Intellectual Deficits in First-Episode Schizophrenia: Evidence for Progressive Deterioration

by Robert M. Bilder, Lauren Lipschutz-Broch, Gail Reiter, Stephen H. Geisler, David I. Mayerhoff, and Jeffrey A. Lieberman

Abstract

The developmental processes leading to neuropsychological deficits in schizophrenia are poorly understood. Both early developmental defects and subsequent deterioration may occur. Intelligence test profiles are often used to estimate premorbid ability and deterioration from prior levels of functioning. These characteristics were assessed in samples of first-episode (n = 51) and chronic (n = 50) schizophrenic patients. Although the groups showed few differences on tests to estimate premorbid intellectual ability, the chronic group performed worse on measures considered sensitive to deterioration. Dextral (right-handed) patients tended to have better performance; this effect was marked in the first-episode sample, especially on verbal tests. Male patients showed more evidence of deterioration than female patients. Subgroups differing in the time course of premorbid social dysfunction also differed in intelligence test profiles, suggesting that estimates of social and cognitive deterioration may have concurrent validity. The results support the hypothesis that patients differ in the course of cognitive decline and suggest that deterioration of function may follow the onset of overt psychosis in some patients. Prospective longitudinal studies of first-episode schizophrenic patients could directly test this hypothesis.

Despite agreement that the distinction between developmental and deteriorative processes may be critical to understanding the pathophysiologic bases of schizophrenia, there is no clear understanding of the longitudinal course of functional deficits in this syndrome. While it is assumed that significant deterioration of functioning occurs, the overall incidence, severity, and time course of this process are not well characterized. Most relevant evidence, which comes from detailed case histories documented by highly experienced clinician-investigators, points to significant deterioration leading to "pure deficit syndromes" in 10 to 15 percent of patients (Bleuler 1972; Huber et al. 1975; Ciompi 1980; Zubin 1980). There is agreement that the most severe deterioration may occur primarily in the first 5 years of illness (Payne 1961; Hamlin 1969; Bleuler 1972; Huber et al. 1975; Ciompi 1980; Zubin 1980; Abrahamson 1983; Kolakowska et al. 1985). Following the initial decline, subsequent functioning may remain stable or even improve slightly (Bleuler 1972; Huber et al. 1975; Stephens 1978; Ciompi 1980), although later deterioration, particularly progression of persistent negative symptom states, may also occur (for a review see McGlashan and Fenton 1992). Milder yet significant deterioration may be more prevalent, may precede the overt onset of schizophrenic symptoms, and may affect many more patients (Parnas et al. 1982; Parnas and Schulsinger 1986; Fish 1987).

The presence of neuropsychological (NP) deficits in schizophrenia is amply documented; 50 to 80 percent of schizophrenic patients have been classified as "brain damaged" using NP methods (Heaton et al. 1978; Flor-Henry and Yeudall 1979; Kolb and Whishaw 1983; Seidman 1983; Bilder 1992). NP studies also have

Reprint requests should be sent to Dr. R.M. Bilder, Long Island Jewish-Hillside Medical Center, 75-59 263rd St., Glen Oaks, NY 11004.

shown some promise in defining subsyndromes of schizophrenia with distinctive patterns of symptoms, premorbid social adjustment, responses to treatment, tardive dyskinesia, residual disability, and abnormal patterns of brain physiology and morphology (for reviews see Seidman 1983; Goldberg and Seidman 1991; Bilder and Degreef 1991; Bilder 1992).

While there is a consensus that NP deficits are central characteristics of schizophrenia, little attention has been paid to distinguishing deficits that reflect abnormal development from those that reflect deterioration of acquired abilities. A sparse literature documents NP abnormalities in preschizophrenic individuals (Pollack et al. 1970; Parnas et al. 1982; Aylward et al. 1984; Mirsky et al. 1985; Parnas and Schulsinger 1986), but also shows that significant deterioration of NP functioning may accompany the onset of symptoms (Payne 1961; Hamlin 1969) and that progressive deterioration may continue through subsequent years of illness (Payne 1961; Schwartzman et al. 1962; Smith 1964; Silverberg-Shalev et al. 1981). Later improvements in NP functioning have also been observed, possibly associated with improvements in clinical status (Schwartzman et al. 1962; Haywood and Moelis 1963; Hamlin 1969; Klonoff et al. 1970; Heaton and Crowley 1981).

Previous studies have involved primarily chronic, institutionalized patients with long histories of somatic treatments. In addition to introducing sampling biases, such studies confound both illness duration and treatment effects with effects of primary pathologic processes. Thus, it is still unclear to what extent findings of NP deficit (1) reflect patterns of cerebral dysfunction that are "primary" and pathophysiologically relevant to schizophrenia; (2) may apply only to a subgroup of patients with particularly poor treatment response and outcome; (3) may be secondary to long-term treatment; or (4) may be secondary to long-term illness and/or institutionalization. Attempts to control statistically for duration of illness or long-term treatment effects are flawed in the absence of random, epidemiologic sampling or long-term controlled treatment trials. Studies involving careful characterization of patients as soon as possible following the onset of psychosis, combined with longitudinal followup may offer the best opportunity to differentiate these possible sources of neurocognitive compromise.

In the absence of prospective longitudinal data, NP methods can nevertheless provide insights into the course of cognitive development and dissolution. Techniques for estimating premorbid abilities and subsequent deterioration are used widely in clinical neuropsychology (for reviews see McFie [1975] and Lezak [1983]). Estimates of premorbid ability usually are based on test scores that are relatively resistant to the effects of deterioration, such as tests of general knowledge, word knowledge, or reading skill. Possible deterioration of function is suggested when, relative to these estimates of premorbid ability, there is poorer performance on tests that are sensitive to deterioration, such as measres demanding attentional control, speeded performance, or cognitive flexibility.

Application of similar techniques to the study of schizophrenia offers an opportunity to distinguish longstanding developmental compromise from deteriorative processes (Bilder 1985; Bilder et al. 1985, 1988; Goldberg and Seidman 1991). In prior research, we found that structural abnormalities of the brain (ventricular and sulcal enlargement) were more clearly related to indices of deterioration than to absolute levels of NP performance (Bilder 1985; Bilder et al. 1988) and that indices of poor premorbid intellectual ability were most strongly related to symptoms of "conceptual disorganization" (Bilder et al. 1985), partially supporting the validity of these test-based indices in schizophrenia.

We report here the application of comparable methods in a sample of patients who participated in comprehensive NP exams after initial treatment for their first episode of schizophrenia. If first-episode patients showed evidence of deterioration as severe as that found in a chronic sample, it would suggest that the process of cognitive dissolution may precede or occur near the time of onset of overt psychotic symptoms. If, on the other hand, indices of deterioration were less severe in first-episode patients, this would leave open the possibility that NP dysfunction is progressive and indicate a need for prospective assessment of NP function following the onset of psychosis to determine the possible causes and correlates of the deteriorative process(es).

Method

Subjects. Three groups of subjects were included in data analyses: (1) a first-episode schizophrenia patient group; (2) a chronic schizophrenia patient group; and (3) a healthy control group. Sample characteristics are shown in table 1.

The first-episode patients were recruited from consecutive admissions to the inpatient service of Hillside Hospital during the period from 1988

Table 1. Sample characteristics

Variable	Group			Group differences
	Control (n = 22)	First episode (n = 51)	Chronic (n = 50)	
Male (n)	18	33	34	NS
Dextral (n)	17	40	39	NS
White (n)	18	27	35	NS
Age (yr)	25.9 ± 6.2	25.6 ± 5.9	31.8 ± 8.7	(Co = FE) < Ch
Patient education (yr)	14.9 ± 6.2	13.4 ± 2.3	12.2 ± 2.4	Co > FE > Ch
Parental education (yr)	3.1 ± 1.4	3.5 ± 1.5	NA	NS
Parental occupation	2.8 ± 1.2	3.5 ± 1.6	NA	NS
Age at onset	NA	21.3 ± 6.3	19.7 ± 3.7	NS

Note.—Values for variables 4–8 are mean ± SD. Group differences were tested using ANOVA followed by post-hoc Scheffé tests (for continuous variables) or chi-square analyses (for categorical variables). Group differences of $p > 0.05$ (two-tailed) are coded nonsignificant (NS). Variables either not applicable or not available are coded NA. Levels of parental educational and occupational attainment use Hollingshead-Redlich (1958) codes (1 is highest, 6 is lowest). Co = control; FE = first episode; Ch = chronic.

to 1991. Subjects were between 16 and 40 years of age and had received fewer than 12 weeks of prior cumulative lifetime neuroleptic treatment. Diagnosis of definite or probable schizophrenia or schizoaffective disorder (mainly schizophrenic subtype) according to Research Diagnostic Criteria (RDC; Spitzer et al. 1978) was based on the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) interview and other information. Patients were included in this sample only if they were actively psychotic, that is, required hospital admission and had a current rating of 4 or more on at least one of the psychotic items (severity of delusions and hallucinations, thought disorder, bizarre behavior) of the SADS. Also the patient's family had to be willing to participate in the consent process. Patients were excluded if they had any medical contraindication to the use of neuroleptics or any history of serious neurologic or endocrine disorder (e.g., severe head trauma, brain damage, seizure disorder, Cushing's disease, or thyroid disorder). Further information about this sample has been reported elsewhere (see Lieberman et al. 1992, this issue; Lieberman et al. in press *a*, in press *b*). All first-episode patients were receiving treatments according to a standardized algorithm, and none had dose changes within 2 weeks preceding NP assessment. A set of operationalized criteria based on symptom rating scale data also was employed to ensure clinical stability during the conduct of these exams.

The chronic sample was recruited from inpatient units and studied at the New York State Psychiatric Institute Division at Creedmoor Psychiatric Center from 1982 to 1987. Diagnoses of schizophrenia or schizoaffective disorder (mainly schizophrenic type) also were according to RDC based on SADS interview and other sources. Patients were excluded for current or past neurologic or endocrine disorder or for a history of substance dependence. All chronic patients had been stabilized on typical antipsychotic treatment regimens by research physicians before testing, and none had dose changes within 2 weeks preceding NP assessment. This sample has been the subject of previous reports (Bilder 1985; Bilder et al. 1985; Bilder and Goldberg 1987; Pandurangi et al. 1988; Barr et al. 1989*a*, 1989*b*; Mukherjee et al. 1990).

Control subjects were recruited from the community at the same time as the first-episode patients and screened for lifetime history of psychiatric illness, medical illness, and drug abuse by the Structured Interview for *DSM-III* (SCID; Spitzer and Williams 1985), physical exam, and laboratory testing. These subjects were selected to match the first-episode patient group on distributions of age, sex, race, and parental socioeconomic status. The control subjects were paid for their participation. Subjects in all three groups gave written informed consent before participating.

Procedures. Because NP inferences about premorbid ability and deterioration have been based principally on intelligence test data, analyses were restricted to the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981). All subjects were given the complete WAIS-R according to standard procedures as part of more comprehensive NP assessments. To minimize possible effects associ-

ated with normal aging, analyses were conducted on age-corrected IQ scores and individual subtest age-corrected scaled scores (ACSS).

In the first-episode patient group we tried to conduct NP exams as soon as possible after the onset of illness. However, because the goal of these NP exams was to assess relatively stable ("trait") aspects of performance, it was important to examine patients only following resolution of the acute psychotic phase of illness. Following an analysis of the time course of initial treatment response, it was decided to conduct NP exams 6 months after the start of treatment. The actual median time from the start of treatment to the date of testing was 29.8 weeks. The chronic patients were tested on average almost 12 years after the onset of illness (see table 1).

Data analyses aimed to determine whether WAIS-R indices of premorbid ability and deterioration might distinguish the groups. Although a variety of different test-based indices of premorbid ability have been devised (Lezak 1983), there is general agreement that the WAIS-R Information and Vocabulary subtests are relatively insensitive to deterioration ("hold" tests); as in prior research, we used the mean of these subtests as an index of premorbid ability. Selection of deterioration-sensitive ("no-hold") measures from the WAIS-R has been more variable. Reanalysis of data reported by McFie (1975) revealed that of all WAIS-R subtests, Digit Symbol is the most sensitive to brain damage, regardless of lesion location (Bilder 1985). For that reason, we selected this subtest score for contrast to the premorbid estimate. A "deterioration index" (DI) was computed, following the method of Wechsler (1958): [hold − no hold]/hold).

Handedness was assessed using a modification of the Edinburgh Inventory (Oldfield 1971). In the original version, subjects state which hand they use to perform each of 20 unimanual activities; to avoid the possibility of inaccurate reporting of preference, we asked subjects to perform each of the activities so that hand preference could be determined empirically. The number of activities performed with right and left hand was recorded, and a laterality quotient (LQ = 100 [total right − total left]/[total right + total left]) was devised. Subjects were classified as dextral (LQ $\geq$ +70) or nondextral (LQ $<$ +70) using cutoffs similar to those described by Geschwind and Galaburda (1987).

Because we were interested in IQ test results as a possible window on premorbid development, we assessed the relationship of WAIS-R scores to summary scores from the National Institute of Mental Health modification of the Premorbid Adjustment Scale (PAS; Gittelman-Klein and Klein 1969; Cannon-Spoor et al. 1982), which were available for the first-episode group. These ratings were completed by trained research staff based on all available information from patient interview, family interview, and chart information.

Results

Subject Characteristics. Group comparisons of subject characteristics are shown in table 1. The first-episode patient and healthy control groups did not differ significantly on means or distributions of age, sex, hand preference, or race. The healthy controls had more years of education, although the group did not differ from the first-episode group in parental educational attainment, reflecting the matching strategy.

The chronic patient group did not differ from the first-episode group on mean age at onset of psychiatric symptoms or on distributions of sex or race, but they were significantly older and had longer duration of illness and fewer years of education. These differences in demographic and course-of-illness variables are consistent with expected discrepancies between a sample of chronic, primarily poor-prognosis, long-stay inpatients and the more representative sample of patients recruited from consecutive admissions for first-episode schizophrenia.

Intelligence Test Results: Estimates of Premorbid Ability and Deterioration. Comparisons of IQ test scores for the three groups (controls, first-episode patients, and chronic patients) are shown in table 2. Analysis of variance (ANOVA) on the IQ scores revealed large main effects of group; multivariate analysis of variance (MANOVA) on the subtests showed a large group effect (Wilks lambda = 0.56; $F = 3.42$; $df = 22,218$; $p < 0.001$); and univariate F tests revealed large effects of group on each subtest. In line with expectations, post-hoc tests confirmed that the control group had significantly higher scores on every variable than either of the patient groups. Further analyses focused on differences between the two patient groups.

The first-episode group had significantly higher Performance IQ (PIQ) than the chronic group, but the differences in Full Scale IQ (FSIQ) and Verbal IQ (VIQ) were not statistically significant. The first-episode sample was superior to the chronic sample on Digit Span, Arithmetic, Picture Arrangement, and Digit Symbol subtests, but the two patient groups did not differ significantly on other subtest scores (see table 2). In-

Table 2. Wechsler Adult Intelligence Scale—Revised results

IQ score/subtest ACSS	Group			t
	Control	First episode	Chronic	
FSIQ	110.0 ± 13.3	87.8 ± 16.3	82.4 ± 11.9	1.93
VIQ	112.1 ± 12.0	91.9 ± 15.6	88.2 ± 14.9	1.21
PIQ	104.9 ± 13.6	84.2 ± 16.8	77.7 ± 11.5	2.27[1]
Information	12.3 ± 2.5	8.6 ± 3.4	8.6 ± 3.5	−0.02
Digit Span	11.7 ± 2.9	9.6 ± 2.9	8.5 ± 2.4	1.96[1]
Vocabulary	13.1 ± 2.8	9.1 ± 3.1	8.6 ± 3.5	0.73
Arithmetic	12.0 ± 3.1	8.4 ± 3.1	7.1 ± 2.8	2.12[1]
Comprehension	12.0 ± 2.5	8.1 ± 3.5	7.2 ± 3.6	1.31
Similarities	11.6 ± 2.0	8.7 ± 2.9	8.0 ± 3.9	0.97
Picture Completion	9.8 ± 2.3	7.1 ± 3.5	6.6 ± 2.8	0.86
Picture Arrangement	11.6 ± 3.2	7.4 ± 3.0	6.3 ± 2.2	2.13[1]
Block Design	11.4 ± 2.3	8.3 ± 3.1	7.4 ± 2.5	1.53
Object Assembly	10.8 ± 2.3	7.8 ± 3.8	6.5 ± 3.2	1.83
Digit Symbol	10.1 ± 2.6	7.4 ± 2.9	5.9 ± 2.1	2.91[2]

Note.—The control group scored significantly higher on all measures than either patient group. Values of *t* are for differences between first-episode and chronic groups. ACSS = age-corrected scaled score; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ.

[1] $p < 0.05$, two-tailed.
[2] $p < 0.005$, two-tailed.

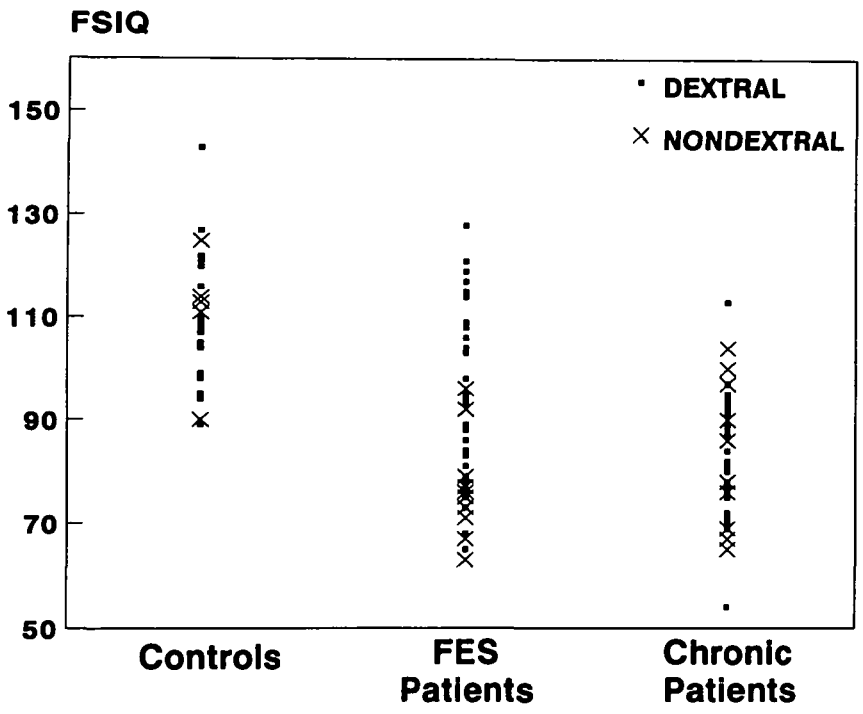
spection of the WAIS-R subtest profiles and effect sizes on post-hoc tests revealed relatively small and nonsignificant differences on the two "hold" tests used to estimate premorbid ability (Vocabulary, Information subtests). In contrast, the largest single difference between first-episode and chronic patient groups was observed on the Digit Symbol subtest. This pattern was consistent with the impression of greater deterioration in the chronic group, and deterioration index scores (mean ± SD) were significantly lower in the first-episode group (0.11 ± 0.35) compared to the chronic group (0.24 ± 0.37) (t[98.5] = 1.89; $p < 0.05$).

Sex and Handedness Effects. Although IQ scores did not differ between the sexes, MANOVA on individual subtest scores revealed a significant sex effect ($F = 3.93$; $df = 11,111$; $p < 0.001$), without a significant Sex × Group interaction. A similar analysis in the patient groups showed a similar effect of sex ($F = 3.16$; $df = 11,87$; $p < 0.001$), and followup univariate tests showed that male and female patients differed on the Information subtest (men performed better) and the Digit Symbol subtest (women performed better). This pattern suggested greater deterioration among males. DI scores (mean ± SD) were significantly higher in men (0.29 ± 0.22) than in women (−0.05 ± 0.48) (t[40.8] = 3.92; $p < 0.001$); this was caused by a nonsignificant trend for men to have higher scores on the premorbid index (t[70.9] = 1.73; $p < 0.10$) but significantly lower scores on the Digit Symbol subtest (t[59.0] = −2.02; $p < 0.05$).

Because of unequal numbers of dextral and nondextral subjects and to the inequalities of variance in subgroups defined by hand preference, Mann-Whitney tests (corrected for ties) were used to assess hand preference effects. Dextrals tended to have higher FSIQ than nondextrals across the entire sample of controls and patients (Mann-Whitney U-test corrected for ties, $Z = 1.69$, $p = 0.09$, two-tailed). Inspection of the FSIQ score distributions for dextral and nondextral subjects in each group made it clear, however, that this effect was greatest in the first-episode patients (see figure 1).

Within the first-episode group, the effect of hand preference on FSIQ was strong ($Z = 2.82$; $p = 0.0024$, one-tailed). Inspection of the WAIS-R profiles of dextrals versus nondextrals suggested that the group differences were greater on Verbal compared to Performance subtests, but MANOVA using VIQ and PIQ as within-subject factors failed to reveal a statistically significant interaction of hand preference with IQ scale. Similar analyses using the hold and no-hold tests or all WAIS-R subtests as within-subject factors also

Figure 1. Full Scale IQ (FSIQ) in subgroups defined by hand preference



Note.—Subjects with laterality quotient (LQ) ≥ 70 were classified dextral; others were classified nondextral. FES = first-episode schizophrenia.

failed to reveal significant interactions, thus failing to support the hypothesis that hand preference effect on FSIQ might be specific to certain subtests.

To assess the possibility that the broad classification of nondextrality (LQ < +70) might obscure possible differences between patients with strong left-handedness and those with intermediate (possibly ambiguous) handedness, we also assessed relations between LQ and IQ scores. There were no significant correlations between LQ and IQ scores or subtests in either the total sample or the chronic sample. Within the first-episode group, however, LQ was correlated significantly with FSIQ ($r = 0.32$; $p = 0.01$, one-tailed). The largest effects were seen on VIQ ($r = 0.36$; $p = 0.005$, one-tailed) and the verbal subtests Similarities ($r = 0.41$; $p = 0.0015$, one-tailed) and Digit Span ($r = 0.38$; $p = 0.003$, one-tailed). Correlations with other Verbal scale subtests ranged from 0.30 to 0.38. Correlations with Performance scale subtests ranged from 0.13 to 0.28, and the correlation with PIQ was 0.27. Although this pattern suggested stronger relations of LQ to Verbal than Performance subtests, the difference between the correlations of LQ with VIQ and PIQ was not significant (Hotelling's test of the difference between correlated correlation coefficients). Scatterplots of LQ by IQ or other subtest scores failed to reveal a "J" distribution that might indicate better relative performance among a strongly left-handed subgroup of nondextrals. Further analyses using a three-group handedness classification, with right-hand (LQ > +70), left-hand (LQ < 0), and mixed (70 > LQ > 0) groups also failed to yield any distinctive pattern among those with stronger patterns of left-hand preference.

Associations With Premorbid Social Adjustment. In the first-episode group, PAS summary scores increased from childhood, to early adolescence, to late adolescence, to adulthood (means ± SD were 1.2 ± 0.94, 1.3 ± 0.89, 1.6 ± 1.1, and 1.8 ± 1.4, respectively). This pattern suggesting deterioration of social functioning has been described elsewhere (Mukherjee et al. 1990). There was considerable heterogeneity among these scores, however; some patients showed poor childhood adjustment and no subsequent decline, while other patients showed relatively good early functioning with substantial later deterioration. To distinguish among these patients, we formed three subgroups: (1) poor childhood social adjustment (childhood PAS score ≥ 2); (2) declining social adjustment during adolescence (increase in PAS score from childhood to early adolescence or from early to late adolescence of ≥ 1); and (3) declining social adjustment during adulthood (increase in PAS score from late adolescence of ≥ 1). No patient showed PAS score increases of greater than 1 in more than one period. FSIQ scores for these groups are shown in table 3.

Table 3 shows a monotonic progression, with lowest IQ in the poor childhood function group, higher IQ in the adolescent decline group, and highest IQ in the adult decline

Table 3. Wechsler Adult Intelligence Scale—Revised scores in subgroups with different courses of premorbid social adjustment

IQ score	Poor childhood (n = 8)	Adolescent decline (n = 12)	Adult decline (n = 6)	F_{lin}	p
FSIQ	75.5 ± 9.9	86.2 ± 13.7	96.5 ± 19.4	3.81	0.01
VIQ	77.4 ± 8.7	90.7 ± 12.9	102.7 ± 17.7	13.1	0.0015
PIQ	75.8 ± 15.0	82.3 ± 15.8	88.7 ± 17.2	2.31	0.14

Note.—See text for grouping criteria. F_{lin} = F value for linearity effect; FSIQ = full-scale IQ; VIQ = verbal IQ; PIQ = performance IQ.

group. There also appeared to be a stronger effect of group on VIQ compared to PIQ, corroborated by a significant linearity effect for VIQ (r = 0.60) but a nonsignificant effect for PIQ (r = 0.31). Hotelling's test for the difference between correlated correlation coefficients further supported the impression that the classification of subgroups according to premorbid social function was more related to VIQ than PIQ ($t_{dr}[23]$ = 2.42, $p < 0.002$).

Profiles of individual subtest scores are plotted for the three groups in figure 2. MANOVA with subtests as within-subject factors yielded a significant main effect of group (F = 3.91; df = 2,23; $p < 0.05$) and a significant Group × Subtest interaction (approximate F = 2.10; df = 20,24; $p < 0.05$), suggesting that the group profiles differed. Post-hoc tests showed significant ($p < 0.05$) main effects of group on all Verbal subtests except Information and Similarities, while none of the Performance subtests showed differences (all $p >$ 0.10; see figure 2).

Deterioration index scores followed a monotonic progression across the groups (poor childhood = −0.14, adolescent decline = 0.09, and adult decline = 0.17), yielding a significant linearity effect (r = 0.36; F = 3.2; df = 2,23; $p < 0.05$).

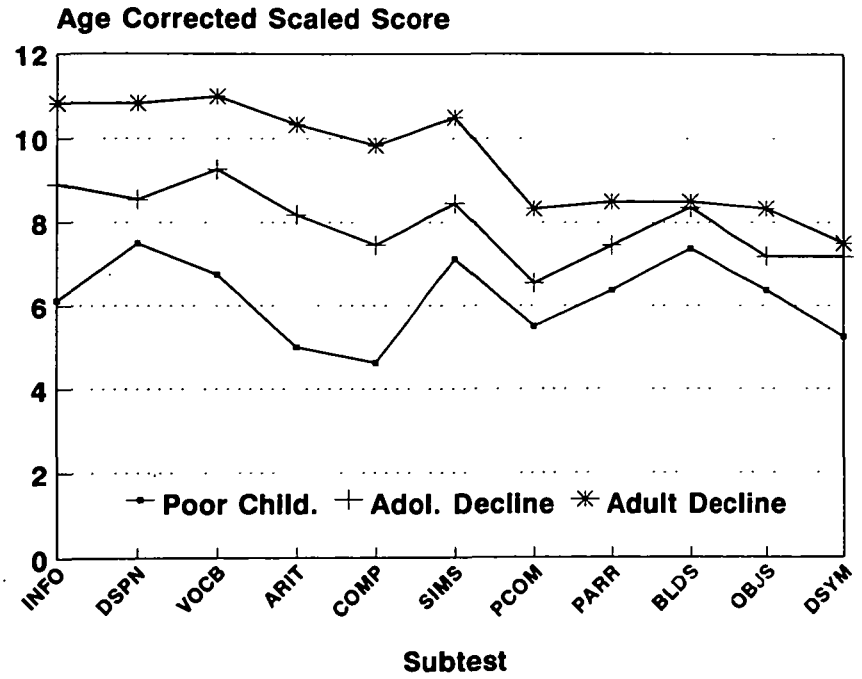
Discussion

The results of this study are consistent with the hypothesis that patients with schizophrenia may suffer both early developmental and deteriorative effects on intellectual functions. The sample of first-episode patients had substantial deficits when compared to controls, but these deficits were less severe than those found in the sample of chronic patients, leaving open the possibility that significant deterioration of intellectual functioning may occur after the onset of overt psychotic symptoms. Although these groups did not differ in VIQ or on estimates of premorbid intellectual ability, they showed significant differences in PIQ, and largest differences were found on those WAIS-R subtests considered sensitive to deterioration. Specifically, the smallest differences between groups were found on Information and Vocabulary subtests from the Verbal Scale, and on the Picture Completion subtest of the Performance Scale (which is considered the least deterioration sensitive of the Performance subtests). In contrast, the largest group difference was observed on the Digit Symbol subtest, which is the most sensitive to deterioration among all WAIS-R subtests. The next largest group differences were observed on the Digit Span and Arithmetic subtests of the Verbal Scale (which are most sensitive to left hemisphere damage) and on the Picture Arrangement subtest of the Performance Scale (which is the most sensitive to right hemisphere damage) (McFie 1975; Bilder 1985).

Analysis of DI values further supported the hypothesis of more severe decline among chronic patients. The mean DI of the first-episode sample was 0.11, while the mean DI in the chronic sample was significantly higher at 0.24. Wechsler (1958) suggested that a DI greater than 0.10 suggested "possible deterioration" while a DI of 0.20 or more suggested "definite deterioration." This classification-based approach to interpreting the DIs therefore suggests on average mild deterioration in the first-episode sample and more severe deterioration in the chronic sample.

There were no significant sex differences on IQ scores, but men and women varied in their subtest profiles, with men showing more evidence of deterioration. This finding supports the hypothesis that men with schizophrenia may be relatively vulnerable to a more severe form of the illness and is consistent with evidence that they have more focal or lateralizing abnormalities on NP, neurologic exams, cerebral blood flow studies, and MRI scans, along with a greater risk for nonfamilial forms of the illness (for reviews see Lewine 1988; Goldstein et al. 1990; Lewine et al. 1990). It has been suggested that men generally have more focal and highly lateralized organization of cerebral representations, such that they are more vulnerable to the functional consequences of brain injury (for a review see Filskov and Catanese 1986). The findings of this

Figure 2. Wechsler Adult Intelligence Scale—Revised profiles in first-episode patients with different courses of premorbid social dysfunction



Note.—Poor Child. = poor childhood functioning group; Adol. Decline = adolescent decline; INFO = Information; VOCB = Vocabulary; ARIT = Arithmetic; COMP = Comprehension; SIMS = Similarities; PCOM = Picture Completion; PARR = Picture Arrangement; BLDS = Block Design; OBJS = Object Assembly; DSYM = Digit Symbol.

study could be seen as supporting the hypothesis that men with schizophrenia are more likely than women to have NP profiles suggesting acquired brain damage. If women do have less localized (more distributed) organization of cerebral representations, they may be less likely to show functionally specific deficits following brain damage. Further research is needed to determine whether the pattern of sex differences observed in schizophrenia is different from that found among healthy individuals.

Evidence of early developmental (premorbid) cognitive impairment was found in both the first-episode and the chronic groups. Both groups performed more poorly than a healthy control group on indices of premorbid intellectual ability. It is noteworthy that the first-episode and the chronic groups did not differ in estimates of premorbid intellectual ability despite differences in educational achievement. This suggests that, for most patients, acquisition of general knowledge and vocabulary was largely complete before the illness could disrupt academic progress.

Attempts to further specify which patients might show the poor premorbid pattern focused on individual differences associated with handedness and premorbid social adjustment. A striking effect of hand preference was found in the first-episode sample, with nondextrals having significantly lower IQ than dextrals. The distribution of IQ scores in the first-episode and the chronic groups suggested that dextrals might be more likely to show a deterioration pattern, while nondextrals might be more likely to show a pattern of early developmental compromise. All nondextral first-episode patients had IQ scores within the range of the chronic group, but only dextral first-episode patients had IQ scores above the chronic range (see figure 1). If the distribution of IQ in the first-episode sample does indeed approach that of the chronic sample over time, it will be due to deterioration among dextral patients. This possibility is compatible with the hypothesis that nondextral patients may have an increased frequency of developmental failures (Green et al. 1989). Morever, it is compatible with the hypothesis that dextral patients (perhaps like males) may be at increased risk for deterioration due to a more localized pattern of cerebral organization. This argument was advanced to explain an association of tardive dyskinesia with dextral hand preference and with normal patterns of occipital asymmetry (Barr et al. 1989*b*).

It is interesting that degree of right-handedness (as indicated by higher values of LQ) tended to correlate more with Verbal than with Performance subtests, and LQ was correlated most robustly with the Digit Span and Similarities subtests, both of which are sensitive to left temporal lobe dysfunction (McFie 1975). These results thus support, in part, the hypothesis that faulty development of the left hemisphere may be more likely among nondextral pa-

tients and could be seen as compatible with Crow's hypothesis (Crow et al. 1989; Crow 1990) that failure in the normal development of cerebral asymmetry, and particularly in the development of the temporal lobe, may be a prominent feature of schizophrenia. The findings are also consistent with the hypothesis that a more general failure in functional-anatomic specialization and cerebral lateralization may mark a pathologic process that is most common among schizophrenic patients whose illness is dominated by signs of impaired verbal development and conceptual disorganization (Bilder et al. 1985; Bilder and Degreef 1991).

Differentiating familial from nonfamilial types of nonright-handedness offers one approach to distinguishing genetic from environmental factors. In the data described here, family history of nondextrality was not clearly related to IQ test scores. Moreover, strongly nondextral subjects were not clearly distinguishable from those with intermediate (possibly ambiguous) degrees of handedness. The results thus failed to support the concept that ambiguous handedness comprises an index of especially severe neurodevelopmental compromise (Satz et al., in press). Because our sample had relatively few nondextral patients with family history of nondextrality or with strong nondextrality, the failure to detect effects on IQ scores may simply reflect a lack of statistical power. It is also possible that more sophisticated methods for detecting ambiguous handedness (Green et al. 1989) would yield different results.

The use of current IQ subtest scores to draw inferences about premorbid ability and deterioration was supported by analyses of premorbid social adjustment. Ratings of premorbid social adjustment revealed distinctive patterns of impairment, with prominent dysfunction in childhood among some patients and later decline in function among others. Subgroups defined by these retrospective ratings of premorbid social adjustment showed relatively clear differences in WAIS-R performance (see figure 2). The poor childhood functioning group had lowest VIQ and relatively flat WAIS-R profiles. In contrast, the groups with later decline in social adjustment had higher scores on most Verbal subtests along with more striking deterioration profiles. DI values also showed a monotonic progression, with least estimated deterioration among the poor childhood adjustment group and progressively more deterioration among the adolescent and adult decline groups. These results suggest parallel progression in the ages of onset of intellectual and social/academic decline: the earlier the social/academic compromise, the more profoundly basic verbal abilities appear to be affected.

In general, contrasts of scores on different tests are difficult to interpret as evidence of a specific, rather than a generalized, deficit, because one test may have superior psychometric discriminating power and thus be more sensitive to generalized deficit (Chapman and Chapman 1973, 1978). Several strategies have been proposed to address this problem, including (1) the use of psychometrically matched tasks or (2) contrasting experimental tests with other tests that are known to have high discriminating power over a wide range of ability, such as the relatively well-standardized subtests of the intelligence scale (Chapman and Chapman 1973, 1978). The contrast of intelligence subtests here applies the latter strategy. Of course, the WAIS-R was not devised to draw inferences about specific functional systems of the brain, and there are clear limits to the NP inferences that can be drawn from intelligence test results alone. Nevertheless, the WAIS-R comprises perhaps the most widely used and best standardized set of measures of human cognitive function, and, through its use in countless studies of patients with known neurologic illness, it has accrued substantial predictive and concurrent validity.

A final note of caution must be voiced against drawing firm conclusions about deterioration from cross-sectional, test-based indices. An alternative explanation of the findings presented here is that a long-standing, static, pathologic process selectively impaired performance on the deterioration-sensitive tasks; and this process was simply more prevalent in the poor prognosis chronic group, among males, among dextrals, and among patients with a relatively late decline of premorbid social function. The DI approach has had only mixed success even in the classification of patients with known neurologic insults; thus it must be applied cautiously in studies of schizophrenia. Even when they are effective, these test-based methods offer little insight into the precise timing of deterioration, which may well occur before overt signs of illness. Detailed followback studies using objective, prospectively obtained data such as academic test scores may be helpful in determining the time course of functional deterioration during the premorbid period. Only prospective longitudinal assessment of patients early in the course of illness appears adequate to determine whether deterioration follows onset. Conducting this combination of followback and followup assessments is a major goal of our ongoing

research on the course of NP deficits in first-episode schizophrenia.

References

Abrahamson, D. Schizophrenic deterioration. *British Journal of Psychiatry*, 143:82–83, 1983.

Aylward, E.; Walker, E.; and Bettes, B. Intelligence in schizophrenia: Meta-analysis of the research. *Schizophrenia Bulletin*, 10:430–459, 1984.

Barr, W.B.; Bilder, R.M.; Goldberg, E.; and Mukherjee, S. The neuropsychology of schizophrenic speech. *Journal of Communication Disorders*, 22:327–349, 1989*a*.

Barr, W.B.; Mukherjee, S.; Degreef, G.; and Caracci, G. Anomalous dominance and persistent tardive dyskinesia. *Biological Psychiatry*, 25:826–834, 1989*b*.

Bilder, R.M. *Subtyping in Chronic Schizophrenia: Clinical, Neuropsychological, and Structural Indices of Deterioration*. Ann Arbor, MI: University Microfilms, 1985.

Bilder, R.M. Structure-function relations in schizophrenia: Brain morphology and neuropsychology. In: Walker, E.F.; Dworkin, R.H.; and Cornblatt, B.A., eds. *Progress in Experimental Personality and Psychopathology Research*. Vol. 15. New York: Springer, 1992. pp. 183–251.

Bilder, R.M., and Degreef, G. Morphologic markers of neurodevelopmental paths to schizophrenia. In: Mednick, S.A.; Cannon, T.D.; Barr, C.E.; and La Fosse, J.M., eds. *Developmental Neuropathology of Schizophrenia*. New York: Plenum Press, 1991. pp. 167–190.

Bilder, R.M.; Degreef, G.; Pandurangi, A.K.; Rieder, R.O.; Sackeim, H.A.; and Mukherjee, S. Neuropsychological deterioration and CT-scan findings in chronic schizophrenia. *Schizophrenia Research*, 1:37–45, 1988.

Bilder, R.M., and Goldberg, E. Motor perseverations in schizophrenia. *Archives of Clinical Neuropsychology*, 2:195–214, 1987.

Bilder, R.M.; Mukherjee, S.; Rieder, R.O.; and Pandurangi, A.K. Symptomatic and neuropsychological components of defect states. *Schizophrenia Bulletin*, 11:409–419, 1985.

Bleuler, M. *The Schizophrenic Disorders: Long-Term Patient and Family Studies*. New Haven: Yale University Press, 1972.

Cannon-Spoor, H.E.; Potkin, S.G.; and Wyatt, R.J. Measurement of premorbid adjustment in chronic schizophrenia. *Schizophrenia Bulletin*, 8:470–484, 1982.

Chapman, L.J., and Chapman, J.P. Problems in the measurement of cognitive deficit. *Psychological Bulletin*, 79:380–385, 1973.

Chapman, L.J., and Chapman, J.P. The measurement of differential deficit. *Journal of Psychiatric Research*, 14:303–311, 1978.

Ciompi, L.C. The natural history of schizophrenia. *British Journal of Psychiatry*, 136:413–420, 1980.

Crow, T.J. Temporal lobe asymmetries as the key to the etiology of schizophrenia. *Schizophrenia Bulletin*, 16:433–443, 1990.

Crow, T.J.; Ball, J.; Bloom, S.R.; Brown, R.; Bruton, C.J.; Frith, C.D.; Johnstone, E.C.; Owens, D.G.C.; and Roberts, G.W. Schizophrenia as an anomaly of development of cerebral asymmetry. *Archives of General Psychiatry*, 46:1145–1150, 1989.

Endicott, J., and Spitzer, R. Schedule for affective disorders and schizophrenia. *Archives of General Psychiatry*, 35:837–844, 1978.

Filskov, S.B., and Catanese, R.A. Effects of sex and handedness on neuropsychological testing. In: Filskov, S.B., and Boll, T.J., eds. *Handbook of Clinical Neuropsychology*. Vol. 2. New York: John Wiley & Sons, 1986. pp. 198–212.

Fish, B. Infant predictors of the longitudinal course of schizophrenia. *Schizophrenia Bulletin*, 13:395–409, 1987.

Flor-Henry, P., and Yeudall, L.T. Neuropsychological investigation of schizophrenia and manic depressive psychosis. In: Gruzelier, J., and Flor-Henry, P., eds. *Hemisphere Asymmetries of Function and Psychopathology*. New York: Elsevier Science Publishers, 1979. pp. 341–362.

Geschwind, N., and Galaburda, A.M. *Cerebral Lateralization: Biological Mechanisms, Associations, and Pathology*. Cambridge, MA: MIT Press, 1987. pp. 72–75.

Gittelman-Klein, R., and Klein, D.F. Premorbid asocial adjustment and prognosis in schizophrenia. *Journal of Psychiatric Research*, 7:35–53, 1969.

Goldberg, E., and Seidman, L. Higher cortical functions in normals and in schizophrenia: A selective review. In: Steinhauer, S.R.; Gruzelier, J.H.; and Zubin, J., eds. *Handbook of Schizophrenia: Neuropsychology, Psychophysiology, and Information Processing*. Vol. 5. New York: Elsevier Science Publishers, 1991. pp. 553–597.

Goldstein, J.M.; Santangelo, S.L.; Simpson, J.C.; and Tsuang, M.T. The role of gender in identifying subtypes of schizophrenia: A latent class analytic approach. *Schizophrenia Bulletin*, 16:263–275, 1990.

Green, M.F.; Satz, P.; Smith, C.; and Nelson, L. Is there atypical handedness in schizophrenia? *Journal of Abnormal Psychology*, 98:57–61, 1989.

Hamlin, R. The stability of intellectual function in chronic schizophrenia. *Journal of Nervous and Mental Disease*, 149:495–503, 1969.

Haywood, H., and Moelis, I. Effect of symptom change on intellectual function in schizophrenia. *Journal of Abnormal Psychology*, 67:76–78, 1963.

Heaton, R.K.; Baade, L.E.; and Johnson, K.L. Neuropsychological test results associated with psychiatric disorders in adults. *Psychological Bulletin*, 85:141–162, 1978.

Heaton, R.K., and Crowley, T.J. Effects of psychiatric disorders and their somatic treatment on neuropsychological test results. In: Filskov, S.B., and Boll, T.J., eds. *Handbook of Clinical Neuropsychology*. New York: John Wiley & Sons, 1981. pp. 481–525.

Hollingshead, A.B., and Redlich, F.C. *Social Class and Mental Illness*. New York: John Wiley & Sons, 1958.

Huber, G.; Gross, G.; and Schütter, R. A long-term follow-up study of schizophrenia: Clinical course and prognosis. *Acta Psychiatrica Scandinavica*, 52:49–57, 1975.

Klonoff, H.; Fibiger, C.H.; and Hutton, G.H. Neuropsychological patterns in chronic schizophrenia. *Journal of Nervous and Mental Disease*, 150:291–300, 1970.

Kolakowska, T.; Williams, A.O.; Arden, M.; Reveley, M.A.; Jambor, K.; Gelden, M.G.; and Mandelbrote, B.M. Schizophrenia with good and poor outcome. I: Early clinical features, response to neuroleptics, and signs of organic dysfunction. *British Journal of Psychiatry*, 146:229–246, 1985.

Kolb, B., and Whishaw, I.Q. Performance of schizophrenic patients on tests sensitive to left or right frontal, temporal, or parietal function in neurological patients. *Journal of Nervous and Mental Disease*, 171:435–443, 1983.

Lewine, R.R.J. Gender and schizophrenia. In: Tsuang, M.T., and Simpson, J.C., eds. *Handbook of Schizophrenia*. Vol. 3. Amsterdam: Elsevier Science Publishers, 1988. pp. 379–397.

Lewine, R.R.J.; Gulley, L.R.; Risch, S.C.; Jewart, R.; and Houpt, J.L. Sexual dimorphism, brain morphology, and schizophrenia. *Schizophrenia Bulletin*, 16:195–203, 1990.

Lezak, M.D. *Neuropsychological Assessment*. 2nd ed. New York: Oxford University Press, 1983.

Lieberman, J.A.; Alvir, J.M.J.; Woerner, M.; Degreef, G.; Bilder, R.M.; Ashtari, M.; Bogerts, B.; Mayerhoff, D.I.; Geisler, S.H.; Loebel, A.; Levy, D.L.; Hinrichsen, G.; Szymanski, S.; Chakos, M.; Koreen, A.; Borenstein, M.; and Kane, J.M. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophrenia Bulletin*, 18:351–371, 1992.

Lieberman, J.A.; Jody, D.; Alvir, J.M.J.; Ashtari, M.; Levy, D.; Bogerts, B.; Degreef, G.; Mayerhoff, D.I.; and Cooper, T. Brain morphology, dopamine, and eye tracking abnormalities in first-episode schizophrenia: Prevalence and clinical correlates. *Archives of General Psychiatry*, in press *a*.

Lieberman, J.A.; Jody, D.; Geisler, S.; Alvir, J.M.J.; Loebel, A.; Szymanski, S.; Woerner, M.; and Borenstein, M. Time course and biologic correlates of treatment response in first episode schizophrenia. *Archives of General Psychiatry*, in press *b*.

McFie, J. *Assessment of Organic Intellectual Impairment*. London: Academic Press, 1975.

McGlashan, T.H., and Fenton, W.S. The positive-negative distinction in schizophrenia: Review of natural history validators. *Archives of General Psychiatry*, 49:63–72, 1992.

Mirsky, A.F.; Silberman, E.K.; Latz, A.; and Nagler, S. Adult outcomes of high-risk children. *Schizophrenia Bulletin*, 11:150–154, 1985.

Mukherjee, S.; Reddy, R.; and Schnur, D.B. A developmental model of negative syndromes in schizophrenia. In: Greden, J., and Tandon, R., eds. *Negative Schizophrenic Symptoms: Pathophysiology and Clinical Aspects*. Washington, DC: American Psychiatric Press, 1990. pp. 173–186.

Oldfield, R.C. The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia*, 9:97–114, 1971.

Pandurangi, A.K.; Bilder, R.M.; Rieder, R.O.; Mukherjee, S.; and Hamer, R.M. Schizophrenic symptoms and deterioration: Relation to computed tomographic findings. *Journal of Nervous and Mental Disease*, 176:200–206, 1988.

Parnas, J.; Schulsinger, F.; Schulsinger, H.; Mednick, S.; and Teasdale, T.W. Behavioral precursors of schizophrenia spectrum: A prospective study. *Archives of General Psychiatry*, 39:658–664, 1982.

Parnas, J., and Schulsinger, H. Continuity of formal thought disorder from childhood to adulthood in a high-risk sample. *Acta Psychiatrica Scandinavica*, 74:246–251, 1986.

Payne, R. Cognitive abnormalities. In: Eysenck, H.J., ed. *Handbook of Abnormal Psychology*. New York: Basic Books, 1961. pp. 193–261.

Pollack, M.; Woerner, M.; and Klein, D.F. A comparison of childhood characteristics of schizophrenics, personality disorders, and their siblings. In: Roff, M., and Ricks, D.F., eds. *Life History Research in Psychopathology*. Minneapolis: University of Minnesota Press, 1970. pp. 208–225.

Satz, P.; Green, M.F.; Ganzell, S.; Bartzokis, G.; Gledin, A.; and Vaclav, J.F. The neuroanatomy of atypical handedness in schizophrenia. In: Coren, S., ed. *Left-Handedness: Behavioral Implications and Anomalies*. Amsterdam: Elsevier Science Publishers, in press.

Schwartzman, A.; Douglas, V.; and Muir, R. Intellectual loss in schizophrenia: Part II. *Canadian Journal of Psychology*, 16:161–168, 1962.

Seidman, L.R. Schizophrenia and brain dysfunction: An integration of recent neurodiagnostic findings. *Psychological Bulletin*, 94:195–238, 1983.

Silverberg-Shalev, R.; Gordon, H.W.; Bentin, S.; and Aranson, A. Selective language deterioration in chronic schizophrenia. *Journal of Neurology, Neurosurgery and Psychiatry*, 44:547–551, 1981.

Smith, A. Mental deterioration in chronic schizophrenia. *Journal of Nervous and Mental Disease*, 139:479–487, 1964.

Spitzer, R.L.; Endicott, J.; and Robins, E. Research Diagnostic Criteria: Rationale and reliability. *Archives of General Psychiatry*, 35:773–782, 1978.

Spitzer, R., and Williams, J.B.W. *Structured Clinical Interview for DSM-III*. New York: Biometrics Research Department, New York State Psychiatric Institute, 1985.

Stephens, J.H. Long-term prognosis and followup in schizophrenia. *Schizophrenia Bulletin*, 4:25–47, 1978.

Wechsler, D. *The Measurement and Appraisal of Adult Intelligence*. Baltimore, MD: Williams & Wilkins Company, 1958.

Wechsler, D. *WAIS-R Manual*. New York: Psychological Corporation, 1981.

Zubin, J. Chronic schizophrenia from the standpoint of vulnerability. In: Baxter, C., and Melnechuk, T., eds. *Perspectives in Schizophrenia Research*. New York: Raven Press, 1980. pp. 269–294.

Acknowledgments

This work was supported in part by USPHS grants MH-41646 and MH-41960 from the National Institute of Mental Health and by a Faculty Research Award (3-926) from Long Island Jewish Medical Center. The authors thank members of the Psychiatry Research Department at Hillside Hospital who assumed responsibility for patient care and assisted in data collection and management.

The Authors

Robert M. Bilder, Ph.D., is Chief of Clinical Neuropsychology at Hillside Hospital, Long Island Jewish Medical Center, Glen Oaks, NY, and Assistant Professor of Psychiatry at the Albert Einstein College of Medicine, New York, NY. Lauren Lipschutz-Broch, Ph.D., and Gail Reiter, M.A., are staff, Neuropsychology Unit, Department of Psychiatry Research, Hillside Hospital, Long Island Jewish Medical Center. Stephen H. Geisler, M.D., is Director of the Schizophrenia Clinic and Assistant Professor of Psychiatry, Albert Einstein College of Medicine. David I. Mayerhoff, M.D., is Research Psychiatrist at Hillside Hospital, Long Island Jewish Medical Center, and Assistant Professor of Psychiatry, Albert Einstein College of Medicine. Jeffrey A. Lieberman, M.D., is Director of Psychiatric Research at Hillside Hospital, Long Island Jewish Medical Center, and Associate Professor of Psychiatry, Albert Einstein College of Medicine.