Genetic Determinants of Borderline Conditions*

Larry J. Siever and John G. Gunderson

Abstract

Evidence about the genetic determinants for borderline conditions is reviewed. The research data are too limited and the diagnostic practices followed in existing studies are too varied to allow firm conclusions to be drawn. Thus, the need for new studies starting with well-defined samples of borderline patients is clear. Previous work implicates genetic factors in the etiology of at least some borderlines, but it is unclear that borderlines by any definition will, as a group, have uniformly strong and specific genetic determinants. With further research, partially overlapping subgroups might be defined on the basis of careful examination of borderline patients' clinical characteristics and family histories. Such characterization could have potential clinical value since there may be subgroups of borderlines who respond differently to various psychopharmacologic treatments (Klein 1975) or to exploratory versus ego supportive psychotherapy (Stone 1977). Characterizations based on genetic considerations may have their limitations, since the genetics of these disorders probably involve complex interactions of a variety of factors that may be more or less specifically related to other major diagnostic groups.

The term “borderline” has become increasingly popular, and thus a great deal of interest has been focused on its validity, etiology, prognosis, and treatment. The literature on borderlines has largely emphasized psychogenic origins for the condition. This article will explore the possibility that borderline conditions have significant genetic determinants by analyzing the evidence available from adoptive, family, and twin studies. No attempt will be made to critique or analyze the methods and conclusions of the studies reviewed except insofar as they pertain to concerns about the more specific issues of borderlines.

Although the genetic determinants of borderline conditions are of potential significance to both clinicians and clinical researchers, there have been few studies that have been systematically designed to address the concerns of these groups. Clinicians, faced with the need to understand and treat a particularly troublesome group of patients whose disorder seems to fall somewhere between the neuroses and the psychoses, are confronted by a variety of descriptive and dynamically formulated definitions. Some recent clinical studies have attempted to operationalize these definitions and distinguish borderline conditions from schizophrenia, on the one hand, and the neuroses on the other (Grinker and Werble 1977; Gunderson 1977; Gunderson, Carpenter, and Strauss 1975; Gunderson and Kolb 1978; Willeit et al. 1973). However, there is still considerable controversy about the borderline diagnosis (Perry and Klerman 1978). In most cases, the existing studies have not included extensive family histories, and hence the possible value of genetic

* Reprint requests should be addressed to Dr. Siever at Clinical Neuropharmacology Branch, NIMH Intramural Research Program, NIH, Bldg. 10, Rm. 3D48, 9000 Rockville Pike, Bethesda, MD 20014.
factors in helping to define borderline patients is in need of exploration.

Most information about the role of genetic factors in borderline conditions derives from studies designed for quite a different purpose—to elucidate the genetic basis of schizophrenia. The earliest family studies of schizophrenics noted the presence of "eccentric" relatives, who had schizophrenia-like symptoms but neither the deteriorating clinical course nor the full-blown psychosis characteristic of schizophrenia. A number of the twin studies of schizophrenia also encountered such individuals. Originally termed "schizoid," the eccentric relatives of schizophrenics more recently have been included under the rubric of "borderline" relatives by Kety, Rosenthal, and Wender in their adoptive family studies (Kety et al. 1971; Rosenthal et al. 1971).

For genetic researchers, the presence of milder forms of disturbance in the unhospitalized relatives of psychiatric patients has implications for the role of genetic factors in the etiology of the major psychiatric disorders. However, the designs of genetic schizophrenia studies are such that they include limited sample cases of borderlines.

Just as there is disagreement among clinicians about the definition of borderline, the descriptions applied by genetic researchers to the borderline relatives of schizophrenics are not uniform and overlap to varying degrees with the clinically defined borderline. The critical overlapping characteristic from both areas is the presence of an enduring tendency to brief losses of reality testing and psychotic-like experiences. In this review, we are faced with the problem of trying to synthesize data based on differing diagnostic systems and sample sizes. In general, we will apply the term "borderline" to persons who have transient psychotic-like characteristics accompanied by an enduring personality disturbance. When explicit diagnostic criteria have been used in the studies reviewed, however, they will, of course, be noted. Thus, the term "borderline" as used in this review is an inclusive one—a usage somewhat different from the more specifically elaborated clinical definitions of borderline personality disorder (Gunderson and Singer 1975) or borderline personality organization (Kernberg 1975). We will address some of the diagnostic issues presented by this broad definition at the conclusion of our review. Recognizing the limitations of the small sample sizes, we will report p values for all statistical analyses so that the reader can note those which reach significance. We will also note suggestive but nonsignificant trends in the data which have cumulative weight and may represent areas worthy of further investigation. Thus, the goal of our review will be to sum up what is known, but also to provoke speculation and inquiry into still-unanswered questions.

Adoptive Studies

Extended Family Study

In the extended family study, Kety et al. (1968, 1975, 1976) attempted to isolate, to the greatest degree possible, the influence of genetic factors in the etiology of schizophrenia. To minimize shared environmental influences acting on the schizophrenic and his biological relatives, Kety et al. located a unique sample of adopted schizophrenics who had not been reared by their biological parents. As a control, they compared the prevalence of schizophrenic disorders in the biological relatives of both the index schizophrenic adoptees and matched nonschizophrenic adoptees. They also compared the prevalence of such disorders in the biological relatives with that in the adoptive relatives of both the schizophrenic and the control adoptees. Prevalence rates were determined first by an examination of the records of all hospitalized relatives of index and control cases (Kety et al. 1968) and subsequently by interviews with these relatives (Kety et al. 1975).

In the 1975 study, Kety et al. screened the controls, deleting those who were questionably schizophrenic or could not be interviewed. They collected a sample of 34 schizophrenic adoptees on whom they could reach a consensus diagnosis of definite schizophrenia, including three subgroups: chronic, acute, and borderline, coded B1, B2, and B3, respectively (see table 1). Together these diagnoses were considered as the "schizophrenic spectrum" disorders. Relatives were rated according to the same classification, expanded to include uncertain schizophrenic diagnoses: either D1, D2, or D3 depending on the subgroup. The presence of schizoid or inadequate personality, rated C, as well as other psychiatric diagnoses and criminal records, was noted in the relatives as well.

Those individuals who were
designated as having borderline states were originally characterized by a broad list of signs and symptoms (see table 1). Kety et al. formulated this category on the basis of their clinical experience and the clinical literature on such syndromes as pseudoneurotic and ambulatory schizophrenia. Recently Spitzer, Endicott, and Gibbon (1979) have examined this sample of borderlines and developed operational criteria for identifying such people (see table 2). Both the hospital records study

Table 1. Diagnostic classification system used in adoptive studies

A. Definitely not schizophrenia (specify diagnosis).

B. Chronic schizophrenia (chronic undifferentiated schizophrenia, true schizophrenia, process schizophrenia).
   Characteristics: (1) Poor prepsychotic adjustment; introverted; schizoid; shut-in; few peer contacts; few heterosexual contacts; usually unmarried; poor occupational adjustment. (2) Onset: gradual and without clear-cut psychological precipitant. (3) Presenting picture: presence of primary Bleulerian characteristics; presence of clear rather than confused sensorium. (4) Posthospital course: failure to reach previous level of adjustment. (5) Tendency to chronicity.

B2. Acute schizophrenic reaction (acute undifferentiated schizophrenic reaction, schizoaffective psychosis, possible schizophreniform psychosis, [acute] paranoid reaction, homosexual panic).
   Characteristics: (1) Relatively good premorbid adjustment. (2) Relatively rapid onset of illness with clear-cut psychological precipitant. (3) Presenting picture: presence of secondary symptoms and comparatively lesser evidence of primary ones; presence of affect (manic-depressive symptoms, feelings of guilt); cloudy rather than clear sensorium. (4) Posthospital course good. (5) Tendency to relatively brief episode(s) responding to drugs, electroshock therapy, etc.

B3. Borderline state (pseudoneurotic schizophrenia, borderline, ambulatory schizophrenia, questionable simple schizophrenia, "psychotic character," severe schizoid individual).
   Characteristics: (1) Thinking: strange or atypical mentation; thought shows tendency to ignore reality, logic, and experience (to an excessive degree) resulting in poor adaptation to life experience (despite the presence of a normal IQ); fuzzy, murky, vague speech. (2) Experience: brief episodes of cognitive distortion (the patient can, and does, snap back, but during the episode the idea has more the character of a delusion than an ego-alien obsessive thought); feelings of depersonalization, of strangeness, or of unfamiliarity with or toward the familiar; micropsychosis. (3) Affective: anhedonia—never experiences intense pleasure—never happy; no deep or intense involvement with anyone or anybody. (4) Interpersonal behavior: may appear poised, but lacking in depth ("as if" personality); sexual adjustment—chaotic fluctuation, mixture of heterosexuality and homosexuality. (5) Psychopathology: multiple neurotic manifestations that shift frequently (obsessive concerns, phobias, conversion, psychosomatic symptoms, etc.); severe widespread anxiety.

C. Inadequate personality.
   Characteristics: A somewhat heterogeneous group consisting of individuals who would be classified as either inadequate or schizoid by DSM-II. Persons so classified often had many of the characteristics of the B3 category, but to a considerably milder degree.

D1, 2, or 3. Uncertain B1, 2, or 3 either because information is lacking or because even if enough information is available, the case does not fit clearly into an appropriate B category.

---

Table 2. Schizotypal personality disorder

Operational criteria for Schizotypal Personality Disorder

At least four of the following are characteristic of the patient's long-term functioning and are not limited to discrete episodes of illness.

1) Magical thinking, e.g., superstitiousness, clairvoyance, telepathy, "6th sense," "others can feel my feelings."

2) Ideas of reference, self-referential thinking.

3) Social isolation, e.g., no close friends or confidants, social contacts limited to essential everyday tasks.

4) Recurrent illusions, sensing the presence of a force or person not actually present (e.g., "I felt as if my dead mother were in the room with me"), depersonalization, or derealization not associated with panic attacks.

5) Odd communication (not gross formal thought disorder), e.g., speech that is tangential, digressive, vague, overelaborate, circumstantial, metaphorical.

6) Inadequate rapport in face to face interaction due to constricted or inappropriate affect, e.g., aloof, distant, cold, superficial.

7) Suspiciousness or paranoid ideation.

8) Undue social anxiety or hypersensitivity to real or imagined criticism.

Essential features. Although no single feature is invariably present, patients with this disorder manifest various oddities of thinking, perception, communication, and behavior, but never severe enough to meet the criteria for Schizophrenia. The disturbance in thinking may be expressed as magical thinking, ideas of reference, or paranoid ideation. Perceptual disturbances may include recurrent illusions, depersonalization, or derealization (not associated with panic attacks). Often there are marked peculiarities in communication; concepts may be expressed unclearly or oddly, words used deviantly, but never to the point of formal thought disorder. Frequently, but not invariably, the behavioral manifestations include social isolation and constricted or inappropriate affect that interferes with rapport in face to face interaction.

Associated features. Frequently there are varying admixtures of anxiety, depression, and other dysphoric moods. Frequently, there are features of Borderline Personality Disorder.

Differential diagnosis. Schizotypal Personality Disorder is distinguished from Asocial Personality Disorder and Avoidant Personality Disorder by the presence of the oddities of behavior, thinking, perception, and communication that are only present in Schizotypal Personality Disorder. Frequently patients with Schizotypal Personality Disorder will also meet the criteria for Borderline Personality Disorder. In such instances, both diagnoses should be given.

1 From: DSM-III draft, 4/15/77.
and interview study indicated that the syndromes of chronic schizophrenia and borderline states seemed to be related as part of a schizophrenic spectrum, but failed to indicate such a relationship with acute schizophrenia (B2) or schizoid personality (C). When one examines these data with a view toward understanding better the genetic basis of borderlines, there is a suggestion of a genetic relationship to chronic schizophrenia. More borderlines are found among the relatives of the index cases (6/173 or 3.5 percent) than among the biological relatives of controls (3/113 or 2.7 percent), but the difference fails to reach significance \((p = .25)\) with these small numbers. The corresponding comparison for chronic schizophrenics (5/173 or 2.9 percent among index biological relatives versus 0/113 among controls) is significant \((p = 0.03)\) despite similarly small numbers (Kety et al. 1975). This suggests that genetically transmitted factors specifically related to schizophrenia may play a more important role in the etiology of chronic schizophrenia than in the etiology of the borderlines, although the small numbers preclude any definite conclusions.

Since there is no evidence that the acute schizophrenic group is genetically related to the other two disorders in either of the two studies, we reanalyzed the data using only the B1 and B3 probands (see table 3). For these analyses we have used a prevalence based on the interview diagnoses supplemented by hospital record diagnoses when necessary. 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) \((p = .039)\) (see table 3). Including the uncertain borderlines, which neither the authors (Kety, personal communication) nor Spitzer, Endicott, and Gibbon (1979) are able to distinguish reliably from the definite borderlines, we find a highly significant difference between the index and control biological relatives \((p < .001)\).

We then isolated the borderline probands and the chronic schizophrenic probands to find if there is a significant concentration of one disorder in the relatives of the other subgroup (see table 3). Starting with the 17 B1 probands, we find highly significantly greater numbers of borderlines, certain and uncertain, among the biological relatives of the chronic schizophrenics than in those of the screened controls \((p < .001)\). Since such a comparison allows for the possibility of a few deviant families skewing the distribution, we can compare the number of families of index probands containing a certain or uncertain borderline member versus those of controls and also find a highly significant difference \((p < .001)\). Even if only certain borderlines are used for these analyses, the differences still reach significance. However, taking the nine borderline (B3) schizophrenics as index cases, we do not find any chronic schizophrenics among the relatives. These data are consistent with the conclusion that borderlines, on the average, have less of a genetic loading for schizophrenia than the chronic schizophrenics. It is also consistent with the possibility that only a subgroup of borderlines shares a genetic relationship to chronic schizophrenia.

When we compare the prevalence of borderlines in the biological families of borderline (B3) probands compared to those of normal screened controls, we find a significant difference \((p = .049)\), which becomes highly significant when the uncertain borderlines are included \((p = .004)\). It is noteworthy, however, that the comparison using the analysis by families leads to a nonsignificant result. Only 2/9 families of the borderlines include a relative with a definite borderline diagnosis versus 1/23 of the screened control families \((p = .18)\). Even if the uncertain borderline diagnoses are included in the family. analysis, the comparison still only approaches a significant difference \((p = .057)\)—in contrast to the highly significant comparison by relatives. The lower significance of the analysis by family compared to the analysis by individual relatives (a disparity in the reverse direction from that we see for the B1 probands) suggests that the difference in individuals could represent the contribution of a subgroup of the families.

The only diagnosis assigned in significantly greater numbers to the relatives of the B3 probands than to those of controls was the borderline diagnosis itself. In both the hospital record and interview study, there is a slight trend for minor affective disorders to be found more often in the relatives of borderlines than in those of either controls or chronic schizophrenics, but the numbers are far too small to reach significance. Thus, for the B3 sample alone, there is no evidence for genetic relatedness of borderlines to schizophrenia, a hint of a relation to minor affective disorders, and suggestive evidence for a
### Table 3a. Interview study with B3 probands

<table>
<thead>
<tr>
<th>Diagnoses of relatives</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 B3 D1 D3 C</td>
<td>5/38</td>
<td>8/174 (4.6%)</td>
<td>2/113 (1.8%)</td>
<td>.061</td>
<td>.011</td>
<td>3/9</td>
<td>33.3%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B1 B3 D1 D3</td>
<td>5/38</td>
<td>8/174 (4.6%)</td>
<td>2/113 (1.8%)</td>
<td>.061</td>
<td>.011</td>
<td>3/9</td>
<td>33.3%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3 C</td>
<td>5/38</td>
<td>7/174 (4.0%)</td>
<td>1/113 (0.9%)</td>
<td>.043</td>
<td>.004</td>
<td>3/9</td>
<td>33.3%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3</td>
<td>5/38</td>
<td>7/174 (4.0%)</td>
<td>1/113 (0.9%)</td>
<td>.043</td>
<td>.004</td>
<td>3/9</td>
<td>33.3%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3</td>
<td>3/38</td>
<td>3/174 (1.7%)</td>
<td>1/113 (0.9%)</td>
<td>.072</td>
<td>.049</td>
<td>2/9</td>
<td>22.2%</td>
<td>3/34 (8.8%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

#### Significant at p < .05.

#### Significant at p < .01.

Note—Probability levels listed in the column under the heading p' derive from comparisons between indexes and unscreened controls, whereas those listed under p derive from comparisons between indexes and screened controls.

### Table 3b. Interview study with B1 and B3 probands

<table>
<thead>
<tr>
<th>Diagnoses of relatives</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 B3 D1 D3 C</td>
<td>24/142</td>
<td>18.9%</td>
<td>8/174 (4.6%)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>13/26</td>
<td>50%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B1 B3 D1 D3</td>
<td>24/142</td>
<td>18.9%</td>
<td>8/174 (4.6%)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>12/26</td>
<td>50%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3 C</td>
<td>18/142</td>
<td>12.7%</td>
<td>7/174 (4.0%)</td>
<td>.004</td>
<td>.001</td>
<td>12/26</td>
<td>46.2%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3</td>
<td>18/142</td>
<td>12.7%</td>
<td>7/174 (4.0%)</td>
<td>.004</td>
<td>.001</td>
<td>12/26</td>
<td>46.2%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3</td>
<td>8/142</td>
<td>5.6%</td>
<td>3/174 (1.7%)</td>
<td>.057</td>
<td>.030</td>
<td>7/26</td>
<td>26.9%</td>
<td>3/34 (8.8%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

#### Significant at p < .05.

#### Significant at p < .01.

### Table 3c. Interview study with B1 probands

<table>
<thead>
<tr>
<th>Diagnoses of relatives</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
<th>Index</th>
<th>Unscreened controls</th>
<th>Screened controls</th>
<th>p'</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 B3 D1 D3 C</td>
<td>19/104</td>
<td>18.3%</td>
<td>8/174 (4.0%)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>10/17</td>
<td>58.8%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B1 B3 D1 D3</td>
<td>19/104</td>
<td>18.3%</td>
<td>8/174 (4.0%)</td>
<td>&lt;.001</td>
<td>&lt;.001</td>
<td>10/17</td>
<td>58.8%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3 C</td>
<td>13/104</td>
<td>12.5%</td>
<td>7/174 (4.0%)</td>
<td>.009</td>
<td>.002</td>
<td>9/17</td>
<td>52.9%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3 D3</td>
<td>13/104</td>
<td>12.5%</td>
<td>7/174 (4.0%)</td>
<td>.009</td>
<td>.002</td>
<td>9/17</td>
<td>52.9%</td>
<td>5/34 (14.7%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
<tr>
<td>B3</td>
<td>5/104</td>
<td>4.8%</td>
<td>3/174 (1.7%)</td>
<td>.133</td>
<td>.088</td>
<td>5/17</td>
<td>29.4%</td>
<td>3/34 (8.8%)</td>
<td>1/23</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

#### Significant at p < .05.

#### Significant at p < .01.

Note—Probability levels listed in the column under the heading p' derive from comparisons between indexes and unscreened controls, whereas those listed under p derive from comparisons between indexes and screened controls.
subgroup of borderlines sharing a common genetic basis. The evidence for the relatedness to schizophrenia derives only from the chronic schizophrenic proband data. Since we do not yet have corresponding data starting with affectively disordered probands, we cannot conclude that a very specific relationship between the borderlines and schizophrenia exists which excludes the affective disorders.

Although the size of the borderline sample is too small to permit firm conclusions to be drawn, the results all converge in suggesting a genetic relationship between borderlines and chronic schizophrenics. The more detailed analyses go further by raising the possibilities that: (1) Some, but not all, borderlines have this genetic relatedness; (2) some borderlines may share common genetic factors that are not specifically related to chronic schizophrenia; and (3) borderlines may be a more genetically diverse group (i.e., less etiologically specific) than chronic schizophrenia.

Adopted-Away Study

This study (Rosenthal et al. 1968, 1971) looks at the psychopathology of adoptees who had a biological parent diagnosed as schizophrenic (chronic, acute, or borderline) or manic-depressive according to hospital records in Denmark. Rosenthal et al. located 76 such parents of adoptees, including 30 definite and 14 possible chronic schizophrenics, 4 borderlines, 4 acute schizophrenics, 7 manic-depressives, and 17 parents whom at least one judge had diagnosed as manic-depressive but in whom the possibility of a diagnosis within the schizophrenic spectrum had not been ruled out. Rosenthal et al. attempted to test whether schizophrenia is a genetically determined disorder by comparing diagnoses of the adopted-away offspring of these 76 index parents with a control group of 67 adoptees whose biological parents had never been psychiatically hospitalized.

The percentage of schizophrenic spectrum diagnoses among the index offspring group, 31.6 percent, was significantly greater than the corresponding percentage among the control offspring, 17.8 percent ($p = .045$). This comparison includes acute schizophrenia, schizoid personality, and uncertain diagnoses as part of the schizophrenic spectrum. We reanalyzed the data, coding the offspring diagnoses using the authors’ diagnostic abbreviations (see table 4), to determine the prevalence of the various schizophrenic spectrum diagnoses among offspring of the parental diagnostic groups. We then note in table 5 that the strongest relationships are found if one includes definite and uncertain chronic schizophrenics and definite borderlines as the diagnoses for the index parents and compares the number of definite chronic schizophrenics and definite borderlines among their offspring to that among control offspring ($p = .035$). This again argues for a genetic relatedness between chronic schizophrenia and borderlines but does not support the inclusion of acute psychoses, schizoid personalities, and uncertain borderlines in the spectrum.² By casting a wider net (i.e., using a broad definition of schizophrenic spectrum disorder) we include more individuals among the index adoptees, but we also increase the number among the controls, making the diagnoses less effective in isolating the hypothesized genetic factors. Perhaps the most discriminating diagnosis is again chronic schizophrenia, applying to 3/76 index adoptees as opposed to none of the controls, but even here the numbers are too small to be significant ($p = .34$).³

The three chronic schizophrenic adoptees are all children of the definite or uncertain chronic schizophrenic parents. Most of the borderline (definite or uncertain) offspring are also born of chronic schizophrenic parents (6/9 definite and 9/17 uncertain borderlines). In contrast, there are no chronic schizophrenics among the offspring of the four borderline parents. The four offspring of the borderline parents did include two spectrum diagnoses, however: one paranoid borderline and one paranoid character. These are somewhat “softer” diagnoses in the schizophrenic spectrum than those found in the offspring of chronic schizophrenics. As with the extended family study, these results support a hypothesis that there are common genetic factors in the etiology of borderline and chronic schizophrenia, but also suggest these factors are weaker in the case of the borderlines.

Furthermore, careful scrutiny of the data from this study again

---

² The discrepancy between this study and the extended family study with regard to uncertain borderlines may reflect the fact that parents of control adoptees were not screened in this study and thus may have included individuals with milder borderline disorders.

³ More recent data with a larger sample further support the premise that in fact the diagnosis of chronic schizophrenia most specifically discriminates the relatives of the index cases from those of controls.
### Table 4a. Diagnoses in the schizophrenia spectrum of Index children and their biological parents

<table>
<thead>
<tr>
<th>Diagnosis of Index parent</th>
<th>Children’s diagnoses (from study)</th>
<th>Classification by review authors of children’s diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1 (N = 30)</td>
<td>1 Schizophrenia (not hospitalized)</td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td>3 Borderline schizophrenia</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>2 Schizophreniform borderline</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>1 Significant paranoid tendencies: beginning paranoid schizophrenia?</td>
<td>D3</td>
</tr>
<tr>
<td>B1/ (N = 14)</td>
<td>1 Schizophrenia, chronic (hospitalized)</td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td>1 Schizophrenia, simple (not hospitalized)</td>
<td>B1</td>
</tr>
<tr>
<td></td>
<td>1 Borderline paranoid</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>1 Probably borderline paranoid; schizoid</td>
<td>D3</td>
</tr>
<tr>
<td></td>
<td>1 Schizoid; schizophreniform borderline?</td>
<td>D3</td>
</tr>
<tr>
<td>B2 (N = 4)</td>
<td>None</td>
<td>B3</td>
</tr>
<tr>
<td>B3 (N = 4)</td>
<td>1 Paranoid borderline</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>1 Paranoid character</td>
<td>D3</td>
</tr>
<tr>
<td>M (N = 7)</td>
<td>1 Manic-depressive or schizophreniform psychosis (hospitalized)</td>
<td>B2/M</td>
</tr>
<tr>
<td></td>
<td>1 Pseudoneurotic borderline</td>
<td>B3</td>
</tr>
<tr>
<td>B2/M (N = 6)</td>
<td>1 Psychotic or near psychotic</td>
<td>B2/M</td>
</tr>
<tr>
<td></td>
<td>1 Schizophrenic borderline, well-compensated</td>
<td>B3</td>
</tr>
<tr>
<td></td>
<td>1 Schizoid, prepsychotic</td>
<td>D3</td>
</tr>
<tr>
<td></td>
<td>1 Schizoid character</td>
<td>C</td>
</tr>
<tr>
<td>B/D/M/A (N = 11)</td>
<td>1 Almost pseudoneurotic schizophrenic</td>
<td>D3</td>
</tr>
<tr>
<td></td>
<td>1 Paranoid borderline?</td>
<td>D3</td>
</tr>
<tr>
<td></td>
<td>1 Possible paranoid borderline</td>
<td>D3</td>
</tr>
<tr>
<td></td>
<td>1 Schizoid personality</td>
<td>C</td>
</tr>
</tbody>
</table>

Note—Bi = process schizophrenia, diagnosed by all judges; Bi/ = process schizophrenia diagnosed by at least one judge but not by all judges; B2 = reactive schizophrenia; B3 = borderline or pseudoneurotic schizophrenia; M = manic-depressive psychosis; B2/M = judges could not agree which of these two diagnoses were correct; B/D/M/A = judges could not agree which of these diagnoses applied to a particular case (A = not in the schizophrenia spectrum; D = doubtful schizophrenia).

1 Information in this table except where otherwise noted is from Rosenthal et al. (1971).

2 These classifications are based on the study diagnoses of the offspring as listed in this table under "Children’s Diagnoses."

brings up a question of the specificity of these genetic factors. For example, of the seven offspring of manic-depressive parents, one was borderline (see table 4). If we add the other 17 index cases in which at least one judge diagnosed a parent as manic-depressive, we find 6/24 (25 percent) of their offspring carry a diagnosis of definite or uncertain borderline compared to 11/67 or 16.4 percent of the control offspring (p = .26). Current research would suggest that a psychosis with symptoms associated with both schizophrenia and mania may be at least as closely related to manic-depressive psychosis as to schizophrenia (Pope and Lipinski 1978; Taylor, Gaztanaga, and Abrams 1974). Among the offspring...
Table 4b. Diagnoses in the schizophrenia spectrum of control subjects (N = 67)

<table>
<thead>
<tr>
<th>Children's diagnoses (by study)</th>
<th>Classifications by review authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Schizophrenic-like border case</td>
<td></td>
</tr>
<tr>
<td>2 Borderline schizophrenia</td>
<td></td>
</tr>
<tr>
<td>1 Paranoid borderline</td>
<td></td>
</tr>
<tr>
<td>1 Psychotic borderline</td>
<td></td>
</tr>
<tr>
<td>1 Close to borderline psychotic</td>
<td></td>
</tr>
<tr>
<td>1 Conceivably paranoid borderline</td>
<td></td>
</tr>
<tr>
<td>1 Pronounced preschizophrenic diathesis</td>
<td></td>
</tr>
<tr>
<td>1 Schizophrenic diathesis (with some doubt)</td>
<td></td>
</tr>
<tr>
<td>1 Pronounced prepsychotic features: suspicion of organic brain syndrome</td>
<td></td>
</tr>
<tr>
<td>1 Schizoid: beginning schizophrenia?</td>
<td></td>
</tr>
<tr>
<td>1 Moderately schizoid</td>
<td></td>
</tr>
</tbody>
</table>

of the definite and uncertain manic-depressive parents, 10/24 or 41.7 percent carry any of the schizophrenic spectrum diagnoses compared to 12/67 or 17.8 percent of the controls (p = .022) (see table 5). Although only the last comparison reaches significance, the trend is suggestive enough with these small numbers to cause us to wonder if there may be common genetic factors between the borderlines and the affective disorders as well.

Although a relationship of borderlines to minor affective disorders was suggested by the extended family study, there was no evidence for a relationship with manic-depressive psychosis. The discrepancy with the results from the adopted-away study may in part be attributable to the difference in design between the two studies. In the extended family study, the authors were diagnosing relatives specifically through a lens designed for detecting schizophrenic diagnoses, while in the adopted-away study, the authors by design specifically included parents carrying a manic-depressive diagnosis. Furthermore, in the extended family study, there were no relatives of the subsample of borderline index cases with either a chronic schizophrenic or a manic-depressive diagnosis. The design of the adopted-away study allows the selection of an index group of parents with manic-depression, presumably a more severe and genetically pure disorder than borderline conditions, and finds a parallel increase in the number of offspring with borderline diagnoses from this group. The high number of schizophrenic spectrum diagnoses in the control offspring also is consistent with the possibility of a less specific genetic diathesis for the borderline and uncertain borderline diagnoses.

The assortative mating data presented by Rosenthal (1975) are also consistent with the hypothesis that the softer spectrum disorders, including borderlines, are characterized by less specific genetic vulnerability factors than either schizophrenic or manic-depressive disorders. Rosenthal looked at the prevalence of spectrum disorders in the co-parents of the index parents and found that index parents tended to assortatively mate with spouses who also had spectrum disorders. He then showed that the frequency of spectrum disorders in the offspring is about three to five times as frequent when the co-parent also has a spectrum disorder than when he or she does not. He believes that this finding supports the view that all the spectrum disorders are genetically related to process schizophrenia. If Rosenthal is correct, the question still remains: How specifically are they related to schizophrenia, and to what degree are they a manifestation of a less specific genetic vulnerability to a range of psychopathology? If an individual with genetic factors predisposing to nonspecific psychopathology mates with an individual...
Table 5. Prevalence of various schizophrenic spectrum diagnoses among offspring for each parental diagnostic group

<table>
<thead>
<tr>
<th>Offspring diagnoses</th>
<th>Parental diagnoses</th>
<th>B1 (N = 30)</th>
<th>p&lt;sup&gt;1&lt;/sup&gt;</th>
<th>B1/(N = 14)</th>
<th>p</th>
<th>B2 (N = 4)</th>
<th>p</th>
<th>B3 (N = 4)</th>
<th>p</th>
<th>M (N = 7)</th>
<th>p</th>
<th>B2/M (N = 6)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>B1</td>
<td></td>
<td>1/30 (3%)</td>
<td>.31</td>
<td>2/14 (14%)</td>
<td>.028&lt;sup&gt;2&lt;/sup&gt;</td>
<td>—</td>
<td>0/4</td>
<td>—</td>
<td>0/7</td>
<td>—</td>
<td>0/6</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td></td>
<td>5/30 (17%)</td>
<td>.15</td>
<td>1/14 (7%)</td>
<td>.72</td>
<td>—</td>
<td>1/4 (25%)</td>
<td>.30</td>
<td>1/7 (14%)</td>
<td>.46</td>
<td>1/6 (17%)</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>B3 D3</td>
<td></td>
<td>6/30 (20%)</td>
<td>.44</td>
<td>3/14 (21%)</td>
<td>.45</td>
<td>—</td>
<td>2/4 (50%)</td>
<td>.15</td>
<td>1/7 (14%)</td>
<td>.63</td>
<td>2/6 (33%)</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>B1 B3</td>
<td></td>
<td>6/30 (20%)</td>
<td>.076</td>
<td>3/14 (21%)</td>
<td>.14</td>
<td>—</td>
<td>1/4 (25%)</td>
<td>.30</td>
<td>1/7 (14%)</td>
<td>.46</td>
<td>1/6 (17%)</td>
<td>.41</td>
<td></td>
</tr>
<tr>
<td>B1 B3 D3</td>
<td></td>
<td>7/30 (23%)</td>
<td>.29</td>
<td>5/14 (36%)</td>
<td>.10</td>
<td>—</td>
<td>2/4 (50%)</td>
<td>.15</td>
<td>1/7 (14%)</td>
<td>.68</td>
<td>2/6 (33%)</td>
<td>.29</td>
<td></td>
</tr>
<tr>
<td>B1 B3 D3 C</td>
<td></td>
<td>7/30 (23%)</td>
<td>.36</td>
<td>5/14 (36%)</td>
<td>.13</td>
<td>—</td>
<td>2/4 (50%)</td>
<td>.17</td>
<td>1/7 (14%)</td>
<td>.64</td>
<td>3/6 (50%)</td>
<td>.10</td>
<td></td>
</tr>
<tr>
<td>B/M</td>
<td></td>
<td>0/30 —</td>
<td>—</td>
<td>0/14 —</td>
<td>—</td>
<td>—</td>
<td>0/4</td>
<td>—</td>
<td>1/7 (14%)</td>
<td>.95</td>
<td>1/6 (17%)</td>
<td>.08</td>
<td></td>
</tr>
<tr>
<td>B1 B3 B/M D3 C</td>
<td></td>
<td>7/30 (23%)</td>
<td>.36</td>
<td>5/14 (36%)</td>
<td>.13</td>
<td>—</td>
<td>2/4 (50%)</td>
<td>.17</td>
<td>2/7 (29%)</td>
<td>.40</td>
<td>4/6 (67%)</td>
<td>.019&lt;sup&gt;2&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Offspring diagnoses</th>
<th>(N = 11)</th>
<th>M&lt;sup&gt;+&lt;/sup&gt; (N = 24)</th>
<th>p</th>
<th>(N = 24)</th>
<th>p</th>
<th>(N = 48)</th>
<th>p</th>
<th>(N = 76)</th>
<th>p</th>
<th>(N = 67)</th>
<th>p</th>
<th>(N = 67)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>p</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>p</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td>B/D/M/A</td>
<td></td>
</tr>
<tr>
<td>B1</td>
<td>0/11 —</td>
<td>—</td>
<td>—</td>
<td>0/24 —</td>
<td>—</td>
<td>1/34 (3%)</td>
<td>.34</td>
<td>3/48 (6%)</td>
<td>.07</td>
<td>3/76 (4%)</td>
<td>.15</td>
<td>0/67</td>
<td></td>
</tr>
<tr>
<td>B3</td>
<td>0/11 —</td>
<td>.46</td>
<td>2/24 (8%)</td>
<td>.60</td>
<td>6/34 (18%)</td>
<td>.11</td>
<td>7/48 (14%)</td>
<td>.18</td>
<td>9/76 (12%)</td>
<td>.28</td>
<td>5/67 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B3 D3</td>
<td>3/11 (27%)</td>
<td>.31</td>
<td>6/24 (25%)</td>
<td>.26</td>
<td>8/34 (24%)</td>
<td>.27</td>
<td>11/48 (23%)</td>
<td>.26</td>
<td>17/76 (22%)</td>
<td>.25</td>
<td>11/67 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 B3</td>
<td>0/11 —</td>
<td>.46</td>
<td>2/24 (8%)</td>
<td>.50</td>
<td>7/34 (21%)</td>
<td>.058</td>
<td>10/48 (21%)</td>
<td>.04&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12/76 (16%)</td>
<td>.10</td>
<td>5/67 (7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 B3 D3</td>
<td>3/11 (27%)</td>
<td>.31</td>
<td>6/24 (25%)</td>
<td>.26</td>
<td>9/34 (27%)</td>
<td>.18</td>
<td>14/48 (29%)</td>
<td>.08</td>
<td>20/76 (26%)</td>
<td>.11</td>
<td>11/67 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 B3 D3 C</td>
<td>4/11 (36%)</td>
<td>.16</td>
<td>8/24 (33%)</td>
<td>.10</td>
<td>9/34 (27%)</td>
<td>.23</td>
<td>14/48 (29%)</td>
<td>.12</td>
<td>22/76 (29%)</td>
<td>.09</td>
<td>12/67 (18%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B/M</td>
<td>0/11 —</td>
<td>—</td>
<td>2/24 (8%)</td>
<td>.67</td>
<td>0/34 —</td>
<td>—</td>
<td>0/48 —</td>
<td>—</td>
<td>2/76 (3%)</td>
<td>.28</td>
<td>0/67 —</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B1 B3 B/M D3 C</td>
<td>4/11 (36%)</td>
<td>.16</td>
<td>10/24 (42%)</td>
<td>.22&lt;sup&gt;2&lt;/sup&gt;</td>
<td>9/34 (27%)</td>
<td>.23</td>
<td>14/48 (29%)</td>
<td>.12</td>
<td>24/76 (32%)</td>
<td>.045&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12/67 (18%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup> All p values reflect comparisons with control populations listed in last column.
<sup>2</sup> p < .05.
carrying genes more specifically predisposing to schizophrenia, the presence of these factors in the offspring in conjunction with the more specific schizophrenogenic genetic factors might easily contribute to a higher probability of the offspring’s manifesting a schizophrenia-related disorder.

Rosenthal argues that the softer schizophrenic spectrum diagnoses are genetically related to schizophrenia by virtue of their increased prevalence in index over control relatives. Suicide was also found in the extended family study to be more prevalent in the biological relatives of the index schizophrenic adoptees than in the biological relatives of the controls. To argue that suicide is a function of the schizophrenic spectrum predisposition is misleading, however, since suicide is also found in the families of individuals with major affective disorders—a group of disorders which are specifically not found in the families of schizophrenics in the extended family study. Rosenthal’s logic may imply a degree of specificity that the data do not warrant.5

Thus, the apparent lack of genetic relatedness of these soft spectrum diagnoses to the index schizophrenics in the extended family study is not due to their decreased prevalence in the index half-sibs, but to their high prevalence in the control group. This suggests that if there is any genetic commonality between these diagnoses and chronic schizophrenia, it is a rather broad and nonspecific one.

An important implication of this study is that as we move down the schizophrenic spectrum from process schizophrenia toward the softer spectrum disorders, genetic factors related to schizophrenia, while still present, seem to become less determining and less diagnostically specific. Borderlines seem somewhere between these two extremes in the spectrum. As in the extended family study, a definite borderline diagnosis is correlated with chronic schizophrenia, but the strength and specificity of this genetic relationship is not clear. The adopted-away study also offers further suggestions that borderlines may be genetically related to affective disorders.

Adoptive Parents Studies

The adoptive parents study (Wender et al. 1968, 1971, 1977) noted the presence of one chronic and two borderline or doubtful schizophrenics in the adoptive parents of the schizophrenics. Among the biological parents of the schizophrenics, on the other hand, there were one chronic schizophrenic, five borderline or doubtful schizophrenics, and nine schizoid personalities. Again the sample size is small. However, the distribution of borderlines is consistent with the impression from the extended family studies: Borderlines seem to be found more frequently in the biological relatives of chronic schizophrenics than in their adoptive relatives.

Cross-Fostering Studies

To separate still further the role of experiential factors from genetic factors, Wender et al. (1974) employed the cross-fostering technique (see also Wender 1976, 1977). In this new strategy, four groups were compared: (1) the index group, 69 adopted-away offspring of schizophrenic biological parents reared by normal parents; (2) the normal controls, 79 adopted-away offspring of normal biological parents reared by normal adoptive parents; (3) the cross-fostered group, 28 adopted-away offspring of normal biological parents reared by adoptive parents with diagnoses in the schizophrenic spectrum; and (4) the nonadoptees, 40 offspring born to and reared by schizophrenic parents. Wender et al. found a trend toward a greater prevalence of probable borderline or schizophrenic psychopathology6 among the index

---

5 The finding of a significant difference in the softer spectrum disorders between the index and control groups is also not confirmed by other studies (see Family Studies section), including the extended family study. Rosenthal explains the latter discrepancy by noting that he is looking at first degree relatives of schizophrenics while Kety’s extended family study looks preferentially at the half-sibs due to the composition of the sample, and that the prevalence of schizophrenia drops off in the second degree relatives, as noted in previous studies. However, this does not explain why a greater prevalence of borderlines discriminates the index half-sibs from the control half-sibs, while the diagnoses in the schizoid or inadequate personality (C) category in fact are greater in the control half-sibs (in part attributable to the greater number of index half-sibs with borderline diagnoses which might override the C diagnosis).

6 We only know the percentage rated in the upper quartile of a forced quasi-normal distribution of psychopathology. Wender states these individuals include schizophrenics and doubtful schizophrenics and, by implication, probable borderline
schizophrenics as well. The distribution between the borderlines and schizophrenics among the offspring has not been described. The index group is presumably identical to the Rosenthal et al. adopted-away group and thus includes predominantly borderline offspring. There is no information as to the distinction in the cross-fostering and nonadoptee group, but since in other discussions Wender cites similar figures to those used in the cross-fostering study for the prevalence of "borderlines" (Wender 1976) rather than "borderlines and chronic schizophrenics," we can only guess that most of the offspring in the other groups were borderline as well. Such a finding would be consistent with the extended family and adopted-away studies, where the most prevalent spectrum diagnosis is definite or uncertain borderline.

Table 6. Percentage of offspring in upper quartile of psychopathology in forced normal distribution for all groups

<table>
<thead>
<tr>
<th></th>
<th>Adopted control group (AC)</th>
<th>Adopted index group (AI)</th>
<th>Cross-fostered group (CF)</th>
<th>Nonadoptees (NA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sample</td>
<td>8/79 (10.1%)</td>
<td>13/69 (18.8%)</td>
<td>3/28 (10.7%)</td>
<td>9/38 (24%)</td>
</tr>
<tr>
<td>Purified</td>
<td>8/75 (10.7%)</td>
<td>13/66 (19.7%)</td>
<td>1/21 (4.8%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC vs AI</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>AC vs CF</td>
<td>0.59</td>
<td>0.37</td>
</tr>
<tr>
<td>AC vs NA</td>
<td>0.05*</td>
<td>0.063</td>
</tr>
<tr>
<td>AI vs CF</td>
<td>0.26</td>
<td>0.094</td>
</tr>
<tr>
<td>AI vs NA</td>
<td>0.36</td>
<td>0.44</td>
</tr>
<tr>
<td>CF vs NA</td>
<td>0.15</td>
<td>0.062</td>
</tr>
<tr>
<td>AC + CF vs AI</td>
<td>0.083</td>
<td>0.05*</td>
</tr>
<tr>
<td>AC + CF vs AI + NA</td>
<td>0.029*</td>
<td>0.017*</td>
</tr>
<tr>
<td>AC + AI vs NA + CF</td>
<td>0.29</td>
<td>0.43</td>
</tr>
<tr>
<td>AC + AI vs CF</td>
<td>0.44</td>
<td>0.18</td>
</tr>
</tbody>
</table>

The authors find a significant difference (p < .03) by using the test of proportional differences for the same comparison.

Genetic factors play a role in the etiology of borderlines because schizophrenic pathology in the biological parents made a significant difference in the outcome of their biological offspring. They found no evidence supporting a role for familial psychopathology, because an adoptive parental diagnosis of schizophrenia (in the cross-fostering group) did not correlate with an increase in borderline pathology. In a further refinement of this study, the authors “purified” the control and cross-fostered samples by removing those infants who demonstrated some behavioral deviance before adoption or those whose biological parents were found to carry a previously undetected psychiatric diagnosis; these adoptees were felt to be individuals with
possible genetic predispositions that would confound the separation of the etiologic roles of familial psychopathology versus genetic factors. When the samples were purified, the level of significance was slightly higher. This confirmed their earlier conclusions and suggested that some of the unscreened controls had carried a genetic predisposition to psychopathology (see table 6).

To test the hypothesis that familial psychopathology can be influential in the development of schizophrenia when an antecedent genetic predisposition is present, Wender (1977) used yet another comparison group—the nonadoptees. He reasoned that if family factors were contributory, then individuals reared by their schizophrenic biological parents would have a higher prevalence of borderline psychopathology than individuals born to schizophrenic parents but reared by presumably healthier adoptive parents (the index group). Wender found no such increase in psychopathology among the nonadoptees (24 percent borderlines) compared to the index group (13/69 or 18.8 percent) (p = .36). Thus, he concluded that no additive environmental influence of parental psychopathology on the development of schizophrenia spectrum disorders could be detected, even in a group of genetically vulnerable individuals.

The studies of Wender and his associates imply that a significant proportion of the offspring of chronic schizophrenics may become borderlines, irrespective of rearing factors. However, the numbers are too small to establish the authors' hypotheses. Furthermore, this design cannot clarify whether the etiology of the borderline diagnosis in an index sample of borderlines (as, for example, selected in the extended family study) is likely to be primarily genetic rather than environmental. It suggests that genetic factors are especially important in that subgroup born to mainly chronic schizophrenics. Even in this group, the study does not allow us to rule out a role for environmental variables.

**Family Studies**

Most genetic studies focus on classical schizophrenia and only incidentally offer information about borderlines—the latter diagnosis was not commonly used, after all, when the bulk of such studies were carried out. Some more psychosocially oriented investigators have reported large numbers of borderlines in the close relatives of schizophrenics. Litz, Fleck, and Cornelson (1975) identified 5 borderlines in 15 sibs of 15 inpatient schizophrenics. Alanen (1966) found that of the 60 parents of 30 schizophrenics, only 4 were overtly schizophrenic, but 12 (20 percent) were borderline schizophrenics. Of 49 siblings, 6 were schizophrenic. When Waring and Ricks (1965) studied the families of children who later were diagnosed as chronic schizophrenic, they characterized 35 percent of mothers and 40 percent of fathers as psychotic or borderline. Wynne and Singer (1963) also noted that borderline psychopathology is common in the parents of chronic schizophrenics. However, European workers such as Bleuler (1968), using a narrower definition of schizophrenia, only found 4 certain and 3 doubtful schizophrenics among 200 parents of schizophranics. None of these studies started with an index group of borderlines.

Of the family studies based on a borderline index sample, Grinker and his associates (Grinker, Werble, and Drye 1968; Grinker and Werble 1977) reported that familial disturbance and serious physical and mental parental illness were prominent in their sample, but they are not explicit as to the particular type of parental psychopathology uncovered. The investigation of Stone (1977) is perhaps the most extensive and explicit in this respect to date. He started with 18 hospitalized cases, diagnosed according to psychostructural criteria (Kernberg 1975) as having borderline personality organization, and compared them to a group of 23 psychotic inpatients. Of the 27 psychiatically ill relatives of the borderlines (rated by the hospital staff according to the author's questionnaire) none were clearly schizophrenic, 11 percent were schizoaffective, and 89 percent were manic-depressive. The 28 ill relatives of the psychotic inpatient group, on the other hand, included 32 percent with schizophrenic spectrum disorders, 11 percent with a schizoaffective diagnosis, and 54 percent with manic-depression. There were thus significantly more schizophrenics among the ill relatives of psychotics (p = .01).

Stone then compared a group of 28 somewhat healthier borderline outpatients with 25 neurotic and 15 psychotic outpatients. He found more families with ill relatives in the borderline group (68 percent) than in the neurotic group (28 percent) (p = .01) as well as a greater number of ill relatives per patient (1.19 compared to .32). However, this outpatient borderline sample
had 33 ill relatives, of whom 16 were either schizophrenic or schizo-affective, and the psychotic patients (mostly schizophrenic) had 20 ill relatives of whom 14 were schizophrenic. He did not note the presence of manic-depressives in either group. Thus, in this latter sample, there was no significant difference between the percentage of schizophrenic relatives of borderline versus psychotic probands.

There are a number of problems with this study including the idiosyncratic diagnostic system, questions about the selection and therefore representativeness of the samples, nonblind ratings of unknown reliability, and the unclear but probably incomplete means of screening relatives. More complete pedigree data as in the Kety et al. extended family study would certainly have been helpful.

However, this study is important in that it tends to support the hypothesis that borderline patients, even when diagnosed by psychostructural criteria, share familial factors with the major psychoses. Furthermore, the inpatient group of borderlines shows a striking predominance of affective disorders in their relatives. Again, however, there is heterogeneity of psychoses, since schizoaffective and schizophrenic diagnoses are found in these relatives as well. The schizophrenic versus manic-depressive relatives could be well discriminated using the criteria of Cohen et al. (1972) for the borderline inpatients but not for the outpatient group. These data support the suggestions, seen in the extended family study and strengthened by the adopted-away study, that borderline may represent a genetically heterogeneous disorder. The fact that the relatedness to affective disorders is more striking in this study is probably related to the different criteria for diagnosing the borderlines. Borderlines diagnosed using psychostructural criteria, particularly those subject to hospitalization, are likely to include a number of patients who could be classified as having affective disorders in the standard psychiatric categories (Stone, personal communication). It is also noteworthy that the presumably better compensated outpatient borderlines and psychotics could not be distinguished on the basis of family history. This is consistent with the hypothesis suggested earlier that in less severely disordered individuals, the genetic antecedents are harder to discriminate symptomatically.

Winokur (1977) carried out an interesting study of nonschizophrenic paranoid inpatients. He concluded that paranoia, which is sometimes considered to overlap with the borderline diagnosis and to be part of the schizophrenic spectrum, may run in families but does not bear a close relationship to chronic undifferentiated schizophrenia. In another family study, Akiskal et al. (1977) reported that individuals they diagnosed as having a cyclothymic personality—some of whom had been diagnosed borderline by previous clinicians—had a higher proportion of manic-depressive relatives than controls.

In summary, these nonadoptive family studies confirm that a number of borderlines are found among the relatives of schizophrenics. They also suggest that patients diagnosed borderline using a variety of approaches will also have a large number of relatives with major psychoses, including both the affective disorders and schizophrenia.

**Twin Studies**

Twin studies are the classical means of studying genetic elements of psychiatric disorders. Comparison of concordance rates in monozygotic and dizygotic twins indicates the relative etiologic contribution of genetic elements to the development of disorder. Although twin studies do not separate environmental and genetic factors as well as the adoptive strategy, they have the compensating virtue of allowing greater insight into the nature of environmental determinants. In this review we will examine seven twin studies for the prevalence of borderline disorders in the co-twins of chronic schizophrenics. The data are summarized in Table 7. Because the investigators used a variety of diagnostic categories, we have tried to isolate the categories that might include borderlines and look at these individuals separately.

**Gottesman and Shields**

Gottesman and Shields (1972) studied both monozygotic (MZ) and dizygotic (DZ) twins selected from the twin register at Maudsley Hospital. Their sample comprised 24 MZ and 33 DZ twin pairs; at least one member of each pair was admitted to Maudsley Hospital during a 16-year period. Index schizophrenic twins were rated, as were their co-twins, on the basis of information extracted from the hospital records by a panel of six “blindfolded” judges, with a special independent rating by a Scandinavian judge, Essen-Moller. These individuals were also evaluated using an extensive range of psychometric assessment measures.

The unique contributions of this study were its rigorous methodology...
Shields' analysis, however, none of the above group of borderline diagnoses, examined together or individually, is able to improve the specificity of the MZ-DZ ratio.

Responding to Gottesman and Shields (1972) asserted that the ratio of MZ to DZ concordance rates might not be the best way of determining those characteristics that define schizophrenia. He argued as follows: One might suppose, for example, that the biological lesion, which is the basis of schizophrenia, is a function of a dominant gene with complete penetrance. All affected individuals, however, might not show the full-blown syndrome of schizophrenia, but instead present a very attenuated picture of a few schizophrenic-like features. If this were true, then one would expect to find concordance rates of 100 percent among MZ twins and 50 percent among DZ twins. Stimulated by Meehl's suggestion, Shields, Heston, and Gottesman (1975) re-examined the twin study data to determine what kind of concept of schizoidia (or schizotypy in Meehl's terms) would be necessary to obtain a 50 percent concordance rate among the DZ twins. They concluded it would require much too broad a concept to be clinically useful outside of schizophrenic family studies.

Essen-Moller was asked to "blindly" diagnose the 114 twins in Gottesman and Shields' sample as an example of the Scandinavian point of view. He allocated the twins to one of six categories: (1) true schizophrenia; (2) schizophreniform psychosis; (3) other diagnosis but possible schizophrenia; (4) schizoid or possibly schizophrenia-related personality; (5) other diagnoses; and (6) normal. The diagnoses corresponding most closely to the definition of borderline employed in the extended family and adopted-away studies would most likely fall within categories 3 and 4, although these categories may include other schizophrenia-related disorders as well. Category 2 seems to correspond to the American diagnosis of acute schizophrenia. Essen-Moller rated all of the co-twins in those nine pairs in which at least one twin was rated as a true schizophrenic as falling into the first four schizophrenia-related categories, yielding a concordance rate of 100 percent. In six pairs in which he did not rate the co-twins as having a schizophrenia-related disorder, none of the probands were rated as true schizophrenia.

It is interesting to note that in the nine pairs in which an index proband was diagnosed by Essen-Moller as true schizophrenia (category 1), four co-twins (44 percent) were concordant for this diagnosis and the other five co-twins (56 percent) were all in categories 3 (two co-twins) or 4 (three co-twins), while none was in category 2. Once again, the idea of a genetic relatedness between true or chronic schizophrenia and schizophrenia-related personality (which would probably include borderlines), but not acute schizophrenia, is supported. If one starts with the three index probands diagnosed as schizophrenia-related personality, category 4, none of the co-twins are diagnosed as true schizophrenia, two are diagnosed in category 4 (one questionable), and one in category 2. This is consistent with the conclusions from the adoptive studies: Borderline individuals may share a common genetic basis, in some cases perhaps distinct from chronic schizophrenia, and probably carry less of a genetic load for the schizophrenic features.

In reviewing the consensus diag-
Table 7. Percentage rates of chronic schizophrenics, borderlines, and all schizophrenia-related disorders in co-twins of schizophrenics

<table>
<thead>
<tr>
<th>Study</th>
<th>Pairwise % concordance</th>
<th>Pairwise % co-twins borderlines</th>
<th>Pairwise % other possible schizophrenia-related disorders</th>
<th>Pairwise % all schizophrenia-related disorders</th>
<th>Concordance ratios</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
<td>DZ</td>
<td>MZ</td>
</tr>
<tr>
<td>1. Gottesman &amp; Shields (consensus) proband: def. schiz.</td>
<td>8/20 (40%)</td>
<td>3/31 (10%)</td>
<td>4/20 (20%)</td>
<td>2/31 (7%)</td>
<td>12/20 (60%)</td>
</tr>
<tr>
<td>2. Gottesman &amp; Shields (consensus) proband: includes? schizophrenic</td>
<td>11/20 (50%)</td>
<td>3/33 (9%)</td>
<td>2/22 (9%)</td>
<td>2/33 (6%)</td>
<td>13/22 (59%)</td>
</tr>
<tr>
<td>3. Gottesman &amp; Shields (Meehl) proband: chronic or acute schiz.</td>
<td>11/22 (50%)</td>
<td>3/33 (9%)</td>
<td>2/22 (9%)</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>4. Gottesman &amp; Shields (Meehl) proband may include borderlines or schizotypes</td>
<td>14/24 (58%)</td>
<td>8/33 (24%)</td>
<td>0/24</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>5. Gottesman &amp; Shields (Essen-Möller) proband: (1) &quot;true schizophrenic&quot;</td>
<td>4/9 (44%)</td>
<td>1/18 (6%)</td>
<td>5/9 (56%)</td>
<td>1/18 (56%)</td>
<td>9/9 (100%)</td>
</tr>
<tr>
<td>6. Gottesman &amp; Shields (Essen-Möller) proband: broader definition Cat. 1–4</td>
<td>12/20 (65%)</td>
<td>3/32 (9%)</td>
<td>13/20 (65%)</td>
<td>3/32 (29%)</td>
<td>7.2</td>
</tr>
<tr>
<td>7. Kringen proband: chronic schizophrenic</td>
<td>14/45 (31%)</td>
<td>3/32 (9%)</td>
<td>3/45 (7%)</td>
<td>17/45 (38%)</td>
<td></td>
</tr>
<tr>
<td>Probands</td>
<td>Classification</td>
<td>Concordant Cases</td>
<td>Non-Concordant Cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------</td>
<td>---------------------------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Kringlen proband: schizophreniform psychosis</td>
<td>3/10 (30%)</td>
<td>0/10 (0%)</td>
<td>3/10 (30%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Essen–Möller</td>
<td>2/7 (29%)</td>
<td>1/7 (14%)</td>
<td>4/7 (57%)</td>
<td>6/7 (86%)</td>
<td></td>
</tr>
<tr>
<td>10. Inouye proband: chronic schiz.</td>
<td>11/23 (48%)</td>
<td>3/23 (13%)</td>
<td>9/23 (39%)</td>
<td>23/23 (100%)</td>
<td></td>
</tr>
<tr>
<td>11. Inouye proband: relapsing schizophrenic</td>
<td>4/7 (56%)</td>
<td>0/7 (0%)</td>
<td>2/7 (29%)</td>
<td>6/7 (86%)</td>
<td></td>
</tr>
<tr>
<td>12. Inouye proband: mild schizophrenic</td>
<td>3/23 (13%)</td>
<td>2/23 (9%)</td>
<td>18/23 (78%)</td>
<td>23/23 (100%)</td>
<td></td>
</tr>
<tr>
<td>13. Fischer proband: C</td>
<td>5/21 (24%)</td>
<td>4/41 (10%)</td>
<td>5/21 (24%)</td>
<td>12/21 (57%)</td>
<td>14/41</td>
</tr>
<tr>
<td>14. Fischer proband: C'</td>
<td>10/21 (48%)</td>
<td>8/41 (20%)</td>
<td>2/21 (10%)</td>
<td>6/41 (15%)</td>
<td>12/21 (57%)</td>
</tr>
<tr>
<td>15. Tienari</td>
<td>1/16 (6%)</td>
<td>4/16 (25%)</td>
<td>7/16 (44%)</td>
<td>12/16 (75%)</td>
<td></td>
</tr>
</tbody>
</table>

1 Two of the co-twins classified as borderline in above row are now included as concordant for this broader proband classification.
noses of the co-twins, Gottesman and Shields (1972) noted that at most four co-twins would qualify as schizoid/eccentric psychopaths or borderline schizophrenics of the type Kety et al. would place in the schizophrenic spectrum—two MZ twins and two DZ twins. Thus, pairwise there is a prevalence of only 2 out of 22 or 9 percent of such co-twins in the MZ group versus 2 out of 33 or 8 percent in the DZ group. This, of course, is not a significant or even suggestive difference. If the borderline diagnosis were strongly determined by genes shared with schizophrenics, a larger difference would have been expected.

Gottesman and Shields were unable to identify aspects of the twins’ shared environments that distinguished concordant twin pairs from discordant pairs. The only trend differentiating the schizophrenic index and the nonschizophrenic co-twin was that the index tended to have been more submissive in childhood. The most important other finding derived from the data of Gottesman and Shields’ study is that discordant pairs included a nondextral proband more often than the concordant pairs (Boklage 1977) and that these probands were more often atypical cases. The fact that twins in the discordant pairs were opposite handed and that many of these probands were not rated as “true” schizophrenics by Essen-Moller suggests the following alternative explanations: (1) Many of the schizophrenic probands in the discordant pairs may have been schizophrenic on other than a genetic basis; or (2) the phenotypic expression of this genetic basis in the nonschizophrenic co-twins was so modified by unknown environmental factors as to render any relationship to schizophrenia unrecognizable at the time of study.

Kringlen

Kringlen’s (1967) study of Norwegian twins included two groups of probands: chronic schizophrenics and those with schizophreniform psychosis. Among the diagnoses applied to the co-twins was “borderline states,” based on the presence of psychotic personality traits, diffuse anxiety, vagueness in less structured interviews, and disturbed ability to get close. The criteria appear similar to those used by Kety et al. in the adoptive studies. Kringlen found a pairwise concordance of 31 percent in the MZ twins, with a 7 percent pairwise prevalence of borderline states in the co-twins, similar to Gottesman and Shields’ 9 percent. Neither typical schizophrenia nor borderline states were found in the co-twins of the schizophreniform psychotics (corresponding to acute schizophrenia). This study leaves one with the impression that there is probably a genetic basis for the borderline psychopathology found in the co-twins of schizophrenics. However, the lack of such features in 50 percent of the co-twins suggests the following alternative explanations: (1) Many of the schizophrenic probands in the discordant pairs may have been schizophrenic on other than a genetic basis; or (2) the phenotypic expression of this genetic basis in the nonschizophrenic co-twins was so modified by unknown environmental factors as to render any relationship to schizophrenia unrecognizable at the time of study.

*Non-dextral means an individual who is lefthanded or displays some signs of mixed dominance. Such individuals do not have the normal left hemisphere dominance.

*Percentage of all pairs of monozygotic twins (with a schizophrenic proband) in which the co-twin is borderline.
Essen-Möller

In a study including eight MZ twin pairs with a chronic schizophrenic proband, Essen-Möller (1970) diagnosed two of the co-twins as having clear-cut schizophrenia, giving a concordance rate of 29 percent. However, four additional co-twins had one or more symptoms suggestive of schizophrenia or a schizoid adaptation—for example, ideas of reference in two; thoughts of telepathy and mood swings in one. The pairwise concordance including these co-twins is 86 percent. The implication from this study, as from that of Gottesman and Shields, is that given a strong enough genetic loading for schizophrenia, one or more manifestations of this diathesis will be present and recognizable as schizophrenia-related. The nature, severity, and quality of these manifestations, however, will be determined by environmental features, whether biological, psychosocial, or a combination of both.

Inouye

Inouye (1961) studied 53 MZ twin pairs in which at least one member was diagnosed schizophrenic. His concordance rate for chronic schizophrenia was 48 percent. An additional 13 percent were diagnosed as “chronic neurotic states with symptoms resembling schizophrenia.” Analogous to borderline patients, such co-twins manifested, for example, transient ideas of reference or fixed psychotic-like beliefs. In Inouye’s judgment, all of the co-twins had some symptoms of schizophrenia or schizoid personality. However, his diagnostic system is complicated and dissimilar to those discussed in connection with previous studies. Furthermore, co-twins were not “blindly” diagnosed. Both these factors make it difficult to interpret his results.

Fischer

Fischer (1972) used the Danish twin register to find concordance rates for schizophrenia among MZ twins. Like Gottesman and Shields, she had a control group of DZ twins and determined MZ:DZ ratios of pairwise concordance rates. The ratio remained the same whether Fischer included only those co-twins diagnosed as having “strict schizophrenia” (resulting in an MZ pairwise concordance rate of 24 percent and a DZ rate of 10 percent, with a ratio of 2.4) or also included psychotic co-twins who did not meet “strict” criteria (yielding higher concordance rates of 48 percent for MZ and 20 percent for DZ pairs, but the same ratio of 2.4). Including co-twins described as “nervous” or “odd” reduced the ratio to a nonsignificant level. The psychotic co-twins not satisfying the criteria for “strict” schizophrenia appeared to have chronic maladaptive traits, including paranoid symptoms, and could possibly fit into the borderline classification. If this rather questionable fit is valid, the study supports the hypothesis of a closer and more specific relationship of borderlines to chronic schizophrenics than exists for other milder conditions that might be considered schizophrenia-related.

Tienari

In a study of Finnish twins, Tienari (1963, 1968, 1971) found 16 schizophrenic MZ probands. In an initial publication (Tienari 1963), psychotic symptoms were not reported in any of the co-twins. Later one of the co-twins was judged schizoaffective. Although the author did not consider them borderline, the co-twins in three or four cases displayed what might currently be considered borderline features, such as chronic anxiety, paranoia, and hypochondriasis. Seven co-twins were characterized by schizoid features—broadly defined in terms of introversion and tenseness. Interestingly, Tienari found a fairly large proportion of co-twins with borderline (27–36 percent) or schizoid (63 percent) features, but an exceptionally low proportion of schizophrenics (9 percent). More subtle schizotypal traits appeared to characterize the co-twins in Tienari’s study far more than chronic schizophrenia or borderline personality.

Pollin

Pollin and co-workers (Pollin et al. 1966; Pollin and Stabenau 1968) intensively studied 11 pairs of MZ twins discordant for schizophrenia, with a focus on better understanding the environmental conditions that may have been responsible for this discordance. Of the 11 probands, four were considered “borderline” schizophrenic (meaning questionably schizophrenic). Although this category was designed to refer to lack of diagnostic unanimity, rather than to a strict diagnostic group, it corresponds to the definition of borderline used in several investigations (e.g., Gunderson, Carpenter, and Strauss 1975; Willett et al. 1973). The investigators were able to isolate several variables that differentiated the schizophrenic probands from their nonschizophrenic co-twin
controls, including a lower birth weight, a more intense ambivalent relationship with the dominant parent (usually the mother), slower development, more instability, and greater submissiveness. These trends were present to a lesser degree in the borderline probands than in those who were diagnosed clearly schizophrenic. Pollin et al. (1966, pp. 500-501) suggested that there may have been "less organic disparity between the twins, less biological favoring of the control in these 'borderline' families . . . ." While selecting discordant pairs in which the proband is clearly schizophrenic seems to isolate pairs showing a clear organic disparity, selecting borderline discordant pairs does not. The clinical descriptive disparity between twins in these pairs was also less. Perhaps the etiology of chronic schizophrenia in the probands of the discordant pairs reflects organic environmental rather than genetic factors. In the borderlines, however, genetic factors may be more sensitive to environmental interactions, so that even without the intervening influence of readily detectable organic environmental factors, more subtle biological or psychosocial environmental influences could have contributed to the discordance. It is interesting that the borderlines, who were noted to have more prominent affective psychopathology than the schizophrenics, were perceived during childhood as being more impulsive, having more of a temper, and were given to throwing things, as compared to the co-twins.

Mosher et al. (Mosher, Pollin, and Stabenau 1971; Mosher, Stabenau, and Pollin 1973) later reexamined the discordant co-twins of their schizophrenic subjects for indications of schizoidness, which was described primarily as avoidance of close relationships and detachment. Although they found no evidence of increased schizoidness in the co-twins of the schizophrenics as compared to normal twins, three of the co-twins of the borderlines and one co-twin of a schizophrenic were described as having a tendency to disorganization, fragmentation, or rambling without overt thought disorder and without an accompanying personality disorder; none of the descriptions of the controls included these characteristics. The subtype diagnoses of the index twins (i.e., schizophrenic or borderline) in these four cases were residual schizophrenia in two cases, obsessive-compulsive neurotic with borderline features of schizophrenia in a third, and paranoid schizophrenia in remission in the fourth. The co-twin of another borderline, although without the cognitive characteristics cited, was impulsive with acting-out tendencies and suicidal ideation—symptoms associated by some authors with borderlines (Gunderson and Singer 1975). This patient was later hospitalized as noted in a followup study (Belmaker et al. 1974). Thus all four borderline probands had co-twins with borderline symptoms. None of the index cases diagnosed as acute or chronic undifferentiated schizophrenics had co-twins who manifested the above characteristics. The more marginal discordance for the borderlines suggests that genetic factors may be important determinants for these borderline-like symptom pictures. Moreover, these determinants may be partially independent of those underlying more severe chronic undifferentiated schizophrenia.

In summary, the twin studies do not greatly clarify the relationship of the borderlines to chronic schizophrenia. This is in large part due to lack of explicit or homogeneous diagnostic criteria, as well as appropriate controls. If a relationship between borderline and chronic schizophrenia exists, it is not a simple one. The presence of mild psychotic-like symptoms correlates better with genetic relationship to chronic schizophrenia than any identifiable personality type such as borderline or schizoid. Nevertheless, there is some evidence that a borderline adaptation is seen more frequently in the co-twins of chronic schizophrenics than any other identifiable personality disorder. Other genetic factors—not necessarily shared with chronic schizophrenia—and environmental factors—whether biological or psychosocial—may play a more important role in the genesis of the borderline than of the classic chronic schizophrenic in these twins.

Discussion

Implications of Genetic Studies

In this review we have attempted to examine those studies that might shed light on the possible genetic determinants of borderline conditions. We have further looked for evidence that could delineate the strength and specificity of such genetic determinants. The diagnostic criteria have been too varied and the sample sizes too small to allow us to draw definite conclusions. However, the following six tentative impressions have emerged from our review:

1. Some borderline conditions have important genetic determin-
.borderlines in significantly greater number than the appropriate controls. Borderlines and chronic schizophrenic parents than controls. Some borderlines, defined by the same diagnostic criteria, may be affected by genetic factors distinct from those implicated in schizophrenia, or may share with the schizophrenics less specific genetic vulnerability factors.

3. Borderlines with genetic relatedness to chronic schizophrenia have some common clinical characteristics. The characteristics described by Kety et al. (1968) and refined recently by Spitzer, Endicott, and Gibbon (1979) are similar to those observed in the co-twins of chronic schizophrenics. These so-called “schizotypal” characteristics emphasize psychotic-like cognitive distortions and atypical mentation. Although Spitzer, Endicott, and Gibbon include in their criteria a lack of depth in interpersonal relationships, they have not systematically examined the characteristics of schizotypal individuals that relate to personality style, such as the quality of interpersonal relations, impulsivity, and social adaptation.

4. Borderlines may be genetically related to other psychiatric disorders, particularly the affective disorders. The family study by Stone (1977) provides the strongest evidence that clinically diagnosed borderlines are genetically related to patients with major affective disorders, and that this relationship is at least as strong as that to chronic schizophrenics. The borderlines studied by Stone were diagnosed using Kernberg’s (1975) psycho-structural criteria but also conformed to the clinical syndrome of borderlines defined by Gunderson and Singer (1975). Because both these sets of criteria allow for transient psychotic experiences, they would appear to encompass—while still being more extensive than—the schizotypal criteria derived from the extended family study. This impression is further supported by Spitzer, Endicott, and Gibbon’s study, which showed that two thirds of the patients with schizotypal characteristics also meet the clinical criteria for Gunderson and Singer’s proposed diagnosis of borderline personality disorder. Thus, the presence of schizotypal symptoms is unlikely to discriminate borderlines who are genetically related to chronic schizophrenia from those related to affective disorders. Moreover, even when the borderline sample is limited to individuals with schizotypal characteristics, there are still intriguing suggestions of a relatedness to the affective disorders. In the adopted-away study, for example, borderlines were found as frequently in the offspring of parents with affective disorders as in the offspring of chronic schizophrenics. A second example is provided by the extended family study, even though there were no probands with major affective disorders to test the hypothesis that borderlines are related to those disorders. Here we found a suggestion of more minor affective disorders in the borderline biological relatives than in the chronic schizophrenic biological relatives or control biological relatives. Schizophrenia

---

Spitzer’s schizotypal criteria have not been applied to this as yet unoperationally characterized group (Wender, personal communication).
and manic-depressive disorders are the most extreme and universally recognized diagnostic groups and, thus, it is natural to look for genetic relatedness to these groups. It remains a possibility that if genetic relationships to a third or even fourth major diagnostic group were investigated, still other associations could be found. It is possible, if not probable, that a variety of genetic factors predispose to the borderline diagnosis in addition to those shared with the "schizophrenic spectrum" disorders. Perhaps some of these factors are shared with the "depressive spectrum" disorders as well, and both of these spectrums become less specific and increasingly overlapping as one moves away from the parent disorders.

5. Chronic schizophrenics seem to share a stronger common genetic predisposition with each other than they do with borderlines. On the one hand, genetic factors shared by borderlines and chronic schizophrenics have a less determining role in the diagnosis of borderline than in the diagnosis of chronic schizophrenia. On the other, genetic factors other than those implicated in chronic schizophrenia may be important in the etiology of borderline conditions. This impression is gained from the observations in the extended family study that chronic schizophrenics or borderlines are more highly concentrated among the biologic relatives of chronic schizophrenics than among those of borderlines and that relatives with diagnoses in the schizophrenic spectrum were not confined to a smaller subgroup of the schizophrenics' families as they were for the borderlines.

6. Nonborderline individuals may share a common genetic composition with chronic schizophrenics. The evidence for this impression comes from the twin studies: Gottesman and Shields' (1972) sample as diagnosed by Essen-Möller, Essen-Möller's (1970) own sample, and the studies of Inouye (1961), Fischer (1972), Tienari (1963), and Pollin et al. (1966). All of these studies contained many MZ co-twins of chronic schizophrenic index cases who were specifically not diagnosed as borderline personalities or even necessarily schizoid personalities. In some cases these nonborderline co-twins presented characteristics in history or interview that seemed related to schizophrenia to the diagnosticians, even when diagnosed blind, as in Essen-Möller's case. When specified, these characteristics seemed to resemble the cognitive distortions and atypical mentation found in the adoptive studies (see tables 1 and 2) rather than any uniform personality type or style of social adaptation. Since these characteristics are mild and do not impair the individual's personal functioning, it would seem unwise to assign a psychiatric label to such individuals.

Models of Transmission

It is not now possible to arrive at an adequate formulation of genetic transmission for borderlines. However, some tentative conclusions can be made about the strength and specificity of the genetic factors important in the etiology of at least the schizotypal borderlines. When there is a shared genetic predisposition to both chronic schizophrenia and borderline schizophrenia, it does not seem to manifest itself as a definite constellation of personality traits, symptoms, and life course. The schizophrenogenic potential may find expression in characteristics varying in quality and severity, such that they might be noted only on a careful mental status examination and would be difficult to identify reliably. Less ambiguous delineation of individuals with a schizotypal genotype will depend upon finding more discriminating clinical features or upon isolation of physiological or biochemical parameters.

The conclusions outlined above are compatible with a variety of genetic models. The schizotypal borderline may be regarded as a forme fruste of schizophrenia such that the two diagnostic groups share the same genetic load. This hypothesis, particularly compatible with a monogenic theory, implies that although borderlines share the same genotype as process schizophrenics, more favorable modifying genes and/or environmental factors forestall the development of chronic psychosis. Another possibility, more compatible with the polygenic hypothesis (although conceivable in a monogenic model including homozygotes and heterozygotes), is that borderlines carry a lower genetic loading for schizophrenia and, for this reason, are less severely clinically disordered. In a polygenic model, one can also allow for the contribution of less specific genetic factors,4 which might explain the

---

4 This heterogeneity is consistent with a polygenic model in which there are various subgroups of borderlines, one more closely related to the affective disorders and another to chronic schizophrenia, though these subgroups may not present easily distinguishable clinical pictures. An arbitrary example of this model would be one in which
two alleles $A_m$ and $B_m$ were necessary for an individual to manifest manic-depressive disorder, while two other alleles $C$ and $D$ are necessary for an individual to manifest chronic schizophrenia. Individuals with only one of these variant alleles might present a borderline clinical picture, but the underlying genetic etiologies would be different.

It is also consistent with a second model (not mutually exclusive), in which borderlines may share common genetic vulnerability factors (or even a single factor). The vulnerability factors predispose an individual to either disorder but require other more specific genetic and/or environmental factors to determine whether and in which direction this occurs.

The following is an example of such a model. At locus $A$ there may be a wild-type allele, $A_w$; an allele strongly and specifically predisposing to schizophrenia, $A_s$; and another allele strongly and specifically predisposing to manic-depressive psychosis, $A_m$. (These alleles need not be at the same locus to demonstrate this point.) As both $A_s$ and $A_m$ are rare genes and at the same locus, their probability of occurring in the same individual, or even in the same family, would be low. At locus $B$ there may be a wild-type allele, $B_w$ or $B'$, the “genetic vulnerability” gene. The presence of $B'$ may weakly increase the likelihood of an individual’s presenting borderline symptomatology and also be associated with an increased prevalence of more specific and severe psychoses such as manic-depressive psychosis and chronic schizophrenia when associated with either allele of the $A$ gene. Thus, individuals carrying such a vulnerability gene may be clinically normal or, under adverse environmental conditions, appear borderline, but in most cases, would require either of the $A$ variants for a relationship of borderlines to both the affective and schizophrenic disorders.

Both models allow for the possibility of individuals who represent phenocopies; that is, individuals whose clinical picture is much like that of a genetic disorder, although their similar-appearing disorders are not in fact genetically based. If only a proportion of the schizotypal borderlines shared a specific genetic basis in common with process schizophrenia and in the rest, other, perhaps less specific genetic factors and/or environmental determinants were the crucial causative factors, one might see this as a disorder of a much more heterogeneous etiology. Accordingly, genetic factors would perhaps be relatively less important in many individuals with this diagnosis. In this case, one would see (as was found in the family and fostering studies) a large number of borderlines who have no family history of schizophrenia or schizophrenia-related disorders.

At this point, even for chronic schizophrenia, we cannot fully distinguish between a monogenic and polygenic model (Matthysse and Kidd 1976), although the data so far favor a polygenic one. It would nevertheless seem that a polygenic mode of transmission would more comfortably accommodate the genetic heterogeneity of borderlines.

### Future Research Directions

In reviewing the existing research, we repeatedly encountered two major limitations. The first was the wide variation in criteria for borderline disorders. It was not clear that the samples in any of the studies were comparable populations, yet they seemed to share some common characteristics. However, because of the second limitation—small sample sizes—no single study permitted us to draw conclusions with any degree of confidence.

With respect to the first limitation, it is essential that future research use replicable criteria to arrive at a borderline diagnosis. The recent work by Spitzer, Endicott, and Gibbon (1979) and by Gunderson and Kolb (1978) provides two approaches to the problem. Moreover, such samples should be surveyed for
a broad range of clinical characteristics. This may permit the retrospective identification of subgroups that have special genetic loadings. An example of this would be to select a sample using schizotypal characteristics. There are suggestions that within such a sample there is a subgroup which is closely related genetically to chronic schizophrenia. The presence of social isolation in these schizotypal borderlines may, for example, discriminate this group from those with the intense unstable relationships found in most patients diagnosed borderline, who also have psychotic-like symptoms.

Clear borderline criteria might also be productively applied to the samples in the existing genetic studies. One could examine the adoptive sample as Spitzer, Endicott, and Gibbon have done, or look at the relatives of samples of other index diagnostic groups (e.g., psychopaths or manics). Along this line, we are currently examining the co-twins of chronic schizophrenics for evidence of borderline psychopathology.

The problem of sample size stems largely from the fact that with the exception of Stone, all of the investigators whose work has been described have included borderlines as a subgroup in studies primarily directed at understanding the genetics of schizophrenia. The research strategies reviewed here—adoptive studies, twin studies, and family studies—could profitably be employed to look for the prevalence and types of psychiatric disorders in the relatives of an index sample of borderlines.

There is no doubt that genetic studies would be enhanced if some biological marker or antecedent clinical indicator were found. In the latter instance, longitudinal studies could be done to study gene-environment interactions. In the former instance, tighter samples which may overlap with other diagnoses such as affective disorders or schizophrenia could be studied.

**Diagnostic Implications**

At this point, there is not enough evidence from genetic studies to definitively resolve questions about the validity and specificity of the borderline diagnosis. Spitzer, Endicott, and Gibbon (1979) have argued that borderline patients who share genetic determinants with chronic schizophrenics should be made a distinct diagnostic category “Schizotypal Personality Disorder.” They feel that their work with the adoptive study sample has provided a means of identifying such patients; furthermore a questionnaire study they conducted has demonstrated that clinicians find such schizotypal characteristics in a large fraction of patients diagnosed as borderline. Acceptance of Spitzer, Endicott, and Gibbon’s conclusion would appear to demand that the following three preconditions be met: (1) People with schizotypal characteristics can be discriminated from patients with borderline personality disorder; (2) such people have a clearly defined genetic relationship to chronic schizophrenia; (3) conditions 1 and 2 constitute sufficient evidence to warrant an independent diagnostic status. We believe that the existing data do not support these conclusions.

With respect to the first point, many clinicians have always viewed brief, psychotic-like experiences as a central characteristic of borderline personality. Thus, examples of brief psychotic-like thinking are contained in the descriptions of borderline patients by Knight (1953) and Kernberg (1975), and in the systematic studies by Grinker and Werble (1977). The work of Gunderson and his associates has also demonstrated that brief psychotic experiences and, particularly, paranoid ideation and ideas of reference are central characteristics of borderlines. Moreover, these characteristics are highly interrelated psychologically and highly correlated statistically with other characteristics of patients with a borderline personality disorder (Gunderson 1976; Gunderson, Carpenter, and Strauss 1975; Gunderson and Kolb 1978; Gunderson and Singer 1975). Even in the questionnaire study by Spitzer, Endicott, and Gibbon, two thirds of the patients with schizotypal characteristics also were found to have clinical characteristics of borderline personality disorder. All of this evidence combines to indicate that the psychotic-like characteristics Spitzer, Endicott, and Gibbon define as schizotypal are unlikely to demarcate a new diagnostic entity discriminable from borderline personality disorder.

With regard to the second point, existing evidence for a genetic relationship between schizotypal individuals and chronic schizophrenics stimulated interest in creating the new diagnostic category “Schizotypal Personality Disorder.” It seems likely, however, from this review that even should people with schizotypal characteristics be discriminable from borderline personality disorder, they may have neither a strong nor necessarily specific relationship to chronic schizophrenics. Although such a close relationship need not be a prerequisite for a separate diagnostic entity, the nature of this relationship needs to be better estab-
lished and clarified. With further research, it might be possible to define subgroups of borderlines along genetic lines, particularly if differences in the quality of the psychotic-like symptoms, affect, and interpersonal relations can be reliably discriminated. If this were possible, it still seems likely from this review that there might be considerable overlap between such subgroups. It appears the less severe and clear-cut the diagnosis is, the more likely a variety of genetic factors, specific or nonspecific, and environmental factors, psychosocial or biologic, become important. The possibility remains that a subgroup of patients with schizotypal characteristics will be found to have a strong relationship with chronic schizophrenics. In our view, patients with schizoid personality disorder in conjunction with schizotypal features are most likely to form such a subgroup, discriminable from borderline personality disorder. This, however, needs to be demonstrated.

With respect to the third component of Spitzer, Endicott, and Gibbon's argument, even should the schizotypal characteristics be shown to be indicative of a specific genetic relationship with chronic schizophrenia, there are problems involved in giving them independent diagnostic status as a schizotypal personality disorder. In the first instance schizotypal characteristics (table 2) are symptom-oriented largely in the cognitive sphere and do not describe a personality disorder. They are probably associated with a variety of personality types, as has been suggested by the twin studies. In the presence of severe dysfunction, it might be preferable to revitalize latent or ambulatory schizophrenia. In the absence of any significant functional disorder, it becomes an ethical problem to give a psychiatric label to such persons. Those with schizotypal features in the presence of clearly defined personality disorders such as schizoid personality or borderline personality disorder might be considered a subgroup of these disorders as noted above. However, this review suggests that the clinical characteristics of such individuals related to chronic schizophrenics may overlap partially with characteristics of individuals genetically related to other major psychiatric syndromes. Finally, although we have illustrated how the mode of transmission could fit either a monogenic or polygenic mode of transmission, we believe that the polygenic mode is more likely. One implication of a polygenic mode of transmission is that single genetic factors are unlikely to be sufficiently powerful determinants of adult psychopathology to provide a meaningful basis for defining a diagnostic group (Kidd and Matthysse 1976). A monogenic model would have to allow for a correspondingly larger role for environmental influence to account for the genetic data. In summary, the formation of a new psychiatric diagnosis based on evidence of a weak and variable genetic relationship has complicated scientific problems and could have serious ethical problems as well. We thus conclude that the separation of the borderline patients who are genetically related to chronic schizophrenics into a distinct diagnostic category is premature.

References


Acknowledgment

This research was supported in part by McLean Hospital Biomedical Research Support Grant FR05484. Special thanks are due to Lynne Montcrieff without whose help this article would not have been possible.

The Authors

Larry J. Siever, M.D., is Staff Psychiatrist, Clinical Neuropharmacology Branch, National Institute of Mental Health, Intramural Research Program, NIH Clinical Center, Bethesda, Md. Dr. Siever was formerly Clinical Fellow, Department of Psychiatry, Harvard Medical School, and Resident in Psychiatry, McLean Hospital, Belmont, Mass. John G. Gunderson, M.D., is Assistant Professor, Department of Psychiatry, Harvard Medical School, and Director of Psychotherapy, McLean Hospital, Belmont, Mass.

The Switch Process in Manic-Depressive Illness

In manic-depressive illness, the process of change from a severely depressed to a manic phase can occur anywhere between a few minutes and a few days. Analysis of the “switch process” has given psychobiologists important insights into the chemical processes associated with changes in brain neurons in affective illnesses.

Dr. William E. Bunney, Jr., Chief of the Biological Psychiatry Branch of the National Institute of Mental Health’s Intramural Research Program, has studied manic-depressive patients, focusing on the neurotransmitter mechanisms that carry impulses from one neuron to another at the synapse. He theorizes that elevated or reduced levels of the neurotransmitters, norepinephrine and dopamine, may be responsible for the sudden shift from one state to the other. In the 14-page monograph, Bunney discusses the switch process and his study of what happens in the brain during the switch.

Published by: The National Institute of Mental Health
Division of Scientific and Public Information