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CHEMICAL CORPS MEDICAL LABORATORIES
SPECIAL REPORT

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MLSR No. 71

FIRST PSYCHOCHEMICAL CONFERENCE (C)

12 May 1954

by

Amedeo S. Marrazzi
Chairman and Coordinator

September 1955



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**CHEMICAL CORPS
MEDICAL LABORATORIES
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CMLRE-ML-52

Medical Laboratories Special Report No. 71

FIRST PSYCHOCHEMICAL CONFERENCE (C)

12 May 1954

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**Amedeo S. Narrazzi
Chairman and Coordinator**

September 1955

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FIRST PSYCHOCHEMICAL CONFERENCE
DIRECTION OF FURTHER WORK
Cml C Medical Laboratories
Army Chemical Center, Maryland

12 May 1954

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I. Opening Remarks

Dr. Marrazzi: I think we had better start although all our guests have not yet arrived. It hampers me in welcoming them, but I do so in any case. I have also been asked by General Creasy to convey his welcome and to express his very special interest in this field and his regret that his new duties make him unable to attend this meeting.

I want to spend just the briefest time in orienting you and devote the rest of the time to the speakers. This actually is one of our biweekly research conferences, this one being devoted almost exclusively to contract reports on psycho-chemical aspects of warfare. It is perfectly obvious that a military objective is to produce incapacitation and, although not the most dramatic form of incapacitation, certainly one of the most telling is the derangement of coordination - in other words, mental incapacitation with the whole train of events which it involves and the drain it places upon the military resources of a great number of people. Obviously such an objective might be accomplished in large groups or small groups or even in single individuals. Chemical Corps' interest is in the larger groups. It involves the selection of sufficiently potent substances with such characteristics that they could be disseminated on a sufficiently large scale. To achieve that end, a joint committee of Medical Laboratories and Chemical and Radiological Laboratories surveyed compounds known to have mental effects starting out with very familiar ones. We were aided in that brief survey by a number of consultants, including Dr. Seevers on one occasion, and we finally selected as those of immediate interest though not exclusively these few: the mescaline series, the lysergic acid diethylamide and marijuana series. This started the program which has had very strong support from Dr. L. Wilson Greene, Scientific Director of Chemical and Radiological Laboratories. Dr. C. L. Butler has been the coordinator, Dr. B. Witten has synthesized or supervised the synthesis of a large number of these compounds. We are interested in the effects in humans, and thus it became quite clear that it was necessary in the beginning to determine these effects in humans. This necessitated setting up a number of contracts with individuals sufficiently interested and expert in the field. Medical Laboratories has been responsible for the biological testing and evaluation, and I have coordinated these activities.

II. Goals of the Conference

A presentation of this type is open to two courses. One would be to fit the pieces together into a more or less coherent whole. The other would be to start out with the major picture and try to break it down into its components, and, if there is enough time and ingenuity, we can reconstitute them into some understandable hypothesis. I have chosen the latter course because it will serve to emphasize the whole picture, that in humans who exhibit it in its most complete form and who uniquely are able to communicate it to us in a complete or understandable fashion. I am going to call first, three speakers who will each have twenty minutes followed by a ten minute

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discussion period. There will then be a short ten minute presentation and time left for general discussion. First we shall call on Dr. Paul Hoch, Principal Research Psychiatrist at New York Psychiatric Institute which has a contract with us. Dr. Hoch is a pioneer in the field of correlating experimental pharmacology and clinical psychiatry. He will tell you about the results on his contract and some of his ideas.

III. Psychotic Manifestations in Artificially Produced Psychoses Dr. Paul H. Hoch, New York State Psychiatric Institute

At first I would like to discuss the reaction of patients to mescaline and LSD25 which were given orally, intravenously, and intraspinally. Six patients received mescaline intraspinally. These patients had received mescaline previously intravenously.

<u>Mescaline</u> <u>intravenously</u>	<u>Mescaline</u> <u>intraspinally</u>
125 mgm. -	50 mgm. -
250 mgm. --	75 mgm. ----
500 mgm. ---	100 mgm. ----

As this table indicates, much less mescaline is needed intraspinally to produce alterations in the vegetative nervous system and perceptual and emotional changes. If mescaline is given orally, clinical symptoms occur about 30 minutes to an hour after ingestion. When mescaline is given intraspinally in adequate quantities the clinical manifestations appear in about 2 to 3 minutes. Intraspinally, the clinical symptoms are practically immediate, massive, and an almost shocklike toxic picture with higher doses. While oral and intravenous application of mescaline is rarely followed by after effects, after intraspinal application generalized discomfort, autism, and unreality feelings remained two to three days after the injection. The impression is that mescaline acts suddenly on the nervous system after being introduced intraspinally. This immediate action on the nervous system precludes that it acts through the liver or other organs as was assumed by some investigators. The mode of this sudden action is unclear and it is not known whether it interferes with the synapses or with the enzymatic system in the nervous system. As a matter of fact, it is not clear why the clinical symptoms should appear more rapidly and more severely after intraspinal application than after intravenous ones.

LSD25 was given in the dose range from 3 γ to 100 γ orally, intramuscularly, intravenously, and intraspinally. When given orally the clinical symptoms appear after 30 minutes; when given intramuscularly after 15 minutes; intravenously after about 7 minutes. Intraspinal application leads nearly immediately to a psychotic picture. To produce clearcut clinical symptoms of a psychosis 60 to 100 γ are necessary. The quantitative relationship between dose and clinical manifestations is not as striking as when mescaline is used. For instance, 100 γ of LSD25 given orally produces

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the same intensity of symptoms as that given intravenously or intraspinally. However, the clinical manifestations appear more quickly. Based on the clinical picture, it is not possible to tell which route of administration was used.

We used mescaline on normal controls and on schizophrenic patients. In normal persons under the influence of drugs we saw vegetative manifestations like paleness, flushing, anorexia, and insomnia. The pupils are often dilated, there is an increased pulse rate and blood pressure is present. Alterations of the psyche like perceptions are changed, especially those concerning time, space, and body image; depression and euphoria are common. Depersonalization is frequently seen and ambivalence, negativism is often observed. Formal intelligence is not impaired. Consciousness is only slightly affected, or not at all. The person under the effect of mescaline remains in contact with the environment. However, amnesia often is present later on concerning the experiences. In many persons, in addition to the above changes, hallucinations, delusions (paranoid, grandiose, somatic, etc.) catatonic symptoms, and regressive patterns occur. Many of the clinical manifestations seen in normal individuals strikingly resemble schizophrenia.

The question arises as to how regularly these above described manifestations occur. In any drug action we have to differentiate between so-called chemical factors and personality factors. Discarding the tendency in some persons to adapt themselves to the drug, we find that many patients show similar reactions to mescaline on repeated administration. Often basic patterns of response remain the same. The content, however, of the same emotional response varies. For instance, a person displays an anxious or paranoid or euphoric attitude, but what he verbalizes in the framework of this emotional state is different in different sessions. In some persons, however, a change occurs in their reaction and, whereas at one time they respond in a paranoid manner, the next time they may display euphoria. Releasing repressed psychic material is not as common as believed. This is especially true if the patient's emotional structure is well known to the examiner. Of course, if the person is known only superficially under the influence of the drug he will release repressed material which was not possible to obtain in only one or two psychiatric interviews. In a minority of patients even though they are well known psychodynamically, under the impact of the drug and especially those patients where intense anxiety has been produced, new material can be obtained during mescaline interviews.

Mescaline was also administered to persons already suffering from schizophrenia and the differences with normal persons under the influence of the drug were studied. It was found that the alterations of the vegetative nervous system are the same in both. Hallucinations, unreality feelings, and delusions occur in both. Euphoric reactions are more common in normals. Sexual content and behavior under the influence of the drug is much more common in schizophrenics. In non-deteriorated schizophrenics much more intense anxiety is produced by the drug and a much more marked disorganization of their thoughts and emotional patterns is seen. Normal

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persons under the influence of the drug retain a better reality control. The normal is more an observer of the perceptual and other sensory changes produced by the drug, whereas the schizophrenic patient is dominated by these experiences. The schizophrenic symptomatology is markedly reinforced by the drug in non-deteriorated cases and mescaline is capable of underscoring the existing schizophrenic symptoms. In pseudoneurotic and latent schizophrenics the drug is able to produce a full fledged schizophrenic psychosis with marked exaggeration of the existing phobic, obsessive and other symptoms and with disorganization of reality controls. It was an interesting observation that chronic and especially deteriorated schizophrenics usually remain bland, unproductive, and unchanged under the influence of mescaline. Many of these patients showed physical symptoms and even some visual hallucinations under the drug, but no underscoring of the psychotic phenomena appeared. Their response to mescaline was less than that of a normal control and very much less than that of an acute schizophrenic. This torpidity of response under mescaline was also observed in this group of patients to insulin, adrenalin, histamine, etc.

We also studied the relation of mental phenomena under mescaline to the alterations of the vegetative nervous system. This relationship is still not clear, and is under investigation.

The investigation with LSD25 showed that vegetative symptoms, perceptual changes, illusions and hallucinations were very common. More than with mescaline, lassitude, euphoria, and an impaired ability to concentrate was seen with LSD25. On some individuals, it seemingly has a somewhat more sedative effect than mescaline. In many other ways LSD25 produces similar psychotic manifestations as mescaline, and has the same underscoring properties with mescaline in schizophrenic patients. The diagnostic use of these compounds is now under investigation. At present we did not find any great therapeutic use for them. They are very important drugs in the study of the psychodynamic structure of individuals under intoxication.

We also used mescaline and LSD25 on psychiatric patients who showed a good improvement after psychosurgery. It was possible to demonstrate that the neurotic or psychotic mental symptomatology could be activated into existence in these patients under the influence of the drug. After surgery these clinical pictures appeared to be the same as before, with the exception that quantitatively-speaking they were more mild. This would indicate that in psychosurgery the treatment is essentially a quantitative one, but qualitatively speaking the matrix of the disorder remains and can be activated with the drug which has such properties.

I would like to spend a little time on discussing the so-called counter-acting agents. Mescaline and LSD25 can be influenced by different drugs such as sodium succinate and glutamic acid, but these did not work out too well in our hands. In our studies the most effective counteracting drugs were sodium amylal and pervitin, especially if given combined. After an injection of a mixture of sodium amylal and pervitin the psychotic manifestations produced by mescaline or LSD25 were eliminated in about 15 to 20

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minutes. These drugs also have some preventative value. If a patient receives an injection of sodium amytal and pervitin, and mescaline or LSD25 is given to this patient later on, the psychosis-producing drugs are not able to produce clinical symptoms of the same intensity or their action is much delayed by the application of sodium amytal and pervitin.

Recently we have made investigations with thorazine on mescaline and LSD25 intoxication. In a few cases we are able to demonstrate that thorazine counteracts the action of mescaline and LSD25 and eliminates the psychotic symptoms. Seemingly it also has a preventative value. The interesting interaction of thorazine on mescaline and LSD25 is now under intensive investigation. It is not quite clear how these drugs act on mescaline and LSD25. Because they are of a very different chemical constitution the action is most likely not a straight chemical one. It is possible that any sedation of the nervous system is able to prevent the occurrence of psychotic symptoms produced by mescaline and LSD25. Seemingly if stimulation produced by these drugs in the nervous system is reduced, psychotic manifestations cannot appear. Further investigations are necessary to see if the action of these drugs is a generalized one or as is possible with thorazine a more circumscribed one affecting especially the reticular substance and diencephalic and mesencephalic structures.

We believe that further investigations in this line would contribute a great deal in the understanding of how psychotic manifestations occur and can be abolished at least in the artificially produced psychoses.

IV. Discussion

Dr. Marrazzi: Thank you, Dr. Hoch. I'd like to start the discussion by asking you two questions. First, would you give us some idea of the dosage used, comparatively speaking, and second, on the basis of your findings in psychiatric and in normal individuals, how near do you think this group of drugs comes to being a candidate for the production of an incapacitation in a sense of being unable to carry out a pattern designed to achieve a military objective?

Dr. Hoch: While the dosages used varied with mescaline we found that mild symptoms are produced with about 125 milligrams, become a little more marked with 250, and rather impressive with 500 mgm. With lysergic acid the dosages are between 40 and 100 gammas. Of course, these dosages are varied when given orally, intravenously, or intraspinally. We mainly gave the drug intravenously. We have the largest experience with that. The intraspinal application we did to settle the question of how the drug acts intraspinally after it was done in animal experimentation, but there much lower doses of course are sufficient to produce the same result. Now, to answer the second question. Mescaline in my opinion, as it is used today, cannot be used for any of our warfare purposes because its application is rather difficult and cumbersome. This is not the case for lysergic acid. Lysergic acid, and compounds related to it, would be highly potent agents to make a whole population psychotic just as we know it from persons who

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became psychotic from ergot poisoning. This is provided adequate means are found to administer sufficient amounts of lysergic acid to large groups of people. Lysergic acid is odorless and tasteless. Therefore it can be put into any drink or food and the person would not know it; after a half hour, if the dose is sufficiently great, practically every person in this room could be made psychotic. Of course, this varies in the clinical manifestations. These drugs therefore, from our point of view and from that of chemical warfare, could play quite an important role. As you know we experimented on how lysergic acid acts by inhalation. These experiments were not fully pursued because the inhalation was done by use of an inhalator and not with a proper dispersion of lysergic acid in the inspired air. However, with this inhalator it was possible to produce psychotic manifestations in the same way as with the oral administration or with injection. From the point of view of chemical warfare this would have to be thoroughly investigated. We don't know for instance if lysergic acid were to be put into drinking water how long it would stay as lysergic acid. At least, I don't know if it would disintegrate very quickly or if it would remain toxic for a long time.

Dr. Herget: I didn't hear how long the effect could be expected from an adequate dose.

Dr. Hoch: From an adequate dose the duration of reaction is about 4 to 8 hours. I would say an average of 6 hours, with decreasing intensity. Given orally or intravenously the action comes on in a few minutes, lasts for a few hours and disappears after six or eight hours with no after effects with one exception. Those patients who received the drug intraspinally showed after effects of two, three or four days after administration which these patients normally do not show if you administer the drug intravenously.

Dr. Butler: Were you speaking of LSD or mescaline?

Dr. Hoch: Both.

Col. Batlin: You spoke of disorganization of the psyche. Do these people who have received these drugs show in their response to personality tests any basic change in their personality?

Dr. Hoch: No, the basic personality doesn't change, but some basic personality traits are exaggerated, and of course disorganization symptoms can occur. In other words, a person will become completely panicky; for example, if you give it to a latent schizophrenic he will become extremely anxious, panicky, very much upset, and will ask for help. In some persons these disturbances are very similar to those in schizophrenia. These individuals are unable to organize themselves properly. In many of these persons delusions and hallucinations occur in which the person tries to focus and cannot. One of the interesting psychiatric observations was for us to follow the alterations of the psyche in these patients step by step. For instance, mescaline or lysergic acid produced a great deal of anxiety, and

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after a while the patients became aggressive, and began to express paranoid delusions. And then, of course, you can follow the same thing in reverse.

Dr. Schmidt: How consistent is this response? Do different individuals vary a great deal in their pattern?

Dr. Hoch: Different individuals vary and even the same individual varies. Some basic patterns often remain the same, but that is by no means invariably so. It is interesting that some of the basic mood reactions (for instance, a great deal of anxiety or euphoria or depression) are repeated quite often, but the content is not necessarily the same. In other words, if the patients have a paranoid behavior, the same ideas are not necessarily expressed in connection with this emotional state. There are patients, however, where changes occur and if you apply the drug two or three times, the patient does not respond in the same way as he responded the first time. Full reliance cannot be had, and you cannot, for instance, predict for certain that if the patient responded in a certain way the first time and you administer it four or five times, the reaction would be always the same, but in many patients it is the same.

Col. Batlin: Would the reaction be very severe in a person who is already under anxiety? An infantryman in combat is under considerable anxiety. What would the effect be on him?

Dr. Hoch: I can only speculate on the answer. We did not examine normal persons who were under stress or under a great deal of anxiety. We examined however, a lot of patients, including psychotic patients who labored under a great deal of anxiety of different kinds or sorts, and these compounds in these persons increased the anxiety very much; the anxiety often became so great that they were unable to control it. The drug has a strong anxiety reinforcing effect, at least in persons who are already suffering from anxiety. I have no data on its effects in a normal individual, say for instance facing a combat situation with anxiety, but I believe it would be somewhat similar.

Dr. Fremont-Smith: When you spoke of the difference in the reaction that the same person would have in a second or third or fourth trial, did you mean to suggest that the reaction might become less and less in the sense of acquiring tolerance?

Dr. Hoch: No, I didn't mean it that way, although tolerance does occur in a number of persons. However, if you increase the dose you again are able to produce the effect. I meant it this way, for instance, the first time the patient shows depression under the influence of the drug. The third or fourth time he may come through with a different reaction.

Dr. Fremont-Smith: With approximately equal severity?

Dr. Hoch: Yes. However, it is a different psychic response to the situation and the difference may be more marked in psychic content.

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However, we have quite a number of patients where the background remained remarkably similar.

Dr. Marrazzi: I am going to ask Dr. Freeman and others that we have not yet heard to hold their further questions and comments for the general discussion period a little later so that we may keep on schedule.

I'd like to pass on to the next presentation. I think it has been perfectly apparent and obvious that it is very difficult to quantitate mental phenomena. However, an effort has been made to do just that in a parallel series of studies on the same individuals by Dr. Carney Landis who is the Principal Research Psychologist at New York Psychiatric Institute and who has devoted many years to quantitative evaluation of psychological changes in individuals; he has written an article on flicker fusion in a current issue of Psychological Reviews.

V. Sensory and Motor Psychophysical Thresholds After Administration of Drugs

Dr. Carney Landis
New York State Psychiatric Institute

Dr. Landis: It should first be made clear that Dr. Hoch's report and the findings I am about to report are quite independent. Although we have applied our battery of tests to many of the same patients whose reactions Dr. Hoch has reported, his findings were not available to us nor were ours to him. His group administered the drug being studied, made their tests and clinical observations, and then turned the patients over to us for testing. Not until later did we know the number of the drug which had been given or the dosage applied. In fact, although I will report in terms of drug numbers and dosage in mg./kg., I do not, at this instant, know the name or chemical constitution of these drugs. In order to provide a background of material I will summarize briefly and then pass on to a more detailed statement of the action of these drugs on the tests we have used.

The hypothesis has been advanced that the effect of drugs on psychophysiological functions in the human can be objectively measured particularly in terms of the changes brought about in the temporal aspects of the response. In order to test this hypothesis we have developed new apparatus and new procedures to measure the critical threshold of visual flicker-fusion, decision reaction time, ballistic reaction time, time to make twenty alternate taps on two plates separated 155 mm, and tests of finger dexterity. This equipment and these procedures were utilized with more than 50 cooperative, undeteriorated psychiatric patients who were tested on five or more occasions in order that we might establish reference standards both in terms of group performance and individual performance. Of the first 35 patients tested, eleven received only psychotherapy during the period covered by our tests; eight underwent psychosurgery; four, electric convulsive therapy; five, insulin coma; and five, ambulatory insulin therapy. (The same individual may have received more than one variety of active therapy.) From these groups

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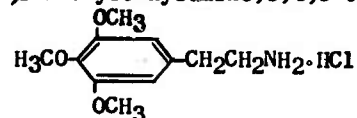
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we have derived and present tentative average scores which serve for a basis of comparative evaluation.

Six synthetic drugs provided to us by the Chemical Corps (*1297, 1298, 1302, 1316, 1319, and 1322) were given at two or more dosage levels to two or more of a group of five psychiatric patients, constituting 19 experiments.

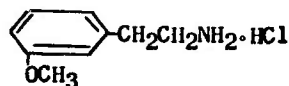
EA 1306 Mescaline HCl

β -Phenylethylamine, 3,4,5-trimethoxy HCl



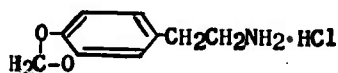
EA 1302

β -Phenylethylamine, 3-methoxy HCl



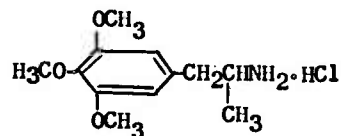
EA 1297 Homopiperonylamine HCl

β -Phenylethylamine, 3,4-methylenedioxy-, HCl



EA 1319

β -Phenylethylamine, α -methyl-3,4,5-trimethoxy HCl

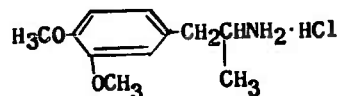


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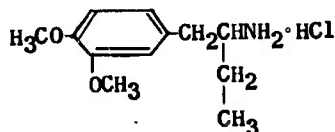
EA 1316

β -Phenylethylamine, 3,4-dimethoxy- α -methyl-, HCl



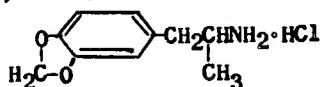
EA 1322

β -Phenylethylamine- α -ethyl, 3,4-dimethoxy HCl



EA 1298

β -Phenylethylamine, α -methyl-3,4-methylenedioxy-, HCl



A variety of scoring methods was developed and applied to the scores obtained with these six drugs. Our conclusions are: (1) that drug 1298 acts to prolong the refractory phase of the visual sensory cortical component in the discrimination between steady and intermittent light; (2) drug 1316 given in 10 mg./kg. dose markedly, definitely and differentially increased decision reaction time which under the circumstances of these experiments is an indicator of the rate of cortical integration; and (3) drug 1319 at low dosages stimulates motor reaction time and at higher dosages depresses it. Its effects on finger dexterity (Purdue Assembly) were profound at all dosages.*

*Dr. Marrazzi: Dr. Landis, could you also supply the mescaline data for comparison, since it is the starting member of this series?

Dr. Landis: I am sorry. I don't have them with me.

Mescaline produces a marked drop in Tapping and Purdue Peg-board score tests which is apparent even 24 hours after injection. The effects on critical flicker fusion frequency are much less definite and probably are exerted only at low intensity thresholds.)

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The tests we have utilized were as follows: (1) Critical threshold for flicker-fusion. This was determined at one fixed level of brightness and a light-dark ratio of 0.50 with a Krasno-Ivy flicker photometer and at three fixed levels of brightness with a modified Strobotac instrument which gave a light-dark ratio of 0.001. (2) Reaction time and Speed of Tapping. A specially constructed instrument measuring in thousandths of seconds units provided a measure of (a) the delay between the flash of a signal lamp and the initiation of the motor response (decision reaction time); (b) the elapsed time between the initiation of the motor response and touching the appropriate plate (ballistic reaction time); and (c) the elapsed time of twenty alternate taps on each of the plates which were separated by 155 mm. (3) Finger dexterity was measured by means of the Purdue Pegboard. This provides a measure of the finger movements with the hands used separately or simultaneously. The score (Purdue RLB) is the total number of pegs the subject can place during the three periods. He was also required to make assemblies of small parts (pegs, washers, collars) in a designated fashion on the pegboard, using both hands as rapidly as possible during a 1-minute interval. The score (Purdue Assembly) is the number of pieces assembled during the minute interval.

A total of 36 psychiatric patients, resident at the New York State Psychiatric Institute, were included in the study. Diagnosis and sex are as follows: schizophrenia, 8 male, 17 female; pseudoneurotic schizophrenia, 5 male, 1 female; neurosis, 2 male, 1 female; involutional psychosis, 1 male; manic-depressive (depressed), 1 male; total, 17 male, 19 female. All patients had entered the hospital voluntarily. No one of them showed any signs of mental deterioration. Patients who for one reason or another could not give adequate cooperation in the tests were excluded from the study. The average age of the total group was 29.8 years ranging from 19 to 49 years. Average age of the 19 female patients was 29.4 years (range 19-47), and of the 17 male patients 30.3 years (range 20-49).

The patients included in the study were tested at varying intervals during their stay in the hospital. The routine procedure was to test them twice during the first week of residence before any active treatment had been started. These two testing periods will be referred to as the "Pre-I" and "Pre-II" tests, respectively. During the duration of their active treatment they were tested repeatedly, number of tests and interval between them depending upon the treatment given, and finally they were tested once or twice after termination of the treatment, and before discharge from the hospital. These final tests will be referred to as the "Post-I" and "Post-II" tests.

Psychotherapy cases. Eleven patients (6 males and 5 females) were given psychotherapy or supportive therapy. As the treatment for these cases started immediately after admission and continued until the time of discharge, no clear "Pre" and "Post" testing can be distinguished to contrast with the tests before and after active treatment. In general, the psychotherapy patients were tested at six-week intervals.

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Psychosurgery cases. Eight patients (4 males and 4 females) underwent brain surgery. Four of them were diagnosed as schizophrenia, and 4 as pseudoneurotic schizophrenia. The type of operation was precoronal lobotomy in seven of the cases, and medial lobotomy in the remaining case. These patients were tested at least twice before the operation, and 1, 2, 4, 7, and 10 weeks following operation.

Electric convulsive therapy and insulin coma therapy. The patients in the ECT group received a total of from 7 to 20 standard treatments. The testing took place 3-4 hours after the treatment. Four of the patients were diagnosed as schizophrenia and one as involutional psychosis.

The eight patients who had IC were given a regular series of 50 comas with six treatments a week. They were tested with intervals of two weeks during the treatment period.

Standards for the various treatment groups. The standards which we are presenting must be regarded as preliminary, since the number of cases included in the various subgroups are still too small to provide really stable baselines. This is particularly true for the ECT group.

The standards are presented in the form of graphs. (Graphs taken from the Final Report made on contract #DA18-108-CML-4915 were displayed and passed around in the conference.) In the graphs we have used the mean score obtained on each particular test procedure at the second test period with the psychotherapy group of patients as our reference point, and expressed all other group averages as percentage deviation from this reference point.

The four CFF test scores are thresholds in cps; the two Purdue tests yield scores expressed as the number of completed tasks; and the two reaction time and tapping score tests are expressed in milliseconds of time elapsed. Consequently improvement in performance is indicated by higher scores in the threshold and task categories and by lower time scores. In order to make our percentage deviations directly comparable for all scores, we have reversed the signs expressing the change in millisecond scores. In the graphs, therefore, all percentage changes in plus direction indicate improvement in performance relative to the reference point, and changes in the minus direction indicate loss.

The effects of individual drugs were as follows:

Drug 1297: This was given by injection to patient M.K. in doses of 5.0 and of 1.0 mg. per kilogram body weight; to J.G. in the same dosages; and to H.B. in a 5.0 mg./kg. dose. Drug 1297 for patient M.K. reduced all CFF measures more or less markedly. The particular patterns of this patient's CFF scores occurred only twice among 14 psychotherapy cases. The majority of the psychosurgery patients, however, show a more marked drop in CFF than this patient does after having had 1297. Drug 1297 (10 mg./kg.) given to patient J.G. lowered the score for the brightest level of CFF; LDR .001, and for CFF; LDR 0.5; 20 ml., resulting in patterns which occur four and two

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times for the respective measures among 14 psychotherapy cases. In patient H.B., 1298 (5 mg./kg.) seemed to have but little effect on CFF. Drug 1297 did not alter markedly any of the psychomotor functions.

Drug 1316: This drug was given to patient S.M. in a 0.87 mg./kg. dosage, and to patient H.B. in dosages of 1 and 10 mg./kg. The only change in scores with the lower dosage with patient S.M. was the slowing of Decision Reaction Time and of Tapping Time. Patient H.B. with the 10 mg./kg. dosage gave a markedly slower Decision Reaction Time and lower Purdue RLB and Assembly scores. His reduced efficiency on the psychomotor tests was quite unique when compared to the psychotherapy case reference standards. They are more marked than the changes brought about by any drug in any of the patients. The CFF measures with S.M. at low dose level showed no changes. For H.B., 1316 (1 mg./kg.) acted as a stimulant for all four CFF scores, while 1316 (10 mg./kg.) seemed to have a stimulating effect for the lowest and intermediate brightness level of CFF; LDR .001, and depressing effect on the brightest level for this measure. It had no effect on CFF; LDR .5; 20 ml.

Drug 1298: One mg./kg. of this drug was given to patient S.M. while 0.4 mg./kg. was given to patient H.B. In patient H.B., the smaller dose acted as a stimulant on all four flicker measures, contributing to a pattern which was not shown by the control cases. This patient's Purdue RLB and Assembly scores were reduced by the injection of this drug.

Drug 1302: This was administered to patient M.K. in a dosage of 1 mg./kg. and to patient J.G. in a dosage of 0.4 mg./kg. The only change in any test score was a slight increase for J.G.'s CFF; LDR .001; 5.8 ml. after the drug, which change is of doubtful significance.

Drug 1322: This was given to M.K. (1.0 mg./kg.) and J.G. (0.67 mg./kg.). The only changed scores of possible significance following 1322 administration were that CFF; LDR .001; 9.72 ml. and 5.9 ml. for J.G. were slightly increased.

Drug 1319: This drug was given to patient Gel on four occasions at dosages of 15 mg./kg., 39 mg./kg., 50 mg./kg. and 79.4 mg./kg., respectively. Between experiments with 50 mg./kg. and 79.4 mg./kg. separated two days from either dose, a dose of mescaline 50 mg./kg. was administered. This patient was not particularly cooperative even without the drugs. Much scatter in performance was always apparent. Despite his somewhat erratic test behavior, 1319 gave clear-cut changes in test performance. All doses slowed the time in making a motor decision but speeded the ballistic or muscle movement time. Speed of tapping was decreased by the two larger doses. Both finger dexterity scores were markedly reduced at all dosage levels. The effect on flicker-fusion thresholds was either slight or too erratic to be trustworthy.

In summarizing these observations, we can make the following statements:

1. It is possible to obtain stable measures of sensory and motor psychophysical thresholds from mental patients after the administration of

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drugs whose action is to an extent unknown so far as humans are concerned. Although not as yet completely certain that these changed thresholds are invariably associated with one or another psychological or physiological change or with the subjective changes produced by the drug, such evidence and theory as do exist indicate test validity.

2. Drug 1297 had clear effects on the flicker-fusion thresholds.
3. Drug 1316 had a marked effect on motor test scores, particularly on decision reaction time.
4. Drug 1319 had a marked effect on motor test scores, particularly on finger dexterity.
5. Drug 1298 which other indicators showed to have a high toxicity had but little effect on test scores.
6. Drugs 1297, 1322, and 1302 produced but slight changes at the dosage levels employed.

VI. Discussion

Led by Dr. Paul H. Hoch
New York State Psychiatric Institute

Dr. Hoch: This gives me an opportunity to mention some points which I didn't go into before. Clinically speaking, 1298 was a very toxic compound and 1319 has also some properties which would indicate that it has some toxic components. The others clinically did not differ from the ordinary mescaline reaction and in some instances didn't reach the mescaline potency, so, seemingly, you can produce compounds which are highly toxic, compounds which are very similar to mescaline and compounds which are less effective than mescaline if you vary the structure.

I think Dr. Landis' experiments relate to the clinical experiments in the following way. He tries to measure certain partial functions. We, of course, try to judge clinically the patient's behavior and actions, shall we say, in a global manner. Clinically, the patient very often shows no signs of any reaction where, maybe, some changes in partial functions can be picked up. This is true not only for psychochemical drug intoxication; it is also true that, if the patient receives electroshock, insulin, or psychotherapy, some of these elementary functions which Dr. Landis tested show some deviation from the normal. I should say that at the same time the all over clinical picture of the patient was unchanged. It will have to be decided later on how far this partial function deviation relates to some dosage reaction. I would like to mention here one other thing which probably is of importance, which I had no time to go into. We used these compounds to see how far we are able to activate psychoses or neuroses after they are treated, and here the larger series which we have are the psychosurgical patients. Such patients, before the operations were done, were tested with these drugs to see how they behaved and how they reacted, and

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after they were operated upon they were retested. The interesting observation was made that in those patients, who responded well to the operation and lost their clinical symptoms or their clinical symptoms were markedly ameliorated, under the influence of these compounds the whole psychosis in every detail was reactivated as it was before the operation. However, their reactivated clinical symptoms were not as intense as before the operation, clearly indicating that the matrix of this disorder (I have schizophrenia in mind) remains unchanged with psycho-surgical operations and a reactivation of the psychosis is possible. However, the symptoms are much less marked after the operation than before. Similar investigations will have to be done with other patients, but I have very little doubt that they will come out in the same way. Quantitatively, the symptoms of these patients are usually reduced. It indicates what I alluded to that seemingly if you clamp down on certain stimulation which is not able to reach the cortex probably some of the psychotic manifestations are reduced or cannot go through.

Dr. Marrazzi: Do you have a question, Dr. Landis?

Dr. Landis: Yes. In the table there, 1298, which Dr. Hoch says was very toxic, produced in two patients very minor changes so that neither the motor nor visual responses showed anything.

Dr. Marrazzi: Did you use the same doses?

Dr. Landis: There were two doses. (Both doses were much smaller than the ones with which toxic symptoms were observed.)

Dr. Freeman: My question pertains to both speakers equally well. I wonder whether you view these reactions, psychiatric or psychometric, as unique for these particular compounds or whether we have acquaintance with more familiar compounds having similar reactions.

Dr. Landis: So far as my testing goes, three of the Chemical Corps compounds took the individuals to whom they were administered outside the range of anything we had gotten by psychosurgery, by mescaline, by LSD, by electroshock or even by insulin coma. That is as far as I can go in answering that question.

Dr. Fremont-Smith: How about other toxic materials? Has there been any experience say with alcohol or some other toxic materials that have been in general use?

Dr. Landis: I am unable to say. Mostly, this kind of thing has not been done under the same conditions by two different experimenters ever.

Dr. Marrazzi: Do you want to answer that, Dr. Hoch?

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Dr. Hoch: Yes. I would like to add that, of course, I could see partial alteration of the psyche. What you see with these drugs you can also produce with other drugs. However, if you take the whole complex especially schizophrenic type symptoms, in which the clear status of the consciousness* of

*The most definite manifestations of schizophrenia, such as hallucinations and delusions, occur typically in a clear setting of consciousness, i.e., without disorientation, confusion, mental obtunding, and genuine memory defects. The schizophrenic patient often describes his hallucinatory and delusional experiences in an orderly and logical fashion (except insofar as his thought processes are impaired by schizophrenic-type intellectual deterioration). The artificial psychoses after parent psychochemical agents, such as mescaline and LSD25, are considered schizophreniform in type because of the nature of the psychopathological reaction which include non-impairment of consciousness.

the patient is not much affected, mescaline, lysergic acid and probably one or two other compounds are the only ones which can produce this picture. Now, occasionally the same observations were made in some persons with DFP. Interestingly enough thorazine which I mentioned, which is used to counteract psychoses in some individuals, produces experiences which partially are similar as those produced with lysergic acid or mescaline, i.e., the feeling of depersonalization, but I would say that mescaline and lysergic acid today are rather unique producing strikingly similar symptomatology to schizophrenia in normals in a state of clear consciousness.

Dr. Marrazzi: I would like to call attention to four points which have not been stressed. (1) The doses used by Dr. Landis are not always comparable to those used by Dr. Hoch. (2) Patients used were not always the same ones studied by Dr. Hoch. (3) The conclusions under the section for 1298 and in the final summary do not agree completely. (4) The psychological measurements evidently are not measurements of toxicity. I think we should move on once more and come back later.

Dr. Macy: In referring to lysergic acid do they mean LSD25? In the future we may have lysergic acid. We should clear that up.

Dr. Marrazzi: Yes, I think that is quite right. We have the diethylamide. We will have the monoethylamide and the acid itself. Apparently, although the picture that we are interested in is fully developed as we understand it in humans, we have had only partial success in elucidating the phenomena in humans and so it seems quite appropriate, if any defense were necessary, to carry on experiments in animals. I now call upon Dr. Seevers who is Professor of Pharmacology at the University of Michigan and Consultant at United States Public Health Service, who has had long experience on action of drugs having a euphoric and addictive action, and who was kind enough to accept our contract for the study of some of these compounds.

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VII. Toxicity of Psychochemical Compounds

Dr. Maurice Seavers
University of Michigan

We have had experience with some twenty-two homologues of mescaline, or twenty-one in addition to mescaline. Our objective in this contract was to determine toxicity in these compounds preparatory to clinical trial, and to ascertain, if possible, any screening technique for evaluating what might be expected in man. From a standpoint of great increases in potency, we can say that none of these compounds has been found to be more than ten-fold in increase of potency over mescaline. The most potent in the series that we have had, is the 1298 which was indicated by Dr. Hoch, in which the potency in the monkey is at least fourteen times that of mescaline.

It should be brought clearly to your attention that what we see when we observe an animal is somewhat different than the criterion that is used in man. The best animal for the standpoint of what we interpret to be bizarre mental reactions, if you can make such interpretation, is the dog. The monkey does not appear to get a similar type of response to these drugs, as in the case of the dog. The dog gets a peculiar reaction. He crawls under the table, stays away from the dark, leaps out at imaginary objects, and as far as one can interpret, may be having hallucinations. It would appear even to the untrained observer that this dog is not normal. He suddenly jumps out, even without any stimulus, and barks, and then crawls back under the table. The monkey doesn't respond in that fashion, so that most of our data is based simply on toxicity which in the case of this whole class of compounds is convulsions.

These convulsions are all antidotable by the barbiturate that was indicated by Dr. Hoch's discussion. We haven't attempted to determine how many lethal doses can be antidoted, but I expect a considerably, high number. From a chemical point of view in this series, one or two points seem to be of interest. All of these twenty-two compounds have been subjected to the LD50 in the mouse. The LD50 in the mouse is not too reliable a statistic on which to base toxicity in man - as we found later. I'll put a few of the results on the board, showing the difference in the different species. On the other hand, it gives us some idea, based on mouse toxicity, of the changes in this structure. For instance, the methylene-dioxy structure seems to enhance toxicity, especially in the case of substitution to make the isopropyl derivative. All of this class of compounds in which the methylene-dioxy substitution is made, in which there are substitutions on the side chain, are fairly highly toxic. In fact, in this whole class of twenty-one compounds, the more toxic ones are those which have a substitution of the side chain, either the isopropyl or, in most cases, the ethyl substitution. So if there is any common denominator in this series with respect to toxicity, you might say that substitution of the side chain does modify toxicity. Whether it modifies the psychic response is something else again.

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Compound 1298 is much more toxic as a convulsant. Our figures are based upon that data. I might give you here, for instance, the comparative study of five different species on two or three of these compounds. This compound is 1298 and we have used the ratio of the LD50 of the compound 1306, which is mescaline-chloride, over the LD50 of x. That is the compound given at the ratio which I'll put on here.

$$\frac{\text{LD50} - 1306}{\text{LD50} - x} = R$$

With respect to the mouse, rat, guinea pig, dog and monkey, we find that 1298 is the most potent compound. We get this by determining the ratio. This is the most potent compound we found in the monkey, largely because it is a convulsant. Given large doses, the animals died very rapidly. We can get some idea here of species variation within this series. The next most potent compound that we studied is compound 1475 which is identical with 1298, except that there is a methyl substitution for one of the hydrogens in this position. That substitution reduces the toxicity somewhat.

The next most potent compound is 1319, where you have a lesser toxicity in the mouse. The only difference between mescaline and this compound is the fact that we have an isopropyl derivative here rather than the other one which acted less toxic in the mouse and rat, but gets more potent in higher species. It gives a pretty good index in the mouse toxicity alone.

Compound 1296, which is another example of a less potent compound, is the -1 methoxy group. I have substituted methoxy rather than di-methoxy mescaline. This compound is less potent than the mescaline itself. In that particular incidence, the species correlation is excellent. Some of these marked differences in toxicity may relate to methods of detoxication by the different species. It seems very queer that in the case of the monkey with mescaline, the drug has very low toxicity, so this ratio may be out of line in the sense that it may not be a fair means of estimating toxicity. The monkey certainly can handle mescaline very rapidly and detoxify it, while we can knock off this amino group here (1302) and convert it to a less potent effect. We have given large doses of mescaline chronically to monkeys over periods of several months, and found that they learned to tolerate very large doses after a while. For this reason I am not sure that the monkey is a very satisfactory test object in this series.

	Mouse	Rat	Guinea Pig	Dog	Monkey
1298	3.2	4.8	10.2	7.0	14.0
1475	2.1	2.9	3.6	3.5	6.3
1319	0.8	0.9	2.2	2.3	4.3
1296	0.6	0.4	0.8	0.4	0.5

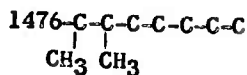
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Generally speaking, we have been not impressed with any qualitative differences between these compounds. This fits in, more or less, I think with the findings of Dr. Hoch, and I'm rather of the opinion, from a pharmacological point of view, that we're not likely to find compounds in this series that would have a great utility from the standpoint of chemical warfare.

We have more recently received some members of another series of compounds - the cannabinal. This group of compounds are of this general type structure with a variable side chain, cannabinal itself to amyl. This tetrahydro compound is cannabinal. I have never been impressed too much with the potentialities of this class of compound, until I received these compounds that we have been examining recently. This compound was first prepared by Adams not too many years ago. The tetrahydrocannabinal itself is opening up this ring and is a much weaker compound. Apparently the pyran ring, a stable ring, is necessary to increase potency, so that if we can get anything which will increase the potency of this compound it is of a considerable interest. We have studied two compounds, 1476 and 1465.

Compound 1476 which is a longer side chain is substituted in three positions. This is the most potent compound that we have determined. This compound in the dog in a dose of as small as 100 micrograms per kilogram, and up to 1 milligram per kilogram will produce exceedingly profound effects. As a matter of fact, if you go up to 1 or 2 milligrams per kilogram, the dog goes in a state of almost suspended animation for two or three days, appears to be dead, and then revives. He can hardly walk. The monkey is in the same category. As a matter of fact, with a dose of one-half a milligram per kilogram, it produces a type of effect in an animal which I have never seen before, and this seems to appear both in the monkey and dog equally well. These animals lie on their side; you could step on their feet without any response; it is an amazing effect, and a reversible phenomenon. It has greatly increased our interest in this compound from the standpoint of future chemical possibilities, particularly in modifications of this side chain. There hasn't been very much done in this group of compounds in the past. Baily who worked at Cornell worked a great deal with this class of compounds.



These are figures relating to potencies from Loewe's observations and relate to the length of the side chain in tetrahydrocannabinal. The methyl actually is of interest in comparative potencies. We used the amyl in the base line because that is the tetrahydrocannabinal itself. The hexyl falls off again when you increase the tetrahydro chain considerably. The most potent in this group was the hexyl. If you hydrogenate this ring and make the hexyl hydro series, the hydrogenation reduces the potency of all of these compounds to almost zero, whereas it doesn't affect the hexyl very much.

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It would appear as if a side chain of that length on the base of what evidence we have to date is about the optimum for maximal effectiveness. This compound, however, where there have been substitutions in the branching of the chain with great increases in potency, seems to suggest that it is a line of approach which might be worth while.

Methyl	-	0.16
Propyl	-	0.40
Butyl	-	0.37
Amyl	-	1.00
Hexyl	-	1.82
Heptyl	-	1.05
Octyl	-	0.66

We have also studied one other compound, the 1465 which has only one branch chain, which would have 1-methyl octyl or secondary nonyl depending on how you want to designate it. This compound is of intermediary potency between the mother compound and 1476. How much further work has been done on this compound, we don't know. We don't know of any public work, but Dr. Woods, my associate who is a chemist, made several suggestions that might be of interest. Of course, a chemist can see numerous modifications on that side chain, if you operate on the premise that this basic structure is of interest. It seems that there could be a great number of chemical modifications on the side chain which might make it of considerable potency. I should think that a compound of this type which has such a great duration of action, capable of incapacitating individuals for long periods of time with survival, and at the same time rendering an individual analgesic, is a compound which deserves further chemical evaluation. In fact, we have been much more impressed with this compound than any of the mescaline compounds we have seen, partly because it represents a type of action that I don't know a duplicate of in the central nervous system of pharmacology. These animals are really completely knocked out for 48 hours, and they gradually get back on their feet over a period of a day or two.

VIII. Discussion

Dr. Schmidt: Have you had any experience with bulbocapnine?

Dr. Seevers: A little, but not too much. I have not had much experience with bulbocapnine. But from what I know of bulbocapnine it doesn't produce nearly as long an effect as this does. Have you had any experience with it?

Dr. Schmidt: No.

Dr. Marrazzi: You asked for a chemist's commentary and we have a galaxy of them present. We should have a comment from one of them.

Dr. Seevers: I think it has to be in the chemical field because we don't have any more pharmacological information about this classic compound.

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Now, as to what type of compound one should make I suppose you could think in terms of branch and ring structure.

Dr. Butler: We've had some speculation on this and I think some of the possible variations have been made by the people in Chemical Division.

Dr. SeEVERS: We would be very much interested in looking at some of them. The one fundamental defect in these compounds is their solubility. Parenteral administration has to be in propylene glycol or something of that type. It is interesting though that with these compounds, particularly this one, that the difference between oral and parenteral administration is very little. It might be expected in a compound of such duration of action, that any difference between oral and parenteral administration would be leveled out because of the great duration of action but an oral dose of 250 micrograms per kilo in a dog will produce a very profound effect. We are getting into potencies with this class of compounds that I think we will never achieve in the mescaline series. Furthermore, it is a much different qualitative type of response. I am personally very much interested in seeing this class of compound pursued further because anything that will knock an animal out for three days and have him survive is of considerable interest.

Dr. Greene: What was that dosage again please?

Dr. SeEVERS: The effective doses are in the order of 250 micrograms per kilo.

Dr. Butler: Will that dosage have a positive effect in the dog?

Dr. SeEVERS: It won't knock him out, but it will produce an effect of shorter duration of several hours. I have forgotten the exact dosages, 1 to 5 milligrams will knock out an animal for a long period of time. Occasionally an animal will die from probably some intercurrent infection. He dies sometime later and any animal that is knocked out for such a long time always has a chance of dying of pneumonia. As far as we can see it leaves no permanent residue in the animal. It is a rather remarkable drug. We haven't the slightest idea what happens to these compounds in the body, but I think on the basis of the cannabinol analogy you might say that anything that would stabilize the pyran ring might greatly increase the duration of action.

Col. Batlin: Do these animals show anything else except unconsciousness?

Dr. SeEVERS: As with smaller doses the monkeys present a most bizarre picture; they act as if they are blind. They will charge around the cages and bang into things and then they will ultimately relapse into a state in which they can be prodded and partially aroused but they stay there. We had a dozen or fifteen monkeys lying around; everyone was wondering when they were going to die. They kept lingering and hanging on for days, and finally commenced to get back on their feet.

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Dr. Pennes: Is there any motor limpness or rigidity during this time, Dr. Seevers?

Dr. Seevers: Very little. They are limp with large doses. It depends entirely on the dose.

Dr. Michaelis: You mentioned the pyran ring is essential.

Dr. Seevers: I don't say it is essential, but the only analogy you have is the cannabidiol in which the ring is open. This compound, cannabidiol is much less active than the cannabinol itself.

Dr. Michaelis: It resembles phenanthrene somewhat in its skeletal structure and one might think of substitutions in the side chain with cyclopentane, resembling morphine structures.

Dr. Seevers: It isn't very far off.

Dr. Michaelis: It isn't very far off chemically. How is it pharmacologically?

Dr. Seevers: That's what has been studied, the general possibilities of acting very much like morphine. It is the analgesic properties that interest us a great deal at the moment.

Dr. Oberst: About twelve or fifteen years ago the Public Health Service was interested in marijuana; they were doing some work on this as a compound.

Dr. Seevers: I think it is a hexyl compound, a parahexyl. It had a tremendous similarity between the reaction in dogs and that of marijuana, the picture you describe is essentially the same as what we got in our dog.

Dr. Butler: Parahexyl is very similar to the tetrahydrocannabinol.

Dr. Seevers: The only difference is that it is a little more potent according to the figures of Loewe, but am I correct in saying that relatively little further chemistry has been done in this area. We haven't been able to find anything after that series of papers that Adams published.

Dr. Butler: We have been making some variations on that field.

Dr. Seevers: In view of all the interesting aspects of it, it is amazing that it hasn't been investigated pharmacologically. It is a fact that it is a nuisance to handle because of solubility but I don't think that is an absolute deterrent.

Dr. Marrazzi: We had better move on for the moment to work that has been done right here actuated by two interests: one - the hallucinations with mescaline which are conspicuously visual hallucinations; two - a possibility of obtaining a measurable pertinent change in animals that might be

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correlated empirically with the clinical change and therefore used as a screening procedure in animals. I am going to call on Dr. Hart, Chief of the Neurology Branch, to present this work.

IX. Neuropharmacological Screening Technique in Animals

Dr. E. Ross Hart
Neurology Branch, Cml C Medical Laboratories

Dr. Marrazzi has indicated our obvious interest in developing some sort of a screening procedure. I think we will all agree that screening in the human is a process which has many deficiencies. I would like to illustrate with the first slide the reasoning which preceded our experiments with mescaline and LSD25. These are formulae. Adrenaline we have studied on a number of animals and it has consistently inhibited synaptic transmission. We have also studied amphetamine and it also inhibits synaptic transmission. Now, we know that to a very small extent adrenaline has a central nervous system action and amphetamine affects the central nervous system to a considerable extent. Mescaline we knew had a central nervous system action, but we did not know its effect on synaptic transmission. It seemed sufficiently close, structurally, to adrenaline and amphetamine to justify investigation of a suspected synaptic action.

The second slide illustrates diagrammatically the type preparation which we have studied most intensively. One can stimulate the lateral gyrus on one side of the cerebral cortex and record from the symmetrically located point on the opposite hemisphere. This provides a recording of the activity in a transcallosal pathway and in a synapse which is located on the side opposite the stimulus. In these experiments, injections are ordinarily made into the carotid artery on the same side as the recording electrodes so that the synapse under study will be subjected to relatively high concentrations while the systemic effects will be minimal.

In the third slide, we see the effect of mescaline on the preparation. This is the typical sort of potential which is recorded. The downward deflection we believe is an index of the activity in the fiber approaching the synapse under study. Negativity in that fiber would cause positivity under our electrode and this is the conventional means of recording with positive deflections downward. When the impulse crosses the synapse the deflection goes negative and in particularly favorable preparations there is another wave of positivity later. The time trace is 100 cycles or 10 milliseconds between peaks.

The pictures clearly show that transmission as indicated by the negative deflection has been markedly inhibited, but does recover. The conduction ahead of the synapse has not been affected as indicated by constancy of the positive component of the response.

These are sample traces taken from a series. Stimuli were delivered every two seconds and every response recorded. We simply selected from the series, the traces which show the control, maximum effect and recovery.

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Now, the fourth slide illustrates the action of LSD25 on this preparation. Eight micrograms of LSD25 when injected into the carotid artery produce the extent of synaptic inhibition shown. The maximum effect occurred about 2 minutes after the injection and within another 2 or 3 minutes the potential had returned to its control status. Conduction in the presynaptic fiber was unaffected.

Again, these are selected from records taken every two seconds in this preparation.

For technical reasons which will be obvious to any of you who have ever done an experiment of this sort, this "screening" procedure is attended by difficulties. Several hours of surgery are required to prepare such an animal before the first injection. One such experiment can be done per day and with good luck one might be able to give half a dozen injections. The problems of comparing one animal to another leave much to be desired when comparing this to an optimal screening procedure. However, there is clear indication of a qualitative uniformity in the type of action being produced in the central nervous system by these drugs. We must await more of these experiments with additional compounds and additional data from work such as Dr. Hoch and Dr. Landis have reported this morning in order to attempt correlation of the ability of these compounds to interfere with synaptic transmission in the nervous system with their ability to produce disturbances in motor or visual phenomena or the more complex phenomena which Dr. Hoch has described. Only after such correlations have been established can we say that we do have an adequate screening technique. I think, however, it is worth knowing that there is a technique which can be used on animals which will show some effects of these types of compounds.

X. Discussion

Dr. Frank Fremont-Smith
Josiah Macy Jr. Foundation
et al.

Dr. Marrazzi: Thank you, Dr. Hart. We have considerable time, so I am going to call first on three of our consultants who have long been associated with us in an advisory capacity. I take pleasure in calling first upon Dr. Frank Fremont-Smith who is Medical Director of the Macy Foundation.

Dr. Fremont-Smith: I have nothing to add because of my inexperience in this area. I have two questions I would like to ask. One of them is with respect to this last presentation of Dr. Hart's. Were the animals under anesthesia? I assume they were.

Dr. Hart: Relatively light nembutal anesthesia.

Dr. Schmidt: This would undoubtedly be taken into consideration since we know that certain physiological responses may be reversed by differences in anesthesia. Thus, if possible, it could eventually prove worthwhile to try it out with other anesthetics, or if you could carry it to the point

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where you had anesthesia. That was one point. My second question had to do with Dr. Hoch's presentation. It may be a little bit remote from your immediate interest here but I was very much struck with the immediate effect that you reported on the intraspinal injections. I assume those were intralumbar and I would like to ask for some comment on the mechanisms by which this takes place because it seems to be very striking. I have thought for sometime how it is possible for one to get such immediate central nervous system effects from material injected into the spinal fluid. My own interpretation has been that there was a penetration, a diffusion into the arterioles and in the cerebrospinal fluid space and then an immediate carrying of the toxic material to the capillary bed, a diffusion outward at the capillary bed and an immediate effect upon the neurons. Now this may be fantasy on my part. I remember watching an operation Dr. Tracy Putnam did many years ago on the meninges of the cat and injecting fluoresce intravenously and you immediately saw a color fluoresce around both of the veins and the smallest arterioles and venules and since fluoresce would diffuse out through an arterial wall, at least I thought it was tenable that other molecules could diffuse in. However, if this mechanism which I am suggesting operates, I don't see how it can operate at the cerebral level when you inject a few cc. of fluid in the lumbar region, which we have reason to believe does not get up to the cortex very rapidly.

Dr. Hart: There are two points which I might make in response, one is that we have had a series of experiments on other synapses including such experiments as flashing light into the eyes and recording the potentials observable at the cortex, in response to these flashes of light. This has been carried out primarily by Captain Pennes where so far as we have gone the effects are qualitatively similar. I should also say that we have a fairly considerable background of experience with these types of synapses with other drugs (adrenaline, acetylcholine, anticholinesterases, atropine, tetraethyl ammonium, curare) all of which indicate the type of action that one would expect of these drugs and would tend to oppose your suggestion that the actions are very significantly influenced by anesthesia.

Dr. Schmidt: I just said they might be.

Dr. Hart: One can't deny the possibility but our experience would indicate that it is not too likely.

Dr. Marrazzi: If you accept the premise that the actions at these and other synapses are qualitatively alike - in the other synapses and in ganglia we have tried a variety of anesthetics and gotten the same type of response. Your point is still valid; we haven't tried a variety at this particular situation. What is the difference in time between the intravenous injection and this intraspinal injection?

Dr. Hoch: If you apply mescaline or lysergic acid intravenously, usually vegetative symptoms occur one or two minutes after injection. The psychotic manifestations also appear after two to five minutes. If mescaline or lysergic acid is introduced intraspinally, it seems to act practically immediately.

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Dr. Schmidt: How many cc.'s do you inject?

Dr. Hoch: About 4 cc.'s are injected. We took out 2 cc., 3 cc., 4 cc. and replaced by the solution slowly.

Dr. Fremont-Smith: Did you measure the spinal pressure at the end; do you know what the pressure was?

Dr. Hoch: It was not abnormal; the pressure was practically 10 or 15 millimeters H₂O, probably more, so the action is immediate.

Dr. Fremont-Smith: And full fledged?

Dr. Hoch: Yes. You have full fledged hallucination within seconds.

Dr. Marrazzi: How many such experiments do you have?

Dr. Hoch: Six each.

Dr. Fremont-Smith: This is really very exciting.

Dr. Hoch: Incidentally, there is something which I think is interesting which Dr. Seevers already alluded to, that there are reports introducing mescaline and lysergic acid into the animals intrathecally, and the toxicity there is much less than in humans.

Dr. Fremont-Smith: There is no increased intensity over the period of the first five minutes when you give it intrathecally?

Dr. Hoch: Well, there is an increase, the symptoms become more marked but actually a pretty intensive drug effect comes on immediately, and then becomes more intense. The shock comes on immediately and I am pretty sure that whatever mechanism you assume is behind this (and I don't know what it is) the compound immediately affects the nervous system and it is not through some intermediary.

Dr. Fremont-Smith: Not back through the circulation?

Dr. Seevers: I am not certain but what you can expect to find small quantities of the compound in the ventricle a very short time after lumbar injection; procaine gets there and all compounds ultimately get there, even though it may not be in an effective concentration. You can find procaine in the ventricle in any spinal anesthesia. I don't know how fast it gets there. I guess that it would take longer than a few seconds.

Dr. Marrazzi: How much is the quantity of the injection?

Dr. Hoch: The dose was small.

Dr. Marrazzi: The volume?

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Dr. Hoch: The volume was much less.

Dr. Marrazzi: I am looking only for mechanical effect.

Dr. Fremont-Smith: I might add that older experiments seem to indicate that there was a very slow movement of medication put into the lumbar sac, unless it was put under high pressure, and that it actually did not reach the ventricles. It would reach the cisterna magna and then get over the cortex but never get into the ventricles unless you did something to remove fluid from the ventricles osmotically or otherwise. This goes back to Weed's earlier experiments with potassium ferri-cyanide so that I think that we may have been under a misapprehension. I am very much interested in what you said about procaine in the ventricles. Have you any data on that?

Dr. Seevers: Methodology was inadequate in the old days; it may be a very small amount.

Dr. Hoch: I believe that 125 milligram of mescaline intravenously gives a 1 plus reaction, the same 1 plus reaction that is obtained by 50 mg. intraspinally. Also, 250 milligrams intravenously gives 2 plus, the equal of 75 milligrams intraspinally. With 500 milligrams you get three or four plus reactions intravenously, and with 100 milligrams intraspinally you get the reaction which comes instantly.

Dr. Marrazzi: What puzzles me, Dr. Seevers, is that ordinarily intraventricular injections of drugs don't produce such immediate reactions.

Dr. Seevers: If you inject ephedrine intraspinally - you get a terrific rise of blood pressure.

Dr. Marrazzi: Yes, but that's a spinal injection.

Dr. Fremont-Smith: That could be attributed to splanchnic stimulation.

Dr. Seevers: It's feasible. This may be a reflex of some kind.

Dr. Fremont-Smith: Didn't Dr. Cushing put pilocarpine into the ventricles? He got a very prompt reaction there.

Dr. Marrazzi: It was and enough time elapsed so it could have been absorbed into the circulation although he didn't believe so.

I think I'll call next on Dr. Carl Schmidt, Professor of Pharmacology at University of Pennsylvania - also one of the consultants we rely on most frequently.

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XI. Discussion
Dr. Carl Schmidt
University of Pennsylvania
et al.

Dr. Schmidt: I too am very much interested in this matter of instantaneous effects. The one thing that occurs to me here is that we are probably dealing with a very unusual type of drug action as evidenced by the extremely small total dose that one gives. Your dosages of lysergic acid diethylamide are in the order of less than one-tenth of a milligram where as with the others you are dealing with 50 gamma and then you are dealing with the mescaline order of dosage which is 500 times this. So presumably a few molecules of this compound getting in contact with certain nerve cells can produce its effect whereas the other apparently needs a good many more. Perhaps that is part of the story, but I too have difficulty in seeing how this can work as nearly instantaneously following intralumbar injection of a small volume of fluid. For example, a few years ago a brain surgeon in Brooklyn performed an operation on the head under spinal anesthesia by means of procaine and justified the procedure on the basis that procaine does not get into the circulation and thus doesn't penetrate into the brain. Actually it did, but I suppose its rate of detoxification did keep up pretty well with the rates of absorption, and he got away with it successfully in most cases. I remember seeing published records of individuals on whom he had done a mastoid operation. These people were blind, they couldn't smell, and he was able to operate on their heads entirely under spinal anesthesia by means of procaine, the justification being that it wouldn't get in contact with nerve cells. What the effects may be I don't know, it is a much smaller molecule than the one you are dealing with here. On the other hand the lysergic acid molecule gets into the steroid order; when you get into that, specific affinity or specific transfer mechanisms or what-not may be involved here. I haven't anything to offer; it is a large question and a great deal of congratulations are in order to the people who have been working on this for a beautiful job in a most highly developed form of pharmacology dealing with the human psyche. If there is anything more difficult than managing that - I don't know what it is. And when Dr. Seevers gets at it from the animal viewpoint and you people from the human viewpoint I think we can readily expect to learn something interesting.

XII. Discussion
Dr. Harold Abramson, Mt. Sinai Hospital
and
Dr. Jacob Finesinger, University of Maryland Psychiatric Institute

Dr. Marrazzi: Dr. Harold Abramson is not only a consultant, but for a long time he participated very actively in Chemical Corps activities at the Army Chemical Center. He is an allergist at Mt. Sinai Hospital and Clinical Physiologist at Columbia University.

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Dr. Abramson: I became interested in LSD25 about three and one half or four years ago, when I read that it really set up what could be called a model for schizophrenic state and was capable of study in the laboratory under pretty safe conditions. As a result, I gave it to some private patients who were receiving psychotherapy. I used small doses (about 30 to 40 micrograms) and got the usual effect. However, at one of the Macy Foundation conferences where I discussed this work, several of the participants said to me "how do you know that it is not due to suggestion"? I scoffed, but nevertheless went back home and proceeded to give the same patients water flavored with tartaric acid and much to my amazement I got phenomena which were identical to the LSD effect. That stumped me for a while and I realized that, if one were to study the effects of a drug of this type on the psyche, one should have a laboratory controlled situation in which the clues which previously had been given to the subjects were controlled by statistical procedure.

Now, in the experiments in progress we use a questionnaire of 47 items. We find it very difficult not to let the subjects know what they are supposed to feel and report. Very briefly we find that with placebos certain of our subjects will give a zero response on the questionnaire. However, others of our subjects will give typical LSD25 effects with water. In other words, if one makes a statistical study of normals under the laboratory conditions of a hospital or private office, one is surprised by the difficulty, as Dr. Landis pointed out, of getting statistically significant data. We have now given the drug on approximately several hundred occasions to groups which I believe fairly different from Dr. Hoch's and therefore I was very much interested in following his data. These are volunteers who have been carefully screened by interviews and by psychometric tests and we consider them ambulatory "nonpsychotic". Very briefly nearly everything that Dr. Hoch has found we have found also. There are slight differences in time relationship, for example, on a statistical basis we find that the symptoms reported for zero doses start early and taper off whereas the effects of the LSD25 reach a peak depending on the dosage at approximately 1 1/2 to 2 1/2 hours when taken by mouth. We have quite a lot of data which will be reported shortly and which can be made available to you.

There is another program in progress at the Biological Laboratory in Cold Spring Harbor on the effect of lysergic acid and other derivatives on brain metabolism. We have Dr. Geronimus and Mrs. Ingram studying oxygen consumption on guinea pig brain homogenate and minces and the latest results are that the mince is apparently a better substance to study than the homogenate. The LSD25 does reduce the oxygen consumption of the minces much more effectively than other ergot compounds that we've studied so far. We have not as yet studied the monoethyl-amide or the monobrom compounds, but we hope to get those in pure form soon. We are also studying and searching for the enzyme system which Dr. Hoch has apparently been able to hit very effectively by intraspinal injection.

Finally, I'd like to emphasize one point which answers the question in regard to the use of compounds in combat situations in chemical warfare.

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I feel, and this is slightly different from Dr. Hoch, that there are other factors in the experimental situation which are just as important as the drug itself. They are the individual who is doing the experiment, and the stress situation. In my office patients can take rather large doses up to 150 micrograms and not show too much anxiety. They will show typical schizophrenic reaction, including depersonalization, yet they are in a protected environment and I am there; if they become upset they talk to me about it. If, however, we take certain subjects and go with them to the cafeteria downstairs, some of them will panic just being in the presence of other people, and rush upstairs to the office. In the hospital just taking a subject who is in the laboratory situation and saying "let's go out to the cafeteria" will throw him into a panic. We must distinguish between the protected situation response and the nonprotected situation response.

Last evening I ran an experiment on a subject who has had it at least 50 times. He is one of my trained subjects. I must say that in general I confirm Dr. Hoch's statement that there may be fluctuations in the response. We find, however, if we keep the protective nature of the situation constant and there has been no recent psychological trauma in the personal life of the individual, by using our questionnaire we get pretty much the same response with the same person. The personality of the individual seems to be about as important as the drug in determining the reaction. We have gone much higher in our dosages on one of my assistants; I've given as much as 225 micrograms, five to ten times and he always goes through the same process. "Have you given me anything", he says, "well I am sleepy", and he lies down. He will get up, but is always withdrawn. On only one occasion did he show a tremendous amount of anxiety. His method is withdrawal and he very effectively uses it. To go back to the combat situation, I feel that if this drug is given even in small quantities under any type of stress situation whatsoever with very few exceptions, according to our psychosometric test, performance may be enhanced. It is the situation that will determine the reaction about as much as the dose of the drug and I predict that from the point of view of the Army Chemical Corps and its combat problems that a stress situation would lead to very effective production of a chaotic state.

Dr. Marrazzi: Another of our friends and contractors that we haven't heard from this morning is Dr. Jacob Finesinger, Director of the Psychiatric Institute, University of Maryland.

Dr. Finesinger: I don't think I have very much to add. I have found the presentation extremely interesting. I want to underline the remarks of Dr. Abramson. I don't know the way out except by trying these things in other situations and actually seeing what really is the effective agent in determining the changes going on. The questions I had in mind in reference to Dr. Hoch's and Dr. Landis' were of this sort. They deal essentially with the reactions of the subject to his hallucinations. I was wondering if it is not possible for a person to have, we will say, hallucinations that do not affect his performance. I have had personal experience with mescaline, with very lovely hallucinations, but they had nothing to do with what I was going about doing. I was aware of them and it was all pleasant;

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I don't know whether that is the usual sort of thing one finds. How much do the hallucinations or disturbed states actually affect performance and do you have any evidence of that sort from your work? Another question. Are these disturbances primarily in this area or do you find disturbances in judgement and the capacity to solve problems? Dr. Landis, you had a chance of doing performance tests on these subjects and in those situations; how did they react?

Dr. Landis: Not one of the Chemical Corps compounds we used produced, so far as we knew, hallucinations during the time we were testing these subjects. The same was true when we were working previously with the patients that had mescaline or patients who had mescaline during the last week. In the case of the lysergic acid patients, some of those had hallucinations, but we made no effort to find out about them. We asked psychiatrists later if they had any report on it. That wasn't our job, but to the best of our knowledge during our studies on all the Chemical Corps compounds, there was no hallucinatory interference. The patients, half of them, at any rate, are "sick". They want to rest, they'll actually, in the middle of the test, get off the chair and lie down on the floor for a quarter of a minute and then get up and resume the test. In spite of the fact that those things occur, the general level of what they are doing for us holds rather regular at that particular session. The one thing I have a great deal of faith in is particularly the battery of tests we are using at the present, which gives nice, regular results, measured out to thousands of seconds, which is pretty good for a psychologist in this field. The question Dr. Abramson raised with individual differences - I think that in psychopharmacology we must give up any group statistics and simply report that, let us say 22 out of 25 patients or individuals were affected in such and such a way with such and such a dosage. Lower the dosage and then you only get 17 out of 25 who responded in such and such a way. It is also true that you get with all the things we have done, about one out of seven so-called ambulatory non-psychotics who give suggested reactions, that is placebo reactions. Right through any series of so-called normal individuals, one out of seven gave such reactions and not one was picked up by any other test. They just happened to come through. Whether they are more susceptible to the agent which we are using or whether they have been guided by clues or people they have seen around them I don't know, but that is our regular experience with such things as phenobarbital, dexedrine, dormisone and compounds of that sort.

Dr. Abramson: I was very much impressed with one accidental experiment. This trained subject that I have used for a couple of years came over to run the experiment at dinner one evening when I had a guest for dinner. The subject took his dose. He is a scientist, and the guest listened to my asking him the questionnaire. His response was essentially negative, but my guest said - "I have got the symptoms", and she proceeded to give, although having no LSD whatever, a violent LSD response going into an anxiety state. She spent the night and the next day she was still very anxious from a clinical point of view. It was a very exciting phenomenon to me to see an almost psychotic state produced by identification with the subject.

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Dr. Hoch: I would like to answer Dr. Abramson first. I think you have to consider all the points which you mentioned and I didn't go into some. First you have to consider the dosage. If you use this drug in the small dosage range, the ability to use suggestion or let the patient himself use a great deal of suggestion is great. When you are getting up in the higher ranges however, usually the action of the drug is so dominant that even to modify some of these drug experiences by suggestion or by hypnosis, which we do try, is extremely difficult. I believe that when the drug action is very great, external modification is as difficult as external modification of a psychotic phenomena in an active state. Because such dominance of phenomena characterizes the picture that you are not able to change, and when you get subjective reports from these persons, the most outstanding thing is, in all these individuals (either volunteers or mental patients) that they are unable to shut off this particular experience which bothers them. Therefore there is no doubt that suggestive influences should be taken into consideration very much since in any drug experiments this can intrude. Nevertheless, I would like to suggest that that is far less in persons who have a sufficiently large dose and in whom dominance phenomena or impulsive phenomena are produced.

I fully agree with the statement that you have the drug, you have the personality and you have the situation. The situation is an important factor. Our patients, for instance are all in a protected situation. In other words the patients were always with a doctor or with a nurse or even with several other people, therefore they were not alone. However, if as happened several times, a doctor wanted to leave the room - then a patient, who had an anxiety response, begged the doctor to remain or even tried to hold the doctor. Another thing which is very important from a situational point of view - we did not study systematically. However, some such studies are made now I think in Boston. This is a study of what happens if you let such drugged individuals interact among normal individuals. It has of course a very strong demoralizing effect for a group if they think that they can be made psychotic too. I don't know if this guest who was present in Dr. Abramson's experiments exhibited purely a reaction of identification or also probably had the idea or the notion that she could be made psychotic by taking something. I wouldn't be surprised if you let loose a few drugged people in the population you could have a mass psychotic reaction simply because they believe they are drugged too.

I am also in full agreement with Dr. Abramson that if a person is under stress probably these drugs act differently. This is, I think, similar to a question which was posed early in the morning, how a person in anxiety actually responds. We find especially in our explorations in schizophrenic patients that the drug acts differently than in the normal, since they are already under stress. The reality relationship in the schizophrenic is different. Their ability to organize perceptions and organize sensory phenomena is different under stress and when you put on another stress they fold completely. How far the same would happen to the normal person in anxiety I don't know.

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This relates to some extent to the question of Dr. Finesinger - are they actual hallucinations capable of producing an upset, or are they the response to the hallucinations. Here we have interesting material comparing, for instance, normal persons hallucinating and schizophrenics, especially a group of schizophrenics with very strong anxiety, the pseudoneurotics. The interesting thing is that normal individuals make their experiences much more fascinating - like a movie. They see very beautiful geometric figures, or they have exceptionally intense emotional experiences. Schizophrenics usually become quite upset, quite disorganized by the same hallucinations and their reactions to this experience are different. Another thing, however, which is of greater interest is that some schizophrenics take elementary optic hallucinations produced by the drug as a drug effect, but the intensification of his own hallucinations is very upsetting, which is similar to the experiments which were done several years ago in which such schizophrenics were able to differentiate between hallucinations.

I have no material to answer the second question of Dr. Finesinger - how far the judgement of this person is impaired. I am pretty sure, simply based on clinical observations, that judgement is impaired. Judgement is very much under emotional pressure, and actually in these patients who have this anxiety structure, I am sure that the judgement is impaired, so much so that I don't know what they would have done.

Dr. Abramson: I have some data which will answer your questions. We have been studying immediate memory solving arithmetical problems, nonsense syllables, tachistoscope experiments with reaction time.

Dr. Marrazzi: I think we'd better discuss that after lunch.

Dr. Fremont-Smith: I wanted to say one word and reemphasize something that Dr. Abramson and Dr. Hoch spoke of from the practical point of view in chemical warfare. If you go back to what happened in World War I when chlorine was used, the evidence showed that about twenty men were incapacitated by anxiety for every man that was incapacitated by chlorine. This one would expect to happen from any drug, and therefore if you have a drug with which you can knock out 10 percent of troops you have a drug which for practical purposes is going to be extraordinarily effective.

Dr. Abramson: Psychologically?

Dr. Fremont-Smith: Psychologically, yes. But also I think the element of suggestion is important, and the breakdown of morale. In modern warfare, people are very much interdependent and group relationships and recognition that other people in your group will support you so much influences and strengthens morale that something of this sort which would knock out 10% (an also if it became known that any were being knocked out) would have a profound effect on the morale situation. I think therefore from the practical point of view it would not necessarily have to wait until you have the perfect material you could plan on using something which had 10 percent effectiveness.

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Dr. Dill: I would like to suggest that those directly concerned, the consultants, the contractors, and representatives from Chemical and Radiological Laboratories, reassemble after lunch to talk about plans.

Dr. Marrazzi: Our lunch will not be served until 12:45 or 1:00 o'clock, so I'd like to recognize any others who have something to say.

Col. Batlin: The work of Woolley, reported at the National Academy of Sciences recently, has come into this field. He proposes the theory that serotonin is a metabolite that can antagonize lysergic acid and its derivatives and he also looks upon yohimbine as another antimetabolite to serotonin. I'd just like to ask if you people think that there is a possibility that this theory may be valid.

Dr. Hoch: As a matter of fact, Dr. Woolley and myself have collaborated on that project to use serotonin on humans. It has only been used in animals. This is only hypothesis and I don't know if anything will come out of it. One great difficulty with serotonin is that it is extremely volatile and I don't even know that it can be really introduced in the nervous system. Some of the animal experiments indicate that serotonin influences the function of the nervous system, also the metabolism most likely at enzymatic level in humans. In about four or six weeks we should have an answer to whether it works or not. One difficulty is that it very easily disintegrates; in addition, it most likely doesn't pass the spinal fluid barrier.

Dr. Marrazzi: I think it is interesting to point out how parallel growth takes place. For example, in the slides that Dr. Hart presented this morning, the parallelism drawn between substances having a similar chemical structure and producing a similar action on synaptic transmission starting with adrenaline, amphetamine and mescaline. Now serotonin is closely related and does have at least on ganglia the same type of synaptic inhibitory action. Adrenochrome being an oxidized adrenaline belongs in that series. Adrenochrome has also been implicated as a possible metabolite inducing schizophrenia and we have obtained some adrenochrome in order to test it in this preparation that was described this morning.

Dr. Marrazzi: Dr. Greenhill is our Principal Investigator on the University of Maryland contract and is Associate Director of the Psychiatric Institute. Dr. Greenhill?

Dr. Greenhill: I'd like to ask Dr. Hoch a question that might have some pertinence to the military situation. Dr. Hoch mentioned earlier in his presentation that the administration of lysergic acid diethylamide for example, does not seem to improve the acquirement of verbal material or information, and I'd like to ask whether lysergic acid diethylamide modifies verbal communication in any fashion or whether there are any characteristic patterns of verbal communication that seem to come through while the person is under the influence of lysergic acid diethylamide.

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Dr. Hoch: Release of material, which was suppressed or repressed, does occur under influence of the drug just as produced by amytal or one of the amphetamines. If you know the patient well, quite a number of these patients don't tell you anything you didn't know before. However, material revealed is usually with much stronger emotional charge, which is especially true of schizophrenics. There is a group of patients who release this new material under the influence of the drug and, of course, several times the question was posed if such a drug could be used to reveal information. Now, I don't believe that the drug is a reliable releaser of information. That doesn't mean that, in certain situations especially where the person is under a great deal of tension or anxiety, he would not reveal some, but I don't know that in this respect the drug is superior to the drugs which are already used for this purpose.

Dr. Marrazzi: Dr. Dill, I know you will want to comment extensively this afternoon, but do you want to make some remarks now?

Dr. Dill: I don't believe so, other than to make the suggestion that those directly concerned including the representatives of Chemical and Radiological Laboratories assemble here at 2:00 o'clock to discuss the direction of further work.

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RECOMMENDATIONS

1. Promising results reported appear to warrant intensification of neurological, psychological and psychiatric studies along with mechanism studies.
2. Present progress warrants the study of dissemination problems. Aerosols suggest themselves as the most practical form of dissemination. Water and food contamination should also receive attention.
3. Intensification of study of antidotes and prophylactics.
4. Field trials are now indicated. These should include the effectiveness of performance of soldiers subjected to psychochemicals in the execution of war games all the way from desk levels to field levels.
5. It is suggested that administration of small doses of LSD25 would constitute a very valuable method of screening personnel, particularly those in certain critical situations, for anxiety proneness and more important the effects of anxiety on their conduct, judgment, ability to make decisions, execute tasks and maintain security.

AMEDEO S. MARRAZZI, M.D.
Chairman

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LIST OF CONFEREES

Dr. Harold Abramson, Mt. Sinai Hospital, New York
Dr. Rupert Anderson, Cml C Medical Laboratories
Lt. Col. Alexander Batlin, Office of Assistant Secretary of Defense
(Research and Development)
Dr. Courtland L. Butler, Chemical and Radiological Laboratories
Dr. William H. Chambers, Cml C Medical Laboratories
Dr. Neville Creasey, Cml C Medical Laboratories
Mr. Ira A. DeArmon, Cml C Medical Laboratories
Dr. D. B. Dill, Scientific Director, Cml C Medical Laboratories
Colonel Norman W. Elton, Commanding Officer, Cml C Medical Laboratories
Captain M. Epstein, Cml C Medical Laboratories
Dr. Jacob Finesinger, University of Maryland Hospital, Psychiatric Institute
Dr. Gustave Freeman, Cml C Medical Laboratories
Dr. Frank Fremont-Smith, Josiah Macy Jr. Foundation
Dr. Robert Fox, Cml C Research and Engineering Command
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First Psychochemical Conference (C)

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1. Neuropharmacological screening technique in animals
2. Psychochemical compounds, toxicity
3. Psychotic manifestations in artificially produced psychoses
4. Sensory and motor psychophysical thresholds after administration of drugs

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REPLY TO
ATTENTION OF

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

RDCB-DPS-RS

30 MAR 2015

MEMORANDUM THRU Director, Edgewood Chemical Biological Center, (RDCB-D, Mr. Joseph L. Corriveau), 5183 Blackhawk Road, Aberdeen Proving Ground, MD 21010-5424

FOR Office of the Chief Counsel, US Army Research, Development and Engineering Command (RDECOM), (AMSRD-CCF/Ms. Kelly Knapp), 3071 Aberdeen Boulevard, Aberdeen Proving Ground, MD 21005-5424

SUBJECT: Operations Security/Freedom of Information Act (FOIA) Review Request

1. The purpose of this memorandum is to recommend the release of information in regard to RDECOM FOIA Request, FA-13-0099.
2. The Edgewood Chemical Biological Center (ECBC) received RDECOM FOIA Tasker #FA-13-0099 from Ms. Kelly Knapp, the RDECOM FOIA Officer. The request originated from the United States Army Research Laboratory (ARL).
3. The following documents were reviewed by Subject Matter Experts from ECBC:
 - a. Research on New Capacitating Agents Final Summary Report for 1963-1966, AE 490687, date unknown.
 - b. Quarterly Report No. IITRI-C6011-21, Non-Hazardous Dissemination and Delivery Concepts, AD 356349, dated Jan 1965.
 - c. Quarterly Report No. IITRI-C6011-40, Non-Hazardous Dissemination and Delivery Concepts Final Comprehensive Report, AD 380969, dated Mar 1967.
 - d. Psychochemical Warfare: Substances Causing Mental and Other Sub-Lethal Effects of Psychochemical Interest. Preliminary Survey Supplement 1, dated 1951.
 - e. Special Report: First Psychochemical Conference, AD 077032, dated Sep 1955.
 - f. Staff Paper: Incapacitating Agents for Use in Tactical Combat, AD 307806, dated Jun 1959.
 - g. United States Army Chemical Corps Summary of Major Events and Problems, Fiscal Year 1957, dated Oct 1957.
 - h. United States Army Chemical Corps Summary of Major Events and Problems, Fiscal Year 1958, dated Mar 1959.

RDCB-DPS-RS

SUBJECT: Operations Security/Freedom of Information Act (FOIA) Review Request

- i. United States Army Chemical Corps Summary of Major Events and Problems, Fiscal Years 1961-1962, dated Jun 1962.

4. ECBC has determined that documents 3a, 3b and 3c should remain limited distribution under Exemption b (1) and not be publically released. All other documents have been deemed suitable for distribution change with the Defense Technical Information Center to be released publically; however, authority for release of the information in 3f lies with the originating agency, Johns Hopkins University.

5. The point of contact is Mr. Ronald L. Stafford, ECBC Security Specialist, (410) 436-1999 or ronald.l.stafford.civ@mail.mil.



RONALD L. STAFFORD
Security Manager