searches for the mode of genetic transmission in schizophrenia: reflections and loose ends*

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Although the idea that mental illnesses might be heritable has existed in Western civilization for many centuries, it was research conducted early in this century which clearly documented the fact that such mental disorders tended to cluster in families. Pedigrees were established to document such findings. Investigators examined twins, both monozygous (MZ) and dizygous (DZ), and found that MZ twins were much more concordant than DZ twins with respect to the mental disorder. The first such studies were carried out primarily with respect to schizophrenia. Even with this earlier evidence, skeptical scientists still maintained the position that these findings were not crucial, and were still inconclusive in establishing the heredity hypothesis. However, the findings of the adoption studies carried out in the 1960s and 1970s (Heston 1966, Karlsson 1966, Kety et al. 1968 and 1975, Rosenthal et al. 1971, and Wender, Rosenthal, and Kety 1968) developed new findings that strongly indicated an inherited basis for schizophrenia. Most scientists have now accepted this long-standing idea. In fact, the findings of the adoption studies stimulated a rash of research which intended to discover the biological root causes of schizophrenia.

It had long been known, beginning with Rüdin's monograph in 1916, that the mode of genetic transmission in schizophrenia did not follow any simple Mendelian pattern. With the new evidence that hereditary factors played a major role in the development of schizophrenia, however, scientists began to develop new strategies for determining the mode of genetic transmission in this illness, and the passion for carrying out such studies has continued. Much ingenuity has been expended in these attempts. At times it seemed that we were about to find the evasive mode, but the search still goes on.

Currently, however, many scientists belittle the importance of a genetic factor in schizophrenia. Such a finding, they claim, by itself throws little light on the problem and adds little to our understanding of schizophrenic illness. But if we could identify the mode of genetic transmission in schizophrenia, the acceptance of the relative contributions of genetic factors in schizophrenia could be increased appreciably. Thus, apart from the current pharmacological studies of schizophrenia, a major task at this time is to unravel the mystery of the mode of genetic transmission in this illness.

For these reasons, an attempt to review some of the different major efforts to nail down the mode of transmission problem, evaluate the effectiveness of the concepts or strategies employed, explore the preferences of the investigators regarding the mode of transmission problem, and discuss some related issues should be worth the effort. This attempt will confine its comments to studies that were carried out by investigators since 1950.

Some Selected Models of the Mode of Transmission

Kallmann (1953) proposed a model for a recessive single gene that could be modified by another variable which he called the "constitutional resistance to manifestation." Kallmann believed that the constitutional resistance variable was a polygenically determined trait. With respect to the culpable single gene, an individual could be homozygous or heterozygous. Individuals who
were homozygous for the gene were much more likely to develop schizophrenia than individuals who were heterozygous. Degrees of constitutional resistance could increase or decrease the tendency to develop schizophrenia even in a homozygote, however, depending on whether the constitutional resistance was weak or great. With various combinations of homozygosity or heterozygosity reacting with high or low degrees of constitutional resistance, Kallmann believed that he could account for cases called schizoid, mild schizophrenia, and deteriorating schizophrenia. It is somewhat ironic that Kallmann, who was so well known for his twin studies of schizophrenia, should propose such a theory. Since MZ twins share the same genes and presumably the same degree of constitutional resistance, except for a minimal number of cases, it would be difficult for him to explain why almost all MZ twins should ever be discordant at all. This fact by itself diminishes the possible validity of his theory.

Although the early attempts to discover the mode of transmission through the use of pedigrees were not productive, they eventually helped to generate new ways of looking at pedigrees, with the hope that a fresh look at this research strategy might be revealing. Probably the best designed study for this purpose was carried out by Mitsuda in Japan (1967). Mitsuda collected 88 schizophrenic patients who had been hospitalized from 2 to 5 years. These patients were defined by Mitsuda as recovered, chronic, or periodic, according to their respective outcome. Mitsuda then divided the subjects into four groups, according to their respective outcome. The four groups were (1) no defect, (2) psychic rapport well preserved, (3) psychic rapport nearly absent, and (4) severe defect. Mitsuda then examined all cases for the apparent mode of inheritance, and divided the subjects roughly into three groups: dominant, recessive, and intermediate. Mitsuda found that, with respect to clinical course, chronic subjects were much more numerous than recovered subjects in the recessive group. An opposite tendency was found in the dominant group, and the intermediate group had a position about in between. Mitsuda concluded that, according to the genetic classification, the dominant group contained more prognostically favorable cases, while the recessive group had relatively more prognostically unfavorable cases, and the intermediate group was somewhere in between. Although many questions can be raised about this study, the research strategy is an interesting one; perhaps it should be replicated with more stringent criteria. In effect, Mitsuda proposes a theory of heterogeneity, in which at least two, and possibly three modes of genetic transmission are implicated. Although theories of heterogeneity are fairly popular, it should be clear that, if they are correct, our prospects of unraveling the mode of genetic transmission in schizophrenia are less than we have hoped. For this reason, it may be preferable to assume a single mode of transmission and try to disprove the single mode theory.

In 1963 Rosenthal proposed to reduce the abundant theories of the cause of schizophrenia to three classes of theory, which he named Monogenic-Biochemical Theory, Diathesis-Stress Theory, and Life-Experience Theory. In 1970 he showed how the theories compared with one another regarding fundamental issues of the causes of schizophrenia; e.g., biological or genetic unity, what is inherited, how it is manifested, role of environment, clinical subtypes, severity of illness, remission, and premorbid personality. This classification provided a conceptual framework which could possibly reduce the dead ends in the search for causes.

The first more modern and sophisticated attack on this problem was carried out by Slater (1965), who built his model upon the earlier work of Böök (1953). The Slater-Böök model assumes that the mode of genetic transmission involves partial dominance of a single major locus with two alleles. Slater also made a second assumption—that all individuals homozygous for the pathological allele will manifest the illness, but that heterozygotes may or may not become ill. A third assumption involved the best estimate of the population incidence of the illness. Accepting the reports of earlier studies, he assumed that the population incidence of schizophrenia was 0.8 percent. Employing these assumptions, Slater was now in a position to calculate the proportion of heterozygotes in the population who manifest the illness as a function of different possible gene frequencies. For additional data, Slater employed Kallmann's figures for the rates of schizophrenia in the siblings and the parents of a proband schizophrenic. Slater also used Elsässer's (1952) figure for the frequency of schizophrenia in children born to two schizophrenic parents. These data agreed well with an expectation for a gene frequency of 0.015 and a corresponding manifestation rate of 26 percent in heterozygotes. Homozygotes accounted for 3 percent of all schizophrenics, whereas 97 percent of all schizophrenics were heterozygotes. The
Slater-Böök approach to the problem set the general style for most of the later, more contemporary studies. Such a research strategy, however, raises many questions. Is there any way to prove or disprove the model? Would the figures have been changed appreciably if figures from studies other than Kallmann's or Elsässer's had been chosen? Slater also found it difficult to fit the known twin data into his model.

During the same year of Slater's report, another novel imaginative approach to the problem was published (Falconer 1965). The author's goal was to determine heritability values in diseases not inherited in a simple manner, using quantitative genetic methods. Heritability was estimated from the degree of resemblance between relatives, expressed as a correlation or regression coefficient. When the mean liabilities of two groups are compared, one must make the assumption that the variance of liability is the same in both groups. Several important concepts were included in this model, especially two that were originally proposed by Carter (1961 and 1963). One was the concept of liability, which Falconer explained as follows: "To overcome the difficulty of the all-or-none character of a disease we have to suppose that there is in fact an underlying gradation of some attribute immediately related to the causation of the disease" (p. 52). Falconer rejected the term susceptibility because it implied innate tendencies, as distinct from external circumstances. Liability included both innate tendencies and external circumstances that might be involved in the development of the disease.

The concept of threshold represents the point on the scale of liability above which all individuals are affected and below which all are normal. The variation of liability is arranged so that it is normally distributed, and the degree of liability can be measured in terms of the standard deviation. The method is not applicable to single-gene diseases or to situations in which the variation of liability is discontinuous, but it does apply to diseases with a polygenic component or to conditions with few genes where their effects are small, relative to the nongenetic variation. Variables involved in the analyses include the mean liability of the general population, the mean liability of affected individuals in the general population, the mean liability of relatives, and the proportion of individuals with liabilities exceeding the threshold—i.e., affected. Thus, the model permits the possibility of determining the heritability of various polygenic diseases, including schizophrenia, should that illness prove to have a polygenic basis.

With such an attractive model so readily available, its application to the genetics of schizophrenia was bound to occur quickly. Gottesman and Shields (1967) were the first to carry out such an analysis, using MZ and same-sex DZ twins, parents, sibs, children, and aunts and uncles, and setting the population incidence at both 1 percent and 2 percent. Thus, many heritability values were obtained, using different samples of subjects. The values of the heritability of the liability to schizophrenia, Falconer's $h^2$, ranged between 45 percent and 106 percent [sic]. The size of the standard errors ranged between 3 percent and 23 percent. The authors acknowledge that the method is subject to errors, that their "findings are far from monolithic," and that probably the underlying assumptions have not been fully met. They note that the heritability of liability to schizophrenia across samples is quite substantial, however, and they caution that the heritability is a property not only of the trait but also of the population sampled and its related environmental milieu.

Falconer was concerned about sources of error in his model. He noted two chief limitations from which error may arise: (1) the assumption of a continuous distribution of liability, and (2) the assumption of equal variances. He pointed out, too, that the method breaks down if a major gene is contributing to the cause of the disease. A gene that did not produce Mendelian ratios and that manifested incomplete penetrance could cause a discontinuity in the distribution of liability. Nongenetic sources of error included the fact that family members are exposed to similar environmental factors and life styles and that their liabilities to a disorder might be correlated for purely environmental reasons.

Thus, there are several possible factors that could have brought about the heterogeneous findings in the Gottesman-Shields analysis. From the standpoint of discovering the mode of genetic transmission, however, one can infer only that a multifactorial mode is possible but it will be difficult indeed to prove. It is possible, too, that a major gene is causing a discontinuity in the distribution of liability and that we are confronted with a confounding of both a major single gene and a polygenic system, a possibility that Kallmann had earlier envisioned.

It is important to note that the concept of heritability is controversial, and that it applies primarily to populations rather than to traits. In earlier years, some formulas for computing heritability were devised and were later roundly criticized. In an earlier article, Kidd and Cavalli-
Sforza (1973), who used a mathematically more precise method for estimating $h^2$, judged that the mean heritability estimate from among the several Gottesman-Shields analyses with the Falconer model was about 80 percent. They then calculated heritability for schizophrenia as an all-or-none trait, using discrete scores for normal and affected individuals, and found that the heritability values were between 20 and 40 percent for a single gene model. In another analysis, they constructed a single gene model with an underlying continuous liability that was not normally distributed and obtained a heritability of liability in the range of 0 to 15 percent. The authors conclude that heritability provides no information about etiology and that the heritability of schizophrenia is not a meaningful concept or statistic.

A two-gene theory of the mode of transmission was proposed by Karlsson (1966), who thought that in schizophrenia we were dealing with a mechanism of modified dominance. The mechanism involved a basic gene designated S, with a mutant counterpart designated as s. The frequency of the s gene was calculated to be 0.03. The genotype Ss leads to a phenotype that differs from that occurring with the genotype SS, but usually no disease results from the s gene. A gene $P$, with a mutant allele $p$, was possibly metabolically related to the $S$ gene, but the two were inherited independently. The $p$ gene frequency was calculated to be 0.4, and it acted as a classic recessive. $PP$ and $Pp$ individuals were phenotypically the same, but only $pp$ persons showed abnormality. Different combinations of the two genes led to personality types named normophrenic, tensesphrenic, superfrenic, schizophrenic, and autistic or retarded.

Karlsson's model has some attractive features. Unlike any other, it predicts distinctive personality types that derive from specific genotypes that he describes at fair length, but there have been no independent studies to validate the model, as far as can be determined.

Kidd (1975) combined the mode of inheritance problem with the problem that schizophrenia continues to be maintained in the population at a high frequency, even though it is evolutionarily detrimental, and even though schizophrenics manifest lower fertility than the population at large. Kidd thought selective mechanisms that could lead to a balanced polymorphism might be involved. He noted that, since the heterogeneity of values for the incidence of affected relatives of schizophrenics was so great, a precise estimate was not possible. Employing analyses he had carried out with his colleague (Kidd and Cavalli-Sforza 1973), he used the “solutions” they had obtained as the basis of his report.

The genetic model employed postulated only two alleles, $S_1$ (normal) and $S_2$ (pathological). Two assumptions were made: (1) random mating resulting in Hardy-Weinberg ratios of the genotypes, and (2) absence of correlation in environmental factors among relatives. The model is general, encompassing all other two-allele single locus models, from recessive to dominant to intermediate, and allows nongenetic factors to produce the schizophrenia phenotype. In the single major locus model, the general incidence and the incidences for two classes of relationship (parent-offspring and sibling-sibling) combine to yield an infinite number of solutions.

Equations are employed which relate general incidence, additive variance, and dominance variance to the allele frequency and the penetrances for the genotypes with 0, 1, and 2 schizophrenogenic alleles, respectively. The variances are based on the observed correlations, which are calculated by arbitrarily coding the individuals 0 or 1 for absence or presence of the trait.

Following this procedure, Kidd found the general incidence to be 0.0087. The predicted incidence for different groups of relatives of an affected proband are as follows:

- MZ co-twins, incidence = 0.375
- DZ co-twins, incidence = 0.122
- parent-offspring, incidence = 0.052
- aunt-uncle or niece-nephew, incidence = 0.030
- dual matings, incidence = 0.341
- matings of an affected and a normal person, incidence = 0.052.

$S_2S_2$ homozygotes never constitute more than 90 percent of those affected, and $S_1S_1$ homozygotes never constitute less than 9 percent of those affected.

Kidd finds considerable uncertainty in parameter values and in the magnitude of possible selective factors. If a single major locus is involved, the frequency of the pathological allele is about 10 percent, and the average selective advantage of unaffected heterozygotes would not need to be more than 5 percent to maintain the allele in the population. Searching for a selective advantage among unaffected relatives of schizophrenics therefore appeared futile.

Thus, Kidd presents a highly sophisticated approach to the problem, but his goal evades him. He concludes that “though present analyses are very ambiguous, many possible avenues for future research are suggested.”
The possibility exists that bisexuals may be more fertile than the population at large, and that such individuals contribute to the maintenance of homosexuality, but I am unaware of any evidence regarding a possible increased fertility in bisexuals. However, there is no reason to believe that homosexuality, which has a history at least as long as schizophrenia's is gradually disappearing, and it may in fact be increasing, although good data on this point are not easy to find. Is there any reason to suppose that a physiological-advantage hypothesis (e.g., Huxley, Mayr, and Hoffer 1964) might apply equally to homosexuality and schizophrenia? Or is it possible that we are overlooking other explanations regarding the maintenance in the population of major behavioral disorders that involve a genetic input?

Matthysse and Kidd (1976) have provided us with the most up-to-date attack on the transmission problem. In the main, they have compared the two competing models, the single major locus or monogenic model, and the multifactorial or polygenic model. They note that neither model incorporates cultural transmission, and they assume that environmental factors are randomly distributed for both models. As in previous studies, unknown parameters had to be estimated. In the monogenic model, these parameters are the frequency of the pathological allele, the likelihood of “phenocopies,” and the incidence of schizophrenia in heterozygotes and homozygotes. Both models are said to predict genetic heterogeneity in schizophrenia.

In their discussion of the multifactorial model, which assumes a large number of independent genes that contribute small amounts respectively to risk, the authors compare this model to IQ in an innovative way. Just as IQ scores are based on scale tests that involve an underly-

ing normal distribution, in the same way, values could be postulated for a scale of vulnerability to schizophrenia—this scale called the SQ, or schizophrenia quotient. As in IQ, the scale has a normal distribution, with a mean of 100 and a standard deviation of 15. SQ below 100 is associated with a risk near zero, while SQ well above 100 involves a risk near 100 percent. The authors then try to fit the appropriate parameters into the monogenic model, and SQ (50 percent) and SQ (99 percent) into the polygenic model. The data used in the analyses include incidence in MZ twins, in offspring of two schizophrenic parents, in siblings, and in the general population. The calculations require in both models that the risk for offspring does not exceed the risk for siblings.

It would take too long to describe all the findings of this study, but we will mention some that may have special interest.

In the monogenic model, the calculated values for MZ twins and dual mating offspring are lower than the values cited in the literature. The authors conjecture that the low values may have been much influenced by special environmental effects. For the lowest gene frequency used, 0.3 percent, 100 percent of the homozygotes become schizophrenic. In the population as a whole, 99.3 percent are genetically normal, 0.7 percent are heterozygotes, and 0.001 percent are homozygotes.

In the multifactorial model, the predicted values for MZ twins and dual mating offspring are better than those in the monogenic model, but the errors are in the opposite direction. With respect to SQ, 9.1 percent of the schizophrenic population are predicted to have a genetic vulnerability (SQ) so high that their risk would be 99 percent or greater were they to start life over again in a new environment. The model implies that, in 1 out of 11 schizophrenics, the illness is almost completely genetically determined. Matthysse and Kidd have provided us with the most heuristic analysis of the genetic contribution to schizophrenia thus far. Whether the SQ analogy can lead to new conceptualizations of the problem remains to be seen. One problem in their analysis arises from their requirement that the risk for offspring must not exceed the risk for siblings. In comparing studies of morbidity risk for siblings and offspring of a schizophrenic (Rosenthal 1970), however, it was found that the median risk for offspring was 9.7 percent, whereas the median risk for siblings was 7.5 percent. Perhaps these differences can be accepted as close enough to equality. Among offspring, the risks in the
studies available ranged from 7.0 percent to 16.9 percent, whereas for siblings, the risks ranged between 3.3 percent and 14.3 percent. Thus, the preponderant findings suggest that morbidity risk may not be equal in the two groups, and that the risk tends to be consistently higher for offspring, but only moderately higher. It is not clear what might lead to this inequality, but the authors' equality assumption may have been a bit misleading. The authors point out that, according to any mode of genetic transmission, the incidence in sibs must be greater than, or at least equal to, the incidence in offspring. Any deviation from this must be caused by other factors, which, of course, might be hard to identify.

Discussion

After having reviewed these diverse approaches to the mode of transmission in schizophrenia, we must raise the key question: What have we learned about the transmission problem from these studies? We find a modest consensus among investigators concerning the single major locus model that the implicated major gene functions as a dominant or partial dominant, rather than as a recessive. Karlsson, however, thinks that a recessive gene is involved in schizophrenia, as well as a partial dominant, and Kallmann also thought in terms of a recessive gene. Thus, even in assessing this issue, there is no clear consensus regarding the mode of action of the single gene.

However, there does seem to be agreement on zygosity. For example, three studies emphasize the relatively low frequency of homozygotes in the schizophrenia population and the very high manifestation rate in these patients, which is thought to be close to 100 percent. Unfortunately, no empirical data are available to validate these predictions. Marked differences, ranging from 0.015 to 19 percent, also occur in the estimates of the frequency of the pathological gene in the population at large.

Perhaps it is even more distressing to be reminded that we still are unable to decide whether a single gene or a multifactorial model is correct. Clearly, the authors who have searched for the mode of transmission have exercised considerable ingenuity in their efforts, but, for their own reasons, they have not always considered aspects of schizophrenia other than the frequencies of the illness in relatives and populations. Some of these aspects may suggest additional approaches. For example, the authors appropriately bemoan the wide range of values that occur in different studies of the frequency of schizophrenia in relatives of probands. They reasonably fall back on averaged values, none of which may be meaningful. It is at least possible that the respective values found in the original studies are true values for the samples evaluated and that these true values vary so much across samples because of factors we do not yet understand, or cannot yet identify, be they genetic or not.

None of the authors have taken into account cases that might not be diagnosed as chronic schizophrenia but that may be genetically related to that illness. Rosenthal (1975a and 1975b) and his colleagues refer to such cases as schizophrenia spectrum disorders. The authors of searches may have ignored such cases because they may have thought that there was not yet enough data to warrant an acceptance of the spectrum concept; indeed, a conservative position on this matter is fully justified. However, it might be helpful in future studies to include such cases. Support for the concept of spectrum disorders was published by Reich, James, and Morris (1972).

In the studies presented above, none dealt with the group of cases described as preadolescent schizophrenia. It is true that such cases are not purported to occur in abundance: but since systematically obtained samples of such subjects are rare, many cases may be overlooked or not reported. The point to be made is that the values employed by the authors may be highly fallible because we still do not have sufficiently stable data around which we can launch such studies with at least some promise of a worthy yield. It is clear that the multifactorial model is a prime candidate for the mode of transmission. Indeed, Matthyssse and Kidd (1976) note that the fit of the multifactorial model to the incidence estimates for MZ twins and offspring of dual matings is somewhat better than for the single major locus model. However, Falconer's (1965) approach to the polygenic model has added a new look to it, especially in regard to the key concepts of liability and threshold. Falconer's major goal is to estimate heritability values in polygenic diseases, especially the heritability of liability. Precisely what the liability to schizophrenia involves is just what we want to know. That is, what makes a person more or less vulnerable in different degrees? The models cited
above do not help us to understand the nature of the
liability. Whether they help us to determine the degree of
liability is another matter. This issue is approached by
determining the heritability of the liability as it was
discussed earlier. We noted then that the concept of
heritability was controversial and probably not robust.
Others have pointed out that heritability values vary,
depending on the range of relevant environments—the
greater the range, the lower the heritability. Heritability
values are changeable. McMahon (1968) reminds us that
heritability was controversial and probably not robust.
Heritability depending on the range of relevant environ-
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heritability was controversial and probably not robust.
Discussed earlier. We noted then that the concept of
determining the heritability of the liability as it was
likely to distinguish the subtypes in searches and models of the mode of transmission.

Other aspects of schizophrenia are also overlooked in
the searches reviewed, some of which may bear on the
transmission issue. For example, although it is generally
accepted that the incidence of schizophrenia is the
same for males and females, there are instances in which
sex ratios vary. If we concern ourselves only with pre-
adolescent schizophrenia, we find a predominance of
males in both singletons and twins. Male-female ratios
are 12:5, 15:10, and 37:13 for MZ, DZ, and single-born
index cases, respectively (Rosenthal 1970). These sex
differences are striking indeed: what causes the differ-
ces is another matter. Also worth noting is a repeated
finding that among adult schizophrenics, although ad-
mision rates are about equal for the sexes, males are
more likely to be admitted earlier than females. Various
explanations of the earlier admissions for males have
been proposed, almost all involving familial or environ-
mental factors. The situation is reversed, however, in
the affective disorders with females tending to be
admitted earlier than males. Thus, although environ-
mental factors may well contribute to the age of first
admission, it is likely that the nature of the illness,
as well as genetic factors associated with the illness, is
an important factor in age of admission. We know, too,
that most cases of schizophrenia occur during puberty,
adolescence, and postadolescence, and it may be that the
genetic factors associated with onset of these physio-
logical changes are the same ones associated with time
of first admission in the sexes. Searches for mode of
transmission may need to take these factors into ac-
count.

One of the most tantalizing aspects of schizophrenia
is the large range of symptoms manifested in this ill-
ness—alteration of thinking, feeling, and relation to the
external world; loss of unity in the personality; frag-
mentation of ideas that become connected in illogical
ways; loss of continuity in thought associations; emo-

tional deterioration; ambivalence; autism; deterioration of attention or lack of active interests; abulia; lack of goal; disregard of reality; confusion; hallucination; delusion; excitatory periods; mutism; mannerisms and stereotyped movements; and peculiar motoric signs. There is no need to list them all.

The point at issue is this: Should we expect a single gene to generate such an extraordinary range of symptoms? We know that pleiotropy does occur in other single gene diseases, but in this illness its range would seem to be unusually wide, especially when compared to most other psychiatric disorders. In considering a multifactorial model, what is the likelihood that multiple genes of small effect can generate such an exceptional variety of such serious symptoms? We do not know the answer to these questions, but we can at least speculate about them. We can, for example, assume alternative models. Among these, the simplest may be a two-locus model. We noted earlier that Karlsson favored such a model, which generates four different genotypes. It seems probable that four different genotypes are more likely to generate a much wider range of symptoms than a single-locus model. Perhaps we should explore the two-locus model more thoroughly, since it allows for many more combinations of gene interaction. It is noteworthy that, as a result of his study, Karlsson could identify and describe four personality subtypes as well as a smaller group that he regarded as retarded or autistic. In the classical subtypes of Kraepelin and Bleuler, although changes occurred, in the end the subtypes fell into three or four groups—depending on how simple schizophrenia was regarded at any time. The rough parallel in which both Karlsson and Kraepelin-Bleuler discriminate approximately four subtypes may be without meaning, but perhaps the association should be explored. In any case, there may be some grounds, not very strong or convincing, for exploring further the two-locus model. As of now, the major locus and multifactorial models have not been especially productive in increasing our understanding of schizophrenia, but perhaps new approaches to the problem will be forthcoming.

It may be that a fresh start is in order, one which would require a national or international collaborative study that would use “blind” examiners and tests of various kinds—behavioral, biological, and pharmacological. The value of such a study would be in employing standard diagnostic criteria and sophisticated assessments of the incidence of schizophrenia and its genetically related disorders in extraordinarily large numbers of probands, in the relatives of schizophrenics, and in a control group as well. Even so, we should be prepared to wait a long time before we can nail down the mode of transmission in schizophrenia, though we need not despair of eventually giving the final blow to the nail.

References


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