PROCEEDINGS OF THE ROUND TABLE ON

Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry

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Edited by

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Today psychiatry feels itself somehow to be at the crossroads. It may be the same crossroads that investigators of mental diseases have seen many times in the past when important information seemed forthcoming. It is an era when many segments of scientific understanding are in the process of an integration which offers significant hope for major advances in our knowledge.

We have lately developed many tools—chemical, electronic, physiologic, psychological and sociological. These tools are being coordinated toward the fuller awareness of normal mental functioning, and the meanings of the dysfunctions we call the psychoses. At this moment in psychiatry, it is difficult to say just what major clarity has emerged from the rapid technical advances in these disciplines. It is hoped that these advances are preliminary to significant progress in our comprehension of the psychic state we have termed psychosis. The clinical data on these psychoses are plentiful, the technical methods in so many disciplines seem competent; but the coordination and the integration of these materials and tools seem somehow lacking. It may not be fanciful to hope that this lack may be overcome by the discovery of the “model psychoses.”

The key to understanding psychiatry’s deepest mystery, schizophrenia, might lie in the production of an experimental, predictable, controllable, reproducible state—an artificial psychosis. Such are the hopes that some investigators hold for the state of mind induced by giving lysergic acid diethylamide (LSD). One might ask why one should hope for such information with LSD. These hopes were not fulfilled in the hundred years or more that mescaline has been known and described. But possibly during this time a coordinated attempt to understand the mescaline-induced state was not at a level of development technically and conceptually, to exploit its potentialities of information. For great advances do not spring full-grown from the scientific community, rather they emerge from the maturation and fruition of scientific moieties which offer new levels of insight.
This symposium attempts to utilize the tools of lysergic acid diethylamide and mescaline in a multi-faceted assault on the problem of the psychoses. Underlying this investigative attack is a conceptual construct that these drugs have a meaningful relationship to the naturally occurring psychotic states. Some investigators study the possibility that the naturally occurring psychotic states are directly or indirectly a result of either these drugs or their derivatives. Some investigators presume simply that these drugs can cause a momentary psychotic state, and hesitate to even consider that schizophrenia, for instance, is related in any way to the LSD produced state. Others feel that LSD can cause a schizophreni-form state and we therefore can investigate some aspects of the psychoses from this artificially induced state. Some simply study the nervous system abnormalities that emerge from the ingestion of these drugs. They do not want to evaluate the question in terms of the psychotic states. Some are occupied with the pharmacological desire to study the physiologic effects of two very strangely acting drugs. Others may be interested in studying the potential therapeutic effects of these drugs. All are earnestly using LSD as a tool. Some study the body with this tool, some the mind, others the relationship. All are grateful for the discovery of a new tool.

Let us think for a moment of an ideal tool to help us understand the state of being we call schizophrenia. This ideal tool might well be the artificial production of the disease. It must be safe, so that it would not hurt a volunteer; it must reproduce schizophrenia exactly; it must be short acting; it must be controllable, so that we might study partial effects; it must be reproducible, so that effects can be checked; and lastly, this tool must allow the subject of an experiment to communicate subjective data to the investigator.

Some of the forthcoming discussion will point out that many of these criteria for the ideal experimental tool are found in the state induced by LSD and mescaline. So many of these criteria are found, that the question is naturally presented as to whether the LSD induced state is not in reality a schizophrenic state. This question which cannot be answered with any clarity now, underlies many of our present investigations and discussions.

In another aspect of the problem, the ideal experimental tool for the study of psychoses would chemically and physiologically reproduce the schizophrenic state. These areas are now under painstaking study. The answers that are not present now will undoubtedly be learned within the next few years. The major problem which presents itself, however, is whether we are asking the right questions, both of our data and our
tools. It is but one expression of our lack of understanding of the psychotic state, that so many different questions and concepts can be raised to explain the same state of psychic functioning.

Pasteur once said, "It is characteristic of science that new horizons and new directions constantly present themselves." The writer, for instance, in studying the equilibrium disturbing effect of LSD in chronic schizophrenic patients, came upon the unusual tolerance phenomena manifested by LSD. His studies must necessarily then take a new and unexpected road. Many others in this work have found themselves exploring unexpected pathways. It is perhaps naive optimism to conceive that one of these pathways, possibly unknown at the present moment, may lead us to an understanding of the enigma of the psychoses. A consequence of the search for new answers is the emergence of new questions.

This book records the proceedings of the American Psychiatric Association's Round Table on Lysergic Acid Diethylamide and Mescaline in Experimental Psychiatry, held in Atlantic City in May, 1955. This symposium aimed at no weighty answers to the problem of the psychoses. Rather, it was organized in an attempt to offer a workshop for the exchange of data among some of the many investigators who work with these two drugs. It also offered an opportunity for the membership of the A.P.A. to learn of developments in this area of experimentation. The large and enthusiastic audience who could endure a round-table discussion lasting until nearly midnight, testified to the importance and relevance of the symposium. Unfortunately, due to time limitations, many important contributors in this field could not be represented. Also, time did not allow our participants a full discussion of their work. The reader will have to determine the validity of what was accomplished for himself. However, all who took part in its presentation felt enriched by this experience.

The editor wishes to acknowledge his deep appreciation for the help of the many colleagues who offered their thoughts and efforts in the preparation of this panel. He must mention the patience of Dr. David Young, Chairman of the Program Committee who facilitated the organization of the Roundtable; Dr. Paul H. Hoch, always ready with sound and considered advice; and Dr. Carlo Henze of the Sandoz Pharmaceutical Company whose kind and ready assistance made the preparations for the Round Table and the publication of this volume so great a pleasure. He wishes also to thank Myra Cholden, his wife, who patiently bore the brunt of the more tedious aspects of the editorial duties.
Pharmacology of LSD-25

E. Rothlin and A. Cerletti

In recent times, an unusually wide and growing interest has developed for the substance known as LSD-25* (lysergic acid diethylamide). The peculiar and frequently described effects of LSD on psychic functions, in conjunction with the modern concept that mental illness also may be a biochemical phenomenon, are responsible for this interest. It has been known for a long time that certain pharmacologic agents may elicit characteristic disturbances of the intellect and psyche. For this reason alone, LSD would not warrant any greater interest than cocaine, hashish, mescaline, opium, etc. The peculiarity of LSD however, does not rest so much in what it produces, but how it produces its effect. We are still quite remote from an understanding of the latter question, but elucidation of this mechanism may be of eminent importance for the understanding of the pathogenesis of mental illness, as well as its prophylaxis and therapy. With these considerations in mind, we feel justified, as pharmacologists, in taking part in a psychiatric discussion.

LSD was first synthetized in the Sandoz research laboratories seven teen years ago. Starting with lysergic acid, a specific component of all ergot alkaloids, Stoll and Hofmann¹ in 1938, succeeded in synthetically producing the natural alkaloid ergonovine, as well as a larger number of new lysergic acid amides, among which LSD-25 was included. In accordance with its close relationship to ergonovine, we were able to show that LSD exhibited oxytocic activity only slightly weaker than that of ergonovine. Particular attention, however, was directed towards LSD in 1943 when A. Hofmann, stimulated by an apparent laboratory intoxication, discovered the specific psycho-activity of this substance in a series of reproducible experiments on himself. As a result of further experiments on members of the staff and associated co-workers in the laboratory, the observations of Hofmann were fully confirmed. It was soon learned that an effective oral dose in normal subjects was

¹ Known as Delysid, a registered trade-mark of Sandoz Pharmaceuticals.
between 0.5 to 1.0 /Kg. body weight. This tremendous activity was characteristic for LSD, since other similarly active substances, such as mescaline, require doses 5,000 times greater, and more, to produce psychic effects. A more extensive psychiatric analysis of the LSD activity seemed indicated, and the young psychiatrist, W. A. Stoll undertook the project. His investigations, partly carried out in our laboratories and partly in the Department of Psychiatry of the University Hospital in Zurich, were published in 1947, in the framework of a basic study of the problem. The detailed description of the clinical picture of the acute LSD effect on normals and schizophrenics given by W. A. Stoll, was subsequently confirmed by numerous other investigators. We must abstain from discussing the many clinical papers on LSD which have since appeared, as it is not within our scope to discuss specific psychiatric aspects of the LSD problem, but rather to contribute to the knowledge of this substance in the realm of pharmacology. Moreover, it must be said that it is hardly possible today to understand the enormous activity which LSD exercises on the human psyche in terms of its pharmacodynamic action. Nevertheless, the systematic analysis of the pharmacologic properties of LSD is an important pathway in the understanding of the pathogenesis of emotional and mental disturbances, from a biologic and biochemical point of view.

CHEMISTRY

LSD is the diethylamide of lysergic acid which constitutes an essential component of all natural ergot alkaloids. Since, aside from lysergic acid, an isomeric isolysergic acid exists and both are optically active, there are correspondingly four stereo-isomers of lysergic acid, as well as four different LSD isomers. From a pharmacological point of view as well as in regard to effectiveness in man, only d-lysergic acid diethylamide is interesting, inasmuch as the 1-form and the d and 1 derivatives of isolysergic acid are pharmacologically inactive.

ABSORPTION, DISTRIBUTION and EXCRETION

LSD-25 is easily soluble as a salt of tartaric acid and as such is highly active by mouth. Contrary to the complicated molecular structures of the peptide-containing ergot alkaloids, the simple derivatives of lysergic acid, ergonovine or LSD, are quickly and completely absorbed.

Investigations on the distribution of LSD in the body have given a
PHARMACOLOGY OF LSD-25

surprisingly clear picture. At first we studied the problem with a biological method, using the inhibition of serotonin (5-oxytryptamine) by LSD for determination of small quantities of LSD in tissue extracts. As a result of the availability of tagged LSD, a second means of studying the fate of this substance in the body was found. On the basis of the studies carried out in two different laboratories, the following may be said:

LSD administered intravenously disappears relatively rapidly from the blood and can be found within a very short time in different organs, the highest tissue concentration being reached ten minutes after administration. LSD is clearly demonstrable also in the brain though in much lesser concentration than in many other organs, particularly liver, spleen, kidney, adrenals. Tissue concentration of LSD declines rapidly, since, within a short time, all the LSD is excreted through the liver and bile into the intestinal tract from which it is eliminated. In the course of the elimination process through the liver, LSD is altered in its properties in that it is present in bile in the form of metabolites which still appear to be closely related to LSD chemically. The fact that in warm-blooded animals LSD is not truly broken down, and/or enters the general metabolism, is suggested by the observation that of the total C\textsubscript{14}-LSD radioactivity, hardly any appears in the urine or is exhaled through the lungs (CO\textsubscript{2}). However, the greater portion of radioactivity is found within a few hours in the content of the intestinal tract. Further studies on the LSD metabolites excreted through the liver are in progress, but there is reason to assume that these differ only slightly from LSD inactivated by some detoxification process.

TOXICOLOGIC DATA

The acute toxicity of LSD differs considerably according to animal species. Relatively speaking, mice tolerate the highest doses so that in determining the LD\textsubscript{50}, 50-60 mg./Kg. must be injected intravenously. In the rat the intravenous LD\textsubscript{50} of LSD drops to 16.5 mg./Kg. and is thus approximately four and one-half times smaller than that of ergonovine. An even higher toxicity of LSD in relation to ergonovine is present in the rabbit where 0.3 mg./Kg. LSD i.v. constitutes the LD\textsubscript{50}. Among all the natural ergot alkaloids no representative is known which exhibits such high activity in the acute toxicity experiment. The picture of LSD poisoning is devoid of any specific features. Ataxia, paralysis and sometimes increased reflex response may be seen in addition to various vege
tative symptoms. Death occurs as a result of respiratory failure. Disturbances of respiration which sometimes develop into respiratory arrest may occasionally be seen in animals after the relatively small LSD doses of 50-100 /Kg., and seem to be the expression of the LSD effect on the respiratory center.

In chronic experiments in rats we have been able to give 2.5 mg./Kg. LSD daily i.v. for a period of 30 days without losing any animals. Since the maximum tolerated single dose in the rat is approximately 3.2 mg./Kg., no cumulative factors seem to be present in the light of what we know about the excretion of LSD. Vice versa, no toleration appears to develop in that the animals pretreated with LSD require the same LD$_{100}$ as the untreated animals. Rats submitted to chronic LSD effects exhibit tremor, increased reflex response and pilo-erection. These symptoms, however, are relatively unspecific and decline in intensity within a few days. Nevertheless, the animals are retarded in weight increase compared with the controls. Histologic tissue examinations of these animals are not available at the present time. Following chronic administration in dogs degenerative changes of ganglionic cells in the brain have been described.

**PHARMACOLOGY**

The most important pharmacodynamic properties of LSD may be grouped as follows:

*Peripheral Effects*

1. LSD increases the contractility of the uterine muscle and in this respect practically has the activity of ergonovine.

2. The smooth muscle of the vasculature contracts after large doses of LSD, but this effect is manifested only in isolated vessels and spinal animals. In the presence of intact nervous innervation, the effect of LSD on the central nervous system predominates and decreases the vasomotor tone.

3. The specific adrenolytic action so characteristic of the peptide alkaloids of ergot is not demonstrable for LSD. However, LSD exhibits a marked antagonism toward 5-oxytryptamine (serotonin, Enteramine), as detailed below.

*CNS Effects*

LSD precipitates a multiplicity of vegetative reactions, some of which are sympathetic and others parasympathetic in nature:
1. Characteristic of LSD is the mydriatic action present in various animal species and which can be inhibited by adrenosympatholytic agents.

2. In the rabbit, LSD produces a hyperglycemia which can be inhibited by the hydrogenated ergot alkaloids.

3. High sensitivity toward LSD is exhibited by the centers of heat regulation. In the cat, dog, and rabbit LSD provokes an increase in body temperature. The rabbit particularly is so sensitive that doses of 0.5-1 /Kg. i.v. regularly produce a pyrogenic response. Under anesthesia and by pretreatment with hydrogenated ergot alkaloids of the ergotoxine group, this pyrogenic effect (similar to the glycemia) can be inhibited.

4. Animals treated with LSD have an increased pilo-erection indicating increased sympathetic activity.

5. In contrast to the LSD effects already mentioned, other symptoms seem to be essentially of vagal origin. Thus, increased salivation and lacrimation are particularly evident in the dog.

6. 50-100 /Kg. LSD in the anesthetized cat produced bradycardia by a central vagal mechanism. At the same time, a blood pressure decrease may be observed which also is of central origin since it is absent in the spinal cat.

7. Respiration is effected by LSD doses of 10-50 /Kg. which are distinctly active both in terms of inhibition or stimulation. Large doses of LSD produce respiratory standstill and death.

8. Other CNS effects appear only with doses exceeding 100 /Kg., and include increased intestinal peristalsis, vomiting, ataxia, paralysis of the extremities, etc.

In summarizing, we can say that LSD produces a multiplicity of pharmacologically well-defined effects, the majority of which appear to be of CNS origin. Of greatest interest are effects which are reproducible with very small doses and in this relation the action of LSD on body temperature regulation in the rabbit is outstanding. The minimum effective doses are readily comparable to those effective in man. This does not imply any identity of the two effects—the pyrogenic action in the rabbit and the psychic effect in man. At most, however, there is an analogy which may be confirmed further, in that both in man and the rabbit, tachyphylaxis and tolerance develop quickly. Moreover, it must be emphasized that a considerable number of simple lysergic acid derivatives as well as the natural ergot alkaloids equally
raise body temperature, however, large doses are usually required. Also others of the aforementioned pharmacologic actions of LSD are not specific in the sense that they are produced by other substances chemically related to LSD. Marked vegetative stimulation similar to that of LSD was observed by us in animals and man following administration of substances which, though structurally closely related to LSD, would be devoid, in the doses used, of any psychic effect (lysergic acid dimethylamide, lysergic acid pyrrolidine, etc.). So far only the monoethylamide of lysergic acid (LAE 32) proved to be qualitatively similar to LSD, even though the dose required was ten times larger. It may be possible that the ethyl groups may be of decisive importance for the psychic effect of LSD, the vegetative effects being common to a greater number of lysergic acid amides.

The marked antagonism between LSD and serotonin first found by Gaddum as well as the presence of serotonin in the brain have given rise to new ideas concerning the possible mechanism of action of LSD. More recent observations render any formulation of such hypotheses very difficult at the present time.

THE ANTAGONISM TO 5-OXYTRYPTAMINE

A number of peripheral effects of 5-oxytryptamine can be selectively inhibited by LSD. Our own observations cover not only LSD, but a large number of LSD derivatives and LSD homologues. Without discussing details, it can be said that more or less marked inhibition of serotonin is characteristic of a large number of lysergic acid derivatives. It is of interest that the psychic action of LSD and serotonin antagonism do not run parallel as was most clearly established for an LSD derivative in which bromine is substituted in position 2. In investigation of this substance shows that serotonin effects on smooth muscle (uterus, vessels, bronchial musculature), is at least as strongly inhibited as by LSD. On the other hand, both in pharmacologic tests and in human experiments, all other effects of LSD were not inherent in the bromine derivative. No psychic effect of bromine LSD could be elicited with doses of 1-2 mg. We are thus faced with the fact that an LSD derivative has lost all properties typical of LSD and yet exhibits definite serotonin antagonism. It is therefore not possible to relate the unique psychic effect of LSD to its serotonin inhibitory properties. One might well assume that bromine LSD does not enter the central nervous system and its serotonin-inhibitory effect may, therefore, be limited to the periphery only. However, the presence of
bromine LSD in the brain could be demonstrated in the same manner as for LSD itself. If, in addition to the purely peripheral smooth muscle action of serotonin, the potentiation of barbiturates is used for testing, the serotonin effect may be equally inhibited with bromine LSD as with LSD. Without wishing to exclude the possibility that serotonin may be somehow involved in the production of the “LSD psychosis,” the relationship seems to be considerably more complicated than the assumption of a simple competitive serotonin-LSD antagonism on smooth muscle.

In reviewing all the facts that pharmacologic analysis has so far yielded, we must admit that we are far from a satisfactory explanation of the mechanism of action which is responsible for the unusual psychic effects of the minute parts of this substance. The assumption of involvement of enzymatic processes is obvious, but despite considerable research in this direction (LSD and cholinesterase, LSD and amino-oxydase, and enzymes of carbohydrate metabolism) no results have yet been obtained which contribute to the understanding of the problem. It is to be hoped, however, that the great efforts made in psychoneuropharmacologic research today may allow new insight into the relationship between psychic function and biochemical processes, and that in the course of these developments LSD may yield more and more of its secrets.

REFERENCES

I would like to discuss some aspects of LSD studies which I carried out in the New York Psychiatric Institute in cooperation with Doctor Pennes, Doctor Malitz and Doctor Douglas.

We are interested in applying, by different routes of administration, LSD-25 and mescal, which have similar clinical symptoms; to find out the qualitative and quantitative differences that might exist when the drug is given by different routes.

We first gave the drugs orally, intramuscularly, then intravenously, and finally we applied these drugs intraspinally. When given orally, the dosage of LSD varied between 100 and 250, with an average of about 120. The onset of symptoms was usually noted after 30 or 45 minutes, the peak effect after 1 1/2 to 2 1/2 hours, and total duration of effect from 9 to 12 hours. The intramuscular route produced an initial response in about 15 to 20 minutes, with the peak effect after about an hour, and total duration of effect about 9 to 10 hours. The intravenous route of application was used to apply 40 to 180 of LSD, the average dose being about 100. Symptoms appeared within several minutes, and showed a peak effect, if the drug action was not interrupted, in about an hour. It lasted about 9 to 10 hours.

Intraspinal administration brought about the most rapid onset and quickest peak effect. We used 20 to 60 of LSD in those experiments. The intraspinal application of the LSD-25 brought on autonomic changes and the psychotic manifestations nearly instantaneously, when the drug was introduced. The intensity of the manifestations was about the same as those observed with the intravenous application of the drug. It would be well to note that intraspinal application of these drugs occasionally leads to toxic manifestations, and I believe it should not be done routinely, and not without great precautions.

There are no qualitative differences in results, regardless of the
route of administration. The differences were chiefly of a quantitative nature, the onset of the symptoms being less rapid in an oral than an intramuscular route of administration; and especially rapid with the intravenous or intraspinal application. We cannot yet explain why the intraspinal application of LSD-25 brings on symptoms even more rapidly than when it is given intravenously. Our observations, however, would indicate that the drug acts instantaneously on the nervous system.

For a long time we were also interested in studying how far it was possible to influence the LSD psychosis. We used different methods such as hypnosis, electroshock and sodium succinate to influence the psychotic reaction, without too much effect. Then we began using sodium amytal and pervitin (desoxyn) intravenously. They were effective alone, but if given in combination their efficacy was greater in ameliorating the psychotic symptoms and vegetative disturbances produced by the drug. We used sodium amytal in doses of about 200 to 500 mg., and pervitin in doses of 20 to 40 mg. These drugs exert their effect in about three to five minutes after intravenous injection. They served to shorten the total time over which the psychosis producing drug would exert its effect, provided the action of LSD was not completely neutralized.

The usual action of LSD given intravenously, which lasts nine to ten hours, was shortened after giving sodium amytal and pervitin, to two or three hours. Seldom are the autonomic and psychic effects completely eradicated. There is a tendency for the psychotic symptoms to recur, but much less intensively after the effects of amytal and pervitin have worn off.

Chlorpromazine is seemingly an even more potent and effective antidotal agent when administered intravenously at the height of the psychotic reaction. For instance, if about 50 mg. of chlorpromazine is administered intravenously in about 10 cc. of diluent over a five minute period, rapid and complete disappearance of autonomic phenomena such as nausea, vomiting and dizziness is obtained in 30 to 60 seconds after the injection. Vegetative symptoms are usually the first to disappear, and then a marked reduction of motor activity and verbal productivity takes place.

The patient often states he is no longer anxious. Following this phase, the patient may state that his feelings of unreality and depersonalization are gone, and that hallucinatory manifestations induced by the drug have also disappeared. It is interesting that in some patients hallucina-
tory and some delusional ideas may remain, but the patient no longer reacts to them nor is dominated by them. This is similar to what is seen in some schizophrenic patients who are maintained under chlorpromazine as a therapeutic measure and is interpreted by some as a chemical lobotomy.

Varying degrees of drowsiness may develop with the chlorpromazine injection. This usually occurs after the vegetative and motor manifestations are eliminated. There is no disturbance of the sensorium and the patient remains well oriented throughout. It has been observed that the more intense and clearcut are the symptoms brought on by the psychosis producing drug, the more effective is the eradication of the symptoms by chlorpromazine. If chlorpromazine is given as an antidotal agent, the change in the patient's psychosis shows a certain sequence. This, of course, cannot be followed in every patient, for they are not absolute rules; but they are indications discerned in a number of patients.

The first picture which we observed is an improvement in contact and a more clear relationship to reality. At the same time, motor restlessness and verbalized feelings of anxiety are reduced or eliminated. The abnormal thought content, however, often continues for a while, but with the absence of great emotional pressure. Later on, the content of the patient's expressions reverts back to the same expressions noted prior to the application of the drug. In many patients there is a feeling of detachment and impairment of reality control. These symptoms were not relieved until the anxiety was reduced. Similar observations were made in patients who showed visual hallucinations and those who expressed obsessive ruminations or paranoid ideation.

In figure 1, a solid line indicates the duration of the reaction; we see that the drug action is slowly falling down, and is finished in the 10th or 11th or 12th hour. The dotted line indicates how the application of the chlorpromazine suddenly eliminates the psychotic symptoms, and of course, also the duration of the whole psychotic manifestation is shorter than when chlorpromazine was not given to the patient.

Figure 2 indicates the same after the application of a mixture of sodium amytal and pervitin.

We also used rauwolfia preparations to counteract LSD-25 and mescal. These experiments are not complete, but our impression is that rauwolfia does not act immediately on the experimentally produced psychosis of
Figure 1: The usual course of the reaction to D-LSD can be altered by the administration of various antidotal drugs after the reaction has reached its maximum intensity. The graph demonstrates the typical obliterating effects of the antidotal drugs with later return of some of the intensity of the reaction and followed by spontaneous waning of the drug effects. In particular instances, the antidotal drug may obliterate the D-LSD reaction more completely and permanently, while in other instances, the antidotal effects are less dramatic than shown. The more complete obliteration can often be achieved by using relatively larger doses of the antidotal drug as compared with dose of D-LSD.

Figure 2: The intensity of the reaction to D-LSD can be dampened or minimized by administration of antidotal drugs prior to, or simultaneously with the administration of D-LSD in some instances. Relative dosages of the psychosis-inducing drugs and the antidotal drugs are of special importance in this preventive aspect of these reactions.
LSD as does chlorpromazine. Some of our patients experienced disagreeable reactions from the injection of rauwolfia, independent of the autonomic disturbances that are produced by LSD. Chief among these effects of rauwolfia were nausea, vomiting, malaise and abdominal pain.

There are now several known substances which counteract the action of LSD. For instance, sodium amytal, methamphetamine and chlorpromazine. You will hear from Doctor Himwich about the new drugs Frenquel, serotonin, and so forth. Because these antidotal drugs have a different chemical constitution, it was not possible to evolve until now a common denominator explaining their action.

We feel that it is possible that different chemical processes can produce the same clinical results and it is not necessary to assume that we are dealing with one single mechanism which would explain the action of all these different compounds. The action of LSD on the nervous system on one hand and the action of chlorpromazine on the other, is still more or less obscure. In both, the mode of reaction is more in the realm of speculation or in a state of working hypothesis, than established fact.

It will be very important not to present research hypotheses for those who work in this field as factual evidence for clinical purposes; and it is, especially, too early to draw clinical conclusions from some of these experiments. For instance, it is unclear if LSD as a psychosis producing agent, and chlorpromazine as an antidote, act differently on the nervous system. How they do act will have to be further elucidated. It is quite possible that, for instance, LSD-25 or chlorpromazine produce some of their effects diffusely, based on some metabolic alteration of the brain. It is also possible, however, that both compounds have something to do with the function of the midbrain, especially with the function of the reticular substance.

I believe that research will have to continue in both the neurophysiological and the chemical areas to elucidate whether we are dealing with a more localized or with a diffuse mechanism in the production and elimination of psychotic manifestations.

I will not be surprised if the answer to our questions from biochemical and neurophysiologic sources will come from ideas and observations which we do not know anything about today.
Biochemical Reflections
on the Psychosis Problem

Max Rinkel

These biochemical reflections are the result of experiments in progress since 1949 at the Boston Psychopathic Hospital. In order to study the psychosis problem, we produced an experimental psychosis in normal human beings. This experimental psychosis, usually of not more than 6 to 8 hours duration, was induced by the oral administration of mere traces (1 microgram, or less, per kilogram body weight) of the diethylamide of d-lysergic acid (LSD). This chemical is a semisynthesized derivative of ergot, a fungus which grows on rye. It was first produced in the Sandoz Research Laboratories, in Basel, Switzerland. A. Hofmann, a chemist, accidentally discovered that this colorless, odorless, and tasteless drug, when taken by mouth, produces symptoms of psychosis. This observation was subsequently confirmed by us, and a great number of authorities. In our studies, LSD has proven itself of inestimable importance as a tool for the experimental investigation of psychiatric problems, and, in many ways, of practical value.

Nurses of our hospital, who had volunteered for an LSD experiment, stated that the experience had given them greater understanding of the feelings and behavior of their mental patients, and consequently the general ward care became substantially improved. Many subjects who had taken this drug, and under its influence experienced mental changes and alterations in behavior, became aware of their own problems, which resulted in their better adjustment. The experimental LSD psychosis became a useful model for testing counteracting chemicals, and stimulated research in the development of drugs for the chemical treatment of psychosis. Pharmacologic, physiologic, biochemical, clinical, psychologic and socioanthropologic investigations of the LSD induced psychosis has brought to light facts which led us to a new “chemical,” concept of the cause and nature of mental illness.
Some of the recent suggestions as to chemical causes of schizophrenia which offer interesting leads to its study, even though valid arguments may be raised against them, are as follows:

Fiamberti,\(^5\) at the first world congress of psychiatry in Paris (1950), suggested that schizophrenia is caused by an acetylcholine deficiency and proposed that it be named “acetylcholine psychosis.” He submitted the following evidence for this physio-chemical concept of schizophrenia: First, reports by Fahowich, Arnon and Rablom that the brain of schizophrenics is deficient in acetylcholine as the direct result of an increase of cholinesterase in the blood; and secondly, the successful treatment of schizophrenics with convulsions produced by massive intravenous acetylcholine infusions.

Woolley and Shaw\(^{18,20}\) advanced the theory that schizophrenia is the result of a deficiency of serotonin in the brain, brought about “by failure of the metabolic processes which normally synthesize or destroy the hormone.” The intensive research of these authors had indicated that serotonin (5-hydroxytryptamine) plays an important part in the maintenance of normal mental processes. Any interference with serotonin therefore would necessarily cause abnormal mental symptoms. Such interference, for instance, is the result of the antagonism between serotonin and LSD. The “schizophrenia-like condition evoked by lysergic acid diethylamide,” therefore, must be considered as the result of a “pharmacologically induced cerebral serotonin deficiency.”

Another biochemical concept of the schizophrenia process, involving the liver, was advanced by Patzig and Block\(^{1,2,14}\). These authors and their associates reported that following intraperitoneal injection of radioactive mescaline into mice, the greatest accumulation of radioactive activity was found in the liver and kidneys; the smallest concentration in the brain and spinal cord. They also observed that mescaline had completely disappeared from the brain and spinal cord (within about 30 minutes) before the time when, in man, mescaline-induced mental alterations become manifest. Because of this time interval, and on the basis of other experimentally established physio-chemical evidence, the authors concluded that mescaline enters into a new protein combination which causes mental symptoms, and that this biochemical process takes place in the liver.

Fischer, Georgi and Weber\(^6\) also consider the liver as an etiological factor in the causation of schizophrenia.

Mental phenomena, produced by mescaline, were especially the object
of intensive research in England by Osmond and Smythies.\textsuperscript{13} On the basis of the similarity of mescaline induced psychic effect with those occurring in natural psychosis, the authors postulated the presence of a chemical substance, "M" in psychotics as the cause of mental disturbances. In their search for this substance, they were guided by the intuitively recognized similarity of the molecular structure of mescaline and adrenalin, and suspected "M" to be a metabolite of adrenalin. They joined the research group of our distinguished guest, Dr. A. Hoffer,\textsuperscript{12} at the Saskatchewan Hospital, Saskatchewan, Canada; and under his direction, proceeded to investigate several chemical substances. One of these, adrenochrome, an adrenaline metabolite, attracted their interest. They reported the results of a number of experiments with adrenochrome, which they administered in the amounts from 0.1 mg. to 10 mg. by subcutaneous or intravenous routes (in later publications they stated that 25 to 50 mg. are necessary). They observed marked psychological changes. One subject became overactive, showed poor judgment and lack of insight; another subject "became deeply depressed for four days and endured a condition which was indistinguishable from an endogenous depression." In discussing their observations, the authors state that "adrenochrome is the first substance thought to occur in the body which has shown to be a hallucinogen." However, they cautiously raise the question "whether adrenochrome, itself, plays any part in schizophrenia," and refer to further work in this field.

Our own studies,\textsuperscript{3,15-17} are based on the observation of the mental phenomena in more than one hundred volunteer subjects who have taken LSD by mouth. First results of our experiments were reported in May, 1950, at the annual meeting of the American Psychiatric Association. In subsequent papers, we reported clinical and physio-chemical observations which indicated great similarities between LSD induced mental manifestations and those which occur in schizophrenia and other psychoses. Of interest was the observation that disturbances of the autonomic nervous system preceded mental symptoms.

The examination of the function of the autonomic nervous system with polygraphic recordings and pharmacodynamic techniques brought to light the fact that, under the influence of LSD, the heart rate became increased, but was more stable. It was further revealed that LSD caused a greater variability in length and depth of the respiration cycle than was indicated on control days; also, the rate of respiration was faster
and there was more sighing. The systolic and diastolic blood pressure, which was taken with ordinary clinical methods before and after psychodynamic interviews, was very little affected by LSD, although the blood pressure readings before an interview, were slightly lower after LSD than on control days. However, following the psychodynamic interview, the blood pressure was somewhat higher (average 132/94 mm. Hg) while the reverse was observed on control days, when the blood pressure was slightly lower after the interview (average 125/98 mm. Hg).

A consistent observation was the increase in the size of the pupils. Measured by the same observer, under identical light conditions, it was noted that the diameter of the pupils gradually increased from 3 mm. to 5.25 mm. during a two and three-quarter hour observation time. This progressive dilatation of the pupils must be attributed solely to the influence of LSD and not to the psychodynamic interview, since on control days no such dilatation of the pupils took place.

The pharmaco-dynamic examination of the autonomic nervous system indicated an antagonism between LSD and epinephrine. On the injection of .025 ml. of a 1:1000 solution of synthetic epinephrine, the mean value of the rise in the systolic pressure on LSD days was 57.6 mm. Hg, as compared to 85.4 mm. Hg on control days; with a standard deviation of 10.3 and 14.6 respectively. The \( t \)-value between means was .01. These results were even more striking in a case of bilateral prefrontal lobotomy, an operation which causes the autonomic nervous system to become particularly responsive.

Antagonism between LSD and epinephrine was also reported by J. D. P. Graham and Alaa iddeen Khalidi of the Department of Pharmacology of the Royal Faculty of Medicine, Baghdad. It may also be speculatively interpreted into Witt's demonstration of the spider web built under the influence of LSD. This web seemed to show a much weaker tensile quality. This might indicate that LSD interfered with the normal production of adrenalin, in view of the long-known fact that the main chemical constituent of the spider web is adrenalin.

From our own experimental observations and the various reports in the literature, especially Feldberg and Sherwood's intensely interesting observation of the catatonic phenomena which result from intraventricular injection of adrenalin in cats, and Funkenstein's work on the relationship of epinephrine and nor-epinephrine to extra- and inappro-punitive phenomena, we arrived at a chemical concept of psychosis.
We hypothesized the involvement of the adrenalin cycle in the production of psychoses. In agreement with Hoffer and associates, we suggested that an enzymatic disturbance within the adrenalin cycle may originate, possibly one or more noxious metabolites, which, among other factors, may well be operative in the development of psychosis. Of such adrenalin metabolites, two have been described: adrenochrome, which has been isolated, and adrenoxine, which has not yet been isolated. P. Heirman,9,10,11 however, obtained adrenoxine by carrying enzymatic adrenalin oxidation beyond the adrenochrome level. Pharmacologic and physiologic effects of adrenoxine, according to his description, seem to be similar to those obtained by LSD administration. The isolation and further study of this chemical may well provide valuable information which may advance our understanding of psychosis. The assumption of an involvement of the adrenalin cycle in psychosis is based on our clinical and pharmaco-physiologic observations. An involvement of the adrenalin cycle in psychosis cannot be considered particularly unusual in the light of such clinical entities as phenyl-pyruvic acid oligophrenia, tyrosinosis, alcaptonuria, and albinism which are indisputably known to be the result of enzymatic disturbance of the adrenalin metabolism.

I have presented some biochemical reflections on the psychosis problem which resulted from our research in experimental psychiatry. We believe that the comprehensive study of experimentally produced psychosis will eventually bring under control mankind's most disruptive and least understood disease—mental illness; just as poliomyelitis and other diseases have been brought under control by the classical method of producing the disease experimentally, in order to study its causes, process and cure.

REFERENCES

4. Feldberg, W., and Sherwood, S. L.: Injections of drugs into the


The Effect of Frenquel on EEG Changes Produced by LSD-25 and Mescaline

Harold E. Himwich

We have used Frenquel* as a tool to study the actions of LSD (d-lysergic acid diethylamide) and mescaline (figure 1). Because our analysis depends upon the power of the hallucinogens to evoke the alerting EEG reaction, it may be well to view such a reaction (figure 2). These records were obtained with superficial and deep electrodes inserted into the brain of a rabbit that was artificially resired under curare and without any general anesthetic. Bilateral coaxial electrodes were placed superficially on the limbic and motor cortices, while the deep electrodes were inserted into the head of the caudate nucleus and into the medial portion of the thalamus.1

Beginning on the left side of figure 2 you will observe first the sleep pattern: slow high amplitude waves, interrupted, especially in the motor cortex and caudate nucleus, by spindles of fast low amplitude frequencies. This pattern continues until it is stopped by a stimulus and is then replaced by another one, characteristic of the alert, awakening or arousal EEG reaction. The cortical waves are desynchronized and rapid undulations up to 20 to 30 cycles per second of low amplitude are observed, especially in the motor area. On the other hand, the thalamus reveals, characteristically, a change to regular waves 4 to 6 per second in frequency. As we continue with figure 2 we observe that the drowsy pattern reappears only to be followed again by another alert period.

The presence of the alert pattern depends on the stimulation of the activating system.2 The physiology of this system is well known and I shall therefore mention it only briefly. Stimuli from the periphery of the body, for example, advance centripetally and pass through the lemnisci to the specific sensory areas of the cortex. The lemnisci,

* Frenquel is the trade-mark of the William S. Merrell Company, Cincinnati, Ohio, for alpha-4-piperidyl benzhydrol hydrochloride.
however, in addition, send collaterals to the reticular formation of Moruzzi and Magoun, which is thus excited and in turn carries impulses which stimulate the cerebral cortex via the thalamic diffuse projections of Jasper. These two structures, the reticular formation and the thalamic diffuse projections, may act as a unit, the mesodiencephalic activating system, called for brevity, the activating system. The reticular formation also sends branches to the hypothalamus which is therefore involved in the activation of the EEG. In figure 3 you will observe the sleep pattern of the rabbit injected with Frenquel (called gamma-pipradrol in the figure). When this animal was touched lightly the activating system was stimulated and the alert pattern appeared. Thus we see that Frenquel changes neither the sleep pattern nor that of EEG alertness.

At this point of our investigations I went to Cincinnati and visited Dr. Howard Fabing who had been using Frenquel, finding it beneficial for acute psychotic patients. Our observations on chronic disturbed patients with schizophrenic reactions also revealed a beneficial effect, as reported at these meetings. Dr. Fabing, in addition, performed an experiment on volunteer subjects, in whom he induced an LSD psychotic-like episode. Most interestingly, this episode was cured by Frenquel. Frenquel, too, could prevent the effects of subsequently administered LSD. With this hint, we made comparable experiments with LSD and Frenquel using, however, the rabbit as our test object.

Figure 4 reveals the effect of 15 /Kg. of LSD on a rabbit’s cerebral electrical activity. An enduring pattern of alertness is produced by this dose of LSD. Smaller doses, 1 to 5 /Kg., facilitate the alert response to even minimal stimuli, but with larger ones the alerting reaction may continue uninterruptedly for an hour or more. After the LSD-activated pattern had been produced (figure 4) the injection of Frenquel (figure 5) restored the sleep pattern. Mescaline, in larger doses than LSD, also evoked (figure 6) the alerting reaction. And again (figure 7) Frenquel eliminated this alerting response and reestablished the features of sleep.

This alerting reaction is not a specific one, and cannot be attributed only to the two hallucinogenic agents. Cholinergic drugs like DFP (diisopropyl fluorophosphate) and central nervous system stimulants like Meratran* also call forth the alert pattern. The latter, when evoked

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*Meratran is the trade-mark of the William S. Merrell Company, Cincinnati, Ohio, for alpha-2-piperidyl benzhydrol hydrochloride.
by Meratran, could not be reversed by Frenquel despite the chemical similarities of the two agents (figure 8). Thus Frenquel was able to correct the alerting reaction only when it was produced by the two hallucinogenic agents.

It should be added that the elimination of the alerting response can be accomplished by any drug which depresses the activating system; Chlorpromazine, in small doses, is one of these. Others are atropine or atropine-like drugs and central nervous system depressants, such as the barbiturates.

In our studies on the influence of LSD we were confronted with paradoxical results. By increasing the dosage of that hallucinogenic agent, it was possible to eliminate the first effect of LSD and to evoke EEG arousal. With sufficiently high doses of LSD the sleep pattern was restored. At this point, my co-worker, Dr. Franco Rinaldi, wanted to take a large dose of LSD to determine whether the psychotic-like episode induced by small amounts of LSD could be cured by an excess of the drug. Just after that, the May 2, 1955 number of Chemical and Engineering News appeared, containing an article by W. H. Sebrell, Jr., which showed a photograph of a monkey with a man’s finger in its mouth. Though the monkey normally is an ornery creature, he was not biting the man’s finger. The legend underneath the photograph stated that the monkey had received a thousand times the dose of LSD necessary to produce a psychotic episode. This large amount of LSD was not hallucinogenic but tranquillizing in action.

We have mentioned clinical studies in which we used Frenquel therapeutically for disturbed psychotic patients as well as experiments concerned with the EEG of animals. A third group of observations performed in our laboratory, by Dr. E. Costa, throws additional light on the mechanism of action of Frenquel. Dr. Costa employed the rat uterus as a test object and took the extent of uterine contraction evoked by serotonin as his standard. By using the minimal contractions caused by serotonin he found that the hallucinogenic drugs, LSD and mescaline were synergistic with serotonin and increased the magnitude of the uterine contraction. On the other hand, the tranquilizing drugs, Frenquel, chlorpromazine and reserpine antagonized serotonin and reduced the extent of the contraction. These experiments indicate that LSD and mescaline go to the same receptors as serotonin and in tensify its effect, certainly in the rat uterus and perhaps for the brain.
wave of the rabbit and the behavior of the LSD injected human subjects. Frenquel, chlorpromazine and reserpine likewise go to the same receptors as serotonin but antagonize the effects of serotonin in the rat's uterus, the EEG of the rabbit and the human subject. In contrast to the action of small concentrations of LSD Gaddum and Hameed\textsuperscript{15} have previously shown that large ones inhibit the maximal concentration of the uterus caused by serotonin. Thus again, as in their effects.

![Figure 1: Structural Formulas of Two Steroisomers](image)

Figure 1: STRUCTURAL FORMULAS OF TWO STEROISOMERS

![Figure 2: The Sleep and Alert Brain Wave Patterns](image)

Figure 2: THE SLEEP AND ALERT BRAIN WAVE PATTERNS. Two different brain wave patterns are presented, both obtained from a curarized unanesthetized and artificially resired rabbit. See text for description of these two patterns. The leads from the top tracing downward in: 1) right limbic cortex, 2) ECG, 3) right caudate nucleus, 4) left caudate nucleus, 5) right motor cortex, 6) left motor cortex, 7) right thalamus, 8) left thalamus.
on brain waves of the rabbit and behavior of the monkey, large doses inhibit rather than stimulate.

The main point of this presentation, however, is to report experiments showing that the behavioral effects of Frenquel on psychotic patients as well as in model psychosis, are in line with observations on the effects of Frenquel to correct the EEG abnormalities evoked by hallucinogenic drugs.

Figure 3: EFFECT OF FRENQUEL ON BRAIN WAVES. Frenquel (gamma-pipradrol) affects neither the sleep pattern nor the alert one caused by the stimulation of light touch.

Figure 4: EFFECT OF LSD ON CEREBRAL ACTIVITY OF THE RABBIT. LSD produces the alert pattern consisting of low voltage, fast activity prominent in the motor cortex and also present in the other leads, with the exception of the thalamic ones. In the latter four to six waves per second predominate.
Figure 5: EFFECT OF FRENQUEL ON THE ABNORMALITIES INDUCED BY LSD. The high voltage slow activity and 14 per second spindles which have been eliminated by LSD (see figure 4) are restored by Frenquel.

Figure 6: EFFECTS OF MESCALINE ON CEREBRAL ACTIVITY OF THE RABBIT. Mescaline eliminates the high voltage slow waves and low voltage fast frequency spindles of sleep, replacing them with the characteristics of the alert pattern.
Figure 7: EFFECT OF FRENQUEL ON BRAIN WAVE ABNORMALITIES INDUCED BY MESCALINE. Frenquel (gamma-pipradrol) corrects the changes produced by mescaline (see figure 6) and reestablishes the sleep pattern.

Figure 8: EFFECT OF MERATRAN ON CEREBRAL ACTIVITY OF THE RABBIT. Meratran (pipradrol) induces an alert pattern and the latter cannot be corrected by Frenquel.

REFERENCES


The Clinical Uses of Lysergic Acid Diethylamide

R. A. Sandison

The properties of drugs of the mescaline type (those producing hallucinations, alterations of space and time relationships and some change of consciousness) have been known for centuries. With them must be linked the mushroom preparations anciently used by the North American Indians and the Russians, and the use of Cannabis indica in the near and far east. It seems probable that these drugs have long had some reputation in the treatment of certain forms of insanity but, in general, their action has been little understood, and in deed, suspect by rational therapists. So they stood, in relation to orthodox psychiatry, rather as alchemy in the time of Galen stood to medical treatment. The mysterious alchemistic rites of the middle ages are now being interpreted in terms of the dynamic, and orthodox psychological process. By the same psychological system of thought, the action of the so-called "phantasticums"—such as mescal and lysergic acid diethylamide, can be understood.

It therefore seems possible, that, just as dreams have come to be regarded as a source of material for Freudian and Jungian analysts, so the experiences of patients under the influence of lysergic acid diethylamide might be similarly used. These dreams were regarded by former writers as delirious manifestations. Sir Arthur Mitchell (1905) regarded dreams as "sane hallucinations" and could only reconcile the apparent lack of moral spirit in the dreams of people of the utmost rectitude, by regarding them as equivalent to the delirium of the toxaemic states.

I have commenced with this apologia to prepare you for a rather similar change of attitude which may be occurring towards the psychic manifestations of the so-called mescal or LSD "intoxication." There are good reasons for believing that the LSD experience is a manifestation of the psychic unconscious, and that its material can be used in psychotherapy in the same way that dreams, phantasies and paintings can be used by the psychoanalysts.
RESULTS OF TREATMENT

We have already reported upon the possibilities of using LSD to assist in the psychotherapy of neurotic patients. To quote briefly from our findings, I might remind you that encouraging results were obtained in the treatment of 36 patients; and that obsessional conditions and mental tension as an accompaniment of other forms of neurosis were regarded the most suitable type of case. Since the time of our preliminary report in 1954, my colleagues and I have had an opportunity to extend our work, and now have a total of approximately 90 treated patients. The results of treatment in these cases have been most encouraging, fully confirming our earlier observations. Furthermore, we are happy to report, our most successful earlier cases have kept well.

Rather than introduce a tedious list of figures, I shall refer only briefly to these results and pass on to some speculations about the actual treatment itself. Out of the completed cases, about 55 per cent have recovered and maintained their improvements; 12 per cent have failed, after a reasonable period of treatment, to show any real improvement; the remainder have made various degrees of adjustment compatible with a reasonable life outside the hospital. A few of the failures have been lost to us, others have had other forms of treatment, one has had a rostral leucotomy. On the whole, we have every reason to be satisfied with lysergic acid diethylamide as an aid to treatment, and in many cases the results are so dramatic as to leave one in no doubt as to the value of this remarkable drug.

One of my early obsessional cases, a married woman of 30, who was tortured with all sorts of obsessions regarding water and spent a great part of her life performing washing rituals, has now been entirely free of symptoms for nearly two years. Except for a few months after her marriage, she had not been free of these symptoms since the age of 13. At her worst, she was at times suicidal; at other times she was confined to bed, or spent up to 8 hours a day washing herself, or her own and her child's clothes. The long remission in this case now suggests a permanent cure. I only wish I could demonstrate this patient to you. These successes are being confirmed by personal communications coming from other centers in England carrying out this treatment. It is gratifying to learn that others are finding the drug useful.

The action of a drug which so evidently has a powerful effect on the
patient's psyche is difficult to appraise by comparing its action with an inert placebo. I believe that the patient must be his own control, and that the patient just referred to would still be suffering severe symptoms unless she had been given LSD.

**PATIENTS SUITABLE FOR TREATMENT**

One is constantly being asked which type of patient is most suitable for LSD treatment. While the results make it clear that the tense, driving obsessional patients do best, and that the shallow, affectless hysterics do least well, successes in treatment are not confined to any one class of neurosis. Neither are they confined to psychoneurotics, but I must not yet digress into the effects of LSD on psychotics.

The problem of selection is rather similar to that of selecting patients for leucotomy. It is probable that those patients whose basic personalities and drives have been most satisfactory, respond to treatment. Patients with drive, who have done something with their lives, even if it is the wrong thing, are good cases to take on. Provided they have this drive, it seems to matter little whether they have broken down into an anxiety neurosis, and obsessional state, or into a neurotic depression. This is brought out rather clearly in the effects of LSD treatment in the obsessive-compulsive states.

Let us consider a small group of six female patients. These six patients had very similar fears; i.e., fears of hurting others, compulsive ideas concerning knives and other implements, fears of insanity, and, in four cases, a fear of killing children amounting, in one case, to a belief that she had actually done so by means of tablets. These were all severe cases that failed to respond to other measures of treatment. All were roughly twenty to thirty years old. Three of these patients got well, one greatly improved; while two have obstinately failed to get well despite even more energetic treatment than was accorded to the others. These latter two were co-operative, they abreacted well, and produced plenty of material; but their fears remained and baffled us. The difference in those two cases seems to be partly in the personality, which was weak and ineffective; and partly in their I.Q's, which were lower than the others. Our successes were more active and enterprising, with more drive and initiative. Our failures were patients who had always withdrawn from life, sheltered behind their families or husbands, and were dependent and immature.
**DOSAGE AND METHOD OF ADMINISTRATION**

For the purpose of treatment, we have used LSD in doses varying from 25 to 400 \( (1 = 0.001 \text{ mg.}) \), the most usual doses varying from 50 to 200. The drug is mixed with distilled water and taken by mouth first thing in the morning. No special preparation of the patient is necessary, but the nature of the treatment and the expected action of the drug should be explained to the patient before his first treatment. The drug is given once a week and we commence with a small dose, say 25 and work up by 25 until the desired response is obtained. In the earlier stages, the drug may be given twice a week. The maximum dose will vary with the objects of the therapist. Small doses will suffice where the object is only to free the patient’s mind and to abreact mildly in an uninhibited frame of mind. Medium doses \((100 - 200)\) usually suffice to produce regressive phenomena and deeper emotional responses, while larger doses still may take the patient into primal and archetypal experiences. For full details of the nursing arrangements, a previous paper should be consulted. (Sandison, Spencer and Whitelaw, 1954).

**USE OF RORSCHACH TESTS**

We should next enquire whether psychological tests can help us towards better selection. In September, 1953, it was decided to give all patients a preliminary Rorschach and other tests, and to follow this up a year later with further tests. Although a complete analysis of all the results so far is not available, the evidence is that the Rorschach test is not a very satisfactory guide to selection, but that it does provide some help in evaluation of the cure by follow-up tests. Among the recoveries there are indications of a definite change of approach to the test in a proportion of cases that is not found in the patients who have not done so well. Furthermore, we think the Rorschach test definitely points to a permanent alteration of outlook in a significant number of cases, and it will be interesting to see whether this correlates with permanent freedom from neurosis. Looking through the results, I have been impressed by the quite remarkable changes that have taken place in the tests over a period of 12 months.

**MODE OF ACTION**

I should like now to return to the question of what LSD actually does to the patient. There have been a number of classic descriptions
of the effects of the drug on normal persons. The best of these is probably that given by Hofmann, reported by W. A. Stoll in 1947. These accounts are like those of solid and animated dreams, as if it were a waking dream, in which the real exterior world becomes blended with the dream world or modified by it. Hence the similarity of this state to schizophrenic thinking noted by some writers, including Tayleur Stockings, (1940), and the hypnagogic states noted by others. The random observations of normal subjects under LSD appear confused, disintegrated and haphazard, compared with the much more orderly train of events which occur in patients undergoing LSD treatment. This is probably because the patient is under the control of the-therapist where he is taught to concentrate upon each image as it appears and to follow it to its conclusion. More important, he is taught a way of studying his mental processes so that he may get more from the LSD experience. Thus, for many patients, the hallucinatory experiences are not of great importance; the subjective feelings and flow of thought are the really significant things. Our patients are also encouraged to concentrate on the primal or regressive phenomenon. A high proportion of them re-enter their childhood with remarkable clarity, to return to very early experiences. Most of us who have worked with LSD have encountered patients that regress to a birth experience. Usually, this is a feeling on the part of the patient that he himself is being born and sometimes, in female patients, that the birth of a child is taking place. Some of these experiences are felt with remarkable clarity, and the following is a brief description:

I feel I am ready to be born but that I am safe here in the womb. I can only think of the womb as a dark wall of soft tissue like the inside of one’s mouth ... I am going to make the effort of being born now. I am pulling back great walls of thick slime to find an opening, but I have not found an opening yet ... I have found the vaginal passage and I have found the great lips of the vagina sealed ... I must get out. I am pressing against them with my feet and hands and the seals are giving way ... I can feel my young body starting to make an effort ... I feel I must grow away from the womb, I feel I have left it, but not quite. I have been returning to the womb and seeing myself as a sperm swimming about, and others dying, clinging to the wall of the womb and then falling away.

LSD EXPERIENCES AND PSYCHOANALYTIC THEORY

It has been noticed that the experiencing of these early memories and primitive states has been an affair of great significance for the patient,
often marking a turning point in treatment, or rapidly being followed by a sense of integration and a relief of symptoms. One is reminded of the significance attached by R. O. Scott to the birth experience in patients undergoing insulin treatment. I have myself observed clearly described birth phantasies which marked the end of the schizophrenic regression and formed the point of commencing recovery. One must add to this the recognition by many religions of the importance of re-birth, and our own Christian gospel that “Except a man be born again he cannot enter into the Kingdom of God.” The importance of these experiences in analytic treatment is indicated by the significance accorded them in the Freudian and Kleinian systems. There has been much discussion on whether these birth experiences are real memories or whether they are phantasies. Their extraordinary reality under LSD tempts one to think that the patient has vividly stored memories of his own birth. Personally, I do not think it matters which view we take; the important thing is that the patient shall make contact with the archetype of the birth experience, that he shall feel separate from his mother, and also, perhaps, that he can realize, no matter what happened later in childhood, there once was a time when he was connected to his mother with the bonds of mother love.

I turn now to the significance of other experiences. Just as a dream of a patient early in treatment may reveal the patient’s inner problem and his faulty methods of setting about his life, so the early LSD experiences frequently lead one straight to the core of the patient’s problem. They do so, more surely and frequently than is normal in psychotherapy, and many months of time can be saved. I am convinced that patients under LSD come to the central problem long before they could possibly realize it ordinary analytical methods. Many do this who would probably never do so by other means. If anyone wants confirmation of the great analytical principals laid down by Freud and Jung, let him study patients having LSD. The classical complexes and archetypes show in their abundance.

Time does not permit a detailed study of the LSD material. It might be summarised under three headings, each with its special significance. First, the reliving and emotional working out of earlier, often forgotten, traumatic memories. Second, the experiencing of a second, inner self; the neglected side of the personality, which must be integrated into consciousness if the personality is to be developed. Third, contact with the archetypes, of which the birth experience is only one. In
Jungian language, however, Mandala symbolism is frequently found and runs true to its peculiar integrative qualities.

**LSD TREATMENT FOR PSYCHOTICS**

I should like to make some reference to the possibilities of using LSD in the treatment of psychotics. Most reports have dismissed psychosis from this sphere of study by recording that LSD produces little alteration in the psychic scene. The picture is rather different in the case of well preserved psychotics who have passed the florid stage but who are in danger of gradual deterioration into dementia. Last year, I successfully treated a patient with puerperal schizophrenia who showed little improvement with E.C.T. and insulin. Dr. Stafford Clark told made of a similar case treated with hashish that dramatically recovered after a “re-birth” experience—interesting when we recall the similarity of action between LSD and hashish. Some recent cases are showing promising results. We might do well to investigate this field further, bearing in mind that the follow-up at home of many treated schizophrenics reveals that numbers of them have severe residual disabilities. Many have to lead sheltered lives and others, although working, are conscious of an emotional deadness which is very distressing to them.

I believe that we may be on the threshold of a new era of treatment now that we are commencing to gain access to drugs which compel the unconscious, willy-nilly, to unlock its secrets. It may be that we shall have to take warning from Charles Williams’ story of the stone of “many dimensions” that reached England from the East. We may have to realise that the healing of neurosis is only one use to which these drugs may be put. We may not like the Dominicans’ criticism of Aldous Huxley that in mescal he has found “Heaven in a capsule,” but we ought to pay attention to it. If these drugs can help us to understand more about life as well as to treat our patients, we shall have learned something.

From the patient’s point of view, LSD is something definite that constitutes a real treatment of his own mind. This is of great importance, because it holds his interest, and helps him to get down to his problems. Reinforced by group treatment, the techniques of analysis are easily grasped by most patients. As a result of this, few patients discontinue treatment, in fact, enthusiasm and eagerness to continue are among the features of LSD patients. Furthermore, without in any way negating the importance of formal psychiatric training, it does give
the doctor of lesser talents, provided he uses the drug with care, an opportunity to investigate and treat patients without recourse to deeper, longer analytic techniques. I think we can claim to do in weeks, as much as it would take months of ordinary analysis to accomplish.

REFERENCES

The LSD Psychosis as a Transaction between the Psychiatrist and Patient

The study of the LSD psychosis enables us to learn about the psychotic process and about the transactions of the psychiatrist and patient; we learn what things we do that make the psychosis better, and what things we do that make it worse. In short, from working with the LSD psychosis we can, perhaps, learn something about the management of naturally occurring psychoses. I am going to describe two of our series of model psychoses and see what speculations we can derive from them.

The first is a young woman in her early thirties, normal to all appearances and testing. She is an amateur artist who customarily paints landscapes and other conventional themes. She is in analysis because of recurrent feelings of depression. However, she was completely blocked in the early analytic situation. She asked that I give her some LSD in the hope of spurring on her analysis. (Previously she had had sodium amytal with no relief of blocking.) The first illustration shows the effect of LSD. It represents a composite of three separate experiences, one with 50, one with 100, and one with 150 of LSD.

The second illustration is a key to the various parts of the picture:

This painting is an accurate representation of many of her unconscious conflicts. Let me illustrate how one of them was elucidated in the course of analysis. Take the staring yellow eyes: “Eyes popping out—whose eyes—those goddam ever present watching eyes—popped out with my thumbs to stop the ever present evil eye. They must watch all the time, even when you’re asleep, because they know all the evil you’ve ever done, or thought, and follow you around so much that everything you do must be bad. What did I do? It must be something. I don’t know what but I’m sick of it. God knows how many bad things you’ve done but the worst is more awful than you can ever think about.”

In the course of several months of working over the material of this painting she recovered the following memory:
I went to bed last night tired and became extremely fearful of something, expressed with great restlessness, crying, etc.; again of an infantile nature but which I could not suppress. I had to curl up into a ball and cover both my face and genitals, as though fearful of some terrible complete destruction.

1. Eyes popping out
2. Me meeting myself at a party
3. Self-image—one's body a gray curved undefined blob
4. Crossed arrows or lances that do not allow one to pass
5. Partial self-image with red indicating my arm—made up of many interwoven pieces of red twine or rope
6. Writhing person—a shadow of the proper self one wanted to be, now pierced with 7.
7. Flaming blue sword destroying the last of what one wanted to be
8. The hideous mocking, cold face
9. Part of a human form—female—now grotesque, as a dead, burnt, naked tree
10. Fragment of double or reflected thorn of a thistle
11. Shrubbery
12. The road to nowhere
Suddenly in my fantasies I saw the headlight of an automobile, the glass of which was cracked and shattered—like an eye, a staring eye that had been destroyed as mine would be for seeing. I remembered standing at the foot of my parents’ bed during the night, in the dark, having entered to announce I was about to “throw up” again and remaining to stare at the two dark figures in bed together, doing I do not know what because the remembrance of the darkness, the shadows, and the foot of the bed was what was recalled. In remembering this I could not close or cover my eye enough—they had been or would be hit. Then I knew why the eyes in the crazy painting were coming out. They were mine for having seen too much.

With the help of the continuous recall and release of such repressed material and with a new found ability to express herself and overcome resistances, her analysis now begins to move.

The LSD experiences have been valuable. But it was not an easy victory nor something to undertake lightly. This woman became very depressed and suicidal during the LSD experience, and I felt it wise to discontinue giving her LSD. But, because she had found the LSD experiences helpful she wanted to continue them and took 150 of LSD without my knowledge. She became intensely depressed. Four hours after she had taken the drug she told me about it. I stayed with her for 18 hours until she recovered. She later told me, “I would have died if you hadn’t been there.”

I want to stress that the person with an acute LSD psychosis needs someone with him all the time. The very presence of the other person minimizes the effects of the psychosis.

We have found that self-experiments are sometimes more productive of psychopathology than experiments in which an objective experimenter is present. Early in our work we found that while many were eager to take LSD to learn about its effect, there was a potential danger in this. The average subject was unable to judge when the effect of the drug had terminated. After he had considered himself recovered, he might get a renewed or secondary effect of the drug. For example, one subject found himself in a class on infra-red spectrophotometry while still under the influence of LSD. Another who had taken LSD at home while alone became so terrified that he had to call the hospital. Consequently we forbade anyone to take the LSD in the absence of medical supervision. One person decided to take LSD anyway. He took 100 of LSD and holed up with an audograph to record his experiences; at the same time he felt moderately guilty about the procedure and had some misgivings as to the consequences and appre
hension about having his experiment discovered. Nevertheless, he was confident in his ability to snap out of it and act normal, if he wanted to. During the first hour he had many intense somatic sensations. For a while he felt pleasant. He had left his body and was floating on a cloud. He was on a barge floating down the Nile with slaves rowing the barge. This idyll did not persist. He had to get up to change the record. When he did so he found he was surrounded with a blinding haze. He felt as though he were wrapped around with gauze and that an electric field insulated him from the rest of the world. He could barely change the record. He felt that he was being sucked or drawn into the machine. He was then faced with the fact that he was completely unable to shake off the effect, that he was overwhelmed by it, that he had lost control, and that he was totally incapacitated.

Immediately he went to the phone to call me to come to his rescue but was stopped by the thought—what if I did not answer the phone, he would have played his ace in the hole and he was afraid to risk it. He then developed the fear that someone else would answer the phone, and that they would come over and discover him. He later developed the delusion that his thoughts were being broadcast to the world, that there was no need to phone me since I knew of his plight anyhow, and that some hostile influence was keeping me away from him. Disturbing and horrible as the fantasies were, they were less horrible than the attempt to cope with the real world. Some of his comments are quoted:

I heard a noise, thought it was the repair man coming to replace me. I thought I heard the repair cart. Somebody's going through my pockets. They turned on this machine to shake me. I'll put my watch back on, and prove I'm not crazy, that this whole thing is a plot to get me to talk. The third degree. Having the truth shaken out of me. This is broadcast all over the world. All right, I'll talk; you don't have to beat it out of me any more. It certainly is a good torture device, being hooked up to a mind-reading outfit, thoughts being broadcast to the whole world.

He continued in this vein for about 6 hours, continually searching for some vestige of reality to cling to, yet afraid to test his reality. He continued to record during this time because somehow the recorder gave him an occasional reminder that it was all only an experiment. This reminder was not particularly helpful because he felt that, yes, it was an experiment, but that underneath there was a plot to incriminate him and drive him crazy. At the same time, he hated the recorder, felt chained to it, wanted to smash it, but was not sure if he would
not be destroying himself. The experiment was the unreality, a plot to drive him insane and incriminate him was the real reality. After six hours he felt recovered and started to leave. The very act of leaving frightened him. His delusions now returned. He had turned off the recorder and had put it away. Now the walls became lines with dictaphones. He was in a prison; he was afraid to set foot outside the door. Finally, he telephoned me but was unable to say how desperate he was because the wires were tapped. He was surprised that I was unaware of the experiment. He managed to elicit from me the suggestion that I come to see him, but without any hint of urgency. He was then faced with a wait, during which time he alternatedly paced the floor, and sat and stared at a piece of candy he had. He wanted desperately to eat the candy but felt that it was his last link with reality, and that if he ate it his last hold on reality was gone and he would be permanently crazy.

When I arrived, he was in a most intense anxiety state. For a few minutes he could not believe that it was me. When he had convinced himself that this was the case, he sat down and cried and related what a horrible experience it had been. In the course of talking about his delusions they gradually disappeared. He spent the night watching hallucinations untroubled by delusions. The next morning he had very strong feelings of unreality which persisted all day. In addition he felt people could read his mind. That night he was afraid to go to sleep lest he talk in his sleep and someone could overhear him. During the following week he persisted in the fear that someone would steal the records.

Both subjects had much more severe reactions than on previous occasions. In both instances guilt feelings over their defiance of me, and their loneliness, seemed to have shaped the course of the psychosis.

THE DETERMINANTS OF THE PSYCHOSIS

The prime determinant of the LSD psychosis is, of course, LSD itself. It causes disturbances in ego functioning which makes possible the emergence of the psychosis. The greater the amount of LSD, the greater likelihood of a psychosis: with small amounts the subject can fight off the effects or give into them as he chooses; with large amounts he feels overwhelmed by a force over which he has no control, which leads to attitudes of suspicion, distrust and paranoid thinking.

However, the amount of LSD is insufficient to decide why one sub
ject develops a psychosis, and another not; why a subject may develop a psychosis on one occasion and not on another. For this we must look to the subject himself and the experimental setting. The physiological state of the subject makes a difference. No food and no sleep make for a more severe reaction. The basic personality structure of the subject, his defenses and his underlying psychopathology are important. Those who are well defended, do not show a marked reaction. On the other hand, some pre-schizophrenics may develop a full unfolding of their basic psychosis under the influence of LSD.

The mental set of the individual at the time of the experiment contributed in good part to his reaction, as well as his reasons for taking the drug. Some introspective psychiatrists anxious to squeeze the last drop of psychopathology out of the drug experience, may on the surface appear to have a more profound psychotic reaction; nevertheless, for them these experiences are often conceived as ego alien and not really happening to them. It seems true of the LSD experience that the more you look, the more you find. In a similar vein subjects who are anxious to please the doctor by turning up nuggets of psychopathology tend to do so. By contrast, moderate states of anxiety and apprehension tend to denial of the experience. Where the anxiety and apprehension are overwhelming and the loss of reality is seriously threatened, the psychotic reaction is intensified. Such neurotic motivations for taking the drug in order to be cared for, tend to make for a more severe reaction because of the guilt engendered over giving into hostile dependent wishes. A subject who takes the drug at one time in a relatively anxiety free state, and at another time with a relatively severe anxiety state, will then have a more severe reaction.

The experimental setting shapes the reaction. We notice a less profound effect when subjects are kept busy doing psychological tests; this is a relatively non-stress situation which gives them more points of reality to cling to. A stress situation increases the severity of the reaction. A situation which points up the individual's incapacity makes him worse: "When I have to do dishes, there are always people standing behind me, leering over my shoulder; when I can lie down, they go away."

A major contributor to a heightened psychotic effect is the factor of loneliness. Loneliness must be qualified as a sense of isolation rather than the presence or absence of another person. For example, having to participate or being urged to participate in a group activity increases
the sense of loneliness if the subject is the only one who has had LSD. But where two or more in the group have received the drug at the same time, the experience is different. The subjects may then take this as a license for acting out of repressed impulses, tease and flirt with the nurse and tell off the doctors and act like mischievous boys. In similar fashion, talking and being talked to may decrease loneliness, but having to talk and having to listen may increase it. As one subject put it: “You don’t want to be alone and yet you don’t want the fellow you’re with to say anything. You just want him to be there.” The same subject commented that it was possible to talk with someone who understood, and that being able to talk to someone who understood was helpful. So intense is the fear of loneliness that one subject commented: “If you hadn’t been there I would have had nightmares for three days.” While leaving the subject alone usually results in an intensification of symptoms, the degree of intensification is in part a measure of the setting. For example, subjects who are unfamiliar with my office find the cluttered disorder and weird paintings disturbing, an additional threat to their hold on reality. Subjects who are familiar with my office find this very disorder reassuring, a reminder of something familiar, of my presence.

THERAPEUTIC IMPLICATIONS FOR SCHIZOPHRENIA

It is my belief that certain things we learn from studies of LSD are applicable to the treatment of the acute schizophrenic outset. This belief is founded upon my own observations of acute schizophrenic reactions, my observations of both subjects and patients who have had LSD, and from the reports of some of the subjects who, while naive to psychiatry, had the opportunity to compare their reactions with those of the patients with whom they were housed.

First, I would suggest that we be more alert for the early onset of schizophrenia, which is commonly accompanied by strong feelings of unreality and perceptual distortions. Very often the schizophrenic makes early appeals for help, often repeatedly calling his friends or his family; yet he is so blocked that he does not get his message across. Such patients make frequent appeals to the doctor. These appeals are often couched in terms of somatic complaints and complaints about the perceptual disturbances. Very often they consult the eye doctor, because things look different to them. I believe that if we can recognize them at this point and somehow reduce the level of anxiety, we can
materially impede the perceptual distortions and the rapid disintegration of the ego. Perhaps the new tranquilizing drugs which do not, apparently, cloud the sensorium might be helpful at this point.

Second, I would like to suggest that our treatment of the acute schizophrenic reaction is all wrong. At a time when the schizophrenic is desperately trying to hold on to some vestige of reality, we do everything in our power to destroy his hold on reality. We take him from his home, to a police station; from there to the emergency hospital, then to the admission ward, and finally either to the treatment ward or to the mental hospital. We cloud his sensorium with soporifics and shock, dealing a blow to his grasp on reality. We isolate him, putting him in a quiet room—as unreal an environment as one could ask for. We change his doctors and nurse; every eight hours a new shift comes on and several new faces appear. We view psychotherapy as we do penicillin in oil, as though one shot a day could carry over 24 hours. I suspect that the interpretations offered at this point are not nearly as effective as having the presence of another individual. I would think that round-the-clock specialing gives him the opportunity to talk if he wants to, not to talk if he doesn’t want to; and the opportunity to have the attendant talk to him if he wants. The talking is important, but more important is the presence of another person, whom he can learn to trust and whom he feels is capable of understanding. I think that during an experience when time is meaningless, to have the attendant disappear for prolonged intervals is devastating. As one subject with LSD put it, “Your physical reality disappears, and then your body disappears, and you have only another person and something gets between you and the other person, and you’re cut off from the only thing that can save you.”
Research psychiatrists no longer need apologize for either the words "model psychosis" or for the use of these interesting drugs to produce psychologic changes. There have been many objections hurled at the research psychiatrist because he has played around with these drugs. Some of the objections I consider frivolous, some of them I consider very serious and constructive.

An example of the frivolous type of objection is the statement that LSD produces a toxic psychosis. If you heard Doctor Hoch, you will understand that it does not produce a disorientation, nor a decrease in consciousness, nor memory loss. So it is not, by definition, a toxic psychosis.

A serious objection has been the statement that the majority of subjects who have taken LSD noted predominantly visual phenomena, and that very few schizophrenics show the same degree of visual change. This is a serious criticism against the LSD experience as a representative of real schizophrenia. It is true that in a small group of acute, very excited schizophrenics we do find changes that are practically indistinguishable from LSD. We have taken a verbatim recording of the LSD interview and of a schizophrenic interview, and we have given the interviews to eminent psychiatrists, to see if they could distinguish them; they were not able to do so.

However, we have been trying to modify the LSD experience. You have heard Doctor Hoch discuss some of the compounds, amytal and dextadrine compounds; and Doctor Himwich briefly referred to his use of Frenquel. We have been working with nicotinic acid, or niacin, vitamin B₉; and we find that the vitamin, when given in adequate dosages, produces a remarkable modifying action on the LSD psychosis. We have run two types of experiments. In the first we have given the subject 100 of LSD; at the height of the experience we injected intravenously 200 mg. of nicotinic acid. Our experience has been that, within a matter of two to five minutes, almost all of the LSD phenomena disappeared, and the subject claimed that he was entirely normal.
The most striking example was that of a very serious psychologist, who, under the influence of LSD merely sat and giggled for two hours. When we subjected him to a T.A.T. test, all he could find were race horses in it. We gave him the nicotinic acid and five minutes later he became quite sober and normal; the rest of the afternoon he got to work and did some psychological problems that he had been putting off for the past two months. He claimed that he was entirely normal, although I don’t think that he was. The rest of the afternoon he still had recurring waves of slight perceptual changes.

This is the most typical example of this type of experiment. We have done the reverse type of experiment where we premedicated the subjects with niacin for three days, with a dose of three grams per day; then on the test day the subject was given 100 of LSD. With this type of experience the phenomena occurred much later—it took more than the usual fifteen minutes to half hour, usually about an hour before any change occurred. With this type of medication the niacin appears to prevent most of the perceptual changes from occurring. In this type of change, which we think is also a type of psychosis, the subject is able to describe with great clarity his experiences. He is not over whelmed by the perceptual disturbances, and he is able to delve into himself to describe exactly what he is experiencing. The chief changes are in the areas of feelings of unreality and depersonalization. One of our subjects felt that he was seven beings at one time, that he was looking down in never ending spirals at this poor real world in which we are living.

Now, these two types of experiments have raised very interesting questions. I cannot explain chemically why giving the niacin before LSD produces a certain type of change, and giving the niacin after LSD produces another type of change. It has occurred to me that when a subject is experiencing the real LSD phenomena and he is brought back to normal, that he compares himself to the state he was in previously; a state he considers normal. Whereas, in the other type of experiment where the subject has not experienced the vivid perceptual changes, he then becomes aware of the changes that he is experiencing in relevance to the previous state.

We don’t feel that the niacin normalizes the LSD subject, although it certainly does so in the areas of perception. If you will permit me to split the changes into the neurological and psychiatric, it appears that niacin prevents most of the neurological changes, the autonomic changes; yet permits many of the psychiatric changes to run their course.
Mescaline and the "Other World"

Aldous Huxley

My purpose tonight is to discuss the mescaline experiences, not of neurotics, but of those, who like myself, are relatively sane. Classic descriptions of this experience were given, many years ago, by Weir Mitchell and Havelock Ellis, whose accounts tally very closely with what I myself and all the experimenters with whom I am personally acquainted were able to report. These classic mescaline experiences differ in many respects from those we have heard discussed tonight. Almost all of those we have heard discussed tonight are colored by fear and anxiety. Moreover, they abound in references to the subject's personal memories and to the traumatic experiences of his childhood. How different is the classic mescaline experience! Here the most striking feature, stressed emphatically by all who have gone through it, is its profound impersonality. The classic mescaline experience is not of consciously or unconsciously remembered events, does not concern itself with early traumas, and is not, in most cases, tinged by anxiety and fear. It is as though those who were going through it had been transported by mescaline to some remote, non-personal region of the mind.

Let us use a geographical metaphor and liken the personal life of the ego to the Old World. We leave the Old World, cross a dividing ocean, and find ourselves in the world of the personal subconscious, with its flora and fauna of repressions, conflicts, traumatic memories and the like. Traveling further, we reach a kind of Far West, inhabited by Jungian archetypes and the raw materials of human mythology. Beyond this region lies a broad Pacific. Wafted across it on the wings of mescaline or lysergic acid diethylamide, we reach what may be called the Antipodes of the mind. In this psychological equivalent of Australia we discover the equivalents of kangaroos, wallabies, and duck-billed platypuses—a whole host of extremely improbable animals, which nevertheless exist and can be observed.

Now, the problem is, how can we visit the remote areas of the mind,
where these creatures live? Some people, it is clear, can go there spontaneously and more or less at will. A few of these travelers were great artists, who could not only visit the Antipodes, but could also give an account of what they saw, in words, or in pictures. Much more numerous are those who have been to the Antipodes, have seen its strange inhabitants, but are incapable of giving adequate expression to what they have observed. At the present time they are reluctant to give even an inadequate expression to their experience. The mental climate of our age is not favorable to visionaries. Those who have such spontaneous experiences, and are unwise enough to talk about them, are looked on with suspicion and told that they ought to see a psychiatrist. In the past, experiences of this kind were considered valuable and those who had them were looked up to. This is one of the reasons (though not perhaps the only reason) why there were more visionaries in earlier centuries than there are today.

Those who cannot visit the mind’s Antipodes at will (and they are the majority) must find some artificial method of transportation. One method which works in a certain proportion of cases is hypnosis. There are persons who, under moderately deep hypnosis, enter the visionary state.

More certain in their effect are the so-called hallucinogens, mescaline and LSD. Personally I have never taken LSD, so I can speak, from experience, only of mescaline. Mescaline transports us very painlessly—for there is hardly any of that horrible nausea which follows the ingestion of the peyote cactus, and there is no hangover—to the mind’s Antipodes, where we find a fauna and a flora strikingly different from the fauna and flora of the familiar Old World of personal consciousness. But just as marsupials, though improbable, are in no sense random or lawless phenomena, so it is with the inhabitants of the mind’s Antipodes. They conform to the laws of their own being, they can be classified and their strangeness possesses a certain regularity of pattern. As Klüver has pointed out in his book on peyote; visionary experiences, though varying from individual to individual, belong nevertheless to one and the same family. Mescaline experiences of the classic kind exhibit certain well-marked characteristics.

The most striking of these common characteristics is the experience of light. There is a great intensification of light; this intensification is experienced both when the eyes are closed and when they are open. Light seems praetematurally intense in all that is seen with the inward eye. It seems also praetematurally strong in the outside world.
With this intensification of light there goes a tremendous intensification of color, and this holds good of the outer world as well as of the inner world.

Finally there is an intensification of what I may call intrinsic significance. That which is seen, either with the eyes closed or open, is felt to have a profound meaning. A symbol stands for something else, and this standing for something else is its meaning. But the meaningful things seen in the mescaline experience are not symbols. They do not stand for something else, do not mean anything except themselves. The significance of each thing is identical with its being. Its point is that it is. In a paradoxical, but (to those who have experienced this heightening of intrinsic significance) an entirely self-evident way, the relative becomes absolute, the transient particularly universal and eternal.

Intensified light, intensified color and intensified significance do not exist in isolation. They inhere in objects. And here again the experiences of those who have taken a hallucinogen, while in a good state of mental and physical health, and with a proper degree of philosophical preparation, seem to follow a fairly regular pattern. When the eyes are closed, visionary experience begins with the appearance in the visual field of living, moving geometries. These abstract, three-dimensional forms are intensely illuminated and brilliantly colored. After a time they tend to take on the appearance of concrete objects, such as richly patterned carpets, or mosaics, or carvings. These in turn modulate into rich and elaborate buildings, set in landscapes of extraordinary beauty. Neither the buildings nor the landscapes remain static, but change continuously. In none of their metamorphoses do they resemble any particular building or landscape seen by the subject in his ordinary state and remembered from the near or distant past. These things are all new. The subject does not remember or invent them; he discovers them, “out there,” in the psychological equivalent of a hitherto unexplored geographical region.

Through these landscapes and among these living architectures wander strange figures, sometimes of human beings (or even of what seem to be superhuman beings), sometimes of animals or fabulous monsters. Giving a straightforward prose description of what he used to see in his spontaneous visions, William Blake reports that he frequently saw beings, to whom he gave the name of Cherubim. These beings were a hundred and twenty feet high and were engaged (this is characteristic of the personages seen in vision) in doing nothing that could be thought of as being symbolic or dramatic. In this respect
the inhabitants of the mind's Antipodes differ from the figures inhabiting Jung's archetypal world; for they have nothing to do either with the personal history of the visionary, or even with the age-old problems of the human race. Quite literally, they are the inhabitants of "the Other World".

This brings me to a very interesting and, I believe, significant point. The visionary experience, whether spontaneous or induced by drugs, hypnosis or any other means, bears a striking resemblance to "the Other World," as we find it described in the various traditions of religion and folklore. In every culture the abode of the gods and of souls in bliss is a country of surpassing beauty, glowing with color, bathed in intense light. In this country are seen buildings of indescribable magnificence, and its inhabitants are fabulous creatures, like the six-winged seraphs of Hebrew tradition, or like the winged bulls, the hawk-headed men, the human-headed lions, the many-armed, or elephant-headed personages of Egyptian, Babylonian and Indian mythology. Among these fabulous creatures move superhuman angels and spirits, who never do anything, but merely enjoy the beatific vision.

The costumes of the inhabitants, the buildings and even many features of the landscape in "the Other World" are encrusted with precious stones. Interestingly enough, the same is true of the inner world contacted under mescaline or in spontaneous vision. Weir Mitchell and many of the other experimenters, who have left an account of their mescaline experience, record a profusion of living gems. These gems which, in Mitchell's words, look like clusters of transparent fruit, glowing with internal radiance, encrust the buildings, the mountains, the banks of rivers, the trees. One is reminded, as one reads these descriptions of the mescaline experience, of what is said of the next world in the various religious literatures of the world. Ezekiel speaks of "the stones of fire," which are found in Eden. In the Book of Revelation, the New Jerusalem is a city of precious stones and of a substance which must have seemed to our ancestors almost as wonderful as gem-stones—glass. The wall of the New Jerusalem is of "gold like glass"—that is to say of a transparent, self-luminous substance having the color of gold. Glass reappears in the Celtic and Teutonic mythologies of Western Europe. The home of the dead, among the Teutons, is a glass mountain, and among the Celts it was a glass island, with glass bowers.

The Hindu and Buddhist paradises abound, like the New Jerusalem, in gems; and the same is true of the magic island which, in Japanese mythology, parallels Avalon and the Isles of the Blest.
Among primitive peoples, ignorant of glass and having no access to gemstones, paradise is adorned with self-luminous flowers. Such magical flowers play an important part in the Other World of more advanced peoples. One thinks, for example, of the lotus of Buddhist and Hindu mythology, the rose and lily of the Christian tradition.

It may be objected that paradise is merely “pie in the sky,” and that the reason all paradises are adorned with precious stones is precisely their preciousness here on earth. But why should gems ever have been regarded as precious? What has induced men to spend such enormous quantities of time, trouble and money on the finding and cutting of colored pebbles? In times of any kind of utilitarian philosophy, the fact is entirely inexplicable. My own view is that an explanation for the preciousness of precious stones must be sought, first of all, in the facts of visionary experience. Gem-like objects, bright, self-luminous, glowing with praeternatural color and significance, exist in the mind’s Antipodes, are seen by visionaries and are felt by all who see them to be of enormous significance. In the objective world, the things which most nearly resemble these self-luminous visionary objects are gems. Precious stones are held to be precious, because they remind human beings of the Other World at the mind’s Antipodes—the Other World of which visionaries are fully conscious, and ordinary persons are obscurely and, as it were, subterraneously aware. There is a magical kind of beauty, which we say is “transporting.” The adjective is well chosen; for it is literally true that certain spectacles do carry away the mind of the beholder—carry it out of the everyday world of common, conceptualized experience into the magical Other World of non-verbal, visionary awareness.

Flowers are almost as transporting as precious stones, and I would be inclined to attribute the almost universal passion for flowers, the almost universal use of flowers in the rites of religion, to the fact that they remind men and women of what is always there, praeternaturally bright, colorful and significant, at the back of their minds.

Of the connection between visionary experience and certain forms of art, I have no time to speak. Suffice it to say that the connection is real, and that the almost magical power exercised by certain works of art springs from the fact that they remind us, consciously or, more often, unconsciously, of that Other World, which the natural visionary can enter at will, and to which the rest of us have access only under the influence of hypnosis or of a drug such as mescaline or LSD.
Some Observations on Normal Volunteers and Patients

Harold A. Abramson

Dr. Cholden mentioned that the whole problem of communication between the disciplines was enhanced by the discovery of LSD. It was a source of great inspiration to me to see the enactment of cross-fertilization among the disciplines actually taking place vigorously, at the meeting of the American Psychiatric Association. It is, of course, all the more important because the stimulus is the discovery of a new and safe technique for a model psychosis in man.

I am reminded, somewhat, of the progress made in understanding biological reactions and behavior in the 1920's and early 1930's. This period, the renaissance of general physiology, saw the joint efforts of physical chemistry, pharmacology, classical physics, physiology, neurology, organic chemistry, mathematics and modern physics, applied to biological systems. Tonight we have witnessed the same phenomenon occurring in the field of mental illness. This integration and application of the scientific disciplines in the study of psychotic processes is an event that must lead to a new and better knowledge.

It marks a departure from the standard set by the remarks of a well-known physician* concerning the attitude of the therapist in treating certain cases of schizophrenia.

Mention may be made of the personality of the therapist if he is to have a good chance of successfully treating the acute phase of schizophrenia. He should believe in his own omnipotence—therapeutic failure must be unacceptable to him, the patient's recovery must be of high emotional importance to him, the whole gamut of emotionality must be at his quick command, and the activation of psychic manifestations close to the primary processes must be uninhibited. He must be endowed with the ability to dramatize, time spent on the patient must count, the gravity of the situation must challenge him, and the possibility of failure must mean to him the imminence of a traumatic, therapeutic defeat.

The patient will then feel that he has been placed in the center of the thera


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L. C. Greenfield. Choose the correct response:

pist's life. The higher the stakes which the therapist places on the patient, the greater will be his response.

I feel quite sceptical about the miracles which are reported in the Gospels. But I am convinced that the Saviour cured schizophrenics in the acute phase. Like most psychiatric reports, the Gospels also omit the tidings of the second phase. Nevertheless, the more the therapist can evoke in the patient a modern approximation to the Christ image, the greater will be his therapeutic chances.

I only wonder why the churches, which usually guard their prerogatives with jealousy, so easily surrendered to science the privilege of treating schizophrenics.

I foresee that the psychiatrist, with the help of the experimental method, with the insight obtained from the studies of the model psychosis in non-psychotic subjects, instead of having to believe in his own omnipotence, will be able to bear the humilities embodied in the experimental method. Failure will not mean, to the psychiatrist, the imminence of the "traumatic therapeutic defeat", but the emergence of a new problem for him to investigate in the laboratory.

Dr. C. S. Savage emphasized that an important transaction had occurred between the physician and the patient. That, I believe, is a clue to understanding the usefulness of LSD-25. The pharmacologic action of LSD-25 by itself can hardly be as valuable as the LSD-25 experience in response to an interested therapist. The response of the subject, therefore, will depend markedly upon the attitude of the therapist toward the use of his drug. In particular, if the therapist is not anxious about the use of the drug, anxiety in the patient will be much decreased.

Most important are the relationships occurring when LSD-25 is administered to groups. Dr. Jarvik and I have studied the reaction of groups for several years at the Mount Sinai Hospital, New York City. I have also studied group responses in my office, and as a matter of fact, have frequently observed group reactions of from two to five subjects in my own home at Cold Spring Harbor. During the past four years we have administered the drug hundreds of times to non-psychotics in doses up to 225 by mouth, without difficulty.

Before discussing what occurs within the group I would like to mention the effects of chlorpromazine administered with LSD-25 to groups of four to five in a social situation at my home. The drug was administered before dinner and the experiments were carried out during the course of the evening. If chlorpromazine is given to the subjects two hours before or two hours after LSD-25, the psychomotor activity
decreases. However, if given simultaneously with LSD-25, potentiation of the LSD reaction may occur. 50 mg. of chlorpromazine were usually given by mouth in these experiments. Our results are not contrary to those of Dr. Hoch because our dosage was lower.

In the group reactions a remarkable relationship often occurs among the group under LSD. It is probably connected with what Mr. Huxley was discussing. Those who have participated in these groups are nearly always definitely benefited by their experiences. Almost invariably they wish to return and to participate in new experiments. The improvement in ego structure that I have observed is due, I believe, in part to the following mechanism. Under the influence of LSD an experimental stress situation is produced. Psychodynamically, the subjects of the experiment repeatedly go through threatening situations in which they are constantly reassured by their own success in dealing with the experimental stress. Ego-depression produced by the drug is well balanced by ego-enhancement which persists as an ego lesson learned. This, I believe, leads to improvement of ego structure; at least it has with many of my subjects.

It may be of interest that one subject has had LSD eighty times in doses varying from 25 to 100. Several have had it at least twenty times. I believe that in all cases where the drug has been taken repeatedly in group situations even though active psychotherapy was not part of the experimental program, some mechanism like that proposed, improved the ego structures of some members of the group.

I was very glad to have Dr. Sandison say that I was trying to determine the orderly aspect of the LSD psychosis. This I have especially tried to do where the doses of 20 to 40 are administered as an adjuvant to psychotherapy. Interviews with me often last as long as four hours. I believe that I have utilized in therapy, not only the depression in ego functioning but also the ego enhancement or reinforcement which occurs simultaneously. Patients under LSD have been able to utilize the mobilization of preconscious material. Their interpersonal relationships improved not only with the therapist, but also with others. So I must emphasize that, when LSD acts in the dose range indicated, we must take advantage of the ego-enhancement as well as the ego-depression. The ego adaptive forces are ready and waiting for the therapist to activate them.

Finally, it must be important to have someone always with the subject or protecting the subject in a nearby room. Subjects under LSD are
readily placed in, and are particularly sensitive to, stress situations. Going alone on the cafeteria line may produce a severe anxiety state. One subject developed a process grossly resembling a paranoid psychosis, when he went alone to the men's room.

REFERENCES


THE point of view from which I will discuss LSD is a bit different from the one which the other speakers have presented. Much of what has been said tonight has been directed toward developing data which will lead to an understanding of the basis of the effects of LSD in man; the work which I will present will not, at the present time, enable us to do this. We believe, however, that by studying certain neurophysiological effects of LSD, we may be able to learn something of the brain mechanisms underlying the effects of this drug in animals. I would like, however, to emphasize the need of exerting caution in using the data which one obtains from animal studies as an explanation of the effects of LSD in man.

We have approached studies of the effects of LSD in animals from two general points of view. First of all, we have attempted to discover the structure of additional chemicals whose actions are similar to those of LSD. In approaching this problem, we were very interested in Gaddum’s observation that LSD is a potent serotonin antagonist in vitro. The second general aim of our animal studies with LSD has been to discover certain specific LSD effects in animals; it seemed reasonable that such specific effects might be related to the mechanism of action.

We have carried out detailed studies of the actions of three indole derivatives, LSD, serotonin and bufotenine. On the basis of Gaddum’s work, we thought that in addition to LSD, serotonin analogues of other sorts, or serotonin competitors, might share some of the properties of LSD. This hypothesis led us to investigate bufotenine (dimethylserotonin), an alkaloid which has been isolated from seeds of piptadenia peregrina. We found that bufotenine and LSD produce a similar syndrome in the conscious monkey. We observed that the monkeys became blind at a certain stage in either LSD or bufotenine intoxication. This finding led us to investigate the effects of LSD and
bufotenine on neural transmission in the visual system. We studied the visual system of the nembutalized cat in three ways. First of all, we photically stimulated the retina and recorded the action potential complex from the optic tract. LSD and bufotenine had little effect on the optic tract response to photic stimulation of the retina. We examined synaptic transmission in the lateral geniculate nucleus by stimulating the optic nerve and recording the resultant potentials in the lateral geniculate nucleus. LSD and bufotenine caused a marked decrease in the amplitude of the post-synaptic geniculate potential. We then examined the effects of LSD and bufotenine on the cortical response to geniculate radiation fibre shock. We found that this cortical response was highly resistant to both of the drugs.

Several of the speakers this evening have discussed LSD antagonists. The idea has been expressed that such antagonists might be of some value in the treatment of schizophrenia; a priori, it would be difficult to be at all certain that this is so. Perhaps the notion of an LSD-antagonist should be defined more precisely. One might think of several types of antagonists: a nonspecific antagonist, which alters the psychological effect of LSD in man without acting as a biological competitor. There might be two additional types of antagonists: one, an antagonist in the sense that n-allylmorphine is an antagonist to morphine, and two, an antagonist in the sense that acetylcholine is an antagonist to curare. It would be most interesting to find antagonists like these latter two; if they were to be obtained, we feel that it would be valuable to study the interaction between these antagonists and LSD in man.
We are engaged in a study of the metabolism of LSD by using radioactive carbon 14 labeled LSD. This work is not as exciting as some which has been presented here, but we hope that eventually it may lay some of the groundwork for the better biochemical understanding of the mode of action of LSD.

We would like to say just a few words about the distribution, excretion and metabolism of LSD.

Table 1 shows the relative concentrations of radioactivity in various tissues of the rat three hours after the intraperitoneal administrations of labeled LSD. This labeled LSD had an activity of 5.4 mc./mg., and a dose of 1 mg./Kg. given either intraperitoneally or intravenously was used in all our experiments. I should perhaps emphasize that the data in this table is for the rat and is not necessarily applicable to any other species. It should also be pointed out that this data represents total radioactivity and includes, therefore, LSD itself and any metabolites of it which have been formed in the body.

The distribution shown in this table, except the data on the gut and its contents, represents what I would call a relatively normal distribution with a high activity in the liver and kidney, which are two of the major routes of elimination, and a relatively low activity in the brain. However, it can be seen from the table that the administered LSD, or at least its radioactivity, is very unevenly distributed. About 70 per cent of the dose is in the gut contents, and about 10 per cent in the gut itself. The high level in the gut wall is probably due, at least in part, to incomplete separation of the gut from its contents.

Studies on the transfer of radioactivity from the liver to the gut by the way of the bile, indicate that about 80 per cent of the radioactivity in the gut and its contents reaches this site via the bile secretion in three hours.

Experiments have also been done in which urine, feces, and expired air were collected for twelve hours after the administration of labeled
LSD. The amount of radioactivity excreted by all of these routes in twelve hours was relatively small. About 3 per cent was found in the expired air; 3 per cent in the urine; and 1 per cent in the feces. The radioactivity in the urine and feces has not yet been identified but that in the expired air has been shown to be in the form of carbon dioxide.

The gross distribution of radioactivity twelve hours after administration of labeled LSD is summarized in table 2.

**CONCENTRATION OF RADIOACTIVITY**
**AND PER CENT OF DOSE AT THREE HOURS**

<table>
<thead>
<tr>
<th>Tissue</th>
<th>%</th>
<th>mc./mg. (wet) x 10^-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gut Contents</td>
<td>70.2</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>2.31</td>
<td>3.89</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.08</td>
<td>1.33</td>
</tr>
<tr>
<td>Brain</td>
<td>0.02</td>
<td>0.21</td>
</tr>
<tr>
<td>Heart</td>
<td>0.03</td>
<td>0.55</td>
</tr>
<tr>
<td>Lung</td>
<td>0.12</td>
<td>1.13</td>
</tr>
<tr>
<td>Skeletal Muscle</td>
<td>0.09</td>
<td>0.40</td>
</tr>
<tr>
<td>Kidney</td>
<td>0.44</td>
<td>3.28</td>
</tr>
<tr>
<td>Uterus and Ovaries</td>
<td>0.06</td>
<td>0.74</td>
</tr>
<tr>
<td>Adipose Tissue</td>
<td>0.04</td>
<td>0.24</td>
</tr>
<tr>
<td>Gut (less contents)</td>
<td>10.2</td>
<td>17.8</td>
</tr>
<tr>
<td>Blood</td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td>Rest of Carcass</td>
<td>7.55</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Table 1: Distribution of radioactivity among the tissues of the rat three hours after administration of 1 mg/kg. of labeled LSD intraperitoneally.

**GROSS DISTRIBUTION OF RADIOACTIVITY**
**TWELVE HOURS AFTER ADMINISTRATION**

<table>
<thead>
<tr>
<th>Component</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total excreted</td>
<td>6.8</td>
</tr>
<tr>
<td>Gut and Contents*</td>
<td>79.7</td>
</tr>
<tr>
<td>Various tissues</td>
<td>1.2</td>
</tr>
<tr>
<td>Rest of carcass</td>
<td>10.4</td>
</tr>
</tbody>
</table>

Table 2: Gross distribution of radioactivity in the rat twelve hours after intraperitoneal administration of 1 mg./Kg. of labeled LSD.

*Of the 79.7%, at least 71.2% was in the contents of the gut.
With regard to metabolites, we have so far isolated two from the bile. And there are indications that at least two more are formed in the rat. The two which we have isolated are formed rapidly, and as far as we can tell at the present time, small amounts of them are probably distributed fairly widely in the body. Thus they may account for a significant proportion of the radioactivity found in the various tissues. These two metabolites isolated from the bile account for close to 50 per cent of the administered LSD within a period of an hour and a half to two hours after administration.

In general these data indicate that in the rat LSD is picked up from the peritoneal cavity and carried mainly to the liver. Here much of it is rapidly metabolized and excreted via the bile into the gut. From here some of the LSD and metabolites are probably recirculated to the liver and back to the gut. Only 10 to 20 per cent of the administered dose seems to reach the systemic circulation. Part of this is excreted by the kidneys and part is distributed in a fairly even manner throughout the remainder of the body.
Summary and Discussion

Harry Pennes

I have the happy experience of being the summarizing discussant of these excellent papers. I expect that I shall apply the Socratic method and bring up some questions which I hope the previous speakers will answer. The speakers have all been clear and explicit and the evening has been full of material. Our chairman has impressed on me the desirability of brevity and I shall endeavor to comply without neglecting anyone.

The majority of contributions tonight were on LSD rather than on mescaline. While listening, I have been wondering what the reasons might be for this partition of interest. Mescaline has been known much longer than LSD and of course was introduced into psychiatry first. Is there a fascination, perhaps, with the much lower absolute dosage of LSD required to produce effects as compared with the dosage of mescaline? Or is it possibly because we want our patients to be as comfortable as possible while under these drugs—the mescaline experience is usually more distressing to the subject because of the frequent nausea and vomiting. Actually, as you all know, mescaline is much closer structurally to a natural body constituent than is LSD, and in the long run may turn out to have more physiological significance. I refer to the similarity in structure between mescaline and adrenalin and nor-adrenalin.

Dr. Hoch, in the first presentation of the evening, gave us a succinct resumé of the effects of various blocking agents against the mescaline and LSD psychoses. He referred to the nonspecificity of these various blocking agents at a chemical level, referring to sodium amytal, methamphetamine, chlorpromazine and to some degree, Serpasil. Other speakers also mentioned Frenquél and nicotinic acid. In addition, there has been an unpublished report that serotonin modifies the LSD reaction; and also a published account of the blocking action of succinic acid and glutamic acid. So there is non-specificity at a chemical level with a rather broad spectrum of blocking agents, but in addition there is non-specificity at a clinical level with respect to a given agent. Chlorpromazine, one of the most effective blocking agents mentioned by
Dr. Hoch, tends to reduce the same symptoms in all the naturally occurring mental disorders in which it is effective. These symptoms are mainly increased tension, agitation, disturbed behavior and pathologically increased psychomotor activity. The beneficial effects of the drug occur in various diagnostic categories—schizophrenia, manic-depressive psychosis, some of the acute toxic psychoses and other conditions. And now, the symptoms of tension and agitation occurring in the model psychoses produced by mescaline and LSD may be added to the list of symptoms which may be attenuated by chlorpromazine. The final point I should like to make in connection with Dr. Hoch’s presentation is something he referred to in a single sentence, namely that the more intense the psychotic symptoms under mescaline and LSD, the more effective the relief provided by the blocking agents. This observation, so far as chlorpromazine is concerned, also agrees with the action of this drug in naturally occurring psychosis—excessive states of agitation and tension are more effectively reduced than minor degrees of these symptoms. Thus we have another sort of parallelism between the effects of chlorpromazine on the model psychoses and the naturally occurring mental disorders.

Turning now to Dr. Himwich’s presentation, I shall content myself by asking two obvious questions which I am sure must have occurred to Dr. Himwich himself. First of all, would he tell us about the EEG effects of mescaline and LSD in schizophrenics and how they compare with the electrocortical arousal reaction he has observed in his unanesthetized rabbits? Secondly, does the EEG of schizophrenics in the resting state show evidence for a tonic electrocortical arousal reaction? At this point, if I may have your indulgence for a moment, I should like to present some personal neuropharmacological work done with mescaline on the primary optic system of the cat. I recently had the opportunity, in collaboration with Dr. Amedeo S. Marrazzi, of studying the effects of this drug on evoked cortical optic responses in the anesthetized cat. The results were quite consistent. With either intravenous or intracarotid administration, primary evoked responses of optic cortex were regularly depressed or eliminated, often for periods lasting up to 45-60 minutes before full recovery. The minimal effective intravenous dose for this effect was 5-10 /Kg. body weight, a dose which produces characteristic behavioral changes in the unanesthetized cat and in man. The minimal effective intracarotid dose was approximately one-tenth of the intravenous dose, a reasonable ratio. Inhibition occurred of optic responses evoked either by electrical or photic stimu-
lation. Type of anesthesia was immaterial—Nembutal, chloralosane, or chloralosane-urethane. There is evidence from the electrical stimulation-studies that the inhibitory action occurred primarily at a cortical rather than a subcortical (lateral geniculate body) locus. With topical administration of mescaline to cortex, the results were quite different. Although the results have not been analyzed in full yet, topical administration produced no consistent change in the primary evoked response but did cause spontaneous cortical discharge and also facilitated repetitive after-discharge following the primary evoked response.

The relationships of these findings to those of Dr. Himwich are speculative since he worked with a different species, used no anesthesia and studied a different neurophysiological system. Perhaps this will come up in the later discussion. The inhibition I just reported for mescaline is in accord with the data presented by Dr. Evarts with LSD on the same system in the cat in the sense that depression of transmission occurred with both drugs. However, with LSD the primary locus of action was subcortical in Dr. Evarts experiments rather than cortical.

Dr. Rinkel gave us in succinct form his reasons for implicating the adrenalin cycle in the generation of the LSD psychoses. In so doing, he has joined hands to some extent with Dr. Hoffer's group in Canada, who arrived independently at the hypothesis of a toxic "M" substance by a different line of reasoning. I wonder whether Dr. Rinkel, or anyone else, has given adrenalin itself as an agent which might modify the LSD or mescaline reactions. Theory would not appear securely enough established to predict the result and no effect, increase, or decrease of symptoms might occur.

Turning now to some of Dr. Hoffer's previous ideas, I should like to present some data relevant to the indole nucleus hypothesis. As you know, Dr. Hoffer and his group have pointed out that the known hallucinogens (with the exception of mescaline) are characterized structurally by the presence of an indole nucleus, examples of this fact being LSD and harmine. With mescaline, it is assumed that the aliphatic side-chain may be closed after absorption of the compound to form an indole structure. Their reasoning has been quite stimulating to others and has resulted in that much to be desired effect—the experimental testing of specific hypotheses. Our own group, however, recently had the opportunity of testing two hallucinogenic agents in mental patients which do not possess an indole nucleus. One of these, known
commercially as Win 2299, has the following formula: 2-diethylaminoethyl cyclopentyl-(2-thienyl)-glycolate hydrochloride. In animals, it is said to have a scopolamine-like action although its structure is entirely different from that of scopolamine. The second agent is better known, namely N-allyl normorphine hydrochloride.

Win 2299 produces a full-fledged mescaloid reaction in mental patients, complete with perceptual disturbances in most modalities, visual hallucinations, emotional changes, unreality feelings, and difficulties with the thought-speech processes. The dosage range employed was 2—10 mg., orally; at the highest dose, definite evidence of a delirioid component began to appear. N-allyl normorphine, 10—20 mg. intravenously, is more restricted in its action. It produces primarily a visual hallucinosis (without much involvement of other perceptual spheres; there is also a certain amount of central depression manifested as clinical sedation-relaxation and drowsiness. Along with these effects, about half our patients reported a therapeutic type of action, principally a reduction of anxiety, tension and other emotional aberrations.

There is considerable interest in the relationship of the structures of these two drugs to those of mescaline and LSD. Here we can generalize only broadly. All are basic in reaction, possess a ring structure and an aliphatic side-chain; the side-chain either contains a terminal amino group (mescaline) or a terminal substituted nitrogen atom. Even this broad generalization fails if another hallucinogen, harmine, is considered: there is no aliphatic side-chain in harmine. Only two of the five compounds possess an indole nucleus (LSD, harmine). The Win 2299 is of particular interest because of the composition of its side-chain: please note the asymmetric carbon atom, which is the first carbon atom on the left; it is followed by a C = 0 group; and on the right of the chain, the nitrogen with a diethyl substitution. All these features are present in LSD. The obvious issue is the degree to which LSD actively is dependent on these features and the degree to which it is dependent on its tetracyclic structure. Certainly the cyclic portions of LSD and Win 2299 are grossly dissimilar. With N-allyl normorphine, a curious structure even for the organic chemist, the nitrogen atom has an allyl attachment and also enters into the CH₂—CH₂ bridge.

Doctor Savage gave us a very vivid account of LSD psychosis, and the experience of our group, by and large, confirms his excellent clinical description. We, too, have found if the patient is left alone the intensity
of the experience does usually increase markedly; and we have found this to be particularly true for the emotional experiences. We have tended to divide the reactions to LSD and mescaline into two categories: the basic experiences under the drug or the effects which are directly produced by toxic drug action; and what we call the personality specific experiences under the drug. By the personality specific experiences, we use a broad definition and refer to the total sum of the patient's previous capacity for dealing with stress, his life situations, and the particular content of his psychopathological status. Tentatively we feel that some of the basic disturbances are the hallucinations and alterations in other perceptual spheres, and certain emotional changes, these being considered to be directly drug produced. Certain features of the experience seem to operate, however, at a personality level, perhaps broadly reactive or secondary to these basic drug experiences. In certain quarters there has been a tendency to consider the entire LSD experience as a personality induced experience, and it is not uncommon to hear statements, for example, that the hallucinations or the disturbances of body image originate at a psychologic level. I wonder if Doctor Savage would be good enough to give us his views on this question.

Dr. Sandison has given us a refreshing approach, that is to say, the use of the temporary psychotic experience provided by LSD as a means of providing symptomatic relief in the neuroses when given in proper hands. You might summarize his approach, I suppose, as "first you make them worse and then you get them better." Actually, the getting better, although he has perhaps been too modest to stress this, may be a function of the total therapeutic situation in which these patients find themselves. Those of you who have been fortunate to read his papers in the Journal of Mental Science will realize that competent individual psychotherapy has been as sine qua non; and moreover, Doctor Sandison has apparently been quite devoted in this regard. Also I note with interest that the patients had, in addition, group psychotherapy, and that there was much interpersonal communication between the various patients after the LSD experience. I won't belabor the obvious point of the contribution of these factors in producing the observed therapeutic effects. I hope that Doctor Sandison will give us his opinions on the degree to which they contributed.

Now, in conclusion, I want to mention Mr. Huxley's presentation. Some of us in this field like to think of psychiatry as the universal science, and I should like to thank Mr. Huxley for bringing this home to us again, especially with the implement of his enormous erudition.
Dr. Calloway: I was particularly curious about the difference between Doctor Evarts' work and Doctor Savage's reports in the transmission of the lateral geniculate in the cortical responses, and in the relationship to Doctor Himwich's work and the relationship between this and the ascending reticular system. Not meaning to put everything there, but it seems to end up there frequently. Also the work more recently reported by Jasper on the effect of stimulating the reticular system in blanking out the evoked potential from stimulating the thalamic nuclei. And you didn’t mention the anesthesia which you used on the animals.

The two questions are:

1. Could your results, Doctor Evarts, have been due to the effect on the reticular system, which Doctor Himwich has so nicely demonstrated, and the difference be due to the fact that Doctor Pennes was using a Nembutal anesthesia?

2. Would that much Nembutal anesthesia be enough to prevent any effect on the reticular system by showing up as blocking the transmission of the potentials?

The reason behind these questions is my interest in the general notion of diminishing the amount of afferent information, if you want to put it that way, that an individual has to work on. The relationship between this and the more recent work in Montreal, for instance, on the production of psychoses by limiting afferent information in other fashions.

Doctor Cholden: Thank you, Doctor Calloway. I think I should like to ask for a number of questions, and then the panel shall answer en masse, rather than have each question answered separately. Doctor Geronomous of Cold Spring Hospital.

Doctor Geronomous: This is just a very simple and perhaps technical question of Doctor Boyd. I am associated with Doctor Abramson's project. Now, I would like to ask Doctor Boyd exactly where the LSD was labelled, and whether he has any idea what these two derivatives are.
Doctor Choden: Doctor Ian Stevenson of New Orleans.

Doctor Stevenson: I should like to make two comments and add to them, also, some questions.

The first has to do with Doctor Hoch's brief reference to sodium succinate, which I gather from his neglect of it this evening, and his published comments, he has not found an effective antidote. Our experience in New Orleans on the other hand has been that sodium succinate is of considerable value as an antidote, at least to the mescaline psychosis.

I suppose the reason for this might lie in several factors. We may be using larger doses than he did. In fact, we did find the effect quite variable. In some of our subjects it seemed to have almost no effect, while in others it had a very definite effect; so that they quite rapidly described almost a melting away of the visual imagery, starting first of all with a loss of the vivid colors to which Mr. Huxley referred. These colors lost their quality of intense saturation, becoming duller, then finally fading into browns and greys.

Another reason for the difference in these results may be the fact that the succinate seems to be oxidized more rapidly—or at any rate, destroyed more rapidly than the mescaline itself. So that after a brief remission the subject may then re-enter the psychosis and experience all his symptoms once again. In any case I should like to ask Doctor Hoch to elaborate, if he will, on his experience with the substance, which we have found quite effective.

Secondly, emboldened by Mr. Huxley's comments, I should like to confess that my experience with mescaline was an exceedingly pleasant one. I found myself in my enthusiasm using words like "mystical" and "ecstatic," until I found my colleagues raising their eyebrows at this, and looking at me askance; after which I simply described it as "very pleasant." I mention this tonight, not to testify to my normality, but to point out that we have really studied insufficiently, I think, the differences in the psychotic experiences, or the toxic experiences, of the different subjects. I think we need to find out more about the personal factors which influence the occurrence in one person of a really quite different experience from that which other people have.

Now, it may be that the difference lies in the actual content of the unconscious of these different people. But I think the answer may also lie elsewhere, namely, in the differences by which people digest their experiences; if it doesn't sound too clumsy, the differences in the way
they experience their experiences. Some people have an increased capacity apparently to deal with unusual perceptive experiences, and some simply have different ways of viewing the world. In any case, we have begun, in New Orleans, some tentative efforts to explore this, so far as I know, undeveloped field. We hope to find out something about the relationships between the previous personalities of the subjects and the experiences which they undergo under the influence of these drugs.

I should be very grateful if anyone here would share with me the experiences they may have already had in this area.

Doctor Cholden: Thank you, Doctor Stevenson. It is fortunate for Mr. Huxley that his colleagues don't raise their eyebrows when he uses the words “mystical” and “beautiful.”

Certainly there is some evidence—and I think of Doctor Stoll's work, and some of the Rorschach studies, that point up the fact that you can't make a silk purse, so to speak, out of a sow's ear. The material of the receiver, determines the material of the response. The person who can experience beauty and a different state of being without fear, will then be able to communicate to others his feelings. Perhaps these are the essential ingredients for the satisfying response we have heard about.

Now a question from Doctor Roland Fisher of Canada.

Doctor Fisher: Allow me to answer the previous question in a somewhat sophisticated way. Doctor Masserman, yesterday afternoon, pointed out that, in his experiments, the response depends much more upon the species of monkey used, than upon the drug used. Not everybody has the same personality structure, and some of us are visionaries and others are just dry scientists. I think that from Mr. Huxley's mescaline experience there is 99 per cent Aldous Huxley and only one half gram mescaline. This doesn't distract at all, but we, unfortunately, cannot afford to be Aldous Huxley.

As to the specificity and the nonspecificity of the action of blockers and antidotes to LSD, there is an interesting question here. As Mr. Huxley pointed out, he and some other talented visionaries are not interested in being blocked in their experience, and I wonder whether some schizophrenics—some very talented ones—need to be cured in the very same sense.

Our culture still may be in a stage in which the blood letting and
purging is done in a routine way. Possibly this gathering here is initiat
ing a new era of scientific approach to a problem in which we have a
basic lack of knowledge, puzzling us in such a way.

For instance, we found that the best blocker of LSD, is LSD served in
a higher dosage, and similar puzzling questions.

Doctor Cholden: Thank you, Doctor Fisher. Doctor Karl Menninger.

Doctor Menninger: Doctor Cholden and members of the panel, I
was hoping—and I still hope—that in the future discussion, something
more will be said about what might be called the constructive aspects
of this experience which is variously described as an intoxication, a
model psychosis, a delirium, and so on. Mr. Huxley, it seems to me,
approached this more nearly than did most of the others, but I am
sure that this is only because they haven’t gotten to it yet.

It seems to me most important to know what is the scientific analogue
of the experience described by the Navahoes and other Plains and
Southwest Indians. What are the renewing and reassuring aspects of
the nature of the experience which leads one of the colleague’s patients
to have 80 experiences of this kind with pleasure. What is the positive
side, and in what way—I don’t mean to get too practical about some
thing which I realize at the present time is only in the most experi-
mental stage—but what are the aspects of this which are capable of
being exploited further in a constructive way?

Several have said it is a beautiful experience, a mystical experience,
and as the Indians, I believe, felt, an experience of an almost divine
nature. Mr. Huxley pointed out that it had some parallels with phan-
tasies of paradise. It seems to me that this is something of utmost
importance ideologically, and I would like to hear more about it. I
am sure I will from later speakers.

I want to add one other thing. I remember very well earlier meetings
of the American Psychiatric Association, and the American Psycho
analytic Association, when we got the first reports of some of the
individuals who had had personal analysis. I can still remember one
of the first Americans who went over to see Professor Freud, and came
back and reported in some detail the various steps in the treatment. I
can remember the half a dozen or maybe a dozen of us who clustered
around and listened to these amazing experiences, little realizing that
25 or 30 or 35 years later they would seem so unnecessary to talk about
in a public meeting.
Perhaps some of you will remember this meeting in a similar way 30 years from tonight.

**Doctor Cholden:** Thank you, Doctor Menninger. One can always—I can remember from my earliest training days—know that Doctor Menninger will bring out the philosophical and constructive things that we might otherwise have missed.

I think we ought to add a few more questions. Doctor Denber of New York.

**Doctor Denber:** Doctor Stevenson's remarks prompted me to get up and share a mescaline experience which was stimulated by our distinguished speaker's book. I swallowed the mescaline, as Aldous Huxley did, and through it learned the answers to some of the rather amazing things we had found at our hospital. Last July when we started studying extensively the blocking action of chlorpromazine on mescaline, and after the second test case that was run where chlorpromazine was administered, about an hour after the mescaline, to a patient who had a long history of the phobic feelings, intense anxieties and intense fears; the ward nurse came down and said, "You know, Doctor, your patient is cured. You can send him home now, because he isn't afraid any more, he walks around and doesn't hang onto the wall, and goes downstairs to eat."

But, unfortunately, 48 hours later he relapsed, so we gave him some more mescaline and some more chlorpromazine; and he was all right for about a month. Then we began to follow this thing sequentially, no longer looking at the blocking action but at the therapeutic action, the constructive action, as Doctor Menninger suggested. And more patients began to show complete remissions of their psychotic symptoms. A whole concept was constructed, and it looked pretty new. Then I came across Doctor Sandison's article, and apparently our unconscious had been in communication across the ocean because we had the same ideas.

So to test this further I took some of the stuff. I feel that there is no question that the basic result is a function of one's antecedents, perhaps the way Jung has described it, one's past experiences, one's present state and one's future aspirations. I found myself floating around in the uterus, afterwards recalling toilet training experiences; and so on down the line. It had one very beneficial effect upon me. Those of you who live in New York know that the speed limit on the Pequannock Parkway is 45 miles an hour. I live about 40 miles out of the city and
usually go about 55 miles an hour. After the mescaline experience I started going 45 miles an hour. So that it did have some therapeutic action, at least, it saved me a lot of money.

In this series of patients, there were 40 who were acutely ill, with a short duration of illness. There were 17 who were chronically ill for 2—25 years. We got, in the acute group, 18 complete remissions of symptoms out of some 40. The frame of reference we used was that the mescaline experience is neither an intoxication—and the rebel in me rebels absolutely against the use of the word “intoxication”—or a neurosis or a psychosis. These two words give it a purely descriptive sense, and psychiatry has been stuck long enough in this descriptive phase.

It is simply a state of being, as Mr. Huxley has so brilliantly described. In that sense, the state of being taken in its dynamic implication with the free associations become constructive and meaningful, and the patients who, in the past, have been simply saying, “I see red,” and “I see blue, and like the flowers that I saw that were so beautiful, which actually I knew were three or four days old, but—and color-blind as I am—knew that they weren’t the colors I saw. But the colors were brilliant.” It was the free association to these things that became therapeutically meaningful. In this sense then the patient who sees red and asked, “What does it mean to you,” will say, as one patient said, “This red reminds me of my first menstrual period. That reminds me I never wanted to be a girl, I always wanted to be a boy.” That led into the homosexual conflict, and this was worked through. At the end the patient said, “I never felt like this before.”

We have not been able to corroborate Doctor Hoch’s findings in terms of the effect of chlorpromazine in blocking at the acute states. This may be due, I suppose, to a rather inferior action in the chronic states. One patient who had tremendous response with an extraordinary emotional discharge to mescaline required first 50 mg. of chlorpromazine; and again, another 50 mg. of chlorpromazine, before the whole thing was blocked.

In essence, I think that tonight’s meeting indicates a new line of approach, the constructive angle, as Doctor Menninger has pointed out. The dynamic implications, as Doctor Sandison and Doctor Savage have pointed out, are really the angles for the clinicians to work through.

It is extraordinary what one can find if one looks for it. And if one looks for it, one finds it.
**Doctor Cholden**: Thank you, Doctor Denber. I have been to very few of these meetings that have evidenced the amount of interest and patience on the part of the audience at this late hour.

I see two more questions.

**Doctor Brenninger**: I would like to ask the members of the panel, or anyone, if they know of one of these drugs being given to a patient who had always been blind; and if so, what they saw, if anything.

**Doctor Cholden**: There is one more. After this question our panel will answer.

**Doctor Monroe**: Two questions were raised which we had some experience with, and I thought I just might mention it.

One is that Doctor Rinkel might be interested to know that in a few patients—very few, so far—we have found adrenalin oxidation impaired after the LSD.

The second thing is that in human beings, subcortical recordings in the hippocampus can set up, not invariably, but oftentimes, if the patient gets a good clinical effect, very high amplitude delta activity.

We still don't know what this means, but Doctor Pennes brought up the question of what happens to the EEG's in human beings.

**Doctor Cholden**: Now, I would like to call on the panel, in the order of the first presentation, to answer the questions that strike them as most urgent.
Doctor Hoch: Because I am in daily communication with Doctor Pennes, I will not answer his questions so that I will be able to save some time.

I would like to comment on several questions by other speakers, first, concerning the discrepancies which were mentioned in connection with sodium succinate. The action of sodium succinate, chlorpromazine and other blocking agents does not depend on the compound alone, but also on its dosage. In the beginning, experiments usually do not cover all the dosage ranges. If all the dosage ranges were studied, it would be found that some compounds will not block in some doses, whereas in other dosage ranges, they will. In my opinion this explains quite a number of the discrepancies reported. Furthermore, in all these experiments, usually the general observations made on the majority of patients is stressed, but there are exceptions to be found, in all of these drug actions. Of course, the exceptions will have to be studied experimentally because they will enlighten us on many points we do not know.

I believe it has to be stressed again, that the psychosis producing agents and the blocking agents, as far as we know, are non-specific; and any tendency to make them specific simply does not jell with the facts as we know them today.

There was some discussion about where these drugs act. I think that we are not fully prepared to say at present if the action of these drugs is cortical, subcortical, or even ganglioplegic. The site of the action is not fully investigated, and I think many more observations will be necessary at the different action levels, before we will be able to localize the actions of these compounds securely. For instance, the claim that the psychosis producing drugs and the counteracting drugs essentially act on the subcortical region of the brain is not conclusively demonstrated, even though there is enough evidence to assume that they have a certain predilection for this region. We do not know if the action of these compounds is a diffuse one all over the nervous system or only a local one. We feel that the research investigations in the future will have to concentrate on clarifying this point.
Questions were raised concerning whether the abnormal mental states produced by the drugs are states of psychosis or not. This depends entirely upon one's understanding of what a psychosis is. There are those who call them psychomimetic reactions. In other words, states which indicate a psychosis. I do not believe that this is a very happy designation, because I do not know how a psychosis can be imitated on an organic level. If somebody calls them schizophrenic-like psychoses, this would be acceptable for some of these drugs, but not for all of them. I believe, for clarity's sake, that if a person develops a certain group of symptoms which we observe and describe by present rules of psychiatry as a psychosis, and then observe a similar phenomenon caused experimentally, we have to call it by the same name. We cannot introduce two or three different systems to describe the same clinical manifestations. The d-LSD-25 and mescal produced mental states have a symptomatology identical to that of an acute organic mental state which resembles schizophrenia. Even if they did not resemble anything, they would be psychotic states because of the symptoms they produce, such as hallucinations, delusions, distortions of reality, and marked impairment of ego functioning.

It is also important to discuss the different reactions of different individuals under the influence of these drugs. The New Orleans group is doing some interesting work along these lines. They will run, however, into the difficulty, quite often, that even the same individual, at different times, shows a different reaction to the drug. This is a very interesting phenomenon, for, in some patients, the basic reaction to the drug remains the same, but the content of the patient's productions may change. However, a considerable number of patients show a change in reaction. For instance, they can display a depressive reaction under the drug at one time, and a paranoid reaction another time. The personality structure of the patient surely plays a role, but not alone the personality structure as we understand it today. I would like to call your attention to the thought that, in addition to the differences in the psychic personality structure, we also must have differences in the somatic personality structure. There are many hints which would indicate that the metabolic organization of persons are not identical. How this is then linked with specific personality structures on the psychic level is unclear, further investigations will have to be made.

Differences in observation are also due to the fact that the ability to verbalize experiences in the drug induced psychotic states is different persons. Our communication with the person during such
a drug produced state is not fully worked out. Some patients are not able to report experiences, while others may have them, but cannot report them. Discrepancies in clinical observations are sometimes due to incomplete communication.

Finally, a word as to the therapeutic use of d-LSD-25 and mescal. I would like to ask those who are stressing the therapeutic achievement with these compounds, how far they have made comparative studies with other drugs, for instance sodium amytal, desoxyn, CO₂, etc. As far as I am concerned, I do not see any specific value in the therapeutic application of mescal or d-LSD-25 at present. We were able to produce similar results with other procedures in patients who also received psychotherapy. We feel that mescal or other compounds can be used as adjuncts to psychotherapy, and that it will depend on the therapist and the patient which procedure is to be preferred. Here, I am only arguing the point that a great deal more evidence will have to be presented that d-LSD-25 and mescal have specific value in connection with or within a psychotherapeutic procedure, which other compounds do not have.

**Doctor Rinkel:** There are two questions I believe I can answer. The first question was with regard to adrenalin and its antagonism to LSD. Such an antagonism seems to exist. We have found it in our pharmacodynamic studies in human subjects, and it has also been reported from the Department of Pharmacology of the Royal Faculty of Medicine, in Baghdad, Iraq.

The second question refers to the effect of LSD in blind people. We gave LSD to a scientist in nuclear physics, who went blind as a child—I think about three months after birth. He received 1 /Kg. body weight, and on another occasion 2 /Kg. body weight. In both instances, the results were negative; the subject had no visual experiences.

**Doctor Himwich:** Doctor Pennes asked two questions: What is the effect of LSD on the EEG of human subjects and whether we see similar EEG records in unmedicated patients with schizophrenia? Fortunately, the literature contains data in regard to these questions. Rinkel and co-workers reported diminished responsiveness to hyperpnea and interference with the production of slow high voltage waves characteristic of overbreathing. Gastaut and associates observed low voltage and fast rhythms while Bradley et al. found that human subjects with poor re
response to eye opening and to attention presented a better desynchroni-
zation after LSD. Thus, in general, it may be said that the effects of
LSD on human beings, though obtained with lower dosage than used
for the animal experiments, nevertheless revealed the same kinds of
changes: a flattening of the record due to diminution of voltage with
faster frequencies and the disappearance of the slower waves. Pauline
Davis had reported earlier the development of flat records after the
administration of mescaline to human subjects. She applied the term
“choppy” to the low voltage fast activity. This “choppy” activity ob-
literated the premedication EEG and was present during the time
the subject exhibited behavioral changes resembling those of schizo-
phrenia. Both the behavioral and EEG alterations faded away together
as the mescaline wore off.

In answering Doctor Pennes’ second question, in regard to the EEG
of psychotic patients, I might say that Pauline Davis pointed out that
in many psychotic patients the alpha activity, is poorly organized and
is replaced by a “choppy” activity. Instead of the usual alpha waves
she found faster and smaller undulations. Though they occur in but
a small percentage of normal individuals they are observed in about
one-third of patients with schizophrenia, manic-depressive psychosis and
more than half the patients with involutional psychosis. It would seem
of interest to determine whether these “choppy” EEG recordings could
be normalized by Frenqnel. I should like to conclude my discussion by
quoting Pauline Davis in regard to the choppy rhythm she observed
in her psychotic patients. “The choppy activity is regarded as indi-
cating primarily overstimulation or irritation of the cortex which is
due to unsynchronized activity within the central nervous system.”
Our results suggest that a site of the “unsynchronized activity within
the central nervous system” is an overactive activating system.

Doctor Sandison: I think Doctor Hoch and Doctor Pennes asked
very much the same question, that is, whether we would achieve the
same results by just having the patient in the therapeutic situation—
which we so often have in the hospital and the clinic. I think the
answer to that must be that a number of these patients have been treated
very energetically in the same surroundings and with other forms of
psychiatric treatments, group therapy, drug abstractive techniques,
and so on, previously, under very much the same conditions, without
the LSD. The only significant alteration was the introduction of LSD,
and it seems to me that we have got here, too, a means of producing material from the unconscious which does so more efficiently and more quickly, in a way both we and the patient understand more clearly.

Just cogitating on what had been said this evening, I am reminded of this book, *Many Dimensions*, which was written by Charles Williams, in which he refers to a magical stone which was brought from the East, and which had been lost for many centuries. Then it came to England, and he describes the effect of the stone on various people. Although some people used this magical stone as a means of transport, some used it as a means of healing, some used it as a means of gaining philosophical insight into the world’s problems, and some used it as a means of gaining political power.

I think the eventual approach to LSD is something of this order, the way in which we get a hold on it must depend on our personality. Those of us who are primarily faced by the immense burden of treating the neurosis we have in the community—and feel that something has to be done about it, are trying to use LSD as a weapon in means of treatment. Others may feel a greater need for theoretical knowledge before we commit ourselves to treatment, and are more interested, maybe, in these theoretical approaches to the subject.

**Doctor Savage** About the effect of these substances on the blind, as I recall, Zador in 1930, gave mescaline to blind persons. The congenitally blind developed somatic hallucinations, but no visual or auditory phenomena. Those with acquired blindness had visual hallucinations.

Now, as to the question: Do hallucinations originate at the psychological level? I will answer that “yes and no.” Initially you get phenomena, such as flashing lights, that are similar to what one might expect from stimulation of some part of the visual system. Then, for example, you get rather formalized hallucinations, such as hexagons, as are illustrated in Stoll’s original article. Then, sometimes, one sees microptic hallucinations or caricature-like structures of a rapidly changing character.

Many of these experiences seem to be quite foreign to the individual. Later on, the hallucinations slow down and become realistic. For example, one individual reported that as he was looking at a woman he saw her change into a corpse; he saw her at a later time and observed that all her clothes came off. She then seemed to be having intercourse with an isolated penis; and then before his eyes she delivered a child.
This illustrates the considerable unconscious conflict which he had about this woman.

Even where hallucinations seem to be quite foreign, we can sometimes find residues in the person’s previous experience.

For example, let us refer to the illustration on page 37. Notice the lances here. The subject reports the three crossed lances have turned up frequently in her doodlings. So this hallucination was a repetitive pattern with her.

In the same way that mask, that mocking face up on the right there, is also to be seen in some of her previous scribblings. During the LSD intoxication she had an hallucination of that same face, which she later recognized as being something she had experienced before.

So, I would say that while initially hallucinations seem to be almost beyond the psychologic level, in other instances they can be clearly correlated with psychologic material.

Doctor Hoffer: In connection with the question of the blind, we have given it to three subjects. One subject was a young man who received 200, and was blindfolded, from the time of administration, for two hours. As far as we could make out there was absolutely no reaction, but when we took the blindfold off he became violently seasick; this, he explained later, was due to the violent movement that he saw about him.

We thought we had something, so we tried it on another subject with 100y, who was blindfolded throughout the whole experience. But we found with him that there was an experience, although slightly different, and it lasted throughout the entire session.

We have done another subject blindfolded, and again we have found more subtle but very definite changes persisting throughout the experience.

Mr. Huxley: I am very glad that Doctor Menninger should have raised this point of a constructive use of the so-called hallucinogens. In this context, it is important to examine the words we currently use. Take the word “hallucination,” for example. The word carries with it a certain pejorative overtone. To call an experience a hallucination is, implicitly, to condemn it as unreal and in some way discreditable. But now let us consider what happens when we take mescaline. Looking out at the eternal world, we perceive it as being quantitatively very
much as it was before, but qualitatively quite different, for everything has become inconceivably beautiful and significant. What reason have we for thinking that beauty and significance are less real than ugliness and dullness? A person who has taken mescaline sees the world as Wordsworth describes it in his great *Ode on the Intimations of Immortality in Childhood*. Was Wordsworth the victim of a hallucination because, as a child and youth, he saw all things glorified, transfigured, clothed in celestial light? Or is it we who are living in hallucinatory illusion, because we fail to see anything in the world around us that is not drab, commonplace, lifeless and without significance?

If Wordsworth and the other seers of spontaneous and induced visions are the victims of hallucinations, they are so only in a statistical sense. The majority of men and women perceive the world as a collection of all too familiar and extremely boring objects. That is why they have to spend so much time looking at television.

But statistical normality is not the only kind of normality. There is also something that may be called absolute normality. An absolutely normal human being may be defined as one whose psycho-physical organism is functioning at its highest potential, to the limit of its native capacities. The statistically normal, but absolutely abnormal majority of human beings perceive the world as stale, boring and meaningless. The absolutely normal, but statistically abnormal minority suffer from what the majority call a hallucination, and perceive it as fresh, living, blazing with light and color and charged with infinite significance.

**Doctor Abramson:** Doctor Hoch brought up some points which I should like to discuss further. I feel the LSD-25 reaction, when given in low dosage, has certain elements, from a psychotherapeutic point of view, which are not easy to achieve with other methods.

1) The patient is fully conscious.
2) The toxicity of the material is negligible between 20 and 40.
3) The patient, in my limited experience, shows two phenomena simultaneously which are ideal for psychotherapy; at least, when I am the therapist: ego-enhancement and ego-depression occur simultaneously, which enables a better synthesis to occur. Not a *narcosynthesis* but an elated type of synthesis that I have termed *hebesynthesis* occurs.
4) Finally, the patient remains this way for a period of three to four hours.
I would like to discuss one other point that Doctor Hoch brought up. Doctor Hoch said that possibly some of the discrepancies might be due to the fact that we cannot communicate with the patient, or the patient cannot communicate with us. I agree with that, but also, I wonder if we do not need more statistical material to validate our present views.

Doctor Evarts: In answer to Doctor Callaway's question, the effects which I have described occurred in animals that received sodium pentobarbital or, similarly, in animals that had been decerebrated by midcollicular section; the dosage of LSD required to produce a given reduction in post-synaptic spike amplitude was two to three times greater in the decerebrated then in the nembutalized preparation.

I might add that the work which Doctor King has done in Doctor Magoun's laboratory, to which Doctor Callaway referred, was done on the somesthetic system. At the present time we do not have data on the effects of alteration in reticular activity upon the excitability cycle of the lateral geniculate.

Doctor Boyd: The first question, I believe, was as to where the LSD used was labeled. The labels are the two carbon atoms in the diethyl side chain.

In regard to the second question, we do not know what the two metabolites are, except that they are, I will say that most of the LSD molecule is still present in them. We naturally are very interested in finding out what they are and what kind of pharmacological or psychologic activity they have, if they have any.

Doctor Pennes: With regard to Doctor Callaway's questions on the effects of mescaline on evoked optic responses. These experiments were done in cats anesthetized with Nembutal, chloralosane or chloralosane-urethane. The observed effect was depression of the primary evoked optic response, recorded with a surface cortical electrode, and the main locus of action was cortical. This inhibition could be the result of a direct depression of cortical excitability by a local action of mescaline; or else cortical excitability may have been depressed by an action of mescaline elsewhere in the brain, producing a variation in the tonic afferent inflow to optic cortex.

As Doctor Callaway mentioned, the brain stem reticular activating system might be one of the sources of such a tonic afferent inflow.
Since Doctor Himwich has found an effect of mescaline on this system, conceivably this effect might be tied in with the observed inhibition. The necessary correlating link would be that primary evoked cortical responses are inhibited during the elicitation of the electrocortical arousal response produced by stimulation of the reticular activating system. However, my experiments were done with moderately deep anesthesia to ensure reasonable uniformity of amplitude of successive evoked responses in the control period. The spontaneous EEG, as evaluated by comparison of successive CRO sweeps was probably quite low. These conditions are not favorable to securing stimulation of the brain stem reticular activating system, at least in response to noxious sensory stimulation. Accordingly, I think it would be accurate to state that stimulation of this system was probably not occurring in these preparations in response to the drug.

Now, going a step further, some speculation is due on the possible psychophysiologic implications in man of this finding with mescaline in the cat. First of all, it may be a species action or an artifact related to the Nembutal anesthesia. Doctor Hoch told us that amytal, another barbiturate, tends to block mescaline actions in man. Since most of the cats were under Nembutal and if Nembutal likewise blocks mescaline actions, one must wonder whether the observed inhibition represents the true activity of mescaline in the unanesthetized state. However, inhibition also occurred under other anesthetics.

Going a bit further out on a limb and accepting the inhibition as representative of the action of the drug on unanesthetized man, one is tempted to speculate further and correlate this with various clinical observations. These observations may be interpreted to the effect that decreased input to the visual system appears to facilitate the occurrence of visual hallucinatory activity. I refer to the fact that after a cataract operation, elderly patients with a bandage over the eyes for several days, not uncommonly have visual hallucinations. Psychotic patients at night, particularly those with acute toxic psychoses, are reported to have more hallucinations than during the day. Doctor Callaway, in his question, referred to the recent Montreal experiments with restriction of variation of the sensory environment: a normal subject, isolated in a cubicle, and further restricted sensory-wise often reports visual hallucinations after a lapse of several days.

The depression of transmission produced in the primary optic system by mescaline might thus be comparable to reduction in visual in
put—in both cases, the common result would be decreased activity in the primary visual system at a cortical level. Furthermore, with mescaline and LSD both, the visual hallucinations are often reported to be more vivid, more intense with the eyes closed than with the eyes open. With n-allyl normorphine, subjects report hallucinations only with the eyes closed, the images disappear immediately when the eyes are open.
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