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Biochemical Theories of Schizophrenia

Part I of a two-part critical review of current theories and of the evidence used to support them.

Seymour S. Kety

The concept of a chemical etiology in schizophrenia is not new. The Hippocratic school attributed certain mental aberrations to changes in the composition of the blood and disturbances in the humors of the brain, but it was Thudichum (*1*), the founder of modern neurochemistry, who in 1884 expressed the concept most cogently: "Many forms of insanity are unquestionably the external manifestations of the effects upon the brain substance of poisons fermented within the body, just as mental aberrations accompanying chronic alcoholic intoxication are the accumulated effects of a relatively simple poison fermented out of the body. These poisons we shall, I have no doubt, be able to isolate after we know the normal chemistry to its uttermost detail. And then will come in their turn the crowning discoveries to which our efforts must ultimately be directed, namely, the discoveries of the antidotes to the poisons and to the fermenting causes and processes which produce them." In these few words were anticipated and encompassed most of the current chemical formulations regarding schizophrenia.

It may be of value to pause in the midst of the present era of psychochemical activity to ask how far we have advanced along the course plotted by Thudichum. Have we merely substituted "enzymes" for "ferments" and the names of specific agents for "poisons" without altering the completely theoretical nature of the concept? Or, on the other hand, are there some well-substantiated findings to support the prevalent belief that this old and stubborn disorder which has resisted all previous attempts to expose its etiology is about to yield its secrets to the biochemist?

An examination of the experience of another and older discipline may be of help in the design, interpretation, and evaluation of biochemical studies. The concepts of the pathology of schizophrenia have been well reviewed recently (*2*). As a result of findings of definite histological changes in the cerebral cortex of patients with schizophrenia which were described by Alzheimer at the beginning of the present century and confirmed by a number of others, an uncritical enthusiasm for the theory of a pathological lesion in this disease developed, and this enthusiasm penetrated the thinking of Kraepelin and Bleuler and persisted for 25 years. This was followed by a period of questioning which led to the design and execution of more critically controlled studies and, eventually, to the present consensus that a pathological lesion characteristic of schizophrenia or any of its subgroups remains to be demonstrated.

Earlier biochemical theories and findings related to schizophrenia have been reviewed by a number of authors, of whom McFarland and Goldstein (*3*), Keup (*4*), and Richter (*5*) may be mentioned (*6*). Horwitt and others (*7–9*) have pointed out some of the difficulties of crucial research in this area. It is the purpose of this review to describe the biochemical trends in schizophrenia research of the past few years, to discuss current theories, and to examine the evidence which has been used to support them.

Sources of Error

Because of the chronicity of the disease, the prolonged periods of institutionalization associated with its management, and the comparatively few objective criteria available for its diagnosis and the evaluation of its progress, schizophrenia presents to the investigator a large number of variables and sources of error which he must recognize and attempt to control before he may attribute to any of his findings a primary or characteristic significance.

Despite the phenomenological similarities which permitted the concept of schizophrenia as a fairly well defined symptom complex to emerge, there is little evidence that all of its forms have a common etiology or pathogenesis. The likelihood that one is dealing with a number of different disorders with a common symptomatology must be recognized and included in one's experimental design (*8, 10, 11*). Errors involved in sampling from heterogeneous populations may help to explain the high frequency with which findings of one group fail to be confirmed by those

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of another. Recognition that any sample of schizophrenics is probably a heterogeneous one would seem to indicate the importance of analyzing data not only for mean values but also for significant deviations of individual values from group values. The biochemical characteristics of phenylketonuria would hardly have been detected in an average value for phenylalanine levels in blood in a large group of mentally retarded patients.

Most biochemical research in schizophrenia has been carried out in patients with a long history of hospitalization in institutions where overcrowding is difficult to avoid and where hygienic standards cannot always be maintained. It is easy to imagine how chronic infections, especially of the digestive tract, might spread among such patients. The presence of amebiasis in a majority of the patients at one large institution has been reported (*12*), and one wonders how often this condition or a former infectious hepatitis has caused the various disturbances in hepatic function found in schizophrenia. Even in the absence of previous or current infection, the development of a characteristic pattern of intestinal flora in a population of schizophrenic patients living together for long periods and fed from the same kitchen is a possibility which cannot be dismissed in interpreting what appear to be deviant metabolic pathways.

In variety and quality the diet of the institutionalized schizophrenic is rarely comparable to that of the nonhospitalized normal control. Whatever homeostatic function the process of free dietary selection may serve is often lost between the rigors of the kitchen or the budget and the overriding emotional or obsessive features of the disease. In the case of the "acute" schizophrenic, the weeks and months of emotional turmoil which precede recognition and diagnosis of the disease are hardly conducive to a normal dietary intake. Kelsey, Gullock, and Kelsey (*13*) confirmed findings of certain abnormalities in thyroid function previously reported in schizophrenia and showed that in their patients these abnormalities resulted from a dietary deficiency of iodine, correctable by the introduction of iodized salt into the hospital diet. It is not surprising that a dietary vitamin deficiency has been found to explain at least two of the biochemical abnormalities recently attributed to schizophrenia (*9, 14–16*). It is more surprising that the vitamins and other dietary constituents, whose role in metabolism has become so clearly established, should so often be relegated to a position of unimportance in consideration of the intermediary metabolism of schizophrenics. Horwitt (*17*) has found signs of liver dysfunction during ingestion of a diet containing borderline levels of protein, while nonspecific vitamin therapy accompanied by a high protein and carbohydrate diet has been reported to reverse the impairment of hepatic function in schizophrenic patients (*18*).

Another incidental factor which sets the schizophrenic apart from the normal control is the long list of therapies to which he may have been exposed. Hypnotic and ataractic drugs and their metabolic products or effects produce changes which have sometimes been attributed to the disease. Less obvious is the possibility of residual electrophysiological or biochemical changes resulting from repeated electroshock or insulin coma.

Emotional stress is known to cause profound changes in man—in adrenocortical and thyroid function (*19*), in the excretion of epinephrine and norepinephrine (*20*), and in the excretion of water, electrolytes, or creatinine (*21*), to mention only a few recently reported findings. Schizophrenic illness is often characterized by marked emotional disturbance even in what is called the basal state and by frequently exaggerated anxiety in response to routine and research procedures. The disturbances in behavior and activity which mark the schizophrenic process would also be expected to cause deviations from the normal in many biochemical and metabolic measures—in volume and concentration of urine, in energy and nitrogen metabolism, in the size and function of numerous organic systems. The physiological and biochemical changes which are secondary to the psychological and behavioral state of the patient are of interest in themselves, and understanding of them contributes to total understanding of the schizophrenic process; it is important, however, not to attribute to them a primary or etiological role.

An additional source of error which must be recognized is one which is common to all of science and which it is the very purpose of scientific method, tradition, and training to minimize—the subjective bias. There are reasons why this bias should operate to a greater extent in this field than in many others. Not only is the motivation heightened by the tragedy of this problem and the social implications of findings which may contribute to its solution, but the measurements themselves, especially of the changes in mental state or behavior, are so highly subjective, and the symptoms are so variable and so responsive to nonspecific factors in the milieu, that only the most scrupulous attention to controlled design will permit the conclusion that a drug, or a diet, or a protein fraction of the blood, or an extract of the brain is capable of causing or ameliorating some of the manifestations of the disease. This is not to suggest that the results of purely chemical determinations are immune to subjective bias; the same vigilance is required there to prevent the hypothesis from contaminating the data. In a field with as many variables as this one, it is difficult to avoid the subconscious tendency to reject for good reason data which weaken a hypothesis while uncritically accepting those data which strengthen it. Carefully controlled and "double blind" experimental designs which are becoming more widely utilized in this area can help to minimize this bias.

Obvious as many of these sources of error are, it is expensive and difficult, if not impossible, to prevent some of them from affecting results obtained in this field, especially in the preliminary testing of interesting hypotheses. It is in the interpretation of these results, however, and in the formulating of conclusions, that the investigator has the opportunity, and indeed the responsibility, to recognize and evaluate his uncontrolled variables rather than to ignore them, for no one knows better than the investigator himself the possible sources of error in his particular experiment. There are enough unknowns in our guessing game with nature to make it unnecessary for us to indulge in such a sport with one another.

Schizophrenia Program of the Laboratory of Clinical Science

Since 1956, the Laboratory of Clinical Science of the National Institute of Mental Health has been developing and pursuing a program of biological research in schizophrenia designed to minimize many of the sources of error discussed above while increasing the opportunity to detect, and to correlate with psychiatric and behavioral information, true biological characteristics if they exist. One of the wards houses a group of approximately 14 clearly diagnosed schizophrenic patients, representative of as many clinical subgroups as

possible, chosen from a patient population of 14,000. In selecting these patients an attempt was made to minimize the variables of age, sex, race, and physical illness and, on the basis of careful family surveys, to maximize the likelihood of including within the group individuals representative of whatever genetic subgroups of the disease may exist (*10*). These patients are maintained for an indefinite period of time on a good diet, receiving excellent hygienic, nursing, medical, and psychiatric care. Each patient receives a careful and sophisticated psychiatric and genealogical characterization, and detailed daily records are kept on his psychiatric and behavioral status; these, it is hoped, will be of value in a more complete interpretation of biological findings. No specific therapy is employed or even found to be necessary, and drugs or dietary changes are introduced only for research purposes and for short periods of time. The other ward houses a comparable number of normal controls, who volunteer to remain for protracted periods of time on the same diet and in a reasonably similar milieu. We recognize, of course, that only a few of the variables are thus controlled and that any positive difference which emerges in this preliminary experiment between some or all of the schizophrenics and the normal population will have to be subjected to much more rigorous examination before its significance can be evaluated. Such reexamination has rarely been necessary, since our schizophrenic patients, individually or as a group, have shown little abnormality in the biological studies which have thus far been completed (*9, 14, 22–24*).

Oxygen, Carbohydrate, and Energetics

A decrease in basal metabolism was found in schizophrenia by earlier workers, although more recent work has not confirmed this (*5*), and theories attributing the disease to disturbances in the fundamental mechanisms of energy supply or conversion in the brain have enjoyed some popularity, but on the basis of extremely inadequate evidence, such as spectroscopic oximetry of the ear lobe or nail bed (*25*). Our finding of a normal rate of cerebral circulation and oxygen consumption in schizophrenic patients (*26*) was confirmed by Wilson, Schieve, and Scheinberg (*27*) and, more recently, in our laboratory by Sokoloff and his associates (*28*), who also found a normal rate of cerebral glucose consumption in this condition. These studies make it appear unlikely that the moderate decrease in these functions reported by Gordan and his associates (*29*), but only in patients with long-standing disease, is fundamental to the disease process. These studies do not, of course, rule out a highly localized change in energy metabolism somewhere in the brain, but cogent evidence for such a hypothesis has yet to be presented.

Richter (*5*) has pointed out the uncontrolled factors in earlier work which indicated that a defect in carbohydrate metabolism was characteristic of the schizophrenic disease process. The finding in schizophrenia of an abnormal glucose tolerance in conjunction with considerable other evidence of hepatic dysfunction (*30*), or evidence of an abnormally slow metabolism of lactate in the schizophrenic (*31*), do not completely exclude incidental hepatic disease or nutritional deficiencies as possible sources of error. Horwitt and his associates (*32*) were able to demonstrate and correct similar abnormalities by altering the dietary intake of the B group of vitamins.

Evidence for greater than normal anti-insulin or hyperglycemic activity in the blood or urine of a significant segment of schizophrenic patients was reported in 1942 by Meduna, Gerty, and Urse (*33*) and as recently as 1958 by Moya and his associates (*34*). Some progress has been made in concentrating or characterizing such factors in normal (*35*) urine as well as in urine from schizophrenics (*36*). Harris (*37*) has thrown some doubt on the importance of such anti-insulin mechanisms in the pathogenesis of schizophrenia, and it is hoped that further investigation may clarify the nature of the substance or substances involved and their relevance to schizophrenia.

Defects in oxidative phosphorylation have been thought to occur in this disease. Reports of alterations in the phosphorus metabolism of the erythrocyte (*38*) await further definition and independent confirmation.

Two recent reports of a more normal pattern of carbohydrate metabolism and of clinical improvement following the infusion of glutathione (*39*) in psychotic patients, some of whom were schizophrenic, are perhaps of interest. There is little verifiable evidence for a reduction in the blood glutathione index in schizophrenia (*9*); one group which has repeatedly postulated this reduction has done so on the basis of decreasingly convincing data (*16, 40*), while our laboratory has failed to find it at all (*14*), and a very recent report publishes identical figures for the schizophrenic and normal groups (*41*). Clinical and biochemical improvement in a variety of psychoses following glutathione infusion, even if it is accepted without the necessary controls, suggests at best that glutathione is of secondary and nonspecific import.

It is difficult for some to believe that a generalized defect in energy metabolism—a process so fundamental to every cell in the body—could be responsible for the highly specialized features of schizophrenia. On the other hand, a moderate lack of oxygen, an essential requirement of practically every tissue, produces highly selective manifestations involving especially the higher mental functions and as suggestive of schizophrenia as manifestations produced by many of the more popular hallucinogens. It may not, therefore, be completely appropriate that, in a search for biochemical factors etiologically related to schizophrenic psychoses, the center of interest today appears to have shifted to other, more specialized aspects of metabolism.

Amino Acids and Amines

The well-controlled studies of the Gjessings (*42*) on nitrogen metabolism in periodic catatonia arouse considerable interest in that they suggest the possibility of a relationship between intermediary protein metabolism and schizophrenia, although earlier workers had postulated defects in amino acid metabolism in this disease (*43*). The hallucinogenic properties of some compounds related directly or indirectly to biological amines reawakened this interest, and the techniques of paper chromatography offered new and almost unlimited opportunity for studying the subject.

The first group to report chromatographic studies of the urine of schizophrenic and control groups found certain differences in the amino acid pattern and, in addition, the presence of certain unidentified imidazoles in the urine of schizophrenics (*44*). Although a normal group of comparable age was used for comparison, there is no indication of the extent to which dietary and other variables were controlled, and the authors were properly cautious in their conclusions. In a more extensive series of studies, another group has re-

ported a significantly higher than normal concentration of aromatic compounds in the urine of schizophrenic patients (*45*) and has suggested that there are certain qualitative differences in the excretion of such compounds (*46*). Others have reported the abnormal presence of unidentified amines (*47*) or indoles (*48*), and one group has reported the absence of a normally occurring indole (*49*) in the urine of schizophrenic patients. In some of these studies there appears to have been no control relative to possible drug therapy or to volume or concentration of urine, and in few of them was there control of diet. There are numerous mechanisms whereby vitamin deficiencies may cause substantial changes in the complex patterns of the intermediary metabolism of amino acids. In addition, the fact that a large number of aromatic compounds in the urine have recently been shown to be of dietary origin (*50*) suggests the need for considerably more caution than has usually been employed in drawing conclusions with regard to this variable. Another point which has not been emphasized sufficiently is that chromatographic procedures which make possible the simultaneous determination of scores of substances, many of them unknown, require statistical analyses somewhat different from those which were developed for the testing of single, well-defined hypotheses. It is merely a restatement of statistical theory to point out that in a determination of 100 different compounds carried out simultaneously in two samples of the *same* population, five would be expected to show a difference significant at the 0.05 level! It is interesting to note that a more recent study was able to demonstrate considerably fewer differences between the urines of normal and schizophrenic populations and drew very limited and guarded conclusions (*51*). In our own laboratory, Mann and LaBrosse (*24*) undertook a search for urinary phenolic acids, in terms of quantity excreted in a standard time interval rather than in terms of concentration, which disclosed significantly higher levels of four compounds in the urine of schizophrenics than in that of the normal test subjects. These compounds were found to be known metabolites of substances in coffee, and their presence in the urine was, in fact, better correlated with the ingestion of this beverage than with schizophrenia.

The hypothesis that a disordered amino acid metabolism is a fundamental component of some forms of schizophrenia remains an attractive though fairly general one, chromatography as a means of searching for supporting evidence is convenient and valuable, and preliminary indications of differences are certainly provocative. Proof that any of these differences are characteristic of even a segment of the disease rather than artifactual or incidental has not yet been obtained.

The Epinephrine Hypothesis

The theory which relates the pathogenesis of schizophrenia to faulty metabolism of epinephrine (*52–54*) is imaginative, ingenious, and plausible. It postulates that the symptoms of this disease are caused by the action of abnormal, hallucinogenic derivatives of epinephrine, presumably adrenochrome or adrenolutin. By including the concept of an enzymatic, possibly genetic, defect with another factor, epinephrine release, which may be activated by stressful life situations (*22*), it encompasses the evidence for sociological as well as constitutional factors in the etiology of the schizophrenias.

The possibility that some of the oxidation products of epinephrine are psychotomimetic received support from anecdotal reports of psychological disturbances associated with the therapeutic use of the compound, especially when it was discolored (*52*), and from some early experiments in which the administration of adrenochrome or adrenolutin in appreciable dosage was followed by certain unusual mental manifestations (*54*). A number of investigators failed to demonstrate any hallucinogenic properties in adrenochrome (*55*), and the original authors were not always able to confirm their earlier results.

Meanwhile, reports were emerging from the group at Tulane University, suggesting a gross disturbance in epinephrine metabolism in schizophrenic patients. Five years previously, Holmberg and Laurell (*56*) had demonstrated a more rapid oxidation of epinephrine in vitro in the presence of pregnancy serum than with serum from the umbilical cord and had suggested that this was due to higher concentrations of ceruloplasmin in the former. There had also been a few reports of an increase in levels of this protein in the blood of schizophrenics. Leach and Heath (*57*) reported a striking acceleration in the in vitro oxidation of epinephrine in the presence of plasma from schizophrenic patients as compared with that from normal subjects and shortly thereafter implicated ceruloplasmin or some variant of ceruloplasmin as the oxidizing substance (*58*). Hoffer and Kenyon (*59*) promptly reported evidence that the substance formed from epinephrine by blood serum in vitro was adrenolutin and pointed out how this strengthened the epinephrine hypothesis.

All of the evidence does not, however, support the epinephrine theory. In the past few years the major metabolites of epinephrine have been identified: 3-methoxy-4-hydroxymandelic acid, by Armstrong and his associates (*60*), and its precursor, metanephrine, by Axelrod and his coworkers of this laboratory (*61*), where, in addition, the principal pathways of epinephrine metabolism in animals (*62*) and man (*63*) have been demonstrated. The metabolites of C^{14}-labeled epinephrine in the urine of schizophrenic patients (*64*) and in normal man (*65*) have been studied independently by others. No evidence has been found for the oxidation of epinephrine via adrenochrome and adrenolutin in any of these populations. Although it has been reported that there are appreciable amounts of adrenochrome in the blood of normal subjects and that these amounts increase considerably following administration of lysergic acid diethylamide (*66*), Szara, Axelrod, and Perlin, using techniques of high sensitivity, have been unable to detect adrenochrome in the blood of normal test subjects or in that of acute or chronic schizophrenic patients (*22*). In a recent ingenious study of the rate of destruction of epinephrine in vivo, no difference between normal subjects and schizophrenic patients was found in this regard (*67*). Finally, it has been shown, by McDonald (*9*) in our laboratory and by members of the Tulane group themselves (*16*), that the low level of ascorbic acid in the blood is an important and uncontrolled variable in the rapid in vitro oxidation of epinephrine by plasma from schizophrenic patients. The fact that McDonald has been able to produce wide fluctuations in the epinephrine oxidation phenomenon, from normal to highly abnormal rates, in both normal subjects and schizophrenics merely by altering the level of ascorbic acid in the blood by dietary means, and that this has had no effect on the mental processes of either group, is quite convincing evidence of the dietary and secondary nature of the phenomenon.

It should be pointed out that none of this negative evidence invalidates the

theory that some abnormal product of epinephrine metabolism, existing somewhere in the body, produces the major symptoms of schizophrenia; it does, however, considerably weaken the evidence which has been used to support the theory. In addition, there is the bothersome observation of numerous workers (*68*) that the administration of epinephrine to schizophrenics, which, according to the theory, should aggravate the psychotic symptoms, is not accompanied by appreciably greater mental disturbance than occurs in normal subjects.

Quite recently a new report on inconstant psychotomimetic effects of epinephrine oxidation products in a small number of subjects has appeared (*69*), with evidence suggesting that the psychotoxic substance is neither adrenochrome nor adrenolutin, that it is active in microgram quantities, and that it is highly labile. This report, like the previous ones which described the psychotomimetic effects of epinephrine products, is highly subjective and incompletely controlled. Even if these conclusions are accepted, the relevance of such hallucinogens to, or their presence in, schizophrenia remains to be demonstrated.

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