progress and regress in the research on the genetics of schizophrenia*

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The evidence reviewed by Gottesman and Shields (1976) strongly supports the involvement of genetic factors in the development of schizophrenia. This view was widely adopted following the 1967 Puerto Rico conference at which the preliminary results of the Kety-Rosenthal research (Kety et al. 1968 and Rosenthal et al. 1968) were presented. Subsequent work has strengthened the evidence.

I would like to make a few comments on some of the genetic aspects of the Gottesman and Shields review and then deal briefly with one or two broader issues. First, it needs to be remembered that Gottesman and Shields are researchers who have primarily used twin studies in their investigations. They have a tendency to conceptualize genetic problems in terms of the relative contributions of heredity and environment to the causation of a trait—the very kind of information that the twin methodology was designed to elucidate. Thus, as they discuss the less-than-perfect rates of concordance for schizophrenia among monozygotic twins, they are quick to note that low concordance does not necessarily mean that there is low heritability. The use of heritability in this context implies that heritability represents a measure of the strength of the genetic determination of schizophrenia. This is an unfortunate implication and a misuse of the heritability concept.

Heritability is a term useful to the animal and plant breeder because it provides a predictive handle on the rate of change that can be effected through selective breeding. Its use outside this realm is questionable (Falconer 1960).

The causes of variation for a given trait in a population can be broken down into major components of variance representing genotypic, nongenotypic (environmental), and interactional contributions. The genotypic part can be further subdivided into components representing the contributions of individual alleles (additive variance), pairs of alleles at a locus (dominance variance), and other variance components. Heritability represents the proportion of the phenotypic variation in a population due to additive genetic variance. What Gottesman and Shields call heritability is more properly called the "degree of genetic determination" (Falconer 1965), which includes other variance components in addition to the additive one. Thus, the degree of genetic determination is an inflated estimate of the true heritability. At the present time, there is no way of teasing apart the components of the genotypic variation so that the true heritability of the liability to schizophrenia can be calculated.

The problem is actually more complex. Calculations of the degree of genetic determination or of heritability require that there be no variance contributions arising from gene-environment interactions and gene-environment correlations. If genetically predisposed individuals are subjected to environments that promote schizophrenia—a not unlikely possibility—then such gene-environment correlations would preclude the valid estimation of the genotypic and other contributions to the phenotypic variance. Correlation "makes it impossible to know how much of the phenotype similarity arises from similarity of genotype and how much from similarity of the environment" (Feldman and Lewontin 1975, p. 1164).
The estimation of heritability is also dependent on the underlying assumptions made about the genetic transmission of a trait. For example, Matthysse and Kidd (1976) have recently shown that the heritability (or rather the degree of genetic determination) of the liability to schizophrenia can vary anywhere from 0 to 80 percent depending on the genetic model of transmission assumed to be operative. They found that the lower estimates of heritability were associated with single major locus models, whereas the polygenic models yielded the higher estimates of heritability.

Very much because of the work of Jensen (1972) and others concerning the genetics of IQ differences and the determinants of intergroup differences in IQ, the concept of heritability has been recently subjected to critical reexamination. Matthysse and Kidd (1976) have commented that "heritability does not provide information on etiology... and cannot be unambiguously estimated from data. Therefore, it is our conclusion that heritability of schizophrenia is not a meaningful concept or statistic, even though the disease has a clear genetic component" (p. 186). Feldman and Lewontin (1975) echo the sentiment of many American geneticists when they state that the "estimate of heritability... is nearly equivalent to no information at all for any serious problem of human genetics" (p. 1168). Perhaps Gottesman and Shields are not willing to go that far. Nonetheless, it needs to be recognized that their use of heritability estimates is more in the service of convincing the reader that there are major genetic inputs in the liability to schizophrenia than in providing meaningful genetic information.

The problem of the gene-environment correlations in the development of schizophrenia fostered the use of the adoption strategy as a means of separating hereditary from environmental influences. Heston's (1966) classic study in Oregon was the first of this type to be reported. It was quickly followed by the reports of Kety, Rosenthal, and their colleagues (Kety et al. 1968 and Rosenthal et al. 1968) of work being carried out in Denmark. It may be years before we will be able to assess fully how successful or unsuccessful the Kety-Rosenthal strategy has been. As the data accumulate, it becomes apparent that the adoption method is not without its peculiar set of quirks and problems.

The Danish data, as Gottesman and Shields point out, are not as clean as one would wish. For example, in contrast to Heston's (1966) findings of a significantly higher rate of schizophrenia in index adoptees than in control adoptees, Wender et al. (1974) reported no significant difference in the rate of schizophrenia (definite or uncertain) between index and control groups.

Wender et al. (1974) believe that their results are due to an inflated rate of psychopathology in the control group. Control adoptees were selected because of the absence of psychiatric hospitalization in their biological parents. More careful assessment through interviews, however, revealed an inordinately high rate of schizophrenia spectrum diagnoses among the biological parents of the controls. Careful sampling procedures, the pride of the Kety-Rosenthal group, and one of the great strengths of their strategy, may yet turn out to be an Achilles' heel.

If, as the Kety-Rosenthal group now claims (Wender et al. 1974), the control adoptees are not representative of individuals with parents free of psychopathology, one is left wondering, how valid are any of the comparisons between the control and index adoptee groups? Also, how representative are the index adoptees of children with an affected parent? To what extent do the adoptees resemble or differ from Danish nonadoptees with and without schizophrenic parents? To what extent will the Danish findings accord with previous family studies of schizophrenia? It is to be hoped that we shall have answers to these and other questions within the next few years.

Another problem in the adoption studies is revealed by the results of the Kety strategy in which the rates of schizophrenia spectrum disorders are compared in the biological or adoptive families of schizophrenic and control adoptees. The rate of psychopathology among the biological half siblings of schizophrenic adoptees was found to be 19.2 percent, whereas among the biological parents of these adoptees, the rate of schizophrenia (definite or uncertain) was 12.1 percent (Kety et al. 1975). Unfortunately, half siblings only share one-quarter of their genes in common with their schizophrenic relatives, whereas biological parents share one-half. No genetic model can account reasonably for data in which the incidence of a trait is as high or higher among more remotely related relatives than among closer ones. Again, the adequacy of the sampling might be questioned. Gottesman and Shields raise and then dismiss the possibility that the interviewers in the Danish study had a mental set not to miss schizophrenia-related disorders, thus implying that the Kety-Rosenthal work is not so free of investigator bias as we had hoped it was.
Gottesman and Shields state that "the major accomplishment of the adoption studies was to determine that numerous alleged environmental factors were neither necessary nor sufficient for the occurrence of schizophrenia..." (p. 366, italics added). In a sense this is hardly flattering to the Kety-Rosenthal work. I am sure that Kety and his colleagues believe that the principal aspect of their research was to establish unequivocally that some genetic factors that promoted the development of schizophrenia were indeed transmitted. Before their work, this was a fact under considerable dispute despite, or perhaps because of, the classical twin and family studies.

If schizophrenia has a major genetic component, then the pertinent gene(s) involved must have some lawful pattern of transmission. In the past few years it has become painfully evident that currently available family and twin data are hopelessly inadequate to elucidate the mode of inheritance of schizophrenia. Besides differences in diagnostic criteria, sampling, populational characteristics, and other such problems, the data fit multiply different genetic models equally well or poorly. In the latest attack on the problem, Matthysse and Kidd (1976) examined the extreme genetic models—single major locus (monogenic) and multifactorial (polygenic) models. From the available data, these workers calculated estimates of the parameters of the two models. Also, knowing the rates of schizophrenia in the general population and in the siblings and children of schizophrenics—that is, the cases that provide the largest body of data in the literature—it is possible to determine the expected incidence among monozygotic twins and in dual matings (children of two schizophrenic parents). The expected and observed rates are shown in table 1.

Matthysse and Kidd found that neither of these models accounted adequately for the observed data. The predicted incidence in monozygotic twins and in offspring of dual matings was too low in the single major locus model and too high in the multifactorial one; a decision as to which model provided the best fit could not be made. Nevertheless, the two models provided some interesting perspectives. In the single major locus model, the genetic composition of the schizophrenia population varied according to the frequency of the allele that promoted the development of the disorder. At relatively low frequencies of this allele, about 60 percent of schizophrenics are phenocopies (i.e., environmentally induced mimics of the genetically determined form of the disorder). In other words, these schizophrenics would be genetically "normal" persons and the disorder would develop because of environmental influences. The remainder of the cases would be mostly heterozygotes. At relatively high frequencies of the schizophrenia-promoting allele, the number of phenocopies drops, and the proportion of heterozygotes increases correspondingly. At all allelic frequencies, the proportion of schizophrenics who are homozygotes is low. Thus, "according to some versions of the SML [single major locus] model, genes play an extremely important role when they are present in double dose; but such individuals are very

<table>
<thead>
<tr>
<th>Group</th>
<th>Observed percentage</th>
<th>Expected percentage</th>
<th>Single major locus model</th>
<th>Multifactorial model</th>
</tr>
</thead>
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<tr>
<td>General population</td>
<td>0.87</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Siblings</td>
<td>8.7</td>
<td></td>
<td></td>
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<tr>
<td>Children</td>
<td>12.0</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Children (both parents schizophrenic)</td>
<td>39.0</td>
<td>19.9</td>
<td>54.0</td>
<td></td>
</tr>
<tr>
<td>Monozygotic twins</td>
<td>47.0</td>
<td>19.9</td>
<td>61.0</td>
<td></td>
</tr>
</tbody>
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Based on data presented in Matthysse and Kidd (1976).
rare, even among schizophrenics” (Matthysse and Kidd 1976, p. 189).

In the multifactorial model, Matthysse and Kidd found that about 9.1 percent of schizophrenics had such a high genetic risk that 99 times out of 100 they would become schizophrenic virtually irrespective of environmental circumstances. Thus, according to this model, in 1 of 11 schizophrenics, the disorder is almost totally genetically determined.

Both the single major locus and multifactorial models predict genetic heterogeneity among schizophrenics. Not every schizophrenic will have the same genetic makeup with respect to the schizophrenia-promoting genes. This could be a serious problem for both biologically and psychologically oriented investigators as it will make it difficult to obtain relatively homogeneous groups of affected individuals for research purposes. In turn, this might significantly reduce the chances of detecting and isolating a specific biochemical or neurophysiological factor reliably associated with the disorder. Matthysse and Kidd (1976) address themselves to methods of maximizing the frequency of homozygosity in schizophrenia research, particularly by using the offspring of dual matings. This approach is limited by the magnitude of the genetic heterogeneity. If the magnitude is very high, the schizophrenia-promoting genotype would tend to differ from case to case.

Gottesman and Shields approach the mode of inheritance problem somewhat differently than Matthysse and Kidd, but arrive at similar conclusions in that they are unable to determine whether monogenic or polygenic models provide the best fit for existing data. Gottesman and Shields seem to favor a threshold polygenic model with high heritability, genetic heterogeneity, and a Thoday-like system (Thoday 1967) in which some of the genetic factors in the polygenic system involved in the development of schizophrenia make disproportionately greater contributions than others. They appear to want to cover all bases! This may not be possible. For example, some conditions of genetic heterogeneity are not compatible with high heritability (see Edwards 1969 for a discussion of this point). Nonetheless, the possibility that a Thoday-like polygenic system might be operative in the case of schizophrenia may move proponents of multifactorial and single major locus models closer together. Once a major segregating unit is detected, the polygenic system can be treated as a single major locus system.

Gottesman and Shields allude to a model of genetic heterogeneity involving low-grade mental deficiency. Dewey et al. (1965) made a study of this disorder using populational incidences and inbreeding data and found that many cases of severe mental defect could be divided into a high risk group, consisting of cases from families in which the recurrence risk (or segregation frequency) was appreciable, and a group in which the risk of recurrence was low. These workers calculated that 88 percent of the cases were sporadics or of the low risk type. The remaining majority of the cases represented fresh mutations, phenocopies, and (classically additive) polygenic complexes. Thus, in some respects the model of severe mental defect is compatible with others discussed above in that it suggests that not all cases of a disorder have equal risks of recurrence and that substantial genetic heterogeneity exists.

The possibility that a substantial number (perhaps the majority) of cases of schizophrenia are phenocopies or have a negligible recurrence risk is an intriguing idea, not incompatible with several known pieces of information: the high rate of discordance among monozygotic twins (roughly half or more are discordant), the relatively low rates of the disorder among offspring of dual matings, the erratic patterns of transmission in some kinships, what appears to be a negligible effect of natural selection in reducing the general incidence of the disorder over time, and the notable inability of researchers to find a biochemical or developmental defect as a specific cause of schizophrenia, despite decades of intensive searching. Of course, there are alternative explanations for these phenomena—genetic heterogeneity for one. If the magnitude of the genetic heterogeneity is very high, however, there is the danger that although the illness is genetically determined, each affected individual is so genetically unique (with respect to the schizophrenia-promoting genes) that the knowledge of genetic determination becomes a trivial fact.

The Gottesman and Shields review may have provided a turning point. There seems to be a movement away from the feelings generated at the Puerto Rico conference—feelings that regardless of our stance, we are together in trying to understand the phenomenon of schizophrenia. Their statement that “the burden of proof has shifted from showing that genes are important to showing that environment is important...” (p. 367)
is like a page out of the recent past in which many human problems were conceptualized as either being due to nature or to nurture. In contrast to several decades ago, the geneticists now appear to be holding the trump cards.

Some of the recent findings of the adoption studies can easily be misconstrued as meaning that relative to heredity, environmental factors play a minor role in the development of schizophrenia. Gottesman and Shields appear to be of two minds on the subject. On the one hand, they say that both genes and environment are necessary but not sufficient for developing the disorder, but then they also state that "...the adoption work...disconfirms the...hypothesis that the high schizophrenia rate observed in the children of schizophrenics was due to an interaction between schizophrenogenic rearing and genetic predisposition..." (p. 367). This assessment of the pertinent data (Rosenthal et al. 1975 and Wender et al. 1974) is subject to dispute (Reiss 1976). It is not as if the Kety-Rosenthal group actually observed the rearing transactions between the adoptee and his or her adoptive parents. The evaluation of rearing environments was based largely on retrospective information provided by the subjects. The reliability of such reports needs to be established.

One also senses in the Gottesman and Shields review that the gulf between the researcher and academician on the one hand and the clinician on the other appears to be growing wider. Geneticists have not made clear what the relevance of genetic contributions to schizophrenia may be either for the treatment of an affected individual or his or her family or for understanding the schizophrenic process itself. To most clinicians the psychological environment in which the patient has functioned and is currently functioning appears to have a more direct connection to the development and maintenance of schizophrenic symptoms than the fact that he or she may have some intangible vulnerability on account of genetic factors. Someday we might demonstrate a correlation between a gene or genes and a specific biochemical factor in some group of schizophrenics, and this discovery might then open the way for the development of new treatment modes. For the present, the clinician will have to rely on drugs for management and for various modes of treatment in which a psychodynamic, social system, communications, or some other environmentally based model serves as a guide. At this stage of our knowledge, information on the genotype appears to have a minimum value for the therapist.

If geneticists have little to offer on the subject of the treatment of schizophrenia, it is certainly not out of any lack of interest in this problem. On the contrary, there is considerable interest, generally moving along a single track—namely, pharmacogenetics. This track is consistent with the faith of many geneticists in the reductionistic approach in science and in the medical model of schizophrenia. I do not wish to become embroiled here in attacking or defending this model. The disease or medical model of schizophrenia has much to commend it, and Kety (1974) has recently presented cogent arguments against many of the unwarranted criticisms of the model. Nevertheless, the medical model of schizophrenia is neither the only valid nor the only scientific approach to the problems posed by schizophrenia. Alternative psychosocial models are not incompatible with scientific research methods or with the known biological and genetic facts. By buying a single conceptual line, behavioral geneticists have limited their understanding of the schizophrenic process and have restricted their ability to investigate, among other things, the gene-environment interactions involved in the precipitation of a schizophrenic episode, the maintenance of symptoms, and the response to differential modes of treatment.

Gottesman and Shields suggest that we let many flowers bloom in future genetics research, and I agree. It is to be hoped, however, that not all of the seeds will come from a single conceptual packet.

References


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**dean research award**

The 14th annual Stanley R. Dean Research Award was presented recently to Dr. Margaret Thaler Singer and Dr. Lyman C. Wynne in San Diego, Calif. The award of $2,500 was established by the Fund for the Behavioral Sciences and is granted each year, jointly with the American College of Psychiatrists, in recognition of "basic research accomplishment in the behavioral sciences contributing to our understanding of schizophrenia."

Dr. Singer is Clinical Professor of Psychiatry (Psychology), University of Rochester, and Lecturer, Department of Psychology, University of California at Berkeley. Dr. Wynne is Chairman and Professor, Department of Psychiatry, University of Rochester School of Medicine and Dentistry, and Psychiatrist-in-Chief, Strong Memorial Hospital.

The Dean Award lecture presented by the two recipients was entitled: "Schizophrenics, Families, and Communication Disorders: I. Overview of Research Findings" (Dr. Singer) and "II. Therapeutic Implications" (Dr. Wynne).