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The Biochemistry of Schizophrenia

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Abstract

For many years there have been two schools of thought concerning the aetiology of Schizophrenia. Some psychiatrists have been impressed by the disturbed family relationships and early upbringing that is commonly seen in cases of schizophrenia and have felt that the condition is largely psychogenic: that is that anyone subjected to these malign influences would develop the disease. Other psychiatrists have felt that schizophrenia results from a genetically determined metabolic disorder and that the disturbed behaviour results from a brain with specific faults in its biochemical mechanism.

Two recent studies of what happens to the children of schizophrenic mothers who have been removed from their mothers shortly after birth and reared in foster homes have provided powerful, and I believe conclusive, evidence in favour of the latter view. This work was carried out by Heston in Oregon and by Rosenthal and Kety in Denmark. The results showed that these children in foster families nevertheless developed schizophrenia at the same rate (about 12% — as compared with the normal expectancy of 0.8%) as do the children of one schizophrenic parent reared by their biological mother. A control group of adopted children of normal mothers reared in similar foster homes showed no increased incidence. Then the foster families in which these children actually developed schizophrenia were compared with those in which the children remained normal, and no difference could be detected between them. Both lots appeared to be ordinary families. Thus what counts for the development of schizophrenia appears to be the genes and not the early family environment.

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THE BIOCHEMISTRY OF SCHIZOPHRENIA

J. R. Smythies, M.D.

For many years there have been two schools of thought concerning the aetiology of Schizophrenia. Some psychiatrists have been impressed by the disturbed family relationships and early upbringing that is commonly seen in cases of schizophrenia and have felt that the condition is largely psychogenic: that is that anyone subjected to these malign influences would develop the disease. Other psychiatrists have felt that schizophrenia results from a genetically determined metabolic disorder and that the disturbed behaviour results from a brain with specific faults in its biochemical mechanism.

Two recent studies of what happens to the children of schizophrenic mothers who have been removed from their mothers shortly after birth and reared in foster homes have provided powerful, and I believe conclusive, evidence in favour of the latter view. This work was carried out by Heston in Oregon and by Rosenthal and Kety in Denmark. The results showed that these children in foster families nevertheless developed schizophrenia at the same rate (about 12% — as compared with the normal expectancy of 0.8%) as do the children of one schizophrenic parent reared by their biological mother. A control group of adopted children of normal mothers reared in similar foster homes showed no increased incidence. Then the foster families in which these children actually developed schizophrenia were

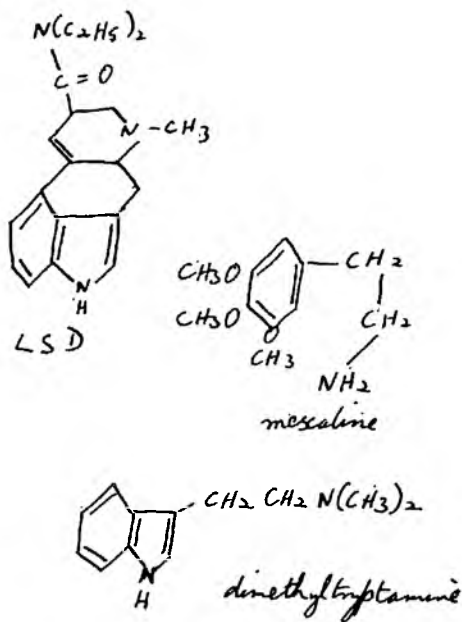
compared with those in which the children remained normal, and no difference could be detected between them. Both lots appeared to be ordinary families. Thus what counts for the development of schizophrenia appears to be the genes and not the early family environment. Moreover many of the children of a schizophrenic mother, who did not develop actual schizophrenia, were abnormal having various severe forms of psychopathic personality. This would therefore account for the fact that many of the relatives of schizophrenics have abnormal personalities and for the fact that many schizophrenics come from peculiar families. However environmental influence also play a role in the genetic expression, which is of course true for any genetically determined condition, such as diabetes, and even for infections, such as tuberculosis. In identical twins, if one twin has schizophrenia, the other is affected in only about 40% of cases. But the affected twin is almost always the smaller and weaker with signs of relatively defective intra-uterine nourishment.

The prognosis of the illness also depends, of course, on environmental and psychogenic factors. But the present evidence is that most schizophrenics are fated from birth to develop the condition.

If then schizophrenia is genetically determined, presumably the faulty gene or genes are expressed by some faulty enzyme(s) whose

malfunction leads to disorders in the brain mechanisms underlying thinking, emotional responses and the generation of belief and behaviour. In search for clues as to what the system concerned might be people have studied the mode of action of drugs that can induce a schizophrenia-like reaction (i.e. hallucinogens such as LSD) and those that are of therapeutic value in the illness (i.e. the phenothiazines and butyrophenones). To take these in turn. The hallucinogens produce many different effects in different people, but sometimes they include a 'bad trip' which is an acute psychosis with many points of similarity with an acute schizophrenic breakdown. The formulae for some well-known hallucinogens is shown in figure 1. It will be noted that many are close chemical relations to the neurotransmitters serotonin and dopamine, the simplest relation being O-methylation, N-methylation or both.

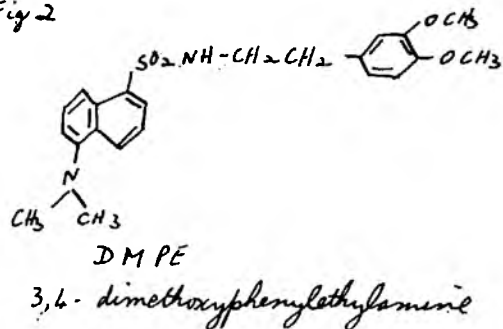
Fig. I.



This relation ship led Osmond, Harley-Mason and Smythies to suggest in 1952 that schizophrenia might be associated with some disorder of catecholamine metabolism so that mescaline-like compounds were produced in the brain such as DMPE (fig. 2). Although this compound has been shown to be a normal constituent of urine (possibly of dietary origin)

there is evidence that its levels are not raised in schizophrenics. However it is possible that schizophrenics may be abnormally sensitive to it, particularly since it has been reported that schizophrenics are abnormally sensitive to the psychotoxic properties of its close chemical relative 2,3,4-trimethoxy phenylethylamine (fig. 3). This possibility can easily be tested by experiment.

Fig 2



Another approach to this problem derives from the discovery made by Pollin et al in 1961 that some chronic schizophrenics react to 1-methionine with an acute psychosis. This has now been confirmed by four groups of workers. In some cases the psychosis shows features of a toxic psychosis and in others of an acute schizophreniform psychosis. About 50% of schizophrenics react and the rest show no reaction at all. It is not possible to predict on clinical grounds which patients will react and which will not. The dose of 1-methionine required is quite small (10-20 C/day) and this dose produces no reaction in normal people. Recently an unconfirmed report from Poland claims that methionine increases the excretion of dimethyltryptamine in schizophrenics but only in those that react to methionine. Thus the basis of the methionine effect may be to increase transmethylation processes in the brain since methionine is the origin of the methyl groups in all transmethylation reaction in the body. Other unconfirmed reports in this field are that schizophrenics do not react with a toxic psychosis as normal people do to the methionine antimetabolite MSO (methionine sulphoxamine) at a dosage of 300 mg/day. Also that schizophrenics methionine metabolism is different from normals. Methionine with a C_{14} label on the labile methyl group was given to schizophrenics and normal controls and the rate of excretion of $C_{14}O_2$ was measured.

This was much slower in the schizophrenics indicating an overactive transmethylation pool.

However we cannot assume that methionine induces its effects by some action on the transmethylation system, for it has other potent biological actions. For example 20 G 1-methionine a day will cause an upset in the uptake of all the other amino acids and it will also affect secondarily tryptophan metabolism. The problems of how it does produce its effects in schizophrenics can only be settled by further experiment.

We can now ask how do hallucinogens produce their effects on brain function for that may give us a clue as to the site of the disorder in schizophrenia. Their most marked property is to block central serotonin mechanisms.

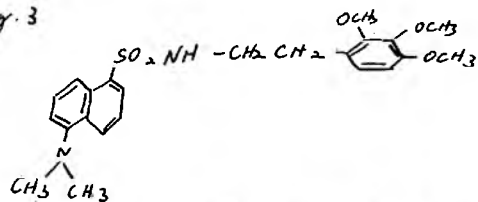
This has been determined both by micro-injection techniques onto the surface of individual neurones and by the following technique. Most of the serotonin containing neurones in the brain locate their cell bodies in the raphe nuclei of the brain stem. From here the axons are distributed all over the rest of the brain. This system seems to control slow-wave sleep amongst other things. If recordings are made from this nucleus and d-LSD injected intravenously an abrupt cessation of firing results.

In addition to these drugs that mimic schizophrenia, we now know of several classes that alleviate it and are used in its clinical treatment. This includes the phenothiazines (such as chlorpromazine), the butyrophenones (such as haloperidol) and certain diphenylbutylpiperazines (such as pimozide). These have a very wide range of biological effects but prominent amongst them is the inhibition of catecholamines. Pimozide, in particular, has potent anti-dopamine actions. This suggests that schizophrenia may be associated with excess activity in the adrenergic and particularly the dopamine system, or it may not be the absolute level of activity in these systems that may be as important as their relative level or balance. If the serotonin system is blocked there may be a relating imbalance of the adrenergic or dopamine systems. The therapeutic action of the anti-psychotic drugs may thus depend on their ability to reduce this (relative) excess activity in the adrenergic system so that it comes back into balance with the serotonin system again.

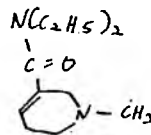
Another way to treat schizophrenia would be to develop drugs that would so act on the serotonin receptor in brain that the binding

of hallucinogens (such as dimethyltryptamine) would be blocked but serotonin itself could still bind. We are currently working on developing such a drug based on the 'top half' of LSD. Figure 3 shows a compound we have called THPC (N-methyl-1,2,4,6 tetrahydropyridine carboxamide). This is a close approximation to the top half of d-LSD. If it were to bind in the same locus as where d-LSD itself acts, clearly d-LSD itself could no longer bind, but mescaline itself, which approximates in shape to the A + B rings of d-LSD, could. Therefore one would predict that THPC would block the effects of d-LSD but potentiate the effects of mescaline. This prediction was tested using a conditioned avoidance test in rats that enables us to measure the 'psychotomimetic' activity of a drug and was confirmed. THPC was also shown to block the effects of dimethyltryptamine. Clearly then THPC may be useful in the treatment of an LSD psychosis and if schizophrenia is caused by a compound like dimethyltryptamine, THPC might prove

Fig. 3



2, 3, 4-trimethoxyphenylethylamine.



THPC

of therapeutic benefit, whereas if the compound responsible was more like mescaline, THPC should exacerbate the illness. Thus THPC can be used as a molecular probe to try and determine the nature of the psychotoxin of schizophrenia. Even if it had no effect, this would provide useful evidence — i.e. that no compounds similar to dimethyltryptamine or to mescaline were involved.

Now although the bulk of recent research

in schizophrenia has been based on the trans-methylation hypothesis, other lines of study have produced some promising results. It has been known for years that chronic schizophrenics have a peculiar odour. Recently a claim has been made that the substance responsible has been identified (fig. 4). This was found in the sweat of 10/10 schizophrenics and in no normal controls. It did not appear to be the product of some bacterial flora peculiar to chronic hospital wards. The compound certainly has a most characteristic and penetrating odour. However it belongs to a chemical family — a branched chain unsaturated fatty acid — never before connected with brain function. In fact the only compounds I know of related to it that have a known biological activity are the bee ovarian hormones, Queen Substance and Royal Jelly, but this may be no more than a coincidence. At any event if this report is confirmed, vigorous efforts should be made to trace its metabolic origin.

A very large number of other investigations have been carried out in schizophrenics but none has achieved any very notable results. Sometimes positive results have been claimed but subsequent work has shown these to be artefactual or due to malnutrition, non-specific stress and other similar factors. This very lack of success has had negative results. The answer to the problem of schizophrenia can only come from an intensive research effort directed towards discovering its biochemical basis. Unfortunately the skilled biochemists

and other biological scientists needed to work on such a programme are not attracted to what has proven over the last 50 years to be so unrewarding a field. The bulk of biochemical research in psychiatry is currently focussed on the biochemical basis of depression, in the form of very extensive work on the biochemistry of cerebral amines — their metabolism, uptake, storage and release mechanisms — which has already paid handsome dividends including Nobel Prizes to two of the main workers in this field. In contrast the field of schizophrenia research is almost totally neglected both in Europe and North America which is strange when one considers the enormous economic cost to the community and the cost in human suffering and blighted lives that schizophrenia brings about. It is not commonly realized that about one in 120 people will develop the illness at some point during their lives and that slightly less than one-quarter of the hospital beds in the country are occupied by schizophrenics.

However, now that we possess at last one valid fact about the physiology of schizophrenia — the methionine effect — the immediate way ahead is clear. The biochemical basis of the effect must be determined. Is it due to altered transmethylation reactions, to changed patterns of aminoacid uptake, to disturbances in tryptophan metabolism or to some other factor? The answer to this question may well lead to other research programmes that in turn may further our understanding of the biochemical basis of one of the still outstanding problems of medicine.