greater importance since they can be studied by others in a similar frame of reference.

Various studies have suggested that mescaline and lysergic acid diethylamide have therapeutic possibilities, both in the neuroses and psychoses, although this point of view is disputed by some. Additional work is needed to carefully define the parameters within which this therapeutic activity takes place.

It was with the hope of stimulating further thinking and research in this fascinating field that a Round Table was organized at the 1956 Annual Meeting of the American Psychiatric Association in Chicago. All of the participants had done considerable work, either in the laboratory, on the wards, or in private practice.

As more and more knowledge is accumulated from chemistry, anatomy, physiology, genetics, psychodynamics and sociology, it will be possible to develop an integrated and scientific theory of human behavior. Experimental psychiatry offers the tools to further explore some of these intricate problems.

THE EDITORS

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PHARMACODYNAMICS OF LSD AND MESCALINE

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LSD ("Delysid") and mescaline are alkaloids which occur in plants but have now been synthesized, and are used for experimental and therapeutic purposes. LSD is derived from the ergot fungus which grows on rye; mescaline is present in the cactus peyotle. Chemically, LSD is the diethylamide of d-lysergic acid, and mescaline is a trimethoxy-phenyl-ethanolamine. LSD (50 micrograms) and mescaline (500,000 micrograms) have in common that they produce mental alterations of a psychotic-like nature and, therefore, have been used as tools in experimental psychiatry. The mescaline effects have been described by many authors. Aldous Huxley gave a most impressive account on the basis of self-experiments (1). The mental effects of LSD were discovered by Hofmann. They were confirmed and systematically explored by Stoll (2) who, in 1947, published a comprehensive report on "lysergic acid diethylamide, a phantasticum of the ergot alkaloids." Since then, a number of papers have been published confirming the original observations of both Hofmann and Stoll.

LSD was first studied in this country at the Boston Psychopathic Hospital in 1949. A preliminary report of our experiments was presented at the annual meeting of the American Psychiatric Association in 1950 (3) The psychotic phenomena caused by LSD are similar to those of mescaline. They are characterized by a schizophrenic-like turmoil state of short duration, associated with delusions, hallucinations, illusions, changes in mood, feelings of depersonalization. and catatonic signs. The neurophysiological and biochemical actions of these chemicals were correlated with their mental effects. This led to a chemical concept of psychosis and various chemophysiologic theories about the nature and origin of mental illness. This study is confined to reporting some pertinent pharmacodynamic observations and theories which tend to explain the "psychosomimetic" action of these drugs.

Much information about these drugs has been obtained from studies with radioactive mescaline and LSD. Mescaline, made radioactive by introducing a C^{14} isotope into the side chain of the molecule, was injected into mice. Block *et al.* (4–5), of the Max-Planck Institute, Marburg, Germany, determined the distribution of the radioactive mescaline in the organism. They reported that it is diffused in all tissues; the brain showed the lowest concentration, while the greatest accumulation was found, e.g., in the liver and kidneys. Mescaline had disappeared from the brain after 30 minutes, which in man is the time that the first mental phenomena occur. Further chemical research by these authors provided evidence that mescaline was transformed, within the liver, into a new protein bound chemical. The authors believe this new chemical compound to be the agent causing the mental phenomena commonly ascribed to mescaline. Patzig and Block (6) then speculated that a

similar process may be operative in the origination of an otherwise gene-bound psychosis.

Experiments to study the distribution and metabolism of LSD were undertaken with a compound which had been made radioactive by introducing a C^{14} isotope into the side chain of the LSD molecule. Stoll *et al.* (7) used mice in these experiments, and Hodge *et al.* injected the radioactive LSD into rats. Both research groups worked independently and reported similar observations (7–8). The smallest concentrations of radioactive LSD were found in the brain, and the largest accumulations in the liver, intestines, and kidneys. The resemblance of this distribution to that of mescaline is striking.

The action of LSD and mescaline upon the nervous system has been reported in many publications. At the Boston Psychopathic Hospital, we studied the effects of LSD in human beings, observing that the very first symptoms which follow its administration involved the Autonomic Nervous System. Clinical and pharmacological examinations of the Autonomic Nervous System yielded the following observations: Increased dilatation of the pupils, rise in blood pressure, acceleration but greater stability of heart beat, increased respiration and other sympathetic phenomena. From these and similar observations (9–16), it was theorized that LSD may interfere with the normal metabolism of the adrenal cycle leading to the production of a noxious adrenaline metabolite which, in turn, may cause the mental phenomena. This concept was then enlarged to include psychosis in general. It was speculated that in the origination of psychosis a similar process may take place, i.e., an endogenous, possibly gene-bound disturbance within the adrenaline cycle resulting in the occurrence of a noxious, psychotogenic, metabolite of adrenaline. Osmond and Smythies (17) in England arrived at a similar concept for the action of mescaline on the basis of the molecular similarity between mescaline and adrenaline. They postulated the presence of a substance "M" in psychotic patients as the cause of psychosis. In the search for the substance "M", they came upon adrenochrome and, with Hoffer in Canada, described mental disturbances following the administration of adrenochrome to a few volunteers (18). Experiments in this country with adrenochrome, prepared by the Research Laboratory of Eli Lilly, were done independently at the Boston Psychopathic Hospital, at the Psychiatric Institute in New York, under Paul Hoch (19), and at Emory University School of Medicine, Atlanta, Georgia, by Carl Pfeiffer (20). According to personal communications from these authors, the intravenous administration of the Eli Lilly adrenochrome to humans was not followed by any particular mental alterations (19–20). This was also true with our own experiments. In the light of these studies, the question is still unanswered regarding the role of the adrenaline metabolite, adrenochrome, in the origin of experimental or natural psychosis. Further research will be needed and may include the investigation of adrenoxine obtained when adrenaline is enzymatically oxidized beyond the adrenochrome level. It was first described by Heirman (21–23) in France, and seems to have similar physiological effects upon the autonomic nervous system as were described with LSD administration.

Another chemical theory of psychosis is based upon the presence of serotonin in the brain. Serotonin (5-hydroxytryptamine) was shown by Page (24) and Gaddum (25) to be normally present in the brain. This discovery led to the speculation that it may be of importance in the maintenance of normal mental function. Woolley and Shaw (26–28) found that a variety of compounds which cause hallucinations and other central effects were anti-metabolites of 5-hydroxy tryptamine, i.e., structural analogues of serotonin which function as specific and reversible antagonists of serotonin on smooth muscles. Such compounds are the ergot alkaloids (of which LSD is hallucinogenic), some of the harmala alkaloids (notably harmine, yohimbin) and its derivatives such as reserpine, and synthetic analogues of serotonin, such as medmain and 2-methyl-3-ethyl-5-nitroindole. The anti-metabolites cause a deficiency of the hormone serotonin in the classical manner of anti-metabolites by competition for the same cell receptors. On the basis of these and other pertinent observations, especially on human and rat oligodendroglial cells of the brain which were cultured *in vitro*, the authors theorized that interference with the serotonin of the brain would result in

abnormal mental phenomena. Either raising or lowering of the functioning concentration seems to cause profound disturbance. Woolley (28) recently presented "evidence for the participation of serotonin in mental processes." The serotonin theory of Woolley and Shaw (26) was challenged by Cerletti and Rothlin (29) on the basis of the observation that 2-brom-d-lysergic acid diethylamide (BOL 148) *in vitro* is as powerful an antagonist of serotonin as LSD and, at the same time, does not cause mental changes in humans. The latter, therefore, expressed the opinion that one is "not justified in assuming a causal relationship between the psychic effects of lysergic acid diethylamide and its anti-5-hydroxytryptamine property" at the present time.

A chemophysiological theory for the action of LSD and mescaline was proposed by Marrazzi (30–31). He investigated the effects of mescaline, LSD, adrenaline, nor-adrenaline, serotonin and others upon transcallosal monosynaptic transmission, and demonstrated that these substances caused inhibition of synaptic transmission. He theorized that "synaptic inhibition could readily result in release from normal restraining influences with consequent stimulation," and speculated that hallucinations may represent a stimulatory phenomena. From the study of the effects of adrenaline and structurally related compounds, he further concluded that a disturbance of adrenergic or related cerebral neurohumoral mechanisms appears to be implicated in the action of mescaline and LSD.

In summarizing the various observations, theories, speculations and opinions on the action of LSD and mescaline, the fact seems to emerge that neither drug acts directly but by the mediation of or interference with other chemicals (adrenaline metabolites, 5-hydroxytryptamine), or by causing inhibition of synaptic transmission in the brain.

As can be seen, the psychosomimetic drugs, LSD and mescaline, were originally used as tools for research in experimental psychiatry. Their use for therapeutic purposes was only recently investigated, independently, at about the same time in Germany, England, and in this country. Frederking (32–33) in Germany reported that LSD as well as mescaline could be used successfully in psychotherapy. Similar reports on LSD were published by Sandison *et al.* (34) in England. In this country, Denber and Merlis (35–39) concentrated especially on the therapeutic use of mescaline, and Abramson (40) on that of LSD.

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BIOLOGICAL CHANGES IN MAN FOLLOWING INTRAVENOUS ADMINISTRATION OF MESCALINE

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This report concerns a research investigation carried out under the supervision of Professor Jean Delay, in collaboration with Drs. M. Raclot, J. Thuillier, and M. Ropert. Its main purpose was to study the biological reactions to intravenous mescaline, of which little is known. Renewal of interest during the last few years in the hallucinogens, or "psychosomimetic" compounds, has been concerned particularly with the psychological aspects. Mescaline and LSD have been used experimentally to create psychopathological states comparable to some psychotic disturbances. The ability of various substances to reverse these states has confirmed, in addition, the therapeutic effectiveness of chlorpromazine. "Psychosomimetic" compounds have been used therapeutically as an aid in accelerating psychoanalytic therapy.

It was felt useful to determine if mescaline, besides its specific psychodynamic properties, could bring about any biological reactions similar to those described in connection with shock or stress reactions. This would be of importance in the interpretation of various therapeutic results.

Heffter (1), who isolated the drug in 1894, initiated biological research with mescaline.