Developmental Processes in Schizophrenic Disorders: Longitudinal Studies of Vulnerability and Stress

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Abstract

The Developmental Processes in Schizophrenic Disorders project is a longitudinal study of schizophrenic patients who have recently had a first episode of psychosis. The project focuses on discriminating characteristics of schizophrenic patients that are "stable vulnerability indicators," "mediating vulnerability factors," and "episode indicators" by comparing normal subjects to schizophrenic patients assessed in clinically remitted and psychotic states. A parallel project goal is to identify predictors of relapse, social and work impairment, and illness course among potential psychobiological vulnerability factors and environmental potentiating factors. Hypothesized vulnerability factors and potential environmental stressors are examined first under standardized maintenance antipsychotic medication conditions for at least 1 year. Patients showing stable remission of psychosis after 1 year of maintenance antipsychotic medication are invited to enter drug crossover and withdrawal protocols to determine the need for continuous antipsychotic medication. Vulnerability and stress factors are again assessed. A summary of results to date is presented. Deficits in early components of processing visual arrays and in sustained discrimination of successive ambiguous perceptual inputs are relatively stable across psychotic and clinically remitted states in the schizophrenic patients. Performance on a vigilance task demanding active, working memory also remains abnormal during clinical remission but covaries significantly with psychotic state and is a candidate for a mediating vulnerability factor. Autonomic activation level does not appear to be an enduring vulnerability factor, but it predicts the extent of short-term symptomatic recovery and may mediate the impact of stressors. Under conditions of standardized, injectable antipsychotic medication, independent stressful life events and highly critical attitudes toward the patient in the social environment predict relapse risk. Prospective data suggest that signs and symptoms prodromal to psychotic relapse may be present in about 60 percent of patients.

The clinical course following a first psychotic episode often fluctuates, including periods of psychotic remission as well as psychotic exacerbation and relapse, and the degree of work and social impairment is highly variable across patients (Bleuler 1972/1978; Zubin and Spring 1977; Strauss et al. 1978; Shepherd et al. 1989). Because most patients now return to the community after a relatively brief hospitalization, knowledge of the predictors and determinants of the subsequent outpatient course are of enormous practical importance. Following patients through the fluctuating early course of schizophrenic disorder also provides an excellent opportunity to clarify the extent to which measures that have been proposed as indices of vulnerability factors in schizophrenia represent trait or state aspects of schizophrenia or a combination of each (Zubin and Spring 1977; Nuechterlein and Dawson 1984a; Holzman 1987; Nuechterlein 1990; Szymanski et al. 1991). Identification of measures...
ures that detect abnormalities that endure into periods of clinical remission should provide insights into processes underlying schizophrenic symptoms. In addition, given the very strong evidence for the role of genetic factors in the development of schizophrenia (Gottesman and Shields 1976, 1982; Kendler 1988), the identification of enduring vulnerability factors may help to delineate a schizophrenia-related genotype that has greater utility for studies of genetic transmission than does the clinical diagnosis of schizophrenia itself (Holzman and Matthyse 1990; Levinson and Mowry 1991).

Follow-through longitudinal designs have many advantages over cross-sectional designs in the study of schizophrenia. Because schizophrenic disorders are not static conditions, many of the most significant issues concern processes in the development and course of symptomatology and of impaired work and social functioning (Strauss 1973; Strauss and Carpenter 1981; Keith and Matthews 1989). Cross-sectional comparisons of patient groups who are in different stages of illness (e.g., psychotic vs. clinically remitted) are likely to be confounded by sampling biases that create differences not due to intra-individual processes (Strauss 1973). For example, patients whose illness course is particularly benign after a psychotic episode are probably more likely to discontinue their contact with treatment facilities unless specific efforts are made to maintain their involvement and, thus, allow longitudinal comparisons of patients in contrasting clinical states.

Longitudinal study of patients during the initial years following onset of psychosis should provide particularly valuable information because results will not be confounded by the effects of prior treatment or by chronic patterns of adaptation to the illness. Beyond a better understanding of vulnerability-linked and episode-linked variables, greater knowledge of predictors of early course should provide targets for interventions aimed at decreasing the odds that more severe, chronic illness patterns will develop. The study of the early course of schizophrenia is, of course, tremendously enhanced if contemporary treatments are provided in a standardized fashion so that the relationship between initial patient characteristics, environmental factors, and illness course can be detected.

**Stable Vulnerability Indicators, Mediating Vulnerability Factors, and Episode Indicators**

Longitudinal study is essential to determine whether the prominent information-processing, psychophysiological, and other psychobiological abnormalities in schizophrenia reflect traits, clinical states, or a combination of the two. We have suggested that the following three types of abnormalities among schizophrenic patients be distinguished (Nuechterlein and Dawson 1984a), as summarized in figure 1.

Stable vulnerability indicators are stable, trait-like individual characteristics of schizophrenic patients that are consistently different from normal even during remission and do not become more abnormal during psychotic episodes. Some of these characteristics are specific to schizophrenia and related disorders. They would, in many cases, be expected to show substantial genetic influence and would occur with abnormally high frequency in populations at heightened risk for schizophrenia. Variables with these qualities help to identify schizophrenia-prone individuals and may help to define an extended phenotype relevant to studies of genetic transmission.

Mediating vulnerability factors are variables that show abnormalities during clinical remission as well as during psychotic periods, but that also become more severely deviant during and possibly somewhat before psychotic exacerbations. The word "mediating" signifies that some variables showing this pattern may be involved in subclinical processes leading to formation of schizophrenic symptoms. Many abnormalities in this class, like stable vulnerability indicators, are likely to be genetically influenced, are expected to be present with abnormally high frequency in high-risk populations, and can help to identify schizophrenia-prone individuals. However, mediating vulnerability factors are expected to be more likely candidates than stable vulnerability factors for links in causal chains that are close to psychotic symptom formation.

Episode indicators or "symptom-linked" characteristics are abnormalities occurring during psychotic periods that return to normal levels during clinical remission. Episode indicators may predict short-term clinical outcome and are extremely useful in the evaluation of clinical improvement and treatment efficacy. However, they do not represent enduring characteristics associated with vulnerability to schizophrenia.

Deficits in attentional functioning, information processing, smooth pursuits eye movements (SPEM), and possibly autonomic functioning are among the most promising indicators of vulnerability found in cross-sectional studies of post-psychotic schizophrenic patients and persons at risk for future schizophrenic disorders (Garmezy 1974; Ohman 1981;
Figure 1. Stable vulnerability indicators, mediating vulnerability factors, and episode indicators as distinguished by presence and degree of abnormality in patients during asymptomatic and symptomatic states

Stable Vulnerability Indicator

Mediating Vulnerability Factor

Episode or Symptom Indicator

ASYMPTOMATIC  PSYCHOTIC

Potential Stress Factors Related to Psychotic Relapse

It is clear that genetically transmitted vulnerability factors play an impor-
tant role in etiology, relapse, and course in schizophrenia. Several models posit that these factors also combine with biological and social environmental factors to influence the course of schizophrenia (Rosenthal 1970; Gottesman and Shields 1972; Kendler and Eaves 1986). Possible environmental factors in psychotic relapses have received particular attention (Leventhal et al. 1984). It is important to emphasize that evidence of a role for environmental triggers in psychotic relapses does not imply that these same factors contributed to the initial development of schizophrenia, as some factors could be relevant to illness course but not to etiology.

Earlier studies have suggested that stressful life events judged to be independent of the patient's behavior are more frequent in the weeks immediately before relapse (Brown and Birley 1968; Leff and Vaughn 1980; Day et al. 1987). The possible role of these environmental triggers in relapse and the processes by which they affect the course of schizophrenic disorder may be understood more fully through prospective research with a follow-through design. Earlier studies assessed recall for prior stressful life events after relapse had occurred and may, therefore, have included retrospective memory biases. Brown and Birley (1968) have termed this retrospective memory bias a "search for meaning" as the patient attempts to understand what may have led to a psychotic episode. The current project examines the role of stressful life events within a prospective design under standardized medication conditions.

Studies originating in Britain (Brown et al. 1972; Vaughn and Leff 1976a) and replicated in California (Vaughn et al. 1984; Karno et al. 1987), Illinois (Moline et al. 1985), and India (Leff et al. 1987) have indicated that highly critical, hostile, or emotionally overinvolved attitudes (summarized by the term "high expressed emotion" (EE)) toward the patient expressed by a significant other in an interview during the patient's hospitalization, predict relapse rates that are 2 to 4 times higher in the 9 to 24 months following hospitalization than those of patients whose significant others do not express such attitudes (Bebbington and Kuipers 1988). These studies do not suggest that all expressions of emotion are correlated with higher relapse rates, however. In the initial British studies, the level of warmth and the number of positive comments about the patient were also rated. Their relationship with relapse was found to be nonlinear, apparently due to a complex interaction with the rating of emotional overinvolvement. This led to an emphasis on the measures of critical comments, hostility, and emotional overinvolvement. Critical or emotionally overinvolved attitudes in the social environment appear to be predictors of relapse risk that are not diagnostically specific (Vaughn and Leff 1976b; Hooley et al. 1986; Miklowitz et al. 1988) and that generalize to at least some physical disorders (Fishman-Havstad and Marston 1984; Szmukler et al. 1985). Furthermore, these dimensions are not specific to familial settings, but pertain to living environments generally, including residential therapeutic environments.

Studies of the predictive relationship between high EE and relapse have rarely controlled medication patterns or dosages. Thus, the extent to which selection of different medications or dosages contributes to the predictive relationship is largely unknown. Furthermore, some recent studies that have varied the conditions under which the critical or emotionally overinvolved attitudes are assessed (e.g., during a patient's nonpsychotic period or through assessment of only one significant other) or that have used broad definitions of relapse (e.g., rehospitalization not necessarily including psychotic symptoms) have found weak or nonsignificant relationships between these attitudes and relapse (Dulz and Hand 1986; Hogarty et al. 1988; McCreddie and Phillips 1988; Parker et al. 1988). The possibility that longer exposure to the patient's symptoms leads others to react with more critical or emotionally overinvolved attitudes has also been emphasized in two recent studies (MacMillan et al. 1986; Parker et al. 1988).

It is possible that these attitudes, like the occurrence of major life events, contribute to a high level of environmental stress that interacts with preexisting biological vulnerability factors to increase the likelihood that psychotic symptoms will return (Brown et al. 1972; Leff 1987). Another possibility is that these critical and emotionally overinvolved attitudes at least partially represent reactions to the heavy burden that mental illness places on significant others, and that the patients who have a more severe, relapse-prone form of illness place the heaviest burden on significant others (Brown et al. 1972; Kanter et al. 1987; Leff 1989). According to this alternative model, there might not be a causal relationship between high EE of significant others and relapse; they might be jointly related to a third variable, severity of illness (MacMillan et al. 1986). Thus, it is not clear whether attitudes of significant others have a direct influence on relapse risk, although the positive im-
pact of psychoeducational and problem-solving interventions with patients and their significant others suggests this possibility (Goldstein et al. 1978; Falloon et al. 1982; Leff et al. 1982; Hogarty et al. 1986, 1991; Tarrier et al. 1988). Of course, it is quite possible to combine these two models by positing feedback loops from patient behaviors to attitudes and behaviors of significant others, thereby producing bidirectional influence patterns (Nuechterlein and Dawson 1984a; Liberman 1986; Nuechterlein 1987). Repeated measurement of the social environment during the initial course of schizophrenia is very important in addressing the possibility of bidirectional influence, because attitudes of significant others are particularly likely to be changing during this period as these individuals adapt to the impact of the patient’s psychotic symptom onset.

The roles of social support and stress factors in other aspects of the early course of schizophrenia also require further prospective longitudinal examination (Wing 1978; Bebbington and Kuipers 1988). Initial findings (e.g., Hogarty et al. 1988) suggest that significant associations with social functioning might be present.

**Conceptual Framework**

The earlier studies cited above and many others reviewed in the *Schizophrenia Bulletin* (Vol. 10, No. 2, 1984) led to a tentative heuristic model of factors in schizophrenic psychotic relapse, work impairment, and social impairment. This model is an elaboration of diathesis/stress or vulnerability/stress conceptions such as those proposed by Meehl (1962, 1989), Gottesman and Shields (1972), and Zubin and Spring (1977), but with a primary focus on clinical course rather than etiology. Recognizing that any working model of such a complex interactive system will greatly oversimplify nature, we present in Figure 2 a tentative heuristic schema for variables being studied in this project, adapted from earlier versions presented by Dawson and colleagues (1983), Nuechterlein and Dawson (1984a), Liberman (1986), and Nuechterlein (1987).

We recognize that this framework does not specify the underlying neurobiological pathways and omits some common stressors (e.g., street drugs) that are not principal variables of our current protocols. We view this schema as an evolving organizing framework rather than a formal hypothetico-deductive model. The input components fall into four major classes: (1) enduring personal vulnerability factors, (2) personal protective factors, (3) environmental potentiators and stressors, and (4) environmental protective factors. Genetic and other psychobiological vulnerability factors are hypothesized to interact with psychosocial and biological protective factors and stressors over time to influence the likelihood that the individual will develop hypothesized intermediate internal states. In addition to fluctuations in biological or social environmental stressors, gene regulation processes may also result in changes in the “effective genotype” over time (Gottesman 1991). Thus, fluctuations in either vulnerability factors or environmental stressors might move the patient toward the hypothesized intermediate states preceding a return of psychotic symptoms. In this schema, development of the intermediate states of overloaded information-processing resources and tonic autonomic hyperactivation is viewed as a possible precursor to schizophrenic relapse and to impaired work functioning, consistent with subjective reports of the early stages of psychotic episode onset (Docherty et al. 1978). Continued increases in the subclinical disturbances represented by the intermediate internal states lead the vulnerable individual to develop prodromal symptoms.

A feedback loop from prodromal symptoms is hypothesized to highlight the view that prodromal symptoms often exacerbate the level of stress, evoke increases in protective factors, and might even temporarily alter levels of vulnerability factors. Hypothetically, the interaction of heightened psychobiological vulnerability and stress continues to increase the severity of intermediate states and prodromal symptoms, unless protective factors are successful buffers. A threshold for development of psychotic symptoms is finally exceeded and a psychotic relapse results, often accompanied by disturbances in social and occupational functioning.

What follows is a description of the research design and the specific measures being used in each of two phases of the Developmental Processes in Schizophrenic Disorders project and a summary of the major published findings to date. After reading this introductory section, readers interested in a particular substantive area may wish to turn to the Results section for that area. A detailed description of the research design allows this article to serve as an overall methodological reference for the project, but the reader may find that these details are not necessary to understand results in a particular area of interest.

Phase 1 of the project involves an examination of potential vulnerability and stress factors in recent-onset schizophrenic patients during an in-
Figure 2. A tentative heuristic framework for some of the possible psychobiological vulnerability factors, nonspecific environmental stressors, and protective factors in schizophrenic relapse and illness course.

Personal Vulnerability Factors
- Dopaminergic Dysfunctions
- Reduced Available Processing Resources
- Autonomic Hyperreactivity
- Schizotypal Personality Traits

Personal Protectors
- Coping and Self-Efficacy
- Antipsychotic Medication

Environmental Protectors
- Effective Family Problem Solving
- Supportive Psychosocial Interventions

Environmental Potentiators & Stressors
- Critical or Emotionally Overinvolved Attitudes Toward Patient
- Overstimulating Social Environment
- Stressful Life Events

Intermediate States
- Information Processing Overload
- Tonic Autonomic Hyperactivation
- Deficient Processing of Social Stimuli

Outcomes
- Social Functioning
- Schizophrenic Psychotic Symptoms
- Occupational Functioning

Feedback Loop

Remission Period → Prodromal Period → Episode

dex hospitalization, a stabilization period, and at least 1 year of a standardized dosage of injectable maintenance antipsychotic medication and psychosocial intervention. Following at least 1 year on the standardized antipsychotic medication, patients who have shown sufficiently stable remission of psychosis are invited to enter Phase 2; the remainder are urged to remain on antipsychotic medication. Phase 2 involves a 24-week placebo-controlled drug crossover period to determine whether patients require continuous prophylactic antipsychotic medication and to examine the impact of short-term antipsychotic withdrawal on hypothalamic vulnerability and stress factors. Patients who show no adverse clinical effects during the crossover period are then entered into an open medication withdrawal period for up to 18 months while they continue to be monitored for any signs of exacerbation or relapse. Potential predictors of risk for exacerbation or relapse during this period are being tested, based on the same set of potential vulnerability and stress measures used in Phase 1. A followup assessment battery is completed about 3 years after the initial outpatient test battery.

Measures assessing several key components of the overall conceptual schema are included in this ongoing follow-through study of the initial phase of schizophrenia. Potential
The frequency and prospective nature of the symptom ratings have led us also to examine signs and symptoms that might be prodromal to psychotic relapse. This article also includes initial results on the persistence of fluphenazine in plasma during the placebo period of the drug crossover protocol.

**Experimental Design for Phase I**

**Phase 1: Developmental Processes in Outcome in the Early Course of Illness.** Phase 1 involves a longitudinal follow-through study of schizophrenic patients after their initial episode of psychosis, using standardized antipsychotic medication conditions for at least 1 year of prophylactic treatment. Measurement of information-processing, psychophysiological, psychopharmacological, psychological, and social variables at an initial inpatient point and during later standardized outpatient treatment is used to examine predictors of psychotic relapse, negative symptoms, social functioning, and work functioning (table 1). Information-processing and psychophysiological abnormalities are also examined in symptomatic remission and at any psychotic exacerbation or relapse to differentiate stable vulnerability indicators, mediating vulnerability factors, and episode indicators.

Standardized prospective assessment of symptom fluctuations, social functioning, and work/school functioning are obtained to provide outcome measures as well as to test hypotheses about the temporal sequencing of fluctuations in these domains. The inpatient and first outpatient testings are the main sources of predictor variables for examination of illness course over the first outpatient year. The first outpatient testing has the advantage of being completed when medication is standardized and florid psychotic symptomatology is not dominating the measurement of other factors. This initial outpatient battery taps residual deficit levels after the acute psychotic episode that presumably are most relevant to the outpatient course of the disorder.

The expanded Present State Examination (PSE; Wing et al. 1974) and the inpatient intake test battery are completed as early as possible in the hospitalization, typically while the patient is still actively psychotic. Following hospital discharge, patients are followed through the Aftercare Clinic at the University of California at Los Angeles (UCLA) Neuropsychiatric Institute and Hospital (NPI/H) and placed on the standardized injectable dosage of fluphenazine decanoate (12.5 mg every 2 weeks). A first outpatient testing is completed using a full battery of procedures 1 month after the standardized medication level is achieved, typically 8 to 16 weeks after clinic admission. Another full test battery is administered 1 year from this initial outpatient assessment to evaluate the extent to which key measures show stability, increasing abnormality, or normalization. If the patient qualifies immediately for the next project phase and consents to participate, this 1-year followup also defines a baseline for Phase 2.

Life Events Interviews (Dohrenwend et al. 1978) are completed monthly to allow the impact of stressful life events to be assessed prospectively. Ratings of symptomatology on an expanded version of the Brief Psychiatric Rating Scale (Expanded BPRS; see Overall and Gorham 1962 and Lukoff et al. 1986b) and on the Psychiatric Assessment Scale (PAS; Krawiecka et al. 1977) are completed every 2 weeks to provide continuous monitoring of periods of remission, psychotic exacerbation, and relapse. The Strauss/Carpenter Social Contact and Work Outcome ratings (Strauss and Carpenter 1972) and the UCLA Social Attainment Survey ratings (Goldstein 1978) are completed every 3 months by the case manager.

Additional testing sessions during Phase 1 are triggered by clinical state criteria based on BPRS ratings. Rehospitalization and clinical global judgments of exacerbation or relapse were rejected as criteria for retesting due to their frequent dependence on nonsymptomatic factors (e.g., loss of housing or employment, end of family tolerance of symptoms). Instead, we adopted exacerbation and relapse criteria that could be more clearly
Table 1. Phase 1: Schedule of assessment procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Time of Administration</th>
<th>Initial outpatient (8-16 wk postdischarge)</th>
<th>Remission or best clinical state</th>
<th>Relapse or psychotic exacerbation</th>
<th>1 yr after initial outpatient</th>
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<td><strong>Symptomatology and personality characteristics</strong></td>
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Table 1. Phase 1: Schedule of assessment procedures—Continued

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<th>Procedure</th>
<th>Time of Administration</th>
<th>Initial outpatient (8–16 wk postdischarge)</th>
<th>Remission or best clinical state</th>
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Note.—PSE Int. = interviewer administering the Present State Examination; CFI Int. = interviewer administering the Camberwell Family Interview; Case Mgr. = Aftercare Clinic case manager for the patient; Lab = staff research associates trained to complete laboratory measures; M.D. = clinic psychiatrist monitoring the patient; R.N. = research nurse; Snyder = Karen Snyder, M.A.; Ventura = Joseph Ventura, M.A.

Scales.—PSE = Present State Examination (Wing 1974); Rorschach Thought Disorder Index (Johnston and Holzman 1979); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962; Lukoff et al. 1986b); PAS = Psychiatric Assessment Scale (Krawiecka et al. 1977); SANS = Schedule for the Assessment of Negative Symptoms (Andreasen 1982); HAM-D = Hamilton Depression Rating Scale (Hamilton 1967); Wisconsin Psychosis-Proneness Scales (Chapman and Chapman 1987); MMPI = Minnesota Multiphasic Personality Inventory (Hathaway and McKinley 1967); CPT = Continuous Performance Test (Rosvold et al. 1956; Nuechterlein 1991); Span of Apprehension Task (Asamow et al. 1991); Digit-Span Distractibility Test (Olman and Neale 1975); WAIS = Wechsler Adult Intelligence Scale (Wechsler 1955); Cognitive Slippage Vocabulary Test (L.J. Chapman, unpublished test); Shipley-Hartford Vocabulary and Abstraction (Shipley 1946); CFI = Camberwell Family Interview (Vaughn and Laff 1976b); Life Events Interviews (Dohrenwend et al. 1978); Social Network Interviews (unpublished forms); UCLA Social Attainment Survey (Goldstein 1978); Strauss/Carpenter Prognostic Scales (Strauss and Carpenter 1974); Phillips Premorbid Scale (Phillips 1953).

operationalized and that emphasized return to a state of active psychotic symptoms, as recommended by Falloon (1984). To improve interrater agreement, we developed behavioral anchors for the BPRS rating points (Lukoff et al. 1986b). Criteria for other forms of relapse were also developed, including three BPRS scales (Bizarre Behavior, Self-Neglect, and Suicidality) specifically designed to reflect other possible forms of symptomatic relapse in schizophrenia (Lukoff et al. 1986a). Criteria for milder symptomatic worsening and for remission were also specified in terms of this Expanded BPRS. Clinical remission is defined as ratings of 3
psychotic relapse involves a scales. Another form of first-year by a rating of 6 or 7 on one of these completed test batteries during periods of psychotic symptoms, criteria for initiating test batteries at exacerbations were deliberately set lower than criteria for classifying the patient as having had a psychotic relapse as the overall first-year outcome during Phase I. The first-year outcome distinguished three subtypes of psychotic relapse based on the Expanded BPRS Hallucinations, Unusual Thought Content, and Conceptual Disorganization scales. The patient is classified as showing a “remission followed by a significant exacerbation.” In this case, the patient is rated 3 or below on the three psychotic scales for at least 1 month and is later rated 5 (moderately severe) on one of the psychotic scales with an accompanying increase of 2 points on another psychotic scale or is rated 5 for more than two consecutive biweekly ratings. Finally, a patient is classified as showing “persisting psychotic symptoms followed by a significant psychotic exacerbation” if ratings of 4 (moderate) or above on a psychotic scale continue throughout the period, but at least one 2-week BPRS rating shows an increase of 2 or more points to a 6 or 7 or shows a 1-point increase to a 6 or 7 with an accompanying 2-point increase on another psychotic scale. Although these BPRS criteria for first-year psychotic relapse seem rather technical and somewhat arbitrary, they were designed to parallel prior criteria based on other instruments, and in practice they appear to correspond rather well to occasions when clinicians view psychotic symptoms as reaching relapse levels (Lukoff et al. 1986a; Lukoff et al., in press).

**Subject Selection for Phase 1.** Schizophrenic patients entering this protocol must meet the following criteria: (1) recent onset of a psychotic disorder with symptoms lasting at least 2 weeks and a first psychotic episode starting not more than 2 years before project entry; (2) diagnosis by Research Diagnostic Criteria (RDC; Spitzer et al. 1978) of schizophrenia or schizoaffective disorder, mainly schizophrenia; (3) age between 18 and 45 years; (4) no evidence of an organic central nervous system (CNS) disorder (e.g., epilepsy, encephalitis); (5) no evidence of significant and habitual drug abuse or alcoholism in the 6 months before hospitalization, no evidence that substance abuse triggered the psychotic episode or makes the diagnosis ambiguous, and no evidence that substance use will be a prominent factor in the course of illness; (6) premorbid IQ not less than 70; (7) Anglo-American, Native American, or acculturated Hispanic or Asian background (including fluency in English); and (8) residence after hospital discharge likely to be within commuting distance of the UCLA Aftercare Clinic.

Patients with other known CNS disorders, significant drug or alcohol abuse, or mental retardation were excluded because these conditions could produce symptoms or effects on key dependent variables that could either mimic or be confounded with those of schizophrenia. Because many features of schizophrenia, and possibly of vulnerability to schizophrenia, involve alterations in normal thought patterns, language usage, and processing of information, reasonable English fluency was required for valid, standardized application of research measures that evaluate subtle anomalies in thinking, language usage, and processing of verbal information. Patients of primarily Afro-American background were not included in this protocol because electrodermal activity, a key autonomic variable in the a priori multivariate model for predicting clinical outcome, is substantially altered in this population due to differences in peripheral skin composition (Johnson and Corah 1963; Bernstein 1965; Johnson and Landon 1965). To have taken this factor into account would have required a much larger subsample of Afro-American first-episode schizophrenic patients than we could have obtained. An unfortunate consequence is that we cannot...
evaluate the generalizability of our findings to Afro-American patients, although we would expect the same psychobiological vulnerability factors to be applicable.

Schizophrenic patients for Phase 1 are selected from admissions to four major public hospitals in the Coastal and San Fernando Valley regions of the Los Angeles County Department of Mental Health (UCLA Neuropsychiatric Hospital, Harbor/UCLA Medical Center, Olive View Medical Center, and Camarillo State Hospital) as well as from referrals to the outpatient service of the UCLA NPI/H. Project staff confirm diagnosis using RDC and seek patient consent for participation in the outpatient longitudinal study. After inpatient treatment, the schizophrenic patients are followed within an outpatient research program at the Aftercare Clinic, located at the UCLA NPI/H, and participate in standardized treatment: medication, individual case management, behaviorally oriented therapy, and group social skills training and therapy activities. After an initial stabilization period using variable dosages of medication, antipsychotic medication is administered by intramuscular injection at a standardized dosage of 12.5 mg fluphenazine decanoate every 2 weeks. Antiparkinsonian medication, typically benztropine mesylate or trihexyphenidyl hydrochloride, is prescribed as needed for side effects. In unusual cases in which side effects on 12.5 mg of fluphenazine decanoate remain intolerable despite antiparkinsonian medication, a lower dosage is established (as low as 6.25 mg every 2 weeks).

The RDC, rather than DSM-III or DSM-III-R (American Psychiatric Association 1980, 1987) criteria, are used as the diagnostic basis for inclusion in the project for several reasons. First, because a major aim of the research is to provide better predictors and a better understanding of the early course of disorders involving characteristic schizophrenic symptoms, using a diagnostic system demanding a continuous period of illness of 6 months or more (as in DSM-III and DSM-III-R) for the inclusion criterion would be counterproductive. This duration criterion would exclude study of the earliest months of active symptomatology and limit our ability to address initial predictors of outcome that might be available from cross-sectional testing during this initial phase. Use of a 6-month duration of illness as a diagnostic inclusion criterion also tends to narrow the range of psychotic cases to those with poorer prognosis (Helzer et al. 1981) without shedding any light on possible determinants of the poor prognosis. Second, the RDC include explicit criteria for schizoaffective disorder and for subtyping of schizoaffective disorder, and DSM-III did not. Cases that have major psychotic symptoms typical of schizophrenia, including Schneiderian first-rank symptoms (Schneider 1959), only during periods in which a full affective disorder syndrome is also present are diagnosed schizoaffective disorder, mainly affective, by RDC. These cases are placed in a bipolar affective disorder sample rather than the schizophrenic sample. Third, the RDC have high interrater reliability (Fenton et al. 1981) and identify schizophrenia as a disorder with significant heritability, one form of evidence for construct validity (McGuffin et al. 1984).

The inclusion of RDC schizoaffective, mainly schizophrenic, cases in the schizophrenic sample reflects the view that some schizoaffective cases are similar to schizophrenic disorders, whereas others are similar to affective disorders (e.g., Baron et al. 1982; Harrow and Grossman 1984; Meltzer et al. 1984; Tsuang and Simpson 1984; Kendler et al. 1986). We adopted the RDC standard for making this division. In practice, only 17 of 106 cases (16%) entered into Phase 1 have been in the RDC schizoaffective disorder, mainly schizophrenia, category. All of these cases showed depressive rather than manic syndromes that overlapped temporally for part, but not all, of the period of typical schizophrenic psychotic symptoms.

All patients are cross-diagnosed by DSM-III-R so that the implications of this alternative diagnostic system can be examined. The FSE was expanded with appropriate items from the Schedule for Affective Disorders and Schizophrenia (SADS; Endicott and Spitzer 1978) and other sources to allow RDC and DSM-III-R criteria for schizophrenia to be evaluated for each case.

Normal comparison subjects are recruited primarily through newspaper and periodical advertisements. Individual matching of age, sex, educational level, and race provides matched pairs of schizophrenic and normal subjects. In addition, normal comparison subjects must meet the following criteria: (1) no evidence of major psychopathology based on an expanded FSE adapted for a lifetime perspective and a Minnesota Multiphasic Personality Inventory (MMPI; Hathaway and McKinley 1967) profile; (2) self-report of no prior treatment for psychiatric disorder; (3) no evidence of organic CNS disorder; (4) no evidence of significant and habitual drug abuse or alcoholism; and (5) no evidence that a first-degree relative has been treated for a major psychiatric disorder (including schizophrenia, major affective disorder, or alcoholism). Normal subjects
are administered the major measures at the same intertest intervals as patients. The BPRS/PAS and Life Events Interview are administered only at major testing points for normal subjects.

Bipolar affective disorder patients are recruited in a manic state from two of the hospitals (UCLA Neuropsychiatric Hospital and Olive View Medical Center). Their selection criteria are the same as those for schizophrenic patients except that their RDC diagnosis must be either bipolar disorder or schizoaffective disorder, mainly affective. The manic patients are administered the same test battery as the schizophrenic patients, but are tested only twice—once during a manic period and once during an outpatient period of relative clinical remission. Medication of the bipolar patients is recorded but not standardized. Patients experiencing a manic episode were chosen as a psychopathological comparison group because their acute cognitive disturbance shows many similarities to schizophrenic disturbance (Oltmanns 1978; Strauss et al. 1984; Nuechterlein and Asarnow 1989), but bipolar disorder typically has a different course and may involve a separate genetic predisposition.

As of December 1991, 106 schizophrenic patients had been entered into the standardized-medication outpatient period and 57 matched normal control subjects had reached this same point (second major test battery). In addition, 30 bipolar affective disorder patients had been entered into the Phase I protocol. The demographic characteristics of this sample at project entry are presented in table 2. As would be expected for a sample with a recent onset of schizophrenia, the patients are typically young adults with an average educational level slightly above high school graduation. The predominance of males was somewhat surprising, because schizophrenia has traditionally been regarded as distributed equally by sex. A survey of admissions at the public hospitals from which we draw subjects indicates that the sex ratio among recent-onset schizophrenic patients is very similar to the ratio entering Phase 1, so the predominance of males does not reflect a differential rate of refusing participation. In any case, the relatively small number of females in our sample limits our ability to evaluate definitively whether vulnerability, stress, and protective factors in schizophrenia differ significantly by gender.

The total lifetime duration of psychiatric symptoms for the schizophrenic patients, including symptoms prodromal to the initial psychotic symptoms, before project entry averaged 16.0 months (standard deviation [SD] = 13.1). The total lifetime duration of psychotic symptoms for the bipolar patients, including prodromal symptoms, was 10.3 months (SD = 8.2). Thus, the patient groups had only very brief periods of psychiatric symptoms before project entry, even when prodromal symptoms were included. At project intake, about 70 percent of the schizophrenic patients were in the midst of a first episode that had lasted less than 6 months. The remainder were in the midst of a first psychotic episode that had lasted more than 6 months or had experienced a first episode that began less than 2 years before project contact. Sixty percent of the schizophrenic patients had no hospitalization before the index admission; 29 percent had one prior hospitalization, 8 percent two, and 3 percent three. Prior hospitalizations were typically just before the index admission, but in some cases were for an earlier nonpsychotic disorder or for a first psychotic episode that had occurred earlier in the 2-year period used to define a recent onset of psychosis. Mean lifetime duration of psychiatric hospitalization for the schizophrenic patients at discharge from the index hospitalization was 6.0 weeks (SD = 7.8). The mean duration of the index hospitalization

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Gender</th>
<th>Ethnicity/race</th>
<th>Education (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenic patients (n = 106)</td>
<td>23.3 (4.3)</td>
<td>87 M</td>
<td>91 Anglo</td>
<td>12.4</td>
</tr>
<tr>
<td>Normal comparison subjects (n = 57)</td>
<td>23.7 (4.0)</td>
<td>42 M</td>
<td>52 Anglo</td>
<td>13.4</td>
</tr>
<tr>
<td>Bipolar-manic comparison patients (n = 30)</td>
<td>22.3 (4.1)</td>
<td>15 M</td>
<td>27 Anglo</td>
<td>13.6</td>
</tr>
</tbody>
</table>

Note.—Numbers in parentheses are standard deviations.
was 4.7 weeks (SD = 5.7), and 66 percent of the schizophrenic patients had never taken antipsychotic medications before the index hospitalization. In the remainder, the mean duration of prior neuroleptic use was 2.7 months (SD = 3.1).

The mean time interval from the initial inpatient assessment battery to the first outpatient battery on a standardized dosage of fluphenazine decanoate for the schizophrenic patients was 108 days (SD = 57). The outpatient battery was completed about a month after the standardized medication dosage was established. The treating psychiatrist gradually changed antipsychotic medication to the standardized dosage as judged appropriate based on resolution of the acute psychotic symptomatology. The relatively low level of psychiatric symptoms remaining at the initial outpatient assessment on standardized medication (Phase 1 entry) is evident in the BPRS factor scores and total score from this point, as presented in table 3. For comparison, the even lower BPRS scores for subjects entering into the later drug crossover protocol are shown at their Phase 2 entry point. During Phase 1, an adjustment in the fixed dose of medication was found to be necessary for 11 patients (10%) due to intolerable side effects on 12.5 mg fluphenazine decanoate every 2 weeks. The fixed dosage was changed to 10 mg for four patients, to 7.5 mg for one patient, and to 6.25 mg for six patients. Five patients were judged to need antidepressant medication and were prescribed supplementary medication as needed during the standardized antipsychotic medication period. Medications to aid sleep were also used if required, but this was uncommon. If a patient had a psychotic exacerbation or any form of relapse, the treating psychiatrists changed or added medications as necessary.

### Table 3. Mean Brief Psychiatric Rating Scale scores for schizophrenic patients at outpatient entry points for Phase 1 and Phase 2

<table>
<thead>
<tr>
<th>Project phase</th>
<th>Total score</th>
<th>Anxiety-depression</th>
<th>Anergia</th>
<th>Thought disturbance</th>
<th>Activation</th>
<th>Hostile suspicion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1: Initial outpatient test</td>
<td>27.2 (9.0)</td>
<td>1.8 (1.0)</td>
<td>1.7 (0.8)</td>
<td>1.4 (0.7)</td>
<td>1.3 (0.5)</td>
<td>1.3 (0.7)</td>
</tr>
<tr>
<td>(n = 106)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase 2: Entry to drug crossover</td>
<td>22.4 (4.2)</td>
<td>1.3 (0.4)</td>
<td>1.6 (0.8)</td>
<td>1.0 (0.2)</td>
<td>1.1 (0.2)</td>
<td>1.1 (0.4)</td>
</tr>
<tr>
<td>(n = 48)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1Total score and factor scores are for the 18 items included in the 5-factor solution presented by Guy (1976). Possible range for total score is 18 to 126 and for factor scores is 1 to 7. Numbers in parentheses are standard deviations.

### Experimental Design for Phase 2

**Phase 2: Double-Blind Crossover and Withdrawal of Neuroleptics in Recent-Onset, Remitted Schizophrenia.** Schizophrenic patients showing sufficient remission of psychotic symptoms after at least 1 year of maintenance antipsychotic medication are invited to participate in Phase 2 of the project. Phase 2 involves a drug crossover design, including a trial period of 12 weeks on placebo, to determine whether continuous neuroleptic medication is required, followed by an open medication withdrawal period for patients who show no return of psychotic symptoms during the crossover period. Patients who do not meet criteria to enter Phase 2 or who choose not to enter are invited to continue treatment on maintenance antipsychotic medication.

The first part of Phase 2 involves a 24-week double-blind drug crossover design, as diagrammed in figure 3. The assessment battery is nearly identical to that of Phase 1, including measures of plasma levels of fluphenazine and prolactin, information processing, SPEM, autonomic nervous system activity, attitudes of significant others, stressful life events, social network, psychiatric symptoms, social functioning, and work functioning. The span of apprehension procedure in the drug crossover and withdrawal protocols is adapted to examine more specifically the nature of information-processing abnormalities in schizophrenia and the impact of antipsychotic medication on these processes. A forced-choice, partial-report condition is retained, but a full-report condition is added as a contrast (Asarnow et al. 1991). Heart rate recordings are added to the electrophysiological session to distinguish between orienting responses, defensive responses, and startle responses, particularly in response to 98-decibel (dB), fast rise-time bursts of white noise (Graham 1979). To make the test battery more manageable during the frequent assessments of the drug crossover protocol, the
Figure 3. Schematic summary of the research design and timing of key measures in the protocols of Phase 2

<table>
<thead>
<tr>
<th>Months Since Stabilized on 12.5 Mg. Prolixin Decanoate</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>19</th>
<th>20</th>
<th>21</th>
<th>22</th>
<th>23</th>
<th>24</th>
<th>25/36</th>
</tr>
</thead>
<tbody>
<tr>
<td>FPZ</td>
<td>FPZ</td>
<td>Placebo</td>
<td>FPZ</td>
<td>Placebo</td>
<td>Off Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPZ</td>
<td>Placebo</td>
<td>Off Medication</td>
<td></td>
<td></td>
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<td></td>
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</tr>
</tbody>
</table>

Measures

- Information Processing: (continues at monthly intervals)
- Smooth Pursuit Eye Movements: (continues at 3-month intervals)
- Electrodermal Activity & Heart Rate: (continues at monthly intervals)
- Plasma Assays: (continues at monthly intervals)
- Atitudes of Significant Others: (Retest only if necessary)
- Life Events: (continues at monthly intervals)
- Social Network: (continues at monthly intervals)
- Strauss/Carpenter Outcome Scales: (continues at monthly intervals)
- BPRS/PAS: (continues at monthly intervals)
- Depression (Hamilton Depression): (continues at monthly intervals)
- Negative Symptoms (SANS): (continues at 3-month intervals)

Note.—FPZ = fluphenazine decanoate; Strauss/Carpenter Social Contact and Work Outcome Rating (Strauss and Carpenter 1972); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962; Lukoff et al. 1986b); PAS = Psychiatric Assessment Scale (Krawlecka et al. 1977); Hamilton Depression = Hamilton Depression Rating Scale (Hamilton 1967); SANS = Schedule for Assessment of Negative Symptoms (Andreasen 1982).

digit-span distractibility task and the cognitive slippage vocabulary test are omitted during this period. However, at the major testings in the later open drug withdrawal protocol, these two measures plus the span of apprehension procedure from Phase 1 are added to allow examination of trait/state issues for these potential vulnerability factors in an unmedicated state. At the patient’s entry into the crossover protocol, the Camberwell Family Interview (CFI; Vaughn and Leff 1976b), the Five-Minute Speech Sample technique (FMSS; Magaña et al. 1986), and a Thematic Apperception Test (TAT; Jones 1977) of communication style are administered to all significant others living or in weekly contact with the patient. The TAT procedure measures unclear or idiosyncratic communication of themes or ideas, language anomalies, disruptive speech, lack of
In order to further our understanding of information processing and psychophysiologic functioning during psychotic exacerbation. Information-processing and psychophysiological variables that change with psychotic state during a medication-free period might be candidates for early warning signals of impending psychotic symptoms.

To evaluate relatively long-term stability of potential vulnerability factors relevant to schizophrenia, schizophrenic patients are administered a test battery with the same measures 3 years after the initial outpatient assessment in Phase 1.

Subject Selection for Phase 2. The schizophrenic patients who complete the Phase 1 standardized treatment form the base population from which Phase 2 subjects are recruited. The paired normal subject for each schizophrenic patient from Phase 1 serves as the normal comparison subject for Phase 2. Thus, normal subjects are not only matched individually with the schizophrenic patients for age, education, gender, and race, but also for time intervals between tests in the preceding phase. Patients completing Phase 1 are considered for this protocol if they (1) have received at least 1 year of maintenance antipsychotic medication in the Af-
through both conditions of the drug crossover protocol and the open drug withdrawal protocol unless they withdraw permission for the study or they experience psychotic exacerbation or clinical relapse. The following criteria are used during this project phase: (1) psychotic exacerbation is defined as any 2-point total change in the sum of the three BPRS psychotic scales (Hallucinations, Unusual Thought Content, and Conceptual Disorganization), not counting changes at or below 3 on each scale (nonpsychotic levels); (2) psychotic relapse is defined as a 6 or 7 on BPRS scales for Hallucinations, Unusual Thought Content, or Conceptual Disorganization; (3) relapse of a nonpsychotic type is defined as 6 or 7 on scales of Bizarre Behavior, Self-Neglect, Hostility, Depressive Mood, or Suicidality; and (4) a clinical relapse is declared if the treating psychiatrist decides to break the double-blind code for clinical reasons, even if these reasons are not reflected in the first three exacerbation/relapse criteria.

If a patient experiences a psychotic exacerbation or relapse, information-processing and psychophysiological testing is done, a blood sample is drawn, and the patient is then treated according to the clinical needs of the situation.

Results and Discussion

The results to date from this ongoing project will be summarized by substantive area. Selected summary variables were chosen a priori from major substantive domains for a multivariate predictive model (figure 4). Indices of possible vulnerability factors include the patient’s familial loading for schizophrenia, information-processing abnormalities, and autonomic activation levels. Familial loading is an index of possible genetic predisposition based on the weighted prevalence of schizophrenia spectrum disorders in first- and second-degree relatives of the proband. Information-processing abnormalities are represented primarily through vigilance and forced-choice span of apprehension performance, while autonomic activity is measured by electrodermal activation level. Premorbid social adjustment level is included to reflect earlier influences on interpersonal functioning. Independent life events and the presence of critical or emotionally involved attitudes in the immediate social environment are the a priori indices of potential stress factors. Patient symptomatic level at entry is included to allow an examination of the extent to which other predictive relationships are independent of patients’ initial symptom levels. In addition to these individual predictive relationships, the predictive roles of selected interactions between hypothesized internal vulnerability and external environmental factors are being tested.

The final application of the full multivariate model for prediction of outcome in the two project phases is being reserved until subjects complete the respective follow-through periods. However, analyses have been completed to assess the interrelationship of variables within substantive domains and to examine the relationship of key variables to concurrent symptomatic levels. A priori predictors have been examined in Phase 1 to determine their univariate relationship to psychotic exacerbation or relapse. Several potential vulnerability indicators have
been examined during Phase 1 to determine whether longitudinal data support their role as stable vulnerability indicators, mediating vulnerability factors, or episode indicators. The signs and symptoms that precede relapses have been examined in a supplementary analysis (Subotnik and Nuechterlein 1988) to determine the extent of distinctive prodromal features. Finally, the persistence of fluphenazine in plasma for subjects entering the drug crossover protocol was presented in a preliminary report (Gitlin et al. 1988). The reader will note that sample sizes vary with the point in ongoing data collection at which a given form of data analysis was completed. Major data analyses were completed in 1985 and 1988 and are underway at this writing in late 1991.

Information Processing. The first analyses in this area focused on the concurrent relationships between information-processing performance and symptomatic levels for 40 schizophrenic patients at the initial inpatient and outpatient assessments during Phase 1 (Nuechterlein et al. 1986a). Cross-temporal relationships between these two initial testing points were also examined. The 5-factor solution for the 18-item BPRS (Guy 1976) was used to summarize symptom dimensions. Information-processing impairments were indexed by tachistoscopic signal/noise discrimination in a forced-choice span of apprehension task, which is a measure of early components of visual processing (Estes and Taylor 1964; Asarnow et al. 1991) and by two versions of the Continuous Performance Test (CPT), a test of visual vigilance or sustained attention (Rosvold et al. 1956; Nuechterlein 1991). The forced-choice span of apprehension involves detecting which of two target letters are present in very briefly presented letter arrays of varying size, while CPT tasks involve detecting occurrences of target characters within a rapidly paced, quasi-random sequence of letters or numbers that typically lasts 5 to 15 minutes. One CPT required the subject to detect occasions when a “3” preceded a “7” in a series of single digits (3-7 CPT), while the other required the detection of the blurred digit “0” in a series of blurred single digits (degraded-stimulus CPT). Signal/noise discrimination deficits on the memory-load CPT (3-7 CPT), the CPT using degraded numerals to burden early perceptual processes, and a forced-choice span of apprehension task during the inpatient period were found to be mildly but significantly correlated (p < 0.05) with the presence of concurrent negative symptoms (indexed by the BPRS Anergia factor and particularly the Blunted Affect and Motor Retardation items), but not with the presence of hallucinations or delusions (BPRS Thought Disturbance factor and particularly the Hallucinations and Unusual Thought Content items). Based on prior research with offspring of schizophrenic patients (e.g., Asarnow et al. 1977; Rutschmann et al. 1977; Nuechterlein 1983; Cornblatt and Erlenmeyer-Kimling 1985), we hypothesize that these tachistoscopic signal/noise discrimination indices are vulnerability factors for development of schizophrenic symptoms rather than part of the acute symptomatic picture. Therefore, we predicted that similar relationships would be found between performance on these three information-processing tasks measured at a point of clinical stability and negative symptoms during episodes. Indeed, low scores for the signal/noise discrimination index (d') from each CPT measured at the clinically stabilized outpatient point were found to be significantly related to negative symptoms during the inpatient period. This cross-temporal relationship occurred without a concurrent association between these same variables at the initial outpatient testing point, an occasion at which both positive and negative symptoms had generally subsided. Thus, signal/noise discrimination levels on these tasks are related to negative symptoms in a fashion consistent with their hypothesized role as vulnerability factors and are not just correlates of acute symptomatology.

Low outpatient signal/noise discrimination during the degraded-stimulus CPT was also significantly related to high inpatient formal thought disorder characteristic of schizophrenia as measured by the Rorschach Thought Disorder Index, particularly the Fluid Thinking factor (Johnston and Holzman 1979; Holzman et al. 1985). Similar relationships were present for the outpatient 3–7 CPT and forced-choice span of apprehension and the inpatient BPRS Conceptual Disorganization rating. Because these cross-temporal relationships could not be accounted for by cross-sectional relationships between these variables, they are also consistent with the view that impaired signal/noise discrimination on these tasks is a vulnerability factor for the development of schizophrenic formal thought disorder (Nuechterlein et al. 1986a).

Subsequent analyses have directly addressed the distinction between stable vulnerability indicators, mediating vulnerability factors, and episode indicators that was diagrammed in figure 1. We selected those schizophrenic patients who were tested in a clinically remitted state and in a psy-
schotic state while on identical levels of antipsychotic medication. Clinical remission was defined as having no BPRS rating in the 4 to 7 (pathological) range for at least a month, reflecting an absence of positive and negative symptoms of schizophrenia and also of other psychiatric symptomatology. Psychotic states were defined by a return to ratings of 4 (moderate) or higher on the Unusual Thought Content, Hallucinations, or Conceptual Disorganization items and an increase of at least 2 points in the sum of these three scales. Most patients entering Phase 1 (current \( n = 106 \)) have met criteria for clinical remission during the initial outpatient year. However, only about one-third of the entered patients can be used for analyses of the extent to which characteristic information-processing or psychophysiological anomalies reflect traits rather than clinical states in schizophrenic patients. Most patients are excluded from this form of analysis by an absence of any returning psychotic symptoms during the standardized-medication period.

Preliminary analyses reported by Nuechterlein and colleagues (1991a), based on data collected through mid-1988, involved 17 schizophrenic subjects and 17 matched normal controls tested at comparable intervals. To allow inclusion of six patients who did not yet have a matched control at that point, tested normal controls who were appropriate matches in demographic variables were used for these analyses. As shown in figure 5, the patients and normal subjects had comparable mean scores on the BPRS Thought Disturbance factor at the patients’ remission point, but not at the patients’ psychotic point. Our selection criteria led to a substantial separation of the groups on the mean Thought Disturbance factor score at the patients’ psychotic point; Cohen’s \( d \) (Cohen 1988), an index of effect size in SD units, was 3.82. The patients were particularly likely to meet criteria for a psychotic point through return of delusions or hallucinations (see Unusual Thought Content rating, figure 5); clinically noteworthy increases in conceptual disorganization were rare.

Performance on the 1- and 10-letter arrays of the forced-choice span of apprehension at these same points is shown in figure 6 for the 13 of 17 schizophrenic and normal pairs for whom complete span data were available for the normal controls (Nuechterlein et al. 1991a). (Four test sessions from the substitute matched normal controls did not include this span version because they were drawn from drug crossover test batteries of normal subjects, used to equate number of prior testing sessions.) Performance on the 1-letter forced-choice span was used as an index of understanding task directions, cooperation, and ability to master the forced-choice response format. In the left panel, it is apparent from the \( p \) values for the planned \( t \) tests at each testing point that patients did not differ from normal controls at either occasion on this control task. Each of the mean scores approached a perfect score of 40 in this condition. However, for the 10-letter arrays, significant defi-
Figure 6. Mean number of correct target identifications on forced-choice span of apprehension task at test occasions chosen for remitted and psychotic states within the same patients


Note.—n = 13 patients, 13 matched controls.

cits were found for the schizophrenic patients at both the clinical remission and the psychotic point, as summarized in the right panel of figure 6. The extent of this deficit in early visual information processing was comparable at the two test points. The educational matching of schizophrenic and normal controls eliminates education as a source of these deficits and also makes it unlikely that premorbid differences in general intellectual ability were the source (Chapman and Chapman 1973). These preliminary analyses suggest that this anomaly in the number of letters that can be scanned in early visual processing fits the pattern of a stable vulnerability indicator for schizophrenia. The deficit is associated with conditions demanding rapid processing of a high input load by components of visual processing that precede active, short-term memory (Sperling 1960; Estes and Taylor 1964).

Parallel analyses were completed with CPT data from the 17 pairs of schizophrenic patients and normal controls (Nuechterlein et al. 1991a). As shown in figure 7, signal/noise discrimination level (d') in the degraded-stimulus CPT (Nuechterlein et al. 1983) is very clearly deficient for these recent-onset schizophrenic patients in both the psychotic and the clinically remitted state. The tendency for schizophrenic patients to have slightly larger d' deficits during their psychotic state was not significant, as is evident in the interaction p value. Thus, the degraded-stimulus version of the CPT, which like the forced-choice span of apprehension particularly burdens early perceptual analysis aspects of information processing, also appears to be a promising stable vulnerability indicator for schizophrenia.

In contrast to these two measures, signal/noise discrimination level (d') in a memory-load CPT (3-7 CPT) also significantly differentiated the 17 patients from the 17 matched normal controls during both the remission and psychotic states of the patients in these preliminary analyses, but the patients' target discrimination also declined strikingly during their psychotic state (figure 8). The greater deficit among the schizophrenic patients during the psychotic state as compared to the clinical remission state was demonstrated by a highly significant interaction, p < 0.002. This pattern is characteristic of a potential mediating vulnerability factor (Nuechterlein and Dawson 1984a). Rather than the demand for difficult and immediate perceptual discriminations that characterizes the degraded-stimulus CPT, the 3-7 CPT requires memory of the prior stimulus to determine whether the current stimulus is a target (Nuechterlein et al. 1986a). Thus, the 3-7 CPT demands use of both contextual cues (Cohen and Servan-Schreiber 1991) and active, working memory (Goldman-Rakic 1991). A tentative hypothesis derived from our forced-choice span and CPT results is that an early perceptual component of information processing is a stable trait associated with vulnerability to schizophrenia, whereas a disturbance in the use of active, working memory to cue relevance of current stimuli becomes more severe during the psychotic state. Labeling the 3-7 CPT d' as a
Figure 7. Mean signal/noise discrimination level (d') during the degraded-stimulus Continuous Performance Test (DS-CPT) at test occasions selected for remitted and psychotic states within the same patients.


Note.—n = 17 patients, 17 matched controls. DS-CPT (Nuechterlein et al. 1983).

Potential mediating vulnerability factor highlights the possibility that increased disturbance in the use of working memory to cue current stimulus selection might actually precede the appearance of psychotic symptoms and serve as one of the causal factors for such symptoms.

These preliminary results from comparisons of the schizophrenic patients and the normal controls do not address the issue of the specificity of these findings to schizophrenia. Thus, we have also recently completed an initial set of parallel analyses with the first 7 bipolar manic patients who could be tested in both a manic state and a clinically remitted state as well as an expanded sample of 25 schizophrenic patients and matched normal controls tested in psychotic and clinically remitted states (summarized briefly in Nuechterlein et al. 1991b).

Of note here is that bipolar patients during their manic state had significant d' deficits on both CPT versions compared to normal controls and similar, but nonsignificant, deficits for the 10-letter arrays of the forced-choice span. However, the task performance of the bipolar patients during clinical remission did not differ from that of normal controls. Thus, preliminary analyses suggest that these information-processing deficits are trait-like aspects of vulnerability in schizophrenia but are generally state-linked in bipolar disorder.

To examine the internal structure of these information-processing variables, a principal components analysis of the primary signal detection theory indices from the degraded-stimulus CPT, 3-7 CPT, and forced-choice span of apprehension was completed for the schizophrenic patients. The signal/noise discrimination indices (d' level for the CPTs and P(C) for the forced-choice span) loaded on one factor, which we named "Tachistoscopic Signal Discrimination," and the response criterion indices from the CPTs (beta) loaded on a second factor, named "Response Caution" (Nuechterlein et al. 1989). This factor solution is similar to that found by Nuechterlein (1983) for five conditions of the CPT among 9- to 16-year-old normal subjects, but in this case also shows that target discrimination on the forced-choice span shares variance with signal/noise discrimination on CPT tasks. Thus, although the individual indices within the two factors from these schizophrenic patients correlate in the 0.30 to 0.50 range and therefore have substantial unique variance, for some purposes composite scores across these three visual information-processing tasks may serve as useful summary measures.

One such application of summary dimensions has involved a test of whether the information-processing abnormalities in the patients measured by the CPT and forced-choice span might show familial transmission consistent with a genetic vulnerability factor. In an initial test of the relationship of these patient deficits to subtle perceptual or cognitive anomalies in other genetically related individuals, we used parental measures of atypical perceptions and language usage during the TAT. Although the measures of "communication deviance" (Jones 1977) have
Figure 8. Mean signal/noise discrimination level (d') during a memory-load Continuous Performance Test (CPT) at test occasions selected for remitted and psychotic states within the same patients.

![Graph showing mean signal/noise discrimination level (d') during a memory-load Continuous Performance Test (CPT) at test occasions selected for remitted and psychotic states within the same patients.](image)

CLINICAL STATE OF PATIENTS

- Schizophrenic Pts
- Normal Controls

Note.—3-7 CPT refers to the target sequence, a “3” followed by a “7” in successive trials. Working memory must be used to store the prior stimulus in order to determine whether the current stimulus requires a response. CPT (Rosvold et al. 1956; Nuechterlein 1991).

traditionally been associated with research on environmental factors in schizophrenia, at least two factor scores (Contorted, Peculiar Language and Misperceptions) derived from these stories about the ambiguous TAT cards can also be viewed simply as indicators of subtle, subclinical thought disorder and perceptual anomalies. In these initial analyses with 40 schizophrenic patients, only mothers' TAT scores could be examined because only 18 of the biological fathers participated in the TAT assessment. As hypothesized, we found significant correlations between low Tachistoscopic Signal Discrimination factor scores from patient CPT and forced-choice span performance and high parental scores for Misperceptions (r = -0.34) and Contorted, Peculiar Language (r = -0.40) (Nuechterlein et al. 1989). Although the magnitude of these correlations might seem low at first, their relative strength is apparent when one considers that a trait transmitted by a simple additive genetic model would not be expected to have a correlation magnitude higher than 0.50 between the midparent and offspring values (midparent refers to the average of the scores of the biological parents). These findings extend the results of Wagener and colleagues (1986), who also found a relationship between Misperceptions of biological mothers and aspects of schizophrenic patients' forced-choice span and CPT performance. Of course, we cannot at present rule out environmental contributions to these parent-child correlations, but further examination of genetic transmission of these subtle perceptual and cognitive abnormalities relevant to schizophrenia certainly appears to be warranted.

We have also addressed the issue of whether smooth pursuit eye-tracking impairment, a promising vulnerability indicator sometimes described as measuring an involuntary form of attention (Holzman et al. 1978), is related to impairments on the CPTs and the forced-choice span. Stoddard (1989) found that qualitative smooth pursuit eye-tracking scores showed modest but significant relationships (r = 0.25 to 0.35) with signal/noise discrimination in each of the CPTs and the forced-choice span for 99 schizophrenic patients tested at the initial inpatient screening point. Degraded-stimulus CPT performance was also significantly related to eye-tracking performance in 44 normal subjects (r = 0.42 at initial test), although 3-7 CPT and forced-choice span performance was not. Thus, some common variance among these promising vulnerability indicators is indicated, particularly within the schizophrenic sample, but each of the measures also clearly has substantial unique variance as well.

In preliminary analyses examining the prediction of outcome during the 1-year, standardized medication period, a summary factor score from the two CPTs and the forced-choice span did not predict likelihood of psychotic relapse. However, it did show promise for predicting occupational outcome (amount of useful work) in the first outpatient year.
In summary, analyses to date suggest that signal/noise discrimination levels in the degraded-stimulus CPT, 3-7 CPT, and the forced-choice span identify deficits among schizophrenic patients that often continue into clinically remitted periods. These promising indicators of vulnerability factors share some variance with each other and with SEMP dysfunctions and are related to measures of subtle language and perceptual anomalies among biological parents. The memory-load (3-7) version of the CPT is also quite sensitive to changes from remission to psychotic states, suggesting that disturbances in use of working memory for contextual cueing of responses accompanies and might contribute to psychotic symptoms.

Autonomic Nervous System Activity. Primary analyses in this domain have addressed (1) the presence of characteristic schizophrenic abnormalities in electrodermal activity during the early phase of schizophrenia; (2) relationships among electrodermal activity, concurrent symptom levels, and recovery from the index episode; and (3) the extent to which skin conductance abnormalities during the standardized-medication period reflect state-sensitive episode indicators versus enduring vulnerability factors. Because methods and a recent wave of analyses in this area have been summarized in a separate article (Dawson et al. 1992a), our description of them here will be relatively brief.

A recent comparison of 98 schizophrenic patients who exhibited psychotic symptoms at the initial inpatient assessment and 40 normal comparison subjects indicated that a disproportionately large number of patients were skin conductance nonresponders during conditions in which loud white noise bursts were stimuli or tones were given task significance—both conditions in which the stimuli require attention (Dawson et al. 1992a). These findings indicate that the electrodermal nonresponsivity typically found to characterize a subgroup of chronic schizophrenic patients (Ohman 1981; Dawson and Nuechterlein 1984; Bernstein 1987) is also present during the initial phase of illness, although in this case the abnormality is not elicited in an innocuous tone condition, probably due to an unusually high number of nonresponders among normal subjects in this condition. Schizophrenic patients who did show a skin conductance orienting response (responders) showed significantly more (p < 0.02) nonspecific skin conductance responses than normal subjects who showed skin conductance orienting responses, suggesting that they were more electrodermally activated than the normal comparison subjects. Thus, both the disproportionate number of nonresponders and the excessive electrodermal arousal of the responders that have been found among chronic schizophrenic patients were also found among these recent-onset patients (Dawson et al. 1992a).

The second topic, the symptomatic correlates of electrodermal activity within the schizophrenic sample and prediction of the extent of symptomatic recovery from the index episode, has been examined recently by Dawson and colleagues (1992b) in 69 of the patients who had electrodermal data available from both the initial inpatient and the initial outpatient assessment points. In the 56 males, heightened electrodermal activity (nonspecific skin conductance responses and trials to habituation) was found to be concurrently associated with higher BPRS Activation at the initial inpatient test and with BPRS Total Psychopathology score and four of the five factor scores at the initial outpatient test. Heightened electrodermal activity at the initial inpatient assessment also significantly predicted higher outpatient symptom levels (BPRS Total Psychopathology score and four of five factor scores) at the initial outpatient testing point, which occurred approximately 3 months after hospital discharge. In female patients, these correlations were near zero and never significant, but the sample of females was too small (n = 13) to allow definite conclusions. These results indicate that heightened autonomic activation is correlated across subjects with the level of symptoms in schizophrenia, at least in male patients, and has a role in predicting the extent of short-term symptomatic recovery from the initial episode in these recent-onset patients.

To address the within-subject relationships between autonomic activity and clinical state and the distinction between stable vulnerability indicators, mediating vulnerability factors, and episode indicators, we have recently completed analyses with 24 schizophrenic patients who were tested in a clinically remitted state and in a psychotic state on the same standardized dosage of antipsychotic medication and 24 demographically matched normal controls (Dawson et al., in preparation). These pairs of patients and normal controls are identical to the ones described in the information-processing performance section, with the exception of one whose electrodermal data were invalidated by equipment failure. The tonic electrodermal measures—frequency of nonspecific skin conductance responses and skin conductance level—were found to correspond well
to the pattern characteristic of episode indicators. That is, they yielded a significant interaction between diagnostic group and clinical state ($p < 0.05$) in which schizophrenic patients showed normal electrodermal activation during remission but had significantly higher activation than normal controls during their psychotic states. For the number of skin conductance orienting responses during the three auditory stimulus conditions, the schizophrenic patients did not differ significantly from the normal controls in either of their clinical states, although schizophrenic patients during their remitted state were more likely than normal subjects to be nonresponders to innocuous tones by a strict definition of nonresponder.

Thus, the clearest evidence from these trait/state analyses suggests that abnormally high tonic electrodermal activation accompanies schizophrenic psychotic states and qualifies as an episode indicator (Dawson et al., in preparation). Because electrodermal activation level is known to be affected by at least some antipsychotic medications (Ohman 1981), this conclusion will need to be examined again for remission and psychotic exacerbation states that occur during the drug withdrawal phase of the project to determine whether it generalizes to unmedicated conditions. These results suggest that electrodermal activation level is not an enduring vulnerability factor, at least not while patients are receiving antipsychotic medication, but leaves open the possibility that electrodermal activation plays a role in psychotic relapse as a transient intermediate state (Nuechterlein and Dawson 1984a; Dawson and Nuechterlein 1987). As described by Dawson (1990) and Dawson and colleagues (1992a), initial evidence from two of three schizophrenic patients who were assessed just before a psychotic exacerbation suggests that increased electrodermal activation sometimes actually precedes psychotic symptoms.

In the heuristic vulnerability/stress model that serves as an organizing tool for this project (see figure 1), autonomic activation level is hypothesized to be a mediating process affected by the interaction between the patient and the environment during the prodromal period. To shed light on this possibility, we examined electrodermal activation levels of patients who had experienced a prominent life event not under their influence during the month preceding electrodermal assessment. Although these occurrences were rare, patients with such preceding independent life events were found to have significantly higher electrodermal activation levels than other patients (Ventura et al. 1986; Nuechterlein et al. 1989).

In summary, our electrodermal analyses to date are most consistent with the view that autonomic activation level is not an enduring vulnerability factor in schizophrenia, at least not during medicated periods, but serves as a psychophysiological index of clinical state, helps to predict recovery from the index episode, may be a mediator of the impact of the environment on the schizophrenic individual, and might have promise as an early indicator of increased risk for return of psychotic symptoms.

Stressful Life Events. The possible role of stressful life events in triggering psychotic exacerbations and relapses has been examined in the initial standardized-medication period and in the subsequent drug withdrawal period. An adaptation of the Psychiatric Epidemiology Research Interview for Life Events (Dohrenwend et al. 1978) is used to assess life events monthly. Our initial test of the relationship between life events and psychotic exacerbation or relapse focused on the medicated period (Ventura et al. 1989). Life event frequencies in the months immediately preceding psychotic exacerbation or relapse for 11 patients were carefully contrasted with life event frequencies of the same 11 patients during other periods and with life event frequencies for 19 nonrelapsing patients. The frequency of all life events, total negative events, and events that were of sufficient magnitude to be considered life changes by the Brown and Harris (1978) standard were examined. As we hypothesized, a significantly higher number of independent life events was found in the month before relapse (mean = 0.73; $SD = 1.00$) compared with an analogous month for the same patients that did not precede a relapse (mean = 0.07; $SD = 0.24$; $t = 2.32; df = 10; p < 0.025$; one-tailed, paired test), as shown in figure 9. A McNemar test for correlated proportions also indicated that the number of patients who had an independent life event in the month before relapse (5 of 11) was significantly higher than in the analogous month during the nonrelapse period (1 of 11).

To provide a comparison to life event rates for nonrelapsing patients, the average number of life events per month during a 1-year standardized medication period was computed. The rate of life events during the month before the 11 psychotic relapses was also significantly higher than the 1-year average rate of independent life events for nonrelapsing patients (Ventura et al. 1989). Thus, we have found critical support for
the view that independent life events in some cases may trigger psychotic episodes in schizophrenic patients being maintained on antipsychotic medication. Unlike prior studies suggesting such a relationship (Brown and Birley 1968; Day et al. 1987), this study involves life event data collected before the psychotic episodes occurred. Thus, the relationship between independent life events and psychotic relapse cannot be due to selective retrospective memory for events as a function of knowing the outcome at the time of life event reporting.

This confirmation of a relationship between recent independent life events and psychotic relapse while on maintenance medication led us to test whether a similar relationship existed during the Phase 2 drug withdrawal protocol, during which the need for continued medication was assessed. An early study by Leff and colleagues (1973) suggested that the increased incidence of independent life events before relapse might be limited to periods of maintenance medication. If this finding could be confirmed, it would lend support to the view that antipsychotic medication raises the threshold for return of psychotic symptoms such that occurrence of psychotic symptoms is less likely unless stressful life circumstances increase liability above this higher threshold (Nuechterlein and Dawson 1984a; Leff 1987).

To test this possibility, we (Ventura et al., in press) compared the frequency of recent life events for 10 patients who had a psychotic exacerbation or relapse while on a fixed dose of injectable fluphenazine and 13 patients who had a psychotic exacerbation or relapse after being off medication for a minimum of 12 weeks. Significant exacerbations and relapses were combined for data analyses. In addition to events independent of the patient's influence and symptomatology, we examined the frequency of personally influenced events, events secondary to the patient's illness, and all life events. We focused on life events that had been reported for the 3 months before the relapse.

As described in more detail by Ventura and colleagues (in press), a significant Medication Status × Time interaction occurred for the frequency of independent events meeting Brown and Harris (1978) criteria and the frequency of all independent events. As hypothesized, the mean number of independent life events was significantly higher in the 1-month period just before a relapse for patients on medication (mean = 0.80) than in the parallel month for drug-free patients (mean = 0.06). We also determined that 5 of the 10 patients (50%) who relapsed while on medication had experienced at least one independent life event during the month before relapse, while only 1 of the 13 patients (8%) who relapsed while drug-free had experienced such an event ($\chi^2 = 5.25; df = 1; p < 0.03$). These findings support the hypothesis that major stressful life events that are not under the patient's control or secondary to symptomatology play a stronger role in psychotic relapse during maintenance medication periods than during unmedicated periods. They also indirectly support the view that antipsy-
chotic medication may serve as a protective factor by raising the threshold for development of psychotic symptoms.

An intriguing tendency that only approached significance ($p < 0.10$) in these initial data was a higher frequency of personally influenced events among unmedicated patients than among medicated patients in the second and third months before psychotic relapse (Ventura et al., in press). Personally influenced events typically include expansions of life experiences, such as returning to work, promotion, or beginning a dating relationship, and major disappointments. We will examine further in subsequent data the possibility that the increase in nonindependent life events 2 to 3 months before return of psychotic symptoms while drug free represents a tendency for such patients to expand their life experiences beyond the stress levels that they can tolerate.

In summary, our results to date in this domain support our vulnerability/stress conception of the course of schizophrenia, which hypothesizes that stressful life events may in some cases serve as environmental potentiators for relapse in persons who have high psychobiological vulnerability to schizophrenia. In this conception, genetically influenced vulnerability factors are viewed as major determinants of proneness to schizophrenia (Gottesman and Shields 1982; Nuechterlein and Dawson 1984a; Nuechterlein 1987). Stressors in the biological and social environment may serve to trigger a reappearance of psychotic symptoms in persons whose liability to schizophrenia is already near a critical threshold for such symptoms. Our initial results also support the view that the role of independent life events in psychotic exacerbations and relapses may, ironically, actually be greater when patients are on maintenance neuroleptic medication than when they are off medication. This result is consistent with the view that neuroleptic medication serves as a protective factor by increasing the threshold for psychotic symptom formation, such that fluctuations above this threshold are less likely unless major life stressors occur.

**Attitudes of Significant Others.** Our analyses in this area have focused on the following: (1) determining whether the basic predictive relationship between attitudes of significant others toward the patient and relapse risk is present when standardized administration of maintenance antipsychotic medication is ensured by using an injectable, long-acting form; (2) determining the interrelationships among the patient’s age at illness onset, duration of the illness before hospitalization, EE attitudes, and psychotic relapse; (3) examining the bidirectional nature of interactions between patients and their significant others; and (4) determining whether a family education session with relatives of these recent-onset schizophrenic patients affects knowledge about schizophrenia, feelings of being supported by the treatment team, and attitudes toward the schizophrenic patient.

In a preliminary analysis, Nuechterlein and colleagues (1986b) examined data from the first 26 subjects who completed the 1-year, standardized-medication protocol and had significant others with whom CFIs could be completed. Previous studies of the relationship between high EE and relapse had not employed a standardized, fixed dose of antipsychotic medication and, with one exception (MacMillan et al. 1986), had not restricted their samples to recent-onset schizophrenic patients. Likelihood of psychotic relapse was significantly higher among patients whose significant others showed high EE, with relapse rates of 37 percent (7 of 19) for patients in high EE environments and 0 percent (0 of 7) for patients in low EE environments. Unlike the results of MacMillan and colleagues (1986), which suggested that longer duration of untreated illness predicted higher relapse rates and might account for the predictive relationship between high EE attitudes and psychotic relapse, duration of illness before index hospitalization in this sample was not related to either relapse or the level of EE attitudes.

To further resolve the differences between our results and those of MacMillan and colleagues (1986), we completed a more detailed examination of only those patients recruited during a strictly defined first psychotic episode. Mintz and colleagues (1989) found that the level of high EE among significant others was not related to the best estimate of illness duration before initial hospitalization. Best estimates were derived from a pooling of all information sources. Consistent with the finding of MacMillan and colleagues (1986), a relationship between long reported duration of illness and high EE was found when only direct parental observation of illness onset was considered. The discrepancy between parental report and best estimate of illness duration was primarily accounted for by underestimates of illness duration by parents with low EE. Illness duration reports from parents with high EE were generally quite accurate; overestimates were limited to parents of patients who had been living away from home before hospitalization. These findings indicate the difficulties of establishing
illness duration and suggest that a common attitudinal set may be reflected in both illness duration estimates and ratings of levels of EE. Further consideration of relationships among illness duration, EE attitudes, and relapse will require careful evaluation of the method used to establish illness duration.

We have also applied path analysis procedures to clarify relationships among patient background variables, EE attitudes, and relapse among the first 43 patients with relevant data who completed the Phase 1 protocol (Nuechterlein et al., in press). We continued to find support for the basic predictive relationship between high EE among significant others at the index hospitalization and higher relapse rates during the 1-year, standardized-medication period. Among these 43 patients, the rate of relapse was 39 percent (12 of 31) for patients who had at least one family member with attitudes toward the patient that were highly critical or emotionally overinvolved and 0 percent (0 of 12) for patients whose family members showed low EE (Nuechterlein et al., in press). Thus, the predictive relationship continues to hold even when antipsychotic medication compliance is enhanced by injectable medication and the overall relapse rate is relatively low. We also found a relationship between living at home before the index hospitalization and greater likelihood of highly critical or emotionally overinvolved attitudes among significant others at this hospitalization (Mintz et al. 1989), which we felt might reflect a tendency for such high EE to develop as a result of direct exposure to a patient's psychiatric symptoms. In subsequent analyses, we noted that patients with an earlier age of illness onset were more likely to be living at home before the index hospitalization. Path analysis allowed us to move beyond the basic predictive relationship between EE attitudes and relapse risk to examine possible specific alternative models relating age at illness onset, living with family members before the index hospitalization, EE attitudes, and later relapse. Path analyses evaluate the strength of hypothesized paths of influence between variables in a model with the alternative paths between the variables in the model statistically controlled (Loehlin 1987).

As Nuechterlein and colleagues (in press) report, a set of significant path relationships was found to link (1) earlier patient age at illness onset to greater likelihood of living at home with relatives before index hospitalization, (2) living with relatives before hospitalization to presence of high EE, and (3) presence of high EE to a higher relapse rate during the subsequent 1-year standardized-medication period. The direct paths from patient age at illness onset to subsequent relapse and from living with relatives before hospitalization to relapse were clearly not significant. These results suggest that high EE may develop, in part, through direct exposure to the patient during the period immediately before hospitalization, which is more common for patients who are younger at illness onset and thus more likely to be living at home. High EE then, in turn, appears to serve as a significant mediating factor in relapse risk, consistent with a vulnerability/stress conception of the course of schizophrenia.

The possibility that EE in significant others is a reflection of bidirectional influences between patients and persons in their immediate social environment has also been examined in several recent publications that use inpatient CFI data from this project as well as outpatient FMSS and direct interaction data gathered with a subset of the same families by a collaborating group led by Goldstein (Goldstein et al. 1989). Hahlweg and colleagues (1987, 1989) found through sequential analyses that families classified as high in EE based on critical comments about the patient during a FMSS showed an escalating interactive pattern of criticism between patient and significant others at the same time point; this was not true of other families of schizophrenic patients. The same negative sequence occurred whether started by a patient or a relative behavior (Hahlweg et al. 1987). Significant others who expressed critical attitudes about the patient in the FMSS made more criticisms and offered fewer positive solutions in direct interaction with the patient than significant others who showed either low EE or emotional overinvolvement with the patient in the same test. Patients from families in which at least one relative expressed critical attitudes showed significantly higher numbers of negative nonverbal behaviors, disagreements, and self-justifications in direct interaction with family members than did patients from families classified as low in EE based on the FMSS (Hahlweg et al. 1989). Thus, behaviors of patients and of significant others appear likely to contribute to a stressful emotional climate in families showing critical attitudes toward the patient.

Goldstein and colleagues (1989), Miklowitz and colleagues (1989), and Strachan and colleagues (1989) have further examined the probable bidirectional nature of EE by contrasting the coping styles of patients and the affective styles of relatives in families classified by EE level. As
compared to patients whose relatives showed low EE at the inpatient interview point, patients with a family member who showed highly critical or emotionally overinvolved attitudes at that earlier point exhibited more criticisms and fewer autonomous interests or wishes in a direct interaction task with the relatives 2 months later, regardless of whether the family members showed high EE at that outpatient point (Goldstein et al. 1989; Strachan et al. 1989). The affective styles of relatives in direct interaction with the patient were found to be significantly related to EE level rated from a concurrent FMSS but not to EE level rated from the CFI completed at the patient's index hospitalization (Miklowitz et al. 1989). The most common change in family EE level was from high at the inpatient point to low at this initial outpatient point. Combined with findings from prior studies, these results suggest that substantial change in attitudes and behaviors of significant others might occur immediately following the patient's hospital discharge, thereby lowering the correspondence between attitudes at the inpatient CFI and parental affective style during the outpatient period. This change, if confirmed through use of the same measure of EE at both points, would occur during a period in which patients' symptoms have decreased dramatically and might be expected to be a reaction to these decreased symptoms. No simple relationship between level of symptoms and either EE level or affective style of significant others, however, could be found (Goldstein et al. 1989; Miklowitz et al. 1989). Thus, additional measures of more subtle patient behaviors and of adaptational processes of significant others in response to the stress of the patient's psychotic episode may be needed to address these issues.

Results of a doctoral dissertation examining the impact of a 3-hour educational session with significant others that occurs after the initial CFI and FMSS measures deserve mention (Cozolino et al. 1988). This educational session is completed with groups of 6 to 10 relatives of patients, typically 2 to 3 months after the patient's admission to the UCLA Aftercare Clinic. Informal presentations by the clinic staff cover, in layman's language, the symptoms of schizophrenia, common misconceptions about schizophrenia, typical schizophrenic deficits in processing of information, biological factors in etiology, psychopharmacologic treatment, and basic practical advice regarding living with a family member with schizophrenia. Results of this dissertation indicate that, relative to a control condition, family members did experience an increased sense of support from the treatment team after this session and a nearly significant decrease in self-blame regarding the schizophrenic illness of their relative. The message from clinic staff that the family members are not to blame for the schizophrenic illness appeared to be one of the most helpful ingredients of this educational session.

Presence of Psychiatric Disorder Among Biological Relatives. The prevalence of major psychiatric disorder in first- and second-degree relatives is being examined as an index of familial genetic loading for major psychiatric disorders. An initial publication in this domain (Fogelson et al. 1991) has examined interrater reliability for the symptom dimensions used to diagnose personality disorders based on the Structured Clinical Interview for DSM-III-R, Axis II (SCID-II; Spitzer et al. 1987). Pairs of diagnostic interviewers rated symptoms for 45 SCID-II interviews, one based on a line interview with a first-degree relative of a schizophrenic or bipolar affective disorder patient and the second based on the audiotape of this interview. The interrater reliability ranged from 0.60 to 0.84 (intraclass correlation) for the symptom dimensions for five personality disorders, including 0.71 for paranoid and 0.72 for schizotypal personality disorder. Given the greater ambiguity of the boundaries for personality disorders compared to disorders such as schizophrenia and bipolar affective disorder, these levels of agreement suggest that the reliability of rating these personality disorder dimensions from the SCID-II is acceptable and is comparable to the levels in most other studies that have used structured interviews to assess DSM-III-R personality disorders.

We have also examined the correspondence between a personal history of psychiatric disorder in biological parents of the schizophrenic patients and the presence in the same parents of distinctive communication styles or of high EE attitudes toward the patient (Goldstein et al., in press). These analyses address the possibility that the communication styles or EE attitudes that have typically been considered psychosocial stress variables are associated with traditional psychiatric diagnostic constructs. We examined consensus best-estimate psychiatric diagnoses from the modified Diagnostic Interview Schedule (DIS; Robins et al. 1981) and PSE psychosis section for Axis I and from the SCID-II for Axis II for the biological parents of the schizophrenic patients. To provide adequate sample sizes within cells for the purposes of this initial analysis,
diagnoses for parents were grouped into the three categories of schizophrenia and bipolar spectrum disorders, other psychiatric disorders, and no psychiatric disorder. The communication styles were scored from the TAT using the modification of the Wynne and Singer (1963) scoring categories and the six factor scores derived by Jones (1977).

Of 56 biological parents of 41 recent-onset schizophrenic patients who also had EE and communication style data available from an earlier assessment, 7 were classified as having schizophrenia or bipolar spectrum disorders, 23 met criteria for other psychiatric disorders (primarily unipolar depression, including mild variants meeting RDC, substance abuse, or personality disorders outside the schizophrenia spectrum), and 26 had no psychiatric disorder (Goldstein et al., in press). The disorders ranged widely in severity, and their onset was usually reported to be many years before the onset of schizophrenia in the offspring, so most could not be viewed as wholly reactive to the occurrence of schizophrenia in the child. (This observation does not imply, however, that the onset of the child's schizophrenia did not result in severe additional distress for parents.) No significant relationships were found between the diagnostic categories and the six communication style factor scores from the TAT, although a tendency in the expected direction was present for the Misperceptions score.

For the indices of EE attitudes, a complex pattern emerged. Attitudes toward the patient rated as high in EE (criticism or emotional overinvolvement) based on the CFI were not significantly related to the categorization of the parents into the three diagnostic groups. Five of the seven parents with schizophrenia or bipolar spectrum disorder were rated as displaying high EE attitudes by this method. However, 61 percent of parents with high EE attitudes but also 28 percent of parents with low EE attitudes were judged to evidence some psychiatric disorder, contributing to an overall nonsignificant relationship (Goldstein et al., in press).

As categorized by the FMSS collected 5 to 6 weeks after the patient's hospital discharge, high EE attitudes were less frequent but significantly related to the presence of psychiatric disorder among biological parents. Of biological parents who exhibit high EE attitudes by this method at this point, 85 percent were judged to also show evidence of a psychiatric disorder, while 44 percent of parents with low EE attitudes showed evidence of a psychiatric disorder (Goldstein et al., in press). Combining the two EE rating methods to yield a pattern of EE over two points in time also resulted in a significant relationship with psychiatric disorder in the biological parent, such that parents rated as showing high EE attitudes toward the patient across two methods and two points in time were particularly likely to show evidence of some psychiatric disorder.

These findings raise important questions that we hope to address in further research with these recent-onset schizophrenic patients and in associated research with their relatives. First, it appears that the EE construct, at least as measured by the FMSS method after the patient has returned to the community, is not wholly independent of the presence of psychiatric disorder in the person whose attitudes are evaluated. Given the different timing of the CFI and the FMSS in the current data, at least two alternative interpretations are possible: Either the FMSS method is unduly sensitive to effects of psychiatric distress in the significant other as compared to the longer CFI method, or those relatives who show high EE attitudes toward the patient that do not change after the patient's acute episode are more likely to have sufficient psychiatric distress to meet criteria for a psychiatric disorder. Perhaps a psychiatric disorder experienced by a relative limits the ability to shift attitudes as the patient's clinical state improves (Goldstein et al., in press). The influence of the onset of the offspring's schizophrenia on the development and severity of psychiatric distress in parents also needs more specific examination, as clinical experience suggests that the emotional distress triggered by the onset of schizophrenia in a family member is often quite severe.

Another major issue to be addressed concerns prediction of the patients' short-term outcome based on these factors. How does presence of psychiatric disorder and of high EE attitudes in relatives combine to predict relapse risk for patients? Does the extent of a family history of psychiatric disorder account for some of the predictive power of highly critical or emotionally overinvolved attitudes in relatives? As the number of family members assessed increases, we also plan to examine whether the nature of any disorders in family members helps to predict psychotic relapse risk. Prior work (Vaughn and Leff 1976a) indicates that the presence of high EE attitudes in spouses of depressed patients predicts increased relapse risk, so the general predictive relationship is not limited to attitudes of biological relatives. However, as far as we are aware, the differential predictive power of familial psychiatric history and of high EE attitudes has not been directly examined.
If a relationship between stable high EE attitudes and presence of psychiatric disorder in biological relatives is confirmed when EE is evaluated at two points by the traditional CFI procedure, the mechanisms by which this relationship occurs also need further consideration. The origins of high EE attitudes remain rather obscure, although our path analytic results suggest that these attitudes may in some cases be a reaction to living with a patient during the development of schizophrenia. Our initial data make it clear that highly critical or emotionally involved attitudes toward the patient can develop in many significant others who have no personal psychiatric disorder, so the two dimensions are not isomorphic. However, if later data suggest that a relationship between high EE attitudes and personal psychiatric disorder is particularly strong for psychiatric disorders with genetic components, it might be helpful to consider whether genetic and other biological factors could predispose to development of high EE attitudes toward the patient.

Finally, while the report by Goldstein and colleagues (in press) has emphasized a possible relationship between stable high EE attitudes and presence of psychiatric disorder in relatives, it should be noted that the familial psychiatric loading for schizophrenia spectrum disorders and major affective disorders within these families is also being examined in ongoing analyses in relation to the course of the probands' illness and to the psychobiological vulnerability factors described earlier.

**Prodromal Symptoms.** The nature and frequency of any signs and symptoms prodromal to psychotic relapses have been examined using the Expanded BPRS ratings completed every 2 weeks by Aftercare Clinic staff. To determine whether prodromal signs and symptoms of psychotic relapses and nonpsychotic relapses can be detected in the immediately preceding 6-week period, we analyzed the BPRS factor scores and then the individual BPRS items (Subotnik and Nuechterlein 1988). For these supplementary analyses, we defined psychotic relapse as only those occasions that involved a return to a rating of 6 (severe) or 7 (very severe) on one of the psychotic scales. Several BPRS factor scores and individual item ratings were found to be elevated in this prodromal period relative to a comparison period for the same subjects, including small elevations in odd thoughts, unusual perceptual experiences, depressed mood, somatic concern, and guilt. A discriminant analysis using a jackknifing procedure indicated that 59 percent of prodromal periods from patients with psychotic relapses and 82 percent of comparison periods from nonrelapsing patients could be correctly classified from the BPRS Hostile-Suspiciousness and Thought Disturbance factors (Subotnik and Nuechterlein 1988). These results indicate that detection of signs and symptoms prodromal to psychotic relapses is possible for many, but not all, schizophrenic patients through regular BPRS assessments. The ability to detect such prodromal symptoms in prospective clinical ratings extends prior results (e.g., Docherty et al. 1978; Herz and Melville 1980; Marder et al. 1984b) and makes intermittent or targeted medication strategies (Carpenter and Heinrichs 1984; Herz 1984) a consideration for patients with a stable remission of psychosis on typical neuroleptics after a first episode of illness. Herz and colleagues (1991) note that, although an intermittent medication strategy showed no net advantage with chronic schizophrenic patients, it might nevertheless be useful for first-episode patients who remain free of psychosis after 1 year of continuous maintenance medication. A trial of intermittent medication for such patients might lower total exposure to typical neuroleptics and the accompanying risks of tardive dyskinesia and possibly also of lower occupational outcome (Johnstone et al. 1990), but an increased risk of psychotic exacerbation would also be expected. Thus, until neuroleptics without side effects such as tardive dyskinesia are available, benefits and risks of such medication strategies will need evaluation. Further discrimination of prodromal signs and symptoms should also aid development of early intervention strategies for patients taking low maintenance dosages of antipsychotic medications.

**Persistence of Fluphenazine Levels After Drug Withdrawal.** A final topic addressed to date is the persistence of fluphenazine in plasma after maintenance fluphenazine decanoate administration at a fixed dosage (Gitlin et al. 1988). Although controlled clinical trials and clinical experience with fluphenazine decanoate are plentiful, data regarding its persistence in plasma and optimal intervals between injections are relatively sparse. Thus, for the first 12 patients to enter the Phase 2 drug crossover protocol, plasma levels of fluphenazine during the 12-week placebo period were contrasted with those of the same patients during the 12-week active drug period. Radioimmunoassay was completed in the University of Saskatchewan laboratory by Kamal Midha, D.Sc., where it was also verified by comparison to a gas chromatographic-mass spectrometric
method. The mean fluphenazine level at entry into the drug crossover protocol was 0.86 ± 0.52 nanograms per milliliter. Mean plasma fluphenazine level did not drop significantly until 8 weeks after the last injection, at which point it reached 0.38 ± 0.16 in the placebo condition (Gitlin et al. 1988). Although a larger sample size and refined assay techniques will lead to greater statistical power to detect smaller declines in plasma levels not apparent in these initial data, our finding that plasma levels in these patients did not decline significantly for the first 6 weeks after the last injection is similar to those of Wistedt and colleagues (1981, 1982). Thus, our initial findings suggest that plasma levels of fluphenazine remain relatively unchanged well past the 2-week intervals at which fluphenazine decanoate injections have customarily been given.

Summary

This article has provided details of the research design and measures of the Developmental Processes in Schizophrenic Disorders project as well as a review of the major published findings to date. Given the length of this article and the authors' acute awareness of the limits of human processing resources, a brief synopsis of selected results will no doubt be useful.

1. The discrimination of ambiguous perceptual information presented in rapid succession and the ability to apprehend simultaneous information remain impaired in a relatively stable way during the early course of schizophrenia even if all psychiatric symptoms go into remission. Performance on a vigilance task demanding active, working memory for prior stimuli also remains impaired but varies significantly in patients across psychotic and remitted states, suggesting that increased disturbances in use of active memory for contextual cuing accompany and might contribute to psychotic symptoms.

2. These subtle information-processing impairments share some common variance with SPEM abnormalities and are significantly correlated with subtle perceptual and language anomalies in some biological parents, suggesting that they continue to be promising indicators of psychobiological vulnerability factors in schizophrenia. Although direct evidence is clearly needed, these data are consistent with the hypothesis that subtle information-processing anomalies are genetically transmitted components of vulnerability to schizophrenia.

3. Autonomic activation level in our recent-onset schizophrenic subjects, as judged from electrodermal activity, serves as a psychophysiological index of clinical state and predicts the extent of short-term symptomatic recovery from the acute schizophrenic episode. However, autonomic activation level normalizes when patients achieve a clinically remitted state and, thus, does not appear to be an enduring vulnerability factor. Our data support the view that electrodermal activity may be a mediator of the impact of stressors in the environment. Furthermore, pilot data suggest that increased electrodermal activity might serve as an early indicator of increased risk for psychotic exacerbation.

4. We have confirmed through rigorous prospective methods that stressful life events independent of the patient's illness and beyond the patient's control occur with disproportionately high frequency in the month before psychotic exacerbations and relapses. Thus, the triggering effect of independent stressful life events suggested in prior retrospective research cannot be explained by retrospective memory bias. This significant excess of independent life events before psychotic exacerbations and relapses involves patients whose exacerbation or relapse occurs while on maintenance antipsychotic medication. Initial analyses suggest that independent life events of stably remitted patients who later show a return of psychotic symptoms while off antipsychotic medication may not show the same pattern. Independent stressful life events occur before slightly less than half of psychotic episodes experienced by patients on maintenance medication, suggesting that they are one of several factors contributing to relapse risk.

5. Highly critical or emotionally overinvolved attitudes toward the patient in the immediate social environment are predictive of higher risk of psychotic relapse even if antipsychotic medication administration is ensured by using standardized dosages of injectable medication. Path analyses suggest that such attitudes are more likely to develop among immediate relatives in this initial period of psychosis if patients are living at home during the development of their psychotic symptoms, which is somewhat more likely if the patient is younger at first onset of illness. These data are consistent with the view that critical or emotionally overinvolved attitudes toward the patient are partly a reaction to the patient's symptoms and support a possible role for such social environments in mediating relapse risk. The probable bidirectional nature of social influence is also suggested in analyses of the direct interactions of patients and significant others following discharge from the hospital. Evaluation of a family education ses-
sion suggests that providing information about schizophrenia to family members during this early period of their relative’s illness may lead to an increased sense of support from the treatment team and tends to reduce self-blame.

6. Prospective BPRS ratings indicate that it might be possible to identify signs and symptoms prodromal to psychotic relapses in about 60 percent of patients during the early period of schizophrenia. The prodromal symptoms are of varied types, but the dimensions contributing to the BPRS Hostile-Suspiciousness and Thought Disturbance factor scores made significant contributions to a discriminant function.

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Announcement of Available Resource Funds

The Theodore and Vada Stanley Foundation in collaboration with the National Alliance for the Mentally Ill welcomes applications for its 1992 grant awards program. The purpose of the awards is to support research directly related to the causes of serious mental illnesses (schizophrenia, bipolar disorder, major depression). The grant awards are intended to attract established scientists from other areas of biology and medicine (e.g., biochemistry and neurology) into research on serious mental illnesses, as well as to provide support for innovative research by established scientists already in the field whose funding sources are limited. Grants are for 1 or 2 years and may be up to $50,000 per year. In the first 3 years of the program, 38 researchers have been funded.

Applications must be submitted by April 1. Notification of awards will be presented in June and funding will begin in August. Application forms, which should be requested from the address below, consist of a brief outline of the proposed project, a budget, and a list of current and pending sources of funding. Funds may be used for salaries, supplies, or equipment; but it is the policy of the Stanley Foundation not to pay indirect costs. The grant applications are reviewed by a six-person professional selection committee consisting of Dr. E. Fuller Torrey, Chairperson, and Drs. Julius Axelrod, Charleton D. Gajdusek, Seymour S. Kety, Robert M. Post, and Janice R. Stevens. Requests for applications and questions should be directed to:

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