Infant Predictors of the Longitudinal Course of Schizophrenic Development

by Barbara Fish

Abstract

This study was begun in 1952 to test the hypothesis that specific neurointegrative disorders in infancy predict vulnerability to later schizophrenia and schizotypal disorder. Twelve offspring of chronic schizophrenic mothers and 12 controls from similar low socioeconomic status (SES) backgrounds have been studied since their births in 1952–53 and 1959–60. The infants were ranked according to the severity of their neurointegrative disorder, or "pandysmaturation" (PDM), based on analysis of Gesell tests and physical growth measures repeated 10 times between birth and 2 years. Twenty-three subjects (96 percent) completed all 10-, 15- and 20/22-year followup examinations. PDM was significantly related to maternal schizophrenia but not to obstetrical complications, SES, sex, or ethnic background. The severity of PDM was significantly related to the blind evaluations of the severity of psychopathology at 10 years. One 26-year risk subject has been chronically schizophrenic since age 17. The author, nonblind, provisionally diagnosed six other risk subjects as schizotypal or paranoid personality. All seven had PDM; six required 6 to 18+ years of treatment; four with "negative" symptoms remain severely impaired. All six sick subjects had severe social-affective symptoms by 3–6 years of age; four had perceptual deficits by 2 years. Some social-affective, cognitive, academic, and vocational impairments included in the "negative" symptoms and "process" traits of schizophrenia had antecedents before 2 years of age. Primary prevention requires research into the mechanisms underlying these dysfunctions in infancy.

This study was begun in 1952 to test the hypothesis that specific neurointegrative disorders in infancy predict vulnerability to later schizophrenia and schizotypal disorder. Twelve offspring of chronic schizophrenic mothers and 12 controls from similar low socioeconomic (SES) status backgrounds have been studied since their births in 1952–53 and 1959–60.

Characteristics of the Sample

Definition of Risk Status. Risk status was defined by a State hospital diagnosis of schizophrenia for the mother. For the 10 subjects born in 1959–60, this meant having a mother who was hospitalized during her pregnancy and whose infant would be available for examination 12–18 hours after birth.

Diagnostic Criteria for Parents. The initial diagnoses, made in 1945–60, the era of *DSM-I* (American Psychiatric Association 1952), were based on the consensus of an experienced chief of staff and the psychiatrists in charge of the individual patients. They depended on the clinical judgments of these senior staff psychiatrists in the two major New York State hospitals used in the study.

We plan to have independent *DSM-III* (American Psychiatric Association 1980) diagnoses made later, using the often voluminous hospital charts in our files. However, 10 of the 12 mothers have required more than 4 years of hospitalization (up to 35 years; see column b, table 1). Most of these were known to have

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Table 1. Risk Group: Data on schizophrenic mothers and offspring's PDM, rearing family, 10-year & 20/22-year diagnoses and blind MMPI; high school, job & sexual adjustment

a **Name** **Subject's** **Ident# =** HR rank Ethnic Sex **±PDM**	b **Sc M** Min. No. Yrs Hosp	c **Rearing** **Family** Parent resp's before & after S's Sx	d **10 yr: Blind** **Independent** **Evaluation** Rank, Diagnosis Severity	e **15 yr** V–IQ & [Max sch'l year pass]	f **Job** H–R class & Age when Indep	g **Sex Rel'ns** Married/(Live with > 1 yr) age yrs = [1] 0 live-in = [3] **brief/0 = [5]**	h **22 yr: Nonblind** **Provisional Diagnosis** (global rating) **[Blind MMPI: 15#– or 22-yr]** Ages in treatment: **Hospital, /Residential/** **(Court),** [Remedial], OPD
Peter #1 WM **PDM #1**	**27**	**Sc M+** agency **Abused**	1 **Schizophrenia** ***Severe**	87 ***[9]** **left**	***7** **–0–**	— **0 partners** **< 25.9y**	***Schizotypal PD** (6) **[Borderline Sc/ Paranoid]** **/5–11/, (17–18)**
Linda #2 BF **PDM #2**	0.6	**Sc M+** agency **Abused**	2 **Schizophrenia** **Severe**	100 [12]	4 23	— bisexual	**Schizotypal PD** (4) **#[Psy: Paranoid Sc/ PD]** 6, **7–10, /10–17/,** 18, 25–26+
Edwin #3 WM **PDM #3**	**35** F = Sc?	Ad MF warm ambiv	4 **Schizoid** **Severe**	110 [12]	***> 7** **–0–**	— **0 partners**	***Schizophrenia** (7) **#[Psy: prob early Schiz]** 8–20, **19, 20, 25, /20–26+/**
Herman #4 WM **PDM #4**	5+	Ad MF warm solid	3 **Paranoid** **Severe**	87 [12]	**7** 22 army	—	**Paranoid PD, depr** (4) **#[Cyclothymic PD, depr]** 5–12, **/12–15/, (19)**
Pia #5 PF **PDM #5**	4+	MGM warm **reject**	11 Withdrawing, depressed ***Moderate**	**58** ***[8]** **left**	***> 7** **–0–**	—	***Schizotypal PD** (7) **#[Psy: Paranoid Sc/ PD]** 13–14, **14, /14–19/**
Rachel #6 BF **PDM #6**	8+	Ad MF warm solid	8 Withdrawing **Moderate**	79 [12]	**7** 19 army	— **casual** **homosexual**	**Schizotytpal PD, Alc Ab** (5) #[PD: adolescent turmoil] —
Minna #7 PF **PDM #7**	**24+**	MGM inadeq ambiv	7 Schizoid ***Moderate**	79 ***[7]** **left**	***> 7** **–0–**	—	***Schizotypal PD, depr** (5) **#[Borderline psy Sc/ PD]** **(13–16), /14/, (18),** 18–26+
Valerie #8 PF	1.2	Ad MF warm solid	9 Withdrawing **Moderate**	79 [12]	4 20	— homosexual	Mildly schizoid (3) **#[Psy: Sc; may look better]**
Billy #9 BM	4+	Ad MF warm solid	10 Immature, anxious **Moderate**	**72** **[9]** failed	**7** **–0–**	— dates, sex	Dependent PD, **halluc** (4) **#[Psy: Sc/ borderline MR?]** [6–16 remedial reading]
John # 10 BM	8+	PGM warm solid	16 Reactive depression Mild	91 [15]	4 22 grad	(19–22) 23– married	No mental disorder (2) #[NI; not happy; observe] [10: reading class]
Charles #11 WM	4+	Ad MF enmesh **reject**	17 Vulnerable to depression Mild	123 [11] to Work	4 18	— live-in < 1 yr	Depressed 13–15, impr (2) #[PD: adolescent react'n?] 9, 14

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Conrad #12 WM ? PDM	4+	Sc M+ agency 7 moves	6 Schizoid, psychopathic *Severe	99 [10+] Certif	7 18	(19–21) [1] 25– married	Adjusting [NI; mildly narcissistic] 8–11, /11–17/ (2)

Morbid features in the text of tables are in **boldface.**
• = S had some negative symptoms of schizophrenia at period noted (author, nonblind).
a: Name = Pseudonym used in all publications.
Rank # = Rank order, within each group, of severity of developmental symptoms.
c: M = mother, F = father, Ad = adoptive, MGM/PGM = maternal/ paternal grandmother.
e: V–IQ = Verbal IQ on 15-year WISC.
Certif = passed later examination for high school certificate.
f: H–R class = Hollingshead-Redlich rating of job type; **>7** = unable to hold menial job.
h: OPD = other psychiatric disorder, Sc = schizophrenia, S'd = some schizoid traits, PD = personality disorder, MR = Mental retardation, chr = chronic, impr = improved, Sx = symptoms, NI = normal.

been transferred or readmitted to other State hospitals, but since these later charts were not available to us, the exact durations of these additional periods of hospitalization are not known. At a minimum, the median hospitalization of the 10 mothers was 6.5 years and the mean was 12.3 years. Their initial diagnoses were confirmed on later hospitalizations and will probably meet generally accepted criteria for chronic schizophrenia.

The diagnoses of the two mothers with a single short hospitalization need to be reviewed. One mother was dependent on a series of men after a 1.2-year hospitalization. She had been disturbed for years as a child, and her father was chronically hospitalized with psychosis. The other mother was supported by homosexual partners after a 7-month hospitalization, but has been working in recent years. From her early history and reports of her recent functioning, she may well meet criteria for schizotypal personality disorder.

Dimensionalized Assessments. We have not yet attempted to dimensionalize the status of the psychotic mothers, but hope to do so later. There is sufficient information in most of the hospital charts to analyze premorbid functioning, the severity and duration of psychosis, and certain positive and negative symptoms, but most charts lack sufficient data to score affective symptoms or the severity of thought disorder.

Other Criteria. One newborn was excluded because his severe congenital gastrointestinal anomaly required immediate surgery and would have confused any evaluation of psychomotor or personality development. No other criteria were used; all the other offspring born to schizophrenic mothers in the two cooperating State hospitals during 1959–60 were accepted for study. Three infants were lost early to uncooperative social agencies and were never included in the analyses.

Comparison Group. Our 1952–53 cohort, which provided all 12 infants for our comparison group, was initially intended as a pilot study to test the feasibility of our method for predicting vulnerability to later schizophrenia (Fish 1957). Fourteen infants were drawn at random from the lower-class population of New York City served by the Bellevue Hospital well-baby clinic. Recent immigrants who spoke too little English to give a detailed history were excluded. This eliminated many psychiatrically normal parents and left a population that the author had known, as a pediatrician, to have a high incidence of pyschopathology and developmental disorders. That 2 of 14 disadvantaged mothers were later hospitalized and diagnosed as schizophrenic suggests how much pathology can be found in such a low SES group. Their infants became members of our high-risk group.

The 12 remaining infants constitute our comparison sample. This was not expected to be a "normal" group, but was drawn from a disadvantaged population similar to that served by the State hospitals; it proved to be relatively well-matched with the risk group for socioeconomic variables (Fish 1984).

Sample Biases. It is clear from column b, table 1, that our method of selecting the risk sample yielded a group of mothers most of whom had severe, chronic schizophrenia. This was ideal for our purpose, since we had hypothesized that neu-

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rointegrative disorder in infancy, severe enough to be measurable on behavioral developmental tests, would be the antecedent primarily of early onset, chronic schizophrenia (Fish 1957, 1977, 1984). Theoretically, the offspring of very chronic schizophrenic mothers should be somewhat more likely to have that type of disorder.

Fortunately for the research and the children, the severity of the mothers' illnesses also led to 9 of the 12 risk infants being reared by others: three grandmothers and six carefully selected adoptive homes, seven of which were genetically unrelated to the mother (see column c, table 1). Since most of the infants at risk had stable and generally supportive parenting, we were able to observe the viscissitudes of neurointegrative disorder in optimal environments that were not influenced by the mothers' disorders.

Although the controls were chosen at random from a disadvantaged population, our method of selection also biased the group in the direction of severe psychopathology, as had originally been expected. This bias became increasingly apparent as we followed the families and children, especially as they entered adolescence. Thus, while we were unable to study a psychiatric comparison group in any formal way, we did obtain longitudinal data on infants who subsequently had a variety of disturbed as well as normal outcomes (see column h, table 2).

Our method of sample selection also introduced the expected ethnic and other socioeconomic biases into our sample (see column a, tables 1 and 2). Approximately half of both groups were Puerto Rican or black and the rest were Caucasian, a distribution that was fairly representative at that time of the population of New York City served by Bellevue and the two State hospitals.

Most infants were born to SES class IV and V mothers, but were reared in homes that were, or became, class III and IV. The families who did not move up out of class V were generally those headed by single mothers, or with more severe psychopathology. Approximately half of both groups were reared in single-parent homes, but the quality of mothering and the reason for the mother's single status (maternal psychosis or neurosis, father's death or desertion, and cultural factors) appeared to have more effect on the offspring than the simple absence of a father. The most devastating effects were seen in the three risk subjects who had intermittent and chaotic rearing by their psychotic mothers, interrupted by periods in large foundling institutions and/or a series of foster homes.

The impact of these biases appears to be reflected in the high incidence of psychopathological outcomes in both groups. Genetic factors, implicated in the mothers' schizophrenia (and the possibly schizophrenic father of #3), would increase the predisposition of the risk group. In two control subjects, inadequate parenting appeared to be related to their deprived SES background. The SES background of the controls may also have selected a group at higher genetic risk for depression and personality disorders.

Attrition. Attrition has not been a major problem, apparently because of the close, supportive relationships we established with our subjects and their families over the years. One control subject was "too busy" to make an appointment for his 15-year examination and his mother was too overwhelmed with her marital problems and the demands of raising five children to help us gain his cooperation; he was also "too busy" at 23 years, but did fill out a Minnesota Multiphasic Personality Inventory (MMPI) form. Luckily, he is one of the three subjects who were omitted from the developmental analyses because they had too few exams in infancy. The remaining 23 subjects (96 percent) have been followed through the entire series of examinations.

Two other subjects who were reluctant to complete the entire 15-year battery were also well controls. They were quite content to be examined by the principal investigator (PI) and agreed to a second "blind" psychologist, but balked at the prospect of a 15-year interview with yet another strange psychiatrist. In response, we modified our procedures for subsequent followups: the author administered the adult interview and psychological battery, and the 15-year battery for the 1959–60 cohort (tape recording these for subsequent verbatim transcription and blind, independent evaluations) and encountered no further resistance.

It has required considerable effort and persistence to maintain our precious sample. Several long trips were required for the PI and the psychologists to complete the 10-year, 15-year, and adult followup examinations. Interim contact has generally been maintained by mail and telephone. More frequent contacts have been made by us, the families, agencies, and by the subjects themselves in the case of subjects who required more help. In some instances where contact had lapsed before the 10-year followup, only the ingenious tracking skills of our research social worker (Renee Wile Jackson) saved us.

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Procedures for Index Offspring Assessment

Initial Assessments. The initial developmental assessments of our subjects in infancy were used to make our original predictions of vulnerability to schizophrenia (Fish 1957, 1963, 1976, 1977, 1984).

The analysis of infant development was based on Gesell (1947) tests and physical measurements, repeated at key ages 10 times between birth and 2 years. Separate developmental quotients were obtained for gross motor, visual motor, and language development. Visual motor items were analyzed for specific integrative functions (Fish and Hagin 1973). Height, weight, head circumference, and overall body growth ("Auxodrome") were plotted on the Wetzel (1946) grid. The diagnosis of neurointegrative disorder, later abbreviated as pandysmaturation (PDM), which was based on these assessments, and its possible value as a predictor of later schizotypal development, are discussed in the section on **Predictors of Vulnerability.** The initial rankings of the subjects on the severity of their PDM are listed in column a, tables 1 and 2.

To measure the "abnormally quiet" behavior observed clinically in subject #1 (Fish 1957), behavioral state was recorded in the second cohort through 4 months of age, in 5-minute intervals throughout the 2-hour presentation of a standard series of stimuli, from mild (vision, sound, touch) to more strenuous (Gesell gross motor tests, passive manipulation, caloric vestibular test) (Fish 1963; Fish and Dixon 1978).

Subsequent Assessments. These were carried out at 9–10, 15–16, 18–19, and 20–22 years of age on all subjects (except for #32 who was not examined after age 10 years). The subjects of the 1952–53 cohort who were symptomatic at 22 years were reinterviewed at age 26–27 years.

Developmental Problems in Assessments. The psychiatric interview and clinical psychological battery used for our followup assessments cover similar areas of functioning and psychopathology at the three ages covered; they are appropriate for children at 10 years, as well as adolescents and adults. These instruments therefore yield information that can be compared to some extent across the three developmental epochs of late prepuberty, midadolescence, and early adulthood. However, since children show less tolerance for an extended interview and have less verbal facility and less ability to conceptualize and be introspective about subjective experience, the material obtained is not precisely comparable, even when the same questions are asked. Normally, there is a greater tendency to projection and denial in the younger age groups, with more false negative information. When our subjects were 18, they often told us about symptoms in early adolescence that they had denied at the time.

Psychiatric Assessments. The psychiatric interviews conducted before 1971 were not structured interviews, although similar probes were used for all subjects. Since 1974 (for the 1959 cohort at age 15 years and all subjects as adults) we have used a structured interview, and all interviews and psychological tests have been audiotaped. This interview includes Goldstein's (see Goldstein, this issue) followup interview (covering past and current functioning), the schedule for Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer 1978), and Rieder's Schizophrenia Spectrum Schedule (Rieder 1978), which permits one to score the symptoms for a *DSM-III* diagnosis of schizotypal personality disorder. The interview is supplemented at appropriate points by questions drawn from the Strauss/Carpenter Prognostic Scale and Personal and Social History (Strauss and Carpenter 1972, 1974, 1977) and, when indicated, from Robins' (1966) Interview for Antisocial Personality Disorder.

From the first followup at 10 years, the psychological battery has consisted of the thematic apperception test (TAT), Wechsler Intelligence Scale for Children/Wechsler Adult Intelligence Scale (WISC/WAIS), Rorschach, Bender-Gestalt (BG), and Human Figure Drawings (FDs). In 1974 we added the Benjamin Proverbs Test, a version of the Word Association Test, and the MMPI. Irving I. Gottesman is evaluating the MMPIs, blind to all other information. Verbatim transcripts of the audiotaped testing are also being scored blindly by our consultants: Jeri Doane is scoring the TATs and Rorschachs for communication deviance, and Hollis Johnston is scoring the Rorschachs and the verbal subtests of the WISC and WAIS, using the Thought Disorder Index she and Holzman developed (Johnston and Holzman 1979). The major problems we encountered involve issues of identifying early and milder preschizotypal traits and symptoms on the assessments at age 10 years.

Current Psychiatric Status of Index Offspring

Age Groups. All our controls and two risk subjects are 33+; 10 risk subjects are 26 years old (in 1986).

Breakdowns and Dysfunctions to Date. On the blind evaluations at 10

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Table 2. Control group: Data on offspring's PDM, rearing family, 10-year & 20/22-year diagnoses and blind MMPI; high school, job & sexual adjustment

a **Name** **Subject's Ident# =** C rank Ethnic Sex **±PDM**	c **Rearing Family** Parent's response before & after S' Sx	d **10 yr: Blind Independent Evaluation** Rank, Diagnosis Severity	e **15 yr** V–IQ & [Max school year pass]	f **Job** H–R class & Age when indep	g **Sex Rel'ns** Married/(Live with > 1 yr) age yrs = [1] 0 live-in = [3] **brief/0 = [5]**	h **22 yr: Nonblind Provisional Diagnosis** (global rating) **[Blind MMPI: 22-year]** Ages in treatment: **Hospital, /Youth Home/ &** **/Prison/,** [Remedial], OPD
Frank #21 WM **PDM #8**	M enmeshed protective	5 neurotic/ **paranoid** **Severe**	126 [15]	**> 7** **–0–** M supp	— **[5]** **0 partners < 23** **rare sex < 28**	**Depr, chr, impr** (S'd?) **(4– > 3)** [NI; mild depr homsexl?] [6: remedial reading]
Wilma #22 BF	M warm supportive	12 obsessive, **paranoid** **Moderate**	102 [12]	4 17	(22–24) [1] (24–27)	compulsive, adjusted (2) **[Schizoid-paranoid PD]**
Vera #23 PF	MF M narcis F warm	21 slight phobic asymptomatic Mild	97 [12]	4 17	19–married [1]	slightly phobic, no Sx (1) [NI; sugg mild PD, rage]
Carol #24 WF	MF favor Sib **rejecting**	15 reactive depr inhibited Mild	118 **[9]** drugs	4 21	(20–22) [1] 22–24 married 25–2° marriage	**Unstable PD; Opioid Abuse:** **improved, relapsed (3–4±)** [NI; mild PD drugs delus] **19**–22, 28– Methadone + Rx
Ramona #25 PF	M±F M depres **derogate**	13 depressed, hysterical **Moderate**	95 [10] Certif	4 18	(21–22) [1] 22–29 married 29 divorce	**Depr, chr** (hys); **impr (4– > 3)** **[Psychotic; Sc = impr; depr]** 24
Grace #26 WF	M, 2 aunts protective **critical**	19 inhibited, introverted Mild	109 [16]	3 22 = grad	(23—) close homosexual "marriage" [1]	**Maj Depr, 4 epis; impr** (2) [NI; neurotic, anx, depr] 19, 25, 28
Virginia #27 PF	MF warm favored	14 phobic, depressed Mild	82 [12]	4 18	22–married [1]	No mental disorder (1) [NI; obsessive, phobic]
Marie #28 PF	M±F warm supportive	20 compliant, adjusted Mild	93 [12]	4 17	22–married [1]	No mental disorder (1) [NI; conforming, controlled]
Sara #29 WF	MF warm supportive	24 well- integrated asymptomatic	100 [13]	4 18	(22—) [1]	No mental disorder (1) [NI; self-confident]
Sam #30 WM	MF immature **rejected**	18 depr/inner aggression Mild	100 [10] Certif	4 20 Marine	23–married [1]	**Antisocial PD; improved (3)** **[Sociopathic PD, hostile]** **/15–17/,** & **/18–20/**
Anne #31 WF ? PDM	MF warm supportive	23 well-endowed, good adjustment	106 [11]	5 17	22–married [1] 23–separated	No mental disorder (1) [NI; somewhat unhappy]

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Chris #32 WM ? PDM	MF immature F paranoid	22 conforming asymptomatic	NA [12]	NA 17	?? steady girl-friends + sex, adol—	appar adjusted; no Px [NI; not introspective]	(NA)

Morbid features in the text of tables are in **boldface.**
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a: Name = Pseudonym used in all publications.
Rank # = Rank order, within each group, of severity of developmental symptoms.
b: Sc M = schizophrenic mother.
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e: V–IQ = Verbal IQ on 15-year WISC.
Certif = passed later examination for high school certificate.
f: H–R class = Hollingshead-Redlich rating of job type; **>7** = unable to hold menial job.
h: OPD = other personality disorder, Sc = schizophrenia, S'd = some schizoid traits, PD = personality disorder, MR = Mental retardation, chr = chronic, impr = improved, Sx = symptoms, NI = normal.

years, two risk subjects were diagnosed as schizophrenic and three risk subjects and one control as severely schizoid or paranoid (see column d, tables 1 and 2). The provisional diagnoses of the 20–22 year interviews were made immediately after scoring the SADS and are tabulated in column h, tables 1 and 2. These must be considered highly tentative since they were made by the author, who was not blind, and before the case histories had been drafted, much less reviewed in detail. Blind, independent, consensus diagnoses and psychometric assessments will be obtained when the case histories and verbatim transcripts of the adult interviews have been completed.

The only blind evaluations available to date are Gottesman's evaluations of the 1974–75 MMPIs, when 10 of the risk subjects were only 15 years old (their MMPIs are marked "#" in column h, table 1). As one might expect, the clinical diagnoses are more conservative than psychometric evaluations made in the absence of case history information. The ages when the subjects required treatment, as well as their global ratings, and their vocational and sexual functioning, are tabulated in columns f–h, tables 1 and 2.

In the risk group (column h, table 1) one subject is schizophrenic, five met criteria for schizotypal personality disorder, and one for paranoid personality disorder. All seven had had PDM in infancy (column a, table 1). Six have been chronically disturbed since early childhood, requiring 6 to 18+ years of treatment independent of the research (mean = 11 years); three required treatment in hospitals, followed by prolonged residential treatment; three are currently in treatment. The two diagnosed schizophrenic at 10 years appear schizotypal following treatment (Fish 1976, 1977, 1982; Fish et al. 1965, 1966; Fish and Hagin 1973). The schizophrenic who broke down at 17 remains chronically disabled (Fish 1986). Two of the personality disordered subjects have only moderate dysfunction currently.

Four risk subjects (33 percent) did not manifest any type of diagnosable *DSM-III* disorder at 20 to 24 years. One had been dysthymic and was referred for psychotherapy by his school as an adolescent, and one hallucinated at 11 years, and gradually improved during 7 years of residential treatment.

In the control group (column h, table 2), one subject had four major depressive episodes and two had prolonged dysthymic disorders; all three improved later. None of the three required pharmacological treatment, but two sought brief psychotherapy for neurotic problems with a parent or a spouse. One subject met criteria for a "probable" antisocial personality disorder, requiring detention as a juvenile and later in prison, but improved in a supportive marriage. One subject has an unstable borderline personality disorder and continues to function erratically, sporadically entering psychotherapy or treatment for her chronic drug abuse.

Six (54 percent) of the 11 controls assessed as adults have not manifested any type of diagnosable *DSM-III* disorder. One has had mild paranoid traits, observed clinically and on psychological tests since 10 years, but she functions relatively well and has never required treatment.

Measures of Social, Interpersonal, or Role Competence

School Performance. Attitudes and

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feelings about school, behavior in class, grades received, special help required, and classes that had to be repeated were recorded at followup as reported by subjects, parents, and teachers. The maximum school grade that was passed is tabulated in column e, tables 1 and 2.

Of the six risk subjects who were chronically disturbed from childhood on, three left school before grade 10. Symptoms akin to "negative" symptoms in schizophrenia appear to have played a role in their "giving up." Dropping out was not simply related to IQ, although the verbal IQ of one had fallen below 60 by 15 years. However, when she stopped school at age 16.9, she was in residential treatment, receiving individual teaching in an ungraded class; her involvement in treatment, always minimal, simply petered out. The other two subjects who dropped out had borderline IQs, equal to the IQs of three risk subjects who completed 12th grade. All three of these subjects had been characterized since their infancy or preschool years by apathy and passivity. Their habitual methods of coping with difficult situations were to submit and just endure them, or to run away. It was as if they could expend no effort, even that involved in treatment. Only one other risk subject had negative symptoms in childhood, and then to a milder degree. Negative symptoms became marked in the schizophrenic man after he graduated from 12th grade and 1 year before his first hospitalization.

Another risk subject tried to pass 10th grade for 3 years and failed. He had no negative symptoms or apparent schizotypal traits, and we thought his failure was due only to his severe dyslexia, but we now question this. At 18 he reported that he had been hallucinating since 7th grade, a fact he denied at the time; the hallucinations may well have contributed to his preoccupation in class.

Job Performance. The vocational histories of both risk and control subjects have paralleled the severity of their psychiatric disorders (see column f, tables 1 and 2). The schizophrenic man and the three schizotypal subjects with longstanding negative symptoms have not been able to cope with even menial jobs on their own.

The only control subject who did not achieve financial independence was still supported by his mother at age 28. He is also the only control who had PDM in infancy. The control with antisocial personality disorder worked in the Marines, following a year in prison, took a year of college, and then continued to work after his marriage. The other disturbed control subject has held high-paying jobs for years, interrupted by periods of increased depression and drug abuse. The remaining 8 (of 11) controls and 5 (of 12) risk subjects became financially independent shortly after finishing school.

Social Functioning. Gross acceptance or rejection of subjects by peers, ability to make and keep friends, ability to take the initiative in social contacts, and the number and depth of such relationships were recorded at followup as reported by subjects, parents, teachers, and others. The subjects' feelings of closeness and trust with friends, and later with sexual partners, were elicited on all interviews and were scored on Rieder's Schizophrenia Spectrum Schedule at the adult followup. The overall quality of relationships with sexual partners was rated on a 5-point scale and tabulated in column g, tables 1 and 2.

Of the risk subjects, only two (rated [1]) had lived with sexual partners for a year or more by the time they were 23 years old; these two men married subsequent partners at ages 23–25. A total absence of stable, close relationships with sexual partners (rated [5]) characterized six of the seven risk subjects who were diagnosed as having schizophrenia spectrum disorders on their adult interviews.

In contrast, 10 of the 11 controls who were assessed as adults were living with long-term or permanent sexual partners at the time. The only control who was sexually dysfunctional was the one who had PDM as an infant; he had no intercourse by age 23 and only rare casual contacts by age 26.

The three other controls who were disturbed at the time of the adult assessment had milder problems in their sexual relationships, which were congruent with their diagnoses (chronic dysthymia, borderline unstable, and antisocial personality) and consistent with their individual family and personal dynamics.

In our sample, an inability to establish and maintain an intimate sexual relationship in early adulthood was a more sensitive indicator of schizotypal disorder than school or vocational function. The four severely disturbed schizotypal subjects who had no negative symptoms in adolescence were able to graduate from high school, and three of these achieved financial independence by 19–23 years of age, although two did so only by joining the Army; the fourth had been hospitalized with schizophrenia 1 year after graduating.

Predictors of Vulnerability

Neurological Studies. The diagnosis

of PDM was based essentially on an analysis of neurological maturation, using the Gesell in conjunction with measures of physical growth (see Fish 1959, 1963, 1976, 1977, 1984; Fish and Dixon 1978). It required a transient lag and disorganization of gross motor and/or visual motor development, which was associated with a lag in physical growth on the Wetzel grid. PDM was hypothesized to be a marker in infancy of an inherited schizotypal trait. The predictions of vulnerability consisted of ranking the infants according to the severity of PDM between birth and 2 years (column a, tables 1 and 2).

The entire course of psychobiological development after 2 years was to be the test of these predictions, but in a sample of this size we could not expect to establish "predictive validity," whatever the adult outcomes of our subjects. The potential value of PDM as a predictive measure was supported by the 10-year followup. The severity of PDM was significantly related to the blind, independent evaluations of the severity of psychopathology at 10 years (χ^2, $p < .01$; columns a and d, tables 1 and 2). The broad category of moderate severity included some pathology that at 10 years did not appear to be specific to schizophrenia spectrum disorders. That PDM might be an expression in infancy of a schizotypal trait, rather than a nonspecific precursor of childhood psychopathology in general, is suggested by the fact that PDM was significantly related to maternal schizophrenia (χ^2, $p < .05$) but not to obstetrical complications, SES, sex, or ethnic background.

Six of the seven risk subjects with PDM continued to be the sickest adolescents and adults in our sample, requiring the most treatment, independent of the research (see column h, table 1). This author's nonblind provisional diagnoses of these subjects as of 22 years, as well as the blind evaluations of their MMPIs at 15 or 22 years, suggest that some of the moderately severe psychopathology that appeared to be nonspecific at 10 years may be more specifically related to schizotypal disorders (see column h, table 1). If future blind diagnoses confirm this, PDM should be investigated further as a marker of infant vulnerability to later schizophrenia spectrum disorders.

Along with most investigators, we believe, from observing the changes in the severity of symptoms in our subjects over time, that the emergence and remission of psychosis in individuals who fall within the schizophrenia spectrum depends on factors other than a genetically determined schizotypal trait. We never expected to predict such changes in state from events as remote as those we observed in infancy (Fish 1957, 1959, 1960).

Nonlocalizing Neurologic Signs. Dyslexia, associated with failures on the Block Design subtest of the WISC, high Koppitz scores and distortions on the Bender-Gestalt, poor fine coordination, and defective finger schema, occurred significantly more often in our risk subjects (χ^2, $p < .05$), similar to the findings of Erlenmeyer-Kimling et al. (1984), Marcus (1974), and Rieder and Nichols (1979) in larger studies.

However, high Koppitz "developmental scores" on the Bender-Gestalt result from several different types of visual-motor disorders (Fish and Ritvo 1979). Lauretta Bender evaluated the 10-year Bender-Gestalts of our subjects, without any other information available. Of the eight risk subjects with dyslexia, she considered five to show signs typical of schizophrenia, one to resemble an organic brain disorder, and two to be indistinguishable from the Bender-Gestalts of ordinary dyslexic children.

There was no significant relationship between soft neurological signs at 10 years and PDM in infancy, although other investigators often discuss these conditions together under "neurological" findings in preschizophrenics. More importantly, there was no relation between soft neurological signs at 10 years and the nonblind provisional diagnoses of schizophrenia spectrum disorders at 23 years. Subject #3, who was independently diagnosed as schizophrenic at 19, had had no dyslexia or soft signs at 10 years, although Bender considered his 10-year Bender-Gestalt to be typically schizophrenic. At age 19, after 3 months of hospitalization, he was found on an exhaustive neuropsychological battery to have "some form of longstanding, diffuse CNS deficit," including "left hemisphere and frontal lobe problems with concentration and symbolic reasoning" (Fish 1986). It appears that while some neurological signs may define a more severely impaired subgroup of chronic schizophrenics (Hertzig and Birch 1968; Tucker et al. 1975; Quitkin et al. 1976; Weinberger et al. 1979), as measured here, soft signs were not sensitive enough and included too many nonspecific developmental disorders to provide an adequate predictor of later schizotypal outcomes in children at risk.

Early Prodromal Signs

Psychological Evaluations. We have not yet analyzed our data in detail for possible early prodromal signs of mental disorder in our subjects. There was a continuity, however, between the blind ratings of severity of psychopathology on the 10-year

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psychological testing and the blind evaluation of mental disorder on the 15- or 22-year MMPIs. Gottesman's diagnoses of schizophrenia, borderline schizophrenia, or severe schizoid or paranoid personality disorder correlated with the 10-year ratings of severe and moderately severe disorder (χ^2, $p < .005$); and his diagnoses of normal profiles correlated with the 10-year ratings of mild or no disorder (χ^2, $p < .005$).

The blind ratings of severe pathology at 10 years included the evaluation of subtle indications of lapses in logical thinking and reality testing on the WISC and projective tests done by highly skilled and experienced clinicians (Rosa Hagin and Florence Halpern). Now that the Thought Disorder Index (Johnston and Holzman 1979) has been standardized on child patients and normals (Arboleda 1982), and has been found to characterize psychotic children and the children of psychotic parents, using this quantitative measure of thinking on the WISC and Rorschach should improve our ability to predict later schizotypal disorder on the basis of these clinical tests.

Psychiatric Evaluations. A comparison of columns h and d, table 1, suggests that schizotypal symptoms could be identified in severely disturbed subjects at 10 years, even on the unstructured psychiatric interview used before 1971. But we could not identify precursors of milder forms of schizophrenia spectrum disorder in those who were only moderately disturbed at age 10. Either the symptoms had not yet emerged clearly or the clinical and psychometric instruments we used were not sufficiently sensitive to detect them. Both factors seem to have been operating. Clearly, for the psychiatrist to diagnose *DSM-III* schizotypal traits in prepubertal children, we need valid and reliable criteria for detachment and paranoid defensiveness on interview, illogical and paranoid ideation, and the morbidity of illusions and bizarre fantasies in children.

During childhood, the six sickest risk subjects (those who required treatment at 5–13 years of age) showed the same clusters of symptoms that have been found in the much larger risk studies (see Asarnow and Goldstein 1986), symptoms that also characterized preschizophrenics as children in the "follow-back" studies. All had poor interpersonal relationships and feelings of depression, loneliness, isolation, and rejection by peers. Poor affective control was seen in three. Schizoid behavior appears to be the most specific predictor of the three clusters since the first two clusters occur frequently in other types of disturbed children. More importantly, schizoid behavior characterized our four subjects with persistent negative symptoms who had the poorest adaptation in adolescence and adulthood.

The seventh risk subject with PDM had mild "socially immature" behavior at 10 years (fearful, inhibited, withdrawn), appeared to be less impaired socially than the other six, required no treatment, and was considered to be only "moderately severe" on her psychological testing. Of the two other risk subjects rated as moderately severe at age 10, one was somewhat inhibited and withdrawn but was not anxious and had what appeared to be good peer relationships; the other was very immature, hyperactive, impulsive, and distractible, and revealed only a glimpse of bizarre ideation. The controls with severe to moderate symptoms at 10 years appeared to have neurotic symptoms, but two of them also had paranoid features observed clinically or on psychological testing.

Longitudinal Observations. Other prodromal signs of mental disorder became apparent in reviewing the longitudinal course of the subject who had his first "acute" psychotic break at age 17 and his first hospitalization for schizophrenia at age 19 (Fish 1986). A comparison of his WISC/WAIS scores at 10, 15, and 19 years revealed a deterioration in effective intellectual functioning that paralleled his increasing psychopathology. His school test scores first showed impairment just before he cut off the legs of his pet turtle at 8 years: his reading scores did not progress and his arithmetic score actually regressed. At 11, right after signs of physical puberty, his reading level regressed and he erupted with inappropriately blunt and sometimes irrelevant remarks. This suggested that there might be a beginning of disordered thinking, but he was too guarded and taciturn to manifest this on interview.

In five of our risk subjects, a drop in a subject's Wechsler Comprehension subtest score of 2–7 points, between 10 and 15 years, was correlated with the author's nonblind evaluation of an increase in schizotypal symptoms ($p = .015$, Fisher test). Two of these subjects were hallucinating at 14 to 15 years; two began to show withdrawal and acting-out behavior at 13 years; one blocked so severely that her 15-year TAT had to be terminated. The scores did not drop in the four controls who became depressed in adolescence or the one who developed an antisocial personality disorder. Seven risk subjects had drops in Vocabulary scores of 3–6 points, but this was less regularly associated with increasing schizotypal pathology.

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Other Life Events

In a small sample such as ours, suggestions about the impact of life events can only be regarded as anecdotal. The major life events that affected three of our risk subjects negatively stemmed from the presence of their psychotic mothers in the rearing environment. The consequences included inadequate rearing, multiple placements, institutionalization, severe physical abuse, and threatened homocide (see column c, table 1). The occurrence of schizophrenia by 10 years in two of these subjects was significantly related to a risk subject's being reared by a psychotic mother ($p = .045$, Fisher test). These two subjects also had the most severe PDM. How such extremely negative environments interacted with their genetic vulnerability and affected the manifestations of disordered development and PDM is a matter for conjecture. That both infants then showed accelerated spurts in development, while still in these environments, points to the operation of genetic factors as well as deprivation (see Fish 1957, 1976, 1977, 1982; Fish and Hagin 1973).

The early development of these three subjects suggested that the positive or negative impact of separation or institutionalization depended on the developmental stage of the child, the severity of any genetic vulnerability, the nature of the institution, and what type of rearing the child was being separated from. In these three subjects, even institutional care was more supportive than what they received at home, and good foster home care was better than a large institution. We are therefore inclined to attribute the relation between a poorer outcome and institutional care and parental separation in the first 5 years (Mednick et al. 1984) to genetic or other factors that may be associated with these events, rather than to separation or institutional care alone, unless the chronically schizophrenic mothers in the study of Mednick et al. (1984) provided very different homes from the ones we studied. That Heston (1966), in his study of adoptees, could find no effect on outcome related to the duration of institutionalization appears to support this view.

The biological event of puberty also deserves study. It was associated with cognitive regression, an early prodromal sign of mental disorder, in our subject #3 (4 years before his breakdown), and the beginning of behavioral deterioration in subject #5 and subject #7. This is hardly surprising, in view of the usual age of onset of schizophrenia. We hope that the larger risk studies can shed some light on the underlying mechanisms.

A number of life events, as well as genetic predisposition, appeared to play a role in the symptoms of our three depressed control subjects. All three mothers were subject to periods of depression; all three subjects lost their fathers by death and/or desertion. The dysphoric mothers of the two girls projected their own self-derogation onto their daughters, insisting that the girls were "slow" despite all evidence to the contrary and the PI's repeated demonstrations and assurances that the girls were bright. Both girls had suffered neonatally after severely traumatic births and both had partially disabling medical illnesses for prolonged periods (rheumatic fever, asthma, duodenal ulcers, Legg Perthe's disease).

Possible Protective Factors

To equate the hypothesized risk in two or more of our subjects, in order to evaluate protective factors, we would have had to demonstrate not only that they had PDM of the same magnitude, age of onset, and duration, but also that their developmental profiles showed comparable assets and impairments (Fish 1977). As yet we do not know enough to match for all the significant differences in the developmental profiles of infants with or without signs of genetic vulnerability to schizophrenia, even assuming that we could identify the latter, that it was the overriding determinant of outcome, and that one had a sufficiently large sample.

Additional risk factors that cannot be evaluated in a small sample are the severity of schizophrenia in the mother and the number of affected relatives. Three of the four risk subjects with the worst outcomes, those with persistent negative symptoms and a chronic inability to function in school, job, or social relationships, were also the offspring of the mothers with the most chronic hospital courses (see columns b, e–h, table 1).

Individual Characteristics. High IQ alone did not appear to be a protective factor in our sample, occurring as it did in four depressed subjects, one risk subject, and three controls (one with unstable borderline personality) (see columns f and h, tables 1 and 2). Whether or not our subjects used their assets seemed to depend on other individual characteristics and family transactions. However, the severe dyslexia of two risk subjects appeared to be an additional factor in their vocational inadequacy.

In addition to the lines of development and gross disorganization (PDM) that could be measured on infant tests, we noted individual

characteristics, such as vivid affect or apathy, which were described qualitatively, and more global individual differences which we labeled "organization," "drive," "persistence," and so on, for want of more precise terms. It was our clinical impression that these qualities played a role in helping some infants and children use their relatively limited capacities better than others who had higher IQs; they overcame environmental handicaps, and mild dyslexia in 2, and then advanced further in school and jobs. But we have yet to analyze the components of these qualities and how they changed over time and with differences in environmental support.

Family Environment. Given the limitations on our ability to equate risk and predict outcome, we are left only with our clinical impressions that the major protective factor for some of our subjects at risk was the consistent support and stimulation provided by one parent capable of responding to their changing needs. This was particularly true of 4 of the adoptive parents and the paternal grandmother of #10 (see column c, table 1).

It was our clinical impression that some of the earlier and milder developmental symptoms, such as irritability and apathy, could be modified by early intervention and optimal parenting. Later, optimal treatment at critical times appeared to help lessen the symptoms, and possibly even abort a full-blown breakdown, at times of crisis during the lives of the four sickest risk subjects, as noted below for subject #1. But these efforts did not prevent chronic impairment or alter schizotypal or paranoid personality disorders substantially, although they seem to have improved the adaptation or circumstances of some. At best, treatment provided secondary prevention and was limited to reducing pathology that was already present.

Longitudinal Observations

When completed, the essential contribution of this project will be to provide an in-depth study of the evolution of personality and psychopathology, from birth to 26+ years, of 24 risk and control subjects with a high incidence of psychopathology. Only a few peaks and valleys of their lives are captured in two tables, but one can trace subjects longitudinally on table 1 and compare the very different courses of the three most vulnerable infants, now three sick risk subjects, two with negative symptoms and one without.

Subject #1 was an "abnormally quiet" infant and has been apathetic since then, lacking the additional stimulation he needed. He had disorganized speech by 3 years, and has been withdrawn ever since. Then abused at home, he was institutionalized and treated from age 5 to age 11, but was "schizophrenic" and hallucinating at 10, and "like a chronic schizophrenic" on psychological testing. He compensated by 15, and his IQ increased, but he remained isolated, paranoid, and hopeless; he dropped out of school and became addicted to heroin. Yet, despite this past, and few assets, he was able to stop heroin and make a marginal, dependent, but nonpsychotic adjustment (now age 33+) after a father figure rescued and "adopted" him at age 18.

Subject #3 was an "abnormally quiet," bright infant, but had a flat affect from birth, despite a warm adoptive home. He was odd, detached, rejected by peers from age 6, a "severe schizoid" at age 10, and insidiously regressed after 8 years, with declining cognitive function, becoming clearly schizotypal, with vague hallucinations, by age 15 (see the section on **Early Prodromal Signs, Longitudinal Observations,** above). He first became psychotic at age 17, but completed high school on neuroleptic treatment. After graduation he regressed, "like a simple schizophrenic," before being hospitalized at 19, paranoid and hallucinating, with an "acute schizophrenic break." He has been unable to function outside of hospitals or group homes since that time (now age 26+) (Fish 1982, 1986).

In contrast to the subjects with negative symptoms, subject #2 was a "normally active" infant who was apathetic for her first months in a foundling institution, but spontaneously improved there, developing vivid affect by 2 years and noncompliant, explosive behavior by age 3. This worsened after she was forcibly discharged to her fiercely rejecting mother at age 4; she was "psychotic" by age 6, but gradually improved in a State hospital from 7 to 10 years. She was still "schizophrenic" at 10 years, stormy, paranoid, and with loose associations. Her symptoms lessened in residential treatment from 10 to 17 years, and her IQ increased. She was unable to function on her own, but with agency support she became self-supporting at 23. She has always had schizoaffective features and seemed eminently treatable to the author; her initial psychotic break appeared to be precipitated by life with her angrily rejecting and abusing mother (Fish 1982).

Recommendations

The aim of all risk research into schizophrenia is to identify targets

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for early prevention, before decompensation and chronic deficits occur. Observation of the six sickest risk subjects in this study convinced me that 3–6 years of age is already too late to prevent cognitive and social-affective impairment in some genetically vulnerable children. All six needed treatment by that age: they were already isolated and lonely, with blunted, detached, and/or explosively hostile relating. Four had chronic perceptual deficits and academic difficulty from the very beginning of school, which dated back to their failures on the Gesell formboard at 18–24 months of age (Fish and Hagin 1973). The "negative" symptoms of schizophrenia, and the deficits conceptualized as "process" traits, seemed to have very early antecedents. Our prospective observations suggest that the anlage for some of the early social-affective and perceptual-cognitive-academic impairments can be found in the first 2 years of life.

If the optimal adoptive homes in our study were unable to modify these impairments substantially, it is clear that more specific intervention techniques are needed for the developmental disorders that occurred before 2 years of age. For true primary prevention, we need to study the mechanisms underlying these dysfunctions in vulnerable infants and then design specific interventions to remedy them, measuring the effect on social-affective and perceptual-cognitive development at 2–3 years. Certain abnormalities, observed in the vulnerable infants at the times when development was severely disorganized, suggest possible targets for such intervention research:

- **The "abnormally quiet" state,** which occurred in the first month of life in three of the "sick" risk subjects, included a peculiar depression of "arousal," which was limited to gross motor, proprioceptive, and vestibular responses (Fish 1957, 1959, 1960, 1963, 1977; Fish and Alpert 1962; Fish and Dixon 1978). This seemed to be continuous with their later affective blunting. The neurophysiological, neuromuscular, and biochemical correlates of this early state need to be studied, in conjunction with studies of early mother-infant motor play and social-affective interaction.
- **Transient delays in skeletal growth and decreased arousal** during periods of PDM (Fish 1977; Fish and Dixon 1978) suggest that a temporary disturbance of neuroendocrine regulation and hypothalamic function accompanied the periods of greatest developmental disorganization. Techniques are now available to investigate and possibly treat such dysfunctions.
- **Failures of midline bimanual skills** at 4, 7, or 10 months of age occurred in all eight risk infants in the second cohort who developed severe to moderate psychopathology at 10 years (Fish and Hagin 1973). This disturbance of midline integration of both hands should be studied further, in conjunction with studies of interhemispheric integration.
- **Deficits in the organization of visual-spatial perception,** seen in failures on the Gesell formboard at 18–24 months, persisted as failures on the Block-Design subtest of the WISC at 10 years, and were associated with dyslexia (Fish and Hagin 1973). It is important to determine the antecedents for this persistent defect. Our observations of additional visual-motor disorders in these infants suggest that modern techniques for studying early focused attention, pattern recognition, and the integration of visually directed reaching and depth perception could explicate some of the mechanisms underlying the dysmaturation in vulnerable infants between birth and 2 years.
- **PDM could be measured in the same infants** at 4, 8, 16, 28, and 40 weeks, and at 15 and 24 months. The incidence of PDM in the offspring of schizophrenic, depressed, and normal controls would provide one test of its potential utility as a provisional marker for infants hypothesized to be vulnerable to later schizotypal disorder. We hypothesized earlier (Fish 1977) that the periods of increasing PDM may reflect increased "activity" of the schizophrenic process. These measurable fluctuations in development might then underscore the significance of any associated neurophysiological or biochemical changes that occurred in these periods.

A series of 2-year studies could screen the most promising measures of specific dysfunctions, suggest possible specific intervention techniques, and test these interventions for their ability to modify the targeted behaviors. When a specific dysfunction could be modified, the effect on social-affective or perceptual-cognitive development at 3–4 years could be measured. Such intervention research could, in turn, increase our understanding of the mechanisms underlying key dysfunctions in schizotypal infants and children. Even if some of these dysfunctions prove not to be specific to schizotypal infants, reducing the early impairments should improve their subsequent premorbid adaptation, although it may have no effect on subsequent breakdown.

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