The Danish American Adoptees’ Family Studies of Kety and Associates: Do They Provide Evidence in Support of the Genetic Basis of Schizophrenia?

JAY JOSEPH
California School of Professional Psychology
Alameda, California

ABSTRACT. This review is a critical re-analysis of the Danish American Adoptees’ Family Studies, by Kety and colleagues, which are perhaps the most frequently cited studies in support of a genetic predisposition for schizophrenia. As noted by previous reviewers and as examined in detail here, these studies, conducted primarily between 1968 and 1994, contain problems that include (a) their design, (b) the definition of schizophrenia (in particular, the concept of a schizophrenia spectrum) they used, (c) the validity of their method for counting second-degree relatives, (d) their questionable methods for counting diagnoses in certain statistical comparisons, (e) their likely violation of the assumption of independent observations (by individually counting relatives who grew up in the same families), and (f) their failure to study environmental variables. Most important, the author argues that the policies of Danish adoption agencies led index adoptees to be placed into environments inferior to those into which control adoptees were placed. He also concludes that methodological problems and likely environmental confounds call into question the investigators’ conclusions that their studies furnished evidence supporting the genetic basis of schizophrenia. Given the problems associated with family, twin, and other adoption studies and the failure of molecular genetic studies to identify postulated genes, the entire body of evidence cited in support of a genetic predisposition for schizophrenia should be re-evaluated, and the debate over the existence of genetic factors in schizophrenia should be re-opened.

Key words: adaptive studies, genetics, Kety, psychiatric genetics, schizophrenia, selective placement
Joseph, 1998a, 1999b; Lewontin, Rose, & Kamin, 1984; Lidz, 1976; Lidz & Blatt, 1983; Lidz, Blatt, & Cook, 1981; Pam, 1995). This article’s objective is to look closely at the key issues raised by these critiques to determine whether the conclusions reached by Kety and his associates are consistent with the evidence.

The Adoptees’ Family method begins with a group of adoptees diagnosed with the condition in question (called index adoptees, or probands) and compares the prevalence of the particular condition both among the index adoptees’ biological and adoptive relatives and among the relatives of a group of control adoptees. In theory, adoption studies should be able to separate out the influences of genetic and environmental factors, because adoptees receive their genes from one family but are reared in the environment of another.

The first phase of the Danish American Adoptees’ Family Study took place in the greater Copenhagen area. The most important articles coming out of this work were published in 1968 and 1975. The first article (Kety, Rosenthal, Wender, & Schulsinger, 1968) was based entirely on institutional records; the second article (Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1975) was based in part on interviews conducted with the biological and adoptive relatives of both index and control adoptees. Following the publication of the 1975 Copenhagen Study, the work was extended to the rest of Denmark; this second phase of the study included preliminary reports on this new Provincial sample (Kety, Rosenthal, & Wender, 1978; Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978), which were based on institutional records only. The final article, which was published 16 years later (Kety et al., 1994), presented the results of the study of the interviews from the Provincial Study sample. There were also results reported for a Danish national sample, which combined the diagnoses of the Copenhagen Study and the Provincial Study.

Analysis of the Studies

The 1968 Copenhagen Study

Kety, Rosenthal, Wender, and their Danish associates presented their first article on the Danish American adoption work at the Dorado Beach schizophrenia conference in the summer of 1967; their Copenhagen Study was published the following year (Kety et al., 1968).

The investigators established an index group of 34 adoptees who had been diagnosed with chronic schizophrenia (designated as B1; \( n = 16 \)), acute schizophrenia (designated \( n = 10 \)).

Index cases granted in the City of Copenhagen and in the remainder of Denmark were screened, and a group of control cases who were not adoptees and were not diagnosed with schizophrenia were also established.

Kety and Wender transferred the adoptees to the adoptive families and interviewed the adoptees and their adoptive families. The central goal of the study was to determine whether the pairs of adoptees who were adopted together were more similar to each other than they were to other adoptees who were not adopted together.

Diagnoses that were made at the time of the study were based on the criteria used at the time of the study. The diagnostic categories used were schizophrenia, affective disorder, and other psychiatric disorders.

Four copies of the study were made for each adoptee, and each copy was mailed to a different set of relatives. The relatives were asked to rate the adoptee on a scale of 1 to 5, with 1 being the most severe and 5 being the least severe. The ratings were then converted to a score, and the scores were compared between the adoptees and their relatives.

Address correspondence to Jay Joseph, Box 5653, Berkeley, CA 94705-5653; jayjoseph2@aol.com (e-mail).

---


2 The index group consists of monozygotic twins.
The objective is to look nine whether the con-
with the evidence.
adoptees diagnosed bands and compares index adoptees’ bio-
f a group of control rate out the influences give their genes from
family Study took places coming out of this ity, Rosenthal, Wen-
ril records; the second . 1975) was based in tive relatives of both 1975 Copenhagen second phase of the ample (Kety, Rosen-
; & Jacobsen, 1978), ile, which was pub-
s of the study of the results reported for of the Copenhagen

d research method, see et al., 1984; Pam, 1995.

ized their first ar-
reach schizophrenia was published the
adoptees who had been = 16). acute schizo-

phrenia (designated as B2; n = 7), or borderline schizophrenia (designated as B3; n = 10). Index cases were selected from the records of all adoptions that had been granted in the City and County of Copenhagen between 1924 and 1947; from this group of adoptees, 507 had been recorded as being admitted to a psychiatric facility. The investigators were granted access to the Danish adoption records of the State Department of Justice; the Folkeregister (Population Register); the Psychiatric Register of the Institute of Human Genetics; records of the Mother’s Aid Organization; and police, court, and military records. The records of these adoptees were screened, and when a consensus B1, B2, or B3 diagnosis was made by Kety, Rosenthal, and Wender, that person became an index case. A control group was also established, consisting of 33 adoptees who had no record of admittance to a psychiatric facility.

Index and control adoptees were matched on the basis of age, gender, age at transfer to the adoptive parents, and the socioeconomic status of the adoptive family (Kety et al., 1968, p. 350). After the index and control groups were established, the researchers attempted to locate the records of the adoptees’ biological and adoptive relatives; 463 of these relatives were identified. Kety and his colleagues then searched for any existing psychiatric records for these relatives; when such records were found, a blind consensus diagnosis was made by Kety et al. (1968). The codes concealing the identity and group status of the relatives were then broken, and each case was then assigned to either the biological-relative or adoptive-relative category of the appropriate group (index or control). All diagnoses were based on information obtained from institutional records. There was no personal contact between the investigators and any of the adoptees or their relatives.

Diagnoses that fell into what was called the schizophrenia spectrum of disorders (Kety et al., 1968, p. 353) were counted as schizophrenia in comparisons between index and control relatives (see the discussion that follows). Diagnoses were made according to a global (or consensus) diagnostic system. This method, which was used during the entire series of studies (spanning more than 25 years), was described as follows:

Four copies of the edited summary were prepared and distributed to the four authors who served as raters and who independently characterized each subject according to the classification described below. The individual ratings were then tabulated and those cases in which there was disagreement among the raters were discussed at a conference of all four authors where an effort was made to review additional edited information which it was possible to obtain and to arrive at a consensus diagnosis acceptable to all. In 4 cases there remained an evenly split opinion regarding the presence of schizophrenia or doubtful schizophrenia, and these were not included in those categories. (Kety et al., 1968, pp. 351–352)

The index group consisted of 34 participants but only 33 cases because 2 of the index adoptees were B3 monozygotic twins.
Although high interrater reliability was claimed (Kety, 1974), each investigator approached the diagnostic process somewhat differently. According to Kety (1987), each rater’s “individual definitions of schizophrenia varied by virtue of [their] training and experience, from a substantial reliance on Kraepelin and Bleuler to the broader psychodynamic concepts which were taught in the 50s” (p. 424).

The distribution of spectrum diagnoses among index and control relatives, adoptive and biological, can be seen on pages 354–355 of the 1968 paper. Schizophrenia was defined as the aforementioned designations B1, B2, or B3, and it was also defined as uncertain chronic schizophrenia (designated as D1), uncertain acute schizophrenia (designated as D2), uncertain borderline schizophrenia (designated as D3), or schizoid and inadequate personality (designated as C) (Kety et al., 1968, p. 352). In addition, several psychiatric diagnoses outside of this spectrum were made by the authors. Kety and his colleagues found a higher prevalence of spectrum disorders among index biological relatives than among control biological relatives:

Of 150 biological relatives of index cases, 13, or 8.7%, had a diagnosis of schizophrenia, uncertain schizophrenia, or inadequate personality, compared to 3 of 156, or 1.9%, with such diagnoses among the biological relatives of the controls. The difference is highly significant (p one-sided probability from exact distribution = .0072). (Kety et al., 1968, p. 353)

Kety and colleagues concluded that “genetic factors are important in the transmission of schizophrenia” (p. 361).

Before re-analyzing Kety and his colleagues’ results, I will discuss six important topics relating to the 1968 study and to all the subsequent Danish American Adoptees’ Family reports as well: (a) the schizophrenia spectrum concept, (b) questions relating to the studies’ design, (c) the failure to study environmental variables, (d) the counting of half-siblings in statistical calculations, (e) the counting of individual relatives versus the counting of families, and (f) the evidence of selective placement in the Danish adoption process.

The schizophrenia spectrum concept. Although only chronic B1 “process” cases were traditionally counted as schizophrenia by Danish psychiatrists (Kety, 1978), the Danish American Adoptees’ Family Studies’ researchers broadened this definition of schizophrenia considerably to include what they considered to be related diagnoses. The doubtful validity of the Kety et al. concept of a schizophrenia spectrum has been discussed in great detail elsewhere (Joseph, 1998a, 2000a), and the main problems with the concept are summarized here.

1. The evidence suggests that the spectrum was created after the diagnoses of adoptees and relatives revealed very few cases of chronic schizophrenia. Thus, the researchers were compelled to widen the definition of schizophrenia in order to achieve statistical power, as opposed to the more frequent stated spectrum concept.
2. The investigators’ arbitrary definition of schizophrenia was found in relatives versus controls.
3. In spite of Kety et al., certain criteria were used to distinguish “schizophrenia” from “schizotypal,” and this distinction was important for a “very narrow” diagnosis of schizophrenia.
4. As noted by Kety et al., schizophrenia was found in relatives versus controls.
5. The spectrum conditions are found to be the same in all of the groups.

Because of the spectrum, chronic schizophrenia can be found in various settings.

Questions relating to the conclusions from the 1968 study were based on the findings of the Danish American Adoptees’ Family Studies. However, the original research data of relatives under study were not available. The investigators found a significant difference in spectrum biological (CB) (IA) and control adoptees and relatives.

A higher incidence of schizophrenia was found among the adoptees reared by biological parents, of, or not reared by adoptive parents.
quently stated purpose of desiring to test the hypothesis that the other spectrum conditions were genetically related to chronic schizophrenia.

2. The investigators’ rationale for the inclusion of a particular diagnostic category in the spectrum was based on finding a significantly greater number of diagnosed people among index biological relatives versus controls. However, with the exception of the vaguely defined “uncertain borderline schizophrenia,” no spectrum category in either the 1968 or 1975 studies was found in significantly greater numbers among index biological relatives versus controls.

3. In spite of Kety’s reliance on E. Bleuler’s description of latent schizophrenia (see Kety, 1985), Bleuler did not believe that it was possible to distinguish “milder cases of schizophrenia” from people who were merely “whimsical” (1911/1950, p. 294). Bleuler therefore called on clinicians to use a “very high diagnostic threshold value” in making a schizophrenia diagnosis (p. 294).

4. As noted by the researchers themselves, it was often difficult to distinguish spectrum disorders from similar, nonspectrum diagnoses (see Kety, Rosenthal, & Wender, 1978).

5. The spectrum concept was based on the logical fallacy of believing that conditions are genetically related simply because they are (allegedly) found together. As Gould noted, “The invalid assumption that correlation implies cause is probably among the two or three most serious and common errors of human reasoning” (1981, p. 242).

Because of the doubtful validity of Kety and his colleagues’ schizophrenia spectrum, chronic schizophrenia is the only recognized diagnosis in comparisons between the various relative groups made here.

Questions relating to the studies’ design. Beginning with those in the 1968 study, the conclusions from all of the Danish American Adoptees’ Family Studies reports were based on significant differences in the diagnoses of spectrum disorders found between the index biological relatives and the control biological relatives. However, there are questions about whether these comparisons reflect the original research design of the Danish American investigators. The four groups of relatives under study are represented in Figure 1.

The investigators’ conclusions were based on finding a statistically significant difference in spectrum diagnoses between the index biological (IB) and control biological (CB) groups and on finding no difference between index adoptive (IA) and control adoptive (CA) groups. According to Rosenthal,

A higher incidence among the biological relatives of index cases than of controls indicates that heredity is contributing significantly to the disorder. A higher incidence among the adoptive relatives of index cases than of controls supports the view that rearing by, of, or with schizophrenics contributes to the development of the disorder. (Rosenthal, 1970, p. 57)
The design of the study was questioned by Lidz and Blatt (1983), who made the unsupported claim that the study's original intent had been to compare the schizophrenia rates of IB and IA families: "The investigators sought to differentiate genetic from intrafamilial environmental factors by comparing the occurrence of such disorders in the biological and adoptive relatives of schizophrenic patients who had been adopted at a very early age" (Lidz & Blatt, 1983, p. 426). According to Lidz and Blatt, the fact that Danish adoptive parents had been screened for psychiatric disorders compelled Kety and associates to create a control group of nonschizophrenic adoptees and their relatives. Lidz and Blatt concluded that "the major interest of the study became the comparison of the biological relatives of the schizophrenic and control adoptees rather than the original purpose of the project" (p. 427).

Kety (1983a) replied that Lidz and Blatt incorrectly described the aim of study and misunderstood the logic of its design. Furthermore, according to Kety,

We anticipated that there would be differences between adoptive and biological relatives in age, socioeconomic status, life style, and other variables. For that reason we planned not to make comparisons between these two groups of relatives but, instead, as described fully in the original publications and outlined above, to compare each group with their respective controls in evaluating separately the significance of genetic or family-related environmental factors. (Kety, 1983a, p. 721)

It is true that the 1968 study discussed the importance of making direct comparisons between index relatives and control relatives from each group. However, a paper delivered by Rosenthal in 1967, 3 months before the first public presentation of the study, suggests that Lidz and Blatt were correct—that the intent of the researchers had been to compare the biological and adoptive relatives of index adoptees, as well as the biological and adoptive relatives of controls:

---

4I am unaware of any previously published description of the design and method of the 1968 study prior to its publication. Apart from Kety's (1959) article discussing the need to study adopted children, none are cited in any Danish American Adoptees' Family study paper.
Adoptive Relatives

IA
(Index Adoptive)

CA
(Control Adoptive)

In Denmark, with the collaboration of Dr. Fini Schulsinger and others, we began with adoptees who are now schizophrenic. *We compare the incidence of schizophrenic disorders in their biological and adoptive families* [italics added]. The same procedure is carried out for a matched group of normal adoptees, who serve as controls. (Rosenthal, 1967, p. 25)

Rosenthal is therefore on record as stating, in March of 1967, that the design of the study had been to compare the difference between Groups IB and IA with the difference between Groups CB and CA, but it was not until April of 1967 that all of the data were collected and the diagnoses were made (Kety et al., 1968, p. 346). When comparisons were made according to Rosenthal’s description, the difference was not statistically significant with either group. Kety et al. (1968, p. 355) found 13 spectrum diagnoses out of 150 index biological relatives (8.7%) and 2 diagnoses out of 74 index adoptive relatives (2.7%); the difference was not statistically significant (*p* = .076, Fisher’s exact test, one-tailed).

Thus, had the Danish American investigators analyzed their data using Rosenthal’s stated approach, they would have had to conclude that there were no significant differences between the groups and that their study had found no evidence in support of the genetic transmission of schizophrenia. Interestingly, neither Kety nor Rosenthal cited Rosenthal’s 1967 article in any of their subsequent publications on the genetics of schizophrenia.

The failure to adequately study environmental variables. Two years before the publication of the 1968 study, Kety wrote, “Although genetic factors undoubtedly operate in schizophrenia, they do not constitute a sufficient explanation for the genesis of this disorder” (1966, pp. 230–231). If Kety then had little doubt that genetic factors were operating, he might have instead concentrated more on discovering the environmental component of schizophrenia—for why should so much time and money be spent on investigating something that is “undoubtedly” true? Kety continued, “We must continue to look for environmental factors that operate to produce what we call schizophrenia in the genetically vulnerable individual. Fortunately, this seems to be the attitude of most investigators in the field” (p. 231).

---

1. used Fisher’s exact test in all statistical comparisons because it was used by Kety and associates in all of their important articles. Although other methods were available, I preferred to reanalyze the data using the same statistical tests found in the original articles.

2. Psychiatric geneticists Fanone and Tsuang (1995) described the Adoptees’ Family method, which they call the “adoptive-as-proband design,” as follows:

As its name suggests, the adoptee-as-proband design starts with ill and well adoptees and examines rates of illness in both biologic and adoptive relatives. If the biologic relatives of ill adoptees [IB] have higher rates of illness than the adoptive relatives of ill adoptees [IA], then a genetic hypothesis is supported. In contrast, if the adoptive relatives show higher rates of illness, then an environmental hypothesis gains support. (p. 92)

The likelihood that Kety et al. (1968) abandoned this comparison in favor of another that produced significant results did not hinder Fanone and Tsuang, two paragraphs later, from citing this study as evidence in favor of the genetic basis of schizophrenia.
Unfortunately, however, Kety generally abandoned any idea of looking for environmental factors; his studies considered only one environmental variable, and that for the likely purpose of answering anticipated objections to his research design. In 1970, Kety wrote,

We are really examining only one environmental factor and that is the presence of a person in the adoptive family with a mental illness. There are thousands of environmental factors which we have not examined: the personality of the family, their child-rearing practices, the diet which the individual has had, the lead in the drinking water and many perhaps undreamed of. Therefore, these data by no means rule out the operation of environmental factors. They simply indicate that at least one of these factors, namely, having a mentally ill person with a schizophrenic form of illness in the immediate environment, is not an important or significantly operating variable. (Kety, 1970, p. 240)

Kety wrote of the family-rearing environment as just another possible environmental influence on schizophrenia, one on par with lead levels in the drinking water, for instance, or diet. But this variable happens to be a major psychosocial explanation of a schizophrenia diagnosis, and therefore it deserves closer study. In a subsequent schizophrenia adoption study, Tienari and associates in Finland found that “all adoptees who had been diagnosed either as schizophrenic or paranoid had been reared in seriously disturbed adoptive families” (Tienari et al., 1987, p. 482; also see Joseph, 1999a). The Danish American Adoptees’ Family Studies would have been substantially more interesting and important had Kety followed his own advice from 1966 and, like Tienari and colleagues, taken a serious look at the psychosocial environments of the people under study.

The validity of counting half-siblings in statistical calculations. The Danish American investigators counted diagnoses among first-degree relatives and second-degree relatives (or biological half-siblings) equally. Most critics of the 1968 report have noted that only a single diagnosis of chronic schizophrenia—of a half-sibling—was made among the 150 index biological relatives. The statistically significant index spectrum rate was dependent on counting non-B1 diagnoses among index biological half-siblings. There were 9 spectrum diagnoses found in this group, whereas there were no such diagnoses among the control biological half-siblings. In the 1968 report, half-siblings were 57% of all biological relatives (173/306) and constituted 69% of diagnoses among index biological relatives (9/13). As we will see, the 1975 study rested its case for compelling evidence of genetic factors on the distribution of spectrum disorders among index and control paternal half-siblings.

In the mid-1970s, there was a debate among several prominent schizophrenia researchers over the importance in the study of the cases of half-sibling relatives. Gottesman and Shields (1976) noted that there was a higher rate of spectrum diagnoses among half-siblings than there was among full siblings, an ob-
d any idea of looking for an environmental variable, objections to his research and that is the presence of a are thousands of enironment-related, their child-lead in the drinking water no means rule out the operat at least one of these fac-ticantly operating variable.

and another possible envi-lead levels in the drink-ens to be a major psy-nd therefore it deserves tudy, Tienari and associ-agnosed either as schiz-red adoptive families” The Danish American life more interesting and nd, like Tienari and col-ments of the people

culations. The Danish degree relatives and sec-

Most critics of the 1968 ic schizophrenia—of a l relatives. The statistic-counting non-B1 diag-9 spectrum diagnoses among the control biere 57% of all biologi-mong index biological ase for compelling ev-risorders among index

prominent schizophrenies of half-sibling rela-
a higher rate of spec-
g full siblings, an ob-
ervation that led them to comment that “genetic theory predicts a much higher risk for full siblings” (p. 370). Kruglen argued that the higher rate among half-siblings “is, from a genetic point of view, meaningless” (1976, p. 430). Kety et al. (1976, p. 416) admitted that he and his associates had “toyed with the idea of giving them half-weight as soon as we realized how many were being identified, but rejected it as being too pretentious.” Later, Boyle (1990) commented, “It is difficult not to wonder whether the idea was also rejected because it leads to a quite different set of conclusions” (p. 144). Benjamin (1976) noted that “this finding is peculiar and contradictory. It shows, in effect, that the less consanguinity, the greater the ‘genetic’ effect. Differences should be weakest, not strongest, in the half-sibling category” (p. 1131). Kety (1976) argued in response that Benjamin’s observation was incorrect because the difference was not statistically significant. He explained further that, had a significant difference been found, it could have then been explained by “socioenvironmental” and other fac-

tors (p. 1135).

Lidz and Blatt (1983) argued that Kety and his colleagues, in counting half-siblings, should have given them a weighting on the basis of the status of the common parent, of whether the identity of the other parent was known, and of the type of genetic model used. They pointed out that there was no information in the study either about the half-siblings’ other parents or about family-rearing environments. Kety (1983a) replied that the findings from the 1975 report would have been significant even if half-siblings had only been accorded a half weight-
ing, and that in his opinion there was as much justification to give half-siblings a weighting of two as to give them a half weighting. He accused Lidz and Blatt of giving half-siblings no weight at all, because they had focused their attention on rates among first-degree relatives.

In this report, I argue that only first-degree relatives should have been counted. From the standpoint of genetics, knowing only half of the genetic background makes it difficult to determine genetic factors. In a discussion of other schizo-

phrenia adoption studies, Rosenthal (1974a) noted that investigations that have only half of the genetic equation are dealing in “confusion and folly” and that “a proper genetic study must be based on who mates with whom. In fact, although genetics has been defined in various ways, the simplest and perhaps best defini-
tion of genetics is: the science of matings” (p. 168). In the case of the Danish American Studies’ half-siblings, there is little known about the “who” and nothing known about the “whom,” yet the diagnoses from the products of these often-anonymous matings were decisive in the Kety-led studies.

From an environmental standpoint, it is unacceptable to count people about whose families and social environments little or nothing is known. In another comparison, Kety and his colleagues (1968, 1975) stressed that there were no significant differences in psychiatric diagnoses, either within the spec-

trum or “outside the spectrum,” between index and control adoptive families, thereby implying that both sets of adoptees grew up in comparable rearing en-
environments (although as we will soon see, Lewontin, Rose, & Kamin, 1984, found otherwise).

Suppose, for example, that most index adoptees had been raised by adoptive parents diagnosed with schizophrenia or another psychiatric disorder, whereas most or all of the control adoptees had been raised by parents without psychiatric disorders. Given this scenario, it is likely that Kety and his associates would have concluded that the significantly higher level of index adoptive-family distress was a factor in the higher rate of index-adoptive schizophrenia. This type of comparison cannot be made for the Danish American Adoptees’ Family Studies’ half-siblings, however, because there was no information provided about their family environments. Yet Kety and his associates have acknowledged that one needs such information to identify potentially pathological family-rearing environments.

Furthermore, the studies provided no information on how many biological parents of half-siblings actually lived with their children. An index father, for example, could have sired the half-sibling in question without actually raising the child. Quite literally, a spectrum-diagnosed half-sibling could have grown up eating out of garbage cans on the streets of Copenhagen, whereas a nondiagnosed half-sibling could have been raised in an exceptionally nurturing and loving environment.

Even Gottesman and Shields noted the problems of assessing the environments of the Danish half-siblings:

The high degree of psychopathology seen in the half sibs could have a major environmental component and could reflect cultural transmission. That is, the half sibs might have stayed with a disturbed biological parent or been subjected to various kinds of institutional care. Although such happenings may not be sufficient to produce schizophrenia, they may have produced “inadequate personalities” of the kind that might have been diagnosed as definite or uncertain latent or borderline schizophrenia (B3 or D3). (1982, pp. 144–145)

Gottesman and Shields bring up an important point: How many of these half-siblings were raised in institutions? This has never been discussed in any of the papers from these Danish American studies, however.

After giving a talk on the genetics of schizophrenia and the results of his studies, Kety was asked, “In your data on the paternal half siblings, how can we be sure that those fathers might not have sought out a schizophrenogenic mate repeatedly?” Kety replied to this question as follows:

That is a very good question. Frankly, we cannot rule it out; but this hypothesis requires the assumption that the fathers have some uncanny ability, greater than that of any psychiatrist I know, to pick out schizophrenogenic mothers. Furthermore, if the father had the propensity for picking schizophrenogenic mothers, this would still not be as effective as being the schizophrenogenic mother. On the basis of the hypothesis you propose, we would expect the biological maternal half siblings to have more schizophrenia than the paternal half siblings. That is not what we find. . . . so this hypothesis finds no support. (Kety, 1978, p. 67)
Kety's response contained one clear error: The rate of schizophrenia among the biological maternal half-siblings is irrelevant to the questioner's hypothesis because they were not raised by the same mother who raised the adoptee. Kety should have responded that children in the adoptive homes were the group of interest, because that was the location of the theorized schizophrenogenic environment. There were only 4 full siblings and 2 half-siblings raised in the adoptive homes of B1 index adoptees, so this question could not have been looked at in the 1975 study. However, the evidence from schizophrenia family studies indicates that the siblings of people diagnosed with schizophrenia are more likely to be diagnosed with schizophrenia than randomly selected members of the population are. Theoretically, this increased risk could be due to genes, environment, a combination of both, or methodological error. From a psychosocial perspective, family studies demonstrate that schizophrenogenic environments do exist, and nothing in Kety's data suggests that such environments do not also exist in the homes (or institutions?) of the paternal half-siblings.

According to Rosenthal, to "demonstrate that genes have anything to do with schizophrenia," the investigator must show that "the frequency of schizophrenia in relatives of schizophrenics [is] positively correlated with the degree of blood relationship to the schizophrenic index cases" (1974b, p. 589). That the series of Adoptees' Family Studies failed this test speaks to the operation of environmental factors causing the high rate of spectrum diagnoses among index-adoptee half-siblings.

In conclusion, the counting of half-siblings—for whom no biographical information is provided—is untenable on both genetic and environmental grounds and suggests that there is no basis on which they should be counted in the Danish American adoption studies. Following Lidz and Blatt (1983), therefore, the focus of this investigation is on the diagnoses that were found only among first-degree biological relatives.

**The counting of individual relatives versus the counting of families.** Benjamin (1976) observed that counting each biological relative separately and combining them into totals, for both index and control groups, is a violation of the assumption of independent observations:

The procedure of counting up all the possible relatives of each index case and pooling them as if they were independent samples ... would allow some families to disproportionately affect the results. ... This group of people, who were likely to have been reared together and to have had the same health care system supplying records used in the study, could falsely inflate the "significance" of the difference. (p. 1130)

According to Benjamin, the 1975 study should have reported a sample size of 67 (the combined number of index and control biological-relative families); instead, Kety and his colleagues reported a sample size of 347 (the number of biological relatives overall). Kety (1976) replied that his study did indeed recognize the importance of counting families in addition to counting individuals. By
Kety and his colleagues’ calculations, spectrum disorders were found in 17 of 33 biological index families and in only 5 of 34 biological control families (p = .0014; Kety et al., 1975, p. 163). However, they had to redefine the spectrum to find statistical significance in this comparison.⁶

According to Loren Mosher, then editor of Schizophrenia Bulletin and the Director of Schizophrenia Research at the National Institute of Mental Health,

The actual sample size of all the adoption studies is, at least for genetic purposes, the number of index probands [adoptees], not the number of relatives identified. The power of the adoption methodology is its separation of heredity and environment for genetic analysis; therefore, when n’s are reported as the number of biological relatives seen, it leaves the misleading impression that the genetic/environmental separation is applicable in this group, whereas, in point of fact, it is not. Basically, studying either biological or adoptive relatives is just a special family study. (Mosher, 1975, p. 3)

Benjamin’s and Mosher’s observations have merit because clusters of schizophrenia in particular families could be explained by exposure to common environmental influences or by siblings receiving similar hospital diagnoses because they were viewed as sharing the same familial “tainting.” For Mosher in particular, counting all biological relatives individually in statistical comparisons transformed the Adoptees’ Family method into little more than a “special family study.” Thus, using a sample size of 347 in the 1975 interview study (and a sample size of 306 in the 1968 study) does seem to violate the independence assumption of the statistical procedures used.

The evidence of selective placement of adoptees. There is evidence that the selective placement of adoptees was a major factor influencing the Danish adoption process, meaning that the Adoptees’ Family Studies were likely confounded by environmental factors. Although it is not frequently discussed by adoption researchers, the validity of adoption studies depends on the assumption that placements were made randomly:

Adoption studies are based on a critical theoretical assumption: that factors relating to the adoption process (including the policies of adoption agencies) did not lead to the placement of experimental (index) adoptees into environments compared to the placement of adoptees into homes correlated with the status of their biological family. (Joseph, 1999b, p. 133)

I begin with the findings of criminality adoption researchers Hutchings and Mednick:

⁶As noted by Lidz and Blatt (1983), spectrum Category C was omitted from this comparison. If Category C had been included, the results would have been 23/33 index families affected versus 16/34 affected control families. A Fisher’s exact test revealed that the probability for this difference was not significant (p = .05108). In another article Kety et al. (1976, p. 418) acknowledged that the comparison was not significant, writing “NS” below the totals (see my discussion of the 1975 study).
The most important limit of the adoption method is the possibility that the adoption procedure results in selective placement, promoting correspondence between the adoptive home and the characteristics of the biological parents. ... The Danish organization which arranged many of the adoptions examined in this study states clearly that they do aim at matching in certain respects. (Hutchings & Mednick, 1975, p. 115)

Hutchings and Mednick (1975) found a statistically significant correlation between the social classes of the biological and adoptive fathers. Teasdale (1979) studied all 14,427 national-sample adoptees identified by Kety and his associates and found a significant correlation between the socioeconomic status of the adoptees’ biological parents and the adoptees’ adoptive fathers. Teasdale concluded that “some selective placement has occurred in the sample; i.e., the adoption agencies tended to place children into adoptive homes as a function of their biological background” (p. 108).

Kety and his colleagues believed that placement policies in Denmark did not create a major problem for their study:

Since the etiological role of environmental variables remains obscure at present, it is not likely that a social agency, even if it set about doing so deliberately, could find sufficient of the unknown variables in the prospective adoptive parents to materially affect the risk of [schizophrenic] illness in the adoptee. (Kety et al., 1994, p. 452)

According to Kety and associates, it was therefore unlikely that agency policies led to the placement of index adoptees into more schizophrenia-producing environments. But is this really the case?

The potentially confounding influence of selective placement can be seen by looking at pellagra, a disease that is characterized by digestive, skin, and nervous disturbances that are followed by mental deterioration. Because of its tendency to cluster in certain families, pellagra was once thought to have an important genetic component. It was later shown that the disease is caused by a niacin deficiency. Pellagra was found mainly in poor families where there was not enough niacin in the diet (Joseph, 2000c). As observed elsewhere,

According to Kety’s logic, an early 20th-century adoption agency, unaware of the true causes of pellagra, could not have systematically placed certain classes of adoptees into more “pellagrogenic” environments. However, if an agency had placed adoptees into homes corresponding to the socioeconomic status of the adoptee’s biological family, then adoptees born into poor families would have been placed into poorer adoptive homes, where they would have been more likely to develop pellagra. All of this would have occurred without the adoption agency having any idea what the “unknown variables” of pellagra were. And Kety and associates (1994, p. 452) have acknowledged that schizophrenia, like pellagra, is correlated with lower socioeconomic status. (Joseph, 1999b, p. 134)

In the opinion of Kety and his associates (1994, p. 453), knowledge of the parents’ psychiatric status did not influence the results of their studies because “in practically every case” index adoptees were born to parents who had no record of mental disorders at the time of adoption. But as will be seen, a prospective adoptee’s biological parents were not the only relatives checked for
a history of mental disorder. As can be seen in the 1946–47 annual report of the Mother’s Aid Organization of Copenhagen, which was the largest adoption service in the country, the family background of a potential adoptee was of great concern to the Danish authorities. Recall that adoptees in the Copenhagen Study and Provincial Study were placed between 1924 and 1947:

Before a child is cleared for adoption, it is investigated with respect to health, and an attempt is made to obtain detailed information on the child’s family background and to form an impression of its developmental potential. Not only for the adoptive parents, but also for the child itself, these investigations are of great importance for its correct placement. Information is obtained on the child’s mother and father; on whether or not there are serious physical or mental illness in the family background [italics added]; criminal records are obtained for the biological parents; and in many cases school reports are obtained. By means of personal interview with the mother an impression of her is formed. Where information is uncovered on convicted criminality or on mental retardation, mental illness, etc. in the family background [italics added], the case is referred to the Institute of Human Genetics of Copenhagen University, with whom there exists a valuable cooperation for advice on the advisability of adoption. (Mother’s Aid Organization for Copenhagen, Copenhagen County and Frederiksberg County. Annual Report for 1946–47; Quoted in Mednick & Hutchings, 1977, p. 163)

This passage demonstrates that selective placement was operating in Denmark during the period when the Kety et al. adoptees were being placed for adoption. Potential adoptees were carefully screened for a family history—which went well beyond that of the biological parents—of mental disorders. Where there were suspicions of a family history of mental disorders, the case was turned over to the Institute of Human Genetics, which was the keeper of the National Psychiatric Register. It is likely that a more thorough check of that family’s psychiatric records was then undertaken. Therefore, the fact that an adoptee’s biological parents had no record of mental disorder at the time of adoption does not diminish the likelihood that adoptee placements were influenced by the prevalence of mental disorders among other members of the adoptee’s biological family. Because mental disorders were considered to have an important genetic component—which would therefore brand a potential adoptee as “tainted”—the family background of an adoptee (who often was only an infant) was considered “of great importance for its correct placement.” Potential adoptees with a family history of mental disorders were considered to have poor “developmental potential”—that is, poor “genetic potential”—and were likely placed with less qualified adoptive families.

It is critically important to understand that the country in which these adoptions took place had a long history of governmental and social support for eugenic practices. Denmark became the first European nation to pass national legislation for the purpose of promoting eugenic sterilization, predating by 4 years

the Nazi Germany's sterilized sterilization in not include the work of production must be Hansen, 1996, p. 34. According to Hansen, 'ment among all policies in 1935 a new cases, typically those by the under a sterilization performed 1960s that compulsive Manfred Bleu the so-called "hered As we have seen, the early-to-mid part of During much of many more Danish ones to adopt. As des: Many of these as: It was more diffic the relative una adoptees avail: Apparently, the ado shish history, and in th biological parents v less they refused the shports of children v "Every weekend (i: would visit the orph adoptive parent is: (Mednick, 1996, p.

1 No mention of the adoptee's biological diagnostic status at the time of adoption was made in the Kety et al. (1968 or 1975) articles.
the Nazi Germany sterilization law of 1933. The 1929 Danish legislation legalized sterilization in cases of retardation or mental disorder. Although the law did not include the word “eugenic,” it allowed sterilization “where suppression of reproduction must be regarded of being of great importance to society” (quoted in Hansen, 1996, p. 38). The law easily passed in the Danish Parliament and according to Hansen, “The Danish version of eugenics seemed to command agreement among all political parties” (p. 39).

In 1935 a new law was passed allowing compulsory sterilization in certain cases, typically those labeled “mentally abnormal” (Hansen, 1996, p. 41). Compulsory eugenic sterilization was now widely accepted in Denmark: “While everybody up to and during the passing of the 1929 law had recommended caution, they now spoke of eugenics legislation as something that was urgently needed” (Hansen, 1996, p. 45). According to Hansen, there were nearly 6,000 eugenic sterilizations performed in Denmark between 1929 and 1950, and it was not until the 1960s that compulsory eugenic sterilization was legally abolished in Denmark.

Manfred Bleuler, who was well acquainted with European attitudes toward the so-called “hereditary taint” of schizophrenia, gave the following description of the effect of these attitudes on the afflicted families:

If one knows schizophrenics and their families well, it is sometimes a matter for despair to see how much they suffer under the terrible concept of “familial tainting.” Like a sinister shadow it darkens the lives of many people and of entire families. The stifling, uncertain fear of coming from an “inferior breed,” of carrying within one’s self the seeds of something pathological, morbid, and evil (I am speaking in the jargon of the afflicted) to themselves, like a curse that you must pass on to someone else, causes oppressive feeling of inferiority. (1978, p. 473)

As we have seen, there is good reason to believe that attitudes in Denmark in the early-to-mid part of the 20th-century were similar to those described by Bleuler.

During much of the period when these adoptees were placed, there were many more Danish children available for adoption than there were families wanting to adopt. As described by Mednick, Gabrielli, and Hutchings,

Many of these adoptions took place during the Great Depression and World War II. It was more difficult to find willing adoptive homes in these periods owing partly to the relative unavailability of adoptive parents and to the additional number of adoptees available. (1987, p. 78)

Apparently, the adoption process was a buyers’ market during this period of Danish history, and in the words of Mednick and Hutchings, “serious deviance in the biological parents was routinely reported to the prospective adoptive parents unless they refused the information” (1977, p. 161). Mednick discussed the case reports of children who were put up for adoption but who were never placed: “Every weekend (at least in the 1930s), Danish people who wished to adopt would visit the orphanages and pick children... Children whose selection by an adoptive parent is delayed may be less attractive physically and behaviorally” (Mednick, 1996, p. 134). It is likely that many children were also less attractive
genetically. To put it crudely, each weekend Danish prospective adoptive parents arrived at the orphanage and picked children as they might have selected apples at the market. Healthy, attractive, and non-"hereditarily tainted" children were picked by the most qualified parents as they would have chosen the most attractive apples. The "best" families would have obtained the most desirable children, leaving the less desirable ones either unadopted or placed with families who provided a less favorable rearing environment (Joseph, 2001c).

To continue with this analogy, it might be expected that all buyers would have had an equal chance to select the best apples. This was unlikely the case in the Danish adoption process, however, because placement officials had the ultimate authority to determine where children would be placed. Most probably, children with the best "developmental potential" were placed into more stable and nurturing family environments, leaving the rest to be placed into less stable families.

An important indication of the impact of selective placement was discovered by Lewontin and colleagues (1984), who were granted access to the Danish American data. It turned out that a notation had been made in each file if a relative had been placed in a mental institution. Lewontin et al. found that in 8 of the 33 index adoptive families, a parent had been admitted to a mental hospital, whereas this was true for none of the control families. Lewontin and colleagues concluded:

A credible interpretation of the Kety et al. results [is] that the schizophrenic adoptees, who indeed had been born into shattered and disreputable families, acquired their schizophrenia as a result of the poor adoptive environments into which they were placed. The fact that one's adoptive parent goes into a mental hospital clearly does not bode well for the psychological health of the environment in which one is raised. (1984, p. 223)

It appears that the single environmental variable assessed by Kety and associates—the prevalence of mental disorders among adoptive family members—showed a significantly higher psychiatric hospitalization rate among index adoptive parents versus control adoptive parents. This finding is consistent with the previously discussed evidence of selective placement in the Danish adoption process. As Mednick, who had intimate knowledge of the Danish adoption process, acknowledged, "In Denmark, the national adoption agency had a policy of selective placement" (1996, p. 134), although he believed that "the agency was not successful" (p. 134). However, the evidence suggests that the agency was indeed "successful" in many respects.

To summarize, it is likely that the placement of Danish adoptees was influenced by the socioeconomic and psychiatric background of their biological families, leading to the placement of "tainted" children into more psychologically harmful rearing environments. Therefore, before any conclusions about the role of genetic factors can be drawn from the Danish Adoptees' Family Studies, it must be shown that index adoptees were not systematically placed into family-rearing environments placed.

Re-analysis of the 19th environmental factors' post-1968 data the first-degree biological criteria measure of the difference observed between the 16 B1 index adoptees compared with 1 such control adoptees. A closer relative with such a dichotomy, the 1968 study schizophrenia. Kety's comparisons by greatly c second-degree relative

The Kety and Colleagues

Method and results. The study was published from the 1968 study at the time of attempt as possible. They believe, which had not among these relatives. The interviews with language transcripts v States, who made blind

The interviews were conducted in check lists and face to face interviews were transcribed. There were now 174 control. One diagnosis was B1, mean 9 B3s, and 7 B2s. A "somatic" was identified; this gives
potential adoptive parents might have selected apples "tainted" children were
that all buyers would
placement was discovered
at the schizophrenic adoptees,
assessed by Kety and asso-
Danish adoption
Danish adoption
Danish adoptees was influ-
more psychologically
rearing environments that were inferior to those in which control adoptees were
placed.

Re-analysis of the 1968 study. The study’s methodological flaws and confounding environmental factors aside, I argue here that (according to Kety and his associates’ post-1968 design) the prevalence of chronic B1 schizophrenia among the first-degree biological relatives of B1 index and control adoptees is the only valid measure of the genetics of schizophrenia. Utilizing these criteria, the difference observed between index and controls for affected individuals or families was not statistically significant. Among the 34 first-degree biological relatives of the 16 B1 index adoptees, there were no diagnoses of chronic B1 schizophrenia, compared with 1 such diagnosis among the 68 first-degree biological relatives of control adoptees. A comparison of families with at least 1 first-degree biological relative with such a diagnosis yielded similar results. Thus, on the basis of these criteria, the 1968 study provided no evidence in favor of the genetic theory of schizophrenia. Kety and colleagues found significant differences for both comparisons by greatly expanding the definition of schizophrenia and by counting second-degree relatives.

The Kety and Colleagues 1975 Study

Method and results. The next major report from the ongoing Adoptees’ Family Studies was published in 1975 (Kety et al., 1975). Using the same index adoptees from the 1968 study and adding 1 more control adoptee, the researchers faced the difficult task of attempting to interview as many adoptive and biological relatives as possible. They believed that there were many “schizophrenia-related disorders,” which had not been identified through the use of institutional records, among these relatives.

The interviews were conducted by Danish members of the team. English-language transcripts were sent to Kety, Wender, and Rosenthal in the United States, who made blind global diagnoses. According to the authors:

[The interviews] were extremely exhaustive, 35 pages in length, including many check lists and much narrative material, and covered the major aspects of the life experience: sociological, educational, marital, occupational, and peer relationship history from birth, medical background, and a careful mental status examination. These interviews were transcribed in English... and the transcripts were edited to remove any clues which a sophisticated reader might use to guess that this was a biological or adoptive relative of an index case or of a control. (Kety et al., 1975, p. 150)

There were now 347 identified biological relatives in the study (173 index and 174 control). One record-based, B3-diagnosed index adoptee (S3) was re-diagnosed as B1, meaning that index adoptee diagnoses now consisted of 17 B1s, 9 B3s, and 7 B2s. A “screened control” group of 23 control adoptees (out of 34) was identified; this group consisted of control adoptees who had been inter-
viewed and had been judged free “from the suggestion of schizophrenic disorder” (1975, p. 155).

The investigators found a significantly greater number, and higher percentage, of spectrum disorders in the index biological-relative group compared with the control biological-relative group (37/173 versus 19/174, \( p = .006 \)). From the table provided by Kety and associates (1975, p. 154), the numbers of various spectrum diagnoses found in the group of index biological relatives versus the group of control biological relatives were as follows: For B1 diagnoses, there were 5 in the index group versus none in the control group; for B3 diagnoses, there were 6 in the index group versus 3 in the control group; for the sum of D1, D2, and D3 diagnoses, there were 13 in the index group versus 3 in the control group; and for C diagnoses, there were 13 each in the index group and control group. A full 65% of noncategory-C spectrum diagnoses were made on half-siblings, and nearly one half were “uncertain.” Of the 5 diagnoses of chronic (B1) schizophrenia among index biological relatives, only 1 was of a first-degree relative. No significant differences were found between index adoptive relatives and control adoptive relatives.

Although the investigators’ calculations showed the combined spectrum diagnoses to be significantly concentrated among the index biological relatives, this finding was, according to Kety et al., “compatible with a genetic transmission for schizophrenia,” but not “entirely conclusive” (1975, p. 156). Because of possible factors such as birth trauma, in utero influences, and early mothering experiences, “one cannot, therefore, conclude that the high prevalence of schizophrenia illness found in these biological relatives of schizophrenics is genetic in origin” (p. 156).

However, Kety and his colleagues pointed to another comparison which, they argued, provided stronger evidence in favor of genetic factors:

The largest group of relatives which we have is, understandably, the group of biological paternal half-siblings. Now, a biological paternal half-sibling of an index case has some interesting characteristics. He did not share the same uterus or the neonatal mothering experience, or an increased risk in birth trauma with the index case. The only thing they share is the same father and a certain amount of genetic overlap. Therefore, the distribution of schizophrenic illness in the biological paternal half-siblings is of great interest. (Kety et al., 1975, p. 156)

The investigators noted that there were 16 spectrum diagnoses, based on records and interviews, among these paternal half-siblings, but that this distribution was “highly unbalanced” (14 index, 2 control). Kety and his colleagues concluded, “We regard this as compelling evidence that genetic factors operate significantly in the transmission of schizophrenia” (p. 156).

As noted earlier, the investigators realized that counting individual relatives might not be “entirely appropriate” because of cases clustering “into a limited number of biological and adoptive families” (Kety et al., 1975, p. 156). A table was presented that showed, on the basis of their criteria, that index families were more

affected at the .001 level of the evidence.

The inclusion and exclusion of cases was not dropped from the analysis. After breaking the data into category by category, Kety et al. found that all diagnoses except C were significantly higher in the index category. For example, the table includes Category C totals a spectrum.” Therefore, spectrum. Kety et al. noted that diagnoses of chronic (B1) schizophrenia among index biological relatives, only 1 was of a first-degree relative. No significant differences were found between index adoptive relatives and control adoptive relatives.

Although the investigators’ calculations showed the combined spectrum diagnoses to be significantly concentrated among the index biological relatives, this finding was, according to Kety et al., “compatible with a genetic transmission for schizophrenia,” but not “entirely conclusive” (1975, p. 156). Because of possible factors such as birth trauma, in utero influences, and early mothering experiences, “one cannot, therefore, conclude that the high prevalence of schizophrenia illness found in these biological relatives of schizophrenics is genetic in origin” (p. 156).

However, Kety and his colleagues pointed to another comparison which, they argued, provided stronger evidence in favor of genetic factors:

The largest group of relatives which we have is, understandably, the group of biological paternal half-siblings. Now, a biological paternal half-sibling of an index case has some interesting characteristics. He did not share the same uterus or the neonatal mothering experience, or an increased risk in birth trauma with the index case. The only thing they share is the same father and a certain amount of genetic overlap. Therefore, the distribution of schizophrenic illness in the biological paternal half-siblings is of great interest. (Kety et al., 1975, p. 156)

The investigators noted that there were 16 spectrum diagnoses, based on records and interviews, among these paternal half-siblings, but that this distribution was “highly unbalanced” (14 index, 2 control). Kety and his colleagues concluded, “We regard this as compelling evidence that genetic factors operate significantly in the transmission of schizophrenia” (p. 156).

As noted earlier, the investigators realized that counting individual relatives might not be “entirely appropriate” because of cases clustering “into a limited number of biological and adoptive families” (Kety et al., 1975, p. 156). A table was presented that showed, on the basis of their criteria, that index families were more

affected at the .001 level of the evidence.
number, and higher percent-ative group compared with 9/174, \( p = .006 \). From the t, the numbers of various logical relatives versus the s: For B1 diagnoses, there l group; for B3 diagnoses, 1 group; for the sum of D1, 1 up versus 3 in the control e index group and control ses were made on half-sib-diagnoses of chronic (B1) 1 was of a first-degree rel-index adoptive relatives and he combined spectrum di-index biological relatives, with a genetic transmis-1975, p. 156). Because of s, and early mothering ex-igh prevalence of schizophrenies is genetic in other comparison which, ectic factors:

standably, the group of bio-half-sibling of an index case e same uterus or the neon-trauma with the index case, amount of genetic overlap, biological paternal half-sib-gnoes, based on records that this distribution was is colleagues concluded, tors operate significantly nating individual relatives lustering “into a limited 975, p. 156). A table was index families were more

affected at the .001 level of probability. Kety and associates concluded that the weight of the evidence was strongly in favor of a genetic basis of schizophrenia.

The inclusion and noninclusion of Category C. A critique of the 1975 study should begin with a discussion of how it defined a schizophrenia spectrum. It is important to understand that Category C (schizoid and inadequate personality) was not dropped from the schizophrenia spectrum; rather, it was simply not included in the most important statistical comparisons (Lidz & Blatt, 1983).

After breaking the code and assigning interview diagnoses to their respective categories, Kety et al. found that Category C cases were equally distributed between index biological relatives and control biological relatives; each had 13. That this diagnosis was nevertheless still considered part of the schizophrenia spectrum is reflected by Kety and his colleagues’ Table 3 (1975, p. 154). This table includes Category C under the “schizophrenia spectrum” heading, and the Category C totals are likewise included in the column “total in schizophrenia spectrum.” Therefore, Category C remained a component of their schizophrenia spectrum. Kety and his associates noted that this diagnosis did not differentiate between index biological relatives and control biological relatives, thereby casting doubt on its relationship to B1 schizophrenia. However, they “were not prepared to dismiss the possibility that there is a schizoid or inadequate personality which is genetically related to schizophrenia” (p. 155).

As has been noted, Kety and his colleagues found “compelling evidence” for the genetic transmission of schizophrenia in the differences in spectrum diagnoses found among paternal half-siblings. However, they had to exclude Spectrum Category C to obtain a significant difference, as seen in a comparison published (but not referred to) by Kety and his colleagues (Kety et al., 1976, p. 418, Table 2a). In this table—including Category C—the comparison of the index paternal half-siblings and control paternal half-siblings is listed as index 18/63 (28.5%) and control 11/64 (17.2%), yielding a nonsignificant \( p \) value of .094. Thus, Kety and his associates omitted Category C from their calculations, even though they still considered it to be a schizophrenia spectrum disorder. Lidz and Blatt (1983) called the removal of Category C from this comparison a “post hoc change in criteria” (p. 430) and correctly called the procedure invalid. The “significant difference” cited by Kety and his associates as “compelling evidence” of the genetic transmission of schizophrenia turned out to be, in fact, statistically nonsignificant—a fact that most psychiatry textbooks published since the mid-1970s have failed to mention (Joseph, in 2001b).

---

8When the comparison is limited to the B or “definite” cases, Kety and his colleagues reported that the rate of affected index families was significantly higher than the control rate (index 14/33 vs. control 3/34, \( p = .002 \); Kety et al., 1975, p. 163). However, this comparison reflects an error on the part of Kety et al. because there were only 8 index biological families with a member receiving a 1968 or 1975 B diagnosis, rendering the comparison statistically nonsignificant (8/33 vs. 3/34, \( p = .08 \), Fisher’s exact test, one-tailed). See Boyle (1990) for more details.
David Rosenthal was a coauthor of the Kety et al. 1975 study; his "compelling evidence" for the genetic basis of schizophrenia was based on the "confusion and folly" of looking at participants for whom he knew (at best) only half of the genetic picture and on omitting the schizoid (Category C) diagnosis, which in the same year he had written was "indeed genetically related to process schizophrenia" (Rosenthal, 1975, p. 201).

Problems with the interview method. Although the 1975 study is typically referred to as "interview-based," only 72% of the 347 identified biological relatives and 48% of the 165 identified adoptive relatives were actually interviewed (see Kety et al., 1975, p. 151). Of the biological relatives, 79% were alive and accessible; the rest had died, had disappeared, or had emigrated outside of Scandinavia.

Although these are common characteristics of studies of this type, there is a problem here, in that all 347 identified biological relatives were counted in the study’s statistical calculations. The investigators decided that 347 was "the most unbiased and conservative denominator" (p. 153). In counting all of the relatives, however, there was a dilemma: what to do with those diagnosed in 1968 who in the intervening 7 years either had died or were otherwise unavailable for interviewing. There are clear inconsistencies in how these deceased or otherwise unavailable diagnosed relatives were counted (Lidz & Blatt, 1983). For example, in a comparison of a table on page 154 (Kety et al., 1975, p. 154) with a related table on page 158, it is apparent that 1 of the 3 relatives who had received (based on records) a Category D diagnosis in 1968, and who in the intervening 7 years had either died, emigrated, or refused to be interviewed, was nevertheless given a spectrum diagnosis in 1975; the other 2 relatives, however, were not. However, all record-based Category B and Category D diagnoses were counted in the comparison of paternal half-siblings.

The case of 1 control adoptee’s (identified as C9) biological father highlights the inconsistent and often arbitrary way that family members were counted. This individual had received a B1 diagnosis in 1968 but had died before he could be interviewed. Although by 1975 his B1 diagnosis was no longer incorporated into the statistical calculations, this individual was still counted as a nonspectrum relative. To add to the confusion, he was also counted as a control, screened, record-based diagnosis in Table 4b (Kety et al., 1975, pp. 160–161), but not in Table 3 on page 154. The omission of this relative from Table 3 makes it appear as if the B1 diagnoses were significantly concentrated among index biological relatives as opposed to control biological relatives (5 to 0), when in fact, if this particular control biological relative (C9’s biological father) is included in the count of B1 diagnoses among controls, the difference becomes a nonsignificant 5 to 1 (index 5/173 versus control 1/174, p = .10, Fisher’s exact test, one-tailed).

This first-degree biological relative was both a screened as well as a B1 matched control. The probable reason this person was not counted is subsequently revealed in the report, but it cannot be accepted that he was not, especially because he we...
t al. 1975 study; his "com- 
mitment was based on the "con- 
trolled" he knew (at best) only half 
category C) diagnosis, which 
ally related to process schiz-
5 study is typically referred to 
ied biological relatives and 
ually interviewed (see Kety 
 were alive and accessible; 
outside of Scandinavia. 
udies of this type, there is a 
atives were counted in the 
 that 347 was "the most 
counting all of the relatives, 
diagnosed in 1968 who in 
wise unavailable for inter-
deceased or otherwise-un-
at, 1983). For example, in 
75, p. 154) with a related 
 who had received (based 
in the intervening 7 years 
ed, was nevertheless given 
 ever, were not. However, 
 were counted in the com-
ological father highlights 
bers were counted. This 
ed died before he could be 
 longer incorporated into 
ted as a nonspectrum rel-
trol, screened, record-
t-161), but not in Table 3 
 makes it appear as if the 
ex biological relatives as 
 fact, if this particular 
cluded in the count of B1 
insignificant 5 to 1 (index 
one-tailed). 
screened as well as a B1 
is not counted is subse-
ent that he was not, espe-
cially because he was counted in some statistical calculations but not in others. Fortunately, this issue was eventually resolved, because in 1988 Kety began counting C9's biological father in the Copenhagen Study as a B1 diagnosis of a control biological relative (Ingram & Kety, 1988, p. 122; Kety et al., 1994, p. 452). Therefore, no dispute exists between Kety et al. and my present study in counting this participant as a B1 control relative.

The treatment of C9's biological father is an example of how a single diagnosis was handled differently in different sets of statistical calculations. The 1968 study counted this individual's record-based B1 diagnosis, but that he was the only first-degree biological relative diagnosed with schizophrenia was deemed unimportant when he was compared with the significant clustering of spectrum disorders found among index biological relatives. In contrast, the 1975 study did not count the chronic schizophrenia (B1) diagnosis of C9's biological father, an exclusion that allowed the comparison of B1 diagnoses between index and control biological relatives to become statistically significant. By 1988, this individual had been recategorized as a Copenhagen Study B1 relative, but by then he could be mixed in with those from the Provincial Study diagnoses, and the comparison remained significant (see Ingram & Kety, 1988, p. 122).

Of the 364 biological and adoptive relatives who were alive and accessible, 12 refused to be interviewed; nevertheless, according to the report, there was "adequate information" available about them to make a diagnosis. According to the investigators, "even though the individual persistently refused to give an interview, Dr. Jacobsen nevertheless obtained considerable information in the process" (Kety et al., 1975, p. 150). How this "considerable information" on these reluctant individuals may have been obtained is described in a 1974 article by Paikin et al. In this article, the authors described the problems that the investigators had with participants who did not want to be interviewed. The following illustrates a scenario in which the researchers felt they had obtained enough information from a home visit to determine whether a participant was in or out of the schizophrenia spectrum:

In those cases where the psychiatrist was not invited into the house, the face-to-face contact varied between a few minutes to twenty minutes. In general, it was found that if the subject was seen for less than five minutes, the amount of information gained was not sufficient for a judgment to be made as to whether the subject was psychiatrically inadequate or not. . . . It must be stated that much of the information obtained was somewhat superficial; it was necessary to give some weight to a general impression of the subject with particular emphasis being placed on disturbances in emotional contact, language use and thought processes. The diagnostic presentation has, therefore, been restricted to three broad categories: outside the schizophrenia spectrum, suspected schizophrenia spectrum, and schizophrenia. (Paikin et al., 1974, pp. 308-310)

It appears, then, that the Danish American investigators considered a 5-minute conversation at the front door of a participant's house sufficient to determine whether that individual should be included in the schizophrenia spectrum.
Although Paikin et al. (1974) described the interview process of a different Danish American schizophrenia adoption study, it is possible that several relatives in the Adoptees’ Family Studies were diagnosed in a similar fashion.

Next, I consider the pseudo-interviews, which were first brought to public attention in 1984. According to Lewontin and colleagues (1984), who had been in contact with one of the psychiatrists who had conducted the interviews,

In several cases, when relatives were dead or unavailable, the psychiatrist “prepared a so-called pseudo interview from the existing hospital records.” That is, the psychiatrist filled out the interview form in the way in which he guessed the relative would have answered. (p. 225)

In other words, Danish members of the team made up interviews for several relatives. Lewontin and colleagues described the case of Index Adoptee S11’s biological mother, who had received a Category C diagnosis of inadequate personality in the 1968 study. By 1975, her diagnosis after her “interview” was changed to Category D3 (uncertain borderline). In fact, this woman “had committed suicide long before the psychiatrist had attempted to locate her, and so—from the original hospital records—she was ‘pseudo-interviewed’” (Lewontin et al., 1984, p. 224). It turned out this woman had been hospitalized on two different occasions for manic depression, a condition outside the schizophrenia spectrum and one considered genetically unrelated to schizophrenia by Kety, Wender, and Rosenthal (Kety et al., 1976).

The use of these pseudo-interviews, left unmentioned in the published Danish American papers, seems to explain the case of Control Adoptee C9’s biological father. As stated earlier, he had been diagnosed B1 in the 1968 report; he then died and was assigned no diagnosis in the 1975 follow-up study, although he was still counted as a case at that time. Apparently, this individual had been pseudo-interviewed and, on the basis of this “information,” was subsequently reclassified as nonschizophrenic.

Another description of the pseudo-interviews is contained in Kendler and Gruenberg’s (1984) re-analysis of the Copenhagen results:

Based on an extensive review of hospital records, detailed pseudointerviews were constructed for all of the index adoptees. These pseudointerviews contained more detailed information on the index adoptees than had been available to Kety and co-workers when they made their initial diagnoses. However, although they contained a detailed account of the psychiatric illness, the hospital records did not contain all the information normally present in sections of the real interviews dealing with such factors as personal history or living environment. This difference in information content as well as other differences in format made it impossible to be “blind” to whether an adoptee interview was a real interview with a control adoptee or a pseudointerview with an index adoptee [italics added]. (Kendler & Gruenberg, 1984, p. 556)

It appears that Kety and his colleagues’ “blind” diagnoses might not have been as blind as they implied. Kendler and Gruenberg could tell the difference between a real interview and a pseudo-interview, and it is possible that Kety, Rosenthal, and Wender knew from the 1968 biological relatives (13) relatives (3), and the re-interviews were more likely to be introduced into the data.

As Kendler and colleagues evaluated the diagnosis among index C11 diagnosed as a B3 in the interview, as a B1 in the final study, a half-sibling reared by the adoptive parents, Gruenberg’s account, changed in the absence of the pseudo-interviewed relative, would not have been reclassified as chronic.

To summarize, the 64% of biological and that the 1975 report’s interviews,” is misleading on whether to methodological errors and justified in any of these interviews were used.

Re-analysis of the 1975: The differences in biological relatives as B1-diagnosis rate among B1-diagnosis rate among affected index families included in the 36 index families among the 70 affected index families of the 1975 study provides no support.

The 1994 Provincial Study:

Most critics of the study concentrated on the 1994 Provincial Study’s beginning. In th
ew process of a different Dan-
possible that several relatives in
similar fashion,
were first brought to public at-
gues (1984), who had been in
acted the interviews,
ilable, the psychiatrist "prepared
ital records." That is, the psychi-
ch he guessed the relative would
up interviews for several rel-
of Index Adoptee S11’s bio-
gnosis of inadequate person-
her "interview" was changed
woman "had committed sui-
cocate her, and so—from the 
ved" (Lewontin et al., 1984.
ized on two different occa-
schizophrenia spectrum and
ia by Kety, Wender, and
ioned in the published Dan-
control Adoptee C9’s bio-
 from the 1968 report; he then
study, although he was
sidual had been pseudo-
s subsequently reclassified
contained in Kendler and
ults:
tailed pseudointerviews were
views contained more de-
, although they contained a
records did not contain all the
views dealing with such fac-
t to be "blind" to whether an
adopte or a pseudointerview
nberg, 1984, p. 556)
oses might not have been
ld tell the difference be-
it is possible that Kety,
Rosenthal, and Wender could also tell the difference. Kety and his colleagues
knew from the 1968 records that there were more spectrum-diagnosed index bi-
ological relatives (13) than there were spectrum-diagnosed control biological rel-
atives (3), and the recognition of a pseudo-interview meant that the participant
was more likely to be an index biological relative. Thus, a bias may have been
introduced into the diagnostic process.

As Kendler and Gruenberg noted, all index adoptees’ diagnoses were re-
evaluated on the basis of a pseudo-interview. There was only one change in di-
agnoses among index adoptees from 1968 to 1975: Index Adoptee S3, originally
diagnosed as a B3 in 1968, was rediagnosed, apparently as a result of a pseudo-
interview, as a B1 in the 1975 report. Index Adoptee S3 had a biological mother
and a half-sibling receiving a 1975 B1 diagnosis. On the basis of Kendler and
Gruenberg’s account, it appears that the diagnosis of Index Adoptee S3 was
changed in the absence of any actual interview with the participant. Had this
pseudo-interviewed adoptee’s diagnosis been left unchanged, the 1975 study
subsequently would not have produced a single index first-degree biological-rela-
tive case of chronic schizophrenia.

To summarize, the interview process was plagued by many difficulties. Only
64% of biological and adoptive relatives were actually interviewed, suggesting
that the 1975 report’s subtitle, “A Preliminary Report Based on Psychiatric In-
terviews,” is misleading. The use of pseudo-interviews in place of an a priori de-
cision on whether to count deceased or unavailable 1968 cases is a serious
methodological error in this study. The procedure should have been discussed
and justified in any of the Adoptees’ Family Studies reports in which pseudo-
interviews were used.

Re-analysis of the 1975 interview-based study. I used the same criteria to cal-
culate the differences in diagnoses between index biological relatives and control
biological relatives as were used during the 1968 study; that is, I compared the
B1-diagnosis rate among the first-degree biological relatives of B1 index with the
B1-diagnosis rate among the first-degree biological relatives of controls. Look-
ing at affected individuals, I found 1 person diagnosed with chronic B1 schizo-
phrenia out of 36 index first-degree biological relatives compared with 1 B1 di-
agnosis among the 70 first-degree biological relatives of controls; there was 1 af-
fected index family and 1 affected control family. I therefore conclude that the
1975 study provides no evidence supporting the genetic basis of schizophrenia.

The 1994 Provincial Study

Most critics of the Danish American Adoptees’ Family Studies have con-
centrated on the Copenhagen component, and with good reason—the final arti-
cle on the Provincial Study was not published until 1994, over 30 years after the
Study’s beginning. In the present investigation, I attempt what is possibly the first
detailed critical analysis of the Provincial Study. The reader should bear in mind that most of the methodological flaws and potential environmental confounds discussed in relation to the 1968 and 1975 studies are applicable to the Provincial Study as well.

The preliminary results of the Provincial Study were first published in 1978 (Kety, Rosenthal, & Wender, 1978; Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978). Interviewing began in 1980, but the first report on interview diagnoses did not appear for another 8 years (Ingraham & Kety, 1988), and the first article listing diagnoses for each family member did not appear until 4 years later (Kety & Ingraham, 1992). Two years after that, the final Provincial Study article was published (Kety et al., 1994), which is the starting point of the present investigation.

Method and results. The group of adoptees for the Provincial Study was selected from a total of 8,944 Danes given up for adoption between 1924 and 1947. These adoptions took place in the Danish provinces outside of the greater Copenhagen area; this Provincial Study therefore looked at adoption records in the rest of Denmark. As was done in the Copenhagen Study, the names of Provincial Study adoptees were checked against those in the National Psychiatric Register to determine how many of them had been admitted to a psychiatric facility. When the records indicated that an adoptee’s symptoms were compatible with a diagnosis of schizophrenia, a summary of the institutional records was translated into English, edited to remove family-related information, and then sent to the United States. There Kety, Rosenthal, and Wender performed blind consensus diagnoses. This process produced 41 index cases, consisting of chronic, latent, and acute diagnoses.

A matched control group was established on the basis of age, sex, socioeconomic status (SES), and time of transfer from the biological family. By the end of the study, the control group consisted of 24 adoptees and their 121 biological and 55 adoptive relatives. Because acute schizophrenia was dropped from the spectrum of diagnoses, the final index group consisted of 29 B1 (now called “chronic schizophrenia”) and 4 B3 (now called “latent schizophrenia”) adoptees. Biological and adoptive parents and their offspring were identified through population registers. The chronic-schizophrenia index adoptees had 171 biological and 71 adoptive relatives. The first stage of the relative work consisted of checking these names against the National Psychiatric Register, after which blind diagnoses were made in much the same way as they had been made for the index adoptees.

The task of interviewing relatives began in 1980. Although nearly 90% of the available relatives were interviewed, this group represented only 63% of all identified relatives (see Kety et al., 1994, p. 445). As with the previous studies, the researchers used the global diagnostic method, in spite of the fact that the DSM-III (American Psychiatric Association, 1980) and its operationalized diag-

nostic system had been applied for index biological relative in this study. The results were consistent with the findings of many other studies, with a higher risk of schizophrenia among biological relatives (p = .013, Fisher’s exact test). The control biological relative group had a lower risk (p = .12), but the difference was not statistically significant. The assumption of a genetic component is supported by the finding of a higher rate of schizophrenia among biological relatives compared to adoptive relatives (4/8 vs. 1/8, Fisher’s exact test, p = .04).

As stated earlier, the Provincial Study was a part of the larger Danish American Adoption Project, which aimed to understand the genetic and environmental factors influencing schizophrenia. The study included a control group of adoptees who were not included in the main analysis. The differences between the adoptive and biological relatives were analyzed using Fisher’s exact test, which showed a statistically significant difference (p = .04).

The 1994 group
The reader should bear in mind that environmental confounds are applicable to the Provincial Study was selected between 1924 and 1947, outside of the greater Copenhagen adoption records in the rest of the study, the names of Provincial National Psychiatric Register of a psychiatric facility. When records were compatible with a diagnosis was translated into a psychiatric diagnosis, and then sent to the reformed blind consensus diagnosis of chronic, latent, and basis of age, sex, socioeconomic family. By the end of their 121 biological criteria was dropped from the index of 29 B1 (now called schizophrenia") adoptees. There were identified through the pool of the 171 biological work consisted of checklist, after which blind diagnosis was made for the index

Although nearly 90% of represented only 63% of all with the previous studies, in spite of the fact that the its operationalized diag-

nostic system had been published. Only two spectrum diagnoses were made on relatives in this study: chronic schizophrenia and latent schizophrenia.

The results were: (a) for chronic schizophrenia, 8 diagnoses (4.7%) among index biological relatives and no such diagnoses among control biological relatives (p = .013, Fisher's exact test, one-tailed); (b) for latent schizophrenia, 14 diagnoses (8.2%) among index biological relatives and 3 diagnoses (2.5%) among control biological relatives. Both differences were statistically significant. The combined diagnoses (chronic plus latent) for index biological relatives were 22 out of 171 (12.9%) and for control biological relatives were 3 out of 121 (2.5%). These findings led Kety and associates to the following conclusion:

This study and its confirmation of previous results in the Copenhagen Study speak for a syndrome that can be reliably recognized in which genetic factors play a significant etiologic role. These findings provide important and necessary support for the assumption often made in family studies; observed familial clustering in schizophrenia is an expression of shared genetic factors. (Kety et al., 1994, p. 442)

Latent schizophrenia in the Provincial Study. It has been argued both briefly in this investigation and in detail elsewhere (Joseph, 1998a, 2000a) that a diagnosis of latent schizophrenia should not have counted as schizophrenia in the Danish American Adoptee's Family Studies. However, in spite of the evidence in favor of this assertion, the Provincial Study retained this diagnosis as part of its dependent variable. There were 14 diagnoses of latent schizophrenia among the index biological relatives; however, only 4 of these were first-degree relatives. The remaining 10 diagnoses were of half-siblings. Among controls, 1 first-degree biological relative and 2 second-degree biological relatives received a latent schizophrenia diagnosis. This means that a comparison of the rate of latent schizophrenia among the first-degree biological relatives of chronic schizophrenia index adoptees (4/82) to the rate of latent schizophrenia among the first-degree biological relatives of controls (1/59) was not statistically significant (p = .30, Fisher's exact test, one-tailed). But this is only the beginning of the story.

As stated earlier, the researchers selected matching control participants for the Provincial Study (Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978). In a later article, Kety (1983b) reported that there were 42 adoptees in this control group. As reported in the 1994 final article, however, there were only 24 adoptees in the control group. It turns out that several controls were eliminated in the interim through a screening process quite different from that used in the Copenhagen Study. As previously noted, the 1975 study designated 23 control adoptees as "screened controls" on the basis of their having been interviewed and determined to be free from the "suggestion of schizophrenic disorder" (Kety et al., 1975, p. 155). Although separate statistical calculations were performed both for index versus controls and for index versus screened controls in the 1975 report, the relatives from the nonscreened group were displayed in a table, and they were not eliminated from the study.

The 1994 group consisted of screened controls of a quite different type. At
an undisclosed point in the study, Kety and his colleagues decided that all 13 controls who had been interviewed by a psychiatrist and had been diagnosed with a "serious or confounding mental illness" should be dropped from the study (Kety et al., 1994, p. 446). These "confounding illnesses" were primarily nonspectrum affective disorders (Kety & Ingraham, 1992). It may be permissible to eliminate a control adoptee on the basis of receiving a diagnosis of schizophrenia, but for the study to remove adoptees on the basis of nonspectrum affective disorders is a serious error. From a genetic perspective, finding that a control adoptee has a particular nonspectrum psychiatric diagnosis would not "confound" the results of the study.

An interviewed 1975 control adoptee diagnosed with an affective disorder not only was retained in the study but also qualified as a screened control. The following is a description of interviewed control adoptees from the 1975 report:

Nine of these we called normal, one was diagnosed neurotic, one as affective disorder [italics added], and 12 were called personality disorders other than schizoid or inadequate personality. These 23 controls we designate as "screened" to indicate that there was no suggestion of schizophrenic disorder among them. (Kety et al., 1975, p. 155)

Apparently, a diagnosis that certified a control adoptee as screened in 1975 was enough to remove him or her from the Provincial Study. In 1992, Kety and Ingraham wrote of their control group:

In the Provincial sample, we have found latent schizophrenia in 5 of 37 (13.5%) biological relatives of probands screened out of the study due to a diagnosis of major affective disorder, a rate comparable to that in the biological relatives of the schizophrenic adoptees. It is possible that more precise diagnostic criteria could characterize a specifically schizophrenia-related syndrome. (1992, p. 250)

In other words, these controls were excluded, in part, because their biological relatives had spectrum diagnoses at rates comparable to those found among index adoptees. The genetic basis of schizophrenia was therefore assumed in the process of investigating it. Though diagnosed with a major affective disorder, according to Kety and Ingraham, they may have been misdiagnosed schizophasias and therefore had to be dropped from the study.

Had the study retained these control adoptees, the difference in latent schizophrenia between index and controls for all biological relatives (first-degree and second-degree) would have been nonsignificant (14/171 index versus 8/158 control, p = .18, Fisher's exact test, one-tailed). This finding (though with different percentages) was confirmed by Kendler and Diehl, who had viewed the final Provincial Study data while in preparation. They reported that before the reduction of the control group, "latent and uncertain schizophrenia was not found to be significantly more common in the biologic relatives of the schizophrenia

adoptees than in those of (Kendler & Diehl, 1993)

Like the 1975 Kety blind re-evaluation by R 
(1994). They looked at the disorder, and paranoid per
control adoptees and among na
atives. Of the 37 controls di
agnoed with major de
was diagnosed with schiz
adopte (the one with schizi
ing a spectrum disorder,

Five additional controls were not examined in the 1975 study, but the adoptees had been screened.

In 1992, Kety and Ingraham wrote:

The Provincial Study's first article in 1978 began by control adoptees had bee tween the announcement announcement of the red fered tampering with the validity of the entire study.

There is also the question of the Provincial Study. It has schizophrenia, uncertain sonality (Joseph, in 2000) fixation in the 1994 publication, 1980) was publis al-diagnostic method an egory, schizotypal perso

differentiating symptom: D3, and C relatives (Spi using DSM-III criteria, a must demonstrate at least thinking," (b) "ideas of r
confidants," (d) "recurre

This did not prevent the 1975 Copenhagen screened controls (with an affective disordered adopte) from being combined with Provincial screened controls (affective disordered adoptees removed) to constitute the 47 National sample "Control Adoptees With No History of Major Mental Illness" (Kety et al., 1994, p. 452).
agues decided that all 13 con-
tact had been diagnosed with a
stroke from the study (Kety
were primarily nonspectrum
be permissible to eliminate
hiphenia, but for
spectrum affective disorders is
that a control adoptee has a
not "confound" the results of

adoptees than in those of the control adoptees (6.5% vs. 5.5%, respectively)" (Kendler & Diehl, 1993, p. 265).

Like the 1975 Kety et al. report, the Provincial Study sample was subject to a
blind re-evaluation by Kendler and associates (Kendler, Gruenberg, & Kinney,
1994). They looked at the rates of *DSM-III* schizophrenia, schizotypal personality
order, and paranoid personality disorder both among interviewed index and con-
trol adoptees and among those adoptees' interviewed first- and second-degree rela-
tives. Of the 37 control adoptees, 25 were given no psychiatric diagnosis, 6 were
diagnosed with major depression, 5 were diagnosed with anxiety disorder, and 1
was diagnosed with schizotypal personality disorder (p. 458). Thus, only 1 control
adoptive (the one with schizotypal personality disorder) could be suspected of hav-
ing a spectrum disorder, and none were diagnosed with chronic schizophrenia.

Five additional control adoptees were dropped from the Provincial Study on
the grounds that they had refused (or had been unable) to be interviewed. This
was also a questionable move. There were 11 noninterviewed control adoptees
in the 1975 study, but they were not removed from the control group. If these
adoptees had been selected on the basis of matching criteria and had been
checked against a national register of psychiatric hospitalizations, this should
have been sufficient to retain them in the control group. At no point are we told
what diagnoses were found among this group's biological relatives, and at no
point did Kety et al. (1975) indicate that they were unaware of these diagnoses at
the time these 5 adoptees were excluded.

The Provincial Study investigators began their work in 1975, published their
first article in 1978, began interviewing relatives in 1980, but first reported that
control adoptees had been dropped in 1992. In other words, 14 years elapsed
between the announcement of the establishment of a control group in 1978 and the
announcement of the reduction of this group. It could be argued that the unjustifi-
ted tampering with the Provincial Study control group is reason enough to in-
validate the entire study, but let us move on.

There is also the question of how latent schizophrenia was defined in the
Provincial Study. It has been argued that there is little difference among latent
schizophrenia, uncertain latent schizophrenia, and (nonspectrum) schizoid per-
sornality (Joseph, in 2000a; Lidz & Blatt, 1983), and this position received con-
firmation in the 1994 study. In 1980, the *DSM-III* (American Psychiatric Asso-
ciation, 1980) was published. The third edition moved away from the older, glob-
al-diagnostic method and toward an "operationalized" system. A new *DSM* cat-

eralogy, *schizotypal personality disorder* (SPD), was created on the basis of the
differentiating symptoms of Kety and his colleagues' Copenhagen Study's B3,
D3, and C relatives (Spitzer & Endicott, 1979). To receive a diagnosis of SPD
using *DSM-III* criteria, a person must not meet the criteria for schizophrenia and
must demonstrate at least four of the following eight symptoms: (a) "magical
thinking," (b) "ideational reference," (c) "social isolation, e.g., no close friends or
confidants," (d) "recurrent illusions," (e) "odd speech (without loosening of as-
sociations or incoherence), e.g., speech that is digressive, vague, overelaborate, circumstantial, metaphorical.” (f) “inadequate rapport in face-to-face interaction due to constricted or inappropriate affect, e.g., aloof, cold.” (g) “suspiciousness or paranoid ideation.” (h) “undue social anxiety or hypersensitivity to real or imagined criticism” (American Psychiatric Association, 1980, p. 313).

Kety frequently referred to SPD as comparable to the Danish American latent schizophrenia diagnosis, for example, “The components of the spectrum have assumed different names in DSM-III: schizotypal personality disorder takes the place of our latent or uncertain schizophrenia, from which its characteristics were derived” (1983a, p. 724). In Kety and Ingraham’s 1992 update the terms schizotypal personality disorder and latent schizophrenia were used interchangeably.

Schizotypal personality disorder carries the distinction of being, in the words of Gunderson and Siever, “the first diagnostic category introduced into standard diagnostic usage that is built on a genetic rationale and explicitly gives familial relationship primacy as a validating criterion” (1985, p. 532). For the architects of the SPD classification, schizotypal personality disorder was “merely a subdivision of what has for years been referred to as Schizoid Personality Disorder” (Spitzer & Endicott, 1979, p. 98). By 1983, Kety had definitively removed schizoid and inadequate personality from the spectrum: “There was . . . no justification for believing that schizoid and inadequate personality, as we had diagnosed them in the interview study, were related to schizophrenia, and were therefore excluded from the subsequent analyses” (Kety, 1983a, p. 723). It therefore becomes even more evident in the Provincial Study that SPD/latent schizophrenia is barely distinguishable from nonspectrum schizoid personality disorder. According to the DSM-III, the only symptom differentiating SPD from schizoid personality was the former’s “eccentricities of communication or behavior” (American Psychiatric Association, 1980, p. 310). Even Kety and his associates acknowledged that “it is doubtful that we could demonstrate a significant differentiation between” latent schizophrenia, uncertain schizophrenia, and schizoid/inadequate personality (Kety, Rosenthal, & Wender, 1978, p. 220).

In their 1994 article, Kety and his associates listed the “criteria regarded as important in our diagnosis of schizophrenia and their presence or absence in the adoptees for whom we made that diagnosis” (Kety et al., 1994, p. 445). There was a table provided for chronic schizophrenia adoptee diagnoses, and there was another table listing symptoms of relatives diagnosed with latent schizophrenia. A review of the table for latent schizophrenia (p. 447) demonstrates just how few symptoms were necessary to make a spectrum diagnosis and how often latent schizophrenia was essentially indistinguishable from the schizoid diagnosis.

According to my calculations, only 5 of 17 relatives met the criteria for the supposedly comparable DSM-III schizotypal personality disorder, and 2 relatives were diagnosed on the basis of only one major symptom. One of these, a member of Family 420, was diagnosed on the sole criterion of “inappropriate or constricted affect”; the other, from Family 936, was diagnosed on the basis of “odd or digressive speech.” A lack of any meaningful personality. This individual “no close friends/seeking. However, in the same frequently reflect[ing] several others, the diffuse spectrum schizoid perigastic system.

How much further teachings of Eugen Ble tract to the Danish American study should be diagnosed could be utilized in recog nosis threshold value’s. Danish American invest individuals demonstrating fact,” and, in Rosenthal quote” people (1979, p. 6).

In Kendler, Gruent 3, p. 460), the SPD rat compared with all Prov acently significant (index one-tailed). When con remained nonsignificant test, one-tailed).

The evidence suggest to be counted as s or 1975. Kety claimed schizophrenia was real Provincial Study recon gree biological relative Blatt’s (1983) observati ple considered odd and labeled as (nonspectr Chonic (B1) schizophreni here that the B3 latent schizophrenia, the fact index biological relati agnostes among the cor ures require closer exa
gressive, vague, overelaborate, port in face-to-face interaction oft, cold;" (g) “suspiciousness or hypersensitivity to real or ulation, 1980, p. 313).

To the Danish American latent iments of the spectrum have as-personality disorder takes the which its characteristics were 1992 update the terms schizoi were used interchangeably.

distinction of being, in the tic category introduced into rationale and explicitly gives on” (1985, p. 532). For the ar-onality disorder was “merely Schizoid Personality Dis-
Kety had definitively removed um: “There was . . no just-personality, as we had diaglschizophrenia, and were there-
, 1983a, p. 723). It therefore that SPD/schizophrenia
dersonality disorder. Ac-nating SPD from schizoid nunciation or behavior” (even Kety and his associates constructs a significant differ-certain schizophrenia, and Wender, 1978, p. 220).

ied the “criteria regarded as presence or absence in the et al., 1994, p. 445). There e diagnoses, and there was 1 with latent schizophrenia. demonstrates just how few nosis and how often latent the schizoid diagnosis.

ees met the criteria for the ity disorder, and 2 relatives tom. One of these, a mem-
a of “inappropriate or con-nosed on the basis of “odd

or digressive speech.” A member of Family 871 is even more illustrative of the lack of any meaningful difference between latent schizophrenia and schizoid personality. This individual was diagnosed with latent schizophrenia on the basis of “no close friends/exclusive/withdrawn,” and “suspicious/paranoid ideation.” However, in the same report schizoid personality was described as “most frequently reflect[ing] severe introversion, suspicious or referential symptoms in otherwise psychiatrically unremarkable individuals” (Kety et al., 1994, p. 445). In other words, the difference between spectrum latent schizophrenia and nonspectrum schizoid personality is known only to the practitioners of the global diagnostic system.

How much further could Kety and his associates have strayed from the teachings of Eugen Bleuler, the inventor of the schizophrenia concept? In contrast to the Danish American investigators, Bleuler believed that schizophrenia should be diagnosed conservatively: “Only a few isolated psychotic symptoms can be utilized in recognizing the disease, and these too, have a very high diagnostic threshold value” (E. Bleuler, 1911/1950, p. 294). On the other extreme, the Danish American investigators were prepared to count as schizophrenia those individuals demonstrating the single symptom of “inappropriate or constricted affect,” and, in Rosenthal’s case, simply those who were “cold, distant and inadequate” people (1979, p. 23).

In Kendler, Gruenberg, and Kinney’s independent re-analysis (1994, Table 3, p. 460), the SPD rate among all Provincial Study index biological relatives compared with all Provincial Study control biological relatives was not statistically significant (index 10/140 versus control 5/162, \( p = .09\), Fisher’s exact test, one-tailed). When considering only first-degree relatives, the difference remained nonsignificant (index 7/51 versus control 3/60, \( p = .10\), Fisher’s exact test, one-tailed).

The evidence suggests that a diagnosis of latent schizophrenia did not deserve to be counted as schizophrenia in 1994 any more than it did in either 1968 or 1975. Kety claimed that the association of latent schizophrenia with chronic schizophrenia was reaffirmed in this study. In fact, the opposite is true; the Provincial Study reconfirmed its nonsignificant clustering among index first-degree biological relatives (see Joseph, 2000a), and it also supported Lidz and Blatt’s (1983) observation that latent schizophrenia describes nonpsychotic people considered odd and exclusive, who are not easily distinguishable from people labeled as (nonspectrum) schizoid personalities.

**Chronic (B1) schizophrenia in the Provincial Study.** Although it has been argued here that the B3 latent-schizophrenia diagnosis is unworthy of being counted as schizophrenia, the fact remains that Kety and associates (1994) diagnosed 8 index biological relatives with chronic schizophrenia compared with no B1 diagnoses among the control biological relatives (\( p = .013\)). As always, these figures require closer examination. According to a chart on page 448, 2 of the 8
index B1 diagnoses were maternal half-siblings, who were second-degree relatives. The remaining 6 B1 diagnoses were 2 biological fathers, 1 biological mother, and 3 biological full siblings. Concerning these 3 biological full siblings, Kety et al. indicated that although the Copenhagen Study suffered from a lack of biological full-siblings that “prevented a meaningful estimate of disease prevalence in first-degree relatives” (although Kety et al. studied 131 biological parents), with the Provincial Study sample

There were a substantial number of full siblings (24 biological index siblings compared with three in the Copenhagen Sample), probably the result of differences in lifestyle from that of the large city. Schizophrenia was found in three (12.5%) of the 24 full siblings, nearly six times the rate in the half-siblings (two [2.2%] of 90) (one-tailed p = .062). (Kety et al., 1994, pp. 447–448)

However, this stated chronic-schizophrenia rate of 3/24 (12.5%) among biological full siblings is misleading because all 3 of these full siblings were from the same family (Kety et al., 1994, p. 448, Figure 1). And what a family this was! Index Biological Family 69 consisted of a mother, father, their 3 full daughters, 2 full sons, and 3 paternal half-siblings. As always, there was no information on where these children had been reared. In the likely case—that they had been reared in the same home—a plausible explanation would be that environmental conditions contributed to the level of psychological disturbance in this family.

In addition to the daughter and 2 sons from Family 69 that were diagnosed with chronic schizophrenia, one of the other 2 full daughters received a diagnosis of nonspectrum “bipolar illness.” In addition, 2 of the 3 paternal half-siblings in Family 69 were diagnosed as nonspectrum schizoid. Because the Provincial Study sample was drawn from the small towns and rural communities of Denmark, one can envision this family living together in the Danish countryside, possibly on a farm. The parents, neither of whom received a psychiatric diagnosis, were perhaps hard-working people tending to their land, but, from a psychosocial perspective, they raised some pretty screwed-up kids.

What kind of a household could this have been in which, of the 8 children, 3 were diagnosed with spectrum chronic schizophrenia, 2 were diagnosed with nonspectrum schizoid, and 1 was diagnosed with nonspectrum bipolar illness? And what were the circumstances surrounding the abandonment of a child (the index adoptee) by parents who raised 8 biological children together? As is always the case in a Danish American Adoptees’ Family Study, one can only speculate, because of a total lack of information about the environments in which these people lived.

Of the remaining 20 index biological full siblings (who were born to 6 different sets of biological parents), not one of them received a diagnosis of chronic schizophrenia. A valid conclusion would therefore be that family environ-

---

10Although Kety et al. (1994) counted 24 index biological full-sibs, the pedigree chart on page 448 indicates that there were 25.
who were second-degree related: fathers, 1 biological mother, biological full siblings, Kety (a victim of disease prevalence died 131 biological parents),

biological index siblings com- mit the result of differences in is found in three (12.5%) of the blings (two [2.2%] of 90) (one-

of 3/24 (12.5%) among bio-

nese full siblings were from And what a family this was! ther, their 3 full daughters, here was no information on case—that they had beenould be that environmental insuriance in this family. lly 69 that were diagnosed ughters received a diagno-

the 3 paternal half-siblings id. Because the Provincial ural communities of Den-

e Danish countryside, pos- ed a psychiatric diagnosis, nd, but, from a psychoso-

which, of the 8 children, a, 2 were diagnosed with spectrum bipolar illness? donment of a child (the en together? As is always; one can only speculate, nents in which these peo-

(who were born to 6 different families) had a diagnosis of chronic schizophrenia that family environ-

ment, rather than genetic background, best explains the clustering of chronic schizophrenia among the siblings of one family. This underscores the observation by Benjamin (1976), Mosher (1975), and Kety et al. themselves (1975) that it could be misleading to count affected individuals, as opposed to families, because a common environment violates the assumption of the independence of individual observations.

The 3 remaining diagnoses of chronic schizophrenia among first-degree biological relatives were made on 2 fathers and 1 mother. A consideration of the case of the chronic schizophrenic adoptee from Family 139 demonstrates how comparatively few symptoms are necessary to obtain such a diagnosis when the global diagnostic method is used. According to a table listing the course and symptoms of the adoptees diagnosed with chronic schizophrenia (Kety et al., 1994, p. 446), this individual demonstrated these five symptoms: (a) "insidious onset," (b) "schizoid features observed premorbidly," (c) "chronic course observed," (d) "withdrawal from social interaction," and (e) "flat affect." Other symptoms that this adoptee did not demonstrate included "autistic behavior," "poverty of thought/speech," "loose associations," "suspicious/ideas of reference," "delusions," "auditory hallucinations," and "other hallucinations."

Thus, this adoptee presented no uniquely psychotic symptoms or even one symptom that would have differentiated him from a person receiving a latent schizophrenia or schizoid diagnosis. In addition, this adoptee would not have been diagnosed with chronic schizophrenia according to the criteria of DSM–I through DSM–IV. The diagnosis of chronic schizophrenia for this individual is therefore questionable; in fact, it calls into question the validity of every chronic schizophrenia diagnosis in the entire series of Adoptees' Family Studies.

Of the original 42 index adoptees (29 of whom were diagnosed with chronic schizophrenia by Kety et al.), Kendler, Gruenberg, and Kinney diagnosed only 19 with chronic schizophrenia (1994, p. 458). Although it is unclear how many of these were diagnosed with Kety and his colleagues' 29 chronic schizophrenia index adoptees, at least 10 of the latter were diagnosed with conditions other than chronic schizophrenia. Among the 28 first-degree biological relatives of chronic schizophrenia index adoptees, Kendler et al. (1994, p. 460) found 2 cases of chronic schizophrenia and, among the 60 first-degree biological relatives of controls, they found a single case (p = .24, Fisher's exact test, one-tailed) of chronic schizophrenia.

Re-analysis of the 1994 study. I used same criteria that were used for the 1968 and 1975 studies to re-analyze the Provincial Study. Before looking at the numbers, I must re-emphasize that this study is plagued by serious methodological problems. Almost one half (43%) of the control adoptees were eliminated from the study on questionable grounds, and there were several latent schizophrenia diagnoses among their biological relatives. How many relatives were diagnosed on the basis of a 5-minute doorstep interview? How many by pseudo-interview?
How many index adoptive parents had been admitted to a mental hospital? How many deceased hospital-diagnosed relatives were excluded from statistical calculations? In short, as Lewontin et al. (1984) noted when discussing the Provincial Study in its preliminary phase, “there is no reason to suppose that the more recent work is free of the invalidating flaws we have outlined above” (p. 225). Most important, the results of this study are confounded by the selective placement of adoptees, meaning that the critical theoretical assumption of all adoption studies was violated.

The 6 cases of first-degree index biological-relative chronic schizophrenia (diagnosed by Kety et al., 1994) produced the first statistically significant comparison in the series of Adoptees’ Family Studies. These diagnoses were made among a group of 82 first-degree relatives. Among controls, no chronic schizophrenia diagnoses were made in the group of 59 first-degree biological relatives (6/82 versus 0/59, $p = .036$, Fisher’s exact test, one-tailed). If Adoptee 139 and his 2 first-degree relatives are removed, however, the comparison no longer has statistical significance (5/80 versus 0/59, $p = .06$). The first-degree relative chronic schizophrenia rate among affected families was not significant (index 4/29 versus control 0/24, $p = .08$, Fisher’s exact test, one-tailed). On the basis of all of these calculations and of the previously discussed flaws in this study, I conclude that, like the results of the 1968 and 1975 studies, those of the Provincial Study do not support a genetic basis for schizophrenia.

The National Sample

Kety and his associates (1994) tabulated the results of what they called the National sample: the combined diagnoses of the Copenhagen Study and the Provincial Study. The investigators reported highly significant differences for chronic and latent schizophrenia rates among all index biological relatives and controls (Kety et al., 1994, p. 452). However, as Kety and his colleagues acknowledged, the Provincial Study constituted a “replication of the Copenhagen Study in the rest of Denmark” (1994, p. 442). By its very nature, an attempt to replicate must stand on its own merit; otherwise, two nonsignificant results could be combined into one large significant result, or a nonsignificant replication could be added to the significant original study and thus lead to a completely different conclusion than it would have led to standing alone (Gottfredson & Hirschi, 1990). Therefore, the results of the National sample are not re-analyzed here.

The Adoptees’ Family Studies: Summary and Conclusions

The Danish American Adoptees’ Family Studies of Kety and his associates are the most widely cited studies in support of the genetic basis of schizophrenia. However, in this report I have argued that the conclusions of its authors are faulty for two main reasons: placement factors, and the genetic hypothesis of adoptive offspring is framed by the National Psychiatric Adoptions by most sectors of Denmark, in fact, had whose victims include the Danish adoptees, experienced inferior treatment by control adoptive adoptive relatives with months before the press time. Rosenthal (1967) wrote that the basis of significant differences were. Previous discussion of the schizophrenia diagnosis rates among all index biological relatives and controls (Kety et al., 1994, p. 452). However, as Kety and his colleagues acknowledged, the Provincial Study constituted a “replication of the Copenhagen Study in the rest of Denmark” (1994, p. 442). By its very nature, an attempt to replicate must stand on its own merit; otherwise, two nonsignificant results could be combined into one large significant result, or a nonsignificant replication could be added to the significant original study and thus lead to a completely different conclusion than it would have led to standing alone (Gottfredson & Hirschi, 1990). Therefore, the results of the National sample are not re-analyzed here.

The Adoptees’ Family Studies: Summary and Conclusions

The Danish American Adoptees’ Family Studies of Kety and his associates are the most widely cited studies in support of the genetic basis of schizophrenia. However, in this report I have argued that the conclusions of its authors are faulty for two main reasons: placement factors, and the genetic hypothesis of adoptive offspring is framed by the National Psychiatric Adoptions by most sectors of Denmark, in fact, had whose victims include the Danish adoptees, experienced inferior treatment by control adoptive adoptive relatives with months before the press time. Rosenthal (1967) wrote that the basis of significant differences were. Previous discussion of the schizophrenia diagnosis rates among all index biological relatives and controls (Kety et al., 1994, p. 452). However, as Kety and his colleagues acknowledged, the Provincial Study constituted a “replication of the Copenhagen Study in the rest of Denmark” (1994, p. 442). By its very nature, an attempt to replicate must stand on its own merit; otherwise, two nonsignificant results could be combined into one large significant result, or a nonsignificant replication could be added to the significant original study and thus lead to a completely different conclusion than it would have led to standing alone (Gottfredson & Hirschi, 1990). Therefore, the results of the National sample are not re-analyzed here.

The Adoptees’ Family Studies: Summary and Conclusions

The Danish American Adoptees’ Family Studies of Kety and his associates are the most widely cited studies in support of the genetic basis of schizophrenia. However, in this report I have argued that the conclusions of its authors are faulty for two main reasons: placement factors, and the genetic hypothesis of adoptive offspring is framed by the National Psychiatric Adoptions by most sectors of Denmark, in fact, had whose victims include the Danish adoptees, experienced inferior treatment by control adoptive adoptive relatives with months before the press time. Rosenthal (1967) wrote that the basis of significant differences were. Previous discussion of the schizophrenia diagnosis rates among all index biological relatives and controls (Kety et al., 1994, p. 452). However, as Kety and his colleagues acknowledged, the Provincial Study constituted a “replication of the Copenhagen Study in the rest of Denmark” (1994, p. 442). By its very nature, an attempt to replicate must stand on its own merit; otherwise, two nonsignificant results could be combined into one large significant result, or a nonsignificant replication could be added to the significant original study and thus lead to a completely different conclusion than it would have led to standing alone (Gottfredson & Hirschi, 1990). Therefore, the results of the National sample are not re-analyzed here.
ed to a mental hospital? How excluded from statistical call when discussing the Provin-
und the selective place-
relative chronic schizophrenia statistically significant com-
These diagnoses were made controls, no chronic schiz-
degree biological relatives tailed). If Adoptee 139 and
the comparison no longer has
first-degree relative chron-
ist significant (index 4/29 ver-
ated). On the basis both of
aws in this study, I conclude
ose of the Provincial Study
result of what they called the
Copenhagen Study and the
significant differences for
x biological relatives and
Kety and his colleagues ac-
lication of the Copenhagen
very nature, an attempt to
onsignificant results could
onsignificant replication
us lead to a completely dif-
ing alone (Gottfredson &

and Conclusions
of Kety and his associates
etic basis of schizophrenia.
ions of its authors are faulty
for two main reasons: (a) it is likely that the results were confounded by selec-
tive placement factors, and (b) the studies were methodologically unsound.
It is unlikely that index and control adoptees were randomly placed into their
respective adoptive homes. Rather, a potential adoptee with a family history of
“mental illness” (going well beyond the biological parents and checked through
the National Psychiatric Register) was considered an undesirable “tainted” child
by most sectors of Danish society, including the adoption agencies themselves.
Denmark, in fact, had a long history of legally sanctioned eugenic sterilization,
whose victims included people diagnosed with schizophrenia. Selective place-
ment in the Danish adoption process points to the likelihood that index adoptees
experienced inferior rearing environments when compared with those experi-
enced by control adoptees. Thus, like the schizophrenia family and twin studies,
the Danish American adoption studies were confounded by environmental fac-
tors (Joseph, 1999b).
There is evidence that Kety and his associates’ original intent was to com-
pare the schizophrenia or schizophrenia spectrum rates of index biological and
adoptive relatives with those of control biological and adoptive relatives. Three
months before the presentation of the Copenhagen Study’s record-based report,
Rosenthal (1967) wrote that this was indeed the design of the study. Had this de-
sign been the basis of comparison between the index and control groups, no sig-
ificant differences would have been found in the 1968 study.

Previous discussions (Joseph, 1998a, 2000a) presented evidence against the
validity of the schizophrenia spectrum concept as defined by Kety and his associ-
ates, and the main points are summarized here. In short, the Kety et al. spec-
trum is invalid on empirical, theoretical, and historical grounds.
I further determined by this investigation that half-siblings should not have
been counted in the series of Adoptees’ Family Studies. In the 1975 Copenhagen
Study, Kety and his associates concluded that the spectrum rate among paternal
half-siblings produced “compelling evidence” in favor of the genetic basis of
schizophrenia. However, a statistically significant difference was found only by
omitting Category C, which two pages earlier in the report had been counted as
a spectrum diagnosis.

Benjamin (1976) observed that it is more appropriate to compare rates
among affected families than among affected individuals. Even Kety and his asso-
ciates acknowledged that the counting of individuals might constitute a viola-
tion of the principle of independence of observations. Although in this investiga-
tion I re-analyzed the results pertaining to affected individual relatives, I also
note that counting affected families is a more valid comparison.

I also examined the researchers’ methods for conducting interviews and for
making blind diagnoses. There were clear inconsistencies in the way that relative
diagnoses were counted. Fewer than three quarters of the biological relatives
were actually interviewed, and there are persisting questions about the com-
pleteness of the interviews that were undertaken. The so-called pseudo-inter-
views were created as a substitute for real interviews, meaning that the researchers made up interviews for many adoptees and their relatives. Strikingly, the use of these pseudo-interviews was not discussed in any Danish American Adoption Study paper. According to Kendler and Gruenberg (1984), all index adoptees were diagnosed via pseudo-interview in the 1975 Copenhagen Study. I also criticized the vaguely defined "global diagnostic method" on the grounds that it increased the subjectivity of the diagnoses and allowed relatives to be diagnosed on the basis of a minimal number of symptoms.

In summary, there is good reason to disagree with Kety and his associates' conclusion that the results of the 1968, 1975, and 1994 studies support a genetic basis for schizophrenia. Serious methodological problems, questionable research practices, and environmental confounds due to selective placement lead to the conclusion that these studies are far too flawed to be considered as evidence in favor of the genetic position. Given the problems associated with family, twin, and other adoption studies (Joseph, 1999a, 1999b), and the failure of molecular genetic studies to identify postulated genes (DeLisi, 2000; Tsuang & Faraone, 2000), the entire body of evidence cited in support of a genetic predisposition for schizophrenia should be re-evaluated, and the debate over the existence of genetic factors in schizophrenia should be re-opened.

REFERENCES


reviews, meaning that the re-
and their relatives. Strikingly,
seed in any Danish American
Gruenberg (1984), all index
he 1975 Copenhagen Study. I
stic method” on the grounds
and allowed relatives to be di-

tomus.

with Kety and his associates’
994 studies support a genetic
blems, questionable research
active placement lead to the
considered as evidence in
associated with family, twin,
and the failure of molecular
i, 2000; Tsuang & Faraone,
: a genetic predisposition for

e over the existence of ge-

1 statistical manual of mental
associates study of genetic fac-
Journal of Psychiatry, 133,

schizophrenias. New York: In-
patient and family disorders.

York: Routledge.

in’s Press.

schizophrenie: Réévaluation
on of a consensus]. Psychia-
tes to genetic mechanisms in

tric genetics. In M. Tsuang,
epidemiology (pp. 81–134).

t adoption, twin, and fam-
vases. Schizophrenia Bulletin,

n genetic puzzle. New York:

crime. Stanford, CA: Stan-


in the schizophrenic syndrome. In 233–244). New York: Brunner/R
ic Journal of Psychiatry, 131,
cie and environmental variables in 1 answers. American Journal of
show (Ed.), Schizophrenia: Scie
adoptive relatives of schizophrenic
tal factors in etiology. American
mental influences in the etiologic
rels. In S. Kety, L. Row
virological and psychiatric dis
erational definition of Bleuler’s
etiology of schizophrenia: Re-
ion and improved diagnosis of
Psychiatric Research, 26,
relationships within the schiz-
R. Spitzer & D. Klein (Eds.), New York: Raven Press.
(1968). The types and preva-
iiation of adopted schizophren-
ssion of schizophrenia (pp.
F. (1976). Studies based on a
hy they were necessary, what
Jacobsen, B. (1975). Mental
iduals who have become
pectives. In R. Fieve, D.
try (pp. 147–165). Baltimore:
Jacobsen, B. (1978). The bi-
became schizophrenic: Preva-
ynne, R. Cromwell, & S.
aches to research and treat-
son, L., Faber, B., & Kinney,
ve relatives of schizophrenic
est of Denmark. Archives of
Lidz, T. (1976). Commentary on a critical review of recent adoption, twin, and family
studies of schizophrenia: Behavioral genetics perspectives. Schizophrenia Bulletin, 2,
402–412.
Lidz, T., & Blatt, S. (1983). Critique of the Danish American studies of the biological and
adoptive relatives of adoptees who became schizophrenic. American Journal of Psy-
chiatry, 140, 426–435.
adopted-away offspring of schizophrenic parents. American Journal of Psychiatry,
138, 1063–1068.
Mednick, S. A. (1996). General discussion III. In G. Bock & J. Goode (Eds.), Genetics of
criminal and antisocial behavior (pp. 129–137). New York: Wiley.
of criminal behavior. In S. Mednick, T. Moffitt, & S. Stack (Eds.), The causes of crime:
New biological perspectives (pp. 75–91). New York: Cambridge University Press.
Danish adoption studies in relation to asocial behavior. In S. Mednick & K. Chris-
tiansen (Eds.), Biosocial bases of criminal behavior (pp. 159–164). New York: Gar-
nier Press.
Paikin, H., Jacobsen, B., Schulsinger, F., Godtfredsen, K., Rosenthal, D., Wender, P. H.,
& Kety, S. S. (1974). Characteristics of people who refused to participate in a social
and psychopathological study. In S. Mednick, F. Schulsinger, J. Higgins, & B. Bell
(Eds.), Genetics, environment and psychopathology (pp. 293–322). New York: Ameri-
can Elsevier.
(Eds.), Pseudoscience in biological psychiatry: Blaming the body (pp. 7–84). New
York: Wiley.
Rosenthal, D. (1967). An historical and methodological review of genetic studies of schiz-
ophrenia. In J. Romano (Ed.), The origins of schizophrenia: Proceedings of the first
Rochester international conference on schizophrenia, March 29-31, 1967 (pp. 15–26).
New York: Excerpta Medica Foundation.
(Eds.), Genetics, environment, & psychopathology (pp. 167–176). New York: Ameri-
can Elsevier.
American handbook of psychiatry (2nd ed., revised and expanded) (pp. 588–600). New
York: Basic Books.
Rosenthal, & H. Brill (Eds.), Genetic research in psychiatry (pp. 199–208). Baltimore:
The Johns Hopkins Press.
(Eds.), Psychiatry, genetics and pathography: A tribute to Eliot Slater (pp. 22–33).
London: Oxford University Press.
Spitzer, R. L., & Endicott, J. (1979). Justification for separating schizotypal and border-
line personality disorders. Schizophrenia Bulletin, 6, 95–104.
Teasdale, T. W. (1979). Social class correlations among adoptees and their biological
adoptive parents. Behavior Genetics, 9, 103–114.
Tienari, P., Sorri, A., Lahtti, I., Naarala, M., Wahlberg, K., Moring, J., Pohjola, J., and

Received July 3, 2000

---

**Services from Heldref Publications**

**Reprints** of Heldref journal articles—professional reproduction on excellent quality 60-lb. white enamel (glossy) paper. Minimum order 50 copies.

For further information, write to the **Reprints Manager**.

**Bulk Orders** for classrooms and conferences

**Subscriber list rental**

**Advertising**—All copy subject to publisher’s approval

**Sample copies**

For further information concerning these services, write to:

**Heldref Publications**

1319 Eighteenth Street, NW
Washington, DC 20036-1802
(202) 296-6267 • fax (202) 293-6130
(800) 365-9753 • www.heldref.org