THIS FILE IS MADE AVAILABLE THROUGH THE DECLASSIFICATION EFFORTS AND RESEARCH OF:

THE BLACK VAULT

THE BLACK VAULT IS THE LARGEST ONLINE FREEDOM OF INFORMATION ACT / GOVERNMENT RECORD CLEARING HOUSE IN THE WORLD. THE RESEARCH EFFORTS HERE ARE RESPONSIBLE FOR THE DECLASSIFICATION OF THOUSANDS OF DOCUMENTS THROUGHOUT THE U.S. GOVERNMENT, AND ALL CAN BE DOWNLOADED BY VISITING:

HTTP://WWW.BLACKVAULT.COM

YOU ARE ENCOURAGED TO FORWARD THIS DOCUMENT TO YOUR FRIENDS, BUT PLEASE KEEP THIS IDENTIFYING IMAGE AT THE TOP OF THE .PDF SO OTHERS CAN DOWNLOAD MORE!
August 20, 2009

Office of the Chief Counsel

Mr. John Greenewald, Jr.

Dear Mr. Greenewald:

This is the final response to your FOIA request dated June 10, 2009 and assigned RDECOM FOIA #FA-09-0034 where you seek a copy of the report titled, “The Effects of Fluphenazine in Psychologically Normal Volunteers: Some Temporal, Performance, and Biochemical Relationships”, Report Number EA-TR-4348, Accession Number AD-865341.

The redacted record enclosed was subject to FOIA exemption, (b)(6). FOIA Exemption (b)(6) along with a Department of Defense policy allows for the withholding of government employee names, email addresses, and other personal information.

If you consider this response to be an adverse action, you may administratively appeal, in writing, to the Secretary of the Army. However, prior to appealing directly to the Secretary of the Army, the Initial Denial Authority, (Mr. Patrick R. Sheldon), must review the appeal. Therefore, any such appeal should be addressed to this office. We will review your appeal and forward your appeal to the Army Office of General Counsel, the designated Army Freedom of Information Act appellate authority.

Additionally, if you choose to appeal, the appeal must be received by the appellant authority (Army General Counsel), no later than 60 days following receipt of this letter. Please send correspondence to the following address:

Brian A. May
RDECOM, ATTN AMSRD-CCF
5183 Blackhawk Road, E4435
Aberdeen Proving Ground, MD 21010-5424
Should you have any questions or concerns regarding your request I can be reached at (410) 436-2289 or brian.may3@us.army.mil

Sincerely,

//SIGNED - BAM//
Brian A. May
FOIA Officer, HQ RDECOM

Enclosure
The Effects of Fluphenazine in Psychologically Normal Volunteers: Some Temporal, Performance, and Biochemical Relationships

EDGEWOOD ARSENAL ABERDEEN PROVING GROUND MD

FEB 1970

Redistribution Of DTIC-Supplied Information Notice

All information received from DTIC, not clearly marked "for public release" may be used only to bid on or to perform work under a U.S. Government contract or grant for purposes specifically authorized by the U.S. Government agency that is sponsoring access OR by U.S. Government employees in the performance of their duties.

Information not clearly marked "for public release" may not be distributed on the public/open Internet in any form, published for profit or offered for sale in any manner.

Non-compliance could result in termination of access.

Reproduction Quality Notice

DTIC's Technical Reports collection spans documents from 1900 to the present. We employ 100 percent quality control at each stage of the scanning and reproduction process to ensure that our document reproduction is as true to the original as current scanning and reproduction technology allows. However, occasionally the original quality does not allow a better copy.

If you are dissatisfied with the reproduction quality of any document that we provide, please free to contact our Directorate of User Services at (703) 767-9066/9068 or DSN 427-9066/9068 for refund or replacement.

Do Not Return This Document To DTIC

UNCLASSIFIED / LIMITED
EDGECWOOD ARSENAL
TECHNICAL REPORT

EATR 4348

THE EFFECTS OF FLUPHENAZINE
IN PSYCHOLOGICALLY NORMAL VOLUNTEERS:
SOME TEMPORAL, PERFORMANCE,
AND BIOCHEMICAL RELATIONSHIPS

February 1970

DEPARTMENT OF THE ARMY
EDGECWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010
DISCLAIMER NOTICE

THIS DOCUMENT IS BEST QUALITY AVAILABLE. THE COPY FURNISHED TO DTIC CONTAINED A SIGNIFICANT NUMBER OF PAGES WHICH DO NOT REPRODUCE LEGIBLY.

REPRODUCED FROM BEST AVAILABLE COPY
Distribution Statement

Each transmittal of this document outside the agencies of the US Government must have prior approval of the Commanding Officer, Edgewood Arsenal, ATTN: SMUEA-TSTI-T, Edgewood Arsenal, Maryland 21010.

Disclaimer

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

Disposition

Destroy this report when no longer needed. Do not return it to the originator.
THE EFFECTS OF FLUPHENAZINE IN PSYCHOLOGICALLY NORMAL VOLUNTEERS: SOME TEMPORAL, PERFORMANCE, AND BIOCHEMICAL RELATIONSHIPS

by

(b)(6)

Clinical Research Department

February 1970

Each transmittal of this document outside the agencies of the US Government must have prior approval of the Commanding Officer, Edgewood Arsenal, ATTN: SMUEA-TSTI-T, Edgewood Arsenal, Maryland 21010.

Task 1B562602AD1202

DEPARTMENT OF THE ARMY
EDGECWOOD ARSENAL
Research Laboratories
Medical Research Laboratory
Edgewood Arsenal, Maryland 21010
FOREWORD

The work described in this report was authorized under Task 1B562602AD1202, Incapacitating Chemical Agent Investigations, Biomedical Evaluation of Incapacitating Agents (U). This work was started in February 1967 and completed in June 1968.

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

Reproduction of this document in whole or in part is prohibited except with permission of the Commanding Officer, Edgewood Arsenal, ATTN: TSTI-T, Edgewood Arsenal, Maryland 21010; however, DDC is authorized to reproduce the document for US Government purposes.

The information in this document has not been cleared for release to the general public.

Acknowledgements

The authors wish to thank (b)(6) for the cholinesterase analyses reported in this paper.
DIGEST

Fifty healthy young male volunteers were given 10 to 40 μg/kg of fluphenazine dihydrochloride intramuscularly. All subjects were studied at regular intervals for behavior and symptom appraisal, arithmetic performance, and physiological changes. Twelve subjects were also tested for manual dexterity and digit recall. Blood cholinesterase activity of eight subjects was measured just prior to intramuscular administration of a series of 0.8- or 1.0-mg doses of physostigmine. Four subjects were also tested for fine visual-motor coordination by use of a track-tracer test.

The major findings were as follows: (1) Fluphenazine caused extrapyramidal signs (EPS) and fine visual-motor coordination impairments in some subjects, but these signs usually did not appear until 24 hours after administration of the drug; all other drug effects occurred primarily within the first 24 hours. (2) The probability of the occurrence of EPS was strongly dose related (r = 0.9). (3) Drug-produced irritability occurred primarily on the first day, showed a positive correlation both to dose and to the score on the MMPI Paranoid scale, and was not related to EPS. (4) Slight, clinically insignificant, dose-related plasma cholinesterase depressions occurred on the first but not on the second day after fluphenazine. (5) Repeated customary doses of physostigmine did not influence any parameters of the fluphenazine effect. (6) Fine visual motor impairments did not respond to the customary treatment for EPS.

The results suggest both that the drug-induced EPS forms a curious late phase of the drug action which apparently may not directly involve cholinergic mechanisms, in contrast to EPS occurring in Parkinson’s disease, and that the drug-induced irritability may well have a direct organic etiology in addition to a psychological proclivity. The results also suggested that impairment of fine visual-motor coordination may not be directly related to the appearance of gross EPS.
CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. INTRODUCTION</td>
<td>7</td>
</tr>
<tr>
<td>II. METHOD</td>
<td>7</td>
</tr>
<tr>
<td>A. Subjects</td>
<td>7</td>
</tr>
<tr>
<td>B. Test Procedures</td>
<td>8</td>
</tr>
<tr>
<td>C. Tests and Measurements</td>
<td>8</td>
</tr>
<tr>
<td>D. Special Procedure for Testing of Cholinergic Factors</td>
<td>9</td>
</tr>
<tr>
<td>E. Treatment for EPS</td>
<td>9</td>
</tr>
<tr>
<td>III. RESULTS</td>
<td>9</td>
</tr>
<tr>
<td>A. The Effect of Physostigmine on Subjects Given Fluphenazine</td>
<td>9</td>
</tr>
<tr>
<td>B. EPS-Dose Relationships</td>
<td>10</td>
</tr>
<tr>
<td>C. Temporal Occurrence and Type of EPS</td>
<td>10</td>
</tr>
<tr>
<td>D. Performance Ratings</td>
<td>13</td>
</tr>
<tr>
<td>E. Signs and Symptoms Other Than EPS</td>
<td>13</td>
</tr>
<tr>
<td>F. Physiologic Findings</td>
<td>19</td>
</tr>
<tr>
<td>G. Personality Relationships to Dysphoric Drug Effects</td>
<td>19</td>
</tr>
<tr>
<td>H. Blood Levels of Cholinesterase</td>
<td>19</td>
</tr>
<tr>
<td>IV. DISCUSSION</td>
<td>19</td>
</tr>
<tr>
<td>A. EPS, a Later-Phase Phenomenon</td>
<td>19</td>
</tr>
<tr>
<td>B. Track-Tracer Performance Impairments and EPS</td>
<td>22</td>
</tr>
<tr>
<td>C. Cholinergic Factors in EPS</td>
<td>22</td>
</tr>
<tr>
<td>D. The Irritability Response to Fluphenazine</td>
<td>22</td>
</tr>
<tr>
<td>E. Comparison With Other Fluphenazine Studies</td>
<td>23</td>
</tr>
<tr>
<td>V. SUMMARY AND CONCLUSIONS</td>
<td>24</td>
</tr>
<tr>
<td>LITERATURE CITED</td>
<td>25</td>
</tr>
<tr>
<td>DISTRIBUTION LIST</td>
<td>27</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Tables
1. Effects of Repeated Physostigmine Treatment ........................................ 10
IIA. EPS-Dose Relationship ............................................................................... 11
IIB. Probit Analysis ........................................................................................... 11
III. Time of Onset of First EPS at Each Dose .................................................. 11
IV. Track-Tracer Scores Compared With EPS .................................................... 18
V. Occurrence of Symptoms .............................................................................. 18
VI. Subjects With Signs and Symptoms Other Than EPS .................................. 20
VII. Irritable Responders as a Function of Dose and MMPI Paranoid (Pa) Scores .......................................................... 20

LIST OF FIGURES

Figures
1. Time for Occurrence of EPS for Each Subject .............................................. 12
2. Median Number-Facility (NF) Percent Scores ............................................... 14
4A. Track-Tracer-Number of Hits (Error) .......................................................... 16
4B. Track-Tracer-Error Time ............................................................................. 17
5. Average Plasma Cholinesterase Levels ......................................................... 21
THE EFFECTS OF FLUPHENAZINE IN PSYCHOLOGICALLY NORMAL VOLUNTEERS: SOME TEMPORAL, PERFORMANCE, AND BIOCHEMICAL RELATIONSHIPS

I. INTRODUCTION.

Although over 1200 articles have been published on the phenothiazine tranquilizer fluphenazine (Prolixin), the only published study on the psychopharmacology of the drug in normal subjects was one by Kitzes. He reported that the effects of fluphenazine include a mild impairment in performance of an addition test during the first 24 hours after drug administration, and that the extrapyramidal signs (EPS)—akathisia, dystonia, muscle spasms, etc.—occur almost entirely between 24 and 32 hours after intramuscular (im) administration of the drug.

The case records of Kitzes' subjects were reviewed; it was found that the EPS occurred 8 to 12 hours after the peak behavioral effects of the drug. It was also noted that irritability and restlessness, which occurred frequently, were apparently dose related.

To obtain further information about these drug effects, we gave doses of fluphenazine (im) to 14 additional normal male volunteers (1) to replicate the above-mentioned findings; (2) to study drug effects on memory, manual dexterity, and visual-motor coordination; (3) to determine whether cholinergic mechanisms can account for EPS; and (4) to note whether personality factors can account for some of the irritability caused by the drug, as has been reported for other tranquilizers.

This paper is a report of the data obtained from these 14 subjects combined with the data obtained from Kitzes' 36 subjects.

II. METHOD.

A. Subjects.

All subjects were male volunteers 19 to 35 years old. Their weights ranged from 134 to 186 lb, except for one who weighed 118 lb and one who weighed 227 lb. Of the 36 subjects tested by Kitzes, 32 were prisoners; the remaining four and the 14 tested recently were US Army enlisted men.

Subjects were screened before testing to assure that they were mentally and physically sound on the basis of a psychiatric examination and a physical examination that included chest X-ray and routine blood and urine analyses. The Minnesota Multiphasic Personality Inventory (MMPI), the Picture Frustration Test, and a personal-history questionnaire were also used in the psychiatric screen of the subjects. The Picture Frustration Test consisted of six pictures taken from the complete test designed by Rosenzweig. The test was scored for externally directed hostility as described by Rosenzweig. The inter-rater reliability of the scoring was 0.84.

*Blood analyses included hemoglobin (Hgb), hematocrit (Hct), total and differential white cell count (WBC), serum glutamic oxaloacetic transaminase (SGOT), blood urea nitrogen (BUN), bilirubin, total protein, red cell and plasma cholinesterase, and alkaline phosphatase.
B. Test Procedures.

All subjects were tested in a hospital ward atmosphere under the supervision of physicians. Each subject was observed by nurses and trained technicians. Subjects were assigned to doses by a random method and were told that they would receive a well-known tranquilizer. Only the investigators knew the doses administered.

On the morning of the injection, control tests were conducted as described in the next section. Fluphenazine dihydrochloride (10 to 40 µg/kg, *im) was then administered to three or four subjects at around 9 a.m. During the next 2 days, physical signs and behavioral ratings were recorded; psychological tests were given hourly for the first 6 hours, then at 2-hour intervals, except that they were suspended from 10 p.m. until 7 a.m. Each testing session required about 20 to 30 minutes, and subjects were allowed to spend their free time in a ward lounge area.

C. Tests and Measurements.

1. Physical Signs.

Blood pressure (supine), heart rate, and pupil size were recorded at the regular testing intervals. Pupil size was estimated by a disk pupillometer under standard lighting conditions. These physical signs were measured at least twice before drug administration.

2. Behavioral Rating and Definition of Irritability.

The completeness of the nurses' notes varied between 1965 and 1968, but the comments recorded at the regular testing intervals generally covered the subjects' moods, symptoms, complaints, feelings, and behavior.

The nurses' records were reviewed by two independent raters, who scored each subject for the presence or absence of irritability. For rating purposes, the irritability syndrome was defined to include the descriptors "irritable," "nervous," and "tense," except when the subject explicitly claimed he was nervous or tense because he feared a recurrence of EPS. The inter-rater agreement was 78%. The statistics for occurrence of all other symptoms were based on the presence in the nurses' notes of the actual description; e.g., sleepy, restless, blurred vision, etc.


At the regular test interval, all subjects took the Number Facility Test (NF), which is part of Moran and Mefferd's repetitive psychometric measures. The NF allows 3 minutes for a series of subject-paced simple addition problems and is scored for the number of correct additions. Baseline scores were the average of the five highest out of 25 obtained before the drug was administered. Three of these 25 scores were obtained the morning the drug was to be given. Subsequent scores were expressed as percentage of baseline.8

Four subjects who received doses of 23 µg/kg were tested for visual-motor coordination with a track-tracer test9 in which the subject guided a metal stylus through a

*The total doses ranged from 0.8 to 2.8 mg.
curved, enclosed metal path. Each hit on the rim or bottom of the path was considered an error. The number of hits (errors) and the cumulative time during which contact was maintained with the path limits (error time) were scored electronically. Each test consisted of two repetitions of the tracking task, giving two measures for both errors and error time. Baseline scores were the average of four tests given the day before the drug was administered.

Twelve subjects who received 10 to 40 μg/kg of fluphenazine were tested before and after drug administration on a standard digit-recall test, which measures auditory memory, and on the Minnesota Manipulation Test, which is a pegboard test of manual dexterity. The test of digit recall consisted of a series of numbers, read one digit at a time, at approximately two digits per second. The subject was to repeat the number, a digit at a time, starting on a signal given about half a second after the last digit was read. The largest complete digit series he could recall correctly for at least two out of three trials was the basis for his score; a different digit series was used in each trial. The mean of two control scores on the digit-recall test and the mean of the last five of the 10 control manual-dexterity tests were considered baseline scores. The baseline scores were all obtained the day before the drug was administered.

D. Special Procedures for Testing of Cholinergic Factors.

Physostigmine salicylate was given to eight subjects in doses of either 0.8 or 1.0 mg (im) at 5, 8, 11, 24, 26, 28, and 30 hours after fluphenazine was administered. These doses were selected to correspond with those used by Duvoisin in a similar study with patients having Parkinson's disease. The clinical effects of physostigmine at these doses are over in less than 2 hours. The dose of 0.8 mg was administered to four subjects who received 15 μg/kg of fluphenazine. The dose of 1.0 mg was given to four subjects who received 23 μg/kg of fluphenazine. Red-blood-cell and plasma cholinesterase activity of these eight subjects was measured in blood samples taken before the test and at both 5 and 24 hours after fluphenazine had been administered. The cholinesterase activity was measured by the method described by Groff et al.

E. Treatment for EPS.

The subjects that showed EPS were treated with either 50 mg (im) of diphenhydramine hydrochloride (Benadryl), 1 mg (iv) of benztropine methanesulfonate (Cogentin), or 1 mg (orally) of trihexyphenidyl (Artane). This treatment is effective for about 1.5 to 3 hours. Three subjects were given treatment after EPS disappeared to prevent its recurrence.

III. RESULTS.

A. The Effect of Physostigmine on Subjects Given Fluphenazine.

The eight subjects who received physostigmine were compared with 11 subjects who received only fluphenazine. Table I gives the doses, the percentage of subjects that showed EPS, and the onset times for the first EPS. The differences between the physostigmine-fluphenazine and fluphenazine-alone groups are not significant. The behavioral performance measures and other physiological measures also failed to show any differences between these groups of

---

The blood samples were taken 4 weeks before the test for all eight subjects and on the morning of the test for the four subjects given 23 μg/kg of fluphenazine. The values showed no significant change over the 4-week period.
Table I. Effects of Repeated Physostigmine Treatment

<table>
<thead>
<tr>
<th>Dose of physostigmine</th>
<th>Dose of physostigmine*</th>
<th>Fraction of Ss with EPS</th>
<th>Percentage of Ss with EPS</th>
<th>Times for onset of EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/kg</td>
<td>mg</td>
<td></td>
<td></td>
<td>Hours after drug</td>
</tr>
<tr>
<td>15</td>
<td>0.8</td>
<td>0/4</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>none</td>
<td>1/7</td>
<td>14</td>
<td>12</td>
</tr>
<tr>
<td>23</td>
<td>1.0</td>
<td>2/4</td>
<td>50</td>
<td>24, 28</td>
</tr>
<tr>
<td>23</td>
<td>none</td>
<td>1/4</td>
<td>25</td>
<td>27</td>
</tr>
</tbody>
</table>

* Administered 5, 8, 11, 24, 26, 28, and 30 hours after fluphenazine.

subjects. Because these doses of physostigmine had no significant effects upon the subjects, their data are combined with those of other subjects in the following analyses. Removing these eight subjects would not change the findings, but it would reduce the sample sizes and give uneven dose categories.

B. EPS-Dose Relationships.

Sixteen of the 50 subjects tested developed EPS. The occurrence of EPS was clearly dose-related (tables II A and II B). The Pearson Product-Moment Correlation Coefficient of 0.92 suggests that, within a select age and weight group of healthy young men, the predictability of gross extrapyramidal effects from fluphenazine is good, much better than is apparently commonly assumed.

C. Temporal Occurrence and Type of EPS.

Of the 16 subjects who developed EPS, six had two or more episodes of EPS, with two men at the highest dose each showing three or more episodes of EPS. Fourteen subjects had their first reaction on the second test day, between 22 and 33 hours after administration of the drug (table III), and the remaining two subjects had a second or third episode of EPS during this interval. All the episodes occurring during this interval were dystonic and included spasms of the muscles of the back (3), legs (3), tongue (7), neck (9), and jaw (3). One oculogyric crisis occurred at 28 hours. The two subjects who experienced EPS prior to 22 hours showed akathisia at 5 and 10 hours and dystonia at 12 hours. At 53 hours, one subject had, as a second EPS episode, an occurrence of parkinsonian rigidity and posture; other than this episode, EPS did not occur after 33 hours. Figure 1 presents the time and type of occurrence of EPS for each subject.

In the subjects at the highest doses, EPS occurred earlier and more repeatedly. Considering only the subjects with EPS, the percentage at the highest dose range (35 to 40 µg/kg) exceeded the percentage at all other doses for both occurrence of EPS within the first 12

*A probit analysis yields an ED50 dose for EPS of 29.5 µg/kg with 95% confidence limits (CL) of 20.9 to 41.7 µg/kg.

**Some of EPS episodes included more than one of these reactions.
### Table II.A. EPS-Dose Relationship

<table>
<thead>
<tr>
<th>Dose of</th>
<th>Fraction of</th>
<th>Percentage of</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluphenazine</td>
<td>S with EPS</td>
<td>S with EPS</td>
</tr>
<tr>
<td>µg/kg</td>
<td>µg/kg</td>
<td>µg/kg</td>
</tr>
<tr>
<td>10-15</td>
<td>0/8</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>1/7</td>
<td>14</td>
</tr>
<tr>
<td>20</td>
<td>3/10</td>
<td>30</td>
</tr>
<tr>
<td>23</td>
<td>3/8</td>
<td>38</td>
</tr>
<tr>
<td>25-27</td>
<td>4/8</td>
<td>50</td>
</tr>
<tr>
<td>35-40</td>
<td>5/9</td>
<td>56</td>
</tr>
</tbody>
</table>

### Table II.B. Probit Analysis

<table>
<thead>
<tr>
<th>Percentage of</th>
<th>Dose predicted</th>
<th>95% CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>S with EPS</td>
<td>µg/kg</td>
<td>µg/kg</td>
</tr>
<tr>
<td>1.0</td>
<td>8.0</td>
<td>2.4-25.9</td>
</tr>
<tr>
<td>16.0</td>
<td>16.8</td>
<td>17.3-27.8</td>
</tr>
<tr>
<td>50.0</td>
<td>29.5</td>
<td>20.8-41.7</td>
</tr>
<tr>
<td>84.0</td>
<td>51.6</td>
<td>21.1-126.2</td>
</tr>
<tr>
<td>99.0</td>
<td>109.3</td>
<td>20.2-591.8</td>
</tr>
</tbody>
</table>

### Table III. Time of Onset of First EPS at Each Dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>Hours after drug</th>
<th>Average of log time</th>
</tr>
</thead>
<tbody>
<tr>
<td>µg/kg</td>
<td>Hours after drug</td>
<td>Hours after drug</td>
</tr>
<tr>
<td>38-40</td>
<td>5.0, 24.0, 26.0, 27.0, 30.0</td>
<td>19.1</td>
</tr>
<tr>
<td>25-27</td>
<td>23.0, 25.0, 27.0, 29.5</td>
<td>26.0</td>
</tr>
<tr>
<td>23</td>
<td>24.0, 27.5, 28.0</td>
<td>26.4</td>
</tr>
<tr>
<td>20</td>
<td>26.5, 27.5, 28.0</td>
<td>27.3</td>
</tr>
<tr>
<td>17</td>
<td>12.5</td>
<td>12.5</td>
</tr>
</tbody>
</table>
Figure 2. Median Number-Facility (NF) Percent Scores

10-20 μg/kg (N=25)
23-40 μg/kg (N=25)
Figure 4B. Track-Tracer-Error Time

N = 4
σ = STANDARD DEVIATION FROM CONTROL SCORES

EXPERIMENTAL TIME, HOURS AFTER DRUG

Figure 4B. Track-Tracer-Error Time
Table IV. Track-Tracer Scores Compared With EPS

<table>
<thead>
<tr>
<th>Subject</th>
<th>Tests showing impairment</th>
<th>Maximum score</th>
<th>EPS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 1</td>
<td>Day 2</td>
<td>Day 3</td>
</tr>
<tr>
<td>1</td>
<td>14%</td>
<td>30%</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>14%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>0%</td>
<td>80%</td>
<td>50%</td>
</tr>
<tr>
<td>4</td>
<td>0%</td>
<td>20%</td>
<td>0%</td>
</tr>
</tbody>
</table>

A test was considered to show impairment if both repeated measures of error time and number of errors exceeded the average of the repeated measures on the predrug test. About 17% of the tests should be abnormal by chance, provided there is no significant order effect. Total number of tests were: day 1, 7; day 2, 10; day 3, 2.

Table V. Occurrence of Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>First day</th>
<th>Second day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sickness</td>
<td>% Ss</td>
<td>% Ss</td>
</tr>
<tr>
<td>Sleepiness</td>
<td>90</td>
<td>4</td>
</tr>
<tr>
<td>Restlessness</td>
<td>32</td>
<td>6</td>
</tr>
<tr>
<td>Irritability</td>
<td>40</td>
<td>8</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>26</td>
<td>2</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>22</td>
<td>0</td>
</tr>
</tbody>
</table>
Sleepiness also showed no relation to the chances that EPS would occur; actually, nearly all the subjects were sleepy on the first day. In fact, two subjects who later showed EPS were among the few who were not even noted to be sleepy on the first day.

F. Physiologic Findings.

No appreciable pulse or pupil-size changes occurred following the administration of fluphenazine. A slight but consistent drop in systolic and diastolic blood pressure occurred in 72% of the subjects from 2 to 4 hours after drug. Neither the magnitude nor the occurrence frequency of this hypotension was dose related.

G. Personality Relationships to Dysporic Drug Effects.

Because many investigators have found that personality variations can influence behavioral and subjective responses to phenothiazine drugs, the pretest scores available for 20 subjects* on the MMPI the Picture Frustration Test were analyzed for the relationship between the irritability response and personality. For each personality measure, the Mann-Whitney U statistic was calculated for the group that became irritable compared with the group that did not. The analysis showed that those that became irritable had significantly \( P < .01 \) higher scores on the paranoid (Pa) scale of the MMPI than did the other subjects. To a lesser extent, the irritable group also showed higher scores on the hypochondriasis (Hy) scale of the MMPI \( P < .05 \). None of the other eight MMPI scales showed a relationship in this regard, nor did the Picture Frustration Test scores. Furthermore, the arithmetic performance of the irritable subjects was not different from that of the other subjects.

Table VII presents the percentage of irritable responders as a function of the dose above or below 24 \( \mu \)g/kg and Pa scores above or below the mean of the standard college norms. The data in the table suggest that both dose and Pa scores relate to the percentage of irritable responders, as indeed was seen when each factor was considered separately.

H. Blood Levels of Cholinesterase.

At 5 hours after fluphenazine, plasma cholinesterase activity was slightly but consistently depressed, but red-cell cholinesterase activity was not consistently changed. The range of depression of plasma cholinesterase tended to be dose related: 0.05 to 0.38 \( \mu \) moles substrate/ml sample/min for those four men who received 15 \( \mu \)g/kg of fluphenazine, and 0.25 to 0.45 \( \mu \) moles/ml/min for the four men who received 23 \( \mu \)g/kg (Mann-Whitney U = 2, \( P = .06 ** \)). At 24 hours, plasma cholinesterase levels had returned to their control levels (figure 5). While the changes in cholinesterase levels at 5 hours are consistent, they are small and of uncertain significance.

IV. DISCUSSION.

A. EPS, A Later-Phase Phenomenon.

It is somewhat puzzling that for 90% of the subjects who showed EPS, it occurred only on the second or third day after drug administration—a time when the behavioral, mental, and gross motor effects of fluphenazine were either mild or no longer present. One possible

*Complete scores were available only for the 18 Army subjects and two of the prisoners.
**The coefficient of variance in these measures is 2.5%, which is a change of about 0.1 \( \mu \) moles/ml/min.
### Table VI. Subjects with Signs and Symptoms Other Than EPS

<table>
<thead>
<tr>
<th>Dose of fluphenazine (µg/kg)</th>
<th>Number of Ss</th>
<th>Subjects with Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Restlessness</td>
</tr>
<tr>
<td>10-15</td>
<td>8</td>
<td>12</td>
</tr>
<tr>
<td>17-20</td>
<td>17</td>
<td>29</td>
</tr>
<tr>
<td>23-27</td>
<td>16</td>
<td>44</td>
</tr>
<tr>
<td>35-40</td>
<td>9</td>
<td>33</td>
</tr>
<tr>
<td>Significance*</td>
<td>NS**</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

* Determined by $\chi^2$ test with Yates correction, comparing the 25 subjects at low doses with the 25 subjects at high doses.
** Not significant.

### Table VII. Irritable Responders as a Function of Dose and MMPI Paranoid (Pa) Scores

<table>
<thead>
<tr>
<th>Pa “T” score</th>
<th>Dose of fluphenazine (µg/kg)</th>
<th>Number of Ss</th>
<th>Subjects who became irritable</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50*</td>
<td>10-23</td>
<td>8</td>
<td>1 13</td>
</tr>
<tr>
<td></td>
<td>25-40</td>
<td>2</td>
<td>1 50</td>
</tr>
<tr>
<td>≥ 50*</td>
<td>10-23</td>
<td>6</td>
<td>4 67</td>
</tr>
<tr>
<td></td>
<td>25-40</td>
<td>4</td>
<td>4 100</td>
</tr>
</tbody>
</table>

* The mean of the norms is a “T” score of 50.
Figure 5. Average Plasma Cholinesterase Levels
explanation of this delayed effect is that somnolence inhibited the expression of EPS, as has been suggested from clinical observation.14, 15 This position, however, can only explain the lack of EPS on the evening and night of the first day, when most of the subjects were sleepy. Also, two subjects who did not show EPS until the second day were not observed to be sleepy on the first day. There was no clinically observed relation between sleepiness and EPS. One important evidence against a relation between EPS and sleepiness is that onset time does not increase with increasing dose, but, if anything, decreases with increasing dose.

B. Track-Tracer Performance Impairments and EPS.

The temporal agreement between track-tracer impairment and EPS was not surprising. Haase14 found that handwriting changes occurred in an average of 95% of the patients taking phenothiazines, and he felt that these changes were fine extrapyramidal signs. If fine-motor-task impairment reflects EPS, it would be reasonable to expect these impairments to be reversed, like EPS, by the antiparkinsonian drugs. Haase claims this to be the case, but the limited data from this report suggest the opposite. Although treatment reversed the EPS, it did not reverse the decrement in track-tracer scores. On the one hand, this may only be a problem of dose; reversal of the fine motor impairments may require a larger treatment dose than do the gross EPS. On the other hand, it is quite possible that separate mechanisms are involved in these different effects of the phenothiazines.

C. Cholinergic Factors in EPS.

The failure of physostigmine to alter the occurrence of EPS provides a striking contrast to the impressive work by Duvoisin.11 He showed that 1 mg (iv or subcutaneously) of physostigmine salicylate dramatically intensifies EPS in patients with Parkinson's disease. The logical basis for Duvoisin's study was the following assumption. If atropine* and physostigmine cause quite different effects on a biological system and antagonize each other's influence on that system, there is strong, indirect evidence that cholinergic mechanisms are operating on the system. The converse argument cannot be made as strongly. The results from this study, nonetheless, failed to show that drug-induced EPS involves cholinergic mechanisms, in contrast to the work with EPS occurring with parkinsonism.** These results also conflict somewhat with the conclusion of Morpurgo16, 17 who stresses the importance of cholinergic factors in EPS, which she relates to phenothiazine-induced catatonia in animals. Higher doses of physostigmine would be required to make more positive assertions, but these results certainly suggest a possible basic difference between drug-induced and parkinsonian EPS.

D. The Irritability Response to Fluphenazine.

Irritability and heightened anxiety following the administration of neuroleptic drugs has not been an uncommon occurrence in psychiatric patients. However, in these carefully chosen, healthy volunteers, the frequent occurrence of these reactions was unexpected.

The etiology of these so-called paradoxical reactions to neuroleptics is still in doubt. Theories of the psychological school include that of Sarwer-Foner,4 who sees the anxious...
response to neuroleptics as a reaction to the unacceptable passivity that these drugs can cause; and that of Goldman, who feels that the antipsychotic effects of these drugs rob psychotic patients of their customary compensatory mechanisms. Kornetsky and Humphries and Forrest et al. found that highly anxious, psychologically normal subjects react with anxiety to phenothiazines, and Frostad et al. and Heninger et al. reported that athletic, extroverted volunteers responded most dysphorically.

Although the above-mentioned psychological reports do not have mutually exclusive conclusions, they demonstrate a lack of agreement in emphasis. On the organic side, Di Mascio et al. found that chlorpromazine, but not perphenazine and trifluoperazine, caused irritability in normal volunteers. In a further study, Gardos et al. found that chlordiazepoxide increased hostile and aggressive feelings in volunteer subjects, whereas oxazepam decreased these feelings.

The findings of the present study support the fact that psychological factors are important in the proclivity to the reaction of irritability. Although marginal, the relationship between the Hy scale and irritability is hardly surprising, because a high score on the scale suggests a tendency to be expressive and active. The relationship between irritability and the Pa scale seems less obvious. Normal people who score high on Pa are often described as sensitive, emotional, and prone to worry, according to S. R. Hathaway and P. E. Mehl. Perhaps it is not too surprising that this type of person should be prone to irritable reactions. The failure of either the psychasthenia (Pt) or social introversion (Si) scale to relate to irritability is somewhat surprising, considering the earlier studies discussed above. Apparently, neither anxiety or introversion is as important for irritability as is sensitivity or the tendency to express emotions.

It is important to note that all these subjects had MMPI scores well within normal ranges. Indeed, the selection of subjects was aimed at insuring that they were psychologically healthy. The high frequency of drug-induced irritability in healthy volunteers, along with the relation to dose, supports the argument that direct organic factors, as well as indirect psychological factors, play an important etiologic role in this response.

E. Comparison With Other Fluphenazine Studies.

The studies reported in this paper are exceptional in that they have taken advantage of both normal volunteers and a “one-shot” administration of a long-acting phenothiazine. Because of the prolonged drug effects, the single dose permits a more careful description of the relation between the various symptoms. The use of normal volunteers permitted a more reliable description of the symptoms.

Certain other factors should be noted in comparing this study with others. Young adults have more dystonic reactions than do their elders, and males have more dystonic reactions than do females. Oral doses of fluphenazine have been reported to produce perhaps fewer sedative effects and fewer dystonic EPS than parenteral administration.

V. SUMMARY AND CONCLUSIONS.

Fifty healthy young male volunteers were given 10 to 40 µg/kg (im) of fluphenazine dihydrochloride. All subjects were studied at regular intervals for behavior and symptom appraisal, arithmetic performance, and physiological changes. Twelve subjects were also tested for manual dexterity and digit recall. Blood cholinesterase activity of eight subjects was measured just prior to a series of 0.8- or 1.0-mg doses (im) of physostigmine. Four subjects were also tested for fine visual-motor coordination by use of a track-tracer test.

The major findings were as follows: (1) Fluphenazine caused extrapyramidal signs (EPS) and fine visual-motor coordination impairments in some subjects, but these signs usually did not appear until 24 hours after administration of the drug; all other drug effects occurred primarily within the first 24 hours. (2) The probability of the occurrence of EPS was strongly dose related ($r = 0.9$). (3) Drug-produced irritability occurred primarily on the first day, showed a positive correlation both to dose and to the score on the MMPI Paranoid scale, and was not related to EPS. (4) Slight, clinically insignificant, dose-related plasma cholinesterase depressions occurred on the first but not on the second day after fluphenazine. (5) Repeated customary doses of physostigmine did not influence any parameters of the fluphenazine effect. (6) Fine visual-motor impairments did not respond to the customary treatment for EPS.

The results suggest both that the drug-induced EPS forms a curious late phase of the drug action, which apparently may not directly involve cholinergic mechanisms, in contrast to EPS occurring in Parkinson's disease; and that the drug-induced irritability may well have a direct organic etiology in addition to a psychological proclivity. The results also suggested that impairment of fine visual-motor coordination may not be directly related to the appearance of gross EPS.
LITERATURE CITED


This work was started in February 1967 and completed in June 1968.

A study of 50 psychologically normal male volunteers given 10 to 40 μg/kg of Fluphenazine dihydrochloride (Prolixin) showed that extrapyramidal signs (EPS) occurred commonly on the second day and were dose related. Irritability also occurred frequently, and was related to dose and personality. Both motor and cognitive performance were related to dose, but only fine motor functioning was related to EPS. Small doses of phystostigmine were used to explore possible cholinergic mechanisms involved in EPS. When given in repeated small doses, phystostigmine had no effect upon the EPS.
[ This page is intentionally left blank. ]