TRANSMETHYLATION PROCESSES IN SCHIZOPHRENIA

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It is generally agreed today that the etiology of schizophrenia is compounded of a genetically determined predisposition, in the form of some vulnerable enzyme system or systems in the brain possibly concerned with reactions to stress, together with various environmental factors that determine whether the genotype is actually expressed as the phenotype. There is very little information, however, on what the biochemical lesion is, and only a handful of hypotheses about what the lesion could be. The so-called transmethylation hypothesis is based on the observation made in 1950 by Harley-Mason, Osmond, and Smythies that mescaline is an O-methyl derivative of dopamine. Many other psychotomimetic drugs have been discovered since then, and most of these are either O-methyl, or N-methyl (or both) derivatives of the central neurotransmitters, noradrenaline, dopamine and serotonin.

The transmethylation theory simply states that schizophrenia may be associated with a defective enzyme system concerned in transmethylation reactions, so that toxic levels of some psychotomimetic agent builds up in the brain. The enzyme, N-methyltransferase, has been discovered in brain (Mandell 1971), and several groups have reported the detection of dimethyltryptamine in the body fluids of schizophrenic patients (e.g., Tanimukai et al. 1970).

I will discuss (1) the experimental data, (2) the transmethylation hypothesis in more detail, and (3) some recent work on transmethylation in the brain brought about by methionine.
The Data

When we consider what the alleged biochemical fault in schizophrenia may be, we find, alas, very few facts on which to build. Fifty years of research have yielded the following meager harvest relevant to the transmethylation hypothesis.

(a) Many workers have reported that schizophrenics are less reactive to histamine than normal people. This may be seen most clearly by measuring the size of the wheal produced by an intradermal injection of histamine. It is consistently smaller in schizophrenics than in normal people and returns to normal size upon clinical remission.

(b) Seymour Kety and his group then at the National Institute of Mental Health found that some chronic schizophrenics react with an acute psychosis to methionine plus an inhibitor of the enzyme, monoamine oxidase. Other schizophrenic patients, clinically indistinguishable from the former, do not react at all. This observation was confirmed by several groups, and the monoamine oxidase inhibitor was shown to be unnecessary (Smythies and Antun 1970; Antun et al. 1971); the active agent is the methionine. This period of acute psychosis is often followed by a period of clinical remission.

(c) Schizophrenic patients also react more commonly than normal with an acute psychosis to antabuse, a drug given to chronic alcoholics to prevent their drinking.

(d) The drugs that alleviate schizophrenic symptoms—that is, the phenothiazines and butyrophenones—have a wide range of biological activity, but one of their most potent effects is in inhibiting the adrenergic synapses in the central nervous system and, in particular, the dopamine receptors.

(e) The drugs that can produce an acute psychosis (a "bad trip") in normal people—that is, the hallucinogens like d-LSD and mescaline—have been shown to inhibit brain serotonin mechanisms and to potentiate certain adrenergic mechanisms.

Interpretation of the Data

These are the clues currently available, and we can ask, meager as they are, whether they suggest the nature of the metabolic lesion—or, at least, what system in the brain might be involved. The evidence presented in sections (c) and (d) suggests that schizophrenia may be associated with an overactive central adrenergic system and, in particular, with the mechanisms involving dopamine. Antabuse nonspecifically inhibits the enzyme that converts dopamine