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THE EFFECT OF INJECTED MONOMETHYLHYDRAZINE ON PRIMATE PERFORMANCE

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HERBERT H. REYNOLDS, MAJOR, USAF

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Foreword

This experimentation, which began on 26 October 1964 and was completed on 29 October 1964, was performed jointly by members of the Aeromedical Research Laboratory, Holloman Air Force Base, New Mexico, and the Aerospace Medical Research Laboratories, Wright-Patterson Air Force Base, Ohio. The research was conducted in support of Project 6302, "Toxic Hazards of Propellants and Materials," Task 630202, "Pharmacology-Biochemistry," for the Toxic Hazards Branch, Physiology Division, Biomedical Laboratory, Aerospace Medical Research Laboratories.

This technical report has been reviewed and approved.

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Abstract

Nine macaque monkeys were injected on two occasions with either 2.5 or 5.0 mg/kg of monomethylhydrazine (MMH). Operant task performance was measured, and clinical symptoms were noted. No difference in performance resulted from the two dosage levels, but there was a greater incidence of clinical symptoms in those subjects exposed to 5.0 mg/kg. In over half the cases a performance decrement preceded clinical symptoms, but in no instance did clinical symptoms precede a performance decrement. In 3/18 cases clinical symptoms did appear without a performance decrement, but in 4/18 cases a performance decrement occurred in the absence of clinical symptoms. When initial 2.5 or 5.0 mg/kg injections are made one might predict that performance decrements will occur between 1 and 2 hours and clinical symptoms between 2 and 2.5 hours in about half the subjects. A second exposure might be expected to produce performance decrements between 1 and 2 hours and clinical symptoms between 2 and 3 hours in the majority of subjects. If a subject is influenced by MMH, clinical symptoms will likely disappear between 3 and 9 hours following injection, and performance should return to baseline level between 3 and 30 hours.

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SECTION I.

Introduction

Over the years considerable experimental data have been gathered and published concerning the hydrazines. Most of the experiments have dealt with the toxicology-pharmacology and associated physiology-biochemistry-pathology of 1, 1-dimethylhydrazine (UDMH), 1, 2-dimethylhydrazine (SDMH), monomethylhydrazine (MMH) and hydrazine per se. As early as 1956 Witkin (ref 1) studied the acute toxicity of hydrazine, UDMH, SDMH, and MMH. He demonstrated that when the intravenous, intraperitoneal, and oral routes of administration were compared there was no difference in the toxicity in any of the compounds. Witkin and Weatherby had previously studied the pharmacological effects of MMH (ref 2), Back and Thomas provided the toxicological-pharmacological information on UDMH (ref 3), and Krop (ref 4) published on the toxicity of hydrazine, citing the pharmacological investigations of Thienes and Roth.

It was not until 1961 that the central nervous system effects of the hydrazines were subjected to study. In that year, and throughout 1962, Reynolds and Back (ref 5) investigated the overt behavioral changes resulting from injections of UDMH. *Macaca irus* were used as subjects, and further research on UDMH followed in 1963 (ref 6), suggesting that 30 mg/kg of UDMH administered intraperitoneally has a significant effect on performance, especially as the tasks become more complex and as they are presented in quick succession. It was further demonstrated that performance decrements occurred from 1.5 to 2 hours following injection, but that complete recovery to a baseline performance level might be expected by the ninth hour.

Since the earlier study of UDMH via performance media had proven of value, as well as the later study of decaborane (ref 7), it was decided that MMH should be subjected to similar study at minimal dosage levels. Thus, the purpose of this investigation was to evaluate the effects of low levels of MMH on primate performance.

SECTION II.

Method

Subjects

The subjects were nine macaque monkeys weighing between 3.1 and 6.8 kg. All monkeys had been trained on the performance tasks to various levels of proficiency over a period of several months. The reason for lacking complete asymptotic behavior in each instance was due to Mogenson (ref 8) and Singh's (ref 9) findings that more highly trained responses are less susceptible



Figure 1. Performance Chambers and Master Programming Console

to the deleterious effects of depressant agents and that there is increasing susceptibility at lower habit strength levels. It thus appeared wise to train the subjects to differential levels to more accurately evaluate the effect of MMH.

Apparatus

The apparatus was composed of two major groups of items: individual performance chambers, especially designed for psycho-pharmacological research, and a master electronic console for programming the tasks for the individual chambers (fig. 1). The inside dimensions of the work area

of each chamber were 24 by 24 by 26 inches, and the performance panel measured 13.5 by 14 inches. The performance panel included two red stimulus lights and two response levers, one set mounted on each side and slightly below a stimulus response key (SRK) from which a low intensity visual stimulus was presented.

Performance Schedule

The schedule was of 15 minutes duration and was comprised of two integrated tasks. At the onset of the red stimulus lights above the left and right levers, the subject had to press each lever at least once every 15 seconds for the full 15 minutes. If the monkey failed to respond as often as required, it received a 3-8 milliamp shock at 300-650 VAC to the soles of its feet. Since the subject diligently presses the lever to insure against shock, this task has been labeled continuous avoidance (CA) as distinguished from the Sidman avoidance schedule in which a shock-shock interval is employed. The requirement that the subject continually press both levers has further altered the Sidman schedule; thus the designation Dual CA has been given to the task just described. Throughout the 15-minute work period the visual stimulus from the SRK was presented at 0.50, 1.25, 3.00, 4.50, 5.25, 5.50, 7.5, 9.00, 10.00, 12.00, 12.75, and 14.00 minutes. The subject was required to turn off the stimulus by pressing the response key within 2 seconds (visual reaction time - VRT). Failure to respond within the allotted time resulted in a shock with the same parameters as for Dual CA.

Procedure

Subjects were rank-ordered on the performance tasks. The sum of the ranks was then calculated and two groups were formed on the basis of the sum of the ranks. After being restrained in squeeze cages, the subjects were injected ip with either 2.5 or 5.0 mg MMH per kg of body weight. The MMH was prepared in distilled water at 50 mg per cc or 0.57 cc MMH diluted to a total volume of 10 cc with distilled water. The dosages of MMH were selected on the basis of Back's previous toxicological-physiological research which indicated that these were below the lethal dosage level but probably high enough to elicit changes in overt behavior.

All subjects were injected between 0845 and 0910, and the first 15-minute performance program began at 0930. The program was presented on the half hour, i.e., 1030, 1130, etc., thereafter for a total of eight programs for each day throughout the experiment. A new solution of MMH was prepared for the second exposure and injections were accomplished between 0745 and 0800, 48 hours following the initial exposure. The performance program was then presented beginning at 0830.

SECTION III.

Results

Objective Data

The performance data are presented graphically for each subject in Figures 2-10, along with the upper and lower baseline limits. Statistically significant decrements in performance are reported in Table I. A comparison of the significant performance decrements experienced by the two groups was accomplished by the Wilcoxon matched-pairs signed-ranks test (ref 10), using the

TABLE I.
Summary of Statistically Significant Decrements*
 $p^* < .01$ (one-tailed test)

Subject No.	Continuous Avoidance (CA) Left Lever Exposure		Continuous Avoidance (CA) Right Lever Exposure		Ratio of Left Lever (CA) to Right Lever (CA) Exposure		Visual Reaction Time Exposure	
	1	2	1	2	1	2	1	2
<i>Group I (2.5 mg/kg of MMH)</i>								
2	X	X	X			X		X
9	X			X	X	X		X
58				X		X		
60								
Sub-Total	2	1	1	2	1	3	0	2
<i>Group II (5.0 mg/kg of MMH)</i>								
7	X	X	X			X		
8								X
22	X	X	X	X				X
25								
59				X			X	X
Sub-Total	2	2	2	2	0	1	1	3
<i>Possible Instance of Effect and % Affected</i>								
Group I	4(50%)	4(25%)	4(25%)	4(50%)	4(25%)	4(75%)	4(0%)	4(50%)
Group II	5(40%)	5(40%)	5(40%)	5(40%)	5(0%)	5(20%)	5(20%)	5(60%)

eight pairs of performance data resulting from: two exposures x four performance variables. The Wilcoxon test yielded a T value of 19.0, but the T had to be four or less for eight pairings to be significant at the .05 level. Thus, the null hypothesis of no difference between the two dosage levels could not be rejected.

2.5 mg/kg MMH

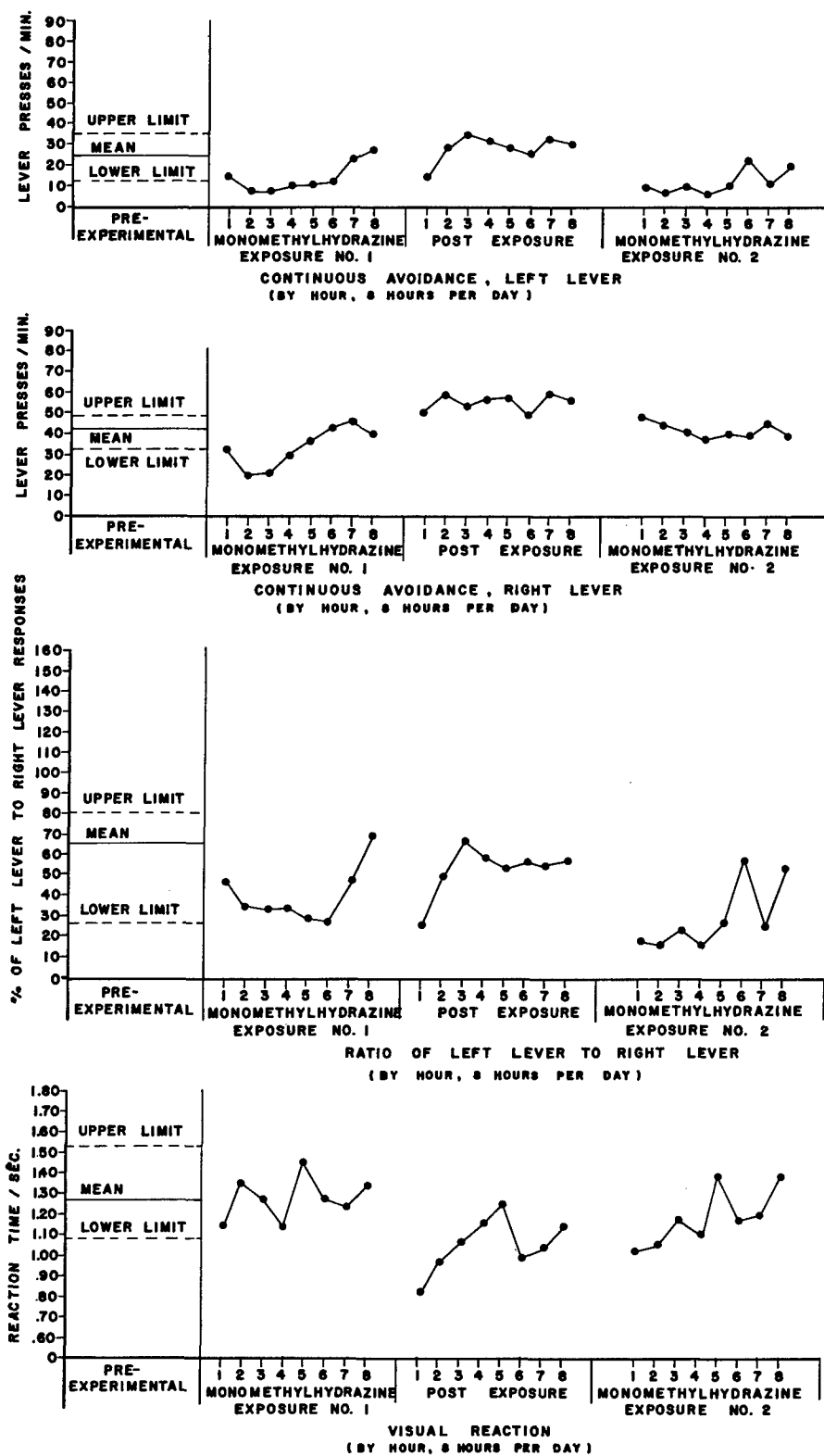


Figure 2. Baseline and Experimental Performance, Subject No. 2

2.5 mg/kg MMH

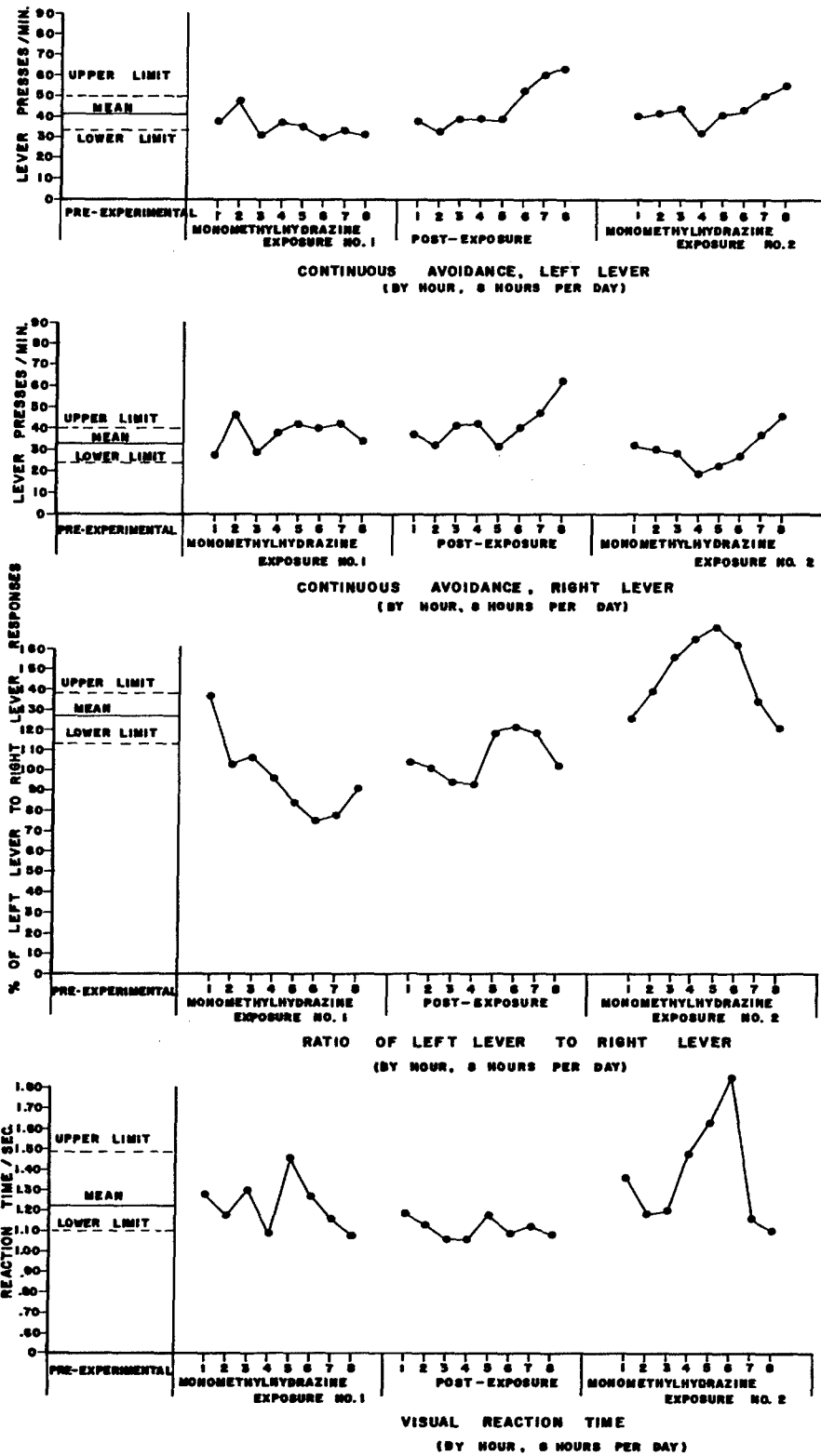


Figure 3. Baseline and Experimental Performance, Subject No. 9

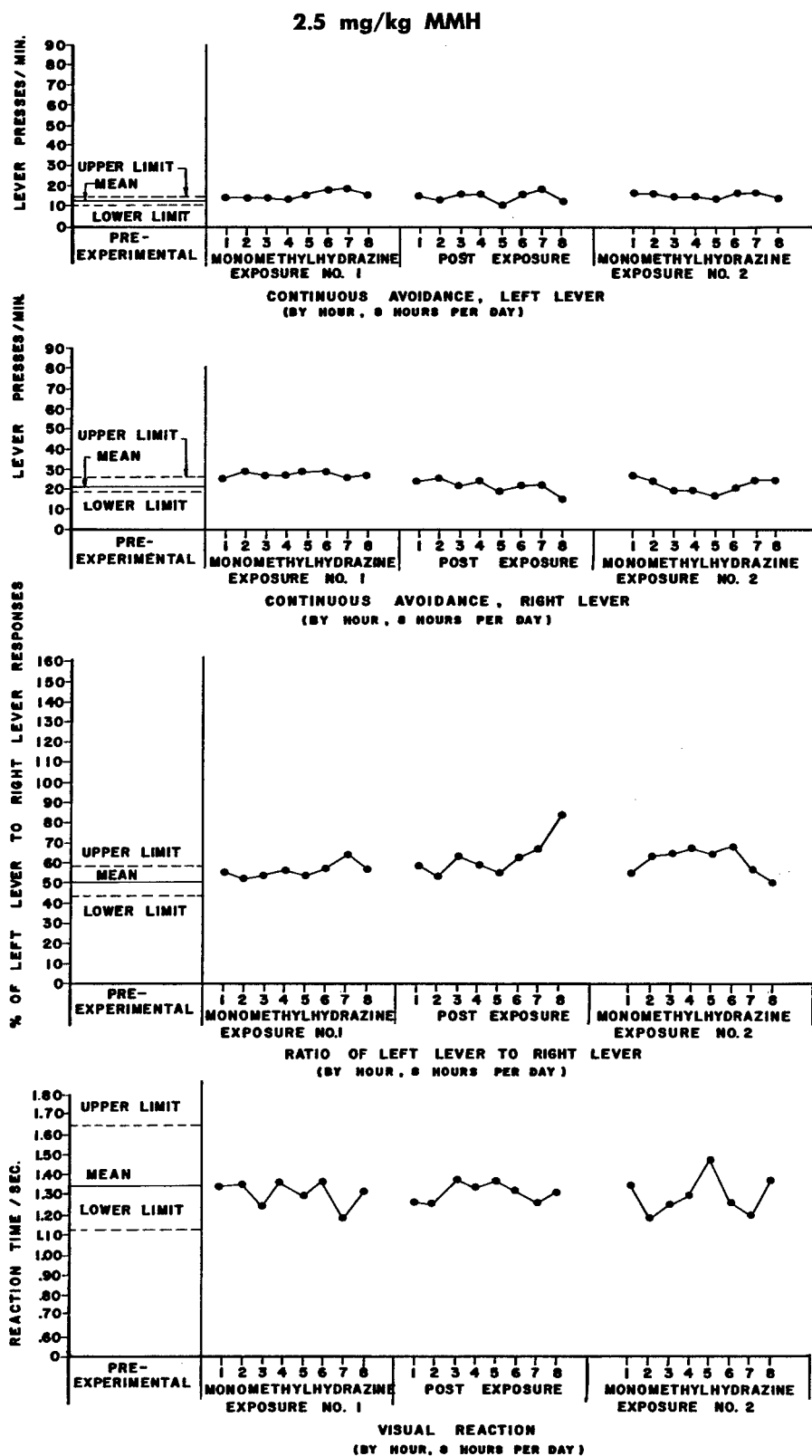


Figure 4. Baseline and Experimental Performance, Subject No. 58

2.5 mg/kg MMH

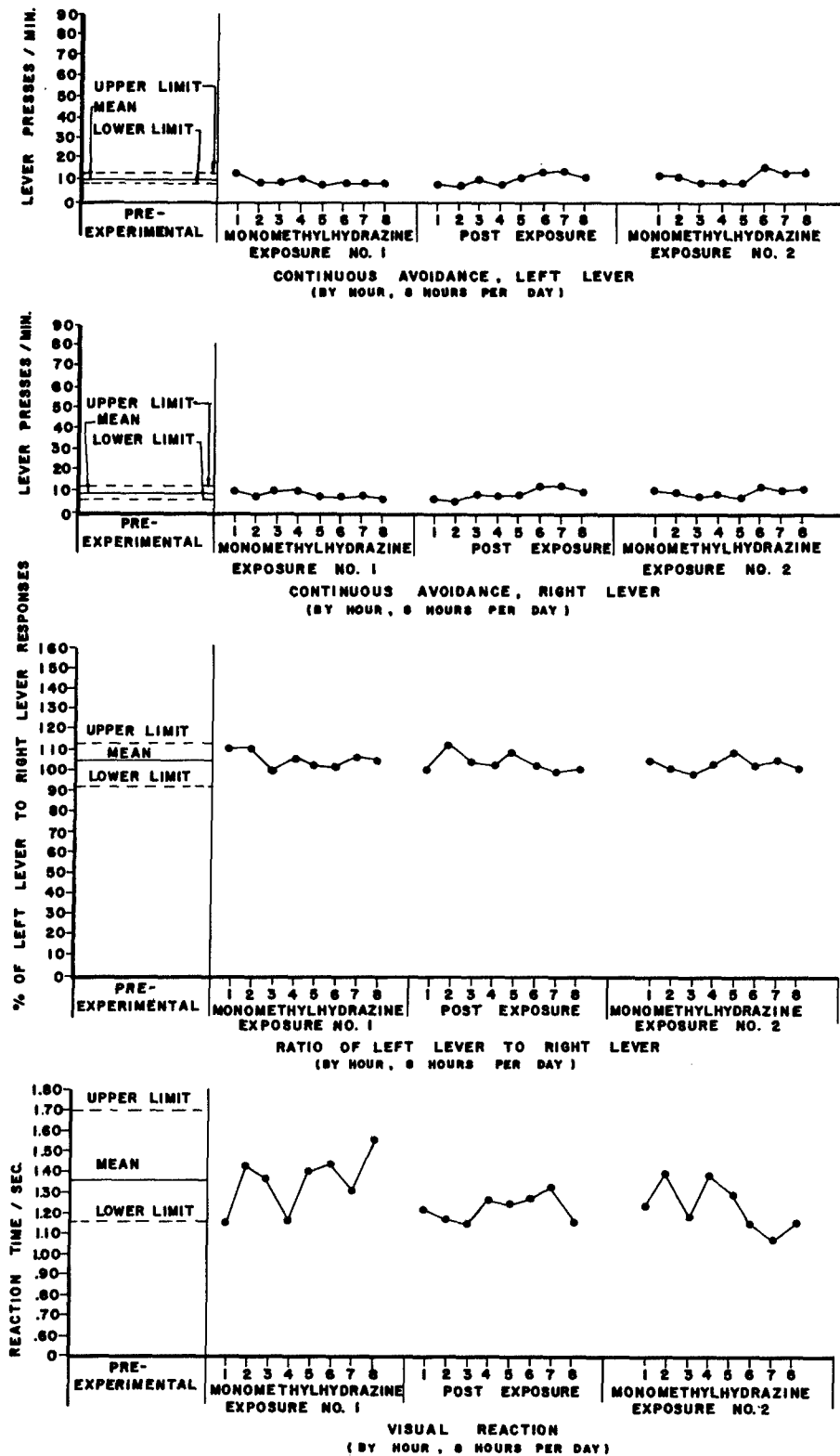


Figure 5. Baseline and Experimental Performance, Subject No. 60

5.0 mg/kg MMH

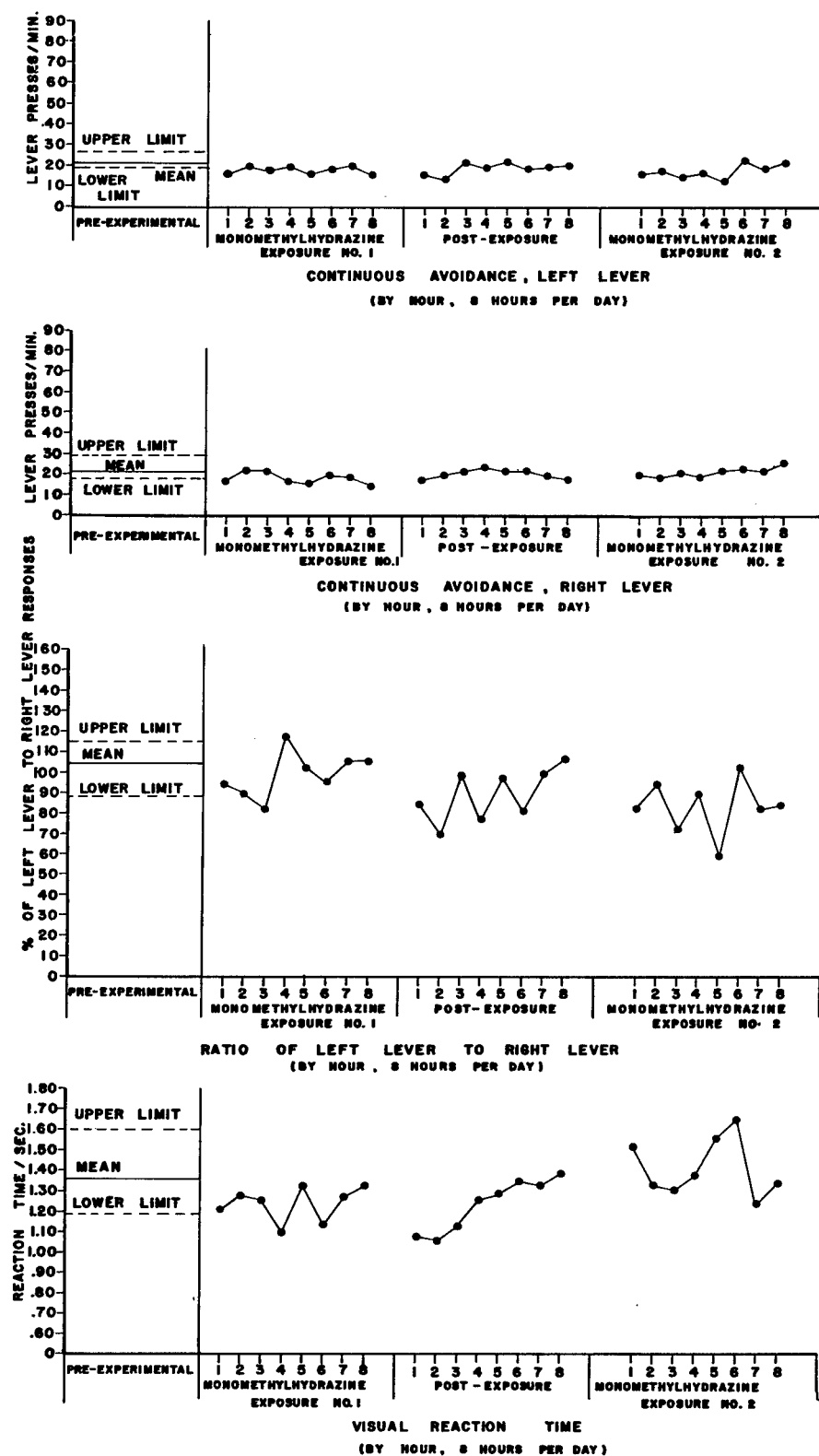


Figure 6. Baseline and Experimental Performance, Subject No. 7

5.0 mg/kg MMH

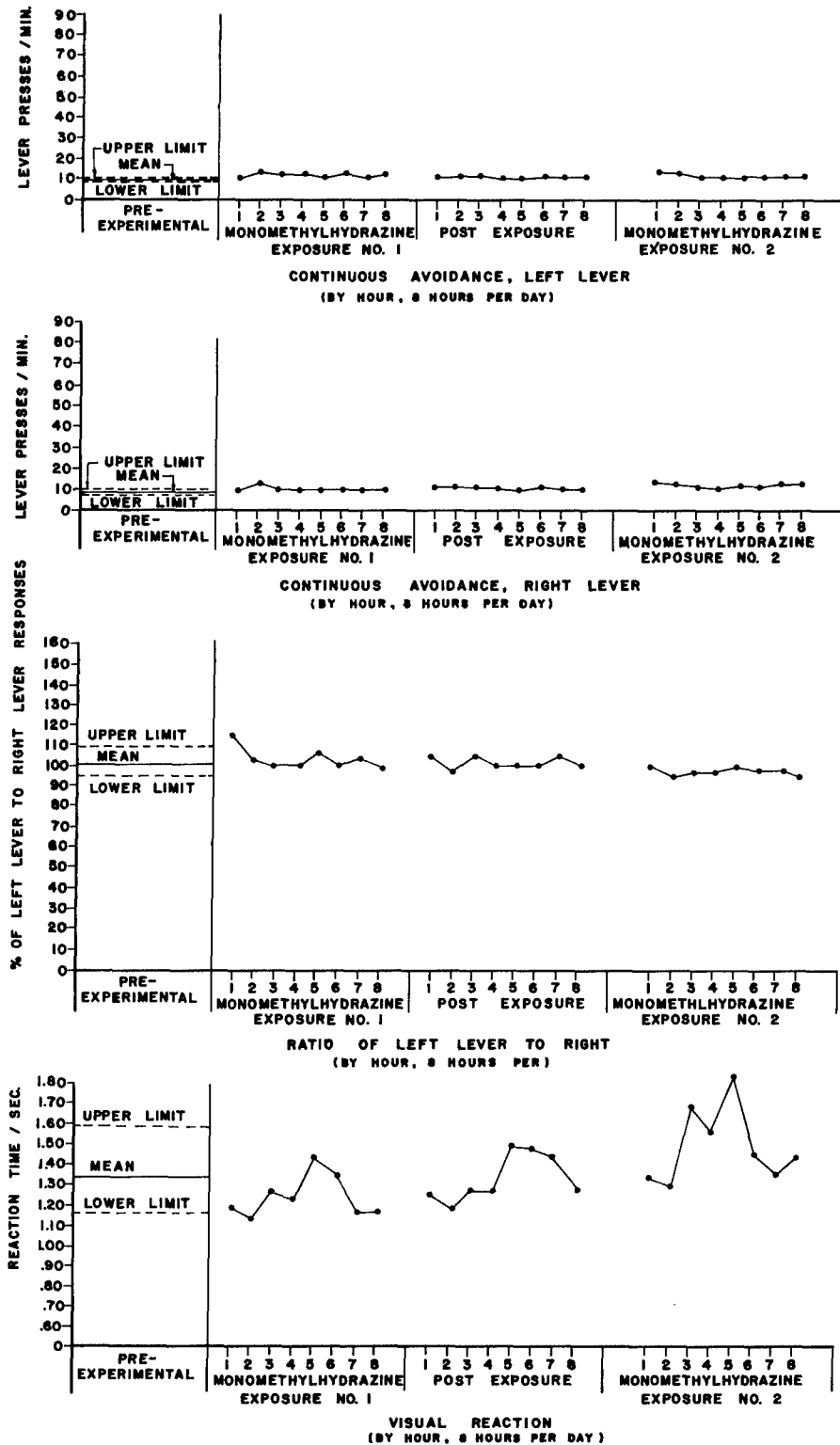


Figure 7. Baseline and Experimental Performance, Subject No. 8

5.0 mg/kg MMH

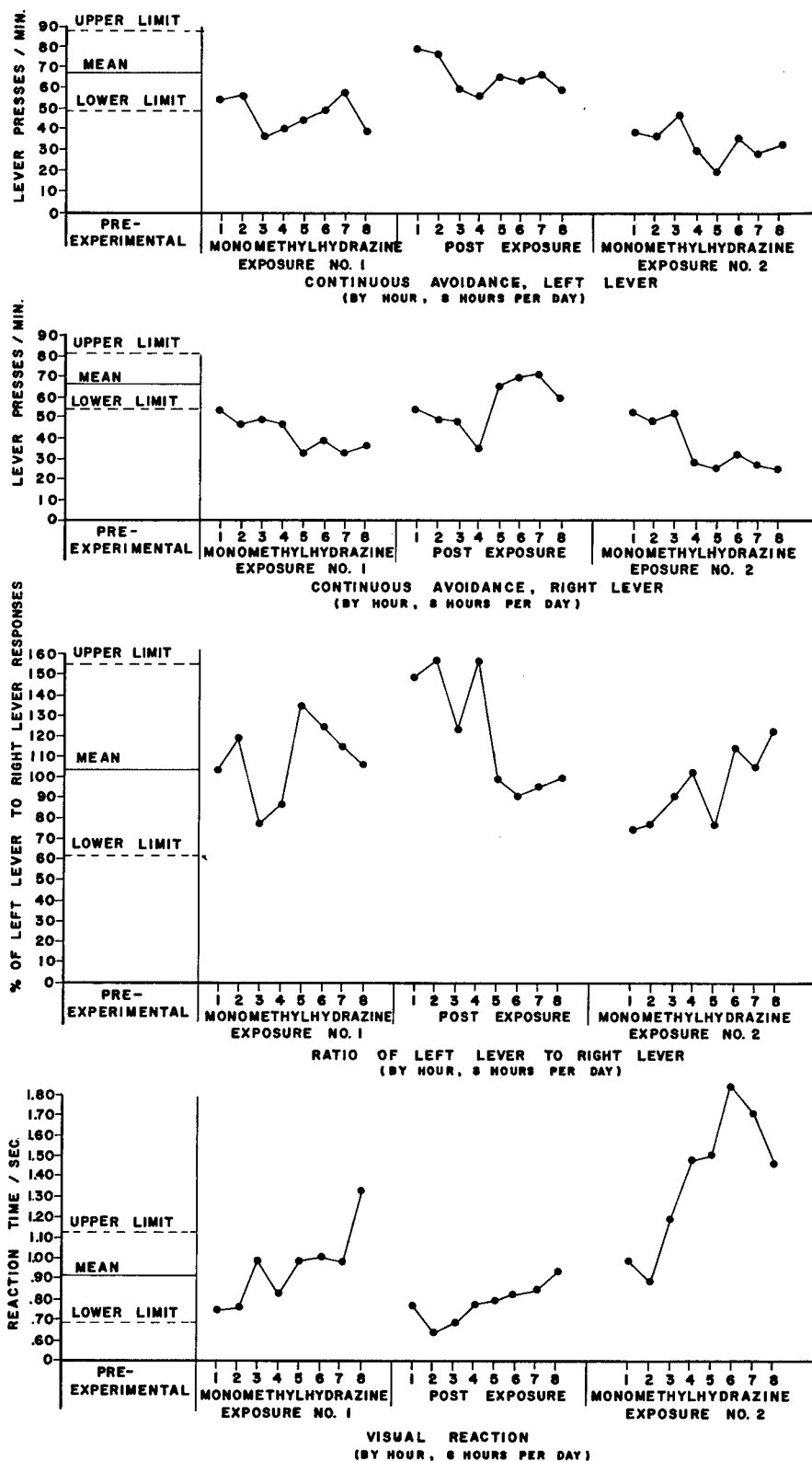


Figure 8. Baseline and Experimental Performance, Subject No. 22

5.0 mg/kg MMH

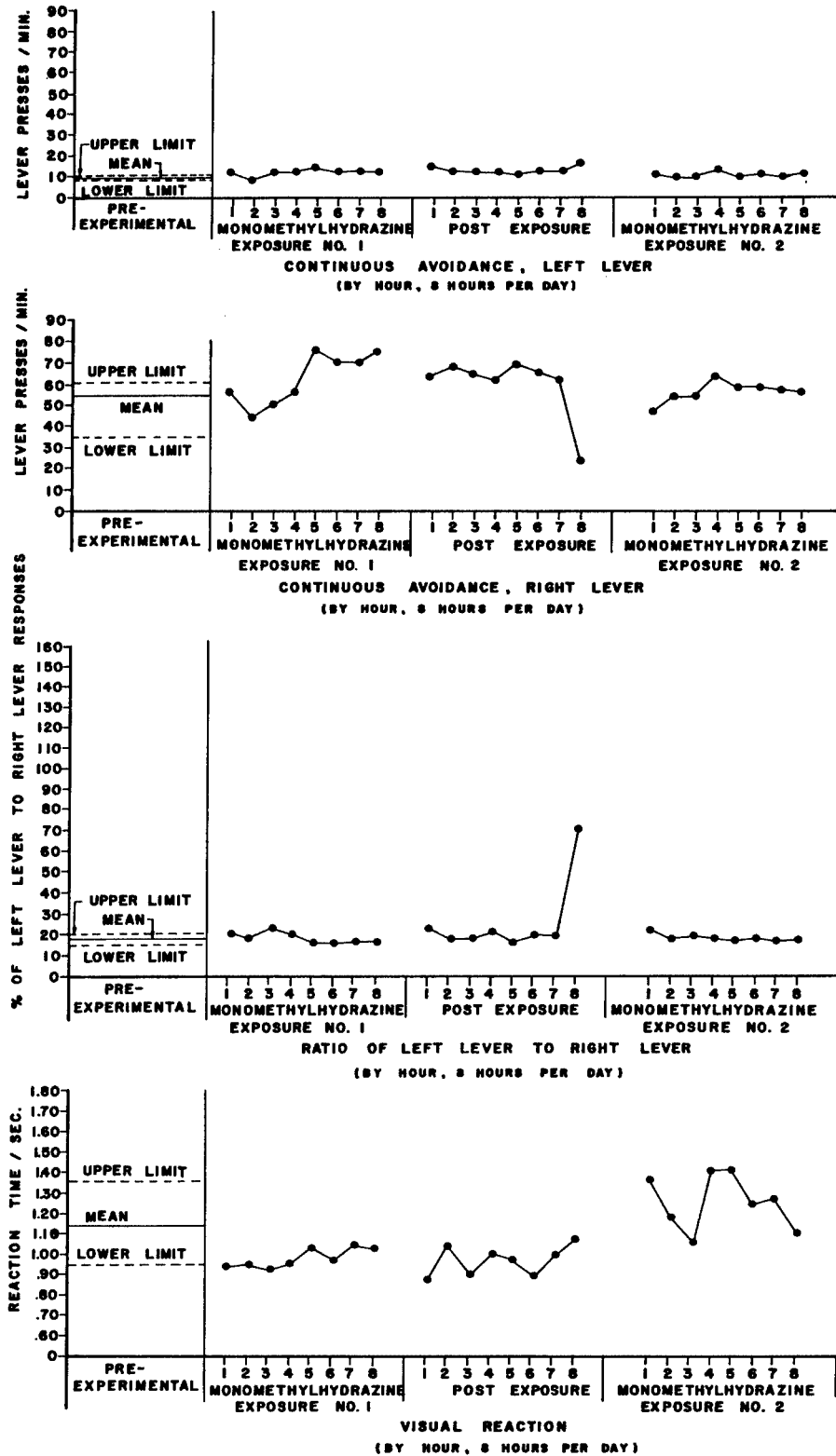


Figure 9. Baseline and Experimental Performance, Subject No. 25

5.0 mg/kg MMH

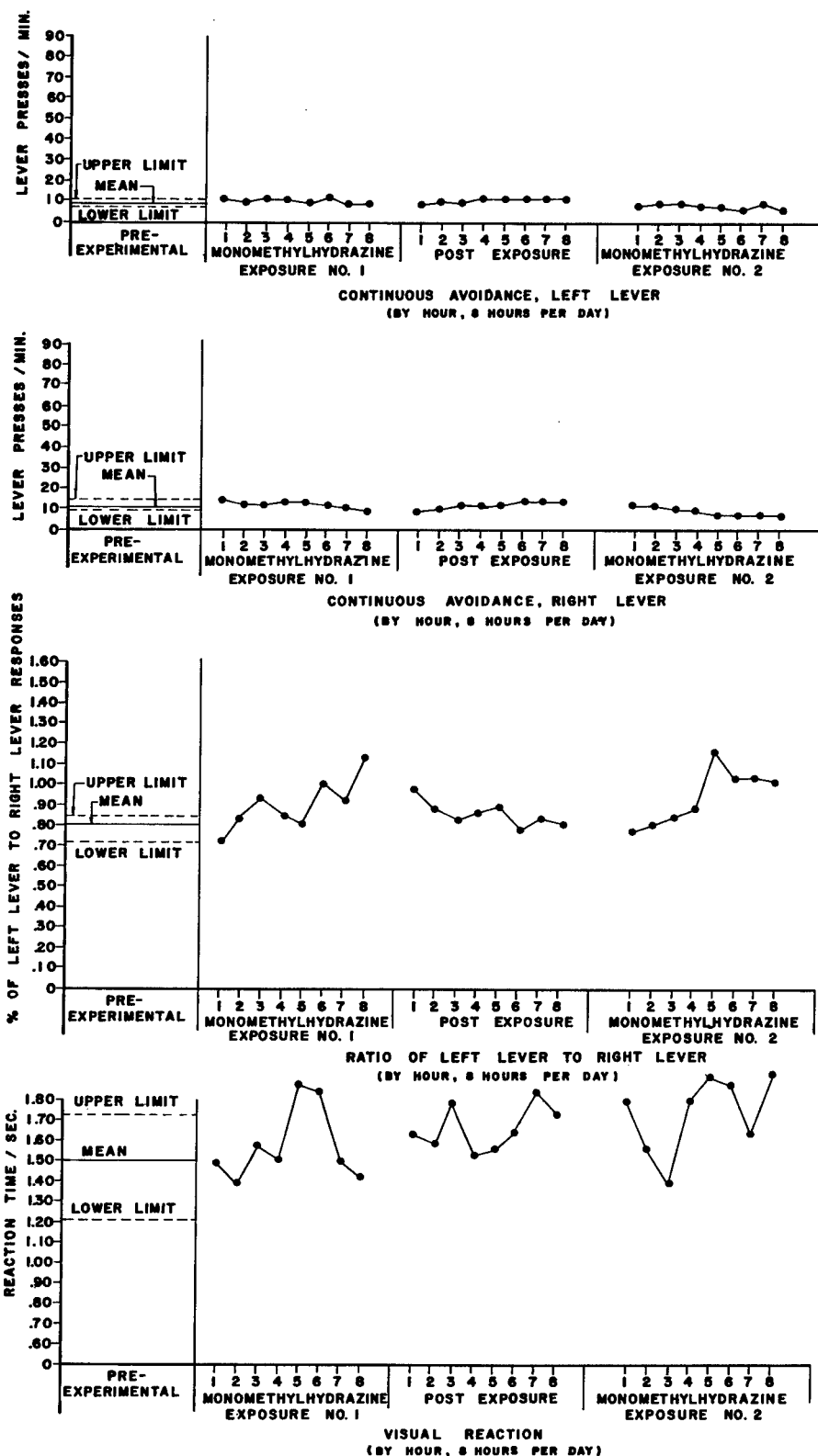


Figure 10. Baseline and Experimental Performance, Subject No. 59

Observational Data

Each subject was carefully monitored from the clinical point of view. Observations of import are reported for each of the exposures to MMH.

GROUP I (2.5 mg/kg)

Subject No. 2

Exposure No. 1 (26 Oct 64)

1056 — Emesis

1226 — Emesis (3X)

1320 — Emesis

1405 — Coughing or gagging

Exposure No. 2 (28 Oct 64)

0942 — Emesis

1007 — Emesis (3X)

1020 — Coughing

1044 — Coughing and emesis

1106 — Emesis

1105 — Emesis (3X)

1302 — Emesis

Subject No. 9

Exposure No. 1 (26 Oct 64)

No clinical symptoms

Exposure No. 2 (28 Oct 64)

No clinical symptoms

Subject No. 58

Exposure No. 1 (26 Oct 64)

No clinical symptoms

Exposure No. 2 (28 Oct 64)

No clinical symptoms

Subject No. 60

Exposure No. 1 (26 Oct 64)

No clinical symptoms

Exposure No. 2 (28 Oct 64)

0903 — Emesis

1309 — Coughing

GROUP II (5.0 mg/kg)

Subject No. 7

Exposure No. 1 (26 Oct 64)

0955 — Considerable emesis

0957 — Emesis

1050 — Emesis

1355 — Retching

Exposure No. 2 (28 Oct 64)

0826 – Gagging, coughing and chewing

0830 – Emesis, just at start of work session; however,
the subject promptly went to work.

0840 – Emesis

0852 – Emesis

1012 – Emesis

1040 – Emesis

1055 – Emesis (2X)

1120 – Emesis

1150 – Emesis

1302 – Emesis

1402 – Emesis (2X)

Subject No. 8

Exposure No. 1 (26 Oct 64)

1100 – Retching

Exposure No. 2 (28 Oct 64)

1312 – Emesis (2X)

1510 – Emesis

Subject No. 22

Exposure No. 1 (26 Oct 64)

1124 – Retching

1211 – Emesis

1410 – Retching

1625 – Lying on side on chamber floor

Exposure No. 2 (28 Oct 64)

1012 – Emesis

1128 – Emesis

Subject No. 25

Exposure No. 1 (26 Oct 64)

No clinical symptoms

Exposure No. 2 (28 Oct 64)

0853 – Saliva in cage, possibly slight emesis.

0929 – Emesis

1010 – Emesis

1318 – Emesis (2X)

Subject No. 59

Exposure No. 1 (26 Oct 64)

No clinical symptoms

Exposure No. 2 (28 Oct 64)

1011 – Emesis

1028 – Emesis

1048 – Emesis

1121 — Emesis
 1152 — Emesis (2X)
 1300 — Emesis
 1326 — Emesis
 1409 — Emesis
 1502 — Emesis (3X)

Table II indicates the hours that clinical symptoms were first and last observed for each subject.

TABLE II.
*Onset and Cessation of Clinical Symptoms
 Following Injection (in hours)*

Subject No.	Onset		Cessation	
	Exposure 1	Exposure 2	Exposure 1	Exposure 2
<i>Group I (2.5 mg/kg of MMH)</i>				
2	2	2	5	5¼
9	N/A	N/A	N/A	N/A
58	N/A	N/A	N/A	N/A
60	N/A	1	N/A	5¼
<i>Group II (5.0 mg/kg of MMH)</i>				
7	1	1	5	6¼
8	2	5¼	2	7¼
22	2½	2¼	7½	3¾
25	N/A	1½	N/A	5½
59	N/A	2½	N/A	7¼

Table II shows that clinical symptoms were observed more frequently in Group II than in Group I. In the first exposure the ratio was 3:1, and in the second exposure the ratio was 5:2.

Summary Data

Since an important question concerns the relationship between clinical symptoms and performance decrements, Table III was constructed. This table demonstrates the relationship in terms of the time of occurrence of either sickness or a decrement. Percentage values are provided to highlight the differences in sensitivity of the two variables.

TABLE III.

Relationship Between Performance Decrements and Clinical Symptoms

Subject No.	Instances of Clinical Symptoms Preceding Performance Decrements	Instances of Performance Decrement Preceding Clinical Symptoms	Instances of Clinical Symptoms Occurring Simultaneously	Instances of Clinical Symptoms Without Performance Decrement	Instances of Performance Decrement Without Clinical Symptoms	Neither Performance Decrement nor Clinical Symptoms
<i>Group I (2.5 mg/kg)</i>						
2		2				
9					2	
58		1			1	
60				1		1
<i>Group II (5.0 mg/kg)</i>						
7		1	1			
8			1	1		
22		2				
25				1		1
59			1		1	
Summary	0(0%)	6(33.3%)	3(16.7%)	3(16.7%)	4(22.2%)	2(11.1%)

Note: 9 Ss x 2 Exposures = 18 possible Instances of Effect

SECTION IV.

Discussion and Conclusions

The results indicate that low dosages of MMH definitely have an effect on the central nervous system as evidenced by significant performance decrements at both 2.5 and 5.0 mg/kg. Wilcoxon's test provided further information to the effect that there were no differences in performance between the two dosage levels. On the other hand, there was evidence that clinical symptoms appeared more often in the subjects receiving the higher dosage.

With regard to the relationship between the onset of clinical symptoms versus performance decrements, Table III shows clearly that in over half the cases (10/18) a performance decrement preceded clinical symptoms or occurred without concomitant clinical symptoms. In no instance did clinical symptoms precede a performance decrement and in only 3/18 cases did clinical symptoms appear without a performance decrement. Thus, the value of performance measures in toxicological research is readily apparent.

In summary, when initial 2.5 or 5.0 mg/kg injections are made one might predict that performance decrements will occur between 1 and 2 hours and clinical symptoms between 2 and 2.5 hours in about half the subjects. A second exposure might be expected to produce performance decrements between 1 and 2 hours and clinical symptoms between 2 and 3 hours in the majority of subjects. If a subject is influenced by MMH, clinical symptoms will likely disappear between 3 and 9 hours following injection and performance should return to a baseline level between 3 and 30 hours.

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14. **KEY WORDS:** Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical content. The assignment of links, rules, and weights is optional.