EXHIBIT J

EDGEWOOD ARSENAL TECHNICAL REPORT

EATR 4678

RELATIONSHIPS AMONG DOSE, TIME, AND VARIOUS MEASURES OF LABORATORY AND MILITARY PERFORMANCE IN VOLUNTEERS RECEIVING A CENTRALLY ACTIVE CHOLINERGIC BLOCKING AGENT (EA 3580) (U)

by

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(U) FOREWORD

The work described in this report was authorized under Task 1W062116AD1901, Techniques of Evaluating Effects of Chemicals, Performance Evaluation of Chemically Exposed Personnel. This work was started in July 1967 and completed in June 1970.

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.

Acknowledgments

The authors are indebted to the members of the Clinical Research Branch and the Psychology Section of the Experimental Medicine Branch for providing support and conducting the field study described in this report.

(C) DIGEST

(C) Forty normal US Army enlisted men who volunteered for this study were given intramuscular doses of [(1-methyl-4-piperidyl)α-cyclobutylmandelate] (EA 3580) in a range from zero (placebo) to a high dose (0.375 mg/man). Serial laboratory and military performance tests were administered and the percentage decrement for each of 13 performance measures relative to dose and elapsed time was measured. Intercorrelations among the various performance measures and the doses were also computed for dose groups separately and combined and for time periods separately and combined. The degree of correlation between laboratory and military measures was found to be related to the range of dosage and the elapsed time of drug effect.

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RELATIONSHIPS AMONG DOSE, TIME, AND VARIOUS MEASURES OF LABORATORY AND MILITARY PERFORMANCE IN VOLUNTEERS RECEIVING A CENTRALLY ACTIVE CHOLINERGIC BLOCKING AGENT (EA 3580) (U)

I. (U) INTRODUCTION.

Previous studies with centrally active glycolate compounds (i.e., those resembling atropine and the belladonna alkaloids in both chemical structure and pharmacological properties) have shown them to produce effects upon human performance which are related to both the dose and the elapsed time following administration of the drug. In most of these studies, however, performance has been measured solely by laboratory instruments requiring the subject to solve arithmetic problems, to move pegs from hole to hole, to estimate time intervals, or to perform other somewhat artificial tasks. There remained some doubt as to whether such measures could be relied upon to predict the ability of an individual to carry out more "natural" or "meaningful" tasks related to his normal duties. Earlier investigations of this question reported the correlation between laboratory and military performance scores to be either high[1,*] or quite low,** depending in part, it appeared, on the range of drug effects present. The present study was undertaken to explore again the correlation between military and laboratory performance in a population more heterogeneous with respect to the degree of drug effect present.

II. (C) METHODS.

(U) The subjects were forty-eight young US Army enlisted men, all in excellent health, who freely volunteered to participate in the experiment, following a briefing on its nature and purpose. Each man underwent a comprehensive series of medical, psychological, and clinical laboratory examinations before he was accepted into the program. Throughout the period of study they were housed in separate, specially designed rooms in which safety and comfort were primary considerations. Nursing care was continuous and vigilant. The performance tests were administered by medical officers, psychology technicians, and registered nurses, depending on the complexity of skills required. Motivation was maintained at a high level by encouragement and approval, and no material inducements were required. Observers generally agreed that the men made a maximum effort even when their capability was reduced to very low levels by the effects of the drug.

(C) Subjects were tested in groups of four. In each of eight such groups, two subjects were given 250 μg of [(1-methyl-4-piperidyl)α-cyclobutylmandelate] (EA 3580) by intramuscular

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[1] Ketchum, J. S., Tharp, B. R., Crowell, E. B., Jr., Sawhill, D. L., and Vancil, M. E. EATR 4140. The Human Assessment of BZ Disseminated Under Field Conditions (U). November 1967. CONFIDENTIAL Report.

* Kysor, K. P. The Effect of BZ on the Relationship Between the Number Facility Test and Military Field Performance Ratings. In Preparation.

** Allen, R. P. Preliminary Correlation of Field Performance with Laboratory Tests for Medical Volunteers. Memorandum for Record. 24 May 1968. SMUEA-RME.

injection, and two subjects were given saline placebo. In the last four groups, no placebo was used; and two subjects were given 125 μg (a low dose), whereas the other two were given 375 μg (a high dose). The assignment of doses to subjects within each group was randomized, with dose assignment being known only to the senior physician.

(U) Table I summarizes the dose design. Only 8 of the 16 placebo subjects are included because at the time the results were analyzed it was decided to reduce the number of placebo subjects so that the number of cases at each dose would approximate more closely a Gaussian

Table I (U). Dose Design

Dose (mg/man)	Number of subjects
0 (saline)	8
.125	8
.250	16
.375	8

distribution. This notion is predicated on the military concept that in an actual attack with an incapacitating agent, the doses would be distributed among the affected population in a roughly Gaussian manner. Figure 1 shows that if the cases are represented as a cumulative frequency with respect to increasing dose, using a probit transformation on the y-axis, they fall passably close to the theoretical straight line required of a Gaussian distribution. Furthermore, each of the dose subgroups, with the exception of the no-dose group, shows its own distribution of dose values to be approximately normal.

(U) At prescribed intervals, a variety of indoor laboratory and field military performance measures were administered to the subjects. The Laboratory measures included:

1. The Number Facility (NF)[2] Test – requires the subject to complete as many simple addition problems as possible within a 3-minute period. Only correct solutions are counted.

2. The Track Tracer (TT)[2] – primarily a measure of hand steadiness and eye-hand coordination. Three scores are obtained electronically: speed of tracking, steadiness (as reflected in number of contacts made with the sides of the track), and accuracy (as reflected in the total time spent in contact with the sides).

[2] Baker, W. J., Elkin, E. H., VanCott, H. P., and Fleishman, E. A. The Effects of Drugs on Human Performance: The Development of Analytical Methods and Tests of Basic Human Abilities. Technical Report No. 2. March 1966. UNCLASSIFIED Report. American Institutes for Research. DA18-035-AMC-282(A).

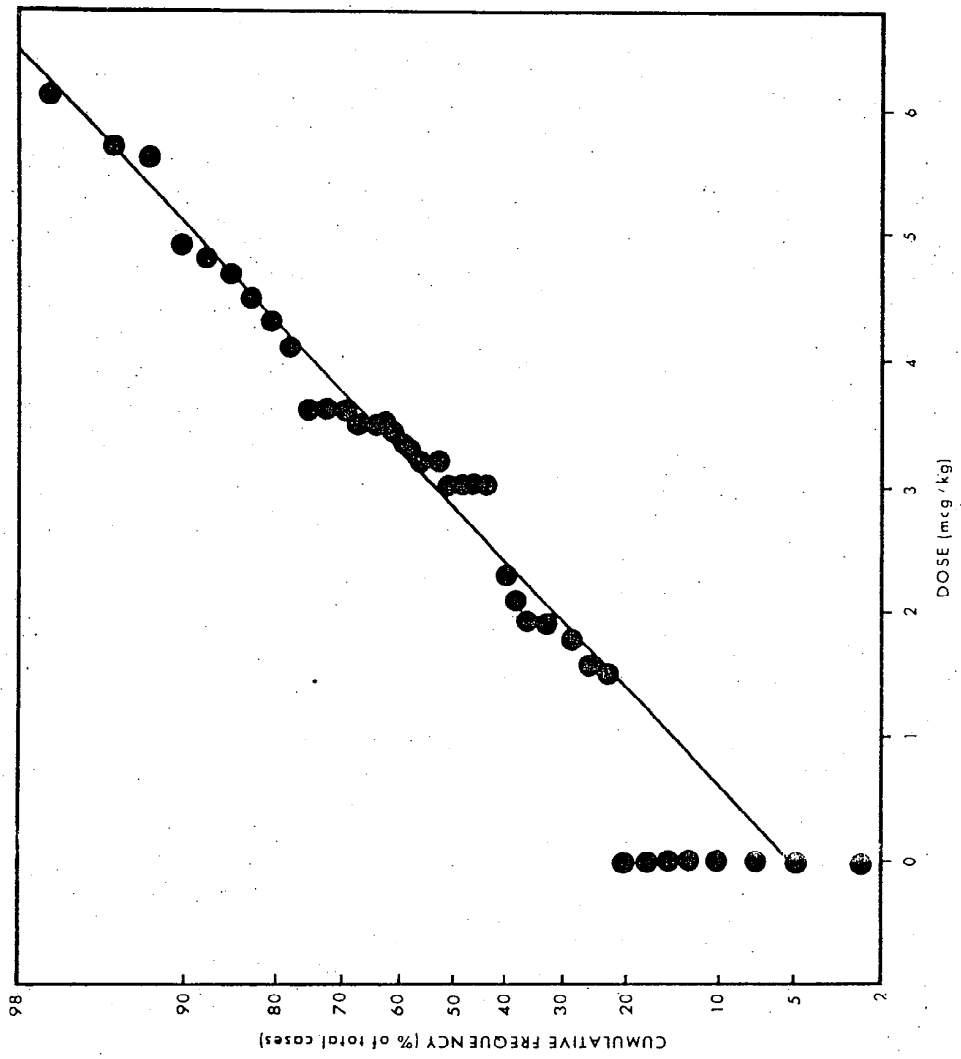

Figure 1 (U). The Distribution of Cases in This Study is Plotted in Order of Dose Using a Probit Transformation of the Cumulative Frequencies

3. The Minnesota Manipulation or Pegboard (PB)[2] Test – hand-speed and dexterity are the prime factors. The score is the number of pegs moved in a 60-second period.

4. The Orthorater[2] – a device for measuring visual acuity using interchangeable visual displays and lenses. The subject is required to discriminate the location of certain patterns within the overall display.

5. The Bend, Twist, and Touch (BTT)[2] – a test of physical proficiency that requires the subject to bend, twist, and touch the wall and floor alternately as many times as he can in 20 seconds.

(U) The military performance tasks,[3] more elaborate than the laboratory measures, consisted of:

1. The Obstacle Course – measures physical proficiency and endurance by requiring subjects to negotiate a series of barriers in a prescribed manner. After 1 week of training, the course takes from 3 to 5 minutes to complete. Score is the rate (feet/second) at which the course is traversed.

2. Rifle Accuracy – using live ammunition and a special cage and tether to restrict the range of the weapon to a safe angle of fire. A total of 40 rounds are fired at a silhouette target 200 yards away. Score is one point for each electronically recorded hit.

3. The Grenade Assault – subject advances between bursts from a machine gun simulator and throws six grenades at a bunker opening from a distance of 50 feet. Score is one point for landing within a prescribed area and a bonus point for throwing through the opening.

4. Masking Speed – measured during each obstacle course run by giving the signal "Gas!" at a predetermined point in a course. Score is the rate (percent of task completed per second) at which masking is accomplished.

5. Terrain Surveillance – measured by having the subject report by telephone all significant events he observes from a foxhole. A scenario enacted by aggressor troops includes vehicular movements, use of weapons, smoke grenades, and other special props. Score is the number of events correctly reported during a 17-minute scenario.

(U) Baseline performance was established for each man in each of the performance tasks. For the laboratory measures, as many as 25 distributed practice trials preceded the drug administration. For the military tasks, the number of practice trials was smaller, but in general, sufficient to provide a reliable baseline.

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[3] Linder, W. K., Smith, R.G., Grover, D. E., Morrissey, P. A., and Allen, R. P. EASP 100-57. Test Manual: Measurement of Incapacitation with Selected Infantry Skills. June 1969. UNCLASSIFIED Report.

(U) The scheduling of measures presented some difficulties because of the time required for each and because of the physical distance between certain test stations, such as the rifle range and the obstacle course. Each group of four was divided into group A and group B, each with two members. The schedules of testing are shown in figure 2. It may be seen that there is some overlap among the times of testing of various tasks and that considerable time separates the A and B groups during the first few hours. For purposes of analysis, however, it was considered expedient to consider all scores within a certain block of time as being essentially comparable, granting that, in fact, appreciable changes in intensity of drug effect may have occurred during this period, differentially affecting the scores in various tasks. After the 2- to 5-hour period, however, these time differences would seem to be of negligible importance.

III. (U) RESULTS AND DISCUSSION.

The results may be considered from several standpoints. First, figure 3 shows the mean effect upon each of 12 performance measures for each of the three dose groups. In each graph, the mean scores of the placebo group are equated with 100% throughout the time series. The mean score for each dose group at each time is then represented as a percentage of the placebo group mean score at that time. The upper margin of the darkened area in each graph represents the serial adjusted means for the low-dose group, and the lower margin represents those for the high-dose group. The middle-dose group means are shown by the heavy black line. It can be seen that all 12 measures are affected to a remarkably similar degree. Some measures are affected earlier and for longer periods, whereas some are relatively resistant, but the similarities are more striking than the differences. Likewise, the times of maximum effect vary somewhat, but are all between 2 and 6 hours.

In a second approach to the analysis, intercorrelations were computed for all the tasks, using individual raw scores rather than averaged or adjusted scores. (The only exception to this is the NF which has always been calculated as a percentage of the individual's baseline, and this convention was not altered in the current study.)

In figure 4, the correlation matrices for pretest, 0- to 2-hour, 2- to 5-hour, 7- to 9-hour, and 30-hour periods are compared. Symbols are substituted for decimal values to enhance visual appreciation of differences. A solid black square represents a coefficient of .88 or higher, an open square represents .71 to .87, a dot represents .50 to .70, and a blank is used for all correlation coefficients below .50. (For an N of 40, a correlation above .50 is significant at the .001 level; therefore, all nonblank squares contain highly significant values.) The matrix has been rank-ordered from left to right and from top to bottom to produce a gradient extending from upper left to lower right. The grand mean for the matrix is shown just to the left of each display.

During the pre-drug period, only one highly significant correlation is present, and that is the expected association between near and far visual acuity. As drug effects develop, however, the

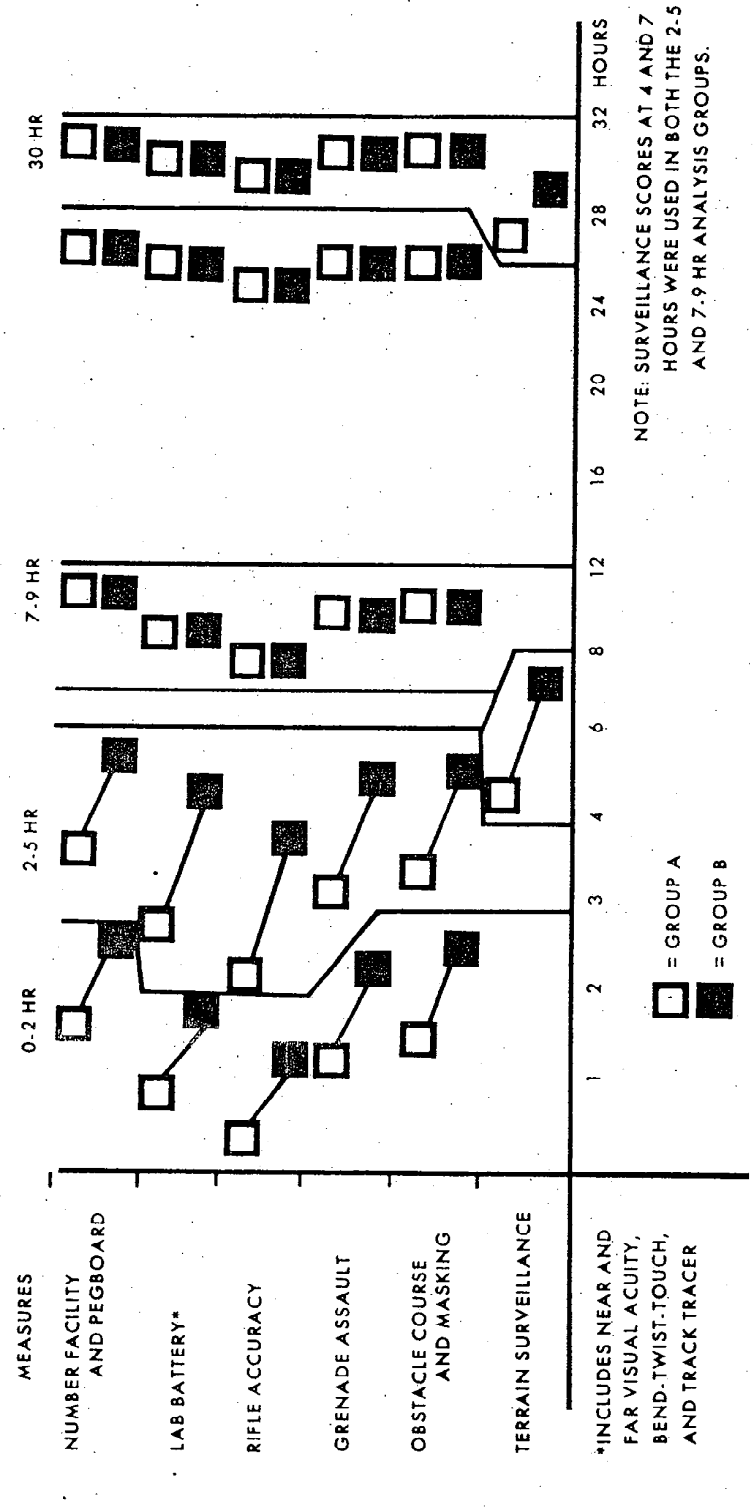

Figure 2 (U). The Schedule of Testing for the Performance Measures

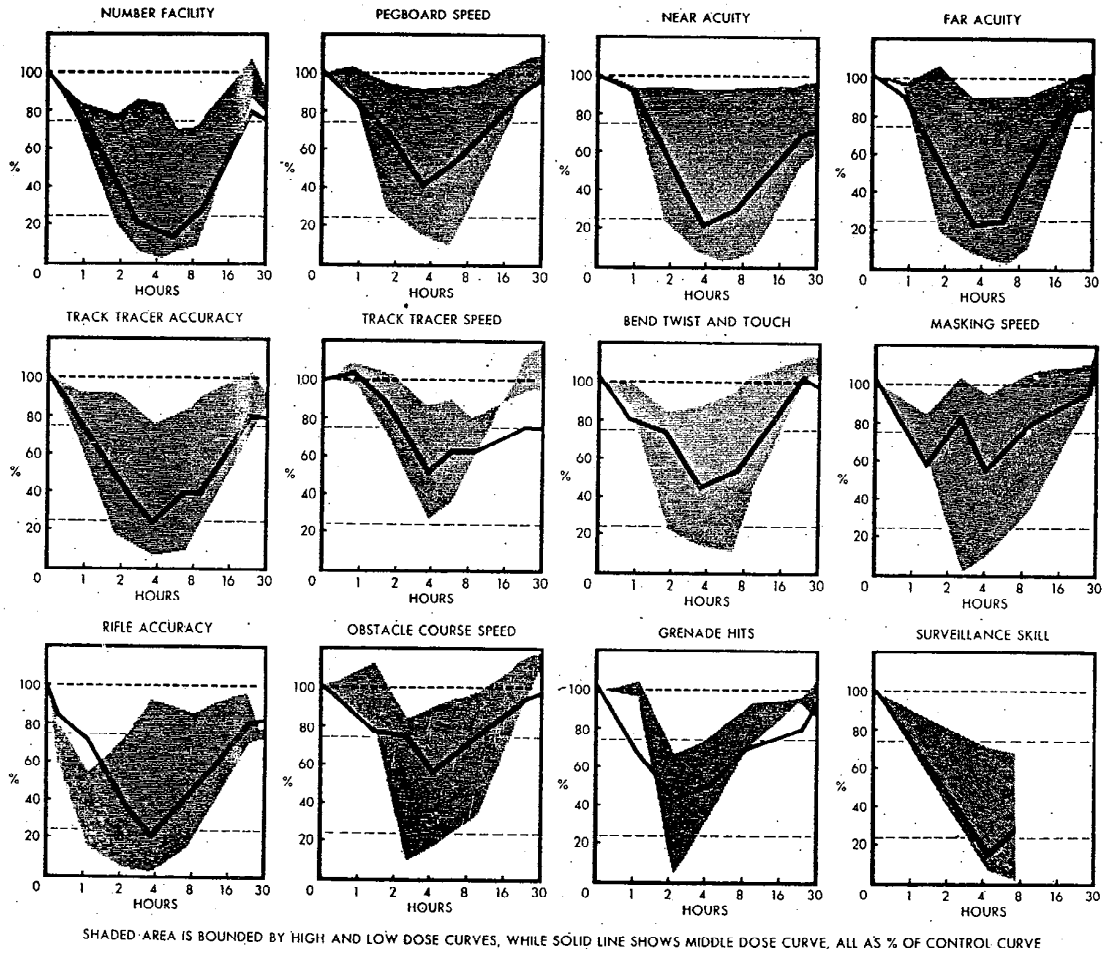

Figure 3 (U). The Effect of the Drug on the Performance Measures as a Function of Dose and Elapsed Time

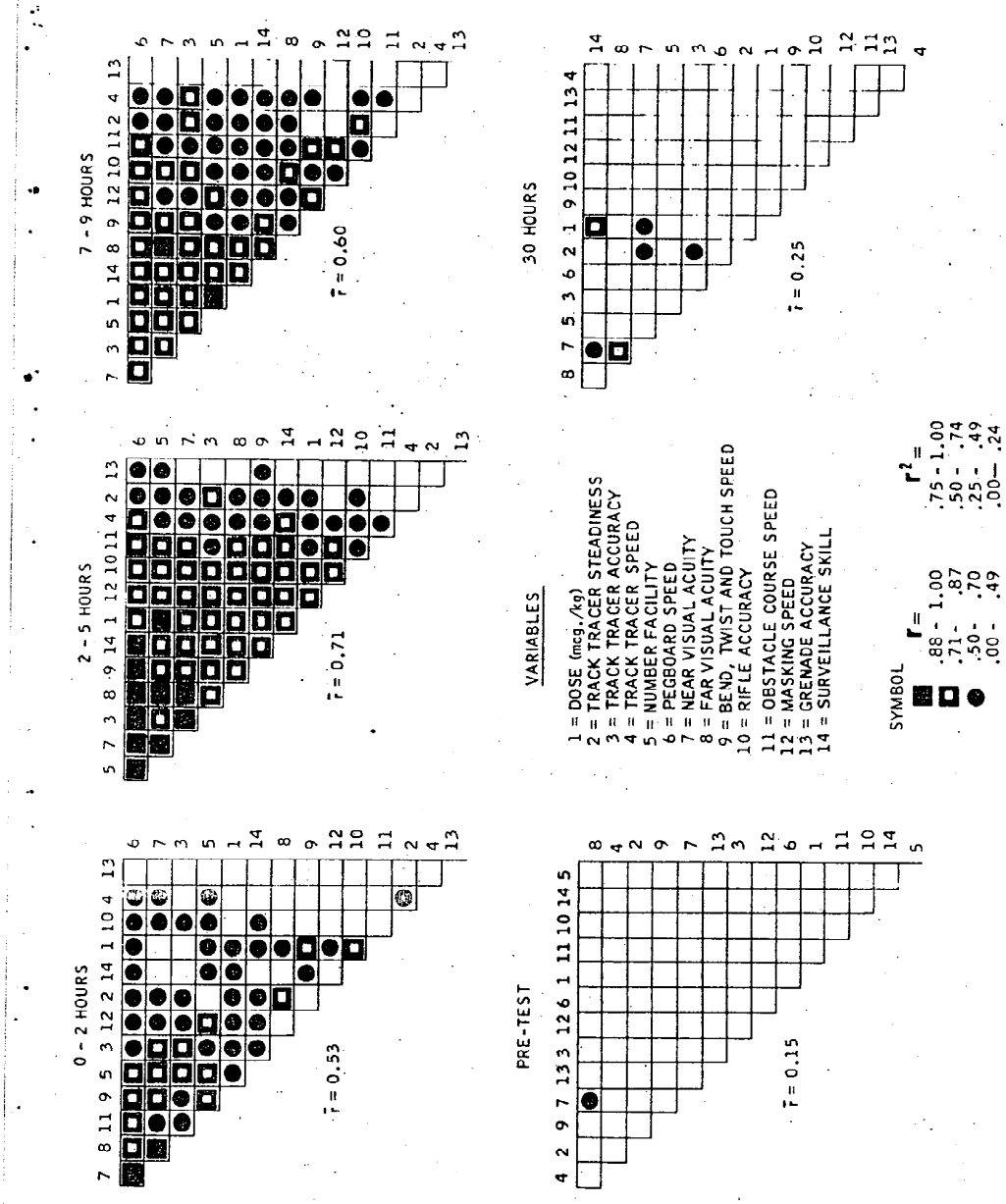

Figure 4 (U). The Effect of the Drug on the Intercorrelations of the Performance Measures

intercorrelations rapidly rise to high values, maximal in the 2- to 5-hour period, corresponding to the time of peak effect for most individual measures. Thereafter, the intercorrelations decline until, at 30 hours, only a few elevated values remain.

The higher correlation between dose and most of the performance measures during the period of maximal drug effect (2 to 9 hours) suggests that the elevated intercorrelations among the various performance measures themselves may be due to a significant covariance with dose (or, more directly, with intensity of drug effect). A preliminary examination of the partial correlations (not presented here) supports this supposition.

Table II shows the rankings of the 14 variables with respect to their average intercorrelation with all other variables during the 0- to 9-hour period of maximum drug activity. In a sense, this ranking may help in the selection of a small number of measures whose efficiency as predictors of scores in other tasks is maximal. Such a battery could be used routinely in future drug studies. Some judgment is required in the selection, since measures like near and far acuity may acquire higher rank than that merited by their intrinsically high correlation with each other. If they are excluded and if the TT also is omitted since only one of its three component scores ranks high, the Pegboard, the NF, and the BTT would seem to make up a logical triad, especially since they have been shown to measure psychomotor, cognitive, and physical proficiency skills, respectively.

Finally, table III presents the average intercorrelations for each dose group and for the combined groups. If we consider only the period of maximal drug effect (2 to 9 hours), it is apparent that for each dose group, the average intercorrelation values are (with one exception) lower than for all doses combined. Mean correlations for the low-dose group alone, actually, seem not to differ significantly from the placebo (no dose) group. On the other hand, the high-dose group in one instance exceeds, and in another roughly equals, the value for the combined doses. An examination of the data showed that this latter result may be explained by the presence of several subjects in the high-dose group who were untestable and were therefore recorded as zero for all tasks during these time periods. This causes a spuriously high intercorrelation among measures in this group.

With this exception, the intercorrelations for "all doses" are higher than for any single dose group, illustrating the general rule that whenever the range of either variable in a correlation is restricted, the correlation will be lower. This, however, raises a practical question: What is to be considered a "restriction of range" in a population of drugged subjects? Nature controls the range for many experimental variables, but the experimenter controls the range of drug effects by his selection not only of the doses, but of the times following administration at which he will make his measurements. The correlation, or lack of of correlation, between measures of effect is thus quite sensitive to the design of the study. If, for example, only low doses had been given in the present study one might have concluded that intercorrelations among performance scores are unchanged by the administration of EA 3580.

Table II (U). Serial Mean Correlations for Each Variable with all Other Variables

Name of Variable	Pre-test	0-2 hr	2-5 hr	7-9 hr	30 hr	Rank
Pegboard Speed	.14	.65	.81	.71	.28	1
Near Acuity	.17	.63	.78	.70	.33	2
Number Facility	.10	.59	.80	.69	.31	3
Track Tracer Accuracy	.15	.56	.77	.69	.30	4
Far Acuity	.22	.62	.76	.66	.35	5
Bend-Twist-Touch Speed	.18	.61	.76	.62	.25	6
Surveillance Accuracy	.11	.49	.75	.67	.35	7
Dose (mcg/kg)	.13	.48	.74	.67	.28	8
Masking Speed	.15	.53	.72	.62	.19	9
Rifle Accuracy	.11	.44	.71	.61	.19	10
Obstacle Course Speed	.13	.62	.69	.59	.19	11
Track Tracer Steadiness	.19	.49	.58	.56	.25	12
Track Tracer Speed	.20	.37	.60	.56	.12	13
Grenade Accuracy	.16	.36	.47	.08	.14	14
Grand Means	.15	.53	.71	.60	.25	

Table III (U). Grand Mean Correlations for Each Dose Group and for All Groups Combined

	Pre-test	0-2 hr	2-5 hr	7-9 hr	30 hr
No dose	.36	.34	.35	.30	.36
Low dose	.26	.35	.32	.35	.32
Mid dose	.20	.39	.46	.42	.27
High dose	.32	.61	.72	.53	.33
All doses	.15	.53	.71	.60	.25

IV. CONCLUSIONS.

Special care must be taken, it would seem, in defining the population in any drug study seeking correlations among observed effects. Ideally, the doses should span a range sufficient to produce near maximal effects at the highest doses, and minimal ones at the lowest doses. The time course of the drug should be thoroughly understood so that measurements may be taken not only at the time of peak effects, but at other periods of intermediate intensity.

V. RECOMMENDATION.

Since not all investigators conduct their work in a setting where a wide range of dosage may feasibly be employed, it would seem desirable to devise a statistical method by which work done under conditions of restricted range can be appropriately related to results obtainable from studies in which range of dosage is essentially unrestricted. Such an approach would help to resolve many apparent contradictions in the psychopharmacological literature.

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