Brit. J. Pharmacol. (1965), **24**, 14–23.

DIFFERENTIAL EFFECTS OF TWO AMPHETAMINE-BARBITURATE MIXTURES IN MAN

BY

D. W. DICKINS*, M. H. LADER† AND HANNAH STEINBERG

From the Department of Pharmacology, University College London

(*Received April* 10, 1964)

Mixtures of amphetamine and a barbiturate continue to be fairly widely used in psychiatry, especially in the treatment of mild anxiety and depression (*Lancet*, 1962; *British Medical Journal*, 1962; Ornstein & Whitman, 1963), but relatively little is known about the effects of such mixtures from laboratory experiments on man. In a previous investigation (Legge & Steinberg, 1962) a mixture of 15 mg of amphetamine sulphate and 300 mg of cyclobarbitone and the two ingredients separately were studied in normal human subjects, and it was found that the mixture produced a different pattern of effects from the separate ingredients: it impaired the efficiency of the performance of three simple tasks less than did the barbiturate alone; it produced almost as big a rise in the pulse rate as did amphetamine alone; and it produced spontaneous reports suggesting " elation " from more subjects than did either drug separately, though there was no corresponding increase in reports of other feelings and sensations. The mixture used contained proportionally several times as much barbiturate as a widely used commercial preparation, Drinamyl (Smith, Kline & French), which contains dexamphetamine sulphate and amylobarbitone sodium in a ratio of 1 : 6.5. In the experiments to be reported the earlier mixture was therefore compared with a mixture which contained the two drugs in approximately the same proportions as Drinamyl, except that for practical reasons amphetamine sulphate and cyclobarbitone were again the compounds used. Since the main clinical aim of using these drug mixtures appears to be to induce favourable changes in subjective reactions, especially in moods, a standardized and detailed method was adopted to elicit reports of the subjects' feelings. Otherwise the test methods were similar to those previously used.

METHODS

The subjects were preclinical medical students in their fourth term, and the experiments were carried out in the course of practical classes in which the students learned simple ways of assessing in man effects of drugs acting on the central nervous system. Before the experiment it was explained that each student would receive a tablet containing either amphetamine, or cyclobarbitone, or one of two mixtures of the two, or lactose as a control; the main effects of amphetamine and barbiturate drugs were described in general terms. Regarding the mixtures, the subjects were told that combinations of depressant and stimulant drugs were fairly widely used in medicine, and that the effects would be discussed at the end of the class. The following were studied:

* Present address: Psychology Department, University of Liverpool.

† Present address: Institute of Psychiatry, Maudsley Hospital, Denmark Hill, London, S.E.5.

Pulse rate. The pulse rate was taken for 30 sec.

Performance tests. Arithmetic: the subject added sums of four two-digit numbers as quickly as possible. The score was the number of sums correctly added in 2 min. *Tapping:* using the first finger of his preferred hand, the subject tapped a key as quickly as possible. The key was connected to a resettable counter. The score was the number of taps in 60 sec. The subject could not see the counter while tapping, but he was told his score after each trial. *Dotting:* a modified McDougall/Schuster disc-dotting machine was used. It consisted of a disc on which was marked a spiral of irregularly placed brass dots. The disc rotated behind a window. Starting at the centre of the spiral, the subject hit as many dots as possible with a metal stylus which was connected to an electric counter. The task required accurate hand-eye co-ordination. The score was the number of hits during one complete exposure of the spiral which took 2 min. As in the tapping test, the subject could hear but not see the counter while working, but he was told his score after each trial. In the course of explaining the three tests to the students it was stressed that they should throughout aim at making the highest possible scores. Details of the test methods are given in Steinberg (1954).

Subjective effects. Sheets were provided on which were printed twenty-six adjectives describing various feelings. These adjectives had been selected from spontaneous reports of feelings made by students in previous experiments. The subjects were instructed to tick those words that described how they felt at the time (Nowlis & Nowlis, 1956).

Students worked in pairs, and each member of a pair acted in turn as subject and as observer for his partner. The experiments were carried out in small laboratories with one or two pairs of students and a demonstrator in each. The general arrangements were similar to those described in previous papers (Wilson, Crockett, Exton-Smith & Steinberg, 1950; Paton & Steinberg, 1956). The observations were always made in the order in which they have been listed, and a complete set of observations occupied about 7 min. Before the experiment began the students were given a standard amount of practice on all the test methods. Tablets were taken on a relatively empty stomach at about 1.30 p.m., and immediately afterwards a set of observations was begun. Twenty minutes after taking his tablet each subject ate a light lunch. Forty minutes after taking the tablet, and every 20 min thereafter, further sets of observations were begun; the last set of observations began 100 min after the tablet had been taken. At the end of the afternoon, after the results had been tabulated and the subjects had said what they thought their tablet had contained, they were told what it had actually contained.

Drugs. Each of the following had been compounded in the form of a single yellow tablet with a bitter flavour and was administered with a draught of water: (1) amphetamine sulphate, 15 mg; (2) cyclobarbitone, 300 mg; (3) these two combined in a mixture ($Mixture_{300}$); (4) a second mixture containing amphetamine sulphate, 15 mg, and cyclobarbitone, 75 mg ($Mixture_{75}$); and (5) lactose as control. The smaller cyclobarbitone dose in the second mixture was chosen so as to have an approximately similar ratio to 15 mg of amphetamine as the amylobarbitone has to dexamphetamine in Drinamyl. Estimates differ of the relative potencies of cyclobarbitone and amylobarbitone. Some authorities (Sollman, 1957; Osol & Farrar, 1955) seem to regard the two drugs as roughly equipotent; others (British Pharmacopoeia, 1958) give dose-schedules implying that cyclobarbitone has about half the activity of amylobarbitone. For the present purpose it was regarded as about two-thirds as potent. Amphetamine sulphate seems to be regarded by some as of the same potency as dexamphetamine sulphate (British Pharmacopoeia, 1958), and by others as half as potent (Goodman & Gilman, 1955; Laurence, 1962). For the present purpose it was regarded as about half as potent.

RESULTS

The subjects were divided into five groups according to the content of their tablet. Results were computed separately for each of these groups and differences between the groups were evaluated statistically.

Pulse rate and tests of performance

For the pulse rate and for each performance test the results obtained at the first trial that is immediately after the tablet had been swallowed when there was no reason to suppose that the drugs had as yet had any effect, were taken as " basal." The basal results for each

of the four kinds of measure were compared between the five groups of subjects by means of one-way analyses of variance, and were not found to differ significantly. All subsequent scores were expressed as differences from these basal scores and were analysed statistically; since some of these difference scores were not suitable for analysis by parametric statistical methods because of heterogeneity of variance, the comparisons were made between all possible pairs of groups for each subsequent trial by means of the Mann-Whitney " U " Test (Siegel, 1956). The number of subjects in the five groups ranged between ten and fourteen.

Pulse rate

After 40 min from taking the tablet the pulse rates of the control and cyclobarbitone groups had increased by about 7 beats/min, and they remained so for the rest of the afternoon. In the other three groups, that is the groups given amphetamine either alone or in combination with either dose of cyclobarbitone, the pulse rates had by the end of the afternoon risen by between 16 to 22 beats/min, and these increases were significantly greater ($P<0.05$) than those in the other two groups, but not significantly different from each other.

Tests of performance

All three tests of performance were affected in fairly similar ways by the drugs. Figs. 1 and 2 show the results for the tapping and dotting tests; the dotting test had, as before, a particularly steep learning curve. Cyclobarbitone greatly reduced scores, and the differences in mean change between the cyclobarbitone and control groups were statistically significant at every trial except at the 40-min trial for tapping. The scores with amphetamine were throughout slightly above the scores of the control group, but the differences were not

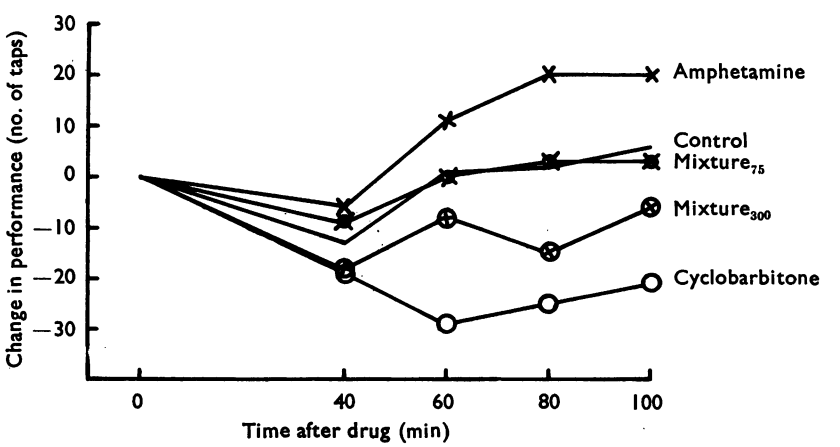

Fig. 1. Tapping test. The mean scores of five groups of subjects are expressed as differences from initial scores at 0 min after the drug. The groups received respectively (1) amphetamine sulphate, 15 mg, (2) cyclobarbitone, 300 mg, (3) these two combined in a mixture, (4) amphetamine sulphate, 15 mg, and cyclobarbitone, 75 mg, combined in a mixture, and (5) lactose as control. Each group repeated the test at 40, 60, 80 and 100 min after taking the drug, and positive scores mean that performance improved compared with initial scores.

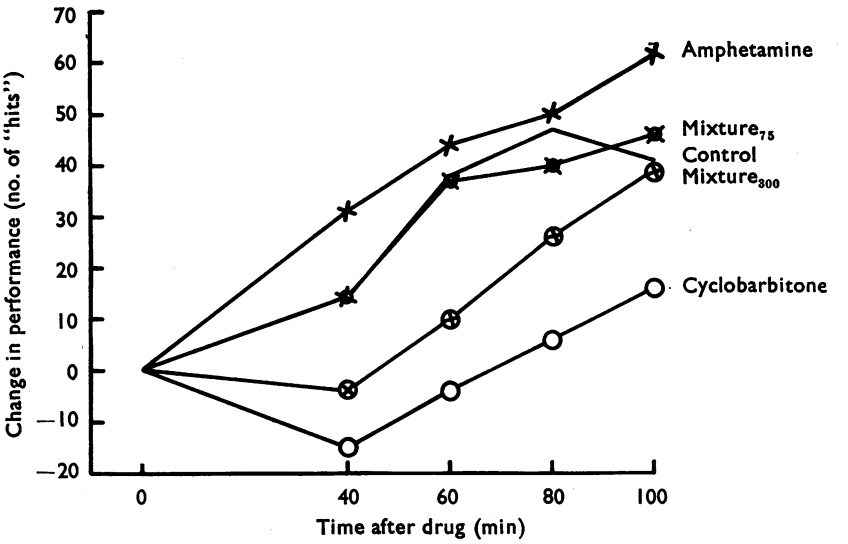

Fig. 2. Dotting. The mean scores of five groups of subjects as for Fig. 1.

statistically significant except at 100 min in the dotting test. The mixture of these two doses ($Mixture_{300}$) gave scores which were consistently intermediate between those obtained with cyclobarbitone alone and those obtained by the controls, though the differences only reached statistical significance at a few points. In the tapping test the $Mixture_{300}$ results were significantly different from the controls at 80 min, and from the cyclobarbitone group at 60 min. In the dotting test the $Mixture_{300}$ scores were significantly different from the control group at each trial except at 100 min, and from the cyclobarbitone group only at the 100-min trial. In both tests, the scores with the $Mixture_{300}$ were throughout significantly lower than those obtained with amphetamine alone. $Mixture_{75}$ gave results which were almost indistinguishable from the scores of the control group: the scores with this mixture were also slightly though consistently lower than the results obtained with amphetamine alone (significantly so at 40 min for dotting and 100 min for tapping), and significantly higher throughout than the scores obtained with cyclobarbitone alone ($P<0.005$). Because of the large variances the only comparisons between the two mixtures which reached statistical significance were scores at 80 min for tapping and at 60 min for dotting. The results of the arithmetic test showed trends which were throughout similar to those in the tapping and dotting tests, but fewer of the differences between the groups were statistically significant.

Subjective effects

Each subject was scored " yes " for an adjective if he ticked it on at least one of the trials from 40 to 100 min after ingestion of the tablet, and " no " if he did not tick it on any of these occasions. The distributions of yeses and noes within each of the five groups were determined for each adjective. Comparisons were made between all possible pairs of drug groups for each of the twenty-six adjectives, using the Fisher Exact Probability test for small independent samples (Finney, 1948; Latscha, 1953); there were 260 comparisons in all. Thirteen adjectives which gave significant results on at least two comparisons are

shown in Table 1, and Fig. 3 shows the percentage of subjects in each group which reported these adjectives. The adjectives have been arbitrarily divided into those which might be considered " desirable " and " undesirable " effects. None of the comparisons between the control and the amphetamine groups were statistically significant.

Further analyses were made by assigning two scores to each subject according to the number of " desirable " and " undesirable " adjectives, out of the thirteen, which he had

TABLE 1

RESULTS OF ANALYSIS OF THE FREQUENCIES WITH WHICH DIFFERENT ADJECTIVES DESCRIBING SUBJECTIVE REACTIONS WERE REPORTED BY FIVE GROUPS OF SUBJECTS

Thirteen adjectives, out of twenty-six, gave two or more significant differences between groups, and they have been divided into " desirable " and " undesirable " reactions. Blank spaces indicate that the comparison did not yield a significant difference. Cy=cyclobarbitone, 300 mg; A=amphetamine, 15 mg; M_{300}=A+Cy; M_{75}=A+cyclobarbitone, 75 mg; C=control group

	Significance levels (*P*)								
Reaction	C v. M_{75}	C v. M_{300}	C v. Cy	A v. M_{75}	A v. M_{300}	A v. Cy	M_{75} v. M_{300}	M_{75} v. Cy	M_{300} v. Cy
" *Desirable* "									
Clear-headed		0·034	0·017			0·040	0·034	0·017	
Alert			0·040			0·040	0·003	0·002	
Sociable								0·040	0·026
Efficient			0·027					0·027	
Elated			0·013					0·013	
Energetic						0·045		0·002	
Absorbed					0·024		0·046		
Quick-witted	0·048						0·020	0·005	
" *Undesirable* "									
Drowsy	0·020	0·002	0·003	0·030	0·003	0·002			
Mentally slow		0·015	0·003		0·024	0·002		0·007	
Confused		0·005	0·003		0·009	0·018			
Dizzy	0·020	0·002	0·031		0·003		0·029		0·029
Unsteady		0·003			0·009		0·013		0·030

ticked. The maximum scores were therefore 8 and 5 respectively. The five groups were compared by means of Kruskal & Wallis' (1952) one-way analyses of variance, and there was a significant overall difference due to groups ($P<0.001$) for both " desirable " and " undesirable " adjectives separately. Comparing groups (Mann-Whitney *U*-test), the following differences were found at the $P<0.05$ level of significance or beyond. With " desirable " adjectives there were more reports per subject from the control, amphetamine, and $Mixture_{75}$ groups than from the $Mixture_{300}$ and cyclobarbitone groups, and the $Mixture_{300}$ gave more than the cyclobarbitone group. The control, amphetamine, and $Mixture_{75}$ groups did not differ among themselves. With " undesirable " adjectives, the cyclobarbitone and $Mixture_{300}$ groups reported more than the other three groups, but were not significantly different from each other. The $Mixture_{75}$ group gave more " undesirable " reports than the control group, but was not significantly different from amphetamine. The subjects in the $Mixture_{75}$ group reported altogether more adjectives, both " desirable " and " undesirable," than those in the amphetamine group ($P<0.025$), and also significantly more than those in the control group ($P<0.01$) and the cyclobarbitone group ($P<0.01$).

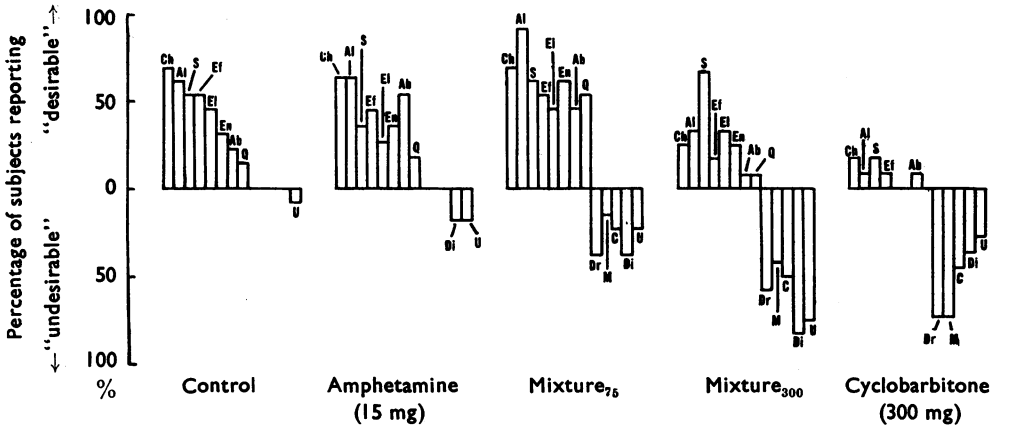

Fig. 3. Subjective effects. The incidence of 13 " desirable " and " undesirable " effects expressed as the percentage of subjects who reported each effect in the five groups of subjects. Ch=clear-headed; Al=alert; S=sociable; Ef=efficient; El=elated; En=energetic; Ab=absorbed; and Q=quick-witted. Dr=drowsy; M=mentally slow; C=confused; Di=dizzy; and U=unsteady.

The subjects' statements as to what they thought their tablet had contained are shown in Table 2. Of forty-two subjects given a drug, six thought they were controls; of twelve subjects given control tablets, four thought they had had a drug; this distribution of estimates is significantly different from chance ($P<0.001$). The expected frequencies are too small to allow χ^2 tests to be made on the results in Table 2 as a whole, but of those

TABLE 2

DISTRIBUTION OF ASSESSMENTS MADE BY FIVE GROUPS OF SUBJECTS OF WHAT THEIR TABLET HAD CONTAINED

Actual content of tablet	No. of subjects reporting	Subjects' assessments of content of tablet					
		Control	Amphet-amine	Mixture$_{75}$	Mixture$_{300}$	A mixture (unspecified)	Cyclo-barbitone
Control	12	8	2	2	—	—	—
Amphetamine	10	2	5	1	—	2	—
Mixture$_{75}$	12	4	5	2	1	—	—
Mixture$_{300}$	11	—	3	2	—	2	4
Cyclobarbitone	9	—	1	1	—	2	5

correctly guessing that they had received a drug those receiving amphetamine alone and cyclobarbitone alone seemed to identify the correct drug more often than would be expected by chance, while those receiving mixtures showed no tendency to guess correctly.

DISCUSSION

In general, mixtures in the present investigation showed antagonistic effects of the two drugs on efficiency of performance, amphetamine-like effects on the pulse rate, and effects suggesting opposition on some subjective reactions and mutual augmentation on some others. The results also suggest that an amphetamine-barbiturate mixture which is similar to the clinically used Drinamyl can produce a pattern of effects which may be potentially more useful than effects of a mixture containing four times as much barbiturate. The

Drinamyl-type mixture produced no significant impairment of the performance of simple tasks compared with responses of control subjects, though performance was slightly worse than with amphetamine alone. It made many subjects report feeling " desirable " effects (for example, alert, clear-headed, sociable, energetic) but relatively few " undesirable " ones. The total incidence of subjective effects with this mixture, both desirable and undesirable, was greater than with amphetamine alone, and this suggests that, as in the case of the performance tests, the effect of amphetamine was modified by adding the small dose (75 mg) of barbiturate. This low dose of barbiturate was not studied by itself, but from other experiments (Nash, 1962) it seems unlikely that it would have any significant effects alone. The mixture which contained four times as much barbiturate, on the other hand produced some impairment of performances, though less than the constituent dose of barbiturate alone, and this confirmed previous findings (Legge & Steinberg, 1962). Like the first mixture and the control it produced reports of feeling " sociable," but otherwise the subjective effects were different. There were few " desirable " effects, but a large proportion of subjects reported " undesirable " effects, for example that they felt dizzy, unsteady, drowsy and confused. Feelings suggesting " elation " which were prominent with this mixture in the previously reported study (Legge & Steinberg, 1962) were reported only fairly frequently by subjects in both the present mixture groups, and the effect only reached statistical significance in the Drinamyl-type mixture group as compared with cyclobarbitone alone. This may have been partly due to the different way of eliciting subjective sensations in the present investigation; the word " elated " did not seem a very natural one for the students to make use of. Feeling " unsteady " was reported by a large proportion of the subjects in the $Mixture_{300}$ group but hardly at all in the Drinamyl-type mixture group. This is compatible with results in animal experiments where a Drinamyl-ratio mixture produced greatly increased exploratory activity in rats without causing ataxia, while a mixture containing proportionally about five times as much barbiturate and, therefore, similar in ratio to the present $Mixture_{300}$ produced almost as much exploratory activity but also marked ataxia (Rushton & Steinberg, 1963). Recent experiments on man (Dickins, Rushton, Montagu & Steinberg, unpublished) in which 10 mg of dexamphetamine were substituted for 15 mg of amphetamine produced results essentially similar to the present investigation, and this suggests that the assumptions about the relative potencies of amphetamine sulphate and dexamphetamine discussed earlier in this paper were reasonable. In these experiments a digit symbol substitution test (Wechsler, 1955) was used instead of the arithmetic test and results were also essentially similar.

Other investigators who have studied the effects of barbiturates and amphetamine together on performances in man have reported predominantly antagonistic effects (Dureman, 1962), or predominantly amphetamine-like effects, that is improvements (Nash, 1962; Laties, 1961). As regards the subjects' feelings, the work of Nowlis & Nowlis (1956), Lanzetta, Wendt, Langham & Haefner (1956) and Laties (1961) suggests that with amphetamine-barbiturate mixtures subjects were apt to feel expansive, elated and sociable. Dureman (1962) and Nash (1962) have especially reported increased " alertness " with mixtures. These various investigators have used various compounds and dose-ratios, and the ingredient drugs and doses were not in all cases studied separately; the test methods and experimental conditions usually also differed. Taken together, the results of these investigations, those of the present investigation and those of animal experiments (Steinberg, Rushton & Tinson, 1961; Rushton, Steinberg & Tinson, 1963; Rushton & Steinberg,

1963; Weiss & Laties, 1964; Rutledge & Kelleher, 1964), show that patterns of effects can be obtained with amphetamine-barbiturate mixtures which are different from those produced by the separate ingredients, that on some reactions there can be a marked mutual potentiation of the two drugs, and that much depends on the precise doses, dose-ratios and experimental conditions involved. For example, in rats a mixture markedly stimulated their exploratory activity in a new environment but not if the animals had become familiar with the environment by previous exposure to it (Steinberg *et al.*, 1961; Rushton *et al.*, 1963). As regards mutual potentiation of the two drugs, the most definite effects so far have also been obtained in animal experiments, for example with exploratory activity where the stimulant effect of some mixtures of dexamphetamine and amylobarbitone was greater than the effect of any dose of the separate drugs and also greater than the sum of the maximal effects of the separate ingredients (Rushton & Steinberg, 1963). In these experiments also it seemed that mixtures could often produce more ataxia than the separate constituents. Recently Rutledge & Kelleher (1964) have also reported mutual potentiation with a form of learned behaviour in pigeons, and the results of Weiss & Laties (1964), using a learned response in dogs, are also consistent, and include results obtained with a mixture of amphetamine and ethyl alcohol as well as with amphetamine mixed with a barbiturate.

As regards actions in man, the present results do perhaps support the view that more marked subjective effects can be obtained with mixtures than with the separate drugs; for example, as is illustrated in Fig. 3, the $Mixture_{75}$ group had a rather higher incidence of reports of feeling " quick-witted " than all other groups, though the actual efficiency of performances with this mixture was no greater than among the controls. The total incidence of reports, both favourable and unfavourable, in the $Mixture_{75}$ group was also significantly greater than in all other groups except in the $Mixture_{300}$ group. Moreover, the $Mixture_{300}$ group gave significantly more reports of " unsteadiness " than did all other groups. But these and the other human experiments referred to have, of necessity, been carried out with few dose combinations and manipulations of the experimental conditions, and this is also true of the clinical reports on amphetamine-barbiturate mixtures, both the earlier ones which have been listed in Legge & Steinberg (1962) and more recent clinical trials (Wheatley, 1962; Hare, McCance & McCormick, 1964). Aspects of their results might be worth following up, especially since there is now growing clinical interest both in drug mixtures in general and in ways in which effects of drugs can be modified by environment and personality (Rinkel, 1961; Hamilton, Hordern, Waldrop & Lofft, 1963; Steinberg, 1964; Lennard, 1965).

SUMMARY

1. Two mixtures of amphetamine sulphate and cyclobarbitone (15 mg+75 mg and 15 mg+300 mg, respectively, the first ratio being similar to that in Drinamyl) and the separate ingredient doses of the second mixture were studied in man.

2. In general, the mixtures showed antagonistic effects of the two drugs on the efficiency of simple performances, amphetamine-like effects on the pulse rate, and effects suggesting opposition on some subjective reactions and mutual augmentation on some others.

3. The first mixture seemed potentially the more useful; it did not impair the efficiency of performances compared with those of control subjects, though efficiency was slightly worse than with the ingredient dose of amphetamine alone. Subjective reactions were generally

amphetamine-like, that is mostly " desirable," and the incidence of reactions reported, both " desirable " and " undesirable," was somewhat greater than with amphetamine alone.

4. The second mixture somewhat impaired performances, but less than did the ingredient dose of barbiturate alone. Subjective reactions were mostly " undesirable " and similar to those with the ingredient dose of the barbiturate alone, except for a higher incidence of reports of " sociability."

5. The second mixture also produced more reports of " unsteadiness " than any other treatment, including the ingredient dose of barbiturate, and this was congruent with results of animal experiments where spontaneous activity and ataxia had been measured following administration of drug mixtures with similar dose-ratios.

We are grateful to Mr J. K. Hall, Mr D. Legge and Dr N. W. Please for statistical help, to Dr C. Kornetsky for advice about the digit symbol test, to Dr T. D. Whittet for preparing the drugs and to Dr D. H. Jenkinson for suggestions. The work was supported by research grants MH-03313 and MH-03561 from the National Institute of Mental Health, U.S. Public Health Service.

REFERENCES

BRITISH MEDICAL JOURNAL (1962). Leading article : *Drugs under Suspicion. Amphetamine-barbiturate Combinations*, **i**, 1456–1457.

BRITISH PHARMACOPOEIA (1958). London: Pharmaceutical Press.

DUREMAN, E. I. (1962). Behavioural patterns of antibarbituric action after 5-phenyl-2-imino-4-oxo-oxazolidine, amphetamine, and caffeine. *Clin. Pharmacol. Ther.*, **3**, 163–171.

FINNEY, D. J. (1948). The Fisher-Yates test of significance in 2×2 contingency tables. *Biometrika*, **35**, 148–156.

GOODMAN, L. S. & GILMAN, A. (1955). *The Pharmacologic Basis of Therapeutics*, p. 141. New York : MacMillan.

HAMILTON, M., HORDERN, A., WALDROP, F. N. & LOFFT, J. (1963). A controlled trial on the value of prochlorperazine, trifluoperazine and intensive group treatment. *Brit. J. Psychiat.*, **109**, 510–522.

HARE, E. H., MCCANCE, C. & MCCORMICK, W. O. (1964). Imipramine and " Drinamyl " in depressive illness : a comparative trial. *Brit. med. J.*, **i**, 818–820.

KRUSKAL, W. H. & WALLIS, W. A. (1952). Use of ranks in one-criterion variance analysis. *J. Amer. Statist. Ass.*, **47**, 583–621.

LANCET (1962). Leading article : *Interactions between Drugs*, **ii**, 818–819.

LANZETTA, J. T., WENDT, G. R., LANGHAM, P. & HAEFNER, D. (1956). The effects of an " anxiety-reducing " medication on group behaviour under threat. *J. abnorm. soc. Psychol.*, **52**, 103–108.

LATIES, V. G. (1961). Modification of affect, social behaviour and performance by sleep deprivation and drugs. *J. psychiat. Res.*, **1**, 12–25.

LATSCHA, R. (1953). Tests of significance in a 2×2 contingency table : extension of Finney's table. *Biometrika*, **40**, 74–86.

LAURENCE, D. R. (1962). *Clinicel Pharmacology*, 2nd ed. London : Churchill.

LEGGE, D. & STEINBERG, H. (1962). Actions of a mixture of amphetamine and a barbiturate in man. *Brit. J. Pharmacol.*, **18**, 490–500.

LENNARD, H. L. (1965). A proposed program of research in socio-pharmacology. In *Symposium on Psychological Approaches to Social Behavior*, in the press.

NASH, H. (1962). Psychologic effects of amphetamines and barbiturates. *J. nerv. ment. Dis.*, **134**, 203–217.

NOWLIS, V. & NOWLIS, H. H. (1956). The description and analysis of mood. *Ann. N.Y. Acad. Sci.*, **65**, 345–355.

ORNSTEIN, P. H. & WHITMAN, R. M. (1963). Drug therapy. In *Progress in Neurology and Psychiatry*, pp. 631–658, ed. SPIEGEL, E. A. New York : Grune & Stratton.

OSOL, A. & FARRAR, G. E. (1955). *United States Dispensatory*, 25th ed. New York : Lippincott.

PATON, W. D. M. & STEINBERG, H. (1956). A class experiment on ganglion block in human subjects. *Brit. med. J.*, **ii**, 622–626.

RINKEL, M. (1961). *Psychopharmacology*. New York : Philosophical Library.

RUSHTON, R. & STEINBERG, H. (1963). Mutual potentiation of amphetamine and amylobarbitone measured by activity in rats. *Brit. J. Pharmacol.*, **21**, 295–305.

RUSHTON, R., STEINBERG, H. & TINSON, C. M. (1963). Effects of a single experience on subsequent reactions to drugs. *Brit. J. Pharmacol.*, **20**, 99–105.

RUTLEDGE, C. O. & KELLEHER, R. T. (1964). Interactions between the effects of methamphetamine (MA) and pentobarbital (PB) on operant behavior in the pigeon. *Fed. Proc.*, p. 103.

SIEGEL, S. (1956). *Nonparametric Statistics for the Behavioural Sciences*, pp. 116–127. New York: McGraw-Hill.

SOLLMAN, T. (1957). *A Manual of Pharmacology*, 8th ed. Philadelphia : Saunders.

STEINBERG, H. (1954). Selective effects of an anaesthetic drug on cognitive behaviour. *Quart. J. exp. Psychol.*, **6**, 170–180.

STEINBERG, H. (1964). Aspects of psychopharmacology : drug-induced changes in emotions and personality. In *Readings in Psychology*, pp. 142–154, ed. COHEN, J. London : Allen & Unwin.

STEINBERG, H., RUSHTON, R. & TINSON, C. M. (1961). Modification of the effects of an amphetamine-barbiturate mixture by the past experience of rats. *Nature (Lond.)*, **192**, 533–535.

WECHSLER, D. (1955). *Manual for the Wechsler Adult Intelligence Scale.* New York: Psychological Corporation.

WEISS, B. & LATIES, V. G. (1964). Effects of amphetamine, chlorpromazine, pentobarbital, and ethanol on operant response duration. *J. Pharmacol. exp. Ther.*, **144**, 17–23.

WHEATLEY, D. (1962). Evaluation of psychotherapeutic drugs in general practice. *Psychopharmacol. Service Center Bull.*, **2**, 25–31. U.S. Government Printing Office, Public Health Service.

WILSON, A., CROCKETT, G. S., EXTON-SMITH, A. N. & STEINBERG, H. (1950). Clinical evaluation of effects of drugs on medical students as a teaching method. *Brit. med. J.*, **ii**, 484–488.