EFFECTS OF HYOSCINE AND MECLOZINE ON VIGILANCE AND SHORT-TERM MEMORY

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An investigation was made of the effects of 1 mg. hyoscine hydrobromide and of 50 mg. meclozine hydrochloride on the performance of tasks of vigilance and short-term memory. In further trials the effects of these drugs were measured after ingestion of 32 g. ethyl alcohol. Efficiency was impaired by hyoscine taken alone, but meclozine alone had no significant effect. The effect of hyoscine was substantially increased by the presence of alcohol and under these conditions the effect of meclozine was equally great. The vigilance task appeared to be more sensitive to the effects of the drugs than the memory task, and possible reasons for this are considered in the discussion.

The efficacy of both 1 mg. hyoscine hydrobromide and 50 mg. meclozine hydrochloride in allaying the physiological effects of motion have been amply demonstrated (Glaser and McCance, 1959; Report of study by Army, Navy, and Air Force motion sickness team, 1956), and since existing studies typically report that doses of 0·65 mg. hyoscine or 50 mg. meclozine (Payne and Moore, 1955), or even of 1·2 mg. hyoscine (Holling, McArdle, and Trotter, 1944) do not exert any significant influence on performance, it might be concluded that the use of these drugs in small doses is quite safe. However, whereas these studies usually take as a criterion the level of skill displayed at some kind of motor task such as tracking, it is noteworthy that in an experiment measuring quite a different capacity, *i.e.* memory for verbal material, Payne (1955) found that 0·65 mg. hyoscine or 50 mg. meclozine significantly impaired retention. This suggests that although motor functions may remain unimpaired by small doses of these drugs, processes of a primarily perceptual kind may be more sensitive to their effects. If this were found to be the case, the use of these drugs by persons employed on work where such processes are involved might be contra-indicated in certain cases.

The present experiment was designed to investigate the effects of 1 mg. hyoscine and of 50 mg. meclozine on the performance of tasks in which the primary measures were of perceptual efficiency and memory function. The motion-sickness compounds were tested both in isolation and in conjunction with 32 g. ethyl alcohol, in view of the possibility that their effects might be increased in the presence of a depressant drug.

Two main performance tests were employed. One of these was of the "vigilance" type, in which, although motor activity is minimal, constant alertness is required over a prolonged period. Since vigilance performance is known to be affected by various physiological conditions (Mackworth, 1950; Wilkinson, 1960) it was considered that a test of this kind would provide a sensitive indication of any effect of the drugs. The task selected was the digit-checking test of Kappauf and Powe (1959), adapted for group administration.

The other main test was of short-term memory in a self-paced situation. The task used here was the sequence-following procedure shown by Broadbent and Heron (1962) to be sensitive to the effects of distraction and ageing.

In an additional short test an attempt was made to measure "higher" levels of behaviour by requiring subjects to generate a random series. Baddeley (1962) has shown that when subjects are tested individually at this task under carefully controlled conditions, performance is related to intelligence and is sensitive to ageing effects. The present employment of the task as a group test was intended primarily as an exploration of its value in this relatively uncontrolled form.

TABLE 1

SCHEDULE OF EXPERIMENTAL SESSIONS

Day 1	Day 2	Day 3	Day 4	Day 5
All subjects practice on tests	Half subjects: placebos I and II* Half subjects: no treatment	One-third subjects (Group A): placebo I One-third subjects (Group B): meclozine One-third subjects (Group C): hyoscine	Group A: placebo II Group B: alcohol† Group C: alcohol‡	Group A: placebos I and II Group B: meclozine and alcohol§ Group C: hyoscine and alcohol§

* Placebo I = motion sickness drug placebo   Placebo II = alcohol placebo.

†Meclozine remains in the body for more than 24 hours after ingestion. This group was therefore tested under the influence of alcohol plus a residue of meclozine.

‡Hyoscine is fully metabolized in under 12 hours. This group was therefore tested under the influence of alcohol alone.

§Both these groups were assumed to be free of residual dosages of alcohol and motion sickness drugs from Days 3 and 4.

Experimental Design

The following treatments were investigated: (1) meclozine alone, (2) hyoscine alone, (3) alcohol alone, (4) meclozine with alcohol, (5) hyoscine with alcohol, (6) alcohol with the residue of a meclozine dose taken 24 hours previously. Two control conditions were considered necessary: (i) no treatment, (ii) placebo.

Since for administrative reasons the experiment had to be completed within a period of five consecutive days, it was not possible to test each subject's performance under all conditions. Instead, each subject was tested on four occasions only. On the first of these an assessment was made of individual levels of performance under control conditions. Half the subjects received no treatment on this occasion, the other half placebo, in order that the effects (if any) of the latter might be determined. The subjects were then divided into three groups of equal number. On the second and subsequent testing occasions, one of these groups received (unknown to them) placebo only. This group served as a control group for the two remaining groups who received the drug treatments in accordance with the schedule shown in Table 1.*

Since it was desired to test performance at a time when the concentrations of the drugs were relatively stable, meclozine and hyoscine were administered two hours, and alcohol 30 minutes before test sessions began, in order that absorption would be completed beforehand. However, as testing continued for 90 minutes, the latter part of the testing programme was carried out during a period when certainly the alcohol and possibly the hyoscine concentrations were falling from peak value, owing to the relatively rapid rate of elimination of these drugs from the body.

*It should be noted that, since this design is not of the "crossover" type, the validity of the results on all testing occasions other than the first rests on the assumption that performance on these occasions is determined solely by the drugs then present in the body, and is independent of previous treatments.

Drug Administration.—The meclozine, hyoscine, and placebo (lactose) doses were made up into tablets of identical size, shape, and colour, which were swallowed whole with water.

The alcohol dose consisted of 70 ml. of 90·5% proof spirit, equivalent to 32 g. absolute alcohol. It was diluted with 20 ml. of ginger cordial and 10 ml. of "Coca-Cola". For control purposes a drink which was closely similar in both taste and appearance was made up by floating 7 ml. of the spirit on the surface of a mixture of 30 ml. ginger cordial, 40 ml. "Coca-Cola" and 23 ml. water.

Consumption of tablets and drinks took place immediately on issue, and was closely supervised by personnel who were unaware of the treatment assigned to each subject.

Performance Tests.

Test 1: Vigilance.—The subject listened to a long, continuous series of random digits presented over a loudspeaker from a tape recording at the rate of one per second. His task was to check an almost identical series presented in a mimeographed test booklet, and mark the booklet whenever he detected a discrepancy between the two series. There were 450 digits on each page of the booklet, arranged in rows of thirty. Each successive pair of pages contained 10 discrepancies, distributed at random with the sole constraint that no single page contained less than three or more than seven discrepancies. Ten sets of booklets were prepared, each containing a unique set of discrepancies. Each subject had a different booklet. In order to make the test of indeterminate length, all booklets contained more pages than were actually used.

The score obtained from this test was the percentage of discrepancies correctly marked off (signal detection efficiency). This score was calculated separately for each page of digits in the booklet, and also for the entire series.

Test 2: Sequence Following.—The subject again checked through a series of random digits, but this

time the numbers were presented in single rows of 10 through a viewing aperture, and the task was self-paced, a new row of digits being brought into the aperture by the operation of a knob. The digits were read from left to right, the first "0" occurring being marked off with a pencil, then the next "1", then the next "2", and so on up to "9". On reaching "9" marking off recommenced at the next "0". The test continued for 20 minutes, instructions being given to work as fast as was consistent with accuracy. Every second occurrence of a "key" digit (*e.g.* "1") was clearly labelled, in order that any previous error on the part of the subject might have no further cumulative effects beyond this point. The subject started at a different point in the sequence on each occasion of testing; this starting point was identified by a labelled "key" digit which also differed. No part of the sequence was therefore ever the same for any single subject on successive occasions of testing.

The scores obtained from this test were (1) the number of rows of digits checked through in the time allowed (speed of work), (2) the number of errors of *omission* (failure to mark off the first example of the digit next in the sequence), (3) the number of errors of *memory* (marking off a digit which was not the correct one in the sequence at that point). These scores were expressed as totals for the complete run.

Test 3: Random Sequence Generation.—The subject was required to write down, in columns of 10, a sequence of 120 letters of the alphabet similar to one he might obtain by drawing the letters from a hat containing an infinitely large number of each letter. Successive letters were written at one-second intervals to the beat of a metronome. Instructions were given to avoid constructing meaningful words, and also naturally occurring sequences such as "ABCD".

This test can be scored in several ways, but the two measures used here were first the total number of different digrams employed, and second the percentage of stereotyped digrams (a stereotyped digram is defined as one that occurs in the natural sequence of the alphabet, *e.g.* LM).

These three tests were given in the order 2, 3, 1, on each occasion of testing. Test 2 lasted for 20 minutes, Test 3 for two minutes, and Test 1 for one hour. The additional time required for instructions, changeover of test material *etc.* brought the total test time to approximately 90 minutes.

Subjects.—The 33 volunteers for this experiment were all young healthy Servicemen who were members of a group undergoing special combat training. Morale was good in this group and the level of motivation in the volunteers was high. Only one subject had had previous experience with a motion-sickness drug, but all subjects were used to taking alcohol in small or moderate amounts at fairly frequent intervals. Scores obtained on the AH4 test (Heim, 1955) indicated that as a group the subjects were of somewhat above average intelligence, and ratings obtained from the Heron personality inventory (Heron, 1956) showed that they were on the whole slightly more sociable and emotionally stable than the typical male Serviceman of this age-group.

Procedure.—During the course of the experiment subjects were excused all but light duties, but were confined to barracks and were not permitted to take alcohol in any form. Smoking was not restricted except during test sessions, and normal meals were taken. Subjects were under the direct observation of the author or his assistants during the forenoon of each day, but were not supervised at other times. During test sessions subjects sat at individual work-desks in a single large hall. No two subjects receiving the same treatment sat next to each other. Watches were not worn.

On Day 1 subjects were given an introductory briefing on the general purposes of the experiment, and were told that they could all expect to receive both motion-sickness tablets and spirits in the course of the succeeding four days. The three performance tests were explained, and then practised until all subjects were fully conversant with the procedures. Intelligence and temperament tests then followed, and details of age, body weight, and drug experience were obtained by questionnaire.

On Day 2, 17 subjects, selected at random, were given placebo tablets and "dummy" alcohol at 10.00 a.m.; the remaining 16 subjects were given nothing at this time. The three performance tests were then taken in the order previously described, commencing at 10.30 a.m. and finishing at approximately 12 noon. At this point, the 16 "no treatment" subjects were given the placebo tablets and "dummy" alcohol in order to equate their "drug" experience with that of the others.

The subjects were then divided into three groups of 11 (Groups A, B, and C in Table 1), matched as far as possible on the basis of their performance scores in the three tests. On Days 3, 4, and 5 treatments were administered to these groups in accordance with the schedule given in Table 1. Tablets were issued at 8.30 a.m., drinks at 10.00 a.m., when detailed. Performance tests were carried out as for Day 2 on each occasion.

At 10.25 a.m. and again at 12 noon on each of Days 2 to 5 subjects completed a short questionnaire, adapted from Glaser and Whittow (1954), which was

TABLE 2

MEANS AND RANGES OF DAY 2 PERFORMANCE SCORES

Group	Test 1 Vigilance	Test 2 Sequence Following			Test 3 Random Sequence Generation	
	Detections (%)	Speed (Rows Completed)	Omission Errors (No.)	Memory Errors (No.)	Digrams (No.)	Stereotyped Digrams (%)
A	95·7 (90·0-100·0)	392 (261-594)	7·1 (0-16)	†	76·9 (64-92)	25·3 (13-46)
B	95·7 (90·0-100·0)	409 (282-601)	7·5 (0-23)	†	76·9 (44-97)	17·5 (4-40)
C	96·8 (90·0-100·0)	401 (304-529)	6·8 (0-15)	†	81·5 (62-102)	19·6 (10-32)

†Insufficient data for analysis.

TABLE 3

MEANS AND RANGES OF PERSONAL VARIABLES

Group	Age (years)	Bodyweight (lb.)	Intelligence (AH4)	Emotional Instability (Heron: Pt. I)	Unsociability (Heron: Pt. II)
A	18·7 (18-21)	163 (145-190)	72·2 (50-96)	6·0 (1-11)	3·2 (1-9)
B	19·0 (18-22)	162 (142-216)	77·5 (55-102)	6·9 (2-12)	3·4 (1-6)
C	20·4 (18-25)	157 (133-189)	71·8 (54-104)	6·7 (1-14)	2·7 (1-4)

TABLE 4

MEAN PERFORMANCE SCORES OF "PLACEBO" AND "NO TREATMENT" CONDITIONS ON DAY 2

Condition	Test 1 Vigilance	Test 2 Sequence Following			Test 3 Random Sequence Generation	
	Detection (%)	Speed (Rows)	Omission Errors (No.)	Memory Errors (No.)	Digrams (No.)	Stereotyped Digrams (%)
Placebo	96·2	400	8·2	†	79·7	21·2
No treatment	96·2	396	5·9	†	76·6	20·6

†Insufficient data for analysis.

TABLE 5

VIGILANCE TEST: MEAN DETECTION SCORES (%) ON DAYS 3, 4, AND 5

Group	Day 3		Day 4		Day 5	
	Condition	Score	Condition	Score	Condition	Score
A	Placebo	94·0	Placebo	96·1	Placebo	93·6
B	Meclozine	91·7	Alcohol and meclozine residue	84·7	Alcohol and meclozine	75·6
C	Hyoscine	82·1	Alcohol	90·0	Alcohol and hyoscine	65·0

TABLE 6

VIGILANCE TEST: PROBABILITIES OF DIFFERENCES BETWEEN TREATMENT CONDITIONS BEING DUE TO CHANCE ALONE (p ≤ 0·05 only shown)

Treatment Conditions						
1	2	3	4	5	6	7
Placebo	Meclozine	Hyoscine	Alcohol	Meclozine plus Alcohol	Hyoscine plus Alcohol	Meclozine Residue plus Alcohol
1		<0·02	=0·05	<0·002	<0·002	=0·05
	2			<0·002	<0·002	<0·02
		3			<0·002	
			4	=0·05	<0·002	
				5		<0·02
					6	<0·02
						7

designed to elicit information concerning subjective symptoms such as nausea, headache, and dry mouth.

Results

Interrelationships of Performance Test Scores.— The performance scores obtained on Day 2 were examined to test the hypothesis that the three performance tests were in fact independent measures of behaviour. No significant degree of relation (measured by the rank correlation coefficient "tau") was observed between any score from one test and any score from another, nor between different scores from a single test. Thus it appears that different aspects of performance were being tested in each case.

Intergroup Matching.—The means and ranges of the Day 2 scores for each of the three experimental groups A, B, and C are shown in Table 2. Matching between groups was reasonably good in all cases except on the score of "percentage stereotyped digrams" from Test 3.

The three groups were also reasonably well matched for age, bodyweight, intelligence, and temperament (see Table 3).

Effect of "Placebo" Treatment.—The mean performance scores returned by the "placebo" and "no treatment" groups on Day 2 are shown in Table 4. The scores in Test 1 were identical, and the differences between the groups in Tests 2 and 3 were not statistically significant at the 5% level of confidence.* It cannot be said, therefore, that the placebo treatment had any effect on performance.

Effect of Drug Treatments on Vigilance (Test 1).— The mean overall detection scores for Groups A, B, and C on Days 3, 4, and 5 are shown in Table 5. On Day 3 the detrimental effect of the motion-sickness drugs was found to be statistically significant in the case of hyoscine but not in the case of meclozine (see Table 6). However, when meclozine was taken in conjunction with alcohol (Day 5) performance was significantly impaired, and the presence of only a residue of the drug when alcohol was taken (Day 4) increased the impairment (slight, but statistically significant) due to the latter. The effect of hyoscine was significantly increased by a concurrent dose of alcohol (Day 5) in much the same manner. It is clear, in fact, that the combination of either meclozine or hyoscine with alcohol impaired efficiency to a

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*The procedure for assessing the statistical significance of the various treatment effects is described in the Appendix.

greater extent than would be predicted by the simple addition of the effects of alcohol and either one.

The mean detection score for each consecutive page of digits checked is shown in Fig. 1. The temporal action of hyoscine with or without a concurrent dose of alcohol, and of meclozine with either a concurrent or a delayed dose of alcohol appeared to be rather similar. In each case performance appeared to be almost unaffected initially, but as time progressed efficiency dropped rapidly to reach a minimum level somewhere about the middle of the test period (somewhat earlier in the case of alcohol with meclozine residue). The detection score tended to rise again after this point. The decrement with alcohol alone was less rapid in onset, and continued throughout the entire test period.

(Note: The fact that the drug effects on Days 4 and 5 were not evident at the start of the test is supporting evidence for the assumption of no Treatment by Day interaction that is required for the assessment of the results on these days. It seems reasonable to suppose that any adverse "carry-over" effects in Groups B and C arising from their previous day's testing under drug conditions would have been apparent at this stage of the test session. Also pertinent to this point is the fact that there was a partial end-recovery in the drug groups even on the final day of testing.)

Effect of Drug Treatments on Sequence Following (Test 2).—The mean scores for the three measured aspects of performance on this task are given in Table 7. Each drug treatment produced a fall in speed of work, and (except in the case of meclozine alone) an increase in the number of errors made. However, only the effects of hyoscine with alcohol were statistically significant at the 5% level of confidence.

Although the results on this test were less clear cut than on the vigilance test, it is noteworthy that the rank order of the mean scores both of speed of work and of errors of omission for the three Groups on each day was almost identical with that for the corresponding detection scores in the vigilance test; the probability that this could have occurred by chance alone in either case is only 0·032 (by "tau").

Effect of Drug treatments on Random Sequence Generation (Test 3).—Since Groups A, B, and C were not adequately matched on their Day 2 "percentage stereotyped digrams" score, only the "total number of digrams" score was analysed. No significant change in this score was produced by any of the drug treatments. The average number of digrams recorded remained relatively constant throughout Days 2 to 5 in each Group. The rank order of the mean scores for the three Groups on

TABLE 7

SEQUENCE FOLLOWING TEST: MEAN PERFORMANCE SCORES ON DAYS 3, 4, AND 5

Group	Day 3				Day 4				Day 5			
	Condition	Speed	Omission Errors	Memory Errors	Condition	Speed	Omission Errors	Memory Errors	Condition	Speed	Omission Errors	Memory Errors
A	Placebo	479	8·1	0·5	Placebo	501	7·4	0·2	Placebo	548	8·9	0·2
B	Meclozine	463	7·0	0·6	Alcohol and meclozine residue	484	11·9	1·5	Alcohol and meclozine	505	9·6	1·4
C	Hyoscine	453	11·7	0·3	Alcohol	466	8·4	0·9	Alcohol and hyoscine	436	9·8	1·5

TABLE 8

PERCENTAGE OF SUBJECTS REPORTING ONE OR MORE SYMPTOMS BEFORE AND
AFTER TEST SESSION

Day 2			Day 3			Day 4			Day 5		
Condition	Before	After	Condition	Before	After	Condition	Before	After	Condition	Before	After
Placebos I and II	41	82	Placebo I	18	64	Placebo II	36	54	Placebos I and II	54	82
No treatment	6	75	Meclozine	36	73	Alcohol plus meclozine residue	64	82	Alcohol plus meclozine	82	100
			Hyoscine	73	73	Alcohol	36	54	Alcohol plus hyoscine	100	91
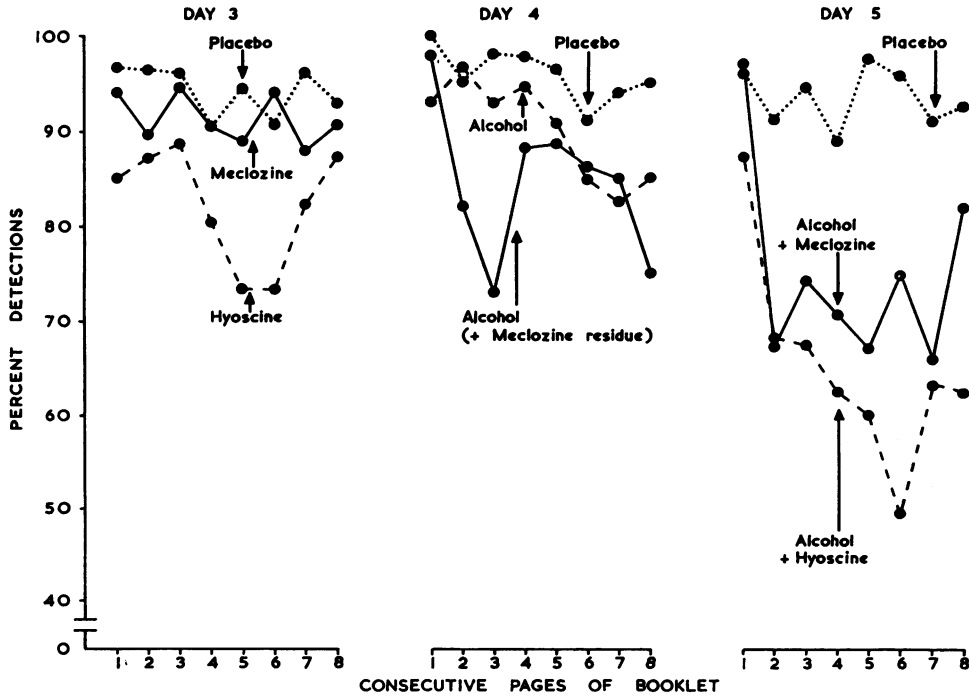
FIG. 1.—Vigilance test: mean detection score for each consecutive page of digits checked on Days 3 to 5.

each of Days 3 to 5 did not correspond with that for the scores on either Test 1 or Test 2. Thus it cannot be said that the drugs had any effect on performance on this test.

Individual Differences.—The range of scores obtained from the initial testing session on Day 2 varied in the three tests, being very small in Vigilance, and considerable both in Sequence Following and in Random Sequence Generation (see Table 2). The differences between subjects were not related either to intelligence or to temperament.

The effect of each drug treatment differed considerably in individual subjects, but again no correlation was found between degree of performance impairment and intelligence or temperament. Body weight was also unrelated to drug effect.

Subjective Symptoms.—The most commonly reported symptoms were sleepiness, dry mouth, inability to concentrate, and headache. The percentage of subjects reporting one or more symptoms under the various conditions is shown in Table 8.

On average, more symptoms were reported at the end of each session than at the beginning, and there was also an increase in reported symptoms over the four days on which they were recorded. However, with the exception of the "alcohol alone" case the proportion of subjects in both of the "drug" groups reporting one or more symptoms was greater than the proportion in the control group on each day (this was true even on Day 2 where the "drug" was actually placebo). Examination of the records showed that this greater incidence of symptoms was chiefly due to a rise in the proportion of subjects reporting headache or inability to concentrate.

Before the test session began hyoscine produced rather more symptoms than meclozine (possibly on account of its relatively quicker absorption rate). By the end of the session there was little difference in the gross incidence of reported side-effects from the two drugs, although detailed analysis showed that at this time dry mouth was reported more than twice as frequently after hyoscine as after meclozine. There was a tendency for more symptoms to be reported by individuals whose performance was affected to a greater extent by the drugs, but the degree of correlation between symptom incidence and performance decrement was not statistically significant.

Discussion

The finding on the first of the three experimental test days that 1 mg. hyoscine impaired performance in a situation where 50 mg. meclozine had no significant effect may have implications for the selection of a drug for use by persons whose efficiency cannot be permitted to deteriorate as a result of anti-motion-sickness medication. However, it should be noted that the actual dose recommended by the manufacturers of motion-sickness preventives that contain hyoscine or meclozine are smaller than those investigated here. Recommended single doses are usually 0·3 mg. hyoscine and 25 mg. meclozine. Thus it might be argued that the quantities of the drugs used, particularly in the case of hyoscine, were unnecessarily large for practical purposes, and that neither of the *recommended* doses would have impaired performance. Although this may well be true, the writer knows of no experimental proof that 0·3 mg. hyoscine is actually effective in preventing motion-sickness and there is definite evidence that meclozine in a dose of 25 mg. only does *not* provide protection (Glaser and McCance, op. cit.). Thus the dosages used were those which on the available evidence appeared to be appropriate in each case.

If it is accepted that the doses of meclozine and hyoscine used were of approximately equal strength, their differential effect on performance might be considered to arise from a difference in their mode of action on the nervous system; this seems plausible in view of their differing chemical constitution. An alternative possibility is that the temporal action of the drugs is dissimilar, *i.e.* that whereas the effects of hyoscine on behaviour are clearly observable at the time after ingestion at which performance was measured, those of meclozine appear either earlier or later than this. This is unlikely, since both drugs were tested at near peak concentrations where maximal effects would be expected.

Whatever the reason for the difference between the two drugs may be, the practical conclusion is that meclozine is to be preferred, as far as short-term effects on performance are concerned. However, a drawback to the use of meclozine is the excessive length of time during which this drug continues to circulate in the bloodstream. Thus it has been objected (Glaser, 1959) that for short exposures to motion it is undesirable to employ a drug that remains active for more than 24 hours after ingestion. The results obtained on the second day of the experiment provide some reason for sustaining this objection, since it appeared there that the effect of a relatively small dose of alcohol on performance was increased by the presence of the residue of a dose of 50 mg. meclozine taken some 27 hours earlier. Although the evidence for this residual effect of meclozine was not conclusive, the enhancement (on the final day's testing) of the effect of a peak concentration of this drug by the presence of alcohol was clear, as was the increment to the effect

of a peak concentration of hyoscine provided by this added depressant. There was no significant difference between the effects of the two drugs in this respect. Thus when alcohol is likely to be taken both hyoscine and meclozine are contraindicated if efficiency is to be maintained.

Although the effects of the drug treatments were well defined in the Vigilance test, they were less reliably established in the case of Sequence Following; this was apparently due to greater inter-individual variability in the latter case. Thus it appears that these two tasks may be differentially sensitive to the drugs in the sense that the capacity to remain constantly alert in order to make a series of sensory discriminations at a rate which is externally determined is more readily impaired than the ability to work efficiently at a more complex task involving memory where the flow of events can be controlled. Performance of the additional test of Random Sequence Generation was apparently quite unaffected by the drugs, but since this may have been due to the relatively uncontrolled conditions under which the test was administered no conclusion can be drawn about its true sensitivity.

Further research is needed before the apparent difference in the sensitivity of the Vigilance and Sequence Following tests can be accepted as proved, since certain differences existed between the two test situations in the present case which may have been influencing the results. These differences were: (1) *task duration*—the vigilance test was three times as long as the memory task; (2) *sequence of testing*—the vigilance test was the last task performed in a series which entailed one and a half hours of almost continuous work; (3) *time since ingestion of the drugs*—this was somewhat greater in the case of the vigilance test. Thus the observed difference between the tests may have resulted from an interaction of the drug effects with either task length, general work fatigue, or time, rather than from differential impairment of the specific skills involved in the two tasks. However, since the concentration of alcohol (and possibly also of hyoscine) was falling during the Vigilance test, and was therefore lower at that time than during the Sequence Following test, the supposition that greater sensitivity to the drugs was shown by the former task because of the longer period elapsing between drug ingestion and performance in that case is unlikely to be true. Again, the very high level of the detection score returned by the control group in the vigilance test suggests that the amount of general work fatigue generated during the whole test session was insufficient to affect performance at this task. On the other hand the known ability of individuals to compensate successfully for the otherwise depressing effect of alcohol when the task is a short one (Drew, Colquhoun, and Long, 1959) suggests that the relatively longer period for which the vigilance task had to be performed may have contributed to its apparently greater sensitivity to the drugs. The fact that impairment increased as a function of time on this test supports this interpretation.

These considerations suggest that until further evidence has been obtained it would be unwise to accept the ostensibly greater sensitivity of the vigilance test as being due to anything other than its relatively long duration. Even if the task duration was shown to be irrelevant, it could not then be said with certainty that any task of the vigilance type would be more sensitive to the drugs than the memory task. Most vigilance tasks involve the detection of a standard difference in certain members of a series of stimuli of constant form, occurring in a single sensory modality. The stimuli in the present vigilance task, on the other hand, were of varying form; they were presented simultaneously to two senses for comparison; and the "signal" to be detected varied according to the particular digit being checked. It is possible that the greater susceptibility of this task to drug effects depends on its possession of one or more of these particular characteristics rather than on those features which it holds in common with other vigilance tasks. Should this prove not to be the case, further research would be required to determine the most important of these common features, one of the more obvious of which is the fact that the task is externally paced.

The absence of a significant degree of correlation between individual performance levels under the drugs and either temperament, intelligence, or body weight should not be taken as evidence that these variables are irrelevant. Temperament has been shown to be a significant factor in at least one previous study on alcohol (Drew *et al.*, op. cit.), and the failure to show a relation in the present case may well have been due to the restricted range of Heron test scores obtained. Intelligence is perhaps of less importance when, as here, the motivational level of subjects is high. Although impairment might be expected to be related to bodily concentration of the drugs, and hence inversely to the amount of absorptive tissue, the measure of gross body weight available in the present case provides only a crude estimation of the latter, and the rate of diffusion of the drugs from the stomach is likely to have varied considerably owing to the very small quantities ingested.

The relatively large incidence of subjective symptoms in subjects receiving placebo only, and the fact that the number of such symptoms increased during each test period confirms the finding of

Glaser and Whittow (op. cit.) concerning response to placebo treatments. It also demonstrates once again the importance of including a placebo group as a control when drug effects are evaluated by questionnaire. The finding that the number of symptoms reported increased over the four-day experimental period shows that the use of such a control group is particularly vital when different treatments are to be given to the same subjects on successive occasions. On the other hand, the lack of significant correlation between the number of symptoms reported by individual subjects and the actual degree of task impairment shown emphasizes the importance of obtaining objective measures of performance in addition to introspective comments.

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APPENDIX

Procedure for Assessing Statistical Significance of Treatment Effects

For each test, the performance score (S 1) for each subject on Day 2 was subtracted from his score on each of Days 3, 4, and 5 to obtain difference-scores (S 2) which represented the effects of particular treatments on that subject. In the case of Group A these S 2 scores represented "learning" or "practice" effects; in Groups B and C they reflected both these effects and those due to the drugs administered on each day. The effect of each of the six drug treatments was therefore assessed by comparing the sets of S 2 scores computed for Groups B or C with those for Group A on each Day (the "placebo" effect on Day 2 was of course assessed on the basis of S 1 scores). Evaluation of the differences between certain of the drug treatments was carried out by comparing the S 2 scores for Group B with those for Group C on any one Day (three comparisons) and the differences between the scores for each of Groups B and C on different Days with the corresponding Group A differences (six comparisons). Where the Group A scores indicated that "learning" or "practice" effects were absent, comparisons were also made between drug treatments given to different Groups on different Days (six comparisons).

In Test 1 the S 1 scores on Day 2 all fell within 10% of the maximum possible score. Since this suggested that the distribution of the scores was being limited, the non-parametric Mann-Whitney U-test of ranks (Siegel, 1956) was used to evaluate the differences between treatment conditions. Where the S 1 score for any individual subject in a "drug" group was the maximum possible score (in which case the S 2 score was either 0 or had a positive value) the S 2 score was adjusted to a value which just exceeded the greatest positive S 2 score in the "placebo" group. This procedure allowed for the possibility that performance was being limited in these cases, and ensured that the tests of statistical significance were conservative.

For the sake of consistency of statistical treatment in inter-test comparisons the Mann-Whitney test was also used in the analysis of the results from Tests 2 and 3, although in these cases the scores were not limited in the same manner.

In no treatment condition was the distribution of any score sufficiently skew to disallow the use of the mean score as an approximate measure of central tendency; these means are accordingly given in the Tables to indicate the extent of the differences between conditions.

Test 1 (Vigilance).—Since the scores for Group A on Days 2, 3, 4, and 5 indicated that practice effects were absent, all 21 comparisons between treatment conditions

were made. The figures given in Table 6 are the probabilities, for a two-tailed test, of obtaining the observed or a more extreme value of "U" by chance alone in each comparison.

Test 2 (Sequence Following).—Since practice effects were clearly evident those comparisons between drug treatments given to different Groups on different Days could not validly be made. Thus 15 comparisons were made on each of the three performance variables.

Test 3 (Random Sequence Generation).—Analysis was carried out as for Test 1 on the one score for which adequate inter-Group matching was obtained on Day 2.

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