Journal of Abnormal Psychology
1977, Vol. 86, No. 6, 575-588

#111

Genetic Theories and the Validation of Psychiatric Diagnoses: Implications for the Study of Children of Schizophrenics

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The success of prospective methods for studying the development of schizophrenia in those few offspring of schizophrenics who also become schizophrenic (high-risk method) depends on using valid diagnostic criteria for selecting the parent probands. Data from a high-risk study in which the affected parents were diagnosed by five clinicians are used to illustrate the impact different diagnostic standards may have on the composition of high-risk samples and control samples of children of other psychiatric patients. Publicly reporting careful assessments of affected parents will also facilitate comparisons among different high-risk samples and will allow estimates of the risks for individuals within each high-risk sample. Genetic theory and empirical data suggest that children with severely affected parents and children with many affected relatives will have the highest risks, while samples of children with only one mildly affected parent may have risks that approach the population base rates. Genetic theory further suggests that some children of validly diagnosed schizophrenics will have *no* genetic risk for schizophrenia, and some of those who do have the genetic predisposition will enjoy a lifetime of adequate mental health even without intervention, thus confounding the effort of high-risk research to validate indicators of the high-risk genotype with follow-up status. High-risk researchers are cautioned against premature implementation of intervention strategies based on unvalidated indicators of the risks to individuals.

The omissions and distortions in retrospective accounts of the origins of abnormal behaviors led Pearson and Kley (1957) to propose a plan that would allow prospective investigations of infrequent disorders while maintaining sample sizes within practical limits. For any *familial* disorder, the offspring of affected parents will be affected much more frequently than individuals sampled from the general population; thus, Pearson and Kley argued that these high-risk subjects deserved intensive, longitudinal scrutiny. Subsequent to the pioneering work on schizophrenics' offspring by Fish (Fish & Alpert, 1962; Fish & Hagin, 1973) and Sobel (1961), the major impetus for the rapid expansion in prospective studies of children of schizophrenic patients came in 1968 with two publications by Mednick and his colleagues (Mednick & McNeil, 1968; Mednick & Schulsinger, 1968). Recent tallies (Erlenmeyer-Kimling, 1975; Garmezy, 1974) show that at least 20 high-risk projects are now under way and that the vast majority of these studies utilize the familial model for defining high risk.

All of these investigations are being conducted with the hope that prospective methods will lead to the early (premorbid) detection of the schizophrenic process and will

This research was supported in part by a Mental Health Training Grant in Biological Sciences (MH10679) awarded to S. C. Reed and I. I. Gottesman at the University of Minnesota and the Charles M. Goethe Memorial Fund of the Dight Institute for Human Genetics. Support for the preparation of this article came in part from a grant from the Ontario Mental Health Foundation (OMHF 579-75A) awarded to D. R. Hanson.

We thank Rosalyn Rubin and V. E. Anderson of the University of Minnesota and Roland Peek and other members of the Minnesota Department of Public Welfare and Minnesota State Hospital System for their valuable cooperation and assistance.

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uncover potentiating or protective factors (genetic and environmental). Everyone hopes that the early detection of vulnerable individuals and an understanding of the pathophysiological and pathoenvironmental contributors to schizophrenia will lead to rational methods of treatment and, ultimately, to workable strategies for prevention. So far, these goals have not been realized. Some 20 years after the appearance of the Pearson and Kley (1957) article, it is an appropriate time to examine some of the data, logic, and assumptions that form the rationale for studying children of schizophrenic parents (also see Garmezy, 1977; Shields, 1977).

High-Risk Research and the Validity of Psychiatric Diagnoses

In contrast to the majority reports (some might say *ideologies*) of a decade or two ago, current research (cf. Cooper et al., 1972; Endicott & Spitzer, 1972; Fischer, 1974; Shields & Gottesman, 1972; Spitzer, 1975; Wing, Cooper, & Sartorius, 1974; World Health Organization, 1973) shows that the diagnosis of schizophrenia can be made with high reliability when, to paraphrase Meehl (1972, p. 358), competent and motivated diagnosticians have accurate and detailed information with which to work. Even though many different criteria for diagnosing schizophrenia can be applied with high reliability, there are considerable differences of opinion on what constitutes the most valid and useful working definition. For high-risk researchers, the issue of the predictive validity of the diagnoses of schizophrenia is of central importance in two respects. First, fulfillment of the high-risk researchers' hopes for early detection of schizophrenia requires the adoption of definitions of schizophrenia for affected parents that *do* accurately predict schizophrenia in the offspring. A lack of predictive validity will mean that the children studied are not at high risk for schizophrenia, and many years of expensive longitudinal research will come to nought. Second, the high-risk method itself provides a powerful way to test the predictive validity of schizophrenia diagnoses, though few prospective high-risk projects have attempted to capitalize on this aspect of the strategy. The predictive validities of current diagnostic criteria for schizophrenia are not established, and consequently, it seems reasonable to employ a range of alternative criteria for parental probands when assembling a high-risk population. Follow-up results can then be used to evaluate which of the criteria deliver the optimal "yield." Data from our own study of children of schizophrenic mothers or fathers (Hanson, Gottesman, & Heston, 1976) illustrates the impact that different definitions could have on the composition of a high-risk sample.

Hanson, Gottesman, and Heston's (1976) Schizophrenic Sample

Our sample was ascertained by searching for reports of mental illness in mothers or fathers of the first 2,500 births in the Minnesota subsample of the Collaborative Study of Cerebral Palsy, Mental Retardation, and Other Neurological Disorders of Infancy and Childhood, a prospective study of child health and development sponsored by the Perinatal Branch of the National Institute of Neurological and Communicative Diseases and Stroke (Broman, Nichols, & Kennedy, 1975; Niswander & Gordon, 1972). At the time of the 7-year follow-up, 221 of the 5,000 parents (4.4%) had a history of hospitalization for psychiatric care. We excluded 54 cases who did not meet our sampling requirements, which specified native-born Caucasians with no physical or sensory handicap who had been hospitalized for at least 1 week in a Minnesota hospital. After reviewing the hospital records for the remaining 167 patients, we excluded 97 more cases because there was insufficient information to make a diagnosis (e.g., records lost or sealed by the courts [15 cases]), because the affected parent was unquestionably alcoholic with no indication of psychosis (25 cases), or because the patients' illnesses appeared very mild and transient (e.g., grief reactions [57 cases]). Full details of the sampling procedures can be found in Hanson et al., (1976) and Hanson (1974).

After these exclusions, there remained 70 patients with a variety of hospital diagnoses who had to be confirmed as schizophrenic or

Table 1
Comparison of the 24 Cases called Schizophrenic by Meehl and Called Nonschizophrenic by Consensus Opinion

Consensus diagnosis of nonschizophrenics	Meehl's diagnosis of schizophrenia				
	Pseudo-psycho-pathic	Schizo-affective	Pseudo-neurotic	Other	Chronic
Character disorder/psychopath	6	0	1	0	3
Affective psychosis	0	4	0	0	1
Neurotic/inadequate personality	0	1	3	0	3
Other	0	1	0	1	0

not. For each patient, detailed life histories, usually with results from repeated testing with the Minnesota Multiphasic Personality Inventory (MMPI), were submitted to five senior clinicians[1] who made totally independent blind diagnoses and who rated the patients on an 8-point scale of global pathology (see Gottesman & Shields, 1972, p. 229) and a 5-point scale of anxiety level (1 = extremely low and 5 = extremely high). Twenty-nine of the 70 cases were judged to be schizophrenic by at least three diagnosticians, which constituted our consensus schizophrenic sample. For 83% of these consensus schizophrenic diagnoses, the five judges agreed unanimously or with one dissenting vote. The 29 consensus schizophrenics represented 13% ± 2% of the 221 hospitalized parents and .6% ± .1% of the 5,000 parents in the initial sampling frame. A psychiatric control sample contained 34 parents (from the 70) who were judged to be other than schizophrenic by consensus; these patients comprised a heterogeneous cluster of organic syndromes, affective illnesses, and character disorders. Four additional consensus nonschizophrenics were excluded because of diagnostic disagreement (two votes schizophrenic vs. three votes nonschizophrenic), and three other consensus nonschizophrenics were mates to the schizophrenics. Of the 70 × 5 = 350 individual diagnoses, 87% agreed with the consensus diagnosis.

Tellegen's adaptation of the Kuder–Richardson 20 formula (see Gottesman & Shields, 1972, p. 216) provided an interrater reliability coefficient of .89. For diagnoses of schizophrenia versus nonschizophrenia, the average pair-wise agreement among the judges was 77%. However, one judge (Meehl) consistently had the lowest agreement with the other four judges. His average pair-wise agreement with the others was 62%. Whereas consensus opinion (including Meehl) designated 29 of the 70 cases as schizophrenics, Meehl diagnosed schizophrenia 53 times.

A comparison of Meehl's diagnoses with the consensus diagnoses for the 24 cases called schizophrenic by Meehl but called nonschizophrenic by consensus opinion is shown in Table 1. The majority (17/24, or 71%) of the disagreements occurred when Meehl used a diagnosis of "qualified" schizophrenia (i.e., pseudoneurotic, pseudopsychopathic, and schizoaffective). There is close agreement between Meehl and the other four judges for perceived symptomatology. That is, Meehl often made a diagnosis of pseudopsychopathic schizophrenia when the other judges said psychopath, schizoaffective schizophrenic was often used by Meehl when the others reported an affective psychosis, and cases called pseudoneurotic by Meehl were usually just

[1] The five judges were (a) I. Gottesman, Professor of Psychology and Psychiatry and Director of the Behavioral Genetics Center, at the University of Minnesota, Minneapolis; (b) L. Heston, Professor of Psychiatry and Director of Psychiatric Research at the University of Minnesota, Minneapolis; (c) P. Meehl, Regents Professor of Psychology, Psychiatry, and Philosophy at the University of Minnesota, Minneapolis; (d) V. Tuason, Chief of Psychiatry at Saint Paul-Ramsey Hospital, Saint Paul, Minnesota; and (e) H. Gilberstadt, Chief Research Clinical Psychologist at Minneapolis (Minnesota) Veterans Hospital.

Table 2
Indicators of Severity for the Three Diagnostic Groups

Indicator of severity	Consensus schizophrenics	Consensus psychiatric controls	Consensus nonschizophrenics called schizophrenic by Meehl
Average age (in years) when first hospitalized	24	23	22
Average age (in years) at follow-up	35	32	31
Average no. psychiatric hospitalizations	4.3	3.0	3.0
% hospitalizations less than 6 months	21	59	63
% hospitalizations 6 months to 1 year	41	26	29
% hospitalizations 1–2 years	10	12	8
% hospitalizations more than 2 years	28	3	0
Average weeks in hospital	95	26	21
% ever in state hospital	76	41	29
% committed by court order	45	32	21
% not working at follow-up	66	44	38
Average severity rating	5.6	5.0	5.0

Note. For consensus schizophrenics, $n = 29$; for consensus psychiatric controls, $n = 34$; and for consensus nonschizophrenics called schizophrenic by Meehl, $n = 24$.

neuroses in the opinion of others. Most of the apparent diagnostic disagreement appears to reflect a theoretical difference in opinion on what constitutes valid indicators of schizophrenia rather than a lack of reliability in recognizing and rating patients' attributes. However, these differences in opinion between Meehl and the consensus opinion of all five judges cannot be dismissed too easily in light of reports that claim a link between typical schizophrenia and a "spectrum" of possibly genetically related psychopathologies (e.g., Kety, Rosenthal, Wender, Schulsinger, & Jacobsen, 1975; H. Schulsinger, 1976, Note 1).

Table 2 details some of the characteristics of our consensus schizophrenic parents, the consensus controls, and members of the total sample of consensus nonschizophrenics (including the four excluded cases and the three mates to schizophrenics) who were called schizophrenic by Meehl. The consensus schizophrenics tended to be a severely affected, chronically ill group. About three fourths of the consensus schizophrenics were state hospital patients, and nearly half of them had been hospitalized under court order. More than a decade (on the average) had elapsed since first hospitalization, yet two thirds of the consensus schizophrenics were still hospitalized, on welfare, or under the guardianship of relatives. One judge (Gottesman), who regularly applied Kraepelinian subtype descriptors, considered 45% of the consensus schizophrenics to exhibit catatonic or hebephrenic features. The control sample, on the average, is less severely affected in all respects and the consensus nonschizophrenics who were called schizophrenic by Meehl comprised a relatively mildly affected group who have spent only about 5 months (on the average) in the hospital during the 9 years since first hospitalization.

Sixty-six of the 70 diagnosed cases had at some time been administered the MMPI, and their scores provide another way of describing our sample. Marks, Seeman, and Haller (1974) have derived detailed descriptors for 16 MMPI profile types that are frequently seen among adult psychiatric patients. Nine of the 16 Marks et al. MMPI code types are most commonly (though not exclusively) observed in schizophrenic patients (see Gottesman & Shields, 1972, p. 272; Marks et al., 1974, Appendix C), and these 9 profile types characterized 22/27, or 81%, of our consensus schizophrenics. The heterogeneous group of consensus nonschizophrenic controls showed a wide variety of code types as expected. Forty-four percent of the controls had code types

that were most commonly (but not exclusively) associated with schizophrenia. Notably, none of the controls had Marks et al. MMPI profile types involving both the Schizophrenia scale (8) and the Paranoia scale (6); instead, they usually had elevations on scales for Depression (2), Psychopathic Deviate (4), or Hypomania (9) in addition to any elevation on 8 or 6.

Throughout this diagnostic exercise, Meehl has remained true to his broad concept of schizotypy (Gottesman & Shields, 1972; Meehl, 1962) and has identified as schizophrenic a number of relatively mildly affected ambulatory patients who did have some of the characteristics of more narrowly defined schizophrenics. Yet, on the whole, the symptom patterns of these patients did not resemble schizophrenia sufficiently in the opinion of the majority of diagnosticians. Which point of view is correct? Shields and Gottesman (1972) argue that diagnostic criteria between very broad and very narrow points of view make the most "genetic sense." However, the controversy over the validity of various definitions of schizophrenia and schizophrenia-related disorders is far from settled (see Gottesman & Shields, 1976a; Kety, Rosenthal, Wender, & Schulsinger, 1976; Shields, Heston, & Gottesman, 1975) and is of vital interest to high-risk researchers.

If, for example, a significant proportion of *presumed* nonschizophrenic psychiatric control parents could transmit a diathesis for schizophrenia to their children (as Meehl's diagnoses indicate for about one half of our psychiatric controls), then the contrasts between high-risk and control samples will be blurred, and the specificity of the genetic contribution to the development of schizophrenia may be questioned (cf. Rosenthal, 1975). However, if the broad point of view should prove to be false, there will be other serious consequences for the high-risk studies that adopt it: Many of the children of presumed schizophrenics will not have an increased risk for schizophrenia, the "yield" from the project will be much less than expected, and the potency of specific genetic factors in schizophrenia will be underestimated. Long-term follow-ups of children born to patients who have been screened through a variety of strict and loose criteria for schizophrenia will provide powerful tests of the predictive validities of the many definitions now in use. The employment of a range of potentially valid diagnostic criteria for schizophrenia will greatly broaden the scope of every high-risk project.

Table 3
Age-Corrected Morbidity Risk for Schizophrenia in Children with One Schizophrenic Parent

Investigator	Children		Morbidity risk (% ± *SE*)
	N[a]	Affected	
Hoffman, 1921	85.5	6	7.0 ± 2.8
Oppler, 1932	289.5	28	9.7 ± 1.7
Gengnagel, 1933	96.9	8	8.3 ± 2.8
Kallmann, 1938	678.5	94	13.9 ± 1.3
Garrone, 1962	77.0	13	16.9 ± 4.3
Heston, 1966[b]	30.5	5	16.6 ± 6.8
Reisby, 1967	201.8	7	3.5 ± 1.3[c]
Lindelius, 1970	243.0	17	7.0 ± 1.6
Fischer, 1973	31.2	3	9.6 ± 5.2
Bleuler, 1972	115.8	10	8.7 ± 2.6
Rosenthal et al. 1971[b]	69[d]	8	11.6 ± 3.8
Reed et al., 1973	108.0[e]	21	19.4 ± 3.8
Karlsson, 1974	82[d]	2	2.4 ± 1.7[f]
	46[d]	1	2.2 ± 2.2[f]
Schulsinger, 1976	87	9	10.3 ± 3.3[g]

[a] *N* is corrected for age distribution, except where noted, and is equal to risk lives observed (see Slater & Cowie, 1971).
[b] Children were raised apart from the schizophrenic parent.
[c] Risk for schizophrenia or schizophreniform psychoses was 10.4 ± 2.2.
[d] This datum is not age corrected.
[e] Age correction was not required; only schizophrenic psychoses were included.
[f] Risk for all "functional psychoses" was 8.5 ± 3.1 and 4.6 ± 3.1.
[g] Hospitalized cases only were included; inclusion of six additional diagnosed cases gave 17.2% risk or 23.8% by an alternative method.

The ways in which high-risk investigators define their samples also have important short-term consequences. Until childhood predictors of adult schizophrenia can be confirmed by the realities of follow-up results, or until a state independent biological endophenotype is discovered, the only major indicator of the validity of preliminary results will be their replicability—although, of course, replicability does not guarantee validity (cf. Herman, Mirsky, Ricks, & Gallant, 1977; Rutschmann, Cornblatt, & Erlenmeyer-Kim-

Table 4
Age-Corrected Morbidity Risks for Schizophrenia for Children of Schizophrenic Parents as a Function of Mating Type and Severity of Illness (Data are from Kallmann, 1938)

Schizophrenic parents	Children		
	N[a]	% morbidity risk for definite schizophrenia	% morbidity risk for definite or doubtful schizophrenia
Both schizophrenic	23.5	53.3	68.1
One parent as indicated and second parent not specified			
Hebephrenic	265.5	17.3	20.7
Catatonic	106.5	18.8	21.6
Paranoid	212.0	8.5	10.4
Simple	94.5	10.6	11.6
One parent as indicated and second parent normal			
Hebephrenic	144.5	13.1	17.3
Catatonic	49.5	14.1	16.2
Paranoid	118.0	6.8	8.5
Simple	57.0	1.8	1.8

[a] *N* is adjusted for age distribution of the sample and is equal to "risk lives" observed, or *Bezugsziffer*.

ling, 1977). Replication of results will require the assembling of similar samples, and without thorough descriptions of the diagnosed schizophrenic parents, replications are likely to fail.

Genetic Theories and Epigenetic Realities

A summary of the age-corrected lifetime morbidity risks for the occurrence of schizophrenia in individuals who have one schizophrenic parent is shown in Table 3. Children with schizophrenic mothers have the same risk as children with schizophrenic fathers (Bleuler, 1972; Kallmann, 1938). Individuals who have two schizophrenic parents have risks for schizophrenia that range from about 35% to 50% (Erlenmeyer-Kimling, 1968; Rosenthal, 1966). By comparison, the risks to individuals in the general population are about .85% to 1.0% (Slater & Cowie, 1971) when rather strict European diagnostic criteria are applied and are about 3% when broader North American diagnoses are used (Yolles & Kramer, 1969).

All of these risk values are empirical and therefore atheoretical, but the important genetic contribution to schizophrenia evidenced by twin (Gottesman & Shields, 1972), family (Bleuler, 1972), foster (Heston, 1966), adoption (Kety et al., 1975; Rosenthal, Wender, Kety, Welner, & Schulsinger, 1971), and cross-fostering (Wender, Rosenthal, Kety, Schulsinger, & Welner, 1974) studies boosts genetic interpretations (see review by Gottesman & Shields, 1976a). The mode of transmission of schizophrenia is not known, but the patterns of transmission are consistent with polygenic theory:[2] (a) Polygenic traits are more common in the general population than deleterious Mendelian traits with full penetrance, (b) polygenic disorders are found with varying severities, (c) the risks are greater in families

[2] Transmission via a dominant gene with variable expressivity cannot be ruled out; at the population level, such a theory generates predictions that are indistinguishable from polygenic expectations using available data. Two of us (Hanson and Gottesman) prefer polygenic models because they are more general and include monogenic models when the number of polygenes is set equal to one, or when monogenic models specify variable expressivity as a result of modifying genes.

with many affected relatives compared to families with few affected members, (d) risks to second- and third-degree relatives of affected individuals drop off more sharply than dominant-gene theory expectations, and (e) the risk to a person increases as a function of the severity of a relative's illness. Curnow and Smith (1975) provide a further guide to multifactorial models for familial diseases.

Kallmann's (1938) data (see Table 4) illustrate some of these patterns in samples of children of schizophrenic parents. As we have seen, children with two affected parents have a greater risk than children with one affected parent. The more severely affected catatonic and hebephrenic parents have more affected children than do parents with less devastating paranoid and simple forms of schizophrenia. Many of the nonschizophrenic parents in Kallmann's sample had some type of possibly schizophrenia-related psychopathology; specifying that the nonschizophrenic parent is normal results in a reduction of the overall risks. These relations between magnitude of risk and number of relatives affected or severity of affected relatives' illnesses have been observed in other family (Hallgren & Sjögren, 1959. Lindelius, 1970; Ødegaard, 1972) and twin studies (Gottesman & Shields, 1972). It is apparent that the risk values to samples of children of schizophrenic parents can range anywhere from a low that approaches the general population risk to a high of about 50% depending on the composition of the parent sample. It also appears that at least half (Heston, 1970) and maybe as many as 75% (Bleuler, 1972) of the children with one schizophrenic parent will grow up to be normal and not eccentric. Every high-risk sample will be genetically heterogeneous; those children who receive the necessary genes for schizophrenia will be the true high-risk individuals, and those children who receive none of the necessary genes for schizophrenia will have *no genetic risk* for schizophrenia, even though they are children of schizophrenic parents.

The situation here is like a problem in "sampling without replacement." If all individuals with the high-risk genotypes for schizophrenia (say 10% to 50% of the subjects) are removed from the sample, there remains a large group of individuals who are not at high risk for schizophrenia unless a completely unprecedented set of stressors is brought to bear, thus making "traditional" risk values inapplicable. Genetic theorizing further suggests that there will be individual differences in the magnitude of the necessary diathesis corresponding to the number and potency of predisposing genes inherited. Those individuals with a relatively mild diathesis will be resistant to all but the most severe environmental stressors, while individuals with very strong predispositions might be vulnerable to breakdown in the face of even the mild stresses of everyday life. The goals of high-risk research include detecting the high-risk genotypes and specifying the life events that actualize the predisposition to schizophrenia. The net result of a dynamic combination of genetic and environmental sources of liabilities and assets determines whether and when a predisposed individual will become a diagnosible schizophrenic.

Table 5
Age Distribution of Risk for Schizophrenia (Data are from Slater and Cowie, 1971)

By age (in years)	Proportion of total risk up to age 55 (percent)	
	Male	Female
15	0·6	0·8
20	11·4	10·6
25	31·4	25·3
30	50·8	43·5
35	70·2	59·7
40	80·6	71·6
45	91·0	83·4
50	95·5	91·7
55	100·0	100·0

The lifetime risk estimates discussed above are useful for estimating the final number of high-risk subjects who will eventually break down by the end of the age risk period for schizophrenia. Traditionally, the period of risk for schizophrenia has been thought to extend from age 15 years to age 45 or 50, though Slater and Cowie (1971) have extended the range upward to age 55; and elsewhere, we (Hanson & Gottesman, 1976) have suggested that a downward extension may also be warranted. In addition to lifetime risk

estimates, high-risk researchers will also want to estimate how many individuals will break down within a realistic follow-up time.

Table 5 provides the distribution of ages at first hospitalization for schizophrenia and, in conjunction with Table 3, allows easy calculation of the percentage of high-risk subjects expected to break down before any given age range. For example, by age 20 years, a male has been exposed to 11% of the lifetime risk (i.e., 11.4% of all schizophrenic males break down by age 20), and a female has been exposed to 10.6% of the total risk. If we estimate that 10% of a high-risk sample will break down by age 55, then we would expect ($.10 \times .114 \times 100 =$) about 1.1% of the high-risk males and ($.10 \times .106 \times 100 =$) about 1.1% of the high-risk females to break down by age 20. By age 30, the respective values are 5.1% and 4.4%. Thus, a researcher who starts with a sample of high-risk infants would expect to ascertain only about one half of the eventual schizophrenics after a 30-year follow-up. Any shorter follow-up may provide a distorted view of the natural history of schizophrenia by focusing on the minority of severely affected early-onset cases. Conversely, investigators who report large percentages of affected individuals after short follow-ups are likely to be beating the odds with atypical, severely affected samples or are overdiagnosing schizophrenia.

Genetic theory *does* suggest that schizophrenics who have one or two schizophrenic parents *will* be more severely affected on the average than schizophrenics who have no schizophrenic parents. A recent follow-up of Mednick's (Mednick & Schulsinger, 1968) Danish high-risk sample (H. Schulsinger, 1976) may illustrate this phenomenon. By the time the sample reached a mean age of only 23 years (range of 18 to 30), 9 of 173 (5.3%; 10.3% with age correction) high-risk subjects had been hospitalized for schizophrenia. Application of CATEGO (Wing et al., 1974) diagnostic criteria obtained a similar rate of 5.8%, uncorrected for age, while application of broader DIAGNO II (Endicott & Spitzer, 1972) criteria boosted the uncorrected rate to 17.3%. Schizophrenics with schizophrenic parents may represent a subgroup of all schizophrenics who have atypically strong genetic and environmental diatheses. This would be especially true if the second parent is also schizophrenic or psychiatrically abnormal, as are some of the fathers in the Danish sample (B. Mednick, 1973). The actualization of these strong diatheses would require relatively mild additional stresses from the environment, and these environmental contributors might be so mild and so much a part of everyday life that they pass by unnoticed. Even if the relevant stressors are recorded, they may occur with similar frequencies in high-risk and control samples and may be discounted by investigators not accustomed to thinking in terms of gene-by-environment interactions (cf. Erlenmeyer-Kimling, 1972; Gottesman & Shields, 1976b).

Table 5 may underestimate the rate of breakdown among children of schizophrenics but can serve, at least, as a check on the minimum number of cases expected to break down at any given age. Table 5 also reminds us that even after extensive follow-ups, there may still be a number of individuals in the high-risk sample who will break down at some later date. The presence or absence of breakdown at follow-up is critical to the high-risk method because, in the absence of biological endophenotypic indicators (Shields & Gottesman, 1973) of the schizophrenic genotype, the only proof that certain childhood characteristics are harbingers of adult psychoses comes when forecasted schizophrenics do break down. When the Mednick and Schulsinger (1968) high-risk sample was followed up in 1972 at a mean age of 23.9 years (H. Schulsinger, 1976, Note 1), more overt schizophrenics were found *outside* of the so-called "sick" high-risk subsample than in it. Of 15 consensus-diagnosed schizophrenics in the 173 reinterviewed high-risk subjects, only 4 had been identified in 1962 as in the high-risk sick group.

Some of the possibilities that a high-risk researcher might face at the time of follow-up are illustrated in Figure 1, which shows the phenotypic and genotypic compositions of a high-risk sample of 100 individuals that have been followed up until about age 30 years. The proportion of individuals who eventually break down has been set at 10%. The high-

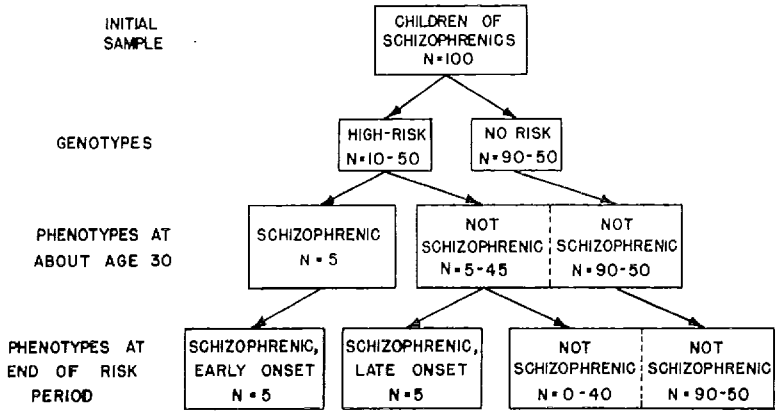

Figure 1. Possible outcomes of a longitudinal study of 100 children with schizophrenic parents.

risk genotypes include all children who have the necessary genes for schizophrenia; those without the necessary genes have no-risk genotypes. In this illustration, the minimum proportion of high-risk genotypes is 10%, while the maximum has been set at 50% to coincide with Mendelian expectations for dominant inheritance. To keep the graphics simple, we have omitted intermediate-risk genotypes and borderline outcomes. At follow-up, 5 individuals have schizophrenia. Among the 95 who are not schizophrenic, there are 5 more individuals who will develop schizophrenia at a later date, and there are perhaps as many as 40 individuals who have the necessary genotype for schizophrenia but who will never break down. We know there are many individuals with the genetic diathesis for schizophrenia who do not show the trait because only about half of the identical twins of schizophrenics are concordant.[3] Clinical follow-up status, even at the end of the risk period, may not be a sufficient criterion for validating proposed indicators of the high-risk genotype.

Without valid indicators of the high-risk genotypes, high-risk researchers will be hard pressed to fully evaluate the environmental contributors to schizophrenia. Such evaluations require comparisons of those individuals who have the genes and who break down early to those individuals who have the same genetic liability but who break down late; and both of these groups must be compared to the group of individuals who have high-risk genotypes, but who do not break down at all. Without some heroic "boot-strapping" (Cronbach & Meehl, 1955), the high-risk strategy will have difficulty using fallible indicators to identify either the genetic or the environmental contributors to the development of schizophrenia. The discovery of endophenotypic indicators of the schizophrenic genotype is both a goal of high-risk research and a requirement for the success of the high-risk design.

Discussion

Both Kraepelin (1919) and Bleuler (1911/1950) believed that the first signs of developing schizophrenic illnesses are often present many years before the appearance of psychotic symptoms. Follow-up studies of abnormal children and follow-back studies of schizophrenic adults (for reviews, see Garmezy & Streitman, 1974; Offord & Cross, 1969) support these beliefs, but only about half of all schizophrenics show any retrospective evidence of abnormal prepsychotic behaviors (Slater & Roth, 1969). The known behavioral precursors of schizophrenia are not

[3] Further evidence that both the affected and discordant twins have the necessary genotype (and therefore are not examples of "environmentally produced" schizophrenia) comes from the observation of a 13% risk to the children ($n = 27$) of nonaffected members of the discordant MZ pairs, which is similar to the risk for children of the affected twins (Fischer, 1973).

pathognomonic and include irritability, excitability, anxiety, and unsocialized aggression in addition to apathy and withdrawal. Apparently, normal personalities also precede schizophrenia. Simple shyness alone does not foretell schizophrenia (Michael, Morris, & Soroker, 1957; Morris, Soroker, & Burruss, 1954), and there is little evidence that schizoid behaviors, as they are popularly perceived, are useful predictors (Mellsop, 1973a; Shields, et al., 1975). The fact that some preschizophrenics do have documented histories of abnormal childhood behaviors stands as a warning that the cause–effect ambiguities constantly facing those who study schizophrenia will not be automatically resolved by prospective methodologies. Anytime a high-risk child is identifiable on behavioral measures as a candidate for adult schizophrenia, there is reason to suspect that an important threshold in the disease process has already been passed.

The fact that many schizophrenics do show evidence of abnormality long before psychosis is also the best evidence supporting the contention that prospective studies of children of schizophrenic parents will be able to discern the beginnings of schizophrenia. However, these efforts will be successful only if predictively valid criteria for schizophrenia are used to define the schizophrenic parent sample. Concentrating on severely affected families or families with many affected relatives will increase the chances of including future schizophrenics among presumed high-risk children. Even if the broad definitions of schizophrenia that encompass pseudoneurotic and pseudopsychopathic cases are valid, the relatively milder severity of these varieties reduces their utility for high-risk studies.

There are at least three important realistic goals for high-risk research. The first goal is to define the range and specificity of the childhood characteristics that precede adult schizophrenia. Retrospectively, some preschizophrenics appear behaviorally normal, while some seem "different," and others are markedly disturbed. It does seem clear that childhood psychopathology is often associated with adult psychopathology, but childhood symptomatology is a poor predictor of adult diagnosis (Fish, 1975; Mellsop, 1973b; O'Neal & Robins, 1958a, 1958b; Pritchard & Graham, 1966; Roff, Knight, & Wertheim, 1976). Children of schizophrenic parents must be compared to children at risk for other kinds of psychopathology to resolve the specificity issue.

A second important goal for high-risk researchers is to quantify the relation between predictors and outcomes. The usefulness of predictors will, of course, be directly proportional to the accuracy of the predictions. The predictors' false positive and false negative rates will have to be determined by extensive follow-ups, and the frequency of the predictor traits in high-risk samples will have to be compared to estimates of the population base rates (Meehl & Rosen, 1955) obtained from control samples of children born to normal parents. Base rates may vary as a function of social class or other demographic characteristics, so both matched and unmatched (general-population) comparison groups will be useful.

A third goal of high-risk research is to determine whether valid childhood predictors of adult schizophrenia identify the etiological roots of schizophrenia. At least three possibilities must be considered. First, the predictor variables might be indicators of the high-risk genotype. Such predictors could help elucidate specific neurobiological deficits associated with the development of schizophrenia and would denote individuals with the potential for future schizophrenia, even though some of these individuals will remain behaviorally normal throughout their life. Second, valid childhood predictors of adult schizophrenia might identify potentiators (Meehl, 1973) or correlates of potentiators that lead to breakdown. Such potentiators might be parts of predisposed individuals' environments or general genetic backgrounds (Gottesman & Shields, 1972). For example, let's say school failure in high-risk children often predicts breakdown. Such a school-failure sign might be due to family pathology (or low IQ), and the family pathology (or low IQ) might be a potentiator of schizophrenia in predisposed individuals. Yet, the school-failure sign is neither a consequence of the high-risk genotype nor, by itself, an early sign of schizophrenic behavior. Third, child-

Table 6
Percentage of Children Who Exhibited Proposed Preschizophrenic Indicators

Indicator	% children of parents who are			
	Consensus schizophrenic (n = 30)	Other psychiatric patients (n = 30)	Normals, matched (n = 29)	Normals, not matched (n = 27)
Poor motor skills	30	10	21	7
Large within-person test score variance	53	30	28	19
Schizoid behavior at 4 and 7 years	27	3	10	0
Only two indicators	10	10	17	0
All three indicators	17	0	0	0

Note. One sample of children of normal parents was matched to the children of schizophrenics for social class, mother's age when the study child was born, and number of prior live-born children. The other normal comparison sample was selected by taking the next child of normal parents who entered the collaborative study after each high-risk child.

hood predictors might represent the earliest signs (or effects) of already potentiated schizophrenias. Such predictors would indicate when schizophrenic behaviors begin but would not necessarily shed light on either the genetic or environmental contributors to the development of schizophrenia.

It seems likely that, at least, some early developing schizophrenics will be detected by high-risk researchers. In our own sample (Hanson et al., 1976), 5 out of 30 (17%) 7-year-old children of our consensus schizophrenics were categorized by having poor motor skills, large within-individual inconsistencies in performance on cognitive tasks, and enduring patterns of withdrawal, emotional flatness, irritability, negativism, and emotional instability. None of the 30 children of consensus psychiatric controls and none of 56 children born to normals (see Table 6) had all three "indicators." The 5 children exhibited behaviors found in adult schizophrenics (e.g., loose, bizarre thoughts and extreme anxiety), but none were reported to have delusions or hallucinations, and none fit the syndrome of adult schizophrenia. Most have severely schizophrenic parents, and two children have a second parent with psychiatric problems. If past behavior predicts future behavior, and if a diathesis-stress model of schizophrenia is valid, these 5 children have a higher risk for schizophrenia than all the other children studied. It might be possible to detect some symptoms of the syndrome early in the life of predisposed individuals, but any sample of high-risk children will have to be followed well into adulthood to establish the validity of proposed preschizophrenic traits.

The detection of *some* schizophrenias in childhood will not imply that *all* schizophrenias can be predicted from childhood. Even if a perfect indicator of the high-risk genotype is discovered, prediction of all cases of schizophrenia will be impossible as long as the environmental contributors to schizophrenia are unpredictable. So far, *no* specific environmental source of liability is known; the most likely environmental contributor, stress, may come from many sources and, apparently, may come during any stage of development. Prenatal or birth complications, early deprivations, broken homes, censuring parents, the death of someone close, failures in school, work or social relationships, childbirth, a "bad trip," as well as all kinds of good fortune may have effects on a predisposed individual that are obvious in retrospect. In prospect, it will be impossible to prophesy the events themselves, let alone their effects.

The laudable goal of preventing schizophrenia shares problems with the goal of prediction. Even if a good indicator of the high-risk genotype is discovered and an effective preventative treatment becomes available, the treatment will still have to be applied judiciously, since many individuals with the necessary genetic predisposition for schizophrenia

enjoy a lifetime of adequate mental health *without any intervention,* as evidenced by the concordance rate for schizophrenia in identical twins being only about 50%. The accuracy of the predictions, the cost-effectiveness of the treatment, the short-term and long-term risks from side effects of the treatment, and the burden of worry imposed by focusing the targeted individual's attention on a potential problem (cf. the controversy surrounding attempts at early detection of Huntington's disease, Freeman, 1973; Goodman, Ashkenazi, Adam, & Greenfield, 1973; Lyle & Gottesman, 1977) are just a few of the issues that require evaluation. Subjecting otherwise normal individuals to symptomatic but powerful treatments on the basis of theoretical but unvalidated indicators of future schizophrenia is improvident.

It seems unlikely that high-risk research will quickly point the way to cures or preventions for schizophrenia. However, if investigators are wise enough to study the "right" variables, and if they are lucky enough to be on the scene when important events occur, the high-risk method will provide accurate and detailed descriptions of the natural history of schizophrenia. Documenting the age at which the earliest abnormalities (or "oddities") appear and recording the life events that precipitate, exacerbate, or ameliorate these abnormalities are not the same as explaining schizophrenia. In addition, we need to know how these developmental events interact with predisposed individuals' genotypes. If cures or preventions are forthcoming, they will come from an understanding of the joint actions of environmental and apparently specific genetic factors. Claiming specific genetic etiological contributors to the development of schizophrenia does not diminish prospects for treatment; genetics cannot be equated with determinism (Meehl, 1973, 1977). Hopefully, high-risk investigators will incorporate both environmental and genetic theorizing into their research designs and, thus, help bridge the gap between descriptive psychopathology and molecular biology.

Reference Note

1. Schulsinger, H. *Clinical outcome of a ten-year follow-up of children of schizophrenic mothers.* Paper presented at the meeting of the Society for Research in Life History and Psychopathology. Fort Worth, Texas, October 1976.

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Received February 28, 1977
Revision received August 11, 1977 ■