Philadelphia, Detroit, Boston, San Francisco-Oakland, Pittsburgh, St. Louis, Cleveland, Washington, Baltimore, Minneapolis-St. Paul, and Buffalo, plus 15 million persons more.

For me, these are sobering if not staggering figures. When against this backdrop one reviews the problem, implications that I have tried to outline as well as others, both economic and noneconomic in character, that might be added, and considers how ill prepared we in this predominantly urban nation are to deal with them intelligently and in time, he may be pardoned if he concludes that this country has a few things to worry about besides the Sputniks. The metropolitan outlook is grave, in my opinion, not because its problems are impregnable, but because our poor preparation for dealing with them is found on so many fronts—in basic understanding of the problems themselves, in governmental and private institutional means for deciding on policies and pressing forward with them, and in public appreciation of the scale and seriousness of the issues.

In the lifetimes of most of us, not only the face but also the physique of urban America is going to be changed —radically changed. In my opinion we simply cannot afford to muddle along as we are now doing—building a parking garage here or there, transferring a bankrupt transit company to public ownership, tearing down a few blocks of old houses, hiring another junior planner or two when we can find them, nursing our petty, parochial prejudices, whether in central city or suburb, trying to decide if we should not raise the dog license fee a dollar to keep our local government out of the clutches of that evil foreign octopus that is headquartered in Washington, and tentatively suggesting that maybe it is about time to begin to think about setting up a metropolitan planning body or a special authority responsible for *both* water supply *and* sewage disposal. If we continue in this vein, well before 1975 we will have lost one of the finest opportunities any generation of Americans ever had: the opportunity to make our rapidly growing urban localities into things of economy, beauty, and livability, appropriate settings for metropolitan communities that we and our children can live in and take part in with pride.

References and Notes

1. "Civilian population of the United States, by type of residence, March 1956 and April 1950," *U.S. Bur. Census, Ser. P-20, No. 71 (1956)*. This report is the source of other figures cited in this article.
2. V. Jones, "Economic classification of cities and metropolitan areas," in *Municipal Year Book* (International City Managers' Assoc., Chicago, 1953), pp. 49–57.
3. *Housing in the United States* (U.S. Housing and Home Finance Agency, 1956), pp. 54, 75. The study here reported was made by the Bureau of Labor Statistics.
4. "Family income in the United States: 1955," *U.S. Bur. Census, Ser. P-60, No. 24 (1957)*, p. 21.
5. *Housing in the Economy, 1955* (U.S. Housing and Home Finance Agency, 1956), p. 18.
6. *Housing Statistics* (U.S. Housing and Home Finance Agency, Oct. 1957), pp. 5, 21.
7. "Projections of the number of households and families: 1960 to 1975," *U.S. Bur. Census, Ser. P-20, No. 69 (1956)*, p. 1.
8. "Statistical abstract of the United States, 1957," *U.S. Bur. Census,* Table No. 486, p. 406, and "Summary of governmental finances in 1956," *U.S. Bur. Census,* Table No. 17, p. 33.
9. "Statistical abstract of the United States, 1957," *U.S. Bur. Census,* Table No. 562, p. 466.
10. "Illustrative projections of the popluation of the United States, by age and sex: 1960 to 1980," *U.S. Bur. Census, Ser. P-25, No. 187 (1958)*, p. 2.

Biochemical Theories of Schizophrenia

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

Seymour S. Kety

In part I of this article [*Science,* **129,** 1528 (1959)], an attempt was made to discuss the possible sources of error peculiar to biological research in schizophrenia, including the possible heterogeneity of that symptom complex and the presence of certain biological features—such as adventitious disease, nutritional deficiencies, disturbances associated with abnormal motor or emotional states, and changes brought about by treatment, all of which may be said to result from the disease or from its current management rather than to be factors in its genesis. The difficulty of avoiding subjective bias was emphasized. Some of the hypotheses relating to oxygen, carbohydrate, and energy metabolism, to amino acid metabolism, and to epinephrine were presented, and the existing evidence relevant to them was discussed. Among the recent or current concepts there remain to be discussed those concerned with ceruloplasmin, with serotonin, and with the general genetic aspects of schizophrenic disorders.

Ceruloplasmin and Taraxein

The rise and fall of interest in ceruloplasmin as a biochemical factor significantly related to schizophrenia is one of the briefest, if not one of the most enlightening, chapters in the history of biological psychiatry. The upsurge of interest can be ascribed to a report that a young Swedish biochemist had discovered a new test for schizophrenia. The test depended upon the oxidation of N,N-dimethyl-*p*-phenylenediamine by ceruloplasmin (*1, 2*). It is difficult to understand the exaggerated interest which this report aroused, since Holmberg and Laurell (*3*) had demonstrated previously that ceruloplasmin was capable of oxidizing a number of substances, including phenylenediamine and epinephrine, and Leach and Heath (*4*) had already published a procedure based on epinephrine oxidation which was equally valid as a means of distinguishing schizophrenics from normal subjects and had identified the oxidizing substance as

The author is chief of the Laboratory of Clinical Science, National Institute of Mental Health, National Institutes of Health, Bethesda, Md.

This article is based on the Eastman Memorial Lecture, delivered at the University of Rochester, December 1957, and on a paper presented at the Third International Neurochemical Symposium, Strasbourg, August 1958.

ceruloplasmin (*5*). All of these observations were compatible with earlier reports in the German literature (*6*) of an increase in serum copper in schizophrenia and with the demonstration that practically all of the serum copper was in the form of ceruloplasmin and that the levels of this compound in blood were elevated during pregnancy and in a large number of diseases (*7, 8*). There had even been preliminary observations of an increase in blood ceruloplasmin in schizophrenia (*8*). Following the announcement of the Akerfeldt test, however, interest in copper and ceruloplasmin rose, and very soon a number of investigators reported this reaction, or some modification of it, to be positive in a high percentage of schizophrenics (*2, 9*), although as a diagnostic test the Akerfeldt procedure was discredited because of the large number of diseases, besides schizophrenia, in which the results were positive. Both Akerfeldt and Heath recognized that ascorbic acid could inhibit the oxidation of phenylenediamine and of epinephrine, respectively, but neither felt that this was crucial to his findings, since each had satisfied himself that the feeding of large doses of ascorbic acid to the patients had not influenced the respective reactions (*2*). In addition, Abood (*9*), who used a modification of the Akerfeldt procedure which was not affected by ascorbic acid, was able to obtain a positive reaction indicating abnormally high ceruloplasmin levels in two-thirds of the more than 250 schizophrenics he had examined.

In the past 18 months there has been a remarkable decline in the interest in, and the reported levels of, ceruloplasmin in schizophrenia. In May of 1957, McDonald (*10*) reported his findings on three groups of schizophrenics, one group from the wards of the National Institute of Mental Health, where the patients had been maintained on a more than adequate diet, and two groups from state hospitals. He performed the Akerfeldt test and the Abood modification of it, as well as independent tests to measure ascorbic acid and copper, on these groups and on three groups of controls. In none of the schizophrenic groups was there an increase in serum copper or other evidence of increase in ceruloplasmin. In the state-hospital patients and one group of controls, however, ascorbic acid levels were low and the results of Akerfeldt tests were positive, whereas in schizophrenic patients from the National Institute of Mental Health, levels of ascorbic acid were normal and the results of Akerfeldt tests were negative. It was clear that a high ceruloplasmin level was not characteristic of schizophrenia and that a positive response to the Akerfeldt test, where it occurred, could be completely explained by a dietary insufficiency of ascorbic acid.

In findings of the Tulane group, the mean values for serum copper in schizophrenia have decreased from a high of 216 micrograms per 100 milliliters in 1956 (*5*) to 145 micrograms per 100 milliliters at the end of 1957 (*4*), mean normal values having remained at 122 and 124 micrograms per 100 milliliters during the same period. Other groups have found slight differences or no differences at all with respect to blood levels of ceruloplasmin or copper between schizophrenic and normal subjects (*11*) and no support for the theory that the Akerfeldt test is a means of distinguishing between schizophrenic and nonschizophrenic patients (*12*). It is not clear why some schizophrenics apparently show an elevated level of ceruloplasmin in the blood; among suggested explanations are dietary factors, hepatic damage, chronic infection, or the possibility that excitement tends to raise the level of ceruloplasmin in the blood, as preliminary experiments appear to indicate (*13*).

Quite early in their studies, members of the Tulane group recognized that the potent oxidant effects of the serum of schizophrenics on epinephrine in vitro could not be satisfactorily explained by the ceruloplasmin levels alone (*5*). Before they recognized the importance to this reaction of ascorbic acid deficiency (*14*), they had postulated the presence in the blood of schizophrenics of a qualitatively different form of ceruloplasmin (*5*), which they proceeded to isolate and to test in monkey and man, and to which they have given the name *taraxein* (from the Greek root *tarassein,* meaning "to disturb"). They have reported that when certain batches of this material were tested in monkeys, marked behavioral and electroencephalographic changes occurred. When samples of these active batches were injected intravenously at a rapid rate into carefully selected prisoner volunteers, all of the subjects developed symptoms which have been described as characteristic of schizophrenia—disorganization and fragmentation of thought, autism, feelings of depersonalization, paranoid ideas, auditory hallucinations, and catatonic behavior (*15–17*).

Demonstration of toxic materials in the blood and in the body fluids of schizophrenic patients is not new. The voluminous and inconclusive work of earlier investigators was well reviewed by Keup in 1954 (*6*). Since that time, many new reports have appeared, although there has been no extensive substantiation of any of them. The results of one, on the toxicity of serum and urine of schizophrenic patients for the larvae of *Xenopus laevis* (*18*), were disputed by the laboratory in which the work was done (*19*). Edisen (*20*) was unable to demonstrate toxicity of such serum for the species of tadpole previously used, or for other species and other genera. A report that serum from schizophrenic patients is toxic to cells in tissue culture (*21*) lost some of its significance when 1 year later the same laboratory reported that the sera of surgical patients (*22*) was of comparable toxicity. Reports that injection of certain extracts of the urine of schizophrenic patients induces electroencephalographic and behavioral changes in rats (*23*) or disturbances in web construction in spiders (*24*) have not yet received confirmation in the scientific literature. Such urine, however, has been reported to have no effect on the Siamese fighting fish, which is remarkably sensitive to certain hallucinogens (*25*). Contrary to earlier findings, a recent attempt to demonstrate behavioral changes in rats following the injection of cerebrospinal fluid from catatonic patients was unsuccessful (*26*). A highly significant decrease in rope-climbing speed in rats injected with sera from psychotic patients as opposed to sera from nonpsychotic controls has been reported by Winter and Flataker (*27*). Their later finding (*28*) that the phenomenon occurs with sera of patients with a wide variety of mental disorders, including mental retardation and alcoholism, and that there is a considerable variation in this index between similar groups at different hospitals, coupled with the inability of at least one other investigator (*29*) to demonstrate this phenomenon in the small group of schizophrenic patients under investigation in this laboratory, suggests that the quite real and statistically significant phenomenon originally observed may be related to variables other than those specific for, or fundamental to, schizophrenia. More recently, Ghent and Freedman (*29*) have reported their inability to confirm the observations of Winter and Flataker.

It has been reported that rabbits pretreated with serum from schizophrenics

do not exhibit a pressor response following the local application of an epinephrine solution to the cerebral cortex (*30*). No difference between the action of sera from normal subjects and that from schizophrenics was demonstrated by means of this procedure in tests of sera from a small number of individuals on our wards.

The significance of all of these studies in animals, whether the studies are successful or unsuccessful in demonstrating a toxic factor in schizophrenia, is quite irrelevant to, and considerably dwarfed by, the implications of the taraxein studies. It is because of the tremendous implications which these results could have in the etiology and rational therapy of this important disorder that a reviewer must evaluate them with even more than the usual care.

In the first place, the important biochemical phenomena originally reported in schizophrenia—lowered blood levels of glutathione and rapid oxidation of epinephrine in vitro—which prompted the search for taraxein and directed work on its isolation toward the ceruloplasmin fraction of serum (*15, 16, 17*), have since been controverted by data reported by the same group, as well as by others and have been regarded by most workers as spurious or at least unrelated in any direct way to the schizophrenic process (*14, 31*). This, in itself, does not preclude the possible validity of the taraxein phenomenon, since bona fide discoveries have occasionally been made on the basis of erroneous leads; it does, however, reduce the probability of its occurrence from that involved in a logical interrelationship of sequential proven steps to the extremely small chance of selecting this particular and heretofore unknown substance from the thousands of substances which occur in blood and which might have been chosen.

One attempt by Robins, Smith, and Lowe (*32*) to confirm the Tulane findings, in tests in which they used comparable numbers and types of subjects and at least equally rigorous controls, was quite unsuccessful. In 20 subjects who at different times received saline or extracts of blood from normal or schizophrenic donors, prepared according to the method for preparing taraxein, there were only five instances of mental or behavioral disturbance resembling those cited in the original report on taraxein, and these occurred with equal frequency following the administration of saline, extracts of normal plasma, or taraxein. It is easy to dismiss the negative findings with taraxein on the basis of the difficulty of reproducing exactly the 29 steps described in its preparation; it is considerably more difficult to dismiss the observation that a few subjects who received only saline or normal blood extract developed psychotic manifestations similar to those reported with taraxein.

During the preliminary investigations it was stated, on the basis of unpublished studies (*5*), that taraxein was qualitatively different from ceruloplasmin. A physicochemical or other objective characterization of taraxein would do much to dispel some of the confusion regarding its nature. Is it possible, for example, that taraxein is, in fact, ceruloplasmin but ceruloplasmin that derives its special properties from the psychosocial characteristics of the situation in which it has been tested? This question was raised more than a year ago (*33*), and since then additional evidence has become available which tends to support it. This is a detailed report from a psychoanalyst at Tulane of the experience of one of his patients who received taraxein (*34*). Even though a "double blind" procedure was said to have been used, there are enough possibilities for the operation of unconscious bias in this one case, if it is at all typical of the means used to demonstrate the psychotomimetic properties of taraxein, to raise some doubts concerning the validity of these properties. The subject, a psychiatric resident, knew before the injection that he was to get either saline or a potent sample of taraxein which had made a monkey catatonic for several hours. Immediately following the injection he noted venous distension, tachycardia, a swollen feeling of the head, and flushing of the head and face, which, a footnote explains, was probably a reaction to the ammonium sulfate in the taraxein solution. Following these symptoms, which the subject could hardly have attributed to saline, there ensued a period of introspective cogitation, with occasional mild mental disturbances quite compatible with the anxiety-producing nature of the situation, with the preparation and cues which the subject had received, and with his anticipation of marked psychotic reactions and not necessarily symptomatic of a chemical toxin at all. The changes were not qualitatively dissimilar to those which Robins and his associates had on a few occasions obtained with their control solutions (*32*). The report of the observer who injected the material was longer and mentioned more numerous and more bizarre subjective feelings than the subject himself reported. The observer's summary of the subject's reactions as blocking of thought processes, autism, bodily estrangement, and suspiciousness seems incompletely supported by the subject's retrospective report.

The possibility, remote as it may be, that the reported effects of taraxein are the result of a combination of suggestion, nonspecific toxic reactions from ammonium sulfate or other contaminants, and reinforcement of these cues by the unconscious biases of subject and observer through the device of an unstructured interview, is one which has not been ruled out. Hypotheses related to the mechanism of action of this material have moved from concern with abnormalities in the blood to concern with abnormalities in the blood-brain barrier; but the question of whether taraxein acts as a biological cause or as a mediator of some of the symptoms of schizophrenia is by no means resolved. I have already mentioned the only attempt of which I am aware on the part of an independent group to confirm the original results in a controlled series of significant size, and that attempt was unsuccessful.

Serotonin

Serotonin, an important derivative of tryptophan, was first shown to exist in the brain in high concentration by Amin, Crawford, and Gaddum (*35*). Interest in its possible function in the central nervous system and speculation that it might even be related to schizophrenia were inspired by the finding that certain hallucinogens, notably lysergic acid diethylamide, could, in extremely low concentration, block the effects of serotonin on smooth muscle. Thus, Woolley and Shaw in 1954 (*36*) wrote: "The demonstrated ability of such agents to antagonize the action of serotonin in smooth muscle and the finding of serotonin in the brain suggest that the mental changes caused by the drugs are the result of a serotonin-deficiency which they induce in the brain. If this be true, then the naturally occurring mental disorders—for example, schizophrenia—which are mimicked by these drugs, may be pictured as being the result of a cerebral serotonin deficiency arising from a metabolic failure. . . ." Simultaneously, in England, Gaddum (*37*) was speculating, "it is possible that the HT in our brains plays an essential part in keeping

us sane and that the effect of LSD is due to its inhibitory action on the HT in the brain." Since that time additional evidence has appeared to strengthen these hypotheses.

Levels of serotonin have been found to be considerably higher in the limbic system and other areas of the brain which appear to be associated with emotional states (*38*) than elsewhere. Bufotenin, or dimethyl serotonin, extracted from a hallucinogenic snuff of West Indian tribes, was found to have some properties similar to those of lysergic acid diethylamide (*39*). A major discovery was the finding that the ataractic agent, reserpine, causes a profound and persistent fall in the level of serotonin in the brain (*40*), a process which more closely parallels the mental effects of reserpine than does its own concentration in the brain. By administration of the precursor, 5-hydroxytryptophan, the levels of serotonin can be markedly elevated in the brain, with behavioral effects described as resembling those of lysergic acid diethylamide (*41*)—a finding quite at odds with the original hypotheses. On the other hand, administration of this precursor to mental patients, along with a benzyl analog of serotonin to block the peripheral effects of the amine, has been reported, in preliminary trials, to suppress the disease (*42*), while confusion is compounded by the report that the benzyl analog alone is an effective tranquilizing drug in chronically psychotic patients (*43*).

Still another bit of evidence supporting the hypotheses of a central function for serotonin was the accidental discovery of toxic psychoses in a certain fraction of tuberculous patients treated with iproniazid (*44, 45*), which has led to the therapeutic use of this drug in psychic depression. It is known that iproniazid inhibits the action of monoamine oxidase, an enzyme which destroys serotonin, and it has been shown that iproniazid increases the levels of this amine in the brain (*41*).

There are certain inconsistencies in the data cited above to support the serotonin hypotheses, and no single theory has been found to explain all of the findings, even though full use is made of the concept of "free" and "bound" forms and of the common pharmacological principle of stimulant and depressant effects from the same drug under different circumstances. Moreover, certain weaknesses have appeared in each of the main supporting hypotheses, and these should be noted.

Although the ability of the hallucinogen lysergic acid diethylamide to block effects of serotonin on smooth muscle prompted the development of the hypotheses relating serotonin to mental function or disease, a number of lysergic acid derivatives have since been studied, and the correlation between mental effects and antiserotonin activity in the series as a whole is quite poor (*46*). One of these compounds is 2-bromo-lysergic acid diethylamide; this has 1.5 times the antiserotonin activity of lysergic acid diethylamide, and through this property, its presence in the brain, after systemic administration, can be demonstrated, but in doses more than 15 times as great it produces none of the mental effects of lysergic acid diethylamide (*46*). A recent report that, at least in one preparation, lysergic acid diethylamide in low concentration behaves like serotonin and does not antagonize it (*47*) seems to reconcile some of the empirical inconsistencies in the field, although it is quite at odds with the original hypotheses based on the antagonistic action of lysergic acid diethylamide.

Levels of norepinephrine as well as serotonin are markedly lowered in the brain following administration of reserpine (*48*). In fact, the brain concentrations of these two amines follow each other so closely in their response to reserpine as to suggest some mechanism common to both and perhaps obtaining as well for other active amines in the brain. In one study, 3,4-dihydroxyphenylalanine, a precursor of norepinephrine, was capable of counteracting the behavioral effects of reserpine, whereas the precursor of serotonin was ineffective (*49*). Moreover, the effects of iproniazid are not limited to brain serotonin; a comparable effect on norepinephrine has been reported (*50*), and it is possible that other amines or substances still to be discovered in the brain may be affected by what may be a nonspecific inhibitor of a relatively nonspecific enzyme. Of great interest in this connection are recent studies of Olds and Olds (*51*) indicating a positive behavioral response for iproniazid injected into the hypothalamus but not for serotonin or norepinephrine.

Chlorpromazine, which has the same therapeutic efficacy as reserpine in disturbed behavior, is apparently able to achieve this action without any known effect on serotonin. In addition, the provocative observation that iproniazid, which elevates serotonin levels in the brain, can cause a toxic psychosis loses some of its impact when one realizes that isoniazid, which does not inhibit monoamine oxidase and can hardly raise the brain serotonin concentration, produces a similar psychosis (*45, 52*).

It seems reasonable to conclude that the serotonin as well as the norepinephrine in the brain have some important functions there, and the evidence in general supports this thesis, even though it also suggests that their roles still remain to be defined.

If the picture of the role which serotonin plays in central nervous function is blurred, the direct evidence to support the early speculations that it is involved in mental illness is meager and contradictory. From all of the evidence cited above, one could find a basis for predicting that in schizophrenia the serotonin levels in the brain, if they are altered at all, should be quite low or quite high. Results confirming both predictions have been reported.

The urinary excretion of 5-hydroxyindoleacetic acid has been used as an indicator of the portion of ingested tryptophan which is metabolized through serotonin to form that end product. Although excretion of 5-hydroxyindoleacetic acid is normal in schizophrenic patients under ordinary circumstances (*53*), it may be altered by challenging the metabolic systems with large doses of tryptophan. Zeller and his associates have reported a failure on the part of schizophrenics, under these circumstances, to increase their output of 5-hydroxyindoleacetic acid, while nonpsychotic controls double theirs (*54*). Banerjee and Agarwal, on the other hand, have reported exactly the opposite results; in their study it was the schizophrenics who doubled their output of the serotonin end product, while the output of the controls remained unchanged (*55*).

Kopin, of our laboratory, has had the opportunity to perform a similar study on schizophrenics and normal controls maintained on a good and reasonably controlled diet and given no drugs. In each group there was a slightly greater than twofold increase in output of 5-hydroxyindoleacetic acid following a tryptophan load, and there was no significant deviation from this pattern in any single case (*56*).

That the heuristic speculations of Woolley and Shaw, and of Gaddum, have not yet been established does not mean that they are invalid. The widespread experimental activity which they stimulated has broadened and deepened our knowledge of the metabolism and pharmacology of serotonin and of its ef-

fects on behavior and may lead the way to definitive evaluation of its possible role in normal and pathological states.

Genetics and Schizophrenic Disorders

Many of the current hypotheses concerning the schizophrenia complex are original and attractive even though, up to this time, evidence directly implicating any one of them in the disease itself is hardly compelling. There is, nevertheless, cogent evidence that is responsible to a large extent for the present reawakening of the long dormant biochemical thinking in this area and sufficiently convincing to promote its continued development. Genetic studies have recently assumed such a role, and it appears worth while briefly to review them in the present context.

In earlier studies on large populations, a remarkable correlation was reported between the incidence of schizophrenia and the degree of consanguinity in relatives of known schizophrenics (*57*). These findings were not conclusive, however, since the influence of socioenvironmental factors was not controlled. Better evidence is obtained from the examination of the co-twins and siblings of schizophrenics; a number of such studies have been completed and are summarized in Table 1 (*57–59*). The concordance rate for schizophrenia is extremely high for monozygotic twins in all the studies, while that for dizygotic twins is low and not significantly different from that in siblings, to which, of course, dizygotic twins are quite comparable genetically. Even these studies, however, are not completely free from possible sources of error, and this makes it difficult to arrive at a definitive conclusion regarding the role of genetic factors in this disease. One cannot assume that environmental similarities and mutual interactions in identical twins, who are always of the same sex and whose striking physical congruence is often accentuated by parental attitudes, play an insignificant role in the high concordance rate of schizophrenia in this group. This factor could be controlled by a study of twins separated at birth (of such twins no statistically valid series has yet been compiled) or by a comparison of the concordance rates in monozygotic twins and in dizygotic twins whose zygosity had been mistakenly evaluated by the twins themselves and by their parents and associates. Another possible means of better controlling the environmental variables would be to make a careful study of schizophrenia in adopted children, with comparison of the incidence in blood relatives and in foster relatives. Perhaps only a survey on a national scale would provide the requisite numbers of cases for any of these studies.

A less satisfactory resolution of this problem can be obtained by an appraisal of environmental similarities in normal fraternal and identical twins. Such a study, on over 100 specific aspects of the environment, has been made (*60*), and I have assembled the results into a rough index of environmental similarity (Table 2). Although a difference is apparent, in the crude measurement of environmental congruence, between identical and fraternal twins of like sex, it is not statistically significant and can account for only a small fraction of the large difference in concordance with respect to schizophrenia between these types of twins. On the other hand, there is a highly significant difference in environmental similarity between fraternal twins of like and unlike sex which is sufficient to account for the difference in concordance with respect to schizophrenic psychosis between them, for which, of course, there is no tenable genetic explanation.

Two recent reports have been used, but by no means conclusively, in support of the position that too much significance has been attached to environmental factors as determining causes in this disease group. Chapman (*61*), reporting a case of concordant early infantile autism in identical twins, points out that this disorder has never been reported as concordant in fraternal twins, whereas it has been described in three sets of identical twins. Since fraternal twins occur nearly three times as frequently as identical twins, the evidence cited is suggestive, in spite of the small numbers involved; furthermore, the disease may develop before the personal identifications and interactions peculiar to monozygotic twins have had much chance to operate. Another interesting finding in over 150 families with a single schizophrenic member is that no ordinal position in the family appears to carry specific vulnerability to schizophrenia (*62*)—a finding completely compatible with genetic theory but more difficult to reconcile with theories of environmental etiology if the assumption is correct that different positions within the family are subject to varying degrees of stress. Of course one may argue quite properly that schizophrenogenic stress exists and can be evaluated only in terms of the reaction between each individual and his own environment, so that any position on a social, economic, occupational, or birth-order scale may be associated with greatly different degrees of stress for different individuals.

Another possible source of error in the twin studies which have been reported is the personal bias of the investigators who made the judgment of zygosity and the diagnosis of schizophrenia in the co-twins. Until a more definitive study is carried out in which these judgments are made independently, a rough evaluation is possible, at least for the diagnosis of schizophrenia, if not for zygosity, on the basis of diagnoses arrived at in the various hospitals to which the co-twins may have been admitted before or irrespective of their involvement in the study—diagnoses which are not likely to have been contaminated by knowledge about their zygosity. Kallmann has been kind enough to review the material collected in his 1946–49 survey from that point of view. Of 174 monozygotic co-twins of schizophrenic index cases, 103, or 59 percent, had been diagnosed schizophrenic by Kallmann, while 87, or 50 percent, had received a psychiatric hospital diagnosis of schizophrenia prior to any examination made by him. On the other hand, he had made the diagnosis of schizophrenia in 47, or 9.1 percent, of 517 dizygotic co-twins as compared to a hospital diagnosis in 31, or 6 percent. Although the concordance rates based only on hospital diagnoses are lower in both types of twins, for obvious reasons, the striking difference between the two concordance rates remains. Slater (*59*) has published individual protocols of his cases from which I have made judgments of zygosity and schizophrenia. Of 21 pairs of twins who could be considered definitely uniovular, 15, or 75 percent, were concordant with respect to the simple criterion of admission to a mental hospital, whereas in only 12, or 10.3 percent, of 116 binovular or questionably binovular pairs was there a history of the co-twin's having been admitted to a mental hospital for any psychosis. On the basis of this analysis of the two most recent series, it seems that only a small component of the great difference in concordance rates reported for schizophrenia between uniovular and binovular twins can be attributed to the operation of personal bias in the diagnosis of the disease in the co-twin.

Even the most uncritical acceptance of all the genetic data, however, cannot

lead to the conclusion that the schizophrenic illnesses are the result of genetic factors alone. In 14 to 30 percent of the cases in which schizophrenia occurs in one of a pair of monozygotic twins, the genetically identical partner is found to be free of the disorder (Table 1). Attention has already been called (Table 2) to the higher concordance with respect to schizophrenia and the greater environmental similarities in like-sexed fraternal twins or siblings than in those of unlike sex, and from the same source (*57*) a difference in concordance is reported between monozygotic twins separated some years before the study (77.6 percent) as opposed to those not separated (91.5 percent). Neither of these observations is compatible with a purely genetic etiology of the disease, and both suggest the operation of environmental factors. Rosenthal (*63*) and Jackson (*64*) have pointed out the striking preponderance of female over male pairs concordant for schizophrenia in all of the reported series, whether they be monozygotic or dizygotic twins, siblings, or parent-child pairs. If sampling errors resulting from the greater mobility of males are excluded and the observations are taken as a reflection of the true incidence of this phenomenon, several explanations for it on the basis of social interaction can be given, but none based on purely genetic grounds, unless sex linkage is invoked, for which there is no other evidence.

Clausen has critically reviewed the extensive literature supporting the importance of environmental factors in the etiology of schizophrenic disorders (*65*). The evidence there seems quite as suggestive as the genetic evidence but by no means more conclusive, since few studies in either field have been completely objective or adequately controlled.

It is both interesting and important to note that even if the conclusions of both the genetic and the environmental approaches to the etiology of schizophrenic psychoses are accepted uncritically, they are not mutually exclusive. Both are compatible with the hypothesis that this group of diseases results from the operation of socioenvironmental factors on some hereditary predisposition, or from an interaction of the two, each being necessary but neither alone sufficient. An excellent example of such a relationship is seen in tuberculosis, where the importance of the environmental microbial factor is undisputed and where, as Lurie (*66*) has shown, genetic susceptibility is likewise important; a population sufficiently heterogeneous with respect to susceptibility and exposure to tuberculosis yields results in contingency and twin studies (*67*) which, before the discovery of the tubercle bacillus, could easily have been used to prove a primary genetic cause—almost as convincingly as the results of similar studies have been used to prove such a cause in schizophrenia. Interestingly enough, studies of tuberculosis made from the socioenvironmental point of view would obviously provide data offering equally convincing proof that exogenous, social, and economic factors play a part. One hypothesis with respect to the schizophrenic psychoses which remains compatible with all the evidence from the genetic as well as the psychosocial disciplines is that these disorders, like tuberculosis, require the operation of environmental factors upon a genetically determined predisposition.

Table 1. Concordance rates for schizophrenia found in studies of twins.

Investigator	Number of pairs		Concordance rate* (%)	
	Dizygotic	Monozygotic	Dizygotic	Monozygotic
Luxenburger (1928)	48	17	2	59 (67)
Rosanoff *et al.* (1934)	101	41	10	61
Kallmann (1946)	517	174	10 (15)	69 (86)
Slater (1953)	115	41	11 (14)	68 (76)

* Figures in parentheses indicate rate after correction for the chance that a co-twin, normal at the time of observation, may develop the disease later.

Résumé

Although the evidence for genetic and therefore biological factors as important and necessary components in the etiology of many or all of the schizophrenias is quite compelling, the sign-posts pointing the way to their discovery are at present quite blurred and, to me at least, illegible.

Genetic factors may operate through some ubiquitous enzyme system to effect general changes in one or another metabolic pathway—changes detectable through studies of blood or urine—and it is to be hoped that the currently active search in these areas will continue.

It is at least equally possible, however, that these genetic factors may operate only through enzymes or metabolic processes peculiar to or confined within the brain, or even within extremely localized areas of the brain. We are in need of new hypotheses such as those of Elkes (*68*) and many already discussed. In this connection, gamma-amino-butyric acid appears to be just as interesting a substance about which to construct working hypotheses as are the catechols or the indoles. It has been isolated only from nervous tissue, and its metabolism in such tissue has been investigated in some detail (*69*), while its neurophysiological properties appear to be better defined than are those of the other two groups (*70*); in addition, its inhibitory properties may have special relevance to diseases where a failure in central inhibition seems to be involved.

Amphetamine possesses remarkable psychotomimetic properties which should not be overlooked. Its ability to produce a clinical syndrome often indistinguishable from schizophrenia (*71*) and the possible relation of amphetamine to the naturally occurring catechol amines make it at least as inter-

Table 2. Environmental factors in studies of schizophrenia in twins.

Sex	Environmental similarity in normal twins* (%)	Number of pairs	Concordance with respect to schizophrenia† (%)	Number of pairs
		Identical twins		
Same	61	70	86	174
		Fraternal twins		
Same	53	69	18	296
Different	26	55	10	221
		Siblings		
Same			16	
Different			12	

* Estimated from data of P. T. Wilson (1934).
† From data of F. J. Kallmann (1946).

esting as lysergic acid diethylamide.

In addition to techniques at present available in neurochemistry, neurophysiology, and behavioral pharmacology, the development of new methods designed to yield information on processes occurring within the psychotic brain will be needed before our explorations in this field have been exhausted.

But the biochemist must not lose sight of the possibility, which is certainly as great as any of the others, that the genetic factors in schizophrenia operate to determine inappropriate interconnections or interaction between chemically normal components of the brain; if that should prove to be the case, the physiological psychologist, the neurophysiologist, or the anatomist is likely to find meaningful information long before the biochemist does. It would take many biochemists a long time to find a noisy circuit in a radio receiver if they restricted themselves to chemical techniques.

These possibilities are mentioned only to indicate how large is the haystack in which we are searching for the needle; one cannot avoid a feeling of humility when one realizes how slight the chance is that any one of us has already found it, or will find it in a relatively short time.

That is no cause for discouragement, however. It is not necessary that one be convinced of the truth of a particular hypothesis to justify devoting one's energies to testing it. It is enough that one regard it as worth testing, and that the tools be adequate. Modern biochemistry, with its wealth of new knowledge of intermediary metabolism and its array of new techniques for the separation and identification of compounds and the tracing of their metabolic pathways, has provided the biologist interested in mental illness with an armamentarium which his predecessor of only a generation ago could hardly have envisioned. If he chooses from among the approaches which may lead to a definition of the biological factors in schizophrenia those which will in any case lead to a better understanding of the nervous system and of thought processes and behavior, the present surge of enthusiasm will not have been misdirected.

References and Notes

1. S. Akerfeldt, *Science* 125, 117 (1957).
2. F. A. Gibbs, Ed., *Blood Tests in Mental Illness* (Brain Research Foundation, Chicago, 1957).
3. C. G. Holmberg and C. B. Laurell, *Scand. J. Clin. & Lab. Invest.* 3, 103 (1951).
4. B. E. Leach and R. G. Heath, *A.M.A. Arch. Neurol. Psychiat.* 76, 444 (1956).
5. B. E. Leach, M. Cohen, R. C. Heath, S. Martens, *ibid.* 76, 635 (1956).
6. W. Keup, *Monatsschr. Psychiat. Neurol.* 128, 56 (1954).
7. C. G. Holmberg and C. B. Laurell, *Acta Chem. Scand.* 2, 550 (1948).
8. H. Markowitz, C. J. Gubler, J. P. Mahoney, G. E. Cartwright, M. M. Wintrobe, *J. Clin. Invest.* 34, 1498 (1955).
9. L. G. Abood, F. A. Gibbs, E. Gibbs, *A.M.A. Arch. Neurol. Psychiat.* 17, 643 (1957).
10. R. K. McDonald, "Plasma ceruloplasmin and ascorbic acid levels in schizophrenia," paper presented at the annual meeting of the American Psychiatric Association, Chicago, Ill., 1957.
11. I. H. Scheinberg, A. G. Morell, R. S. Harris, A. Berger, *Science* 126, 925 (1957); M. K. Horwitt, B. J. Meyer, A. C. Meyer, C. C. Harvey, D. Haffron, *A.M.A. Arch. Neurol. Psychiat.* 78, 275 (1957); C. E. Frohman, M. Goodman, E. D. Luby, P. G. S. Beckett, R. Senf, *ibid.* 79, 730 (1958); M. H. Aprison and H. J. Grosz, *ibid.* 79, 575 (1958).
12. M. H. Aprison and A. L. Drew, *Science* 127, 758 (1958).
13. A. M. Ostfeld, L. G. Abood, D. A. Marcus, *A.M.A. Arch. Neurol. Psychiat.* 79, 317 (1958).
14. C. Angel, B. E. Leach, S. Martens, M. Cohen, R. G. Heath, *ibid.* 79, 500 (1957).
15. R. G. Heath, S. Martens, B. E. Leach, M. Cohen, C. A. Feigley, *Am. J. Psychiat.* 114, 917 (1958).
16. R. G. Heath, B. E. Leach, L. W. Byers, S. Martens, C. A. Feigley, *ibid.* 114, 683 (1958).
17. R. G. Heath, S. Martens, B. E. Leach, M. Cohen, C. Angel, *ibid.* 114, 14 (1957).
18. R. Fischer, *Proc. Intern. Physiol. Congr., 19th Congr.* (1953), pp. 350–351.
19. F. Georgi, H. P. Rieder, R. Weber, *Science* 120, 504 (1954).
20. C. B. Edisen, *Diseases of Nervous System* 17, 77 (1956).
21. S. Fedoroff, *Anat. Record* 121, 394 (1955).
22. ——— and A. Hoffer, *J. Nervous Mental Disease* 124, 396 (1956).
23. J. Wada, *Proc. Soc. Biol. Psychiatrists, 12th Ann. Conv.* (1957).
24. H. P. Rieder, *Psychiat. et Neurol.* 134, 378 (1957).
25. K. Smith and A. C. Moody, *Diseases of Nervous System* 17, 327 (1956).
26. A. K. Shapiro, *J. Nervous Mental Disease* 123, 65 (1956).
27. C. A. Winter and L. Flataker, *Proc. Soc. Biol. Psychiatrists, 12th Ann. Conv.* (1957).
28. ———, *A.M.A. Arch. Neurol. Psychiat.* 80, 441 (1958).
29. C. Kornetsky, personal communication; L. Ghent and A. M. Freedman, *Am. J. Psychiat.* 115, 465 (1958).
30. B. Minz and E. J. Walaszek, *Compt. rend.* 244, 1974 (1957).
31. R. K. McDonald, *J. Chronic Diseases* 8, 366 (1958); A. J. Barak, F. L. Humoller, J. D. Stevens, *A.M.A. Arch. Neurol. Psychiat.* 80, 237 (1958).
32. E. Robins, K. Smith, I. P. Lowe, in "Neuropharmacology," *Trans. Josiah Macy, Jr. Foundation, 4th Conf.* (1957).
33. S. S. Kety, in *ibid.* (1957).
34. H. I. Lief, *A.M.A. Arch. Neurol. Psychiat.* 78, 624 (1957)
35. A. H. Amin, T. B. B. Crawford, J. H. Gaddum, *J. Physiol. (London)* 126, 596 (1954).
36. D. W. Woolley and E. Shaw, *Science* 119, 587 (1954).
37. J. H. Gaddum, in *Ciba Foundation Symposium on Hypertension* (Little, Brown, Boston, 1954).
38. D. F. Bogdanski, H. Weissbach, S. Udenfriend, *J. Neurochem.* 1, 272 (19[illegible] M. K. Paasonen, P. D. MacLean, N. J. Giarman, *ibid.* 1, 326 (1957).
39. E. V. Evarts, *A.M.A. Arch. Neurol. Psychiat.* 75, 49 (1956); H. D. Fabing and J. R. Hawkins, *Science* 123, 886 (1956).
40. P. A. Shore, A. Pletscher, E. G. Tomich, A. Carlsson, R. Kuntzman, B. B. Brodie *Ann. N.Y. Acad. Sci.* 66, 609 (1957).
S. Udenfriend, H. Weissbach, D. F. Bogdanski, *ibid.* 66, 602 (1957).
42. D. W. Woolley, *Science* 125, 752 (1957).
43. L. H. Rudy, E. Costa, F. Rinaldi, H. E. Himwich, *J. Nervous Mental Disease* 126, 284 (1958).
44. G. E. Crane, *ibid.* 124, 322 (1956).
45. H. Pleasure, *A.M.A. Arch. Neurol. Psychiat.* 72, 313 (1954).
46. E. Rothlin, *Ann. N.Y. Acad. Sci.* 66, 668 (1957).
47. J. H. Welsh and A. C. McCoy, *Science* 125, 348 (1957).
48. M. Holzbauer and M. Vogt, *J. Neurochem.* 1, 8 (1956); M. Vogt, in *Metabolism of the Nervous System*, D. Richter, Ed. (Pergamon, London, 1957), pp. 553–565.
A. Carlsson, M. Lindqvist, T. Magnusson, *Nature* 180, 1200 (1957).
50. S. Spector, D. Prockop, P. A. Shore, B. B. Brodie, *Science* 127, 704 (1958).
J. Olds and M. E. Olds, *ibid.* 127, 1175 (1958).
52. S. L. O. Jackson, *Brit. Med. J.* 2, 743 (1957).
53. G. A. Buscaino and L. Stefanachi, *A.M.A. Neurol. Psychiat.* 80, 78 (1958); A. Feldstein, H. Hoagland, H. Freeman, *Science* 128, 358 (1958).
E. A. Zeller, J. Bernsohn, W. M. Inskip, J. W. Lauer, *Naturwissenschaften* 44, 427 (1957); J. W. Lauer, W. M. Inskip, J. Bernsohn, E. A. Zeller, *A.M.A. Arch. Neurol. Psychiat.* 80, 122 (1958).
55. S. Banerjee and P. S. Agarwal, *Proc. Soc. Exptl. Biol. Med.* 97, 657 (1958).
56. I. J. Kopin, *Science* 129, 835 (1959).
57. F. J. Kallmann, *Am. J. Psychiat.* 103, 309 (1946).
58. H. Luxenburger, *Z. ges. Neurol. Psychiat.* 116, 297 (1928); A. J. Rosanoff, L. M. Handy, I. R. Plesset, S. Brush, *Am. J. Psychiat.* 91, 247 (1934).
59. E. Slater, "Psychotic and Neurotic Illnesses in Twins," *Medical Research Council Special Report No. 278* (H.M. Stationery Office, London, 1953).
60. P. T. Wilson, *Human Biology* 6, 324 (1934).
61. A. H. Chapman, *A.M.A. Arch. Neurol. Psychiat.* 78, 621 (1957).
62. H. J. Grosz and I. Miller, *Science* 128, 30 (1958).
63. D. Rosenthal, *J. Nervous Mental Disease*, in press.
64. D. D. Jackson, in "The Study of Schizophrenia," D. D. Jackson, Ed. (Basic Books, New York, in press).
65. J. A. Clausen, *Sociology Today*, Merton, Broom, and Cottrell, Eds. (Basic Books, New York, 1959).
66. M. B. Lurie, S. Abramson, A. Heppelston, *J. Exptl. Med.* 95, 119 (1952).
67. K. Planansky and G. Allen, *Am. J. Human Genet.* 5, 322 (1953).
68. J. Elkes, in "Neuropharmacology," *Trans. Josiah Macy, Jr. Foundation, 3rd Conf.* (1956).
69. E. Roberts and S. Frankel, *J. Biol. Chem.* 187, 55 (1950); E. Roberts, M. Rothstein, C. F. Baxter, *Proc. Soc. Exptl. Biol. Med.* 97, 796 (1958).
70. D. P. Purpura, M. Girardo, H. Grundfest, *Science* 125, 1200 (1957); K. Iwama and H. H. Jasper, *J. Physiol. (London)* 138, 365 (1957).
71. P. H. Connell, *Biochem. J.* 65, 7p (1957).