Effects of Centrally-Acting Drugs on Human Motor and Psychomotor Performance

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The dose-effect and duration of action of several stimulants and tranquilizers were determined using motor and psychomotor performance tests with humans. Three doses of each of the following drugs were employed: placebo, caffeine, *d*-amphetamine, phenmetrazine, methyl phenidyl acetate, phenobarbital, chlorpromazine, meprobamate, and oxanamide. Phenmetrazine and methyl phenidyl acetate were also studied with additional tests designed to measure fatigue. Deanol and placebo groups were tested weekly for 8 weeks of daily administration crossing treatments at 4 weeks. The tranquilizers did not affect performance as measured by the tests employed, while all stimulants produced some improvements in all tests. Phenmetrazine and methyl phenidyl acetate were the most promising central stimulants tested. These were found to mitigate fatigue by elevation of the initial performance level and by decreasing the time-related decrement. The action of deanol was equivocal with some indication of an interaction between the drug and subject interest.

PROBLEMS inherent in the guidance of aircraft or anticipated spacecraft have increased to the point where, despite refinements in instrumentation, they have begun to exceed man's physiologic and psychologic limits. The obvious solution to the problem is to alter man himself. This might be accomplished through education and training and (or) through the mediation of centrally acting drugs. While it is perhaps self-evident that the improved control of rapidly moving objects is a worthwhile objective, an even more important objective could be the production of periods of enhanced efficiency under conditions of stress or fatigue. Although many studies have been conducted to determine the effects of centrally acting drugs upon human performance, most of these have been clinical in nature, lack proper controls, or they have been oriented toward the treatment of mental illness. It is therefore difficult to compare the effects of such drugs upon normal performance.

The minimum requirements for the proper evaluation of a drug affecting performance would seem to be that: the temporal and dose effects of the drug must be measured with several types of performance; the subjects employed must be adequate in number and be reasonably uniform, physiologically and psychologically; and the experimental design must provide adequate controls and employ suitable techniques to avoid bias.

In the studies which follow every effort was made to meet these requirements, although, as noted in the discussion, it became necessary to reach certain compromises dictated by the limitations of time.

EXPERIMENTAL

Central Stimulant Study.—Subjects consisted of 15 volunteer, male, college students between the ages of 22 and 27, and weighing between 145 and 185 pounds. All were experimentally naive prior to testing and were of approximately the same intellectual capacity as indicated by the rank in their class. Subjects were instructed in the test procedure by means of detailed printed instructions and an oral orientation period. They were then repeatedly tested in practice sessions until a stable level of performance was achieved for each test. Treatments consisted of the following drug doses: placebo; caffeine, 100, 200, and 300 mg.; *d*-amphetamine, 2.5, 5, and 10 mg.; phenmetrazine, 12.5, 25, and 50 mg.; and methyl phenidyl acetate, 5, 10, and 15 mg. Doses were selected by bracketing what was thought to be the amount of the drug which would induce definite physiological and psychological effects.

All testing was performed between 1:00 and 5:00 p.m. At approximately 12:00 p.m., 1 hour prior to the administration of the drug, subjects ate a light lunch consisting usually of a sandwich, a glass of milk, and some fruit. They were instructed to refrain from drinking caffeinated beverages and from smoking following breakfast. Five subjects were each tested four times in one afternoon at hourly intervals. The first test for all subjects, or control, was conducted one hour after lunch. Immediately

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following this test a No. 1 pink capsule containing the drug was administered with a glass of water. The selection of the drug-dose was randomized and double-blind conditions were maintained throughout the study. Testing was repeated three times at hourly intervals following the first test and the administration of the drug.

As each subject was to be tested with each of 13 drug or placebo doses, it was anticipated that boredom or disinterest might influence the results after the novelty of early testing wore off. In an attempt to minimize this possibility and yet not introduce new factors of variability, two techniques were employed in order to maintain positive motivation. Competitive motivation was used to the extent that the three highest individual scores for each test were posted weekly with the previous record score. No further efforts were made to induce individual or group competition because such methods have been found to create variable secondary effects (1). Self-competition related to knowledge of performance (2) was difficult to induce because of the changing drug factor. Subjects were not allowed to observe another's performance nor did they receive information concerning their own scores except as indicated. The second measure designed to stimulate motivation was the encouragement of subjects to maintain a record of their own subjective responses to each treatment. They were informed that at the conclusion of the study they would be provided with their own test results and the drugs employed at each period. This procedure provoked considerable speculation and maintained interest in the effects of each treatment. Subjects were not informed of the drugs that were to be employed other than that moderate doses of nontoxic agents were to be used.

All experiments were conducted in an isolated laboratory equipped specifically for this purpose. The room was well lighted with overhead fluorescent lamps as the sole source of light. Room temperature was held between 70 and 72°F. Ambient noise consisted of the sound of the fan motor in the counter and the motors of the tracking test. These were kept running continuously throughout the entire afternoon of testing and provided a low steady noise level sufficient to mask external sounds. Conversation between subject and experimenter was not permitted except for necessary signals and instructions.

Tests

Tapping Rate.—A microswitch with a roller contact was used as a key in the tapping tests. The switch had a lever arm of 1 in., a pretravel distance of $^1/_4$ in., and required an actuating force of 140 Gm. The roller materially reduced finger friction and in the preliminary testing gave more consistent results than similar keys without the roller. It was mounted at table height so that the subject sat facing the switch with his arm comfortably bent at the elbow and his forefinger on the key. The thumb and remaining fingers were folded beneath the hand and kept in constant contact with the table. This precaution was necessary in order to avoid actuation of the switch with the muscles of the hand rather than of the finger. Use of the hand enabled subjects to obtain higher scores, especially in the 60-second test in which finger fatigue became marked. Conformity with this provision was assured by careful preinstruction and continual observation by the experimenter.

The key was wired into an electric timing circuit in such a manner that the first tap activated an adjustable timer previously set for the desired period over which the tapping rate was to be measured. Starting the timer simultaneously closed a relay connecting the key to an electric four-digit counter. The stopping of the timer at the end of the preset interval opened the relay and discontinued the counting. In this manner subjects could begin tapping whenever they felt that they were ready and the total count for the specified period was recorded automatically. The circuit for this counter system is shown in Fig. 1.

One objective of the tapping test was to determine the maximum speed at which a voluntary movement could be repeated. For this purpose the test must be conducted over an accurately measurable time interval yet one that is short enough to prevent fatigue. A 5-second period was employed. It was repeated four times at each of 4 hourly test periods.

The rate of tapping may also be used to observe the effect of fatigue on the motor activity of the discrete group of muscles controlling finger movement. For this purpose the test was conducted over a 60-second interval. Because of the problem of cumulative fatigue, it was possible to perform this test only twice in any one period, before and after an 8-minute interval during which the other tests were being performed.

Simple Visual Reaction Time.—The visual stimulus for this test consisted of the light from a 120-v., 6-watt, Sylvania S6 lamp mounted in a holder behind a 1-in., clear, jeweled lens. The lamp was placed in a cabinet about 3 ft. from the subject and was 6 in. above the desk top. The subject was seated before the light with his index finger on a snap-action switch having a pretravel distance of $^1/_{16}$ in. With the subject in position, the experimenter, seated behind the cabinet, gave a verbal signal of "ready," at which time he simultaneously closed a switch in a time-delay circuit. This circuit was previously and at random varied by the experimeter between time intervals of from 2 to 5 seconds. At the completion of the time-delay, the circuit to the lamp and a Beckman time interval meter model 7250C were activated, turning on the light and starting the counter. When the snap switch was then closed by the subject, the timer was stopped and the time was measured to 0.1 msec. The circuit diagram of this apparatus is presented in Fig. 1. Four replicates of this test were conducted at each test period.

Complex Reaction Time.—This test was modified from one described by Borkenstein (3) which was termed "choice reaction." The apparatus for this test consisted of a 9 × 9 inch panel of opalescent plexiglas mounted on the sloping front of the cabinet containing the simple reaction time light. The panel was divided into sixteen 1.5 in. square spaces in a 4 by 4 arrangement. Each space had a black 1-in. number arranged in the order from top row to bottom row: 9-6-3-5, 6-2-4-7, 7-8-9-8, and 5-2-3-4. These numbers were on the reverse side of the plexiglas panel and were not visible until individual lights, mounted separately behind each number, were lit. The lights could be lit in either of two manners. First, they could be lit two lights at a time in a con-

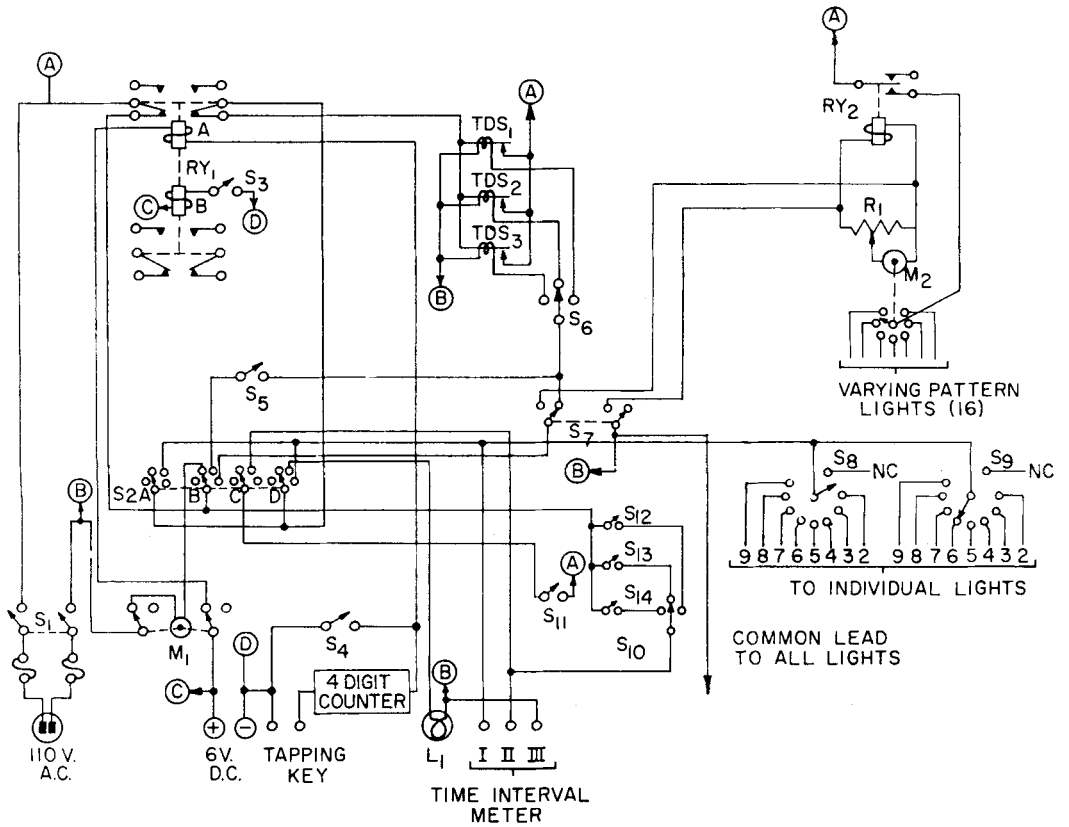


Fig. 1.—Circuit diagram of the unit controlling tapping tests and simple and complex reaction times. All switches except $S_{11, 12, 13, \text{and } 14}$ are mounted on the rear of the cabinet. S_1, SPDT switch controlling 110 v. a.c. power. S_2, 4P 4-position switch controlling test function; A, B, C, and D represent switch gangs; positions are 1, 2, 3, and 4 beginning to the left of the pole and proceeding clockwise; all gangs are shown in position 2; position 1, off; position 2, tapping rate; position 3, visual reaction time; and position 4, complex reaction time. S_3 and S_4, momentary SPDT, NO switches controlling RY_1 relay position. S_5, SPDT off-on time delay switch. S_6, SP 3-position switch for selection of time-delay circuit. S_7, DP 2-position switch to turn on motor switching varying pattern lights (M_2) and lights through relay RY_2 or to activate one of three time-delay switches ($TDS_{1, 2, 3}$). S_8 and S_9, SP 10-position switches controlling lighted number pair of complex reaction time test. S_{10}, SP 3-position switch for selection of odd, even, or odd-even pairs, as indicated by positions of S_8 and S_9. S_{11}, SPST momentary switch thrown by subject to complete visual reaction time. S_{12}, S_{13}, and S_{14}, SPST momentary switches thrown by subject to complete odd, even, or odd-even pairs for complex reaction time. RY_1, SP, 2-position, 2-section latching relay controlling a.c. power. RY_2, SP, 2-position relay to supply power to motor-driven switch prior to activating time delay switches by S_7. $TDS_{1, 2, 3}$, Amperite 2, 3, and 5-second delay relays. M_1, Industrial Timer Corp., TDAF-60-second series timer. M_2, varying pattern lights switch motor. I, Start position on Beckman time interval meter. II, Stop position. III, Common. Circled letters represent common connections.

tinuously varying pattern by means of a motor-driven rotating multicontact switch. Secondly, any two selected numbers could be lit by the experimenter following a time delay of from 2 to 5 seconds. The test was performed as follows: the subject sat facing the panel of numbers with his thumb and forefinger on a 1.25-in. control stick of a Grumann automatic pilot controller, model GR2. When the subject was ready, the experimenter threw the first switch, causing various pairs of numbers to flash off and on in an irregular manner. After approximately 10 seconds of this irregular flashing of the numbers, a second switch was thrown, activating the previously selected time delay relay and disconnecting the rotating switch. The panel of numbers now remained dark for the selected time period. This alerted the subject to be ready for the appearance of the two numbers previously selected by the experimenter. With the closing of the circuit lighting the selected pair of numbers, the Beckman time interval meter was activated. The subject at this time seeing a pair of numbers, had to decide whether the pair was even, odd, or an odd-even combination. For an even combination the stick switch was to be pressed to the right, for an odd combination to the left, and for an odd-even combination, forward. Moving the stick in the correct direction closed a microswitch which stopped the counter. If the wrong combination was chosen, the counter remained activated and the result was recorded as an error. The circuitry of this device is seen in Fig. 1.

It had been previously determined in an initial study of this apparatus that an individual's score for a given number pair was quite consistent, but that there were considerable differences in the times

between different pairs. For this reason, ten odd-even pairs in which the numbers were approximately the same distance apart on the panel had been tested repeatedly with a group of subjects. It was found that four of these pairs gave consistent reaction times varying between 825 and 875 msec. Each test consisted of five reaction times, two of which were obtained from the four consistent pairs. In the preliminary testing it was determined that the subjects were not aware of the fact that certain number pairs were being repeated.

Tracking Test.—The apparatus used to measure motor coordination was similar in principle to many previously employed and is shown in Fig. 2. The object of the test was to hold a 15 mm. spot of light from a pistol-like flashlight on a circular 1-cm. photocell that was moving at a distance of 2.5 ft. from the end of the light gun. The photocell unit consisted of a basic motor which moved a 7-in. arm through a vertical 70° arc, requiring 20 seconds for a complete cycle. To the end of this arm was connected a 15 r.p.m. synchronous motor, which in turn continuously rotated a second arm 6 in. in length, also in the vertical plane. At the end of the 6-in. arm was a 2-in. white circular target with a 1-cm. circular photocell in the center. The combined movements of both motors caused the photocell to travel at an irregular speed and in a varying pattern. The speed with which the photocell moved relative to the subject depended upon the relative motion of the component motors. When the directions of movement were the same, the photocell would move in a gradually accelerating or sudden burst of speed, or if moving in opposite directions, the photocell might almost stop or move very slowly. In order to induce irregularity further and prevent smooth continuous tracking, a universal joint was used to connect the 15 r.p.m. motor to the 6-in. target arm. By adjustment of this joint it was possible to cause the target to make a bobbing movement at four points with each circular motion of the 15 r.p.m. motor. As these irregular movements occurred at varying positions of the photocell and were dependent upon the relative positions of the two arms, the bobbing could not be anticipated. The entire apparatus

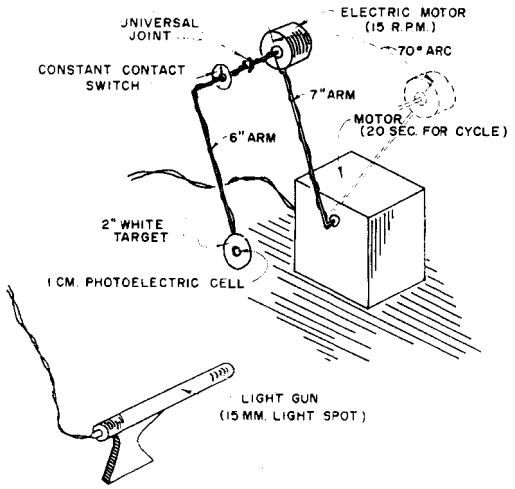


Fig. 2.—Diagram of mechanical portion of the tracking test apparatus.

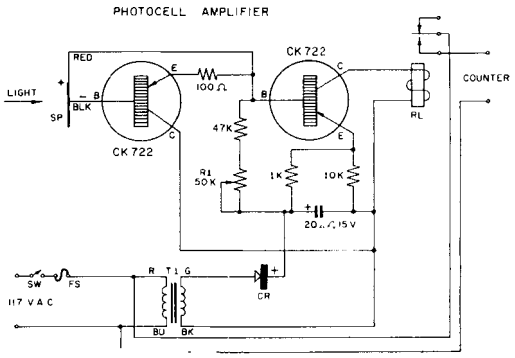


Fig. 3.—Circuit diagram of amplifier used to control the sensitivity of the tracking test photocell.

was placed in the rear of a blackened box with the open end to the front. The dimensions of the box were 26 in. high by 26 in. wide and 34 in. deep. A black screen with a slot through which the blackened rotating arm extended concealed the apparatus from the subject who saw only an erratically moving 2-inch white circular target with a 1-cm. black center.

The photocell was electrically connected through a constant contact rotating switch on the 6-in. arm to an amplifier relay circuit shown in Fig. 3. Adequate light upon the photocell induced a signal which, when sufficiently amplified, activated a relay and, in turn, closed a 60-cycle, 110 v. circuit connected to the Beckman time interval meter. Therefore, every second that the photocell was adequately illuminated, 60 counts would be recorded.

The experiment was performed with the subject sitting squarely before the target box having both feet flat on the floor. At a signal from the subject who was tracking the target, the experimenter threw a switch which simultaneously connected the Beckman time interval meter to the photocell circuit and started a 40-second timer. A perfect score for continuous contact throughout the 40-second period was a count of 2400. However, in order to allow for drug-induced increments or decrements in performance, the amplification of the photocell output was so adjusted that the average control score was less than half the perfect score. This test was repeated four times during each period.

Central Depressant Study

The study to determine the effect of central depressants upon performance was also conducted with 15 new subjects, but with the same experimental design and tests described for the stimulants. The drugs employed and their respective doses were: placebo, three doses; phenobarbital (as a standard sedative), 15, 30, and 45 mg.; chlorpromazine, 25, 50, and 100 mg.; meprobamate, 200, 400, and 800 mg.; and oxanamide, 200, 400, and 800 mg.

Central Stimulants Fatigue Study

This study was designed to elaborate further upon certain results obtained with the initial central stimulant experiments. One objective was to determine the effects of phenmetrazine and methyl phenidyl acetate upon muscular fatigue. Each of these drugs had appeared promising in the 60-second tapping test and no indication was found in the literature that they had been tested for this effect.

A second objective was to answer a hitherto unexplained question of how the central stimulants affect fatigue. The question was whether psychomotor drugs act to maintain the base-line level of performance by suppressing the sense of fatigue or whether, by actually raising the initial level of performance, they simply negate a fatigue-induced decrement. Two tests were conducted to determine these objectives. As the rate of tapping had been previously noted to decline steadily throughout the period of 60-second tapping, this test was extended to 3 minutes. Readings of the counts were made at half-minute intervals. The second test employed the tracking apparatus and was performed by extending the period of testing to 6 minutes, during which time readings were made at minute intervals. To induce fatigue further, the subjects were required to hold their arm with the light gun straight before them rather than with the elbow bent and touching the side.

Five subjects participated in this study. The treatments employed were: placebo, methyl phenidyl acetate 15 mg., and phenmetrazine 50 mg. Subjects received each treatment twice in randomized allocation and according to the manner previously described.

Chronic Deanol Study

Eighteen volunteer, male, college students between the ages of 21 and 33, weighing between 135 and 205 pounds, served as subjects. Orientation and tests were the same as for the studies with central stimulants and depressants. Subjects were randomly divided into two groups with nine subjects in each group. Group 1 received a daily capsule containing a placebo during the first four weeks and a capsule identical in appearance containing 75 mg. of deanol (dimethylaminoethanol) for the next four weeks. Group 2 received these treatments in the reverse order. Double blind conditions were maintained throughout. The five tests were administered in the same manner as in the central stimulant and depressant studies except that the testing of each subject was repeated at regular weekly intervals from the onset of treatment. In addition to the usual tests, subjects were also examined for changes in mood and any other subjective responses. For the analysis of a possible effect upon mood, the adjective check list of Nowlis (4) was employed. This list consisted of 145 adjectives descriptive of mood, feelings, or states of mind. Each adjective could be categorized as being either positive (cheerful, self-confident, etc.) or negative (depressed, unsure, etc.) in character. At each test period the subject checked those adjectives on the list which definitely described his feelings, using a single check were applicable, a double check mark where the adjective strongly applied, and a question mark when there was some uncertainty. In addition to the adjective list, subjects were further asked to describe any change from normal in their mental or physiological functions, such as the presence of pain, amount of sleep required, or changes in appetite, libido, study habits, and similar effects.

RESULTS

Central Stimulant Study.—In order to compensate for normal diurnal variations and to increase the precision of the tests of significance, the means of 12,480 raw scores were first adjusted for regression upon the corresponding control values. These adjusted scores were examined by an analysis of variance (5). The results are shown in Table I. The principal experimental variables were drugs, doses, and times. In each test, drugs constituted a significant source of variation. This means simply that not only were the drugs employed capable of affecting performance, but also that the tests selected were adequate to detect these changes. The absence of significant variations in dose response, except for the 60-second tapping rate, would indicate

TABLE I.—ANALYSIS OF VARIANCE OF ADJUSTED[a] POSTTREATMENT SCORES OF CENTRAL STIMULANTS

Source of Variance	*df*	Mean Square	*F*	*P*
		Pursuit Test		
Drug	3	6,266	11.33	<0.01
Dose	2	1,385	2.50	
Time	2	9,921	17.94	<0.01
Drug × dose	6	12,565	22.72	<0.01
Drug × time	6	1,989	3.60	<0.05
Dose × time	4	372	0.67	
Drug × dose × time	12	553		
Total	36			
		Five-Second Tap		
Drug	3	0.5849	3.63	<0.05
Dose	2	0.4688	2.91	
Time	2	0.9747	6.04	<0.05
Drug × dose	6	0.9610	5.96	<0.01
Drug × time	6	0.2665	1.65	
Dose × time	4	0.0884	0.55	
Drug × dose × time	12	0.1613		
Total	36			
		Sixty-Second Tap		
Drug	3	63.4259	6.53	<0.01
Dose	2	301.2100	31.01	<0.01
Time	2	125.5413	12.93	<0.01
Drug × dose	6	41.9323	4.32	<0.05
Drug × time	6	6.5628	0.68	
Dose × time	4	12.9989	1.34	
Drug × dose × time	12	9.7120		
Total	36			
		Visual Reaction		
Drug	3	1,255,955	6.19	<0.01
Dose	2	758,429	3.74	
Time	2	21,562	0.11	
Drug × dose	6	687,697	3.39	<0.05
Drug × time	6	171,169	0.84	
Dose × time	4	235,488	1.16	
Drug × dose × time	12	202,746		
Total	36			
		Complex Reaction		
Drug	3	37,381,699	3.56	<0.01
Dose	2	34,867,787	3.32	
Time	2	3,810,247	0.36	
Drug × dose	6	85,377,907	8.13	<0.01
Drug × time	6	11,104,987	1.06	
Dose × time	4	15,545,967	1.48	
Drug × dose × time	12	10,504,450		
Total	36			

[a] Adjusted score is the difference between mean treatment score and mean control score.

TABLE II.—EFFECT OF CENTRAL STIMULANTS AS MEAN PER CENT DEVIATIONS FROM CONTROL[a]

Treatments	Tracking Test			Five-Second Tap			Tests and Trials[b] Sixty-Second Tap			Visual Reaction			Complex Reaction		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Placebo	7.12	9.51	10.36	3.30	−2.01	−0.80	2.01	−0.10	−2.91	−6.33	−4.16	−6.37	4.81	1.90	−3.14
Caffeine, 100 mg.	25.43[c]	27.80[d]	31.95[d]	3.01	4.12	5.81	2.17	4.11	3.90	−3.68	−2.61	−5.63	14.00	7.75	10.84
Caffeine, 200 mg.	20.74	19.72	20.58	2.16	2.84	2.79	5.49	8.87[d]	6.32[c]	−0.28	−2.46	−4.20	6.51	0.17	7.24
Caffeine, 300 mg.	5.06	6.10	6.84	1.88	1.17	0.63	5.44	4.78	5.40[c]	1.32	−0.70	0.27	−1.43	−0.42	−3.40
d-Amphetamine, 2.5 mg.	7.92	15.34	21.07	1.78	2.67	2.30	3.86	5.06	4.75[c]	1.62	0.50	0.33	6.11	−4.15	−0.55
d-Amphetamine, 5.0 mg.	11.03	16.36	18.63	0.37	3.30	−0.14	2.94	5.59	4.41	−1.55	−1.14	0.49	−2.90	0.14	1.96
d-Amphetamine, 10.0 mg.	0.82	10.88	17.08	2.21	4.36	3.53	4.87	8.40[c]	6.42[d]	−0.15	4.47	1.47	5.41	10.89	9.84
Phenmetrazine, 12.5 mg.	5.14	7.21	10.28	0.76	3.14	4.22	2.41	3.62	2.34	2.51	3.41	8.95[d]	9.13	8.18	−0.35
Phenmetrazine, 25.0 mg.	13.52	19.26	23.17	2.91	3.89	4.89	3.40	6.09	6.66[d]	−0.23	0.44	−2.45	6.22	11.54	4.37
Phenmetrazine, 50.0 mg.	20.61	26.04[d]	29.43[d]	5.43	6.74[c]	3.85	7.95	7.20[c]	7.59[d]	−0.08	1.92	2.46	−3.57	−8.86	−9.83
Methylphenidate, 5 mg.	6.45	15.09	21.26	0.74	3.52	−1.18	1.35	2.47	0.59	1.00	−1.15	0.16	−1.93	−3.87	3.34
Methylphenidate, 10 mg.	15.89	22.33	26.35	3.13	5.34[c]	2.13	1.65	5.92	3.87	−1.05	1.23	−2.71	−4.28	−3.32	0.38
Methylphenidate, 15 mg.	23.08[c]	27.25[d]	29.96[d]	4.04	5.57[c]	3.87	3.21	6.86	5.87[c]	2.57	1.31	3.88[c]	0.34	6.91	−5.75

[a] Controls are those test values obtained immediately preceding drug administration. [b] Trials 1, 2, and 3 are those test values obtained 1, 2, and 3 hours after drug administration. [c] Significantly different than placebo ($P < 0.05$). [d] Significantly different than placebo ($P < 0.01$).

that either the tests were not sufficiently sensitive to detect the overall effect of the dose as a variable or that the differences in the sizes of the dose were not adequate to demonstrate such an effect. This does not, of course, preclude the possibility that individual doses may induce significant variations from corresponding control values. The fact that time was significant for all tests except the reaction times tells that the length of time following drug administration also influenced the response.

In order to determine which drug-dose-time performances were significantly different from those of the placebo, the *t*-test of Dunnett (6) was applied to the differences between the mean test scores and control values for the drugs and placebo. These data are presented in Table II and in Figs. 4–13. From Table II it is apparent that the tracking test was the most sensitive gauge of stimulant drug activity and that the lowest dose of caffeine, 100 mg., and the highest doses of phenmetrazine and methyl phenidyl acetate, 50 mg. and 15 mg., respectively, were generally the most effective.

The numerical values employed in Table II and their graphic presentation in Figs. 4–13 demonstrate the discrete changes resulting from the drug-dose-time interaction. Although with such presentations the individual values and treatments may be observed to vary significantly from those of the corresponding placebo or control, total drug-dose effects are not easily compared. In order to simplify such a comparison, the time-effect was integrated by measuring the areas under the graph curves with a planimeter. These values, measured in square centimeters, were obtained from original graphs in which the coordinates measured 7.6 cm. and 15.3 cm. for the x and y axes, respectively. The values obtained are the algebraic sums of the areas above and below the zero or control level, and are presented in Table III.

The 5-second tapping test afforded an objective index of the speed of a simple repetitive muscular movement rather than a measure of precision. It is most apparent from Table III and from Figs. 4 and 5 that methyl phenidyl acetate and phenmetrazine can significantly improve 5-second tapping. As might be anticipated, peak activities appeared at the second hour posttreatment. While it is not

Fig. 4.—Five-second tapping rate.

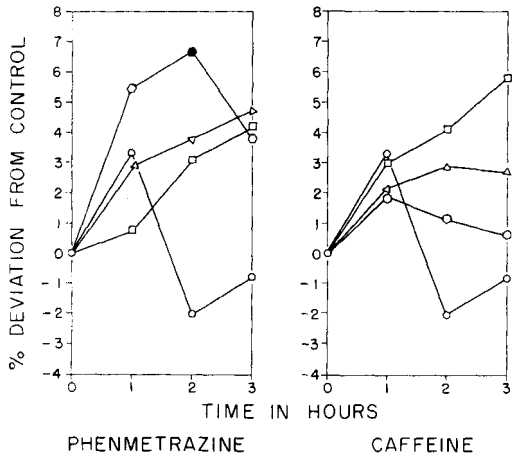


Fig. 5.—Five-second tapping rate.

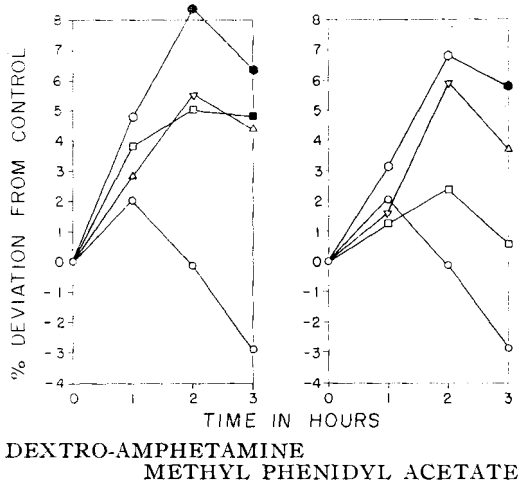


Fig. 6.—Sixty-second tapping rate.

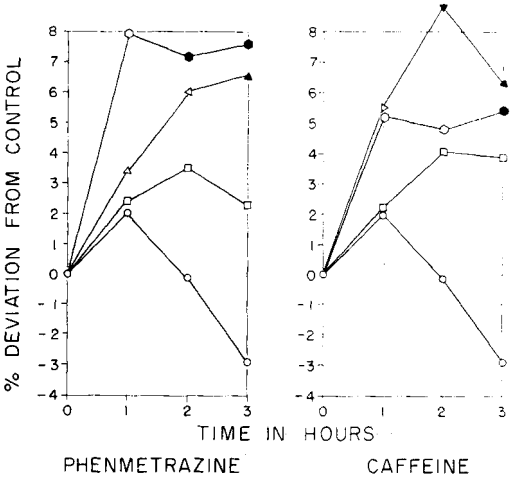


Fig. 7.—Sixty-second tapping rate.

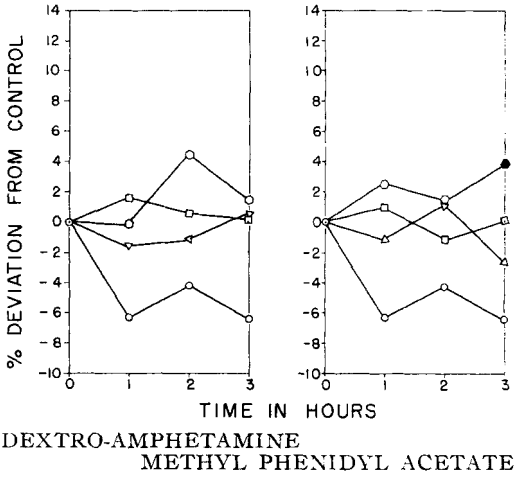


Fig. 8.—Simple visual reaction time.

surprising to find that central stimulants are capable of improving this type of performance, it is rather surprising that *d*-amphetamine did not cause a significant improvement. From Fig. 4 and Table II, it can be observed that *d*-amphetamine, while raising the level of performance over that of the placebo, was not as effective as the larger doses of phenmetrazine or of methyl phenidyl acetate. Further, these latter agents induce a dose-related effect. These differences may be the result of an improper selection of doses or they may reflect real differences in the actions of these drugs. The results with caffeine, although not significant, are most interesting because of the inverse relationship between dose and effect.

The information obtained from the 60-second tapping test is quite similar to that from the 5-second test, although the longer test appears to be a somewhat more sensitive measure of the drug effect. The principal difference in these two was the factor of fatigue in the longer test. All drugs demonstrated a significant improvement in performance at one or more of the times tested (Table II). From

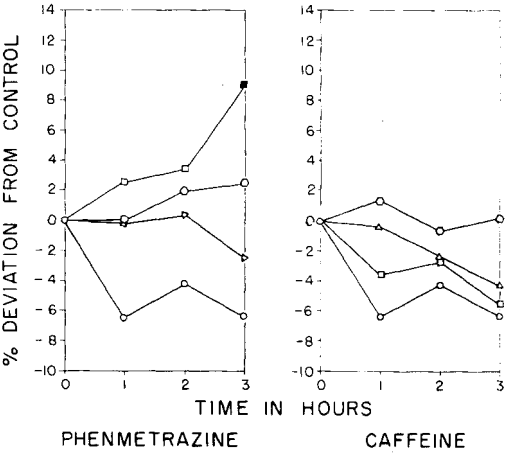


Fig. 9.—Simple visual reaction time.

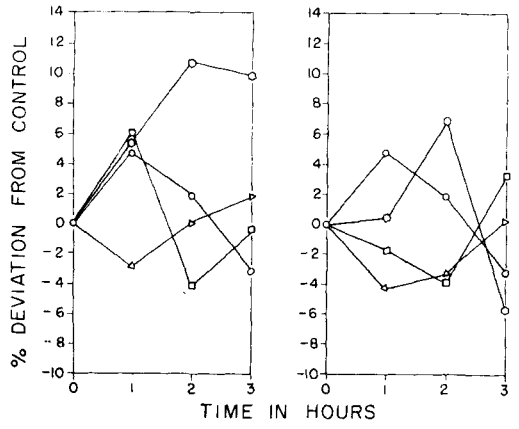


Fig. 10.—Complex reaction time.

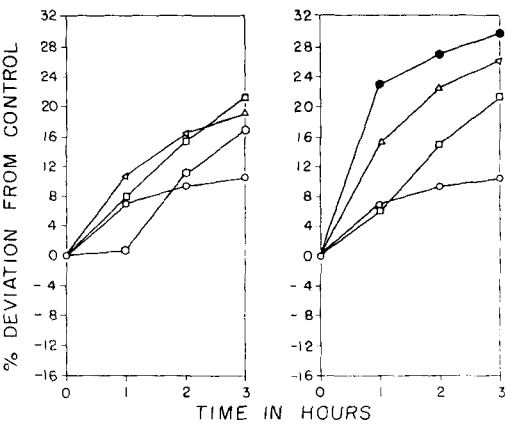


Fig. 12.—Tracking test.

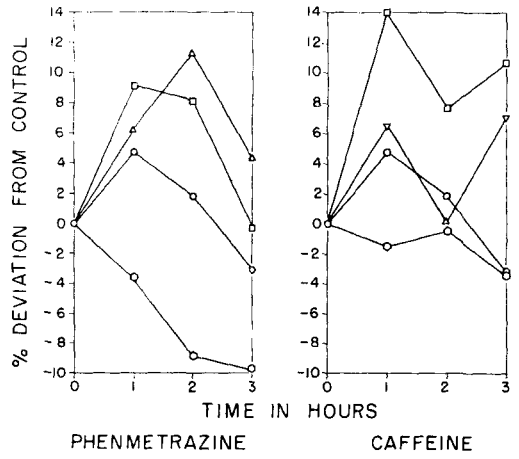


Fig. 11.—Complex reaction time.

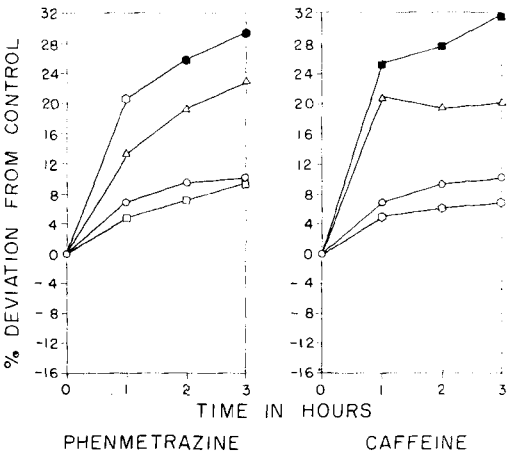


Fig. 13.—Tracking test.

Figs. 4—13.—Placebo, ○; *d*-amphetamine, □, 2.5 mg., △ 5 mg., ⬡ 10 mg.; methylphenidyl acetate; ⊏ 5 mg., △ 10 mg., ⬡ 15 mg.; phenmetrazine, □ 12.5 mg., △ 25 mg., ⬡ 50 mg.; caffeine, ■ 100 mg., △ 200 mg., ⬡ 300 mg. Filled-in symbols indicate a significant difference ($P < 0.05$) from corresponding placebo values.

TABLE III.—INTEGRATED DOSE-TIME EFFECTS OF CENTRAL STIMULANTS[a]

Treatments	Tracking Test	Five-Second Tap	Sixty-Second Tap	Visual Reaction	Complex Reaction
Placebo	17.9	2.0	1.9	−21.4	6.7
Caffeine, 100 mg.	56.0	32.5	27.6	−14.4	44.2
Caffeine, 200 mg.	41.1	21.0	55.5	−8.2	16.7
Caffeine, 300 mg.	12.2	12.6	40.9	1.0	−6.3
d-Amphetamine, 2.5 mg.	27.4	18.2	35.4	3.7	3.1
d-Amphetamine, 5.0 mg.	29.7	15.8	33.3	−9.9	−2.6
d-Amphetamine, 10.0 mg.	16.5	22.1	52.1	10.4	34.4
Phenmetrazine, 12.5 mg.	13.1	19.3	24.6	17.8	29.0
Phenmetrazine, 25.0 mg.	35.2	30.1	40.3	−2.5	31.9
Phenmetrazine, 50.0 mg.	49.2	45.8	60.4	5.4	−27.8
Methyl phenidyl acetate, 5.0 mg.	26.1	10.4	12.9	−0.3	−7.0
Methyl phenidyl acetate, 10.0 mg.	41.2	30.9	31.6	−1.7	−13.0
Methyl phenidyl acetate, 15.0 mg.	52.2	38.7	43.2	9.6	6.1

[a] The areas under curves were measured with a planimeter from original graphs in which the coordinates measured 7.6 cm. and 15.3 cm. for the *x* and *y* axes, respectively. Values are the algebraic sums of the areas above and below the zero or control level.

Table III and Figs. 6 and 7, it may be observed that the improvement was dose-related except in the case of caffeine. For reasons that are not apparent, the order of activity with caffeine was 100 < 300 < 200 mg.

The effects of the drugs upon both simple and complex reaction times were not as marked nor as consistent as those obtained with the tapping tests. This may be seen from examination of Tables II and III and Figs. 8–11. Generally some improvement over the control values can be noted, but of greater meaning is the fact that the time-related performance decrement of both tests, as seen by comparison with the placebo values, was prevented by most of the drug doses. Several effects stand out. First, in contrast to most of the other tests, in the simple reaction time, caffeine induced a slight improvement that was directly related to the dose. With the complex reaction time, however, the 100-mg. dose of caffeine produced significantly greater improvement than the higher doses, again demonstrating an inverse relationship between the dose and the effect of this drug. This effect of a high dose of a stimulant causing a decrease in the complex reaction time performance was marked with the 50-mg. dose of phenmetrazine.

From Tables II and III and Figs. 12 and 13, it is apparent that the tracking test was the most sensitive gauge of stimulant drug activity. Both methyl phenidyl acetate and phenmetrazine produced improvement in performance. In each case the effect was directly related to the size of the dose, and with the highest doses it was significant. Caffeine, on the other hand, once again demonstrated an inverse relationship between dose and effect with the 100-mg. dose inducing significant improvement. *d*-Amphetamine did not significantly affect this performance test at any dose nor at any time tested.

The side-effects observed with the central stimulants were minimal and usually consisted of no more than a marked increase in excitability and physical activity with the highest dose of each drug. All subjects were normotensive and no symptoms were elicited from the cardiovascular system other than moderate increases in the heart rate. One subject, who did not drink coffee, became quite agitated after the first dose of 100 mg. of caffeine and was given no further doses of this drug. Generally the subjective response to all the drugs was a feeling of well being, although the 300-mg. dose of caffeine had a tendency to induce nervous tension that might be best described as the "jitters."

Central Depressant Study.—Dunnett's *t*-test was applied to the data from the study of the central depressants in the same manner as previously described for the stimulants. The results are summarized in Table IV. Inspection of the mean values reveals that only one score was significantly improved. This was the simple reaction time with chlorpromazine 50 mg., at the 2-hour test period. Examination of the raw data from which this significant value was obtained gave no indication as to the reason for the apparent improvement.

While the values obtained in the various tests are seemingly quite variable in terms of the placebo effects, the per cent deviation from the control (initial) values are uniformly low (Table IV) in comparison with the results from the same tests using central stimulants (Table II). In the stimu-

Table IV.—Effect of Central Depressants as Mean Per Cent Deviation from Control[a]

Treatments	Tracking Test			Five-Second Tap			Tests and Trials[b] Sixty-Second Tap			Visual Reaction			Complex Reaction		
	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
Placebo	3.24	6.73	5.42	1.46	0.68	0.85	0.53	0.93	1.33	−2.42	−4.78	−5.83	3.04	2.32	0.11
Chlorpromazine, 25 mg.	6.80	5.23	5.36	0.16	−2.72	−4.25	2.00	1.88	1.73	−2.85	−6.61	−6.61	10.24	3.41	8.22
Chlorpromazine, 50 mg.	0.88	1.89	−0.13	0.88	−0.94	−1.66	−0.57	−1.31	−1.88	3.21	6.10	3.83[c]	1.42	−1.23	−5.02
Chlorpromazine, 100 mg.	5.30	−0.25	−3.66	0.50	−2.20	−7.10	0.40	−2.07	−3.77	0.73	−3.88	−6.40	−14.31	−4.72	−4.72
Meprobamate, 200 mg.	2.62	2.86	4.11	0.03	−1.27	−2.78	1.65	3.55	3.39	−3.19	−3.66	−4.60	−1.38	−6.60	−3.30
Meprobamate, *400 mg.*	10.27	9.73	9.33	−0.32	0.82	1.83	1.27	1.05	1.05	−0.09	−0.27	−4.93	0.64	5.50	−1.15
Meprobamate, 800 mg.	4.29	6.24	7.61	0.92	0.48	−0.35	0.46	0.34	2.82	−3.49	−1.10	−3.30	−0.96	−12.33	−11.23
Oxanamide, 200 mg.	2.55	4.98	5.11	4.43	0.98	0.03	0.72	1.02	−4.09	−7.72	−7.86	3.71	1.06	5.30	
Oxanamide, 400 mg.	8.13	5.21	5.46	−0.28	−0.60	−2.62	0.82	1.58	1.77	−1.56	0.96	−6.75	0.27	−2.46	−3.69
Oxanamide, 800 mg.	−1.10	−2.44	−1.71	1.42	−0.03	−2.24	−0.68	−2.29	−1.43	−1.54	−4.90	−5.37	−0.40	−3.44	−5.83
Phenobarbital, 15 mg.	7.06	5.36	8.10	5.88	3.47	6.51	3.18	1.85	0.62	−0.52	−4.15	−3.35	−1.05	8.04	−2.50
Phenobarbital, 30 mg.	1.32	4.21	4.47	0.23	−0.97	−0.84	0.63	0.51	0.24	−4.74	−3.30	−5.16	−9.08	−7.15	−7.98
Phenobarbital, 45 mg.	3.47	3.59	5.57	3.03	−0.47	1.23	0.51	1.74	1.50	−1.16	−0.98	−4.41	−0.14	8.05	3.83

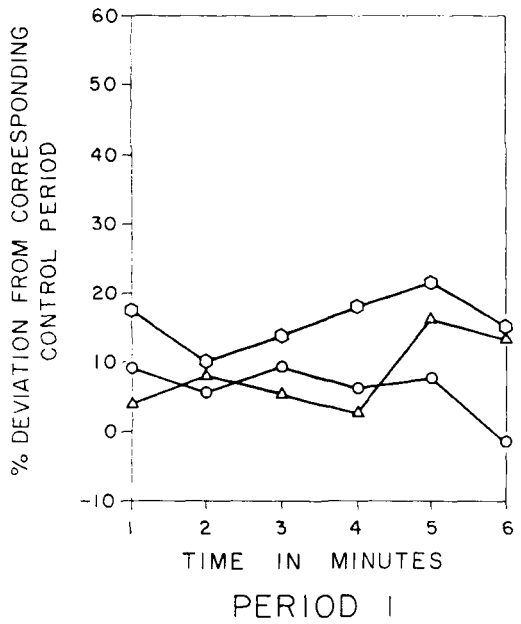
[a] Controls are those test values obtained immediately preceding drug administration. [b] Trials 1, 2, and 3 are those test values obtained 1, 2, and 3 hours after drug ad ministration. [c] Significantly different from placebo ($P < 0.05$).

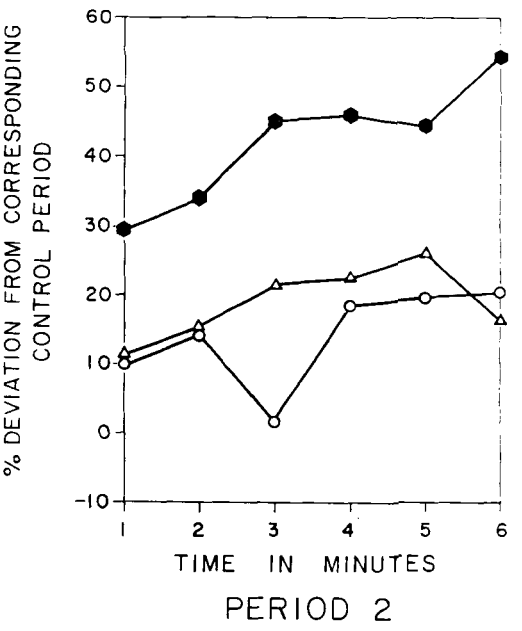
lant tests, the mean per cent deviation was frequently in the range of a 20 to 30% positive deviation, while with the central depressants, it seldom exceeded 8% in either direction.

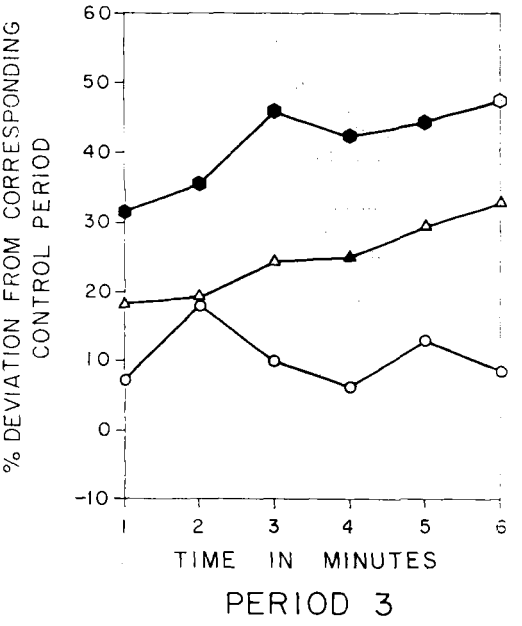
Central Stimulants Fatigue Study.—The results of this study are presented in Figs. 14–19. While the manner in which the data are presented does not indicate any apparent time-related decrement in performance, it should be noted that the points in each curve represent the per cent deviation from the corresponding points measured during the control period. Therefore, while the relative values shown in the curves may indicate an increase or little change in performance, a plot of the absolute values would result in curves having a definite downward trend in almost all cases. With this in mind, it may be seen that phenmetrazine induced a greater percentage improvement with the 6-minute tracking test than with the 3-minute tapping test. The prevention of fatigue with the stimulants, as anticipated from the results of the previous 60-second tapping test, was most prominent 2 hours after taking the drug. In the 6-minute tracking test the results were significant ($P < 0.01$) at all times throughout the 2-hour period and in all but one point at 3 hours. In the 3-minute tapping, only two points in the 2-hour test period were significant at $P < 0.01$ and $P < 0.05$, while none were significant at period three. Methyl phenidyl acetate significantly improved performance only at one time, 3 hours after the drug in the 6-minute tracking test.

Chronic Deanol Study.—The results of the performance tests were analyzed with a nested 2 × 2 factorial type design in order to measure the significance of each of the following effects: drug effect *vs.* placebo; order of administration, i.e., drug first, placebo last *vs.* placebo last, drug first; and finally the interaction between the drug and the period tested, i.e., drug-test period differences (7).

The mean values for the motor and psychomotor tests at 4 and 8 weeks are presented in Table V. In







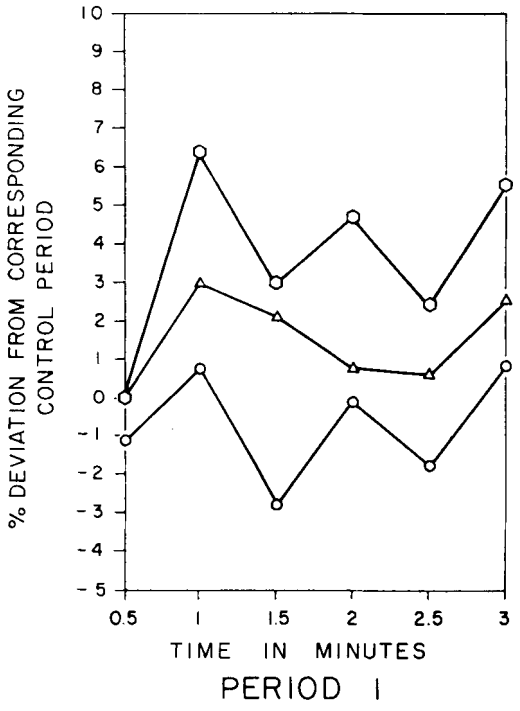
Figs. 14—16.—Six-minute tracking test; placebo, O; methyl phenidyl acetate 15 mg., △; and phenmetrazine 50 mg., ⬡.

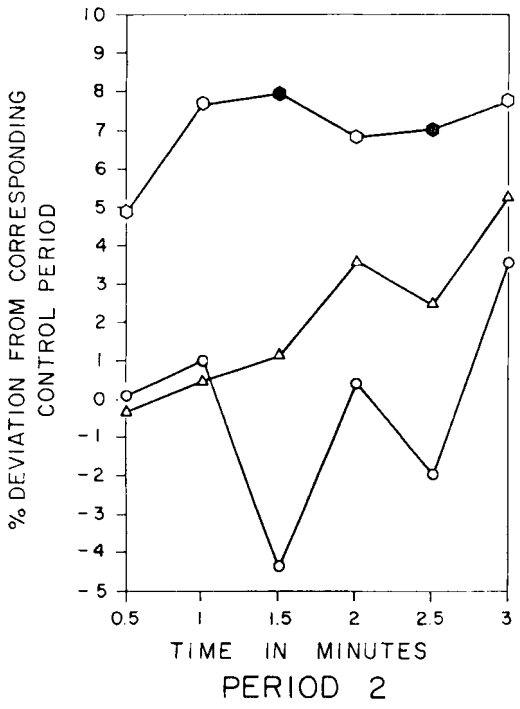
TABLE V.—MEAN CHRONIC DEANOL SCORES AT 4 AND 8-WEEK TEST PERIODS[a]

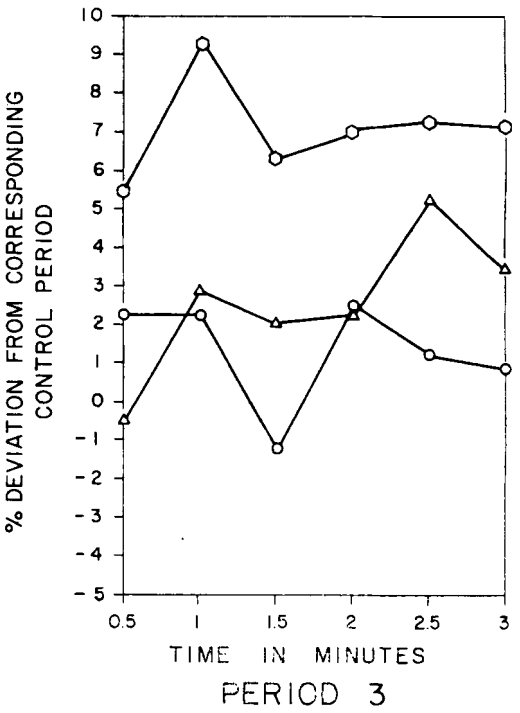
	Four Weeks		Eight Weeks	
	Placebo Group 1	Deanol Group 2	Placebo Group 2	Deanol Group 1
Tracking Test	660.2	720.7	649.8	635.2
5-Second tap	31.7	31.9	32.9	31.7
60-Second tap	326.0	333.4	329.1	321.2
Visual reaction	228.3	221.2	216.1	222.9
Complex reaction	814.2	764.0	728.3	733.2

[a] Group 1 received 75 mg./day of deanol for first 4 weeks while group 2 received a placebo. For the next 4 weeks, the treatments were reversed.

Table VI the analysis of variance of the data indicates a significant interaction only between order and drug for the pursuit test. It is apparent that the reason for the significance lies in the relatively high score obtained with the drug when it was administered in the first 4-week period. This score, when compared with the other three values in the pursuit test by a *t*-test, was found to be significant at $P < 0.001$ (8).







Figs. 17—19.—Three-minute tapping test, placebo, ○; methyl phenidyl acetate 15 mg., △; and phenmetrazine 50 mg., ⬡.

TABLE VI.—ANALYSIS OF VARIANCE OF CHRONIC DEANOL SCORES

Source of Variation	*df*	Mean Square	*F*	*P*
Tracking Test				
Order	1	12,656	0.96	...
Error term	16	13,233		
Drug	1	4,738	2.84	...
Drug × order	1	20,688	12.41	<0.01
Error term	16	1,667		
Five-Second Tap				
Order	1	4.41	0.12	...
Error term	16	36.51		
Drug	1	2.25	1.20	...
Drug × order	1	1.87	0.79	...
Error term	16	2.38		
Sixty-Second Tap				
Order	1	529.00	0.12	...
Error term	16	4,296.62		
Drug	1	0.44	...	...
Drug × order	1	186.78	0.99	...
Error term	16	189.42		
Visual Reaction				
Order	1	434.03	0.44	...
Error term	16	995.05		
Drug	1	0.25	...	...
Drug × order	1	250.70	1.03	...
Error term	16	243.03		
Complex Reaction				
Order	1	6,834	0.16	...
Error term	16	43,331		
Drug	1	4,624	0.34	...
Drug × order	1	30,625	2.28	...
Error term	16	13.458		

The results of the adjective check list test for mood were analyzed in several ways in order to obtain any possible indication of drug effect. As each adjective had a positive or negative mood characteristic, those that were checked were graded 3 points for a double check, 2 points for a single check and 1 point if they were undecided. The total number of positive points over the total negative points was expressed as the mood index. These values ranged from a low of 0.26 to a high of 79.0. Comparison of the 4 and 8-week values revealed no significant difference between drug and placebo. Neither was there any tendency for the mood index to increase during the 4 weeks of deanol administration when compared with the placebo administration. In some individuals, marked fluctuations in the mood occurred from week to week while with others, the values were relatively constant. Neither the direction nor the magnitude of the change could be related to the presence or absence of the drug nor to the period of testing. The comments of subjects concerning changes in mental or physiological functions were equally variable and unrelated to the drug or the period.

DISCUSSION

In any study of human behavior the selection of test procedures not only can influence the results but, unfortunately, is rather empirical. The general types of tests that may be employed can be categorized as: conditioned response, affect change, neurophysiological, perceptual, motor, mental, and perceptual-motor tests. Tests employed in these studies were selected in order to meet several criteria. Because of the large total number of individual drug-test scores (34,860) in addition to the pretest training, it was necessary to consider carefully the amount of time required for the actual performance of each test. In a more limited study, it might have been possible to select tests which would have been more sensitive to drug effects, although there is little information on this subject. Further requirements of each test were that the results must be reproducible, quantitative, and complement the other tests employed rather than measure essentially the same parameters. The simple visual reaction time met these requirements for reaction time tests. While the complex reaction time test employed was not a well-known procedure, it combined both simple mentation and reaction time, and it was thought that when compared with the results of the simple reaction time test it might serve to separate the complex reaction time into the time required for mentation and that needed to complete the simple reflex. Because of the variance within the complex reaction times, such a comparison was not feasible. The tapping tests provided objective indexes of motor activity in terms of the speed at which a simple voluntary movement could be repeated and the effect of fatigue upon an extended performance. The pursuit, perceptual-motor in nature, integrates visual perception with a complex motor response. It has been suggested that tests requiring a complex response are most sensitive to central drug effects (9, 10).

As caffeine was the first psychomotor drug to be known, a considerable number of performance tests have been conducted with this agent. Unfortunately, much of the evidence is conflicting. Its effect upon reaction time presents a case in point. In our study, caffeine induced a significant dose-related improvement in simple visual reaction time. It has, however, been reported to: decrease the reaction time (11–14), lengthen the reaction time (15, 16), produce no change in the simple reaction time after doses as large as 600–900 mg. of caffeine citrate (17–20), and to produce either a decrease or an increase dependent upon the size of the dose (21). Small doses between 60 and 240 mg. produced longer reaction times than the placebo, while larger amounts, 300–360 mg., shortened the times.

There are several possible reasons for these divergent results with such a seemingly simple test. In some of the investigations, cups of coffee were employed to measure the dose of caffeine, a technique which raises suspicion as to the actual amount of caffeine administered (13, 16). Further, the measurement of the reaction time (RT) is dependent upon numerous variables which makes the test fairly complex to administer. For one thing, it has been demonstrated that the reaction time is a function of the sense modality stimulated, auditory RT's being faster than visual RT's. Further, the number of sense organs stimulated affect the times, as any combination of auditory, visual, and electrical or shock stimuli induce faster RT's than do the individual stimuli. Additional factors influencing the RT include: stimulus duration and intensity, period of readiness, stress, age, body position, and the responding member (22). It is entirely possible that some of the reported effects may have been the result of uncontrolled variables. For example, the optimum period of readiness before the stimulus is presented has been determined to be between 1.0 and 4.0 seconds, a longer delay resulting in a lengthened RT. This was the approximate range employed in our study although, in some of the results cited, the authors have used indefinite periods of readiness or periods up to 10 seconds.

Perhaps the most significant finding with regard to caffeine was that in three of the five tests, that is 5-second tapping, complex reaction time, and the tracking tests, an inverse relationship was found to exist with regard to dose and effect. The only other drug which caused this effect was the 50-mg. dose of phenmetrazine in the complex reaction time. That increasing the dose of caffeine might be detrimental to performance has been previously reported for tracking tests (18, 22, 23). The doses employed in these observations were in the 200 to 300-mg. range. We observed that with a dose of 200 mg., performance was still improved and that it required 300 mg. to induce a modest and nonsignificant decrease in performance. Such minor differences could be related to subject or test variables.

The reason for the impairment of performance with a task such as tracking may be related to the fact that caffeine has been reported to reduce steadiness of the hand in doses of 300 mg. or more (13, 17, 18, 20, 21, 24–26). While there has been no mention of an improved steadiness with lower doses of caffeine, an inverse dose-effect relationship has been reported in a test of coordination in which the time required to thrust a stylus into a series of holes was measured. In this test, 60 to 120 mg. of caffeine improved the performance, while doses above 180 mg. slowed the response (21). This same

inverse effect that we also noted with the 5-second tapping test may help to explain reports that caffeine increases (17, 20, 21, 23), decreases (13), or produces no change (18, 27) in the tapping rate.

Obviously the effects of caffeine upon performance are dose-related and complex. It is suggested that the impaired steadiness or tremor induced by the high doses of caffeine may be the primary factor, or a direct extension thereof, in the tests in which the drug reduced performance, although it is difficult to equate muscle tremor directly with a test such as complex reaction time. Reasons for the improved performances with caffeine are presumably similar to those applying to the other psychomotor stimulants tested. It has been determined by others that caffeine heightens excitability, improves vigilance, facilitates simple intellectual tests, improves the mood, and decreases fatigue. Whether these are different expressions of the same effect is difficult to say, but any or all would likely have influenced the performance tests in this study. One may conclude that if caffeine is to be employed for the general improvement of performance, the dose should not exceed 100 mg. unless it can be definitely determined that the detrimental effect of larger doses is not a direct extension of the beneficial effect. In this case perhaps, the impairment can be negated through the concomitant administration of appropriate central depressants.

The results of the *d*-amphetamine testing were in general agreement with those previously reported. It had been found to induce somewhat equivocal results in the tapping rate. Both an increase (20) in the rate and no change (18, 28) have been reported. We observed a dose-related trend toward improvement which was not significant, although we did not use as high a dose as some of the reports which found improved performance. An important variable in this test is the state of fatigue. As indicated in the 60-second test, *d*-amphetamine produces a significant increase in the rate at both the 2 and 3-hour periods. Other workers have demonstrated that *d*-amphetamine can prolong the time that an individual can perform physically fatiguing work (29–32). Repeated testing, or testing with intervals longer than 5 seconds would be expected to increase further the minimal improvement which we noted in the 5-second test. While the *d*-amphetamine was not significantly effective in any test except 60 second tapping, which is a measure of fatigue, it has been reported that 5 mg. of the drug significantly improves the score in a multidimensional pursuit test (33). This difference may be attributed to the greater sensitivity of the multidimensional pursuit test.

Phenmetrazine and methyl phenidyl acetate significantly improved the performance in the 5 and 60-second tapping rate, visual reaction time, and the tracking test. It has been previously observed that subjects depressed with phenobarbital were able to perform simple arithmetic calculations faster when they received 20 mg. of methyl phenidyl acetate (34). Phenmetrazine was found to improve mental performance approximately 9% in well-rested subjects and 40% in the presence of fatigue (35). Studies comparable to those reported in this paper have not been disclosed, but within the limitations imposed by the drug doses and the tests employed, these agents gave indication of greater promise for the improvement of performance than did either caffeine or *d*-amphetamine.

The fact that the central depressants did not significantly affect the performance tests is not surprising. Low doses of central depressant drugs have been generally found to be without effect upon simple performance tests similar to the types which we used (36, 37). Kornetsky found that meprobamate did not affect learning or reaction times in a dose of 800 mg., but in a 1600-mg. dose, impairment of performance was observed (38). In general, tests requiring integration of several functions, such as a simulated automobile driving apparatus (8) or a multidimensional pursuit test (39) are sensitive to moderate central depression. While the statistical analysis of the data did not demonstrate any depressant drug effects, a less sophisticated approach of simply observing trends gives some indication of a depressed performance. For example, as seen in Table IV, the greatest reduction in performance with the complex reaction time occurred with the largest doses of the tranquilizers. Further, the two larger doses of chlorpromazine (50 and 100 mg.) produce a deteriorated performance in four out of the five tests. It had been reported that chlorpromazine at the 100-mg. level impairs the pursuit test, tapping rate, and hand steadiness (40).

The tranquilizers should not be necessarily considered as agents which reduce performance, as the ability to perform certain tasks may actually be improved in the presence of fear, anxiety, or tension. This action has been demonstrated with both oxanamide (41) and meprobamate (42) using subjects having demonstrable nervous tension. Unfortunately, the experimental production of anxiety or tension in human subjects has not been adequately studied. It has been demonstrated that with an increase in muscle tension, performance will improve, but beyond a certain amount of tension it will rapidly fall off (43). It was previously noted in the discussion of the central stimulants that increasing the dose of caffeine beyond 100 mg. generally resulted in a performance decrement. These larger doses of caffeine were also found to induce tremor and other signs of muscle tension. It is possible with high dosage levels of caffeine, and perhaps of other central stimulants as well, that the concomitant administration of a tranquilizer may improve the level of performance above that obtainable with a stimulant alone.

A number of investigators have suggested that both caffeine and the amphetamines prolong the period over which an individual can maintain the level of performance in physically fatiguing tests (29–31, 44–47). There has been little evidence, however, to indicate the exact mechanism by which fatigued performance is mitigated. These drugs may either maintain the base-line level of performance, thereby preventing a performance decrement, or they may elevate the initial performance level, thus allowing a decrement to occur without dropping below the base-line. Neither caffeine nor *d*-amphetamine were tested in this phase of the work as both phenmetrazine and methyl phenidyl acetate appeared to be equally or more active, resulted in a better dose-response relationship, and had not been previously tested for their effect upon fatigue. Phenmetrazine in a 50-mg. dose was significantly effective in both the 3-minute tapping and 6-minute

pursuit tests. From the initial points in Figs. 15, 16, 18, 19, it can be seen that the effect upon fatigue is accomplished in part by elevation of the initial level of performance and, as best seen in the tracking test curves, also by the time-related widening of the difference between the points for the placebo and phenmetrazine. This increase in difference reflects a reduction in the rate of fatigue-induced decrement.

From the results obtained with deanol, several possible conclusions may be reached. As there was no indication of activity with the mood test and most of the psychomotor tests, it may be concluded that in the dose and with the duration tested, deanol does not produce central stimulation of the magnitude observed with the other stimulants. The reason for the highly significant ($P < 0.001$) difference between the effect of deanol at the end of the first 4 weeks of the 8-week test period and at the end of the second 4 weeks, is not clear. If this difference is related to the drug, then there must have been an interaction between the drug and some unknown, uncontrolled factor that differed between the first and the last 4 weeks of testing. It is suggested that the factor might have been the heightened interest or motivation during the early stages of testing. Although this type of interaction has not been reported, it is of interest to note in Table V that both the drug and placebo scores in the pursuit test were highest at 4 weeks.

The observed effect of the deanol treatment upon mood and other subjective responses is at variance with reported results (48). The responses described by others: a more affable mood, greater ability to concentrate, the ability to stop smoking, increased tolerance of contact lenses, and less stimulation from amphetamines, were presumably obtained with low daily doses of from 10 to 30 mg. of the drug. Similar conclusions might be drawn from a casual or uncritical inspection of our own data. We found that nervousness was reported five times by individuals taking deanol and four times by the controls. An increased incidence of headaches was noted four times by the controls. An increased incidence of headaches was noted four times by deanol subjects and six by the placebo group. There were six reports that more sleep was needed with deanol and five with the placebo. Conversely, the need for less sleep was indicated nine times in the placebo group and eight times in the deanol subjects. An increase in libido was noted once in each group. It may be of some consequence that during the first 4 weeks both drug and placebo groups made a total of 96 comments concerning subjective responses, while during the last 4 weeks, only 54 comments were made. The suggestion, previously advanced, that the significant effect of deanol upon tracking performance during the first 4 weeks might be related to an interaction with a heightened initial interest, would tend to be supported by this evidence.

Any final interpretation of the experimental results, in terms of their possible application to useful tasks, must be predicated upon the specific tests which were employed. Because a particular drug could not be demonstrated to affect a specific test does not mean that activity might not be observed, perhaps, in a more appropriate or total measure of performance. Conversely, if a drug was demonstrated to be effective, it may generally be assumed that while more sensitive test procedures would also be affected, total performance may still not be improved.

REFERENCES

(1) Miller, R. B., "Handbook on Training and Training Equipment Design," WADC Technical Report 53–136, 1953, p. 252.

(2) Ammons, R. B., "Knowledge of Performance," WADC Technical Report 54-14, 1954, p. 1.

(3) Borkenstein, R. F., "A Practical Experiment on the Effects of Alcohol on Driving Skill," The Southern Police Institute, University of Louisville, 1956, p. 24.

(4) Nowlis, H., Nowlis, V., Riesen, A. H., and Wendt, G. R., "Chemical Influences on Behavior, III. The Effects of Dramamine and Scopolamine on Emotional and Social Behavior with Comparison Data on the Effects of Other Drugs," Technical Report, Officer of Naval Research, U. S. Navy, Contract N6or1-126, Project NR 144, 1953, p. 3a.

(5) McNemar, Q., "Psychological Statistics," 2nd ed., John Wiley & Sons, New York, N. Y., 1955, pp. 311–325.

(6) Dunnett, C. W., *J. Am. Stat. Assoc.*, **50**, 1096(1955).

(7) McNemar, Q., "Psychological Statistics," 2nd ed., John Wiley & Sons, New York, N. Y., 1955, pp. 332–335.

(8) Scheffe, H., *Biometrika*, **40**, 87(1953).

(9) Loomis, T. A., and West, T. C., *J. Pharmacol. Exptl. Therap.*, **122**, 525(1958)

(10) Goldstein, A., Searle, B. W., and Schimke, R. T., *ibid.*, **130**, 55(1960).

(11) Cheney, R. H., *ibid.*, **53**, 304(1935)

(12) Cheney, R. H., *J. Exptl. Psychol.*, **19**, 357(1936).

(13) Gilliland, A. R., and Nelson, D., *J. Gen. Psychol.*, **21**, 339(1939).

(14) Horst, K., and Jenkins, W. L., *J. Pharmacol Exptl. Therap.*, **53**, 385(1935)

(15) Schilling, W., *Psychol. Rev.*, **28**, 72(1921).

(16) Hawk, P. B., *Am J. Physiol.*, **90**, 380(1929).

(17) Thornton, G. R., Holck, H. G. O., and Smith, E. F., *J. Abnormal Social Psychol.*, **34**, 96(1939).

(18) Alder, H. F., Burckhardt, W. L., Ivy, A. C., and Atkinson, A. J., *J. Aviation Med.*, **21**, 221(1950).

(19) Seashore, R. H., and Ivy, A. C., *Psychol. Monog.*, **67**, 1(1953).

(20) Lehman, H. E., and Csank, J., *J. Clin. Exptl. Psychopathol.*, **18**, 222(1957).

(21) Hollingworth, H. L., *Arch. Psychol.*, **3**, 1(1912).

(22) Horst, K., Buxton, R. E., and Robinson, W. D., *J. Pharmacol. Exptl. Therap.*, **52**, 322(1934).

(23) Horst, K., Robinson, W. D., Jenkins, W. L., and Bas, D. L., *ibid.*, **52**, 307(1934).

(24) Hull, C. L., *J. Gen. Psychol*, **13**, 249(1935).

(25) Switzer, S. A., *ibid.*, **12**, 78(1935).

(26) Switzer, S. A., *J. Comp. Psychol.*, **19**, 155(1935).

(27) Flory, C. D., and Gilbert, J., *J. Appl. Psychol.*, **27**, 121(1943).

(28) Simonson, E., and Enzer, N., *J. Exptl. Psychol.*, **29**, 517(1941)

(29) Alles, G. A., and Feigen, G. A., *Am J. Physiol.*, **136**, 392(1942).

(30) Cuthbertson, D. P., and Knox, J. A. C., *J. Physiol.*, **106**, 42(1947).

(31) Knoefel, P. K., *Federation Proc.*, **2**, 83(1943).

(32) Smith, G. M., and Beecher, H. K., *J. Am. Med. Assoc.*, **170**, 542(1959).

(33) Payne, R. B., and Moore, E. W., *J. Pharmacol. Exptl. Therap.*, **115**, 480(1955).

(34) Drassdo, A., and Schmidt, M., *Med. Monatsschr.*, **8**, 393(1954).

(35) Lienert, G., *Psychiat. Neurol. u. Med. Psychol*, **6**, 237 (1954)

(36) Kristofferson, A. B., and Cormack, R. H., *Clin. Res.*, **6**, 416(1958).

(37) Seward, G. H., and Seward, J. P., *Arch. Psychol.*, **29**, 1(1936)

(38) Kornetsky, C., *J. Pharmacol. Exptl. Therap.*, **123**, 216 (1958).

(39) Pearson, R. G., THIS JOURNAL, **46**, 702(1957)

(40) Kornetsky, C., *J. Mental Sci.*, **104**, 1093(1958)

(41) Procter, R. C., *Diseases of Nervous System*, **18**, 223 (1957).

(42) Dickel, H. A., Wood, J. A., and Dixon, H. H., *Ann. N. Y. Acad. Sci.*, **67**, 780(1957).

(43) Courts, F. A., *J. Exptl. Psychol.*, **25**, 235(1939).

(44) Rivers, H. W. R., and Webber, H. N., *J. Physiol.*, **36**, 33(1907).

(45) Foltz, E. E., Ivy, A. C., and Barborka, C. J., *Am. J. Physiol*, **136**, 79(1942).

(46) Foltz, E. E., Ivy, A. C., and Barborka, C. J., *J. Lab. Clin. Med.*, **28**, 603(1943).

(47) Foltz, E. E., Schiffrin, J. J., and Ivy, A. C., *ibid.*, **28**, 601(1943).

(48) Pfeiffer, C. C., in "International Review of Neurobiology," Vol. 1, Academic Press, New York, N. Y., 1959, p 220.