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Hallucinogenic Drugs

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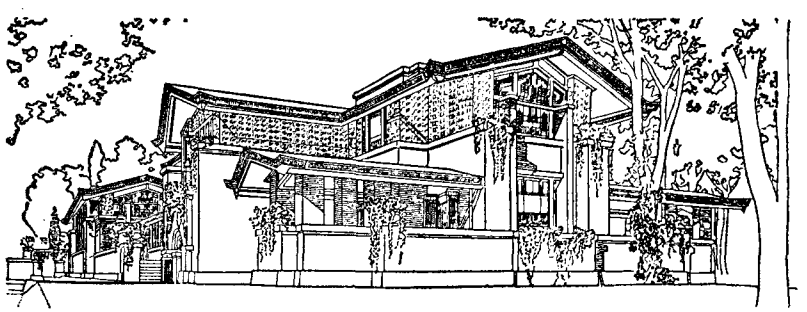

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FOREWORD

OUR LIVING CHEMISTRY SERIES was conceived by Editor and Publisher to advance the newer knowledge of chemical medicine in the cause of clinical practice. The interdependence of chemistry and medicine is so great that physicians are turning to chemistry, and chemists to medicine in order to understand the underlying basis of life processes in health and disease. Once chemical truths, proofs and convictions become sound foundations for clinical phenomena, key hybrid investigators clarify the bewildering panorama of biochemical progress for application in everyday practice, stimulation of experimental research, and extension of postgraduate instruction. Each of our monographs thus unravels the chemical mechanisms and clinical management of many diseases that have remained relatively static in the minds of medical men for three thousand years. Our new Series is charged with the *nisus élan* of chemical wisdom, supreme in choice of international authors, optimal in standards of chemical scholarship, provocative in imagination for experimental research, comprehensive in discussions of scientific medicine, and authoritative in chemical perspective of human disorders.

Dr. Brown of Memphis unravels the dim haze of mystery on the psychoactivity of hallucinogens with enchantment in its pursuit. These "mind drugs" produce varied experiences—psychotic, psychodynamic, cognitive, aesthetic, mystical to ease the uncertainties of the day and avoid psychic pain, to achieve pleasure, to find faith, to reach experiential transcendence, to seek the imagery of rebirth. Once the quest is on, the individual relinquishes the core of his existence, his individuation, for the potion becomes the master. First he takes the drug, then the drug takes him. Once the Rubicon is crossed, the barriers are gradually let down for destruction.

An hallucinogen interferes with brain metabolism producing uncontrolled stimulation and altered perception. It is mind-expanding or psychedelic reducing the perceptual filter to give the user a "trip." He experiences distortion of time, space and colors and hears colors and sees colored sounds. There is regression into the past and the individual feels as if he is coming out of his body experiencing vivid revelatory hallucinations. The "mind drugs" serve the new mood for mysticism and exploration of internal space.

Man has been an inveterate experimenter with chemicals, usually derived from plants, that made him happier or livlier or altered his perception and awareness. Natural hallucinogenic drugs like marijuana, hashish, and peyote have been known since prehistoric times and used in religious rites down to the present. Artificial hallucinogens like LSD and THC have become well known for two decades. The same drug in the same dose in the same person may produce very different effects, according to the events which precede or follow a particular medication. Hallucinogens are illegal because of their presumed harmful effects. Unlike opium derivatives, none is addicting; unlike barbiturates, none is a cerebral depressant. Like sedatives and anesthetics, they alter subjective states of awareness pleasurably in mind-expanding sensations. They may cause temporary psychoses, dreamy states and delusional withdrawals from reality which may produce permanent damage. Nevertheless, the hallucinogens constitute behavior-control devices for the future once their specificity and selectivity are delineated. The hallucinogen is like the finger of God, it can slake and it can smite.

What is this I hear of sorrow and weariness
Anger, discontent and drooping hopes?
Degenerate sons and daughters
Life is too strong for you
It takes life to love Life.

I. NEWTON KUGELMASS, M.D., Ph.D., Sc.D., *Editor*

PREFACE

Part of my duties at the University of Tennessee Medical Units is to participate in the teaching of freshman medical students. For the past two years, several groups of young men have worked with me in a varied and continuing study of hallucinogenic drugs. Together we have examined the literature; the history, biogenesis, pharmacology, toxicity and psychoactivity of these materials have been explored. We have probed the chemical properties, searching for a clue to the mystery of their psychoactivity. Also, we have discussed, sometimes objectively, but at times with individual personal commitment, the social and cultural ramifications of drug-taking.

In this monograph, I have tried to retain, or rather, to capture, some of the essence of those sessions; the casual concern, the exuberance, the willingness to accept and/or to modify reality, the disappointments that so often accompany knowledge, especially when the latter interferes with the stuff from which dreams are made, and, above all, honesty. That is not to say that all of my own personal bias and opinions as related to drug-taking and the effects thereof have been excluded. Bidden or not, bias and opinion have an insidious way of creeping into every thoughtful endeavor. But I have tried to be honest with myself and the reader. In those areas where opinions, as opposed to a physical property such as say, aqueous solubility, may influence the evaluation of a drug or the response to a drug, I have tried to present the various views. However, I may have made no effort to conceal my own evaluation of the concept under discussion.

As for organization, the book has been built around the chemical distinctiveness of the drugs. Medically trained individuals, in my opinion, tend to shy away from chemistry, par-

ticularly if it appears to be irrelevant to a working concept. The key word, of course, is *relevance*. Students readily shed their timorous regard for the chemistry of drugs when confronted with the molecular intrigue built into each compound—and to the necessity for knowing that the intrigue is there. One can almost see the mental machinations evoked by the realization that substances such as psilocin and serotonin are chemically very similar compounds. Using the chemical structure as a base, the dosage, pharmacological, biochemical, and psychological properties can be more meaningfully discussed.

For information I have relied extensively on literature reviews and published symposia. In the past five years, these have appeared in respectable numbers in the literature of pharmacology, biochemistry, psychiatry, as well as in the neurosciences, psychopharmacology, and so forth. Thus, it is possible to derive a broad based view of drugs and attendant problems. For the most recent developments of the past year or two, journals, periodicals and books have been searched for current research results and articles of topical interest.

The author is indebted to several people for help in the preparation and appraisal of this manuscript. Dr. W. G. Struve, Assistant Professor of Biochemistry, and Dr. A. O. Battle, Associate Professor of Clinical Psychology at the University of Tennessee Medical Units read the manuscript and offered constructive suggestions for improving it. I am also indebted to the nimble fingers of Mrs. W. G. Struve (Nancy) for typing the final draft. Lastly, I must thank Mrs. Jerry Defoor and Palmer Gordon for many hours of tedious proofreading. Without the help of these generous people, the task of putting this book together would have been much more difficult.

F. CHRISTINE BROWN

CONTENTS

HALLUCINOGENIC DRUGS

Chapter I

GENERAL CONSIDERATIONS

THERE ARE MANY substances which will, if taken in the appropriate quantities by normal subjects, produce distortion of perception, vivid images, or hallucinations. Most of these compounds will produce powerful peripheral as well as central nervous system effects. A few agents are characterized by the *predominance* of their actions on mental and psychic functions. This group of compounds has been called the *hallucinogens*. Several other terms have been used: *psychotomimetics*, *psycholytics*, *psychotogens*, the theatrical-sounding *phantastica*, and *psychedelic*. Of these titles, psychedelic, a term coined by Osmond[1] meaning "mind manifesting" and which has been called an "etymologically impossible word" by Schultes,[2] is the most widely known to the general public. In recent years, the term has become a synonym for the morals, mores, and actions resulting from the use and misuse of the most famous of the hallucinogens, LSD. Psychotomimetic, which means *mimicking psychoses*, was introduced to describe the capacity of these agents to induce a so-called model psychosis. Because of the diverse nature of the symptoms observed under different conditions of administration and dosage, the variety of chemical structures included, and a general lack of knowledge as to the underlying mechanisms involved in the physiological and psychological effects, none of the names suggested to date are adequately descriptive. This writer prefers the term hallucinogen for mostly negative reasons. It does not imply any knowledge, or suggest a hypothesis, as to how, why or where, these agents elicit the observed effects, but it does describe one specific property which most of them have in common.

Classification of the Hallucinogens

The major hallucinogens of current interest may be classified into five groups of chemically distinct compounds and a sixth group composed of substances of diverse chemical identities:

1. lysergic acid derivatives
2. indolealkylamines
3. phenylethylamines
4. piperidylbenzilate esters
5. cannabinoids
6. other

Except for the benzilate esters and a related group of compounds, the phenylcyclohexyls, which are products of a more practical "manifestation of mind," synthetic organic chemistry, drugs representing all of these classes have been isolated from natural products. Most of the hallucinogens identified to date are alkaloids, that is, having alkaline properties. The one major exception is the cannabis group. Alkaloids are found abundantly in plants. Out of the total number of plant species, variously estimated to be from 400,000 to 800,000,[3] only about five thousand or so are known to be alkaloidal. Surprisingly few of these, about sixty, produce hallucinogens. Ethnobotanical researchers, who go into remote inaccessable areas of the world in search of rapidly disappearing primitive cultures, say that there are appreciable numbers of hallucinogenic plants still unknown to scientists.

Current interest in psychoactive compounds has stimulated an intense search for these unknown plants, and a closer look at the active ingredients of those that are known. Recent evidence[3] has shown that the active ingredients of fly agaric from the mushroom, *Amanita muscaria*, is not muscarine or bufotenine, both of which are present in small amounts, but muscimole, an unsaturated hydroxamic acid, and ibotenic acid. Although Hofmann and Tscherter[4] found lysergic acid derivatives in morning glory seeds, Cook and Kieland[5] isolated a glucoside from an extract (ololiuqui) of these seeds which is five times as active as the original extract. Thus, the list of

classes above may have to be altered and expanded as our knowledge of the versatility of plants increases. But that information may become even more difficult to ferret out as aboriginals become less original and their cultures yield to the advancing technologies of transportation and communication. Primitive cultures are disappearing, and with them the native knowledge which has been so helpful in the discovery and development of useful plant products.

Drug Dependence

The terms *addiction* and *habituation* have been almost as controversial as the conditions they describe. Uncertainties over the definitions of these words have plagued scientists, sociologists, legislators, and theologians for years. The term addiction, for instance, acquired a sociological significance with which scientists, particularly, are reluctant to deal. Drug *addiction* came to have an evil connotation, more definitive of public mores and attitudes toward a substance than of the capacity of that substance to induce disorders of behavior. The Expert Committee on Addiction-Producing Drugs of the World Health Organization made several attempts to solve some of the semantic problems peculiar to the terms *addiction* and *habituation*. In 1957, they defined the two terms as follows:[6]

> Drug addiction is a state of periodic or chronic intoxication produced by the repeated consumption of a drug (natural or synthetic). Its characteristics include
>
> 1. an overpowering desire or need (compulsion) to continue taking the drug and to obtain it by any means;
> 2. a tendency to increase the dose;
> 3. a psychic (psychological) and generally a physical dependence on the effects of the drug;
> 4. a detrimental effect on the individual and on society.
>
> Drug habituation (or habit) is a condition resulting from the repeated consumption of a drug. Its characteristics include:
>
> 1. a desire (but not a compulsion) to continue taking the drug for the sense of improved well-being which it engenders;
> 2. little or no tendency to increase the dose;
> 3. some degree of psychic dependence on the effects of the

drug, but absence of physical dependence and hence of an abstinence syndrome;
4. detrimental effects, if any, primarily on the individual.

In 1964, the WHO Expert Committee revised its recommendations and included a suggestion to replace the terms *addiction* and *habituation* with the expression *drug dependence* of a particular type in each specific case, that is "drug dependence of marihuana type" or "drug dependence of morphine type." It was thought that *dependence* was a general term which described a common feature of all types of drug abuse. Furthermore, the term could be used without invoking or implying the social stigma which was attached to the old terms, particularly to *addiction.*[7]

Psychoactive drugs are usually classified into two broad categories:[8]

Depressants. The depressants, which reduce mental and physical performance, include alcohol, barbiturates, anesthetics, and other sedative-hypnotic agents. Colloquially, depressants may be called "downers." These compounds can cause loss of consciousness and complete loss of motor function. Dependence of the depressant type may not cause immediate overt antisocial behavior, but chronic abuse is always accompanied by physical dependence. Termination of the drug is characterized by a distinctive abstinence syndrome. Thus, drug dependence of morphine-type or alcohol-type leads to antisocial behavior indirectly. These materials are expensive, and the dependent subject, sooner or later, turns to crime to obtain the drug and to avert the compelling need brought on by withdrawal.

Stimulants. These compounds excite and enhance psychic function and increase motor activity. The groups include psychomotor stimulants such as the amphetamines. Hallucinogens are considered to be stimulants. A common property of this class is the capacity to induce psychotoxicity, distortion of perception, hallucinations, illusions and other disorders of behavior. The major difference between hallucinogens and psychomotor stimulants such as cocaine or amphetamine is one of dose; the latter require much larger doses to induce

psychotic-like behavior.[8] No physical dependence occurs with hallucinogenic drugs and there is no clearly defined abstinence syndrome. Nonorganic dependence, which may and often does occur, is a factor common to all forms of drug dependence.

One of the important characteristics of stimulants is that they, unlike "downers," elicit antisocial behavior. Delusions, false bravery and extremes of perceptual distortion may occur, while physical capacities remain intact. Coupled with a loss of mental control, this condition often results in aggressive, if not violent, behavior.

In the continuing effort to understand the mechanisms of drug action, the phenomena of tolerance and physical dependence have been rigorously investigated. Tolerance develops with chronic ingestion and modifies drug actions by reducing effectiveness. Most hallucinogens induce tolerance, but not physical dependence. A great deal of scientific and medical effort has been expended in the study of these two related, but independent, phenomena. Both conditions can be produced at will in the laboratory in either animals or man, and physical dependence can be effectively treated. Many hypotheses have been proposed over the years to explain the development of tolerance and physical dependence. Past and current theories, and the results of current investigative endeavors, have been reviewed in several recent articles.[9-11] Despite the intensive concentration on these two drug-induced conditions, we do not understand the cellular mechanisms that determine their existence. However, the research is likely to continue because tolerance and physical dependence are considered to be the most important factors in ultimately understanding the conditioning and maintenance of drug-seeking behavior.

Why Do We Take Drugs?

Current public concern, bordering on panic, over the drug problem has stimulated a revival of the philosophy of conjecture relative to man's propensity for drugs. Messer[12] recently added some new thoughts to an old hypothesis[13] to explain why men (and women) take drugs. According to him, the present drug problem is a part of the "end of a myth" or the end of

a cultural era. The "age of reason and enlightment" which brought capitalism, music, art, and science, especially science, has become "overripe"; the goals have been achieved. Affluence is an important part of the achievement and is also the shared historical experience of the age group who seek to "cop out." Their subjective experience of the successful economic is that the project is completed. They are not concerned with the "struggle for existence" but seek to "pacify existence" or to "indulge in existence." Messer concedes that members of the so-called psychedelic revolution are parasites. However, he exhorts us to accept the historical reality of our position in time; to *live off machine* rather than *like machines.* When the concept of "work" becomes culturally irrelevant, then so will the concept of parasites. Because of their historical location, a considerable portion of today's youth can perceive that we are "running out of era," and they are busy inventing a new myth. The taking of drugs is a part of a search for a new reality.

Clausen[14] offers some timely, well-frayed thoughts. He suggests that drug dependence "is, indeed, primarily a symptom of a deeper pathology that derives from our failure to integrate into the social fabric the more deprived migrants to our metropolitan centers, especially those disadvantaged by minority-group status. Subjected to all the stimuli which beckon Americans to participate in the joy of an affluent society, yet lacking the legitimate, socially approved means to achieve the gratifications and material rewards promised by this society, some of these persons turn to deviant and illegal means." Seevers[8] suggests a more realistic, and surely less myopic, view when he fatuously (his own evaluation) says that the individual having had no experience with psychoactive agents will never become dependent. This, in Seever's words, is the only means to eliminate drug dependence in the human society. "Having once experienced drug effects, a large majority of the world population will inevitably become drug dependent." Some drugs are weak and little harm results, but some are extremely powerful reinforcers and could, under the

right conditions, cause a social disaster. "It should be clearly understood by those who decry the depravity of the drug addict that susceptability is only relative, and if conditions are optimal, almost any individual can be made drug dependent, even against his will."[8] There is considerable experimental evidence to support this view. Lower animals, such as the monkey and the rat, having once experienced a drug like cocaine will, without exception, self-administer the drug until they die.[15] In a recent symposium, experiments utilizing this behavioral component in animals to study the psychological approaches to dependence and tolerance were described.[16,17]

In this book, it is not the author's aim to probe deeply into the moral, legal, or philosophical considerations[18] implicit to a discussion of why people take drugs. Rather, some of the drugs which have profoundly influenced the mind and emotions of man will be described; facts will be presented; properties will be discussed. It is the author's hope that this type of information can serve the reader when, and if, he himself chooses to delve into the many considerations involved in drug-seeking behavior.

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Chapter II

PHENYLALKYLAMINES: MESCALINE AND AMPHETAMINES

IN THIS CHAPTER, two important groups of hallucinogenic agents will be considered. Historically the β-phenylethylamines, typified by naturally occurring mescaline, are the most interesting. In recent years a structurally related group, the phenylisopropylamines, have become important drugs. The latter compounds are derivatives of amphetamine, but hallucinogenic activity is found only in those which are methoxylated; thus, they could be considered as mescaline derivatives, and in the past many authors have classified them in this way. However, several psychoactive substituted amphetamines have been synthesized recently and there is a growing literature on their chemistry, pharmacology and psychopharmacology. I will classify them correctly as phenylisopropylamines but discuss them as amphetamines. The amphetamine terminology is improper, but it is familiar and therefore useful.

PHENYLETHYLAMINES

The phenylethylamines occur abundantly in both the plant and animal kingdom, are nitrogen containing, and have basic properties, but their classification as alkaloids is open to question.[1] Unlike more typical alkaloids, the structures are relatively simple; the nitrogen atoms are not incorporated into heterocyclic skeletons; and they can be derived from amino acids by a few simple reactions. For example, decarboxylation of most amino acids gives rise to simple amines which are certainly not regarded as alkaloidal. However, these simple amines may be hydroxylated or methylated to give compounds

which are sometimes classified as alkaloids. Robinson[1] proposes the adoption of the name "protoalkaloid," suggesting both a simple structure and a possible role as precursor of more typical alkaloids for these borderline compounds.

Many, if not most, of the β-phenylethylamines, whether derived from animal or plant sources, are sympathomimetic. For many years "sympathin" activity was attributed to epinephrine, but within the last ten years norepinephrine has been identified as the neurohormone. Both of these compounds are phenylethylamines and are structurally very similar to mescaline. Of the many protoalkaloids of this type which have been isolated from both plant and animal sources, only mescaline has been shown to have hallucinogenic activity in man.

Mescaline is a natural constituent of certain species of cactus which grow in the more arid regions of the American continents.[2,3] Centuries before the white man came to this area of the world, Indian tribes of what is now the southwestern part of the United States and of Mexico used and revered peyote as a sacrament. In some territories it was called mescal or mescal buttons; on the Rio Grande it was called pellote, peyote, or peyotle.[2] The first literary reference to peyote was made by a missionary, one of the many who religiously followed in the white man's wake and served perhaps a greater function by observing and recording information about what was to them new faces, new places, and odd new cultures. Thus a Franciscan monk, Bernardino de Sahagan, succintly summarized in 1560 a large part of our knowledge of peyote and the effects it can produce. There were also references to the cactus and its remarkable effects in books written by Spanish naturalists and historians who came to the new world as a result of the Spanish conquest of Mexico. The use of peyote for either divinatory or devilish purposes was abhorrent to the teachings of the Catholic Church, which waged an ideological and legal effort to stamp out the cult. However, in spite of church and state prohibitions, peyotism not only remained alive among Indian tribes, it spread. In 1918, the American Church of North America was incorporated. The "peyote church," composed of a once numerous sect restricted to Indians, is a synthesis of old Mexican, Christian, and local religious rites[4] which includes the imbibing of peyote as a part of the sacrament. Over the years some efforts have been made, under the aegis of the law, to prevent the use of the cactus in the rites of this church. In recent years, much has been made of this sort of so-called religious persecution. Various Supreme Courts in the United States have ruled that, as applied to religion, drugs are no affront to the law or to society.[5]

Little or nothing was known of the nature of the peyote until 1886 when Lewin, the intrepid traveler, came to know the plant. He was not only fascinated with the bizarre symptoms which he personally experienced with the drug, but was aware of its potential for exploring mental functions.[6] His interest led indirectly to identification of the cactus plant as a species of *Anhalonium*, and directly to knowledge of the alkaloidal nature of its extract. He crystallized anhalonine, which is not, however, responsible for the sensory effects. Heffter isolated several protalkaloids from various species of cacti, and, in 1896, isolated and identified the active hallucinogenic agent, mescaline, from *Anhalonium lewinii*.[7] In 1919, Späth published the first of a long series of papers in which he and his collaborators were to clarify the chemistry, establish the structure, and synthesize several of the cactus alkaloids. Among these were mescaline,[8] N-methyl mescaline[9] and N-acetyl mescaline.[10] They also isolated, identified, and characterized a large number of alkaloidal isoquinolines, which are thought to be derived from simple protalkaloids. None of the isoquinolines are hallucinogenic.

Chemistry

The chemistry of the naturally occurring phenylethylamines has been known for at least a half-century, probably because they are substances of fairly simple structures. Reti[2] summarized the knowledge of these compounds up to 1950. The structures of several phenylethylamines which are found in a variety of natural sources, but not necessarily in cactus, are shown in Figures 1 and 2.

When it is freshly picked, cactus has a water content of

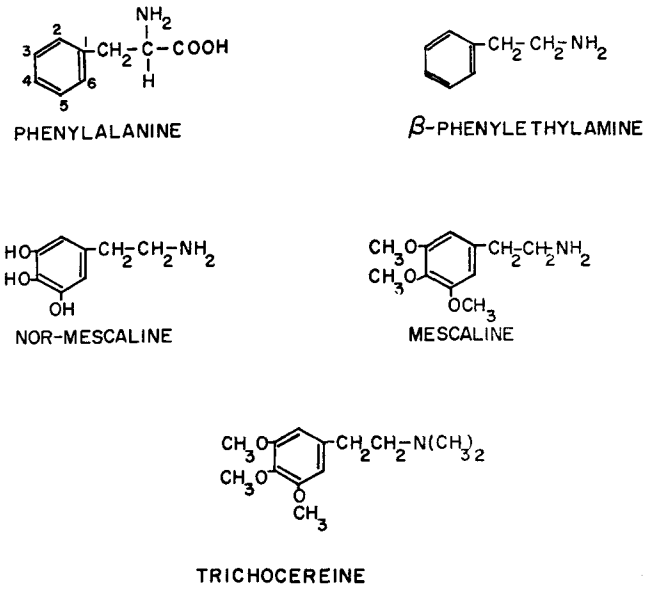

Figure 1. Mescaline and some related compounds.

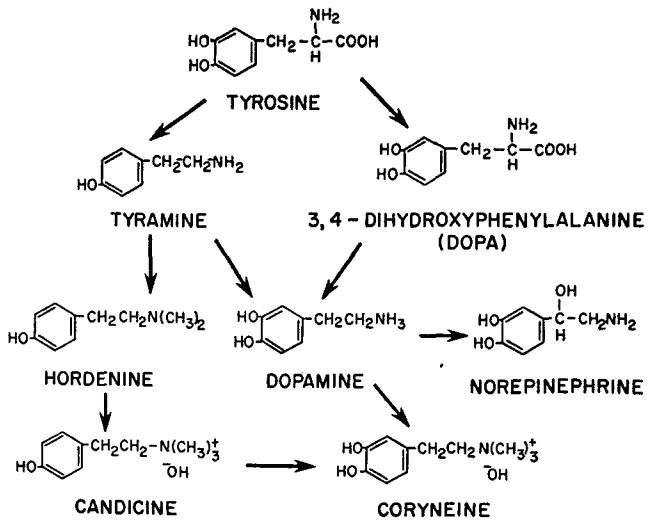

Figure 2. Pathways for the biogenesis of protalkaloids.

90 to 95 per cent and is difficult to handle, so the protoalkaloids, including mescaline, are preferably extracted from the dried cactus. To avoid losses, the plant should be dried at a low temperature as soon as it is collected. Späth and Becke[11] prepared mesaline as follows: The dried powder from the cactus was extracted with cold alcohol and the latter was removed *in vacuo.* An aqueous solution of the resulting syrup was treated with dilute HCl and filtered. The filtrate was made alkaline with NaOH, and the nonphenolic bases were extracted into ether. After removing the ether, the free bases were distilled *in vacuo.* On treatment with dilute H_2SO, mescaline sulfate crystallized. Peyote contains about 6 per cent mescaline.

The free base of mescaline is a colorless oil which can be crystallized when highly purified. It dissolves in H_2O, alcohol and chloroform, but is only slightly soluble in ether. The sulfate salt is preferred for isolation because it is insoluble in ethanol, slightly soluble in cold H_2O, very soluble in hot H_2O, and forms brilliant prisms which melt at 183° to 186°. The hydrochloride forms colorless crystals which melt at 181°.

Mescaline has been synthesized by a large number of investigators using different procedures of varying degrees of complexity.[2] Most have used either trimethoxybenzoylchloride or trimethoxybenzaldehyde as starting material. Späth's[8] original synthesis is given in Figure 3.

As indicated earlier, phenylalanine, tyrosine or dihydroxyphenylalanine may be precursors in the biogenesis of protoalkaloids of the β-phenylethylamine type. Phenylethylamine derived from phenylalanine is of widespread occurrence in plants, but derivatives of this base are much less commonly found than those of tyramine, therefore phenylalanine is probably converted to tyramine before undergoing other reactions. Dopamine, which occurs in both plants and animals,[12] comes from dihydroxyphenylalanine by decarboxylation. However, dihydroxyphenylalanine (L-DOPA) is not widely distributed in either plants or animals. Figure 2 shows the metabolic pathway by which several of the protalkaloids can be derived as indicated by tracer experiments. Such experiments have shown

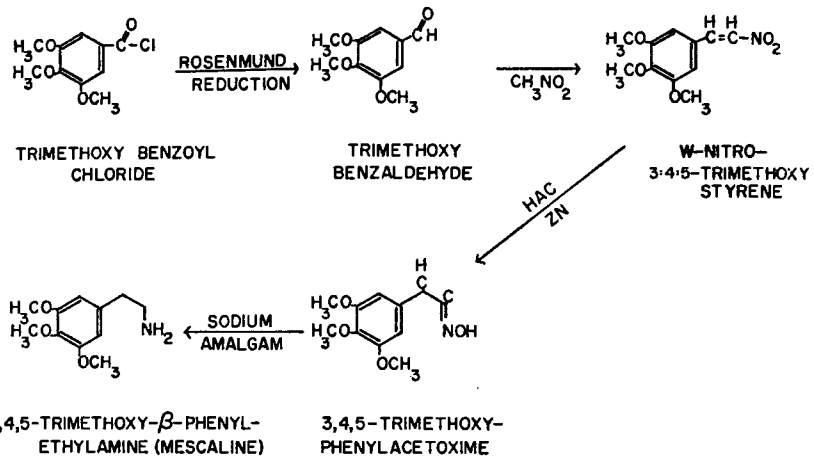

Figure 3. Spath's procedure for the synthesis of mescaline.[8]

that at least for hordenine, the N-methyl group is derived from methionine. The best precursor for mescaline is dopamine, however it can be derived either by decarboxylation of dopamine or by hydroxylation of tyramine.[13] Relative per cent recoveries of radioactivity from α-^{14}C-labeled compounds were phenylalanine 0.025, tyrosine 0.32, tyramine 1.53, dihydroxyphenylalanine 1.58, and dopamine 1.90. The source of the O-methyl group has not been determined. And it should be noted that as yet, no trihydroxy precursors, such as normescaline, have been isolated from natural sources.[2]

Dosage and Symptoms

Mescaline was long the drug of choice for producing experimental hallucinations. In recent years, LSD has replaced it mostly because of the difference in dosage required to bring about the desired result. The average dose in man is from 5–7 mg/kg compared to about 1.5 μg/kg for LSD. Thus on a weight basis, LSD is from three thousand to five thousand times more effective than mescaline, but the pharmacological and psychic effects are similar. Mescaline produces somatic and autonomic effects similar to those observed with LSD, such as nausea, tremor, blurred vision, dilated pupils, incoordination, and ataxia. The somatic symptoms which last about one to two hours precede the perceptual and psychic changes. The latter are described in detail in Chapter III. Vivid, detailed reports of the mescaline reaction, based in part on subjective responses, were made long ago by men like Lewin, Printess and Morgan, Mitchell, and Klüver. Their thoughts, observations, and experiences, though often expressed in superlatives, stimulated no cataclysmic social or ideological revolution. Apparently, the time was not yet right for mind-manifestation on a major scale. The mescaline reaction is conditioned by ill-defined variables and suggestability as is the LSD-induced phenomena.

Absorption and Metabolism

For the most part, absorption, distribution, and tissue metabolic studies of drugs are by necessity limited to experimental animals, and, as for most drugs, these types of experiments with mescaline have been performed in a variety of species. Extrapolating data obtained from one species to considerations involving another, particularly people, can be precarious. Conclusions or even speculation should be made with this danger well in mind.

Mescaline is readily absorbed from the gastrointestinal tract in all species studied, including man. It is rapidly distributed into all tissues, but the highest concentrations are found in the kidney, liver and spleen,[14,15] The brain concentrations are low. Neff *et al.*[16] studied in cat brain the uptake and distribution of mescaline-^{14}C labeled in the side chain. It was distributed throughout the gray matter and reached its highest concentration in brain at the time of onset of symptoms. The biological half-life was calculated to be about 90 to 120 minutes. Only two radioactive compounds were found in the tissues, mescaline and trimethoxyphenylacetic acid. Neff *et al.*[16] concluded that trimethoxyphenylacetic acid is the chief metabolite in the cat. Recently, Charalampus *et al.*[17] reported on the metabolic fate of orally administered mescaline-^{14}C in human subjects. An average of 87 per cent of the radioactive dose was excreted via the urine in the first twenty-four hours.

This radioactivity was distributed as follows: mescaline 55–60 per cent, 3,4,5-trimethoxyphenylacetic acid 27–30 per cent, N-acetyl-β-(3,4-dimethoxy-5-hydroxyphenyl)-ethylamine 5 per cent, and acetyl mescaline less than 0.19 per cent. These four compounds were also detected in the cerebrospinal fluid. The biological half-life was found to be six hours. As an illustration of species differences, a greater amount of radioactivity was found in the whole blood of cats than in plasma,[16] whereas in humans[17] greater concentrations were found in plasma. Radioactivity was strongly protein-bound in human plasma.

Apparently, the major route of mescaline metabolism in man is via deamination to yield trimethoxyphenylacetic acid, which is not a psychoactive compound. The expected metabolic intermediates in this reaction would be 3,4,5-trimethoxyphenylethanol or its immediate precursor, the corresponding aldehyde. The alcohol derivative was detected in rat urine, and was shown to have mescaline-like activity in rabbits.[18] It was suggested that the aldehyde was actually the "active" intermediate, but no definite evidence was presented to support this idea.

Pathways involving O-methylation and O-demethylation of mescaline compounds have been investigated in rat and rabbit liver.[19] Small quantities of several methylated and demethylated derivatives were detected, but apparently these pathways are of minor importance.

It has been known for many years that mescaline is oxidatively deaminated to trimethoxyphenylacetic acid. However, it is not oxidized by monamine oxidase, which is somewhat surprising since this enzyme has such an indescriminate specificity. Zeller *et al.*[20] have reported that diamine oxidase degrades mescaline. Another mescaline "oxidase," distinct from diamine oxidase, is inhibited by semicarbazide and other carbonyl-group reagents, and there are data[21] which suggest that the enzyme is more specific than many of the amine oxidases.

As mentioned earlier, mescaline has an extraordinary structural resemblance to naturally occurring neuroactive agents such as norepinephrine, and is believed to be derived from

dopamine. This similarity has stimulated much research into possible relationships between mescaline and the catecholamines.[22] As of this time, there is no unequivocal evidence that mescaline activity is mediated through aberrations or functional changes in catecholamine metabolism. Although it is reasonable to hypothesize that either mescaline or the catecholamines could serve as precursors for psychoactive indoles, no such compounds have been detected indogenously.

Many structural analogs of mescaline have been prepared and studied.[23,24] Changes in the ring substituents give compounds with an interesting array of properties, some depressant, some stimulatory, and some inactive, but none with significant psychoactivity. For the latter, substituting a methyl group in the α-position of the side chain is effective, but this gives amphetamines which will be described next.

PHENYLISOPROPYLAMINES

Amphetamine (1-phenyl-2-amino propane) was synthesized[25] in 1887, but its effects on the central nervous system were discovered by Alles in 1927.[26] This drug has been a useful medicine for almost fifty years. Many of us (the unenlightened generation) grew up with the naivè notion that the "Benzedrine"® nasal inhalator contained nothing more exciting than a decongestant, useful only for relieving the symptoms of a head cold. Benzedrine (Smith, Kline and French) is the trade name for dl-amphetamine, which because of its slow volatility has been one of the most useful of the vasoconstrictive phenylisopropylamines. However, the stimulating effects of the amphetamines on the central nervous system is by far their most interesting and outstanding property. Shortly after the introduction of the amphetamines as effective therapeutic agents, they received a great deal of adverse publicity in much the same way as LSD. Expressions, such as "confidence drugs," "pep pills," "take a pill instead of a cocktail" analogous to our current flamboyant terminology, were used to describe them. During World War II, they were known as "energy drugs," because of their capacity to offset fatigue and the need for sleep. Lessons learned from wartime experiences

were applied to therapeutic advantage during the years that followed.

The dextrorotatory isomer of amphetamine, introduced under the trade name "Dexedrine" is more potent, faster- and longer-acting than is the levorotatory or racemic form. This is generally true of amphetamine-type substances, where the d-form is effective in doses of from one-half to two-thirds of that required with the l-form or racemic mixtures. Figure 4 shows the structure of amphetamine and some of its congeners.

For many years, amphetamine and its derivatives have been a boon to the physician in the treatment of mild or minor neurotic depression, for the control of narcolepsy, and as an appetite depressant.[27,28] At the present time, the amphetamines are available in a variety of chemical structures specifi-

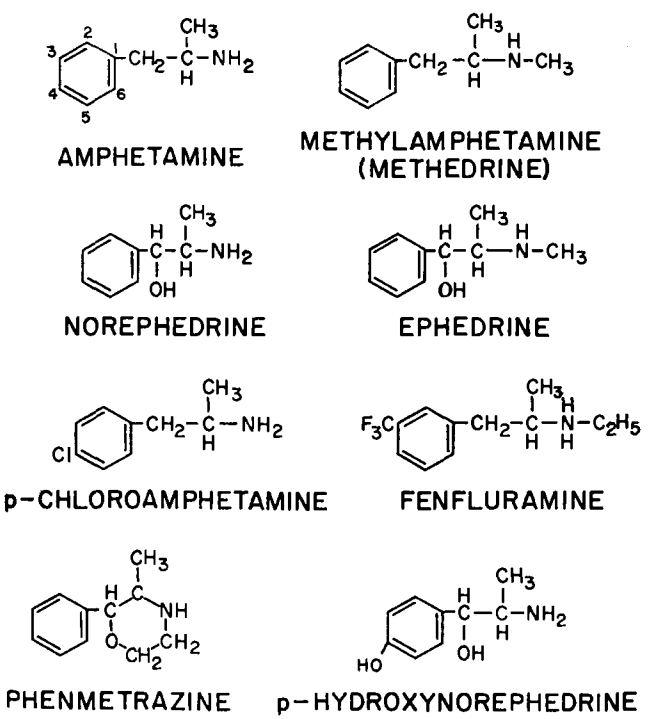

Figure 4. Chemical structure of amphetamine and some related compounds.

cally designed to enhance one or another of these properties at the expense of the others. With the introduction of the proper substituents, such as a chlorine group or a trifluromethyl group in the 3 or 4 position of the phenyl ring, the central nervous system stimulation may be diminished, whereas the anorectic properties remain.[29,30] Relatively potent peripheral effects are encountered when an OH function is present in the same position as in noradrenaline or ephedrine. Norpseudoephedrine, having the OH group in the opposite position, is a stronger central stimulant than ephedrine, but a weaker sympathomimetic. Thus, there is a dissociation between the psychomotor and the peripheral sympathomimetic effects of the amphetamines.[29] The central stimulant and antifatigue effects can be retained without the production of tolerance, marked anorexia, or cardiovascular side-effects by forcing the alkyl-substituted side chain into a heterocyclic ring system.[31]

Over the years, amphetamines have been used by millions as stimulants, and in the control of obesity or other weight problems. Until recently, they were considered to be of such low toxicity that they could be taken without producing toxic manifestations or inducing tolerance or resistence to their action. Considering the large number of individuals who have taken these compounds over long periods of time, the evidence of noxious effects or addiction is rare.[32] Connell[33] has recently shown, however, that following continued usage in some people a condition clinically indestinguishable from paranoid schizophrenia may occur. Griffith *et al.* have elicited an amphetamine psychosis with large daily oral doses of d-amphetamine.[34] Intravenous administration creates a rapid dependence on the drug and produces a stage of intoxication characterized by more psychotic manifestations than does oral abuse.[35] Among other symptoms, there are delusions and hallucinations.

Metabolism, Absorption and Distribution

The metabolism of amphetamine varies from species to species. In the rat, p-hydroxylation is the main metabolic route. In man and rabbit, deamination to phenylacetone and eventual excretion as hippuric acid are the major pathways.

In dogs, both pathways occur to about the same extent.[36-38] In rabbit liver, deamination is catalyzed by an enzyme in the microsomes and requires NADP. A minor pathway for amphetamine metabolism is β-hydroxylation, catalyzed by dopamine-β-oxidase.[39] In the cat, small amounts of p-hydroxynorephedrine were found in the spleen,[40] and stimulation of the splenic nerve resulted in the release of p-hydroxynorephedrine. These results suggest that the β-hydroxylated metabolite may be localized at, or in, sympathetic nerves in such a fashion as to serve as a false transmitter. It has been suggested that the psychosis produced after prolonged administration of large doses of amphetamine is a result of an accumulation of p-hydroxynorephedrine in the peripheral nerve terminals and in the central nervous system. The abnormal behavior possibly results from a disturbance of transmission in the central sympathetic nervous system caused by the accumulation of the false transmitter, p-hydroxyamphetamine.[38]

The distribution of amphetamine in dogs was studied by Axelrod years ago.[41] One hour after administration the drug was found in most tissues, with highest concentrations in the liver, brain, kidney, lung and spleen. There was no blood-brain barrier to its entry into the brain. In dogs, the plasma half-life of amphetamine and of p-hydroxyamphetamine was about seven and one hour respectively. In man, early results indicate that the plasma half-life is about eight hours when subjects are kept on an acid diet. On an alkaline diet, the plasma half-life in man was extended to twenty-two hours.[38] The urinary excretion of amphetamine depends upon the urinary pH which may vary from day to day and from subject to subject. The diet greatly influences the pH of the urine, of course. Thus any study of the effects of substituents on the distribution, metabolism and excretion of amphetamines, based on urinary analyses, requires control of urinary pH if meaningful results are to be obtained. The fluctuations can be abolished and the logarithmic rate of excretion versus time plots made linear by the oral administration of ammonium chloride to keep the urine acid. Much greater percentages of unchanged drug is then excreted. Under normal conditions,

the ratio of a metabolite to unchanged drug in the urine varies greatly, but a reproducible ratio can be obtained if the urine is kept acid.[42] Such considerations are of fundamental importance in the study and understanding of metabolic degradation and plasma decay rates.

Considering the number of years that the amphetamines have been under fairly intense investigation, it is not surprising that our knowledge of these compounds is relatively broad-based. Over the years, several theories as to how they elicit their peripheral and central effects have been offered and discarded[28] in the light of new information which has marked our increasing understanding of nerve transmission. However, the extent of that understanding is not of the proportion to generate smugness, and with time the new ideas, barely conceived in a haze of ambiguities, may be profoundly altered or discarded altogether.

Axelrod has recently summarized information relative to the effect of amphetamine on catecholamines as follows:[38,43]

1. blockage of norepinephrine (NE) uptake by nerve endings;
2. release of NE from nerve endings;
3. inhibition of monamine oxidase.

It has been postulated that amphetamine has a direct action on adrenergic receptors and that it may give rise to a false transmitter. There is a growing body of evidence that the false transmitter concept has some degree of validity even though other factors may also be involved. For instance, both amphetamine and reserpine cause a release of norepinephrine in the brain, yet amphetamine causes excitation whereas reserpine is a depressant. In a study on the development of tolerance to the anorexigenic effects of d-amphetamine, it was shown that the accumulative effects of amphetamine on NE stores were inconsistent with the short half-life of this drug in the body. In support of the previous mentioned role of p-hydroxynorephedrine, Brodie *et al.*[44] found this compound in tissues in amounts that were related to the NE deficiency. They concluded that the persistent depletion of NE after a

single large dose of d-amphetamine is due to the presence of p-hydroxynorephedrine in the nerve endings. Essentially the same results were reported by others[45-47] who found that animals receiving p-hydroxynorephedrine-^{3}H accumulated the compound in the tissues; the stored metabolite could then be released by nerve stimulation. These promising results, coupled with the intensive investigative effort stimulated by them, may bring the long sought answer to the question of how amphetamines work. They may also bring unexpected dividends in the search for new information about neurotransmitters and receptor sites in the central nervous system.

Abuse of Amphetamines

Until about 1966, amphetamines were not considered to be a major drug abuse problem.[48] In that year, Griffith[49] and Lemere[50] warned of the extent of danger of abuse, and in 1967 Kalant *et al.*[51] reported on the effects of intravenous use of amphetamines. Since then there has been an explosive increase in the use of "speed," the street name for metamphetamine. In practically every city of any size there is a "speed" colony, made up of saddening, mostly young, people who use massive amounts of amphetamines intravenously. The problem has reached such proportions in the United States that the Federal Drug Administration in August 1970 appealed to drug manufacturers and physicians to voluntarily limit the use and production of amphetamines. A spokesman for the Agency reported that in 1969, 3.5 billion amphetamine dose units, mostly in the form of pills, were made in the United States. This amounts to fifteen pills for each man, woman and child in the country. The tremendous production, for which there must be a legal market, makes easy the diversion of large supplies into the illegal market, and, it would appear to make a mockery of the so-called public concern about the drug abuse problem. The speed "shooting" (intravenous injection) phenomena has not been confined to the United States but has been reported in Sweden[34,52] in Great Britain[53] and Japan.[54]

Effect of Intravenous Use of Amphetamines

The prescribed daily dose of amphetamine varies from 5 mg to no more than 20 mg daily; the user who regularly takes the drug intravenously may inject from 100 to 1000 mg daily, depending upon the degree of tolerance that has been acquired. These massive doses are accompanied by a behavioral and physical syndrome which may result from a variety of factors. The drug causes insomnia, anorexia, paranoia, compulsivity, and, according to experienced observers,[55,57] a tendency toward violent reactive behavior. Intravenous injection of metamphetamine (a hit), which comes in a crystalline form and is prepared and injected like heroin, causes a quick, powerful and direct reaction known as a "rush" or "flash." After the initial ecstasy, there is a period of euphoria characterized by hyperactivity, hyperexciteability, volubility, paranoia and aggressiveness. During this period (a run) which may last from three to six days, the "speed freak" does not sleep and rarely eats. He gets more tense, tremulous and paranoid as the "run" continues and may lose up to ten to twenty pounds in weight. The "runs" are followed by a day or two of sleep, which, with the depression that follows it, is known as "crashing." The "crash" is so devastatingly uncomfortable that the user often starts another "run" even though he may be in a state of physical, emotional and mental exhaustion.[57] Users of high doses of metamphetamine sooner or later experience paranoia of such intensity that they turn to "downers" such as opiates, tranquilizers and sedatives.[55]

In addition to the generalized mental and physical deterioration brought on by the self-imposed torture (it would be interesting to compare the relative degree of physical and mental impairment brought on by "police brutality"), many "speed" users are victims of hepatitis[58] which is acquired through the use of dirty contaminated needles. Smith *et al.*[58] listed this as one of the major medical problems associated with chronic use of metamphetamine intravenously. Acute psychiatric problems were divided into four categories: the acute anxiety reaction, the psychotic reaction, the exhaustion

reaction, and the withdrawal. One reaction, reminiscent of delirium tremens, is described as the occurrence of "crank bugs," imaginary bugs under the skin. Smith[56] quotes a twenty-four year old "speed freak" as follows:

> It's just that when you're shooting speed constantly you start to feel like there's bugs going around under your skin and you know they're not there, but you pick at them anyway. You go through all these changes scratching. Once in a while you'll see a little black spot and you'll watch it for 10 minutes to see if it moves. If it doesn't move it isn't alive. You can feel them on your skin. I'm always trying to pick them out of my eyebrows.

Chronic amphetamine abuse appears to be a game for the young (they can have it!) Older people can't stand the accelerated pace; they wear out sooner and "crash" harder and longer.

To the physician, the diversity of physical and psychiatric complaints presented by the user of massive doses of amphetamines can be extremely confusing. Once he diagnoses the problem, acute treatment consists of sedative medication and counseling. The sedation should be controlled so as not to go rapidly from an excited to an exhausted state. If the patient is already exhausted, bed rest and adequate diet are suggested.[58] Kramer[55] states that anyone concerned with the welfare of amphetamine users and the users themselves, should recognize that most, if not all, can recover from even the most profound intellectual disorganization and psychosis, given six months or a year of abstinence.

Hallucinogenic Amphetamines

Although amphetamine as such is not a hallucinogenic compound, derivatives containing methoxy substituents on the benzene ring have hallucinogenic properties similar to mescaline. Thus, 3,4,5-trimethoxyamphetamine (TMA, α-methylmescaline) is twice as psychoactive as mescaline. An extensive number of these dimethoxy-, trimethoxy- and methoxymethylenedioxyamphetamines have been synthesized[59-62] and the psychoactivity has been evaluated relative to mescaline. The

mean effective does of mescaline was taken to be 3.75 mg/kg. This mescaline unit (M.U.) is subject to much variation and the degree of uncertainty was estimated to be about 25 per cent.[63] Nevertheless, the mescaline unit is a useful reference in estimating the potency of amphetamine derivatives.

In Table I a list of substituted amphetamines is given and their potency in M.U. is shown. Shulgin *et al.*[63,64] and Snyder and Richelson[65] have discussed the structure-activity relationships of these compounds at length. Adding a methyl group to the α-position in the mescaline side chain gives the active 3,4,5-TMA mentioned above. The presence of the methyl group in this position may prevent or decrease the rate of degradation by amine oxidases, thus making the drug more effective. The optimum length of the alkyl group is three carbons. The most active TMA derivative is the 2,4,5; the least active is the 2,3,4-compound (Fig. 5).

TABLE I
RELATIVE HALLUCINOGENIC POTENCY OF SUBSTITUTED AMPHETAMINES

Compound	*Ring Position of Substituent*	*M.U.*
Mescaline	3,4,5	1
Trimethoxyamphetamines (TMA)	2,3,4	<2
	3,4,5	2.2
	2,3,5	4
	2,3,6	13
	2,4,6	10
	2,4,5	17
Dimethoxyamphetamines (DMA)	3,4	<1
	2,4	5
	2,5	8
Methylenedioxyamphetamines (MDA)	3-4	3
Methoxymethylenedioxyamphetamines (MMDA)	3,4-5	2.8
	2,4-5	12
	2,3-4	10
Dimethoxymethylenedioxy-amphetamines (DMMDA)	2,3-4,5	12
	2,3,4-5	5
Methoxyamphetamines (MA)	4	5
Dimethoxymethylamphetamine (DOM)	2,(4)5	80
Dimethoxyethylamphetamine (DOET)	2,(4)5	—

The cyclic substituent is indicated by a dash between the numbers of the ring carbons involved. Parentheses indicate position of the nonoxygen containing substituent. From A. T. Shulgin: Efron, D. H. (Ed.), *Psychotomimetic Drugs.* New York, Raven, 1970.

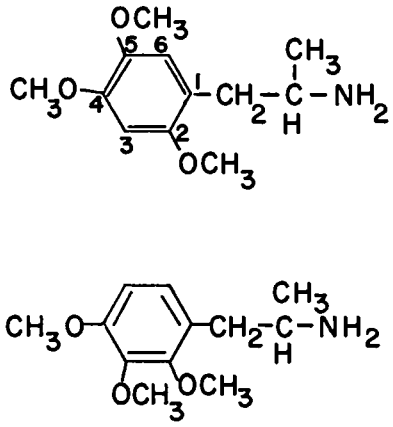

Figure 5. Trimethoxyamphetamines. The top structure is the highly hallucinogenic 2,4,5-trimethoxyamphetamine. The lower compound is the weakly active 2,3,4-trimethoxy derivative.

Among the more chemically interesting and more psychoactive compounds in Table I are the methylenedioxyamphetamines, Figure 6. These materials resemble naturally occurring myristicin which has been proposed as the active ingredient of nutmeg.

The most important of the substituted isopropylamines in terms of potency (Table I) and abuse is 2,5-dimethoxy-4-methylphenylisopropylamine (DOM), the active ingredient of the street scene STP (Fig. 6). Given orally, DOM produces hallucinogenic effects in doses greater than 3 mg and mild euphoria in lower doses.[66] Symptoms are similar to those ob-

Figure 6. Examples of hallucinogenic amphetamines. I. 2,5-dimethoxy-3,4-methylenedioxyamphetamine. II. 2,5-dimethoxy-4-methylamphetamine (STP).

served with LSD, mescaline and other hallucinogenic drugs. Effects begin in about one hour after administration, and the peak reaction occurs in three to five hours. In seven or eight hours, the effects subside. Snyder *et al.*[66,67] did not confirm reports that the effects of STP (serenity, tranquility, peace) are long-lasting, nor did they find potentiating effects with chloropromazine. However, Smith[68,69] reported on a hundred or more cases which were treated at the Haight-Ashbury Medical Clinic in San Francisco. There were a large number of so-called "bad" trips. At the street level dose (10 mg versus 2 to 3 mg used in the laboratory tests), the peak often lasted from sixteen to twenty-four hours. In some cases, the reaction continued for two to three days. The duration of the effects and the intensity of the physiological and psychological changes probably combine to produce a panic reaction. The subject thinks the reactions will never end and that he or she is going crazy, that normality is gone forever. Smith also noted several cases in which exacerbation of symptoms occurred after chloropromazine. He recommends that other types of sedative be used, along with sympathetic counseling.

The analogous ethyl compound, 2,5-dimethoxy-4-ethylamphetamine (DOET) produces euphoria and enhanced self-awareness in the absence of hallucinogenic or psychotomimetic effects.

As can be seen in Table I, shifting or changing the substituents on the benzene ring can markedly change the psychotropic potency of the amphetamines. In the TMA group, the most active 2,4,5-derivative and the least active 2,3,4-compound were labeled with radioactivity and studied in rats (Mitoma, cited in ref. 70). No differences could be detected in their excretion rate, in their disappearance from the body, their metabolism by liver microsomes, or in their rate of entry into the brain. Using these limited results as justification, some[63,70] have concluded that metabolically induced changes alone cannot account for the differences in potency, and seek an explanation in the fundamental structures of the molecules. Thus Shulgin[63] speculates upon the possibility, as have many others, that these materials possess biological activity by

virtue of the fact that they may imitate or form indoles during the course of their metabolism. With this in mind, he comments on the fact that *ortho* substitution in the benzene ring gives greater activity, whereas *meta* substitution gives compounds with decreased potency. Activity appears to parallel the ease with which substituents, generally speaking, add to and activate a benzene ring. Thus, one cannot challenge the proposal that indoles would be more easily formed by *ortho*- as compared to *meta*-substituted compounds. Snyder *et al.*[65,70] suggests an explanation in so-called quantum theory. In essence, this theory is concerned with speculations on possible steric and conformational changes, as well as interaction of sigma-π bonds, which would make molecules like psilocybin fit an LSD model, or transform mescaline into an indole, as discussed earlier. Evidently the idea is to try to fit these diverse molecules into a common molecular mold in order to understand a certain amount of similarity of action, or to explain why cross-tolerance can be elicited by some of these chemically diverse structures. The hypotheses are based on the premise that hallucinogens interfere in some way with the normal functioning of a constituent or pathway. Current concepts of synaptic transmission and of mechanisms of enzyme action suggests receptor sites of precise chemical specificity. Thus, any model which purports to reconcile the chemical diversity of compounds such as LSD, mescaline, and psilocin to fit a common site of action is likely to be challenged. The best, and as far as I know the only, evidence to support the idea of a common site of action is that the drugs, in some cases, can elicit cross-tolerance, one for the other. Since there is little information as yet to explain the development of tolerance to any one drug, I can see no reason to invoke an oversimplified explanation of cross-tolerance between drugs. Perhaps there are multiple, integrated receptor sites, a series of interconnected chemical events. A hallucinogen could disrupt the series or pathway at any one of various points, depending upon its chemical affinity for a specific site. At the present level of knowledge of the central nervous system, hypotheses as to how hallucinogens work are as numerous and

seem as ephemeral, and sometimes as bizarre, as the responses elicited.

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Chapter III

LYSERGIC ACID DERIVATIVES

THE BEST KNOWN of the lysergic acid derivatives is lysergic acid diethylamide (LSD-25), a compound which has created an aura of excitement and magic from the moment of its discovery. Indeed, some element of its "mind-expanding" property may have been acting on Albert Hofmann on April 16, 1943, when he was able to distinguish "a peculiar sensation of vertigo and restlessness" and being "unable to concentrate"[1] from an ordinary case of Friday afternoon doldrums. In so doing, he was to discover a heretofore unknown property of a drug and initiate a new era in the continuing effort to understand the underlying mechanisms which control human behavior. Hofmann had, in fact, accidentally ingested minute quantities of one of the most powerful of drugs. A few years later, this potency in producing bizarre psychic phenomena, plus a lack of addictive and toxic properties, and the minimal side effects, were to impress and excite many behavioral scientists who were concerned with mental illness, particularly schizophrenia. There was a reawakened interest in the possibility of natural chemical activators in the schizophrenic process. Among the concepts re-introduced was the possibility of using drugs to initiate so-called model psychoses. Advocates reasoned that compounds such as LSD-25 could be used to induce a "schizophrenic-type" state analogous to a natural psychosis; biochemical and physiological mechanisms of the drug action could provide clues to mechanisms involved in schizophrenia; drugs counteracting the drug-induced psychoses could provide a therapeutical approach to schizophrenia. The underlying premise of these ideas is that natural psychoses could be caused by the production of a minute, perhaps undetectable, amount of aberrant metabolite by the organism.

The model psychoses theory, attractive in its simplicity, resulted in a deluge of publications, but has produced neither a cure for nor a better understanding of the causes of schizophrenia. Although it was not completely discarded, it was rapidly displaced by a more pervading, insidious, and much more difficult to evaluate concept, namely, that LSD-25 and other hallucinogens can be used for constructively expanding one's mental existence and of permanently altering human personality and behavior, ostensibly for the better. As Hollister[2] has so aptly observed, what was once regarded as insanity was now heralded as insight. The change in emphasis seemed to parallel the degree to which observers became participants in the LSD experience. Justification for this view is expressed by Blum[3] who noted:

> It was when people shifted from using the drug to see what *it* was like or what *it* could do, to using it to see what *they* themselves were like or what *they* could do, that LSD *use* rather than LSD effects became an intriguing subject for investigation.

As will be shown on the following pages, neither the model psychoses theory nor the expanded psyche concept can be proved or disproved by the investigative methods and/or philosophy that are presently available to the biochemist or to the behaviorist.

Source

Lysergic acid compounds, which can be chemically manipulated to yield various hallucinogens, are found as natural molecular components of ergot. The latter has had an intriguing history of mixed horror and magic in its own right.[4] Ergot is a biological product of a growing fungus, specifically *Claviceps purpura*, which parasitizes cereal grains. Various types of grains can be affected, but the history and distribution of ergot parallels that of its favorite host, which is rye. Rye was introduced into Southern Europe by the Teutons in the early Christian era. During the Middle Ages, rye bread was eaten largely by the poor, since wheat at that time, because of vicissitudes in agricultural conditions, was regarded

as a luxury crop. Rye and ergotism were largely restricted to districts of poor soil and poorer people.

The first description of ergot as such was made in 1582 along with a description of its use by women in producing pains of the uterus. Although ergot had been used as an oxytocic agent for centuries by European midwives, its use for that purpose was introduced into modern medicine in 1808 by an American physician, Dr. John Stearns. In his scholarly and exhaustive monograph on ergot, Barger[4] credits a "New World" freedom from prejudice for the eventual, but belated, recognition of ergot as a useful medicinal agent. This view would be hotly contested in the "New World" of today. But he also recognized that the Old World had suffered much from the toxic properties of ergot; its good had been obscured more by pain, suffering and ignorance than by any prejudice against its use by the medical fraternity.

During the middle ages and after, infected rye was used in bread and animal feed and caused major widespread epidemics of ergotism in both people and livestock. Ergot poisoning was of two types, gangrenous and convulsive. The early symptoms of gangrenous ergotism were tingling in the fingers and toes, vomiting, and diarrhea. These were followed by a dry type of gangrene in the extremities, affecting the entire limb which would separate spontaneously at the joint without pain or loss of blood.[4] In convulsive type, early symptoms were much the same, but were followed by painful contractions and distortions of the limbs, and by convulsions. If the victims survived either type, they were left mentally incompetent. Although there were cases of ergotism reported in the early 1900's, improved agricultural methods, coupled with governmental regulation and inspection of grains, has made it an insignificant modern disease. Ergot is grown commercially now in most countries of the world and processed for medicinal purposes. Spain and Portugal are among the world's major producers.

Chemistry

The basic structural component of ergot is lysergic acid upon which various chemical groups can be arranged to give

compounds of diverse chemical and physiological properties.[5,6] The isolation of lysergic acid and its derivatives from ergot, and the characterization and proof of structure involved many years of meticulous work and study. As is so often the case in chemistry, each intricate bit of information was obtained in a painfully slow, but always fruitful, step by step process. It is not within the scope of this discussion to explore the chemical history of the development of the ergot horror into a plethora of drugs, but there are some names which marked milestones along the way. There was Tanret[7] who isolated the first crystalline, but heterogenous product, ergotinine; Barger and Carr[8] who isolated crystalline but heterogenous, ergotoxine; Stoll[9] who recognized that these crystalline substances were actually mixtures and proceeded to isolate the first homogenous substance, ergotamine, which possessed all the typical biological properties of ergot; Jacobs and Craig who isolated lysergic acid from ergot[10] and contributed much to the elucidation of its structure; and Kornfeld *et al.*[11] who accomplished the total synthesis of lysergic acid in 1954.

Among the ergot alkaloids, ergometrine is of particular significance because of its pharmacological value, and because Stoll's work with this and related lysergic acid amides led to the synthesis of LSD. Ergometrine was isolated from ergot by four different laboratories independently in 1935. It was named ergometrine in England, ergobasine in Switzerland and ergonovine in the United States. The compound, which has oxytocic properties and is used as an uterotonic agent, was synthesized by Stoll and Hoffman[12] in 1938. Using the same procedure, which is shown in Figure 7, they produced a large number of lysergic acid derivatives of the acid-amide type among which was the diethyl amide.[1] In the original synthesis, hydrazine was used to cleave ergot alkaloids to lysergic acid hydrazide. The latter was treated with nitrous acid to give the azide which can be used to prepare the desired amide by acylation of an appropriate amine. The conditions must be mild because of the lability of the indole part of the structure. In addition this procedure has several serious disadvantages. Hydrazinolysis of ergot causes racemization and isomerization

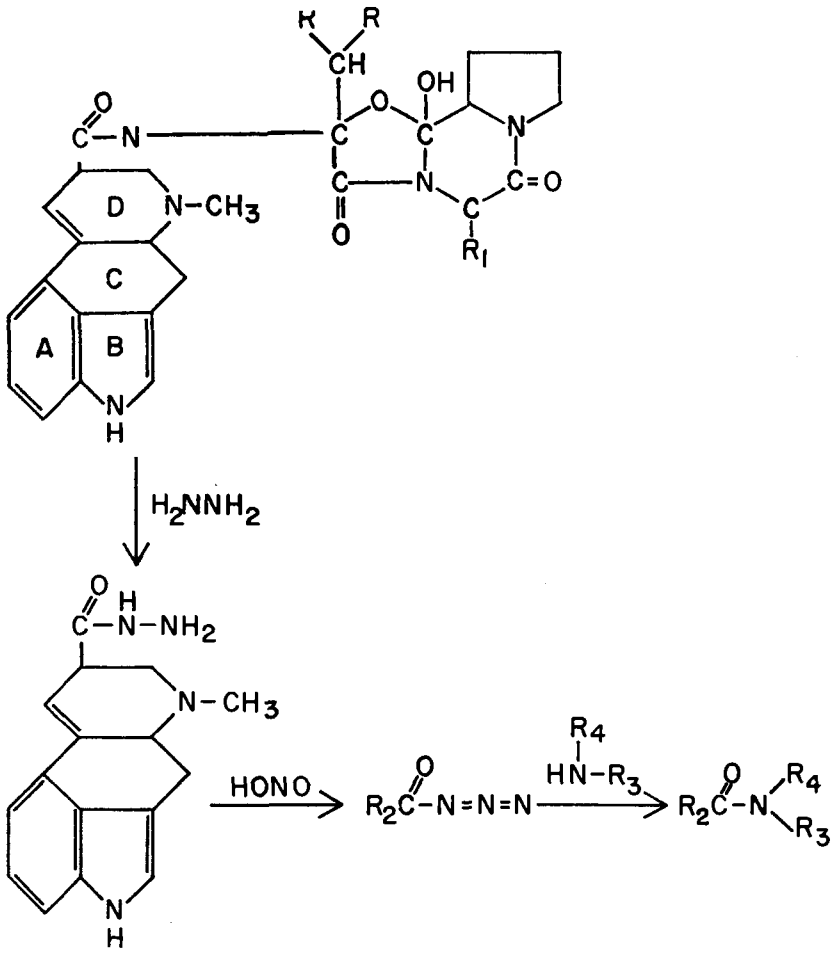


Figure 7. Synthesis of LSD-25 by the procedure of Stoll and Hoffmann.[13] Substituent groups can be varied as follows to give a variety of related compounds: R = –H, $-CH_3$; $R_1 = -CH_2Q$ (Q is the benzene ring), $-CH_2CH(CH_3)_2$, $-CH(CH_3)_2$; R_2 = ABCD rings, R_3, R_4 = –H, alkyl.

of the products which reduces the yield of the active ingredient. Collection of the azide requires large volumes of ether, and the acylation step requires several hours.

By starting with free d-(+)-lysergic acid, which can be made by treating ergot alkaloids with aqueous alkali,[13] an unracemized product can be easily obtained. Garbrecht's[14]

useful synthesis is shown in Figure 8. The entire reaction sequence can be carried out very quickly since all the steps are instantaneously completed. The entire reaction takes no more than thirty minutes and goes well in a temperature range of from −20° to 35°C. Given the starting material, a minimum of laboratory equipment, and a few standard organic reagents, the synthesis of LSD can be affected in good yield in a short time. The compound is isolated as the crystalline maleate or tartrate and purified by recrystallization from methanol-ether. Pioch's method[15] uses the mixed anhydride of lysergic acid, and the yields are not as good as Garbrecht's synthesis.

Many of the ergot alkaloids share the same basic tetracyclic ring structure, which encompasses three familiar ring systems,[16] naphthalene (A+C), N-methylquinoline (C+D), and indole (A+B) (Fig. 9). The latter is a tantalizing, frustrating chemical entity to the neurochemist. Its occurrence in a wide variety of substances which effect brain function titillates the imagination. Paradoxically, the indole nucleus may be found in psychotogens, such as LSD, compounds such as serotonin, which occurs naturally in the brain and is believed to be a neurohormone, and tranquilizers, such as reserpine

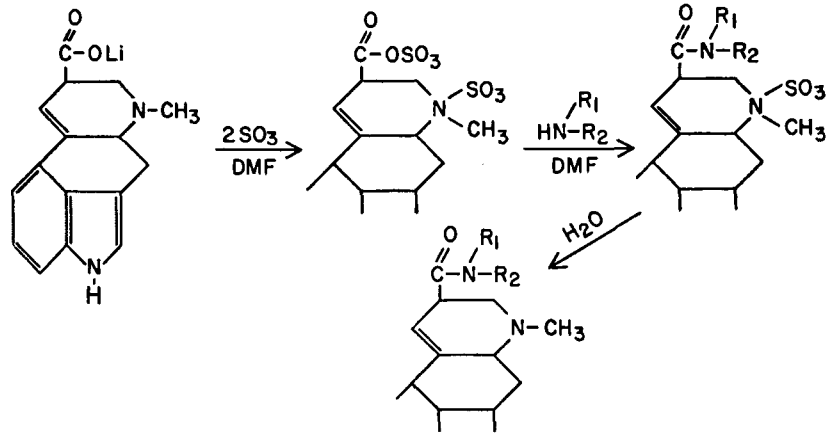
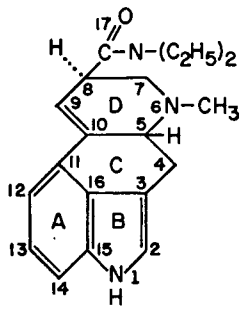
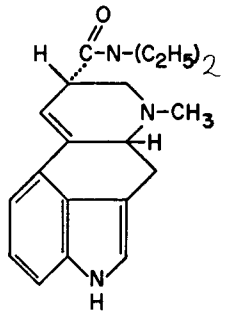


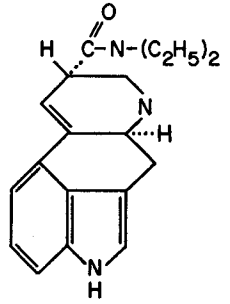
Figure 8. Synthesis of LSD-25 by the method of Garbrecht.[14] DMF = dimethylformamide; R_1 = R_2 = alkyl.



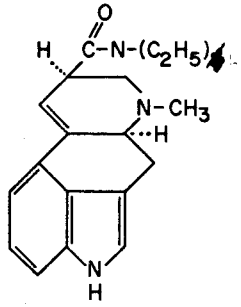
d-LYSERGIC ACID DIETHYLAMIDE (LSD-25)



d-ISOLYSERGIC ACID DIETHYLAMIDE



l-LYSERGIC ACID DIETHYLAMIDE



l-ISOLYSERGIC ACID DIETHYLAMIDE

Figure 9. LSD-25 and isomeric congeners.

which relieve mental disturbances. In recent years, much attention has been devoted to indole metabolism in man, and it is safe to say that indole-containing compounds play an important, perhaps a neuro-transmitter, role in mental function. However, the same comments can be made about other types of compounds. In any event, the crucial experiments to define the neurochemical role of the indole ring remain to be done.

The tetracyclic structure constitutes the gross skeletal framework of lysergic acid and is necessary for hallucinogenic activity. However, minor modifications in specific substituent groups can profoundly alter the characteristic response to

these compounds. Of the various derivatives of lysergic acid, LSD is by far the most potent hallucinogen. As indicated previously, it is the most powerful psychotogen yet devised. The potency depends upon a precise configurational arrangement of the molecule. Figure 9 shows that there are two asymmetric centers in LSD, i.e. carbons 5 and 8 have four dissimilar groups attached to each. This asymmetry allows for a difference in the spatial orientation of the groups attached to these carbons. As a result, LSD may exist as four isomers, differing only in spatial configuration around carbons 5 and 8. Of these, only the d-form has hallucinogenic activity.[17]

Modifications of LSD at the amide nitrogen attached to carbon 17 also drastically changes the properties of the compound. The free amine has approximately 10 per cent of the psychological effect in man as does LSD-25. The monoethylamine and dimethylamide derivatives have the same degree of potency as the free amine in this respect. Of all the changes which have been made in the LSD molecule, for instance, reduction or hydrolysis of the double bond at carbon atoms 9–10, halogenation (bromine, chlorine) at carbon atom 2, modification at the quinoline nitrogen, and substitutions on the indole nitrogen, only two yield compounds having the psychological potency of LSD.[17,18] The compounds are d-l-acetyllysergic acid diethylamide and d-l-methyl-lysergic acid diethylamide.[18] Their activity is believed to be due to the ease with which groups substituted on the indole nitrogen can be removed to give LSD. Thus, LSD remains the King of Psychedelia and for this reason will be the focus of the remainder of this chapter.

Dosage and Symptoms

The original dose of LSD taken by Hofmann was 250 μg, which from his own account[19] gave him quite a ride. His more conservative colleagues took lesser amounts[18] and found the effective oral dose for the production of psychic phenomena in normal subjects to be from 0.5 to 1.0 μg/kg. The customary clinical dose used by some psychotherapists is in the 1 to 2 μg/kg range (70–140 μg for an individual weighing 70 kg).

However, dosage is subject to a great deal of individual selectivity among psychiatrists, and one could say that it depends a great deal on the philosophy of the prescriber. Spencer reported using 1.5 mg per individual,[20] which Hoffer and Osmond[21] suggest is the upper safe limit when given to an individual for the first time. They also roughly estimate the LD-50 for man to be about 14 mg. In a recent report, two dosage levels were used; a low dose of 50 μg and a high of 450 μg per patient.[22]

LSD is equally effective by whatever route it is administered; only the time of onset of symptoms differs. The drug is usually taken by mouth in the form of tablets or aqueous solutions of the tartrate salt.

The degree of toxicity of LSD varies with the species to which the drug is given. In animals, the intravenous acute LD-50 is 46 mg per kg for the mouse; 16.5 mg per kg for the rat and 0.3 mg per kg for the rabbit.[23] Acute poisoning is not specific, both autonomic and somatic effects are observed. These are mydriasis, piloerection, salivation, vomiting, ataxia and spastic paresis; death results from respiratory failure.[17] In chronic toxicity experiments, rats tolerated 2.5 mg/kg intravenously daily for thirty days. There were no cumulative effects and the animals required the same LD-100 as untreated rats, indicating no development of tolerance.[23] LSD has a pronounced effect on the uterus of the rabbit *in vitro* and *in vivo*, but its toxicity is high as compared to ergotamine.

Most animals also show a rise in temperature. In this respect, the rabbit is particularly sensitive, showing hyperpyrexia with doses of LSD as low as 0.5–1.0 μg/kg which are analogous to amounts needed for psychic effects in man.

In man, hyperflexia, nausea, tremor, muscular weakness, hyperthermia and mydriasis may occur. Of these, pupillary dilation is almost always present. In the dosage ordinarily used to bring about psychic changes, the peripheral and autonomic effects are insignificant and occur with minimal intensity if at all. At high levels, the drug is extremely toxic, and it was for this reason that it was set aside in 1938 as being of no medicinal importance.

The onset of symptoms varies with the dosage and with the sensitivity of the individual. Oral administration produces effects in from one-half to 1½ hours. Intramuscularly, the time is shortened to about ten minutes; intravenously to a few minutes. Introspinal injection illicits instantaneous effects.

Although the peripheral (i.e. uterotonic, vasoconstriction), autonomic, and somatomotor effects of LSD are well known and have been described at length, the psychic effects are by far the most important. Starting with Hofmann, who may well be the only naive recipient, there has been no dearth of eloquent and ineloquent descriptions of what can be viewed only as a disquieting experience. Summarized without embellishment, there is overwhelming agreement that this compound produces periods of altered perception without marked changes in the consciousness, or in the physiological state of the recipient. In general, some mental processes which may under normal conditions be dormant, variable, or transient, become fixed into a persistent state. The usual boundaries which structure thought and perception become fluid. There is a heightened awareness, while control over input is diminished or lost. The mundane reception and evaluation of stimulatory input becomes novel, illusory, profound, and leads to the loss of a sense of reality. The subject may grasp at the surroundings, at preconceived notions, or transcendentalism bordering on the mystique[24] (many times of a religious nature[25]) for the support which can no longer be found in himself.

Little would be accomplished by trying to describe the plethora of specific hallucinations which have been experienced. Some investigators distinguish the bizarre psychic imagery of the LSD experience from "true" hallucinations. The recipient knows that the images are drug-induced and that they are not real. Since the cerebral mechanisms which produce either "real" or "unreal" hallucinations are obscure, this difference may be one of semantics or of conjecture.

The psychological responses to LSD are confusingly numerous and diverse, which is not surprising in view of the number of variables influencing and shaping their occurrence. Among a large number of nonspecific factors which may alter,

influence, or control the LSD experience are (a) personality, (b) education and vocation, (c) drug sophistication, (d) the setting, which includes the physical environment as well as the objective of the drug session, (e) the set, which defines the expectation of the subject. These factors are listed by most of the behavioral scientists and therapists whose use of LSD qualifies them to speak authoritatively. An exhaustive list would include somatotype, age, health, circadian rhythm, the degree of fullness of the stomach,[21] and, of course, dosage. Some of these factors imply that the hallucinogenic drugs enhance suggestability. A study in this regard[26] showed that LSD and other drugs do indeed increase the sort of suggestability which can be produced by the induction of hypnosis. However, no one has attempted to measure whether suggestion influences the expected action of the drug.

Reading the multiplicity of reports which proliferate by the hundreds each year on the hallucinogenic drugs is a mind-numbing task. Apparently, no aspect is left untouched. Studies on LSD have ranged from its effects on life's fundamental molecular entity, DNA,[27] to the elephant[28] (it was bound to DNA, and killed the elephant). Along the way, it was shown that the hallucinogenic activity of LSD correlates with motility in the liver fluke,[29] and that the Siamese fighting fish assumes a nose-up, tail-down position in solutions of LSD.[30] The difficulties in becoming familiar with the voluminous literature are compounded by the controversy which surrounds so much of it. Seemingly, for every investigator who reports a positive finding, there is one who furnishes a negative. Thus, the uninitiated reader can become quickly confused, and the experienced reader just as quickly disillusioned.

Absorption and Distribution

Orally administered LSD is readily absorbed in all species. Generally it can be said that the drug disappears rapidly from the blood and that it can be assimulated into most tissues. Maximum concentrations are rapidly obtained. There is good agreement that it is not concentrated in the brain of any of the species studied so far.

In animal studies, the fate of administered LSD has been investigated by three different methods. The first, which was used in some of the early studies[31] is a bioassay and is based on the antagonistic action of LSD to 5-hydroxytryptamine (serotonin, 5HT). In the second, LSD is extracted from the tissue into heptane from which it is returned to aqueous solution and estimated spectrofluometrically.[32] The third depends upon determining the distribution of radioisotope[33] after giving a dose of LSD-^{14}C. All of the procedures suffer from a lack of specificity, i.e. they do not distinguish between LSD and structurally similar metabolites.

A great deal of species variation is reflected in the metabolic fate of LSD. In mice and rats, the half-life of LSD was found to be about 10 minutes;[32,33] in the cat and monkey, the half-life is one hundred and 130 minutes, respectively.[32] In man, the rate of disappearance from plasma was measured by the fluorometric method and the half-life was calculated to be about 175 minutes.[34] This value has been corrected to 109 minutes by these investigators[35] whose calculations were based on a two compartment model in which it was assumed that LSD was equally distributed throughout the tissues. As we shall see, this assumption is a precarious one if animal studies can be extrapolated to humans.

Using LSD labeled with ^{14}C in the diethylamide portion of the molecule, Boyd[36] determined the distribution of radioactivity in the tissues of the rat. The drug was administered both intravenously and intraperitoneally with similar results. After the injection of 1 mg/kg, relatively large amounts of radioactivity were found in the liver, spleen, kidney and lung. In these organs, the isotope reached a maximum concentration quite rapidly; low amounts were present in blood, adipose, and brain. The latter contained not over 0.01 per cent of the administered dose. Radioisotope rapidly accumulated in the bile which contained from 60–80 per cent of the dose in three hours. This radioactivity was excreted by way of the feces in which 80 per cent of the administered dose was found after a period of thirty-six to sixty hours. Oxidation of the amino side chain to CO_2 was a minor degradation route since only 4 per cent

of the radioactivity was found in CO_2 expired over a period of 12 hours. About 8 per cent of the dose appeared in the urine. The bile contained four radioactive compounds of which none were identified unequivocally. Boyd suggested that one was unchanged LSD (amounting to about 10% of the radioactivity in the bile) and that the other two were glucuronides of 12-hydroxylysergic acid amide. For the latter observation, Boyd has some support in the work of Slaytor and Wright.[37] who also found metabolites which were identified by paper chromatography, fluorescence and color reactions to be β-glucuronides of 12-hydroxy-LSD and 12-hydroxy-iso LSD.

Although there are some minor points of divergence, these results are fairly consistent with observations made by others with different methods.[31,32] In summary, they suggest that LSD is rapidly disseminated into all tissues, but that it is mainly and rapidly metabolized in the liver, from whence it is secreted into the bile and excreted via the gut. Evidently, the lysergic acid ring is not cleaved or degraded and little destruction of the substituted amide side chain occurs. The work of Boyd[36] and Slaytor and Wright[37] suggests that hydroxylation occurs at ring carbon 12. They did not find the 2-oxy LSD which Axelrod *et al.* found in guinea pig liver microsomes.[32] Axelrod *et al.* used several species of animals in their study, but evidence for the formation of 2-oxy-LSD was reported only for guinea pig liver.

In an interesting study, Haley and Rutschman[38] measured the concentration changes of LSD-^{14}C, labeled in the amide group, in the brain of rats after intracerebral and intravenous injection. They found immediate behavioral changes after intracerebral injection, whereas there was about a three minute lag by the intravenous route. The effects were however qualitatively and quantitatively identical. The behavioral changes were still apparent after the intracerebrally administered radioactivity had fallen to very low levels. The authors conclude therefore that the low concentrations of LSD found in the brain after intravenous injection (or other routes of administration) are sufficient to produce the behavioral changes. However, the radioactivity was lost from the brain very rapidly to the bile via the liver. This rapid clearance supports the

possibility of a trigger mechanism, whereby LSD *per se* is not the active agent, but its presence in some manner causes another reaction or reactions to become aberrant.

Mechanism of Action

Among the observations that most stimulated interest in the mechanism of LSD action was that of Gaddum,[39] who showed that LSD would antagonize the action of serotonin on isolated rat uterus. Although the antagonism was demonstrated on smooth muscle not on cerebral function, Gaddum suggested[40] that LSD action in the central nervous system was mediated through its antagonism to serotonin. Independently, Wooley and Shaw[41] extrapolated the reasoning further, and proposed that a mental disease, such as schizophrenia, could result from an error in the metabolism of serotonin in the brain. Thus, serotonin was conceived as playing a highly significant role in mental function (which it does) and that LSD and other chemicals such as harmine, yohimbine and reserpine, all of which have an indole nucleus in common with serotonin, act as antimetabolites to the latter. Gaddum's original hypothesis that the psychic effects of LSD are caused by an antagonism of serotonin in the brain analogous to that in muscle was almost immediately discredited.[42] Although 2-Brom-LSD (BOL) is a potent inhibitor of serotonin action *in vitro* and *in vivo*, it is without any effect on the psyche in man.[23] Both LSD and BOL readily penetrate the blood brain barrier and they show a similar pattern of distribution and elimination. Furthermore, it was shown that the capacity of reserpine to decrease brain serotonin levels was uneffected by LSD, which at the same time ameliorated the depressant effects of this drug.[43] Conversely, pretreatment with reserpine enhanced and prolonged the LSD reaction in animals and in man. Later Costa *et al.*[44] concluded that the central effects of LSD have nothing to do with its antiserotonin action. However, using a bioassay technique, Freedman and Giarman[45] found that LSD causes an increase in cerebral serotonin in reserpinized rats. The increase was attributed to an increased binding of serotonin by brain granules.

At the time of this writing, there appears to be no com-

pelling evidence that the psychic effects of LSD are in any way mediated through the biogenic amines. In two recent and exhaustive symposia on the catecholamines[46] and on the mechanisms of biogenic amine release,[47] neither LSD or any of the well known psychoactive agents are mentioned. The omission is indicative of a waning interest in using the hallucinogens as tools for probing brain function. The scientific disciplines represented at these symposia, namely pharmacology, biochemistry, neurophysiology, and morphology among others, are those from which answers to the LSD phenomena are likely to come. Whether the apparent indifference results from a conviction that these drugs *per se* offer little toward understanding CNS function, or whether the increasing notoriety has lead to disenchantment in certain scientific disciplines, is a subject of conjecture.

Another interesting, but poorly understood, facet of LSD action is the rapid tolerance[48] and cross tolerance which can be demonstrated on repeated use of the drug. Cross tolerance occurs between LSD and some of its derivatives such as lysergic acid monethylamide and d-2-brom-lysergic acid diethylamide;[49] between LSD and psilocybin;[50] and between LSD and mescaline.[51,52] These observations led to a proposal that mescaline, psilocybin and LSD constitute a physiologically related group of psychotomimetics and that these substances act through the same physiological or biochemical mechanism or on some final common pathway. However, compounds such as N,N-dimethyltryptamine which elicit effects similar to those produced by LSD,[53] and d-amphetamine[54] which is chemically related to mescaline, give no cross tolerance. Furthermore, a certain molecular configuration is required for the LSD reaction, and the reaction is stereospecific, which leads to the belief that highly selective sites might be involved. Isbell and Jasinski[55] compared LSD and Δ^1-tetrahydrocannabinol (Δ^1-THC) and checked for cross tolerance. The pattern of so-called objective tests such as temperature and blood pressure increases, pupillary dilation, and hyperreffexia are characteristic of LSD but did not appear with Δ^1-THC. The subjective effects caused by the two drugs were quite similar. However,

patients tolerant to LSD showed no cross tolerance to Δ^1-THC. The authors concluded that different underlying mechanisms are responsible for the psychic effects produced by the two drugs.

Recently Smythies *et al.*[56] proposed a general hypothesis based on an interaction between serotonin and either RNA or DNA. Apparently, these authors are proposing that hallucinogens in some way act as central antagonists to serotonin, but they readily admit a lack of supporting evidence. This illustrates one of the weaknesses of the extensive research effort on hallucinogenic drugs, particularly LSD. Too much of it has been directed toward determining the effects on this or that system, or on the therapeutic and adverse consequences of the drug. There is relatively little conclusive data on the mode of action of any of these agents.[57]

Needless to say, there has been a deluge of studies on biochemical parameters both in man and in animals. LSD administered intravenously had no significant effect on cerebral blood flow, cerebral vascular resistence, oxygen or glucose utilization, or respiratory quotient.[58] Only two of the wide variety of systems examined have shown consistent change. After LSD, the excretion of inorganic phosphate is diminished, and free fatty acids are increased in the plasma. However, these effects could be due to nonspecific stress.[59] In man, LSD does not effect serum creatinine, plasma urea, NPN, sodium chloride or osmolality. Serum cholesterol and total lipids are essentially unaltered. The activities of serum GOT, pseudocholinesterase, and ceruloplasmin are unchanged. Liver function is uneffected, and no significant results have appeared from the examination of urinary constituents.

As has been indicated earlier, LSD produces a mild hyperglycemia. It inhibits oxidative phosphorylation[60] in the rat brain mitochondria while oxygen consumption in the intact animal is increased.[61] This increased metabolic rate would be consistent with the pyretonic effect mentioned earlier. Enzyme systems may be either inhibited or activated depending upon the dose of the drug, the species, and the part of the brain examined. Thus, LSD increased oxidation of glucose in

rat cerebral homogenates, but reduced it in cerebellar tissue.[62] These results on glucose utilization differ from the observations made in man.[58] 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.[62,63] Many of the reports describing effects on enzymes and other biochemical systems are conflicting. For the most part, these studies project an aura of indecision and as a whole offer little convincing evidence on the biochemistry of LSD, or on its mechanism of action.

LSD as a Therapeutic Agent

Of all the so-called mystic phenomena which have been generated from the discovery of LSD, none are more mystifying than how this compound metamorphosed from a psychosis-simulating agent into a psychotherapeutic device in a period of less than ten years. Perhaps one oversimplified and unsatisfactory explanation can be distilled from these words:[64] "In the late 1950's some physicians thought they had discovered a new reality of the mind and were not only struck by the drug-induced phenomena, but addled by them."

Whatever the explanation, the fact is that by 1960 LSD was being considered and seriously tested in the treatment of a variety of mental disorders. Among these were included manic depressive reactions of various types; schizophrenic reactions of paranoid, catatonic and hebephrenic types; involutional psychotic reactions; psychoneurotic reactions of mixed types; alcoholism; chronic psychoses; character and behavior disorders, including homosexuality; pseudoneurotic and borderline schizophrenia.[65] By 1960 LSD had been used in the treatment of practically every type of mental affliction known to man, including drug addiction. Most of the author's reported efficacy of treatment as either good or promising.

From these early studies, a variety of techniques and methods were evolved. With some overlap, most of these can be summarized into two major techniques: psycholytic and psychedelic therapy. The psycholytic[63] or psychoadjuvantic method[21] depends upon a drug-induced loosening of defenses

and dissolution of ego.[66] Some elements of insight, recall, reliving, abreation and catharsis are involved. The drug facilitates the efforts of the therapist in helping the patient to confront, understand and accept certain factors and events which may have been contributory to his or her past and present behavior. Some psychotherapists place emphasis on the process of abreation, a cathartic exercise resulting from recalling and reliving a profound or traumatic experience of the past. LSD is considered to be an effective agent for opening mental sluices through which an outpouring of suppressed or hidden emotion can occur.[67-70] Others have found LSD to be no more effective than placebo or no drug treatment at all.[71-72] Significantly, the latter studies, which incorporated controls as a part of the experimental design, reported *improvement* in *all* categories of subjects; those who received placebo, those who received no drugs, and those who received LSD. However, there was no significant difference between the groups.

In psycholytic therapy, LSD is considered to be an adjuvant to conventional psychotherapy. In psychedelic therapy, it is also used for this purpose, but in addition, one major aim is to achieve the psychedelic reaction, sometimes called "experience" or "peak." The "experience" and the procedures for bringing it about have been described at length by various investigators.[21,66,73,74] The "mind-manifesting" experience is assumed to be of such impact that the subject becomes aware of new and different avenues for personality change and development. However, investigators have difficulty in describing just what the experience is. Terms such as "transcendental" and "mystic" are used, followed many times by a long wordy direct quote of a *subject* describing the experience.

Psychedelic therapy is said to be a highly specialized form of brief intensive psychotherapy.[66] In this context, much has been made of reported successes in the treatment of alcoholics with LSD.[21,75-77] In controlled experiments, of which there is a dearth in this area of research, LSD was shown to be no more effective than placebos or no drugs at all.[78-80] The latter investigators formulated criteria for objective evaluation, and in each study *all* groups, whether they had received LSD, pla-

cebo, or no drugs, showed improvement as judged by follow-ups on from 87 to 97 per cent of the subjects. Thus, we are led to conclude that the use of LSD for treatment of alcoholism is of questionable value and that appropriate controls may have been lacking in some of the more optimistic reports of success.

There have been reports of beneficial effects of LSD in the treatment of patients with malignancies[81] or with terminal cancer.[82] These were uncontrolled, subjective studies, conducted on patients who could be expected to be extremely vulnerable to suggestions, so the conclusions are suspect. However, in this case, if not in the other categories of mental distress, the proposed therapy can do no harm.

In summary, the simplest, most easily understood rationale for investigating the use of LSD in the treatment of various mental disorders is that there is no other simple, consistently effective drug or tool which works. One can sympathize with the almost insurmountable barriers to the design of sound experimental approaches to these human problems. However, the problems, difficult as they are, have been compounded by an incredible naiveté, if not downright ignorance, as to how and what conclusions can be made from any one or more series of observations. In his discussion of obsolete or outmoded paradigms, Colby[83] states that chaos prevails in psychotherapy; that psychotherapy, as presently defined and practiced, is no science and may never be. To him, psychotherapy consists of remedial techniques which looks to science for help with difficulties. But science is only a method, a model, a paradigm, which many investigators of LSD have chosen to ignore, or of which they are not aware. Colby calls for new paradigms in psychotherapeutics, but he apparently foresees no increased significance for the scientific approach, in spite of the growing body of information on the efficacy of pharmacological agents.

Adverse Reactions

No established, experienced, creditable investigator of LSD and its use has claimed in print that it is not a dangerous drug. In 1959, the year in which the drug became a black-market

item,[84] this point was stressed repeatedly by Hoch, Fremont-Smith, West and others.[86-87] In fact, most responsible advocates of the use of LSD in therapy or research admonish that the drug be given to humans only under carefully controlled conditions, with experienced medical supervision, and that every precaution be taken before, during and after the administration of the drug. In spite of this awareness of the potential hazards, prior to 1960 practicing professionals dispensed and used LSD with a casualness that belied respect for the toxicity of the compound. At the conference on LSD sponsored by the Josiah Macy, Jr. Foundation in 1959, one participant lightly referred to having given LSD to his wife; another had given the drug to pregnant women, and nearly all of the twenty-six conferees had taken the drug themselves. Thus, it is not too difficult to understand why, during the period from 1950 to 1959, the use of LSD spread from the research laboratory to practicing professionals, who gave it to their friends, relatives and patients.[84] Shortly after physicians had access to the drug for experimentation, informal black-market use occurred.[84]

At the 1959 Conference on the use of LSD, only a few untoward problems were reported as a result of administering LSD to over two thousand patients and/or experimental subjects. Among the incidents listed were one suicide, one disrobing, one paranoid reaction, "variable" problems and "aggressive psychopaths." These and other data embodied in a deluge of published work, much of which lacked scientific discipline and value, apparently led to an *attitude* that LSD was a reasonably safe drug in spite of warnings to the contrary. At that time, a relatively small number of people had ingested LSD. Of those who had, a large percentage were mentally ill and had received the compound in a therapeutic or hospital situation. The lack of knowledge and the lack of respect for the potential dangers of the drug lead ultimately to the highly publicized so-called "unfortunate Harvard Affair" and its aftermath. LSD, which offered such great promise as a research tool for probing mental function became an alluring lady of the streets, and was now offering "creativity to the uninspired, *kicks* to the jaded, emotional warmth to the cold and inhibited,

and total personality reconstruction to the alcoholic or the chronic neurotic."[88]

In a very short span of from four to five years, articles which stressed primarily the bizarre, intriguing, or beneficial effects of LSD proliferated in newspapers, magazines and books. Its capacity to "expand the consciousness," to open new doors to self-understanding, to unveil latent powers of creativity, and to bring about a general reformation of personality were highlighted. Not surprisingly, this type of sensationalism led to widespread indescriminate self-administration of material by impressionable people, particularly young folk. Often the drug was obtained from illegal black-market sources and was neither pure nor safe.

As has been indicated earlier, when LSD is used experimentally a great deal of caution is exercised. Despite this care, there have been and continue to be a number of reports of brief or even prolonged adverse effects. In 1960 these incidents were estimated to be less than 1.0 per cent.[89] This was considered to be quite low, but assumes significance if one considers that 1 per cent of one million is ten thousand and this under conditions which should minimize the chance of bad reactions, panic, or prolonged complications. In any event, with the upsurge in the numbers of persons who were taking the compound, or something reputed to be the compound, in nonsupervised situations, there was a marked increase in the number of persons hospitalized as a result.[90-94] Frosch reported[93] that from 1965 to 1967, there were two hundred admissions to the Bellevue Psychiatric Hospital in New York City resulting directly from the ingestion of LSD. About 5 per cent of the admissions to the Psychiatric Hospital had had at least one experience with LSD. Of the patients who had used the drug, about 15 to 20 per cent were admitted as a direct result of the drug effects. Thus, of the 20,000 to 26,000 psychotic cases admitted, two hundred were a result of adverse reactions to LSD. Louria[95] has recently reported on the increased number of patients admitted as a result of adverse LSD effects.

Psychological Syndromes

There have been several classifications and descriptions of adverse psychological reactions following the ingestion of LSD.[90-94,96,97] In general, there is good agreement among those who have published explicitly on the various types of untoward reactions and those who mention *an occasional* adverse reaction as to symptomology and effect. The following description has been summarized from the paper by Frosch.[93]

There are three overlapping categories of adverse reactions to LSD; acute reactions, recurrent reactions in which there is a recurrence of symptoms without reingestion of the drug, and prolonged reactions.

Acute Reactions

These reactions arise concomitantly with the ingestion of the drug and are short lived; however, persons in whom these symptoms occur may also later report recurrences. Under the direct influence of the drug, some individuals experience a so-called psychotoxic reaction which Cohen[96] called acute paranoia. These individuals may attempt suicide or try to inflict harm on themselves. Such actions may result from grandiose or persecutory illusions. Some of the acute reactions are bizarre and newsworthy so that an increasing number of such incidents are reported in newspapers. Recently, the eighteen-year-old daughter of a well-known entertainer leaped to her death, reportedly under the influence of LSD. Advocates of the use of LSD in therapy and research insist that reactions of this sort arise from a lack of supervision during the period of drug action.

Differentiated from the psychotoxic reaction, which appears to be a direct effect of the drug, is the panic reaction, which is a response of the recipient to the drug-induced symptoms. There may be an overwhelming anxiety, fear of going crazy, a sense of helplessness and a loss of control (note that these reactions are implicit in the general psychological effects mentioned earlier). These individuals fear that they will not re-

turn to reality. Both the setting in which the drug is taken and the psychological state of the person at the time of ingestion are important in precipitating panic. Frosch[93] reports that in their patient population, panic reactions occurred both in the novice and in the experienced drug user.

Recovery from acute reactions to the drug occurs usually within a period of two to three days. A supportive environment and sympathetic hospital personnel are usually sufficient to alleviate the terror. Although chloropromazine is the drug most often used clinically to reverse the LSD reaction, it is by no means a complete antagonist, nor is it a panacea for "bad trips." Nevertheless, Hollister[2] recommends it for those situations in which the LSD syndrome gets out of hand, either for the patient or the physician. Usually, the dose is from 25 to 50 mg, intramuscularly, repeated every thirty minutes until the situation is controlled. Caution should be exercised however, since chlorpromazine exacerbates the symptoms of STP[91] and others have questioned its use even with LSD.[102]

Recurrent Reactions

There have been reports of recurrent episodes after ingesting LSD, at least since 1959.[98] However, in the last few years increasing numbers of cases are being hospitalized as a result of symptom recurrence. In Frosch's study[93] of fifty-seven LSD-using patients, 33 per cent were cases of recurring symptoms. Others[99] report an increasing number of teenagers who, having had LSD once at a party, got over the episode in twelve to sixteen hours, but then presented at a hospital a few months later with recurring symptoms. However, recurrent symptoms are not restricted to "first-time" or "once-only" users, but may occur in more experienced drug users.[93,99,100]

Recurring symptoms are analogous to those experienced at the time of drug ingestion. The time of onset may vary from a week to months or even up to a year or more after the last drug session. Recurrent episodes may last only a few seconds, or they may last over an extended period of time. There may be again the heightened awareness, perception, etc. There may also be anxiety, depression, paranoia, feelings of futility,

and a sense of lost reality. There is almost always fear, sometimes bordering on terror, when individuals experience these effects without having taken the drug. They think they're going crazy.

Among the persons who experience recurring effects, there are a preponderance of "unstable" types.[64,100] Also important to this phenomenon of return is a factor which could be called "susceptibility to suggestibility." Most authors stress the importance of set, the attitude with which the recipient approaches the drug session, and the setting, the environment in which the session is conducted. These obviously attest to a "suggestible" state. After the drug session, persons who may be more prone to suggestion excessively dwell on the drug session; what they felt, thought and saw. Thus, they transport themselves back into the realm of phantasy. The question is, did they transport themselves into phantasy by way of suggestion *at the time* of the drug ingestion? Most psychotherapists who use LSD and similar drugs readily admit that LSD opens the door, so to speak, to the therapist. Hypersuggestibility may be the most important, if not only, role in therapy.

Prolonged Reactions

Although somewhat similar to schizophrenia or chronic depression, chronic anxiety and chronic psychotic states resulting from the use of LSD show a preponderance of visual phenomena, depersonalization and body image distortions. Chronic anxiety states consisting of depression, somatic problems, and difficulty in functioning are not uncommon and may last for periods of months. These chronic psychotic states may develop in persons who were not psychotic prior to using LSD. The condition is partly explained by assuming that once having experienced feelings of ecstasy and omnipotence, and of having achieved a new level of being, the recipients could not return to reality. Further complications arose when their new concept of themselves was not accepted by those with whom they had to function in everyday life. As a result, they withdraw. Freedman[64] recognizes the possibilities of impairment of

good sense and maturation with habitual long term use of LSD.

In summary, LSD is obviously a dangerous compound, a fact which has been recognized since it was first used as a psychotomimetic agent in the early 1950's. However it is not now and has never been other than an experimental drug. Even when used in this capacity, under medical supervision, and with the most attendant care, it can and often does cause varying degrees of harm, which at the present time is thought to be mostly of a psychological nature. The fact that an experimental compound can be harmful, even when used under proper supervision, should be no cause for alarm. There are few drugs which won't cause adverse reactions and few chemicals which are absolutely harmless to everyone—strawberries cause severe adverse reactions in some people, and poison ivy is not completely innocuous to everyone. LSD, unlike strawberries, is an important research tool which may, if used with intelligence, common sense, and possibly a great deal more diligence than it has been in the past, give us some clues to the nature of the very adverse reactions that it induces.

At a recent conference on LSD, one participant stated that the words "LSD" and "scientific objectivity" are mutually exclusive.[101] If this is true, and past events certainly lend credence to the statement, LSD may become a bane or a boon to human existence, or it may be a passing fad, but it will never fulfill its promise as a tool of science. At the same conference, one conferee stated[102] that "there's very little hope that when most psychiatrists have their first contact with this drug they are going to be particularly sensible about viewing the phenomena induced by LSD." From the very beginning, as noted above in the 1959 Macy Conference on therapeutic effects of LSD, this fact was implicit to a discerning reader of articles on the effects, the uses, and the personal and impersonal observations on LSD.

> For myself, my experiences with these substances have been the most strange, most awesome, and among the most beautiful things in a varied and fortunate life. These are not escapes from, but enlargements, burgeonings of reality. In so far as I can judge they occur in violation of Hughlings Jackson's principle, because the brain although its function is impaired, acts more subtly and complexly than when it is normal. Yet surely, when poisoned, the brain's actions should be less complex, rather than more so? I cannot argue about this because one must undergo the experience himself. Those who have had these experiences know, and those who have not had them cannot know and, what it more, the latter are in no position to offer a useful explanation.[103]

Few authors are possessed of such evangelical zeal, but there is an aura of permissiveness in some articles. The statement that "Its dangerous, if the person is dangerous,"[104] is neither a novel or convincing argument in support of LSD use by the layman. The same thing could be said of dynamite. And another, "I've tried to describe that from time to time but there's no question that the split of the self, that is, the entire experience of the self seeing the self, and the self seeing the self seeing is an astonishing experience."[102]

At the present time, there is a need for scientific objectivity in the search for knowledge about LSD. Whether it's supplied by someone looking at himself looking at himself or by someone looking at an organism as an organism, or both, is irrelevant.

Chromosomal Aberrations

In March of 1967, Cohen *et al.*[105] published a paper describing a marked increase in chromosomal abnormalities in human leukocytes which had been incubated with LSD in tissue cultures. Almost immediately several papers appeared which reported a greater incidence of chromosomal aberrations in leukocytes of LSD takers as compared to nontakers.[106-108] At the same time an equal number of papers appeared disclaiming LSD-induced chromosome damage in human leukocytes.[109-111] Cohen *et al.* [112] followed up their original *in vitro* study with an experiment involving eighteen LSD users in whom they found two to four times greater incidence of chromosomal aberrations than in fourteen controls. Interestingly, this patient group was described as "inveterate experimenters with other drugs" and every subject had taken either one or more of the amphetamines, barbiturates, cocaine, hallucino-

gens, opiates and phenothiazines. One subject had had phenothiazine at the time blood was drawn. These authors also studied six patients who had not taken LSD, but some other drug, mainly chlorpromazine. Of these, all but one showed an abnormally high incidence of chromosome damage. One detects some lack of candor in describing this study as "chromosome damage induced by LSD-25." Recently, Tjio *et al.*[22] selected thirty-two patients for a controlled study of chromosome damage before and after ingesting LSD. None of the patients had ever been exposed to LSD prior to the study. There was no significant difference between the before and after-LSD chromosomal aberration rates. Although these patients had been exposed to a wide variety of psychoactive and other drugs for varying times prior to the experiment period, the number of chromosomal defects in the pre-LSD lymphocytes was insignificant. White blood cells from five persons who had used black-market LSD were examined before and after LSD, but no chromosome defects were noted. These workers also studied eight subjects who had received pure LSD, but were not patients, and two subjects who were not patients, but had never had LSD prior to participating in the study. In none of these groups was there a significant change in white blood cell chromosomes before and after LSD ingestion.

Perhaps a more interesting facet of the LSD chromosome controversy is whether LSD may be mutagenic or teratogenic. The latter effect was reported after LSD was administered to rats,[113] mice[114] and hamsters.[115] However, such changes have not been detected by others.[116,117] Two studies, referred to as "preliminary" by one of the authors, [118] have shown aberrations in meiotic chromosomes in male mice germ cells.[119,120] As yet, these data have not been supplemented by the authors, and others have not confirmed the observations.[121]

In view of the thalidomide tragedy, and perhaps because of it, reports of teratogenicity in humans as a result of LSD ingestion during pregnancy are of much interest. Zellweger *et al.*[107] reported one such case. A child with a malformed leg was born to a mother who had apparently taken LSD on the

forty-fifth day of pregnancy. Two other cases have been recorded where mothers, who had reputedly ingested LSD and marihuana during pregnancy, gave birth to babies with malformed limbs.[122,123] Another case report showed no abnormalities in a baby born to a mother who had ingested LSD during and before pregnancy.[124] In early[125] and recent studies[126] no defects or abnormalities were found in children born to patients who had received LSD.

Among the many factors which should be assessed in evaluating reported LSD chromosome damage *in vitro* and/or *in vivo* are radiation, viral infections,[127-129] other psychoactive agents [109] and some tranquilizers, as noted by Cohen *et al.* with chlorpromazine.[112] In addition, there are a wide assortment of radiomimetic compounds,[130-133] among which ethyl alcohol and caffeine have been included. Significantly, the latter[134,135] was shown to cause chromosomal aberrations in Hela cells and human leukocytes, apparently by binding to DNA and preventing effective replication. When patients are used as test subjects, alcoholics for instance, the nutritional status and the general state of health could also be pertinent factors.

Chromosome damage is not an uncommon occurrence, and at the present time its significance in altering normal functions is unknown. Therefore, the recent rash of conflicting articles concerning LSD-induced chromosomal damage should be viewed with some skepticism. These reports, which are apparently published at will in journals with benign editorial review policies, have evoked sensational inferences concerning reproduction and health. The inferences are given the guise of veracity by widespread dissemination in an everpresent, all-encompassing mass news media. Subtly composed nonconclusions based on preliminary and possibly tainted data cannot substitute for the pains-taking, time-consuming check and balance methodology which is so often required to ferret out one small truth. One can question the wisdom, if not the morality, of sacrificing a fruitful tradition of scientific discipline for social expediency.

In summary, there is overwhelming agreement that LSD

can initiate dangerous psychological reactions and that it should be ingested only under the supervision and guidance of a physician experienced in its use.

Data implicating LSD in chromosome damage are fragmentary, conflicting and confusing. Much more work is needed and experimental conditions should be more carefully controlled before useful conclusions can be drawn. However, ingesting the drug during pregnancy is counterindicated at the present time.

OLOLIUQUI

The mission of the Spanish Priests, who came to Mexico following the Spanish Conquest, was to prosecute evil and indoctrinate heathens in a new faith.[136] To do this effectively, the more conscientious and learned of these Churchmen thoroughly studied the indigenous rites, religions, history, knowledge and morals of the conquered Aztec people. Fortunately, some of them became seriously interested in the real values of the civilization and went to great lengths to obtain and record information on various aspects of the culture. The most distinguished of these was Bernardine de Sahagun who, according to Del Pozo,[136] was a true pioneer in the use of scientific methods for ethnological research. In "General History of things of New Spain" originally published in 1560, Sahagun[137] explicitly described teonanacatl, peyotl and ololiuqui. The active ingredients of these ancient drugs are among the most famous of modern hallucinogens. Ololiuqui was described by Sahagun and others[138] as a sacred hallucinogenic vine, the seeds of which were used for divinatory and religious purposes. In his monumental study of over three thousand plants, Francisco Hernandez,[138] a Spanish physician, described and illustrated the plant and its seeds. Although the description and drawing by Hernandez were accurately indicative of a species of morning glory (Convolvulaceae), the plant was incorrectly classified as a species of *Datura*, in spite of the insistence of Mexican botanists that the plant was a morning glory. Ethnobotanists were misled by the knowledge that, in contrast to Solanaceae, no intoxicating constituents had hitherto been found in convolvulaceous plants. The identity of ololiuqui was the subject of a botanical impasse until Schultes work[139] in 1941. He confirmed an earlier identification of ololiuqui as *Rivea corymbosa* Hall and described its history, botanical properties and uses.

The peoples of Aztec Mexico used ololiuqui for divinations and medicine, perhaps even more than peyote and teonanacatl.[140] Modern Indians grind the seeds, which have a tough outer coat, on a stone, soak them in water or alcoholic drinks, filter them, and drink the filtrate. If the seed coat is not crushed, the intact seed may pass through the gastrointestinal tract without yielding up its magic potent.

Chemistry

Hofmann *et al.*[141-144] extracted and identified several ergot derivatives from *R. corymbosa* seeds. The main component of the ergot indole fraction was d-lysergic acid amide (LAA), plus d-lysergic acid methylcarbinolamide (LAM) and a few minor alkaloids.[16,144] This finding was unexpected because hitherto lysergic acid alkaloids had been found only in lower fungi such as *Claviceps*. This was the first time they had been found in higher plants. Some botanists (and a few pharmacologists) were difficult to convince, but Hofmann's results were confirmed in other laboratories and in other species of morning glory.[146-149] The structures of LAA and LAM are shown in Figure 10 along with the minor ergot constituents of ololiuqui.

Although the presence of ergot alkaloids in ololiuqui and the seeds of morning glories is an important discovery, it has not been unequivocally established that the psychic activity of ololiuqui is due solely to lysergic type compounds. None of the ergot indole derivatives except LAA have hallucinogenic activity. The amide is about one-tenth as active as LSD.[21] LAA had been known for years as a constituent of the hydrolysis products of ergot alkaloids.[150] Solms[151] showed that it was psychoactive and contained a strong narcotic component. Hofmann confirmed these results. Another major component

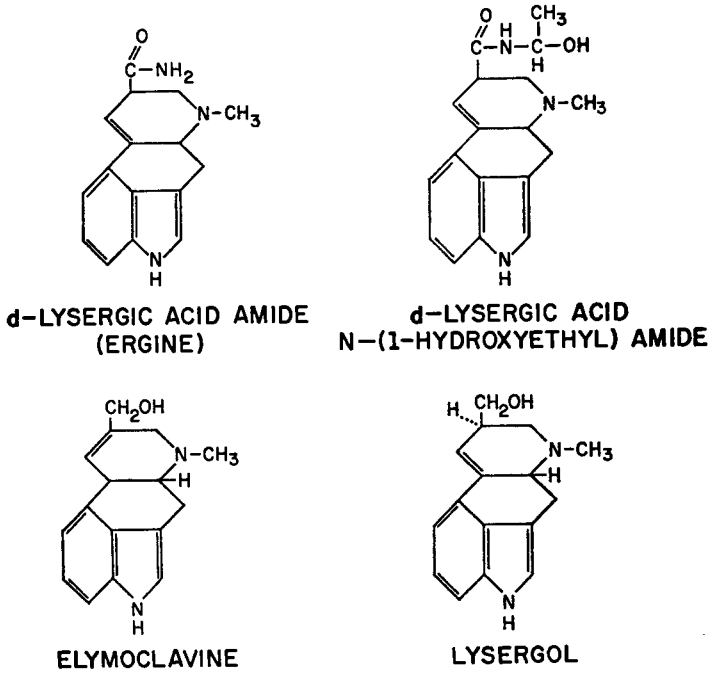


Figure 10. Lysergic acid derivatives which have been isolated from ololiuqui.

of ololiuqui is a glucoside which was isolated by Cook and Killand.[152] The presence of a glucoside was confirmed by Perezamador *et al.*[153] who identified it as turbicaryn. Hoffer[21] ingested a glucoside which had been extracted from *R. corymbosa* and concluded that it had a psychological effect of an inhibitory nature.

Until all the constituents of ololiuqui have been isolated, identified, and assayed for activity, knowledge of the active ingredients will be incomplete.

Pharmacological and Psychological Effects

After reading Schultes work[139] and combing other sources for information about the use of ololiuqui for producing intoxication, sense distortion, and hallucinations, Osmond studied the effects of the drug on himself[21] His subjective evaluation

of his results[154] were published in 1955. For reasons which are not clear, others[155] were unable to confirm Osmond's results. Hofmann's subsequent discovery of the ergot compounds in *R. corymbosa* amply justify Osmond's confidence in his analysis of his own behavior.

Starting with fourteen seeds, Osmond (who apparently possesses unusual gustatory accouterments) increased the dosage gradually. In doses of sixty to one hundred seeds, which were pulverized and washed down with water, ololiuqui produced anergia and irritable apathy, combined with alert thought processes and increased hypnagogic phenomena. Effects appeared rapidly (within 20 minutes), were of short duration, and left no hangover. In doses of 0.5 mg,[144] LAA caused slight nausea, and a tired, dreamy, apathetic state. One hour after ingestion, the subject fell into a sleep which lasted for three hours. There were no after effects. Thus, Osmond's original observations with morning glory seeds were born out by later experiments with a purified compound extracted from those seeds.

In recent years, several cases of morning glory seed intoxication have been reported.[156-159] The patients, all young people who had taken seeds of locally available species of morning glory, admitted with strikingly similar symptoms. Autonomic effects were nausea, flushed skin, extremely dilated pupils, low blood pressure and a slightly increased pulse rate. The number of seeds used to bring on the syndrome varied from 150 to 309. Subjects reported hallucinations and visions. They were much concerned with the reality of objects and people. Periods of apathy alternated with short periods of excitement. Recent and remote memory was affected.

The morning glory seeds were from several varieties: Heavenly blue (*R. corymbosa*), Pearly gates (*I. viol*) or Flying Saucers. Some of the students reported taking dramamine to ward off nausea.

In one case[156] Promethazine hydrochloride was used intramuscularly as effective therapy. Five weeks later, this subject readmitted and was treated for a "recurrence." Other cases[157] used counseling in conjunction with barbiturates as therapy.

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Chapter IV

THE INDOLES

IN THE PRECEDING discussion of LSD, the importance of indole compounds to mammalian physiology was mentioned. Indole analogues are of no less importance to other forms of life, and their distribution reflects that fact. Among naturally occurring alkaloids, there is a large and complex group of indole-containing compounds. These comprise about one-fourth of all known alkaloids,[1] but they may have such diverse chemical structures that group identity is obscured. For instance, there is little similarity in the chemical properties of reserpine, LSD, and physostigmine, and even less similarity in their pharmacological action. On the other hand, LSD and psilocybin differ markedly in chemistry but elicit very similar psychological reactions. These compounds, all of which have an indole moiety as a part of their structure, are shown in Figure 11.

Indole alkaloids are widely distributed, but little information on the metabolism or biogenesis of these complex materials has been forthcoming. One generally accepted assumption is that the indole nucleus is derived from the amino acid, tryptophan. The intermediates between this simple amino acid and complex alkaloids such as ibogaine, lysergic acid, and their derivatives are unknown.

With the exception of LSD, which is not a naturally occurring substance, the hallucinogenic indoles can be classified into three groups of related compounds. These are the simple indolealkylamines which are protalkaloids and because of their close chemical relationship to serotonin have received much study. The other two groups are the β-carbolines of which

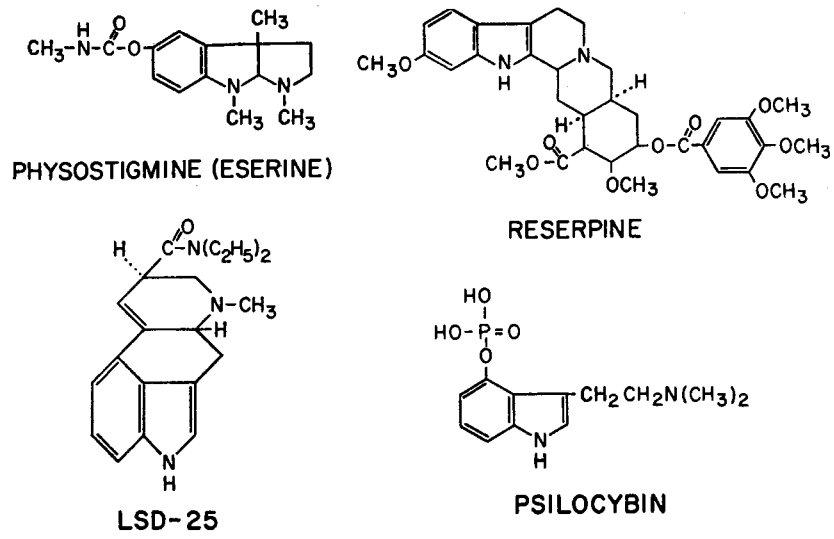


Figure 11. Structurally dissimilar indole-containing alkaloids.

harmine is an example, and the iboga alkaloids, typified by ibogaine.

INDOLE ALKYLAMINES

Tryptamines

The simplest indole protalkaloid which has hallucinogenic activity is N,N-dimethyltryptamine (DMT). As is often the case with simple compounds, DMT was synthesized[2] long before it was isolated from natural sources. It was first identified as a constituent of snuff made from the seeds and pods of *Piptadenia peregrina* and *Piptadenia macrocarpa* Benth, which are leguminous plants.[3,4] Along with DMT, Fish *et al.*[4] found dimethyl-N-oxide, 5-hydroxydimethyltryptamine, or bufotenine, and its corresponding N-oxide, as constituents of the cohoba snuff. Since bufotenine was present in the highest concentration, Fish *et al.* assumed that it was the active ingredient. A short time later, Szara[5] investigated DMT and found it to be inactive if ingested orally. However, intramuscular injection of relatively small quantities gave a rapid and strong hallucinogenic reaction.

Dimethyltryptamine is one of the more widely distributed hallucinogens. In addition to the plants above, DMT has been identified as an active ingredient in the hallucinogenic snuff made from *Prestonia amazonica.*[6] The validity of this observation has been vigorously contested[7,8] on the grounds that the source material was probably *B. rusbyana* rather than *P. amazonica.* DMT also occurs in *Lespedeza bicolor japonica,*[9] and in the root of *Mimosa hostilis* Benth.[10] These plants have been used for centuries by some Indian tribes of South America and the Caribbean as the source of a ceremonial, psychoactive snuff. The snuff which is called cohoba or yopo may be prepared in different ways from different plant species by various tribes. This native individuality has created havoc in the efforts of more sophisticated cultures to identify the ingredients of the snuffs. For instance, a snuff called yakee, parica, epena or nyakwana is prepared from the bark of several jungle trees of Virola[8,11,12] belonging to the Myristicaceae family. The active ingredients of epena and cohoba are apparently the same. However, the question of which plants are used to make the intoxicating epena, or yakee, is still not unequivocally established[13] because plants of types other than Virola are used simultaneously and as mixtures. This could explain the contradictory findings that completely different compounds may be isolated from snuff of the same name, but of various origins. Holmstedt[14] found 5-methoxy-N,N-DMT as the main component of epena obtained from Indians in northwest Brazil; whereas harmine derivatives were found in the epena made by the Surara Tribe.[15] Whatever the variety or source, the snuff is almost always ingested by inhalation through the nostrils by means of bifurcated or straight tubes. Interesting articles on the botanical sources, preparation, and use of these snuffs have appeared.[11,12]

Bufotenine was first isolated[16] from the secretions of the toad, *Bufo vulgaris* in 1893, but it was not fully characterized until much later.[17] There are many syntheses of the compound, the most useful of which is the procedure of Speeter and Anthony.[18] Bufotenine is present in significant proportions in practically all of the various plants from which hallucinogenic

snuffs are made. *P. peregrina* seeds contain 0.94 percent and *P. colubrina* seeds as much as 2.1 per cent.[19] However, snuff made from these materials also contain DMT and 5-methoxydimethyltryptamine in about the same amounts.[20] There has been some controversy as to whether bufotenine has any hallucinogenic activity. Fabing and Hawkins[21] injected from 2–16 mg per kg intravenously into man and reported psychic activity. Others have refuted this,[22] partly on the basis that amounts of bufotenine needed to produce hallucinations could not be inhaled in snuff. Isbell was unable to find any psychic effects of bufotenine after inhalation or oral ingestion. However, he warned against premature conclusions about the efficacy of bufotenine as a hallucinogen.[23] This compound has extremely painful and dangerous cardiovascular effects and cannot be used without caution in man. It would be difficult to differentiate whether a psychotic reaction were due to central effects or cardiovascular action.

Sheep feeding on a grass, *Phalaris tuberosa L.*, developed a condition known as "staggers" and stimulated a search for an active psychotogen. A substance identified as 5-methoxy-N-methyltryptamine was isolated from a related species of grass, *P. arundinacea L.*[24] This compound and 5-methoxy-N,N-dimethyltryptamine were both later shown to be present in the bark of *P. peregrina* (Fig. 12).[25]

Psilocybin

Although they have not been found in the plants from which psychoactive snuffs are made, the 4-hydroxy derivatives of N,N-dimethyltryptamine are among the more potent naturally occurring hallucinogens. The story of the rediscovery of the "magic mushroom" cult of Mexico by a New York businessman turned ethnologist and his wife has been well-chronicled, not only by them[26] but by the press and by every writer who treats the subject of hallucinogenic drugs. It is an interesting episode and bears up well under retelling.

Spanish historians[27,28] who wrote about peyote and ololiuqui also described the "sacred mushroom," teonanacatl. The intoxicating mushrooms were eaten by the Indians at feasts and

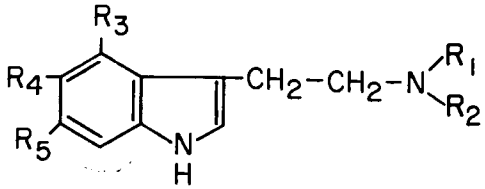


Figure 12. Indole alkylamines. Various substituents give the following compounds:

DMT: R_1, R_2 = CH_3; R_3, R_4, R_5 = H.
Psilocin: R_1, R_2 = CH_3; R_3 = OH; R_4, R_5 = H.
Bufotenine: R_1, R_2 = CH_3; R_3, R_5 = H; R_4 = OH.
5-MEO-DMT: R_1,R_2 = CH_3; R_3, R_5 = H; R_4 = OCH.
6-OH-DMT: R_1, R_2 = CH_3; R_3, R_4 = H; R_5 = OH.

religious ceremonies, and by special classes of folk, such as witch doctors and soothsayers. Imbibers were subsequently endowed with clairvoyance and divine powers. Descriptions of the response to ingestion of selected types of mushrooms are entirely analogous to those written about peyote ingestion.

The use of mushrooms in Mexico and Central America for social and religious purposes had apparently disappeared except for a few isolated Indian tribes in remote mountainous districts of Mexico. Stimulated by reports that mushrooms were still being eaten for purposes of magic in southern Mexico, the Wassons[26] made several trips into these regions in search of the culture and the mushrooms. In 1955, Gordon Wasson actively participated in an Indian mushroom ceremony in Huautla de Jimenez, Oaxaca. On a subsequent expedition in 1956, the Wassons were accompanied by Roger Heim, a botanist, who identified and classified the mushrooms. They were of the family Strophariaceae and mostly of the genus *Psilocybe*. Heim collected spores, and upon his return to Paris artificially cultivated the mushrooms in the laboratory. One variety *Psilocybe mexicana* Heim, grew especially well under these conditions and was later subjected to chemical analyses by A. Hofmann, the discoverer of LSD, and his associates.[29,30] The original extracts were tested in animals using pupillary and piloerection criteria to evaluate the activity. The results were equivocal, and there was some doubt as to whether the mushrooms, cultivated and dried in Paris, were still active. Hofmann, settled the question personally by ingesting thirty-two dried specimen of *Psilocybe mexicana* weighing 2.4 grams. He described the results as follows.[13]

> Thirty minutes after taking the mushrooms the exterior world began to undergo a strange transformation. Everything assumed a Mexican character. As I was perfectly well aware that my knowledge of the Mexican origin of the mushrooms would lead me to imagine only Mexican scenery, I tried deliberately to look on my environment as I knew it normally. But all voluntary efforts to look at things in their customary forms and colors proved ineffective. Whether my eyes were closed or open I saw only Mexican motifs and colors. When the doctor supervising the experiment bent over me to check my blood pressure, he was transformed into an Aztec priest and I would not have been astonished if he had drawn an obsidian knife. In spite of the seriousness of the situation it amused me to see how the Germanic face of my colleague had acquired a purely Indian expression. At the peak of the intoxication, about 1½ hours after ingestion of the mushrooms, the rush of interior pictures, mostly abstract motifs rapidly changing in shape and color, reached such an alarming degree that I feared that I would be born into this whirlpool of form and color and would dissolve. After about six hours the dream came to an end. Subjectively, I had no idea how long this condition had lasted. I felt my return to everyday reality to be a happy return from a strange, fantastic but quite really experienced world into an old and familiar home.

Thus having established that the mushrooms were active, Hofmann *et al.*[29] proceeded to extract the active ingredients from the dried material and to purify and crystallize them. The main active component, 4-phosphoryloxy-N,N-dimethyltryptamine, was named psilocybin, and an accompanying compound, present in much smaller amounts, was called psilocin. The latter was later found to be (Fig. 12) 4-hydroxyl-N,N-dimethyltryptamine, a hydrolysis product of psilocybin.

Absorption, Dosage and Metabolism

In humans, orally administered N,N-dimethyltryptamine has no effect in doses ranging up to 150 mg. The optimal intramuscular dose for psychotic activity is from 0.7–1.0 mg per

kg.[31] Effects appear within three to four minutes after injection and last for about one hour. N,N-diethyltryptamine (DET) elicits the same response in about the same dosage and time. Symptoms that precede or accompany the psychic phenomena, which are quite similar to those observed with LSD, are increased blood pressure, pupil dilation, nausea and vomiting, visual and auditory distortions, bizarre somatic complaints, sweating, distortion of time sense, etc.[32] Subjects find the experience to be unpleasant.

In 1962, Szara and Hearst[33] reported that rats excrete about 60 per cent of an injected dose of N,N-diethyltryptamine as the 6-hydroxylated derivative; smaller percentages were excreted unchanged and as 3-hydroxyindoleacetic acid (HIAA). In man, 5 per cent is excreted as 6-hydroxy-DET, 12 per cent as 3-HIAA, and a very large percentage of the dose could not be found. This led to speculation that the 6-hydroxy metabolites were responsible for the psychological effects. However, others have not confirmed that 6-hydroxy-DET is active,[34] and recently Szara has finally agreed that it is not.[35]

Bufotenine, possibly because of its questionable psychoactivity or low potency has not been a popular drug for study. Gessner *et al.*[36] described its vasopressor effects. In anesthesized rats, these effects lasted for thirty minutes while those from serotonin and psilocybin were three and sixty minutes respectively. The times appeared to correlate with the destruction of these compounds by monamine oxidase; serotonin is rapidly destroyed, whereas bufotenine and psilocybin serve as poor substrates. This is a general characteristic of N,N-dialkylated tryptamines.[37] In these studies bufotenine was excreted unchanged as 5-HIAA, and the glucuronide. In rats, doses of 100–125 mg per kg were toxic. Neither psilocybin or bufotenine exerted any characteristic effects on rat uterus or pig intestine, but they did antagonize the effect of serotonin on these tissues.

In 1962, Gessner and Page,[38] using a conditioned avoidance response system in rats, evaluated the potency of 5-methoxy-N,N-dimethyltryptamine relative to DMT, DET and LSD. The methoxy congener was found to be more potent than

tryptamines, with activity approaching that of LSD. Originally detected in plants by Pachter *et al.*,[39] 5-MEO-DMT was shown to be a major constituent of some of the intoxicating South American snuffs mentioned earlier.[20,40] These observations stimulated much work on 5-MEO-DMT and its closely related derivatives.[41] In animals, low doses of 5-MEO-DMT caused slight excitation, some salivation and tremors.[42] Tremors were a characteristic response and were dose dependent in the range from 1–10 mg per kg when administered intraperitoneally. After a dose of 10 mg of 5-methoxy-N,N-dimethyltryptamine-2-^{14}C per kg, rats excreted about 50 per cent of the radioactivity in the urine in twelve hours. About 60 per cent of the dose was excreted in forty-eight hours. The major excretion product was 5-methoxyindoleacetic acid.

A few of the tryptamine compounds have been tested in man. It was reported that 5-MEO-DMT is more active in man than DMT,[43] and like DMT, it is only effective if taken parenterally. It is much less active than LSD, but is more active than psilocybin.

Psilocybin and psilocin produce hallucinogenic effects which are entirely analogous to those produced by LSD and mescaline, but the frequency and intensity of the effects vary with the dose. The dose required to elicit LSD-like symptoms is from 4 to 8 mg. However, a dose of from 115 to 160 μg per kg orally is sufficient to elicit a minimum response. The threshold dose is about 60 μg per kg. The syndrome pattern becomes apparent within thirty minutes of an oral effective dose; parenterally, these symptoms appear within five minutes of injection.[44] Doses of 6 to 20 mg cause much more profound psychic changes than the lower amounts and lead to illusions and hallucinations. The hallucinogenic properties of psilocybin, psilocin, LSD and mescaline are essentially identical,[45] except that the time course for the tryptamines is shorter.

Indolealkylamines which have a hydroxyl in the 4-position do not exhibit typical effects on isolated organs such as rat uterus. They are however, powerful inhibitors of the actions of serotonin in this respect.[46] Some of the autonomic effects are dilation of the pupil, piloerection, temperature increase,

etc. The pharmacologic effects of psilocin and psilocybin are practically identical. Thus, the phosphoric acid radical appears to contribute little or nothing to the pharmacological efficacy of psilocybin. Since dephosphorylation is readily accomplished by alkaline phosphatase, it has been suggested that psilocin is the active component *in vivo*.[47] The administration of psilocybin to mice results in an accumulation of psilocin in the kidney, liver and brain. In these organs, the highest concentrations were reached in from twenty to thirty minutes. The peak concentration in the liver and kidney preceded that in the brain by about ten minutes. Behavioral effects closely followed the increase in brain levels of psilocin and there is evidence that the CNS effects are exerted only after psilocybin is converted to psilocin.[48] The distribution of ^{14}C-psilocin in the brain could not be correlated with any of the properties of the brain, including such parameters as volume cell density and capillary density.[49]

The toxicity of psilocybin is low. In mice, it is 2.5 times less toxic than mescaline, while it is fifty times more effective as a hallucinogen in man.[13]

Using psilocybin labeled with ^{14}C in the 2'-position or in the N-methyl group, Kalberer *et al.*[50] studied the absorption, distribution and metabolism in the rat. After a standard oral dose of 10 mg per kg, it was shown that about 50 per cent of the injected dose was absorbed into the gastrointestinal tract. The isotope was evenly distributed throughout most tissues, including brain. Within twenty-four hours about 65 per cent of the radioactivity appeared in the urine and from 15–20 per cent was in the bile and feces. Most of the radioactive material was excreted in eight hours, but small amounts continued to appear in the urine up to seven days after ingestion of the drug. Only about 4 per cent of psilocybin is converted to 4-hydroxyindoleacetic acid; another 25 per cent is excreted unchanged. The fate of the remaining 70 per cent is unknown, but it is not converted to ^{14}CO since the side chain of psilocybin was shown to be remarkably stable to metabolic alteration. The main metabolic products appeared to be highly hydrophilic substances. In this connection it is interesting to note that

heart and kidney contain an oxidase which transforms psilocin into a blue-colored quinone-like compound.[51]

Chemistry

Psilocybin and psilocin are relatively rare among the alkaloids because they have a hydroxyl group substituted in the 4-position. When hydroxyl functions are present in other naturally occurring indole alkaloids, they are in the 5, 6, or 7 position. A recent paper on the biogenesis of psilocybin in *Psilocybe cubensis*[52] indicates that N-methyltryptamine, tryptamine and tryptophan all serve as better precursors for psilocybin than 4-hydroxytryptamine.

Synthetic preparation of the N,N-dialkyltryptamines is by far the preferred method for obtaining them. Yields from synthetic methods vary with the particular compound being prepared, but range from 50 to 90 per cent. By comparison, yields of the various hallucinogenic indoles isolated from natural sources range from about 0.2 to 2.1 per cent.[53]

Although a relatively large number of synthetic routes for preparing the dialkytryptamines have been devised, for the most part they are of historical or academic interest. A good general route, which gives good yields and has been most used, is that of Speeter and Anthony.[18] In the procedure (Fig. 13), oxalyl chloride is reacted with indole to give 3-indoleglyoxylyl chloride. This intermediate may be treated with a primary or secondary amine to yield glyoxylamide. Reduction of the amide with lithium aluminum hydride will produce the N,N-dialkyltryptamine. Speeter and Anthony[18] first used this procedure with 5-benzyloxyindole (Fig. 14) as starting agent to synthesize bufotenine. Later Benington *et al.*[54] modified the method slightly and got 5-MEO-DMT in about 50 per cent yield from 5-benzyloxindole. Hofmann *et al.*[55] started with 4-benzyloxindole and synthesized psilocin.

Szara and Hearst[33] used the Speeter-Anthony procedure to make N,N-dimethyl, N,N-diethyl and higher homologues of tryptamine. The N,N-dipropyl and N,N-diallyl derivatives were shown to be hallucinogenic in man at about the same level of potency as N,N-diethyltryptamine, but the N-N-dibutyl

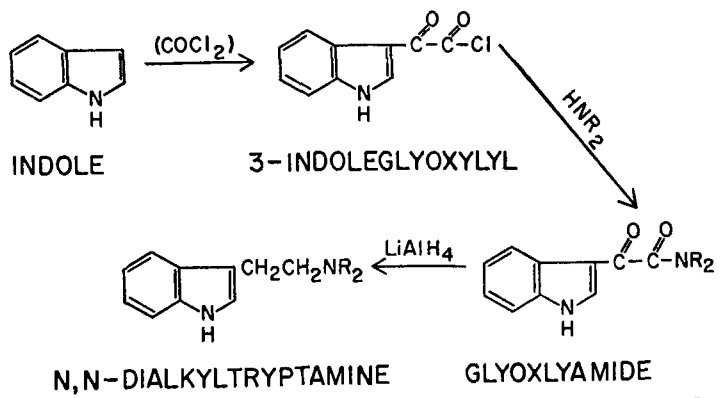


Figure 13. The procedure of Speeter and Anthony[18] for the synthesis of indolealkylamines.

and higher homologues were inactive. N,N-dialkyl-6-hydroxyltryptamines can be made from 6-benzyloxindole by the Speeter-Anthony procedure.[18]

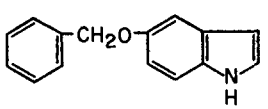


Figure 14. An important starting compound in the synthesis of a variety of indole-substituted hallucinogens.

THE β-CARBOLINES

The β-carbolines are a group of heterocyclic indole compounds among which are included the harmala alkaloids. Hallucinogenic compounds of this type have been identified as the active ingredients of a group of bizarre "magic drinks" prepared from the Malpighiaceae family of plants. The most widely used species are from the genus, *Banisteriopsis*. From *Banisteriopsis caapi*, *B. inebrians*, and *B. rusbyana*, Indian tribes in parts of Brazil, Bolivia, Colombia, Ecuador, Peru and Venezuela make hallucinogenic extract which has been given a variety of names. A related genus *Tetrapteris methystica* has also been used for this purpose.[7,56] Although the magic potion is

called by many vernacular names, ayahuasca, caapi, natema, pinde, and yajé, among others, the active ingredients are the same. For the most part the same, or closely related, plant is used in making the decoction. Usually only one type of plant is used, but in some areas of the Amazon the preparation may include the bark of *B. caapi* and the leaves of *B. rusbyana*.[8] Sometimes plants which have toxic properties are added—*Alternanthera*, *Psychotria*, *Nicotiana*, and *Datura*. The active ingredients of the latter are atropine and scopolamine.

The first descriptions of the use and effects of caapi and ayahuasca were recorded by the British botanist, Richard Spruce.[56] He tells of a woody vine, later known as *B. caapi*, from which Indians of the upper Rio Negro made an intoxicating drink. The result of caapi-intoxication can vary widely, but normally begins with giddiness, nausea, profuse sweating and eventually leads to lassitude and a sort of detachment.[8] Then a period marked by realistically colored hallucinations follows. Synesthesias may or may not occur. Muscle coordination is not effected since many Indian caapi ceremonies may involve dancing. The caapi is taken for purposes of divination, prophecy, diagnosis and treatment of diseases, preparation for war, male adolescent rites, etc.

Much difficulty and confusion occurred in the course of botanical and chemical identifications of the hallucinogenic plants and the extracts thereof. Schultes[7,8,56,57] has critically analyzed some of the older literature on the botanical sources and history of the interesting beverage made from *Banisteriopsis*. The advent of modern methods of isolation and identification has simplified the chemical operations, so that isolated compounds are now known with exactness. Some uncertainty remains in the methods of evaluating the psychoactivity of the pure materials.

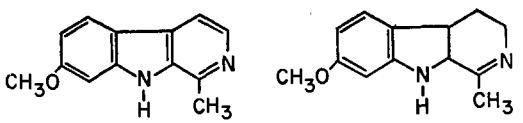
Chemistry

Early investigation of extracts of *B. caapi* resulted in the isolation of an alkaloid which was named telepathine by Zarda Barron.[58] The first crystalline product, which was probably impure, was obtained by B. Villalba[59] and was called yajeine

after the vernacular name Yaje for the plant source. Villalba incorrectly identified the source as *Prestonia amazonica* Spruce. He is said to have corrected this error in a later paper[58] and identified the plant as *B. caapi.* As indicated above the lack of rigorous botanical identification of source materials by chemists has led to chaos in the study of naturally occurring hallucinogens, as well as in the study of other natural products. In these areas, it is essential that the botanist and chemist find some means of communication and collaboration.

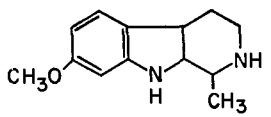
The confusion about the plant source of caapi or ayahuasca was compounded by the use of names like telepathine[60] and banisterine[61] for alkaloids isolated from *B. caapi.* Elger,[62] Wolfes and Rumpf[63] and others [64] identified the active ingredient of *B. caapi* as a single alkaloid, harmine, a well known base which had been isolated from the Asian shrub *Peganum harmala* (Zygophyllaceae) over a century ago.[65,66] Hochstein and Paradies[6] using more modern techniques investigated *B. caapi* Spruce from which they isolated harmine, harmaline, and (+)-tetrahydroharmine. The two latter bases were found in relatively large amounts.

All the bases isolated from *B. caapi* have a β-carboline structure with different degrees of hydrogenation of the pyridine ring (Fig. 15). The correct structures were suggested[67] in 1919 and confirmed by the synthesis of Manske *et al.*[68]



HARMINE

HARMALINE



d-1,2,3,4-TETRAHYDROHARMINE

Figure 15. Chemical structures of the β-carbolines.

Several methods of synthesis are now available and these have been summarized.[69]

Pharmacology

Very few studies on the pharmacological properties of harmine and related compounds have been reported and little is known about the metabolism and biochemistry of these substances. In large doses harmine causes tremors, reminiscent of some of the indole alkylamines, and clonic convulsions. With toxic doses, respiratory arrest occurs, and there is a fall in temperature. The drug causes a weakening of cardiac muscles which results in a vasodepressant effect. Partial reduction of harmine leads to a greater toxicity since harmaline is about twice as toxic to experimental animals as is harmine. The minimum lethal dose[70] for the three compounds harmine, harmaline and tetrahydroharmine in the rabbit are 2:1:3. The effects of harmine and derivatives in animals, particularly the excitant effects, are related to their capacity to inhibit monoamine oxidase.[71] This well-known enzyme catalyzes the oxidation of amines such as epinephrine, norepinephrine, and serotonin. Its inhibition results in an accumulation of these compounds in the central nervous system, as well as in other organs, and leads to excitant or antidepressant effects.

Although there is no doubt that caapi or ayahuasca is hallucinogenic, there is considerable skepticism about the psychic effects of harmine and related compounds. Lewin[61] reported that subcutaneous doses of 25–75 mg caused euphoria in man. Pennes and Hock[72] found that mental patients given 150–200 mg intravenously responded as if they had received LSD. Oral application of from 300–400 mg produced a minimum of perception disturbance. Turner *et al.*[73] did not consider harmine to be hallucinogenic. However, recent studies confirm that harmaline is hallucinogenic in doses of 1 mg per kg intravenously, or 4 mg per kg orally.[74] In humans, subjective effects occur with doses of 35–45 mg of harmine injected intravenously. The material is rapidly lost from the blood, suggesting rapid distribution to the tissues. In both man and rat, harmol, harmol sulfate, and harmol glucuronide are found

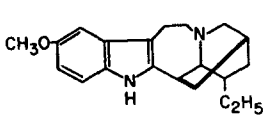
in the urine after a dose of harmine. These metabolites account for the major portion of the injected dose.[75]

Some of the responses to harmaline are nausea, dizziness, and general malaise; parasthesias of the hands, feet, and face occurs, followed by numbness. Distortions of body image and of objects in the environment, so frequent with LSD and mescaline, are not present. The same is true in regard to color enhancement.

The consensus among workers in the field is that the psychotomimetic effects of ayahuasca, etc. are caused by compounds other than harmine and its derivatives. Gas chromatographic techniques should offer a means to the solution of this problem in the very near future.

IBOGA ALKALOIDS

Alkaloids obtained from the root bark of the African shrub, *Tabernanthe iboga* are another series of indole-containing compounds which are of possible interest in the study of hallucinogenic drugs. The natives of West Africa, especially of Gabon, chew the root of *T. iboga* to offset hunger and fatigue.[76] Extracts of the plant are said to be used by natives while stalking game to enable them to endure motionless periods for as long as two days while remaining mentally alert.[77] In large doses, iboga causes excitement, mental confusion, and a drunken madness characterized by prophetic utterances. The principle alkaloid of at least twelve which can be isolated from these extracts is ibogaine (Fig. 16). The latter was first obtained from *T. iboga* as early as 1901,[78,79] and much of the chemistry has been elucidated.[80,81] However, as usual, much uncertainty and confusion exists in the evaluation of the psychic properties of the drug. Although central effects such as excitation and tremor are produced in doses of 10–20 mg per kg (S. C.) in



IBOGAINE

Figure 16. Chemical structure of ibogaine.

animals,[82] and ibogaine is said to have cocaine-like effects in man,[8] Turner *et al.*[73] doubt whether ibogaine is hallucinatory. A few animal studies have been reported,[69,83] but as far as the author could ascertain, the behavioral effects of the pure compound in man have not been reported.

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Chapter V

MARIHUANA

MARIHUANA is a name for one of the several types and kinds of hallucinogenic preparations which can be obtained from *Cannabis sativa* L. (family Moraceae). The name of the preparation depends upon the part of the world in which the plant is grown, as well as from what part of the plant the preparation is made. The potency however, depends on the genotype rather than the soil and climate as was previously thought.[1]

Cannabis sativa L. is a dioecious (separate male and female) plant of which there are two varieties, *indica* and *non-indica.* It is a tall weed, which occurs as an annual and will grow almost anywhere. The staminate male plant is usually taller than the pistillate female plant. It is generally thought that the hallucinogenic principle of marihuana is found only in the female plant, however recent results show that the active material can be isolated from the male plant as well.[1,2] This particular distinction in the sex of the plant has been questioned for many years[3] but is propagated in the modern literature. The flowering top (Fig. 17) and adjacent leaves (bracts) of the plant are covered with glandular hairs which secrete a sticky resin. Formation of the latter ceases when the seeds mature, and it has been proposed that the function is to protect them during the ripening season. Whatever its natural function, cannabis resin has acquired several uses for which it probably wasn't intended. It is known in the Middle East and Europe as "hashish"; in India as "charas." If the entire flowering top is collected and used, it is known as "ganga" in India, "kif" in North Africa, "dagga" in South Africa, "maconha" in Brazil, etc. The cheapest and least po-

tent preparations are made from cut tops of uncultivated plants, which have low resin content. In India, these are called bhang and are of about the same grade as marihuana which is smoked in the United States. In the United States, marihuana may be called "weed," "stuff," "Indian hay," "grass," "pot," "maryjane," "tea" and God only knows what else.

In his monograph Walton[3] presents an excellent summary of the history and distribution of marihuana use. There is evidence that the Chinese Emperor, Shen-Nung taught his people to cultivate hemp for its fiber in the twenty-eighth century B.C. Although its medicinal and narcotic properties were known to the Chinese, and references to it can be found in their literature, there were no descriptions of generalized abuse of the drug. Apparently, it could not compete with opium.

In India, the Susruta, which was probably compiled before 100 B.C., mentions bhang as a remedy. Early Hindu literature indicates clearly that the euphoria producing qualities of the hemp plant were known. The drug was not indigenous to India, but was brought from somewhere in Central Asia. It became a part of Hindu life and custom and a part of certain phases of the Hindu religion:[4]

> To the Hindu the hemp plant is holy. A guardian lives in the bhang leaf. . . . . To see in a dream the leaves, plant, or water of bhang is lucky. . . . A longing for bhang foretells happiness. . . . . It cures dysentery and sunstroke, clears phlegm, quickens digestion, sharpens appetite, makes the tongue of the lisper plain, freshens the intellect, and gives alertness to the body and gaiety to the mind. Such are the useful and needful ends for which in his goodness the Almighty made bhang. . . . . It is inevitable that temperaments should be found to whom the quickening spirit of bhang is the spirit of freedom and knowledge. In the ecstasy of bhang the spark of the Eternal in man turns into light the murkiness of matter. . . . . Bhang is the Joy-giver, the Skyflier, the Heavenly-guide, the Poor Man's Heaven, the Soother of Grief. . . . No god or man is as good as the religious drinker of bhang. . . . . The supporting power of bhang has brought many a Hindu family safe through the miseries of famine. To forbid or even seriously to restrict the use of so holy and gracious an herb as the hemp would cause widespread suf-

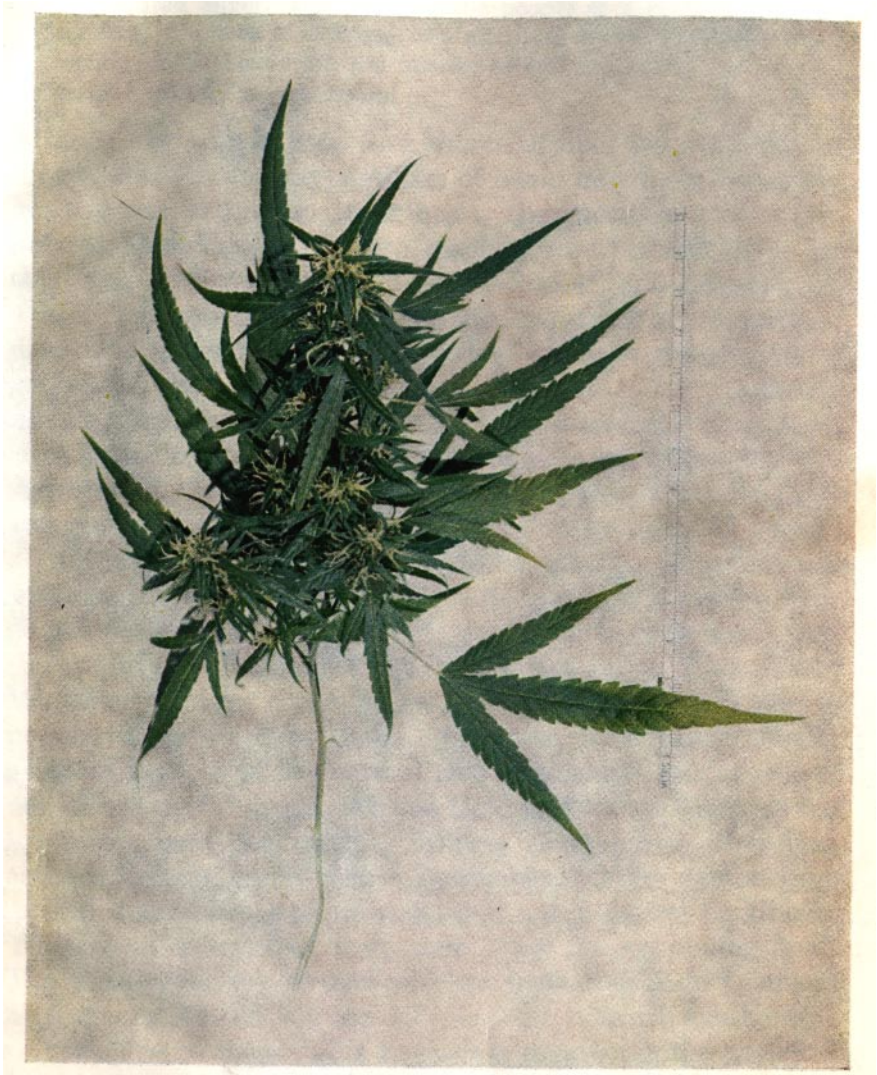

Figure 17. Marihuana flowers.

> fering and annoyance and to large bands of worshipped ascetics deep-seated anger. It would rob the people of a solace in discomfort, of a cure in sickness, of a guardian whose gracious protection saves them from the attacks of evil influences. . . . So grand a result, so tiny a sin!

Although hemp was used as a source of fiber for centuries by diverse peoples, and preparations of hemp may have been used by ancients to produce anesthesia, the cannabis drugs were not introduced generally into medicine until about 1840. At this time O'Shaughnessy,[5] Aubert-Roche[6] and Moreau de Tours,[7] recommended its use for the treatment of a variety of disorders. Their activities resulted in widespread and general use of the drug in Europe and in America. This popularity can be attributed partly to the fact that the drugs were introduced prior to the appearance of synthetic hypnotics and analgesics. At that time, the only drug commonly used for these purposes was morphine. Hemp drugs do not exhibit certain of the notorious disadvantages of the opiates. They do not constipate, they increase rather than decrease appetite, they do not depress the respiratory system even in high doses, and the liability of developing addiction is not great. These were attractive features and were responsible for the rapid rise in popularity of use in medicine. However, their use gradually declined because of the central side effects and the advent of new, more useful drugs. At one time or another cannabis extract was used for coughs, fatigue, rheumatism, neuralgia, asthma, tetanus, hydrophobia, headaches, uterine dysfunction, mental depression, and to ease labor pains during childbirth. There is no record that it was ever tried for embalming fluid! The therapeutic use of cannabis is a matter of history, unless as suggested,[8] some use can be found for it in psychotherapy. Garattini[9] even denied that hashish is a narcotic, the property for which it was originally introduced into medicine.

Physiological and Psychological Effects

In view of the long history of hashish use by practically every nationality and culture, the degree of ignorance about the drug, its pharmacological properties and effects, is appalling.

Perhaps the lack of information is a result of restricted priorities rather than a lack of interest. There are literally millions of naturally occurring and synthetic pharmacological agents to be evaluated and studied. Perhaps there has been some justification for focusing attention on areas such as cancer chemotherapy, antibiotics, or hormones at the cost of neglecting substances for which no therapeutic value is known, such as alcohol, marihuana, etc. If the latter are to become a greater scourge to mankind than cancer or infection, then attention must be and of course, will be, diverted to them.

Much has been written, but little has been told about marihuana. Except for information concerning the chemistry of the various constituent compounds of cannabis extract, I found the 1965 Ciba Foundation Study to be of less value than Walton's monograph published in 1938. There was a spurt of interest in the chemistry of cannabis in the late 1930's and early 1940's lead by Roger Adams.[10] During this period, considerable progress was made. Shortly thereafter, probably because of the war, interest in cannabis declined and until quite recently little or no research was done on this substance. At the present time, a well-financed, concerted research effort is producing information about as fast as it can be assimilated. A relatively large number of papers have appeared in 1969 and 1970.

Hemp drugs may be introduced into an organism by smoking, oral ingestion, and by intravenous or intraperitoneal injection. The two latter routes are used primarily in experimental animals. In man, smoking, chewing or sniffing are the main modes of administration. The technique of imbibing varies in different areas of the world. In North America, smoking is preferred to either eating or chewing. Watt reports[11] that this route produces a more intense intoxication and results in more harmful effects. The various techniques of taking pot (imbibing cannabis) have been elaborately described.[3]

The dosage of marihuana depends upon the source, variety, and part of the plant from which it is made. Folk preparations and extracts, which were described in early papers[5,6] and were consistent only in their variability, were taken in the

amount of 10 to 30 grams. In Europe and America, attempts to use Indian hemp as a therapeutic agent caused some totally unexpected and often undesirable hashish experiences. An overdose of cannabis given to a patient who was seriously weakened by an affliction of unknown origin sometimes led to severely untoward reactions.

During this period of more or less exploratory use of cannabis in medicine, some efforts were made to observe and record the effects of the drug. However, dosages were only of approximate significance. Bioassays of any degree of reliability were not available prior to 1900, if then. And, to this day, there is no good, rapid, sensitive chemical assay for the active ingredient of cannabis. In any event, one of the first efforts to objectively record a case history was submitted by Brown[12] in 1862. He treated a patient who had taken, in graded amounts, a total of six grains of a solid extract. About three to four hours later, the patient became nervous and dizzy, felt an irresistible inclination to run, a great desire to urinate, a great thirst, and a general feeling of disorientation. In this patient, the severe symptoms lasted about one hour, then gradually diminished. Kelly[13] described a typical hallucinogenic reaction in a patient who had received 30 mg of a cannabis extract for treatment of severe rheumatic pains. Strange[14] reported a patient who was accidentally given an overdose of cannabis extract. Three hours later the patient had a marked reaction, but sleep was induced after about an hour. The next morning the patient ate a ravenous breakfast. Sticker[15] gave "Cannabinon" to about thirty patients without any peculiar effects except for one case who took about 100 mg of the drug. In this subject, the effects began in about thirty minutes and for a few hours there were several long periods of psychic exaltation.

There are many papers which describe incidences of clinical marihuana intoxication. One of the more interesting efforts to describe the effects is the following which is quoted from Adam's lecture[10] describing synthetic marihuana preparations. The narrative was taken from a log kept by the subject, beginning two to three hours after he took the drug.

6:00 to 8:30 P.M Very much in the fog. Had alternate waves of hilarity and depression. Sat in smoking compartment looking at myself in the mirror, writing notes on the experiment, and feeling very silly and stupid. Would feel the onset of a surge of hilarity and break into a raucous, rippling laugh. This gayety was not particularly pleasant, however, for throughout I felt wholly dissociated from myself, knew that I was at the mercy of the drug, and greatly resented this lack of control. The feeling was very different from that of being at one or another stage of intoxication, for I looked perfectly clear and normal and I could stand erect without swaying and execute motions with considerable precision. I could not, to my annoyance and as I was well aware, speak or write or think coherently. This bothered me particularly in the waves of depression, when my lips would feel very parched and salty and I would long to break the spell and regain my consciousness. A very pressing and persistent sensation was that of extreme hunger, but I had sense enough to wait until the laughing spells were under control before going to the diner.

At 8:30 I devoured an enormous steak dinner with great rapidity and thoroughness and left no trace of any of the fixings . . . .

It was an interesting experiment, but I can't write too enthusiastic an endorsement for this drug you fellows are synthesizing. The feeling of well-being would not, in my estimation, equal that from about three highballs and the penalty seemed to me to be pretty severe. The outstanding impressions were the feeling of detachment from myself and the extreme hunger. . . .

The highly purified active ingredient of marihuana, Δ^1-trans-3,4-tetrahydrocannibinol (Fig. 18) (Δ^1-THC), can be detected in amounts of about 50 μg per kg when smoked. If taken orally, about 120 μg per kg is the minimum detectable dose. Psychotomimetic effects are produced by about 200 μg per kg by smoking; whereas 480 μg per kg are required by the oral route.[16] Weil *et al.*[17] who used crude marihuana estimated that these dosages are roughly equivalent to the quantities consumed by their subjects. The Δ^1-THC content of their marihuana was estimated to be about 0.9 per cent. The Δ^1-THC content[18] of one relatively fresh (10–15 months old) sole was about 0.4 per cent.

The immediate effects of ingesting or smoking marihuana

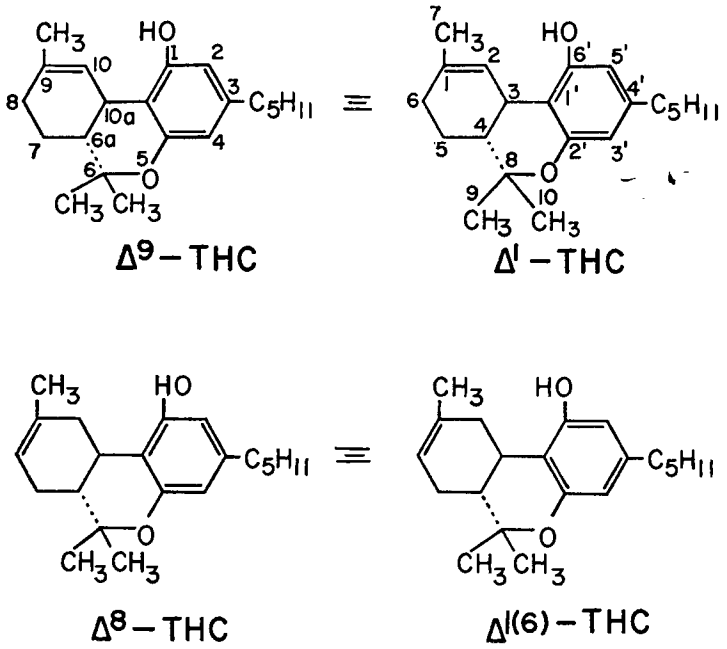

Figure 18. The relationships between Δ^9- and Δ^1-THC, and between Δ^8- and $\Delta^{1,6}$-THC.

may be nausea, vomiting, diarrhea, dryness of mouth and a burning thirst.[19] Ataxia, muscle tremors, and cold extremities plus a few days of colicky stomach pains may also ensue. Marihuana intoxication is manifested by euphoria, motor excitation, and hilarity followed by mental confusion. These symptoms may be accompanied or followed by psychic phenomena such as depersonalization, hallucinations and usually depression. There is no dearth of lucid descriptions of the psychic effects.[19-21] Many of these have been partially quoted and summarized by Walton.[3] As with LSD, the effects seem to come in waves of varying intensity. Time and space appear distorted. There appears to be increased sensual perception and a sense of profound insight, at least in some people. (These serious-sounding symptoms probably have been experienced at one time or another by tobacco smokers and/or

alcohol drinkers, particularly those who overindulge.) Intravenously, marihuana causes severe chills, tachycardia, and fever after a brief latent period. In one or two hours, nausea, vomiting, and general aching pains were present.[22] Regardless of the route of administration, Δ^1-THC (marihuana) causes an increase in pulse rate and a dilation of conjunctival blood vessels,[16,17] but in moderate to large doses there is no change in pupil size, respiratory rate, blood pressure, blood sugar or knee jerk reflex.

In a neutral setting, the physiological and psychological effects of smoking marihuana appeared to reach a maximum intensity within thirty minutes and to be completely dissipated after three hours.[17]

Metabolism

Until recently, the identity of the hallucinogenic agent in marhuana has been obscure. Most research on cannabis was done with mixtures of compounds of unknown potency. Even now, the number and kinds of metabolites produced in the body are unknown. These factors, plus the lack of a reliable assay, the extremely low aqueous solubility of cannabis extracts, and the use of extracts from plants grown in different parts of the world make a large part of the literature questionable and of little value.

In 1965, Miras[23] presented data on the distribution and metabolism of ^{14}C-tetrahydrocannabinol. At that time, the active agent (Δ^1-THC) had been identified[24] but had not been synthesized. The ^{14}C-THC was obtained from cannabis plants grown in an atmosphere of $^{14}CO_2$, and was isolated from plant extracts by repeated column and thin-layer chromatography. This material was injected intraperitoneally as a colloidal suspension in 4 per cent Tween-80 into male rats. The dose was about 6 mg per kg.

The largest amounts of radioactivity found 1½ hours after injection were in the liver, kidney and testis. Radioactivity appeared in the urine within thirty minutes after injection and this was about the time of onset of symptoms. Only 6

or 7 per cent of the dose was recovered. With doses of about 100 mg per kg, cannabis resin caused a definite hypothermic effect in rats.

Recently Agurell *et al.*[25,26] have synthesized Δ^1-THC labeled with tritium or ^{14}C. After the intravenous injection of tritiated Δ^1-THC into rats, the radioactivity was eliminated very slowly. In the first twenty-four hours, only 2 to 6 per cent of the dose appeared in the urine. One week after administration, one-half the dose still remained in the tissues. Approximately 80 per cent was eventually excreted in the feces and the other 20 per cent appeared in the urine. Less than 0.006 per cent was eliminated as unchanged drug; the rest appeared as metabolites. These results are consistent with Miras' observations.

In the rabbit however, the story is entirely different. Intravenously administered ^{3}H-Δ^1-THC is excreted rather rapidly, as polar metabolites. About 35 per cent of the dose is excreted via the urine during the first twenty-four hours and about 10 per cent appears in the feces.[27] Distribution in the tissues reflects the elimination through the liver and the kidney; the spinal cord and brain show the least radioactivity. Two hours after intravenous administration, the lung has a large amount of radioactivity. However, the highest concentrations are in the urine and bile. The latter contains by far the most radioactivity after seventy-two hours. Since the feces accounts for only 10 per cent of the excreted dose, the rabbit may have a system of reabsorption from the gut. The half-life of tritiated Δ^1-THC, as measured by the rate of disappearance from blood, is from seven to sixteen minutes.

Rabbit liver homogenates metabolize Δ^1-THC to the psychoactive 7-hydroxy-Δ^1-THC.[28] After one hour, 40 per cent of Δ^1-THC-^{14}C was converted to a group of polar compounds of which the hydroxy compound was the major constituent. The rabbit also converts tritiated $\Delta^{1,6}$-THC to the 7-hydroxy-$\Delta^{1,6}$-THC derivative[29] as does the rat.[30] The 7-hydroxy metabolites (Fig. 19) produced behavioral effects in rats and mice, but 6,7-dihydroxy-THC was inactive. As yet, these compounds have not been tested in man. As a matter of fact, very little

metabolic work with marihuana has been done in humans. This deficit should be corrected under the impact of the large sums of money currently being spent on drug research by the United States Government.

Although none of them have been isolated or identified, several metabolites, other than the 7-hydroxy compounds, are produced from Δ^1-THC and $\Delta^{1,6}$-THC by the organism. In the absence of convincing evidence pro or con, there is much speculation that it is one of these metabolites which is ultimately responsible for the observed biological effects.[31] Chronic users say that marihuana has no effect when taken for the first time. Also, both Δ^1-THC and $\Delta^{1,6}$-THC are more active when administered intraperitoneally than when injected subcutaneously. Such observations could be explained on the basis of enzyme induction. For instance, if the liver hydroxylating enzyme which catalyzes the formation of 7-hydroxy-Δ^1-THC were inducible, the initial dose could stimulate synthesis of this enzyme. Subsequent use of the drug would result in significant concentrations of the psychoactive agent. Or, if the active metabolite or metabolites were formed in the liver, intraperitoneal injection would lead to higher concentrations than would subcutaneous or intramuscular routes. These ideas are

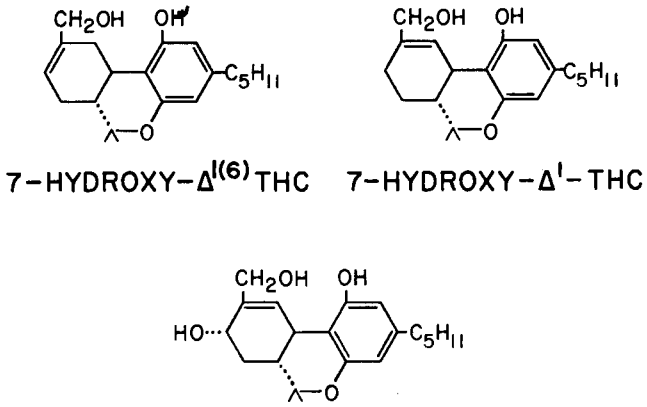

Fig. 19. Metabolites of tetrahydrocannibinols.

little more than educated guesses and are based on trivial evidence. One should keep in mind that the effects of marihuana are difficult to evaluate for various reasons, one of which is that the effects may be influenced by subjective psychological responses.[17] Others can be mentioned; Δ^1-THC Acid A, an ingredient of cannabis extracts, is inactive, but is converted by smoking to the active Δ^1-THC.[31,32] However, the burning process also partially destroys Δ^1-THC, which is an unstable compound; its properties in mixtures, or in the pure state are difficult to predict. In spite of the very recent and compelling progress in the chemistry of cannabinols, an aura of uncertainty, if not mystery, still lingers in the smoke of the marihuana story.

Chemistry

From the earliest studies to the present, the same general procedures have been used by all investigators to extract and process hemp resin. Organic solvents of one type or another were used to extract the plant material. The resulting suspension was then filtered, the solvent removed, and vacuum distillation of the residue gave a highly viscous, physiologically active red oil. Fractional distillation of the oil gave an active fraction boiling at 180–190° which is commonly known as "purified red oil." Chemists have been analyzing, or trying to analyze, this famous "red oil" for a very long time. Only recently have the active ingredients been isolated and unequivocally identified. However, as we shall see, the identity was known, but without precision, thirty years ago.

Nomenclature

In any discussion of the chemical, physiological or other properties of the cannabinoids, a clarification of the nomenclature is a necessity. Originally, confusion arose from the use of four separate and distinct procedures for numbering the cannabinoid ring systems, and it has been propagated by the continued and current use of two of these methods. Figure 20 shows the cannabinoid structure and the four methods of numbering it. The structure of Δ^1-THC with its two most common names is also illustrated. Adams[10] used the *dibenzo-*

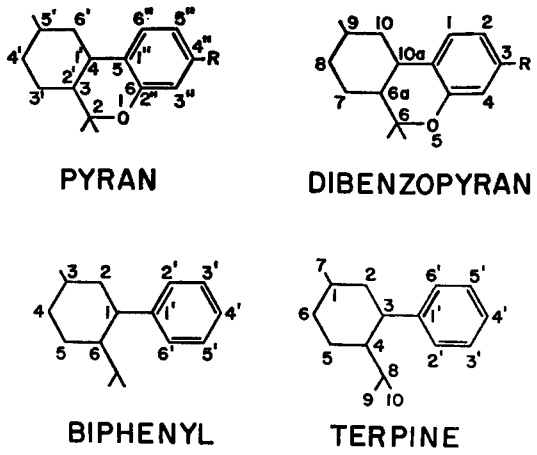

Figure 20. The numbering systems used in the naming of cannabinoids.

pyran method which is approved for use by the Chemical Abstracts. This system, as well as the *pyran* and *biphenyl* methods, is not easily adapted to changes involving the pyran ring (heterocylic O-containing ring). For instance, cannabis resin contains compounds in which the ring is open and some in which it is closed. In recent years, the terpene system was adopted to circumvent these difficulties. It appears to be the most widely used of the two systems now in vogue; the other being the dibenzopyran method. However, the same compound may appear as Δ^1-THC[18,27,31] or Δ^9-THC[33,34] or some other name depending upon whether the author uses the dibenzopyran, the monoterpene, the pyran,[35] or the diphenyl[36] numbering system. The monoterpene system is the most logical and adaptable, and in my opinion, is the method of choice.

Early History

In 1857, T. and H. Smith[37] showed that the active ingredient of hashish was alkali insoluble, high-boiling, and, most significantly, that it was not an alkaloid. Thus, the formal chemistry began. Forty years later, Wood, Spivey and Easterfield[38] discovered that the high-boiling fraction was a mixture and isolated an active, glassy product which they called cannabinol. Some thirty years later, Cahn[39] took up the study of cannabis and elucidated the structure of cannabinol which he described in a short series of elegant papers. A few years following the work of Cahn, two of the more brilliant organic chemists of this century undertook to clarify the hashish problem. Todd in England, and Adams in the United States, began their studies at about the same time. Working independently, they proceeded to throw a great deal of light on hashish chemistry; however, neither of them succeeded in isolating and identifying the active ingredient.

Adams *et al.*[40] could not repeat the work of Cahn, but instead isolated a new substance and largely elucidated its structure. The compound was cannabidiol. Later,[41] cannabinol was isolated and crystallized. Neither of these was the active hallucinogenic agent of "red oil." In the process of establishing the structure of these compounds by synthesis, several tetrahydrocannibinols were prepared as intermediates.[10,35] Some of these synthetic compounds, particularly Δ^3-THC, were found to be active in animals and man. This fortuitous discovery led to the synthesis and pharmacological examination of a series of related compounds in the hopes of elucidating the relationship between chemical constitution and hashish activity. That goal was not attained, and has not been reached unequivocally to this day, but some of the results obtained independently by Todd[35] and Adams [10] were of considerable interest and importance.

Adams *et al.*[42] showed that cannabidiol can be cyclized under acid conditions to yield mixtures of optically and physiologically active tetrahydrocannabinols. These were the so-called "low" and "high" rotating compounds. The latter was shown to be $\Delta^{1,6}$-THC.[43] It is quite likely that Δ^1-THC was also present since it can be prepared easily from cannabidiol under these conditions. Another active compound synthesized independently by Adams and Baker[43] and Todd's group[44] was Δ^3-THC, which was about one-eighth as active in humans as $\Delta^{1,6}$-THC. For many years, Δ^3-THC served as a standard for animal testing of cannabinoids, but it was recently[16] shown to be inactive in man (smoking) at levels of 400 μg per kg.

Derivatives of this compound, containing substituents for the benzyl n-alkyl group at the 4′ position, showed gradually increasing activity up to the n-hexyl isomer. The synthetic Δ^3-n-hexyl compound was dubbed Synhexyl and was about one-fourth as active in humans as $\Delta^{1,6}$-THC.

At about this time, others[45] reported the isolation of a highly active "THC" by fractional distillation, but offered no criteria of identification or purity. They probably had a mixture of isomers.

The chemists of this time (early 1940's) recognized the limitations of fractional distillation techniques for separating the natural cannabinoids from hemp extract.[10] Most of the compounds boil within the same temperature range and form mixtures which have complex chemical and physical properties. Although these scientists did not succeed in isolating the active ingredient of marihuana, they supplied a wealth of information which was to make the later studies possible.

Recent History

After about 1945, there was a lull of almost twenty years in the development of the chemistry of marihuana. In the early 1960's, Mechoulam and Gaoni and their co-workers, and a group in Germany led by F. Korte took up the problem of the elusive ingredients in the "red oil" resin from hemp. They were able to use advantageously the new techniques which had been developed over the intervening years. Thus, in the last decade much progress has been made in the separation, identification, and structural elucidation of this complex and confusing group of compounds. The stubborn "red oil" yielded it's secrets to the elegant onslaught of column, gas and thin-layer chromatography, ultraviolet and infrared spectrophotometry, mass spectrometry, and nuclear magnetic resonance, among other techniques.

The structures and name of the major and better known neutral cannabinoids which have been isolated from hemp are given in Figures 18 and 21. Mechoulam and Gaoni based their separation method on column chromatography[46,47] and were able to isolate nine different compounds from hashish. Korte

et al. used counter current distribution and adsorption chromatography to isolate many of the same compounds.[48,49] Among these, Mechoulam and Gaoni isolated and identified the active ingredient of hashish.[24] This compound (Δ^1-THC) is reported[50] to be the only major hallucinogenic agent in hashish.

For almost every neutral constituent, hashish contains an analogous acid. The cannabinoid acids are not hallucinogenic. When they are heated,[51] they are rapidly converted into the respective neutral compound. As mentioned earlier, this may well be one of the reasons why marihuana has a higher activity if it is smoked than if ingested. Cannabidiolic acid is the predominant cannabinoid in nature. Some of the important cannabinoid acids are illustrated in Figures 18 and 21.

In 1965, Mechoulam and Gaoni[52] reported the first total synthesis of dl-Δ^1-3,4-trans-THC. This synthesis is of little practical value; the yield is low and it gives a racemic mixture. A useful synthesis is a procedure which was originally devised by Taylor *et al.*[53] but was modified[31] to give fairly high yields of Δ^1THC. This synthesis is shown in Figure 22A. The most

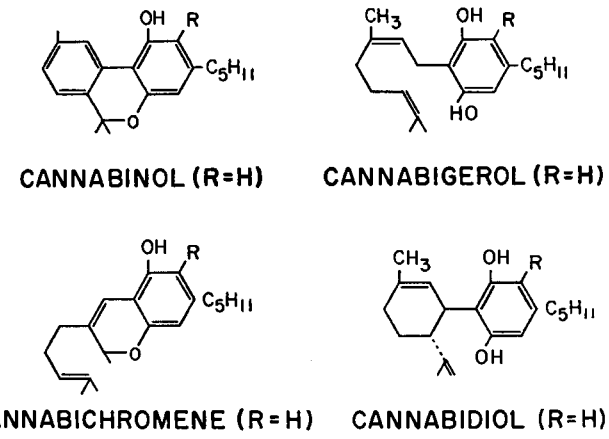

Figure 21. Four of the major neutral constituents of cannabis and their respective acids.

recent method which is stereospecific and gives the desired optically active isomer in a yield of about 25 per cent was devised by Petrzilka *et al.*[54] This procedure is shown in Figure 22B.

Most of the naturally occurring cannabinoids have been synthesized. The literature describing the various synthetic procedures and the ingenious techniques used by organic chemists to establish the correct structures has been summarized by Mechoulam.[31] A good account of the chemical and physical properties of the various constituents of hashish is also presented.

Assay Procedures

The Beam test[56] was devised in 1915 and is still widely used to detect and to assay cannabinols. In keeping with the many other paradoxes associated with marihuana, the Beam test is quite specific for the drug, but gives negative tests for the active ingredients, Δ^1-THC and $\Delta^{1,6}$-THC. Compounds such as cannabidiol and cannabigerol are oxidized by ethanolic potassium hydroxide to hydroxyquinones,[56] the ionic forms of which give a pretty purple color. Another color test, also purple, is the Duquenois-Negm reaction (cf ref #31) which is more sensitive, but not as specific as the Beam test. Applying

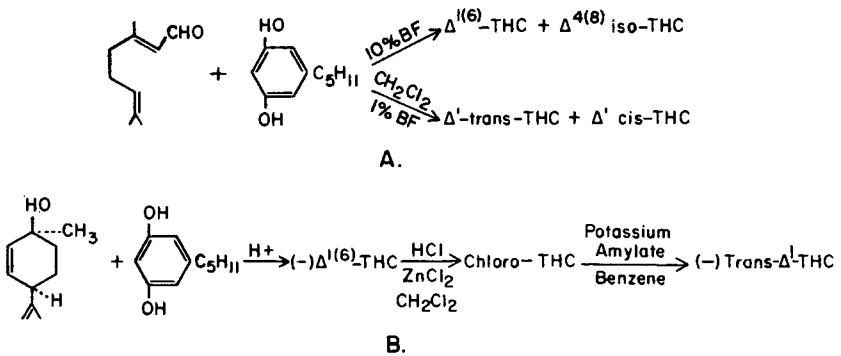

Figure 22. Procedures for the synthesis of THC. *A.* The method of Taylor *et al.*[55] *B.* The procedure of Petrzilka *et al.*[54]

both tests to an unknown sample will almost surely allow one to decide whether it is or is not marihuana.

In the laboratory, qualitative analysis and identification of cannabis compounds are easily accomplished with thin-layer chromatography. For quantitative analysis, gas-liquid chromatography (GLC) plus mass spectrometry is very elegant. However, all the cannabinoid acids are decarboxylated at the temperatures required for GLC.[31] For routine analysis, this could be an advantage because it duplicates the reactions in the smoking process. When a quantitative determination of the exact ingredients is required, decarboxylation of the acids is prevented by esterification.

The physiological testing of cannabinoids leaves much to be desired. For many years, the degree of incoordination produced in dogs has been a method for estimating biologic activity,[3,57] and it is still used.[47] In mice, cats and rabbits, the Gayer[58] test in one form or another is still used. In these animals, marihuana induces a corneal anesthesia or an analgesic effect which is roughly proportional to the concentration of the active ingredient. Recently[59] the adult rhesus monkey has been used as a test animal. And, of course, man is the only organism in which the psychotomimetic effects can be evaluated.

Biogenesis

Several years ago Todd[60] suggested that cannabinoids originated in the plant by the condensation of a terpene moiety with olivital. Although the suggestion has led to a system of nomenclature, and a number of recent syntheses has employed this very combination, paradoxically again, there is no evidence that the plant actually does it this way. The occurrence of acidic compounds and their respective neutral derivatives suggests that neutral compounds could be formed by decarboxylative reactions. An alternative idea is that parallel biogenic sequences exist. Experiments in plants using labeled precursors have been disappointing because of very low incorporation of radioactive material into the cannabinoids.[33]

Marihuana Abuse

The use of marihuana in the United States, particularly among young people, has increased enormously over the past few years. As a result of the increase vociferous groups advocating the legalization of marihuana have sprung up. These writers[61] and speakers base their arguments on the fact that marihuana, as grown and used in the United States *at this time* (the italics are the author's), is physiologically and pharmacologically harmless. Marihuana does not have dramatic acute toxicity[62] nor does it produce physical dependence. Others say[62,63] that, contrary to widely held opinion, marihuana does not serve to induce a more dangerous drug habit, i.e. it is not a stepping-stone to heroin. Almost without exception, marihuana advocates cite the abuse, dangers, and toxicity of alcohol, which is of course legally available in most areas of the earth, in defense of the legalization of marihuana. "If one assumes then that the rational of regulation of a drug should be in proportion to its abuse potential, then one would expect the regulation of marihuana and alcohol to be approximately equal."[62] Not one author or speaker who has used this argument has yet cited evidence that the legalization of alcohol has in any way deterred its use and abuse.

At the present time, the determination of the abuse potential is very difficult. The question is beset with social and intellectual bias and generates emotional controvery. In effect marihuana is much like alcohol; the degree of toxicity depends upon the quality and quantity of the dose. Furthermore, if taken chronically, deleterious results can be expected. Eastern and Middle-Eastern countries have been coping with the hashish problem for centuries in much the same way that Western countries have handled the alcohol problem—with a notable lack of success.

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Chapter VI

PIPERIDYL BENZILATE ESTERS AND RELATED COMPOUNDS

ONE OF THE RICHEST alkaloidal plant families, members of which grow in almost every part of the world, is the Solanaceae, typified by often narcotic herbs, shrubs, and trees. The Solanaceae encompass the more mundane potato and eggplant, as well as the belladonna or deadly nightshade. A number of the plants, perhaps the most important of which is the genus *Datura*, have been recognized as poisons and narcotics since antiquity, and some have been used in religious and magic rites.[1] Various species may be found in parts of Asia and Africa where they were ingested specifically for hallucinatory effects. Several species of *Datura* were used also in Mexico as medicinal plants and for hallucinogenic divinations. In spite of its toxicity, *toloache* (*Datura*) is still used by several Indian tribes in the North American Southwest for religious and hedonistic purposes.

Although methods of preparing and using *Datura* differ widely, it and related plants have been employed by various South American Indian tribes since classical times. Pulverized seed are taken as a drink or infusion; leaves and twigs may also be used. The partaker undergoes an initial violent reaction, followed by a deep sleep, marked by hallucinations. During the quiescent period, the witch doctor, if such is his profession, acquires divine powers from spirit visitations. An interesting use is made by the Jivaro tribes. Unmanageable children are given *Datura* seeds in the hope that the spirit of their forefathers may come to admonish them. It is indeed unfortunate that such optimism, and the philosophy, if not

the custom, cannot be exported to more enlightened cultures. Among ancient tribes of the Bogota area, wives and other slaves of departed masters were given *Datura* to induce stupor prior to being interred alive with the deceased. In more recent times[2] a case of mass poisoning of British troops by *Datura stramonium* during the American Revolution resulted in odd, at times comical, unmilitary behavior which lasted in some men for several days. Hallucinations and amnesia occurred. This episode which happened in the Jamestown area gave rise to the vernacular name "Jimson" (Jamestown) weed.

Most, if not all species of *Datura* of North America, Europe and Asia, as well as the tree species of South America, contain similar tropane alkaloids such as hyoscyamine and its racemic isomers, atropine, and scopolamine. The belladonna alkaloids are anticholinergics, and have been used as medicines for at least a century. In small doses, they are prescribed as antispasmodics, sedatives, muscle relaxants, and for Parkinsonism, etc. In large doses, they may produce delirium, characterized by peripheral anticholinergic effects such as tachycardia, dry mouth, and myridiasis. They are extremely toxic, and in large doses can lead to respiratory failure and death.

Atropine has been used to induce a psychotic state[3] similar to schizophrenia. Large doses were reported to produce hallucinations, mood changes, and depersonalization.[4,5] The central effects of a number of atropine-like anticholinergics have been overshadowed by their parasympathetic depressant properties. Many compounds which were synthesized for the latter purpose have not even been tested for central effects.

In 1958, Abood *et al.*[6] tested a series of compounds in which the piperidine ring of atropine had been retained, but which had been modified so that the tropic acid side chain was replaced by various substituted glycolate acids. The position of the side chain relative to the heterocyclic nitrogen atom was changed from *para* to *meta*. The resulting compounds, substituted glycolate esters of N-alkyl-3-hydroxy piperidines, elicited powerful, long lasting psychotomimetic and antidepressant effects in man. In rats, Biel *et al.*[7] found them to be potent central stimulants as measured in activity cages. These initial

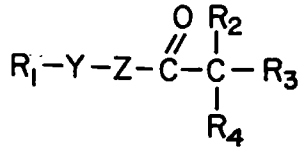


Figure 23. A general formula for glycolate esters.

observations[8] led to a broad investigation of other structural types and the relationship between anticholinergic activity and central stimulation.[9,10]

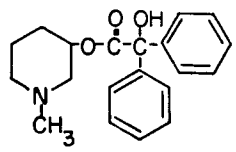
Chemistry

The glycolate esters have the general formula, shown in Figure 23, where R_1 is a heterocyclic N-substituted imino alcohol such as piperidinol, pyrrolidinol, quinuclidinol, granatanol or tropanol; R_3 and R_4 are a combination of phenyl, cycloalkyl, and saturated or unsaturated alkyl; R_2 is OH, Cl or acyl; Y is a chemical bond or lower alkyl; and Z is O or S.

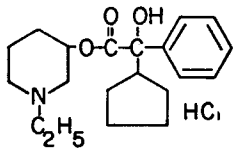
In the original report[6] the most psychotomimetically active compound was said to be 1-methyl-3-piperidyl benzilate, but it was later found that Ditran (Fig. 24) and other cycloalkyl derivatives were more active. Recently, esters of heterocyclic imino alcohols, such as 3-quinuclidinol have been found to be among the more potent of psychotomimetic glycolate esters.[12,13] Abood and associates have published widely on the relationship of chemical structure to psychotomimetic activity, particularly in reference to the piperidyl and piperazinyl glycolates.[4,8,11]

In the case of the piperidyl and pyrrolidyl esters, the relationships may be summarized as follows:

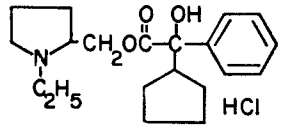
1. For maximum hallucinogenic, but not necessarily for anticholinergic activity, the N-substituent must be a lower alkyl. Quaternization of the heterocyclic N-atom abolished CNS, but not anticholinergic activity.
2. R_2 must be an OH group for maximal psychic and anticholinergic activity.
3. For CNS activity, R_3 and R_4 must be one of the follow-



1-METHYL-3-PIPERIDYL BENZILATE



PIPERIDYL ISOMER
30%



METHYLPYRROLIDYL ISOMER
70%

DITRAN

Figure 24. Chemical formuli for some of the benzilate esters.

ing combinations, arranged in decreasing order of potency.

Cycloalkyl + Q
Q + Q
Q + unsat alkyl
Cycloalkyl + unsat alkyl
Q + alkyl
Cycloalkyl + alkyl
alkyl + alkyl

If R_4 is an alkyl group (when R_3 is Q or cycloalkyl) an increase in the length or branching of the carbon chain enhances CNS activity. Maximum potency and duration of action is obtained with the cyclopentyl derivatives. In general, substituents on the phenyl or cycloalkyl decrease activity.

4. When substituted in the 2 or 3 position of the ring, the piperidyl and pyrrolidyl esters are comparable in both CNS and anticholinergic potency. With both types, potency is maximal if substitution at Y is direct; if Y is an alkyl, CNS activity diminishes with length and branching of the chain.
5. In the piperidyl series, the most active compounds are substituted in the 4 position, followed by the 3 and 2 positions, respectively.
6. The thioesters obtained by replacing O with S in the Z position are less active in both CNS and anticholinergic activity than are the esters.

Among the other heterocyclic glycolate esters, the 3-quinuclidinols are comparable to the 4-piperidyl-cyclopentyl esters in potency. Esters of 3-tropanol and 3-granatanol are somewhat less active, but all of these are more active than the piperazino compounds.

In general, there is a close relationship between anticholinergic potency and central nervous system stimulatory effects in the sense that potent anticholinergic activity is a pharmacological prerequisite of CNS action. The reverse is not true; not every potent anticholinergic acts necessarily as a central stimulant.[8] Receptor site specificity must also play a part for there is a preference for certain structural types among the piperidyl and pyrrolidyl esters. Changing an N-methyl to an N-allyl or N-(β-phenethyl) abolishes the central effects while the potent cholinergic properties are retained.

The glycolate esters and related compounds are synthetically derived materials. Biel *et al.*[14] were responsible for the original group of piperidyl benzilates and later extended their efforts[7] to both the piperidyl and pyrrolidyl glycolates. Reaction of 1-alkyl-3-hydroxypiperidine with an acid chloride, or of 1-alkyl-3-chloropiperidine with an appropriate glycolic acid gives a glycolate ester. The synthesis of the most potent hallucinogenic preparation, Ditran, proceeds through an unusual rearrangement. Reaction of 1-ethyl-3-chloropiperidine with cyclopentylphenylglycolic acid gives a mixture of the expected

1-ethyl-3-piperidylcyclopentylphenylglycolate (30%) and the ring-contracted isomer, 1-ethyl-2-pyrrolidylmethylcyclophenylglycolate (70%). This mixture is the drug, Ditran. During the reaction, one of the methylene groups of the piperidine ring becomes extra-annular; distillation of the rearranged product results in a reversal of the ring contraction.[15]

Pharmacology and Dosage

The compounds of major interest among the glycolate esters are 1-methyl-3-piperidyl benzilate (JB-336), 1-ethyl-3-piperidyl benzilate (JB-318) and Ditran (JB-329). In most of the early and more recent studies on the psychotomimetic effects and pharmacology of the glycolate esters one of these compounds was used.

The piperidyl benzilates may be administered orally, subcutaneously or intravenously[16] in doses of from 1 to 25 mg (0.02 to 0.35 mg/kg). The route of administration is of little significance to the onset and duration of drug action.

In comparison to the extensive knowledge on structural-activity relationship, little is known about the distribution, metabolism and elimination of these compounds. In one of few such studies,[17] tritium labeled N-ethyl-3-piperidyl benzilate was given to rats. In less than two hours over 95 per cent of the drug was excreted in the urine, however the identity of the compounds containing the radioactivity was not established. It is not unusual for tritium to undergo exchange with body H_2O and other ingredients, so unless identity is established such data has little meaning. Only 0.1 per cent of the total dose was found in the central nervous system, and the largest concentrations were in the caudate nucleus and hypothalamus. Less than 20 μg of drug was estimated to produce the powerful effects of Ditran. The latter has no effect on blood pressure[18] and no antiserotonin activity. The report that these drugs exert few effects on any of the known enzymes of the body [4,8] is a far-reaching conclusion and I doubt that there is sufficient evidence for it.

Central Nervous System

Generally speaking, the glycolate esters are classed among the so-called psychotomimetics, but many do so with misgiving. Hofmann[19] rejects them as specific hallucinogens, and relegates their psychotomimetic properties to side effects or toxicity. The primary objection appears to be that they elicit effects differing markedly from those observed with LSD, mescaline, etc., which are considered by some to be the "true" hallucinogens. However, the confusion may be semantic, centering around the use of the word psychotomimetic as an all-inclusive term. The term implies that the agent produces a condition in man resembling a psychoses or symptoms normally associated with psychoses. Abood[10] and others[16] equate the basic thinking disturbances seen in schizophrenia with those produced by Ditran. Thought processes are severely disrupted. Speech is disorganized and incoherent; confusion, disorientation, and amnesia occur often and may be long lasting. These symptoms wax and wane, typical of a true delirium. The amnesia is striking, particularly following doses great enough to produce delirium. At lower doses, memory may not be significantly affected, but the ability to concentrate may be altered. A subject may start to answer a question, but change to a completely irrelevant thought in midsentence. He may then suddenly become aware of an inability to control or concentrate thought, and become bewildered, often returning to the original topic or asking that a question be repeated.

The affective disturbance produced by these drugs closely resembles those observed in some types of schizophrenia. Hallucinations, which ordinarily would create fear, panic or great emotion, are experienced with little or no reaction, whereas mild perceptual distortions may result in fright or wild hilarity. Tactile, auditory and visual hallucinations occur, the latter being less intense than those from comparable doses of LSD or psilocybin.[20,21] With Ditran the onset is rapid (20–30 minutes) and the effects prolonged. At the upper dose range, mental disturbance may last for twenty-four hours with some confusion remaining for days. Subjects find the Ditran experi-

ence to be entirely unpleasant and few will agree to more than one trial. Significantly, there has been a dearth of Ditran cults.

In trying to assess whether the glycolate drug syndrome is psychotomimetic, one should bear in mind that such symptoms are not necessarily characteristic of schizophrenia. And, there are many symptoms observed in schizophrenia which are certainly not found in the drugged state, whether it is induced by LSD, mescaline, psilocybin, or glycolate esters. Hollister has frequently[20] commented on this facet of chemically-induced psychoses. However, to my mind, the syndrome above is about as psychotomimetic as one could want a syndrome to be.

Mechanism of Action

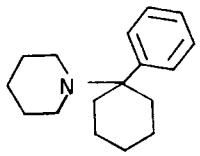
In their clinical studies, Gershon and Olariu[16] showed that tetrahydroaminoacridine antagonized the central and peripheral action of Ditran, but not those of LSD, mescaline or 1-(1-phenylcyclohexyl)-piperidine (Sernyl®). Tetrahydroaminoacridine is a potent cholinesterase inhibitor, as is yohimbine, which was found to be an even more effective antagonist of the glycolate esters in dogs.

In view of the fact that most of the effective antagonists are anticholinesterase agents, it would be logical to conclude that cholinergic mechanisms are involved. Also, since there appears to be a relationship between the peripheral anticholinergic action of the glycolate esters and their psychotomimetic activity, it follows that the central action of the drugs could very well involve cholinergic blockade or antagonism. Although Abood, who with his associates has been the greatest source of information on the glycolate esters, recognizes the possibilities, he[23] appears, out-of-hand, to reject the hypothesis on the basis that we don't know much about central cholinergic transmission *per se*. Instead attention has been concentrated on the availability of "an electrophilic center on a presumptive receptor (synaptic) site" at which a nucleophilic nitrogen atom (the heterocyclic nitrogen) can interact. Studies on stereochemical relationships to drug potency using conformational analysis in conjunction with a "behavioral disturbance index (BDI)" has, according to Abood, clearly established the validity of the hypothesis that the availability of the nonbonded electron pair in the ring is correlated with the psychotomimetic potency of the glycolate esters.[24]

In his analysis of the relationship between the physical and chemical properties of the glycolate esters and mechanism of drug action, Abood[10] suggests that the gylcolates substitute and interfere with the regulatory action of calcium on some ill-defined excitatory membrane. The crux of the argument is that the drugs can replace Ca^{+2} which is bound to phosphate groups on a hypothetical membranous lipid. After a series of studies involving surface potentials, pressure, viscosity and absorption, on surface films made from brain and purified lipid.[25,26] it was concluded that the drug was capable of substituting for Ca^{+2} and that it exerted similar as well as dissimilar physical effects upon the lipid monolayers. Abood's arguments are impressive and interesting, but to my mind, much of the conjecture involving conformational analysis, charge-transfer complexes, and molecular models of drug-lipid surface interaction, is premature. Serious investigations of possible interference with central cholinergic mechanisms would appear to be a more fruitful approach, at least until we learn more about the chemistry of membranes as such.

SERNYL

Sernyl is the trade name (Parke Davis and Co) for 1-(1-phenylcyclohexyl) piperidine, a compound which was originally synthesized in a search for a fast-acting intravenous anesthetic. During clinical trials of the drug as an analgesic in humans the existence of behavioral side effects were noticed.[27,28] Myer *et al.*[29] and Chen *et al.*[30] characterized these unusual symptoms in terms of sensory deprivation. Anxiety, illusions, delusional and hallucinatory phenomena, with a feeling of displacement, and interference with the thinking process were noted. The effects of Sernyl are centrally mediated. The drug appears to have a selective action on the sensory cortex, the thalamus, and midbrain region, resulting in an impairment of pain, and touch proprioception, and in discriminative aspects of sensation.



SERNYL

Figure 25. The structure of Sernyl.

Luby *et al.*[31] found psychotomimetic effects of Sernyl to be somewhat distinctive. The substance was unusual in its effects because, although the primary characteristics of schizophrenia, such as loss of ability to sustain thought, fluctuations in experiencing time and space etc., were marked, the secondary characteristics, such as hallucinations, delusions etc. were absent. Comparatively minor somatic symptoms were experienced. However, Meyer *et al.*[29] Levy *et al.*[32] and others[16,33] have found that responses may be unpredictable depending somewhat on the route of administration and other factors.

The dosage of Sernyl ranges from 0.05 to 0.2 mg per kg. Intravenously, striking effects may be obtained in minutes; intramuscularly, the effects are less marked, but may be prolonged. Orally, the drug is much less effective. In patients with various mental dysfunction, tachycardia, sweating, excessive salivation, some motor effects, loss of deep pain sensation, and anesthesia may occur.[32] Psychoneurotic patients showed a period of apathy after Sernyl followed by anxiety, disturbances of body image, feeling of depersonalization and thought disorder. Body image disturbances were recalled after the effects of the drug wore off. Feelings of "floating in space" were frequently described. N-ethyl-1-phenylcyclohexamine, although similar in structure, has very few of the effects of Sernyl. Apparently, the phenylcyclohexyl moiety is not the hallucinogenic determinant. In these patients, chloropromazine seemed to antagonize the psychotomimetic effect.

In some schizophrenic patients, Sernyl caused a reactivation of psychoses and an exacerbation of symptoms. The action of Sernyl is quite different from that of LSD, mescaline,

or psilocybin, and at one time it was believed to be the most "schizophrenic" of all the psychotomimetics. However, as others have noted, the fact that Sernyl intensifies the symptoms of schizophrenia is not particularly compelling if one considers that a large number of chemicals, both hallucinogenic and nonhallucinogenic, have this property. Schizophrenia, like personality, and perhaps embodying some of the intangible facets of the latter, is a concept which seems to defy definition. A recent symposium began with a lengthy discussion of the problems of defining drug states in terms of schizophrenia. The discussion ended with a conclusion that the use of drugs as models for schizophrenia, or vice versa, is premature in light of the fact that we don't know what schizophrenia is.[34]

Metabolism

Few studies have been conducted on the metabolism of Sernyl. One of these was done in monkeys using a drug labeled with radioactivity. After a dose of from 2 to 6 mg per kg about 60 per cent of the dose appeared in the urine in twelve hours. After eight days, 75 per cent of the dose appeared in the urine. Practically all the recovered radioactivity was in the form of metabolites. In the urine, the major metabolite was a conjugated nonphenolic dihydrophenylcyclidine. No oxidation to CO_2 occurred, and fecal recovery was from 1 to 2 per cent of the dose.[35]

Abuse

Ban *et al.*[36] reported a study in which fifty-five patients were given Sernyl intravenously. Among these, only three became euphoric, laughed, or expressed any evidence of pleasure. Indeed, the Sernyl experience was overwhelmingly unpleasant and extremely frightening. Patients spontaneously asked that they not be given the drug again. In comparison with an LSD or mescaline experience, Sernyl was much more traumatic.

The unpleasant reaction to Sernyl is analogous to that reported for the glycolate esters, and there are few reports of abuse of these drugs. One interesting exception was recently

included in a paper by Hammar *et al.*[37] The Swedish investigators were asked to help identify a substance called "hog,"* a supposedly new drug of some sort with extremely weird effects. The compound had come to the attention of the New York judiciary by way of a young man who described the drug as giving much more bizarre and satisfying trips than "acid," so much so that it had become the rage of the California hippie community. Using combined gas chromatography and mass spectrometry, and a little intuitive chemistry, Hammar *et al.* unequivocally identified the weird, active ingredient of "hog" to be phencyclidine, once again illustrating that one man's poison relative to tea may well depend on the cup.

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* David Smith identifies "hog" as Benactazine in the Editor's Note, *Current Marijuana Issue, J Psychedelic Drugs, II* (Issue I), 1968. Sernyl is known as "P.C.P." or "peace pill."

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Chapter VII

SOME MINOR HALLUCINOGENS

WHETHER they be mushrooms, cacti, shrubs, trees, or toads, natural products yield their pharmacologic secrets slowly. Some of the more interesting enigmas still lurk in the deserts of Mexico, in the Amazonian forests of South America, and in the West and South of Africa.[1] On the other hand, interesting substances of natural origin can be found in places no more remote than the ordinary kitchen spice shelf. Very little information is available about most of these minor hallucinogens, but, for some, considerable knowledge has been accumulated.

FLY AGARIC

There are only two areas of the world, one in the west and the other in the northeast of vast Siberia, where fly agaric has been used commonly as an intoxicant.[2] Fly agaric, which grows throughout northern Europe and Asia, is the common name for the mushroom, *Amanita muscaria Fr.* The mushroom is eaten for its inebriant properties, swallowed whole in a dried state, or else by infusion after soaking four or five days in water. According to Wasson,[2] the effects of ingesting fly amanita are apparent within fifteen to twenty minutes, but may last for hours. The first reaction is soporific—the recipient falls into an abnormal sleep, marked by colored visions. After waking from this sleep, some subjects express feelings of elation that lasts for three or four hours. During this state, the subject is often capable of extraordinary physical feats and enjoys performing them. One of the most extraordinary features of fly agaric is that the hallucinogenic properties pass into the urine. Thus, one may enjoy the euphoriant over and

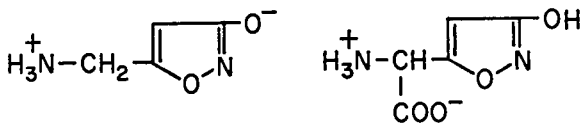
over again or pass it among friends (or enemies)! Obviously, the active ingredient is ingested and excreted unchanged. Or, an inactive constituent may be activated by metabolic processes *in vivo*.

Chemistry

Muscarine, the history and chemistry of which is well-known,[3] is present in fly agaric, but it is not considered to be the centrally active constituent. Although bufotenine, atropine, hyoscyamine and scopolamine have been suggested as the cause of the central effects of *A. muscaria*, there is controversy as to whether they are even present in the plant.[4] Actually, there is very little evidence that bufotenine has any central effects.

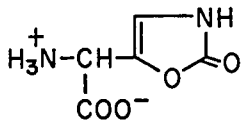
In recent years, muscimole and ibotenic acid have been isolated from *A. muscaria*[5,6] (Fig. 26). Pharmacological tests (narcosis-potentiation) which were used as aids in the isolation process, showed these materials to be centrally active. Several syntheses are available.[7-9]

As indicated by its structure, muscimole is very polar and extremely water soluble. It is the enol-betaine of 5-aminomethyl-3-hydroxyisoxazole, in other words, an unsaturated hydroxamic acid. It may be formed by the decarboxylation and loss of water from ibotenic acid.[8] The latter is an amino



MUSCIMOLE

IBOTENIC ACID



MUSCAZONE

Figure 26. Compounds isolated from *Amanita muscaria* (fly agaric).

acid, α-amino-α-[3-hydroxy-isoxazoylyl-(5)] acetic acid monohydrate and is probably a principal active constituent of *A muscaria*, being present to the extent of 0.3–1.0 gm per kg.

In the laboratory, ultraviolet irradiation of ibotenic acid gives muscazone,[10] which is pharmacologically less active. The variation in toxicity of *A. muscaria* may be a result of fluctuations in the ibotenic acid-muscazone ratio.

Pharmacology

The central effects of muscimole and ibotenic acid were evaluated in mice using the sedative/hypnotic effect. Sedative action was obtained with 4–8 mg of ibotenic acid per kg and 1–2 mg muscimole per kg injected intraperitoneally. Oral administration was about one-half as effective as intraperitoneal injection. Toxicity for mice was rather high; typical signs of toxicity were nervousness, excitation, dilated pupils, convulsions, twitches, catalepsy, irregular respiration, later sedation and sleep. Rats are somewhat less sensitive.

Waser[11] reported the results of self-administration of ibotenic acid and muscimole. With 20 mg of ibotenic acid, there was little change except for lassitude. Muscimole in doses of 10–15 mg orally created a toxic psychosis with confusion, dysarthria, disturbance of visional perception and hearing, delusions of color vision, muscle twitching, disorientation in situation and time, weariness, and sleep with dreams. Also, muscimole was found in the urine.

NUTMEG

Nutmeg is known as a condiment to millions of people in all areas of the world. It comes from the nutmeg tree, *Myristica fragrans*. There are about one hundred species of the genus Myristica, but of these, *M. fragrans* is the only one that is cultivated. It is a tropical plant, growing particularly well in the East Indies and in the Caribbean.

M. fragrans is a dioecious species, having male and female flowers. Nutmeg comes from the seeds; mace, another well-known spice, is prepared from the aril, a bright red covering which can be peeled away from the seedcoat.

History

M. fragrans was not known in European countries until about the time of Marco Polo. At that time, the Portuguese controlled the trade in nutmeg and mace. Later, the East Indies came under the control of the Dutch, who, for economic reasons, limited the cultivation of the nutmeg tree. French and British traders managed to successfully break the monopoly and gradually the cultivation of *M. fragrans* spread throughout the tropic world.

The use of nutmeg as a medicant was first recorded by the Arabs about 600 A.D. It was used for kidney disease, pain and other ailments, particularly digestive disorders. Inevitably, it was described as an aphrodisiac; in some Arabian countries men still take it to increase virility.[12]

In Hindu medicine, nutmeg was used for fevers, respiratory dysfunction and heart disease. It is still used as an analgesic and sedative by folk doctors and is given in small doses to quell hysterical or unmanageable children, the number of which seems to always increase in direct proportion to increased virility.

Early European physicians, following the lead of their Arabian colleagues, prescribed nutmeg for many different types of ailments. With the development of modern pharmacy in the early 19th Century, the use of nutmeg in medicine declined. However, near the turn of the 20th Century, a mistaken belief that nutmeg would induce abortion and bring on overdue menses caused many incidences of nutmeg poisoning.[13] A summary of symptoms described in these cases[14] were restlessness, dizziness, fear of death, coldness of extremities, nausea, vomiting, and abdominal pain. Patients were likely to be extremely agitated and delirious with weak rapid pulses and decreased body temperatures. These symptoms resulted from the oral ingestion of one to three nutmegs.

In the forty years preceding the 1960's, the use of nutmeg or mace as a psychoactive agent was rare to unknown. However, during the last ten years its use has increased, particularly among students and prisoners. The latter, of course, use the spice as a replacement for standard drugs.[15] Students[12] use it as a first experience which, because of the unpleasant side effects, is usually and fortunately their last. Among students, doses range from one teaspoon to a whole can of ground nutmeg, taken with water or a glass of juice. The onset of action is from two to five hours, a delay the naive recipient does not anticipate. A person takes a goodly amount of nutmeg, then sits around waiting for the expected euphoria, but when nothing happens either takes more or goes off to bed. Next morning, he awakes with a blooming headache, dry mouth, tachycardia, dizziness and general malaise—all of which suggest a mean "hangover."

Psychological reactions are not likely to occur with small doses of nutmeg. However, with higher doses reactions may range from no mental changes to hallucinogenic experiences analogous to those caused by LSD or mescaline. There is no direct correlation between dose and psychoactivity. This variability is probably due to differences in potency of different batches of nutmeg or to differences in sensitivity of the recipients.

Chemistry and Pharmacology

Nutmeg can be processed to yield fixed oil, volatile oil, and residue fractions.[16] The fixed oil fraction (nutmeg butter) consists essentially of triglycerides, and myristic acid is the principal ingredient.[17] The volatile fraction (oil of nutmeg) is composed primarily of terpenes (80%), but also has a percentage of aromatics, consisting of ethers and phenols. The solid residue, or pulp, which remains after the fixed and volatile oils have been removed, constitutes about 50 per cent of the original mass of the nutmeg. The pulp is assumed to be mostly cellulose and has no psychoactivity.[18] Although it is generally accepted that the effective agent of nutmeg is in the volatile oils, no definitive analysis of the three fractions has actually been made.[17]

Using gas chromatography in conjunction with infrared and high resolution mass spectroscopy, several compounds were isolated and identified. The terpine fraction has properties similar to turpentine, known well for its irritant properties,

but not as an intoxicant. Thus, the aromatic fraction would seem to be the most likely source of psychotropic activity. Tests with the major constituents, myristicin, elemicin and safrole, in animals and humans,[19] indicate that they cannot account for the psychoactive efficacy of nutmeg oil.

An interesting proposal that the psychoactive agent may be generated *in vivo* has been offered. In Figure 27, the formuli for the constituents of the aromatic fraction of the oil of nutmeg are shown. With the addition of nitrogen, several of these, specifically myristicin, elemicin, and safrole, would be identical to phenylisopropylamines of known psychotogenic activity. Addition of ammonia[20] could occur to give methoxylated amphetamines. However, Casida *et al.*[21] using methylene-^{14}C-dioxyphenyl-labeled myristicin, have shown that the methylenedioxy side chain is lost as CO_2 in a mouse liver microsomal

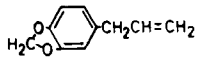
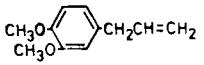
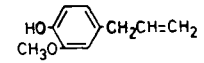
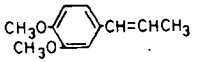
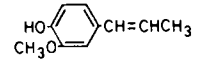
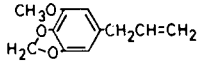
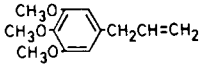
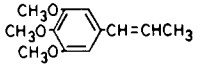
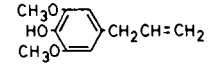
STRUCTURE	NAME	AMOUNT TO BE FOUND IN 20 GRAMS TOTAL NUTMEG (IN MILLIGRAMS)
	SAFROLE	39
	METHYLEUGENOL	18
	EUGENOL	5
	METHYLISOEUGENOL	11
	ISOEUGENOL	6
	MYRISTICIN	210
	ELEMICIN	70
	ISOELEMICIN	3
	METHOXYEUGENOL	8

Figure 27. Constituents of the oil of nutmeg, from Shulgin *et al.*[17] with permission.

system, requiring NADPH. This does not disprove the theory of ammonia fixation, which is a relatively rare biochemical event in mammalian systems, but it does suggest that the idea may be an oversimplification.

KAVA

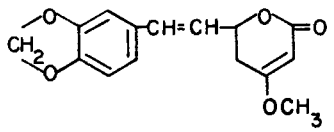
The Polynesian beverage, kava, is prepared by steeping the pulverized roots of the Kawa, or Kava-Kava plant (*Piper methysticum* Forster) in water until a cloudy, khaki-colored liquid is produced. In times past, the extraction was preceded by a mastication step, that is, the roots were chewed for a time by selected members of the group, usually young boys, before the water was added. In Samoa,[22] kava drinking and its attendant ceremonies has a mythological etiology and is intimately related to indigenous religious, social and political organizations. In contemporary Samoan society, kava drinking is an integral part of the social life and has been compared to the Western cocktail or highball,[23] in that it produces a relaxed and friendly atmosphere, conducive to social cooperation.

Although the drink is prepared in much the same way throughout Western Polynesia, the potency and therefore the effects of the extracts varies from one area to another. Samoans use the dried root which apparently yields a refreshing, astringent drink. Drinkers experience a tingling sensation in the mouth and a short-lived numbness of the tongue. In the New Hebrides, green root is used and the mastication process has been retained.[24] One hour or so after ingesting a preparation made in this way, the drinker goes into a dreamy, stuporized state, which is not sleep. Although he resents being disturbed, or the "breaking of the kava," he responds rationally and shows no loss of orientation as to time, place or person. This initial state is followed by sleep from which the subject awakes appearing fresh and without any hangover or other sequelae. During the euphoriant stage, there is a heaviness and weakness of the extremities and a paraesthesia described as "numbness," "tingling," or "coldness." No change in pulse rate or blood pressure occurs; respiration is shallow, but regular, and deep tendon reflexes remain intact.

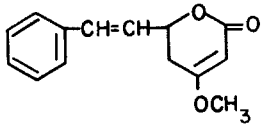
Chemistry and Pharmacology

For over a century, the intriguing properties of kava have stimulated research into the active ingredients. Until recently, most of the information on the chemistry of kava came from the laboratories of Borsche and co-workers, who published a series of fourteen papers between 1914 and 1933 (see ref. 25). They isolated and characterized kawain and dihydrokawain. In addition they elucidated the structures of methysticin and dihydromethysticin, both of which had been isolated much earlier. All of these compounds are substituted 5,6-dihydro-α-pyrones. In more recent times, several related α-pyrones, the yongonin series, have been isolated from kava (Fig. 28).

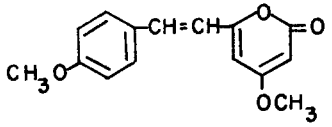
In physiological tests involving changes in motor function, reflex irritability, seizure thresholds and patterns, the kava pyrones were shown to have activity.[26] In mice, kawain and dihydrokawain were absorbed rapidly from the gastrointestinal tract. The time of peak effect was about ten minutes; methysticin and dihydromethysticin required about thirty to forty-five minutes.



METHYSTICIN



KAWAIN



YANGONIN

Figure 28. Chemical structures of some α-pyrones.

Studies by Meyer and his co-workers have dealt with the water-insoluble α-pyrones of kava.[26] There is no doubt that these materials possess pharmacological activity, however there is question as to whether they are the psychoactive components of kava. Using water-soluble preparations from kava, Buckley *et al.*[27] have suggested that substances other than α-pyrones are physiologically active. On the other hand, studies in animals and man[28] have shown that the main pharmacological action of extracts of kava is that of a central relaxant, that is, antagonistic to strychnine. Generally speaking, the hallucinogenic properties of kava are considered to be of minor importance.

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