

Table IV—Relative specific activity of phosphorus compounds in mouse brain.

Samples	AS		LP		TP		DNA		RNA		RS	
	V	C	V	C	V	C	V	C	V	C	V	C
1	71.7	75.7	8.4	11.9	10.0	13.9	2.2	1.8	17.1	18.9	13.4	14.8
2	65.2	74.2	11.5	10.5	12.8	13.6	1.4	2.4	18.6	15.4	14.5	16.5
3	57.1	45.3	12.3	8.3	9.9	11.9	2.5	1.9	16.3	14.8	11.2	13.9
4	60.6	54.4	10.6	9.8	9.0	9.2	3.2	1.7	14.6	19.4	9.7	9.8
5	175.1	47.5	19.2	10.2	21.4	9.5	4.3	2.0	44.4	12.9	28.4	11.0
6	140.0	65.8	20.5	9.1	20.7	12.4	4.4	2.5	38.5	17.5	25.4	13.7

The authors wish to express their gratitude to Dr. TATSUO KARIYONE, and Dr. TOMOJI SUZUKI, of Kyoto University, for valuable advice and suggestions. Their thanks are also due to scientists of the Department of Bacteriology, the University of Utah College of Medicine, U.S.A., for critical discussions.

R. KIMURA, S. HOTTA, T. FUJII¹,
I. TANABE, Y. HASHIMOTO,
T. INOUE, and T. FUJITA

From the Microbiological Institute and Department of Pharmacy, Faculty of Medicine, Kyoto University, Kyoto, Japan, October 2, 1954.

Zusammenfassung

Die Verteilung von radioaktivem Phosphor im Gehirn virusinfizierter weisser Mäuse ist geprüft worden. Im Zeitpunkt maximaler Virusvermehrung nimmt die Aufnahme des radioaktiven Phosphors in den Phosphorverbindungen der infizierten Gehirne deutlich zu. Virologische und biochemische Aspekte wurden diskutiert.

¹ Present address: Department of Medical Chemistry, Gifu Medical College, Gifu, Japan.

DISPUTANDUM

Possible Biosynthesis of D-lysergic Acid Diethylamide-like Compounds from Mescaline¹

There are some data in the literature suggesting that the intact mescaline molecule is not involved directly in the model psychosis elicited by its administration.

Any one of 500 mg mescaline, 1 mg D-lysergic acid ethylamide (LAE) or 100 μ D-lysergic acid diethylamide (LSD) causes experimental (model) psychosis of similar intensity and duration in healthy volunteers. This decreasing order of dosage was related recently to the increasing affinity for wool protein of the same compounds (0, 1.1, 2.6 $\times 10^{-2}$ mM per gram wool) indicating that high activity as well as high affinity for wool are concomitant characteristics². Since mescaline displays no affinity for wool, this might suggest that the intact molecule as such is not the active compound.

SCHUELER³ as well as BLOCK, BLOCK and PATZIG⁴, emphasize that the inhibition of rat brain respiration by 0.12% mescaline (substrate, glucose) as reported by QUASTEL and WHEATLEY⁵ in their WARBURG-experi-

ments is brought about after a 2–3 h (!) contact of the brain-homogenate with mescaline. Such a time lag points to the possible transformation of mescaline to an active compound¹.

BLOCK *et al.*² have shown that the metabolism of mescaline by the white mouse resembles that by man. Still, the peak of hallucinations in humans upon administration of mescaline and the presence of the highest amounts³ of radioactive labelled C¹⁴-mescaline in the brain of the white mouse do not coincide in time. This discordance might suggest the possibility of a transformation of the mescaline into the active compound.

Enzymatic incorporation of only 20–60 γ of C¹⁴-labelled mescaline (i.e. around 1% of the amount administered) into the liver protein⁴ of the white mouse as well as the peak of the phenomena of a model psychosis in humans on administration of mescaline coincide in time⁵; an observation not inconsistent with our hypothesis.

According to RICHTER⁶, 58% of the mescaline administered to human volunteers can be recovered unchanged in the urine after 18 h; small amounts of trimethoxyphenylacetic acid were also found. This result is not contradictory to our hypothesis and suggests that only part of the mescaline might be transformed into an active compound.

2, 3, 4-trimethoxyphenylethylamine (iso-mescaline) an isomer of the symmetrical 3, 4, 5-compound (mescaline), does not cause model psychosis in normal volunteers⁷ and was found to display no affinity for wool⁸; thus it behaved as an inactive compound like, for instance, mescaline itself⁹. It is also reported¹⁰, that none of the

¹ The 0.12% mescaline concentration used in QUASTEL's experiments is far above that which might occur in the organism [F. W. SCHUELER, J. Lab. Clin. Med. 33, 1297 (1948); W. BLOCK, K. BLOCK, and B. PATZIG, Z. Physiol. Chem. 290, 160 (1952)], and it can be argued that smaller amounts would need either an even longer time lag or would not cause an inhibition at all.

² W. BLOCK, K. BLOCK, and B. PATZIG, Z. Physiol. Chem. 290, 230 (1952).

³ These "highest amounts" are, however, relatively very small quantities.

⁴ If the mescaline-protein complex itself might cause the model psychosis as postulated by B. PATZIG, Naturwissenschaften 40, 13 (1953), an immunity towards mescaline, or at least an anaphylactic shock might be expected to occur after readministration of the drug. According to our own observations, this is not the case.

⁵ B. PATZIG, Naturwissenschaften 40, 13 (1953).

⁶ D. RICHTER, Biochem. J. 32, 1763 (1938).

⁷ K. H. SLOTTA and J. MUELLER, Z. Physiol. Chem. 238, 14 (1936).

⁸ R. FISCHER, to be published.

⁹ R. FISCHER, Exper. 10, 435 (1954); J. Ment. Sci. 100, 623 (1954).

¹⁰ L. RETI and J. A. CASTRILLON, J. Amer. Chem. Soc. 73, 1767 (1951).—L. RETI, β -Phenethylamines; see R. H. F. MANSKE and H. L. HOLMES "The Alkaloids", Vol. 3, Chapter 22 (Academic Press. Inc. Publ., New York, 1953).

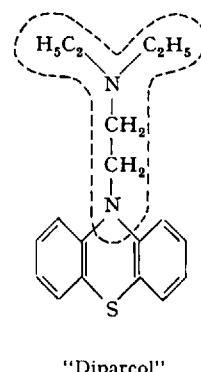
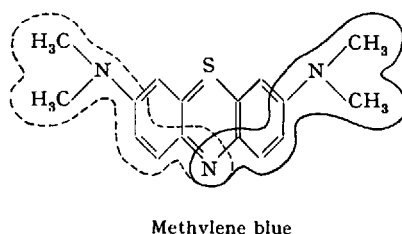
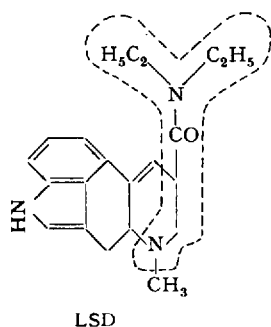
¹ Saskatchewan Committee on Schizophrenia Research. Supported by the Department of National Health and Welfare, Ottawa.

² R. FISCHER, Exper. 10, 435 (1954); J. Ment. Sci. 100, 623 (1954).

³ F. W. SCHUELER, J. Lab. Clin. Med. 33, 1297 (1948).

⁴ W. BLOCK, K. BLOCK, and B. PATZIG, Z. Physiol. Chem. 290, 160 (1952).

⁵ J. H. QUASTEL and A. H. WHEATLEY, Biochem. J. 27, 1603 (1933).



N-substituted derivatives of mescaline cause model psychosis.

There is a similarity between the psychopathological phenomena caused by 500 mg mescaline and by 100 γ LSD¹, and 300 mg of mescaline or 90 γ or more of LSD cause an apparently similar alteration of the liver function in humans as measured by the glucuronic acid test².

Inhibition of an LSD-produced model psychosis may be brought about by previous administration of certain compounds of the phenothiazine series, e.g. methylene blue, β -diethylaminoethyl-N-phenothiazine ("Diparcol", Poulenc Ltd.) etc., displaying some apparently essential features of the LSD molecule³ (see dotted lines).

LSD⁴ has uterotonic properties; mescaline does not exhibit uterotonic action when added to the excised organ but only when administered *in situ*⁵. Thus, transformation of the mescaline molecule *in situ* is suggested to be a prerequisite for its activity.

The foregoing suggest that mescaline is transformed *in vivo* to a compound resembling LSD in its main structural features and also having an affinity for wool, and that the observed physiopathological and psychopathological properties of mescaline are due to this LSD-like compound. Whether the biosynthesis is brought about by small amounts of partially demethylated mescaline with a tyramine-like compound, or whether it results, e.g. through condensation of very small amounts of mescaline with *nor*-adrenalin (or 5-hydroxytryptamine⁶) both recently identified in the brain⁷, is still in the realm of speculation.

BLOCK⁸ has shown that tyramine is the most powerful activator of the enzymatic incorporation of C¹⁴-mescaline in the mouse liver without affecting mescaline oxydase. This evidence suggests that the formation of small amounts of a compound derived from mescaline and similar in structure to LSD might occur in the liver and could be connected with the "etiology" of the model psychosis elicited in humans after the administration of mescaline.

Acknowledgment. The stimulating discussions with Professors J. PEPPER, C. McARTHUR, V. WOODFORD, University of Saskatchewan,

Saskatoon, and Dr. M. KATES, National Research Laboratories Ottawa, are gratefully acknowledged.

R. FISCHER

Psychiatric Research Unit, Research Laboratory, Munroe Wing, General Hospital, Regina, Saskatchewan, Canada, August 5, 1954.

Zusammenfassung

Die Hypothese einer Biosynthese von D-Lysergsäure-diäthylamidähnlichen Substanzen aus Meskalin in der Leber und im Gehirn wird postuliert.

PRO LABORATORIO

A Scanning and Computing Microphotometer for Cell Analyses

The development of complicated technical tools in cytology automatically produces new technical problems. One of the main problems in quantitative cytology is the time it takes to obtain data from many measurements on each cell, and then to repeat them on many cells in order to get statistically significant results. Every problem on differentiation, cell growth or function involves this difficulty, when the sample is a section through a number of cells. There is little point trying to draw conclusions from observations on a few cells in such studies. The scanning and computing microphotometer described in this paper can be used for quantitative studies of cell sections, and is applicable for the various wave-length ranges now used in cytology. Our aim was to obtain information on transmission values integrated over the cytological preparation point by point with a sufficient resolution and within a short time. For the construction we have used the information theory in its most elementary form, applying a technique commonly used within this field: the pulse technique.

The principle is to convert light intensity to time. The apparatus is thus a type of information machine with a receptor, a microscope system and a scintillation tube with a scanning system, a computing unit, a memory unit, and a printing unit - the effector. 12,000 measurements are made on the sample under examination and the results are computed and recorded in numbers with retained spatial localization. The computation of the 12,000 values takes four minutes. The area of the sample covered by a single measurement is usually 3 μ^2 . An ultimate resolution of about 1 μ is possible, and the permissible error of the apparatus has been set to 1%.

Let us consider the general construction (Fig. 1). The unit at A contains the microscope system and the scanning mechanism. B is the computing unit with its con-

¹ R. FISCHER, F. GEORGI, and R. WEBER, *Schweiz. med. Wschr.* 81, 817 (1951).

² R. FISCHER, F. GEORGI, and R. WEBER, *Schweiz. med. Wschr.*, 81, 817 (1951).

³ R. FISCHER and N. AGNEW, *Naturwissenschaften* 41, 431 (1954).

⁴ E. ROTHLIN, unpublished data (1939).

⁵ G. S. GRACE, *J. Pharmacol.* 50, 359 (1934).

⁶ The biogenesis of LSD in the fungus has recently been described, postulating that oxidized 5-hydroxytryptophan is a precursor [D. HARLEY-MASON, *J. Chem. Ind.* 1952, 172].

⁷ M. VOGT, Communication to the British Pharmacol. Soc., 5. Jan. 1952. - A. H. AMIN, T. B. B. CRAWFORD, and J. H. GADDUM, Communication to the British Pharmacol. Soc., 7. July 1952.

⁸ W. BLOCK, *Z. Physiol. Chem.* 294, 49 (1954)