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DTIC-R (FOIA 2009-151)

Mr. John Greenewald, Jr.
[redacted]

Dear Mr. Greenewald:

This is in response to your enclosed Freedom of Information Act (FOIA) request dated August 17, 2009. The FOIA request and one document were referred to this Office by the Defense Technical Information Center on October 15, 2009. This Office has determined that the document may be released in full. There are no assessable fees associated with this response.

Sincerely,

Paul J Jacobsmeyer

Paul J. Jacobsmeyer
Chief

Enclosures:
As Stated

Akers, Kelly CIV DTIC R

From: John Greenewald, Jr. [john@greenewald.com]
Sent: Monday, August 17, 2009 10:50 AM
To: FOIA
Subject: FOIA REQUEST

Dear Sir,

This is a non-commercial request made under the provisions of the Freedom of Information Act 5 U.S.C. S 552. Pursuant to the U. S. OPEN Records Act of 2007, my FOIA requester status as a "representative of the news media" -- a status entitling me to an unlimited search processing my request, and the first 100 pages free of charge. For examples of my various publication credits in this regard, I refer you to my radio network, and my own personal radio show (syndicated on FM and AM stations) at http://www.blackvaultradio.com. My internet website http://www.theblackvault.com which holds a vast government document database, along with many freelance articles that I have written, which have also been published in magazines and websites, including OpEdNews.com, UFO Magazine, FATE Magazine, and others.

Additionally, the DTIC bibliography lists the document as under 100 pages, so it should not incur a charge.

I respectfully request a copy of the following document:

Accession Number: ADA3100965
Title: Psychotoxic Substances
Date: 16 Nov 1964
Pagination: 45
Report Numbers: JPRS-27373

Thank you so much for your time, and I am very much looking forward to your response. Please know that electronic delivery of the requested material or correspondence related to this case is preferred and accepted in lieu of paper copies via snail mail.

Sincerely,

John Greenewald, Jr.
[redacted]

Psychotoxic Substances.

JOINT PUBLICATIONS RESEARCH SERVICE ARLINGTON VA

16 NOV 1964

JPRS: 27,373

TT: 64-51629

16 November 1964

PA 21,006

PSYCHOTOXIC SUBSTANCES

by Kurt Stade

- East Germany -

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JPRS: 27,373

PSYCHOTOXIC SUBSTANCES

- East Germany -

/Following is a translation of Section 28. of the book Pharmakologie und Klinik Synthetischer Gifte (Pharmacology of and Clinical Experience with Synthetic Poisons) by Kurt Stade, M.D., published by the German Military Publishing House, Berlin (East), 1964; translated pages 394-442./

28.1 General

During recent years, this group of substances[1] has gained in importance among the synthetic poisons. In a publication of the Chemical and Engineering News[2] an expression of opinion by the former Chief of the Army Chemical Corps was reported, in which it is said verbatim: "...new developments in nerve gases and psychochemicals (lysergic acid derivatives) may be ready for major battlefield use in five or 10 years." At another place it is said that the synthetic poisons may be just as fatal as the atomic weapons, but that they may also be "more humane". They can be adapted to the various occasions in such a way that the will of an individual to fight may be destroyed and armies can be conquered without killing a person. Communications of this kind, without more detailed information on the [illegible] of these substances, have in the past appeared in several issues of the U.S. Armed Forces Chemical Journal. For this reason, substances with psychotomimetic or hallucinogenic properties, which are already known from the literature, have been included in the framework of this study.

The synthetic or semi-synthetic poisons described in this section have not as yet been described as destined for war use, but they certainly could be so used after suitable aerosolization. Therefore we want to describe here the most important psychic and autonomic deficiency symptoms caused by them and the influence of therapy on them, if any.

According to Raruk[3], substances are called psychotropic if they cause objectively provable central symptoms or cause psychic changes which may be subject only to recognition by personal experience.

By contrast, psychotoxic substances are of the kind which produces in man symptoms known from psychopathology as psychosis-equivalents or true psychoses. The limits between psychotropic and psychotoxic substances cannot always be clearly defined, because a psychotropic substance, in suited dosage or with application over considerable periods of time, can likewise result in psychotoxic effects.

Whether the substance as such exerts a primary effect on the normal psychic functions, or whether this occurs by way of metabolic products, is not of interest for their classification with one or the other group.

Another possibility of development of a psychotoxic effect lies in the liberation of very active body substances which disturb the psychic functions.

Psychopathologic symptoms after or during intoxication have always been of great medical interest, but formerly only the symptoms were recorded, while research which aimed at the connections between the drug and the psychic condition was lacking. This work was started first by Kraepelin in the second half of the 19th century.

28.2 Lysergic acid diethylamine (LSD)

28.2.1 Historic Notes on the Effect

The psychic effect of the semi-synthetically produced amine of the D-lysergic acid, which belongs to the group of ergobarsins, was first discovered in 1943, in experiments in the laboratory of Sandoz Ltd.. Hofmann, after having once experienced an involuntary condition simulating drunkenness, after work with few milligrams of the substance, reported an experiment on himself in which he ingested 250 µg of the substance. After 40 minutes he experienced slight dizziness, nervousness, disturbances of concentration and vision, and compulsory laughing. Because of the exact description of the development of the experiment, Hofmann's record is quoted verbatim[4]:

"...I asked my laboratory assistant to see me home..., but already on the way home by bicycle it became evident that all symptoms were more marked than the first time. I had extreme difficulty in speaking clearly, and my field of vision varied and was distorted as in a crooked mirror. I also had the feeling that we were not moving, while my laboratory assistant told me later that we rode with good speed."

In the further course of the intoxication, he saw faces like "colored grimaces", and at times there was again a "clear recognition of the

situation", "whereby sometimes I noted as an outside neutral observer how I shouted like half-mad, or blabbered mixed-up stuff".

After 6 hours, only the visual disturbances were still marked.

"Everything seemed to totter and was distorted in its proportions (similar to an image on an agitated water surface). Moreover, everything was dipped in changing, unpleasant, predominantly poisonous green and blue color tones..., particularly strange was how all acoustic perceptions, such as the noise of a passing automobile, were transposed in optical sensations, so that every sound and every noise induced a corresponding colorful picture, changing kaleidoscopically in shape and color."

The next day, the symptoms had disappeared.

Stoll[5] continued Hofmann's experiments by testing LSD on several test individuals. Because of its effects, Stoll designated LSD as "phantasticum", because the unique psychic changes did not permit the classification of the substance with the so-called psychotomimetics.

Starting from these effects of a psychic nature, there began an intensive research for the clarification of the mechanism of the effect of psychotomimetic substances. In addition to the semi-synthetically produced D-lysergic acid diethylamine, a number of similar compounds were synthesized[6] and tested as to their psychotoxic effect[7]. It was shown that most LSD derivatives were devoid of a psychotoxic effect. Central effects, however, were demonstrable with most compounds, namely by potentiation of barbiturate narcosis without a hypnotic effect of its own[8].

An important factor of the LSD effect is the extraordinarily high effectiveness in in-vivo experiments. The minimal quantity of LSD which induces psychic changes in man after oral administration was determined by Stoll and Rothlin in experiments on themselves with 0.5 to 1.0 µg per kg body weight. For comparison with other substances, Table 28/1 by Blickensdorfer[9] is quoted; it shows the relationships of quantitative effects of psychotropic substances[10].

After ingestion of amounts between 0.5 and 1.0 µg, optic hallucinations started in 30 minutes, according to Stoll[11]. The kind of hallucinations differed; mostly they were connected with synesthesias. At the beginning there were mainly prolonged afterimages, which during the further course of the experiment were replaced by scenic hallucinations. Changes in the area of the other senses (sense of smell and of taste) did not occur, likewise no acoustic hallucinations, with the exception of the above-mentioned acoustic transformations which, however, cannot be considered as true hallucinations.

Table 28/1
Quantitative Relationships of the Effect of
Psychotropic Substances
(in µg per person)

Glutamic acid	p.o.	10,000,000 ... 40,000,000
Ethanol	p.a.	7,000,000 ... 20,000,000
Chloral hydrate	p.a.	1,000,000 ... 2,000,000
Dibenamine	i.v.	200,000 ... 600,000
Ethyl ether	p.o.	200,000 ... 400,000
Cocaine	s.c.	80,000 ... 300,000
Mescaline	p.o.	10,000 ... 20,000
Morphia	s.c.	5,000 ... 10,000
Atropine	s.c.	3,000 ... 10,000
Dilaudid	s.c.	2,000 ... 4,000
Pervitin	p.a.	1,500 ... 3,000
LSD	p.o.	10 ... 35

A striking relationship existed between mood and hallucinated color. With an elated mood, predominantly light red, yellow, and light green shades were hallucinated, while, if the mood was more dysphoric, blue and dark green colors were dominant.

In addition to these experiences, "ego" disturbances were particularly marked. The participants in the experiments felt isolated from their surroundings and alone, although the mood, with the majority of individuals, was euphoric, and depressive tendencies occurred only occasionally. All individuals remained oriented as to place and time, but there was flight of ideas, perseveration tendencies, levitation phenomena, and disturbances of body orientation.

28.2.2 Toxicity

The LD_{50} of lysergic acid diethylamine depends very much on the examined animal species, as the compilation of values after i.v. administration shows:

Mouse	46 mg/kg
Rat	16.5 mg/kg
Rabbit	0.3 mg/kg

A comparison of these values shows a proportion of 1:28:150. LSD shows the highest effectiveness among all homologous compounds of natural or synthetic origin. Animals show, with suitable dosages, besides autonomic signs also somatic symptoms.

28.2.3. Absorption, Distribution, Elimination

LSD is usually used as salt, is therefore well soluble in water, and is easily absorbed if given by mouth. The distribution of LSD in the organism was studied with LSD marked with C^{14}, [12] and at the same time on the uterus by means of the antagonism of 5-hydroxytriptamine[13], and the results of both methods were in good agreement.

The distribution in the various organs showed this sequence:

Intestine > liver > kidney > adrenal > spleen > pancreas > heart > muscle > skin > brain.

The concentration in the brain was even less than in the blood. As the distribution series shows, LSD is found in almost all tissues. In the blood, LSD is not long demonstrable, because it is very quickly excreted via liver and bile. Discrepancies relating to the time of half the LSD amount in the blood were caused by the two methods of determination. With the isotope technique, it is 7 to 10 minutes, while it is 35 minutes with testing of the serotonineantagonism. Two hours after intravenous administration, only traces can be found in the blood and in various tissues.

Lysergic acid diethylamine is changed by the body metabolism, since, in contrast to LSD, a large part of the excreted compounds is water-soluble. Elimination takes probably largely place via the bile, because three fractions were demonstrated in it by paper chromatography, which, however, could not be identified chemically.[14] According to the biochemical studies by Axelrod and collaborators[15], LSD, in presence of oxygen and TPN-H_2, is enzymatically transformed in vitro by guinea-pig liver mitochondria into 2-oxy-LSD, a substance having no psychotoxic properties.

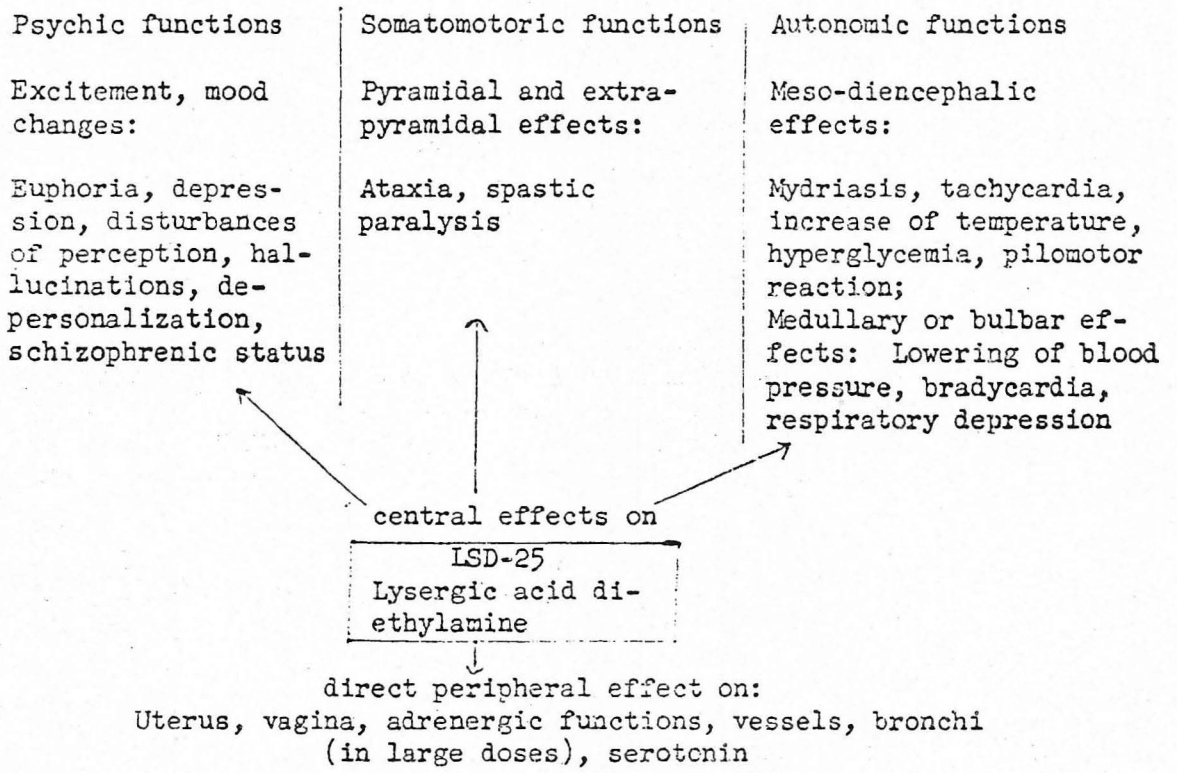
The data on type of distribution, half-value time, and catabolic products in the literature are not uniform and only in partial agreement.

Concerning the distribution, Axelrod and collaborators[15] found a similar sequence:

Bile > plasma > lung > liver > kidney > brain > small intestine > spleen > muscle.

The half-value times were 100 minutes in monkeys and 130 minutes in cats. While Rothlin was able to test the total activity, Axelrod found the LSD in the plasma of cats firmly bound to protein. The data on elimination products are likewise contradictory; according to Axelrod they are unchanged LSD.

The various effects produced by lysergic acid diethylamine in the body are schematically presented (see next page).



28.2.4. Psychic Effects

The psychic effects produced in man by LSD are similar to those of mescaline, but LSD is about 5,000 times as effective as mescaline.

Beginning with the first observations by Hofmann, the field of the psychic effects of LSD has been experimentally studied with great intensity. Important points were that the psychic symptoms after LSD start only after a certain period of latency (40 to 60 minutes), while the autonomic effects begin after about 20 minutes.

The maximum of the psychic symptoms starts two to three hours after application, while the effect lasts altogether about 8 to 12 hours. With the new, entirely synthetic psychotimimetic substances the psychic effect lasts longer still. The time lag before appearance of the symptoms depends on the type of administration, whereby the symptomfree interval becomes shorter in the following sequence:

oral > intramuscular > intravenous > intraspinal.

After intravenous and intraspinal administration, the maximum of symptoms is attained in one hour and therefore decreases somewhat earlier

than with oral administration. The LSD symptomatology is very much intensified and also lengthened by pervitin.[17]

With the LSD effect it is striking that this substance is able in such extraordinarily small quantities to influence so basically the perception system which has been acquired, learned, and stabilized in the course of decades of life. According to Mattusek[18], extremely strong toxic influences or extreme emotional burdens are necessary in order to loosen the perceptive connections. This loosening is characteristic for the beginning of schizophrenic psychoses.[18]

Normally there is a definite dosage-effect relationship[19], and with doses up to 1 µg/kg of body weight, unmotivated actions occur sometimes during the hallucinatory stage. It is, however, mainly the affective sphere which is effected. By contrast, with a dosage of more than 1 µg/kg "schizophrenic pictures" are observed.

According to the studies by Anderson[20], it is not permissible on the basis of these symptoms to consider LSD as a so-called schizophrenomimeticum, because, in spite of the great similarity of the syndromes, there are considerable differences. E.g. schizophrenics have beside "ego disturbances" also disturbances of thinking, while such a combination does not occur with LSD intoxication. In addition, there are, however, as has been described at the beginning, changes in the field of body perception and in the sphere of body sensation occurring in the psychosis. Such disturbances are counted among the "Ego-nucleus-disturbances" and therefore do display certain parallels with the psychic changes which are often observed in beginning schizophrenia.[21] LSD does show - in suitable dosages - phenomena which are also observed with beginning schizophrenia; on the other hand, certain disturbances which are typical for schizophrenia are lacking, and therefore one cannot speak of a "schizophrenomimeticum".

28.2.5. Autonomic Effects

The LSD effects on the autonomic nervous system are sympathetic as well as parasympathetic.

The most sensitive autonomic function is the temperature regulation of the rabbit which reacts already to doses of 0.5 to 1 µg/kg.[22] The cat, dog, and rabbit show, besides the increase in body temperature, also an increase in blood pressure. The line of clearly sympathetic autonomic effects is further supplemented by reactions of the pilomotors and by mydriasis which is observed in various animal species - but also in man.[23]

All described sympathetic effects are triggered by stimulation of mesodiencephalic or bulbar centers, because these central reactions to LSD can be inhibited by preceding administration of ganglion blocking agents or by adreno-sympathicolytically active substances.

In contrast to these autonomic effects of a sympathetic nature, LSD also produces parasympathetic effects such as nausea, vomiting, increased salivation, and tears.

The influence of LSD on the blood pressure depends basically on the dosage. Very small doses do not influence the blood pressure. Quantities which produce psychic symptoms in man, increase the frequency of pulse and respiration and the blood pressure.[24] With identical dosage, the effects are much less outspoken in schizophrenics than in healthy test persons.

With high dosage (50 to 100 µg/kg), LSD produces in the cat, via central vagus stimulation, bradycardia and a decrease in blood pressure. According to Sokoloff[25], the latter is produced by a depressor effect of LSD on the vasomotor center, because in the spinal cat LSD makes the blood pressure rise and there is no bradycardia.

The increase of blood pressure in man coincides with the maximum of psychic symptoms, while even with intense psychic symptoms the vascular resistance, the cerebral blood flow, and the arterio-venous oxygen difference are not significantly influenced. The effect on respiration likewise depends on the dosage. With a low dosage, there is mostly stimulation, while with higher doses, an inhibition and death by apnea are observed.[26]

28.2.6. Somatomotoric Effects

They make their appearance only with dosages way above the minimal amounts necessary for the production of psychic symptoms. With high doses, disturbances of a pyramidal and extrapyramidal nature develop in the animal experiment, which lead to ataxia and spastic paresis.

28.2.7. Biochemistry

In order to clarify the specific effects of lysergic acid diethylamine, many metabolic processes and the influence of LSD on them were examined.

As to the distribution of LSD in the brain, tests with LSD marked with C^{14} showed the following pattern[27] (Table 28/2):

Table 28/2
Percentage of LSD, with theoretically equal distribution of counts

Hypothalamus	16	Cortex	31
Cerebellum	26	Thalamus	28
Brain stem	17	Liver	135

As these values show, no part of the brain shows a particularly obvious affinity for binding LSD.

A hint of a possible action mechanism of LSD is given by the finding that, after administration of LSD, the acetylchlorine contents of the guinea-pig brain increased.[28] Systematic studies showed further that LSD in concentrations of 5×10^{-6} M inhibits the activity of human brain and plasma cholinesterase,[29] while acetylcholinesterase from erythrocytes or brain is only slightly inhibited by LSD concentrations up to 5×10^{-5} M.[30] This inhibitory effect could explain the increase in the acetylcholine contents of the brain of animals treated with LSD, which Poloni has found.[28] The question whether LSD in vivo produces its central, autonomic, and psychic effects primarily via the mechanism of accumulation of acetylcholine, must be handled with great caution, because in acute alkyl phosphate intoxication these substances, while also producing central effects, have never resulted in an observation of psychic symptoms similar to those caused by LSD, and yet the cholinesterase-inhibiting effect of the alkyl phosphates is higher by several tens of potencies than that of LSD.

The differences in concentration between the in-vivo and the in-vitro effect of LSD also weigh against the assumption of a significant participation of cholinesterase in bringing about the psychic changes.

In the in-vitro experiment, LSD exerts an inhibiting influence on the esterase not below 5×10^{-6} M, while an influence on psychic functions is seen already with 0.5 to 1 µg/kg. This corresponds approximately to a mol value of 2×10^{-9} M.

Because of the unusually small quantity necessary for the effect, Mayer-Gross and collaborators[31] presented the theory that LSD triggers the picture of a psychotic condition by way of formation of a cerebral anti-enzyme. Their experiments on the influence of LSD on the carbohydrate metabolism showed that the carbohydrate metabolism is influenced very little. The finding, however, was notable that in guinea-pigs' brain pulp, in the presence of 4×10^{-9} M LSD, glucose oxidation was stimulated by 30%, while the catabolism of hexamonophosphates was lessened by 40%.[32] One related therefore the psychic phenomena partly to this blockage of hexamonophosphate. Based on other studies on the effects of LSD on carbohydrate metabolism, an inhibition of the catabolism of glycogen on the level of the hexamonophosphate was shown.[33] If this inhibition of glycogen metabolism is in reality an important factor in the LSD effect, a parenteral administration of glucose must compensate the LSD effect, which actually seems to be the case if the glucose level is elevated to 200 mg%. Unfortunately, the number of experiments was too small to allow significant statements.

Other authors did not find an increase of glucose oxidation, but rather an inhibition[34] if brain sections of guinea-pigs were electrically stimulated in the presence of 5×10^{-5} M LSD. Sections which were not so stimulated showed no reaction.

Other biological systems, such as non-protein nitrogen or the liver functions demonstrable by means of the cephalin-cholesterol flocculation

reaction, are not changed even after administration of medium doses of LSD.[35]

The liver, according to comparative studies with mescaline and LSD, seems to be relatively unsensitive to LSD, although both - even though in different dosages - bring about similar psychic phenomena. The LSD effect on the liver is of shorter duration.[36]

For a better survey of the biochemical effects of LSD, Bain's summary[37] (Table 28/3) is reproduced below.

28.2.8. Biogenic Amines and LSD

It has been known for some time[45] that a number of amines, among them mescaline (3,4,5-trimethoxyphenol ethylamine), act as potent inhibitors of the pyruvate, glucose, and lactate oxidation by brain enzymes; also that a number of biogenic amines, such as tyramine, 5-hydroxytryptamine, and adrenaline, function as substrates of the monoamine oxidase of the brain.[46] These biogenic amines have long ago been recognized as having special significance in the development of psychic diseases. Therefore it is understandable that the psychic changes under the influence of LSD were likewise considered as connected with the metabolism of 5-hydroxytryptamine. According to this, these changes are supposed to be based on two developmental possibilities:[47]

- Can the 5-hydroxytryptamine contents of the brain be lowered by the antagonistic effect of LSD?

- Can a much elevated 5-hydroxytryptamine level be caused by competitive inhibition of monoaminooxidase by LSD?

According to these hypotheses, endogenous psychoses, as well as schizophrenias, develop by either too much or too little 5-hydroxytryptamine. These hypotheses, however, must be considered as obsolete by virtue of the present state of research in the field of the monoaminooxydase inhibitors.

Table 28/3

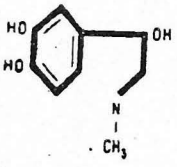
In-vitro Effects of LSD on biochemical Systems

System	Effect	Concentration
Psychotomimetic effect in vivo		10^{-9} M
Glucose oxidation by guinea-pig brain pulp	30% activation	$4\ 10^{-9}$ M
Glucose oxidation by guinea-pig liver pulp	10% inhibition	$4\ 10^{-9}$ M

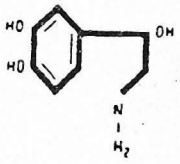
(Table continued)

System	Effect	Concentration
Hexosemonophosphate consumption of guinea-pig brain pulp	40% inhibition	$4\ 10^{-9}$ M
Hexosemonophosphate consumption by guinea-pig liver pulp	10% inhibition	$4\ 10^{-9}$ M
Glucose oxidation in electrically stimulated guinea-pig brain sections[39]	40% inhibition	$5\ 10^{-5}$ M
Lactate formation in electrically stimulated guinea-pig brain sections	40% inhibition	$5\ 10^{-5}$ M
Glucose oxidation in non-stimulated guinea-pig brain sections	no effect	$1\ 10^{-4}$ M
Lactate formation in non-stimulated guinea-pig brain sections	10% inhibition	$1\ 10^{-4}$ M
Succinic acid dehydrogenase from brain[40]	23% inhibition	1 m M
Cytochromoxidase from brain	13% activation	1 m M
Glucose oxidation by rat brain pulp[41]	no effect	$1\ 10^{-6}$ M
Glucose oxidation by rat liver pulp	no effect	$1\ 10^{-6}$ M
Glucose oxidation by non-stimulated rabbit brain sections[42]	10% inhibition	$3\ 10^{-5}$ M
Glucose oxidation by rabbit brain sections stimulated by dinitrophenol	10% inhibition	$3\ 10^{-5}$ M
Oxidation phosphorylization in rat brain or liver mitochondria[43]	no effect	$1\ 10^{-4}$ M
Cholinesterase from human plasma or brain[44]	50% inhibition	$5\ 10^{-6}$ M
Acetylcholinesterase from human erythrocytes and brain	10% inhibition	$5\ 10^{-5}$ M

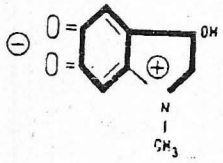
The question of the relationship between the psychic effect of LSD, mescaline, or other psycho-active substances and their influence on the metabolism of the biogenic amines is not easily answerable. An important point in question seems to be the structural similarity of the biogenic amines and the compounds with psychotomimetic properties, as is shown by the following formulas:



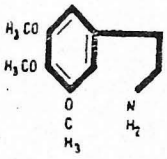
Adrenaline



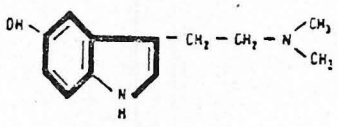
Noradrenaline



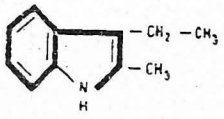
Adrenochrome



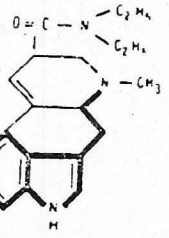
Mescaline



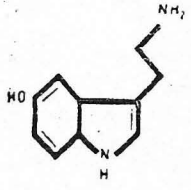
Bufotenin



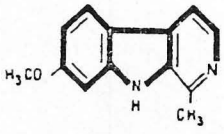
Medmaine



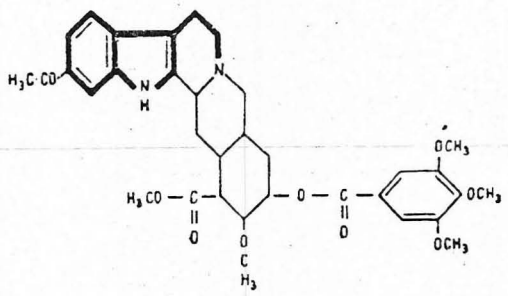
Lysergic acid diethylamine



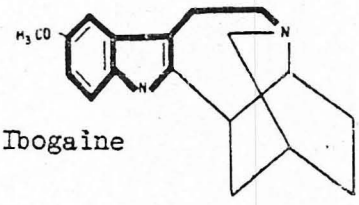
5-Hydroxytryptamine



Harmine



Reserpine



Ibogaine

The interest in the indole structure and the role which it plays in the nervous symptomatology, goes back to the studies on the role of nicotinamine and its precursor, tryptophane, in the pellagra syndrome. There, one observes, beside dermatitis and diarrheas, central deficiency symptoms. The interest in the indole structure increased again in the nineteen fifties, when for the first time the occurrence of considerable amounts of 5-hydroxytryptamine in the normal brain substance was shown.[48] Thereafter, extensive studies on the distribution of 5-hydroxytryptamine in the brain[49] and its relationships to neuromuscular transmitter substances such as noradrenaline were undertaken.[50]

The observations made in more recent times that 5-hydroxytryptamine as well as adrenaline and noradrenaline are potent inhibitors of synaptic transmission, offered a new posibility to connect the indole structure with psychic symptomatology.[51]

The observation that compounds the structure of which is similar to that of 5-hydroxytryptamine have a schizophrenogenic effect[52] resulted in the assumption that the substances with hallucinogenic effect owe their pharmacodynamic properties to a predominant influence of the effect of 5-hydroxytryptamine[53] and that, therefore, their effect is based on the formation of antimetabolities.

Based on the experiments by Gaddum[54] on the antagonistic effect of LSD against 5-hydroxytryptamine in vitro, there exist at present a considerable number of compounds which either operate in vitro as antimetabolites of 5-HT (5-hydroxytryptamine) or have a psychotogenic effect, or show both antagonistic effects.

The influence of various substances on the 5-hydroxytryptamine level in the brain has been used therapeutically. In the animal experiment, reserpine lowers the 5-HT contents[55], and with the phenothiazides, the 5-HT-blocking ability goes parallel with the ability of psycho-sedation.[56]

Because it was thus shown that 5-HT functions as neuro-humoral transmitter in the brain, the interpretation that 5-HT was the key to the changes caused by LSD, offered itself in a fascinating manner. Unfortunately, the situation proved not to be as simple as it had seemed at the beginning.

The first difficulties occurred in the interpretation of the effect of LSD derivatives, because many substances with strongly marked in-vitro activity showed no effect in vivo.

However, there also exist some LSD derivatives, such as 2-bromine - LSD, which are strong inhibitors of 5-HT in vivo as well as in vitro, but have no influence whatever on the human psychology. Even a dose of 650 µg has no more than a little sedative effect, and even 7,500 µg[58] resulted in no significant psychic changes. Of all tested LSD derivatives, only the monoethylamine, the diethylamine, and the l-acetylamine of d-lysergic acid cause psychic changes in man. Quantitatively, the derivatives act rather similarly, however 8-10 times more monoethyl lysergic acid amine is needed for the production of psychic changes than of the diethyl derivative. But these substances, too, resulted in typical mood changes in the sense of euphoria or dysphoria, besides changes of behavior, mainly optic hallucinations, disturbances of body perception, depersonalization symptoms, and a "psychotic" status.

Also with the derivatives, the individual reaction, the surroundings, and the basic psychic mood existing at the time, are partly decisive for the psychotic picture manifested under the influence of the toxic substance.

The effects of LSD and 2-bromine-LSD show partly a certain likeness, but partly not. The reactions of the sympathetic system known as due to LSD, such as mydriasis, increase of body temperature and blood sugar, pilomotor reaction, EEG activation and the psychic phenomena, do not occur after 2-bromide-LSD. Here one finds a general sedation which is also shown in the EEG, which presents no signs of activation. The sedating effect becomes particularly obvious in the inhibition of the excitatory effect of amphetamine.

Amphetamine results in certain ways in similar effects on autonomic and somatic functions, in that it produces a sympathetic waking reaction and reverses the 5-HT potentiating effect on barbiturates, just as LSD does.[59] A similar behavior is shown by ergometrin.[60]

As the experiments show, the LSD effect does not seem to come about only by way of influencing the 5-HT metabolism. Above all, the psychic

phenomena cannot be related only to a disturbance of the metabolism of the neurohumoral amines. Although the cause of the development of endogenous psychoses has not become very clear so far, there are at least several working hypotheses which indicate the trend to be taken in research on basic problems.

The adrenochrome hypothesis was supported by Hoffer and Osmond[61] on the basis of the psychotomometic properties of adrenochrome and adrenolutin. In experiments with schizophrenics it was shown that these patients have less ability to catabolize injected adenochrome than normal persons. According to Hoffer, adrenochrome was supposed to be a normal metabolic product, while others[62] considered Hoffer's adrenochrome as artifact.

In the theory of a disturbance of adrenaline metabolism as cause of psychoses[63], the possible methylization of the phenol groups was supposed to play a role in the development of schizophrenia. However, the examination of the adrenaline metabolism in healthy persons and in schizophrenics did not show any differences in the proportion and the amount of the various methylated decomposition products.[64]

The theory of a metabolic disturbance of 5-hydroxytryptamine as cause of schizophrenia, or the correlation of 5-hydroxytryptamine with the biochemical processes of the psychotic could not be sustained despite many studies, because there are no differences in the 5-HTA balance between healthy persons and schizophrenics. Similarly to 5-HTA, the theories relating to indoles, indole bases, and indole acids, had to be dropped, because differences in indoles in the urine of schizophrenics or depressives could be explained by a specifically directed, nutrition-dependent bacterial metabolism.

At this time, the toxic factors in the plasma of schizophrenics seem to have assumed a greater importance. This observation goes back to experimental findings according to which the plasma - but not the serum - of schizophrenic patients is significantly more toxic for rats than the plasma of healthy persons.[65] Permeability experiments proved the small molecular size of the substance. The concentrated toxic principle, called taraxeine, brought about catatonic-like symptoms in rhesus monkeys shortly after injection.[66] LSD resulted in symptoms similar to those after taraxeine.

The effect of taraxeine was interpreted by the hypothesis that it increases the susceptibility of the brain against different non-specific low-molecular constituents of the blood, which then secondarily exert a toxic effect. In addition to these attempts at explanation, there are those of alteration of the copper level, the plasma oxidase activity, and of the tryptophane metabolism, which, however, are also explained by a nutrition-dependent hypovitaminosis of schizophrenics.

As this enumeration shows, many individual studies on the problem of psychogenesis have been undertaken, without, however, clarifying the real

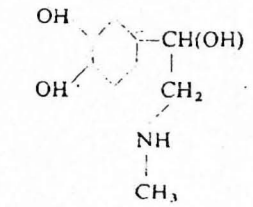
effective mechanism in the development of psychotic reactions. This clarification probably will require again as much time as the solution of the problem of the mechanism of the effect of psychotomimetic substances.

28.3 Mescaline

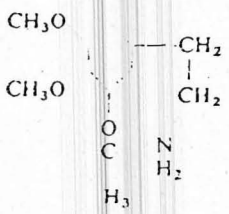
28.3.1. Historic Notes on the Effect

Mescaline was used for a long time by the inhabitants of Mexico for purposes of religious cult. It occurs in nature in the cactus species "Echinocactus Williamsii lem."[67], popularly called "peyotl". It was ingested as slices of cactus over which alcohol had been poured. Because of its strong hallucigenic effect, peyotl was reversed like a deity.

Mescaline, the effective substance, was isolated for the first time in 1918.[68] It has a structure which invited comparisons with adrenaline:[69]



Adrenaline



3,4,5-trimethoxy-phenylethylamine Mescaline

In the opinion of Osmond, disturbances of the adrenaline metabolism result in toxic catabolic products, which are then able to bring about psychoses.

Further experiments resulted in research on adrenochrome[70], an oxidation product of adrenaline, which probably is produced in the body and, in sufficiently high dosage, is able to produce psychosis equivalents. The assumption that adrenochrome is one of the primary causes of schzophrenia was understandable, particularly because also adrenolutin, likewise an oxidation product of adrenaline, showed psychotomimetic properties.

Just as peculiar as the effect of the substance is its history, which is similar for all psycho-active substances which occur in nature. Most of these substances had been in use for a long time, though without knowledge of the effective principle, with the people on whose territory they occur naturally, such as the mescaline of the Mexican peyotl, the D-lysergic acid amine of the Mexican ololiuqui, or the ibogaine from Tabernanthe iboga in the Belgian Congo.

A good insight in the history and the cult significance of various substances with psychotropic effect, particularly those of the American

continent, gives Reco.[71] It is interesting that the effective substances of some of the medicinal plants described by him, such as the ololiuqui, have been isolated and identified only recently.[72]

Although the powerful psychic effects of the peyotl were known in Europe already at about the middle of the 16th century,[73] the plant remained unused for a long time. Only Lewin[74] described it and its use by the primitive peoples in greater detail.

In the animal experiment, central excitatory conditions with the appearance of tetanus were seen. Psychological studies in man were undertaken later;[75] in these- in contrast to the tetanus-like conditions in animals - hallucinations occurred. However, the colorful visions and the "rhythmic ondulations of colored forms" occurring after use of mescaline cannot well be considered as true hallucinations. Striking were the constantly appearing disturbances of time perception.[76]

Reviews on mescaline and mescaline psychoses were recently published by Fischer[77] and Schueler.[78]

Descriptions of experimental mescaline psychoses are quite common in the literature. However, the best description is probably that by Knauer[79], who made experiments with physicians. The dosage was between 0.1 and 0.2 g. Approximately 60 minutes after the injection, the first symptoms appeared as nausea, as also Reco has described. It was followed by a stage of increased urge to talk and to move about. The reactions of the participants in the experiment varied. Some displayed a dysphoric mood with depressive tendencies, others unmotivated hilarity. All experimental persons remained in constant contact with the person undertaking the experiment and could be influenced by him. The alterations of perception brought about by the effect of the substance occurred mainly in the optical sphere, similarly as with LSD. All colors seemed to be brighter and the contours of the hallucinated pictures were sharper.

Kaleidoscope-like pictures appear, which, however, remain without inner associations. Characteristic for the mescaline intoxication is the "jewel rain" which occurs at least in the early stages.[80] Besides, objects such as patterns, ornaments, panoramas, people, or animals are hallucinated. Because these objects, too, are experienced without associations, they remain without a threatening character.

Hallucinations in the acoustic field occur almost never, while haptic deceptions of the senses, as also described by Reco, are more common. Disturbances in the haptic sphere result in disturbances in body perception. During the whole course of the experiment, the criticism relating to occurring hallucinations remained intact, while a delusional misconception of the surroundings or of perceptions was always accepted without criticism. A purposefully directed development of the occurring pictures by the person conducting the experiment, similar to the catathymic visual experiences, is

not possible in mescaline psychosis. The acute symptoms with a dosage of 0.1 to 0.2 g last 3 to 4 hours on the average, the stimulation of the optical system, however, up to 24 hours. The deceptions of the senses, which are induced by mescaline, depend very much on the dosage. With an increase of the dose to 0.5 g, not only the act of perception changes, but there are also qualitative changes in the mental sphere. However, even with these high dosages, the acoustic sphere is least influenced.

After transient vegetative stimulation symptoms, the true mescaline psychosis occurs, representing the main stage. The mental changes occurring during the psychosis consist mainly in experiences being given abnormal meaning, having principally paranoid features. The disturbances of time perception which are seen with low dosages, increase, as do the disturbances of body perception which in the end result in the experience of "ego doubling". The stupor syndromes which occur quite frequently, and the change in the general mood were the original reasons for the usage of this substance for mythological acts.

In individual cases, toxic transformations occur. They are not in the acoustic sphere, as with LSD, but show up as change in cutaneous function. Tactile stimulation of the skin is not any more experienced as such, but rather as painful stimuli, whereby the after-duration of the sensation is unusually prolonged.[81]

In contrast to LSD, there is no inner connection between the psychic condition and the contents of the hallucinations. In mescaline psychosis, therefore, there could occur pleasurable hallucinations in spite of a dysphoric mood, and vice versa.[82]

The main phenomena of the deception of the senses which Guttmann has observed are the pictures which either have a movement of their own or stand still, the disturbances of taste, and the disturbances in the sphere of bodily sensation which result in levitation phenomena and flying sensations.

With hallucinations of a threatening character, Guttmann observed "personality cleavages". This phenomenon was also mentioned in Reco's report. With it, there exists next to the personality which anxiously experiences the toxic effects, one which coolly registers and records. Despite the intensity with which the hallucinations are experienced, they are never considered as real. Similarly as in Knauer's experience, an influencing of the hallucinations from the conceptual side could not be seen. Alterations in mood from apathy to quarrelsomness and vice versa were often observed.

A peculiarity of mescaline intoxication is the alteration of the experience of time and space.

The opinion formerly expressed by Mayer-Gross, that the phenomena occurring in mescaline psychosis could represent a kind of schizophrenic

model psychosis, is, according to newer studies, not quite correct.[83]

According to them, the peculiarity of the mescaline intoxication rests mainly in the fact that, while consciousness is retained, the subjective experiences, by displacing the world of objective perceptions, are pushed in the foreground.

The hallucinations are accepted without criticism, but can be recognized as such in conscious observation. According to Wolf, mescalinized persons, after transient kaleidoscopic pictures, experience hallucinations in which space is felt as expanded and widened. The experimental person can see the whole room at one time and is not able any more to distinguish between top and bottom, or right and left. This phenomenon increases in intensity, and during the maximum of effect, the mescalinized identifies himself with the room. E.g., the space experiences are presented as follows: "I was on a lonely island, floating in the ether. But then, nothing. An entirely empty space. The room seemed deprived of space."[84] "I have ceased to be, my ego has dissolved in space."

The experience of time is likewise disturbed during mescaline intoxication, in that the time concept is lost. Time is felt as standing still, and past and future have ceased to exist.

In addition to these changes in the concept of space and time, there are very often disturbances of body perception; during those, disfigurements and changes of size of the body or of certain parts of it are seen.[86]

A likewise constant finding are the synesthesias which occur under mescaline, namely the occurrence of sensations in an organ of sense if another one is stimulated, which is explained by an increased sensitivity of all sense organs.[87] In spite of the hypersensitivity - also in the acoustic sphere - deceptions of the acoustic sense are not experienced. The sensitization has been explained by a lowering of the stimulation threshold.

In the optic sphere, the contrast and plasticity phenomena increase. All hallucinated objects and actions show a strong mobility, which likewise is characteristic for the mescaline psychosis. During the maximum of symptoms, the thinking requirement of causality was disturbed, probably mainly due to the synesthesias.

28.3.2. Influence of Mescaline on the EEG and ERG

With intravenous application of mescaline to cats, intermittent spikes and slow waves were seen in the electroencephalogram, which were accompanied by a disturbance of behavior. Each time when spikes and waves occurred, crying, scratching, and howling attacks went parallel.[88]

In man also, there are typical changes of the EEG under mescaline. The amplitude of the activity of the α-waves decreases. During the

occurrence of an optic hallucination, the α-activity is blocked. Even after the subjective symptoms have abated, the α-activity remains decreased for several days.[89]

The influence of mescaline on the spontaneous electrical activity of the curarized rabbit shows hardly any difference in comparison with LSD.[90]

E.g., mescaline, in an intravenous dosage of 5 to 10 mg/kg, produces in the EEG an arousal reaction, as it can also be induced by LSD. Azacyclonol (15 to 25 mg/kg) was able to normalize this EEG finding. This is in conformity with the result achieved by Fabing[91], who succeeded with 200 mg of azacyclonol (intravenously) to terminate an LSD psychosis.

The assumption that also animals, if under the influence of hallucinogenic drugs, such as LSD or mescaline, have optic hallucinations, is made likely by experiments on the influence of psychoactive substances on the electroretinogram of cats.[92]

As Fig. 28.1. shows, there occur after LSD and mescaline administration spontaneous action potentials which have the characteristics of the B waves of the electroretinogram, meaning that a pronounced positive potential is followed by a lesser negative one. These potentials make the existence of optic hallucinations likely, which also seems to be shown by the behavior of the animals.

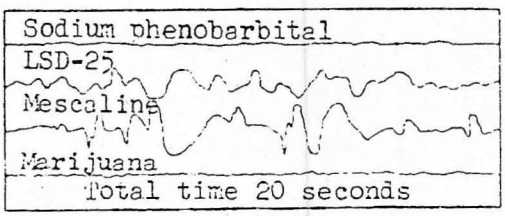


Fig. 28.1. Spontaneous potentials of four cats, each under influence of a different substance[93]

28.3.3. Biochemical Changes under Influence of Mescaline

Mescaline is a substance with psychotomimetic effect, of which the oldest description of biochemical in-vitro effects exists. Already in 1933, papers on the effect of amines on the cerebral metabolism showed[94] that mescaline inhibited the oxidation of glucose, lactate, pyruvate, and glutamate in sections of guinea-pig brain, but not the oxidation of succinate. Under certain experimental conditions (with pre-incubation of the inhibitors), an average inhibition of 65% could be found for the mentioned substances, with a mescaline concentration of 4×10^{-3} M. Because the inhibition occurred also with other amines, Quastel and Wheatley assumed that a liver injury results in a faulty amine catabolism and thereby possibly secondarily

in a development of psychoses. However, experiments with C^{14}-mescaline showed that only a very small part of the marked compound is found in the central nervous system.[95]

Because of this fact, the concentrations which Quastel tested were way above those which are achieved by mescaline administration in vivo. However, by way of a damaged liver an accumulation of considerable amounts of toxic amines, which in turn damage the central nervous system, would be possible. That the liver is able to play a large role in the pharmacologic effect of centrally effective substances was shown in a recently published paper on activation of tremorine (1,4-dipyrolidino-2-butyne)[96]. According to this, tremorine develops its central effect only after having passed through the liver and after having been changed there into an active form, which has recently been identified, by means of microsome enzymes.

The most important biochemical reactions which have been examined in vitro as to their capability of being influenced by mescaline, are summarized in Table 28/4.

Table 28/4
Summary of the Biochemical Effects of Mescaline in Vitro (according to Bain[97])

System	Effect	Concentration
psychotomimetic effects in vivo		10^{-5} M
Glucose, lactate, pyruvate oxidation by guinea-pig brain sections (not succinate)[98]	65% inhibition	4×10^{-3} M
Glucose, lactate, pyruvate oxidation in rat brain sections (not succinate)[99]	55% inhibition	4×10^{-3} M
Oxalacetate and oxalsuccinate-carboxylase-transaminase[100]	no effect	
Succinic acid dehydrogenase and cytochromoxidase[101]	no effect	10 m M
Pyruvate oxidation by brain pulp[101]	42% inhibition	10 m M
Glucose oxidation in electrically stimulated guinea-pig brain sections[102]	50% inhibition	1×10^{-3} M

(table continued)

System	Effect	Concentration
Lactate formation in electrically stimulated guinea-pig brain sections	50% inhibition	1×10^{-3} M
Glucose oxidation in non-stimulated guinea-pig brain sections	no effect	1×10^{-2} M
Lactate formation in non-stimulated guinea-pig brain sections	no effect	1×10^{-2} M
Oxidative phosphorylization in rat brain mitochondria[103]	no effect	1×10^{-3} M

The results found by Quastel were checked by Schueler.[104] The same discrepancy between the in-vivo and the in-vitro experiment was found. Important were the studies relating to a therapeutic effect on mescaline hallucinations. By intravenous administration of sodium succinate the mescaline psychosis could be interrupted at once. Yet no substances were employed, the oxidation of which in the tissue is interrupted by mescaline.

It is probably one of the most interesting tasks of experimental psychiatry to develop chemical model substances having psychotomimetic properties and, by utilization of the results achieved with them, to synthesize substances which act as antidotes. Schueler was probably the first to utilize such model substances on the basis of the in-vitro experiments by Quastel and Wheatley. The finding that intravenous administration of succinates can neutralize the mescaline effect could thereafter be confirmed.[105] The succinate was also able to block the behavioral disturbances of mice, which had been induced by mescaline, as well as those induced by LSD.[106]

Likewise, the psychic phenomena induced by these psychotomimetics in man can supposedly be blocked by succinate.[107]

28.4 Ibogaine

In the Congo, the aborigines chew the roots of "Tabernanthe iboga" as part of their cult activities. If larger amounts are chewed, phenomena are produced in the central nervous system[108] which have been described by observers as follows:

"Soon his nerves became extraordinarily tense, he was engulfed in an epileptiform/condition, he became confused and stammered words which were interpreted by the older members of the group in such a way that he had the gift of prophesy and that the fetish (spirit) had gotten hold of him."[109]

These and other reports in the French literature show that the raw extracts of Tabernanthe iboga produce central excitation, "drunkenness", mental confusion, and - with sufficiently large dosage - also hallucinations.[110] The aborigines of the Congo region, however, used the plant also in small dosage for stimulation of efficiency, when great physical strain made such an increase necessary. This is a parallel to the use of cocaine by the Indians of the Andes, who, if subject to physical strain, chew the leaves of "Erythroxylon coca".

The isolation of the effective principle in the form of the pure alkaloid from the plant took place at the turn of the century.[111] The alkaloid was called ibogaine or ibogine. The pharmacological testing of ibogaine likewise took place at that time.[112]

In the animal experiment, rabbits, dogs, rats, and guinea-pigs presented an unusual type of stimulation. In addition, the substance had also local anesthetic properties. After clinical testing, ibogaine was then used as stimulans for neurasthenics and convalescents[113] and also for symptomatic therapy of trypanosomiasis.[114]

The drug was then forgotten for 30 years, until Rothlin and collaborators[115] went back to the formerly commenced work. In these experiments, the influence of ibogaine on the cardiovascular system and on isolated organs was studied.

A summary report on the botany, chemistry, and pharmacology, and his own results concerning the influence of ibogaine on the cardiovascular system were written up by Delourme-Houde.[116] In the animal experiment it is possible to induce with dosages from 2 to 10 mg/kg ibogaine hydrochloride a very typical behavior in dogs and cats.

After intravenous administration, the reaction occurs immediately. Cats become clearly excited, show dilated pupils, salivation, and pilomotor reaction. The excitement increases and becomes, via a stage of tremors, a wild rage. In this stage, the animal stays at one place, slightly trembling, with stretched out tail. It emits a hissing sound, as is usually done in defense reactions, even if no threatening objects are nearby. Apparently there are optic hallucinations, because the animal tries to hide in corners and to climb up the walls, obviously in order to flee. During the maximum of the phenomena there is an ataxia, which however, need not always be present but depends on the dosage. With a higher dosage, peculiar clonic extensions of the paws occur, so that the animal is not able any more to stand, but lies on his stomach, with all extremities stretched out. In this phase, the respiratory frequency is elevated and there is increased salivation. Urinary and fecal incontinence do not occur either in the phase of rage nor in that of fear. The duration of the effect of the compound can by no means be compared with that of lysergic acid diethyl amine, because with ibogaine the stage of maximum excitement is reached 10 to 20 minutes after intravenous administration, and normalization occurs mostly after 1 to 2 hours.

The short duration of the effect indicates that ibogaine induces a central stimulation, but no definite statements can be made as to the location in the central nervous system at which this effect is exerted. With doses around 10 mg/kg, there are regularly reactions of fear and tension. The animals try by all means to flee from a situation which scares or frightens them. If an attempt at flight is prevented, the animal turns aggressively against real or imaginary objects or adversaries. With this dosage, ataxia, which otherwise is seen only occasionally, occurs regularly.

Magoun[117] examined the question of the possible point of action of ibogaine in the central nervous system more closely, and put it in the ascending part of the formatio reticularis of the brain stem, because stimulation of this region induces an arousal reaction. The probability that the point of action is in fact in the formatio recticularis was supported by EEG tracings and surgical procedures on the brain stem.

Thus, an electroencephalogram after electric stimulation of the formatio reticularis[117] and an EEG after intravenous administration of ibogaine are completely similar. A further proof that the formatio reticularis is the point of action of ibogaine could be provided by high decerebration (cerveau isole; see Chapter 27.), because thereby the influence of a large part of the formatio reticularis is eliminated, and there is in fact a weakened and shortened excitatory phase after ibogaine.

Additionally, the excitatory phase can be eliminated by atropine. Therefore, in addition to the effect of central stimulation, a cholinergic mechanism must also play a part in the effect of ibogaine. This mechanism is also suggested by the inhibition of serum cholinesterase by ibogaine.[118]

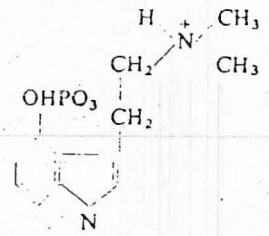
The effect of ibogaine seems to be almost exclusively of a central nature, because a direct influence on the voluntary muscles or the neuromuscular transmission has not been found. A component similar to strychnine likewise could not be established. It is also remarkable that, in spite of the very pronounced extensor spasms the reflex activity remains small.

28.5. Psilocybine

In addition to peyotl, the Mexican Indians used for centuries two other "miracle drugs" for the performance of religious ceremonies. One of these medicinals, called "teonanacatl", is a fungus of the species psilocybe (Psilocybe mexicana; Heim),[119] the other, "ololiuqui", consists of the seed of a bindweed (Rivea corymbosa (L.) Hall.f.).[120]

The isolation of the effective principle of psilocybe was accomplished during the last years,[120] as well as that of ololiuqui.[121]

The substance has an indole structure, which is esterized with a phosphoric acid group in the 4-position, as the structural formula shows:



Also with psilocybine and psilocin, the non-esterized product, the basic structural similarity with other psychotomimetic substances, such as lysergic acud diethyl amine, is striking.

In the animal experiment, the substance showed in high doses a sedating effect on mice, without causing a loss of response to stimulation in normal mice. In dancing mice, the rotating movements were weakened for a period of 20 to 40 minutes. The phenomena are somewhat different from those caused by LSD. The autonomic sympathetic reactions occurring under influence of LSD, such as salivation, pilomotor reaction, and tremors, are not observed with psilocybine. The effects also start more quickly than with LSD.[122] In clinical experiments on the effect of the substance it was shown that psilocybine is absolutely able to imitate many of the known phenomena related to other psychotomimetics. In comparison with LSD, it showed a great similarity pharmacodynamically, although its effect is much weaker. A dose of 114 µg/kg of psilocybine is approximately equivalent in intensity of effect to 1 µg/kg of LSD.[123]

Probably the best study on the clinical and psychic phenomena produced by psilocybine was performed by Hollister[124]. He used various routes of administration, namely orally with doses of 60 to 209 µg/kg, and parenterally with doses between 37 and 205 µg/kg. A special advantage of the experiments was that all experimental persons had a basic knowledge of psychologic problems, and that blind studies were performed. A suggestive influence by other persons could be excluded.

The threshold value for oral doses was determined as 60 µg/kg. The quickness and intensity of the clinical symptoms depended on the dosage, but with 115 to 160 µg/kg there were unequivocal characteristic symptoms, which are recorded in the following chronologically and completely.

After oral administration, the following characteristic symptoms were observed:

Within the first 30 minutes:
Vertigo;
Weakness, muscular pains and twitching, tremors;
Nausea, abdominal complaints;
Anxiety, tension, restlessness;

Numbness of the tongue, the lips, or the mouth;
Feeling of heaviness or lightness of the extremities;

Between 30 and 60 minutes:
Blurred vision, more intensive colors;
Prolonged after-images, clearer recognition of objects;
Seeing of patterns (with closed eyes);
Increased acuity of hearing;
Yawning, lacrimation, perspiration, blushing;
Dream stage, loss of attentiveness and the ability to concentrate, slowed-down thinking, feeling of unreality;
Depersonalization phenomena, loss of coordination;
Difficult and trembling speech;

Between 60 and 90 minutes:
Increased visual phenomena (colorful patterns and bands, generally of a pleasant character but occasionally inducing fear, mainly with closed eyes, at times covered up by objects which are seen);
Ondulations (wave-like movements) of surfaces looked at, perception of distance is impaired;
Euphoria, general stimulation, stage of rumination;

Between 90 and 120 minutes:
Prolongation of many of the above-described effects in varying intensity, in particular an introspective status;
Intensified physical sensations and increased mental perception;

Between 120 and 180 minutes:
Fading out of the above-described effects;
Almost complete recovery from the effects induced by the substance.

With parenteral administration of psilocybine the effects were similar, but the first clinical symptoms occurred after 5 minutes already, in contrast to oral administration after which the symptoms started only after 20 to 30 minutes, and in addition the phenomena were stronger and longer-lasting with the same dosage.

After parenteral application, the experimental persons complained more often of difficulties in thinking, uncontrollable laughing, paresthesias, and difficulties in breathing. Less constant were decreased salivation, decreased appetite, synesthesias, and transient sexual stimulation. None of the experimental persons observed paranoid ideas, or hallucinations in the field of smell, taste, or touch. A few experienced acoustic hallucinations consisting either of misinterpretations of the surrounding voices or of hallucinated conversations. Only rarely there were disturbances of body perception which occurred parallel with the maximum of the visual disturbances.

An unusual psychological effect of the substance, which occurred almost constantly, was the ability to perceive the feelings of the persons nearby as well as one's own reactions.

Psychic aftereffects were relatively rare and consisted of headaches and tiredness.

Several had a prolonged condition of contemplation and meditation with a mood of unusual serenity, while most had regained their normal psychologic ability.

Clinical symptoms under the influence of the substance were few. The systolic and diastolic pressure rose somewhat. Changes in pulse frequency were not beyond the physiological limits. During the maximum of phenomena there was always a mydriasis, with an average dilatation of 3 mm. With the majority of experimental persons the deep tendon reflexes were increased and at times had a clonic character. Disturbances of coordination generally were more of a subjective than of an objective character.

Biochemical studies did not disclose any important changes during the effect of psilocybine. Only the urinary excretion of inorganic phosphate, and the number of circulating eosinophils decreased significantly. However, there were no changes of the titer of the serum glutamine-oxalacetate-transaminase, or of serum cholesterol, the serum cholinesterase, or the activity of the alkaline serum phosphates.

Because there is hardly a clinical symptom caused by psilocybine which is not also produced by LSD and mescaline, the question arises in what way the effect of psilocybine differs from that of the two other substances. The duration of the psilocybine effect is shorter than that of mescaline and LSD, and its maximal effect occurs between 90 and 120 minutes. In addition, the somatic effects after psilocybine are considerably weaker than after LSD, and lastly, psilocybine, in doses which do not produce a definite intoxication, brings about a dream state in which past things come into the foreground again and are experienced plastically.

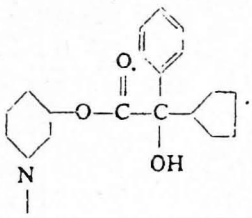
This re-living of the past, deja-vu experiences, misinterpretations of stimulation from outside, and the production of a dream state are phenomena as they are observed by stimulation of the interpretive cortex of the temporal lobe.[125]

28.6. Synthetic Psychotomimetics

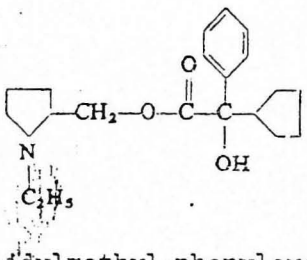
28.6.1. Piperidylglycolate and Sernyl

In the recent past, various compounds from the group of piperidylglycolates have been developed[126] which are able to produce psychosis

equivalents or psychoses on an even larger scale than LSD or mescaline can do.[127] Ditran, a mixture of the following two compounds, was found to be the most effective one:



C_2H_5 N-ethyl-3-piperidyl-phenyl-cyclopentyl-glucolate H Cl

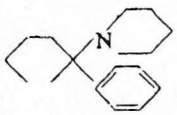


N-ethyl-2-pyrrolidylmethyl-phenylcyclopentyl-glucolate H Cl

This substance displays extraordinarily strong hallucinogenic properties, which in some respects were even more interesting and more similar to schizophrenia than those observed with LSD.

The dosage in these experiments ranged from 5 to 15 mg orally, corresponding approximately to 70 to 200 µg/kg.

A related compound, 1-(1-phenylcyclohexyl-) piperidine hydrochloride, which was called sernyl



likewise produced schizophrenoid psychoses in man, for which reason the effect of this compound was termed "schizophrenomimetic".[128]

Pharmacological studies showed that ditran has a weak antihistaminic effect and is not a serotonin antagonist, but by contrast has very strong anticholinergic properties. The assumption, however, that the anticholesterases eserin, neostigmin, and DFP would act as antagonists to the central effects of ditran, has not been confirmed.[129]

Comparative tests with mescaline and LSD showed only a small psychotomimetic effect for mescaline. LSD was considerably more effective in this respect; but LSD produced mainly disturbances in the optical field. The effects of sernyl varied considerably from individual to individual. In part of the tested persons it produced tiredness or restlessness and sometimes a condition of stupor. Ditran, on the other hand, produced, in addition to true hallucinations, very severe psychic reactions. The duration of the effects was 12 to 24 hours with ditran, and with sernyl up to 48 hours.

After intramuscular administration of 10 to 20 mg ditran, there appear 20 minutes after the injection autonomic reactions mainly of sympathetic character, similarly to LSD, namely mydriasis, tachycardia, dryness of the mouth, and muscular weakness.

The central effects start approximately 45 to 60 minutes after administration, and consist of confusion, difficulties of speech, weakness of concentration, disorientation, and hallucinations. In contrast to other psychotomimetic substances, these hallucinations are not confined to one sense organ, but include hallucinations of an optic, acoustic, or tactile character.

The duration of the phenomena was 24 hours on the average, whereby mainly former experiences were re-lived or non-real experiences were hallucinated. The hallucinations were accompanied by strong distortions of objects or persons. A number of persons expressed paranoid ideas and ideas of grandeur. In some, a complete loss of contact with the surrounding world occurred. They reacted only to their hallucinations, while others displayed a syndrome of massive stupor.[130]

28.6.2. Psychic Reactions after Pyperidylglycolates

All persons who are under the effect of ditran display disturbances of the line of thought. Mainly, the ability to follow a logical sequence of thought is lost first. The effect differs individually. Some persons display complete disturbances of word finding, others an echolaly. During intoxication, the mood is subject to strong fluctuations and includes the whole scale of moods from euphoria to dysphoria. Partly there are friendly, partly aggressive, partly bellicose tendencies. Other persons display a quiet, even mood approaching euphoria. In a number of cases there are connections between the mood and the contents of the hallucinations. Some find them funny and amusing, while others develop a syndrome of anxiety with a fear that the symptoms will resist therapy. Mood changes from euphoria to sadness and depressions are also observed. Besides these phenomena, various degrees of sleepiness appear, although the persons always react to external stimulants. The period during which the mental confusion persists, differs individually and can, on one hand, represent a

lasting condition, on the other hand occur in phases. Contact with the reality of the world around is lost just as the insight in the artificial character of the happenings or the phenomena.

Sensitivity in the tactile, optic, and acoustic sphere is considerably disturbed by this group of substances. The optic hallucinations consist to a small extent in scenic proceedings of actions, more frequently, however, in objects, persons, animals, and scenery. Persons may be built into the scenery, mainly such who have personal or family relationships to the experimental person, as parents, friends, or other participants in the experiment. Persons under the influence of ditran react to the optic hallucinations as if they were real, pick up invisible objects, drink from imaginary cups,[131] eat imaginary foods, dance, and in some cases tend to violence.

Besides the optic hallucinations, there also develop some in the acoustic sphere. Under the influence of hallucinated human voices, unmotivated laughter and even aggressive actions occur often. In a certain percentage, particular with acoustic hallucinations, there occur paranoid features with ideas of reference.

With the described dosage range, toxic symptoms are hardly to be expected, at the most nausea and vomiting. Only in cases of a hypertonus of long standing, circulatory effects with quick rise of blood pressure and giving out of the heart can occur under the influence of ditran.

As the experiments with the piperidylbenzylates show, these compounds are able to imitate schizophrenia symptoms almost completely. With these compounds, it is amazing that they have a psychotomimetic and hallucinogenic effect without having the indole nucleus of the naturally occurring psychotogenic substances. The indole nucleus, therefore, does not seem to represent an absolute condition for a hallucinogenic effect. If the intensity of the effect of LSD and ditran is compared, however, it is shown that LSD is much more effective, because it was extrapolated from rat experiments that, for the production of psychotomimetic effects, the brain level must be about 100 µg.

Experiments relating to the excretion of ditran marked with tritium[132] show that 90% of the ditran which has been taken up are excreted within 2 hours. In the central nervous system only a negligible fraction of 0.1% is fixed, and there is even a specific distribution, because the substance accumulates predominantly in the nucleus caudatus and the hypothalamus.

As to its psychic effect, the psychotomimetic effect of ditran has a wider scope than that which LSD or mescaline are able to produce.[133] This behavior was also confirmed in later experiments,[132] in which also qualitative differences in the effects were shown in that the appearance

of kaleidoscope-like pictures, which are characteristic for LSD and mescaline, did not occur with ditran.[134]

Comparisons of schizophrenic and non-schizophrenic persons[132] did not show any quantitative differences in the effect following the same dose of ditran. The schizophrenics showed hereby an intensification of their primarily existing psychotic phenomena and a reactivation of the total psychotic picture. Surprising are also the differences in the behavior of chronic schizophrenics with respect to the various psychoactive substances. On one hand, such patients are relatively resistant to the effect of mescaline or LSD and are furthermore able to distinguish between the effect induced by the poison and the normal manifestations of their disease,[135] while, with respect to ditran, they cannot distinguish between the symptoms of the endogenous psychosis and the effect of ditran.

28.6.3. Relationships between Structure and Effect

Studies on the relationship between chemical constitution and pharmacodynamic effect do not only permit statements concerning the chemical groups of the substances but also on the character of the chemical receptors or the reactive spots in the central nervous system. It is therefore understandable that in recent years the group of piperidylglycolates has been examined because of its strong psychotomimetic effects, particularly with respect to the relationship of their structure and effectiveness.[136]

Pharmacologically, these piperidylglycolates are powerful anticholinergics and therefore related to acetylcholine. According to Abood, a threedimensional acetylcholine molecule can to a certain extent be compared to substances such as N-methyl-3-piperidylbenzylate. The reactive sides of the compounds are formed, on one hand, by the cationic nitrogen atom of the aminoalcohol, and on the other, by the carbonyl group of the acid which is able to go into hydrogen linkage.

Although the real chemical-structural difference between cholinergic and anticholinergic substances is relatively small, the change expresses itself in a complete reversal of the pharmacodynamic effect. With increasing length of the chain of the aminoalcohol, the cholinergic effect decreases strongly, while a lengthening of the chain of the aliphatic acid causes the anticholinergic effect to increase, as is shown in Table 28/5.

The introduction of one or two aromatic groups causes, as the table shows, the anticholinergic effect, and also the lipoid solubility, to increase very strongly. With two aromatic groups, the optimum of the anticholinergic effect is reached. This is seen best with the N-methyl-3-piperidylbenzylate, which, in addition to its strong anticholinergic effect, is at the same time the most effective known psychotomimetic of this group. The reactive group of this substance is the piperidine nitrogen. A change

in the character of the charge results in a lessening of the anticholinergic as well as of the psychotomimetic effect.

Table 28/5
Properties of some Esters of Acids and Aminoalcohols*
(after Abood[137])

Acid	Aminoalcohol R = N-$(CH_3)_3$	Cholinergic effect	Anticholinergic effect
Acetic	$-(CH_2)_2R$	100	
Acetic	$(CH_2)_3 \cdot R$	0.1	
Acetic	$CH_2C(CH_3)_3R$	0.02	
Isovalerianic	$CH_2C(CH_3)_3R$		1
Allylisopropionic	$CH_2C(CH_3)_3R$		10
Tropinic	$CH_2C(CH_3)_3R$		200
Benzylic	$CH_2C(CH_3)_3R$		2,000

* The cholinergic effect was determined by hypotension of the narcotized cat, the anticholinergic effect on the isolated rat ileum. Only the relative effectiveness is stated.

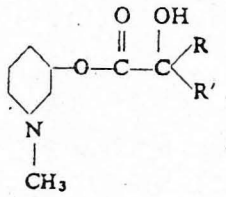
To what extent the lipoid solubility influences the psychotomimetic effect, is shown in experiments in which the benzylate remainder was exchanged for a cyclopentyl remainder or other remainders. Table 28/6 shows the influence of the exchange of the phenyl groups.[138]

Experiments with tritium-marked compounds[139] relating to the possible mode of the effect of the piperidylglycolates showed that the substances were bound to a fraction of large mitochondria, in which there are also substances such as acetylcholine, noradrenaline, and serotonin. Measurements of the optical density of mitochondria suspensions showed that the piperidylglycolates cause impairments of the mitochondria structure, although a whole number of enzymes, including the ferments of the system of electron transport, esterases, phosphatases, and oxidases, are not influenced. The binding of the piperidylglycolates to the mitochondria can be influenced by a whole number of psychotropic substances, such as chlorpromazine, reserpine, meprobamate, and 1,2,3,4-tetrahydro-9-aminoacridine.

From the results which have been arrived at up to now, it must be concluded that the point of attack of the substances is to be found in the mitochondria which contain the cholinergic receptors. The biochemical reactions induced there may be primarily of a physical nature, namely changes of permeability and thereby a secondary influence of the synthesis

of structural and functional elements, such as proteins, lipids, or transmitter substances.

Table 28/6
Influence of the Replacement of Phenyl Groups on the Psychotomimetic and Anticholinergic Effect of Piperidyglycolates



R	R'	Anti-cholinergic ED_{50}*	Psychoto-mimetic effect**	Duration in hours
Phenyl	Phenyl	0.003	4	5
Phenyl	Cyclohexyl	0.01	4	12
Phenyl	Cyclopentyl	0.003	5	18
Phenyl	Thienyl	0.001	3	1
o-Cl-phenyl	o-Cl-phenyl	0.5	1	1
m-Cl-phenyl	m-Cl-phenyl	0.1	0	-
m-CH_3-phenyl	m-CH_3-phenyl	0.5	0	-
Phenyl	Propyl	0.02	1	2
Fluorenyl		0.005	4	3

* ED_{50} shows the concentration of the substance necessary to inhibit by 50% a contraction of the isolated rat ileum induced by acetylcholine.

** The psychotomimetic effect in man was determined on the basis of the following phenomena: hallucinations, delusions, confusion, loss of contact, capacity in answering questions and psychological tests. Maximal effects were indicated by "5", no effect by "0".

Despite the many individual results concerning the effect of the piperidylglycolates, contemporary research is still very far remote from an exact explanation of the production of hallucinations or other psychotomometic effects. The most likely explanation still relates to an influence on the various neurohumoral amines of the central nervous system.

Such substances as 5-hydroxytriptamine, noradrenaline, dopamine, and histamine are concentrated in the hypothalamus and in other structures of the limbus system.

Because this part of the central nervous system is closely connected with affect and emotional behavior, an influence on these functions

by substances imitating the effect of neurohumoral substances is likely, and an explanation of their central effect is possible this way.

The amine structure appears to have a great, at this time not yet estimable, importance for the psychic phenomena. In recent times, various volatile amines were found in the mammalian brain.[140] In addition to aliphatic amines, pyrrolidine and piperidine were found in quantities of 30 µg/kg, and dimethylamine in an amount of 550 µg/kg. Piperidine itself has recently been used as psychotropic substance and proved to be very effective in the treatment of paranoid schizophrenias.[141]

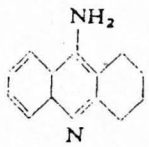
Even though the more detailed mechanism of psychotomimetic substances has been clarified only to a small extent, there are at least directions established in which research promises fruitful developments.

28.6.4. Therapy

The sternyl-induced psychosis with its stupor symptoms was favorably influenced by administration of succinates. The succinate reversed the peripheral as well as the central effects of sernyl and brought the experimental persons back to the condition prevailing before sernyl had taken effect. The only reaction which it was impossible to influence, a massive nystagmus, remained after succinate administration.

Against ditran, however, succinate was ineffective, although otherwise it is a very good antidote against other psychotomimetics and various types of depression, drug-induced as well as endogenous.[142]

Against the effects of ditran, 1,2,3,4-tetrahydro-9-aminoacridine



given intravenously, 30 mg during 5 minutes, proved to be effective. It was, however, not effective with sernyl so that it must be assumed that sernyl and ditran exert their effect at different spots in the central nervous system.

With ditran, tetrahydroaminacrine is effective at any time during the psychic or clinical symptoms. The blood pressure and heart frequency become normalized, regardless of whether there had been an elevation or a lowering of blood pressure. In addition, tetrahydroaminacrine is also a good de-curarizer[143] which reverses the depressor effect of morphine in the dog[144], and in man lowers the central morphine effects significantly.

These experiments are of interest because tetrahydroaminacrine is a cholinesterase inhibitor, and other cholinesterase inhibitors, such as eserine, neostigmine, or diisopropylfluorphosphate, do not influence the central effects of ditran.

Because of these findings it has been considered to use tetrahydroaminacrine in the therapy of schizophrenia, because the concentration of acetylcholine and its changes are capable of influencing psychic phenomena.[145]

Bibliography

1 Readers interested in the chemistry of these substances are referred to the summary by D. F. Downing: Quarterly Rev., 16, 133-162 (1962).

2 Chemical Engin. News 37, 20 (1959).

3 H. Baruk, Schweiz. Med. Wschr. (Swiss Medical Weekly), 1517 (1953).

4 A. Hofmann, quoted by W. De Boor, Pharmakopsychol. u. Psychopath (Pharmacopsychology and Psychopathology), 1956.

5 W. A. Stoll, Schweiz. Arch. Neurol. Psychiatr (Swiss Archive of Neurology and Psychiatry), 60, 279 (1947).

6 A. Stoll, A. Hofmann, Helv. Chim Acta 26, 944 (1943), and 38, 421 (1955).

7 E. Rothlin, Bull. Schweiz. Akad. med. Wiss. (Bulletin of the Swiss Academy of Medical Sciences), 2, 249 (1947).

8 E. Rothlin, Schweiz. med. Wschr. (Swiss Medical Weekly), 64, 188 (1943).

9 E. Blickenstorfer, Arch. Psych Z. Neurol. (Archive of Psychology and Neurology Journal) quoted by W. De Boor, Pharmakopsychol. and Psychopath., 1956.

10 E. Blickenstorfer, Arch. Psych. Z. Neurol. (Archive of Psychology and Neurology Journal), 188, 226 (1952); quoted by W. De Boor, Pharmakopsychol. and Psychopath., 1956.

11 W. A. Stoll, Schweiz. Arch. Neurol Psychiatr (Swiss Archive of Neurology and Psychiatry), 60, 279 (1947).

12 E. S. Boyd, E. Rathlin, J. F. Bonner, I. H. Slater, H. C. Hodge, J. Nervous Mental Disease 122, 470 (1955).

12 E. S. Boyd, E. Rathlin, J. F. Bonner, I. H. Slater, H. C. Hodge, J. Pharmacol. exp. Therap. 113, 6, (1955).

13 U. Lanz, A. Cerletti, E. Rathlin, Helv. Physiol. Pharmacol. Acta 13, 207 (1955).

14 Stoll, Rathlin, Rutschmann, Schalch, Exper. 11, 396 (1955).

15 J. Axelrod, R. O. Brady, B. Witkop, E. V. Evarts, Ann. N. Y. Acad. Sci. 66, 435 (1957).

16 E. Rathlin, Psychotropie Drugs, Elsevier Publ. Co. N. Y. 1957, S. 38.

17 G. Tonini, G. Montanari; quoted by H. Osmond, Ann. N. Y. Acad. Sci. 66, 417 (1957).

18 P. Mattusek, Arch. Psychiatr. and Z. Neurol. 189, 279 (1952).
P. Mattusek, Schweiz. Arch. Neurol. (Swiss Archive of Neurology) 71, 189 (1953).

19 M. Rinkel, R. W. Hyde. H. C. Solomon, Dis. Nerv. Syst. 15, 259, (1954).

20 E. W. Anderson, K. Rawnsley, Mschr. Psychiatr. (Psychiatric Monthly), 128, 38 (1954).

21 O. H. Arnold, H. Hoff, Wien. Z. Nervenheilk, Vienna, (Journal of Neurology), 6, 129, (1953).

22 A. Horita, Y. M. Dille, Science 120, 1100 (1954).

23 L. Sokoloff, S. Perlin, C. Kornetsky, S. S. Kety, Ann. N. Y. Acad. Sci. 66, 468 (1957).
M. Rinkel, Am. J. Psychiatr. 108, 572 (1952), and 111. 881 (1955).
A. Cerletti, Neuropharmacol. II. 1955).

24 M. Rinkel, Am. J. Psychiatr. 108, 572 (1952), and 111. 881 (1955).
J. D. P. Graham, A. I. Khalidi, J. Fac. Med. Iraq, 18. 1 (1954).
S. Katzenelbogen, A. D. Fang, Diseases Nerv. Syst. 14. 85 (1953).

25 L. Sokoloff, S. Perlin, C. Kornetsky, S. S. Kety, Ann. N. Y. Acad. Sci. 66, 468 (1957).

26 J. D. P. Graham, A. I. Khalidi, J. Fac. Med. Iraq. 18. 1. (1954).
S. Katzenelbogen, A. D. Fang, Diseases Nerv. Syst. 14. 85 (1953).
E. Rothlin, A. Cerletti, Ann. N. Y. Acad. Sci. 66. 668 (1957).

27 H. Hoagland, Neuropharmacol. Trans. Zud. Conf. Josiah Macy Jr. Found. (1956); quoted by J. A. Bain, Ann. N. Y. Acad. Sci. 66. 459 (1957).

28 A. Poloni, G. Maffezoni, Sistemia nervosa 4, 578 (1952).

29 R. H. S. Thompson, A. Tickner, G. R. Webster, Brit. J. Pharmacol. 10. 61 (1955).

30 K. Zehnder, A. Cerletti, Helv. Physiol. Acta 14, 264 (1956).

31 W. Mayer-Gross, W. McAdam, J. W. Walker, Nature 168. 827 (1951).

32 W. Mayer-Gross, W. McAdam, J. W. Walker, J. Mental Sci. 99. 804 (1953).

33 W. Mayer-Gross, W. McAdam, J. W. Walker, Nervenarzt 23. 30 (1952).

34 J. L. Lewis, H. McIlwain, Biochem. J. 57. 680 (1954).

35 G. R. Forrer, R. D. Goldner, Arch. Neurol. Psychiatr. 65. 581 (1951).

36 R. F. Fischer, F. Georgi, R. Weber, Schweiz. med. Wschr. 81. 817 (1951).

37 J. A. Bain, Ann. N. Y. Acad. Sci. 66, 459 (1957).

38 W. Mayer-Gross, W. McAdam, J. W. Walker, J. Mental Sci. 99. 804 (1953).

39 J. L. Lewis, H. McIlwain, Biochem. J. 57. 680 (1954).

40 L. C. Clark, R. P. Fox, F. Benington, R. Morin, Fed. Proc. 13. 27 (1954).

41 Bain and Hurwitz unpublished; quoted by Bain, Ann. N. Y. Acad. Sci. 66. 459 (1957).

42 Bain and Morrison unpublished; quoted by Bain, Ann. N. Y. Acad. Sci. 66. 459 (1957).

43 Bain unpublished; in: Bain, Ann. N. Y. Acad. Sci. 66. 459 (1957).

44 R. H. S. Thompson, A. Tickner, G. R. Webster, Brit. J. Pharmacol. 10. 61 (1955).

45 J. H. Quastel, A. H. M. Wheatley, Biochem. J. 27. 1609 (1933).

46 P. J. G. Mann, J. H. Quastel, Biochem. J. 34. 414 (1940).

47 D. W. Woolley, E. Shaw, Brit. Med. J. 2. 122 (1954).

48 I. H. Page, Physiol. Rev. 34. 563 (1954).
M. Rinkel, R. W. Hyde, H. C. Solomon, H. Hoagland, Am. J. Psychiatr. 111. 881 (1955).

49 E. Costa, M. H. Aprison, J. Nerv. Ment. Dis. 126. 289 (1958).

50 A. H. Amin, T. B. B. Crawford, J. H. Gaddum, J. Physiol. 126. 596 (1954).
M. Vogt, J. Physiol. 123. 451 (1954).

51 M. I. Gluckmann, E. R. Hart, A. S. Marrazzi, Science 126. 448 (1957).

52 D. W. Woolley, E. Shaw, J. Pharmacol. exp. Therap. 108. 87 (1953).

53 D. W. Woolley, E. Shaw, Brit. Med. J. 2. 122 (1954).

54 J. H. Gaddum, J. Physiol. 121. 15 P (1953).

55 A. Pletscher, P. A. Shore, B. B. Brodie, J. Pharm. 116. 84 (1956).
B. B. Brodie, J. S. Olin, R. G. Kuntzman, P. A. Shore, Science 125. 1293 (1957).
D. C. Bonnycastle, M. K. Paarsonen, N. J. Giarman, Nature 178, 990 (1956).

56 E. P. Benditt, D. A. Rowley, Science 123. 24 (1956).

57 E. Rothlin, Psychotropic Drugs, Elsevier publ. Co N. Y., 1957.

58 P. J. D. Snow, J. E. Lennard-Jones, G. Curzon, R. S. Stacey, Lancet 269, 1004 (1955).

59 M. Teaschler, Intern. Congr. Physiol. 21. Congr. Brussel 873 (1956).

60 J. H. Gaddum, M. Vogt, Brit. J. Pharmacol. 11. 175 (1956).

61 A. Hoffer, H. Osmond, J. ment. Sci. 105. 653 (1959).

62 A. Feldstein, Amer. J. Psychiatr. 116. 454 (1959).

63 J. Harley-Mason, quoted by H. Osmond, J. R. Smythies, J. ment. Sci. 98. 309 (1952).

64 O. Resnick, F. Elmadjian, Amer. J. Physiol. 187. 626 (1956).
G. Cohen, B. Holland, M. Goldenberg, A.M.A. Arch. gen. Psychiat. 1. 228 (1959).
O. Resnick, J. M. Wolfe, H. Freeman, F. Elmadjian, Science 127. 1116 (1958).

65 J. R. Bergen, R. B. Pennell, H. Freeman, H. Hoagland, J. R. Smythies, A.M.A. Arch. Neurol. 2. 146 (1960).

66 B. Melander, S. Martens, Acta psychiatr. Kbh. 34. suppl. 136. S. 344 (1959).

67 M. J. Poisson, Ann. pharmaceut. franc. 18, 764 (1960).

68 E. Spath, Mh. Chem. (Wien) 40. 139 (1918).

69 H. Osmond, J. Smythies, J. Mental Sci. 98. 309 (1952).

70 A. Hoffer, H. Osmond, J. Smythies, J. Mental Sci. 100. 29 (1954).

71 V. A. Reco, Magische Gifte, Stuttgart 1938, (Magic Poisons)

72 A. Hofmann, A. Cerletti, Dtsch. med. Wschr. (German Medical Weekly) 86. 885 (1961).

73 V. A. Reco, Magische Gifte (Magic Poisons), Stuttgart 1938.

74 L. Lewin, Arch. exp. Path. Pharm. 24. 401 (1888).

75 L. Lewin, Arch. exp. Path. Pharm. 34. 374 (1894).

76 Heffter, Arch. exp. Path. Pharm. 34. 2975 (1894), and 40. 385 (1898).
S. Mitschell, Weir, Brit. med. J. 1896. 1625 (1896).

77 R. Fischer, Rev. Canad. Biol. 17. 389 (1958).

78 F. W. Schueler, L. lab. Clin. Med. 33. 1297 (1948).

79 A. Knauer, Allg. Z. Psychiatr. 69. 115 (1912).

80 V. A. Reco, Magische Gifte, Stuttgart 1938. (Magic Poisons)
K. Zucker, J. Zador, Z. Nuer. 127. 15 (1930). (Journal of Neurology)

81 W. Mayer-Gross, H. Stein, Z. Neurol. 101. 354 (1926).

82 A. Guttmann, Mschr. Psychiatr. 56. 161 (1924).

83 R. Wolf, Deutsch. Med. Wschr. 77. 168 (1952).

84 Beringer; quoted by R. Wolf, Deutsch. Med. Wschr. (German Medical Weekly) 77. 168 (1952).

85 R. Wolf, Deutsch. Med. Wschr. 77. 168 (1952).

86 A. Serko, J. Psychiatr. 34. 355 (1913).
R. Klein, Mschr. Psychiatr. 67. 78 (1928).
E. Forster, Z. Neur. 127. 1 (1930).

87 H. Stein, W. Mayer-Gross, Dtsch. Z. Nervenheilk (German Journal of Neurology) 89. 112 (1926).

88 B. E. Schwarz, K. G. Wakim, R. G. Bickford, F. R. Lichtenheld, Arch. Neurol. Psychiatr. 75. 83 (1956).

89 A. Chweitzer, E. Geblewicz, W. Liberson, Compt. rend. soc. biol. 124. 1296 (1934) and Ann. Psychol. 37. 94 (1936).

90 F. Rinaldi, H. E. Himwich, Science 122, 198 (1955).

91 H. D. Fabing, Neurology (Minneapolis) 5. 319 (1955).

92 J. T. Apter, C. C. Pfeiffer, Ann. N. Y. Acad. Sci. 66. 508 (1957).

93 Ibid

94 J. H. Quastel, A. H. Wheatley, Biochem. J. 27. 1609 (1933).

95 W. Block, A. Block, B. Patzig, Z. Physiol. Chem. (Journal of Physiological Chemistry) 291. 119 (1952).

96 R. M. Welch, J. J. Kocsis, Proc. Soc. exp. Biol. Med. 107. 731 (1961).

97 J. A. Bain, Ann. N. Y. Acad. Sci. 66, 459 (1957).

98 J. H. Quastel, A. H. Wheatley, Biochem. J. 27, 1609 (1933).

99 F. W. Schueler, J. Lab. Clin. Med. 33. 1297 (1948).

100 W. Block, A. Block, B. Patzig, Hoppe-Sylers Z. physiol. Chem. 290. 220 and 230 (1952).

101 L. C. Clark, R. P. Fox, F. Benington, R. Morin, Fed. Proc. 13. 27 (1954).

102 J. L. Lewis, H. McIlwain, Biochem. J. 57. 680 (1954).

103 J. A. Bain, Unveroff. Erg.; in: Ann. N. Y. Acad. Sci. 66. 459 (1957). (unpublished work)

104 F. W. Schueler, J. Lab. Clin. Med. 33. 1297 (1948).

105 R. Fischer, Rev. Canad. Biol. 17. 389 (1958).
I. Stevenson, A. J. Sanchez, Amer. J. Psych. 114. 328 (1957).

106 S. Gershon, E. M. Trautner; unpublished, quoted from S. Gershon, J. Olariu, J. Neuropsychiatr. 1. 283 (1960).

107 O. H. Arnold, G. Hofmann, Wien, Z. Nervenheilk. 11. 92 (1955).

108 A. Landrin, Bull. sci. pharmacol. 11. 319 (1905).

109 J. A. Schneider, E. B. Sigg, Ann. N. Y. Acad. Sci. 66. 765 (1957).

110 A. LeRoy, quoted from C. A. Burckhardt, dissertation, Univ. of Basel, 1953.

111 J. Dybowski, E. Landrin, Compt. rend. 133. 748 (1901).
A. Haller, E. Heckel, Compt. rend. (Transactions) 133. 850 (1901).

112 M. Lambert, Arch. int. Pharmacodyn. 10. 101 (1902).
M. C. Phisalix, Compt. rend. Soc. biol. (Transactions of Biological Society) 53. 1077 (1901).

113 G. Pouchet, J. Chevalier, Bull. gen. therap. 149. 211 (1905); quoted from Schneider, Sigg. Ann. N. Y. Acad. Sci. 66. 765 (1957).

114 Kuborn, Centr. Bacteriol. Parasiten K. (Central Bacteriological Parasite Control) 31. 562 (1902).

115 Raymont-Hamet, E. Rothlin, Arch. int. Pharmacodyn. 63. 27 (1939).
E. Rothlin, Raymont-Hamet, Compt. rend. soc. biol. (Transactions of Biological Society) 127. 592 (1938).

116 J. Delourme-Houde, Thesis. Univ. Paris, France (1944).

117 H. W. Magoun, Physiol. Rev. 30. 459 (1950).

118 E. Vincent, M. Sero, Compt. rend soc. 136. 612 (1942).

119 A. Cerletti, Dtsch. Med. Wschr. 84. 2317 (1959).

120 A. Hofmann, R. Heim, A. Brack, H. Knobel, A. Frey, H. Ott, Th. Petrzilka, F. Troxler, Helf. chim. Acta XLII 1557 (1959).

121 A. Hofmann, A. Cerletti, Dtsch. Med. Wschr. 86. 885 (1961).

122 J. Delay, J. Thuillier, H. Nakagema, M. C. Durandin, Compt. rend. Soc. Biol. 153. 244 (1959).

123 H. Isbell, Psychopharmacologia 1. 29 (1959).

124 L. E. Hollister, Arch. int. pharmacodyn. CXXX. 42 (1961).

125 W. Penfield, Science 129. 1718 (1959); quoted from L. E. Hollister, Arch. int. Pharmacodyn. Therap. CXXX. 42 (1961).

126 J. H. Biel, E. P. Sprengler, H. A. Leiser, J. Horner, A. Drukker, H. L. Friedman, J. Am. Chem. Soc. 77. 2250 (1955).
J. H. Biel, US Patent 2 995 492 8. Aug. 1961.

127 L. G. Abood, A. Ostfeld, J. H. Biel, Arch. int. Pharmacodyn. 120. 186 (1959), and Proc. Soc. exp. Biol. N. Y. 97. 485 (1958).

128 E. D. Luby, B. D. Cohen, G. Rosenbaum, J. S. Gottlieb, S. Kelly, Arch. Neurol. Psych. 81. 363 (1959).

129 Lakeside Labs. Res. Div. Chem. Pharmacol.; quoted from S. Gershon, J. Olariu, J. Neuropsychiatr. 1. 283 (1960).

130 S. Gershon, Nature 186. 1072 (1960).

131 S. Gershon, J. Olariu, J. Neuropsychiatr. 1. 283 (1960).

132 L. G. Abood; quoted from Gershon, Olariu, J. Neuropsychiatr. 1. 283. (1960.

133 L. B. Abood, L. J. Meduna, J. Nerv. Ment. Dis. 127. 546 (1958).
L. G. Abood, A. M. Ostfeld, J. Biel, Proc. Soc. Exp. Biol. Med. 97, 483 (1958).

134 F. W. Schueler, J. Lab. Clin. Med. 33, 1297 (1948).

135 G. Confrau, Acta Psychiatr. Kbh. 24. 9 (1949).
W. Stoll. Schweiz. Arch. Neurol. Psychiatr. 60. 1 (1947).

136 L. G. Abood, J. Med. Pharm. Chem. 4. 469 (1961).

137 Ibid.

138 Ibid.

139 L. G. Abood, A. Ostfeld, J. H. Biel, Proc. Soc. exp. Biol. N. Y. 97. 483 (1958).

140 C. G. Honegger, R. Honegger, Nature (London) 185. 530 (1960).

141 D. Tasher, L. G. Abood, F. A. Gibbs, R. Gibbs, J. Neuropsychiatr. 1. 266 (1960).

142 O. H. Arnold, G. Hofmann, Wien. Z. Nervenheilk. 11. 92 (1955).
R. H. Barnett, Curr. Res. Anesth. 27. 326 (1948) and 26. 74 (1947).
P. Boisson, Acta chirurg. Belg. 49. 953 (1950).
R. H. Burrell, New Zealand Med. J. 45. 565 (1955).
R. Fisher, Rev. Canad. Biol. 17. 389 (1958).

142 S. Gershon, F. H. Shaw, J. Pharmac. und Pharmacol. 10. 22 (1958).
S. Gershon, E. M. Trautner, Med. J. Austr. 1, 783 (1956), and 2. 291 (1957).

143 W. S. Feldberg, Lancet 2. 900 (1955).

144 F. H. Shaw, S. Gershon, G. A. Bentley, J. Pharm. Pharmacol. 9. 666 (1957).

145 L. H. Cohen. T. Thal, M. J. Tissenbaum, Arch. Neurol Psychiatr. 51. 171 (1944).
W. S. Feldberg, Physiol. Rev. 25. 596 (1945), and Lancet 2. 900 (1959).
W. H. Funderburk, T. J. Case, J. Neurophysiol. 10. 179 (1947).
D. Grob, A. M. Harvey, D. R. Langworthy, J. L. Lilienthal, Bull. Johns Hopkins Hosp. 81. 257 (1947).
A. S. McKail, S. Obrador, W. J. Wilson, J. Physiol. 99. 312 (1941).
C. C. Pfeiffer, E. H. Jenney, Ann. N. Y. Acad. Sci. 66, 753 (1957).
D. W. Rowntree, S. Nevin, A. Wilson, J. Neurol. Neurosurg. and Psychiatr. 13. 47 (1950).
R. Suttel, S. Ratsimilia-Ratandra, Presse Med. 63. 1073 (1955).
D. W. Woolley, E. Shaw, Brit. Med. J. 2. 122 (1954).

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