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The Psychotomimetic Agents

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1. Introduction

The group of psychotomimetic agents (also called fantastika, hallucinogens psychedelics, psychodysleptics, and mysticomimetics) plays a double role in our consideration of them. They are not only valuable chemical aids in assisting us to understand the chemistry of the brain and the psychology of mental functioning. In addition, they have presented us with new and expanding medicolegal and sociological problems.

Originally, these agents were principally of plant origin, but more recently, long series of psychotomimetic substances have been synthesized. The number of synthetic members of this group now range in the hundreds with only the desire and ingenuity of our chemists being the limiting factors in developing new ones.

1.1 *Definitions*

The psychotomimetic agents were originally considered producers of a model psychosis. They were supposed to induce loss of reality contact, dysphoria, disorganized or delusional thinking states and hallucinations. It was to provide a laboratory, temporary, reversible psychosis that they were originally used in research. In recent years, the concept of their action has broadened to include other profound alterations of consciousness which depend upon the dose taken, the personality of the subject, the conditions under which the experiments are conducted, the expectations of the subject and the researcher, and other variables.

The hallucinogenic plants were traditionally employed to provide an intoxication, an aid to religious experiences, divinatory or prophetic insights, an ordeal or rite of passage, or elevation of mood.

The changes in perception may include an intensified subjective meaning of the percept, marked distortions of time, space, color and depth perception, illusions, pseudohallucinations, and hallucinations. Synesthesias, or crossing over of the sensory signal to another sensory pathway, can occur.

Emotional alterations are often euphoric and may include blissful or ecstatic periods. The range of affectual change is considerable. The subject can experience anxiety, depression, or horror. Mood swings may be pronounced during any single exposure to a psychotogen.

The shifts in thought provide a multitude of congitive states. They include dream-like, fantasy-laden, eidetic activity, or a manic flight of ideas, or a catatonic absence of thinking activity, or paranoid, delusional thought sequences which are usually grandiose, or a hebephrenic silliness. Non-rational, non-logical thinking processes tend to prevail.

Unusual ego transformations are frequent. These range from changes in body image to duplications and triplications of the self, to a complete loss of the ego boundaries and of self identify (depersonalization). The derealization of the external world is also described.

It is true that similar unusual shifts of mental functioning occur with other

classes of drugs. In predisposed individuals, or when used in large amounts, stimulants, sedatives, narcotics, and anesthetics mimic these changes. The separation of the hallucinogenic experience from the delirial experience seen with other classes of pharmacologic agents is incomplete and overlapping. The latter are more frequently associated with confusion and disorientation; the hallucinogenic state is more frequently associated with relative mental clarity.

Neither can we assume that the psychotomimetic condition is a temporary schizophrenia, although occasional subjects under the influence of an hallucinogênic drug will be difficult to distinguish from an acutely schizophrenic patient. Others appear to be undergoing an experience described as oneirophrenia, a living dream with all the distorted, non-sequential, symbolic qualities of dreaming sleep. The predominance of visual over auditory hallucinations, the sympathomimetic autonomic effects, the retention of insight that one has taken a drug – all these factors seem to differentiate the state induced by various psychodysleptics from the schizophrenic reactions. It is certainly true that the stress of an LSD (d-lysergic acid diethylamide) experience has precipitated a schizophrenic psychosis. The assumption under these circumstances is that a predisposed individual became and remained disorganized following exposure to the hallucinogen.

1.2 *Epidemiology*

The current upsurge in the use of psychotomimetic agents is only ten years old, although they have been used for centuries, indeed millenia, in certain cultures. In the early 1960's, the ego dissolving property of LSD was rediscovered by a group at Harvard University, and this event led to a sensational and seductive dissemination of esoteric claims for the drug. It was hailed as a solution to all of one's personal problems and a solution to the world's woes if it were universally utilized. The widespread publicity, disseminated by the mass media, led to brisk experimentation, and the dawn of a psychedelic revolution was proclaimed. About 5 to 10 percent of all college students in the United States have tried LSD at least once, and perhaps one percent are regular users. Because of the adverse reactions encountered, and because the promised resolution of conflicts did not result, many desisted from further use. However, others formed psychedelic subcultures which had their peak during the summer of 1967. Since then, the many inhabitants of the drug using ghettos have gone on to intravenous methamphetamine abuse, and more recently have become involved with heroin. A few of the LSD devotees have attempted to form communes in rural areas. Meanwhile, LSD is being increasingly used by very young school children at this time.

Since the 1950's there has been a gradual increase in the use of *Cannabis* in the form of marihuana in the United States. During the mid 1960's, its use rose steeply, and it has been tried by ten million or more Americans. Although most experimenters stop using marihuana, substantial numbers continue to smoke 'pot' occasionally. A much smaller number are daily users, some of whom are continually intoxicated during their waking hours.

The other psychotomimetic substances have been sampled. Dimethyltryptamine (DMT) had a vogue. Mescaline and psilocybin are being used, except that analysis shows them to contain neither mescaline, nor psilocybin, but LSD [1]. 2,5-dimethyoxy-4-methylamphetamine (DOM or STP) is being used in certain areas. What is being sold as Δ^9-tetrahydrocannabinol (THC) turns out to be LSD or phencyclidine, an anesthetic used in veterinary medicine. Other drugs, such as 3,4,5-trimethoxyamphetamine (TMA) and 3,4-methylenedioxyamphetamine (MDA) are sporadically consumed.

At this time, the use of *Cannabis* is definitely increasing. The more potent psychedelics appear to have leveled off in use and would be declining were it not for the junior high school and high school youngsters who have recently taken up the practice in an effort to mimic the behaviour of college age contemporaries.

2. Ethnopharmaceutical History[1])

In this section, a number of the vegetable substances which can provide a psychotomimetic experience will be briefly mentioned. In some instances, their active constitutents will be discussed later in the chapter. Some of these plants are definitely psychotomimetic, others could just as correctly be classified with the deliriants.

2.1 *Peyote*

Peyote (*Lophophora williamsii*) is a turnip-shaped cactus that grows in the basin of the Rio Grande between Mexico and the United States. It contains mescaline and a large number of other alkaloids. Mescaline is produced in the peyote cactus from tyrosine via tyramine and dopamine. Another pathways is from tyrosine through dihydroxy-phenylanaline (DOPA) and dopamine. This has been demonstrated by feeding radioactive tyrosine [2]. It is a bitter and nauseating material to chew. The 'buttons' or crescent shaped tops are used in the rituals of the Native American Church of North America. This Indian religious order extends from Mexico to Canada, and can legally use peyote in its ceremonies in the United States.

2.2 *Psilocybe Mushrooms*

A number of the species of the Psilocybe mushrooms, for example, *Psilocybe mexicana* Heim, are traditionally employed in a semi-religious context in southeastern Mexico. It was from these slender mushrooms that HOFFMANN [3] extracted psilocybin and psilocin. These are the Mexican magic mushrooms that WASSON [4] described in his search for hallucinogenic mushrooms.

[1]) Detailed accounts of a number of hallucinogenic plants can be found in Public Health Publication No. 1645, *Ethnopharmacologic Search for Psychoactive Drugs: 1967* (US Government Printing Office, Washington, D.C.).

2.3 *Kava*

Kava (*Piper methysticum* Forst) is an ancient beverage squeezed or chewed from the rootstock. It is a ceremonial drink in Samoa, Fiji, and other South Sea islands. Chemically, kava is a mixture of six C_6-aryl-substituted pyrones. It is a mild intoxicant and sedative. It also has muscle relaxant, anticonvulsant, and local anesthetic activity.

2.4 *Nutmeg*

Nutmeg (*Myristica fragans*) is the well known spice which is intoxicating when swallowed in large amounts. It cantains myristicin (3-methoxy-4,5-methylenedioxy-allylbenzene) along with related substances including safrole and elemicin. Since these are non-nitrogenous analogues of ring substituted amphetamines, it is assumed that the aromatic components induce hallucinatory effects by altering norepinephrine metabolism in the central nervous system.

2.5 *Cohoba Snuff*

Cohoba (*Piptodenia peregrina*) snuff is a traditional intoxicant in the Caribbean area. Special tubes for blowing the snuff up the user's nostrils are still seen today among the indigenous tribes. Both bufotenine (5-hydroxy-dimethyltryptamine) and DMT have been identified in cohoba. In addition to their hallucinogenic capability, they release considerable autonomic activity including hypertension, tachycardia, mydriasis, and dyspnea.

2.6 *Fly Agaric*

The Siberian fly agaric (*Amanita muscaria*) contains muscinol and ibotenic acid as the probable active ingredients. It also has some muscarine, but this substance does not cross the blood-brain barrier. Bufotenine, which was once postulated to be the active ingredient, cannot be detected. Muscinol is excreted unchanged in the urine. This accounts for the high value placed upon the urine of those intoxicated with the red spotted mushroom. It is reported that the Karyak tribemen of the Kamchatka peninsula no longer use the fly agaric. It has been replaced by alcohol.

2.7 *Yagé*

Yagé (*Banisteriopsis caapi*) also known as ayahuasca and caapi is still used in the Amazonian basin. A series of beta-carbolines are responsible for its activity. The major ones are harmaline, harmine, and tetrahydroharmine. When first isolated, harmine was called telepathine, a tribute to the supranatural powers attributed to the vine. Generally, yagé is mixed with another local plant such as *Prestonia amazonica*, which has been found to contain DMT. It is used by the local shamans as a divinatory drug.

2.8 *Iboga Bean*

The Congolese ordeal bean (*Tabernanthe iboga*) contains ibogaine among other substances. It is a mind altering drug with many unpleasant to dangerous side effects. In addition to visions, it produces hyperexcitable states, epileptic seizures and coma. It is also sometimes given to young males as a rite of passage. If they do not succumb, they have achieved manhood.

2.9 *Morning Glory Seeds*

A half dozen varieties of American tropical morning glory seeds (*Ipomoea violacea* and *Rivea corymbosa*) have been found by HOFMANN [5] to contain d-lysergic acid amide and d-isolysergic acid amide. Elymoclavine, chanoclavine, lysergol, ergometrine, and lysergic acid-a-hydroxyethylamide have also been identified. When sufficient amounts of what the Central American Indians call *ololiuqui* seeds are chewed, a drowsy, hallucinatory state results. When LSD was in short supply a few years ago, many turned to morning glory seeds for their chemical fantasies despite the nausea and vomiting that sometimes accompanied the event. Cold extremeties and uterine contractions are presumable due to the ergonovine content. Prolonged dissociative states are occasionally reported. COHEN [6] reported a suicide precipitated by the spontaneous recurrences of a morning glory seed experience.

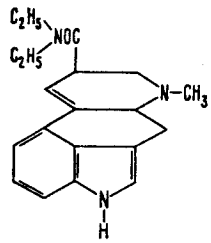
Another member of the Convolvulaceae can serve as a source of psychotomimetic material. The Hawaiian Baby Wood Rose (*Argyreia nervosa*), closely related to the genus *Ipomoea* contains similar alkaloids and can induce hallucinogenic effects [7].

Cannabis sativa will be described under the cannabinoids (3.4).

3. Classification

3.1 *Indolealkylamines*

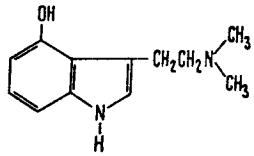
3.11 d-Lysergic acid diethylamide tartarate (LSD)



The rye fungus, ergot, (*Claviceps purpurea*) is not hallucinogenic. It contains lysergic acid and many other ergot alkaloids. In 1938, HOFMANN and STOLL [8] synthesized LSD. Five years later, HOFMANN [9] accidentally discovered its extraordinarily potent psychotomimetic properties. A long series

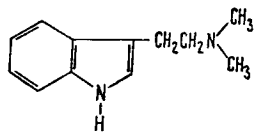
of LSD substituted derivations has been prepared. None exceeds the potency of LSD insofar as psychic activity is concerned, although better serotonin antagonists are represented. No hallucinogenic action is found in *l*-LSD or d-iso-LSD, but d-*l*-acetyl LSD (ALD) and d-*l*-methyl LSD (MLD) approach LSD in activity. LSD will be used as the prototype of a psychotomimetic agent and further discussion will be continued in later sections of this chapter.

3.12 Psilocin and Psilocybin (4-hydroxydimethyltryptamine and 4-phosphoryl-dimethyltryptamine)



These substances have an action similar to, but shorter than LSD. They last over a 3 to 4 hour period in contrast to 8 to 10 hours for LSD. Psilocybin is converted to psilocin in vivo.

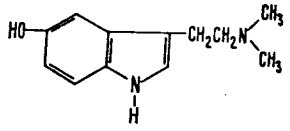
3.13 The Dimethyltryptamine Series (DMT, DET, DPT, etc.)



A series of substituted tryptamines exists which are known to be hallucinogenic. In addition to *a*-methyltryptamine, dimethyltryptamine, diethythyltryptamine, and dipropyltryptamine, their 6-hydroxylation products are more active than the parent compounds. SZARA [10, 11] has investigated this group. He points out that the 6-hydroxylated members can be produced in rat liver microsomes, and these may be the active compounds. Humans can convert DMT to the 6-hydroxy form. It should be mentioned that amine oxidation, not 6-hydroxylation, is the major metabolic pathway in man. Tryptamine is deaminated to 3-indoleacetic acid, and most of the serotonin (5 HT) is excreted as 5-hydroxy-indoleacetic acid.

DMT is ineffective by mouth in doses up to 350 mg. Intramuscular injections of 50 mg will call forth marked autonomic and hallucinogenic symptoms. It is also active when smoked or sniffed. Pretreatment with an amine oxidase inhibitor will diminish the effect of DMT. Apparently increasing brain serotonin levels impairs the DMT response. On the other hand, pretreatment with a strong serotonin antagonist such as 1-methyl-d-lysergic acid butanolimide (UML) potentiates the DMT effect. DMT has a brief duration of action and an intense onset. In less than an hour, a very strenuous experience will have occurred.

3.14 Bufotenine (5-hydroxydimethyltryptamine)

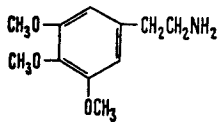


The claim that this compound is hallucinogenic is not established. Although found in cohoba snuff, and the parotid gland and skin of the toad (*Bufo marimus*), its autonomic activity is undoubted, but it is questionably hallucinogenic. Very small amounts have been found in the urine of acute schizophrenics. Chronic schizophrenics given an amine oxidase inhibitor have a reactivation of their florid psychosis, and an increased bufotenine excretion.

SAAVEDRA and UDABE [12] have recently reviewed the literature and added their results of urinary bufotenine determinations in a variety of subjects. Normal subjects showed values of 1.7 ± 0.27 μg%. Non-schizophrenic mental patients had values of 2.4 ± 0.28 μg%. Four conversion hysterics averaged 6.8 ± 0.9 μg%. Schizophrenic patients under treatment with psychotropic drugs had a mean of 3.5 ± 1 μg%. Acute, non-treated schizophrenics had a bufotenine value of 16 ± 2.27 μg%, significant beyond the 0.01 level as compared to the control and other groups. In their opinion, excessive methylation of 5 HT could be etiologically related to schizophrenia. Their findings are in confirmation of a number of earlier studies.

3.2 *Phenylalkylamines*

3.21 Mescaline (3,4,5-trimethoxyphenylethylamine)



Mescaline seems to be only active hallucinogenic agent of the phenylethylamine series. It is so named because peyote was first used by the Mescalero Indians. It has nothing to do with the mescal bean from which an alcoholic beverage is made by fermentation in Central America. Its chemical similarity to biogenic amines like dopamine and norepinephrine is interesting to those who assume that an aberrant catecholamine metabolic process has some relationship to endogenous psychoses.

The psychotomimetic equivalent dose of mescaline is some 4,000 times greater than that of LSD. SPECK [13] obtained an LD_{50} of 370 mg/kg in rats when it was administered intraperitoneally. Death was preceded by flexor convulsions and respiratory arrest.

The typical mescaline EEG using scalp electrodes is a dyschronized, low voltage, fast wave recording. When rats are given 50 mg/kg chronically, adrenal cortical hyperplasia is found at autopsy.

NEFF [14] studied the distribution of mescaline in cat brains using ^{14}C-labeled material given intravenously. High concentrations were detected in the cortical and subcortical gray matter. Maximum concentrations were achieved in 30 to 120 minutes. The only radioactive products identified were mescaline itself and 3,4,5-trimethoxyphenylacetic acid (TMPA), an inactive metabolite. Both substances could be found in brain tissue, cerebrospinal fluid, plasma, and urine.

In man, a biologic half life of six hours was determined [15]. This is consistent with the subjective and observable clinical effects. During the first 24 hours, 87% of the orally administered radioactive mescaline had been excreted in the urine. By 48 hours, a 92% recovery had been obtained. Measurable quantities remained in the brain for $9^1/_2$ hours. Mescaline and TMPA were the principal substances recovered.

Despite the disparate chemical structures of LSD and mescaline, their behavioral, cognitive, and autonomic effects are distinctly similar. Experienced LSD subjects, when given equivalent amounts of LSD or mescaline blind, are unsuccessful in distinguishing between the two agents. Cross-tolerance between LSD, psilocybin, and mescaline has been established in many species including man. Thus, the assumption is that mescaline, LSD, and psilocybin act over common neurochemical pathways.

When AGHAJANIAN [16] found a specific network of neurones in the rat midbrain raphé nuclei that was exquisitely sensitive to LSD, he repeated the work with mescaline to see whether a similar inhibition of firing of the single neuronal units could be duplicated with mescaline. These raphé midbrain nuclei have been proven to contain 5HT. Neither chlorpromazine, amphetamine or norepinephrine inhibits all raphé activity. DMT and BOL in concentrations consistent with their behavioral potency in the rat do produce inhibition. However, BOL does not inhibit all raphé units completely. Mescaline in equivalent doses did inhibit certain raphé cells as completely as LSD. Interestingly, not all raphé cells were inhibited by mescaline. Those located in the ventral portion of the dorsal raphé nucleus were inhibited. Other cells were not affected by mescaline. The explanation of this discrepancy may be in a differential catecholamine fiber input in specific cells, but this remains unproven.

3.3 *Substituted Amphetamines*

A long series of trimethoxyamphetamines and methoxymethylendioxyamphetamines has been synthesized and found to be hallucinogenic in man. They vary in their potency, for example, 3,4,5-trimethoxyamphetamine (TMA) the amphetamine analogue of mescaline, has double the activity of mescaline. The 2,4,5-trimethoxyamphetamine (TMA-2) is 18 times as active. However, 2,3,4-trimethoxyamphetamine (TMA-3) is inactive. These variations may be due to the steric ability of the methoxy groups to fold and approximate the B and C rings of LSD as SNYDER [17, 18] has postulated.

Of the substituted amphetamines, the best known is 2,5-dimethoxy-4-methylamphetamine (STP or DOM). It is the 4-methyl analogue of TMA-2 and

is about five times as active as the latter compound, and eighthy times more potent than mescaline. Apparently, its increased activity is due to slower degradation by avoiding demethoxylation at the C-4 position.

STP may have been the first synthetic hallucinogen which has been widely used in man before its animal pharmacology had been clarified. During the summer of 1967, tablets containing large amounts of the drug were distributed freely in the Haight-Ashbury district of San Francisco and an unusual number of adverse reactions were seen. These consisted of prolonged psychiatric states lasting 24 to 48 hours, associated with dry mouth, dilated pupils, some systolic hypertension, a temperature elevation, and increased heart rate. Many of these uncomfortable symptoms were high dose effects.

STP has been shown to accumulate in specific areas of cat brains and to remain there for at least six hours. The cortex was an area of high radioactivity after tritiated STP was administered. The hypothalamus, amygdala, hippocampus, putamen, and medial and lateral geniculate bodies all gave high counts in comparison to other areas.

In the rabbit FUJIMORI [19] found that the amphetamines evoked EEG alerting at the midbrain area, whereas STP reacted at the medullary level. In the rabbit, EEG alerting requires an intact midbrain center, and the medullary center is the locus of the resting EEG. It is postulated, therefore, that STP, by inhibiting the medullary mechanism, removed its restraints on midbrain activating systems and resulted in EEG alerting.

The ethyl analogue of STP is DOET (2,5-dimethoxy-3-ethylamphetamine). It is slightly more potent. In low doses it is euphoriant and increases self awareness. It has had some therapeutic trials as an aid to psychotherapy. In large doses, it reproduces the usual psychotomimetic continuum of actions. This dose related response is probably true of all other drugs in this group.

Numerous other congeners exist, some active and some without psychic effect according to their stereochemical properties. It appears that at intervals new members of this series will appear as 'the newest, safest psychedelic'. Since it is the profound psychologic properties of these chemicals which make them unsafe for some persons, the hope that a safe psychotomimetic agent will be produced is hardly possible by definition.

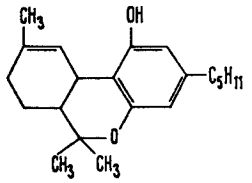
3.4 *Indian Hemp and Its Active Ingredients*

Because of its expanding use, and since considerable new information has recently become available, *Cannabis sativa* and its active components will be reviewed in some detail.

3.41 The Indian Hemp Plant

The flowering bracts and leaves of *Cannabis sativa* contain a series of cannabinols, tetrahydrocannabinols, and cannabidiol, along with their acidic compounds. It is generally assumed that Δ^9-tetrahydrocannabinol (THC) and,

to a lesser extent, Δ^8-tetrahydrocannabinol account for its hallucinogenic and mildly sedative qualities. Both male and female plants have THC in similar amounts.



The leaves and tops are variously called marihuana (marijuana), ganja, kif, bhang, and other numerous local and colloquial designations. Two genotypes are described: one high in THC content, such as many Nepalese, Mexican, and Vietnamese varieties, and the second which is low in THC and high in cannabidiol content, such as some North American, Swedish, French, and Italian variants. Under similar conditions of soil, moisture, and sunlight, the two genotypes may breed true, but this point has not been precisely determined. Wild Minnesota or Iowa plants may assay at about 0.08% Δ^9-THC, while Mexican seeds cultivated under identical conditions might have 1.4% Δ^9-THC.

The resin, hashish or charas, can be obtained only from high quality plants, and it is 5 to 10 times more potent than the plant from which it is obtained. Like marihuana, the resin slowly loses its potency when kept at room temperature in sunlight. This may be due to conversion from Δ^9 to Δ^8-THC, the latter being about three times weaker. Conversion to the inactive cannabinol is also a possibility.

The stems, seeds, and roots of Indian hemp are inert. The stems have commercial value in the manufacture of rope and cloth. The sterilized seeds constitute a good proportion of birdseed. There is an often quoted account from Herodotus about the Scythians who threw hemp seeds onto hot stones and covered themselves with skins to enclose the vapor. When they 'howled for joy', it could only have been due to the pleasure of a stimulating sauna bath. Certainly no THC inhalation was involved. Marihuana smokers manually eliminate the seeds and stems from the crude material that they purchase.

When *Cannabis* is smoked, its effects are quickly noted. Especially if it is deeply inhaled and kept in the lungs, symptoms can be discerned within a few minutes, and they last for one to three hours. Although effective when eaten, the onset is delayed, and three times as much must be consumed to produce an equivalent effect.

Cannabis has been used for millenia, especially in those cultures where alcohol was forbidden by religious taboo. It has been praised and blamed since ancient times. Claims that it was a facilitator of meditation on one hand and of assassination on the other are probably both partially correct in that it can loosen rational controls and permit primary process mentation to emerge.

More recently, the smoking of *Cannabis* has escaped from traditional boundaries, and the young people of Western societies have taken to indulging. Of

this group, the great majority are experimenters or infrequent users. Some 5 to 10 percent of all users are 'potheads'. They are frequent and chronic smokers. It is this latter group who are characterologically disturbed when measured psychometrically, and who use *Cannabis* in an effort to treat their inability to enjoy sober existence, cope with the frustrations of ordinary life, or handle their underlying aggressive or sexual problems. Individual 'potheads' tend to escalate to the use of more dangerous drugs.

The symptoms of smoking strong *Cannabis* closely resemble the smoking of low doses of THC. No lethal overdose of *Cannabis* has been clearly proven. Instances of severe collapse from injecting a liquid extract of marihuana intravenously are in the literature [20, 21].

Psychological dependence, not physical addiction, occurs. Tolerance is not evident, but this is due to the low dose range involved. 'Reverse tolerance' is simply a learned effect of knowing what to detect from the smoking procedure, and an increase in the efficiency of retaining the smoke in contact with the pulmonary alveoli. Chronic bronchitis is familiar to regular users, but emphysema and carcinoma are not known. A minor withdrawal syndrome is described in the consistent user of high grade material. This consists of irritability, dysphoria, and restlessness. Whether *Cannabis* leads to crime or sexual disinhibitory activity depends more on the reason for which the drug was taken than because of any specific pharmacologic action. An amotivational syndrome has been described consisting of passivity, lack of future orientation, impairment of functioning, and loss of drive and goal direction.

Reporting from a student health center, KEELER [22] mentioned recurrences of the marihuana state (flashbacks) as a possible undesirable effect. WURMSER [23] listed reports of sixteen patients who required psychotherapy following their marihuana use for anxiety, paranoid states, depression, rage reactions, inability to concentrate, and psychotic breaks. Toxic psychoses lasting one to eleven days have been reported from Vietnam [24, 25].

WEST [26] mentions that chronic marihuana users are apt to demonstrate 'decreased drive, apathy, distractibility, poor judgment, introversion, depersonalization, diminished capacity to carry out complex plans or prepare realistically for the future, magical thinking, a peculiar fragmentation of thought and progressive loss of insight'.

The adverse effects of long term use of potent *Cannabis* have been the subject of numerous articles in the older literature. These do not measure up to the scientific standards of modern observation, data collection, experimental design or data evaluation. In an effect to obtain a more accurate answer to this question, studies are underway in countries where the use of *Cannabis* is traditional. Matched groups of users and controls are being examined physically and psychologically to determine whether significant differences occur as the result of chronic *Cannabis* use over many years.

Human research with *Cannabis* has long been handicapped by the inability to assay the material, the problems associated with delivering a known amount of the substance into the organism, and the effect of non-drug variables such

as expectation, bias of the subject or the observer, and the conditions under which the drug was taken. A number of these problems remain unresolved. Some 1,860 references on *Cannabis* were collected up to 1965 by the United Nations Economic and Security Council. Many hundreds of articles have appeared since, and a comprehensive, unbiased review of the entire literature is not available. Perhaps the quality of the material is not satisfactory enough for such an effort.

The effects vary as may be expected of any psychotropic agent, but most frequently a sense of relaxation, euphoria, reduction of ego controls and loosening of affect are described. Color and form become more intense, subjective time is often slowed. The critical function of the self is diminished. Thought becomes dreamlike. Occasionally, laughing or crying bouts without apparent cause are experienced. Less frequently, paranoid feelings of a suspicious nature, anxiety and dizziness are expressed. Especially when beginners smoke potent material, a rare toxic psychosis lasting a day or two can occur.

In a number of surveys, almost half of those who try their first marihuana cigarette notice no effects. In WEIL's nine naive subjects [27], they likewise reported little or no subjective symptoms after smoking the equivalent of 18 mg of THC (2.0 g of marihuana containing 0.9%-THC). These same subjects did demonstrate impaired performance on simple intellectual and psychomotor tests after marihuana as compared to their control scores. Chronic users smoking similar amounts did become 'high' and showed no significant change in performance on testing. Subtle difficulties with speech may reflect interference with retrieval of immediate memory [28].

Defects in immediate recall have been reported in the past [29]. Recently this issue has been put to more rigorous scrutiny. TINKLENBERG [30] administered 20, 40, and 60 mg of THC by mouth, which is the equivalent of smoking ordinary amounts of marihuana. His subjects performed the digit span forward test worse under every dose of the drug than during the placebo period ($p < 0.05$). Digit span backward was also adversely affected ($p < 0.01$).

The waxing and waning quality of the marihuana experience has been cited as another source of experimental error. This ability to 'pull oneself together' is mentioned by a number of investigators. Reaction times of various complexity, digit code memory, time estimation, hand steadiness and reading comprehension were tested. In all instances except hand steadiness, which improved under the dose of marihuana (equivalent to 1 or 2 cigarettes), the other tasks were performed more poorly. CLARK [31] indicates that the capacity to maintain sequential thought and emit chains of goal directed behaviour that are required for successful adaptation to the environment is a complex process. These include selective awareness of external stimuli, rapid retrieval of old information, recall of immediately preceding thoughts or events, and the ability to maintain the mental set productive of patterned sequences of behavior. It is these processes that may be sensitive to impairment by marihuana.

JONES [32] calculates that his smoked dosages ranged from 0, 7, 21, and 70 mg of THC. His oral extract dose ranged from 5 to 80 mg of THC. The

smoked route can be controlled by experienced subjects while equivalent amounts given orally may cause dysphoric reactions. In addition to commonly confirming the observed rise in pulse rate and conjunctional injection from marihuana, he noted a diminished salivary flow and reduced skin temperature. The EEG revealed only minimal, inconsistent changes. His placebo was the residue of marihuana after complete alcohol extraction. It produced no physiologic changes and contained no THC. Nevertheless, only 11 of 70 experienced users called it a placebo. In general, experienced marihuana users were found to be rather poor judges of the quality of marihuana. Significant ($p < 0.01$) decrements were found in the digit symbol substitution test in ten experienced smokers after smoking 1.0 g of *Cannabis* (0.9 %) THC. Time estimation tended to be poorly performed.

Only one study of driving skills in which alcohol and marihuana were compared has been reported [33]. The deficiences in this investigation make additional studied of this sort necessary. Two marihuana cigarettes of unknown quality were smoked until a 'social marihuana high' was obtained. The alcohol requirement was to drink two ounces (63 cc) of 43% alcohol in fruit juice within a half hour for each 20 lb. of body weight. The testing was done one hour after the drugs were taken. The alcohol state produced marked errors on all scores. The marihuana state was found to produce only speedometer errors. It is evident that the alcohol and marihuana doses were hardly comparable, and that by one hour the effects of marihuana had begun to wane. If two or three different dosage levels had been used, and a dose-response curve obtained, this would have been a valuable study.

3.42 The Tetrahydrocannabinols

The natural tetrahydrocannabinols can be extracted from high quality *Cannabis* by distillation, and if special procedures are used, a very pure product can be obtained. Six years ago MECHOULAM [34] succeeded in synthesizing Δ^8- and Δ^9-THC from verbenol and olivetol. Δ^9-THC is a gummy, labile, hydrophobic substance which is readily isomerized to Δ^8-THC. In air it oxidizes to cannabinol which is inert. All of the effects of *Cannabis* are reproduced by Δ^9-THC [35]. The burning process destroys part of the THC, therefore the amount absorbed on smoking may be lower than the actual content. On the other hand, smoking may increase the availability of the tetrahydrocannabinols because their acid forms are converted under these conditions. It could be that this conversion explains the greater activity of cannabis following smoking as compared to ingestion.

Δ^8-THC is approximately a third as potent as its Δ^9-isomer, but generally duplicates its psychophysiological properties. It was first administered by ADAMS [36] three decades ago to human volunteers.

PETRZILKA's [37] synthesis is considered the most efficient for large scale manufacture. It is a condensation of olivetol and mentha-2,8-dien-1-ol. At present sufficient supplies of Δ^8-THC, Δ^9-THC, cannabidiol, marihuana extract

distillate (an alcohol and hexane extraction followed by molecular distillation which contains 20% Δ^9-THC, 5% cannabinol, and 2.5% cannabidiol) are available at the National Institute of Mental Health. Tritiated and ^{14}C-labeled Δ^8- and Δ^9-THC have been manufactured for metabolic studies. Further pyrolytic studies to determine the fate of the cannabinoids are proceeding. Some of the active material condenses in the proximal end of the cigarette. About 50% of the Δ^9-THC can be lost under these conditions.

The first principal metabolite of THC has been identified as an hydroxylated compound which has biologic activity. The Battelle Memorial Institute group [38], the Israeli workers [39] and the Karolinska Pharmacy [40] researchers have found that Δ^8-THC and Δ^9-THC are converted to their 11-hydroxy derivatives. Instead of its exocyclic position, the possibility that the hydroxy group attached on the 7 position of the ring has been considered [39]. The compound has already been synthesized [38]. It shows hallucinogenic properties as demonstrated by a potentiation of the barbiturate sleeping time and an increase in the amphetamine induced locomotor activity in rats. It produces catatonia, passivity, clumsiness, biting when provoked, increased startle and vocalization.

Monkeys may be the most satisfactory animal bioassay for THC [41], being more sensitive than the dog ataxia test. They become tame and assume a 'thinker's' position supporting their heads on one hand and gazing out into space. Decreased activity is noted in a number of species including the mouse and rat. Hypothermia and hypotension are regularly found to exist. A biphasic stimulation and depression with loss of ability to perform complex tasks is reported in a number of species. At high doses the impairment may last for days after the drug was administered.

When tritiated Δ^9-THC is injected into pregnant hamsters early in pregnancy, radioactivity crosses the placental barrier quickly. These animals contain three times as much radioactivity as those exposed during late pregnancy. A significant degree of radioactivity is present in all fetuses after 24 hours, and the count is higher over the fetus than over the maternal plasma or brain [42].

The distribution of the cannabinoids was studied by AGURELL [43]. THC remains far longer in the organism that the other psychodysleptic drugs. Most of the labeled material is found in the liver and gall bladder. After three days, the central nervous system contains very little radioactivity. In the rat, the bulk of THC is excreted in the feces. In the rabbit most can be recovered in the urine. Man seems to resemble the rabbit in his elimination of THC. Probably due to lipoprotein binding, small, measurable amounts can be detected for many days in all species.

Tolerance to the effects of THC occurs when the drug is given in large doses over a period of a week or more. This is in contrast to marihuana in which lower dosage rangers are used. Cross-tolerance between THC and other hallucinogens has not been found.

The mechanism of action of THC is unknown. Slight reductions in brain serotonin levels, and both increases and decreases in norepinephrine levels have been reported.

Acute LD_{50}'s for the mouse have been determined to be 42 mg/kg for Δ^9-THC by intravenous injection [44]. For the rat it is 29 mg/kg. Intraperitoneal and intragastric LD_{50}'s were over ten times the intravenous amounts. Death was due to respiratory failure.

Doses of 0.34 mg/kg and 2.7 mg/kg of Δ^9-THC as marihuana extract distillate were injected intraperitoneally in cats for 23 to 120 days [44a]. The cats became apathetic and less interested in their surroundings during their waking hours. Those receiving the higher doses developed persisting 4 to 6 per second high voltage, slow waves, and also high voltage fast spike-like activity particularly over the parietal and occipital areas. These EEG changes persisted for up to ten weeks after discontinuance in the animals kept on the 2.7 mg/kg dose for seven weeks. The cats given the 0.34 mg/kg daily dose have shown similar EEG alterations except that they took longer to develop. This same group reported that 16 of 19 individuals who had used marihuana (11 had used marihuana in combination with other drugs) showed abnormal tracings. Slow waves and spikes were recorded over the occipital and temporal lobes, less frequently over the frontal and parietal area.

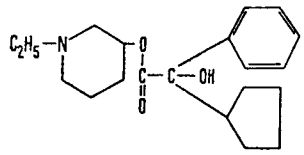
The psychophysiologic effects of the naturally occurring Δ^9-THC was first studied under varying dosages in man by ISBELL [34]. He found a consistent tachycardia, increased conjunctival injection even when the preparation was swallowed, no hypoglycemia and no consistent pupillary dilation. At the higher dosage levels, delusional thinking and hallucinatory phenomena analogous to those produced by LSD were elicited. Some drowsiness was present at all dosages. HOLLISTER [46] adds that a greater euphoria and fewer perceptual distortions occurred with 30 to 70 mg of THC than with 100 to 200 µg of LSD. THC was more like a dreamlike state. He compares the THC effect as similar to a combination of alcoholic and LSD intoxication. LSD produces increased plasma free fatty acid levels reflecting a sympathomimetic, hyperalert stress state. The elevation of free fatty acids was found to be minimal with THC.

These studies have used dosage ranges which are somewhat elevated when compared to the intake of THC by most *Cannabis* smokers. A cigarette of good quality will not provide much more than 10 mg of THC. However, if THC is only a third as active when swallowed, the ISBELL and HOLLISTER experiments are not excessive in comparison to the quantity smoked by a heavy user.

The determination of cannabinoids can be readily performed by thin layer chromatography. If more accurate methods are required, gas chromatography alone or combined with mass spectrometry with the results analyzed by an on-line computer can provide very sensitive and reliable data. This latter technique, mass fragmentography, may be capable of detecting THC in urine and plasma. Another possibility under study consists of creating a fluorescent compound out of THC and measuring it by fluorescence spectroscopy [47].

3.5 *Anticholinergic Hallucinogens*

Ditran



A number of the 3-*N*-substituted piperidyl benzilates are psychotomimetic. Some of this series are as potent by weight as LSD. JB-329 (Ditran) is a combination of two isomers: *N*-ethyl-2-pyrrolidyl-methylphenylcyclopentyl glycolate and *N*-ethyl-3-piperidylphenylcyclopentyl glycolate. The glycolate esters are central anticholinergics, but ABOOD [48] believes that their cholinergic blocking ability and their hallucinatory properties do not correlate well. However, GIARMAN [49] found a good relationship between brain acetylcholine levels after Ditran administration, and the behavioral changes in rats. In contrast to LSD and psilocybin, Ditran does not alter the chromatophore pattern of minnows, nor does it produce hyperthermia in rabbits, neither does it reverse reserpine-induced depression. Cross-tolerance to the indole and phenylalkylamine hallucinogens does not occur. This indicates that another neurochemical mechanism induces the striking psychic alterations seen with Ditran, atropine, and scopolamine. The anticholinergic group manifests cross-tolerance to each other, and tolerance to them is quickly acquired.

The brain does not preferentially concentrate Ditran, but within that organ the caudate nucleus and hypothalamus have the highest concentrations. Tetrahydroaminocrine, a potent anticholinesterase, reverses the central and peripheral effects of Ditran. This would provide additional support that its psychotomimetic properties are the result of central anticholinergic activity.

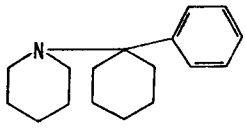
The oral dosage range is 2 to 20 mg in adults. It is an uncommonly unpleasant drug to take, so that abuse of the substance is exceedingly rare. Some of the autonomic-neurological actions of the glycolate esters in man include: mydriasis, dry mouth, tachycardia, hypertension, muscle tremors and rigidity, convulsions, ataxia, restlessness, aphasia, and drysathria. The psychic-behavioral effects resemble a toxic psychosis: euphoria, depersonalization, intellectual impairment, disorientation, delusions, hallucinations, confusion, panic, and amnesia.

Ditran has been used in the treatment of apathetic depressive states after other therapies have failed. A single dose is sufficient if it works. It has not been widely accepted as a therapeutic agent.

3.6 *Miscellaneous Hallucinogens*

3.61 Phencyclidine (Sernyl, Sernylan, PCP)

Phencyclidine is an anesthetic which is marketed for veterinary use. In sufficient dosage, it provokes a severe disorganization of thought and feelings



of strangeness which exceed those induced by LSD. Complete loss of insight into one's psychotic state can occur. It has a sedative action which may culminate in a coma. According to some investigators, phencyclidine mimics the symptoms of early, acute schizophrenia better than other hallucinogens. LAWES [50] found that a combination of phencyclidine and sensory deprivation diminished the effects of the drug. He therefore made the assumption that it acted primarily on the coding of incoming sensation. When the sensory input is reduced, the miscoding is less evident. This is not exclusively the property of phencyclidine for the same is often true of LSD. However, it must be admitted that certain schizophrenics do seem to have a chronic inability to code sensory signals properly. They do well in a sensorily deprived environment.

4. Pharmacology of LSD

4.1 *Potency and Dosage*

LSD may be one of the most potent drugs known. It is certainly the most powerful mind altering substance. Table 1 gives some relative strengths of various hallucinogens. Amounts as low as 0.02 μg/kg can induce discernible effects in a majority of individuals. An average dose is about 1.0 μg/kg. Much higher amounts have been consumed. To achieve complete out of the body states, 3 to 12 μg/kg have been taken orally. The author knows of one instance where 10 mg was swallowed without a fatal result.

Table 1 *Comparative strengths of LSD and other hallucinogens (approximate)*

Marihuana (potent leaves and tops of *Cannabis sativa*, swallowed)	30,000	mg
Peyote buttons (*Lophophora williamsii*)	30,000	mg
Nutmeg (*Myristica fragans*)	20,000	mg
Hashish (resin of *Cannabis sativa*)	4,000	mg
Mescaline (3,4,5-trimethoxyphenylethylamine)	400	mg
Psilocybin (4-phosphoryltryptamine)	12	mg
STP (2,5-dimethoxy-4-methylamphetamine)	5	mg
LSD (d-lysergic acid diethylamide tartarate)	0.1	mg

The approximate LD_{50} in a variety of species is given in Table 2. It can be seen that the LD_{50} correlates better with brain weight than body weight. The LD_{50} for man is an estimate based upon brain weight. A dose of 297 mg (0.1 mg/kg) was placed intramuscularly into one male elephant [51]. This was done to determine the effects of LSD *musth*, a periodic form of deranged behavior in certain elephant species. *Musth* is accompanied by secretions from the temporal

gland. The animal died within two hours in larygospasm and status epilepticus. When death occurs in human beings in connection with LSD, it is not caused by overdosage.

Table 2 *LD_{50} for LSD*

Animal	Body Weight (kg)	Brain Weight (gm)	LD_{50} (mg/kg)
Mouse	0.035	0.5	46
Rat	0.5	1.7	16.5
Rabbit	3.5	85	0.3
Man (?)	70	1400	0.2
Elephant (?)	4500	3600	0.15

Certain kinds of people are more resistant to the effects of LSD than others. Schizophrenics have a resistance to all medications including the psychotomimetics. Those individuals who want to resist the effects of the drug consciously or unconsciously may be able to prevent average amounts from having the usual impact. Chronic alcoholics may require more than ordinary doses to produce changes characteristic of the LSD experience.

4.2 *Absorption*

LSD is readily absorbed from the gastrointestinal tract, and definite psychic effects from average doses are reported in 30 to 120 minutes. It passes through all mucous membranes and the abraded skin. Subcutaneous, intramuscular and intravenous injections increase the rapidity of onset. When administered intraspinally or intracisternally, its action is instantaneous. Large doses have a more rapid onset of action and a longer period of activity than lesser amounts.

The amount required to produce an effect is so small that instances of accidental inhalation or ingestion are known. Scientists have unwittingly developed symptoms because a minute amount of the powder or solution came in contact with their fingers and was subsequently transferred to their lips.

4.3 *Tolerance and Cross-Tolerance*

Another remarkable characteristic of LSD is the tachyphylaxis that develops. Tolerance is complete within a few days, and enormous amounts can be ingested by a tolerant individual without effect. It has been shown [52] that tolerance is phasic with periodic waxing and waning of the effects in both animals and man. In goats, the rhythm appears to be four days, in man about nine days. The mouse is very resistant to the effects of LSD.

Cross-tolerance occurs between all members of the LSD series, including 2-brom-LSD, which is essentially non-hallucinogenic. Cross-tolerance can also be developed between LSD, mescaline, and psilocybin, but not to amphetamine [53], phencyclidine, or other central anticholinergic hallucinogens.

Both tolerance and cross-tolerance are lost within days after the psychotomimetic agent is discontinued.

4.4 Withdrawal Syndrome

A true abstinence syndrome is not identifiable for the psychotomimetic agents. Even in individuals who attempt to overcome the rapid onset of tolerance by doubling the dose each day, abstinence produces no characteristic pattern. Some EEG changes persist for weeks, but minimal or no clinical evidence for a withdrawal syndrome is apparent. Lethargy, disinterest in daily activities, a tendency to avoid here-and-now problems are more likely to be a recovery phase than anything that can be called abstinence on the basis of an altered physiology by enzyme induction.

4.5 Distribution in the Organism

The earliest radioactive studies in mice demonstrated that tagged LSD disappeared from the brain and blood within an hour. The half life for mice is ten minutes. This led to the earlier theory that LSD acted as a trigger for a sequence of aberrant neurochemical reactions that continued for many hours. The mouse data, although correct, cannot be extrapolated to human metabolism of the drug. Mice are capable of dealing with enormous amounts of LSD. They may almost be considered permanently tolerant to the drug, so effective are their mechanisms for metabolizing it.

Monkeys have an LSD half life of 100 minutes, and cats have a 130 minute half life. Spectrophotofluorometric measurements on human plasma provide us with a calculated half life of 175 minutes [54]. One half hour after the intravenous injection of 2 μg/kg, plasma levels reach 7 ng/ml. During the next 8 hours plasma levels gradually decline approximating the improvement in performance test scores. By the end of 8 hours, 2 ng/ml were still detectable in the plasma. It therefore is unnecessary to invoke a trigger action for LSD since it remains in the organism during the entire period of its activity.

The brain does not receive more LSD than it should by weight. Between 1.0 to 1.5% of the absorbed LSD reaches the brain and is soon detectable in the cerebrospinal fluid. If the dose is 100 μg, then about 1 μg is distributed to the brain. Very small amounts, from 2 to 7 ng/ml in the brain will provide intense psychic changes.

Localization within the brain is not by diffusion. Certain areas receive differential concentrations as studied by SNYDER [55] in the squirrel monkey. Twenty minutes after an intravenous injection, the blood, the cerebral cortex, the cerebellum, the white matter and the brain stem all had approximately similar concentrations. The thalamus and extrapyramidal system had 1.5 times as much, the hypothalamus and limbic system 2 to 3 times as much, the auditory and visual cortex had 2 to 5 times as much, the posterior pituitary and pineal glands had 5 to 7 times as much, and the anterior pituitary 10 times as much. These spectrofluorophotometric results were quite comparable to those obtained with ^{14}C-labeled LSD using an autoradiographic technique. These findings of a variable concentration within the central nervous system may help explain certain of the psychological phenomena. Inhibition of synaptic

transmission in the lateral geniculate body (a visual reflex area) could explain the disinhibiting effects of LSD on perception. In human subjects with subcortically implanted electrodes, LSD induced paroxysmal EEG activation of the limbic system, and particularly the posterior hypothalamus. The limbic system is involved with emotionality, the hypothalamus with the overall autonomic eleboration of emotion, and the anterior pituitary with the stress response.

4.6 *Metabolism*

The original proposal of WOOLEY [56] that the hallucinogenic productivity of LSD was due to serotonin antagonism was refuted by the demonstration that the non-hallucinogenic BOL is an even stronger serotonin antagonist on peripheral tissues and also crosses the bloodbrain barrier. MARCHBANKS [57] has pointed out that LSD enhances the binding of serotonin to neuronal macromolecules, and that BOL does not.

FREEDMAN [58] states that LSD causes a binding of serotonin in the nerve endings and a slowed metabolic rate of this neurohumor. The release of the norepinephrine which can be measured is contingent upon the state of hyperexcitation [59]. The significance of these finds is enhanced by the observation that, following the use of serotonin-depleting drugs such as reserpine, which impairs storage, or those that block the synthesis of 5HT, the effects of LSD are both enhanced and prolonged [60, 61]. On the other hand, after pretreatment of several days or weeks with monoamine oxidase inhibitors, or by feeding a serotonin precursor like 5-hydroxytryptophan, there is a diminuation of LSD symptoms [62]. Apparently LSD acts either by imitating serotonin at the receptor sites and blocking them, or by reducing the amount of serotonin at the synaptic cleft. LSD, then, decreases the firing of serotogenic neurons and decreases serotonin availability where it acts. Although brain 5HT levels may be increased while LSD is present, it remains intracellular and ineffective as a neuronal transmitter.

To substantiate these findings, investigators have found that LSD decreases the rate of biogenic amine depletion at 5HT nerve terminals [63, 64]. They demonstrate a decrease in turnover rate of 5HT. BOL in doses five times as large did not alter 5HT conversion from tryptophan [65]. LSD and serotonin seem to have similar CNS actions, and LSD is capable of stimulating serotonin receptors. The direct stimulation of serotonin receptors may call forth a negative feedback on presynaptic serotogenic neurons. This would result in a total decrease in activity of these neurons. Nonhallucinogenic compounds of the LSD series such as BOL do not produce these effects. In very large amounts, LSD can induce similar effects on norepinephrine levels and noradrenergic receptors.

4.7 *Cytogenetic Effects*

Since the original report of chromosomal fragmentation in 1967 [66], considerable study of all aspects of this problem has continued [67–90]. Human leukocytes have been exposed in vitro to varying concentrations of LSD.

People who have taken LSD have had their white blood cells examined. Their offspring have had cytogenetic studies. Animals have been given LSD, and various tissues, including testes and ovaries, studied. The early reports mentioned chromosomal breaks and exchanges. The percentage of chromatid and isochromatid breaks, exchange figures, and acentric fragments was found to be three times that found in nondrug controls in some series. These alterations in chromosomal morphology resembled those due to deep irradiation, certain viral infections and the use of antineoplastic agents. ^{14}C-labeled LSD administered to pregnant mice passed through the placental barrier. In the early stages of pregnancy, 2.5% of the dose was found in the fetus. In later stages of pregnancy, 0,5% of the injected dose appeared in the fetus [91]. Uptake in the placenta began in five minutes, was maximal in thirty minutes with a significant amount remaining in the fetus for two hours.

Children born of parents who had taken LSD were found to have similar chromosomal changes in some studies. An infrequent instance of a congenital deformity was reported. In one study of the abortuses of mothers who had taken LSD prior to or during pregnancy, a surprisingly large number of instances of exencephaly were reported [92]. Up to this date, this defect, incompatible with life, has not been definitely confirmed elsewhere. A small number of cases of acute leukemia have been reported in people who have used LSD [93]. Whether this number exceeds the number to be expected 'spontaneously' is unknown. The interest in acute leukemia was generated by reports of the Philadelphia chromosome in slides of LSD patients, since it is found in instances of acute leukemia.

During the time when the chromosomal anomalies were being reported, other investigators were finding that they could not duplicate these positive results. Considering the highly variable content of illicit LSD, and the pattern of multiple drug use, it may be too much to expect that a final answer to the important question of genetic structural change due to LSD will be quickly forthcoming. A number of investigators who had given pure LSD to their patients previously, found no significant changes in their chromosomal patterns when they were re-examined.

In October 1969, the National Institute of Mental Health sponsored a conference to attempt to answer the questions posed by the conflicting reports [94]. The early cytogenetic studies on LSD were reviewed and found difficult to interpret because of poor experimental design, inadequate controls, drug contaminants, exposure to other drugs, malnutrition and infections. Well planned, serial, in vivo animal studies would avoid some of these problems. It was not possible to make a definite statement at this time regarding the carcinogenicity, teratogenicity, or mutagenicity of drugs of abuse. However, precise, relevant, and practical investigations are badly needed in this and other areas.

4.8 *Excretion*

Over 90% of radioactive LSD is excreted within 24 hours. Large amounts can be scanned in the liver, gall bladder, and intestines four hours after an

intravenous dose. The excretory products are a 2-oxy-LSD [95], a 13-hydroxylated LSD [96], and glucuronides, all inert forms. These detoxification reactions all have been demonstrated in liver microsomes. The major portion of excretion products have been identified in feces, lesser amounts are present in urine.

5. Psychophysiology of LSD

5.1 *Autonomic Effects*

LSD stimulates central sympathetic, and to a much lesser degree, central parasympathetic activity. Pupillary dilation, piloerection (or gooseflesh), salivation, loss of appetite, lacrimation, tachycardia, and hyperglycemia is detectable in most species. Of these, mydriasis is the most constant. Most animals will manifest a rise in body temperature, with the rabbit being particularly sensitive. Doses of LSD as low as 0.5 to 1.0 μg/kg will produce hyperpyrexia. Hyperreflexia can be seen in man and many other animal species. Restlessness and peripheral vasoconstriction are regularly mentioned. The head shaking movements of mice can persist for weeks after a single high dose of LSD. Rats also demonstrate head shaking, motor hyperactivity, crawling movements and, at a later stage, inactivity. Incoordination is frequent after moderate or high doses in most animals. The blood pressure, heart rate, and respiratory rate respond more to the varying emotional state than to the pharmacologic effects of LSD. Tameness, calming, spacial disorientation, and ataxia are observed in monkeys.

In man the most obvious autonomic effect is dilation of the pupils up to 6 mm. They react partially to light. Quickened tendon reflexes, nausea, rarely vomiting, a tremor, sometimes muscle weakness, and flushing can develop. There is no change in cerebral blood flow, cerebrovascular resistance or cerebral oxygen or glucose utilization.

5.2 *Electrographic Effects*

The most frequent surface EEG finding is an alerting pattern in which low amplitude, high frequency, desynchronized activity is noted over the entire cortex. EEG arousal in man and the intact animal is a routine finding. The lower brain stem is the locus of EEG activity as determined by transection experiments. This site corresponds to the reticular formation.

Evarts [97] had the theory that changes in the conductance in the visual pathway may be a neural correlate of hallucinations. If the retinal input is impaired while the cortical projection site is more excitable because of the reduced inhibitory influence of subcortical structures, then hyperarousal may cause internally produced imagery.

It should be remembered that the EEG arousal state may be similar to that of rapid eye movement (REM) sleep. In both conditions, the cortex is alert, the difference between the two states being activity in the subcortical brain

areas. The LSD condition might be thought of as an electrographic waking dream state. In minute doses, LSD increased REM sleep [98], but large amounts reduced it [99]. ADEY [100] found that cats under the influence of LSD showed hippocampal and entorhinal seizures of 4 to 5 cps waves, a pattern which is also observed during REM sleep. LSD is supposed to facilitate REM sleep, but this may be a dose related phenomenon. He also noted an effect of LSD when he used computer averaging techniques which lasted up to a week [101].

The quantified EEG's of schizophrenics and of controls given LSD both show sustained excitation. Whereas LSD decreases the variability of the record in normal subjects, it increases the variability of schizophrenic tracings. The latter are known to be less variable under ordinary conditions. Chronic schizophrenics with implanted depth electrodes showed paroxysmal hippocampal, amygdaloid and septal activity if their psychosis exacerbated under LSD.

5.3 *Endocrine Effects*

The organism exposed to LSD shows evidence of nonspecific stress. Leukocytosis, eosinopenia, a slight elevation of 17-ketosteroids and a moderate elevation of the 17-hydroxycorticoids, have all been recorded. Urinary phosphate excretion is diminished, and plasma free fatty acids are increased. This rather good evidence that ACTH and adrenal cortical function is increased is accompanied by suggestive evidence of diminished thyroid and gonadal activity. While under the effects of LSD, the antidiuretic hormone of the posterior pituitary is elevated. The prior administration of steroids have been reported to block the effects of LSD [102].

6. Psychological Effects of LSD

The psychological effects in man are numerous, diverse, and variable. The action of psychotomimetic agents, more than any other class of drugs, is difficult to predict. They are markedly influenced by non-drug variables such as the personality of the subject, the conditions under which the drug is taken, the expectations of the investigator and of the subject, the relationship between these two individuals and many other factors. These are the non-specific factors which may play an enormous role when a drug which releases ego controls is administered [103].

Vast changes may occur during a single session due to the hypersuggestibility of the subject or patient whose critical functioning may be in abeyance. It is therefore with some difficulty that the psychological effects of LSD are described with accuracy.

6.1 *Perception*

A great difference between the subjective impression of what is perceived, and the ability to objectify that sensory percept exists. In fact, attempts to

measure the state seriously interfere with the course of the experience. It is the perceptual alterations that are most notable about the LSD experience. The state is one of hypervigilance, as though every sensory cue required intense scanning. As in any prolonged hyperalert state, the ability to sort and code the input may break down.

6.11 Visual Perception

One of the first subjective effects following the ingestion of LSD may be a colorful, moving display of patterns slanting past one's closed eyes. Later, complex forms and scenes may be fantasied. When the eyes are opened, these changes disappear, but as the state intensifies, the color and depth of viewed objects become more intense and more pronounced. An inner luminosity seems to glow out of ordinary materials. Textures become more pronounced. Illusions are frequent and consist of the movement of stationary objects or the erroneous reading of a sensory cue. For example, a spot on the wall may be mistaken for an eye. Faces may change. The afterimage is measurably prolonged.

Pseudohallucinations also occur. These are complete misperceptions, but with the retained awareness that they are drug induced, and therefore not real. True hallucinatory experiences are rare, but they do occur at higher dosage levels, and are responded to with an affect appropriate to the hallucination. These are concepts projected as percepts onto the outside world. The meaningfulness of the percept may be overwhelming. A hair may take on the entire significance of the universe. There is a complete cathexis between the object and the self.

6.12 Auditory Perception

Sounds are, for some, profoundly altered during the LSD experience. Music may be apprehended as never before. Background noises are heard with new awareness. Auditory hallucinations are very rare. Auditory illusions certainly occur. A dropped ashtray may be interpreted as a shot fired at the subject. Some subjects have hyperacusis.

Crossing over of sensations are a hallmark of the LSD experience. These are synesthesias in which a color is heard or a sound is smelled. Their genesis has been incompletely investigated.

6.13 Tactile Perception

Subjects relate that their sense of touch has become much more sensitive, and that stroking an object has become a more sensual experience.

As an example of the discrepancy between the subjective report and the objective verification, we [104] examined tactile thresholds, pain thresholds, color discrimination and a list of other sensory tasks. None was changed in the direction of improvement.

6.14 Taste and Odor Perception

Differences in these sensory modalities occur. They often reflect the emotional status of the moment. Ordinary food may taste 'better than anything I ever ate', or a foul odor may be complained of which no one else in the room could detect.

6.15 Time Perception

The internal clock is greatly disordered under LSD. Time slows down or stops completely. Time estimation is impaired. The slowing down of subjective time may be due to the flood of thoughts that make seconds seem like hours. Subjects are generally amazed at the length of time that an LSD session takes. Although it ordinarily lasts six to ten hours, it seems like years. This can be pleasant if the experience is an euphoric one, but it may be very frightening if it is anxiety ridden. Then the notion that it has gone on interminably and will last forever is believed.

6.2 *Cognition*

Mental functioning under LSD is often eidetic: the thought is seen. Logical thinking may give way to paralogical thought processes. Ideas of omnipotence are common, though paranoid notions of suspicion and persecution are also known. The ability to read people's minds, transmit thoughts, fly, walk on water, have all been held by some subjects.

Ideas seem unusually creative and brilliant, and the idea of consciousness expansion arises from the alleged expanded conceptual activities that seem unique, original, and novel. Again, on testing, the great insights and enlightenments turn out to be less than unusual. It is the lack of the ability to discriminate one's thought processes and the loosening of the critical functions of the ego that makes the experience seem to be the real reality so vivid and believable.

In tests of intellectual functioning, a deficit is invariably found [105]. In part, this is due to lack of motivation to perform, interfering thought sequences or perceptual distortions. In tests of parapsychological ability, LSD subjects did no better than under their control state despite their strongly held idea that they could be telepathic, precognitive, or clairvoyant.

6.3 *Emotion*

As with all other disinhibiting agents, LSD provides a loosening of affect, sometimes inappropriate extremes of emotion along with considerable lability. Feelings can range from ecstasy to horror with all intermediate feeling tones. It is surprising how two ordinarily incompatible emotional feelings can coexist at times. The 'good trip' is a blissful or euphoric experience with appropriate perceptual and cognitive elements. The 'bum trip' is anxiety or panic ridden with sensations and thoughts consistent with this mood. Since the LSD state is an hypersuggestible one, these 'trips' can be manipulated at will.

Some people who suffer from an inability to feel deeply in their sober state find the LSD experience attractive because it allows them to experience strong emotions.

6.4 *Ego Function*

Changes of ego function may be imperceptible at the lowest dosages and completely disrupted at the higher ranges. Initially, one's ordinary repertoire of ego defenses come into play to cope with the peculiar changes that LSD brings. Eventually, they may be overwhelmed, and one can either become terrified at the loss of controls or joyful at the ability to relinquish them.

Gross distortions of body image are common. One may think that one is a giant or a dwarf. One part of the body may seem larger than the other. One's face may appear entirely unrecognizable in the mirror. Duplication or triplication of the self has occurred. The ultimate is complete depersonalization in which self identity disappears. Derealization is a pervasive belief that all things have become strange.

It is obvious that these alterations mimic both those of psychosis and of the mystical state. When they are terrifying and disorganizing, they are called psychosis. When they are perceived as a beautific fusion with the universe, this is interpreted as the mystical state.

6.5 *Learning and Conditioning*

The LSD state can be a learning event since it is a new experience. Some professionals have said that it has enhanced their ability to empathize with their psychotic patients. Certain conditioning and programming may be lost in connection with LSD. This results in abrupt attitude changes and value shifts. The psychotomimetics affect a wide variety of instinctual as well as learned behaviors in all species. Thus, they have some general biological significance.

Reward behavior is generally depressed by ordinary doses of LSD. Aversive conditioning is not blocked. This is opposite to the approach-avoidance behavior of antipsychotic drugs in animals.

Low doses of LSD in the cat increase the level of physiological arousal, and decrease the ability of the animal to habituate to environmental stimuli which were once relevant. Behaviorally, it is as though an enhanced sensory impact occurs. This increased arousal and generalization of sensory imput may induce changes in the animal's ability to discriminate events in the environment. Whether such changes result in increased or decreased accuracy of perception depends upon many factors such as dose, complexity of task, and many environmental factors.

6.6 *Behavior and Performance*

Behavioral patterns are often more predictable than other facets of human functioning. Under moderate or large doses of LSD, the subject is inclined to

be passive, sitting quietly or lying down with eyes closed attempting to deal with or integrate the unusual state. Task orientation is grossly impaired. Sleep is unusual. Other behaviors are possible. Attempts to maintain control by talking incessantly are known. Hostile acting out occurs in instances where loss of control unleashes repressed aggressive tendencies. Disrobing is mentioned at times. When panic and a loss of insight into the situation occur, the subsequent behavior can reflect this condition. A person may respond actively to a paranoid delusion. It is to deal with the infrequent behavioral disruptions that a skilled person should be in attendance.

Performance as measured by tests are almost invariably impaired. Psychomotor skills suffer, verbal fluency, ability to abstract, all types of reaction time are prolonged and the more complex the task, the worse the performance [106].

6.7 *Semantics*

The vocabulary used to describe and understand the LSD state has its impact on the individual's response to the drug. The use of words with positive or negative implications colors the comprehension of the experience. Table 3 indicates how a drug effect may be perceived as an event which is psychotic or integrating.

Table 3 *The semantics of LSD*

Psychotomimetic	← Drug Effect →	Mysticomimetic
(Hallucinatory)		(Psychedelic)
Depersonalization	← Ego Loss →	Mystical union; fusion
Illusion, hallucination	← Perception →	Visionary
Delusion, irrational	← Thought →	Non-rational
Euphoria	← Emotion →	Ecstasy

7. Psychotherapeutic Efforts with LSD

Because of the impressive altered state of awareness, the psychotomimetic agents were tried as therapeutic agents almost as soon as they became available.

7.1 *Psycholytic Psychotherapy*

The use of modest amounts of LSD to intensify the affectual response, increase the transference relationship, retrieve repressed, unconscious material and remove the ordinary blocks to insight have been tried especially, but not exclusively, in numerous centers in Europe [107]. In a patient well known to the therapist, it seems possible that emotional working through could occur with occasional LSD sessions. These must be reinforced during non-LSD interviews. Abreactions may occur, ego defenses may be reduced, and reconstructive work accelerated. The procedure has not been proven on a scientific level, but a

number of therapists feel that LSD-assisted psychotherapy can be helpful in selected cases.

7.2 *Psychedelic Psychotherapy*

In North America, single or a few large dose sessions which are aimed at a dissolution of the ego boundaries and the achievement of a transcendental experience have been tried, primarily in alcoholics whose progress can later be measured by the subsequent drinking patterns. Insight may or may not be achieved. What is sought is simply a psychological death-rebirth experience with the opportunity for a new beginning. The old feelings of guilt and self-hate can be set aside and destructive drinking patterns changed.

The original workers reported very promising results from this quick attempt at behavioral change. As soon as controlled studies were performed, investigators reported uniformly non-significant results. Apparently, more than a massive emotional experience is necessary to alter the noxious habits of a lifetime. Combined with intensive followup psychotherapy, this technique still may have some promise [108].

Hypnodelic psychotherapy is a variant of psychedelic treatment which includes the enhancing power of suggestion of hypnosis plus the quality of the LSD state. It has had insufficient trial to make an informed judgement about it [109].

8. Complications of Psychotomimetic Agents

During the first 15 years of research with LSD, it was unavailable on an uncontrolled basis, and the adverse reactions were rare. When subjects and patients were carefully selected and adequately protected, the incidence of complications was negligible [110]. After it became widely used in non-medical settings, a startling increase in adverse reactions were seen. These can now be categorized [111, 112].

8.1 *Immediate Reactions*

In the course of an LSD exposure, three major events can occur which are undesirable. One is the panic or severe anxiety state. People responding to the dissolution of their ordinary world with fear may become frightened and attempt to run away. This can cause injury or a fatality.

A second untoward occurence is the paranoid reaction which becomes so real that the person responds to the delusion. Typically, attempts to fly have been made. This sort of accident is illustrative of how strongly these ideas can be held.

A third complication is a confusional state in which disorganized behavior gets the individual into difficulties. He may be disoriented, his thoughts may be chaotic, and his control over his behavior so attenuated that he gets into difficulty. Typically he may wander into the path of an oncoming car.

For these acute reactions, the patient should be brought to a secure place and reassured that he will recover. At times he can be talked out of his anxiety

or paranoid notions. When sedatives are required, barbiturates may be safest because of the questionable contents of black market psychedelics.

On rare occasions LSD has caused grand mal convulsions in people who were not epiliptic. The usual anticonvulsant treatment for such an event is adequate. Seizures are not likely to recur during the drug-free interval.

8.2 *Recurrent Reactions*

For reasons incompletely understood, the person who has tried LSD, especially one who has used it many times, may have recurrences without exposure to the drug. These 'flashbacks' may be anxiety provoking since the person thinks that he is going mad. They can also be very upsetting because they often happen under psychological or physical stress conditions. Certain unassociated medications may bring on a 'flashback'.

An occasional suicide has been attempted in connection with a recurrence. Actually, they usually subside spontaneously, and the patient requires support and reassurance or mild tranquilization for his anxiety.

8.3 *Chronic Reactions*

A variety of prolonged reactions can be listed. Following an LSD event or a 'flashback', the person may become anxious, depressed, or both. Some LSD-like phenomena may persist. These non-psychotic states rarely last more than a few weeks.

The prolonged psychotic reaction is more serious. If the patient does not recover over a period of days following his LSD exposure, he should be vigorously treated as an acute schizophrenic reaction. The outlook is not always favorable for recovery.

Table 4 *Median number of drug experiences in LSD and control groups (30 in each group)*

Drug	LSD Group		Control Group	
	Number of subjects	Number of experiences	Number of subjects	Number of experiences
LSD	30	70	...	...
Marihuana	30	500	6	11
Amphetamines (oral)	18	100	...	...
Amphetamines (sniffed or injected)	15	40	...	...
Dimethyltryptamine (DMT)	9	10	...	...
Codeine cough syrup	8	4	...	...
Barbiturates	7	50	...	...
Psilocybin	6	5	...	...
Heroin	6	4	...	...
Cocaine	6	3	...	...

Sufficient numbers of chronically confused, disoriented individuals who complain of poor memory and inability to concentrate have been seen, that the

question of temporary or permanent organic brain damage arises in the therapist's minds. Studies [113] have not yet conclusively proven that LSD in large quantities produces brain cell changes, but the clinical picture of a chronically brain impaired individual can be seen in 'acidhead' colonies. Were these brain damaged individuals who gravitated into these groups? Did their frequent exposure to LSD and a host of other substances produce the picture of brain damage? To show how many other drugs are used by heavy LSD users, Table 4 is presented. It demonstrates the multiple use of drugs among 30 individuals who had used LSD 50 or more times.

9. Summary

As we come to know more precisely how picogram quantities of a psychotomimetic agent deposited on specific nerve cells for a short period of time can profoundly alter mental processes, an enormously important advance in our knowledge of brain functioning will occur. The derangement we call 'psychosis', the state we call 'mystical', even the condition we call 'normal' will be illuminated.

By what cerebral mechanism do we sense, think, and feel under the influence of a psychotogen? How is it that our hold on reality is so tenuous that a few molecules of LSD can enormously alter it?

The use of the psychotomimetic agents for pleasure, to shatter the structure of ordinary reality, for phantasmagorias of sight and sound, for 'religious' purposes – these all pose a question which is well worth our consideration. Is this a chemical trick played upon the delicately counterbalanced mind of man, or is it the release of inhibitory activity toward his full potential to perceive and integrate his universe?

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