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THE GENETICS OF SCHIZOPHRENIA

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Chapter 25
THE GENETICS OF SCHIZOPHRENIA[1]

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It should be clear at the outset that if we understand the genetics of schizophrenia, we are in a favorable position to develop optimal preventive and therapeutic measures with respect to this grave mental disturbance. The fact is that we do not understand the genetics of schizophrenia. In truth, the primary task of genetic research on this disorder over the past six decades has been to show that heredity has anything to do with schizophrenia at all. The burden of proof has not been borne easily, despite the fact that the conception of the disorder by its originators, Kraepelin and Bleuler, took place in an intellectual climate which assumed almost without question that the disorder was indeed inherited. In this article, we will review the main body of genetic evidence gathered to date and try to place a fair evaluation on it.

Determining That a Disorder Is Genetic

First, the reader ought to be reminded of the kinds of information that permit us to make decisions about the role of genes in various disorders. The genetics issue is most readily resolved, and perhaps can only be resolved

conclusively, if we can demonstrate that a disorder (the phenotype) follows a Mendelian distribution in families. To make such a demonstration requires that we examine at least two generations. Such research has been done extensively with regard to schizophrenia, and although theorists have advocated a single gene theory, in the main, they have never been able to demonstrate a consistent, simple Mendelian distribution of the disorder within families, nor have they been able to agree on whether the postulated mode of genetic transmission follows a dominant or recessive pattern. In fact, investigators have been able to find families that simulated a pattern of dominance, recessiveness, or no pattern at all, and one investigator has taken the view that the families in which the distribution of schizophrenia represents a dominant, recessive, or intermediate pattern actually constitute three different genetic disorders. This latter view—that there may be a number of major single genes, each of which can respectively be responsible for schizophrenic illness—is referred to as heterogeneity theory. In different forms, it is a view that is not uncommonly held, and indeed it was advocated by E. Bleuler himself, who thought of the illness as a group of schizophrenias.

Failing to find evidence for a clear Mendelian distribution, we might advance our understanding of the genetics of schizophrenia if we could point to a specific metabolic disturbance that is clearly associated with the disorder. To date, however, no such finding has been made, although, as in most bodies of literature on schizophrenia, a large number of theories have

been put forward over the years, some of them based on suggestive empirical findings. Until such a finding is forthcoming, our understanding of the genetics of schizophrenia must remain limited and questionable.

A third kind of information that could be helpful would derive from studies analogous to breeding experiments carried out with animals. In such studies the experimenter is able to develop different strains of a species and to inbreed or crossbreed them in various ways over several generations. Fortunately, scientists cannot exercise such controls with regard to humans who mate as they will. The best that the scientist can hope for is to find naturally transpiring matings that follow along the lines he would have chosen had he been able to control the matings in a laboratory-like situation. In fact, it is information from just such matings and from twin studies which provides us with whatever we do know about the genetics of schizophrenia. To demonstrate that genes have anything to do with schizophrenia, the investigator, lacking the desiderata noted above, must marshal the following group of statistical findings:

1. The frequency of schizophrenia must be greater in the families of schizophrenics than in the families of nonschizophrenic controls or in the population at large.

2. The frequency of schizophrenia in relatives of schizophrenics should be positively correlated with the degree of blood relationship to the schizophrenic index cases.

3. The concordance rate for schizophrenia must be higher in monozygotic than in dizygotic twins.

Familial Evidence and Twin Studies

Table 25-1 indicates the expected rate of schizophrenia in the sibs of schizophrenic index cases and in the corresponding population at large. Clearly, the rates are always significantly higher for the sibs than for the general population, thus meeting the first criterion. With respect to the second criterion, a median risk value for second-degree relatives is about 2.1 percent, which is lower than the median risk value for sibs in Table 25-1, and a median risk value for third-degree relatives is about 1.65 percent, which is lower than the median rate for second-degree relatives and higher than the median rate for the populations shown in Table 25-1. Thus, the data provide support for the second criterion, but the differences between median values, once one moves beyond first-degree relatives, are slight indeed, and involve a fair amount of overlap when one looks at the individual studies separately.

Table 25-2 presents the main studies regarding the third criterion. With the exception of one study, the concordance rate for MZ twins is always significantly higher than that for DZ twins, thus meeting the third criterion strongly.

Table 25-1. Morbidity Risk Estimates for Sibs of Schizophrenic Index Cases and

for the Population at Large

	Morbidity risk estimate in percent	
Study	*Sibs*	*General Population*
Brugger, 1928	10.3	1.53
Schultz, 1932	6.7	0.76
Luxemburger, 1936	7.6	0.85
Stromgren, 1938	6.7	0.48
Kallmann, 1938	7.5	0.35
Bleuler, 1941	10.4	1.53
Book, 1953	9.7	2.85
Hallgren & Sjögren, 1959	5.7	0.83
Garrone, 1962	8.6	2.40

Table 25-2. Approximate Concordance Rates for Schizophrenia in Monozygotic and Dizygotic Twins

	Estimated concordance rate in percent	
Study	*MZ Twins*	*DZ Twins*
Luxemburger, 1928-1934	55	2.1
Rosanoff et al., 1934-1935	61	10.0
Essen-Moller, 1941	42	13.0
Kallmann, 1946	73	12.2
Slater, 1953	70	12.3
Inouye, 1961	48	9.0

Tienari, 1963, 1968	6	4.8
Gottesman and Shields, 1966	50	9.1
Kringlen, 1967	31	9.0
Fischer et al., 1969	37	9.5
Pollin et al., 1969	15.5	4.4

Note: These are not necessarily the rates reported by the investigators. They indicate this author's estimate of the rate that might best represent the data in each study, but the reader should know that a simply expressed concordance can be misleading, that it masks or disregards much information necessary to understand the basic data on which the rates are based.

Once we have met the primary three criteria, we can add a fourth. We may now make the reasonable tentative assumption that individuals who have the disorder also have the genotype that leads to that disorder. When they mate, they should pass this genetic loading on to their children in appreciable degree, depending on the mode of genetic transmission. In fact, children who have a schizophrenic parent have about a 10 percent median risk of developing schizophrenia themselves. With *both* parents schizophrenic, the assumed genetic loading transmitted increases proportionately, and the median risk of developing schizophrenia in children of such dual matings increases to about 40 percent. Thus, these findings are also consistent with the genetic hypothesis and provide additional support for it.

An Alternative Hypothesis

Nevertheless, it is time to pause in our discussion to look at the matter more broadly. It is true that all the data mentioned are consistent with what genetic theory predicts, but might the data not be explained in some other way as well? If schizophrenia runs in families, could it be that there are certain behavioral and psychological events that occur in these families that induce schizophrenic symptoms and behavior in some of their members? Investigators who have observed such families intensively have long called attention to behavioral patterns in mothers whom they call "schizophrenogenic." Some have thought that families with strong mothers and weak, dependent fathers produce schizophrenic children. Others have pointed to parents who "double-bind" their children or who create an impalpable "rubber-fence" around the family, or non-genuine relationships among themselves called "pseudo-mutual", or who fragment the child's foci of attention in various ways, especially through loose or garbled forms of verbal communication, or who create a family climate that has been called "skewed" or chaotic, and that such familial characteristics induce schizophrenic disorder in children subjected to them. Some evidence suggests that families in the lowest socioeconomic status breed a disproportionately large number of schizophrenics.

Let us then for the moment make another reasonable but tentative assumption, namely, that those observations listed above do indeed indicate that familial interaction patterns play a causal role in the development of

schizophrenia. How could such an hypothesis account for the four groups of findings noted above?

First, the fact that sibs of schizophrenics develop schizophrenia more often than the population at large is not surprising, since the sibs grow up in the same family as the schizophrenic index cases. Both have been victimized by the same noxious influences, which in turn do not apply to the general population, at least not with the same intensity or frequency. The fact that there is a correlation between the rate of schizophrenia in relatives and the degree of blood relationship to schizophrenics might also be predicted by our tentative hypothesis. First-degree relatives should show the highest rate since all are subjected to the same noxious influences. Second-degree relatives, such as aunts or uncles, grew up in the same environment as the mothers and fathers of the schizophrenic cases, and may have developed behavioral patterns similar to those of the schizophrenics' parents, thus abetting the production of schizophrenia in their own children, but to a lesser extent. These shared environments occur to lesser extents as the degree of blood relationship becomes further removed, thus accounting for the observed correlation.

A similar line of argument would apply to families in which one of the parents is schizophrenic. Of course, a psychotic parent will be more likely than a normal parent to produce a chaotic family, with increased

schizophrenia among his offspring. When both parents are schizophrenic, conditions for complete familial chaos are ripe indeed, and it is no wonder that the rate of schizophrenia among their offspring increases about fourfold, a rate of increase not strictly predicted by genetic theory. It may be, too, that some of the children identify with the schizophrenic parent, see themselves as being like that parent or even being a "part" of her (which, genetically speaking, is true), and eventually come to a schizophrenic denouement in which the identification with the parent reaches its fullest expression.

Now, what about the MZ and DZ twins, in which both members of the pair grew up in the same home? Why should the concordance rate be higher for the MZ pairs? Well, the tentative hypothesis under scrutiny is a psychological one. Two people may grow up in the same home but have completely different psychological experiences in it. This point applies especially to twins. DZ twins should share experiences much as ordinary siblings do, although they also share some additional ones that have to do with the fact that they were born together and are the same age. However, MZ twins have a unique psychological experience which pervades their entire lives. Identification with another person reaches its strongest point in such genetically identical individuals. The literature on twins is replete with all kinds of experiences and lore that bear on this intense communality or psychological bond.' If one twin develops an illness, the other is likely to do so as well. This sharing of fates is an ongoing, integral part of their development

and learning. Therefore, if one twin develops a schizophrenic illness, the likelihood of the second twin's developing that illness is increased inordinately, and the concordance rates for MZ pairs should be appreciably higher than that for DZ pairs, according to the tentative hypothesis.

Studies Separating the Genetic and Rearing Variables

Thus, we see that the same basic data can be explained plausibly by at least two competing hypotheses which are completely different from one another, and which have vastly different implications with regard to our understanding, treatment, and research on schizophrenia. Such a situation is scientifically intolerable, and it becomes incumbent on scientists working on the problem to determine which hypothesis is correct. Resolution of the issue is no simple matter since both hypotheses depend on familial distributions to support their veridicality, and both the hypothesized genes and the reported behavioral-psychological factors are confounded in the same families. The scientist's task is to unconfound the two implicated variables, and this can best be done by taking advantage of naturally occurring adoptions.

In a study carried out in western U.S.A. by Heston, the index cases were adults who had been born of hospitalized, actively schizophrenic women and who had been placed at birth in foundling homes or in the care of paternal relatives, or adopted away. A matched control group consisted of subjects

who had been placed in the same foundling homes. Of the forty-seven index cases five, or 16.6 percent, were hospitalized chronic schizophrenics, but none of the controls was schizophrenic.

Karlsson, in a study done in Iceland, compared the biologic and foster sibs of schizophrenics who had been adopted in their first year of life. Six of twenty-nine biologic sibs (20.7 percent) were found to be schizophrenic, as compared to none of the twenty-eight foster sibs.

In an eastern U.S.A. study carried out by Wender et al., the index cases were adult schizophrenics who had been adopted by nonrelatives in their first year of life. One control group consisted of matched schizophrenics who were reared in the parental home, and a second control group consisted of matched adult adoptees who were psychiatrically normal. The adopting parents of the index cases had less severe psychopathology than the biologic parents of the schizophrenic controls, but more psychopathology than the adopting parents of normals.

In a study done in Denmark by Kety et al., the index cases were adults who had been given up for nonfamily adoption in their first four years of life and who were diagnosed as having a schizophrenic disorder. A control group consisted of matched adoptees who had had no known psychiatric admission. The adoptive and biologic parents, sibs and half-sibs of both groups were

evaluated with respect to schizophrenia and schizophrenic disorders called acute, borderline, severely schizoid, paranoid, or inadequate. These diagnoses combined were called *the schizophrenia spectrum.* There was one case of chronic or process schizophrenia among 150 biologic relatives of the index cases and one among the 156 biologic relatives of the controls, but with regard to all schizophrenia spectrum disorders, thirteen occurred in relatives of index cases as compared to three of controls, a difference significant at the .01 level. No differences in such disorders occurred among the adoptive relatives of the index and control subjects.

A second study carried out in Denmark by Rosenthal selected adult index cases who had had a schizophrenic biologic parent but who had been adopted away in the first four years of life. A control group consisted of matched adoptees whose biologic parents had never had a psychiatric admission for a schizophrenia spectrum disorder. Both groups of adoptees were examined in an interview lasting three to five hours by a psychiatrist who did not know if the subject was an index or control case. Among the index cases, three were diagnosed as schizophrenic, only one of whom had been hospitalized, but none of the controls was so diagnosed. With respect to all schizophrenia spectrum diagnoses combined, the rate was almost twice as high in the index cases as in the controls, the difference being statistically significant.

Problems in the "Unconfounding" Studies

Thus, we now have five independent studies in which the genetic and rearing families have been unconfounded. All five point strongly to the conclusion that genes do in fact determine to an appreciable extent whether schizophrenic types of disorder will or will not occur.

Nevertheless, each of the five studies leaves some lingering questions. In the Heston study, the biologic mothers were actively schizophrenic, and were hospitalized and treated while pregnant with the index cases. Could such prenatal influences foster a schizophrenic outcome? Also, many of the rearing families knew about the schizophrenic mother, and conceivably some may have had the common expectation of "like parent, like child," and may have communicated this expectation to the child in various ways and behaved toward him accordingly. Could such factors have been implicated in the index case disorders observed?

In the Karlsson study, we are provided with too little information about the methodological details, especially in regard to diagnosis. Moreover, among the separated biologic sibs of his index cases he finds 20.7 percent schizophrenic. A glance at Table 25-1 will show that this rate is twice as high as the highest rates shown in the table. Why should this be so, especially when the index cases and their sibs are *not* reared together?

In the Wender et al. study, the number of subjects was smaller than one would like, and the major examiner was not blind with respect to which parents being interviewed were related to which proband group. This study has been repeated with a new sample to address itself to these problems, but the data are not yet available.

In the Kety et al. study, there was no significant difference between the biologic and adoptive relatives of index and control subjects with regard to clear-cut schizophrenia. Perhaps, this result could be traced to the fact that the number of clear-cut schizophrenic index cases was relatively small. This study has been expanded and additional findings may change this statistical picture. The findings that did discriminate the biologic relatives of index and control subjects depended on mental disturbances tentatively assumed to be milder forms of schizophrenic disorder that are genetically linked to process schizophrenia. This assumption of a genetically unified spectrum of disorders needs further testing and clarification, and indeed these investigators are working to provide it.

In the Rosenthal study, only one index case was a hospitalized schizophrenic. Two additional index cases diagnosed schizophrenic by the examining psychiatrist were managing their lives in the community and never required hospitalization. Of the offspring of thirty process schizophrenics, not one was hospitalized for schizophrenia, and only one was diagnosed

schizophrenic (3.3 percent, not age corrected, as compared to Heston's 16.6 percent, corrected for age). Among offspring of a schizophrenic generally, the median rate of schizophrenia reported is approximately 10 percent. Thus, a possible interpretation of the Rosenthal finding is that rearing in an adoptive home may indeed protect children of a schizophrenic parent from developing the disorder themselves.

With respect to twins, the best way to unconfound the genetic and psychological variables that may account for the high concordance rates in MZ pairs is to separate them early in life. Although this obviously cannot be done in any systematic way, Slater has compiled from eight sources a series of MZ pairs in which the twins were separated early in life and at least one was schizophrenic. Of the sixteen twin pairs compiled, ten were concordant and six were discordant. The concordance rate of 62.5 percent may be compared with the rates for MZ twins in Table 25-2, in which the median concordance rate is 48 percent. As a matter of fact, only two of the eleven rates in Table 25-2 are higher than the rate for the separated twins.

This finding again points to the importance of genetic factors in schizophrenia and certainly indicates that at least not all instances of concordance in MZ twins arise from psychological factors unique to such twins. Does not the high concordance rate of 62.5 percent indicate that such psychological factors are really irrelevant? No, because the twin pairs do not

constitute a systematic sample. For example, the first five pairs of separated twins reported were *all* concordant. Among the eleven pairs reported later, when sampling problems in genetic studies were being discussed with increased concern, five pairs were found to be concordant and six pairs were discordant. We do not know what the concordance rate would be for a systematically collected sample of separated twins, and indeed it might be an insuperable task to try to collect such a sample. Of the three pairs found through birth registers, all were discordant. Thus, the high rate of 62.5 percent might simply reflect the fact that concordant pairs were more likely than discordant pairs to find their way into samples, a factor that might also have accounted in part for the three highest MZ concordance rates in Table 25-2. If the true concordance rate for separated MZ twins could be shown to be less than the rate for reared-together MZ twins from the same population, the rate increment among the together-reared twins could reflect the influence of the psychological factors common to MZ twinship.

Summing the Major Evidence

What conclusions can we draw from such research findings with respect to the genetics of schizophrenia? Most important is the fact that all statistical findings are consistent with a genetic hypothesis, whether they derive from studies of two-generation families, of first-, second- or third-degree relatives, of twins reared together or apart, or of studies in which the principally

implicated variables of heredity and rearing are separated or unconfounded. In fact, if we were asked to foretell which persons are most likely to become schizophrenic, the best predictor now available to us is the simple fact of blood relationship to another schizophrenic: The more genes the individual shares with a schizophrenic, the greater is the probability that he will become schizophrenic. Our predictive success may not be great, except in the case of MZ twins, but it will be the best we can do. Since no other predictive criterion can presently approach blood relationship as a predictor of schizophrenia, almost all investigators who embark on so-called high risk longitudinal studies to explore the precursors of schizophrenia, even those who favor environmentalist explanations of the disorder, prefer to have index cases who are children of schizophrenics.

For such reasons, it seems reasonable to make the operating or working assumption that the case for considering a hereditary factor in the etiology of schizophrenia has been sufficiently demonstrated, and that further research will continue to support this assumption. Such a position does not by any means imply that we should rule out the possible contribution of environmental factors to the disorder. In fact, we know that such factors must play a role in schizophrenia because among all MZ twin pairs in which one twin is schizophrenic, in as many as half the pairs, or sometimes more, the co-twin, who has exactly the same genes, may not be clinically schizophrenic. Unfortunately, we have up till now only crudely formulated notions of what

some of these non-genetic factors may be, but knowledge of them will surely increase.

On the other hand, our operating assumption amounts to an open admission that we understand very little about the genetics of schizophrenia. True enough, we have an abundance of genetic theories that try to account for the statistical distributions obtained in a large number of studies that vary appreciably among themselves in many ways, but we are not yet in a position to make a clear choice among these theories. As a matter of fact, it may be that we should not really be talking about the genetics of schizophrenia at all, but about the genetics of schizophrenic disorders, a point that is implied in the studies that concern themselves with a broader spectrum of possibly schizophrenia-related disorders.

The Genetic Unity of Schizophrenic Disorders

The term "schizophrenia" has been applied to a wide variety of behavioral disorders that differ clinically to an appreciable extent, although they also share a number of common features or symptoms. Some of these disorders are represented by the classical Kraepelinian subtypes: simplex, catatonia, hebephrenia, and paranoia. Others are designated borderline, pseudoneurotic, or pseudopsychopathic. Some make a distinction between process and reactive, or nuclear and peripheral forms of schizophrenia. Some

disorders labeled symptomatic, atypical, or schizophreniform, are sometimes thought not to be true schizophrenia. Many people are called schizoid, many schizoaffective. Some age-related disorders such as preadolescent schizophrenia or early infantile autism are often thought to be variant forms of schizophrenia. Can there be a simple genetic explanation for all these forms of clinical disorder? Is it possible that some are genetically related and that some are not, and if so, how can we tell?

This is a key problem which we must resolve if we are to obtain any real understanding about the genetics of schizophrenic disorders. The topic and the research done on it are too extensive to review in appreciable detail here, but it has been thoroughly reviewed and evaluated elsewhere. We may state briefly, however, that decisions about whether two different forms of illness are genetically related are based on the finding that both occur in families and in twinships at a greater than chance frequency. On this basis, we may tentatively draw the following conclusions from the known literature:

1. The classical subtypes, catatonia, hebephrenia, and paranoia, are genetically related. Not enough research has been done with regard to the simplex form, which is apparently diagnosed with very low frequency, to draw any conclusion about its genetic relatedness to the other subtypes.

2. The process-reactive delineation is based primarily on a continuum of severity with regard to the clinical outcome of

schizophrenic disorders. Clearly, outcomes can be graded in many ways, all of which may have a dimensional character. In the main, it appears that most forms of schizophrenic disorder intermediate between the most hapless outcomes and those in which the subject eventually manages to achieve a fair to good level of social and occupational adjustment in the community are genetically related. However, the cases at the extreme end of the reactive continuum, those who have a good premorbid social, sexual, and personality history, who have a single schizophrenic-like episode of modest duration, and who make a full and relatively rapid recovery with no indication of residual integrative defects, probably do not share the genetic background that is implicated in other schizophrenic disorders.

3. Cases called borderline, pseudoneurotic, or severely schizoid or paranoid, are probably genetically related to cases with full-blown schizophrenia.

4. Preadolescent forms of schizophrenia are probably genetically related to adult forms of schizophrenia, but the literature on early infantile autism is too sparse and contradictory to permit any conclusions about its etiology or its possible genetic relatedness to schizophrenia.

5. To complicate the matter even further, there is some evidence to suggest that some other types of disorder, not usually thought of as being in the schizophrenia spectrum, may also be related to schizophrenia. These include some forms of

> neurosis, especially certain severe obsessive-compulsives, and the disorder called depersonalization neurosis; some forms of personality, e.g., those called odd or eccentric, cold and schizoid, or paranoid; some forms of psychopathy, including those with prison psychosis, cases called pseudopsychopathic schizophrenia, and cases called schizoid psychopathy. There is even some suggestion of genetic overlap between schizophrenia and manic-depressive psychosis. Some investigators have also linked schizophrenia with epilepsy and mental deficiency.

Clearly, this morass must be straightened out. Some influential psychiatrists and most clinical psychologists have proposed that we throw out the genetic hypothesis altogether, as well as all diagnostic labels, and the whole concept of mental illness to boot. However, proponents of such views are merely turning their backs on all the evidence for a genetic factor in schizophrenic disorder. Moreover, traditional psychiatric nosology, if it is to have any meaning at all, will probably best find vitality and real psychiatric relevance when at least some of the currently accepted diagnostic categories are grouped according to whether they share a common genetic etiological basis or not.

Genetic Theories of Schizophrenia

Modern theorizing about the genetics of schizophrenia began in 1916. Since then, we have never had a dearth of such theories and new ones

continue to turn up regularly. Rosenthal grouped them all into two main classes which he called monogenic-biochemical and diathesis-stress theories. These were in turn counter-posed to a class of theories that assumed no genetic basis at all for schizophrenia, and which he called life-experience theories. Monogenic-biochemical theories assume that a single pathological gene is necessary, if not sufficient, to produce schizophrenia. The schizophrenic phenotype itself may be dominant, recessive, or intermediate. The genotype is responsible for a specific metabolic error that produces the patterns of behavior that are pathognomonic of schizophrenia. Theories that invoke two single major genes in the etiology of the illness really belong in the monogenic-biochemical class as well, because they, too, assume that the two genes in combination produce a particular biochemical abnormality that causes the illness and its lingering psychological defects. It is such theories, and the research material on which they are based, that lead many scientists to devote their professional lives to search for *the* metabolic error in schizophrenia and the chain of biochemical aberrations it is assumed to produce.

According to diathesis-stress theories, what is inherited in schizophrenia is a predisposition to develop the illness. The nature of the assumed predisposition is usually vaguely conceived. Most often, it is formulated in terms of personality characteristics manifested early in life, such as social avoidance behavior, high anxiety, unusual habits or

predilections, lack of interests, self-preoccupation, or some other characteristics thought to be signs of deviance. However, since some hereditary deviation is postulated as an essential contributor to the illness, some metabolic digression must be assumed to have taken place. In diathesis-stress theory, however, this digression is usually thought to have manifested itself prenatally in some structural anomaly in the central nervous system itself, primarily in the form of a neural integrative defect. Thus, a diathesis-stress theorist would hold out little hope of finding a particular abnormal metabolite whose ebb and flow make for lesser or greater manifestation of schizophrenic pathology. Instead, he would be more concerned with trying to find aberrations in CNS neurophysiology. But he also would be especially interested in life stresses, biological or psychological, which he assumes are necessary to precipitate the schizophrenic psychopathology. Thus, this class of theories invokes a model of heredity-environment interactionism, as contrasted with monogenic-biochemical theory in which the role of environmental factors is thought to be minimal, or even in some instances, nonexistent. The implicated diathesis could result from a single gene, but most likely it involves a sizeable number of genes of small effect, called polygenes, whose combined effects are accumulative or additive, i.e., the more of these genes the individual harbors, the more vulnerable he is to stresses that trigger schizophrenic manifestations, and the more psychopathology he is likely to show.

Theories of genetic heterogeneity are difficult to fit into any particular model. Such theories hold that there may be several major single genes which are not alleles of one another, each of which may underlie schizophrenia. The concept has a kind of attractiveness in a clinical sense, since the range of clinical manifestations in schizophrenia is wide indeed, especially, for example, as compared to manic-depressive psychosis, and it is tempting to postulate a different gene for each different type of clinical manifestation. However, it will be difficult enough to show that even one major gene lies at the roots of schizophrenia. To demonstrate that there are *n* such genes will require an extraordinary research effort. Moreover, as has been pointed out above, the available literature on this problem provides considerable support for the view of genetic homogeneity (or unity) with respect to most forms of schizophrenic disorder. Vartanyan and Gindilis, however, cite evidence to support the view that chronic, deteriorating forms, and periodic forms with temporally discrete, acute attacks and complete recession of symptoms during remission, with only slight personality changes, are two genetically different forms (morphisms) of schizophrenia. In further support of heterogeneity theory, it should be noted that recent findings have turned up a greater than chance frequency of chromosomal abnormalities in schizophrenic populations. However, it may well be that the chromosomal abnormality does not provide any specific *Anlage* for schizophrenia, but rather that it imposes an unusual degree of psychological stress on the

affected individual, and that this increased stress makes for heightened vulnerability to the illness. This would be especially true of XXY phenotypic males (Klinefelter's syndrome) who suffer prolonged intense crises around their sex role and identity, and who may tend to develop schizophrenic disorders at a frequency greater than that of the population at large. Moreover, the possibility exists that some aneuploidic schizophrenics may represent phenocopies of the illness, in the same sense that some cases of Huntington's disease, lues, temporal lobe epilepsy, head injury, or amphetamine toxication, may present clinical pictures that simulate schizophrenia.

Which genetic theory is the most plausible, in the light of all the evidence to date? Actually, there are four competing theories that need to be mentioned.

In the 1940s, Kallmann's influence was at its height and his theory was the most highly regarded. He postulated a single recessive gene in a typical monogenic-biochemical model to account for his research findings. Thus, a schizophrenic had to receive one pathological allele from each parent. However, to account for deviations from expected Mendelian ratios, he postulated polygenic modifiers which made for more or less resistance to clinical manifestation. Most homozygotes—who carried the pathological gene in double dose—would develop schizophrenia, but those whose resistance to

manifestation was high would have a mild form of the illness, or would merely be schizoid. Some homozygotes, with very high constitutional resistance would even be clinically normal. Heterozygotes who carried only one allele would be schizoid or normal, depending on their degree of resistance.

In the 1950s, Böök introduced a theory in which the major gene was a partial dominant. This theory, as reformulated by Slater, attempted to account for data obtained in several studies. It was statistically more sophisticated and elegant than Kallmann's, and supplanted it in general favor. The theory assumes that only relatively few individuals are homozygous for the pathological gene, but that all these homozygotes become schizophrenic. Assuming an estimated 0.8 percent frequency of the illness in the population, Slater was able to show the rate of schizophrenia expected in sibs and children of a schizophrenic, as well as in children with both parents schizophrenic, with varying degrees of the gene frequency in the population and varying degrees of gene penetrance. A best fit to the selected known data indicated a gene frequency of fifteen per thousand, and a manifestation rate of 26 percent in heterozygotes who accounted for 97 percent of all schizophrenics, the other 3 percent being homozygous.

In the 1960s, two noteworthy theories appeared. One, by Karlsson, has not caught on, but it is interesting in that it assumes two separate major genes

in the causation of schizophrenia, one recessive, the other dominant, and attempts to account genetically for schizophrenics' relatives who are productive leaders, gifted and creative. Along with the theories of Kallmann, Book, and Slater, it is essentially a monogenic-biochemical theory.

The second genetic theory to be launched successfully in the 1960s is the one most widely accepted today, not only by genetically minded psychiatrists, but by many investigators who had previously rejected any genetic role in schizophrenia. It is a simple polygenic theory that also postulates a threshold effect in regard to process schizophrenia. It is a model that is prototypical for diathesis-stress theories and it accounts most readily for all the known statistical distributions regarding schizophrenic disorders without postulating such variables as genetic modifiers, constitutional resistance, manifestation rate, or penetrance. It also accounts nicely for the gradation of disorders subsumed in the schizophrenia spectrum and for the relatively important role played by non-genetic factors in the etiology of clinical schizophrenia. The threshold effect implies that process schizophrenics harbor relatively more of the polygenes and/or are subjected to greater life stresses, the latter potentiating the former, so that latent biological capacities for the development of secondary and gross primary Bleulerian signs are unleashed. The task for adherents of this theory is to identify the implicated genes and their number, to determine how they achieve the quality of additivity, and to understand how environmental

factors trigger the threshold effect that culminates so often in chronic schizophrenia.

It is to be hoped that the 1970s will be the decade in which clear and irrefutable findings will settle at least some of the issues regarding this fundamental psychiatric problem. Despite all the statistical evidence to support their position, proponents of the genetic viewpoint will probably not be able to maintain the high credibility of their position in the long run, unless the implicated biological defect is finally discovered and elucidated. At the present time, many laboratories and independent investigators are searching for the presumed metabolic or enzymatic abnormality that they believe must be present in schizophrenia, but as of this writing the most provocative findings are only suggestive. With respect to a possible neurological integrative defect, in a study as yet unpublished but described briefly by Rosenthal et ah, Marcus was able to discriminate children who had a schizophrenic parent, and matched controls with normal parents on the basis of a neurological examination. This finding is promising but needs to be replicated. Many researchers and theoreticians are optimistic about a breakthrough in the 1970s. We can only wait and see.

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Notes

1 The opinions expressed herein are those of the author and do not necessarily express the position of the National Institute of Mental Health.