DEPARTMENT OF THE ARMY
US ARMY RESEARCH, DEVELOPMENT AND ENGINEERING COMMAND
5183 BLACKHAWK ROAD
ABERDEEN PROVING GROUND MD 21010-5424

REPLY TO
ATTENTION OF:

August 20, 2009

Office of the Chief Counsel

Mr. John Greenewald, Jr.
[redacted]

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.

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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

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EDGEWOOD ARSENAL
TECHNICAL REPORT

EATR 4348

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

by

(b)(6)

February 1970

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

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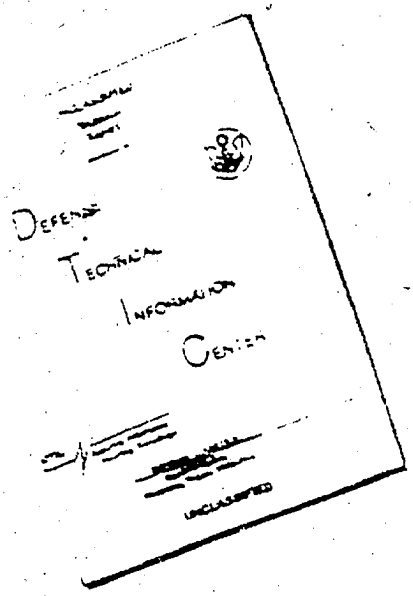

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EDGEWOOD ARSENAL TECHNICAL REPORT

EATR 4348

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

by

(b)(6)

Clinical Research Department

February 1970

Task 1B562602AD1202

DEPARTMENT OF THE ARMY
EDGEWOOD 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.

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.

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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),[1] the only published study on the psychopharmacology of the drug in normal subjects was one by Kitzes.[2] 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 behavorial 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.[3, 4, 5]

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.[6] 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), serumglutanic 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 pupilometer 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.

3. Performance Tests.

At the regular test interval, all subjects took the Number Facility Test (NF), which is part of Moran and Mefferd's repetitive psychometric measures.[7] 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 test[9] 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,[10] 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[11] 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.[12] 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.[13]

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.

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Table I. Effects of Repeated Physostigmine Treatment

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

*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 IIA and IIB).* 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 IIA. EPS-Dose Relationship

Dose of fluphenazine	Fraction of Ss with EPS	Percentage of Ss with EPS
μg/kg		
10-15	0/8	0
17	1/7	14
20	3/10	30
23	3/8	38
25-27	4/8	50
35-40	5/9	56

Table IIB. Probit Analysis

Percentage of Ss with EPS	Dose predicted	95% CL
	μg/kg	
1.0	8.0	2.4-25.9
16.0	16.8	17.3-27.8
50.0	29.5	20.8-41.7
84.0	51.6	21.1-126.2
99.0	109.3	20.2-591.8

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

Dose	Hours after drug	Average of log time
μg/kg		*Hours after drug*
38-40	5.0, 24.0, 26.0, 27.0, 30.0	19.1
25-27	23.0, 25.0, 27.0, 29.5	26.0
23	24.0, 27.5, 28.0	26.4
20	26.5, 27.5, 28.0	27.3
17	12.5	12.5

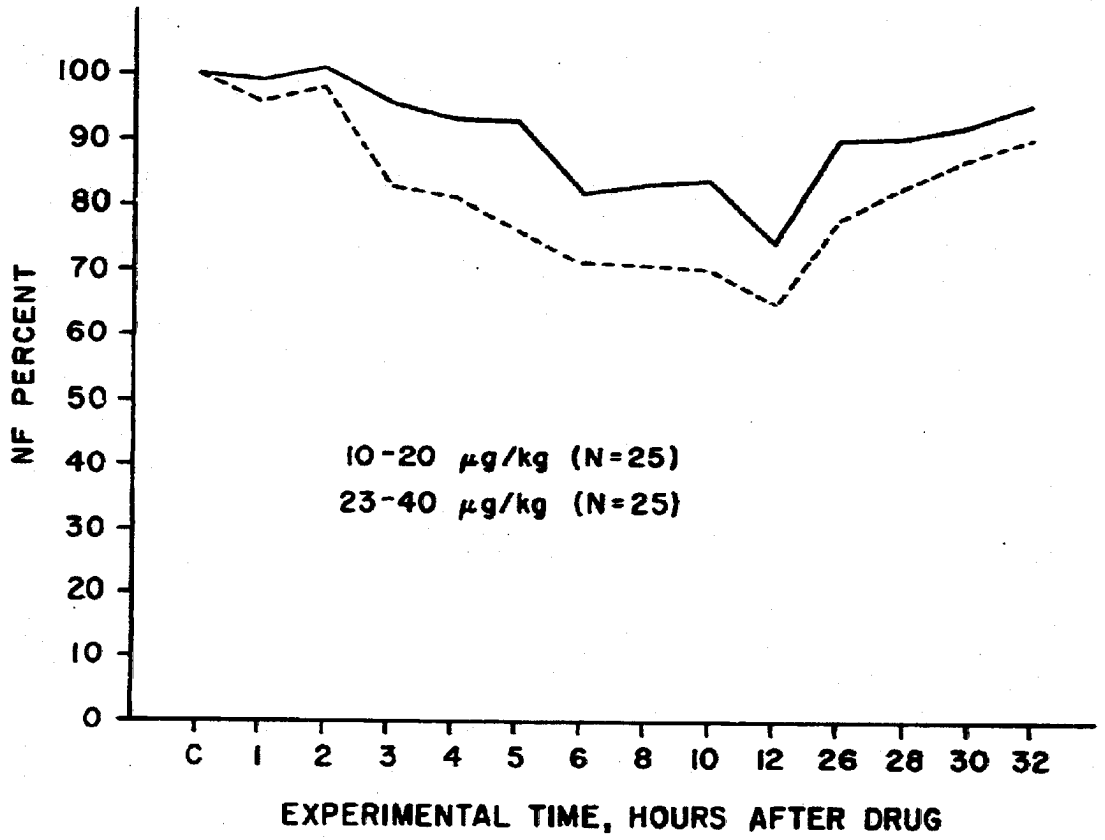

Figure 2. Median Number-Facility (NF) Percent Scores

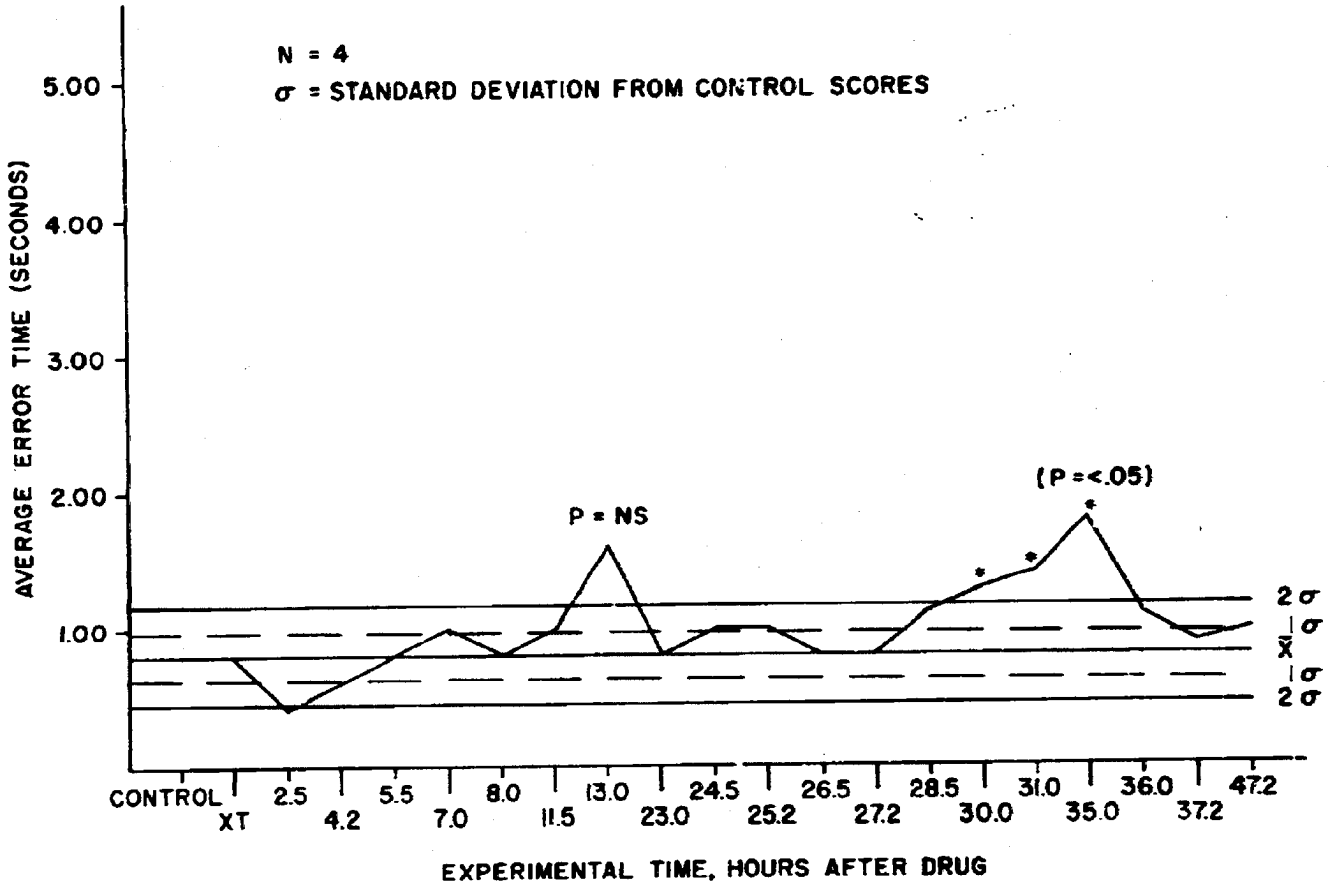

Figure 4B. Track-Tracer-Error Time

Table IV. Track-Tracer Scores Compared With EPS

Subject	Track-tracer test					EPS	
	Tests showing impairment*			Maximum score			
	Day 1	Day 2	Day 3	Error time	No. of errors	No. of episodes	Type
	%			% of control			
1	14	30	0	400	227	0	–
2	14	40	0	286	155	0	–
3	0	80	50	242	293	3	Dystonic
4	0	20	0	109	388	2	Dystonic, oculogyric crises

*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

Symptom	First day	Second day
	% Ss	
Sleepiness	90	4
Restlessness	32	6
Irritability	40	8
Blurred vision	26	2
Dry mouth	22	0

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 and 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 μg/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 μmoles substrate/ml sample/min for those four men who received 15 μg/kg of fluphenazine, and 0.25 to 0.45 μmoles/ml/min for the four men who received 23 μg/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 μmoles/ml/min.

Table VI. Subjects with Signs and Symptoms Other Than EPS

Dose of fluphenazine	Number of Ss	Subjects with Signs and Symptoms				
		Restlessness	Irritability	Dry mouth	Sleepiness	Blurred vision
μg/kg				*%*		
10-15	8	12	25	12	100	0
17-20	17	29	24	12	100	12
23-27	16	44	62	19	88	50
35-40	9	33	44	44	89	33
Significance*		NS**	< 0.05	NS	NS	< 0.05

*Determined by χ^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

Pa "T" score	Dose of fluphenazine	Number of Ss	Subjects who became irritable	
	μg/kg		*No.*	*%*
< 50*	10-23	8	1	13
	25-40	2	1	50
≥ 50*	10-23	6	4	67
	25-40	4	4	100

*The mean of the norms is a "T" score of 50.

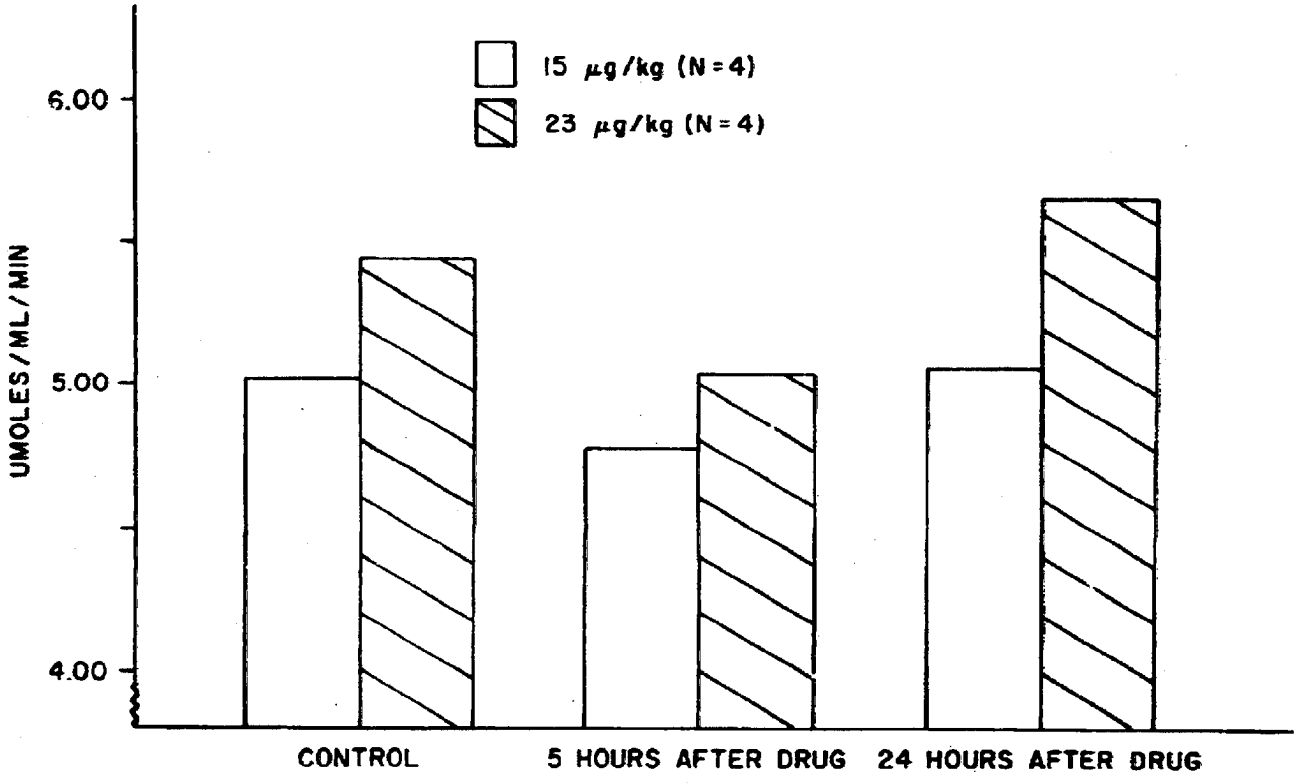

Figure 5. Average Plasma Cholinesterase Levels

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. Haase[14] 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 Morpurgo[16,17] 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

*Atropine-like compounds such as Benadryl and Cogentin reverse EPS.

**It should be noted that the fluphenazine-induced EPS observed in the present study were predominantly dystonic rather than parkinsonian. The highest dose of fluphenazine did, however, produce EPS similar to that observed in parkinsonism.

response to neuroleptics as a reaction to the unacceptable passivity that these drugs can cause; and that of Goldman,[18] who feels that the antipsychotic effects of these drugs rob psychotic patients of their customary compensatory mechanisms. Kornetsky and Humphries[19] and Forrest et al.[5] found that highly anxious, psychologically normal subjects react with anxiety to phenothiazines, and Frostad et al.[20] and Heninger et al.[3] reported that athletic, extroverted volunteers responded most dysphorically.

Although the above-mentioned psychological reports do not have mutually exclusive conclusions they do demonstrate a lack of agreement in emphasis. On the organic side, Di Mascio et al.[21] found that chlorpromazine, but not perphenazine and trifluperazine, caused irritability in normal volunteers. In a further study, Gardos et al.[22] found that chlordiazopoxide 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 relationships 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. Meel.* Perhaps it is not too surprising that this type of person should be prone to irritable reactions. The failure of either the psychaesthenia (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.[23] Oral doses of fluphenazine have been reported to produce perhaps fewer sedative effects[24] and fewer dystonic EPS[25, 26] than parenteral administration.

*S. R. Hathaway and P. E. Meal, Adjective Check List Correlates of MMPI Scores. Unpublished materials at University of Minnesota. 1952.

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.

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13. ABSTRACT

(U) A study of 50 psychologically normal male volunteers given 10 to 40 µg/kg of Fluphenazine dihydrochloride (Proxlixin) 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 physostigmine were used to explore possible cholinergic mechanisms involved in EPS. When given in repeated small doses, physostigmine had no effect upon the EPS.

14. KEY WORDS

Physostigmine
Cholinesterase
Extrapyramidal signs (EPS)
Incapacitation
Prolixin
Fluphenazine
Performance measurement
Psychopharmacology
Irritability
Minnesota Multiphasic Personality Inventory (MMPI)
Number Facility Test (NF)
Trail-Tracer Test

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