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U. S. Army

Chemical Research and Development Laboratories

Technical Report

CRDLR 3074

Clinical Investigation of EA 1729 (U)

by

Van M. Sim

June 1961

ARMY CHEMICAL CENTER, MD.

~~SECRET~~

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CLINICAL INVESTIGATION OF EA 1729 (U)

by

Van M. Sim

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(U)

FOREWORD

The work described in this report was authorized under Project No. 4C08-02-022, Medical Aspects of Chemical Warfare (U). The work was started in 1955 and completed in 1960.

Acknowledgments

The author wishes to make it clear that the studies reported in this document represent the work of many individuals, both within these Laboratories and under contract. A number of the studies described have been reported in the open literature, but several are being reported here for the first time. Particular acknowledgment is made of the collaborative efforts of Capt. Joseph R. Bertino, Capt. Duane Collier, Capt. Leslie E. Geiger, and Dr. Gerald Klee in the studies on dose-response effects; the work of Capt. Ernest R. Clovis in planning, coordinating, and evaluating many of the demonstrations; and the work of Dr. Kazuo K. Kimura, Dr. Alvin I. Goodman, and Dr. Bernard J. Clark, who conducted many of the experiments reported. The author also wishes to thank Mrs. Marion P. Royston for her assistance in compiling this report.

(S) DIGEST

EA 1729 (lysergic acid diethylamide, LSD25) has been studied extensively in animals and in humans as a possible incapacitating CW compound. Clinical, physiological, and psychiatric studies have been conducted.

From the standpoint of biological effectiveness, EA 1729 incapacitates man at doses as low as 1 μg/kg, the degree of incapacitation increasing with the dose. Its effects endure for periods ranging from 6 to 24 hours. There is a very wide margin of safety between the incapacitating and lethal doses.

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(S) CLINICAL INVESTIGATION OF EA 1729 (U)

I. (S) INTRODUCTION.

(S) The ability of EA 1729 (lysergic acid diethylamide, LSD25) to produce aberrant mental behavior in humans came to the attention of the U. S. Army Chemical Corps about 1947, and this material has been one of the most promising CW incapacitating compounds since that time. It is the most potent of the incapacitating agents studied to date and has the very important attribute of a large safety margin between the incapacitating and lethal doses.

(U) The objectives of the project under which the reported work was carried out are:

1. To supply fundamental knowledge concerning the nature of the mechanism and sites of action in man of CW agents and of prophylactic and therapeutic drugs.

2. On the basis of this information, to suggest the development of novel or more effective agents, as well as to develop diagnostic, protective, antidotal, and therapeutic devices and procedures applicable to poisoning by such compounds.

(U) A research and development program on agents that temporarily incapacitate but do not kill requires a more complex structure of research than is necessary for a program on lethal agents. Quantitating the lethality of a compound does not require the extensive knowledge of the physiological and pharmacological effects of the material that is required when dealing with an incapacitating compound, especially one that produces effects on the mind. It has therefore been necessary to extend the program of these Laboratories to include studies that will yield the more detailed information on incapacitating agents required to meet the program objectives.

(C) Because of its profound effect on the mental processes of man, EA 1729 is of interest to investigators in many parts of the world. It has been used extensively to produce experimental model psychoses that sometimes mimic the acute schizophrenic patient. The survey of open publications continues, keeping the Laboratories cognizant of the work being done and permitting an economy of effort. These Laboratories have restricted studies to those questions that would probably not be considered by private research because they are especially applicable to the search for and evaluation of CW agents and the treatment of casualties therefrom.

(U) Since the establishment of the Medical Research Volunteer Program in 1955, numerous studies in volunteers have yielded sufficient data to delineate essentially the physiological and psychological effects of this material in man. Dose-response relationships also have been determined, and the effectiveness of a number of antidotal and blocking agents has been evaluated.

(C) The effect of EA 1729 on the ability of small groups of individuals to participate in activities that require group cooperation has been assessed. These demonstrations were followed by field tests designed to measure this agent's disorganizing and disrupting influence on a disciplined military unit.

(U) An extensive and systematic investigation of the nervous system of lower animals has been undertaken as a step toward arriving at a more complete understanding of the mechanism and site of action of psychotomimetic agents in man. The continuing need for improved methods of recognizing potent psychochemical agents in animals, in order to permit the effectual and expeditious evaluation of the large number of compounds that the Chemical Corps must screen, motivated many of the animal studies reported.

(C) The potency of several analogs and homologs of EA 1729 has been studied to determine whether they merit consideration as CW incapacitating agents.

(U) The data reported fall into two categories:

1. Work that has been done in these Laboratories or performed in cooperation with other military organizations which is being reported for the first time.

2. Work in universities by contractors, which may have been reported in the open literature, as a classified contractor's report, or in a collaborative study at this facility.

II. (C) HUMAN STUDIES.

A. (C) Clinical, Physiological, and Psychiatric Studies.[1, 2, 3, 4]

(C) A conservative estimate is that approximately 3,000 doses of EA 1729 have been given to some 1,500 individuals either in clinical studies at Army Chemical Center, in group demonstrations and exercises conducted at other military installations, or in contract programs at the University of Maryland Psychiatric Institute; Tulane University, Department of Neurology and Psychiatry; New York Psychiatric Institute; and University of Washington Medical School, Department of Pharmacology. These studies indicated that

the effects elicited by EA 1729 increase more or less proportionately to the dosage, up to 2 μg/kg. Above this dose, there was no clear-cut relationship between dose and response. Subjects have had very distinct effects from only 25 μg(total dose), but they were relatively mild compared with those produced by higher doses. Most subjects received total doses of approximately 70 to 150 μg. At this dose range, the majority of men had marked effects. After considerable numbers of clinical trials, it was found that, for field demonstration purposes, total doses of 100 to 150 μg (without strict regard to body weight) were sufficient to cause incapacitation.

(C) The general physiological effects of EA 1729 are mild, consisting of pupillary dilatation and a slight increase in blood pressure and pulse rate. Nausea and dizziness and an increase or a decrease of appetite are also reported by some subjects. The only consistent neurological change noted was an increase in deep tendon reflexes, such as knee, ankle, wrist, and elbow hyperreflexia. The major and most consistent physiological effect was disturbance of visual perception, evidenced by distortion of shapes and objects, and, subjectively, by hallucinations of colors and geometrical patterns. The latter were more pronounced in darkened rooms.

(U) Psychological changes were consistent and profound. Almost all the subjects had difficulty in concentrating, making decisions, and communicating. The particular type of observed reaction depended on the total personality of the individual. The broad term "personality" in this sense means the evaluation of psychological and psychometric testing, as well as the psychiatric evaluation of the individual's ability to cope with his social environment, either in military or in civilian life.

(U) The observed reactions ranged from tenseness to panic and from friendliness to (rarely) verbal manifestation of aggressiveness without physical action.

1. (C) Dose-Response Effects.

(C) In an experiment to determine the dose-response effects of EA 1729, 18 volunteers were given a different dose of the drug at weekly intervals for a total of 3 weeks. The oral dosages used were 1, 2, 4, 8, and 16 μg/kg body weight, dissolved in distilled water and administered on a double-blind basis. Even at the highest concentrations used, the drug was found to be odorless, colorless, and tasteless.

a. (C) General Effects.

With increasing doses, the onset of signs and symptoms became more rapid and more severe. At the 16 μg/kg dose level, symptoms were noted 5 to 10 minutes after ingestion. Severe psychic effects lasted 10 to 24 hours, and, in a few instances, 24 to 48 hours. Tingling, numbness, lightheadedness, and "woozy" feelings were reported by the majority of subjects. Impaired time sense and slurring of speech were frequent results.

b. (C) Other Effects.

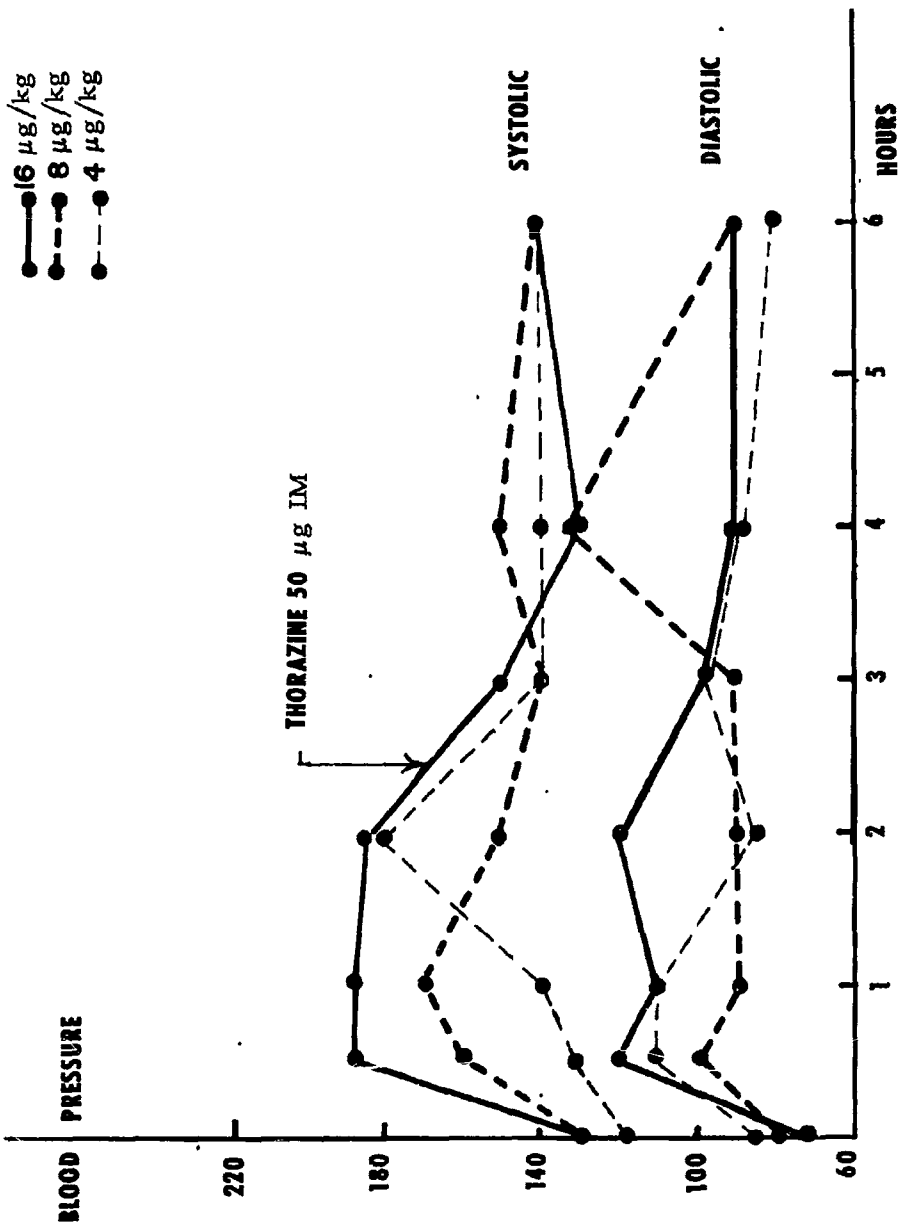
(1) (C) Neurological Changes.

At the 4 μg/kg dose level, difficulty in walking was evident. Some volunteers preferred not to leave their beds, but two subjects at this dose level exhibited extreme restlessness and paced up and down with little difficulty in walking. Confusion and severe perceptual disturbance seemed to be responsible for the impairment of locomotion. Tests of cerebellar function gave normal results; only slight incoordination was seen. Mutism was observed in two volunteers at the higher dose levels, and at 16 μg/kg one volunteer became totally uncommunicative for 4 hours.

Increased deep tendon reflexes were noted in some subjects at the 1 and 2 μg/kg dose, and all subjects given doses of 4, 8, and 16 μg/kg exhibited hyperreflexia. Above the 4 μg/kg level, there seemed to be no correlation between the degree of hyperreflexia and dose.

(2) (C) Circulatory Systemic Changes.

Generally, it was found that blood pressure increased with the drug dose. Systolic and diastolic pressure rises were maximal 2 to 3 hours after a dose of 1 to 2 μg/kg. When the dose of EA 1729 was 4 μg/kg or higher, the maximum blood pressure was observed 30 minutes after drug administration. In almost every subject, blood pressure returned to control levels within 6 hours postingestion. Blood pressure effects were most pronounced when anxiety, restlessness, and panic were predominant symptoms. However, regardless of the psychological reaction, a blood pressure rise was noted in every subject given doses of 4, 8, and 16 μg/kg. Figure 1 illustrates the effects on blood pressure of 3 doses of EA 1729. Due to the apprehension and hyperactivity of this subject, 50 μg/kg of Thorazine was given intramuscularly and was followed by a rather rapid decrease of both systolic and diastolic pressure. Figure 2 indicates the change in blood pressure in an individual receiving doses of 4, 8, and 16 μg/kg of EA 1729 at 1-week intervals. It would appear that the difference in these two subjects (figures 1 and 2) is that



(C)

FIGURE 1

BLOOD PRESSURE CHANGES RESULTING FROM THREE DOSES OF EA 1729 AND AFTER TREATMENT WITH THORAZINE (U)
(Subject C. A.)

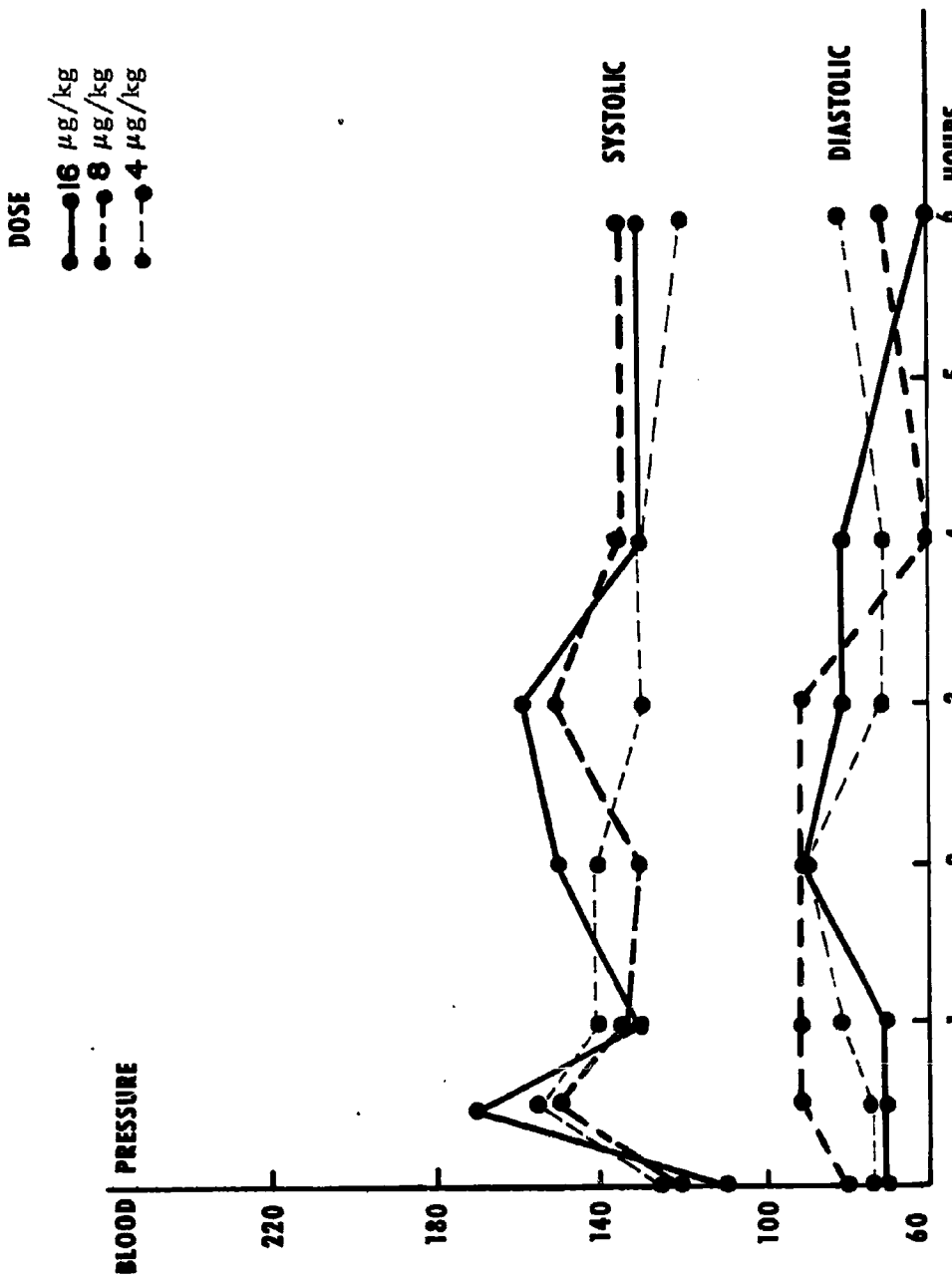


FIGURE 2

(C)

BLOOD PRESSURE CHANGES RESULTING FROM THREE DOSES OF EA 1729 (U)
(Subject A. B.)

in the hyperreactor both the diastolic and systolic pressures rose rather rapidly in the first 30 minutes whereas in the subject described by figure 2 the systolic pressure rose without a concomitant marked increase in the diastolic pressure. Acceleration of the pulse rate was observed in all volunteers given more than 2 μg/kg, and pulse rate changes paralleled blood pressure increases. No instances of abnormal rhythm or extrasystoles were recorded.

(3) (U) Pupillary Size Changes.

Pupillary dilatation could not be measured accurately because of the difficulty in getting the subjects to cooperate, to move into a room with constant illumination. Estimates of pupillary size were made on the basis of 0 for no change to 4^+ for maximum dilatation. Subjects given 4 μg/kg had an average of 3^+ change in pupil size, while higher doses produced no apparent increase of this near-maximum dilatation. Light reflex and accommodation were normal. Table 1 summarizes these changes.

(C)

TABLE 1

CHANGES IN PUPILLARY SIZE RESULTING FROM EA 1729 (U)

Number of subjects	Dose EA 1729	Average increase in pupillary size*
	μg/kg	
6	1	1+ (0-2+)
6	2	2+ (1+-2+)
18	4	3+ (2+-3+)
12	8	3+ (2+-4+)
11	16	3+ (3+-4+)

* (U) 0 = no change
4+ = maximum dilatation

(4) (C) Nausea and Vomiting.

At low doses of EA 1729, nausea was usually transient; at higher doses, it became more persistent. No subject given a dose of 1 and 2 μg/kg vomited. Both the severity and frequency of nausea and vomiting increased with dosage, as seen in table 2.

(C)

TABLE 2

FREQUENCY OF NAUSEA AND VOMITING AFTER ADMINISTRATION OF EA 1729 (U)

Number of subjects	Dose EA 1729	Nausea	Vomiting
	μg/kg		
6	1	2/6	0/6
6	2	3/6	0/6
18	4	10/18	1/18
12	8	10/12	4/12
11	16	8/11	5/11

(5) (C) Respiratory Changes.

Changes in respiration were not evident at low doses of EA 1729. At 4 μg/kg, one subject developed hyperventilation, respiratory alkalosis, and a positive Chvostek sign. Four of the 12 volunteers who received 8 μg/kg and 4 of the 11 volunteers who received 16 μg/kg also exhibited hyperventilation with signs of alkalosis. Carbon dioxide levels in blood, taken 3 hours after drug administration, were determined in 6 subjects at various dose levels, and the results are summarized in table 3.

(C) TABLE 3

CO_2 LEVELS BEFORE AND AFTER ADMINISTRATION OF EA 1729 (U)

Subject	Dose	Hyperventilation	CO_2 content (venous whole blood)	
			Predrug	Postdrug
	μg/kg		vol %	
J.G.	4	+	63.7	56.3
R.R.	4	-	62.1	61.0
R.T.	8	-	51.3	55.5
W.L.	8	-	60.4	47.6
D.B.	16	-	48.9	51.9
R.B.	16	+	59.3	41.7

(6) (U) Electrocardiogram (ECG) Findings.

(U) ECG's were taken on 12 subjects, both under control conditions and at the height of the drug reaction (table 4 summarizes the data obtained). The most significant change in the ECG was a prolongation of the P-R interval, but this bore no relationship to the dose of drug ingested. There does, however, appear to be some relationship between P-R changes and the occurrence of nausea.

(U) In all except one case, prolongation of the P-R interval at a given dose was followed by an equal or longer P-R interval at the higher doses.

(U) There were several other ECG findings, but these were inconsistent. The findings which were not consistent were changes in voltage and small but insignificant changes in S-T segment patterns.

(C)

TABLE 4

PROLONGATION OF P-R INTERVAL AFTER ADMINISTRATION OF EA 1729 (U)

Dose EA 1729	Prolongation of P-R interval (.01 sec)					
	-1	0	1	2	3	4
µg/kg						
4	0	2	2	2	2	0
8	0	1	4	2	1	0
16	1	1	1	3	2	1
Total	1	4	7	7	5	0
Nausea	0	1	5	4	5	0

(7) (C) Electroencephalogram (EEG) Findings.

EEG's were recorded on two subjects given a 16 µg/kg dose of EA 1729. The recordings taken at the height of the EA 1729 reaction were difficult to interpret because of excessive muscular activity over the frontal and temporal leads. No reliability was placed on these records. Other studies by contractors have covered the EEG findings.

(8) (C) Blood Chemistry Changes.

Electrolyte studies included calcium, magnesium, chlorides, sodium, and potassium determinations and showed no significant change after administration of EA 1729. Blood glucose determinations of six volunteers given doses of 4, 8, and 16 µg/kg showed a slight rise 2 hours after drug ingestion.

(9) (U) Temperature Changes.

Skin and body temperatures were also measured on these subjects. In general, body temperatures fell slightly (0.5° to 1.0°C) at doses of 8 and 16 µg/kg.

(10) (U) Insomnia.

Insomnia, a common complaint of the volunteers, could be related to the dose of drug administered. Subjects with insomnia were effectively treated with 100 mg secobarbital.

2. (C) Correlation of Oral and Aerosol Doses.

In a test to determine the comparative effectiveness of inhalation and oral doses of EA 1729, four volunteers were first exposed to aerosols of the agent and then administered oral doses 2 weeks to 1 month later. Aerosol total doses (particle size MMD = ca 2.4μ) ranged from 11.8 μg to 67.7 μg; oral total doses were 70 and 72 μg. It was found that the agent produced similar reactions by both routes, results differing only in rapidity of onset. After oral doses, onset occurred within 30 to 40 minutes; after inhalation doses, onset occurred within 15 to 25 minutes.

3. (C) Effect on Human Tracking Ability and Discriminability of Radar Symbols.

Several tests were conducted to evaluate the effects of EA 1729 on the performance of military tasks that require quick, accurate, visual discrimination.

In one test of 11 volunteers, 5 served as controls and 6 received oral doses of 150 μg of EA 1729 2 hours before testing. Differently shaped symbols were presented to the subjects on a Planned-Position-Indicator Radar Display, which is integral to the Antiaircraft Fire Control System. One symbol was designated the target symbol during each display, and subjects were required to recognize and count the frequency with which the target symbol appeared among varying numbers of three different symbols. A total of 24 symbols appeared on each display; the frequency of the target symbol was varied from 2 to 4. Statistical comparison of scores for the control group versus the drugged group indicated that the mean scanning time and number of trials during which an error occurred increased significantly for the drugged group at the 5% and 0.1% level, respectively (table 5). In the control group, the mean scanning time was 2.74 seconds; in the drugged group, it was 4.53 seconds. In the control group, the total number of errors was 15; in the drugged group, it was 57.

In another test, 16 volunteers participated in a study to evaluate the effects of 3 dose levels of EA 1729 on tracking proficiency. The tracking device used responded to steering much like a tracked vehicle, and the

accuracy with which operators tracked a moving target of light was scored automatically by photo cells and counters. For example, when the subject deviated 1° from perfect tracking, 3 or 4 photo cells were stimulated. Each subject had five 15-minute trials per day for 4 days. On the second and fourth days, the men were given placebo. On the third day, 2 men were given an oral dose of 50 μg of EA 1729, 6 received 100 μg, and 8 received 150 μg. Only those subjects who received 150 μg showed a significant decrement in their tracking ability. The minimum decrement in performance for the 150-μg-dose group was twice as large as the maximum decrement in the performance of the 100-μg-dose group. The maximum decrement in the 150-μg-dose group was nearly six times greater than the maximum decrement of any operator in the 100-μg-dose group.

(C) TABLE 5

INDIVIDUAL AND GROUP SCORES FOR SCANNING TIME AND NUMBER OF ERRORS COMMITTED IN CONTROL AND DRUGGED GROUPS (U)

Performance criteria	Control-group subjects					Drugged-group subjects*				
	A	B	C	D	E	F	G	H	I	J
Mean scanning time (in sec)	3.06	2.75	3.40	1.94	2.75	5.27	6.10	3.74	4.58	4.68
Group mean scanning time			2.74 sec					4.53 sec		
Total number of errors committed	2	5	4	3	1	28	6	6	8	9
Number of trials during which one or more errors occurred	2	4	4	3	1	10	6	6	4	7

* Dose = 150 μg

4. (C) Effects on Humans as Determined by Self-Rating Tests.

A group of ten volunteers was given 100 μg of EA 1729 by mouth. These subjects rated themselves by the Clyde Mood Scale* four times: once before taking the drug, and again at 1, 2, and 6 hours after taking the drug. Table 6 lists their responses to the six general factors into which the 133 adjectives were categorized. The "jittery" factor is the one that most clearly differentiates the subjects' drug and nondrug self-descriptions. "Clear thinking" is depressed at 1 and 2 hours after drug, but by 6 hours subjects have largely recovered.

(C) TABLE 6

MEDIAN FACTOR SCORES ON THE CLYDE MOOD SCALE (U)

Factor	Predrug	Postdrug		
		1-hr	2-hr	6-hr
Friendly	50.5	47a/	44.5	44.5b/
Energetic	53	50	49	49c/
Clear-thinking	55.5	49a/	40b/	51.5
Aggressive	45	42	43	40
Jittery	42	54c/	68b/	51a/
Depressed	42	44	48c/	43

a/ 0.02, least significant difference
b/ 0.01, least significant difference
c/ 0.05, least significant difference

NOTE: Ten subjects received 100 μg of EA 1729 by mouth. Significance of the difference between each postdrug test value and the predrug value for that factor was tested by the Wilcoxon Signed Ranks Test.

* (U) The Clyde Mood Scale is a self-rating test consisting of 133 cards, each bearing an adjective that is descriptive of feeling. The subject sorts these cards into four groups, according to the degree to which he feels a given adjective describes him at the moment. The degrees are: "not at all," "a little," "quite a bit," and "extremely."

5. (C) Effects on Personality Factors.

Paranoid reactions to EA 1729 have frequently been noted in normal subjects. In most cases this reaction can be related to definite personality factors of the subject. It was found that the amount of drug and the environmental conditions may influence the degree of EA 1729 reaction, but the predrug personality appeared to be the determining variable in paranoid reactions.

6. (C) Effect on Body Image.

Figures drawn by 18 college graduates, when they were experiencing the effects elicited by ingestion of 72 μg of EA 1729, showed less attention to detail, a greater number and higher severity of distortions, and a more disturbed line quality than figures drawn by the same subjects when normal. The figures drawn under drug also tended to be larger than the control figures.

7. (C) Effect on Intellectual Functions.

Sixteen subjects were tested on two forms of the Wechsler Memory Scale and Gorham Proverbs test under a control state and after ingesting 72 μg of EA 1729. Of the Wechsler Memory tests, only the abilities to draw geometric figures from memory, to reproduce brief prose passages, to count backward, to say the alphabet, and to perform serial addition were adversely affected by the drug. There was a significant difference between performance during the Gorham Proverbs test under control and drug conditions.

8. (C) Effect on Sense of Time.

Twenty-four subjects tested after ingestion of 1 or 2 μg/kg of EA 1729 for any alteration in their sense of time showed that external events are perceived as passing more slowly. This was a fairly consistent finding in most of the studies of this drug. In an Air Force study,[5] a comparison was made of the effects of isolation and the effects of EA 1729. It was found that the drugged volunteers felt a loss of their sense of time more frequently than did the undrugged, isolated volunteers. They also found that a few of the drugged subjects had the sensation that time was passing faster than usual. This acceleration of time was never observed in the studies performed in these Laboratories; in fact, the opposite has been true.

9. (C) Effect on Selected Subjective Reactions.

(C) Drugged subjects were tested for visual effects under three oral doses of EA 1729:

No. of Subjects	Dose μg
10	100
4	150
5	200

Each subject was tested twice: once in the normal state and once at the presumed peak of drug action (1-1/2 to 2 hours after administration). This testing included:

a. (C) Acuity: Snellen charts were projected one line at a time, with parallel series, to negate the effects of learning.

b. (C) Manifest Refraction: Nearsightedness, farsightedness, and astigmatism were checked objectively with a retinoscope and subjectively with a fogging technique.

c. (C) Muscle Balance: With the subject focusing at 20 feet, the Maddox rod was used; with the subject focusing on a near object, the Von Graph method was used.

d. (C) Color Discrimination: A series of 44 pseudo-isochromatic plates was shown to subjects.

e. (C) Depth Perception: The Verhoeff test was used to assess this function. The subject was presented with three vertical bars, one of which was either nearer to him or farther from him than the other two. He was asked to state which bar was out of line for each of a series of such presentations. This test permits the elimination of size as a systematic cue by varying size independent of distance.

(U) With scattered exceptions, these subjects did not reveal disturbances of vision. One of the 100 μg subjects showed a slight acuity drop in one eye, as did two of the 150 μg subjects. But at the 200 μg dosage, none of the subjects showed lessened acuity except for one subject who showed a changed refraction under the drug and failed one portion of the color test.

(U) A probable reason for this negative finding of visual effects is that no time limits were placed on these tests. Subjects took longer to read a given line of the Snellen chart under drug, commenting that "it comes and goes" or "now I see it; now I don't." It may be that strict time controls in the visual tests should be introduced along with other tests to check on motivation, concentration, ability to communicate, etc.

10. (C) Effect on Associative Processes and on Learning and Memory.

From the responses of 25 normal subjects to the Rapaport word association test after ingestion of 2 μg of EA 1729, it can be concluded that the learning of simple, specific, nonemotional, verbal material presented to the subjects orally is not affected at this dose.

11. (C) Effect on Funkenstein Test.

The effect of EA 1729 on cardiovascular changes resulting from injection of epinephrine and methacholine bromide (Mecholyl bromide, Funkenstein test) was studied in 14 volunteers. No subject showed a hyper- or hyporeactivity to methacholine (as defined by Funkenstein). The usual response to methacholine is an initial decrease in blood pressure associated with an increase in heart rate. This is followed in a short time by a heart rate that is below control values. Two hours after ingestion of 1.5 μg/kg of EA 1729, the subcutaneous injection of 10 mg of methacholine produced a relatively greater drop in blood pressure and a slower return to initial blood pressure levels than in the control. However, an analysis of covariance indicated that these results were probably attributable to the greater initial elevation of the blood pressure caused by EA 1729.

Subjects pretreated with EA 1729 had significantly smaller elevations of blood pressure (compared with their control values) after intravenous administration of 0.025 mg of epinephrine.

The results suggest that the cardiovascular mechanisms that react to a hypotensive stimulus respond normally in an EA 1729-drugged individual. The smaller rise in blood pressure following administration of epinephrine, although not correlated with the higher initial blood pressures caused by EA 1729, may still reflect the higher level of sympathetic activity seen clinically. It appears that as the initial level of sympathetic activity is increased the magnitude of physiological response, such as that seen with epinephrine, is decreased.

B. (C) Field Demonstration of Effects of EA 1729 in Humans.

(C) On 17 December 1957, a demonstration was conducted primarily to determine the problem of controlling a small group influenced by EA 1729 and also to provide a filmed record of the effect of the agent.

(C) Nine soldiers were ordered by a typical Army drill sergeant to "fall in." The squad responded like well-trained soldiers; the drill sergeant's commands were obeyed accurately and with precision. After the squad was given 2 μg/kg of EA 1729 orally and the undrugged drill sergeant again ordered the men to fall in, the response was entirely different. The men were euphoric and disorganized; commands were either disregarded or obedience was haphazard and indifferent. In a marching exercise, the men started fairly well but soon began to break ranks and straggle out. When a second drill sergeant who was drugged was given command of the squad, he did not perform effectively. In fact, when an officer ordered him to drill the squad, he responded with, "You want 'em drilled? You drill 'em!"

(C) On 18 December 1957, in another demonstration, eight volunteers were each given 2 μg/kg of EA 1729 orally. This group, before receiving the drug, had defeated another group in a volleyball game by a score of 21-5. After receiving the drug, they again defeated their undrugged opponents 21-17. It is believed that one individual, an Army private who demonstrated exceptional leadership, was instrumental in holding the group together. When he was removed from the game, there was a tendency for his team to slacken play.

(U) These two demonstrations indicated that individual reactions to this agent are varied: a drugged group can continue simple functions, but there is reduction in their effectiveness and teamwork is less efficient.

1. (C) Demonstration of Effects of EA 1729 to U. S. Army Chemical Corps School Personnel.

(C) The Chief Chemical Officer desires all officers assigned to the Chemical Corps to be thoroughly familiar with the current standard agents that the Corps has developed and those experimental or research compounds that show the most promise of ultimate development into effective agent or weapons systems. For this reason, several demonstrations of the effects of EA 1729 were conducted at the U. S. Army Chemical Corps School, Fort McClellan, Alabama, in which students and members of the staff and faculty participated. It was felt that actually experiencing the effects of EA 1729 would enable members of the Advanced Class to discuss more intelligently the potential of the compound, recognize its symptoms, and that additional clinical data could be gathered upon which to base a determination of the value of EA 1729.

(C) In these demonstrations, doses from 100 to 150 μg/man were administered orally to the participants, and then the individuals engaged in such activities as map exercises, target analysis, arithmetic problems, bridge and blackjack games. Some staff and faculty personnel attempted to give platform presentations and to conduct seminar-type discussions. It was found that under stress, in a platform presentation of familiar material, personnel were unable to complete a lecture successfully. In a similar group situation, previously rehearsed 5-to-10-minute presentations on completely familiar subjects, i.e., the diagnosis and treatment of tuberculosis by a medical officer, or a concise description of select problems of radioactive fallout by a trained radiological safety officer, were never completed by the subjects under drug. The results of the map-reading test taken by 68 subjects are contained in table 7.

(U) TABLE 7

RESULTS OF MAP-READING TEST (U)

Day	Mean score		Mean difference	Difference required for 0.05 confidence level
	Control	Experimental		
1	79.7	63.8	15.9*	11.8
2	79.8	59.8	20.0*	13.7
3	76.5	56.7	19.8**	12.9

* Significant 0.01 level

** Significant 0.05 level

2. (C) Demonstration of Effects of EA 1729 to XVIII Airborne Corps, Fort Bragg, North Carolina.

(C) After enough experiments in individual and small groups of volunteers had been carried out to ascertain that large-group studies were feasible, arrangements were made by CG, USCONARC, to conduct a test at Fort Bragg, North Carolina, in September 1958. Chemical Corps personnel supplied the necessary medical support for all test operations, but operational evaluation of the tests was made by members of the XVIII Airborne Corps. All scoring was based on standard artillery proficiency tests. Such an evaluation allows some judgment to be made of the military effectiveness of the agent. All evaluations of test results that appear in this report were furnished by the evaluation team of the XVIII Airborne Corps.

(U) Of the 70 men from the XVIII Airborne Corps Artillery who volunteered to compose the teams, 11 were rejected for either psychiatric or medical reasons. The crews selected represented above-average, skilled Army units, with exceptional morale. The tests were conducted in the field under anticipated operating conditions, with only minor deviations from normal procedure to insure the safety of individuals and to allow for photographic coverage.

(C) The total dose of 150 μg/man of EA 1729 was selected on the basis of previous clinical experience as a dose which would (1) produce measurable effects that would endure for the period of the test; (2) permit the degree of physical activity necessary; and (3) not be so severe as to result in a termination of the test before missions were accomplished. Although several of the volunteers received the compound more than once during the 5-week testing period, there was no evidence that the performance of these men was improved by previous drug experience.

(C) A double-blind procedure was used on all tests; EA 1729 in water and plain water as placebo were administered to the volunteers.

(U) The criteria used for selecting the types of teams to be used in the test were:

(U) a. Team missions should require the collective efforts of the individual team members to produce results.

(U) b. The success or failure of the accomplishment of the team mission should have a maximum effect on related operations.

(U) c. Maximum opportunity to supervise the safety of individuals composing the team should be possible.

(U) Two of each of the following groups participated in the tests outlined below:

(1) (C) Meteorological Section.

The mission of this section is to furnish necessary weather data* that will affect artillery projectiles or rockets in flight and will furnish winds-aloft data for prediction of fallout after an atomic burst.

* (C) Data obtained by this section are disseminated to artillery units throughout the Corps sections and can affect the firing accuracy of several artillery units.

(C) At 0820 on 3 September 1958, EA 1729 in water was administered to one of the meteorological sections; the other section received placebo. Both sections were assigned the mission of making weather balloon releases at 0830, 0930, and 1030 hours and reporting weather data gained from the releases. The section which received placebo disseminated completed messages at 0900, 1000, and 1100 hours. The drugged section disseminated a completed message at 0900 hours, but was unable to produce any part of a message after the next two balloon releases.

(U) Identical results were achieved when the same procedure was followed on 9 September 1959, the only change in the procedure being that the drugged and control sections were reversed.

(C) The evaluation team of the XVIII Airborne Corps concluded from this phase of the test that a meteorological section subjected to attack with EA 1729 would not be able to fulfill its mission.

(2) (C) Survey Section.

(C) The mission of this section is to furnish survey control data needed by artillery units to locate firing positions and targets.

(U) On 4 September 1958, both survey sections were given data for a survey control point and the mission of extending this control to another area. Under normal conditions successful accomplishment of this mission should be achieved within 2-1/2 hours.

(C) Immediately after EA 1729 and placebo were administered, the teams began survey operations. The drugged team required 5 hours 50 minutes to complete the task. The accuracy of the survey was within allowable tolerances only because the recorder was undrugged and was able to assure that all angles and taped distances were rechecked until he was certain of their accuracy. (When the test was repeated on 10 September and all members of the same section were drugged, the team required 3 hours 40 minutes to complete the survey, and accuracy was not within tolerable limits.) The undrugged (control) section completed its mission in 2 hours 5 minutes, and the results were accurate.

(C) The evaluation team of the XVIII Airborne Corps concluded that although a survey team subjected to attack with EA 1729 might be able to produce acceptably accurate results, the time required for completion of even the simplest type of survey would be so great as to make the survey section's accomplishment of its mission unsatisfactory.*

(3) (C) Fire Direction Team.

(C) The mission of this section is to control battery or battalion firing by converting information furnished by an observer into commands for guns to fire; to convert without adjustment data furnished by survey and meteorological sections into commands to deliver fire on targets when no observer is available.

(C) On 16 September 1958, the two fire direction teams were given a series of identical fire missions that were typical of their normal operations. An hour after receiving EA 1729, the drugged team was much slower in processing fire commands than the control section. Although the members of the drugged team were able to perform the necessary computations for delivering area-type fire on target with acceptable results, they could not fire precision missions with any degree of accuracy, mainly because of their inability to concentrate.

(U) Identical results were obtained when the test was repeated on 23 September 1958, the only change in procedure being that the drugged and control teams were reversed.

(C) The evaluation team of the XVIII Airborne Corps concluded that an artillery fire direction team would be unable to perform its mission satisfactorily while experiencing the effects of EA 1729.

(4) (C) 40-mm Antiaircraft Automatic Weapons Gun Section.

The mission of this section is to provide air defense for forward combat arms and to attack and destroy hostile targets on land or water, as required.

* (U) It should be borne in mind that the recorder was not drugged in the test on which this conclusion is based. That this would be the case in an actual situation is not probable.

(C) On 5 September 1958, the 40-mm antiaircraft automatic weapons gun sections were emplaced on a ridge which afforded a field of fire in all directions. Cameras were mounted parallel to the gun tubes, and an L-19 aircraft was used as the target. The tracking by the undrugged group was smooth and continuous, and the gun camera film indicates this group was able to accomplish its mission of defense against hostile aircraft. The tracking by the drugged group was jerky and not coordinated; the gun camera film proved that the only hits obtained by this group were accidental.

(U) When the test was repeated on 11 September, with the drugged and control groups alternated, similar results were obtained.

(C) The evaluation team of the XVIII Airborne Corps concluded that a 40-mm antiaircraft automatic weapons gun section subjected to attack with EA 1729 would be unable to track an aircraft that was using evasive tactics and, therefore, would not be able to accomplish its mission of furnishing antiaircraft protection.

Over-all Results

(C) The over-all results of the tests conducted at Fort Bragg (XVIII Airborne Corps) indicate that an artillery unit attacked with EA 1729 would be unable to deliver artillery fire effectively in support of ground operations.

3. (C) Demonstration at U. S. Army Special Warfare School, Fort Bragg, North Carolina.

On 29 September 1958, eight members of a Special Forces Group stationed at Fort Bragg were assigned guard posts and given specific instructions for restricted access to the area. Then they were given a dose of 150 μg/man of EA 1729 orally. Six posts, manned by drugged subjects, were penetrated successfully at least once and in some cases several times by personnel without proper identification. Two subjects did not permit unauthorized personnel to enter their posts. With one exception, none of the guards knowingly let an unauthorized visitor pass through his post. However, the men were easily confused and deceived as to what constituted the correct identification. The one exception was a subject who experienced an extreme reaction to the drug and would not remain on his post. Although the agent affected the men's sense of responsibility and duty, they also lost physical control, were unable to read the printing and signatures, and were easily confused.

It was concluded by personnel of the school that the use of EA 1729 in higher doses against enemy personnel would enable an exploiting force of small size to overcome the enemy force very rapidly and without violence.

On 30 September, six subjects were given an assumed tactical situation and told not to divulge this information during the course of a subsequent interrogation. After receiving a dose of 150 μg/man of EA 1729 orally, three of the men were successfully interrogated. When the test was repeated on 1 October, the six subjects did not show the usual reaction to the drug, and interrogation was generally unsuccessful. However, the men were confused to the extent that one unknowingly signed a confession of germ warfare.

A slightly higher dosage of EA 1729 would be effective in enabling an interrogator of limited experience to compel a subject to compromise himself and sign documents which would place his existence in jeopardy with the enemy.

4. (C) Demonstration at Infantry School, Fort Benning, Georgia.

(C) Forty-one officer-students of the Infantry School at Fort Benning participated in a test designed to familiarize combat arms groups with the effects of psychochemical agents. On the morning of 8 January 1960, oral dosages of 100 μg, 150 μg, and 200 μg of EA 1729 (the dosage increasing with the weight of the subject) were given in distilled water to test subjects. Thirty-four men actually received the drug; the remaining seven were unaware that they had received only water. When in the afternoon the test subjects were asked to indicate by a show of hands those who felt they had received little or none of the test material, only the seven control subjects responded.

(U) Comments written by the volunteers while in the drugged condition and after recovery revealed a variety of subjective responses. Visual perception hallucinations were manifested by blurring of images, and objects and people changing to a green or yellow color. For most, time seemed to come to a almost complete standstill. There was euphoria, inability to concentrate, confusion, and an almost complete lack of concern about anything.

(U) A basic arithmetic test, designed for students at the eighth-grade level, was administered to the group when under the influence of the drug and after recovery. When drugged, the group averaged a score of

13 out of a possible 100. After recovery, the class averaged a score of 89 out of a possible 100.

(U) In an English test, composed of many uses of everyday English and problems in correct-word selection, the class averaged a score of 55 out of a possible 136 when under the influence of the drug. After recovery, the class average was 112 out of a possible 136.

(U) Some of the comments on the value of the agent and the demonstration were:

"No amount of research on the effect of a psychochemical could have prepared me for the actual effect."

"The impressive thing about the drug is that so many of the normal students didn't detect anything particularly wrong. This would have a tremendous effect on an executive officer who knew his commanding officer wasn't behaving in a normal manner but who hesitated to relieve him and assume command."

"I had lost all sense of urgency as to the situation and duties that I was performing. During this period I never felt that I was incapacitated or that I was unable to perform what I desired to do. If the decision to request someone to take over my responsibilities and duties was to be mine, then it would never be accomplished."

"I do not think that any time during the day I was physically or mentally able to perform in my present MOS."

"I can never forget the effects the agent had on myself or other personnel. The thought of what could be done to an entire command or population is beyond comprehension."

5. (C) Demonstration of Effects of EA 1729 on Polygraph Examination.

(C) Fourteen subjects took part in a test (August 1958) to determine whether an individual experiencing the effects of EA 1729 is capable of persisting in deliberate falsehoods.

(U) During the control session, each subject was told to give a false answer deliberately to one question of a series asked him while he was undergoing a polygraph examination. The purpose of this control session

was to determine if each subject's response to a lie could be picked out of the polygram.

(C) In the drug sessions, each subject was also instructed to falsify one answer deliberately, and the machine record of the individual's reaction was read to see if the operator could detect the falsehood and select this area as one potentially valuable for further questioning. Subjects received a total oral dose of 100 μg to 150 μg of EA 1729.

(U) It was observed that:

(C) While under the influence of EA 1729, subjects are capable of falsification and persistence in a previously contrived falsehood.

(U) Falsification while under the drug appears to be limited to a "yes" or "no" type of response; the mental state of subjects appears to render them incapable of a complex false response.

(C) Polygraph examination of subjects experiencing EA 1729 effects indicates a more effective reaction to unexpected key questions than when the same or similar questions are put to the same subjects under normal conditions.

(C) The stress of the polygraph examination appears to be increased for subjects under the influence of the drug.

(C) In the spring of 1960, polygraph testing was again undertaken to determine whether it is more advantageous to polygraph a subject while under the influence of EA 1729 than in his normal state.

(U) It was observed that:

(C) In spite of some strong evidence pointing in that direction, it is impossible to state definitely that it is more advantageous to polygraph a subject while under the influence of EA 1729 than in his normal state. The principal limitation to a distinct advantage appears to be the inability of the polygraph operator to interpret the machine's charted graphs rather than the state of the subject under examination. The subject's condition under the drug's influence appears to be such that he is less capable of persisting in a precontrived falsehood because of mental confusion between the truth and a deliberately distorted response.

6. (C) Demonstration of Effects of EA 1729 in a Contrived Social Situation.

(C) In two tests (August 1958 and September 1959), subjects were a part of a contrived social situation (cocktail party). In the test conducted in August 1958, 6 of the 13 "naive" (inexperienced with the drug) subjects were surreptitiously administered 100 μg to 150 μg of EA 1729 in their first drink under double-blind conditions. In the test in September 1959, 12 (10 naive, 2 experienced) of 20 subjects received the drug. Otherwise, the conditions of the two tests were similar. The monitors assigned to each subject observed their behavior throughout the evening.

(U) It was specifically concluded that:

(C) It is possible to administer EA 1729 surreptitiously in alcohol. Most naive subjects are unaware that they are under the influence of a drug; however, there is a possibility that certain subjects, by comparing their drug reaction with their known reaction to alcohol, may relate their strange feeling to drugs.

(U) Subjects are reluctant to withdraw from the psychological support afforded by their remaining in a group situation.

(U) An uninformed observer cannot tell that a drugged individual's behavior is not attributable to alcohol. An observer who is familiar with the external physical symptoms of the drug's reaction is not able to state with certainty in all cases that an individual is drugged.

7. (C) Demonstration of Effects of EA 1729 When Subjects are in Isolation.

(C) Eleven subjects participated in a test (2 to 21 November 1958) of the combined effects of a 150 μg dose of EA 1729 and deprivation of external sensory stimuli (by confinement in an isolation chamber) to determine whether the combined effects of isolation and drug are different from those elicited by drug alone.

(C) Seven volunteers had prior experience with EA 1729 (sophisticated); three had no experience with the drug (naive); and one subject, although he had never taken EA 1729, had observed individuals who were under the influence of the drug.

(U) The three naive and three of the sophisticated subjects fled the unlocked isolation chamber before the arbitrary time limit of 4 hours (which the subjects did not know had been set).

(U) All of the sophisticated subjects reported that the combination of the drug and isolation generally intensified the over-all effects elicited by the drug alone. It would appear that naive subjects were more strongly affected.

8. (C) Demonstration of Effects of EA 1729 on Retentiveness and Recall.

(C) A program for testing retentiveness and recall under the effects of EA 1729 was conducted (3 November 1959 to 17 December 1959).

(U) Twelve subjects were verbally given a set of detailed instructions; they were permitted to take notes, ask questions, and repeat instructions over a period of 1 hour. Three hours later, after oral drug administration, the subjects were recalled and asked to repeat the given instructions to the monitor. The degree of completeness and accuracy of the subjects' recall of instructions was scored by the monitors according to preset weighted values.

(C) It was apparent that individual ability to absorb, retain for a period not exceeding 2 hours, and verbally communicate a body of new data of simple, logical, but detailed content was impaired by EA 1729.

(U) Similar ability in respect to a body of previously learned data of the same type is variably affected. Variability appears to be dependent upon the degree of sophistication of the individual with regard to previous experience with the drug. Impairment does not appear to be related to individual intelligence, training, or undrugged experience in similar situations.

III. (C) ANIMAL STUDIES.

A. (C) Neurophysiological Studies.

(U) It is not possible to restrict investigations into the problems of pharmacological psychoses to man because most neurophysiological techniques are not applicable to man. The alternative has been selected of studying the electrical activity of the brain of animals and correlating neurophysiology with behavior in so far as possible.

1. (C) The Pharmacological Properties of an Evoked Potential in the Midbrain Reticular Formation.[6,7]

(C) A study of the effect of EA 1729 on several electrophysiological properties of the cat brain revealed that even in massive doses EA 1729 failed to alter the evoked potentials in the electrocorticogram; the evoked potentials in primary visual, auditory, and somatic cortex; the direct response of the cortex; the transcallosal-evoked potential; and the somatic-evoked responses in the thalamus and midbrain reticular formation. EA 1729 does appear to exert a definite effect on electrical activity of the lateral geniculate nucleus, but the dose required to inhibit the postsynaptic potential in the lateral geniculate is probably 100 times the quantity needed to produce visual hallucinations in man.

(C) There is evidence that the process involved in visual hallucinations is in some manner associated with the lateral geniculate nucleus, and this might be evidence that the physiological effects of EA 1729 on the lateral geniculate are of clinical significance. This would, however, require human investigations, because hallucinations are a subjective phenomenon and no means of detecting hallucinations in animals is yet known. Also, paranoia and depersonalization are not applicable to the behavior of animals. No clinical study to date reports that EA 1729 has produced a definite neurological deficit, and in only a few reports has this drug been related to the organic toxic psychoses. This is of importance in interpreting the lateral geniculate effects of the drug since the most logical clinical manifestation of the effect would be decreased visual acuity, which has not been observed in man. One hundred times the hallucinating dose in man is required to alter the electrical properties of the lateral geniculate in cats and monkeys, and larger doses in monkeys appear to produce blindness. Therefore, decreased vision must be considered a toxic effect of the drug that is unrelated to its hallucinatory properties.

2. (C) The Effect of EA 1729 on Spinal Reflexes in Cats.[8,9]

(U) Zoxazolamine*, reported to be a centrally acting skeletal-muscle relaxant, was studied in cats to establish the validity of the techniques of studying inhibition of spinal reflexes. Electrophysiological techniques were used to analyze the mode of action of zoxazolamine. Interference from possible block at the neuromuscular junction or from interaction of afferent proprioceptive responses, inherent in techniques of muscular recording, was thus [illegible].

(U) A 10% solution of the drug dissolved in polyethylene glycol was administered intravenously. No significant blood pressure changes were observed at doses up to 50 mg/kg. Discharges in response to afferent-nerve

* (U) Flexin, 2-amino-5-chlorobenzoxazole

stimulation were recorded from ventral roots in 13 spinal cats. The monosynaptic and first polysynaptic spikes were unchanged by doses of less than 20 mg/kg. Above 30 mg/kg, the amplitudes of these complexes were reversibly decreased. The later polysynaptic spikes were reversibly inhibited at doses between 15 and 30 mg/kg. The dorsal roots of nine other spinal cats were stimulated with intense shocks to activate repetitive discharges, which were recorded from thin ventral root filaments. The frequency of discharge evoked by the stimulus and the background activity were found to be depressed by intravenous doses greater than 10 mg/kg or by 3 mg/kg injected into the upper abdominal aorta. The duration and degree of depression paralleled the dosage.

(C) After establishing the methodology and determining the effect of zoxazolamine on spinal reflexes, the effects of EA 1729 on spinal reflexes of cats were evaluated by measurement of changes in magnitude of the reflex volley in ventral roots rather than by recording muscular contraction. A gastrocnemius, tibial, or peroneal nerve was stimulated with single square wave stimuli (0.08 to 3 volts intensity and 0.1 to 0.4 msec duration). Twenty preparations of dosages ranging from 4 to 1,000 μg/kg of EA 1729, dissolved in sterile physiological saline, were administered in 36 injections through a cephalic vein. The characteristic modification of reflex activity after administration of EA 1729 was the increased height of monosynaptic response observed in 11 out of 16 injections of more than 200 μg/kg. Below this dose, only 1 out of 20 injections resulted in facilitation. The increased amplitude of the monosynaptic spike became apparent within 15 seconds after the injection and lasted from 4 minutes to 3 hours. Maximum facilitation was observed with 250 to 300 μg/kg doses. Higher doses prolonged the duration of facilitation, but did not increase the magnitude.

(C) This study indicates that EA 1729 may modify spinal reflexes in a manner analogous to that of epinephrine. Thus, EA 1729 may interact with proposed adrenaline-like transmitters.

3. (C) Localization of EA 1729 Action in the Brain.[10]

To attempt localization of EA 1729 action in the brain, the effect of chlorpromazine*, pentobarbital**, and EA 1729 were studied in

* (U) 2-Chloro-10-(3-dimethylaminopropyl)phenothiazine; 3-chloro-10-(3-dimethylaminopropyl)phenothiazine; N-(3-dimethylaminopropyl)-3-chlorophenothiazine; Torazina; 4560 R. P.; Novomazina; Propaphenin; Aminazine; Largactil; Ampliactil; Amplictil; Megaphen; Hibernal; Promazil; Thorazine; Wintermin.

** (U) Sodium 5-ethyl-5-(1-methylbutyl)barbiturate; Nembutal; Embutal; Pentyl; Pentone; pentobarbitone sodium; Sopental; Sagatal; Sotyl; Barpental.

cats with electrodes permanently implanted in the region of the hypothalamus. Upon electrical stimulation, these animals constantly responded with excellent patterns of behavioral rage. Although chlorpromazine produced definite behavioral depression or tranquilization, the hypothalamic rage response was little affected. Chlorpromazine may act by decreasing afferent input to the hypothalamus, thereby reducing its activity. In contrast to chlorpromazine, pentobarbital produced a marked decrease in the electrical excitability of the hypothalamus. EA 1729, in doses of approximately 400 μg/kg, produced a striking rage behavior. It has been postulated that this rage reaction is produced by activating some region, such as the amygdaloid nuclei, which then fires the hypothalamus.

4. (C) Effects of EA 1729 on the Medullary Vagal Center in the Decerebrate Cat.[11]

EA 1729 produced bradycardia, a decrease in respiratory rate, and hypotension in the intact cat anesthetized with pentobarbital, but this drug caused the reverse effects of hypertension and tachycardia in the spinal animal. An explanation advanced for this divergence of effects is that in the intact animal the hypertension and tachycardia due to peripheral vasoconstriction are masked by the more potent effects of EA 1729 on higher centers. Earlier work demonstrated that, in the decerebrate cat, ergot alkaloids caused hypotension and bradycardia via medullary vagal centers. Therefore, the possible vagal effects of EA 1729 in the decerebrate cat were studied.

EA 1729 appeared to have a medullary-stimulating action. The dose of this compound which produced clear-cut behavioral effects in the unanesthetized animal approximates the dose that produces a conduction disturbance in the decerebrate animal (0.4 mg/kg) and is approximately 400 times the amount that produces behavioral effects in man. In both the unanesthetized and the decerebrate cat, severe autonomic disturbances occur at this dose level, whereas in man pronounced changes in the autonomic nervous system occur at a dose of 4 μg/kg with behavioral changes occurring at 1 μg/kg.

5. (C) Effects of Lysergic Acid and its Derivatives on Rhinencephalic Electrograms of Monkeys.[12]

(C) Subcortical paroxysmal activity recorded from the septal and hippocampal regions in patients suffering from schizophrenia have been reported,[13,14] and rhinencephalic electrograms of humans under the influence of EA 1729 and mescaline have been studied.[15] It was found

that paroxysmal activity induced in the hippocampal, amygdaloid, and septal regions seemed to correlate with overt expressions of psychotic behavior. Because of this, 6 Macaca mulatta monkeys with chronically implanted subcortical electrodes in these rhinencephalic structures were given lysergic acid derivatives (d-LSD25, ALD52, MLD41, LSM, DAM, LPD, l-LSD25, BOL, and UML) with varying degrees of psychotogenic effects, and the monkeys were studied to determine whether this paroxysmal hypersynchronous activity in the rhinencephalic region is a spurious or an essential neurophysiological mechanism in individuals demonstrating psychotic behavior that is either spontaneous or pharmacologically induced. If a gross correlation could be made between the extent of hypersynchronous activity in the rhinencephalic structure and the overt behavior of the Macaca mulatta monkey, and then a gross correlation could be made between this rhinencephalic activity and the psychotogenic effects in man of various lysergic acid derivatives as established by Harris Isbell,[16] it would offer a screening device for both psychotogenic activity and tranquilizing drugs.

(U) No correlation was found between the pyretogenic, antiserotonin, or psychotogenic effect as found by Isbell studying these same drugs on humans. However, there did appear to be a good correlation between the behavioral effect in monkeys (which had the appearance of either disturbed catatonic-like or agitated behavior) and rhinencephalic paroxysmal hypersynchronous activity, particularly in the septal studies. Mescaline also showed a similar correlation. Studies on a combination of monoamine oxidase (MAO) inhibitor (phenylisopropylhydrazine)* and 5-hydroxytryptophane (a serotonin precursor which crosses the blood-brain barrier), showed minimal effects in the subcortical areas as well as minimal behavioral changes.

(U) Rhinencephalic paroxysmal hypersynchronous abnormality appears to be a good indication of the psychotogenic effects of such drugs.

B. (C) Biochemical Studies.

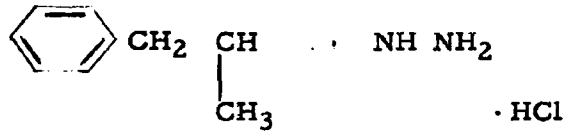
(C) Studies on β-Phenylisopropylhydrazine Hydrochloride.[17,18]

(C) If the postulate that an increase in brain levels of serotonin cause a response like that produced by EA 1729 and 5-hydroxytryptophane (hyperthermia, rage-like reaction, etc.), it should be possible to elicit these responses by preventing the destruction of the endogenous serotonin formed

* (U) JB516; 1-phenyl-2-hydrazinopropane; Catron, CS 2570.

by the tissues. Until recently the most effective MAO inhibitor in vivo was iproniazid*. Although iproniazid potentiates the effects of serotonin in animals, it causes little behavioral change unless given in near-lethal doses.

(U) Recently another hydrazine, β-phenylisopropylhydrazine (PIH), has been discovered that is an effective MAO inhibitor both in vitro and in vivo. The structural formula of this compound is:



(U) PIH in doses as small as 5 to 10 mg/kg was effective in potentiating the actions of 5-hydroxytryptophane in rabbits. In vitro, PIH was 50 times as effective as iproniazid as an MAO inhibitor when measured in rat-brain and liver homogenates, using serotonin as a substrate.

(U) When rats were treated with 20 mg/kg of PIH, it was found that maximum MAO inhibition occurred on the day of injection, but even after 7 days the liver had regained only about 80% of its original activity.

(U) PIH in a dose of 5 mg/kg had no effect on the rectal temperatures of rabbits. However, if this was followed by 10 mg/kg of 5-hydroxytryptophane, a marked rise in temperature resulted, followed by death of the animal.

(C) A dose of 20 mg/kg of PIH in cats produced such EA 1729-like effects as hissing, pupillary dilatation, salivation, tachypnea, fear, and rage reaction. Peak activity occurred about 8 hours after injection and effects persisted over a period of 25 hours.

(U) The slow onset of action suggests that PIH itself was not producing the symptoms, but that the inhibition of MAO (which develops rather slowly) was responsible for them. The action of PIH may be similar to the action of alkyl phosphates against cholinesterase enzymes, causing an irreversible inhibition of MAO and causing the accumulation and toxic actions of the endogenously formed amines.

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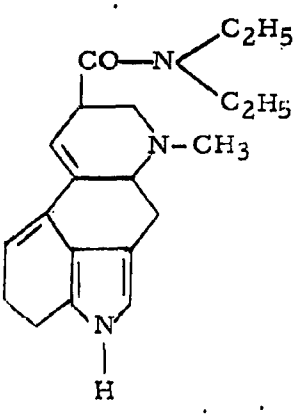
*(U) Isonicotinic acid 2-isopropylhydrazine; 1-isonicotinoyl-2-isopropylhydrazine; 1-isonicotinyl-2-isopropylhydrazine; Marsilid.

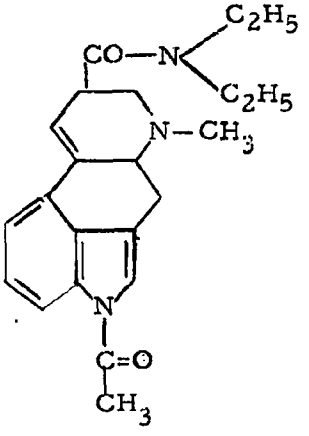
IV. (S) ANALOGS AND HOMOLOGS OF EA 1729.[19]

(C) EA 1729, ALD52 (1-acetyl-lysergic acid diethylamide), and MLD41 (1-methyl-lysergic acid diethylamide) were administered orally to 52 non-hallucinating, hospitalized, psychiatric patients and 34 normal volunteers. A comparison of the clinical effects produced by these compounds was made. It was found that 1.6 times more ALD and 1.7 times more MLD than EA 1729 are required to induce clinically apparent responses in both normal volunteers and psychiatric patients. The responses to ALD and MLD do not differ significantly from those experienced when EA 1729 was given. In contrast to the EA 1729 subjects, the ALD and MLD subjects did not seem to be disturbed by the drug reaction after the effects wore off. There were no problems presented in their psychotherapy relating to the study, as frequently happened after an EA 1729 study. Many individuals in the EA 1729 volunteer group were upset after the study and did not want to repeat it.

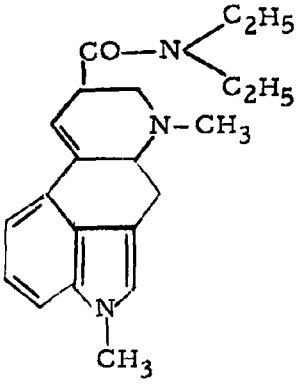
(S) The following are the structural formulas of d-LSD25, ALD52, and MLD41:



lysergic acid diethylamide d-LSD25 (EA 1729)



1-acetyl-lysergic acid diethylamide ALD52



1-methyl-lysergic acid diethylamide MLD41

V. (C) ANTIDOTAL OR BLOCKING AGENTS.

(C) Chlorpromazine (Thorazine) and dibenzylamine attenuate the acute EA 1729 reaction if given in doses of from 10 mg to 50 mg by intramuscular injection or by intravenous infusion about 30 minutes before EA 1729 is

administered. Frenquel*, Promazine**, Amytal sodium ***, and a combination of Amytal sodium and Desoxyn**** have been less effective in attenuating the acute symptoms of EA 1729 intoxication.

(C) Studies of Trilafon (perphenazine) as a blocking agent for EA 1729 revealed that onset of action is 30 minutes after intravenous administration of Trilafon. Therefore, it is considered to be inferior to chlorpromazine, which acts within 30 seconds after administration.

(C) Dibenzyline, an adrenolytic compound with adrenergic-blocking properties, was studied in 14 volunteers for its effect on the response to EA 1729 and to observe the psychological effects of dibenzyline itself. All were given 0.16 to 0.51 mg/kg of dibenzyline by intravenous infusion. Eleven of these volunteers received EA 1729 orally in doses of 1 μg/kg 1 hour after receiving dibenzyline. When given dibenzyline alone by intravenous infusion, seven of the volunteers developed orthostatic hypotension lasting 3 to 4 hours; one volunteer had orthostatic hypotension that persisted for 3 days. T-wave changes were noted in leads II, III, AVF, V4 to V6 of the ECG, which reverted to normal the following day. Six of the volunteers experienced impairment of concentration. One volunteer reported a dream-like state,

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* Azacyclonol, α,α-diphenyl-4-piperidenemethanol; α-(4-piperidyl)-benzhydrol; MER-17; gamma-pipradol.

** 10-(3-dimethylaminopropyl)phenothiazine; 3276 R.P.; WY 1094; Liranol; Prazine; Sparine; A 145; Verophen; Neo-Hibernex; Protactyl; Ampazine; Esparin.

*** 5-Ethyl-5-isoamylbarbituric acid; barbamyl; barbamil; amylobarbitone; 5-ethyl-5-isopentylbarbituric acid; Somnal; Dormytal; 5-isoamyl-5-ethylbarbituric acid; pentymal; Isomytal; Amytal.

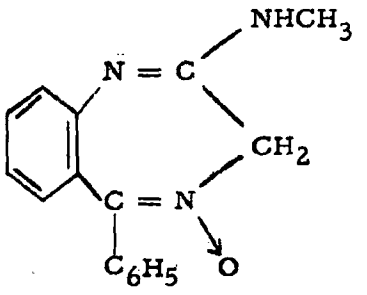
**** d-Desoxyephedrine hydrochloride. d-N,α-dimethylphenethylamine hydrochloride; phenylmethylaminopropane hydrochloride; the hydrochloride of dextro-1-phenyl-2-methylaminopropane; of d-phenylisopropylmethylamine; of d-N-α-methyl-β-phenylisopropylamine; of d-N-methylamphetamine. Norodin hydrochloride; Desoxyn; Pervitin; Drinalfa; Desoxyfed; Methylisomyn; Methedrine; Isophen; methamphetamine-HCl; Syndrox; Dexoval; Efroxine; Doxephrin; Semoxydrine; Hiropon; Soxysympamine; Destim; Gerovit; Tonedron; Adipex; Amphedroxyn.

subjective numbness of the body, a loss of time sense, and feelings of depersonalization and unreality. Another volunteer experienced considerable tension and vague apprehension. A third volunteer reported thought disorder, nervousness, slight numbness of the body, and subjective slowing of the passage of time.

(C) All subjects who received EA 1729 plus dibenzyline experienced reactions similar to those with EA 1729 alone, except for the mydriasis produced by EA 1729.

(C) BOL148 (2-bromo-d-lysergic acid diethylamide) has also been studied for its effect as a prophylactic compound against EA 1729.[20] Fifteen subjects received a daily oral dose of 200 μg to 300 μg of BOL148 for 3 to 5 days prior to a challenging dose of 1 to 4 μg/kg of EA 1729. The men were examined for changes in blood pressure, pulse, pupillary size, reflexes, and psychic and physical symptoms. It was found that pretreatment with 200 μg to 300 μg of BOL148 for several days before and on the day of EA 1729 challenge prevented to a large degree the psychic changes caused by 1 to 4 μg/kg of EA 1729. The physical signs and symptoms were also diminished by BOL148 pretreatment, and psychomotor tests confirmed the protection afforded by this compound. The BOL148 did not cause any consistent physiological or psychological changes.

(C) Librium (RO 5-0690) was tested for its therapeutic or prophylactic effects against EA 1729. One hour before receiving 2 μg/kg of EA 1729, three volunteers received total doses of 25, 50, or 75 mg of Librium, respectively, and one man was given a placebo. In another group of four volunteers, three received total doses of 25, 50, or 75 mg of Librium and one received placebo 1 hour after each had received 2 μg/kg of EA 1729. No modification of the reaction to EA 1729 was noted in those individuals who were given Librium. The following structural formula is that of Librium:



(C) Because various reports appearing in the literature stated that substances such as nicotinic acid were effective EA 1729 antidotes, some vitamins were studied.[21] Nicotinic acid, histamine phosphate pyridoxine, and thiamine were not found to be effective antidotes.

VI. (C) DISCUSSION.

(C) In 1955, the chairman of the Technical Advisory Panel on Biological and Chemical Warfare* appointed an ad hoc study group (the so-called Wolff Committee) to examine the problem of psychochemical agents, with a view to advising the Chemical Corps in regard to its future program. Based on an intensive investigation into the preliminary work the Corps had completed on psychochemicals and a survey of the open literature, the Wolff Committee recommended that:

(C) 1. A quasi-realistic experiment (outlined in detail in its report)[22] be carried out with EA 1729 and volunteer units as soon as practicable.

(C) 2. The potential and promise of the use of psychochemical agents in warfare be re-evaluated upon completion of the experiment.

(C) 3. Increased efforts be placed on screening chemicals in the lysergic acid class to find a substitute for EA 1729.

(U) 4. Conditioned reflex studies, using psychochemical agents, be made on dogs and additional higher animals other than man.

(U) 5. The dog or similar larger animals be employed in long-term toxication and lethal-dosage studies.

(C) All of the Wolff Committee's recommendations concerning EA 1729 have been carried out and are reported either in this document or in those mentioned in the bibliography.

(C) EA 1729 was selected as the model to be used in studies to provide some conception of the worth in warfare of materials that produce aberrant mental behavior because of its known action and because a tremendous amount of work already had been done with this compound in psychiatric research with humans.

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* Office of the Assistant Secretary of Defense, R&D

(C) Among the conclusions of the Wolff Committee is the following:

> The promise offered in this field can be determined only by assaying the effect of psychochemical agents on military units. If LSD25, used as outlined in the experiment, should fail to produce disorganizing and disrupting effects on the military unit, it would be evident that there is no military promise in this field. However, if the use of these agents should, under the specified conditions, produce serious disruptions in the ability of the unit to carry out its missions, then it could be reasonably stated that these agents offer great promise for use in military operations.

(C) The Fort Bragg field test described in this report is comparable to the experiment recommended by the Wolff Committee and certainly proved that EA 1729 will "produce serious disruptions in the ability of the unit to carry out its missions." If more realistic doses had been used (250 μg to 300 μg total per man), the men probably would have been so incapacitated that they would never have attempted to perform their mission requirements.

(C) From the studies reported in this document, the biological activity of EA 1729 can be summarized as follows:

1. (C) Effective Dose for Various Routes.

With respect to dose, EA 1729 is twice as effective as the next most potent CW incapacitating agent and psychologically incapacitates man by either the oral or the inhalation route. The effective dose ranges from 1 μg/kg upward, the degree of incapacitation increasing with the dose.

There has been insufficient work on the percutaneous application of EA 1729 to permit a conclusion on its effectiveness by this route.

In all the studies that have been conducted with this material, no human insensitive to EA 1729 has ever been encountered. Although it is possible to build up a tolerance to small doses by taking the drug over a period of time, no one has succeeded in developing a tolerance to doses of 300 μg/man or higher.

2. (C) Safety Factor Between Effective and Lethal Doses.

There is a very wide margin of safety between the incapacitating and lethal doses of EA 1729. Although the LD50 for man is not known, no

untoward effects were seen in dose-response studies ranging from 0.1 μg/kg to 16 μg/kg. No physiological effects have been seen at the highest doses given that would lead one to suspect that the limits of safety were even approached.

3. (U) Speed of Onset of Incapacitation.

Effects invariably were noted within 20 to 30 minutes following ingestion, autonomic physiological and perceptual changes appearing promptly and reaching a peak between 1 and 2 hours. Onset of effects occurred within 15 to 25 minutes after inhalation of 70 μg, and after large oral doses, within 5 to 10 minutes. Peak psychotic incapacitation usually developed by 3 to 4 hours after exposure. The predictability of the time of onset and duration of effects are valuable tactical assets.

4. (U) Duration of Incapacitation.

Subjects were incapacitated for periods ranging from 6 to 24 hours, depending on the dose received.

5. (C) Type of Action.

(C) EA 1729 produces consistent and profound psychological changes in man.

> Because the drugged individual is extremely confused, making decisions and communicating thoughts is almost impossible. Haphazard and indifferent obedience to commands is characteristic. The drugged subject has a distorted time sense; time passes extremely slowly and experiences cannot be related to time. Vision is impaired, waves of clear perception being followed by distortion. Because psychomotor coordination is impaired, the subject moves more slowly.

The appendix contains two excellent examples of individual subjective responses to this compound.

(U) The general physiologic effects are mild, being manifested in pupillary dilatation, a slight increase in blood pressure and pulse rate, nausea, and dizziness. At higher doses than those used in the studies reported here, psychological changes would be compounded by an increase in the severity of the physiological changes.

(C) To the untrained eye, EA 1729 intoxication is extremely difficult to recognize. Even when it is detected and treated with the compound of choice, chlorpromazine, the acute EA 1729 effects are attenuated, but the subject becomes a medical casualty.

6. (C) Degree of Incapacitation.

(C) Psychological incapacitation is difficult to scale in degrees. If one considers inability to accomplish an assigned mission as the criterion for complete incapacitation, the tests of EA 1729 with the XVIII Airborne Group at Fort Bragg certainly qualify this compound as one that produces complete incapacitation. After receiving EA 1729, the inability of trained instructors to deliver lectures that they have given time and again indicates a drastic mental incapacitation that has far-reaching possibilities when one considers the effect on subordinates of the mental derangement of a superior.

(U) At total doses above 300 μg, physical incapacitation would be almost complete.

7. (C) Routes of Entry.

EA 1729 is effective by both the oral and inhalation routes in comparable doses. The inhalation studies admittedly are meager and should be continued to provide a stronger basis for correlating the oral and inhalation effectiveness of this compound.

8. (U) Completeness of Recovery.

Every one of the exposures reported in this paper and about which the author has personal knowledge was followed by complete recovery.

9. (C) Species Variation.

Since such extensive work in humans has been done with EA 1729, it is not necessary to consider species variation in evaluating the potential effectiveness of this compound.

10. (C) Predictability of Military Effects.

In the one large field test conducted with EA 1729, every unit was so affected it could not perform its assigned mission. The diversity of the missions involved is significant. In this instance, a meteorological section, a survey section, a fire direction team, and an antiaircraft section were all rendered ineffective by EA 1729.

When interpreting the results of the demonstrations and field test, one should bear in mind that it was necessary to make a number of compromises that would not occur in an actual combat situation. All these compromises reduced the apparent effectiveness of EA 1729 and did not permit the attainment of the full potential of this agent. For instance, an artificial population of subjects resulted from the elimination of those who did not meet the standards of the physical and psychological examinations. In an actual combat situation, the effect of this compound on psychologically unstable individuals (who would most assuredly be found in any large group) might result in utter chaos.

Another artificial factor is that all of the subjects knew they would be given some kind of drug and that medical personnel would be constantly monitoring their response. By materially decreasing the stress that would normally accompany the development of bewildering psychic changes, one of the most profound effects of EA 1729, anxiety, was considerably diminished. Anxiety in the subjects under study was also reduced because these men had the advantage of a supportive group situation.

The dosages used in the field test and demonstrations (100 μg to 150 μg) were not as high as could be expected in a realistic battlefield situation. They were selected for their ability to produce measurable effects without so physically incapacitating the men that the experiment would be over before it began. Needless to say, higher doses would produce even more disrupting results. In spite of all these hindrances to achieving the full potential of EA 1729, every unit was rendered ineffective.

Because there is a fair percentage of hyperreaction to EA 1729, the question may arise as to whether people in a battlefield situation will be so affected that they will become menacing fighters. The author feels that should the drug cause an individual to become more aggressive, it would be of no consequence because his mental state would make it very difficult for him to distinguish the enemy from his own forces.

An interesting and significant outcome of the studies with this compound is that all military personnel who received EA 1729 were so impressed by their individual experience that they have enthusiastically advocated its military application.

VII. (S) CONCLUSIONS.

From the standpoint of biological effectiveness, EA 1729 incapacitates man at doses as low as 1 μg/kg, the degree of incapacitation increasing with the dose. Its effects endure for periods ranging from 6 to 24 hours. There is a very wide margin of safety between the incapacitating and lethal doses.

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(C) APPENDIX

TWO PERSONAL REACTIONS TO EA 1729 (C)

(Dose: 100 μg/kg)

I. (U). I experienced a multitude of strange, unusual sensations impinging upon me from every quarter. Visually, new bizarre colors and shapes flashed across my visual field. My hearing was changed. Sometimes things seemed to be louder, sometimes softer, and at times they seemed to come from a distance when actually they did not. At times my voice sounded as if it were not my own. The outer world was seen in separate, divided, jagged units, units that at times seemed to overlap, divide, and move independently. Things would often seem to jiggle as I walked. My body parts did not seem to be in the familiar relationship. I had to concentrate to be sure that my legs were there. It was a repeated surprise to find that I was able to stand up. My hands felt icy and different; my sense of touch was not as good as usual, and rubbing my hands together gave me little feeling. Swallowing a drink of water revealed quite well this inability to perceive accurate relationships between my body parts, for it felt as if the water was going down in a right, left, halting, circuitous fashion, and that at any moment it would decide that it could not go down at all, not because of any feeling of nausea, but because it seemed as though the water was getting lost and would have to come back. Waves of empty, icy, unfamiliar feelings gave me a feeling of bodily tottering in oceanic waves. Each time a wave hit me, I would have to try to redefine my relationship to space. These bodily sensations seemed to have an anticipatory relationship to a sensation of blindness that overtook me from behind and to the side. As I looked to the side, I could see but felt as if I wouldn't be able to. I was continuously being surprised by my capacity to function. I felt as if I could hardly talk, and yet when I put in the effort, I could. I felt like I would be very ataxic, but really was not. I felt that time was going much slower than it really was.

The more commonplace and usual things I could see, hear, and do, the better I felt. To talk, walk, and listen to others talk was anxiety-relieving. To be alone with my eyes shut was most disturbing. I began to worry that possibly this experience was not going to be just temporary. When I began coming out of the reaction, wonderful feelings were connected with seeing, touching, and being close to the common, usual, and familiar things. Whether or not these things were good, pleasant, or distasteful had little bearing. As long as they were familiar, they were highly reassuring.

II. (U) The first symptoms began to appear in 15 to 20 minutes after taking the drug. The first thing I noticed was a heavy feeling in my arms and legs. I felt as if I were glued to the chair in which I was seated. Faces appeared to have a reddish glow. The walls began to move back and forth in about three or four planes. Everything was in technicolor, so to speak, and each color was in its own separate dimension.

At about this time, I noticed that time began to stand still. My mind was racing ahead many, many hours, while those around me were living in minutes. This was the most confusing of the experiences I felt. Time had no meaning. I could not relate experience with time, nor could I concentrate on any one thing long enough to accomplish anything that I tried to do.

I would start to write something down and forget what it was before I could lift my pencil. So many things, sights, and sounds entered my mind in a second that it was extremely difficult to maintain a continuous train of thought.

When I would close my eyes, I witnessed the most beautiful display of designs and colors I have ever seen. When my eyes opened, they disappeared. I also experienced a sensation of leaving this world that can only be described as just not being here. In these out-of-the-world flights, I would live for weeks, it seemed, and yet, when I returned, only a matter of seconds would have elapsed from the time I left.

I actually thought days and nights were passing and that they had slipped us a larger dose than the others. I felt depressed for short periods and then extremely elated. All this over nothing. After awhile I noticed that the flights were becoming less frequent and that the periods of rationality were increasing. Finally, after about eight hours, all of the symptoms were just about gone. Under combat conditions I could not have performed my mission.

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107 President, U.S.A. Chemical Corps Board, Building 483, Army Chemical Center, Md.
108 School of Aviation Medicine, USAF, Attn: SAMLIBR, Brooks Air Force Base, Texas
109 Senior Army Representative, Department of Health, Education & Welfare, Room 2078 South Building, Washington 25, D. C.
110 Senior Standardization Representative, U.S.A. Standardization Group-UK, Attn: Chemical Representative, Box 65, USN 100, FPO, New York, N. Y.
111 - 112 Technical Library, Room G-2B, Office of Civil and Defense Mobilization, Attn: Director, Technical Library, Battle Creek, Michigan
113 - 114 3415th Technical School, USAF (TORF), Lowry Technical Training Center (ATC), Lowry Air Force Base 30, Colorado
115 U. S. Army Chemical Corps Advisory Council, Building 330, Army Chemical Center, Md.
116 U. S. CONARC Liaison Officer, Building 330, Army Chemical Center, Md.
117 Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington 12, D. C.
118 British Liaison Officer, Building 330, Army Chemical Center, Md.
119 - 128 Commander, Armed Services Technical Information Agency, Attn: TIPCR, Arlington Hall Station, Arlington 12, Virginia

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CLINICAL INVESTIGATION OF EA 1729 (U) - Van M. Sim

CRDLR 3074, June 1961
Project 4C08-02-022, SECRET REPORT

(C) LSD25 has been studied extensively in animals and in humans as a possible incapacitating CW compound. Clinical, physiological, and psychiatric studies have shown that this drug psychologically incapacitates man at a very low dose.

CONFIDENTIAL

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2. LSD25, animal studies
3. LSD25, field tests
4. LSD25, biological activity
5. Incapacitating agents, LSD25

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