CHEMICAL, PHARMACOLOGICAL AND MEDICAL ASPECTS OF PSYCHOTOMIMETICS*

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Hallucinogens are a sub-group of the large class of psychotropic compounds, that is, substances which exert some influence or other on the psyche. Psychotropic substances have always played a large role in medicine but their importance has increased greatly in recent years. The psychotropic compounds could be divided into the following six groups:

TABLE I

PSYCHOTROPIC SUBSTANCES

1. *Analgesics and Euphoriants* ...	opium (morphine, heroin, etc.) pethidine, methadone, etc. amidopyrine
2. *Sedatives and Tranquillizers* ...	rauwolfia (reserpine, etc.) phenothiazines (chlorpromazine, etc.) meprobamate, etc.
3. *Hypnotics*	barbiturates (luminal, dial, etc.) hydantoins chloralhydrate
4. *Intoxicants*	alcohol chloroform, ether benzene
5. *Stimulants*	"Weckamine" (amphetamine, etc.) caffeine cocaine iproniazid, etc.
6. *Psychotomimetics and Hallucinogens*	peyotl (mescaline) hashish d-lysergic acid diethylamide (LSD 25) psilocybin, etc.

The psychotropic effects of these groups of substances overlap to a quite considerable extent so that a somewhat different classification may also be made. Thus, cocaine may be included not only in the group of stimulants but also in the group of analgesics and euphoriants. Alcohol, a prominent representative of psychotropic agents, can be included in the euphoriants and also in the intoxicants.

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The substances in group 6, the psychotomimetics or hallucinogens, with which we are more particularly concerned, differ from the other five groups in exerting their own characteristic effects. Whereas the psychotropic effect of the substances in groups 1 to 5 consists basically in an influence on mood or the production of sedation, sleep or stimulation, the effects of the psychotomimetics are much more profound. In a specific manner they elicit profound psychic changes associated with changes in the perception of reality of space and time, two of the basic features of our existence. They produce profound changes in body image and personality. Nevertheless, consciousness is retained. In this respect there is an important difference between the effects of psychotomimetics and the analgesics and euphoriants such as morphine or alcohol, the effects of which are associated with more or less marked clouding of consciousness. The psychotomimetics transfer the subject into a new world, into a sort of dream world, which is experienced as quite real, generally more real and more intense than the every-day world. In this dream world everything seems to be of heightened significance; objects lose their symbolic character; they stand detached, radiating their own intense existence. Colours are more brilliant and assume a greater significance. The condition elicited by the psychotomimetics is generally accompanied by a visual hypersensitivity which may even lead to illusions and hallucinations. However, true hallucinations do not always occur; they usually occur only after very high doses. Hallucinations are not a characteristic feature of these substances and it would therefore be more correct to call them not hallucinogens but psychotomimetics, that is substances which mimic a sort of psychosis. Another expression for these substances is "mind changing drugs", which does not sound so scientifically but describes their effects fairly well.

Table II shows a series of compounds which can be classified as psychotomimetics. Most of these substances are known as magic or esoterical drugs. They were used in rituals and in religious ceremonies; some are still used today for these purposes, e.g., by some Indian tribes in the mountains of South Mexico. As their effects cannot be explained and are not without danger they are tabu to the natives. Only the priest doctors, the magicians, may use them. To a certain extent this restriction applies also to the use of these substances in our

TABLE II

PSYCHOTOMIMETICS

Anhalonium Lewinii (peyotl)	...	mescaline
Cannabis indica (hashish) ...	...	tetrahydrocannabinols, etc.
Peganum harmala } ...	...	harmine (banisterine, yagcine, telepathine),
Banisteria caapi (yage) }		harmaline
Piptadenia peregrina (cohoba)	...	bufotenin, dimethyltryptamine
Piper Methysticum (kawa-kawa)	...	active principles unknown
Amanita muscaria ...	...	active principles unknown
Psilocybe spec. } (teonanacatl)	...	psilocybin, psilocin
Stropharia cubensis }		
Rivea corymbosa (ololiuqui)	...	lysergic acid derivatives
LSD 25	...	d-lysergic acid diethylamide

scientifically enlightened world ; they should not be taken by lay persons without medical supervision but only controlled by the modern successor of the priest doctor, the psychotherapist.

After a brief review of the drugs listed in this, I shall deal in greater detail with the psychotomimetics derived from our own investigations—LSD 25, the active principles of the Mexican magic mushroom, and ololiuqui, another magic mexican drug.

Mescaline is the main active principle of the Mexican drug peyotl, the cactus species Anhalonium Lewinii. The chemical structure of mescaline was elucidated by Späth who also synthesized this alkaloid (1). Very many publications have appeared on the peyotl cult of the Mexican Indians and on the effects of mescaline (2, 3). I shall only mention a few aspects which are of interest in connection with the effects of lysergic acid diethylamide and psilocybin.

Of particular interest is the high dosage of mescaline which is necessary to elicit intoxication. The usual doses of mescaline are between 0·3 and 0·6 g. Soon after the drug has been taken, unpleasant autonomic symptoms are experienced: these are nausea, tremor and sweating. The hangover actually precedes the intoxication. After one to two hours, when these unpleasant effects are slowly wearing off, the actual dream-like state of intoxication ensues. This is usually accompanied by coloured visions. A brilliant description of mescaline intoxication has been provided by Aldous Huxley in his book "The Doors of Perception" (4).

Hashish is an intoxicant poison from the Near East which has been known for thousands of years. It is derived from Indian hemp Cannabis indica (5). Hashish has also found some fame in the literature since the French poet Charles Baudelaire described his experiences under this drug in his book "Les Paradis Artificiels". More recently, hashish has turned up in the new world, particularly in Central America, where it is widely used in the form of Marihuana cigarettes, particularly by youths and by the demi-monde. Of the numerous substances which have been isolated from hashish it seems to be the tetrahydrocannabinols which are primarily responsible for the psychotomimetic effect (6). The tetrahydrocannabinols are diphenyl derivatives, the only non-nitrogenous psychotomimetics.

From two plants used for mystical purposes in different parts of the world, *Peganum harmala* (7), which grows on the Asian steppes, and the South American creeper, *Banisteria caapi* (7, 8), the same active principles, harmine, and a closely related compound, harmaline, have been isolated. The name "telepathin" instead of harmine indicates the use of the drug for mystical and telepathic purposes.

The seeds and leaves of the mimosacea, *Piptadenia peregrina*, are used by some Indian tribes in the Orinoco region in South America to prepare a snuff called "cohoba" which is supposed to render the warriors fearless and insensitive to pain. From this plant the two substances bufotenin and dimethyltryptamine have been isolated (9).

The psychotomimetically active principles of *Piper methysticum* have not yet been elucidated. Piper methysticum is used as an intoxicant in the South Sea Islands (10) where it is known as kawa-kawa.

Certain tribes in Siberia eat particular varieties of the mushroom *Amanita muscaria* to produce a state of intoxication as well as for mystical purposes. The psychotomimetic active principle is still unknown. The muscarine and slight traces of bufotenin (11) found in European varieties of Amanita muscaria cannot account for the psychotomimetic effects of the Siberian variety (12).

After this brief review I should like to deal in greater detail with the psychotomimetics resulting from our own investigations.

d-Lysergic Acid Diethylamide (LSD 25)

Lysergic acid diethylamide, which is also known as LSD 25, is extraordinarily effective both qualitatively and quantitatively. Evidence of this is provided by almost 800 papers reporting on pharmacological and clinical studies of this compound. I shall have to confine myself to discussing our own experiments and experiences with this substance. First some remarks concerning the history of LSD.

Lysergic acid diethylamide was prepared in the course of the investigations, over a period of some decades, on the ergot alkaloids (Fig. 1) in the SANDOZ Research Laboratories at Basle. Fig. 1 shows some spikes of rye infected with the fungug claviceps purpurea. The grains infected with the fungus grow large

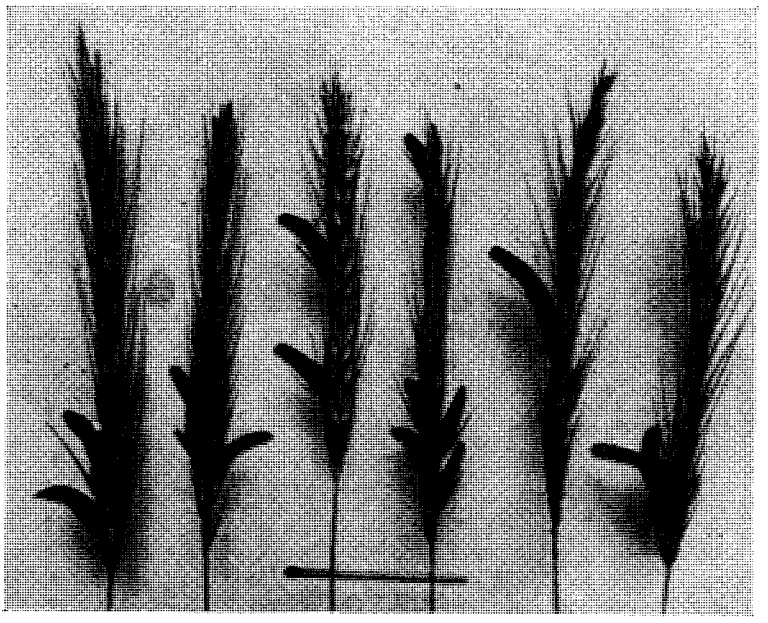


FIG. 1.

and become dark coloured. They constitute that what is named ergot. Ergot contains as everybody knows therapeutically important alkaloids. We were able to synthesize one of these alkaloids named ergometrine, the oxytocic principles of ergot. That is the structural formula of ergometrine. Ergometrine is the propanolamide of lysergic acid. Lysergic acid is the characteristic nucleus of all ergot alkaloids. Subsequently we prepared a large number of other acidamide-like derivatives of lysergic acid, including the diethylamide (13). This derivative was prepared in the hope that it would be an analeptic, as might reasonably be expected in view of the structural relationship between ring D of lysergic acid, and that of nikethamide, a well-known analeptic (see formulae fig. 2).

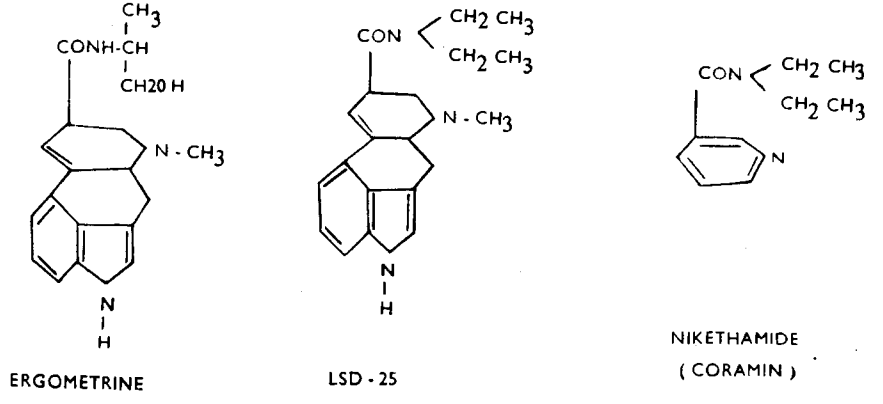


FIG. 2.

When I was preparing lysergic acid diethylamide tartrate I experienced a strange, not unpleasant, transient state of intoxication. I attributed this to some exogenous factor. In order to ascertain the cause, I took 0·25 mg. d-lysergic acid diethylamide tartrate. This first, planned study of LSD had dramatic results: the dose of 0·25 mg. which I thought would be very low subsequently proved to be five to ten times higher than the normally effective dose. All the symptoms experienced were pronounced and intense, so that in my report on that first personal study all the fundamental effects of LSD could be described (14). The first systematic study of the clinical effects of LSD in normal subjects and in mental patients was then carried out by Psychiatrist W.A. Stoll in the University Psychiatric Clinic in Zurich (15).

LSD is by far the most active and the most specific psychotomimetic known. The effective oral dose in human beings is 0·02 to 0·05 mg. Thus, LSD is about 200 times more active than cocaine or amphetamin or 10,000 times more active than mescaline. This high potency of LSD is not just a curiosity, it is also of major pharmacological interest. The extremely high potency of LSD indicates that it acts on very profound structures. It probably acts on a central site of regulation.

In order to assess the specificity of a substance it is important to know not only the high potency but also the relationship between effective and toxic doses, that is, the therapeutic margin. So far as we know, in no case toxic symptoms have resulted from the ingestion of LSD, although innumerable experiments have been made with this drug. In animals the LD_{50} varies greatly from species to species. It is 46 mg./kg. in the mouse, 16 mg./kg. in the rat and 0·3 mg./kg. in the rabbit. Death is due to respiratory paralysis (16). The effective dose in human beings is 0·5 μg./kg. It is of course not possible to compare toxicity in animals and effectiveness in human beings. Nevertheless, these figures do reveal the quite unique and specific nature of the psychic effects.

In the case of such a specific psychotomimetic as LSD it is of interest to know how it is distributed in the organism. It would be expected that such a compound would accumulate in the brain. Investigations have shown, however, that this is not the case.

The distribution in the body and the excretion was studied in mice with the aid of LSD labelled with ^{14}C (17). As Fig. 3 shows, LSD gives by intra-

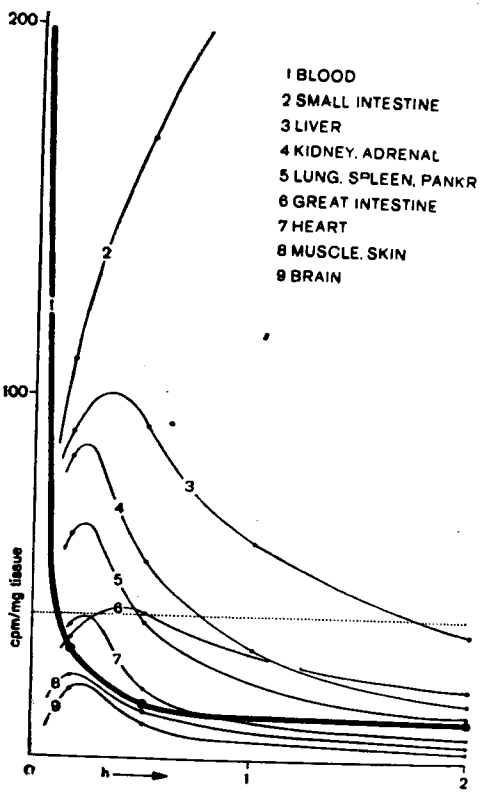


FIG. 3

venous injection disappears rapidly from the blood and is then found in various organs. Suprisingly enough, the concentration is lowest in the brain. The concentrations in the organs reach peak values after 10 to 15 minutes and then decrease very rapidly. One exception is the small intestine where activity rises to a maximum over a period of two hours. Excretion is mainly, *i.e.* about 80%, through the liver, bile and the intestinal tract. Extraction studies of various organs made two hours after administration showed that only 1 to 10% of the activity is present in the form of unchanged LSD ; the remainder consists of water-soluble metabolites of LSD. As the psychic effect reaches its peak when most of the LSD has disappeared from the organs, it can, with a great decree of probability, be concluded from these studies that even minimal doses of LSD can set off a chain of reactions culminating in the psychic symptoms.

The principal investigations of the pharmacological properties of LSD were performed in the Sandoz Pharmacological Laboratories under the leadership of Professor Rothlin and his successor, Dr. Cerletti. The most important pharmacological effects of LSD (18) are depicted in Fig. 4.

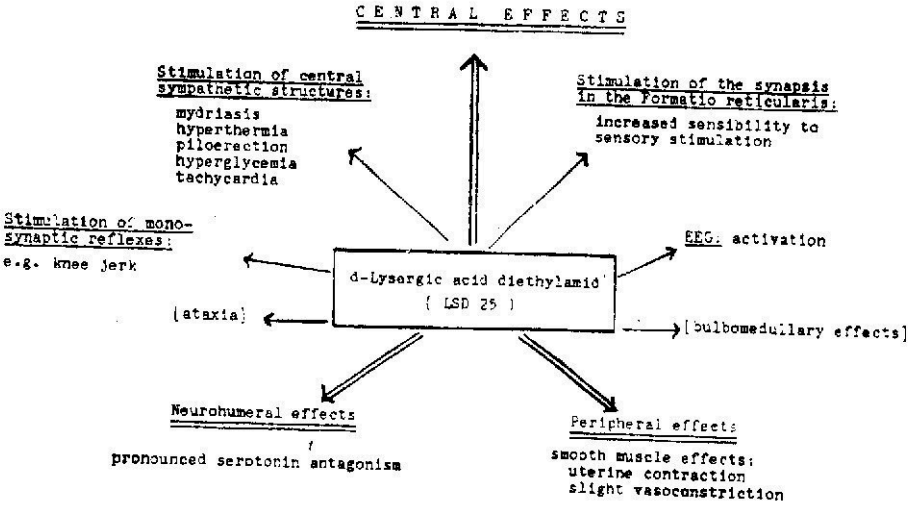


FIG. 4.

The effects of LSD can be divided into three main groups: central, peripheral and neurohumoral.

Of the peripheral effects special mention must be made of the direct action on smooth muscle, particularly the oxytocic effect, which is characteristic of the ergot alkaloids.

As a neurohumoral effect the antagonism of LSD to serotonin (5-hydroxytryptamine) is of importance. In extraordinarily low concentrations, LSD

antagonises the peripheral effects of serotonin. Reference to this effect will be made later.

The central effects of LSD are manifold. They may be summarised as forming a syndrome of ergotropic stimulation. This syndrome comprises:

(*a*) Activation in the EEG.

(*b*) Stimulation of the synapses in the reticular formation, leading to increased sensitivity to sensory stimuli.

(*c*) Stimulation of central sympathetic structures, manifested by mydriasis, hyperthermia, piloerection, etc.

(*d*) Stimulation of monosynaptic reflexes, *e.g.* the patellar stretch reflex.

Ataxia and bulbomedullar effects, such as vomiting, occur only after very high, toxic doses.

Not all the effects of LSD are stimulant. In certain tests and in certain animals LSD elicits marked depressant effects. Thus, barbiturate anaesthesia in the mouse and the rat is enhanced by LSD, and body temperature and oxygen consumption are reduced.

In general, the doses required to produce these pharmacological effects in animals are significantly higher than those which exert psychic effects in human beings. The only exception is the rabbit in which certain autonomic effects, *e.g.* hyperthermia, can be elicited by the same minimum doses, *e.g.* 0·5 to 1 μg. per kg. body weight.

But the particular feature of LSD lies not in these pharmacologically determinable effects, which are of minor importance in human beings, but in its extraordinary psychic effects.

Our knowledge of psycic function is still very limited. A highly active substance such as LSD offers new possibilities for the experimental study of psychosomatic relationship. One of the pathways by which psychopharmacological research can gain an insight into psychosomatic relationships is provided by making modifications to the structure of a psychotropic agent and comparing the pharmacological effects of the various derivatives with their psychic effects in human beings. This provides correlations between biochemical, peripheral and central effects on the one hand and psychic effects on the other. This procedure will be now demonstrated in the case of LSD and its derivatives.

We modifield the molecular structure of LSD in the following ways:

1. Variations in the acid amide residue (19).
2. Variations in the spatial arrangement of the atoms (19).
3. Saturation of the double bond in ring D (19, 20).
4. Substitutions in the ring system (21).

A more or less comprehensive pharmacological analysis of the many derivatives was carried out. Some of them were also studied in human beings. In order to compare the pharmacological effects and psychic activity Cerletti (22) selected 18 typical products (Fig. 5) as depicted in this figure.

On the left-hand side the psychotomimetic activity is indicated in relative

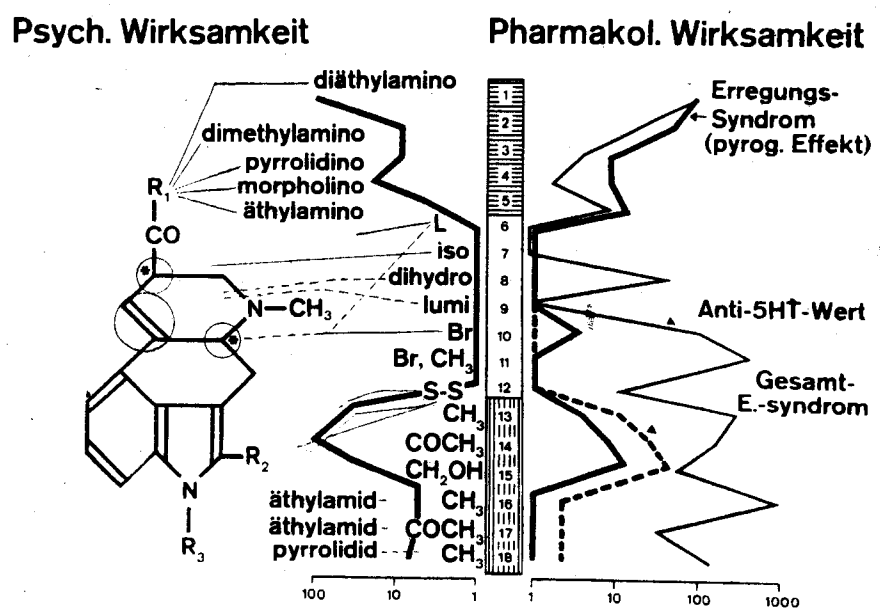


FIG. 5.

logarithmic values, LSD being taken as 100 (standard). The value derive mainly from investigations by H. Isbell in U.S.A. (23) but some were also derived from personal studies (24). It can be seen that when the diethylamide group is replaced by other amide groups psychic effects are still present but to a lesser degree. Even the closely related dimethylamide is only approximately one-tenth as active as LSD. The stereo-isomers of LSD and the derivatives in which the double bond in ring D has been saturated with hydrogen are practically devoid of psychic activity. Other derivatives that are almost without effect are those with a substituent group in position 2, for instance 2-bromo-LSD (also known as BOL 148), and the bimolecular product with an S-S bridge in position 2. By contrast, the derivatives with substituent groups at the indole nitrogen include some with considerable psychic activity. Thus, 1-acetyl-LSD is as potent as LSD. The combination of substitution in the amide group and in position 1 always led to compounds with weaker effects, their activity being less than 10% of that of LSD. Of all the many compounds related to LSD which we have prepared, none has been so far found which exceeds LSD in psychic activity.

The right-hand side of the table shows the pharmacological effects of these derivatives expressed in relative logarithmic values. This strong line is a manifestation of the syndrome of excitation which, as already mentioned in the case of LSD, is due to stimulation of sympathetic centres and consists of mydriasis, piloerection, hyperthermia, etc. The hyperthermic effect in rabbits

is a good index of the central autonomic stimulation. With some compounds, *e.g.* compounds 1-9, the hyperthermic effect parallels the general syndrome of excitation (continuous line). In the case of compounds with substitution in position 1 the hyperthermic effect is weaker than the other symptoms of sympathetic stimulation therefore an average value is marked by the dotted line.

The thinner line of this diagram is an expression of the antagonism of these agents to serotonin. The antagonism to serotonin is a characteristic feature of LSD, as already mentioned before.

A comparison of anti-serotonin activity and psychic activity reveals some interesting findings. When the LSD was discovered to be a potent antagonist of serotonin, it was postulated that the psychic effects of LSD might be due to its blocking brain serotonin, which apparently plays a role in the regulation of central nervous processes. However this comparison shows that this hypothesis cannot be correct. Compounds such as bromo-LSD or, more particularly, 1-methyl-2-bromo-LSD, and 1-methyl-lysergic acid ethylamide, are far more potent than LSD as antagonists of serotonin but exert little or no effect on the psyche. The serotonin antagonism does not parallel the psychotomimetic activity.

On the other hand a comparison of the excitation syndrome, strong line, and psychic effects reveals interesting parallels. The compounds with the most marked psychic effects, LSD and acetyl-LSD, elicit the most marked syndrome of excitation. The series of compounds which are devoid of psychotomimetic activity (compounds No. 6 to 12) are barely effective in elicitating the syndrome of excitation.

From these investigations it can be concluded *that there exists within the group of LSD and related compounds a relationship between psychotomimetic activity on the one side and the syndrome of a general central sympathicotonic stimulation on the other side.*

This result can be regarded as a contribution to our knowledge of the pharmacological basis of psychic processes.

Psilocybin and Psilocin the psychotropic principles of the teonanácatl

"Teonanácatl", the "sacred mushroom", played an important part in the pre-Columbian cultures of Central America. The famous chronicle of the Franciscan Father Bernardino de Sahagun, entitled "Historia General de las Cosas de la Nueva Espana" covering the years 1529-1590 gives a splendid picture of the culture, the history and the destruction, by Cortez, of the Aztec Empire. It also contains data on the use of intoxicant sacred mushrooms which were eaten by the Indians of Mexico at their feasts and religious ceremonies. From Sahagun's chronicle and from other reports it can be seen that Teonanácatl was not only ingested at social, festival occasions but also by the priest-doctors and the soothsayers: these became endowed by the mushroom god—the Christian missionaries said by the devil—with clairvoyant properties which

enabled them beside other things to identify the causes of disease and indicate the way in which they could be treated.

The use of these mushrooms and the worship of them by the Indians of Central America must be very old. In Guatemala so-called "mushroom stones" have been found. These are stones carved in the form of a pileate mushroom in the stem of which the head or entire figure of a god is depicted (Fig. 6). The

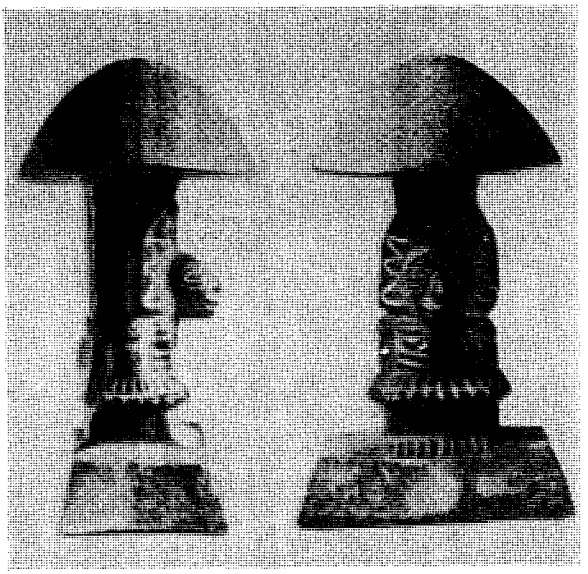


FIG. 6.

oldest specimens found are over three thousand years old. It can therefore be concluded that the mushroom cult of the Indians dates back to more than thousand years before Christ (25).

Although this mushroom cult is very old, our knowledge about it is very recent. For some centuries the reports in the old chronicles were given surprisingly little attention, probably because they were regarded as extravagances of a superstitious age. However, between 1936 and 1938 American investigators, Robert J. Weitlaner, Blas Pablo Reko, Jean Basset Johnson and Richard Evans Schultes, ascertained that mushrooms were still eaten in our day for magic purposes by natives in certain districts of South Mexico.

Systematic studies of the mushroom cult in its present form were then made later by the amateur investigators R. Gordon Wasson and his wife, Valentina Pavlovna. Between 1953 and 1955 they made several expeditions to the remote mountainous districts of South Mexico to study the current use of the magic mushrooms. On a further expedition, in the summer of 1956, Wasson was accompanied by the well-known mycologist, Professor R. Heim,

from Paris. Heim succeeded in classifying the most important types of mushroom used for magic purposes by the Indians. These were foliate mushrooms (Agaricales), mostly new types, almost all of the genus Psilocybe (26).

Subsequently it proved possible to grow culutres of some of these species in the laboratory (27). Artificial cultivation provided a very good yield especially of one of these sacred mushrooms, namely of Psilocybe mexicana Heim (Fig. 7).

FIG. 7.

Co-operation between the Laboratoire de Cryptogamie du Muséum National d'Histoire Naturelle in Paris and the SANDOZ Laboratories in Basle made it possible to obtain sufficient material from Psilocybe mexicana Heim chemical studies (28).

If there is no evidence of the chemical nature of the substance which is sought, as was the case with these magic mushrooms, then the attempt at isolating the active principle must be based on pharmacological tests. We first tested the mushroom extracts in animals. Studies were made of pupillary reaction and of piloerection in mice and of general behaviour in dogs. The results were not clear-cut and led to disagreement in the evaluation of the various extract fractions. After most of the very rare and valuable material, (or rather, the extracts) had been given to the animals without effect, there was some doubt whether the mushrooms cultivated and dried in Paris were still active. I therefore decided to make a personal trial to settle this fundamental point. I ate 32 dried specimens of Psilocybe mexicana, a medium dose used by the Indians. They weighed 2·4 g. The mushrooms exerted a marked psychotomimetic effect as the following extract from my laboratory records show:

"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 colours proved ineffective. Whether my eyes were closed or open I saw only mexican motifs and colours. 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 colour, reached such an alarming degree that I feared that I would be torn into this whirlpool of form and colour 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 every day reality to be a happy return from a strange, fantastic but quite really experienced world into the old and familiar home".

This personal study showed that the negative results of the animal investigations were due not to the mushroom material but to the animals studied and that human beings provide a more sensitive index of substances with psychic effects than animals do. We therefore found ourselves compelled to employ this sensitive, realiable test in human beings for working up the remaining mushrooms. Based on this personal study just described it was possible to select the samples in such a way as to prevent overdosage and therefore minimise the danger of the experiments. As 2·4 g. of the dried mushroom had elicited a marked reaction lasting several hours, we subsequently took samples of the extracts to be examined corresponding to only one-third of this amount, *i.e.* 0·7 to 0·8 g. dried mushrooms. These samples, of them contained the active principle, exerted merely mild effect. Nevertheless, the effect was sufficiently clear-cut for us to make a distinction between those fractions containing the active principle and those containing none.

With the aid of this reliable test in human beings it was then possible to extract the active principle from the mushroom, to purify and to cristallize it (29).

We called the new substances from the magic mushroom Psilocybe mexicana: *Psilocybin.* Psilocybin gave a violet colour, characteristic of indole derivatives, in the KELLER and VAN URK reactions. With the aid of these colour reactions, which now replaced the personal studies, the isolation and purification could be carried out more comfortably.

In addition to psilocybin, the mushroom extracts contained very small amounts of another psychotomimetically active indole compound. This gave a blue colour in the KELLER reaction and was called *Psilocin* (29).

Fig. 8 shows crystals of psilocybin and psiolocin as they separate from methanol.

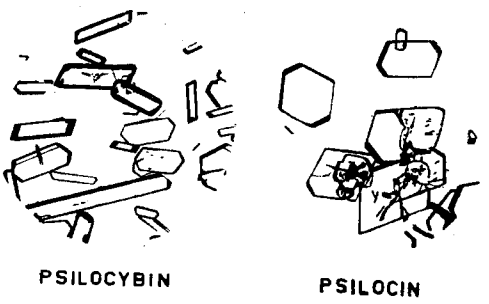


FIG. 8.

It is beyond the scope of this paper to indicate how the chemical structure of psilocybin was elucidated. These investigations have been carried out with my colleagues Drs. A. Frey, H. Ott, Th. Petrzilka and F. Troxler.

Degradation studies lead to a structural formula of Psilocybin as depicted in fig. 9. Psilocybin proved to be 4-phosphoryloxy-ω-N, N-dimethyl-tryptamine.

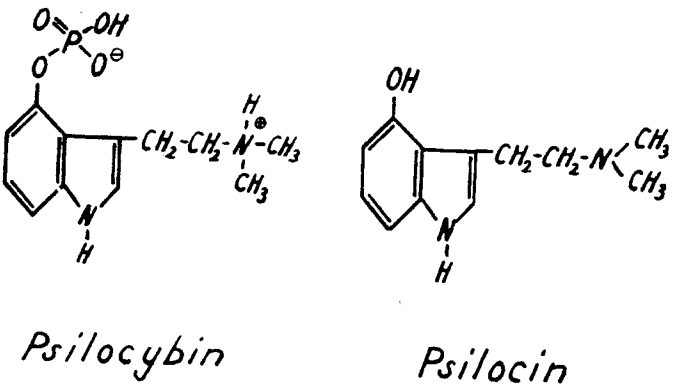


FIG. 9.

Psilocin is dephosphorylated psilocybin, *i.e.* 4-hydroxy-ω-N, N-dimethyl-tryptamine (30, 31).

Psilocybin is in two respects a chemically novel compound: it is the first natural indole compound which contains phosphorus; together with psilocin it is the only natural indole derivative with a hydroxyl group in position 4 of the indole ring.

These structural formulae were confirmed by the total synthesis of psilocin and psilocybin(30, 31). This scheme (fig. 10) demonstrates the procedure followed.

This synthesis of psilocybin which starts from o-nitrocresol comprises ten stages. Psilocybin can be produced by this way in an industrial scale. The

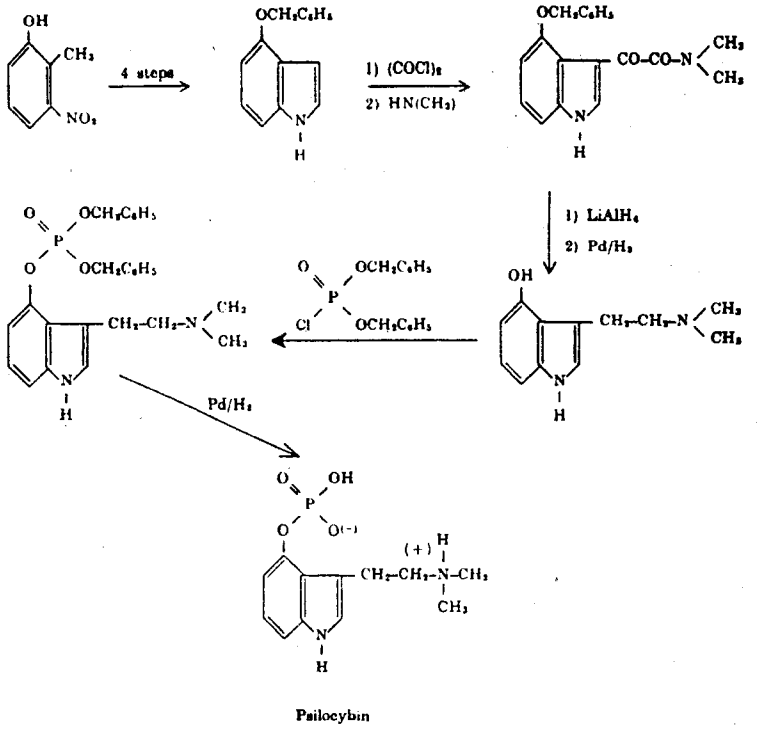


FIG. 10.

synthetic production of psilocybin is much more rational than obtaining it from the mushrooms.

It was in this way that the mystery of Teonanácatl, the magic mushroom was solved. The substance that's magic effects led the Indians to believe for centuries that a god resided in the mushroom has been elucidated with regard of its chemical structure and it can be synthesised in glass flasks. The tiny mushrooms growing in the remote mountains of Mexico are no longer needed.

The effect of psilocybin on human beings. The effects of the pure substance are identical with those of the mushrooms as depicted in the old chronicles and in the reports of personal studies by Wasson, Heim, Hofmann and others. A preliminary analysis of the effects of psilocybin was made in the University Psychiatry Clinic in Basle based on personal studies made by several members of the staff of the SANDOZ Research Laboratories (32). More detailed investigations have since been carried out by Delay and his associates in Paris (33). As a result of these and further investigations, some of which have not yet been published, the effects of psilocybin can be reported as follows: Oral doses of a few milligrams lead, after 20 to 30 minutes, to changes in the psychic sphere. The psychic symptoms produced by small doses, *i.e.* up to 4

mg., comprise effects on mood and environmental contact in that there frequently is a subjectively pleasant sensation of intellectual and bodily relaxation and divorcement from the environment. Not infrequently, these effects are associated with a pleasant feeling of physical tiredness and heaviness but sometimes they are accompanied by a feeling of extraordinary lightness, a bodily hovering. With higher doses, 6 to 12 mg., more profound psychic changes are prominent and are associated with alterations in spatial and temporal perception and with changes in the awareness of the self and the body image. Visual hypersensitivity is present and may lead to illusions and hallucinations. In the dream-like state long-forgotten memories, even some from early childhood, are often recalled.

The toxicity of psilocybin determined in animals is very slight by comparison with the doses effective in human beings. The LD 50 in the mouse is 280 mg./kg., *i.e.* psilocybin is 2·5 times less toxic than mescaline in the mouse although it is 50 times more powerful as a psychotomimetic in human beings.

That was a short report on the active principles of the magic mushrooms of Mexico.

Besides the teonanácatl and the peyotl, an other magic drug, the ololiuqui is used by certain Indian tribes of South Mexico. Since about 1 year we have started chemical investigations on ololiuqui. The following is a short preliminary report on this subject.

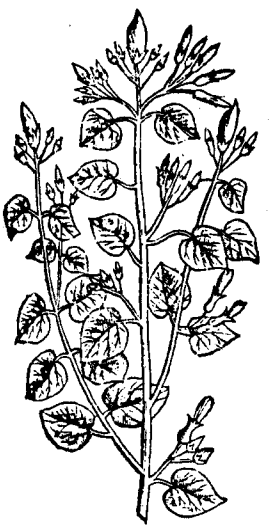
Ololiuqui

Ololiuqui is the aztec name of the seeds of certain convolvulaceous plants, which have been used since prehispanic times by the aztecs and related tribes, just as the sacred mushrooms in their religious ceremonies and for magic purposes. Ololiuqui is still used in our day by certain tribes, such as the Zapotecs, Chinantecs, Mezatecs and Mixtecs who live in the remote mountains of South Mexico in comparative isolation, little or not at all influenced by christianity (34).

One of the first description and the first illustration of ololiuqui is given by Francisco Hernandez, a Spanish physician, who between 1570-1575 carried out for Philip II extensive research on the flora and fauna of Mexico, in his "Rerum Medicarum Novae Hispaniae Thesaurus". Fig. 11 is a copy of this first account. An extract of the translation of the latin version reads as follows: "Ololiuqui, which some call Coaihuitl, which means snake plant, is a twining herb with green cordate leaves and long white flowers—formerly, when the priests wanted to commune with their gods and to receive a message from them, they ate this plant. A thousand visions and satanic hallucinations appeared to them (34)."

Two different seeds of Ololiuqui collected by a Zapotec Indian near Oaxaca, South Mexico were sent to us through the good offices of R. G. Wasson, the amateur ethnomycologist, who had participated successfully in the investigation

De OLILIVHQVI, seu planta orbicularium foliorum. Cap. XIV.



OLILIVHQVI, quam *Coaxihuitl*, seu herbam Serpentis alij vocant, volubilis herba est, folia viridia ferens, tenuia, cordis figura. caules teretes, virides, tenuesq;. flores albos, & longiusculos. semen rotundum simile Coriandro, vnde nomen. radices fibris similes. calida quarto ordine planta est. luem Gallicam curat. dolores è frigore ortos sedat. flatum, ac præter naturam tumores discutit. puluis resina mixtus pellit frigus. luxatis aut fractis offibus, & lumbis fœminarum laxis, aucto robore mirum auxiliatur in modum. Seminis etiam est vsus in medicina, quod tritum, ac deuoratum, illitumq; capiti, & fronti, cum lacte & *Chilli*, fertur morbis oculorum mederi. deuoratum verò, venerem excitat. Acri est sapore, & temperie, veluti & planta eius, impensè calida. Indorum sacrifici cum videri volebant versari cum Superis, ac responsa accipere ab eis, ea vescebátur planta, vt desiperent, milleq; phantasmata, & dæmonũ obuersãtium effigies circumspectarent. qua in re Solano maniaco Dioscoridis similis fortasse alicui videri possit.

FIG. 11.

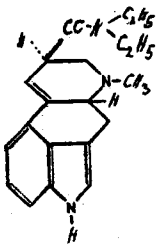
of the sacred mushrooms. One sample consisting of brown seeds, called "badoh" in the Zapotec language, proved to be identical with Rivea corymbosa (L.) Hall.f., the other sample, black seeds, called "badoh negro" could be identified botanically as Ipomoea tricolor Cav. The chemical investigation of both seeds gave the same, quite unexpected, result: The active principles proved to be lysergic acid derivatives. Three of the six components could be identified so far, namely d-lysergic acid amide, d-isolysergic acid amide and chanoclavine (35). The formulae of these compounds (see fig. 12) show the close chemical relationship of the active principles of ololiuqui with the well-known semic-synthetic LSD 25.

This result is of considerable interest from the phytochemical point of view, since lysergic acid derivatives had been found until now only in lower fungi of the genus Claviceps. It was quite unexpected to find these very special alkaloids also in higher plants such as of the family of convolvulaceae.

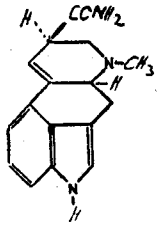
Another aspect of these findings is amusing and remarkable. Lysergic acid amide has been synthesized and investigated pharmacologically in our laboratories together with lysergic acid diethylamide (LSD) long before it was found now in nature to be one of the active principles of a magic plant.

Observations on the chemical structure of psychotomimetics

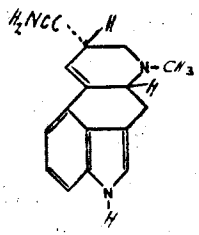
A review of the structural formulae of natural psychotomimetics as depicted on fig. 12 shows that, with the exception of the non-nitrogenous active principle



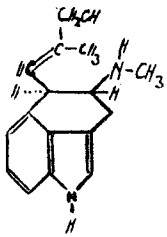
LSD



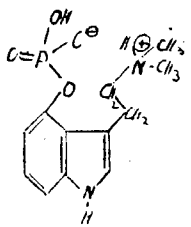
Lysergsäure-amid



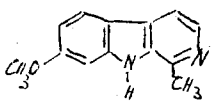
Isolysergsäure-amid



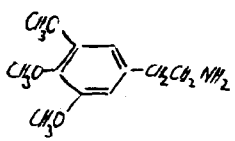
Chanoclavin



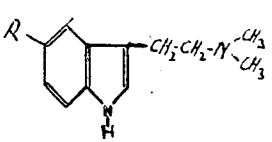
Psilocybin



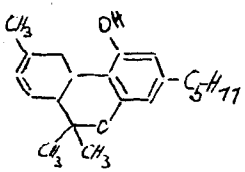
Harmin



Mescalin



Bufotenin (R=OH)
Dimethyl-tryptamin (R=H)



Tetrahydro-cannabinol

Fig. 12

of hashish and mescaline, they are all indole derivatives or, more accurately, tryptamine derivatives. But even mescaline exhibits a certain structural relationship to the indoles. It is not impossible that mescaline may to a small extent be converted to an indole derivative in the organism and that this actually exerts the effects attributed to mescaline.

It is hardly only a coincidence that most psychotomimetics are chemically

related to the neurohumour serotonin. Serotonin (5-hydroxytryptamine) is one of the products on which biochemical research is at present concentrated. It is widely distributed in warm-blooded animals. It accumulates in the brain where it plays a role in the chemistry of central nervous processes (36). *The structural relationship of the psychotomimetics with the brain factor serotonin, which all are tryptamine derivatives, suggests that certain indole structures are of importance in the biochemistry of psychic functions.* The biochemical investigations of the connections between endogenous indole metabolism and psychotomimetics with an indole structure may be a rewarding topic for psychopharmacological research.

Within the group of psychotomimetics which contain a tryptamine residue an especially close structural relationship can be seen between LSD and psilocybin in that both compounds are indole derivatives with substitutions in position 4. The active principles from the Mexican magic mushroom, psilocybin and psilocin, and the active principles from ergot of rye, the ergot alkaloids, from which LSD is derived, are the only natural indole compounds with substitution in position 4. Further research will show to what extent this common structural feature determines the highly specific psychotomimetic activity of LSD and psilocybin.

The use of psychotomimetics in experimental and practical psychiatry

The psychotomimetic agents have proved to be valuable tools in experimental neurology and psychiatry. The resemblance borne by the effects of psychotomimetic substances to the symptoms of certain mental disorders led to the term "model psychosis" being coined. Such model psychoses are of value in the experimental study of the biochemical processes involved in mental disorders. It is basically since the discovery of LSD that considerable progress has been made in this direction.

Whereas the psychotomimetics have for some time been generally recognised to be valuable aids in experimental psychiatry it is only in recent years that they have been more widely employed in therapy. Promising results have been obtained with their use as drug aids in psychotherapy. The literature already contains a considerable number of papers which stress the value of LSD as a drug aid to psychotherapy. Equally good results have also been reported with the use of psilocybin (37).

What is the basis for use of these agents in psychotherapy? Primarily, two effects are of value:

Firstly, their ability to release the patient from his autistic fixation and isolation by shattering and transforming his customary setting. As a result, the patient can re-establish rapport with the therapist.

Secondly, these drugs reactivate forgotten or repressed memories. Even experiences of very early childhood may be reactivated. This is of major

importance for the success of psychotherapy, particularly when the experiences involved are those which have led to psychic trauma.

The discovery of highly active psychotomimetics such as LSD and of the tranquillisers such as reserpine, chlorpromazine, etc., offers new possibilities of pharmacological influence on psychic spheres and has led to the term "psychopharmacology". The use of psychotomimetics and of tranquillizers in therapy is due to their contrasting effects. Whereas the tranquillizers, as their name suggests, elicit sedation and conceal conflicts, the psychotomimetics activate and reveal psychic trauma. In this way the conditions predisposing to real recovery by psychotherapy are created.

Agents such as the psychotomimetics with their profound and unforeseeable effects may not be taken by patients without medical supervision. In most cases that would be useless, in others it might even prove dangerous. But in the hands of the skilled, capable psychotherapist, these substances are new drug aids which facilitate the task of the doctor in his objective recognition of the conflicts involved and subjectively enable the patient to attain self-awareness and gain insight into his disease. It is in this sense that this new agents deserve the term "mental drugs".

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