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EDGEWOOD ARSENAL

SPECIAL PUBLICATION

EASP 100-11

PROCEEDINGS OF A CONTRACTORS' CONFERENCE ON BEHAVIORAL SCIENCES

14 and 15 October 1965

edited by

Charles C. Berdjis, LTC

February 1967

Medical Research Laboratory

Research Laboratories

EDGEWOOD ARSENAL

EDGEWOOD ARSENAL, MARYLAND 21010

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EDGEWOOD ARSENAL SPECIAL PUBLICATION

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PROCEEDINGS OF A CONTRACTORS' CONFERENCE ON BEHAVIORAL SCIENCES

14 and 15 October 1965

edited by

Charles C. Berdjis, LTC

Experimental Medicine Department

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Project 1C522301A079

Medical Research Laboratory
Research Laboratories
EDGEWOOD ARSENAL
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FOREWORD

The increasing importance of psychology and psychopharmacology in the modern sciences calls for further emphasis on human and animal performance. Although psychology and its related behavioral studies constitute an autonomous basic science, it borrows freely from and has contributed immensely to many medical techniques and procedures. Each has acted as a stimulus, and each has contributed to the other. The clinical application of psychopharmacological concepts is and has been for a number of years a matter of great concern to the Medical Research Laboratory, Research Laboratories, Edgewood Arsenal.

To keep pace with the latest developments in this field and to cope with the problems inherent in our research program, a meeting on behavioral sciences was organized to bring together on an informal basis the in-house investigators, interested contractors, and other competent scientists to provide authoritative and timely coverage of significant psychological and psychopharmacological developments.

This program constitutes a comprehensive, up-to-date study of major psychopharmacology subjects under investigation within the Medical Research Laboratory under Project 1C522301A079, Non-Defense Medical Aspects of Chemical Agents (U).

The papers presented at this meeting are the product of several years of continuous effort and experience. The formal and informal discussions that followed the papers and the comments made by the participants, panel members, and attendees covered most of the subjects and problems inherent in our research program.

This 2-day meeting was divided into two parts: the first part dealt with animal performance and the second part emphasized human performance.

An attempt was made to cover the essential facts and questions often encountered in the evaluation of human performance on a psychological test. Some of the information may be subject to debate, but the aim of this conference was to exchange information and new ideas among the elements of the Research Laboratories and other governmental and nongovernmental research groups. Perhaps this exchange will be helpful for future research projects and will be an aid and stimulus for original tasks.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care" as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences—National Research Council.

The human subjects in the tests conducted by this installation are enlisted US Army volunteers. There is no coercion or enticement to volunteer. The most stringent medical safeguards surround every human test.

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Acknowledgments

The preparation of this manuscript and the editorial proceedings would have been impossible without the skilled assistance of the authors and the most efficient editorial help of Mrs. Marion P. Royston. The cooperation of the authors, panel members, and other participants is greatly appreciated. The contribution of Mrs. Royston in compiling the papers, discussions, and comments and in the arduous task of proofreading is gratefully acknowledged.

DIGEST

This is a report of the major psychopharmacology subjects under investigation within the Medical Research Laboratory, both on the premises and under contract. The compilation consists of papers presented at a conference on behavioral sciences that was divided into two parts: animal performance and human performance. The subject covered include techniques of testing, philosophy of testing, and results of drug evaluation.

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CONTENTS

Page

Opening Remarks by the Chairman, LTC Charles C. Berdjis, Chief, Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal..... 23

Introduction, COL Joseph R. Blair,* Director of Medical Research, Edgewood Arsenal 23

SESSION I. ANIMAL PERFORMANCE - 14 October 1965..... 25

Moderator: Dr. Milton H. Joffe
Office of Chief, Medical Research Laboratory
Edgewood Arsenal

1. Introduction of Panel, Dr. Milton H. Joffe..... 27

2. Psychopharmacological Studies of Complex Behavior in Animals, Dr. Vincent J. Polidora, University of Wisconsin..... 29

3. Motor and Sensory Effects of Chemical Compounds, Dr. Leon S. Otis, Stanford Research Institute 43

4. Simplified Cortical Electrode for Recording Brain Electrical Activity in Restrained Animals, CPT Frank J. Macchitelli (with Mr. Nicholas Montanarelli, Jr.), Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal..... 69

5. Changes in Behavior and Electrocortical Activity in the Monkey Following Administration of 5-Hydroxytryptophan (5HTP), CPT Frank J. Macchitelli (with Mr. Donald Fischetti and Mr. Nicholas Montanarelli, Jr.), Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal..... 75

6. Gomparison of Various Operant-Behavior Techniques for Performance-Decrement Testing, Dr. Thomas R. A. Davis, Arthur D. Little, Inc. 87

* Now Deputy for Medical Sciences.

7. Effects of LSD-25 on a Variety of Delayed-Response Tasks in the Monkey, Dr. Perry Black (with Dr. Salvatore N. Cianci, Mr. Jack D. Maser, and Mr. Pericles Spyropoulos, Friends of Psychiatric Research, Inc. 105

8. Drug Effects on a Rapidly Trained Conditioned Avoidance Response in Rats, Dr. Robert Clark, E. I. du Pont de Nemours & Co., Inc. 117

9. Monitoring Visual Acuity in the Rhesus Monkey, Dr. William B. Coate, Hazleton Laboratories, Inc. 123

10. Complex Behavior and Its Disruption, Dr. Jack D. Findley (with Dr. Peter K. Levison), Institute for Behavioral Research 139

11. Drug Effects on Learned Behavior in the Squirrel Monkey and the Rat, CPT Donald Meltzer (with Mr. Norman L. Merkler and Mr. George C. Maxey), Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal. 147

12. A Sequential Response Test for Use With the Albino Rat, Mr. LeRoy W. Metker (with Mr. Robert D. Armstrong, Miss Lea M. Somers, and Dr. John F. O'Leary), Physiology Department, Medical Research Laboratory, Edgewood Arsenal. 155

13. Spontaneous Physical Activity of the Rat: A Criterion for Assessing Anticholinergic Incapacitators and Their Antagonists, Mr. Robert D. Armstrong (with Mr. LeRoy W. Metker, Miss Lea M. Somers, CPT Carvel G. Tiekert, and Dr. John F. O'Leary), Physiology Department, Medical Research Laboratory, Edgewood Arsenal 163

14. Effects of Hallucinogenic Drugs on Avoidance Performance and Bar Pressing of Gerbils, Dr. Jack Pearl (with Dr. Franklin J. Rosenberg, Mr. John Fitzgerald, and Mr. Edward Ferguson), Sterling-Winthrop Research Institute 177

15. Comparative Behavior Study of Diverse Organisms Subjected to Drug Action, Dr. Elmer G. Worthley (with Mr. C. Donald Schott and Dr. Milton H. Joffe), Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal 187

16. General Discussion 195

SESSION II. HUMAN PERFORMANCE - 15 October 1965 199

Moderator: Dr. Van M. Sim
Deputy Director of Medical Research
Edgewood Arsenal

1. Introduction of Panel, Dr. Van M. Sim 201

2. The Development of Tracking Tasks as Indicators of Stress, Mr. Norman K. Walker (with Miss Janet F. Burkhardt), Norman K. Walker Associates, Inc. 203

3. A Model for Predicting the Effect of Anticholinergic Compounds on Cognitive Performance, MAJ James S. Ketchum (with Mr. Kragg P. Kysor), Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal 239

4. Bias in Color Discrimination, Dr. Michael H. Siegel, Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal 261

5. An Approach to Studies of Human Drug Behavior, Dr. Peter K. Levison (with Dr. Jack D. Findley), Institute for Behavioral Research 269

6. Standardization Studies With the Repetitive Psychometric Measures: Assessing the Effects of Motivation on Test Performance, CPT James J. Hart, Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal 283

7. Use of Chess as a Technique in Studying Psychochemical Effects, CPT Charles J. Wickstrom (with CPT David L. Kitzes), Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal 289

8. The Effect of Monetary Reward on NF Performance in Prison Volunteers, CPT David L. Kitzes (with 1LT Harlan L. Linsley), Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal 295

9. The Effects of Drugs on Human Performance. Laboratory Testing and Military Prediction, Dr. Edwin H. Elkin (with Dr. Harold P. Van Cott and Dr. Edwin A. Fleishman), American Institutes for Research 305

10. The Baseline Concept as Used in Assessing the Effects of Drugs on Human Performance, CPT Harlan L. Linsley, Experimental Medical Department, Medical Research Laboratory, Edgewood Arsenal 321

11. Extrapolation: Application of the Results of Animal Experimentation to Man, LTC Charles C. Berdjis 325

12. Closing Remarks, Dr. Van M. Sim 349

DISTRIBUTION LIST 351

DD FORM 1473 (DOCUMENT CONTROL DATA - R&D) 363

LIST OF FIGURES

Figure		Page
1.	Diagram of Sequential-Response Test Compartment Used for the Rat	30
2.	Aquisition Curves for Both Simple and Complex Sequences Using Door Responses (Upper Graphs) and Floor-Pedal Responses (Lower Graphs)	32
3.	Intrasession Performance in Training and Rotated Sequences	32
4.	Intersession Relearning of Three-Site Sequences That Have Been Changed in Direction	33
5.	Intrasession Transfer Between Various Combinations of Simple and Complex Sequences	33
6.	Modified Visual-Cliff Apparatus for Testing Mice	44
7.	Underwater Swim Alley for Testing Rodents	47
8.	Effects of Mescaline and LSD-25 on Swimming Performance of Rats in the Underwater Swim Alley	50
9.	Four-Channel Underwater Swim Alley	51
10.	Underwater Swim Maze	52
11.	Effects of Standard Reference Compounds on Swimming Performance of Rats in the Underwater Swim Maze	53
12.	Chamber for Measuring Spontaneous Motor Activity of Rodents	56
13.	Distribution of Scores of 5-min Spontaneous Motor Activity on Counters 1 and 2 for Selected Compounds	57
14.	Life-Space Chamber for Testing Rats	61
15.	Psychophysical Response Curves of Rats	62
16.	Effects of Drugs on Tests Involving Changes in Shock, Sound, and Light Stimuli	65
17.	Size-Difference Threshold Curves for Eight Squirrel Monkeys	[illegible]
18.	Schematic Drawing of Snap-On Fastener Connection Cable and Snap Stud for Use in EEG Recording of Electrocortical Activity of Anesthetized and Unanesthetized Animals	71

LIST OF FIGURES (contd)

Figure		Page
19.	Illustration of Dog Preparation for EEG Recording of Cortical Activity	71
20.	Cutaway View of Chronic Implant of Snap Stud in Animal Skull	72
21.	Recording on Grass Model IIID, 8-Channel EEG of Anesthetized Rhesus Monkey	72
22.	Number of Responses Emitted by Monkey A1 Cumulated Against Time After 5HTP Injections	80
23.	Effects of 5HTP on Response Rate of Monkeys A1, A2, and A3 During First 300 min (Control-Session Time)	81
24.	Comparison of Control EEG's and EEG's Obtained From Monkey A2 After 100-mg/kg Injection of 5HTP	83
25.	Multiple FI/FR (3/30) Schedule	88
26.	Sidman-Type Shock-Avoidance Schedule	89
27.	Tracking-Type Schedule	90
28.	Motor-Performance Schedule	91
29.	Schedule to Measure the Functions of Coordination, Ataxia, and Muscle Weakness	92
30.	Horizontal-Bar Schedule	94
31.	Effects of Two Anticholinergic Agents on FI/FR Schedule	95
32.	Effects of Two Benzomorphans on FI/FR Schedule	97
33.	Effects of Chlorpromazine on Four Schedules	98
34.	Vertical-Activity Schedule Showing Duration of Action of EA 1476	100
35.	FI/FR Schedule Showing Effects of EA 1476	101
36.	Steadiness Schedule Showing Effects of EA 1476	102
37.	Vertical-Activity Schedule Showing Effects of EA 1476	103
38.	Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (10 μg/kg)	111
39.	Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (70 μg/kg)	111

LIST OF FIGURES (contd)

Figure		Page
40.	Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (130 μg/kg)	112
41.	Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After Placebo (Sterile Water)	112
42.	Gap-Size Performance Records With Saline, Methylatropine, and Atropine	127
43.	Gap-Size Performance Records With Saline and Two Dosage Levels of dl-Amphetamine	128
44.	Gap-Size Performance Records With Saline and BZ	129
45.	Gap-Size Performance Records With Saline and LSD Maleate	130
46.	Psychometric Functions Relating Performance to Gap Size With Saline and Three Cycloplegic Agents	132
47.	Stop System Distribution of Responses	136
48.	Interaction of Effects Between Radiation Series and Level of Accuracy on a Matching-to-Sample Baseline in the Monkey	142
49.	Effects of 6-mg/kg Dose of Chlorpromazine Upon Baboon's Accuracy of Counting Problems 1 Through 5	143
50.	Interaction Between Magnitude of Drug Effect and Frequency of Earned Shocks in Rats	145
51.	Effects of LSD on Accuracy of Three Monkeys in Matching-to-Sample Response Test	149
52.	Effects of Sodium Pentobarbital (7.5 mg/kg) on Accuracy of Three Monkeys in Matching-to-Sample Response Test	150
53.	Effects of Sodium Pentobarbital (10 mg/kg) on Discrimination Reversal During 3 Training Days	154
54.	Apparatus for Testing Rats in Sequential-Response Test	156
55.	Probit Plot of BZ Dose-Response Relationship in Sequential-Response Test	159
56.	Probit Plot of BZ Dose-Response Relationship in Sequential-Response Test	161

LIST OF FIGURES (contd)

Figure		Page
57.	Jiggle-Cage Unit	164
58.	Jiggle Cages in Sound-Retarding Chamber	166
59.	Dose-Response Curves for Various Compounds Administered Ip to Rats	169
60.	Probit Analysis of Dose-Response Data	171
61.	Results of an Individual's Performance in a Tracking Task	204
62.	ZITA (Type IIIb) With Visicorder and Hand Control	206
63.	Typical ZITA Record for Task B	208
64.	Rubric Tracking	210
65.	The Learning Process for a Particular Subject - Task A (Acceleration Control, No Lag)	211
66.	Collected Learning Curves for Four Subjects - Task A (Acceleration Control, No Lag)	212
67.	Standard Variation of Mean Modular Error With Stiffness - Task A (Acceleration Control, No Lag)	214
68.	Effect of Lag at High Stiffness - Task B	215
69.	Effect of CBR Suit on Tracking	217
70.	Effect of Auditory Shadowing on Tracking	218
71.	A Typical ZITA Record With Auditory Discrimination Task	220
72.	Subject Tracking on ZITA Equipment While Responding to Auditory Discrimination Task	222
73.	Collected Results for Similar Stressors	223
74.	Variation of "Remnant" With Input Amplitude	231
75.	Balancing a Billard Cue on the Finger	234
76.	General Shape of Time Versus Score Relationship	240
77.	Diurnal Cycle of Performance in Normal Subjects	242
78.	Median Performance Scores Versus Residual Dose	243

LIST OF FIGURES (contd)

Figure		Page
79.	Gompertz Curve Fitted to Median Performance Scores at Various Residual-Dose Levels	246
80.	Logistic Curve Fitted to Median Performance Scores at Various Residual-Dose Levels	247
81.	Graphical Estimation of Pharmacological Half-Life	248
82.	Concentration of Agent at Site of Action	250
83.	Composite Theoretical Curve of Drug Level Versus Time.	251
84.	Predicted Versus Actual Serial Performance Scores (Dose, 1.8 Units/kg)	252
85.	Predicted Versus Actual Serial Performance Scores (Dose, 2.4 Units/kg)	253
86.	Predicted Versus Actual Serial Performance Scores (Dose, 3.4 Units/kg)	254
87.	Predicted Versus Actual Serial Performance Scores (Dose, 4.8 Units/kg)	255
88.	Response Frequency as a Function of Size of Variable Stimulus	264
89.	Color Discrimination as a Function of the Number of Stimulus Repetitions	267
90.	Matching-to-Sample Console and Typical Problem	270
91.	Accuracy of Simultaneous Matching (a) and Delayed Matching (b) on Successive Experimental Days	270
92.	Accuracy and Rate of Response for Delayed Matching	274
93.	Multiple Activities Chamber	274
94.	Matching-to-Sample Console With Problem Stimulus Projected on Screen	275
95.	Subject Responds Following Offset of Comparison Stumulus	276
96.	Subject Obtains Food From the Food and Cigarettes Dispenser	277
97.	Subject Obtains Water From the Water-Dispensing Unit	277
98.	Subject Rests on Cot	278

LIST OF FIGURES (contd)

Figure		Page
99.	Subject Reads While Pressing Hand Switch to Provide Light	278
100.	Subject Selects a Programmed Activity by Pressing Button on Master Panel	280
101.	Mean NF Performance for High- and Low-Nach Subjects	287
102.	Comparison of Percentage Drop in Win-Loss Record of Chess Games and NF Tests Versus Pair Number of Subjects Given Scopolamine	293
103.	Comparison of Percentage Drop in Win-Loss Record of Chess Games and NF Tests Versus Pair Number of Subjects Given LSD	294
104.	Effects of Scopolamine on Simple Reaction Time	313
105.	Effects of Scopolamine on Near Visual Acuity	316
106.	Comparison of Effects of Scopolamine on Performance Tests	317
107.	Comparitive Time Histories of Scopolamine Effects on Representative Performance Tests	319
108.	Relationship Between Average Basal Metabolic Rate per Kilogram per Day of Different Species	343

LIST OF TABLES

Table		
I.	Results of Visual-Cliff Test of Mice	46
II.	Effects of Standard Reference Compounds on Swimming Behavior of Rats in Underwater Swim Alley	48
III.	Brightness-Discrimination Performance of Rats in Underwater Swim Maze	55
IV.	Evaluation of Standard Reference Compounds by Squirrel Monkey Rough-Limits Test	59
V.	Mean Ratio of Percent Positive Responses After Injection of Selected Compounds to Percent Positive Responses After Injection of Saline	63

LIST OF TABLES (contd)

Table		Page
VI.	Disruptive Doses of Standard Compounds on Easy and Difficult Size Discriminations in the WGTA	67
VII.	Percent Alteration in Performance Score as a Function of Task and LSD Dose	109
VIII.	Comparison of Four Standard Compounds in Conditioned-Avoidance-Response Test in Rats	119
IX.	ED50 Values for Five Behavioral Measures in BZ Sequential-Response Test	160
X.	Chappel-Abood Paradigm for General-Activity Test	167
XI.	Activity Counts	168
XII.	Summary Agent-Antagonist Studies	173
XIII.	Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Reference Drugs	179
XIV.	Change in Spontaneous Motor Activity With Reference Drugs, Benzomorphans, Other Narcotic Antagonists, and Anticholinergic Compounds	181
XV.	Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Reference Hallucinogenic Compounds, Benzomorphans, and Other Narcotic Antagonists	182
XVI.	Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Anticholinergic Compounds	184
XVII.	Comparison of Mammalian and Nonmammalian Screens	191
XVIII	Medians and Distribution of NF Scores Associated With Residual-Dose Levels	244
XIX.	Estimation of Pharmacological Half-Life for Each Subject	249
XX.	Analysis of Variance in Tests 1 to 20	297
XXI.	Mean NF Performance	298,299
XXII.	Analysis of Variance in Tests 21 to 50	300
XXIII.	Analysis of Simple Main Effects of Tests 21 to 50 at Pay-Contingency Levels Used on Tests 41 to 50	301

LIST OF TABLES (contd)

Table		Page
XXIV.	A Priori Comparison of Tests 21 to 40 Versus Tests 41 to 50 for Each Pay Contingency on Tests 41 to 50	301
XXV.	Initial Selection of Criterion Military Tasks	307-309
XXVI.	Tests Used in Three Performance Batteries	311
XXVII.	Mean Near-Point Visual Acuity Scores	325
XXVIII.	Comparison of Baseline to Postdrug Scores by Method 2: Number Facility Subtest (NF) for One Subject	326
XXIX.	Comparison of Baseline to Postdrug Scores by Method 3: Two-Hand Coordination for One Subject	327
XXX.	Visual Acuity Analysis of Variance: Main Effects	328
XXXI.	Visual Acuity Analysis of Variance: Simple Main Effects	329

Speakers and Discussants

1.	Mr. Robert D. Armstrong	Physiology Department, Medical Research Laboratory, Edgewood Arsenal
2.	LTC Charles C. Berdjis	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
3.	Dr. Perry Black	Friends of Psychiatric Research, Inc., Baltimore, Maryland
4.	COL Joseph R. Blair	Director of Medical Research, Edgewood Arsenal
5.	Dr. William N. Boyer	University of Wisconsin, Madison, Wisconsin
6.	Dr. Eugene B. Brody*	Psychiatric Institute, University of Maryland, College Park, Maryland
7.	Dr. J. Carr	Army Research Office, Washington, D. C.
8.	Dr. Robert Clark	E. I. du Pont de Nemours & Co., Inc., Newark, Delaware
9.	Dr. William B. Coate	Hazleton Laboratories, Inc., Falls Church, Virginia
10.	Dr. Thomas R. A. Davis	Arthur D. Little, Inc., Cambridge, Massachusetts
11.	Dr. Peter B. Dews*	Harvard Medical School, Cambridge, Massachusetts
12.	Dr. Joel Elkes*	Department of Psychiatry, Johns Hopkins Hospital, Baltimore, Maryland
13.	Dr. Edwin H. Elkin	American Institutes for Research, Washington, D. C.
14.	Dr. Jack D. Findley	Institute for Behavioral Research, Silver Spring, Maryland
15.	CPT James J. Hart	Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal

* Panel member for discussion of papers.

16.	Dr. Milton H. Joffe	Office of Chief, Medical Research Laboratory, Edgewood Arsenal
17.	MAJ James S. Ketchum	Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal
18.	CPT David L. Kitses	Clinical Research Department, Medical Research Laboratory, Edgewood Arsenal
19.	Dr. Peter K. Levison	Institute for Behavioral Research, Silver Spring, Maryland
20.	Dr. John C. Lilly*	Communication Research Institute, Miami, Florida
21.	1LT Harlan L. Linsley	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
22.	CPT Frank J. Macchitelli	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
23.	CPT Donald Meltzer	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
24.	Dr. Millard M. Mershon	Medical Research Laboratory, Edgewood Arsenal
25.	Mr. LeRoy W. Metker	Physiology Department, Medical Research Laboratory, Edgewood Arsenal
26.	Mr. Nicholas Montanarelli	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
27.	Dr. Leon S. Otis	Stanford Research Institute, Menlo Park, California
28.	Dr. Jack Pearl	Sterling-Winthrop Research Institute, Rensselaer, New York

* Panel member for discussion of papers.

29.	Dr. Franklin J. Rosenberg	Sterling-Winthrop Research Institute, Rensselaer, New York
30.	Dr. C. R. Shuster	University of Michigan, Ann Arbor, Michigan
31.	Dr. Michael H. Siegel	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal
32.	Dr. Van M. Sim	Deputy Director of Medical Research, Edgewood Arsenal
33.	Dr. Harold P. Van Cott	American Institutes for Research, Washington, D. C.
34.	Mr. Norman K. Walker	Norman K. Walker Associates, Inc., Bethesda, Maryland
35.	Mr. Kenneth M. Wilson	Medical Research Laboratory, Edgewood Arsenal
36.	Dr. S. Russell Wilson	Peninsular Chemical Research, Inc., Gainesville, Florida
37.	Dr. Elmer G. Worthley	Experimental Medicine Department, Medical Research Laboratory, Edgewood Arsenal

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OPENING REMARKS BY THE CHAIRMAN

LTC Charles C. Berdjis
Chief, Experimental Medicine Department
Medical Research Laboratory
Edgewood Arsenal

I am sorry Dr. Silver is sick and could not attend this meeting. COL Blair is going to give us the introduction and the official welcome to this conference. It is my great pleasure and privilege as chairman of this meeting to welcome all of you most warmly.

INTRODUCTION

COL Joseph R. Blair
Director of Medical Research
Edgewood Arsenal

Good morning, ladies and gentlemen. We are delighted to have everyone with us for this meeting. I am very sorry that Dr. Silver, our laboratory director, cannot be here to make the introduction. He had been looking forward to it and wanted to be here, but he is ill.

This meeting was set up by LTC Berdjis and his staff, to whom we have to give the credit for the very fine program. We hope it will be of great interest to everyone here. We know that it will be of great value to all of us. It will mean very much to our research program and to the accomplishment of our research mission here in the Medical Directorate at Edgewood Arsenal. I want to welcome everyone who is here and everyone who will be contributing to this program. We know that you have a busy schedule at home; probably you will find your desk heavily cluttered with unfinished business when you get back. But we want you to know that we appreciate your taking the time to be here with us these 2 days.

We are very glad that the program that has been arranged is an unclassified one, one that will lend itself to the free exchange of information among the various participants. We hope everyone will take an informal approach to this meeting, feel free to ask questions, participate in the discussions, and make contributions to the program. You have copies of the abstracts of the papers that are to be presented; however, there is much more to be gained by hearing the fine presentations that will be made.

Regarding the personal exchange of information, there will be ample opportunity at various social functions and luncheons to talk with different

people. We hope everyone will take advantage of that opportunity. If any of you want to visit our laboratories or our facilities, we would be most delighted to make arrangements for you to visit and to talk with the people who are working on these various projects.

Behavioral studies in both animals and man are critical to our research program here. They are vital to the accomplishment of our military mission, which, to a large extent, depends upon our being able to observe in both animals and man certain behavioral responses. We must also be able to correctly interpret the data presented by these experiments. Your presence here, your criticism of the papers that we will present on our in-house program, and your contributions will be of value in helping us to accomplish this mission.

Again, on behalf of COL Batte, our Post Commander, and Dr. Silver, I want to extend to you a most hearty welcome. I extend to you their hopeful wishes that the conference meeting here will be successful, thoughtful, and most pleasant. Thank you very much.

I. ANIMAL PERFORMANCE

14 October 1965

Moderator: Dr. Milton H. Joffe
Office of the Chief
Medical Research Laboratory
Edgewood Arsenal

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INTRODUCTION OF PANEL

Dr. Milton H. Joffe
Office of Chief, Medical Research Laboratory
Edgewood Arsenal

The two panel members we have here this morning are both, fortunately, friends of mine; I'm delighted to introduce them both. Dr. Dews is presently at Harvard University, and I think those of you who are in this field are certainly familiar with a great deal of the work that he has done. Dr. Dews, I am sure, will be able to take a critical and unbiased look at the studies that we will be presenting this morning, and I hope that he will be rather free with his comments.

I have fortunately known Dr. Lilly for the last 20 years. His work at present is concerned with some of the highest functions that animals are capable of, as embodied in his experiments with dolphins and their possible use of communications. I say "possible," but perhaps he can be a little more emphatic about it. Because a great deal of this conference will be devoted to animal studies that will have some predicted value for humans, I am very delighted to welcome Dr. Lilly here.

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PSYCHOPHARMACOLOGICAL STUDIES OF COMPLEX BEHAVIOR IN ANIMALS

Dr. Vincent J. Polidora*
University of Wisconsin

Research at the University of Wisconsin Primate Laboratory is concerned primarily with the development and methodological evaluation of techniques for studying the effects of drugs upon the complex behavior of rats and monkeys. However, since most of the work done in the first 4 yr has already been published in the open literature, this presentation will be restricted to a brief description of our four research programs and a summary of recent results in each.

Our first research program is concerned with studying the effects of drugs upon sequential behavior in rats and monkeys. In this procedure, the animal is required to respond to a certain sequence of response sites within a cylindrical test compartment in order to obtain rewards. Figure 1 shows the test compartment used for the rat. There are four equally spaced response sites located on the wall of the compartment. Each response site consists of a floor pedal and a top-hinged door that conceals a water-reward fountain. The rat is simply required to go to a certain combination of these sites in a given sequence in order to obtain a small amount of water at each. The general strategy is to train each rat on one sequence, rerun it daily until its performance is stable, and then determine the effect of the drug on the ability of this highly trained animal to execute its spatial pattern of responding.

One of the most important properties of this method is that drug effects can be studied as a function of behavioral complexity. That is, each rat of a test battery is trained to perform one sequential pattern, but the range of sequence complexities, from simple sequences to more complex ones, is represented by other rats in the battery. As was reported previously,** the magnitude of the disruptive effect of hallucinogenic agents, such as Ditran, is a direct function not only of dose, but also of sequence complexity. The more complex the sequence the rat is required to perform, the greater the detrimental effect of a given drug dose.

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* Presented by Dr. William N. Boyer.

** Polidora, V. J. A Sequential Response Method of Studying Complex Behavior in Animals and Its Application to the Measurement of Drug Effects. J. Exptl. Anal. Behav. 6, 271-277 (1963).

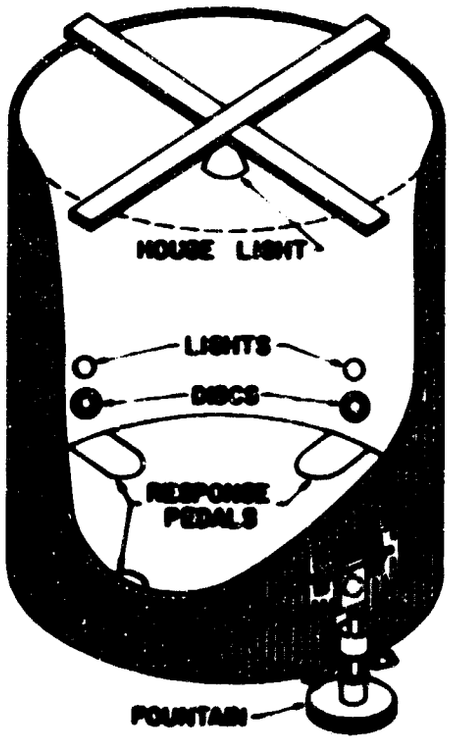

Figure 1. Diagram of Sequential-Response Test Compartment Used for the Rat

Some normative acquisition data have been presented for both simple and complex sequences using two methods for recording responses. The designations simple and complex were based upon performance on these sequences. The upper graphs of figure 2 represent performance employing door responses (pushing a top-hinged door concealing a water fountain), and the lower graphs represent performance using floor-pedal responses. The door-response procedure is a more sensitive technique (note the differences on a two-site opposite, B-D pattern) and, therefore, is currently being employed.

Most of our recent efforts have been directed toward a psychological characterization of this class of sequential behavior of rats. We sought to determine first whether the rat was performing a spatial response sequence or a series of responses to a sequence of specific sites. To answer one part of this question, we required rats that had already asymptotically learned a given sequence to perform the same spatial pattern displaced by rotation. For example, if a rat had learned an A-B-D sequence (where the four sites are arbitrarily labeled A, B, C, and D), it was required to obtain its rewards from sites C-D-B or perhaps B-C-A. Another animal having a B-D pattern might be required to perform an A-C sequence in the test session. The results of this rotation experiment are summarized in figure 3.

Regardless of the sequence involved, all rats took only about 5 min to orient themselves to the rotated sequence. From that point on, they performed as well as they had on their initial sequences. In fact, rats could transfer to a rotated sequence even in the middle of a session (figure 3).

A second experiment required the rat to perform a sequence that was reversed in direction. For example, an A-B-D animal would be required to perform a C-B-D sequence. Figure 4 shows performance results for both an original and a reversed three-site sequence. Again, transfer was slight, but learning the reversed sequence required four to five sessions. Since a naive rat would require from 10 to 15 sessions to learn the same sequence, we can conclude that although transfer about specific reversed sequences is negligible, there is an appreciable learning-to-learn effect in this situation.

In our next series of experiments, the transfer characteristics between classes of sequences were investigated. After learning an initial sequence, the rat was required to perform an entirely new and different sequence. In figure 5, the results of these experiments are summarized. Complex sequences transfer almost completely to more simple sequences (figure 5, upper graphs), but simple sequences transfer negligibly to more complex ones (figure 5, lower graphs). For example, an A-B-D rat required only a few minutes to perform asymptotically on a C-D sequence, whereas a C-D rat required about the same number of sessions to learn an A-B-D sequence as does a totally naive animal.

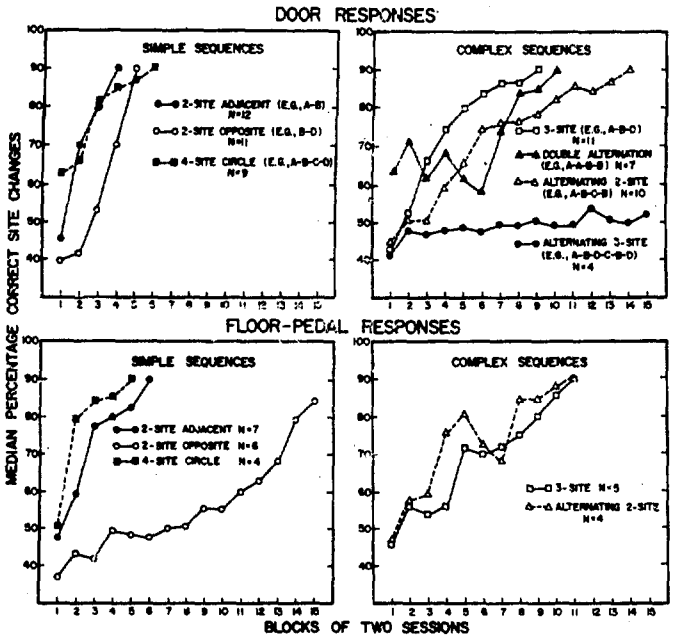

Figure 2. Acquisition Curves for Both Simple and Complex Sequences Using Door Responses (Upper Graphs) and Floor-Pedal Responses (Lower Graphs)

(Acquisition curves are based upon median percentage of correct site changes)

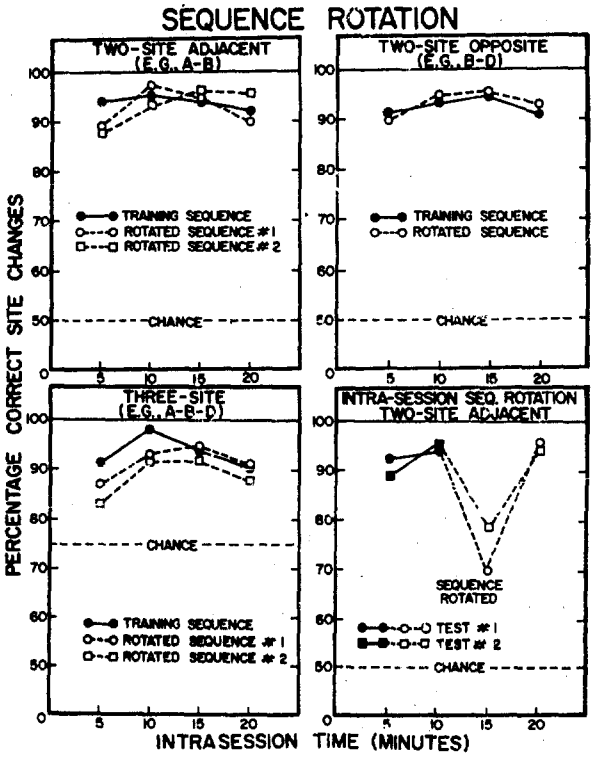

Figure 3. Intrasession Performance in Training and Rotated Sequences

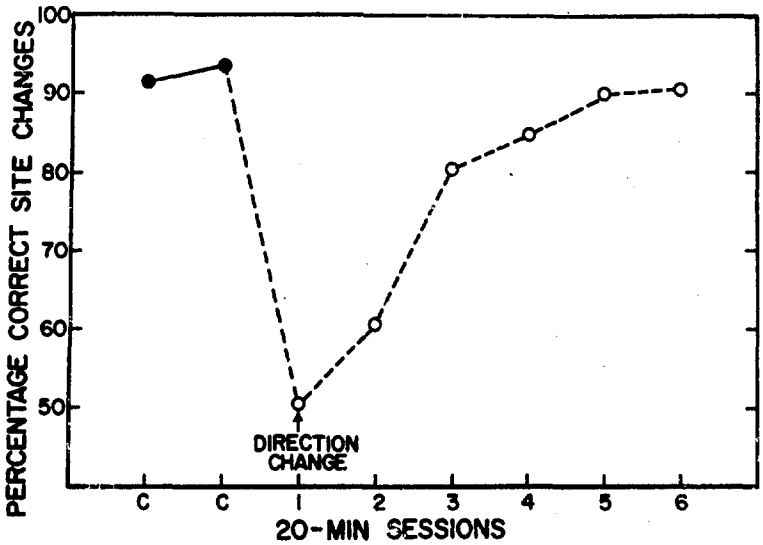

Figure 4. Intersession Relearning of Three-Site Sequences That Have Been Changed in Direction

—— Performance on original problem
--- Performance with sequence reversed in direction

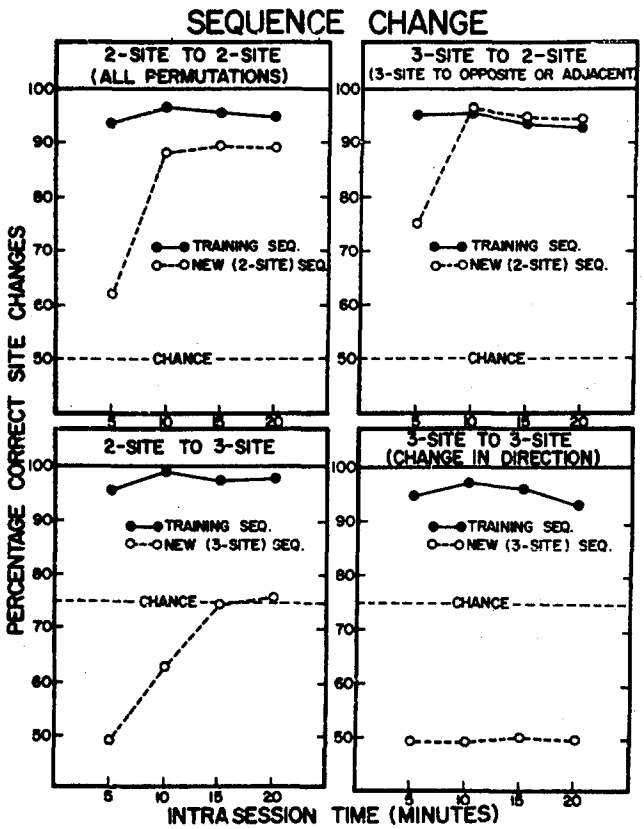

Figure 5. Intrasession Transfer Between Various Combinations of Simple and Complex Sequences

On the basis of these findings, we may conclude that sequential response habits consist of a patterned chain of spatial responses rather than a sequence of responses to specific sites. One implication of these findings is that a drug that selectively interferes with this type of sequential behavior has the general characteristic of disturbing some aspect of the rat's ability to integrate its behavior in space.

This latter conclusion, however, is empirically based and not merely an assumption. We emphasize this point because you expect us to report only the results of drug experiments. Instead, we are reporting results that seem to be purely from psychological experiments. It is our view that a specification, description, and, hopefully, even an explanation of the behavior that is affected by a drug are at least as important as a catalog of drug effects upon arbitrarily selected, convenient, or merely conventional behavior tests. Regrettably, a natural consequence of our position regarding psychopharmacological research will be that you will probably evaluate much of our research as being only peripherally related to your main interests in drug research. We disagree.

We design these methodological experiments to determine the important parameters of an assay. In the same sense that a researcher in biochemistry must determine the factors that make his assay for compound X more accurate, specific, precise, and replicable, we are attempting to identify and evaluate the factors that influence our behavioral assays. With such data available, predictions and extrapolations to drug effects in human subjects will, hopefully, be more accurate.

There have recently been two important outcomes of our Vigilance research program. First, we will briefly review this experimental situation. A monkey is in a 2-ft cubic cage, and it views a visual display through the transparent front wall of the cage. The visual display consists of 121 lights in an 11 by 11 matrix; these lights are continuously blinking on and off at random. Superimposed upon this visual "noise" there occurs at unpredictable intervals a visual "signal," which consists of some combination of these lights remaining on continuously. When a signal is presented, the monkey is required to make an avoidance response in order to avoid an electric shock that is programmed to occur 10 sec later. Thus, we are studying avoidance behavior in the monkey where the parameter being experimentally manipulated is the nature of the visual stimulus for avoidance. By adjusting the detectability of the signal embedded in the noise, we can adjust the complexity of the signal-from-noise detection behavior that we require of the monkey.

We have already reported* that this behavioral assay is differentially sensitive to chlorpromazine but not pentobarbital and that the detection of smaller signals is more drug sensitive than that of larger ones. Subsequently, we studied the effects of chlorpromazine on six signals that were of equal size but of differential detectability. All signals consisted of 36 lights, but they were formed (in decreasing order of detectability) into (1) a 6 by 6 solid square, (2) a cross, (3) an outline cross, (4) broken segments of a cross, (5) an outline square, and (6) a random array. As predicted, the decrement in detection behavior induced by 0.25 mg/kg of chlorpromazine was greater as the signal became less detectable.

The second important result of our Vigilance research program is the finding that there are several significant advantages to using airblast as an unconditioned stimulus rather than electric shock. We have found in several preliminary experiments that airblast-motivated behavior in the monkey is in many ways superior to shock-motivated behavior. Naive animals, for example, are less severely disturbed by the airblast so that they are capable of learning faster. Also, the noninjurious airblast is so noxious to monkeys that stable avoidance behavior can be maintained over extended periods of time without their becoming adapted to it. Finally, an apparatus to deliver an airblast costs several hundred dollars less than one for electric shock. We are currently building a shuttle box that is equipped for shock as well as airblast delivery so that comparative experiments can be performed.

Our third research program is our newest, so this report must be restricted to a description of the problem and initial experiments. This research is concerned with investigating the effects of drugs upon monkeys' persistent motivations to explore their environment visually. Our expectation is that this rather subtly motivated behavior may be very sensitive to drug effects. To facilitate collation and analyses of the huge volume of data that is obtained, we are using an IBM key punch to record the visual exploration responses of batteries of six monkeys. Since the data are thereby recorded on punched cards, we are using the computer to do most of our calculations. The program has just begun, however, and only two batteries of six monkeys each have been adapted to the apparatus. Our initial drug experiment is scheduled to begin in 2 wk, at which time we shall begin determining the effects of several prototype compounds.

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* Polidora, V. J., and Urbanek, R. J. Drug Effects Upon Visual Signal-From-Noise Detection by Monkeys. Psychon. Sci. 1, 237, 238 (1964).

Our fourth and final research program concerns the study of discriminative behavior of primates. As in our work with sequential responses, we have in this program been occupied recently with a series of methodological experiments that relate directly to the important parameters of the behavior under study. Because the main goal of our psychopharmacological research is to study the interactive effects between drugs and behavioral complexity, we have devoted a considerable effort toward establishing useful means of scaling the difficulty, or discriminability, of visual-pattern-discrimination problems. We have sought to determine the physical attributes of visual patterns that are utilized by monkeys discriminating between these patterns. We reasoned that if we could determine which physical dimensions of visual patterns were correlated with the monkeys' discriminative proficiency, we could then select patterns so that the difficulty of the problems would be known before the experiment began. In this way, we could study drug effects upon the continuum of complexity of discriminative behavior.

Fortunately, there is a rather simple set of physical correlates of visual metric patterns that predict the discriminative proficiency of primates. Before giving these results, however, perhaps we should describe the problem more precisely.

We have studied visual metric patterns that are formed by the lighting of certain lights of a 4 by 4 matrix of lights. Simultaneous discrimination problems are constructed by presenting the monkey with two patterns, one of which is arbitrarily designated the "correct" pattern, and by rewarding the monkey with a sugar pellet only if it responds to the correct pattern By presenting each pair of patterns several times, we allow the monkey to obtain as many rewards as it can. The number of rewards obtained on a given problem by a battery of highly trained monkeys was assumed to be inversely related to the difficulty of the problem, because learning and other important factors were controlled.

The experiments consisted of presenting thousands of problems to our battery of 14 extremely test-sophisticated monkeys and correlating performance with the physical dimensions of the pairs of visual patterns. Again, to provide more precise control of these experiments and to collect the data in a computer-compatible format, we used an IBM key punch to program the stimuli and record the data simultaneously.

In the course of 4 yr of experimentation on this problem, we have collected over a million responses to such visual, metric, pattern-discrimination problems. Since the results of most of these experiments have already

been reported in the literature,* only the results of our recent and extensive reanalysis of these data will be reported here. In one sense, the chaff of our early experiments has been dispersed, and the kernels can now be exposed by taking a careful look at the data of the entire research program.

We extracted from our data estimates of the relative contributions to discriminability provided by 18 physical dimensions of visual patterns. These dimensions included the several we have worked with as well as those proposed by researchers working with random shapes. All of these dimensions were incorporated into multivariate analyses of the data—multiple regression techniques, discriminant function analyses, and analyses of variance and covariance. Fortunately, the results of these complex analyses were mercifully simple, and they can be reported very briefly.

More than 80% of the variability of discriminative performance was accounted for by a single physical dimension, one that we call unique elements. Consider the two patterns of a problem. Number the lights in each 16-element display from left to right as 1 through 4 in the top row, 5 through 8 in the second row, and so on through 16. The number of unique elements in a problem is determined by comparing the states of the lights in the two displays; that is, by comparing light No. 1 in one display with light No. 1 in the other, light No. 2 with the other light No. 2, and so on. The total number of corresponding lights that are in different states is the number of unique elements for that problem. A moment's reflection will reveal that what the dimension of unique elements expresses is the number of dissimilar components of the two patterns. It is this dimension that has the highest partial correlation, multiple regression β-weight, F-ratio, and discriminant function weighting of any dimension we have analyzed, and we think we have analyzed them all.

By additional analyses, other aspects of the general problem have been examined, but none of them violate the main conclusion. Considering the objective of this meeting, these additional findings should probably be reported in full only when we write them for publication. The main point we make at this time is that on the basis of these results, we can now predict the discriminability of this class of visual metric patterns. Thus, we can design drug

* Polidora, V. J., and Thompson, W. J. Stimulus Correlates of Visual Pattern Discrimination by Monkeys: Area and Contour. J. Comp. Physiol. Psychol. 58, 264-269 (1964); Polidora, V. J. Stimulus Correlates of Visual Pattern Discrimination by Monkeys: Sidedness. Percept. Motor Skills 20, 461-469 (1965); Polidora, V. J. Stimulus Correlates of Visual Pattern Discrimination by Humans: Area and Contour. J. Exptl. Psychol. 69, 221-223 (1965); Polidora, V. J., and Thompson, W. J. Orienting Behavior and the S-R Spatial Discontiguity Effect in Monkey. J. Comp. Physiol. Psychol. 59, 240-245 (1965).

experiments with the discriminability factor as one of the important independent variables. Furthermore, we can provide the same information to any researcher who wants to achieve the same control of the stimulus in his visual-pattern-discrimination experiments.

DISCUSSION

Dr. Joffe (Edgewood Arsenal): Before we have questions I would like to make one remark. We are asking the contractors for the development, the validation, and the reliability of these test methods. We are not in most instances asking for an assay of our materials. The assay of our materials is our business and responsibility. We are asking for the development of test methods that we must then evaluate for their applicability to our mission. I would like to make this very plain at this time. We appreciate Dr. Polidora and Dr. Boyer's efforts in this area. They have developed tests and have done exactly what we asked of them. Not only have they developed the tests, but they have given us figures for the reliability and validity of the tests, and without this information, a test is worthless. The application of it to our business is our problem.

Dr. Otis (Stanford Research Institute): Dr. Boyer, can you give us some idea of comparative differences between the monkey and the rat in learning these procedures and in the kind of transfers that you discussed?

Dr. Boyer (University of Wisconsin): We have used an enlarged version of the same apparatus for monkey studies, but we have not been able to get the monkeys to learn a sequence. We are now considering presenting a panel in front of the monkey so that he can pull levers or push buttons in sequence. In other words, we were not able to train monkeys to perform a complex sequence in a cylindrical apparatus, but we are working on other approaches to the problem.

Dr. Joffe: The last time I talked to Dr. Polidora, he told me that it was Dr. Harlow's opinion years ago that the monkey would never learn this sort of thing! Maybe rats are smarter than monkeys.

Dr. Dews (Harvard Medical School): I have a number of technical questions to raise that start with the last type of work you were describing, the visual-pattern discrimination. You mentioned that 80% of the variance was accounted for in terms of the unique-elements differences between the stimuli. I was surprised that the total brightness would not be an important element. In some of the displays that you gave as examples, there were different numbers of lights on in the two patterns: one had 11 and the other had 6. I wondered if you had looked for a relationship between ease of discrimination and the number of bulbs you had on in the patterns. Related to this, what sort of ambient illumination did you have when you were doing the experiment?

Dr. Boyer: The dimension you described, one that we have called element disparity or the difference between the number of "on" elements in the two displays, was investigated in the initial experiments in this program. As has been reported in the literature by Dr. Polidora and his coworkers [which includes, in addition to those footnoted previously, Polidora, V. J., and Thompson, W. J. Stimulus Correlates of Visual Pattern Discrimination by Monkeys: Pattern Complexity. Percept. Motor Skills 21, 71-79 (1965)], element disparity as well as several other dimensions predicts discriminative performance fairly well. However, we have recently reanalyzed our data using multiple and partial regression techniques and discriminant function analyses and have found that when all other dimensions are held constant, the unique-elements dimension predicts the great bulk of the variance. These latter data will be written for publication shortly. In reply to your second question, the ambient illumination around the displays was very low when the monkey was making these discriminations. A house light in the back of the box provided ambient illumination, but when the animal was masked, its body and head blocked most of the house light from the area of the displays.

Dr Dews: In the first experiment of the sequential behavior of rats, I understood from your slide on the apparatus that it was an entirely symmetrical arrangement with respect to all of the positions. Therefore, what exactly do you mean by rotation? I would have thought that since A is equal to B, which is equal to C, which is equal to D, rotation would leave the situation unchanged except with respect to cues outside the apparatus, such as the magnetic pole.

Dr. Boyer: The apparatus for the rat was designed to be completely quadrilaterally symmetrical, and A (hopefully) is identical to B, C, and D. By "rotation" of a sequence, we mean that the same pattern of responding in space to a new set of specific response sites in the apparatus was required. An A-B-D sequence rotated 180° would be a C-D-B sequence; that is, it would be the same pattern of responses but to different sites in the apparatus. Our use of the term rotation is unfortunate and, perhaps, even misleading. We shall have to use a better one in the future.

Dr. Dews: In connection with your main thesis that it is the complexity of the problem that determines the sensitivity of the performance to disruption by drugs, are you able to differentiate completely between the complexity of the problem per se and the perfection of the discrimination that is developed? In other words, are the control performances at the different complexities absolutely identical in percent level of success? If there is a difference in the control performances, how do you know that it is not the difference in the level of performance rather than the complexity per se that is determining the sensitivity to disruption?

Dr. Joffe: Since I was there when some of these drug experiments were run, I think perhaps I can answer your question better, Dr. Dews. The data have generally been graphed or calculated by making three curves: the first being the number of responses, the second the number of rewards, and the third the total number of trials. From these, one could distinguish between a drug that simply increased activity without changing discrimination and a drug that changed discrimination without changing activity, because you had a total number of responses, a total number of correct responses, and, by calculation, a number of errors. You could get a value for the percentage correct even though the task was exactly the same. Does this answer your question?

Dr. Dews: I'm not sure. The more complex the task, the longer it took for the animal to acquire a respectable performance and the more susceptible the performance was to disruption by the drugs. Many other things, such as inappropriate stimuli, make a discrimination more difficult. Can you identify complexity per se, as opposed to any of these other things that make performance less perfect, as influencing the sensitivity to disruption by the drugs?

Dr. Boyer: Complexity is inferred from several data. First, we have made the assumption that the relative rates of acquisition of the various classes of sequences (the data shown on one of the slides) represent the relative levels of sequence complexity. By using the median sessions-to-criterion data (that is, the number of sessions to attain 90% correct site changes), we obtain one estimate of at least the ranking of sequence complexity. Next are the drug data, with which we have shown that some sequences are disrupted more by a given drug dose than others. Complexity rankings based on the acquisition data agree favorably with the rankings based upon the drug data. We have concluded that these two means of estimating complexity (perhaps the only difficulty) provide an empirical ranking of sequential behavior that is at least internally consistent.

Your question about complexity with respect to level of performance is an important one. In all our drug experiments with sequential behavior, we have administered the drug in the first session after the animal has performed in excess of 90% correct site changes for three consecutive sessions. In other words, we have kept level of performance constant, regardless of the complexity of the sequence. Although we have thus made an attempt to control for the complexity-performance problem, we nevertheless are confronted with another problem as a byproduct of exerting this control. Because more complex sequences take longer to learn, the animals assigned the complex sequences receive more practice than do those assigned simple sequences. We have not yet developed a means of controlling, or even estimating, the effects of the obvious confounding between sequence complexity and practice. Training all animals for a fixed number of sessions (at least as many as are required to learn the most complex sequences) does not seem to us to be an answer because

the experience of overlearning a simple sequence must certainly be qualitatively different from learning a complex sequence, even though the same number of sessions is involved. In any event, the practice-complexity confounding must be recognized when our data are evaluated, but I think it is a criticism that applies equally to most other research on this problem.

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MOTOR AND SENSORY EFFECTS OF CHEMICAL COMPOUNDS*

Dr. Leon S. Otis
Stanford Research Institute

For the past two years, we have been interested in developing methods for evaluating two classes of compounds: those that may affect visually dependent behavior and those that may severely impair motor performance. We have emphasized simplicity and economy and have favored methods that require a minimum of training.

The Visual-Cliff Test.

Although cats and rats performed quite adequately using the Visual-Cliff test described by Gibson,** several modifications of the apparatus have been necessary in order to evaluate the performance of mice. The modified apparatus, shown in figure 6, consists of a box 3 × 3 × 3 ft. Half of the top is a shelf and the other half a well. The shelf, floor and the inside of the well are covered with black-and-white-squared cloth. A sheet of plate glass lies across the top of the box, covering the shelf and well. From above the box, the impression gained is that of a cliff with a 3-ft drop into the well.

In the original apparatus, mice failed to jump from the center walkway. To overcome this problem, several changes were introduced:

1. A circular platform, 9 in. in diameter and raised to a height of 4 in., was used.

2. An infrared bulb was suspended about 10 in. above the platform, thereby heating the platform to a temperature of about 50°C. The heat eventually forced the animal to jump off the platform; most animals jumped within 2 min.

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* This work was supported in part by Contract DA18-108-AMC-215(A) from Edgewood Arsenal and in part by Contract Nonr-2993(00) from the Office of Naval Research and Grant MY 08311-02 from the National Institutes of Health. The collaboration of Dr. Gordon Ball (currently at Yale University), Dr. Ronald Schusterman, Mr. Lawrence Sharpe (currently at Purdue University), Dr. David Reynolds, and Dr. Gordon Pryor is acknowledged..

** Gibson, E. J., and Walk, R. D. The "Visual Cliff." Sci. Am. 202 (No. 4), 64-71 (1960).

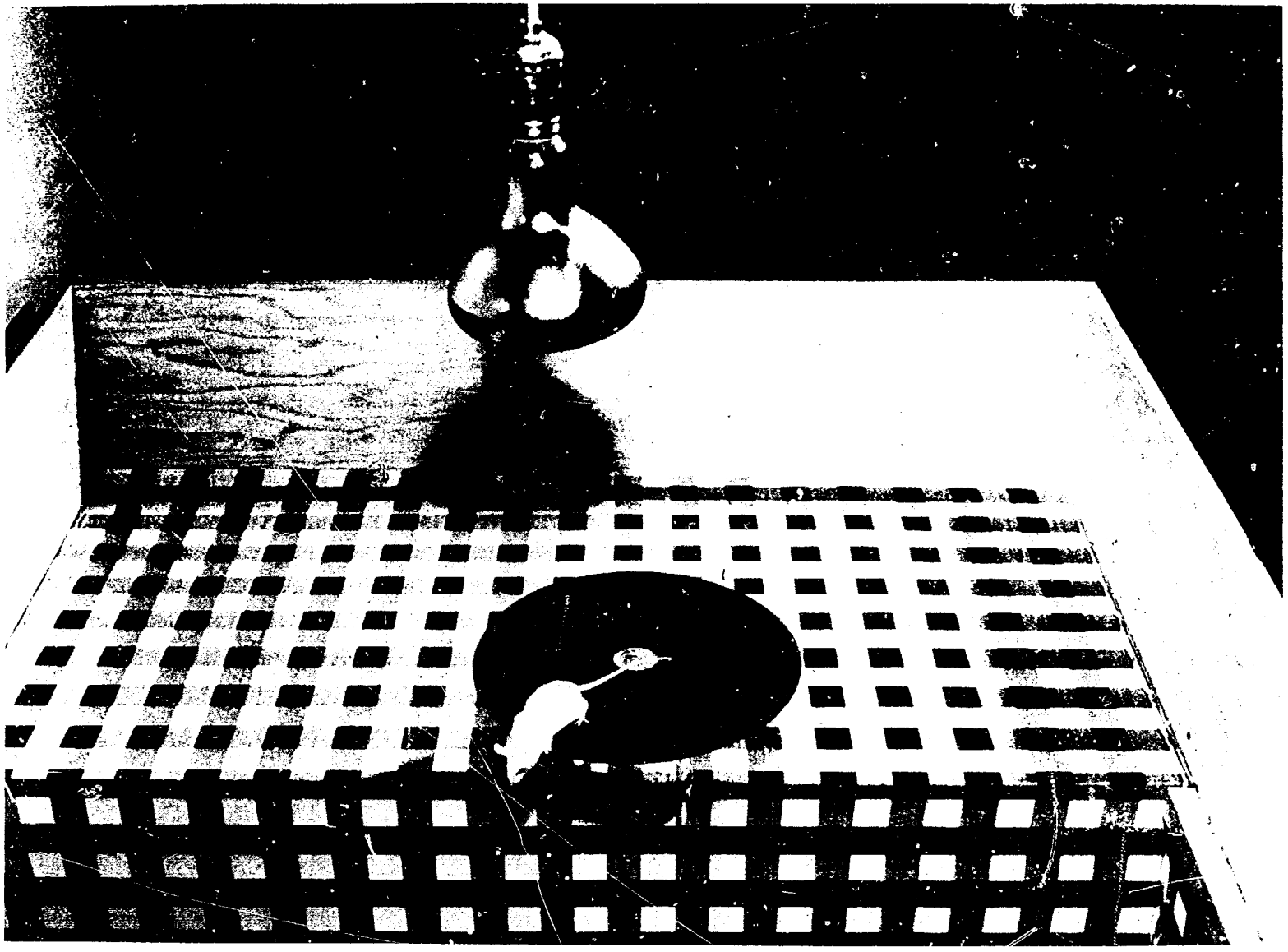

Figure 6. Modified Visual-Cliff Apparatus for Testing Mice

3. The heat lamp was placed slightly off center in order to assure a temperature gradient across the platform. This forced the mouse to a position on the platform immediately overlooking the edge between the shelf and the well. It was found that, under such conditions, the probability of the animal's jumping to the higher of the two sides was increased to between 90% and 100%.

The test consisted of placing the mouse on the center of the platform and noting whether it jumped to the well or the shelf. After the animal had responded, it was returned to its cage until the next trial. Intertrial intervals varied from 5 to 10 min. Apart from the light from the heat lamp, the room was unlighted. Administration of drugs was by the intraperitoneal (ip) route. The results for several standard compounds are shown in table I.

The result of a "blindness" control test is shown in the upper part of the table. Vision was obliterated by covering the eyes of the mice with an opaque adhesive cement (rubber-to-metal cement). These animals performed at chance level, and their locomotion was normal. The results of the blindness control test showed that the Visual-Cliff test does, in fact, discriminate between mice with good and poor vision.

Only those compounds that result in less than 77% response to the ledge and that are not accompanied by abnormal gross responses are considered to significantly affect this rather primitive form of visually dependent behavior. Compounds that meet these criteria are LSD-25, mescaline, morphine, and scopolamine. All of these compounds are known to produce visual disturbances in man.

The Underwater-Swim-Alley Test.

The Underwater-Swim-Alley test (USA test) resulted from our attempts to develop a procedure that would maximally motivate performance under conditions of extreme stress. The rat's natural aversion to water serves to maximally motivate escape behavior in this test. The test consists of underwater swimming in a linear tank shown in figure 7. The alley is 72 in. long, 4 in. wide, and 6 in. deep. Photocells with red filters are mounted 10 in. from the starting point and at the escape holes at the far end of the tank. A starting chamber is slipped into the tank at the beginning of each trial, thereby totally submerging the animal. The animal is released from the starting chamber through a guillotine door 1 sec after immersion and swims through a clear plastic tube immersed in the water; the tube prevents the animal from escaping to the surface during the swim. The times required to swim past the first photocell (the orientation time) to the escape hole (the swimming time) are recorded to the nearest 0.1 sec.

Table I. Results of Visual-Cliff Test of Mice

Group	Dose, ip	Response to ledge	Abnormal gross behavior
	mg/kg	%	
		A. Control	
Experimentally blinded	–	53*	None
Normal	–	90-100	None
		B. Treated	
Atropine	80.0	–	All subjects failed to respond; prostration; death (30%)
	40.0	83	None
Benactyzine HCl	7.0	42*	Hypersensitive; subjects immediately ran off edge
	3.5	94	None
Chlorpromazine	2.0	61*	Popcorn reaction; ataxia
	1.0	89	None
Phenobarbital	100.0	–	Some subjects fell off platform; prostration and acute ataxia
	50.0	78	None
Scopolamine	160.0	61*	None
	80.0	94	None
LSD-25	0.45	60*	None
	0.20	82	None
Mescaline	50.0	57*	None
	25.0	92	None
Morphine	3.125	71*	Normal locomotion but analgesic to heat; had to raise temperature to obtain a response

Note: Overall performance at each drug level is assessed from 18 responses from 6 subjects tested at 3, 15, and 30 min postinjection; the performance level is obtained by using the number of responses to the ledge as percentages; the probability of 77% response to the ledge is >0.05, and it is assumed that animals reaching this criterion have reasonably normal vision.

* Indicates performance at chance level.

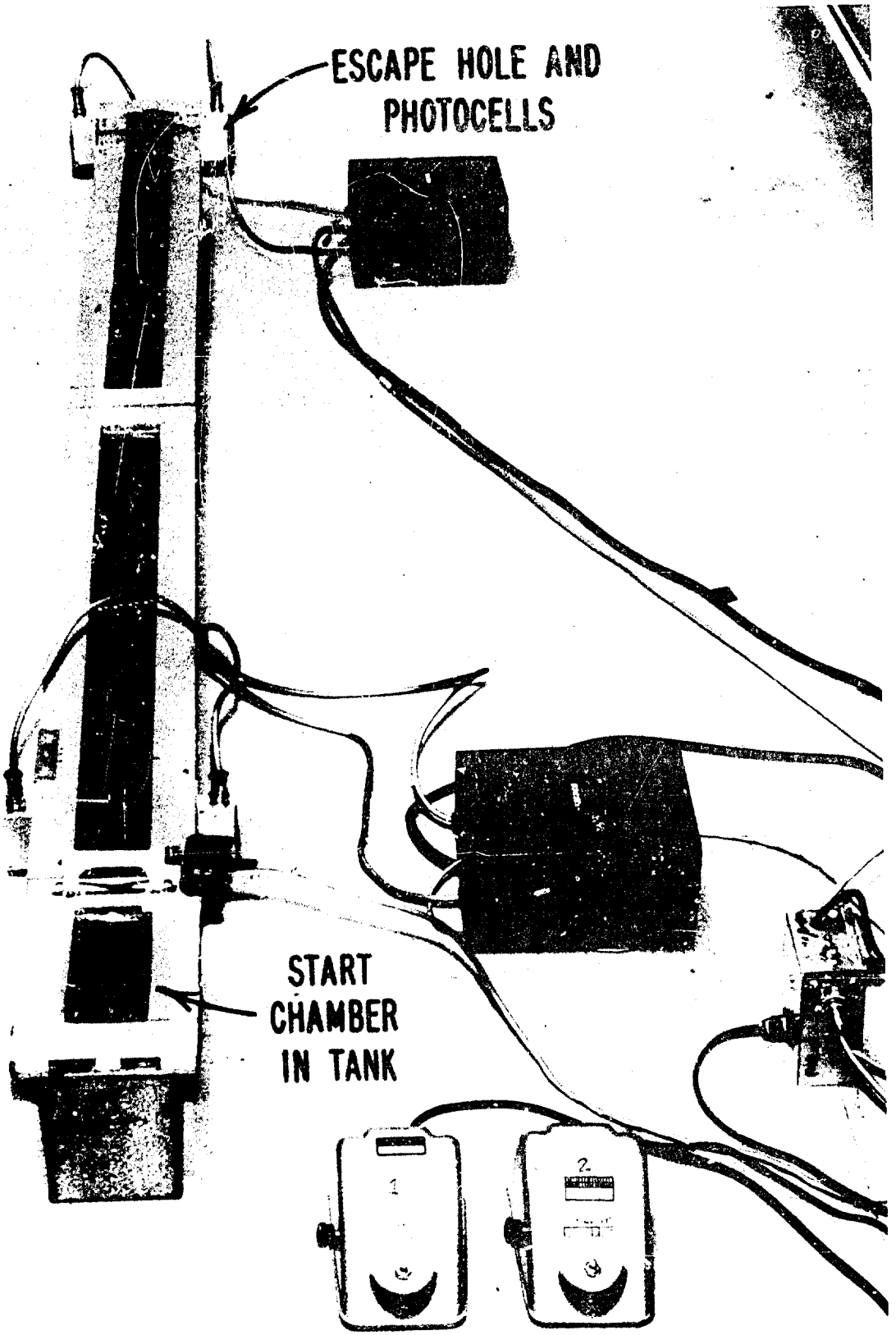

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Figure 7. Underwater Swim Alley for Testing Rodents

The naive animal learns to swim the tank almost immediately. The asymptote is typically reached within 5 trials; the average orientation time for the last 5 of 10 training trials is about 1.3 sec, and the average swimming time is about 3.9 sec. Experiments have shown that swimming performance does not improve noticeably after 10 trials (20 or 30 consecutive trials were given in one experiment, and 3 days of 10 trials/day were given in another). After approximately five trials, the trial-to-trial variability for each rat is very small (40 to 75 msec).

After 10 training trials, the animals are given a test compound or a placebo and are retested for 10 more trials at a predetermined, peak-effect time.

Table II shows that performance in this test is highly stable over a wide dose range of different drugs. We have found that almost total incapacitation is required before the animal will show a deficit in swimming performance in this test.

Table II. Effects of Standard Reference Compounds on Swimming Behavior of Rats in Underwater Swim Alley

Drug	Dose range	Median orientation time	Median swimming time
	mg/kg	sec	
Placebo	–	1.3	3.9
Dexedrine	0.078 - 2.5	1.3	4.1
Imipramine	3.75 - 30.0	1.3	4.0
Iproniazid	6.25 - 50.0	1.3	3.8
Scopolamine	0.1 - 4.0	1.4	3.8
Perphenazine	0.125 - 3.0	1.6	4.3
Chlorpromazine	0.625 - 2.5	1.3	4.2
Trifluoperazine	0.25 - 4.0	1.6	3.8
Pentobarbital	2.5 - 15.0	1.2	5.1*
Reserpine	0.25 [illegible]	1.8	3.8
Meprobamate	12.5 - 100.0	1.1	4.0

* Significant response.

A different picture is seen when hallucinogenic-type compounds are evaluated. Figure 8 shows that orientation time is impaired at dosages that have little or no effect on swimming time.

Figure 9 shows the latest version of this test. We doubled the length of the tank to 12 ft and built four alleys side-by-side, so that now we are able to run four animals at a time.

The Underwater-Swim-Maze Test.

The USA test is primarily a test of coordinated motor performance and is limited in its ability to detect possible deterioration of visual processes, except in a very rudimentary sense (that is, orientation time). Accordingly, we developed a second test, the Underwater-Swim-Maze test (USM), shown in figure 10, which more clearly requires vision for its solution.

Swimming time and orientation time are measured in the USM test (as in the USA test), but the USM test also measures the animal's ability to perform a brightness-discrimination task. Essentially, the USM is a USA with a two-choice discrimination problem attached at the end, forming a T-maze. The animal is trained to select the darker arm (the brightness is controlled by means of a small bulb mounted at the end of each arm) to escape from the water.

The general procedure for running animals in the USM is as follows: The subjects are given 5 trials/day until a criterion of 10 correct responses has been reached (that is, 2 consecutive days of errorless trials). This criterion is typically reached within 6 days. Animals then perform at 100% efficiency in subsequent trials, even after several days of rest.

Three measurements are recorded for each trial: (1) the time the subject takes to leave the start box (orientation time), (2) the time the subject takes to swim to the escape hole (swimming time), and (3) the number of errors. A correct discrimination is recorded when the subject swims directly to the escape hole (the darker of the two sides). A correction technique is used during both training and testing.

Figure 11 shows the effects of selected compounds on orientation time and swimming time. The high dose of dexedrine affected swimming time, and both orientation time and swimming time were affected by LSD-25 and mescaline. The other compounds were without effect. The increase in swimming time after LSD-25 and mescaline is not surprising, because an orienting response is required at the choice point as well as at the starting point of the maze.

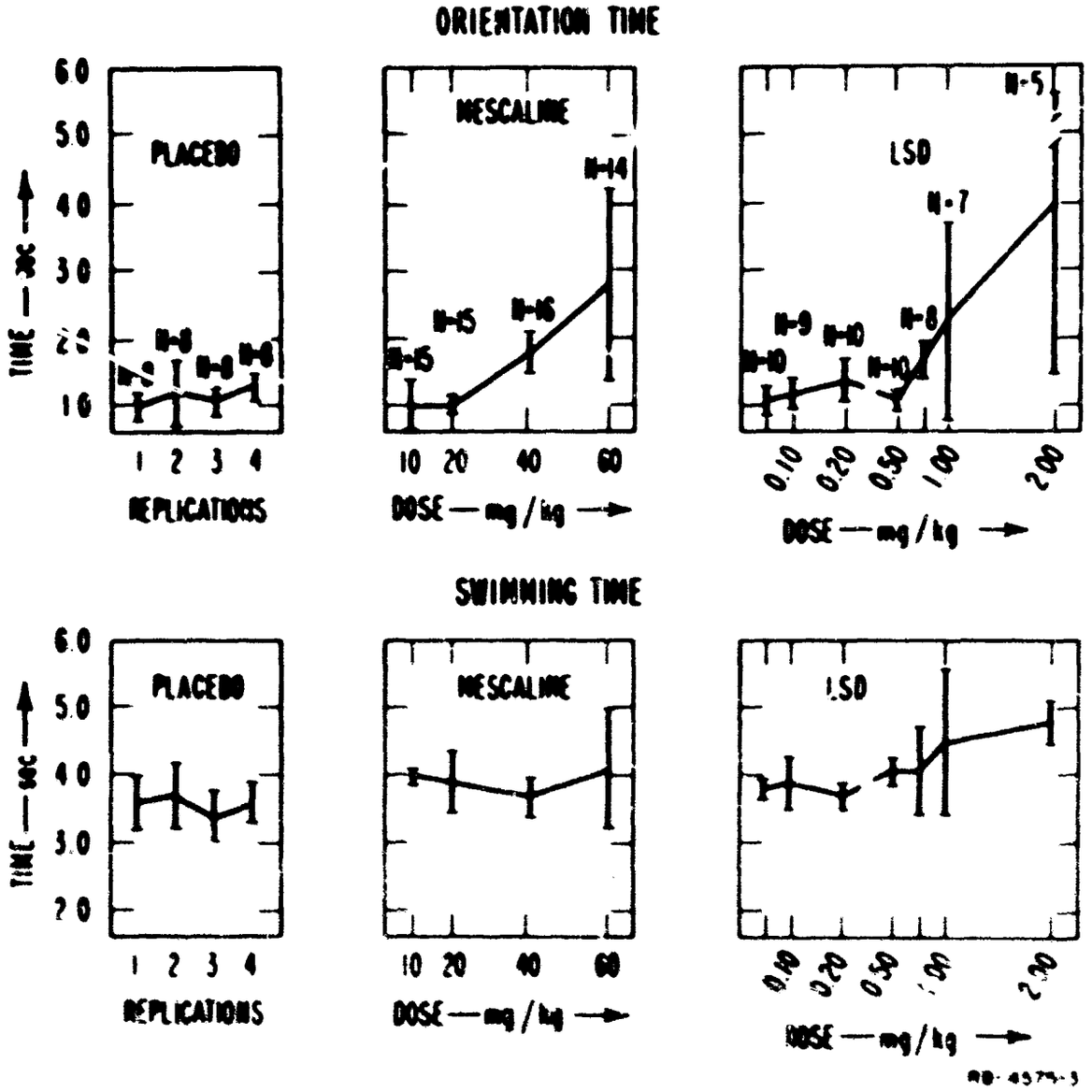

Figure 8. Effects of Mescaline and LSD-25 on Swimming Performance of Rats in the Underwater Swim Alley

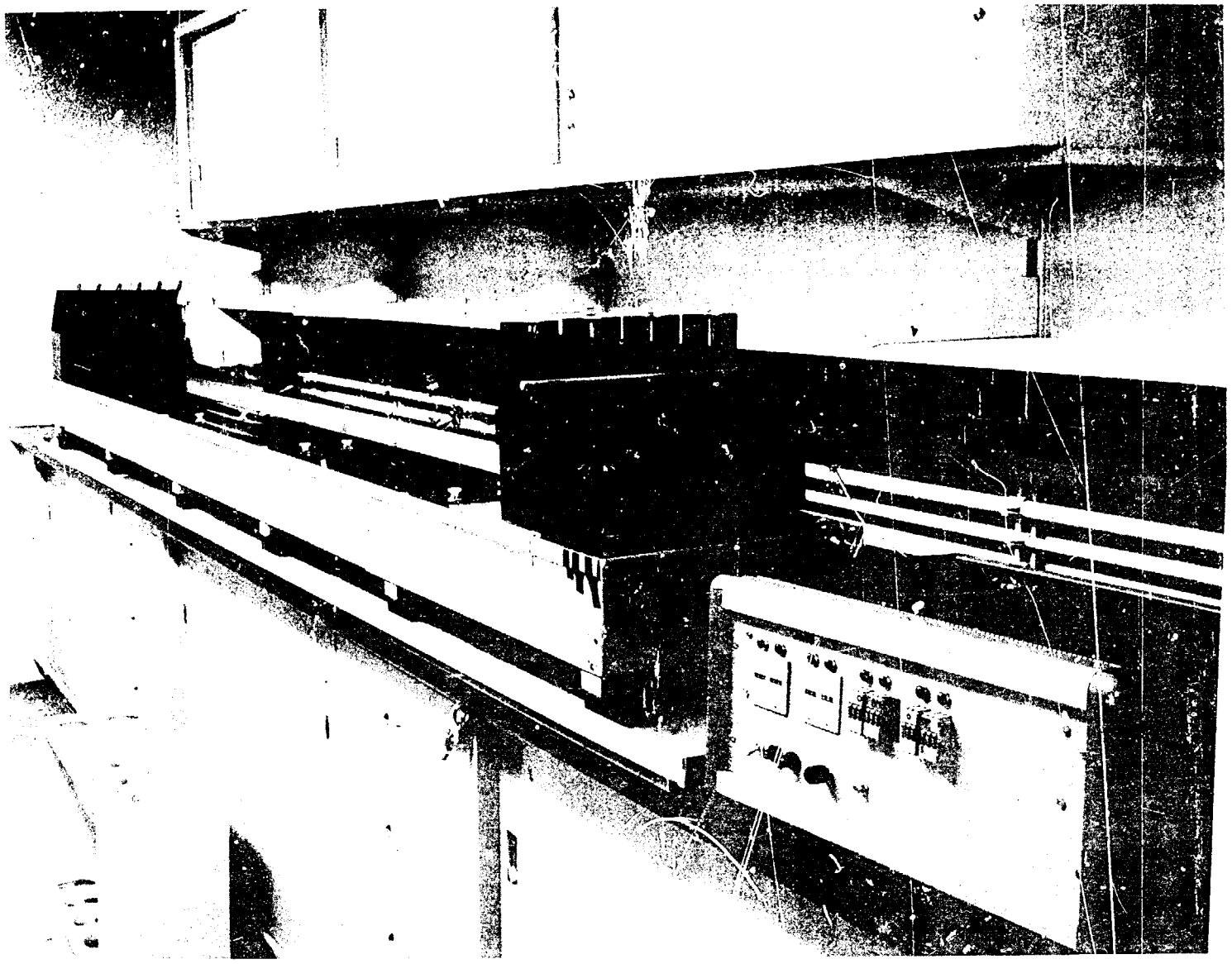

Figure 9. Four-Channel Underwater Swim Alley

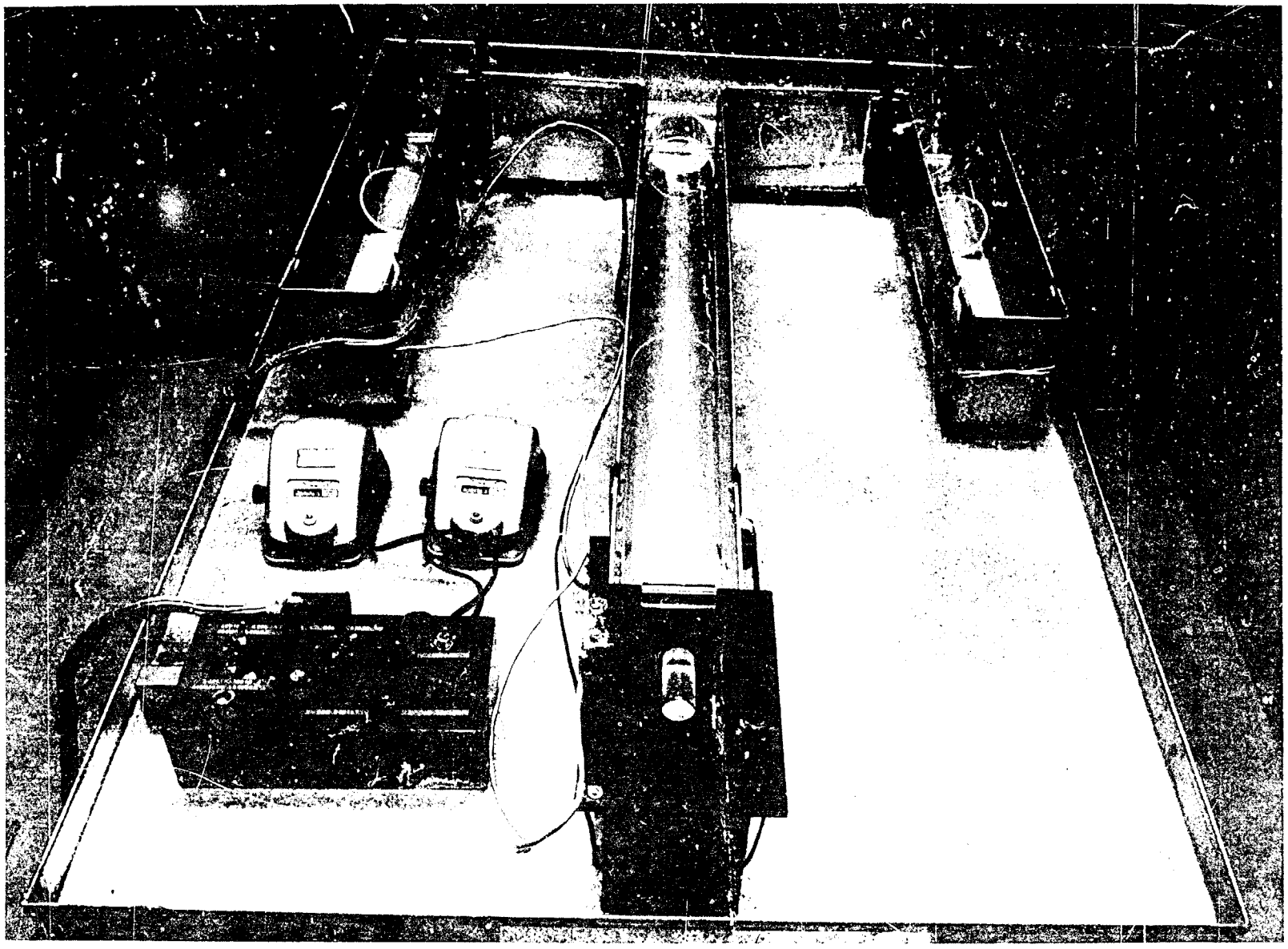

Figure 10. Underwater Swim Maze

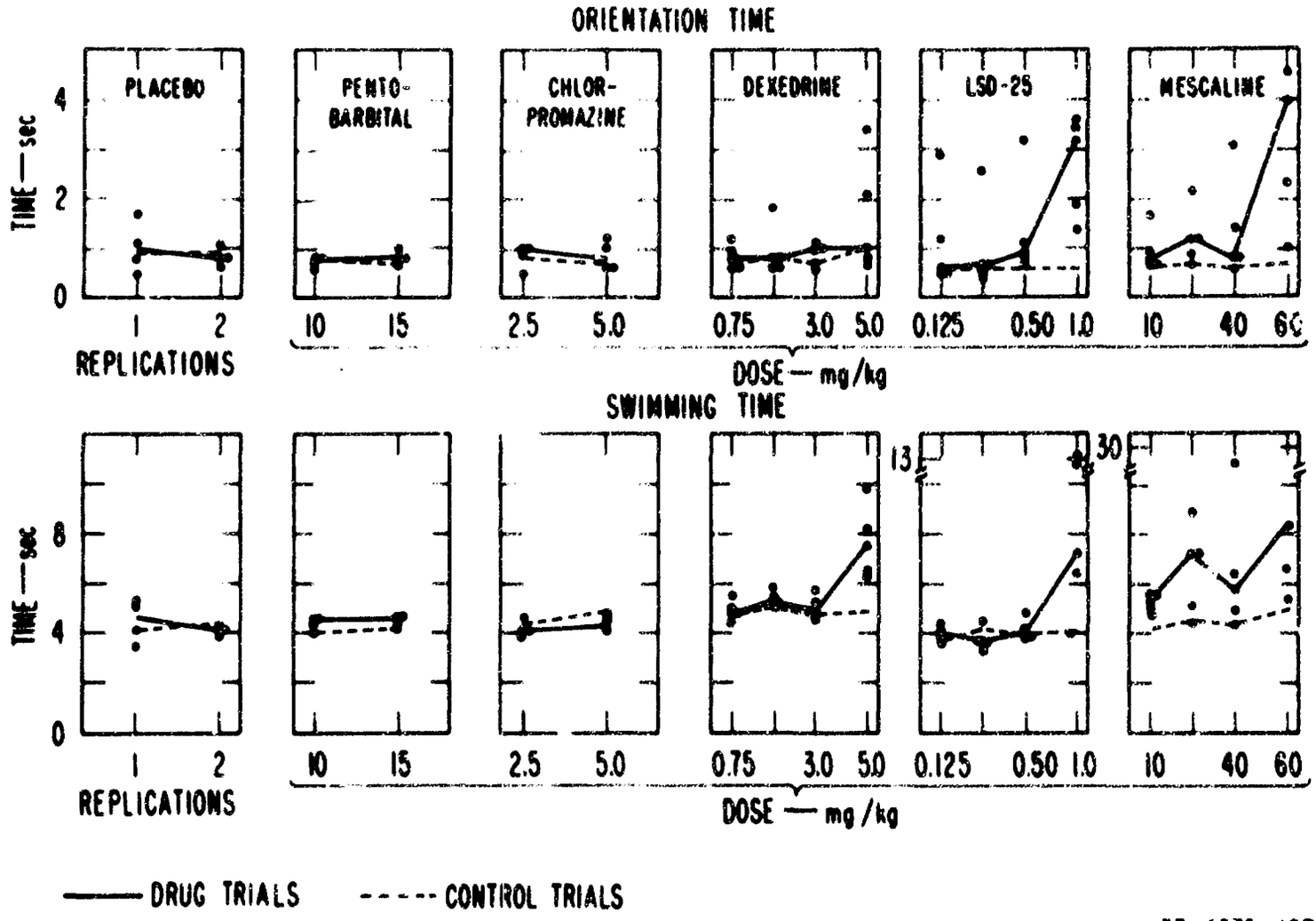

Figure 11. Effects of Standard Reference Compounds on Swimming Performance of Rats in the Underwater Swim Maze

(Each point is for a single animal)

The errors are shown in table III. Note the absence of errors for all compounds except those known to produce visual-perceptual disturbances in man. Even though the frequency of errors is low, we tend to place considerable significance on them because of their almost-complete absence with a placebo or under other drug conditions.

The Measurement of Spontaneous Motor Activity.

Special circuits and equipment have been designed for measuring spontaneous motor activity in a chamber that senses floor displacement. Although the present chamber was designed for the rodent and other small animals, any reasonably small animal (including primates) may be tested; all that is required is the construction of a chamber large enough to house the species.

The rodent chamber, shown in figure 12, consists of a circular plastic cage with a grill floor. Forces imparted to the floor by a moving animal are sensed by a displacement-sensitive transducer mounted on the roof. The signals are amplified and applied to amplitude-discrimination circuits, which operate electromechanical counters or electronic counters. Several of these "quantifying" circuits may be adjusted to respond to different signal amplitudes (which correspond, of course, to progressively greater amplitudes of activity in the cage) to derive a spectrum, or distribution, of activity. Thus, the apparatus can give an estimate of the relative amounts of activity over a period of time. The upper limit of sensitivity is sufficient to detect the slightest tremor or movement.

Figure 13 shows the advantage of recording different intensities of motor activity. When data from both counters 1 and 2 are considered, differences between similarly acting compounds become evident. For example, 2.5 mg/kg of dl-amphetamine and 5 mg/kg of pipradol are indistinguishable from each other, on the basis of counter-1 data, but when counter-2 data are considered, the effects of these two compounds on activity are quite different. The figure also shows that the low doses, except in the case of pipradol, have a more stimulating effect on activity than the higher doses.

The Monkey Rough-Limits Test.

The Monkey Rough-Limits test (MRL) was developed to provide a rapid evaluation of a large number of compounds for incapacitation effects. In addition, the MRL has proved useful for establishing dose levels appropriate for use in test procedures that require considerable training, such as the Wisconsin General Testing Apparatus (WGTA).

Table III. Brightness-Discrimination Performance of Rats in Underwater Swim Maze

Compound	Dose, ip	No. of animals*	No. of animals making:		Remarks
			One error	Two or more errors	
	mg/kg				
Saline	–	22	0	0	–
Pentobarbital	15	5	0	0	–
Chlorpromazine	5	5	0	0	–
Dexedrine	5	5	0	0	–
LSD-25	1	5	1	0	–
Mescaline	60	5	1	0	One animal failed to complete the test
BZ	10	4	1	0	–
DMT (N,N-dimethyltryptamine)	8	4	2	0	One animal failed to complete the test
	4	4	1	0	–
NIH 7607	0.0125	10	1	1	One animal failed to leave the start box
	0.00625	10	1	0	–

* For each compound, the same animals were tested at the different doses shown; 48 hr of rest and a control retest preceded each test at a different dose.

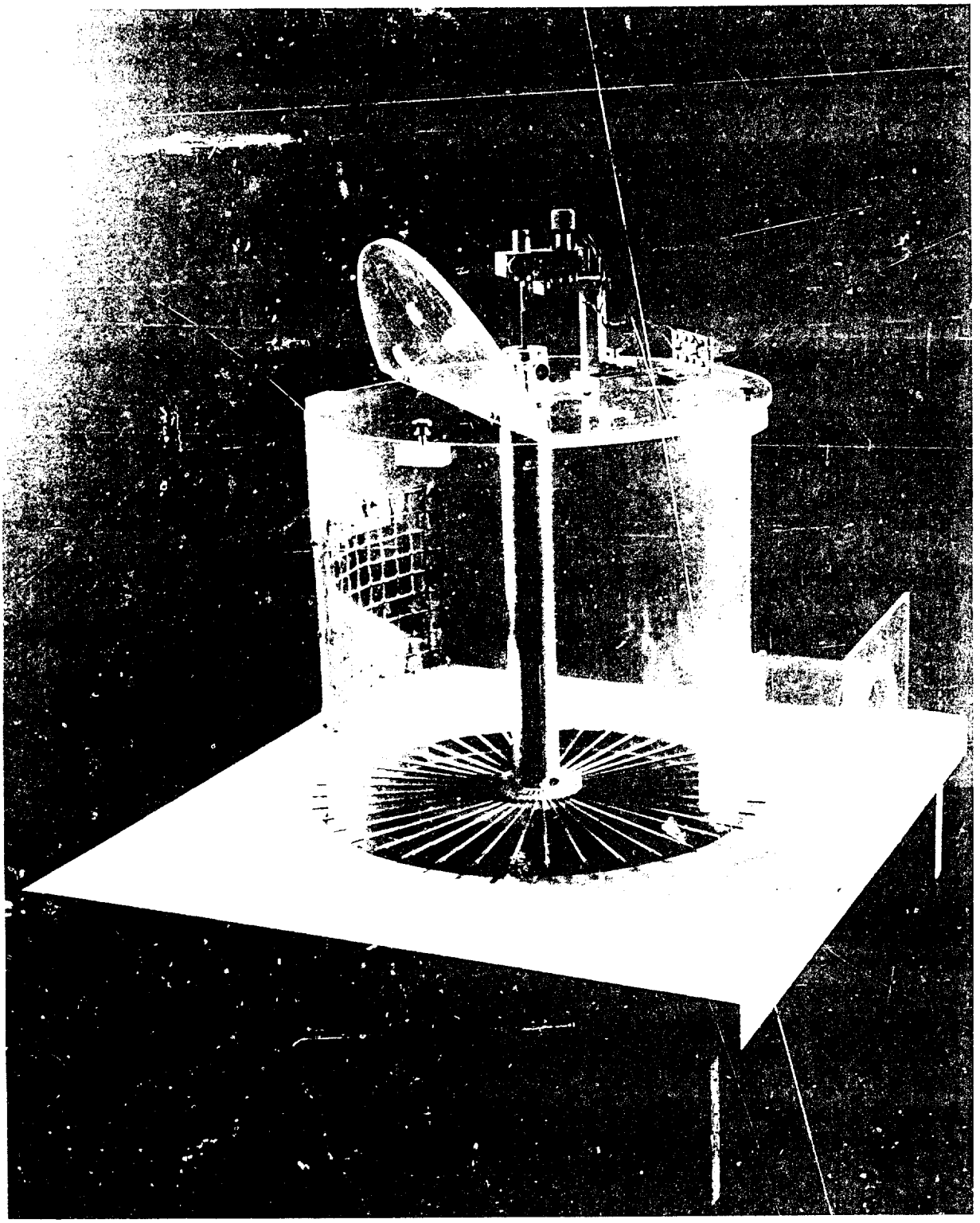

Figure 12. Chamber for Measuring Spontaneous Motor Activity of Rodents

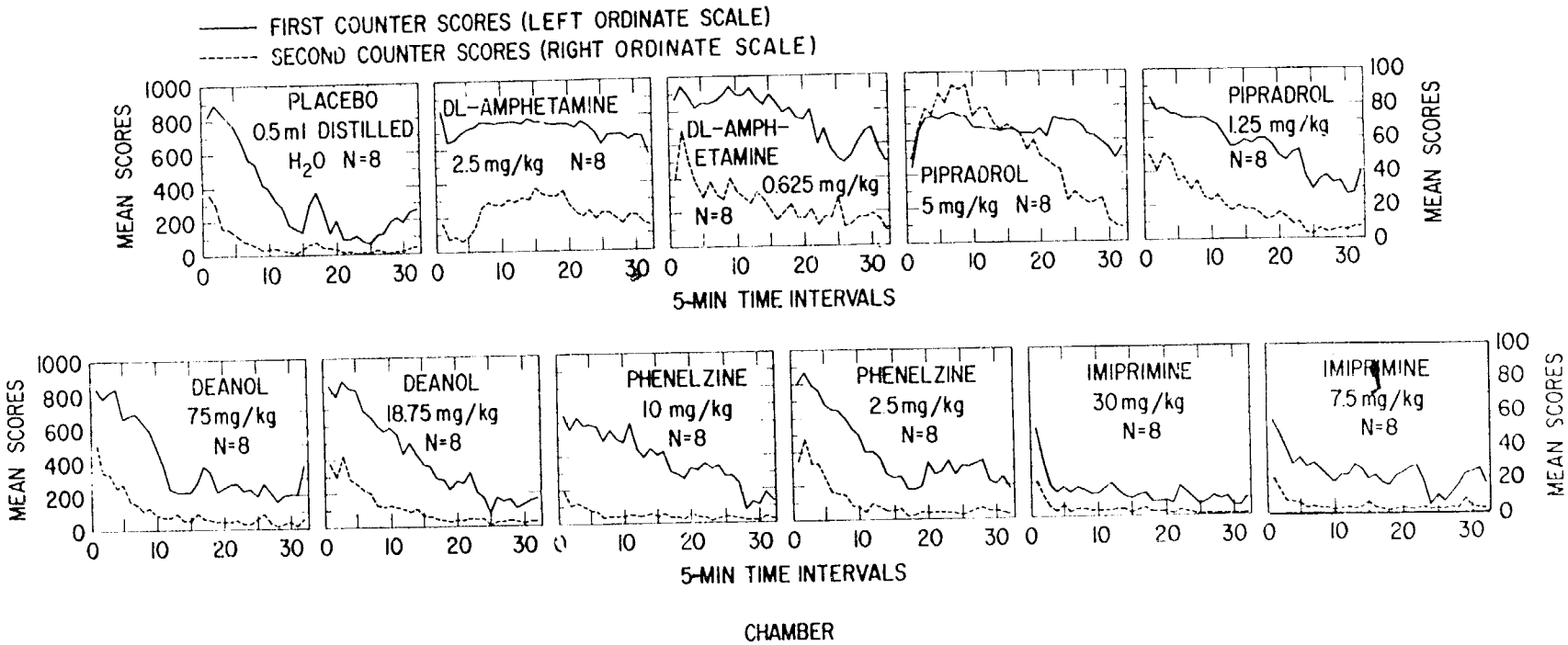

Figure 13. Distribution of Scores of 5-min Spontaneous Motor Activity on Counters 1 and 2 for Selected Compounds

(Scores on counter 3 were 0, with few exceptions, and are not shown)

The MRL includes 16 standardized observations of squirrel monkey behavior before and at specific intervals following intravenous (iv) injection of test compounds. These 16 behavioral items are rated on a scale from +3 to -3, with the midpoint, 0, indicating no effect, and are as follows: (1) activity - general frequency and level of movement when the animal is given access to the test room; (2) aggression - rated intensity with which an animal resists being handled by the experimenter; (3) startle - responsiveness to a loud unexpected noise or quick movement by the experimenter; (4) biting - as a response to restraint; (5) locomotion - smoothness and extent of movement about the test room; (6) coordination - ability of an animal to balance upon and to negotiate an 8-ft horizontal rope; (7) jumping - ability to leap 4 ft from the experimenter's gloved hand to the home cage; (8) evasion - vigor with which the animal avoids capture by the experimenter in an open-field situation; (9) strength - tenacity with which the monkey holds onto a cage when pulled away by the experimenter; (10) vocalization - qualitative or quantitative changes in sounds emitted by the animal; (11) regurgitation - dry heaves or vomiting; (12) pain sensitivity - response to pressure applied to the tail of the animal; (13) tremor - usually most noticeable in the limbs; (14) respiration - any change in normal breathing; (15) muscle tone - degree of muscular relaxation; and (16) excessive scratching - change in severity or frequency of scratching. In addition, provision is made on data sheets for recording other behavioral responses.

No special equipment or training is required for the MRL procedure. After an observation period of several minutes, a compound is injected iv into two squirrel monkeys at a standard dose level of 1 mg/kg. Compounds that are not effective at this dose are discontinued. When the dose of 1 mg/kg is effective, animals are tested at successively lower doses (0.1, 0.05, and 0.01 mg/kg) until the minimum effective dose (MED) is determined.

Each animal is observed and scored on the checklist during the first 5 min, at 5-min intervals for the next 15 min, and then at regular intervals for the next several hours. Then observations are made at 1-hr intervals until the effects of the injected compound have disappeared. All animals are further checked at 24 and 48 hr for possible residual effects.

Table IV shows the sensitivity of this procedure for detecting the MED's of a series of compounds. The drugs are listed in a descending order of effectiveness.

Table IV. Evaluation of Standard Reference Compounds by Squirrel Monkey Rough-Limits Test

Compound	Number of animals affected					
	1.0 mg/kg	0.1 mg/kg	0.05 mg/kg	0.01 mg/kg	0.001 mg/kg	0.0005 mg/kg
Sernyl	2/2	3/3	2/3	2/3	4/4	0/4
LSD-25	2/2	2/2	2/2	1/3	1/4	
BZ	2/2	3/3	3/4	1/2		
Haloperidol	2/2	3/3	4/4	0/3		
Morphine sulfate	2/2	1/1	2/2	0/2		
Scopolamine	2/2	0/2				
Tremorine	2/2	0/2				
Arecoline	0/2					
Isonicotinic acid	0/2					
Dextrorphan tartrate	0/2					
Histamine	0/2					
Pipecolinic acid	0/2					

The Life-Space Chamber.

A preliminary experiment was conducted in a special chamber designed to evaluate behavior of the rat under simultaneously existing contingencies involving different motivational dynamics, different response patterns, and different sensory systems. The animals were trained to respond to any changes in ambient light, sound, or shock (the ambient condition for shock was 0 intensity) in order to receive water or food or to avoid painful shock to the feet, respectively.

Two test chambers were employed, both operating simultaneously from the control equipment. The chambers, shown in figure 14, are housed in sound-deadened, lead-lined boxes to minimize extraneous sound cues. The floor of each chamber is constructed of radial spokes that serve to transduce the animal's spontaneous movements into electrical signals; thus, activity may

be continuously monitored. In addition, the floor serves as a grid through which a noxious, scrambled shock can be delivered to the feet of the animal. A pole suspended from the ceiling of the chamber serves as an escape, or avoidance, perch; the weight of the animal displaces the pole slightly downward, thereby activating a microswitch that terminates the shock, conditioned stimulus or prevents the occurrence of the shock, unconditioned stimulus. A lever and pellet dispenser are provided on one side of the chamber and a drinkometer nipple on the other. Pressing the lever or licking the nipple supplies food (0.45-mg pellets) or water, respectively, during designated periods. Feeding and drinking periods are signaled by an increase in the intensity of a tone emitted from a loudspeaker or a light mounted in the ceiling of the chamber, respectively. The tone and light are kept at low ambient intensities during the nonresponse intervals. Impending shock via the grid floor is signaled by a low-level shock for 15 sec just prior to the onset of the painful shock.

Six male rats were used as subjects. After an initial food-deprivation period, they were taught in practice boxes to press a bar to obtain a pellet of food on a continuous-reinforcement schedule. They were also trained to drink water by licking the drinkometer nipple. The animals were maintained on a 22-hr food- and water-deprivation schedule and were then trained daily in the chambers until they responded to sizeable changes in the intensity of light, sound, or shock with the appropriate responses.

Visual, auditory, and somesthetic responses to a wide range of intensity changes were then evaluated by a varied presentation of changes in light, sound, or shock stimuli at several intensities ranging from below to well above threshold. Figure 15 shows the combined psychophysical response curves of the six animals to the shock, sound, and light stimuli used.

If shifts in response frequencies at the various intensities occur after drug administration (that is, certain compounds might tend to either enhance or degrade visual, auditory, or somesthetic sensitivity), such changes should be detected using this procedure.

After the baseline performance was determined, the effects of LSD-25, brom-LSD, phenipraxine, and a placebo (0.9% saline) were evaluated. Animals were given 1.0 mg/kg of the appropriate solutions ip just prior to being placed in the chambers. The testing session lasted for at least 100 min after the injections, during which time approximately 50 sound, light, or shock stimuli were presented.

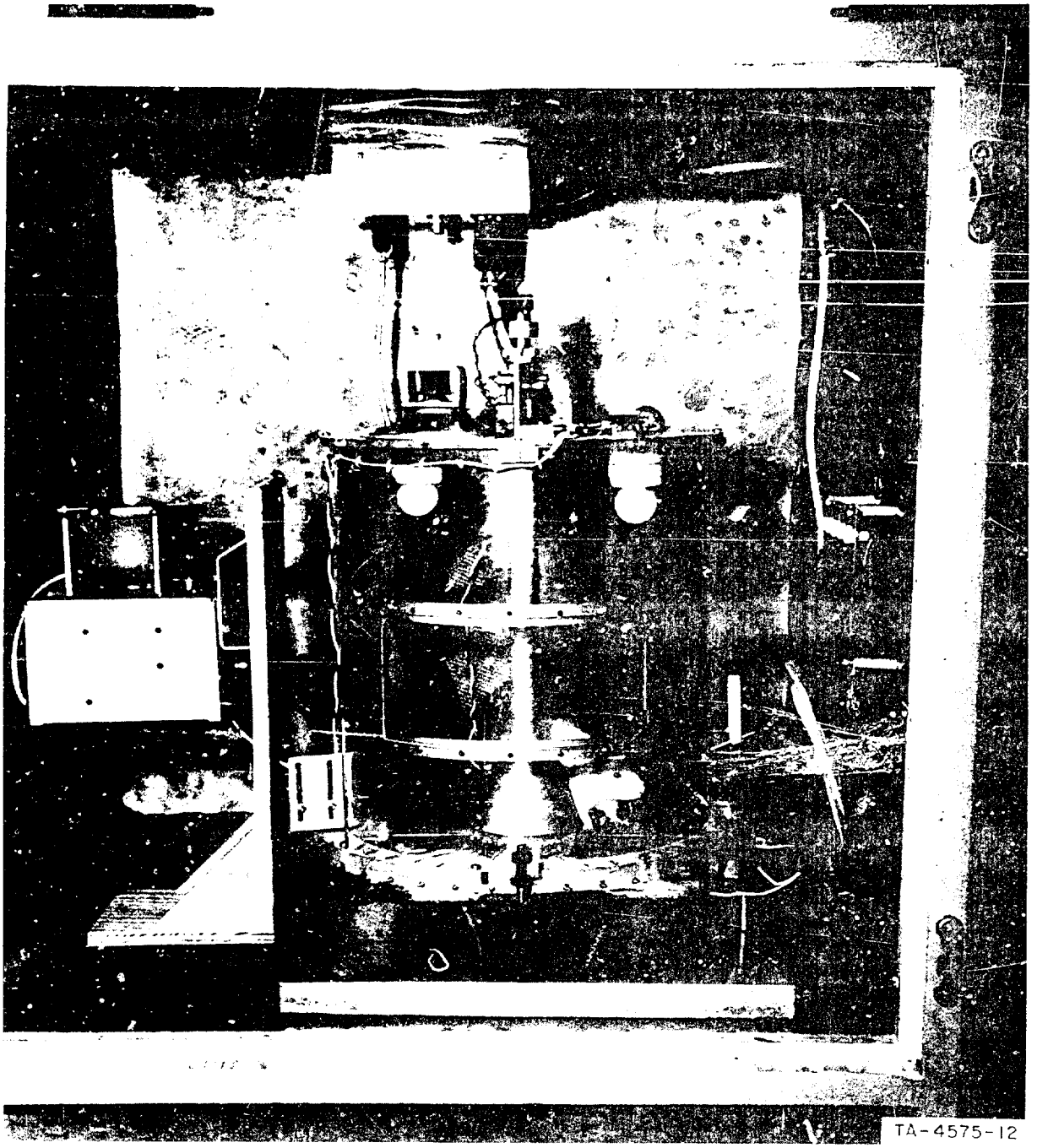

Figure 14. Life-Space Chamber for Testing Rats

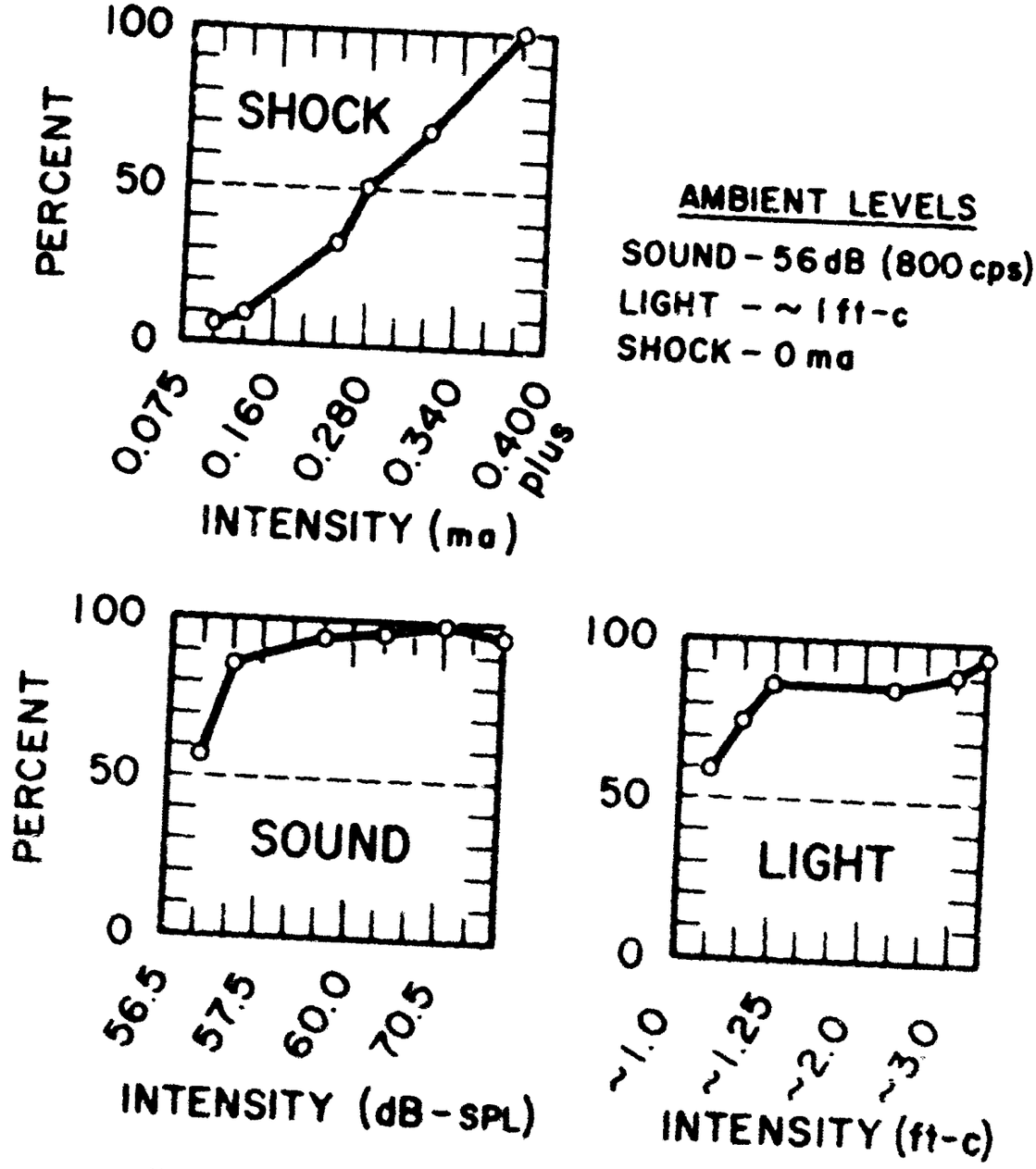

Figure 15. Psychophysical Response Curves of Rats
(Given as percent of correct responses)

Table V shows the results for animals given the highest doses used in these experiments. The data are expressed as the mean ratio of the percent of positive responses (that is, responses made during presentation of the stimulus) after injection of the drugs as compared with the percent of positive responses after injection of the saline. In other words, the animal's performance after being given a drug is compared with his performance after the placebo. A ratio of 1.00 indicates no change in performance, a ratio greater than 1.00 indicates an improvement, and a ratio less than 1.00 indicates a decrement.

Table V. Mean Ratio of Percent Positive Responses After Injection of Selected Compounds to Percent Positive Responses After Injection of Saline

Drug	Dose	No. of animals	Sound	Light	Shock
	mg/kg				
Saline	1.0a/	6b/	0.91	0.85	1.00
LSD-25	1.00	2	0.70	0.29	1.00
Brom-LSD	1.00	2	1.00	1.00	1.00
Pheniprazine	10.00c/	1	0.67	0.00	1.00
	10.00d/	1	0.95	0.86	0.93

a/ All solutions were given ip in concentrations such that all the animals received 1.0 ml/kg.

b/ Animals administered saline were also subjects in the drug experiments.

c/ This animal had received an injection of 5 mg/kg of pheniprazine the previous day.

d/ This animal had received an injection of saline the previous day.

LSD-25 caused a decrement in response to the tone and light, but had no effect on escape from shock. Responses of animals given brom-LSD, on the other hand, did not differ from those of controls administered saline. Pheniprazine, a monoamine oxidase inhibitor that is reported to cause retinopathology after chronic administration, caused a pronounced decrement in response to changes in illumination after two administrations of the compound, but not after only one.

One problem we encountered using the life-space approach was that we had no way of knowing whether failure to press the bar for food or lick the nipple for water indicated a change in appetitive motivation or an inability to detect the change in sound or light from the ambient levels. Another problem was that the animals had to be deprived of food and water in order to perform satisfactorily in this test situation. Also, the pole-jumping avoidance response was learned considerably faster than the responses of pushing the lever and licking the drinkometer nipple. Accordingly, we are currently attempting to condition a single response, pole jumping, to changes in light, sound, or shock level. The results of the single experiment we have performed are shown in figure 16.

In this experiment, the animals were trained to jump in order to avoid a 1.5-ma shock to the feet whenever the light, sound, or grid current changed from the ambient levels to the highest cue intensity previously used. After 20 days of training, the animals were matched and arranged into three groups. The groups received saline, 1 mg/kg of LSD-25, and 1 mg/kg of BOL-148 (5-bromo-N,N-diethyl-d-lysergamide) ip, respectively, and 20 trials distributed over a 2-hr period were started immediately. LSD-25 depressed response to all three cues, whereas BOL-148 and saline had no effect. These results may have been due to the high dose of LSD-25 used; two of the LSD-25 animals were found dead the next day. We are currently trying lower doses to see whether LSD-25 will selectively depress response to the visual cue, but not to sound or shock.

The WGTA.

We trained squirrel monkeys (*Saimiri sciureus*) to make a size discrimination for a grape reward. The stimuli consisted of round plastic disks painted flat black and varying in size from 1.02 to 3.92 sq in. Size-threshold curves for each animal were determined through the use of the psychophysical method of constant stimuli. The threshold curves are shown in figure 17.

From these data, easy and difficult discriminations were identified for use in the drug-testing phase; the easy discrimination was defined as that resulting in over 90% correct responses and the difficult, between 70% and 80% correct responses. Since some animals performed below 90% on the 1.48:1 size ratio, the 1.96:1 size ratio was designated as the easy discrimination. All animals had achieved at least 90% correct responses on this discrimination before threshold testing was initiated.

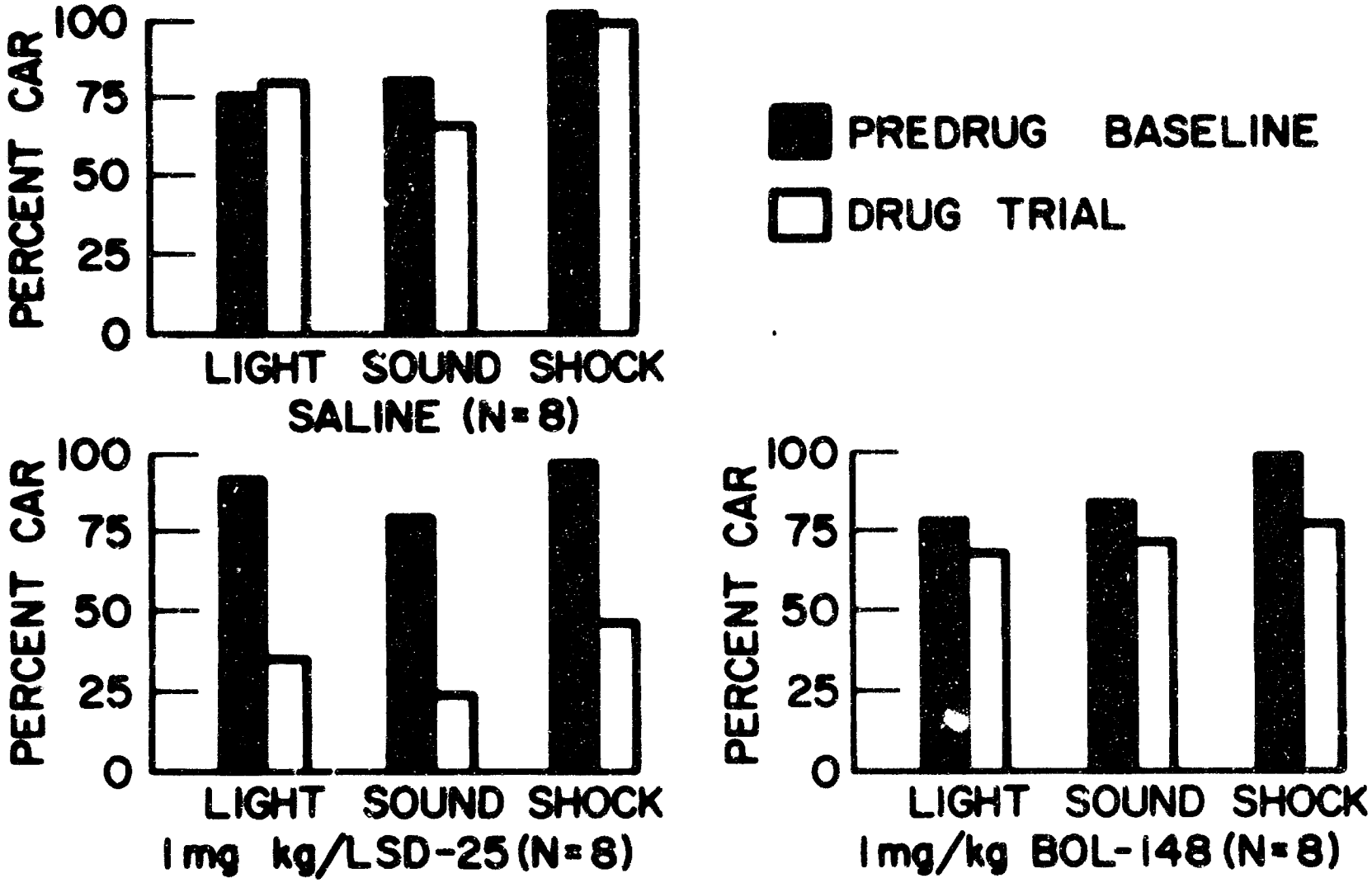

Figure 16. Effects of Drugs on Tests Involving Changes in Shock, Sound, and Light Stimuli

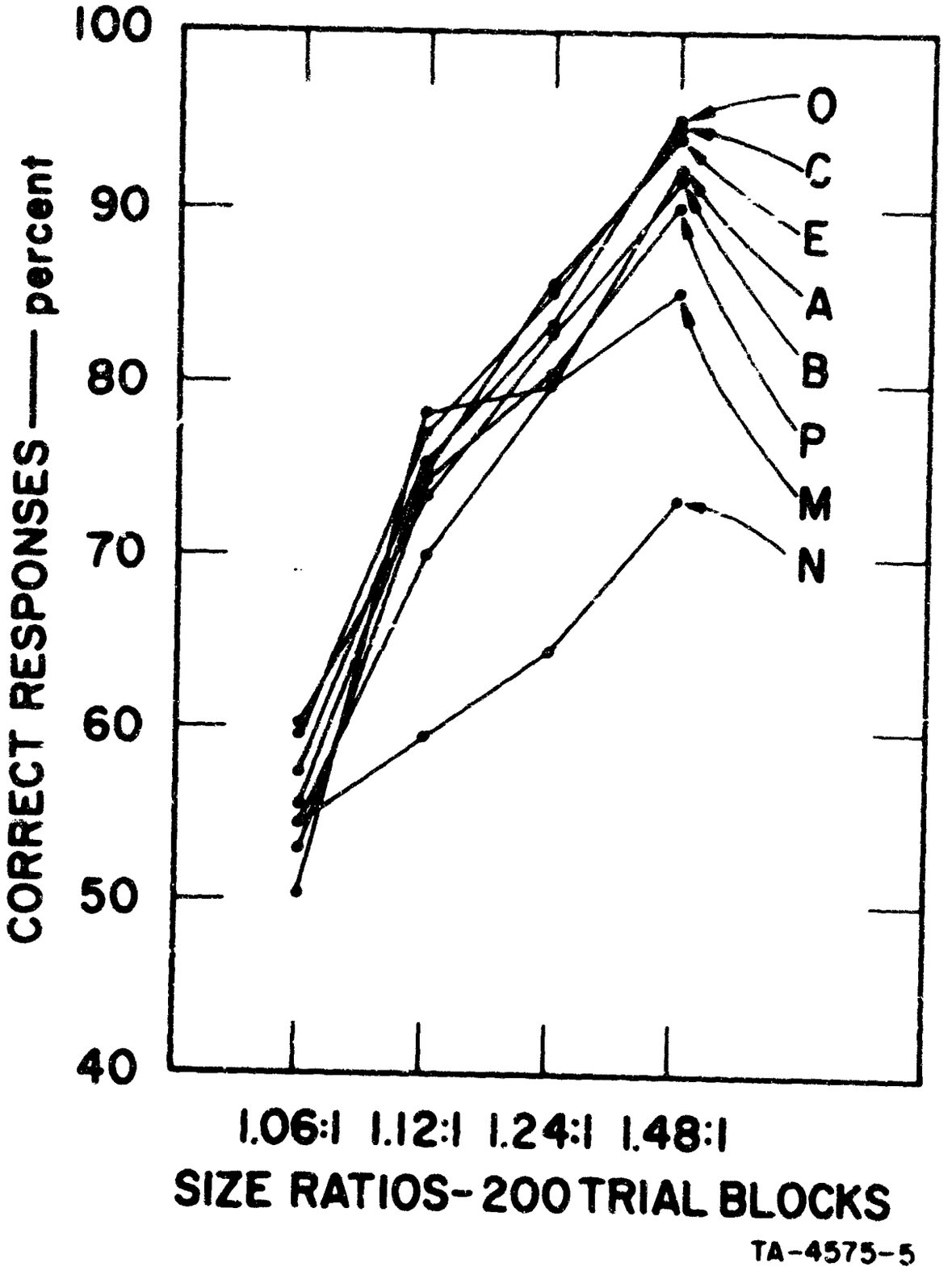

Figure 17. Size-Difference Threshold Curves for Eight Squirrel Monkeys

Table VI shows the effects of four reference compounds on easy and difficult discriminations. The data show that, with the exception of BOL-148, which was used as a control compound for LSD-25, the difficult discrimination was selectively affected in all but one animal by from 0.01 to 0.10 mg/kg of the compounds evaluated. The easy discrimination was also affected by Sernyl and BZ. These results demonstrate that this procedure is sensitive to relatively low doses of compounds and should prove useful for detecting compounds that may influence visual processes.

Table VI. Disruptive Doses of Standard Compounds on Easy and Difficult Size Discriminations in the WGTA

Drug	Monkey	Disruptive dose*	
		Easy discrimination	Difficult discrimination
		mg/kg	
Sernyl	A	0.02	0.02, 0.01
	N		0.05
	P		0.02
BZ	E	0.10	0.10
	M		0.01
LSD-25	A		0.01
	C		0.04
	M		0.02
	N	(No effect up to 0.25)	
	P		0.02
BOL-148	B	(No effect up to 0.50)	
	E**	(No effect up to 0.10)	
	O	0.20	0.20

* The drug was considered disruptive if the discrimination response changed at least 15% from baseline.

** Use of animal was discontinued because of suspected illness.

I have stressed method development and have given a cursory idea of the approaches we have been using to sharpen the discriminatory power of our drug-evaluation procedures. Our underlying philosophy has been that psychopharmacologists probably have settled too early on too few methods and that this trend needs to be reversed in order to increase the probability of developing test procedures with more predictive power.

DISCUSSION

Question: Inaudible..

Dr. Otis: Surprisingly, rats do quite well under water. This is not true of mice, incidentally. They drown quite readily. But rats can stay under water for up to 1 or 1-1/2 min without resurfacing. We very seldom lose one from drowning. In describing the training procedure, I left out a lot of detail. Initially, when we train rats in the underwater tests, we release them very close to the escape hole. Then we just keep moving them back to the starting point. But it only takes two or three trials for them to find out what is expected of them, and then they perform adequately. We use a 40-sec underwater criterion. If the animal is having difficulty during drug testing and he doesn't show up at the escape hole within 40 sec, we simply retrieve him (our tubing is cut so we can lift out any piece of it). We have a very low mortality rate; we lose about 1 in a 100.

SIMPLIFIED CORTICAL ELECTRODE FOR RECORDING BRAIN ELECTRICAL ACTIVITY IN RESTRAINED ANIMALS

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Experimental Medicine Department
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Edgewood Arsenal

EEG recordings of the electrical activity of the brain of animals in behavioral and physiological studies are being employed with increasing frequency. This is especially true in studies where the behavioral and physiological changes are drug-induced. By recording the EEG of the animals, the investigator is better able to clarify the role of the central nervous system (CNS) in these changes. These studies are being performed on anesthetized as well as restrained, unanesthetized animals. In many situations, however, it is usually necessary to obtain measurements in a large number of animals to clearly elucidate the effects of experimental manipulations. Unfortunately, the conventional techniques for the construction and implantation of cortical electrodes, in both chronic and acute preparations, require a great expenditure of time and the labor of skilled individuals. Reviews of various types of electrodes and implantation are given in other literature.**,† It is important, therefore, that simplified procedures for the preparation and installation of recording electrodes be developed.

The method described in this report is concerned with the preparation of animals (cats, dogs, and monkeys) for recording electrocortical activity in chronic or acute studies of anesthetized or unanesthetized animals. The advantages of this method include the simplicity of materials, the ease and rapidity of preparation and implantation, and the excellent quality of the EEG's obtained.

Materials

The materials used consist of two inexpensive items, Nu Way snap studs and snap-on fasteners (obtainable from Allied Electronics, Chicago, Illinois). These items are electrical components normally used to make or

* Presented by Mr. Montanarelli.

** Bures, J., Petran, M., and Zachar, J. Electrophysiological Methods in Biological Research. Academic Press, New York, New York. 1960.

† Delgado, J. M. R. In: Electrical Stimulation of the Brain Sheer, D. E., ed. University of Texas Press, Austin, Texas. 1961.

break connections in low-voltage dc circuitry. The snap studs, which are screwed into the skull of the animal, are used as the cortical electrodes. The connections between the snap stud (attached to the animal) and the EEG (the recorder) are made with a vinyl-covered, 18-gage, stranded conductor. This conductor has a Nu Way snap-on fastener crimped to one end and a banana or pin-jack soldered to the other end. A schematic drawing of these items is shown in figure 18.

Procedure.

The animal is anesthetized and held by a stereotaxic instrument. The head is shaved and sterilized with Merthiolate, and a midline incision is made. The length of this incision is dependent on the number of electrodes to be implanted and the areas from which recordings are to be obtained. The scalp is reflected, and the cutaneous muscles are separated from the skull. The points selected for insertion of the snap studs are marked and holes are drilled to the surface of the dura using a 3/32-in. drill. Care must be taken to insure that the dura is not punctured or damaged in any way. The holes are tapped (No. 6-32), and the snap studs are screwed into the bone to the dural level. At this point, the procedure is completed for an acute study. Figure 19 represents the preparation of a dog for an acute study using the described procedure. Control records can now be taken from the animal by connecting it to the recorder.

For the chronic preparation, several more steps are required. The first of these steps requires the fixation of the studs to the skull with dental acrylic cement (Yates Manufacturing Company, Chicago, Illinois). During this cementation, it is imperative that the area be free from blood or cerebral spinal fluid to insure the adhesion of the cement to the skull. After the cement has hardened, the scalp is joined to cover the snap studs. A small incision (8 to 10 cm in length) is made over each snap, and the scalp is pushed down around the studs, allowing them to protrude above the scalp. Figure 20 is a schematic representation of the chronic implant at this point in the procedure. The midline incision is then sutured, and the animal is administered an antibiotic and placed in its home cage. When performed under aseptic conditions, the entire operation takes approximately 60 min.

Discussion.

Utilizing the method for the chronic preparation, we have obtained excellent EEG's from cats, dogs, monkeys, and chimpanzees. The quality that is typical of these records can be seen in figure 21, which is an EEG of an anesthetized monkey recorded simultaneously with polygrams of respiration, blood pressure, and heart rate, and an electrocardiogram.

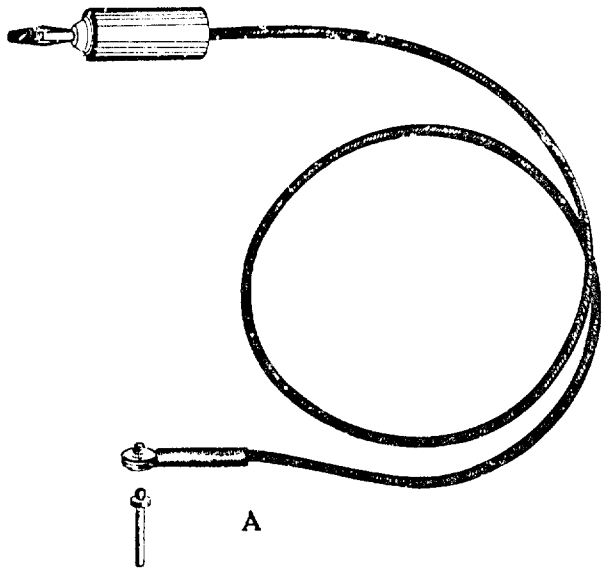

Figure 18. Schematic Drawing of Snap-On Fastener Connection Cable and Snap Stud for Use in EEG Recording of Electrocortical Activity of Anesthetized and Unanesthetized Animals

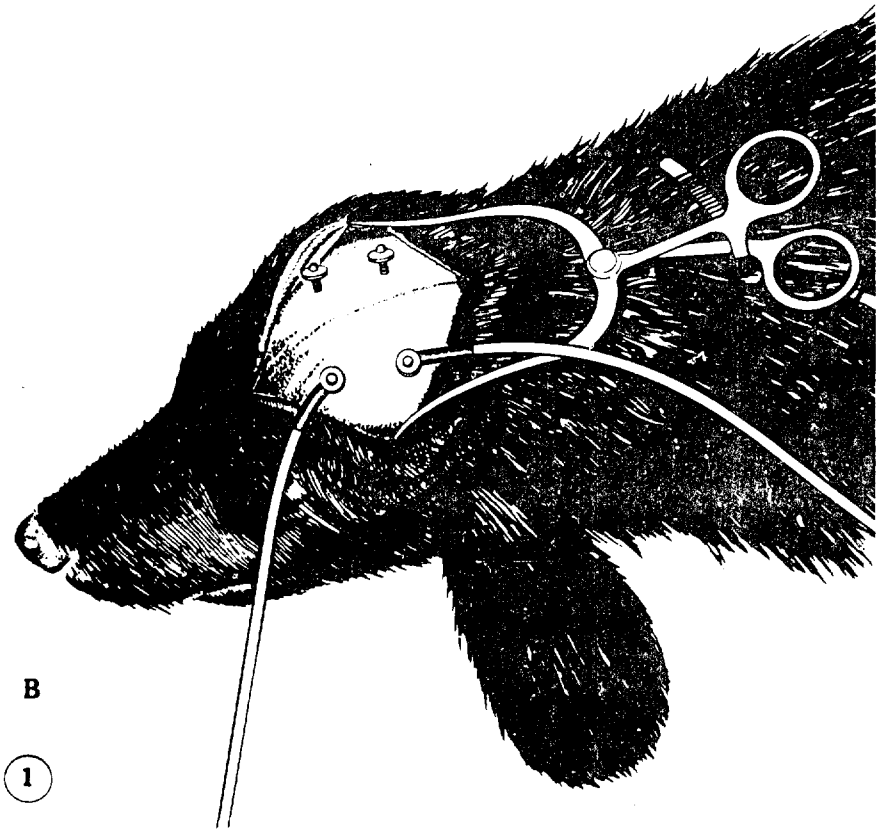

Figure 19. Illustration of Dog Preparation for EEG Recording of Cortical Activity

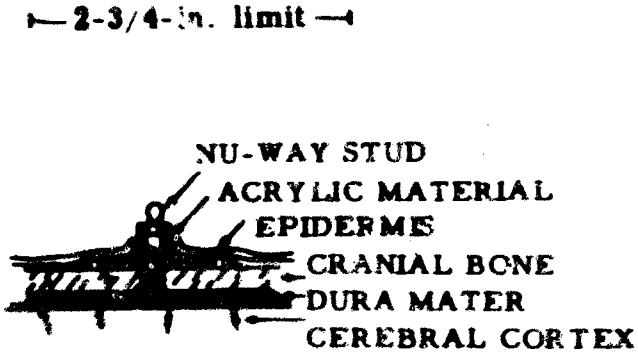

Figure 20. Cutaway View of Chronic Implant of Snap Stud in Animal Skull

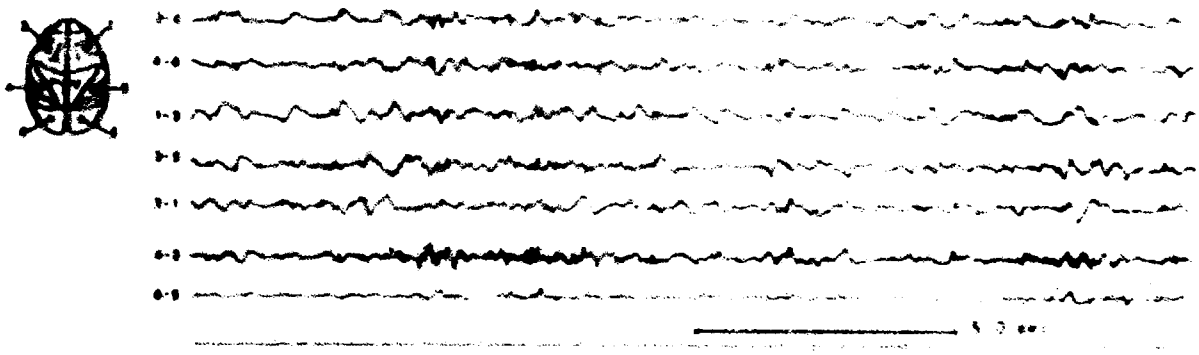

Figure 21. Recording on Grass Model IIID, 8-Channel EEG of Electrocortical Activity of Anesthetized Rhesus Monkey

(Calibration, 100 μv)

The chronic preparation has been successful in a series of 10 rhesus monkeys. Each animal had six implanted electrodes, one each in the frontal, association, and occipital areas of the right and left hemispheres. There have been no complications with these animals 6 mo postsurgery. The EEG's obtained from these monkeys while they were in an operant-conditioning, bar-pressing situation were excellent, with little or no 60-cycle interference or movement artifact.

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CHANGES IN BEHAVIOR AND ELECTROCORTICAL ACTIVITY IN THE MONKEY FOLLOWING ADMINISTRATION OF 5-HYDROXYTRYPTOPHAN (5HTP)

CPT Frank J. Macchitelli, Mr. Donald Fischetti,
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Edgewood Arsenal

During the past decade, substantial evidence has been accumulated that suggests that serotonin (5-hydroxytryptamine, 5HT) may have an important role in brain function and that changes in the serotonin levels of the brain can lead to gross changes in the behavior of men and animals.* In most instances, these behavioral effects have been qualitatively described. There have been only a few behavioral studies that have attempted to alter levels of brain serotonin and to correlate these changes with changes in behavior measured objectively.

One of the first of these studies was conducted by Aprison and Ferster,** who examined the effect of an increase in brain serotonin on the behavior of pigeons trained to peck a disk for intermittent food reinforcement. The elevation of brain serotonin was produced by injecting the precursor to serotonin, 5-hydroxytryptophan (5HTP), into the birds. This amino acid rapidly penetrates the "blood-brain" barrier where it is decarboxylated to form serotonin.† The results showed that the drug lowered the rate of responding in proportion to the amount of 5HTP injected.

In an experiment using rats trained on a discrete avoidance schedule, Joyce and Hurwitz‡ found that injections of 5HTP affected both the

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* Woolley, D. W. The Biochemical Basis of Psychoses. John Wiley & Sons, Inc., New York, New York. 1962.

** Aprison, M. H., and Ferster, C. B. Neurochemical Correlates of Behavior: I. Quantitative Measurements of the Behavioral Effects of the Serotonin Precursor, 5-Hydroxytryptophan. J. Pharmacol. Exptl. Therap. 131, 100-107 (1961).

† Udenfriend, S., Weissbach, H., and Bogdanski, D. F. Increase in Tissue Serotonin Following Administration of its Precursor 5-Hydroxytryptophan. J. Biol. Chem. 224, 803-810 (1957).

‡ Joyce, D., and Hurwitz, H. M. B. Avoidance Behaviour in the Rat After 5-Hydroxytryptophan (5-HTP) Administration. Psychopharmacologia 5, 424-430 (1964).

reaction time and the number of shocks received. Joyce and Hurwitz interpreted the behavioral change as being primarily depressant.

Hingtgen and Aprison* investigated the effect of decreased levels of brain serotonin on the behavior of pigeons trained on a reinforcement schedule similar to that used by Aprison and Ferster. The birds were given α-methyl-m-tyrosine (α-MMT), a compound that, in large amounts, differentially depletes serotonin and norephinephrine in brain tissue as well as in peripheral tissues.** According to these authors, the birds exhibited a marked decrease in response rate that was followed by a gradual return to normal within 9 hr.

The purpose of this study was to extend the quantitative behavioral work in this area by examining the effect of an increase in serotonin level on the behavior of monkeys trained to press a lever for food reward. The electrocortical activity of the monkeys was also recorded on an EEG simultaneously with behavior to determine if changes in performance after 5HTP administration are correlated with the EEG phenomena.

Subjects and Apparatus.

The subjects were three female adolescent rhesus monkeys (*Macaca mulatta*) weighing 3 to 5 kg. The reinforcement histories of the animals did not include the injection of other compounds. Six months prior

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* Hingtgen, J. H., and Aprison, M. H. Behavioral Response Rates in Pigeons: Effect of α-Methyl-m-tyrosine. Science 141, 169-171 (1963).

** Costa, E., Gessa, G. L., Hirsch, C., Kuntzman, R., and Brodie, B. B. On Current Status of Serotonin as a Brain Neurohormone and in Action of Reserpine Drugs. Ann. N. Y. Acad. Sci. 96, 118-131 (1962); Hess, S. M., Connamacher, R. M., Ozaki, M., and Udenfriend, S. The Effects of α-Methyl-DOPA and α-Methyl-meta-tyrosine on the Metabolism of Norepinephrine and Serotonin In Vivo. J. Pharmacol. Exptl. Therap. 134, 129-138 (1961); Sourkes, T. L., Murphy, G. F., Chavez, B., and Zielinska, M. The Action of Some α-Methyl and Other Amino Acids on Cerebral Catecholamines. J. Neurochem. 8, 109-115 (1961); Udenfriend, S., and Zaltman-Nirenberg, P. On the Mechanism of Norepinephrine Release Produced by α-Methyl Meta-tyrosine. J. Pharmacol. Exptl. Therap. 138, 194 (1962).

to the start of the experiment, silver-ball electrodes were implanted bilaterally and extradurally on the frontal, parietal, and occipital cortex of the animals. These electrodes were attached to a connector held on the skull by nylon screws and dental acrylic cement. The EEG was recorded on an 8-channel Grass EEG (Model III D).

Throughout the experiment, the animals were maintained at 80% of their free-feeding weights and were held in chair-type restraining apparatus. Attached to the chair support frame were a lever, a pellet hopper, a speaker, and a water bottle. The chairs were housed in semisoundproof cubicles (Lehigh Valley Electronics No. 1330C). The cubicles were placed in a sound-damped room into which masking white noise (68 db) was introduced during the experimental sessions. A closed circuit television system was used to observe the gross behavioral changes in the animals. The television monitors, the EEG, and all programing and recording equipment were placed in an adjacent room.

Procedure.

A multiple fixed-interval/fixed-ratio schedule (FI/FR, 5/30)* was used to provide a predictable performance pattern. The two components of the schedule were under the control of auditory stimuli (a clicker and a tone). The session began with the clicker on and the FR 30 component in operation. A reinforcement (D and G monkey pellet, 0.15 gm) followed every 30th lever press. After four such reinforcements, the tone started, and the FI component was in operation. The first lever press made by the animal 5 min later yielded a reinforcement. A limited hold procedure (lasting 15 sec) was used with the FI component so that a failure to respond after 5 min, 15 sec would cut short the FI component and produce the FR component again. The two components operated in this alternating manner until the end of the session.

All sessions lasted 5 hr, except on drug-administration days, when the animals were allowed to work until the control level of 250 reinforcements was achieved. The animals were tested at the same time each day, 5 days a week.

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* Ferster, C. B., and Skinner, B. F. Schedules of Reinforcement. Appleton-Century-Crofts, New York, New York. 1957.

Injections were made 1/2 hr after the start of the experimental session. Control saline injections were administered 2 days before and in volumes comparable to the drug injections. The compound dl-5HTP, in doses of 50, 75, or 100 mg/kg, was used to elevate brain serotonin levels in the animals. The compound was made up 1/2 hr before injection in 5% HCl adjusted to pH 7.3 with anhydrous 10% NaOH and expanded to volume with distilled water. Final injection volumes were kept to approximately 4.0 ml. All injections were made im into the posterior thigh muscles of the monkeys. Twenty control days intervened between successive drug tests to allow for recovery of normal performance and to avoid the effects of tolerance development.

Control EEG tracings were taken on drug, no drug, and saline control days and were begun 1/2 hr before the start of the experimental session. A recording was then taken every 15 min for a duration of 5 min until the end of the session. Behavioral data were simultaneously recorded on digital display counters and graphic cumulative recorders.

Results.

Gross Behavioral Changes.

At all doses, the animals exhibited gross behavioral changes characterized by agitation and excitement within 10 min after injection. These changes consisted primarily of champing movements of the mouth, shaking of the head, retching, and sometimes vomiting. Approximately 15 to 20 min postinjection, retching, vomiting, and head shaking ceased, but the champing movements persisted throughout the duration of the drug effect. At this time, the animals went into a period of relative inactivity, the length of which was a fun on of dosage. The animals alternated between periods of dozing with their eyes closed and staring blankly into space while in rigid positions.

Quantitativ Behavioral Changes.

Corresponding in time with the onset of the gross behavioral effects was an almost-complete cessation of responding during the FI component of the schedule. At this time, the response rate during the FR component was depressed considerably, and it deteriorated rapidly, becoming progressively slower with increasingly longer pauses after each reinforcement. The animals then ceased lever responding completely as they went into the period of inactivity described previously.

Following the period of inactivity, the animals did not immediately return to the control pattern of behavior. Sporadic pressing during the FR component was the first sign that an animal was beginning to come out of the inactive state induced by the injection. At this time, however, the animals usually dozed during the FI component. As the response rate during the FR component became progressively more steady, dozing during the FI component became less pronounced and gradually approached the control rate.

Figure 22 represents graphically the onset and recovery of an animal's performance after injection of various doses of 5HTP. The effect of the injections is expressed as the number of responses emitted cumulated against time. The control values include averaged data of sessions in which saline injections were made and noninjection sessions preceding the experimental ones. This figure summarizes the data for one animal and is illustrative of the effect of 5HTP on the other two animals.

A dose-response curve for each animal is shown in figure 23. Here, the behavioral effect is more simply expressed as the number of responses emitted per minute in 300 min. Zero on the abscissa represents an average of the data derived from both the saline injections made 2 days before 5HTP injection and the control noninjection sessions preceding the experimental ones. Examination of these figures shows that the behavioral effect of 5HTP increases approximately linearly with dose.

Electrocortical Changes.

The control electrocortical activity of the monkeys was characterized by low-voltage activity in the intermediate fast and β ranges when the monkeys' eyes were open and moderate voltage α-range activity when their eyes were closed.

One-half hour following the administration of 5HTP (at all doses), changes in the animals' electrocortical activity became evident. When the animals' eyes were open, the EEG exhibited an increase in voltage and slower activity, with the dominating frequency in the θ range. When the animals' eyes were closed, the electrocortical activity slowed down, exhibiting both θ and δ activity. The α and intermediate fast activity seen in the control tracings was almost completely absent. These changes in electrocortical activity were most prominent when the animals were behaviorally inactive

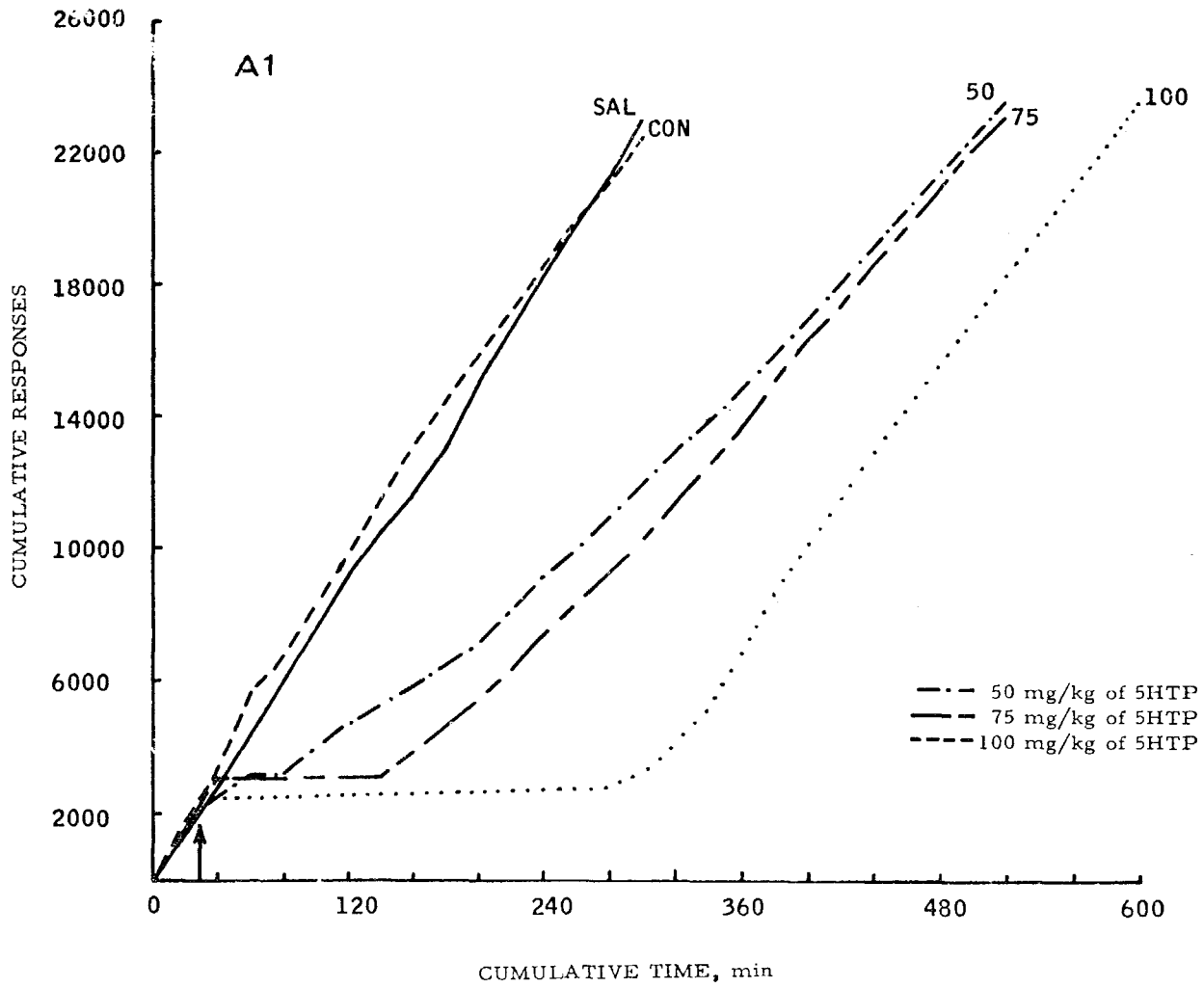

Figure 22. Number of Responses Emitted by Monkey A1 Cumulated Against Time After 5HTP Injections

(Saline and control curves represent averaged data collected preceding each drug administration; plots and doses of experimental sessions are marked on curve)

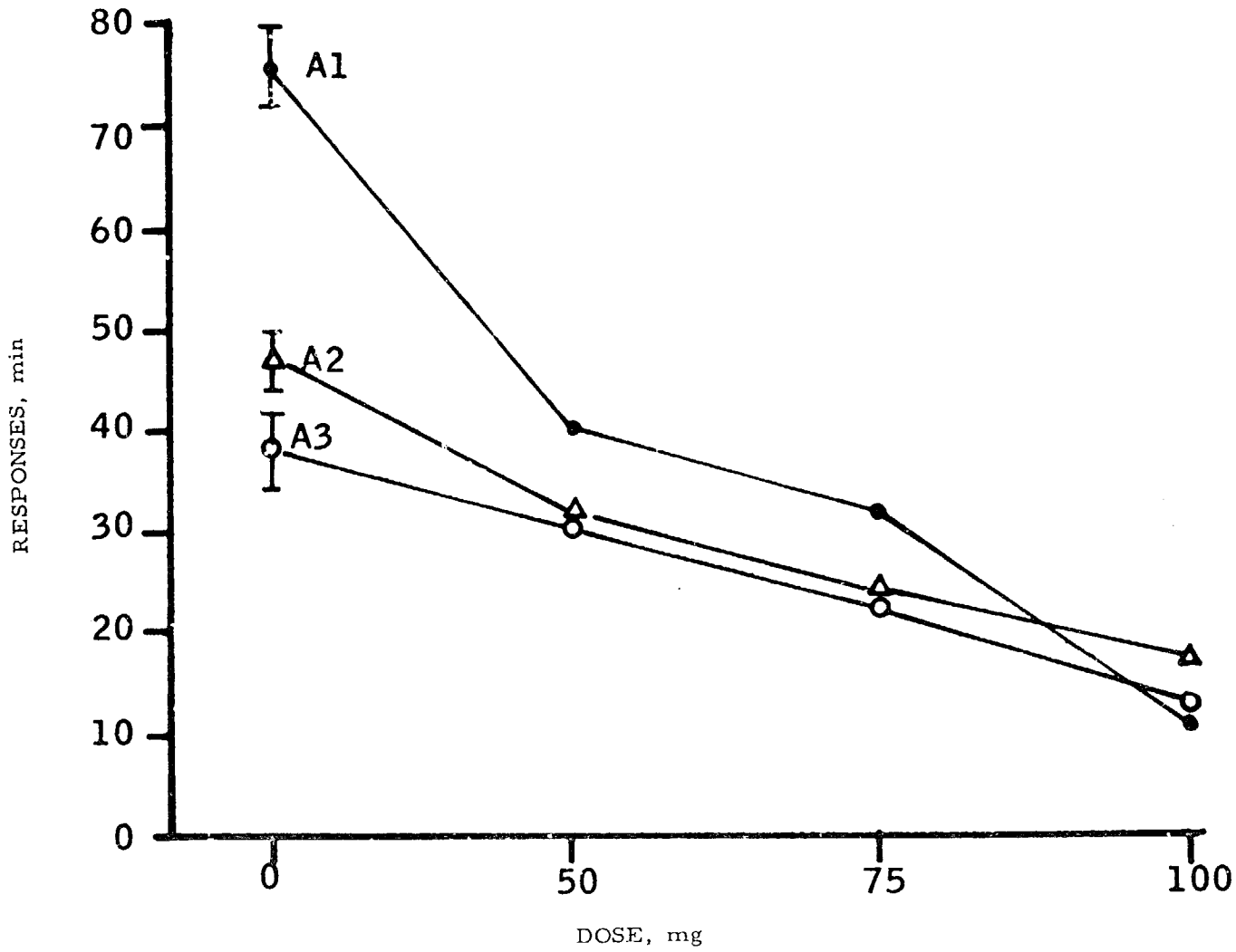

Figure 23. Effects of 5HTP on Response Rate of Monkeys A1, A2, and A3 During First 300 min (Control-Session Time)

(Standard error is represented by vertical lines)

When the monkeys began pressing the lever again, there was a corresponding change in the EEG. The voltage decreased, and there was a gradual return of the intermediate fast and the β-range frequencies. This type of activity continued to increase until the electrocortical activity returned to the control level. As the EEG recovered to the control level, there was a corresponding return in performance to the baseline.

A comparison of the control EEG's with those seen 1 hr after the administration of 5HTP (100 mg/kg) can be seen in figure 24.

Discussion.

The administration of 5HTP depressed lever pressing for a food reward. The magnitude and duration of the behavioral effect increased with dose. These findings are in agreement with other behavioral studies. Joyce and Hurwitz found that as the dosage of 5HTP increased, there was a general increase in reaction time and the number of shocks received by rats in a discrete avoidance situation. These results were obtained with very low doses (6.25, 12.5, and 25.0 mg/kg of 5HTP).

The results obtained by Aprison and Ferster in their study with pigeons are more comparable to those obtained in the present study because similar reinforcement schedules and dose ranges were used. The behavioral effects of 5HTP injections were quite similar in both studies, suggesting that the effect of the injections is the same in both species.

The gross behavioral changes observed in the monkey were similar to those observed by Aprison and Ferster in pigeons, by Costa and Rinaldi in rabbits,* and by Bogdanski and coworkers in cats and dogs.** The latter group found that at low or intermediate doses (5 to 30 mg/kg of 5HTP), the animals were at first alert but later appeared sedated. At larger doses (40 to 60 mg/kg), the animals showed widely opened eyes, a steady gaze into space, and, also, excitement and disorientation. All these behavioral changes were observed in the monkeys at one time or another. However, no agitation

* Costa, E., and Rinaldi, F. Biochemical and Electroencephalographic Changes in the Brain of Rabbits Injected With 5-Hydroxytryptophan (Influence of Chlorpromazine Premedication). Am. J. Physiol. 194, 214-219 (1958).

** Bogdanski, D. F., Weissbach, H., and Udenfriend, S. Pharmacological Studies With the Serotonin Precursor, 5-Hydroxytryptophan. J. Pharmacol. Exptl. Therap. 122, 182-194 (1958).

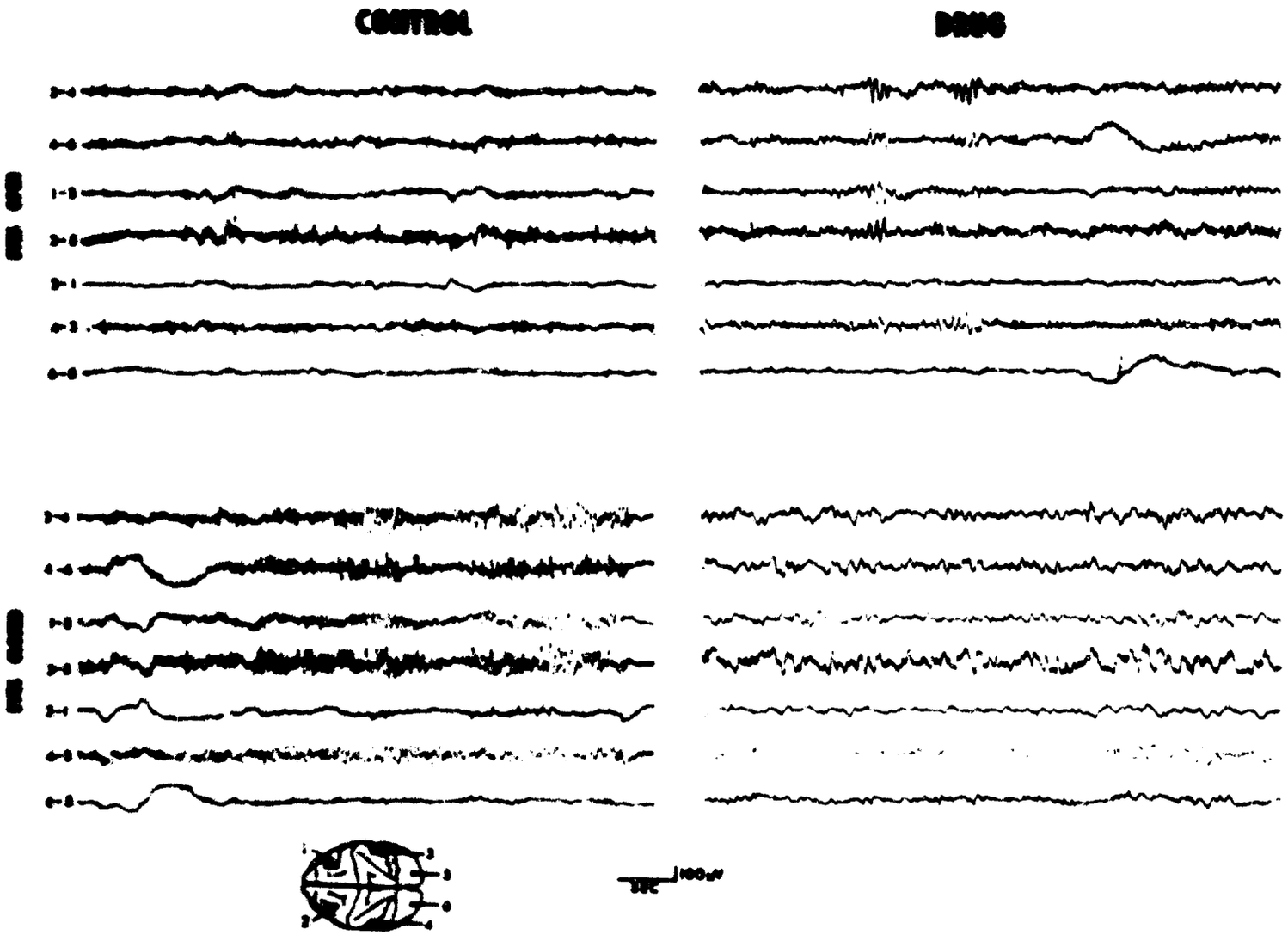

Figure 24. Comparison of Control EEG's and EEG's Obtained From Monkey A2 After 100-mg/kg Injection of 5HTP

or excitement was observed after the monkeys stopped pressing the lever. They appeared to be extremely lethargic, staring blankly into space or dozing. Their other movements were occasional champing. This pattern of behavior occurred at all doses. An increase in dose increased the magnitude and the duration of the effect but did not change its basic character.

The fact that Hingtgen and Aprison found similar behavioral results in pigeons after a depletion of serotonin does not necessarily contradict the results in this and other studies mentioned previously. In the present experiment, the injection of the serotonin precursor introduced the free form of serotonin in the brain. In the Hingtgen and Aprison experiment, most of the serotonin depletion caused by the injection of α-MMT was of the bound or inactive form. It is possible that, with both 5HTP and α-MMT, more free or active serotonin can be formed or released than in the normal state.* Another factor that must be considered is the possibility that α-MMT may cause anorexia. Hingtgen and Aprison's birds worked for a food reward. It has recently been demonstrated that α-MMT increased lever pressing in a continuous avoidance situation, but decreased food intake in rats.**

The EEG changes observed in the monkeys were similar to those seen by Costa and Rinaldi in rabbits within the first half hour after iv injection of 75 mg/kg of 5HTP. They observed monorhythmic, diffuse, high-voltage activity and a disappearance of cortical fast activity. These changes, however, were followed within the second half hour by an overall generalized depression of voltage. This diminution of voltage in the EEG was not observed in the monkeys and may be due to the difference in route of administration or the difference in species, or both, in the two experiments. In correlating the behavioral and EEG changes observed in the rabbits, Costa and Rinaldi noted that both changes occurred after the same period of latency (30 min) and had an almost equal period of duration (2 hr).

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* Aprison, M. H., and Ferster, C. B. Neurochemical Correlates of Behavior: I. Quantitative Measurements of the Behavioral Effects of the Serotonin Precursor, 5-Hydroxytryptophan. J. Pharmacol. Exptl. Therap. 131, 100-107 (1961).

** Carlton, P. L., and Furgiuele, A. R. Appetite Suppression Due to α-Methyl-m-tyrosine. Life Sciences 4, 1099-1106 (1965). Carlton, P. L. Behavioural Stimulation Due to alpha-Methyl-meta-tyrosine. Nature 200, 271 (1963); Scheckel, C. L., and Boff, E. Behavioral Stimulation in Rats Associated With a Selective Release of Brain Norepinephrine. Arch. Intern. Pharmacodyn. 152, 479-490 (1964).

In the present experiment, behavioral changes occurred approximately 20 min before changes in electrocortical activity became obvious. The changes observed, however, in the electrocortical activity of the monkeys first became obvious after the same period of latency (30 min) as in the Costa and Rinaldi experiment. This change in the EEG correlated with the onset of the period of behavioral inactivity in the monkeys. From this point on, as in the Costa and Rinaldi experiment, the recovery of performance and of electrocortical activity to the control level was correlated in time.

It is difficult to explain the difference in latency in onset of behavioral change in the two experiments, especially when there is agreement in results in other respects. Again, it might be due to the difference in species or route of administration, or both. The fact that the monkeys were engaged in a behavioral task at the time of the administration of the 5HT might also contribute to this difference. Also, Costa and Rinaldi depended solely upon visual observation of the rabbits. It is possible that the initial behavioral changes observed in the monkey were not obvious to visual observation in the rabbit. Since, in the present experiment, quantitative as well as qualitative measurements of behavior were obtained, it is possible to specify more exactly the onset of drug-induced behavioral changes.

Other studies are now in progress in our laboratory to further elucidate the effect of altered levels of brain 5HT on the behavior of monkeys.

Summary

Simultaneous measurements of the behavioral and electrocortical effects of the serotonin precursor, 5HTP, have been made in rhesus monkeys. Im injections of 50, 75, and 100 mg/kg of 5HTP depressed the monkeys' rates of responding in proportion to the amount of the compound injected. The changes in the electrocortical activity of the animals were correlated with the changes in their behavior.

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COMPARISON OF VARIOUS OPERANT-BEHAVIOR TECHNIQUES FOR PERFORMANCE-DECREMENT TESTING

Dr. Thomas R. A. Davis
Arthur D. Little, Inc.

Introduction.

The program at Arthur D. Little was instituted with the objective of using a variety of operant-behavior techniques in order to evaluate candidate agents in primates following evaluation with screening techniques in other animal species. The approach was based upon developing new techniques or using existing techniques, each of which would represent a particular function as its primary behavioral component. The program was in operation only 15 mo, including time taken for training the animals.

Methods.

Several techniques were used in this program with each technique having a predominating factor that involved a particular functional biological component. Two of these are commonly used operant-behavior schedules with only minor modifications; namely, a multiple fixed-interval/fixed-ratio (FI/FR, 3/30) schedule (figure 25) and a Sidman-type, shock-avoidance schedule with no visual or auditory stimuli (figure 26).

A tracking-type schedule (figure 27) that uses multiple levers and visual stimuli on a reinforcement schedule was instituted in an attempt to measure reaction time, but this schedule turned out to be similar to an FR schedule, so it was discontinued.

A motor-performance schedule (figure 28) was developed using a vertical pole, 2 m long, with a lever and a feeder at the top, and another lever at the bottom. In order to obtain a reinforcement, the animals had to operate both upper and lower levers on a variable-ratio schedule. Since the distance of vertical traverse and the animal weights are known, the work done during a session can be calculated. Also, the time taken on upward traverse was measured and, from this, work intensity could be calculated.

Another schedule was developed to measure the functions of coordination, ataxia, and muscle weakness (figure 29). The animal was required to hold a pinged stylus in a 2-cm hole without touching the edge. A successful hold for 7 sec produced a reinforcement. Failure within 7 sec returned the requirement for the duration of hold back to 7 sec. This schedule, by itself,

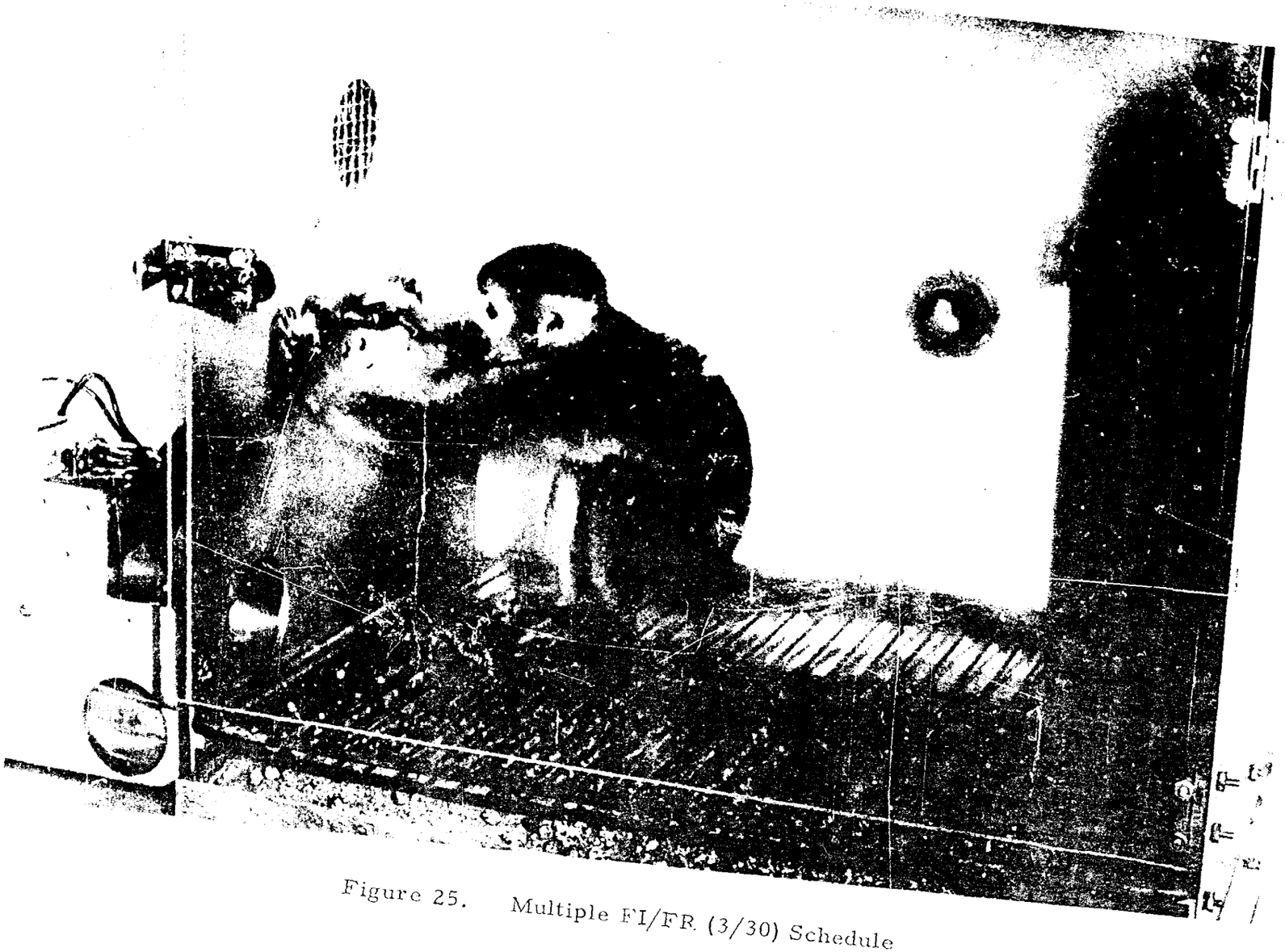

Figure 25. Multiple FI/FR (3/30) Schedule

Figure 26. Sidman-Type, Shock-Avoidance Schedule

Figure 27. Tracking-Type Schedule

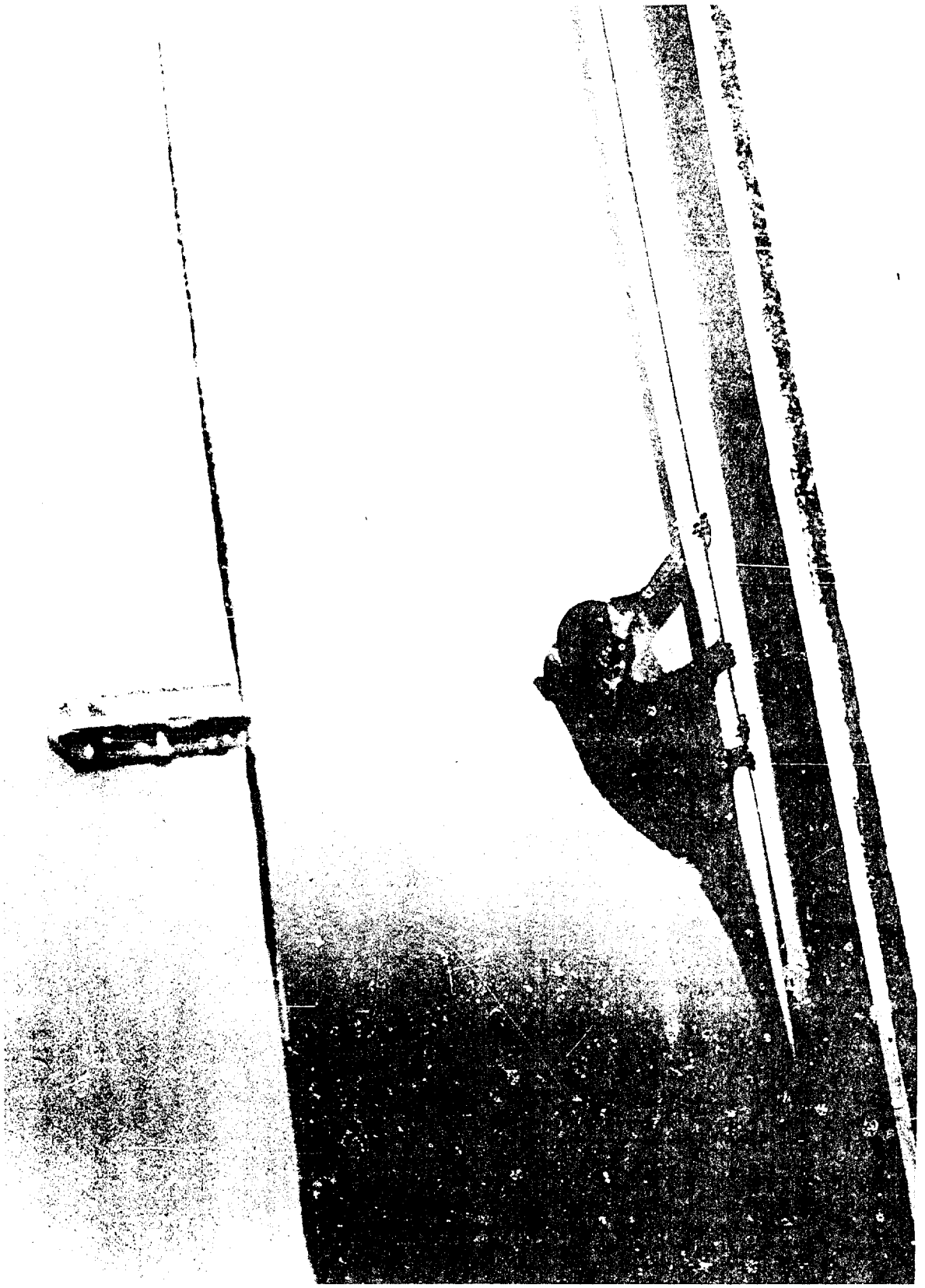

Figure 28. Motor-Performance Schedule

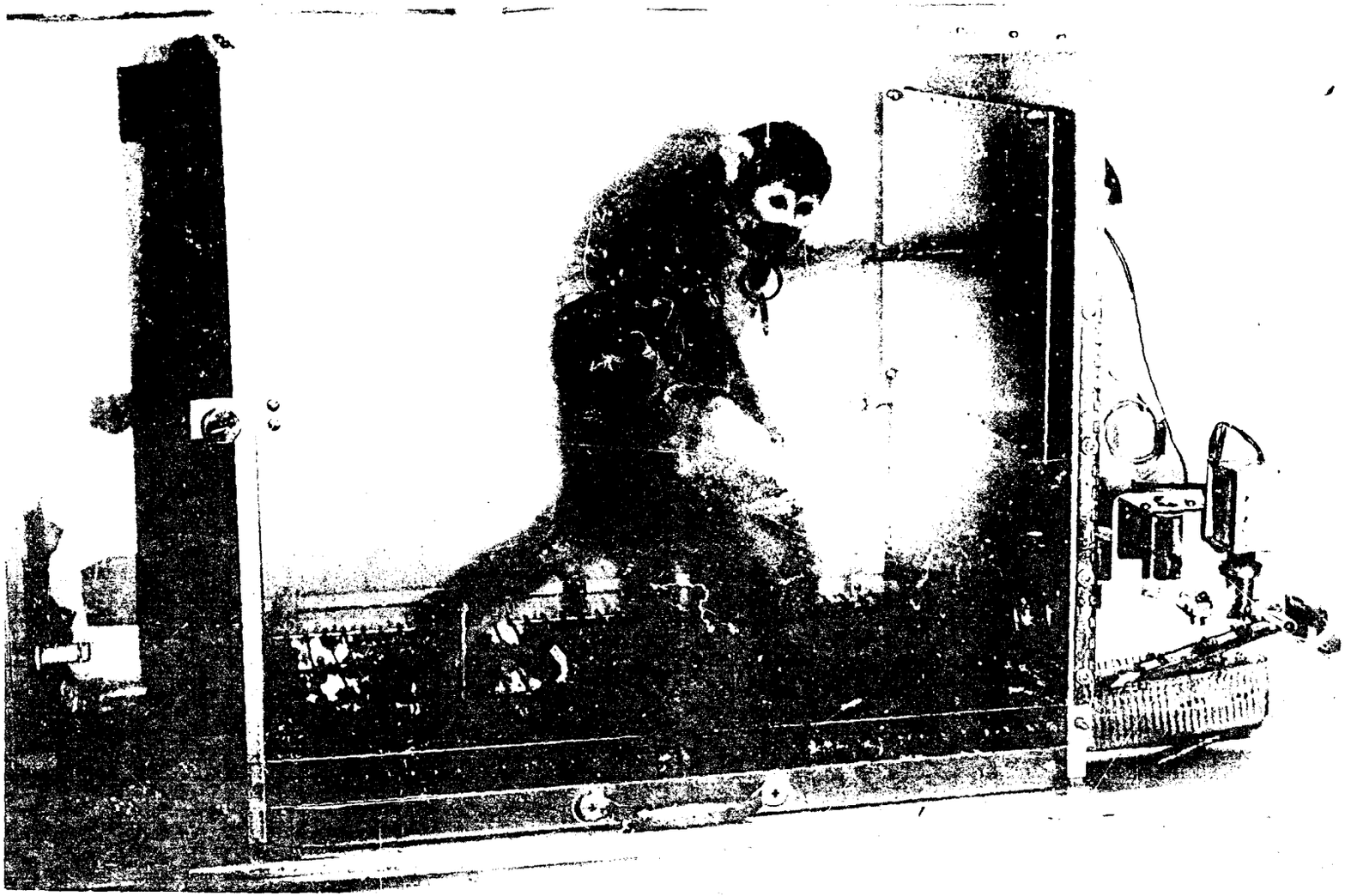

Figure 29. Schedule to Measure the Functions of Coordination, Ataxia, and Muscle Weakness

could not be expected to distinguish between a decrement in coordination, ataxia, or muscle weakness, since one of these, when specifically affected, would probably produce the same results. However, in combination with the vertical-motor-activity schedule, the component of muscular weakness could be distinquished from ataxia and coordination. There has not been enough time, however, to permit the development of schedules that allow separation of coordination, ataxia, or the disturbance of vestibular function.

Preliminary investigations with a horizontal-bar schedule (figure 30) to measure vestibular function indicated that this schedule was sensitive to tropanol anticholinergics at much lower doses than those required for FI/FR and vertical activity.

In all these schedules, the squirrel monkey was used as the experimental animal, and six animals were trained for each schedule. Four dose levels were used for each compound except the tetrahydrocannabinols and azatetrahydrocannabinols, in which a 1/2-log increase to the highest dose level usually produced prostration that, for the 1,2-dimethylheptyl derivative of tetrahydrocannabinol (EA 1476), lasted as long as 4 to 6 days and required hand feeding and nursing care of the animals.

Each animal acted as its own control for each dose given. The controls were given an injection of the vehicle of the compound and were run the day before a compound dose was given. Statistics on a paired-data basis were used to determine significance from control data. Although this program was started 16 mo ago, the length of time has been insufficient to explore fully the potential of the techniques developed.

Results.

Anticholinergic compounds such as atropine, BZ, and tropanol derivatives and other drugs such as benzomorphans, chlorpromazine, and tetrahydrocannabinols have been examined in one or another of the above described schedules. Only the tetrahydrocannabinols and chlorpromazine have been examined in most of the schedules, and several of these will be used to illustrate differences among the results obtained in the different schedules.

Figure 31 shows the effects of two anticholinergic agents on the multiple FI/FR schedule. The FI is only slightly affected by one of the tropanyl glycolates tested; there are no significant differences from the control at a of the doses examined. On the other hand, the FR is significantly affected ($p < 0.01$) at doses of 0.01 mg/kg and higher. Data obtained with BZ showed both FI and FR to be affected to the same extent. This response was qualitatively the same as that seen with atropine but at much higher doses (× 100).

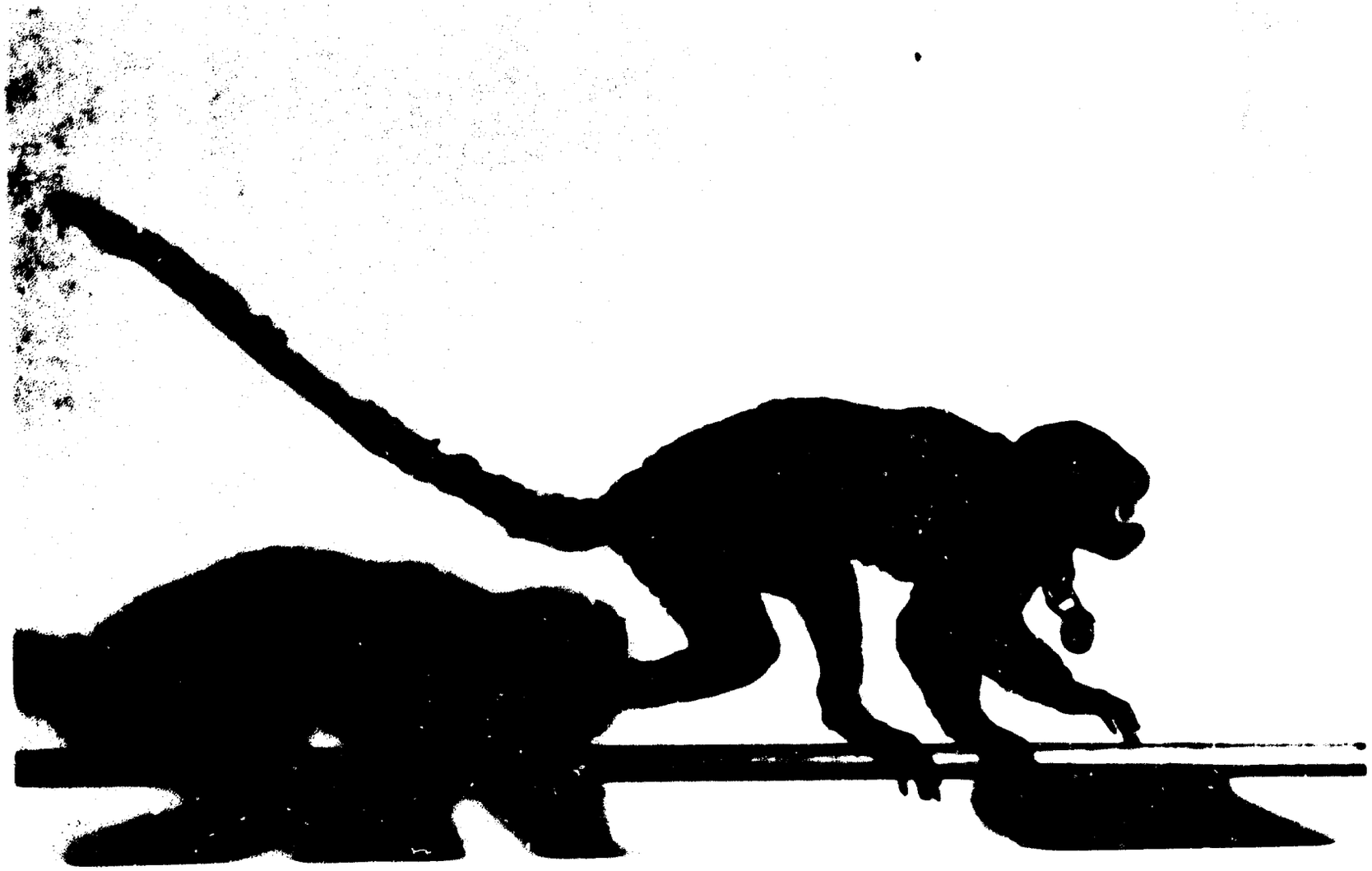

Figure 30. Horizontal-Bar Schedule

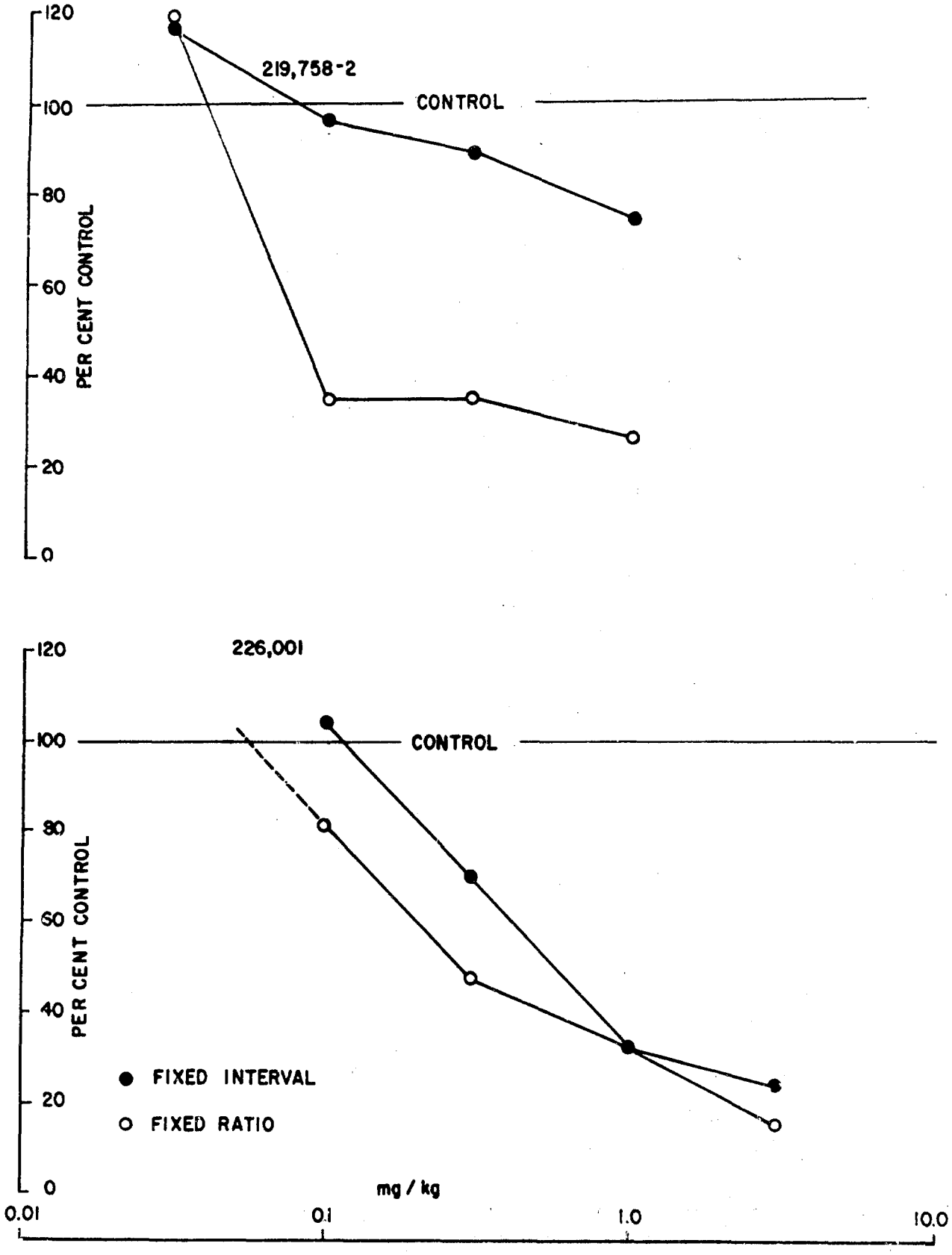

Figure 31. Effects of Two Anticholinergic Agents on FI/FR Schedule

Figure 32 shows the effect of two benzomorphans on the FI/FR schedule. As with BZ, both the FI and FR are equally affected but at much higher doses (× 10). There were no differences between the effects of these two compounds.

Figure 33 shows the effect of im chlorpromazine on four schedules. The FR was affected at doses of 0.3 and 1.0 mg/kg, whereas the FI was not affected except at the highest dose of 1.0 mg/kg. The difference between the FI and FR at 0.3 mg/kg is statistically significant ($p < 0.01$). The apparent enhancement in the FI and FR at 0.03 mg/kg is not statistically significant.

The effect of chlorpromazine on vertical activity shows that, except at the 0.3-mg/kg dose, the work done and the intensity with which it is done are affected equally. The differences at 0.3 mg/kg are significantly different at the 95% confidence level. The effect of chlorpromazine on the tracking schedule is almost identical to that seen in the FR schedule.

Chlorpromazine has a distinct effect on the number of shocks received by the animal in the shock-avoidance schedule, as compared with its effect on the response rate. The reciprocal of the number of shocks received was used in the calculations so that some idea of the decrement in performance could be gaged.

The im doses of chlorpromazine to produce a 50% decrement in performance for different schedules are given below.

Schedule	Dose to produce a 50% decrement in performance mg/kg
FI	0.45
FR	0.20
Work done	0.20
Work intensity	0.30
Tracking	0.20
Response rate	>1.00
Shock-avoidance	0.08

The values indicate that the same dose (0.2 mg/kg) is required for FR, work done, and tracking responses; approximately double this dose was required

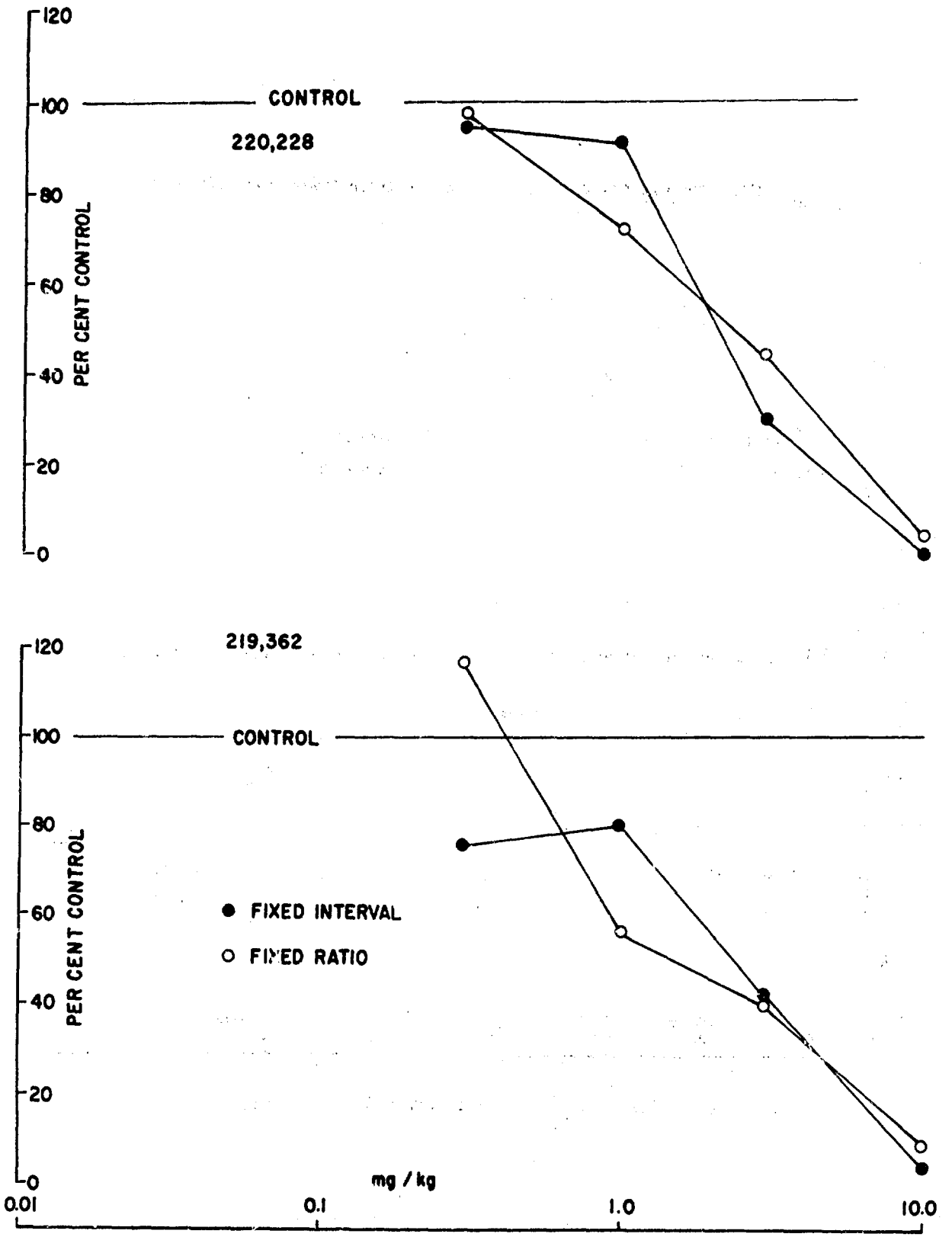

Figure 32. Effects of Two Benzomorphans on FI/FR Schedule

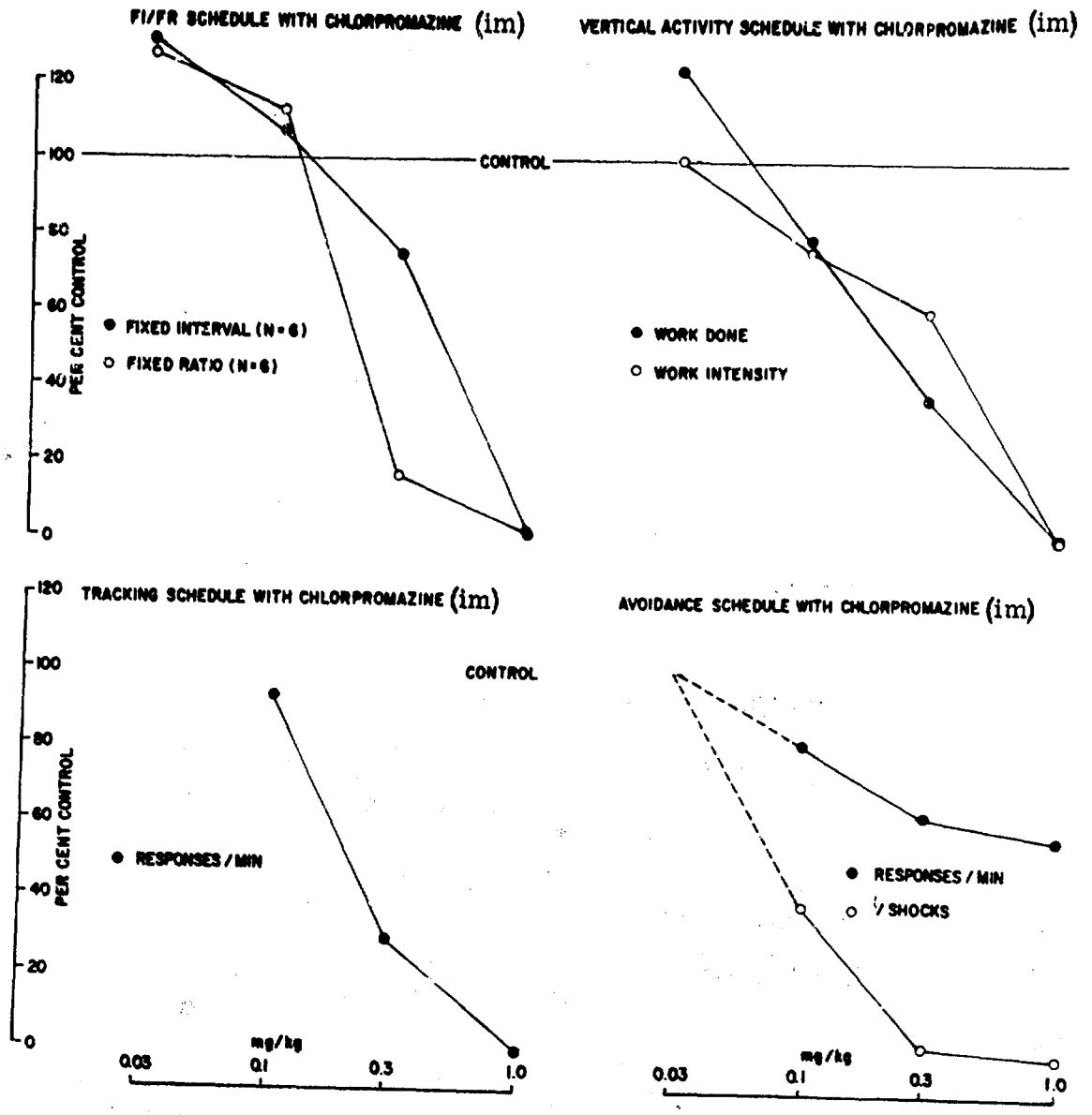

Figure 33. Effects of Chlorpromazine on Four Schedules

to affect FI, work intensity, and responses to avoid a shock; a very small dose (0.08 mg/kg) was sufficient to obtain a 50% decrement in ability to avoid shocks.

Figure 34 shows the effect of 0.3 mg/kg of EA 1476. This compound has a slow onset and a prolonged duration of effect. At doses of 3 mg/kg and higher, the effect lasted as long as 4 to 5 days, during which time nursing care and hand feeding were necessary.

Figure 35 illustrates the 24-hr postinjection effect of EA 1476 on the multiple FI/FR schedule for doses up to 1.0 mg/kg. At 0.1 mg/kg the enhancement of performance for both the FI and FR was significant ($p < 0.05$). This enhancement was also observed for the ratio of successful to unsuccessful attempts in the steadiness schedule, as illustrated in figure 36, but was not observed for mean steadiness time. The vertical-activity schedule data (figure 37) show no evidence of enhancement. Instead, a significant decrement of performance occurred at 0.1 mg/kg.

Discussion.

Atropine (data not shown) and the tropanol derivative demonstrated a dissociation that affected the FR to a significantly greater extent than the FI, whereas BZ affected both the FI and FR equally. This type of response was also seen for the benzomorphans, indicating that, in addition to the anticholinergic effect, BZ also had other effects that may be common to benzomorphans. Where both the FI and FR are affected, a depressant component may be in effect.

The data obtained with chlorpromazine indicate varying sensitivities of the various schedules. Shock avoidance is the most sensitive, and response rate to avoid a shock is the least sensitive. Unfortunately, other compounds have not been tested by the avoidance schedule to determine whether or not this finding is general or specific to chlorpromazine.

EA 1476 showed some interesting characteristics that were also observed in other tetrahydrocannabinol derivatives that showed activity. The slow onset of action and the prolonged duration of effect were fairly unique. The enhancement of performance in the FI/FR schedule and in the steadiness schedule was seen not only 24 hr after administration but also as early as 1 hr after administration. This suggests that these observations have some basis in fact. On the other hand, this enhancement was not seen in a schedule requiring a motor-type performance as its major component.

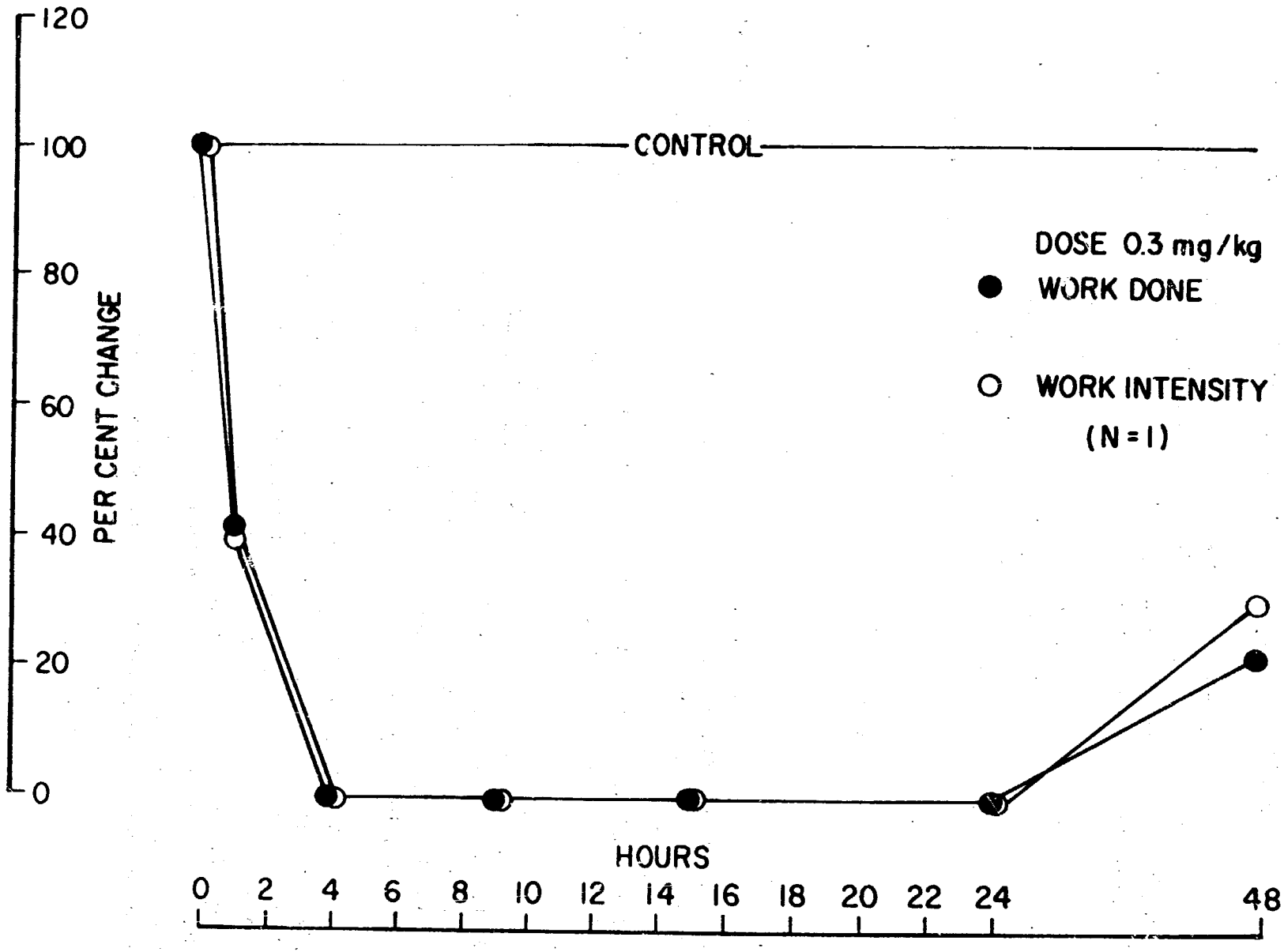

Figure 34. Vertical-Activity Schedule Showing Duration of Action of EA 1476

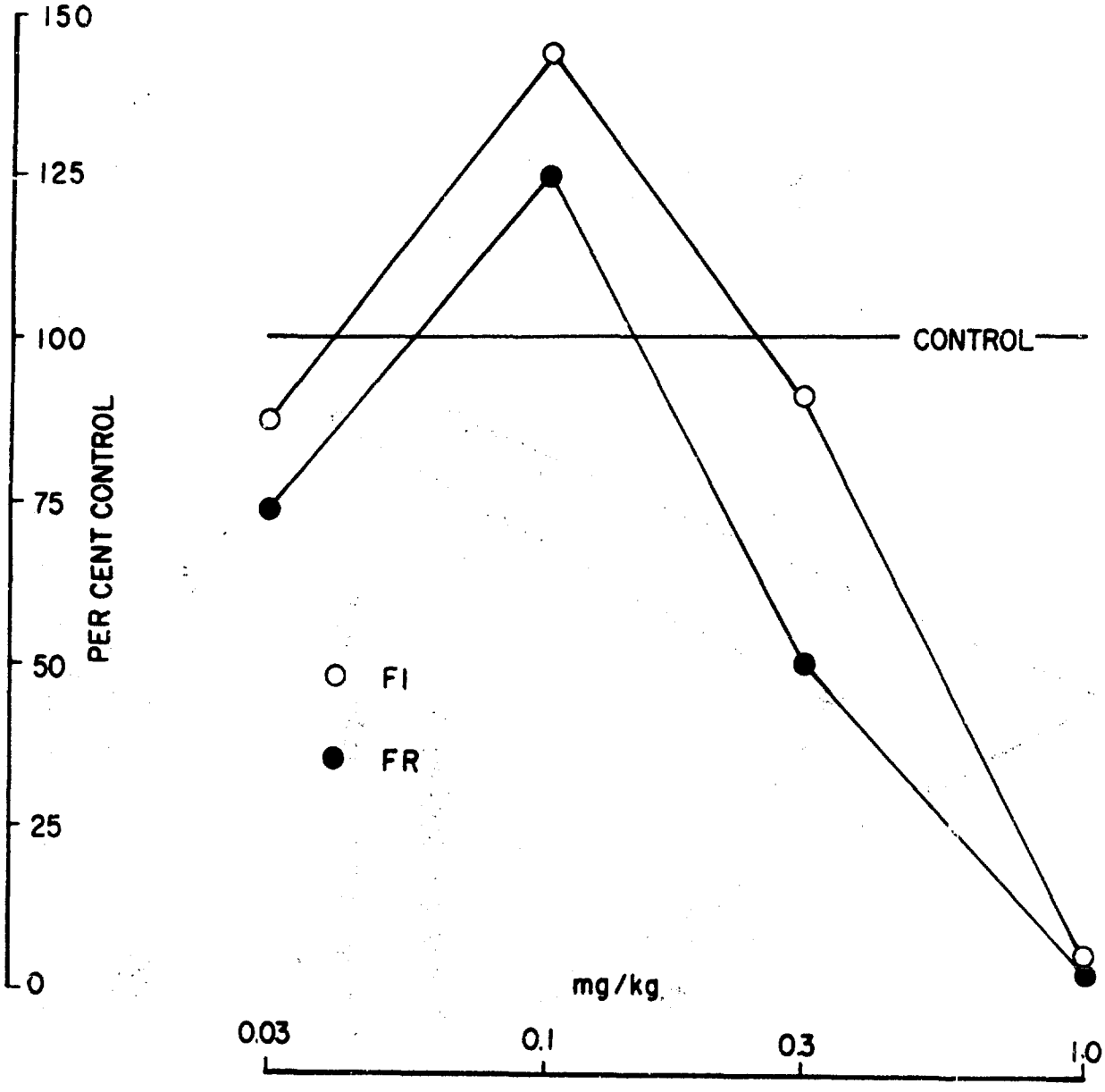

Figure 35. FI/FR Schedule Showing Effects of EA 1476

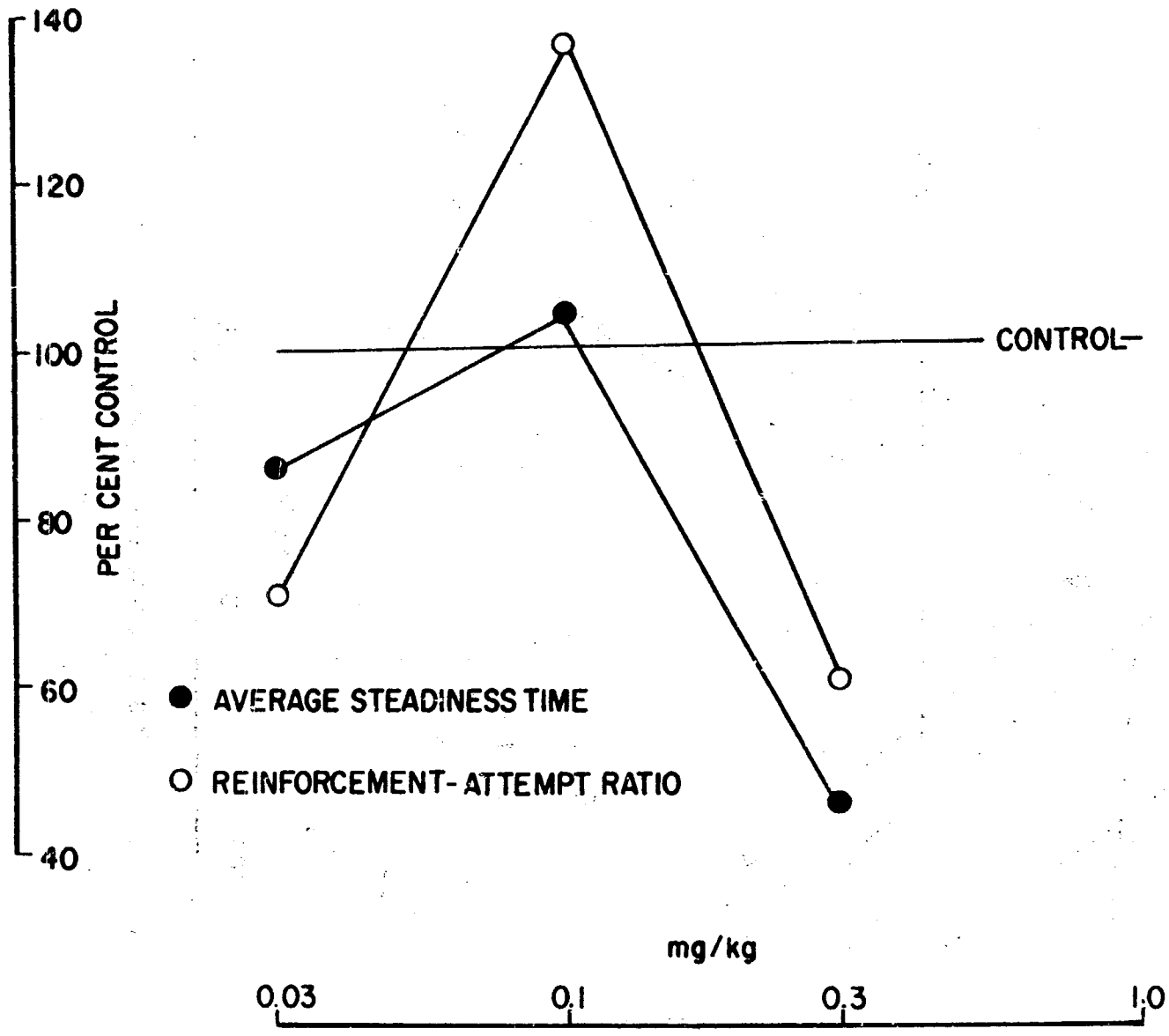

Figure 36. Steadiness Schedule Showing Effects of EA 1476

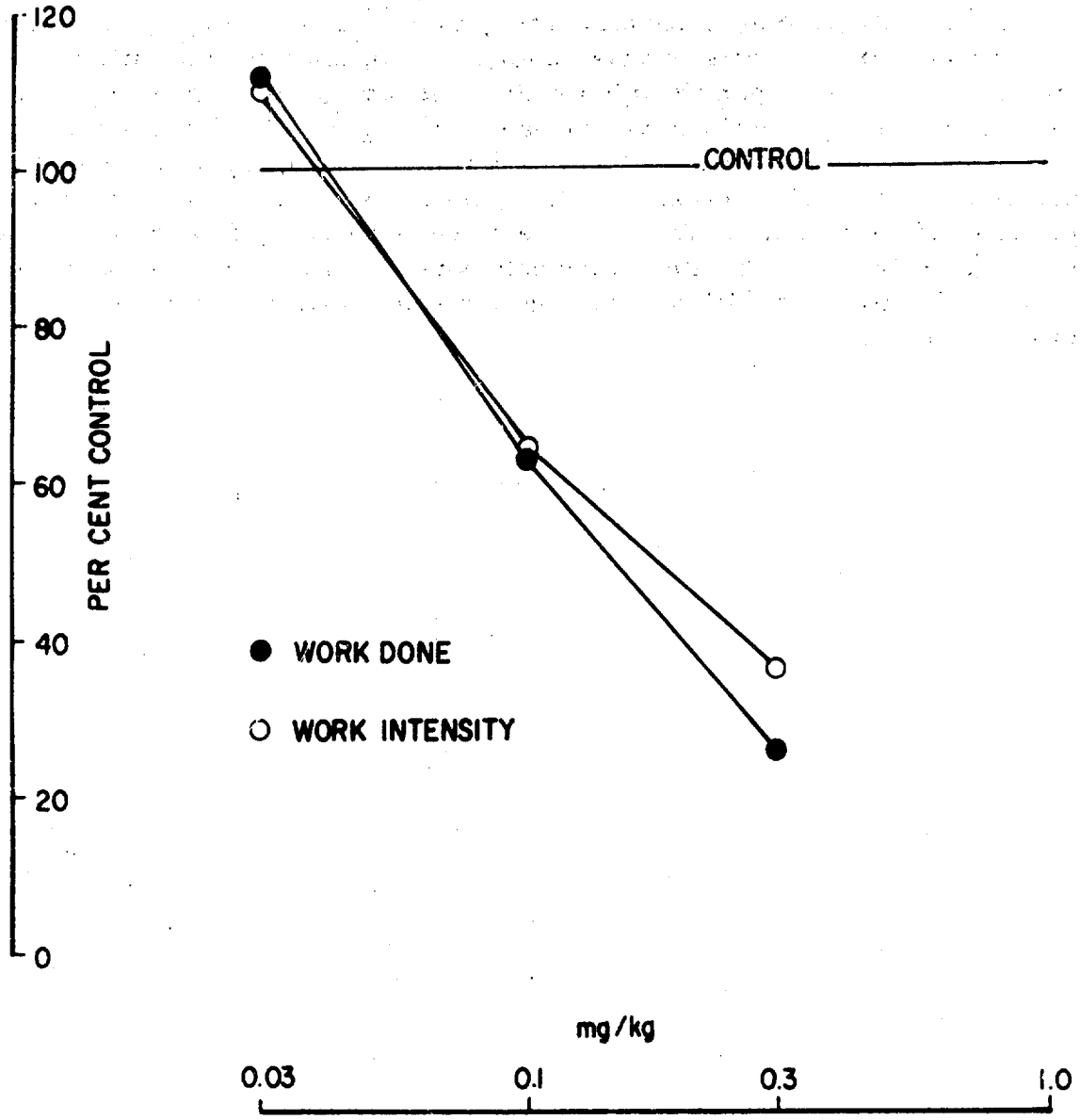

Figure 37. Vertical-Activity Schedule Showing Effects of EA 1476

On the basis of the data presented, it is reasonable to conclude that a battery of different types of schedules, each designed to elicit disturbances of a particular functional component of the biological system, is able to show decrements that may be dependent upon the major biological action of a particular compound. If this is true, then the capability of this battery to discriminate may depend upon the spectrum of action of the compound. A compound that affects many functions will not show specificity for a particular type of behavioral schedule, whereas the reverse would be true for a compound that is relatively discrete in its action. In the context of the Edgewood Arsenal incapacitating-agent program, it would seem undesirable to depend upon crude indexes for selection of candidate compounds when such indexes might cause the exclusion of a more specifically acting compound with highly desirable incapacitating properties.

EFFECTS OF LSD-25 ON A VARIETY OF DELAYED-RESPONSE TASKS IN THE MONKEY

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Laboratory of Neurological Sciences
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Introduction.

LSD has been shown in the past decade to alter "higher functions" in both man and animal.* Although many hypotheses have been advanced to explain its mode of action, none has clarified the perplexing variability of behavioral effects following LSD administration.

The principal purpose of this study is to investigate the possible differential effects of LSD as a function of procedural variations in the performance of delayed-response tasks. If such a differentiation exists, it may be inferred that performance of the tasks is subserved by diverse neural mechanisms. That differences in procedure are important was demonstrated by Pribram and Mishkin** employing the object-alternation task. In the same context, Battig, Rosvold, and Mishkin† showed that monkeys trained and tested in an automated apparatus manifested no deficit on a delayed-alternation task after bifrontal ablation. However, the classical finding of postoperative impairment was seen in animals trained and tested in the manually operated Wisconsin General Testing Apparatus (WGTA). This finding has been corroborated in our laboratory.

These procedural differences may account for some of the apparent discrepancies in the LSD literature. Jarvik and Chorover†† reported that LSD produced impairment in accuracy of performance of a delayed-alternation task

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* Hoffer, A. D-lysergic Acid Diethylamide (LSD): A Review of Its Present Status. Clin. Pharmacol. Therap. 6, 183-255 (1965).

** Pribram, K. H., and Mishkin, M. Analysis of the Effects of Frontal Lesions in Monkeys: III. Object Alternation. J. Comp. Physiol. Psychol. 49, 41-45 (1956).

† Battig, K., Rosvold, H. E., and Mishkin, M. Comparison of the Effects of Frontal and Caudate Lesions on Delayed Response and Alternation in Monkeys. J. Comp. Physiol. Psychol. 53, 400-404 (1960).

†† Jarvik, M. E., and Chorover, S. Impairment by Lysergic Acid Diethylamide of Accuracy in Performance of a Delayed Alternation Test in Monkeys. Psychopharmacologia 1, 221-230 (1960).

in monkeys trained in an automated apparatus. Employing the WGTA, Evarts* reported no deficit in delayed-response performance following LSD administration in monkeys trained to high-level criterion. Since the ability of animals tested in the WGTA to perform delayed-response or delayed-alternation tasks is affected by prefrontal ablation, it may be hypothesized that the paradoxical findings reported with LSD are related to the procedural differences of manual versus automated training. In order to test this hypothesis, monkeys in the present study are being trained in one or more of three types of delayed-response tasks, each differing in the manner of cue presentation and the environmental situation.

An additional concern of this study is that of dose-effect relationships with respect to the three tasks under consideration. Widely discrepant dose-response results have been reported by other workers. Evarts found little or no effect on accuracy of delayed-response performance in monkeys after total iv doses up to 950 μg of LSD. By contrast, Jarvik and Chorover reported impairment of delayed alternation with doses as low as 5 μg/kg of body weight. In pilot testing prior to the present formal study, we evaluated dose effects of LSD in doses ranging from 10 to 140 μg/kg in increments of 10 μg/kg. The highest doses tended to produce generalized behavioral alterations so that the animal would frequently remain unresponsive in the test situations; therefore, doses higher than 140 μg/kg were not employed. After this information on dose limits was obtained, an investigation was undertaken that forms the basis of the present report. The doses of LSD that are being studied are 10, 70, and 130 μg/kg. Sterile water (which is used as the diluent for the LSD) serves as a control.

Methods.

Experimentally naive monkeys in the weight range of 2.2 to 4.1 kg serve as subjects in this investigation. Seven groups, consisting of four animals per group, are trained in one, two, or all three variations of the delayed-response task, as shown in the list. The various task combinations will permit an evaluation of the relative significance and interaction of the respective procedural variations in relation to the effects of LSD.

* Evarts, E. V. Neurophysiological Correlates of Pharmacologically-Induced Behavioral Disturbances. In: The Brain and Human Behavior. Proc. Assoc. Res. Nervous Mental Diseases 36, 347-380 (1958).

Group	Assigned tasks
1	Direct
2	Indirect
3	Direct and indirect
4	Automated
5	Direct and automated
6	Indirect and automated
7	Direct, indirect, and automated

The three variations of the task are as follows:

1. Direct method in the WGTA - In this the classical method of training and testing in delayed response, the animal observes the baiting of one of two adjacent food cups by the experimenter, who then covers them with identical lids. Direct viewing of the food reinforcement by the subject constitutes the critical feature of this method. An opaque barrier is then interposed so that the animal is unable to view the covered cups for a 6-sec period. At the end of the delay, the barrier is raised, and the animal is permitted to respond in the absence of any cue.

2. Indirect method in the WGTA - In this situation, the monkey views the two adjacent cups, one covered by a lid with a grey surface and the other by a lid with a central white disk on a grey background. The cup bearing the lid with the white disk signifies the cup that will yield the food reward. The subject is not cued by the food. After the animal views the choices, a barrier is interposed for 6 sec. During this delay period, the experimenter removes the lid with the white disk and replaces it with one having a uniform grey surface, so that now both lids are identical. The animal subsequently responds in the absence of the critical cue.

3. Automated method - Employing electromechanical relay circuitry, the apparatus, as developed in this laboratory for the present experiment, cues and rewards or punishes the animal automatically. A restraining chair is employed to enhance the probability of the animal's attention to the cueing stimuli that are presented on one of two adjacent translucent windows approximately 12 in. in front of the animal's head. The cue consists of a circular beam of light on one window for 6 sec while the other window remains unilluminated; the right-left sequence is predetermined by the Gellermann series. When the projectors are turned off, a 6-sec delay period ensues. An opaque barrier is not interposed between the animal and the windows. The animal is prevented from responding prematurely by an air-driven door that allows accessibility to the windows only at the conclusion of

the delay period. The monkey then responds by pressing one of the two windows. A correct response is rewarded by food that drops into a midline food well in front of the animal. Incorrect responses result in mild punishment, a puff of air directed at the animal's head.

Drug testing is introduced after the animal has achieved a criterion performance of 90% correct responses per test session for 5 consecutive days. When the criterion is met, a specified dose of LSD or sterile water is administered daily for 5 days. The animal is tested daily on each of the tasks in which it had received training, starting 15 min after ip administration of the agent. The sequence of tasks on a particular day follows a predetermined order to overcome possible differential effects of the drug related to the length of time following administration. After a particular dose of the drug has been given for 5 consecutive days, testing continues until the monkey again achieves 5 consecutive days of criterion performance. Testing with the next dose of LSD is then begun. A counterbalanced order of drug doses is employed so that the effect of dose sequence may be evaluated.

For the preliminary analysis of the data, statistical significance is determined by the binomial approximation to the normal distribution. The 5-day predrug sessions are used to establish the normative values for each animal. The percent of correct responses over 5 days for any given dose is then compared to the animal's normative scores. Each animal thus serves as its own control.

Results and Discussion.

Preliminary results are available on the performances of eight monkeys. Table VII summarizes the observations to date, the percent alteration in correct responses reflects the alteration in performance over 5 days for each of the animals at a particular dosage.

As might be expected, the most significant changes were those seen at the highest dose level, 130 μg/kg, but the impairment was not uniform for all tasks. Although all animals in the automated situation, with the exception of one,* were deleteriously affected, only half of the animals tested in the WGTA were significantly impaired, regardless of whether the direct or indirect procedure was employed.

* Monkey No. 622 failed to respond during the first 2 days of testing, but on the subsequent 3 days, its performance was not significantly impaired. Failure to respond was commonly seen in monkeys trained in the automated situation, but only rarely in the WGTA.

Table VII. Percent Alteration in Performance Score as a Function of Task and LSD Dose

Dose	Monkey No.	Percent alteration in performance score		
		Automated method	Indirect WGTA method	Direct WGTA method
μg/kg				
130	403	-6.00*	-15.00*	-13.60*
	515	-16.00*	+2.70	+1.10
	516	-39.00*	-11.00*	-1.00
	522	-2.20**	—	—
	568	-28.00*	—	—
	557	—	-7.6	-4.8
	550	—	+0.4	-5.8
70	403	-4.00*	-15.00*	+1.00
	515	-15.00*	+2.30	-51.00*
	516	-8.00*	+1.00	+2.30
	568	-16.00*	—	—
	522	-15.04*	—	—
	449	—	-9.80*	+0.6
	550	—	0.00	+2.6
	557	—	-1.6	-5.8*
10	403	-4.00*	-16.00*	+1.00
	515	-2.00	+0.70	-1.10
	516	+1.20	-0.04	+2.30
	449	—	-7.00	-0.20
Sterile water (1 ml/kg)	403	-2.00	-1.00	+1.00
	515	-13.00*	+3.70	-1.10
	516	-5.00*	+1.00	+2.30
	571	+1.0	—	—
	568	+3.20	—	—
	557	—	+1.40	+4.2

* $p < 0.001$.

** No response for 2-1/2 days.

At the intermediate dose level, 70 μg/kg, a result qualitatively similar to that at the highest dose was obtained. Again, the scores of all animals in the automated situation were significantly decreased; on the other hand, in the direct and indirect WGTA situations, the scores of only one-third of the subjects showed statistically significant impairment. At the lowest dose, 10 μg/kg, the difference between the automated and the nonautomated procedures was less evident; only one subject of the eight tested in the nonautomated situations exhibited the deficit due to LSD, and only one of three subjects thus far tested at this dosage in the automated apparatus was affected. With sterile water, the control, no alteration in performance occurred in the direct or indirect WGTA tasks. In the automated situation, two of the five monkeys thus far tested showed a significant decrease in their scores, which is difficult to explain. These animals had previously been subjected to high doses of LSD, and the needle puncture for drug injection may have served as a stimulus for a conditioned emotional response. Additional control animals, especially those administered sterile water as the first "drug," may clarify this finding.

With regard to the question of a differential effect of LSD on procedural factors, there is a clear distinction between the automated and nonautomated methods at the high and intermediate doses. The former method appears to be the more sensitive indicator of LSD effects. In the free-ranging WGTA situation, animals tested by either the direct or indirect method show great variability in degree of impairment, ranging from nil to severe.

From the standpoint of dose-effect relationships, the results suggest a positive correlation between magnitude of dose and extent of functional impairment. This holds true, in general terms, for both the automated and WGTA situations. Although the nonautomated tasks appeared to be relatively resistant to LSD, there was a positive relationship between dose and degree of impairment. At the highest dose, performance deteriorated in 50% of the monkeys tested in the WGTA. This dose may be expressed as a significant impairment dose (SID50) of 130 μg/kg. Similarly, the SID50 for the automated task lies between 10 and 70 μg/kg.

Although statistical analysis has not been completed with regard to drug-tolerance effects, data in figures 38 to 41 show a tendency toward rapidly developing tolerance. The maximal effect of LSD is seen on the first day, following which there is an apparent trend in the direction of criterion performance. These observations corroborate those of Jarvik and Chorover, who similarly concluded that tolerance effects occurred. Evarts had suggested that the apparent improvement in performance was an effect not of tolerance but rather of continued training of the animal. That drug tolerance rather than overtraining accounts for the improved performance is suggested by the fact that, in the present study, the animals had to meet a criterion of stable

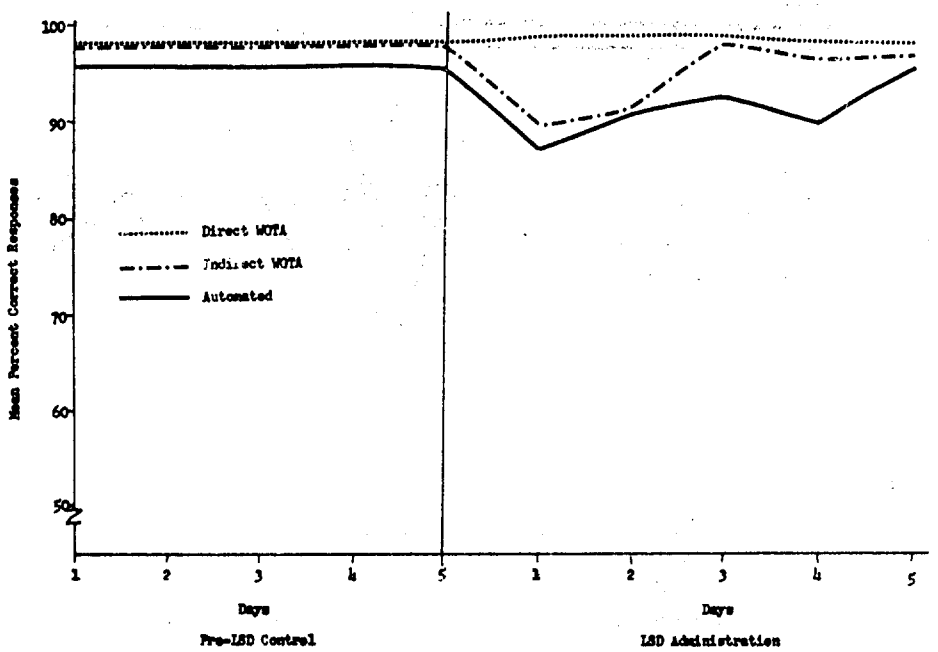

Figure 38. Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (10 μg/kg)

(The pre-LSD control portion of graph reflects mean level of performance during 5-day sessions prior to drug administration)

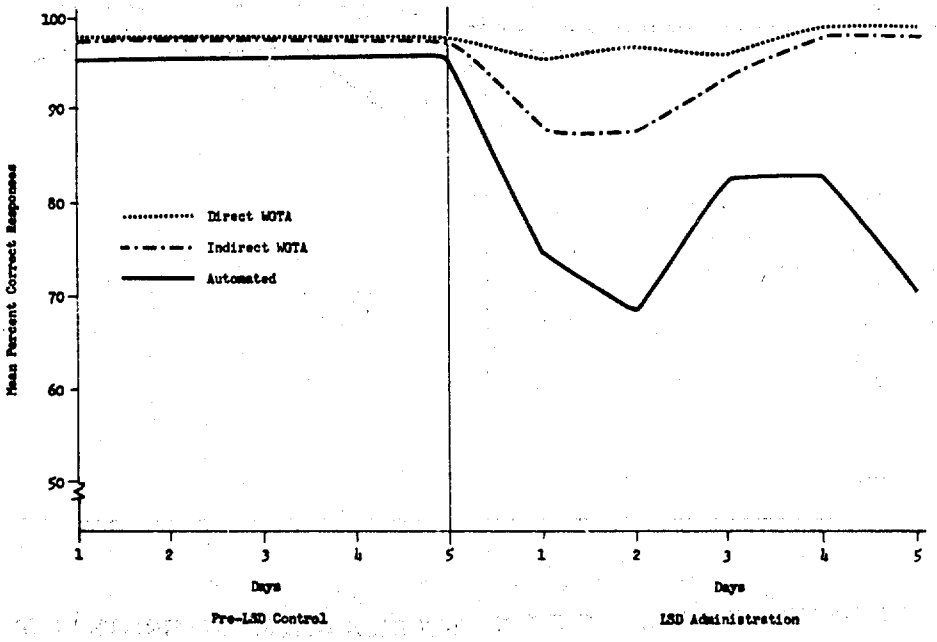

Figure 39. Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (70 μg/kg)

(The pre-LSD control portion of graph reflects mean level of performance during 5-day sessions prior to drug administration)

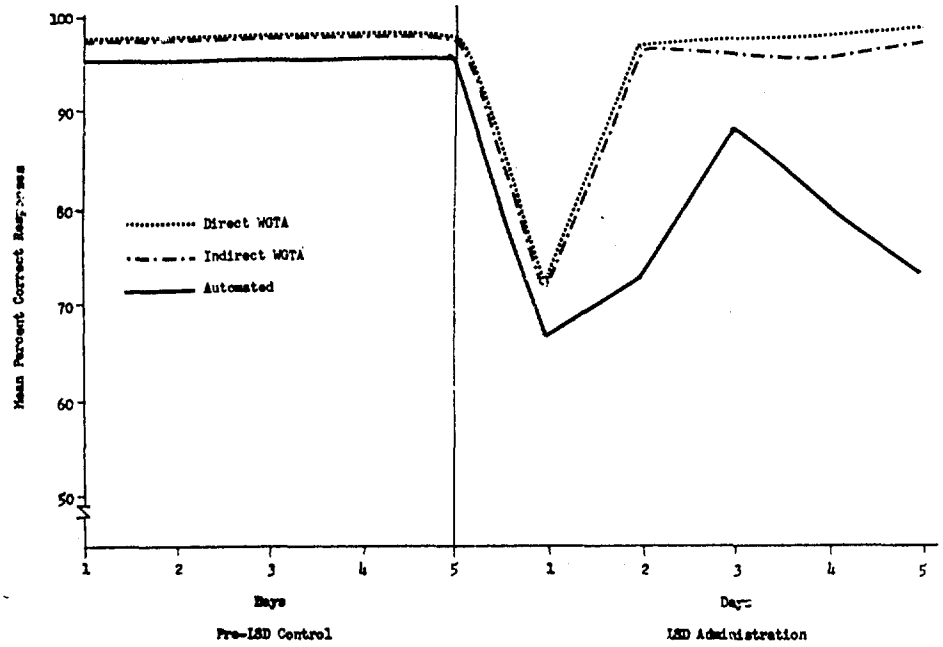

Figure 40. Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After LSD (130 μg/kg)

(The pre-LSD control portion of graph reflects mean level of performance during 5-day sessions prior to drug administration)

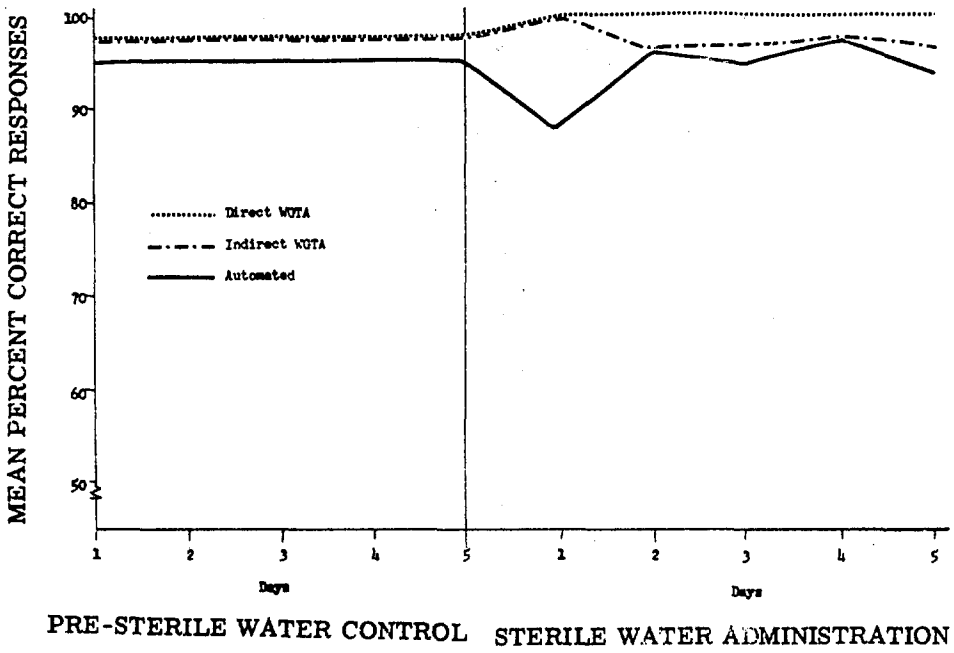

Figure 41. Mean Percent of Correct Responses of Monkeys on Three Delayed-Response Tasks After Placebo (Sterile Water)

(The preplacebo portion of graph reflects mean level of performance during 5-day sessions prior to placebo administration)

performance prior to the administration of the drug; additional training in itself would not be expected to improve their performance.

The differential effect of LSD on versions of the delayed-response task demonstrated in this study indicates the importance of procedural factors in training and testing. It is interesting to note that the differential effect of LSD appears to be directly opposite that observed in frontally ablated animals by Battig, Rosvold, and Mishkin.* Conceivably, the procedural differences in the apparently similar delayed-response tasks may be subserved by different neural systems that are selectively affected by LSD. These findings are consistent with those of Evarts, who found only minimal LSD effect on performance in the WGTA. The results of the present study are also in agreement with those of Jarvik and Chorover; using an automated apparatus, they reported a decrement in delayed-alternation ability. The method employed in each of the studies cited above may have accounted for the apparent disparity in the LSD effect.

DISCUSSION

Dr. Joffe (Edgewood Arsenal): Thank you very much, Dr. Black. Are there some questions for Dr. Black?

Dr. Levison (Institute for Behavioral Research): Some procedural questions. Were there any changes in latency in the response; that is, once the monkey had access to the food and particularly in relation to the dose of LSD?

Dr. Black: Attention in this study is directed primarily to the analysis of delayed-response ability under LSD as a function of procedural variations. Although response latencies are not systematically measured, we have observed long pauses by some of the subjects prior to making the initial response. This initial failure to respond occurs mainly at the highest LSD dose level. In these instances, the monkey sits quietly in the test apparatus for 10 to 15 min and then, with few exceptions, spontaneously begins to respond.

Dr. Levison: You didn't have any hold on it; that is, the subjects could wait as long as they wanted to, prior to responding?

Dr. Black: If a response is not made within 20 sec after the delay interval, it is recorded as a no-response trial, and the next trial is presented. In the rare instances when an animal fails to respond on successive trials, the test session is terminated after 30 min.

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* Battig, K., Rosvold, H. E., and Mishkin, M. Comparison of the Effects of Frontal and Caudate Lesions on Delayed Response and Alternation in Monkeys. J. Comp. Physiol. Psychol. 53, 400-404 (1960).

Dr. Levison: Is there any suggestion that if you had tested latencies at the very low levels, perhaps you would get changes in latencies where the subjects would be discriminating as well as they had on baseline?

Dr. Black: The available evidence does not lend itself to an answer to this question.

Dr. Levison: These tests were on rhesus monkeys, weren't they?

Dr. Black: All rhesus.

Dr. Levison: What were their weights?

Dr. Black: They were 2.2 to 4.1 kg.

Dr. Wilson (Peninsular Chemical Research, Inc.): In the automated situation, I believe you had an air puff that was punishment for the animal. Was there any similar punishment in the direct method?

Dr. Black: No, there is not a similar punishment. The only punishment for incorrect responses that is uniform across tasks is the absence of the food reward.

Dr. Coate (Hazleton Laboratories): Did all animals do this work?

Dr. Black: The animals are assigned to one, two, or all three variations of the delayed-response task. The full experimental design consists of seven groups of animals, each group representing one of the seven possible task combinations. When the data of all the groups are available at the conclusion of the study, it should be possible to estimate the contribution of each of the tasks separately and in combination, relative to the LSD effect.

Dr. Dews (Harvard Medical School): Forgive me if I missed this. Did you lower a partition in the automated situation during the 6-sec delay?

Dr. Black: No, a partition is not lowered in that situation. During the cueing and the delay periods, the animal can see the response panels but is not given access to them. A solenoid-driven door is then opened, permitting response.

Dr. Otis (Stanford Research Institute): You implied early in your presentation that your methodology here involved a short-term memory. My question is related to your distinction between a short-term memory process and, perhaps, a maintenance postural cue, particularly in the automatic situation.

Dr. Black: If postural cues operate to sustain delayed-response performance, one might expect that the restraint in the automated situation would facilitate postural cueing more effectively than in the WGTA situations, in which the animal is permitted more freedom of movement. The fact, however, that the greatest impairment in performance is seen in the automated situation tends to minimize the importance of postural cues.

Some of the animals with impaired delayed-response performance while on LSD were also tested and showed proficiency on a visual-discrimination task. The discrimination task consisted of zero-delay trials in the indirect WGTA and in the automated situations. This observation suggests that the LSD deficits are probably not perceptual in character, but rather that they reflect impairment in the neural mechanisms subserving associative or retentive processes, or both.

Dr. Coate: I would like to suggest to you that you run some longer delay periods to see if you could get a relationship between the length of delay and the decrement. We have done this up to 120 sec, at which level we do not get any greater effect than we do at 6 sec. It does not sound like a short-term memory process; it sounds more like the animal hyperacts or starts to look around right after the onset of the delay. A greater effect is not produced by increasing the delay.

Dr. Black: Although both associative and retentive elements seem to be implicated in delayed response, there is no clear indication that one is more critical than the other. There is, however, evidence in the literature of a retention or delay limit beyond which performance rapidly deteriorates.

Dr. Cianci: I would like to comment on the question of short-term memory and why delayed response is considered to be a short-term memory task. It is short term in the sense that, in each and every trial, the animal is called upon to make a new association, be it right or left. Whether it is 6, 20, or 120 sec is really quite aside from the issue of its being a short-term memory in that a new association has to be formed. Long-term memory, by contrast, is characterized by visual discrimination in which the animal makes the same kind of response from trial to trial, always going to a triangle or a circle or whatever the cueing stimulus happens to be. The delayed response is considered to be a paradigm for one-trial learning and may be regarded as a short-term process.

Dr. Otis: I would like to raise one other point. What are the considerations regarding changes in appetitive behavior on the relatively high doses of LSD?

Dr. Cianci: With few exceptions, the monkeys respond actively and eat each of their food rewards. If the appetitive factor were to play a prominent role, we might expect that the animals would ignore the food, and the decrement in performance would be similar in all three variations of the task. There is seen, instead, a clear-cut difference in performance between the WGTA situations on the one hand and the automated situation on the other, regardless of any appetitive influence.

Dr. Lilly (Communication Research Institute): I was very interested to see this difference on the automated side versus the nonautomated side, and I was wondering how much of this is purely a physical spatial factor, in which you

separate the point of the reinforcement in space from the point of the stimulus itself. In the WGTA, the food reward is put directly under the signal, so there is a proximity of each in space. You might expect that, in the automated apparatus, a complex, long, spatial difference between the point of reinforcement and cue signals might prove more difficult for the animal under LSD because of the necessary longer chains of cerebral activity to arrive at the same end point.

Dr. Black: Dr. Lilly's suggestion may well be a factor that may account for the differential effect of LSD as a function of the automated and the WGTA situations. A number of other possible contributory factors may be listed, including Dr. Dews' observation of the absence of an opaque barrier in the automated apparatus, and that of Dr. Wilson concerning the question of punishment. Further behavioral analysis of the individual variables will be necessary to isolate the critical elements. Regardless of the significance of any of these possible factors, the main feature emerging from the present data is the importance of procedural variations in producing significant alterations in behavior. Inherent in this observation is the possibility, as Dr. Lilly implied, that the behavior in the different situations may be subserved by different neural mechanisms.

DRUG EFFECTS ON A RAPIDLY TRAINED CONDITIONED AVOIDANCE RESPONSE IN RATS

Dr. Robert Clark
E. I. du Pont de Nemours Co., Inc.

Rapid, dependable test methods are a prerequisite for screening the biological activity of any significant quantity of test compounds. With this objective, a rapid training procedure has been developed to measure the effect of drugs on the conditioned-avoidance-response (CAR) behavior of rats. By use of this technique, which will be described, rats are taught to perform reliably after only brief training. The method appears usable for advanced screening or developmental tests on selected compounds.

Test Method.

Carworth Farm male CFE rats weighing 60 to 85 gm are used. The animals are trained to avoid electric shock by passing through a 3- by 3-in. opening in a partition dividing a 12- by 9-1/2- by 10-1/2-in. chamber into two compartments of unequal size. The smaller of these is 4-1/2 in. long, the larger 7-1/2 in. The animals pass from the smaller chamber, which has a grid floor of 1/4-in. stainless steel rods spaced 1/2 in. apart, to the larger compartment, which has a solid floor raised 1 in. above the level of the grid floor. If the animal responds (that is, passes from the smaller to the larger compartment) within a 10-sec interval timed from the onset of an overhead light (10 w) and a "white noise",* the light and sound are turned off and a completed avoidance trial is recorded. If the animal fails to respond within the 10-sec avoidance interval, a missed avoidance trial is recorded, and a continual scrambled electric shock (0.8 ma, 1000 v of dc**) is then applied to the animal's feet through the grid floor of the smaller compartment. A response within 10 sec of shock onset terminates the shock, the light, and the noise; this is recorded as a completed escape trial. If the animal fails to respond within the 10-sec shock period, the shock, the light, and the noise are terminated, and a missed escape trial is recorded.

For purposes of initial training, each rat is given four successive escape trials in which the light, noise, and shock are presented simultaneously. Escape trials are separated by a 10-min interval. Following escape training, each animal is given either one or two avoidance trials spaced 10 min apart, in which the light and noise are presented 10 sec prior to shock onset. Animals that fail to avoid on one of the two avoidance trials are discarded. Less than 5% of animals tested failed to pass the avoidance criterion indicated.

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* At 68 db, recorded on 20-kc scale of Type 1551-C sound-level meter, General Radio Corporation, Concord, Massachusetts.

** Produced from Lehigh Valley Electronics constant-current shock power supply, Fogelsville, Pennsylvania.

Drug Effects.

The effects of chlorpromazine, chlordiazepoxide, meprobamate, pentobarbital, and BZ were evaluated in the new procedure. Conditioned animals were divided into groups of 9 or 10 rats and were given graded doses of test compound (6 to 10 doses of each compound, 1 dose per group) or control vehicles at a constant volume to body weight ratio of 1.0 ml of solution (or fine suspension) for each 100 gm of body weight. No animals received more than a single dose of test compound or control vehicle. Each rat was given a single avoidance trial at 30, 60, 120, 240, and 1440 min after injection. Compounds were administered ip in order to compare the results of these experiments to literature values obtained from comparable CAR procedures. *

The following data are summarized in table VIII:

1. The ED50 values for avoidance- and escape-response failures, slope functions, and 95% confidence limits are shown. All values were calculated according to the methods of Litchfield and Wilcoxon** and are based on data obtained at the time of peak compound effect.

2. The ratio of the ED50 value for escape-response failure to the ED50 value for avoidance-response failure is shown. This ratio measures the degree of separation between dosage values that blocked avoidance performance and those that blocked escape performance. The 95% confidence limits of each ratio value are indicated.

3. The approximate duration of effect, which was the time interval between the avoidance trial in which more than 10% of the animals failed to avoid shock and that in which 10% or less of the animals failed to avoid shock, is shown. The duration of effect was estimated from time-response curves at dosage levels near the ED50 value for avoidance failure. Data obtained from approximately 70 concurrently treated and tested control animals indicated by the chi-square test that avoidance failures of 10% or more were significantly different from control values at or beyond the 0.05 level.

4. The time to the peak compound effect at the ED50 value for avoidance failure is also shown.

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* Herz, Albert. Drugs and the Conditioned Avoidance Response. Intern. Rev. Neurobiol. 2, 229-277 (1960).

** Litchfield, J. T., Jr., and Wilcoxon, F. A Simplified Method of Evaluating Dose-Effect Experiments. J. Pharmacol. Exptl. Therap. 96(2), 99-113 (June 1949).

Table VIII. Comparison of Four Standard Compounds in CAR Test in Rats

Compounds	Avoidance failure* (ED50)	Avoidance slope*	Escape failure* (ED50)	Escape slope*	Escape failure, ED50/ avoidance failure, ED50*	Duration of effect at avoidance failure (ED50)	Time to peak effect (avoidance failure)
	mg/kg (ip)		mg/kg (ip)			hr	hr
Chlorpromazine HCl	2.5 (1.6 - 3.9)	1.8 (1.4 - 4.7)	16.0 (8.4 - 30.4)	3.6 (1.2 - 11.4)	6.4** (2.9 - 13.8)	>4, <24	2
Chlordiazepoxide HCl	6.4 (3.4 - 12.2)	4.3 (1.5 - 12.1)	48.0 (32 - 72)	1.3 (1.2 - 1.6)	7.5** (5.3 - 10.5)	>4, <24	1
Meprobamate	60.0 (48.0 - 75.0)	1.7 (1.3 - 2.1)	135.0 (108.0 - 168.7)	1.6 (1.2 - 2.1)	2.25** (1.7 - 3.0)	>4, <24	0.5
Pentobarbital Na	18.0 (15.4 - 21.0)	1.4 (1.2 - 1.6)	24.5 (20.4 - 29.4)	1.35 (1.2 - 1.6)	1.36 (1.0 - 1.8)	>4, <24	1
BZ	0.013 (0.005 - 0.4)	2.7 (1.6 - 4.6)	0.030 (0.010 - 0.080)	2.8 (1.5 - 4.9)	2.3** (1.6 - 3.2)	>4, <24	0.5

* Confidence limits 95%.

** Significantly greater than 1.0 at the 0.05 level or beyond by t-test.

The data in table VIII are in good agreement with literature values for the same compounds evaluated in comparable CAR procedures. Traditional CAR techniques, however, require considerably longer training periods and often result in the rejection of 20% to 25% of the animals as "learning failures." The present method requires less than 1 min total training time per animal, and less than 2% of the nearly 2500 animals trained to date have failed to learn the avoidance response.

The data in table VIII indicate that the present CAR test is quite sensitive to BZ. The ED50 value for avoidance loss was 0.013 mg/kg (ip).

DISCUSSION

Dr. Joffe (Edgewood Arsenal): Dr. Clark's paper was very clear to me, perhaps because it was familiar to me. But maybe you have some questions about it.

Dr. Carr (Army Research Office): I have no discussion on your paper, but my colleagues who are interested in nutritional problems have impressed on me more and more in the last few years that one should be careful about problems involving visual acuity in animals and man since we apparently do not appreciate vitamin A deficiencies in animals and man. Perhaps we might exercise a little bit of caution in some of these experimental situations where the animal is required to respond to a visual cue in a dim light. As I have been listening to some of these reports, I have been thinking of this.

Dr. Joffe: From my own somewhat ancient knowledge of the situation with respect to vitamin A in rats, I would say that it is impossible to produce a vitamin deficiency — at least for a nutritional experiment in any rat raised on a normal laboratory diet or in an adult rat. I don't recall any experiments that tested for a correlation in nutritional deficiency and visual difficulties in adults. For other physical parameters, it is virtually impossible to produce a deficiency state.

Dr. Clark: I, perhaps, should have made clear that the light was for the experimenter's benefit, so that he could see the rat in this case. We actually have done a number of experiments and showed quite conclusively that the rat doesn't respond to this light and that the sound is the real stimulus. This light merely enables us to see the running rat.

Dr. Joffe: The albino rat is known to respond more to sound than to light because its vision is rather poor in the first place.

Dr. Shuster (University of Michigan): In this situation, when does the response cause the cessation of the shock and the light? When the animal enters? Or does he have to go completely into the next compartment? It occurs to me that

when I was running shuttle-box situations, I used to get into the problem that the animal would get halfway through and if you would terminate the conditioned stimulus or the shock, in this case, you would get into trouble. How did you handle that?

Dr. Clark: The animal passed through from a grid floor to a solid floor. [When four feet were on the solid floor, the experimenter terminated the light and the sound if it was an avoidance trial or terminated the shock if it was an escape trial.] Now, at times the animal would terminate its own shock, for example, by putting its two front feet on the solid floor, and the hind paws might be on one grid bar. The animal would not be shocked under these circumstances. The animals did go through very rapidly. Generally they didn't hang in the doorway; they either went through or they didn't.

[redacted]

MONITORING VISUAL ACUITY IN THE RHESUS MONKEY*

Dr. William B. Coate
Hazleton Laboratories, Inc.

The present study was undertaken to develop a method that would permit continuous, unattended monitoring of drug effects on and clear-cut measurement of visual acuity in the rhesus monkey during prolonged test sessions. A basic requirement of such a method is that the animal's normal performance be independent of motivational conditions likely to be affected adversely by the dosages of the drugs of interest. For this reason, shock avoidance rather than hunger or thirst motivation was employed in the present method. A second requirement is that some way be provided for distinguishing between loss of stimulus control from weakened attention and disrupted discrimination or response bias and decreased visual acuity, per se.

In brief, the test method was a discriminated, discrete-trial avoidance procedure that involved successive presentation of either a broken or unbroken ring stimulus with two response keys, requiring a choice response without correction. Continuous monitoring of acuity performance level was accomplished by the use of a response-adjusted, stimulus-titration schedule adapted from the method pioneered by Békésy.** Errors on broken and unbroken rings were recorded independently.

Subject.

The subject was a young male rhesus monkey weighing about 3.0 kg, which had never previously been the subject of any training or testing. He had water available at all times and was fed twice daily, once 2 hr prior to his daily training or test session and again about 6 hr later. He was continuously confined to a plastic restraining chair except on weekends, when he was caged alone.

Apparatus.

Stimulus presentations were accomplished by transprojecting 2- by 2-in. slides from a Kodak Carousel projector through a light tunnel onto a 3.5- by 3.5-in. viewing screen constructed of a sheet of oiled tracing paper

* This work was supported by Contract DA18-035-AMC-120(A) with the US Army Edgewood Arsenal.

** Békésy, G. V. A New Audiometer. Acta Oto-laryngol. 35. 411-422 (1947).

sandwiched between two pieces of 1/16-in. Plexiglas. The screen was located at eye level directly in front of and 9 in. from the monkey's eyes. The response keys were symmetrically placed laterally with respect to the screen but were below the neck plate of the restraining chair. The screen and response keys were located in a dim, indirectly lighted isolation booth. The projector was located outside the booth. A photosensing head positioned between a solenoidal shutter and the light tunnel permitted a coded-stimulus presentation.

Slides were prepared by photographing a black ring mounted on a light table. The stimuli consisted of white Landolt rings on a grey background with gaps ranging from 90° to 0.1° of a circle as well as identical unbroken rings. The gaps were all centered at 8 o'clock on the screen. The projector was operated on its 300-w setting.

Shock was provided by an 800-v, constant-current generator set to deliver 5.0 ma through a limiting resistor in series with the subject. Shock could be delivered either through the feet (escape shock) or through the incorrect key knob and the buttocks or feet (punishment shock).

Training.

The training procedure was adopted after two false starts with two other monkeys. As described, it represents only a tentative idea of an efficient training procedure for this test method.

A. Preliminary training.

After 2 days of booth adaptation with both keys in place and with a vertical divider to restrict the hands to their respective keys, the left-hand key was removed and a 5.0 ma, 800-v, shock-escape training was given. A red unbroken ring was projected starting 10 sec prior to the untimed shock onset that could be avoided by pressing the right-hand key. After 20 trials with the right-hand key, the left-hand key was substituted, and a blue ring with a 90° gap was presented for 20 trials. This procedure was repeated on the next day and was followed immediately by 100 trials with both keys in place and a single alternation of the two stimuli using a correction procedure in which only the appropriate key response could end the trial. For the next 23 days, the stimuli were alternated randomly and a 0.2-sec shock was delivered through the feet for each incorrect response. Daily sessions consisted of 100 to 400 trials. By the end of this phase of training, the monkey exceeded 90% correct on initial responses and avoided 100% of the shocks.

During the next 5 days (400 trials/day), the colors were faded, first by removing the blue from the broken ring and then by decreasing the redness of the unbroken ring. Transfer was nearly perfect by the end of each step. After 3 days with the colorless stimuli, the stimulus-titration schedule was programed.

B. Threshold training.

The entire set of 29 broken-ring slides were serialized and interspersed randomly with unbroken rings in the projector magazine. For 15 days (400 trials/day), training was given in which the monkey progressively drove the stimulus schedule from 90° toward the smallest gap size in the series. The projector was programed to advance one position trial-by-trial with each correct initial response and similarly to reverse after an incorrect response until the next initial correct response on a broken (larger-gap) ring. The next phase of training was to deliver shock for incorrect responses through the incorrect key rather than through the feet. After 3 days of this training, errors on gaps larger than 0.8° were almost totally eliminated.

Finally, the correction procedure was abandoned in favor of a noncorrection procedure in which the first key response ended the trial (and removed the stimulus), regardless of whether or not it was a correct response. Punishment for errors on 0.8° and smaller gaps was discontinued as it was for errors on unbroken rings in this region of the stimulus series. During training, punishment continued to be delivered for the rare errors above this region; this forestalled continued carelessness but did not punish errors in the animal's normal region of uncertainty (error range). Throughout the training, a variable intertrial interval was used that ranged from 10 to 40 sec with a mean of 30 sec.

Total training prior to the first saline test lasted 51 days. Retraining was given every weekday except on test days.

Testing.

Prior to injection on test days, a 60-trial warmup was given with the training procedure. Testing was carried out with the noncorrection procedure and without punishment for errors in any region of the series. The escape shock continued to be programed. Responses were recorded on an operations recorder that transported the paper a fixed distance on each trial. The tape was decoded by reference to the known order of the slides in the magazine on the particular test. Test sessions normally lasted 3 hr and began immediately after administration of the compound or saline (control). A minimum of

7 days separated compound tests, which were preceded by saline tests on the previous day. All materials were administered iv unless otherwise indicated.

Results.

Figures 42 through 45 represent performance records for approximately the first 2 hr after administration of one or more doses of several reference compounds and saline. To read these records, the following should be noted: (a) a downward deflection from the horizontal indicates a correct response at the corresponding stimulus (gap-size) value read from the ordinate, (b) an upward deflection similarly indicates an error at that value, (c) responses to unbroken rings do not affect the ups and downs and were correct unless otherwise indicated on the record by a vertical line, and (d) missed avoidance responses are indicated by a solid dot.

Figure 42 shows the effect of 1.0 mg/kg of atropine methylnitrate and of a similar dose of atropine sulfate, as well as the intervening saline run. It was expected that methylatropine, as a peripheral cycloplegic agent, would produce some elevation in the acuity threshold but would have no other behavioral effects. In contrast, it was expected that atropine, as a central anticholinergic agent, would produce both an elevation in the acuity threshold and manifestations of its central action (for example, missed avoidance trials or errors on unbroken rings, or both). These expectations were clearly met. After about 30 min, methylatropine raised the acuity threshold from approximately 0.4° to approximately 2.0°, and there were only one incorrect unbroken-ring response and no missed avoidance responses. Atropine, on the other hand, produced 7 errors on unbroken rings and 20 missed avoidance responses during the same postinjection interval, while raising the acuity threshold to approximately 4.0°.

Figure 43 shows the effects of 1.0 and 3.16 mg/kg of dl-amphetamine and the intervening saline run. A very slight effect on the acuity threshold without other behavioral indications appeared with the lower dose. At the higher dose, however, after about 45 min postinjection, a marked effect appeared that was followed in about 15 min by a complete loss of stimulus control, in which the monkey adopted a consistent left-key response resulting in alternate presentation of the 2.4° break and an unbroken ring. No missed avoidance responses were made.

Figure 44 shows the gradual onset of a marked effect on the acuity threshold produced by 0.032 mg/kg of BZ. Only one missed avoidance response and two errors on unbroken circles accompanied this effect. Thus it appeared to be almost entirely a visual one.

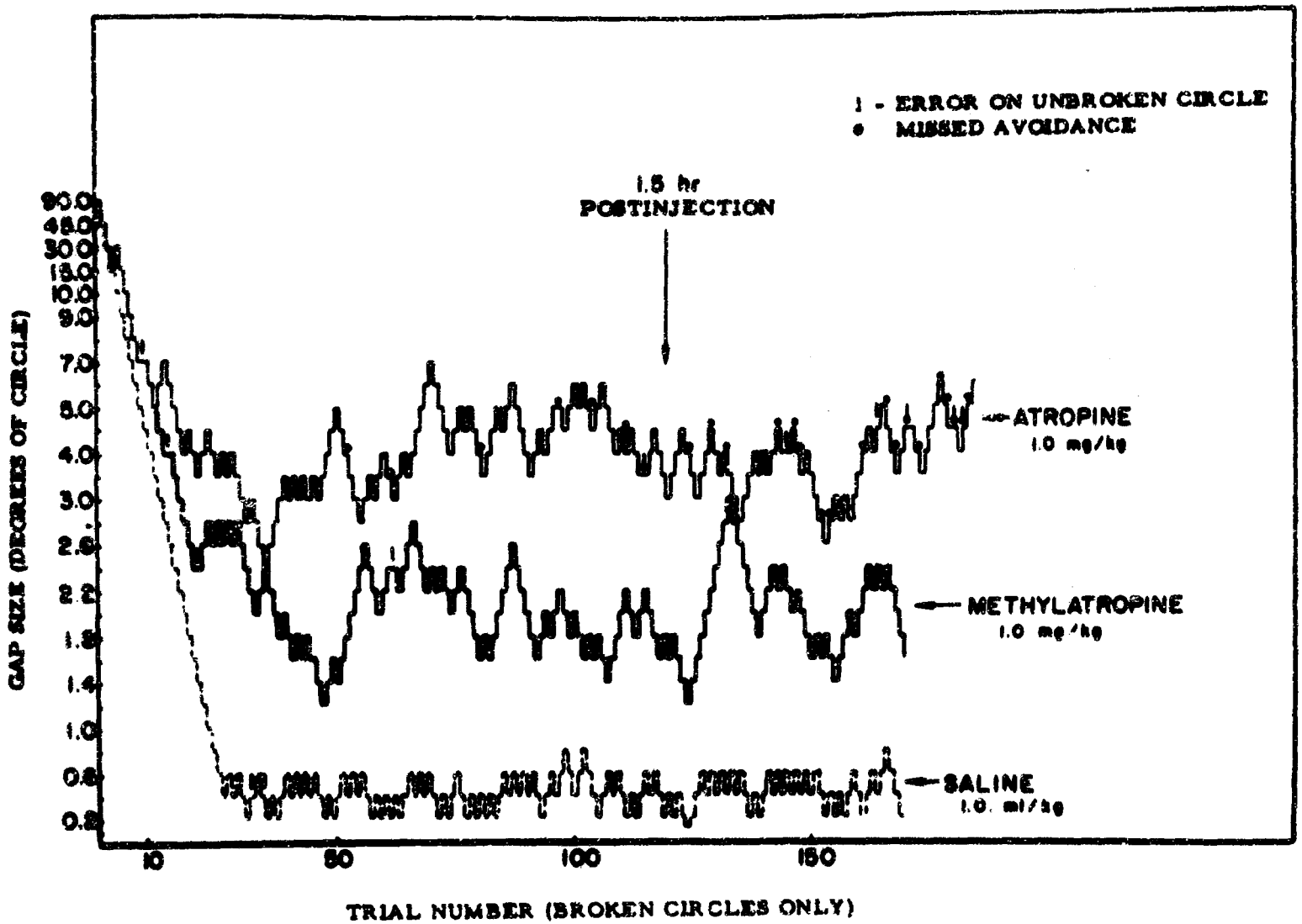


Figure 42. Gap-Size Performance Records With Saline, Methylatropine, and Atropine

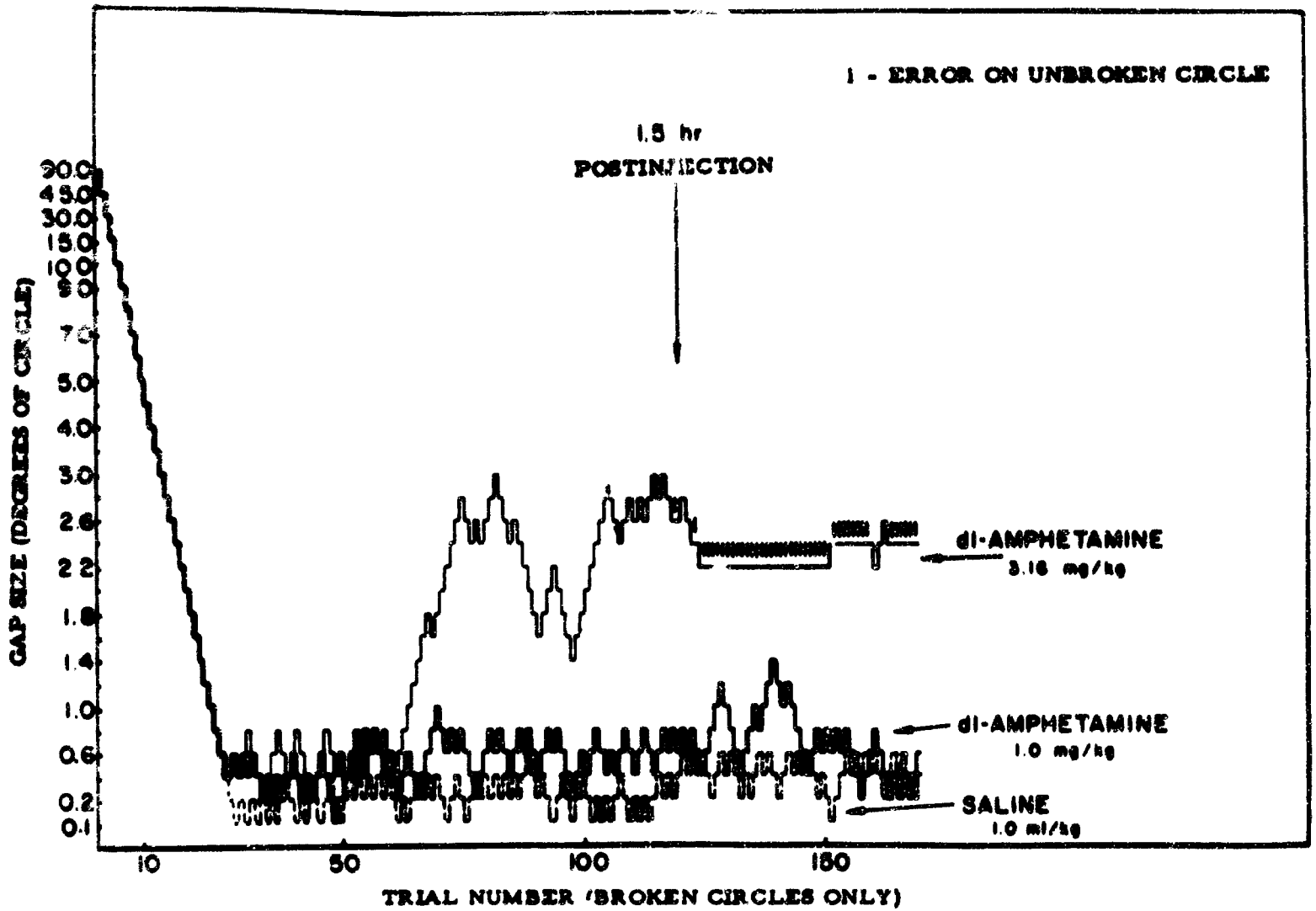


Figure 43. Gap-Size Performance Records With Saline and Two Dosage Levels of dl-Amphetamine

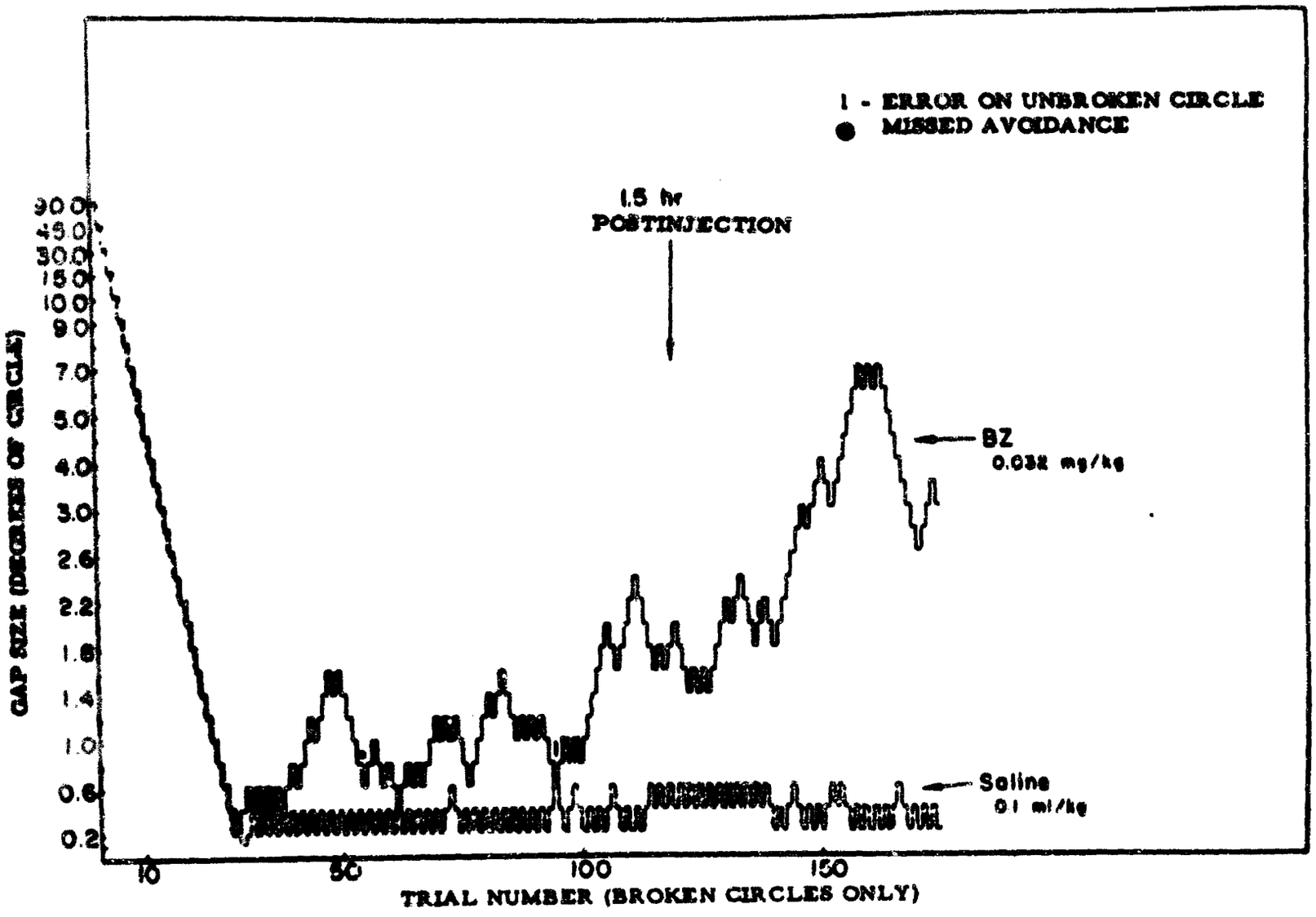


Figure 44. Gap-Size Performance Records With Saline and BZ

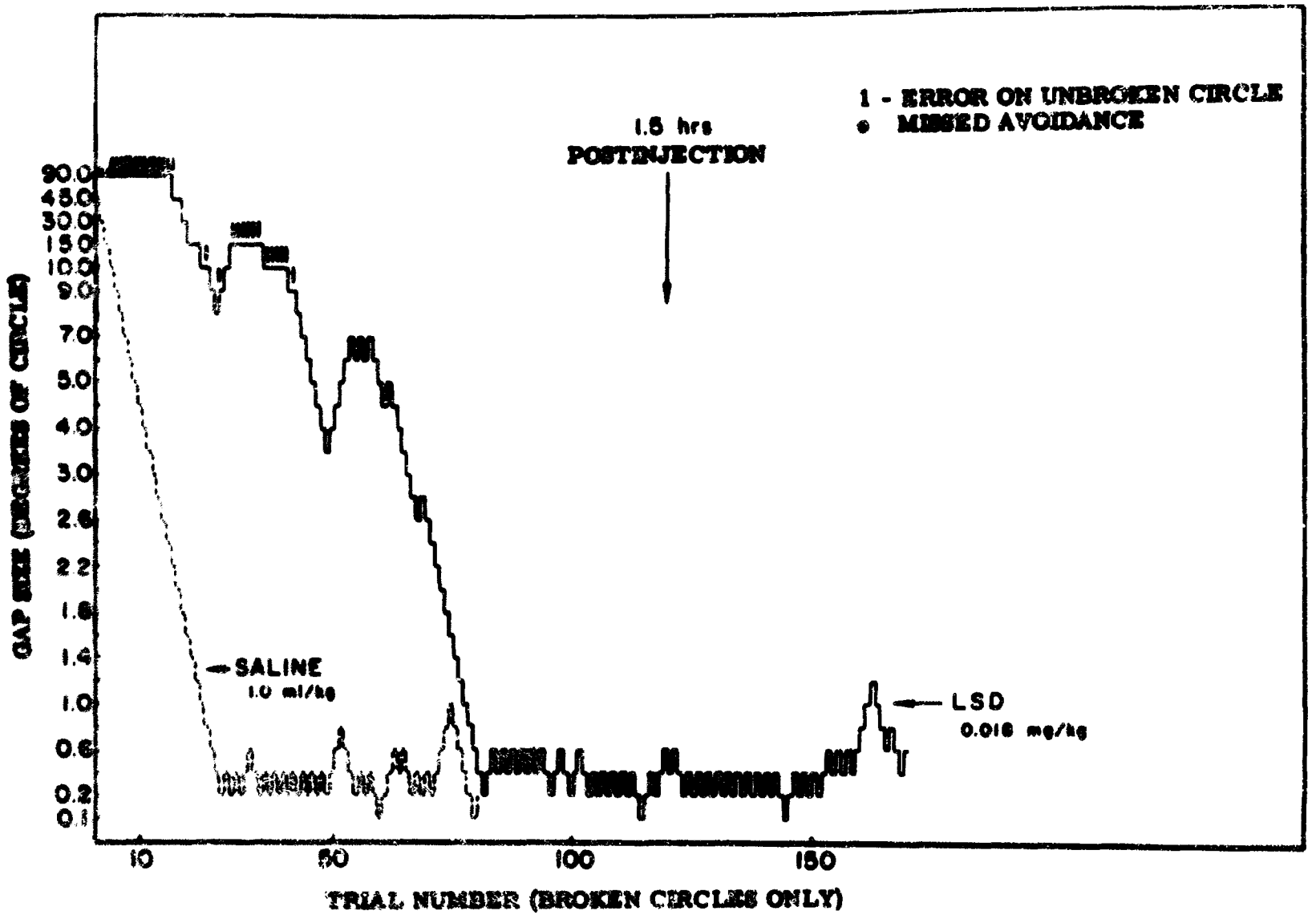


Figure 45. Gap-Size Performance Records With Saline and LSD Maleate

Figure 45 depicts the rapid decline of a marked, short-lived, but immediate effect of 0.018 mg/kg of LSD maleate. Of the first 32 avoidance responses, 8 were missed, and on the first 13 trials with unbroken rings, 13 errors were made (due to persistent left-hand-key responding). During the remainder of the first postinjection hour, 11 additional errors were made on unbroken rings, and no further avoidance responses were missed. Up to this point, it appears that any possible visual-acuity effect was completely obscured by the profound nonvisual central effects of the drug. Aside from one brief setback, recovery was quite dramatic and was essentially completed by 90 min postinjection (trial 60 in figure 45). The saline run of the previous day is not shown in its entirety, but it did not differ appreciably from the LSD run between trials 80 and 150. This indicates that recovery from the LSD was complete by trial 80. The momentary rise in the record at trial 161 was probably not a drug effect since, again, recovery was almost immediate. Thus the record contains no positive evidence for a purely sensory effect of LSD.

Figure 46 shows, in the form of psychometric functions, the effects of saline, methylatropine (1.0 mg/kg), atropine (1.0 mg/kg), and cyclopentolate (0.5% solution instilled one drop to each eye) on the monkey's performance with respect to broken rings only. The three drugs had a rapid onset to peak effect (<30 min) and more than 2 hr duration of this action. This permitted use of all the data from the test sessions in the construction of these functions. The linearity and slope invariance of these functions are noteworthy.

Discussion.

Whether visual acuity in this monkey was, in fact, measured with the present method is questionable. Fletcher, Bowman, and Boelkins* have argued that since the range of gap sizes on which their trained monkeys continued to make errors was far in excess of the range which a purely sensory function should encompass, it was doubtful that visual acuity, per se, was being measured at all. Furthermore, since they were able to show a good fit between their data and a model based on the concept of a stimulus-sampling response that was assumed to be a linear function of the logarithm of the gap size, they concluded that the stimulus-sampling model was as appropriate as

* Fletcher, H. J., Bowman, R. E., and Boelkins, R. C. Discrimination of Broken Circles by Normal and X-Radiated Monkeys. J. Comp. Physiol. Psychol. 58, 312-314 (1964).

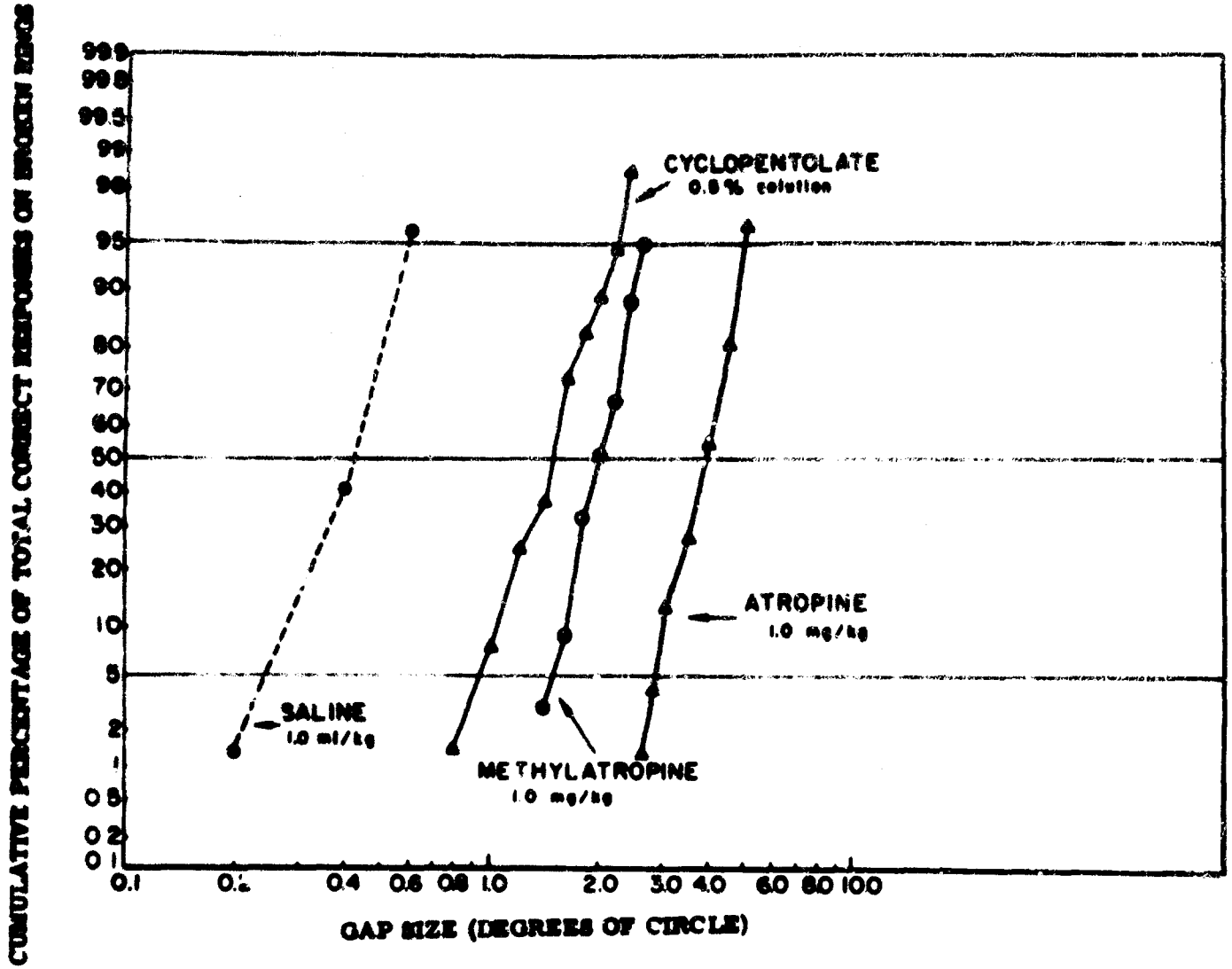


Figure 46. Psychometric Functions Relating Performance to Gap Size With Saline and Three Cycloplegic Agents

the sensory-acuity model in all similar experiments.* In the present experiment, the range of gap sizes in which the monkey made errors when tested with saline was restricted more highly than those reported for the monkeys tested by Fletcher and coworkers. Because of this narrow range of uncertainty and because of the excellent day-to-day stability of the performance, it may be argued that this monkey's visual acuity was being measured, if it is possible to measure minimum separable visual acuity by operant-behavioral techniques. It must be admitted that under different stimulus conditions, a lower normal acuity threshold might have been found for this monkey by using diffraction gratings to produce fields of stripes**; nevertheless, the essential thing is that under the given conditions, a gap size was tested to which the monkey consistently failed to respond correctly, even after weeks of repeated training and testing.

Perhaps the most telling advantage of the present method over previous methods is that it contains a methodological check on whether the monkey's change in performance under drugs was due to some function other than acuity. An independent measure of the rate of false positive responses (errors on unbroken rings) is available, which permits a more valid inference than would be possible in the more usual situation of simultaneous stimulus presentation, where there is but one kind of error measured. In such a situation, it is not possible to conclude with impunity that an increase in errors is or is not due to some function other than acuity. In the present study, the results with atropine provide a good case in point. Behavioral effects other than those ascribable to a raised acuity threshold were present. On the other hand, a reasonably stable performance with respect to gap sizes was achieved. The function plotted in figure 46 for atropine is independent of the other behavioral effects and may be interpreted as showing the maximum drug effect on acuity per se. This dose of atropine apparently did not decrease the precision of the discrimination of broken rings from unbroken rings once the errors on the latter were discounted. Figure 46 shows that the slope of the atropine function

* Brown, W. L., and McDowell, A. A. Visual Performance of Normal and Chronic Irradiated Monkeys. J. Genet. Psychol. 96, 133-137 (1960); Lovelace, W. E., and Davis, R. T. Minimum Separable Visual Acuity of Rhesus Monkeys as a Function of Aging and Whole-Body Radiation With X-Ray. J. Genet. Psychol. 103, 251-257 (1963); McDowell, A. A., and Brown, W. L. Visual Acuity Performance of Normal and Chronic Focal-Head Irradiated Monkeys. J. Genet. Psychol. 96, 139-143 (1960).

** Weiskrantz, L., and Cowey, A. Striate Cortex Lesions and Visual Acuity of the Rhesus Monkey. J. Comp. Physiol. Psychol. 56, 225-231 (1963).

was as steep as the other functions, including that for saline, which indicates merely that there was an increase in the magnitude of the gap consistently required to evoke a left-key (correct) response with the same degree of variability as under normal conditions.

For the specific purpose of drug testing, there is a great advantage to an avoidance procedure in which neither correction nor punishment for errors is employed. This allows one to test for the effect of the drug without interaction either between the drug and the reinforcement (as would be the case with an anorexic drug in a food- or water-reward procedure) or between the consequences of errors and the drug (as would be the case where frustration ensues following errors in a reward procedure or where shock punishment follows errors in an avoidance procedure). The present method constitutes a pure test unconfounded with the elements of a training situation. In this respect, it is quite analogous to the clinical testing situation.

Summary.

A discrete-trial, shock-avoidance procedure is described in which a response-adjusted, stimulus-titration schedule using Landolt rings permitted continuous monitoring of the visual acuity threshold of a rhesus monkey. Results of tests with saline and with five reference compounds were presented to demonstrate the validity of the method.

DISCUSSION

Dr. Joffe (Edgewood Arsenal): This most interesting paper is open for discussion.

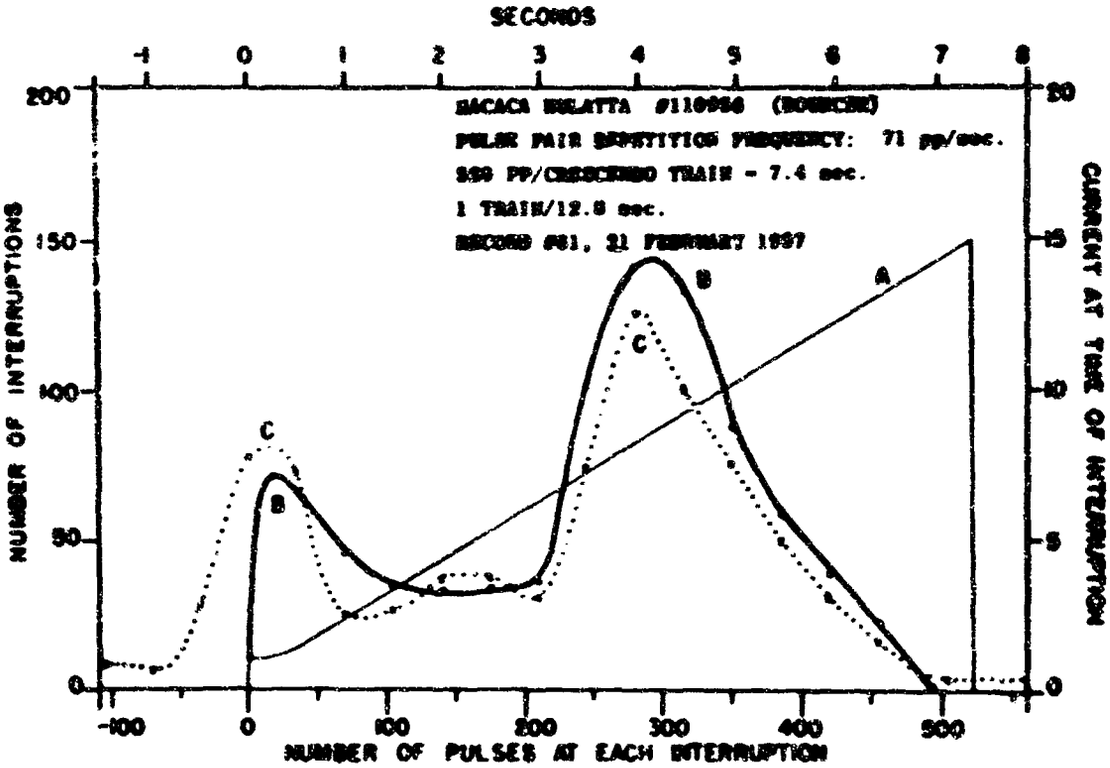
Dr. Otis (Stanford Research Institute): After administering various compounds, Dr. Coate, do you bring your animals back to baseline or test them on baseline before going on to another compound?

Dr. Coate: Yes. Animals were repeatedly tested. Each was tested every day and had a saline run before the drug run.

Dr. Dews (Harvard Medical School): Dr. Coate has gotten a very nice drug effect with his procedure. I am a little curious, though, as to why he did not use a procedure closer to the Blough technique, which would have avoided the difficulty of working in extinction. He could have allowed the monkey actually to guide the angle down toward zero with the right key and to be able to escape from a stimulus correlated with shock by response on the left key only when the circle was complete. By intermittently changing from the Landolt ring to the complete circle on the right key, he would permit the monkey to go to the left key and turn off the warning signal. Thus, one could be sure that the warning light could be turned off only when the circle was complete.

Dr. Coate: I can't give you a very good answer to that except that in trying to work out that procedure on a shock-avoidance schedule, it seemed quite possible that the animal would receive too much shock. This way, you see, unless the animal is suffering from a central effect clearly blocking avoidance behavior, he gets no shock whatsoever throughout the entire session. Frankly, I was hoping to develop a procedure in which there would be no shock-drug interaction or contamination. I didn't want the animal to be wakened from some momentary lapse by a shock. Otherwise, I really have no explanation for why I didn't use those techniques.

Dr. Lilly (Communication Research Institute): Some years ago, we applied a similar technique to the study of central avoidance and escape by using a central stimulus. This technique probably could be applied quite easily to peripheral shock avoidance. The stimulus from the electrodes increased in a linear fashion with time, shut itself off, and then rose again every 13 sec. The monkey was able to use a minimum-effort switch and shut it off at any level that he chose. We plotted the number of times that he shut it off at each value of current against time. This gives the solid curve shown in figure 47. The small bump at low currents is the monkey's detection threshold. The large bump can be explained as follows: If you watch the monkey's behavior at the same time, you find that the turn-over-time point at the top (his maximum number of hits) indicates the start of an escape pattern; his best performance at slightly lower current levels is the period and syndrome of shock avoidance.



Stop-capture: distribution of 750 crescendo interruptions. Curve A is the trace of the crescendo starting at zero pulses, zero seconds and at about 1.0 ma., and ending at 520 pulses, 15 ma., and 12.8 seconds, if not interrupted by the animal. C is the distribution of the touches preceding the effective triggering releases, which are plotted as curve B. Touches occur all the way through the whole cycle; releases only from 0 to about 490 pulses (at values less than the peak).

Figure 47. Stop System Distribution of Responses

In other words, once the current exceeds avoidance levels, the escape pattern became so strong that his learned response of shutting it off is being suppressed, and the instinctual pattern of escape becomes more demanding. He, therefore, shut it off less and less frequently. This technique is very useful (along with those of Blough and Von Békésy) to evaluate drug effects. At that time, we were much more interested in the place we were stimulating in the brain rather than in drug variables. The method goes far beyond appearances; quantitative analysis of affective, emotional, and learned behavior is here.

Dr. Coate: All I can say is that practically all the errors the animal made on unbroken circles were on this avoidance trial.

COMPLEX BEHAVIOR AND ITS DISRUPTION

Dr. Jack D. Findley and Dr. Peter K. Levison
Institute for Behavioral Research

The behavioral effects of drugs, radiation, or other such agents, short of death and extensive disruption, are not easily determined and quantified. Also, generalizations from one study to another and from one species to another are all too frequently embarrassing. I believe that these difficulties, in part, rest with our diverse conceptions of behavior and why it changes. Constant observation of organisms in the natural environment may be one factor that creates a bias in the wrong direction. If we think of the total environment as all the conditions affecting the organism, whether they are within the skin or external, it is not surprising that our observations of behavior under constantly and widely changing conditions lead us to a view of inherent variability and assumed difficulty in prediction.

The bias I would like to stress is one pointed in the opposite direction; namely, that if the total laboratory environment is held sufficiently constant, the resulting stability of behavior is often at a level that would have delighted the most mechanistic of the 18th-century physicists. Such stability is, perhaps, artificial and found only in the laboratory, but it is real and holds broad implications for our current efforts to understand and manage behavioral phenomena. I will focus upon a general structure of behavior that such laboratory stability suggests, and then, in turn, point out three major dimensions or behavioral parameters that appear critical in the evaluation of agents directed at the disruption of behavior.

The behavioral phenomenon to which I refer is not of our own interpretive language nor is it the behavior of the everyday world; it is rather the highly specific and circumscribed performance of laboratory organisms that have been subjected to equally specific and circumscribed environmental manipulations. In essence, an organism responds totally and in an integrated fashion to changes in its internal and external environment. These changes in the environment, where identified and effective, are traditionally designated as stimuli, and the changes in the organism are designated as responses. Many internal changes in the organism and particularly those requiring a minimum of past experience or conditioning history are thought of as unconditioned behavior and are frequently examined within the context of other bodily changes and functions. That class of behavior that is heavily dependent upon a unique training history defines broadly the behavior thought of as voluntary or operating upon the external environment. The structure of this latter class of behavior is best viewed by reference to the various units from which such behavior is compounded. The basic unit of analysis, at present, is a single

class of responses, defined experimentally by manipulation of variables that control instances of this class. An example of such a response class, or operant, would be lever pulling, wheel turning, or any other objective behavior for which designations of class limits are provided and that could be shown experimentally to function as a unit. When the stimulus conditions under which instances of a given operant occur are identified and controlled, larger units of behavior may be created by compounding two or more of the simple units. One larger unit, for example, is a chain in which instances of one specific operant produce the stimulus occasion for a second, and so on.

Another unit, even more involved, is one in which the conditions defining two separate operants are simultaneously present and the organism is essentially presented with a choice or option. Combination and elaboration of simple operants, chains, and options can result in an almost infinite series of structures that increase in complexity and form. When established in the laboratory piece-by-piece and under known conditions, such structures are generally regarded as complex behavior (text table). The structure of behavior in the laboratory differs from the behavior in the natural environment in that definitions are less arbitrary and are tied to specific operations. Lacking in both areas, however, are the kinds of units that would allow a common denominator.

Unit	Notation	Properties
Operant	Op → S^R	1. Identified response class 2. Prevailing stimulus conditions 3. Contingencies for reinforcement 4. Nature of reinforcement
Chain	Op1 → Op2 → S^R	Serial arrangement
Option	Op1 → S^R Op2 → S^R	Parallel arrangement
Tree	Op1 → Op2 → S^R Op1 → Op3 → S^R	Combination

Accepting the definitions and units shown in the list, let us turn to the problem of disruption as best we can at present. The view of complex behavior previously outlined would suggest that its disruption would logically follow any alteration of the variables by which it is defined and maintained. One obvious implication is that the administration of drugs, radiation, or other agents for either disruptive or facilitative effects represents changes in the environment and, hence, if effective, logically results in a different behavior. Thus, one way of viewing the effects of such agents is to picture them

as shifting the behavior under scientific observation. In the case of a disrupting agent, for example, one might observe fewer instances of the behavior originally being measured while at the same time obtaining a large increase in other undefined and unmeasured behaviors. Since it is not feasible to measure all possible behaviors, the experimental evaluation of agents or variables potentially affecting behavior is always limited to samples of given behavior from an almost infinite population.

These samples of specific behaviors established prior to the administration of a given agent represent the baselines against which an agent is effective or not, and from which we try to generalize to overall behavior. Critical to these purposes, consequently, are the samples that are selected. With respect to the difficult problem of selecting the right sample for a given task, I would like to suggest, briefly, three dimensions along which most samples can vary and that probably determine the sensitivity of specific procedures and, eventually, the generality of results.

The first of these I call accommodation, a general term that encompasses the learning process and all other variables producing a transitory baseline. For example, when an organism is presented with a new set of contingencies by which food is obtained, or when it is subjected to a new light-dark cycle, its performance moves through a transitory phase in which it may be said to accommodate to the new conditions. The importance of this dimension in determining the outcome of an experiment is illustrated in figure 48. The data are taken from an experiment examining the effects of low-dose radiation upon a complex matching-to-sample task maintained by electric shock in monkeys. The radiation series was begun before a final level of accuracy had been reached, and the results generally show that a dose of 40 r produces a transitory decrement in matching accuracy only prior to full mastery of the task. The total food intake, on the other hand, remains sensitive throughout the series.

The second dimension is the complexity of the behavior sample under observation. Complexity may be defined as the gross number of individual response units and multiple stimulus conditions involved in the total performance. There is a growing body of information suggesting that long chains, for example, are more sensitive to disruption than short ones and that performances with several options are more sensitive than those with fewer options, etc. Figure 49 illustrates the effects of a 6-mg/kg dose of chlorpromazine upon a baboon's performance on five counting tasks. The subtasks required an exact count to 1, 2, 3, 4, or 5, and each higher count problem substantially increased the behavioral options leading to possible error. This figure shows that the more difficult count problems, 3, 4, and 5, are the most subject to disruption.

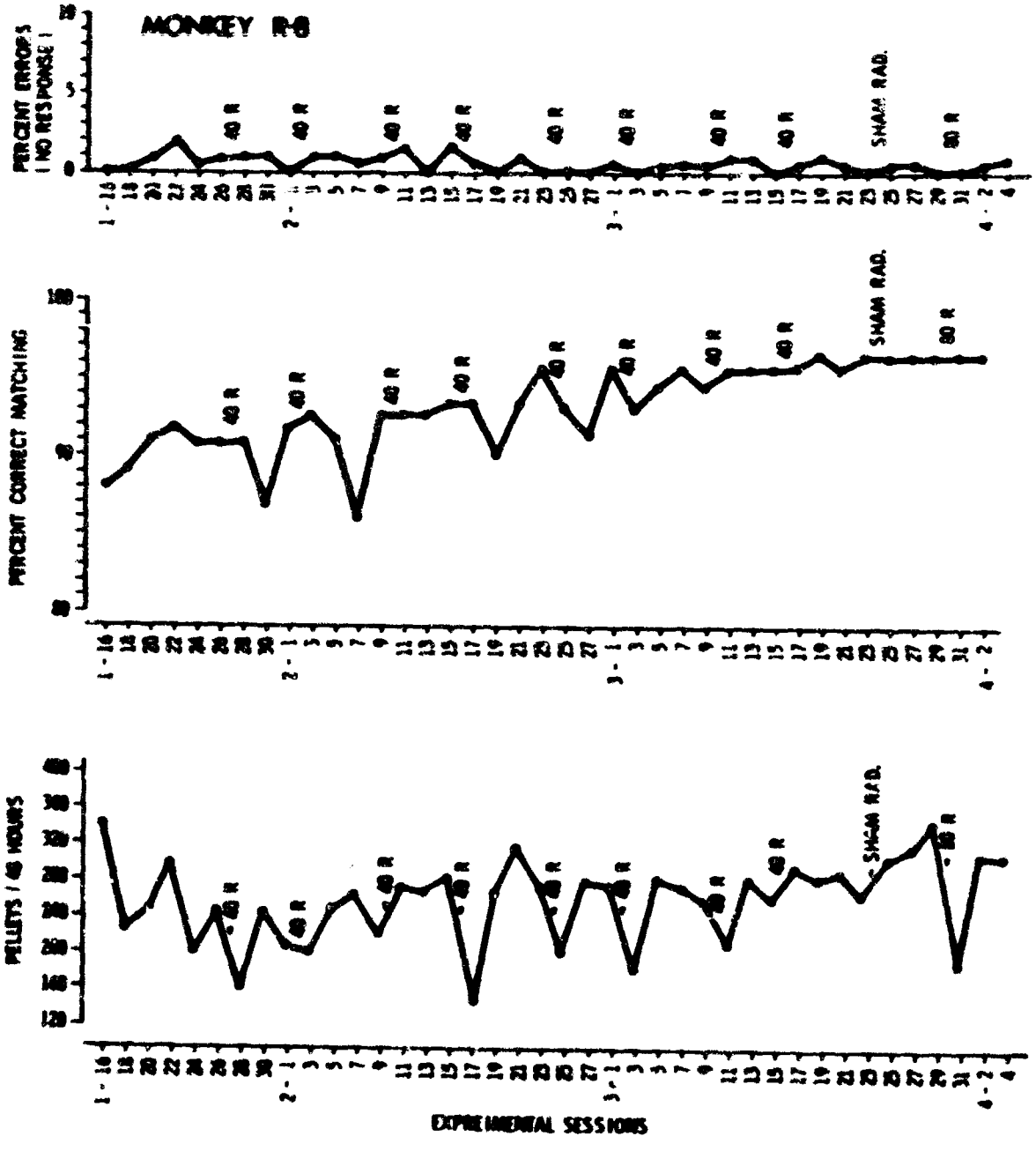


Figure 48. Interaction of Effects Between Radiation Series and Level of Accuracy on a Matching-to-Sample Baseline in the Monkey

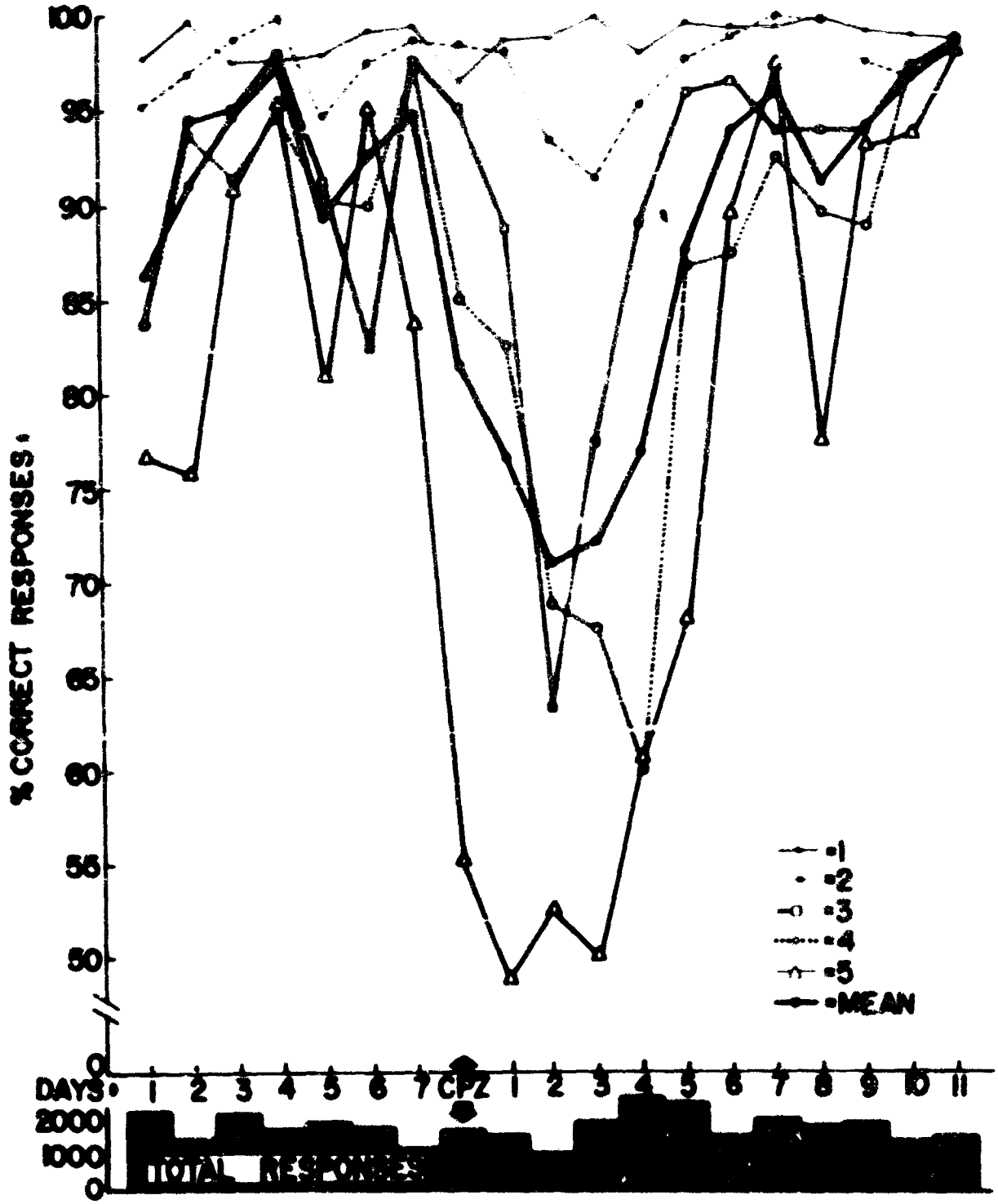


Figure 49. Effects of 6-mg/kg Dose of Chlorpromazine Upon Baboon's Accuracy of Counting Problems 1 Through 5

A final dimension along which a wide variety of behavior samples can vary is that of motivation level. In many experiments, the level of shock or the amount of positive food reward could be varied as a parameter during the course of the experiment and the testing of various agents. Typically, this is not done. The potential importance of this dimension, however, is illustrated by data from an experiment by Sidman* shown in figure 50.

In this experiment, Sidman established avoidance responding in rats by allowing a lever response to postpone a potential shock for 20 sec. A previous experiment had shown that about the same level of responding was obtained with 20% delivery of earned shocks as with 100% shock, and in this experiment, the shock frequency was varied over successive sessions during a course of administration of reserpine. A decline in the rate of responding on the 20% shock schedule may be seen during the period of drug administration. Each time the 100% shock level was introduced, however, the rate of responding rose to its normal level. Changing the shock contingency eradicated the drug effect, even though the two shock schedules showed no differential effects in the untreated animal.

My general point is this: A clear conception of the structure of behavior and our appreciation of its important parameters will become increasingly important both from the measurement of the effects of various agents and for appropriate generalization to the state of flux we call the everyday world. In the laboratory, samples of behavior may be stable or transitory, simple or highly complex, weakly or strongly maintained, and in all combinations of these three dimensions. For example, a complex task might be well mastered but weakly maintained.

We need, then, to be particularly careful about our specifications of behavior as a dependent variable and to examine agents against a background of major parameters. Otherwise, we are likely to miss the effectiveness of some agents, overestimate the effectiveness of others, and weaken our generalizations.

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* Sidman, Murray. Drug-Behavior Interaction. Ann. N. Y. Acad. Sci. 65, 282-302 (1956).

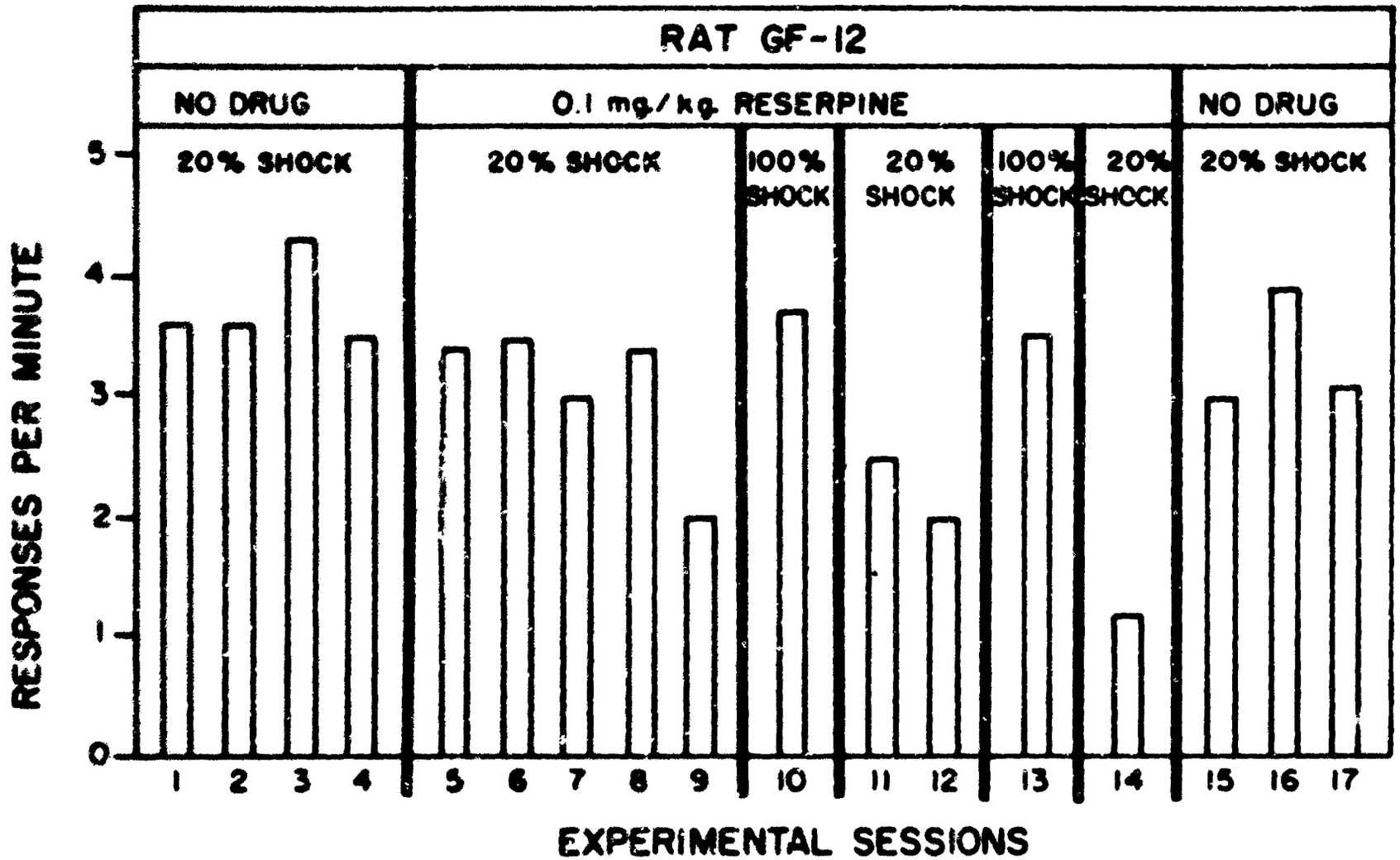

Figure 50. Interaction Between Magnitude of Drug Effect and Frequency of Earned Shocks in Rats

(Taken from Sidman, 1965)

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1. Findley, J. D. Institute for Behavioral Research, Silver Spring, Maryland. Contract 49-193-MD-2607. Studies of Low Dose Radiation Upon Complex Behavior Patterns. Progress Report. June 30, 1965. UNCLASSIFIED Report.

2. Findley, J. D. An Experimental Outline for Building and Exploring Multi-operant Behavior Repertoires. Monograph. J. Exptl. Anal. Behav. 5 (Suppl), 113-166 (1962).

3. Levison, P. K., Findley, J. D., and Ferster, C. B. Institute for Behavioral Research, Silver Spring, Maryland. Contract DA18-108-AMC-26-A-CP3-4025. Drug Effects in Complex Behavioral Repertoires in Monkeys, Baboons, and Man. Technical Report. June 3, 1964. UNCLASSIFIED Report.

DRUG EFFECTS ON LEARNED BEHAVIOR IN T SQUIRREL MONKEY AND THE RAT

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We have developed a procedure for obtaining a symbolic matching-to-sample response in the squirrel monkey. The apparatus used was an ice chest that was divided into two parts. On the front wall of the animal's section, two translucent keys were located about 2 in. apart. The key on the animal's left was the sample key and the one on the right, the comparison key.

When the monkey was in the chamber, a response had to be made on the sample key to start the trial. The sample key turned on either a red, white, or green 7-1/4-w bulb, in the bulb section behind it. The bulb that came on at this time stayed on for the rest of the trial. The comparison key, which had been inoperative, became functional when the sample light was turned on. The comparison key turned on either a blue, yellow, or lavender bulb behind it. Additional responses on the comparison key changed bulb lights behind it in a random sequence. The monkey had to respond on the comparison key until an arbitrary color match had been achieved. If the sample bulb was red, responses had to be emitted on the comparison key until the comparison bulb was blue. A white sample bulb and a yellow comparison bulb or a green sample bulb and a lavender comparison bulb were the other matches.

After a match, an additional sample-key response turned off the lights behind both keys and a food pellet was delivered. If the sample and comparison matched and the monkey continued to respond on the comparison key, the response was called an overstep and was recorded, but no penalty was imposed. If, however, the monkey responded on the sample key when the sample and comparison stimuli did not match, a 60-sec timeout was programed.

We felt that this procedure would be quite sensitive to drugs such as LSD and decided to explore the effect of relatively small doses of the compound in each of our three monkeys (Lucy, Shoulders, and Adolph). Doses of 0.005, 0.01, and 0.02 mg/kg im were given to all three animals. One of the main effects of LSD was to block the monkeys' performance for a period of time after injection. We recorded our data at 20-min intervals and waited until at least 15 trials had been completed in a drug session before we used the data for comparison with baseline accuracy. In other words, the first

time a total of 15 or more trials was recorded at a 20-min reading, the data were regarded as comparable to the first 20-min reading in a control session.

For Lucy and Shoulders, the interval between the resumption of responding and the disappearance of drug effects on accuracy lasted approximately 1 hr. Adolph needed between 1 and 2 hr to reach baseline accuracy. Figure 51 sums up these results.

Lucy's accuracy during the 1-hr recovery period was significantly lower at all drug doses than at similar points during the first hour of the saline baseline sessions. Shoulders' accuracy, which was normally 10 to 15 percentage points lower than that of the other two monkeys, was unaffected by the two low doses of LSD but showed some impairment when 20 μg/kg was injected. After receiving this dose of LSD, Shoulders took 2 hr to complete the first 15 trials. No suppression of comparable duration was noted for either of the other two monkeys at this dose. Adolph showed reduced accuracy after all three doses of the drug, as stated previously.

LSD also affected overstepping, but the direction of the change varied among the animals. The one monkey (Lucy) that maintained a low overstepping per trial ratio before drug administration increased overstepping while the drug effect was in progress. The other two monkeys had relatively high overstepping per trial ratios before the drug was given, but showed a decrease in overstepping during the period of drug effect.

Rate changes during control sessions generally showed a downward trend as the session progressed. The response rate in a 20-min segment was defined as the number of trials initiated by the subject divided by 20 min minus the total time spent in the timeout condition; that is, rate = number of trials/20 min - timeout. During drug sessions, however, the rate increased as the animal recovered. There was a clear positive correlation between accuracy and rate.

After the LSD tests were completed, each monkey was given 5.0 and 7.5 mg/kg of sodium pentobarbital administered im. The 5.0-mg/kg dose stopped responses in two of the three animals for periods ranging from 1 to 2 hr, but there were no changes in accuracy of any of the animals in that session.

Figure 52 shows that all three animals were less accurate following doses of 7.5 mg/kg than during control sessions. Lucy had returned to baseline levels of accuracy approximately 40 min after injection. The accuracy of the other two animals remained below baseline for over an hour after they began responding.

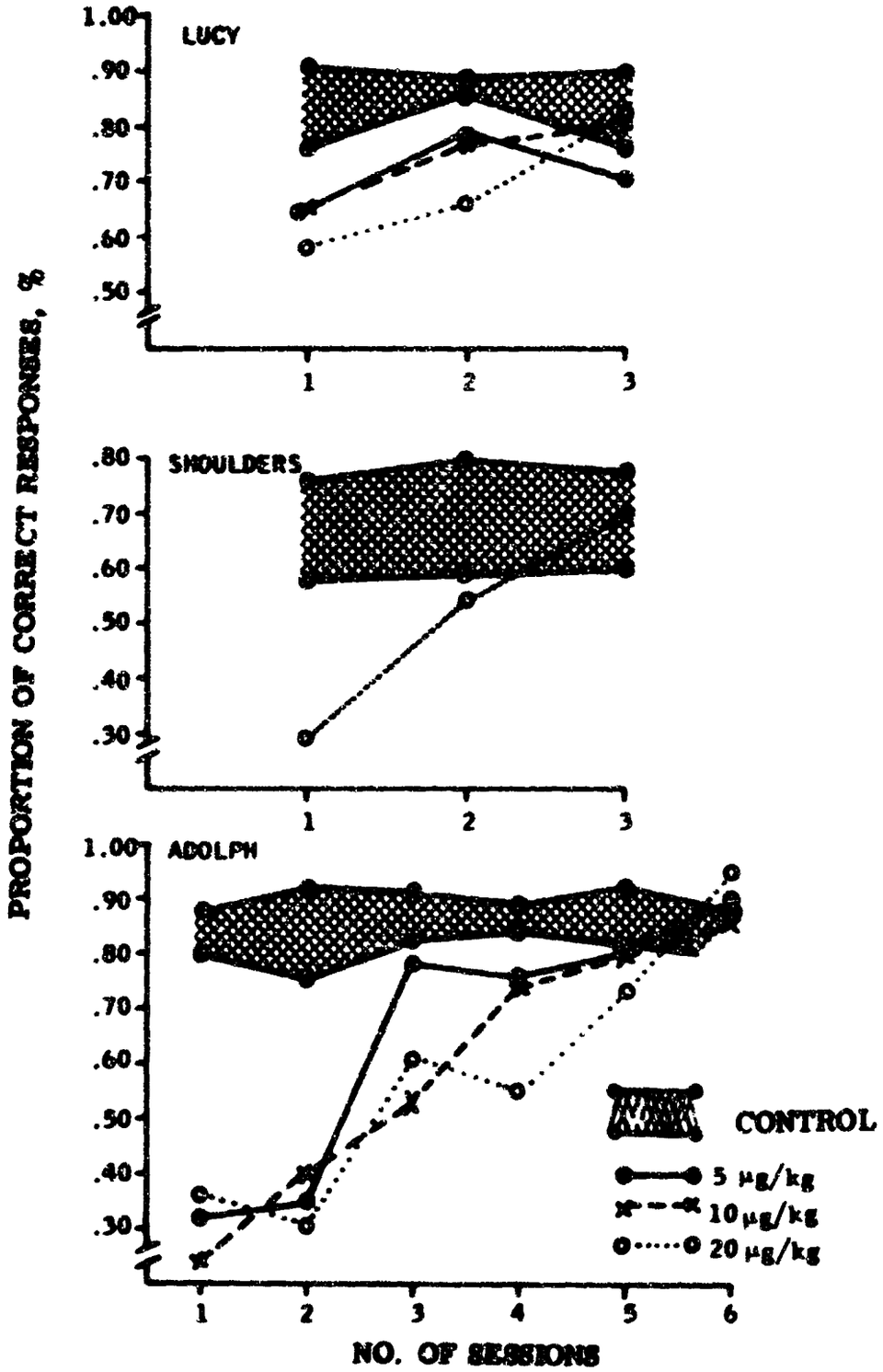

Figure 51. Effects of LSD on Accuracy of Three Monkeys in Matching-to-Sample Response Test

(Cross-hatched areas are the saline control sessions)

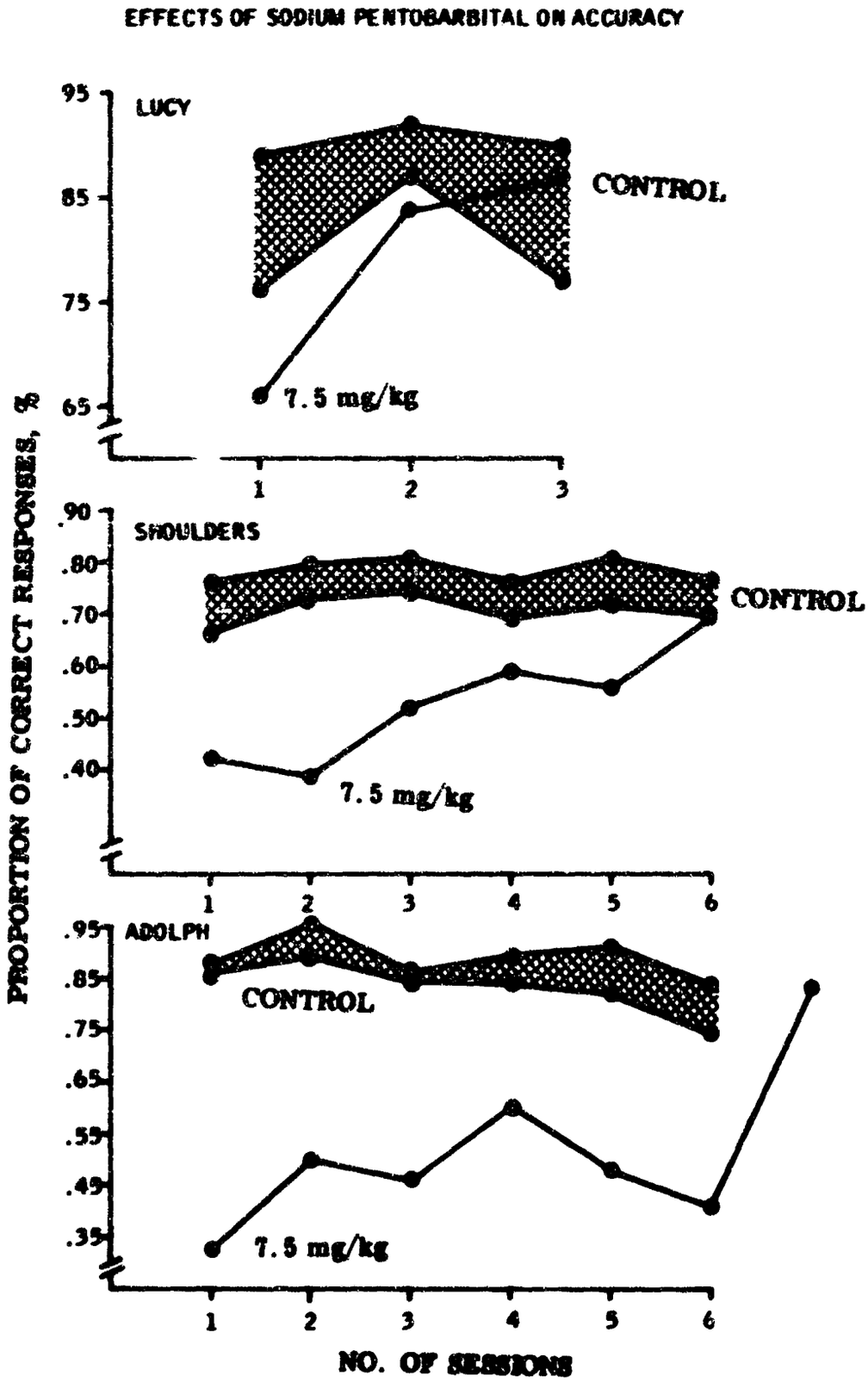

Figure 52. Effects of Sodium Pentobarbital (7.5 mg/kg) on Accuracy of Three Monkeys in Matching-to-Sample Response Test

Drug effects on overstepping are difficult to describe. As with LSD, the effects with pentobarbital varied among animals and were unpredictable. The response rate was reduced, as might be expected.

Our interest in the effects of barbiturates on learned behavior led us to perform another set of experiments. Overton* showed that rats could learn an escape discrimination response in a T-maze under high doses of sodium pentobarbital. In an undrugged state, the subjects were unable to make the response learned under the drug at greater than chance accuracy. The degree of dissociation between the two conditions depended on the drug dose. When pentobarbital and a placebo were administered on alternate days, the rats could learn a different response for each drug state. Learning was faster than that observed in nondrugged subjects that were exposed to exteroceptive discriminative stimuli on alternate days.

An earlier study by Barry, Wagner, and Miller,** showed that 20 mg/kg of amobarbital significantly increased the resistance to extinction when rats that had been trained under nondrug conditions were drugged during the extinction trials themselves. These results were observed while water reinforcement was used in a runway situation. There were major differences between the studies, including the type of motivation and the specific drug used. If Overton's results are compared, however, they lead to the prediction that a barbiturate administered during the acquisition of a learned response should facilitate discrimination reversal later. The study by Barry and coworkers suggests that a barbiturate administered during reversal training, which must include extinction of the prior habit, should impede this training.

The subjects in our experiments were 24 Long-Evans hooded rats approximately 90 days old at the beginning of the experiment. They were given a sufficient water ration after each session to keep their weights between 225 and 275 gm during the course of the experiment. Food was available ad libitum in the home cage.

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* Overton, D. A. State Dependent or "Dissociated" Learning Produced With Pentobarbital. J. Comp. Physiol. Psychol. 57, 3-12 (1964).

** Barry, H., Wagner, A., and Miller, N. Effects of Alcohol and Amobarbital on Performance Inhibited by Experimental Extinction. Ibid. 55, 464-468 (1962).

A Lehigh Valley Electronics Skinner box equipped with two retractable levers was used. Reinforcements were delivered from a 0.06-cc liquid dipper located at the middle of the base of the front wall. The dipper was available to the subject at all times except when in operation.

The subjects were magazine-trained and then placed on continuous reinforcement (CRF). There were three additional 1-hr sessions of CRF during which only one of the levers was available to the subject. Each lever was present on alternate days, with the preferred lever on the first day determining the sequence. Following the CRF sessions, there were six 1-hr sessions of variable-interval (VI), 1-min reinforcement for responses on the one available lever. Then, each lever was again retracted and available on alternate days.

The experiment proper consisted of 5 sessions of 15 reinforcements each. Both levers were available to the subject during this training. Responses on one of the levers were reinforced on a VI 1-min schedule, and an extinction schedule was in effect on the other lever. After the training sessions there were 2 days of rest, followed by three sessions of reversal training, during which responses on the previously positive lever were never reinforced; responses on the other lever were reinforced on a VI 1-min schedule.

The subjects were divided into three groups. Group 1 (12 rats) was given a placebo injection (isotonic saline) before each training and reversal-training session. Group 2 (6 rats) was given pentobarbital before each training session and the placebo before each reversal session. Group 3 (6 rats) received placebo injections before training sessions and pentobarbital before reversal sessions.

The drug or placebo was administered 20 min before each experimental session. Pentobarbital was always administered in 10-mg/kg doses and prepared in concentrations of 10 mg/ml. The placebo was injected in the same volume-to-weight ratio as the pentobarbital.

The data were analyzed in terms of proportion of total responses emitted on the correct lever and total number of responses. There were no significant differences during acquisition on either measure when drugged and nondrugged animals were compared.

The total number of responses did not differ significantly among the three groups during reversal training. Drug treatment, however, had a significant effect on the proportion of responses emitted on the correct lever on day 1 ($F = 6.39$, $df = 2/21$, $p < 0.01$) and day 2 ($F = 3.7$, $df = 2/21$, $p < 0.05$)

of the reversal training session. Figure 53 shows the mean percent correct responses for each group on each day. Group 2, which received pentobarbital before the original training session, was able to make a relatively quick shift to the new reinforcing lever. The superiority of this group over the control group had disappeared by the second day of training. Group 3, which received pentobarbital before reversal training, made a lower percentage of correct responses than the control group until after the third day of reversal training.

We then trained a fourth group of animals using the same procedures described, except that they received pentobarbital before both the acquisition and the reversal training. When this group was compared to the control group, there were no significant differences in any of the responses.

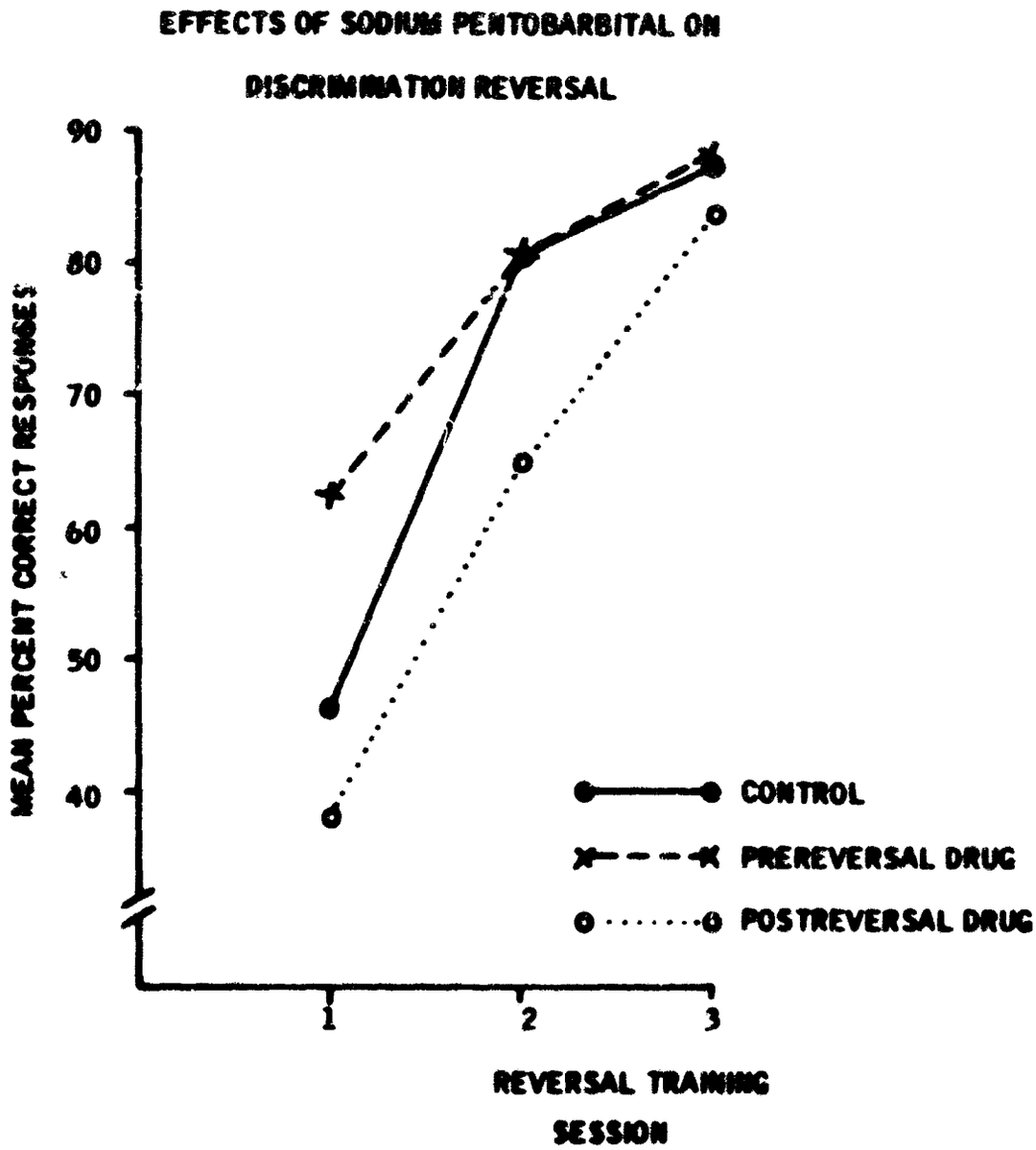

Figure 53. Effects of Sodium Pentobarbital (10 mg/kg) on Discrimination Reversal During 3 Training Days

●—● Group 1, x- - -x Group 2, o· ·o Group 3

SEQUENTIAL RESPONSE TEST FOR USE WITH THE ALBINO RAT

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Introduction.

The current and continued interest at Edgewood Arsenal in the psychotomimetic chemical agents has generated a need for reliable behavioral testing procedures. One such test in current use in our laboratory is the Sequential Response test, which is a modification of the procedure originally described by Polidora.*

Methods and Materials.

Test Apparatus.

The test apparatus is shown in figure 54. The core of this test apparatus consists of an intelligence panel with a centrally mounted Gerbrands liquid dipper. This device is programmed to operate for 5 sec, delivering 0.2 ml of water, and is spotlighted from above when operated. Four transilluminated levers for the rat are spaced equally across the panel, with two on each side of the dipper. A house light located above the feeder and a speaker for the introduction of masking background noise are also provided. The entire unit is housed in a Grason-Stadler sound-attenuating chamber in a quiet room, with the programming and recording equipment located in an adjacent room.

Behavioral Situation.

The test animal is required to perform a 4-lever response chain in this experiment; that is, one response per lever in the sequence 1, 2, 3, and 4, starting from the left. If this is done correctly, the house light goes out, the feeder light goes on, and the dipper rises into position, allowing the rat access to the water reinforcement for 5 sec. This response is counted as a reinforcement whether the animal actually drinks the water or not. Each

* Polidora, V. J. A Sequential Response Method for Studying Complex Behavior in Animals and Its Application to the Measurement of Drug Effects. J. Exptl. Anal. Behav. 6 (2), 271-277 (1963).

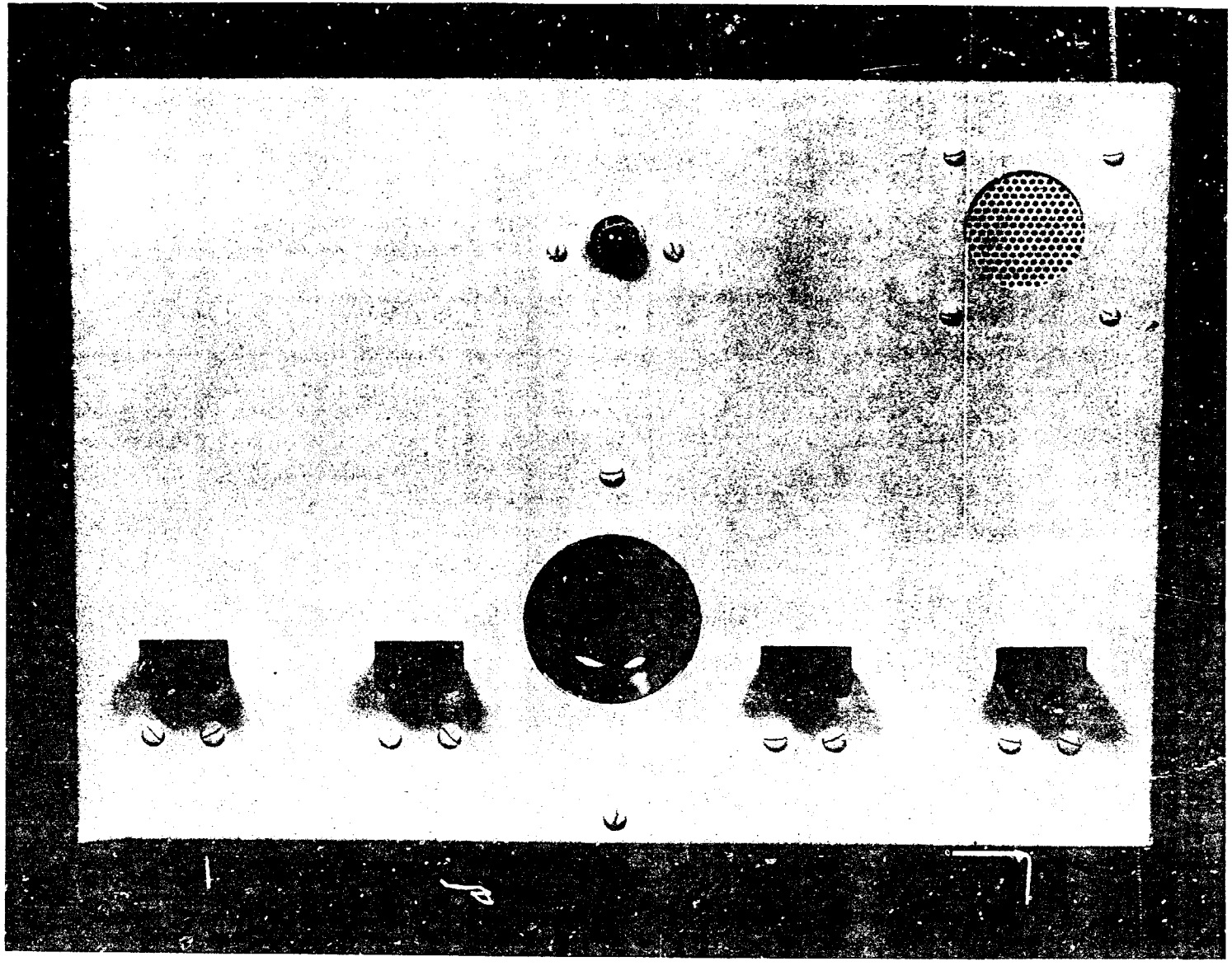

Figure 54. Apparatus for Testing Rats in Sequential-Response Test

lever is illuminated after the correct response is made. An incorrect response (any response not made in the correct order or more than one response per lever) resets the program and turns off the lever lights, and the animal has to begin a new trial starting again from the first lever.

Conditioning Procedure.

Thirty-six experimentally naive, male albino rats, initially weighing 250 gm, were water-deprived for 48 hr prior to conditioning. Starting with the first conditioning session and continuing thereafter, the rats obtained all their water during their 30-min test period. The exception to this procedure occurred over weekends, during which time the animals were not tested. They were given water ad libitum from Friday at 4 PM to Saturday morning at 9 or 10 AM, at which time the water bottles were removed.

The time required to condition the rats to this 4-lever response chain varies from 2 to 7 half-hour training sessions. Once this response chain has been acquired, 10 to 15 additional sessions are required before behavior becomes stable in terms of the variables measured.

Data Generated.

Five variables of behavior were recorded daily for each animal: (1) total responses; (2) total trials; i.e., a sequence ending either in an error or a reinforcement; (3) percent responses leading to rewards; (4) percentage of correct responses; and (5) total rewards. An analysis of variance in 10 test sessions per rat revealed that there were no significant differences in the time of day, day of the week, or particular chamber in which the animal was tested. However, significant variation among animals was noted in the behavioral variables previously mentioned. In view of this latter finding, each animal was used as its own control. The five test sessions prior to each treatment session were used to establish baseline behavior for each animal.

Drug Testing.

Thirty of the conditioned animals were divided into five groups of six animals per group for drug testing. This grouping was based upon a distribution study of percent correct responses only and yielded six groups with a mean of 73%, which varied no more than 2% from group to group.

Prior to drug testing, the subjects were tested several times with ip injections of saline. Response data obtained on the saline days were then compared with the mean values of responses recorded the preceding 5 days using the five variables. A statistical analysis of these data indicated no significant differences between the saline days and the nontreatment days in all parameters examined. To establish a dose-response relationship, the five groups were then given BZ (100, 150, 200, 250, and 300 μg/kg). These animals were dosed by the ip route 30 min prior to actual testing; then, the changes in all five of the behavioral variables during the following 30 min were noted. Twenty-eight days later, these same test animals were regrouped into 3 groups of 10 animals each. Control data were established in the same manner as for the prior testing. Three dose levels of BZ (75, 150, and 300 μg/kg) were selected from the results of the first study and were used in tests employing the same procedure previously described.

Results and Discussion

BZ Dose-Response Relationship

In order to obtain probit information from these data, an empirical method was employed to determine the effect–no effect level of BZ. An affected animal was considered to be any animal whose test-day values fell below 95% confidence limits (CL) of the 5-day control mean values in any or all of the five behavioral parameters measured. We examined these parameters individually and as a composite of all five.

Table IX shows the ED50 values obtained (104 to 174 μg/kg) for the five behavioral variables: both test days are combined, and data are plotted by the method of Bliss.* The individual parameters show varying degrees of sensitivity. A statistical comparison of the ED50's and slopes, however, revealed that there was no statistically significant difference between these values. The last line on the table shows the values obtained from a composite of the five variables. The ED50 calculated in this manner is 136 μg/kg and approximates most closely the value obtained for the percent correct responses.

Considering the probit plot (figure 55) for the first BZ test day on a composite basis, we obtain an ED50 of 139.72 μg/kg with a slope of 3.27. From this plot, we picked the doses used in our second BZ test session to examine the reproducibility of the initial drug effect. These doses (75, 150, and 300 μg/kg) approximate the ED19, ED54, and ED86 values, respectively.

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* Bliss, E. I. The Statistics of Bioassay. Academic Press, New York, New York, 1952.

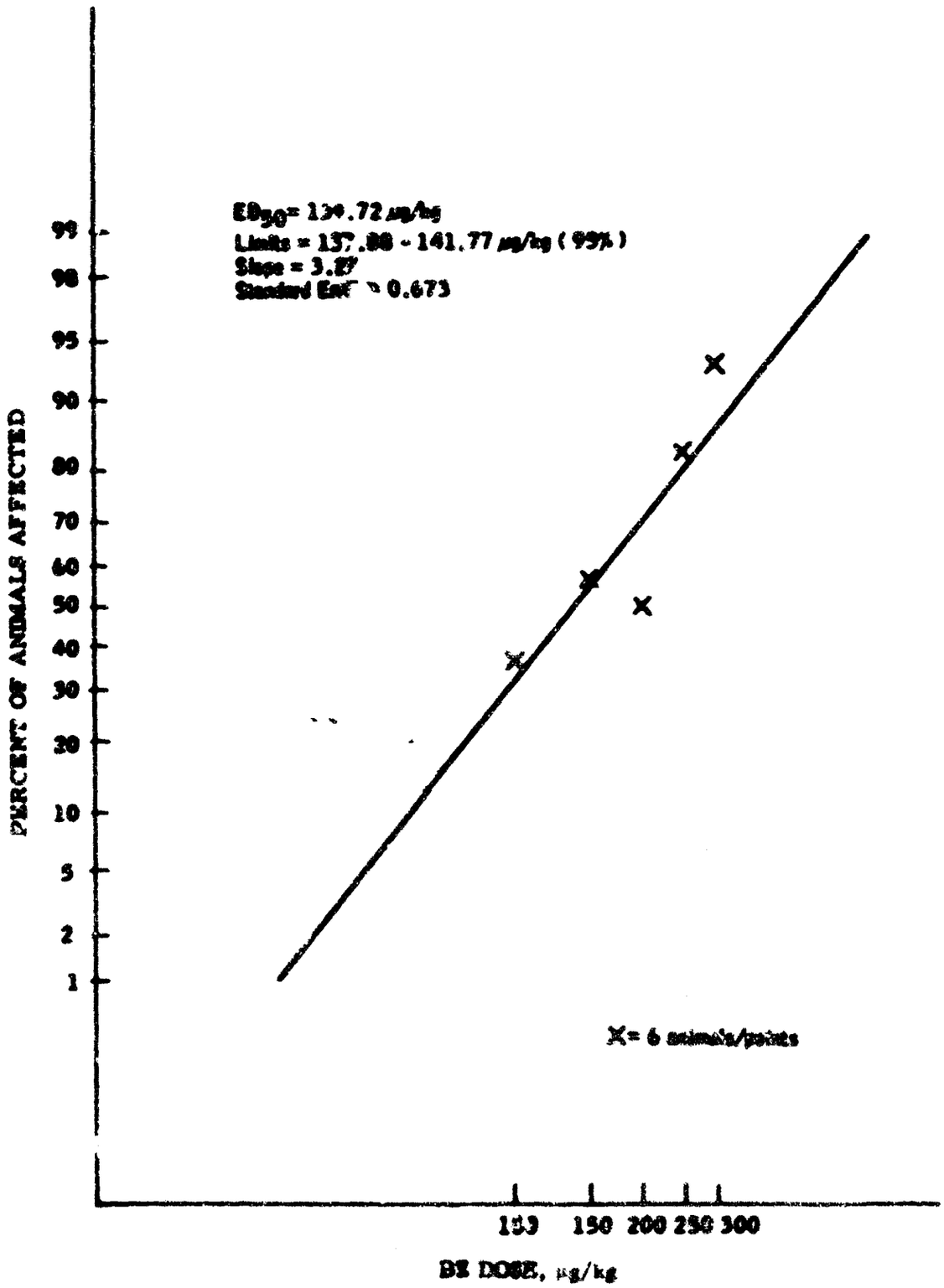

Figure 55. Probit Plot of BZ Dose-Response Relationship in Sequential-Response Test

Table IX. ED50 Values for Five Behavioral Measures in BZ Sequential-Response Test

	ED50 (95% CL)	Slope	SE slope
	μg/kg		
Total rewards	104 (81 - 132)	5.03	1.22
Total R's (responses)	134 (106 - 170)	3.99	0.95
Percent correct R's	136 (104 - 179)	3.33	0.88
Percent R's ⟶ reward	160 (113 - 227)	2.27	0.81
Total trials	174 (127 - 238)	2.57	0.83
Composite	136 (120 - 154)	3.12	0.386

Considering the composite probit plot combining both drug studies (figure 56), we can see that the experimental probit values obtained were an ED22 versus an expected value of 19, an ED56 versus an expected value of 54, and an ED86 versus an expected value of 86—or extremely close to the predicted values. The broken line in figure 56 indicates the probit plot for the first drug test and shows clearly the reproducibility of this drug effect.

Summary.

The primary mission of our group is the search for antagonists to the anticholinergic psychotomimetic agents. The work described represents the necessary prelude to our basic mission and provides us with a necessary behavioral tool to accomplish this purpose. Results from the Sequential-Response tests indicate that:

1. The behavioral procedures employed led to stable performance by the animals.

2. The behavior emitted as the result of these procedures appears to be sensitive to the effects of BZ.

3. The results of the two BZ dose-effect studies demonstrated that the effect is consistent and reproducible.

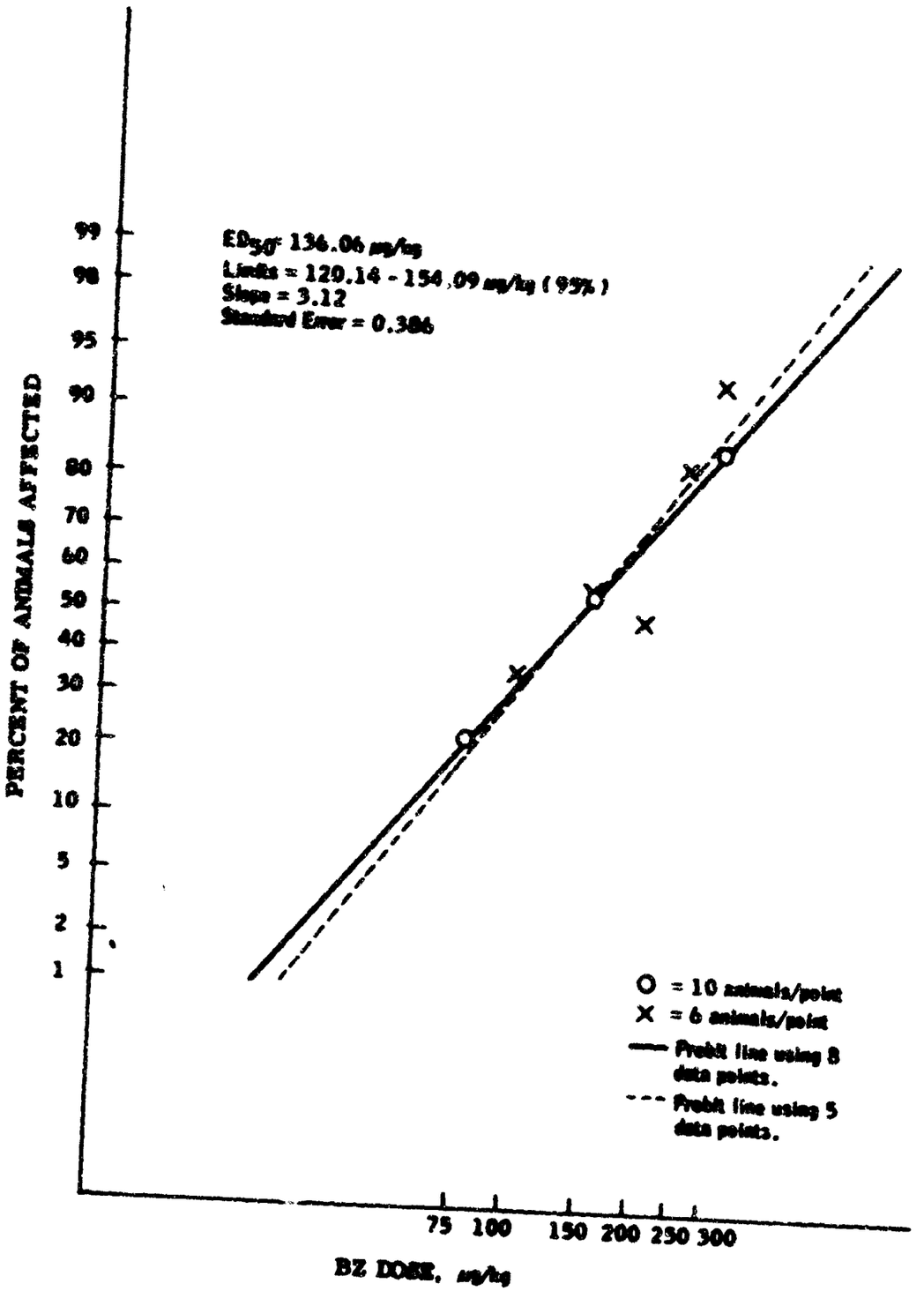

Figure 56. Probit Plot of BZ Dose-Response Relationship in Sequential-Response Test

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SPONTANEOUS PHYSICAL ACTIVITY OF THE RAT: A CRITERION FOR ASSESSING ANTICHOLINERGIC INCAPACITATORS AND THEIR ANTAGONISTS

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The need for reliable behavioral tests that can be used to either screen for and study psychoactive chemical agents or to test for their antagonists in small animals is a current problem. This problem is being worked on in several laboratories in Edgewood Arsenal and by a number of outside contracting organizations.

In the Pharmacology Branch, we are investigating the efficacy of a number of different types of behavioral tests for this purpose. Three of these tests that utilize the rat as a test subject will, we believe, be useful for testing more rigorously those compounds that have passed primary screening as antagonists to anticholinergic psychotomimetic agents. One of these is a physical-activity test described by Chappel and coworkers.* For the time allotted, I will describe our experience with this system and present the results of a number of studies that illustrate its usefulness.

The rationale for its use initially was based in part on the finding by Abood and Biel** that a good correlation can be demonstrated between the psychotomimetic potency of piperidyl glycolates in man and increased physical activity in the rat measured in this system.

Materials and Methods.

The activity apparatus is a modified Chappel-type jiggle cage. The modifications were those of Abood, and the design and dimensions for our units were supplied to us by Abood.† Figure 57 is a photograph of one of the jiggle-cage units.

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* Chappel, C. I., Grant, G. A., Archibald, S., and Paquette, R. An Apparatus for Testing the Effect of Drugs on the Spontaneous Activity of the Rat. J. Am. Pharm. Assoc. 46, 497-500 (1957).

** Abood, L. G., and Biel, J. H. Anticholinergic Psychotomimetic Agents. Inst. Rev. Neurobiol. 4, 217-273 (1962).

† Abood, L. G. Private communication.

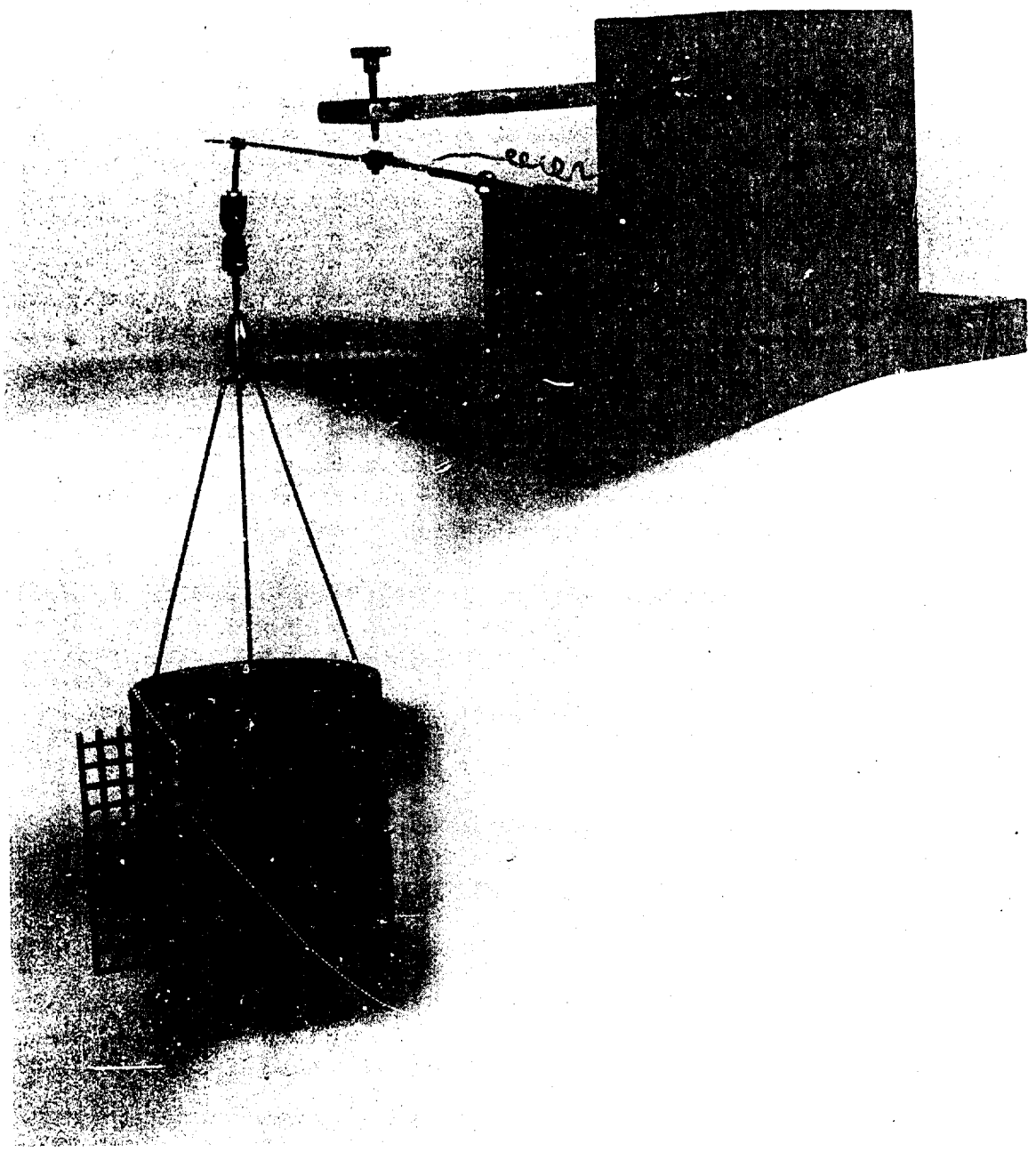

Figure 57. Jiggle-Cage Unit

Each unit consists of a cylindrical wire cage with a solid metal bottom and top suspended from a cantilever beam of stainless spring steel. The upper beam is a rigid iron bar with an adjustable brass screw tapped through it. With a rat in the cage, the gap between the contact surface on the cantilever beam and the brass screw is adjusted so that only legitimate movements of the animal cause the cage to bounce and close the contacts. The two beams are wired in series with a 28-v dc source and a digital counter. Each contact closure produces one activity count, which is the basic datum obtained. Activity counts are measured simultaneously from each of four units over a period of 25 min.

Since a wide variety of environmental factors, such as temperature, background noise, and illumination, can influence activity (Chappel and coworkers and Abood and Biel), the units are operated in a sound-retarding chamber without light (see figure 58). The room temperature is maintained at $71^{\circ} \pm 2^{\circ}F$ by an air conditioner.

All of the recording and controlling equipment is located in another room and connected via cables with the units in the sound chamber.

The test scheme employed requires 48 rats for a single study. The rats are used only once. Experimentally naive male rats weighing between 170 and 200 gm were obtained 16 to 20 hr prior to the test period and housed in the room containing the activity units. Room lights were kept on, and the rats were subjected to a low-level masking noise during this period. Also, all food was withheld, but water was available ad libitum in the storage cages.

In all studies, the rats were divided into six experimental groups of eight animals each. In dose-response studies, one group served as a saline control and the remaining five groups received graded doses of the agent; in an agent-antagonist study, one group served as a saline control, another group as an agent control, and the remaining four groups received a single dose of the agent plus graded doses of the proposed antagonist. All drugs were administered ip.

Table X shows the test paradigm. The Roman numerals refer to the six groups and identify the approximate time of day and the cage (lettered A, B, C, and D) in which each of the six groups of eight rats were run in a study.

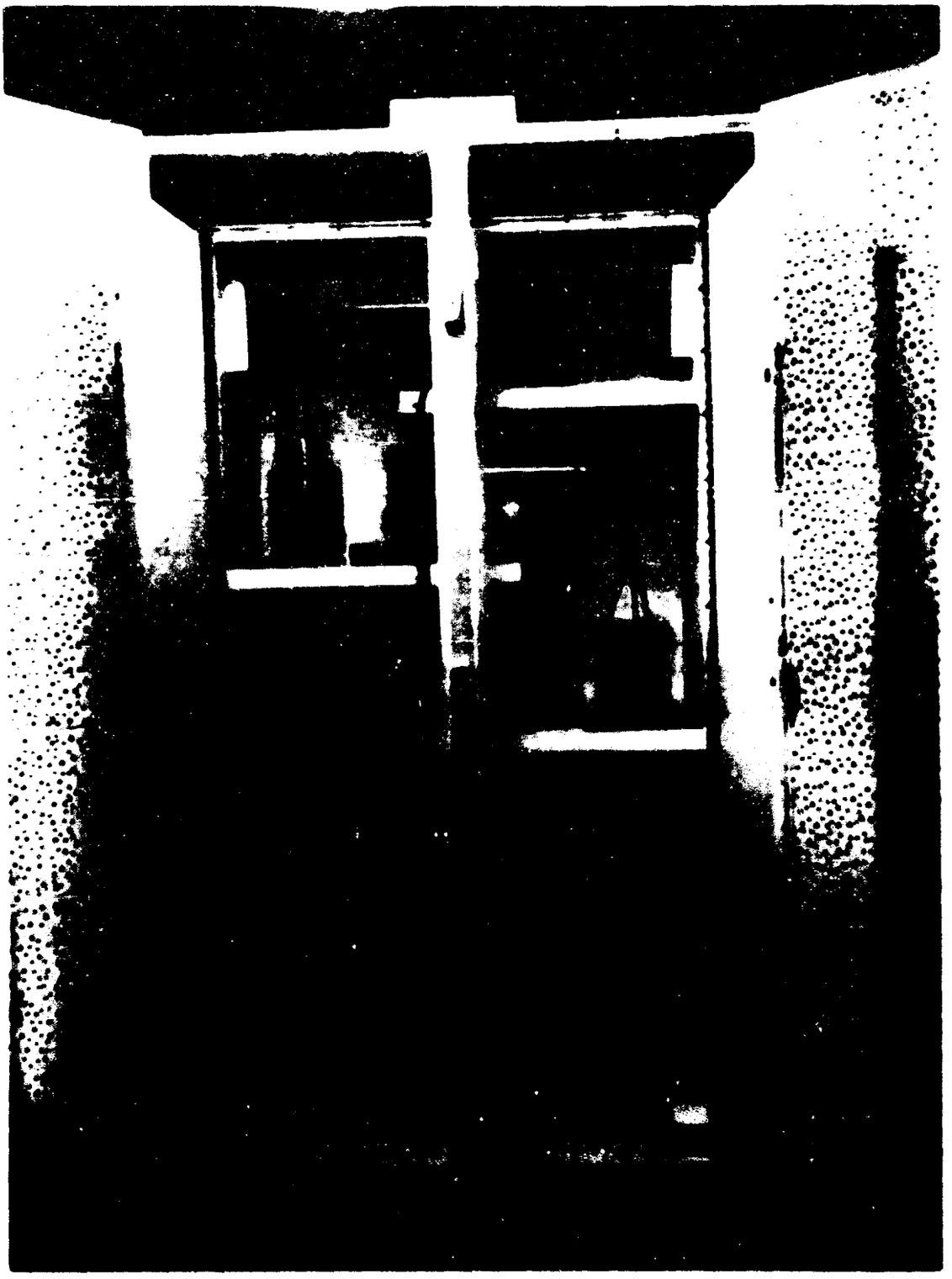

Figure 58. Jiggle Cages in Sound-Retarding Chamber

Table X. Chappel-Abood Paradigm for General-Activity Test

Trial number	Start count time	Group			
		Cage A	Cage B	Cage C	Cage D
1	0850	III	VI	I	IV
2	0930	IV	II	V	I
3	1010	I	III	VI	III
4	1050	V	IV	II	VI
5	1130	VI	I	III	II
6	1210	II	V	IV	III
7	1250	III	VI	I	IV
8	1330	IV	II	V	I
9	1410	I	III	VI	V
10	1450	V	IV	II	VI
11	1530	VI	I	III	II
12	1610	II	V	IV	V

Table XI is a summary of a three-factor analysis of variance on 7 different saline-control studies involving a total of 336 rats. It is evident from the analysis that the time of day and the cage employed had no significant effect on the activity counts. The between-day difference was highly significant. Each of these studies was performed in a different month, and a further analysis revealed this difference was in reality a reflection of a seasonal variation, a finding also reported by Chappel and coworkers. Controls run on successive 2- to 3-day periods do not show significant difference in counts. However, as was already pointed out, one group in each study was always used as a saline control, and all treated groups were compared with it.

Agent Studies.

The effects on activity of graded doses of BZ, BD, BB, and BC have been assessed in this system. In each study, the agent was administered 25 to 30 min prior to the counting period.

Table XI. Activity Counts

Sources of variation	Three-factor analysis of variance			Significance
	Degrees of freedom	Mean square	F-ratio	
Time of day	5	2076	1.019	NS
Cages	3	3270	1.605	NS
Days	6	8282	4.066	$p < 0.001$
Cages - time of day (A)	15	3062	1.503	NS
Time of day - days (B)	30	2569	1.261	NS
Cages - days (C)	18	3049	1.497	NS
A × B × C	90	1947	0.956	NS
Error	168	2037	—	—

Note: Grand mean activity counts for 7 days = 751.

Figure 59 shows the dose-response curves for each of the agents on a semilog plot. All agent doses are expressed as the free base. The control value is the mean control count for the five studies described in figure 59 [± the largest standard error (SE) encountered in an individual test]

When proposed antagonists are investigated, varying doses of the antagonist are tested against a single dose level of the agent. The agent dose employed is the lowest dose in the dose-response study that produced a group mean count significantly different from the group mean control at the 95% confidence level. For BZ, BD, BB, and BC these doses are 400, 250, 100, and 75 μg/kg, respectively. The SE range is indicated for each of these values in figure 59.

The compound BZ methyl bromide is a quaternary BZ. It was tested primarily to obtain some insight into the orgin of the activity induced by

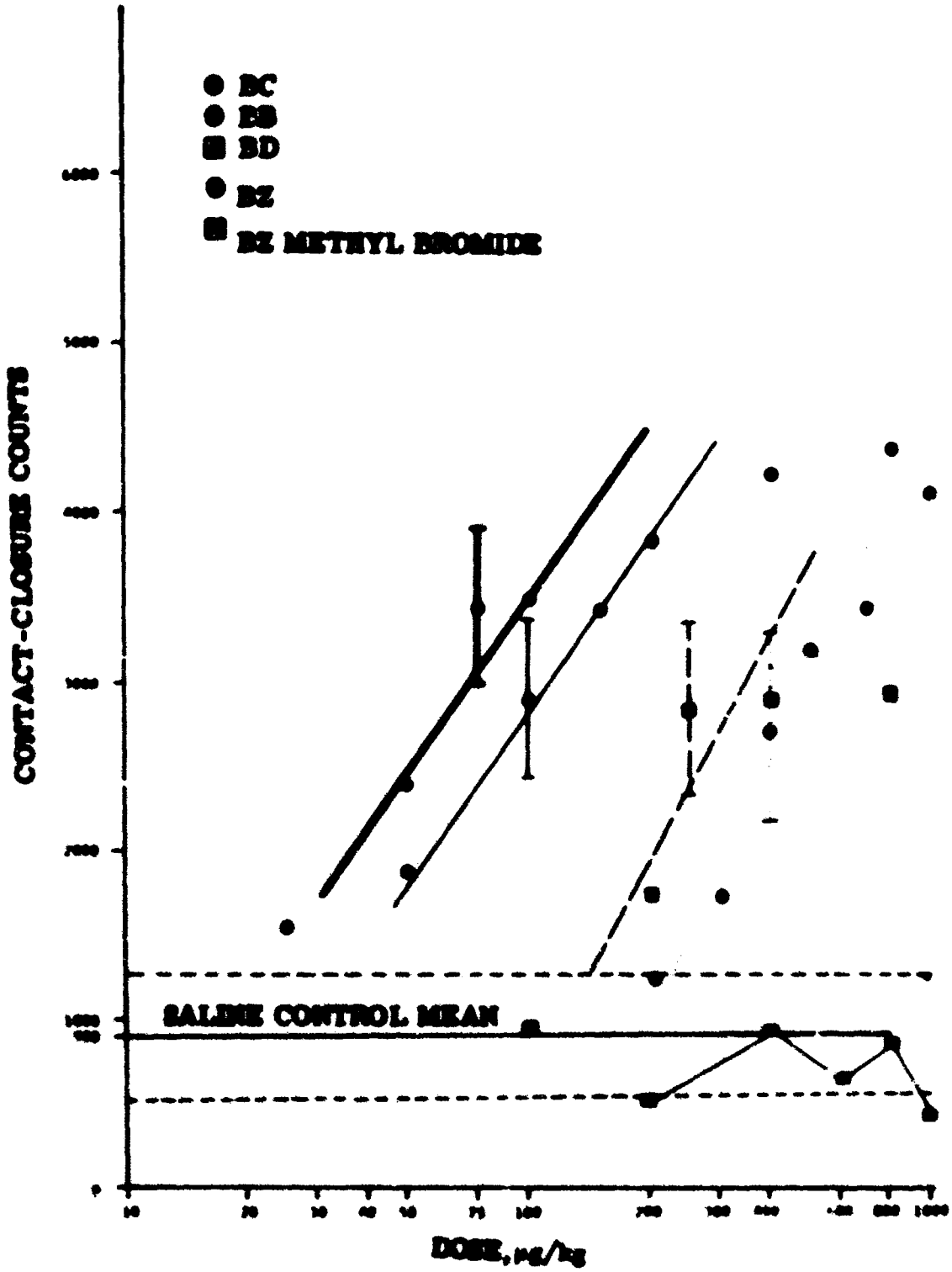

Figure 59. Dose-Response Curves for Various Compounds Administered Ip to Rats

the anticholinergic agents. The Toxicity Screening Branch* has determined that this compound in mice is as potent peripherally as BZ but lacks any discernible central actions. Since it is a quaternary compound, it should not pass into the CNS readily. The fact that it had no more effect on activity than saline is good presumptive evidence that the physical activity generated by these agents in rats is centrally inspired and not due to some peripheral effect.

Using an empirical method, we have been able to convert the data obtained in these studies into probit information. To determine the effect-no effect level for agent-treated animals, we simply considered any individual animal whose counts fell below the upper 95% confidence limits for the control as a no-effect animal.

Figure 60 contains the probit lines for the four compounds when these data are treated in this manner and plotted according to the method of Bliss.** The ED50 values for the agents are indicated in the key and by the two direction arrows on each curve. The ED50's for BZ, BD, BB, and BC are 294, 166, 40, and 25 μg/kg, respectively. The potency ratio between the ED50's for BZ and BD is not significant, and the same is true for the difference between BB and BC. However, the differences between the potencies of BB or BC compared with those of BD or BZ are significant. This latter difference of the ED50's is from twofold to fourfold. It is interesting to note that at the ED99, these differences in potency are of the order of 1.5 to 2.5 and are not significant.

The doses of the agents employed in the agent antagonist studies to be presented were between the ED75 and ED85, as defined by the plots in figure 60.

Antagonist Studies.

The Clinical Research Department† has determined that eserine, THA (tetrahydroaminoacridine), and VX will antagonize the psychotomimetic effects of BZ in volunteers. To test the efficacy of this system, we have also

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* Lennox, W. J. Toxicity Screening Branch, Edgewood Arsenal. Private communication.

** Bliss, E. I. The Statistics of Bioassay. Academic Press, Inc., New York, New York. 1952.

† Ketchum, J. S. Clinical Research Department, Edgewood Arsenal. Private communication.

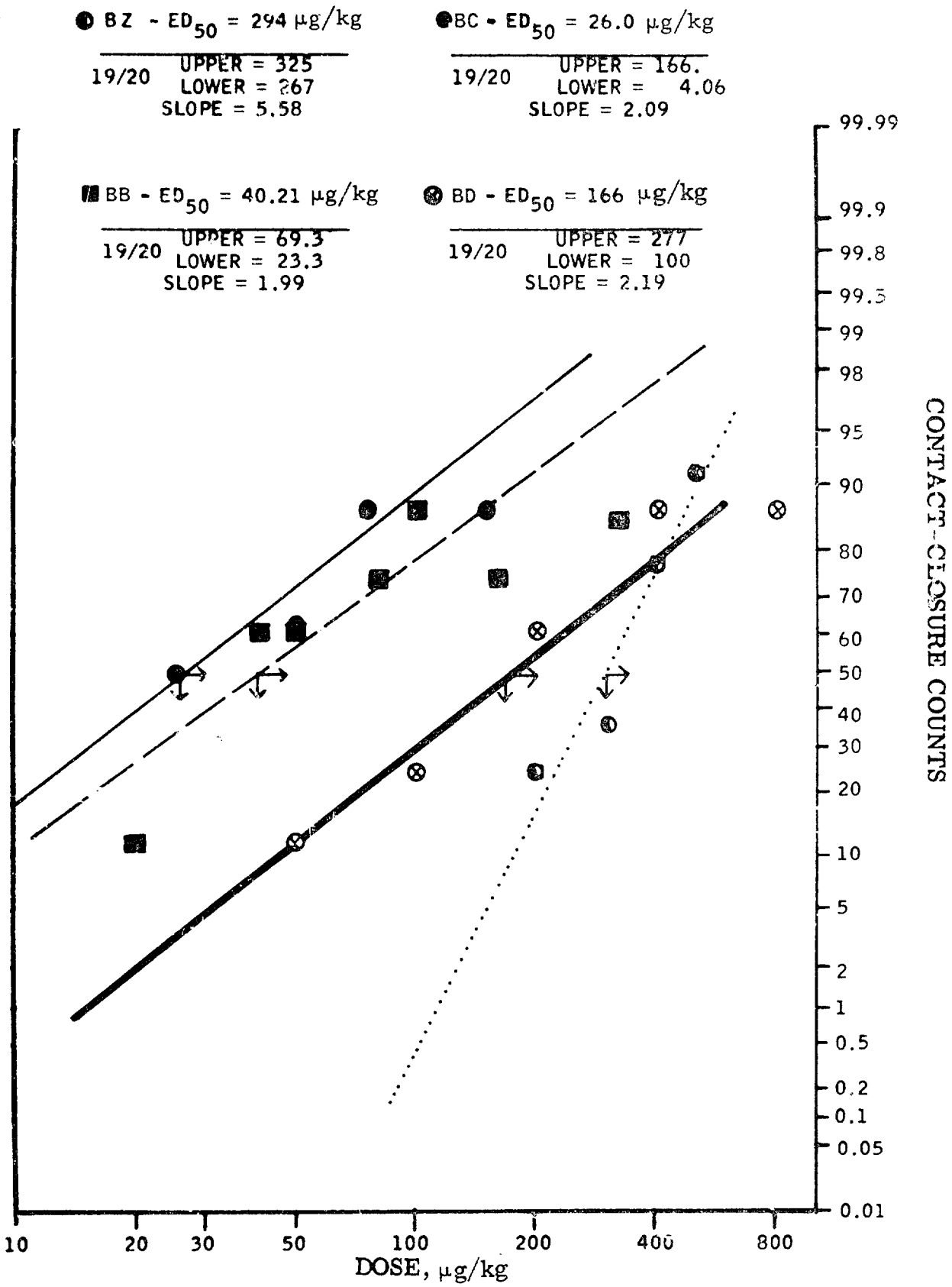

Figure 60. Probit Analysis of Dose-Response Data

investigated the effects of eserine, THA, and VG against three of the incapacitating agents. In each of the studies, the antagonist was administered 20 to 25 min after the agent was injected.

Table XII contains a summary tabulation of the results. The three agents were BZ, BB, and BC. The agent doses, as mentioned before, were 400 μg/kg for BZ; 100 μg/kg for BB, and 75 μg/kg for BC.

There are three features of this tabulated summary (table XII) to which I would like to direct your attention: (1) With the exception of VG versus BC, only those dose levels of a particular antagonist that produced statistically significant antagonism in each of the nine studies represented are included in the table; (2) there are two scoring methods indicated, a count-reduction score and a probit score; (3) the results themselves as expressed by these two scoring methods.

The count-reduction score utilized a 3-point scoring method based upon a statistical comparison of the mean counts of each of the antagonist-treated groups with the saline control and with the agent control in each study. A value of 1 indicates no antagonism because the treated group was different from the saline control but like the agent control. A value of 2 indicates partial antagonism because the treated group is like both controls. And a value of 3 indicates complete antagonism because the treated group was like the saline control but unlike the agent control.

The probit score in the sixth column of table XII is derived from the data starting in the fourth column. The probit value (percent effect) of the treated group is derived from individual counts, as previously described. The fifth column indicates the dose corresponding to the probit values in the fourth column. It is obtained from the probit plot in figure 60. The sixth column shows the percent decrease in the agent-dose effect. For example, 500 μg/kg of eserine administered to rats previously treated with 400 μg/kg of BZ produces an effect similar to a dose of 280 μg/kg of BZ or a 30% reduction in effect.

Eserine and THA produce at least a partial antagonism to all three agents as judged by both scoring methods. The most dramatic results, however, were obtained with THA against BB, as judged by the probit score method. The sensitivity of the latter method is obvious, as it delineates the degree of antagonism found by the first method. VG worked well against BB and BZ but was completely ineffective in doses up to 200 μg/kg against BC in this system.

Table XII. Summary Agent - Antagonist Studies

Agent / Antagonist	Effective antagonist dose	Count-reduction score*	Probit value	Agent dose-equivalent from probit analysis	Probit score
	mg/kg		%	mg/kg	% decrease in agent-dose effect
BZ (0.400 mg/kg)					
Eserine	0.500 - 1.000	2 - 2	44 - 38	0.280 - 0.260	30 - 35
THA	5.0	2	67	0.350	18
VG	0.200	2	38	0.260	35
BB (0.100 mg/kg)					
Eserine	5.0	2	57	0.048	48
THA	2.5 - 5.0	3 - 3	25 - 14	0.019 - 0.012	81 - 88
VG	0.200	2	50	0.040	47
BC (0.075 mg/kg)					
Eserine	0.250	2	63	0.038	49
THA	2.5	2	72	0.049	35
VG	up to 0.200	1	88	0.095	+20

* 1 = no antagonism, 2 = partial antagonism, 3 = complete antagonism.

Discussion and Summary.

The quantitative differences between effective doses of these agents for psychotomimetic effects in man and increased physical activity in the rat are considerable, ranging in the rat from 60 to 350 times the dose required for man.

There are three basic qualitative similarities that make this test valid: (1) The potency differences among the four agents are similar and in the same direction as encountered in man; Ketchum's group* has not found a significant difference in potency between BD and BZ nor between BB and BC, but BB and BC are more potent than BD and BZ by a factor of roughly 2. The potency of these two sets of agents as measured in the rat in this system is different by a factor of 2 to 4 and in the same direction. (2) the antagonists that are effective against these agents in human subjects are also effective against agent-induced activity in the rat; (3) the degree of antagonism is essentially the same for a single injection. For example, a single injection of eserine in a human subject previously treated with an incapacitating dose of BZ will produce, as a rule, only a partial recovery as judged by a performance test, and may amount to 70% or less. Repeated treatments every 40 min are required for full recovery to occur in several hours.

It is of interest to determine whether or not an increase in physical activity is a psychotomimetic effect. The question, of course, cannot be answered. From a pragmatic point of view, however, the answer is unimportant, even if it were negative, as long as this effect continues to parallel, in most respects, the psychotomimetic effects or potency of these agents and their response to treatment in man. The fact that BZ methyl bromide does not produce any changes in rat activity, as already stated, is good presumptive evidence that the increase in physical activity produced by these anticholinergic agents is of central origin.

The possibility of false positive tests is a problem yet to be investigated in our laboratory. In regard to this question, Abood and Biel** have tried a number of tranquilizing agents as antagonists to Ditran, and they work

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* Ketchum, J. S. Clinical Research Department, Edgewood Arsenal. Private communication.

** Abood, L. G., and Biel, J. H. Anticholinergic Psychotomimetic Agents. Inst. Rev. Neurobiol. 4, 217-273 (1962).

only if given prior to treatment with the agent. They found that the barbiturates do not have much effect, even when administered beforehand.

The efficacy or validity of this test for the purposes mentioned has been partially demonstrated previously. The work just presented reinforces that information. The only new features presented were the use of more controls and the application of probit analysis to these data. By doing so, we believe we have enhanced the reliability, sensitivity, and utility of this simple behavioral test.

DISCUSSION

MAJ Ketchum (Edgewood Arsenal): I found your paper most fascinating. Did you find any reduction in activity with low doses? We see this clinically in the volunteers, either with low doses, or perhaps, early during the initial onset.

Mr. Armstrong: Do you mean reduction in activity with the agents? Yes, we've seen this every now and then at very low doses. When we first started studying the agents, we started out at very low doses. We didn't pay too much attention to it until we found that three or four of the agents did the same thing. We haven't had time to look into this any further to see what it might mean.

Dr. Rosenberg (Sterling-Winthrop): In working with some anticholinergics (I don't know whether they are the same) in another type of activity test, I found that we could increase the sensitivity to these compounds manyfold by introducing a stress into the cycle. This consisted of a 30-sec period of noise every 3 min, and the noise was a loud bell programed in at about 100 db. We found that we could remarkably increase the sensitivity of the psychomotor test to the potency of the compounds. I don't know whether or not this would work in your cages. But it was a fascinating phenomenon.

Mr. Armstrong: We haven't tried it yet.

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EFFECTS OF HALLUCINOGENIC DRUGS ON AVOIDANCE PERFORMANCE AND BAR PRESSING OF GERBILS

Dr. Jack Pearl, Dr. Franklin J. Rosenberg, Mr. John Fitzgerald, and Mr. Edward Ferguson
Sterling-Winthrop Research Institute

Method.

Why use gerbils, rather esoteric rodents, rather than mice or rats? We chose to work with gerbils because of their sensitivity to drugs, their high level of activity, and their ease in acquiring avoidance responses. The gerbils were trained to press a bar to avoid shock when a 5-sec warning noise was presented. (Details of the method will be given later.) Three indicants of performance were the total number of bar presses, avoidance responses, and escape responses. The most useful indicant was the number of bar presses. Because this indicant may in part be a function of the general level of activity, spontaneous motor activity was measured in photocell units. All drugs were given subcutaneously (sc), most of them 30 min before testing; some drugs (phenothiazines, for example) were given 60 min before testing. For the avoidance test, each animal served as its own control by receiving all doses of a given drug and control vehicle. Seven to nine gerbils were assigned for testing with each drug. For the activity test, independent groups of four to six gerbils were used for each dose.

Apparatus and Programing.

From six to nine Grason-Stadler Model E 3125A Skinner boxes were available. Each box was modified by removing the original bar and substituting a Lehigh Valley Model 1352 bar in a corner of the box. A force of about 18 g's acting through a distance of 1/16 in. depressed the bar sufficiently to operate the switch and to count as a bar press. The warning stimulus, delivered by a Grason-Stadler Model 901 generator, was white noise of a level of about 74 db. The shock was delivered by Grason-Stadler Model E 1064 GS generators set at 1-ma calibration.

Control racks were programed to present the noise every 30 sec for a total of 50 times. The bar ended the noise and prevented the delivery of the shock or ended both the noise and the shock, depending on when the gerbils pressed the bar. In the absence of a bar press, the noise acted alone for 5 sec and then was joined by shock for another 5 sec. Holding the bar down had no effect on the experimental operations. The bar had to be released after each press for the next press to count. Impulse counters recorded the total number of bar presses, avoidance responses, and escape responses.

Spontaneous motor activity was recorded in 12 circular metal cages, 16 in. in diameter and 3-3/4 in. high. Impulses were registered on counters when the animal broke the photocell beam that intersected the diameter of each cage. Activity for two consecutive 30-min test sessions was recorded with one gerbil in each cage.

Medication Procedure.

Most drugs were given 30 min before testing. Those that were given 60 min before testing were chlorpromazine, trifluoperazine, and imipramine. On the avoidance test, gerbils were medicated and tested only once The drugs were injected at a volume of 1 ml/kg. (The results are reported in mg/kg of the salt.)

Statistics.

For the avoidance test, the mean number of bar presses, avoidance responses, and escape responses were computed for each dose and for the control condition. The difference in the means between the drug and the control conditions are shown in the tables. The significance of differences between the means was evaluated with the Wilcoxon assigned-rank test.

For the activity test, the percent of change in activity was computed as follows:

The percent increase in activity was $\left(\frac{\text{drug mean}}{\text{control mean}} - 1\right) \times 100$

The percent decrease in activity was $\left(1 - \frac{\text{drug mean}}{\text{control mean}}\right) \times 100$

The Kruskal-Wallis analysis of variance was the statistical test.

Results and Discussion.

Reference Drugs

To illustrate the gerbil's pattern of response to drugs, results with several well-known drugs will be given: chlorpromazine, imipramine, d-amphetamine, atropine, morphine, caffeine, and phenobarbital (table XIII)

Chlorpromazine at 1 mg/kg and trifluoperazine at 0.1 mg/kg decreased bar presses, avoidance responses, and escape responses. In the

Table XIII. Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Reference Drugs

Drug	Dose	Bar presses	Avoidances	Escapes
	mg/kg			
Chlorpromazine HCl	0.5	-12	-8	-5
	1.0	-14	-18	-10
	2.0	-56*	-41*	-29*
Trifluoperazine HCl	0.01	-6	-2	0
	0.05	0	-9	-6
	0.10	-75*	-24*	-22*
	0.25	-84*	-38*	-28*
Imipramine HCl	10.0	-22	+1	0
	20.0	+1	0	0
	40.0	+13	-4	0
d-Amphetamine SO_4	1.0	+10	+1	0
	2.0	+94*	-1	0
	4.0	+25	-3	-1
d-Amphetamine SO_4 (replication)	1.36	+27	0	0
	2.72	+47	-5*	-1
	5.44	+26	-8*	-2
Atropine SO_4	4.0	-31	-7*	-1
	8.0	+3	+3	-1
	16.0	-24	-9*	-1
Morphine SO_4	0.25	-1	+1	0
	1.0	-15	+1	0
	3.0	+53	-1	0
	6.0	+133*	-5	0
Caffeine	1.0	+11	0	0
	2.0	+6	0	0
	6.0	+5	0	0
	20.0	+4	-1	0
Phenobarbital sodium	0.1	-7	0	0
	1.0	-4	+1	0
	10.0	+1	0	0
	15.0	-5	0	0
	20.0	+3	-2	0
	50.0	+26*	-7*	0

* $p \leq 0.05$.

photocell cages, somewhat higher doses were needed to decrease spontaneous activity (table XIV).

Imipramine had no effects in Skinner boxes at 10 to 40 mg/kg. Higher doses were not used because they would kill gerbils.

d-Amphetamine at 2 mg/kg increased bar presses. Higher doses decreased the number of avoidance responses. Spontaneous activity increased at 1 mg/kg.

Atropine at 4 to 16 mg/kg decreased avoidance responses and increased spontaneous motor activity.

Morphine at 3 mg/kg increased spontaneous activity, and 3 to 6 mg/kg increased bar pressing without affecting avoidance responding.

Caffeine within a dose range of 1 to 20 mg/kg increased bar pressing only slightly at best. At 10 mg/kg and lower, spontaneous motor activity increased.

Phenobarbital decreased avoidance responding and increased bar pressing at 50 mg/kg.

Reference Hallucinogenics.

Within a dose range of 0.1 to 10 mg/kg, LSD, psilocin, and mescaline (listed according to their decreasing activity) increased bar pressing (table XV). Although this rank order corresponds with the hallucinogenic potency of the drugs in man, the results fail to indicate the full magnitude of the differences in potencies of these drugs in man. (LSD is a much more potent hallucinogenic than mescaline.*) Furthermore, these hallucinogenics were not too much more active than d-amphetamine in accelerating bar pressing, and phenobarbital gave a profile similar to LSD on the avoidance test. Both types of drugs increased bar pressing and decreased avoidance responding. An increase in bar pressing, therefore, is not necessarily an indicant of hallucinogenic activity nor of an increase in spontaneous motor activity. LSD, for example, increased bar pressing at doses that decreased spontaneous motor activity. Here, the increase in bar pressing may be related to an increase in the number of shocks received because gerbils usually persevere in pressing the bar after being shocked.

* Barron, F., Jarvick, M. E., and Bunnel, S., Jr. Sci. Am. 210, 20 (1964).

Table XIV. Change in Spontaneous Motor Activity With Reference Drugs, Benzomorphans, Other Narcotic Antagonists, and Anticholinergic Compounds

Drug	Dose	Percent change
	mg/kg	
A. Reference Drugs		
Chlorpromazine HCl*	0.5	-2
	1.0	+19
	2.0	-30
	4.0	-74
Trifluoperazine SO_4*	0.5	-80
	2.0	-70
d-Amphetamine SO_4	1.0	+62
	2.0	+112
Atropine SO_4*	4.0	+235
	16.0	+233
Morphine SO_4*	1.0	+38
	3.0	+211
LSD tartrate*	0.1	-45
	0.5	-69
Mescaline	1.0	-15
	10.0	-37
Caffeine*	1.0	+11
	3.0	+46
	10.0	+88
B. Benzomorphans and Other Narcotic Antagonists		
ℓ-Cyclazocine	0.5	+67
d-Cyclazocine	0.5	-4
Cyclazocine*	0.25	+250
dℓ,trans-Cyclazocine	1.0	+247
Pentazocine	1.0	+15
220,548-3	1.0	-65
C. Anticholinergics		
219,758-2*	0.05	+68
	0.25	+235
	0.50	+317
226,054*	0.01	+15
	0.10	+294
226,056*	0.01	+17
	0.05	+296
	0.25	+262
226,060*	0.01	+6
	0.05	+57
	0.25	+202
BZ*	0.01	-40
	0.10	+269
	1.0	+148

* $p \leq 0.05$.

Table XV. Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Reference Hallucinogenic Compounds, Benzomorphans, and Other Narcotic Antagonists

Drug	Dose	Bar presses	Avoidances	Escapes
	mg/kg			
	A. Hallucinogenics			
LSD tartrate	0.1	+25	-8*	-2
	0.5	+49*	-36*	-14
Psilocin	0.5	+14	-1	0
	1.0	+40	-2	0
	5.0	+39	-5	-1
Mescaline	0.5	+15	0	0
	1.0	+16*	0	0
	10.0	+11	-1	0
	B. Benzomorphans and Other Narcotic Antagonists			
dℓ-Cyclazocine	0.25	+12*	+1	0
	1.0	-3	-13*	-3
dℓ-Cyclazocine (replication)	0.10	+27	0	0
	1.0	+50*	-1	0
d-Cyclazocine	0.05	+15*	0	
	0.25	+9	-1	
	1.0	+21	-2	
d-Cyclazocine (replication)	0.10	-14	0	0
	1.0	-17	0	0
ℓ-Cyclazocine	0.05	+28	0	0
	0.10	+79*	-3	-1
	1.0	+137*	0	0
Cyclazocine (dℓ, trans- isomer)	0.05	+14	0	0
	0.10	+20	0	0
	0.25	+31	-2	0
	0.50	+173*	0	0
	1.0	-63*	-43*	-35*
Cyclazocine (d, trans- isomer)	0.1	-11	+1	0
	1.0	-20	0	0
Cyclazocine (ℓ, trans- isomer)	0.012	-3	+1	0
	0.025	+4	+1	0
	0.05	+16	+1	0
	0.10	+24	+1	0
220,548-3	0.25	-10	0	0
	1.0	+30*	0	0
220,548-3 (replication)	0.1	-10	-1	0
	1.0	-17*	+1	0
219,362	0.25	+7	0	0
	1.0	+17	0	0
Pentazocine	0.25	-10	0	0
	1.0	+13	+2	0

* $p \leq 0.05$.

Benzomorphans.

To further evaluate the usefulness of bar pressing as an indicant of hallucinogenic activity, nine benzomorphans were tested (tables XIV and XV). In man these benzomorphans are potent narcotic antagonists with various degrees of analgesic and of hallucinogenic effects.*, **, † Although some of the more potent hallucinogenics, such as cyclazocine, increased bar pressing, the hallucinogenic 220,548-3 did not increase bar pressing consistently. So again, among the benzomorphans, an increase in bar pressing does not appear to be a good indicant of hallucinogenic activity.

Because the results of a monkey overt-behavior test indicated that the *l*- isomer of cyclazocine was more potent than the d- isomer, both the isomers and the racemic mixture were given to gerbils. The bar-press measure indicated that most, if not all, of the activity is in the *l*- isomer both for the cis- and trans- stereoconfiguration.

Anticholinergic Compounds.

Included among the 20 anticholinergic compounds tested were six groups and within each were drugs differing in the α- and β- conformation and in the d-, *l*-, and d*l*- isomerism (table XVI). Three of the drugs, scopolamine, 219,758-2, and BZ, are known to be hallucinogenic. The main finding, with increases in bar pressing as the indicant, was that most of the activity was shown to reside in the drugs with the α- conformation and the *l*- isomer. Increases in bar pressing for some of the drugs with the α- conformation and the *l*- isomer occur at least as low as 0.05 mg/kg and probably lower. The avoidance and escape indicants failed to give any meaningful relationship. The results for mydriatic and antitremorine activity agree with the results for bar pressing.

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* Archer, S., Harris, L. S., Albertson, N. F., Tullar, B. F., and Pierson, A. K. Advan. Chem. Ser. 45, 162 (1964).

** Gates, M., and Montyka, T. A. J. Med. Chem. 7, 127 (1964).

† Keats, A. S., and Telford, J. Advan. Chem. Ser. 45, 170 (1964).

Table XVI. Change in Mean Number of Bar Presses, Avoidance Responses, and Escape Responses With Anticholinergic Compounds

Drug	Conformation	Isomer	Dose	Presses	Avoidances	Escapes
			mg/kg			
219,758-2	α	–	0.10	+6	0	0
			0.25	+80	-7	0
			0.50	+15	-3	0
			4.0	+12	-2	0
226,053	β	–	0.05	+27	-1	0
			0.25	+18	0	0
			1.0	+41	-2	0
226,054	α	Enriched	0.01	-6	+1	0
		d	0.10	+44	-14*	-4
226,061	β	Slightly	0.25	+28	+3	0
		d	1.0	+24	-1	0
226,081	α	ℓ	0.25	+46	-1	0
			1.0	+40	-1	0
226,056	α	dℓ	0.10	+17	0	0
			0.50	+60*	-3	0
			2.0	+35	-1	0
226,060	β	dℓ	0.10	+2	0	0
			0.50	+40	0	-3
			2.0	+25	-7	-3
226,087	α	d	0.25	+29	-2	0
			1.0	+25	-4	0
226,086	α	ℓ	0.25	+57*	-4	0
			1.0	+60*	-1	0
226,058	α	dℓ	0.05	+24	-1	0
			0.25	+87*	-1	0
			1.0	+51	-1	0
226,079	α	d	0.25	+22	-2	0
			1.0	+32	0	0
226,078	α	ℓ	0.25	+57	-6	0
			1.0	+90	-2	0
226,062	α	Enriched	0.05	+17	0	0
		d	0.25	-12	-3	0
			1.0	+12	-2	0
226,077	α	d	0.25	+23	0	0
			1.0	+26	-1	0
226,075	α	ℓ	0.25	+53*	-3	0
			1.0	+26	-2	0
226,057	α	dℓ	0.05	+31	0	0
			0.25	+47	0	0
			1.0	+95*	-4*	0
226,100	α	d	0.25	+10	-2	0
			1.0	+16	-7	0
226,101	α	ℓ	0.25	+54*	-4	0
			1.0	+60*	0	0
BZ**	–	–	0.05	+143	-5	0
			0.25	+42	-18*	-1
			1.0	-10	-20*	-1
Scopolamine HBr	–	–	0.05	+55	-4	0
			0.25	+62	-4	-1
			1.0	+57	-2	0

* $p \leq 0.05$.

** Independent groups of gerbils tested at each dose and with control vehicle.

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1. Foldes, F. F., Swedlow, M., and Sike, E. S. Narcotics and Narcotic Antagonists. Charles C. Thomas, Springfield, Illinois. 1964.

2. Keats, A. S. Personal communication.

3. Telford, J., Papadopoulas, C. N., and Keats, A. S. J. Pharmacol. Exptl. Therap. 133, 106 (1961).

DISCUSSION

Dr. Joffe (Edgewood Arsenal): Dr. Pearl's results show an increase in bar pressing with the gerbil. I'm sure this is definitive; it works with enough compounds. Yet when the chimpanzee is given BZ or other anticholinergics of the same type that Dr. Pearl was talking about, a very marked decrease in bar pressing occurs. This again devolves into our own problem here; that is, on occasion we are looking for a task that will detect changes in behavior in an animal as an indication that it may do something in man. Whether the compound will increase or decrease bar pressing is not significant; what is significant is whether the compound will cause a change in behavior. Another part of the program that we need to worry about is the following; Does the change in the animal reflect in any way the change that will occur in man? Apparently, changes in the chimpanzee are more parallel to changes in man. I simply offer this to show that we have to look at both sides of the problem, and here we have both of these things to look at—predictability to man in terms of quantity and quality.

Dr. Schuster (University of Michigan): This is actually more of a direct statement than a question. It distresses me a bit for you to speak of bar pressing as if this is a definition of a "behavior." I think that one of the points that should be made is that bar pressing is the topography of a response and that it does not define the behavior you are studying. It is not only the description of the behavior but of the controlling contingencies as well, and, as a consequence, you might expect marked differences between the chimpanzee and the gerbil, depending upon the controlling contingencies. I think it is important that you understand that the behavior you are studying is defined not only by the physical act or the topography of the response but by all the controlling contingencies that are involved in it.

Dr. Pearl: That may be so. I favor the interpretation, however, that it's a species difference because, in the previous paper and in our own results, the motor activity of gerbils and rodents is obviously stimulated. I don't think it comes as too much of a surprise that they are going to rap the bar more if

they scratch it, jump on it, press it with their paw, or hit it with their tail. They are more active. I don't know if the chimpanzee is depressed by BZ or not. I couldn't say, but I suspect it is more of a species difference at this point than an environmental difference.

Dr. Schuster: Was this an avoidance performance as well in the chimpanzee?

Dr. Pearl: It was.

Dr. Joffe: The chimpanzee actually exhibits more, qualitatively, of what the human shows. They show a dysphoria as well, but the dysphoria is not noticeable until you start to make them perform. If you simply have them sit there, you don't see the great increase in activity that you see in rodents. You may not know they are affected at all until you try to make them perform.

Dr. Schuster: I am certainly not questioning that there will be species differences in response to these drugs. The only point I am trying to make is that it is important to specify all the conditions. Frequently, all people will say is "bar pressing in the rat" or "bar pressing in the chimpanzee." That's an absolutely meaningless statement unless you specify the contingencies controlling that response.

Dr. Otis (Stanford Research Institute): It also should be pointed out that the kind of response that is asked for from the animal can make a lot of difference in what the effects of the compounds are going to be. For example, avoidance behavior, where a lever-pressing response is called for, is highly stimulated by amphetamine in the rodent. But if the animal is trained in a pole-jumping response, also avoidance behavior, amphetamine knocks it out.

Dr. Pearl: In agreement with that point, I tried amphetamine once in the gerbil and its jumping up and breaking the photocell beam was the avoidance response. Amphetamine decreased avoidance response in that situation.

MAJ Ketchum (Edgewood Arsenal): I would also like to add that I would be interested in knowing the interaction with time and with dose. In man, for example, with BZ, there may be a reduction or increase in activity depending on the phase of the drug action or the time. Also, as mentioned earlier, depending on the dose, you can get the paradoxical or U-shaped function of the relationship to dose.

Dr. Pearl: We didn't see any U-shaped relationship as far as time goes. BZ was given 30 min prior to testing on the avoidance test, which only lasted 20 min. There wasn't much change occurring during that 20 min. The spontaneous-motor-activity test was an hour long. We can't say that there is any difference because the operant rate of activity will go down over the hour anyway. So, we are not in a position to evaluate time effects at this point.

THE MOUSE COMPARED TO A NONMAMMALIAN ORGANISM FOR DRUG SCREENING*

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Introduction.

Natural-products researchers have used a variety of organisms for testing compounds for biological activity in their search for new drugs. One of the most popular of these organisms or test animals is the mouse. It has long been used in the primary screening stage because it is small, easily handled, and relatively inexpensive; therefore, many different extracts can be tested in a short time. During the past two years, the Natural Products Laboratory at Edgewood Arsenal and its contractors have tested chemically and screened about 3600 extracts.

We wanted to screen more extracts at a reduced cost and, at the same time, not overlooking information now obtained through the mouse screen. We attempted, therefore, a nonmammalian screen consisting of 10 different tests that utilized 6 species of plants, 1 of fish, 2 of echinoderms, and 1 of crustacean. In the first 10-mo period, 3000 extracts were tested. The nonmammalian screen proved to be far less expensive and faster than the mouse screen.

The question then arose, were we overlooking any interesting compounds because of insufficient data?

Methods and Materials.

Sixty-four standard drugs were tested by the nonmammalian screen. We possess complete data on only five: reserpine, serotonin

* The data for this preliminary study were obtained through Contract DA18-108-AMC-255(A). Hazleton Laboratories, Inc., Falls Church, Virginia. The nonvertebrate screen was set up and operated by Dr. Ivor Cornman, University of the West Indies, Mona, Kingston 7, Jamaica.

creatinine sulfate, yohimbine hydrochloride, d-amphetamine sulfate, and physostigmine salifylate. The least effective doses (LED's)* for each compound, as obtained by both screening methods, were compared. Their empirical formulas are as follows**:

Drug	Empirical formula
Physostigmine salicylate	$C_{15}H_{21}N_3O_2$
Yohimbine hydrochloride	$C_{21}H_{26}N_2O_3$
d-Amphetamine sulfate	$C_9H_{13}N$
Serotonin creatinine sulfate	$C_{10}H_{12}N_2O$
Reserpine	$C_{33}H_{40}N_2O_9$

The nonmammalian screen is described in the following steps:

A. Stock Solutions.

The stock solution for the mouse was made by combining the drug to be tested with isotonic saline in concentrations of 25, 50, and 100 mg/ml.

The stock solution for all other organisms was made by adding 1 gm of the drug to be tested to enough distilled water to make a 10% solution.

B. Mouse.

Replicate groups of two male, Swiss albino, cesarian-derived, 20- to 30-gm mice are given each drug iv (at 0.5 log-dose intervals) and retained for observation up to 3 days. Food and water are available ad libitum. The time of injection, reactions displayed, and times of death are observed and recorded.

C. Fish—Top Minnow or Mosquito Fish.

One *Gambusia affinis* is placed in a bowl containing 100 ml of sea water and 1.0 ml of stock solution. The fish is observed for alteration of behavior and for distress, indicating toxicity. The time of the first observed

* Cutting, Windsor F. Handbook of Pharmacology. 2nd ed. Appleton-Century-Crofts, Inc., New York, New York. 1964.
Sollman, Torald. A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. 8th ed. W. B. Saunders Company, Philadelphia, Pennsylvania. 1957.

** LED is the lowest dose at which a reaction was obtained in an entire test population; it could be termed ED100 (effective dose at which 100% of the test population showed an effect or reaction to the drug administered).

effect and the time to death are recorded. Any unusual behavior is noted for verification. Also, 10% dilutions of the stock solution are made until the no-effect concentration is found.

D. Sea-Urchin Eggs.

Eggs are removed from the *Lytechinus variegatus* and fertilized. After 6 to 10 min, a drop containing several hundred eggs is transferred to a shallow dish containing 10 ml of sea water and 0.1 ml of stock solution. The eggs are observed for morphological changes in the cells and for modification or retardation of development. Delay in the first and second cleavages is noted, and subsequent observations are timed to detect abnormality and delay in the blastula, gastrula, and pluteus (free-swimming, fully developed larva) stages.

E. Nerve Muscle.

Fragments of body wall of the sea urchin, *Diadema antillarus*, are placed in sea water and tested for response to shadow, to touching of the tip of the spine, or to prodding of the body surface. They are then placed in 20 ml of sea water containing 0.2 ml of stock solution. The normal response is a convergence of spines at the point of stimulation, followed by a brief period during which the spines wave about. These responses can be inhibited so that there is no response to stimulation, or the response may be weak and unoriented. Any noted effect is verified on a second fragment, and the response threshold is determined by 10% dilutions.

F. Brine Shrimp.

Many *Artemia salina* (about 2 days old) are placed in 2.0 ml of sea water containing 0.1 ml of stock solution. They are observed for changes in swimming behavior and time of death. Ten percent dilutions are made until a no-effect level is found.

G. Seedlings.

Garden mustard (*Brassica nigra*) and rye grass (*Secale cereale*) seeds are placed in a layer of Avicel. Eight to ten drops of stock solution are dripped on each group of seeds. They are then transferred to a moist chamber and observed for retardation, or blocking, of germination, for changes in morphology or tropisms, and for abnormal color. If retardation or changes in the growth of the seed occur, the stock solution is diluted 10% and the process repeated until a no-effect level is found.

H. Microorganisms.

Aspergillus niger, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis* are plated on agar. Antibiotic assay discs are dipped in the

stock solutions and placed on the inoculated plates. The plates are incubated at 37°C and read the next day for zones of inhibition (in millimeters). If zones of inhibition occur, the antibiotic assay discs are dipped in stock solution diluted 10%. This process is repeated until the zones of inhibition disappear.

Results and Discussion.

The results obtained from each screen are as follows:

Drug	LED of mouse screen mg/kg*	LED of nonmammalian screen mg/ℓ*	Ratio of nonmammalian: mouse screen.
Physostigmine salicylate	0.1	0.02	0.2
Yohimbine hydrochloride	3.2	1.0	0.3
d-Amphetamine sulfate	1.0	1.0	1.0
Serotonin creatinine sulfate	3.2	100.0	31.3
Reserpine	0.003	20.0	6700.0

Only at high dose levels did serotonin creatinine sulfate and reserpine produce unusual reactions in the nonmammalian screen. Had the nonmammalian screen been used as the only basis for selection of interesting compounds, reserpine and serotonin would have been passed by.

The results from these organisms indicate that these conditions are not ideal for screening all drugs. Although more drugs and organisms should be surveyed to establish the relative usefulness of nonmammalian types of screens, the present study shows promise for more efficient, rapid, and cheaper screening methods. Table XVII summarizes the results.

Summary and Conclusions.

With yohimbine, d-amphetamine sulfate, and physostigmine salicylate, the LED obtained from the mouse screen for compounds affecting the peripheral nervous system in mammals is about equal to the LED obtained from the nonmammalian screen. Physiologically speaking, these reactions are basically the same in the invertebrates, fish, and mammals used; muscles either contract or relax from stimulation of the neuromuscular junction or direct action on muscle tissue.

* mg/ℓ = mg/kg.

Table XVII. Comparison of Mammalian and Nonmammalian Screens

Drug	Mammalian (mouse) screen					Nonmammalian LED screen					
	LD100	LD50	LED	ED50	ED0	A	B	C	D	E	F
	mg/kg a/					mg/l b/					
Physostigmine sulfate	0.32	0.2	0.1 c/	0.05	0.03	100.0	20.0	500.0	0.02 c/	10,000	20,000
Yohimbine hydrochloride	32.0	17.8	3.2 c/	1.8	1.0	20.0	1.0 c/	100.0	100.0	20,000	10,000
d-Amphetamine sulfate	12.0	10.0	1.0 c/	0.5	0.3	20.0	100.0	500.0	1.0 c/	10,000	20,000
Serotonin creatinine sulfate	320.0	178.0	3.2 c/	3.2	1.0	1000.0	2000.0	100.0 c/	100.0 c/	10,000	20,000
Reserpine	50.1	44.7	0.003 c/	0.002	0.001	200.0	20.0 c/	1000.0	500.0	20,000	20,000

Note: A - *Lytechinus variegatus*, B - *Gambusia affinis*, C - *Artemia salina*, D - *Diadema antillarum*, E - *Brassica nigra* and *Secale cereale*, and F - *Aspergillus niger*, *Staphylococcus aureus*, *Escherichia coli*, and *Bacillus subtilis*.

a/ Milligrams of drug per kilogram of mouse.

b/ Milligrams of drug per liter of isotonic saline.

c/ Denotes figures used for comparisons discussed in the text.

Serotonin creatinine sulfate and reserpine showed a wide disparity in their LED in the mammalian versus the nonmammalian screen. The mouse screen showed activity at much lower levels than the nonmammalian screen for these two drugs.

DISCUSSION

Dr. Schuster (University of Michigan): When you give your drugs to the fish, do you put the drug in the surrounding water?

Dr. Worthley: Yes.

Dr. Schuster: Do you vary the pH? For example, we have been working with morphine sulfate, and we simply put it into the enviornment of the fish. The pH, of course, determines whether or not the drug will dissociate, and there is a considerable difference in absorption that is dependent on the form of the drug. Perhaps it would be useful to get some indication of the pK value for each of the drugs and to work with that rather than dosage per se.

Dr. Joffe: I think in most of these instances the drugs were in such small amounts that there would be no effect on the physical parameters.

Dr. Schuster: No, I am not saying that at all; I am not saying you are going to change the pH of the water. I am saying that the amount of dissociation of the drug that will take place will differ as a function of pH. We know that in the case of morphine, for example, we can vary its toxicity, the lethal dosage, greatly by maintaining the same concentration but just changing the pH because the fish only absorb the nondissociated morphine.

Dr. Joffe: I follow this, but let me go back one step. These techniques were developed for the specific purpose of running a screening program in the field, and other factors, such as you mentioned, were not considered. This was a field procedure, and what we were trying to do at this time was to get a rapid and easily usable field screen in order to avoid the necessity of having to make extracts and send them all back to the laboratory for mouse screening.

Dr. Schuster: The only point I wanted to make was that perhaps some of the drugs not picked up or absorbed would be at a different pH.

Dr. Joffe: Yes, this is quite true.

MAJ Ketchum (Edgewood Arsenal): Again, right along the same line, do you have any way of knowing how much drug gets into these animals that you surround with material?

Dr. Worthley: No, we have made no attempt in this preliminary study to do this, nor at this point are we particularly interested. The main thing attempted

here was to try to get a screen that picked up activity, and we don't care about the details so much at this point. In other words, the feeling at this preliminary stage is that we aren't going to worry about minor changes in pH or dissociation because we intentionally are using a wide variety of organisms, in some of which these factors are very important and, we hope, in others, not so important. So if we can develop a group of organisms which will pick up activity, we don't care, and we expect that some of the organisms will miss some of the drugs.

GENERAL DISCUSSION

Dr. Dews (Harvard Medical School): I would like to go back to the point I tried to make this morning and see if I can confuse the issue a little further. A number of people today have made comments about the effect of the complexity of the behavioral task on the degree of effect that you would expect from a drug. The point I was trying to make this morning can be illustrated. An animal can be trained in a situation in which a red light alone is positive and a blue light alone is negative, but a red light plus a white light is negative and a blue light plus the same white light is positive. This is a conditional discrimination. What the red means depends on whether or not the white light is there. You will find that animals can do this with a high degree of success. Then, if you test the effects of a drug such as amphetamine, there is a considerable increase in the amount of responding to the negative stimulus under these circumstances. If you compare the amount of responding to the negative stimulus in the conditional discrimination with the amount of responding to the negative stimulus in a simple discrimination, you find that there is much more responding in the conditional discrimination than in the simple discrimination. When these observations were first made, they were interpreted as showing that conditional discrimination is a more complex task and is, therefore, more sensitive to disruption by amphetamine. However, if you study an animal when a simple discrimination is in an early state of development and the animal is doing a fair amount of responding to the negative stimulus, you have a degree of increase with amphetamine comparable to that seen in a conditional discrimination that has been allowed to develop to a steady state. An extreme example of the same process is that if you subject an animal to a simple discrimination procedure for a very long time so that there are essentially no errors, then the sensitivity to amphetamine disappears.

There are now techniques whereby you can train an animal so that he never makes a response to the negative stimulus, never in his lifetime. In animals so trained, discriminations do not break down under the influence of drugs. The point I am making is that what seems to matter in this situation is not the degree of complexity but the level of performance, the drug superimposed on very small differences in the levels of performance can make big differences in the effects of the drug. People today have been talking about the complexity of the behavioral task as an independent variable that determines and influences the effect of the drug. What they have been saying may well be true, but you've got to be very careful and very cautious in this, unless you can show that you are studying identical performance levels.

CPT Meltzer (Edgewood Arsenal): I wonder if a good part of these results aren't tied very tightly to the specific stimulus complex presented to the animal so that, in the example of the red and blue light, you might very well find an effect that disappeared as the animal was overtrained; whereas, by

choosing more complicated stimuli or multidimensional stimuli, you would eventually reach a level of performance that proximated the discrimination between red and blue lights, but you would still be able to disrupt that performance far more readily.

Dr. Dews: I am not denying the possible influence of complexity. All I am saying is that you've got to be very careful not to casually infer that it is complexity per se that is determining the drug effects. This is one caution that could be generalized to practically all behavioral studies. When you set up your test to compare levels of complexity, types of motivation, or drug effects as related to any variables, the particular variables you had in mind when you set up your procedure tend to dominate your thinking about the situation. You have to be very careful when you have the results. Just because you were thinking about a particular variable when you set up the procedures doesn't necessarily mean that this variable is the prime determining factor in the differences in drug effects you may be seeing. In the example I gave, we were thinking in terms of complexity. It turned out that complexity was a red herring. It was irrelevant to drug effects. My colleagues have set up experiments making fixed intervals for escape comparable to fixed intervals for food. They find that as the performance becomes more and more alike under the two procedures, the effects of drugs on the two procedures become more and more alike. They find this to be true for barbiturates, for amphetamines, and even for morphine. It doesn't matter whether the animal is escaping or working for food; if the performance under study is identical, the effects of the drugs are identical under these circumstances. Nature of motivation also turned out to be a red herring. If you set up experiments to compare, for example, avoidance versus positive reinforcement and the schedules are different, the performances you are dealing with will be different. If you then get different effects of drugs, you are not entitled to say that they are due to the difference between avoidance as opposed to positive reinforcement. The differences are much more likely to result from the different schedules.

Dr. Joffe (Edgewood Arsenal): I think Dr. Dews has a good point here. It has often occurred to me that what we call levels of complexity really involves a very anthropomorphic situation. We decide that this ought to be more difficult or less difficult for the animal. And then I sort of brush it off by saying, "Everybody knows this," and we are simply putting a label on the thing, saying that we are setting up a task that is different. I don't believe anyone really means, or, at least, I hope no one really means, to say that this task is or is not more complex or more difficult for an animal, as we can't have a very good idea of just what constitutes difficulty for it.

Dr. Lilly (Communication Research Institute): What has impressed me here is the fact that the definition of complexity, in which we are also so involved with the dolphins, is not too clear. I propose the idea of using a computer to do a feedback job with the animals so that we are no longer inhibited by our own inventiveness in terms of complexity. In other words, if we set up a computer so that its response is a function of the past responses of the human or animal, we can stack the cards toward complexity as he learns. I believe that we can thus satisfy your criteria, Dr. Dews, for complexity as opposed to learning. We are introducing a continuous increase in the novelty of the task and, hence, introducing the increasing complexity that we desire. We can have novelty; that is, we are on the rising portion of the learning curve. This is a substitute for obvious complexity because the task now is to eliminate the nonessential stimuli and to select the essential ones. So, in a sense, the beginning of each of these tasks is very complex. But once learned, once embedded in the animals, it is now an almost-mechanically reproduced habit pattern, conditional-response complex, or, as I prefer to call it, a new program at an automatic level.

We find that when the dolphin gets to that degree of perfection with any task, he drops the task. So he not only reaches a plateau on the learning curve, but he reduces it to zero. It is very convenient to have the animal do this; he announces at that point that he is not going to be tested that way anymore. A criterion of 18 out of 20 cannot be obtained. In effect, he says, "I will go to 3 out of 4 and that's it." The task must immediately be varied. If he is given a new task, he is intrigued again and goes at it. We have done this with vocalization kinds of operant conditioning in which the dolphin is expected to give a different vocal response each time. If we make a sufficiently variegated ensemble of stimuli and response, we obtain a continuous interest and a continuous set of solutions. He will hit, say, an average error rate of only 10% and stay there. Suddenly he goes to 100% error; in other words, no performance. It's a distinctly different situation from the classical learning curve going up and leveling off. It's a classical learning curve starting up, beginning to level off, and then stopping. Boredom is a real problem for the large brain.

Dr. Joffe: I think this is a very good point. As many experiments have shown, when you present a man and a monkey or chimpanzee with exactly the same operant lever-pressing task, for the first, perhaps, 5 min or so until the man catches on, or for 2 or 3 min after he catches on (it may take the chimp an hour or so), human performance will be considerably better than that of the animal. But once the animal has caught on to the task, he is content to do this task for a great length of time. But because of boredom incorporated in the task, the human performance falls off markedly. As Dr. Lilly says,

with the porpoise, it becomes no task any more, and he says, "I quit." Perhaps this is directly related to the degree of intelligence or to factors of motivation that we certainly know very little about.

MAJ Ketchum: I would like to comment on the difference between complexity and difficulty as it appears to me. Complexity, as Dr. Findley seemed to be defining it, is related to the information-theory view: namely, how many options are available to the responder. If he only has a single option of making or not making a response, this is rather simple behavior. If he has a tree with many branches, this response that he is making is a more informative one, and, therefore, this is possibly more-complex behavior. The question of difficulty as it was brought up this morning by Dr. Boyer related to the difficulty of discriminating between two patterns in one illustration — two patterns of lights in which the number of dissimilar elements appears to be related to the difficulty of making a discrimination. So, in this case, the response may be simple, but the problem may be difficult.

Dr. Otis (Stanford Research Institute): I would like to restate what I think Dr. Dews said, principally to see if I'm right and secondly because I agree with it. As I got it, the implication as to complexity per se is not at issue here. What is important is the baseline performance of the animal in the particular task he's performing before he is given the compound. To say that a drug has differential effects on complex or simple behavior — what does this really tell us about drug action — because, as you just pointed out, Dr. Ketchum, the issue of complexity or difficulty of a task is a matter of definition.

Dr. Dews: Needless to say, I agree with Dr. Otis, Dr. Ketchum, and Dr. Lilly. I think Dr. Ketchum's distinction between difficulty and complexity is very well taken. All I was trying to say was that if you set up an experiment with two different situations with different complexities, and you do get a difference in the effect of a drug, this is not sufficient evidence to say that the effect of the drug is determined by the complexity. You need to analyze very carefully the performance in the two situations.

II. HUMAN PERFORMANCE

15 October 1965

Moderator: Dr. Van M. Sim
Deputy Director of Medical Research
Edgewood Arsenal

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INTRODUCTION OF PANEL

Dr. Van M. Sim

We are fortunate this morning to have with us as a panel member Dr. Joel Elkes, who is head of the Department of Psychiatry at Johns Hopkins Hospital. Dr. Elkes and I have crossed paths many times in the last 12 or 13 yr. When I first knew Joel, he was scientific director of the Department of Experimental Psychiatry at Birmingham, England. He has been very active in the biochemical and physiological aspects of CNS metabolism, and he has been interested in international psychiatric work. So it is a great pleasure to introduce to you this morning Dr. Joel Elkes.

Dr. Lilly gave an extremely stimulating talk last evening, and for those of you who were not there, if you ever get a chance to hear Dr. Lilly, I think you should listen to that story.

Here this morning are some of the people who, 10 yr ago, were instrumental in starting the Volunteer Program. It has been in effect since late 1955. MAJ John Jarvis used to go out on recruiting trips and come back all excited about having signed up three people who would be volunteers in our program; by the time he got back to the laboratory, two of them would have cancelled out—sometimes all three. This was strictly a labor of affection and love in those days, and I am sure that at that time John thought it had a chance of success, but he didn't know when. It is successful today because of the help of everybody in the Army who has had a chance to see this program, has become enthusiastic about the necessity of such a program being conducted somewhere, and, this being the place, has seen fit to help us.

Today we are going to talk about man and his relationship to some of the testing that we heard about yesterday—whether or not the tests are comparable, can be transferred, and can be related to man's situation. At this time, I would like to call on Mr. Norman Walker, who has been interested and instrumental in the development of certain types of instrumentation for measurement of man's ability to perform both with and without stress.

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THE DEVELOPMENT OF TRACKING TASKS AS INDICATORS OF STRESS

Mr. Norman K. Walker and Miss Janet F. Burkhardt
Norman K. Walker Associates, Inc.

Introduction.

Tracking tasks have often been used to measure the effects of stress on human performance. Garvey and Henson of the Naval Research Laboratory have published studies that are typical of the type of work that has been done in this area: The movements of a spot of light are governed by a complex wave input. After being trained to use his right hand in the tracking task, a subject tracked the moving spot of light using various incompatible psychomotor control systems. This produced serious degradations in tracking performance, and the cause was attributed to "task-induced stress." Since an individual's performance is very variable, the results are in arbitrary and undefined units (figure 61).* Consequently, they cannot be correlated with other tracking studies.

We believe that the variability of results that Garvey and Henson found was a function of the type of tracking tasks they used. It is our belief that a tracking task must meet certain criteria if it is to be used as an indicator or a measure of the magnitude of the stress. These criteria are:

(a) The task must be accurately defined and easily reproducible.

(b) The task must be unambiguous.

(c) A training technique must be devised so that the subject can be trained to a certain plateau of efficiency that must be reasonably constant during an experiment.

(d) The difficulty of the task must be easily variable to accommodate different levels of stress.

(e) The performance of a wide variety of subjects should not differ excessively in the unstressed condition.

(f) The various parameters defining the task must be easily calibrated.

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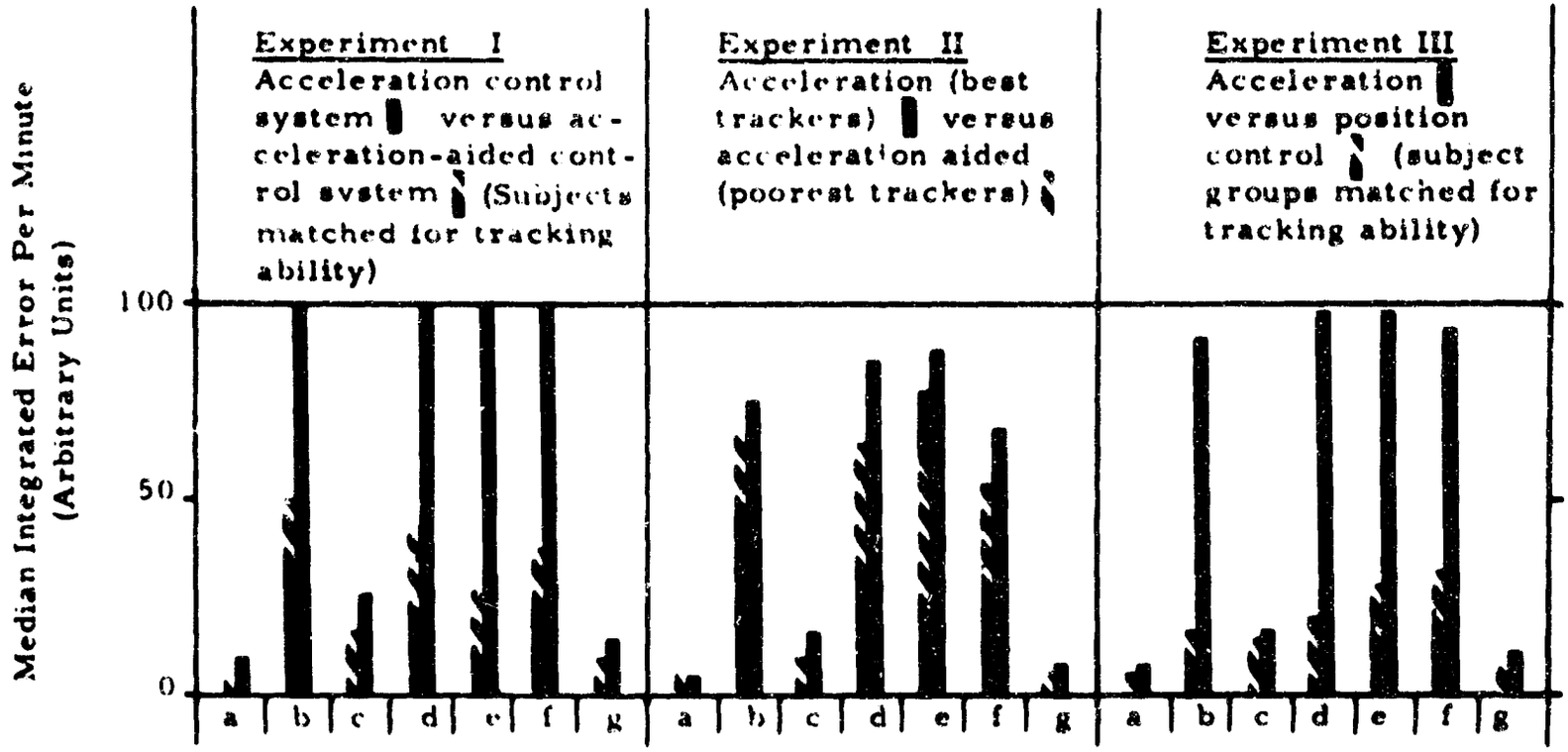
* Garvey, W. D. Naval Research Laboratory. Report No. 5015. The Effects of "Task-Induced Stress" on Man-Machine System Performance. September 9, 1957. UNCLASSIFIED Report.



Stress Conditions -:
a) Unstressed
b) Incompatible display-control relationship
c) Left-handed tracking (trained on R. hand)
d) Two handed tracking (on two identical systems)
e) Two coordinate (x-y) tracking -one hand
f) Secondary visual task
g) Secondary arithmetic task

Figure 61. Results of an Individual's Performance in a Tracking Task

(Taken from the work of Garvey)

(g) The equipment must be stable and give consistent results.

(h) A simple readout of the results and a permanent record of performance are desirable.

(i) The results must be in a form that can be correlated with other tracking investigations.

The formulation of these criteria was influenced by the past experience of Norman K. Walker Associates, Inc., in the design of guided-missile systems. In this field, even though some of the inputs are statistical in nature, complete systems of great complexity are assembled with very great confidence in their predicted performance. This is achieved by studying and defining the ideal performance of each subsystem in considerable detail, adding them together, and then optimizing the results for minimum error while allowing for statistical errors in information. It is believed that this same basic approach will be fruitful in analyzing a man's tracking degradation due to stress; unfortunately, the chief source of "noise" in the system is the man himself. The first step must be to analyze the performance of the man, including the random noise he generates, under the simplest possible conditions. There is little hope for using this method to analyze previous experiments, such as those of Garvey and Henson, because they disturbed a man-machine system of unknown characteristics to an unknown degree by a large input, and they affected the system with a stressor that produces unknown effects.

Fortunately there are systems that can be used to meet the previous criteria. When the subject cannot prevent himself from making small errors in holding an indicator on zero, even though there is no disturbance from electrical inputs, the system can be calibrated without stress. The effect of an added stress would then be indicated as an increase in the subject's error when compared with his original unstressed error score. Since this system has only three components, the man, the task, and the stressor, there is a good possibility that the results can be analyzed and interpreted by using an approach similar to that used in designing guided-missile systems.

Description of ZITA Equipment.

The Zero Input Tracking Analyzer (ZITA) was developed to meet the previous list of criteria in order to quantify the effects of stress on a man's tracking performance. The ZITA has three basic components: the signal processor, the error analyzer, and the display recorder unit. The first two are combined into a single unit, the ZITA, and the display recorder is a Minneapolis-Honeywell Visicorder (figure 62).

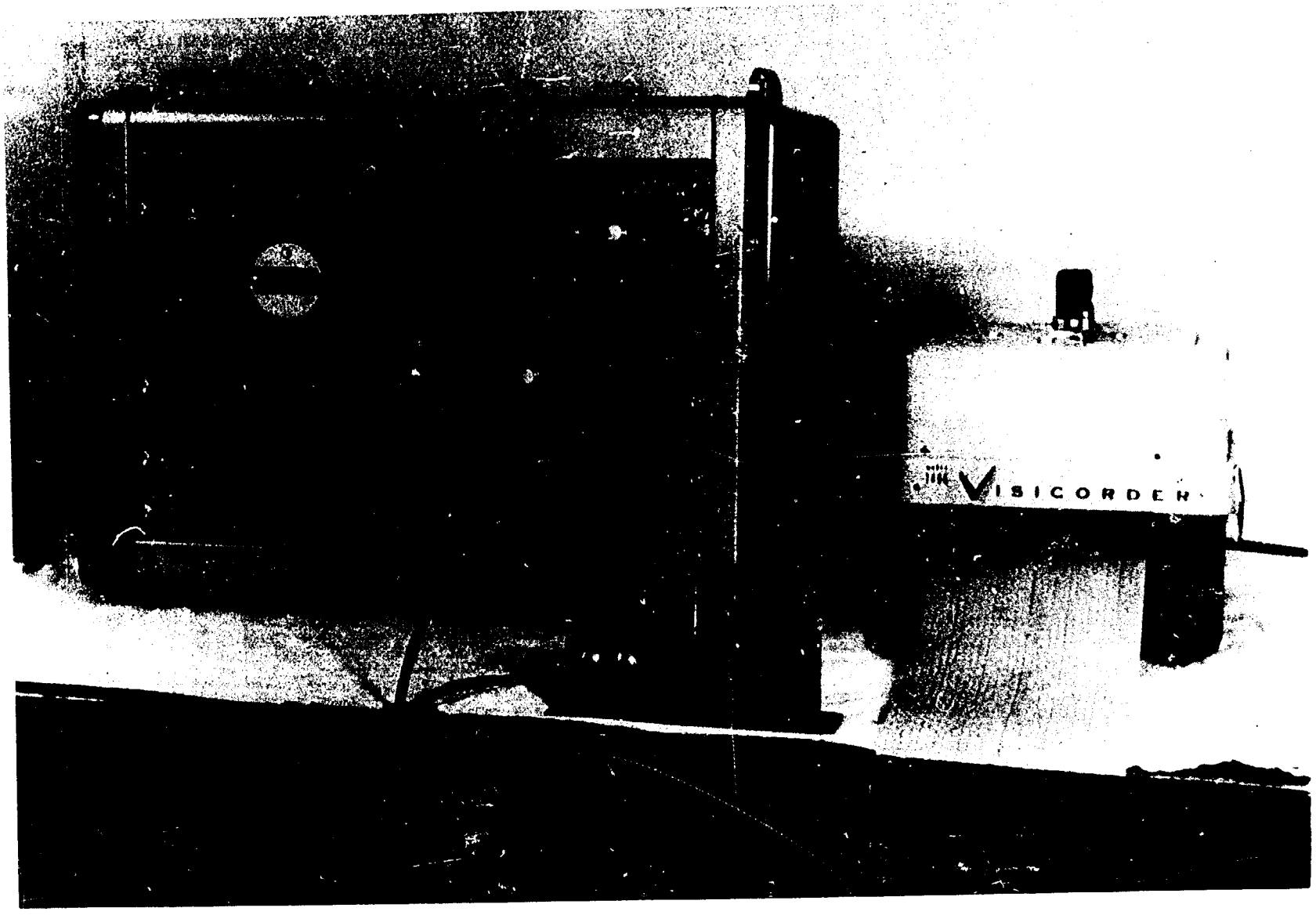


Figure 62. ZITA (Type IIIb) With Visicorder and Hand Control

The ZITA equipment provides a one-dimensional tracking task for the operator in which he is required to centralize a spot of light in the display window of the Visicorder. This is done by applying control commands (left or right) to which the light spot responds either in velocity or acceleration, depending on which has been selected for the test. A wide range of "stiffness," which is a measure of angular acceleration, is available in each mode, and various amounts of time lag or lead may be introduced into the response. The display record (figure 63) includes stick movements, integrated mean error, and rectified error and is permanently recorded. The operating cycle is indefinite, but the integrated error, from which the mean modular error for each cycle is readily derived, resets to zero in 1-min cycles. Other information is displayed on the panel of the cabinet, and all preselected conditions set on the panel are clearly marked and easily seen during the operation.

The ZITA equipment can be used with various control sticks. The "proportional" type gives a smooth variation of control. The "bang-bang," or "switching," type may have a two-position (left and right) or a three-position (left, zero, and right) control setting.

Explanation of the ZITA Task.

The Naval Research Laboratory investigators have found that the difficulty increases with the mathematical order of the control system that connects the operator's control stick to the display. Therefore, the basic task chosen was acceleration control in which the operator observes a displacement error of the spot of light on the display, makes a given stick movement to correct it, and observes that the spot accelerates in the direction required to reduce this error. The acceleration control system is considered to be adequately difficult to detect the effects of stress. Previous experiments by ourselves and others indicate that the effect of stress is difficult to detect if a task is too easy and that as the task is made more difficult, the effect of stress becomes more apparent.

Since it is believed that fundamentally the man responds to the angular error when he is tracking, the error is expressed in milliradians (mrad), a nondimensional unit that is more basic than measuring an angle in degrees. The spot of light is considered to be a point, and the response of the spot is defined by the angular acceleration of the line of sight caused by a fixed stick movement. This is called the control stiffness ($\ddot{\Delta}$). Because the measurements are concerned with angles, the stiffness can be varied either by changing the electronic gain or the optical magnification of the system. For a bang-bang control system, there is only one available stick deflection and, hence, one particular stiffness, $\ddot{\Delta}$ max, for any given gain or magnification.

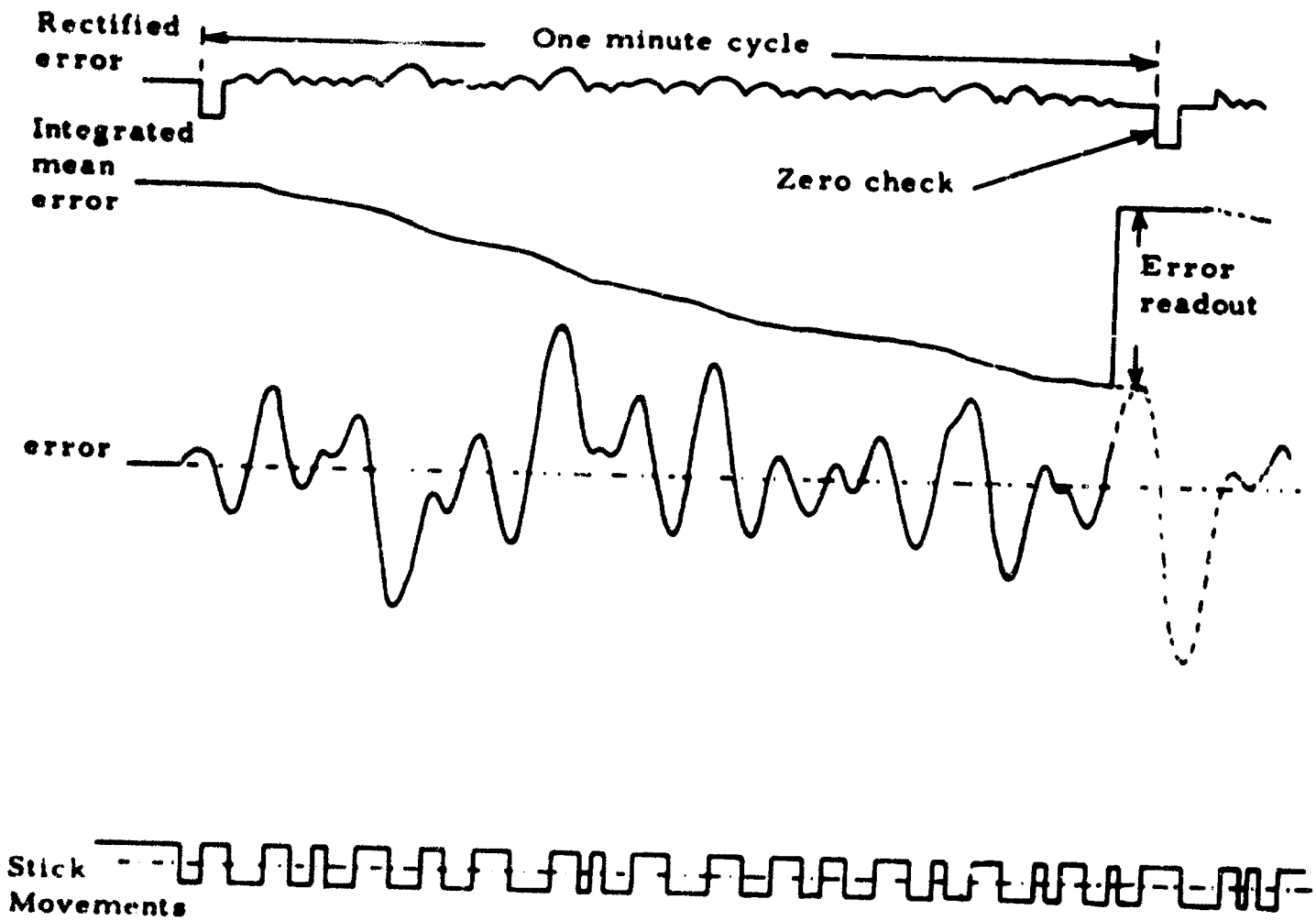


Figure 63. Typical ZITA Record for Task B

ZITA Training.

The variability of the results obtained in other tracking studies may have been due to the excessive complexity of the tasks and the multiplicity of the possible responses. Since this would not have permitted the development of a precise training technique, the operators may have used various tracking strategies.

In order to permit precise training, the tracking task was simplified by eliminating the electrical input that was used in some studies to produce a seemingly irregular movement of the spot of light. This was replaced by a tracking task in which the operator continually corrects an error produced by his own control input. The difficulty of defining the correct response that was encountered when using the proportional control stick was eliminated by using a bang-bang control stick. This will give only three control positions (maximum left, zero, and maximum right). Since the center zero position is not used by skilled operators, it is normally removed by changing a switch on the ZITA panel. Now the operator has only two control positions (left and right), and he is forced to oscillate his control stick. The spot moves to the left with a left stick movement, and the stick must be moved to the right to prevent the spot from overshooting the desired position. The stick movements are continual, and by using a particular tracking technique called Rubric tracking (figures 64 and 65), a subject can be quickly trained to a plateau level. According to this technique, the subject must reverse control when the spot is halfway back to the desired position. This gives an immediate correction for odd large errors. This rule applies only to task A (acceleration control, no lag). When different tasks are used, other rules tell the subject when to reverse control. In task B, for instance, control must be reversed immediately after the spot reaches the peak of its movement.

Figure 66 shows that the plateau level attained by individuals with similar ages and vision and using the Rubric tracking technique is substantially constant. The tracking task has been accurately defined in regard to the controlling parameters and is easily reproducible. The training instructions are unambiguous, and the base results achieved are consistent.

Stiffness.

Figure 67 shows a set of results on task A for one skilled subject. The entire available stiffness range is covered. At high stiffnesses, the error is proportional to the stiffness. This indicates that the subject is responding to a stimulus and moving the stick as fast as possible. At lower stiffnesses, the error tends to a constant value that is the minimum error to which the subject can give a response. Since the subject must wait for an

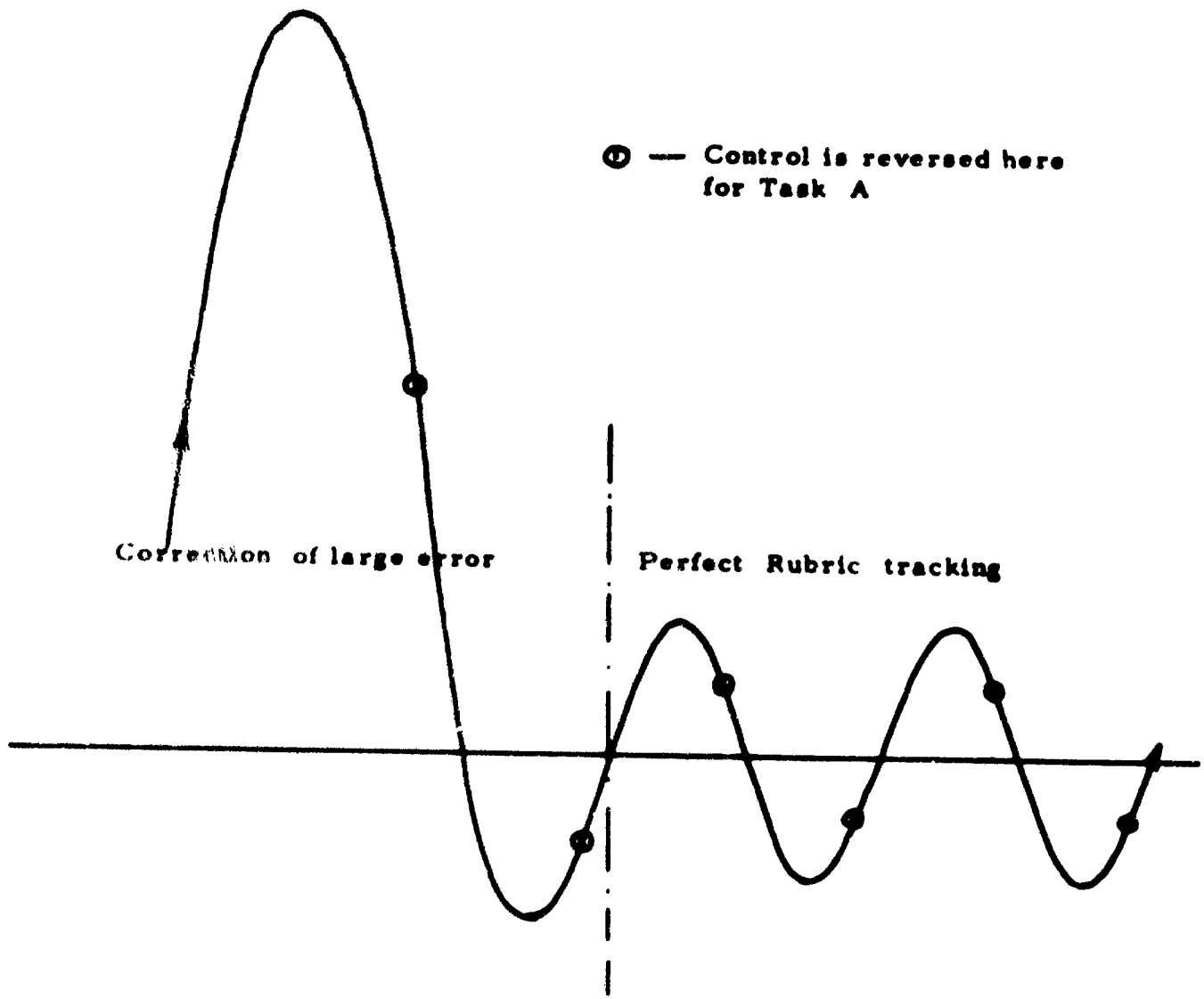
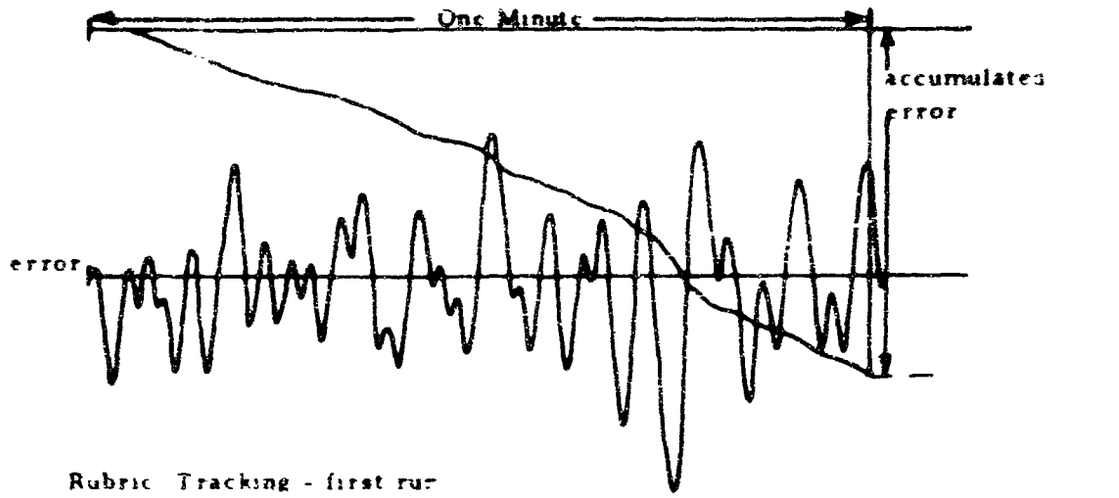
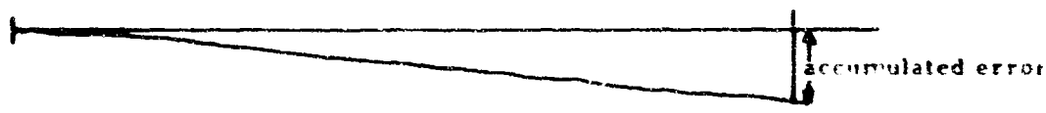
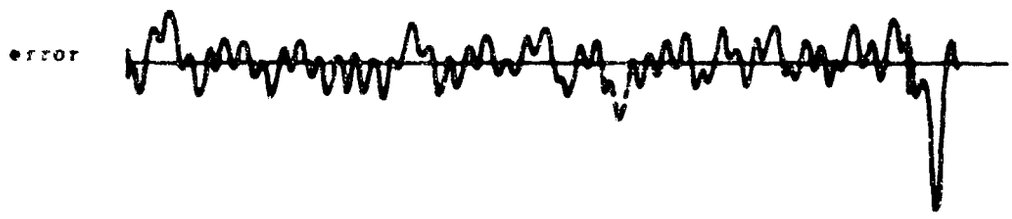


Figure 64. Rubric Tracking



Rubric Tracking - first run
Total time - 2 minutes





Rubric Tracking - tenth run
Total time - 11 minutes

Figure 65. The Learning Process for a Particular Subject - Task A (Acceleration Control. No Lag)

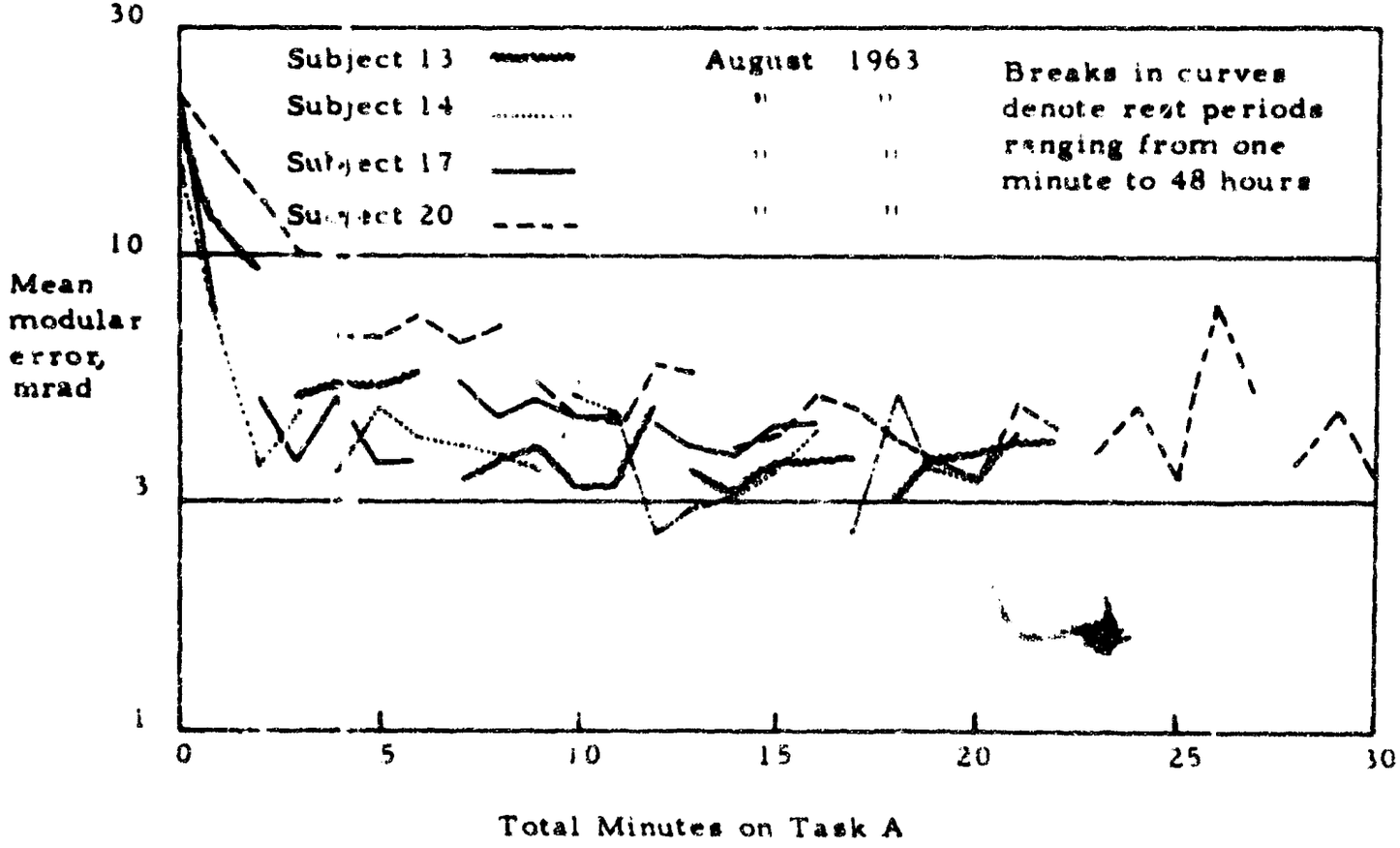


Figure 64 Collected Learning Curves for Four Subjects - Task A (Acceleration Control, No Lag)

appreciable error to build up, the rate of stick commands is decreased. The shape of the curve is consistent and does not vary over time.

The work done by the Naval Research Laboratory relates the difficulty of a tracking task to the number of integrators comprising it. The difficulty of a task, therefore, will not be expected to vary with the stiffness since the number of integrators remains constant, but the resulting error will vary with changes in stiffness. One investigation showed that the effect of a particular stressor was roughly constant over a stiffness range of 1,000:1.* This supports the reasoning used at the Naval Research Laboratory.

Lag.

The tracking task could be made more difficult by adding an additional stage of integration, but this would negate the definition of stiffness as angular acceleration. The same results were achieved, instead, by adding a lag to delay the effect of applying a control signal. Tests have shown that a lagged system seems more difficult to the operator, produces a considerably larger base error for a given stiffness, and is more affected by stress. Furthermore, the effect of the stress is roughly independent of the control stiffness but varies with the amount of lag.

Figure 68 shows a complete set of results for the same operator taken at different times. Task B, which includes a 1.25-sec. first-order lag, was used over the entire range of stiffness, and the resulting curve is similar in general shape but higher than the task A (acceleration control, no lag) curve in figure 67.

Stressors.

Having devised an appropriate tracking and recording instrument, the problem of defining and producing stress effects on tracking performance was attacked by defining a stressor as anything that disturbs tracking. Through preliminary investigations, various stressors have been found, and a series of experiments have been conducted in which human tracking performance was measured while the subjects were subjected to selected stress conditions. Some of the conditions found were ineffective, but one of the early

* Walker, Norman K. Norman K. Walker Associates, Inc. Contract No. DA49-193-MD-2369. Report No. 7. The Effect of a Particular Stress on One Man's Performance of Various Tracking Tasks. September 1963. UNCLASSIFIED Report.

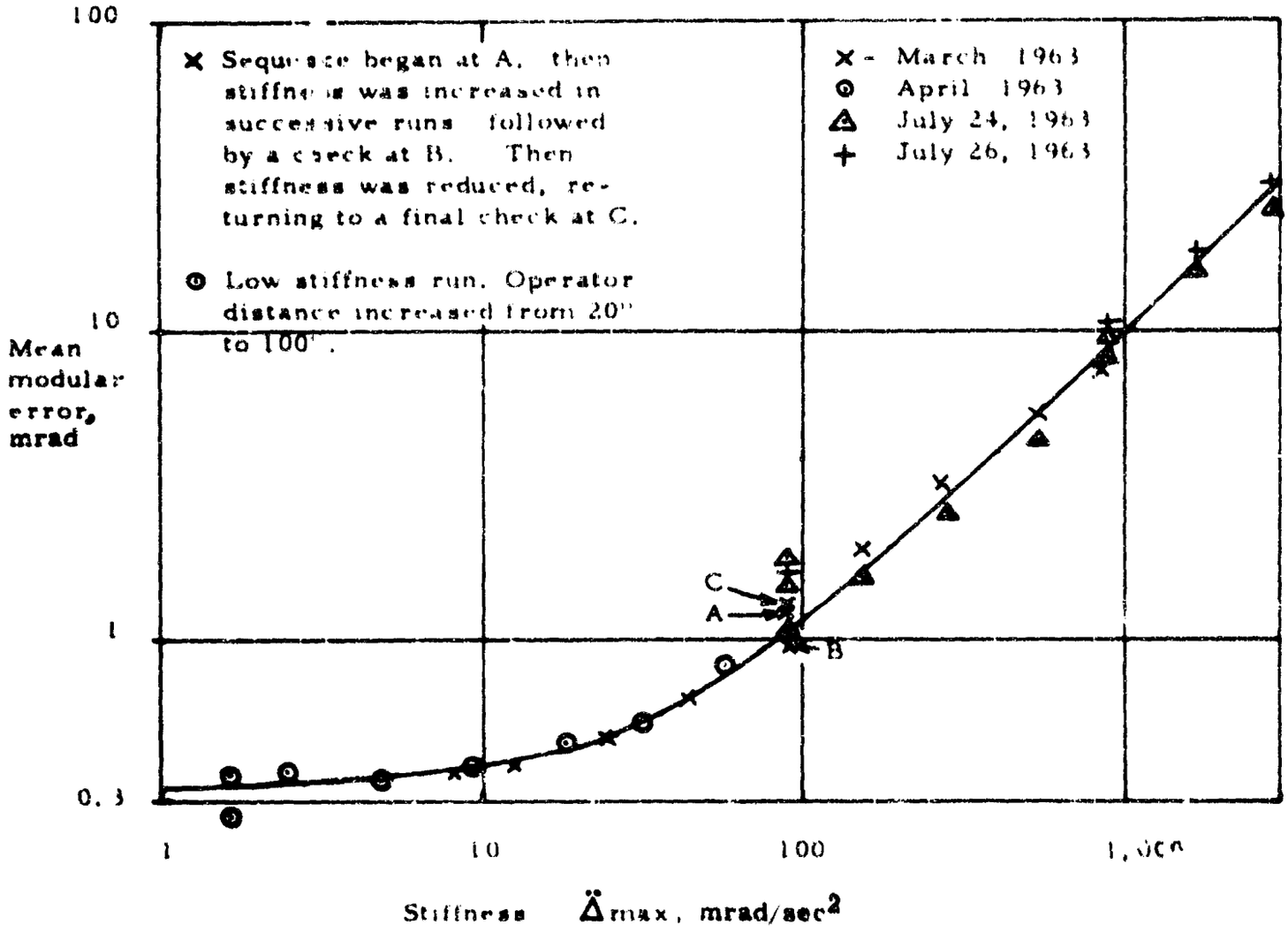


Figure 67. Standard Variation of Mean Modular Error With Stiffness - Task A (Acceleration Control, No Lag)

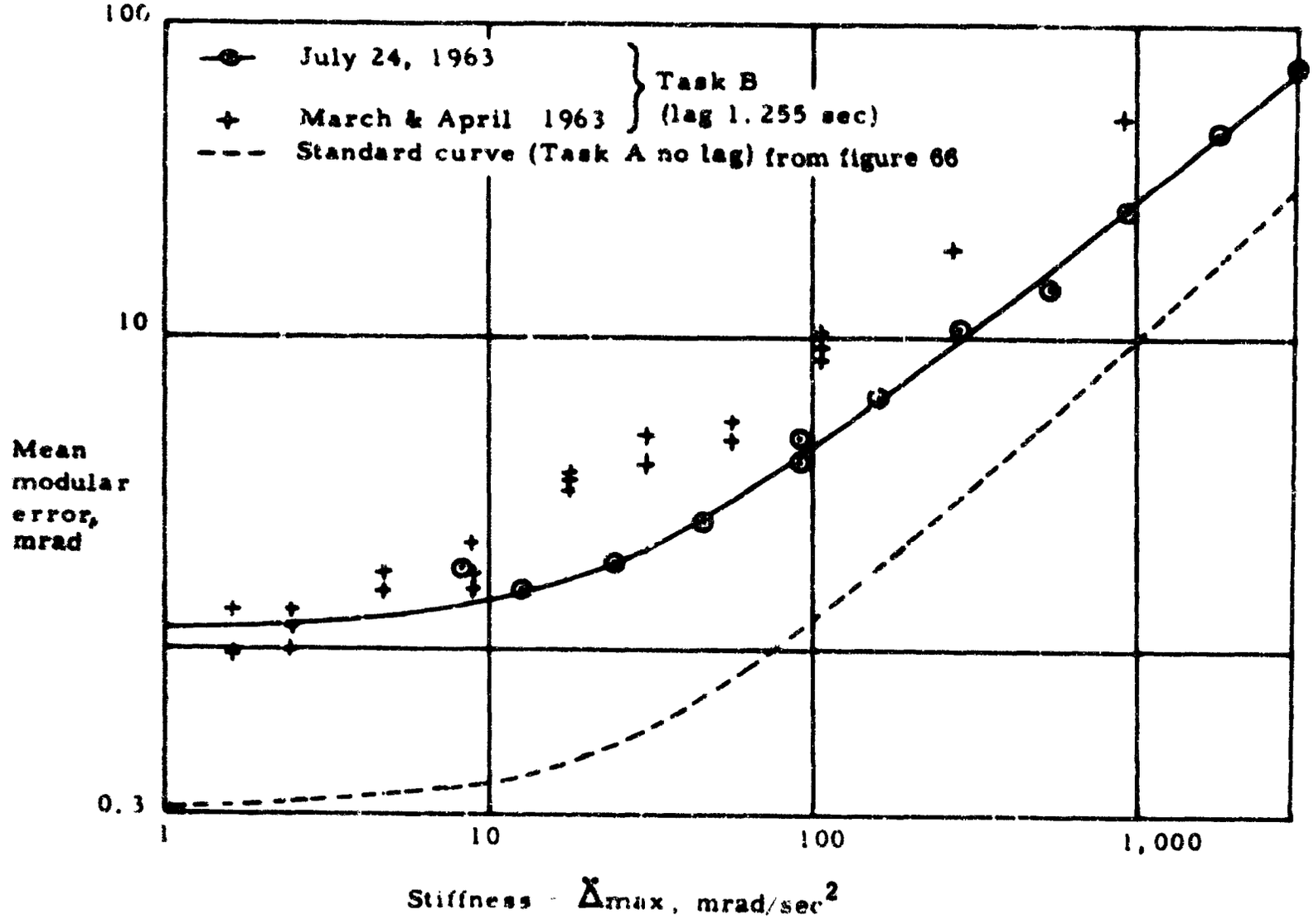


Figure 68 Effect of Lag at High Stiffness - Task B

successful stressors found was the acute physical discomfort produced by wearing a "thermal," or CBR suit (figure 69). The tracking performance of the subject degraded progressively as his body temperature rose. There were also indications that the effects produced were strongly dependent on psychological factors.*

The most consistent results have been obtained with a distraction-type stressor, such as auditory shadowing, in which the subject repeats aloud a list of random numbers fed to him from a tape while he is tracking. Auditory shadowing (figure 70) produces major degradations in the performance of tracking tasks and the results are considered to be similar to those obtained using the CBR suit.**

Similar Stressors.

For one stressor, a, to be replaceable by another stressor, must produce the same results on the same tracking task. This implies : F is some measure of tracking performance under stress, two stressors w be identical in their effects on a particular tracking task if $F_a = F_d$ on the same task. In general, however, the effect of a stressor depends upon its intensity and upon the subject's susceptibility. It may be desirable to produce greater numerical degradations in tracking accuracy by using a stressor which is more effective than auditory shadowing. In this case, the above could be simplified by stating that two stressors are similar in their effects on various tracking tasks if for all subjects and intensities of stress the following ratio holds:

$$\frac{F_a \text{ (task A)}}{F_d \text{ (task A)}} = \frac{F_a \text{ (task B)}}{F_d \text{ (task B)}}$$

Combat Stress.

The degradation in tracking obtained with auditory shadowing is similar to the degradation found when the combat results of missile systems

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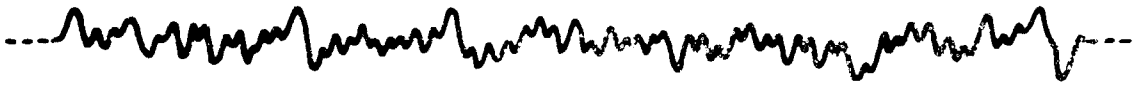
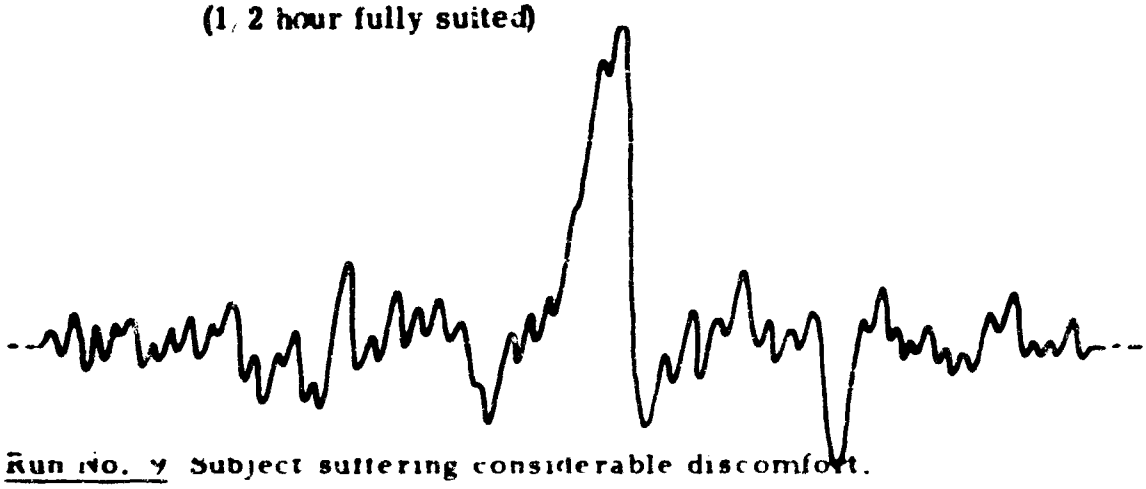
* Walker, Norman K., and Fricker, Charles J. Norman K. Walker Associates, Inc. Contract No. DA49-193-MD-2208. Report No. 4. The Use of Tracking Tasks as Indicators of Stress. August 1964. UNCLASSIFIED Report.

** Walker, Norman K., and Shectman, F., and DeSocio, E. Norman K. Walker Associates, Inc. Contract No. DA49-193-MD-2369. Report No. 10 Further Work on the Use of Tracking Tasks as Indicators of Stress. October 1964. UNCLASSIFIED Report.



Run No. 6 Subject acclimatized to CBR suit and not appreciably distressed (1/2 hour fully suited)



Run No. 9 Subject suffering considerable discomfort. (1-1/2 hours fully suited)

Run No. 12 Subject removed from suit, towelled down and tested immediately.

Figure 69. Effect of CBR Suit on Tracking

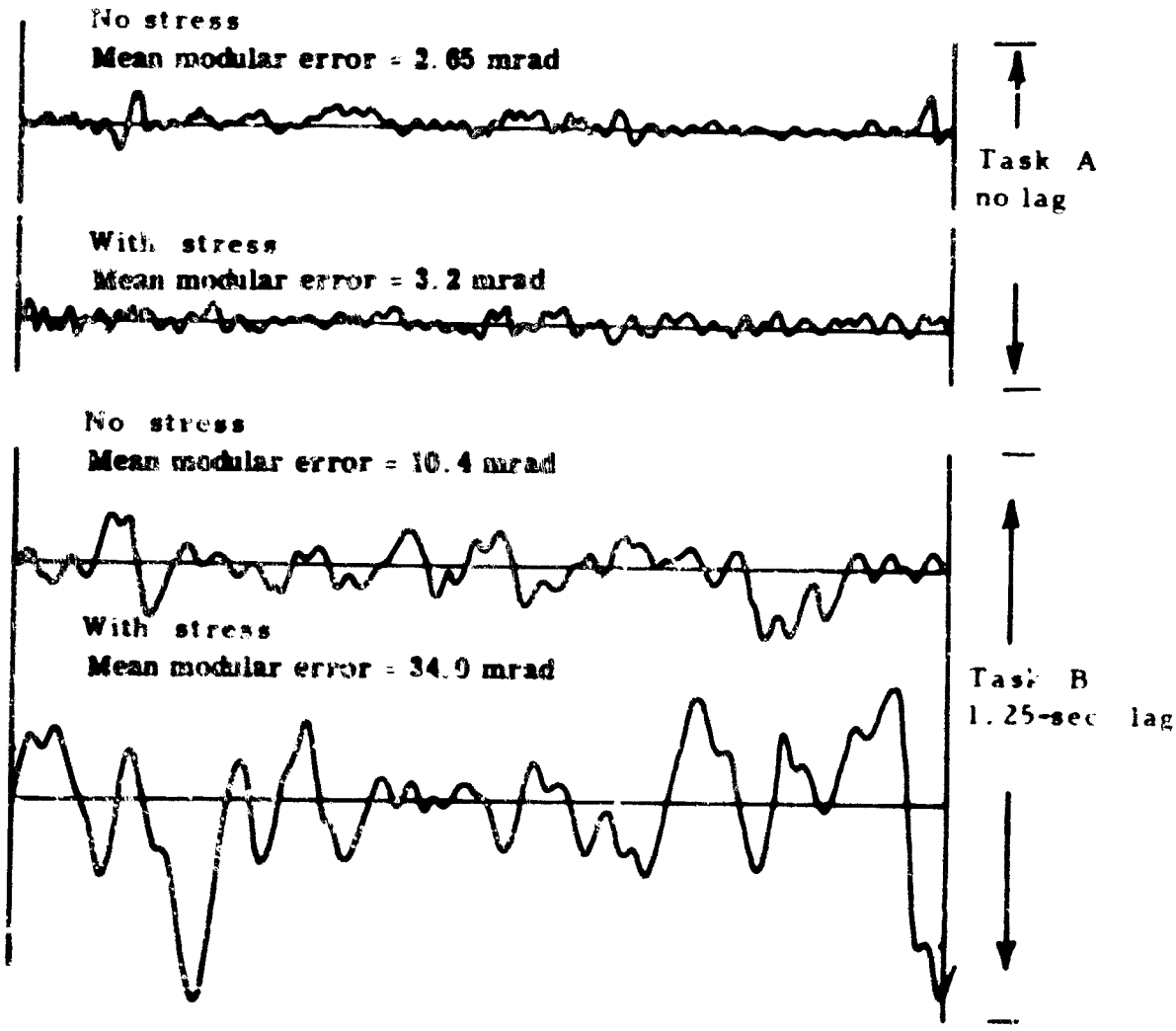


Figure 70. Effect of Auditory Shadowing on Tracking

used in World War II and the Korean War were analyzed.*,** The relative degradation of two acceleration control tracking tasks, task A, which has no lag, and task B, which has a 1.25-sec lag, is almost the same as the relative degradation produced by combat stress on two types of systems having the same characteristics as the two ZITA tasks. It is believed, therefore, that the laboratory stressed performance on the two ZITA tracking tasks can be used as an indicator of the probable degradation of certain system types in combat situations.. (To avoid classifying this paper, the figure is omitted.)**

For a stressor to be effective as a predictor of combat effects, it should produce the same results as combat on the same tasks. Since the effect of various stressors varies in intensity and can reach a limit, while the effect of combat varies with the severity of the combat, it is necessary that the stressor be similar to combat and desirable that it be able to produce results of the same magnitude. Auditory shadowing, although effective, has not produced the acute loss of control experienced in severe combat. A more effective stressor, therefore, was needed, and the auditory discrimination task appears to meet the requirement.

Auditory Discrimination Task.

In the auditory discrimination task, a tone is substituted for a vocal digit, and a manual response is substituted for the verbal response that is difficult to score (figure 71). Although the use of a manual response destroys the original concept of the stressor being independent of the psychomotor task (tracking), it has many substantial advantages over auditory shadowing.

The auditory discrimination task produces greater tracking degradations than auditory shadowing.† In order for it to replace auditory shadowing as representing combat stress, the two must be shown to be

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* Walker, Norman K. Norman K. Walker Associates, Inc. Contract No. DA36-034-AMC-0032R. Report No. 8. The Accuracy of the Azon Guided Bomb as Affected by Battle Conditions in World War II. May 1964. UNCLASSIFIED Report.

** Walker, Norman K., and DeSocio, E. Norman K. Walker Associates, Inc. Contract No. DA36-034-AMC-0032R. Report No. 9. The Effect of Combat on the Accuracy of Various Human Operator Control Systems. April 1964. CONFIDENTIAL Report.

† This would be expected from the Garvey and Henson results for various combinations of two-handed tracking.

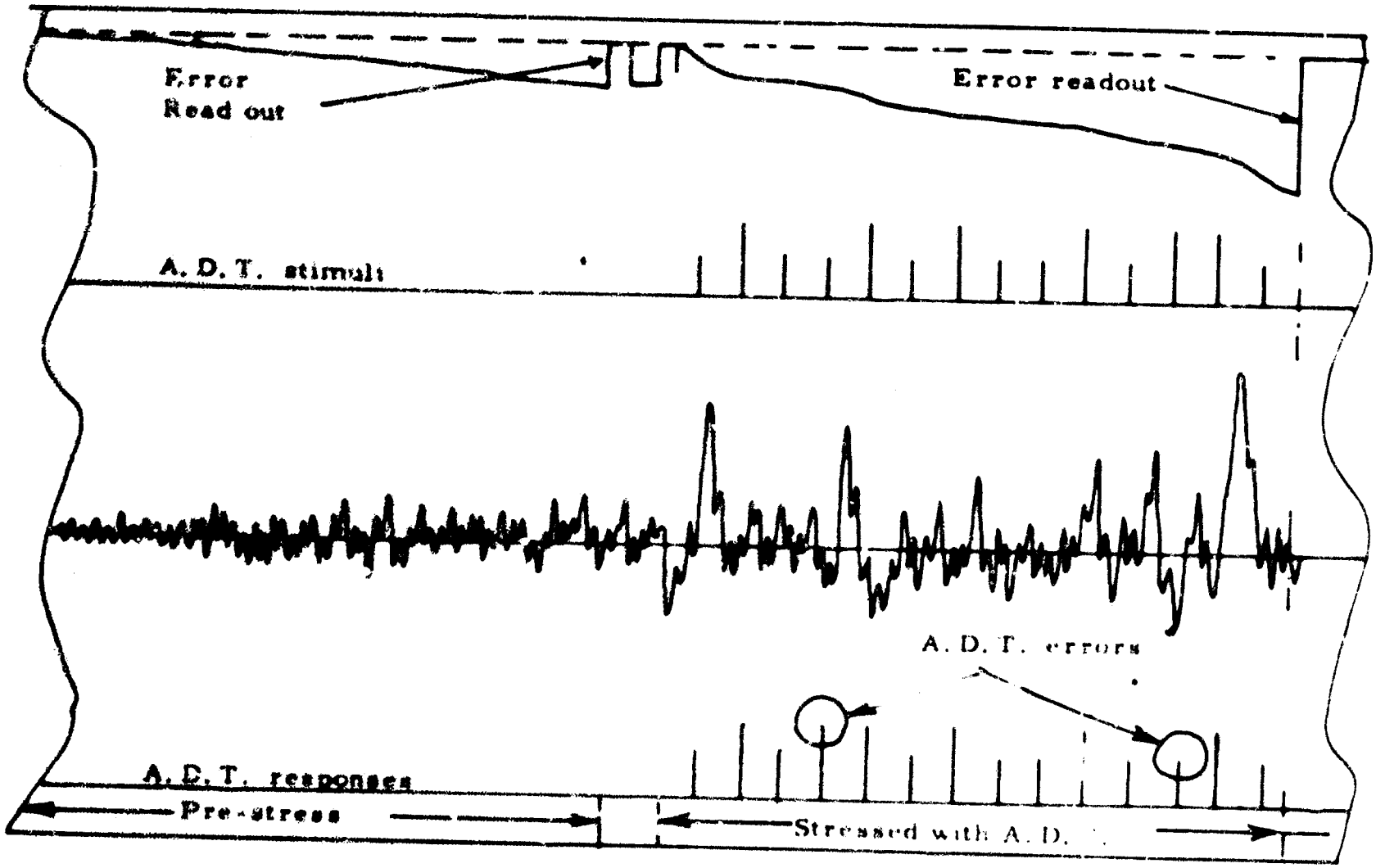

Figure 71 A Typical ZITA Record With Auditory Discrimination Task

mathematically similar. If this can be done, the auditory discrimination task, which in preliminary studies has produced degradations as severe as those found in heavy combat, may be useful in designing future systems for combat. The auditory discrimination task can be scored and recorded on the Visicorder record (figure 72). This facilitates data processing and permits the analysis of possible refractory time intervals.

Figure 73 shows the collected results from auditory shadowing tests on eight university students and four Army-trained SS-11 gunners compared with tests of auditory discrimination tasks on one subject at two levels of stress; i.e., auditory discrimination task repetition rate. The function of F in this instance is $\sqrt{(E - 1) \times A}$, where E is the tracking-error ratio (stressed to unstressed) and A is the number of auditory shadowing or auditory discrimination task errors per minute. This composite error score makes some allowances for performance on both the tracking and the stressor tasks. It has been found that subjects can trade off errors on one task against errors on the other and that the combined score is more consistent than either the tracking error ratio or the auditory discrimination task score. There are theoretical objections to this particular combined score, and improved formulations are being studied.*

The results shown in figure 73 support the hypothesis that the auditory discrimination task is similar to auditory shadowing, even though the added confusion due to the left-hand response has enormously increased the effectiveness of the auditory stressor at a given presentation rate. Direct correlation of the Garvey and Henson experiments with the auditory discrimination task results may now be possible.

Future Work.

Although there are many fields of study in which ZITA's precise quantifications and great range of sensitivity can be used, future experiments by Norman K. Walker Associates, Inc., will follow two lines. The first is to validate the assumptions upon which ZITA is based. This can be done by using a larger number of subjects. It is hypothesized, for instance, that the results to be achieved by Navy pilots operating real missile systems in combat at a stiffness level of 10 mrad/sec^2 or less can be inferred from tests on

* Walker, Norman K., Shectman, F., and DeSocio, E. Norman K. Walker Associates, Inc. Contract No. DA49-193-MD-2369. Report No. 10. Further Work on the Use of Tracking Tasks as Indicators of Stress. October 1964. UNCLASSIFIED Report.

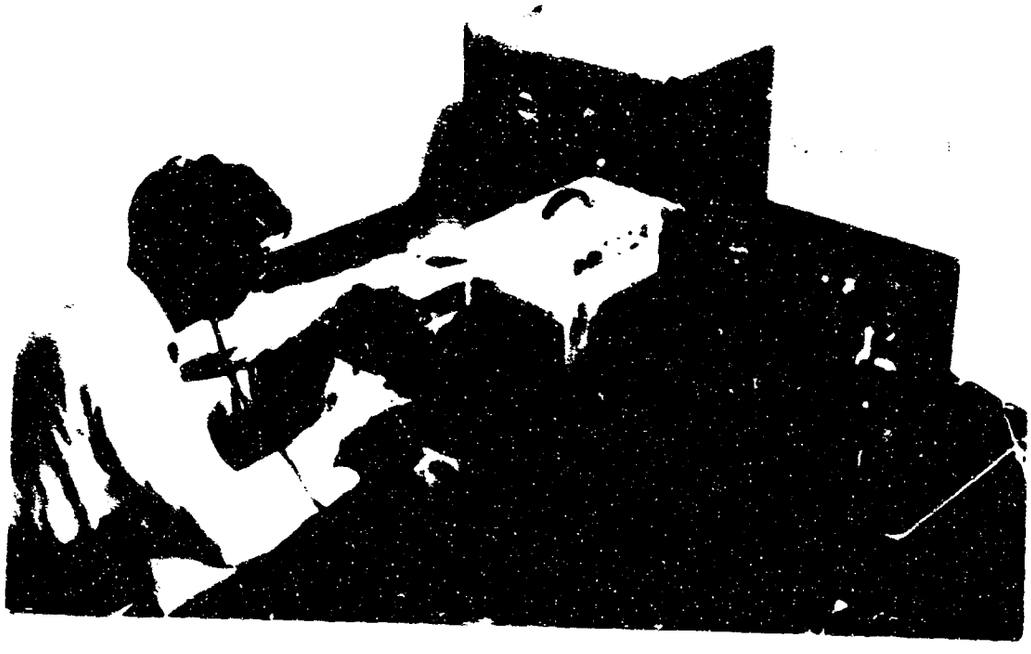

Figure 72 Subject Tracking on ZITA Equipment While Responding to Auditory Discrimination Task

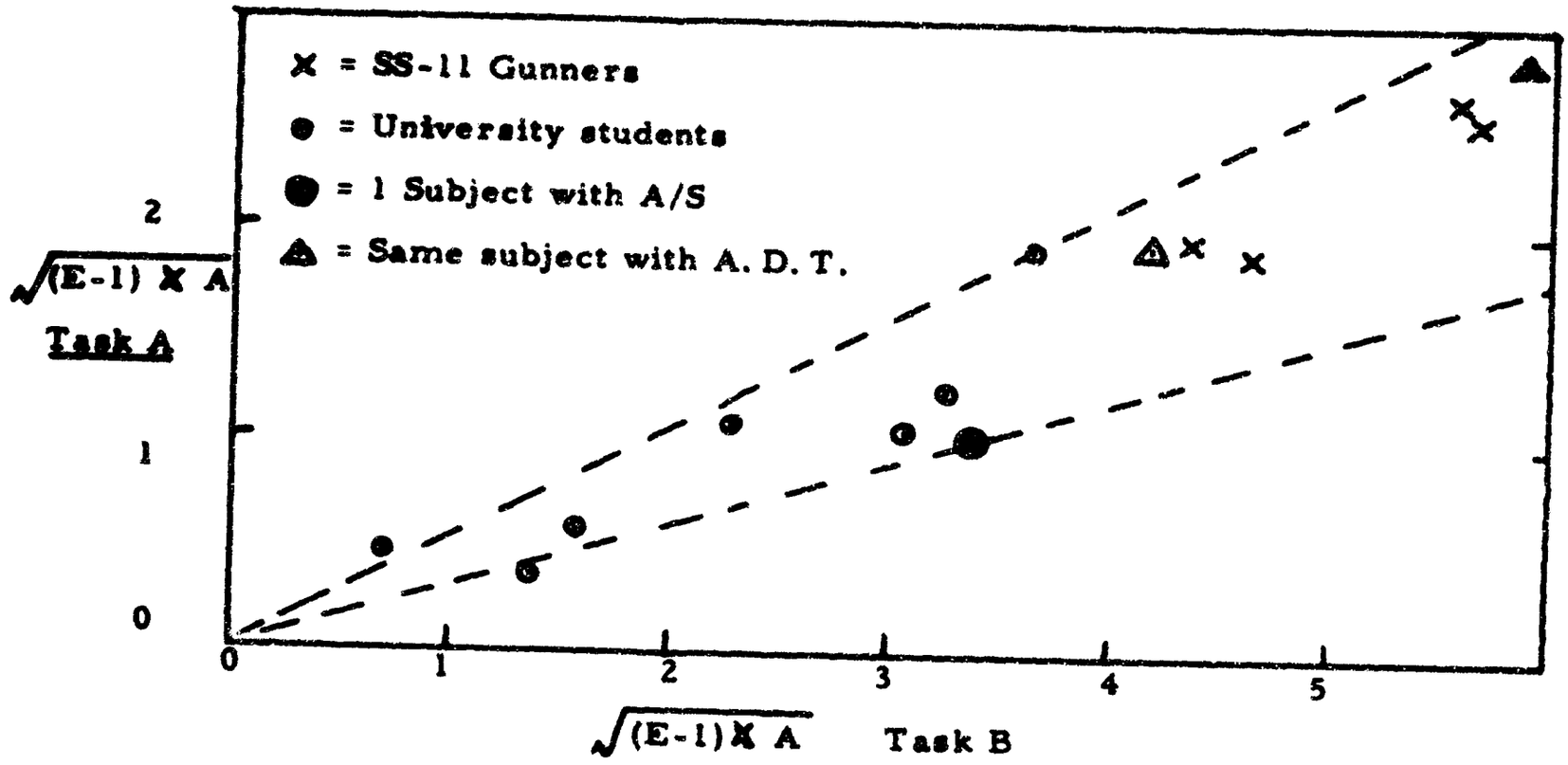

Figure 73. Collected Results for Similar Stressors

a small number of college students under artificial stress conditions in the laboratory with the arbitrary ZITA tasks A, B, and C at a stiffness level of 100 mrad/sec^2. Large numbers of Navy cadets and pilots are to be tested by using a lab stressor and ZITA tasks, which have the same characteristics as missile systems now in use in Viet Nam. By these tests, it will be possible to determine the extent to which combat degradation of a system corresponds to degradation of ZITA tasks under lab stress. If this correspondence is as expected,* it will then be possible to predict the combat effectiveness of a given system in various combat conditions. This will be done by studying performance on representative ZITA tasks under laboratory stressors such as auditory shadowing or the auditory discrimination task.

The other area of present interest is the design of a critical experiment to test a possible theoretical explanation of the results which have been obtained. All stressors used thus far have been quantitatively similar. It appears, therefore, that the stressors interfere with the same part of the man-machine system responsible for tracking performance.

The results are consistent with an assumption that there is a refractory time within which the response to one stimulus inhibits the response to another stimulus.**, † This would lead to a combined error score of the following form:

$$C_s = f_1 f_2 (E-1) + A$$

C_s = combined score
f_1 = constant numerical factor
f_2 = numerical factor depending on the tracking task and possibly the gain of the task

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* Walker, Norman K., and DeSocio, E. Norman K. Walker Associates, Inc. Contract No. DA36-034-AMC-0032R. Report No. 9. The Effect of Combat on the Accuracy of Various Human Operator Control Systems (U). April 1964. CONFIDENTIAL Report.

** Walker, Norman K., and Shectman, F., and DeSocio, E. Norman K. Walker Associates, Inc. Contract No. DA49-193-MD-2369. Report No. 10. Further Work on the Use of Tracking Tasks as Indicators of Stress. October 1964. UNCLASSIFIED Report.

† Welford, A. T. The Psychological Refractory Period and the Timing of High-Speed Performance--A Review and Theory. Brit. J. Psychol. 43, 2-19 (1952).

E = error ratio of $\frac{\text{error with stress}}{\text{error without stress}}$

A = stressor score on auditory shadowing or auditory discrimination task in errors per minute

Previous experiments on auditory discrimination tasks have indicated that this refractory period may exist and with further refinement of experiments, it will be able to be determined if the following hold:

(a) The refractory period on a given stressor is independent of the tracking task.

(b) The refractory period for a tracking task is constant, and, hence, independent of gain.*

(c) The refractory period in a tracking task is a constant proportion of the time interval between successive stick movements under the no-stress condition as implied by Walker.**

If (a) is correct, or at least if this period is short compared with the others, then (b) implies that the effect of a reduction in gain is to reduce the effect of stress as shown by E. If (c) is correct, the reduction in gain will lead to a considerable increase in E for a given stressor. The evidence suggest that the effect of stress is substantially independent of the gain, which would imply that some intermediate condition between (b) and (c) is correct. Therefore, carefully planned experiments using the auditory discrimination task as a stressor could settle this point, since the difference in E between (b) and (c) is a large factor.

The ZITA technique is basically the application of well established principles used in designing missile systems to solve a psychological problem—that of human performance degradation under stress. The results obtained thus far have many interesting implications. It is easy to speculate about the causes of the observed effects, but it must be remembered that

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* Welford, A. T. The Psychological Refractory Period and the Timing of High-Speed Performance--A Review and Theory. Brit. J. Psychol. 43, 2-19 (1952).

** Walker, Norman K., and Shectman, F. and DeSocio, E. Norman K Walker Associates, Inc. Contract No. DA49-193-MD-2369. Report No. 10, Further Work on the Use of Tracking Tasks as Indicators of Stress October 1964. UNCLASSIFIED Report.

these results have been obtained on very small samples. During the next year, much larger samples will be tested both by us and other experimenters. The experiments will include the effect of various drugs used as stressing agents and a comparison of the ZITA technique with other standard psychomotor tasks, such as the pursuit rotor, which is not as obviously related to real tasks as is the ZITA.

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4. Hick, W. E., and Bates, J. A. V. Permanent Records of Research and Development. No. 17-204. Ministry of Supply. United Kingdom. The Human Operator of Control Mechanisms. UNCLASSIFIED Report.

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APPENDIX

The Relation Between Pursuit Tracking, Compensatory Tracking, and Zero Input Tracking

by

Norman K. Walker

(Not read at the Conference but inserted in view of later discussions with conferees).

1. INTRODUCTION.

Psychologists have commonly used two forms of tracking tasks, distinguished as pursuit and compensatory tracking in their investigations. Zero Input Tracking is a new and apparently different task, with a high degree of face validity, and it is important to define how it is related to other two as an aid to:

(a) The correlation of the effects of stress on Zero Input Tracking with the effects of stress on other tasks

(b) The interpretation of stress effects on "real world" tasks

(c) A possible future application of factor analysis to the Zero Input Tracking results.

2. THE VARIOUS TASKS.

Pursuit Tracking.

In pursuit tracking, the subject is shown a target, which in a one-dimensional task similar to Zero Input Tracking might be a colored spot of light. He is instructed to hold his indicator, which might be represented by another colored spot of light, as closely as possible to the target spot by manipulating his control. Any desired type of control system can be interposed between his control stick and the indicator.

In early work of this type, the target spot was moved suddenly from one point to another and the subject's response with the indicator was studied. The error score was the transient difference in the position of the target and the indicator. Sine wave motions of the target were then studied, and these were later replaced by complex sine waves or random noise inputs,

since it was found that the subject could acquire a mental "set" and anticipate a regular sine wave.

If the subject does not respond, the error will be equal to the input. If the subject responds perfectly, the indicator and target will always coincide, but will move together in space relative to the display panel. Note that it is possible to imagine perfect performance as being attainable by anticipating the required control signals.

Compensatory Tracking.

In compensatory tracking the subject is shown only one spot, the indicator, and is told to hold this as nearly as possible on a fiducial marker or zero that does not move.

The disturbing inputs are applied to the indicator spot, and the subject is required to compensate for these with opposing motions. If the subject does not respond at all, the motion of the indicator is simply the input. If the subject does respond perfectly, the indicator will not move. Clearly, the latter case is almost impossible since there would be no direct signal to the operator that control is required.

In this case, the error score is measured by the displacement of the spot from the zero mark.

Zero Input Tracking.

Zero Input Tracking, in which the input is given zero amplitude can be used with various control systems. With certain control systems, a small error remains, which is due to the inability of the operator to function perfectly. This represents a residual compensatory tracking task. Zero Input Tracking represents the limit of both compensatory and pursuit tracking, for as the input of pursuit and compensatory tracking tasks is reduced to zero, a residual task remains.

3. THE ANALYSIS OF TRACKING PERFORMANCE IN TERMS OF LINEAR COMPONENTS AND THE REMNANT.

Pioneer analysis by North, Tustin, and others showed that the response to a step function input, with either compensatory or pursuit tracking

could be approximated by a linear transform.*, **

Later, more detailed work by Westbrook and McRuer† and others, especially for the USAF and NASA, showed that this was not quite true but that:

(a) The "best-fit" transfer function required variable gain and lead coefficients that were varied by the human operator during the experiment to obtain the best results

(b) After extracting the "best-fit" result a nonlinear component remained, which McRuer christened the "remnant

Let us assume that the variation of error with input amplitude may follow a line such as PQ_1 in figure 74 for pursuit tracking and a line such as PQ_2 in figure 74 for compensatory tracking.

Note that PQ_1 and PQ_2 are quite arbitrary variations. They may be linear, convex, or concave, but they are almost certainly monotonic.

From these, the linear component may be extracted in each instance, thereby giving PQ'_1 and PQ'_2, which represent the remnant. Again, the lines PQ'_1 and PQ'_2 may be linear, convex, or concave, but almost certainly monotonic.

Assuming that the linear variations are as shown, the following are implied:

(a) Zero Input Tracking represents the final limit of the remnant in either the compensatory or pursuit tracking mode. As we believe that this limit is due to a

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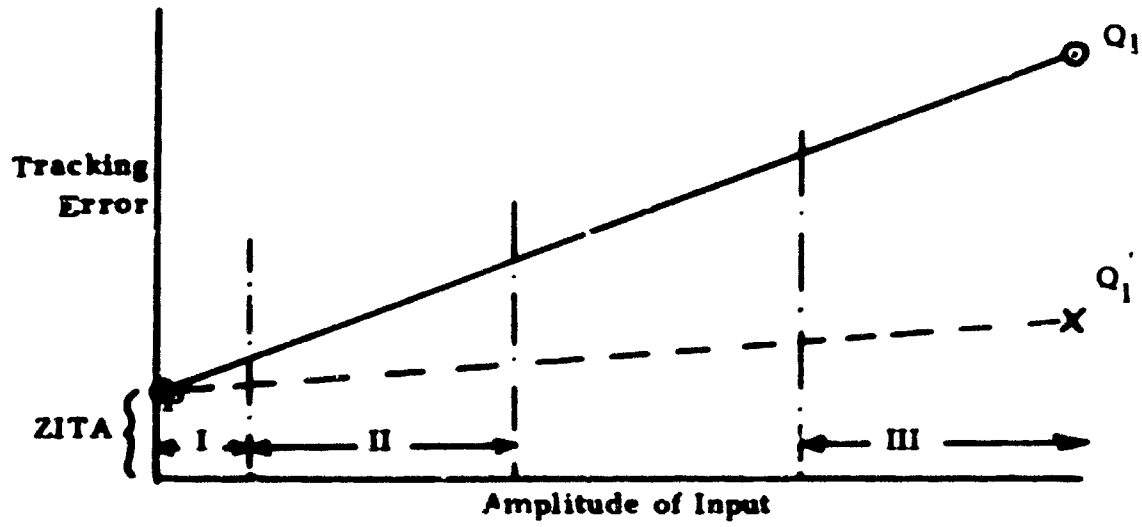
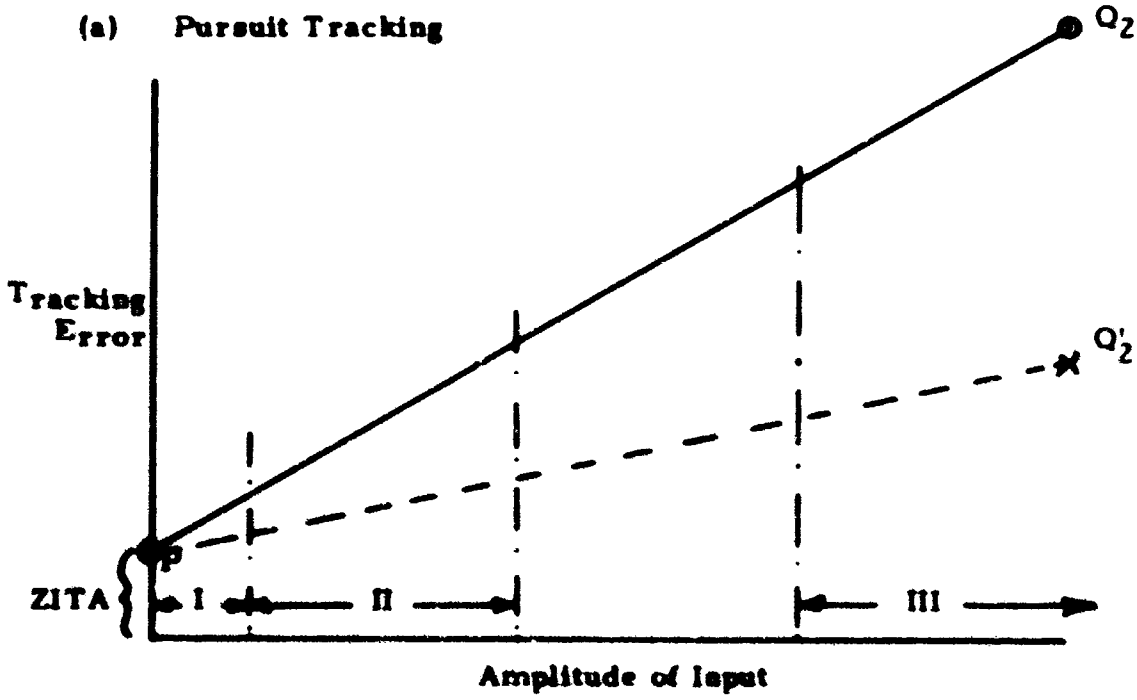
* North, J. D. The Human Transfer Function in Servo Systems. Automatic and Manual Control. Butterworth's Scientific Publications. London. pp 473-501. 1952.

** Tustin, A. The Nature of the Operator's Response in Manual Control and Its Implications for Controller Design. Institute of Electrical Engineering. United Kingdom. May 1947.

† Westbrook, C. B., and McRuer, D. T. Report No. 125. Aircraft Handling Qualities and Pilot Response Characteristics North Atlantic Treaty Organization Advisory Group for Aeronautical Research and Development. May 1957. UNCLASSIFIED Report.



(a) Pursuit Tracking



(b) Compensatory Tracking

I. Human Operator Guided Missiles
II. Recent NASA Tests on Piloted Aircraft
III. Early Experiments (McRuer and others)

Figure 74. Variation of "Remnant" With Input Amplitude

discontinuous response in the man, even with a proportional control, this residual remnant is nonlinear.

(b) The proportion of the nonlinear component, or remnant, to the total error steadily decreases as the input increases. In the early studies of the control of aircraft (by Duane and McRuer, for example), there were large inputs, and it was possible to speak of the remnant as small. In later studies by NASA, in which the pilot's ability to hold a steady course was measured, the remnant amounts to perhaps 50% of the total error. In instances in which the true, or apparent, target motion is small and other inputs are small, as in the instance of the antitank missiles Malkara or ENTAC, the remnant accounts for almost all the error.

The Effect of Stress.

The experiments of Garvey and Henson were performed with compensatory tracking tasks with a large complex sine wave input. *

It is obviously impossible to analyze the relative effects of stress on the linear component and the remnant without first finding the proportion of errors due to each without stress, and then with stress. Furthermore, critical experiments are needed to isolate the stress effects of the two components.

This will obviously take an appreciable effort, but the result may be simpler than it appears at first sight. If the overall stress degradation is of the same order with an input as without and if the measurements of refractory period from stress tests confirm Walker's simple interference hypothesis, then there is hope of correlating all three forms of tracking with and without stress.

* Garvey, W. D. Report No. 5015. The Effects of "Task-Induced Stress" on Man-Machine System Performance. Naval Research Laboratory. September 9, 1957. UNCLASSIFIED Report.

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DISCUSSION

Dr. Levison (Institute for Behavioral Research): Would you clarify the analogy between billiard-cue balancing and zero input tracking?

Mr. Walker: Suppose you balance a billiard cue (or more properly a light, stiff rod with a weight on the top) vertically on your finger (figure 75a).

If everything is perfect, it will remain vertical indefinitely. There will always be some slight departure from the vertical, however, say θ, and the result will be that the rod begins to fall over with an acceleration proportional to sin θ, the error angle increasing more and more rapidly with time (figure 75b).

You can overcome this and prevent the billiard cue from falling by moving your finger even faster until the error angle is reversed (figure 75c). The resulting acceleration will then cause the rod to slow down and stop. You will, however, be unable to do this perfectly, and you will settle down to a condition where you are always moving your finger to and fro or from side to side. The rod is always roughly vertical, but it is never stationary.

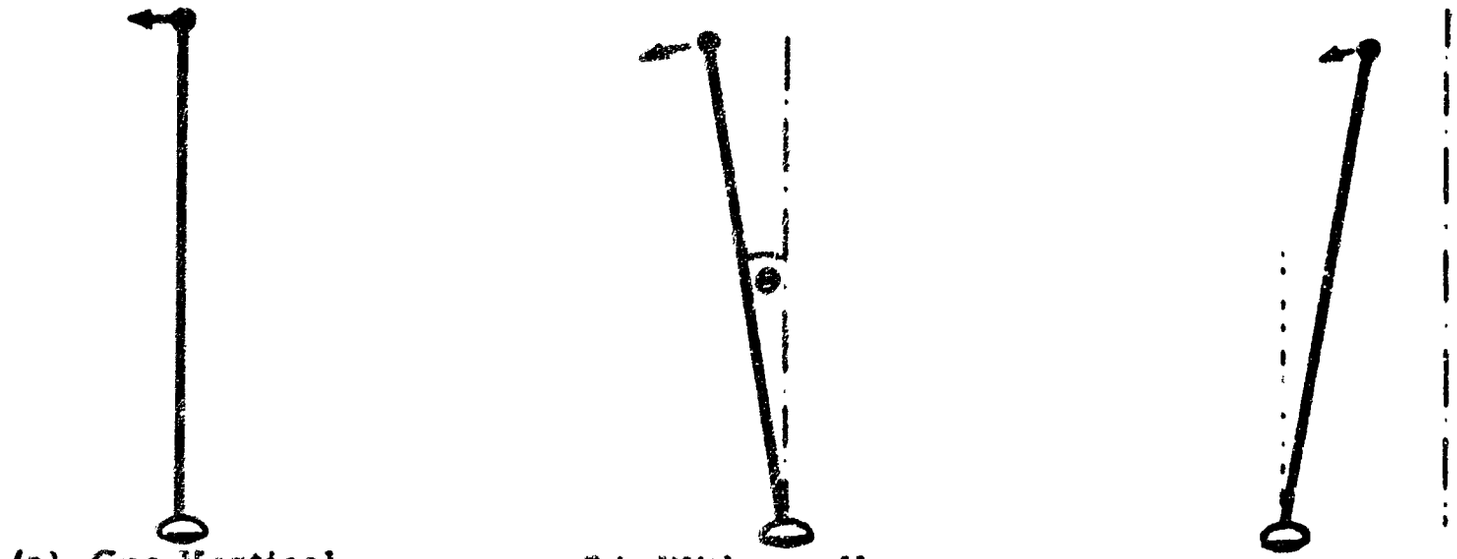
Note that once this condition is established, there is no error input from outside; there is only the residue from your previous errors. This is closely analogous to zero input tracking on the ZITA with task A (acceleration control, no lag) except that:

(a) One must control in two directions at once.

(b) The optical and tactile cues are not as well defined as the error displayed on ZITA.

Nevertheless, to the operator the two tasks are substantially the same.

Since the general concept of difficulty of control may be unfamiliar, I have here a diagram that may clarify this point. This diagram shows the control movements required to completely cancel small errors in three types of systems which we encounter frequently in daily life.

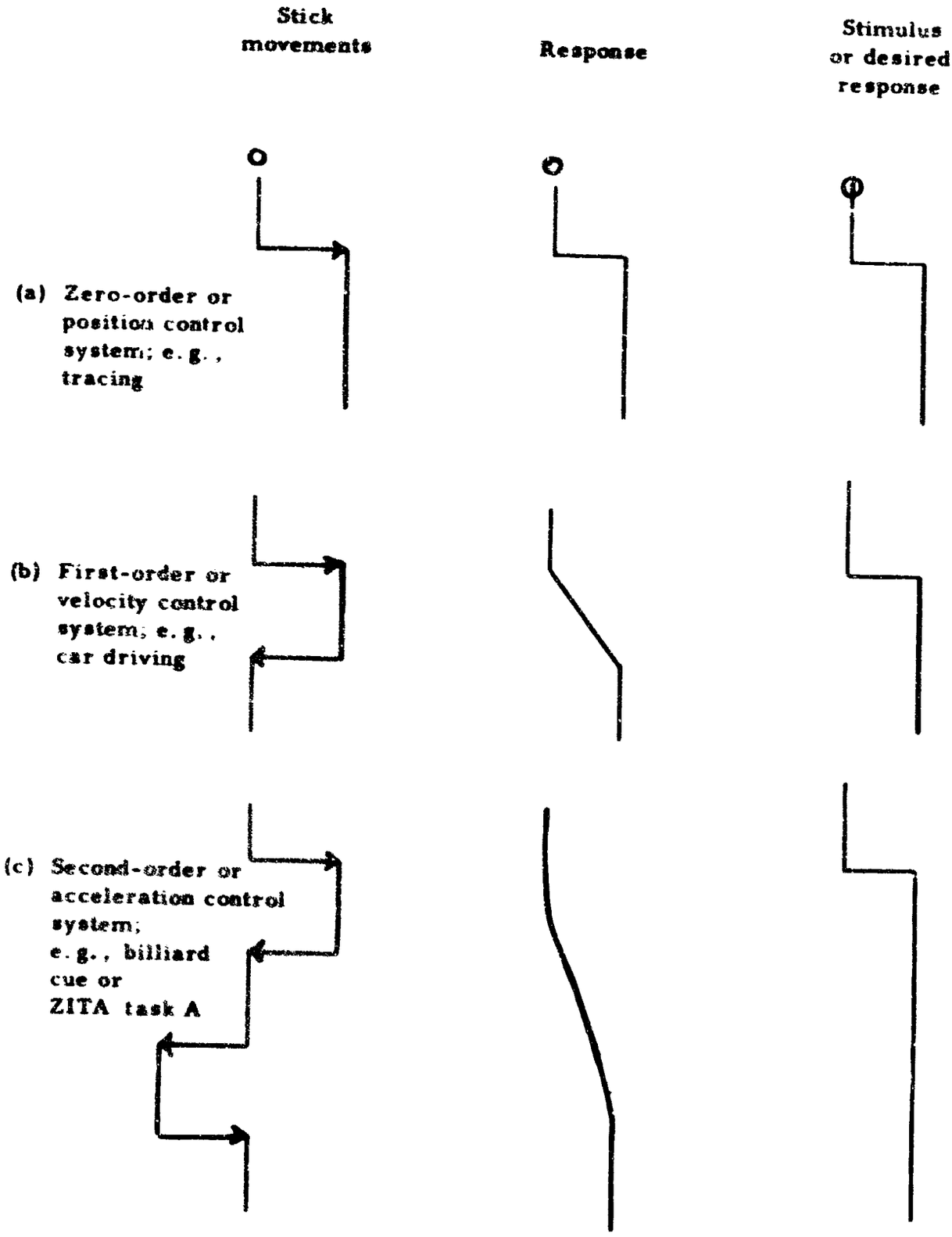


(a) Cue Vertical

(b) With small error (weight accelerates sideways with acceleration g sin θ)

(c) Correction by movement of finger (weight now has acceleration opposing velocity)

Figure 75. Balancing a Billiard Cue on the Finger


Stick movements
Response
Stimulus or desired response
(a) Zero-order or position control system; e.g., tracing
(b) First-order or velocity control system; e.g., car driving
(c) Second-order or acceleration control system; e.g., billiard cue or ZITA task A

The first column shows the stick movements and the second the response of the system. The third, in each case, shows the desired result.

The first illustration, a, is of a position control or zero-order system in which movements of the stick are preproduced faithfully by the indicator. Such systems are roughly representative of signing one's name, tracing, etc. In this case, only one movement is required to correct the error.

The second illustration, b, is of velocity control in which a movement of the control element (hand, finger, or stick) produces a velocity or rate of movement of the indicator. This task is really like driving a car along a straight road toward a distant object. Suppose you observe that you are not pointing, i.e., moving directly toward the object: you make a small movement of the wheel and the car turns at a steady rate toward the object. When it is lined up, you center the steering wheel and the error is eliminated. Note that with this control system, it takes two stick movements to cancel an error.

The third illustration, c, is of an acceleration control or a second-order etc. system such as balancing the billiard cue or ZITA task A, in which a movement of the stick opposes the observed error by applying acceleration. When the error is obviously being reduced by the velocity increment due to the acceleration, you restore the stick to center. This kills the acceleration but leaves the velocity. When error is reduced to exactly the right amount again, you again move the stick to apply opposite control and kill the velocity. Finally, when the velocity is zero, you center the stick, and this leaves the system with no acceleration, no velocity, and no error. To achieve this happy result of three zeros at once, however, takes such accurate timing of four separate control movements that it is in fact impossible.

Dr Levison: I think at this one point I could ask you just one question. You said that on these systems you do not impose any stimulus change on the subject. Now isn't this track that is to my right a stimulus change that you are imposing?

Mr. Walker: No it isn't imposed from outside in the way that we use the ZITA device. It is imposed by the subject himself. The illustration shows the response to an isolated disturbance of the system.

What happens in practice is that there would always be some tiny disturbance of the system at some time or other. The man would get bored, and he would touch the stick. As soon as he touched the stick, the spot would respond and start to move. As soon as he sees the spot move, he takes corrective action to kill the movement and now finds that just as in the case of

the billiard cue, he is in a continuous repetitive situation in which his average error does not depend on the initial error at all but only on his own characteristics and on those of the system he is controlling.

What we are doing with ZITA, therefore, is measuring some sort of combined reaction, decision, and thinking time all together at the rate of about 100 repetitions per min. Since we usually average several 1-min runs, we get a pretty good readout.

Note again that the man cannot stop. The error he sees at any time is due to the error left over from his previous correction.

Dr. Levison: So the only other solution to this is not to touch the stick.

Mr. Walker: Correct, but this is not a permitted solution. You cannot guarantee that the errors are zero, zero, zero in the beginning—not in a real world situation. If they were, the skilled operator would in fact do nothing. (We have discovered one case in several hundred actual drops of a guided bomb in which this occurred.) The real solution to this situation is to find a way of getting around it. There are ways, and we have written a classified report on one of them. *

This was not, however, our primary concern with ZITA. We needed a reproducible task that exercised certain parts of a man's mind in a certain manner; we could, therefore measure what happened under stress or the influence of drugs.

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* Walker, Norman K., and Silverman, Stephan M. Norman K. Walker Associates, Inc. Contract No. DA49-092-ARO-36. Report No. 19. An Investigation into the Effect of Auditory Shadowing on the Accuracy of 'Flick' Tracking (U). September 1964. CONFIDENTIAL Report.

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A MODEL FOR PREDICTING THE EFFECT OF ANTICHOLINERGIC COMPOUNDS ON COGNITIVE PERFORMANCE

MAJ James S. Ketchum and Mr. Kragg P. Kysor
Clinical Research Department
Medical Research Laboratory
Edgewood Arsenal

Introduction.

Most reported studies of effects of drugs on behavior have been concerned with measuring behavioral changes at the time of presumed maximum action of the drug. Relatively little attention has been given to the rate at which these effects increase and decrease during the course of the drug's action.

From inspection of the serial cognitive-performance scores of a number of individuals receiving centrally active, cholinergic-blocking agents, it is apparent that the scores (when plotted on ordinary graph paper) follow a characteristic "trajectory" over time, as shown in figure [illegible].

For some time, this curve has been an intriguing puzzle for which no simple equation or function could be found. Although an equation could no doubt be computed that would explain much of the observed variance, validation of such an equation would be most difficult unless a large number of subjects could be tested, since considerable individual variation is known and might easily obscure small deviations in the trend from the supposed model.

A method by which some of these difficulties may be reduced is presented in this paper. Basically, the approach involves the "factoring out" of the effect of time on the intensity of the response. Time is treated as an operator that continually modifies the concentration of the drug at the site of action in a manner that can be predicted by using the half-life concept of drug metabolism. Therefore, by suitable transformations, the starting dose and elapsed time, which are normally considered as separate variables, can be combined into a single variable that might be referred to as the "residual dose." Since from 10 to 30 different residual doses, each associated with the test score, can be obtained for each subject, the analysis of the relationship between the residual dose and the score can be expected to yield a much more reliable estimate than would be possible from the usual one man—one score approach.

The procedure followed, the results of the analysis, and some of the theoretical implications of these results will be presented here.

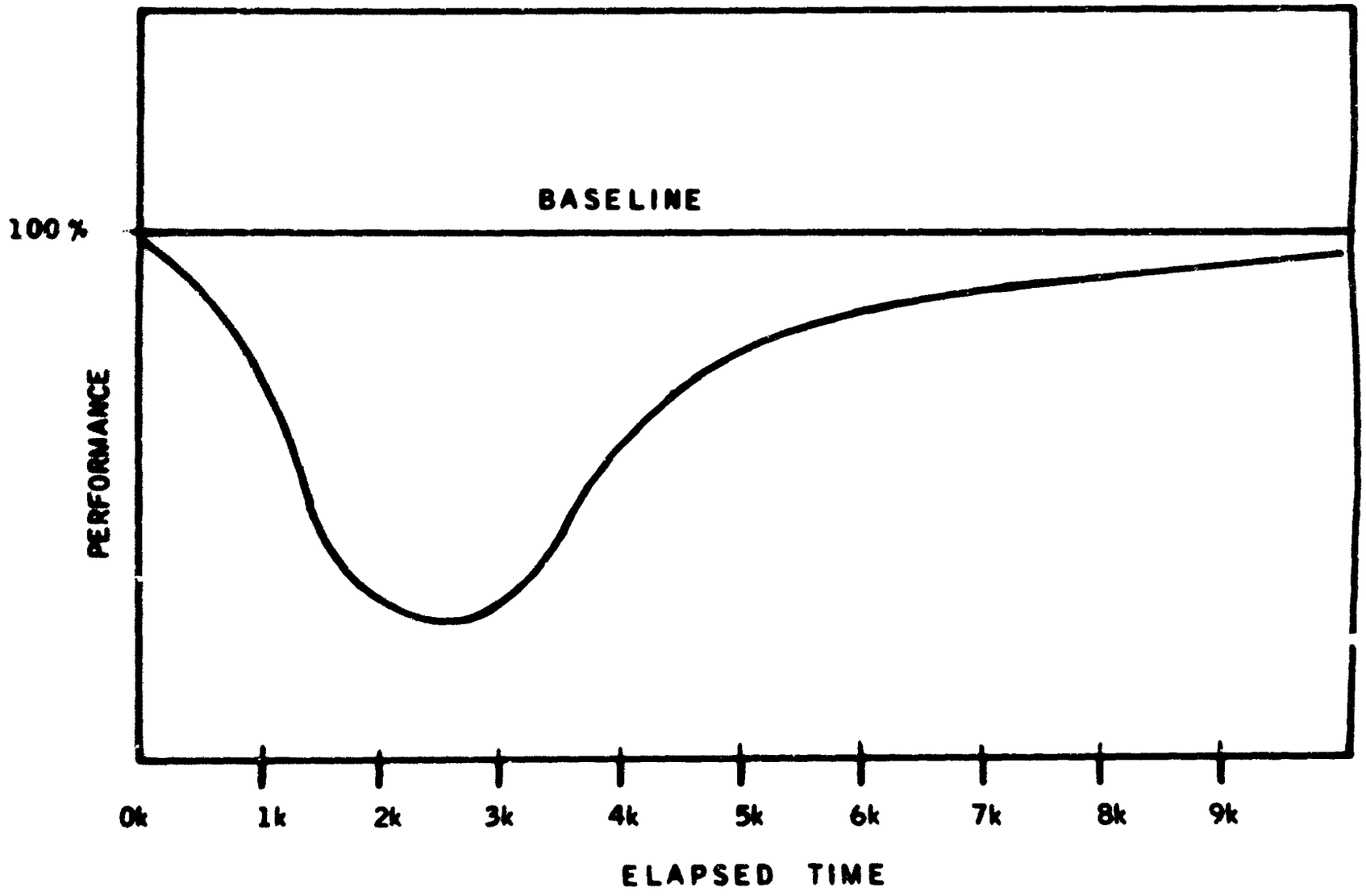

Figure 76. General Shape of Time Versus Score Relationship

Twenty healthy enlisted military volunteers were given a glycolate (atropinelike) agent by the im route. Doses, expressed in arbitrary units of agent weight per kilogram of body weight, ranged from 1.8 to 4.8. The subjects remained under continuous medical observation for a period of 96 to 124 hr following administration of the agent and were tested at regular intervals, using the 20 equivalent forms of the Number Facility test (NF) designed by Mefferd and Moran.*

Methods.

NF scores following exposure were expressed as a percentage of the baseline (the mean of the five highest scores attained during a preexposure series of 10 to 20 distributed practice trials). These percentage scores were then adjusted by converting them to a percentage of an "expected score" for the particular time of day at which the test was given (figure 77).

From the approximate regression lines fitted to graphed data for the entire group of subjects, an estimate of the pharmacological half-life was made and from this, residual-dose levels were inferred for the various experimental times at which the NF scores were obtained.

The dose-score pairs for all the subjects were then pooled, and the median score associated with each residual-dose value was determined (figure 78). Curve-fitting operations were then applied to the residual-dose–median score pairs.

Results.

The scores and medians associated with each residual-dose level are given in table XVIII. The residual dose–median score relationship was satisfactorily fitted by a Gomperts curve,** which has as its equation:

$$Y_c = ka^{b^x}$$

This may be put in logarithmic form:

$$\log Y_c = \log k + (\log a)b^x$$

* Moran, L. J., and Mefferd, R. B., Jr. Repetitive Psychometric Measures. Psychol. Rept. 5, 269-275 (1959); Hart, J. J. CRDLTM 2-17. Standardization Studies with the Repetitive Psychometric Measures. I. Determining Equivalence of Forms. 1965. UNCLASSIFIED Report.

** Croxton, F. E., and Cowden, D. J. Applied General Statistics. 2nd ed. 1955.

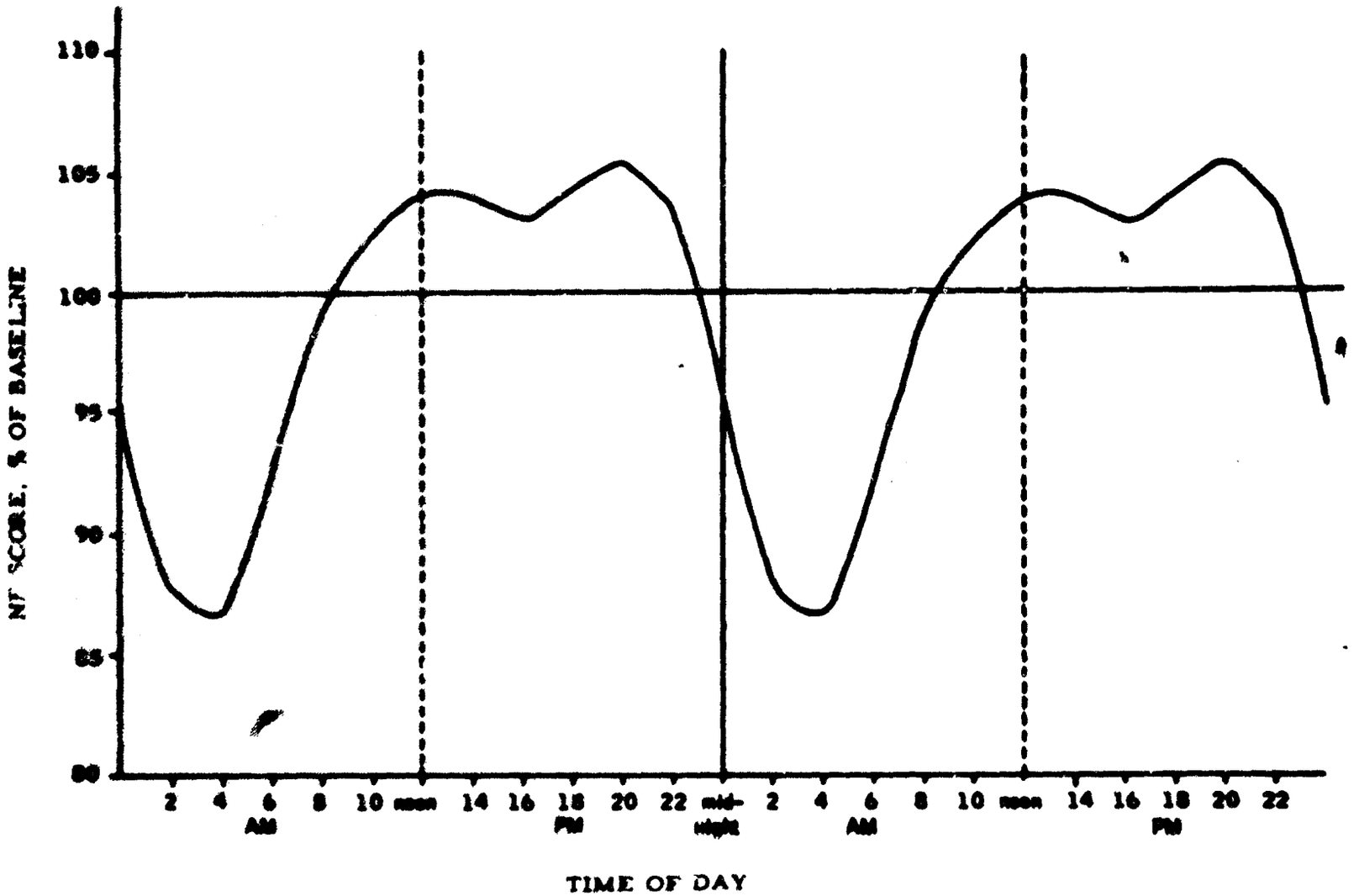

Figure 77. Diurnal Cycle of Performance in Normal Subjects

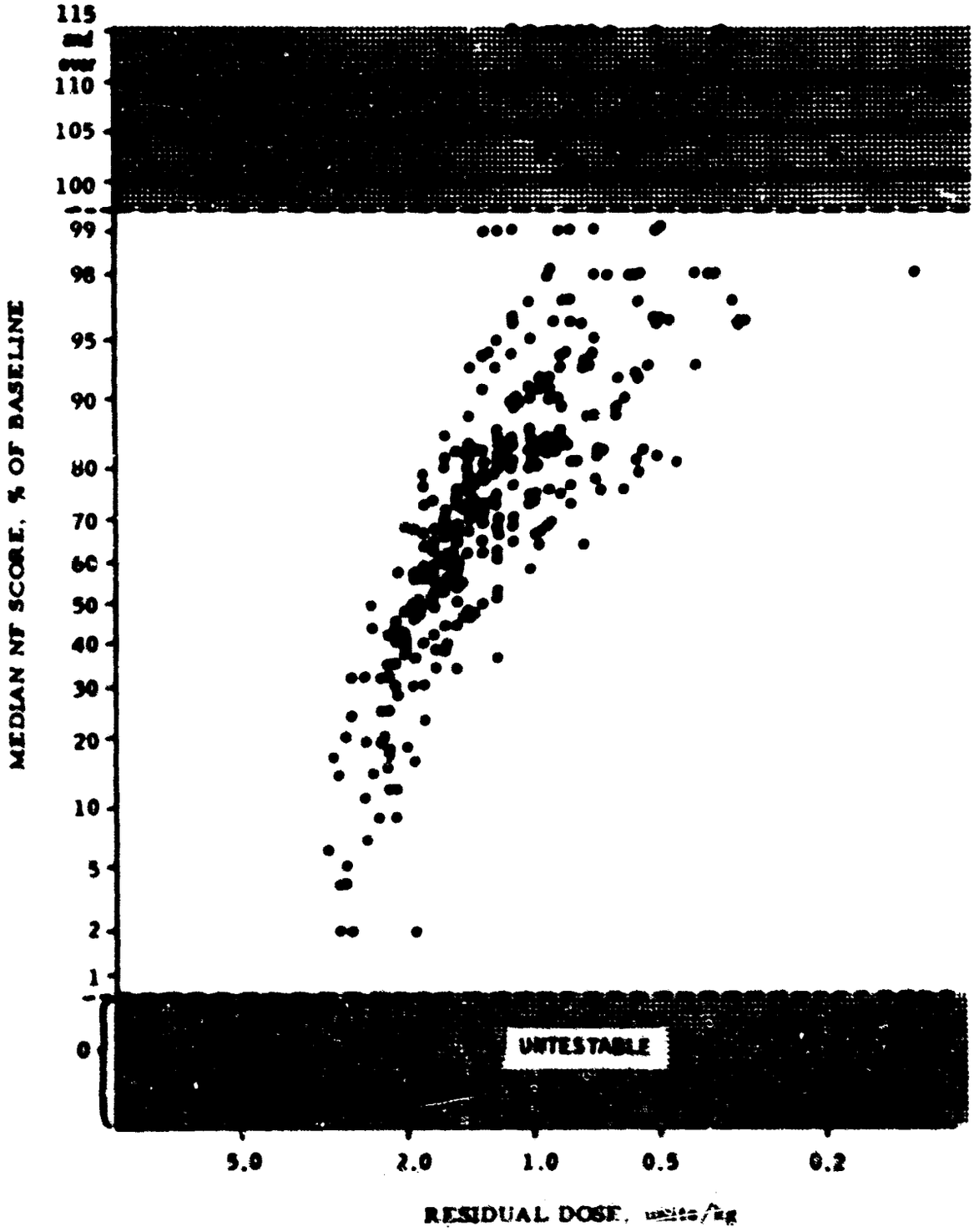

Figure 78. Median Performance Scores Versus Residual Dose

Table XVIII. Medians and Distribution of NF Scores Associated With Residual-Dose Levels

Residual dose	NF scores (in rank order)	Median score
units/kg	%	%
3.1	6	6
3.0	0, 0, 17	0
2.9	2, 5, 14	5
2.8	0, 0, 4, 5 | 20	4
2.7	2, | 22, 32	22
2.6	0, 0	0
2.5	7, 11, 19, 31	15
2.4	0 | 14, 44 | 49	29
2.3	0, 9, 19, 19, 25, 31	19
2.2	12, 15 | 17, 18, 25, 32, 35, 42	21.5
2.1	9, 12, 29, 30, 35, 40, 55 | 58, 63	35
2.0	0, 18 | 38, 40, 42, 48 | 61, 68	41
1.9	2, 16, 30 | 37, 47, 48, 48, 49, 50 | 52, 57, 66	48
1.8	23, 30, 40, 49, 56, 59, 64, 67 | 73, 77, 79	59
1.7	0, 34, 37, 38, 41, 49, 50, 56, 58, 59, 63 | 65, 68, 74, 87	56
1.6	39, 44, 52, 55 | 59, 60, 61, 64, 66, 66, 68, 70 | 72, 80, 82, 85	65
1.5	34, 35, 50, 54 | 54, 60, 64, 67, 69, 69 | 74, 75, 76, 83	65.5
1.4	46, 46, 46, 62, 67 | 70, 71, 72, 73, 73, 75, 76, 77, 78, 79, 82, 83 | 83, 84, 84, 88, 93	75.5
1.3	50, 65, 69, 71 | 71, 72, 72, 73, 79, 81, 83 | 91, 94, 99, 103	73
1.2	38, 51, 51, 61, 63, 64 | 69, 70, 73, 75, 80, 80, 81, 82, 83, 84, 85, 86 | 86, 93, 95, 99, 104, 108	80.5
1.1	65, 68, 70, 73, 77 | 80, 80, 81, 84, 85, 89, 89, 90, 94, 96 | 96, 99, 103, 107, 128	87
1.0	73, 74, 75, 80, 81 | 81, 82, 83, 85, 86, 90, 91, 95 | 97, 102, 105, 111, 121	85.5
0.9	58, 64, 67, 67, 68 | 69, 76, 80, 83, 83, 84, 84, 84, 91, 91, 94, 98, 98 | 102, 104, 105, 105, 120	84
0.8	73, 75, 77, 81, 81, 84 | 86, 89, 90, 93, 93, 94, 94, 96, 97, 97, 99, 99, 100 | 100, 105, 106, 111, 115, 123	94
0.7	64, 76, 78, 82, 83, 88, 88, 93, 93, 93, 94, 95, 96, 98, 99, 101, 102, 104, 106 | 107, 108, 109, 110, 120, 126	96
0.6	76, 78, 81, 88, 90 | 92, 98, 98, 98, 100, 101, 103, 104, 105, 106 | 106, 107, 107, 108, 117	100.5
0.5	79, 81, 82, 83, 91 | 92, 93, 96, 96, 97, 98, 99, 104, 105, 105 | 107, 110, 110, 111, 115	97.5
0.4	53, 93 | 96, 98, 100, 104, 106, 108 | 110, 118	102
0.3	96, 96 | 97, 98, 98, 104, 105, 105, 108, 113	101

Note: The approximate interquartile range (Q_1 - Q_3) is indicated by the vertical bars in each row.

The equation was solved as follows:

$$\log (NF) = 2.06 + (2.53)0.87^{x}$$

where x is an expression of dose such that x = 32 - (10 × units/kg). The graphic representation of this curve and the data points (median NF scores) are given in figure 79.

When the data points are plotted on arithmetic-probability paper, a remarkably linear trend is obtained, as shown in figure 80. Although departures from the line are present above 90% and below 10%, they are small in absolute magnitude.

Estimates of individual pharmacological half-lives were made for each subject by replotting the NF scores as residual doses on semilog graph paper. The calculations for an illustrative case are shown in figure 81. The half-life for each subject, estimated by the graphic method described, is given in table XIX.

The first 5 hr, during which equilibration is presumably occurring between the concentration of agent at the site of action and that remaining in the general circulation, was omitted from the initial analysis. This period, which appears to be about 6 hr, was later analyzed by using the calculated relationship between dose and score as given by the Gompertz curve.

Scores for each subject during the first 5 hr were first transformed to their corresponding residual doses. The latter were then pooled by expressing them as percent of the administered dose. The pooled values are shown in figure 82.

It appears that the rising dose levels during the onset period can be fairly well described as a logarithmic growth curve that asymptotes at about 88%. A composite curve describing the rise and fall of the dose level over the entire time course (assuming a half-life of 33 hr) is shown in figure 83.

From this theoretical curve, "most probable" serial NF scores were predicted for each dose administered. These predictions, together with the actual median NF scores for the subjects receiving that dose, are presented in figures 84 through 87.

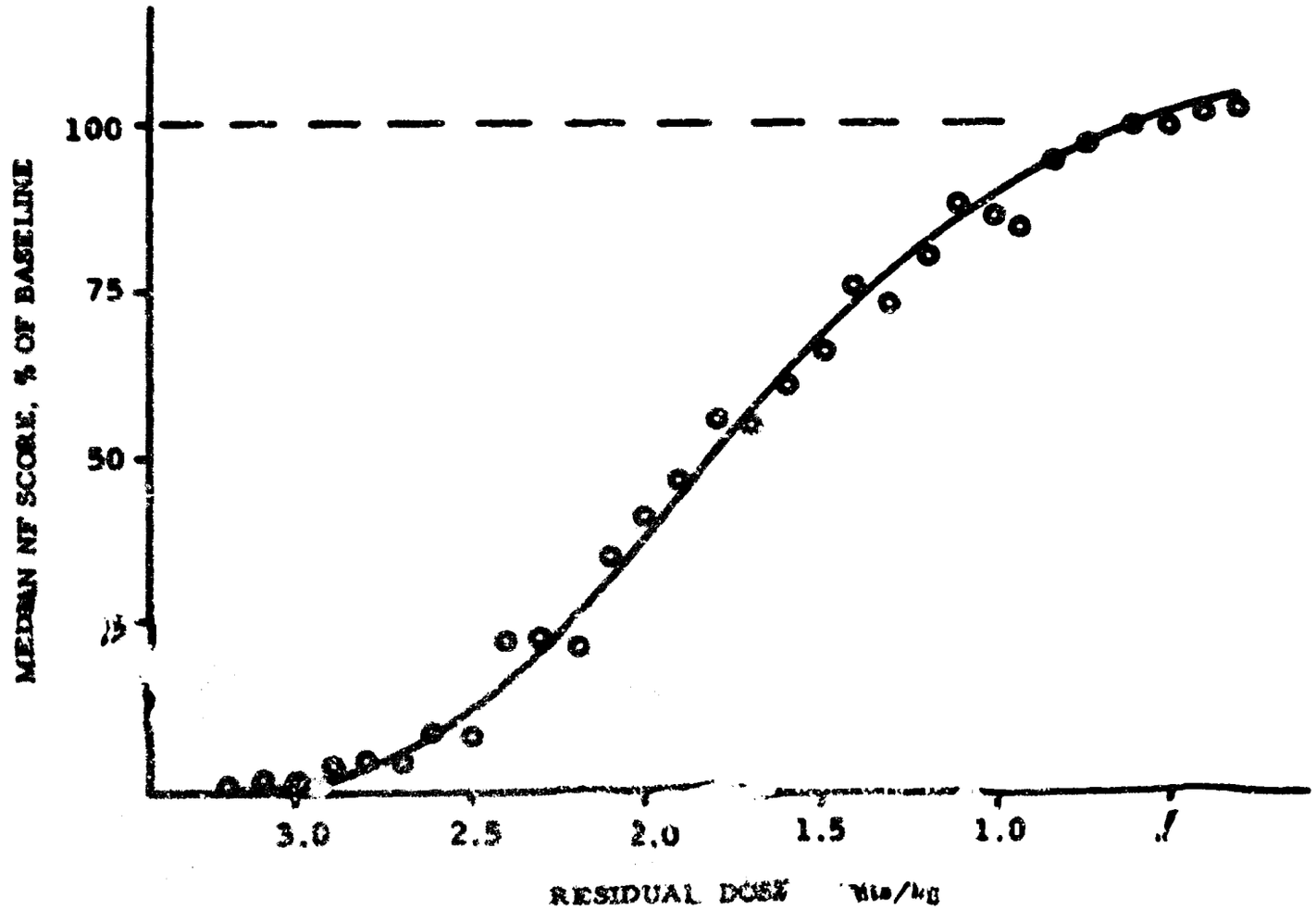

Figure 79. Comperts Curve Fitted to Median Performance Scores at Various Residual-Dose Levels

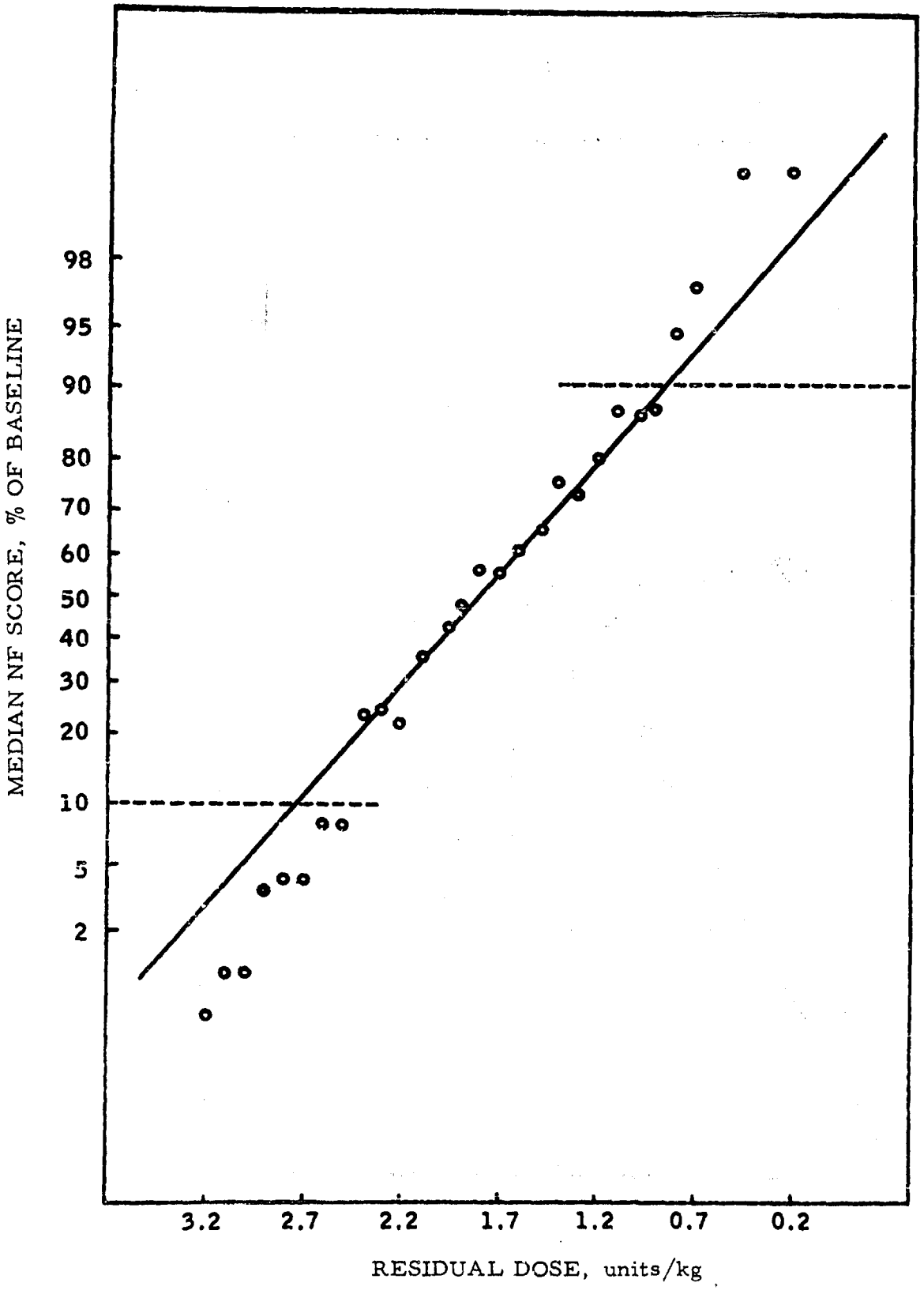

Figure 80. Logistic Curve Fitted to Median Performance Scores at Various Residual-Dose Levels

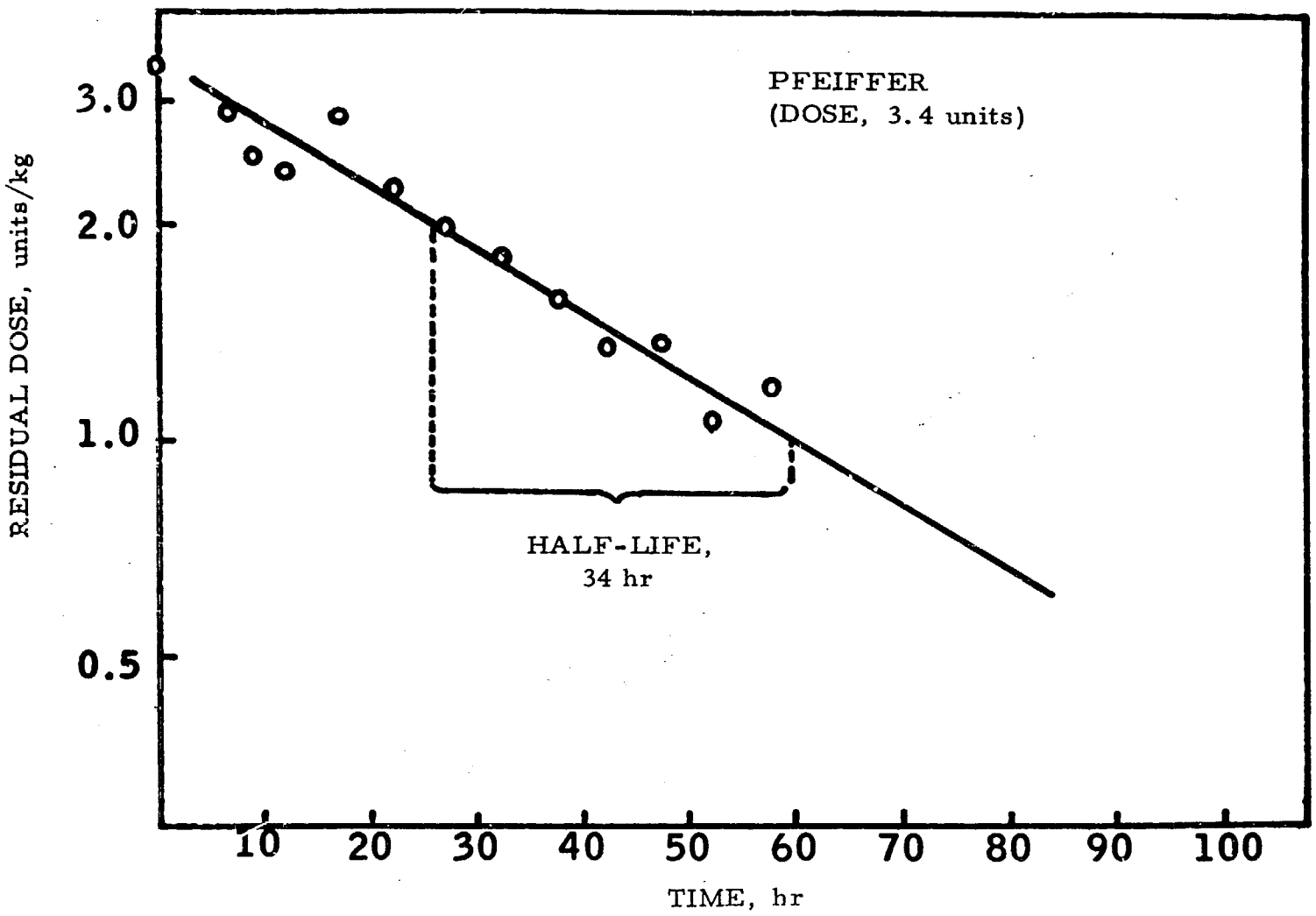

Figure 81. Graphical Estimation of Pharmacological Half-Life

Table XIX. Estimation of Pharmacological Half-Life for Each Subject

Dose	Subject	Estimated half-life
units/kg		hr
1.8	Hughes	42
	Miskey	40
	Winston	29
	O'Neill	31
	De La Rosa	16
2.4	Williams	35
	Neilson	32
	Cox	23
	Lee	45
	Mullins	34
	Pender	43
3.4	Pfieffer	34
	Johnson	33
	Samson	21
	Bishop	39
	Kemp	30
4.8	Benton	36
	Armstrong	41
	Bok	43
	Fernandez	43

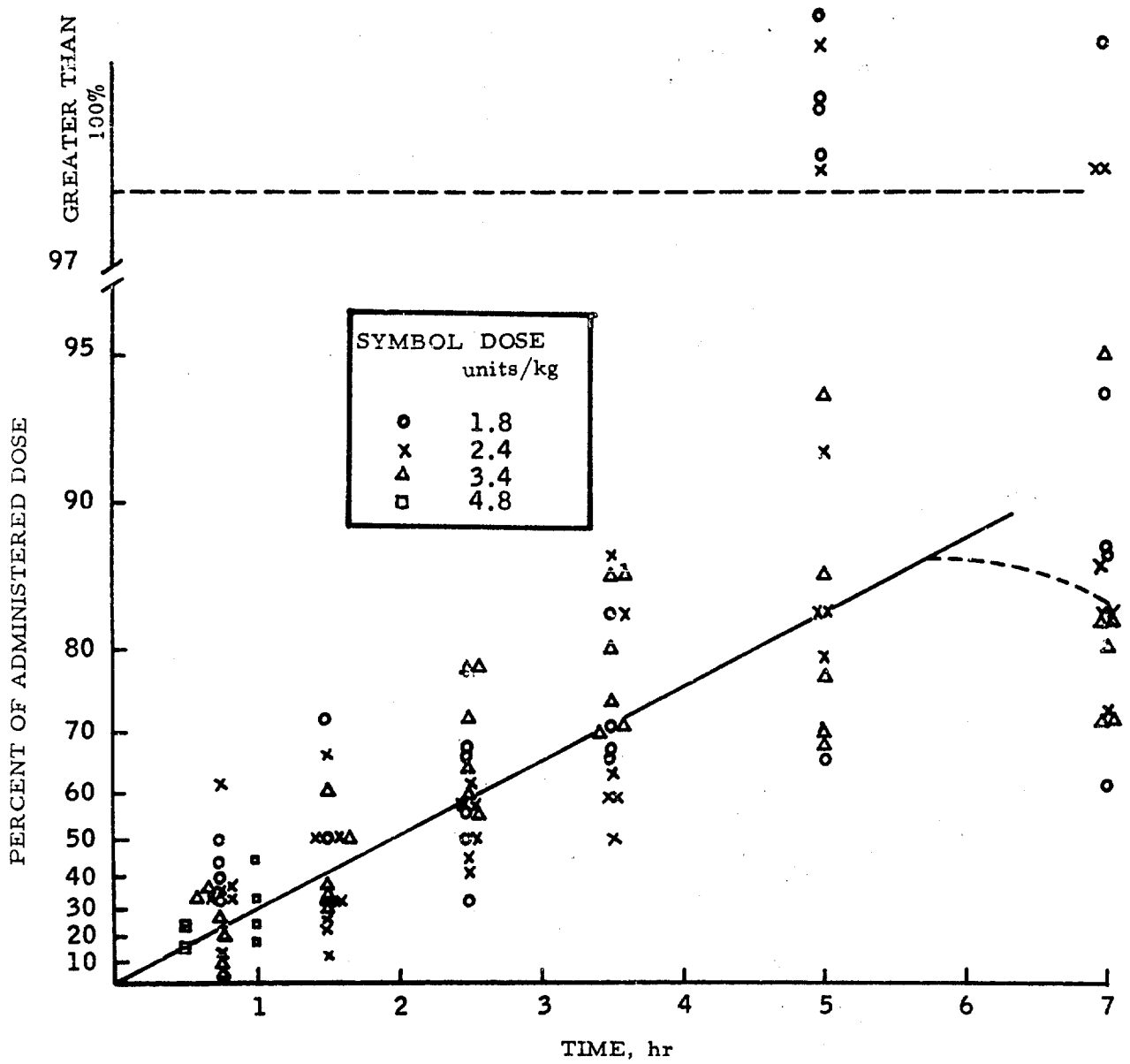

Figure 82. Concentration of Agent at Site of Action

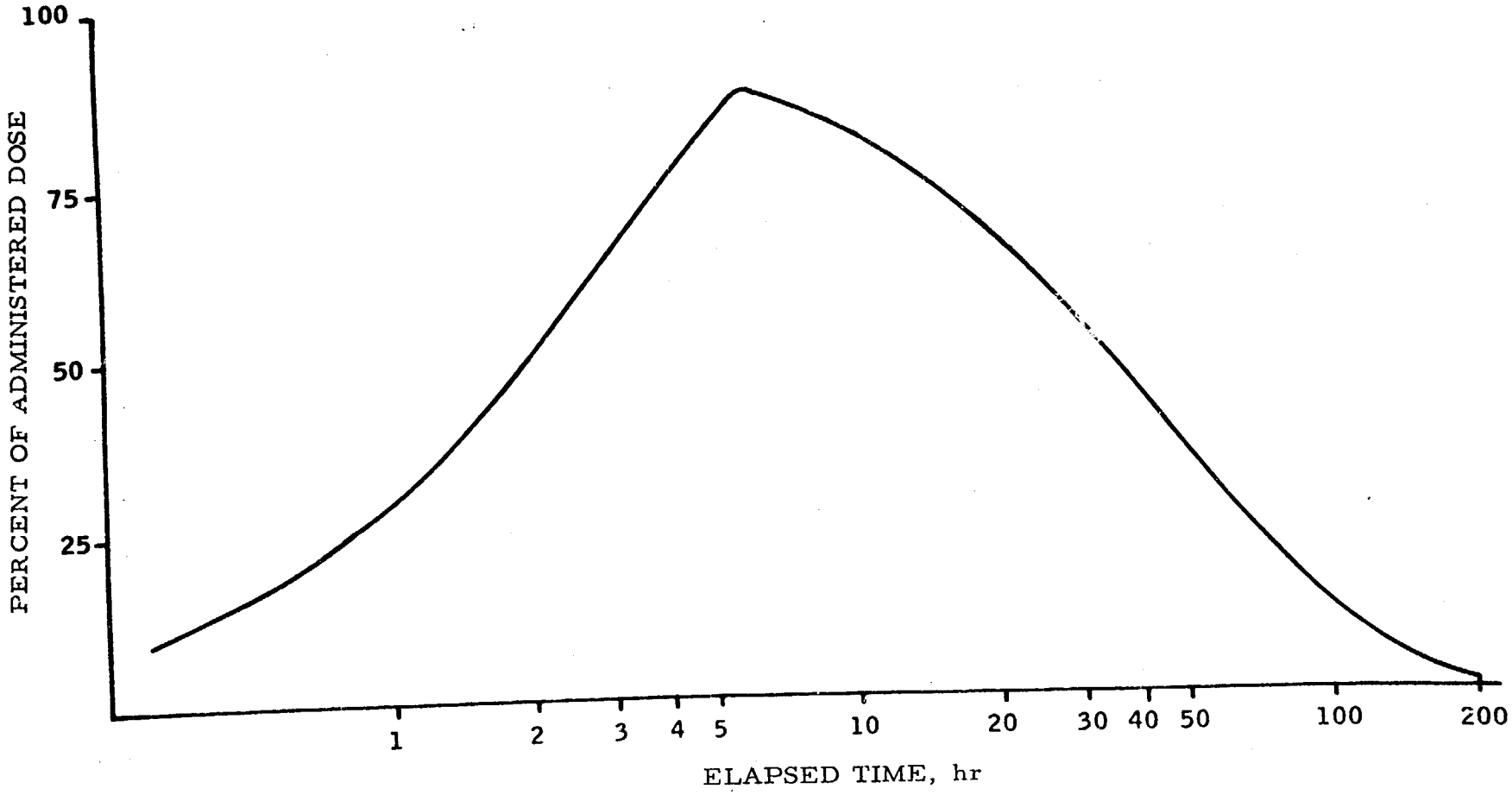

Figure 83. Composite Theoretical Curve of Drug Level Versus Time

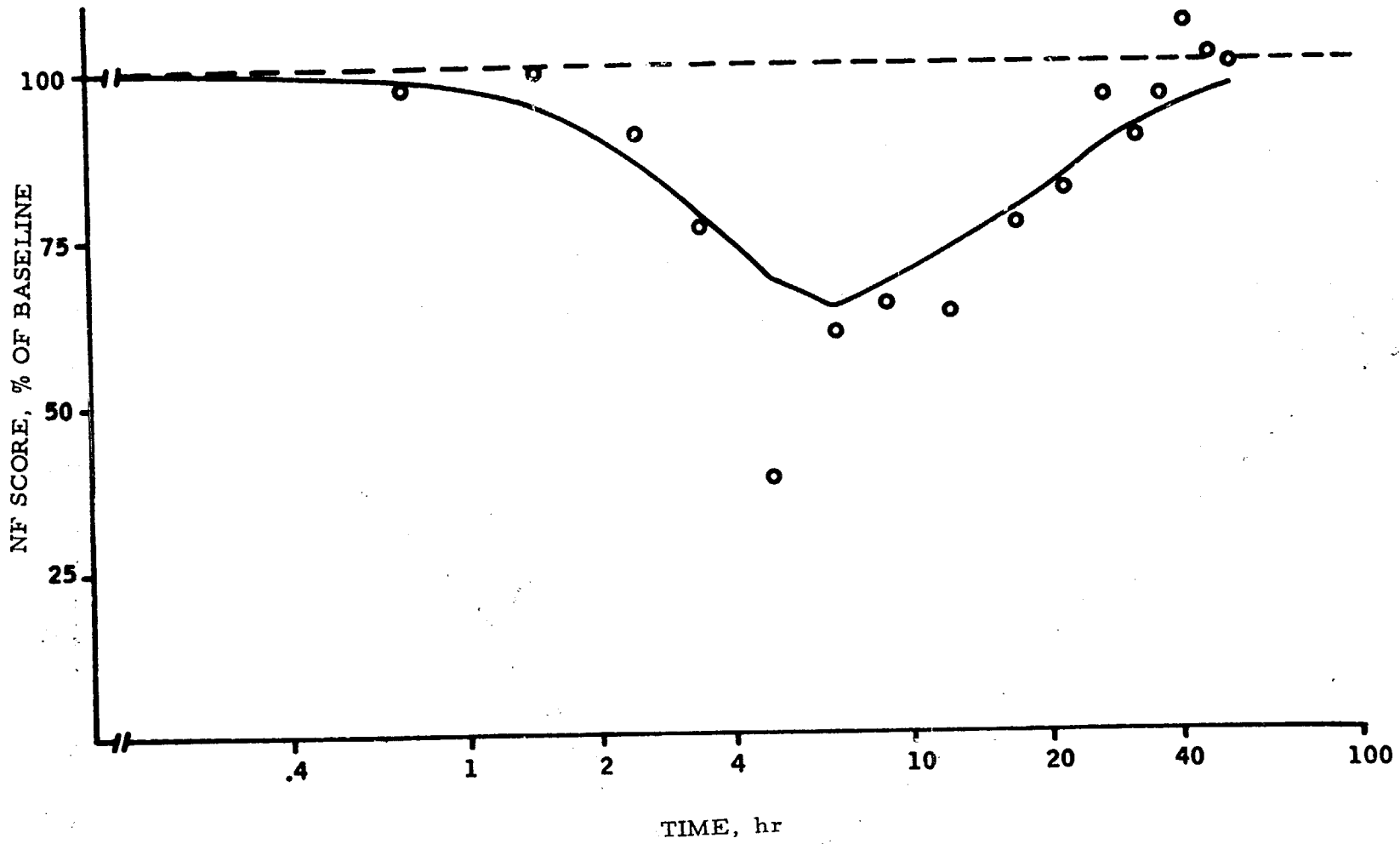

Figure 84. Predicted Versus Actual Serial Performance Scores (Dose, 1.8 Units/kg)

(Circles indicate actual median NF score; solid line indicates predicted NF score)

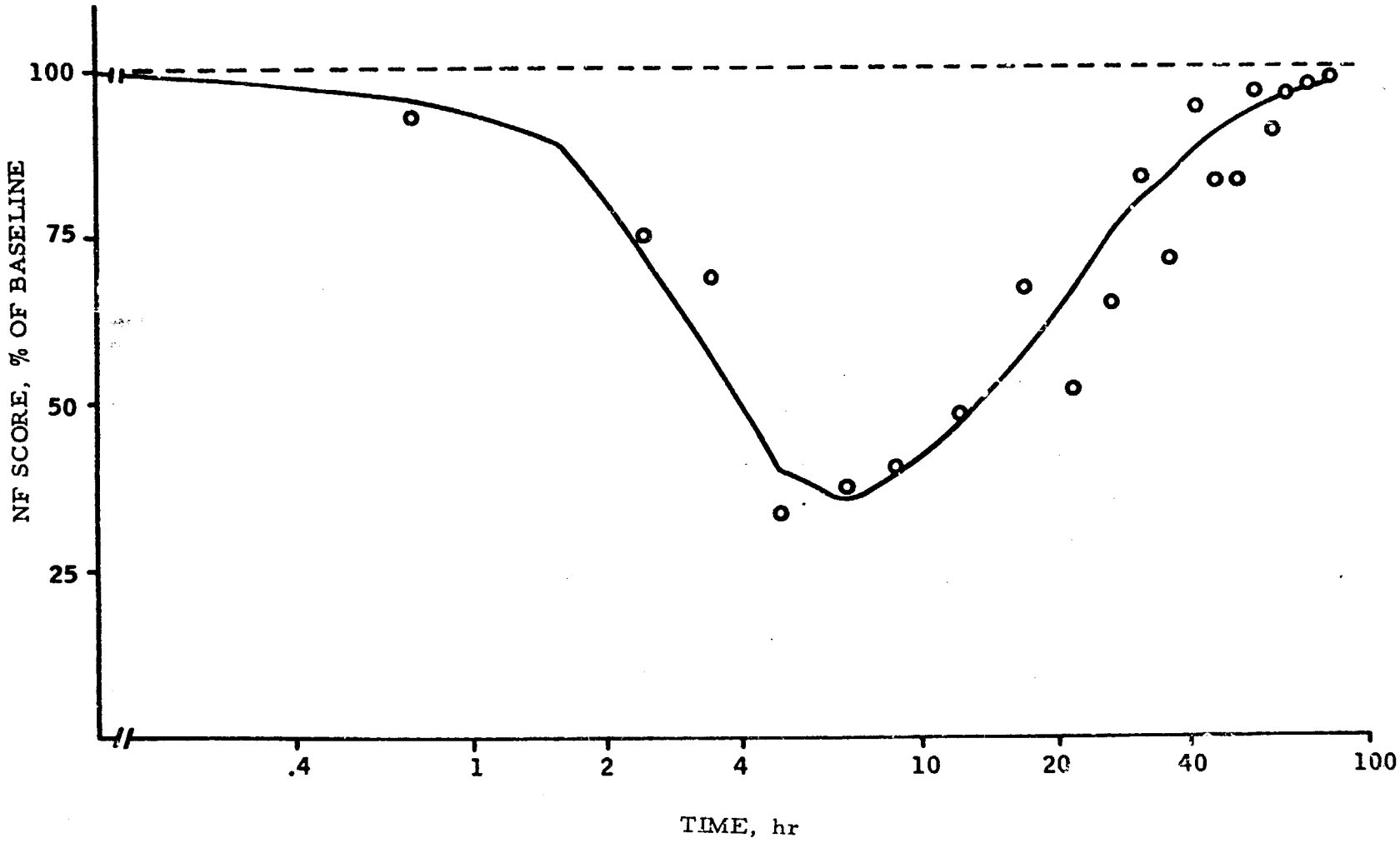

Figure 85. Predicted Versus Actual Serial Performance Scores (Dose, 2.4 Units/kg)

(Circles indicate actual median NF score; solid line indicates predicted NF score)

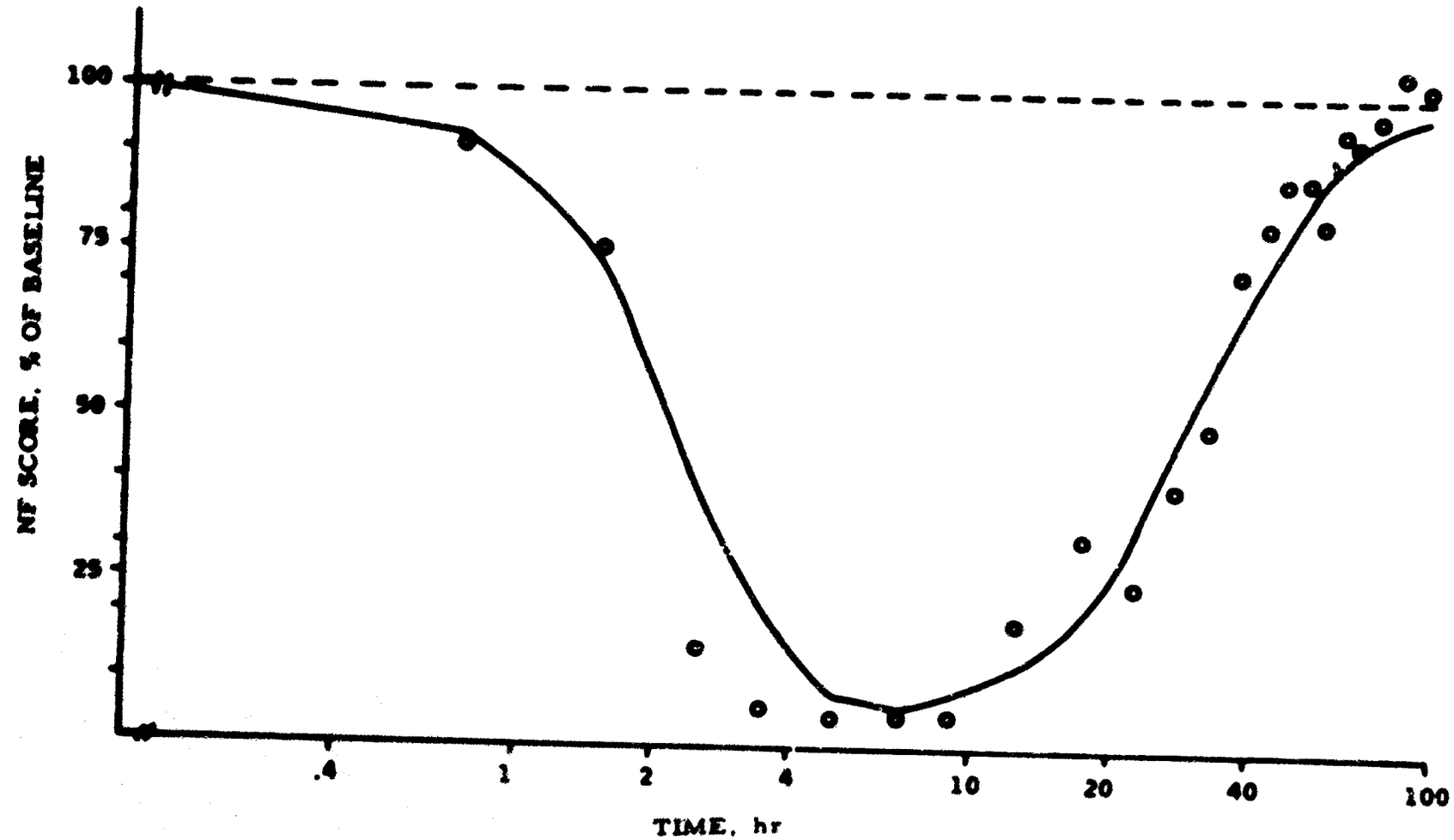

Figure 86. Predicted Versus Actual Serial Performance Scores (Dose, 3.4 Units/kg)

(Circles indicate actual median NF score; solid line indicates predicted NF score)

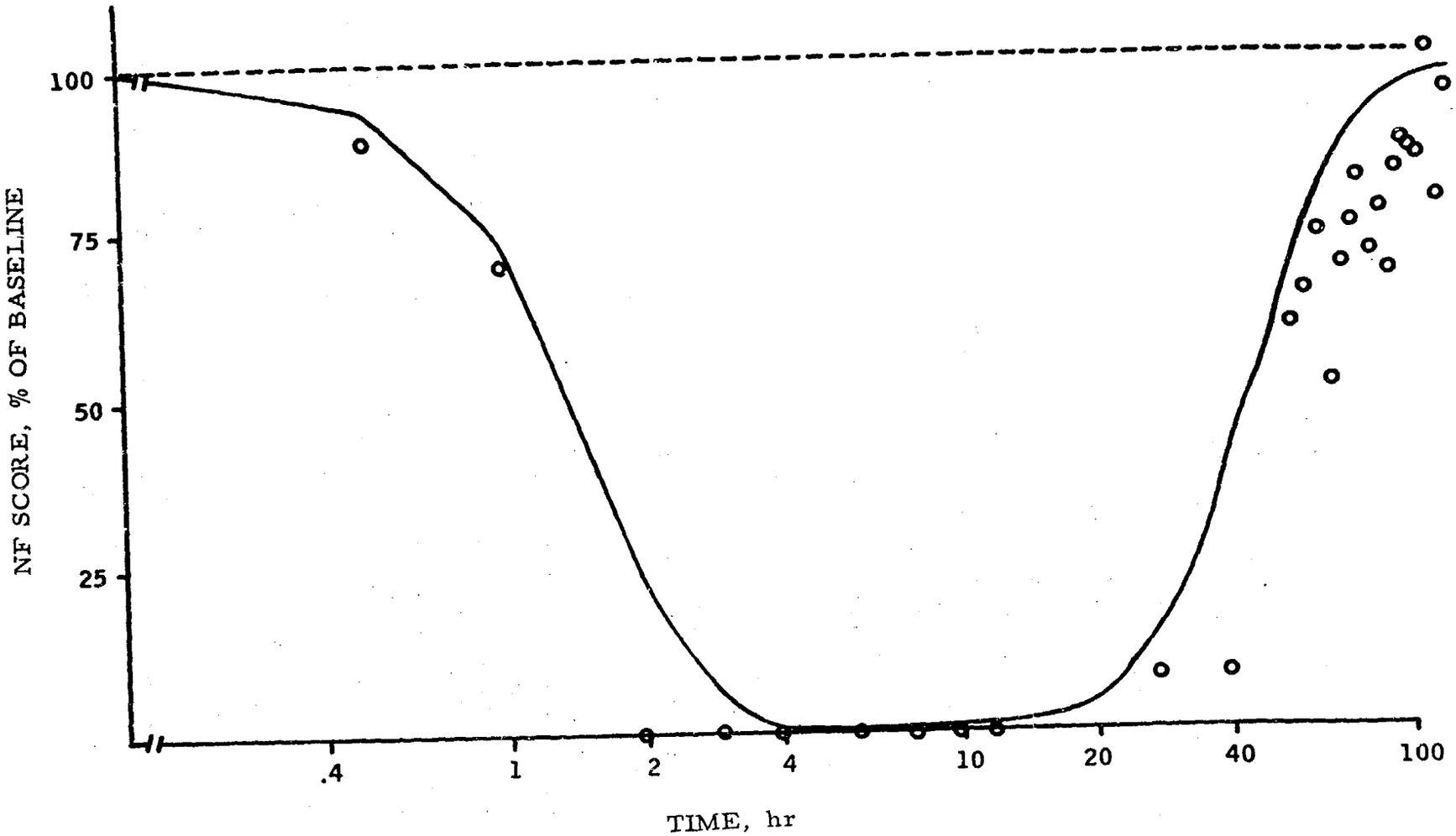

Figure 87. Predicted Versus Actual Serial Performance Scores (Dose, 4.8 Units/kg)

(Circles indicate actual median NF score; solid line indicates predicted NF score)

Discussion.

The model described in this paper is based on the major assumption that the chemical agent under consideration is metabolised in a uniform manner such that its rate of disappearance in percent from the site of action is constant for each individual and varies for the population as a whole about 2% to 4% per hour. An additional assumption is that a given concentration of the agent at the site of action (which, in this case, is obviously not a topologically discrete space) will reliably alter the probability of a correct response to an arithmetic problem to some predictable degree that is independent of individual differences in ability.

Neither of these assumptions is likely to be entirely correct, and the most that can be expected is that they are approximately correct. The justification for making the first assumption is that it permits a relatively simple transformation of the data to be carried out, a transformation that, in effect, eliminates the time factor and increases manyfold the number of observations relating dose to response. Since the result seems to be the uncovering of a striking linearity between dose and probability of correct response, the assumption has, at least, heuristic value.

The second assumption is justified if we can be assured that the differences in individual effects at various dose levels are randomly distributed within our sample. There seems no reason to doubt this, granting, of course, that the subjects themselves are not randomly selected from the general population but are from a smaller population of "acceptable" subjects.

There is, finally, no guarantee that this is a valid model just because it has the virtue of simplicity and compatibility with certain familiar biological concepts. Certain things are not appealing about it. First, it seems to predict an effect that is a bit too long at the lowest doses and that is not long enough at the highest dose. This could be a reflection of variations in half-life in the subjects, but somehow this rationalisation seems inadequate. Second, the demonstrated linearity of transformed scores on arithmetic-probability paper is at variance with the usual straight-line relationship between the log of the dose and the probability of response. The latter is so well accepted that the ordinary probit analysis is designed to solve the regression equation describing this very relationship.

The validity of the model can, of course, be tested to some extent by replication of the experimental data and by extension of the range of observations to higher dose levels or to other agents in the same pharmacological class. Whether or not such observations fulfill the predictions of this particular model is a matter of interest, but more important, we believe, is the incentive that one

derives from such endeavors to construct a better model. From good models grow good theory, and good theory is something that is urgently needed in the field of behavioral pharmacology.

Summary.

From an analysis of the NF performance scores of 20 normal male enlisted volunteers exposed to an anticholinergic agent, the following conclusions were reached:

1. If elapsed time is treated as an operator continuously modifying the residual dose at the site of action, the transformed dose values can be paired with each performance score, and the resulting distribution can be satisfactorily fitted by a Gomperts curve ($Y_c = ka^{bx}$).

2. A logistic curve, which is mathematically simpler,

$$Y_c = \frac{k}{1 + 10^{a+bx}}$$

gives a fit, which is nearly as good from a descriptive standpoint and, in addition, yields an interesting model that relates probability of correct response to estimated dose at the site of action.

3. Scores approximating the serial median response values may be generated using either equation, which makes a critical comparison of their validities difficult. A preference for the logistic function is expressed, inasmuch as it is simpler and easier to interpret.

4. Although the model is compatible with certain familiar biological concepts and may be pragmatically useful, it presents certain theoretical difficulties, and, even descriptively, is not fully adequate. Its value is considered to be in its emphasis on a combined theoretical and descriptive approach to the effect of drugs on human behavior, an approach that is urgently needed in behavioral pharmacology.

DISCUSSION

Dr. Nodine: In testing blood levels of various psychopharmacologic agents administered by different routes and noting the intervals for various effects, we have found that a 5- to 10-hr time of peak action, as was indicated in your graphs, is inordinately long for most of the drugs that we have administered. Certainly, in terms of most of our cholinergic and anticholinergic drugs, you would expect a peak action much earlier. And I wondered if you had any studies with labeled materials indicating that the blood levels were actually correlating with your calculated residual-dose values or if this approach might not be fruitful in considering whether the main drug administered is acting, or whether some metabolic conversion or transfer rate to a cell site is resulting in this inordinate delay that was observed in your study.

MAJ Ketchum: Of course, at the doses we're using in man, none of the ordinary assay techniques has been feasible. There is one I have heard of that involves labeling the material after it is extracted from the blood and then counting the labeled material in a scintillation counter. Dr. Brody, I believe, has described this technique, and we hope to find out more about it. We have had success with LSD. One of our psychiatrists adapted a method developed by Axelrod for following clinical levels of LSD in blood, and this method did, in fact, show that it took about half an hour after iv injection for a steady state to be reached in the blood, after which logarithmic decay occurred. There was also a correlation with the performance scores. He has published this in the open literature.

In regard to your second question, it is my thinking that, although we do know from other studies that these glycolates pass rapidly into the brain and so forth, the site of action may not be reached that rapidly. That is my fantasy about it. Certainly, clinically, there is this rather late peak, and it occurs regardless of route. Of course, it is a little slower orally. But, regardless of route, there is a delay of several hours; there is also a delay in the peak central effect of quite a period of time after the peak peripheral effects can be observed. So there is some reason for this lag. Whether it is also due to a secondary chain of events or a delay in reaching the peripheral site, I don't know.

Dr. Sim (Edgewood Arsenal): I think this is true, Dr. Nodine. There seem to be two fractions in this particular type of drug—one with a half-life of about 4-1/2 hr in the brain and the other with a half-life of several days. This does interpose a problem in relation to the time factor.

Dr. Elkes (Johns Hopkins Hospital): I would like to compliment Dr. Ketchum on this elegant study. The question of tachyphylaxis and tolerance could be very nicely investigated by this method, as could also be the interaction of drugs

competing for the same receptor sites (such as reserpine and LSD). I wonder whether you have applied the same approach to the experimental animal in which drug action in relation to intermediate metabolism could be followed?

MAJ Ketchum: No, Dr. Elkes, we just formulated this approach at rather the last moment. But if it appears to have merit or be worth trying, we may be able to look at some of the animal data from this standpoint. It might be interesting.

Mr. Walker (Norman K. Walker Associates): Again, I don't know anything about drugs, but I am very interested in numbers and fitting curves and making sense of thousands and thousands of data points. The first thing I would like to do is congratulate Jim Ketchum on what seems to be a major advance in how to handle this information. It has a weak point in it which worries me a little; I know it worries him, and it worries other people. This is this 5-hr line where you change from one curve to another. Now it seems to me that this is where you can do some crucial experiments. The first thing is that you shouldn't joint on the second branch curve at 5 hr. It is a discontinuity. This destruction of the drug has been going on ever since it started, at time zero. The 5-hr cutoff occurs when the supply of the drug is, perhaps, exhausted and isn't getting circulated any more. One of the things that might effect this cutoff is the concentration of the drug in the liquid you inject. If you had injected the same total amount of drug but in a larger volume of diluent, you might get another answer because you diffused it over a bigger area. So this is something that one could look into; but I think it would improve the fit of the curve if the second branch started at zero.

MAJ Ketchum: Well, it actually does, Norman. We made that turning point a bit acute. However, that turning point came at about 88% of the administered-dose value. This is the calculated amount that would be left, assuming elimination began immediately at the time of injection; the drug was going out of the body at the same time it was going into the site of action. It was able to build up to only that degree as a maximum because, after 5 or 6 hr, about 10% to 12% was actually gone.

Mr. Walker: My suggestion is that you multiply the two things together instead of starting with one and going to the other.

Dr. Mershon (Edgewood Arsenal): I have a comment on Dr. Nodine's question here. On some of the work that we have done on animals with relatives of these compounds, we found considerable difference in the peak times for optical isomers of these compounds. So it would seem that the distributions would be equated there. What the reasons are for these differences, we don't know.

Mr. Wilson (Edgewood Arsenal): I'm going to quarrel with Dr. Mershon. I think we do know. I think, with the isomers of the drugs under study, the competition for the site of action has been demonstrated many times in smaller systems. I think you know the one I am referring to, which is Dr. Mershon's and my own studies with the iris muscle. For instance, the curve that you show, which is the Sigmoid dose-response curve, is the tool that you should use, because, if you do the same series of analyses with many different dose levels, it is then possible to construct a log-log regression, the slope of which indicates whether there is competition or not. If you do have a thing like atropine, for instance, which has the two components, the d- and l-hyoscyamines, competing for the site, only one of which is active, this slope will change. So I think you have the information in your hands already. Extension of the analyses is needed.

Dr. Lilly (Communication Research Institute): Have you applied this to LSD-25 data, say for dose analyses, arithmetical test scores, or any of these other things at different doses?

MAJ Ketchum: No. We are anxious to try this as soon as we have the time.

BIAS IN COLOR DISCRIMINATION

Dr. Michael H. Siegel
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Medical Research Laboratory
Edgewood Arsenal

Introduction.

It has become abundantly clear that a number of experimental variables can affect sensitivity to color differences. The choice of psychophysical method,[*,**] the availability of response categories,[†] the wavelength composition of the standard stimulus,[††] and the duration of the stimulus exposure[‡] are but a few of the variables which have profound influences on color discrimination. In the present report, we have investigated the effect of the order of presentation of stimuli upon color discrimination sensitivity.

It has become standard practice for this laboratory to present several variable stimuli in a random order to an observer. Would sensitivity scores change if the order were made nonrandom?

Two reasons prompted us to consider the presentation of a nonrandom order. A random sequence requires frequent changes of instrument settings. This leads to lengthy sessions, which in turn fatigue the observers. If stimuli were presented in repeated blocks rather than at random, at least part of this problem would be solved. There is some indication from the

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* Blackwell, H. R. Studies of Psychophysical Methods for Measuring Visual Thresholds. J. Opt. Soc. Am. 42, 606-616 (1952).

** Siegel, M. H. Discrimination of Color. I. Comparison of Three Psychophysical Methods. Ibid. 52, 1067-1070 (1962).

† Siegel, M. H. The Selection of Judgment Categories in Color Discrimination. Psychon. Sci. 2, 151-152 (1965).

†† Siegel, M. H., and Dimmick, F. L. Discrimination of Color. II. Sensitivity as a Function of Spectral Wavelength, 510 to 630 mμ. J. Opt. Soc. Am. 52, 1071-1074 (1962); Siegel, M. H. Discrimination of Color. IV. Sensitivity as a Function of Spectral Wavelength, 410 through 500 mμ. Ibid. 54, 821-823 (1964); Connors, Mary M., and Siegel, M. H. Differential Color Sensitivity in the Purple Region. Ibid. 54, 1374-1377 (1964).

‡ Siegel, M. H. Color Discrimination as a Function of Exposure Time. Ibid. 55, 566-568 (1965).

literature that nonrandom sequences do not adversely affect discriminations of lifted weights* or of certain auditory stimuli**; however, no direct evidence is presently available on how such a procedure influences color discrimination.

A second reason for adopting a nonrandom order was to assess a growing body of research purporting to measure various aspects of sensitivity by presentation of stimuli in blocks. An early and well-known example of this form of stimulus presentation is the neural quantum theory.† A review of the then current literature on this theory was performed a decade ago.†† Although the theory is derived from studies in audition,‡ some vision research has also been directed upon it.‡‡,§

The original theory was concerned with the sensory intensity continuum. It was assumed that the neural structures involved in the perception of a sensory continuum are divided into functionally distinct units. At a particular instant, a stimulus of a given magnitude excites a certain number of these quantal units, and in order for an increment to be noticeable, it must excite at least one additional quantum.

The neural quantum theory predicts a discontinuous steplike increase in response probability as the stimulus value is changed. The more typical psychophysical curve, by contrast, shows a continuous increase in response

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* Shaad, Dorothy J., and Helson, H. Group Presentation in the Method of Constant Stimuli as a Time-Saving Device. Am. J. Psychol. 43, 422-433 (1931).

** Jerger, J. F. On the Independence of Successive Responses in the Quantal Psychophysical Method. Ibid. 68, 145-147 (1955).

† Stevens, S. S., Morgan, C. T., and Volkmann, J. Theory of the Neural Quantum in the Discrimination of Loudness and Pitch. Ibid. 54, 315-335 (1941).

†† Corso, J. F. The Neural Quantum Theory of Sensory Discrimination. Psychol. Bull. 53, 371-393 (1956).

‡ Békésy, G. V. Experiments in Hearing. McGraw-Hill Book Company, Inc., New York, New York. 1960.

‡‡ Mueller, C. G. Frequency of Seeing Functions for Intensity Discrimination at Various Levels of Adapting Intensity. J. Gen. Physiol. 34, 463-474 (1951).

§ Blackwell, H. R. Studies of Psychophysical Methods for Measuring Visual Thresholds. J. Opt. Soc. Am. 42, 606-616 (1952).

probability as the stimulus is changed. Both types of curves are presented in figure 88.

In order to be able to detect the quantal increases in response, the experimenter must depart from the usual psychophysical procedures in which stimuli appear in a random order.* In this way, the quantal distribution will not be masked by shifts in the observer's criterion. This departure from standard psychophysical procedure, necessary as it may be, is worthy of careful attention. Since the experimental evidence for the neural quantum theory rests upon data in which the same stimulus value is presented 25 consecutive times, it is of some significance to know whether or not the order of presentation affects discrimination data.

Apparatus.

A Farrand monochromator and a xenon arc produced the stimulus. A sector shutter with a clutch provided discrete, 0.2-sec stimulus exposures. The stimulus field was circular and subtended two degrees at the observer's eye. The upper half served as the standard. It was set to a wavelength of 570 mμ, which most observers call yellow-green, and a luminance of 0.2 ft-l. Calibrations were made both before and after the experiment upon the wavelength setting of the monochromator, the luminance level of the stimulus, and the duration of the exposure time. No change in the preexperimental level could be detected.

Observers.

Four members of the laboratory staff served as observers. All received extensive training in making the required discrimination before data were collected. All observers were free from color-vision defects, and the nonemmetropic observers wore corrective lenses. All observations were made with the right eye.

Procedure.

Before each experimental session, a pretest was performed to allow the observers to equate the brightness of each of the variable stimuli to that of the standard and to determine the range of variable stimuli to be presented. For each experimental condition, the stimulus range consisted of 5

* Stevens, S. S., Morgan, C. T., and Volkmann, J. Theory of the Neural Quantum in the Discrimination of Loudness and Pitch. Am. J. Psychol. 54, 315-335 (1941).

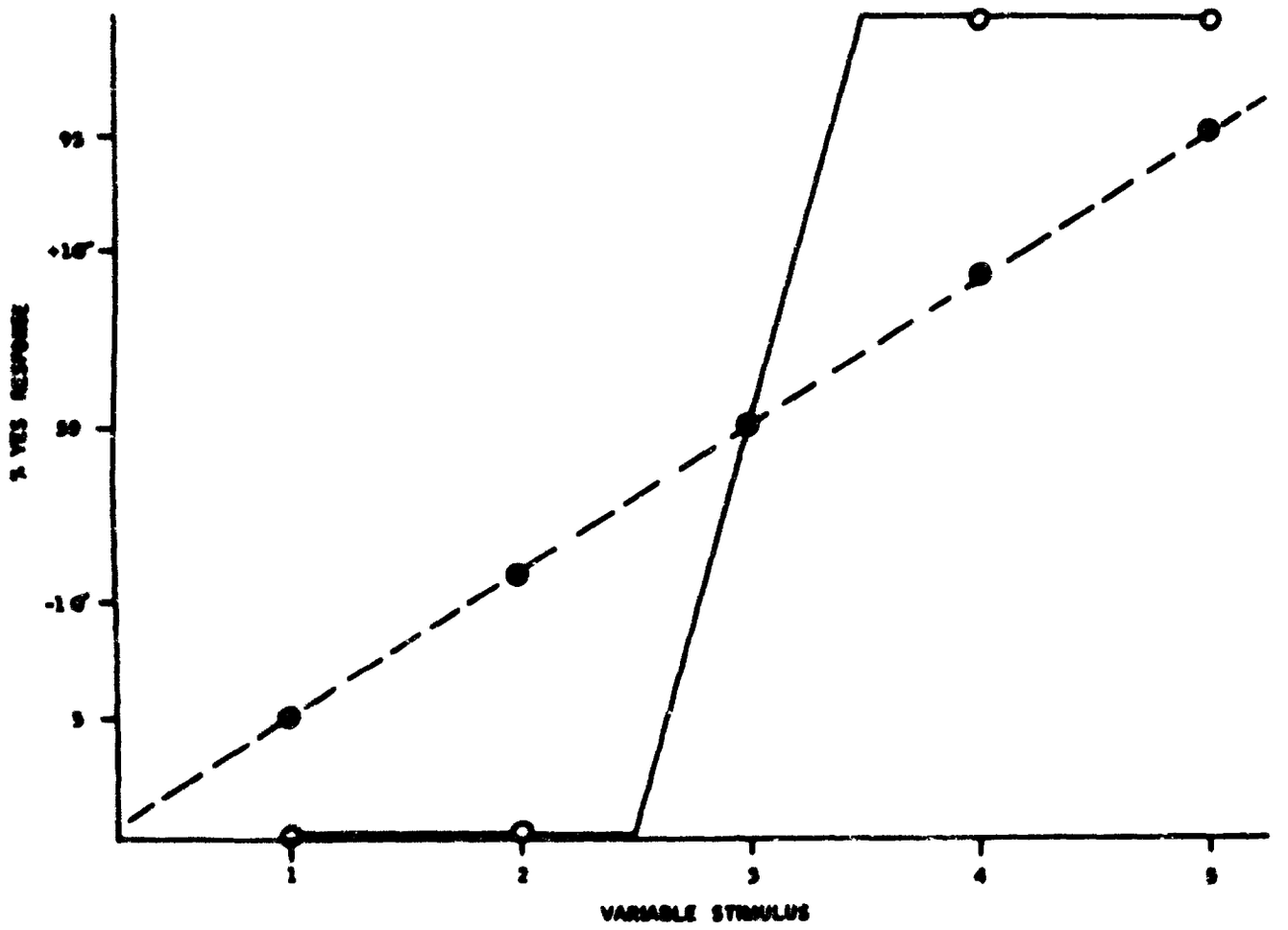

Figure 88. Response Frequency as a Function of Size of Variable Stimulus
----The usual psychophysical curve in which the phi function of gamma is presumed to hold
——The curve predicted by the neural quantum theory

steps, each of which was presented a total of 10 times. At each session, two separate measurements were made: the first for wavelengths shorter than the standard and the second for wavelengths longer than the standard. This procedure is more fully discussed elsewhere.*

Experimental Conditions.

1. In the first condition, there was a standard method of constant stimulus differences. Fifty stimuli that consist of 5 variable stimuli were presented a total of 10 times each in a random order.

2. In the second condition, each stimulus difference was presented two consecutive times before another randomly selected stimulus difference was presented.

3. In the third condition, each stimulus was presented five consecutive times.

4. In the fourth condition, each stimulus difference was presented 10 consecutive times.

The order of appearance of each of the four conditions was randomized and then reversed for each observer. The resulting order of these eight sessions was then repeated twice. This permitted each observer to experience each of the four conditions six times.

Results.

Curves of frequency of positive responses were recorded on normal probability paper. The measure of sensitivity, the standard deviation (SD), was defined as the difference in wavelength between the points at 50% and at approximately 84%. A more complete treatment of this response measure has been presented earlier.*

Figure 89 presents the experimental results for this study. The four points on the abscissa from left to right represent conditions one through four. The ordinate is the size of the SD in mμ. The first and most obvious result is that large individual differences occur among the four observers. There is no apparent relation between the sensitivity scores obtained in the

* Siegel, M. H. Discrimination of Color. I. Comparison of Three Psychophysical Methods. J. Opt. Soc. Am. 52, 1067-1070 (1962).

first condition and the scores in the other conditions. There is a relation, however, among conditions 2, 3, and 4. With the exception of one point for one observer, sensitivity scores are improved as the number of stimulus repetitions is increased.

Discussion.

The finding of extensive individual differences is not at all unusual. It would be naive to expect that all normal observers have the same sensitivity at any point in the spectrum. More important is the finding that each of the observers was reliable.

In speculations prior to this experiment, a decreasing monotonic relationship among the four conditions was predicted. It was predicted that the first condition would lead to the poorest discrimination and the fourth condition, to the best. Data for two of the four observers support this position; but for the remaining two observers, discrimination scores in the second condition were poorer than those in the first condition. These latter two observers had had a great deal of experience observing in condition 1. Conditions 2, 3, and 4, in which stimuli were repeated, represented a departure from the normal method of observing for them. By contrast, the other two observers, CS and JF, had had very little experience with any of these conditions. The unexpected deterioration in sensitivity from condition 1 to condition 2 for two of the observers is probably simply the effect of practice.

The major experimental finding is that sensitivity scores are in fact dependent upon the stimulus order. Our finding that sensitivity is directly related to the number of times a stimulus is repeated strongly suggests that any procedure in which stimuli are presented in large blocks can be expected to generate seemingly better discrimination scores than procedures in which stimuli are presented in a random order. Effects such as this are not new in psychological literature. Some time ago it was suggested that stimulus repetition leads to channelization of responses.* In a typical psychophysical curve, such as the straight line depicted in figure 88, there are several stimulus values for which the associated response probability is neither 0% nor 100%. The observer will be able to detect a difference at one time but will fail to detect the same difference another time. This variability is presumed to reflect random fluctuations in sensitivity. If channelization occurs, intermediate response values are forced either to 0% or 100% limits as variability is eliminated. This results in a rectilinear distribution with a very steep slope.

* Blackwell, H. R. Studies of Psychophysical Methods for Measuring Visual Thresholds. J. Opt. Soc. Am. 42, 606-616 (1952).

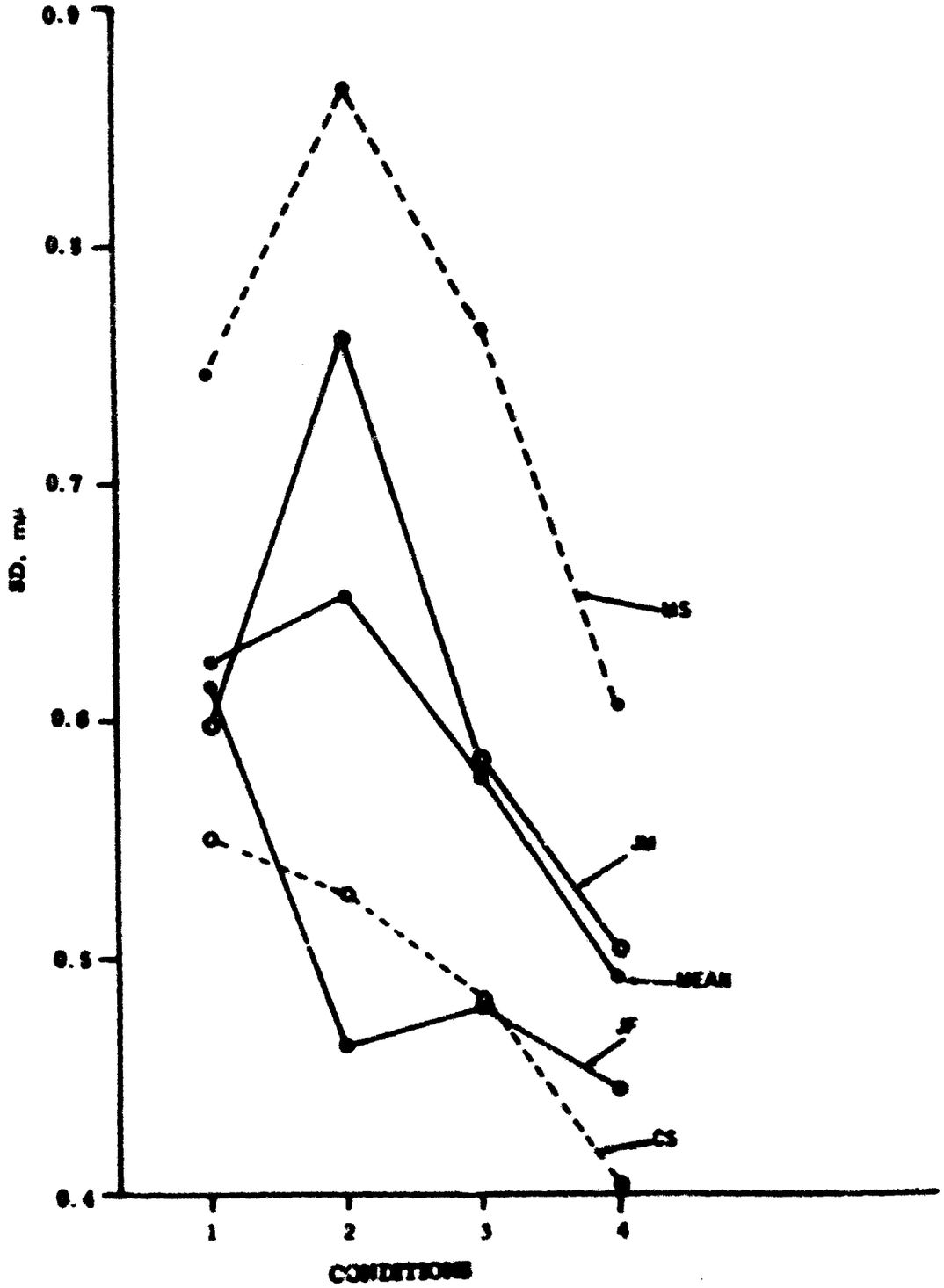

Figure 89. Color Discrimination as a Function of the Number of Stimulus Repetitions

(The values on this figure are all SD)

Exactly such a curve is predicted by the neural quantum hypothesis and depicted in figure 88. Therefore, the operations employed to gather the data for the quantal hypothesis insured the generation of the curve predicted by this hypothesis.

Although this study cannot and should not be considered as a test of the neural quantum theory directly, since the theory concerns itself with sensory intensity, it does cast serious doubt on the validity of psychophysical procedures that employ presentation of stimuli in blocks. This experiment has demonstrated clearly that diviating from a random order presentation of stimuli does indeed change color-discrimination scores. Although it is apparent that the improvement in these scores is artifactual, there appears to be no way a priori to determine what the extent of the change will be. In order to allow meaningful comparisons of different research ventures, it is concluded that, whenever possible, stimuli be presented in a random order.

DISCUSSION

Dr. Lilly (Communication Research Institute): Several years ago we did some experiments with the minimum duration detectable flash in a study of the phi effect (apparent movement). The subjects attempted to judge right or left movements. We kept the judgment in digital form. If you presented the stimulus pairs once, the subjects couldn't give an answer. If you presented them twice (within one-tenth of a second), they could give you an answer, but an answer in error. With three presentations, they gave answers that were absolutely correct; they were sure of it consciously. With only two could you show that their scores were better than chance, even though they thought otherwise. In other words, there seems to be a multiple set of thresholds operating as soon as you decrease the stimulus duration. Duration is critical. The repetition rate is also critical. This is in addition to the variables that you are speaking of here. Once you could program the man (get him thoroughly trained on that kind of thing), you could then go on with five presentations, and he would show no improvement over his score at three presentations.

Dr. Siegel: Right. One possible explanation for that, in addition to what you have already mentioned, is the persistence of afterimages. Sometimes it takes two or three presentations for a good afterimage to form, and people can learn to detect a stimulus that appears very, very quickly.

Dr. Lilly: Right. We were using background light levels and contrasting light levels. The afterimage was very weak. Also, we checked it out with two clicks to the two ears and got similar results there. We checked it out with pairs of tactual skin stimuli and made crossed modal comparisons. Here the effect holds up well, but not quite as well as the duration of the effect increases giving an afterimage.

AN APPROACH TO STUDIES OF HUMAN DRUG BEHAVIOR

Dr. Peter K. Levison and Dr. Jack D. Findley
Institute for Behavioral Research

Introduction.

The work I will describe represents part of our effort to develop baselines of complex or higher-order behaviors in man and primates in order to evaluate the effects of chemical agents. Part I of this paper presents human drug data from an extended period of time on a representative higher-order performance, a matching-to-sample task. Part II describes an experimental method that was developed from an analysis of our earlier experiments. We believe this method will provide two major improvements on the work described in the first part of the paper: (1) a more comprehensive evaluation of the effects of compounds upon higher-order performances and (2) a more extended analysis of potential behavior changes relevant to clinical situations following drug administration. In addition, the experimental situation described in Part II provides for a more economical use of subject effort and monetary payment.

Part I.

It was our intention to design an experimental environment in which problems are automatically presented, and the consequences of behavior are clearly and immediately specified by the apparatus. The positive consequences selected were the payments of varying amounts of money because these consequences are known to maintain large amounts of behavior in a natural environment. It was hoped that the scheduling of these consequences would influence the level of accuracy and the rapidity at which the subject worked on the problems.

A model situation was selected from a type of complex problem used extensively with both animals and humans, a procedure called matching-to-sample. This procedure is displayed in figure 90. The first step is the presentation of a sample stimulus in the center window of the console. The stimulus is typically an abstract symbol. Symbols also appear in each of the windows on either side of the sample. The subject is conditioned by reinforcement and punishment procedures to make a response associated with the symbol that stands in a specifiable relationship to the sample. The relationship most typically used is one of similarity or identity. For example, if a plus sign is projected on the center window and also on the left window and a triangle on the right, the reinforced response is to the left or identical stimulus. The subject may be reinforced immediately after making the response or according to some intermittent schedule of reinforcement.

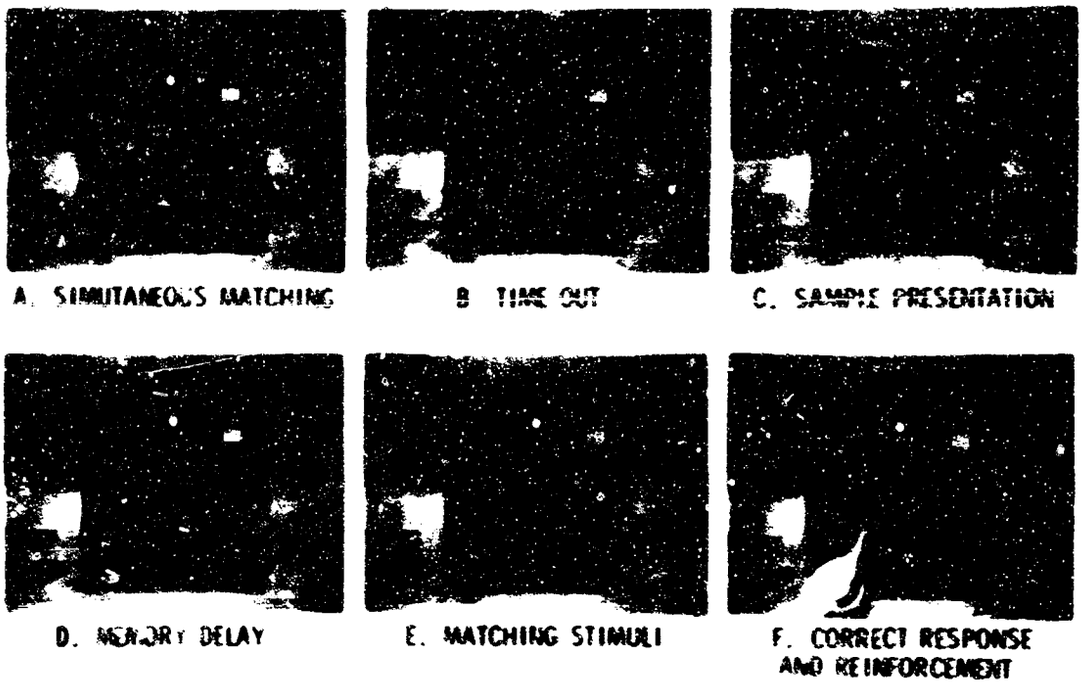

Figure 90. Matching-to-Sample Console and Typical Problem

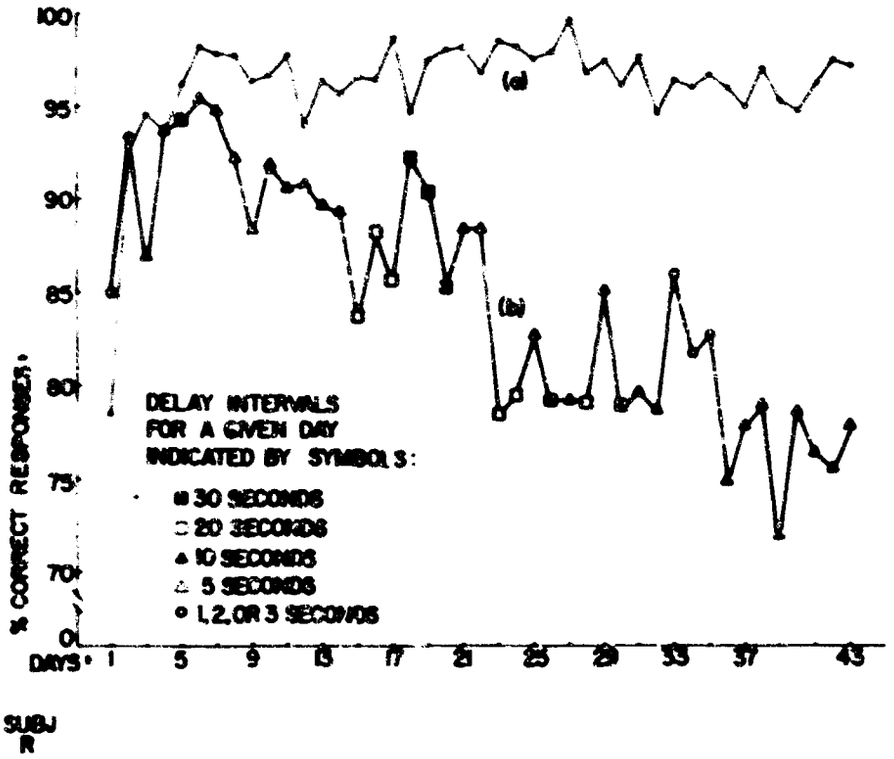

Figure 91. Accuracy of Simultaneous Matching (a) and Delayed Matching (b) on Successive Experimental Days

A 20-year-old female subject worked from 3 to 4 hr a day for several months on matching-to-sample. When the programmed contingencies for correct solution were satisfied, the subject was reinforced with points on a numerical counter. These were later converted to money. She typically earned $8 to $9 in a 3-hr session. Incorrect responses were punished by the immediate occurrences of timeout periods in which the problems were not available. I would like to add at this point, in reference to Dr. Lilly's talk last evening, that our human subject, unlike the dolphin, was willing to work on this reptitive, dull, and boring task with the same 25 problems being presented for several months. These data demonstrate that, at least with humans, very monotonous behavior can be maintained for extended periods of time when appropriate extrinsic rewards are contingent upon the behavior.

Two variations of matching-to-sample were used. These are called simultaneous matching and delayed matching (figure 90, A and D). In simultaneous matching, the three symbols appear simultaneously and remain visible until the subject gives her answer. In delayed matching, the sample appears briefly, followed by a dark period of several seconds before the comparison stimuli appear in the side windows. The subject must remember the sample stimulus and respond appropriately in its absence.

A variable-interval, 3-min schedule of reinforcement was in force when the present data were obtained. The subject was reinforced with a counter tally for the first correct response after a time interval of variable duration with a mean value of 3-min. Therefore, it was not necessary to perform at high rates of accuracy continuously in order to achieve nearly maximum income for the task, nor would a very high response rate appreciably increase the take-home pay.

The subject readily mastered the 25 problems that were wired into the apparatus (figure 91). This level of achievement is represented by her nearly perfect performance on the simultaneous matching, which was maintained throughout the experiment. Her delayed-matching scores, however, regularly declined with some fluctuations until they stabilized at 75% to 80% after 1 mo. This relationship can be seen in figure 91. The curve for simultaneous matching is approximately horizontal, whereas the delayed-matching curve declined and then finally leveled off between 70% and 75%.

Our interpretation of these data includes two principal points: (1) the additional demands upon attention and memory in delayed matching would seem to be involved in the considerably reduced accuracy scores compared with simultaneous matching, and (2) the subject's behavior was maintained increasingly by the schedule of reinforcement alone, and other behaviors, such as working to obtain more money for better performance or working to please the experimenter, were extinguished in the absence of reinforcement.

Figure 92 shows decreases in both the accuracy and rate of responding over time, irrespective of the delay interval programmed. The curves are separated into the different delay intervals: 2, 5, 10, 20, and 30 sec. The effects of two dose levels of chlorpromazine, 25 and 50 mg, are also shown. Decrements in both the rate and accuracy were noted on the drug days with delayed matching. Simultaneous-matching accuracy was unaffected, and decrements in response rates were smaller than those for delayed matching. Hence, we can see a differential drug effect dependent upon differences in the complexity of tasks that involve the same symbolic stimuli and consequences. This result can be well ordered in the framework of yesterday's paper by Findley and Levison. The baseline later proved to be sensitive also to 10-mg doses of d-amphetamine, which selectively increased the rate of responding on both simultaneous and delayed matching without affecting the accuracy levels. This result is consonant with the known behavioral properties of the compound.

In our experimental situation, we achieved three major objectives:

1. We brought a subject's behavior under the control of realistic consequences.

2. We developed a stable baseline upon which to assess drug effects.

3. We noted differential sensitivity of components of different complexity to disruption by chemical agents.

Part II.

We believe that it would be scientifically and economically sound, however, to develop an experimental environment in which much more drug-behavior information could be obtained at a lower expenditure of subject time and payment. A situation was required in which several behaviors, in addition to problem-solving, are available to a subject. These activities can include basic

maintenance functions, such as obtaining food, liquids, and sleep or rest. Recreational activities that are engaged in frequently in natural environments, such as reading or listening to music, can provide subjects with reasonable behavioral options to problem-solving. It seemed appropriate to arrange a microenvironment in which access to various natural behaviors could be carefully controlled experimentally and objectively measured. These activities would also provide a meaningful background for problem-solving tasks. The major return from such an effort would be a relatively broad range of behaviors from a multidimensional drug baseline. Drug administration might be expected to produce drug- and dose-effect profiles that would be of value in predicting clinical effects in natural environments. Also, such a profile would give more meaning to performance changes on the problem-solving task. For example, if access to a bed had been programmed into the environment of the experiment described earlier, an immediate, objective measurement of a side effect of chlorpromazine might have been obtained when the subject reported drowsiness on the postsession questionnaire. Measures of the frequency and duration of lying on the bed in the drug session relative to a control baseline of bed use on nondrug days would have contributed to the interpretation of the drug effect.

For these reasons, we constructed a multiactivities environment enclosed in a high-sound-attenuated room that measured 6 by 10 by 7 ft. Figure 93 is a floor plan of the room indicating the location of various activities. The matching task was modified and programmed on 16-mm film to permit an indefinitely large number of problems to be used. Figure 94 shows the new matching-to-sample console with a problem stimulus projected on its screen. The subject is about to indicate that the sample and comparison stimuli are different by pressing the left-hand button. The rectangular unit on the right-hand side with numerals on it is the reinforcement counter. The stimulus lights are in a vertical column on the left-hand side and the tone that accompanies reinforcement is on the right of the counter. Figure 95 shows the subject responding following offset of the comparison stimulus. The screen is blacked out; the comparison stimulus has been turned off. Figure 96 shows the food and cigarette dispenser; the subject is pressing the plunger to obtain food. Figure 97 shows the subject pressing the button at the side of the water-dispensing unit to fill a cup with water; the cup was filled automatically. Figure 98 pictures the subject resting on the cot. Figure 99 shows the subject reading and pressing a hand switch to keep the reading light on. An activity consisting of speaking into a microphone and having the voice amplified with immediate feedback proved to be very unpopular with the pilot subjects and was later replaced with listening to a radio.

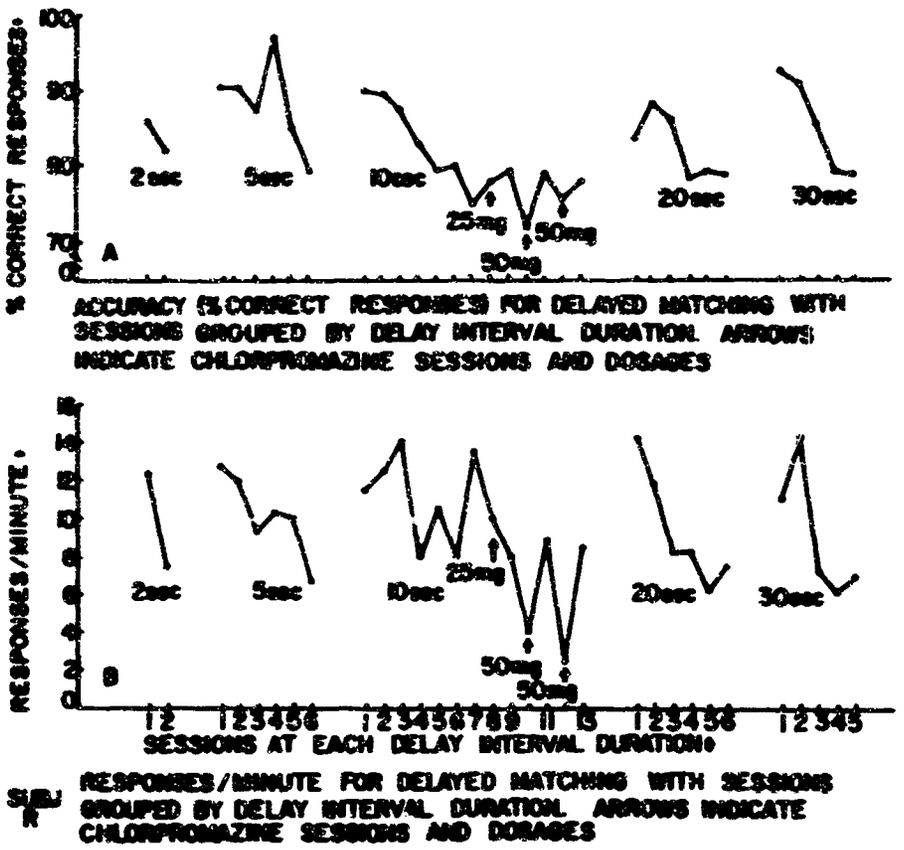

Figure 92. Accuracy and Rate of Response for Delayed Matching

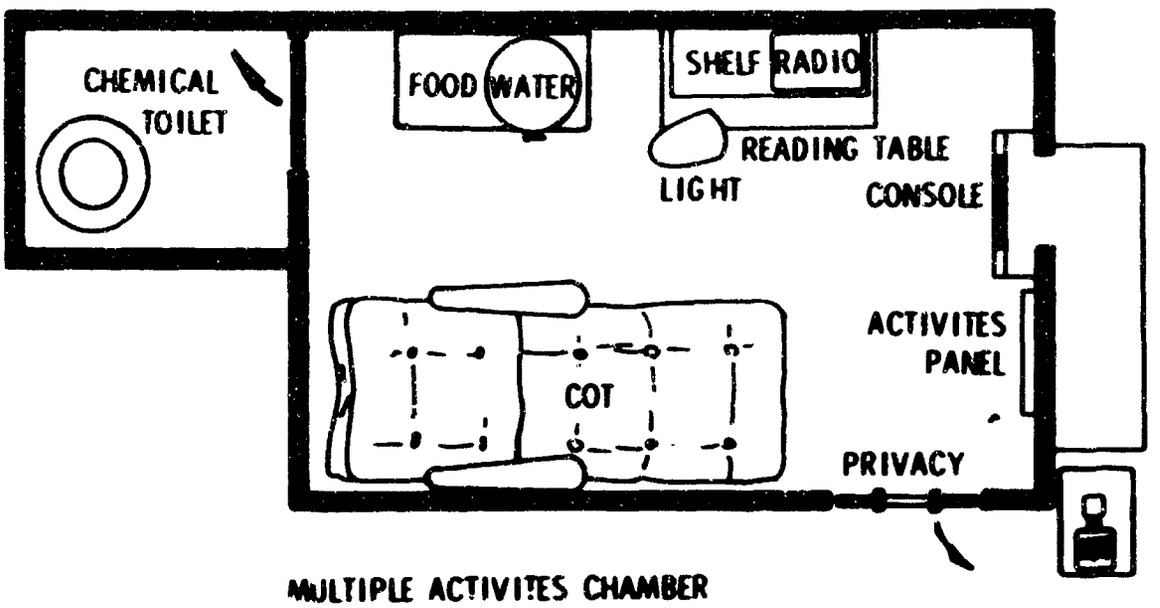

Figure 93. Multiple Activities Chamber

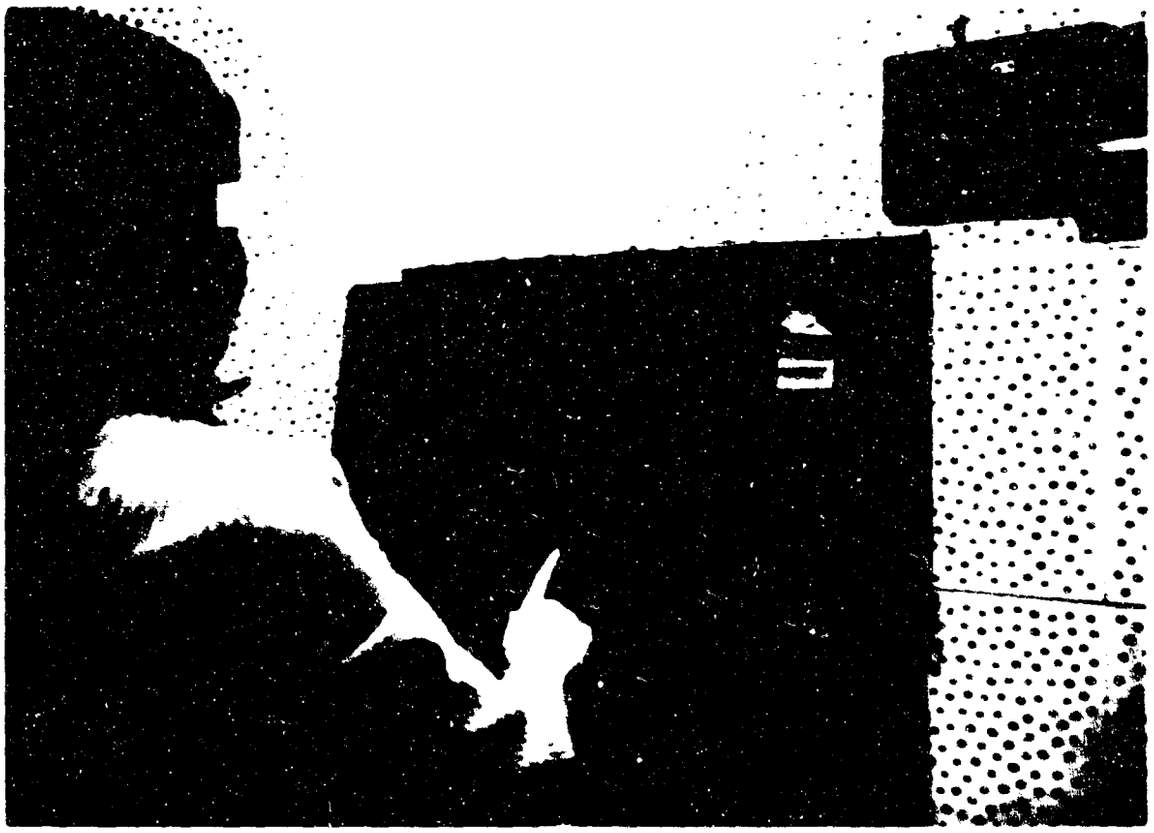

Figure 44. Matching-to-Sample Console With Problem Stimulus Projected on Screen

Figure 95. Subject Responds Following Offset of Comparison Stimulus

Figure 96. Subject Obtains Food From the Food and Cigarettes Dispenser

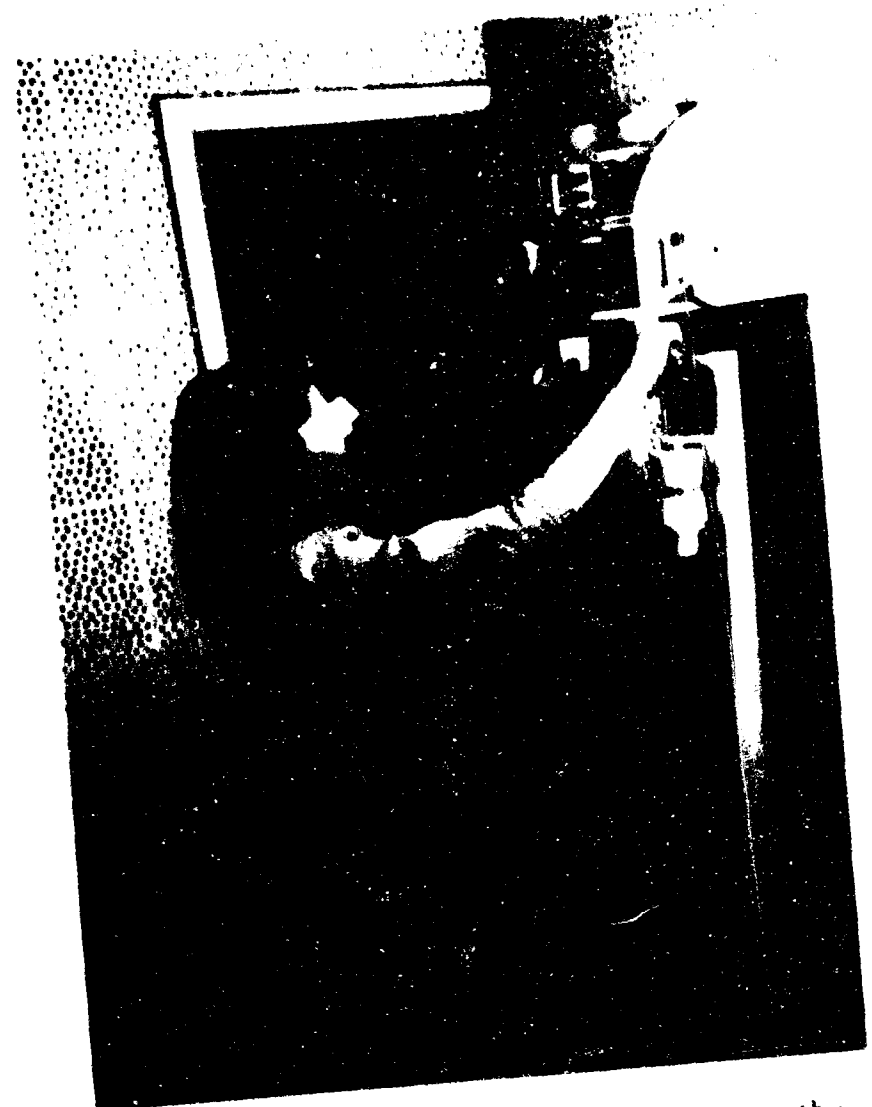

Figure 97. Subject Obtains Water From the Water-Dispensing Unit

Figure 9a. Subject Rests on Cot

Figure 9b. Subject Reads While Pressing Hand Switch to Provide Light

Access to all of these activities is completely controlled by a prearranged experimental program. Depending upon programmed availability, the subject may press a button on a master panel to select various activities. Figure 100 shows the master panel with the subject making an activity selection. Availability may be scheduled so that the activities are mutually exclusive or concurrently available. Also, the selection of one activity, such as matching, may be a prerequisite to engaging in another.

The chamber also contains a clock, the face of which can be illuminated by a button press, a chemical toilet located in a separate room, and a wide-angle observation system that may be shut off by the subject. The level of illumination is too low to permit reading without the reading light. The room is ventilated and temperatures are moderate.

To date, several subjects have been tested in 1-, 2-, and 3-day pilot experiments, 7 to 8 hr per session. Preliminary results indicate that it is completely practical to run 3-day experiments with 8-hr sessions in this environment. The subjects engaged in most of the available activities. Matching-to-sample was selected frequently enough to provide a useful problem-solving baseline.

In summary, we have placed a problem-solving task that was useful for drug evaluation in a complex environment, which offers the following advantages for human drug research:

1. Multidimensional baseline for the evaluation of chemical agents, resulting in a drug- or dose-effect profile.

2. A meaningful behavioral background against which drug effects on a performance task may be interpreted.

3. A closer approximation to natural environments than is typical in human drug experiments for prediction in clinical situations.

4. The economical use of the subjects' time and effort to obtain a large return for the experimental cost.

5. The relative stability of a single experimental setting.

Figure 100 Subject Selects a Programmed Activity by Pressing Button on Master Panel.

The final point is important. Drug subjects progress through a succession of tasks in separate experimental settings to provide a drug-behavior profile. However, the early data we reported as well as the experience of a host of psychopharmacologists indicate that marked behavioral adjustments occur in novel experimental situations. Obviously, drug effects on behavior will be influenced by these ongoing changes. An internally coherent environment, such as the one that has been described, can offer the best of two types of experimental programs, the rich information harvest of profile analysis and the relative stability of a single experimental setting.

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STANDARDIZATION STUDIES WITH THE REPETITIVE PSYCHOMETRIC MEASURES: ASSESSING THE EFFECTS OF MOTIVATION ON TEST PERFORMANCE

CPT James J. Hart
Clinical Research Department
Medical Research Laboratory
Edgewood Arsenal

Introduction.

The Number Facility subtest (NF) of the Repetitive Psychometric Measures is used extensively by the Psychopharmacology Branch as a measure of behavioral incapacitation. The assumption has been that if NF score decreases below baseline level, ability to function is impaired. Not everyone has accepted this interpretation; they argue that with certain classes of compounds, at least, ability remains the same but motivation is decreased.

The effect on performance in the laboratory may be the same whether ability or motivation is affected; however, the implications for performance in a field situation may be far different, depending upon which factor is contributing most heavily to the decrease in performance. If ability is primarily affected, the individual would not be able to perform in any type of situation. If motivation is primarily affected, performance in a laboratory may be low enough to reflect incapacitation. However, in a field situation where an individual's life or death is contingent upon his performance, this performance might increase to an acceptable level. Thus, it is important to have some method for assessing motivation as well as performance.

The problem is that of effectively controlling for and assessing the effects of motivation. Our discussion will be restricted to motivation as it influences the NF score, although the issue is of decisive significance to all behavioral performance measures.

Several methods of controlling and increasing motivation have been attempted. One is to encourage a subject to "do his best" whenever he takes a test. Such an approach is not unlike the various psychometric approaches used to insure that the subject is maximally motivated. This method has its disadvantages in that the amount of motivation cannot be directly assessed, and comparisons between one subject and another are difficult. A second approach has been taken by Kitzes.* In his study, subjects were paid varying rates for

* Kitzes, D. L., CPT. The Effect of Monetary Reward on NF Performance in Prison Volunteers, p 295 of this report.

their performances on the NF, and the number of correctly completed NF problems was measured. A third method makes use of intrinsic motivators such an approach has been taken in this study.

Our purpose is to demonstrate that under no-drug conditions one can distinguish between "high" and "low" performance on the NF by measuring the level of motivation. This approach is taken with the hope that, if differences can be demonstrated under no-drug conditions, these differences may also carry over to performance after drugs.

The intrinsic-motivation method used in this study assumes that individuals with a certain type of need pattern will perform better on a given task than will other individuals. To determine which persons these are, some measure of quality and quantity of motivation is necessary. The Edwards Personal Preference Schedule (EPPS)* was used for this purpose. This measure is an objective test of personality and gives a classification of needs and motives similar to those derived by Murray** for the analysis of the Thematic Apperception Test (TAT).

The EPPS, when scored, results in a list of 15 needs; for each need a score is obtained indicating the strength of that particular need in a person's life. In this experiment, the "need for achievement" (Nach) was chosen for study. Nach is measured by the desire to do one's best, to be successful, to accomplish tasks requiring skill and effort, to be a recognized authority, to accomplish something of great significance, to do a difficult job well, to solve difficult problems and puzzles, to be able to do things better than others, and to write a great play or novel. In other words, persons who preferred the above listed activities would be high in Nach.

It was thought that those individuals scoring high in Nach would be more motivated to do well on a task like the NF and, therefore, would solve more problems correctly than those who scored low in Nach. It was further believed that those persons scoring high in Nach would work harder in a competitive situation to improve their performance than those scoring low in Nach.

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* Edwards, A. L. Edwards Personal Preference Schedule. The Psychological Corporation, New York, New York. 1959.

** Murray, H. A. Thematic Apperception Test. Harvard University Press, Cambridge, Massachusetts. 1943.

Since our hypothesis deals with level of performance on the NF, it is necessary to equate subjects on all variables known to influence level of performance. One such variable is intelligence.*

Assuming intelligence to be equivalent for both groups, it is predicted that:

a) Those persons scoring high in Nach will also score consistently higher on the NF than those persons scoring low in Nach.

b) When competition is introduced, persons scoring high and low in Nach will all improve their performance, with those high in Nach improving the most.

Method.

Forty-eight male subjects were given the EPPS and 20 trials on the NF. The NF consists of 90 addition problems per form. Each item consists of three one- or two-digit numbers. The numbers for each item are randomly drawn from all the numbers from 1 to 99. The score is the number of correct answers given in 3 min. Twenty alternate forms of the NF were used in this study. Twenty trials on the NF were given, five in a series. Each series was separated by an afternoon or an evening.

Ten additional NF trials were administered to the same 48 subjects in 5 groups of approximately 10 subjects each. Each group of 10 was divided into 2 teams of 5 men per team. The 2 teams were equated on their mean performance on the NF for the previous 20 trials. The 2 teams were then given an additional 10 trials on the NF: 2 trials in the morning and 2 trials in the afternoon for 2-1/2 consecutive days. After each two trials, the scores for each team were put on the board and the high-scoring team was singled out. In addition, the task was structured as a competitive one between the two teams. A group of 10 men were tested in this manner every week for 5 wk. During all testing, the order of the NF forms was counterbalanced so that everyone did not receive the same form during a particular trial.

* Hart, J. J., and Kysor, K. P. EA Technical Memorandum 114-1. Standardization Studies With the Repetitive Psychometric Measures. III. Determining the Effects of Ability and Practice on Level of Performance. March 1966. UNCLASSIFIED Report.

After these data were collected, the 48 subjects were ranked according to their Nach scores on the EPPS. The 24 highest in Nach were designed as the high-Nach group; the remaining 24 subjects comprised the low-Nach group. The means for the high- and low-Nach groups were then computed.

Results and Discussion.

The mean NF performance for the high- and low-Nach subjects is presented in figure 101.

The performance of those scoring high in Nach was consistently above the performance of those in the low-Nach group. These results correspond to a pilot study with 10 subjects in each group, in which essentially the same results were obtained. It is difficult to determine whether the performance levels for the last 10 trials (when competition was introduced) were significantly higher than those for the previous 20 trials. To answer this question, control subjects (no competition) would have to be tested with the same intervals between trials as occurred in our sample. The higher scores obtained in both the high and low group after trial 20 may be explained by learning as easily as by the introduction of competition.

The better performance of the high-Nach group does make the first prediction seem plausible; (i. e.; persons scoring high in Nach will also score consistently higher on the NF than persons scoring low in Nach. However, since the General Technical Area Test score (GT), which is an estimate of IQ, is related to level of performance on the NF, it is necessary to compare the two groups on GT.

When the mean GT scores of both groups are calculated, the difference between the two mean scores is about 1.2 of a point—hardly enough to account for the differences obtained between the mean level of performance on the NF for the low- and high-Nach groups.

Our measure of Nach may not have been the best one for distinguishing between the highly motivated subjects and those less highly motivated. Some of the subjects seemed a little bored by the task. Some of the items keyed for Nach (e.g., to do one's best and to be able to do things better than others) make no reference to achievements of skill or significance. However, other items (e.g., to accomplish something of greater significance and to solve difficult puzzles and problems) would seem to be negatively related to high performance on the NF in that performance on NF can hardly be viewed as solving a difficult problem or solving a problem of great significance. A combination of Nach items and items from another scale that measures the

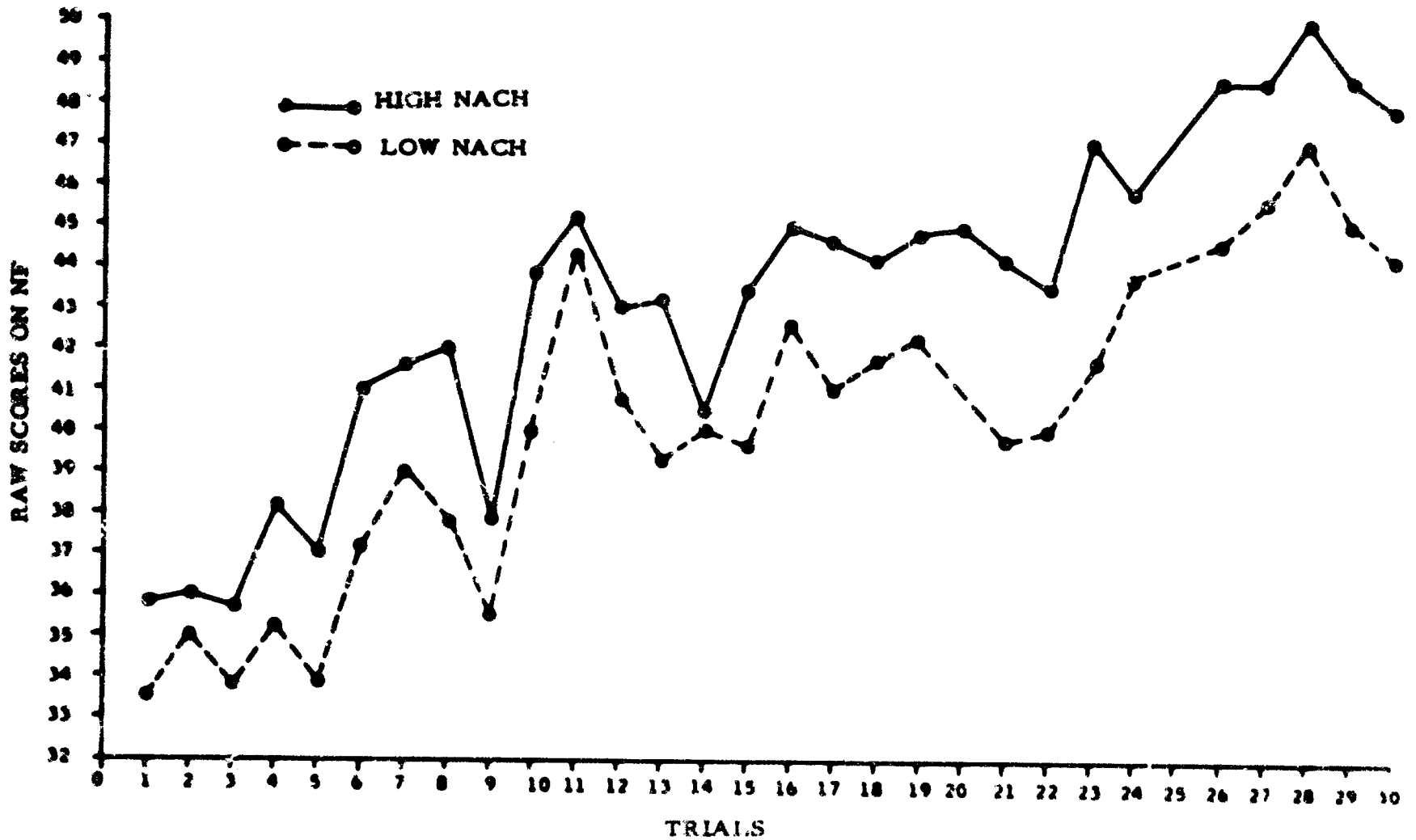

Figure 101. Mean NF Performance for High- and Low-Nach Subjects

need for endurance would probably be the most adequate scale for distinguishing between a high and a low performance on the NF. The need for endurance is a measure of perseverance in pursuit of a task and would probably be more appropriate than Nach to the extent that it requires sticking to a boring task rather than solving a problem of great difficulty or significance.

DISCUSSION

Dr. Sim: Thank you, CPT Hart. I think before we ask questions, since the next two papers will be given by the same man, we'll have Dr. Kitzes go on, and then, at the end, we'll ask questions on any of the preceding papers. The author of this next paper actually is a man who was not assigned to these laboratories but who has an intense interest in gaming theories and gaming practices. CPT Wickstrom is absent at this time on duty outside of this country. Dr. Kitzes will give his paper and then will follow with his own.

USE OF CHESS AS A TECHNIQUE IN STUDYING PSYCHOCHEMICAL EFFECTS*

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Introduction.

To evaluate the effects of psychochemicals, various tests to cognitive function have been used. Most games involve cognitive function, but the element of chance (luck) is important in almost all games except duplicate bridge and full-information games such as chess, Go and checkers. It was, therefore, decided to use chess as a measure of cognitive function in subjects given minimal doses of LSD and scopolamine. Subjects were graded on blunder percent, or percentage of bad moves.

Subjects and Materials.

Twelve male volunteers were selected from a group of 80 on the basis of intelligence, social history, Minnesota Multiphasic Personality Inventory (MMPI), and an interview. Only two had any extensive experience playing chess. Chess sets and Pal Benko chess timers were used in the experiment.

Procedures.

The subjects were given extensive instruction in six 3-hr sessions for 2 wk. Not only were the rules explained, but basic strategy and example games were demonstrated. The subjects were taught the standard method of recording chess games so that their games could later be replayed and analyzed. They were taught to play using a Pal Benko chess clock. Each player was required to make 30 moves within 20 min. If a player did not complete 30 moves within the prescribed time he lost the game. If neither player completed 30 moves within the prescribed time, the game was considered terminated. At this point, the game was adjudicated. Of course, games that reached a conclusion before the time ran out were considered terminated. After the first few days of competition, only the weakest player lost a game because of failure to complete 30 moves within the designated time.

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* The senior author of this paper who is now in Viet Nam, has all of the experimental data. However, I have compiled what little information I have. Detailed statistical analysis could not be performed on blunder percent and time per move because the raw data are not presently available.

A maximum amount of information could be obtained from pairs that were as closely matched in ability as possible. (If, for example, subject A won 95% of his games with subject B, there would be no point in drugging subject B, and to change the results by drugging subject A might require a large dose). The subjects played a round-robin tournament, after which they were paired so that the best player played the second best, the third best played the fourth best, and so forth. The subject played six games with his now standard opponent.

The actual experiment was divided into 3 days. On day 1, all subjects received a cup of juice at 8:40 AM. One subject in each pair had 50 μg of LSD in his juice. From about 9:00 AM until about 12:30 PM, the subjects played four to six chess games. Between each game, the subjects took one Number Facility (NF) test, which is a speed arithmetic test requiring the subject to add as many three-number problems (of not more than two digits) as possible in a 3-min period. This test of cognitive function has been extensively used in the evaluation of the effects of psychochemicals. On day 2, all men received a cup of juice, and the test was conducted in the same manner. On day 3, the subjects received either 12 μg/kg of scopolamine or a saline placebo. In general, the partner of the subject who received LSD was given scopolamine, except for two instances in which it would have meant that a subject who had a small win percentage was to be drugged. In these two pairs (Reis and Mihlebach, Sandifer and Peck), the same man received LSD and scopolamine. One percent of Neo-Synephrine was instilled in the pupils of all subjects so that they could not tell who had received the drug by observing each other's pupil size.

Results.

To evaluate the results of the experiment, win-loss percentage, blunder percent, and time per move were recorded. The win-loss record of the subjects is given below.

I. Starr - Renton

	Win	Loss
P	3-1/2	2-1/2
L	4-1/2	1/2*
C	4	1
S	2*	4

II. Grufman - Cavalier

	Win	Loss
P	3	3
L	4	2*
C	4	2
S	1/2*	4-1/2*

III. Mihlebach - Reis

	Win	Loss
P	4	2
L	3-1/2*	1-1/2
C	5	0
S	1-1/2*	3-1/2

IV. Meisner - Smith

	Win	Loss
P	3	3
L	3*	3
C	2	4
S	1/2	4-1/2

V. Hoge - Pratt

	Win	Loss
P	2	4
L	3	2*
C	3-1/2	1-1/2
S	1-1/2*	2-1/2

VI. Sandifer - Peck

	Win	Loss
P	5	1
L	4-1/2*	1/2
C	4	1
S	0*	5

Note: The results are for the underlined player of each pair.

P = Practice
L = LSD
C = Placebo results
S = Scopolamine
* = Drugged subject

If we regard P and C together as a control standard, the drug effect is in the expected direction in every case except VI, L, in which a slight difference goes in the wrong direction. In the 11 other LSD cases, the drugged individual did more poorly than his control standard.

In evaluating win-loss percentage, a simple 2 by 2 Chi square ($\chi 2$) technique was used. The wins and losses of practice and placebo games were added together for each pair of subjects. This represented their performances versus one another. A win and loss record was obtained for each day's drugged group. This was compared with the group's performance on the drug day. The $\chi 2$ for the LSD experiment was 0.38, which is not significant. The $\chi 2$ for the results under scopolamine was 6.34, which is significant at the 0.02 level. The evaluation of the win-loss percentage is given below.

		Win	Loss
LSD subjects	(A) $\Sigma P + C$	39	68
	(B) ΣL	15X	16X
Scopolamine subjects	(A) $\Sigma P + C$	43	25
	(B) ΣS	10	20

LSD χ^2	Win	Loss	Total
Baseline (P + C)	39	29	68
Drug run	15.5	16.5	32
	54.5	45.5	100

Scopolamine χ^2	Win	Loss	Total
Baseline (P + C)	43	25	68
Drug run	10	20	30
	53	45	98

$$\chi^2 = \frac{[(ad - bc) - 1/2N]^2 \, N}{(a + b)\,(a + c)\,(B + D)\,(C + D)}$$

LSD $\chi^2 = 0.38$ Scopolamine $\chi^2 = 6.34$

In figure 102, the percentage drop in performance in win-loss is closely parallel to the average NF percentage fall during the period of chess playing. The win-loss percentage for the LSD experiment seems to be more sensitive than for the NF, which changed very little (figure 103).

When subjects received LSD, their blunder percent was 15.4, but when they were given a placebo, it was 12.4, a difference of 6.0. Time per move was determined by dividing the time used by each subject by the number of moves made. It was desirable to make as many good moves as possible in the shortest time, thereby reserving time for difficult situations. When subjects received LSD, their average was 32.8 sec/move, whereas when they were given a placebo, it was 30.9 sec/move. The subjects who received scopolamine had an average of 36.5 sec/move, but their baseline value was 32.3 sec/move, a difference of 4.2 sec/move.

Discussion.

The purpose of this experiment was to test the feasibility of using chess as a measure of cognitive function in subjects who had received only a minimal dose of a psychochemical.

The change in win-loss percentage for the LSD part of the experiment was not significant, but it was in the expected direction. The change in the win-loss percentage for the moderate dose of scopolamine used was significant at the 0.02 level. The results of the time per move and blunder percent analyses were all in the right direction. The only change that seems significant is the increase in blunder percent of 6.0 under scopolamine.

It seems that chess is an effective measure of cognitive function and is more sensitive than the NF test, which has been used extensively for measuring cognitive function.

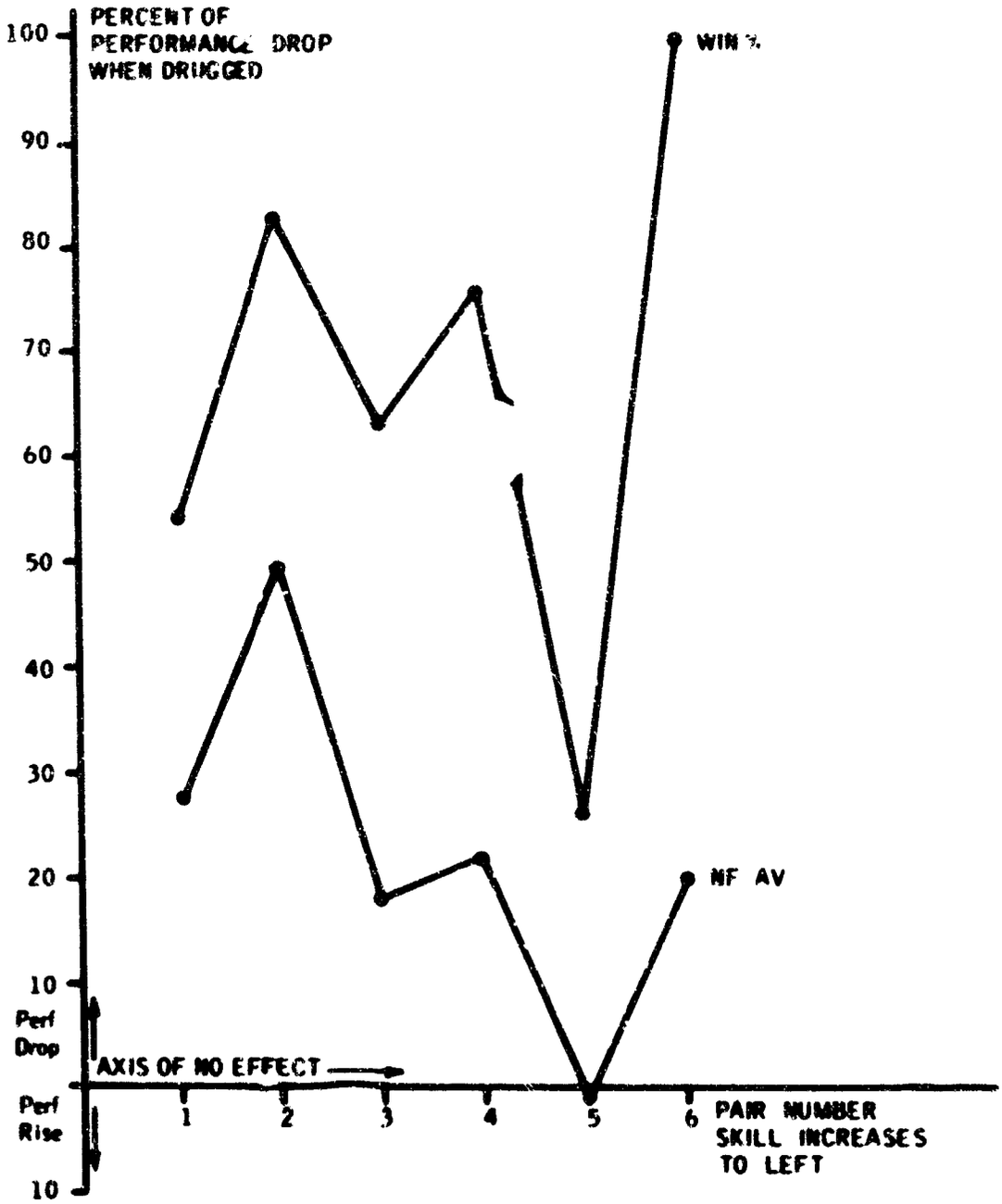

Figure 102. Comparison of Percentage Drop in Win-Loss Record of Chess Games and NF Tests Versus Pair Number of Subjects Given Scopolamine

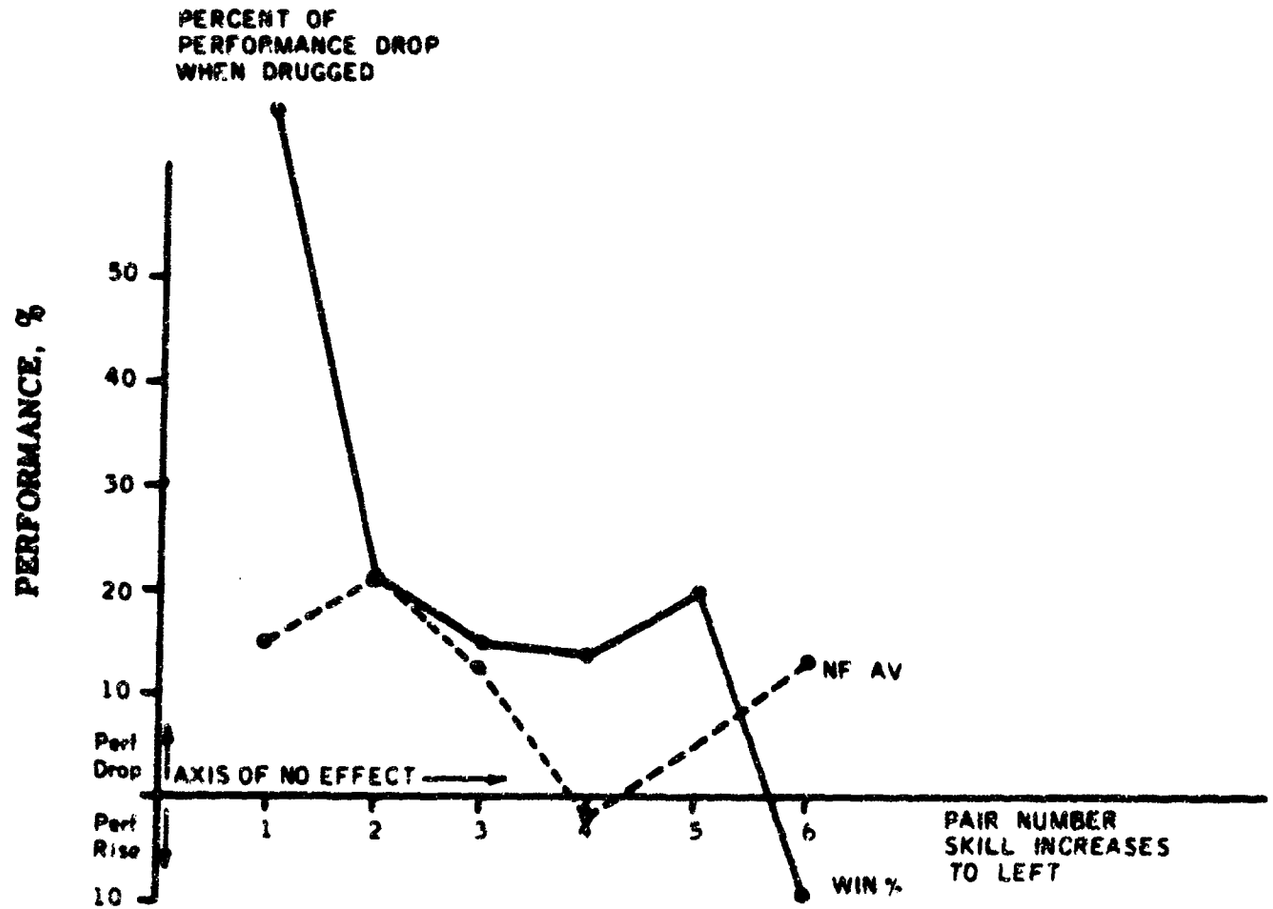

Figure 103. Comparison of Percentage Drop in Win-Loss Record of Chess Games and NF Tests Versus Pair Number of Subjects Given LSD

THE EFFECT OF MONETARY REWARD ON NF PERFORMANCE IN PRISON VOLUNTEERS

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Introduction.

In evaluating the effects of incapacitating agents, tests of cognitive function are used. In the Psychopharmacology Branch at Edgewood Arsenal, the Number Facility (NF) test, which is part of the Texas Battery of Moran and Mefferd,* has been used extensively. The subject's task is to add as many groups of three numbers of not more than two digits as he can within a 3-min period. In evaluating the results of experiments utilizing the NF test, the question is often asked if subjects' performance would have been higher if they had been more motivated.** It was, therefore, decided to try to determine whether different monetary rewards would affect performance on the NF test.

Subjects and Materials.

Thirty male subjects between the ages of 22 and 31, who were prisoners at Holmsberg Prison, Philadelphia, Pennsylvania, were selected on the basis of their social histories and the Minnesota Multiphasic Personality Inventory (MMPI).

The test materials were 20 forms of the NF test and a stopwatch.

Procedures.

The subjects were given the test forms in sequential order beginning with form No. 1. The subjects were tested in groups of five; they were given 10 forms per session with a 5-min rest period between each form.

Experimental Design.

The 30 subjects were given 20 NF forms. The subjects were paid $0.02 per right answer for each of these tests.

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* Moran, L. J., and Mefferd, R. B., Jr. Repetitive Psychometric Measures. Psychol. Rept. 5, 269-275 (1959).

** Moran, L. J., Kimble, J. P., Jr., and Mefferd, R. B., Jr. Repetitive Measures: Equating Alternate Forms. Ibid. 14, 335-338 (1964).

The subjects were then divided randomly into 2 groups of 15, group I and group II. Group I received 10 NF tests for which they were paid a flat rate of $10. They then received 10 more tests for which they were paid $0.30 per right answer. Group II first took 10 NF tests for which they were paid $0.03 per right answer; then, they took 10 tests and were paid a flat rate of $10.

Then groups I and II were both divided randomly into three subgroups (A, B, and C) of five men each, giving a total of six subgroups. Subgroups IA and IIA received 10 NF tests for which they were paid a flat rate of $10. Subgroups IC and IIC received 10 NF tests and were paid $0.01 per right answer. In addition, a bonus level was determined by taking the average of the highest decade of NF's (i.e., either 1 to 10, 11 to 20, 21 to 30, or 31 to 40). The men were paid $0.50 for each right answer per test higher than this bonus level.

Results.

Two analyses of variance, the first on the data from tests 1 to 20 and the second on the data from tests 21 to 50, were done according to the techniques described by Winer* for a multiple factorial design. The analysis on data of tests 1 to 20 was done in order to determine if the six subgroups of five subjects each were matched with respect to baseline NF ability. The analysis on data of tests 21 to 50 was done in order to determine the different effects of the various conditions of monetary reward upon NF performance.

The data for tests 1 to 20 were analyzed as a 6 × 20 factorial design with a different subgroup of five subjects each nested under each of six levels of the first factor and with repeated measures over all 20 levels of the second factor. The two factors and the levels of each follow:

First factor - subgroup subjects

Subgroups IA, IB, IC, IIA, IIB, and IIC

Second factor - tests (forms 1 to 20)

The results of the analysis of variance in data of tests 1 to 20 are summarized in table XX. The F-ratio for the main effect of subgroups was not significant at the 0.05 level, nor was the interaction of subgroups times tests significant at the 0.05 level. This indicates that, on the average, in all of the first 20 tests, there were no significant differences among the subgroups and that

* Winer, B. J. Statistical Principles in Experimental Design. McGraw-Hill Book Company, Inc., New York, New York. 1962.

there was no significant interaction between the subgroups and the test forms. The F-ratio for the main effects of tests was significant beyond the 0.01 level, indicating there were, on the average, significant differences in the average performance by the subjects among the forms.

Table XX. Analysis of Variance in Tests 1 to 20

Source	df	MS	F
Between subjects		3049.02	
Subgroups	5	3543.80	1.20
Subgroups within subgroups	24	2945.94	
Total	29		
Within subjects		11.20	
Tests 1 to 20	19	83.20	9.54*
Subgroups X tests	95	8.69	1.00
Tests X subjects within subgroups	456	8.72	
Total	570		
Overall total	599	158.27	

* Indicates significance beyond the 0.01 level.

The data for tests 21 to 50 were analyzed as a 2 X 3 X 30 factorial design with a different subgroup of five subjects each nested under each of the six combinations of levels of the first and second factors and with repeated measures over all the levels of the third factor. The three factors are as follows:

First factor - pay contingency for tests 21 to 40

$10 flat rate (tests 21 to 30), $0.03 per correct answer (tests 31 to 40)
$0.03 per correct answer (tests 21 to 30), $10 flat rate (tests 31 to 40)

Second factor - pay contingency for tests 41 to 50

$10 flat rate, $0.03 per correct answer
Reward payed on bonus level + $0.01 per correct answer

Third factor - tests 21 to 50

This design with the mean NF performance for each of the 2 X 3 X 30 treatment conditions is summarized in table XXI. The results of the analysis of variance appear in table XXII.

Table XXI. Mean MF Performance

First factor	Second factor	Test No. 1				Test No. 5					Test No. 10				
Level 1	Level 1	52.4	50.6	48.0	50.0	50.6	52.8	51.4	50.2	51.8	49.4	51.0	50.4	51.6	52.0
Level 1	Level 2	44.2	42.8	40.8	44.2	44.2	41.6	41.0	43.6	44.6	42.8	41.2	41.8	42.4	45.4
Level 1	Level 3	39.2	37.0	36.4	36.8	36.8	36.6	35.6	36.8	38.0	36.0	38.8	36.8	39.2	41.8
Level 2	Level 1	36.6	35.2	34.6	36.2	36.2	35.4	36.0	36.0	36.6	35.0	34.6	34.2	42.2	37.4
Level 2	Level 2	44.6	40.4	41.8	45.2	42.0	42.2	42.6	45.0	42.8	46.2	42.8	42.2	43.6	43.6
Level 2	Level 3	42.2	40.2	36.0	37.4	39.8	40.8	37.2	38.4	37.8	34.0	38.6	40.4	37.8	42.4

Note: Level 1 = $10 then $0.0,
Level 2 = $0.03 then $10

Level 1 = $10
Level 2 = $0.03
Level 3 = Bonus system

Table XXI. Mono MF Performance (horizontal continuation)

Test No. 15					Test No. 20					Test No. 25					Test No. 30
54.2	54.2	53.6	54.2	53.2	57.6	56.6	52.6	50.6	52.0	52.2	52.0	50.2	52.2	51.2	49.2
45.6	44.6	43.8	47.0	41.8	40.2	45.6	45.4	43.6	46.2	45.2	45.8	43.6	45.2	44.4	44.4
41.0	41.8	39.8	43.6	40.0	46.6	41.6	40.4	38.2	49.2	3[illegible].2	42.4	36.8	40.8	40.0	42.0
39.4	38.2	43.8	41.2	35.0	41.6	39.4	38.8	35.6	37.[illegible]	43.2	39.4	35.4	38.2	37.8	36.8
46.2	43.8	43.6	44.8	41.8	41.2	48.4	47.0	44.0	48.4	45.2	54.0	45.2	46.6	43.4	44.8
42.2	41.4	38.6	43.2	41.0	40.0	46.8	45.4	44.0	44.6	44.0	45.2	42.0	42.8	44.0	45.0

Table XXII. Analysis of Variance in Tests 21 to 50

Source	df	MS	F
Between subjects		5130.86	
Pay contingency, tests 21 - 40	1	3778.15	0.70
Pay contingency, tests 41 - 50	2	1764.06	0.33
Pay contingency, tests 21 - 40 × pay contingency, tests 41 - 50	2	6287.25	1.17
Subjects within subgroups	24	5371.46	
Total	29		
Within subjects		14.81	
Tests 21 - 50	29	81.98	6.67*
Pay contingency, tests 21 - 40 × tests	29	7.41	0.60
Pay contingency, tests 41 - 50 × tests	58	20.33	1.65*
Pay contingency, tests 21 - 40 × pay contingency, tests 41 - 50 × tests	58	9.52	0.77
Tests × subjects within subgroups	696	12.30	
Total	870		
Overall total	899		

* Indicates significance beyond the 0.01 level.

The F-ratio for the main effect of pay contingency for tests 21 to 40 was not significant at the 0.05 level. This indicates that, on the average, there were no differences in performance between the two pay contingencies for tests 21 to 40. The F-ratio for the main effect of pay contingency for tests 41 to 50 was not significant at the 0.05 level. This indicates that, on the average, there were no differences in NF performance among the three pay contingencies for tests 41 to 50. The F-ratio for the main effect of tests was significant beyond the 0.01 level, indicating that, on the average, there were significant differences among the tests over all other conditions.

The F-ratios for the interactions of pay contingency for tests 21 to 40 times tests and pay contingency for tests 21 to 40 times pay contingency for tests 41 to 50 times tests were not significant at the 0.05 level. The F-ratio for the interaction of pay contingency for tests 41 to 50 times tests was significant at the 0.01 level. The occurrence of this significant interaction made interpretation of the main effects for the pay contingency for tests 41 to 50 ambiguous and required further data analysis. Therefore, an analysis of variance was done on the simple main effects of tests 21 to 50 at each of the three pay contingencies used on tests 41 to 50. This analysis is summarized in table XXIII.

Table XXIII. Analysis of Simple Main Effects of Tests 21 to 50 at Three Pay-Contingency Levels Used on Tests 41 to 50

Source	df	MS	F
Tests: $10 flat rate (41 - 50)	1	5.42	0.44
Tests: $0.03 per correct answer (41 - 50)	1	318.28	25.89*
Tests: bonus rate (41 - 50)	1	584.02	47.51*
Tests × subjects within subgroups	696	12.30	

* Indicates significance beyond the 0.01 level.

The F-ratio for tests on $10 flat rate was not significant at the 0.05 level. This indicates that there were no significant differences in NF performance among tests 21 to 50 for those men who received a $10 flat rate on tests 41 to 50. The F-ratios for tests on a $0.03 per right answer basis and on a bonus level were both significant at the 0.01 level. These indicate that there were significant differences in NF performance among tests 21 to 50 for those men who received either a $0.03 per right answer or bonus-level rate on tests 41 to 50.

To more specifically locate where the change in NF performance occurred, a priori orthogonal comparisons were made between tests 21 to 40 versus tests 41 to 50 under each of the pay contingencies for forms 41 to 50 The results of these comparisons are summarized in table XXIV.

Table XXIV. A Priori Comparison of Tests 21 to 40 Versus Tests 41 to 50 for Each Pay Contingency on Tests 41 to 50

Comparison	df	MS	F
Tests 21 - 40 versus tests 41 - 50 under $10 flat rate on tests 41 - 50	1	5.42	0.44
Tests 21 - 40 versus tests 41 - 50 under $0.03 per correct answer on tests 41 - 50	1	318.28	25.89*
Tests 21 - 40 versus tests 41 - 50 under bonus rate on tests 41 - 50	1	584.02	47.59*
Tests × subjects within subgroups	696	12.30	

* Indicates significance beyond the 0.01 level.

The F-ratio for the comparison of tests 21 to 40 versus 41 to 50 for the subgroup paid $10 flat rates on tests 41 to 50 was not significant at the 0.05 level. This indicates that changing the pay contingencies between tests 21 to 40 to 41 to 50 did not produce a differential effect in NF performance.

The F-ratios for the comparisons of tests 21 to 40 versus tests 41 to 50 under either $0.03 per right answer or the bonus-rate pay contingencies were significant beyond the 0.01 level. This indicates that changing the pay contingency between tests 21 to 40 and tests 41 to 50 in either way produced a differential effect in NF performance.

Discussion.

The results of analysis of variance of the first 20 tests were interpreted as evidence that the random assignment of subjects to the six subgroups had, in fact, resulted in groups matched with respect to NF ability. The fact that, for the first 20 tests, the F-ratio for the main effects of tests was significant was interpreted as evidence that repetitive testing on the NF may lead to a significant increase in average NF performance. Assuming that the forms are indeed equivalent, it is suggested that learning contributes to NF performance. A similar effect has been observed by Hart.*

The results of the analysis of variance of the last 30 tests were interpreted as evidence that there was a significant change in NF performance within the last 30 forms. The significant interaction between pay contingency for tests 41 to 50 times tests was interpreted as a partial indication that change in pay contingency results in a differential effect on NF performance. More specifically, the analysis of simple main effects indicated that the $0.03 per right answer for tests 41 to 50 and the bonus level for tests 41 to 50 both produced significant changes in NF performance. The a priori comparisons between tests 21 to 40 versus 41 to 50 were interpreted as further evidence that a change in pay contingency from tests 21 to 40 to either $0.03 per right answer or bonus level, but not to $10 flat rate, produced a significant change in average performance. From inspection of the mean scores in table XXI, it seems apparent that the trend was toward increasing average NF performance with a change in pay contingency to $0.03 per right answer or bonus level. This would seem to suggest that, in future evaluations of the effects of psychochemicals on cognitive function, strong consideration should be given to the possible utilization of monetary rewards to increase motivation.

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* Hart, J. J. CRDL TM 2-17. Standardization Studies with the Repetitive Psychometric Measures. I. Determining Equivalence of Forms. (1965). UNCLASSIFIED Report.

DISCUSSION

Dr. Levison (Institute for Behavioral Research): Could you describe the reinforcing situation?

CPT Kitzes: Before each test contingency, the subjects were told how they would be paid. They didn't know what the next contingency would be.

Dr. Levison: Did they receive their pay the moment they obtained the right answer?

CPT Kitzes: The prison does not allow them to have money. They can use credit to buy things while in prison or get cash when they are released.

Dr. Levison: Well that's not so critical, but what I was wondering was the point at which the subject ought to answer correctly. Would he, at that point, know how many he had correct or incorrect?

CPT Kitzes: After taking the form, he would know how many he had completed, they are arranged in columns of 10, and that would be very close to the number correct.

Dr. Lilly (Communication Research Institute): I would like to go back to Dr. Levison's paper, if I may, on the assessment of behavior for long periods of time. At the beginning of his talk, he brought up something that I said last night in regard to so-called complex organisms and the onset of monotony or boredom in their performances. Last night, I was discussing a test devised for rats, applied to dolphins, resulting in reactivity of the dolphin to the monotony. I was not comparing test devices for humans with those for dolphins. I think a better and more apt comparison was the remark by the trainer that when he had a dolphin with a brain the same size as a human and one with a brain larger than a human, the "military precision" could be gotten from the smaller-brained dolphin but not from the larger-brained dolphin.

Dr. Levison: This point is well taken. However, if you were a subject for 9 mo in an experiment 3 to 4 hr a day, 5 days a week, doing 25 matching-to-sample problems of two crosses versus a plus, I think you might agree that this was not a problem that was appropriate for a human organism either.

Dr. Lilly: There is also a sex difference. I noticed you chose a female subject. I, too, find that they will do very boring tasks over a very long period of time. Whether this is a brain size difference or a sex difference, I can't say.

Dr. Elkes (Johns Hopkins Hospital): I wanted to ask Dr. Levison whether he had used any drugs other than chlorpromazine and amphetamine. Could you please go over these again in a little more detail?

Dr. Levison: No, I didn't use any other drugs. We did not use any drugs in the pilot work that was subsequently described. The effects were slight decrements in accuracy of matching the sample, with 50 mg of chlorpromazine—on both accuracy and rate of responding. With 25 mg (this is an absolute dose, not by body weight) the effects were not reliable. With 10 mg of amphetamine, we got an acceleration or rate of responding, but there were no effects on accuracy.

Dr. Elkes: Do you have any suggestions to account for the difference?

Dr. Levison: I don't know quite how to answer that. The rate changes are consistent with the kind of rate changes we expected to observe with amphetamine. I think that in order to disrupt accuracy at those dose levels, it would have to be the subject's interpretation that the drug generated a lot of competing behavior—she was distracted, couldn't concentrate on the stimulus, and so forth—and apparently we didn't reach these dose levels for this particular subject. We used 5 mg of d-amphetamine with little effect.

Dr. Carr (Army Research Office): Twenty-five or fifty milligrams of chlorpromazine is almost a homeopathic dose.

Dr. Levison: At 25 mg, she had chronic administrations, and she did report some side effects initially, but not after she had two or three doses of the drug. I might add she weighed 100 lb, to give you some idea of the dimensions of the organism.

Dr. Elkes: I would also like to ask Dr. Hart whether he has any other data, perhaps, than the "need for an achievement" score. This score, on one hand, reflects the need to achieve, and, on the other hand, of course (if correlated with other personality scores), it may reflect some compensating mechanisms that are at work, and could possibly show up. In fact, I was quite surprised when these curves were as parallel as they were. Has he any other data?

CPT Hart (Edgewood Arsenal): We did give the people the EPPS, and there are I think, 14 other needs on it, such as a need for endurance, a need for affiliation, wanting to be with other people, and aggression. We do have all this information on all these subjects, but we haven't analyzed it. So we do have the information on all these other needs for the same subjects.

Dr. Elkes: What I am really saying is that real achievers may not have any "need for achievement."

CPT Hart: Yes, I think that is an important point in that perhaps it isn't one need, for example, the need for achievement, that is important, but perhaps a whole pattern of two or three needs. I agree with you.

THE EFFECTS OF DRUGS ON HUMAN PERFORMANCE*

Laboratory Testing and Military Prediction
Dr. Edwin H. Elkin, Dr. Harold P. Van Cott, and
Dr. Edwin A. Fleishman
American Institutes for Research

The American Institutes for Research (AIR) project at Edgewood Arsenal began in July of 1964. Its aim has been the development of a comprehensive test battery with which the Army will be able to study the effects of incapacitating agents on human abilities, especially those abilities that are considered basic to the performance of military tasks. Essentially, we are seeking a means of predicting the effects of chemical agents on military performance from their effects on the basic human abilities that underlie that performance. We are not certain at this point that such predictions can reliably be made, but we recognize the value of such prediction, and we are attempting (1) to define the variables involved, (2) to establish the best tests of human abilities available, and (3) to eventually determine whether the predictions can be made.

This paper presents a brief résumé of AIR's accomplishments at Edgewood Arsenal during the past year and illustrates some of the preliminary findings. The scope of this report precludes any detailed discussion of each aspect of our research. However, it does give some of the "flavor" of the work, which is described more fully in a series of reports by Elkin and coworkers.**

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* Based on a paper presented at the Experimental Medicine Division Contractor's Meeting. 14 - 15 October 1965. U.S. Army Chemical Research and Development Laboratories, Edgewood Arsenal, Maryland.

** Elkin, E. H., Freedle, R. O., and Fleishman, E. A. AIR Contract DA18-035-AMC-282(A). Effects of Drugs on Human Performance. First Quarterly Report. 15 October 1964. UNCLASSIFIED Report; Elkin, E. H., Freedle, R. O., Horowitz, H., and Van Cott, H. P. Ibid. Second Quarterly Report, 10 January 1965. UNCLASSIFIED Report; Elkin, E. H., Horowitz, H., and Van Cott, H. P. Ibid. Third Quarterly Report, 10 April 1965. UNCLASSIFIED Report; Elkin, E. H., Freedle, R. O., Van Cott, H. P., and Fleishman, E. A. Ibid. The Effects of Scopolamine on Representative Human Performance Tests. Technical Report 1. 31 August 1965. UNCLASSIFIED Report; Elkin, E. H., Fleishman, E. A., Van Cott, H. P., Horowitz, H., and Freedle, R. O. Ibid. Phase I. Research Concepts, Test Development, and Preliminary Studies First Annual Summary Report. 31 October 1965. UNCLASSIFIED Report.

From the beginning, we have kept three broad objectives in mind First, we intend to establish a laboratory facility that will incorporate a test battery of basic human abilities. Second, we plan to evaluate the battery's usefulness in dealing with the full range of drug effects we expect to encounter here. Third, we plan to validate the laboratory results by determining just how well predictions can be applied to criterion military tasks.

The first year's effort was concentrated on the first two objectives of establishing the laboratory and trying some of the newly developed tests on drugged subjects. However, work was initiated on the third objective to the extent that a rationale was developed for selecting criterion military tasks, and an initial selection of such tasks was made for an eventual Edgewood Arsenal test program.

The initial selection of tasks is outlined in table XXV, which lists five specific military skills recommended as suitable for initial testing. Also shown in the table are: (a) the particular performance tests recommended, based primarily on the Human Resources Research Office work in this field; (b) the specific kinds of scores obtained from each test; (c) the special test conditions required, if any; and (d) the abilities that are considered basic to the particular skill being tested. Plans for implementing this phase of the research effort are not presented here, but the table should provide a better idea of the criterion task's relation to the basic-abilities tests, the development of which constituted the greater part of the first year's work.

The major accomplishments of the year were as follows:

1. We considered the broad range of human performance and decided to have five major categories of abilities, which we named psychomotor, physical proficiency, cognitive, sensory-perceptual, and social.

2. We recommended some 50 ability tests for development and experimentally studied 20 of these with drugs, using a total of 82 medical volunteers.

3. In the laboratory, we conducted a total of six experiments. Three major studies (called studies I, II, and III) used scopolamine as a "standard" agent; three exploratory studies used classified agents of current interest to Edgewood Arsenal. The latter studies were conducted jointly with the Psychopharmacology Branch, and, in this coordinated effort, we were able to compare the effects of several candidate agents on our tests with their effects on psychological and medical tests previously established at Edgewood Arsenal.

Table XXV. Initial Selection of Criterion Military Tasks

Military skill	Performance test	Kind of score obtained	Special physical terrain and apparatus requirements	Related basic abilities
Weapon-firing	Simulated firing with the Hit-Indicator a/	Total number of hits obtained, rate of fire, rate of effective fire	Small (90 - 450 m) open field with no obstacles, IR sensor and source units, stopwatch	Multiple-limb coordination, reaction time, arm-hand steadiness, visual acuity, control precision
	Actual firing with M14 rifle suspended in safety harness b/	Same as above	Outdoor, small-arms firing range modified with safety-harness stand b/, pop-up targets, stopwatch	Same as above
	Assembly and disassemb'y of rifle	Time to disassemble and reassemble a rifle	Indoor or outdoor facility with small stand, stopwatch	Associative memory, spatial visualization, finger dexterity, manual dexterity
Individual CBR measures	Donning gas mask after gas alarm is given	Total time to don mask, rating of adequacy of gas-mask fitting	None	Manual dexterity, reaction time, speed of arm movement

a/ Formerly known as the Technique of Fire Trainer.

b/ The proposed safety-harness stand consists of a triangular metal frame that has three chains (one from each corner) attached with some slackness to permit maneuverability of different points of the weapon's stock. This arrangement gives the firer complete freedom to aim the weapon at any point downrange but completely prevents his removing the weapon from the frame or his aiming the weapon outside the "fan of fire."

Table XXV. Initial Selection of Criterion Military Tasks (contd)

Military skill	Performance test	Kind of score obtained	Special physical terrain and apparatus requirements	Related basic abilities
Target detection	Target detection and range estimation (with no difficulty phasing) c/	Total number of targets correctly identified, accuracy in estimating range	Outdoor target-identification range as described in FM 23-71, Rifle Marksmanship, July 1964	Visual acuity, spatial visualization, perceptual speed, spatial orientation
	Target detection and range estimation (with difficulty phasing of targets) c/	Total number of targets correctly identified at each phase of difficulty, accuracy of range estimation at each phase of difficulty	Same as above	Same as above
Individual tactical action	Selection of appropriate camouflage material	Total number of correct items selected minus the number of incorrect items selected, rating of adequacy of application of camouflage material	Modified tactical training course as described in ATP-21-114	Associative memory, visual acuity
	Crawling test	Time to crawl	Same as above	Static flexibility, dynamic flexibility, multiple-limb coordination

c/ In a difficulty-phasing version, each trial in the test involves the appearance of several targets; the first target is the most difficult to detect and identify, thereafter, targets become progressively easier to detect.

Table XXV. Initial Selection of Criterion Military Tasks (contd)

Military skill	Performance test	Kind of score obtained	Special physical terrain and apparatus requirements	Related basic abilities
	Simulated barbed-wire crawl	Time to crawl course, number of contacts with wire	Same as above with barbed wire simulated by electrical wire that makes contact when touched	Same as above
	Fire and movement	Time for two men to cover terrain, time for each man to cover his designated sector	Modified tactical training course as described in ATP-21-114	Reaction time, manual dexterity, dynamic flexibility, spatial visualization
Physical combat proficiency	Overhead ladder climb	Time to climb distance of ladder, length of distance climbed on ladder before man loses grip	Modified Physical Combat Proficiency Course (protective padding as needed at critical points along route)	Gross body equilibrium, dynamic strength
	Flat run	Time to run course	Same as above	Explosive strength
	Grenade throwing	Accuracy in hitting target with grenade from each of four throwing positions	Same as above	Explosive strength, visual acuity

Emphasis in this paper is on scopolamine studies I and II, in which the drug's effects on 17 different performance tests (primarily in the psychomotor and physical-proficiency areas) were investigated.

The third study also used scopolamine but differed from the first two insofar as its prime concern was the feasibility of assigning corrective lenses to compensate for the loss in visual accommodation that was induced in the drugged subjects. Such loss, if left uncorrected, would lead to poor performance on any test requiring good vision, not because of a true drug effect on the subject's ability or interest but because of its action on the visual mechanism.

One important point to keep in mind relating to the research reported here is that it is not intended as a study of scopolamine effects, per se; rather, the drug is being used as a generally well-known reference agent to determine the utility of the test apparatus and testing procedures. Once these have been established, we will then be able to undertake the rigorous experimentation that is essential for the accurate assessment of drug effects.

Table XXVI presents the abilities and the tests involved in this year's effort. Many of these abilities and the tests to best measure them were identified during the course of 14 yr of research by the principal investigator, Fleishman, and his associates. Summaries of this research and elaborations of the conceptual framework on which it is based have been extensively reported. *

In Table XXVI, the tests are grouped according to four of the ability categories worked with this year. Tests of the social-abilities category, which involve multiple-subject situations, were not conducted and will be postponed until adequate experience has been gained in the simpler individual-subject test situations.

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* Fleishman, E. A. Psychomotor Tests in Drug Research. In: Drugs and Behavior. Miller, J. C., and Uhr, L., eds. pp 273-296. John Wiley & Sons, Inc., New York, New York. 1960; Fleishman, E. A. The Description and Prediction of Skill Learning. In: Training Research and Education. Glaser, R., ed. pp 137-175. University of Pittsburgh, Pittsburgh, Pennsylvania. 1962; Fleishman, E. A. The Structure and Measurement of Physical Fitness. Prentice-Hall, Inc., Englewood Cliffs, New Jersey. 1964; Fleishman, E. A. Human Abilities and the Acquisition of Skill. In: The Acquisition of Skill. Bilodeau, E. A., ed. Academic Press, New York, New York. 1965; Fleishman, E. A. Individual Differences and Motor Learning. In: Learning and Individual Differences. Gagne, R. M., and Glaser, R., eds. Charles E. Merrill Books, Inc., Columbus, Ohio. 1966. (In press); Gagne, R. M., and Fleishman, E. A. Psychology and Human Performance. Holt, Rinehart, and Winston, Inc., New York, New York. 1959.

Table XXVI. Tests Used in Three Performance Batteries

Category	Ability	Test	Admin time
			min
Sensory-perceptual	Visual acuity a/	Orthorator (near and far)	4.0
	Time estimation a/	Empty-interval judgments (10 sec)	4.0
Psychomotor	Reaction time a/	Simple reaction time	3.0
	Manual dexterity a/	Minnesota rate of manipulation (displacement)	3.0
	Multiple-limb coordination b/	Two-hand coordination	5.0
	Finger dexterity b/	Purdue pegboard	2.5
	Arm-hand steadiness b/	Track tracing	2.5
	Manual dexterity b/	Block turning	2.5
Physical proficiency	Static strength a/	Dynomometer	1.0
	Gross body equilibrium a/	Balance-A test	2.0
	Dynamic flexibility b/	Dynamic flexibility	1.5
	Explosive strength b/	Broad jump	1.0
	Dynamic strength b/	Pullups	1.5
Cognitive	NF a/ c/	Addition	4.0
	Short-term memory a/	Auditory number span	4.0
	Speech intelligibility b/	Auditory verbal discrimination	5.0
	Associative memory b/	Recognition memory	5.0
	Perceptual speed c/	Canceling numbers	3.0
	SC c/	Circling words	3.0
	Visualization c/	Visual line tracing	3.5

a/ Battery I
b/ Battery II
c/ Battery III

Each test is keyed to the battery in which it was included. Thus, battery I includes sensory-perceptual tests of visual acuity and time estimation, psychomotor tests of reaction time and manual dexterity, physical-proficiency tests of static strength and gross body equilibrium, and cognitive tests of number facility (NF), and short-term memory. Together, these tests provide a representative cross-section of the ability areas.

Similarly, battery II includes tests of multiple-limb coordination, finger dexterity, arm-hand steadiness a second test of manual dexterity, dynamic flexibility, explosive strength, dynamic strength, speech intelligibility, and associative memory.

Battery III exclusively uses the cognitive-area tests, as indicated, and includes measures of perceptual speed, speed of closure (SC), visualization, and NF.

Figure 104 shows the effects of scopolamine on the simple reaction time test and illustrates the experimental design employed as well as the initial technique used to obtain the results. The test was administered to 4 control subjects, whose mean performance is shown by the dotted line, and to 11 experimental subjects, whose mean performance is shown by the solid line. The control subjects were given an im injection of scopolamine in a dose strength of 12 μg/kg of body weight. The curves for each of the subject groups are divided into two parts, showing the trend in performance on each of two successive test days. Between the two parts, a baseline value is shown that is the average of the last two baseline scores.

Groups of four subjects each were given the battery of tests on a staggered schedule. Generally, one man was a control and three were drugged in each group; four such groups were tested during a 2 wk period.* In this particular study, 8 tests were combined into a battery from which 10 performance measures were derived. The total time for each subject to complete one round of tests in the battery constituted a test session, which generally lasted 1/2 hr.

On the first day, each man had an orientation session followed by four baseline sessions; on the second day, he had a fifth baseline session just prior to injection, followed by five test sessions after injection. The first test session, d1, occurred at 1000 hr, 3/4 hr after injection, and the

* The first group consisted of one placebo, or control, and only two drugged subjects.

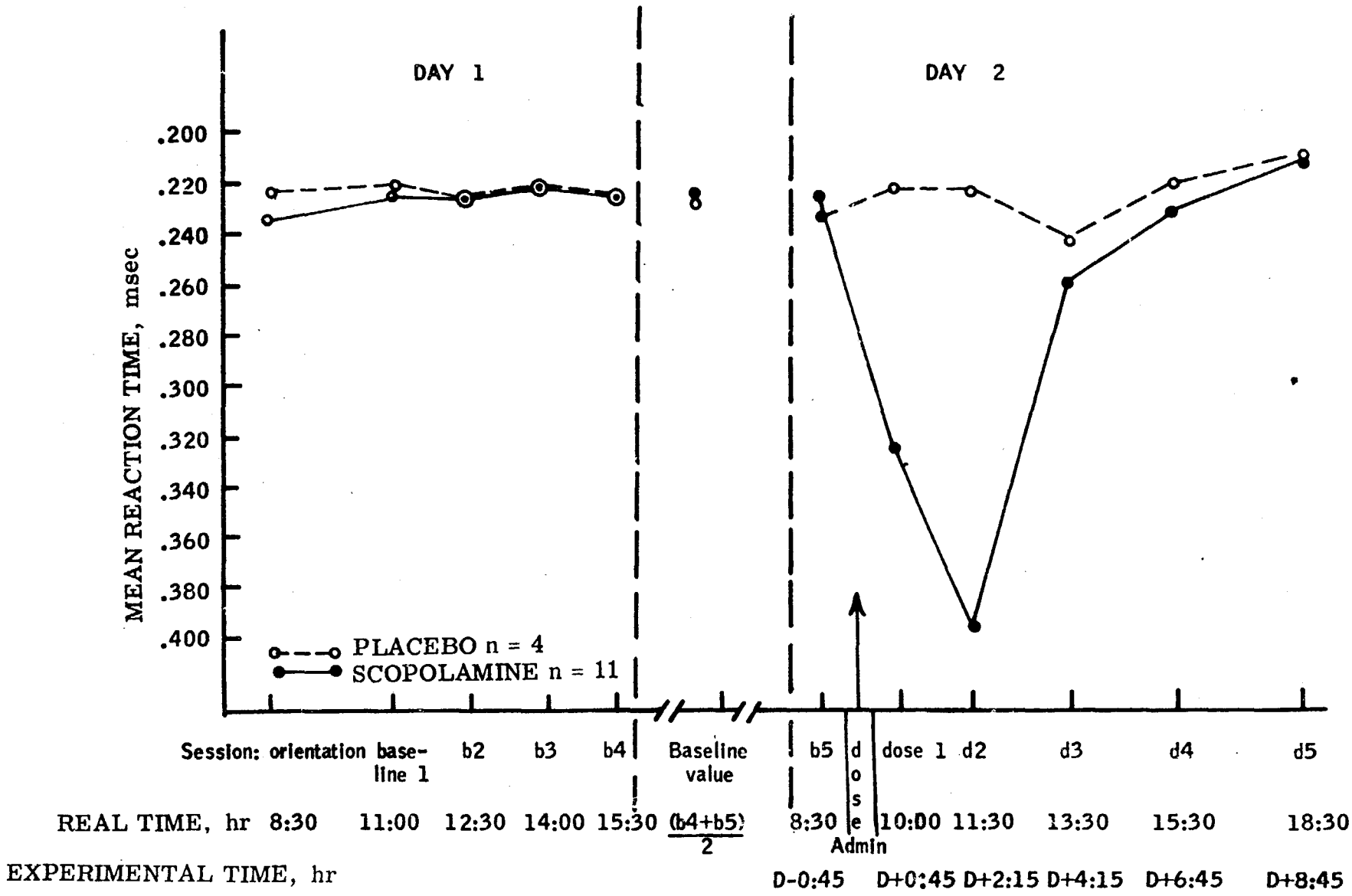

Figure 104. Effects of Scopolamine on Simple Reaction Time

last, d5, was at 1830 hr, 8-3/4 hr after injection. The time of injection, indicated by the arrow in the figure, occurred at about 0915 hr on the morning of the second day. The three interrelated time factors are all represented along the X-axis: the test-session sequence, the actual clock time, and the experimental time in relation to the time of injection. The simple reaction time to a light stimulus was recorded for 20 stimulus presentations, and the mean was computed as the score. The Y-axis shows mean reaction times, ranging from 200 to 400 msec.

Several major trends are noticeable in figure 104 that are characteristic of the results of both studies I and II. It must be remembered, though, that these curves are based on average values and do not represent the sometimes-wide range of responses that are possible on a given test, which is a factor of considerable importance and which will be dealt with in subsequent presentations.

First, the control and drug groups were effectively "matched" insofar as no significant differences between them were detectable. Thus, the results of the control group may be considered to represent those of the drug group if no drug had been administered.

Second, in the control group, there was no evidence of learning, facilitation, or fatigue, insofar as no significant trends (positive or negative) appeared during the total time period tested. Thus, the baseline value may be taken as a single value representative of "normal" performance, against which subsequent changes in performance may be compared. However, if significant trends during the course of control-group testing had occurred, then the baseline value, as computed here, would cease to represent undrugged performance, and a correction factor based on the control-group performance would be required.

Third, the agent had a marked effect on the test performance of the drug group. It changed the group's average reaction time from a baseline value of 226 msec to a value of 396 msec during the second drug session.

Fourth, recovery was completed by the last session, insofar as the mean reaction time had returned to its baseline value.

The patterns of results from the other tests have been plotted in a similar manner. However, the pattern of loss and recovery of ability for some tests differed greatly from those of other tests. This confirmed our belief that, except for instances of gross incapacitation, drugs do act differently on different abilities, and the generalization of effects from one kind of performance to another can rarely be made.

For example, although the performance of many tests, such as reaction time, was poorest during the second drug session, the performance of others, such as the one presented in figure 105 for near visual acuity, was poorest during the third drug session. The baseline value is approximately 1' of arc, but the performance continues to worsen through the first and second drug sessions and reaches its low point during the third session, when the average acuity threshold was 3.8' of arc. Moreover, reaction-time recovery is complete by the fifth session, whereas recovery of near visual acuity is clearly not complete at that time.

The performance of still other tests, especially those in the physical-proficiency area, was poorest during the first drug session, and recovery tended to be more rapid than for either reaction time or near visual acuity.

What about comparisons of performance decrement across tests? Although the X-axis represents a time scale that remains the same for all tests reported, the Y-axis changes as a function of the particular scoring system used for each test. As long as each test decrement is reported in terms of its own unique scale system, direct comparisons of magnitude and pattern of effect are impossible. To deal with this problem, a standard technique has been employed to permit precisely this kind of across-test comparison through the use of a Z-score as a common denominator of drug effects.

The Y-axis of figure 106 represents a change from the baseline to terms of the Z-score, where a Z-value of 0 represents the baseline for all tests. The X-axis shows the five successive drug sessions, as indicated by their experimental time. The numbers 1 through 10 at the top of each bar represent the 10 performance tests compared in study I. With the Z-score technique of comparison, a Z-score of -2 on test 1 is, relatively speaking, as serious as the same Z-score on test 2 or, for that matter, on any test.

With these relationships in mind, we can see from the graph that tests 1 and 2, which measure far and near visual acuity, respectively, do not differ greatly during the first test session. However, on subsequent sessions, far acuity worsens only slightly, while near acuity worsens considerably and, relative to the other tests, continues to be the most severely affected performance.

Similarly, test 5, which measures balance, shows the greatest performance decrement during the first session, but its performance gradually improves until the decrement, relative to the other tests, is negligible during later sessions.

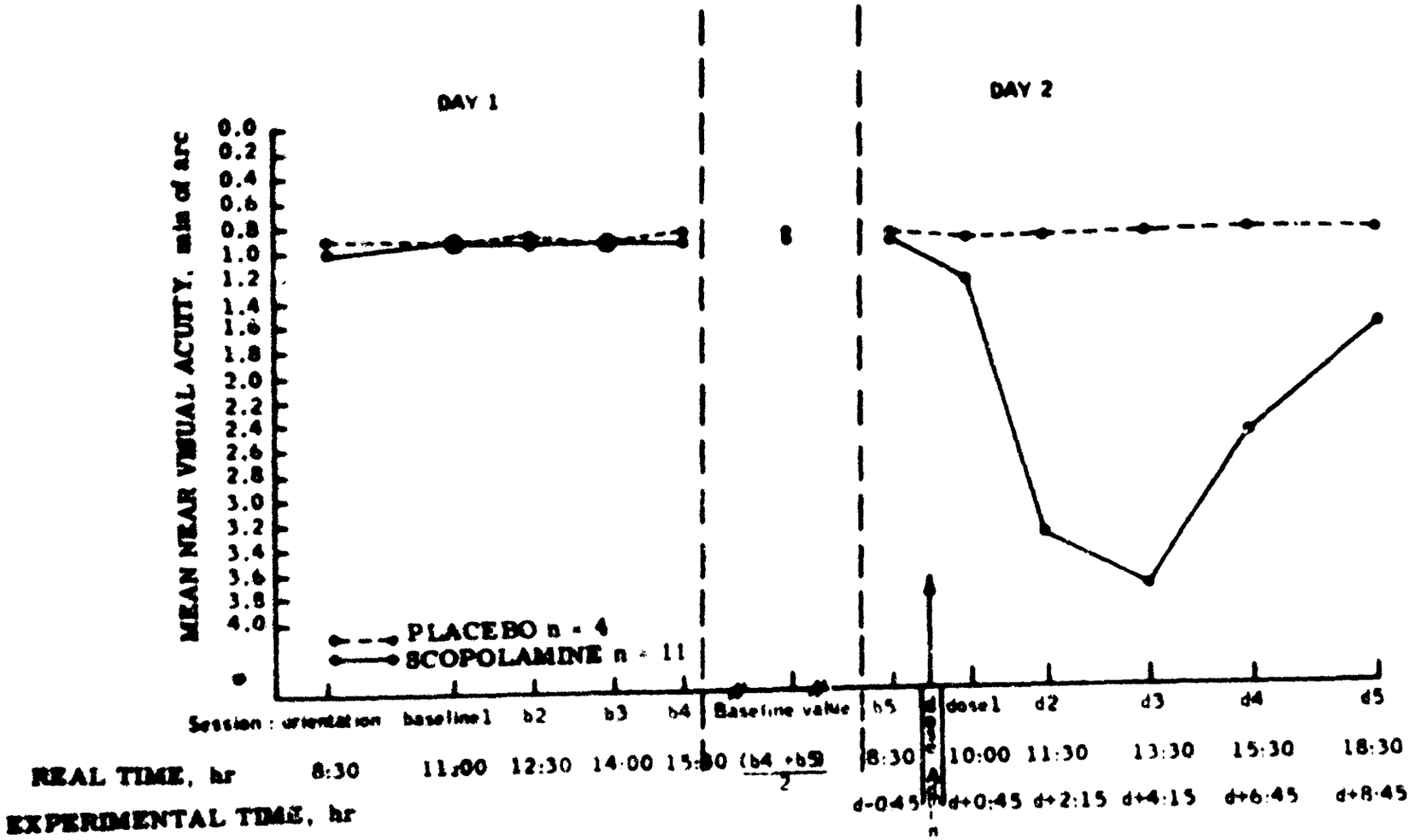

Figure 105. Effects of Scopolamine on Near Visual Acuity

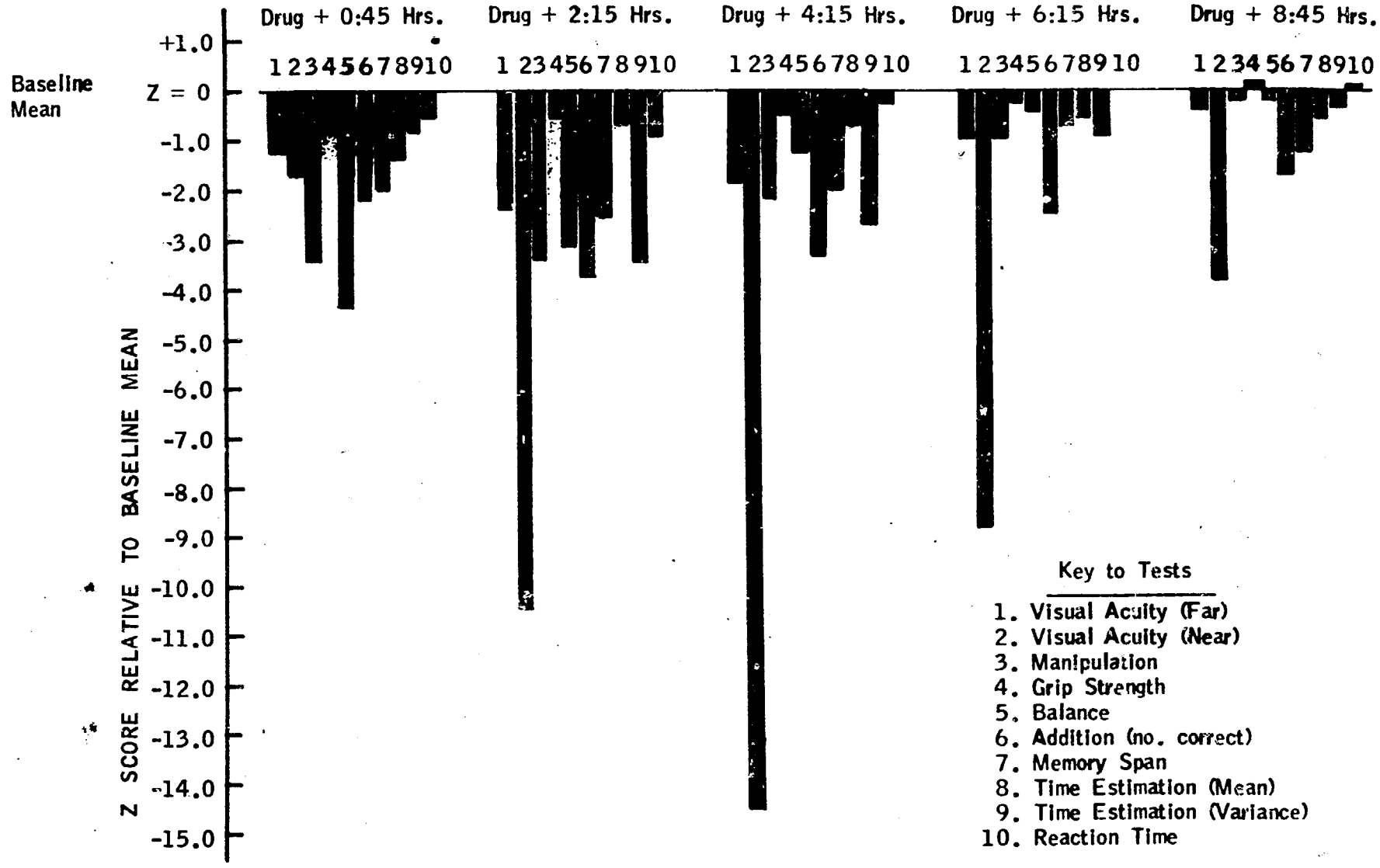

Figure 106. Comparison of Effects of Scopolamine on Performance Tests

Lastly, test 10, which measures reaction time, is severely affected in terms of its own score range but is not, in the Z-score comparison, nearly as "bad off" as the other tests; it remains only slightly affected throughout the five test sessions.

With presentations such as these, we have effectively produced what we hope will develop into a profile of ability loss, so that the drug effect or any number of tests may be compared to show which are the most and least affected at any particular point in time. The continued refinement of measures such as these for across-test comparison is now under way. Figure 107 presents a preliminary example of such refinement by combining the actual time, X-axis, with the comparable Z-score, Y-axis, in a single graph for each of eight performance tests. The area under each baseline represents the relative performance decrement with time.

Even now, as we approach the point where tests of basic abilities are developed and where the techniques for assessing the effects of drugs on such tests are perfected, we must return to the ultimate question of prediction.

Of what value are the highly controlled laboratory studies for telling us what to expect in actual field situations? Can we ever hope to obtain enough information to predict significant changes in performance without incurring the expense and logistical problems of such field operations? We believe that these goals are practical and achievable in the sense that Edgewood Arsenal can develop reliable means for extrapolating from relatively inexpensive laboratory research to field operations by means of the correlation of laboratory performance measures with carefully designed and limited field-test situations.

The value of such extrapolation is great, and the effort that goes into determining its feasibility is well worthwhile. But the development of human performance tests and prediction techniques is only a part of this development program. In order to fully explore the potential for predicting from drug effects on abilities to drug effects on "real-world" performance, a broader scope of research must be conducted, ranging from the tactical doctrine and system concerns of the Military Operations Research Analyst to the physiological concerns of the psychopharmacologist and the physician. Although the psychological aspect is indeed important, the maximum value of this broad-scope research program will not be realized until it is subsequently integrated with the other parts of the job at hand. The goal continues to be the fuller understanding of the relationship between drugs and human behavior

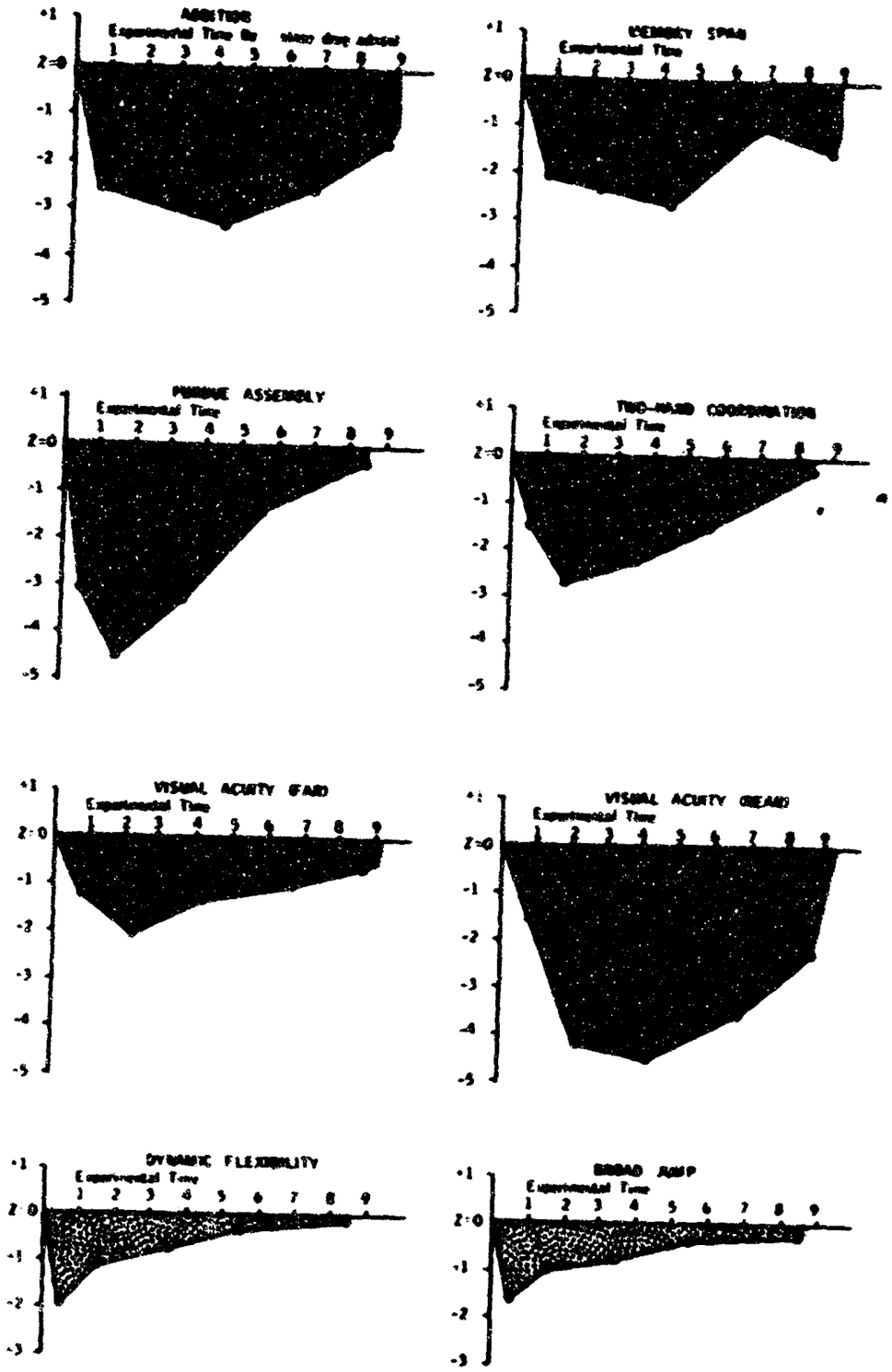

Figure 107. Comparative Time Histories of Scopolamine Effects on Representative Performance Tests

DISCUSSION

Dr. Carr: How many subjects did you use in your tests?

Dr. Elkin: In the first study we used only 4 placebo and 11 drug subjects. In the second study, we used only five. We are starting out with small numbers in order to develop our measures. These are medical volunteers supplied through Psychopharmacology Branch.

Dr. Carr: Do you have any feeling for the reaction of the tactical military man to this type of test?

Dr. Elkin: They seem to enjoy some of the tests. They find some boring after a little while. We haven't had too many questions such as, "What does this mean in terms of military performance?" We haven't had any opinions from the volunteers, the test subjects themselves. The military people we talked to down at the CBR Agency asked us what the value of this is in terms of real military performance, and we tried to explain it to them.

THE BASELINE CONCEPT AS USED IN ASSESSING THE EFFECTS OF DRUGS ON HUMAN PERFORMANCE

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Much research at Edgewood Arsenal with psychochemical agents has employed a concept of baseline performance as a norm to assess the degradation of human performance associated with certain of these agents on various psychological tests. A single baseline value for a particular test has typically been calculated for an individual subject. An average of several pre-drug test scores has often been employed as this baseline value. Comparisons have then been made of subjects' baseline values with their performances at varying time intervals after receiving a drug. Most commonly, the subjects' postdrug test performances have been expressed as either percentages of their baseline values or as standard scores of some type.

The procedure just described for deriving baseline estimates may be adequate for those types of tests on which performance improves only minimally with repeated testing. However, for tests on which performance improves noticeably with repeated experience, a procedure which yields a single baseline value is inappropriate because the possible contribution of learning to subsequent test performance is not taken into consideration. Since the possibility that learning may occurr during repetitive experience can seldom be excluded entirely, the contribution of learning should be estimated in the derivation of baseline values.

Three Baseline-Derivation Methods.

Because test performance may change continually as a result of learning, a variable or dynamic baseline may be required. Such a dynamic baseline should represent the expected levels of performance that would be attained by subjects if they were given additional practice on a test while not under the effects of a drug. The major problem to be solved, therefore, is that of determining the most appropriate estimates of the subjects' expected levels of future performance. Three methods of obtaining such estimates are presented for consideration.

Method 1.

Some subjects may be given a placebo while others are given a drug, then the performances of the placebo and drugged subjects may be compared on postdrug test sessions. The average performances of the placebo

subjects, tested at specified intervals after administration of the placebo, can be taken as baseline values to which the average performances of the drugged subjects, tested at similar intervals after administration of the drug, may be compared.

Data obtained by this method may be analyzed appropriately by the powerful techniques of analysis of variance. One such technique is described by Winer* for a two-factor factorial design. Drug versus placebo conditions may be regarded as two levels of a first factor, and a series of test sessions may be regarded as multiple levels of a second factor. A different group of subjects is nested under each of the two levels (drug or placebo) of the first factor, and repeated measures are taken over all levels of the second factor (test session). Relatively powerful and unambiguous tests for statistical significance of differences may be made on all the comparisons of experimental treatments that are of interest to the experimenter.

Although this method provides excellent experimental controls, it has some disadvantages. Each subject cannot serve as his own control, since different groups of subjects are assigned to the placebo and drug conditions. Therefore, comparisons of these two conditions are "between-subjects" effects.** Consequently, individual differences among subjects are completely confounded with some of the experimental treatment effects. This difficulty may be partially alleviated by assigning subjects matched on the basis of their predrug test performances to the placebo and drug conditions. Alternatively, if subjects are randomly assigned to placebo and drug conditions, the result should, on the average, be matched groups of subjects. Regardless of the manner in which subjects are assigned to treatment conditions, individual differences will still be confounded with some of the treatment effects. Another disadvantage of this method is that a large number of subjects should be used, particularly when subjects are assigned to groups randomly. If a large number of subjects is not available or if the medical support required for the experiment is extensive, then this method may not be feasible.

Method 2.

Each subject may be tested and retested until his performance has approached an asymptotic level; then an estimate of the asymptote can be used as a baseline value to which subsequent postdrug test scores may be compared.

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* Winer, B. J. Statistical Principles in Experimental Design. McGraw-Hill Book Company, Inc., New York, New York. 1962.

** Winer, B. J. Op. cit.

An average of the last several test scores in a series of predrug test sessions during which the subject's performance appears to have reached a stable level can be taken as an estimate of his asymptotic level.

This method has the major advantage of permitting each subject to serve as his own control. Comparisons of a subject's baseline estimate with his postdrug test scores are "within-subjects" effects.* Drug effects and individual differences in initial ability among subjects are not confounded. It is possible that satisfactory data can be obtained with a smaller number of subjects by this method than by the first method. Practical circumstances may make this method more feasible than the first.

This method also has its disadvantages. The number of predrug practice sessions required for a subject's performance to reach a stable level may be prohibitively large. Also, it may be untenable to assume that a stable level of performance is necessarily a final asymptotic level. The possibility exists that a curve of performance versus time may be characterized by "plateau" effects. Another disadvantage of this method is that the number of practice sessions required for performance to reach a stable level will vary among subjects. That all subjects will have received equivalent predrug experience cannot be assured; thus, another source of between-subjects variation may be introduced into the data.

Method 3.

Each subject's performance during postdrug test sessions may be predicted statistically from a "best-fitting" function of performance versus time derived from a series of predrug test scores by means of a curve-fitting technique then, each subject can have a variable baseline with a predicted level of potential performance under nondrug conditions to which his actual performance during each postdrug test session may be compared. Any of several functions may possibly provide satisfactory descriptions for a set of data. A Gompertz function, as described by Lewis,** may be particularly suitable because such a function can easily be rationalized as a type of learning function. A Gompertz function is a double exponential curve having the following general form:

$$Y = vg^{h^x}$$

* Winer, B. J. Op. cit.

** Lewis, D. Quanititative Methods in Psychology. McGraw-Hill Book Company, Inc., New York, New York. 1965.

where Y represents level of performance, x represents time, and v, g, and h are constants. The constants may be rationalized as follows: v represents the asymptotic level of performance that may be attained by a subject; g represents the initial ability level of a subject; and h represents that rate at which the performance of a subject improved over time. Procedures for fitting a function of this type to a set of data have been described. *

This is perhaps the most mathematically sophisticated of the three methods. It provides a dynamic baseline in which the contribution of learning is represented in a theoretical function. From this function, a predicted level of performance can be calculated for each postdrug test session. Like the second method, this method allows each subject to serve as his own control because the subject's postdrug levels of performance may be compared with his own predicted levels of potential performance. Unlike the second method, this method need not allow the occurrence of situations in which subjects may be given different numbers of predrug practice sessions in order to approach an asymptotic level; all subjects can be given the same number of predrug test sessions. Thus, the amount of predrug experience can be held constant over all subjects. The major comparisons of interest to the experimenter are within-subject effects.

This method is not without its disadvantages. It must be assumed that the proper type of function has been fitted to the data and that sufficiently accurate predictions of expected levels of performance are possible. The proportion of error variation in the data may be so great as to make accurate prediction impossible. In order to increase the accuracy of prediction, it may be necessary to give the subjects a large number of predrug test sessions, which may not be practical. Extrapolation from a curve is always a risky procedure. Finally, the computational effort involved in curve-fitting can become quite laborious. High-speed computational services with rapidly available output are required for this method to be maximally useful.

Illustrations.

Data from Study I and Study II by Fleishman and coworkers** of the American Institutes for Research will be used to illustrate each of the previously described methods numerically. In both of these studies, medical

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* Lewis, D. Op. cit.

** Fleishman, E. A., Elkin, E. H., Van Cott, H. P., Freedle, R. O., and Horowitz, H. Contract DA18-035-AMC-282(A). Effects of Drugs on Human Performance. 1965. To be published.

volunteers at Edgewood Arsenal were tested repeatedly on a variety of performance tests both before and after im injection of either a drug or a placebo. The drugged subjects received 12 μg/kg of scopolamine, and the placebo subjects received normal saline.

In both of these studies, all subjects underwent an orientation session, five predrug baseline test sessions, and five postdrug test sessions. The times in hours after the beginning of the orientation session at which each of the other test sessions began are shown in tables XXVII to XXIX. The im injections were administered at 25.25 hr for Study I and at 24.75 hr for Study II, after the beginning of the orientation session.

Table XXVII. Mean Near-Point Visual Acuity Scores*

Test session No.	Time**	Placebo group score (N = 4)	Drug group score (N = 11)
	A. Predrug		
1	2.5	10.75	10.73
2	4.5	11.25	11.05
3	6.0	10.88	10.82
4	7.5	11.38	10.91
5	24.5	11.12	10.91
	B. Postdrug		
6	26.0	10.88	8.77
7	27.5	10.75	5.05
8	29.5	11.12	5.05
9	31.5	11.25	6.50
10	34.0	10.88	7.77

* Level attained on the orthorator.

** Time after beginning of orientation session.

Table XXVIII. Comparison of Baseline to Postdrug Scores by Method 2: Number Facility Subtest (NF) for One Subject

Test session No.	Time a/	NF score b/	Percent of baseline c/
A. Predrug			
1	2.5	66	–
2	4.5	62	–
3	6.0	64	–
4	7.5	63	–
5	24.5	69	–
B. Postdrug			
6	26.0	38	56
7	27.5	6	9
8	29.5	18	27
9	31.5	32	47
10	34.0	46	68

a/ Time after beginning of orientation session.

b/ Number of correct responses.

c/ Baseline is defined as the mean (67.5) of the two highest predrug scores.

Illustration of Method 1.

This method will be illustrated with data from an orthorator test of visual acuity included in Study I. A total of 15 subjects, of whom 11 received scopolamine and 4 received saline, were tested repeatedly according to the schedule shown in table XXVII. The data chosen for purposes of illustration were the near-point acuity levels attained by the subjects at each of the test sessions. The chosen data were treated as a 2 × 10 factorial design of the type previously discussed under method 1. The 2 levels of the first factor were the placebo and drug conditions; the 10 levels of the second factor were the 10 serial test sessions (5 predrug and 5 postdrug). The mean near-point acuity levels attained by the subjects under each of the 2 × 10 conditions are also shown.

Table XXIX. Comparison of Baseline to Postdrug Scores by Method 3: Two-Hand Coordination for One Subject

Time* (x)	Observed score (Y)	Predicted score (Y')	Percent of baseline** (100 Y/Y')
	min of arc		
	A. Orientation		
0	0.345	0.397	–
	B. Predrug		
2.5	0.357	0.410	–
4.0	0.410	0.424	–
5.25	0.465	0.435	–
6.75	0.521	0.449	–
24.0	0.571	0.594	–
	C. Postdrug		
25.25	0.377	0.603	63
26.25	0.140	0.611	23
28.25	0.174	0.625	28
30.25	0.260	0.640	41
33.25	0.582	0.661	88

* Time after beginning of orientation session.

** Baseline is defined by the following function:

$$Y' = (0.388)^{0.975^x}$$

An unweighted means analysis of variance for the main effects of the drug and placebo on visual acuity was performed first. F-ratios significant beyond the 0.05 level were obtained for each factor and for the interaction of the two factors. This analysis is summarized in table XXX.

Table XXX. Visual Acuity Analysis of Variance: Main Effects

Source	df	MS	F
Between subjects	14	39.70	
Placebo versus drug	1	151.21	4.86*
Subjects within groups	13	31.12	
Within subjects	135	6.94	
Test sessions	9	19.04	7.03**
Placebo versus drug × test sessions	9	17.89	6.61**
Test sessions × subjects within groups	117	2.71	
Total	149	10.02	

* Significant beyond the 0.05 level.

** Significant beyond the 0.01 level.

The F-ratio for placebo versus drug indicates that on the average overall test sessions, the performances of the placebo and drug groups were significantly different beyond the 0.05 level. The F-ratio for test sessions indicates that over both the placebo and drug conditions, there were significant differences in average performance among the test sessions. These differences were significant beyond the 0.01 level. The F-ratio for the placebo versus drug × test sessions interaction indicates that the average performance curves for the placebo and drug groups were significantly different in shape beyond the 0.01 level.

Because of the significant interaction effect, further analysis was required. An analysis of variance was performed on the simple main effects, both with respect to the placebo versus drug conditions and with respect to the test sessions. This analysis is summarized in table XXXI.

Table XXXI. Visual Acuity Analysis of Variance: Simple Main Effects

Source	df	MS	F
Test sessions × placebo versus drug			
Test sessions; placebo group	9	0.30	0.11
Test sessions; drug group	9	36.66	13.54*
Test sessions × subjects within groups	117	2.71	
Placebo versus drug × test session			
Placebo versus drug; session 1	1	0.00	0.00
Placebo versus drug; session 2	1	0.12	0.02
Placebo versus drug; session 3	1	0.01	0.00
Placebo versus drug; session 4	1	0.64	0.11
Placebo versus drug; session 5	1	0.14	0.02
Placebo versus drug; session 6	1	12.96	2.34
Placebo versus drug; session 7	1	95.45	17.20*
Placebo versus drug; session 8	1	108.42	18.48*
Placebo versus drug; session 9	1	66.18	11.92*
Placebo versus drug; session 10	1	28.23	5.09*
Within cell	130	5.55	

* Significant beyond the 0.01 level.

** Significant beyond the 0.05 level.

For the simple main effect of test sessions, the F-ratio for the placebo group was not significant at the 0.05 level; the F-ratio for the drug group was significant beyond the 0.01 level. The F-ratio for test sessions for the placebo group indicates that there were no significant differences in the average performance among the 10 test sessions by the placebo subjects; that is, there was no placebo effect. The F-ratio for test sessions for the drug group indicates that there were differences in average performances. Assuming that all other relevant variables were held constant, there was a significant drug effect.

For the simple main effects of the placebo versus drug conditions, the F-ratios were not significant for sessions 1 through 5 (the predrug sessions) or for session 6 (the first postdrug session) at the 0.05 level; the F-ratios for sessions 7 through 10 (the remaining postdrug sessions) were all significant beyond the 0.05 level. The nonsignificant F-ratios for the placebo versus drug conditions for sessions 1 through 5 indicate that there were no significant differences in average performance between the placebo and drug groups during the predrug test sessions, and the two groups were matched. The F-ratio for the placebo versus drug conditions for session 6 indicates that by the beginning of that session a significant difference in average performance had not yet appeared. The F-ratios for the placebo versus drug conditions for sessions 7 through 10 indicate that there were differences in average performance between the placebo and drug groups, significant beyond the 0.01 level for sessions 7 through 9 and significant beyond the 0.05 level for session 10.

In brief summary, it appeared that 12 μg/kg of scopolamine administered im produced a significant loss in near-point visual acuity, which could be measured at 2.25 hr after administration of the drug, and perhaps earlier. This loss of acuity continued until at least 8.75 hr after administration of the drug, although the effect of the drug became less significant at that time.

Illustration of Method 2.

This method will be illustrated with data from the Number Facility subtest (NF) developed by Moran and Mefferd* and used in Study I. The NF scores for one subject who received scopolamine will be used. This subject's NF scores for 10 test sessions (5 predrug and 5 postdrug) appear in table XXVIII.

The subject had been tested on NF many times previously. It was assumed that his performance on the five predrug sessions had approached an asymptotic level and that the major source of variability among these predrug scores was a lack of form equivalence among the various forms of the NF test. It was decided arbitrarily to define the subject's baseline level as the mean (67.5) of his two highest predrug scores. For purposes of comparison with the subject's baseline, his five postdrug scores were converted to percentages of the baseline level. These percentages revealed the pattern of degradation in NF performance following administration of the drug. The maximum degradation appeared during test session 7 with gradual recovery toward the baseline level thereafter. However, the subject's performance had not yet returned to baseline level when testing was terminated with session 10.

* Moran, L. J., and Mefferd, R. B., Jr. Repetitive Psychometric Measures. Psychol. Rept. 5, 269-275 (1959).

The example just presented was a simple descriptive method for summarizing the effects of a drug on the performance of a single subject. However, the method could easily be extended to groups of subjects by calculating group mean baseline levels for comparison with group mean performance scores. Also, no attempts were made to determine the statistical significance of the drug effects. If mean baseline levels and mean performance scores were compared for a group of subjects, then the significance of drug effects could readily be evaluated by standard statistical procedures.

Illustration of Method 3.

This method will be illustrated with data from a test of two-hand coordination included in Study II. The "time-on-target" scores for one subject who received scopolamine will be used for the illustration. The subject's scores for 11 test sessions (1 orientation, 5 predrug, and 5 postdrug sessions) appear in table XXIX.

A Gompertz function of the type previously mentioned was fitted to the data in table XXIX. The constants g and h were estimated by the procedures described by Lewis.* The constant v was set equal to 1 min, which was the maximum time-on-target score allowed by the testing procedure.

The resulting function was as follows:

$$Y' = (0.388)^{0.975^x}$$

Y' represented the predicted score in minutes, and x represented the time in hours after the beginning of the orientation session. From this function, the predicted scores were calculated for all test sessions.

As a check on the accuracy of fit of the Gompertz function, the observed scores (Y) and the predicted scores (Y') were compared. The mean of the absolute values of the residuals (Y - Y') over the orientation session and the five predrug sessions was 0.0407. The variation (sum of the squares) of the residuals over these same sessions was 0.0122. Because both the mean of the absolute values and the variation of the residuals were relatively small, the Gompertz function was arbitrarily considered a sufficiently accurate fit to the data.

In order to estimate the predictive validity of the Gompertz function, the Pearson correlation coefficient between the observed values (Y) and the predicted values (Y') over the orientation and the five predrug sessions

* Lewis, D. Op. cit.

was calculated; this correlation was 0.841. Although a higher correlation would have been desirable, the value 0.841 was arbitrarily accepted as an indication that the Gompertz function should have sufficiently high predictive validity for practical use. The predicted scores (Y') for the five postdrug test sessions were taken as baseline values for comparison with the observed scores (Y) for these same sessions.

For purposes of easy comparison with the subject's predicted baseline, his five observed postdrug scores were converted to percentages of the corresponding baseline values. These percentages revealed the pattern of degradation in two-hand coordination following administration of the drug. The maximum degradation occurred during the second and third postdrug test sessions between 0.50 and 1.50 hr postdrug, with gradual recovery toward the baseline levels thereafter. However, the subject's performance had not yet returned to 100% of baseline by the last test session, which began 8.5 hr postdrug. It might have been expected that the subject's performance would not have approached 100% of baseline until many hours after the drug was administered, since the predicted baseline values were gradually increasing to a maximum possible score of 1 min time-on-target.

Like the example presented for method 2, the example just presented described the effects of a drug on the performance of a single subject. However, there is no reason why this method could not be extended in a similar manner to groups of subjects.

Final Considerations.

The most appropriate method for arriving at baseline values may be determined empirically for various performance tests. It should be possible to compare the results of all three methods for several sets of data. The most appropriate method may not always be the same but may depend upon the specific tests being used.

In selecting the most appropriate baseline technique to be used, one final question should be considered. Is a baseline value for an individual subject really needed, or are group baseline values required? The answer to this question depends upon the goals of a particular study. If primary concern is with the performance of individual subjects, as in a clinical setting, then baseline values for individual subjects are desirable in order to provide the experimenter with criteria for evaluating recovery from drug effects. However, if primary concern is with the average performance of groups of

men, as in a combat situation involving large numbers of men and where casualty estimates are required, then there is only limited need for individual baselines. The simplest experimental procedure would then involve comparing the mean performance of a group of placebo subjects with one or more experimental groups of drugged subjects.

In conclusion, it appears that there is no single procedure for arriving at baseline values that will be generally appropriate, but a concept of baseline as a single value is certainly too limited.

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EXTRAPOLATION: APPLICATION OF THE RESULTS OF ANIMAL EXPERIMENTATION TO MAN

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Introduction.

Within recent years, clinical investigation has contributed largely to elucidating the problems of psychology. In many instances, clinical research not only revealed the true nature of a psychological concept, but cast a light into some dark corners of this science. Psychology, in turn, by animal experimentation, contributed immensely to the solution of many clinical problems. The rapid progress and prodigious success of psychological concepts made our pace such that continuous readjustments became necessary from year to year.

Most psychological problems can be approached only by animal experimentation, because animals furnish a valuable source for studying the mechanism of action of drugs.* On the other hand, many problems can be elucidated only by observations of man. "The normal human subject as an experimental animal possesses unique advantages for many types of investigation."** The application of the results of animal experimentation to man, however, is one of the unsolved and most pressing problems of our time.

Extrapolation is by no means a private problem of psychopharmacologists or psychologists. It was a headache for the early investigators in immunology, in the evaluation of toxic and infectious agents, in irradiation, in the program of anticancer drugs, and in many other circumstances as well. The contribution of extrapolation to the development of immunological processes and to the evaluation of some biochemical and toxic agents is well-known. Jennerian vaccination and Pasteur's antirabies vaccine

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* Himwich, H. E. Stimulants. p 356. In: The Effect of Pharmacologic Agents on the Nervous System. Braceland, F. J., ed. Williams & Wilkins Company, Baltimore, Maryland. 1959.

** Best, C. H., and Taylor, N. B. The Physiological Basis of Medical Practice. Williams & Wilkins Company, Baltimore, Maryland. 1961.

illustrate this point. "Extrapolation is nevertheless a major problem when our goal is the identification and development of drugs for their clinical usefulness in man."*

Although there is no solid basis for extrapolation from experimental animal evidence to human populations, the evaluation of the variables "drug," "animal," and "human" by statistical and experimental design techniques must be meticulously followed for the results of the experiment to be trusted.** It is seldom possible to predict, with confidence, whether a compound that produces lesions in experimental animals will produce similar lesions in other species.†

The fruits of the labor of thousands of scientists in laboratories, the mountains of data amassed by the investigators, and the millions of words spawned about various agents all must be beamed to a single spot—to the brain of the individual scientist or physician,** who must decide whether the results can be extrapolated from animal to man.

Certain problems that are inherent in research related to extrapolation from animals to man are implicit in the discussion that follows, and there are many pitfalls.

Analogies and Homologies.

Science is frequently enriched through analogies; some are satisfactory, some fail us.†† If ontogenic evolution of an individual is intimately related to phylogenesis, as claimed by some anthropologists, some behavioral analogies might conceivably exist between man and animals.

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* Russell, R. W. Relevance of Behavioral Effects of Drugs in Animals to Their Effects in Man. pp 410-418. In: Animal Behavior and Drug Action. Ciba Symposium. Little, Brown and Company, Boston, Massachusetts. 1964.

** Chessick, R. D., and McFarland, R. L. Problems in Psychopharmacological Research. J. A. M. A. 185(4), 237 (1963).

† Paget, G. E. The Morphological Evaluation of Toxic Action. In: Evaluation of Drug Toxicity. Walpole, A. L., and Spinks, A., eds. Little, Brown and Company, Boston, Massachusetts. 1958.

†† Eiseley, L. The Freedom of the Juggernaut. In: Mayo Centennial Symposium: Mirror to Man. Man's Adaptation to His Expanding Environment. Mayo Clin. Proc. 40, 7 (1965).

Although man is the highest form in the evolutionary scale of life and the highest form of life on this planet,* the brain is conceivably a common site of feeling, storage, and external exchanges in all species.

Behavioral patterns center around homologies and analogies, which constitute the the theoretical aspects of extrapolation. Russell,** in 1951, described homologous as being alike in origin and fundamental structure and analogous as being alike in form but different in origin. The role played by analogy or homology, or both, in behavioral patterns (listed below) was also discussed by Dews.† He stated that superficially similar patterns may be produced, but the effect of drugs on these analogous behavioral patterns may be quite different.

1. Predictive validity
2. Concurrent validity
3. Reliability of measuring instruments
4. Selection of behavior patterns to be measured
5. Identification of drugs with new behavioral modes of action
6. Evaluation of success in predicting

In 1964 Russell maintained that "from a theoretical point of view we would expect the accuracy of prediction or extrapolation from one animal species to another to be affected by the extent to which the behavior patterns involved are homologous or merely analogous."

In predicting drug effects from animals to man, one assumes that animals are organized in a manner sufficiently similar to man so that their responses to drugs are also similar.†† Authors do not always agree with this

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* Effendi, Shoghi. Baha'u'llah. The Hidden Words. Hazell, Watson, and Viney, Ltd., London, England. 1933.

** Russell, R. W. The Comparative Study of Behavior. H. K. Lewis & Company, Ltd., London, England. 1951.

† Dews, P. B. Modification by Drugs of Performance on Simple Schedules of Positive Reinforcement. Ann. N.Y. Acad. Sci. 65, 268 (1956).

†† Irwin, S. Prediction of Drug Effects from Animals to Man. pp 269-280. IntAnimal Behavior and Drug Action. Ciba Symposium. Little, Brown and Company, Boston, Massachusetts. 1964.

concept. Bradley,* for instance, is cautious in saying that "we must not attempt to draw too close an anology between abnormal behavioral states in animals which have been induced by experimental procedures and abnormal mental states in man." It is obvious that a gap exists between the effects of drugs in animal experiments (scientific concept) and in clinical usage (medical practice), and no pretense is made here of solving this problem.

In agreement with Russell (1964), this discussion engenders two essential questions that warrant ample discussion:

1. Are similar behavioral patterns in different species homologous or analogous?

2. If not, how can one extrapolate to man the observations of the effects of drugs on behavior in infrahuman species?

Psychology and Behavioral Science: Discussion and Controversial Views.

There has been a steady increase in the number of research procedures and investigations concerning behavioral studies. In recent years, attention has been focused upon the interrelationship of psychology and behavioral study. Behavioral science has exerted a profound influence upon the field of psychology, and psychology has illustrated beautifully some of the problems inherent in behavioral studies. Each has acted as a stimulus, and each has contributed to the other. There is considerable confusion, however, in the interpretation and evaluation of psychological tests; few authors agree on semantics.

The problem of extrapolating or measuring human behavior, or both, in an experimental situation is the fundamental challenge to psychology. There are two extremes in the way this problem is handled. Some investigators prefer to be extremely operational and cautious** and refuse to extrapolate at all from basic behavioristic data, others attempt to reach highly speculative and extremely generalized conclusions.†

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* Bradley, P. B. Methods and Analysis of Drug-Induced Behavior in Animals. pp 11-19. In: Neuropsychopharmacology. Bradley, P. B., Deniker, P., and Radouco-Thomas, C., eds. Elsevier Publishing Company, Amsterdam, the Netherlands. 1959.

** Beecher, H. K. Measurement of Subjective Responses: Quantitative Effects of Drugs. Oxford University Press, London, England. 1959.

† Chessick, R. D., and McFarland, R. L. Problems in Psychopharmacological Research. J. A. M. A. 185(4). 237 (1963).

There is no concensus because we never have sufficient knowledge of all the variables involved in extrapolation. Paget* claims that the safety of a compound for clinical use can never be conclusively demonstrated by animal experimentation. Testing in animals may provide clues to the possible action of a drug, but the results of such testing cannot be extrapolated to man.**

"It is seldom possible to predict with confidence, never with certainty, that a compound which produces the lesions seen in the experimental animal will produce similar lesions in other species, including man."*

Fuller† stated that the analyses of the basic nature of hereditary differences in learning ability—for instance complex tests such as maze running—are unsuitable, since success depends upon so many factors. He further stated that there is, as yet, no good evidence in animals for assuming a general factor of intelligence that operates in all learning situations. Brady†† however stated that the effects of drugs on learning and memory can readily be studied in man as well as in animals.

Zbinden‡ emphasized the great variety of adverse reactions to medicaments and the multiplicity of mechanisms by which toxic drug effects are caused. He further stated that "transition from the animal experiment to human patients is certainly one of the most important steps in the development of a new drug, but it is not a hazardous and dangerous phase as it is sometimes believed to be by people not involved in drug research."

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* Paget, G. E. The Morphological Evaluation of Toxic Action. In: Evaluation of Drug Toxicity. Walpole, A. L. and Spinks, A., eds. Little, Brown and Company, Boston, Massachusetts. 1958.

** Fraser, F. C. Humans Offer Sole Proof of Drug Teratology. J. A. M. A. 185(7) 39 (1963).

† Fuller, J. L. In: The Behavior of Domestic Animals. Hafez, E. S. E., ed. Williams & Wilkins Company, Baltimore, Maryland. 1962.

†† Brady, J. V. Operant Behavior and Operant Conditioning. p 104. In: The Effects of Pharmacological Agents on the Nervous System. Braceland, F. J., ed. Williams & Wilkins Company, Baltimore, Maryland. 1959.

‡ Zbinden, G. The Problem of the Toxicologic Examination of Drugs in Animals and Their Safety in Man. Clin. Pharmacol. Therap. 5, 537 (1964).

The magnitude of drug-induced psychological effects is significantly related to the reactivity of the subject. According to von Felsinger and coworkers,* those subjects who respond atypically to one drug are likely to respond atypically to other drugs. If this statement is correct, one is inclined to believe that if two species respond atypically to one drug, other species, including man, are likely to respond atypically to this drug. Subsequently, the question of extrapolation from animals to man seems considerably simplified: any reactivity observed in animals is likely to occur in man. Unfortunately, in experimental conditions, the situation is entirely different.

In animal experiments, it is generally possible to control, quite strictly, the conditions of the experiment so that only the factor under investigation is varied, whereas in a human population, the interpretation must be made against an infinitely variable background.**

This subject is debated extensively in the literature, and there is no concensus because of innumerable factors and "interfering variables."† The following data, selected from a long list of reported papers, illustrate the major factors influencing extrapolation. These factors are related to the variables "drug," "animal," and "man."

Factors influencing extrapolation related to drug

Experimental conditions and procedures
Doses and routes of administration
Toxicity, lethality, and effectiveness
Tolerance
Side effects
Allergic reaction
Repeated administration
Cumulative and synergistic effects

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* von Felsinger, J. M., Lasagna, L., and Beecher, H. K. Drug-Induced Mood Changes in Man. Personality and Reactions to Drugs. J. A. M. A. 157, 1113-1119 (1955).

** Milier, J. W. The Application of the Results of Experimental Research Work on Animals to Man. Bull. Swiss Acad. Med. Sci. 20, 417 (1964).

† Lehman, H. E. The Place and Purpose of Objective Methods in Psychopharmacology. pp 107-127. In: Uhr, L. M., and Miller, J. G. Drugs and Behavior. John Wiley & Sons, Inc., New York, New York. 1960.

Mechanisms of action
Dose-effect relationship
Neurotropism and vicerotropism
Physiopathologic reaction

Factors influencing extrapolation, related to animal and man

Controllable variables	Uncontrollable variables
Race, species, strain	Genetic and hereditary factors
Sex, age	Reactivity of the subject or individual susceptibility
Experimental conditions and procedures	Endocrinological and neuro-physiological conditions
Dose and route of administration	Metabolic activities
Environmental conditions	Stress and autonomic responses
Economic circumstances	Psychological disturbances
Social status	Adaptability and learning Cooperation and communication
Dietary habits	
Cooperation	

Uncontrollable factors influencing extrapolation and offering no solid basis for comparison

Intelligence
Conscience
Feeling, emotion, etc.
Motivation
Aspiration
Learning ?
Mental activity or status
Intuition, initiation, and skill
Communication

An attempt was made to divide the factors in the first grouping into controllable and uncontrollable variables in the second grouping, but in many instances they overlap. Some of these factors are not only uncontrollable, but they also do not offer any solid basis for comparison. Nonetheless, the behavioral patterns that were summarized previously (Dews)

clearly indicate that the validity of a test depends not only on a pondered experimental design, but also on many other conditions as well.

There is an astonishing variety of scales and measures from which many highly questionable extrapolations have been made. These scales run all the way from how many times a rat climbs a pole to the "recovery of intrauterine experience,"* and the number of permutations and combinations is infinite. According to Fuller,** complex tasks such as maze running are unsuitable, simply because learning ability varies with the basic nature of hereditary differences. Besides, adds this author, success depends upon so many factors; we never have sufficient knowledge of all the variables involved in extrapolation, nor are we aware of the basic reaction from one species to another or from one individual to another.

Brodie† has made a strong statement for this view that "the greatest difficulty in projecting data from animal to man arises from specific differences in biotransformation of the drug." Perhaps I should use an example in order to illustrate this point. The study of amphetamine, for instance, showed that there is marked difference in the metabolism of Dexamphetamine in different species of animals; dogs and rats hydroxylate considerable amounts of the drug; rabbits and guinea pigs, on the other hand, apparently metabolize Dexamphetamine by another pathway.††

The consequence of the above observation is that several gaps exist: namely (a) biotransformation, (b) metabolic activities (figure 108), (c) modes of action, etc., and above all (d) the gap between the scientific concept in laboratory practice and the clinical investigation in the hospital.

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* Chessick, R. D., and McFarland, R. L. Problems in Psychopharmacological Research. J.A.M.A. 185 (4), 237 (1963).

** Fuller, J. L. In: The Behavior of Domestic Animals. Hafez, E. S. E., ed. Williams & Wilkins Company, Baltimore, Maryland. 1962

† Brodie, B. B. Symposium on Clinical Drug Evaluation and Human Pharmacology. VI. Difficulties in Extrapolating Data on Metabolism of Drugs from Animals to Man. Clin. Pharmacol. Therap. 3, 374 (1962).

†† Axelrod, J. Studies on Sympathomimetic Amines. II. The Biotransformation and Physiological Disposition of D-Amphetamine, D-Hydroxyamphetamine, and D-Methylamphetamine. J. Pharmacol. Exptl. Therap. 110, 315 (1954).

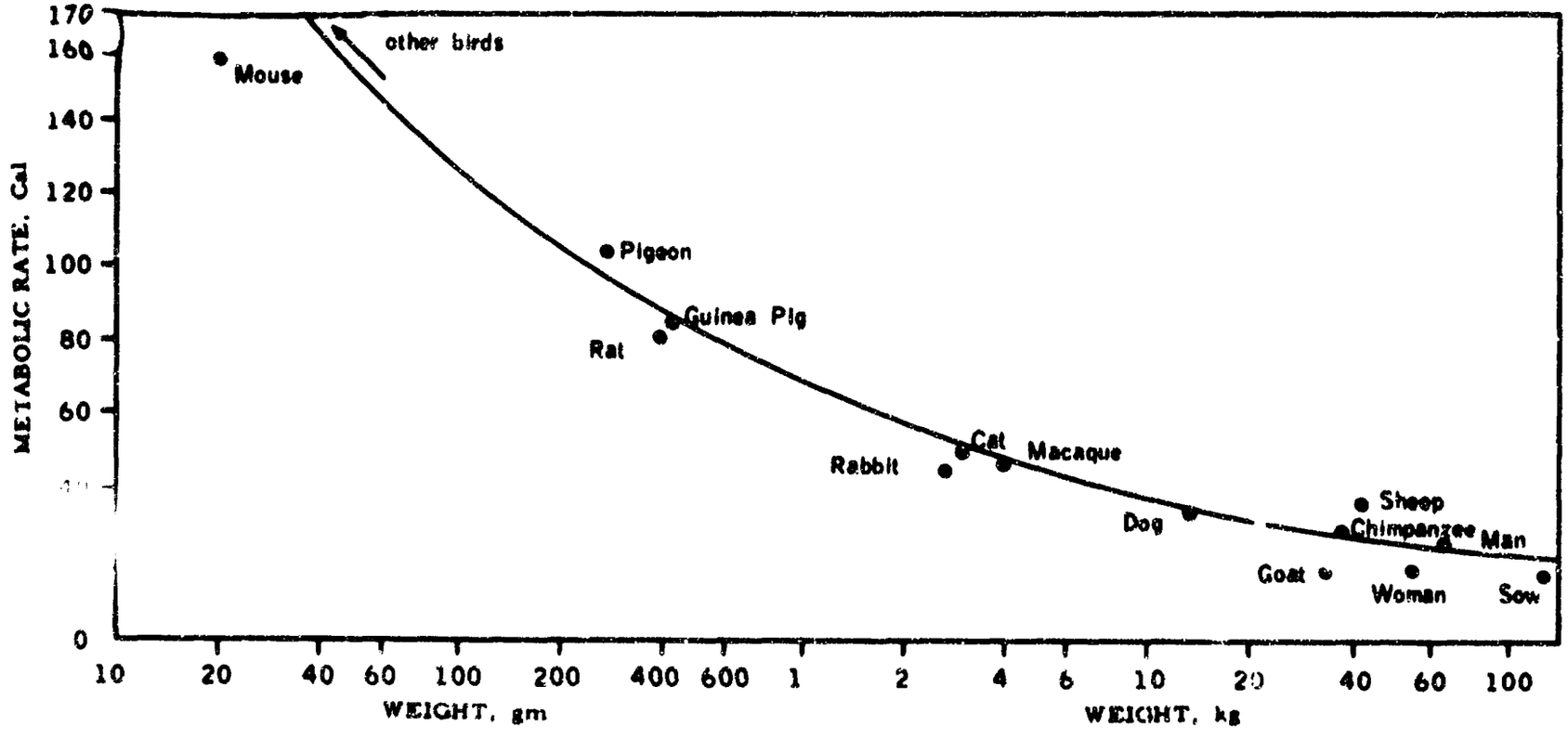

Figure 108. Relationship Between Average Basal Metabolic Rate Per Kilogram Per Day of Different Species

[Benedict. Carnegie Inst. Wash. Publ. No. 503 (1938)]

Experimentation in Man.

The final proof of extrapolation, whether in behavioral studies or evaluation of a new drug, must necessarily come from human experimentation.

The oldest experimental work in human subjects goes back to Persia, where "it was the practice for the king to hand over condemned criminals for experimental purposes in science."*

Although Galen is considered the founder of experimental physiology and the father of medical experimentation, the first controlled experiments in animals and in man were performed by Harvey in 1628. Thus, human experimentation remained in a dormant status and was almost forgotten for about 14 centuries. Isolated or multiple human experimentations were accomplished for various experimental purposes during the last three centuries. Nevertheless, Ladimer** stated that "so far, planned and directed medical research on human beings has not been tested." "Paradoxically enough, in the last century at least, those who experiment in man have been freer of attack than those who carry out animal experimentation. . . Man as the essential final test site has come into adequate prominence only in recent decades."*

According to Fraser,† the final proof of whether a drug is likely to be harmful to man must be sought in man. Here, we rely on animal experimentation, here we fail. Nevertheless, there are favorable circumstances in which the tissues from animals dosed with a potential drug may indeed be of great intrinsic interest. This kind of experiment is intended to assist in arriving at a decision as to whether a compound should be given to man. "While prior experimentation in animals is absolutely necessary when possible, the crucial study of new techniques and agents must be carried out in man."*

Summary.

The problem of extrapolating or measuring human behavior, or both, in an experimental situation is a fundamental challenge to psychology. The rapid progress and prodigious success of psychology in recent years

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* Beecher, H. K. Experimentation in Man. Charles C. Thomas, Publisher, Springfield Illinois. 1958.

** Ladimer, I. Human Experimentation: Medicolegal Aspects. New Engl. J. Med. 257. 18 (1957).

† Fraser, F. C. Humans Offer Sole Proof of Drug Teratology. J. A. M. A. 185(7). 39 (1963).

make extrapolation a problem of utmost urgency. The application of the results of animal experimentation to man is not a private problem of psychopharmacologists: it is equally shared by other scientists in a number of fields. Although there is no solid basis for extrapolation from experimental evidence to human populations, the evaluation of the variables related to drug, animal, and human is of prime importance.

The factors influencing extrapolation are innumerable. Often, the results are extrapolated either by analogy or similitude, or by physiopathologic evaluation. There is considerable confusion, however, in the interpretation and evaluation of psychological tests and behavioral work in general. We never have sufficient knowledge of all the variables involved in extrapolation, nor are we aware of the reaction from one species to another. Nevertheless we rely on animal experimentation as a last resort.

DISCUSSION

Dr. Sim: I am going to ask Dr. Lilly to make a few comments because I know he has to leave, and then we will have open discussion.

Dr. Lilly (Communication Research Institute): I am very gratified to see this very thorough and extensive comparison. My particular interest in research is exactly in this area of the problem of carrying data from animal work to human work and also in the reverse direction. I just want to put in one additional factor that I think is important. (I am sure Dr. Berdis thought of this and that he has mentioned it implicitly in his paper.) With man, one is sometimes very much limited by some very stringent legal and social considerations. One can do certain things with animals that one couldn't possibly do with man at the present time. We are in this position with the dolphins. We do work of the type that one could not do with man without getting into severe moral, legal, or ethical problems. In other words, we can for example obtain brains under ideal conditions for neuroanatomical studies. I don't know how long this situation will last. At the present time we are still able to use animals who have brains as large and larger than ours and have an intelligence (even though alien and different from ours) that is probably comparable with ours in their own medium, the sea. I don't see any other way of interpreting the data we have accumulated, to date, on structure and on function in this particular species. The extrapolations to man from dolphins are very difficult, and the reverse direction is very difficult also. We do have one exchange channel with this particular species that is lacking with the other species, namely, the beginnings of a vocal-communication channel. The complexity of communication between dolphins is great. (We can't go into that at great length here.) Their willingness to attempt our communication mode (as I showed last night) in the vocal sphere as well as in

the behavioral sphere allows us another channel. We hope to develop this channel over the next 10 yr to the point where it will be a useful channel to operate with experimentally. That same channel is lacking with every other animal. We have it with man; this makes man so valuable. We can get subjective reports from informed observers about drug effects. We gain insights by means of the verbal exchange with the subject that we can't get from any other animal. I think this is an important point. There are objective ways of arriving at certain other kinds of data directly from the subjective data. With some of these drugs, such as LSD-25 this is a very important route to knowledge.

Dr. Elkes (Johns Hopkins Hospital): I, too, would like to echo what Dr. Lilly has just said and to thank Dr. Berdjis for a very thoughtful and convincing plea for the need for human experiment. He really raised questions that are fundamental to psychopharmacology, namely, the relation of subjective to objective observation, the relation of somatic to the symbolic transaction the limitations of language, the need for new languages, and the need for training observers in communication in these highly subjective states.

He also raised, by inference, Roger Williams old genotropic concept of chemical individuality in terms of the handling of drugs, which is a state of affairs that both plagues and provokes much that is new in human psychopharmacology. I think the importance he attached to the difficulty of carrying over behavioral observation to subjective observations cannot be overstated Certain behavioral tasks (many having been developed by industry) are measurable and, in this sense, satisfying and safe. But in other areas (in the more subtle areas with which one is concerned in psychiatry and, I presume, areas that are also the concern of this center) one would have to resort much more to subjective reports, again may I reiterate what Dr. Lilly said in a different context: the training of subjects in subjective reporting. One has to develop a kind of mental deep-sea-diving school that employs special techniques and trains people to look for certain things that they have a chance to see for a few hours at a time and to report accurately on these to themselves and to others. This really means that one has to develop means for perceiving many phenomena and answering many questions all at once and condensing the ideas to convey meaning to somebody who is outside the phenomena In fact I think we are probably talking about two fundamental ways in which we process information, namely, asking many questions concurrently and then putting them in sequence—a sort of starting "in parallel" and repeating "in series." As Dr. Lilly puts it, when the noise level is high (or as I put it, selective inhibition is low), these questions crowd in at tremendous speed. The verbal readout is a very slow and clumsy way of conveying information. This, however, is all we have in man. So, really, what we have to think through is new kinds of shorthand, notation, and symbols.

We may need new languages that may ultimately develop into new kinds of mathematical languages. The sooner we encourage mathematical colleagues to look at these phenomena and develop a form of notation for them, the sooner, I think, we will have the tools that scientists always need to develop a new field. The history of science is really the history of the languages of sciences.

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CLOSING REMARKS

Dr. Van M. Sim

After the presentation by LTC Berdjis and comments by Dr. Dews yesterday and Dr. Lilly and Dr. Elkes this afternoon, there is a storehouse of ideas for thought but little time for further discussion. This meeting, its presentations and discussions, clearly indicated that we have learned a great deal in the 7-yr interval between this conference and the first one held here on the same subject. One of the most satisfying findings is that we are beginning to understand one another. During the first meeting, the psychologists and psychiatrists were not only unable to agree on testing between disciplines, but were not in any agreement within their own disciplines. The interchange of information between these disciplines, at this meeting, has been excellent. We are far from speaking a common scientific language, but, like Dr. Lilly's dolphins, we are learning the new language slowly.

The purpose of animal studies is really twofold. First and foremost, for practical purposes, we hope to utilize this information for better prediction and insight as to what may be expected of man. We are also interested in the mechanisms by which animals react to and stabilize to specific and specialized environments. Previously, most of the correlations of animal drug studies had to be done after the fact—after man received the drug. Then, observations made were rechecked with previous animal studies to see if there was any information that had been overlooked or not emphasized. Now we appear to be making headway toward using the animal data for predictability of reactions in man.

I hope our guests benefited as much from this conference as I know we have. Thank you all for attending.

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13. ABSTRACT
(U) This is a report of the major psychopharmacology subjects under investigation within the Medical Research Laboratory, both on the premises and under contract. The compilation consists of papers presented at a conference on behavioral sciences that was divided into two parts: animal performance and human performance. The subjects covered include techniques of testing, philosophy of testing, and results of drug evaluation.

14. KEYWORDS

Behavioral science	Hallucinogenic drugs
Animal performance	Psychometric measures
Human performance	Psychochemicals
Psychopharmacology	Drug effects
Psychology	Testing
Electrocortical activity	Conditioning
Anticholinergic agents	Learning
Conference	Motivation
Proceedings	Extrapolation
Contractors' conference	Discussion
Brain activity	LSD-25
Dose-response studies	Number Facility test

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