**The Genetics of Schizophrenia: A Review**

by Seymour Kessler

Abstract

The evidence suggesting that genetic factors are involved in the etiology of schizophrenia is reviewed. Despite methodological and other difficulties, independent lines of research—family, twin, and adoption studies—point in a common direction: Persons genetically at risk for schizophrenia are more likely to become affected than those who are not. Current attempts to understand the mode of inheritance of the gene or genes involved have become increasingly sophisticated and, consequently, less accessible (and possibly useful) to clinicians and nongeneticist researchers.

Guidelines are provided for the provision of genetic counseling to affected persons and their relatives. Such counseling is frequently enmeshed with multiple psychosocial (rather than strictly medical) issues and should be provided by professionals with appropriate training and experience in psychotherapy.

In retrospect, I realize that the tendencies of polarization and regression are inherent within the very subject matter about which we are concerned. Schizophrenia touches us in very personal ways in our struggles to understand its nature and etiology. Its mystery and elusiveness attract us to any sign of certainty or glimmer of understanding, be it biochemical or psychodynamic. Thus, possibilities and hypotheses quickly become dogmas. Also, as schizophrenic families are marked by disturbances of communication, perhaps we too, students and researchers of schizophrenia, are not immune to communication difficulties among ourselves. No wonder then, humor is mistaken for hostility and irony read as ire.

With these thoughts as a preamble, I will move on and attempt to review briefly here the pertinent contemporary evidence suggesting that genetic factors contribute to the etiology of schizophrenia. I then plan to comment on some recent lines of research pertinent to genetic investigations of schizophrenia, and lastly, I will address myself to some of the issues present in the genetic counseling of this disorder. No attempt will be made to be totally comprehensive, and the reader desiring a more thorough overview should consult Rosenthal (1970), Slater and Cowie (1971), Gottesman and Shields (1976), and other appropriate reviews of the literature.

There are three major lines of evidence implicating a genetic involvement in the etiology of schizophrenia: family studies, twin studies, and...
and adoption studies. Each will be discussed in turn.

**Family Studies**

The family study method is based on the observation that genetic disorders show a familial concentration. Relatives of a proband or index case share a greater proportion of their genes in common than unrelated persons. Thus, to the extent that a disorder is genetically determined, relatives of affected individuals are more likely to have inherited the predisposing gene or genes than persons in the general population. A common strategy in human genetic studies, then, is to compare the prevalence of the disorder among relatives of affected persons to the base rate of the disorder in the general population. If the rate of the disorder among the former is significantly higher than among the latter, a genetic contribution to the etiology of the disorder is suspected. Further study of specific pedigrees frequently reveals information on the mode of transmission of the gene or genes involved. Thus, a disorder which shows a pattern of transmission from unaffected mothers to one-half of their sons suggests that an X-linked mode of inheritance is involved; a pattern involving affected parents with affected children is suggestive of a dominant mode of transmission, and when groups of unaffected parents have one-quarter of their children affected, a recessive mode of transmission is suggested. These traits or disorders are the ones that follow relatively simple, Mendelian patterns of inheritance and yield predictable ratios of affected to nonaffected progeny in specified kinds of matings. As we shall see, schizophrenia does not fall into this category.

Many studies have been carried out worldwide to determine the incidence rate of schizophrenia in the general population. The rates found range from 0.35 to 2.85 percent, with a mean around 0.85 percent. This mean is a widely accepted base rate of schizophrenia in the general population in the United States and in European countries. The differences between various countries with respect to the incidence of schizophrenia may reflect changes in diagnostic criteria, sampling biases, and/or varying psychosocial and other environmental conditions predisposing to schizophrenia. It is also conceivable that the different populations represent differing gene pools, and hence differential frequencies of the gene or genes predisposing to schizophrenia.

The frequency of schizophrenia among different classes of relatives of probands is shown in Table 1. The table shows the pertinent data as compiled by two different investigators in the field, Rosenthal (1970) in the United States, and Slater and Cowie (1971) working in Great Britain. The former tends to use median values whereas the latter investigators favor means. Irrespective of the method of averaging used, the results are quite similar for any given degree of relation to an index case. Thus the risk for a sib of an affected individual, given that neither parent is affected, ranges from 6.7 to 8.2 percent. When one parent is affected, the risk rises to between 12.5 and 13.8 percent.

Examination of Table 1 reveals that for all close relatives of an index case, the risk for schizophrenia is decidedly higher than that for individuals in the general population; the rates vary from between 2 and 46 times higher than the average risk for schizophrenia in the population. Among first-degree relatives of a proband, the average risk for schizophrenia is roughly between 8 and 10 percent. The risks for relatives are also graded so that relatives who share relatively less of their genes in common with an affected individual show a lower expectancy for schizophrenia than those who share more of their genes in common. Thus, overall, first-degree relatives show higher risks for schizophrenia than second-degree relatives and the latter, taking into consideration some amount of sampling error, appear to show a higher risk for schizophrenia than their third-degree relatives.

This distribution of risks among relatives of affected individuals is consistent with a genetic hypothesis. Also consistent is the fact that the risk for schizophrenia increases as the genetic loading increases; children, both of whose parents are affected, show a decidedly higher risk than those with only one affected parent.

An apparently consistent finding among first-degree relatives of schizophrenic probands is that sibs and children seem to have a higher risk for schizophrenia than do parents. This phenomenon has been found in several different studies, and the reasons for it are not entirely clear. Rosenthal (1970) has speculated that multiple factors may affect the self-selection for parenthood of preschizophrenic individuals. These include the ability to find and hold employment, assume marital responsibilities, sex drive, socioeconomic, cultural, personality, and other variables.

**Twin Studies**

Another classical line of approach used to demonstrate genetic involvement in the etiology of schizophrenia is the twin method.
Table 1. Estimates of the risk for schizophrenia among relatives of schizophrenics (%)

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Parents</td>
<td>4.2</td>
<td>4.4</td>
</tr>
<tr>
<td>Sibs (neither parent affected)</td>
<td>6.7</td>
<td>8.2</td>
</tr>
<tr>
<td>Sibs (one parent affected)</td>
<td>12.5</td>
<td>13.8</td>
</tr>
<tr>
<td>All sibs</td>
<td>7.5</td>
<td>8.5</td>
</tr>
<tr>
<td>Children</td>
<td>9.7</td>
<td>12.3</td>
</tr>
<tr>
<td>Children (both parents affected)</td>
<td>35.0(^1)</td>
<td>36.6–46.3</td>
</tr>
<tr>
<td>Half-sibs</td>
<td></td>
<td>3.2</td>
</tr>
<tr>
<td>Aunts and uncles</td>
<td>1.7</td>
<td>2.0</td>
</tr>
<tr>
<td>Nephews and nieces</td>
<td>2.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Grandchildren</td>
<td>2.6</td>
<td>2.8</td>
</tr>
<tr>
<td>First cousins</td>
<td>1.7</td>
<td>2.9</td>
</tr>
</tbody>
</table>

\(^1\)Excludes Kallmann's (1938) study.

This method is based on the observation that there are two classes of twins, monozygotic (MZ) and dizygotic (DZ) twins; identical and fraternal twins, respectively. The former derive from a single fertilized ovum, whereas the latter result from two separate fertilizations. MZ twins are genetically alike, whereas DZ twins are no more genetically alike than ordinary siblings. If a disorder is genetically determined, then one might expect that pairs of MZ twins would show significantly higher concordance rates than pairs of DZ twins.

Nearly a dozen major twin studies of schizophrenia have been carried out worldwide, and all show higher rates of concordance among MZ than DZ twin pairs. In the studies carried out before 1965, MZ concordance rates are 60 percent or more, whereas in those conducted since that time, average MZ concordance rates tend to be lower. These differences probably reflect changing diagnostic styles and variations in sampling and statistical procedures. The older studies generally involved chronically affected resident hospital populations, whereas the more recent studies, summarized in table 2, employed consecutive admissions or data gathered from birth registers.

Concordance rates may be calculated in one of several ways. Table 2 shows the results of two common methods of determining concordance, the pairwise and the probandwise methods. In the pairwise method, one calculates the proportion of all pairs in which both twins are affected, whereas in the latter method, the concordance rate is based on independently ascertained affected twins. Since members of any given pair of twins might be counted twice using the proband method, concordance rates calculated this way tend to be higher than those of the pairwise method. Calculated in either way, the results are impressive and demonstrate in each case that the concordance rates among MZ twins exceed their corresponding rates among DZ twins. The fact that there is less than perfect concordance reveals that environmental factors also play a major role in the etiology of schizophrenia.

Studies of MZ twin pairs reared apart also point to the involvement of genetic factors in the etiology of schizophrenia. Slater and Cowie (1971) compiled 17 such pairs, and 11 of these (65 percent) were reported to be concordant for schizophrenia.

The family and twin studies of schizophrenia have a major methodological flaw. Both types of studies cannot differentiate between the influences of what is inherited biologically from what an individual acquires from the sociocultural and familial context in which he or she is reared. Thus, for such disorders as schizophrenia, genotype-environment correlations are likely to occur, i.e., disordered environments (e.g., disordered intrafamilial communication patterns) may occur concurrently with a genetic predisposition for schizophrenia. In such instances, it is not possible to separate the effects of genetics from those of nongenetic influences, i.e., the environment. In recent years, investigators have turned to adoption studies as the means of separating the respective influences of heredity and rearing environment.

Adoption Studies

The most compelling, if not convincing, evidence that genetic factors are involved in the etiology of schizophrenia comes from a series of elegantly designed studies on adopted children. The first such study was that of Heston (1966) carried out in Oregon. This investigator studied a group of 47 individuals born to a group of hospitalized schizophrenic mothers, separated from them at birth and reared in foster homes. A control group of 50 individuals was selected from among children whose mothers had no psychiatric disorder but, nevertheless, had placed them
Table 2. Concordance rates in recent twin studies of schizophrenia (\%)\(^1\)

<table>
<thead>
<tr>
<th>Studies</th>
<th>Location of study</th>
<th>MZ twins</th>
<th></th>
<th></th>
<th></th>
<th>DZ twins</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n (pairs)</td>
<td>Pairwise</td>
<td>Proband-</td>
<td></td>
<td>n (pairs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>wise</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kringlen (1968)</td>
<td>Norway</td>
<td>55</td>
<td>25-38</td>
<td>45</td>
<td></td>
<td>90</td>
<td>4-10</td>
<td>15</td>
</tr>
<tr>
<td>Fischer, Harvald, and Hause (1969)</td>
<td>Denmark</td>
<td>21</td>
<td>24-48</td>
<td>56</td>
<td></td>
<td>41</td>
<td>10-19</td>
<td>26</td>
</tr>
<tr>
<td>Pollin et al. (1969)</td>
<td>U.S.A.(^2)</td>
<td>95</td>
<td>14-27</td>
<td>43</td>
<td></td>
<td>125</td>
<td>4-5</td>
<td>9</td>
</tr>
<tr>
<td>Tienari (1971)</td>
<td>Finland</td>
<td>17</td>
<td>0-36</td>
<td>35</td>
<td></td>
<td>20</td>
<td>5-14</td>
<td>13</td>
</tr>
<tr>
<td>Gottesman and Shields (1972)</td>
<td>U.K.</td>
<td>22</td>
<td>40-50</td>
<td>58</td>
<td></td>
<td>33</td>
<td>9-10</td>
<td>12</td>
</tr>
</tbody>
</table>

\(^1\) Data from Gottesman and Shields (1976).

\(^2\) Only male twins studied.

into the same foundling homes as the experimental group. Heston interviewed most of the subjects and found that none of the controls and five of the experimental group were schizophrenic. Also, he found a relatively lower mean Menninger Mental Health-Sickness score and higher mean rates of criminality, mental deficiency, neurosis, and sociopathy among the experimental subjects as compared to the controls.

A study with somewhat similar design was carried out by Rosenthal et al. (1968, 1971) in Denmark. Names of about 5,500 individuals who had been given up for nonfamilial adoption early in life were obtained from an Adoption Register of the greater Copenhagen area. From the records it was possible to learn the names and other identifying information of the biological and adopting parents. In this way the names of about 10,000 biological parents were obtained. A search was then made in a second register, the Psychiatric Register, for those parents who had been admitted to a psychiatric facility. A Danish psychiatrist first reviewed each of the hospital records and prepared an abstract which was transmitted to the American collaborators who independently rated each record and made their own diagnostic assessment. Where full diagnostic consensus was reached that a parent was in the schizophrenic range, the child given up for adoption was selected as an index case. From the remaining adoptees, controls were selected whose biological parents had no known psychiatric history. The controls were matched to the index cases for age, sex, age at transfer to the adopting family, and the socioeconomic status of the adopting parents. A total of 76 index and 67 control adoptees were subsequently interviewed by a psychiatrist who did not know to which group a particular subject belonged. Among the index adoptees, 30 percent received a diagnosis of schizophrenia or schizophrenia spectrum disorder\(^1\) as compared to 17.8 percent among the controls. The three cases with diagnoses of chronic or process schizophrenia were all index cases whereas no such diagnosis was found among the controls.

The frequency of schizophrenia spectrum disorders among the controls is surprisingly high, leading to a search to refine diagnostic methodology. When three blind independent clinical judges attempted to reach a consensus diagnosis for each subject, 32 percent of the index group and 25 percent of the controls received a schizophrenia spectrum diagnosis (Haier, Rosenthal, and Wender 1978). However, when a schizophrenia spectrum diagnosis required both a consensus diagnosis and a divergent profile on at least one clinical scale of the Minnesota Multiphasic Personality Inventory (MMPI), 21.9 percent of the index cases (including the three chronic schizophrenic cases) and 6.3 percent of the controls received spectrum diagnoses (Haier, Rosenthal, and Wender 1978). The possibility that parents who give their children up for adoption may include persons with a substantially higher rate of psychiatric disturbances than parents in the general population may account somewhat for the elevated rates found among the controls (Horn et al. 1975).

In contrast to Heston’s (1966)
study, Rosenthal et al. (1968) found no mental retardation, criminality, or sociopathy among the Danish index adoptees. Several factors may account for the differences between the two studies; these are discussed by Shields, Heston, and Gottesman (1975). Despite the differences, both studies agree in their main finding, i.e., that the offspring of a schizophrenic parent have substantially the same risk for the disorder whether or not they are raised by that parent. This finding strongly suggests the operation of genetic factors.

Further evidence comes from another study of the Danish adoptees carried out by Kety et al. (1968, 1975). From the Psychiatric Register and other files the names were obtained of adoptees who had been admitted to a psychiatric facility; 33 such index cases were found. From the remaining adoptees a matched control group was selected—free of psychiatric history. The Psychiatric Register was searched once again for the names of the adopting and biological relatives of the index and control adoptees. The histories of the relatives found in this Register were abstracted and, as in the previous study (Rosenthal et al. 1968), all precautions were taken to minimize investigator bias. The results are shown in table 3.

The data clearly show a concentration of schizophrenia spectrum disorders among the biological relatives of the schizophrenic index cases. The frequency of these disorders among the biological relatives of the index cases was significantly higher than that among the controls; among the adopting relatives there was no significant difference. If disordered rearing led to the development of schizophrenia in children, then it might have been expected that a greater frequency of schizophrenic disorders would have been found among the adopting rather than the biological relatives of the index adoptees. The concentration of psychopathology among the biological relatives strongly supports the genetic hypothesis.

Kety et al. (1975) reported the results of psychiatric interviews of these biological and adoptive relatives. In all, 345 relatives were either interviewed or supplied adequate information about themselves. The interviews were carried out by a Danish psychiatrist who did not know to which group a particular relative belonged. Edited transcripts of the interviews were independently assessed by the American collaborators who arrived at a consensus diagnosis. The results are shown in table 4.

These investigators confirmed that a significantly greater frequency of schizophrenia spectrum disorders occurred among the biological than among the adoptive relatives of the schizophrenic adoptees. In the initial report (Kety et al. 1968), less than 5 percent of the relatives received a schizophrenia spectrum diagnosis, whereas in the more recent report nearly 20 percent of the relatives were so diagnosed—a four-fold increase. This finding suggests that considerably more psychopathology occurs in the population than reaches the attention of psychiatric facilities.

Table 4 also shows data on the frequency of psychopathology among the relatives of a group of 23 “screened” controls, all of whom were interviewed and shown to be free of a schizophrenic disorder. Again, there was a significantly higher rate of schizophrenic spectrum disorders among the biological relatives of the index cases than among the relatives of the “screened” controls.

Among the biological relatives, Kety et al. (1975) found 63 paternal

Table 3. Schizophrenia spectrum disorders among the biological and adoptive relatives of index and control adoptees

<table>
<thead>
<tr>
<th>Biological relatives</th>
<th>Index adoptees</th>
<th>Control adoptees</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number in schizophrenia spectrum</td>
<td>Number in schizophrenia spectrum</td>
</tr>
<tr>
<td>Parents</td>
<td>63 (3)</td>
<td>63 (2)</td>
</tr>
<tr>
<td>Sibs</td>
<td>2 (1)</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Half-sibs</td>
<td>85 (9)</td>
<td>88 (0)</td>
</tr>
<tr>
<td></td>
<td>150 (13)</td>
<td>156 (3)</td>
</tr>
<tr>
<td>Adoptive relatives</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parents</td>
<td>63 (2)</td>
<td>66 (0)</td>
</tr>
<tr>
<td>Sibs</td>
<td>8 (0)</td>
<td>17 (3)</td>
</tr>
<tr>
<td>Half-sibs</td>
<td>3 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>74 (2)</td>
<td>83 (3)</td>
</tr>
</tbody>
</table>

1 Data from Kety et al. (1968).
half-sibs of index cases and 64 of controls. In this group of half-sibs, there were 16 individuals who received a diagnosis of schizophrenia spectrum disorder; of these, 14 were among the relatives of the index cases and only 2 were related to the controls. Since paternal half-sibs share a father rather than a mother in common, the findings suggest the absence of maternal effects, i.e., that prenatal and perinatal factors are not involved in the etiology of schizophrenic disorders, at least in these relatives. The data again strongly implicate genetic factors.

Wender, Rosenthal, and Kety (1968) studied the psychological characteristics of a group of biological parents who had raised their own schizophrenic children, as compared to a group of matched parents who had adopted either a child who became schizophrenic or a normal child. These investigators found that the adopting parents of schizophrenic children were less disturbed than the biological parents of such individuals, suggesting that parental psychopathology was not a precondition for the development of schizophrenia in the offspring.

Wender et al. (1974) examined the role of parental psychopathology in the production of schizophrenia in offspring who were not known to be genetically predisposed to this disorder. A group of 69 Danish adoptees born to a schizophrenic parent but reared from an early age by unrelated adopting parents (index group) and a group of 69 matched control adoptees whose parents had no recorded psychiatric history were compared to a group of 28 adoptees who, like the latter group, had nonschizophrenic biological parents, but unlike them, had an adoptive parent with a schizophrenia spectrum diagnosis. These latter subjects constituted the cross-fostered group. All subjects were interviewed, and efforts were made to maintain blind procedures in order to determine an unbiased relative rating of psychopathology for each individual. These researchers found that the control and cross-fostered groups were not significantly different in their degree of rated psychopathology. When tested against the mean score of the index adoptees, those of the control and cross-fostered subjects were significantly lower. These data suggest that the experience of being reared in a schizophrenic home does not increase the risk for schizophrenia in individuals unless a genetic predisposition for the disorder is already present.

Wender et al. (1974) also found that the mean psychopathology score of children of schizophrenic mothers was not significantly different from those of schizophrenic fathers and that there were no greater psychopathogenic effects of the schizophrenic parent on the same-sexed child.

Rosenthal et al. (1975) have suggested that although genetic predisposition and the quality of rearing both may affect the development of psychopathology, the amount of variance accounted for by rearing tends to be low. These workers rated the degree of psychopathology and the quality of the parent-child relationship in index, control, and cross-fostered adoptees and in a group of nonadopted individuals, born to and reared in a home with a schizophrenic parent. The individuals in this latter group and the index adoptees (both groups with a biological schizophrenic parent) showed the most severe psychopathology. The worst parent-child relationships were found in the cross-fostered and

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**Table 4. Frequency of schizophrenia spectrum disorders in the relatives of schizophrenic and control adoptees**

<table>
<thead>
<tr>
<th>Group</th>
<th>Biological relatives</th>
<th>Adoptive relatives</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Number interviewed</td>
</tr>
<tr>
<td>Index cases</td>
<td>173</td>
<td>118</td>
</tr>
<tr>
<td>All controls</td>
<td>174</td>
<td>140</td>
</tr>
<tr>
<td>Screened controls</td>
<td>113</td>
<td>86</td>
</tr>
</tbody>
</table>

**Note:** Data from Kety et al. (1975). **p < 0.01; NS, not significant.
nonadoptive groups. Rosenthal et al. (1975) found that the cross-correlation between child psychopathology and quality of parent-child relationship was higher for the two groups without a schizophrenic biological parent (i.e., the control and cross-fostered groups) than for the index adoptees and nonadoptive group. Thus the rearing environment appeared to play a relatively greater role in producing normal or psychopathological behavior in individuals without a genetic loading for schizophrenia than it did for individuals with such loading.

Rosenthal et al. (1975) also found that there were no significant differences between index and control adoptees with respect to the quality of the (adoptive) parent-child relationship. Nevertheless, index adoptees scored higher than controls on their psychopathology scores, suggesting that the greater psychopathology of the former group was due to genetic factors rather than to disordered rearing.

Evidence of another sort is presented by Wynne, Singer, and Toohey (1976). Working blindly, Singer analyzed the Rorschach protocols of the biological and adopting parents of the Wender, Rosenthal, and Kety (1968) study and, with astonishing high accuracy, was able to differentiate the biological and adopting parents of schizophrenic individuals from the adopting parents of normal individuals. The same degree of Rorschach psychopathology was shown by both the adopting and biological parents of schizophrenics, and both groups were significantly different from the adopting parents of normal subjects. In an attempt to replicate the study on another sample, Wender et al. (1977) found that the biological mothers of schizophrenics tended to show more Rorschach psychopathology than either the adopting mothers of schizophrenics or the biological parents of a group of nonadopted retarded children. Wender et al. (1977) suggest that test set might account for the differences between the Wynne, Singer, and Toohey (1976) study and theirs. The adopting parents of schizophrenics were, in one case, informed, before testing that they had been chosen because of their adopting status, whereas in the more recent study they were recruited on the basis of a consecutive sample of hospital admissions and their adopting status was purportedly not highlighted. Wender et al. suggest that as a result of this latter strategy, the adopting parents did not show any greater test anxiety than the other parents and, under such conditions (of presumably constant anxiety for all groups), only the mothers of schizophrenics showed significant Rorschach psychopathology. If these latest findings can be replicated, it might suggest that dysfunctional communication styles have a genetic component, and should not be treated as an environmental variable as has been done in the past.

Kety et al. (1975) found that diagnoses of questionable schizophrenia and of schizoid or inadequate personality were distributed equally among the biological relatives of schizophrenic and nonschizophrenic adoptees, whereas the diagnoses of chronic, latent or borderline, and uncertain schizophrenia tended to cluster together among the biological relatives of schizophrenic adoptees. Thus, the latter disorders appear to constitute a group of genetically related disorders, whereas the relationship of the former ("soft-spectrum") disorders to the gene or genes that produce schizophrenia is less clear. Differences of opinion exist as to the inclusion of sociopathic behaviors in the schizophrenia spectrum. Data of Heston (1966) and of Bender (1975) suggest that they should be included. Data of Kety et al. (1975) suggest that they should not.

Rosenthal and his co-workers believe that a relationship exists between the "soft-spectrum" diagnoses and schizophrenia. Preliminary data (Rosenthal 1975) suggest that "soft-spectrum" diagnoses occur among a substantial fraction of the co-parents (i.e., the mating partners of the biological index parent) of schizophrenic adoptees. When the coparent had a "soft spectrum" diagnosis, it appeared to increase the risk for a schizophrenia spectrum diagnosis in the adoptee. When the former diagnosis was absent in the co-parent, it was also likely to be absent in the adoptee. Rosenthal (1975) has suggested that the genetic input from a soft spectrum co-parent adds to the genetic input from a chronic schizophrenic parent to promote an increased schizophrenic manifestation in the offspring. Rosenthal's data also strongly suggest that substantial assortative mating occurs between individuals who have a predisposition to schizophrenic disorders.

A full detailed report of all the findings of the Danish adoption studies is not yet available, and it may be years before we can assess the full implications of the Kety-Rosenthal work. Like the family and twin studies, the adoption studies are not without their sampling and other methodological difficulties. Some of the replications are not always consistent with the main trends in the data. For example, Wender et al. (1974) did not find a significant difference between index and control.
groups with respect to the rate of
definite or uncertain schizophrenia.
These investigators accounted for
their results by suggesting that there
was an inflated rate of psychopathol-
yogy among the individuals in the
control group. Also, examination of the
data of Kety et al. (1975) suggests
that the rate of psychopathology
among the biological half-sibs of
schizophrenic adoptees was 19.2
percent, whereas among the biologi-
cal parents of these adoptees, the
rate of schizophrenia (definite or un-
certain) was 12.1 percent. Unfortu-
nately, half-sibs only share one-
quarter of their genes in common
with their schizophrenic relatives,
whereas biological parents share
one-half of their genes in common
with their affected children. Genetic
models cannot reasonably account
data in which the frequency of a
trait is as high or higher among more
remotely related relatives than
among closer ones. These apparent
inadequacies may yet be accounted
for when the full report is in, and in
no way do they weaken the major
thrust of the Danish adoption
studies.

Individual studies—family, twin,
adoption—all contain methodologi-
problems and flaws, and can be
subjected to greater or lesser criti-
cism. Nevertheless, the overwhel-
ing direction of the findings of all
these studies, carried out in different
countries and at different times, is
remarkably consistent in confirming
that genetic factors are involved in
the etiology of schizophrenia. Also,
these studies confirm that although
in many cases a genetic predisposi-
tion to schizophrenia may be a
necessary precondition, it is by no
means a sufficient condition to pro-
duce the disorder. Both genes and
environment play a substantial role
in the etiology of schizophrenia.

A few words need to be said about
the mode of inheritance of the gene
or genes involved in the etiology of
schizophrenia. Rosenthal (1977) has
recently reviewed this topic.

It has been known for many deca-
des that schizophrenia is not trans-
mitted in a simple Mendelian way.
Of course, many traits in many dif-
ferent species, including humans, do
not show a Mendelian pattern of in-
heritance, yet have important genetic
determinants. For example, such
commercial traits as animal size, egg
production, milk yield, etc., have all
been shown to have a complex
non-Mendelian, multifactorial ge-
etic determination and have been
responsive to artificial selection pro-
cedures. Also, many important
human characteristics (e.g., IQ,
height, etc.) show a pattern of inheri-
tance which can best be understood
as being multifactorially determined
and which can be analyzed by quan-
titative genetic methods. Some traits
diseases seem to show a quasi-
continuous distribution; that is, they
manifest all-or-none characteristics
and do not follow a Mendelian mode
of inheritance.

Using a quantitative genetic
approach, a field to which he had
already contributed, the geneticist
Falconer (1965) advanced a model to
account for such quasi-continuous
diseases as schizophrenia, pyloric
stenosis, diabetes, cleft lip (±) cleft
palate, etc. The model presupposes
that underlying the etiology of a dis-
order is a continuously distributed
variable, liability, that encompasses
all the endogenous and exogenous
factors predisposing to the disorder.
The distribution of the liability can be
conceived as being represented by a
normal, bell-shaped curve, at one
end of which is a point called the
threshold, which demarcates indi-
viduals who are affected from those
who are not. The point at which the
threshold is placed on the curve can
be determined by the prevalence of
the disorder in the general popula-
tion. Given the prevalence rates
among different classes of relatives of
affected individuals, it is possible to
use the model to calculate the herita-
bility of the liability to the disorder.
Gottesman and Shields (1966) were
the first to apply the Falconer model
to the inheritance of schizophrenia
and calculated that the heritability of
the liability to schizophrenia was
about 85 percent. Simply put, herita-
bility represents the proportion of
the degree of resemblance between
relatives accounted for by genetic
factors.

The major problem with the
Falconer/Gottesman/Shields ap-
proach was that it left many inves-
tigators intellectually dissatisfied.
The model introduced "new" concepts—liability, heritability—
both of which had limiting defini-
tions and generalizability and could
only be understood in terms of popu-
lations rather than of individual
pedigrees. Furthermore, the model
did not appear to be of much use to
researchers who were trying to un-
derstand the biochemistry and
neurophysiology of schizophrenia.
These investigators were hoping for
a more simple model, one more like
that of phenylketonuria (PKU) or
other inborn errors of metabolism
which appeared to have a more
straightforward pattern of inheri-
tance associated with a specific chem-
ical defect. Given the new impetus
supplied by the results of the adap-
tion studies, the problem of the
mode of inheritance of schizophrenia
was subjected to renewed attack.

Using currently available family
and twin data and rather sophisti-
cated computer programs, Kidd and
Cavalli-Sforza (1973) and Kidd (1975)
found that the data were compatible with a single gene model which incorporated a threshold concept. From their calculations it appeared that the gene had a frequency of about 10 percent and a threshold such that 50 percent or more of the homozygotes would be affected.

Matthysse and Kidd (1976) expanded on this approach by investigating the extreme genetic models, i.e., a single major locus or monogenic model (SML) and the multifactorial or polygenic model (MF). These workers calculated estimates of the parameters of the two models including the gene frequency, the likelihood of phenocopies, and the relative incidence of schizophrenia in heterozygotes and homozygotes. Based on the rates of schizophrenia in the general population and among sibs and children of schizophrenics (i.e., the cases which provide the largest body of data in the literature), it is possible to determine the expected incidence among MZ twins and in dual matings (children of two schizophrenic parents). The expected and observed rates are shown in table 5.

Matthysse and Kidd found that neither of the models accounted adequately for the observed data. The SML model provided estimates that were too high relative to the actually observed incidences among children of two affected parents and MZ twins. Nevertheless, the two models provided some interesting perspectives. In the SML model, the genetic composition of the affected population varied according to the frequency of the allele that promoted the development of the disorder. At relatively low frequencies of the allele, about 60 percent of schizophrenics were estimated to be phenocopies, i.e., environmentally produced mimics of the genetically determined form of the disorder. In other words, these affected individuals would be genetically “normal” persons, and the disorder would develop because of environmental influences. The remainder of the cases would be mostly heterozygotes. At relatively high frequencies of the schizophrenia-promoting allele, the number of phenocopies drops and the proportion of heterozygotes increases correspondingly. At all allelic frequencies, the proportion of schizophrenics who were homozygotes is low. Thus under some conditions of this model, genes play an extremely important role when they are present in double dose, but such individuals would be rare, even among affected individuals.

Under the MF model, Matthysse and Kidd found that about 9.1 percent of schizophrenics had such a high genetic risk that 99 times out of 100 they would become schizophrenic virtually irrespective of environmental circumstances. According to this model, in 1 of 11 schizophrenics, the disorder is almost totally genetically determined.

Both models predict genetic heterogeneity among schizophrenics. Not every schizophrenic will have the same genetic makeup with respect to the schizophrenia-promoting genes. This, of course, would pose serious difficulties for investigators who would like to obtain a relatively homogeneous group of affected individuals for research purposes.

Kidd and Matthysse (1978) addressed themselves to the future research strategies that may need to be adopted in the study of schizophrenia, particularly in an attempt to resolve the underlying heterogeneity. Kidd and Matthysse (1978) suggest that the screening of large samples of unrelated individuals be done to identify individuals with markedly deviating values on biochemical and neurophysiological variables. These may be followed by classical family studies of such individuals. Other research possibilities include the study of children of twins, separation studies on groups such as half-sibs, adoptees, and MZ twins reared apart. Perhaps the most useful kinds of studies are those involving nuclear families and multigenerational pedigrees, that is, large families encompassing several generations and several sibships. Both Kidd and Matthysse (1978) and Rieder and Gershon (1978) argue that these groups probably constitute the best material on which to test genetic hypotheses linking various variables.

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Table 5. Observed and expected rates of schizophrenia

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed (%)</th>
<th>Single major locus model</th>
<th>Multifactorial model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dual matings</td>
<td>39.0</td>
<td>19.9</td>
<td>54.0</td>
</tr>
<tr>
<td>MZ twins</td>
<td>47.0</td>
<td>19.9</td>
<td>61.0</td>
</tr>
</tbody>
</table>

1 Data from Matthysse and Kidd (1978).
2 Data based on observed incidences of 0.87 percent in the general population, and 8.7 and 12.0 percent among sibs and children of probands, respectively.
biological and psychological, to schizophrenia.

Genetic Counseling in Schizophrenia

Discussion of this topic may be found in articles by Heston and Gottesman (1966), Kay (1978), Kety, Matthysse, and Kidd (1978), and Tsuang (1978). Several difficulties are encountered in providing adequate genetic counseling to patients and their relatives. Available empiric risk figures are averages derived from a wide range of individual values from diverse populations. An average figure may not be appropriate to the individual seeking counseling. Also, as Kety, Matthysse, and Kidd (1978) point out, empiric risk figures are derived from and are only applicable to cases of classical chronic schizophrenia and not to the other forms, such as latent or borderline schizophrenia and acute schizophrenia about which less is known with respect to recurrence risks. Furthermore, the mode of inheritance of the gene or genes involved in the etiology of schizophrenia is not known. The models currently available are too subtle and abstruse for most counselees to comprehend; the models are likely to be perceived as intellectual exercises. It is also important to keep in mind that risk figures only have relevance for any given person and any given pregnancy, the individual will either have or not have an affected child.

The genetic counselor needs to have a good understanding of how individuals process ego-threatening information under conditions of uncertainty (Janis and Mann 1977; Kessler 1976; Pearn 1973; Tversky and Kahneman 1974) to appreciate this point.

Schizophrenia has enormous impact on the family; parents of affected individuals have a profound sense of failure, inadequacy, guilt, and shame. To imagine that one has transmitted a gene or genes to one’s offspring that are responsible for the child’s illness often exacerbates these feelings and further erodes the parent’s self-esteem. If parents have not blamed themselves for their child’s illness, it is not unusual that they have been blamed by other relatives and, not infrequently, by the professionals with whom they have come in contact. It is no wonder then that parents of affected individuals come for genetic counseling relatively infrequently (Reed 1972) and, when they do come, do so with high levels of defensiveness.

Since many cases of schizophrenia have their onset in the postpubertal years, many parents of schizophrenics have either completed or almost completed their reproduction. Nevertheless, such individuals may request genetic counseling, often on behalf of their children, affected and unaffected. Concern for one’s children may be used as a means of obtaining personal help from a professional. By focusing on the children, the parents may evade or avoid needing to deal with the interpersonal difficulties which have been precipitated by the illness of the child. In some cases, when the genetic counselor becomes complicit with the parents in focusing on the child at the expense of not dealing with the parental dynamics, genetic counseling may actually exacerbate family dysfunctions.

In my own experience, the genetic counseling of affected individuals generally takes one of two forms: Most often, genetic counseling is requested on behalf of the affected individual and/or the person is referred to genetic counseling by a public health nurse, physician, or other health professional because the professional is disquieted by the reproductive plans of the affected individual. In such cases, the professional generally makes either an explicit or implicit demand on the genetic counselor to persuade the individual not to have children. Such referrals are generally nonproductive, as the counselee comes in already suspicious, and the confidence that needs to develop for effective nondirective genetic counseling to occur cannot be established.

Less frequently, the affected individual or the spouse requests the counseling. If either or both counselees are in psychotherapy, consultation with the psychotherapist should be sought, and the genetic counseling should become an integrated part of the psychotherapeutic process. Such requests for counseling often involve important therapeutic issues, and the management and timing of the counseling may have important consequences for the therapeutic outcome for the individual or family.

Affected individuals and/or their spouses sometimes request genetic counseling because of the psychotropic medications to which they may have been subjected and their concerns about the effects of such pharmacological agents on the genes they carry and about the possible consequences for a healthy fetus. Unfortunately, this is another area about which hard facts are not available.

The unaffected sibs of schizo-
Sometimes also request genetic counseling. The timing of requests for such counseling should be carefully explored by the counselor. The fear that one is going mad or may already be mad may motivate the quest for genetic counseling, particularly if precipitated by some family crisis (which may or may not be related to the affected individual). Not infrequently, genetic counseling is sought by one spouse as a means of obtaining a professional ally or support for his or her side in an interpersonal conflict or over reproduction. The counselor needs to explore carefully the motivation for obtaining genetic counseling at a particular time in the life cycle of a family, to avoid exacerbating already existing family dysfunctions.

Children of a schizophrenic parent are another group that may seek genetic counseling. Here, too, the motivations for requesting counseling, the meaning of the risk figures, and the consequences of knowing or not knowing that one is at risk for schizophrenia all need to be explored.

Tsuang (1968) has described seven basic steps in the genetic counseling for psychiatric disorders. These will be listed with some additional commentary of my own. The steps include:

1. Making an accurate diagnosis. Tsuang points out several caveats in this area. The counselor needs to remember that at the present state of our knowledge it is not possible to differentiate unequivocally between cases of schizophrenia with high genetic loading, phenocopies, folie à deux, etc., even within the same family.

2. Obtaining a family history. Not infrequently the counselor may need to rely on medical records of doubtful value and on secondhand information provided by relatives who are neither objective nor unbiased. In the discussion of family history, family myths may emerge about the affected individual and his or her relationship with other family members. These myths may be based on mistaken notions and may play a key role in maintaining dysfunctional family dynamics. Although the correction of mistaken notions may be a worthy goal in genetic counseling, achieving this goal may be difficult. Family members may resist new input and reject ideas which run counter to their own system of beliefs. Alteration of these belief systems may have important consequences for the family, not always of a negative kind. However, the counselor may need to engage in longer term work with the family if an attempt is made to alter the myths on which family functioning is based. Also, in discussing various relatives, strong feelings of anger, disappointment, bitterness, love, longing, etc., may emerge with which the counselor may need to deal.

3. Estimation of the recurrence risk. There is a plethora of models that the genetic counselor may use in estimating a recurrence risk, including single gene, multifactorial, and models of genetic heterogeneity. All may be consistent with existing data. Most counselees would neither appreciate nor understand the complex models with which geneticists deal. In general, counselees come to an expert like a genetic counselor for unequivocal certainties and, unfortunately, this is what we seldom can provide at the present state of affairs. The fact that there are ambiguities in our understanding of the mode of transmission of schizophrenia may tend, as ambiguities usually do, to increase the counselees' already existing anxieties, and not infrequently erode their confidence in the counselor.

4. Psychosocial evaluation of the counselee. Perhaps this should be the first step in the process of genetic counseling, and should occur before the counselor becomes locked into a procedural course which may turn out to be inappropriate in light of the counselee's needs and motivations.

5. Dealing with the risk/burden ratio. The counselor attempts to help the counselees weigh the estimated recurrence risk against the burden of the disorder. Unfortunately, risk and burden are not orthogonal variables; counselees generally experience the risk as an integral part of the burden of genetic disease (Lippman-Hand and Fraser 1979). Also, discussions of risk/burden ratios presuppose that human cognitive-emotional mechanisms are geared toward such discussions. Evidence suggests that they are not (Janis and Mann 1977). In the evaluation of risks and burdens, individuals take simplifying steps and shortcuts which may lead to end points unanticipated by the counselor.

6. Formulating a plan of action. Tsuang (1978) suggests that the counselor needs to play a relatively directive role in this area. This presupposes that "doctor knows best" with respect to other peoples' reproductive plans and health decisions, a supposition which may not necessarily be the case.

7. Followup. The counselor needs to have a clear sense of his or her own motivation and goals in providing followup. If, on followup, the counselor discovers that the information provided during the course of genetic counseling has been distorted or misunderstood, what course will be followed then? To attempt to reeducate and inform at that
point may be as futile as the first attempt, if the defensive, coping, or other conditions which led to the distortion in the first place continue to prevail.

One needs to remember, in the provision of genetic counseling in schizophrenia, that the disorder itself involves, among other things, a distortion of reality and an illogical thinking and connection of ideas in which the entire family, affected and nonaffected, participates in many subtle ways. The frequent distortion of genetic information found in genetic counseling (Shaw 1977) occurs even more so in the genetic counseling of schizophrenia. All the issues usually seen in genetic counseling (Kessler 1979a, 1979b) are present, often in an extreme or distorted form. Similarly, the feelings of fear, guilt, shame, confusion, etc., frequently manifested in genetic counseling may be present in an exacerbated or distorted way. Requests for counseling, the perception of the information provided by the counselor, the interpretation of the recurrence risk, and the perceived need to reach reproductive or health decisions frequently contain hidden agendas and are intertwined with a mishmash of intrapsychic and interpersonal issues. Thus, the genetic counselor needs to be trained and skilled in dealing with these issues and needs to be willing to engage in more than a brief fact-finding and fact-giving activity (Kallmann 1956; Rainer 1975).

Unfortunately, genetic counseling in this area is sometimes done in a very cavalier way without taking into consideration the possible short- and long-term consequences the counseling might have for the individual and his or her family. It is my strong belief that genetic counseling in schizophrenia should only be given by persons trained in the skills of psychotherapy and, optimally, within the confines of the psychotherapeutic encounter.

References


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