SUMMARY

THE HYPOTHETICAL RELATIONSHIPS BETWEEN AMINES AND MENTAL ILLNESS; A CRITICAL SYNTHESIS

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LET me begin with some considerations of epistemology. I should like to ask: What does one require of a good hypothesis? We would want it to be plausible, and to be capable of explaining phenomena parsimoniously; to be heuristic, that is, be testable, stimulate good research and the acquisition of new and useful knowledge. We would ask that it have predictive value, and that it continue to be compatible with new data which it stimulates and with other information which becomes available. We should want it to be capable of being modified and elaborated in line with new information without losing its parsimonious qualities. We would also want it to be capable of being rejected and ourselves willing to scrap it when crucial evidence against it is obtained.

Numerous current hypotheses have formed the basis of this meeting, some have been broad and general, and others have been subsidiary to these. Have any of them been proven? I think we will agree that no hypothesis in this Symposium was proven except, perhaps, the very specific hypothesis that there may be a reduction of cystathionine synthase in the liver of patients with homocystinuria which Mudd *et al.* (this Symp., p. 247) seem to have proven rather rigorously.

But we did not really expect to prove any hypotheses in so short a time. What we must ask ourselves and answer, not so much as a group but each individually, with regard to any of these hypotheses is simply this: Is there enough evidence to reject it? And, having satisfied ourselves on that point: Is it sufficiently attractive, plausible or relevant to our own interest and competence to motivate us to devise and carry out appropriate tests of it? The answers to these questions do not demand the same kind of rigorous proof that the hypothesis itself requires. There have been no statistical techniques worked out to establish when a hypothesis is worth entertaining or when it is

viable, interesting, or plausible enough to make it worth one's effort to test it.

The discovery of the psychotomimetic effects of mescaline and later of LSD was responsible for a broad and rather ill-defined hypothesis that chemical substances, or more specifically, certain amines may be crucially involved in the symptomatology of some forms of schizophrenia. It was pointed out by Smythies this morning, and others have emphasized as well, that these agents are not properly described as hallucinogens because they produce true hallucinations in only a small percentage of individuals. The interesting thing about them is that they produce a wide variety of mental changes, including delusions, hallucinations, thought disturbances, paranoid states, affective changes, in different individuals at different times. All of these are found in patients with schizophrenia. That there are differences between the effects of these drugs and schizophrenia is undoubtedly true, but one wonders exactly what the logical implications of the psychotomimetic drugs are to a toxin hypothesis of schizophrenia: dissimilarities do not disprove it since the drug is administered to the patient at different times and in different situations from those which might attend an endogenous toxin. But even if such substances were to produce a syndrome indistinguishable from schizophrenia (which I believe amphetamine may sometimes do), that, in itself, would not prove the hypothesis although it would be compatible with it.

About 15 years ago Smythies, Osmond and Harley-Mason (*J. Ment. Sci.* **98,** 309, 1952) went further with this broad hypothesis and, recognizing that mescaline was a threefold-methylated congener of the normal metabolite, dopamine, they proposed the hypothesis that an alteration in biological transmethylation, resulting in the production of abnormal methylated products, played a crucial role in some forms of schizophrenia. I may have added a few modifiers to their hypothesis, but they are not very important. This hypothesis is parsimonious in that it can incorporate within a single concept the bulk of hallucinogens which are methylated compounds. It is heuristic in that many of the studies which were discussed here resulted from that hypothesis and, as I mentioned before, if that hypothesis did no more than stimulate some of the research which we heard today—research on some of the basic aspects of S-adenosylmethionine metabolism in the brain (Baldessarini, this Symp., p. 199), the development of neurophysiological (Himwich, this Symp., p. 137) or behavioral tests (Smythies, this Symp., p. 5) for hallucinogenic activity, correlations between hallucinogenic activity and quantum molecular properties (Snyder and Merril, this Symp., p. 229)—the hypothesis would have served a valuable purpose. The hypothesis, in addition, however, has been predictive and seems capable of being compatible with new information. Harley-Mason, in what was a remarkable insight, predicted before anyone had demonstrated it, a methylation of catecholamines—in fact, he needed it as part of his hypothesis—and we have since seen only recently, through the work of Axelrod, that O-methylation is one of the most important pathways

in the metabolism of catecholamines. Interestingly enough, Harley-Mason (*J. Ment. Sci.*, **98,** 309, 1952) also suggested that 3,4-dimethyoxyphenylethylamine was a provocative compound in connection with this hypothesis. He based this on its similarity to mescaline and the report by Noteboom, who observed that DMPEA was most potent in producing a catatonia-like state in animals. When a prediction as far out as that is followed by a report, 10 years later, that such a compound occurs in the urine of schizophrenics (Friedhoff and Van Winkle, *J. Nerv. Ment. Dis.* **135,** 550, 1962) a greater credence is attached to the hypothesis.

There is the report by Holmstedt (this Symp., p. 151) of the discovery of a new compound which is probably hallucinogenic and, interestingly enough, both N- and O-methylated. I must confess that I find it interesting that this new hallucinogen, which could have had any structure in all of organic chemistry, turns out to be another methylated compound. There has been reviewed considerable evidence which can be taken to support a transmethylation hypothesis of schizophrenia. The evidence does not rigorously support the hypothesis, but much is at least compatible with it. We have heard about the effects of methionine administration which can produce an exacerbation of psychosis in some schizophrenic patients (Pollin, Cardon and Kety, *Science*, **133,** 104, 1961), an observation which appears to have been confirmed in other laboratories (Brune and Himwich, *J. Nerv. Ment. Dis.* **134,** 447, 1962; Alexander *et al.*, ibid., **137,** 135, 1963). I feel that there are few more aware of the deficits in those observations than the investigators who have made them. Much remains to be done to rule out alternative hypotheses to the one that methionine exacerbates psychosis by stimulating transmethylation. As a matter of fact, we freely admitted that it was rather naïve to expect a simple increase in the ingestion of methionine to stimulate so basic a process as transmethylation. *A priori* it would seem strange that nature would have permitted a process so important in the biology of the organism to be sensitive to alterations in the nutritional intake of methionine.[1] Although the idea seemed somewhat far-fetched biochemically, it seemed at least worth while to test the effects of methionine along with a number of other amino acids which were precursors of centrally occurring amines. As I have indicated, the psychotic activation by methionine is certainly compatible with the hypothesis. The ability of betaine to do the same thing, which was demonstrated by Brune and Himwich (in *Recent Advances in Biological Psychiatry*, N.Y., Plenum Press, **5,** 144, 1963), is also compatible with the hypothesis and, as a matter of fact, as Smythies mentioned yesterday, restricts the number of alternative explanations. That methionine causes an increase in S-adenosylmethionine in the brain, as reported by Baldessarini (this Symp., p. 199),

[1] On the other hand, since methionine does not occur in nature unassociated with other amino acids in proteins, nature may not have been required to protect against overriding doses of simple methionine.

is most interesting as is his finding that monoamine oxidase inhibitors depress the concentrations of that methyl donor. On the basis of these findings, perhaps, our speculation that transmethylation could be facilitated by methionine loading may not have been naïve; at least the procedure seems capable of increasing the brain concentrations of the important methyl donor. Axelrod's finding (*Science*, **134,** 343, 1961) of what appears to be an enzyme present in mammalian tissue and capable of converting tryptamine to dimethyltryptamine, is also compatible with the transmethylation hypothesis but hardly constitutes very strong evidence since he found this in normal rabbit lung, which simply suggests that some mammalian tissues can, with a methyl donor, under certain conditions methylate a normal metabolite to a psychotomimetic compound.

Himwich's group (Berlet *et al.*, this Symp., p. 69) has reported increases in tryptamine excretion with exacerbations of schizophrenia and although this requires one or two more steps, it can certainly be made compatible with a transmethylation hypothesis in terms of providing more substrate for the formation of methylated indoles. Sprince (this Symp., p. 97) found increased tryptamine excretion in activated schizophrenics under the influence of methionine loads and he indicated why this finding was compatible with the transmethylation hypothesis. The presence of schizophrenia in the family of a homocystinuric patient (this Symp., p. 247) I find rather interesting. It could possibly be made compatible with the transmethylation hypothesis of schizophrenia, as Baldessarini valiantly attempted to do. This family could have shown many diseases—why did they have to pick on schizophrenia, if not simply to tantalize us?

Finally, we had the report by Friedhoff and Van Winkle (this Symp., p. 19) of the presence of 3,4-dimethyoxyphenylethylamine, the compound which Harley-Mason had indicated as being of special interest, with a much greater frequency in the urine of schizophrenics than in normals. This observation and Friedhoff's subsequent contributions to the problem have received careful scrutiny at this meeting. Although we do not know whether this particular compound is psychotomimetic in man, we have the interesting evidence of Noteboom, which one need not take very seriously, since what is catatonia in cats may be quite different from schizophrenia in man. But we have in addition the interesting predictions made independently by Smythies, Himwich and Snyder (this Symp., that this particular compound, whether by behavioral changes, physiologic effects, or structure, should have psychotomimetic activity. In any case, Friedhoff's observations have been confirmed by Kuehl (this Symp., p. 23) and very cogently by Bourdillon and Bridges (this Symp., p. 43), although Bourdillon was careful to point out that he has not clearly established his pink spot, which correlates so well with the probable incidence of schizophrenia in his various samples, as 3,4-dimethoxyphenylethylamine. Perry (this Symp., p. 31), on the other hand, has not found this substance in

either normal urine or that of schizophrenic patients on plant free diets. That evidence is not as cogent as it would have been had he found the compound equally in both types of urine and then shown it to disappear by dietary means.[1] If its excretion is more frequent in schizophrenics, finding that it depended on dietary factors would not indicate that it was unimportant. The excretion of phenylpyruvic acid in phenylketonuria requires the presence of phenylalanine in the diet.

Further research appears to be indicated. We need more blind studies with attention to diagnostic classification, like Bourdillon's, reinforced by rigorous control of diet, drugs and of every other non-disease variable which could conceivably have been operating. Such studies could help to establish whether or not the excretion of this compound was characteristic of certain forms of schizophrenia. We have heard the reasons which indicate that dimethoxyphenylacetic acid or other metabolites of DMPEA may be more significant or more readily identified. It would seem worth while to learn whether these or other methylated compounds are excreted to a greater extent by schizophrenics during methionine loading and whether this correlates with the mental changes. Interestingly enough, the transmethylation hypothesis is in a relatively unassailable position here. If the validity and relevance to schizophrenia of DMPEA should become clearly established, that would clearly support the transmethylation hypothesis. If DMPEA is eventually found to be a will-o'-the-wisp, that does not necessarily force rejection of the transmethylation hypothesis which can then go merrily on to another metabolite which could become methylated.

This conference has provided an opportunity to present and discuss much of the evidence relevant to that hypothesis and for each line of evidence many alternative interpretations can and must be formulated in addition to the one which we would like to believe. Yet, though each bit of supporting evidence has only a small chance of being valid and relevant, it would be rather surprising, to paraphrase Dr. Richter, if all of this were unrelated to the hypothesis of transmethylation in schizophrenia. That hypothesis has by no means been proven nor is it likely to be proven very easily. It remains, however, a remarkably parsimonious explanation of a mass of otherwise disparate information and, for that reason, appears to be worth entertaining and testing.

[1] Such a report has now appeared (Studnitz, W. von and Nyman, G. E., Excretion of 3,4-dimethoxyphenylethylamine in schizophrenia, *Acta psychiat. scand.*, in press). These workers found a substance which they identified as 3,4-dimethyoxyphenylethylamine in the urine of two out of three mentally healthy hospital patients and in four out of six schizophrenics, and demonstrated its disappearance from the urine when the same subjects were placed upon an exclusively carbohydrate diet. The numbers in both samples were not large enough, however, to constitute definitive evidence against the thesis that the compound appears more frequently in schizophrenics, although its disappearance from the urine in all of six individuals on a restricted diet strongly suggests that its presence requires some dietary factors.

But we have discussed other hypotheses at this conference which relate amines to human behavior. One of these is the possibility that amines may be important in mood. We may briefly summarize the evidence which has suggested it: the correlation between the depressant drug reserpine and its ability to diminish the amines in the brain, and the almost predictable property of any monoamine oxidase inhibitor which gets into the brain and retards the degradation of amines there to act as an antidepressant drug. Straughan (this Symp., p. 219) has thrown a little cold water on even this very general hypothesis in pointing out that by micro-injection of amines into various sites in the brain, the only effect which seems to be produced is inhibition. One would expect *a priori* to see some kind of stimulatory activity, although it is not impossible that selective inhibition could result in stimulation. In addition, microinjection may not constitute a crucial test, since such application into the brain substance may not exactly simulate the manner by which these substances are actually released and the site at which they act in the nervous system.

Other hypotheses were discussed which were more specifically related to the relative importance of indoleamines or catecholamines with respect to mental state. Richter (this Symp., p. 169) reviewed considerable evidence which suggested that indoleamines had something to do with mental state, mood, or depression: the tryptamine excretion studies by Brune, Himwich and Pscheidt, the low levels of 5-hydroxyindoleacetic acid in the cerebrospinal fluid of depressed patients, what appeared to be a decrease in 5-hydroxytryptophan decarboxylation in clinical depression which was reversed by treatment, and finally the ability of tryptophan in conjunction with lower doses of monoamine oxidase inhibitors to restore the mood of depressed patients; all of which evidence is clearly compatible with a hypothesis that one or another of the indoleamines plays an important role in the regulation of mood. There has not been as much opportunity to discuss the corresponding hypothesis for catecholamines, some of the evidence for which was presented by Schildkraut (this Symp., p. 213). This includes the antagonism of reserpine depression in animals by dopa which is remarkable and prompt, Everett's compelling correlation between brain dopamine level and the behavioral effects of either a monoamine oxidase or a dopa precursor. I should like to mention very briefly some new data which bear on the relationship between catecholamines in the brain and mood. First let me recall for you the findings of Kopin and Gordon (*J. Pharmacol.* **140,** 207, 1963), who labeled the norepinephrine stores in the sympathetic nerve endings of the isolated heart with tritiated norepinephrine and studied the effects of certain drugs and of sympathetic stimulation. When norepinephrine was released by nerve stimulation or by tyramine, both of which are associated with a sympathetic effect on the heart, there was an increase in O-methylated derivatives. When the norepinephrine was released by reserpine which has no sympatho-

mimetic effect, the O-methylated derivatives were unchanged and the deaminated derivatives were increased. On the basis of these findings it was reasonable to suggest as a tentative generalization that O-methylation of norepinephrine is associated with its release at functional sites while deamination occurs when it is released in a non-functional way. Now, it would be very interesting to know what was happening to norepinephrine in the brain under different circumstances, but until quite recently that was not possible. Recently, however, Jacques Glowinski, a young man who had developed a technique for injecting materials into the lateral ventricle of the rat brain, came to work with Axelrod and, with him, injected tritiated norepinephrine into the lateral ventricle. They found evidence that the radioactive substance was labeling rather faithfully the endogenous norepinephrine of the brain and by using such a preparation it was possible to study the metabolism of norepinephrine in the brain and to test the effects of various drugs (*J. Neurochem.* **12,** 25, 1965). It was found that reserpine causes an increase in deaminated products while, on the other hand, monoamine oxidase inhibitors, imipramine and amphetamine, were all associated with an increase of O-methylated products in the brain. If one is permitted to draw an analogy between what was found in the brain and what was known about the heart, one could suggest that the functionally active release of norepinephrine in the brain was a mechanism by which the antidepressant drugs acted while a diversion of normal norepinephrine through monoamine oxidase accounted for the depressant actions of reserpine.

Fortunately, as I have mentioned before, we are not forced to accept any one of these hypotheses at the present time. They are all sufficiently plausible and heuristic that it seems sensible to keep entertaining and evaluating them. I, for one, would be surprised if some increased understanding of schizophrenia, normal mood or abnormal affective states does not emerge from that process.