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Overview: A Current Perspective on Twin Studies of Schizophrenia

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The author reviews the results of twin studies of schizophrenia from the perspective of recent advances in our understanding of the twin method and of the transmission of schizophrenia. The evidence suggests that twin studies of schizophrenia are not likely to be substantially biased by the greater similarity in social environment of identical versus fraternal twins. Raw concordance figures from twin studies of schizophrenia are quite variable. When models to estimate the etiologic importance of genetic factors are applied to these figures, the results from all studies are similar. According to these models, genetic factors are as etiologically important in schizophrenia as in such medical conditions as diabetes and hypertension. Twin studies of schizophrenia probably provide a valid measure of the major etiologic role genetic factors play in schizophrenia.

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Schizophrenia is a disorder that tends to run in families (1). For more than 50 years, a major focus of psychiatric genetics has been to determine to what extent the familial clustering of schizophrenia is due to genetic versus nongenetic factors. Until the 1960s, the major method used to address this question was twin studies. Since that time, the focus of research on the genetics of schizophrenia has shifted toward adoption studies and family studies analyzed with sophisticated methods, such as complex segregation analysis and linkage analysis. However, twin studies remain an important source of information about the etiologic role of genetic factors in schizophrenia.

In recent years, advances have been made in our understanding of the transmission of schizophrenia and of the twin method itself. The impact of these advances on our interpretation of twin studies of schizophrenia is the subject of this review. Following a brief review of the twin method, five areas relevant to our understanding of twin studies of schizophrenia will be explored: 1) empirical examinations of the validity of the twin method, 2) the role of nongenetic familial factors in the transmission of schizophrenia, 3) overlooked variables that could produce a "reverse bias" in twin studies of schizophrenia, 4) examination of the apparent heterogeneity of results of twin studies of schizophrenia, and 5) a comparison of the etiologic importance of genetic factors in schizophrenia and various medical conditions as revealed by twin studies.

VALIDITY OF THE TWIN METHOD

The traditional twin method used to evaluate the etiologic role of genetic factors in a qualitative trait such as schizophrenia consists of a comparison of concordance rates for the disorder in monozygotic or identical twins and in same-sex dizygotic or fraternal twins. Monozygotic twins are genetically identical, while same-sex dizygotic twins, like full siblings, share on average 50% of their genes. According to the traditional view, because monozygotic and same-sex dizygotic twins share environmental factors to approximately the same extent, differences in concordance

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between the two twin types must be due to the influence of genetic factors.

A precondition for the meaningful application of the twin method to schizophrenia is that the disorder in twins is etiologically similar to that found in the overall population. One objection to twin studies of schizophrenia has been that monozygotic twins, because of their physical similarity and potentially unique psychological relationship, may be more susceptible to schizophrenia than nontwins (2). Contrary to this hypothesis, several studies have examined the frequency of schizophrenia in monozygotic and dizygotic twins and/or in the general population and have found no significant differences (3–4).

The major criticism of twin studies stems from the observation that monozygotic twins share more of their social environment than do same-sex dizygotic twins. Compared with same-sex dizygotic twins, monozygotic twins are treated in a more similar fashion by their parents and more frequently have the same friends (5–8). Critics of twin studies argue that these observations invalidate the twin method because it cannot be ruled out that the similarity in social environment and not the genetic similarity makes monozygotic twins more alike than dizygotic twins. This conclusion, however, is premature.

Three facts are known for a pair of monozygotic twins: 1) They are genetically identical, 2) they have very similar phenotypes (i.e., they behave in a similar way), and 3) they have similar social environments. Two major hypotheses can be put forward to explain the causal relationship between these facts. The first is that the similar phenotypes in monozygotic twins are caused by their similar social environment. This hypothesis would predict that only monozygotic twins exposed to very similar social environments would develop similar phenotypes. The second hypothesis is that the similar phenotypes in monozygotic twins are caused by their genetic similarity. The similar phenotypes of these twins are then responsible for creating their similar social environment. This hypothesis would predict that monozygotic twins would develop similar phenotypes regardless of the similarity of their social environment. If the first hypothesis is correct, then critics of twin studies are justified in their criticism. However, if the second hypothesis is correct, the greater similarity of social environments of monozygotic versus dizygotic twins is the product, not the cause, of the phenotypic similarity of the monozygotic twins. It would then be hard to argue that the greater similarity in social environment of monozygotic twins constitutes a major bias in twin studies.

The last decade has seen the use of several experimental paradigms to evaluate these two hypotheses. Because schizophrenia is a relatively rare disorder, these studies have mostly examined other behaviors, such as personality and cognitive, perceptual, and language skills, for which monozygotic twins are more similar than dizygotic twins. Most of these studies have evaluated one of two particularly plausible ways in which the social environment might differentially influence the behavior of monozygotic and dizygotic twins. First, the knowledge of the zygosity of twins could influence the way twins are treated. For example, if a twin pair was considered monozygotic, then their parents, teachers, and friends might expect them to behave in a very similar fashion and treat them accordingly. Second, the similarity with which twins are treated by their social environment might relate to their degree of physical similarity. Twins who are particularly physically similar would, according to this view, be treated in a particularly similar way by their social environment. Because, on average, monozygotic twins are more physically similar than dizygotic twins, monozygotic twins would tend to be exposed to more similar social environments.

When twins are blood-typed for zygosity determination (i.e., to determine if they are monozygotic or dizygotic), the true zygosity of some twins does not agree with the belief of the twins and/or their parents regarding their zygosity (i.e., the perceived zygosity). Twins for whom true and perceived zygosity differ represent a natural experiment. If the expectations of the social environment are crucial in shaping the behavior of twins, then these twins should behave on the basis of their perceived and not their true zygosity. If genetic factors and not social expectations shape twins' behavior, these twins should behave on the basis of their true and not their perceived zygosity. Four studies have examined normal twins who were misclassified regarding their zygosity (6, 9–11) (table 1). In nearly all cases, these studies found that these twins behaved on the basis of their true and not their perceived zygosity. In other words, twins who were really monozygotic but thought they were dizygotic were behaviorally more similar than twins who were really dizygotic but thought they were monozygotic. The twins tended to behave on the basis of their genetic similarity rather than on the basis of social expectations.

A second approach to evaluating the plausibility of an "environmental bias" in twin studies takes advantage of another natural experiment. Although genetically identical, monozygotic twins differ considerably in their degree of physical similarity (14). If the behavioral similarity of twins resulted from the similarity in their treatment by the social environment and the similarity of their treatment by their social environment resulted from their degree of physical similarity, then the more physically similar monozygotic twins are, the more behaviorally similar they should be. Two studies, both using large sample sizes, have examined this question in normal twins (12, 13) (table 1). Neither found significant correlations in monozygotic twins between the degree of physical similarity and their similarity of IQ, personality, or perceptual and reading performance. Again, possible differences in treatment by the social environment seemed to have little effect on twin behavior.

Two other approaches have been used to evaluate a

TABLE 1. Studies Examining the Validity of the Twin Method

Study	Year	Method	Sample	Measures	Results
Scarr (6)	1968	True versus parent-perceived zygosity	Mothers of 52 female twin pairs	Interview and checklist given to mother	Monozygotic twins considered dizygotic were judged more similar than dizygotic twins considered monozygotic on nearly all variables
Munsinger and Douglass (9)	1976	True versus parent-perceived zygosity	74 twin pairs aged 3–18 years	Two measures of language ability of twins	Similarity of language ability was determined almost entirely by true and not perceived zygosity
Plomin et al. (12)	1976	Physical and personality similarity	228 same-sex twin pairs aged 2–16 years	Parents' ratings of twins' similarity of appearance and four personality traits	No significant correlation in monozygotic twin pairs between degree of physical and personality similarity
Matheny et al. (13)	1976	Physical and test performance similarity	191 twin pairs aged 3–13 years	Parents' ratings of twins' similarity; twins' performance on IQ, perceptual, reading, and personality tests	No consistent correlations in monozygotic twins between degree of physical and test performance similarity
Loehlin and Nichols (7)	1976	Environmental similarity in childhood and ability and personality in late adolescence	850 twin pairs, high school juniors	Questionnaire to parents; twins' performance on California Personality Inventory and National Merit test	No significant correlation between similarity of experience as children and personality or intellectual ability as late adolescents
Lytton (8)	1977	Direct observation of twins and parents	46 male twin pairs, average age 2½ years, and their parents	Naturalistic observations in the home	Monozygotic twins treated more similarly than dizygotic twins in all parental behavior; no difference between monozygotic and dizygotic twins in parent-initiated behavior
Matheny (10)	1979	True versus parent-perceived zygosity	172 twin pairs	Stanford-Binet IQ Test	Similarity in IQ determined entirely by true zygosity, not affected by perceived zygosity
Scarr and Carter-Saltzman (11)	1979	True versus self-perceived zygosity	400 twin pairs aged 10–16 years	Four cognitive and two personality tests	Similarity in performance on cognitive tests for all twins and on personality tests for true monozygotic twins determined entirely by true zygosity, not affected by perceived zygosity. Perceived zygosity had a small effect on similarity of personality in true dizygotic twins
Kendler and Robinette (unpublished)	1982	Physical similarity and concordance for schizophrenia	164 monozygotic twin pairs (at least one twin had schizophrenia) from the NAS-NRC[a] Twin Registry	Physical similarity at induction into the armed services	No correlation between degree of physical similarity and concordance rate for schizophrenia

[a]The National Academy of Sciences-National Research Council Twin Registry.

possible environmental bias in twin studies. If similarity in social environment significantly influenced twin behavior, then twins whose social environments as children were especially similar should as late adolescents be particularly behaviorally similar. However, in a study of 850 same-sex normal twins, correlations between the similarity of childhood social environment and personality and cognitive similarity later in life were, with rare exception, nonsignificant (7).

Lytton (8) clarified the relationship between social expectation and twin behavior by direct observations of young twins and their parents in the home environment. In accord with other investigators, he found that parents treated monozygotic twins more similarly than dizygotic twins. However, when he divided parental behavior into those actions which were in response to twin behavior and those actions which were initiated by the parents, he found that the parent-initiated behavior was equally similar for monozygotic and dizygotic twins. The similarity of the overall parental behavior toward the monozygotic twins resulted entirely from the parental responses to the twins' behavior. The parents treated monozygotic twins more similarly because the twins behaved more similarly. Lytton concluded that "parents respond to, rather than create, differences between the twins."

The examination of a wide range of behavioral traits according to several different experimental paradigms by a variety of investigators consistently suggests that the behavioral similarity of monozygotic versus dizygotic twins cannot be ascribed to differences in treatment of the twins by the social environment. The first hypothesis articulated above is not supported by the available data. The behavioral similarity of monozygotic twins appears not to result from the similarity in social environment of the twins. Rather, the available evidence suggests that the similarity of the social environment of monozygotic twins is the result of the behavioral similarity of the twins.

Differential treatment of twins by their social environment does not appear to be responsible for the greater similarity of monozygotic versus same-sex dizygotic twins for such characteristics as intelligence, personality, and language and perceptual skills. Therefore, it seems unlikely that such differential treatment could be responsible for the greater concordance for schizophrenia in monozygotic versus same-sex dizygotic twins. To specifically test at least one aspect of this hypothesis, Robinette and I (unpublished data) used the extensive records of the National Academy of Sciences-National Research Council (NAS-NRC) Twin Registry (15) (table 1). In monozygotic twin pairs where at least one twin had schizophrenia, we found no correlation between the degree of physical similarity and concordance for schizophrenia. Monozygotic twins who were very physically similar and hence more likely to be treated similarly by their social environment were no more likely to be concordant for schizophrenia than monozygotic twin pairs who were relatively physically dissimilar. These results suggest that differential treatment by the social environment on the basis of degree of physical similarity between twins is not likely to be a significant bias in twin studies of schizophrenia.

THE TRANSMISSION OF SCHIZOPHRENIA

For a familial-environmental bias in twin studies of schizophrenia to be a tenable hypothesis, nongenetic familial factors must be shown to be of major etiologic importance in the disorder. If nongenetic familial factors play only a minor etiologic role in schizophrenia, it would be difficult to postulate that small differences in concordance for exposure to such factors could account for the large difference in concordance for schizophrenia in monozygotic and same-sex dizygotic twins.

The most plausible nongenetic form of familial transmission for a behavioral syndrome like schizophrenia is "vertical cultural transmission" (16). Vertical cultural transmission means that a particular characteristic is learned by offspring from their parents. Examples of behavioral traits largely transmitted in this manner are religious belief and political affiliation (16). In the last two decades increasing evidence has become available to evaluate the possible importance of vertical cultural transmission in schizophrenia.

In its simplest form, vertical cultural transmission of schizophrenia predicts that the high risk for schizophrenia in the children of schizophrenic parents results from offspring "learning" to be schizophrenic from their parents. Therefore, children of schizophrenic biologic parents who have been reared by nonschizophrenic adoptive parents should have a low risk for schizophrenia, and children of a nonschizophrenic biologic parent reared by an adoptive schizophrenic parent should have a high risk for schizophrenia. Five studies have examined the role of this simple form of vertical cultural transmission in schizophrenia. Two studies have found a significant excess of schizophrenia (17) or schizophrenia plus schizophrenia spectrum disorders (18) in adopted-away offspring of schizophrenic biologic parents compared with the adopted-away offspring of control (nonschizophrenic) parents. Results of one of these studies (18) have been reconfirmed in a blind reanalysis that applied *DSM-III* criteria (19). Using a more informative design, Higgins (20) examined the frequency of schizophrenia in offspring of schizophrenic mothers reared by their natural mothers or reared by adoptive parents who were free of psychiatric illness. The rate of schizophrenia was actually nonsignificantly higher in the children reared by the normal adoptive parents. Fischer (21) found that schizophrenia was equally frequent in the offspring of the schizophrenic and well members of monozygotic twin pairs discordant for schizophrenia. Finally, Wender and associates (22) found no excess of schizophrenia spectrum disorders in biologic offspring of normal parents adopted by parents where one had schizophrenia compared with biologic offspring of normal parents adopted by parents without psychiatric illness.

These results suggest that "simple" vertical cultural transmission (where children learn to be like their parents) is not likely to play a major etiologic role in schizophrenia. This hypothesis could also have been rejected because the great majority of schizophrenic patients do not have a schizophrenic parent. It could be suggested, however, that schizophrenia is passed on by a more "subtle" form of vertical cultural transmission where it is learned from parents who, although they have some of the features of schizophrenia, are not themselves overtly schizophrenic. This hypothesis would predict that schizophrenia-like clinical syndromes (e.g., borderline schizophrenia and schizotypal personality disorder) should be common in the adoptive parents of schizophrenic patients. Three studies have examined this question. Kety and associates (23, 24) found no excess of "schizophrenia spectrum" disorders in the adoptive parents of adoptees from Denmark who developed schizophrenia. A blind analysis of interviews from their study using *DSM-III* criteria found no excess of schizophrenia or schizotypal or paranoid personality disorder among the adoptive parents of the schizophrenic adoptees (25). Wend-

er and associates (26) conducted two studies in the United States examining the psychiatric status of adoptive parents of schizophrenic patients. In the first study they found an excess of schizophrenia spectrum disorders in the adoptive parents of schizophrenic patients compared with the adoptive parents of control subjects, but both groups had less psychopathology than parents of naturally reared schizophrenic patients. These investigators were concerned that the psychopathology in the adoptive parents of the schizophrenic patients might have resulted from the rearing of a disturbed child or lack of rater blindness. They attempted to control for these and other methodologic limitations of this first report in a second independent study (27). In this study, they found that the frequency of schizophrenia spectrum disorders was similar in the adoptive parents of schizophrenic patients and in the natural parents of children with nongenetic mental retardation and much lower than that found in the natural parents of schizophrenic patients. Taken together, these studies are not strongly supportive of the hypothesis that a "subtle" form of vertical cultural transmission (where schizophrenia is learned from parents who display mild "schizophrenia-like" syndromes) is responsible for the familial transmission of schizophrenia.

A yet "subtler" form of vertical cultural transmission has been postulated to occur in schizophrenia. To cause schizophrenia in offspring, perhaps parents need demonstrate neither overt nor subtle symptoms of schizophrenia. Rather, they may manifest some deviant form of behavior that, although clinically unrelated to schizophrenia, can nonetheless produce schizophrenia in an offspring. Put in another way, parents do not have to have schizophrenia or a "schizophrenia-like" disorder to be schizophrenogenic.

The strongest evidence in favor of this hypothesis is the analysis by Singer and associates (28) of parents' Rorschach protocols from the first study of adoptive parents of schizophrenic patients conducted by Wender. They found that the communication deviance of the adoptive and natural parents of schizophrenic patients was similar and significantly greater than that found in the adoptive parents of control subjects. Wender and co-workers (27) were unable to replicate Singer and associates' findings in their second study of adoptive parents of schizophrenic patients. Whether these discrepant results stem from the effects of the stress of rearing an adoptive schizophrenic child or less experience in interpreting Rorschach protocols on the part of Wender and colleagues is uncertain.

One clear prediction of this "subtler" form of vertical cultural transmission for schizophrenia, however, is that stepsiblings of schizophrenic patients should be at high risk for the disorder because they are exposed to the same rearing environment that produced a schizophrenic patient. Two studies have examined the risk for schizophrenia or schizophrenia spectrum disorders in stepsiblings of schizophrenic patients. In his twin family study of schizophrenia, Kallmann (29) collected data on 85 stepsiblings of schizophrenic probands; only 1 (1.2%) of these stepsiblings was schizophrenic. This risk differs little from the population frequency of schizophrenia and is much less than the 7.5% frequency of schizophrenia Kallmann found in the full siblings of schizophrenic probands. Kety and associates (24) found no difference in the frequency of schizophrenia spectrum disorders in 11 stepsiblings of schizophrenic adoptees compared with 23 stepsiblings of control adoptees.

Conflicting information exists regarding the importance of this "subtler" form of vertical cultural transmission in schizophrenia. One problem with this kind of familial transmission of schizophrenia is that it is not self-perpetuating. Like genes, for "cultural phenotypes" to perpetuate themselves they must be passed from generation to generation. However, if schizophrenogenic individuals rear schizophrenic offspring, and schizophrenic individuals are not themselves schizophrenogenic, how can schizophrenia be transmitted through many generations (as shown, for example, by Karlsson [30])? One possible solution to this problem is that schizophrenogenic individuals must rear both schizophrenic and schizophrenogenic offspring. This would explain the increased risk for schizophrenia in the nieces and nephews of schizophrenic probands (1, p. 85). However, if, as noted above, schizophrenic individuals are not themselves schizophrenogenic, this "subtler" form of vertical cultural transmission for schizophrenia can still not explain the high risk for schizophrenia in the children of schizophrenic parents.

An adoption study of schizophrenia currently underway in Finland may help clarify the role of vertical cultural transmission in schizophrenia. Tienari and coworkers are examining the risk of schizophrenia in the adopted-away offspring of schizophrenic and control parents ("Biologic Mothers in the Finnish Adoptive Family Study," presented at the 38th annual meeting of the Society of Biological Psychiatry, April 29, 1983). Furthermore, they are attempting to complete dynamically oriented family evaluations of the adoptive homes while the adoptees are still adolescents. Current results are very preliminary because many adoptees have not completed their age at risk for schizophrenia. The only overt cases of schizophrenia have occurred in adopted-away offspring of schizophrenic parents, but nearly all of these occurred in adoptees who were reared in families rated as disturbed. These results raise the possibility that the "subtler" form of vertical cultural transmission in schizophrenia may be of etiologic importance only in the presence of a genetic diathesis toward the disorder. Perhaps other studies of cultural transmission in schizophrenia will need to be reexamined from the perspective of possible gene-environment interactions in the transmission of schizophrenia. However, current evidence does not support such an interaction for the simple form of vertical cultural transmission. Being reared by a schizophrenic parent does not appear to increase the risk for schizo-

phrenia, whether the individual has a genetic "loading" for the disorder (i.e., is the offspring of a schizophrenic parent) (20) or not (i.e., is the offspring of psychiatrically normal parents) (22).

The available evidence to date does not suggest that schizophrenia is learned from parents in the same manner as religious preference and political affiliation are. Furthermore, it is doubtful that schizophrenia is transmitted by parents who display only mild "schizophrenia-like" symptoms. Current evidence regarding the possibe role of "subtler" forms of familial transmission for schizophrenia involving communication deviance or disturbed family interactions is unclear. Further research will be needed to evaluate these claims more fully.

What are the implications of these findings for the interpretation of twin studies of schizophrenia? The most plausible form of environmental bias in twin studies is that parents would treat monozygotic twins more similarly than same-sex dizygotic twins. As noted above, available evidence suggests in fact that parents treat monozygotic twins more similarly only because these twins behave more similarly. Suppose this were somehow not true for twins destined to be schizophrenic. For an environmental bias to be important in twin studies of schizophrenia, the way parents treat children would have to greatly affect the likelihood of their becoming schizophrenic. A small effect of parental behavior coupled with the likely small difference in the similarity of the way parents would treat monozygotic versus same-sex dizygotic twins could not plausibly explain the large differences in concordance for schizophrenia in the two twin types. To date, firm evidence supporting such an important role for the rearing environment in schizophrenia is not available. Although such support may be forthcoming in the future, as of now the absence of such evidence provides a further limitation to the argument that twin studies of schizophrenia are subject to substantial environmental bias.

A discussion of possible environmental bias in twin studies of schizophrenia would not be complete without mention of the method that would ideally resolve the controversy: the study of twins reared apart. If twins reared in uncorrelated environments and twins reared together had a similar concordance rate for schizophrenia, this would provide powerful evidence that the rearing environment does not bias twin studies of schizophrenia. The problem with this approach is that large, systematically collected samples of schizophrenic twin pairs reared apart do not exist. Farber (31, pp. 152–166) recently completed a careful analysis of all cases of monozygotic twin pairs reared apart in which at least one member developed schizophrenia. She concluded that only nine pairs met her criteria for both separation and diagnosis. Of these, six (67%) were concordant for schizophrenia, a rate quite similar to that found in monozygotic twins reared together (see below). Although most of these twin pairs were found as part of systematic twin studies of schizophrenia, the sample size is too small to permit any definitive conclusions. However, the available evidence from separated twins does not support the view that the high concordance for schizophrenia in monozygotic twins is due to rearing environment.

FACTORS IN POSSIBLE "REVERSE BIAS" IN TWIN STUDIES OF SCHIZOPHRENIA

The importance of genetic factors in the etiology of schizophrenia is estimated in twin studies by comparing the concordance rates for the disorder in monozygotic and same-sex dizygotic twins. Differences in concordance rates for schizophrenia in these two twin types are probably not substantially increased by nongenetic familial factors. However, three factors may produce a "reverse bias" in twin studies of schizophrenia by decreasing the difference in concordance in monozygotic and same-sex dizygotic twins: assortative mating, the "twin transfusion" syndrome, and the possibility that the social environment may act to increase differences in personality in monozygotic twins.

Assortative mating means that individuals with similar phenotypes mate with each other at a rate greater than would be expected by chance. Assortative mating probably occurs both for schizophrenia (32–34) and for the schizophrenia-like personality disorders, which are probably genetically related to schizophrenia (35, 36). Assortative mating, which results in dizygotic twins sharing on average more than 50% of the genes etiologically relevant for schizophrenia, should increase concordance for schizophrenia in dizygotic twins. However, because monozygotic twins already share all their genes, their genetic similarity is unaffected by assortative mating. By increasing dizygotic concordance and not changing monozygotic concordance, assortative mating decreases the difference in concordance rates between the two twin types, thereby causing an underestimation of the importance of genetic factors in schizophrenia. The magnitude of this effect is difficult to estimate precisely. A plausible upper limit is that found for intelligence, where assortative mating results in an 11% underestimation of the importance of genetic factors in intelligence as calculated from twin studies (37).

Although all dizygotic twins in utero have separate chorionic membranes (i.e., are dichorionic), two-thirds of monozygotic twins share the same chorion (i.e., are monochorionic) (38). In monochorionic twins, anastomosis exists in the uterine circulation of the two twins (38). In about 20% of all monochorionic monozygotic twins, a substantial transfusion of blood occurs from one twin to the other during gestation. This "twin transfusion" syndrome, which occurs only in monozygotic twins, can result in large differences in the weight and robustness of the twins at birth (38). Pre- and perinatal complications are probably of etiologic importance in schizophrenia (39, 40). Schizophrenic patients may have lower birth weight than their well

siblings (41, 42). In some (but not other) studies of monozygotic twins discordant for schizophrenia, the ill twin was more likely to have had a low birth weight than the well twin (1, p. 120). These findings suggest that the twin transfusion syndrome might, in certain cases, be responsible for discordance for schizophrenia in monozygotic twins. The plausibility of this hypothesis is increased by the finding that the correlation of IQ in monozygotic twin pairs was substantially lower in those who did versus those who did not have the twin transfusion syndrome (43). For this particular aspect of intrauterine experience, the environment of monozygotic twins is more variable than that of dizygotic twins. By decreasing concordance for schizophrenia in monozygotic twins, the twin transfusion syndrome, like assortative mating, might cause twin studies to underestimate the importance of genetic factors in schizophrenia.

Advocates of an "environmental" bias in twin studies implicitly assume that the close sharing of a social environment by monozygotic twins should lead to increased similarity in the personalities of the twin pair. However, it is also possible that this shared environment in monozygotic twins leads to increased differences in the twins. Such a process might be understood as a need for the twins or persons in their social environment to differentiate the twins from each other. The only available experimental paradigm in which to test these hypotheses involves monozygotic twins reared apart. As reviewed by Farber (31, pp. 45–48), only two studies have compared the personalities of monozygotic twins reared apart and reared together. Both studies found that monozygotic twins reared apart were more similar in personality than monozygotic twins reared together. Furthermore, Farber examined the relationship between global similarity in personality and degree of personal contact in monozygotic twins reared apart (31, pp. 246–253). She found that the more contact the twins had, the less similar they were in personality. Regarding monozygotic twins, she concluded, "The usual assumption is that being reared in the same family and having one's twin present for mutual identification acts in the direction of making sets more alike. Yet evidence suggests opposite effects. Twins with the least overlap in family environment and interaction seem more similar."

The precise implication of these findings for twin studies of schizophrenia is uncertain. However, they suggest that if social environmental factors are of etiologic importance in schizophrenia, it is incorrect to assume that such factors, by increasing the similarity of the personalities of monozygotic twin pairs, will necessarily increase concordance for schizophrenia. Rather, the available evidence raises the possibility that such factors may act to increase the personality differences in monozygotic twin pairs. Therefore, it is at least conceivable that social environmental factors, by promoting the development of distinct personalities in monozygotic twin pairs, could decrease the concordance for schizophrenia in monozygotic twins.

HETEROGENEITY IN RESULTS OF TWIN STUDIES

If raw concordance rates are examined, the results of twin studies of schizophrenia conducted to date are quite heterogeneous (table 2). (See appendix 1 for a discussion of the forms of concordance in twin studies.) Probandwise concordance for schizophrenia ranges from 8% to 28% in same-sex dizygotic twins and from 33% to 78% in monozygotic twins. These variable concordance rates might initially suggest that these studies provide different estimates of the role of genetic factors in the transmission of schizophrenia. However, concordance rates for schizophrenia can differ in twin studies for several methodologic reasons (61). For example, difference in the severity of illness in the index twins, differences in diagnostic criteria for schizophrenia, and differences in completeness of ascertainment can all substantially alter observed concordance rates for schizophrenia. Within any single study, however, these various factors should equally affect concordance in monozygotic and same-sex dizygotic twins. Therefore, instead of examining raw concordance rates, a more useful way to determine whether the results of twin studies of schizophrenia are heterogeneous is to employ methods combining data from both monozygotic and same-sex dizygotic twins to provide a single estimate of the role of genetic factors. By using concordance rates from both twin types, these methods largely correct for variables such as differing diagnostic criteria that could cause substantial differences in raw concordance across studies.

In table 3 and figures 1 and 2, two different methods of this kind are applied to the nine twin studies of schizophrenia in which precise probandwise concordance rates for monozygotic and same-sex dizygotic twins were obtainable. The details of these two methods are outlined in appendix 2. The first method, which produces the variable termed H'_C, was empirically derived by Allen (62) as an improvement over an older statistic applied to twin studies. The H'_C statistic can vary from 0 to 1; higher values reflect greater etiologic importance of genetic factors. The second method, derived from the work of Falconer and Smith (63–65), produces the term G, or coefficient of genetic determination. This term, equivalent to "broad heritability" as defined by quantitative geneticists, is defined as the percent of variance of a postulated normally distributed liability to schizophrenia that is due to genetic factors. Both methods assume that monozygotic and same-sex dizygotic twins share etiologically relevant environmental variables to a similar extent. In addition, the G statistic assumes that the mode of transmission of the disorder is polygenic, with a single threshold of manifestation.

The H'_C values calculated for the nine twin studies of schizophrenia are all similar, and in no case do they significantly differ from one another. In eight of the nine studies, the value of $H'_C \pm$ one standard error overlaps with the weighted mean value of H'_C (.71) from all studies (table 3; figure 1). Values for G

TABLE 2. Probandwise Concordance for Schizophrenia in Monozygotic and Same-Sex Dizygotic Twins and Estimated or Given Population Prevalence in Twin Studies of Schizophrenia Where Probandwise Concordance Could Be Exactly Determined[a]

			Probandwise Concordance								
			Monozygotic			Same-Sex Dizygotic			Population Prevalence (%)		
				Concordance			Concordance				
Author	Country	Year	N[b]	N[c]	%	N[b]	N[c]	%	Estimated	Given	Comment
Essen-Moller (47)	Sweden	1941	11	7	64	27	4	15	1.5		Included twins with schizophrenia-like psychotic disorders and cases followed up by Kaij (48) and Essen-Moller (49)
Slater (50)	England	1953	41	32	78	61	14	23	1		Rates determined from case reports. Slater's category of definite and probable schizophrenia used. Pairs where co-twin died before onset of illness in index twin excluded
Inouye (51)	Japan	1961	55	33	60	11	2	18	1		Inouye's category of schizophrenia and schizophrenia-like disorder used. All twin pairs singly ascertained (E. Inouye, personal communication, Dec 1981)
Kringlen (52)	Norway	1967	69	31	45	96	14	15		.805	Population prevalence calculated by Allen and Hrubec (53)
Fischer et al. (54, 55)	Denmark	1969	23	14	61	43	12	28		.790	Fischer's grade 2 concordance used. Two discordant monozygotic and two discordant dizygotic pairs where co-twin died before onset of illness in index twin excluded
Gottesman and Shields (56)	England	1972	26	15	58	34	4	12	1		Consensus diagnosis of schizophrenia plus schizophreniform psychosis used
Allen et al. (57)	United States	1972	111	42	38	130	11	8		.980	Rates calculated by K.S.K. from final project diagnoses (provided by M. Allen and W. Pollin, personal communication, May 1981)
Tienari (58, 59)	Finland	1975	21	7	33	42	6	14		3.4	Two discordant monozygotic twin pairs where index twin had a probable organic psychosis excluded (after Gottesman and Shields [44])
Leonhard	Germany	1982	44	30	68	34	7	21	1		Data from Leonhard (personal communication, July 1982). Diagnosis of schizophrenia included systematic and unsystematic forms (60)

[a]When twin studies of schizophrenia were reported in several publications, only the most complete report was used in constructing this table. Concordance rates for the twin studies follow, with some exceptions, the judgments of Gottesman and Shields (44, 45). When possible, rates are used that reflect concordance for schizophrenia and schizophrenia-like disorders. No age correction is used. The estimate for the study of Essen-Moller is higher because in that study all the twins were subject to a long-term follow-up; the comparable population prevalence actually equals a lifetime risk. Although the study of Luxenburger (46) should, technically, be included in this table, it is excluded both because of the discrepant concordance rates given in different publications and because the absence of any concordant same-sex dizygotic twin pairs makes an exact calculation of the importance of genetic factors in the etiology of schizophrenia from this study impossible (for a review of Luxenburger's study, see Gottesman and Shields [45, pp. 11–17]).

[b]Total number of co-twins of primarily ascertained index twins (see appendix 1).

[c]Number of co-twins of primarily ascertained index twins with schizophrenia (see appendix 1).

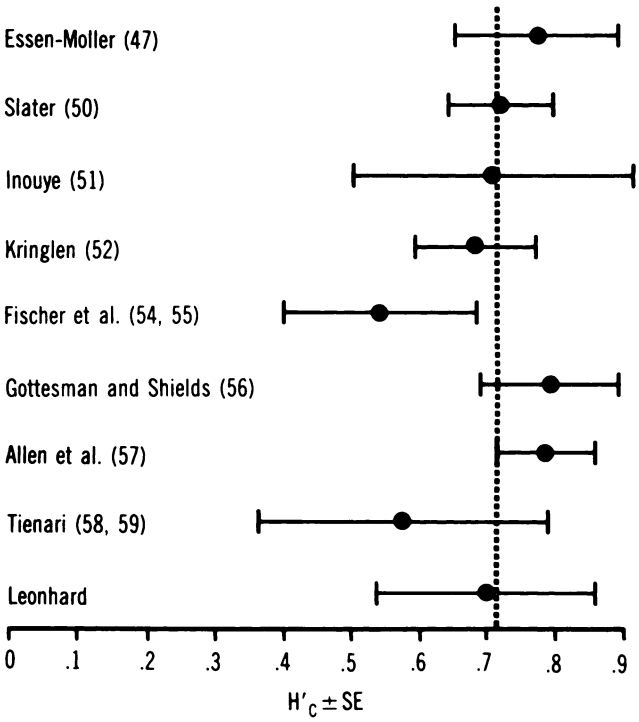
calculated from the nine studies are also quite similar (table 3; figure 2). The values of G±one standard error in all nine twin studies of schizophrenia overlap with the weighted mean of G from all studies (.68). None of the values of G calculated from the nine studies differed significantly from any other. The probable

TABLE 3. Etiologic Importance of Genetic Factors in Schizophrenia as Calculated by Two Methods[a] From Twin Studies Where Probandwise Concordance Could Be Exactly Determined

Study	Year	G	SE	H'_C	SE
Essen-Moller (47)	1941	.87	.36	.77	.12
Slater (50)	1953	.65	.23	.71	.07
Inouye (51)	1961	.66	.35	.70	.20
Kringlen (52)	1967	.61	.20	.68	.09
Fischer et al. (54, 55)	1969	.41	.29	.54	.14
Gottesman and Shields (56)	1972	.86	.32	.79	.10
Allen et al. (57)	1972	.80	.20	.78	.07
Tienari (58, 59)	1975	.53	.33	.57	.21
Leonhard	1982	.63	.24	.70	.16
All studies					
Unweighted		.67	.05	.69	.03
Weighted		.68	.04	.71	.03

[a]See appendix 2 for explanations of the G and H'_C statistics.

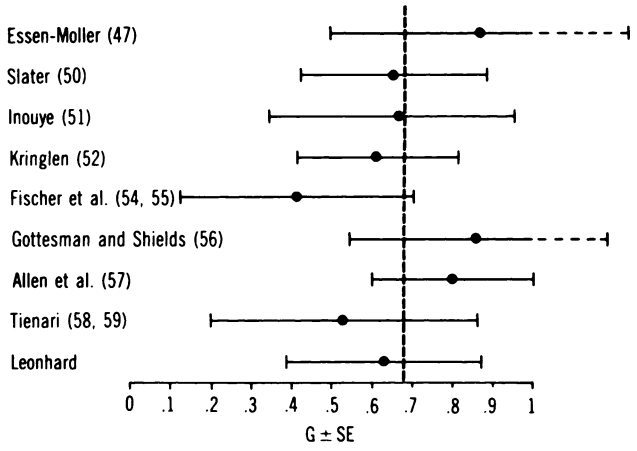
FIGURE 1. Values of H'_C for Twin Studies of Schizophrenia Where Probandwise Concordance for Schizoprenia Could Be Precisely Calculated[a]



[a]See appendix 2 for explanation of the H'_C statistic; the dotted vertical line indicates the weighted mean.

values of H'_C and G were also determined for the two major twin studies of schizophrenia from which exact probandwise concordance rates could not be calculated (29, 66) (see appendix 3). The results were within the range of values found for the other nine twin studies. When the possible methodologic differences between studies are corrected for, the results of all twin studies of schizophrenia are quite consistent. With variation between studies no greater than might be expected by chance, they all suggest that genetic

FIGURE 2. Values of the Coefficient of Genetic Determination (G) for Twin Studies of Schizophrenia Where Probandwise Concordance for Schizophrenia Could Be Precisely Determined[a]



[a]See appendix 2 for explanation of the G statistic; the dotted vertical line indicates the weighted mean.

factors are of major etiologic importance in schizophrenia.

The use of the G statistic is based on the assumption that the mode of schizophrenia is polygenic. How plausible is this assumption? Evidence in favor of a polygenic mode of inheritance for schizophrenia has been reviewed (67, 68). Recently, three different analytic methods have been applied to schizophrenia to determine whether the other most frequently postulated mode of inheritance (a two-allele single-locus model [69]) fits the available data. All three techniques concluded that it does not (70–73, and C.L. Carter, "Segregation Analysis of Schizophrenia in Four Ethnic Groups in Hawaii," abstract presented at the 12th annual meeting of the Behavior Genetics Association, 1982). Applying biometrical techniques to twin studies, Fulker (74) concluded that the transmission of schizophrenia is polygenic. When either a restrictive (75) or more general two-allele single-locus model (73) is applied to twin studies of schizophrenia, the results of certain studies are inconsistent with the model. However, a polygenic model of transmission is very flexible and fits all twin studies of schizophrenia done to date. Furthermore, a path-analytic model based on polygenic transmission has shown a good fit for the risk of schizophrenia in various first- and second-degree relatives (76). Although to date the literature on the mode of transmission of schizophrenia is far from conclusive, it does suggest that a polygenic model is sufficiently plausible to justify its application in the calculation of G from twin studies of schizophrenia.

The values of H'_C and G calculated from twin studies of schizophrenia are relatively high, which suggests that genetic factors play a major role in the familial transmission of schizophrenia. If the assumptions of Falconer's model (63) are correct, these results suggest that about 68% of the variance in liability to schizophrenia is due to genetic factors. This figure,

TABLE 4. Importance of Genetic Factors in the Etiology of Schizophrenia and Common Multifactorial Medical Conditions as Calculated From Twin Studies[a]

Medical Condition	G	SE	H'_C	SE
Diabetes mellitus (67)[b]	.77	.22	.71	.11
Diabetes mellitus (80)[b]	.74	.22	.69	.08
Schizophrenia (this review)	.68	.04	.71	.03
Hypertension (80)	.57	.25	.58	.10
Diabetes (81)[a]	.52	.74	.60	.16
Epilepsy (82)	.50	.33	.56	.13
Coronary artery disease (83)[c]	.49	.57	.49	.17
Stroke (82)	.48	.24	.47	.12
Duodenal ulcer (84)	.46	.13	.46	.09
Breast cancer (85)	.45	.30	.53	.15
Peptic ulcer disease (80)	.41	.25	.48	.12
Bronchial asthma (82)	.29	.24	.40	.08
Myocardial infarction (86)	.29	.61	.33	.35
Myocardial infarction (80)	.11	.23	.18	.13

[a]See appendix 2 for explanations of the G and H'_C statistics. The assumptions of the model for the calculations of G are probably not completely met for a number of the medical disorders listed here. For example, diabetes mellitus and ulcer disease are probably heterogeneous, and single gene effects may be important in some subforms of these disorders (79). Nonetheless, the calculated value of G provides a rough measure of the importance of genetic factors for the disorders listed.
[b]The disease prevalence was estimated rather than calculated from the original report.
[c]Angina pectoris and/or myocardial infarction.

which is quite similar to that found when a biometric (74) or path-analytic (76) approach is used, is somewhat lower than those reported when methods that make no correction for shared environmental effects (77, 78) are used.

GENETIC FACTORS IN SCHIZOPHRENIA AND VARIOUS MEDICAL CONDITIONS AS DETERMINED BY TWIN STUDIES

To provide perspective on the values of H'_C and G found for schizophrenia, it is helpful to compare them with those calculated from twin studies of common multifactorial conditions (table 4). When both statistics are used, the importance of genetic factors in the etiology of schizophrenia is as great as or greater than that found in the various medical conditions. According to these models, genetic factors seem about equally important in the etiology of schizophrenia and diabetes. However, these models suggest that genetic factors are of greater etiologic importance in schizophrenia than they are in several common medical conditions where hereditary factors are usually thought to play an important role, such as hypertension, coronary artery disease, ulcers, and asthma.

SUMMARY

In this article I have attempted to review twin studies of schizophrenia from the perspective of recent developments in twin research and in our understanding of the transmission of schizophrenia. This review is far from comprehensive in that major methodologic issues in twin studies of schizophrenia, such as diagnosis, mode of ascertainment, and zygosity determination, have not been discussed. This article is focused on a single question: Have twin studies of schizophrenia fulfilled their initial purpose in clarifying the role of genetic factors in the familial transmission of schizophrenia? Critics have suggested that twin studies of schizophrenia are flawed by an environmental bias because the greater concordance for schizophrenia in monozygotic versus same-sex dizygotic twins may result not from genetic factors but, rather, from the greater similarity of the social environment of monozygotic twins. This review has suggested that this bias most likely does not apply for two reasons. Most important, studies have shown that the similarity of the social environment of monozygotic twins is the result and not the cause of their behavioral similarity. In addition, studies to date have failed to provide evidence that familial-environmental factors are of major etiologic importance in schizophrenia.

Much attention has been focused on potential biases in twin studies that would tend to increase concordance for schizophrenia in monozygotic twins relative to dizygotic twins. However, at least three potential factors could conceivably cause a "reverse bias" by decreasing the difference in concordance rates for schizophrenia in monozygotic and dizygotic twins: assortative mating, the twin transfusion syndrome, and the tendency for the shared environment in monozygotic twins to lead to increasing differences in personality.

Another criticism directed at twin studies of schizophrenia results from the wide range of raw concordance rates for schizophrenia found in different studies. However, when methods designed to estimate the importance of genetic factors have been applied to twin studies of schizophrenia, the results of all studies have been quite consistent. When these methods were applied to twin studies of common multifactorial medical conditions, they showed that genetic factors are at least as important in the etiology of schizophrenia as they are in the etiology of diabetes, hypertension, coronary artery disease, and ulcers. Twin studies of schizophrenia have consistently suggested that genetic factors play an important role in the familial transmission of schizophrenia. According to our current knowledge, it is not likely that these findings result from major biases in the twin method.

APPENDIX 1. Forms of Concordance in Twin Studies

Two methods are most frequently used to express concordance rates for qualitative traits such as schizophrenia in twin studies (53, 87): pairwise and probandwise concordance. Pairwise concordance is the percent of all twin pairs concordant for the disorder in question. Probandwise concordance is the frequency of the disorder in the co-twins of primarily ascertained index twins (i.e., twins found by the initial selection procedure, such as psychiatric hospitalization). Probandwise concordance is the more genetically

meaningful form of expression for concordance and therefore is used in this review. Probandwise and not pairwise concordance gives an estimate of the segregation ratio for the disorder and can be compared with the frequency of the disorder in other relatives of affected probands or in the general population. When only one member of each twin pair is primarily ascertained, then probandwise and pairwise concordance are equivalent. When both members of some twin pairs are primarily ascertained, probandwise concordance will always exceed pairwise concordance.

APPENDIX 2. Two Methods of Combining Data from Monozygotic and Same-Sex Dizygotic Twins to Provide a Single Estimate of the Etiologic Role of Genetic Factors

The H'_C statistic is calculated from the following formula:

$$H'_C = 1 - C_{dz}/C_{mz}$$

where C_{dz} and C_{mz} equal the probandwise concordance rate for the disorder in dizygotic and monozygotic twins, respectively. The standard errors of C_{dz} and C_{mz} are determined by the standard error of the proportion. From these standard errors, the standard error of H'_C can be estimated by the method of Armitage (88).

The G statistic is calculated as follows:

$$G = 2(r_{mz} - r_{dz})$$

where r_{mz} and r_{dz} are the correlation of liability for monozygotic and dizygotic twins, respectively. The correlation of liability and its standard error are calculated by the method of Smith (65) from the known or estimated population prevalence of the disorder, the probandwise concordance for the disorder in monozygotic and dizygotic twins, and the number of monozygotic and dizygotic concordant pairs. The G statistic provides an estimate of the genetic contribution to the correlation of liability in twins by "subtracting out" the role of the common environment to which the twins are exposed.

The statistical significance of the difference between the values of H'_C or G calculated from two twin studies is estimated by converting the difference to a Z score by the following formula:

$$Z = G_1 - G_2/\sqrt{SE_1^2 + SE_2^2}$$

where SE_1 and SE_2 represent the standard error of G_1 and G_2 (or H'_C), respectively.

APPENDIX 3. Determination of Probable Values of H'_C and G in Two Twin Studies of Schizophrenia Where Exact Probandwise Concordance Rates Could Not Be Determined

In two major twin studies of schizophrenia the available information did not permit the precise determination of probandwise concordance rates for schizophrenia. In the study of Rosanoff and associates (66), the uncorrected probandwise concordance for schizophrenia was within the range of 61% to 76% for monozygotic twins and 13% to 23% for dizygotic twins. If we assume a population prevalence for schizophrenia of 1%, the values of H'_C (±SE) from this study would be between .69±.07 and .78±.08 and the values of G (±SE) would be between .63±.26 and .84±.26. In Kallmann's study (29), although the overall proportions of singly and doubly ascertained concordant pairs are given, these figures are not broken down by zygosity. Given the reasonable assumption that the proportion of singly to doubly ascertained concordant twin pairs was the same in both zygosity groups, the uncorrected probandwise concordance for schizophrenia can be calculated as 78% in monozygotic and 19% in dizygotic twins. If we assume a population prevalence of schizophrenia of 2%, which is plausible given the broad definition of schizophrenia used by Kallmann in this study, the value of H'_C (±SE) from this study would be .76±.04, and the value of G (±SE) would be .90±.13.

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