theoretical commentary on gottesman and shields' review *

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Gottesman and Shields (1976) state: "When the common parent is unaffected [by schizophrenia], we would expect the risk [to half siblings] to approach the population base rate" (p. 368). I have carried out calculations, based on James' (1971) version of the single major locus model, of the expected incidence of schizophrenia in half siblings when the shared parent is affected or unaffected. A population base rate of .87 percent and an incidence in offspring and in siblings of 10.4 percent were assumed. The results are shown in table 1.

The expected incidence in half siblings when the status of the shared parent is unspecified is 5.6 percent. The lower and upper limits of the gene frequencies of .3 percent and 2.2 percent, respectively, are consistent with the assumed rates for siblings, offspring, and the general population (see Matthysse and Kidd 1976). The multifactorial model for the same population, offspring, and sibling incidences gives an expected incidence in half siblings when the shared parent is affected of 11.5 percent, and when the shared parent is unaffected, 2.3 percent. The expected incidence in half siblings when the status of the shared parent is unspecified is 3.3 percent. The method of calculation used was similar to Curnow's (1972). The predicted incidence in half siblings when the shared parent is unaffected remains higher than the population base rate, according to both models.

While I agree with Gottesman and Shields' conclusion that "It is difficult to choose among models..." (p. 387), the conclusions reached by myself and Kidd differ from their opinion that "the predictions from a threshold polygenic model and a monogenic model with incomplete penetrance are not distinguishable from one another..." (p. 387). With the rates for siblings, offspring, and the general population assumed above, we found a predicted monozygotic concordance for the single major locus model of 19.9 percent, and a predicted incidence in offspring of dual matings also of 19.9 percent. The multifactorial model gave approximate predictions of 61 percent for monozygotic twins and 54 percent for dual matings. This disagreement should not be totally unwelcome to the authors, since it favors their polygenic model. I do not, however, agree with the statement that "the relationship between severity and concordance in twins and... between number of relatives affected and the risk for mental disorder favor[s] construing some kind of polygenic model" (p. 387). On a single major locus model, if heterozygotes are affected, but less...
severely than homozygotes, a relationship between severity and monozygotic concordance would be expected. Risk to offspring would be expected to increase with the number of the affected parent's relatives affected for any single major locus model except one in which the gene was fully recessive.

Since the existence of genetic and environmental factors is no longer subject to doubt, both twin and adoption methodologies have to be put to new uses. On the environmental side, the foremost problem is isolation of specific environmental factors that contribute to the etiology; the mere statement of their existence is no longer sufficient. On the genetic side, the most consequential issue is delineation of the genetically determined phenotype or phenotypes at risk for the illness. Granted that the genotype(s) do not cause the illness with certainty, it should be possible to discover what they do cause. These phenotypic expressions may be defined biochemically, physiologically, or psychologically. When they are defined, it is to be hoped that they will have a higher monozygotic concordance than the illness itself. The roles of twin and adoption studies in clarifying genetic and environmental factors may be reversed in the future. Twin studies are useful for revealing phenotypes more directly related to the genotype because, when a co-twin is discordant for the illness, he or she may still be concordant for a biochemical or psychological trait present in the index twin. Adoption studies, conversely, can reveal specific environmental factors because of the separation of the rearing environment.

Although the ultimate understanding of gene effects must be biochemical, the gap between the psychological and neurochemical domains may be too wide to be safely bridged in one step. A promising strategy might include (1) finding a psychological trait that is deviant in monozygotic twins discordant for schizophrenia; (2) studying the pharmacology of that trait in animals to determine the anatomical, neurophysiological, and neurochemical systems that control its expression; and (3) examining brains of schizophrenics postmortem for signs of anatomical, histopathological, or biochemical abnormalities in the relevant regions.

This strategy might, for example, be applied to attentional abnormalities. Holzman et al. (1974) have discovered that errors in pursuit of a smoothly moving target are made, not only by schizophrenics, but by their first-degree relatives who are not ill. These errors, Holzman et al. believe, are related to defective "centering" of attention. It is intriguing that Spohn et al. (in press) have noted changes in the centering of attention to be among the first improvements brought about by antipsychotic drug therapy. (In the experiments of Spohn et al. there was initially excessive fixation, with postdrug reduction in fixation time.) Antipsychotic drugs also counteract stereotyped behavior, a kind of attentional perseveration in animals that can be provoked by dopaminergic agonists like amphetamine or apomorphine. Could it be that among the factors predisposing to schizophrenia are genes causing abnormalities in the deployment and maintenance of attention—the gene products themselves controlling either the organization or the enzymology of the dopamine tracts? This particular hypothesis may not be correct, but the strategy of uncovering deviant psychological traits in relatives of patients and studying the pharmacology, neurochemistry, and neurophysiology of those traits is a hopeful one.

References


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