

PSYCHOTOMIMETIC SUBSTANCES

A. HOFMANN

(Research Laboratories, Sandoz Ltd., Basle, Switzerland)

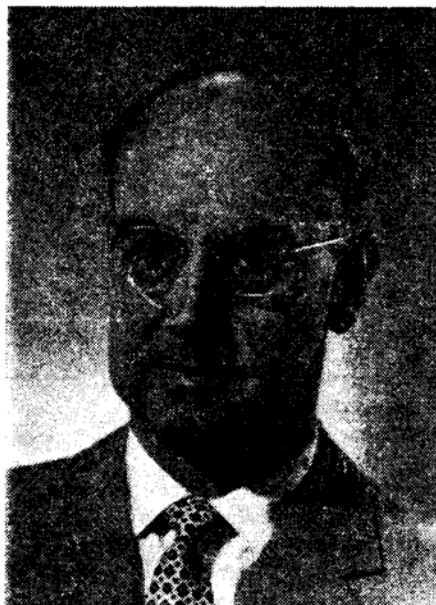
Recent years have been marked by the growth of a new and increasingly important branch of medical and pharmacological research, psychopharmacology as it has been termed. As the name would suggest it relates to influencing psychic processes and states by the use of drugs. Admittedly the treatment of mental diseases with medicaments is not new. In the very beginnings of medical history there is reference to drugs which were administered to counteract psychic disorders such as insomnia, agitation, etc. Mention need only be made of *Rauwolfia serpentina* (sarpagandha) recommended for such purposes in the ancient Ayurvedic medicine. Other noteworthy forerunners of a specific type of psychotropic drugs which are to be the object of special discussion in the present paper are the primeval and until lately mystery-en-shrouded magic drugs which were taken less for therapeutic purposes than as part of religious rites and to induce clairvoyance. Such drugs are "peyotl", "teonanacatl" and "ololiuqui" which occupied an important place in the old Indian cultures of Central America in particular. It is only recently, however, that substances with a highly specific influence on the human psyche have been discovered, submitted to extensive scientific, pharmacological and clinical investigation, and introduced into psychotherapy.

Among the large number of drugs which influence the psyche in one way or another and which collectively may be termed psychotropic substances, a variety of groups can be distinguished according to the quality of their action. The psychotropic drugs may broadly be classified as follows:

I. *Calmatives*: neuroleptics (chlorpromazine, reserpine, etc.), tranquillizers and sedatives (promethazine, meprobamate, etc.).

II. *Hypnotics*: barbiturates, glutarimides, etc.

III. *Stimulants and antidepressants*: sympathomimetic amines, (amphetamine,



Born on January 11, 1906, at Baden (Switzerland).

1925-1929: Course in chemistry at the University of Zürich.

1928-1929: Assistant to Professor Paul Karrer, Nobel Laureate.

1929: Doctorate at the University of Zürich.

Since 1929: Research Chemist in the Research Laboratories for Pharmaceutical Chemistry Sandoz Ltd., Basle, Switzerland, first working as assistant to Professor A. Stoll, then as a group leader and for the last 7 years as director of research of the department for natural products. Main fields of activity: Investigations on the cardioactive glycosides of squill (*Scilla maritima*), on the alkaloids of ergot, on the alkaloids of *Rauwolfia*, on Mexican magic plants.

1960: Visit to India, lectures at Calcutta and Bombay.

etc.), monoaminoxidase inhibitors (iproniazid, etc.), thymoleptics (imipramine, etc.).

IV. *Analgesics and euphorants*: morphine, heroin, pethidine, aminopyrine, etc.

V. *Intoxicants*: alcohol, ether, etc.

VI. *Psychotomimetics*: mescaline, lysergic acid diethylamide, psilocybin, etc.

The latter group of substances, the psychotomimetics, to which this paper is devoted, may be regarded as psychotropic drugs "par excellence" for they are distinguished from the other classes in that in the appropriate dose they act specifically on the psyche without producing any serious disturbances of the autonomic nervous system of bodily functions, and in that their psychic effects are very profound and impressive. Experience of the environment, its forms and colours, as well as a person's own mental and corporal personality are altered by the psychotomimetics. Not only space, however, but also time, the other fundamental category of our existence, is experienced under the influence of psychotomimetics otherwise than in the normal state. Frequently the sense of time seems altogether to have vanished. Yet all these changes in perspective are experienced with undiminished awareness. Fully conscious, the subject is transported into other worlds, dream worlds as it were, but worlds which are experienced quite realistically, generally in fact even more realistically, intensely and meaningfully than the normal everyday world. The senses, especially the sense of sight, are abnormally sensitized; objects appear to be in greater relief, colours more lustrous. With rather high doses this stimulation of the senses is apt to produce visions and hallucinations. It would appear that the control mechanisms in the nervous system, which normally exercise a limiting function, are inactivated and that consequently from the external world the entire store of cosmic experience, and from within, from the subconscious, a vast flow of sensations, images and recollections penetrate the conscious mind. It is not surprising that in its intensity, vehemence and unfamiliarity this experience was frequently interpreted as a religious revelation. The most important currently known psychotomimetics originate in fact from magic plants of antiquity, or else are chemically related to them, and from drugs which were, and, as will subsequently be described in more detail, still are used today for ritualistic purposes.

To characterize the complex, typical reaction pattern of these substances a

variety of terms such as hallucinogens, fantasy-inducing drugs, psychodysleptics and psychotomimetics have been proposed. The term hallucinogens is inappropriate for the simple reason that true hallucinations by no means always occur. The other terms, too, denote only part of the reaction pattern. In this paper the term psychotomimetics has been chosen because many symptoms arising in man after the ingestion of these substances are indicative of the state associated with certain psychoses, i.e. they simulate a type of psychosis. Closer analysis and a comparison with true psychoses of the transient "model psychoses" elicited by psychotomimetics, however, has shown that notwithstanding the many similarities the differences are so great that the true and induced psychoses cannot be equated^{1, 2}.

In medicine and above all in psychiatry the discovery of the psychotomimetically active drugs has roused unusually strong curiosity. At first sight this may seem strange since — it may be wondered — what is the use of substances which produce a kind of mental illness? Medical science is interested in the psychotomimetics for the following reasons:

- (a) The experimental psychoses induced in healthy and in mentally ill persons by psychotomimetics make it possible to study the individual psychotic symptoms and their associated biochemical processes;
- (b) The psychiatrist is able to experience for himself in an experimental psychosis the symptoms and feelings of a patient during an attack;
- (c) Drugs can be tested on the model psychosis for their antipsychotic action;
- (d) The psychic relaxation and the activation of the repressed subconscious which can be achieved by the use of psychotomimetics facilitate psychoanalysis and improve the prospects of successful psychotherapeutic treatment;
- (e) The discovery of substances which in trace amounts are capable of inducing schizophrenia-like states has stimulated research to discover biochemical factors in psychoses

without any underlying organic cause. The discovery of a material agent as the cause of mental illnesses would open up fresh scope for their chemotherapeutic treatment.

The separate psychotomimetically active substances and groups of substances will be discussed below in the order of their activity. Only psychotomimetics in the narrower sense, i.e. substances conforming completely to the reaction pattern described at the outset, will be considered. Substances for which psychotomimetic effects are only part of the spectrum of activity will receive merely cursory mention. Table 1 shows the psychotomimetic drugs in the narrower sense and their effective doses. It will be noted that almost all these drugs are of vegetable origin.

d-Lysergic acid diethylamide
(LSD-25: "Delysid"*)

d-Lysergic acid diethylamide (LSD-25)

* Registered Trade Mark.

is by far the most active and the most specific psychotomimetic known. The effective oral dose in human beings is 0.00002-0.00006 g. Thus it is about 10,000 times more active than mescaline, the well-known alkaloid from peyotl, and about 100 times more active than psilocybin and psilocine—the active principles of the magic Mexican mushrooms. This high potency of LSD is not just a curiosity: it is also of major pharmacological interest. This extremely high potency indicates that LSD acts on very profound structures. It probably acts on a central site of regulation. The importance of LSD in pharmacological and psychiatric research may be derived from the fact that already more than 1200 scientific publications have appeared on this subject.

Lysergic diethylamide is a semi-synthetic compound. The lysergic acid residue is the basis of the natural ergot alkaloids, from which lysergic acid can be prepared by hydrolysis. Ergot is the product of a fungus which grows on vari-

TABLE 1
Psychotomimetics

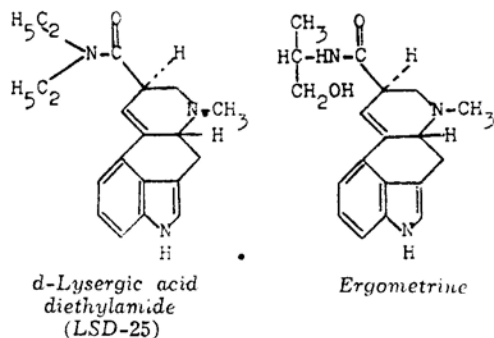
Source	Active principles
Synthetic	d-lysergic acid diethylamide (LSD 25) (active dose: 0.00002-0.00006 g)
Convolvulaceae: <i>Rivea corymbosa</i> "ololiuqui" <i>Ipomoea tricolor</i>	d-lysergic acid amide, d-isolysergic amide, elymoclavine and related compounds (active doses: 0.061-0.002 g)
Mushrooms: <i>Psilocybe</i> spec. "teo-nanacatl" <i>Stropharia cubensis</i> <i>Conocybe</i> spec.	psilocybin, psilocin (active dose: 0.006-0.015 g)
Mimosaceae: <i>Piptadenia peregrina</i> "cohoba" <i>Piptadenia macrocarpa</i>	N,N-dimethyltryptamine, bufotenin (active doses: 0.05-0.07 g)
Malpighiaceae: <i>Banisteriopsis</i> spec. "caapi" <i>Tetrapteryx</i> spec. "yago" "ayahuasca"	harmine, harmaline (active dose: 0.1-0.4 g)
Cactaceae: <i>Anhalonium lewinii</i> "peyotl"	mescaline (active dose: 0.3-0.5 g)

ous kinds of gramineae, especially on rye (Fig. 1).



Fig. 1
Ergot of rye

LSD was first prepared in the course of the investigations on the partial synthesis of ergometrine (formula II) a natural ergot alkaloid, and similar compounds in 1938, but its synthesis was published only later³. Since lysergic acid itself was synthesized in 1954⁴ LSD is now available by total synthesis.



It was not until 1943 that A. Hofmann⁵ in the Sandoz Research Laboratories at

Basle made the observation that profound psychotomimetic effects occur after ingestion of this compound⁶. The first systematic study of the clinical effects of LSD was subsequently carried out by W. A. Stoll in the University Psychiatric Clinic in Zürich⁷.

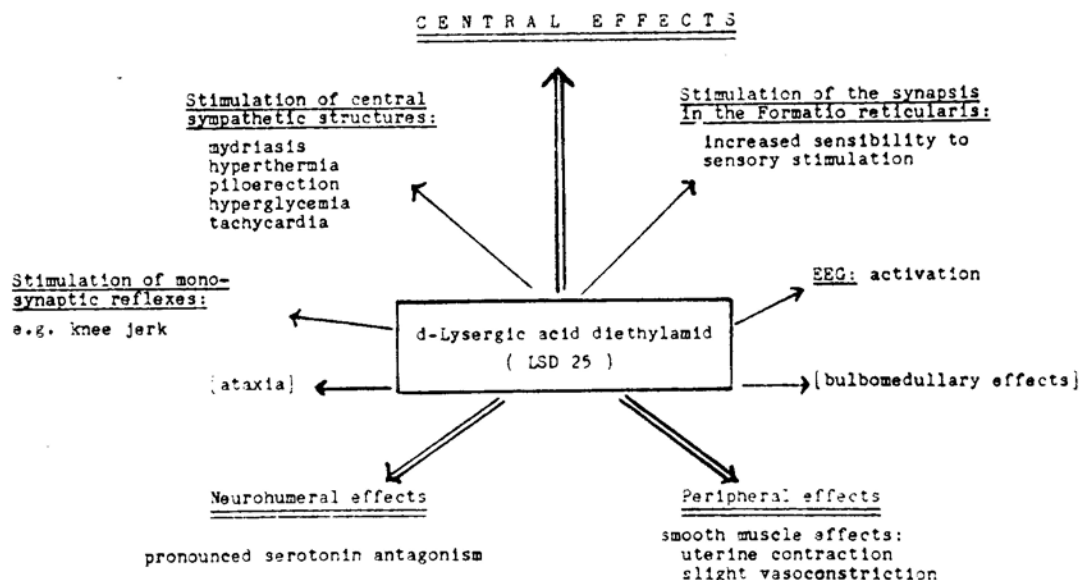
The following survey summarizes the main points of the pharmacological aspects of LSD as established by different studies, mainly in the Pharmacological Laboratories of Sandoz Ltd, Basle (Switzerland) under the leadership of Professor E. Rothlin and his successor Dr. A. Cerletti.

The distribution and fate of LSD in the body have been established on mice with the aid of 14-C-labelled LSD^{8,9}. Intravenously administered LSD disappears rapidly from the blood and is then found in different organs. Surprisingly only a small portion of the total dose administered reaches the brain, and even after intracerebral injection LSD disappears from the brain as rapidly as after intravenous administration. It could therefore be assumed that LSD is mainly responsible for triggering the central reaction.

The complexity of the pharmacological actions of LSD is shown by scheme 1¹⁰.

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, namely 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. In order to gain an insight into the relationship between the spectrum of pharmacological actions of LSD and its psychic activity we modified the molecule of LSD and then compared the pharmacological effects of various derivatives with their psychic effects in human beings^{11, 12, 13}. From these investigations it could be concluded that there exists within the group of LSD and related compounds a relationship between psychotomimetic activity on



Scheme 1

the one hand and the pharmacological effects which result from stimulation of central sympathetic structures (mydriasis, hyperthermia, hyperglycaemia, etc.) on the other.

When LSD was discovered to be a potent antagonist of serotonin, the hypothesis was put forward 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. But in the course of the above-mentioned investigations we found derivatives, e.g. 2-bromo-LSD and 1-methyl-2-bromo-LSD, which 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 and therefore that hypothesis cannot be correct.

The active principles of "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 in the same way as the sacred mushroom, "teonanacatl" and the cactus "peyotl" in their religious ceremonies and for magic purposes. Ololiuqui is currently still used

by certain tribes, such as the Zapotecs, Chinantecs, Mazatecs and Mixtecs who live in the remote mountains of South Mexico in comparative isolation, little or not at all influenced by Christianity. An excellent review of the historical, botanical and ethnological aspects of ololiuqui is given by R. E. Schultes in his monograph: "A Contribution to our knowledge of *Rivea corymbosa*. The narcotic ololiuqui of the Aztecs"¹¹.

The active principles of ololiuqui have been isolated only very recently in the Research Laboratories for Pharmaceutical Chemistry, Sandoz Ltd. Basle, in the same laboratory where 20 years ago lysergic acid diethylamide (LSD) was synthesized and its extremely high psychotomimetic potency discovered. It was therefore a great surprise to find lysergic acid amide and other lysergic acid derivatives to be the psychotropic principles of an ancient magic plant, such as ololiuqui^{15, 16}.

Two different seeds are investigated: brown seeds, the original ololiuqui, which botanically are the seeds of *Rivea corymbosa* (L.) Hall. f. and black seeds, which were identified as those of *Ipomoea tricolor* Cav. The brown seeds are called "badoh" in the Zapotec language and the black ones "badoh negro". Fig. 2 shows

the flowering plants which have been grown from these seeds.

"Badoh" and "badoh negro" contain an alkaloid mixture of nearly the same composition. (*vide* Table 2).

d-Lysergic acid amide is the main con-

stituent in both plants. Lysergol, which is found in *Rivea* seeds, is replaced by ergometrine, the well known uterotonic principle of ergot, in the seeds of *Ipomoea*¹⁷. The alkaloid content in *Ipomoea* is higher than in *Rivea* and cor-



Fig. 2

Rivea corymbosa (L.) Hall

Ipomoea tricolor Cav.

TABLE 2

Alkaloids of the seeds of *Rivea corymbosa* (L.) Hall. f. and *Ipomoea tricolor* Cav.

Thin layer chromatogram (figure 4)		<i>Rivea corymbosa</i> (ololiuqui, badoh)	<i>Ipomoea tricolor</i> (badoh negro)
A	d-Lysergic acid amide (ergine)	0.0065 %	0.035 %
B	d-Isolysergic acid amide (isoergine)	0.0020 %	0.005 %
C	Chanoclavine	0.0005 %	0.095 %
D	Elymoclavine	0.0005 %	0.095 %
	Lysergol	0.0005 %	—
	Ergometrine	—	0.095 %
Total alkaloid content (colorimetrically determined calculated on a mol. weight of 300)		0.012 %	0.06 %

respondingly the priest-doctors of the Mexican Indians use a much smaller quantity of badoh negro than of badoh.

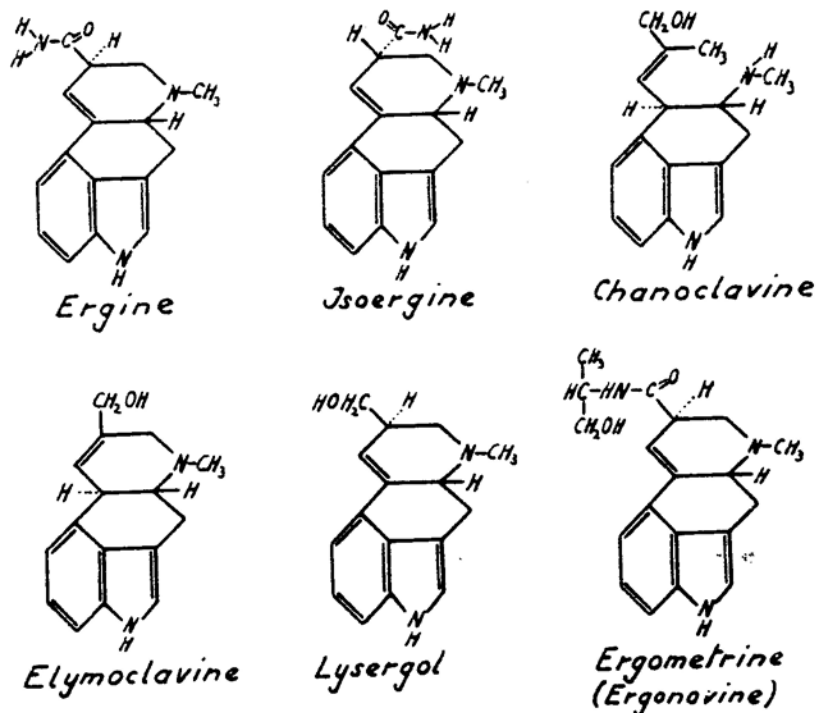
Scheme 2 shows the structural formulae of the 6 ololiuqui alkaloids which were all known hitherto as constituents of ergot. The occurrence of ergot alkaloids in higher plants such as of the family of *Convolvulaceae* is of considerable interest from the phytochemical point of view, since lysergic acid derivatives have so far been found only in lower fungi of the genus *Claviceps*, *Aspergillus* and *Rhizopus*.

It is probable that the psychotomimetic activity of ololiuqui is due mainly to the content of d-lysergic acid amide (ergine), d-isolysergic acid amide (isoergine), elymoclavine and lysergol. The pharmacological properties of ergine were studied in the Sandoz Laboratories long before this compound was discovered in ololiuqui and from personal experimentation it was known that doses of 1 to 2 mg. ergine produce psychotomimetic effects with a pronounced narcotic component. This was later confirmed by H. Solms^{18, 19}. Elymoclavine and lysergol were found to elicit in animals a syndrome of central

sympathetic excitation²⁰. Chanoclavine and ergometrine do not seem to have psychotomimetic properties when administered in low doses. Clinical investigations are in progress to compare the psychic activity of the total alkaloidal fraction of ololiuqui with that of the individual pure alkaloids.

Psilocybin and psilocin, the psychotropic principles of the sacred mushrooms of Mexico

"Teonanacatl" the "sacred mushrooms" played an important part on the pre-Columbian cultures of Central America and are still used today by the priest-doctors and soothsayers at religious ceremonies in remote regions of South America. The existence of a mushroom cult was re-discovered only within the last ten years by the amateur investigators R. Gordon Wasson and his wife Valentina Pavlovna²¹. The botanical identification of the sacred mushrooms has been carried out mainly by the well-known mycologist R. Heim of Paris²². These were foliate mushrooms (Agaricales), almost of the genus *Psilocybe*, one *Conocybe* spec. and *Stropharia cubensis*.



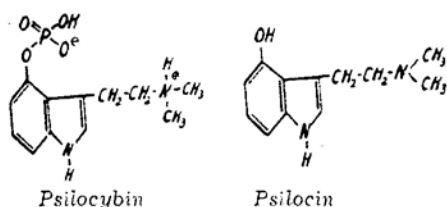
Scheme 2

The isolation, chemical characterization and finally the synthesis of the active principles was realized in the Sandoz Research Laboratories at Basle by A. Hofmann and colleagues²³. The psychotropic agents which could be isolated first from *Psilocybe mexicana* Heim (Fig. 3)



Fig. 3
Psilocybe mexicana Heim

were named psilocybin and psilocin. Psilocybin is the main component (*vide* formulae). These structural formulae were confirmed by total synthesis. The synthetic production of psilocybin is now much more rational than obtaining it from the mushrooms.



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

The effects of psilocybin on human be-

ings 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. 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. With higher doses, 5 to 15 mg., more profound psychic changes are prominent and are associated with modifications 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^{24, 25, 26, 27}.

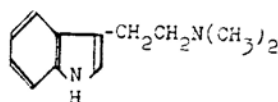
The pharmacological investigation of psilocybin showed that it does not elicit typical effects on isolated organs, with the exception of a pronounced antagonism to serotonin. Tested on the whole animal it produces a syndrome of excitation (mydriasis, piloerection, hyperthermia, etc.) akin to that caused by LSD, which may be explained by central stimulation of sympathetic structures²⁸.

In order to investigate the structure-activity relationship many derivatives of psilocybin were synthesized²⁹ and pharmacologically tested³⁰. The 4-hydroxy-indole derivatives psilocybin and psilocin showed a characteristic stimulatory effect on the patellar reflex of spinal cats, which is limited to 4-substituted derivatives of dimethyltryptamine. In this context it is remarkable that LSD and the other lysergic acid derivatives also contain in their molecules the structural elements of a tryptamine radical with a substituent in position 4.

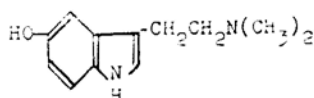
Psychotomimetic tryptamine derivatives in "cohoba"

The seeds and leaves of the mimosacea, *Piptadenia peregrina* Benth. 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^{31, 32}.

The effects of dimethyltryptamine given by the intravenous or intramuscular route have been studied in human beings. Doses of 50 to 70 mg. produced mental effects including anxiety, hallucinations and perceptual distortions. The autonomic effects consisted of pupillary dilatation, increase in systolic and diastolic blood pressure and a decrease in the knee-jerk threshold^{32, 33}. These effects appeared within 15-30 minutes and subsided within 1-2 hours.



Dimethyltryptamine



Bufotenin

Bufotenin, which was first discovered in the skin glands of toads³⁴, has a similar activity to dimethyltryptamine³⁵ when administered by intravenous injection. Other investigators found no hallucinogenic activity after i.v. injections up to 20 mg.³⁶ In personal experiments by the writer doses up to 50 mg. bufotenin taken perorally did not produce any psychic effects¹⁷.

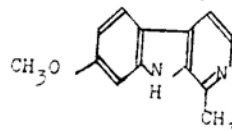
Very recently N-methyltryptamine and 5-methoxy-N, N-dimethyltryptamine were also found to occur in *Piptadenia peregrina* but there are no reports concerning the pharmacological properties³⁸.

It could be that the special application of these substances in the form of a snuff powder modifies in some way their psychic activity.

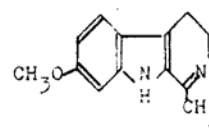
Harmine and harmaline, active principles in South American creepers

A narcotic drink which is known in the Western Amazonian regions as "caapi" (Brazil and Colombia), "yagé" (Colombia) and "ayahuasca" (Ecuador, Peru and Bolivia) is made basically from the same or closely related plants of the family *Malpighiaceae*, i.e. *Banisteriopsis caapi*, *B. inebrians*, *B. rusbyana*, *B. quitensis* and *Tetrapteryx methystica*³⁹. The

main active principle, which has been given the names banisterine, telepathine and yagein, proved to be identical with the alkaloid harmine. Harmine had been isolated first from *Peganum harmala*, a plant which grows on the Asian steppes⁴⁰. The name "telepathine" instead of harmine indicates the use of the drug for mystical and telepathic purposes. Harmaline, which is found as a minor alkaloid in addition to harmine, possesses basically the same activity.



Harmine



Harmaline

Intravenous injection of harmine (150-200 mg.) produced hallucinations. When applied perorally higher doses (300-400 mg.) were needed to elicit psychic symptoms⁴¹. The psychic action is accompanied by disagreeable autonomic effects such as nausea, ataxia, etc. Small doses, e.g. 25-75 mg. s.c. produced euphoria⁴². The stimulant action of harmine may be connected with its inhibitory effects on monoamine oxidase⁴³. This enzyme is responsible for the degradation of physiologically important amines and its inhibi-



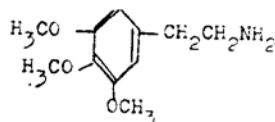
Fig. 4
Lophophora williamsii (Lem.) Coulter

tion leads to accumulation of epinephrine and norepinephrine in the organism.

Mescaline, the hallucinogen from peyotl

The cactus *Anhalonium lewinii* (syn. *Lophophora williamsii*) (Fig. 4) which grows in the northern regions of Mexico is known by its Aztec name "peyotl". In common with the use of the sacred mushroom *teo-nanácatl* and of *ololiuqui* as magic drugs in religious ceremonies and in medicinal practices, that of peyotl dates back to pre-Columbian times. In the 19th century the peyotl cult spread north from Mexico and peyotl became the central religious drug in a Christian institution of the North-American Indians, the Native American Church⁴⁴.

The main active principle of *Anhalonium lewinii*, of which the dried slices are also called "mescal buttons", is mescaline, an alkaloid first isolated by A. Heffter in 1896⁴⁵. The chemical structure of mescaline was elucidated by E. Späth⁴⁶ who also succeeded in synthesizing this alkaloid.



Mescaline

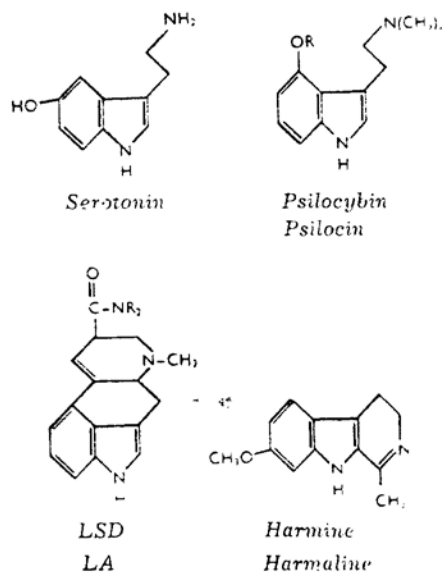
The first pharmacological studies with peyotl were carried out by L. Lewin⁴⁷. Many reports on self-experimentation with peyotl or mescaline have been published^{48, 49, 50, 51}. Mescaline intoxication has been brilliantly described by Aldous Huxley in his books "The Doors of Perception" and "Heaven and Hell"⁵². A survey on peyotl studies during the last 20 years has been published by W. LaBarre⁵³.

Of particular interest are the high doses of mescaline which are necessary to elicit psychic effects, i.e. 0.3 to 0.5 g. Soon after the drug has been taken, unpleasant autonomic symptoms are experienced i.e. nausea, tremor and perspiring. 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.

Common features in the chemical structures of the psychotomimetics

A review of the structural formulae of the psychotomimetics which have been discussed in this article shows that, with the exception of mescaline, all are indole derivatives. They all contain the tryptamine radical. Tryptamine is closely related to the essential amino acid tryptophan which is found everywhere in the organism as a component of proteins and peptides. The fact that all the psychotomimetics which contain the structural elements of tryptamine are chemically connected with the neurohumoral factor serotonin, which is also a tryptamine derivative, i.e. 5-hydroxytryptamine, may be of quite profound biochemical significance. Serotonin plays an important role in present biochemical research⁵⁴.

Serotonin is widely distributed in warm-blooded animals. It accumulates in the brain, especially in the midbrain and in the hypothalamus, which is known to be the site of the structures responsible for central sympathetic regulations. It has been shown that the psychotomimetic activity of LSD and of psilocybin is associated with the syndrome of a central sympathetic stimulation. It seems, therefore, that certain indole-tryptamine structures which are found in the psychotomimetics as well as in neurohumoral factors such as serotonin, may be of im-



portance in the biochemistry of psychic functions. The biochemical investigation of the relationships between endogenous indole metabolism and psychotomimetics with an indole structure is a rewarding facet of psychopharmacological research.

The use of psychotomimetics in psychotherapy

Whereas the psychotomimetics have for some time been generally recognized as valuable tools in experimental neurology and psychiatry, especially for the production of "model psychoses" which permitted the biochemical processes involved in mental disorders to be studied, 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. There are mainly two effects of the psychotomimetics which are of value:

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 achieve a more satisfactory relationship with the therapist.

Following the general psychic activation elicited by these drugs the resistance of the ego disappears and forgotten or repressed memories may be reactivated. Even experiences of the very early childhood are often remembered. This is of major importance for the success of psychotherapy, particularly when the experiences involved are those which have led to a psychic trauma. This kind of abreaction, which often takes place in a dramatic manner under the influence of psychotomimetics, has been named "psycholysis" by H. Leuner⁵⁵. The psychotherapeutic treatment can often be shortened when assisted by the use of these psychotomimetic drugs.

Although some similar experiments have been carried out earlier with mescaline, psycholytic treatment became more general and more successful only after the discovery of LSD and psilocybin. Pioneers of the use of LSD as a drug-aid in psychotherapy in USA were A. K. Busch and W. C. Johnson⁵⁶, H. Abramson⁵⁷ and C. Savage⁵⁸, in England R. A. Sandison⁵⁹, in Germany W. Frederking⁶⁰ and H. Leuner⁶¹. More than 50 publications concerning the successful use of

LSD and psilocybin as drug-aids in psychotherapy have appeared since. Successful treatment was possible in cases of severe character neuroses, psychopathic disorders, chronic neuroses, including those previously regarded as incurable, alcoholism and sexual perversions.

Summarizing, it is true to say that the investigation of ancient magic and religious plants by means of modern scientific methods led to the discovery of potent drugs with a specific action on the psyche. These psychotomimetic substances are very useful tools in experimental psychiatry and valuable drugs in psychotherapy.

REFERENCES

1. Sandison, R. A., *Proceedings of the 1st International Congress of Neuro-Pharmacology, Rome, 1958*. In: *Neuro-Psychopharmacology*. Ed. by P. B. Bradley, P. Deniker and C. Radouco-Thomas, Elsevier Publ. Co., Amsterdam-London-New York-Princeton, 1959, p. 176.
2. de Boor, W. *Pharmakologie und Psychopathologie*. Springer Verlag, 1956, pp. 35-36.
3. Stoll, A. and Hofmann, A. *Helv. chim. Acta*, 1943, 26, 944.
4. Kornfeld, E. C., Fornfeldt, E. J., Kline, G. B., Mann, M. J., Jones R. G. and Woodward, R. B. *J. Am. Chem. Soc.* 1954, 76, 5256.
5. Hofmann, A. *Triangle, The Sandoz Journal of Medical Science*, 1955, 2, 117.
6. Hofmann, A. *Acta Physiol. Pharmacol. Neerlandica*, 1959, 8, 240.
7. Stoll, W. A. *Schweiz. Arch. Neurol. Psychiatr.*, 1947, 60, 279.
8. Stoll, A., Rothlin, E., Rutschmann, J. and Schalch, W. R. *Experientia (Basel)*, 1955, 11, 396.
9. Boyd, E. S. *Arch. Intern. Pharmacodyn.* 1959, 120, 292.
10. Rothlin, E. and Cerletti, A. *Ann. N. Y. Acad. Sci.*, 1957, 66, 668.
11. Stoll, A. and Hofmann, A. *Helv. Chim. Acta*, 1955, 38, 421.
12. Troxler, F. and Hofmann, A. *Helv. chim. Acta*, 1957, 40, 1706, 1721, 2160.
13. Cerletti, A. *Proceedings of the 1st International Congress of Neuro-Pharmacology, Rome, 1958*. In: *Neuro-Psychopharmacology*. Ed. by: P. B. Bradley, P. Deniker and C. Radouco-Thomas, Elsevier Publ. Co., Amsterdam-London-New York-Princeton, 1959, p. 117.
14. Schultes, R. E. *A Contribution to our knowledge of Rivea corymbosa. The narcotic otloliqui of the Aztecs*. Botanical Museum of Harvard University, Cambridge (Mass.), 1941.
15. Hofmann, A. and Tscherter, H. *Experientia (Basel)* 1960, 16, 414.

16. Hofmann, A. *Planta Medica*, 1961, 9, 354.
17. Hofmann, A. Unpublished results.
18. Solms, H. *Praxis (Bern)*, 1956, 45, 746.
19. Solms, H. *J. clin. exp. Psychopath. and Quart. Rev. Psychiat.*, 1956, 17, 429.
20. Yui, T. and Takeo, T. *Jap. J. Pharmacol.*, 1958, 7, 157.
21. Wasson, V. P. and Wasson, R. G.: *Mushrooms, Russia and History*, Pantheon Books, New York, 1957.
22. Heim, R. and Wasson, R. G. *Les Champignons hallucinogènes du Mexique*, Ed. du Muséum National d'Histoire Naturelle, Paris, 1958.
23. Hofmann, A., Heim, R., Brack, A., Kobel, H., Frey, A., Ott, H., Petrzilka, Th. and Troxler, F. *Helv. chim. Acta.*, 1959, 42, 1557.
24. Gnirss, F. *Schweiz. Arch. Neurol. Psychiat.*, 1959, 84, 346.
25. Rümmele, W. *Schweiz. Arch. Neurol. Psychiat.*, 1959, 84, 348.
26. Delay, J., Pichot, P., Lempérière, T. and Nicolas-Charles, P. *Compt. Rend. hebdomad. Séances Acad. Sci.*, 1958, 247, 1235.
27. Delay, J., Pichot, P., Lempérière, T., Nicolas-Charles, P. and Quetin, A. M. *Ann. méd.-psychol.*, 1959, 117, 891.
28. Weidmann, H., Taeschler, M. and Konzett, H. *Experientia (Basel)*, 1958, 14, 378.
29. Troxler, F., Seemann, F. and Hofmann, A. *Helv. chim. Acta.*, 1959, 42, 2079.
30. Weidmann, H. and Cerletti, A. *Helv. Physiol. Acta.*, 1960, 18, 174.
31. Stromberg, V. L. *J. Am. Chem. Soc.*, 1954, 76, 1707.
32. Szara, St. *Experientia (Basel)*, 1956, 12, 441; *ibid.*, 1961, 17, 76.
33. Rosenberg, D. E., Isbell, H. and Miner, E. J. *Psychopharmacologia*, 1963, 4, 39.
34. Wieland, H., Hesse, G. and Mittasch, H. *Ber. deutsch. chem. Ges.*, 1931, 64, 2099.
35. Fabling, H. D. and Hawkins, J. R. *Science*, 1956, 123, 886.
36. Turner, W. J. and Merlis, S. *Arch. of Neurol. and Psych.*, 1959, 81, 121.
37. Fish, M. S., Johnson, N. M. and Horning, E. C. *J. Am. Chem. Soc.*, 1955, 77, 5892.
38. Legler, K. and Tschesche, R. *Naturwiss.*, 1963, 50, 94.
39. Schultes, R. E. *Botanical Leaflets*, Harvard University, 1957, 18, 1-56.
40. Henry, Th. A. *The Plant Alkaloids*, J. and A. Churchill Ltd., London, 1949, p. 488.
41. Pennes, H. H. and Hoch, P. H. *Am. J. Psychiat.*, 1957, 113, 887.
42. Lewin, L. *Arch. exp. Path. Pharmacol.*, 1928, 129, 133.
43. Pletscher, A., Besendorf, H., Bachtold, H. P. and Geigy, K. F. *Helv. Physiol. Acta.*, 1959, 17, 202.
44. Slotkin, J. S. *Trans. Am. Phil. Soc.*, 1952, 42, 563.
45. Heffter, A. *Ber. deutsch. chem. Ges.*, 1896, 29, 216.
46. Späth, E. *Monatsh. Chemie.*, 1919, 40, 129.
47. Lewin, L. *Arch. exp. Path. Pharmacol.*, 1888, 24, 401; *ibid.*, 1894, 34, 374.
48. Prentiss, D. W. and Morgan, F. P. *Therap. Gazette*, 1895, 19, 577.
49. Mitchell, S. W. *Brit. Med. J.*, 1896, ii, 1625.
50. Ellis, H. *Lancet*, 1897, i, 1540; *Popular Science Monthly (N.Y.)*, 1902, 61, 52.
51. Beringer, K. *Der Meskalin-Rausch*, Springer-Verlag, Berlin, 1927.
52. Hudley, A. *The Doors of Perception*, Chatto and Windus, London, 1954; *Heaven and Hell*, *ibid.*, 1956.
53. La Barre, W. *Current Anthropology*, 1960, 1, 45.
54. Cerletti, A. *Helv. med. Acta.*, 1958, 25, 330.
55. Leuner, H. and Holfeld, H. *Psychiatria et Neurologia*, 1963, 143, 379.
56. Busch, A. K. and Johnson, W. C. *Dis. Nerv. Syst.*, 1950, 11, 241.
57. Abramson, H. J. *Psychol.*, 1956, 41, 199.
58. Savage, C. J. *Ment. Dis.*, 1957, 125, 434.
59. Sandison, R. A. *J. Ment. Sci.*, 1954, 103, 508.
60. Frederking, W. *Psyche*, 1953, 7, 342.
61. Lemmer, H. *Wien. med. Wschr.*, 1958, 108, 109.