Brit. J. prev. soc. Med. (1955), **9**, 140–146.

COMPARATIVE EFFICACY OF HYPNOTICS

A SELF-CONTROLLED, SELF-RECORDED CLINICAL TRIAL IN NEUROTIC PATIENTS

BY

E. H. HARE

Barrow Hospital, Bristol

Although insomnia due to neurotic illness is one of the commonest of symptoms, reports on the comparative efficacy of hypnotics in man are rare. Werz and Homann (1939) and Cohen and Beecher (1951) made controlled comparative studies but were concerned with the sedative rather than the hypnotic effects of the drugs they used. Meyers, Cook, and Page (1940) investigated the hypnotic action of five drugs and a placebo in chronically ill patients, but did not attempt to compare the hypnotics with one another. A search through the literature of the past 20 years has not revealed any other relevant work. There are a number of probable reasons why the problem has not been studied more.

In the first place, there is wide individual variation in the response to a hypnotic drug. If it were also true that an individual's response to one hypnotic bore little relation to his response to another, then there would be no value in attempting to compare the efficacy of different hypnotics in a series of patients. Yet this point is one that does not seem to have been established, and on theoretical grounds we might expect that the *comparative* efficacy of different hypnotics would remain the same in different individuals provided the cause of the insomnia was the same.

In the second place, the conditions necessary for a controlled trial of hypnotics in man are not easily or commonly available, for such a trial requires a series of patients, all suffering from insomnia, under continuous night observation for at least several weeks, and, for preference, sufficiently co-operative and intelligent to give an account of how they slept. These conditions, however, may be fulfilled in hospital wards for the treatment of neurotic patients.

In the third place, so many efficacious hypnotics are available that to compare them might seem a work of supererogation. Indeed, in prescribing hypnotics the practitioner suffers an *embarras de richesse*, and in consequence either tends to confine himself to the use of one or two "favourite" hypnotics or administers a succession of newly-marketed drugs, the comparative efficacy of which has rarely been the subject of a controlled trial.

A satisfactory means of comparing the clinical efficacy of hypnotics would have two valuable uses. It would enable new hypnotics to be tested against long-established drugs, and it would permit a comparison of the efficacy of those already in common use. The common hypnotics are usually prescribed in a dosage which experience has shown as that which gives most patients reasonable relief from insomnia and at the same time is associated with a minimum of undesirable side-effects; it has not, however, been clearly established whether there is any significant difference in the efficacy of these drugs when given in their commonly prescribed dosage. If such differences could be established, then, other things being equal, it would be rational to administer the hypnotic which a controlled trial showed to be most effective.

Present Investigations

Hogben and Sim (1953) have outlined a method for determining the effect of treatment in low-grade morbidity by means of a self-controlled and self-recorded clinical trial. The present investigation was planned as an attempt to study, by this method, the comparative efficacy of hypnotics in patients suffering from neurotic insomnia.

In a self-recorded trial it is necessary to demonstrate the reliability of the self-record by checking it against an independent objective assessment. Two main checks were used in the present investigation, where the self-record was the patient's opinion of the quality of his night's sleep: the first, an external check, was the night-nurse's record of the patient's sleep; the second, an internal check, was achieved

by giving the patient the same hypnotic drugs in differently coloured capsules. If the patient's record is in close agreement with that of the night-nurse, and if in addition the recorded quality of sleep on a particular drug was the same whatever the colour of the capsules, then it would seem reasonable to accept the self-record as a reliable indication of the quality of the patient's sleep. The quality of sleep over a series of nights when the patient is receiving one drug could thus be compared with that when he is receiving another drug or a placebo, provided, of course, that the severity of insomnia remains the same during the different trials. There is no way of assuring this provision, but it might be assumed to hold if the different drugs are given in a random order and for a number of nights sufficient to smooth out the many chance factors that influence the quality of any particular night's sleep.

Material

Thirty females, all patients in a neurosis unit, were studied. A patient was admitted to the trial if she:

(*i*) complained of sleeping poorly or badly for the past few weeks or months (no attempt was made to distinguish between patients who had difficulty in getting off to sleep and those who woke early, for in the majority of neurotic patients no clear distinction of this nature is possible);

(*ii*) was able and willing to co-operate;

(*iii*) appeared to be a reliable witness (on this count, patients with low intelligence, with evidence of dementia, or with psychopathic or grossly hysterical personalities were excluded).

The thirty patients suffered for the most part from neurotic states in which anxiety and depression were the prominent symptoms. Their average age was 40, with a range from 18 to 73. They usually received 3 gr. amylobarbitone for the first two nights after admission and then were placed on the trial, remaining on it for as long as hypnotics were indicated or until they took their discharge. Patients who were on the trial for less than fourteen consecutive nights were excluded from the final assessment.

Administration of Hypnotics

Four separate comparative trials were made, as follows:

(*i*) *Trial A* (six subjects).—The effect of butobarbitone gr. 3 was compared with that of carbromal gr. 12 and also with that of a lactose placebo. The capsules containing these drugs were all identical in appearance, but half of the capsules were coloured red and half were coloured blue. They were administered in a pre-arranged random order (known only to the dispenser), such that over a period of eighteen nights a patient would receive each drug six times, three times in a red capsule and three times in a blue. The patients were not told they were receiving different types of drug; to minimize the chance of their noticing a difference in taste, the capsules were taken under the supervision of the night-nurse and the patients were asked to swallow them whole with a drink of water. To ensure that each patient had the correct capsules, these were sent from the dispensary in separate envelopes on which was written the name of the patient and the date on which the dose was to be taken.

(*ii*) *Trial B* (five subjects).—Sodium butobarbitone gr. 3 was compared with methylpentenol 0·3 g. and with a placebo. As methylpentenol is a liquid, it is administered in special soft elastic gelatine capsules. It was therefore necessary to administer the other drugs in a similar manner; to this end, arachis oil was used as a placebo, and the sodium butobarbitone was dissolved in propylene glycol (butobarbitone is insufficiently soluble for this purpose and therefore could not be used).

(*iii*) *Trial C* (thirteen subjects).—Sodium butobarbitone gr. 3 was compared with methylpentenol 0·5 g. No placebo control was used.

(*iv*) *Trial D* (six subjects).—Sodium butobarbitone gr. 3 was compared with carbromal gr. 12, without a placebo control. The drugs were administered in differently coloured capsules as in Trial A. As 3 gr. sodium butobarbitone is equivalent in barbiturate content to 2·72 gr. butobarbitone, we should expect to find that the efficacy of the barbiturate as compared with carbromal would be less in Trial D than in Trial A.

Record Charts

In general, a person will consider she has had a good night's sleep if she:

(*i*) got off to sleep quickly,

(*ii*) slept soundly for about 8 hours,

(*iii*) had no periods of wakefulness,

(*iv*) had no disturbing dreams,

(*v*) felt fresh on waking.

Any scheme that takes account of these factors should give an adequate record. The relative weight that ought to be attached to the factors is debatable, but probably not of great importance. The form of record chart used is shown overleaf. The mark scored by each possible answer is given in parenthesis. In an initial pilot study a question on dreaming was included, but subsequently omitted in the belief that the presence or absence of dreaming was probably not any indication of the efficacy of the hypnotic. It will be seen that a fully satisfactory night's sleep scores no marks, a very unsatisfactory one scores eleven. An adequate reason for halving the scores (toothache, for example) occurred only twice.

SLEEP RECORD

NAME..... DATE.....

1. Was your night's sleep—	*excellent*	(0)
	good	(1)
	fair	(2)
	poor	(4)
	bad	(6)
2. Did you get off to sleep—	*very quickly*	(0)
	normally	(0)
	with difficulty	(1)
3. Was your sleep—	*sound and uninterrupted*	(0)
	of average quality	(0)
	shallow and unsatisfying	(1)
	broken by long waking periods	(1)
4. On waking, did you feel—	*lively*	(0)
	normal	(1)
	stale	(2)
	"drugged" or confused	(3)

5. If you did not sleep well, was there any special reason? (If reason adequate, halve the score)

From the nurse's point of view, a patient slept well if she:

(*i*) was observed to be asleep for the greater part of the night,

(*ii*) was not restless.

The night-nurse kept a record which was scored as follows:

one mark for each half-hour awake between the hour of 10 p.m. and 7 a.m.;

one mark if there were one or two periods of night waking, two marks if more than two such periods;

one mark if a patient was recorded as "somewhat restless", two marks if "very restless".

If there was "considerable" (as opposed to "none" or "slight") disturbance in the patient's ward, one mark was subtracted. A satisfactory night's sleep would thus score no marks, a sleepless and restless night could score 20 marks.

If the records are reliable, then with one factor excepted the score from the nurse's record should show a high correlation with that from the patient's record. The excepted factor is the patient's estimate of how she felt on waking (it may be called the "hangover" score) as this has no counterpart in the nurse's record. Therefore, for the purpose of correlating the nurse's record against the patient's, the hangover score must be omitted.

Other Considerations

All the patients continued, during their period of trial, to have whatever methods of treatment seemed appropriate to their illness. In the course of treatment, most of the patients improved and many ceased to need hypnotics. It might be argued that the effects of a hypnotic cannot be properly evaluated while a patient is undergoing some relatively drastic form of treatment such as electroplexy (sixteen of the thirty patients had this during their hypnotics trial). However, as no patient goes without some form of treatment, and as the type of hypnotic was changed every night or every second night, it seemed justifiable to assume that the effects of the treatment on the insomnia would on the whole be evenly spread and would not seriously influence the comparative quality of the sleep obtained with the different drugs. This question is referred to again in the discussion.

Results

Table I (opposite) shows the patients' and nurse's average nightly scores in the four trials. Remembering that a low score means a good night's sleep, we see that in Trial A the scores obtained with butobarbitone are in every instance lower than those with the lactose placebo and, with two exceptions, lower than those with carbromal. Also, the carbromal scores are lower (in all but one instance) than the placebo scores. In Trial B, sodium butobarbitone scores are consistently lower than those with methylpentenol or the placebo, but there is little difference between the two latter. Consistency is again apparent in Trial C, where in every instance the sodium butobarbitone scores are less than those for methylpentenol, though the difference is less marked than in Trial B. In Trial D there is evidently little to choose between the two hypnotics.

Table II (overleaf) shows the scores in Trials A and D with the differently coloured capsules. It is evident that there is close agreement between the sets of scores obtained with red capsules and with blue capsules.

The "hangover" effects of the different drugs, as scored in the patient's self-record, are shown in Table III (overleaf). It appears that by this method of estimation none of the drugs in the dosages used caused any considerable "hangover" as compared with the placebos, though there is a slight tendency (in Trials A and D) for the scores on carbromal to be less than those on barbiturate.

It is evident from Table I that there is a wide variation between individual patients in the quality of sleep obtained. One way of considering the combined results in each trial is to allot equal weight to each patient's scores and this can be done by adjusting the barbiturate score to a fixed figure, say a hundred, for each patient and expressing the scores for other drugs as a percentage of this figure. When the scores obtained in this way are added together, the combined results for each trial are as shown in Table IV (overleaf). The comparative scores in each

TABLE I

AVERAGE NIGHTLY SCORES BY PATIENTS (SELF-RECORDED) AND NURSE WITH VARIOUS HYPNOTICS

	Trial	Subject	Number of Nights	Patient's Score			Nurse's Score		
				Butobarb.	Carbromal	Lactose	Butobarb.	Carbromal	Lactose
A	Butobarbitone gr. 3 Carbromal gr. 12 Lactose	1	19	1·60	2·29	3·57	1·80	2·50	3·00
		2	19	2·63	2·71	7·25	3·86	6·17	16·00
		3	22	1·40	2·00	2·71	3·57	4·88	6·00
		4	35	1·07	1·64	2·73	3·31	2·26	3·33
		5	35	2·00	1·92	3·80	5·40	6·00	6·40
		6	26	3·50	5·22	5·56	5·75	8·13	8·00
	Total	6	156	12·20	15·78	25·62	23·69	29·94	42·73
				Sod. butobarb.	Methyl-pentenol	Arachis Oil	Sod. butobarb.	Methyl-pentenol	Arachis Oil
B	Sod. butobarbitone gr. 3 Methylpentenol 0·3 g. Arachis Oil	1	14	1·50	2·25	—	4·17	5·75	—
		2	30	0·83	1·50	1·62	0·78	2·17	1·64
		3	18	0·33	0·86	2·00	2·83	3·00	4·60
		4	14	1·00	1·17	1·25	2·25	3·00	2·74
		5	26	1·13	5·27	4·57	6·00	8·18	7·75
	Total	5	102	4·79	11·06	(9·44)	16·03	22.10	(16·74)
				Sod. butobarb.	Methyl-pentenol	—	Sod. butobarb.	Methyl-pentenol	—
C	Sod. butobarbitone gr. 3 Methylpentenol 0·5 g.	1	13	1·83	2·29		4·00	5·15	
		2	14	1·14	2·79		1·57	4·43	
		3	26	1·25	1·50		3·58	4·07	
		4	14	1·00	2·00		2·80	4·29	
		5	33	1·18	1·63		3·89	4·81	
		6	15	1·17	1·50		3·83	5·14	
		7	19	1·20	2·25		2·25	3·08	
		8	30	3·24	4·31		3·60	4·00	
		9	33	2·82	4·75		3·40	4·31	
		10	33	2·71	3·63		5·63	6·63	
		11	36	2·06	2·42		3·00	3·80	
		12	41	3·12	3·25		8·31	9·20	
		13	18	3·16	3·53		6·08	7·62	
	Total	13	335	25·88	35·85	—	51·95	66·53	—
				Sod. butobarb.	Carbromal		Sod. butobarb.	Carbromal	—
D	Sod. butobarbitone gr. 3 Carbromal gr. 12	1	20	1·00	1·00		3·22	2·36	
		2	14	1·83	3·00		6·33	5·80	
		3	25	1·43	1·73		4·69	6·86	
		4	21	2·56	1·83		9·63	8·67	
		5	27	2·92	2·58		6·82	6·83	
		6	17	1·71	1·70		3·13	3·27	
	Total	6	124	11·45	11·84	—	33·82	33·79	—

trial are of the same order as those in Table I. Table IV enables us to make other deductions. From the results in Trial D, carbromal gr. 12 is about as efficacious as sodium butobarbitone gr. 3; but from Trial A, this dose of carbromal is rather less efficacious than butobarbitone gr. 3. Our confidence in the validity of the method is thus supported, for butobarbitone contains 10 per cent. more of the barbiturate radical than an equal dose of its sodium salt and ought, therefore, weight for weight, to be a rather more effective hypnotic. In the same manner, Trials B and C show what is to be expected: that 0·3 g. doses of methylpentenol are less effective than 0·5 g. doses, when each is compared against 3-gr. doses of sodium butobarbitone.

The degree to which the night-nurse's record checks that of the patient on any particular drug can be expressed as the correlation coefficient between the average nightly scores of the patients and of the nurse in each trial. This is shown in Table V. Further, the patients' average nightly scores on the nights they were receiving the barbiturate may be correlated, for each trial, with their scores when they received the other hypnotic; and the nurse's scores for the two drugs may be similarly correlated. These correlation coefficients are shown in Table VI The comparatively low correlation between the patients' scores for sodium butobarbitone and for methylpentenol in Trial B is entirely due to the high average nightly score of Subject 5 when on methylpentenol. With this exception, the correlations are of a high order, indicating that, although there was great

TABLE II

AVERAGE NIGHTLY SCORES BY PATIENTS AND NURSES WHEN THE SAME DRUGS WERE ADMINISTERED IN DIFFERENTLY COLOURED CAPSULES

The patients' "hangover" scores are also shown.

Trial	Subject	No. of Nights	Patients' Score		Nurses Score		Hangover Score	
			Red Capsules	Blue Capsules	Red Capsules	Blue Capsules	Red Capsules	Blue Capsules
A	1	19	2·56	2·34	2·28	2·39	2·00	2·00
	2	19	3·33	3·23	3·42	5·48	1·89	1·63
	3	22	1·33	2·23	3·46	5·81	1·48	1·40
	4	35	1·71	1·84	2·91	2·93	0·95	1·21
	5	35	2·61	2·18	5·57	5·94	1·92	1·89
	6	26	5·06	·440	7·86	7·11	2·92	3·00
	Total	156	16·60	16·22	25·50	29·66	11·16	11·13
D	1	20	1·00	1·00	2·50	3·07	0·33	0·19
	2	14	2·25	2·00	5·83	6·02	2·50	3·00
	3	25	1·00	1·95	4·92	5·70	1·00	1·27
	4	21	2·25	2·17	9·34	9·58	1·00	1·00
	5	27	2·60	3·04	6·43	7·07	2·50	2·33
	6	17	2·00	1·70	3·63	3·03	1·00	1·25
	Total	124	11·10	11·86	32·65	34·77	8·33	9·04

individual variation in the response to a given hypnotic, the *comparative* activity of two hypnotics was practically the same in the different subjects.

DISCUSSION

Two main criticisms may be made of this investigation: that the number of subjects in each trial is small and that over half the subjects were receiving electroplexy during their period of trial. The numbers are admittedly small; but even in a neurosis ward suitable subjects are not very easily found, for in addition to the requirements mentioned above the patient must be prepared to have a few nights of poor sleep (when receiving the placebo) and his sleep must not be consistently excellent on the drugs tested or there would be no difference to record. However, even with the small number of subjects, the results are sufficiently consistent to make the investigation seem worth reporting. The second criticism is more serious, as electroplexy may disturb a patient's judgment. In Trial A, however, only one of the six subjects (Subject 3) received electroplexy, yet all the trials show a similar degree of consistency. On the other hand, the fact that ten of the thirteen subjects in Trial C and four of the six in Trial D received electroplexy might possibly explain the rather lower correlation between the scores of the patients and of the nurses in these two trials.

If these criticisms are met, then the results of the trial allow of four main conclusions:

(1) Reasons for believing the method to be reliable may be summarized as follows:

(*i*) the patients' self-record of the quality of their sleep showed a high positive correlation with the night-nurses' record;

(*ii*) the patients' scores when they received a series of drugs in red capsules were practically the same as when they received the same drugs in blue capsules;

(*iii*) neither patients nor nurses knew when a hypnotic or a placebo was administered; but the quality of sleep recorded on placebo nights was consistently the poorer;

(*iv*) compared against a fixed dose of carbromal, the mean quality of sleep of a series of patients receiving butobarbitone was somewhat better than that of patients receiving the same weight (and therefore a smaller barbiturate equivalent) of sodium butobarbitone; and a similar relation held between patients receiving 0·5 g. and 0·3 g. of methylpentenol when tested separately against a fixed dose of sodium butobarbitone.

TABLE III

AVERAGE NIGHTLY "HANGOVER" SCORE OF PATIENTS ON DIFFERENT HYPNOTICS

Trial	Subject	No. of Nights	Hangover Score		
			Butobarb gr. 3	Carbromal gr. 12	Lactose
A	1	19	2·00	2·00	2·00
	2	19	2·13	1·14	2·25
	3	22	1·86	1·13	1·29
	4	35	0·92	1·18	1·08
	5	35	2·00	2·00	2·00
	6	26	3·00	2·89	3·00
	Total	156	11·91	10·34	11·62
			Sod. butobarb. gr. 3	Methyl-pentenol 0·3 g.	Arachis Oil
B	1	14	1·33	1·38	—
	2	30	1·00	1·55	1·92
	3	18	1·00	1·00	1·20
	4	14	1·00	1·00	1·00
	5	26	2·13	2·09	2·00
	Total	102	6·46	7·02	(6·12)
			Sod. butobarb. gr. 3	Methyl-pentenol 0·5 g.	—
C	1	13	2·67	3·00	
	2	14	2·00	1·86	
	3	26	1·83	1·61	
	4	14	1·00	1·13	
	5	33	1·00	1·13	
	6	15	1·17	1·25	
	7	19	1·07	1·29	
	8	30	1·47	1·54	
	9	33	1·53	2·19	
	10	33	2·22	2·38	
	11	36	1·41	1·58	
	12	41	1·17	1·10	
	13	18	1·69	1·93	
	Total	335	20·23	21·99	—
			Sod. butobarb. gr. 3	Carbromal gr. 12	—
D	1	20	0·00	0·45	
	2	14	3·00	0·45	
	3	25	1·14	1·17	
	4	21	1·00	1·00	
	5	27	2·38	2·22	
	6	17	1·29	1·20	
	Total	124	8·81	8·64	—

TABLE IV

MEAN FOR EACH TRIAL OF THE AVERAGE NIGHTLY SCORES RECORDED BY THE PATIENTS AND BY THE NURSE

In calculating the means, each subject's record has been given equal weight by expressing her score on each drug as a percentage of her barbiturate score

Trial	No. of Subjects	Drug	Patients	Nurse
A	6	Butobarbitone gr. 3 ..	100	100
		Carbromal gr. 12 ..	132	126
		Lactose	212	185
B	5	Sod. butobarb. gr. 3 ..	100	100
		Methylpentenol 0·3 g.	237	159
		Arachis oil	325	155
C	13	Sod. butobarb. gr. 3 ..	100	100
		Methylpentenol 0·5 g.	148	139
D	6	Sod. butobarb. gr. 3 ..	100	100
		Carbromal gr. 12 ..	107	101

TABLE V

CORRELATION BETWEEN AVERAGE NIGHTLY SCORES RECORDED BY THE PATIENTS FOR EACH DRUG AND THE EQUIVALENT SCORE RECORDED BY THE NIGHT-NURSE

Trial	Correlation Coefficient
A	+ 0·85
B	+ 0·82
C	+ 0·51
D	+ 0·63
For all trials combined	+ 0·70

TABLE VI

CORRELATIONS BETWEEN THE PATIENTS' AVERAGE NIGHTLY SCORES WHEN RECEIVING THE BARBITURATE AND WHEN RECEIVING THE ALTERNATIVE HYPNOTIC; AND BETWEEN THE EQUIVALENT SCORES RECORDED BY THE NIGHT-NURSE

Trial	Correlation Coefficient	
	Patients' Scores	Nurses' Scores
A	+ 0·91	+ 0·86
B	+ 0·47	+ 0·97
C	+ 0·85	+ 0·94
D	+ 0·59	+ 0·89

For these reasons it would appear that the self-controlled, self-recorded clinical trial could satisfactorily be used for testing a new hypnotic and comparing its efficacy in combating neurotic insomnia with that of a given dose of an established hypnotic.

(2) Although there was wide individual variation in response to any particular hypnotic, the comparative response to two hypnotics remained almost constant among the subjects in the trials. This constancy of comparative response to hypnotics does not appear to have been clearly established hitherto. If it is a fact, then in general we can no longer suppose that some patients respond well to one particular hypnotic while others may respond better to a different hypnotic.

(3) In the doses given, the hypnotic drugs administered caused no appreciable subjective feeling of "hangover". Goodnow and others (1951) and Felsinger, Lasagna, and Beecher (1953) have nevertheless shown that there may be impairment of physiological performance after barbiturate in the absence of subjective sensations. The patients' estimates of how they felt on waking was in some respects the least satisfactory part of the trial. One or two of the patients with long-standing neurotic disability seemed to feel they owed it to themselves always to complain of waking up "drugged" whenever they believed they had been given a hypnotic. This is an attitude of mind which might explain the statement of Goodman and Gilman (1955) that "hangover from relatively small hypnotic doses (of barbiturates) occurs especially among neurotic patients".

(4) The results suggest that carbromal in a dose of 12 gr. is less efficacious than butobarbitone gr. 3 but has approximately the same efficacy as sodium butobarbitone gr. 3. Carbromal in a dose of 10–15 gr. would thus appear to be a hypnotic of considerable potency and has perhaps been unduly neglected; the National Formulary (1955), for example, states that it is "a weak hypnotic", while Goodman and Gilman (1955) dismiss the monoureides as "somewhat disappointing due to their feeble depressant effects".

Methylpentenol, on the other hand, in a dose of 0·3 g. proved little better than a placebo, and 0·5 g. was sitll considerably less effective than 3 gr. sodium butobarbitone. Hirsh and Orsinger (1952), who administered methylpentenol to 276 patients in doses up to 0·5 g., concluded that it was most effective in "simple insomnia" and less so in agitated states; a similar conclusion was reached by Chevalley and others (1952), and the present trial tends to support these findings.

SUMMARY

(1) This paper describes a self-controlled and self-recorded clinical trial of the comparative efficacy of three common hypnotic drugs in thirty patients suffering from neurotic insomnia.

(2) The reliability of the self-records was checked by several independent methods.

(3) This type of trial appears to yield reliable results and could be used to test the efficacy of new hypnotics.

(4) Butobarbitone gr. 3 was shown to give more relief from insomnia than carbromal gr. 12, which in turn was more efficacious than methylpentenol 0·5 g.

My grateful thanks are due to Mr. E. F. Wellington, dispenser at Barrow Hospital, for his kindness in preparing and dispensing the trial capsules; and to the night-nurses in the neurosis ward for their conscientious co-operation.

ADDENDUM

After this paper had been written, the author's attention was drawn to the work of Straus, Eisenberg, and Gennis (1955). By a self-controlled and self-recorded trial, they have compared the hypnotic activity of an antihistamine with that of phenobarbitone and a placebo. Their method of recording the quality of sleep was somewhat different, and their statistical analysis was more complex than that used in the present investigation; but the underlying principle and general conclusions as to the suitability of the method for comparing the action of hypnotics were the same.

REFERENCES

Chevalley, J., Heminway, N., Meyer, G., Frankhauser, R., and McGavack, T. H. (1952), *N. Y. St. J. Med.*, **52**, 572.

Cohen, E. N., and Beecher, H. K. (1951), *J. Amer. med. Ass.*, **147**, 1664.

Felsinger, J. M. von, Lasagna, L., and Beecher, H. K. (1953), *J. Pharmacol.*, **109**, 284.

Goodman, L. S., and Gilman, A. (1955). "The Pharmacological Basis of Therapeutics", 2nd ed. Macmillan, New York.

Goodnow, R. E., Beecher, H. K., Brazier, M.A.B., Mosteller, F., and Tagiuri, R. (1951). *J. Pharmacol.*, **102**, 55.

Hirsch, H. L., and Orsinger, W. H. (1952). *Amer. Practit. Digest. Treatment (Philad.)*, **3**, 23.

Hogben, L., and Sim, M. (1953). *British Journal of Preventive and Social Medicine*, **7**, 163.

Meyers, F., Cook, E. D., and Page, R. C. (1940) *N. Y. St. J. Med.*, **40**, 12.

Straus, B., Eisenberg, J., and Gennis, J. (1955). *Ann. intern. Med.*, **42**, 574.

Werz, R. von, and Homann, G. (1939) *Arch. exp. Path. Pharmak.*, **193**, 272.