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An OSI Study
on the

STRATEGIC MEDICAL SIGNIFICANCE OF LYSERGIC ACID DIETHYLAMIDE (LSD-25)

NOTICE

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STRATEGIC MEDICAL SIGNIFICANCE
OF LYSERGIC ACID DIETHYLAMIDE (LSD-25)

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Up to this time, there has been no evaluation of the significance of current knowledge about lysergic acid diethylamide, called LSD-25, and related drugs. Knowledge of the unconventional, as well as the therapeutic use to which this most unusual drug might be put, both offensively as well as defensively, is of considerable strategic significance. The broad objective of this study, therefore, is to review, analyze, and evaluate biochemical and pharmacological research on LSD-25 and other psychogenic drugs.

Appendix B, the Global Availability of Ergot, the natural source of lysergic acid, indicates the areas of its growth, both naturally and by cultivation; the approximate amounts obtainable from each country is given for relative comparison of Soviet Bloc and Western capabilities to produce ergot and its derivatives.

A partial list of some known research installations and personnel currently engaged in research on ergot and ergot alkaloids is attached as appendix C. It shows the widespread interest in these products, and the geographical distribution of this work. It is conceivable that they represent potential producers of the chemical substance, LSD-25. At present, the only known foreign source of LSD-25 is Sandoz, Ltd., Switzerland.

In the U.S. the total synthesis of lysergic acid was accomplished in September 1954 by Eli Lilly, Research Laboratories, Indianapolis.

Formal research of this study was closed 1 February 1955, however any pertinent information received up to the date of publication has been included.

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STRATEGIC MEDICAL SIGNIFICANCE OF LYSERGIC ACID DIETHYLAMIDE (LSD-25)

PROBLEM

To determine the strategic medical significance of lysergic acid diethylamide (LSD-25) through a review and an evaluation of the open biochemical and pharmacological research on this psychogenic drug.

CONCLUSIONS

1. LSD-25 is the most potent psychochemical agent available at the present time. Trace quantities of LSD-25 create serious mental confusion of the manic and schizophrenic type and render the mind temporarily susceptible to suggestion.

2. [redacted] but there are as yet insufficient data to confirm or deny its usefulness for eliciting true and accurate statements from subjects under its influence.

3. Because LSD-25 is colorless, odorless and tasteless, it could possibly be used clandestinely for the contamination of food and water although the data on its stability in solution are conflicting.

4. Since the effect of this drug is temporary, in contrast to the fatal nerve agents, there are important strategic advantages for its use in certain operations. [redacted]

5. Although no definite conclusions can be drawn as to the diagnostic and therapeutic value of LSD-25, it does appear to have the potential of being a valuable adjunct in the treatment of certain mental diseases. Methylene blue and phenothiazine derivatives, including chlorpromazine, appear both to modify and inhibit LSD-25 psychosis. The gamma isomer of mevatran also seems to block the psychic effects of LSD-25.

6. Of the other known psychogenic drugs, mescaline produces reactions that are the most similar to those of LSD-25.

7. Sufficiently detailed descriptions of the methods of preparati of both lysergic acid and LSD-25 are available in the open literature t make possible its production by an interested country. Further, the

[redacted]

Method of preparation, except that of synthesis, does not appear to be extremely complex.

8. Although no Soviet data are available on LSD-25, it must be assumed that the scientists of the USSR are thoroughly cognizant of the strategic importance of this powerful drug and are capable of producing it at any time.

DISCUSSION

LSD-25, the diethylamide derivative of lysergic acid (from ergot), is a relatively new chemical agent which affects the human mind. To date, only very small quantities of LSD-25 have been prepared. More widespread use of LSD-25 can now be expected as it has recently been synthesized.

Data on the stability of LSD-25 in solution are at variance with one another. Published methods of preparation, in general, do not indicate the conditions under which the solution was prepared or stored. Consistent results will depend, other things being equal, on the adoption of identical procedures. This has apparently not been considered by all workers.

Research on the physicochemical and toxicological properties as well as the mechanism of action of LSD-25 certainly warrants further consideration, inasmuch as little is actually known.

There does not seem to be good agreement as to the dosage to be used for clinical trials. Further investigation would undoubtedly establish more accurately the limiting dosages for maximum therapeutic efficiency.

A relation seems to exist among such drugs as LSD-25, bulbocapnine, mescaline, hashish, and atropine. Additional research is necessary to determine whether the relation is due to a similarity in the mechanism of action or to some completely new physiological effect not previously considered.

To date little work has been reported on the combined use of LSD-25 with other drugs. Research in this area might indicate the substances which, when administered prior to or concurrently with LSD-25 or other psychogenic drugs, might enhance, modify, or diminish their effects.

Relatively little has been published on the therapeutic use of LSD-25 for mental disorders or even as a diagnostic aid for their classification.

Data on two derivatives of LSD-25 have been published. A method search for other derivatives might be very fruitful.

If LSD-25 is to be used more extensively in the future, a reliable countermgent must be developed. At present phenobarbital and a bromine derivative of LSD-25 are only slightly efficacious for this purpose. However, promising results have been reported with methylene blue and chlorpromazine, but they will have to be verified. The administration of the gamma-isomer of meratran, "Frenquel," reportedly blocks the psychic effects of LSD-25 when given orally as a premedication. In one patient intravenous injection abruptly terminated the effects of LSD-25.

Since minute quantities of LSD-25 are effective, a rapid microbiological or microchemical method of detection should be developed. At present neither is available, although very limited methods of detection and identification are known, such as fluorescence, staining with ninnyerin and spectrophotometry.

APPENDIX A

Discussion of Scientific Data

Summary

While ergot poisoning has been known for many hundreds of years, the parent substance, lysergic acid, from which all ergot derivatives are made, was isolated only 20 years ago. The diethylamide derivative of lysergic acid (LSD-25), a powerful psychogenic drug, was first prepared in 1943 by Sandoz, Ltd., Switzerland, and was fully described in a Sandoz patent application in 1944. Other derivatives of ergot (lysergic acid) have been synthesized which possess sympathicolytic and oxytocic properties.

Lysergic acid diethylamide (LSD-25), a partially synthetic derivative of lysergic acid which is obtained from extractions of ergot, is produced both by straight synthesis and by reacting the azides of d- or dl-lysergic or isolysergic acid with diethylamine. The production and more extensive use of LSD-25 can now be expected since the total synthesis has been accomplished. Other derivatives of lysergic acid have been prepared by reaction with amino acids, dipeptides, and tripeptides.

The use of LSD-25 is relatively safe because of the wide margin of safety between an effective and a lethal dose. In general, LSD-25 is administered orally to humans, although in animals it is usually administered subcutaneously or intravenously. The normal dose is 1 gamma* per kilogram of weight; however, it is active in a total dose as small as 10 gamma. From studies carried out on animals, the lethal intravenous dose was determined to be 65 milligrams or 65,000 gamma per kilogram of weight, and the lethal subcutaneous dose was 285 milligrams or 285,000 gamma per kilogram of weight. By extrapolating the data on animals to humans, the lethal dose is 50 percent of human cases is calculated to be 4,590,000 gamma or 4,590 milligrams. Antidotes for LSD-25 have recently been suggested in the form of inhibitors such as methylene blue, chlorpromazine, and "Frenquel" (gamma isomer of meratran).

LSD-25 usually produces physiological changes in the central nervous system, blood pressure, digestive system, liver, respiration, urogenital system, temperature, salivary secretion, lachrymal secretion, eyes, blood picture, and blood sugar. It also interferes with carbohydrate metabolism; however, these effects can be partially counteracted by barbiturates and by intravenous injection of glucose.

*1 gamma = 1 microgram = .001 milligram

LSD-25 exerts a uterotonic effect in rabbits and inhibits the action of the so called "waltzing mice." Webs woven by spiders under the influence of the drug are more symmetrical than those produced by normal spiders.

LSD-25 does not produce a uniform psychic reaction but two main types are distinguishable, the schizophrenic and the manic. The symptoms produced by LSD-25 are expressions of acute exogenic psychosis analogous to those produced by alcohol, cocaine, hashish, mescaline, and the amphetamines. The characteristic signs observed in LSD-25 intoxication are: changes in thinking and speech and, disturbances of behavior. General symptoms reported are: changes in emotion, mood, affect; subjective feelings; morbid ideas and sensory experiences and disturbances of perception. LSD-25 creates a condition of artificial schizophrenia, and it is hoped that a solution to this form of mental disease may be developed since some indications exist that the human organism may produce toxins similar to LSD-25 which may actually be the cause of mental diseases.

In most cases of depression so far studied, LSD-25 does not appear to have a significant therapeutic advantage over other drugs. However, it did appear to be valuable as an adjuvant in a certain number of cases. The disadvantages of using LSD-25 are that it increases an already present anxiety, anorexia, tendency towards anemia, and insomnia. Like all intoxicants, it discloses pathological tendencies, which permit conjecture of the manner in which a person may become psychotic.

LSD-25 aids psychiatry by facilitating the contact approach between patient and physician. As a therapeutic shock agent, it produces results similar to other types of shock methods.

Other drugs which might be operationally used and which produce reactions somewhat similar to those of LSD-25 are scopolamine, sodium amytal, pervitin, ehtedron, atropine, bulbocapnine, and mescaline. Mescaline is by far the closest in action to LSD-25.

Mescaline and LSD-25 produce the same psychic phenomena although they vary in the quality of their effects, and mescaline must be administered in larger amounts.

Historical Account of Ergot and LSD-25

Ergot, which has been known to countless civilizations, consists of the dried sclerotium of Claviceps purpurea which infects cereal grains most frequently developing on the inflorescence of rye (Secale cereale) plants. Mothers who have benefited during childbirth from the oxytocic efforts produced by the alkaloidal constituents of ergot perhaps have the greatest appreciation for the development and growth of this pitchy fungus sclerotium. But to the men and women who in earlier times suffered from "ergot disease," as the result of eating ergotized cereal grains,

the word has signified pain and death. Since the 6th century, the cry "ergotism" has caused fear and has stressed the need for precautions in gathering grain crops. Farmers whose fields have become infested with fungus know of the damage it will cause to crops. Thus, this drug fungus during the advent of man's use of plants for food and medicine has played both a useful and a destructive role.

Knowledge concerning ergot and its medicinal virtues has rapidly accumulated since the early 19th century. From 500 A.D. to 1800 A.D., accounts of the significance of ergot and ergotized host plants vary considerably and are limited in regard to the early medicinal importance of ergotized grains. Ergotized grains are reported to have been used by the Chinese midwifery at an early date and similarly by Arabian medicine. There is also evidence among the records of the Moorish physician, Avicenna, which indicate that the fungus was used medicinally during the 10th century.

The greatest historical significance of ergot and ergotized grains up to the 20th century was the disease, ergotism. The disease was characterized by the development of gangrene in the limbs of the victim due to the severe vasoconstriction and pressor actions of the ergot alkaloids. Such actions would eventually cause a numbness and shrinkage of the appendages, which finally separated and dropped off. According to the description in the "Annales Xantenses" of 857 A.D., "a great plague of swollen blisters consumed the people by a loathsome rot, so that their limbs were loosened and fell off before death." This disease proved fatal to thousands during the endemic and pandemic plagues of Europe and Russia during the 10th, 11th, and 12th centuries when the peasant classes ingested ergotized grains. The great ergot plagues of the middle ages, which were known as "Holy Fire;","St. Anthony's Fire," and "St. Marvial's Fire," were all associated with ergotized grains of rye. In addition, ergot poisoning plagued whole populations in all parts of the world. 1/ 32/

It was not until 1934 that research on ergot yielded the causative agent of the mental derangement which invariably accompanied ergot intoxication. Lysergic Acid was found to be that portion of the ergot alkaloids which is responsible for the pharmacological action on the mind.

Medical interest was aroused when Dr. Hofmann of Sandoz, Ltd., Switzerland, suffered psychic disturbances while experimenting with LSD-25. Arthur Stoll of Sandoz, Ltd., and his co-workers are responsible for most of the knowledge of this powerful agent, as well as for its partial synthesis. W. A. Stoll studied extensively its psychological effects. 6/ 32/

Sources of Ergot

Ergot is apparently the sole source of material from which Ergotrate is prepared. All the alkaloids of ergot contain either lysergic acid or isolysergic acid as the principal and characteristic constituent of the molecule. The alkaloids of the ergotamine and ergotoxine groups are polypeptides, the lysergic or isolysergic acid segment being joined to other amino acids. [33] [35] The alkaloids of the ergonovine group are amides, the lysergic acid being joined to an amino alcohol.

These groups comprise 12 alkaloids which are regarded as 6 pairs of optical isomers. In addition, ergot contains an unusually large number of pharmacodynamically active substances.

The recent work of Kharasch [60] and Stoll [35] points out that the ergot alkaloids can be classified first into two broad groups namely, peptide and amide compounds of lysergic acid. A second classification indicates the existence of three other categories based on pharmacologic activity. They are called the ergotamine (Group I), the ergovetine (Group II), and the ergonovine (Group III). In Table 1, the chemical compositions of the 12 isomeric ergot alkaloids and the responsible investigators are pointed out. In Group 1, the difference between the 2 alkaloids is due to the presence of only 1 amino acid, either l-phenylalanine or l-leucine. The separation of Group I from Group II is based on the presence of pyruvic acid in the former and dimethylpyruvic acid in the latter. However, the difference between the 3 alkaloids within Group II is due to the exclusive presence of 1 of 3 amino acids, l-phenylalanine, l-valine or l-leucine. Finally, Group III differs from Groups I and II in that the lysergic acid is combined with d-aminopropanol to form an amide derivative rather than a peptide compound as in the first two groups. Only one compound is known to exist in Group III. (See Table 1).

The first member of each of the above pairs occurs naturally in ergot and is an amide derivative of lysergic acid. The second member of each pair is an amide derivative of isolysergic acid. Both members of each pair are called stereoisomers, that is, although they are not identical with each other in pharmacological activity, they are mirror images of each other in structure. This relation in spacial configuration of both members is due to the isomerism between lysergic acid and isolysergic acid, the parent compounds from which all the alkaloids of ergot are derived. However, the second member of each pair is usually found to possess only about 1 percent of the pharmacological activity of the first, its naturally occurring isomer.

In addition, ergot contains various primary amines, especially histamine, isoamylamine, and tyrosine, as well as the quaternary bases, choline and acetylcholine. It is not surprising, therefore, that the

fungus with all its self-contradictory drugs has been an intriguing material for pharmacological research.]/

TABLE I

Alkaloids of Ergot

A. Peptide Alkaloids of Ergot

Group I - Ergotamine Group

Name (formula)	Chemical Composition*		Discoverer
Ergotamine ($C_{33}H_{35}O_5N_5$)	= Lysergic Acid + l-phenylalanine	)	STOLL (1918).
Ergotaminine ($C_{33}H_{35}O_5N_5$)	= Isolysergic Acid + l-phenylalanine)	Pyruvic Acid	
Ergosin** ($C_{30}H_{37}O_5N_5$)	= Lysergic Acid + l-leucine	) + d-proline	SMITH and TIMMIS (1936)
Ergosinine ($C_{30}H_{37}O_5N_5$)	= Isolysergic Acid + l-leucine	) Ammonia	

Group II - Ergotoxine Group

Ergocristine ($C_{35}H_{39}O_5N_5$)	= Lysergic Acid + l-phenylalanine	)	STOLL and HOFMANN (1943)
Ergocristinine ($C_{35}H_{39}O_5N_5$)	= Isolysergic Acid + l-phenylalanine)	Dimethylpyruvic Acid	
Ergocornine ($C_{32}H_{41}O_5N_5$)	= Lysergic Acid + l-valine	)	
		) d-proline	
Ergocorninine ($C_{32}H_{41}O_5N_5$)	= Isolysergic Acid + l-valine	)	
		) Ammonia	
Ergokryptine ($C_{31}H_{39}O_5N_5$)	= Lysergic Acid + l-leucine	)	STOLL and HOFMANN (1943)
Ergokryptinine ($C_{31}H_{39}O_5N_5$)	= Isolysergic Acid + l-leucine	)	

* Products of Hydrolysis
** Not yet introduced into Medicine

TABLE I -- Continued

B. Amide Alkaloids of Ergot

Group III - Ergonovine Group***

Name (formula)	Chemical Composition****	Discoverer
Ergonovine ($C_{19}H_{23}O_2N_3$)	= Lysergic Acid + d-aminopropanol	DUDLEY and MOIR
Ergonovinine ($C_{19}H_{23}O_2N_3$)	= Isolysergic Acid + d-aminopropanol)	KHAVASOF and LECOMTE STOLL and BURCKHARDT THOMPSON (1

*** Known in England as Ergometrine and in Switzerland as Ergobasine
**** Products of Hydrolysis

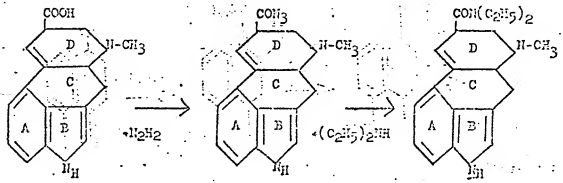
Chemical Preparation and Properties of Lysergic Acid and LSD-25

Since the parent compound of all the ergot compounds is lysergic or isolysergic acid, the preparation of LSD-25 is dependent upon the availability of lysergic acid, a compound which does not occur naturally. Jacobs and Craig, 5/ working with the degradation products of ergot, first prepared lysergic acid in 1934 by the reaction of ergotinine (ergocristine) and methyl alcoholic potassium hydroxide. The alcohol was removed by vacuum distillation. The residue was treated with additional potassium hydroxide and heated on a steam bath, during which time a stream of nitrogen gas was passed through the flask. After cooling, the material was acidified and considerable material crystallized out. This suspension was extracted with ether and the remaining aqueous suspension filtered. The filtrate was evaporated to dryness under reduced pressure. To remove colored impurities, the residue was digested briefly with a small quantity of methyl alcohol. After cooling, the undissolved crystals were collected. The yield was 25 percent. Under ultraviolet rays, lysergic acid has a distinct blue fluorescence. 103/

Lysergic acid, best crystallized from water, appears as slightly colored, very thin hexagonal leaflets which contain one mole of water of crystallization. In reaction, it is amphoteric, that is, it behaves like an acid and also a base. It is soluble in sodium and potassium

hydroxide, sodium carbonate and hydrochloric acid. In most of the neutral organic solvents, it is sparingly soluble, but in pyridine it is quite soluble.

Lysergic acid diethylamide, LSD-25, prepared in 1943 by Stoll and Hofmann, 6/ is a partially synthetic derivative obtained by reacting the azides of d- or dl-lysergic or isolysergic acid with diethylamine. In order to obtain the former, separation is effected by a chromatographic column. This method of preparation 9/ is described in Patent No. 579,454 issued to Sandoz Co., Ltd. of Basel, Switzerland. However, in this patent no mention is made of the method of preparation of lysergic acid, the parent material of LSD-25. Like the natural alkaloids of ergot, their chief component, lysergic acid, is also a sensitive substance. Special, mild methods were therefore necessary in order to convert lysergic acid into a derivative suitable for chemical reactions; such a derivative was found to be the azide of lysergic acid. The structure of lysergic acid was elucidated in 1933 by A. Stoll, and the stages involved in the preparation of LSD-25, according to Rothlin, 40/ are listed below.

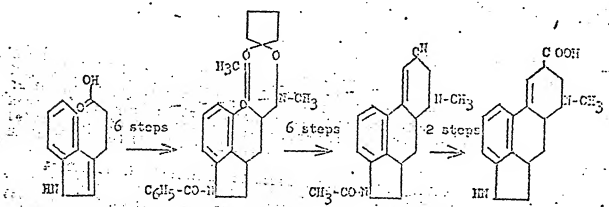


Lysergic Acid | Hydrazine | Lysergic Acid Hydrazide | Diethyl-amide | Lysergic Acid Diethylamide

According to these formulae, the following groupings / atoms may be recognized in the lysergic acid molecule: an indole system (rings A and B), a naphthalene system (rings A and C), and a quinoline system (rings C and D).

Previous attempts at the biosynthesis of ergot in Stoll's laboratory in Switzerland were unsuccessful. 3/ The biosynthesis is, however, currently being attempted in East Germany in the laboratory of Prof. Dr. K. Mothes and H. Silber of the Research Institute for Cultivated Plants, German Academy of Sciences, Gatersleben, in West Germany by Hochstrasser, 1/ 22/ in France by Madame Vialard 102/ and in Japan by Abe. 82/

The total organic synthesis of lysergic acid, including the double bond in ring D, remained unaccomplished until October 1954 67/. This first total synthesis was reported by the Lilly Research Laboratories, Indianapolis, Indiana. Some of the steps involved in the synthesis of lysergic acid are as follows:



LSD-25 is odorless, colorless, and tasteless. The tartrate salt is readily soluble in water and decomposes at 200 degrees centigrade. In strong aqueous solution it is fairly stable. 5/ 23/ For oral use the solution should be made up and stored in a dark glass bottle and not used beyond the third day after preparation. 100/

Recent research 117/ has shown that lysergic acid reacts with p-dimethyl-aminobenzaldehyde in an acid medium. When an oxidant, such as hydrogen peroxide or ferric chloride is added, a blue color is formed. This reaction is considered useful for the quantitative determination of ergot alkaloids.

Derivatives of Ergot and LSD-25

The hydrolytic products of polypeptide alkaloids of ergot were found to contain lysergic acid, succinic acid, amino acids, and ammonia. The close relationship of the peptide segment of the molecule to the amino acids and the ketonic acid was readily recognized by research workers of the Sandoz, Ltd. Thus, the total synthesis of ergot alkaloids has become a possibility. As a result of this research, peptide-like derivatives of LSD-25 were prepared by partial synthesis through the transformation of 6 amino acids, including tryptophane, 2 di- and 2 tripeptides, all of which are known as normal links in the metabolism of man.

Ergotamine, originally believed to be a theoretical compound which did not exist in pure state, was actually discovered by Stoll in 1918. 22/ Ergotamine tartrate is the most important of the ergotamine salts. It is relatively stable and quite readily soluble in water. It is also known as gynergen and is one component of the well-known preparation bellergal. It is officially recognized in the pharmacopoeias of both Switzerland and the United States.

As far as the treatment of certain types of migraine and vasomotor headache is concerned, Krayenbuhl 19/ pointed out that there can be no doubt that ergot preparations - ergotamine tartrate, dihydroergotamine, and cafergot (a combination of ergotamine and caffeine) - eliminate the pain phase of the attack by increasing vascular tonus and reducing the amplitude of pulsations. In a study on a large number of patients, it was shown that prolonged oral treatment with dihydroergotamine-Sandoz or with hydergine exerted a favorable effect on migraine and vasomotor headaches.

The drug hydergine, because of its efficacy in the treatment of peripheral vascular diseases, including trench foot and frostbite, might be very useful in Arctic operations. A stockpile of this drug would be important for human protection. 31/ Hydergine contains the

methanesulphonates of dihydroergocornine, dihydroergocristine and dihydroergocryptine in equal parts. These three substances are obtained by the partial hydrogenation of the corresponding natural alkaloids of ergot and were first prepared by Stoll and Hofmann in 1943 in the Sandoz Research Laboratories. 36/

Recent work has been conducted on the sympathicolytic and oxytocic properties of synthetic derivatives of ergot. 22/

In the search for the true active principles of ergot, various investigators during the course of the past 50 years have isolated from the drug a large number of compounds, demonstrating impressively the power of synthesis which may be possessed by a fungus such as Claviceps purpurea. In addition to the specific ergot alkaloids, other interesting compounds are found in ergot. Rothlin 40/ compiled a list of non-specific compounds which is presented as Table II. In contrast to the ergot alkaloids, however, these compounds are ubiquitously distributed in nature.

TABLE II

Nonspecific Compounds Found in Ergot

Tyramine	Clavine
Histamine	Tyrosine
Agmatine (delta-Guanidyl-butylamine)	Histidine
Putrescine	Tryptophane
Cadaverine	Ergothioneine
Isoamylamine	Ergotinic acid
Trimethylamine	Ergosterin (Ergosterol)
Choline	Vitamin D
Betaine	

The knowledge of the chemical structure of the ergot alkaloids which has been gained as a result of their analysis and degradation has also made it possible to attempt their chemical synthesis. Partial syntheses were accomplished by Stoll and coworkers, Uhle and Jacobs and others. In 1953-54, Uhle completed 11 of the 12 steps which he considered necessary for the complete synthesis. As indicated earlier, in September 1954 Kornfeld and other staffworkers of the Lilly Research Laboratories, Indianapolis, Ind. working with Woodward of the Converse Memorial Laboratory, Harvard University, 67/ completed the total synthesis of both lysergic acid and the ergot alkaloid ergonovine. These partial and total syntheses are of great significance for the manufacture of the known, naturally occurring active principles and closely related derivatives.

Syntheses are also desired for the preparation of compounds, which may possibly be stronger in action, less easily detectable, and longer lasting in effect than LSD-25, for instance, and which might also open the mind to the power of suggestion to a degree never hitherto dreamed possible. In view of these possibilities, the strategic use of such synthetic compounds is self-evident.

Recent work on the preparation of partially synthetic derivatives of lysergic acid had led to compounds which already bear a close resemblance to the natural alkaloids of ergot, having a peptide-like structure. Table III, a list of the derivatives of lysergic acid which have so far been prepared, indicates the great variety of possibilities for preparing new compounds.

TABLE III

Peptide-like, Partially Synthetic Derivatives* of Lysergic Acid
Isolysergic Acid and Dihydrolysergic Acid

Acids	Prepared by Reaction With	Peptide-like Partially Synthetic Derivatives
1. Lysergic acid: 2. Isolysergic acid: 3. Dihydrolysergic acid:	amino acids: ⟷	L-alanine L-leucine a-aminobutyric acid L-phenylalanine L-tryptophane L-histidine
	dipeptides: ⟷	glycyl-glycine glycyl-L-leucine L-seryl-L-leucine
	tripeptides: ⟷	diglycyl-glycine L-seryl-L-leucyl-D-proline

*The compounds described by Rothlin have been termed "partially synthetic" because they have been obtained by chemical reactions with lysergic acid which was derived from natural alkaloids of ergot.

A synthesis of 3-substituted quinolines was developed by Uhle and Jacobs. 44/ This work has made possible the synthesis of a derivative called dihydro-di-lysergic acid.

Wheeler and others 45/ reported the synthesis of four new indole derivatives which have certain structures which are also contained in lysergic acid. However, attempts to prepare substituted amide derivatives by various methods were unsuccessful.

Lysergic acid monoethylamide, a derivative called LAE has been mentioned by Rothlin and Cerletti. 58/ Low doses (0.5-0.75 mg) of LAE produce, according to Solms 106/, a schizophrenic-like condition in normal people and a sedative-like effect in schizophrenics.

As of 1953, it was reported that Sandoz Ltd. was actively searching for an antidote for LSD-25 One compound, a Brom-LSD-25, is available, which seems to check the action of LSD-25 in the "waltzing mice." As an antidote in man, its effect is unknown. 29/

Fischer 107/ attempted to prevent an LSD-caused psychosis by previous administration of a competitive inhibitor. Suitable compounds were found in the phenothiazine series: methylene blue, N-(2-diethylamino-n-propyl)-phenothiazine, 3-chloro-10-(-3-dimethylaminopropyl) phenothiazine, and N-diethylaminoethyl-N-phenothiazine which display a gradually increasing affinity for wool protein as well as modify and inhibit the psychotic experience otherwise caused by LSD. Preliminary experiments suggest that a gradual increase in affinity for wool of a compound might be associated with a more complete inhibition of the experimental psychosis. These inhibiters also display a gradually increasing adrenolytic action.

Most recently Fabing 120/ observed that the gamma isomer of neratran, when given orally as a premedication, blocked the psychic effects due to LSD-25. When administered intravenously, it abruptly terminated the psychotic reactions due to LSD-25.

Pharmacological Effects of LSD-25

Effects of LSD-25 on Man. -- Although the formula for lysergic acid was established in 1934 and the substance was prepared in the same year, LSD-25 was not discovered until 1943. It was Hofmann 59/ who, while working with the amide derivative of lysergic acid, experienced the psychogenic effects of the drug. He felt that it was necessary to leave his work because of dizziness and marked unrest. At home he fell into a state of disagreeable intoxication which lasted for hours, during which he experienced visual hallucinations. In order to verify

the effect, Hofmann later swallowed 250 gamma, a quantity then considered too small to be effective. After 40 minutes vegetative crises appeared, and a violent delirious psychosis developed. He discontinued taking notes in the laboratory record book because he could no longer give sensible answers. A physician had to be summoned. Six hours later there was a spontaneous improvement, and after a night of sleep, the chemist felt completely well again, although still tired.

Studies with LSD-25 were carried out by Forrer and Goldner 13/ in an effort to clarify the physiological and psychic responses attendant on administration of this drug in schizophrenic patients. The drug produced a slight increase in blood pressure, slight increase in pulse rate, no essential change in respiration, increase in salivation and lacrimation, dilation of the pupils, increase in deep reflexes, and slight ataxia. Oral administration produced pupillary dilation of marked degree, whereas topical administration produced very slight dilation. The total white blood cell count was increased during the time of action of the drug. Urinary constituents, the nonprotein nitrogen level, the electroencephalogram, cephalin-cholesterol flocculation, weight, and temperature were not affected by the administration of this drug in doses up to 6 gamma per kilogram. In view of these data LSD-25 seems to be a suitable substance for further therapeutic investigation of the psychoses.

DeShon and others investigated the effect of LSD-25 on the cerebrospinal and autonomic nervous systems. 17/ Dysarthria, which occurred in five experiments, consisted of a transient stumbling over words and was never marked. Involuntary smiling, giggling, and laughing were considered in the nature of "risus sardonicus" where the subject described these phenomena as occurring without or against his will. One subject stated, for example, that, in a smile, he felt as if his facial muscles were like plastic wax being moved by some inexorable force. Equilibratory incoordination, subjectively experienced by some subjects, could never objectively be ascertained. Disturbances in tests of handwriting, reading, gait, station, pupils, nonequilibratory coordination, deep tendon reflexes, and muscle power in the arms were not observed. The autonomic nervous system appeared to be more affected than the cerebrospinal. Flushing, sweating, shivering and chills with goose-pimples occurred many times. Tachypnea, salivation, pallor, sighing, and urgency of micturition were scattered observations. Changes in pulse rate and a rise in both systolic and diastolic blood pressure of 10-20 millimeters of mercury occurred in 1 hour and 30 minutes after administration of LSD-25. Striking changes in handwriting were also recorded. 54/

Other effects of LSD-25 on the body are listed as follows:

CARDIOVASCULAR SYSTEM - Blood pressure slightly increases, within the physiological limits, or not modified; less frequently it was slightly decreased. Two patients developed profound circulatory depression. Heart rate increased in some, decreased in others, not modified in one case.

DIGESTIVE SYSTEM - Anorexia; sometimes nausea with occasional vomiting; also isolated cases of lycorexia.

HEPATIC FUNCTIONS - Only slight changes were observed. However, subjects in whom even slight modification of hepatic function is present such as the protracted sequelae of infectious hepatitis, have a very marked response to LSD-25.

RESPIRATION - Usually not changed, although occasionally deeper and slower.

URINARY SYSTEM - No changes in composition of urine. Diuresis sometimes increased. In isolated cases retention of urine followed by polyuria was present when the effects of LSD-25 had worn off.

REPRODUCTIVE SYSTEM - Uterine cramps in isolated cases.

TEMPERATURE - No change; in exceptional cases, it increased 1°F.

SALIVARY SECRETION - Often increased.

SWEAT SECRETION - Often increased.

LACHRYMAL SECRETION - Sometimes increased.

EYES - Generally dilatation of the pupils; sometime impairment of the reaction to light; mydriasis less pronounced when LSD-25 is instilled into the conjunctival sac.

BLOOD PICTURE - Temporary increase in the total white cell found without modification in the differential count or relative neutrophilia. Slight increase in potassium blood values but no change in calcium blood levels. Some tendency towards anemia appeared during prolonged treatment.

BLOOD SUGAR - Slight rise within physiological limits; less frequently a fall; slight transitory increase in the glucose and hexose monophosphate blood levels; otherwise, carbohydrate metabolism not affected.

According to Wahl 93/, the symptoms experienced by 32 subjects were hyperkinesis, tremors, athetoid-effects, nervousness, sleeplessness, headache, fatigue and other pains, lachrymation, swelling, increased pulse rate, and salivary secretion in the descending order of occurrence.

Electroencephalographic studies were performed by Gastaut and others 61/ on 12 normal subjects who had taken a single oral dose of 40-60 gamma of LSD-25. In these studies it was found that the alpha rhythm was increased by 0.5 to 4.0 cycles per second. In half of the cases the central beta rhythm was initiated, or if already present, was accentuated. Stimulation by means of a flickering light caused an increase in occipital potentials in seven cases. Other workers have reported similar findings. 101/

Effects of LSD-25 on Animals. -- In certain respects LSD-25 resembles ergonovine. It exerts a uterotonic effect on the rabbit, which in situ is 70 percent that of ergonovine. In contrast to the alkaloids of the ergotamine and ergonovine groups LSD-25 exerts no adrenosympathicolytic effect. 27/

However, LSD-25 may be clearly distinguished from all mentioned ergot alkaloids so far investigated in other respects. The injection of small doses of LSD-25 into the anesthetized rabbit produces motor excitation. In the dog the first apparent effects of LSD-25 are of a vegetative (sympathetic) nature, e.g., copious salivation, without any significant change in affective behavior. High doses of LSD-25, like bulbocapnine, cause motor rigidity in man, dog and cat, a condition reminiscent of a cataleptic state. In the normal mouse, LSD-25 has a weak excitatory action which appears only at subtoxic levels. Mice with an hereditary anomaly, the so-called "waltzing mice," are more sensitive to this drug. 55/, 105/

Mayer-Gross et al. 110/ studied the effects of LSD-25 on the metabolism of isolated brain and liver tissue of guinea pigs. As a result, it was concluded that LSD-25 exerted a sparing effect on the hexosemonophosphate metabolism which is greater in brain than in liver tissue, at the same time stimulating the respiration of the brain. It would therefore seem justifiable to relate the psychological action of the drug to these effects on metabolism. However, in in vivo experiments no such relationship between psychological and metabolic changes was noted.

ffects of both LSD-25 and LSD (lysergic acid monethylamide) ...
...ave been studied. 53/ Instead of sedation an apparent ...
... of hydergine, there was an increase in the general excitat...
... with simultaneous suppression of the walking movement.

... of 40 gamma per kilogram injected intravenously or into the ...
...tery of a rabbit caused marked or complete flattening of the ...
... the electrocorticogram. The effect was clear-cut even after ...
... as 15-20 gamma per kilogram; after massive doses (500-... per kilogram), the effect was identical. In addition, ... simultaneous marked motor hyperexcitability 21/ 23/ 105/ due ...
...ct of this LSD-25.

... inhibited the spontaneous rhythmic activity. It did not ... response to electrical stimulation, the epileptic spikes, or ... of rapid spikes produced by the barbiturates, or by ... gamma. Of the vasodilator substances investigated, nicotinic ...amine, hexamethonium, priscol, and alcohol did not modify the ...SD-25. Acetylcholine, given intravenously, in doses of 20-40 ...ilogram, caused the reappearance of bursts of basal rhythm. ...experiments LSD-25 is usually administered intravenously. 22/

... has also been tested for its effects on the central nervous ...spiders. 16/ 57/ It was found that normally spiders exposed ...fecting their central nervous systems lose some of their ...e ability. This was particularly noticeable in the case of ... of spider webs. The webs woven by spiders under the ... of such drugs are asymmetrical and sloppily constructed. The ...SD-25 on the instinct behavior of spiders is, however, quite ...it was discovered that under the influence of this drug, ...e able to weave webs which are more symmetrical and more beauti... way than the webs they are able to weave while under the ... of any other drugs.

...ecent work, 53/ supplemented by photographs of webs woven by ...er the influence of caffeine, chloral hydrate, pervitin and ...arly shows the effects of these drugs on the central nervous ...the spider. It was felt that because of the characteristic w... ...ders under the influence of certain specific drugs, there... ...e may be used to identify the presence of minute and even ...ities of unknown drugs. One disadvantage of this technique, ... that it appears to work only during the summer months. 57/

...of Action of LSD-25

...rough chemical and pharmacological investigations of the

ergot alkaloids which have been carried out during the last 30 years have revealed interesting relationships between chemical structure and pharmacological action. It has now been established 40/ that the fundamental cause of the action resides in the d-lysergic acid part of the molecule. On the other hand, other constituents of the molecule which are coupled with lysergic acid are responsible for the differentiation in the pharmacological action.

The action of the ergot alkaloids is influenced to a very large extent by "the double bond in the D-ring" of lysergic acid which is assumed to be in the 9, 10 position. If this bond is saturated by catalytic hydrogenation, all the natural ergot alkaloids lose their uterotonic effect.

How great the influence of saturating the double bond in ring D can be, may be illustrated by means of the following example. Ergotamine is a powerful oxytocic, characterized by a very strong and protracted constrictory action; but in cases where excessive uterine tonus is liable to hinder the normal progress of parturition, it is able to bring about relaxation of the uterus or to restore the normal tone. As a result of the hydrogenation of the natural alkaloids of the polypeptide type, there is now a considerable prospect that a number of important diseases, such as hypertension, peripheral vascular disorders, and angina pectoris, which were formerly outside the field of indications of the ergot alkaloids, may be treated successfully with the dihydro derivatives. So far the only alkaloids which have attained therapeutic importance are those derived from D-dihydrolysergic 39/ acid.

It has been noted that barbiturates administered to patients under the influence of LSD-25 abolish the psychic effects of the latter drug. It is well-known that the barbiturates act initially on subcortical structures. The site of action of LSD-25 is not known. It is believed 13/ that the drug acts primarily on the cortex to produce a depression, and there is abundant evidence to suggest this, that is, increased deep reflexes, dilation of the pupils, salivation, euphoria, and increased accessibility. One might think of the effects of LSD-25 as being due to a release of the lower centers from cortical control. It would hold, then, that any drug which depresses the subcortical centers would, by blocking the subcortical release effectively, nullify the psychic action of LSD-25. This would be further evidence for and support of the present belief that LSD-25 in the amounts used acts primarily on the cortex, that the neurological symptoms following administration are directly attributable to this cortical effect, and that the psychic phenomena witnessed under its influence are the result of subcortical discharges no longer fall under full control of the cortex.

Mayer-Gross and others 21/ pointed out that the tremendous activity of LSD-25 suggests that the inhibitive symptoms might be caused by an anti-enzymatic mechanism on the cerebral cellular mechanism. Since glucose is normally regarded as the most important and perhaps the only substance required by the nerve cells, it seemed logical to analyze the influence of the drug on human carbohydrate metabolism. Twenty-four persons were given 0.04 to 0.07 milligrams of LSD-25. On the following day, under the same conditions, control experiments were made on 19 persons, 15 of whom were identical with those who had already received LSD-25.

Analyses of blood samples indicated that the hexose monophosphate values and the carbohydrate values increased in those subjects who had been given LSD-25. A plausible explanation, which became at once apparent, was that the carbohydrate metabolism was interrupted in the presence of LSD-25 and could not pass beyond the hexose monophosphate stage. If the theory is adopted that LSD-25 blocks the decomposition of the hexose monophosphate, and furthermore if this blocking action is held responsible for the psychic symptoms, then the direct intake of carbohydrates, which can be utilized without detour via the hexose monophosphate stage, should influence the clinical picture of the intoxication. Although the authors, Mayer-Gross et al., could not arrive at such definite conclusions because of the lack of sufficient data, it was, nevertheless, evident that the symptomatology (optical illusions, alienation of perception, lack of concentration power, euphoria, etc.) was modified and partly disappeared after the intravenous administration of a 33-percent glucose solution.

Since previous research had shown that LSD-25 interfered with the carbohydrate metabolism and there resulted an increased concentration of hexose monophosphate, Mayer-Gross 34/ attempted to solve the time-intensity relationship between the psychological symptoms and the biochemical changes. Since schizophrenic patients are known to have a greater tolerance to LSD-25, it was decided to use them as subjects. Results showed that, although the psychological effects were minimal, there was an increase in blood hexose monophosphate. This average increase was 1.46 milligrams per 100 milliters of blood. Under control conditions there was a mean fall of 1.17 milligrams per 100 milliliters of blood.

Among a group of schizoid patients undergoing treatment with LSD-25, two were diabetics who had to be transferred to the medical service before the treatment was complete. 20/ Curiously, their insulin requirements were lowered temporarily after taking the LSD-25. Although the meaning and validity of this observation are as yet uncertain, it seems evident that LSD-25 does interfere with the carbohydrate metabolism.

In view of the marked similarity between the psychological symptoms of LSD-25 and mescaline, a parallel series of experiments on the influence of mescaline on the blood chemistry was carried out on 9 normal adults. Three-tenths of a gram of mescaline hydrochloride was administered intramuscularly. Analyses were made for glycose, hexose monophosphate, alkali reserve, lactic acid, pyruvic acid, inorganic phosphate, total acid soluble phosphate, lipoid phosphate, adenosine triphosphate. No significant variations could be detected in any of these analyses. The mechanism of mescaline is apparently different from that of LSD-25.

d-N-Methylamphetamine hydrochloride (methedrine) in doses of 40 to 60 milligrams and LSD-25 in doses of 40 to 60 gamma were given by intravenous injection to patients suffering from various mental disorders and their clinical and biochemical effects studied. 37/ After an initial phase of relaxation both drugs produced an aggravation of the clinical picture; while depressive patients became more retarded and depressed, or more agitated, schizophrenic patients showed signs of increased withdrawal and tension and an accentuation of catatonia and cataleptic features. Abreaction frequently occurred, especially in psychoneurotic patients.

Rapid mood swings were sometimes observed after the injection of LSD-25. Methedrine did not produce this effect, but it more readily provoked hallucinations in schizophrenic patients.

The biochemical studies indicated that the effects of both drugs on the plasma adrenaline level were similar. Three phases could be distinguished after the injections: an initial rise of the adrenaline level, a drop below the starting level, and finally a secondary rise. Individual cases mainly differed in the speed with which these phases followed each other. Sometimes, and especially after the injection of LSD-25, the adrenaline level decreased before the initial rise could be observed. When, however, LSD-25 was given by mouth, the initial increase of the adrenaline concentration was clearly evident.

A moderate increase of the blood sugar concentration sometimes followed the injection of methedrine, but the effects of LSD-25 on the blood sugar concentration were hardly significant.

Because LSD-25 intoxication is marked by depersonalization and vegetative symptoms, it probably affects the mid-brain and the inner-brain. The intoxication, in accordance with Stoll's concept, is likely a di- or mesencephalosis. It is still uncertain, however, how extensive the effect of LSD-25 is; how many, if any, peripheral or central metabolic processes are released; and how many intermediary toxic compounds may be developed in the actual release of externally visible symptoms. 38/

According to Arnold and Hoff [19], the LSD effect in the wide sense of its cytostatology resembles that of diluvian trauma, although the degree in each case pronounced in the latter.

Toxin Effects of LSD-25

According to a Polish source, [8] research in the USSR indicated that the human organism can accumulate as much as 0.35 percent of ergot in flour. In animal experiments the use of ergot resulted in gangrene; the ears, hooves, teeth, and hair were affected. Of all animals, cattle were affected the worst.

It is a known fact that the hydrolytic products of the ergotamines consist of the metabolically important substances like ammonia, succinic acid, and the amino acids and that lysergic acid-like substances may also be prepared from physiological metabolic substances. [39] From these facts the analogy can be drawn that the human organism might be able to form toxins similar in nature to LSD-25, which then might become active in peptide combinations. These in turn might then be transformed by the diseased organism into biologically active toxins. There are some indications that such long-suspected but hitherto undected secondary toxins might be identical with LSD-25 or substances closely related to it. Verification of such an hypothesis is contingent upon the development of precise methods for the detection of these toxins.

In order to give some indication of the minute quantities of LSD-25 which are required to influence the human mind, Table 4 is presented.

TABLE IV

Minimum Action Values of Cerebral Agents in Human Therapy

Glutamic Acid	per os	10,000,000 gamma to 40,000,000 gamma
Ethyl Alcohol	per os	7,000,000 to 20,000,000 gamma
Chloral Hydrate	per os	1,000,000 to 3,000,000 gamma
Dibenamine	intravenous	200,000 to 400,000 gamma
Cocaine	subcutaneous	80,000 to 300,000 gamma
Mescaline	per os	10,000 to 20,000 gamma
Morphine	subcutaneous	5,000 to 10,000 gamma
Atropine	subcutaneous	3,000 to 10,000 gamma
Dilaudid	subcutaneous	2,000 to 4,000 gamma
Pervitin	per os	1,500 to 3,000 gamma
LSD-25	per os	10 to 30 gamma

Hoch, 46/ in reporting his personal experiences during LSD-25 intoxication and subsequent intoxication by mescaline, pointed out that the physiological effect of both drugs is similar. In their psychologic effect they differ; LSD-25 produces an hebephrenic-type reaction and mescaline, a catatonic-like state.

Fisher and others 53/ made a comparative study of the effects of LSD-25 and mescaline from the standpoints of psychopathology and physiopathology. They confirmed previous observations of Hochmann and Stoll that LSD-25 produces schizophrenia-like disturbances, bearing particularly on affect, perception, and thought. The comparative toxicology of LSD-25 and mescaline, tested in four subjects, showed that maximum doses of 130 gamma of LSD-25 and 0.5 gram of mescaline effected the same psychic phenomena. However, certain qualitative differences listed in Table V were also noted.

TABLE V

Comparative Effects of LSD-25 and Mescaline

Psychic Phenomena Produced	Effect of LSD-25	Effect of Mescaline
Altered Sense of taste	dampened	enhanced
Altered Sense of smell	unaffected	enhanced
Hallucinations	present	more pronounced
Critical judgment	present	less pronounced
Euphoria	produced	less pronounced
Silly compulsive coloration	produced	not produced
Experiences of splitting	produced	more intense
Paranoid phenomena	uncommon	common
Psychotic picture	hebephrenic	catatonic
Physiopathologic Phenomena		
Hippuric acid test	slightly disturbed	more disturbed
Cinnamic acid test	positive*	positive*

*Also positive in cases of schizophrenia

The psychophysiological and physiopathological differences between LSD-25 and mescaline could possibly be due to the smaller amounts of LSD-25 administered. LSD-25 does, however, appear 100 times more toxic

than mescaline, when tested comparatively, using the larvae of Xenopus laevis Daudin. In humans, LSD-25 is 2000 times more potent than mescaline. Metabolic substances, if actually present during schizophrenia, must be closer akin to mescaline than to LSD-25. Thus, LSD-25 merits a special consideration as a psychotic, not restricted merely to the psychopathological phenomena observed in LSD-25 intoxication, but beyond this in connection with a whole series of new questions and problems in the entire general field of psychophysical correlations and in the special field of schizophrenia. If the current working hypothesis is accepted, namely, that the release of acute schizophrenic "drive" stands in a time relation with endogenous metabolic substances - then the presumably with the secretion of toxic metabolic substances - then the possibility of the existence of such substances must be investigated, using both physiochemical and biological methods.

Anderson et al 113/ administered from 60 to 600 gamma of LSD-25 orally to 4 normal volunteers and 19 psychiatric patients. One male patient with psychogenic amnesia was given 600 gamma LSD-25 which caused a very labile state with the mood fluctuating between aggressive euphoria and agitated depression, transient auditory hallucinations, body image disturbance and time disorder. It was concluded that over a certain minimal dose there is no clear relationship between the clinical picture and the amount of LSD-25 taken.

Blickenstorfer 39/ summarized the following observations of Buscaino 104/ and others in connection with LSD-25 intoxication: (1) schizophrenics possess greater resistance to the drug and have taken up to 500 gamma; (2) related belief in the toxic etiology of schizophrenia and inclusion of LSD-25 with other so-called schizophrenic substances such as atropine, bulbocapnine, and mescaline; (3) records the conclusion that LSD-25 intoxication is an especially suitable psychosis model of schizophrenia as it produces, in contrast to mescaline, hebephronic phenomena; (4) the two fundamental disturbances which control the psychotic syndrome are affect and intentional sphere: (5) LSD-25 has been tested as an aid to psychotherapy; (6) because of the tolerance to LSD-25, it might be one of many therapeutic agents in shock therapy; (7) LSD-25 and histamine may possibly be antagonistic agents; (8) epileptic persons could clearly differentiate LSD-25 hallucinations from common hallucinations; (9) reported the results of Rorschach and other tests of patients under the influence of LSD-25; (10) spiders, under the effects of minute traces of LSD-25, weave nets of most unusual structure.

From studies carried out on animals, scientists have determined that LSD-25 is an extremely safe and relatively nontoxic substance. The lethal intravenous dose was 65 milligrams per kilogram and the lethal

subcutaneous dose was 4.05 milligrams per kilogram in laboratory animals. By extrapolating these data to humans, a procedure open to question, the lethal dose in 50 percent of the cases is calculated to be 4,550,000 gamma. As a comparison, between 70 and 150 gamma are regarded as effective, although it has been reported that 600 gamma have been given to a schizophrenic. Using 50 gamma as a minimum effective dose, this is only 1/90,000 of the lethal dose. Unquestionably, this is an amazing spread between the effective and the lethal dose.

The first workers to carry out research were struck by the analogy between the intoxication produced by LSD-25 and mescaline delirium, although the actived doses of these two products are quite different; LSD-25 is 2000 times more effective than the mescaline on a weight basis. 27/ An analogous relationship has been found when comparing the toxicity of the two substances in cold-blooded animals. The lethal dose of mescaline in tadpoles is 100 to 1000 times greater than that of LSD-25.

In addition, mescaline produces important changes in hepatic function demonstrable by the usual laboratory tests, whereas, LSD-25 produces a much slighter change which is made evident only by an ultra-sensitive test.

Psychophysiological Effects of LSD-25

As far as systemic effects are concerned, both normal and psychopathic subjects respond in almost the same manner to LSD-25 and may, therefore, be considered as one group. However, this is not the case with the mental effects; therefore, normal and psychopathic patients have to be considered separately in this respect.

Up to the present, LSD-25 has usually been administered orally, generally in the morning on an empty stomach. It is active in doses as small as 10 gamma. (Ten gamma would occupy no more space than the point of a pin) A dose of 40 to 100 gamma is active in most cases. Doses as high as 600 gamma have been well-tolerated by psychopathic patients. In general, psychopathic patients show greater resistance to the systemic and mental effects than do normal subjects.

The first effects of an active dose of LSD-25 generally appear within one-half hour with a maximum delay in the onset of three hours. Maximum effectiveness is reached on an average after 2 hours, and the effects persist from 3 to 6 hours. Delayed effects may be observed for 1 or more days but rarely for more than 1 week.

The symptoms produced by LSD-25 have been considered by W. A. Stoll as expressions of acute exogenic psychosis, analogous to those produced

by alcohol, opium, cocaine, hashish, mescaline, and the amphetamines. These latter substances are, however, only active in the higher doses.

There is no uniform reaction to LSD-25. Two main types of reactions may, however, be distinguished: (1) Manic, expansive reaction with psychomotor excitement, euphoria and less frequently depression; (2) A schizophrenic reaction with slowing of mental processes, inhibitions, autism, depersonalization and hallucinations.

The majority of subjects present a mixture of these extreme types. The manic response to the action of LSD-25 is believed to be due to its effect on the sphere of intention, and the schizophrenic reaction to the action on the sphere of affect.

In general, LSD-25 tends to reinforce pre-existing tendencies, producing a caricature of the subject; the cyclothymic patient often becomes euphoric while the schizoid becomes a true schizophrene. Thus, LSD-25 reveals latent tendencies, and its effect may be considered, to a certain degree, as a personality test. Past experience has shown that LSD-25 produces such an overwhelming emotional and intellectual upheaval in the individual that any experiments with this substance must be very rigidly controlled. Once in a Swiss mental hospital, a practical joker sneaked a few grannules of LSD-25 into a staff nurse's coffee. The frantic girl, apparently driven to believe that she had become schizophrenic, leaped to her death from the hospital rooftop. 19/

DeShon, 17/ Rinkel, 47/ Becker, 41/ and others have described in summary articles the mental changes experimentally produced by LSD-25 which was administered 17 times to 15 normal adult volunteers. The drug was administered orally in doses ranging from 20 to 90 gamma (in most cases, one gamma per kilogram of body weight) in about one-half of a glass of water at 0830 hours on the day of the experiment, the subject having eaten no food since the previous evening. The main observations throughout the experiment were on the clinical psychiatric picture. Routine neurological and circulatory system examinations were now done, but signs occurring in these areas were noted if observed.

Results of these investigations are presented in the six following categories:

SUBJECTIVE SYMPTOMS - These symptoms were present in all subjects. They were usually the first to appear, lasting from 15 minutes after administration of the LSD-25 until bedtime. The most common subjective symptom was a decrease in appetite. Frequent complaints were headiness, giddiness, faintness, and tremulousness and shaking. A sense of poor

coordination, which could not be ascertained objectively, was frequent. Next in incidence were subjective feelings of weakness and fatigue; chilliness and coolness of the whole or part of the body; fullness, lump, and "funny feelings" in the abdomen; numbness of the whole or part of the body; headache; warmth; lightness; drowsiness; nausea; and stiffness.

CHANGES IN THINKING AND SPEECH - These symptoms were found in all of the experiments. The most frequent type of disturbance was difficulty in the power of expression and concentration. Next there occurred retardation, press of ideas, hesitancy and indecision, blocking, and impairment of abstract thinking. Less frequently observed were poverty of thought, looseness and disconnection, and distractibility. These changes in thinking and speech appeared within 45 minutes after administration of the LSD-25 and lasted into the late afternoon.

CHANGES IN EMOTION, MOOD, AND AFFECT - These alterations, which were present in all of the experiments, appeared from 15 minutes after the administration of the LSD-25 until evening. Clear cut blunting of affect and suspiciousness were the most common symptoms in this category. Tension and apprehension, as well as feelings of unreality with disturbances in body images, were noted in the majority of observations. Euphoria with a shallow elation and silliness were often seen as were depression, combined with dependency, indecision, insecurity, passivity, and feelings of being "lost." Hostility and resentment were observed in some instances and, on rare occasions, ambivalence and intensified feelings of reality and greater understanding were noted.

DISTURBANCES OF PERCEPTION - These disturbances were common; those of visual perception predominated. Individuals would see rippling, or movements of objects, or the objects would vary in size and shape. Color disturbances were common, such as seeing yellow, orange, or pink colors where there were none. Disturbances of gustatory and auditory perception were less frequent; the latter disturbances were mainly in distinguishing the origin of a sound - distant or near. Time sense was disturbed in 11 of the experiments and was characterized by the feeling of time being either accelerated or retarded. The phenomena appeared from 40 minutes to about 7 hours after the ingestion of the LSD-25.

DISTURBANCES IN BEHAVIOR - These manifestations were seen in 15 experiments from 25 minutes after the administration of LSD-25 until evening. Underactivity, with lack of spontaneity and initiative, was most commonly observed. Overactivity or inappropriate behavior was rarely noted. Often behavior was associated with psychomotor manifestations such as smiling, giggling, and laughing which seemed more

appropriate than inappropriate. Aggressiveness, dramatization, playfulness, perplexity, and negativism occurred only occasionally.

MORBID IDEAS AND SENSORY EXPERIENCES - These experiences included ideas of reference and ideas of influence. The visual hallucinations were all formed images, but in one subject these were preceded by crude flashes of light. Three visual illusions, which appeared in many experiments, were of complex visual interpretation which, however, the subject did not believe; for example, seeing a thermostat on the wall as a crucifix, although really knowing that the experience was an illusion. The one instance of auditory hallucinations was of bells. Two instances of gustatory hallucinations were of metallic and other "funny" tastes. One instance of haptic hallucinations was a rather vivid experience in a subject of his trousers being wet from urine. The morbid ideas and sensory experiences appeared most frequently from 1 hour and 30 minutes after the administration of LSD-25 at 0830 hours in the morning to early afternoon.

The course of reaction to LSD-25 was presented in three phases within the first 12 to 16 hours, and a fourth phase appeared as an after-effect. Phase I, the prodromal phase, represented the period between the administration of the drug and the height of the reaction. The effects were usually subjective symptoms and appeared from 20 minutes to 1 hour and 30 minutes after the LSD-25 had been administered. Phase II represented the height of the reaction or the gross symptomatic departure from normal. It lay within a time span of 1 hour to over 5 hours after the drug had been ingested. Phase III was the period from the height of the reaction until evening. This phase was characterized predominately by a reduced activity, poverty of thought, flat affect, indifference, and a shallow feeling tone comparable to a simple schizophrenic reaction type. None of the 15 individuals who were subjected to LSD-25 had returned to normal when last seen by the authors from 1500 hours to 1900 hours on the day of the experiment. The effects in phase III were not necessarily a continuation of those in phase II. Most of the phases was clearly demarcated, and their time limits for a given experiment could be determined only roughly and in retrospect.

Phase IV included the after-effects which lasted from one to several days. It was not seen in all subjects nor closely observed in any of them. Although all subjects reported that they felt normal the following morning, a few were noted to be more awkward in behavior and speech, more industrious, and perhaps more introspective for several days following the experiment. A striking observation throughout the day of the experiment was the appearance of signs and symptoms in waves. Where symptoms were of long duration, such as indifference and blunting of affect,

there were at least wave-like alterations in their intensity. The subjective symptoms were for the most part transient; although they were scattered throughout the day of the experiment, there was a tendency for them to cluster at the beginning and to a lesser extent at the end of phase II. In general, there was much more uniformity of the clinical psychiatric picture in phase III than in phase II. In 11 experiments, phase II was decidedly schizoid, and in one experiment each, manic-like and schizo-affective.

Katz 12/ published his personal and subjective reactions after taking LSD-25. Further, by describing his visual hallucinations at the time of their occurrence, an artist was able to sketch and then reproduce in vivid colors those bizarre fantasies of the human mind which seem to be somewhat commonplace to the schizophrenic. He stated that for hours he inhabited a nightmare world in which he experienced the torments of hell and the ecstacies of heaven. Since there are no words in the English language to convey the sensations, visions, illusions, hallucinations, colors, patterns and dimensions which his disordered mind revealed, he stated that he will never be able to describe adequately what happened during his excursion into madness.

He volunteered to become a temporary madman in the interests of medical research on mental illnesses. This is one phase of research where some of the guinea pigs have to be humans; animals cannot describe their sensations. The mental condition produced by this drug closely resembles acute schizophrenia, the most prevalent and most serious form of mental disease in Canada. It is reported that one-half of the patients in mental hospitals suffer from some form of this terrible mental torture.

In 1952 Stoll 13/ submitted 11 normal adults to the Rorschach test, these being under the influence of 50 gamma of LSD-25 and repeated it at a later date without the LSD-25. A Rorschach syndrome was produced by the disinhibition of the thought processes with a decrease of precision and wealth of content. In spite of the small number of cases from which to judge, the changes do not seem to be accidental since the relevant factors become changed in a corresponding sense and lead to a logical conclusion. The clinical picture of LSD-25 intoxication, corresponding to the LSD-25 influenced Rorschach syndrome, is regarded as unspecific and as an instance of the exogenous reaction type. Both typical psycho-organic traits occur as do others suggestive of schizophrenia. Upon repetition of the test without LSD-25, similar and often identical results were obtained. The test subjects, however, often mentioned, upon repeating a response, that without the LSD-25 this response would not have occurred to them.

With [illegible] "stereoscopic oximetry", a new psychophysiological procedure, Sloan and Doust 19/ observed significant changes in their LSD experiments. The results indicated increased autonomic lability in 11 healthy controls as well as in 12 patients with predominant depression, but unmodified functioning in the 7 schizophrenics tested.

Therapeutic Use of LSD-25

By artificially creating a condition like schizophrenia, as in the case of Katz, 18/ investigators hope to find the answers to a number of hitherto baffling questions. The psychiatrist wants to know: What does he see? What does he think? How does he think? How can he best be approached by a therapist? Answers to such questions are not easy to obtain from the chronic psychotic who has little or no insight and is usually uncommunicative. The biochemist seeks information which may finally lead to a cure for schizophrenia. What toxic substance is present in the psychotic which is absent from the body of the normal person? If this substance can be identified, then it is conceivable that a chemical agent can be created to counteract it. This could theoretically lead to the cure of half of the mental patients.

Since it was previously shown that LSD-25 usually produced a euphoria in mental patients, a study was made 20/ on the affect, cognition, and expression of 5 "normal" patients and 15 depressed patients. The "normal" patients received a single oral dose of 20 gamma, and the depressed patients received between 20 and 100 gamma by mouth daily for a month. Physiological reactions included rise in blood pressure and pulse rate, mydriasis, and incoordination; but in a few cases there was a profound fall in blood pressure and pulse rate. Unpleasant side effects were nausea, paresthesias, and tension. Mental changes included euphoria or dysphoria, and hallucinations of all modalities. Ideas were transmitted into visual hallucinations of extra-ordinary plasticity. Most patients reacted with anxiety to these distortions in reality and became constricted. Infrequently, the doctor-patient relationship was improved with freedom of affect but not content. Occasionally, the latent content of the hallucinations was elicited by free association. Of the 15 depressed patients, 3 recovered to their pre-psychotic level, 4 recovered from their depression and were considered improved, 4 derived no benefit, and the treatment of 4 was discontinued prematurely.

Within the limits of this sample, LSD-25 does not appear to have a significant therapeutic advantage over other drugs in cases of depression, although it appears to be valuable as an adjuvant in a number of cases. It presents some disadvantages. The anorexia it produces may accentuate

weight loss. There is some tendency for anemia to appear after prolonged dosage, although this may be referable to reduced food intake. Insomnia is often aggravated.

The possibilities of personality explorations through direct communication envisioned by Small have not realized. While LSD-25 was not of value in promoting free verbal exchange, it is of potential use in personality exploration by the analysis of the hallucinations which it produces; for example: one patient reported a colorful medieval pagent and made a sketch of it. After the effects of LSD-25 had worn off, the sketch was presented to the patient who at first could make nothing of it. On free association, the patient brought up the idea that the medieval figures were really psychiatrists, with whom the patient had been associated. One figure was drawn with an open door for a mouth and a window for the one good eye. This psychiatrist talked too much and saw only half of the patients' difficulties. Another figure drawn slantwise or leaning was considered a drunkard. A third was pictured as a knight with a visor drawn both open and closed. Associations to this drawing suggested that the psychiatrist was two-faced. A fourth armored figure was in reality a female, suggesting that he was effeminate. The medieval setting with its rich pageantry and hapless figures suggested the ambivalence and disappointment about psycho-therapy. Thus, neither the patient nor the psychiatrist was left in doubt as to the patient's negative feelings which had previously gone unrecognized.

By contrast, projective testing during LSD-25 intoxication was less revealing than that done during the normal waking state. All patients showed marked constriction in the Form-Interpretation test. It was inferred that the patient attempted to compensate the effects of LSD-25 by an increased effort at adjustment.

These data appear in keeping with Condrau's observation 12/ that no definite conclusions can be drawn as to the diagnostic and therapeutic value of LSD-25.

Benedetti 56/ administered 2 single 50 gamma doses of oral LSD-25 within a span of 2 hours to a patient with an alcoholic hallucinosis. At the beginning of the third hour an acute hallucinatorio psychosis was observed which lasted for four hours. During this psychosis two separate, but simultaneously occurring groups of psychopathological phenomena were observed. The first included those optical and spatial hallucinatorio, and the second was strongly suggestive of the classical alcohol hallucinosis, differing only in the preponderance of optical disturbances.

LSD-25 aids psychiatry in the following manner: 30/ 111/ it is highly suited for the experimental production of intoxication due to its

simple method of application and because it produces no personal antagonism in the patient during introduction; (2) it possesses a diagnostic value in self-experiment of the physician; (3) in psychotherapy it facilitates the contact approach with the patient; (4) as a therapeutic shock agent, it appears to give results similar to other methods. Interestingly, the LSD-25 intoxication, after an initial mania-like stage, can be shaded as depressive catatonic, schizophrenic, or paranoid. Such shades or colorings depend, in all probability, more upon personal disposition than upon direct action of LSD-25, which, like many other poisons, can apparently only produce the unspecific syndrome of an acute exogenous reaction type. It is hardly suitable in the framework of normal psychology as a personality test, in spite of the many individual differences occurring during intoxication. Like all intoxicants it discloses pathological tendencies. These, while not so important in everyday life, permit conjecture of the manner in which a person may become psychotic.

A chemical analysis of normal cerebrospinal fluid has disclosed the presence of 11 amino acids: conspicuous by its absence is the amino acid tryptophane. Tryptophane is, however, one of the constituents of LSD-25. In practically all noxae, resulting in an exogenous reaction type one can expect the following: (a) pathological decomposition of protein; (b) that the substances of protein decomposition may enter the cerebrospinal fluid; (c) that these substances are probably closely related to the amino acid tryptophane which is a constituent of LSD-25. This similarity between tryptophane and LSD-25 may only be accidental. However, it may serve as an indicator that LSD-25 may also occur in human metabolism. Whether the body metabolism is capable of forming such a chemical substance under certain circumstances cannot be theoretically decided.

Busch and others 43/ administered LSD-25 to 29 patients with various type of mental disturbances. They expressed the belief that the drug induces a controllable toxic state within the nervous system which re-activates anxiety and fear with apparently just enough euphoria to permit recall of the provoking experiences. It does this without the sluggishness of speech difficulties so frequently encountered with amytal. On the basis of this preliminary investigation, LSD-25 may offer a means for more readily gaining access to the chronically withdrawn patients. Further, it may serve as a new tool for shortening psychotherapy.

The effects of LSD-25 and mescaline were studied in schizophrenic patients by Hoch and others 18/ It was found that psychological changes were produced in these patients and that their mental symptomatology was

markedly aggravated. The observations made with the above-mentioned drugs on normal individuals were compared with those of schizophrenic patients. Mescaline and LSD-25 are drugs that disorganize the psychic integration of a person. This disorganization is much more apparent in schizophrenics than in normals. The reactions of 59 schizophrenic patients who were given synthetic mescaline sulfate were classified under the following headings: (1) physiological symptoms in the autonomic, motor, and sensory spheres; (2) disturbances of perceptual activity, (3) mental content, (4) emotional alterations. Anxiety increase was the most frequent emotional change in schizophrenic patients under the influence of the drug. Many patients displayed hostility, and paranoid manifestations were very frequent.

Frederking 50/ employed both LSD-25 and mescaline in psychotherapy. In the course of early experiments, he noticed that the state of intoxication, so produced, was meaningful and significant, its content being similar in character to those of dreams. Each period of intoxication brought out particular characteristics of the person on whom the experiment was conducted. It seemed to be an attempt to present and solve his important problems. The author observed that his patients, in their respective states of intoxication, as in their dreams, generally produced those contents that were at the time ripe for expression and for transformation in the direction of a cure. In one particular case, a man accused of murder claimed that he had no recollection of the deed. Under the intoxication of 0.5 gram of mescaline and 75 gamma of LSD-25, the accused admitted that he had not committed the crime but that "another one of him" had done it. It was concluded that although the accused had actually committed the murder, it was done while in a state of subconsciousness, a fact considered earlier by the author (Frederking).

The many phenomena such as colored pictures and experiences of bodily transformation, are either purely symbolic in character, or represent childhood, sometimes to the moment of birth.

The indications for a treatment of this kind must be strictly defined, and particular circumspection is indicated with very anxious patients suspected of schizophrenia. The physician must have submitted to an intoxication himself to be able to realize its possible effects. The effect of mescaline is stronger and more overwhelming. However, LSD-25 is usually more effective in bringing out remembrances.

Delay and others 118/ recently showed that LSD-25 produced 2 syndromes, in addition to other disturbances. The first was the acute exogenous toxic syndrome of Stoll; the second was described as the hypertrophy syndrome of the exterior personality.

Abramson et al. [13] have recently criticized some of the earlier reports on the effects of low doses of LSD-25 on normal subjects. They found that for a given group of individuals suitable evaluation of responses to this drug could not be made without the use of a zero dose control group. Further, at the time when their data were compiled there were no investigations in the literature which justify the conclusions that the symptoms are significantly related to LSD-25 intoxications. On the basis of tests performed on 26 normal psychotic, intelligent adults who were given from one to three doses of LSD-25 (zero, 25-75 gamma, and 100-225 gamma), and to whom a questionnaire investigating changes in the physiological and perceptual phenomena was given at hourly intervals, the following conclusions were drawn by the authors.

1. Symptoms most significantly related to the ingestion of 50 gamma of the drug are (in order of decreasing significance): unsteadiness, dream-like feeling, paresthesias, inner trembling, pressure in ears, difficulty in focusing vision, weakness, lightness of limbs, laps drawn back as if smiling, dizziness, drowsiness, sensitivity of skin, and peculiar feeling of limbs. Less significant, but probably related are: increased salivation, increased appetite, sweating, cold, and fatigue.

2. Symptoms most significantly related to the ingestion of 100 gamma of the drug are (in order of decreasing significance): things moving about subjects, unsteadiness, paresthesias, weakness, dream-like feeling, illness, nausea, dizziness, sensitivity of skin, peculiar feeling of limbs, inner trembling, sweating, lightness of limbs, blurred eyesight, difficulty in focusing vision, and objects seeming too far away. The less significant but probably related symptoms are: feeling of choking, numbness of lips, difficulty in breathing, cold, pressure in ears, and alteration of shapes and colors.

3. There may be differences in subjective severity and quality of the symptoms which are reported under both the 50 - and 100 - gamma doses of the drug. However, several symptoms are common to both the 50 - and 100 - gamma doses, but a greater degree of response was noted under the high dose. The symptoms common to both are: feeling of illness, heaviness of limbs, nausea, funny taste in mouth, objects seeming too far away, and anxiety.

4. For the two drug doses, there is a significant correlation of .83 between the relative position of symptoms, according to frequency of positive response.

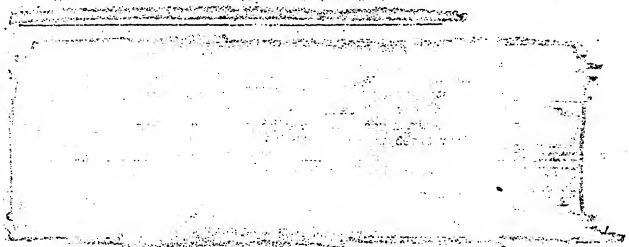
5. The average number of symptoms, out of 44 suggested, under zero dosage is about 3; under 25-75 gamma it is approximately 10; and under 100-225 gamma it is about 14. The differences among the three groups are all statistically reliable at better than the .01 level of significance.

6. The peak effect under zero dosage occurs in the first 1/2 hour, and that of the low dose occurs 1 1/2 and 2 1/2 hours after the drug. The peak for the high dose occurs 1 1/2 hours after the drug, and the effect is longer lasting than for either of the other dosages. These statements were based on group results and individual variability is not considered here.

7. The number of symptoms a subject reports under a low dose correlates .90 with the number he reports under the high dose. Although the average number of symptoms increases, he maintains his relative position within the group. There is also a relationship as high as .65 and .60 between subjects relative position under zero and under low and high doses of LSD-25, respectively. This indicates a fairly high degree of predictability of the number of responses on the basis of the number of responses under the placebo.

8. The reliability of responses to the questionnaire has been found high. Test-retest correlation as high as .77 was obtained in comparing the total number of symptoms reported at two separate testings under the same dosage.

9. The number of symptoms reported and the subject's body weight have been shown either to be unrelated or not related in the expected direction.



Ergot [illegible] human ergot poisoning epidemic [illegible] in Europe has come to light as [illegible] long ago. The epidemic in Pont Saint Esprit, in France, during 1951, where the entire population of the village was believed to have been infected by bread from ergot-bearing rye, is typical. The hallucinations, the general disturbed hysteria, and temporary mental impairment of the victims are typical of reactions to ergot [illegible]

[redacted]

LSD-25 was reported by Weyl 54/ to relax the mind and to produce an increased urge to talk. Advantage of this fact can be utilized both for therapeutic uses and for operational uses. Valuable disclosure may be obtained from persons under LSD-25 intoxication since the ability to think is not markedly impaired. The process of disciplined, logical abstract thinking, retained in almost all cases of intoxication, could however, only be accomplished with considerable effort.

It was reported by a Hungarian scientist that to the best of his knowledge (1954 and earlier) narco-analysis was not employed in examination in that country. Hypno-hypnosis was sometimes used for treatment but never for examination. 21/

Prior to World War II the police were not known to employ aktedron to elicit confessions from prisoners. However, judging by the results of treatments of today, this source believed that this drug was being used, although he has no direct evidence.

In talking with a Hungarian police officer and handwriting experts who had been employed during the early stages of the affair-Mindszenty, the source concluded that the Cardinal was drugged. His confession was induced by the alternate use of aktedron and scopolamine, the former speeding up physiological reactions and the latter slowing them down. The source reports having heard of this method being used. It was estimated that if this procedure were carried on for four days, all of

[redacted]

ie Cardinal's inhibitions would be completely annihilated. Further, would have no concern for moral codes, family, or ethics.

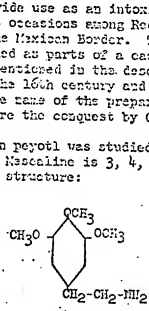
On 20 March 1953, Dr. Imre Zador, a nephew by marriage of Dr. Weil, ie Hungarian Minister in Washington, was arrested for the improper use the drug evipan. This may be a clue to the origin of charges that . Weil was the man who administered the drugs to Cardinal Mindszenty. ther Weil was mistaken for his nephew or it could have been that il was at one time associated with Zador in truth serum research.(23)

lated Drugs

The systematic use of drugs for the production of artificial ychoses is not new, but rather dates from the early work of Kraepelin 1893, according to Mayer-Gross. (25) Experiments have been performed which mescaline, hashish, bulbocapnine, cocaine and similar chemical bstances produced excitation of the central nervous system and ther results which characterized them as strategic medical agents.

Mescaline is found in wide use as an intoxicant to produce ecstatic states for special religious occasions among Red Indian tribes in Mexico and in North America near the Mexican Border. The mescal buttons chewed by the Indians were identified as parts of a cactus plant. Early reports disclose that the drug was mentioned in the description of this part of Mexico by Sahagun early in the 16th century and that the "prophetic" quality of peyotl, the native name of the prepared cactus, was probably known to Aztec medicine before the conquest by Cortez.

The active ingredient in peyotl was studied in 1896, and the formula elucidated in 1918. Mescaline is 3, 4, 5 - trimethoxyphenylethylamine. It has the following structure:



It should be realized that the outward behavior of the subject acutely intoxicated with mescaline is relatively normal. He may be absorbed in his experiences and will talk about freely but rationally. Only if the intoxication has become extreme may he lose control of himself and sink into a sleep-like stupor or delirium. Hashish, in contrast,

addition, it has been suggested that inadequate detoxification of similar substances in the liver may lead to their accumulation in the blood, causing mental disorder. Hence, the study of hepatic function is important in the etiology of psychiatric diseases.

In a recent publication Huxley 52/ pointed out the close similarity of the chemical composition of mescaline and adrenalin. Subsequent work indicated that LSD-25 had a structural biochemical relationship to these compounds. Then came the discovery that adrenochrome, which is a product of the decomposition of adrenaline, can produce many of the symptoms observed in mescaline intoxication. But adrenochrome probably occurs spontaneously in the human body. In other words, each one of us may be capable of manufacturing a chemical, minute doses of which are known to cause profound changes in consciousness. Certain of these changes are similar to those which occur in schizophrenia, a plague of the Twentieth Century. Is the mental disorder due to a chemical disorder? And is the chemical disorder due, in turn, to psychological distresses affecting the adrenals?

The action of mescaline is to inhibit the production of enzymes which regulate the supply of glucose to the brain which is in constant need of sugar. When the normal ration of sugar is reduced, the ability or faculty to remember and think straight is little affected; visual impressions are greatly intensified; the will suffers a profound change for the worse; and, interest in space is diminished and interest in time falls almost to zero.

To most people, mescaline is almost completely innocuous. Unlike alcohol, it does not drive the taker into uninhibited action. Under the influence of mescaline, a man minds his own business and suffers no compensatory hangover. Of the long-range consequences of taking mescaline regularly very little is known. Although superior to cocaine, opium, alcohol and tobacco, it is not the ideal drug. Unfortunately, there is a minority who find in the drug only hell or purgatory.

At different times, Hoch and others 49/ administered sodium amytal, pervitin, and mescaline to each of 16 patients suffering from the pseudoneurotic form of schizophrenia (Group I), 24 patients suffering from an overt form of schizophrenia with slight to moderate deterioration (Group II), and 9 schizophrenic patients with severe deterioration (Group III). In the first group, sodium amytal showed a normalization of 75 percent of the patients. With pervitin, 56 percent of the patients normalized, whereas under mescaline no normalization took place. Instead, in every patient under mescaline an intensification of some aspects of the existing clinical picture was achieved. In Group II, 62.5 percent

of the patients showed normalization with amytal, 29.0 percent normalization with pervitin, and an intensification with mescaline in 5.0 percent. In Group III, normalization with amytal was 44 percent, and with pervitin 22.2 percent. Again mescaline intensified some aspects of the clinical pictures in all patients.

Pennes 102/ administered sodium amytal, pervitin hydrochlorides and mescaline sulfate to 55 schizophrenics. In addition, 25 of these patients received LSD-25. The pharmacological action of sodium amytal was classified as a normalizer of clinical symptomatology; mescaline and LSD-25 as intensifiers; and, pervitin tended to produce an unstable state with equal representation of both normalization and intensification.

Solms 103/ tested the monoethylamide of lysergic acid (LAE) on both normal and mentally sick patients. Small doses administered subcutaneously to normal people produced indifference, paralysis of the mind with intensive depersonalization, and insomnia. Administered to schizophrenics with paranoid-hallucinatoric states, it produced a state similar to a reversible chemical lobotomy. LAE may therefore be regarded as a new type of sedative which is different from the barbiturate and morphine type drugs, and also from the sympathicolytic and parasympathicolytic drugs.

Global Availability of Ergot

Methods for Increasing Production of Ergot

Measures which have been or could be employed by nations to increase their supplies of valuable ergot drugs as well as LSD-25 are listed as follows in ascending order of difficulty of accomplishment from the standpoint of scientific capability:

The Introduction of More Efficient Harvesting and Storage Techniques. -- This could be carried out at a low cost and with a minimum of scientific effort in countries where labor is cheap and in which there is a great deal of centralized control of farming. Such a program might effect a substantial increase in ergot production. Approximately 50 percent of the ergot on grain crops is lost during the harvesting and threshing because the sclerotia being very loosely attached to the host plant are easily jarred loose. They fall to the ground and are overlooked. However, once the ergot is harvested, adequate storage facilities should be made available immediately to prevent deterioration of alkaloid content. Ergot deteriorates steadily unless and until it is properly treated and stored. Exceptionally slow collection and improper storage are some reasons the so-called "Russian ergot" never measured as high in alkaloid content as did the ergots from other countries.

The Selection of Highly Susceptible Host Crops and High Yielding Strains of Fungi. -- Rye is the major crop which is most susceptible to ergot infection and is therefore used commercially. Crop susceptibility is important, but the actual infection is governed by weather conditions. Susceptibility may be altered by the introduction of late or early blooming rye under favorable climatic conditions. Certain strains of ergot produce more of one alkaloid than another. It is also known that ergots are highly mutable and strains are mutable. Strain variation actually occurred in Norway several years ago when a scientist reported that he had discovered ergot which contained absolutely no alkaloids.

In comparative breeding tests Deufel 119/ found that it was more advantageous to grow ergot on tetraploid rye than on diploid Pathisen rye; it not only formed larger sclerotia - due probably to better nutritional conditions - but was more readily infected than the diploid rye. The alkaloid content in percentage is somewhat higher in the larger grains than in the smaller grains. The test area per square meter yielded under like conditions 3 times the amount of alkaloids.

Development of Field Inoculation Techniques. -- The actual mechanics of inoculation are crucial; but tedious. The technique consists of collecting conidia spores from infected plants and applying these spores to the host flower. A. Stoll of Switzerland has developed a machine which punctures the nodes of the rye inflorescence plant, and the method is used in other countries. Actual inoculations requires a great deal of skilled labor as efficient inoculation requires individual attention. Much less efficient techniques might include spraying the plants with sclerotia just before the flowering period or flooding the earth with spores just after the last frost. Despite the technique of inoculation used, the results will depend largely on weather conditions.

The More Efficient Utilization of Alkaloidal Content of Ergot in the Manufacture of Drugs. -- More efficient production of high yields of alkaloid content from a given amount of raw ergot requires the ultimate in pharmaceutical skill. This has been done by Sandoz Ltd., and others. Nevertheless, research in this area offers a definite challenge to scientists.

Biosynthesis. -- Comparatively speaking, research in the biosynthesis of ergot has barely scratched the surface. Claviceps purpurea has been grown on artificial media, and although there are conflicting reports on the quality and commercial value of this product, several countries are actively studying this procedure. If and when complete biosynthesis is accomplished on a practical scale, knowledgeable sources feel that Sandoz will probably be responsible for it. One indication of success in this venture would be the marked curtailment of their raw ergot procurement. The partial synthesis of some of the ergot alkaloids and the total synthesis of one alkaloid - ergonovine - has already been accomplished.

One or all of these steps could be undertaken by any nation, depending upon the long-range demand for ergot drugs and upon the level of scientific effort, personnel, and facilities allotted to this objective. 87/

Switzerland has manifested interest in certain phases of U.S. work which pertains to the biosynthesis of ergot alkaloids. 30/

Cultivation of Ergot in the Soviet Bloc

Naturally occurring ergot is considered of commercial value in Bulgaria, Czechoslovakia, Eastern Germany, Hungary, Poland and Rumania. The ergot of eastern european origin has a lower alkaloid content than most western european varieties.

Bulgaria. -- Special areas have been set aside for growing ergot in ulgaria. [64] Whether the pharmaceutical industry of that country is pable of processing raw ergot is, as yet, unknown. In the past ulgaria has been one of the best sources of supply of ergot containing e alkaloid ergotamine. [65]

Czechoslovakia. -- Successful cultivation of ergot has been reported Czechoslovakia. The methods used are those which reportedly were veloped and published by the Swiss. The ergot cultivation program carried out by the Division of Plant Cultivation of the Ministry of riculture. [65] Czech farmers are being encouraged to cultivate this op. [65] The government is also reported to be paying a good price for . [66]

Eastern Germany. -- Ergot is now cultivated in the Plant Research stitute of the Academy of Science, Gatersleben. The Plant Research stitute undertook the cultivation of ergot as a result of a failure 1951 to obtain from the East German and middle German rye fields ough ergot of sufficient potency to meet the pharmacopoeial standard East Germany. [7]

Large-scale field experiments involving inoculation procedures re carried out in 1952 and 1953; [71] and the constancy of alkaloid ntent of various indigenous strains as well as Hungarian, Portugese, d Finnish strains was recently reported after an extensive and well-umented survey by the Plant Research Institute. [68]

Ergot extract, valued at 50.2 thousand DME (German East Marks), was educed during the first half of 1953, at VEB Arzneimittelwerk, Dresden. enty kilograms of Secale cornutum extract (ergot) were to be delivered the Russian administration in East Germany in 1953. [73] Ergotamine l ergotexine are currently listed as available in the 1954 Arzteka1ender. . Ergot products are not currently listed among the State reserves pharmaceutical supplies. [74]

There is also a laboratory which is exclusively devoted to research ergot alkaloids at Arzneimittelwerk, Dresden (AMD), located in the ser Madaus and Company, Gartenstrass 19/21 in Dresden-Radebeul. addition, work on ergot is carried out in the Biological Institute at plant. [75] This work may be connected with artificial culture eds for growing ergot. One report indicates that an unsuccessful empt has been made at this factory to grow ergot in submerged culture. fungus grew but it contained none of the ergot alkaloids. [71]

Hungary. -- Ergot is grown in Hungary and is known to have been exported before World War II. Hungary was at one time regarded as one of the best sources of supply of ergot containing ergotamine. 3/

Research was reportedly undertaken in 1953 to develop artificial culture of ergot. A Hungarian research installation, located near the city of Budapest, has conducted experiments on field spraying with the spores and conidia of ergot, using 90-100 kilograms (90-220 lbs.) per hectare (2.471 acres).

Poland. -- In Poland, the people are being encouraged by radio to collect ergot and send it to the provincial ergot buying officer because "considerable quantities of raw, unprocessed ergot are needed in a certain chemical process". 69/ Most of the known research on ergot is carried out under the Department of Agriculture. The Institute of Phytopathology of the Agricultural School, Poznan, is doing research on this problem. The artificial cultivation of ergot has reportedly begun in both the field and in the laboratory. "In the laboratory, by cultivating ergot in artificial nutrients, it has proved possible to obtain fungus formations similar to sclerotia". Laboratory produced ergot reportedly contains the three active substances: ergotoxine, histamine, and tyramine which are formed in ergot under natural conditions. 70/

Rumania. -- Ergot was collected for export at least up to mid-1948, and depending upon the climate, 1000 to 3000 kilograms of ergot were collected annually. 68/

Soviet Union. -- Research on ergot cultivation and collection is centered in the Ministry of Agriculture. Some of the work has taken place at the Institute of Plant Protection, Leningrad Academy of Agricultural Sciences, Leningrad. Experiments conducted in 1939 indicated that the spraying of rye with a solution containing ergot conidia was a suitable method for commercial purposes. It has since been reported that there were still further problems to be solved. These included the cultivation of artificial media, the pharmacological testing of sclerotia of other fungi, and the development of new strains of ergot which could be grown on plants other than rye.

In recent years no Russian grown ergot has appeared in foreign markets. Ergot has occurred naturally in the rye fields of Russia for many years, and it probably has not diminished. This may be the result of its low alkaloid content which makes it commercially unattractive. 62/ There is speculation among ergot specialists that Russian ergot is mixed with the Spanish and Portugese quality product and sold as the latter. The mixtures have at times appeared quite obvious.

Cultivation of Ergot in Other Countries

In Western Europe, ergot is cultivated through artificial inoculation of rye in commercial quantities principally in Switzerland, Austria, and West Germany. Ergot in Europe, generally, is produced over an area of some 2500 to 4000 acres with an average yield of 40 kilograms per acre during normal years, the chief producer being Switzerland with some 2000 acres. Ergot is also cultivated to a lesser extent in Japan and India. India also collects large amounts of natural ergot. Natural ergot also occurs naturally in fairly large quantities in the province of Manitoba, Canada, and in the United States, principally in Minnesota. However, it is collected commercially only when the price of the European material becomes so expensive that the cost of labor is not a finaucial deterrent. 4/

Some attempts at artificial cultivation have been made in the United States, but these have not been economically successful because of the foreign competition. The best available information indicates that the annual production in Switzerland is about 50 tons; Austria and Germany produce less than 10 tons each; Japan produces approximately 5 tons. 76/ Portugal and Spain are noted for producing quantities of higher quality ergot, which occurs naturally in these areas where cereals are grown in the Iberian Peninsula. 85/

India. -- In 1952, the government of Madras, India, sanctioned a plan for the cultivation of ergot on a 50 acre plot in the Nilgiri Hills of Madras with a production target of 2500 lbs. per year. According to the director of Agriculture of the government of Madras, experiments have shown that ergot of high alkaloid content can be produced in that area. Some specimens are said to contain double the alkaloid content of the best imported varieties. 26/

It is reported that prior to 1953, 75 tons of wild ergot were shipped to Sandoz yearly for several years. None were shipped in 1953. 86/

Japan. -- Japan grows ergot as a commercial product and there has been some basic research in the field of artificial fermentation. M. Abe and coworkers of the Takeda Research Laboratory, Japan, have published reports on the alkaloid productivity of the ergot fungus. 82/

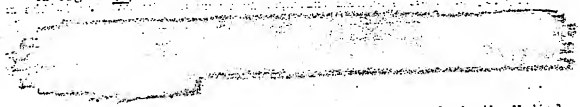
Switzerland. -- During World War II, the Sandoz firm in Switzerland, unable to obtain supplies of ergot because of the exigencies of war, started to grow their own. Switzerland was and still is the main world producer of finished ergot preparations. Currently, Sandoz purchases raw ergot on contract from several countries including the United States.

One source visited Sandoz in June 1951 and reported that the company has a new process for making artificial ergot. Sandoz has been able to isolate this fungus and grow it on tanks, similar to penicillin. 19/ Although this process is possible, no confirmation has been received to date. This process may not be completely satisfactory since Sandoz still obtains ergot from their own rye fields. 2/ The above process may merely be large-scale production of the spore inoculant used to infect rye.

The possibility of tank culture is supported by the fact that some Swiss ergot fields were not harvested and that Indian wild ergot was not imported in 1953. Previous shipments of ergot from India amounted to 75 tons per annum for several years. 86/

Only Sandoz of Switzerland is considered by most sources to be expert at the special technique of inoculation. They are somewhat secretive about this process, and as a result, it is very difficult to learn their degree of success. It is believed that rye is inoculated with a culture of spores suspended in a fluid medium. A wire brush impregnated with the material is drawn by hand across the head of the rye, inoculating the whole head. There are two main reasons for the artificial cultivation of ergot. First, Sandoz hopes to attain a higher yield, a steadier supply, and some control over the costs involved. Second, they are trying to control the alkaloids in the ergot by the preparation of certain strains of fungus.

In Switzerland as in other countries where ergot is produced by artificial inoculation, machines have been developed for the collection of ergot. 76/



United States. -- Recent attempts have been made in the United States by several research groups to produce ergot alkaloids by fermentation methods. The methods were similar to those used for the preparation of antibiotics. Theoretically, at least, since ergot disease of rye is caused by a fungus which can be maintained in culture, this process is feasible. To date, the work has been mainly concerned with the development of suitable growth media. Strain selection of Claviceps has also been started.

Although field inoculation has been successfully accomplished for many years on an experimental basis for laboratory use, inoculation on a profitable commercial scale has not been accomplished in the United States. 57/

The United States has 55 acres for ergot production (1952); 45 are in Michigan and 10 in Minnesota.

Trade in Ergot and Ergot Alkaloids

The latest quotations of February 1954 indicate that ergot can be obtained on prompt shipment from Portugal at 16 shillings ($2.24) per lb. Many sources have stated that small amounts of ergot are processed into the basic alkaloids in various countries, but the largest producer is Sandoz Ltd., Basel, Switzerland. Most international trade is, therefore, conducted with this company. One U.S. company is known to have purchased 100 grams of ergot alkaloids from Sandoz in 1951. 10/

Various sources reported numerous purchases of ergot and its derivatives by the Satellites throughout the world, indicating a notable interest of the Soviet Bloc in these substances. Specific shipment have included:

1. Hungary purchased 35 tons of ergot from Belgium through Centralimpex. 77/

2. A notorious East-West trader contracted to purchase 250 grams of ergotin (80% concentration) from Laboratorios Espanoles Zelta S.A., Madrid. 78/ This shipment went to an Austrian receiver who purchased an additional lot of 250 grams of ergotin, making a total of 500 grams. 79/

3. Portuguese agents also canvassed Spain, purchasing large amounts of ergot at a very high price for shipment behind the "Iron Curtain" through Portuguese ports. 77/

4. Sometime during 1951, the Soviets purchased a large quantity of an ergot derivative from Sandoz, Basel, Switzerland. This was probably the largest order Sandoz ever received. The drug involved was either LSD-25 or d-lysergic acid, probably the former (according to source). The quantity supplied was allegedly sufficient for approximately 50,000,000 normal doses. 80/ This amount far exceeds estimated world production, however, and the amount shipped if any, was probably much less.

5. In 1952, the Yugoslav Government purchased 700 grams of ergotamine from Interzanitas SA, of Lugano, Switzerland. This purchase was for a military office in Belgrade. 81/ 25/

Possibility of Stockpiling Ergot

It is unlikely that raw ergot would be stockpiled as such because of its extreme tendency to deteriorate. There are no ideal facilities for storing it over a period of years. Even the predrying and subsequent vacuum storage of ergot is expensive and not always effective. It is, therefore, assumed that if any stockpiling were undertaken, the total alkaloids of the ergot would be first converted into lysergic acid or that one particular alkaloid would be isolated. In either case the product would then be relatively stable and could be more easily stored. 87/

APPENDIX C

Installations and Persons Associated
With Research on Ergot

I. Soviet Bloc

USSR

All-Union Institute of Plant Protection, Academy of Agricultural Sciences Imeni V. I. Lenin, Leningrad. -- The following persons have been associated with the All-Union Institute of Plant Protection. Their publications relating to ergot are cited.

BILAI, V. A. and PIDOPLICHKA, M. M. Poisonous Fungi on Kernels of Cereals, 1946.

BOLOTNIKOV, S. M. and NOVOSICKAYA, S. A. "Contribution to the Quantitative Determination of the Alkaloids of Secale cornutum," Pharmacy, Moscow, vol 8, no 4, 1945, p 28.

GREBENNIKOV Winter Rye in Siberia, Novosibirsk, 1949, p 53.

LYNOVSKY, I. P. "Ergot and Ergotism (Rafania)," Problems of Nutrition, vol 3, no 5, 1934, p 24.

MASALAB, N. A. Methods of Cultivating Ergot for Medicinal Purposes, State Publishing House of Medical Literature, Moscow, 1941, p 38.

MARKHASEVA, V. A. "Prognosis of the Anticipative Development of Ergot," All-Union Institute of Plant Protection, Leningrad, 1935, p 105.

------ "Method of Prognosis of the Development of Claviceps Purpurea Tul.," Proceedings of the Scientific Research Works of the All-Union Institute of Plant Protection, Leningrad, 2A 1935, 1936, p 535.

------ "The Principal Pests and Diseases of Crop Plants," Lenin Academy of Agricultural Sciences, Leningrad, 1936, p 146.

MUSHNIKOVA, K. S. "Grain Ergots and Measures of Combatting Them," 1934, p 24.

OKOLOV, P. and AKIMOV, I. "Decrease in the Toxic Properties of Ergot in the Process of Bread Making," Translation of the Sanitary Hygiene Institute, Ginsa, Moscow, 1929, p 117.

OSHEV, A. and SHOMEPETKOV, A. "Removal of Ergot from Rye Seed," Selection and Seed Growing, vol 19, no 12, 1952, p 71.

PIDOPLICHKA, M. M. and HILAI, V. I. "Poisonous Fungi on Kernels of Cereals," Ukraine Academy of Sciences, vol 19, no 12, 1952, p 71.

PROKOFEV, N. V. and SHAPIRO, S. D. Production of Liquid Extracts of Ergot (Ergotina) in Ampules for Injection, Medical Industry of the USSR, 1949, p 33.

RIMSKAYA, M. and AKIMOV, I. "Data on Ergot Fat Constants and on the Stability of its Toxic Properties in Relation to the Period of Preservation," Translation of the Sanitary Hygiene Institute, Ginza, Moscow, 1929, p 129.

SMORODINTSEVA, E. D. "Mental Disorders as Remote Sequels of Ergotism," Translation of the Ural Scientific Psychiatric Institute, vol 2, 1935, p 122.

TAT'LANIN, A. R. "Production of Vitamin D_2," Food Industry, Moscow, 1943, p 62.

VLADIMIRSKII, S. V. "Geographical Distribution of Ergot of Rye in USSR and Zones Where Its Harmful Effects Have a Serious Significance," Soviet Botany, no 5, 1939, p 77.

ZABOLOTNAYA, Ye. S. "Alkaloids of Ergot". Tr. VILAR, No X, Medgiz, (All-Union Inst. of Research of Medicinal and Aromatic Plants) Moscow, 1950

Czechoslovakia

1. Charles University, Prague. -- The following persons have been associated with Charles University.

SKARNITZEL, Dr. (fnu) - Is a Professor of Pharmacology. He lectures frequently on ergot and acts as advisor to the ergot cultivation program.

ZDENEK, Dr. Vyslivcek - The Chief of the Psychiatric Clinic in 1952. This clinic, in 1952, was working on various drugs, such as pentothal, evipan, insulin, and ergotin. (Pentothal-sodium was used to interrogate political prisoners at this clinic with some success, according to one unconfirmed report.) 90/

2. Ministry of Agriculture, Division of Plant Cultivation. -- The Division of Plant Cultivation monitors the ergot cultivation program.

NOVAK, Dr. (fnu) - Is known to have worked for the Ministry and on location in the ergot fields.

3. Ministry of Agriculture, Research Institute for the Cultivation of Plants. -- Docent Dr. Rudolf KOMORSKA was directly connected with the ergot program. Currently residing in Zbraslav. 89/

4. Medicinal Herbs National Enterprise, in Zbraslav and Vitavous. -- This enterprise purchases, handles, and processes medicinal herbs. It also organizes their cultivation and collection. 89/

5. Pharmaceutical and Biochemical Research Institute, 17 Kourimska, Prague 12. -- Dr. J. J. NYMAN of this institute has requested reprints of two U. S. articles on ergot and ergot preparations. 91/

6. Other persons who have been connected with research on ergot. -- Their publications are listed.

BERNASEK, J. and VOTAVA, Z. "Study of the Effect of Certain Ergot Substances", Journal of Czechoslovakian Medicine vol 88, p 593 1949.

BLAZEK, Z. and KUCHERA, M. "Current Status of Artificial Ergot Production", Journal of Czechoslovakian Medicine, vol 85, p 1281, 1946.

NEUMANN, J. "Effect of a New Alkaloid of the Ergot Group on the Heart", Journal of Czechoslovakian Medicine, vol 88, p 500, 1949.

POLAK, E. "On the Relation of Ergotamine and the Action of Electrolytes", Bull. Internat. cl. Sc. Math. Acad. Sc., Prague vol 27, p 440, 1925.

SZABO, S. "Ergobasine in labor", Medical Messenger, vol 63, p 24, 1941.

East Germany

1. Plant Research Institute of the Academy of Sciences, Gatersleben, near city of Plant Breeding. -- The following persons have been associated with this Institute.

MOTHES, Prof. Dr. K. and SILBER, H. - Reported 7/ that this Institute decided to cultivate ergot as a result of a failure to obtain sufficient high quality ergot from the East German and Middle German rye fields to meet the pharmacopeial standard of East Germany.

MUEHLE, Prof. Dr. - Is head of an ergot project currently in progress. This project, undetermined in scope, is scheduled for completion by 1956. 83/ 84/ 87/ 88/

2. Arzneimittelwerk Dresden (AWD). -- Complete laboratory engaged in research on the ergot alkaloids is located at the former Madaus and Co., Gartenstrasse 19/21 in Dresden-Radebeul 75/ 85/.

3. Biological Institute of Arzneimittelwerk, (AWD) Dresden -- This Institute is also engaged in research on ergot.

SIEBECK, Dr. Walter - Is head of ergot research at this Institute.

Hungary

1. Agriculture Research Station, Herman Otto 15, Budapest. -- This station covers approximately 15 to 20 acres. The Medical Section covers approximately 4 acres. Work here includes research on medicinal plants.

BEKESY, Dr. Nikolaus - Investigated the alkaloidal content of various European and American ergot samples. He has also worked on artificial cultivation and special apparatus for inoculation. 85/

RUDOLF, Prof. De Giovannini - Is director of the Research Stations. Experiments on medical plants in early 1949 included work on ergot, and intensive research was undertaken to grow ergot on artificial media. 87/

2. University of Szeged. -- In 1949 this University had 3 departments engaged in research on ergot. They were the Department of Pharmacognosy, Department of Pharmacology, and the Department of Bacteriology.

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2. University of Szeged. -- In 1949 this University had 3 departments engaged in research on ergot. They were the Department of Pharmacognosy, Department of Pharmacology, and the Department of Bacteriology.

IVANOVICS, Dr. Gyorgy O Antibiotic specialist, Department of Bacteriology, was involved in aspects of alkaloid investigations in 1949.

JANCSO, Dr. Miklos - Under the Department of Pharmacology, was involved in aspects of ergot alkaloid investigations.

Poland

1. Department of Agriculture, Institute of Phytopathology of the Agriculture School in Poznan. -- Mieczyslaw LASKOWSKI is an assistant at this institute. He has written a paper entitled "Ergot, the Enemy and Friend of Man" which indicates a keen awareness of the therapeutic and unconventional uses to which ergot may be put. 70/

2. Ministry of Health, The Institute of Medicinals, Warsaw. -- This Institute coordinates and plans all scientific research on medicines in Poland and is one of the probable installations which would engage in ergot research. 92/

II. Other Countries

Austria

1. University of Graz. -- The following persons have been connected with this Institute.

HECHT, Dr. Martin (location is not certain) - Has a specific interest in ergot and is the son of Dr. Walter Hecht. He is currently engaged in research on inoculation methods. He claims to have obtained 240 kilograms of ergot per acre with these inoculation methods. He employes a motor driven injection machine with a capacity of one to two acres per hour. 96/

HECHT, Dr. Walter - Is well-trained in botanicals and has had a specific interest in ergot for several years.

Japan

1. Takeda Research Laboratory. -- M. ABE has published reports on research on ergot fungus and the production of alkaloids in ergot fungus in culture medium. 82/

2. Experimental Farm for the Cultivation of Medicinal Plants, Tokyo-fu. -- This farm is attached to the National Hygienic Laboratory. 83/

KAWATANI, Dr. T. - has had a continuing interest in the development of ergot and its alkaloids.

3. Nakazawa-Yoki Co., Inc., Tokyo: -- This Company maintains experimental ergot farms.

TOJO, Katsuo - is managing director of this company and is also interested in ergot production. He has visited the U.S. to obtain information on the subject. 83/

NAKANURA, Taisuke - has visited the United States for information on this subject.

4. Other Japanese scientists -- The following persons have published articles on ergot.

HASHIMOTO, T. Yakugaky Zasshi A. J. Pharm. Soc. Japan, vol 66, 1946, p 22.

OGATA, A. J. Pharm. Soc. Japan, vol 52, 1932, p 25.

OGIU, K. OKAMOTO, T., SIMAMOTO, K. Fol. Pharm. Japan, vol 44, 1948-49, p 76.

OTANI, F. J. Pharm. Soc. Japan, vol 52, 1932, p 25.

SUGIMOTO, S. Fol. Pharm. Japan, vol 31, no 110, 1941.

TAKEMOTO, T. J. Pharm. Soc. Japan, vol 64, 1944, p 225.

Switzerland

1. Sandoz Pharmaceutical Ltd., Basel. -- The following persons are connected with research on ergot.

STOLL, Dr. Arthur - Is President of the Sandoz Pharmaceutical Ltd. He is a world authority on the industrial preparation and use of the ergot drugs. One reference points out that he used ergot in the treatment of animals suffering from the effects of chemical warfare agents. However, when the threat of this type of warfare ceased during the World War II, he stopped his investigations. 80/

HOFMANN, Dr. A. - Was the first investigator to use LSD-25 on himself for the purpose of testing the psychogenic effects of the substance. In addition, he was one of the early investigators

who accomplished the preparation of LSD-25 by converting lysergic acid into the diethyl amide derivative.

West Germany

1. Kali-Chemie, AG, 20 Sahnde bei Hanover. -- Dr. Ing. O. REULLAUX of this firm has stated that work on the isolation of the ergot alkaloids is in progress.

2. Institute of Pharmaceutical Chemistry, Mainz University. -- Prof. Dr. [illegible] reported progress in the production of ergot alkaloids in saprophytic culture at a meeting of the German Pharmaceutical Society in October 1953. 99/

France

1. University of Strasbourg. -- Madame Chauduc VIALARD reported the formation of ergot alkaloids in vitro, obtaining up to 0.7 percent alkaloids in an eight week old culture. 100/

APPENDIX D

Glossary of Scientific Terms

...aluation of an emotion laden experience during its ...ion with an understanding psycho-therapist.

...TION- ...ree d... substance secreted by nerves which sets in motion the ...ding to muscular contractions.

...CHOL... reac... condition marked by coldness and cyanosis of the hands

...TANOS... and f... ...ty of emotional experience.

...T--Am... ...mine or benzedrine.

...TON-- ... a large group of organic basic substances found in plants. ...ally bitter in taste and physiologically active.

ALKALOID- They ... ...ltaneous existence of contradictory and contrasting ...ve and hate) toward the same person.

AMBIVALEN... emot... ...sedrine.

AMPHETAMI... ... loss of appetite for food.

ANOREXIA ... -A psychoneurosis characterized by apprehension and ...companied by a variety of other symptoms such as ... excitability and depression.

ANXIETY fee... ir... ...of muscular coordination.

ATAXIA-... ...aloid from the SOLANACEAE; used as an anti-spasmodic ...o gas poisoning; is also called dl-hyoscyamine.

ATROPIN... and ... ...ation of being dominated by subjective, self-centered ...aught or behavior.

AUTISM- ti... ...S SYSTEM--The functional division of the nervous system ...es the glands, heart and smooth muscles with their ...ervation.

AUTONOM... ... ...alkaloid derived from Corydalis bulbosa. It has an ...effect on the reflex and motor activities of striated ...recognized as a psychogenic agent.

BULBOC... ...

CAFFEINE--An alkaloid extracted from tea and coffee; used as a cardiac, respiratory, renal and psychic stimulant.

CATALEPSY--A condition characterized by a waxy rigidity of the muscles and in which the patient tends to remain in any position that he is placed.

CATATONIA--A form of schizophrenia characterized by negativistic reactions, phases of stupor or excitement, and impulsive or stereotyped behavior.

CENTRAL NERVOUS SYSTEM--The brain and the spinal cord, including their nervous and end organs. Also called cerebrospinal or voluntary nervous system.

CEREBRAL CORTEX--Cortex of the brain composed mainly of gray and cineritious substance.

CEREBROSPINAL NERVOUS SYSTEM--Synonymous with Central Nervous System.

CHLORAL HYDRATE--Used as an anodyne, hypnotic, and antispasmodic in insomnia, mania, delirium tremens, hysteria, tetanus and labor.

COCAINE--An alkaloid from the leaves of Erythroxylon coca; paralyzes the ends of the sensory nerves; stimulates the central nervous system; mainly used as a local anaesthetic.

CHOREO-ATHETOTIC--Referring to both chorea and athetosis, chorea is a nervous affection marked by muscular twitching. Athetosis is a condition marked by slow repeated, involuntary, muscular distortion of parts of a limb or almost the entire body.

COMPULSION--An irresistible impulse to perform some act contrary to one's better judgement.

CYCLOTHYMIA--The recurrent alterations from manic to depression states as seen in certain psychoses.

DEPERSONALIZATION--Loss of the sense of personal identity, or the personal ownership of the parts of one's body.

DEPRESSION--An emotional state characterized by dejection, unpleasant ruminations or forebodings.

DIENCEPHALOSIS--Disease of the posterior division of the prosencephalon or forebrain.

DIBENAMINE (hydrochloride)--N-(2-chloro ethyl) dibenzylamine hydrochloride used for hypertension. Occasionally causes mental confusion and postural hypotension.

DIURESIS--Increased secretion of urine.

DYSARTHRIA--Stammering stuttering or other imperfect utterances due to disorder in the nervous system.

ENDEMIC--Pertaining to or prevalent in a particular district of region. Said of a disease which occurs more or less constantly in any locality and is not sporadic or epidemic.

EPILEPTIC--Pertaining to, or affected with, epilepsy, a disease characterized by fits or attacks of loss of consciousness, with a succession of tonic or clonic convulsions.

ETIOLOGY--The sum of knowledge regarding the causation of any disease.

EUPHORIA--Well-being; absence of pain or distress.

EXOGENIC--Develop or originating outside the body.

HALLUCINOSIS--A psychosis marked by hallucinations.

HAPTIC HALLUCINATION--A tactile hallucination or hallucination of touch.

HASHISH--Female flower tops of Cannabis sativa, a variety of common hemp. Cannabis is antispasmodic and narcotic. In large doses it produces mental exaltation, intoxication and a sensation of double consciousness. Also known as MARIHUANA.

HEBEPHRENIC--Pertaining to hebephrenia, a clinical form of dementia praecox, (schizophrenia) marked by rapid deterioration, hallucinations, absurd delusions, senseless laughter, and silly mannerisms.

HEXAMETHONIUM--The bromide has been recommended as an autonomic nervous system blocking agent. The compound is also used in the form of its iodide.

HYDERGINE--Hydrogenated ergot alkaloids, specifically dihydroergocornine methanesulfonate, dihydroergocristine methanesulfonate and dihydroergocryptine methanesulfonate (used in peripheral vascular disease and hypertension).

HYPERKINETIC--Excessive mobility.

IDEAS OF REFERENCE--An idea which causes the possessor to suppose that the words and actions of others refer to himself or to project the causes of his own imaginary difficulties upon someone else.

ISOMERS--A set of substances which have the same number of atoms, but differ in the order in which the atoms are arranged in the molecule.

LACHRYMATION--The secretion and discharge of tears.

MANIC--Pertaining to or affected with mania, a phase of mental disorder characterized by an expansive emotional state, elation, hyperirritability, overtalkativeness or flight of ideas.

MESCALINE--From mescal buttons, the flowering heads of Anhalonium or Lophophora cactus. A poisonous alkaloid, it produces an intoxication with delusions of color and music.

MESENCEPHALOSIS--Disease of the mid-brain, the smallest of the six divisions of the brain.

METABOLISM--The sum of all the physical and chemical processes by which living organized substance is produced and maintained, and also the transformation by which energy is made available for the uses of the organism.

METEDRINE--Trade name for d-Desoxyephedrine Hydrochloride; also called Pervitin. A central nervous system stimulant.

MICTURITION--The passage of urine.

MYDRIASIS--Dilation of the pupil.

NEGATIVISM--An emotional disorder characterized by stubbornness, refusal, and rebellion against authority. Also an adjustment mechanism by which the individual unconsciously fails to recognize the existence of a problem or obstacle, or of the unpleasant facts that confront him.

NEUTROPHILIA--Increase in the number of neutrophil leucocytes in the blood.

NICOTINIC ACID--Also known as Niacin, anti-pellagra vitamin. Has been used to produce vasodilation.

ONYMACIC--Hastening the process of child-birth. A medicine which accelerates delivery.

PANDEMIC--Widely epidemic.

PARANOIA--A chronic, slowly progressive psychotic disorder marked by the presence of systematized delusions which are built up in a logical form.

PARESTHESIA--Morbid or perverted sensation; an abnormal sensation.

PARTURITION--The act or process of giving birth to a child.

PASSIVITY--A state marked by delusional feelings of being influenced by others or by outside forces or influences.

PATHOLOGICAL--Pertaining to that branch of medicine which treats the essential nature of disease, especially of the structural and functional changes caused by disease.

[illegible]TIN--A derivative of amphetamine identical with methedrine; used to stimulate the central nervous system.

[illegible]--The flowering tops of the Mexican cactus, Anhalonium; used by the natives to produce a state of intoxication marked by feelings of ecstasy. Contains the drug mescaline. 135/

[illegible]PATHOLOGY--The science of bodily functions in disease, or as modified by disease.

[illegible]RIA--The passage of abnormally large amounts of normal urine.

[illegible]OR ACTION--Tending to increase blood pressure.

[illegible]OL--2-Benzyl-2-imidazoline. Used as a vasodilator in peripheral vascular disease.

[illegible]ONEUROSIS--A form of schizophrenia.

[illegible]OGENIC--Originating on the basis of psychological factors; a term also applied to LSD-25, hashish, bulbocapnine, mescaline, and other drugs which cause mental effects.

[illegible]MOTOR--Pertaining to motor effects of cerebral or psychic activity.

PSYCHOSIS--A profound mental disorder, usually involving the total personality; the individual's mental functions are so profoundly disturbed that he is incapacitated from participating in everyday activities.

PSYCHONEUROSIS--A disturbance in bodily function, thinking, feeling, and conduct due to emotional tensions which have developed as a result of deprivations, frustrations, and conflicts; a functional emotional disorder.

PSYCHOPATHOLOGY--The pathology of mental disorders; the branch of medicine which deals with the causes and nature of mental disease.

RORSCHACH TEST--A test for intelligence which also measures the emotional elements of the personality.

SCHIZOID--Resembling schizophrenia; a term applied to the seclusive, asocial and introspective type of personality.

SCHIZOPHRENIA--A psychotic condition, usually occurring during or shortly after adolescence and characterized by disorientation, loss of contact with reality, disorganized patterns of thinking and feeling, and apathy.

SCOPOLAMINE--An alkaloid from the root of certain of the Solanaceae plants. A viscous nerve depressant, mydriatic and hypnotic.

SOMNIFEN--Proprietory name for the monosodium salt of isoamylethyl-barbituric acid. Used as a sedative before general anesthesia.

STEREOISOMER--A compound in which the molecule contains the same number and kind of atoms as another, but in which the spatial arrangement of the atoms is different.

SYMPATHECTOMY--Severing a destructive effect on sympathetic fibers; also interference with the transmission of nerve impulse in autonomic ganglia.

SYNESTHESIA--Secondary sensation accompanying an actual perception; the projection of a sensation in one place due to stimulation in another place; also the condition in which a stimulus of one sense is received as sensation of a different sense, as when hearing a sensation of color.

TACHYPNEA--Rapidity of respiration; a respiratory neurosis characterized by rapid, shallow breathing.

TOXIN--A poisonous substance of microbic, vegetable or animal origin.

VASOCONSTRICTION--The constriction of blood vessels leading to decreased blood flow to a part.

VASOMOTOR--Nervous control over the contraction or dilation of blood vessels.

VEGETATIVE--Vegetative system, the sympathetic nervous system. Also means to function involuntarily or unconsciously.

FIGURES 1-10

Laboratory Experiments Showing
the Effects of LSD-25

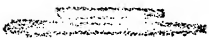


Figure 1. Life Cycle of Ergot, Source of Lysergic Acid

Ergot is the natural source of special alkaloids, yielding lysergic acid as a hydrolysis product. The grain-like ergot is the end result of a special fungus infection (Claviceps purpurea), affecting such crops as rye. The spores are brought to the young ovaries of the rye by wind, insects and most recently and effectively, by large-scale spraying of laboratory cultures.

a. Head of rye with prominent hardened, dark-red fungus bodies: ergot.

b. Sprouting ergot with several stalked globular heads.

c. Flask-shaped cavities imbedded in the surface of a single head.

d. Single cavity with numerous tube-like sexual sacs or asci.

e. Filiform ascospores in closed and open sacs.

f. Single ascospore, capable of infecting rye flowers, forming a mycelium therein.

g. Mycelium, spreading in the grain tissue, forming bead-like, asexual spores (conidia) for further infections.

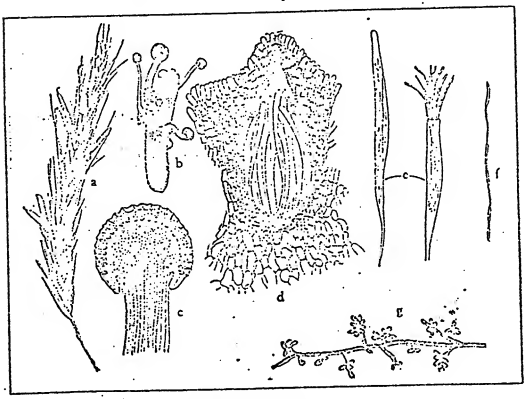
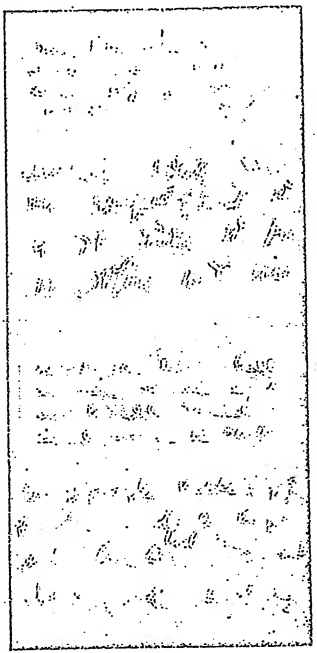


Figure 2. Effect of LSD-25 on Handwriting. 5b/

By Dr. Weyl

The handwriting, under the influence of LSD-25, became shaky; the much enlarged letters spread out, often separated, and frequently became unintelligible.



a. Normal writing test. (Test Person 13.)

b. LSD-25 writing test, 4 hours after 60 gamma LSD-25 administration. (Test Person 13.)

c. Normal writing test. (Test Person 21.)

d. LSD-25 writing test, 3 hours after 60 gamma LSD-25 administration. (Test Person 21.)

Figure 3. Effect of LSD-25 on Drawing Tests. 46

By Laszlo Kateft

The interference of LSD-25 with his ability to draw was strikingly illustrated in self experiments by the author. LSD-25 produced different psycho-pathological reactions of the hebephrenic type. The drawings show a tendency to expansions and some relationship to pictures produced by psychotic patients.

At 9:15, 50 gamma of LSD-25 were taken orally.

At 9:55, test person was completely normal. Drawing A.

At 10:15, an additional 50 gamma of LSD-25 were taken orally.

At 10:40, test person felt less certain, saw object rightly but could not draw it correctly, interrupted drawing repeatedly. Drawings B and C.

At 11:45, test person failed in successive attempts, the contours of the model appeared normal, but not those of the drawings. Drawings D, E, and F.

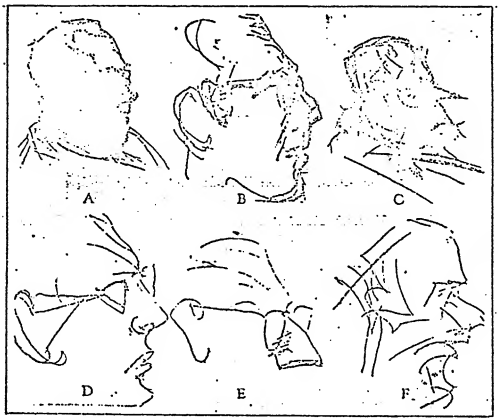
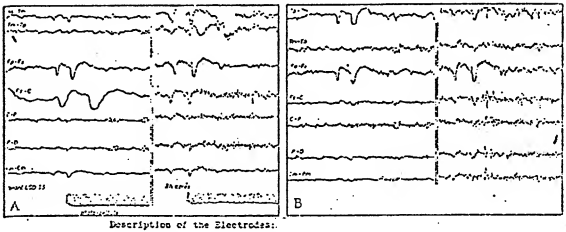


Figure 4. Effect of LSD-25 on the Human Electro-Encephalogram. 01

By Gastaut et al.

The electro-encephalograph records brain waves, or electric potentials originating in the brain, by means of electrodes placed upon the scalp and nearby surfaces, as indicated specifically in the graphs and below. LSD-25 causes a slight increase in the alpha-rhythm and the occurrence of the beta-rhythm in the central regions.



Description of the Electrodes:

Ta-anterior temporal; Tm-middle temporal; Tp-posterior temporal; Fp-polar frontal; Fa-upper frontal; C-central; P-parietal; O-occipital; Fm-median frontal; Cm-median central; Pp-median parietal.

The 7 graphs in A above represent leads from the right half of the scull-hemisphere and the central line.

The 7 graphs in B above represent those from the left half and the central line.

The tracings to the left of the vertical separation-recorded before LSD-25 injection--are characterized by an alpha-rhythm from the parietal, temporal and occipital regions of 10 cycles per second without a central beta-rhythm.

The tracings to the right--recorded 3 hours after injection of LSD-25--show the alpha-rhythm from the same regions with 12 cycles per second, and a beta-rhythm in the central regions with 21 cycles per second.

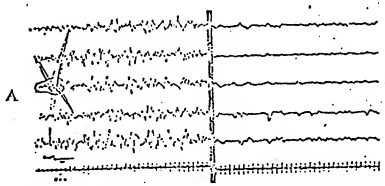


Fig. 1. — Agitationnement du tracé avec 50 gouttes /kg de L S D 25. A gauche, le tracé spontané à droite, le tracé après injection de L S D 25.

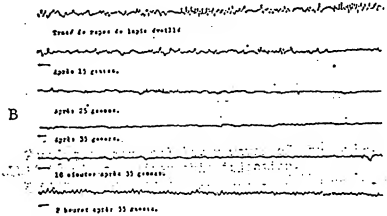


Fig. 2. — Agitationnement progressif du tracé par de petites doses de L S D 25. (Les doses sont indiquées dans leur totalité pour un lapin de 2 kg 500.)

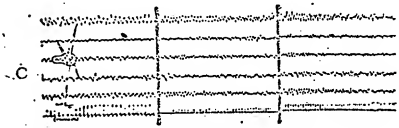


Fig. 3. — Réponses du tracé préalablement agité par le L S D 25 à différentes fréquences du stroboscope.

Figure 5. Effect of LSD-25 on the Electro-Corticograph of the Awake Rat

By J. Delay et al.

The electro-corticograph, as a record, results from the use of electrodes in direct contact with the cerebral cortex. The most characteristic result, so different from the electro-encephalogram, is the flattening of the tracing by LSD-25, signifying the suppression of the spontaneous rhythmic activity of the brain. This contrasts with the persistence of responses to the intermittent light stimulation of the stroboscope.

A. Tracing of cortical layer waves. At left: normal; at right: flattening after injection of 40 gamma/kg LSD-25.

Tracing of cortical layer waves of the awake, resting rabbit.

Tracing of cortical layer waves of the awake, resting rabbit after injection of 15 gamma LSD-25.

Tracing of cortical layer waves of the awake, resting rabbit after injection of 25 gamma LSD-25.

Tracing of cortical layer waves of the awake, resting rabbit, after injection of 35 gamma LSD-25.

Tracing of cortical layer waves of the awake, resting rabbit 18 minutes after this injection.

Tracing of cortical layer waves of the awake, resting rabbit 2 hours after this injection.

B. Progressive flattening of wave tracings by small doses of LSD-25 in rabbit (2.5 kg.)

C. Responses of wave tracings, previously flattened by LSD-25, to different speeds of the stroboscope.

Figure 6. The Rorschach Test for the Effect of LSD-25 on the Mind. [55]

The well-known psychological test, also referred to as the ink-blot test, measures certain traits and general personality trends, based upon the subject's interpretation of ink blots of varying design and color. These tests must be analyzed by experienced diagnosticians, who may gain an insight in the psychological structure of individuals and thus discover hidden emotional tensions, repressions and attitudes. It is logical therefore, to use this test also on individuals under the influence of LSD-25, since this psychogenic substance affects the emotions and personality in general.

This test was actually carried out by W. A. Stoll on 11 adult subjects without apparent mental abnormality, under the influence of LSD-25, after receiving 30 gamma orally. Not less than 3 months later the test was repeated without LSD-25. Comparison of the results with and without LSD-25 indicated a general loosening of mental processes, disinhibition of affectivity and fluency of thought processes. The Rorschach syndrome under the influence of LSD-25 corresponds to the clinical picture of an intoxication that is regarded as unspecific and as an instance of the exogenous reaction type. Besides typical psychoorganic traits others occur suggestive of schizophrenia.

This is, therefore, one further test that may be carried out on humans to examine the effect of psychogenic agents. Ink blots from the Rorschach tests are illustrated to indicate to the reader the greater variety of mental impressions suggested by these indefinite forms. No matter what the patient's interpretations--whether he sees a bat, a gorilla, waiters bowing to each other, a girl riding on a horse or perhaps a man's face in the shadows--he unknowingly exposes his intimate fantasy of life and general personality trends.

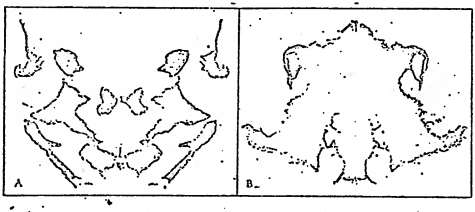
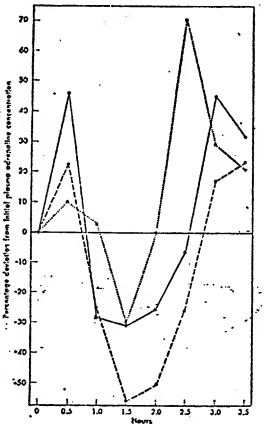


Figure 7. Effect of LSD-25 on the Blood Adrenaline Level and Mental Processes. [1]

By D. W. Liddell and M. Weil-Malherbe

The psychological effects of drugs and their applications in psychiatry are of great interest, although little is known thus far of their mechanism of action. The authors therefore undertook to study the changes of blood adrenaline levels and to correlate them with mental changes. Adrenaline was determined on samples of plasma taken from 3 patients after oral administration of 40 gamma LSD-25, and the results were plotted on the accompanying chart.



These biochemical studies showed that one can distinguish 3 phases in psychotic patients after oral or intravenous administration of LSD-25:

1. An initial rise of the adrenaline level.
2. Its drop below the starting level.
3. A secondary rise.

The rising adrenaline concentration, seemingly associated with tension and anxiety, often with shivering and an appearance of goose flesh; the falling adrenaline concentration apparently connected with relaxation and euphoria.

Figure B. Mental and Muscular Disorder Resulting from Large Amounts of LSD-25.

By U. de Giacomo

The administration of 300 to 500 gamma LSD-25 to psychotic patients led to results not unlike those observed after administration of bulbocapnine-experimental catatonia.

A. Face fixed and inexpressive.

B. Leaning posture of head and trunk.

C. Greatly prolonged muscular inaction; head, arms, and legs raised above the bed level.

Figure 9. Effects of LAE and LSD-25 on the Movements of the waltzing mouse.

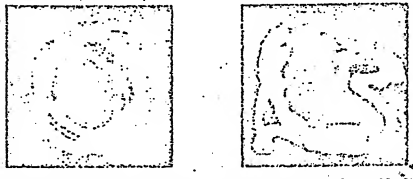
By. E. Rothlin and A. Corlciti

The waltzing mouse represents a special strain, having a congenital and hereditary tendency to carry out characteristic intermittent circular turn or waltzing movements, illustrated below in a slow moving picture record.

These movements are possibly caused by a disturbance of coordinating functions in the brain stem. There is now evidence that psychogenic substances such as ergot alkaloids and their derivatives variously affect this behavior and thus present a new method for their study.

After administration of ethyl- and diethylamide (LAE and LSD-25) derivatives of lysergic acid, (the hydrolysis product of the ergot alkaloids,) only partial turns are carried out with short turns to the left and right.

a. Slow moving picture record of a waltzing mouse.



b. Course of movements of a waltzing mouse before (left), and after (right), the injection of 2 mg. per kg. lysergic acid ethylamide (and LSD-25). Time exposure in the dark, the animal having been rendered luminous.

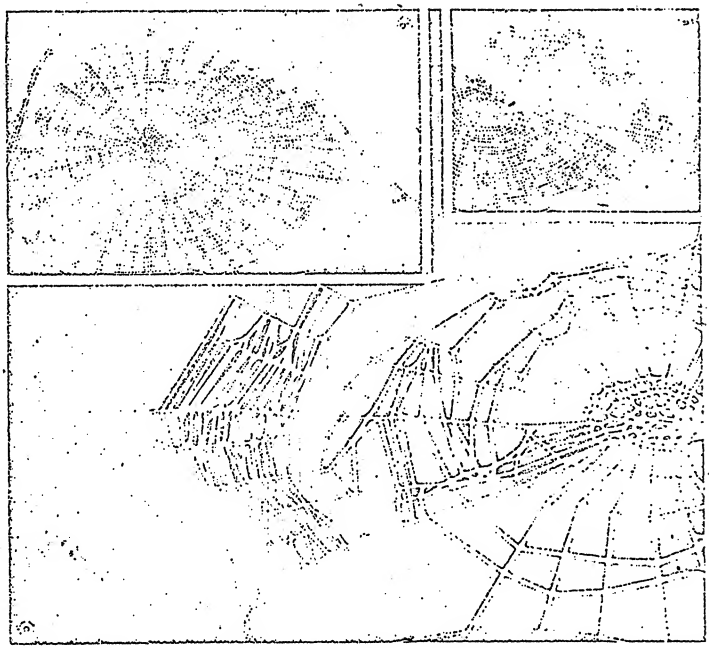


Figure 10. The Effect of LSD-25 on a Spider's Weaving Ability. 55/

By P.Witt

While man shows marked constitutional and temporal fluctuations in both subjective and objective tests, the spider, with a rather highly organized nervous system, shows only slight fluctuations. The urge for web construction may be used as a sensitive qualitative and even quantitative reagent for drug influence, provided the tests are made during the warm season of the year.

With LSD-25 the spider produces a perfect web, since the distractions are evidently dulled; thus he can concentrate on its construction and an improved exactitude of the angles. (In contrast with mescaline there is an increasing irregularity in the construction of the web and a decreased accuracy of the angle structure.) Methedrine or pervetin overstimulates and thus prevents coordination and completion of the web.

a. Normal web; presenting spiral threads, coiled around spokes, which radiate from the hub or the spider's resting place.

b. LSD-25 web; perfected by the improved utilization of stimuli, the greater exactitude of the angles, the check on distractions.

c. Methedrine web; incompleted and spoiled by overstimulated, restless and restricted weaving.