Defining the Schizophrenia Spectrum: Issues for Genetic Linkage Studies

by Douglas F. Levinson and Bryan J. Mowry

Abstract

Genetic linkage studies of schizophrenia depend on accurate psychiatric diagnosis of relatives within multiply affected families. Each investigator makes a series of explicit or implicit decisions to define which relatives will be assumed to share a schizophrenia-related genotype, that is, who is an “affected relative.” In this article we delineate issues that we believe should be considered in such studies and review the relevant literature. Issues include criteria for selecting probands; whether broader criteria should be used to select affected relatives; approaches to including or excluding diagnoses for which family study data suggest a relationship to schizophrenia or to affective disorders or other psychiatric disorders; clarification of diagnostic hierarchy; and issues related to substance abuse and neurological disorders. Also discussed are whether relatives without spectrum diagnoses should be considered unaffected or undiagnosed in linkage analyses, how bilateral familial affectedness should be defined, and provision for independent review of study diagnoses. As an illustration, the clinical model for the authors’ schizophrenia linkage study is described.

Genetic linkage studies of schizophrenia require that clinicians define the set (or alternative sets) of diagnoses assumed to be phenotypic expressions of a common genotype; that is, who is considered “affected” with a schizophrenia spectrum disorder?

Diagnostic accuracy is fundamental to linkage methodology. The linkage study (taking a dominant disease allele as an example) determines whether, within each family, the presence of a deoxyribonucleic acid (DNA) marker allele inherited from an ill ancestor significantly predicts presence of disease. This occurs when the disease-causing allele is close to the DNA marker, so that the two DNA sequences are seldom separated in the genetic shuffling process (recombination) that occurs during the production of sperm and egg cells (meiosis). Incorrect diagnoses thus distort the computation of the association between marker and disease.

This is particularly true for false positive diagnoses. The worst case would be inclusion of an entire family because of a misdiagnosed proband, spuriously weakening evidence for linkage. But even in a family in which the disease and marker are actually linked, false positives can have significant consequences. In linkage calculations, such cases are assumed to represent recombination events. False positives increase the estimated genetic distance between marker and disease (because distance is correlated with frequency of recombinants), until eventually the estimate is so great that linkage cannot be demonstrated. False negative diagnoses are a lesser problem (unless they obscure bilateral inheritance), and their effect depends on the choice of linkage analysis methods. Most or all unaffected relatives are excluded from analysis in sib-pair (Blackwelder and Elston 1985), affected-member (Weeks and Lange 1988), and some pedigree methods (Lander and Botstein 1986), so that false negatives would reduce the power but not the accuracy of the analysis if sample size were

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adequate. (Reasons to use such methods for schizophrenia are discussed below, and by Baron [1990] and Ott [1990].) Both affected and unaffected relatives are included in traditional pedigree analysis, but for incompletely penetrant diseases such as schizophrenia (i.e., where not all genetic carriers become ill), a few false negative cases will be indistinguishable from nonpenetrant carriers, and a larger number of cases would be required to obscure linkage.

Because there are no validating tests for psychiatric clinical diagnoses, we currently face the somewhat circular problem of recognizing that linkage studies depend on accurate diagnoses, while hoping that the same studies will lead to genetic methods for validating diagnostic boundaries.

Diagnosis is only one of many obstacles to studying schizophrenia by means of current linkage techniques, which are best suited to the study of simple single-locus Mendelian (dominant, codominant, or recessive) diseases (Risch 1990). In those cases of schizophrenia that are predominantly genetic in etiology, the disease is probably either genetically heterogeneous (multiple distinct genetic mechanisms) (Lander 1988) or related to one or more major-locus effects with significant polygenic (and possibly nongenetic) modification (Faraone and Tsuang 1985; Matthyse et al. 1986; Karlsson 1988), or to a polygenic mechanism (McGue et al. 1983; Risch and Baron 1984; Faraone and Tsuang 1985; Gottesman et al. 1987).

Should linkage studies be attempted when mode of transmission is unclear and may be polygenic? Many investigators (including the present authors) have taken the position advocated by Kidd (1987), who argues that a major locus effect is compatible with some aspects of schizophrenia family data and that linkage analysis may be the only way to demonstrate such an effect, because it can often withstand erroneous assumptions about genetic parameters. Others take the position recently articulated by Risch (1990), who argues that most schizophrenia is likely to be polygenic and that linkage techniques may prove most useful in identifying common alleles that modestly increase the risk of schizophrenia and provide clues to pathophysiology (analogous to the study of insulin-dependent diabetes or perhaps coronary artery disease). In any event, initial linkage findings may be weak and difficult to replicate. For example, a study might identify a locus that ultimately proved to exert a major locus effect but only in certain samples or in a small proportion of cases, so that the linkage result would be difficult to confirm in independent samples. Or an investigator might find a unique pedigree or geographical region where occurrence of a polygenic disease depended on variation at one or two loci simply because there was considerable homozygosity at other relevant loci, a result that could be difficult to replicate.

In this light, the controversy over the chromosome 5 linkage finding (Sherrington et al. 1988) is not surprising. Sherrington et al. reported linkage between schizophrenia and a group of markers on the long arm of chromosome 5, a region selected for study because of an association between a cytogenetic defect and schizophrenia in a Canadian family (Bassett et al. 1988). Linkage was detected (primarily in Icelandic families) when only cases of nonaffective major psychosis were considered to be ill, but the finding was strengthened when cases with other putatively related disorders (such as schizoid personality) and those with any psychiatric diagnosis were included. Numerous investigators promptly examined these and proximate markers in other samples, but all obtained negative results (Kennedy et al. 1988; Detera-Wadleigh et al. 1989; St. Clair et al. 1989; Aschauer et al. 1990; Crowe et al. 1990; McGuffin et al. 1990). McGuffin et al. (1990) recently reviewed all the chromosome 5 studies to date and concluded that the finding was simply an erroneous result of multiple statistical tests, rather than evidence of genetic heterogeneity as suggested by Sherrington et al. and by several others (Kennedy et al. 1988; Lander 1988); it remains possible that some Icelandic families have an unusual genetic etiology, or that differences in clinical methods could account for the discrepant findings.

This controversy has highlighted a number of the issues to be considered in the present article, such as where to place the boundaries of the schizophrenia-related spectrum of diagnoses, whether to include unaffected relatives in linkage analyses in studies of schizophrenia, and how to conceptualize the relationship between schizophrenic and affective disorders.

Given the number of obstacles to be overcome, it is important that published reports include detailed clinical information so that it can be determined whether differences among samples are associated with linkage results. This article will explore the clinical decisions (table 1) that are involved, explicitly or implicitly, in the formulation of a diagnostic strategy for schizophrenia linkage studies. (Family studies cited are limited [with exceptions as noted] to those in which modern diagnostic criteria were used, interviewers were blind to most proband diagnoses,
Table 1. Issues in selecting a clinical model for schizophrenia linkage studies

1. Selection of index cases (probands)
   a. Criteria for schizophrenia
   b. Include or exclude schizoaffective cases
   c. Criteria for lifetime diagnosis of schizophrenia in presence of some history of affective features.

2. Criteria for schizophrenia in proband's relatives—same as probands versus broader criteria

3. Schizoaffective disorders
   a. Include some or all or exclude
   b. Criteria for subtypes to be included: chronic or nonchronic, mainly schizophrenia or affective, depressed or bipolar, other criteria

4. Other psychoses
   a. Schizophreniform: include or exclude, approach to affective features, minimal followup period
   b. Atypical psychosis: boundaries
   c. Delusional (paranoid) disorder: criteria, include or exclude

5. Schizotypal and paranoid personality disorders
   a. Primary or secondary analysis, or exclude
   b. DSM-III, DSM-III-R, additional criteria (e.g., Gunderson et al. 1983, McGlashan 1987, study-specific)
   c. Define boundary between psychotic-like experience of these disorders and delusional, atypical psychotic disorders

6. Affective disorders
   a. Exclude families that are “too affective”? (Bipolar disorder, depressive psychosis in pedigree, in what degree of relation to included relatives; recurrent major depression: exclude family for a defined density or number of cases)
   b. Include affective disorders as affected relatives? (Which disorders; primary or secondary analysis?)

7. Other disorders
   a. Secondary analysis including all disorders as affected?
   b. Secondary analysis including cases with clinical impression of “broad spectrum” (possible schizotypy)? Criteria?

8. Substance abuse
   a. Exclude cases for abuse of a specific drug?
   b. Exclude for substance abuse during a certain time before onset of schizophrenia?
   c. Criteria for including or excluding cases with concurrent or prior substance abuse in primary and in secondary analyses

This discussion assumes that probands and relatives in a given study will be classified as “affected” or “unaffected” with a schizophrenia spectrum disorder for purposes of linkage analysis, perhaps with alternative sets of diagnoses considered affected in each of a series of analyses. This categorical-diagnostic approach has been the basis for the twin, family, and adoption studies that provide all the compelling evidence for a genetic etiology of schizophrenia, and it lends itself readily to classical linkage analysis methods. Other approaches could be used. One approach would be to consider some family members to be “at risk” (and to assign them this intermediate category in linkage analyses) on the basis of smooth-pursuit eye movement dysfunction or other measures (Matthysse et al. 1986; Lander 1988; Baron 1990). An alternative approach, which has been used successfully in genetic studies of other diseases (e.g., Lalouel et al. 1985), would be to incorporate into linkage analysis a continuous variable that might help to identify genetically vulnerable relatives. This would be consistent with polygenic-multifactorial transmission or with a mixed major gene-polygenic model (Gottesman et al. 1987). For example, questionnaire assessments of schizotypy could be used to assess liability (Claridge 1988; Kendler et al. 1991). Quantitative linkage analysis can be used to determine the influence of individual loci on a continuous measure under some circumstances (Paterson et al. 1988). Moldin et al. (1990) have suggested an approach that uses both overt disease status and a continuous measure of liability (illustrated in the case of schizophrenia by an assess-
Table 1. Issues in selecting a clinical model for schizophrenia linkage studies—Continued

9. Neurological disorders
   a. Excluded disorders
   b. Guidelines for abnormal electroencephalogram, borderline mental retardation, birth or head trauma by history, learning disabilities

10. Diagnostic hierarchy
    a. Approach to multiple diagnoses; "lifetime" diagnosis
    b. Hierarchical model

11. Unaffected relatives
    a. "undiagnosed" or genotypically unaffected in linkage analysis
    b. Selection of penetrance estimate if included in analysis

12. Bilaterality
    a. Criteria for defining a parent as affected
    b. Criteria for assuming positive family history (relatives of parent)

13. Longitudinal diagnostic followup

14. Independent review of study diagnoses

15. Monitoring of diagnostic reliability

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ment of schizotypal diagnostic features) for linkage analysis. One could also incorporate measures such as tests of attention or biological markers into such analyses.

To review all the putative measures of risk for schizophrenia would be beyond the scope of the present article. However, in contrast with the substantial evidence for genetic relatedness between schizophrenia and certain clinical diagnoses (see below), there is much greater controversy surrounding each of the biological and psychophysiological markers. Nor is it clear that we are able to quantify schizotypy or similar constructs accurately; for example, some articulate subjects admit to schizotypy-like experiences that seem clinically insignificant, whereas others deny paranoid and other deviant traits that are suspected by interviewers to be quite significant. It seems likely that schizophrenia linkage studies will continue, for the present, to rely heavily on clinical diagnostic strategies, emphasizing the identification of "definitely affected" individuals. We focus here on issues relevant to formulating such strategies.

Selection of Index Cases

Families are selected for genetic studies by identifying an ill index subject, or proband. A conservative approach would be to select probands who meet relatively narrow criteria for schizophrenia. The Research Diagnostic Criteria (RDC; Spitzer et al. 1978) have several advantages:

- A well-known structured interview schedule—Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978)—is available.
- Compared with other diagnostic systems, the RDC produced the highest heritability estimate for schizophrenia in a retrospective analysis of a major twin sample (McGuffin et al. 1984).
- Relatives of probands with RDC schizophrenia had a significantly increased risk of schizophrenia (Baron et al. 1985b; Gershon et al. 1988) and of schizotypal and paranoid personality disorders (Baron et al. 1985b; Kendler 1988). One study failed to show such differences using RDC (Coryell and Zimmerman 1988).

Most investigators would choose to specify a longer duration of illness than the 2 weeks required by the RDC. The original St. Louis criteria (Feighner et al. 1972) are more conservative than RDC, emphasizing insidious onset and chronicity; they were successful in identifying patients whose diagnosis remained stable over 8 years or more (Guze et al. 1983). The St. Louis maximum age of onset (35) may be too early for female subjects (Bellodi et al. 1986), especially in linkage studies, because later onset females are more likely to have had multiple children. The narrow Taylor-Abrams criteria (Abrams and Taylor 1983) appear not to identify a subgroup that differs from other schizophrenic patients in familial risks for spectrum disorders (Baron et al. 1985a).

An argument can also be made for broader criteria:

- The older family studies of broadly diagnosed schizophrenia showed a genetic effect independent of familial affective disorder (Gottesman and Shields 1982; Gottesman et al. 1987).
- In the St. Louis study, both "probable" and "definite" schizophrenia were associated with increased
familial schizophrenia (but not affective disorders), and most “probable” cases had schizophrenia diagnoses at followup (Guze et al. 1983).

- DSM-III (American Psychiatric Association 1980) schizophrenic probands have increased familial risk of schizophrenia (Frangos et al. 1985; Kendler et al. 1985a) and a heritability estimate similar to RDC (Farmer et al. 1987).

Broader criteria have the disadvantage that, because they require fewer symptoms than RDC, they may include more atypical patients, such as those with chronic hallucinations but no thought disorder or delusions. Investigators might consider whether linkage studies should include families in which the most severely affected individual has this type of clinical picture.

The proband need not be the first identified family member. Unlike segregation analyses (family studies), in which the sampling method affects the outcome and so the probability of ascertaining a given class of proband must be expressed mathematically, linkage studies test the diagnostic and genetic model directly with DNA marker data (Ott 1985).

Can “Affected Relatives” Have a Broader Spectrum of Diagnoses?

Relatives of schizophrenic probands are at risk for a broader spectrum of disorders, perhaps more so than for schizophrenia (see below). The inclusion of spectrum disorders may thus increase the power of linkage studies, despite the possible tradeoff of reduced specificity and accuracy of diagnosis. One strategy is to plan a series of linkage analyses using narrower and broader definitions of the spectrum. For example, Sherrington et al. (1988) found an increasing lod score as broader diagnostic categories were included (as yet an unreplicated finding). It has been suggested that such studies should adjust the threshold of significance of the lod score for the use of multiple tests (Lander and Lincoln 1988; Ott 1990) or compute a significance value based on simulation of actual probability of a given lod score for the pedigrees under study (Green 1990; Ott 1990).

The schizophrenia spectrum can be divided for purposes of discussion into four broad components. Two of these (narrow schizophrenia and broad schizophrenia) have been discussed. Now we consider other non-affective psychoses (including schizoaffective and delusional disorders) and schizotypal and paranoid personality disorders as well as other issues listed in table 1.

Schizoaffective Disorders

There are limited family study data (tables 2–4) on the genetic relatedness of schizoaffective and schizophrenic disorders. Comparison of these samples is difficult because of the many possible ways of subtyping schizoaffective disorders. The RDC include an important dimension of mainly schizophrenic disorders (schizophrenia-like premorbid features, or psychotic symptoms for a week or more after remission of affective symptoms) versus mainly affective disorders (good premorbid functioning, no period of psychosis without prominent affective features). There are also subtypes of manic (or bipolar) versus depressed, and of acute versus chronic (schizophrenia-like symptoms for most of 2 years). Many studies have combined all subtypes into a single schizoaffective group. Only two direct-interview family studies provide information on distinct mainly schizophrenic and mainly affective subtypes (Baron et al. 1982; Kendler et al. 1986). Gershon et al. (1988) studied the chronic subtype, and Coryell and Zimmerman (1988) and Endicott et al. (1986) studied the depressed subtype. No family study has reported on any subgroup defined along all three dimensions, except for Kendler et al. (1986), who provided some information on relatives of schizoaffective manic (mainly schizophrenic) probands.

We interpret the data shown in tables 2–4 as follows:

1. Schizoaffective (mainly schizophrenic) probands have an increased familial risk of schizophrenia without an increased risk of affective disorders (Baron et al. [1982] found a nonsignificantly increased risk of affective disorders).

2. Schizoaffective samples that pool all subtypes typically show an increased familial risk of affective disorders, suggesting that such samples include many probands with variants of affective disorders.

3. Data for chronic schizoaffective probands (Gershon et al. 1988) are difficult to interpret: relatives of schizoaffective probands showed both increased nonaffective psychosis and increased affective disorder ver-
Table 2. Morbid risks of schizophrenia in relatives of schizophrenic, schizoaffective, affective disorder, and normal probands

<table>
<thead>
<tr>
<th>Study</th>
<th>DX CRIT</th>
<th>SA subtype</th>
<th>Morbid risk (%) of SCZ in first-degree relatives of probands with:</th>
<th>Proband groups with significant difference in familial risks of SCZ</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCZ</td>
<td>SA-S</td>
</tr>
<tr>
<td>Baron et al. 1982</td>
<td>RDC</td>
<td>SA-S, SA-A</td>
<td>7.9</td>
<td>4.1</td>
</tr>
<tr>
<td>Kendler et al. 1985a,</td>
<td>DSM-III</td>
<td>SA-S, SA-A</td>
<td>3.7</td>
<td>8.2</td>
</tr>
<tr>
<td>1986</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gershon et al. 1988</td>
<td>RDC</td>
<td>Chronic</td>
<td>3.1</td>
<td>-</td>
</tr>
<tr>
<td>Mendlewicz et al. 1980</td>
<td>RDC</td>
<td>(OWN)⁶</td>
<td>16.9</td>
<td>-</td>
</tr>
<tr>
<td>Scharfetter and Nusperli 1980</td>
<td>ICD</td>
<td>All</td>
<td>8.9</td>
<td>-</td>
</tr>
<tr>
<td>Gershon et al. 1982</td>
<td>RDC</td>
<td>All⁷</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Baron et al. 1985b</td>
<td>RDC</td>
<td>-</td>
<td>5.8</td>
<td>-</td>
</tr>
<tr>
<td>Endicott et al. 1988</td>
<td>RDC</td>
<td>Depressed⁷</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Coryell and Zimmerman 1988</td>
<td>RDC</td>
<td>Depressed</td>
<td>1.4</td>
<td>2.3</td>
</tr>
</tbody>
</table>

Note.—An underlined value indicates that first-degree relatives of those probands had a significantly greater risk than at least one comparison group (p < 0.05), as shown in the rightmost column. DX CRIT = diagnostic criteria; RDC = Research Diagnostic Criteria; SA = schizoaffective disorder; SA-S = RDC SA-mainly schizophrenic subtype; SA-A = RDC SA-mainly affective subtype; SCZ = schizophrenia; AD = major affective disorder; NL = normal; NS = not significant.

¹For comparison, data are shown for unipolar probands (UP), except Endicott et al. (1988) and Coryell and Zimmerman (1988) (UP psychosis), and Kendler et al. (1985a, 1986) (all AD psychoses). For relatives, data shown are all AD combined, except Scharfetter and Nusperli (1980) (all AD psychoses), and Endicott et al. (1986) and Coryell and Zimmerman (1988) (major depression). Most analyses showed similar results for bipolar probands.

²Data for SCZ and NL groups from Kendler et al. (1985a); for SA and AD groups from Kendler et al. (1986).

³Sample overlaps with Gershon et al. (1982); SCZ in relatives includes all nonaffective psychoses.

⁴Groups compared for psychoses (SCZ, SA, UFP [RDC unspecified functional psychosis], and other disorders requiring hospitalization).

⁵Gershon et al. (1988), and Coryell and Zimmerman (1988) used mostly phone interviews; in Mendlewicz et al. (1980), the proportion interviewed in person is unclear.

⁶OWN = authors’ criteria: “Episodic affective syndromes [and] at least one schizophrenic episode not concurrent to an affective syndrome” (Mendlewicz et al. 1980).

⁷Most SA cases were mainly affective subtype.

⁸SCZ in relatives includes four cases of SA-mainly schizophrenic; without these cases, 4.6% of relatives (age adjusted) of chronic SCZ probands had SCZ. Sample overlaps with Baron et al. (1982).
Table 3. Morbid risks of affective disorder in relatives of schizophrenic, schizoaffective, affective disorder, and normal probands

<table>
<thead>
<tr>
<th>Study</th>
<th>DX CRIT</th>
<th>SA subtype</th>
<th>SCZ</th>
<th>SA-S</th>
<th>SA</th>
<th>SA-A</th>
<th>AD</th>
<th>NL</th>
<th>Proband groups with significant difference in familial risks of AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baron et al. 1982</td>
<td>RDC</td>
<td>SA-S, SA-A</td>
<td>5.1</td>
<td>10.9</td>
<td>-</td>
<td>28.1</td>
<td>19.9</td>
<td>-</td>
<td>AD, SA-A &gt; SCZ, SA-S</td>
</tr>
<tr>
<td>Kendler et al. 1985a, 1986</td>
<td>DSM-III</td>
<td>SA-S, SA-A</td>
<td>7.2</td>
<td>7.3</td>
<td>-</td>
<td>14.5</td>
<td>21.9</td>
<td>7.6</td>
<td>AD, SA-A &gt; SCZ, SA-S</td>
</tr>
<tr>
<td>Gershon et al. 1988 &lt;sup&gt;3,5&lt;/sup&gt;</td>
<td>RDC</td>
<td>Chronic</td>
<td>16.0</td>
<td>18.1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7.0</td>
<td>SCZ, SA &gt; NL</td>
</tr>
<tr>
<td>Mendlewicz et al. 1980</td>
<td>RDC</td>
<td>(OWN)</td>
<td>8.6</td>
<td>34.6</td>
<td>-</td>
<td>28.5</td>
<td>-</td>
<td></td>
<td>Not given</td>
</tr>
<tr>
<td>Scharfetter and Nusperli 1980</td>
<td>ICD</td>
<td>All</td>
<td>1.9</td>
<td>9.6</td>
<td>-</td>
<td>12.0</td>
<td>-</td>
<td></td>
<td>AD, SA &gt; SCZ</td>
</tr>
<tr>
<td>Gershon et al. 1982</td>
<td>RDC</td>
<td>All&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>31.3</td>
<td>-</td>
<td>19.6</td>
<td>6.3</td>
<td>SA &gt; AD &gt; NL</td>
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<tr>
<td>Baron et al. 1985a&lt;sup&gt;6&lt;/sup&gt;</td>
<td>RDC</td>
<td></td>
<td>5.5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>5.3</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Endicott et al. 1986</td>
<td>RDC</td>
<td>Depressed&lt;sup&gt;7&lt;/sup&gt;</td>
<td>-</td>
<td>19.2</td>
<td>-</td>
<td>31.3</td>
<td>-</td>
<td>NS</td>
<td></td>
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<tr>
<td>Coryell and Zimmerman 1988&lt;sup&gt;5&lt;/sup&gt;</td>
<td>RDC</td>
<td>Depressed</td>
<td>11.4</td>
<td>22.5</td>
<td>-</td>
<td>25.3</td>
<td>10.4</td>
<td></td>
<td>AD, SA &gt; SCZ; SA &gt; NL</td>
</tr>
</tbody>
</table>

Note.—An underlined value indicates that first-degree relatives of those probands had a significantly greater risk than at least one comparison group (p < 0.05), as shown in the rightmost column. DX CRIT = diagnostic criteria; RDC = Research Diagnostic Criteria; SA = schizoaffective disorder; SA-S = RDC SA-mainly schizophrenic subtype; SA-A = RDC SA-mainly affective subtype; SCZ = schizophrenia; AD = major affective disorder; NL = normal; NS = not significant.

<sup>1</sup>For comparison, data are shown for unipolar probands (UP), except Endicott et al. (1986) and Coryell and Zimmerman (1988) (UP psychosis), and Kendler et al. (1985a, 1986) (all AD psychoses). For relatives, data shown are all AD combined, except Scharfetter and Nusperli (1980) (all AD psychoses), and Endicott et al. (1986) and Coryell and Zimmerman (1988) (major depression). Most analyses showed similar results for bipolar probands.

<sup>2</sup>Data for SCZ and NL groups from Kendler et al. (1985a); for SA and AD groups from Kendler et al. (1986).

<sup>3</sup>Sample overlaps with Gershon et al. (1982); SCZ in relatives includes all nonaffective psychoses.

<sup>4</sup>Number in table represents relatives with bipolar or unipolar disorders; the study also reports a significant increase in unipolar disorder in relatives of schizophrenic probands versus control relatives.

<sup>5</sup>Gershon et al. (1988) and Coryell and Zimmerman (1988) used mostly phone interviews; in Mendlewicz et al. (1980), the proportion interviewed in person is unclear.

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<sup>7</sup>Most SA cases were mainly affective subtype.

<sup>8</sup>SCZ in relatives includes four cases of SA-mainly schizophrenic; without these cases, 4.6% of relatives (age adjusted) of chronic SCZ probands had SCZ. Sample overlaps with Baron et al. (1982).
### Table 4. Morbid risks of schizoaffective disorder in relatives of schizophrenic, schizoaffective, affective disorder, and normal probands

<table>
<thead>
<tr>
<th>Study</th>
<th>DX CRIT</th>
<th>SA subtype</th>
<th>SCZ</th>
<th>SA-S</th>
<th>SA</th>
<th>SA-A</th>
<th>AD^2</th>
<th>NL</th>
<th>Proband groups with significant difference in familial risks of SA^1</th>
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<tbody>
<tr>
<td>Baron et al. 1982</td>
<td>RDC</td>
<td>SA-S, SA-A</td>
<td>2.3</td>
<td>1.4</td>
<td>-</td>
<td>3.2</td>
<td>4.6</td>
<td>-</td>
<td>NS</td>
</tr>
<tr>
<td>Kendler et al. 1985a,</td>
<td>DSM-III</td>
<td>SA-S, SA-A</td>
<td>1.4</td>
<td>2.7</td>
<td>-</td>
<td>0.0</td>
<td>0.1</td>
<td>SCZ, SA &gt; NL</td>
<td></td>
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<td>1986^3</td>
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</tr>
<tr>
<td>Gershon et al. 1988^4</td>
<td>RDC</td>
<td>Chronic</td>
<td>5.0</td>
<td>2.5</td>
<td>-</td>
<td>0.6</td>
<td>-</td>
<td>SCZ, SA &gt; NL</td>
<td></td>
</tr>
<tr>
<td>Scharfetter and Nusperli 1980</td>
<td>ICD</td>
<td>All</td>
<td>0.3</td>
<td>2.5</td>
<td>-</td>
<td>0.3</td>
<td>-</td>
<td>SA &gt; SCZ</td>
<td></td>
</tr>
<tr>
<td>Gershon et al. 1982^5</td>
<td>RDC</td>
<td>All^6</td>
<td>-</td>
<td>6.1</td>
<td>-</td>
<td>0.7</td>
<td>0.5</td>
<td>SA &gt; AD, NL</td>
<td></td>
</tr>
<tr>
<td>Endicott et al. 1986</td>
<td>RDC</td>
<td>Depressed^6</td>
<td>-</td>
<td>1.0</td>
<td>-</td>
<td>1.2</td>
<td>-</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Coryell and Zimmerman 1988^6</td>
<td>RDC</td>
<td>Depressed</td>
<td>0.0</td>
<td>2.5</td>
<td>-</td>
<td>1.0</td>
<td>2.0</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

Note.—An underlined value indicates that first-degree relatives of those probands had a significantly greater risk than at least one comparison group (p < 0.05), as shown in the rightmost column. DX CRIT = diagnostic criteria; RDC = Research Diagnostic Criteria; SA = schizoaffective disorder; SCZ = schizophrenia; AD = major affective disorder; NL = normal; NS = not significant.

1 All SA disorders are combined in all values and significance tests, except for Baron et al. (1982).

2 For comparison, data are shown for unipolar probands (UP), except Endicott et al. (1986) and Coryell and Zimmerman (1988) (UP psychosis), and Kendler et al. (1985a, 1986) (all AD psychoses). For relatives, data shown are all AD combined, except Scharfetter and Nusperli (1980) (all AD psychoses), and Endicott et al. (1986) and Coryell and Zimmerman (1988) (major depression). Most analyses showed similar results for bipolar probands.

3 Data for SCZ and NL groups from Kendler et al. (1985a); for SA and AD groups from Kendler et al. (1986).

4 Sample overlaps with Gershon et al. (1982); SCZ in relatives includes all nonaffective psychoses.

5 Gershon et al. (1982) and Coryell and Zimmerman (1988) used mostly phone interviews.

6 Most SA cases were mainly affective subtype.

The risk of schizoaffective disorder in the relatives of schizophrenic probands is generally low, but in the largest study (Kendler et al. 1985a) there was a statistically significant increase in risk.

5. Most schizoaffective disorders are probably not genetically independent; relatives of these probands have greater risks of schizophrenic and affective disorders. (One of the two studies of psychotic sib pairs found that schizoaffective patients typically had schizophrenic or affective sibs [Tsuang 1967], but the other did find significant concordance for presence or absence of schizoaffective diagnosis [DeLisi et al. 1987].)

The boundary between schizophrenia and mood-incongruent affective...
psychoses is also unclear. Farmer et al. (1987), reanalyzing the twin series of Gottesman and Shields (1972), found a higher monozygotic-to-dizygotic concordance ratio when co-twins with mood-incongruent affective psychosis were considered concordant with schizophrenia. Assuming polygenic inheritance, this finding would support a relationship between the disorders. Another view of their data is that, when affective disorders were excluded and only traditional spectrum diagnoses were considered concordant, the monozygotic-to-dizygotic ratio more closely resembled that seen in a modified dominant disorder (Levinson 1988).

Coryell et al. (1990a, 1990b) examined predictors of chronic delusional outcome in affective psychoses. For mania, this outcome was best predicted by thought disorder at some point with mania in remission (2 of 6 chronically delusional cases) (Coryell et al. 1990b); for depression, by mood-incongruent delusions as a predominant symptom (5 of 16 cases) (Coryell et al. 1990a). Family history was not predictive, but only 4 of 173 patients in this study had any family history of schizophrenia, and few subjects had a mainly schizophrenic type of schizoaffective disorder (10 depressed and 4 manic subjects). It is thus unclear whether chronic course and mood-incongruent delusions represent evidence of a genetic relationship to schizophrenia.

Can schizoaffective (mainly schizophrenic) disorders be reliably diagnosed? There are no data for diagnosticists working totally independently (i.e., not from the same interview material or summaries) or for reliability over time. Patients, families, and clinical records are usually imprecise about the nature and time course of affective features. Endicott et al. (1986) found that 50 percent of schizoaffective subjects exaggerated their affective symptoms.

Further, depression is extremely common in schizophrenias (reviewed in Williams and Dalby [1988] and DeLisi [1990]). In the one relevant long-term, prospective study (Guze et al. 1983; Martin et al. 1985), depressive episodes were reported by 57 percent of subjects who were diagnosed as schizophrenic (by St. Louis criteria) by blind raters at both baseline and 8- to 12-year followup; this depressed schizophrenic subgroup had an elevated familial risk for schizophrenia but not for affective disorders. Manic syndromes may be less common in schizophrenia, but there are no comparable studies. Patients with chronic schizophrenic symptoms who meet current criteria for schizoaffective mania seldom respond to treatments for mania (Levinson and Levitt 1987). Kendler et al. (1986) reported that their schizoaffective manic-mainly schizophrenic probands, when examined separately, had an increased familial risk of schizophrenia and not of affective disorders; no other family study has reported on this subgroup.

We conclude that some RDC schizoaffective (mainly schizophrenic) or DSM-III-R (American Psychiatric Association 1987) schizoaffective disorders are genetically related to schizophrenia. This group may still be heterogeneous, but data for other subtyping dimensions are even more limited. The RDC main affective subtype appears to be related to other primary affective disorders.

Given the limitations of current diagnostic methods, we believe that all investigators draw on their clinical biases to differentiate schizophrenic, affective, and schizoaffective disorders. Considerations may include the relative duration of affective and schizophrenic symptoms, whether affective symptoms are "convincing" (compared with typical affective patients), treatment response, clinical "feel" of remissions, and predominance of depression versus manic or bipolar symptoms. These issues should be subjected to further study, including multicenter and multinational efforts. It may be useful for linkage investigators to describe (and, if possible, to operationalize) their approach to such issues as schizoaffective criteria and subtypes; any study-specific rules used to differentiate schizoaffective diagnoses; whether schizoaffective diagnoses were permitted in probands; any limitations in the number or proportion of schizoaffective cases within a pedigree; and data on interrater reliability.

Other Nonaffective Psychoses

Schizophreniform disorder (schizophrenic symptoms for fewer than 6 months) is usually a prelude to schizophrenic illness (Kane et al. 1982; Guze et al. 1983), but it sometimes precedes affective (usually bipolar) disorders (Guze et al. 1983). One schizophreniform sample had an increased familial risk of affective disorder (Sautter and Garver 1985). A minimum followup period might therefore be required for this diagnosis. Few relatives of schizophrenic probands receive schizophreniform diagnoses, presumably because single lifetime episodes are uncommon.

Such cases might be excluded from studies emphasizing chronicity but included where the emphasis was on a spectrum concept or transmission of psychosis.

Relatives of schizophrenic patients have been found to be at increased risk for DSM-III atypical psychosis
(Kendler et al. 1985a), RDC unspecified functional psychosis (Gershon et al. 1988), and uncertain schizophrenia (St. Louis; Guze et al. 1983); the latter study showed similar familial patterns for definite and probable schizophrenic probands. Thus, considering a broad group of nonaffective psychoses as part of the spectrum in relatives can be justified. The practical dilemma is differentiating such cases from, for example, atypical affective disorders or dissociative disorders.

**DSM-III paranoid disorder (DSM-III-R delusional disorder)** encompasses "nonbizarre" delusions without prominent hallucinations or thought disorder. The largest relevant modern family study (Kendler et al. 1985b) reported significantly more paranoid disorder in relatives of schizophrenic probands versus controls; a smaller study (Baron et al. 1985b) did not, nor did a reanalysis of the relatives of schizophrenic adoptees (Kendler et al. 1981b). The relatives of delusional probands (in older studies, all with methodological limitations) had increased risks for schizophrenia in some studies but not in others, as reviewed by Kendler and Davis (1981), who concluded that this increased risk may be only slight. These data are similar to those for schizotypy and schizophrenia (see below), where the milder disorder is common in the relatives of probands with the more severe disorder, but not the other way around; we suggest caution in prematurely concluding that all delusional disorders are genetically independent of schizophrenia. Winokur (1986) suggested that family studies should differentiate three groups: simple delusional disorder (delusions that are "possible, however implausible;" e.g., reference, jealousy, or persecution); hallucinatory delusional disorder ("possible" delusions with hallucinations); and paranoid schizophrenia ("impossible" delusions, usually with hallucinations).

We have seen a number of relatives of schizophrenic probands with episodic or chronic delusions that have been a challenge to classify along the continuum from schizotypal symptoms (unusual perceptions and beliefs, nondelusional paranoia, "transient" psychotic experiences), to "possible" delusions (delusional disorder), to "impossible" delusions (atypical psychosis or schizophrenia). Further, eliciting the fully delusional nature of the symptoms has sometimes required efforts well beyond the usual structured interview format. We tentatively suggest that interviewing and diagnostic methodologies in this area remain tenuous and that meaningful variations are likely to occur across studies. It would be helpful if investigators reported their approach to these issues and described the features of ambiguous cases.

**Schizotypal and Paranoid Personality Disorders**

Kety et al. (1975) showed that the biological relatives of adopted schizophrenic subjects in Denmark were more likely than relatives of control adoptees to have a "spectrum" of disorders, including longstanding nonpsychotic disorders. A related study reached the same conclusion about the adopted-away children of schizophrenic versus control parents (Rosenthal et al. 1971), a finding confirmed by Tienari et al. (1987). "Latent" or "borderline" schizophrenia was diagnosed in the Kety studies according to previous clinical descriptions and Scandinavian diagnostic practice. Spitzer et al. (1979) used the narrative descriptions of the relatives of these subjects to derive the DSM-III criteria for schizotypal personality disorder. In a twin study, Torgersen (1984) found that schizotypal and borderline personality disorders were genetically independent. Parnas et al. (1982) and Parnas and Jorgensen (1989) studied 15-year-old children of schizophrenic mothers and found that those who later developed schizophrenia or schizotypal personality disorder had more schizotypal traits ("peculiar" and paranoid traits, thought disorder). The history of the schizotypal concept has been reviewed by Kendler (1985); paranoid personality disorder has received less attention.

Table 5 summarizes data from direct-interview family studies on spectrum disorders in the relatives of schizophrenic patients. In four reanalyses of the Danish adoption studies, in which cases were blindly rediagnosed by DSM-III criteria, the biological relatives of schizophrenic subjects continued to show increased schizotypal and paranoid personality diagnoses (Kendler et al. 1981a; Gunderson et al. 1983; Lowing et al. 1983; Kendler and Gruenberg 1984). Only one completed family study (Baron et al. 1985b) fulfills the methodological criteria of mostly blind, in-person interviews with most first-degree relatives by means of a structured interview schedule for
Table 5. Studies of the relationship between schizophrenia and spectrum personality disorders

<table>
<thead>
<tr>
<th>Study</th>
<th>DX CRIT</th>
<th>Design</th>
<th>Personality Disorder Interview Schedule</th>
<th>% of subjects directly interviewed</th>
<th>Risk for index relatives &gt; control relatives?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kendler et al. 1981a</td>
<td>DSM-III</td>
<td>SCZ adoptees(^1)</td>
<td>None</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>Kendler and Gruenberg 1984</td>
<td>DSM-III</td>
<td>SCZ adoptees(^1)</td>
<td>None</td>
<td>90</td>
<td>Yes</td>
</tr>
<tr>
<td>Gunderson et al. 1983</td>
<td>DSM-III, OWN</td>
<td>SCZ adoptees(^1)</td>
<td>None</td>
<td>100(^2)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lowing et al. 1983</td>
<td>DSM-III</td>
<td>Adopted-away(^3)</td>
<td>None</td>
<td>100</td>
<td>Yes(^4)</td>
</tr>
<tr>
<td>Baron et al. 1985b</td>
<td>DSM-III, RDC</td>
<td>Family</td>
<td>SIB/SSP</td>
<td>83</td>
<td>Yes</td>
</tr>
<tr>
<td>Frangos et al. 1985</td>
<td>DSM-III</td>
<td>Family</td>
<td>None</td>
<td>78</td>
<td>Yes(^4)</td>
</tr>
<tr>
<td>Gershon et al. 1988</td>
<td>DSM-III, RDC</td>
<td>Family</td>
<td>SIDP</td>
<td>24</td>
<td>Yes(^4)</td>
</tr>
<tr>
<td>Coryell and Zimmerman 1988</td>
<td>DSM-III, RDC</td>
<td>Family</td>
<td>SIDP</td>
<td>31</td>
<td>No</td>
</tr>
<tr>
<td>Kendler 1988</td>
<td>DSM-III</td>
<td>Family</td>
<td>SISS</td>
<td>((^5))</td>
<td>-</td>
</tr>
</tbody>
</table>

Note.—Study designs: SCZ adoptees = biological relatives of adoptees with schizophrenia were compared with biological relatives of psychiatrically well adoptees; Family = relatives of probands with schizophrenia compared with relatives of controls. DX CRIT = diagnostic criteria; RDC = Research Diagnostic Criteria; SCZ = schizophrenia; SPD = schizotypal personality disorder; PPD = paranoid personality disorder; SIB/SSP = Schedule for Interviewing Borderlines, which includes Schedule for Schizotypal Personalities (Baron and Gruen 1980; Baron et al. 1981); SIDP = Structured Interview for DSM-III Personality Disorders (Pfohl et al. 1982; Stangl et al. 1985); SISS = Structured Interview for Schizophrenia Spectrum (Kendler, unpublished); Yes = schizophrenic probands’ relatives had increased (p < 0.05) risk of the disorder(s); No = there was no significant increase; OWN = authors’ criteria.

\(^1\)The study compared relatives of adoptee probands with (index) and without (control) schizophrenia.
\(^2\)Only the 27 probands and relatives with “borderline schizophrenia” were reviewed, plus 27 comparison cases.
\(^3\)The study compared adopted-away offspring of probands with (index) and without (controls) schizophrenia.
\(^4\)SPD and schizoid personality were combined, plus PPD in Frangos et al. (1985) and in Gershon et al. (1988), plus borderline personality in Gershon et al. (1988).
\(^5\)Preliminary data for direct-interview study, but % interviewed not given.

Preliminary results are available from a study using similar methods (Kendler 1988). These two studies and that of Frangos et al. (1985) confirmed the finding of increased spectrum personality disorders in relatives of schizophrenic probands. Coryell and Zimmerman (1988) found no such increase, but it is not clear whether this was because of differences in the sample or because most interviews were conducted by telephone (Kendler 1988).

Relatives with schizotypal or paranoid personality disorder are thus candidates for inclusion as “affecteds” in linkage analysis, but a number of controversies remain. The specificity of the relationship to schizophrenia is not yet proven: one study found increased schizotypal personality disorder in relatives of affective disorder probands (Squires-
Wheeler and Erlenmeyer-Kimling (1989); a second study did not (Coryell and Zimmerman 1989), but in the second study, most relatives were interviewed by telephone and there was no excess of spectrum disorders among relatives of schizophrenic probands, either. Control relatives have also been reported to have a relatively high incidence of both schizotypal (2.1%) and paranoid (2.7%) personality disorders, although significantly lower than in the relatives of schizophrenic patients (Baron et al. 1985b). There is also considerable overlap among DSM-III personality diagnoses (Zimmerman and Coryell 1989). Further, schizophrenia is not common in the relatives of probands selected for schizotypal personality (Torgersen 1984; Baron and Risch 1987; Siever et al. 1990). This could be due to dissociation of the genetic factors related to schizotypy versus psychosis, to small sample sizes, to less severe expression of the disorder in these families, or to heterogeneity of schizotypal personality (i.e., many probands with these traits have a different etiology than schizotypal relatives of schizophrenic individuals).

Another diagnostic issue is that it is unclear how to validate schizotypal and paranoid personality diagnoses made by structured interviews against other standards; these interview schedules do show good interrater reliability, however (Baron et al. 1981). There is still controversy over diagnostic criteria: Gunderson et al. (1983) criticized DSM-III for emphasizing “positive” psychosis-like symptoms rather than “negative” symptoms such as oddness, anhedonia, and flatness of affect. DSM-III-R partially reflects this criticism, but the modifications of the schizotypal and paranoid personality criteria have not been independently validated. Another issue is whether it was valid to substitute the schizotypal personality construct for the older diagnosis of simple schizophrenia encompassing schizophrenia-like changes in attention, emotions, interest, and speech but without overt psychotic symptoms (Lancet Editorial 1990). The inclusion of this entirely distinct diagnosis in the 10th edition of the International Classification of Diseases (World Health Organization 1989) raises the question whether investigators should report diagnoses of all subjects by multiple systems, including ICD-10, to enhance comparability of studies.

The features of DSM-III-R schizoid personality disorder (emphasizing “negative” symptoms) might also be relevant here (Gunderson et al. 1983; Torgersen 1985). Frangos et al. (1985) and Gershon et al. (1988) combined schizoid with schizotypal and paranoid personality disorders and found that relatives of schizophrenic probands had an increased risk of this group of disorders. Baron et al. (1985b) found a nonsignificant difference in the incidence of schizoid personality disorder in relatives of schizophrenic (1.6%) versus control (0%) relatives. It is thus unclear whether schizoid personality, in the absence of other schizotypal features, discriminates relatives of schizophrenics versus controls.

We conclude that relatives with schizotypal and paranoid personality disorders are likely to provide significant information in linkage studies (evidence is less clear for schizoid personality disorder), but more data are needed to improve diagnostic categories and criteria. Linkage studies will facilitate progress in this area if they provide for the collection of rich descriptive material, including videotapes where possible, in addition to structured ratings.

Affective Disorders as Exclusion Criteria

Many family studies support the genetic independence of schizophrenic and affective disorders (Perris 1966; Mendlewicz et al. 1980; Scharfetter and Nusperli 1980; Baron et al. 1982; Gershon et al. 1982; Guze et al. 1983; Frangos et al. 1985; Kendler et al. 1985b), but there is considerable symptomatic overlap. If these disorders are independent, then excluding families with variants of affective psychoses from schizophrenia linkage studies would be critical. Because relatives of affective disorder probands have high rates of psychiatric disorder, it is plausible that schizophrenia linkage studies could be confounded by families with severe variants of affective psychosis, or families in which assortative mating has resulted in diverse, and sometimes genetically mixed, disorders within the pedigree.

It is unclear when to exclude families for the presence of affective disorders and when to exclude individuals with such disorders. A practical problem is that major depression is too common by current checklist criteria to permit excluding all families with members with this diagnosis. Bipolar and psychotic unipolar diagnoses are less common and more readily identified.

Affective Disorders as Inclusion Criteria

Despite evidence for a “two-psychosis” model, several investigators have urged consideration of a “unitary” model of a schizophrenic-affective continuum (Crow 1980; Gershon et al. 1988; Karlsson 1988). Two linkage studies have treated schizophrenic and affective psychoses...
as genotypically equivalent within the same pedigrees (selected for presence of schizophrenia) (Detera-Wadleigh et al. 1989; St. Clair et al. 1989). Gershon et al. (1988), at variance with most other studies, have recently reported increased major affective disorder in the relatives of schizophrenic probands versus controls. Based on a family study of affective disorders, Endicott et al. (1986) proposed that familial vulnerabilities to psychosis and to affective disorder may be transmitted separately; a similar model can be hypothesized for psychosis and schizotypy, although without supporting data.

One problem is that differentiating between genotypic overlap and the effects of assortative mating is currently impossible. For example, we lack sufficient data on psychiatric disorders in the relatives of unaffected parents of schizophrenic and control probands, data that might determine whether the ancestors of schizophrenic probands have an increased risk of affective disorders or whether the likelihood of having schizoaffective or bipolar siblings is predicted by affective disorders in ancestors.

We favor the view that the greatest clarity will be achieved by identifying linkage in "pure" schizophrenic and affective pedigrees and then determining whether there is an overlap in the relevant loci. However, if there are loci with differential effects on psychosis and schizotypy, then studies of pedigrees with diverse or mixed psychoses might provide information that would be lost in studies including many relatives with nonpsychotic spectrum disorders. We would question the inclusion of classical affective psychoses in such studies.

### Other Psychiatric Disorders and Symptoms

Relatives of schizophrenic probands are probably not at increased risk for anxiety, minor depressive disorders, or alcoholism (Kendler and Gruenberg 1984; Baron et al. 1985b; Kendler et al. 1985a). On the other hand, the schizophrenia spectrum probably extends beyond current diagnostic criteria. Baron et al. (1985b) found increased "probable" schizotypal personality (two to three DSM-III criteria) in the relatives of schizophrenic probands (12.2%), although specificity was poor in that control relatives also had a high risk (6.5%). Sherrington et al. (1988) found 10 relatives in their pedigrees who met RDC criteria for major or minor depressive or phobic disorders or alcoholism, some of whom had been treated with antipsychotic medications; the maximum lod score increased when these relatives were treated as affected. These results have not been replicated. Although identifying such a group for secondary analyses in linkage studies may be useful, it would be helpful if investigators would attempt to specify their definition and describe their cases. For example, Sherrington et al. (1988) did not stress in their original published report that many of these cases were considered odd in ways that did not fit any of the RDC diagnoses (Gurling et al. 1989). (That study's term, "fringe" cases, is unfortunate in our view because of the possible pejorative colloquial connotation, at least in the United States; investigators might keep this in mind when defining and naming their broadest spectrum definition.)

### Substance Abuse as a Complicating Factor

Widespread alcohol and drug abuse among patients with schizophrenia (Mueser et al. 1990) is a potential confounding factor for linkage studies. Anecdotal reports have suggested that stimulant abuse (McLellan et al. 1979; Sato et al. 1983) or alcohol abuse (Cutting 1978) may lead to chronic psychotic illness, an intuitively appealing hypothesis not yet supported by specific data. Bowers (1987) has reviewed the literature in this area and has suggested (on the basis of proportions of State hospital first-admission diagnoses) that a dramatic increase in substance abuse around 1970 may have led several years later to an increased proportion of first-admission diagnoses of schizophrenia and paranoid disorders. Limited family study data have not, however, supported a specific etiologic role. Psychotic emergency ward patients with recent lysergic acid diethylamide (LSD) use had a family history of schizophrenia as frequently as drug-free patients (Vardy and Kay 1983). Three studies have found no significant difference in familial risk of schizophrenia between probands with and without significant substance abuse (Tsuang et al. 1982; F. Henn [personal communication, December 1986, unpublished study of State hospital patients]; Gershon et al. 1988). No studies have selected probands for a particular class of drug. It is therefore not known whether any drug can represent an etiologic rather than a precipitating or complicating factor in schizophrenia.

Two studies found an increased familial risk of affective disorders for substance-abusing schizophrenic...
describe their own approach to using morbid features were present before or exclusion criteria. We or other features as inclusion and whether schizophrenia-like pre-

were abused extensively before onset; drugs (hallucinogens, stimulants) briefer past episodes of substance use; whether psychotogenic acute exacerbations resemble typical syndromes, birth anoxia, or premorbid head trauma with known sequelae, or any premorbid brain disease with potential or observed focal signs or cognitive or personality changes. There are no clear guidelines for mildly abnormal EEGs (presumably, focal abnormalities are more problematic than nonspecific changes), borderline mental retardation, histories of birth or head trauma without known sequelae, learning disabilities, or other nonspecific findings. Because precise differential diagnosis is seldom possible, we suggest that independent diagnostic review is particularly important in such cases and that features of questionable cases be described in linkage reports.

Neurological Disorders

Some neurological disorders can be associated with psychiatric symptoms that closely resemble schizophrenia (Davison and Bagley 1969; Cummings 1985; Goldstein and Levinson 1987). Important issues for the linkage investigator are to determine whether the possibility of neurological disorder has been sufficiently evaluated and, if not, to develop inclusion and exclusion criteria. We believe most clinicians would choose to exclude cases with documented epileptic foci, primary mental retardation syndromes, birth anoxia, or premorbid head trauma with known sequelae, or any premorbid brain disease with potential or observed focal signs or cognitive or personality changes. There are no clear guidelines for mildly abnormal EEGs (presumably, focal abnormalities are more problematic than nonspecific changes), borderline mental retardation, histories of birth or head trauma without known sequelae, learning disabilities, or other nonspecific findings. Because precise differential diagnosis is seldom possible, we suggest that independent diagnostic review is particularly important in such cases and that features of questionable cases be described in linkage reports.

Other Diagnosis-Related Issues for the Linkage Model

Diagnostic Hierarchy. Many subjects receive more than one current or past diagnosis by any given diagnostic system. Most family studies have adopted hierarchies to determine when one diagnosis takes precedence over others. For example, depending on the assumptions of the investigator, certain types of affective diagnoses may take precedence over schizophrenia, or a current diagnosis of schizophrenia may supersede some types of past affective episodes. It also may be necessary to decide on a best lifetime diagnosis for a longstanding disorder that has had different features at different times (such as schizophrenia with intercurrent depression or recurrent bipolar disorder with some episodes meeting criteria for schizophrenia). Most published linkage studies have given sparse clinical information on these issues. It may be valuable to report (1) the approach to such decisions and (2) the decisions made in specific cases.

Unaffected Relatives. In linkage analyses using discrete phenotypes (“affected” vs. “unaffected”), relatives without spectrum diagnoses must be categorized as either unaffected or undiagnosed. The latter designation means that their marker genotypes could help determine parental origin of marker alleles, but they would make no other direct contribution to the lod (linkage) score. Unaffected relatives, however, influence the lod score depending on the estimate of penetrance (the likelihood of becoming ill if one has the disease genotype). A high penetrance estimate (e.g., 0.85) represents an assumption that the disease genotype usually produces illness, so that unaffected relatives are unlikely to have the disease genotype. In this case, affected and unaffected relatives carry similar weight in determining the lod score. Conversely, a low estimate of penetrance is a mathematical expression of uncertainty about unaffected relatives' genotype; these relatives then have minimal effect on the lod score (Levinson and Green 1989). Most schizophrenia linkage analyses have entered nonspectrum relatives into
their analyses as unaffected (see table 6), often using a penetrance estimate calculated from the pedigrees in their own or a similar sample, an estimate that may be inflated because the sample was selected for high density of cases (Diehl and Kendler 1989). Green (1990) has described hypothetical conditions, including overestimation of penetrance, under which a spuriously significant positive lod score could be achieved; Baron (1990) and Risch (1990) have pointed out that spurious negative linkage results could have even more serious effects on progress in this field.

Alternative methods include sib-pair and pedigree analyses where most unaffected relatives are treated as “diagnosis unknown” and thus do not affect the lod score (except by providing information on marker phase). In the Sherrington et al. (1988) study, analysis by such a penetrance-free method (considering unaffected relatives as having unknown diagnosis) yielded a nonsignificant lod score (under 3.0), compared with much higher lod scores based on a penetrance of 0.86 with unaffecteds included. This difference suggests that much of the power of the study derived from the contribution of the unaffected relatives, a contribution dependent on a penetrance model that was unlikely to be accurate. (It is also not stated which of their three diagnostic models was used for the penetrance-free analysis.) We suggest that affecteds-only methods are preferable when a disease allele is hypothesized, at least one parent in each mating must be classified with reasonable certainty as unaffected; with a recessive model, one or two parents must be unaffected to calculate linkage. This raises two sets of issues: (1) What criteria will classify a parent as affected (schizophrenia, psychosis, spectrum disorder, suspicion of a spectrum disorder, any disorder, etc.)? (2) When will bilaterality be assumed based on diagnosis of relatives of an unaffected parent (what threshold of suspicion, for what spectrum of disorders, in relatives of what degree of relatedness)? The thoroughness of the investigation of family history on the unaffected side of each mating (including the various matings on the affected side of the pedigree) may therefore be critical. This issue is discussed below in relation to the strategy adopted in the authors’ study.

Diagnostic Review. Independent consultants may be asked to review diagnoses, particularly when study diagnosticians are not blind to proband diagnosis. This procedure helps guard against the development of idiosyncratic biases within a study and may reduce controversy about diagnostic methods by leading to the exclusion of cases in which diagnostic consensus cannot be reached.

Diagnostic strategies in schizophrenia linkage studies. Table 6 lists some relevant clinical features of recent published linkage studies of schizophrenia; they are restriction fragment length polymorphism (RFLP) studies except for Goldin et al. (1987). RDC diagnoses have been commonly used, often with DSM-III or DSM-III-R diagnoses of personality disorders. Only two studies systematically assessed personality disorders. Strategies have varied widely, particularly in relation to inclusion versus exclusion of affective disorder cases and of families with bipolar disorders; but the impact of these differences has not been determined. Many of the methodological issues raised in this article were typically not clarified. Several issues are not covered in the table: none of the authors shown in the table discussed their approach to substance abuse or bilineality as exclusion criteria; only one study (Sherrington et al. 1988) used independent diagnostic reviews; only two of the studies that included schizoaffective subjects used specific criteria (DSM-III-R in both cases) to include only those with more persistent schizophrenia-like symptoms (Aschauer et al. 1990; Crowe et al. 1990); and two studies excluded families for family history of bipolar disorder (Sherrington et al. 1988; McGuffin et al. 1990) while two performed analyses that included bipolar relatives as part of the schizophrenia spectrum (Detera-Wadleigh et al. 1989; St. Clair et al. 1989). It can be seen in table 6 that studies have varied in their definitions of the schizophrenia spectrum and in their use of alternative models for linkage analyses.

Example of a diagnostic strategy. These issues will be illustrated by describing the present authors’ ongoing schizophrenia linkage study at the Medical College of Pennsylvania (Philadelphia), Graylands Hospital (Perth, Australia), and Wolston Park Hospital (Brisbane, Australia). The sample will eventually consist of 50
Table 6. Diagnostic methods and models in published schizophrenia linkage studies

<table>
<thead>
<tr>
<th>Study</th>
<th>MAJ DIS</th>
<th>PERS DIS</th>
<th>No. of diagnostic models</th>
<th>DX CRIT</th>
<th>SCHED</th>
<th>DX CRIT</th>
<th>SCHED</th>
<th>SA</th>
<th>UFP</th>
<th>SFORM</th>
<th>SPD</th>
<th>PPD</th>
<th>SZOID</th>
<th>MDD</th>
<th>BP</th>
<th>Other</th>
<th>Estimates of penetrance</th>
</tr>
</thead>
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<tr>
<td>Goldin et al. 1987</td>
<td>RDC</td>
<td>SADS-L</td>
<td>D3 SIDP</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>B</td>
<td>B</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>0.50-0.999</td>
</tr>
<tr>
<td>Sherrington et al. 1988</td>
<td>RDC+</td>
<td>SADS-L</td>
<td>D3</td>
<td>3</td>
<td>-</td>
<td>All</td>
<td>All</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>B,C</td>
<td>C</td>
<td>-</td>
<td>C</td>
<td>-</td>
<td>0.73-0.995</td>
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<tr>
<td>Kennedy et al. 1988</td>
<td>D3 + F</td>
<td>SADS-L</td>
<td>-</td>
<td>1</td>
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<td>RDC+</td>
<td>SADS-L</td>
<td>?</td>
<td>4</td>
<td>All</td>
<td>All</td>
<td>D</td>
<td>-</td>
<td>-</td>
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<td>C,D</td>
<td>B,C,D</td>
<td>D</td>
<td>0.66-0.94</td>
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<tr>
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<td>RDC</td>
<td>SADS-L</td>
<td>D3 SIDP</td>
<td>3</td>
<td>All</td>
<td>-</td>
<td>B,C</td>
<td>B,C</td>
<td>B,C</td>
<td>C</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>0.95</td>
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<tr>
<td>Crowe et al. 1990</td>
<td>D3R</td>
<td>CASH</td>
<td>D3R SSP</td>
<td>3</td>
<td>B,C</td>
<td>-</td>
<td>B,C</td>
<td>B,C</td>
<td>-</td>
<td>C</td>
<td>-</td>
<td>-</td>
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<td>0.5-0.9</td>
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<tr>
<td>Aschauer et al. 1990</td>
<td>D3R</td>
<td>DIS</td>
<td>D3R DIS</td>
<td>3</td>
<td>B,C</td>
<td>-</td>
<td>B,C</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>C</td>
<td>-</td>
<td>-</td>
<td>0.54-0.85</td>
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<td>PSE</td>
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<td>-</td>
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DX CRIT = diagnostic criteria; RDC = Research Diagnostic Criteria; SA = schizoaffective disorder; SCZ = schizophrenia; AD = major affective disorder; NL = normal; PPD = paranoid personality disorder; SPD = schizotypal personality disorder; MAJ DIS = major psychiatric disorders; PERS DIS = personality disorders; D3 = DSM-III; D3R = DSM-III-R; F = Feighner et al. (1972) criteria; SADS-L = Schedule for Affective Disorders and Schizophrenia, lifetime version; CASH = Comprehensive Assessment of Symptoms and History (Andreasen 1985); DIS = Diagnostic Interview Schedule (Robins et al. 1981); UFP = unspecified functional psychosis (RDC) or atypical psychosis (D3, D3R); SFORM = D3 or D3R schizotypal disorder, including RDC schizophrenia with duration < 6 months; SZOID = schizoid personality disorder; MDD = major depressive disorder; BP = bipolar disorder; other = other psychiatric disorders.

1Shown is the number of diagnostic sets used for separate linkage analyses; capital letters indicate in which model the diagnosis was included, in addition to schizophrenia (A = model with fewest diagnoses). Some studies permitted more diagnoses than were actually observed; the table shows the latter.

2All psychiatric diagnoses; Sherrington and Aschauer list individual diagnoses including anxiety and minor depressive and substance abuse disorders.

3The estimate, or range of estimates, of disease penetrance used in linkage analyses.

4This study tested linkage to HLA rather than RFLP markers, but used similar methods otherwise.

5Unaffected relatives were also excluded from one analysis (see text).

6Some deceased subjects were diagnosed using old clinical information.

7DSM-III-R delusional disorder only.

8Depressive psychosis with mood-incongruent delusions only.
This study is presented briefly to illustrate the articulation of a diagnostic model. The design of this study raises many issues that are not addressed in this article, such as the selection of “dominant-looking” families and the use of multiple small families drawn from an ethnically mixed population. Of relevance here is the diagnostic model. We do not suggest it is the best model, but rather that it is one of many alternative diagnostic and genetic models that need to be tested to make progress in this area.

The study model assumes that schizophrenic disorders are genetically independent from classical affective disorders (which are thus systematically excluded) and that schizophrenia shares genetic factors with the spectrum disorders. (The highest priority is nevertheless placed on recruitment of families with multiple members with overt psychoses.) Although we have collected preliminary data (in the Australian subjects) on eye-tracking dysfunction and on questionnaire assessment of schizotypy, we believe that diagnostic categories remain the most valid indices of genetic relatedness to schizophrenia. Thus, inclusion and exclusion criteria are based on diagnostic assessment.

1. Selection of probands. One individual in each family must have RDC definite schizophrenia with chronic course (ill for most of 2 years) and must also meet several St. Louis criteria (insidious onset, failure to return to premorbid function, age of onset < 35 for males but modified to < 45 for females). Schizoaffective cases are excluded as probands. There is a set of study-specific criteria (available from the authors on request) for lifetime diagnosis of schizophrenia versus schizoaffective disorder in the presence of affective features. These criteria favor (1) schizophrenia when affective features have been brief, sporadic, or subsyndromal; (2) schizoaffective disorder when affective syndromes have been present during most psychotic exacerbations; and (3) exclusion from either diagnosis in the presence of certain classical manic or psychotic depressive features. The effect of these criteria is to permit probands to be given a lifetime diagnosis of schizophrenia in the presence of the kinds of early, brief, or interepisodic periods of affective symptoms (particularly depression) that are common in schizophrenia, but not if many psychotic episodes include concurrent schizophrenic and affective syndromes.

All other criteria described below apply only to relatives other than the proband.

2. Criteria for schizophrenia in affected relatives. Other relatives are considered schizophrenic if they meet definite or probable RDC criteria (with 6 months’ duration) or DSM-III-R criteria.

3. Schizoaffective disorders. The proband may not have a lifetime diagnosis of schizoaffective disorder. Relatives are included who have RDC schizoaffective disorders and who meet criteria for both the mainly schizophrenic and chronic subtypes; there are additional study-specific criteria to exclude relatives with ambiguous features that are suggestive of primary affective disorder. Pedigrees are excluded if two relatives are schizoaffective. (However, as discussed above for probands, the study-specific criteria permit a lifetime diagnosis of schizophrenia even if affective syndromes have been present briefly or only before or early in the course of schizophrenia.)

4. Other psychoses. DSM-III-R schizoaffective disorder (with minimum 1-year followup), atypical or brief reactive psychosis, and delusional disorder are included in the absence of concurrent prominent affective or dissociative features. Concurrent longstanding spectrum personality diagnoses will also be recorded in cases of atypical psychoses to permit separate examination of cases without schizotypal or paranoid features.

5. Schizotypal and paranoid personality disorders. These criteria are included (DSM-III-R) with a conservative threshold for each (based on a structured interview modified from Baron et al. [1981] and other sources of information), in the absence of prominent concurrent affective features. Additional criteria (Gunderson et al. 1983; McGlashan 1987) are also rated. Subsidiary analyses will be considered if there are “suspected” spectrum cases, including schizoid personality disorder.

6. Affective disorders. Pedigrees, or sections of pedigrees, are excluded if bipolar disorder or depressive psychosis is present or suspected in any affected member’s relative (third de-
gree or closer—the rationale for this criterion is similar to that discussed below for bilateral illness); or if an affected member's parent has recurrent major depression. Affective diagnoses will not be treated as affected cases, with the exception of certain schizoaffective disorders as described above.

7. Other disorders. None are included in the spectrum.

8. Substance abuse. Cases are excluded from the primary analysis if clinically significant stimulant or hallucinogen abuse or alcoholism preceded the onset of the psychiatric disorder, or if there have been no exacerbations without recent abuse.

9. Neurological disorders. Individuals are excluded for epilepsy or other neurological disorders that may produce schizophrenia-like symptoms, unless there was a prior onset of schizophrenia (e.g., longstanding chronic schizophrenia with a recent stroke). No diagnosis is made if mental retardation is sufficiently severe to complicate assessment of symptoms and course of illness. Clinical judgment with independent review is applied in cases of preexisting mental retardation or head trauma; exclusion usually results.

10. Diagnostic hierarchy. A best-estimate consensus lifetime diagnosis is made for each disorder (e.g., if there appears to be a single chronic or recurring disorder, but slightly varying clinical features result in different diagnoses for different episodes, a single lifetime diagnosis is made whenever possible). A diagnostic hierarchy is then applied: affective diagnoses (including RDC schizoaffective-mainly affective subtype) take precedence, followed by schizoaffective-mainly schizophrenic, chronic or subchronic schizophrenia (RDC modified for 6 months' duration, or DSM-III-R), acute or probable schizophrenia, delusional disorder, schizophreniform, nonaffective brief reactive psychosis, atypical psychosis, delusional disorder, and schizotypal or paranoid personality or both.

11. Unaffected relatives are considered undiagnosed for linkage analysis, except for unaffected parents of affected individuals, and obligate carriers. For example, in a dominant model an unaffected individual whose parent and child are both affected would be considered a carrier, but there must be three or more affected family members with definite diagnoses in addition to any obligate carriers for the family to be included.

12. Assessment of bilaterality (bilineality). No affected individual can have bilateral (bilineal) familial illness; that is, on one parental side there must be no relative (within three degrees of anyone entered into linkage analysis as unaffected) with a schizophrenia spectrum disorder or any psychotic disorder by direct interview or by family history report. The bias is toward exclusion for bilaterality, that is, if a deceased grandparent is described as "odd" and isolated, and no additional information is available, that side of the family would be considered affected. This criterion results in the exclusion of any family or branch of a family that would not be informative for linkage without this individual and his or her descendants. For example, a family would be excluded if a living parent and two children were ill but both grandparents on the affected side were reportedly either psychotic or unusually eccentric or suspicious. Or if a subject had two ill parents and was therefore excluded, studying the family constellation of one of the parents and that parent's ill sibling and parent still would be possible.

The criterion of three degrees of relatedness was based on the following rationale. Our goal was to arrive at some approximation of 95 percent certainty that an unaffected parent did not share a nonpenetrant disease allele with an ill relative. Third-degree relatives share 12.5 percent of their genes, so in the simple case of a dominant major locus, the odds of these two relatives sharing an allele at that locus is at most 12.5 percent, but it is actually less because (depending on the penetrance of the disease allele) the well parent is more likely to be genotypically normal than a nonpenetrant carrier. At very low penetrance, the likelihood could be above 5 percent. Therefore, we arrived at the criterion that unaffected parents could have ill relatives only in the fourth degree, which should lower the odds, at least in the simple case, to below 5 percent; further, it is practical to obtain family histories to three degrees in most cases. This criterion also ignores the frequency of schizophrenia in the population because it is so low; for a study of a more common disease (such as depression), this criterion might be too strict. Without knowing the actual mode of inheritance of schizophrenia, it cannot be determined whether this criterion is appropriate, and certainly other approaches are defensible.

13. Longitudinal diagnostic follow-up will be attempted during the study by maintaining contact with families and arranging for repeat interviews at least 1 year after initial assessment.

14. Independent diagnostic reviews are completed by experienced investigators at another institution; consensus diagnoses are reached in cases of disagreement between the two groups.
15. Diagnostic reliability is assessed on an ongoing basis by arranging, at most diagnostic interviews, for an observer-rater in addition to the interviewer. These independent ratings are saved for periodic statistical reliability analysis, and a case conference is held to establish consensus symptom ratings and diagnoses.

Individuals or families may be tagged during diagnostic assessment as excluded from primary data analysis, but they may be considered sufficiently likely to have a spectrum disorder to be included in secondary analyses (e.g., schizophrenia with excessive early substance abuse, but with impressive schizophrenic symptoms and course). When most of the sample has been collected, the investigators and diagnostic consultants (still blind to genotyping data) will consider the distribution of diagnoses and tagged cases in the pedigrees and finalize the alternative diagnostic sets for linkage analysis so that narrower and broader definitions of the schizophrenia spectrum can be tested.

Conclusion

Schizophrenia linkage studies require the formulation of strategies for selecting affected relatives, based on assumptions about the relationship between schizophrenia and other psychiatric disorders. Every such strategy includes explicit or implicit decisions about the issues discussed above. It is proposed that progress in this area will be facilitated by further investigation of these issues. A logical conclusion of this discussion is the suggestion that investigators should specify a diagnostic model or models in advance of undertaking linkage analysis, and that any post hoc testing of alternative models should be acknowledged in published reports. Further, it is recommended that reports of linkage studies should include more detailed clinical information, including both clearly defined inclusion-exclusion criteria and information about particular cases or groups of cases with unusual or ambiguous features. This inclusion may make it easier to compare studies and will contribute to the articulation and perhaps the eventual resolution of the relevant diagnostic issues.

Several issues stand out from the rest. Criteria for selection of probands deserve special attention. Interpretation of the boundaries among schizophrenia and schizoaffective and affective disorders is crucial, yet all current diagnostic criteria give the investigator considerable latitude. Accurate specification of the diagnostic model seems to require both the use of a schizoaffective subtyping scheme and a discussion of the study’s approach to the vagaries of this diagnosis. Similar issues exist in relation to other spectrum diagnoses. The approach to investigating possible bilateral family history is of major importance and has not been adequately stressed or described in psychiatric linkage reports to date.

We again urge investigators in this field to consider the advantages of linkage analysis methods that rely primarily on information from affected family members. Because the mode of inheritance of schizophrenia is unknown and the edges of the diagnostic spectrum are blurred, there is no valid way to estimate standard penetrance functions; the linkage information obtained from “well” relatives is likely to be spurious in many cases. The importance of this point is illustrated by the difference in maximum lod scores reported by Sherrington et al. (1988) between an analysis using a high penetrance estimate versus a form of affecteds-only analysis. As Ott (1990) has also pointed out, reliance on affecteds-only methods for complex diseases would have resulted in a more cautious interpretation of the Sherrington et al. results, a caution that now appears justified in the light of numerous negative studies (McGuffin et al. 1990). In fact, if one considers only the linkage information to be expected from affected relatives (plus obligate carriers and the well parents of affecteds) and the low information content of most available markers, then most of the reported DNA marker studies of schizophrenia must be considered small and preliminary, a point that has been neglected in the highly publicized controversy over the chromosome 5 issue.

In a commentary published after the present article was submitted for publication, Baron (1990) made a number of similar suggestions for linkage studies of psychiatric disorders, including increasing the threshold of significance for the lod score, designation of unaffected relatives as “diagnosis unknown,” clear specification of diagnostic models, avoidance of pedigrees with bilineal illness, and periodic checking of diagnostic reliability. He differs from the illustrative model presented in this article in placing more stress on use of quantitative clinical or biological covariates and in deemphasizing analyses based on spectrum diagnoses.

In our view, the “best” linkage strategy for schizophrenia cannot be determined, but many strategies can be defended on the basis of available data. Progress is likely to result from the testing of diverse approaches. Comparison and understanding of these studies will depend in part on investigators’ willingness to report detailed information about their clinical-diagnostic methods and deci-
sions. If, in addition, we emphasize results based on conservative analytic methods (such as affecteds-only linkage analyses) and are cautious about unreplicated results, we can hope to keep findings in perspective. Failure to do so may bring about premature disillusionment among colleagues and the general public with a field that has barely begun to find its way in what is likely to be a long and arduous search for progress.

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