The Genetics and Biochemistry of Paranoid Schizophrenia and Other Paranoid Psychoses

by Kenneth S. Kendler and Kenneth L. Davis

Abstract

Genetic and biochemical findings in paranoid schizophrenia and other paranoid psychoses are reviewed. Although the data suggesting a lower genetic loading for schizophrenia in paranoid versus nonparanoid schizophrenia are unclear, paranoid schizophrenia does, to a limited extent, breed true within families. Monozygotic twins concordant for schizophrenia tend to be either both paranoid or both nonparanoid schizophrenics. In all studies, the risk for schizophrenia in the relatives of patients with paranoid psychosis is close to that found in the normal population. Genetic studies provide no evidence for a link between affective illness and either paranoid schizophrenia or paranoid psychosis. Although reports of low platelet monoamine oxidase activity in paranoid schizophrenia have not been confirmed, recent results suggest that brain norepinephrine levels may be higher in paranoid than in nonparanoid schizophrenics. Genetic and biochemical findings suggest some differences between paranoid and nonparanoid schizophrenia, but definitive clarification of the relationship between these two syndromes must await future research. From a genetic perspective, paranoid psychosis appears to bear little relationship to schizophrenia.

This article will review the genetics and biochemistry of paranoid schizophrenia and the nonparanoid psychoses. The aim of this review is to apply the genetic and biochemical evidence to the three most frequently posed nosologic questions about paranoid schizophrenia and the paranoid psychoses. First, what is the relationship between paranoid and nonparanoid schizophrenia? Second, what is the relationship between schizophrenia and the paranoid psychoses? Third, what is the relationship between these two disorders and affective illness?

No review can be more precise than the literature being reviewed. As outlined elsewhere in this issue (Kendler and Tsuang 1981), there is great variability in the diagnostic criteria that have been used in the diagnosis of paranoid schizophrenia and the paranoid psychoses. Worse still, many authors do not clearly state their diagnostic criteria for paranoid schizophrenia. The situation is better in the paranoid psychoses where all studies reviewed provide sufficient information to be sure that the paranoid psychotic patients studied meet the general definition of a delusional psychosis without schizophrenic, organic, or prominent affective features. Where possible, the criteria used by each investigator will be outlined in tabular form. Unfortunately, it is not usually possible to determine how much of the lack of consistency seen in the results of different investigators is due to the variability of diagnostic criteria.

Tables will be used to summarize the primary data and the text will be reserved for summary and comment. Statistical analysis is either as presented by the original author, or is by chi-square test (Camilli and Hopkins 1978, 1979).

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<table>
<thead>
<tr>
<th>Study</th>
<th>Par schiz (n)</th>
<th>Relative</th>
<th>Age correction</th>
<th>Age of risk</th>
<th>% morbid risk for schiz in relatives of probands with:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulsz (1932)</td>
<td>31 Sibs</td>
<td>AW</td>
<td>16-40</td>
<td>5.4</td>
<td>18.0*** 5.1 6.8</td>
</tr>
<tr>
<td>Kallmann (1938)</td>
<td>150 Sibs &amp; Child</td>
<td>AW</td>
<td>15-45</td>
<td>6.3</td>
<td>7.4 9.6* 8.2</td>
</tr>
<tr>
<td>Weinberg &amp; Lobstein (1943)</td>
<td>41 Parents &amp; Sibs &amp; child</td>
<td>AW</td>
<td>21-40</td>
<td>3.1</td>
<td>9.7** 8.3** 8.6**</td>
</tr>
<tr>
<td>Hallgren &amp; Sjogren (1959)</td>
<td>24 Sibs</td>
<td>Ind</td>
<td>15-45</td>
<td>4.7</td>
<td>7.0 8.5 7.7</td>
</tr>
<tr>
<td>Garrone (1962)</td>
<td>114 Sibs &amp; Parents &amp; Sibs &amp; parents</td>
<td>AW</td>
<td>15-70</td>
<td>11.1</td>
<td>— — 12.1</td>
</tr>
<tr>
<td>Winokur et al. (1974)</td>
<td>62 Parents &amp; sibs</td>
<td>Ind</td>
<td>15-40</td>
<td>6.8</td>
<td>2.4 — —</td>
</tr>
<tr>
<td>Scharfetter &amp; Nüesperli (1980)</td>
<td>69 All 1st degree</td>
<td>Strømgren</td>
<td>—</td>
<td>6.9</td>
<td>8.4 12.8** 11.0*</td>
</tr>
</tbody>
</table>

Abbreviations: Schiz = Schizophrenia; Par = Paranoid; Heb = Hebephrenic; Cat = Catatonic; AW = Abridged Weinberg method, sets one age of risk for all relatives. Ind = Individual method where age at risk for each family is determined by age when proband became ill; Strømgren = Strømgren (1935) method, which calculates an age correction for relatives on the basis of the distribution of the age of onset in the probands. With this technique, either a single age correction can be applied to all relatives (as done by Scharfetter and Nüesperli 1980), or separate age corrections can be calculated for relatives of different subgroups of probands (as done for paranoid and nonparanoid probands by Tsuang et al 1974).

1 Includes mixed and undifferentiated cases

By x² analysis (Camilleri and Hopkins 1978, 1979), significantly different from morbid risk for relatives of paranoid schizophrenics *p<.10, **p<.05, ***p<.01
or Fisher exact test. Unless noted, all p values reported are two-tailed.

Genetics

Paranoid Schizophrenia. Three questions will be examined regarding the genetics of paranoid schizophrenia. First, is the genetic loading for schizophrenia, as manifest in the risk for schizophrenia in the relatives of schizophrenics, different in paranoid versus nonparanoid schizophrenia? Second, does paranoid schizophrenia tend to breed true in families? That is, are the schizophrenic relatives of paranoid schizophrenics themselves predominantly paranoid schizophrenics? Third, is there a specific genetic relationship between paranoid schizophrenia and affective illness?

The risk for schizophrenia in the relatives of paranoid and nonparanoid schizophrenics. Nine studies have examined the risk for schizophrenia in the relatives of paranoid compared to nonparanoid schizophrenics (i.e., hebephrenic, catatonic, and/or undifferentiated schizophrenics) (table 1). Eight out of nine of these studies reported that the relatives of paranoid and nonparanoid schizophrenics (i.e., hebephrenic, catatonic, and/or undifferentiated schizophrenics) (table 1). Eight out of nine of these studies reported that the relatives of paranoid schizophrenics have a lower risk for schizophrenia than do the relatives of nonparanoid schizophrenics. Seven out of these eight studies used the abridged Weinberg (AW) method for calculating an age-corrected morbidity rate for schizophrenia. Unfortunately, for this kind of comparison, the AW method introduces a systematic bias which makes the findings reported by these studies difficult to interpret.

To outline the nature of this bias, the AW method will be briefly described. The morbidity rate for an illness is the percent of the population under study that will suffer from that illness when all members of that population have passed the age of risk for that illness. While it is ideal in morbidity studies to examine a population of subjects that have all passed through the age of risk, this is often not possible. Therefore, mathematical techniques have been devised to allow an investigator to estimate—based on the frequency of the illness in the population, the age of that population, and the age of risk for the illness—what the true morbidity rate for the illness in question would be. The AW method is one such technique. This method requires that a lower and upper age limit for the "age of risk" for the illness be set. The morbidity rate (MR) is then calculated as follows:

$$MR = \frac{AR}{(0.0) (B) + (0.5) (C) + (1.0) (D)}$$

where:

- $AR = \text{number of affected relatives}$
- $B = \text{number of relatives below the age of risk}$
- $C = \text{number of relatives within the age of risk}$
- $D = \text{number of relatives above the age of risk}$

The numerator is the number of affected relatives in the population under study. The denominator represents the number of relatives "at risk." This number is calculated by not counting any relative below the age of risk, counting as $\frac{1}{2}$ a relative within the age of risk, and counting as 1 a relative above the age of risk.

A crucial, but frequently overlooked assumption is that to compare morbidity rates for schizophrenia using the AW method, the average age of onset of schizophrenia in the populations being compared needs to be similar. This is rarely a problem when comparing different studies since the average age of onset of schizophrenia does not markedly differ in different populations. When the relatives of different subtypes of schizophrenics are compared, however, a problem emerges with the AW method.

There is substantial evidence that the age of onset of schizophrenia is not the same in relatives of paranoid and nonparanoid schizophrenics. The age of onset of paranoid schizophrenia is on the average at least a decade later than the age of onset of nonparanoid schizophrenia (Schulz 1932; Kallmann 1938; Garrone 1962; Larson and Nyman 1970; Kraepelin 1971; Winokur et al. 1974). Paranoid schizophrenia not infrequently begins after the age of 40, often the upper age limit of risk for schizophrenia used in the AW method (Schulz 1932; Wyrch 1942; Garrone 1962; Larson and Nyman 1970; Winokur et al. 1974). The age of onset of schizophrenia is on the average similar in related individuals. This has been shown both for concordant monozygotic twins (table 2) and for pairs of schizophrenic first-degree relatives (table 3). On the average then, the age of onset of schizophrenia will tend to be later in the relatives of paranoid versus nonparanoid schizophrenics. This assumption is supported by the evidence outlined below that the paranoid subtype of schizophrenia, with its later age of onset, is more common among the schizophrenic relatives of paranoid schizophrenics than among the schizophrenic relatives of nonparanoid schizophrenics.
Table 2. Age of onset of schizophrenia in monozygotic (MZ) twins, concordant for schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Relative</th>
<th>Age of onset of twins</th>
<th>Correlation</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Luxenberger (1936)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>84% onset within 6 years of each other</td>
</tr>
<tr>
<td>Kallmann (1946)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>89% onset within 8 years of each other, mean difference in age at onset—3.5 years</td>
</tr>
<tr>
<td>Slater (1953)</td>
<td>MZ twins</td>
<td></td>
<td>.54</td>
<td>79% onset within 8 years of each other</td>
</tr>
<tr>
<td>Kringlen (1967)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>88% onset within 10 years of each other</td>
</tr>
<tr>
<td>Hoffer &amp; Pollin (1970)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>73% onset within 4 years of each other</td>
</tr>
<tr>
<td>Gottesman &amp; Shields (1972)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>80% onset within 3 years of each other</td>
</tr>
<tr>
<td>Fischer (1973)</td>
<td>MZ twins</td>
<td></td>
<td>—</td>
<td>Mean difference in age at onset of 2 years</td>
</tr>
</tbody>
</table>

If the age of onset of schizophrenia is on the average later in population A than in population B, by applying the AW method to both populations using the same age of risk, the morbid risk for schizophrenia will be underestimated in population A relative to population B. Therefore, the AW method will systematically reduce the risk for schizophrenia in the relatives of paranoid schizophrenics compared to the risk for schizophrenia in the relatives of nonparanoid schizophrenics. The younger the age of relatives, the greater will be the bias introduced by the AW method. If most of the relatives are above the age of 50 (generally the upper age limit for paranoid schizophrenia), then the bias introduced by the AW method will be minimal.

To return to the studies outlined in table 1, how much of the difference in risk for schizophrenia seen in the relatives of paranoid versus nonparanoid schizophrenics is real and how much is a result of an artifact of the AW method? In the study of Hallgren and Sjögren (1959) the difference in risk for schizophrenia in the two groups of relatives seen using the AW method is probably entirely the result of statistical artifact. Using the AW method with an age of risk of 15 to 45, they found that the risk for schizophrenia in the siblings of paranoid schizophrenics was 39 percent lower than the risk for schizophrenia in the siblings of hebephrenic and catatonic schizophrenics. These investigators also calculated the morbid risk for schizophrenia in the siblings using a method which accounts for the difference in the age of onset of the disorder in the identified patients. In the so-called “individu-
al” method, the end of the age of risk is set for each family as the age at which the identified patient became ill. Using this method, Hallgren and Sjögren found that the risk for schizophrenia was now 10 percent higher in the siblings of paranoid schizophrenics than in the siblings of hebephrenic and catatonic schizophrenics!

However, two other studies (Tsuang et al. 1974; Winokur et al. 1974) also calculated the morbid risk for schizophrenia in the relatives of paranoid and nonparanoid schizophrenics by both the AW method and a method which corrected for the difference in the age of onset of schizophrenia in the two proband groups. Unlike the study of Hallgren and Sjögren, both these studies found that even after the proper age correction, the relatives of nonparanoid schizophrenics still had a higher morbid risk for schizophrenia than the relatives of paranoid schizophrenics. Like Hallgren and Sjögren, Winokur et al. (1974) used the individual method, while Tsuang et al. (1974) calculated different correction factors for the relatives of paranoid and nonparanoid schizophrenics by the method of Strömgren, which is based on the distribution of the age of onset in the proband group in question. However, neither of these studies after the proper age correction found a difference in the morbid risk for schizophrenia in the relatives of paranoid and nonparanoid schizophrenics that reached statistical significance.

Four other studies (Schulz 1932; Kallmann 1938; Weinberg and Lobstein 1943; Scharfetter and Nüsperli 1980) found differences in the morbid risk for schizophrenia in the relatives of paranoid schizophrenics and at least some forms of nonparanoid schizophrenics which were probably too large to be entirely due to any artifact introduced by age correction. Three of these studies used the AW method only (Schulz 1932; Kallmann 1938; Weinberg and Lobstein 1943), while one used the Strömgren (1935) method (Scharfetter and Nüsperli 1980) but applied a single age correction factor calculated from the age of onset distribution for all the schizophrenic probands to all the relatives (personal communication, C. Scharfetter, April 1981). Using the Strömgren method in this fashion produces a bias very similar to that found when using the AW method, with a single age of risk period, for all the relatives, irrespective of whether the proband was a paranoid or nonparanoid schizophrenic.

The study by Schulz (1932) is unique in finding a lower risk for schizophrenia in the relatives of catatonic patients compared to paranoid schizophrenics. However, the difference between the relatives of paranoid and hebephrenic schizophrenics is so large that it is unlikely to be due entirely to an artifact of the AW method. What makes the results of this study difficult to compare to those of others is the use by Schulz of combined diagnostic categories for his subtyping of schizophrenia (e.g., paranoid-catatonic, catatonic-hebephrenic). These combined diagnoses, which constitute a sizable percentage of his probands, have been eliminated from the present analysis. An inspection of his results on the morbid risk for schizophrenia in the relatives of his pure and combined clinical groups of schizophrenics (see table 20 in Schulz 1932) suggests that the difference in risk in the relatives of the different subgroups is less when the combined forms are also counted.

Kallmann’s study, the largest family investigation of schizophrenia ever conducted, is, unfortunately, also one of the more difficult studies to interpret. By eliminating all probands (identified patients) with an onset of schizophrenia over the age of 40, and examining the family members when the average age of the probands was, if living, over 70 years of age, Kallmann tended to diminish the impact of the artifact introduced by the AW method. That the difference in genetic loading for schizophrenia between paranoid and nonparanoid schizophrenics detected by Kallmann is not entirely due to artifact is further indicated by his results on schizophrenia in the proband’s parents. Kallmann expressed his data on parents as the percentage of probands with a schizophrenic parent. No age correction was attempted as nearly all the parents were dead at the time of evaluation. While 2.9 percent of the legitimate paranoid schizophrenics had at least one schizophrenic parent, the corresponding figures were 6.3 percent for the hebephrenics, 5.8 percent for the catatonic, and 6.1 percent for both combined. While these differences fall short of statistical significance, the trend is clear. However, Kallmann used unusual criteria for paranoid schizophrenia. Not only were such patients defined by the predominance of delusions in their clinical picture, but they also had to demonstrate the absence of “dementia” on long-term followup. The presence of “dementia” on
followup was required for the diagnosis of hebephrenic and catatonic schizophrenia. Therefore, Kallmann's criteria for paranoid schizophrenia were selecting not only for a certain set of symptoms, but also for a relatively good outcome. Since some, but not all, studies examining the question have shown a lower genetic loading for schizophrenics with a good versus poor outcome (Welner et al. 1958; Vaillant 1963), it is possible that the difference in genetic loading found by Kallmann may be due to differences in outcome and not symptoms in his paranoid versus nonparanoid schizophrenics.

Weinberg and Lobstein (1943) found a much lower risk for schizophrenia in the siblings of paranoid compared to nonparanoid schizophrenics. These results are unlikely to be due entirely to the artefact introduced by the AW method because the siblings were old at the time of evaluation, with almost 80 percent of them over the age of 40. The nearly three-fold difference in risk found in these siblings is probably of too great a magnitude to be due only to a statistical artifact. It is not clear if after the artifact is removed the differences would still be statistically significant.

Two studies (Garrone 1962; Tsuang et al. 1980) found minimal or no difference in risk for schiz-

### Table 4. Prevalence of paranoid schizophrenia among the schizophrenic relatives of paranoid and nonparanoid schizophrenics

<table>
<thead>
<tr>
<th>Study</th>
<th>Subtype of schizophrenic proband</th>
<th>Schizophrenic relatives type</th>
<th>n</th>
<th>Paranoid subtype</th>
<th>Nonparanoid subtype</th>
<th>p value of difference in distribution (by χ²)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schulz (1932)</td>
<td>Par</td>
<td>Sibs</td>
<td>4</td>
<td>50</td>
<td>50</td>
<td>NS</td>
<td>Mixed cases excluded. Not blind</td>
</tr>
<tr>
<td>Kallmann (1938)</td>
<td>Par</td>
<td>Children</td>
<td>21</td>
<td>33</td>
<td>67</td>
<td>NS</td>
<td>Paranoid subgroup includes &quot;mixed disease forms.&quot; Not blind</td>
</tr>
<tr>
<td>Slater (1947)</td>
<td>Par</td>
<td>Sibs</td>
<td>18</td>
<td>44</td>
<td>56</td>
<td>.02</td>
<td>Not blind. Subtype diagnosis based on Kraepelinian criteria</td>
</tr>
<tr>
<td>Garrone (1962)</td>
<td>Par</td>
<td>Sibs</td>
<td>38</td>
<td>50</td>
<td>50</td>
<td>NS</td>
<td>Not blind</td>
</tr>
<tr>
<td>Astrup et al. (1962)</td>
<td>Par</td>
<td>1° + 2°</td>
<td>94</td>
<td>78</td>
<td>22</td>
<td>&lt;.0001</td>
<td>Not blind. Based on diagnostic system of Leonhard (1979). Only grandparents, uncles, aunts, parents, and sibs with available case notes included. Series from 1938–50</td>
</tr>
<tr>
<td>Tsuang et al. (1974)</td>
<td>Par</td>
<td>1°</td>
<td>15</td>
<td>60</td>
<td>40</td>
<td>NS</td>
<td>Blind diagnosis</td>
</tr>
<tr>
<td>Scharfetter &amp; Nüsperli (1980)</td>
<td>Par</td>
<td>1°</td>
<td>18</td>
<td>72</td>
<td>28</td>
<td>&lt;.0001</td>
<td>Blind diagnosis</td>
</tr>
<tr>
<td>Tsuang et al. (1980)</td>
<td>Par</td>
<td>1°</td>
<td>6</td>
<td>0</td>
<td>100</td>
<td>NS</td>
<td>Blind diagnoses, based on personal interviews and hospital records. Average age of relatives &gt; 60</td>
</tr>
</tbody>
</table>

Abbreviations: Par = Paranoid; Heb = Hebephrenic; Cat = Catatonic.
In the risk for schizophrenia in the relatives of paranoid versus nonparanoid schizophrenics. In the study of Garrone (1962), the age of risk for schizophrenia, as used in the AW age correction method, was set at 15 to 70 years. This longer age of risk would tend to decrease the artifactual bias of the AW method. It is therefore of interest that Garrone found only a small and nonstatistically significant trend for the risk for schizophrenia to be lower in the relatives of paranoid versus nonparanoid schizophrenics.

Tsuang et al. (1980), in what is probably methodologically the best family study of schizophrenia to date, conducted interviews with relatives 35 to 40 years after the index admission of the schizophrenic probands. Thus at the time of personal interview, nearly all the relatives had passed through the age of risk for schizophrenia, making the effects of any age correction on the calculated morbidity risks quite small and probably of little significance. The inability of this well-designed study to detect any difference in the rate of schizophrenia in the families of paranoid and nonparanoid schizophrenics must call into question the results of previous investigations.

It would be reassuring if a review of the studies outlined in table 1 revealed a clear relationship between the kind of criteria used for the diagnosis of paranoid schizophrenia (which are often only vaguely described) and the presence or absence of a difference in the risk for schizophrenia in the relatives of paranoid versus nonparanoid schizophrenics. Unfortunately, no such relationship is readily apparent, leaving no clear indication of the cause for the discrepant results in the different investigations.

Does paranoid schizophrenia breed true in families? Nine studies were found that addressed the question of whether the schizophrenic relatives of paranoid schizophrenics were more frequently of the paranoid subtype than the schizophrenic relatives of nonparanoid schizophrenics (table 4). Six of these studies were based on thorough family studies, all described in detail in the preceding section. One (Slater 1947) was based on a series of schizophrenic siblings ascertained by family evaluations of sequential psychiatric admissions. Two were based on the clinical picture of relatives for whom hospital records were available (Astrup, Fossum, and Holmoe 1962; Astrup and Noreik 1966). The possibility of an ascertainment bias must be considered when interpreting the results of studies based only on available hospital records.

From a methodologic perspective, in studies comparing the subtype diagnosis of schizophrenic patients and relatives, it is particularly important that the diagnosis of patient and relative be made blindly. Knowledge of the subtype of the schizophrenic proband, for example, could easily bias the investigator in the often subtle task of subtyping the schizophrenic relative. Only three of the nine studies used blind diagnoses (Tsuang et al. 1974, 1980; Scharfetter and Nüsperti 1980). Of these three studies, one examined relatives after a 30- to 40-year followup period and found no cases of paranoid schizophrenia (Tsuang et al. 1980). Previous studies (reviewed in Kendler and Tsuang 1981, this issue) have also found a tendency for paranoid schizophrenia to progress over time into an undifferentiated, residual, or even hebephrenic picture. In studies examining the familial distribution of schizophrenic subtypes, it would probably be best to study the relatives early in their schizophrenic course when the distinctive features of the subtypes are still prominent.

Of the four studies that found a statistically significant tendency for paranoid schizophrenia to breed true within families, three used broad criteria for the definition of paranoid schizophrenia (Astrup, Fossum, and Holmoe 1962; Astrup and Noreik 1966; Scharfetter and Nüsperti 1980). Both the criteria of Leonhard (1979), used by Astrup and his collaborators, and the ICD-9 criteria, used by Scharfetter and Nüsperti, define paranoid schizophrenia by the predominance of delusions and/or hallucinations even in the presence of significant thought disorder and affective deterioration. These criteria are in contrast with the narrow criteria used by Tsuang et al. (Tsuang and Winokur 1974), which exclude patients with significant thought disorder or affective deterioration (see Kendler and Tsuang 1981, this issue). It would be of substantial interest to determine if the tendency for paranoid schizophrenia to breed true in the studies of Astrup and Scharfetter and their associates would still be present if narrower criteria for the diagnoses were used. Unfortunately, the authors do not present data that would permit such an analysis.

The demonstration in most studies of a tendency for paranoid schizophrenia to breed true within
families reinforces the conclusion reached above that it is incorrect to assume that the type and age of onset of schizophrenia will be the same in the families of paranoid and nonparanoid schizophrenics.

Twin studies and the genetic relationship between paranoid and nonparanoid schizophrenia. Eleven twin studies have compared the concordance of schizophrenia in monozygotic (MZ) and dizygotic (DZ) twins (Gottesman and Shields 1966, 1976). In only three of these studies (Kringlen 1967; Gottesman 1968; Fischer 1973) was the subtype of the twins determined, and in only one (Gottesman 1968) was the subtype diagnosis of the twin made blind to the identity of the co-twin.

Because of small numbers and a low concordance rate, little can be gained from analyzing concordance in DZ twins and subtype of schizophrenia. Sufficient information is only present in these studies to examine two questions in the MZ twins. First, what is the concordance rate for any form of schizophrenia when the index (or identified) twin has paranoid versus nonparanoid schizophrenia? Second, in MZ twins concordant for schizophrenia, is paranoid schizophrenia in the co-twin more common when the index twin is a paranoid versus a nonparanoid schizophrenic?

The zygosity of the MZ twins was based on blood typings in 83 percent of the twins studied by Gottesman (1968), 80 percent of those studied by Kringlen (1967), and 43 percent of those examined by Fischer (1973). In the remaining cases, zygosity was based on physical appearance and in some cases fingerprints. One of the three studies (Kringlen 1967) found a significantly lower concordance rate for schizophrenia if the index twin had paranoid schizophrenia (15 percent) than nonparanoid schizophrenia (50 percent) (table 5). Another of the studies (Gottesman 1968) found a nonsignificant trend in the same direction, while the third found essentially no difference in the concordance rate for schizophrenia in twin pairs in which the index twin was a paranoid or nonparanoid schizophrenic. Although fraught with hazard, it is of interest to combine the results of the three twin studies. Of the 38 MZ twin pairs with a paranoid schizophrenic index twin, 12 of the pairs had a schizophrenic co-twin for a concordance of 32 percent. Of the 47 pairs with a nonparanoid schizophrenic index twin, 25 of the co-twins were schizophrenic for a concordance of 53 percent. This difference is significant ($p < .05$).

All three twin studies found that paranoid schizophrenia in a co-twin was only present when the index twin was a paranoid schizophrenic (table 5). This difference was significant or nearly significant in two studies (Kringlen 1967, $p = .02$; Fischer 1973, $p = .06$) in which the diagnosis of the twins was carried out by an investigator who knew the co-twin. In the one study in which the subtype diagnosis in the twins was carried out blind, the difference did not reach significance (Gottesman 1968, $p = .13$). Although by no means valid in a scientific sense because of di-

### Table 5. Twin studies and the genetic relationship between paranoid and nonparanoid schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>No. (%) of all co-twins that are schizophrenic as a function of subtype of index twin</th>
<th>No. (%) of all schizophrenic co-twins that are paranoid schizophrenic as a function of subtype of index twin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kringlen (1967)</td>
<td>2/13 (15) 16/32 (50)**</td>
<td>2/2 (100) 0/12 (0)**</td>
<td>Diagnosis of twins nonblind. A narrower concept of concordance used to examine subtype concordance</td>
</tr>
<tr>
<td>Gottesman (1968)</td>
<td>3/6 (50) 7/9 (78)</td>
<td>2/3 (67) 0/7 (0)</td>
<td>Diagnosis of twins done blindly</td>
</tr>
<tr>
<td>Fischer (1973)</td>
<td>7/19 (37) 2/6 (33)</td>
<td>7/7 (100) 0/2 (0)*</td>
<td>Diagnosis of twins nonblind</td>
</tr>
</tbody>
</table>

Significantly different from results of paranoid subtype by $\chi^2$ or Fischer Exact Test (two-tailed); *$p<.10$, **$p<.05$. 
vergent diagnostic criteria, it is still of interest to combine the results from the three studies. Of the 12 schizophrenic MZ co-twins of paranoid schizophrenic index twins, 11 had paranoid schizophrenia. Of the 21 schizophrenic co-twins of nonparanoid schizophrenics, none had paranoid schizophrenia. This difference is highly significant \( p < .0001 \). Because most of these results are based on studies with nonblind diagnosis, it cannot be currently ascertained how much of this finding may be due to observer bias.

Risk of affective illness in the relatives of paranoid and nonparanoid schizophrenics. If the genetic loading for schizophrenia is less in paranoid than in nonparanoid schizophrenia, could this be due to a genetic link between paranoid schizophrenia and affective illness? Three studies were found that examined the risk for affective illness in the relatives of paranoid and nonparanoid schizophrenics (table 6). If a specific link exists between paranoid schizophrenia and affective illness, the risk for affective illness should be higher in the relatives of paranoid schizophrenics compared to the relatives of nonparanoid schizophrenics.

Of the three studies examining this question, two used blind diagnosis of relatives and standard diagnostic criteria (Fowler et al. 1974; Scharfetter and Nüsperli 1980). None of the studies found a statistically significant difference in the risk for affective illness in the relatives of paranoid versus nonparanoid schizophrenia. Of the two studies using blind diagnosis, one found a slight trend for a greater risk for affective illness in the relatives of paranoid schizophrenics (Fowler et al. 1974) and one found the risk for affective illness to be lower in the relatives of paranoid schizophrenics. The risk for affective illness in the relatives of paranoid schizophrenics resembles the 1 to 4 percent risk found in the general population and not the 10 to 25 percent risk usually found in the relatives of affectively ill probands (Kay 1978; Tsuang 1978).

**Table 6. Risk of affective illness in the relatives of paranoid, hebephrenic, and catatonic schizophrenics**

<table>
<thead>
<tr>
<th>Study</th>
<th>Relatives</th>
<th>Risk of affective illness in relatives of probands with following subtype of schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Par</td>
<td>Heb</td>
</tr>
<tr>
<td>Weinberg &amp; Lobstein (1943)</td>
<td>Sibs &amp; parents</td>
<td>3.8</td>
</tr>
<tr>
<td>Fowler et al. (1974)</td>
<td>1st-degree relatives</td>
<td>5.6</td>
</tr>
<tr>
<td>Scharfetter &amp; Nüsperli (1980)</td>
<td>1st-degree relatives</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Abbreviations: Par = Paranoid, Heb = Hebephrenic, Cat = Catatonic.

By \( \chi^2 \) analysis, significant differences in risk for affective illness in relatives of Heb, Cat or Heb & Cat schizophrenics compared to relatives of paranoid schizophrenics were not found in any study.
larity of subtype among related schizophrenics is due to nongenetic variables. Unfortunately, neither of the two methodologic approaches that can separate genetic from nongenetic variables—MZ twins reared apart and adoption studies—have yet been systematically used to address the question of the genetics of paranoid versus nonparanoid schizophrenia. Given these caveats, what can be concluded from the literature reviewed on the genetics of paranoid schizophrenia?

First, based on the finding of most, but not all, studies of a lower risk for schizophrenia in the families of paranoid versus nonparanoid schizophrenic MZ twin pairs when the index twin has paranoid schizophrenia, it is probable that the genetic loading for schizophrenia is less in paranoid than in nonparanoid schizophrenia. However, since several family studies were unable to demonstrate that finding, this difference is unlikely to be a very substantial one.

Second, paranoid schizophrenia appears, at least to a moderate degree, to run in families. However, all studies show that a substantial proportion (22–67 percent) of the schizophrenic relatives of paranoid schizophrenics have nonparanoid schizophrenia. The results of the twin studies which show a high degree of concordance for paranoid versus nonparanoid schizophrenia among MZ twins concordant for schizophrenia suggest a substantial genetic separation for paranoid versus nonparanoid schizophrenia. Nevertheless, small sample sizes and nonblind diagnoses render these results only suggestive until future attempts at replication are carried out.

Third, the small amount of evidence available does not suggest that paranoid schizophrenia has a genetic relationship to affective illness of any greater magnitude than is found with nonparanoid schizophrenia.

Only future investigations free of the methodologic difficulties outlined above in conjunction with pedigree analysis that will allow for the specific testing of genetic models for the transmission of paranoid and nonparanoid schizophrenia will likely clarify to a satisfactory degree the genetics of paranoid schizophrenia.

**Genetics of the Paranoid Psychoses.** Compared to schizophrenia, little attention has been paid to genetic research in the paranoid psychoses. Sufficient information is currently available, however, to begin to address two important questions on the genetics of the paranoid psychoses: what is the genetic relationship between paranoid psychosis and schizophrenia? and what is the genetic relationship between paranoid psychosis and affective illness?

Paranoid psychosis is here defined as a psychotic disorder characterized by the presence of nonbizarre delusions in the absence of symptoms indicative of an organic, affective, or schizophrenic illness. Symptoms indicative of schizophrenia include a prominent thought disorder, bizarre delusions, prominent affective and personality deterioration, and Schneiderian symptoms (1959). Simple non-Schneiderian hallucinations are permitted within the paranoid psychoses. Schizophrenia as here defined includes both paranoid and nonparanoid forms unless otherwise specified.

**Genetic relationships between paranoid psychosis and schizophrenia.** Six studies have examined the genetic relationship between paranoid psychosis and schizophrenia by examining the frequency of schizophrenia in the families of paranoid psychotic probands (table 7). Unlike the results presented for the family studies on schizophrenia in table 1, all but one of these six studies (Kolle 1931) present uncorrected prevalence rates and not morbidity risks for schizophrenia. Multiplying the uncorrected prevalence rates in table 7 by approximately 1.5 will give a rough approximation of what a corrected morbidity rate would be. (This correction assumes on the average 10 percent of the relatives are below the age of risk for schizophrenia—most of these studies exclude children—and the remaining relatives are evenly divided between those within and those beyond the age of risk for schizophrenia.) The prevalence rate for schizophrenia in the first-degree relatives of patients with a paranoid psychosis ranged in the six studies from 0.7 to 2.4 percent (equivalent to morbidity risks for schizophrenia of roughly 1.1 to 3.6 percent).

Before any attempt to interpret these findings is made, several cautionary notes are in order. First, there are discrepancies in the diagnostic criteria used for paranoid psychosis in these studies. All studies agreed in excluding patients with prominent delusions in the presence of significant affective or organic features. Very brief psychotic episodes were also excluded by all studies. Furthermore, patients demonstrating classic schizophrenic symptoms such as bizarre delusions, thought disorder, and prominent affective dete-
rioration were excluded by all studies. However, some investigators excluded patients with hallucinations (Kolle 1931; Debray 1974; Winokur 1977) while others included such patients (Retterstøl 1967; Watt et al. 1980; Kendler and Hays 1981). Second, Retterstøl’s investigation (1967) has a potential

Table 7. Prevalence of schizophrenia in the relatives of patients with paranoid psychosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Syndrome</th>
<th>Probands (n)</th>
<th>All 1st-degree relatives (n)</th>
<th>Relatives (type)</th>
<th>Prevalence of schizophrenia (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolle (1931)</td>
<td>Paranoia</td>
<td>66</td>
<td>513</td>
<td>All 1st degree</td>
<td>1.0 1.5</td>
<td>Age correction by abridged Weinberg method, age of risk 20–40. Diagnosis of paranoia as by Kraepelin (1971). Figures for certain schizophrenia in relatives reported. High age-corrected prevalence for schizophrenia in children based on 2 cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sibs</td>
<td>1.2 1.7</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Children</td>
<td>1.4 5.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parents</td>
<td>0 0</td>
<td></td>
</tr>
<tr>
<td>Retterstøl (1967)</td>
<td>Paranoid reactive psychosis</td>
<td>206</td>
<td>1,341</td>
<td>Parents</td>
<td>1.6 —</td>
<td>Based on followup proband diagnosis. Sibs &gt; 10 years of age counted. In same investigation, prevalence of schizophrenia in parents and sibs of paranoid schizophrenic was only 1.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>&amp; sibs</td>
<td>1.4 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sibs</td>
<td>2.4 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parents</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Debray (1974)</td>
<td>Deliré paranoïaque chronique (DPC)</td>
<td>21</td>
<td>122</td>
<td>All 1st degree</td>
<td>2.4 —</td>
<td>DPC is a chronic nondeteriorating delusional psychosis without hallucinations. Using similar diagnostic criteria, Brunetti (1964) found a prevalence rate for schizophrenia in the normal population of 1.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sibs</td>
<td>5.2 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Children</td>
<td>0 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parents</td>
<td>0 —</td>
<td></td>
</tr>
<tr>
<td>Winokur (1977)</td>
<td>Delusional disorder (DD)</td>
<td>29</td>
<td>168</td>
<td>All 1st degree</td>
<td>1.2 —</td>
<td>DD defined as psychosis with nonbizarre delusions without hallucinations. Study based on family histories recorded in charts. In original report, prevalence of schizophrenia in 1st-degree relatives reported as 2.4%. However, of 4 cases of “schizophrenia” in relatives, 2 in reality had paranoia. With use of similar method (Winokur et al. 1972) risk for schizophrenia in families of schizophrenics was found to be 2.1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sibs</td>
<td>1.8 —</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Parents</td>
<td>0 —</td>
<td></td>
</tr>
<tr>
<td>Watt et al. (1980)</td>
<td>Paranoid state</td>
<td>24</td>
<td>127</td>
<td>Sibs</td>
<td>0.8 —</td>
<td>Paranoid state defined by presence of systematized delusions without personality change with or without hallucinations</td>
</tr>
<tr>
<td>Kendler &amp; Hays (1981)</td>
<td>Delusional disorder (DD)</td>
<td>12</td>
<td>58</td>
<td>All 1st degree</td>
<td>1.7 —</td>
<td>DD defined by onset of psychosis with ideas of reference leading to persecutory delusions. Hallucinations permitted. Only relatives over age 17 counted. Proband diagnosed blind to status of relatives</td>
</tr>
</tbody>
</table>
serious methodologic deficiency. The author states that he was not
convincled of the thoroughness of his ascertainment method. The
magnitude of this problem is suggested by a prevalence rate for
schizophrenia of only 1.2 percent in the relatives of paranoid schizo-
phrenics found in this study. Since this figure is so much smaller than
that found by other investigators (see table 1), it suggests that the
ascertainment of schizophrenia in this study may have been less than
complete. Thus interpretation of the results of Retterstol's investi-
gation is problematic. Third, the study of Winokur (1977) also used
an ascertainment technique—family histories as recorded in clinical
charts—that is likely to produce an underestimation of the true rate of
schizophrenia. Fourth, none of these studies contained a normal
control group. Debray (1974) utilized the study of Brunetti (1964),
in which similar diagnostic criteria were applied, as a “literature”
control. Fifth, except for the study of Retterstol (1967), which had substantial ascertainment
problems, only one study (Kendler and Hays 1981) contains
a comparison group of schizophrenics that allows a direct com-
parison, using identical diagnostic procedures, of the frequency of
schizophrenia in the families of paranoid psychotic and schizo-
phrenic patients.

Interpretation of these studies must therefore rest in part on a
comparison with other reports of rates of schizophrenia reported in
the literature. Slater and Cowie (1971) calculate that the mean
morbidity risk for schizophrenia in the normal population, based on
20 European studies, is 1.2 percent, ranging in the different in-
vestigations between 0.4 and 2.9 percent. In general, risk figures
above 2 percent are only seen when special populations are being
examined (e.g., the north Swedish isolate population examined by Böök 1953) or particularly
broad diagnostic criteria are being applied (as in the study of Garrone
1962). Combining the numerous family studies on schizophrenia, a
number of which are in table 1, Slater and Cowie (1971) calculate
the average morbid risk for schizophrenia in the relatives of a schizo-
phrenic as follows: parent 4.4 percent, sibling 8.5 percent, and
child 12.3 percent.

Most of the estimated morbid risks for schizophrenia found in
the relatives of patients with a para-
noi d psychosis are in the upper
range of what has been reported in the normal population (see table 8).
Some, however (the results of Debray 1974 and possibly those of
Retterstol 1967 and Kendler and Hays 1981), report risks for schizo-
phrenia slightly above what is
usually found in normal populations. No study finds a risk for
schizophrenia in the relatives of
paranoid psychotics that is in the
range usually found in the relatives
of schizophrenics.

Does the small increased risk for schizophrenia in the relatives of
patients with a paranoid psychosis over that usually found in the normal
population indicate a specific
generic link between paranoid psychosis and schizophrenia? Small increased risks for schizo-
phrenia (usually in the range of 2
to 4 percent) have frequently been
found in groups of relatives of pa-
thents with a wide range of
neuropsychiatric disorders that are
not usually thought to have any
close genetic relationship to schiz-
ophrenia including unipolar and
bipolar affective illness (Slater
1936; Perris 1966; Smeraldi et al.
1977), obsessive compulsive,
hypochondriacal, and anxiety neu-
rosis (Mitsuda, Saka, and
Kobayashi 1967; Sakai 1967), and
general paresis (Slater 1936). These results favor the interpreta-
tion that the small increased risk
for schizophrenia seen in some but
not all studies in families of pa-
thents with a paranoid psychosis is probably not evidence of a specific
genetic link to schizophrenia.

Rather, such small increased risks for schizophrenia probably result
from some nonspecific factor
relating more to psychopathology
in general than to schizophrenia
specifically.

A major methodologic short-
coming of most of the family studies of paranoid psychosis is the ab-
sence of a comparison group of
schizophrenics. Blind to the family
history data, Kendler and Hays
(1981) re-diagnosed 12 of 146 clinic-
ally diagnosed schizophrenics as
having a paranoid psychosis. The
uncorrected prevalence rates for
schizophrenia were lower in the
first-degree relatives of the 12 para-
noi d psychotics (1.7 percent) than
in those of the remaining schizo-
phrenics (7.4 percent) (p = .08).
When the prevalence of schizo-
phrenia in the first- and second-
degree relatives was compared (.6
versus 3.8 percent, respectively),
the results reached statistical sig-
ificance (p = .01). In a controlled
study, with blind diagnosis, the
frequency of schizophrenia was
much less in the relatives of pa-
thents with paranoid psychosis
than in a comparison group of
schizophrenics.

Further support for the lack of a
strong genetic link between para-
Table 8. Prevalence of affective illness in relatives of patients with paranoid psychosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Syndrome</th>
<th>Relatives</th>
<th>Prevalence of affective illness in relatives</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kolle (1931)</td>
<td>Paranoia</td>
<td>All 1st degree</td>
<td>1.1%</td>
<td>Age-corrected risk for &quot;manic-depressive insanity&quot;</td>
</tr>
<tr>
<td>Retterstol (1967)</td>
<td>Paranoiac reactive psychosis</td>
<td>Parents &amp; sibs</td>
<td>0.4%</td>
<td>Prevalence of &quot;manic-depressive illness.&quot; Prevalence in relatives of paranoid schizophrenics was 0%</td>
</tr>
<tr>
<td>Debray (1974)</td>
<td>Delire paraoniaque chronique</td>
<td>All 1st degree</td>
<td>4.9%</td>
<td>Prevalence of &quot;depressive states.&quot; Using similar diagnostic criteria, Brunetti (1964) found a prevalence of depressive states in the normal population reported as 4.9%</td>
</tr>
<tr>
<td>Winokur (1977)</td>
<td>Delusional disorder</td>
<td>All 1st degree</td>
<td>2.4%</td>
<td>Prevalence of affective illness. With the use of a similar method, morbid risk for affective illness in 1st-degree relatives of probands with schizophrenia was 5.5% and with affective illness 13.5%</td>
</tr>
<tr>
<td>Kendler &amp; Hays (1981)</td>
<td>Delusional disorder</td>
<td>All 1st degree</td>
<td>3.4%</td>
<td>Prevalence of unipolar and bipolar illness. Prevalence of affective illness in comparison group of relatives of schizophrenics was 5.3%</td>
</tr>
</tbody>
</table>

Noid psychosis and schizophrenia has emerged from a blind reanalysis of the interviews of the relatives from the Danish adoption study of Kety et al. (1975) (Kendler, Gruenberg, and Strauss 1981). As was found by the original investigators, the schizophrenia spectrum disorders (defined in this study as schizophrenia and schizotypal personality disorder using DSM-III criteria) concentrated heavily in the biological relatives of the schizophrenic adoptees. A similar pattern was not seen for the cases of paranoid psychosis in the relatives. The distribution of cases of paranoid psychosis and schizophrenia spectrum disorders in the relatives was significantly different (p < .01).

Genetic relationship between paranoid psychosis and affective illness. Five studies have examined the prevalence of affective illness in the relatives of patients with a paranoid psychosis (table 8). Although varying widely depending upon diagnostic criteria, the morbid risk for affective illness in the normal population is between 1 and 4 percent, while the risk in relatives of affectively ill probands is usually found to be between 10 and 25 percent (Stenstedt 1952; Kay 1978; Tsuang 1978).

Three of the studies (Retterstol 1967; Winokur 1977; Kendler and Hays 1981) allowed for comparisons using similar methodologies of the prevalence of affective illness in the families of patients with paranoid psychosis and the families of schizophrenics. Since schizophrenia is not thought to be closely genetically related to affective illness, if the families of paranoid psychotics have a higher prevalence of affective illness than the families of schizophrenics, this might be evidence for a genetic link between affective illness and paranoid psychosis. In Retterstol's study, the rates for affective illness were very low and nearly equal in the families of paranoid psychotics and schizophrenics. However, the completeness of ascertainment in this study is questionable, so these results must be cautiously interpreted. Winokur (1977) found a prevalence of affective illness of 2.4 percent in the families of patients with a paranoid psychosis compared to a morbid risk for affective illness of 5.5 percent in the families of schizophrenics. Correcting the prevalence rate to a morbidity risk would still leave the rate of affective illness lower in the families of paranoid psychotic compared to schizophrenic patients. Kendler and Hays (1981), in the only study using blind diagnosis, found the prevalence rate of unipolar and bipolar illness to be lower in the families of patients with a paranoid psychosis than in the families of schizophrenics.

One study (Debray 1974) com-
pared the prevalence rate for affective illness in the relatives of patients with a paranoid psychosis to the rate in the normal population as found by another investigator using similar diagnostic criteria. The rate of "depressive states" was nearly identical in the two populations.

Lastly, one study (Kolle 1931), reported, without a comparison group, that the morbid risk for "manic-depressive insanity" in the families of patients with paranoia was quite low (1.1 percent).

**Genetics of the Paranoid Psychoses:** Conclusion. Although fewer in number, the results of the genetic investigations of paranoid psychoses are less ambiguous than those of paranoid schizophrenia. All studies agree that the frequency of schizophrenia in the relatives of patients with a paranoid psychosis is lower than that usually found in the relatives of schizophrenics and approaches the frequency found in the normal population. Most of these studies, however, were conducted in the absence of a comparison group of either normals or schizophrenics. Nonetheless, the consistency of these results suggests that the genetic relationship between the paranoid psychoses and schizophrenia is probably weak or nonexistent. Further controlled, blind investigations will be needed to confirm these observations.

**Biochemistry**

This section reviews biochemical findings in paranoid schizophrenia and other paranoid psychoses. Two conditions were established for a biochemical finding to be included in this review. First, to avoid the review's becoming a catalogue of miscellaneous results, any biochemical finding here reviewed has to have been replicated by at least one independent group of investigators. Second, the findings could not be limited to comparisons between paranoid schizophrenics (or paranoid psychotics) and controls. A comparison between paranoid schizophrenics (or paranoid psychotics) and one other psychiatric group of interest (e.g., nonparanoid schizophrenics) was required.

**Paranoid Schizophrenia.** Two biochemical findings in paranoid schizophrenia met the criteria for review: the activity of platelet monoamine oxidase and various measures of the functioning of the neurotransmitter norepinephrine. For both of these findings, information was only available comparing paranoid and nonparanoid schizophrenics.

**Platelet monoamine oxidase activity.** Ten studies were found which directly compared the activity of platelet monoamine oxidase (pMAO) in paranoid and nonparanoid schizophrenics (table 9). Controversies regarding the methodology of the pMAO assay, especially the use of different substrates and different platelet preparation techniques, will not be dealt with here. The interested reader is referred to a recent issue of this journal for a discussion of these issues (Schizophrenia Bulletin, Vol. 6, No. 2, 1980). Of the 10 studies, 4 found that pMAO activity was lower in paranoid than in nonparanoid schizophrenics. In two of these studies (Potkin et al. 1978; Wyatt et al. 1978), both done by the same research group, the difference in pMAO activity between paranoid and nonparanoid schizophrenics reached statistical significance. Five studies found essentially no difference in pMAO activity in the two groups of schizophrenics. One study (Landowski 1977) found a nonsignificant trend for pMAO activity to be higher in paranoid than in nonparanoid schizophrenics. One study was found that compared pMAO activity in chronic paranoid schizophrenics and controls. Groshong et al. (1978), using the subtyping criteria of DSM-II, found no difference in pMAO activity in paranoid schizophrenics and controls. Nearly all these studies were done with chronic paranoid and nonparanoid schizophrenics. It is in this group of schizophrenics that the low pMAO activity has been most consistently found (Wyatt et al. 1979). Since differences in the chronicity of illness do not appear to explain the discrepancy of findings in the studies reviewed, could there be other methodologic variables that might account for the observed differences in results?

No consistent difference is found in the substrate used in the pMAO assay in those studies that did versus those that did not find a difference in pMAO activity in paranoid versus nonparanoid schizophrenics. There is a trend for studies using the DSM-II crite-
## Table 9. Platelet monoamine oxidase (MAO) activity in paranoid and nonparanoid schizophrenias

<table>
<thead>
<tr>
<th>Study</th>
<th>Comparison group</th>
<th>Par Schiz (n)</th>
<th>Substrate</th>
<th>Trend</th>
<th>% of comparison group MAO activity seen in Par Schiz</th>
<th>On neuroleptics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wyatt et al. (1973)</td>
<td>CU Schiz</td>
<td>5</td>
<td>Tryptamine</td>
<td>No diff</td>
<td>100</td>
<td>Yes</td>
<td>Chronic schizophrenics. No criteria given for diagnosis</td>
</tr>
<tr>
<td>Demisch et al. (1977)</td>
<td>“Defect” Schiz</td>
<td>12</td>
<td>Phenyl-ethyamine</td>
<td>↓</td>
<td>75</td>
<td>Yes</td>
<td>Chronic schizophrenics. Paranoid schizophrenics defined by presence of delusions of persecution or grandeur often with hallucinations and “cognitive disorders.” “Defect schizophrenia” defined by prominent negative symptoms</td>
</tr>
<tr>
<td>Landowski (1977)</td>
<td>Non-Par Schiz</td>
<td>39</td>
<td>Benzyamine</td>
<td>↑</td>
<td>114</td>
<td>?</td>
<td>No criteria given for diagnoses. Among women, paranoid schizophrenics had significantly increased platelet MAO activity compared to controls.</td>
</tr>
<tr>
<td>Wyatt et al. (1978)</td>
<td>CU Schiz</td>
<td>8</td>
<td>Benzyamine</td>
<td>↓↓</td>
<td>56</td>
<td>Yes</td>
<td>Retrospective chart review study. Chronic schizophrenics by DSM-II and RDC (Spitzer, Endicott, &amp; Robins 1975). Paranoid subtype as defined by DSM-II.</td>
</tr>
<tr>
<td>Potkin et al. (1978)</td>
<td>CU Schiz</td>
<td>8</td>
<td>Benzyamine</td>
<td>↓↓</td>
<td>61</td>
<td>Yes</td>
<td>Prospective study using same criteria. Information gathered by structured interview. Information gathered by structured interview.</td>
</tr>
<tr>
<td>Berger et al. (1978)</td>
<td>CU Schiz</td>
<td>21</td>
<td>Benzyamine</td>
<td>No diff</td>
<td>103</td>
<td>Yes</td>
<td>Chronic schizophrenics diagnosed by DSM-II. Paranoid subtype as defined in DSM-II.</td>
</tr>
<tr>
<td>Sullivan et al. (1978)</td>
<td>CU Schiz</td>
<td>14</td>
<td>Tryptamine</td>
<td>↓</td>
<td>74</td>
<td>Yes</td>
<td>Chronic schizophrenics meeting DSM-II &amp; Feighner et al. (1972) criteria</td>
</tr>
<tr>
<td>Baron, Perlman, &amp; Levitt (1980)</td>
<td>Non-Par Schiz</td>
<td>12</td>
<td>Benzyamine</td>
<td>No diff</td>
<td>—</td>
<td>No</td>
<td>Chronic schizophrenics defined by RDC (Spitzer, Endicott, &amp; Robins 1975). Medication free for 2 weeks. With subtyping criteria of RDC or Tsuang and Winokur (1974), no difference in MAO levels seen between paranoid and nonparanoid schizophrenics.</td>
</tr>
<tr>
<td>Meltzer et al. (1980)</td>
<td>Non-Par Schiz</td>
<td>?</td>
<td>Benzyamine</td>
<td>No diff</td>
<td>—</td>
<td>Yes</td>
<td>Schizophrenia and paranoid subtype as defined in RDC (Spitzer, Endicott, &amp; Robins 1975). No difference in MAO levels seen between paranoid and nonparanoid schizophrenics in entire sample (n=62) or in chronic patients only (n=42).</td>
</tr>
</tbody>
</table>

**Abbreviations:** CU Schiz = Chronic Undifferentiated Schizophrenia; Par Schiz = Paranoid Schizophrenia; Non-Par Schiz = Nonparanoid Schizophrenia; Heb Schiz = Hebephrenic Schizophrenia

**Trends:** No diff = No difference (mean MAO levels within 10% of one another); ↑ = Increased in Par Schiz, not statistically significant; ↓ = Decreased in Par Schiz, not statistically significant; ↓↓ = Decreased in Par Schiz, statistically significant.
ria for paranoid schizophrenia more frequently to find a difference in pMAO activity between paranoid and nonparanoid schizophrenics compared to studies using the subtyping criteria of the Research Diagnostic Criteria (RDC; Spitzer et al. 1975) or of Tsuang and Winokur (1974). However, although the criteria of Tsuang and Winokur define a narrow group of paranoid schizophrenics, an inspection of the criteria for paranoid schizophrenia in the RDC versus DSM-II suggests that the criteria probably define a rather similar group of patients.

Several studies have compared schizophrenics not by subtypes but by symptoms. Low pMAO activity has been associated with hallucinations in some (Becker et al. 1977; Meltzer et al. 1980) but not all studies (Groshong et al. 1978; Mann and Thomas 1979). Hallucinations plus delusions were associated with low pMAO activity in one study (Orsulak et al. 1978). The relationship of these findings to differences in pMAO activity in paranoid and nonparanoid schizophrenics is not entirely clear. While paranoid schizophrenics tend to have hallucinations and delusions more frequently than other subtypes of schizophrenics, these symptoms can certainly be seen in nonparanoid schizophrenics (Helmchen 1975). The fact that in one investigation a relationship was found between the presence of hallucinations (as defined by Schneider 1959) and low pMAO activity but not between the paranoid subtype and low pMAO activity (Meltzer et al. 1980a) indicates that there is no simple relationship between the presence of hallucinations and the diagnosis of paranoid schizophrenia.

As shown in table 9, most of the studies examining pMAO activity in schizophrenia were done with patients on neuroleptic medication. Previous evidence, reviewed by Wyatt et al. (1978), had suggested that neuroleptics did not affect pMAO levels. However, a recent well-designed study (Jackman and Meltzer 1980) has shown a highly significant tendency for neuroleptics to decrease pMAO levels in schizophrenics. These results make interpretation of previous studies of pMAO activity in which patients were on neuroleptics quite problematic. Since patient groups were not carefully matched for the number on and off medication, and for the dose of medication, it cannot be determined if the difference between paranoid and nonparanoid schizophrenics in some studies was an artifact of some difference in neuroleptic intake between the two groups of schizophrenics. The one study (Baron, Perlman, and Levitt 1980) done on drug-free schizophrenics showed no difference between pMAO activity in paranoid and nonparanoid schizophrenics.

Norepinephrine function. Three different approaches have been used in the examination of norepinephrine (NE) function in paranoid versus nonparanoid schizophrenics: the levels of NE or its metabolites in autopsied brain specimens, the levels of NE in cerebrospinal fluid (CSF), and the levels of the enzyme that converts dopamine to NE, dopamine-ß-hydroxylase, in serum.

Farley et al. (1978) first reported that NE concentration was elevated in anterior limbic structures (including the ventral septum and nucleus accumbens) of the brains of paranoid schizophrenics. However, the number of paranoid schizophrenics examined was small (n = 4) and the comparison group was a control population, not a group of nonparanoid schizophrenics. Kleinman et al. (1979) subsequently reported that NE levels were higher in the nucleus accumbens of the brains from two paranoid schizophrenics compared to both controls and nonparanoid schizophrenics. The best study to date on this question has been recently reported by Wyatt et al. (1981). They examined the levels of NE and the main NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in nucleus accumbens and hypothalamus of 22 chronic schizophrenics, subtyped according to the RDC (Spitzer, Endicott, and Robins 1975), and 17 controls. The controls and schizophrenics were matched for age and interval between death and autopsy. Levels of NE in the nucleus accumbens were over twice as high in the paranoid schizophrenics as in the nonparanoid schizophrenics or controls. This difference was highly statistically significant. In the hypothalamus, levels of NE were high compared to controls in both the paranoid and nonparanoid schizophrenics. Free MHPG was no higher in the nucleus accumbens in paranoid schizophrenics than in the other two groups, but in the hypothalamus, free MHPG was nonsignificantly higher in the paranoid versus nonparanoid schizophrenics.

Lake et al. (1980) reported the only investigation to date examining levels of NE in the CSF of medication-free paranoid versus nonparanoid schizophrenics. Using the RDC (Spitzer, Endicott,
and Robins 1975) for the diagnosis of schizophrenia and its subtypes, they found that the NE concentration was 43 percent higher in the CSF of paranoid compared to undifferentiated schizophrenics. This difference was just short of statistical significance. However, while the difference between paranoid schizophrenics and age-matched controls was significant, there was no difference between NE levels in the CSF of the undifferentiated schizophrenics versus controls.

Although the relationship between levels of the NE synthetic enzyme dopamine-β-hydroxylase (DBH) in serum and brain is not entirely clear, since serum DBH has been shown to be under genetic control (Dunnette and Weinshilboum 1977), it is possible that alterations in brain DBH would be reflected in serum levels of the enzyme. Four investigations have compared serum DBH levels in paranoid and nonparanoid schizophrenics (Dunner et al. 1973; Meltzer et al. 1976; Fujita et al. 1979; Meltzer, Nasr, and Tong 1980). In none of these studies was a significant difference found in the DBH levels of paranoid versus nonparanoid schizophrenics.

**Biochemistry of Paranoid Schizophrenia: Conclusion.** Biochemical evidence relevant to the question of the relationship between paranoid and nonparanoid schizophrenia has been reviewed. If a consistent biochemical difference could be found between these two disorders, this would strongly suggest that paranoid schizophrenia and nonparanoid schizophrenia were distinct disorders.

Despite several positive reports, the findings of lower pMAO levels in paranoid compared to nonparanoid schizophrenics have not been consistently replicated. Although in need of further study, the results with pMAO levels do not provide strong evidence for a biological difference between paranoid and nonparanoid schizophrenia.

Three studies have shown elevated NE levels in the limbic forebrain of paranoid schizophrenics. However, only one of these studies had both an adequate number of subjects and a nonparanoid schizophrenic comparison group. The possible validity of these findings is supported, however, by the findings from one study of elevated CSF levels of NE in paranoid versus nonparanoid schizophrenics. Although these findings are suggestive of a true biological difference between paranoid and nonparanoid schizophrenics, given the many methodologic difficulties with postmortem studies, any definitive conclusion in this exciting area must await future studies. Since the elevated NE levels in brain and CSF can result from decreased breakdown and not increased synthesis, the lack of an increase in the synthetic enzyme DBH in plasma does not seriously contradict these findings.

**Biochemistry of Paranoid Psychosis.** No biochemical investigations with patients with paranoid psychosis were located that met the inclusion criteria for this review.

**Conclusion**

Over 80 years have now passed since the nosologic entities of paranoid schizophrenia, the various forms of nonparanoid schizophrenia, and paranoid psychosis were delineated by Kraepelin. We have here reviewed two of the several potential methodologic approaches to the empirical validation of Kraepelin's nosologic divisions: genetic investigations and biochemical studies. Not mentioned, but no less relevant, are demographic, followup, and response to treatment studies.¹

Based on the genetic and biochemical evidence here reviewed, what answer can be given to the three questions posed in the introductory paragraph of this review? The first question was to determine the nosologic relationship between paranoid and nonparanoid schizophrenia. Two sets of findings would support the hypothesis that these two disorders are nosologically distinct: the moderate tendency in families and the stronger tendency in MZ twins for the schizophrenic relatives of paranoid schizophrenics to themselves have paranoid schizophrenia, and the elevation of NE levels in certain brain regions in paranoid but not in nonparanoid schizophrenics. However, because both of these findings are based mostly on studies characterized by small samples and/or serious methodologic flaws, the results must be seriously questioned. A prudent assessment of the findings reviewed would suggest that though there is some evidence of potentially important differences between paranoid and nonparanoid schizophrenia, pending future investigations, it cannot

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¹A more complete review of the data relevant to the nosologic validity of the nonhallucinatory paranoid psychoses has been published (Kendler 1980).
yet be clearly determined whether these two syndromes represent two forms of a single disorder or are two truly distinct disorders.

Only genetic studies were found that addressed the second question: the nosologic relationship between paranoid psychosis and schizophrenia. Although rarely without some methodologic limitations, the results of these studies uniformly suggest that the genetic link between paranoid psychosis and schizophrenia is small or nonexistent. At least from a genetic perspective, the available evidence supports the nosologic distinction between paranoid psychosis and schizophrenia.

Genetic studies were also the only evidence found to address the third question: the nosologic relationship between affective illness and paranoid schizophrenia and paranoid psychosis. The scanty available evidence did not suggest any genetic link between paranoid schizophrenia and affective illness. These results, however, must be regarded as far from conclusive. More evidence was available—most of which was also not free of methodologic flaws—on the relationship between affective illness and paranoid psychosis. All those studies showed no evidence of a genetic link between the two disorders. From a genetic perspective, it appears unlikely that either paranoid schizophrenia or paranoid psychosis is closely related to affective illness.

It is to be hoped that this review will serve not only as a summary of work previously done, but also as a stimulus for future investigations that will provide more definitive answers to the important nosologic questions here considered.

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