EDGEWOOD ARSENAL
TECHNICAL REPORT

EATR 4718

EFFECTS OF DRUGS ON HUMAN OPERANT PERFORMANCE

by

Stanley H. Holgate, CPT, MSC

Biomedical Laboratory

February 1973

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

AD-757 159

EFFECTS OF DRUGS ON HUMAN OPERANT PERFORMANCE

Stanley H. Holgate

Edgewood Arsenal
Edgewood Arsenal, Maryland

February 1973

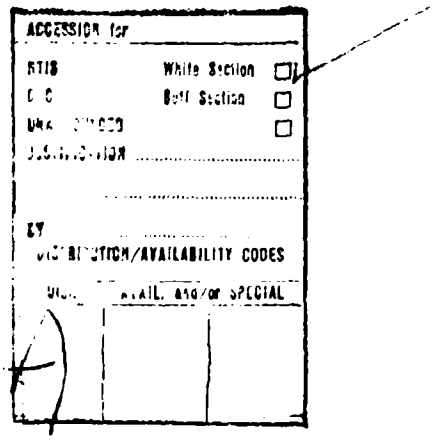
Disclaimer

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

The use of trade names in this report does not constitute an official endorsement or approval of such commercial hardware or software. This report may not be cited for purposes of advertisement.

Disposition

Destroy this report when no longer needed. Do not return it to the originator.



UNCLASSIFIED

Security Classification

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)	2a. REPORT SECURITY CLASSIFICATION
Cdr, Edgewood Arsenal Attn: SMUEA-BL-RCI Aberdeen Proving Ground, Maryland 21010	UNCLASSIFIED 2b. GROUP NA

3. REPORT TITLE

EFFECTS OF DRUGS ON HUMAN OPERANT PERFORMANCE

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)

This work was started in May 1971 and completed in July 1971.

5. AUTHOR(S) (First name, middle initial, last name)

Stanley H. Holgate, CPT, MSC

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
February 1973	14 15	11

8a. CONTRACT OR GRANT NO.	9a. ORIGINATOR'S REPORT NUMBER(S)
b. PROJECT NO 1B061102B71A	FATR 4718
c.	9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
d.	

10. DISTRIBUTION STATEMENT

Approved for public release; distribution unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY
Life sciences basic research in support of material chemical	

13. ABSTRACT

The present experiment is one in a series directed toward the development of an operant task which is sensitive to the effects of low doses of various drugs and agents. Four human subjects were given limited training on an operant task that required both attention and moderately fast response rates. Intravenous injections of 1 ml saline, 5 mg diazepam, 250 mg sodium amobarbital, and 10 mg methylphenidate were given in successive sessions in random order. Numbers of responses and errors were subjected to variance analyses. Overall, saline had no significant effect on either response or error rates. Compared to saline, diazepam produced a slight increase in error rates, but it did not alter response rates. Amobarbital depressed response rates and increased error rates; whereas methylphenidate increased both response rates and error rates.

14. KEYWORDS

Operant conditioning (human)
Drug effects
Diazepam
Sodium amobarbital
Methylphenidate

DD FORM 1 NOV 68 1473 REPLACES DD FORM 1473, 1 JAN 64, WHICH IS OBSOLETE FOR ARMY USE.

UNCLASSIFIED

Security Classification

EDGEWOOD ARSENAL TECHNICAL REPORT

EATR 4718

EFFECTS OF DRUGS ON HUMAN OPERANT PERFORMANCE

by

Stanley H. Holgate, CPT, MSC

Medical Research Division
Biomedical Laboratory

February 1973

Project 1B061102B71A

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

FOREWORD

The work described in this report was authorized under Project 1B061102B71A, Life Sciences Basic Research in Support of Material – Chemical. This work was started in May 1971 and completed in July 1971.

The volunteers in these tests are enlisted US Army personnel. These tests are governed by the principles, policies, and rules for medical volunteers as established in AR 70-25 and the Declaration of Helsinki.

Acknowledgments

Appreciation is extended to the following people for their assistance and cooperation in the completion of this report: Dr. Frederick R. Sidell for his advice and assistance in selecting and administering the dose levels used; the nursing staff on the ward for their assistance in the management of the volunteer subjects; Mrs. Norma Vaught for typing the manuscript, and Mrs. Marion P. Royston for editing the manuscript.

DIGEST

The present experiment is one in a series directed toward the development of an operant task which is sensitive to the effects of low doses of various drugs and agents. Four human subjects were given limited training on an operant task that required both attention and moderately fast response rates. Intravenous injections of 1 ml saline, 5 mg diazepam, 250 mg sodium amobarbital, and 10 mg methylphenidate were given in successive sessions in random order. Numbers of responses and errors were subjected to variance analyses. Overall, saline had no significant effect on either response or error rates. Compared to saline, diazepam produced a slight increase in error rates, but it did not alter response rates; amobarbital depressed response rates and increased error rates; whereas methylphenidate increased both response rates and error rates.

CONTENTS

EFFECTS OF DRUGS ON HUMAN OPERANT PERFORMANCE

I. INTRODUCTION.

In most human drug studies of performance, different tests are used to measure eye-hand coordination, attention, and cognitive ability, etc. These tests, normally given once or twice each hour, require only a few minutes of concentration by the subject. This does not allow the experimenter to observe the rate of the change in performance or the time at which a man might be considered to be incapacitated. Operant conditioning techniques may provide a means of studying several different aspects of performance with a minimum of interruptions in observation of drug effects over time. In the present study, an operant task was used to study the effects of a stimulant (methylphenidate), a tranquilizer (diazepam), and a sedative (sodium amobarbital) on human performance. The object of the experiment was to determine the functional value of the operant task in studying drug effects on human performance.

Ad hoc hypotheses regarding the effects of the drugs used in this experiment are based on the properties attributed to the drugs. Diazepam, a muscle relaxant, may improve or impair performance, depending on the individual subject. The sedating influence of sodium amobarbital should depress response rate and hence result in the subjects not being able to make the number of responses that are required on each trial. Methylphenidate as a stimulant should result in increased response rates and in better attention, which will result in an improvement in performance.

II. METHODS.

The four US Army enlisted men who volunteered to serve in the experiment were given thorough physical and psychological examinations. Except for their weight (mean = 77.6 kg, range 65.9 to 90.0 kg), there was a close similarity between the subjects. For example, their ages ranged from 21 to 24 years; GT scores ranged from 123 to 147, mean = 139; and years of education ranged from 14 to 16 years, mean = 15 years. The subjects reported to the ward for the duration of the experiment.

The subjects worked at the operant task 30 minutes a day for 6 days. Days one and two served to give them practice on the task and to establish baseline performances. During the next 4 days, each subject received intravenous injections of 1 ml saline; 10 mg methylphenidate hydrochloride U.S.P. (Ritalin^{R}, Ciba Company); 5 mg diazepam, N.F. (Valium^{R}, Roche Laboratories); and 250 mg sodium amobarbital, U.S.P. (Amytal^{R}, Eli Lilly and Company). Because of the weight difference between subjects, the dose for each subject (in mg/kg) is presented in the table. The first 5 minutes of each session served as a "warm-up" period and allowed the experimenter to determine if the drug given the previous day had any residual effects on performance. Drugs were administered using a double-blind technique.

Table. Dose Levels[a] and Order of Drugs[b] Given Each Subject[c]

The dose levels in this table represent the mg/kg dose the subject actually received from the constant size dose of 1 ml saline, 5 mg diazepam, 250 mg sodium amobarbital, and 10 mg methylphenidate.

Subject	Weight	Session			
		3	4	5	6
	kg	dose			
S2	76.8	0.130 (D4)	1.000 (D1)	3.255 (D3)	0.065 (D2)
S3	77.7	3.217 (D3)	0.129 (D4)	1.000 (D1)	0.064 (D2)
S4	90.0	0.055 (D2)	0.055 (D2)	0.111 (D4)	2.778 (D3)
S5	65.9	1.000 (D1)	3.794 (D3)	0.076 (D2)	0.152 (D4)

[a] All saline doses are 1.0 ml. All other dose levels are in mg/kg.

[b] D1 = saline; D2 = diazepam; D3 = sodium amobarbital; D4 = methylphenidate.

[c] S1 was given saline each day; therefore, his data were excluded from the analysis. S4 was inadvertently given diazepam on the day he was scheduled to receive saline.

A brief description of the task was given in the initial briefing; and each day before beginning the task, the volunteers read a set of instructions covering the test procedures. The subject sat alone in a room facing a stimulus panel containing three lights (red, yellow, and green), two levers (a green one on the right and a yellow one on the left), and two counters ("points won" and "points lost"). When the green light was lit alone, the subject was required to press and release the green lever. On the 31st release, a yellow light came on in combination with the green light. The subject had to hold the next press of the green lever and press and release the yellow lever four times to turn off the yellow light, thus completing one trial. A "point won" was registered for each correct trial. If the subject failed to complete the trial in 15 seconds, he lost one and a half points. If he made an error such as pressing and releasing the green lever too many times or responding to the yellow lever without holding down the green key, he lost one-half point. The red light came on briefly each time an error occurred.

The reward used in this experiment was time off from normal duties. Time off was calculated by subtracting points lost from points won. The remaining points were converted to minutes on a one to one basis, with 480 points equalling one day. The maximal reward was 3 days off.

III. RESULTS.

Each 30-minute session was divided into six 5-minute periods for analysis purposes. The response and error data were analyzed separately using a repeated measures analysis of variance design.[1] The analysis of variance for numbers of responses revealed that the following were statistically significant: (1) subjects responded at different average rates, (2) drugs affected response rates differently, (3) response rates differed within sessions, and (4) there was an interaction between drugs and time periods.

The first observation reflected the presence of individual differences in the experiment. In addition, the subjects' rates were not equally and (in some cases) similarly affected by the drugs. Paired *t* tests were used to compare the overall rates for all sessions between pairs of subjects; significant differences were found for all pairs. Significantly lower response rates in decreasing order were found for subjects S2, S5, S3, and S4.

A test of simple main effects was performed because the significant interaction between drugs and time periods indicated that the drugs affected performance differently within sessions. For example, amobarbital produced a rapid decrease in the number of responses, whereas the increase in the number of responses after methylphenidate occurred later in the session (figure 1). The results of the variance analysis of simple main effects revealed no differences in performance for the warm-up period. This finding was interpreted to mean that the subjects demonstrated no observable residual drug effects between sessions. Unfortunately, the sessions were not long enough to allow the subjects' performance (after amobarbital or methylphenidate) to return to baseline.

The variance analysis of the numbers of errors revealed a significant block effect representing individual differences in drug sensitivity, indicated by the range of standard deviations in figure 2. Tukey's HSD test was used to compare the mean numbers of errors between pairs of drugs. Subjects made significantly more errors after the injection of diazepam than after the injection of saline. A greater number of errors occurred following sodium amobarbital and methylphenidate than following either saline or diazepam. On the other hand, sodium amobarbital and methylphenidate did not differ significantly.

Absent in the variance analysis was a significant time-period effect, although the data in figure 2 suggest that such an effect was present. The most plausible explanation for the lack of statistical confirmation of the time-period effect is the inter-subject variance. Onset of the depressant action of amobarbital was very rapid. The response rate dropped significantly, and the error rate increased threefold during the first 5 minutes. The response rate remained depressed for the entire session, but the error rate returned almost to the pre-drug level. The error rate associated with methylphenidate increased for the first 15 minutes after the injection and returned almost to the pre-drug level for the last 10 minutes. The error rate associated with diazepam increased transiently during the second 5-minute period and was generally greater than that for saline.

[1] Kirk, R. E. Experimental Design: Procedures for the Behavioral Sciences. Belmont, California: Brooks/Cole (1968).

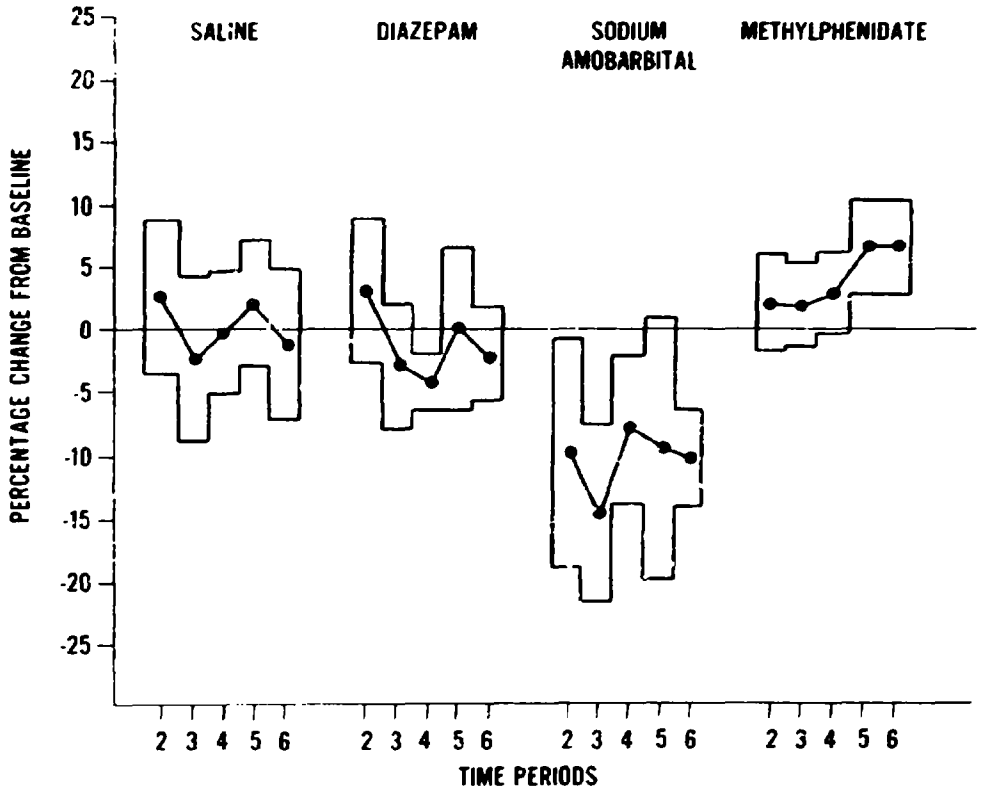


Figure 1. Response Rate Viewed as the Mean Percentage Change from Baseline

The first 5-minute period, the warm-up pre-drug period, is represented by the zero value in the figure. Percentage change from baseline for each subject was calculated using his warm-up period. The data points represent the mean percentages for all four subjects and are encapsulated by the standard deviations which illustrate inter-subject variance. Sodium amobarbital was the only drug to effect a significant change (decrease) in response rate compared to the warm-up rate. It produced a significantly lower rate than did methylphenidate during all post-drug periods and saline and diazepam during time periods two, three, and five. Methylphenidate was associated with a significantly faster post-drug rate than the other three drugs during the last three time periods.

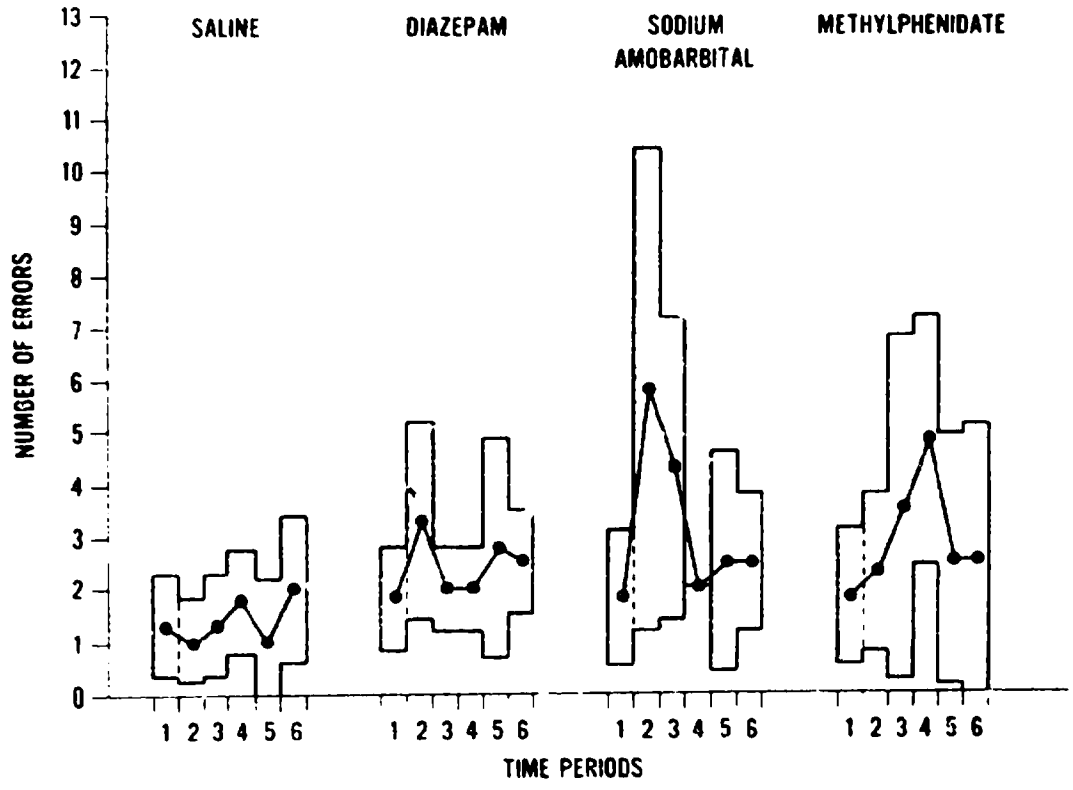


Figure 2. Error Rate Viewed as the Mean Number of Errors Per 5-Minute Periods

The data are means for all four subjects. The data points are encapsulated by the standard deviations which reflect individual differences in sensitivity to drug effect. Period one was the pre-drug warm-up period.

Subjective effects of the drugs were obtained using the symptoms check lists and written statements, both completed by the subjects. The results of the check lists and the written statements generally agreed with the performance data.

IV. DISCUSSION.

Overall, the subjects exhibited small quantitative changes in performance, but these changes differentiated among the drugs statistically. Thus, the operant task was sufficiently sensitive to detect low-dose drug effects. Viewed as group data, the results support some of the *ad hoc* hypotheses of the introduction and fail to support others.

Diazepam has been found to produce both increments and decrements in discriminative conditioned avoidance responding;[2] however, on a continuous, non-signaled avoidance task, rats performed better at low doses than at high doses, as compared to baseline.[3] Cats increased their responding on a fixed-interval schedule of food reinforcement after geometrically increasing dose levels of diazepam.[4] Human subjects given 10 mg intravenously showed transitory decrements in solving arithmetic problems[5] and also increased tolerance to CS, o-chlorobenzilidine malononitrile (CS), a mucous membrane irritant.[6] In the present study, diazepam was given in amounts too small to affect response rate, although it did slightly increase the subjects' tendency to make errors.

Sodium amobarbital shows few manifestations of acting on peripheral mechanisms when given in sedative or hypnotic doses,[7] but it does seem to act as a pharmacological block to consolidation of information input.[8] It has been given in large enough doses in human studies to produce decrements on an arithmetic task.[5,9] The performance decrements on the arithmetic task were found to be functionally related to personality characteristics. In another study, amobarbital inhibited both spontaneous recovery and reconditioning of the galvanic skin response (GSR) conditioned to a light flash followed by electric shock.[10] These findings suggest that the depressed response rate and increased error rate in the present experiment were manifestations of depressed central mechanisms.

---

[2] Jarvik, M. E. Drugs Used in the Treatment of Psychiatric Disorders. In: The Pharmacological Basis of Therapeutics. L. S. Goodman and A. Gilman (Eds). pp 151-203. The Macmillan Company, New York, New York, 1970.

[3] Heise, G. A., and Boff, E. Continuous Avoidance as a Baseline for Measuring Behavioral Effects of Drugs. Psychopharmacologia 3, 264-282 (1962).

[4] Richelle, M. Combined Action of Diazepam and d-Amphetamine on Fixed-Interval Performance in Cats. Journal of Experimental Analysis of Behavior 12, 989-998 (1969).

[5] Hopper, J. A., and McColloch, M. A. TATR 4553. Personality and Reactivity to Tranquilizers. September 1971. UNCLASSIFIED Report.

[6] Hopper, J. A., and McColloch, M. A. TATR 4581. The Effect of Diazepam on Tolerance of a Mucous Membrane Irritant. November 1971. UNCLASSIFIED Report.

[7] [illegible] S. E. Hypnotics and Sedatives: I. The Barbiturates. In: The Pharmacological Basis of Therapeutics. L. S. Goodman [illegible]. The Macmillan Company, New York, New York. 1970.

[8] [illegible] and Weinberger, L. E. Dysnomia and Impairment of Verbal Memory Following Intracarotid Injection of Sodium Amytal. Brain Research 31, 159-168 (1971).

[9] Hopper, J. A., and McColloch, M. A. TATR 4564. Personality and Reactivity to Stimulants and Depressants. November 1971. UNCLASSIFIED Report.

[10] Schneider, R. A., and Costiloe, J. P. The Inhibiting and Facilitating Effects of Amytal, Chlorpromazine, and Phenidylate on the Conditioned Galvanic Skin Response. American Journal of Medical Science 233, 418-422 (1957).

Methylphenidate, considered to be a moderate stimulant for motor and mental activities, may improve attention span.[11] In the GSR conditioning study mentioned above, methylphenidate failed to affect spontaneous recovery, but it did facilitate reconditioning of the response following extinction.[10] It has also been demonstrated to increase continuous avoidance rates in rats[3] and to produce differential increases in human arithmetic performance as a function of personality characteristics.[9] In the present study, response speed was competitive with attention. Methylphenidate increased mean response rate slightly in the last few minutes of the session. This increase was preceded by a transient increase in the number of errors, suggesting a possible lag in the stimulant effects on motor activities in contrast to mental activities.

Further development in the operant task will be directed toward reducing the inter-subject variability. This may be done by imposing more stringent test criteria to reduce the tolerance for error. At the same time, however, the test has to allow enough tolerance for error to reflect dose-response effects. Testing sessions will be lengthened, amount of training will be increased, and several dose levels will be used.

[11] Esplin, D. W., and Esplin, B. Z. Central Nervous System Stimulants. In: The Pharmacological Basis of Therapeutics. L. S. Goodman and A. Gilman (Eds.), pp 348-357. The Macmillan Company, New York, New York. 1970

LITERATURE CITED

1. Kirk, R. E. Experimental Design: Procedures for the Behavioral Sciences. Belmont, California: Brooks/Cole (1968).

2. Jarvik, M. E. Drugs Used in the Treatment of Psychiatric Disorders. In: The Pharmacological Basis of Therapeutics. L. S. Goodman, and A. Gilman (Eds.). pp 151-203. The Macmillan Company, New York, New York. 1970.

3. Heise, G. A., and Boff, E. Continuous Avoidance as a Baseline for Measuring Behavioral Effects of Drugs. Psychopharmacologia 3, 264-282 (1962).

4. Richelle, M. Combined Action of Diazepam and d-Amphetamine on Fixed-Interval Performance in Cats. Journal of Experimental Analysis of Behavior 12, 989-998 (1969).

5. Klapper, J. A., and McColloch, M. A. EATR 4553. Personality and Reactivity to Tranquilizers. September 1971. UNCLASSIFIED Report.

6. Klapper, J. A., and McColloch, M. A. EATR 4581. The Effect of Diazepam on Tolerance of a Mucous Membrane Irritant. November 1971. UNCLASSIFIED Report.

7. Sharpless, S. K. Hypnotics and Sedatives: I. The Barbiturates. In: The Pharmacological Basis of Therapeutics. L. S. Goodman and A. Gilman (Eds.). pp 98-120. The Macmillan Company, New York, New York. 1970.

8. Fedio, P., and Weinberg, L. K. Dysnomia and Impairment of Verbal Memory Following Intracarotid Injection of Sodium Amytal. Brain Research 31, 159-168 (1971).

9. Klapper, J. A., and McColloch, M. A. EATR 4564. Personality and Reactivity to Stimulants and Depressants. November 1971. UNCLASSIFIED Report.

10. Schneider, R. A., and Costiloe, J. P. The Inhibiting and Facilitating Effects of Amytal, Chlorpromazine, and Phenidylate an the Conditioned Galvanic Skin Response. American Journal of Medical Science 233, 418-422 (1957).

11. Esplin, D. W., and Esplin, B. Z. Central Nervous System Stimulants. In: The Pharmacological Basis of Therapeutics. L. S. Goodman and A. Gilman (Eds.). pp 348-357. The Macmillan Company, New York, New York. 1970.