THE
JOURNAL OF MENTAL SCIENCE
[*Published by Authority of the Royal Medico-Psychological Association*]

No. 420 [NEW SERIES NO. 384.] JULY, 1954 VOL. 100

Original Articles

FACTORS INVOLVED IN DRUG-PRODUCED MODEL PSYCHOSES*

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(1) THE PROBLEM AND ITS EXPERIMENTAL APPROACH

THE use of fibrous wool protein as a model of the structural surface of receptors, possibly involved in the mechanism producing a model psychosis by drugs, was suggested by three lines of evidence.

First, the strong affinity (sorption) of certain basic compounds to keratins of low sulphur content as exemplified by the Gram-positiveness of epidermal (Fischer, 1953c) and nervous (Bailey, 1950) tissue.

Second, the accumulating evidence indicating the similarity in behaviour between keratins of high sulphur content (e.g. wool) and the protein component of certain cell membranes (Fischer, 1951; Fischer and Larose, 1952a; *idem*, 1952b; Larose and Fischer, 1952; *idem*, 1953a and 1953b).

Third, some preliminary experiments confirming the role of wool protein as a useful model to simulate some of those receptors for which certain drugs appear to compete.

(1) It was well known that methylene blue, which competes with acetylcholine in causing contraction of an isolated frog heart (Clark, 1937) can be seen by its blue colour absorbed to the tissue from which even prolonged washing does not dislodge it. This example of a competitive absorption (displacement) could be simulated in a model experiment showing the high affinity of methylene blue chloride‡ to wool, i.e. $3 \cdot 3 \times 10^{-2}$ millimoles per 1 gm. of wool, whereas acetylcholine bromide§ could be washed out completely (desorbed) from the wool under the same experimental conditions.‖

* Supported by the Department of National Health and Welfare, Ottawa.
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‡ National Aniline Div. product; C.I. No. 922.
§ An Eastman Organic chemical.
‖ A slight modification of the procedure previously described (Fischer, Hoelle and Seidenberg, 1951) was introduced this time: after equilibrium has been reached, each of the wool samples was rinsed three times by immersion in individual beakers, containing 250 cc. of distilled water at 29-30° C., each rinsing requiring a fresh water change.

https://doi.org/10.1192/bjp.100.420.623 Published online by Cambridge University Press

(2) The adrenergic blocking action of compounds of the Dibenamine (β-haloalkylamine) type (e.g. SKF-501 = N-(9-fluorenyl)-N-ethyl-β-chlorethylamine hydrochloride) was felt to be another example of an inhibition of the action of epinephrine (adrenaline) by means of competitive absorption on a receptor (target) presumably proteinic in nature. Such a hypothesis is supported by some indirect evidence; Sawyer and Parkerson, 1953, namely were able to demonstrate the ability of SKF-501 to block the effects of epinephrine on its target organs, Schayer *et al.*, 1953, on the other hand observed a significant increase in the rate of destruction of l-epinephrine after Dibenamine administration. In line with the foregoing conclusions and results we measured a higher affinity (absorption) of SKF-501 for wool, i.e. $3{\cdot}8 \times 10^{-2}$ millimoles per gm. wool, than that of epinephrine. In order to prevent oxidation of the latter, the determination of its affinity for wool had to be carried out in the presence of very small amounts of ascorbic acid but even so we may make only an estimated comparison.

Based on these premises, the affinity for wool* (Fischer, Hoelle and Seidenberg, 1951) of the following four basic compounds was determined at pH 5·2: mescaline hydrochloride, methedrine 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 100γ respectively, cause a model psychosis characterized by hallucinations and related phenomena of similar intensity and duration (Behringer, 1927; Mayer-Gross *et al.*, 1951, 1953; Stoll, 1947; Liddell and Weil-Malherbe, 1953; Solms, 1953; Fischer, 1946; Fischer, Georgi and Weber, 1951). The method of determining the affinity for wool used in this study gives only relative values but these were found to be proportional to the absolute values obtained by another method (Larose and Fischer, 1953b).

(2) Results

The results are presented in Fig. 1. The logarithms of dosage of each of the four compounds which causes a model psychosis of comparable intensity and duration are plotted against the amount of these compounds sorbed by wool. The results indicate that the higher the affinity of a drug for wool, the lower the amount of that drug required to cause hallucinations.

The results are not contrary to the hypothesis that the mode of action of mescaline and LSD might be different (Witt, 1951; Mayer-Gross *et al.*, 1953). Block and Block, 1952; Block, 1953, have shown that C^{14} mescaline is incorporated enzymatically and not by absorption on the liver protein at the peak of hallucinatory phenomena. The yield and speed of this reaction was found to be in the same range of magnitude as that of radioactive labelled lysine (Block and Block, 1952). Our results are in line with this evidence since they show no affinity of DL-lysine hydrochloride and mescaline hydrochloride for wool. Another analogy: β-phenylethylamine, a sympathomimetic compound which in contradistinction to mescaline, benzedrine, ephedrine, etc., is regarded as a normal metabolite was shown to be degraded enzymatically to phenylacetic acid (Block, 1953). Thus, mescaline has neither its mescalinoxidase nor an affinity to (liver) protein; β-phenylethylamine, however, has its amino oxidase and therefore may be absorbed on (liver) protein. In accordance with this we found that β-phenylethylamine has an affinity of $2{\cdot}2 \times 10^{-2}$ millimoles for 1 gm. (wool) protein.

* The term wool is identical with that of intact wool used in some previous papers, see e.g., Fischer and Larose, 1952b.

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	Affinity i.e. average millimoles $\times 10^{-2}$ of drug sorbed by 1 gm. of wool	Single dose of drug	log. of single dose
Mescaline	0	0·5 gm.	−0·3
Methedrine	0·6	0·1 gm.	−1·0
LAE	1·1	1 mg.	−3·0
LSD	2·6	100γ	−4·0

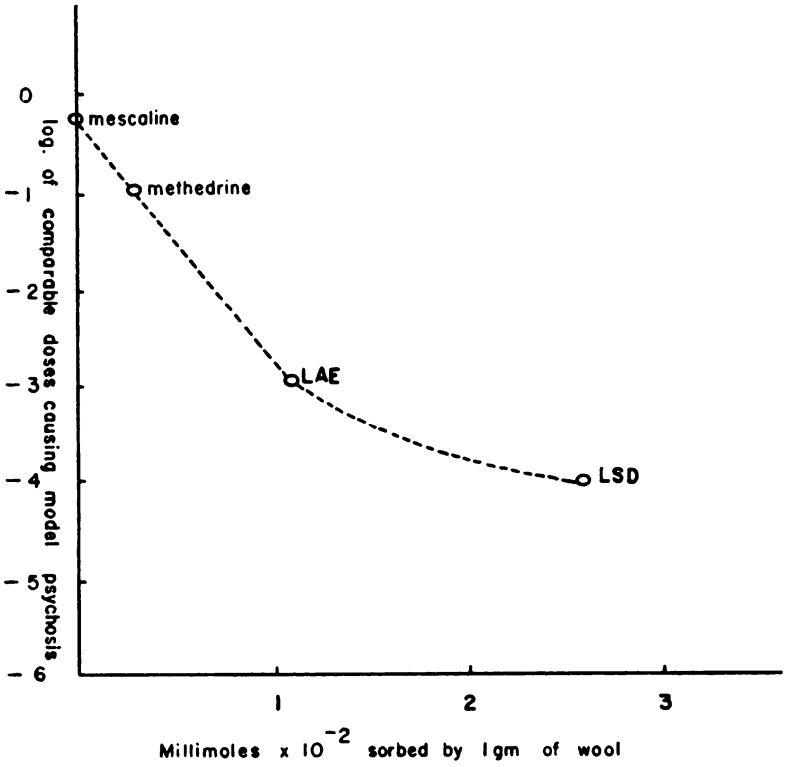


Fig. 1.

(3) Discussion

We are inclined to attribute the increasing affinity of the drugs in question for wool* to their different degrees of specificity simulating a reversible inhibition of an equilibrium involved in the production of hallucinations.

We included only these four drugs in Table and Fig. 1, because it is not easy to find other drugs which precipitate a reversible model psychosis with hallucinatory experience of comparable duration and intensity after administration of a *single* dose. Atabrine (mepacrine), e.g. which is known to produce hallucinations and catatonic excitement (Greiber, 1947; Szatmari, 1953), requires prolonged daily administration.† Another antimalarial, of similar structure and action, Pentaquine, displays an affinity of $3{\cdot}6 \times 10^{-2}$ millimoles per 1 gm. of wool. If Pentaquine is administered daily at a dosage four times higher than usual

* High affinity for wool does not mean the same for us as "selective absorption". An example: Bradley (1951) has shown the selective absorption of one of the optical antipodes by wool from an aqueous or alcoholic solution containing both of the optical antipodes of resolvable acids.

† E.g. 3 gms. per day for 8 days (Halpern, *et al.*, 1953); accordingly we find the affinity for wool of atabrine to be low, i.e. $0{\cdot}9 \times 10^{-2}$ millimoles/gm. This example suggests that compounds of low affinity for wool seem to display their biological activity only in high dosage.

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(0·12-0·24 g./day), it acts as an adrenergic blocking agent (Hoobler and Dontas, 1953). This feature seems to be, among others, a common characteristic of drugs capable of precipitating a model psychosis.

Liddell and Weil-Malherbe, 1953, have shown that methedrine as well as LSD also block adrenergic activity by lowering the blood-epinephrine level, after a short initial increase, during the model psychosis; so might LAE, since it belongs to the family of dihydrogenated ergot alkaloids, which are presumed to act centrally to inhibit sympathetic vasomotor tone (Hoobler and Dontas, 1953); however, it should be noted that the peripheral adrenolytic effects of LAE and LSD are about 300-2,000 times weaker than that of dihydroergotamine (Rothlin, 1953).

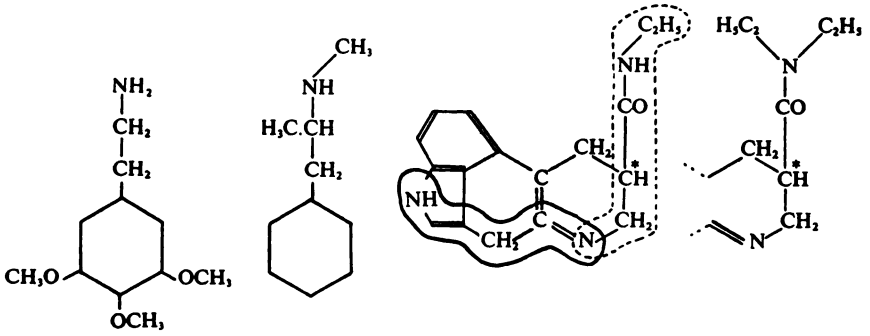
Surgical (sympathectomy) (Harrer and Urban, 1953) or chemical (Dibenamine) (Walter-Buel, 1949) adrenergic blockage also produce psychotic experiences in certain subjects, possessing high epinephrine and nor-epinephrine (Nickerson *et al.*, 1953) levels* to which they apparently are not adapted.

Hence, it appears that drugs which exhibit their central and/or peripheral adrenergic blocking activity in smaller doses than e.g. Dibenamine and simultaneously display a high affinity for (wool) protein, are able to cause hallucinations in very small doses.

(4) Speculations

A. Related to Chemical Structure and Biological Activity

In examining the chemical structure of some of the compounds displaying ncreasing affinity to wool, let us consider one aspect.



Mescaline Mol. w.: 211·6 | Methedrine Mol. w.: 149·1 | LAE Mol. w.: 295 | LSD Mol. w.: 323

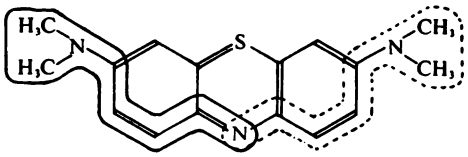
Bovet *et al.*, 1952 and 1953, have shown that the part mainly responsible for specific pharmacodynamic activity of dehydrogenated ergot alkaloids is the molecular configuration centered at the primary NH_2-group and its neighbourhood. We can extend this observation to almost all of our compounds involved in this report and compare in a deliberately oversimplified way the aforementioned groups on these compounds as one factor supposedly influencing their increasing *absorption* (affinity) *for wool.* From mescaline to methedrine: there is an additional monomethyl group on the primary amino N. The third drug, LAE also has an alkylated primary amino group (monoethyl) and then a three C-chain counting up to its additional N in the nucleus of the formula; the latter initiates a second N–C–C–C–N– grouping; LSD, the fourth drug, differs

* Only about 20 per cent. of hypertensive patients react to 0·5 gm. Dibenamine with a model psychosis (Walter-Buel, 1949).

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from LAE only by a higher grade of alkylation on the primary amino group (di-ethyl). Hence we note that (1) a gradually higher grade of alkylation and (2) the presence of two "LSD-tails" (N–C–C–C–N) are among the structural concomitants of our basic drugs displaying an increasing selectivity for wool.

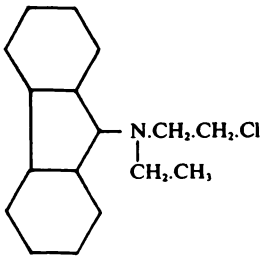
The next formula, methylene blue, shows us a substance of even higher affinity (i.e. absorption) for wool than LSD.



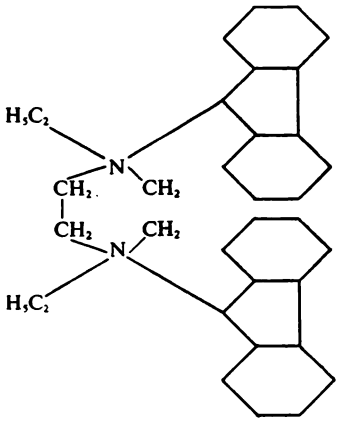
Methylene blue; Mol. weight: 320

Here we observe two dialkylated "LSD-tails" each of which has 4 C atoms (instead of 3, in LAE and LSD) between the primary amino group and the N-atom of the ring.

Before considering some of the structural characteristics of SKF-501 which displayed a high affinity for wool among all the compounds tested in this study and under our experimental conditions, let us draw attention to the findings of Harvey and Nickerson, 1953, which show that compounds of the Dibenamine type, including SKF-501, might occur in the body rather in their ethylenimonium form; these authors also have shown that such a form exerts the same adrenergic blocking activity as the original configuration.



SKF-501



ethylenimonium form of SKF-501
Mol. weight: 314

Summarizing: increasing absorption (higher degree of specificity for wool protein) of basic (cation-active) drugs is accompanied* by the following structural features: (*a*) increased grade of alkylation on the primary amino group, the latter which may be present as quaternary N, in vivo, (*b*) increasing number of such amino-groups, (*c*) increasing number of C atoms (up to 4) between the primary amino group(s) and the neighbouring N of the nucleus, (*d*) the presence of two hidden "LSD-tails" and (*e*) a molecular weight around 320 seems to appear also as one of the characteristics of basic drugs displaying a high affinity

* Among other factors disregarded in this report; further factors, see Fischer and Larose, 1952b.

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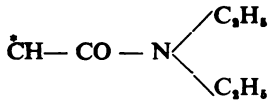
for wool. Some of the aforementioned common structural features of LAE, LSD, methylene blue and SKF-501 remind us that among the phenazathionium compounds substitution in the amino group (alkylation) is accompanied by an increase in basicity; the latter characteristic, however, might be regarded only as one of the factors influencing the affinity of our basic compounds for wool (Fischer and Larose, 1952b).

Since the following data, kindly supplied by the courtesy of Professor E. Rothlin, indicate that there is no increase in basicity if comparing LAE with LSD:

pK_b in H_2O of	Mescaline ..	4·25
	LAE	7·17
	LSD	7·12

the higher affinity for wool of the latter is due to other factors.

There are numerous problems as well as questions arising in connection with the above speculations; e.g. is the optically active Ċ-atom and its adjacent structural part, the



grouping involved in the highly specific action of LSD? Such questions remind us of the limitations of wool in this study, since (*a*) wool protein might be regarded only as a *model* of the protein component of the target organ(s) playing a part in the production of model psychoses by drugs, (*b*) affinity (sorption) of a drug for protein is only *one* of the *factors* considered up to now in this report.

Another factor is suggested by the finding that thioglycolic acid, used in the permanent waving of hair, precipitated a reversible psychotic experience in a healthy individual (Lucy, 1953). Since the above compound alters the cystein part of proteins, namely their –S–S– bonds, one aspect of its mode of action might be a direct one, namely alteration (Schöberl, 1953) of the protein component of the receptor (target) organ itself.

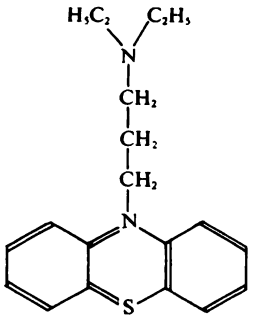
Another problem refers to the adrenergic blocking activity of compounds and the possible relationship of such activity to those common structural characteristics concomitant of drugs exerting high affinity for wool protein.

Finally let me digress in the direction of a very general speculation on biological activity. It might be that different levels of affinity for (wool) protein correspond to apparently different biological activities as viewed by different specialists in biology. Methylene blue, e.g. is a dyestuff capable of staining, among others, the ends of living nerves, it is an analgesic, an antimalarial and an antiseptic, etc.; phenothiazine is an anthelminthic and the base substance of drugs with antihistaminic, fungicidal, adrenolytic, antiemetic and "artificial hibernation"-inducing activity, etc. We could multiply such examples. It seems that derivatives of a compound displaying high affinity for (e.g. wool) protein, exert various biological activities according to the degree of specificity they display toward the available receptors, some of them apparently containing a protein component structurally related to wool.

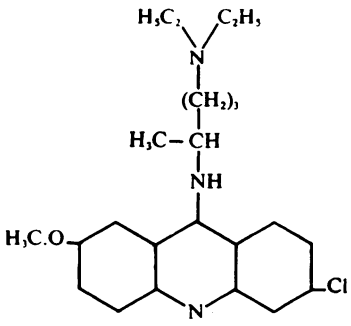
High affinity for wool of basic compounds seems also to be associated with very potent biological activity. This activity is evidenced by the small dose of compounds required to exert their activity; e.g. the affinity of the biologically highly active Largactil for wool is high, i.e. 5·3 millimoles·10^{-2} per gm. wool.

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The low affinity of Atabrine for wool (0·9 millimoles·10^{-2} per gm.) on the other hand explains why it has to be administered in high dosage and for a prolonged period.



Chlorpromazine (Largactil)
Mol. weight: 318.5



Atabrine (Mepacrine)
Mol. weight: 435.9

B. Related to Factors Aggravating and Preventing Model Psychoses Caused by Drugs

Our results as well as previous (Fischer, 1953b) and present reasonings imply the possibility:

First, that stress situations causing sympathetic stimulation and overactivity (e.g. the shock phase of the General Adaptation Syndrome (G.A.S.) of Selye, or administration of 1 mg. of atropine prior to LSD (Forrer and Goldner, 1951)) might diminish that dosage of a drug which is required to cause model psychosis at rest. Analogously it is possible to decrease the intensity of a hallucinatory experience, e.g. caused by LSD if the volunteer is successfully influenced psychologically as to feel freer from anxiety previous to the administration of the drug (Hyde, 1954; Stefaniuk, 1953). The latter observation which we would call an "LSD minus stress"-experiment, confirms our recently published views about model psychoses (Fischer, 1953b).

A similar but even more complete freedom from anxiety and its concomitant sympathetic overtonus might be achieved by administration of drugs causing "artificial hibernation" (Weese, 1953; Laborit, 1953; Benitte, 1953), see Largactil. Such drugs prevent the mediation of the stress response and thus result in a "pure" adrenergic blockage. No model psychosis will result in this case. Such an explanation favours also the understanding of the observation of Walter-Buel, according to whom only one-fifth of *hypertensive* patients, apparently those with high adrenalin and noradrenalin levels to which they were not adapted, experience a model psychosis after Dibenamine, another "pure" adrenergic blocking agent. These patients might also be regarded as being under the stress of their milieu interieur and thus displaying anxiety and sympathetic overtonus. Hence *stress* and *adrenergic blockage* seem to be essential components for the precipitation of model psychoses. Such reasoning means implicitly that drugs causing model psychosis, the latter which might be due to a reversible disturbance of the integration between diencephalon and cortex resulting in a lowered reality threshold, may act by exerting (*a*) a *sympathetic overtonus* due either to a counterregulation after administration of an adrenergic blocking agent, or to the high dosage of the agent in question thus containing also an unspecific alarming stimulus (Fischer, 1953b) and (*b*) an *adrenergic blocking activity*. An analogy: those patients whose hypertension is of psychogenic nature

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and who are characterized by a definite sympathetic overtonus, become mentally disturbed if the symptoms of their hypertension are relieved ("adrenergic blockage") by psychotherapy (Draper, 1935).

Second, that persisting stress situations causing first sympathetic and then parasympathetic stimulation and overactivity (e.g. the counter-shock phase of the G.A.S.) might increase that dosage of a drug which is required to cause hallucinations at rest. Such a reasoning would fit in the manifold observations confirming the strange phenomenon of different reactivity of a schizophrenic towards e.g. methedrine if the drug is administered in different periods of the schizophrenic process; such a different response might be explained by assuming that the schizophrenic—due to his genetically inherited low threshold towards stress—is permanently under stress during the active phases of the schizophrenic process (Williams, 1953) and thus in one or another phase of the G.A.S. (Fischer, 1953b).

Third, that simultaneous administration of one of the four drugs (which cause model psychosis) together with an adrenergic blocking agent may intensify the psychotic experience, and

Fourth, that administration of certain compounds with a high affinity for (wool) protein might prevent by means of competitive inhibition the production of hallucinations caused by LAE or LSD.*

Summary

Factors involved in the production of a reversible model psychosis caused by either 500 mg. mescaline, 100 mg. methedrine, 1 mg. lysergic acid monoethylamide or 100γ lysergic acid diethylamide respectively, are considered.

Wool is used as a model for the protein component of the target organ(s) involved in the production of model psychoses.

Increasing affinity (absorption) of the above-mentioned compounds to (wool) protein goes parallel with the decreasing amounts of the same drugs necessary to cause a model psychosis of similar intensity and duration.

Increasing affinity (absorption) of the above mentioned compounds for (wool) protein goes parallel with the decreasing amounts of the same drugs necessary to cause a model psychosis of similar intensity and duration.

Sympathetic overtonus and subsequent adrenergic blockage are apparently among the factors contributing to the precipitation of a model psychosis.

Speculations are made (*a*) relating chemical structure to biological activity, (*b*) as to the possible aggravation, amelioration and prevention of drug-produced model psychoses.

Acknowledgments

I am indebted to the psychiatric staff of the Saskatchewan (Mental) Hospitals at North Battleford, Weyburn and Regina as well as to N. Agnew, Dr. A. Hoffer, Dr. S. Jedwab, Dr. H. Osmond, Dr. A. Szatmari, A. Trew and V. R. Woodford, jun., for stimulating discussions; to Dr. P. Larose, National Research Council, Ottawa, for valuable advice and criticism as well as for a generous gift of extracted wool; to the Sandoz Pharmaceuticals Ltd., Montreal and especially to Professor E. Rothlin, Director, Sandoz A.G., Basel (Switzld.) as well as to the Smith Kline & French Laboratories, Philadelphia, for their kind assistance in providing LAE, LSD and SKF-501 as well as "pervitine" ("methedrine") respectively. Atabrine and Pentaquine were generously supplied by Winthrop-Stearns, Windsor, Ontario and Abbott Laboratories, Chicago, Largactil and Diparcol by Poulenc Ltd., Montreal.

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* A preliminary experiment (to be published with N. Agnew) seems to indicate that methylene blue for example, a weak adrenolytic compound (Marquardt and Schumacher, 1953) but displaying higher affinity for wool than LSD, is able to reduce by approximately 40 per cent. the intensity of an 80γ-LSD experience. The 0·15 gm. methylene blue is administered intragluteally prior to the LSD. These experiments are being continued using compounds displaying even higher affinity for wool than methylene blue. To date Diparcol (Diethylaminoethyl-N-dibenzoparathiazine hydrochloride)—affinity for wool 5·5 millimoles·10^{-2} per gm. wool—appears to be the most effective compound in blocking out LSD symptoms.

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