PSYCHOTOMIMETIC AGENTS[1,2,3,4]

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The pharmacology of the psychotomimetics is, at present, extensive and somewhat confusing. No well-supported explanation of the action of these drugs (also called hallucinogens, psychedelics, fantastica) exists, although many have been proposed. It is evident that no simple, single effect will be found to explain all of the complex changes that are observed.

The hallucinogens are principally of plant origin although whole series of synthetic chemicals have also been developed. In man, they are capable of producing marked changes in perception, emotion, ego function, and thought. They are differentiated from the deliriants in that, ordinarily, little clouding of consciousness occurs. That some overlap exists is demonstrated by the anticholinergic psychotomimetics which seem to occupy an intermediate position between the two categories of drugs.

The hallucinatory agents can be classified according to their chemical structure. Only the more common ones will be dealt with here (see Fig. 1).

Classification.

I. Substituted indole alkylamines

1. D-Lysergic acid dimethylamide (LSD). Synthesized from lysergic acid in the fungus ergot (*Claviceps purpurea*). A series of lysergic acid compounds are known, some of which are hallucinogenic, for example, D,L-acetyl LSD (ALD) and D,L-methyl LSD (MLD).
2. Lysergic acid amide and isolysergic acid amide. Weak hallucinogens found in species of the American tropical morning glory (*Ipomoea violacea*, *Rivea corymbosa*).
3. Dimethyltryptamine (MDT). Found in cohaba snuff from the seeds of *Piptadenia peregrina*.
4. Diethyltryptamine (DET). Synthetic.
5. 6-Hydroxydimethyltryptamine. May be the active form of DMT *in vivo*.
6. Bufotenine (dimethyl-5-hydroxytryptamine). Found in cohaba snuff, the skin and parotid gland of the toad (*Bufo marinus*), and in small amounts in the fly agaric mushroom (*Amanita muscarina*).

[1] The survey of the literature pertaining to this review was concluded in July 1966.

[2] The following abbreviations will be used: LSD (D-lysergic acid dimethylamide); DMT (dimethyltryptamine); DET (diethyltryptamine); BOL (bromine-labeled brom D-lysergic acid dimethylamide).

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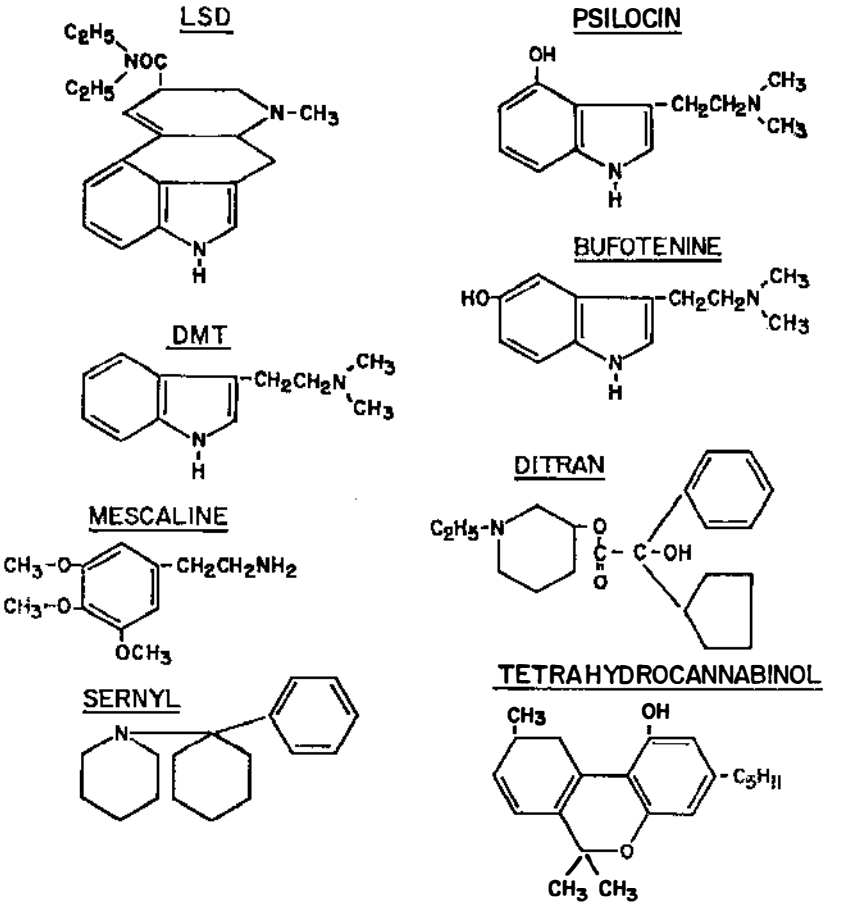

FIG. 1. Formulas of representative psychotomimetic agents.

7. Psilocybin (dimethyl-4-phosphoryltryptamine). Found in *Psilocybe mexicana* Heim and related mushrooms.
8. Psilocin (dimethyl-4-hydroxytryptamine). Found in *Psilocybe mexicana* Heim and other *Psilocybe* species.
9. Ibogaine. Found in the bean and root of *Tabernanthe iboga.*
10. Harmine. Also called telepathine and yageine from *yagé, caapi,* and *ayahuasca* in South America. It is found in the seeds of *Peganum harmala* and in the stems of *Banisteria caapi.*

II. Substituted phenyl alkylamines

1. Mescaline (3,4,5-trimethoxyphenylethylamine). Found in the buttons of the peyote cactus (*Lophophora Williamsii*).

III. Miscellaneous

1. Tetrahydrocannabinol. Found in the resin, flowering tops, and leaves of *Cannabis sativa var. indica*. A non-nitrogenous hallucinogen from hashish (also marihuana, kef, gangha, etc.).
2. Ditran and its analogues. A synthetic mixture of N-ethyl-3-piperidylphenylcyclopentyl glycolate and N-ethyl-2-pyrrolidylmethylphenylcyclopentyl glycolate.
3. Sernyl and its analogues. 1-(1-Phenylcyclohexyl)piperidine, a synthetic.

Although the biochemistry of psychosis will not be discussed, the close chemical relationships between the hallucinogens and the naturally occurring central nervous system neurohumors must be mentioned. Dimethylation of tryptamine yields DMT. Bufotenine is dimethylated serotonin. S-adenosylmethioninemethyl was identified by Axelrod (1) in rabbit lung as one enzyme capable of N-methylating tryptamine to DMT and serotonin to bufotenine. Szara (2) has found a 6-hydroxylase in rabbit liver microsomes, which acts on alkylated tryptamines and enhances the psychotomimetic activity of DMT, DET, and dipropyltryptamine. In man, 6-hydroxylation is not a major pathway of tryptamine and serotonin metabolism, but it might be an alternate one under certain metabolic conditions. Psilocin is an analogue of 6-hydroxy-DMT. Another possible pathway of endogenous psychotomimetic activity is via the skin-lightening hormone melatonin. Clinical observations of the dark complexion of many schizophrenics and of chlorpromazine-induced melanosis may have bearing on this speculation. Melatonin is O-methyl-N-acetylserotonin and is produced in the pineal gland. It may be metabolized to 10-methoxyharmalan which is related structurally and behaviorally to harmine.

Mescaline is a trimethoxylated DOPAmine (dihydroxyphenylethylamine). Friedhoff & Van Winkle (3) have isolated 3,4-dimethoxyphenylethylamine in the urine of schizophrenics. O-methylation with methionine as the methyl donor could be the mechanism of formation. Methionine has been known to worsen the schizophrenic syndrome (4). Friedhoff's compound can be synthesized from the livers of schizophrenics but not from those of nonschizophrenics. The compound produces behavioral changes similar to mescaline in animals but none in man. Recently, Hoffer (5) has brought his adrenochrome hypothesis up-to-date. In Giarman & Freedman's review (6), the correlations between the neurohumors and the psychotogens are well depicted.

LSD

This review will focus on LSD since it has been the hallucinogen most extensively investigated, and since its mechanisms of action seem to be similar to the other indole and phenyl alkylamines.

In 1938 Hofmann (7) synthesized D-lysergic acid diethylamide tartrate, and in 1943 he accidentally discovered its psychotomimetic effects. The compound was prepared in the hope that it might be an analeptic because of the

close structural relationship between nikethamide and the D ring of LSD. Of all the stereoisomers and the substitutions in the ring and amide system that have been prepared, LSD remains the most potent from a psychotogenic point of reference. L-LSD and D-iso-LSD have no psychic activity whatsoever.

Metabolism.—LSD is readily absorbed from the gastrointestinal tract and diffuses into all tissues. The brain does not achieve higher concentrations than other organs [Rothlin (8)]. It is detectable in the cerebrospinal fluid shortly after its appearance in the central nervous system. Very small amounts (less than 3 ng/ml) in the brain produce intense psychic changes. Earlier radioactive studies in mice demonstrated that labeled LSD disappeared from the brain and blood within an hour. The half-life for mice was less than ten minutes. This led to a theory that it acted as a trigger for a sequence of aberrant neurochemical reactions. The mouse data cannot be extrapolated to human excretion of the substance. In monkeys, LSD has a half-life of 100 minutes and in cats, 130 minutes. Recent spectrophotofluorometric measurements on samples of huma plasman resulted in a calculated half-life of 175 minutes (9). One half hour after the intravenous injection of 2 μg/kg, plasma levels reach 7 ng/ml. For the next eight hours plasma levels declined, paralleling the improvement in performance test scores. At this time 2 ng/ml were still detectable in the plasma. According to Kalbhen & Sargent (10), bromine-labeled brom LSD (BOL), a nonhallucinatory analogue, accumulates in the liver and lower abdomen and over 90 per cent is eventually excreted by the kidneys over many days. LSD was also concentrated in the liver and intestines in the mouse scan studies. It seems unnecessary to invoke the trigger mechanism to explain the action of LSD in view of the recent reports.

Depending on the dosage and the sensitivity of the individual, oral administration will produce effects in 20 to 80 minutes. The intramuscular route results in a delay of about 10 minutes. Intravenous administration decreases the delay to a few minutes and intraspinal injection is followed by an almost instantaneous effect. As little as 0.3 μg/kg of LSD is subjectively detectable in man, and 1–2 μg/kg produces intense effects for 6 to 12 hours. Single oral doses of 30 μg/kg evoke a maximally intense depersonalization and derealization experience lasting up to 24 hours. Even higher individual doses have been claimed (4000 μg!) but this was questionable material obtained from black market sources in a partially tolerant individual. Tolerance to the autonomic and psychologic effects is very rapidly acquired in man. It is also lost within days. No withdrawal syndrome following abrupt discontinuance of the drug has been described.

Cross tolerance between LSD, its hallucinogenic congeners, mescaline, psilocin, and bufotenine has been demonstrated. BOL, which has no psychotomimetic activity, blocks the LSD state if administered in sufficient amounts prior to LSD ingestion. The anticholinergic hallucinogens, Ditran, for example, do not show a cross tolerance to LSD, indicating that they may

act over different pathways. The LSD state can be aborted by parenteral barbiturates or chlorpromazine. Succinate, nicotinic acid, and glucose have also been reported to reverse the LSD condition. Amphetamines and other stimulants will prolong or intensify the effect of the drug.

Schizophrenic patients are generally less responsive to LSD than normal subjects. Whether this represents an enhanced capacity to metabolize the drug, or whether it is a part of the schizophrenic's overall refractory state to most chemicals, is unknown.

The rabbit is sensitive to LSD, the LD_{50} being 0.3 mg/kg intravenously. It also develops tolerance to the drug; the rat does not. For the rat and mouse, the LD_{50} is 16 and 46 mg/kg, respectively (11). Rat brains examined after the animals had received 1 mg/kg showed no changes in acute experiments. When 25 mg/kg was given, the cerebral cortical neurons revealed vacuolization of nuclei, depletion and fragmentation of Nissl substance, rarefaction and degeneration (12). Hoffer estimated an LD_{50} for man at 14 mg. A student survived an accidental dose of 10 mg or more without permanent ill effects. He was amnesic and hallucinated for seven hours after which he quickly recovered (L. Eltherington, personal communication). We have no information on the histologic effects of long-term usage of LSD in human beings.

Axelrod et al. (13) found that guinea pig liver microsomes produced 2-oxy-LSD, an inactive metabolite. Szara (14) extracted a 13-hydroxy-LSD as well as its glucuronides from rat liver microsomes.

A differential concentration within the brain of the squirrel monkey was noted by Snyder & Revich (15). Twenty minutes after intravenous injection, the blood, the cerebral cortex, the cerebellum, the white matter, and the brain stem all had approximately similar concentrations. The extrapyramidal system and the thalamus had 1.5 times as much, the limbic system and the hypothalamus 2 to 3 times as much, the auditory and visual reflex areas 2 to 5 times as much, the posterior pituitary and pineal gland 5 to 7 times as much, and the anterior pituitary 10 times as much. These spectrofluorophotometric results were approximately comparable to those obtained with ^{14}C-labeled LSD using an autoradiographic technique. The finding of a variable concentration within the brain substance may help explain some of the psychological phenomena. Inhibition of synaptic transmission in the lateral geniculate body (a visual reflex area) is known to occur. In human subjects with subcortically implanted electrodes, LSD induced paroxysmal EEG activation of the limbic system. Subcortical visual centers are presumably involved in visual misperceptions, the limbic system with emotionality, the hypothalamus with the autonomic elaboration of emotion, and the anterior pituitary with the stress response.

The original proposal of Woolley & Shaw (16) that the hallucinogenic action of LSD was due to its serotonin antagonism was refuted by the demonstration that the nonhallucinogenic BOL is an even stronger serotonin antagonist and crosses the blood-brain barrier (17). Marchbanks et al. (18)

have pointed out that LSD enhances the binding of serotonin to neuronal macromolecules and that BOL does not. Freedman (19) reported that LSD increases serotonin levels and the increase was in the bound fraction. At the same time, brain levels of norepinephrine were decreased. The alterations coincide with the electroencephalographic, autonomic, and behavioral effects in the rat. After serotonin depletion with reserpine, LSD stimulated repletion. Siva Sankar (20) confirmed the binding of serotonin and also reported a drop in 5-hydroxyindole acetic acid, its urinary metabolite, in LSD-treated rats. Both brain norepinephrine and histamine levels declined and their binding was impaired.

LSD inhibits pseudocholinesterase, brain acetylcholinesterase, and amine oxidase. Pretreatment with an amine oxidase inhibitor which elevates biogenic amine levels will attenuate the LSD state in human beings (21). Elevating serotonin levels by administering the precursor, 5-hydroxytryptophan, will also reduce the effect of LSD. Pretreatment with reserpine which depletes the brain of biogenic amines, including serotonin, was found [Resnick et al. (22)] to intensify LSD symptomatology. Some of the LSD-serotonin interactions seem conflicting. It must be remembered that the relative concentration of these substances determines the final response. The well-established antagonism between LSD and serotonin on uterine muscle can be changed to facilitation by lowering the concentration of LSD [Costa (23)].

The impact of LSD on enzyme systems varies according to the dose, the animal, and the part of the brain to be measured. Siva Sankar & Bender (24) state that LSD increases oxidation of glucose in cerebral homogenates but reduces it in cerebellar tissues. Glutamic acid decarboxylase is activated by LSD in the cerebrum but inhibited in the cerebellum. Citrate, succinate, and γ-aminobutyric acid oxidation are increased in both brain fractions. Glycogen phosphorylase levels of rat brain treated with LSD and other hallucinogens tended to be depressed. BOL and tranquilizers increased the concentration of the enzyme (25).

Physiological and behavioral effects.—LSD induces pupillary dilation, pilo-erection, salivation, lacrimation, tachycardia, and hyperglycemia in most species. Of these, mydriasis is most prominent and constant. Most animals will also manifest a rise in body temperature. The rabbit is particularly sensitive, doses of LSD as low as 0.5–1.0 μg/kg will produce hyperpyrexia. Hyperreflexia, restlessness, and some degree of peripheral vasoconstriction may develop. The head shaking movements of mice can persist for many weeks after a single LSD exposure. Rats ordinarily demonstrate head shaking, motor hyperactivity, crawling movements, and later, inactivity. Rats trained in rope climbing have a dose-related prolongation of the time required to accomplish the task. Monkeys manifest ataxia, spatial disorientation, and tameness. Sympathomimetic effects predominate in the LSD-treated animal.

Much evidence of nonspecific stress can be encountered in the LSD-treated organism. Leukocytosis, eosinopenia, slight elevation of 17-keto-

steroids, and a moderate elevation of 17-hydroxycorticoids have been recorded. It is well confirmed that urinary phosphate excretion is diminished. Plasma-free fatty acids are increased.

In man, the most obvious autonomic effect is dilation of the pupils up to 5 mm. They react weakly to light. Hyperreflexia, nausea, rarely vomiting, tremor, gooseflesh, numbness, muscular weakness, and hyperthermia may be detected. In ordinary amounts, vasoconstriction and uterine contraction is minimal. There is no evident change in cerebral blood flow, cerebrovascular resistance, or oxygen and glucose utilization.

Beernink et al. (26) confirmed the increase in rhythmical activity of the liver fluke in an LSD solution. In addition, he demonstrated a good correlation between hallucinogenic activity and liver fluke motility in a series of LSD derivatives. Under LSD, the green sunfish is more aggressive than in the control state (27). Siamese fighting fish assume a nose up, tail down position in solutions of LSD (28). Goats given LSD showed stereotyped, fixed walking patterns (29).

A dose of 297 mg (0.1 mg/kg) was placed intramuscularly into a male elephant by West & Pierce (20). This was done to determine whether the LSD effects would resemble musth, a periodic form of deranged behavior, which is accompanied by temporal gland secretion. The animal died within two hours from laryngospasm and status epilepticus.

In an electrographic study of LSD and nine of its analogues in rabbits, sustained arousal patterns were obtained in those that had an hallucinogenic effect. The locus of EEG action for LSD, as demonstrated by transections, was the lower brain stem level. This site corresponds to the recticular formation (31). This confirms earlier work by Purpura (32).

Transcallosal synaptic inhibition by LSD and other psychotogens has been demonstrated in cats, dogs, and monkeys by Tanaka & Marrazzi (33) and by Marrazzi (34). He also noted an inhibition release effect on visual tract nerves. Pretreatment with chlorpromazine abolished the inhibition. The depression of photic-evoked responses has been demonstrated, again in rats (35).

LSD generally interfered with sleep in cats and reduced the EEG signs of dreaming sleep. On the days following drug administration, a marked increase in dream sleep occurred [Hobson (36)]. In man, small amounts of LSD produced an increase of dreaming sleep, especially during the first dream periods of the sleep cycle. Using a dose of 300 μg, Green (37) also found an increase in dream time during the two nights following LSD after an initial delay in the onset of dreaming.

During the LSD state, the surface EEG in human beings is diminished in amplitude and is of the low voltage, fast type. Desynchrony is noted. Energy content decreases, as does variability. Alpha rhythm tends to disappear. The rhythmic after-discharge of photic-evoked potentials is also lost (38). The quantified EEG's of schizophrenics and of controls given LSD both show a state of sustained excitation. Whereas LSD decreases the variability of the

record in normal subjects, it increases the variability of schizophrenic tracings. These are known to be less variable under nondrug conditions. Quiescent schizophrenics with implanted deep electrodes sustained both an exacerbation of their psychosis and paroxysmal hippocampal, amygdaloid, and septal activity under LSD (39).

LSD and other hallucinogens given to trained, hungry rats blocked the conditional response to food but not to shock (40). This finding is opposite to the approach-avoidance behavior in animals given tranquilizers. In a similarly designed situation, varying the dose of LSD revealed that small doses increased bar pressing for food while large amounts decreased it. Bar pressing to avoid shock was decreased at the lowest dosages but increased in higher doses (41). In general, the experimental animal under a psychotogen will require a longer time to extinguish a conditioned reflex. This is also the case with 3,4-dimethoxyphenylethylamine, the nonhallucinogenic compound found in some schizophrenics' urines. Schizophrenic patients tend to persist in their conditioned response longer than nonschizophrenics after the behavior is no longer rewarded.

A partial cycloplegia is produced by average amounts of LSD. This may be a function of the sympathetic dominance. The ciliary muscles and iris were found to contain much higher than average concentrations of the drug. When given to blind subjects, the congenitally blind did not report color or formed visual hallucinatory experiences. Of 20 subjects who once had sight, 13 reported visual phenomena under the drug. Hallucinatory auditory, tactile, and gustatory experiences were reported more frequently in this group than in other studies when nonblind subjects were tested [Krill et al. (42)].

All types of reaction time were prolonged by 125 μg given normal subjects (43). Visual, auditory, and heat thresholds were elevated. Two-point discrimination was performed more poorly under the LSD condition.

Kast (44) found that 100 μg of LSD gave more prolonged and complete relief of pain than 100 mg of meperidine or 2 mg of hydromorphone in terminal cancer patients. Holliday (45), using D-lysergic acid morpholide, found that her subjects could tolerate more intense heat focused on the forehead than they could under placebo conditions.

Performance tests are almost invariably impaired under LSD. Psychomotor skills, learning, perceptual function, verbal fluency, abstracting capacity, and intelligence are routinely worsened. Whether these results are due to an attenuation of attention and motivation, or whether the sensory-cognitive alterations interfere with performance is not clear. It is likely that the impairment involves a variety of contributing factors.

Psychic and psychotherapeutic effects.—The psychological effects in man are numerous and diverse. They depend, not only upon the dose and the personality of the subject, but upon many other variables. All psychotropic drugs vary in their activity according to nonspecific factors, but the psychotomimetics are particularly influenced by them. The setting in which LSD is

given has a potent influence. It is for this reason that the earlier investigators invariably elicited a "model psychosis." The subject was brought into a strange laboratory setting where unexplained procedures were periodically performed. Furthermore, the investigators expected him to become psychotic. This points up a second variable, the set, or expectation of the observer and of the subject. If the drug is taken with the implied or explicit idea that a transcendental state will ensue, a good liklihood exists that it will. The LSD state is a hypersuggestible one, the rational, critical function of the ego is set aside and one's own "programming" or the investigator's can influence the nature of the response enormously. That LSD and mescaline in average amounts enhance primary suggestibility comparable to the induction of hypnosis has been demonstrated by Sjoberg & Hollister (46). These authors also confirmed the increase in trance phenomena while the drugs were acting. It is on the basis of increased susceptibility to environmental cues that setting and set effects can be explained.

The perceptual alterations are most notable. The first subjective effect may be a colorful mobile display of patterns slanting past one's closed eyes. Later, distinct and complex forms may be fantasied. With eyes open, the color of objects becomes more intense and saturated. The after-image is noticeably prolonged. Flat surfaces assume a depth, fixed objects undulate and flow. Illusions are common, a spot on a wall may be mistaken for a face. Pseudohallucinations, images seen for which no external cue is evident, are apprehended as "not really there" by the subject. True hallucinations are infrequent at ordinary dosages. These are images projected onto the environment which are actually believed to be real. Auditory hallucinations are rare, however, the amplification of background noise is often described and some subjects seem to have hyperacusis. Touch may be more sensitive, and alterations of taste and odor are known, but these are minimal in comparison to the visual changes. Synesthesia, the overflow from one sense modality to another, is a common manifestation of the state. Colors are heard or music becomes palpable. A crossing over of what is emotionally felt with what is perceived or thought can be detected so that a fusion of percept, concept, and affect becomes apparent. Subjective time is seriously altered. Internal time may "stand still." Subjects are almost invariably astounded at how slowly clock time passes.

The emotional responses vary markedly both during any single session, between a series of exposures in the same individual, and between individuals. Initial apprehension is not uncommon, and sustained anxiety may pervade the period of LSD activity. Infrequently the tension may become maximal and culminate in panic. What is more common is an euphoric feeling tone. Elation, bliss, and ecstacy have been described. The mood may be labile, shifting from depression to gaiety and back again. At times, prolonged laughter or tears seem inappropriate to the situation. Rarely, a catatonic flatness or a paranoid rage reaction will be encountered.

The thinking process is substantially altered under the influence of psy-

chotomimetic drugs. A loosening of associations, unusual in content, is regularly noted. Thought sequences are nonlogical, fantasy laden, and eidetic. A few patients, instead of describing a flood of thoughts, report an absence of thought. Intelligence testing is worsened, but this may be due to inattention to the task or preoccupation with the fast moving sensory and mental alterations. Attempts to communicate may be accompanied by blocking. Orientation is ordinarily not impaired, but judgment is by no means dependable. Paranoid grandiosity or ideas of persecution might be elicited.

Changes of ego function may be imperceptible at the lowest dosages or completely disrupted in the higher ranges. At first, the usual ego defense mechanisms come into play to cope with the peculiar mental changes. Eventually, they may be demolished. The ego boundaries may dissolve partially or completely to the point that dedifferentiation of the self from the outer world and separation of internal experience from sensory input is lost. The body image is also distorted with parts of the body becoming larger or smaller or finally disappearing. Depersonalization of all degrees has been described, and derealization of some sort is invariable. One's evaluation and concept of oneself undergoes considerable alterations, usually in the direction of self enhancement, but the opposite may occur. Drives are ordinarily diminished.

Behavioral patterns are often more predictable than other facets of human functioning. Under a moderate or large amount of a psychotomimetic agent, the subject is inclined to be passive, quiet, sitting or lying with closed eyes, attempting to cope with the unusual state. He may withdraw completely or respond minimally. Task orientation is grossly impaired. Of course, other behavior is possible. Attempts to control the state by talking about it incessantly are known. Hostile acting out has occurred in instances where a release of conscious controls unleashes underlying strong aggressive impulses. Disrobing is mentioned from time to time. When panic or a disorganizing loss of insight into the situation develops, the subsequent behavior reflects these affects.

The psychedelic state may be considered equivalent to a chemically induced transcendental event. The neurophysiological implications of a psychic condition similar to those achieved only through strenuous exercise, prolonged meditation, or (rarely) spontaneously, are intriguing. At any rate, such phenomena are far from uncommon and form the basis of the use of these drugs within the context of religious ceremonies. The peyote cactus, for example, is a central item in the rituals of the Native American Church of the American Indian.

Leuner (47), Sandison (48), and other psychiatrists in Europe use LSD in multiple small doses (50–200 μg) as an adjunct to conventional psychotherapy. This is called psycholytic psychotherapy. It depends upon the disinhibiting effects of the drug on the emotions producing abreaction, upon ego defenses producing lessened resistance to recall of repressed memories, and upon primary process thinking producing hallucinatory images which may

have symbolic value for interpretation. The drug sessions are interspersed with nondrug interviews to deal with the material retrieved under LSD.

Psychedelic psychotherapy has been particularly used in North America where Hoffer & Osmond (49) and others employed one or a few high dose (300–1000 μg) experiences primarily in the treatment of chronic alcoholics. The rationale is the induction of a psychological death-rebirth experience, allowing the patient a new start with a new value system and without the burden of the old guilt and self hate. In addition, the loss of ego boundaries permits the alienated patient a transcendental feeling of belonging.

Attempts to employ LSD in psychotherapy ordinarily exclude psychotics, except for autistic children [Bender et al. (50)]. Recently, Simmons et al. (51) presented confirmatory evidence of an increase in visual contacts and positive affects by autistic children under the drug as compared to a placebo.

Complications.—Complications of the controlled use of LSD remain infrequent. During the past two years an increasing nonmedical use has produced increasing numbers of adverse reactions. A classification of the side effects that have been encountered is available [Cohen (52)]. Death directly caused by the toxicity of LSD is unknown. Neurological sequelae are rare; isolated grand mal type convulsions have been reported. The psychiatric complications are more frequent, although their incidence remains unknown. Chronic anxiety and depressive states, somatization reactions and acute panic or paranoid reactions have all been seen. Recurrences of an LSD-like state days to months after the drug has been taken are known. Suicide or accidental death are more apt to occur than homicide. The psychotic complications consist of schizophrenic decompensations or a prolonged hallucinosis. Quick recovery may ensue, but some patients have required hospitalization for years. No reports of permanent brain damage in human beings have yet appeared. Methods for the detection of LSD are available (53).

Ololiuqui

The alkaloids of the seeds of *ololiuqui*, three species of the wild American morning glory, have been determined by Hofmann (54) who had also previously succeeded in synthesizing LSD, psilocybin, and psilocin. They proved to be ergot alkaloids, a surprising finding as, at that time, these chemical structures had only been found in the lower fungi of the genus *Claviceps*. Now they were encountered in a higher plant of the Convolvulaceae family. That fungi contamination is not the source of the hallucinogenic material has been confirmed (55). D-Lysergic acid amide and D-isolysergic acid amide are the more active psychotomimetic ingredients. Elymoclavine, chanoclavine, lysergol, and ergometrine have been extracted. Their pharmacological properties have not yet been completely clarified. In mice, the alkaloidal fraction induces ataxia, ptosis, pilo-erection, and hypersensitivity to stimuli. Convulsions and respiratory arrest occur at lethal doses [Rice & Genest (56)].

Human subjects report a definite sedative quality to morning glory seed

intoxication not noted with LSD. D-Lysergic acid amide has previously been found to induce a dreamy, tired, somewhat clouded state. Nausea and vomiting are not uncommon. The potency of the seeds varies from batch to batch even when *Ipomoea violacea* and *Rivea corymbosa* have been positively identified. Isbell & Gorodetzky (57) reported that former narcotic addicts did not respond to the alkaloidal fraction of *ololiuqui* as they did to LSD. Other observers indicate that when enough seeds are pulverized and taken, the two states are similar. Hoffer (5) suspects that ergotism may follow substantial morning glory seed ingestion.

Other Substituted Indole Alkylamines

A whole series of alkylated tryptamines exist which are known to be hallucinogenic. In addition to α-methyltryptamine, DMT, DET, and dipropyltryptamine, the 6-hydroxylation products of these are even more active than the parent compounds. Szara et al. (58) have investigated this group. They point out that the 6-hydroxylated members can be produced in rat liver microsomes, and they may account for the perceptual and emotional changes. Human beings convert DMT into its 6-hydroxylated congener, and when a flourine atom is placed on the 6 position, 6-hydroxylation is prevented. Under this condition, only the autonomic manifestations of DMT are evident, making it useful as an active placebo (59). Amine oxidation, not 6-hydroxylation, is the major metabolic pathway in man. Most of the tryptamine is converted to 3-indole acetic acid and most of the serotonin to 5-hydroxyindole acetic acid.

Pretreatment with the monoamine oxidase inhibitor, iproniazid, reduces the effects of DMT. This is analogous to similar work cited with LSD (60, 61). Apparently, the increase in brain serotonin levels prevents DMT activity [Sai-Halasz (62)]. Pretreatment with the strong serotonin antagonist, the nonhallucinogenic 1-methyl-D-lysergic acid butanolamide (UML), accentuates the DMT effect. DMT is inactive by mouth; oral doses of 350 mg are without effect. It must be injected, sniffed, or smoked to produce its psychotomimetic effect. Intramuscular injections of 50 mg will induce autonomic and hallucinogenic symptoms.

The N-dimethylated analogue of serotonin is bufotenine. It provokes marked autonomic activity, including a cyanotic flush, nystagmus, mydriasis, tachycardia, and hypertension. This is a remarkably uncomfortable drug to take (63). Very small amounts have been identified in human urine. Fisher & Heller (64) report its presence in acute schizophrenics. Fewer chronic schizophrenics excreted it, and none of the controls did. When chronic schizophrenics were given an amine oxidase inhibitor, bufotenine was found in their urine, and their psychosis was often reactivated.

Psilocybin and psilocin are the active alkaloids in the Mexican magic mushroom. The former is the 4-O-phosphorylated, and the latter is the 4-hydroxylated ester of DMT. The phosphoric acid radical is readily detached *in vivo* by alkaline phosphatase. Hollister (65) estimates that LSD is ap-

proximately 130 times more potent than psilocybin which is 1.5 times weaker than psilocin. Apart from a shorter period of activity (two to six hours), the effects parallel those of LSD. When equivalent doses are given blind, it is impossible for subjects acquainted with the LSD state to differentiate between the two drugs.

Substituted Phenyl Alkylamines

Mescaline, one of the dozen and a half alkaloids in the peyote cactus, was the first of the hallucinogenic alkaloids to be extracted and synthesized. It has already gone through one cycle of scientific, psychotherapeutic, and popular interest. Its close chemical similarity to norepinephrine has made it a subject of interest to those who assume an aberrant catecholamine metabolism hypothesis of psychosis.

The psychotomimetic equivalent dose of mescaline is 4000 times larger than that of LSD. Neff et al. (66) studied the distribution of mescaline in cat brains using ^{14}C-labeled material given intravenously. The cortical and subcortical gray matter showed relatively high concentrations. The biological half-life was 90 to 120 minutes. Maximum concentrations in the brain were achieved in 30 to 120 minutes, corresponding to the period of maximal intoxication. The only radioactive products identified were mescaline itself and 3, 4, 5-trimethoxyphenylacetic acid (TMPA), an inert metabolite. They were both detectable in brain tissue, cerebrospinal fluid, plasma, and urine.

Speck (67) obtained an LD_{50} of 370 mg/kg for rats when mescaline was given intraperitoneally. Death was preceded by flexor convulsions and respiratory arrest. The EEG records showed fast wave, low voltage activity. Bradycardia at the intermediate dose ranges was evident. Mescaline prevented barbiturate hypnosis. The outstanding pathologic finding when 50 mg/kg of mescaline was injected into rats for a month was adrenal cortical hyperplasia.

In man, Charalampous et al. (68) found a biologic half-life of six hours. In the first 24 hours, 87 per cent of the orally administered radioactive mascaline was excreted in urine; in 48 hours, a 92 per cent recovery was obtained. Mescaline and TMPA were the principal metabolites found. Measurable quantities remained in the brain for 9½ hours.

Anticholinergic Compounds

A number of 3-N-substituted piperidyl benzilates are psychotomimetic. JB-329 (Ditran) is a combination of two isomers: N-ethyl-2-pyrrolidylmethyl-phenylcyclopentyl glycolate and N-ethyl-3-piperidylphenylcyclopentyl glycolate. Ditran and the rest of the series are central anticholinergics, but according to Abood et al. (69) their cholinergic blocking and hallucinatory properties do not correlate well. On the other hand, Giarman & Pepeu (70) found a good relationship between brain acetylcholine levels following Ditran and the behavioral changes in rats. Ditran does not exert an effect on the chromatophores of minnows, it does not produce hyperthermia in rabbits,

nor does it reverse reserpine-induced depressions. These are in contrast to the properties of LSD and psilocybin (71).

Ditran is rapidly excreted via the kidneys. The brain does not preferentially concentrate the drug, only about 0.1 per cent is found in the central nervous system. Within the brain itself, the caudate nucleus and the hypothalamus had the highest concentrations. Most of the drug was bound to mitochondria.

Tetrahydroaminocrin, an anticholinesterase, is presumably antidotal to the central and peripheral effects of Ditran [Gershon & Olariu (72)]. This provides additional support for the hypothesis that its hallucinogenic properties are the result of central cholinolytic activity. Tetrahydroaminocrin is ineffective in blocking the symptoms of LSD, mescaline, or psilocybin intoxication. Tachyphylaxis to Ditran occurs rapidly. Cross tolerance between members of the Ditran series is likely, cross tolerance between Ditran and LSD, mescaline, or psilocybin does not exist. The general impression is that Ditran induces a toxic psychosis resembling other anticholinergics like atropine and scopolamine.

The oral dosage range is from 2-20 mg in adult males. The autonomic effects of Ditran exceed those of LSD. Mydriasis, flushing, nausea, vomiting, dryness of the mouth, tachycardia, hyperreflexia, and ataxia are encountered. More mental confusion, speech disturbances and disorientation are seen than with other hallucinogens. Blocking, amnesias, thought disorganization, and feelings of strangeness are often mentioned. All contact with reality and insight into the cause of the mental disruptions may be lost. Alcoholics have likened it to a prior bout of delirium tremens. Ditran has been used in the treatment of severe depressive states after electroconvulsive therapy and antidepressants have failed. Some success has been claimed. Its mechanism of action in the treatment of depression is unknown. Hollister et al. (73) suggest that it may have usefulness in the estimation of individual delirium thresholds.

Phencyclidine (Sernyl) is an anesthetic which induces psychotic-like symptoms in some patients. The disorganization of thought and derealization are greater than with LSD. A complete loss of insight into the situation can be observed. Some sedative action is described. Sernyl is supposed to mimic symptoms of early schizophrenia better than other hallucinogens. Lawes (74) found that sensory deprivation lessened the effects of the drug. He made the assumption that it acted on the coding mechanism of sense data input. When the sensory input is reduced, the miscoding process is not active. The chronic miscoding of information may be one of the mechanisms of the schizophrenic reaction.

Cannabis

The resin from the flowering tops of the female Indian hemp plant has been used in Asia for over 5000 years. The pharmacology of hashish was described in 3000 B.C. by Shen Nung. Although opium eventually displaced it

in China, it later became a part of Indian religious and secular life. It has variously been used as an aid to meditation (by the Yogins), as a thought control agent (by the Assassins), and as a disinhibiting drug (by the Thugs). Its modern use is predominantly as an euphoriant and social relaxant. The drug may be smoked, chewed, or drunk as a beverage.

Marihuana has about a sixth the potency of hashish and consists of the leaves and tops of the plant. Tetrahydrocannabinol has been extracted and a large number of analogues have been synthesized. They are unusual structurally in that they do not contain a nitrogen atom. Marihuana is an hallucinogen rather than a narcotic as it is classified legally. Many of the descriptions of low dosage LSD experiences resemble those of marihuana narrations.

In animals ataxia and tremors, an intensification of the scratch reflex and corneal areflexia are noted on administration of the oil which contains the active ingredients of cannabis.

The LD_{50} in humans is unknown. Very few deaths directly due to marihuana toxicity are recorded. Tachycardia, tremor, and conjunctivities are the more frequent physical signs. Hyperglycemia, dryness of the mouth, and urinary frequency have been mentioned. If the preparation is potent, the pupils are dialated.

Within minutes of inhaling a cigarette, a feeling of release of tensions and inhibitions, a dreamy "high," and of passivity occurs. Synesthesias, alterations of time sense, and changes in auditory and visual perception are described. The duration of the state does not exceed four hours but may be prolonged by smoking additional "reefers." Only a partial tolerance develops and this is rapidly lost. The major differences from the symptoms produced by other psychotomimetics are the drowsiness which may culminate in sleep, and the craving for sweets or other food that often accompanies indulgence in marihuana.

In this country, the usage of marihuana (also called grass, weed, and pot) has increased in recent years among underprivileged and intellectual groups. An occasional psychotic reaction, particularly in the unstable personality, has been seen. Chopra (75) described both acute and chronic toxic psychosis. A very recent letter to the editor (76) speaks of two cases of acute panic and disorganization of thought lasting several weeks after smoking one or two cigarettes. These patients had been seen by a physician prior to their marihuana smoking episode and were neither psychotic nor seriously disturbed. Habituation, not addiction, characterizes the dependency on the drug. Whether escalation to the hard narcotics evolves from marihuana smoking remains open to debate. Crimes of violence following marihuana usage are in police files. This is not surprising since it has a disinhibiting effect. One undesirable use of marihuana consists of its consumption by juveniles who employ it to evade or escape all frustrating or anxiety-provoking experiences.

A bibliography of 1860 references on all aspects of cannabis was issued in 1965 by the United Nations Economic and Social Council (77). Recent

pharmacologic research with this drug in the United States has been negligible.

Summary

It is interesting that some drugs which have either central sympathomimetic or anticholinergic activity are psychotomimetic. The close relationship between neurohumors like norepinephrine and serotonin on one hand and hallucinogens like mescaline and bufotenine on the other, is fascinating. That the hallucinogens may compete with the normally occurring cerebral amines and block the transmission of inhibitory neuronal activity is a speculation which could explain many of their manifestations on a neurophysiological level. A good part of brain function consists of inhibiting or quenching the sensory load and fantasy type mentation. If the inhibitors are depressed, a state similar to the one called psychotomimetic could emerge. As soon as more is understood about the mode of action of the biogenic amines in the brain, the neuropharmacology of the psychotomimetics will become clearer.

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