Etiological Implications of Studies of Identical Twins Discordant for Schizophrenia

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I. Introduction

I should like to share with you our experiences in studying identical twins discordant for schizophrenia, for I believe that these investigations have taught us a number of lessons about the problems inherent in research on schizophrenia. I also feel fairly confident that they have brought us closer to the long-hoped-for day when some answers to the schizophrenia conundrum will be forthcoming.

But despite this guarded optimism, I want most to stress in my remarks here the need for conservatism in interpreting data. We, as investigators, must always be aware of the sometimes damaging effects of our own enthusiasm, which can lead us to report results prematurely. Unfortunately, there are many potentially confounding variables which must be accounted for before meaningfulness — not just statistical significance—can be attributed to data derived from the study of schizophrenia.

Although those of us involved in the twin studies to be reviewed here are relatively "conservative" investigators, we have nonetheless reported findings which have been either over-interpreted or misinterpreted—usually because we failed to provide the definitive data which might have allowed us to draw firm, rather than tentative, conclusions.

Since 1963, the Section on Twin and Sibling Studies in the Adult Psychiatry Branch of the NIMH's Intramural Research Program has been studying identical twins and their families.* Referrals were derived from a nationwide mailing seeking identical twin pairs in which one twin was schizophrenic and the co-twin was not. Each referral was checked out by telephone and letter as to diagnostic status, probability of being identical and willingness to cooperate.

In this way we eliminated, insofar as possible, pairs in which diagnosis was uncertain in the index, pairs in which the co-twin control had been called schizophrenic unbeknown to the referring source, pairs in which one of the parents was dead and finally, pairs in which blood groupings were not identical, indicating the twins were not, in fact, one-egged. In addition to

* The principal investigators have been Drs. W. Pollin and J. Stabenau. Drs. L. Mosher, J. Tupin, A. Hoffer, M. Allen and Mrs. B. Scupi have also made major contributions.
the discordant pairs, sets of twins concordant for schizophrenia and for normality were selected in each instance to match one of our discordant pairs on such variables as age, sex, ethnic group, geographical location and parents' educational level.

The study's primary focus was not genetic factors in schizophrenia; rather, its research strategy was to hold genetic factors constant, while studying constitutional and environmental differences. Thus, the similarities and differences within twin pairs were examined with regard to a whole panoply of variables: physiological, biochemical, psychological, intrafamilial role relationships and so forth. In these twin pairs, genetic, ethnic and social class factors were identical and each twin experienced the impact of family crisis at the same developmental stage—thus eliminating the investigative problem of weighing the age-differential impact of such crises when ordinary sibs are compared.

We feel that these advantages of the twin study method enabled us to understand better how one member of a pair of identical twins can become schizophrenic while his co-twin, with the same genes and raised in the "same" environment, does not.

**Briefings**

Before launching into a detailed description of our studies, I should like to preface my remarks with the following caveats:

1. It is important to remember that our data were derived from a relatively small sample: 24 pairs of identical twins (15 discordant for schizophrenia, five concordant for schizophrenia and four psychologically "normal"), the twins' parents, and in some cases, their sibs.

2. Our sample comprises intact families willing to come to Bethesda, Maryland, as a unit and be studied for two weeks; this, of course, introduces a bias which can never be systematically assessed.

3. Some of our data are derived from retrospective reconstructions and are therefore subject to distortion. Partly to counteract this problem, we made many home visits and interviewed relatives, teachers, friends and acquaintances who knew very little of the subsequent lives of the twins or their parents. In no instances was there a complete turnaround in the reporting of data; that is, we never found a twin who was described by his parents as shy and withdrawn but as extremely sociable, outgoing and friendly by other members of the community.

4. Despite our careful selection procedures, not all of our twins would be universally diagnosed as schizophrenic. However, we feel that our diagnostic criteria are sufficiently stringent that most merit this label. To call a twin clearly schizophrenic, we demanded unanimous agreement from five judges that he was actively psychotic during the course of his two-week stay in the Clinical Center.* In addition, we assessed the certainty of schizophrenia in each person based on an eight-point scale and can, therefore, analyze the data from our sample according to the degree to which the diagnostic consensus was firm or less certain.

Let me turn now to five major areas which our studies have addressed: genetic, constitutional, biochemical, neurological and family factors in schizophrenia.

**II. Genetic**

Recent sophisticated studies of twins based on birth record searches have

* I have recently been in touch with the psychiatrist now treating the index twin whom we viewed as the least schizophrenic member of our entire series. He has read our reports and says that, in his judgment, the patient is at times clearly schizophrenic and that we were far too conservative in drawing diagnostic conclusions.
indicated that between 65 and 75 percent of identical twins with a known schizophrenic co-twin will never develop manifest schizophrenia. This figure should be contrasted with those in the literature of 15 years ago which indicated quite the reverse; that is, that from 65 to 75 percent of identical co-twins of schizophrenics would eventually manifest schizophrenia themselves.

While our study has not contributed directly to the issue of concordance rates, we can say something about Heston's (1970) proposal that this disorder is inherited as a single dominant gene, with "schizoidness" the genotype whose phenotypic manifestation as schizophrenia is relatively rare. Since our non-schizophrenic controls are genetically identical to their schizophrenic co-twins, one would expect them to show—based on Heston's reasoning—an extremely high, if not 100 percent, incidence of schizoid traits. Challenged by this hypothesis, we recently reviewed (Mosher, in press) three psychiatrists' separate reports of interviews with our 15 co-twins of schizophrenics and our eight normal twins. Each time one of the 61 descriptors used by Kallman (1938) and Slater (1953) to define "schizoidness" was applied to a twin he received a score of one to three based on the frequency with which the term was used. Thus, each twin could receive a score from 0 to 183.

Interestingly, we found that our eight normals had a mean score of approximately seven, as compared to our co-twins of schizophrenics whose mean score was six! Looking at our data in a more restricted way, we pursued each interviewer's summary for any mention of the word "schizoid", and found that it had been used to characterize two of the 15 co-twins of schizophrenics and one of the eight normal twins. It is important to note that at no time did more than one of the three psychiatrists refer to a given twin as schizoid. That most of our co-twins were not schizoid is not to say, however, that they were all normal; many of them received some psychiatric diagnosis—most commonly "passive dependent", "passive aggressive" or "obsessive-compulsive" personalities.

III. Constitutional

In preliminary reports we noted that the index schizophrenic in our discordant pairs was in each instance the twin of lighter birth weight (Pollin et al., 1966). But while this held true for the first 11 pairs in our series, the index twins in the next four pairs studied were of higher weight at birth than their non-schizophrenic co-twins. Our initial reports have often been interpreted as indicating either a constitutional or prenatal defect in the schizophrenic-to-be.

We now feel, however, that it is not the birth weight itself which is of great significance (because in many of our pairs the difference is small and the lighter twin's weight would not even have classified him as "premature"), but rather the setting up of differential response patterns in the parents. (See page 65 for further discussion of this issue.)

While we have found more evidence of neonatal complications in the discordant indexes than in their co-twin controls, it is impossible to draw etiological conclusions in the absence of an adequate sample of ordinary twin births to establish a base rate. Several schizophrenic twins in our sample seem to have suffered minor CNS damage secondary to anoxia or infection during their early years, but again, their numbers are too few to allow us to comment meaningfully on this finding's etiological implications.

IV. Biochemical

When the twin study was first undertaken, we decided to look at five biochemical factors thought to be relevant to schizophrenia:
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(1) S-19 macroglobulin levels.

We found that these were not significantly higher in our schizophrenic twins than in our non-schizophrenic subjects; they were, however, significantly higher for females than males (Stabenau et al. 6, 1968). In reviewing Fessel's 7 original report (1962), we found the same relationship in his largely female sample of schizophrenic patients. Thus, it appears that S-19 macroglobulin is actually sex-related rather than schizophrenia-related.

(2) The lactate/pyruvate ratio.

In an intra-pair comparison, we found higher L/P ratios in the index twins in 12 of 14 pairs. Unfortunately, to confound the interpretation, we also found a positive relationship between recent drug intake and elevation of the L/P ratio (Stabenau et al. 8, 1969). This fact, plus similar findings from others (Ryan et al. 9, 1966) who attempted to replicate the original findings of Frohman et al. 10, 11, (1960a and b) led us to conclude that the higher L/P ratio found in many samples of schizophrenics is most parsimoniously explained as a concomitant of treatment, such as hospitalization or phenothiazine intake.

(3) 3,4-DMPEA.

Our studies of this abnormal methylated amine (Friedhoff and Van Winkle 12, 1962) have not clarified the many issues surrounding its possible relationship to schizophrenia. Based on 24-hour urine samples from six twin pairs (analyzed by Dr. Friedhoff), we found DMPEA in the control twins only in three pairs, in both index and control twins in one pair and not at all in two pairs. Thus, in our small sample, four of 11 schizophrenic index twins and four of six co-twin controls had DMPEA isolated from their urine (Stabena et al. 8, 1969). While we were unable to document either the genetic determination of DMPEA or its relevance to schizophrenia, no final conclusions can possibly be drawn from a study containing so few subjects.

(4) Corticosteroids.

While we found no differences in our twin pairs in terms of levels of 17-ketosteroids, 17-hydroxysteroids were higher in the indexes than in their co-twin controls, whose three-day levels were comparable to those of other normal subjects.

(5) Biogenic catecholamines.

Our data are very difficult to evaluate because of the relatively small number of subjects, the number of metabolites run and possible dietary effects. Given all of these provisos, it appears that, in those pairs in which there is a schizophrenic genotype (that is, where there is one schizophrenic member), both members of the pair will tend to have elevated values for urinary epinephrine (Pollin 13, 1971). These are extremely tentative findings, however, and we do not feel our data should be regarded as conclusive.

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A forthcoming review of biochemical factors in schizophrenia (Wyatt, Termini and Davis, 1971), concludes, "To date, no biochemical abnormalities have been consistently and exclusively associated with schizophrenia, although a failure to respond to histamine has frequently been found in schizophrenic patients. Insuring that a given finding is not an artifact due to such factors as diet, drugs and chronic hospitalization remains a major (and all too seldom surmounted) difficulty in conducting biochemical research." Our results are certainly congruent with that summary statement.

The two areas in which we have provided some clarification for the field are

(1) In establishing the confounding effects of sex with regard to S-19 macroglobulins

(2) In replicating earlier work indicating that urinary 17-hydroxysteroids reflect psychological turmoil but are not causally related to schizophrenia.

Thus, our studies have, in the main, elucidated confounding factors! If nothing else, they illustrate the myriad irrelevant factors which must be ruled out before meaningfulness can be attributed to findings.

V. Neurological Factors

We have recently reported neurological findings in our twins (Mosher et al., 1971b). Based on two careful neurological examinations, 11 indexes in the discordant pairs, two schizophrenics in the concordant pairs and two normal twins were judged as having probable or definite neurological "soft" signs. Significantly more abnormal signs were found in discordant indexes than in their co-twins, in schizophrenics than non-schizophrenics and in lower birth weight than in higher birth weight twins. Although two electroencephalograms on each twin revealed few clear abnormalities and striking intrapair concordance, half of the sample had some minor deviation from normal on at least one EEG.

A possible problem with these findings is that both the examining neurologists and the investigator who reviewed their reports knew the psychological state of the subjects (i.e., schizophrenic or not). Because the two neurologists independently agreed quite highly in their evaluations, however, this may not be so serious a problem as it might at first appear. In any case, we plan in the future to subject these reports to blind analyses.

We attempted to interpret our findings as either etiologic (i.e., causal and therefore present prior to illness) or responsive (i.e., due to the illness). To test the etiologic notion, we looked at whether neurological impairment was related to the fact that many of our schizophrenic twins were of lower weight at birth. If this were so, one might expect a relationship between amount of neurological abnormality and birth weights on a rank-order correlation procedure. This did not prove to be the case.

We then explored a second possible interpretation of the findings: Might the neurological impairment found be a result of either the occurrence of schizophrenia or some treatment given for it? This interpretation received its strongest justification from the association of neurological abnormalities with the diagnosis of schizophrenia in both concordant and discordant pairs. The non-schizophrenic co-twins, despite having identical genetic endowment, having been delivered from the same pregnancy and having been raised by the same parents, had many fewer signs of neurological abnormality.

Two variables which might account for the findings in the schizophrenic twins are the administration of psychotropic drugs and ECT. However, we found no significant correlation between previous drug intake or ECT and neurologic abnormality.
In summary, we concluded that we could not provide adequate evidence to substantiate or discredit either an etiologic or a responsive explanation and that one, or both, of these interpretations may be true to differing extents in differing individuals.

VI. Family

Our study—like all studies of the already manifest and diagnosed schizophrenic—can never prove that schizophrenia is a disorder of intrafamilial relationships. Only studies of individuals who are at risk for the development of schizophrenia prior to the onset of illness will allow us to answer questions of causality. We feel, however, that our studies have helped clarify a number of issues and point to several new directions in family research.

In our 15 families containing twins discordant for schizophrenia, we found differential patterns of interaction between one parent and one twin. It was as though one parent (usually the mother) had chosen a twin to rear, leaving the other, more or less by default, to the second parent. This pattern of "selection" seemed to result from the parent's need for a mutual dependency relationship in which he or she could attribute to the child those parts of his personality with which he felt least comfortable (aspects which varied considerably).

Not infrequently, the twin so singled out really did need more care or protection because of some problem; e.g., low birth weight, physical deformity or illness. But severe, prolonged need was rare in our series and, in fact, several of the normal twins could easily have been seen as much more needy because of low birth weight, prematurity and cyanosis; yet the pattern of differential parental involvement did not evolve with these weak normal twins, seemingly because the needs of the parents were met elsewhere or were of a much lesser intensity.

In our normal pairs, there were also the usual numbers of serious illnesses and complications but the parental responses to these crises lasted only until they were no longer needed. Thus, a quality of parental flexibility of response seems to be important to the development of psychological health. In our discordant pairs, however, there was never a reported instance of role change or realignment of twins and parents over time; that is, once a twin was "locked in" with a particular parent, that involvement continued regardless of changes in his cotwin, the other parent or family circumstances.

What other factors may have led to the occurrence of psychosis in one twin and not in the other? We feel that the pattern of differential over-involvement with one parent may have prevented the index twin from developing a close relationship with his co-twin. Indeed, twins in our discordant pairs were more different on almost all variables than were twins in our concordant or normal pairs. Thus, differences are emphasized to an extreme in these cases and the potentially valuable aspects of the twinship are not exploited.

Another interesting issue is, why do these twins grow up to be schizophrenic rather than neurotic? We feel that this may be explained by communication difficulties specific to families with a schizophrenic offspring. The parent who was most intimately involved with the schizophrenic twin in our series was usually the more psychopathologic, cognitively unclear and communicationally confused parent (Moshier et al.16, 1971a). Obviously, the nonschizophrenic co-twin cannot entirely avoid this less healthy parent's influence and it is certainly true that the co-twin controls in our study were not psychologically normal but they were also clearly not schizophrenic. They seem to have had greater freedom than the indexes to seek contact outside of the home. For example, our co-twins reported (almost universally) that in adolescence
they made the decision to leave the twinship behind and seek friends outside of it; they were usually able to negotiate this successfully, unlike the index-to-be, who was still enmeshed in a tight, mutually dependent bond with a parent.

**SUMMARY**

In summary, our model of the development of schizophrenia in one twin and not the other emphasizes differential parental interaction with the schizophrenic-to-be, lack of cognitive and communication clarity and contradictory and incompatible role expectation. Initially, the constitutionally (or perhaps neurologically) less favored twin is "selected" to be the dependent member of the twinship. This continuing role as the "weak" twin is eventually incompatible with the kinds of demands for accomplishment and independence he encounters in the home, school or community. Because of his identification with a communicationally disordered parent, he lacks the ability to think clearly, comprehend, communicate and solve problems in an increasingly complex world.

Thus, "breakdowns" occur at times of greatest stress (e.g., separation from home or co-twin, death of a grandparent, etc.) when his limited resources are overtaxed to the point of disorganization. By way of contrast, the co-twin has many more cognitive, communicational and problem-solving skills available which, if stressed only "normally," are sufficient to carry him over life's hurdles.

**REFERENCES**