gency Service may find its scope extended to meet many general medical and surgical problems which the patient, at least, will deem urgent" — may be the key to a recognition of the fact that the change has already occurred and that it is accelerating at a rate that should be recognized by all. Certainly, the general problem requires much more intensive study, including a critical analysis of statistical material, before any positive declarations can be made about the reaction to the trend. But desirable or otherwise, the trend is a reality and, on the basis of this survey, appears to be one that the majority of people guiding health institutions believe can only be adequately dealt with by adapting the services to meet the challenge.

Summary and Conclusions

Study shows that both in New England and elsewhere there has been a dramatic increase in the use of hospital emergency-room facilities. The rapid growth did not take place during World War II as many believe, but between 1945 and 1955 (although the upward trend did begin during the war). This is out of proportion to the increase in the number of accidents, in population and, probably, in third-party coverage. It is believed to result from physician acceptance of the emergency room as a location preferable to his office or the patient's home for the treatment of injuries and acute illness, probably owing to the facts that he is more likely to be in or near the hospital at the time he is called and that such a facility places at his command a wide variety of services (laboratory, x-ray, operating and so forth) that he may need; public need for the facility because of increase in possibly needed services available in such a facility (if the patient needs surgery or hospitalization, or both, it is immediately available), increase in likelihood of finding a physician and of obtaining prompt attention and increase in the prevalence of hospitalization for injury or illness; public demand for the facility for the reasons given above, in addition to public acceptance of the hospital as the health center of the community; convenience (the patient need not call one to several physicians seeking aid); and third-party coverage (the importance of this may be questioned).

The study reflects an apparent change in thinking upon the part of physicians and public and suggests that physicians and hospitals should plan for the future by increasing emergency-room facilities. It is believed that this trend is dictated by the public. Plans should also be made for modernization of staffing patterns in emergency rooms. As load and complexity increase it is increasingly important that these areas be well staffed with professional personnel of adequate training and mature judgment.

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MEDICAL PROGRESS

THE PHARMACOLOGY OF MESCALINE AND D-LYSERGIC ACID DIETHYLAMIDE (LSD)*

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PHILADELPHIA

DURING the last few years a great revival of interest has occurred in the search for a biochemical basis for schizophrenia and the other types of psychosis. There are several reasons for this. Modern laboratory technics permit the detection and accurate quantitation of substances in the blood and tissues for which satisfactory procedures were not available formerly. The discovery of a partially correctable biochemical defect in one type of mental deficiency, phenylketonuria,[1] has encouraged the hope that other forms of mental disease may be explained in similar terms. Many investigators believe that the Freudian concepts, with their emphasis on the role of early environmental factors in the etiology of psychoses, have in some respects reached an impasse. Although psychoanalytical theory and methods have provided explanations for the development of schizophrenia, such explanations are not amenable to controlled testing and proof. Furthermore, the results of therapy prescribed by the same principles have been disappointing in the majority of seriously disturbed patients. The discovery of causative biochemical factors, if such factors exist, might offer a more tangible basis for both direct proof and successful treatment.

Pharmacology has recently made two important general contributions to psychiatry. In the first place, the introduction of the tranquilizing agents has pro-

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vided a means for the symptomatic treatment of many of the severe external manifestations of schizophrenia, such as excessive psychomotor activity and combativeness. There is general agreement that drugs such as reserpine and chlorpromazine do little or nothing to alter the basic defects in the psychoses. However, they permit a more satisfactory adjustment in a certain percentage of patients and are an aid in rehabilitation. The same thing can be said, with varying percentages, for many classes of unquestionably useful drugs, including the anticonvulsant, antihypertensive and antiarrhythmic agents. The development of effective "mood-elevating" agents could hold similar possibilities in the treatment of abnormal depressive states.

Perhaps of greater theoretical, and in the long range practical, importance has been the recent work with the psychotomimetic or hallucinogenic agents. It has long been known that the ingestion of mescaline and a large number of other drugs produces a temporary state resembling insanity. The finding that a synthetic compound, lysergic acid diethylamide (LSD-25, or LSD), can do so in extremely minute amounts has led to the suggestion that endogenous substances, of similar structure and activity, might be of etiologic significance in the development of spontaneous psychoses. It is, of course, at least equally possible that the effects of LSD represent a highly specific toxic psychosis that bears only a superficial resemblance to naturally occurring psychotic states. However, even if the latter explanation should prove to be correct, the study of the effects of LSD, mescaline and similarly acting drugs should increase knowledge of abnormal psychology and thereby suggest new approaches to therapy.

Several monographs and symposia[2-6] and an extensive bibliography[7] have been published on LSD, mescaline and the other hallucinogenic agents. The present discussion represents an attempt to correlate the findings of studies from several areas, and to evaluate their significance to psychiatry.

The clinical effects of most classes of drugs can be fairly well correlated with their pharmacologic actions in laboratory animals. Thus, the beneficial effects of the digitalis glycosides in congestive heart failure are similar to those obtained on the overtaxed dog heart-lung preparation. Similarly, the actions of the neuromuscular blocking agents, the so-called autonomic drugs, the general and local anesthetics and even the analgesics are all amenable to objective measurements in lower species, and by such means a considerable amount has been learned concerning their relative potencies and sites and mechanisms of action. Mescaline and LSD have so far defied any such straightforward comparison. Although they have been studied extensively, both in the clinic and in the laboratory, it must be admitted that there is still practically no direct information on how or where they act. The reason for this is obvious. The important clinical effects of these two compounds manifest themselves chiefly by interfering with the highest cerebral processes of thought, mood and interpretation. Not only is it impossible to measure such functions in animals, but also it is not even certain that their true animal counterparts exist. Over a half a century ago Heffter[8] described the peculiar behavior of dogs given mescaline; their reactions might be interpreted as indicating that the animals experienced hallucinations. However, this is perhaps an overextension of an anthropomorphic concept. To show how far the gap between the human subject and the laboratory has been bridged, these aspects of mescaline and LSD will be reviewed first, after which the possible bearing of their actions on the etiology of the psychoses will be considered.

Clinical Effects of Mescaline and LSD

Eclectic knowledge of the mescaline psychosis dates back to antiquity, for it has been used by several tribes of American Indians as a part of their religious ceremonies. This phase of its history has been covered in the classic papers of Heffter[8,9] and Lewin.[10] Recent historical reviews of mescaline and other naturally occurring hallucinogens have been presented by Osmond[11] and Fabing.[12] A most interesting subjective account of the mescaline experience is the topic of an essay by Aldous Huxley,[13] who gives a description somewhat reminiscent of that of the hypothetical "soma" of his *Brave New World.* Modern clinical studies with normal and psychotic subjects have been reported by De Jong,[14] Stockings,[15] Hoch,[16] Hoch et al.,[17] Osmond and Smythies,[18] Pennes,[19] Landis and Clausen,[20] Wikler[21] and others.

When mescaline is given to normal subjects in doses of 5.0 to 7.0 mg. per kilogram of body weight, orally or intravenously, the responses are extremely variable and in many respects appear to be conditioned by the personality of the subject and the environmental setting. Diffuse anxiety is one of the commonest and earliest symptoms. Hallucinations are frequent; they are usually visual, and ordinarily experienced only when the eyes are closed. Involvement of the other senses has been reported.[22] Subjects usually retain normal contact, orientation and insight, however, and recognize the hallucinations as such. In addition to actual hallucinations, intensification of color patterns and spatial distortion may occur. Motor abnormalities include shifting coarse tremors, which are more marked at rest, hyperactive tendon reflexes and unsustained ankle or patellar clonus. Some subjects have signs suggestive of sympathetic overactivity, including mydriasis, tachycardia and sweating. These effects are often, but not consistently, accompanied by diffuse electroencephalographic changes in the direction of desynchronization; this is not a specific effect of mescaline but results with numerous drugs or other factors that cause an increase in cortical activity.[21]

Although most of the clinical actions of LSD qualitatively resemble those of mescaline, it has been stated that the former produces a predominantly hebephrenic state, whereas during mescaline intoxication catatonic features are outstanding.[23] LSD is by far the more potent agent; it produces its characteristic effects in oral doses of 1 microgm. or less per kilogram of body weight. Since the original report of its profound psychologic effects by Stoll,[24] in which Hoffman was given credit for the initial observations, there have been numerous clinical investigations of the effects of the drug.[17,18,25-30] In the publication of Rinkel and his associates,[31] involving a controlled study of over 100 normal persons, "a syndrome simulating a moderate acute schizophrenic upheaval of the turmoil or schizoaffective type with or without catatonic features" was produced in the majority of subjects. Additional psychologic effects included various disturbances of thought processes, depersonalizations, hallucinations, abnormal perceptions, delusions, distortions, misinterpretations, disturbances of mood and affect, hostility and suspiciousness. Similar responses have been noted by the authors cited previously. They are illustrated dramatically in the reproductions of paintings and drawings done while artists were under the influence of mescaline and LSD.[32,33] The works were interpreted as demonstrating relaxation of control, some augmentation of perception of dull areas and detachment of details from unity of structure[32]; it was stated that they reflected psychopathologic changes quite similar to those seen in schizophrenia.[33] Motor effects of LSD seem in general to be less than those that follow psychologically equivalent doses of mescaline. Although subjects sense trembling, tremor is rarely seen; deep reflexes are increased consistently only at higher doses.[27] As with mescaline, there is some evidence of sympathetic overactivity, although its appearance is irregular. Objective signs of such overactivity include mydriasis and slight increases in blood pressure and pulse rate.[27,31] Other symptoms suggestive of autonomic dysfunction have been noted. However, the somatic effects are of minor importance in comparison with the profound psychologic changes.

It might be noted that studies of autonomic function in schizophrenic subjects have yielded fairly inconclusive results. Although patients show great variability, there is some delay in reaching homeostatic adjustments.[34] Thus, there is no apparent parallelism with the increased sympathetic activity frequently produced by the hallucinogenic drugs.

Numerous drugs have been reported to antagonize the clinical effects of mescaline and LSD, and results have been by no means consistent. However, both Hoch[35] and Isbell and Logan[36] found chlorpromazine to be effective, and reserpine and azacyclonol to be ineffective in this regard. The former author also reported weakening of the hallucinogenic action by amobarbital sodium and methamphetamine, alone and in combination. In a comprehensive review,[37] he has stressed the lack of parallelism between pharmacologic control of the symptoms of drug-induced and natural psychoses, as the foregoing results indicate. Of the three endogenously occurring substances that have been claimed to modify the actions of LSD—succinic, glutamic[38] and nicotinic[39] acids—the former two were not found to be significantly effective by Hoch and his associates.[37]

The repeated administration of LSD results in the rapid development of a high degree of tolerance to its hallucinogenic actions.[40-42] On the basis of this, arguments have been presented for[41] and against[42] the resemblance of LSD psychosis to those of natural origin. The situation is somewhat analogous to the question of the role of angiotonin in the etiology of natural hypertension, since tolerance develops to its hypertensive effect during prolonged administration.

The absolute effects of both mescaline and LSD are less striking in psychotic than in normal subjects.[25]

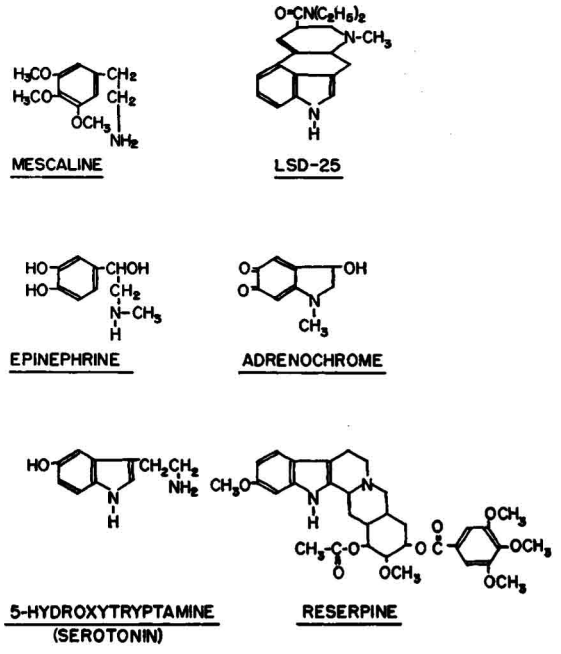

FIGURE 1. *Hallucinogens (Mescaline and LSD-25) and Compounds with Which Their Interactions Have Been Postulated.*

Both drugs produce an intensification of symptomatology in many schizophrenic patients[17]; the percentage so responding has been found to be greater with mescaline.[19]

Several investigators have reported LSD-25 to be a valuable adjunct to psychotherapy, particularly when used properly in conjunction with psychoanalysis.[43-46] Under the influence of the drug repressed material can be elicited more readily than by interview technics

alone, and the number of sessions required can frequently be materially reduced. By itself, LSD is of little or no value in the treatment of depressions,[30] and its reliability as an aid to diagnosis is doubtful.[47]

Laboratory Studies

The chemical structure of mescaline suggests that it may belong to the same pharmacologic group as epinephrine and related sympathomimetic amines (Fig. 1). Certain of its clinical effects, mentioned above, convey the same implication. However, this type of action is not borne out by laboratory investigations. Several years ago, Grace[48] found that in anesthetized cats and rabbits mescaline (10 mg. per kilogram of body weight, given intravenously) produced a fall in blood pressure, no change in heart rate and depression of respiration. After vagal sectioning, atropinization or decapitation, the effect on the blood pressure was reversed, and respiration was no longer affected. Isolated smooth, striated and cardiac muscles were unaffected by moderate concentrations of mescaline. These findings suggest that the cardiovascular and respiratory effects of the alkaloid may be due to a combination of several actions, including the initiation of reflexes by stimulation of chemoreceptors in the heart and lungs (for example, the Bezold reflex), stimulation of autonomic ganglions and actions on the central representation of the autonomic nervous system. Thus, the appearance of increased sympathetic activity in human subjects who have received mescaline is probably the result of indirect effects rather than actions on the effector organs themselves.

Laboratory investigations of LSD, which bears little structural resemblance to epinephrine, have emphasized the importance of its stimulant actions on the sympathetic centers. One of the effects that was first noted after the administration of small doses to various species was a rise in body temperature.[49,50] The initial report indicated that the pyretogenic action was not modified by adrenergic blocking agents. However, it was subsequently found that hyperthermia, as well as several other signs of increased sympathetic activity produced by LSD (hyperglycemia, mydriasis, tachycardia and piloerection), could be prevented by adrenergic or ganglionic-blocking agents, chlorpromazine and general anesthetics.[51,52] Accordingly, these effects are probably the result of a central action of LSD. Like the hallucinogenic action in human subjects, the pyretogenic effect in rabbits exhibits the development of tolerance after repeated administration.[53] The hypothalamic location of the sympathetic centers and the postulated participation of this area in emotional reactions have suggested that the sympathotonic actions of mescaline and LSD may be intimately associated with their psychotomimetic effects.

Early investigators noted that the administration of mescaline to unanesthetized animals had a variety of stimulant effects, followed by depression, and compared these observations with the subjective symptoms it produces in human subjects.[7,8,9,14,54] Because of the much greater potency, and therefore presumably higher specificity, of LSD, it has been employed in most of the modern investigations.

In the conscious cat LSD, like amphetamine, produces alerting behavior accompanied by an alert type of electroencephalographic pattern, but only the former drug abolishes the spindle activity of barbiturate anesthesia.[55] Dogs poisoned with high doses show behavioral and electroencephalographic signs of excitement, followed by depression.[56] The drug causes flattening of the spontaneous activity of the electrocorticogram and motor hyperexcitability in the guinea pig, but does not modify responses to electric stimulation.[57] Extremely small doses of both LSD and mescaline produce arousal patterns in the electroencephalogram of the rabbit, presumably by stimulation of the mesodiencephalic-activating system.[58] These findings thus tend to confirm grossly the conclusions drawn from previous observations of the effects on conscious animals and human subjects. Attempts to localize the critical sites of action of LSD that might account for its hallucinogenic effects have been so far either negative or inconclusive. After administration to cats of doses of LSD (50 to 100 microgm. per kilogram of body weight, intravenously) far in excess of the human psychotomimetic dose, Killam and Killam[59] found little or no effect on the conduction of mixed sensory impulses to the thalamus and cortex via classic afferent pathways, or on the mesodiencephalic-activating or limbic systems.

It is known that visual hallucinations can be produced by lesions at any point in the ascending-visual pathways.[60] Evarts and his associates[61] investigated the sensitivity of synapses at successive levels from the retina to the visual cortex in anesthetized cats. Transmission was selectively depressed in the lateral geniculate nucleus, where fibers from the optic nerve synapse with neurons radiating to the cortex; however, intravenous doses of 160 microgm. of LSD per kilogram of body weight were required. The transcallosal, or cortical-visual-association, pathways of the cat were found by Marrazzi and Hart[62] to be inhibited by the intracarotid injection of LSD (8 microgm. per kilogram of body weight) or mescaline (15 mg. per kilogram), but here too the doses seem quite high in consideration of the route. A more peripheral primary site of action was suggested by Apter and Pfeiffer,[63] who reported that intraperitoneal injection of LSD (100 microgm. per kilogram) or mescaline (140 mg. per kilogram) gave rise to spontaneous action potentials originating from the retina of cats. Purpura[64] has proposed a dual mechanism of action of LSD at low doses (2 to 50 microgm. per kilogram, intravenously) in cats: facilitation of transmission in specific afferent (axosomatic) pathways and inhibi-

tion in nonspecific cortical or reticulocortical (axodendritic) pathways. Further analysis has brought forth the suggestion that the latter inhibitory effect is actually the result of activation of inhibitory axodendritic synapses in the same manner, and with the same recorded effect of "cortical arousal," as results from stimulation of the recticular-activating system. It should be observed that these conclusions, although extremely important so far as possible neurohumoral mechanisms are concerned, are based to a considerable extent on indirect evidence and will require more direct verification. One of the most interesting pharmacologic actions of LSD, which has given rise to considerable speculation, is its highly potent and specific antagonism of several effects of 5-hydroxytryptamine (serotonin, enteramine, 5-HT). The first such report was that of Gaddum,[65] who noted that low concentrations of LSD abolished the spasmogenic effect of 5-HT on the isolated rat uterus. Similar antagonism was reported by Gaddum and Hameed[66] using the guinea-pig ileum and rabbit ear as test objects; they also noted that mescaline failed to block the effect of 5-HT on the rat uterus. There have been subsequent reports of relatively specific antagonism by LSD of several actions of 5-HT, including its constrictor effect on the pulmonary vessels of the cat and the hind-leg vessels of the cat and dog,[67] its bronchoconstrictor action in the cat,[68] its stimulant effect on the mollusk heart[69] and its antidiuretic action in the rat.[70] The physiologic implications of these observations will be discussed further in the following section.

Changes in the blood levels of certain substances have been noted after the administration of LSD to human subjects, but the interpretation of their significance is difficult. In the first place, oral doses as low as 0.5 microgm. per kilogram of body weight appear to stimulate the hypophyseal-adrenocortical axis, and as a result of this several changes in the blood and urinary constituents would be expected to follow.[31] Furthermore, there might then be readjustments in the rate of secretion of other endocrine glands to maintain homeostasis. It has been reported, for example, that the plasma epinephrine level undergoes a rise, followed by a fall and a secondary rise after intravenous doses of LSD in the same range.[71] Hence, it is difficult to assess whether biochemical changes that occur in vivo are due to a direct action of the drug itself or are indirect. Furthermore, in keeping with the old adage that no drug has a single action, many of the biochemical and pharmacologic effects of LSD may be completely unrelated to its hallucinogenic action.

Hoagland and his associates[72] have called attention to the similarity between schizophrenic patients and LSD-treated normal subjects in adrenocortical function and phosphate excretion. After the initial stimulation of the pituitary-cortical axis, noted above, the latter group, like the former, is relatively unresponsive to most of the effects of ACTH. Both groups excrete abnormally low amounts of phosphate, but after the injection of ACTH their urinary phosphate levels rise to much higher values than those observed after ACTH in normal subjects who have not received LSD. These findings were interpreted as indicative of a possible biochemical factor in the primary etiology of schizophrenia.

A rise in the blood level of hexosemonophosphate after the administration of psychologically effective doses of LSD to normal subjects was reported by Mayer-Gross and his associates.[73] At an extremely low concentration (4×10^{-9} M) the drug was found to stimulate respiration and to have a sparing effect on hexosemonophosphate metabolism of homogenates of brain tissue.[74] A direct relation of this action to the psychologic effects seems unlikely, however, since the effect on the blood level of the metabolite was obtained in schizophrenic patients who failed to respond psychologically, whereas psychologically effective doses of mescaline did not change the blood level in normal subjects.

Both LSD and mescaline, as well as several other drugs, were found to inhibit respiration and lactic acid formation in electrically stimulated brain slices to a greater extent than in nonstimulated slices. However, the concentrations required were extremely high compared with those that would be expected to exist in vivo after clinically effective doses.[75] The same thing can be said of the inhibitory effect reported for LSD on nonspecific cholinesterase[76] and various oxidative enzymes.[77] In a recent comprehensive review, Bain[78] concluded that none of the results published thus far indicate a specific enzymatic effect of LSD or mescaline that might account for its hallucinogenic action.

Possible Bearings on the Etiology of Mental Disease

Several reports have called attention to possible relations between the psychologic effects of mescaline and LSD and the metabolism of certain endogenous substances — namely, epinephrine, nor-epinephrine and 5-hydroxytryptamine (5-HT).

In 1952 Osmond and Smythies[18] suggested that a derivative of epinephrine might cause the characteristic mental changes of schizophrenia, on the basis of the compound's aforementioned chemical similarity to mescaline. Two years later, Hoffer, Osmond and Smythies[79] presented an account of the psychologic effects of adrenochrome, an oxidation product of epinephrine, administered to themselves and to additional subjects. They reported that the effects were quite similar to those of mescaline and LSD, and noted the presence of the indole ring in adrenochrome, LSD and certain other alkaloidal hallucinogens. These findings appeared to provide partial substantiation of

their original hypothesis, and it was postulated that an abnormal rate of production or destruction of adrenochrome might be responsible for the symptoms of schizophrenia.

Adrenochrome was first prepared and characterized in 1937 by Green and Richter,[80] who showed that it could be obtained by either chemical or enzymatic oxidation of epinephrine. Although its presence in the body has never been proved, mammals contain at least two enzymes, cytochrome oxidase and tyrosine oxidase, that are capable of producing it.[81] The compound is extremely unstable, and spontaneously passes through a series of subsequent oxidative steps, the structures of which have not been fully established, to form melanin. The quinone structure of adrenochrome allows it to act as a reversible redox system with certain enzymes[80] and is probably responsible for its inhibitory effect on others.[82] Rinkel and his associates,[31] using a stable preparation of the semicarbazone of adrenochrome, were unable to repeat the findings of the Saskatchewan group. This did not detract from the significance of the original report, since the semicarbazide would not be expected to influence enzymatic reactions in the same manner as adrenochrome, and might likewise be devoid of its pharmacologic or psychologic effects. However, subsequent attempts by Osmond and his associates[11] and by other groups to repeat the original observations have been unsuccessful, possibly because of the instability of adrenochrome and its spontaneously formed derivatives. Accordingly, the hypothesis that psychosis is the result of an abnormality in the metabolism of epinephrine is at present no more than conjectural. Minute amounts of both fresh and old solutions of adrenochrome, like LSD, were found by Witt[83] to have distinctive effects on the web-spinning activity of spiders.

The suggestion that 5-HT is involved in the psychotomimetic action of LSD stems largely from the work of Gaddum, described in the previous section, and Woolley and Shaw.[84] This compound was first isolated from beef plasma and identified chemically by Rapport and his associates,[85] who used the designation serotonin. Independently, Erspamer and Asero[86] showed it to be identical with the substance found in the enterochromaffin cells of the gastrointestinal mucosa, which they had called enteramine. Page[87] and Erspamer[70] have reviewed its distribution, actions and possible physiologic roles, and Gaddum[88] has discussed its metabolic synthesis, degradation and interactions with LSD. In the brain, the distribution of 5-HT is very similar to that of nor-epinephrine; both compounds are present in highest concentration in the hypothalamus, where the autonomic centers are located, and in the non-neuronal area postrema.[89,90] The hypothalamus also contains relatively high concentrations of the enzymes involved in the synthesis and destruction of 5-HT.[88]

The common presence of the indole moiety in the structures of LSD and 5-HT, the identification of the latter in the brain, and its specific antagonism by LSD at various peripheral sites led Gaddum[65,91] to postulate that LSD might have its mental effects by interference with a normal cerebral function of 5-HT. From their independent studies, Woolley and Shaw[84] presented much the same hypothesis: that LSD and several alkaloids containing the indole ring might act as antimetabolites to 5-HT. They had shown that these compounds antagonize the action of 5-HT on arterial walls, and deduced a similar effect on the brain. It was suggested that certain forms of mental disorders might be due to a metabolically induced 5-HT deficiency, and that stable derivatives, capable of penetrating the blood-brain barrier, should be synthesized and tested therapeutically.

Further evidence along these lines was offered by Brodie's laboratory at the National Heart Institute.[92-94] Reserpine, a tranquilizing agent that also contains the indole ring, and 5-HT were both found to potentiate the hypnotic effects of hexobarbital in mice. The potentiating effect of each agent was antagonized by LSD, suggesting that the two had some common mechanism of action. When the urinary output of 5-hydroxyindoleacetic acid, a major metabolite of 5-HT, was followed in dogs, it was found to be markedly increased after the administration of reserpine. It was then shown that reserpine produces a marked fall in the 5-HT content of the brain and intestinal tract of rabbits. Although detectable reserpine disappeared from the brain after a few hours, several days were required for restoration of the normal 5-HT content. The duration of the decreased central 5-HT activity paralleled that of the sedative action of the drug. It was demonstrated subsequently that the other sedative alkaloids of the Rauwolfia group produce the same type of 5-HT depletion, whereas the nonsedative Rauwolfia alkaloids do not.[95] From these findings it was deduced that reserpine and its active analogues bring about tranquilization, hypotension and their other pharmacologic effects through interference with cellular binding of 5-HT. As a working hypothesis, Brodie and Shore[96] have proposed that the hypothalamic parasympathetic centers are activated by 5-HT-liberating, or "serotoninergic," nerves, and the sympathetic centers by nor-epinephrine-liberating, or adrenergic, nerves. Dominance of the former centers is suggested to cause sedation or tranquilization, and that of the latter wakefulness or activation. Reserpine, by preventing 5-HT binding in the serotoninergic fibers, would thus cause constant activation of the parasympathetic centers, resulting in signs of parasympathetic hypertonia and sedation. Chlorpromazine, the other potent tranquilizing agent, would bring about the same end results through the opposite mechanism: blockade of adrenergic impulses to the sympathetic and arousal centers. LSD, on the other hand, might block the effects of 5-HT on the parasympathetic

center, thus causing sympathetic dominance and arousal.

Attractive as the foregoing hypothesis seems, its acceptance has been complicated by some recent reports.[88,97] A close analogue of LSD, 2-bromo-D-lysergic acid diethylamide (Brom LSD), was found by Cerletti and Rothlin[98] to be just as effective as LSD in antagonizing several peripheral actions of 5-HT, and its potentiating effect on hexobarbital sleeping time in mice. However, Brom LSD appears to be devoid of hallucinogenic or psychotomimetic action in human subjects.[97,99] On the basis of these and some additional observations, Taeschler[100] has suggested that the central actions of LSD are due principally to sympathetic stimulation rather than to 5-HT-antagonism. It is, of course, possible that the bromoanalogue is preferentially excluded by the human blood-brain barrier, or that some other species factor, or organ-specific factor, can explain its lack of hallucinogenic activity. Nevertheless, the strength of the hypothesis stated above is weakened pending an adequate explanation. It has also been shown that reserpine brings about the liberation not only of 5-HT but also of nor-epinephrine from the brain.[101] The time courses for the restoration of the two substances to normal levels are practically identical.[102] This, of course, raises the questions of whether some heretofore unidentified substances might also be released, and whether their interactions with LSD might be more intimately associated with its pharmacologic effects. It is obvious that much work remains to be done in this field.

The number of gaps in present information concerning the sites and mechanisms of action of mescaline and LSD should be neither surprising nor discouraging. As Kety[103] has pointed out recently, alcohol and the barbiturates have been the subjects of intensive study for several decades, and there is still little understanding of their modes of action. In the space of a few years, investigations of LSD, and renewed studies on mescaline, have stimulated the development of important new concepts in neurochemistry, pharmacology and psychiatry. Some of these may provide essential clues to the discovery of the role of biochemical factors in the etiology of the psychoses.

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