PSYCHOTOMIMETIC DRUGS

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PART I: BACKGROUND

FOREWORD

MODERN interest in the psychotomimetic drugs goes back more than a hundred years[79] and active experimentation more than 75 years.[64,101] In this time a vast literature has accumulated. It is not the intention of the reviewer to attempt to describe all of this. It is important, then, that present purposes be explicitly stated: (a) to cover originally observed facts and statements of concepts; (b) to present current views concerning the effects, the uses, the difficulties, and the possibilities inherent in the psychotomimetic drugs, especially as they have been studied in man; (c) in all of this, to emphasize the well-designed study when encountered—and what seem to be the requirements for such study—and to give suitable emphasis to *quantitative* data wherever it can be found. The reviewer holds with Lord Kelvin that ". . . when you can measure what you are speaking about, and express it in numbers, you know something about it . . . when you cannot express it in numbers, your knowledge is of a meager and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of *Science* . . . ." A final purpose is to arrive at some general conclusions concerning work in this field.

THE AGENTS

Moreau in his monograph *Du hachisch et de l'aliénation mentale* wrote in 1845: "By its mode of action on the mental faculties, hashish gives to him who submits himself to its strange influence the power of studying, on himself, the moral disorders which characterize mental illness, or at least the principal intellectual modifications which are the points of origin of all kinds of mental disturbances." Perhaps he was influenced by Davy[22] and by De Quincey,[25] and Moreau may have stimulated Benjamin Paul Blood's interest in the "Anaesthetic Revelation."[13] This latter work excited William James's interest[57] in the field. These matters have been discussed by Beecher.[7]

For some years there has been widespread interest in the possibility that schizophrenia might be explained on a chemical basis. The beginnings of this modern interest go back to specific experimental work begun 75 years ago. Kraepelin[64] worked on the psychic effects of drugs and this was followed by Schmiedeberg's production[101] of cataleptic phenomena in rabbits and pigeons (but not dogs) with ethyl-urethane. Heffter observed the peculiar effects of mescaline on dogs. A great impetus has been given to work in this direction by studies of mescaline effects over the past 20 years.[42,111] And more recently, study of lysergic acid derivatives has received a great deal of attention (Stoll and Hofmann,[112-114] Stoll,[115-117] Hoch,[52] Hoch, Pennes, and Cattell,[53] Mayer-Gross,[76] Rinkel, DeShon, Hyde, and Solomon,[90] Elkes, Elkes, and Bradley,[28] von Felsinger, Lasagna, and Beecher,[121] Purpura,[86,87] Evarts,[30] Hoagland,[48] Osmond,[81] Osmond and Smythies,[82] Rothlin[95]). In general terms the recent interest in correlating biochemical changes and schizophrenia arises in part, for example, from the demonstration of a relationship between phenylketonuria and mental aberration, in such similarities as exist between mental disease and drug-induced psychoses and, not least, the modern possibilities for measuring minute quantities not only of drugs but also of naturally occurring substances in the body.

While the amount of quantitative data on the effects of drugs in this area is at present meager, it will doubtless increase rapidly in volume and in importance. For these reasons, a fairly extensive background is presented for such quantitative data as are available. This background is described in some detail because it is evident that many effects of the psychotomimetic drugs will lend themselves to quantitative study. Such quantitative values, when established, may mark differences, not now apparent, among the many agents. Such material may also afford insight and avenues of approach not only into differences among the drugs but also, when the drug effects are compared with the signs and symptoms of mental disease, into certain aspects of the nature of such disease. The importance of this area and the possibilities in it, rather than the amount of useful quantitative data now available are reasons enough for discussion.

This new class of agents has received many labels, called variously phrenotropic, psychotogenic, schizophrenogenic, psychehormic, psycherhexic, psychezymic, psychelytic, or psychedelic agents, hallucinogens, schizogens, psychotogens, psychotica, phantastica, or elixirs. A partial list of drugs said to produce psychotic reactions is as follows (Hoch, Pennes, and Cattell)[53]: acetanilid, acetylsalicylic acid, adrenochrome, adrenolutin, alcohol, amphetamine, arsenic, Atabrine, atropine, barbiturates, bromides, bufotenin, caffeine, chloral hydrate, cocaine, diisopropyl fluoro-phosphate (DFP), ergot alkaloids, hormones (various), lead, lysergic acid (both di- and mono-ethyl amides), mercury, mescaline, N-allyl-normorphine, quinine, scopolamine, tetraethylpyrophosphate (TEPP), water (toxic amounts). This is, to say the least, a heterogeneous group of compounds. Here, as always, the difficult problem arises of eliciting a relationship between chemical constitution and pharmacologic effect.[76] This is baffling to the point of impossibility at present. A very wide variety of chemical compounds seems to produce the same or very similar effect. The stakes are high and the challenge great to uncover relationships between structure and psychic effect.

It is believed that these agents on being administered to normal individuals can mimic certain forms of mental disease. Certainly they can produce great subjective change. As Hoagland[48] puts it, "Psychotomimetic drugs are tools capable of producing brief and controllable experimental psychoses in normal persons, and they thus open new channels for the investigator." Just how precise the mimicry of psychotic states is is not yet clear. This capacity may not even be their most important action.[81] Osmond[81] has sought a definition of such agents which leaves out those acting in large part on the body (as well as on the mind). In his definition he wishes to exclude anesthetics, analgesics, hypnotics, alcohol and the derivatives of atropine and cocaine. He suggests, "Psychotomimetic agents are substances that produce changes in thought, perception, mood and sometimes posture, occurring alone or in concert, without causing either major disturbances of the autonomic nervous system or addictive craving, and although, with overdosage, disorientation, memory disturbance, stupor and even narcosis may occur, these reactions are not characteristic." Evarts[30] requires that the psychotomimetic substances produce a psychosis in a high proportion of the subjects who receive them.

It must be emphasized that although our interest in these agents is a limited one, the psychotomimetic agents produce profound subjective change and insofar as this has been dealt with in a quantitative way it is pertinent to the theme of this review. While the quantitative work done to the present time is, as mentioned, meager, unquestionably it will grow rapidly. It will likely arise from the following background.

BRIEF HISTORICAL NOTE

There is nothing new in man's attempt to alter the workings of his own mind. This is as ancient as the history of the human race and doubtless antedates history. Osmond*[81] takes a very long look into the past. He starts with:

> ". . . the still-unidentified soma imported from central Asia into India several thousand years ago and ending with 3,4,5,trimethoxyphenyl-β-aminopropane (TMA), bufotenin, adrenochrome, and adrenolutin whose qualifications for inclusion in this classification are still being examined. As I list these treasures of 5000 years of perilous and sometimes fatal searching, think upon those nameless discoverers and rediscoverers, Aztec and Assassin, Carib and Beserker, Siberian and Red Indian, Brahmin and African, and many others of whose endeavors even scholars do not know. We inherit their secrets and profit by their curiosity, their courage, and even from their errors and excesses. Let us honor them. They do not appear in any list of references.
>
> "There are such substances as soma, hashish, cohoba, ololiuqui, peyote, the Syrian rue, the caapi vine, the fungus teonanacatl, the two Amanitas, pantherina and muscaria, the iboga bean, and the fierce virola snuff obtained from a nutmeglike tree in Amazonia. Who knows what other compounds await the keen inquiries of ethnobotanists such as R. E. Schultes or mycologists such as Gordon Wasson?

*I should like to acknowledge my indebtedness to the interesting review of Osmond for guidance in historical matters.

> "With our modern synthetics we are a little safer, though the ground quakes beneath us. These synthetics include mescaline, introduced by Heffter in 1896, the first, I believe, of these agents to be synthesized; harmine or telepathine, an alluring name whose significance I have never understood; Hofmann's astonishing lysergic acid diethylamide (LSD), whose great activity has made homeopathy seem less improbable; hashish, whose still-uncertain active principles should surely be ascertained; TMA, synthesized by Scott and his co-workers of Imperial Chemicals Ltd., Manchester, England, a synthetic that lies in an area intermediate between mescaline and amphetamine and has recently been the subject of a report by J. R. Smythies; bufotenin, isolated from cohoba, a West Indian snuff; unstable adrenochrome; and the subtle adrenolutin. What an array of substances for daring inquiry! What work for generations to come!"

Recent interest in this field has become very great and many facets of this problem are being attacked in a fairly orderly and sometimes scientific way.

AREAS WHERE PSYCHOTOMIMETIC AGENTS ARE OF INTEREST

The "Model Psychoses."—More than a hundred years ago[79,81] hashish was used to give students of mental disease insight, it was hoped, into what the mentally ill endured. Work in this area has been stimulated in recent years by studies of the effects of mescaline. Osmond[81] credits Schueler[102] with being the "founder of model therapies" in 1934. See the fairly recent work of Stockings,[111] Mayer-Gross,[76] and Hoch.[52] But above all the extraordinary effects of the diethylamide of lysergic acid, the so-called LSD, has aroused interest here, following its introduction by A. Stoll and Hofmann[113] and study by Stoll.[115,117] The papers of Osmond and Smythies,[82] Rinkel, Hyde, and Solomon,[91] and Anderson and Rawnsley[3] should be consulted.

Osmond[81] speaks regretfully of his uncertainty as to whether the psychotomimetic agents mentioned above differ quantitatively or qualitatively, since no studies have "taken into account obvious variables such as body type, height and weight, or skin and eye color, let alone subtle personality or cultural, social, and biochemical factors that may be very important." Important as most of these factors doubtless will be shown to be in the future in determining the effects of drugs that alter subjective responses, the writer knows of no single drug, old or new, which can be said to have been adequately studied from all these points of view. A long-standing interest of Beecher's laboratory has been to devise techniques for correlating, if possible, personality type, for example, with drug action. In some years of work an encouraging mass of data has been accumulated, but only a tentative beginning has been published.[8,9,41,68,108,120] It is true that most of these variables must be taken into account if drugs that alter subjective responses are to be evaluated soundly and understood.

Discussion of the relationship of model psychoses to schizophrenia is at least 50 years old.[81] The work of Osmond and Smythies[82] aided greatly in clarifying the difference between the two. Osmond[81] refers to his work with his associates on ololiuqui, adrenochrome, and adrenolution.

Eventually, model psychoses induced with drugs[81] must be related to those produced by other means such as the specialized "isolated" environments of Heron, Bexton, and Hebb[45] and Lilly.[69]

Psychotherapy With the Psychotomimetic Drugs.—In considering pharmacotherapy in psychiatry Margolis[72] says: "Although chlorpromazine and reserpine have been depicted as highly effective therapeutic agents by a legion of investigators, considerable disagreement still exists as to the actual value of these drugs. They have been considered by some as worthless, or as having only a sedative action, and as having no effect beyond the period of administration. In other quarters they have been regarded as superior to electroconvulsive and insulin-coma therapy and even as 'curative' in nature. They have been described as both a valuable adjunct and as a hindrance to psychotherapy."

Margolis's review provides an abundance of evidence of the confused situation just described: Too many have approached the most complex field of therapy with very nearly complete disregard for the controls that are essential to sound conclusion.

Among the many claims and counterclaims regarding the psychotomimetic agents, it seems to be widely agreed that both physical and psychologic effects of lysergic acid diethylamide are less in schizophrenics than they are in normal individuals. Schizophrenic patients are quite resistant to effects from ordinary doses of lysergic acid diethylamide.[11,21,39,48,100,105]

Osmond[81] and others (following Moreau[79]) maintain that self-administration of these agents is "the essential precondition for such work," that only in this way can an adequate understanding of what these agents are capable of be attained. Several recent studies report the use of these agents in therapy (Sandison,[99] Abramson,[1] Frederking,[33] Busch and Johnson,[17] Anderson and Rawnsley,[3] Osmond[81]).

Part II: Effects

Biochemical Studies

While very little data are at present available on the distribution of the psychotomimetic substances in the body, an excellent start in quantitative terms has been made. Such quantitative work is essential if work on the model psychosis is to be placed on a dependable basis. See, for example, the studies by Axelrod, Brady, Witkop, and Evarts.[5] This work in monkeys indicates that while the lysergic acid diethylamide leaves the plasma rather rapidly following intravenous injection, about half being gone in 100 minutes, this disappearance is presumably due largely to a shift of the drug from the plasma to the tissues. The drug is found (by chemical means) in decreasing order of concentration in bile, plasma, lung, liver, kidney, brain, intestines, spleen, cerebrospinal fluid, muscle, and fat. Lysergic acid diethylamide, according to these investigators, is almost completely metabolized in the body (in monkeys, cats, mice) with only negligible amounts excreted in the urine and stools. The in vitro metabolism of lysergic

acid diethylamide is "markedly" inhibited by chlorpromazine and "moderately" by serotonin.

Hoagland[46] on studying C^{14}-labeled lysergic acid diethylamide in rats found 30 minutes after injection the following percentages of theoretically equal distribution of counts: liver 135, cortex 31, thalamus 28, cerebellum 26, brainstem 17, hypothalamus 16. Further distribution data from other investigators are reported by Hoagland.[48]

There is a growing belief, in some quarters at least, that schizophrenia is to be explained on "chemical" basis. The spur given to study of drug-induced psychoses by the discovery of lysergic acid's effects has led to an increased interest in the biochemical derangements produced by the psychotomimetic drugs and to a comparison of these observations with those found in schizophrenia. These matters have recently been reviewed by Hoagland[48] and cannot be considered in detail here. He and his associates have observed similarity between schizophrenic patients and normal subjects treated with lysergic acid, in adrenocortical function and excretion of phosphate. This group has considered the possibility that this supports the hypothesis of a biochemical factor in the cause of schizophrenia (Hoagland, Feldstein, and Dibner,[50] Hoagland,[46] Bergen and Beisaw,[12] Hoagland, Rinkel, and Hyde,[51] Hoagland and Bergen,[49] Slocombe, Hoagland, and Tozian,[107] and Slocombe.[106]). It is important that techniques for appraising the relative merits of these agents be developed and applied.

The careful review of Koelle on the pharmacology of mescaline and d-lysergic acid diethylamide may be consulted for material relevant to this section but which for reasons of space cannot be included here. His review of laboratory studies is especially useful in augmenting and supplementing the present account.

NEUROPHYSIOLOGIC EFFECTS

Effects of Psychotomimetic Substances on Synaptic Transmission.—(Evarts[30])

Lysergic acid diethylamide: Little work in this area has been done in man, for obvious reasons, and animal work must be consulted. Marrazzi and Hart[74,75] have studied in anesthetized cats the cortical response to stimulation of the contralateral cerebral hemisphere. Lysergic acid diethylamide reduced the amplitude of the postsynaptic component of the transcallosal response. Purpura,[85-87] with unanesthetized cats, found that lysergic acid diethylamide caused facilitation of the primary cortical responses to a click as well as to light stimulation. In his study the cats were immobilized with succinylcholine. Lysergic acid diethylamide also produced changes in the recovery cycles in these two systems. Rovetta[96] with a very large dose of lysergic acid diethylamide (40 mcg./kg.) failed to find in anesthetized cats any clear effect on the cortical responses to photic stimulation. In cats anesthetized with pentobarbital sodium, Evarts, Landau, Freygang, and Marshall[31] in studying the effect of lysergic acid diethylamide on synaptic transmission in the visual system of the cat found an average decrease of 80 per cent in the amplitude of the postsynaptic geniculate response to a single shock to the optic nerve. "Whereas geniculate transmission was blocked by LSD, transmission within the retina and between geniculate radiation fibers and cortical

cells was extremely resistant to inhibition by LSD." There are great differences in the effects of lysergic acid diethylamide on various synapses.[30] Evarts found that pentobarbital sodium sensitized (in comparison with curarized animals) his preparations to the action of lysergic acid diethylamide. This may explain the difference between his work and that of his associates referred to above, and that of Killam and Killam.[59] The latter group used curarized but not anesthetized cats and found that even large doses of lysergic acid diethylamide (up to 100 mcg./kg.) did not alter the thalamic recovery cycle following peripheral stimulation of mixed nerves, nor was the amplitude of the recorded electrical activity changed. The difference might also be due to the fact that the two groups studied different sensory pathways.

Lysergic acid diethylamide blocks the effects of serotonin on the flexion reflex of the cat.[104] The vascular effects of serotonin might possibly have played a role in this result. These must be ruled out.[30]

Mescaline: This agent inhibits the postsynaptic component of the transcallosal response, and this effect of mescaline is blocked by chlorpromazine.[43,44,73] Rovetta[96] has reported that topical application of mescaline chloride to the cortex of anesthetized cats failed to produce any clear effect on the amplitude of the cortical response. Pennes (to be published, referred to by Evarts[30]) has also studied the effect of topical application of mescaline to the optic cortex on cortical potentials evoked by light and by electrical stimulation of the optic nerve.

Spontaneous Cerebral Activity and the Effects of Several Drugs.—The effects of these agents in animals have been reviewed in some detail elsewhere.[30] The effects in man are of greater interest for present consideration.

Mescaline: This agent has been found to decrease the amplitude of alpha activity in man,[19] and when visual hallucinations occur the alpha activity is said to be blocked. Interestingly enough, the diminished amplitude of alpha activity persisted for several days after subjective phenomena had ceased. In psychotic patients, the percentage of alpha was found to be increased in some and decreased in others.[97] No apparent correlation between changes in the electroencephalogram and subjective responses was found.[97] In postaddicts (to narcotics) Wikler[123] found variable responses to oral mescaline (5 mg./kg.). In schizophrenic patients[24] it has been reported that mescaline given intravenously usually produced a decrease in percentage of alpha. In this same study no correlation of electroencephalographic changes and visual hallucinations were found. A decrease in delta activity is produced by mescaline.[23,78]

In a study of the effects on the electroencephalogram of mescaline, morphine, and N-allylnormorphine in 35 experiments on 21 subjects (with previous history of narcotic addiction) Wikler[123] reports that, "Clinical effects of mescaline included the production of anxiety, visual hallucinations, illusions, mydriasis, sweating, tachycardia, hyperactivity of tendon reflexes, and tremors. The frequencies of the tremors were between 6 and 8 cycles per second, and they appeared at rest and were reduced on voluntary intention movement of the affected part. Concomitantly, the electroencephalograms showed no change, intermittent or continuous replacement of alpha activity by low-voltage fast activity and/or increase in frequency of the alpha rhythms. Morphine and tetraethylammonium

chloride were ineffective in relieving the anxiety produced by mescaline. Intravenous injection of barbiturates abolished anxiety promptly."

Lysergic acid diethylamide: At the peak of the lysergic acid diethylamide (1 mcg./kg.) reaction it was found in nine experiments[90] that only slight changes occurred in the electroencephalogram, chiefly increases of 1-3 cycles per second in the alpha rhythm. One subject showed a slowing of about 2 cycles per second. Gastaut, Ferrer, and Castells[36] report that only very slight changes in general were produced in the electroencephalogram. An increase in responsiveness of the alpha rhythm as to photic driving has been reported[15,28,36] in normal subjects. Others[32] found no significant changes in the electroencephalogram in psychotic subjects on 2 mcg./kg. lysergic acid diethylamide, but psychic changes were nonetheless prominent.

N-allylnormorphine: This agent has been reported to have psychotomimetic effects by Wikler, Fraser, and Isbell,[124] by Wikler,[123] and by Lasagna and Beecher.[67] When relaxation and euphoria were produced by the drug an increase in rhythmicity and a decrease in alpha frequency was said to occur. It is reported that a decrease in the amplitude and rhythmicity of the electroencephalogram occurred when anxiety appeared.

Adrenochrome: There are varying reports of the effects of this agent on the electroencephalogram. Szatmari, Hoffer, and Schneider[118] say it does not affect the encephalogram (10 mg. dose in normals) but does in larger doses in epileptics. Hoffer, Osmond, and Smythies[54] say it does affect the electroencephalogram.

Marihuana and Tetrahydrocannabinol: Single doses had little effect on the electroencephalogram but with prolonged medication the dominant frequencies were markedly slowed.[125]

Apter and Pfeiffer[4] have studied the response of the electroretinogram of cats to lysergic acid diethylamide and on the basis of this work have concluded that lysergic acid diethylamide evokes action potentials in the retina of the anesthetized cats. They say, "These experiments demonstrate that cats are capable of having hallucinations as the result of a non-toxic dose of LSD-25." They say further, ". . . the cortical activity induced by the drug is dependent upon nervous transmission from the retina, and does not appear when the connection with the retina is severed." They ". . . conclude that the hallucinations induced by LSD-25 are not similar to illusions induced by psychosis, since the drug has a marked peripheral action." In discussion of this, Brazier[16] raises a question as to how the results might have been influenced through centrifugal efferent action on the retina.[40] In further discussion Börnstein[14] advances the view, based upon his own experimentation, that the retina is not the only region of the organism that is responsible for the occurrence of optical hallucinations.

It is evident that many difficulties lie in the path of those who would like to demonstrate causal relationship between electrophysiologic and psychologic events. Evarts[30] says, ". . . it does not appear that we have reached the point of being able to assign any particular psychological effect of the drug to a demonstrated disturbance of the electrical activity of the nervous system."

INTERACTION OF DRUGS

The demonstration of an antagonism in vitro between lysergic acid diethylamide and serotonin has led to speculation that the in vivo effects of lysergic acid diethylamide are in actuality the result of a serotonin-lysergic acid diethylamide interaction.[30] Research in this field was greatly furthered by the finding of 5-hydroxytryptamine (serotonin, enteramine) in the brain.[34,119] The point of special interest is the role of serotonin in mental processes and the antagonism of lysergic acid diethylamide for serotonin.[127,128] (See Woolley and Shaw's footnote as to priority[129].) Gaddum,[34,35] Twarog and Page,[119] and Salmoiraghi and Page,[98] working independently, also originated and furthered this concept. Support for an in vivo antagonism has been presented by Shore, Silver, and Brodie.[103] In most cases, however, serotonin has failed to antagonize the electrophysiologic effects of lysergic acid diethylamide. Slater, Davis, Leary, and Boyd[104] did find that the effects of serotonin on a flexion reflex were blocked by lysergic acid diethylamide; the opposite effect has not been demonstrated. As Evarts[30] points out, negative evidence is not conclusive. Possibly rapid destruction of serotonin prevents the demonstration in vivo of interaction between serotonin and lysergic acid diethylamide.* Until these relationships are much clearer than they are at present, it is well to bear in mind Rothlin's[95] cautionary statement: ". . . whether there is either an interference or a causal relationship between the inhibition of serotonin and the psychic effect, is more complicated than would appear from the investigations that have been described." A well-recognized difficulty here is the fact that brom-lysergic acid diethylamide has a specific anti-5-hydroxytryptamine effect; brom-lysergic acid diethylamide is as effective as lysergic acid diethylamide in this regard, yet brom-lysergic acid diethylamide has no power to produce mental disturbances although it does produce some sedation.[95] However, as Koelle[61a] points out, it is possible that the bromanalogue is preferentially excluded by the human blood-brain barrier. The references given can be consulted for further information on the complicated subject of serotonin interactions. This controversial field cannot be fully discussed in this brief section.

Isbell[56] could find no evidence that 4-piperidyl carbinol (azacyclonol, Frenquel) could alter the psychologic effects of lysergic acid diethylamide in man. A similar "failure of correspondence" between electrophysiologic and psychologic interaction has been reported in the case of reserpine and lysergic acid diethylamide (Purpura[86,87]). Evarts[30] observes that interactions of tranquilizing and psychotomimetic drugs in animals do not permit dependable prediction of the interactions between the agents in man.

Azacyclonol, a "tranquilizing" agent, has been found to block the effects of both mescaline and lysergic acid diethylamide on the electroencephalogram in curarized rabbits.[88] Demonstration of succinate antagonism of mescaline visions has been reported by Schueler.[102] The succinate produced not only a decrease

*For extensive discussion of the chemistry involved, the role of lysergic acid as an antimetabolite, the drug antagonism involved, and mental changes produced, see the entire symposium, Ann. New York Acad. Sc. **66**:415-840, 1957.

in color intensity but also a decrease in complexity of design. He found that the mescaline "decrease in cooperation and hesitance in speech . . . [was] replaced after succinate by a more normal attitude and readiness to talk."

MENTAL EFFECTS—SUBJECTIVE CHANGES

The psychic effects are of principal concern for present purposes. Two agents, mescaline and lysergic acid diethylamide, have been more extensively studied than all others put together. Since, for reasons already mentioned, this section is intended to present typical examples rather than a thorough-going review, attention will be focused principally on these two agents. One can leave aside the centuries-old knowledge that ergot would cause grave mental derangements and come at once to 1943, when A. Hofmann, a chemist, accidentally received enough lysergic acid diethylamide to produce noticeably abnormal psychic effects and thus ushered in a new era of interest in the field of the psychotomimetic drugs.[95] The psychic effects vary widely from one man to another. The period of latency is long. Autonomic effects appear in about 20 minutes following oral ingestion, but psychic effects may take an hour and become maximal only after one to two hours.

The mental effects fall into several categories and will be discussed forthwith. Of all the mental disturbances produced by these drugs, of most importance are the hallucinations and delusions produced and the personality changes produced, or perhaps exhibited is a better word. According to Klüver,[61] Guttmann,[42] and Stockings,[111] hallucinations are common under mescaline; some authors consider them not to be very common with lysergic acid diethylamide.[90] Others, however, frequently have reported hallucinations under lysergic acid diethylamide; see below. Of all the derivatives of d-lysergic acid only three are known to produce psychic changes: the monoethyl amide, the diethyl amide, and the diethyl amide of d-l-acetyl-lysergic acid.

It is interesting to observe that dictionary definitions of hallucination and delusion do not differentiate clearly enough between them. It is necessary, then, to establish our own working differentiation. *Hallucinations* are distorted sense perceptions (visions, sounds, for example, not based on reality). *Delusions* are distorted thoughts (as "delusions of grandeur," "delusions of persecution").

Speaking of mescaline, Stockings[111] says, "It was found that the constitutional make-up in every case modified the course of the psychosis considerably." Mescaline and the diethylamide of lysergic acid (LSD) are the two most interesting agents at present and will doubtless remain of at least historical importance. While there are quantitative differences between them (for one thing the common dose of mescaline is 5,000 times greater than that of lysergic acid diethylamide) they produce in general the same effects.[53,76,90,95,115]

Hallucinations.—Hallucinations which occur while "contact with reality" is maintained presumably represent very much less mental impairment than hallucinations believed by the subject to be "real." It is regrettable, therefore, that so few authors have specified whether or not a close touch with reality is maintained during the period of hallucination. In 19 normal subjects, 10 under lysergic acid diethylamide and 9 under lysergic acid ethylamide, no loss of contact with the real situation was found by von Felsinger, Lasagna, and Beecher.[121]

It is evident that Stockings[111] in his study of mescaline deals (sometimes at least) with hallucinations during which contact *is* maintained with reality, for he says that mescaline ". . . can reproduce in the normal subject striking psychopathological phenomena without clouding of consciousness . . . ." Later on, in his review of his own experience, Stockings says, "It goes without saying that the subject of mescaline psychoses is entirely lacking in insight . . . ." (Surely many observers would equate a loss of insight with impairment of consciousness.) He says further, and what he really means begins to be blurred: "The mental changes produced are of an almost exactly similar nature to those found in psychotic patients—namely, hallucinations of all senses, delusions, transformations of personality, thought disorders, abnormalities of conduct, affect changes and disorders of temporal and spatial perception." Certainly many psychotic patients (and thus evidently some of Stockings's patients too) are out of touch with reality while experiencing hallucinations. Granting that hallucinations have similar characteristics to those found in psychotic states, "Thus their content is always in line with the subject's past mental experience. They are wish-fulfilling fantasies . . . ."[111]

Visual, auditory, and somatic hallucinations are common, those of smell and taste are rare.[111] In some 60 studies Guttmann[42] found that auditory hallucinations were rare, visual and tactile common. Mayer-Gross[76] speaks of waves of cold under mescaline. He maintained good contact with reality during his hallucinations.

Mayer-Gross,[76] Hoch,[52] and Savage[100] also emphasize the dominance of visual experiences in mescaline intoxication, especially their brilliance of color and intricacy of pattern, the persistence of after images, and the remarkable facility for visual change. Shapes of real objects alter in fascinating ways, and parts of bodies disappear (see also Guttmann[42]). Only the tactile senses and body image sensation successfully compete for attention at times with the visual for attention. Visual hallucinations predominate under lysergic acid diethylamide, as well.[115]

"The psychotic manifestations [of mescaline] occur in a state of clear consciousness."[52] The insistence of the majority of investigators on the persistence of "clear consciousness" under many of the psychotomimetic agents implies a less exact meaning of consciousness than some would prefer. In one approach, at least any drugs which produce amnesia, release self-protecting inhibitions, produce emotional disturbances, and "loosen the tight grip with which patients cling to reality"[65] could be said to have impaired consciousness. It has been repeatedly observed that hallucinations block out normal perceptions. Hallucinations are furthered by "silence, solitude and self-absorption, and mitigated or abolished by simple occupation . . ."[111]

> "The mechanism of their production appears to be as follows: The principal factor in their genesis is an enormous increase in the power of mental imagery and vividness of thought—a true hypertrophy of the imagination; thus, they commence as vivid fantasy, seen on the mind's eye, as it were, not as external objects are seen; at a later stage, when the process of mental dissociation is complete, the imaginalized thought be-

comes entirely split off from the rest of the psychic processes, and the fully-formed hallucination, appearing as a real object outside the subject, is thus produced. All the various stages between thought, vivid fantasy (pseudo-hallucination) and fully-formed hallucination can thus be seen and studied in the mescaline subject.

"Their genesis is also undoubtedly favoured by the characteristic disorder of thinking, the alteration of, and turning away from reality and the preoccupation of the subject with the novel inner life of his psychosis.

"These hallucinations are not influenced by external suggestion, thus differing from the type found in delirium tremens and allied states; the same applies to the auditory hallucinations."[111]

Fifteen normal subjects were studied under lysergic acid diethylamide (1 mcg./kg., orally) by Rinkel, DeShon, Hyde, and Solomon.[90] Disturbances of perception usually appeared within 40 minutes of the intake of lysergic acid diethylamide; they were commonly visual. The subjects realized that their experiences were illusions. No beautiful visions were seen, unlike the experiences of earlier investigators. There were frequent gustatory disturbances, a metallic taste or a "heavy tongue." In their experience hallucinations, although predominant under the influence of most phantastica were "rather meager and never showed the quality of an extraordinarily beautiful or threatening experience." Such hallucinations as they encountered were usually visual. In only one subject out of 15 was an auditory hallucination encountered. Two out of 15 experienced haptic (touch) hallucinations of wetness. Savage[100] reported hallucinations in 5 of 6 normal controls and 4 out of 14 schizophrenics.

On the other hand, Sandison,[99] for example, reports vivid hallucinations under lysergic acid diethylamide and correlates these with repressed material which is thus helpfully exposed, he believes, by the lysergic acid diethylamide.

Von Felsinger, Lasagna, and Beecher[121] report that under lysergic acid ethylamide (LAE) no hallucinations were observed, 1 out of 9 subjects merely reporting that objects "looked pallid."

Delusions.—These have been very well described by Stockings[111]: ". . . it is found that one of the characteristic actions of mescaline intoxication is that it is always accompanied by the presence of morbid suspiciousness and often of fully-developed delusions and ideas of reference, the mechanism of which can be shown in a remarkable way by means of the experimental mescaline psychosis. The delusionary ideas of the mescaline subject are of the same type as those found in psychotic patients, namely, ideas of grandeur, persecution, and bodily change. A description of the mechanism of these as elucidated in these experiments will now be given, and their points of similarity to those of psychotic patients pointed out.

"The basic factor in the genesis of the delusions appears to be a qualitative alteration of the functions of the higher cortical receptive centres, with resulting distortion of their functions, and consequent misinterpretation of external stimuli. The delusions are thus dependent primarily on a disorder of the central perception organs, especially the auditory centres.

"Taking first the delusions of persecution, we find that one of the characteristic actions of mescaline is that of sensitization of the auditory

centres. Sounds appear to be either unnaturally loud, or distorted, and to have acquired strange qualities. They appear to the subject to rush upon him in an extraordinarily purposive and deliberate way, and to have a reference for him which they would not have in the normal state. Thus, to quote actual examples, seen in the writer's experiments, the sound of a typewriter being used in the next room seemed to vibrate and reverberate through the walls and into the subject's body; thus, the typewriter became an infernal machine persecuting him with rays of electricity; in another case a group of people talking in the next room becomes a gang of enemies plotting against him or interfering with him. Similarly, the announcer's voice is sending messages over the wireless specially meant for him.

"In the visual sphere, the strange distorted appearance of people's faces, their movements and conversation all seem to be directed against him, so that he feels as if he was being watched, spied upon or otherwise interfered with.

"Similarly, the strange bodily paraesthesiae readily produce ideas of influence, electrical interference, or bodily changes produced by the machinations of other persons.

"This delusionary state may vary from morbid suspiciousness to fully-developed ideas of persecution, according to the stage of intoxication and the surroundings of the subject. It is apparent that persecutory delusions require some stimulus, in the form of an auditory or visual perception, for their production.

"Grandiose delusions may arise in two ways. One is from the somatic paraesthesiae. One of the commonest of these is a feeling of having grown extremely tall and handsome, and of being possessed of superhuman strength. Appreciation of the weights of objects is always disordered, and common objects may seem extremely heavy to the subject; in this way he imagines, for instance, that in raising a chair he is lifting an enormous weight. The hallucinations of supernatural figures and voices similarly give rise to ideas of communion with God, and of being divinely inspired.

"In these last types of delusions, the disorder of thinking and of association and lack of insight are important contributory factors in their production.

"The striking similarity of the delusional states thus described to those found in schizophrenic and delusional cases will at once be observed."

Hoch[52] has confirmed the findings of others concerning mescaline's effects and reports as common ". . . paranoid, grandiose or hypochondriacal delusions; misinterpretation of environmental situation."

Under lysergic acid diethylamide (1 mcg./kg.), Rinkel, DeShon, Hyde, and Solomon[90] did not observe major delusions as a grandeur or persecution in their normal subjects.

Disturbances of Thought and Speech.—These have been well described by Guttmann[42] and by Stockings.[111] Stockings says:

"The characteristic symptom [of mescaline] is a peculiar slowness and difficulty of thinking, a divorcement of the intellectual functions from the rest of the cerebration, with, simultaneously, a greatly increased output of spontaneous fantasy and imagery. Incoherence and thought-blocking are well shown, and give rise to the peculiar disorders of lan-

guage presently to be described. Flight of ideas, as in the manic states, may occur as a principal feature, or in combination with blocking of thought on the intellectual side. The subject may complain of strange and foreign thoughts being put into his mind, or that each thought is simultaneously repeated as either an auditory or visual perception—the phenomenon of 'double thought' so well exemplified in schizophrenic states. The feelings of passivity, of thoughts foreign to the subject being put into his mind from outside and ideas of influence are also well-known schizoprenic symptoms. Inability to hold a train of thought and follow it up to its logical conclusion, and perseveration and ideational inertia with disorders of association, are also found. A characteristic symptom is that there are several different simultaneous trains of thought running parallel in the mind of the subject. The thought-content is dominated by the subject's particular complex, as in schizophrenic states. The peculiar scattered type of thinking and volitional disorders are at once strongly reminiscent of schizophrenic phenomena, while the psychomotor retardation and flight of ideas bear a striking resemblance to the symptoms found in the depressive and manic psychoses respectively.

"The characteristic change appears to be the peculiar divorcing of the intellectual part of the personality from the rest of the psyche, with disturbance of association, blocking of voluntary intellectual thought, and extreme distractability. These factors, combined with the morbid suspiciousness and non-co-operativeness of the subject, render any proper assessment of the state of the intellectual functions extremely difficult. It is known that the mental efficiency, as measured by psychological tests, shows a great falling-off in performance. The subject can only perform the simplest tests and remember the most elementary facts from his past store of knowledge. The time taken for the performance of any test is increased, and the number of mistakes is also greatly increased."

Thought seems [on occasion] to progress at amazing speed under both mescaline and lysergic acid diethylamide and, at the same time, memory is defective for the recent past.[52,111,115] Doubtless, these effects account at least in part for the disturbances of time sense, discussed below.

"The subject's comprehension of, and memory for, the actual events taking place in the outside world during the period of his [mescaline] intoxication is good; but upon return to normality there is almost complete amnesia for the mental experiences, with the exception of one or two of the more striking hallucinatory scenes. The auditory hallucinations are always much better remembered than the visual. This amnesia for the mental experiences of the psychosis, with a good memory for the actual events in the world of reality, was a striking finding in many schizophrenic cases observed by the writer."[111]

The most prominent psychologic changes observed by Rinkel, DeShon, Hyde, and Solomon[90] in 15 normal subjects under lysergic acid diethylamide (1 mcg./kg., orally) were in thinking and speech. In general, these effects appeared in 30 to 45 minutes and cleared in 3 to 4 hours. There was no clouding of consciousness, they say, and no intellectual weakness, but difficulty in power of expression was frequently observed. "The subjects became more and more slowed down, poverty of thought became apparent, and the flow of speech became increasingly disso-

ciated and blocked." Presumably the reason these authors are so certain no clouding of consciousness recurred was that the subjects could clearly recall the next day all events that occurred during the phase of impaired speech, and ". . . each one was able to give, in a written report, a description of all the experiences he went through."

> "Hesitancy, indecision, and impairment of abstract thinking were frequently present; also looseness of thought and actual disconnection with increased distractibility were common observations." "Gross clouding of consciousness was absent in our experiments, but illusional misinterpretations were not infrequently observed."

One subject out of 15 demonstrated accelerated thought with flight of ideas associated with rhyming and punning. In this instance garrulity and loquacity were like that seen in hypomanic individuals.

Synaesthesia, "colour-hearing and sound-seeing," are reported as characteristic mescaline phenomena.[42,52,76,111] In no instance in 15 normal subjects under lysergic acid diethylamide (1 mcg./kg., orally) did Rinkel, DeShon, Hyde, and Solomon[90]) elicit synaesthesias. They agree that synaesthesias are common under mescaline.

Von Felsinger, Lasagna, and Beecher[121] report no increase in thought or speech processes in their 10 normal subjects under lysergic acid diethylamide, but rather a slowing down of speech and expression, with confusion, difficulty in concentration and in remembering what was read. Eight out of 10 reported difficulty in "paying attention." Lysergic acid ethylamide produced "dulling of thought" in 7 out of 9 cases and also difficulty in concentrating.

Disturbances of Time and Space.—Mescaline acts like cannabis indica, morphine, and cocaine to slow down the passage of time.[42,76,111] With a "small dose," 0.2 Gm. by mouth, this may be the only change perceived; with a large dose, 0.4 Gm. by mouth, mental dissociations occur, and the individual may believe that he is traveling backward or forward in time, or that ". . . in the course of a single afternoon he has lived through thousands of years."[111]

In 11 out of 17 experiments (15 subjects) Rinkel, DeShon, Hyde, and Solomon[90] found that lysergic acid diethylamide (1 mcg./kg., orally) disturbed the time sense, sometimes accelerated, sometimes retarded.

Characteristically, mescaline produces disturbances of space perception.[42] According to Stockings,[111] "Thus, rooms appear as huge fantastic chambers, or endless corridors, and the walls and floor appear to have changed their shape."

Depersonalization.—Alteration of personality is the "basic and fundamental" symptom of the psychosis produced by mescaline.[42,52,76,111] If schizophrenia is literally a split mind, Stockings believes that mescaline temporarily produces it.

> The subject's belief ". . . that something has been taken away from his personality and something strange and foreign substituted, is characteristic. The change consists of a radical alteration of the mind and body. Thus, the subject may feel that he is being several different persons at once—a symptom sometimes found in schizophrenia. More characteristic still is the feeling that he is divided into two separate beings—one purely intellectual and emotionless creature, the other a

fantastic being of delusion and fantasy, the first being able to observe the other in an extraordinarily detached and unemotional fashion.

"A further feature of the personality changes must be mentioned before leaving this subject, namely, the symptom of transformation of the personality—that is, the belief that the patient has been changed into someone else. Thus the subject of the mescaline psychosis may believe that he has become transformed into some great personage, such as a god or a legendary character, or a being from another world. This is a well-known symptom found in states such as paraphrenia and paranoia. As found in the mescaline psychosis, it appears to be due partly to the abnormal bodily feelings referred to in the discussion of delusions of grandeur."

Under lysergic acid diethylamide[76,90,100,121] depersonalization occurred frequently. Often parts of the body were suddenly abnormally large or small or disappeared altogether. The most common feeling was one of unreality for the subject himself and for the outside world.

Mood Changes Effected by Drugs.—Euphoria or dysphoria or depression can be produced by mescaline, depending on the stage of the intoxication.[42,111] Unlike the common sequence of events with alcohol, depression characteristically appears early in the psychosis. "It takes the form of an acute agitated type of depression, associated with intense anxiety and fear, and a sense of impending dissolution. There may be also ideas of unworthiness, of being irretrievably damned and lost, and of intense hopelessness. Associated with this is a terrifying feeling of unreality of self and of the outside world. Objects take on an extraordinarily sinister and vaguely menacing appearance."[42,52,111] Guttmann[42] reports that mescaline is not aphrodisiac, on the basis of his own studies as well as those of others.

Euphoria in response to mescaline appears to be a consequence of direct central action not consequent to the effect of pleasing hallucinations.[111] Emotional instability and fatuousness are common. "The mescaline subject also shows incongruity of affect, with complete indifference to events in the outside world, towards which he displays markedly shallow affective response. Thus, he may simply laugh fatuously at a piece of bad news; or he may wear a mournful and depressed expression whereas he is really inwardly elated and exalted; or he may laugh fatuously while in the depressive stage."[111]

Waves of elation and dejection rapidly alternated under mescaline.[111] This is also true for lysergic acid diethylamide where a periodic or wavelike alternation characterized many of the responses to lysergic acid diethylamide.[121]

Within 15 minutes under lysergic acid diethylamide (1 mcg./kg.) Rinkel, DeShon, Hyde, and Solomon[90] found that "feelings of indifference and blunting tended to be protracted; suspiciousness, hostility, and resentment were always more transient. Changes in mood were twofold: euphoria and depression, which occurred in about equal number." They say further: "In no instance did we observe the happy and dreamy feeling of ecstasy as it has been described by other authors who experimented with L.S.D., mescaline, and other similar chemicals."

In study of "more than 100" normal males and females under lysergic acid diethylamide (1 mcg./kg.) Rinkel, Hyde, Solomon, and Hoagland[93] expressed

particular interest in hostility. They say, ". . . strongly affective relationships of affiliative or hostile nature were distorted to a greater proportion (26%) than were relationship of impersonal, emphathic and nuturient character (6%)." Lysergic acid diethylamide appears to intensify interpersonal relationships.

In the realm of behavior under lysergic acid diethylamide, presumably influenced by mood, Rinkel, Hyde, Solomon, and Hoagland[93] report:

> "Our sociologist, Morimoto, investigated the sociopsychological behavior of 43 normal subjects who were under the influence of LSD. An evaluation was made on each subject before he received LSD, as a basis for comparison. Each subject was classified on 35 attributes which indicated feelings and actions related to his behavior in interpersonal relationships. These attributes were further classified into 4 categories or modes which indicated in which directions one moves in interpersonal relationships. The modes of directions were: away, against, toward, and with.
>
> "The results of this intriguing study revealed that during the influence of LSD the scores in the modes, away, against, and toward, were significantly increased (x^2 significant at .001 level). A significant decrease in scores was found in the "with" mode (x^2 significant at .001 level). These observations mean that the behavior of the subject who is under the influence of LSD is altered from his pre-LSD behavior in the sense that the mode is now one of the moving *away* (avoidance, withdrawal, denial); *against* (hostile, punitive, competitive); and *toward* (seeking of nurturance, support, reassurance); while the *moving with* (brotherly, friendly, reciprocal equalitarian) type of behavior is clearly reduced. This study also indicated that the hospital personnel had more severe reactions than subjects from outside of the hospital. The ability to mobilize appropriate social behavior was reduced during LSD; the directions of change were toward greater rigidity, although a few exhibited an erratic and overreactive type of behavior (x^2 significant at $>.05$ $<.02$ level). Intensity of symptoms subjectively experienced increased in social situations in which there were specific expectations placed upon the subject (x^2 significant at .001). On the other hand, intensity of symptoms was reduced in those social situations that were supportive and nurturant to the subject.
>
> "One cannot escape the impression, from these observations, that the sociopsychological behavior changes showed similarities with the general behavior of the mentally ill and that they provide fundamental implications in the field of psychotherapy."

Loss of emotional control was common under lysergic acid diethylamide.[90] But no consistent trends toward anxiety and tension were found, ". . . possibly because of the peculiar nature of the experience *which preserves insight* in spite of drastic intellectual and emotional changes."*

Comparison of lysergic acid diethylamide and lysergic acid ethylamide: The latter agent has been comparatively little studied. In this, the experiences of von Felsinger, Lasagna and Beecher[121] partly confirm those of Solms.[110] The doses of lysergic acid ethylamide (3 were given 0.25 mg. and 6 were given 0.5

*Italics mine.

mg., subcutaneously) utilized by them were many times greater than those of lysergic acid diethylamide, but no striking difference in severity of symptoms was seen. This confirms Solms's statement about differences in potency. The data[121] on perceptual distortions also suggest that Solms's second statement about the rarity of optic "hallucinations" after lysergic acid ethylamide (as compared with lysergic acid diethylamide) is similarly correct. His third differentiation (relative to differential mental effects), however, cannot find full confirmation in the new data. Both lysergic acid ethylamide and lysergic acid diethylamide seem to produce a general slowing down of mental processes in these subjects. Both drugs show remarkable power in producing definite psychologic changes. These changes are not unique in the experience of this laboratory and other drugs have produced symptoms of even greater degree, but the incredibly small traces of lysergic acid diethylamide that are sufficient to effect change are of considerable significance. Those investigators who choose to view these drug reactions as "schizophrenic" see in this fact considerable support for the conception of schizophrenia as an endotoxicosis. The experience of von Felsinger, Lasagna, and Beecher[121] with the monoethyl amide of lysergic acid, while limited, does not give much support to such a view since with one exception (suspiciousness) the symptoms observed under this drug are not unlike those produced by other agents and do not, clearly, constitute psychotic processes to any greater extent than those produced by other drugs: in this regard it seems important to emphasize the maintenance of voluntary control and, more particularly, of insight and the capacity for reality testing throughout the drug reaction by these subjects.

Four of 10 subjects under lysergic acid diethylamide (usually 1 mcg./kg., p.o.) experienced increase in anxiety; two of these laughed out loud or smiled for long periods.[121] Two of the 10 had erotic sensations.

Rather striking hostility with paranoid tendencies in 4 out of 9 subjects was found under lysergic acid ethylamide (LAE) by von Felsinger, Lasagna, and Beecher.[121] Three considered their reactions pleasant, and 3 considered them unpleasant. One of the latter had a panic reaction with intense fear. One subject of the 9 reported an "overwhelming desire to talk." Five of the 9 felt amused or laughed out loud. As with lysergic acid diethylamide recurrence of symptoms in "waves" was observed.

PHYSICAL EFFECTS, INCLUDING OBJECTIVE CHANGES

Autonomic (Vegetative) Disturbances.—Mescaline appears to have a specific action in abolishing sleep.[111] There is also restlessness and profound anorexia. Sexual function is depressed.[42]

Lysergic acid diethylamide produces numerous disturbances of the autonomic nervous system.[42] Rinkel, DeShon, Hyde, and Solomon[90] report:

> "The most common symptom was change in appetite, which more often was decreased, and associated with nausea, than increased. Complaints of headiness, giddiness, faintness, tremulousness, and shaking were frequently expressed. The subjects complained of chilliness and coolness of whole or part of the body, lump and "funny" feelings in

abdomen, constriction with oppression in chest and precordial discomfort, violent cramps and constriction in the abdomen in a patient who just happened to menstruate. Objectively observed were flushing, sweating, shivering, with goosepimples. Tachypnoea, salivation, pallor, sighing, and urgency of micturation were scattered observations. Changes in pulse rate and blood pressure were of minor magnitude and observed only occasionally. Involuntary smiling, giggling, or laughing were considered in the nature of "risus sardonicus" where the subject described these phenomena as occurring without or against his will. One subject stated that in a smile he felt as if his facial muscles were like plastic wax being moved by some inexorable force. Pupils were often maximally dilated."

In studying lysergic acid diethylamide Rinkel, Hyde, Solomon, and Hoagland[93] report on subjective experiences:

"All subjects who had taken LSD experienced sensations which were the result of dysfunctioning of the muscular, cutaneous, gastrointestinal, genitourinary, cardiovascular, respiratory, and sensory systems. Most common were subjective feelings of trembling, while actual tremor was rarely seen, feelings of numbness, hunger, and nausea; less common were coldness and warmth, perspiration, tingling, throbbing, flushing, sighing, tightness, choking sensation, sexual excitement, and need to urinate."

Physical measurements of pupil size, heart rate, blood pressure, and respiration showed that the heart rate was more stable on lysergic acid diethylamide days than on placebo days, the respiration more variable and the pupils larger. Blood pressure was in general little affected by lysergic acid diethylamide; there was, however, a notable rise in blood pressure under lysergic acid diethylamide following "psychiatric interview." They[93] found further that lysergic acid diethylamide did not significantly alter the response of the autonomic nervous system to norepinephrine, whereas epinephrine was less effective than normal in producing a rise in blood pressure under lysergic acid diethylamide. (These experiments were carried out on mental patients.) Experimental work of this group indicates that lysergic acid diethylamide stimulates the pituitary adrenal axis.

Rothlin[95] concludes that ". . . in the animal, a central sympathomimetic syndrome predominates and that psychic changes are probably present, but difficult to interpret [under lysergic acid diethylamide]. In man psychic changes predominate, while the autonomic symptoms are apparently subordinated."

Motor Disturbances.—A "disinclination for active movement" is common under mescaline.[52,111] Sometimes catatonic states, even, are produced. Such quiet states may alternate with outbursts of aimless motor activity. There is indifference to pain which, though perceived, is not reacted to.

Under lysergic acid diethylamide[90,93] the most striking change found in 15 normal subjects (1 mcg./kg.) was underactivity with lack of spontaneity and initiative. However "psychomotor manifestations, such as smiling, giggling, and laughing, more often appropriate than inappropriate, were frequently observed."

OBJECTIVE EXPERIMENTAL MEASUREMENT

Rorschach.—When the same subjects were given Rorschach tests in their normal state and then under mescaline, it was found, surprisingly,[122] that the latter corresponded closely with the personality as known in normal life; the former was very different and revealed a personality that had been hidden.

Guttmann,[42] working with Vernon, on mescaline, concluded on the basis of Rorschach tests merely that the personality had "changed." He chose not to interpret his data beyond emphasizing that they indicate the "importance of the perceptual sector of the personality."

Stoll[117] found in 11 normal subjects under lysergic acid diethylamide that the Rorschach changes show typically ". . . a general loosening of mental processes . . . [with] disinhibition of affectivity and fluency of thought processes, of which the precision and wealth of contact, however, is decreased." Five subjects were subjected to such study while under lysergic acid diethylamide (1 mcg./kg.) by Rinkel, DeShon, Hyde, and Solomon.[90] All tests showed abnormalities "principally of the schizophrenic or paranoic type." "There was noticed autistic thinking with decreased organization, contamination responses, and lack of logical thinking, also negativism and diminished emotional inhibition indicating anxiety, depression, and aggression. One Rorschach test revealed a moderately schizophrenic picture with autistic thinking and withdrawal."

In another report,[93] Rorschach tests were performed on 29 subjects (these were partial tests, Cards III, VII, and VIII being used.) All but 2 subjects showed significant change under lysergic acid diethylamide from their normal state. In addition, Wechsler-Bellevue Block Designs (No. 2 and No. 4), a Draw-a-Person Test, and 8 Thematic Apperception Cards were used. For the group as a whole the most marked change they found was ". . . a definite reduction in organization and integration of the subjects' response to conventional features of their environment and experience. They showed a lack of concern about their behavior and responses. Their disregard for the environmental stimuli was accompanied by an increased concentration on discrete or minute aspects of experience. The subjects' attention was centered on restricted areas. There was a general loosening of critical appraisal. Intellectual control was impaired with difficulty in concentration and associative thinking."

Von Felsinger, Lasagna, and Beecher[121] carried out fairly extensive Rorschach studies under lysergic acid diethylamide and under lysergic acid ethylamide. Their observations are as follows:

"I. *Lysergic Acid Diethylamide (LSD)*

"All 10 lysergic acid diethylamide subjects were given a second Rorschach examination while under the effects of drugs. The first Rorschach examination was given before the drug was administered, as previously described. These tests were given usually several hours after the drug ingestion when the observers believed the symptomatology was either at its peak or just receding. Seven of the 10 subjects showed distinctive changes in the determinants of their responses. [In an extensive study of the so-called ego-depressant drugs, this is the first time they had found a fairly consistent modification of the Rorschach response by

drug.] In six of these seven cases the changes were in the same direction and of similar meaning. In general, these changes took the form of an expansive release phenomenon in which the postdrug Rorschach was an exaggerated caricature of the predrug one, whereby previous weakness of ego functions was particularly magnified. Intellectual processes tended to regress to an immature level. Thus animal movement responses (FM) became dominant over human movement responses (M). This was particularly evident where the predrug balance was stable or M not especially dominant. Since M dominance is a normal concomitant of mature development, this reversal indicates regressive and immature thought processes, as well as a weakening of intellectual control over affective and emotional impulsivity. In adults, too, the degree of FM dominance correlates with the degree to which productive potential is wasted. The same regressive phenomenon is reflected in the shift in color responses from FC to CF and in a few cases, to C. In adults FC responses should be dominant. They reflect the development in behavior of increased restraint in the regulation of the forms of self-expression, and the modulation and restriction of the behavioral and emotional impulsivity and unpredictability characteristic of younger age groups. These postdrug changes seriously undermined the characteristic mechanisms developed by each personality for the control of behavior and for defense against anxiety. Under these conditions perceptual processes were correspondingly altered with an accentuation of emotional states at the expense of external reality factors. The fact that only three subjects of these seven experienced sensory illusions seems surprising.

"The M:ΣC ratio, reflecting the balance of affective and regulatory spheres in the personality (optimally within 2:1 to 1:2 range), was seriously unbalanced under the drug, the median ratio for the seven cases being 1:3.5 and 0:7.5 following the drug. This severe threat to self-control was reflected in the experience of tenseness, anxiety, and 'jitteriness,' as well as the stated fear of losing control.

"As indicated above, the degree to which the Rorschach was changed was positively correlated with the relative weaknesses of personality development already present. Significantly too, the total amount of reaction to the drug (in terms of objective evidence and subjective description) was also highly correlated with a 'maladjustment' ranking by the psychologist based on an interview and the predrug Rorschach test. The correlation between these maladjustment rankings and the drug reactivity rankings by the pharmacologist was .93. Rankings by the pharmacologist and by the psychologist were performed independently of course."

Case examples are given to illustrate what seems to be a primary psychologic effect of the drug—the exacerbation of existing symptomatology through a weakening of control functions and defense systems.

"II. *Lysergic Acid Ethylamide (LAE)*

"Predrug Rorschach testing and interview were given to seven of the nine lysergic acid ethylamide subjects. Again independent ranking by the psychologist and pharmacologist revealed a high correlation (.80) between 'maladjustment' and degree of drug 'reactivity.' The three best adjusted individuals (ranks 1, 2, 3) had no, or extremely minor, effects, and this group of subjects did not scatter so widely along the adjustment-maladjustment continuum as did the lysergic acid diethylamide subjects.

"The range of reactions and particularly their intermixture in this small sample precludes the analysis of drug reaction and personality structure. However, the four subjects who had paranoid or hostile reactions to lysergic acid ethylamide and the single subject responding in like manner to lysergic acid diethylamide deserve special comment, since the reaction has not been seen (when consciousness was unimpaired) in this laboratory during the study of other drugs. An analysis of the predrug Rorschachs (on four of the five) indicates that while none of them could be called 'paranoid' (except by analytic implication from homosexual trends in two of them) the incidence of 'looking,' 'watching,' and 'eyes' responses in essentially guarded records is suggestive of suspicious attitudes in interpersonal relations. While this implies psychologic predisposition it is noted that one of these subjects had participated in other drug experiments involving five drugs and this reaction had never been noted. He was, however, atypical in his reactions to several of these drugs, where uniformity of reaction was more common among subjects than in the present experiments."

Psychomotor Tests.—Psychomotor tests carried out under mescaline in Guttmann's laboratory[42] were characterized chiefly by the increased incidence of errors made.

No details are given but it has been reported by Rinkel, DeShon, Hyde, and Solomon[90] that lysergic acid diethylamide (1 mcg./kg.) produced in this area a "wide range of responses in abstraction and over-generalized and tangential thinking," similar to those encountered in schizophrenic patients.

Lasagna, von Felsinger, and Beecher[68] have pointed out that "the nature of the subject and the situation in which a drug is administered are important determinants of drug effects," not the drug's "pharmacological" properties alone. This is especially striking in the domain of subjective responses.

Kornetsky, Humphries, and Evarts[62] in a carefully controlled study set out to test in 10 volunteers the hypothesis that "the magnitude of drug induced psychological effects is significantly related to the reactivity of the subject." They considered four classes of centrally acting drugs: meperidine hydrochloride 50 and 100 mg., secobarbital sodium 100 and 200 mg., chlorpromazine hydrochloride 200 and 400 mg., later 100 and 200 mg., lysergic acid diethlyamide 50 μ and 100 μ and two placebos. All agents were administered orally as unknowns ("double blind" system).

A battery of psychomotor tests was presented to each subject who eventually received all drugs and placebos. Lysergic acid diethylamide affected performance on more tests than any other drug but did not significantly affect the pursuit rotor tests (this is in agreement with Abramson, Jarvik, and Hirsch[2] and Jarvik, Abramson, and Hirsch[58]) suggesting that lysergic acid diethylamide has little effect on motor coordination but rather great effect on perceptual and intellectual processes. Chlorpromazine and secobarbital affected complex intellectual tasks (but not simple ones) and also affected motor coordination. However, Landis and Clausen[66] report in schizophrenic patients, impairment on some motor tests and increased critical flicker fusion thresholds under lysergic acid diethylamide. Mescaline usually resulted in lowered motor tests and lowered critical flicker fusion scores.

Kornetsky, Humphries, and Evarts[62] conclude that the "effects of drugs on psychological performance in man are due not only to the specific pharmacological activity of the drug, but also to the specific reactivity of the subject and to an interaction of the two. There is not a significant correlation between the objective and the subjective psychological effects of a given drug. However, the drugs that produce the greater mean objective effect also produce the greater mean subjective effect."

In a further report on this same subject material they found[63] when they examined the data derived from the Minnesota Multiphasic Personality Inventory that "The Depression and Psychoasthenia scales correlated significantly, or almost significantly, with the subjective effects and, to a less extent, with the objective effects of those drugs and dosages that produced significant effects." They say further, "These results support a hypothesis that personality plays a role in determining the extent of drug effect." Thus they support the similar view of von Felsinger, Lasagna, and Beecher.[120]

Part III: Conclusions

Generalizations and Some Questions

Results Expected From Work in This Area.—Guttmann[42] discusses what is gained by a study of mescaline:

> "(a) A new aspect of disintegration of sensory function, namely in the direction towards synaesthesiae. (b) A new idea of the importance of the perceptual sector within the personality. (c) Some therapeutic prospects, especially with regard to depersonalization states. (d) An opportunity of experiencing undescribable mental changes as a help in understanding the mental life of schizophrenics—a point so important for psychiatrists.
>
> "For the future it may be expected that experimental work, as previously outlined, may lead to a better understanding of the complicated interplay of aetiological factors in the origin of psychoses. Careful analysis of one intoxication like mescaline promises a reliable basis for knowledge in the field of toxic psychoses generally, and perhaps hints for the solution of the great problem of psychiatry, that of schizophrenia."

In discussing what is gained from experimental study of drug psychoses, Mayer-Gross[76] emphasizes, as some have before[79,116] and others since, that the pychiatrist as a result of such self-experimentation gains the advantage of increased insight into the problems of deranged patients.

One hopes, of course, that production of the symptoms of mental disease will make it possible to study profitably the mechanism of their production[100] and that these drugs, especially lysergic acid diethylamide, will be useful in the therapy of mental illness.[6,21,100,115]

Persisting Difficulties.—Drug studies in this area are notably unsophisticated in many cases, from the point of view of design, that is, the use of the double unknowns technique and of placebos, the separation of subjects so that they cannot "condition" each other as to what to expect, the use of randomized data,

of correlated or cross-over data, control of possible interaction of drugs, mathematical validation of supposed differences—these essential safeguards are more often ignored than observed. It is rather paradoxical that observers who are most familiar with the complexities of the human mind should pay so little attention to the self-evident difficulties of drug evaluation in this area. The needless waste this inevitably leads to in terms of money, time, and human misery is worth more attention than it has so far received.

In a quotation recorded earlier from Rinkel, Hyde, Solomon, and Hoagland,[93] the comment was made that their hospital personnel when acting as subjects had more severe reactions (behavioral) than subjects from outside the hospital. This arouses suspicion that the hospital personnel had, through intimate contact and discussion with each other, produced a certain amount of "conditioning" which led to this difference. Von Felsinger, Lasagna, and Beecher[121] ran into this problem even when using outside subjects who by coincidence happened to be roommates. The use of personnel who are in communication with each other is likely to lead to distorted and unsound observations.

Drugs which cause psychoses, notwithstanding their wide chemical and pharmacological diversity, give rise to a well-recognized pattern well-described by Hoch, Pennes, and Cattell.[53] It is hazardous to attribute specificity to a given drug or a given group of drugs.

> "The acute organic syndrome (acute toxic reaction, acute delirium, toxic-infectious psychosis, infective-exhaustive psychosis, etc.) following drug administration is basically similar to that produced by other noxae and consists of the following features: 1) Mental clouding with impaired consciousness and fluctuating attention, grasp, retention, and orientation; 2) Perceptual disturbances, mainly visual and auditory illusions and hallucinations; 3) Emotional lability, usually with some degree of anxiety, suspicion, brooding unrest, euphoria, or indifference; and finally 4) Aberrant behavior of various degrees of organized motor activity consistent with the remainder of the reaction. The essential feature for the diagnosis of the syndrome is the presence of the mental clouding and the confused state; the other components may or may not all be present in a given case."

The subject material, whether sick or well, modifies the results observed. In frank schizophrenia, mescaline accentuates the symptoms. In latent schizophrenia the drug precipitates schizophrenic psychoses (Hoch[52] and others). So also lysergic acid diethylamide accentuates pathologic processes already present (Savage[100] and others).

Rinkel, DeShon, Hyde, and Solomon[90] "mention the similarities of the experimental [psychotomimetic] phenomena to actual psychotic states in order to caution against fallacies that may occur in the interpretation of experimental psychotic disturbances. The same caution that is warranted in the application of an animal experiment to a pathological condition in man is needed in the application of the psychiatric experiment to natural psychosis." They continue, "We must bear in mind that, in addition to d-lysergic acid, a great variety of seemingly unrelated chemical substances are capable of producing transitory psychotic-like symptoms."

Some Questions.—There are a number of questions[53] which arise from a survey of the psychotomimetic agents.

Are the symptom patterns characteristic for each drug or each type of drug? The answer to this appears to be that some drugs, notably mescaline and lysergic acid diethylamide, give rise to symptoms which in many respects are similar to those of the toxic psychoses rather than to the acute organic reactions. As indicated above, mescaline and lysergic acid diethylamide typically produce in normal subjects "a hallucinatory-illusional state with emotional changes but without impairment of orientation, comprehension, and memory."[53] These are the findings in the majority whereas only the minority exhibit acute organic reactions to many of the other types of intoxicants.

It has been fairly generally agreed upon that the psychotomimetic drugs do not evoke specific symptoms related to a single drug but do call out general "acute exogenous reactions." It is customary to explain differences among individuals as arising in the person involved, in his conditioning, in his situation. Solms[109] considers the factors just mentioned to be inadequate to explain all of the individual differences encountered as, for example, the differences which appear under three similar ergot derivatives: the mono and the diethyl amides of lysergic acid and lysergic acid amide. He has therefore studied the question of relationship between the chemical structures of these compounds on the one hand and certain subjective responses produced by them on the other hand.

Solms concludes[109]:

> "There are, then, no principal differences in the mental symptomatology produced by LSD and LAE. Both drugs can bring about the same symptoms, but in general one can say that LAE produces lethargy, indifference, drowsiness, apathy, and abulia more often than does LSD. The deterioration of consciousness is slightly greater with the use of LAE. Finally, the hallucinatory phenomena, which are exceptional with small doses of LAE, become frequent, intensive, and impressive (as always with LSD) with high amounts of LAE. . . . The effective doses of LA are the same as for LAE, but LA induces greater indifference, a decrease in psychomotor activity, and a desire to sleep much more strongly than does LAE, until finally an increased clouding of consciousness produces sleep. LA may provoke sleep after one-half to one hour; if the subject is not awakened, sleep lasts approximately two hours. If the dose of LA is increased, no certain hallucinatory experiences can be noticed, but uncomfortable autonomic disturbances do occur, such as, hypersalivation, emesis, dizziness and diarrhea; sometimes irritative depressive moods occur concomitantly. Because of these symptoms the tolerance point was considered reached." Solms then interprets his data as follows:
>
> "Using the greatest prudence the following provisory interpretations are proposed. If ethyl groups are substituted on the amide group of LA, its power to produce hallucinations seems to increase. On the contrary, if the number of substituted ethyl groups [is] decreased, hallucinatory potentials are also weakened; i.e., the visual system seems less affected, but psychomotor activity decreases and clouding of consciousness is augmented until sleep occurs."

He has labeled this approach "comparative pharmaco-psychiatric analysis." The trouble is, no indication at all is given as to whether the most elementary safeguards were observed to control the highly subjective observations made. This approach must of course be used. Surely one day it will be recognized that if sound judgments based upon subtle observations like these are to have meaning, they must be protected by controls not evident in this study.

What individual factors influence reaction to psychotomimetic drugs?[53] In this poorly defined area individual susceptibility and personality type seem to be important (quantitative data here would help greatly). Pennes[53] studied the responses of a group of schizophrenia patients to four agents, amobarbital, "pervitin," mescaline, and lysergic acid diethylamide. He found that 28.8 per cent of the group reacted (presumably the same patients with each drug) with intensification of symptoms. He called these "intensification reactors."

How do psychotic subjects react to drugs which produce psychotic states in normal individuals?[53] A great deal of attention has been devoted by many investigators to answering this question.[53,90,95,115] The major observations have been usefully summarized by Hoch, Pennes, and Cattell[53]:

> "(a) The majority of schizophrenics displayed intensification of their pre-existing symptomatology on administration of mescaline or LSD25; pervitin (desoxyephedrine, methyl benzedrine) was somewhat less effective as an intensifier of abnormal mental phenomena, while sodium amytal was the least effective intensifier of the four drugs employed. (b) The reactions of schizophrenic patients to mescaline and LSD25 are usually marked with severe anxiety and other emotional patterns while disorganization of thought and behavior patterns may be profound. (c) Mescaline psychosis in normal individuals bears only a partial resemblance to natural schizophrenia. . . . The point has been made that chronic administration of mescaline might elicit a reaction more closely approximating the chronic schizophrenic state but the necessary experiments have not been reported. Of the earlier workers, Stockings . . . and Bensheim . . . felt that schizothymic and cyclothymic individuals reacted differently to mescaline. However, Beringer in his exhaustive 1927 monograph was forced to the conclusion that there was no correlation between the previous personality and the reaction to the drug in normals. . . . It would seem, however, that schizophrenic patients do react differently to the drug from normals. In general terms, schizophrenics display severe anxiety and intensification of their original thought and behavior disorganization, whereas normals usually do not pass into a frank schizophrenic episode. In terms of reality control, schizophrenics respond to the intoxication with a further disruption of their faulty reality-handling mechanisms whereas normals tend to cope with the intoxication in a basically adequate fashion."

Is there a relationship between perceptual and emotional changes following administration of mescaline or lysergic acid diethylamide? Hoch, Pennes, and Cattell[53] summarize their wide experience:

> "(a) In the majority of subjects the appearance of anxiety was concomitant with the onset of the perceptual abnormalities. Both the form and content of these perceptual abnormalities apparently served to generate a reactive or secondary anxiety. Apart from this general

relationship, little appeared that could be correlated in a more specific way. For example, (b) different subjects had different emotional reactions (anxiety, depression, hostility, suspicious-paranoid) despite perceptual experiences of the same form. (c) There was often no evident correlation between the apparent intensities of the perceptual and concomitant emotional experiences in different subjects. (d) And finally the same individual on repeat administration of the drug could in some cases experience approximately the same type and degree of perceptual change with a decreasing or qualitatively different emotional reaction.

"It is apparent therefore that perceptual changes may be correlated with the effective responses in acute mescaline or LSD25 psychosis but the relationship is neither qualitatively or quantitatively direct or specific and often appears to involve higher level symbolic reactions. The autonomic and sensori-motor reactions to these drugs are also extremely difficult to correlate with the remainder of the response, either qualitatively or quantitatively."

If the psychosis producing drugs are to be useful in getting at mechanism of action of mental aberrations, a quantitative approach when possible seems essential.

Comment.—The relationship of the predrug personality structure and the type of drug reaction was not as apparent with these drugs as with some others studied, but the correlation of the amount of induced change and the degree of pre-existing maladjustment implies the presence of a significant relationship.[121] This finding suggests McFarland's work[77] on anoxia where he found a high correlation in neurotics between symptom formation, including physical collapse, and low levels of anoxia (induced by simulated high altitudes) where the normal individual was unaffected.

It is important to keep in mind, as von Felsinger, Lasagna, and Beecher[121] point out, that when evaluating drug reactions the primary drug changes can constitute a stressful situation for particular individuals, and they may react with vigorous restitutive activity. The fact that many subjects would respond to perceptual alterations and unusual bodily sensations with anxiety is not strange since experimental studies have demonstrated a similar reaction when external cues to depth or distance are altered or made ambiguous. The complete drug reaction may then be best explained in terms of the individual's defense system or his characteristic reaction to stress or threat in general. The paranoid reactions are a case in point. Thus it might be expected that the poorly adjusted individual would react to drugs with greater diversity and more intensity of behavior than other individuals.

It is easy to appreciate the role of psychologic factors in the "secondary" drug reactions which sometimes supersede the initial, expected one.[121] These reactions are most easily understood as the result of the integrative functions of the personality acting to adjust behavior to an acceptable compromise between internal processes and reality demands or, stated another way, constitute restitutive efforts on the part of a threatened personality organization to preserve its integrity or re-establish its equilibrium. Altering the internal components of this balance may create fear or panic, and great efforts may be made to integrate the change in an emotionally acceptable manner. This may be the best

explanation of religious revelations following ritual drugs and philosophic formulations during the use of mescaline.

The above situation seems analogous to psychologic defense mechanisms developed as a result of threatening disturbances of intrapsychic mechanisms of interpersonal relationships.[121] The defense mechanism of denial is an example in point. It is an interesting, but unexplained, observation in drug experiments in this laboratory that denial appears to be most frequently employed by subjects characterized by a psychopathic personality structure. Another observation of this laboratory is that panic or near-panic as a reaction to drugs seems characteristic of personalities struggling with very strong sexual problems, primarily those of a homosexual nature.[121]

The use of drugs to produce a "psychosis in miniature" and to produce secondary defense reactions in order to study experimentally the relationship of defense pattern and its determinants offers interesting possibilities. An extreme example of drug effect on the development and choice of defense mechanism was the reaction of a young college student (following lysergic acid diethylamide) whose integrative efforts during the drug sessions constituted "the most important experience of my life."[121] The "insight" consisted of a decision that "positive action" was the key to interpersonal relations. When first seen (predrug interview), he was characterized by an excessive desire to please and an anxious ingratiating manner. In the interview he was depressed and anxious over his inability to establish himself in peer groups and showed constant preoccupation with the possibility of acquaintances not liking him. As an example of his difficulties he gave his inability to take any side of an issue under discussion for fear of offending one or the other side. Under lysergic acid diethylamide he was frightened by a feeling of waning contact with reality and doubts of the presence of objects. This was mitigated by self-reassuring statements and positive assertions: "That *is* the chair," "The doctor *is* here," and so on. The effectiveness of this restitutive activity was so anxiety-reducing that the subject suddenly saw it as a key to adjustment and happiness. On return to college he put "positive assertion" into action with friends, girls, classes, and the like, and two months later reported himself to be "successful and happy" in everything he had undertaken. Unfortunately, restitutive activity is rarely so effective.[121]

A basic question is whether drugs create something new in the organism or only release that which is already present. In previous study of other drugs von Felsinger, Lasagna, and Beecher[120] and Lasagna, von Felsinger, and Beecher[68] have been impressed with the apparent meaningfulness of the atypical drug reaction in terms of the individual's personality structure and current personal problems. The small sample and the diversity of response to lysergic acid diethylamide and lysergic acid ethylamide obscure such a relationship if it exists here, but the Rorschach changes are suggestive.

Lysergic acid diethylamide has produced greater and more profound changes in the results of Rorschach testing than any other drug studied in this laboratory.[121] These changes are not striking conversions of normal to psychotic, but rather consistent expansive exaggerations of the predrug personality in which structural weaknesses and immature factors are magnified. In some individuals

already characterized by pathologic signs, such a process may produce a "psychotic" picture. The process itself is better viewed, perhaps, as a release of existing tendencies rather than a creation of new elements.

Quantitative Data.—The writer has no wish to emphasize the need for a quantitative approach to the point of absurdity, where one attempts to quantify the patently unquantifiable. Errors in this direction are likely to be fewer than in the opposite. The pity is, so little has been tried, as Thoreau might have put it. Many are agreed with the need for quantitative data. Gerard[37] says:

> "I am satisfied that the greatest barrier to rapid advance in psychiatric research today is the continuous and anecdotal character of the descriptive material on which psychiatric insights and generalizations are almost exclusively based. When more useful categories have been recognized and at least ordinal scales established; when it is possible to group the phenomena into classes and categories in a meaningful manner, rapid progress is certain to follow. This is really the familiar problem of nosology in disease or typology in individuals or populations. But this implies just the kind of interplay between continuous and discontinuous that has been under discussion. When the input to our biological calculators has been effectively coded, the rules of operation already built into these nervous systems will suffice to grind out important answers in the mental area, as they have already in the physical and biological ones."

A carefully designed experiment carried out in Acheson's laboratory by a large group[38] confirmed the Beecher group's experience[8,9] that introspective data are reliable for scientific investigation in psychopharmacologic relationships.

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