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VI LAE No. 3b (§102d)
LSD No.60b (§102)

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On drug-produced experimental psychoses.
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On Drug-produced Experimental Psychoses *).

Wool protein was used as a model of the structural surface of receptors, possibly involved in the mechanism producing an experimental (model) psychosis by drugs[1]).

Hence the affinity for wool[2]) of the following compounds was determined at p_H 5·2: mescaline hydrochloride, methedrine (pervitine) hydrochloride, lysergic acid monoethylamide (LAE) and lysergic acid diethylamide (LSD), the latter two in form of their methanoltartrates. These drugs, if administered to humans in the approximate range of dosage: 500 mg., 100 mg., 1 mg. and 100 γ respectively, cause an experimental psychosis characterized by hallucinations and related phenomena of similar intensity and duration[1]).

Since ZUPANCIC[8]) and SMITH, *et al.*[9]), among others, claim that certain quaternaries, especially those antagonistic to tubocurarine, act by inhibiting cholinesterase, we suggest that wool protein in this study might be regarded as a model for the latter enzyme.

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[1]) FISCHER, R.: J. Mental Sci. **1954**.
[2]) FISCHER, R., A. HOELLE and S. SEIDENBERG: Helv. chim. Acta **34**, 210 (1951).
[3]) FISCHER, R.: Manuscript forwarded to Experientia.
[4]) VOGT, M., A. H. AMIN et al.: Commun. to the Brit. Pharmacol. Soc., 5. Jan. a. 7. July 1952, respectively.
[5]) BLOCK, W.: Z. physiol. Chem. **294**, 49 (1954).
[6]) FISCHER, R.: Soap a. San. Chemicals **30**, 33 (1954).
[7]) FISCHER, R.: Science (Lancaster, Pa.) **118**, 409 (1953).
[8]) ZUPANCIC, A. O.: Acta Physiol. Scand. **29**, 63 (1953).
[9]) SMITH, C. M. et. al.: J. Pharmacol. **105**, 39 (1952).
[10]) Saskatchewan Committee on Schizophrenia Research.

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Affinity, i.e. average millimoles × 10^{-2} of drug sorbed by 1 gm of wool		Single dose of drug in gm	log. of single dose
Mescaline . .	0	0·5	−0·3
Methedrine .	0·6	0·1	−1·0
LAE	1·1	0·001	−3·0
LSD	2·6	0·0001	−4·0

The results indicate that there is a relation between the affinity of a drug for wool and the ability of the same drug in producing hallucinations.

In the following we will consider only mescaline, LAE and LSD because it can be argued that mescaline in itself is not the active compound when administered to human volunteers but forms compounds similar to the LSD or LAE structure. Such a hypothesis was forwarded recently[3]) postulating that the biosynthesis may be brought about, among others, through condensation of minute amounts of mescaline with nor-adrenalin or 5-hydroxytriptamine both recently identified in the brain[4]).

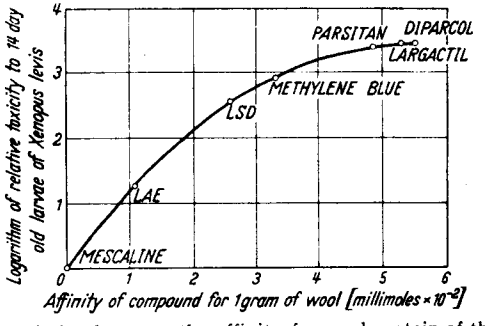

Fig. 1. Relation between the affinity for wool protein of the seven compounds and the log. of their relative toxicity towards 14 day old tadpoles of Xenopus levis.

There are several reasons to believe in such a biosynthesis, one of them being that tyramine is the most powerful activator of the enzymatic incorporation of C^{14}-labelled mescaline in the mouse liver[5]). It was attempted to prevent an 80 γ-LSD-caused psychosis by previous administration of a structurally related substance, a potential competitive inhibitor. Suitable compounds were selected from the phenothiazine series.

It is known that methylene blue, a phenothiazine derivative, is capable of staining, among other things, the ends of living nerves; it is an analgesic, an antimalarial and an antiseptic; phenothiazine, on the other hand, is an anthelmintic and base substance of drugs with antihistaminic, fungicidal, adrenolytic and antiemetic activity; in addition these compounds cause a fall in body temperature, display a ganglionic blocking as well as a curarizing action and even some quinidine-like action[6]). We found that methylene blue, N-(2-diethylamino-n-propyl)-phenothiazine (Parsitan), 3-chloro-10-(-3-dimethylaminopropyl) phenothiazine (Largactil) and β-diethylaminoethyl-N-phenothiazine (Diparcol) display a gradually increasing affinity for wool (3·3, 4·8, 5·3, 5·5 Mmoles × 10^{-2} per gram wool respectively).

If, therefore, wool protein is a model of the neuro-receptors involved in the drug-induced experimental psychoses, then we might expect that this group of compounds will modify the LSD-caused psychosis perhaps by competitive inhibition. 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.

A curvilinear relation was found to exist between the gradually increasing affinity for wool protein of the seven compounds (from mescaline to β-diethylaminoethyl-N-phenothiazine) and the log. of their relative toxicity (0, 1·26, 2·54, 2·9, 3·35, 3·43, 3·43) towards 14 day old tadpoles of Xenopus levis[7]) (fig. 1). Such a relation seems to indicate that apparently the very same type of receptor is involved in the production and inhibition of experimental psychoses. The increasing adrenergic blocking activity of LAE and LSD, as well as the gradually increasing adrenolytic action of the inhibitors mentioned can be evaluated as indirect evidence supporting our contention.

Interpretation of our data can also be based on the hypothesis that "many biologically active substances may produce their specific effects by acting on the enzyme which inactivates them"[8]). We might assume then that adsorption of our compounds on wool simulates the combination of the "cationic head"-s of active compounds with the anionic sides of the cholinesterase receptor. Some further data seem to support such an assumption. Janus green B, a very potent inhibitor of cholinesterase, as well as certain quaternary ammonium compounds exhibit an affinity for wool; especially the quaternaries which display the highest affinity (7·0 Mmoles × 10^{-2} per gram wool).