CHAPTER

5

Does schizophrenia have a substantial genetic component?

PRO	Straube, E. R., & Oades, R. D. (1992). Genetic studies. In E. R. Straube & R. D. Oades (Eds.), *Schizophrenia: Empirical research and findings* (pp. 361–384). San Diego: Academic Press.
CON	Lewontin, R. C., Rose, S., & Kamin, L. J. (1984). Schizophrenia: The clash of determinisms. In R. C. Lewontin et al. (Eds.), *Not in our genes* (pp. 197–231). New York: Pantheon Books.

OVERVIEW OF THE CONTROVERSY: Eckart R. Straube and Robert D. Oades review the evidence from twin and adoption studies of schizophrenia and conclude that schizophrenia is substantially influenced by genetic factors. Richard C. Lewontin, Steven Rose, and Leon J. Kamin find the evidence for the heritability of schizophrenia to be unconvincing and argue that greater attention should be focused on social and cultural factors in the genesis of schizophrenia.

CONTEXT OF THE PROBLEM

The so-called "nature versus nurture" issue has been one of the most persistent and longstanding debates in psychology, including abnormal psychology. This issue, which I will argue in the Discussion of this chapter is essentially a pseudoissue, concerns whether differences among individuals are attributable to differences in their genetic endowment (nature) or to differences in their experience (nurture). The term **heritability**, which is often misused and misunderstood (not least of all by psychologists), refers to the extent to which differences among individuals in a characteristic (for example, their levels of intelligence or extroversion) are due to differences in their genetic makeup. Please note: Heritability does not refer to the importance of genes in the origin of a characteristic. For example, although genes are responsible for producing the proteins that lead to the development of our arms (and are thus extremely important in the development of our arms), the heritability of having both arms is close to zero. Why? Because the *differences* among individuals in whether or not they possess both arms are due largely or entirely to environmental factors (such as accidents), not genetic factors. Keep this point in mind, because a great deal of unnecessary confusion has resulted from the failure to understand what heritability means.

In the arena of psychopathology, the heritability of schizophrenia, which is a severe disorder of thought and emotion frequently associated with delusions and hallucinations, has for decades served as a focal point for the nature versus nurture debate. More recently, that debate in abnormal psychology has to some extent shifted to behavior problems, such as alcoholism (See Chapter 7) and violent criminality. Nevertheless, the same methodological issues that have been bones of contention in the debate concerning the genetics of schizophrenia are also relevant to the investigation of the heritability of these conditions.

Three major **behavior-genetic designs** (that is, research designs that provide information regarding genetic influences on behavior) help to elucidate the heritability of a condition: family studies, twin studies, and adoption studies. Family

studies typically involve a comparison of the prevalence of a condition among the relatives of affected individuals (in other words, those with the condition) with the prevalence of this condition among the relatives of unaffected individuals. Although family studies are quite useful for certain purposes, such as estimating relatives' risk of developing a condition, they are severely limited in one respect. Specifically, because genetic and environmental influences are confounded (inextricably entangled) in intact families, family studies are indeterminate regarding genetic versus environmental causation. In other words, because individuals in intact families share both genes and environment, family studies cannot provide conclusive information regarding the extent to which a condition is influenced by genetic or environmental factors. Family studies do provide useful information about heritability in one respect, however: If a condition does not run in families, it is highly unlikely that it is influenced by genetic factors. (For discussion of an important but presumably rare possible exception, see Lykken, McGue, Tellegen, & Bouchard, 1992). Because of the limitations of family studies, behavior-geneticists have generally turned to more definitive methodologies, particularly twin and adoption studies, to clarify the role of genetic factors in the etiology of mental illnesses.

In the traditional twin study, the investigator compares the concordance (the occurrence in both members of a pair) rate of a condition in monozygotic (MZ) or identical twins, who share 100% of their genes, with the concordance rate of that condition in same-sex dizygotic (DZ) or fraternal twins, who share 50% of their genes on average. (An aside: The word *genes* in the preceding sentence technically refers only to those genes that differ from one human to another, which actually constitute only about one-fifth of one percent of the human genetic material.) DZ twins are thus no more genetically similar or dissimilar than ordinary same-sex siblings. If the concordance of a condition among MZ twins exceeds that among same-sex DZ twins, we can conclude with reasonable certainty that this condition is at least partly heritable. The twin design is, however, premised on an important assumption—the **equal environments assumption.** This assumption, which is more complex than it might appear at first blush, essentially posits that (1) MZ twins are not treated more similarly than are same-sex DZ twins or (2) if MZ twins are in fact treated more similarly than same-sex DZ twins, this greater similarity in treatment does not increase MZ twins' similarity for the characteristic in question relative to that of same-sex DZ twins. If you are confused at this point, do not despair: The equal environments assumption is discussed in greater detail in the reading by Lewontin, Rose, and Kamin and in the Discussion section.

Finally, in the typical adoption study, the investigator compares the prevalence of a condition among the adopted-away biological relatives of affected individuals with its prevalence among the adopted-away biological relatives of unaffected individuals. If a condition is influenced by genetic factors, the prevalence of this condition in the former group should be higher than that in the latter group. In many ways, the adoption design provides the most unequivocal test of genetic influence on a characteristic, because it allows the cleanest separation of genetic and environmental factors. Unlike the family study, in which genetic and environmental influences are hopelessly and inextricably confounded, the adoption study permits investigators to examine the independent effects of genes and environment. Like the twin study, however, the adoption study is premised on a key assumption—**random placement**, which is also discussed in the reading by Lewontin, Rose, and Kamin. Essentially, the assumption of random placement (the opposite of selective placement) posits that adoptees are placed with parents who are no more similar to these adoptees' biological parents than would be expected by chance.

As you will see, many of the differences in the way that Straube and Oades, on the one hand, and Lewontin, Rose, and Kamin, on the other, interpret the data on the heritability of schizophrenia stem from differences in their evaluation of the two principal assumptions of the twin and adoption designs—equal environments (twin studies) and random placement (adoption studies). Whereas Straube and Oades view these assumptions as largely or entirely warranted, Lewontin, Rose, and Kamin do not. For Lewontin, Rose, and Kamin, these assumptions represent serious, if not fatal, stumbling blocks in the effort to detect genetic influences on schizophrenia.

THE CONTROVERSY
Straube and Oades vs. Lewontin, Rose, and Kamin

Straube and Oades

Eckart Straube and Robert Oades first point out that schizophrenia has a pronounced tendency to aggregate in families, although they acknowledge that this finding does not provide definitive evidence for genetic transmission. They then review evidence from several studies demonstrating that the concordance rate for schizophrenia among MZ twins considerably exceeds that among same-sex DZ twins and conclude that these data argue strongly for a genetic component to schizophrenia. Straube and Oades also review the major findings from adoption studies of schizophrenia, which consistently show that the adopted-away biological relatives of schizophrenics exhibit a higher rate of schizophrenia than do the adopted-away biological relatives of nonschizophrenics, or normals, and again conclude that these data indicate a substantial genetic influence on schizophrenia. Straube and Oades next discuss evidence that the offspring of the unaffected MZ co-twins of schizophrenics are at elevated risk for schizophrenia, suggesting that these offspring have inherited a predisposition toward schizophrenia from their parents. In addition, they review

findings suggesting that schizophrenia spectrum conditions—conditions that appear to represent mild or attenuated forms of schizophrenia—are partially under genetic control and are genetically associated with schizophrenia. Straube and Oades discuss several models for the transmission of schizophrenia and conclude that models involving the action of multiple genes, in conjunction with environmental factors, appear to be the most plausible in light of existing evidence. Finally, Straube and Oades review the findings of molecular genetic (linkage) studies of schizophrenia, which involve examining the extent to which known genetic material segregates with schizophrenia within families. They conclude that the results of these studies are inconclusive although promising.

Lewontin, Rose, and Kamin

In this reading, which has been abridged for the purposes of this book, Richard Lewontin, Steven Rose, and Leon Kamin begin by noting the "clash of determinisms"—biological versus cultural—that has bedeviled the study of schizophrenia for decades. They trace the history of the search for the genetic basis of schizophrenia to the eugenics movement of the early part of the 20th century, which aimed to "improve" the gene pool by eliminating genes ostensibly predisposing toward schizophrenia, criminality, alcoholism, and other socially undesirable conditions. Lewontin, Rose and Kamin review Kallman's classic twin studies of schizophrenia and find his results to be highly questionable. They also review the findings from other major twin studies of schizophrenia, including Gottesman and Shield's 1972 study, and again find these results to be unconvincing. Not only are these studies plagued by methodological problems, the reading's authors claim, but the greater concordance among MZ twins than among DZ twins reported by most investigators can be plausibly attributed to greater environmental similarity among MZ twins than DZ twins. Lewontin, Rose, and Kamin then discuss the results of the Danish adoption studies, which are frequently cited as the most persuasive evidence for the heritability of schizophrenia. They argue that close inspection of these studies reveals little or no evidence of a genetic basis for schizophrenia *per se*, as well as serious methodological problems such as selective placement by adoption agencies. Lewontin, Rose, and Kamin conclude that the evidence for the heritability of schizophrenia is extremely weak and that investigators interested in the etiology of schizophrenia must begin to attend seriously to broad social and cultural influences.

KEY CONCEPTS AND TERMS

concordance Occurrence of a given condition in both individuals of a pair (typically a twin pair). Concordance is the opposite of discordance.

cross-fostering design Adoption design in which individuals are raised by adoptive parents who have a particular psychiatric condition. This design allows investigators to determine whether the presence of this condition in the adoptive parents increases the children's risk of developing this condition.

discordance Occurrence of a given condition in only one member of a pair (typically a twin pair). Discordance is the opposite of concordance.

eugenics Policy of attempting to "improve" the gene pool of a population by practices such as mandatory sterilization and limits on immigration.

genotype Organism's genetic endowment. Genotype must be distinguished from phenotype.

Mendelian inheritance Pattern of inheritance characterized by the action of single genes. Mendelian inheritance differs from polygenic inheritance.

penetrance Extent to which a characteristic (for example, schizophrenia) is manifested in individuals with a given genotype. In a genetic condition with a high penetrance, such as Huntington's chorea, many or all individuals with the genotype will develop the condition.

phenotype Observable characteristic of the organism. Phenotypes result from a combination of or interaction between the genotype and environmental influences.

polygenic inheritance Pattern of inheritance characterized by the action of multiple genes. Polygenic inheritance differs from Mendelian inheritance.

schizophrenia spectrum Broad class of conditions including both schizophrenia and milder syndromes thought to be genetically related to schizophrenia. Although investigators disagree somewhat on the boundaries of this spectrum, it typically includes such conditions as schizotypal, paranoid, and sometimes schizoid personality disorders.

schizotypal personality disorder Personality disorder characterized by oddities in thinking, behavior, and appearance and by abnormalities in social relationships.

selective placement Tendency for adoptees to be placed in homes on a nonrandom basis. Typically, selective placement involves the placement of adoptees with adoptive parents who are more similar on relevant characteristics (such as psychopathology, personality traits, and intelligence) to the adoptees' biological parents than would be expected by chance.

zygosity Classification of twins as monozygotic ("identical," originating from the same zygote, or fertilized egg) or dizygotic ("fraternal," originating from two different zygotes or fertilized eggs).

PREVIEW QUESTIONS

1. What are the three major research designs that behavior-geneticists use for examining the influence of genetic factors on a condition, and what is the logic behind each?

What are the potential weaknesses and limitations of each design?
2. What are the major findings from twin studies of schizophrenia? How do Straube and Oades, on the one hand, and Lewontin, Rose, and Kamin, on the other, differ in their interpretations of these findings?
3. What are the major findings from adoption studies of schizophrenia? Once again, how do these two sets of authors differ in their interpretations of these findings?
4. What is the schizophrenia spectrum, and why is it potentially relevant to the genetics of schizophrenia?
5. According to Straube and Oades, what are the most plausible models for the mode of inheritance of schizophrenia? What makes these models more likely than alternative models?

ECKART R. STRAUBE & ROBERT D. OADES

Genetic studies

I. IS SCHIZOPHRENIA INHERITED?

A. Familial Aggregation of Schizophrenia

A schizophrenic is more likely than a nonschizophrenic to have a blood relation who is also schizophrenic. All research reports agree on this point (e.g., Gottesman and Shields, 1982; Frangos *et al.*, 1985; Kendler *et al.*, 1985; Winokur *et al.*, 1985; McGue *et al.*, 1986). The risk of a first-degree relative developing schizophrenia is about 10 times higher than that of a relative of a nonschizophrenic subject (see Table 1). (The risk for someone without close relatives with schizophrenia is approximately 0.85%). . . .

It should be emphasized that about 90% of schizophrenics have no schizophrenic parents, brothers, or sisters (Gottesman and Shields, 1982; McGue and Gottesman, 1989). However, the probability that the monozygotic (MZ) twin of a schizophrenic also suffers in some degree from schizophrenia is higher than that of the twin that comes from another egg and does not share 100% of the genetic material [i.e., dizygotic (DZ); Table 1].

It appears that schizophrenia has a genetic component, but that inheritance may not follow classical Mendelian rules, with dominant and recessive genes for the major features, as for example, Huntington's chorea does. However, other illnesses pose problems similar to those encountered in the study of schizophrenia. There are many illnesses with a psychiatric and/or somatic character in which the hereditary mechanism is poorly understood. For example, the incidence of diabetes mellitus is also higher in the families of those who have the illness but, like schizophrenia, it seems to have a relatively low penetrance. The expression of the phenotype is apparently affected by other factors, since not all of the carriers of the relevant genes succumb to the illness.

Not just the incidence of schizophrenia, but also the incidence for subgroups and for specific symptoms, has been investigated. In earlier reports there seemed to be an increased incidence (concordance) for the symptoms of traditional subgroups in the kindred or twins studied (Fischer *et al.*, 1969; Pollin *et al.*, 1969; Diebold *et al.*, 1977; Kallman, cited in Gottesman and Shields, 1982). However, more recent studies (e.g., Kendler *et al.*, 1988) and a critical review (McGuffin *et al.*, 1987) have questioned these reports.

Even if the question of whether prominent symptom patterns have a genetic basis is disregarded, the reader should be cautioned against assuming that there is enough evidence from family studies alone to understand the genetic influence in schizophrenia, since the putative genetic and the putative environmental influences cannot be separated. If, for example, a child is raised by a mentally disturbed parent, then the poor milieu and a negative influence on the development of the child may theoretically also cause a mental handicap.

It may also be noted that, in most cases, the psychiatrists who were retrospectively attempting to establish diagnoses were often not blind to the type of family to which the subjects be-

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SOURCE: *Schizophrenia: Empirical Research and Findings*, by E. R. Straube and R. D. Oades (Eds.), pp. 361–384.

TABLE 1 Rates of Definite Schizophrenia among Relatives of Schizophrenics[a]

Familial Relationship	*n*	*% Affected*
Offspring of two schizophrenics	134	37
Offspring of one schizophrenic	1678	9
Siblings	7523	7
Grandchildren	739	3
Monozygotic twins	106	41
First cousins	1600	2
Dizygotic twins	149	12
Spouses	399	1

[a]Adapted from McGue and Gottesman, 1989

longed. Bias favoring achievement of a positive result for the investigation(s) may be involved. . . .

B. *Twin Studies*

When searching for semiquantitative information on the degree of influence exerted by hereditary and environmental factors in the etiology of schizophrenia, the measures of concordance from twin studies are the appropriate gauge. If genetic inheritance has a decisive influence, then MZ twins who share the same genetic material should show a far greater incidence of schizophrenia when one of them is schizophrenic than DZ twins. (If dominant genes were involved, the incidence in the MZ twin should approach 100% whereas that in the DZ twin would be about 50%.)

As can be seen in Table 1, the incidence rates of concordance are considerably lower than would be expected from a straightforward Mendelian inheritance. Because of the relatively numerous twin studies carried out, we must select and summarize the information. (For more complete discussions of both results and criticism of methods, see Jackson, 1960; Zerbin-Rüdin, 1972; Neale and Oltmanns, 1980; Gottesman and Shields, 1982; McGuffin *et al.*, 1984; Gottesman *et al.*, 1987; Kringlen, 1987; McGue and Gottesman, 1989.) The more recent studies attempt to consider the criticism of Jackson (1960), among others, of the methods formerly used.

The study of Gottesman and Shields (1982) at the Maudsley Hospital in London shall serve as an example for genetic research with twins. In this study, the selection and diagnosis of the subjects was carefully carried out: six evaluators blind to the zygosity of the subjects were employed. (The authors exerted much effort establishing the zygosity of their subjects. This was not as easy as it might appear and was treated relatively generously in earlier studies.) The degree of concordance depends on the diagnosis, but no matter what diagnostic scheme was used, or how narrowly or generously the criteria were applied, the concordance for schizophrenia was higher with the MZ than with the DZ twins in all cases. On the basis of the judgment of the six evaluators, the concordance was 50% for MZ and 9% for DZ twins (see Table 2; Gottesman and Shields, 1982).

TABLE 2 Effects of Diagnostic Criteria on Twin Concordance for Schizophrenia[a]

	Monozygotic	*Dizygotic*	*MZ:DZ*
Chart diagnoses	10/24 (42)[b]	3/33 (9)	4.6
Consensus of six judges	11/22 (50)	3/33 (9)	5.5
Broad criteria (Meehl)	14/24 (58)	8/33 (24)	2.4
Narrow criteria (Birley)	3/15 (20)	3/22 (14)	1.5

[a]From Gottesman and Shields, 1982
[b]Numbers in parentheses indicate percentages.

The data are in good agreement with concordance rates derived from other more recent studies. However, older studies reported higher concordances. If justifiable criticisms of the methods are disregarded, one of the reasons for this higher concordance is most likely to be the inclusion of subjects with widely varying degrees of illness (i.e., the severity of the illness of the index twin also plays a role in the concordance rates). Relevant here is the reanalysis of an earlier study reported by Gottesman and Shields (1982) in their review. When this group of twins was divided into severely and mildly ill groups, the concordance rates for MZ twins were 75% and 17%, respectively. (The total concordance, without taking the severity of symptoms into account, was 46% for MZ and 14% for DZ twins.)

It is interesting to compare these results with those of Kendler and Robinette (1983) based on the twin register of the American Academy of Sciences. . . . From a base of 16,000 twins, 590 pairs had two or at least one schizophrenic twin. The concordance rate for schizophrenia was 31% for MZ and 6.5% for DZ twins. This concordance can be compared with that for diabetes mellitus, 19% versus 8%, and that for high blood pressure, 26% versus 11%. These concordance values are lower than those found in the Maudsley study, but do confirm the more general experience that concordance rates tend to be higher when the subjects are taken from a purely clinical background, than from the population at large. Once again, selection factors can be seen to play a role. It is also relevant that after Kendler and Robinette divided their population according to the severity of the illnesses, higher

concordance rates were found in the more severely ill, which confirms the findings of Gottesman and Shields (1982).

Of course radical proponents of the influence of environmental factors still object to interpretations of these findings in terms of a genetic component in the transmission of schizophrenia. Some suggest that monozygocity and the necessary similarity of looks and behavior incur problems in the development of the "ego" and of the individual's identity, which are precisely the problems that these psychoanalysts suggest are uppermost in the anomalous development leading to schizophrenia (cf. Arieti, 1955). However, contrary to this argument, it should be noted that the incidence of schizophrenia in samples of MZ-twin probands or DZ-twin probands is no higher than in non-twin samples (Gottesman and Shields, 1982).

In order to counter the criticism of the "environmentalists," the development of MZ twins who were separated immediately after birth and grew up apart must be followed. This is a very rare circumstance. The numbers of cases available do not allow a statistically significant conclusion to be drawn. Evidence from 7 MZ twins (all separated in early childhood) speaks against interpretations that consider an identity problem the cause of the higher concordance rates in MZ twins: 5 of these twins were concordant for schizophrenia (see review and personal observations of Kringlen, 1987).

C. *Adoption Studies*

Adoption studies provide a useful complementary paradigm for investigating the contribution of hereditary and environmental factors in the development of schizophrenia. If there is a hereditary component, there is an increased likelihood of a child of a schizophrenic patient to develop schizophrenia after adoption into a healthy family. The comparison is drawn with children of healthy parents adopted into healthy families. The control and index groups discussed here were carefully matched according to the relevant demographic features.

Several adoption studies have been carried out in Denmark, where there is a particularly comprehensive register of psychiatric illnesses. These studies have mostly been instigated by workers at the National Institutes of Mental Health (NIMH)(e.g., Rosenthal *et al.*, 1968, 1971, who searched the register for schizophrenic patients who had given their children up for adoption, and Kety *et al.*, 1975, 1978, who started with registered adopted probands who had developed schizophrenia). An earlier comprehensive study was carried out by Heston (1966) in the United States with a procedure similar to that adopted by Rosenthal.

The principal finding of the studies of Heston, Rosenthal, and colleagues was that a higher proportion of the children of schizophrenic biological parents than of the children of parents with no recorded illness who were adopted into healthy families eventually developed a schizophrenia-like illness. Some of the individuals concerned were adopted at an early age (i.e., <1 yr). For example, in the study of Heston (1966), 5 (11%) of the 47 adopted offspring of schizophrenic mothers became schizophrenic. None of the children in the control group became schizophrenic. Interestingly, Heston reported that not only schizophrenia, but also "sociopathy, neurosis, and mental deficiency," even greater artistic gifts were more frequent in the index group than in the control group.

The Danish–American study (Rosenthal *et al.*, 1968) and, more recently, a Finnish adoption study (Tienari *et al.*, 1985) reported lower frequencies than Heston (1966). However, cases with schizophrenia were still higher in the index group than in the control group. For example, Rosenthal *et al.* recorded a definitive schizophrenia in 6% of the adopted offspring deriving from a parent with schizophrenia ($n = 52$). This point is emphasized by the re-analysis of their results by Lowing *et al.*(1983). Using more modern diagnostic criteria, only 3% could be diagnosed as schizophrenic (DSM-III). However, as in the Heston study, the authors noted a higher incidence of milder psychiatric problems, especially schizotypal personality disorder, in the index offspring than in the control group. (This finding will be discussed in more detail in a subsequent section.)

It could therefore be claimed that modern diagnostic criteria uncover a lower incidence of fully developed schizophrenia in offspring of schizophrenic patients adopted into healthy families than the earlier studies (see also Tienari *et al.*, 1985, and subsequent text). The reported incidences are slightly lower than those expected from reports in which the offspring was reared by a schizophrenic biological parent and not by a healthy nonbiological parent. In the former case, 10% of the offspring were expected to be affected. This discrepancy permits consideration of the possible role of differences in the familial milieu (i.e., high risk offspring reared by a disturbed or by a healthy person).

This was the starting point for an additional project in Denmark by the NIMH team. Wender *et al.* (1974) wanted to know what the influence of the adoptive father or mother on the adopted child might be. They searched in the Danish registers for those cases in which the adopting parent eventually became schizophrenic after adopting a child from healthy biological parents. (Compared with the previous design, this is the reverse procedure. Adopting schizophrenic *parents*, not the offspring of schizophrenic biological parents, formed the index group. This procedure is called a *cross-fostering* design.)

The result was that no more deviance was observed in the children of healthy biological parents (raised by a schizophrenic parent; $n = 28$) than in those children raised by healthy parents ($n = 79$). [For more details of the design and the results in this and the other two Danish–American adoption

studies, the reader is referred to Gottesman and Shields (1982), who gave an extensive review of the field.] The unavoidable weakness of the study by Wender *et al.* (1974) is that there is no information about the nature of the interaction between the adopting parents and the child, since it is based on retrospective, if blind, analysis of case register data.

Indeed, these results did arouse controversy. Prominent in the debate over the validity of the conclusions have been Lidz and Blatt (1983) at Yale University, who maintained that environmental factors had played a much larger role than had been admitted. They argued that factors such as the age at adoption, the size of the family, and the age of illness onset were not considered. They further criticized that the inclusion of schizophrenia-like illnesses, such as borderline and spectrum diagnoses, may make the picture less rather than more clear. (Other problems include the small number of children appropriate for study and the even smaller number that might be expected to develop schizophrenia.) Thus, in their opinion, evidence from which to attempt to distinguish between genetic and environmental contributions to the development of schizophrenia is limited.

The Finnish team of Tienari and colleagues (1985) also criticized the results of the Danish–American adoption studies, which they felt had not considered sufficiently the different familial environments encountered by the adopted children. This factor can be seen in their own exhaustive study of the fate of 91 children adopted from schizophrenic mothers and 91 control children adopted from healthy mothers. Nevertheless, as in the Danish–American study, they found that more children of schizophrenic mothers developed schizophrenia or schizophrenia-like illnesses. Tienari *et al.* (1985) reported six (7%) schizophrenic cases in the index group and one (1%) psychotic proband in the control group. From 128 (133) matched pairs examined in a later re-analysis (Tienari *et al.*, 1989, 1991), there was no further incidence of illness in the control group, but three cases of paranoia and one of manic-depression had developed in the index group.

However, additional findings from Tienari *et al.* (1991) concerning the role of the family environment are of considerable relevance for a theory of gene-environment interactions in schizophrenia. In contrast to the Danish–American adoption studies, they examined the family members themselves and recorded their patterns of interactions. They found more disturbed offspring in the more disturbed family environments (independent of the index status of the offspring). However, they also found that the likelihood of a severe disturbance (including schizophrenia) was greater if the offspring of a schizophrenic mother was brought up in an adoptive family with a disturbed family atmosphere (compared with the offspring of the control group, who did not have the same risk status). From the index group, 20% of the offspring brought up in a disturbed adoptive family developed a severe character disorder or worse, whereas only 7% of the control group received the same rating (Table 3). These results appear to show the joint effects of genetic vulnerability and family environment (Tienari *et al.*, 1991).

Naturally, Tienari and colleagues (1985, 1989, 1991) asked whether the disturbed family situation could have arisen through the adoption of the potentially psychotic child. However, since similar disturbances of the interactions between members of the family also occurred with the adoption of children from healthy parents, the authors doubt if this was the primary cause. Furthermore, they compared the incidence of clear clinical cases of schizophrenia in children who came directly from the biological parents or came indirectly by way of an institution. The incidence was higher in the latter case. Thus, Tienari *et al.* (1985, 1991) concluded that although a genetic predisposition played a role, unfavorable environmental conditions were important for the development of a complete schizophrenic illness. From this evidence, one might also argue that a "good" family environment can exert a protective effect (Tienari *et al.*, 1985, 1991; Gottesman *et al.*, 1987). However, all these comments must be regarded as tentative; the conclusions may yet be strengthened or weakened. Not all subjects in these studies had reached the critical age for the development of schizophrenia.

TABLE 3 Demonstration of the Putative Gene-Environment Interaction in Adopted Offspring of Schizophrenic or Healthy Biological Mothers as a Function of the Family Atmosphere in the Adoptive Family[a]

	Family Atmosphere		
Offspring	*Healthy*	*Disturbed*	*Severely Disturbed*
Schizophrenic biological mother (n = 133)			
Healthy	33	10	4
Neurotic	7	8	9
Psychotic/personality disorder/borderline	3	8	20
Nonschizophrenic biological mother (n = 131)			
Healthy	31	15	5
Neurotic	12	13	11
Psychotic/personality disorder/borderline	2	5	7

[a]Percentage of offspring with or without a disturbance in the different family groups. Adapted from Tienari *et al.*, 1991.

II. PATTERNS OF DISTURBANCE IN FIRST-DEGREE RELATIVES OF SCHIZOPHRENICS

A. *Offspring of Monozygotic Twins Discordant for Schizophrenia*

Even if the results described so far are accepted as indicative of a heritable component in schizophrenia, it may explain only a part of the variance. At least 50% of the MZ twins with a schizophrenic parent are discordant for the illness. However, it is possible that those who do not develop schizophrenia are carriers. Factors may be present that suppress the release of the symptoms, as suggested earlier (i.e., the threshold for expression of the illness is not exceeded). This interpretation is supported by the conclusions of an elegant study by Fischer (1971, 1973) in Denmark.

Fischer studied the children of the nonschizophrenic twin partners of MZ twin pairs in which the other twin was schizophrenic (n = 25). In this group, she found a 13% incidence of schizophrenia. A recent re-analysis of the same material by Gottesman . . . and Bertelsen . . . (1989) confirms these findings (17% with a schizophrenic or schizophrenic-like psychosis; ICD diagnosis). This percentage is astonishingly close to that expected from a genetic model if one parent was schizophrenic (Figure 1; i.e., healthy twins with the same genetic complement as the schizophrenic partners seem to be carriers). In the offspring of the schizophrenic MZ twin, schizophrenia occurred with about the same incidence (16%) as in the offspring of the schizophrenic DZ twins (18%). The offspring of nonschizophrenic DZ twins had a much lower incidence of schizophrenia (3%; Figure 1).

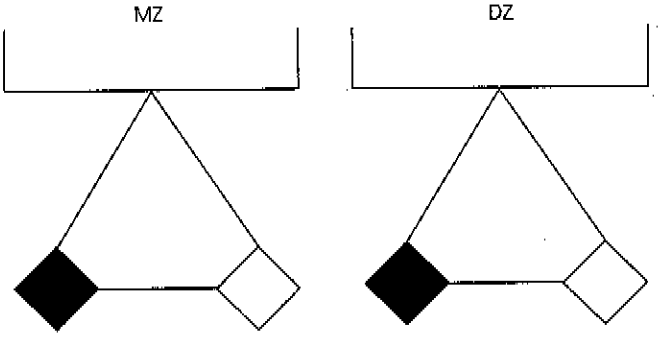
Kringlen (1987) reported similar findings with 155 offspring of discordant MZ and DZ twins. There were 13% schizophrenic offspring in the former group and 3% in the latter. From such results it seems that, although schizophrenia cannot be attributed to genetic factors alone, an increased risk of developing schizophrenia must be genetically transmitted, even if one of the twins does not show a schizophrenia phenotype.

B. *Disturbances in Nonschizophrenic Relatives of Schizophrenics*

It is rather important to provide a little more background at this time. The present concern is the mental health of the nonschizophrenic subjects. As mentioned briefly earlier, it is known from more detailed analyses that many of the discordant nonschizophrenic members of MZ twins are not necessarily completely mentally normal. (All too often the data presented in tables are crude and oversimplified. Subjects who do not develop schizophrenia may be classed along with healthy subjects when, in fact, a category of nonschizophrenic would be more appropriate.) Using data from several reports, Table 4 shows that schizoid disturbances (as far as they were recorded as such) and other psychiatric disturbances are relatively frequent among discordant twins. This does not mean that the evaluators did not find completely normal subjects among the partners of MZ twins that are schizophrenic. However, from the results described earlier, it would be expected that, if disturbed, the nonschizophrenic partners would show a less severe form of a (perhaps) schizophrenia-like personality disturbance.

Let us now return to the adoption studies. One of the earlier investigations (Rosenthal *et al.*, 1968, 1971) reported that many of the offspring adopted from their biological parents could be given a spectrum diagnosis,

FIGURE 1 Schematic Illustration of the Number of Offspring of Members of Dizygotic (DZ) and Monozygotic (MZ) Twin Pairs Who Developed Schizophrenia as a Function of Whether Their Parent Was the Healthy or Ill Member of the Twin Pair (after Propping, 1989)



Twin	n =	11	6	10	20
Children	n =	47	24	27	52
Affected children		16%	17%	18%	3%

TABLE 4 Pairwise Monozygotic Rates for Schizophrenia/Questionable Schizophrenia, Schizoid, Other Psychiatric Conditions, and Normality in Some Schizophrenic Twin Studies[a,b]

	n	*S* (%)	*Si* (%)	*P* (%)	*N* (%)
Luxenburger	14	72	14	—	14
Rosanoff *et al.*	41	61	—	7	32
Kallmann	174	69	21	5	5
Slater	37	64	—	14	22
Kringlen	45	38	—	29	33
Fischer	21	48	5	5	43
Gottesman & Shields	22	50	9	18	23

[a]From Gottesman and Shields, 1982
[b]S, schizophrenia/questionable schizophrenia; Si, schizoid; P, other psychiatric conditions; N, normal

that is, mental disturbances were recorded that could be ascribed to schizophrenia and the periphery of a conventional diagnosis of schizophrenia (e.g., personality disorders with mild schizophrenia-like features). From the index group, 32% of adopted offspring without schizophrenic parents were given a spectrum diagnosis; from the control group, the figure was 16%. Since these diagnoses were somewhat vague, the outcome of this study was criticized (e.g., Lidz *et al.*, 1981). Lowing *et al.* (1983) from the NIMH re-analyzed the material, as already reported. Both analyses were carried out blind to the status of the offspring of the probands. Lowing *et al.* (1983) then used DSM-III criteria. There was some change in the diagnosis of the parents, but the higher incidence of spectrum subjects was confirmed. They diagnosed only one case of schizophrenia (2.5%), but 38% of the index group and 13% of the control group were considered spectrum cases. Within the spectrum diagnosis, schizotypal and schizoid personality disorders had the highest frequency (Table 5). This was also true if only the adopted offspring of chronic schizophrenics were considered.

The incidence of borderline cases and borderline personality disturbances (DSM-III) did not distinguish the two groups re-analyzed by Lowing and colleagues. Kendler and Gruenberg (1984) also found, in their re-analysis of another Danish–American adoption study, an increased incidence of DSM-III-defined spectrum personality disturbances (rated blind) among the biological parents of the adopted children that eventually developed schizophrenia. Prominent were schizotypal and paranoid personality disorders, but not borderline cases.

TABLE 5 Re-analysis of the Rosenthal *et al.* (1968, 1971) Adoption Study by Lowing *et al.* (1983)

	Adopted Offspring	
DSM-III Diagnosis	*Schizophrenic Biological Parent (n = 39)*	*Nonschizophrenic Biological Parent (n = 39)*
Schizophrenia	1	0
Spectrum personality disorder[a]	14	5
No spectrum disorder	24	34

[a]Schizotypal personality disorder, schizoid personality disorder, borderline personality disorder, and "mixed spectrum"

Kendler and Gruenberg used the material of Kety *et al.* (1975), who were interested in adopted offspring with schizophrenia (from the Danish register) and in the rate of schizophrenia in the biological *parents* of these children. [The so-called "Kety strategy" represented the third Danish adoption study of the NIMH, along with the "conventional strategy" of the study of Rosenthal *et al.* (1968, 1971) and the "cross-fostering strategy" of Wender *et al.*, 1974.]

This argument will now be extended to a large-scale study of the incidence of spectrum personality disturbances in first-degree relatives of unequivocally diagnosed chronic schizophrenics (Baron *et al.*, 1983; Baron, 1987). This study was run by the New York Psychiatric Institute at two major hospitals. It found a significantly higher incidence of spectrum personality disturbances in 376 first-degree relatives of 90 schizophrenics (RDC; DSM-III) than in a control group of 346 first-degree relatives of 90 nonschizophrenics.

In detail, Baron found a schizotypal personality disturbance in 15% of the first-degree relatives of the schizophrenics but in only 2% of the control relatives. Paranoid personality disturbances and chronic schizophrenia were less frequent than schizotypal traits among the relatives of the schizophrenics, but were still significantly more frequent than in the controls, with incidences of 7% and 6%, respectively. Kendler and colleagues (1984) from another clinic in New York presented similar results in a study of first-degree relatives. Coryell and Zimmerman (1989) found no differences, but the diagnoses of the relatives were mostly attained through telephone interviews, which may be a disadvantage. Schulz *et al.* (1986) in Pittsburgh wanted to know whether the incidence of schizophrenia or schizotypal disturbances was higher among the first-degree relatives of patients with a schizotypal personality disturbance. They obtained negative results. Unfortunately there were several weaknesses in

the study. In particular, the experimental group used was too small ($n = 22$), and only 44 relatives were investigated. If the incidence is considered, it may be expected from the previous studies that the use of small groups extremely reduces the chance of finding subjects with schizotypal or schizophrenic symptoms. Therefore, little weight can be placed on these negative results.

The reasons for classifying the spectrum diagnosis under the DSM largely arose from the adoption studies (particularly those of Rosenthal and colleagues). Unfortunately, it provides no clear, broadly accepted definition. However, most of the authors cited included schizotypal, paranoid, or schizoid personality disorders. Borderline personality disorder seemed to be less frequent in the first-degree relatives of schizophrenics, but no definitive answer can yet be given. Some of the personality disorders defined in the DSM-III-R do overlap. (See Gottesman, McGuffin, and Farmer, 1987, for an extensive discussion.)

Relevant to whether a narrow or broad definition of the illness relates to the putative common genetic element is a study by Gottesman. . . . This American–English study (Farmer *et al.*, 1987) revealed that the inclusion of schizotypal personality disturbances, atypical psychoses, and mood-incongruent delusions along with definitive cases of schizophrenia markedly increased concordance values for MZ over DZ twins. They calculated the concordance rates for a number of diagnostic constellations, but this particular constellation of diagnoses showed the largest difference between MZ and DZ twins. The other extreme shows that if a very narrow definition of schizophrenia is used (e.g., Abrams and Taylor, 1983, Chicago), extremely few schizophrenic patients are reported from the families of these schizophrenics.

In summary, it can be said that there is an increased incidence of schizophrenic spectrum personality disturbances that are genetically in some way related to schizophrenia among the first-degree relatives of schizophrenics (e.g., schizotypal, schizoid, paranoid, and probably other psychotic disturbances such as atypical psychosis, mood-incongruent delusions, and schizo-affective disorder). Remarkable, though, is the absence in all studies of reports of (DSM-III-R) borderline personality disturbances among the relatives of schizophrenic patients. This is in contrast to prior expectations (see review by Schied, 1990).

These findings could form part of a working hypothesis for current research, to facilitate the assembly of new symptom constellations from an empirical base for studies of the nature of genetic transmission in schizophrenia (cf. Morey, 1988).

III. GENETIC MODELS AND GENETIC ANALYSIS

A. *Single Major Locus Models*

From the data discussed earlier, it seems evident that the classic Mendelian single major locus models cannot adequately explain the observations (i.e., one dominant or recessive gene). In other words, it is unlikely that a direct pathway from the genotype to the phenotype exists. For example, not all the twin partners of affected MZ twins are schizophrenic themselves. They must, however, transmit "something" in their genetic material, since more offspring of the unaffected become ill than would be expected if no transmission had occurred.

Several authors have therefore proposed that a dominant or recessive single gene with reduced penetrance may explain the data. Debray and colleagues (1979) from France ran likelihood estimates for 12 different potential genetic models of transmission, including single major locus models with low penetrance. Their data were based on 1333 individuals from 25 families with a schizophrenic member, covering 4 generations. The authors were not able to decide among several models, since they obtained similar likelihood estimates, but they were able to conclude that modified (low penetrance) single major locus models were untenable (later confirmed by Tsuang *et al.* 1982, and others; see reviews by Faraone *et al.*, 1988; McGue and Gottesman, 1989; see Crow, 1990, for a continuation of the argument for a single locus in a modified form).

B. *Polygenic Models*

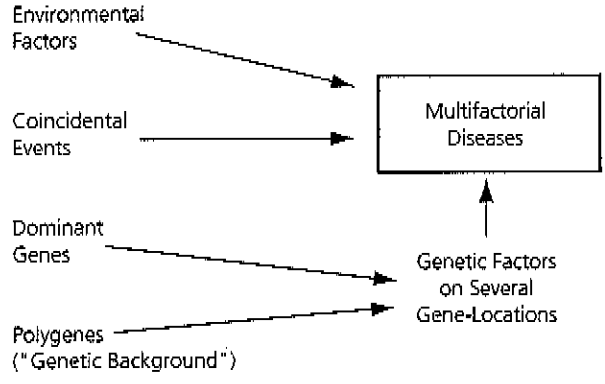
Polygenic models propose that several genes found at several loci may explain the pattern of transmission in schizophrenia. There are three main reasons to propose this alternative: (1) different degrees of severity of schizophrenia may be better explained by differences in the number of loci responsible (additive effects) than by single major locus models; (2) the puzzling heterogeneity may be better explained by different genes (i.e., by different combinations of genes in different schizophrenic patients); or (3) schizophrenia may be the result of the interaction of several genes. Also, (4) the fact that the rate of schizophrenia in the population is constant despite the reduced rate of reproduction of schizophrenic patients cannot be explained by single major locus models.

There have been several studies performed so far, but no clear support has become evident for the one or the other variant two-locus model, several-locus model, and so on. (See reviews by Gottesman and Shields, 1982; Faraone *et al.*, 1988.)

C. *Multifactorial Models*

A multifactorial model assumes that the phenotype is the result of a combination of genetic transmissions *and* environmental influences. A multifactorial model was first proposed by Gottesman and Shields (1967) for the mode of transmission in schizophrenia, but such models have been applied earlier to account for other nonstraightforward familial distributions of (psycho)somatic illnesses, such as high

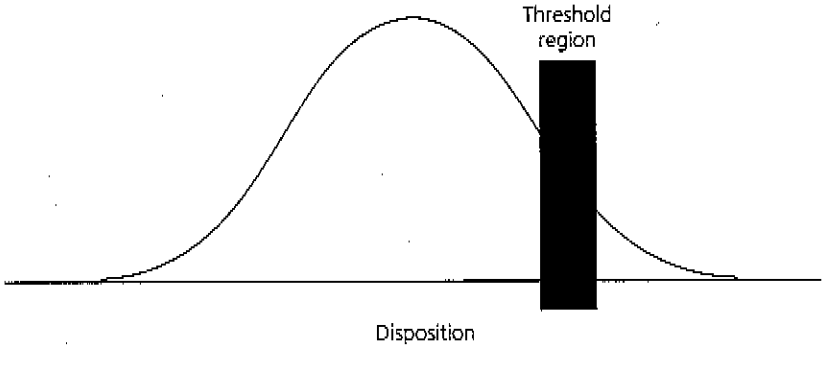
FIGURE 2 Schematic Illustration of the Multifactorial Model. Several genes (most likely a dominant gene and its genetic background) as well as environmental factors contribute to the "multifactorial" illness (after Propping, 1989).



blood pressure, allergies, and diabetes mellitus. In the case of schizophrenia, it is suggested that all individuals have some unobservable liability or predisposition to develop the illness. The model assumes that the mode of transmission is polygenic; therefore the arguments given previously also apply here. The main advantage is that the model also considers environmental factors (Figure 2). Another special feature is that a normal distribution of the predisposition in the general population is assumed. The appearance of the illness is seen as the crossing of a threshold. The model also accounts for spectrum personality disorders (second threshold)(see . . . Figure 3).

There are several old "goodness-of-fit" calculations that have yielded mixed results (cf. Matthysse and Kidd, 1976; review by Gottesman and Shields, 1982). More recent analyses incorporate the two-threshold assumption (i.e., different degrees of the expression of the phenotype from schizoid personality disorder to schizophrenia) and use path analysis in order to disentangle the effects of genetic and environmental factors. Several studies were again initiated by Gottesman and co-workers (see Rao *et al.*, 1981; McGue *et al.*, 1983, 1987) using all information available from several Western European family and twin databases. The results of the "goodness-of-fit" calculations for these data were all similar, favoring the assumption of a multifactorial model and rejecting single major locus models. The authors also concluded that genetic factors accounted for most of the variance (about 60%) but that environmental factors were also important, just to a lesser degree (see review by Faraone *et al.*, 1988, for more details).

FIGURE 3 Gaussian Distribution of the Disposition to Illness in the Population (i.e., the Subclinical Spectrum or Threshold Region). The illness is overt in the area to the right (after Propping, 1989).



D. Mixed Models

A variant of the multifactorial model is the mixed model. The mixed model assumes that a major locus gene exists with a polygenic background and environmental factors (see Figure 2). The model therefore takes into account the heterogeneity and the similarity of the phenotype. Carter and Chung (1980) were not able to find support for a mixed model, but they only used hospital diagnoses to calculate the "goodness-of-fit" with the data from 507 siblings. Baron (1987) also included spectrum disorders in his analysis, using diagnoses based on a standardized interview (79 chronic schizophrenics and their first-degree relatives). The result of this study was discussed already. Baron (1987) found that a single recessive major locus makes the largest contribution to the transmission of the liability (63%). In the model, there was also a statistical likelihood for a polygenic influence, but it was considerably lower (20%). The contribution of environmental effects (random and common sibling environment) to the variance in liability was estimated to be 17%.

In summary, both mixed and polyfactorial models can be supported to some extent. Thus, as yet, no clear decision can be made about which mode of transmission is the most likely, although single major locus models can probably be rejected (see also McGue

and Gottesman, 1989). A problem for these mathematical models and the "goodness-of-fit" estimations is that they depend on the reliability of the diagnosis and, more critically, on the concept of schizophrenia. Therefore, no definitive answers can be expected from this type of calculation. If a researcher decides to include only hospitalized schizophrenic patients, or even only DSM-III-R defined chronic schizophrenic patients, he or she gets a different picture of the mode of transmission than the researcher who believes that spectrum disorders, including schizoid or paranoid personality traits, belong to the genetic concept of schizophrenia. Another problem is, then, to define the borders of the spectrum (see the comprehensive discussion of this problem by Gottesman *et al.*, 1987). Since it is not clear what the appropriate phenotype for analysis should be in schizophrenia research, we must await more precisely defined biological or genetic markers. (These markers will be discussed in the next section.)

E. Molecular Genetic Approaches

Three recent studies conducted by teams from London (Sherrington *et al.*, 1988). Edinburgh (St. Clair *et al.*, 1989), and Yale (Kennedy *et al.*, 1988) have not waited for improved diagnosis and recognition of schizophrenia, but plunged into the material from well-known pedigrees with the newer techniques of molecular biology. Sherrington and colleagues claimed to have demonstrated that the inheritance of a disposition to psychiatric disorders belonging to the schizophrenia spectrum can be associated with genetic material on chromosome 5. The latter two studies, with negative results, have shown that not all cases of schizophrenia can be so explained. How did this all come about?

Three conditions were necessary: the availability of pedigrees providing psychiatric information and genetic material, the methods for locating the genetic fragments responsible, and a sign of where to look among the vast library of genes available.

The analysis of large family clans will be considered first. Sherrington *et al.* (1988) studied two British and five Icelandic pedigrees covering three generations. The Icelandic families were those described by Karlsson (1982, 1988). This database of 104 persons included 39 cases of schizophrenia, 5 with schizoid disturbances, and a further 10 cases of disorders including phobias, anxiety, and depression. Kennedy *et al.* (1988) searched northern Swedish pedigrees. This material covers 157 persons in seven branches. They were able to diagnose 31 cases of schizophrenia and found 50 unaffected subjects. St. Clair *et al.* (1989) used the same phenotypic descriptions as the London group, with 15 families in Scotland. Of 166 members whose DNA was examined, 75 had some mental disturbance; for 44 this was schizophrenia, and, for a further 5 cases, a psychosis or spectrum personality was determined.

We will now discuss the methods. Basically, these tools involve the use of restriction enzymes to identify places at which the different genomes vary. When following the inheritance of parts of a chromosome through a family, one can use the variations of the sequences of DNA as genetic markers. These variations become visible when they disrupt the recognition site for a restriction enzyme. The sequences of DNA marked by these sites are called restriction fragment length polymorphisms (RFLPs). Among the thousands of such sequences already known in humans, it has been possible to track RFLPs that pass from generation to generation with a disease (e.g., Huntington's chorea, manic depression; Egeland *et al.*, 1987). It can be concluded that the genes contributing to the disease lie in a chromosomal region near the RFLP.

Why did these groups look at chromosome 5? The sign was provided by a case reported by Bassett *et al.* (1988). The case concerned an uncle and nephew who were both schizophrenic and had certain unusual facial features in common. They both carried an extra copy of the region known as 5q11–13 translocated to chromosome 1. (Additionally, at the time it was thought that the glucocorticoid receptor was encoded near the 5q region. Disturbance of glucocorticoid metabolism can give rise to psychoses. This locus has since been shown not to be as close as originally thought.)

Sherrington *et al.* (1988) reported finding strong concordance with a putative dominant character predisposing to schizophrenia. The concordance has been improved by including the other psychiatric illnesses, but in view of the relatively inadequate information provided by the individuals concerned, this finding must be treated with reserve. The transmission of schizophrenia and of the genetic markers was $10^{6.49}$-fold more likely if they were genetically linked than unlinked (i.e., the relatively high lod score of 6.49 speaks in favor of a single gene locus[1]). Two features, one in the design and the other in the methods, must qualify this result. There was a deliberately biased sampling of families for signs of genes with a high penetrance. This was deemed a necessary design feature to increase the likelihood of finding what their methods could detect, namely, a single gene locus. However, it is difficult to believe that the lod score increased when they broadened the diagnostic criteria to include various depressive illnesses. Family, twin, and adoption studies have not provided evidence for a genetic link between these two types of psychiatric disturbance (e.g., Loranger, 1981).

However, reasonable criticism can also be made of the reports of negative results (Byerley *et al.*, 1989). The pedigree studied by Kennedy *et al.* (1988) may prove to be an exceptional case. There is reason to suppose that it is also demonstrating segregation for mental retardation. This adds considerable complexity to the analysis. Although the report of St. Clair *et al.* (1989) is laudable for its attempt to test several hypotheses for the linkage of different syndromes, their basic assumption of an autosomal dominant mode for inheritance is unlikely. Byerley is not alone in

suggesting that a recessive mode is more likely (see previous section).

What might the combined results mean? It seems that schizophrenia may rarely be linked to defects in an unknown gene on chromosome 5. It may be a dominant gene, the inheritance of which leads to the inheritance of a susceptibility to schizophrenia. However, carriers do not necessarily develop schizophrenia. It has not been shown that a chromosome 5 defect is sufficient for the development of schizophrenia nor that all schizophrenia develops from this or any other gene. Using five RFLPs, Kennedy *et al.* (1988) found no evidence of a link between chromosome 5 and schizophrenia, but noted that a demonstration of the heterogeneity of schizophrenia would require finding another genetic locus (Lander, 1988).[2] Striking in the results of Sherrington *et al.*(1988) is that apparently several subtypes of schizophrenia may have a common genetic source. Again, the suggestion is that the etiology does not match the results of current diagnostic practices. Future studies should aim to attain more psychiatric and genetic information from more members. This information should be combined with recently developed genetic maps to demonstrate linkage. Such techniques could already be applied to other behavioral and physiological markers correlating with schizophrenia (e.g., pursuit eye movements, sensitivity to amphetamine; Lander, 1988). . . .

[Section IV has been omitted here.]

V. SUMMARY STATEMENTS AND INTERPRETATIONS

A. *Monozygotic (MZ) and Dizygotic (DZ) Twin Studies*

The rate of schizophrenia is higher in MZ than in DZ twins. The concordance is generally less than 50%, but is higher if one of the twins is severely ill.

The numbers speak for a genetic contribution, but are far lower than those expected for a straightforward dominant-recessive model of inheritance.

B. *Adoption Studies*

The adopted (index) offspring of schizophrenic parents are at higher risk for developing schizophrenia than control children. However, the incidence of schizophrenia is lower than in children living with the affected parent. In some adoption studies, schizophrenia is rare, but spectrum personality disorder (e.g., schizotypal personality disorder) is more frequent.

These results demonstrate that both the genetic disposition and the environment play a role in the development of schizophrenia.

C. *First-Degree Relatives of Schizophrenics*

About 15% of the relatives of schizophrenics have personality disorders which have some similarity with schizophrenia (i.e., schizotypal personality disorder and other spectrum features).

A common heritable factor seems to be the basis of both the fully developed illness and the spectrum personality disorder. There may be at least two influences that determine the severity of the expression as spectrum or fully developed schizophrenia: environmental stress and the degree of genetic load (reflected, for example, by the number of afflicted relatives; Odegaard, 1972, in Propping, 1989). The phenotype is the product of a genetic/environment interaction but the genetic predisposition seems to be the necessary condition. Birth complications and slight cortical atrophy seem to play the same unfavorable role as aversive environmental influences. . . . Another possibility is that of a phenocopy, if the same putative pathognomonic area is afflicted by atrophic processes.

D. *Mechanisms of Inheritance*

The exact mode of inheritance is not clear, although most researchers exclude at least the possibility of a single major locus gene. Psychiatric genetics today favor polyfactorial or mixed models (i.e., this is the result of most mathematical likelihood estimations when comparing the model with the appearance of schizophrenia or spectrum disorders in pedigrees).

The polyfactorial model assumes that several genes are responsible for schizophrenia and the additional influence of the environment results in the crossing of a second threshold. The appearance of spectrum disorders is being considered as the crossing of an initial threshold. In general, it is suggested that the liability or the disposition to develop the illness is distributed continuously in the population (Gaussian distribution). The mixed model assumes that, in addition to the factors involved in the polyfactorial mode of transmission, a single major gene locus is responsible.

The mixed and polyfactorial models seem to be plausible with respect to the fact that the phenotype is heterogeneous, the illness can appear without family history of schizophrenia, and schizophrenia does not die out despite the fact that schizophrenic patients have fewer offspring than healthy persons. However, the exact proof for one or the other model is difficult to present because of the variable nature of and the difficulty defining the borders of the various expressions of the phenotype in the general population, from mild spectrum features to severe breakdown.

E. *Molecular Genetics*

A recent claim that the genetic locus is on chromosome 5 is not supported by several other studies.

It is theoretically possible, as discussed earlier, that more than one locus is required to bring about a sufficient liability for developing schizophrenia. If so, a search for a single locus would only make sense if the existence and contribution of a major gene could be assumed. Information pertinent to a decision between the alternatives is not available.

NOTES

1. The "lod" score or "log of the odds" refers to the usual parametric statistic for assessing the strength of a linkage. The conventional threshold for acceptance of linkage is 3.0, whereas that for rejection of a linkage between a polymorphic test marker and a particular disease locus is −2.0. For example, in 1990 the status of combined studies on a marker for Huntington's disease on the short arm of chromosome 4 was 87.7 at a recombination frequency of 0.04; in contrast, for the 11p marker for bipolar affective disorder, the lod score has decreased from 4.08 in the original study to −9.3 after subsequent additional investigations.
2. There are at least two other reports of features with an increased incidence in small groups of schizophrenics, the origin of which has been traced to a locus on chromosome 19 (19p13) (see discussion in Byerley *et al.*, 1989). It should not be overlooked that there may be a number of genetic defects necessary for the expression of the phenotype. It may be a combination of all or only some of these that is sufficient for the illness to appear.

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Schizophrenia: The clash of determinisms

THE CASE OF SCHIZOPHRENIA

The diagnosis and treatment of schizophrenia are paradigms of the determinist mode of thinking, for this is the mental disorder on which more biochemical and genetic research has been lavished than any other, the one in which claims to have discovered *the* cause in a particular molecule or gene have been made most extensively. It is now so widely believed that psychiatry has proved the disorder to be biological that if the case fails here, where it is strongest, it must be even weaker elsewhere. But schizophrenia is interesting from another point of view as well, for in opposition to the biologizing tendencies of medical psychiatry there has grown up a strong countermovement in recent years. Antipsychiatry, in the hands of practitioners like R. D. Laing and theorists like Michel Foucault, has gone far in the opposite direction, almost to the point of denying the existence of a disorder or group of disorders diagnosable as schizophrenia at all. Thus in the case of schizophrenia we find precisely that clash of determin-

isms, on the one hand biological and on the other cultural, . . . which it is one of the purposes of our book to transcend.

What Is Schizophrenia?

Schizophrenia literally means "split mind." The classic picture of a schizophrenic is of a person who feels in some fundamental way cut off from the rest of humanity. Unable to express emotion or interact normally or express themselves verbally in a way that is rational to most others, schizophrenics appear blank, apathetic, dull. They may complain that their thoughts are not their own or that they are being controlled by some outside force. According to the textbooks, dramatically ill schizophrenics appear not to be able to or wish to do anything for themselves—they take little interest in food, sexual activity, or exercise; they experience auditory hallucinations; and their speech seems rambling, incoherent, and disconnected to the casual listener. Some psychiatrists doubt whether schizophrenia is a single entity at all, or speak of core schizophrenia and a wider range of schizophrenia-like symptoms.

The idea of a single disease of schizophrenia may be a hangover from the nineteenth-century definition of madness—so-called dementia praecox—which preceded it. The diagnosis of schizophrenia in a patient with a given set of symptoms can vary between doctor and doctor and culture and culture. It is true that when matched and carefully controlled transnational surveys are done there is some concordance of diagnosis; however, in real life the diagnostic and prescribing practices of doctors and psychiatrists differ sharply from the more controlled procedures of clinical trials. Comparisons of figures in different countries have shown that the most frequent use of the diagnosis of schizophrenia occurs in the United States and the Soviet Union. Nonetheless, even in Britain, where it is defined in a somewhat narrower sense, up to 1 percent of the population is said to suffer from schizophrenia,[1] and 28,000 —or 16 percent—of the admissions to hospitals for mental illness in 1978 were for a diagnosis of schizophrenia or its related disorders.

Faced with the complex phenomena that result in a diagnosis of schizophrenia, the biological determinist has a simple question: What is it about the biology of the individual schizophrenic that predisposes him or her toward the disorder? If no obvious gross brain difference can be found, predisposition must lie in some subtle biochemical abnormality—perhaps affecting the connections between individual nerve cells. And the thrust of the determinist argument is that the causes for these abnormalities, although they might have been environmental, are most likely to lie in the genes. . . .

THE GENETICS OF SCHIZOPHRENIA

The statement that the brain of a person manifesting schizophrenia shows biochemical changes compared with that of a normal person may be no more than a reaffirmation of a proper materialism that insists on the unity of mind and brain. But the ideology of biological determinism goes much deeper that this. It is, as we have reiterated, linked to an insistence that biological events are ontologically prior to and cause the behavioral or existential events, and hence to a claim that if brain biochemistry is altered in schizophrenia, then underlying this altered biochemistry must be some type of genetic predisposition to the disorder. By 1981 psychologists were claiming to be able to detect potential schizophrenics when they are only three years old—up to fifty years before the disease manifests itself. The claim, made by Venables to a meeting of the British Association for the Advancement of Science, is based on a survey of three-year-olds in Mauritius; "potentially abnormal" children were said to show "abnormal autonomic responses."[2]

Push the diagnosis back beyond the three-year-old and we are soon with embryo or gene. But the hunt for a genetic basis for schizophrenia goes far beyond an interest in therapy, as there is no way in which the mere demonstration of a genetic basis for the disorder would aid in its treatment.* As we have seen, the lineage of the effort to find genetic predispositions runs back through the eugenic thinking of the 1930s and 1920s, with its belief in genes for criminal degeneracy, sexual profligacy, alcoholism, and every other type of activity disapproved of by bourgeois society. It is deeply embedded in today's determinist ideology. Only thus can we account for the extraordinary repetitive perseverance and uncritical nature of research into the genetics of schizophrenia. Whatever such research may say about the disorder it proposes to explain, an examination of the claims of its protagonists says a very great deal about the intellectual history of our contemporary determinist society, and hence is worth analyzing in some detail.

The belief that schizophrenia has a clear and important genetic basis is now very widely held. The father of psychiatric genetics, Ernst Rüdin, was so convinced of this that, arguing on the basis of statistics collected by his co-workers,

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*These words were true when we wrote them. However, reductionist science moves faster than the Gutenberg technology of book production. For if it were the case that there were schizophrenia-producing genes, then techniques that excised those abnormal genes from the genome of affected individuals and replaced them with their normal alleles would presumably prevent the expression of the disorder. If schizophrenia were a single or even a two- or three-gene defect, such techniques are not wholly beyond the reach of contemporary molecular genetics—what is sometimes called genetic engineering. There are serious research programs now under way in several laboratories to make gene libraries from schizophrenics and isolate and clone the "schizophrenic genes" with a view to studying their possible replacement. Granted the reductionist premise, the therapeutic logic would be impeccable. And if one can have schizophrenic urine, why not, indeed, schizophrenic genes?

he advocated the eugenic sterilization of schizophrenics. When Hitler came to power in 1933, Rüdin's advocacy was no longer merely academic. Professor Rüdin served on a panel, with Heinrich Himmler as head, of the Task Force of Heredity Experts who drew up the German sterilization laws of 1933.

Perhaps the most influential psychiatric geneticist in the English-speaking world was a student of Rüdin's, the late Franz Kallmann. The blizzard of statistics published by Kallmann seemed to indicate conclusively that schizophrenia was a genetic phenomenon. From his study of a thousand pairs of affected twins, Kallmann concluded that if one member of a pair of identical twins was schizophrenic there was an 86.2 percent chance that the other would be also. Further, if two schizophrenic parents produced a child, there was a 68.1 percent chance that the child would be schizophrenic. These figures led Kallmann to argue that schizophrenia could be attributed to a single recessive gene.

The particular genetic theory espoused by Kallmann has made it possible for latter-day psychiatric geneticists to attempt a spectacular rewriting of their history. Thus, in a recent textbook the following note appears: "Kallmann's [theory] was apparently not based solely on his data. His widow has indicated that Kallmann advocated a recessive model because he could then argue convincingly against the use of sterilization to eliminate the gene. As a Jewish refugee, Kallmann was very sensitive to this issue and afraid of the possible social consequences of his own research."[3] The point here is that if a disease such as schizophrenia is caused by a recessive gene, many carriers of the gene will not themselves display symptoms. Thus, sterilization merely of those who do show symptoms would be inefficient and would fail to eliminate the disease.

The picture of Kallmann as a bleeding-heart protector of schizophrenics, adjusting his scientific theories to mirror his compassion, is grotesquely false. The first Kallmann publication on schizophrenia is in a German volume edited by Harmsen and Lohse that contains the proceedings of the frankly Nazi International Congress for Population Science.[4] There, in Berlin, Kallmann argued vigorously for the sterilization of the apparently healthy relatives of schizophrenics, as well as of schizophrenics themselves. This was necessary, according to Kallmann, precisely because his data indicated that schizophrenia was a genetically recessive disease. Two Nazi geneticists, Lenz and Reichel, rose to argue that there were simply too many apparently healthy relatives of schizophrenics to make their sterilization feasible.

The eugenicist views of Kallmann were not confined to obscure Nazi publications but also made widely available in English after his arrival in the United States in 1936. In 1938 he wrote of schizophrenics as a "source of maladjusted crooks, asocial eccentrics, and the lowest type of criminal offenders. Even the faithful believer in . . . liberty would be much happier without those. . . . I am reluctant to admit the necessity of different eugenic programs for democratic and fascistic communities . . . there are neither biological nor sociological differences between a democratic and a totalitarian schizophrenic."[5]

The extremity of Kallmann's totalitarian passion for eugenic sterilization was clearly indicated in his major 1938 text. Precisely because of the recessivity of the illness, it was above all necessary to prevent the reproduction of the apparently healthy children and siblings of schizophrenics. Further, the apparently healthy marriage partner of a schizophrenic "should be prevented from remarrying" if any child of the earlier marriage is even a suspected schizophrenic, and even if the second marriage is with a normal individual.[6]

These views of the future president of the American Society for Human Genetics are so bloodcurdling that one can sympathize with the efforts of present-day geneticists to misrepresent or to suppress them. They have not, however, suppressed the mountains of published statistics with which Kallmann attempted to prove that schizophrenia (like tuberculosis and homosexuality) was a hereditary form of degeneracy. Those figures are presented to students in today's textbooks as the fruits of impartial science. We begin our review of the data concerning the genetics of schizophrenia with a detailed examination of Kallmann's work, which should make clear that Kallmann's figures cannot be regarded seriously.

KALLMANN'S DATA

The Kallmann data were collected under two very different sets of circumstances. The earlier data, published in 1938, were based upon the records of a large Berlin mental hospital. Working with records from the period 1893–1902, Kallmann made an "unambiguous diagnosis" of schizophrenia in 1,087 index cases. To make these diagnoses it was necessary to ignore "earlier diagnoses or the contemporary notes on hereditary taint conditions in the family of the patient." Then Kallmann attempted to locate, or to acquire information about, relatives of the index cases—many of whom were long since dead. That task often involved

> formidable difficulties . . . we were dealing with inferior people. . . . They sometimes escaped our search for years. . . . Quite a few were bad-humored . . . we had to overcome the suspicion with which certain classes regarded any kind of official activity. . . . Whenever we encountered serious opposition we found ourselves to be dealing with either officials and members of the academic world, or people with exaggerated suspicions, schizoid types, and possible schizophrenics . . . our private sources of information were amplified from the records of police bureaus. . . . In making inquiries about people already dead or living too far away, we employed. . . . local bureaus and trusted agents.[7]

With information gathered in this way, Kallmann felt able to diagnose the relatives of the index cases, and thus to report the probability of schizophrenia for each type of relative. The rates reported by Kallmann in this German

TABLE 1 Age-Corrected Morbidity Rates for Schizophrenia, as Reported by Kallmann

Relationship to Index Case	*Berlin, 1938*	*New York, 1946*	*New York, 1953*
MZ twin	—	85.8	86.2
DZ twin	—	14.7	14.5
Parents	10.4	9.2	9.3
Children	16.4	—	—
Full siblings	11.5	14.3	14.2
Half-siblings	7.6	7.0	7.1
Grandchildren	4.3	—	—
Nephews, nieces	3.9	—	—
Step-siblings	—	1.8	1.8
Spouse	—	2.1	—

sample are reproduced in the left-hand column of Table 1. The reported rates, it should be noted, were "age-corrected." That was necessary because some of the relatives were quite young and might develop schizophrenia as they grew older. The arbitrary correction employed by Kallmann can sometimes produce rates in excess of 100 percent.

The second set of data collected by Kallmann came from a very different sample, studied in New York State. The index cases were now individuals who were schizophrenic twins who had been admitted to public mental hospitals. When Kallmann reported in 1946, there were 794 such index cases.[8] By 1953, the number had increased to 953. There were, of course, some identical (MZ) twins, and some fraternal (DZ) twins. Thus, by obtaining information about the co-twins of index cases, Kallmann could report the probability that both members of a pair were schizophrenic. That probability is called the "pairwise concordance rate." The age-corrected concordances were reported for different types of twins, along with the corrected morbidity rates for various types of relatives. These had been determined by collecting information about the relatives of the twin index cases. There was virtually no information given about the procedures employed in this massive study, but Kallmann wrote that "classification of both schizophrenia and zygosity were made on the basis of personal investigation and extended observation." This obviously allowed for "contaminated diagnosis." That is, the decision as to whether or not a co-twin was said to be schizophrenic could be influenced by the decision as to whether the twin pair was MZ or DZ and vice versa. The Kallmann 1946 data, and the even more sketchily reported data of 1953,[9] are also presented in Table 1.

These data are obviously consistent with an overwhelming genetic determination of schizophrenia—particularly the remarkable rate of 86 percent among MZ twins. Where direct comparisons can be made, the change of countries and of eras—as well as the switch to relatives of twin index cases—has had little effect on the reported figures.

The correspondence between Kallmann's theoretical expectations and the results he discovered is sometimes quite remarkable. Thus, in 1938 Kallmann indicated that the work of earlier twin researchers suggested that schizophrenia manifested itself, even among those with the full genetic predisposition, only about 70 percent of the time.[10] That meant, according to Kallmann's single recessive gene theory, that 70 percent of the children of two schizophrenic parents should themselves be schizophrenic. The Kallmann data indicated that the expectation of schizophrenia in the offspring of two schizophrenics was precisely 68.1 percent. That result, of course, nicely validated Kallmann's theory. Four other studies of the children of two schizophrenic parents suggest a risk of only between 34 and 44 percent.[11]

Kallmann stressed repeatedly that, in his data, the " morbidity figure for the siblings . . . corresponds perfectly with the concordance rate for two-egg twin pairs, whose chance of inheriting a similar genotypical combination is exactly the same as that for any ordinary pair of brothers and sisters."[12] The same close correspondence was described as a notable finding in 1953. We shall soon see, however, that—as an embarrassment to a simple genetic theory—other investigators have not found the close correspondences of data with theory routinely detected by Kallmann. . . .

The research conducted by others who followed Kallmann has in any event made it clear that his extraordinarily high figures cannot be repeated. The Kallmann data are still presented, unblushingly, in purportedly serious reviews of research, but they are now counterbalanced by more recent and more modest results. Perhaps the chief harm brought about by Kallmann's deluge of incredible and poorly documented data was to create a climate in which the findings of subsequent workers seemed so reasonable and moderate that they escaped serious critical scrutiny. Thus, Kallmann's data have faded from the body of acceptable evidence, but the belief for which he was largely responsible—that a genetic basis for schizophrenia has been clearly established—still remains powerful in and out of science.

Family Studies

There are basically three kinds of inquiries that attempt to demonstrate a genetic basis for schizophrenia: family studies, twin studies, and adoption studies. There is no need to spend much time on the first. The simple idea behind them is that if schizophrenia is inherited, the relatives of schizophrenics are likely to display the disease as well.

Further, the more closely related a person is to a schizophrenic, the more likely it should be that the person will be affected. The problem is, of course, that these predictions would also follow from a theory that maintained that schizophrenia was environmentally produced. There is an obvious tendency for close relatives to share similar environments.

For what such data are worth, the major compilation of family studies seems to have been made by Zerbin-Rüdin.[13] The compilation was presented to English-readers in "simplified form" by Slater and Cowie.[14] Their table indicates, e.g., that fourteen separate studies yield a 4.38 percent expectation of schizophrenia among the parents of schizophrenic index cases. The expectation among sibs, in ten studies, was 8.24 percent; and among children 12.31 percent in five studies. For uncles and aunts, grandchildren, and cousins the figures were all under 3 percent, but still higher than the expected 1 percent.

The exactness of these figures, however, is more apparent that real. The same basic set of studies was also summarized by Rosenthal in 1970.[15] The relatives diagnosed in these studies, Rosenthal noted, had often been dead for many years. The studies are quite old, and methods of diagnoses and of sampling are not always spelled out. The combined figures are dominated by Kallmann's massive samples and by data gathered by other members of Rüdin's "Munich school." The Rosenthal tables make clear a fact that is obscured by the Slater and Cowie summary. There are vast differences in the rates of schizophrenia reported in different studies. For parents of index cases, reported risks range from 0.2 percent (lower than in the population at large) to 12.0 percent. For sibs, the range is between 3.3 and 14.3 percent. The risk for sibs is in one study twenty-nine times larger than that for parents; but in another the risk for parents is 1½ times larger than that for sibs. These studies at best demonstrate what nobody would have contested. There is at least a rough tendency for diagnosed schizophrenia to "run in families."*

Twin Studies

[T]he basic logic of twin studies depends upon the fact that while MZ twins are genetically identical, DZ twins on average share (like ordinary siblings) only half their genes. Thus, if a trait is genetically determined, one would obviously expect MZs to be concordant for that trait more often than DZs. The major logical problem with twin studies is that MZ twins, who typically resemble one another strikingly in appearance, are treated much more similarly than are DZs by parents and peers. There is abundant evidence . . . that the environments of MZs are very much more similar than those of DZs. (Twin studies typically compare concordance rates among MZs, who are always of the same sex, with concordance rates among same-sexed DZs.) The demonstration that concordance is higher among MZs does not necessarily establish a genetic basis for the trait in question. Perhaps the difference is due to the greater environmental similarity of MZs. We shall soon discuss evidence which indicates that this possibility is not at all farfetched.

Well-designed twin studies should take as their index cases all schizophrenic twins admitted to a particular hospital during a particular time period. The alternative—feasible in small Scandinavian countries, which maintain population registers—is to start with the entire population of twins and to locate index schizophrenic cases. With either technique, a number of procedural problems are inevitable. The co-twins of index cases are often dead or unavailable for personal examination. Thus, informed guesses often must be made both about whether a given pair is MZ or DZ, and whether or not the co-twin is schizophrenic. The guesses are typically made by the same person, opening the way for contaminated diagnoses. There is sometimes an effort to have blind diagnoses made of individual cases by independent judges, working from written case histories.[17]

The case histories, however, contain selective material gathered and prepared by investigators who were not themselves "blind." Further, the case records of those twins who have in fact been hospitalized—and their diagnoses—had been written up by doctors who questioned the ill twins in detail about possible taint in their family lines. The diagnosis of schizophrenia, as should by now be clear, is by no means a cut-and-dried affair. The fact that a person's relative may have suffered from schizophrenia is often used to help doctors make a diagnosis.

The biases that contaminate twin studies stand out clearly from an attentive reading of the published case history materials. The very first case described by Slater in 1953 is the story of Eileen, a hospitalized schizophrenic, and of her identical twin, Fanny. Eileen had been hospitalized in 1899, "suffering from acute mania," and died in the hospital in 1946. With Eileen as the index case, Slater's task was to investigate the mental status of Fanny, who died, aged seventy-one in 1938. We are told by Slater:

> While still in the twenties she had a mental illness, of which no details are available. . . . Fanny in [1936] proved very difficult to examine . . . so that only the barest details were obtainable. She suppressed all mention of her own mental illness in early years, which fact was obtained from the history of her twin sister given at the time of her admission to hospital. Though there was no sign of any present schizophrenic symptoms, this suspicion and reserve are such as are commonly found as sequelae of a schizophrenic psychosis. Unfortunately, no facts are obtainable about the nature of her past mental illness,

*Even this modest conclusion is not unchallenged in the literature. Two studies in the United States found rates of schizophrenia among the first-degree relatives of schizophrenics which were scarcely above the rate in the general population.[16]

but the probabilities are very greatly in favour of it having been a schizophrenic one . . . she made a fairly complete and permanent recovery . . . though psychologically her reserve and lack of frankness suggest that the schizophrenia was not entirely without permanent after-effect. . . . According to her daughter-in-law, who had not heard of her mental illness, she led a hard life. Neither her family nor the neighbours noticed anything odd about her.[18]

These MZ twins, according to Slater, were concordant for schizophrenia. The only evidence that Fanny had once suffered from schizophrenia was her twin's assertion—while "suffering from acute mania" in 1899—that Fanny had had some kind of mental illness. Fanny herself, in 1936, was difficult and suppressed all mention of her illness. That lack of frankness, Slater noted, was typical of recovered schizophrenics, who otherwise appear normal. Fanny's dead identical twin had clearly been schizophrenic. For Slater this made it obvious that Fanny's supposed mental illness fifty years earlier had been schizophrenia. Fanny's neighbors and family, unlike Slater and other students of the Munich school, had not the wit to detect Fanny's schizophrenia.

Consider now the first pair of discordant DZ twins described by Gottesman and Shields in their 1972 study. Twin A was a hospitalized schizophrenic. What about Twin B? "No psychiatric history. Family unwilling for him to be contacted for Twin Investigation. . . . The pair differs from most in that neither twin was seen by us." The investigators concluded that Twin B was normal: and six blind judges, pondering a case study summary prepared by the investigators, unanimously agreed that Twin B was free of psychopathology. With DZ Pair 16 of the same study, all judges again agreed that the co-twin was normal, making the pair discordant. The diagnosis of the co-twin had not been made under ideal conditions: "He refused to be seen for the Twin Investigation, remaining upstairs out of sight, but his wife was seen at the door. . . . He was regarded as a healthy, levelheaded, solid happy person." That might in fact be the case—but few will agree that diagnoses of co-twins made in this way are solid or levelheaded.

Problems of this sort affect all twin studies, and that should be borne in mind as we review the results reported by various investigators. To obtain reasonable estimates of concordance rates, it seems sensible to require that a study contain at least twenty pairs of MZ and twenty pairs of same-sexed DZ twins. There have been seven such studies, and their results are summarized in Table 2.

TABLE 2 Reported Concordance Rates

	"Narrow" Concordance		*"Broad" Concordance*	
Study	*% MZs*	*% DZs*	*% MZs*	*% DZs*
Rosanoff et al., 1934[19] (41 MZs, 53 DZs)	44	9	61	13
Kallmann, 1946[8] (174 MZs, 296 DZs)	59	11	69	11–14
Slater, 1953[18] (37 MZs, 58 DZs)*	65	14	65	14
Gottesman and Shields, 1966[20] (24 MZs, 33 DZs)	42	15	54	18
Kringlen, 1968[21] (55 MZs, 90 DZs)	25	7	38	10
Allen et al., 1972[22] (95 MZs, 125 DZs)	14	4	27	5
Fischer, 1973[23] (21 MZs, 41 DZs)	24	10	48	20

*There is no simple way to derive separate narrow and broad concordance rates for Slater.

The table presents raw, pairwise concordance rates, without any age correction. Two sets of rates are given for each study, one narrow and one broad. The narrow rates are based on the investigator's attempt to apply a relatively strict set of criteria when diagnosing schizophrenia. The broad rates include as concordant cases in which one twin is described as "borderline schizophrenic" or as "schizo-affective psychosis" or a "paranoid with schizophrenic-like features." The tabled concordance rates, it should be noted, depend upon the different investigators' varying sets of diagnostic criteria. They have not been concocted ad hoc by us.

The table makes clear that in all studies concordance is higher for MZ than DZ twins. But it is also clear that the concordance reported for MZs is much higher in the three older studies than in the four more recent ones. There is in fact no overlap between the two sets of studies. For narrow concordance, the average has plunged from 56 to 26 percent for MZs; for DZs, the corresponding averages are 11 and 9 percent. For broad concordance, MZ rates have dropped from 65 to 42 percent, while the DZ rate remained at a constant 13 percent. These average values, which weight all studies equally, should not be taken too literally. The data do make clear, however, that even in genetically identical MZs environmental factors must be of enormous importance. The concordance for MZs reported by modern researchers, even under the broadest criteria, does not remotely approach the preposterous 86 percent figure claimed by Kallmann.

Those who perform such studies still claim, however, that the higher concordance observed among MZs—a unanimous finding—demonstrates at least some genetic basis for schizophrenia. We

TABLE 3 Reported Risks for DZ Twins and Sibs

	% DZs	% Sibs
Luxenburger, 1935[24]	14.0	12.0
Kallmann, 1946[8]	14.7	14.3
Slater, 1953[18]*	14.4	5.4
Gottesman and Shields, 1972[17]	9.1	4.7
Fischer, 1973[23]*	26.7	10.1
Kringlen, 1976[21]	8.5	3.0

*Probability that the differences between DZs and sibs are due only to sampling error is less than 0.01%.

have already noted that MZs not only are genetically more similar than DZs but also experience much more similar environments than do DZs. The environmental similarity, no less that the genetic similarity, might plausibly account for the higher concordance of MZs.

There are in fact some simple and critical tests that can be made of this environmental hypothesis. There is no doubt that DZ twins experience more similar environments than do ordinary siblings. The DZ twins, however, are genetically no more alike than are ordinary siblings—they are only siblings who happen to have been born at the same time. Thus, from an environmental viewpoint—and only from such a viewpoint—we would expect concordance among DZs to be higher than among ordinary sibs. There have been a number of studies that reported rates of schizophrenia concordance among DZ twins, as well as rates among siblings of the twins. The results of all such studies are summarized in Table 3.

Though the reported differences are very small in the early studies, all studies agree in showing a higher concordance rate among DZs than among sibs. Within more modern studies, the difference is often statistically significant, with the risk for DZs reported as two or three times that for sibs. When we note that similarity of environment can double or triple the concordance of DZs above that of sibs, it seems entirely plausible to attribute the still higher concordance of MZs to their still greater environmental similarity.

The same kind of point can be demonstrated by comparing the concordance rates of same-sexed and of opposite-sexed DZs. Though both types of DZ twins are equally similar genetically, it is obvious that same-sexed pairs experience more similar environments than do opposite-sexed pairs. The available data, summarized in Table 4, again support the environmentalist expectation. There have been statistically significant differences reported by several investigators, always indicating a higher concordance among same-sexed twins. The results of the one study that appears to reverse the otherwise universal trend were not statistically significant.

TABLE 4 Concordance in Same- and Opposite-Sexed DZ Twins

	% Same-Sexed	% Opposite-Sexed
Rosanoff et al., 1934 (53 SS, 48 OS)[19]*	9.4	0.0
Luxenburger, 1953[24]	19.6	7.6†
Kallmann, 1946 (296 SS, 221 OS)[8]*	11.5	5.9
Slater, 1953 (61 SS, 54 OS)[18]*	18.0	3.7
Inouye, 1961 (11 SS, 6 OS)[25]	18.1	0.0
Harvald and Hauge, 1965 (31 SS, 28 OS)[26]	6.5	3.6
Kringlen, 1968 (90 SS, 82 OS)[21]	6.7	9.8

*Probability that differences between same- and opposite-sexed twins are due only to sampling error is less than 0.05%.
†Estimated

Consider, finally, some implications of a finding casually reported by Hoffer and Pollin.[27] Those authors studied the hospital records of the American war veteran twins later reported on by Allen et al. Several hundred diagnosed schizophrenic twins were located by searching through records, but the twins were not personally examined by the investigators. Thus, to determine whether a twin pair was MZ or DZ, questionnaires were mailed to all twins, asking whether they looked as much alike as two peas in a pod, whether they were confused for each other, etc. There were many occasions when only one twin of a discordant pair returned the questionnaire. When the twin returning the questionnaire had been diagnosed as schizophrenic, 31.3 percent gave answers indicating that they were MZ. When the answering twin was not the diagnosed schizophrenic, only 17.2 percent indicated that they were MZ. The difference is statistically significant, and it was produced by an unrealistically small proportion of MZs among the nonschizophrenic twins.

That is easily understandable. When you are normal and your twin is schizophrenic, you are well advised to tell twin investigators and other authorities that you are not a carbon copy of your twin—even if you really are MZs. To admit that you are the MZ twin of a schizophrenic is clearly to invite a similar diagnosis—even, perhaps, sterilization—for yourself. We recall that in all the twin studies some decisions about zygosity are made on the basis of questions put to nonaffected twins and to their relatives. With a little sensitivity to the real lives of people, we must recognize an all-too-human tendency to deny that the nonaffected MZ twins of schizophrenics really are identical. This must be still another source of error, tending to remove some discordant pairs from the MZ and into the DZ cat-

egory. That, of course, artificially inflates the difference in concordance rates between MZs and DZs. There is little wonder in the fact that even psychiatric geneticists have not found twin studies to be wholly convincing, and have turned to studies of adoption. The adoption studies, in theory at least, might be able to disentangle genetic from environmental effects in a way that twin studies cannot.

Adoption Studies

The basic procedure of adoption studies is to begin with a set of schizophrenic index cases, and then to study the biological relatives from whom they have been separated by the process of adoption. Thus—at least in theory—the index case and his or her biological relatives have only genes, and not environment, in common. The question of interest is whether the biological relatives of the index cases, despite the lack of shared environments, display an increased incidence of schizophrenia. To answer that question it is necessary to compare the rate of schizophrenia among the biological relatives with the rate observed in some appropriate control group.

The adoption studies carried out in Denmark in recent years by a collaborative team of American and Danish investigators have had enormous impact. To some critics who could detect the methodological weaknesses of twin studies, the Danish adoption studies appeared to establish the genetic basis of schizophrenia beyond any doubt. The eminent neuroscientist Solomon Snyder referred to these studies as a landmark "in the history of biological psychiatry. It's the best work that's been done. They take out all the artifacts in the nature vs. nurture argument."[28] Paul Wender, one of the authors of the studies, was able to announce: "We failed to discover any environmental component. . . . That's a very strong statement."[29] Though Wender's total excision of environmental factors is extreme, the Danish studies have been universally accepted as an unequivocal demonstration of an important genetic basis for schizophrenia. Clearly these studies require detailed critical examination.

Though they have been described in many separate publications, there are basically two major Danish adoption studies. The first, with Kety as senior investigator, starts with adoptees as the schizophrenic index cases and examines their relatives. The second, with Rosenthal as senior investigator, starts with schizophrenic parents as index cases and examines the children whom they gave up for adoption.

The study that began with adoptees as index cases was first reported by Kety in 1968.[30] Based on Copenhagen records, the investigators located thirty-four adoptees who had been admitted to psychiatric hospitals as adults and who could be diagnosed from the records as schizophrenics. For each schizophrenic adoptee a control adoptee who had never received psychiatric care was selected. The control was matched to the index case for sex, age, age at transfer to the adoptive parents, and socioeconomic status (SES) of the adoptive family.

The next step was to search the records of psychiatric treatment for all Denmark, looking for relatives of both the index and control cases. Those who searched the records did not know which were the relatives of index cases and which were the relatives of controls. Whenever a psychiatric record was found, it was summarized and then diagnosed blindly by a team of researchers who came to a consensus. The relatives were not at this stage personally examined.

The researchers traced 150 biological relatives (parents, sibs, or half-sibs) of the index cases, and 156 biological relatives of the controls. The first point to note is one not stressed by the authors: There were virtually no clear cases of schizophrenia among the relatives either of the index or of the control cases. To be precise, there was one chronic schizophrenic among the index relatives and one among the controls. To obtain apparently significant results the authors had to pool together a "schizophrenic spectrum of disorders." The spectrum concept lumps into a single category such diagnoses as chronic schizophrenia, "borderline state," "inadequate personality," "uncertain schizophrenia," and "uncertain borderline state." With such a broad concept, 8.7 percent of the biological relatives of index cases and 1.9 percent of the biological relatives of controls were diagnosed as displaying spectrum disorders. There were nine biological families of index cases in which at least one spectrum diagnosis had been made, compared to only two such families among the controls. That difference is the supposed evidence for the genetic basis of schizophrenia. Without the inclusion of such vague diagnoses as "inadequate personality" and "uncertain borderline schizophrenia" there would be no significant results in the Kety study.

From the Kety data of 1968 it is possible to demonstrate that such vague diagnoses—falling within the "soft spectrum"—are not in fact associated with schizophrenia. Among the sixty-six biological families reported on in 1968 there were a total of six in which at least one "soft" diagnosis had been made.* There was no tendency for such diagnoses to occur any more frequently in families in which definite schizophrenia had been diagnosed than in other families. However, the "soft spectrum" diagnoses very definitely tended to occur in the same families in which "outside the spectrum" psychiatric diagnoses had been made—that is, such clearly nonschizophrenic diagnoses as alcoholism, psychopathy, syphilitic psychosis, etc. There were "outside the spectrum" diagnoses in 83 percent of the families containing "soft spectrum"

*We here include as "soft" diagnoses the two least certain diagnoses employed by Kety et al.—their D-3 diagnosis ("uncertain borderline") and their C diagnosis ("inadequate personality").

diagnoses, and in only 30 percent of the remaining families—a statistically significant difference. Thus it appears that the Kety et al. results depend upon their labeling as schizophrenia vaguely defined behaviors that tend to run in the same families as do alcoholism and criminality—but which do not tend to run in the same families as does genuine schizophrenia. However, it remains the case that these frowned-upon behaviors did occur more frequently among the biological relatives of adopted schizophrenics than among the biological relatives of adopted controls. What might account for such a finding?

The most obvious possibility is that of selective placement, a universal phenomenon in the real world in which adoptions in fact occur, and a phenomenon that undermines the theoretical separation of genetic and environmental variables claimed for adoption studies. The children placed into homes by adoption agencies are never placed randomly. For example, it is well known that biological children of college-educated mothers, when put up for adoption, are placed selectively into the homes of adoptive parents with higher socioeconomic and educational status. The biological children of mothers who are grade-school dropouts are usually placed into much lower status adoptive homes. Thus it seems reasonable to ask: Into what kinds of adoptive homes are infants born into families shattered by alcoholism, criminality, and syphilitic psychosis likely to be placed? Further, might not the adoptive environment into which such children are placed cause them to develop schizophrenia?

From raw data kindly made available to one of us by Dr. Kety, we have been able to demonstrate a clear selective placement effect. Whenever a record of psychiatric treatment of a relative was located by Kety's team, notation was made about whether the relative had been in a mental hospital, in the psychiatric department of a general hospital, or in some other facility. When we check the adoptive families of the schizophrenic adoptees, we discover that in eight of the families (24 percent) an adoptive parent had been in a mental hospital. That was not true of a single adoptive parent of a control adoptee. That, of course, is a statistically significant difference—and it suggests as a credible interpretation of the Kety et al. results that the schizophrenic adoptees, who indeed had been born into shattered and disreputable families, acquired their schizophrenia as a result of the poor adoptive environments into which they were placed. The fact that one's adoptive parent goes into a mental hospital clearly does not bode well for the psychological health of the environment in which one is reared. There is, by the way, no indication that the biological parents of the schizophrenic adoptees have been in mental hospitals at an excessive rate. That occurred in only two families (6 percent), a rate in fact lower than that observed in the biological families of the control adoptees.

The same set of subjects had also been reported on in a later paper by Kety et al.[31] For this later work as many as possible of the relatives of index and control adoptees had been traced down personally and interviewed by a psychiatrist. The interviews were edited, and consensus diagnoses were then made blindly by the investigators. The basic picture did not change much. There were more spectrum diagnoses among relatives of index cases than among relatives of controls, although the interview procedure greatly increased the overall frequency of such diagnoses. This time, however, diagnoses of inadequate personality had to be excluded from the spectrum, since they occurred with equal frequency in both sets of relatives. The significance of the 1968 results, based on records rather than interviews, had depended upon including inadequate personality in the elastic spectrum.

Personal correspondence with the psychiatrist who conducted the interviews with relatives has revealed a few interesting details. The 1975 paper speaks only of "interviews," but it turns out that in several cases, when relatives were dead or unavailable, the psychiatrist "prepared a so-called pseudo interview from the existing hospital records." That is, the psychiatrist filled out the interview form in the way in which he guessed the relative would have answered. These pseudo interviews were sometimes diagnosed with remarkable sensitivity by the team of American investigators. The case of the biological mother of S-II, a schizophrenic adoptee, is one particularly instructive example.

The woman's mental hospital records had been edited and then diagnosed blindly by the investigators in 1968. The diagnosis was inadequate personality—at that time, inside the spectrum. The 1975 paper—by which time inadequate personality is outside the spectrum—indicates that, upon personal interview, the woman had been diagnosed as a case of uncertain borderline schizophrenia—again inside the spectrum. But personal correspondence had revealed that the woman was never in fact interviewed; she had committed suicide long before the psychiatrist attempted to locate her, and so—from the original hospital records—she was "pseudo interviewed." Perhaps the most remarkable aspect of the story, also revealed by personal correspondence, is that the woman had been hospitalized twice—and each time had been diagnosed as manic-depressive by the psychiatrists who actually saw and treated her. That is, she had been diagnosed as suffering from a mental illness unrelated to schizophrenia, and very clearly outside the schizophrenia spectrum. We can only marvel at the fact that the American diagnosticians, analyzing abstracts of these same records, were twice able to detect—without ever seeing her—that she really belonged within the shifting boundaries of the spectrum.

The Kety study has more recently been expanded to include all of Denmark (rather than merely Copenhagen). The hospital records of relatives have been searched and the results briefly referred to in a couple of publica-

tions. The relatives are also being interviewed. There have been no detailed data published or made available for the larger sample, so critical analysis is not yet possible. Though Kety asserts that results from the expanded sample confirm those earlier reported in detail, there is no reason to suppose that the more recent work is free of the invalidating flaws we have outlined above.

These results must be evaluated together with the results of a companion study reported by Rosenthal et al. using the same Danish files.[32] This study first identified a number of schizophrenic parents who had given up children for adoption. The question is whether those children, not reared by their schizophrenic biological parents, will tend to develop schizophrenia. The control group for the index children was made up of adoptees whose biological parents had no record of psychiatric treatment. The index adoptees and the controls, when grown up, were interviewed—blindly—by a Danish psychiatrist. Based upon those interviews, decisions were made as to whether particular individuals were in or out of the spectrum of schizophrenic disorders. Countless textbooks now indicate that a higher frequency of spectrum disorders were diagnosed in the adopted children of schizophrenics than in children of normal controls. That claim is based on preliminary (and inadequately reported) accounts of the study.

The preliminary reports did claim to observe a barely significant tendency for spectrum disorders to be more frequent among the index cases. (There was only one adoptee who had ever in fact been hospitalized for schizophrenia, and the authors frankly admitted that if they had looked only for hospitalized cases of schizophrenia, "we would have concluded that heredity did not contribute significantly to schizophrenia.")[33] The early papers, however, are entirely vague as to when and how or by whom decisions were made about whether individual cases were in or out of the spectrum. The papers indicate merely that the interviewing Danish psychiatrist made a "thumbnail diagnostic formulation" for each interview, and that these were somehow related to whether or not the interviewee was placed into the spectrum. Personal correspondence with several of the collaborators had made it clear that the "thumbnail diagnostic formulation" of the interviewer did not specify whether the individual was in or out of the spectrum. For the early papers, that decision was made in a manner and by parties unknown.

When consensus diagnoses like those in the Kety study were reported on for the first time in 1978, it developed that there was no significant tendency for spectrum cases to occur more frequently among index subjects.[34] Thus, despite the widely cited misleading early reports of the Rosenthal et al. study, its outcome was in fact negative.

Wender et al. added a new refinement to the Rosenthal study by reporting on a new group of twenty-eight "cross-fostered" subjects.[35] These were adoptees whose biological parents had been normal but whose adoptive parents had become schizophrenic. The new group was added to observe whether the experience of being reared by a schizophrenic adoptive parent would produce pathology in a child. The cross-fostered children, according to Wender et al., did not show more pathology than did the control adoptees. But it is important to note that in this paper the concept of diagnosing a schizophrenia spectrum had been abandoned; instead, the Danish interviews were now being rated for "global psychopathology." Consensus diagnoses—or any other diagnoses—of whether or not the cross-fostered children were in the schizophrenia spectrum have not appeared in any of the many papers concerned with the genetics of schizophrenia.

There is, however, an obscure paper from the Kety and Rosenthal group concerned with the characteristics of people who refuse to take part in psychological studies that contains some important and relevant information.[36] The paper includes as an aside an incidental table (Table 14) showing the percentage of spectrum diagnoses made in each group by a Danish Psychiatrist, Schulsinger. We learn from that table that fully 26 percent of the cross-fostered adoptees were diagnosed as being in the schizophrenia spectrum—a rate not significantly different from that of the index adoptees themselves. Further, that obscure table is the only place where data on an immensely relevant control group have been reported. The Danish investigators, it turns out, also interviewed (and diagnosed) a number of nonadopted children of schizophrenics, who had been reared by their mentally ill biological parents. The rate of spectrum disorder among this group did not differ from that observed among cross-fostered children. Thus, had they taken the design of their own study seriously, the investigators might have concluded that they had shown schizophrenia to be entirely of environmental origin. The cross-fostered biological children of normal parents, when merely reared by schizophrenic adoptive parents, show just as great a frequency of spectrum disorders as do the nonadopted biological children of schizophrenics. The reader may not be surprised to learn that consensus diagnoses of the nonadopted group, like consensus diagnoses of the cross-fostered group, have never been reported.

The weaknesses of the Danish adoption studies are so obvious upon critical review that it may be difficult to understand how distinguished scientists could have regarded them as eliminating all the artifacts that beset family and twin studies of nature and nurture. In fact, a team of investigators from the French National Institute of Medical Research have published, quite independently, an analysis of the Danish adoption studies that reaches the conclusion that they are gravely deficient.[37] Perhaps one factor encouraging the usually uncritical acceptance of the investigators' claims has been indicated by Wender and Klein in an article written for the popular magazine *Psychology Today*.[38] They

cite the Danish adoption study—based upon a broad concept of schizophrenia spectrum—as indicating that "for each schizophrenic there may be 10 times as many people who have a milder form of the disorder that is genetically . . . related to the most severe form . . . 8 percent of Americans have a lifelong form of personality disorder that is genetically produced. This finding is extremely important." The importance of the finding is spelled out by Wender and Klein in the following language: "The public is largely unaware that different sorts of emotional illnesses are now responsive to specific medications and, unfortunately, many doctors are similarly unaware." The logic, erroneous at every step, is as follows: The Danish adoption studies have shown that schizophrenia, and a number of behavioral eccentricities, are genetically produced. Since the genes influence biological mechanisms, it must follow that the most effective treatment for schizophrenia, and for behavioral eccentricity, is drug treatment. Focusing on social or environmental conditions as a cause of disordered behavior would be fruitless.

Yet any materialist understanding of the relationship of brain to behavior must recognize that even if schizophrenia were largely genetic in origin, it would in no way follow that drugs—or any biological, as opposed to social, treatment—would necessarily be the most effective therapy. Just as drugs change behavior, so will altered behavior imposed by talking therapies change brains (as indeed the latent theory behind behavior modification would itself agree). The logic of this does not depend on a belief in any more explicit integration of the biological and the social.

SCHIZOPHRENIA AS SOCIALLY DETERMINED

To reveal, as we have tried, the theoretical and empirical impoverishment of the conventional wisdom of biological determinism in relationship to schizophrenia does not then argue that there is nothing relevant to be said about the biology of the disorder, and still less does it deny that schizophrenia exists. The problem of understanding the etiology of schizophrenia and a rational investigation of its treatment and prevention is made vastly more difficult, perhaps even hopelessly tangled, by the extraordinary latitude and naiveté of diagnostic criteria. Certainly one may wonder about the relevance of biology to the diagnosis of schizophrenia either by the forensic psychiatrists of the Soviet Union or by the British psychiatrist who diagnoses a young black as schizophrenic on the basis of his use of the religious language of Rastafarianism.[39]

Misgivings are not eased when one recalls a well-known study by Rosenhan and his colleagues in California in 1973.[40] Rosenhan's group of experimenters presented themselves individually at mental hospitals complaining of hearing voices. Many were hospitalized. Once inside the hospital, according to the strategy of the experiment, they declared that their symptoms had ceased. However, it did not prove so easy to achieve release. The experimenters' claims to normality were disregarded, and most found themselves treated as mere objects by nurses and doctors and released only after considerable periods of time. A pseudo-patient who took notes in one of the hospitals, for instance, was described by nurses as showing "compulsive writing behavior."

Even more revealing, perhaps, was the drop in hospital admissions for schizophrenia in the area after Rosenhan circulated the results of the first experiment among doctors and indicated that they might be visited by further pseudo-patients in the future, although none were actually sent.

It is this sort of experience that lies behind the argument, developed in its most extreme form by Michel Foucault and his school over the last two decades, that the entire category of psychological disorders is to be seen as a historical invention, an expression of power relationships within society manifested within particular families. To simplify Foucault's intricate argument, he claims that all societies require a category of individuals who can be dominated or scapegoated, and over the centuries since the rise of science—and particularly since the industrial revolution of the nineteenth century—the mad have come to fill this category. In medieval times, he says, houses of confinement were built for lepers, and madness was often explained in terms of possession by demons or spirits.[41] According to Foucault the idea of institutionalizing the mad developed during the eighteenth and nineteenth centuries after the clearing of the leper houses left a gap for new scapegoats to replace the old ones.

In this view madness is a matter of labeling; it is not a property of the individual but merely a social definition wished by society on a proportion of its population. To look for correlates of madness in the brain or the genes is therefore a meaningless task, for it is not located in the brain or the individual at all. To dismiss the suffering and the deranged behavior of the schizophrenic merely as a problem of social labeling by those who have power over those who have not seems a quite inadequate response to a complex social and medical problem. Despite Foucault's historiography and the enthusiasm of its reception in Britain and France at the crest of the wave of antipsychiatry of the 1960s and 1970s, the actual historical account he gives of when and how asylums for the insane arose has been called into question.[42] And by cutting the phenomenon of schizophrenia completely away from biology and locating it entirely in the social world of labeling, Foucault and his followers arrive, from a very different starting point, back in the dualist Cartesian camp, which . . . preceded the full-blown materialism of the nineteenth century. So much has Foucault retreated that at certain points in his argument he even seems to be ambiguous as to whether "physical" quite apart

from "mental" illness exists except in the social context that proclaims it.

More modest than Foucault's grand theorizing but nonetheless culturally determinist are the social and familial theories of schizophrenia developed by R. D. Laing.[43] For Laing—at least the Laing of the sixties and early seventies—schizophrenia is essentially a family disorder, not a product of a sick individual but of the interactions of the members of a sick family. Within this family, locked together by the nuclear style of living of contemporary society, one particular child comes to be picked upon, always at fault, never able to live up to parental demands or expectations. Thus the child is in what Laing calls (in a term derived from Gregory Bateson) a double bind; whatever he or she does is wrong. Under such circumstances the retreat into a world of private fantasy becomes the only logical response to the intolerable pressures of existence. Schizophrenia is thus a rational, adaptive response of individuals to the constraints of their life. Treatment of the schizophrenic by hospitalization or by drugs is therefore not seen as liberation from the disease but as part of that person's oppression.

Family context may be crucial in the development of mental illnesses such as schizophrenia, but it is clear that a larger social context is also involved. The diagnosis is made most often of working-class, inner-city dwellers, least often of middle- and upper-class suburban dwellers.[44] To a social theorist, the argument about the social context that determines the diagnosis is clear. An example of the class nature of the diagnosis of mental illness comes from the studies of depression by Brown and Harris in 1978 in Camberwell, an inner-city, largely working-class area of London, with some pockets of middle-class infiltration.[45] They showed that about a quarter of working-class women with children living in Camberwell were suffering from what they defined as a definite neurosis, mainly severe depression, whereas the incidence among comparable middle-class women was only some 6 percent. A large proportion of these depressed individuals, who if they had attended psychiatric clinics would wave been diagnosed as ill and medicalized or hospitalized, had suffered severe threatening events in their lives within the past year, such as loss of husband or economic insecurity. The use of drugs—mainly tranquilizers—among such groups of women is clearly very high.

Biological determinism faces such social evidence with arguments that, for example, people with genotypes predisposing toward schizophrenia may drift downward in occupation and living accommodation until they find a niche most suited to their genotype. But it would by a brave biological determinist who would want to argue that in the case of the depressed housewives of Camberwell it was their genes that were at fault.

An adequate theory of schizophrenia must understand what it is about the social and cultural environment that pushes some categories of people toward manifesting schizophrenic symptoms; it must understand that such cultural and social environments themselves profoundly affect the biology of the individuals concerned and that some of these biological changes, if we could measure them, might be the reflections or correspondents of that schizophrenia with the brain. It may well be that, in our present society, people with certain genotypes are more likely than others to suffer from schizophrenia—although the evidence is at present entirely inadequate to allow one to come to that conclusion. This says nothing about the future of "schizophrenia" in a different type of society, nor does it help us build a theory of schizophrenia in the present. Neither biological nor cultural determinism, nor some sort of dualistic agnosticism, is adequate to the task of developing such a theory. For that, we must look to a more dialectical understanding of the relationship between the biological and the social.

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DISCUSSION

A discussion of the issues contained in this and similar chapters almost invariably begins with this question: Nature or nurture? In this chapter, the question can be rephrased in the following way: Is schizophrenia caused by genetic factors or by environmental factors? But as you will see throughout this book, the human mind's tendency to oversimplify complicated issues by dichotomizing them into mutually exclusive alternatives often leads us badly astray. The "nature versus nurture" debate is no exception.

Indeed, one could make a reasonable argument that, for all or virtually all forms of psychopathology, the "nature versus nurture" debate is actually a pseudocontroversy. Ponder this simple fact: There are approximately 100,000 genes in the human genome, affecting virtually every aspect of the structure and functioning of the brain and remainder of the nervous system. Is it really plausible to think that not even one of these genes influences, even to the most trivial extent, an individual's risk for developing a condition as enormously complex and multifaceted as schizophrenia? It seems exceedingly unlikely that the heritability of schizophrenia would be precisely zero, because this would imply that individual differences in the propensity to develop schizophrenia are entirely independent of every one of these 100,000 genes. Moreover, an accumulating body of evidence suggests that most or all personality traits—including extroversion-introversion, impulse control, interpersonal alienation, stress reactivity, and fearfulness—are influenced substantially by genetic factors (Tellegen et al., 1988). Again, it seems rather implausible that none of these personality traits would affect, even to a minor degree, an individual's susceptibility to schizophrenia.

But what does the evidence concerning the heritability of schizophrenia indicate? In particular, how are we to reconcile the conclusions of Straube and Oades with those of Lewontin, Rose, and Kamin? As noted in the introduction to this chapter, many of the differences between these two sets of authors can be traced to their differing evaluations of the principal assumptions underlying behavior-genetic designs: Straube and Oades consider these assumptions to rest on reasonably firm ground, whereas Lewontin, Rose, and Kamin do not. In particular, Lewontin, Rose, and Kamin voice serious concerns regarding the equal environments assumption, which, as noted in the introduction, is a crucial presupposition underlying the twin research methodology. Because MZ twins tend to be treated more similarly than DZ twins are (a fact that few researchers would dispute), the higher concordance for schizophrenia among MZ twins is potentially attributable to their greater environmental similarity rather than to their greater genetic similarity. But do the data bear out Lewontin, Rose, and Kamin's criticism of the equal environments assumption?

In fact, the equal environments assumption has stood up surprisingly well to careful empirical scrutiny (Kendler, 1983). This assumption has been tested in several ways. First, researchers have identified MZ and DZ twins whose zygosity has been misclassified—that is, MZ twins who were mistakenly believed by themselves and others to be DZ twins and DZ twins who were mistakenly believed by themselves and others to be MZ twins. If similarity in rearing is the key factor underlying the greater similarity of MZ twins than DZ twins, then perceived zygosity, rather than actual zygosity, should be the best predictor of twin similarity in psychological characteristics. In fact, twin resemblance in personality and cognitive ability is related much more closely to actual, rather than to perceived, zygosity (Scarr & Carter-Saltzman, 1979). Second, investigators have found that similarity in parental rearing among MZ twins is essentially uncorrelated with their actual similarity in either personality or intelligence (Loehlin & Nichols, 1976). Third and perhaps most important, the greater similarity in parental rearing for MZ twins than for DZ twins appears to be due largely or entirely to the fact that MZ twins evoke more similar reactions from their parents than do DZ twins (Lytton, 1977). Thus, the greater similarity of MZ twins than DZ twins seems to be a cause, rather than a consequence, of more similar parental treatment of MZ twins. This conclusion reminds us of an important point: Children's behavior influences their parents' behavior, as well as the converse (Bell, 1968).

Lewontin, Rose, and Kamin have no doubt performed an important service by pointing out methodological shortcomings in many of the twin and adoption studies of schizophrenia. They are surely correct that much of the evidence concerning the heritability of schizophrenia is far from perfect and in some cases has been overstated by overly enthusiastic proponents of genetic explanations of psychopathology. They are also correct that more recent estimates of the heritability of schizophrenia tend to be lower than earlier estimates (Kringlen, 1987), although even these newer estimates suggest that the heritability of schizophrenia is sizable.

Perhaps the weakest link in Lewontin, Rose, and Kamin's reasoning is their failure to explain the consistency of results in studies by different investigators, in different countries, and with different methodologies. Why do virtually all studies in this literature, even with their shortcomings, show a strong genetic influence on schizophrenia? Lewontin, Rose, and Kamin would presumably have to argue that the methodological weaknesses associated with these studies are all systematically biased in the direction of detecting substantial heritability. Although such a uniform bias is possible, it seems rather implausible. Perhaps the most reasonable conclusion one can draw is that, although the evidence concerning the heritability of schizophrenia is far from flawless, converging evidence from multiple sources—studies of MZ twins and DZ twins reared together, studies of offspring of MZ twins discordant for schizophrenia, and adoption studies—implicates genetic factors in the etiology of schizophrenia. It is this consistency of findings across numerous studies (each in isolation admittedly imperfect) that leads most impartial readers to conclude that schizophrenia is strongly influenced by genetic factors. Moreover, the heritability of schizophrenia appears to be comparable to that of many medical conditions in which genetic factors are known to play a major role, such as diabetes, hypertension, coronary artery disease, and breast cancer (Kendler, 1983).

As Straube and Oades note, however, considerable controversy remains concerning the mode of genetic transmission in schizophrenia. To oversimplify matters somewhat, there are two principal camps of researchers. One camp, which currently represents a clear majority, believes that schizophrenia is a polygenic disorder, a disorder produced by multiple genes acting in concert with environmental influences. According to these researchers, schizophrenia is like height and weight in that it is produced by environmental factors and by the combined effects of a large number of genes, each of which makes only a relatively minor contribution to the phenotype of interest. The second camp, which represents a small but active minority of researchers, believes that schizophrenia is a monogenic, single-gene disorder. These researchers maintain that one gene, again in combination or in interaction with environmental factors, is necessary but not sufficient to produce schizophrenia. This gene is necessary in that one cannot develop schizophrenia without it; but it is not sufficient in that environmental factors are required to trigger schizophrenia in genetically predisposed individuals. According to Meehl (1962), Heston (1970), and most proponents of this position (but see Iacono & Grove, 1993, for a dissenting view), this gene is **dominant** in that only one "copy" of it is necessary to produce the vulnerability to schizophrenia.

Some advocates of this second view have conducted **linkage studies**, which, as noted in the reading by Straube and Oades, allow investigators to ascertain whether a psychopathological condition, in this case schizophrenia, is associated with known genetic material within families. Although several investigative teams have reported linkage between areas of certain chromosomes (for example, chromosome 5) and schizophrenia, the search for genetic linkage has been plagued by failures to replicate previous results. Such replication failures may indicate one of three things (Iacono & Grove, 1993):

- Researchers have not yet been fortunate enough to locate the gene predisposing to schizophrenia.
- Schizophrenia is not in fact a monogenic disorder.
- What we currently call schizophrenia is actually a heterogeneous category comprising two or more etiologically different conditions.

With respect to the last point, it is worth pointing out that Eugen Bleuler, the individual who coined the term *schizophrenia*, referred to "the group of schizophrenias" in the title of his classic 1911 book. Bleuler, who was firmly committed to the view that schizophrenia was not one condition but many, would not have been terribly surprised by the inability of modern-day researchers to locate "the gene" underlying schizophrenia. One should not expect to find a unitary etiology for a heterogeneous disorder.

The conclusion that schizophrenia is substantially influenced by genetic factors should not, however, be taken to imply that Lewontin, Rose, and Kamin's critique is devoid of value. Far from it. Indeed, their call for increased attention to the role of environmental influences in the development of schizophrenia is well taken. One fact is not in dispute: Environmental factors play a key role in the etiology of schizophrenia. We can be certain of this conclusion because, in all twin studies, the MZ concordance rate for schizophrenia is well below 100%, with the average figure lying between 40% and 50%. Consequently, an increasing number of researchers have argued that a **diathesis-stress model** provides the most reasonable framework for the etiology of schizophrenia. According to this model, individuals who possess a genetic predisposition to schizophrenia (*diathesis*, by the way, means "predisposition") will develop schizophrenia if, and only if, they are exposed to sufficient environmental stress. If the diathesis-stress model is correct, both genetic factors and environmental factors are necessary but not sufficient to produce schizophrenia. Each set of factors is needed, but neither alone will do the trick. Although the diathesis-stress model has considerable intuitive appeal, it has yet to be tested adequately.

The less than perfect concordance between MZ twins for schizophrenia indicates that nonshared (also known as within-family) environmental factors—factors responsible for making individuals within the same family different from one another—must make a significant contribution to the development of schizophrenia.* A behavior-genetic design that is

*A number of investigators have also examined the potential role of shared (also known as between-family) environmental influences in the etiology of schizophrenia. In contrast to nonshared environmental influences, shared environmental influences make individuals within the same family similar to one another. See Straube and Oades'

ideal for exploring the role of nonshared environmental factors in the etiology of schizophrenia is the study of MZ twins who are discordant for schizophrenia. Because MZ twins are genetically identical, the factors accounting for their discordance are, by definition, environmental. Thus, investigators can use this design to attempt to identify the nonshared environmental variables that are responsible for this discordance.

The literature on MZ twins discordant for schizophrenia has been reviewed by Wahl (1976). Although Wahl's review is somewhat dated, the overall picture he paints has not changed greatly. Wahl concludes that researchers who have sought to pinpoint nonshared environmental influences on schizophrenia have generally come away empty-handed. Factors such as differential patterns of parental treatment in childhood and birth order seem not to have panned out as variables distinguishing the schizophrenic twin from the nonschizophrenic twin. Moreover, even when differences between discordant twins have been reported, they have often been difficult to interpret. For example, several investigators have found that the schizophrenic twin was more submissive, dependent, and fearful in childhood compared with the nonschizophrenic twin. But such personality differences are not necessarily a consequence of environmental influences; they may instead reflect an early manifestation of schizophrenic symptomatology in the preschizophrenic twin. Consequently, schizophrenia researchers find themselves in a peculiar and mildly embarrassing quandary. They know that nonshared environmental factors are relevant to the etiology of schizophrenia, because of the high rate of MZ twin discordance for this condition. Nevertheless, they have had considerable difficulty identifying any of these factors.

There appear to be two major explanations for the failure to detect specific nonshared environmental influences on schizophrenia. These explanations are not mutually exclusive, and there may be some truth to both. The first explanation, which is the most commonly invoked, is simply that investigators have not been clever enough (or fortunate enough) to detect the specific nonshared environmental influences relevant to schizophrenia. The second explanation is quite different from the first and tends to make some readers—not to mention schizophrenia researchers—a bit uncomfortable. According to this explanation, the principal environmental variables that are causally related to schizophrenia are random rather than systematic (Meehl, 1978). Unlike systematic environmental influences, which are experienced by a large number of individuals, random environmental influences are highly unique and idiosyncratic to each individual. Thus, random occurrences—such as losing a close friend at age 6, getting injured in a car accident at age 13, being rejected for a date at age 15, or witnessing a shooting at age 17—might actually be the nonshared environmental factors most critical to the development of schizophrenia. A progressive accumulation of such random events could help to explain why one MZ twin develops schizophrenia while his or her co-twin does not—and, by extension, why one person genetically predisposed to schizophrenia develops this condition while the other remains healthy. From this perspective, chance and luck, especially bad luck, may be among the most crucial etiological factors in schizophrenia (Meehl, 1978).

If this explanation has at least a kernel of truth to it, investigators interested in the environmental causes of schizophrenia may be forced to abandon a purely nomothetic approach to environmental factors in favor of a more idiographic approach, the approach championed by the American personality psychologist Gordon Allport (1937). Psychologists using a **nomothetic** approach attempt to draw generalizations across a large number of individuals. In contrast, psychologists using an **idiographic** approach attempt to understand the unique configuration of personal characteristics and life history factors within a single individual. An idiographic approach may be a bitter pill for some schizophrenia researchers to swallow, because it implies that any attempt to explain the environmental etiology of schizophrenia in terms of a universal set of life experiences is bound to be incomplete or inadequate. At the same time, however, an idiographic approach captures much of the richness and complexity that is often missed by a nomothetic approach, which ignores or deemphasizes experiences that are unique to each person. No less than a full appreciation of such richness and complexity may be necessary for an adequate understanding of the factors that lead a given individual to schizophrenia.

QUESTIONS TO STIMULATE DISCUSSION

1. Lewontin, Rose, and Kamin attempt to refute the equal environments assumption underlying the twin research design with two different sources of data: comparisons of DZ twins with ordinary siblings and comparisons of same-sex and opposite-sex DZ twins. Do you find this evidence compelling? Why or why not?
2. Lewontin, Rose, and Kamin contend that one of the principal underlying agendas of behavior-genetic researchers in the schizophrenia literature is the prescription of antipsychotic medication. Do you agree with them? Is the heritability of schizophrenia relevant to whether it should be

review, in their reading in this chapter, of the adoption studies of Wender, Rosenthal, Kety, Schulsinger, and Welner (1974) and of Tienari et al. (1989) for a discussion of the relationship between shared environmental factors and schizophrenia. Suffice it to say that the evidence that such factors are causally associated with schizophrenia is promising but highly preliminary. The primary difficulty with interpreting these findings is that many of the apparent "environmental" factors (such as disturbed parental communication and parental hostility and criticality) may be a consequence, rather than a cause, of the child's psychopathology.

treated by means of medication (as opposed to psychotherapy or other interventions)?

3. Is it plausible to think that the predisposition to a disorder as complicated as schizophrenia could be produced largely or entirely by a single gene? Explain your reasoning.
4. If schizophrenia is a heterogeneous disorder etiologically, as many researchers have suggested, how should research on the causes of schizophrenia be conducted? What types of research strategies might help to identify meaningful subtypes of schizophrenia?
5. As noted in the Discussion section, the diathesis-stress hypothesis has been an extremely influential model among schizophrenia researchers. How might one attempt to test this model?
6. Judging from what you have read, do you believe any important environmental factors have been ignored or neglected in the search for the causes of schizophrenia? What might they be?
7. If chance and luck were found to play an important role in the etiology of schizophrenia, what would be the implications of this finding, if any, for the treatment of schizophrenia? What might be the implications of this finding for the prevention of schizophrenia?

SUGGESTIONS FOR FURTHER READING

Gottesman, I. I. (1991). *Schizophrenia genesis: The origins of madness*. New York: W. H. Freeman.
This is an interesting and highly readable introduction to research on the characteristics and etiology of schizophrenia. Gottesman intersperses reviews of such topics as the diagnosis, genetics, epidemiology, and neurobiology of schizophrenia with first-person accounts of schizophrenics and family members of schizophrenics. This book is highly recommended for beginning readers who wish to gain an overview of the major research findings and trends in the schizophrenia literature.

Gottesman, I. I., & Shields, J. (1972). *Schizophrenia and genetics: A twin study vantage point*. New York: Academic Press.
Gottesman and Shields review the early behavior-genetic studies of schizophrenia and present the methods and results of their landmark twin study of schizophrenia at Maudsley Hospital. Paul E. Meehl provides an afterword.

Gottesman, I. I., & Shields, J. (1982). *Schizophrenia: The epigenetic puzzle*. Cambridge, England: Cambridge University Press.
This is a superb and comprehensive review of the evidence regarding the roles of genetic and environmental influences in the etiology of schizophrenia. In Sherlockian fashion, Gottesman and Shields lead the reader through the findings from family, twin, and adoption studies, as well as from studies of childhood schizophrenia and autism, environmental influences, and epidemiology and social biology. They conclude with a discussion of models of genetic and environmental transmission. This book is appropriate for advanced readers.

Kendler, K. S. (1983). Overview: A current perspective on twin studies of schizophrenia. *American Journal of Psychiatry, 140*, 1413–1425.
Kendler provides a first-rate review of the major twin studies of schizophrenia. The discussion of the validity of the twin methodology is particularly clear and thorough, and it helps to dispel a number of frequent misconceptions regarding twin studies.

Kringlen, E. (1987). Contributions of genetic studies of schizophrenia. In H. Hafner, W. F. Gattaz, & W. Janzarik (Eds.), *Search for the causes of schizophrenia* (pp. 123–142). Berlin: Springer-Verlag.
This is a clear and readable overview of the major evidence regarding the role of genetic factors in schizophrenia. Kringlen clearly delineates the logic underlying each of the major behavior-genetic designs and reviews the principal findings derived from each. He concludes that, although genetic influences upon schizophrenia are undeniable, many of the earlier studies probably overestimated their contribution.

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologist, 17*, 827–838.
In this seminal article, Meehl introduces his model of the etiology of schizophrenia. According to Meehl, certain individuals inherit a dominant gene (perhaps producing a neuronal abnormality he terms "synaptic slippage") that leads to an "integrative neural defect" called "schizotaxia." Given existing social learning factors, all schizotaxics develop a personality constellation known as "schizotypy"; in turn, however, only a subset of schizotypes develop full-blown schizophrenia. Thus, for Meehl, a dominant gene defect is a necessary but not sufficient condition for schizophrenia. Although this article is not easy to read, it is well worth the effort. Ambitious readers whose appetite is whetted by this paper may want to move on to Meehl, P. E. (1989). Schizotaxia revisited. *Archives of General Psychiatry, 46*, 935–944; and Meehl, P. E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders, 4*, 1–99.

Plomin, R., DeFries, J. C., & McClearn, G. E. (1990). *Behavior genetics: A primer* (2nd ed.). New York: W. H. Freeman.
This is an excellent and relatively nontechnical introduction to behavior-genetic methods and findings. Plomin et al. begin with an overview of basic genetic concepts and methods (such as gene mechanisms, population genetics, and quantitative genetics) and then discuss the application of family, twin, and adoption designs to the study of psychopathology, personality, intelligence, and other psychological characteristics. The book is appropriate for readers with little or no background in genetics.

Sarbin, T. R., & Mancuso, J. C. (1980). *Schizophrenia: Medical diagnosis or moral verdict?* New York: Pergamon Press.
Sarbin and Mancuso put forth their thesis that schizophrenia is more fruitfully conceptualized as a set of behaviors that is condemned in certain societies than as the product of a biological "disease." Chapter 7 contains a critique of the evidence for the genetic basis of schizophrenia.

Torrey, E. F., Bowler, A. E., Taylor, E. H., & Gottesman, I. I. (1994). *Schizophrenia and manic-depressive disorder: The biological roots of mental illness as revealed by the landmark study of identical twins*. New York: Basic Books.

The authors explore the environmental and genetic antecedents of schizophrenia and bipolar disorder in a study of 66 identical twin pairs, many of whom were discordant for these conditions. They conclude that schizophrenia, although influenced substantially by genetic factors, is probably triggered in many cases by a virus or other biological agent in utero or shortly after birth. In addition, they document alterations in brain structure and function among identical twins with schizophrenia.

Wahl, O. (1976). Monozygotic twins discordant for schizophrenia: A review. *Psychological Bulletin, 83*, 91–106.

Wahl provides a comprehensive review of studies of identical twins discordant for schizophrenia. This paradigm offers investigators a unique opportunity to examine the role of nonshared (within-family) environmental influences in the etiology of schizophrenia. As Wahl's review shows, however, this design has generally failed to yield striking differences between schizophrenic and nonschizophrenic co-twins; the major reported differences have been in early personality characteristics and birth weight, and even these findings have not always been consistent across studies.

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