Schizophrenic Illness in the Families of Schizophrenic Adoptees: Findings From the Danish National Sample

by Seymour S. Kety

Abstract

The prevalence of schizophrenic illness in the biological and adoptive relatives of schizophrenic adoptees has been examined in a total sample of adoptees in Denmark. The sample was studied in two stages, beginning with the Copenhagen sample of adoptions granted by the courts in the city and county of Copenhagen, and the results have been reported previously. The adoptions granted by the courts in the remainder of Denmark made up the Provincial sample, the preliminary results of which appear to confirm those obtained earlier. Chronic schizophrenia and milder syndromes described as latent, borderline, or uncertain schizophrenia, and in DSM-III as schizotypal personality disorder, were found in both samples to concentrate significantly in the biological relatives of schizophrenic adoptees as compared to their controls, but not in their adoptive relatives. These milder and marginal syndromes resembling schizophrenia occurring in the families of schizophrenic patients confirm the observations of Bleuler and others who succeeded him. Their presence in the biological families of schizophrenic adoptees indicates not only their familial nature of the disorder, but not in their adoptive relatives. These milder and marginal syndromes resembling schizophrenia occurring in the families of schizophrenic patients confirm the observations of Bleuler and others who succeeded him. Their presence in the biological families of schizophrenic adoptees indicates not only their familial, but also their genetic relationship to schizophrenia, although the specificity of that relationship has not been established.

A problem that has often been a source of difficulty in research on etiology is the confounding of genetic and environmental factors in the development of the individual. In 1962, a collaborative program of research was undertaken in the Intramural Research Division of the National Institute of Mental Health (NIMH) by Drs. Seymour S. Kety, David Rosenthal, and Paul Wender which used adoption as a means of separating genetic and environmental influences in the etiology of schizophrenia and, eventually, a number of other psychiatric disorders. The principal investigators entered into this collaboration from different vantage points and with somewhat different objectives: an examination of mental illness in the two families of schizophrenic adoptees to learn how much of the well-known familial nature of the disorder might be accounted for by genetic or environmental factors (Kety 1959), to evaluate more definitely a diathesis/stress model of schizophrenia (Rosenthal 1963), and to test hypotheses invoking the schizophrenogenic mother or parents without interference by genetic influences (Wender et al. 1968).

Denmark was chosen as the site for these studies because of its relatively homogeneous and stable population, and the excellent demographic and psychiatric records that are maintained there to which the investigators were given access with their assurances of complete confidentiality. With the invaluable collaboration of Fini Schulsinger, it was possible to compile the Danish Adoption Register, first for Greater Copenhagen and more recently for all of Den-

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This article includes data from a study by Kety, Wender, Jacobsen, Schulsinger, Rosenthal, Jansson, Faber, Kenney, and Ingraham, which is in preparation.
mark, which included all individuals legally adopted between 1924 and 1948 by other than biological relatives. A research design was developed to minimize ascertainment, selective, and subjective bias, and to separate to the maximum degree possible the genetic and family-related environmental influences operating in the adoptees and families who would be studied.

Selective placement did not constitute a significant problem in Danish adoptions over that period. The socioeconomic class of the biological and adoptive parents showed a low correlation (.16), and the policy of providing legal abortions to unwed mothers where the mother or the father had a history of mental illness prevented such circumstances or knowledge from affecting all but a very few of the adoptees. When mental illness did occur in a biological parent in the Copenhagen sample, its onset was on the average 11 years after the time of the adoption.

In all research on schizophrenia, the question of diagnosis is the single greatest source of variability since it would not be unusual for one group to find 5 and another 50 schizophrenics in the same sample of patients by virtue of the wide latitude in the concept of schizophrenia that developed since its early description. It was decided to begin with the exhaustive description of the syndrome that Kraepelin had originally defined and which the international and American classifications current at the time the study was undertaken listed as “chronic schizophrenia.” But the standard classifications also listed two putative forms of schizophrenia (“acute” and “latent”) which probably accounted for more of the diagnoses of schizophrenia 25 years ago than the classical Kraepelhian syndrome Bleuler had recognized the existence of a latent form of schizophrenia and the international classification had retained and expanded it to include “pseudoneurotic” and “pseudopsychopathic” schizophrenia as well.

The 34 proband schizophrenic adoptees, selected by unanimous agreement of four raters from the 5,483 individuals legally adopted through the courts of Copenhagen by couples not biologically related to them, represented the gamut of schizophrenia diagnoses—chronic, acute, and latent—accepted at that time by the profession. Borderline schizophrenia was often used in the literature and in classification systems as synonymous with latent schizophrenia and was so used in these adoption studies at first, but the rise and popularity of the “borderline personality” concept, which represents quite a different syndrome, makes the designation “latent schizophrenia” preferable. In the case of the relatives, “questionable,” “uncertain,” or “probable” schizophrenia had to be added if relatives with less certain diagnoses were not to be lost. In addition, two nonschizophrenic disorders most resembling schizophrenia—schizoid and inadequate personality—were included in the spectrum of disorders to be examined. The investigators did not necessarily believe that all of these disorders would be found to be related to schizophrenia, but it would have been inappropriate to exclude any prematurely. Furthermore, if the different components were kept separate, it might eventually be possible to evaluate the relationship of each to paradigmatic schizophrenia.

The hypothesis to be tested in the first study (Kety et al. 1968) was stated as follows. “If schizophrenia were to some extent genetically transmitted, there should be a higher prevalence of disorders in the schizophrenia spectrum among the biological relatives of the index cases than in those of their controls” (p 353). Blind consensus diagnoses based on detailed abstracts of hospital records found a prevalence of that spectrum in the biological index relatives of 8.7 percent compared with 1.9 percent in the biological relatives of the control adoptees (p = .0072), the prevalence in the adoptive index relatives being no higher than that in their controls. Without the inclusion of the two personality disorders, “schizoid” and “inadequate,” the prevalence of chronic or latent schizophrenia, definite or uncertain, in the biological index and control relatives was 7.3 percent versus 1.9 percent (p = .022), and the hypothesis was upheld. Although there were insufficient cases to permit testing individual components of the spectrum with any reliability, an absence of any schizophrenia disorders was noted in the 30 biological relatives of the 7 adoptees diagnosed as acute schizophrenia. On the other hand, 10 of the 13 spectrum disorders in the index biological relatives were diagnosed as “latent” or “uncertain” schizophrenia, confirming Bleuler who rejected “acute” schizophrenia but noted the prevalence of “latent” or “borderline” forms of schizophrenia in the relatives of his schizophrenic patients. These results strengthened the suspicion that schizoid and inadequate personality as well as acute schizophrenia would more appropriately have been omitted from the schizophrenia spectrum, a hypothesis that would be tested later.

To come closer to defining the
boundaries of schizophrenia, it was necessary to enlarge the sample or obtain more information about the mental and behavioral status of the relatives. It was decided to do both by extending the study to all of Denmark and by conducting exhaustive interviews with the relatives. Bjorn Jacobsen joined the collaboration and spent the next 3 years interviewing the relatives in the Copenhagen sample. The structured interviews were more exhaustive than the Lifetime version of the Schedule for Affective Disorders and Schizophrenia (SADS-L), which was not yet available, extending to 36 or more pages with numerous checklists and extensive narrative elaborations designed to elicit response on a complete range of psychiatric symptoms and manifestations, particularly those which had been recorded in schizophrenia, presumptive schizophrenia, and schizophrenia-like syndromes. Dr. Jacobsen succeeded in obtaining interviews with 90 percent of the relatives and control probands still alive and residing in Scandinavia and partial interviews or pertinent information in an additional 5 percent.

Analysis of the interviews amplified the results obtained in the same sample from hospital records alone (Kety et al. 1975). The original spectrum was significantly (p = .006) concentrated as before in the biological relatives of the schizophrenic adoptees, but now in addition to the two cases of schizoid or inadequate personality in the hospitalized relatives, 26 instances were found among the nonhospitalized relatives, dividing themselves evenly between index and control relatives. When these nondiscriminating personality disorders were excluded, the remaining diagnoses (which were forms of DSM-I and the new DSM-II schizophrenia [American Psychiatric Association 1952, 1968]) were highly concentrated in the biological relatives of the schizophrenic adoptees (p = .0004). There were no diagnoses of chronic schizophrenia in the biological relatives of the controls, but five cases of this most severe form occurred in the biological relatives of the schizophrenic adoptees (p = .03). There were, moreover, a large number of latent and uncertain schizoidias among the biological relatives, highly concentrated in the index relatives (11.0 percent vs. 3.4 percent, p = .005). Control adoptees were interviewed blindly along with the relatives, and 23 were found to be free of schizophrenia spectrum or serious mental disorder. When their biological relatives were compared with those of the schizophrenic adoptees, the preponderance of latent and uncertain schizophrenia in the biological relatives of the schizophrenic adoptees was even more striking (11.0 percent vs. 0.9 percent, p = .0004) (Kety et al. 1975).

The concept of latent schizophrenia had been vaguely defined by Bleuler, and our criteria for uncertain schizophrenia were equally ill defined—enough of the features of schizophrenia to make it the most likely diagnosis, but not sufficiently severe or typical to be certain. With all their vagueness, however, which could only increase the opportunity for error and make it more difficult to find a significant difference, these diagnoses, made blindly, were almost exclusively in the biological relatives of the schizophrenic adoptees. Bleuler’s recognition of a mild form of the disorder in the relatives of severely ill schizophrenic patients was confirmed, but now in relatives who grew up apart from the patients and unlikely to have been influenced by the patients’ family environment or their thought processes and behavior.

An opportunity to operationalize the diagnoses of latent and uncertain schizophrenia presented itself when Robert Spitzer and Jean Endicott offered to review the interviews in which we had made those diagnoses, along with a comparable number where we had not, to attempt to define what characteristics distinguished them. Comparing the two sets of interview transcripts, they developed a list of eight discriminators which became the DSM-III (American Psychiatric Association 1980) criteria for schizotypal personality disorder, a category that combined the characteristics of the diagnoses of latent and uncertain schizophrenia in the adoption studies.

The criteria for schizotypal personality disorder were based upon all of the borderline and uncertain schizophrenia diagnoses (plus six diagnoses of schizoid personality) and reinforced by reference to the stereotypes of a large number of psychiatrists selected randomly (Spitzer et al. 1979) but unfortunately not limited to the genetic relatives of schizophrenics which would have given them somewhat greater independent validity. They are apparently better able to discriminate the genotype, however, than any previous descriptors. When Kendler et al. (1981) asked to review Jacobsen’s interviews for the possible relationship of anxiety disorder to schizophrenia, they also agreed to include other DSM-III diagnoses, including schizotypal personality disorder. They found a prevalence of 13.6 percent for this syndrome in the biological relatives
of 16 adoptees diagnosed by the original investigators and by Spitzer and associates as chronic schizophrenia using the Research Diagnostic Criteria, compared to 2 percent in the biological relatives of unscreened control adoptees (Kety 1983). The original global diagnoses had given prevalence rates for latent and uncertain schizophrenia of 17.1 percent and 6.1 percent, respectively, in the same populations. In their hands, DSM-III had greater specificity but less sensitivity than the global diagnoses. Later, when Kendler and Gruenberg (1984) made DSM-III diagnoses on the index probands, the difference in prevalence rates for schizotypal personality disorder between biological relatives of DSM-III schizophrenic adoptees and control biological relatives was even sharper.

The collection of what would be called the Provincial Sample, i.e., the adoptees throughout Denmark outside of Copenhagen, began in 1975, accumulating first the records of adoptions granted outside of the city and county of Copenhagen, approximately 9,300. The same procedures employed in the Copenhagen study were used to select the index adoptees: unanimous agreement on a diagnosis of schizophrenia (chronic, latent, or acute). The matched controls, presumably mentally healthy, or at least with no record of admission to a mental institution, were then selected, their biological and adoptive relatives (parents, siblings, and half-siblings) were identified, and the Psychiatric Registry was searched for any record of admission to these relatives to a mental institution. Blind consensus diagnoses based on institutional records were published in a preliminary report (Kety et al. 1978).

In 1980, Dr. Jacobsen and two associates began interviewing the relatives with the same high rate of compliance which was achieved in Copenhagen. The 36-page English transcripts were blindly rated independently by two raters and a consensus diagnosis was arrived at. This, in conjunction with abstracts and extensive summaries of hospital records of those subjects who had been hospitalized 10 or more years earlier, formed the basis of a final diagnosis made on relatives and probands, both index and control, all arrived at without knowledge of the relationship of a subject to any other (Kety et al., to be published). A preliminary analysis of the findings is possible at this time, based on the prevalence of various diagnoses among identified relatives, although a final updating of the demographic records is now near completion.

The frequency of psychiatric diagnoses outside of the schizophrenia spectrum is almost identical in the biological relatives of the schizophrenic and control adoptees, and no particular diagnosis shows a significant difference. There are significantly more (p = .01) diagnoses of chronic, latent, acute, and uncertain schizophrenia and schizoid or inadequate personality in the biological relatives of the total sample of schizophrenic adoptees than in the biological relatives of the controls. The difference is markedly enhanced when, as was indicated by the Copenhagen Study, the schizoid and inadequate personality disorders as well as acute schizophrenia are removed from the spectrum and comparison is made with controls who were interviewed within the past 5 years and found to be free of serious mental illness (11.6 percent vs. 2.2 percent, p = .007). In each analysis the prevalence in the adoptive relatives is low and no significant difference is found between index and control relatives.

There is good agreement as well between the Provincial and Copenhagen Studies in respect of certain constituents of the schizophrenia spectrum. The relationship of these to classical schizophrenia was explored by examining serially the prevalence of the disorders of the schizophrenia spectrum in the biological relatives of adoptees with classical chronic schizophrenia and of control adoptees who, on psychiatric interview, revealed no evidence suggestive of schizophrenia or other serious mental illness. Chronic schizophrenia, definite or probable, was found at prevalences of 5.2 percent and 5.8 percent in the biological relatives of the Provincial and Copenhagen index adoptees, respectively, compared with 0 percent and 0.9 percent in the control relatives. For latent schizophrenia, definite or probable, the corresponding values were 8.6 percent and 12.5 percent with control levels of 2.2 percent and 0.9 percent. All of the differences between index and control values were significant. When the analysis was made by families instead of relatives, similar differences were found.

In the Copenhagen sample of biological index families, there were only three full siblings—the relatives who under ordinary circumstances provide the highest prevalence of illness in affected families—and for that reason the diagnoses of schizophrenia were relatively few in the first-degree
relatives. In the Provincial sample that was not the case and the 25 biological full siblings of the schizophrenic adoptees provided a prevalence of chronic schizophrenia in the first-degree relatives which was more than twice as high as that in the second-degree relatives and in accord with expectation. It is felt that differences in lifestyle, with more stable monogamous relationships occurring in the Provincial sample, may account for the greater number of full siblings there.

The Provincial Study, which represents a replication of the Copenhagen Study, is confirming many of its results. There is a significant concentration of schizophrenia in the biological families of schizophrenic patients as opposed to those of mentally healthy controls even when they have been reared apart. In addition, confirming Bleuler's observations (Kety 1985) and those of many others, there are one or more milder and marginal syndromes resembling schizophrenia in the families of schizophrenic patients. Their presence in the biological families of schizophrenic adoptees indicates not only their familial but also their genetic relationship to schizophrenia.

Both studies have included a large number of observations on environmental variables that may operate in the development of schizophrenia. Results implicating birth complications have been reported by Jacobsen and Kinney (1980). Other components of the biological and cultural milieu continue to be examined. The psychiatric interviews on the probands and relatives are providing a wealth of information on clinical characteristics some of which may be found sufficiently clustered in the close relatives of schizophrenics by virtue of their genetic overlap to constitute diagnostic criteria with enhanced validity. In addition, systematic analysis of the individual traits may help to ascertain what is genetically transmitted in schizophrenia. Although these adoption studies have not and probably will not in themselves permit a determination of the mode or modes of genetic transmission, the finding that the prevalence of schizophrenic illness in the biological relatives of schizophrenic adoptees is similar to that in the relatives of nonadopted schizophrenic patients warrants the conclusion that the tendency of the disorder to cluster in families is an expression of shared genetic factors. On that basis, the study of families of nonadopted schizophrenic patients to derive information on genetic transmission can be justified, and the application of molecular genetic techniques to informative high-density pedigrees appears reasonable.

References


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