Ethical Human Sciences and Services, Vol. 2, No. 3, 2000

A Critique of the Spectrum Concept as Used in the Danish-American Schizophrenia Adoption Studies

Jay Joseph, PsyD
California School of Professional Psychology, Alameda

The most important schizophrenia adoption studies were based on Danish adoptees and depended on a "schizophrenia spectrum of disorder" in order to find statistically significant results in support of the genetic basis of schizophrenia. This article performs a reanalysis of the Kety and associates spectrum concept for the purpose of determining whether it is a valid construct. On the basis of quantitative and historical evidence, as well as on theoretical concerns, it is determined that the spectrum concept as defined by Kety and is not valid and that chronic schizophrenia is the only diagnosis that should have been used in the Danish-American adoption studies. The results and conclusions of the Danish-American adoption studies therefore are called into question.

Los estudios más importantes de adopción de esquizofrénicos fueron basados en adoptados daneses y dependieron en un "espectro de desorden esquizofrénico" para encontrar resultados estadísticamente significantes en apoyo de la base genética de la esquizofrenia. Este artículo reanaliza el concepto del espectro de Kety y sus asociados, para determinar si es una construcción válida. Basado en la evidencia cuantitativa e histórica, asímismo en las preocupaciones teóricas, se determina que el concepto del espectro como es definido por Kety y sus companeros, no es válido y que "la esquizofrenia crónica" es la única diagnosis que debe haber sido usada en los estudios daneses-americanos de adopción. Por eso los resultados y conclusiones de estos estudios son cuestionados.

Les plus importantes études sur l'adoption de schizophrènes portent sur des adoptés danois et dépendent de l'utilisation d'un "spectre de trouble schizophrènique" pour trouver des résultats statistiquement significatifs qui appuient l'hypothèse génétique de la schizophrénie. L'auteur réanalyse le construit du "spectre" utilisé par Kety et ses collègues afin de déterminer sa validité. Sur la base d'évidence quantitative et historique et de considérations théoriques, il est ici déterminé que ce construit, tel que défini par Kety et al., n'est pas valide et que la schizophrénie chronique reste le seul diagnostic qui aurait dû être utilisé dans ces études. Les résultats et les conclusions des études d'adoption danoises-américaines sont donc remis en question.

The Danish-American adoption studies are the most widely cited evidence in support of the claim that schizophrenia has a genetic basis.[1] Three methods of studying adoptees were used in the Danish-American series:

1. The "Adoptees method" (Rosenthal et al., 1968; Rosenthal, Wender, Kety, Welner, & Schulsinger, 1971), which studied the adopted-away biological offspring of schizophrenia spectrum parents versus controls;
2. The "Adoptees' Family method" (Kety, Rosenthal, Wender, & Schulsinger, 1968; Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1975; Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978; Kety et al., 1994), which studied the biological and adoptive families of adoptees diagnosed with a schizophrenia spectrum disorder and the families of controls; and
3. The "Crossfostering method" (Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974), which looked at the adopted-away biological children of non-schizophrenic parents who were raised by an adoptive parent diagnosed with a schizophrenia spectrum disorder.

The statistically significant results reported in these studies depended on an expanded definition of schizophrenia—the authors created what they called a "schizophrenia spectrum of disorder" (Kety et al., 1968, p. 353; referred to here as the "schizophrenia spectrum," or "spectrum"). The Kety and associates spectrum included chronic schizophrenia (designated "B1") and several other diagnoses supposedly related to B1, which consisted of "acute schizophrenia" (B2), "borderline or latent schizophrenia" (B3), "uncertain chronic schizophrenia" (D1), "uncertain acute schizophrenia" (D2), "uncertain borderline or latent schizophrenia" (D3), and "schizoid or inadequate personality" (C). The purpose of this review is to determine whether the Danish-American schizophrenia spectrum concept is valid.

ORIGINS OF THE SPECTRUM

The spectrum concept has been discussed by several critics (e.g., Boyle, 1990; Breggin, 1991; Joseph, 1998a; Lewontin, Rose, & Kamin, 1984; Lidz & Blatt, 1983; Pam, 1995), since the decision of whom one counts as "schizophrenic" becomes an important issue in analyzing the results of the schizophrenia adoption studies. In the Danish-American series, all spectrum diagnoses were counted equally as schizophrenia in comparisons between the various groups of relatives. Because neither Kety, Rosenthal, nor Wender provided an adequate explanation of how and when they came up with their schizophrenia spectrum, some speculation is unavoidable.

The spectrum concept predates the Danish-American adoption studies but Kety and associates were the first to make it a central aspect of their research. One of the stated goals of the investigators was to test the validity of the spectrum. The Kety and colleagues schizophrenia spectrum definition was first put forward as part of the 1968 Adoptees' Family study, and was justified as follows:

> We had recognized certain qualitative similarities in the features that characterized the diagnoses of schizophrenia, uncertain schizophrenia, and inadequate personality, which suggested that these syndromes formed a continuum; this we called the schizophrenia spectrum of disorders. (Kety et al., 1968, p. 353)

From the time of the formation of the Danish-American team in 1963 until the publication of their 1968 studies, there had been no preliminary reports on the progress of the research or on the theoretical and empirical justification of the spectrum.

In the early 1960s, Kety, Wender, and Rosenthal were brought together by virtue of their mutual dissatisfaction with a perceived inability of family and twin studies to disentangle genetic and environmental influences. As early as 1959, Kety had written:

> Another possible means of better controlling the environmental variables would be to make a careful study of schizophrenia in adopted children, with comparison of the incidence in blood relatives and in foster relatives. Perhaps only a survey on a national scale would provide the requisite numbers of such cases for any of these studies. (Kety, 1959, p. 1594)

Thus, Kety realized at an early stage that the ascertainment of a large sample of adoptees would be necessary to produce a "requisite" number of adoptees diagnosed with schizophrenia. The researchers attempted to obtain subjects in the greater Washington, DC area but it soon became clear that it would be difficult to achieve their goals in the United States (Kety, Rosenthal, Wender, & Schulsinger, 1976). In 1963, the three American researchers began a collaboration with Fini Schulsinger, a Danish psychiatrist whose expertise and language abilities would enable them to obtain the records of a large number of adoptees through the extensive population and psychiatric registers then existing in Denmark. Schulsinger has been credited with convincing the reluctant Danish Ministry of Justice to open up the national Adoption Register for the purpose of scientific research. His persuasiveness finally convinced the authorities to allow access to these records in spite of the fact that earlier Danish researchers had made similar, unsuccessful requests (Strömgren, 1993).

Through the use of the Adoption Register the researchers obtained the records of 5,483 adoptees from the greater Copenhagen area (Kety et al., 1968). Based on rough population expectations it was probably felt that such a large sample would yield a sufficient number of schizophrenic adoptees to be able to compare them to a control group of non-schizophrenic adoptees.The results of prevalence studies conducted in Western countries have placed the lifetime expectancy rate for schizophrenia at between 0.8% and 1% (Rosenthal, 1970; Slater & Cowie, 1971). On the basis of this figure, Kety and associates were probably expecting to find 50-55 schizophrenia-diagnosed adoptees in their sample (5,483 x .01= 54.83). Epidemiological studies conducted in Denmark and summated in Zerbin-Rüdin's 1967 study (quoted in Slater & Cowie, 1971, p. 13) produce a lower age-corrected Danish population prevalence of 0.69%. (In Denmark, only chronic "process" cases were counted as schizophrenia [Kety, 1978].) Based on this relatively low rate the expected number of schizophrenic adoptees from the greater Copenhagen sample would have been 38 (5,483 x 0.0069 = 37.8). However, contrary to genetic expectations Kety and colleagues diagnosed only 16 cases of chronic schizophrenia (B1) among their adoptees. This rate of about three per thousand is less than one-half of the expected rate in the general population.[2]

Thus, even before they began the task of locating the hospital records of the biological and adoptive relatives of their schizophrenic adoptees, the investigators were confronted with a powerful piece of evidence in favor of the

environmentalist position—for the numbers suggested that simply being raised by parents who had been screened for mental health by adoption agencies had reduced the chance of a person being diagnosed with schizophrenia by over 50%. The status of being a Danish adoptee, therefore, placed one in a distinct group when compared to the general population. According to Sarbin and Mancuso (1980), the results "show, quite simply, that the social services agencies have suitably done their job" (p. 138).

One can imagine the researchers' disappointment in finding only 16 cases of chronic schizophrenia among their large sample of adoptees. This number was simply too small to be able to conduct their study, as acknowledged by Rosenthal:

> *The fact that the number of 16 hard-core, process [chronic] schizophrenic, index cases is too small to give the heritability of such disorders the proper opportunity to express itself* [italics added], and the possibility that by relying only on psychiatric records rather than on personal examinations we were missing a number of cases. (1972, p. 68)

In this passage Rosenthal acknowledged that the investigators did not have enough cases with which to conduct the study (that is, they had fallen short of Kety's 1959 "requisite" number). A year earlier, Rosenthal (1971b) made the same point:

> The second [important] feature [of the research] has to do with the fact that we have included a broad spectrum of disorders in the ones I am calling schizophrenic. These include not only the classical chronic, process types of cases, but patients called doubtful schizophrenic, reactive, schizo-affective, borderline or pseudoneurotic schizophrenic, or schizoid or paranoid. *If we dealt only with hardcore schizophrenia, our ns would be too small to make any of these studies meaningful* [italics added]. (p. 194)

He continued,

> However, a more positive reason for including the spectrum of disorders is that in the process, we hope to be able to determine whether any or all of these disorders, which phenotypically have strong resemblances to hardcore schizophrenia, are genetically related to it as well. (p. 194)

A careful reading of this paragraph reveals that, whereas the testing of whether the other diagnoses were related to chronic schizophrenia was a "positive reason" for using the spectrum, the "negative reason" was the necessity of widening the definition of schizophrenia in order to obtain enough subjects to be able to conduct the study. This scenario has been suggested by Lewontin and colleagues (1984) and Pam (1995).

Neither Kety, Rosenthal, nor Wender satisfactorily explained what the next step was after obtaining their low yield. We do not know whether it was at this point that they decided to broaden their definition of schizophrenia, or whether they began searching the psychiatric records of the biological and adoptive relatives of these 16 adoptees.

Assuming the possibility of the latter scenario, the results of the Kety and associates 1968 study (pp. 354-355) demonstrate that there was only one case of chronic schizophrenia among the 82 biological relatives of the B1 index

adoptees (this relative was a half-sibling). If we add the diagnoses in the control group, which also yielded one case of biological relative B1 schizophrenia, only two cases of clear-cut chronic schizophrenia were found among the biological relatives of B1 index and control adoptees. In other words, had Kety and colleagues restricted their definition of schizophrenia to B1 only, they would have had no possibility of achieving statistically significant results in the genetic direction. Rosenthal is clear on this point also: "It should be apparent now that if we had included in our comparisons of index and control relatives only those who clearly had process schizophrenia, we would have found no difference between the two groups of relatives" (Rosenthal, 1972, p. 68).

It then becomes clear that whether,

1. The original sample did not yield enough B1 schizophrenia adoptees to be able to conduct the study, or
2. Significant results could not have been found on the basis of this sample; the schizophrenia spectrum was likely created because of the environmentally caused low yield of B1 index adoptees and B1 biological relative cases.

To put this in frank terms, Kety, Rosenthal, and Wender were confronted with the choice of (literally and figuratively) packing their bags and giving up on several years of hard work, or broadening the definition of schizophrenia in order to obtain more cases. It should be emphasized that it is not implied here that Kety and associates (who were diagnosing blindly) knew into which group (index or control) these cases fell, but that wherever they might have fallen, there were not enough of them to allow even the *possibility* of significant findings.

The evidence points to the conclusion that the schizophrenia spectrum was created by selecting the disorders which seemed closest to chronic schizophrenia in order to have enough cases to conduct the study and not, as its architects maintained in their major papers, in order to test the hypothesis that its components were related to chronic schizophrenia. This idea receives support in a remarkable description of the origins of the spectrum by Rosenthal:

> It seems somewhat ironic that while representing the U.S. Field Center in the WHO International Pilot Study of Schizophrenia, John Strauss and Will Carpenter were working upstairs at the National Institute of Health Clinical Center, trying to hone a definition of schizophrenia as sharply as they could possibly make it, while Paul Wender and I were working downstairs, in concert with Seymour Kety, in effect *broadening the concept of schizophrenic disorder as widely as it may have ever been reasonably conceived before* [italics added] . . .
>
> While Carpenter and Strauss emphasized the limits or boundaries of the process [B1] schizophrenia concept, *our group strained* [italics added] to encompass all disorders that shared salient clinical and behavioral manifestations with process schizophrenia and to group these as a spectrum of schizophrenic disorder.
>
> Of course, we did not know which disorders, if any, should be included in such a spectrum to meet the criterion of genetic or familial commonality. Nevertheless, we selected the ones that we thought had the highest probability of meeting this

> criterion, and introduced them into our research studies as a hypothesis to be tested. It was easy to read through the *APA Diagnostic and Statistical Manual*, second edition, to make such selections. (Rosenthal, 1975, p. 19)

These passages are relevant to the present discussion for several reasons. Because the spectrum was based on *DSM-II* definitions, Rosenthal seemed to date its creation to no earlier than 1967, since it was in February of that year that a draft version of the second edition was distributed to psychiatrists (APA, 1968, p. ix). Assuming that Rosenthal, Kety, and associates did not have access to the draft before it was distributed to psychiatrists for commentary, we discover that as late as 1967 the Danish-American team was "straining" to broaden the concept of schizophrenia "as widely as it may have ever been reasonably conceived before"—well after Kety and colleagues began the collection of adoptees in the Copenhagen study. It must therefore be asked: What circumstances compelled these researchers to widen the concept of schizophrenia so many years after they began their study? Rosenthal's description lends support to the idea that the spectrum was created as a post hoc measure of expediency.

Looking back on their work, Kety and colleagues would write,

> We had previously agreed that for the purposes of this study, "schizophrenia" would include three subgroups: chronic or classical schizophrenia, latent or borderline schizophrenia, an acute schizophrenic reaction. In doing so we made no assumptions that these three syndromes were valid or necessarily related (Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978, p. 26).

The implication is that this definition of schizophrenia was agreed on from the start, but there is no evidence to substantiate this claim. Had Kety and associates truly been interested in testing the hypothesis of a relationship between chronic schizophrenia (B1) and the B2 and B3 categories, they would have limited their index cases to B1 schizophrenia and would then have determined if B2 or B3 cases were found in significantly greater numbers among their biological relatives. In effect they *assumed* that there was a relationship, which is shown by the inclusion of these diagnoses in the Kety et al. 1968 index adoptee group.

The Question of the Inclusion of "Latent Schizophrenia" (B3) in the Schizophrenia Spectrum

The B3 latent or borderline schizophrenia diagnosis was a crucial component in the claims of statistically significant findings in the Danish-American studies. Kety and colleagues (1968, p. 352) diagnosed the B3 condition on the basis of symptoms such as "strange or atypical" thinking, "feelings of depersonalization," "anhedonia never experiences intense pleasure," "lacking in depth," "mature of hereto- and homosexuality," and "multiple neurotic manifestations—severe widespread anxiety." For the Danish-American researchers a condition was considered genetically related to schizophrenia if it affected "a significant concentration in the biologic index relatives compared with their controls," whereas conditions were deemed unrelated if cases fell evenly or non-significantly between index and control biological relatives (Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1978, pp. 29-30).

We will discover that B3 diagnoses were *not* found in statistically significant numbers among index biological relatives when compared with controls, which casts doubt on Kety and colleagues' assertion that this diagnosis is associated/genetically-related to B1 schizophrenia. Both Lidz and Blatt (1983) and Lewontin and colleagues (1984) noted the lack of evidence for such an association, and this observation is elaborated upon here.

In order to test the Danish-American criteria for genetic relatedness, we will look at the number of B3 biological relatives of B1 adoptees plus the number of B1 biological relatives of B3 adoptees. The sum of these totals shall be called the *"B1/B3 relationship"* as it relates to individual relatives. Benjamin (1976) pointed out that in order to assure that the assumption of independent observations is not violated, a more proper method of comparing index and control relatives would be to look at differences between afflicted biological *families*. When making this comparison, the B1/B3 relationship is defined as the number of B3 index adoptees' biological families with at least one B1 member plus the number of B1 index adoptees' biological families with at least one B3 member.

The evidence contradicting Kety and associates' claim that the B1 and B3 categories are related is based on the reanalyzed data displayed in Tables 1-4. In these tables, diagnostic comparisons are made between index biological relatives or families versus controls. The 1975 report by Kety and colleagues did not provide enough information to determine the exact number of matched control biological relatives, which is the reason that the 1968 totals will be used. (The B1/B2 relationship is not calculated here because no B2 biological relative diagnoses were made in the Kety and coworkers 1968 or 1975 studies.) Table 1 calculates the B1/B3 relationship for the Kety and associates 1968 Adoptees' Family study as it relates to individual relatives.

If we look at the B1/B3 relationship from the standpoint of the difference in affected families, the results found in Table 2 are obtained. If we look at Kety and

TABLE 1. The B1/B3 Relationship—Individuals: 1968; Number of B3 Diagnoses Among Biological Relatives of B1 Index Cases Plus B1 Diagnoses Among Biological Relatives of B3 Index Cases—Versus Controls: Cases Based on Records

	N	B1 Index Cases	B3 Index Cases	B1 Biological Relatives of B3 Index	B3 Biological Relatives of B1 Index		B1/B3 Relationship	
Index vs.								
Matched	33	16	10	0/38	3/82*	(3.6%)	3/120*	(2.5%)
Controls	26			0/43	1/78	(1.3%)	1/121	(0.8%)
Probability**					.33	*ns*	.31	*ns*
Vs. All Controls	33				1/156	(0.6%)	1/156	(0.6%)
Probability**					.12	*ns*	.22	*ns*

Note. Based on figures from Kety et al. (1968, pp. 354-355). B1/B3 Relationship defined as total of B3 biological relatives of B1 index cases plus B1 biological relatives of B3 index cases.

*All three cases are paternal half-siblings from the same family.

**Fisher's Exact Test, one-tailed.

TABLE 2. The B1/B3 Relationship—Families: 1968; Number of B1 Index Case Biological Families With at Least One B3 Diagnosis Plus Number of B3 Index Case Biological Families With at Least One B1 Diagnosis—Versus Controls: Cases Based on Records

	N	B1 Index Cases	B3 Index Cases	B3 Adoptee Biological Families With at Least One B1 Diagnosis	B1 Adoptee Biological Families With at Least One B3 Diagnosis	B1/B3 Relationship
Index vs. Matched Controls	33	16	10	0/10	1/16	1/26 (3.8%)
	26			0/10	1/16	1/26 (3.8%)
Probability*					*ns*	*ns*
Vs. All Controls	33					1/33 (3.0%)
Probability*						*ns*

Note. Based on figures from Kety et al. (1968, pp. 354-355). The B1/B3 relationship is defined as the total of the number of B3 index cases' biological families with at least one B1 member, plus the number of B1 index cases' biological families with at least one B3 member.
*Fischer's Exact test, one-tailed.

associates' later study (1975) based on interviews, we find the same results. Table 3 looks at the B1/B3 relationship in terms of individual biological relatives.

If we examine the B3 figures pertaining to affected families in the interview-based study, the results are as shown in Table 4.

Based on the findings in Tables 1-4 it is clear that Kety and colleagues should have concluded that the B3 diagnosis was unrelated to chronic B1 schizophrenia. As they stated, "the schizophrenia spectrum was and still is a hypothesis or group of hypotheses on which we hoped our continuing studies might cast some light" (Kety et al., 1976, p. 417). The light that was cast in the 1968 and 1975 studies clearly illuminated the fact that the sum total of the B3 biological relatives of B1 adoptees, plus the B1 biological relatives of B3 adoptees, was statistically non-significant when compared to the B3 rate in the control group.

A further example of the unwarranted conclusions coming out of the Danish-American studies can be found in a 1970 paper by Kety. Discussing the results of his 1968 study, Kety noted that of the 38 biological relatives of the B3 index adoptees, 3 were diagnosed with borderline schizophrenia, 1 with possible chronic schizophrenia, 1 with possible borderline schizophrenia, and 1 with inadequate personality. Kety concluded, "this finding supports the notion that borderline schizophrenia is a form of schizophrenia and is related to chronic schizophrenia" (Kety, 1970, p. 242). Unfortunately, these results permit no such conclusion. If the only definite cases Kety finds among the relatives of the latent schizophrenic index cases are *latent schizophrenics*, he is not permitted to conclude that this suggests anything about the relationship between *chronic* and *latent schizophrenia*. In this argument, Kety committed the logical fallacy of *assuming* that the B1 and B3 conditions were genetically related in order to *conclude* that they were genetically related.

TABLE 3. The B1/B3 Relationship—Individuals: 1975; Number of B3 Diagnoses Among Biological Relatives of B1 Index Cases Plus B1 Diagnoses Among Biological Relatives of B3 Index Cases—Versus Controls: Cases Based on Interviews

	N	B1 Index Cases	B3 Index Cases	B1 Biological Relatives of B3 Index	B3 Biological Relatives of B1 Index	B1/B3 Relationship
Index vs.	33	17	9	0/38	5/102 (4.9%)[b]	5/140 (3.6%)
Matched Controls[a]	26			0/43	3/78 (3.8%)	3/121 (2.5%)
Probability**					.44 *ns*	.44 *ns*
Vs. Screened Controls	23					1/113 (0.9%)
Probability**						.16 *ns*
Vs. All Controls	34					3/174 (1.7%)
Probability**						.25 *ns*

Note. All biological relative diagnoses based on figures from Kety et al. (1975, pp. 158-161). B1/B3 Relationship defined as total of B3 biological relatives of B1 index cases plus B1 biological relatives of B3 index cases.

**Fisher's Exact Test, one-tailed.

[a]Number of matched control B1 + B3 index and relative cases based on Kety et al., (1968,pp. 354-355). Matching status not provided in the 1975 report.

[b]3 fathers were named in adoption report of index adoptee S-22, counted here as one father.

TABLE 4. The B1/B3 Relationship—Families: 1975; Number of B1 Index Case Biological Families With at Least One B3 Diagnosis Plus Number of B3 Index Case Biological Families with at Least One B1 Diagnosis—Versus Controls: Cases Based on Interviews

	N	B1 Index Cases	B3 Index Cases	B3 Adoptee Biological Families with at Least One B1 Diagnosis	B1 Adoptee Biological Families with at Least One B3 Diagnosis	B1/B3 Relationship
Index vs.	33	17	9	0/9	5/17 (29.4%)	5/26 (19.2%)
Matched Controls[a]	26			0/9	2/17 (11.7%)	2/26 (7.6%)
Probability**					.20 *ns*	.21 *ns*
Vs. Screened Controls	23					1/23 (4.3%)
Probability**						.13 *ns*
Vs. All Controls	34					3/34 (8.8%)
Probability**						.21 *ns*

Note. All biological relative diagnoses based on figures from Kety et al. (1975, pp. 158-161). The B1/B3 relationship is defined as the total of the number of B3 index cases' biological families with at least one B1 member, plus the number of B1 index cases' biological families with at least one B3 member.

Number of matched control index and relative cases based on Kety et al. (1968, pp. 354-355). Numbers not provided in 1975 report.

**Fisher's Exact Test, one-tailed.

The reader may be wondering why, if according to Tables 1-4 category B3 was found unrelated to chronic schizophrenia, Kety and associates did not also recognize this finding. The answer is based on how one counts biological relative cases when comparing B1 schizophrenia to the B3 diagnosis. Looking specifically at B3 borderline schizophrenia cases in Tables 1-4, the prevalence of B3 cases among the biological relatives of B1 index adoptees plus the prevalence of B1 biological relatives among the B3 index adoptees were the only combinations considered—for the simple reason that *the rate of B3 diagnoses among the biological relatives of B2 and B3 adoptees, and the rate of B1 diagnoses among the biological relatives of B1 adoptees, tells us nothing about the relationship between the B3 and the B1 categories*. In the Kety and associates analysis (1975, p. 154), B3 index biological relative diagnoses were combined with the B1 and D biological relatives in order to achieve significant results. Additionally, B3 biological relatives of B2 and B3 adoptees and B1 biological relatives of B1 index adoptees, were combined in the calculation. This was an improper means of comparison.

But even with these errors, the index/control difference for latent schizophrenia (B3) in the interview-based Copenhagen sample was listed as having a non-significant probability of .25 (Kety et al., 1975, p. 154). Even against the "screened controls" only (which consisted of 23 of the 34 control adoptees who had been interviewed and were confirmed as non-schizophrenic) the comparison yielded non-significant results. It was only by combining the B3 category with the other spectrum diagnoses that significant results were obtained. But this comparison was premature because the B3 diagnosis had not yet earned the right to be combined into any schizophrenia spectrum, since it had not passed statistical tests of significance when standing alone. A crucial step in the determination of the B1/B3 relationship had simply been skipped. Therefore, the B3 (and B2) category should have been dropped from the spectrum.

The Kety and colleagues 1994 final report on the Danish Provincial sample reported a significantly higher rate of latent schizophrenia among index versus control biological relatives (which was *not* statistically significant if the comparison is limited to first-degree relatives). However, 18 of the 42 control adoptees (and their relatives) were dropped from the study—over a decade after it began—for insupportable reasons (Joseph, in press-a). Of the 18 excluded control adoptees, 13 were diagnosed with a "serious or confounding mental illness" (typically a major affective disorder; see Kety & Ingraham, 1992) and five could not be interviewed. According to Kendler and Diehl (1993), who viewed the final Provincial study report while in preparation, there was no significant difference in latent schizophrenia diagnoses *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 the control adoptees (6.5% vs. 5.5%, respectively)" (p. 265).

Rosenthal (1971a, p. 96) observed that "in adoption studies, biological relatives separated from schizophrenic family members also developed borderline schizophrenia or schizoid personality." But not in numbers significantly greater than population expectations or significantly greater than controls. Table 5 presents the relevant data from Rosenthal's Danish-American Adoptees study.

TABLE 5. Prevalence of "Borderline Schizophrenia" and Schizoid Diagnoses in the Adopted-Away Offspring of a Parent With a Schizophrenia Spectrum Disorder: Danish-American Adoptees Study—(Rosenthal et al., 1971)

	N	1) Schizoid	2) Borderline Sch.	Total 1 and 2
Index	52	2 (4%)	3 (6.0%)	5 (10.0%)
Controls	67	2 (3%)	3 (4.5%)	5 (7.5%)
Probability*		.59 *ns*	.53 *ns*	.46 *ns*

Note. Based on figures from Rosenthal et al. (1971, pp. 309-310).
* Fisher's Exact Test, one-tailed.
Excludes index cases diagnosed with "manic depressive psychosis."
Index diagnoses: "Schizoid: schizophreniform borderline?" and "Probably borderline paranoid; schizoid." Control diagnoses: "Moderately schizoid" and "Schizoid; beginning schizophrenia?"
Index diagnoses: "Borderline schizophrenia" (3). Control Diagnoses: "Borderline schizophrenia" (2) and "Schizophrenic-like border case" (1)

As discussed elsewhere (Joseph, 1998a), two subsequent reanalyses of Rosenthal's data confirmed these negative results.

Looking back on the formation of the spectrum, Kety (1988, p. 218) would write:

> The investigators did not necessarily believe that all of these disorders would be found to be related to schizophrenia, but it would have been inappropriate to exclude any prematurely. Furthermore, if the different components were kept separate, it might eventually be possible to evaluate the relationship of each to paradigmatic [B1] schizophrenia.

But as we have seen, Kety did not evaluate the B3 category separately. According to Kety, "the number of these illnesses which we found in the relatives was too small to permit a further breakdown of the schizophrenia spectrum" (Kety, 1975, p. 21) and, "there were insufficient cases to permit testing individual components of the spectrum with any reliability" (Kety, 1987, p. 424). By Kety's reasoning, if *zero* B3 cases had been found among index biological relatives, this would have been grounds to drop the category. A non-significant 3.5% B3 rate, however, permitted the retention of the category while constituting "insufficient cases" with which to make a separate comparison. By 1978, Kety and colleagues recognized that "most of the acute psychoses which in America have been labeled 'acute schizophrenia reaction' are not subtypes of schizophrenia" (Kety, Rosenthal, & Wender, 1978, p. 217), and the B2 diagnosis was dropped from the spectrum.

The most explicit rationalization for combining diagnoses which (individually) showed no statistically significant index/control difference among biological relatives was made by Ingraham and Kety (1988). Referring to the 1975 interview-based study they wrote,

> Latent or borderline schizophrenia was found at a 4-5% prevalence in the biological index relatives and 1% to 1.5% in the biological relatives of controls. This is also true where the symptoms are less distinct and the diagnosis is designated uncertain. (Ingraham & Kety, 1988, pp. 121,123)

Ingraham and Kety went on to acknowledge that *none* of these diagnoses was found in statistically significant numbers, followed by a clearly post hoc decision to combine them: "Since neither in chronic nor in latent schizophrenia the results for the definite or uncertain diagnoses are statistically different, *it appears justified to combine them* [italics added]" (p. 123).[3] What Kety failed to understand was that four diagnoses failing tests of genetic relatedness *separately* do not—when combined—constitute a genetically related spectrum of disease. Confronted with the finding that each spectrum diagnosis fell short of statistical significance when compared with controls, Kety could have just as easily concluded that his findings failed to support the spectrum concept or the genetic basis of schizophrenia.

There is another factor relevant to the question of why categories B3 (and therefore D3, because it is an "uncertain" version of the B3 diagnosis) and B2 were not dropped from the spectrum in 1975 in spite of the evidence that they should have been. The Danish-American team had a vital interest in keeping these categories, for losing them would have reduced the index group back to the original 16-17 B1 cases. It already has been demonstrated that the study would not have been viable using this definition of schizophrenia. Thus, in spite of the talk about testing hypotheses, the elimination of B3, D3, and B2 "schizophrenia" would have either meant the unsuccessful conclusion of their work, or the ascertainment of thousands more adoptees in the hope of finding enough B1 cases to continue the study. In the 1975 interview-based study, 24 of the 56 biological relative spectrum diagnoses were either B3 or D3 (24 of 30, excluding category C). Clearly, there was a relationship between the willingness of Kety and associates to remove a diagnosis from the spectrum and that diagnosis' usefulness in statistical calculations or to the study's viability.

One might object that significance levels have been reduced, as Kety complained, by "the simple expedient of dividing the components into smaller groups" (Kety, 1983, p. 723). But this is not at all how the numbers were approached here. The comparisons in the present review were carried out in a series of logical steps based on the idea that each spectrum diagnosis had to prove its worthiness "individually" as a prerequisite to being combined into a spectrum. We have seen that the B3 category failed all tests of relationship to chronic schizophrenia, thereby forfeiting the right to be included in a diagnostic group which included the B1 condition.

The Siever and Gunderson Reanalysis. Siever and Gunderson (1979) reanalyzed the results of the Kety and colleagues (1975) study in order to determine whether there was a relationship between B1 schizophrenia and the lesser B categories. They began by acknowledging that there was no significant difference in B3 diagnoses between index and control biological relatives ($p = 0.25$), while finding that the difference for the B1 diagnosis was significant ($p = 0.03$). They concluded, "This suggests that genetically transmitted factors specifically related to schizophrenia may play a more important role in the etiology of chronic [B1] schizophrenia than in the etiology of the borderlines [B3], although the small numbers preclude any definite conclusions" (Siever & Gunderson, 1979, p. 63).

One might ask how the authors concluded that the B3 condition was genetically transmitted or related to B1 schizophrenia if no significant differences were found between index and control biological relatives. Siever and Gunderson did acknowledge that acute (B2) schizophrenia was unrelated to both the B1 and B3 conditions but they did not explain how they came to that conclusion. One would think that a non-significant B3 index/control biological relative difference would have placed this category alongside B2 as being unrelated to B1 schizophrenia.

Based on their unjustified retention of the B3 category within the spectrum, Siever and Gunderson calculated the rate of B3 diagnoses among the biological relatives of B1 and B3 index cases and compared them to the control group: "In this analysis, the prevalence rate of borderlines in relatives of the B1 and B3 index cases (8/142 or 5.6 percent) significantly exceeded the rate in relatives of screened controls (1/113 or 0.9 percent) ($p = .039$)" (p. 63). In discussing this dubious calculation, one could begin by pointing out that 5 of the 8 index B3 diagnoses the authors are referring to were made on half-siblings. Second, as already observed the rate of B3 diagnoses among the biological relatives of B3 adoptees tells us nothing about the relationship between the B1 and B3 conditions, yet three such cases were figured into the comparison. Third, there was little justification for limiting the comparison to screened controls. The *entire* control group was "unscreened" in the Kety and colleagues 1968 report, which did not prevent the proponents of the genetic theory of schizophrenia from pointing to the allegedly significant results it produced. By Siever and Gunderson's logic, we should completely disregard the results of the 1968 study since all of the controls were potentially non-recorded schizophrenics. Fourth, significant differences were found only by removing the B2 category from the comparison; the criteria for removing the B2 diagnosis were not applied to the B3 diagnosis. As noted, there was equal justification for removing both of these diagnoses. And fifth, 2 of 8 index B3 diagnoses were record-based only. One relative had emigrated, and the other received no diagnosis in the 1975 study. Had Siever and Gunderson applied the same criteria to the B1 index/control comparison, they would have counted the 1968 record-diagnosed B1 biological father of control adoptee C9, meaning that the B1 index/control difference would have been a non-significant 5 to 1.

Siever and Gunderson concluded that "the results all converge in suggesting a genetic relationship between borderlines and chronic schizophrenics" (p. 65)—but if any one of the five errors described above had not been made, they would have obtained non-significant results.

Eugen Bleuler and "Latent Schizophrenia"

Kety and associates consistently justified the inclusion of latent schizophrenia in their spectrum on the grounds that the condition was identified and described by the creator of the schizophrenia concept, Eugen Bleuler. For example, Kety wrote that in addition to the DSM-II description of latent schizophrenia,

> We also took into account Bleuler's description of the symptoms of latent schizophrenia as he observed them in the relatives of overt schizophrenia patients. Bleuler's description of latent schizophrenia actually was the most useful guide since only those observations, like ours, had been made on individuals not hospitalized or seeking treatment. (1985b, p. 592)

Bleuler did indeed identify the condition in his famous book on schizophrenia (1911/1950): "There is also a latent schizophrenia, and I am convinced that this is the most frequent form, although admittedly these people hardly ever come for treatment" (p. 239). However, Kety, Wender, and Rosenthal overlooked a critical element in the way Bleuler proposed that this condition be diagnosed. Had these researchers remained true to Bleuler's teachings they would not have included latent schizophrenia in their spectrum.

Bleuler observed that a latent schizophrenia diagnosis could be made only after a person had demonstrated more serious symptoms. In the following passage, Bleuler noted the important difference between chronic and "milder" cases of schizophrenia:

> As in every other disease, the symptoms must have reached a certain degree of intensity if they are to be of any diagnostic value. Yet in milder cases of schizophrenia we find a number of prominent manifestations, which strongly fluctuate within the limits of what is regarded, if not as healthy, at least as "not mentally ill." Character anomalies, indifference, lack of energy, unsociability, stubbornness, moodiness, the characteristic for which Goethe could only find the English word, "whimsical," hypochondriacal complaints, etc., *are not necessarily symptoms of an actual mental disease* [italics added]; they are, however, often the only perceptible signs of schizophrenia. *It is for this reason that the diagnostic threshold of schizophrenia is higher than that of any other disease . . .* [italics added] (Bleuler, 1911/1950, p. 294)

Here, Bleuler observed that the symptoms of "milder cases" of schizophrenia and the merely "whimsical" are not sufficiently different to be able to make a diagnosis of schizophrenia. He therefore demanded a high diagnostic threshold for schizophrenia precisely in order to eliminate the possibility that people not suffering "actual mental disorders" would be diagnosed as schizophrenic. "Only a few isolated psychotic symptoms," Bleuler continued, "can be utilized in recognizing the disease, and these too, have a very high diagnostic threshold value" (p. 294).

For Bleuler, latent schizophrenia was a *retrospective diagnosis* that could only be made on the basis of a patient's *later* difficulties:

> Such mild cases are often considered to be "nervous" or "degenerated" individuals, etc. But if we follow the anamnesis of those who are admitted to the hospital in later years because of an exacerbation of their difficulties, a criminal charge, a pathological drinking bout or some such episode, we can usually find throughout the entire past history of the individual mildly pathological symptoms *which in the light of their recent illness* [italics added] unquestionably have to be considered as schizophrenic. (p. 239)

For Bleuler, latent schizophrenia could be diagnosed only *in the light of the patient's subsequently more serious condition*. Basing his disease model on the then recently discovered etiology of neurosyphilis (Szasz, 1976), Bleuler viewed schizophrenia as "remain[ing] latent until an acute pathological thrust produces prominent symptoms, or until a psychic shock intensifies the secondary symptoms" (Bleuler, 1911/1950, p. 463).

Kety (1985a) was quite prepared to cite Bleuler in support of the removal of B2 "acute schizophrenia" from the Danish-American spectrum. Kety argued that the DSM-II had "deviated" from Bleuler's teachings by including "'acute schizophrenic reaction' . . . despite Bleuler's admonition that these are 'partial phenomena of the most varied diseases [whose] presence is often helpful in making the diagnosis of a psychosis, but not in diagnosing the presence of schizophrenia'" (p. 6). Here, Kety cites Bleuler's insistence of a high diagnostic threshold for schizophrenia in support of dropping the B2 diagnosis, while ignoring Bleuler's equally stern admonition for the rejection of the *latent schizophrenia* (B3) diagnosis. Thus, Kety's differing set of standards on the statistical plane is paralleled by the selective citation of Bleuler on the historical plane.

For Bleuler, the necessity of maintaining a high diagnostic threshold was necessary in order to avoid errors such as those committed by Kety, Rosenthal, and associates, who applied the schizophrenia label to dozens of "whimsical" relatives in their studies. A comparison of two previously cited quotations will demonstrate just how far Kety and colleagues strayed from Bleuler's teachings:

> Only a few isolated psychotic symptoms can be utilized in recognizing the disease, and these too, have a very high diagnostic threshold value. (Bleuler, 1911/1950, p. 294)

Versus,

> Paul Wender and I were working downstairs, in concert with Seymour Kety, in effect broadening the concept of schizophrenic disorder as widely as it may have ever been reasonably conceived before . . . (Rosenthal, 1975, p. 19)

It appears that the latent schizophrenia diagnosis not only fails statistical tests of significance but lacks even the historical and theoretical legitimacy claimed by Kety and associates.

Other Spectrum Diagnoses

As previously noted, three years after the 1975 interview-based study was published, Kety and colleagues finally concluded that the B2 category did not belong in the spectrum (Kety, Rosenthal, & Wender, 1978). This means that there is no dispute over the exclusion of this category.

Looking at the uncertain or D diagnoses, they must also be excluded from the spectrum because D2 (uncertain acute) and D3 (uncertain borderline) are uncertain versions of the already excluded (by Kety et al.) B2 and (by the present review) B3 categories. D1 (uncertain chronic schizophrenia) seems to be in a gray area regarding its inclusion in the spectrum but there was only one relative with this diagnosis in the entire Danish-American series—the paternal half-sibling of index adoptee S1 as reported in the 1968 study only.

There were 16 biological relative category D diagnoses in the 1975 Kety and colleagues study (13 index and 3 control), representing 28.5% of all spectrum diagnoses. Why should a case deemed "uncertain" be counted as schizophrenia when it "clearly does not fit into an appropriate B category" (Kety et al., 1968,

p. 352)? What is an "uncertain borderline state"? Lidz and Blatt (1983) noted that to be able to tell who is a definite latent schizophrenic and who else may have been an uncertain latent schizophrenic "is a rather extraordinary feat" (p. 407). And even Kety and associates (1976) described the D diagnosis as a "highly subjective and as yet nonexplicit category," and "vague and subjective . . .which hardly qualifies as schizophrenia according to our own or other criteria" (p. 420).

According to Kety (1987), "in the case of the relatives, questionable or uncertain schizophrenia had to be added if relatives with less certain diagnoses were not to be lost [italics added]" (p. 424). Are we to believe that the genetic theory of schizophrenia is based in large part on a classification utilized to help a research team keep track of its subjects? One would think that these relatives could have been prevented from becoming "lost" without being counted in the Danish-American statistical calculations. It seems clear that the D categories should not have been counted as schizophrenia in the Danish-American studies.

Category C (schizoid and inadequate personality) was recognized by Kety as not belonging in the schizophrenia spectrum:

> Our diagnoses of schizoid and inadequate personality in this study [Kety et al., 1975] did not discriminate between the genetic relatives of schizophrenic adoptees and their controls; in fact, the prevalence was the same in both. There was thus 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, 1983, p. 723)

Noteworthy is Kety's justification for the removal of category C on the grounds that its prevalence "was the same in both" groups. From the standpoint of inferential statistics, the exact same statement could have been made about the B3 category, which Kety and associates retained in the spectrum. The criteria used for removing the C category were not applied to the B3 diagnosis.

It has been noted elsewhere that there is a clear overlap between category C and the B3 and D3 diagnoses (Lidz & Blatt, 1983). This point becomes clearer in the following demonstration of just how similar "latent schizophrenia" and non-spectrum schizoid personality were according to Kety and associates' diagnostic criteria. Kety (1985b) acknowledged that the nine 1975 B3 interview diagnoses were made on people displaying milder symptoms than the seven hospitalized 1968 B3 record-based diagnoses. (Only 1 of the 7 record-based B3 diagnoses was sustained by interview, meaning that 8 of 9 B3 diagnoses in the 1975 study were new.) It makes sense that the non-hospitalized biological relatives diagnosed in the 1975 study would display milder symptoms than those whose behavior was severe enough to require hospitalization. What Kety revealed for the first time in his 1985 paper was just how similar the 1975 B3 cases were to those diagnosed with category C schizoid personality—a diagnosis found to be genetically unrelated to schizophrenia.

Table 6 displays a side-by-side comparison of Kety's (1985b) description of his 1975 B3 cases and the DSM-II definition of schizoid personality.

It appears that Kety's 1975 diagnostic criteria for "latent schizophrenia" and DSM-II schizoid personality were remarkably similar. The diagnoses were made on the basis of

1. Flat affect/inability to express feelings,
2. Poor contact/seclusiveness,
3. Poor interpersonal relationships/avoidance of close relationships, and
4. Bizarre thinking/eccentricity.

Spitzer and Endicott (1979) examined the Danish-American relative case records in an effort to define new diagnostic categories for the DSM-III (APA, 1980). The schizotypal personality disorder (SPD) diagnosis was derived from the identification of eight items that distinguished Kety and colleagues' spectrum and non-spectrum relatives. Schizotypal personality disorder was referred to by Kety as "comparable to our diagnosis of latent schizophrenia" (Kety & Ingraham, 1992, p. 250).[4] Consistent with the evidence presented thus far, Spitzer and Endicott discovered that they could not adequately separate schizoid and schizotypal personalities into two distinct diagnostic categories. In fact, they found that SPD "was merely a subdivision of what has for years been referred to as Schizoid Personality Disorder" (Spitzer & Endicott, 1979, p. 98). The similarity of these two diagnoses was codified in the DSM-III, which differ-

TABLE 6. Comparison of Diagnostic Criteria for Schizophrenia Spectrum Latent Schizophrenia and Non-Spectrum Schizoid Personality

Description of diagnoses made in the Adoptees' Family interview study (Kety et al., 1975)	Complete DSM-II definition of schizoid personality
"For our diagnoses made from interviews in the 1975 study...used the DSM-II description of latent schizophrenia, schizoid and inadequate personality. ...Our diagnoses of latent and uncertain schizophrenia in the relatives, therefore, included a majority with flat affect, bizarre thinking, poor contact, and poor interpersonal relationships rather than the positive symptoms which appeared to characterize the [1968] hospitalized group" (Kety, 1985b, p. 592).	"This behavior pattern manifests shyness, over-sensitivity, seclusiveness, avoidance of close or competitive relationships, and often eccentricity. Autistic thinking without loss of capacity to recognize reality is common, as is daydreaming and the inability to express hostility and ordinary aggressive feelings. These patients react to disturbing experiences and conflicts with apparent detachment" (APA, 1968, p. 42).
Summarized version of Kety's 1975 B3 description (schizophrenia spectrum):	Summarized version of the DSM-II schizoid personality (non-spectrum):
1 Flat affect	1 Inability to express feelings
2 Poor contact	2 Seclusiveness
3 Poor interpersonal relationships	3 Avoidance of close relationships
4 Bizarre thinking	4 Eccentricity, autistic thinking

entiated schizoid and schizotypal personality disorders on the sole basis of the latter's "eccentricities of communication or behavior" (APA, 1980, p. 310). It is therefore quite easy to understand why Kety, Rosenthal, and Wender (1978) wrote in reference to the B3, D3, and C diagnoses that "it is doubtful that we could demonstrate a significant differentiation between these categories" (p. 220). This is quite an admission when one realizes that Kety and associates acknowledged that it was doubtful that they could differentiate a "schizophrenia spectrum disorder" from a supposedly unrelated condition.

Although the concept of schizoid personality is widely known, "inadequate personality" is more obscure and was not included in the DSM-III. The complete DSM-II description of the vaguely defined "inadequate personality" is reprinted below:

> This behavior pattern is characterized by ineffectual responses to emotional, social, intellectual and physical demands. While the patient seems neither physically nor mentally deficient, he does manifest inadaptability, ineptness, poor judgment, social instability, and lack of physical and emotional stamina. (APA, 1968, p. 44)

Although virtually no one would diagnose such a person with schizophrenia, Kety (1970, p. 238) wrote that the investigators "had great difficulty making a clear and satisfying distinction between 'inadequate personality' and mild 'borderline schizophrenia.'" This statement becomes even more important when we realize that in a later essay, Kety (1985b) wrote that the 1968 B3 relatives had more "negative symptoms" than the 1975 B3 group. If Kety and associates had "great difficulty" distinguishing "mild" 1968 B3 cases from DSM-II inadequate personality, one can safely assume that the 1975 B3 cases were distinguished only with extremely great difficulty.

The Concepts of "Genetic Relationship" and Association

In the foregoing discussion it was argued that, based on the Danish-American investigators' criteria for determining genetic relatedness, no evidence was found that chronic schizophrenia was related to any other component of the schizophrenia spectrum. But this finding in no way implies endorsement of their criteria for determining the relationship between diagnoses. Even if, for example, "latent schizophrenia" had been found significantly concentrated among the relatives of B1 index cases, this would not necessarily have constituted evidence that it is a related condition.

By Kety and colleagues' definition, if a particular diagnosis is found to *correlate* with another, this suggests that the conditions constitute different manifestations of the same disease entity. However, the fact that two conditions are associated does not prove that they are caused by a common factor. Kety, Rosenthal, Wender, and colleagues overlooked the fact that conditions could be highly correlated and yet have no causal relationship to each other. As Gould (1981) noted, "the invalid assumption that correlation implies cause is probably among the two or three most serious and common errors of human reasoning" (p. 242).

In the following passage Rosenthal (1972) described how the simple correlation of diagnoses led to the conclusion that they were genetically related. Referring to all spectrum diagnoses other than B1, he wrote,

> These combined diagnoses occurred about six times more frequently among the biological relatives of our index cases than among the biological relatives of the controls. *For this reason* [italics added] we feel justified in having broadened the range of schizophrenic disorders studied to include those that we thought might be genetically related to process schizophrenia . . . [the B2 diagnosis] may have to be eliminated from the spectrum. Among the 30 biological relatives of 7 index cases who had this diagnosis, we did not find a single instance of schizophrenic spectrum disorder. (pp. 68-69)

This statement is a clear example of how the spectrum was justified. A condition was considered related to schizophrenia simply because it was (allegedly) found more frequently among the index biological relatives. Little other theoretical justification was deemed necessary. And the claim that non-B1 spectrum disorders were found "six times more frequently" among index biological relatives requires clarification: In the 1968 Kety et al. study, 9 of 13 non-B1 index biological relative spectrum diagnoses were given to half-siblings. Among first-degree relatives the rate was a non-significant 4 to 2.[5]

In his 1938 schizophrenia family study, Kallmann found a correlation between schizophrenia and tuberculosis, which led him to conclude that the two conditions were genetically related:

> Because in our estimate of the causes of death we naturally counted only the absolutely assured deaths from tuberculosis, the assumption will have to be made for the probands that at least one third of them, and possibly even more, died of tuberculosis. Thus no doubt can remain that *within our own proband material the death rate from tuberculosis was also much higher than in the general population, and that, on the whole, a very particular significance must be assigned to tuberculosis in the entire heredity-circle of schizophrenia* [emphasis in original]. (Kallmann, 1938, p. 86)

However, Kallmann's correlation was spurious since he failed to recognize that the high rate of tuberculosis among schizophrenia patients and their relatives was the result of environmental conditions common to both schizophrenia patients and tuberculosis sufferers. Had Kallmann decided to pull together a "schizophrenia spectrum" in 1938, tuberculosis would have likely been a part of it—*and with greater justification than any of the non-B1 Danish-American spectrum diagnoses*. Tuberculosis is a recognizable physical disease which was found in significantly greater numbers in the families of Kallmann's hospitalized schizophrenia patients. "Latent schizophrenia" is a vaguely defined grouping of non-psychotic behaviors found in *statistically non-significant* numbers among the biological relatives of adopted-away schizophrenic index cases. It is quite possible that the greater level of psychological distress among these relatives was the result of differences in rearing environments due to, among other possibilities, the selective placement of adoptees (see Joseph, 1999a, 1999b, in press-a). The conclusion that the spectrum disorders are genetically related to schizophrenia (and to each other) could be the result of a correlation as spurious as Kallmann's.

If we look at the diagnostic criteria for each of the categories described in the 1968 spectrum, we find conditions ranging from possibly "psychotic" individuals (B1) to nonpsychotic people who shun social contact or whose personalities are "inadequate" (C). Looking specifically at the B3 category it is apparent that this is not a description of a person commonly regarded as psychotic. Kety and colleagues made it clear that this diagnosis is given "in the absence of frank delusions or other psychotic symptoms" (Kety et al., 1994, p. 445). The image of a B3 individual is someone whom many people would consider "weird" or reclusive. In essence, they are people who don't conform to the norms of society. They don't think the way that "we" do; they don't understand "our" sense of reality or logic; they can't adapt to "our" society; and they don't always have sexual relations with people of the opposite-sex—which "we" find distasteful. In fact, all three B categories make reference to homosexuality (Kety et al., 1968, p. 353), which obviously became part of the diagnostic formulation. One could imagine a difficult case record being tipped in the direction of diagnosis simply through the knowledge that the person in question was gay or bisexual. And in fact there is at least one documented example of an adoptee being placed in the spectrum on the basis of suspected homosexuality. The complete "diagnostic statement" of this individual read, "Schizophrenia borderline *or perverse (homosexual, transvestite)* [italics added]. Could break down with schizophrenia episode" (Wender et al., 1974, p. 124).

Although homosexuality, or at least "ego-syntonic homosexuality," was removed from the American Psychiatric Association's list of mental disorders in 1974, there was no mention of this fact from the Danish-American investigators or whether their diagnostic criteria had been changed to reflect this decision. Homosexuality was not mentioned in any of the three DSM-II diagnoses upon which the B1, B2, and B3 categories were based, meaning that all such references were inserted by Kety, Wender, and Rosenthal. (Nor was homosexuality mentioned in the DSM-I schizophrenia descriptions.) Rosenthal cited studies which claim that 75% of people diagnosed with schizophrenia are "overt homosexuals" or have had homosexual experiences (Rosenthal, 1979, p. 28). Since for Rosenthal, Wender, and Kety homosexuality was associated with most of their spectrum diagnoses, one might ask why this apparently differentiating "disorder" was not added to the spectrum as well—taking into consideration the large "clinical overlap between schizophrenia and homosexuality" (Rosenthal, 1979, p. 28).

Even if it did not explicitly include homosexuality, Rosenthal's conception of "schizophrenia-related illness" probably included more people than anyone else's definition:

> For every hospitalizable schizophrenic, there are many more people in the community who have a schizophrenic-like type of disorder which is not severe enough to require hospitalization. These individuals are called borderline or pseudoneurotic schizophrenic, schizoid, paranoid, or simply cold, distant and inadequate, or odd and eccentric. (Rosenthal, 1979, p. 23)

Disregarding Bleuler's admonitions, for Rosenthal it was apparently enough to be "cold, distant and inadequate" or "odd and eccentric" to deserve the schizophrenia label. Wender held similar views:

> The heterogeneous group of individuals who are believed by some to be biological—as well as familial—relatives of schizophrenics merges with the group described as having schizoid personality disorder. Called schizotypal, these people vary from the shy, timid and unsociable to the callous, cold, harsh, and distant, from the quiet, empty, and intelligent to the sensitive and poetic or to the militant, rigid, and fanatic (political or religious). (Wender & Klein, 1981, p. 127)

One might ask how many "cold and distant," "sensitive and poetic," or "rigid" people Rosenthal and Wender diagnosed B3, D3, or C in the Danish-American series.

Genetically oriented schizophrenia family and twin researchers have tended to see many of the biological relatives of schizophrenia patients as manifesting less severe forms of the condition (see Kendler, 1985). What they considered schizophrenia-related behaviors are similar to those described in the B3 diagnosis; that is, not psychosis, but socially disapproved, "odd" behavior. Of course, such behavior could be explained on the basis of similarly unhealthy rearing environments as was the case with Kallmann's tuberculosis cases.

In their published reports the Danish-American investigators referred to categories B1, B2, and B3 as "definite schizophrenia," which seems strange when one considers that their studies were supposed to be *testing the hypothesis* that B2 and B3 were related to chronic schizophrenia. Considering that acute schizophrenia was eventually dropped from the spectrum, this diagnosis was apparently not so "definite" after all. Of the B3 diagnosis Lidz and Blatt (1983) commented wryly, yet accurately, "many of the subjects placed in this category were not definitely schizophrenic but, rather, were definitely not schizophrenic" (p. 430).

CONCLUSION

This review began with an exploration into the origins of the Danish-American "schizophrenia spectrum." The evidence suggests that the spectrum was created more by necessity than on the basis of theoretical soundness. Each component of the spectrum was examined and assessed for its relationship to chronic schizophrenia. It was argued that these categories are not related to chronic B1 schizophrenia by statistical, theoretical, or empirical evidence. Because several spectrum categories were subsequently dropped by the Danish-American investigators, there are only two diagnoses for which the present study remains in dispute with Kety and associates: so-called latent or borderline schizophrenia (B3), and uncertain latent or borderline schizophrenia (D3).

Looking specifically at the B3 diagnosis, it was shown that Kety and associates made a crucial error in the way that they counted these cases among index and control relatives. It was argued that the "B1/B3 relationship" formulation is the only valid way of determining whether there is a statistically significant clustering of B3 diagnoses among index biological relatives. According to the statistical calculations presented here, it was shown that there was no such clustering in the Kety and colleagues 1968 or 1975 Copenhagen Adoptees' Family studies. It was argued further that even if such a clustering had existed, it would not have proved a genetic relationship, because mere association

does not necessarily imply a common genetic etiology. It was pointed out that E. Bleuler, the inventor of the schizophrenia concept, would not have diagnosed the Kety et al. B3 adoptees and relatives with latent schizophrenia. Bleuler saw "latent schizophrenia" as a retrospective diagnosis made on the basis of a person's subsequently more serious difficulties.

This article has argued that the schizophrenia spectrum as defined by Kety and associates is not valid on several grounds and that B1 chronic schizophrenia is the only valid diagnosis that can be used to test the genetic basis of schizophrenia. This suggests that the Danish-American studies should be reanalyzed on this basis.[6]

NOTES

[1]Twin studies are also cited, but it is often argued that they are unable to disentangle possible genetic and environmental influences (see Jackson, 1960; Joseph, 1998b, 2000, in press-b, 2001; also see Kety, 1978; Kety et al., 1968).

[2]The difference is still great with the addition of an age-corrected adjustment, although the Danish/American team did not use age-corrected figures in their articles.

[3]Between 1975 and 1988 Kety claimed that the Copenhagen interview-based B1 index/control comparison was a significant 5/173 versus 0/174 (p = .03, Fisher's Exact Test, one-tailed). The Ingraham and Kety 1988 paper was the first post-1975 publication in which Kety counted the record-based B1 diagnosis of the biological father of control adoptee C9, making the comparison a non-significant 5/173 versus 1/174 (p = .10; see Joseph, 1998a, in press-a).

[4]Kendler and Gruenberg (1984) performed a blind reanalysis of the Danish/American results. Of the original 10 Danish B3 index adoptees, Kendler and Gruenberg diagnosed only one with DSM-III schizotypal personality disorder. The remaining 9 diagnoses included 2 cases of chronic schizophrenia, 3 atypical psychosis, 1 bipolar disorder, 1 delusional disorder, and 2 "other" personality disorders (Kendler & Gruenberg, 1984, p. 557).

[5]Discussing the widening of the spectrum, Pam (1995) noted that "with a bigger net, they caught more fish" (p. 29). Expanding on this analogy, one might note that according to the logic of Kety, Rosenthal, and Wender, seagulls and crabs caught up in the net would be classified as fish if the total catch were significantly greater than that of a control group of fisherman.

[6]The Danish/American adoption studies suffer from other serious problems. For details, see Boyle, 1990; Breggin, 1991; Cassou, Schiff, & Stewart, 1980; Cohen & Cohen, 1986; Joseph, 1998a, 1999b, in press-a; Lewontin, Rose, & Kamin, 1984; Lidz, 1976; Lidz & Blatt, 1981; Lidz, Blatt, & Cook, 1983; Pam, 1995.

REFERENCES

American Psychiatric Association. (1968). *Diagnostic and statistical manual of mental disorders* (2nd ed.). Washington, DC: Author.

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders* (3rd ed.). Washington, DC: Author.

Benjamin, L. S. (1976). A reconsideration of the Kety and associates study of genetic factors in the transmission of schizophrenia. *American Journal of Psychiatry, 133,* 1129-1133.

Bleuler, E. (1911/1950). *Dementia praecox or the group of schizophrenias.* New York: International Universities Press.

Boyle, M. (1990). *Schizophrenia: A scientific delusion?* New York: Routledge.

Breggin, P. R. (1991). *Toxic psychiatry*. New York: St. Martin's Press.

Cassou, B., Schiff, M., & Stewart, J. (1980). Génétique et schizophrénie: Réévaluation d'un consensus [Genetics and schizophrenia: Re-evaluation of a consensus]. *Psychiatrie de l'enfant, 23,* 87-201.

Cohen, D., & Cohen, H. (1986). Biological theories, drug treatments, and schizophrenia: A critical assessment. *Journal of Mind and Behavior, 7,* 11-36.

Gould, S. J. (1981). *The mismeasure of man*. New York: W. W. Norton & Company.

Ingraham, L. J., & Kety, S. S. (1988). Schizophrenia spectrum disorders. In M. Tsuang & J. Simpson (Eds.), *Handbook of schizophrenia, Vol. 3: Nosology, epidemiology and genetics* (pp. 117-137). New York: Elsevier Science Publishers.

Jackson, D. D. (1960). A critique of the literature on the genetics of schizophrenia. In D. Jackson (Ed.), *The etiology of schizophrenia* (pp. 37-87). New York: Basic Books.

Joseph, J. (1998a). *A critical analysis of the genetic theory of schizophrenia.* Unpublished doctoral dissertation, California School of Professional Psychology, Alameda.

Joseph, J. (1998b). The equal environment assumption of the classical twin method: A critical analysis. *Journal of Mind and Behavior, 19,* 325-358.

Joseph, J. (1999a). A critique of the Finnish Adoptive Family Study of Schizophrenia. *Journal of Mind and Behavior, 20,* 133-154.

Joseph, J. (1999b). The genetic theory of schizophrenia: A critical overview. *Ethical Human Sciences and Services, 1,* 119-145.

Joseph, J. (2000). Not in their genes: A critical view of the genetics of attention-deficit hyperactivity disorder. *Developmental Review, 20,* 539-567.

Joseph, J. (in press-a). The Danish-American Adoptees' Family studies of Kety and associates: Do they provide evidence in support of the genetic basis of schizophrenia? *Genetic, Social, and General Psychology Monographs.*

Joseph, J. (in press-b). Don Jackson's "A critique of the literature on the genetics of schizophrenia"—A reappraisal after 40 years. *Genetic, Social, and General Psychology Monographs.*

Joseph, J. Separated twins and the genetics of personality differences: A critique. *American Journal of Psychology 114,* 1-30.

Kallmann, F. J. (1938). *The genetics of schizophrenia: A study of heredity and reproduction in the families of 1,087 schizophrenics.* New York: J. J. Augustin.

Kendler, K. S. (1985). Diagnostic approaches to schizotypal personality disorder: A historical perspective. *Schizophrenia Bulletin, 11,* 538-553.

Kendler, K. S., & Diehl, S. R. (1993). The genetics of schizophrenia: A current, genetic-epidemiologic perspective. *Schizophrenia Bulletin, 19,* 261-285.

Kendler, K. S., & Gruenberg, A. M. (1984). An independent analysis of the Danish adoption study of schizophrenia. *Archives of General Psychiatry, 41,* 555-564.

Kety, S. S. (1959). Biochemical theories of schizophrenia, part II. *Science, 129,* 1590-1596.

Kety, S. S. (1970). Genetic-environmental interactions in the schizophrenic syndrome. In R. Cancro (Ed.), *The schizophrenic reactions* (pp. 233-244). New York: Brunner/Mazel.

Kety, S. S. (1975). Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. In H. van Praag (Ed.), *On the origin of schizophrenic psychosis* (pp. 19-26). Amsterdam: De Ervin Bohn BV.

Kety, S. S. (1978). Heredity and environment. In J. Shershow (Ed.), *Schizophrenia: Science and practice* (pp. 47-68). Cambridge, MA: Harvard University Press.

Kety, S. S. (1983). Mental illness in the biological and adoptive relatives of schizophrenia adoptees: Findings relevant to genetic and environmental factors in etiology. *American Journal of Psychiatry, 140,* 720-727.

Kety, S. S. (1985a). The concept of schizophrenia. In M. Alpert (Ed.), *Controversies in schizophrenia: Changes and constancies* (pp. 3-11). New York: Guilford Press.

Kety, S. S. (1985b). Schizotypal personality disorder: An operational definition of Bleuler's latent schizophrenia? *Schizophrenia Bulletin, 11,* 590-594.

Kety, S. S. (1987). The significance of genetic factors in the etiology of schizophrenia: Results from the national study of adoptees in Denmark. *Journal of Psychiatric Research, 21,* 423-429.

Kety, S. S. (1988). Schizophrenic illness in the families of schizophrenic adoptees: Findings from the Danish national sample. *Schizophrenia Bulletin, 14,* 217-222.

Kety, S. S., & Ingraham, L. J. (1992). Genetic transmission and improved diagnosis of schizophrenia from pedigrees of adoptees. *Journal of Psychiatric Research, 26,* 247-255.

Kety, S. S., Rosenthal, D., & Wender, P. H. (1978). Genetic relationships within the schizophrenia spectrum: Evidence from adoption studies. In R. Spitzer & D. Klein (Eds.), *Critical issues in psychiatric diagnosis* (pp. 213-223). New York: Raven Press.

Kety, S. S., Rosenthal, D., Wender, P. H., & Schulsinger, F. (1968). The types and prevalence of mental illness in the biological and adoptive families of adopted schizophrenics. In D. Rosenthal & S. Kety (Eds.), *The transmission of schizophrenia* (pp. 345-362). New York: Pergamon Press.

Kety, S. S., Rosenthal, D., Wender, P. H., & Schulsinger, F. (1976). Studies based on a total sample of adopted individuals and their relatives: Why they were necessary, what they demonstrated and failed to demonstrate. *Schizophrenia Bulletin, 2,* 413-427.

Kety, S., Rosenthal, D., Wender, P., Schulsinger, F., & Jacobsen, B. (1975). Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic: A preliminary report based on psychiatric interviews. In R. Fieve, D. Rosenthal, & H. Brill (Eds.), *Genetic research in psychiatry* (pp. 147-165). Baltimore: The Johns Hopkins Press.

Kety, S. S., Rosenthal, D., Wender, P. H., Schulsinger, F., & Jacobsen, B. (1978). The biologic and adoptive families of adopted individuals who became schizophrenic: Prevalence of mental illness and other characteristics. In L. Wynne, R. Cromwell, & S. Matthysse (Eds.), *The nature of schizophrenia: New approaches to research and treatment* (pp. 25-37). New York: John Wiley & Sons.

Kety, S. S., Wender, P. H., Jacobsen, B., Ingraham, L. J., Jansson, L., Faber, B., & Kinney, D. K. (1994). Mental illness in the biological and adoptive relatives of schizophrenic adoptees: Replication of the Copenhagen study to the rest of Denmark. *Archives of General Psychiatry, 51,* 442-455.

Lewontin, R. C., Rose, S., & Kamin, L. J. (1984). *Not in our genes.* New York: Pantheon.

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 Psychiatry, 140,* 426-435.

Lidz, T., Blatt, S., & Cook, B. (1981). Critique of the Danish-American studies of the adopted-away offspring of schizophrenic parents. *American Journal of Psychiatry, 138,* 1063-1068.

Pam, A. (1995). Biological psychiatry: Science or pseudoscience? In C. Ross & A. Pam (Eds.), *Pseudoscience in biological psychiatry: Blaming the body* (pp. 7-84). New York: John Wiley & Sons.

Rosenthal, D. (1970). *Genetic theory and abnormal behavior.* New York: McGraw-Hill.

Rosenthal, D. (1971a). *Genetics of psychopathology.* New York: McGraw-Hill.

Rosenthal, D. (1971b). A program of research on heredity in schizophrenia. *Behavioral Science, 16,* 191-201.

Rosenthal, D. (1972). Three adoption studies of heredity in the schizophrenic disorders. *International Journal of Mental Health, 1,* 63-75.

Rosenthal, D. (1975). The spectrum concept in schizophrenic and manic depressive disorders. In D. Freedman (Ed.), *Biology of the major psychoses* (pp. 19-25). New York: Raven Press.

Rosenthal, D. (1979). Genetic factors in behavioural disorders. In M. Roth & V. Cowie (Eds.), *Psychiatry, genetics and pathography: A tribute to Eliot Slater* (pp. 22-33). London: Oxford University Press.

Rosenthal, D., Wender, P. H., Kety, S. S., Schulsinger, F., Welner, J., & Østergaard, L. (1968). Schizophrenics' offspring reared in adoptive homes. In D. Rosenthal & S. Kety (Eds.), *The transmission of schizophrenia* (pp. 377-391). New York: Pergamon Press.

Rosenthal, D., Wender, P. H., Kety, S. S., Welner, J., & Schulsinger, F. (1971). The adopted-away offspring of schizophrenics. *American Journal of Psychiatry, 128,* 307-311.

Sarbin, T. R., & Mancuso, J. C. (1980). *Schizophrenia: Medical diagnosis or moral verdict?* New York: Pergamon Press.

Siever, L. J., & Gunderson, J. G. (1979). Genetic determinants of borderline conditions. *Schizophrenia Bulletin, 5,* 59-86.

Slater, E., & Cowie, V. (1971). *The genetics of mental disorders.* London: Oxford University Press.

Spitzer, R. L., & Endicott, J. (1979). Justification for separating schizotypal and borderline personality disorders. *Schizophrenia Bulletin, 6,* 95-104.

Strömgren, E. (1993). Fini Schulsinger's contribution to psychiatric research in genetic epidemiology. *Acta Psychiatrica Scandinavica, Supplement 370,* 11-13.

Szasz, T. (1976). *Schizophrenia: The sacred symbol of psychiatry.* New York: Basic Books.

Wender, P. H. , & Klein, D. F. (1981). *Mind, mood, and medicine.* New York: Farrar, Straus, & Giroux.

Wender, P. H., Rosenthal, D., Kety, S. S., Schulsinger, F., & Welner, J. (1974). Crossfostering: A research strategy for clarifying the role of genetic and experiential factors in the etiology of schizophrenia. *Archives of General Psychiatry, 30,* 121-128.

Acknowledgement. I dedicate this article to the memory of my friend and colleague, Steve Baldwin.

Offprints. Requests for offprints should be directed to: Jay Joseph, PhD, 2625 Alcatraz Ave., #328, Berkeley, CA 94705.