1969

# Variations of visual perceptual discrimination threshold (VPDT) by D-Amphetamine visual perception

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# VARIATIONS OF VISUAL PERCEPTUAL DISCRIMINATION THRESHOLD (VPDT) BY d-AMPHETAMINE

by

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1969

A THESIS

Presented to the Faculty of The College
of Medicine in the University of Nebraska
in partial fulfillment of requirements for
the Degree of Doctor of Medicine

Under the supervision of Dr. Walter Friedlander

Omaha, Nebraska

February 1, 1969

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## INTRODUCTION

The purpose of this paper is to present and evaluate a technique that may measure the higher nervous system function of perception. This was done in a controlled experiment using the subjects as their own controls and measuring the effects of several psychopharmacologic drugs on the speed of perception of a briefly presented visual stimulus.

A brief review of the recent literature on the psychopharmacologic effects of amphetamine, one of the drugs used in the present experiment, is also presented.

## METHOD

Visual Perceptual Discrimination Threshold (VPDT) is defined as the time needed to correctly visually identify the presented stimulus. In this case a three digit number was used. Using a tachistoscope, a three digit number was presented beginning with a 4 millisecond exposure time; this was repeated, with a ten second rest period between exposures, three times or less if the subject recognized it before the third trial. If the number was not correctly identified, it was exposed in similar fashion for 5 milliseconds, etc. until it was correctly identified. The exposure time at which it was correctly identified was the VPDT. A series of five different numbers was presented in each single subexperiment and the mean of the five VPDT values was taken as the mean VPDT. Each subject was tested five times (subexperiments) with each drug. The first test was at time zero ($C_0$) and the second began 20 minutes later ($C_1$). The subject was then given one of the drugs being investigated and was tested again after 20 minutes ($E_1$); 40 minutes after $E_1$ he was again tested ($E_2$), and then again one hour after that ($E_3$).

The experiment was conducted in two parts using the same drugs but in different doses. In part I twelve male medical students from the University of Nebraska College of Medicine were used as subjects. None were taking any drugs or medications. The drugs used were d-amphetamine 5 mg.,

d-amphetamine 10 mg., phenobarbital 30 mg., and a placebo. In part II one female and eleven male medical students, three of whom had participated in part I, were used as subjects, and doses were increased to d-amphetamine 15 mg., d-amphetamine 20 mg., phenobarbital 60 mg., and a placebo. The drugs were prepared by the College of Medicine pharmacy to appear the same and were coded as Rx A,B,C, and D for part I and Rx E, F,G, and H for part II. The code, unknown to the experimenter and the subjects, was broken only when the entire parts of the experiment were concluded. Each subject was given a different drug on four successive weeks so that after four weeks each subject had been tested with each drug. Also, the testing schedule was arranged so that equal numbers of subjects received drug A, for example, on week one, drug B on week one, etc. An attempt was made to conduct the testing at the same time and on the same day every week for each group of two to four subjects tested together, and this was accomplished in most instances.

RESULTS

The mean VPDT values for each subject at the different testing times are shown in Tables I and II. The sums of the mean VPDT values times ten (to eliminate decimals) for all subjects at each testing time are shown as well as the mean of the mean VPDT values for the testing times showing the greatest differences in mean VPDT values.

Using the data obtained, the statistical significance of the differences observed was evaluated using a modification of the t test for small samples which theoretically accounts for the relatively small number of subjects and the occasional value which seems to fall outside of the expected range.[1] The values of p thus obtained are also shown in the tables and are greater than those which could be accepted for significance in all cases.

In an attempt to demonstrate a trend, even if it is not significant

TABLE I

A.

| S. | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1*[1] | 60 | 64 | 56 | 58 | 54 |
| 2 | 82 | 58 | 58 | 64 | 62 |
| 3 | 84 | 90 | 68 | 80 | 72 |
| 4 | 66 | 66 | 70 | 66 | 74 |
| 5 | 80 | 80 | 82 | 78 | 70 |
| 6*[2] | 96 | 96 | 94 | 94 | 80 |
| 7 | 68 | 72 | 76 | 88 | 76 |
| 8 | 152 | 160 | 134 | 134 | 146 |
| 9*[3] | 116 | 126 | 114 | 122 | 104 |
| 10 | 70 | 76 | 78 | 66 | 70 |
| 11 | 66 | 60 | 76 | 76 | 74 |
| 12 | 58 | 58 | 68 | 64 | 62 |
| Total | 998 | 1006 | 974 | 990 | 944 |
| % | 99 | 100 | 96 | 99 | 93 |
| Mean | | 84 | | | 78 |
| P | | | | | $0.1<p<2$ |

B.

| S. | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1 | 56 | 58 | 54 | 56 | 64 |
| 2 | 58 | 50 | 52 | 54 | 54 |
| 3 | 68 | 66 | 72 | 60 | 72 |
| 4 | 80 | 72 | 76 | 88 | 94 |
| 5 | 126 | 104 | 84 | 96 | 86 |
| 6 | 100 | 100 | 92 | 98 | 96 |
| 7 | 68 | 66 | 76 | 90 | 94 |
| 8 | 120 | 108 | 130 | 118 | 126 |
| 9 | 132 | 130 | 132 | 140 | 108 |
| 10 | 80 | 72 | 80 | 62 | 52 |
| 11 | 76 | 70 | 78 | 78 | 74 |
| 12 | 60 | 68 | 72 | 60 | 64 |
| Total | 1024 | 964 | 998 | 1000 | 984 |
| % | 100 | 94 | 98 | 98 | 96 |
| Mean | 85 | | | | 82 |
| P | | | | | $.6<p<.7$ |

C.

| S. | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1 | 62 | 58 | 66 | 58 | 60 |
| 2 | 58 | 48 | 56 | 54 | 62 |
| 3 | 72 | 70 | 72 | 68 | 68 |
| 4 | 88 | 82 | 88 | 74 | 74 |
| 5 | 72 | 82 | 68 | 74 | 70 |
| 6 | 84 | 90 | 102 | 120 | 104 |
| 7 | 114 | 96 | 94 | 102 | 88 |
| 8 | 174 | 140 | 100 | 98 | 108 |
| 9 | 244 | 248 | 186 | 186 | 192 |
| 10 | 64 | 64 | 58 | 70 | 60 |
| 11 | 80 | 74 | 72 | 76 | 62 |
| 12 | 68 | 68 | 64 | 60 | 70 |
| Total | 1180 | 1120 | 1026 | 1040 | 1018 |
| % | 100 | 95 | 88 | 89 | 87 |
| Mean | 98 | | | | 85 |
| P | | | | | $.5<p<.6$ |

D.

| S. | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1 | 52 | 54 | 50 | 48 | 50 |
| 2 | 58 | 52 | 58 | 56 | 62 |
| 3 | 72 | 66 | 72 | 72 | 72 |
| 4 | 72 | 68 | 68 | 60 | 60 |
| 5 | 100 | 98 | 88 | 86 | 82 |
| 6 | 124 | 114 | 102 | 82 | 74 |
| 7 | 106 | 106 | 104 | 90 | 94 |
| 8 | 80 | 86 | 70 | 80 | 74 |
| 9 | 128 | 112 | 90 | 78 | 84 |
| 10 | 84 | 72 | 74 | 66 | 80 |
| 11 | 96 | 66 | 76 | 86 | 80 |
| 12 | 68 | 60 | 64 | 76 | 62 |
| Total | 1040 | 954 | 916 | 880 | 874 |
| % | 100 | 92 | 87 | 84 | 84 |
| Mean | 87 | | | | 73 |
| P | | | | | $.1<p<.2$ |

TABLE II

E.

| S | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1*3 | 118 | 94 | 92 | 82 | 96 |
| 2 | 64 | 62 | 60 | 70 | 60 |
| 3 | 110 | 118 | 94 | 102 | 94 |
| 4 | 92 | 98 | 96 | 88 | 92 |
| 5 | 90 | 84 | 90 | 98 | 86 |
| 6*2 | 114 | 100 | 112 | 104 | 96 |
| 7 | 88 | 76 | 82 | 84 | 86 |
| 8 | 72 | 72 | 70 | 68 | 64 |
| 9 | 64 | 60 | 56 | 64 | 50 |
| 10 | 124 | 118 | 114 | 106 | 96 |
| 11 | 136 | 154 | 138 | 114 | 122 |
| 12*1 | 74 | 70 | 74 | 72 | 68 |
| Total | 1146 | 1106 | 1078 | 1052 | 1010 |
| % | 100 | 96 | 94 | 92 | 88 |
| Mean | 96 | | | | 84 |
| P | | | | | .2<p<.3 |

F.

| S | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1 | 96 | 104 | 94 | 104 | 104 |
| 2 | 60 | 64 | 60 | 60 | 70 |
| 3 | 120 | 100 | 126 | 96 | 84 |
| 4 | 102 | 104 | 90 | 82 | 90 |
| 5 | 132 | 92 | 88 | 106 | 82 |
| 6 | 138 | 116 | 118 | 118 | 132 |
| 7 | 98 | 100 | 120 | 130 | 120 |
| 8 | 72 | 72 | 68 | 76 | 72 |
| 9 | 62 | 64 | 64 | 56 | 60 |
| 10 | 120 | 128 | 132 | 124 | 122 |
| 11 | 150 | 152 | 66 | 70 | 72 |
| 12 | 98 | 78 | 76 | 62 | 74 |
| Total | 1248 | 1174 | 1102 | 1084 | 1082 |
| % | 100 | 95 | 88 | 87 | 87 |
| Mean | 104 | | | | 90 |
| P | | | | | .2<p<.3 |

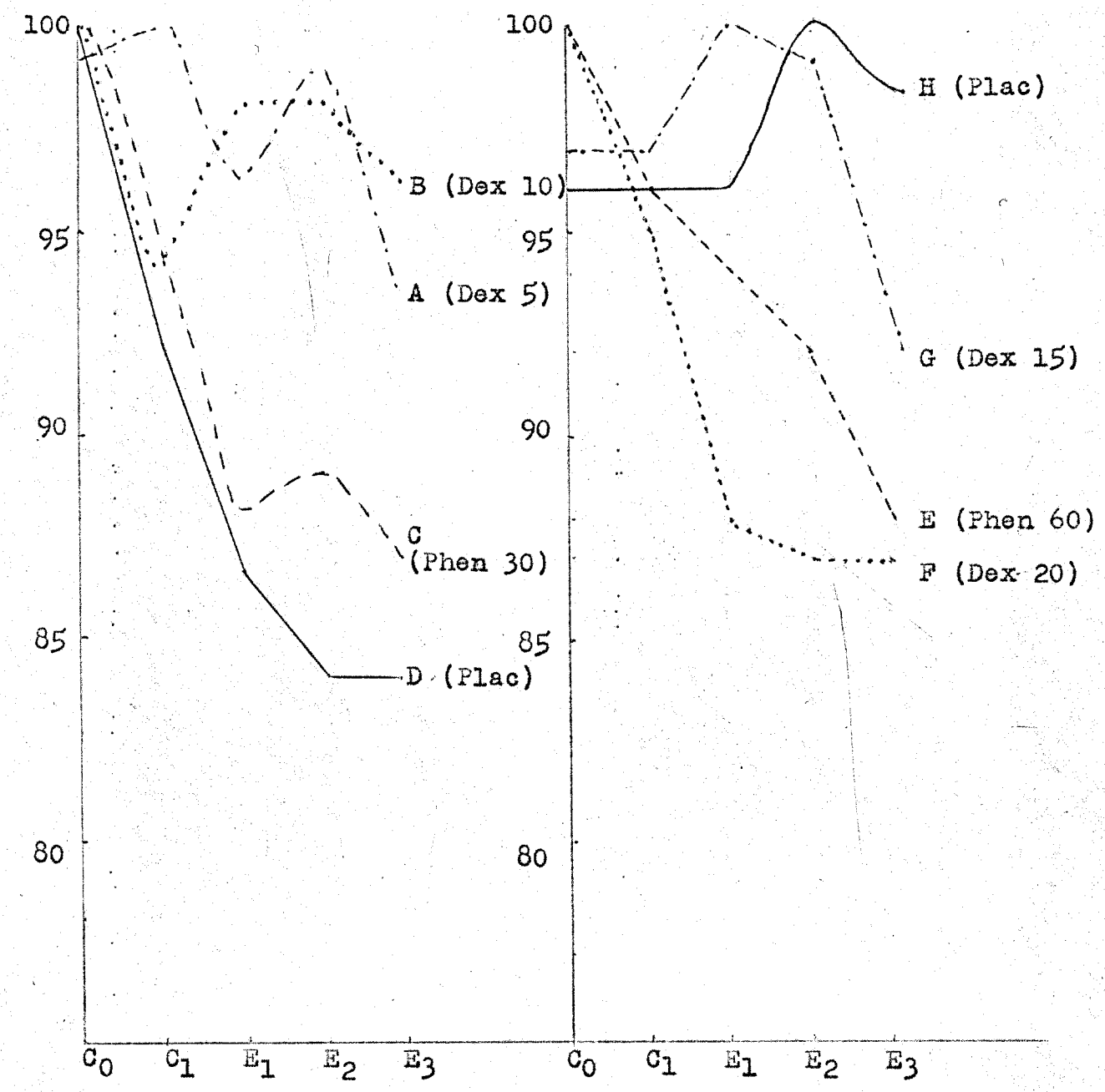
G.

| S | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_2$ |
|---|---|---|---|---|---|
| 1 | 112 | 82 | 96 | 90 | 90 |
| 2 | 66 | 64 | 78 | 66 | 60 |
| 3 | 82 | 76 | 98 | 82 | 104 |
| 4 | 102 | 92 | 102 | 100 | 94 |
| 5 | 68 | 76 | 78 | 104 | 72 |
| 6 | 108 | 110 | 112 | 130 | 118 |
| 7 | 156 | 152 | 134 | 122 | 112 |
| 8 | 78 | 94 | 66 | 76 | 78 |
| 9 | 62 | 62 | 60 | 68 | 58 |
| 10 | 104 | 120 | 162 | 130 | 120 |
| 11 | 120 | 122 | 122 | 134 | 112 |
| 12 | 70 | 80 | 66 | 66 | 58 |
| Total | 1128 | 1130 | 1174 | 1168 | 1076 |
| % | 97 | 97 | 100 | 99 | 92 |
| Mean | 94 | | | | 90 |
| P | | | | | .3<p<.4 |

H.

| S | $C_0$ | $C_1$ | $3_1$ | $3_2$ | $3_3$ |
|---|---|---|---|---|---|
| 1 | 106 | 104 | 104 | 124 | 90 |
| 2 | 60 | 60 | 58 | 62 | 62 |
| 3 | 74 | 88 | 96 | 70 | 100 |
| 4 | 80 | 92 | 90 | 88 | 80 |
| 5 | 76 | 66 | 68 | 70 | 76 |
| 6 | 138 | 158 | 266 | 150 | 148 |
| 7 | 102 | 100 | 102 | 88 | 98 |
| 8 | 78 | 72 | 70 | 66 | 74 |
| 9 | 116 | 88 | 140 | 132 | 114 |
| 10 | 106 | 92 | 106 | 116 | 116 |
| 11 | 102 | 112 | 112 | 120 | 110 |
| 12 | 72 | 88 | 76 | 76 | 74 |
| Total | 1110 | 1120 | 1288 | 1162 | 1142 |
| % | 96 | 96 | 96 | 100 | 98 |
| Mean | 93 | | | 95 | |
| P | .8<p<.9 | | | | |

PER CENT CHANGE IN VPDT WITH TIME




PART I

PART II

A is d-amphetamine 5 mg.
B is d-amphetamine 10 mg.
C is phenobarbital 30 mg.
D is placebo

E is phenobarbital 60 mg.
F is d-amphetamine 20 mg.
G is d-amphetamine 15 mg.
H is placebo

at the 0.05 level, graphs I and II were prepared, showing the per cent change in VPDT values at the different testing times. The per cent change is also shown in Tables I and II. The mean of all the mean VPDT values was taken for each testing time for each drug, and, the highest value being designated 100%, the others were calculated from it. This procedure eliminated the problem of different control values for each subject and allowed a comparison of the effects of the drugs on the VPDT with time. A downsloping left to right curve shows a decrease in VPDT.

Comparing the curves in graphs I and II, the only curves which appear to be consistent are those for phenobarbital. Both show a progressive decrease in VPDT with time. However, this trend has been shown to be insignificant. (phenobarbital 30 mg.: $0.5 < p < 0.6$ and phenobarbital 60 mg.: $0.2 < p < 0.3$).

It is interesting that the curve for d-amphetamine 20 mg. in graph II shows a rapid decrease in VPDT from times $C_0$ to $E_1$ (95-87%), a period of only twenty minutes. It would seem unlikely that significant brain levels of this drug could be reached in only twenty minutes following oral administration; however, no information regarding this point could be found in the literature.

It is also interesting that the curves for phenobarbital resemble that for d-amphetamine 20 mg.

The curves for the placebo are markedly different in graphs I and II. Graph I shows improvement with time, resembling a typical learning curve. However, graph II shows an increase in VPDT with time. The fact that some of the same people were subjects in both parts of this experiment might account for the lack of improvement in part II; that is, they had already reached their peak performance. However, only three subjects were repeats (see asterisks in Tables I and II). Subject 6 is the only one who can be

shown to fit the pattern of improvement in part I and not in part II.

It has therefore been shown that neither placebo (practice) nor d-amphetamine or phenobarbital in the doses tested exerted a significant effect on VPDT as measured in the present experiment. What, then, can be said about the value of the present technique in measuring visual perceptual discrimination threshold? It has not been able to demonstrate a significant difference in a group of individuals' ability to perceive a briefly exposed set of three digits before and after practice and before and after oral administration of d-amphetamine and phenobarbital in the doses used. Clearly, this failure cannot be blamed without qualification on the technique used since multiple factors are involved. Perhaps with more practice a significant improvement could be shown to occur. Also, prolonged testing several more hours after administration of the drugs might show a significant change. More experience with this technique is needed before its value in measuring the nervous system's response to the challenge of a briefly presented visual stimulus can be established.

LITERATURE REVIEW

A brief review of the recent literature discloses little doubt that amphetamine enhances performance of various activities, reduces reaction times to various stimuli, and in general improves accuracy and speed of responses.[2-9] The point or points at which the drug works are open to question. It seems to me that, in general, it can affect the input sensory end, the output or motor end, the integration of the two, or any combination of them. If this is so, then experiments designed to separate these functions and measure the effects of amphetamine upon them may help in pin-pointing the loci of action of this drug.

In an extensive report, Weiss[11] showed that "...amphetamine can produce a significant enhancement of athletic performance, even in events in which, like putting the shot, one cannot see where endurance or fatigue

would play a major role." He concludes that "Amphetamines, then seem to hasten conditioning, to restore in part the degraded rate at which a new discrimination is learned by sleepy subjects, and to increase the rate at which subjects acquire proficiency in a motor skill."

Evans and Jewett[4] showed that reaction times to various stimuli are significantly reduced by amphetamine. This effect is often associated with appreciable improvement in proficiency and accuracy.[7]

Uyeda and Fuster's study[10] measuring the effect of amphetamine on tachistoscopic performance in monkeys, was similar to this experiment except that they measured reaction time and accuracy of response. They were able to show a slight improvement of accuracy, number of correct responses on a series of trials, following administration of the drug, 1.5 mg. I.M., and a significantly shorter reaction time.

All of these results and conclusions seem to point to an enhancement of the motor or output side of the acts. In the tachistoscopic experiment of Uyeda and Fuster, they were able to show improvement of mean accuracy but no actual reduction of threshold.

What about an enhancement of the mechanism which turns sensory input into a meaningful output - a higher function? Smith, et al[8] concluded that "There is much evidence to indicate that amphetamine can improve performance on psychomotor and relatively low level intellectual tests when the dosage (amphetamine sulfate 14 mg./70 kg. body weight) and timing of the present study are employed. Evidence concerning the effect of amphetamine on performance of relatively high level intellectual tests is mostly negative." Whether this is a measure of integrative enhancement in the same sense as that in the simpler task of identifying a stimulus and immediately reacting to it is certainly debatable.

In a different experiment Fuster and Uyeda[6] described the effects

of electrically stimulating several regions of the brain on the responses of monkeys to briefly presented visual cues. They demonstrated that mild stimulation of the mesencephalic reticular formation and central grey matter increased the efficiency of the performance as manifested by an improvement in accuracy and a reduction of reaction time. They attributed these results to a descent of tachistoscopic recognition threshold produced by tegmental influences on the visual system and a concomitant facilitation of integrative processes leading to the motor response. It would be difficult to say definitely that both the recognition threshold decreased and integrative processes were facilitated, but it is possible that one, the other, or both did occur. These same investigators[5,10] have shown that stimulation of the reticular formation results in the same sort of effects produced by amphetamine. This, then, may be one locus of action of amphetamine.

The third consideration is that of the sensory or input mechanism. In six cases studied by Corssen and Domino[3], three of which received 0.05 mg./kg. and the other three of which received 0.1 mg./kg. of d-amphetamine sulfate I.V., none showed any particular change in visually evoked responses as measured by EEG. In addition to this Bradley and Key[2] found the threshold for arousal produced by auditory stimulation decreased as the amount of amphetamine injected increased, while that for click responses from the auditory cortex showed little change. This information could be interpreted as meaning that the threshold for stimuli resulting in impulses in the auditory cortex was not changed because amphetamine does not work on this input side. However, the fact that the arousal threshold produced by auditory stimulation did decrease may mean that amphetamine works on the integrative or output side.

This brief review helps to emphasize the fact that although much information has been gathered regarding some of the effects of amphetamine

on the nervous system, much is still not known about its mode and locus of action.

SUMMARY

In this experiment d-amphetamine in doses of 5, 10, 15, and 20 mg. orally and phenobarbital in doses of 30 and 60 mg. orally were given to subjects who were then required to correctly identify a briefly presented three digit visual stimulus. Results failed to show any significant effect of any of the drugs or of practice on the visual perceptual discrimination threshold. Further work with this technique in humans is needed before its value as a psychopharmacological tool can be established. A brief literature review on the psychopharmacologic effects of amphetamine is presented.

BIBLIOGRAPHY

1. Bancroft, Huldah: Introduction to Biostatistics. Hoeber-Harper, p. 176, 1957

2. Bradley, P.B. and Key, B.J.: The Effect of Drugs on Arousal Responses Produced by Electrical Stimulation of the Reticular Formation of the Brain. Electroenceph. Clin. Neurophysiol. 10:97-110, 1958

3. Corssen, S. and Domino, E.F.: Visually Evoked Responses in Man: A Method for Measuring Visual Effects of Preanesthetic Medication. Anesthesiol. 24:330-341, 1964

4. Evans, W. and Jewett, A.: The Effect of Some Centrally Acting Drugs on Disjunctive Reaction Time. Psychopharmacologia 3:124-127, 1962

5. Fuster, J.M.: Effects of Stimulation of Brainstem on Tachistoscopic Perception. Science. 127, 150, 1958

6. Fuster, J. M. and Uyeda, A.A.: Facilitation of Tachistoscopic Performance by Stimulation of Mid-brain Tegmental Points in the Monkey. Exper. Neuro. 6:384-406, 1962

7. McKenzie, E. and Elliot, L.L.: Effects of Secobarbital and d-Amphetamine on Performance During a Simulated Air Mission. Aerospace Med. 36:774-779, 1965

8. Smith, G.M. et al.: Effects of Amphetamine and Secobarbital on Coding and Mathematical Performance. Pharmacol. Exper. Therapeut. 141:100, 1963

9. Turner, P.: The Changes in Critical Flicker Fusion Frequency Induced by Some Physiologic Procedures and by Drugs, Together with Observations of the Reliability of Olfactory Testing. M.D. Thesis at the University of London, 1961

10. Uyeda, A.A. and Fuster, J.M.: The Effects of Amphetamine on Tachistoscopic Performance in the Monkey. Psychopharmacologia 3:463-467, 1962

11. Weiss, B. and Laties, V.G.: Enhancement of Human Performance by Caffeine and the Amphetamines. Pharmacol. Rev. 14:1-36, 1962