# FACTORS INVOLVED IN DRUG-PRODUCED MODEL PSYCHOSES. II*

By

**ROLAND FISCHER,† M.A., Ph.D.(Basel)**

*University Hospital, Saskatoon, Saskatchewan, Canada*

THE Malleus Maleficarum, the standard textbook of medieval witch-hunting published in 1484 (2), already mentions that "an illusion of sight and touch can be caused . . . by the summoning to the fancy or imagination of certain forms and ideas latent in the mind", and continues by saying that "(the fifth) method of delusion of the devil is by working in the imaginative power, and by a *disturbance of the humours* effecting a transmutation in the forms perceived by the senses". This might be the first working hypothesis ascribing certain behavioural changes of an apparently schizophrenic nature to biochemical influences.

By the administration of certain drugs we can nowadays duplicate that so-called fifth method of the devil and call it an experimental—or *model—psychosis* (1).

The model psychoses, as we know, may be elicited by the administration to normals of a variety of compounds such as mescaline, lysergic acid diethylamide (LSD), atabrine (3), adrenochrome (4), $CO_2$, $O_2$ (5, 6, 7), thioglycollic acid (8), etc., or evoked by certain wave lengths of the stroboscope (9, 10); they can be produced also by a lesion in the temporal lobe of the brain (10) or by continuous lack of (mainly) perceptual stimuli (12), chemical (13) and surgical (14) sympathectomy, as well as through a variety of psychological or physiological stimuli (15) and stressors.

In an over-simplified and generalized way, let me propose the following tentative definition: model psychosis is characterized by symptoms of withdrawal from reality, frequently accompanied by perceptual disturbances, thought-disorders, delusional ideas and sometimes by hallucinations.

Let us recall in this context that there is a *phylogenetic* aspect of schizophrenia.

T. G. Byrne (16) has noted that a choice of three reactions is available to most organisms in response to external stress: an "avoidance", a "still or static" or an "approach" reaction. It is evident that the schizophrenic prefers the first or second of these possibilities, whereas a normal person may choose whichever response appears to him to be most appropriate to the occasion. A "still" reaction has a wide biological usefulness; at the lowest physiological level the still reaction is manifested by feigning death, at an intermediate level by muscular tension, and at a higher psychological level by immobility of emotional expression.

The schizophrenic process is the result of the inability of genetically predisposed people to bear experience.

The *schizophrenic's* "avoidance" as well as "still or static" state can then be compared with the corresponding withdrawal, thought disorder and the

* Based on a paper presented at the Battelle Psychochemistry Symposium, 12-14 October, 1955, in Columbus and Yellow Spring, Ohio. (Part I: *J. Ment. Sci.* (*London*), **100**, 623 (1954).)

† Lecturer in Biochemistry, University of Saskatchewan, Saskatoon.

other symptoms characteristic of a *model psychosis* and it can be assumed that both syndromes contain regressive components from a phylogenetic point of view.

The phylogenetic aspect of mescaline intoxication for instance is emphasized already by Ivanow-Smolenski (17) according to whom the Pavlovian inhibition phase, evoked by mescaline, affects first the most recently acquired artificial conditioned reflexes (C.R.), second the natural C.R.-s, third the unconditioned reflexes thus affecting the subcortical functions. Evidently the inhibition retraces the path of evolution from the youngest to the oldest forms of nervous activity.

The phylogenetic aspect of schizophrenia, on the other hand, was stressed in a research paper where I defined it as a *regressive adaptation syndrome* (18) since certain stages of the General Adaptation Syndrome of Selye seem to be present permanently during certain phases of the schizophrenic process.

Apart from many similarities (1, 19, 20), there are of course differences between the schizophrenic process and a model psychosis, one of them being the chronicity of the former.

However, we should bear in mind that the use of our model is based on a hypothesis, and that, as Goethe remarks in his *Maxims and Reflections*: "Hypotheses are the scaffolds which are erected in front of a building and removed when the building is completed."

There is a group of psychiatrists whose members argue, as does Riebeling (47), that "the mescaline delirium is not a model of schizophrenia".

We could answer to this objection by restating that:

1. Model psychoses contain certain aspects of the acute phase of the schizophrenic process.

2. Can we yet agree on the definition, diagnosis and aetiology of schizophrenia so as to be able to state *ex cathedra* the appropriateness of any model?

3. Anybody criticizing the concept of model psychosis as hypothetical, dogmatic, evanescent or even unscientific should be asked about his psychological reasons for doing so; why did no one venture to criticize the benzene ring for not being a photographic representation of the "true" situation? Scientists are content that a molecular model (e.g. a benzene ring) should represent certain aspects of the compound in question.

4. Synthetic (LSD, etc.) and natural triggering agents utilize a common circuit which converge on the same centres. It is therefore irrelevant whether an impulse is due to a chemical (metabolic) change or has been produced by "artificial" stimulation: the changes will be reflected in the final electrical signs involved.

5. We do not know how compounds with well-established chemical configuration such as LSD or mescaline produce some of those symptoms also present in certain acute phases of the schizophrenic process. Let us find out more about this mechanism instead of reaffirming religiously a dogmatic belief that the model psychoses have no relation to schizophrenia.

### A. Liver Function in Schizophrenia and in Mescaline-Induced Model Psychosis

Among the biochemical similarities let me emphasize the presence of a pathologically low hippuric acid excretion after the administration of sodium benzoate in certain acute schizophrenics on the one hand (20) and in healthy mescalinized (0·5 g. mescaline-hydrochloride s.c.) subjects (21) on the other.

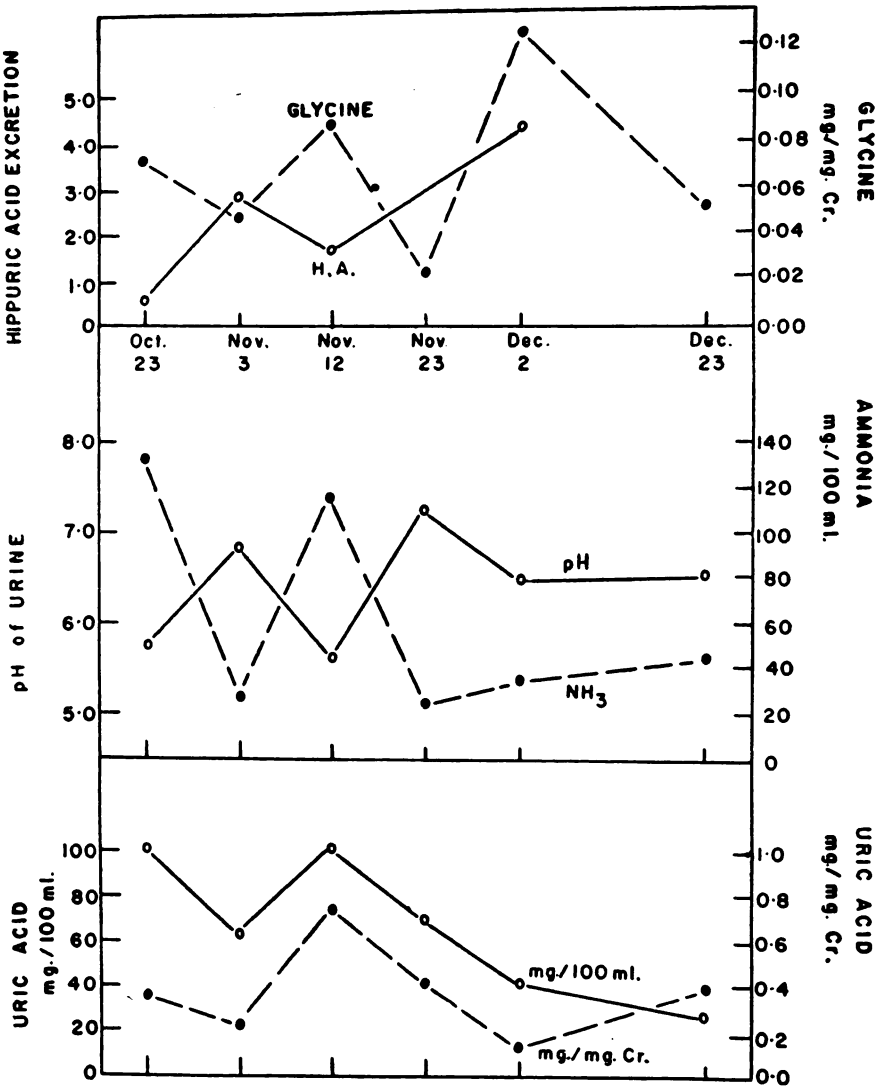


FIG. 1.—Inverse relationship between urinary "free" glycine and subsequent hippuric-acid excretion in a young catatonic schizophrenic male. (23 October—admission to hospital; 23 December—remission.)

It may be recalled that Quastel and Wales (22, 23) were the first to show that in catatonic forms of schizophrenia hippuric acid excretion is lowered after administration of sodium benzoate. We (20) have confirmed these results and extended them to other schizophrenic conditions. Various explanations were later suggested for this "faulty detoxication" in schizophrenia (24, 25, 26). It appears that those investigators who did not confirm the above findings did not use schizophrenic patients prior to treatment or did not supervise appropriately the water intake (52) and the diet of the patients; e.g. oats, prunes, etc., are known to increase hippuric acid excretion (20).

Our present knowledge indicates that the formation of hippuric-acid requires the conjugation of glycine and benzoate in the presence of adenosine triphosphate, magnesium ions, and coenzyme A (27, 28, 29). In some acute

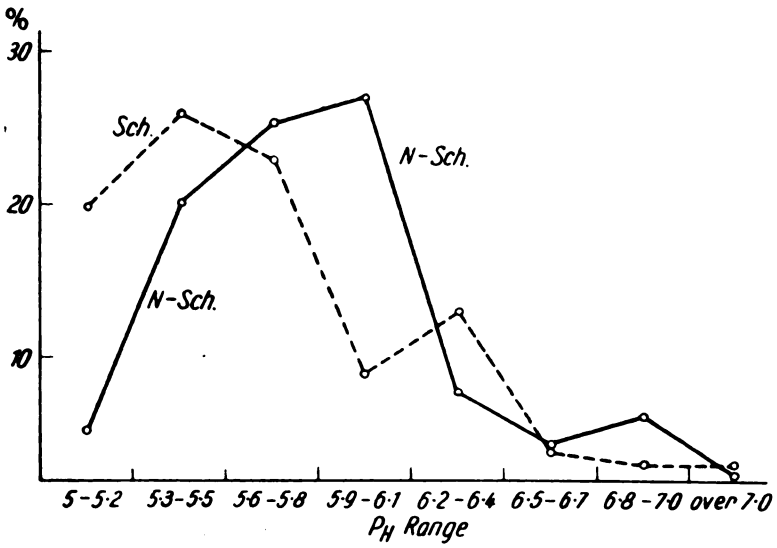


FIG. 2.—Frequency distribution of the pH-ranges of the urines of 130 schizophrenics (Sch) and 114 non-schizophrenics (N.-Sch.); from Fischer, R.: *Naturwissenschaften*, **42**, 301 (1955).

schizophrenics we have found *high* amounts of glycine in the early morning urine (e.g. 90 $\mu$g. per mg. creatinine, as measured by quantitative paper chromatography). These patients had a *low* hippuric acid excretion (approximately 2 g.) during the four hours after the oral administration of 6 g. of sodium benzoate; the amount of glycine in this urine was substantially diminished compared with the glycine in the early morning specimen.

Partial starvation, high protein catabolism (24), decreased thyroid function (30, 31, 32) which is believed to be connected with the regulation of the coenzyme-A level (28) and decreased basal metabolic-rate (24) are among the factors involved in this inverse relationship.

The aforementioned decreased basal metabolic rate and the resulting respiratory acidosis might also be a factor responsible for the significantly higher acidity of schizophrenic urine if compared with a normal and neurotic control population.

Repeated administration of sodium benzoate or surplus of glycine raises significantly the excretion of hippuric acid in certain schizophrenics, but only slightly in normal people (33).

The urine glycine of normal people we found to be higher during the night (40–80 $\mu$g. per mg. creatinine) than in the morning (30–50 $\mu$g. per mg. creatinine). These values were also inversely related to the hippuric-acid values in normal persons after ingestion of sodium benzoate which we had found earlier to be about 10 per cent. lower during the night than in the morning (20).

As to the possible underlying mechanism of the observed data, I should like to present the scheme shown in Fig. 4 overleaf.

Since repeated administration of sodium benzoate or the simultaneous administration of sodium benzoate with a surplus of glycine raises the amount of excreted hippuric acid, it is possible that the surplus of substrate raised the concentration of its enzyme. If this is true, it is likely that decreased conjugation (utilization) of glycine prevails during those phases of the schizophrenic process which are characterized by a low hippuric acid test (35).

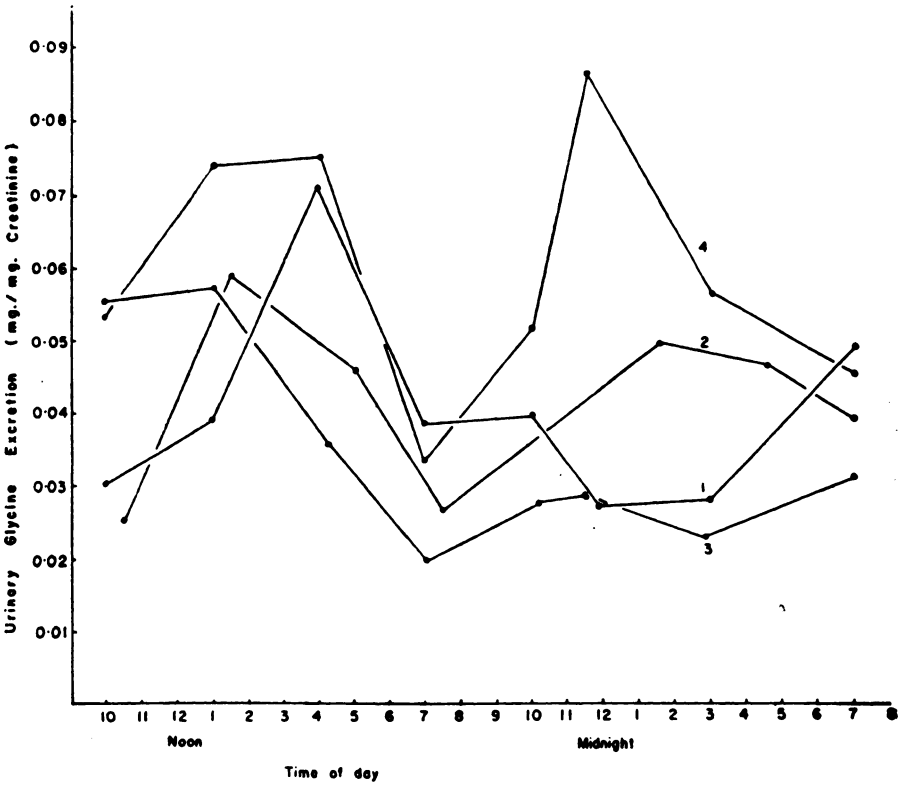


FIG. 3.—Diurnal rhythm of urinary "free" glycine excretion of 4 healthy individuals.

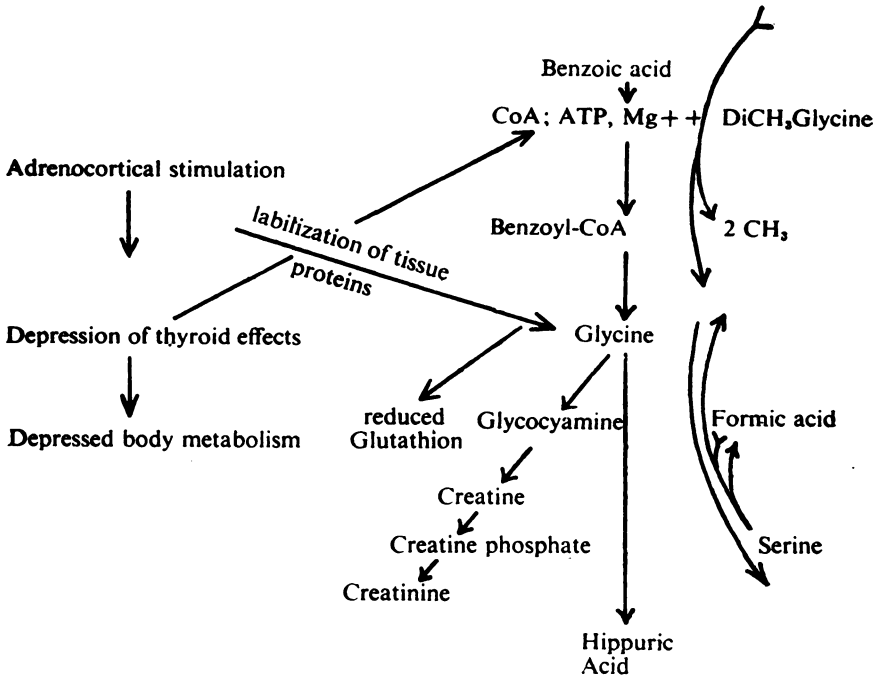


FIG. 4.—Partial scheme of glycine metabolism.

https://doi.org/10.1192/bjp.103.431.392 Published online by Cambridge University Press

It appears therefore that the impaired hippuric-acid synthesis in certain acute schizophrenics might be due to a diminished pyrophosphorylation of CoA by ATP, a step preceding the exchange of the pyrophosphoryl-group for benzoyl- to form benzoyl-CoA which in turn is able to drive the reaction between benzoate and glycine forming hippuric acid.

## B. Studies Using Wool as an Enzyme-Model

In the course of our search for an *in vitro* model of the structural surface of receptors possibly involved in the production of an experimental psychosis, we turned to the use of wool protein (36).

The affinity for wool (37) of the following compounds was determined at pH 5·2: mescaline hydrochloride, methedrine (pervitine) hydrochloride, lysergic acid monoethylamide (LAE) and lysergic acid diethylamide (LSD), the latter two in form of their methanoltartrates. Those drugs, if administered to humans in the approximate range of dosage: 500 mg., 100 mg., 1 mg. and 100 $\mu$g. respectively, cause an experimental psychosis characterized by hallucinations and related phenomena of similar intensity and duration.

The results indicate that there is a correlation between the affinity of a drug for wool and the ability of the same drug to produce hallucinations.

Table

| | Affinity, i.e. average millimoles $\times 10^{-2}$ of drug sorbed by 1 g. of wool | Single dose of drug in g. | 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 |

Continuing these studies it seemed interesting to find out whether LSD has the highest affinity for wool if compared with some of its other biologically active and structurally related derivatives. We determined therefore the affinity for wool of the uterotonics D-lysergic acid 1-propanol-amide-(2) /ergobasine/ and D-lysergic acid (+) butanolamide-(2) /methylergobasine/ compounds with no hallucinogenic activity and found that their affinity for wool was about 1·3 mM $\times$ $10^{-2}$/g.; this is half that of LSD.

Hence it can be stated that LSD, the activity of which in humans is displayed by such small amounts as $\approx$100 $\mu$g., has the highest affinity for wool protein whereas its monoethyl-, propyl- and butyl-derivatives have lower affinity for wool.

In the following, we will consider only mescaline, LAE and LSD. 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. A recent hypothesis (38) postulates that this 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 (39).

Another possibility is to consider the formation of an aldehyde from mescaline as an intermediate in a chain of events leading to an hypothetical active compound *in vivo*.

Block (40) has shown that only 0·03 per cent. of the $C^{14}$ labelled mescaline is incorporated in the mouse-liver-protein 4–6 hours after the administration of the drug; in man this would amount to about 90–180 $\mu$g. mescaline-protein

after administration of 300–600 mg. of mescaline. The order of magnitude of 100 $\mu$g. LSD is similar to that of 90–180 $\mu$g. mescaline-protein.

The affinity for wool of mescaline and its corresponding 3,4,5-trimethoxy-phenyl-ethyl-aldehyde* was determined and it was found that under the experimental conditions prevailing† the affinity of the aldehyde is twice as great (around 4½ mM $\times$ $10^{-2}$/g. of wool) as that of mescaline (2 mM $\times$ $10^{-2}$/g. of wool).

Block (41) believes that the following reaction might take place in the liver:

$$\begin{array}{l} \qquad\qquad\quad CH_2.CH_2.CO.NH..... \\ \qquad\qquad\quad \vdots \qquad\qquad\quad \vdots \\ R.CH_2.CHO + H_2N.CH \qquad\quad . \quad \text{Protein} \\ \qquad\qquad\quad \vdots \qquad\qquad\quad \vdots \\ \qquad\qquad\quad CO.NH.CH_2.CH_2..... \end{array}$$

with subsequent formation of a Schiff's base; the latter hydrolysed would yield the aldehyde again which can be easily oxidized to the corresponding acid; the original amine is also produced by such a split giving rise to mescaline which obtained its $NH_2$-group from the protein. The amount of aminoxidase, necessary to initiate the reaction, is too small to be detected by present-day methods (41). It appears also of some importance to consider another aspect, namely the reversible and competitive inhibition of liver-aldehyde oxidase by epinephrine and its irreversible non-competitive inhibition by adrenergic blocking agents (42).

The situation is quite complex and though it does not simplify matters it should be remarked that Randall (43) has shown that 3,4,5-trimethoxy-phenyl-ethyl-aldehyde does not display any interesting pharmacological properties.

Let us come back again to the earlier-mentioned relation between the affinity of a drug for wool and the ability of the same drug to produce hallucinations. We found that methylene blue, N(2-diethyl-amino-n-propyl)-phenothiazine (Parsitan), 3-chloro-10-(-3-dimethylaminopropyl)-phenothiazine (Chlorpromazine, Largactil) and $\beta$-diethylaminoethyl-N-phenothiazine (Diparcol) display a gradually increasing affinity for wool (3·3, 4·8, 5·3, 5·5 mM $\times$ $10^{-2}$/g. 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 those compounds displaying the highest affinity for wool will modify the LSD-caused psychosis, among others, perhaps by competitive inhibition. Experiments with Largactil (Chlorpromazine) suggest that a gradual increase in affinity for wool of a compound might be one of the factors associated with a more complete inhibition of the experimental psychosis (44).

A curvilinear relation was found to exist between the gradually increasing affinity for wool protein of the seven compounds (from mescaline to Diparcol) 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*.

Such a relation seems to indicate that apparently similar type of receptors may be involved in the production and inhibition of experimental psychoses. The different levels of affinity for wool of certain compounds might imply that many compounds with high affinity display biological properties generally

* Kindly supplied by Prof. J. Pepper, Department of Chemistry, University of Saskatchewan.

† Since the aldehyde is not very soluble in water, the experiments were performed in dissolving 0·2 gm. of each of the substances in a mixture of 30 c.c. ethylalcohol and 20 c.c. of water and determining the affinity for 1 gm. of wool at 85° C. for 10 minutes.

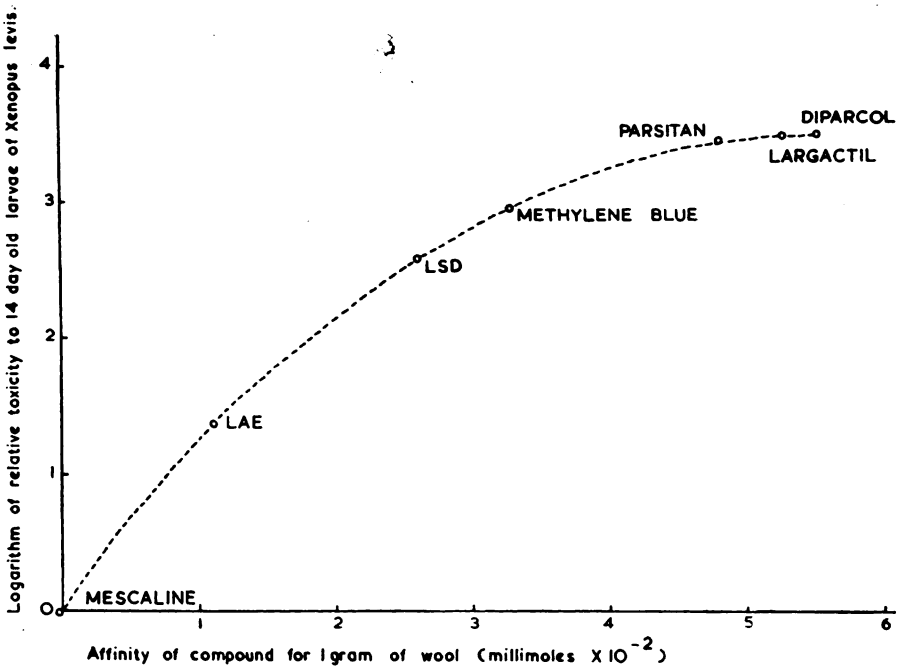


FIG. 5.—Relation between the affinity for wool protein of the seven compounds and the log. of their relative toxicity towards 14-day-old tadpoles of *Xenopus levis*.

including also those associated with compounds of low affinity for wool. The implication may be drawn that there is a hierarchy in terms of biological activity which is associated with the degree of affinity for wool. In general, those compounds of a homologous series which show high affinity have also a wider range of biological activity than those with low affinity for wool. This would be in agreement with the observation that there are many substances each of which acts on more than one enzyme. Ergotamine, for example, inhibits monoaminoxydase, diaminoxydase and cholinesterase (46).

Let me insert here a quotation from Zupancic (45): "The overlapping sensitivity of a few enzymes toward the same substance would be analogous to the retinal cone pigments with their overlapping but quantitatively different, absorption of the same monochromatic light."

*Thema con variazioni*

It could be, of course, that the "fifth method of delusion of the devil" actually works "by a disturbance of the humours". We mean the possibility that, for example, 150$\gamma$ and more LSD might produce a neurohumoral disbalance containing the symptoms of anxiety (24), or in other words certain symptoms of either Cannon's emergency or Selye's G.A.S. shock-phase. Once anxiety has been aroused and is sustained many perceptual thresholds are affected.

Any stimulation then which would affect the same circuit system, could alter the intensity of the model psychosis in either direction.

It is easier to understand in the light of the above hypothesis that a reassuring, familiar environment shortens the LSD-experience as well as diminishes its intensity, whereas stressful stimulations intensify the same experience (48).

"Tolerance to LSD develops more rapidly, is greater in degree, and is lost more rapidly than is tolerance to any other drug with which we are familiar" (49, 50, 51). It does not sound unreasonable to interpret the above observation by assuming that LSD-volunteers develop as well as lose tolerance faster to their own "disbalanced" neurohumours than to body-foreign drugs.

SUMMARY

The concept of model psychosis is discussed. An attempt is made to focus on certain biochemical deviations occurring during both the model psychosis and in schizophrenia. Some of the possible mechanisms involved in the production and modification of model psychosis are described.

ACKNOWLEDGMENT

These studies were supported by the Department of National Health and Welfare, Ottawa, Canada, and the Rockefeller Foundation, New York.

REFERENCES

1. FISCHER, R., GEORGI, F., and WEBER, R., *Schweiz. Med. Wschr.*, 1951, **81**, 817.
2. *Malleus Maleficarum*, 1948, translated by the REV. M. SUMMERS. London: The Pushkin Press.
3. FISCHER, R., *J. Ment. Sci.*, 1954, **100**, 623; *Naturwissenschaften*, 1954, **41**, 431.
4. HOFFER, A., OSMOND, H., and SMYTHIES, J., *J. Ment. Sci.*, 1954, **100**, 29.
5. MEDUNA, L. J., *Carbon Dioxide Therapy*, 1950. Springfield, Ill.: Ch. C. Thomas.
6. HOSKINS, R. G., *The Biology of Schizophrenia*, 1946. New York: W. W. Norton.
7. LOVETT DOUST, J. W., *et al.*, *J. Ment. Sci.*, 1952, **98**, 640.
8. LUCY, J., *see* FISCHER, R., *J. Ment. Sci.*, 1954, **100**, 623.
9. WALTER, W. GREY, *Aspect de l'électrophysiologie des méchanismes mentaux*, 1951. Paris: Presses Univ.; *The living brain*, 1953. New York: Norton.
10. ELKES, J., ELKES, C., and BRADLEY, P. B., *J. Ment. Sci.*, 1954, **100**, 125.
11. WILLIAMS, D., *Lancet*, 1954, *i*.
12. BEXTON, W. H., HERON, W., and SCOTT, T. H., *Canad. J. Psychol.*, 1954, **8**, 70.
13. WALTER-BUEHL, W., *Mschr. Psychiat. und Neurol.*, 1949, **129**, 118.
14. HARRER, G., and URBAN, H. J., *Der Nervenarzt*, 1953, **24**, 63.
15. BOERNSTEIN, W. S., Paper read at the XIII Interntl. Psychol. Congress in Stockholm, 19 July, 1951.
16. BYRNE, J. G., *Studies on the Physiology of the Eye*, 1933. London.
17. IWANOW-SMOLENSKI, *Grundzüge der Pathophysiologie der höheren Nerventätigkeit*, 1954, Berlin: Akademie-Verlag.
18. FISCHER, R., *J. Nerv. and Ment. Dis.*, 1954, **119**, 492.
19. OSMOND, H., and SMYTHIES, J., *J. Ment. Sci.*, 1952, **98**, 309.
20. FISCHER, R., GEORGI, F., *et al.*, *Schweiz. Med. Wschr.*, 1950, **80**, 129.
21. GEORGI, F., FISCHER, R., and WEBER, R., *Schweiz. Med. Wschr.*, 1949, **79**, 121.
22. QUASTEL, J. H., and WALES, W. T., *Lancet*, 1938, *ii*, 301.
23. *Idem*, *ibid.*, 1940, *i*, 402.
24. FISCHER, R., *Mschr. Psychiat. Neurol.*, 1953, **126**, 315.
25. KEUP, W., *ibid.*, 1954, **128**, 56.
26. GRAETZ, B., REISS, M., and WALDON, G., *J. Ment. Sci.*, 1954, **100**, 145.
27. RINGLER, I., and LEONARD, S., *Endocrinology*, 1954, **55**, 363.
28. TABACHNICK, I. I. A., and BONNYCASTLE, D. D., *J. Biol. Chem.*, 1954, **207**, 757.
29. ZIEVE, L., and MANSON, M., *Lab. Clin. Med.*, 1953, **42**, 872.
30. MALIS, G., *Nevropat. i. Psikhiat.*, 1947, **16**, 66.
31. DANZIGER, L., and KINDWALL, J. A., *Dis. Nerv. Syst.*, 1953, **14**, 3.
32. REISS, M., *J. Ment. Sci.*, 1954, **100**, 687.
33. GEORGI, F., FISCHER, R., WEBER, R., and WEIS, P., *Schweiz. Med. Wschr.*, 1948, **78**, 1144.
34. BORSOOK, H., "Peptide bond formation", in *Advances in Protein Chem.*, 1953, **8**, 153.
35. TREW, A., and FISCHER, R., *Lancet*, 1955, *i*, 402.
36. FISCHER, R., *J. Ment. Sci.*, 1954, **100**, 623.
37. *Idem*, HOELLE, A., and SEIDENBERG, S., *Helv. chim. Acta*, 1951, **34**, 210.
38. *Idem*, *Experientia*, 1955, **11**, 162.
39. VOGT, M., AMIN, A. H., *et al.*, Communication to the Brit. Pharmacol. Soc., 5 January and 7 July, 1952, respectively.
40. BLOCK, W., *Z. physiol. Chem.*, 1954, **294**, 49.
41. *Idem*, *ibid.*, 1954, **296**, 108.
42. UNGAR, G., and HUMMEL, F. P., *Proc. Soc. Exp. Biol. and Med.*, 1953, **83**, 126.
43. RANDALL, L. C., personal communication.
44. FISCHER, R., and AGNEW, N., *Naturwissenschaften*, 1954, **41**, 431.

45. ZUPANCIC, A. O., *Acta Physiol. Scand.*, 1953, **29**, 63.
46. FISCHER, R., paper presented at the Symposium on "Molecular structure and functional activity of nerve cells", 3–4 June, 1955, in Washington, D.C., edited by R. G. Grenell and L. J. Mullins, Publ. No. I, 1956, *Amer. Instit. Biol. Sci.*, Washington, D.C.
47. RIEBELING, C., *Fortschr. Neurol. Psychiat.*, 1954, **22**, 181.
48. HYDE, R. W., V. MERING, O., and MORIMOTO, K., *J. Nerv. Ment. Dis.*, 1953, **111**, 266.
49. ISBELL, H., *et al.*, *Fed. Proc.*, 1955, **1**, No. 1, 354; *A.M.A. Arch. Neurol. Psych.*, 1956, **76**, 468.
50. ABRAMSON, H. A., *et al.*, *J. Psychol.*, 1956, **41**, 81.
51. CHOLDEN, L. S., *et al.*, *J. Nerv. Ment. Dis.*, 1955, **122**, 211.
52. RIEDER, H. P., *Helv. Med. Acta.*, 1955, **22**, 210.



https://doi.org/10.1192/bjp.103.431.392 Published online by Cambridge University Press