Overview and Summary: Twenty-Five-Year Followup of High-Risk Children

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Abstract

We report a 25-year followup of a group of 50 children at genetic risk for schizophrenia (by virtue of having a parent with the disorder) and 50 matched controls. The children who eventually developed schizophrenia spectrum disorders, including schizophrenia, were identifiable by cognitive-psychophysiological, neurointegrative, and social/personality traits in the preteenage period. The children at risk were also more likely to develop other Axis I disorders, chiefly affective. Moreover, the risk of Axis I disorders was significantly greater among children raised in the group atmosphere of a kibbutz than among those raised in their own nuclear families in cities and towns in Israel. The study is a unique contribution to knowledge of factors underlying the development of psychopathology.


In 1985 a progress report was presented on a unique longitudinal followup study of children at risk for the development of schizophrenia: the National Institute of Mental Health (NIMH) joint study by the United States and Israel, known as the Israeli High-Risk Study. The study was designed as an investigation of the relative contributions of genetic and environmental factors in the etiology of the disorder. Virtually all of Vol. 11, No. 1, 1985, of the Schizophrenia Bulletin was devoted to that report, which included evaluations conducted at ages 11 and 17 in addition to a 15-year followup at age 25-26. Several articles in the current issue of the Bulletin are devoted to a 25-year followup on the same group of children, who are now in their early to mid-thirties.

This project began between 1964 and 1966, when the probands were being selected. However, the planning for the study by David Rosenthal began as early as 1961-62 and was facilitated by a sabbatical year for Rosenthal, part of which he spent in Israel. Rosenthal invited one of us (A.F.M.) to study attention in the probands in 1962. When this issue of the Schizophrenia Bulletin is published, it will have been 32 years after the study was conceived by Rosenthal.

The Israeli High-Risk Study began in 1964, a time when excitement about genetic studies in schizophrenia was beginning to affect many investigators. At or about that time, the landmark research of Heston (1966), Kety et al. (1968), Mednick and Schulsinger (1968), and others was either being planned or under way, using in some instances the excellent national health records in Scandinavian countries. Somewhat later, in 1971, Erlenmeyer-Kimling et al. (1984) began their New York High-Risk Project.

The concept behind a longitudinal high-risk study, namely, following a group of children at genetic risk for schizophrenia until they enter the age of maximum risk and beyond, is not unique. The virtue of such a study is that it permits the early identification and tracking of variables that might interact with the schizophrenia...
phrenic diathesis to produce a disordered phenotype. In *Children at Risk for Schizophrenia*, there were reports from at least 10 groups of investigators (the high-risk consortium) with that goal (Watt et al. 1984). In at least three of the projects, data were still being collected as of 1991–92: the Israeli High-Risk Study, the New York High-Risk Project (Erlenmeyer-Kimling et al. 1984), and the Jerusalem Infant Development Study (Marcus et al. 1984). Progress reports on some of the remaining projects appeared in Vol. 13, No. 3, 1987, of the *Schizophrenia Bulletin*, and Asarnow (1988) presented a summary of the status of these studies as of 1988.

In the present instance, the fortunate circumstance of the project's location in the NIMH Intramural Research Program afforded a certain degree of long-term stability. Nevertheless, each of the four NIMH intramural research directors during the period 1964–92 had to be sanguine enough about the value of the endeavor to see it continue.

The NIMH–Israeli study was unique in that it capitalized on a child-rearing circumstance found nowhere else in the world—the children's house in the Israeli kibbutz. This method of child rearing owes much to the utopian orientation of the early kibbutz movement. A professional child care worker, or *metapelet*, is responsible for the rearing of the young in a communal children's house and for providing a consistent, stable environment. Most of the children's day is spent in the communal setting, although they usually spend part of the day with their parents. This group experience prepares the children for later communal living and also frees the mother for other occupations and activities.

At the time the study was conceived in the 1960s, theories of the etiology of schizophrenia emphasized heavily the role of the dysfunctional family environment in which the offspring of parents with schizophrenia were raised (Lidz et al. 1957, 1965; Wynne et al. 1958; Wynne 1967, 1968, 1972; Lidz 1972), and promoted the view of the schizophrenogenic mother (Mahler 1952; Mahler et al. 1954). Alternative views, emphasizing the importance of genetic factors, were beginning to be expressed (e.g., Gregory 1960; Shields and Slater 1961), but most research to that point was based on either small samples or samples in which genetic and environmental factors were confounded. Family, twin, and adoption studies would ultimately provide clear evidence of the salience of heredity in the disorder (Gottesman 1990). Rosenthal saw the possible relevance of the kibbutz child-rearing experience for what he labeled the nature-nurture debate about the etiology of schizophrenia. He designed a study that would take advantage of this particular social circumstance: it would be necessary to identify a sample of children at genetic risk (because they had a parent with schizophrenia) who were being raised on kibbutzim and to follow their development over time. Rosenthal theorized that the stability and continuity afforded group-raised children at risk for schizophrenia would have a measurable impact on their development. Such children might be less likely than those raised in their nuclear families to suffer the frequent absences and unpredictable behavior of a mentally ill parent. In this way, the capacity of these vulnerable children to grow and develop normally should be modified, possibly in a favorable direction.

Although the project was conceived initially by Rosenthal, it would not have been possible without the wisdom and influence of the major Israeli collaborator, Shmuel Nagler of the Child Guidance Clinic, Oranim Teachers' College, Tivon, Israel. The kibbutz movement has been the focus of many sociological and psychological studies, but it is very protective of its members. Nagler was able to convince the members of individual kibbutzim of the importance of the proposed study, not only for the scientific world in general but for the kibbutz movement itself. Nagler also sounded a note of caution in his warning in the *Schizophrenia Bulletin* that a firm prediction of the outcome of the study could not be made.

Thus, ... the kibbutz structure ... might have a detrimental effect on the development of children of schizophrenic parents. In such a small, closely knit community, it might be more difficult than in a city or town to keep knowledge of mental illness in the family; parents' bizarre behavior in public might induce feelings of embarrassment and shame in children. Unlike the child in town, the kibbutz child has to stay with his classmates day and night without any possibility of escape. [Nagler and Mirsky 1985, p. 25]

Many Israeli colleagues, whose names appear as authors of articles in the 1985 *Bulletin*, were enlisted by Rosenthal and Nagler to join the enterprise. Summaries of the project design are contained in Nagler and Mirsky (1985), Nagler (1985), and Silberman and Mirsky (1985). In brief, the project involved the assessment of a large
number of clinical variables (including soft neurological signs), observational variables, and objective variables in the four groups of 25 children: the kibbutz index (KI), the kibbutz control (KC), the town index (TI), and the town control (TC) groups. They would be evaluated at regular intervals before and after they entered the period of maximum risk.

To summarize, there are alternative predictions as to the effects on the vulnerable (index) child of growing up in a kibbutz. On the one hand, it is a highly protected, highly organized living arrangement that provides security for the physical needs of the kibbutz members. Only minimal disruptive effects should be expected because of a parent's hospitalization and/or exacerbation of illness. The metapelet provides consistency, which might be a particular advantage for the children of parents with schizophrenia. One might also reasonably expect that growing up in the ideal (or idealized) environment of a kibbutz would act to mitigate, at least partially, the effects of such factors as communication deviance (Singer and Wynne 1966) that have been described in families that have a member who has schizophrenia. The KI cases would therefore be more likely to develop normal personalities than the TI cases.

To execute a satisfactory research design, it would be necessary to recruit children from four groups of families: vulnerable (or index) cases being raised on kibbutzim, similar cases from nonkibbutz environments (i.e., cities and towns in Israel), and control families from both types of environments. The outcome of the two groups of vulnerable children could then be compared after they had entered into the age of maximum risk for the disorder. Four groups of 25 children each, matched in terms of age and sex, were to be studied. While this design did not have the power of the adoption study (in which the offspring of parents with schizophrenia are raised by parents who do not have schizophrenia) it would permit at least partial unconfounding of the effects of nature and nurture.

Arje Latz, the Israeli psychologist who conducted the 15-year followup studies, has pointed out that there may have been more variability within the two environments (and possibly some overlap between the kibbutz and nuclear family environments) than the designers of the study intended. As a result, some metapelets may have been the mothers of some of the kibbutz subjects, thus affording those subjects additional maternal contact; furthermore, kibbutz parents varied in the amount of involvement with their children, so that "family time" in the kibbutz was not the same for all. Moreover, some TI cases were cared for by others from time to time, especially when a mother was hospitalized (A. Latz, personal communication, September 1993). Nevertheless, the two rearing environments appear mainly to differ substantially in the type of socialization and parental contact they afforded.

Conformity to kibbutz norms is greatly encouraged, and deviant or odd behaviors are not tolerated well. The data from the first and second round of interviews, conducted in 1968 and 1973, provided numerous instances of the ways in which index children differed from controls and could therefore be considered odd. The differences involved virtually every area of functioning and included soft neurological signs such as clumsiness, poor left-right orientation, and motor overflow (Marcus et al. 1985b); impaired visual-motor coordination and greater distractibility (Lifshitz et al. 1985); lower sociometric rankings by their peers (Sohlberg and Yaniv 1985); and impaired interpersonal relations, work and play activities, self-esteem, and mood (Nagler and Glueck 1985). It seems likely that such differences could contribute to the impression of oddness in the index children, would be exacerbated in the hot-house environment of the kibbutz, and would add to their feelings of isolation and loneliness. These issues are discussed in Nagler and Mirsky (1985).

Of interest in this regard is the narrative account of contacts with two female index children, one growing up in a kibbutz and the other with her own family (Bonwit 1985). Both subjects (as young teenagers) were identified by Nagler in his interviews as having problems with interpersonal rela-
tionships and as showing paranoid trends, thinking disturbances, and difficulties with speech or language. However, their adult outcomes were very different. The kibbutz-raised subject was diagnosed in 1981 as having dysthymic disorder and in 1989 as having lifetime-major depression, whereas the town-raised subject had no diagnosis at either assessment. The outcomes seen with these two women obviously do not constitute proof of a potentially noxious effect of the kibbutz atmosphere in vulnerable children, but they do encourage detailed examination of environmental circumstances and the role of interpersonal stressors in the development of psychiatric disorder.

An additional, possibly unique source of stress for the kibbutz-raised index child lies in the forced conformity and intolerance for deviation involved in the mandatory military experience. Moreover, kibbutz-raised children are expected to excel as soldiers and to volunteer for the most hazardous assignments (Amir 1969a, 1969b). Persons raised on kibbutzim, in fact, constitute a disproportionately high part of the officer corps in the Israeli Defense Forces, in view of their numbers in the population of Israel (Spiro 1958; Kaffman 1978). The termination of the military experience leads to another stress for all kibbutzniks, which may be heightened for the index cases: they must decide whether to remain in the kibbutz or to seek employment and/or education outside the kibbutz. Nathan et al. (1993) discuss, in part, the probands’ memories of adolescence and the army experience and the differences between index cases with and without diagnoses.

To recapitulate, this article summarizes the results of the 25-year followup of a cohort of 50 at-risk (index) children and 50 matched controls, whose average age was 11 years at the time of their first assessment. There were 46 boys and 54 girls in the cohort. The 50 index children were all offspring of Israeli parents (38 mothers and 12 fathers) who had been diagnosed as having schizophrenia. The controls were classmates of the index children, matched to the index member of the pair by sex and, as nearly as possible, age. Half of the index children and their matched controls were born and raised on kibbutzim; half were raised in their nuclear families in cities and towns throughout Israel. The possible interaction of the circumstances of kibbutz life with the schizophrenic diathesis was the crux of this investigation’s design.

The material we are presenting in this issue of the Bulletin represents a 25-year followup of the cohort originally identified in about 1964 and first assessed in 1966. The test and interview data we present were gathered during the years 1989 and 1990, for the most part, although some information was added as late as the summer of 1991.

Three major themes tie together the studies presented in the articles of this issue: diagnostic outcome, behavioral assessments, and parental rediagnoses.

First, our initial result with respect to diagnostic outcome was that considerably more cases with a diagnosis of psychopathology (including six of the nine schizophrenia spectrum cases) were found in the KI group than in all the remaining groups combined. This result seemed to support the guarded prediction made by Nagler quoted earlier. The degree to which that result had been sustained or modified by the incidence of new cases over the ensuing 8-9 years was obviously of great interest. Therefore, the question arises whether there has been (since the 1981 assessment) an addition to the number of persons who have been identified as suffering from schizophrenia, schizophrenia spectrum disorders, or other Axis I or Axis II disorders. And closely related to that question, how are the new cases, if any, distributed throughout the four groups (KI, KC, TI, and TC)? This theme is the focus of the article by Ingraham et al. (1995, this issue).

Second, numerous behavioral assessments were conducted in 1966, 1972, and 1981. Most of these assessments suggested inferiority in measures of personality, cognition, and neurointegrative organization in the index cases. The question of interest is whether these differences (to the extent that they could be reassessed) existed in 1989-91. This issue was pursued extensively in the 25-year assessment and is the theme of the articles by Frenkel et al. (1995), Ingraham et al. (1995), Kugelmass et al. (1995), and Mirsky et al. (1995) (all in this issue) and Nathan et al. (1993).

Third, questions were raised about the initial selection of the proband parents. It was suggested that some of the parents were misdiagnosed as having schizophrenia, and that they were in fact suffering from schizoaffective or even affective disorders. This criticism stems from the identification of 11 persons with affective disorders (versus 9 with schizophrenia spectrum disorders) among the 90 probands (Mirsky et al. 1985). We
sought to rediagnose as many as possible of the parents of the probands by using DSM-III-R (American Psychiatric Association 1987). These rediagnoses and criteria are presented in the article by Ingram et al. (1995, this issue).

The earlier findings from this longitudinal investigation were published in a series of papers in Vol. 11, No. 1, 1985, of the Schizophrenia Bulletin; some additional analyses derived from the data of the first assessment appear in Mirsky (1988). The information presented here was gathered during 1989-91, when the probands were in their early thirties. The data gathered include neuropsychological assessment, with special emphasis on measures of attention; diagnostic studies (using the Schedule for Affective Disorders and Schizophrenia—Lifetime version [SADS-L; Endicott and Spitzer 1978]) of the probands and of their parents; and measures of locus of control. In addition, some previously unpublished data, collected for the most part at the second assessment (age 17), are presented. These latter data are concerned with cognitive (attention) behavior, personality variables, and electrodermal activity (EDA) considered from two standpoints: as a means of characterizing the at-risk children (i.e., differentiating them from the control children) and as predictors of later psychopathology.

Issues

Three major themes or sets of issues emerged from the 1981 followup and the available data from the 1966 and 1973 assessments that were published in Vol. 11, No. 1, 1985, of the Schizophrenia Bulletin. These themes are (1) diagnoses of the probands, (2) cognitive/personality/psychophysiological characteristics of the index versus the control subjects, and (3) diagnoses of the parents. The discussion of the results around these themes forms the basis of this report.

Diagnoses of the Probands. We wished to know whether additional cases of neuropsychiatric disorder had developed among the cohort of 98 subjects (of the original group of 100) who were alive or traceable in 1989-90. If there were additional instances of disorder, their distribution among the four groups (KI, KC, TI, and TC) of the study was of paramount interest. We wished to know, further, whether the prior diagnoses (as of 1981) were still applicable to the subjects that were rediagnosed in 1989-90. These are the core questions of the investigation, since they relate to the possible protective (or damaging) effects of kibbutz rearing on the long-term development of these genetically vulnerable children.

To review, in our first assessment of the probands as adults in 1981, they were on the average 26 years old, well into the age range of maximum risk for developing schizophrenia. We were able to interview 90 of the cohort, 87 of them in Israel, and to derive a DSM-III (American Psychiatric Association 1980) diagnosis for them based on the SADS-L (Mirsy et al. 1985).

The KI group had the highest incidence of psychiatric disorder. Of the 23 interviewed, 16 had a DSM-III diagnosis distributed as follows: 2 schizophrenia; 1 other schizophrenia spectrum; 1 major affective; 0 minor affective; 3 other diagnosis; and 7 no diagnosis. Corresponding numbers for the 23 members of the TI group, which had a total of 7 diagnoses, were as follows: 2 schizophrenia; 1 other schizophrenia spectrum; 1 major affective; 0 minor affective; 3 other diagnosis; and 16 no diagnosis. There were a total of 4 minor diagnoses for the combined control groups (1 minor affective and 3 other) and 40 control cases with no diagnosis. We obviously could not conclude from this result that the kibbutz environment was associated with significantly more schizophrenia than the nuclear family (i.e., TI) environment; nevertheless, the total amount of psychopathology (16 of 23, or 70% with a psychiatric diagnosis) in the KI subjects was impressive. Moreover, the high incidence of affective disorders (nine in the KI group vs. one in the TI group) suggested that the stresses of the kibbutz environment could interact with the schizophrenic diathesis and be expressed as an affective rather than as a schizophrenia spectrum disorder. Possible misdiagnoses of some of the parents of the probands (i.e., as having schizophrenia rather than a major affective or schizoaffective disorder) could have led to this result as well; this alternative explanation (which is not supported by the data) is discussed in another section of this article. It should be noted, however, that Erlenmeyer-Kimling and associates have also found a high incidence of affective disorders in their long-term followup of the offspring of parents with schizophrenia in their New York study (Erlenmeyer-Kimling and Cornblatt 1987; Moldin et al. 1990a, 1990b; Erlenmeyer-Kimling et al. 1991).
a variety of phenotypic expressions of the same genotype.

In the second round of assessments of the probands as adults, we were able to reinterview 82 of the original 100 probands and collect new information on 3 others. Therefore, 98 of the 100 probands were interviewed at least once in the interval between 1981 and 1989–91 (i.e., 15–23 years after their original assessment as children). In the 1989–91 round, we discovered no new cases of schizophrenia or other schizophrenia spectrum disorder. As in the 1981 assessment, all such diagnoses were found among the index subjects. Also as in the 1981 diagnostic assessment, there was an excess of major affective disorders (6%) among the KI cases. In comparison to the 1981 assessment, when there was a combined total of 11 major and minor affective (lifetime) diagnoses, we have now identified more than twice as many persons with such disorders—25—14 of whom are found in the index groups. The large increase in the number of such diagnoses is found among the control subjects: from 1 in 1981 to 11 in 1989–91. The lifetime prevalence figures for combined affective disorders in this population (i.e., 28% among the index cases and 22% among the controls) appear to be comparable to those found in surveys elsewhere (Weissman et al. 1988; Blazer et al. 1994). For total diagnoses, the figure is 17 of 25 (68%) of the KI group, 15 of 25 (60%) of the TI group, and 7 of 24 (29%) for each of the two control groups. On the average, therefore, the lifetime risk (as assessed for subjects in their early thirties) for any psychiatric disorder among the index cases is twice that of the controls. However, if we confine the comparison to the putatively more severe (Axis I) disorders, the combined risk in the KI group is 11 of 25 (44%) versus 4 of 25 (16%) in the TI group and 4 of 48 (8%) in the pooled control groups. The comparison between KI and TI groups is significant at \( p = 0.031 \) and between the KI and the pooled control groups at \( p = 0.0007 \) (Fisher’s exact test). We conclude, therefore, that kibbutz rearing in vulnerable children increases the risk of their developing a severe form of psychiatric disorder, although not necessarily schizophrenia.

Cognitive/Personality/Psychophysiological Comparisons of Index and Control Subjects. The characterization of the vulnerable person—or, stated somewhat differently, the search for vulnerability markers—is a salient issue in recent research on schizophrenia (Zubin and Spring 1977; Spring and Zubin 1978; Zubin and Stein-hauer 1981; Steinhauer and Zubin 1982). This interest has often involved studies of offspring of schizophrenia patients (Grunebaum et al. 1974; Herman et al. 1977; Nuechterlein 1983; Rutschmann et al. 1986). However, the parents of these probands (and possibly the probands themselves) represent a particular (possibly a less severely ill) subgroup of all persons with schizophrenia, by virtue of their being able to marry and sustain a family.

There is presently an emphasis, as well, on the study of all first-degree relatives of schizophrenia patients (e.g., Mirsy et al., in press). Such studies have the potential to broaden our view of what constitutes vulnerability markers, and they may be less subject to the criticism that the disorder is less severe in these subjects.

In the present investigation, we have identified an extensive series of characteristics of the index cases that differentiated them (at ages 11 and 17) from the controls. Consequently, we supplement the data from the recent assessment, as follows:

1. Index cases were impaired in virtually all examined areas of psychosocial function, including interpersonal relations, work and play activities, self-esteem, and mood (Nagler and Glueck 1985). As adults, the index cases show the same type of impairment: this is manifest in the locus of control measure (Frenkel et al. 1995, this issue), and in their memories of their army experiences (Nathan et al. 1993).

2. Index cases at age 11 showed a significantly lower level of arithmetic proficiency, arithmetic achievement, perceptual-motor functioning, and overall cognitive functioning. They also showed impairment in several specific verbal and thought patterns and in concentration; were more withdrawn; and had a lower social status than controls, as viewed by their peers (Sohlberg 1985; Sohlberg and Yaniv 1985).

3. Index cases at age 11 showed a trend toward slower EDA recovery (i.e., in the direction of hyporausal) versus controls (Kugelmass et al. 1985). However, subjects who would later be diagnosed in the schizophrenia spectrum had an unexpected hyperresponsive skin conductance orienting response to the dishabituation tone in a habituation series (Kugelmass et al. 1995, this issue).

4. Index cases showed poorer
visual-motor coordination and were more distractible in the performance of an attention-cancellation task than controls (Lifshitz et al. 1985). We found trends in this same direction in our neuropsychological assessment of attention in the subjects when they were tested as adults (Mirsky et al. 1995, this issue).

5. Index cases showed a variety of "soft" neurological signs, most commonly involving the following categories: perceptual-sensory, motor coordination, left-right orientation, balance, and motor overflow (Marcus et al. 1985b).

6. Index children were ranked by observers as impaired relative to controls in communication skills, ability to relate to examiners, and motor behavior (Nagler et al. 1985).

7. Index children, as rated by their parents, were more likely than controls to have developed psychopathological symptoms related to mood, social withdrawal, antisocial behavior, eating, and obsessive-compulsive behavior. They also showed poorer self-esteem, adaptability, reliability, task orientation, and relations with family members (Shotten 1985). The studies reported in this issue and elsewhere concerned with personality variables appear to confirm the earlier descriptions of the index cases. Thus, as adults the index cases have less of a sense of coherence, particularly those with a diagnosis (Nathan et al. 1993).

8. Index children, as rated by their teachers, showed impairment or were rated as more disturbed in comparison with controls in school work, mood, suspiciousness, daydreaming, antisocial behavior, hypochondriasis, and accident proneness (Ayalon and Merom 1985).

It is daunting to try to condense all of these characteristics into a few simple summary statements. However, the themes that seem to thread through many of the descriptors are concerned with (1) attention and/or concentration, (2) motor function and perceptual-motor integration, and (3) social adaptation and self-esteem. We shall discuss each of these in terms of the results of our long-term study and relevant research by other investigators.

The strategy that we have followed in this investigation permits us to address the question of vulnerability markers in several ways. We can follow back the data on subjects who later developed schizophrenia or a so-called schizophrenia spectrum disorder to see which of our psychological variables (assessed when the subjects were children or adolescents) correlates highly with psychiatric outcome as adults. We can also assess the characteristics of index cases who did not develop a disorder, to see the extent to which there are trait markers (or environmental circumstances) that characterize these more fortunate persons. The latter (environmental) issue obviously converges on the first major theme—kibbutz versus family rearing—of this series of articles.

**Attention and/or concentration.**

The analyses that we have conducted with respect to vulnerability markers were reported originally in Mirsky (1988). This information (i.e., the significant prediction of later schizophrenia spectrum disorders) indicated that poor attentional skills (on a digit cancellation task) in the preteen to early teenage years (average age 11) were highly correlated with the development of schizophrenia spectrum disorders in adulthood. Scores on the same task administered to the subjects when they were in their late teenage years (average age 17) were less successful as predictors, possibly because the task was not sufficiently effortful as the cohort became older.

These data are consistent with the results of numerous other studies of the cognitive capacities of first-degree relatives of patients with schizophrenia. Most of these data have been concerned with attentional variables, and the usual subject population consists of the offspring of parents with schizophrenia.

The typical finding in those studies (Grunebaum et al. 1974; Gamer et al. 1977; Herman et al. 1977; Nuechterlein 1983) is that the children of persons with schizophrenia are more impaired on attention tests than the children of control subjects. In some of these studies, the controls also comprised children of persons with nonschizophrenic, major psychiatric disorders (Erlenmeyer-Kimling and Cornblatt 1978; Cornblatt and Erlenmeyer-Kimling 1985; Rutschmann et al. 1986). This research has suggested that impaired attention in children at risk for schizophrenia may represent a biobehavioral marker for the disorder. Since various versions of the Continuous Performance Test (CPT; Rosvold et al. 1956) have been the measure of attention in most of these studies, and since elsewhere we have argued that the CPT is a measure of the capacity to sustain attention (Mirsky et al. 1991), these studies suggest that relatives of persons with schizophrenia may share that aspect of the attention deficit seen in schizophrenia patients. Similar impairment was reported in the brothers of male schizophrenia patients by Steinhauer et al. (1991).
Recently we have presented data from a rural sample in western Ireland that confirm the presence of moderate degrees of deficit—in a number of aspects of attention—in the first-degree relatives of persons with schizophrenia (Mirsy et al., in press).

In this issue, we present new information, obtained in 1989–91, on the performance of the index and control cases on attention tasks (Mirsy et al. 1995, this issue); we supplemented that information with scores obtained from schizophrenia patients and normal controls who were participants in NIMH research protocols. The results indicated that the KI and TI groups tended to perform at levels between those of the combined control group (including the KC and TC groups) and the NIMH schizophrenia patients (figure 1, Mirsky et al. 1995, this issue). The result was due largely to the poor scores of the schizophrenia patients, since there were only small differences between the mean scores of the combined index and control subjects. This somewhat disappointing result is likely due to the fact that we were unable to test 12 key index subjects: 7 of 9 schizophrenia spectrum cases and 5 of 10 affective disorder cases as diagnosed in the prior (age 26) assessment. Another contributing factor may be the relatively benign expression of the disorder in the parents of the probands and therefore in the probands themselves (i.e., all the parents with schizophrenia were married, had relatively stable family situations, and may therefore have had late-onset schizophrenia).

Nevertheless, the results are in the expected direction; index cases show reduced attentional skills in comparison with the matched controls. This outcome confirms the persistence into adulthood of an attentional deficit in these offspring of schizophrenia patients that was identified initially when these subjects were 11 years of age.

We add to this review a summary of the results of the reanalysis of the EDA data, from both the age-11 and the age-17 assessments (Kugelmass et al. 1995, this issue). Those probands who would develop schizophrenia spectrum or affective disorders at age 26 were classified as hyposponsive as preteens and teenagers. Unlike the results obtained with the attention/distraction test, in which the poorest scores were obtained by those children who would later be diagnosed as having schizophrenia spectrum disorders, the least responsive subjects at age 11 were the probands who would later be diagnosed as having affective spectrum disorders. The differences among groups were less pronounced at the age-17 EDA assessment.

These results suggest that, as indices of vulnerability, the attentional and EDA/arousal measures are predictive of differing types of psychopathological development within an at-risk population. Ultimately, it may be possible, to develop a profile of vulnerability markers that would predict different outcomes and involve specific remedial and/or preventive strategies.

Motor function and perceptual-motor integration. The studies bearing on motor function and perceptual-motor integration were conducted almost entirely during the first two assessments of the cohort (i.e., when the subjects were 11 and 17 years of age, respectively) and were reported in Marcus et al. (1985a, 1985b).

The findings with respect to motor function and perceptual-motor integration appear, in general, to support the view of Fish and colleagues that there may be a genetic neurointegrative deficit in the offspring of persons with schizophrenia. This condition, which Fish has labeled pandysmaturation, is detectable in infancy and is marked by erratic growth of visual/motor and skeletal systems (Fish 1977; Fish et al. 1992).

It is not clear whether the attentional deficit described in the previous section is the result of the same putative neurological brain disturbance that gives rise to the motoric symptoms of pandysmaturation or whether it stems from an independent pathophysiological cause. Motor and attentional disturbances could represent the sequelae of early injury (by asphyxic insult or other cause) to reticular formation of the brainstem's integrating systems that regulate postural, motoric, sensory, and arousal functions (Hobson and Brazier 1980).

Social adaptation and self-esteem. On the basis of the data reported in Vol. 11, No. 1, 1985, of the Schizophrenia Bulletin, the profile of the index child in this study (at age 11 or at age 17) might be epitomized as follows: he or she was an antisocial person; did not get along well with parents, teachers, or peers; was rated low in social desirability; and had poor communication skills. In addition, the child was hypochondriacal, accident prone, and a daydreamer. In considering the nine probands who later developed schizophrenia spectrum disorders (in terms of 1981 diagnoses) versus those with major
or minor affective disorders, some striking differences emerged. The profile of the individual described above pertains more to the schizophrenia spectrum cases than to the affective cases. The latter, in contrast, were seen as friendly, bright, engaging, eager to please both teachers and examiners, and in some ways more appealing and engaging than the children who developed no disorder. The future affective disorder cases in fact had the highest IQ scores of any of the groups (including subjects who had not developed a disorder by 1981).

This analysis is based primarily on the 1981 psychiatric outcome assessment (when the subjects were on the average 26 years old) and was presented earlier in Mirsky (1988).

In a recent article by Hans et al. (1992), the interpersonal behavior of the children in this study during development is reviewed and compared with that of another Israeli cohort of vulnerable children, subjects of the Jerusalem Infant Development Study (Marcus et al. 1981). The authors conclude that "the two high-risk studies ... replicate one another around the following findings: ... children at genetic risk for schizophrenia are also at risk for interpersonal behavior problems during middle childhood, particularly social withdrawal" (Hans et al. 1992, p. 332).

In a general sense, the additional measures reported for the first time in this issue of the Schizophrenia Bulletin appear to support and illuminate the earlier findings related to social adaptation and self-esteem. Index cases tended to score in the more pathological direction on measures of locus of control and sense of coherence (Nathan et al. 1993; Frenkel et al. 1995, this issue). Index cases (if they had a diagnosis) also had more painful memories of their adolescence (including peer group experiences, sexual experiences, and familial relationships) and of their time in the army (Nathan et al. 1993). An interesting finding emerged with respect to the sense of coherence variable: the highest values obtained by any group, including control subjects free of diagnoses, were found in the index cases who were free of any diagnosis in 1989–91. This result suggests that such a positive self-esteem variable may be a protective factor in subjects at risk for development of a psychiatric disorder. To this result may be added the possibility that higher IQ scores serve to some extent as a protective factor in the development of an affective disorder rather than a schizophrenia spectrum disorder.

Diagnoses of the Parents of the Probands. In the diagnostic assessment conducted in 1981, in which 90 of the probands were interviewed, we found that there were 5 subjects with a diagnosis of schizophrenia and 4 with a diagnosis of other schizophrenia spectrum disorders (Mirsky et al. 1985). This is the expected outcome, more or less; 10 to 15 percent, or 5 to 8, of the offspring of schizophrenia patients would be expected to develop schizophrenia (Gottesman 1991). In addition, however, 11 subjects were identified with affective disorders, 10 of whom were index cases. Moreover, as reported by Ingraham et al. (1995, this issue), the 1989–91 assessment found 25 persons with major or minor affective disorders, 14 of whom were in the index groups. These findings raised the question of possible misdiagnoses of the parents when they were selected in the period when the study was being planned in 1964–66. Is it possible that some of them did not, in fact, have schizophrenia but were suffering from schizoaffective or even affective disorders?

We pointed out in the earlier article that there were few data to support the notion that the probands with affective diagnoses had parents with primarily affective symptoms (Mirsky et al. 1985). The parents of the probands with affective diagnoses had fewer (although not statistically significant) manialike symptoms than parents of probands with schizophrenia-spectrum diagnoses. Moreover, these parents were far less likely than the parents of the schizophrenia-spectrum probands to have the symptom of inappropriate affect (p < 0.01) or catatonia (p < 0.001) listed in their original diagnostic workups. A further argument in favor of the accuracy of the original diagnoses is that (as noted in the earlier report) the parents were diagnosed initially as having schizophrenia by a variety of criteria and methods prevalent in Europe 35 to 45 years ago. At that time, European criteria were more restrictive than those used in the United States.

Nevertheless, to reinforce the validity of the original parental diagnoses and to bring them into conformity with those used with the probands, we sought to rediagnose as many as possible of the parents, using the modern diagnostic criteria of DSM-III–R.

As reported by Ingraham et al. (1995, this issue), the diagnosis of schizophrenia in the parents, based on DSM–III–R criteria that were not in existence in 1964–66, is in
most instances confirmed. Moreover, affective symptomatology in index parents was unrelated to the diagnosis of affective disorders in index probands.

These data confirm the findings that we reported earlier (Mirsky et al. 1985): that the risk for psychiatric disorder in the offspring of parents with schizophrenia is not restricted to the development of schizophrenia or other spectrum disorders; it extends to other Axis I (DSM-III-R) disorders as well, including, but not limited to, major affective illness. As noted earlier, a similar outcome has been reported in the New York High-Risk Project (Erlenmeyer-Kimling and Cornblatt 1987; Moldin et al. 1990a, 1990b; Erlenmeyer-Kimling et al. 1991). Our findings, as well as those of the New York group, must be taken into account in the development of theories about the genetic transmission of psychiatric disorder.

Comment

This series of reports marks the final involvement of the NIMH Laboratory of Psychology and Psychopathology in data gathering in the Israeli High-Risk Study. It would no doubt be valuable to continue to collect information on the life course of these subjects, particularly in view of the fact that schizophrenia can occur up to the seventh decade of life (Gottesman, personal communication, April 1993). And it is likely that some additional studies will be published on this cohort of subjects, since it was not possible to complete all analyses in time for the deadline set for preparation of this issue of the Schizophrenia Bulletin. However, it has become increasingly difficult to secure support for this work. Biochemical, neuroimaging, molecular-genetic, and other such approaches to schizophrenia are currently more fashionable, and it may well be that the hard-wrought behavioral data we report here will be regarded in the future as epiphenomena. Although that view is unlikely, it would be difficult now to try to enlist a team of young behavioral researchers whose interests in the project will not have flagged in 20-30 years. In addition, in the last round of interviews and tests with these subjects (1989–91), a certain degree of ennui or impatience was evident in many of them; some refused to participate or were unwilling to agree to have their parents interviewed or both. Such considerations tend to discourage the notion of further contact.

Nevertheless, we are extremely grateful to all the subjects for allowing us to study them over this 25-year period and permitting us to bring these findings to the scientific community. Special thanks are due to the members of the 26 kibbutzim for their continued participation, which is particularly commendable in view of our results, first published in 1985, suggesting that life on the kibbutzim may present special difficulties for vulnerable children (Nagler and Mirsky 1985). The results of our diagnostic outcome studies, modified to some extent on the basis of the 1991 as compared with the 1981 interviews, have added support for the concept that the development of genetically based disorders may be influenced by environmental circumstances during childhood. It is important to note that we are not referring to parental attitudes and behavior; the children in the TI group had significantly fewer psychopathological diagnoses than those in the KI group, although they had a more intense exposure to their parents, including the one with schizophrenia, during development.

This study can never be replicated, since the conditions in Israel and in the kibbutzim have changed radically since the present cohort were raised (i.e., since the period 1950–70). The number of kibbutzim and kibbutz residents is decreasing (Kaffman 1978). Contact between children and parents on kibbutzim is generally much more frequent and more extensive; consequently, the differences between kibbutz rearing and town rearing appear to be less salient than they were 20–40 years ago. We consider that the information we have gathered is a unique and invaluable contribution to the understanding of the etiology of schizophrenia and other major mental illnesses, and we are grateful to the editors of the Schizophrenia Bulletin for the opportunity to archive this entire series of articles in this issue of the journal.

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