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The New York High-Risk Project: A Followup Report

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Abstract

The New York High-Risk Project began in 1971 as a prospective, longitudinal study of (1) children of one or two schizophrenic parents and (2) comparison groups of children whose parents had other or no psychiatric disorders. The former were examined because they were known to be at high risk—some 10–25 percent for children with one affected parent and 35–45 percent with two affected parents—for developing schizophrenia or schizophrenia spectrum disorders during adolescence or adulthood (Erlenmeyer-Kimling 1977; Gottesman and Shields 1982). Children of parents with affective disorders were included because we wished to determine whether variables that might differentiate the children of schizophrenic parents from the children of normal parents also differentiated them from children of parents with other psychiatric disorders.

Major goals of the program were (1) identification of biological and behavioral indicators of a genetic liability to develop schizophrenia and (2) longitudinal followup of the subjects to assess the predictive validity and specificity of variables tentatively flagged as early indicators. Other goals have included evaluation of the developmental course of such variables and documentation of the history of the development of schizophrenic disorders.

Characteristics of the Samples

The New York High-Risk Project includes two samples of subjects at high and low risk for schizophrenia. Sample A was ascertained during 1971 and 1972. The replication sample, sample B, was ascertained from 1977 to 1979. Children in both samples were between 7 and 12 years old upon entry into the study, were Caucasian and English-speaking, and were without histories of psychiatric treatment, evident psychiatric disturbance, or mental retardation.

Risk for schizophrenia in the children was defined on the basis of a diagnosis of schizophrenia in one or both parents. Mentally ill parents were identified through screening consecutive admissions at several large New York State psychiatric facilities within a 2-hour drive from New York City. To be considered for the study, a patient had to have at least one 7- to 12-year-old child meeting the above criteria, have an intact marriage with the other biological parent of the child, and have none of the following diagnoses: chronic alcoholism, drug addiction, brain trauma, or psychoses of toxic origin. The criterion of an intact marriage was waived for patients who had a child in the target age range by another mentally ill patient with the same diagnosis.

For each sample, two senior psychiatrists (Dr. John Rainer and Dr. Michael Stone) independently made diagnoses from the patient-parents' hospital records, from which hospital diagnoses and medication histories had been removed. The psychiatrists endeavored to use conservative standards for the diagnosis of schizophrenia at the time of ascertaining patient-parents for sample A and followed the Research Diagnostic Criteria (RDC) (Spitzer et al. 1975) in the ascertainment of patient-parents for sample B. For sam-

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ple A, patient-parents for the psychiatric comparison (PC) group were not required to have a specified diagnosis except that it had to meet the exclusionary criteria listed above and be unrelated to schizophrenia. For sample B, however, patient-parents for the PC group were required to have diagnoses of major affective disorder or schizoaffective disorder, mainly affective, according to the RDC. Only those patients for whom there was consensus agreement between the two psychiatrists were accepted for study.

Subsequently, at sample A's third round of testing and at sample B's second round of testing, all available patient-parents were interviewed with the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (SADS–L) (Spitzer and Endicott 1977) and were rediagnosed with the RDC based on the interview and record materials. The SADS–L was administered to spouses about any patient-parents who were unavailable for direct interview.

In both samples, some parents received diagnoses of schizoaffective disorder and were then subclassified according to the RDC distinction between "mainly schizophrenic" and "mainly affective" disorders. In these samples, results of testing on the major biobehavioral variables do not differentiate children of schizophrenic parents from children whose parents are called schizoaffective, mainly schizophrenic, whereas children of parents with schizoaffective, mainly affective disorders are similar to children with major affective disorders. Thus, the children of schizophrenic and schizoaffective, mainly schizophrenic parents were grouped together to form the high-risk-for-schizophrenia (HR) group and children of parents with major affective and schizoaffective, mainly affective disorders were grouped to form the psychiatric comparison (PC) group.

As a result of the rediagnoses, the composition of sample A was altered. After movement of some children from the HR to the PC group because of changes in their parents' diagnoses, plus the addition of three children of a schizophrenic mother and a manic father whom we had not included in earlier data analyses, and removal of two children whose parent did not fit an appropriate RDC diagnosis, the HR group contained 63 children. All parents in the PC group were found to have diagnoses of major affective disorder or schizoaffective disorder, mainly affective, and this group, now expanded by children whose parents were reclassified from schizophrenic to affective diagnoses, contains 43 children.[1] In sample B, the HR and PC groups contain 46 and 39 children, respectively.

For sample A, a normal comparison (NC) group was obtained through the cooperation of two large school districts, in which school officers agreed to send our letters to appropriate families requesting their participation in the project. For sample B, a population sampling firm was retained to generate a pool of families from which the NC group could be drawn. In both samples, the children of the NC groups were between 7 and 12 years old, Caucasian, English-speaking, from intact homes, and without histories of psychiatric problems or mental retardation. Families in which either parent had had psychiatric treatment or a history of psychiatric problems were excluded. In sample B, NC children were matched to HR children based on age, sex, and family socioeconomic status.

[1]With the addition of three children and the subtraction of two children, the effective sample size for data analyses is 206, rather than the 205 described in several earlier publications.

Procedures for Children's Assessments

Sample A has been assessed in four testing rounds and sample B in three, at intervals approximately 2–3 years apart. With the exception of A-4 (the fourth testing round for sample A), each round consisted of a home visit in which the parents and children were interviewed separately and a full day of examinations of the children in the laboratory. (In A-4, the home visit was eliminated.) Examinations in the laboratory consisted of a videotaped psychiatric interview in most rounds and several other types of assessments, including in all rounds, attentional and information-processing measures, at least one neuromotor measure, and interviews about social functioning. Psychophysiological measures were also included in some of the testing rounds, as were IQ tests, personality disorder tests (Minnesota Multiphasic Personality Inventory), the Physical Anhedonia Scale (Chapman et al. 1976), life events inventories, and anthropometric measures. Table 1 lists the main measures that were given during the children's laboratory visits and shows the mean age of the subjects at each testing round. Information about the children's ongoing levels of functioning in school or work, in peer relations, and in the home was also obtained via telephone interviews conducted with the parents at intervals of 3–6 months between the testing rounds. School record data and teachers' evaluations were also collected (Watt et al. 1984).

Table 1. Procedures administered during the children's visit to the laboratory

	Sample A				Sample B		
Testing round[1]:	A-1	A-2	A-3	A-4	B-1	B-2	B-3
Mean age (years):	9.5	12	16	21	9.5	12	15.5
Attention & information processing							
Continuous performance test (CPT)	X	X	X	X	X	X	X
Attention span task (ATS)	X			X		X	X
Digit span/visual aural digit span (DS/VADS)	X		X		X	X	X
Information overload test (IOT)			X	X	X	X	X
Short-term memory lag test (STM-lag)			X				X
Eye tracking				X			X
4-card Rorschach (scored for thought disorder)				X			
Neuromotor measures							
Neurological examination	X	X			X	X	
Lincoln-Oseretsky Test of Motor Impairment	X	X			X	X	
Purdue pegboard			X	X			X
Bender-Gestalt test[2]	X	X			X	X	
Psychophysiology							
Skin conductance (conditioning paradigm)	X						
EEG/event-related potentials		X	X		X	X	
Heart rate		X	X		X	X	
Clinical & social measures							
Psychiatric interview[3]		X	X	X	X	X	X
Friendship & intimacy interview			X	X		X	X
Social Adjustment Scale				X			X
Videotaped general interview	X						
Other domains							
Wechsler IQ scale	X		X		X		X
Life Events Inventory			X	X		X	X
Physical Anhedonia			X	X			X
Minnesota Multiphasic Personality Inventory (MMPI)[4]			X			X	
Anthropometric measures	X	X	X	X	X	X	X

[1]Several procedures given in only one round are omitted.
[2]Given in the home, rather than laboratory, in earlier rounds.
[3]Videotaped in all rounds except A-4.
[4]Given to subjects aged ≥ 14.

Psychiatric Interviews and Other Clinical Assessments. Psychiatric interviews were administered to the children in all testing rounds except for A-1. In A-2, A-3, and B-1, a semistructured interview and the Mental Health Assessment Form (MHAF), developed for this project (Kestenbaum and Bird 1978), were used. The interview was videotaped and rated on the MHAF by at least two child psychiatrists, who also rated the children on a 100-point Children's Global Assessment Scale (CGAS), an assessment of severity of impairment of functioning. In B-2 and B-3, the semistructured interview was replaced by a structured interview, the Columbia Psychiatric Interview for Children and Adolescents (COLPICA) (Shaffer and O'Connor, unpublished), which yields *DSM-III* diagnoses (American Psychiatric Association 1980); the in-

terview, which was videotaped, was also scored on the MHAF and CGAS. In A-4, the subjects (all of whom had entered adulthood) were interviewed with the SADS–L, which had been used in the process of rediagnosing the patient-parents. In all rounds, the interviewing psychiatrist (psychologist in A-4) and raters were unaware of any given child's parental group.

Another approach to the ongoing assessment of the study children's functioning was based on the parents' reports of their children's behavior. The parents' reports are chiefly those obtained in the routine followup calls made by the project social workers every 3–6 months. These reports on the children are rated for degree of behavioral disturbance at any given time on the Behavioral Global Adjustment Scale (BGAS) (Cornblatt and Erlenmeyer-Kimling 1984). The BGAS is a 5-point scale, with rating categories ranging from gross behavioral disturbance requiring hospitalization (a rating of 1) to above-average functioning in all areas of assessment (a rating of 5). Ratings are based on consideration of three major areas of functioning: (1) family relationships and the child's general level of development, (2) peer relationships, and (3) functioning in school or work. BGAS ratings were carried out for sample A in 1978, 1979, 1980, and 1983. BGAS ratings for sample B were carried out in 1980 and 1982.

Other types of assessments administered to the study children may also provide interim "outcome" data. These include the Minnesota Multiphasic Personality Inventory (MMPI) as an assessment of personality disorders, the Physical Anhedonia Scale of Chapman et al. (1976), an interview on friendship and intimacy of relationships (the Friendship and Intimacy Interview) developed by Dr. Dolores Kreisman, the Social Adjustment Scale for adolescents and young adults developed by Dr. Richard Blumenthal, and the Personality Disorder Examination (PDE) (Loranger et al. 1984) for *DSM-III* Axis II diagnoses.

To date, 14 study children in sample A have been hospitalized—seven in the HR group, four in the PC group, and one in the NC group. Of the 190 study children followed through testing round #4, the hospitalized subjects represent approximately 12 percent of the HR group, 10 percent of the PC group, and 1 percent of the NC group. Several other subjects in each group have received substantial amounts of treatment, have been jailed, or are otherwise known to have serious psychological problems; they include 15 HR (25 percent), 8 PC (20 percent), and 10 NC (11 percent) study children who have received some treatment in childhood or adolescence but who are not known to have psychological problems in early adulthood. The remaining subjects in each group are considered to be relatively free of disturbances at present and to have had no major disturbances in the past. These are 28 HR (47.5 percent), 25 PC (62.5 percent), and 66 NC (72.5 percent) subjects.

Predictors of Liability to Psychopathology

One of the primary aims of the project was to identify early indicators of the genetic liability to the development of schizophrenia-related disorders. According to the theoretical model that guided our thinking about risk for schizophrenia, we expected that the most fruitful areas in which to search for such indicators would be the three biobehavioral domains (attentional and information-processing capacities, neuromotor functioning, and psychophysiological processes) and in the genetic histories of the children. We hypothesized that the social functioning of the children might be influenced by disturbances in attention and information processing, and that the latter might therefore precede difficulties in social functioning. Thus, problems in social behavior might be expected to appear closer to the time that clinical symptoms indicative of schizophrenia-related disorders begin to emerge, in contrast to the childhood emergence of dysfunctions in the three biobehavioral domains. Social dysfunctions might, in fact, be considered to be prodromal signs.

We also hypothesized that environmental factors played a role in risk for schizophrenia, although we thought of these as probably being nonspecific and cumulative. Thus, for example, we are examining data collected on stressful life events over the course of the study and are attempting to relate patterns of such variables to the subjects' clinical status in adolescence or very young adulthood. It is also of interest to explore the possible roles of parent and home-environment variables among the children of affected parents, as long as one remembers to be cautious about extending their implications to schizophrenic individuals whose parents are not overtly schizophrenic (Erlenmeyer-Kimling and Cornblatt 1984; Erlenmeyer-Kimling et al. 1984*b*).

In assessing the value of the various types of measures as predictors or early indicators of a genetic liability, we have been concerned with four issues: (1) Can we identify a subgroup of HR subjects who are deviant with respect to this measure (or domain of measures) compared to the remainder of the HR group?

(2) Can we show that deviance on this measure characterizes the HR subjects to a greater extent not only than the NC but also the PC group (i.e., is there specificity)? (3) Can we show that there is a relationship between deviance on this measure and the subsequent development of psychopathology (i.e., is there predictive validity)? (4) Can we show that such a relationship applies specifically to schizophrenia and schizophrenia spectrum disorders? The last question is premature for our samples at their present ages, but the other questions may be considered, especially in sample A.

Attention and Information Processing. Of all the domains of variables that we examined in the search for possible predictors, that of attention and information processing (AIP) has emerged as the most important thus far for sample A. In the initial testing round, which we regard as the key round for prediction, three AIP measures were administered: (1) a version of the Continuous Performance Test (CPT); (2) an auditory Attention Span Task; and (3) the Digits Forward and Backward subtest from the Wechsler Intelligence Scale for Children (WISC). The three tests yield a total of 15 response indices.

One type of response index that we focused on in earlier reports is the signal-detection theory index of sensitivity or discriminability, *d'*, which can be computed for a variety of types of AIP measures. Like Nuechterlein (1983), who obtained *d'* factors for CPT versions administered to high-risk children, we have shown that the children of schizophrenic parents have lower *d'*s on the CPT version administered in A-1, indicating less sensitivity in discriminating among stimuli, than children in either of the other comparison groups (Rutschmann et al. 1977; Cornblatt and Erlenmeyer-Kimling 1984; Erlenmeyer-Kimling et al. 1984*b*). Moreover, we have observed that HR subjects who had been hospitalized or in psychiatric treatment by 1980 had lower *d'*s than the remainder of the HR group, which did not differ from the NC group or the PC group. Thus, the apparent difference between the HR group as a whole and the other two groups is attributable to a subgroup of subjects within the HR group who have manifested psychopathology in late adolescence.

A more recent approach that we have found to be useful for studying AIP variables involves the computation of a composite AIP deviance score across the several response indices. The composite score is derived by establishing as deviant performance for a given response index any score that falls below the cutoff score that identifies the worst 5 percent of performers in the NC group, and then tallying the total number of response indices on which an individual is classified as deviant. The distribution of composite AIP deviance scores ranges from 0 to 10 (out of a possible 15) across the entire sample, but very few subjects have composite scores >6, and a cutting score ≥4 appears to classify the truly deviant subjects most appropriately.

We have reported previously on the composite AIP deviance scores (Erlenmeyer-Kimling et al. 1983, 1984*b*; Cornblatt and Erlenmeyer-Kimling 1984, 1985*b*). To summarize: (1) The HR group contains a significantly ($p = .004$) greater percentage (27 percent) of subjects with composite AIP deviance scores ≥4 than does the NC (6 percent) or PC (11 percent) group. (2) Composite AIP deviance scores correlate significantly ($p = .001$) with 1980 BGAS scores in the HR group but not in the PC or NC group. (3) Slightly more than half (53 percent) of the HR subjects who were classified as functionally impaired on the 1980 BGAS ratings had composite AIP deviance scores ≥4, while none of the PC or NC subjects so classified had such high scores. Conversely, of the subjects with good to superior BGAS ratings, only 7 percent (1 subject out of 14) in the HR group, 5 percent (1 out of 18) in the PC group, and 4 percent (3 out of 69) in the NC group had composite AIP deviance scores ≥4. The composite score appears to have relatively good specificity and moderate sensitivity (Erlenmeyer-Kimling et al. 1983; Cornblatt and Erlenmeyer-Kimling 1985).

In B-1 our interest in recording event-related potentials led us to change the version of the CPT that we had used previously and to introduce two new versions. One version, which required the subject to respond to a constant target stimulus, was too easy and failed to show group differences. However, the other version, which was similar to the CPT version used for sample A in that it required the subject to respond to any stimulus that was identical to the stimulus immediately preceding it, yielded group differences on a number of response indices, with the HR group showing poorer performance than the PC or NC groups (Rutschmann et al. 1986). Furthermore, when a composite CPT deviance score was computed from the 12 response indices of that test in the same manner as described for the composite AIP deviance score for sample A, the results were relatively similar for the two samples: in B-1, 29 percent of the HR subjects had composite CPT deviance scores ≥3 compared to 12 percent of the PC subjects and 8 per-

cent of the NC subjects (Rutschmann et al. 1986). Thus, although the AIP data for B-1 are more limited than those for A-1, the results from sample B corroborate those from sample A.

The domain of AIP variables, therefore, appears to be highly promising in offering relatively specific early indicators of a liability for schizophrenia and schizophrenia-related disorders in this study, as well as in at least two other high-risk studies (Asarnow et al. 1978; Nuechterlein 1983). The relevance of AIP variables to the study of risk for schizophrenia is further indicated by other studies in our laboratory, which have shown (1) schizophrenic patients to have the same types of AIP performance deficits as subgroups of children of schizophrenic parents (Cornblatt et al. 1985) and have demonstrated that performance on AIP measures is highly heritable (in preparation).

Neuromotor Functioning. We have been interested in the assessment of neuromotor functioning in our samples because of reports by other investigators suggesting that disturbances in this biobehavioral domain may be predictors of a schizophrenia-related liability (Fish 1984, 1987). At present, however, we are uncertain about what to say concerning neuromotor disturbances and risk for schizophrenia in our samples.

In A-1, we administered three measures of neuromotor functioning (table 1). In earlier reports (Erlenmeyer-Kimling et al. 1984*b*), we noted that HR subjects as a group scored more poorly on the two tests than did the NC group and that although significant group differences were not found on the neurological examination, there was a trend suggesting greater neurological impairment in the HR group, especially among the younger males. Further examination of the data shows few differences between the HR and PC groups, and a composite measure of neuromotor deviance across the two tests and the neurological examination (derived in the same way as the composite AIP deviance score) does not differentiate the HR children from the PC and NC children. Moreover, there does not appear to be a predictive relationship between neuromotor deviance in A-1 and interim clinical outcome as measured by the Behavior Global Adjustment Scale (BGAS).

Hence, the analyses of sample A neuromotor data suggest neither specificity nor predictive validity thus far. Perhaps we need to use different criteria in examining these data. The approach to deriving a composite deviance score may not be appropriate and may be obscuring important results. It is of interest, for example, that the HR subjects who have been hospitalized or in treatment for psychiatric problems tend to have relatively poor neuromotor scores compared to the HR group as a whole (Erlenmeyer-Kimling et al. 1984*a*). Other approaches to the analysis of the neuromotor data are now being investigated to enable us to determine whether there are specific types of dysfunctions (e.g., fine motor vs. gross motor dysfunctions) that differentiate the HR from the PC and NC children and characterize a subgroup of the former.

Psychophysiology. In A-1 we included an electrodermal conditioning paradigm similar to that of Mednick and Schulsinger (1968), who had reported that those children of Danish schizophrenic mothers who were later considered to have developed psychopathology had shown a different pattern of electrodermal responses on earlier testing than that shown by other high-risk children who were considered to be well-adjusted or by children of normal parents. Rapid recovery was reported to be the measure in Mednick and Schulsinger's battery that best discriminated the high-risk subjects, although the relationship between electrodermal recovery and psychiatric outcome was later reported to obtain only for high-risk males and chiefly those with early separations from their mothers. In our study, we found (1) no relationship between half-time recovery of electrodermal responses in childhood and BGAS ratings in late adolescence or current functional status in young adulthood; (2) no differences in male and female HR subjects with respect to recovery and no association between recovery time and later clinical outcome in males examined alone; (3) no relationship between the severity of impairment of functioning of the schizophrenic parent and recovery time in the HR children; and (4) no differences in recovery time between HR children who had and had not been separated from the parental home for varying lengths of time (Erlenmeyer-Kimling et al. 1985). Thus, in our study, electrodermal recovery is not a good early indicator of a genetic liability for schizophrenia and spectrum disorders.

Event-Related Potentials. The psychophysiological procedures adopted for sample A after round 1 of testing and for sample B focused on the recording of event-related potentials (ERPs) during both auditory and visual stimulation (Friedman et al. 1982). Although earlier reports on data from both samples showed group differences between the HR

and NC groups and/or a subgroup of deviant responders within the HR group (Friedman et al. 1982), those analyses were performed only on the initial HR and NC subjects and were carried out before rediagnosis of the parents. More recent analyses of the entire set of subjects tested in A-3 after rediagnosis of the parents do not show significant differences between the HR and NC subjects and reveal little or no differentiation between the HR and PC subjects. Moreover, recently completed ERP analyses of visual ERPs do not suggest that a deviant subgroup of HR subjects can be detected in that data set (Friedman et al. 1986). Analyses of the longitudinal aspects of the sample B data may help to clarify the status of ERPs as predictors in relation to schizophrenia-proneness.

Other Measures. Two variables that we expected to be related to the children's risk, because they should be indicative of the degree of genetic loading in the ill parent, were the severity of the parent's illness and family history of mental disorders. The severity of impairment of functioning in the patient-parents was rated on the 100-point Global Assessment Scale (GAS) (Endicott et al. 1976) based on the patient-parent's hospital records. The nonpatient-parent's level of functioning was also rated on the GAS based on clinical interviews. Two independent raters (Drs. Rainer and Stone) assigned GAS scores (with an inter-rater reliability of .91), and these were averaged (table 2). Contrary to our expectation, the patient-parents' GAS scores do not relate systematically to the study children's current functional status. That is, the GAS scores of the patient-parents whose children have been hospitalized are not lower or significantly lower than the GAS scores of patient-parents whose children are currently considered to be relatively free of problems. Also unexpected is the fact that the midparent (mean value for father and mother) scores do not relate to the study children's current functional status, although there is a suggestion of a trend in this direction in the NC group. We had hypothesized that not only would the GAS scores of the patient-parents whose children are functioning poorly in young adulthood be worse than the GAS scores of the patient-parents of the higher-functioning children, but also that the same relationship would hold for the GAS scores of the nonpatient-parents. In fact, we had hypothesized that healthy nonpatient-parents might act as protective buffers for their children, environmentally and perhaps genetically. The midparents' GAS scores in table 2 suggest that this is generally not so.

Very crude family history data

Table 2. Mean parental GAS scores and percentage of subjects with definite family history on one or both sides, by group and current functional status (sample A)

Group	Current functional status	*n*	Mean parental GAS scores		Definite family history on one or both sides (%)
			Ill parent	Midparent	
HR	Hospitalized	7	36.1	52.4	71.4
	Substantial treatment	15	38.1	53.3	66.7
	Minimal treatment	9	46.7	58.6	33.3
	No problems	28	41.6	47.4	39.3
	Total	59	37.1	51.2	49.2
PC	Hospitalized	4	48.1	53.4	—
	Substantial treatment	8	36.3	52.8	50.0
	Minimal treatment	3	42.8	68.7	33.3
	No problems	25	36.0	59.4	48.0
	Total	40	47.4	58.2	42.5
NC	Hospitalized	1	—	66.5	—
	Substantial treatment	10	—	72.9	30.0
	Minimal treatment	14	—	72.2	42.8
	No problems	66	—	75.1	33.3
	Total	91	—	74.3	35.2

Abbreviations.—GAS = Global Assessment Scale. HR = high risk. PC = psychiatric controls. NC = normal controls.

were collected in the first rounds of testing. One parent in each family (the nonpatient-parent in HR and PC families, a randomly selected parent in NC families) was asked about physical and emotional or mental disorders and hospitalizations in his/her own and his/her spouse's parents, siblings, and second-degree relatives. Because of the crude nature of the inquiry, we have counted as "definite family history" only those instances in which a first-degree relative (parent or sibling) of a parent was reported to have been hospitalized for a psychiatric disorder. Thus, the relatives being classified for the tally of definite family history are the second-degree relatives (grandparents, uncles, and aunts) of the study children. By this, definite family history was found on one or both sides of the family in 49 percent of the HR families and 42 percent of the PC families (more frequently in the relatives of the patient-parent than the nonpatient parent) and in 35 percent of the NC families (often on both sides). There is some relationship between family history and the study children's current functional status in the HR group, where only 33 percent of the subjects with minimal treatment and 39 percent with no problems had a definite family history, compared to 71 percent and 67 percent of the hospitalized and substantial treatment subgroup, respectively (table 2). In the PC group, however, there is clearly no relationship between definite family history and current functional status, and for the NC group there appears to be no relationship either.

We are currently conducting more detailed inquiries into the family histories of mental illness in our subject families, so that it will be possible to assign *DSM-III* and spectrum diagnoses to affected relatives, carry out appropriate genetic analyses that take into account the number of affected relatives rather than mere presence or absence of any affected relatives, and apply appropriate corrections for sibship size and age at onset.

Possible Protective Factors

Several types of factors that might have protective value for children at risk for schizophrenia have been considered. These include a high level of functioning in the nonpatient parent, a good parent-child relationship, a good social support network in young adolescence, stability of the parental home, physical attractiveness, and high IQ. We hypothesized that a general ambiance that is low in overstimulation and conflicts may be one of the best buffers for individuals at risk for schizophrenia, but this would be very difficult to study in our sample, and, accordingly, we have not attempted to do so.

The first of these potential buffers, a healthy nonpatient-parent, does not appear to relate to the study children's current functional status, as indicated by the fact that the mid-parent GAS scores shown in table 2 are not different for the children with serious impairment than for those who are relatively free of problems. Thus, a high level of functioning in the nonpatient-parent probably does not in itself constitute a protective buffer for the child.

The IQ variable needs further examination, but thus far in our study, it appears that high IQ is not so much a protective factor as that lower IQ may be a potentiator of early emergence of psychiatric illness. We have noted that the first five HR children to be hospitalized had a mean IQ that was 11 points lower than the mean for the HR group as a whole (104) (Erlenmeyer-Kimling et al. 1984*a*), and the sixth HR subject to be hospitalized had a full scale IQ 8 points lower than the group mean. High IQs are found in several of the HR subjects who are now in the substantial treatment category, but it remains to be seen whether these subjects improve or decline further.

We have been interested in the study of protective factors because they might help to explain the relatively low rate of penetrance that is postulated according to some genetic models of schizophrenia. It is difficult to establish a given factor as protective, however, because there is no definitive way to determine that anyone, except the monozygotic cotwin of a schizophrenic person, has a genotypic liability for schizophrenia. Once truly at risk individuals can be identified in DNA studies, it will be easier to determine protective factors. In the meantime, investigators can only identify children showing what are believed to be early indicators or predictors of a genetic liability and then attempt to determine whether children in this group who experience a postulated protective factor differ in "outcome" from children in the same group who are not exposed to that factor.

Recommendations

Ongoing studies need to be completed, and the subjects in several of the studies are sufficiently old that completion can be reached within the next few years, by which time most of the subjects who are going to become schizophrenic or show schizophrenia spectrum disorders will already have done so.

But should there be new research, with new samples? New single-cen-

ter studies using the same types of subject groups that have been examined heretofore and essentially duplicating the approaches and measures of ongoing studies are unlikely to advance risk research beyond its present stage. The second-generation of high-risk studies on schizophrenia needs to be shaped quite differently:

1. New risk research should be collaborative, organized across several centers, with a common core protocol, a common set of specifications for ages of the children and other demographic characteristics, and common diagnostic criteria and practices. The problem of numerous studies with relatively small sample sizes and few shared measures would be eliminated by the collaborative approach in which data could be pooled across centers.

2. Diagnostic groups for the patient-parent should be broadened to include sufficient samples of parents (and their children) with diagnoses of schizoaffective disorder, divided into mainly schizophrenic vs. mainly affective, and schizotypal personality disorder, as well as schizophrenia, to allow for comparison of the children of parents with these different diagnoses.[2] Without a multicenter collaborative effort, it would be very difficult to fill the several cells with numbers sufficient for meaningful comparisons.

3. More attention needs to be paid to possible diagnoses in the nonpatient-parent. There is sufficient evidence of assortative mating between persons with psychiatric disorders and persons with personality disorders to lead to the expectation that many of the nonpatient-parents in studies of children at risk for schizophrenia have personality disorder diagnoses. Thus, it is essential to examine the nonpatient-parents to understand what they are contributing to the increase or diminution of risk in the children.

4. Collaborative high-risk research should take advantage of the major advances that have been made in population genetics with the development of highly sophisticated methods for the analysis of family data and in molecular genetics with the new ability to study DNA and to map the human genome. By careful collection of family history data and establishment of pedigrees, the collaborative study would be able to develop differential risk estimates for each study child, based on his/her family history (relatives from both sides of the family and nonpatient-parent diagnoses), which would substantially increase prediction. Moreover, the collaborative study could supply a number of pedigrees, which would be difficult to obtain in appreciable amounts in any one center and which could be studied with restriction fragment-length polymorphism (RFLP) techniques in the search for a DNA marker (or markers, if schizophrenia is genetically heterogeneous or multifactorial). Establishment of DNA markers would mean that children at true genetic risk could be identified at the very early ages at which intervention strategies might be most appropriate.

5. The collaborative study would be highly appropriate for exploring preventive intervention strategies. It would be possible, for example, to commit relatively small numbers of subjects from each center to a given prevention approach and still have sufficient subjects across centers to be meaningful. What kinds of interventions? The AIP data from the New York High-Risk Project and other high-risk studies suggest that interventions focused on correction of AIP deficiencies at young ages could be useful. Strategies of cognitive intervention (e.g., Kendall and Hollon 1979) could be tried. Other data suggest that working with the social competence of the children or stress reduction of various kinds could be useful areas in which to develop intervention strategies.

Although we do not see new single-center studies that chiefly duplicate existing studies as being advantageous to the further clarification of risk for schizophrenia, we see a definite future for collaborative high-risk research along the lines suggested.

[2]Of course, an affective disorder comparison group needs to be retained also, and it would be advantageous if sufficient numbers of children of both unipolar and bipolar disorders could be examined, so that these groups could be compared separately to the children of parents with schizophrenia and related disorders.

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