Symptomatology of the Initial Prodromal Phase in Schizophrenia

by Philippos Gourzis, Aggeliki Katrivanou, and Stavroula Beratis

Abstract

The initial prodromal symptoms in schizophrenia were studied in 100 *DSM*-diagnosed patients and 100 controls. The median number of symptoms in the patients and the controls was 8 (range 2–13) and 0 (range 0–5), respectively. Patients developed symptoms indicating social, occupational, and affective dysfunction, whereas the controls' symptoms included magical content and disturbance in mood. There were significant differences in the frequency of several symptoms appearing in the subtypes. Initial prodromal symptoms were classified into negative, positive-prepsychotic, and positive-disorganization categories. Patients with the disorganized subtype were more likely to have had negative symptoms in the prodromal state, and patients with the paranoid subtype were more likely to have had positive symptoms in the prodromal state. Observation of the course of symptoms from the prodromal to the psychotic state revealed that 58 percent of the symptoms showed increased intensity, 21 percent remained unchanged, 5 percent decreased, 3 percent evolved into other affective difficulties, 9 percent progressed into delusions, 1 percent progressed into hallucinations, and 3 percent disappeared. The Global Assessment of Functioning Scale showed that functioning is differentially affected among the subtypes even in the prodromal phase. These findings provide a better understanding of the initial prodromal state of schizophrenia, the signs and symptoms that best define it, and their prognostic significance.

Keywords: First episode, initial prodromal phase, positive-negative dimensions, schizophrenia, subtypes, symptomatology.

***Schizophrenia Bulletin*, 28(3):415–429, 2002.**

The prodromal period of schizophrenia, temporally related to the onset of psychosis, is characterized by the presence of a heterogeneous group of behaviors involving several areas of functioning and may continue for weeks to years without prominent psychotic symptoms (Keith and Matthews 1991; Malla and Norman 1994; Lipton and Cancro 1995). The study of the emerging symptoms and their course during the prodromal phase of the schizophrenia disorders is of interest because (1) there is a temporal and possibly nosological association between the prodromal phase and the full psychotic state (Herz 1985) that needs to be further investigated and clarified for possible clinical use in early intervention; (2) knowledge of the presence and duration of specific prodromal symptoms might contribute to a better understanding of the etiology, psychopathology, and prognosis of schizophrenia; and (3) the variability and multidimensionality of the clinical phenomenology of the prodromal phase might help to clarify issues regarding the heterogeneity of schizophrenia, to which the subtypes of the disease and the predominance of the positive or negative syndromes could be related.

The following problem areas, however, have been identified in describing the initial prodromal symptoms of any psychotic disorder: (1) the concept of the prodrome is retrospective and cannot be defined prospectively, and, when it occurs, it does not predict onset of psychosis with certainty (Eaton et al. 1995; Yung and McGorry 1996); (2) the base rates of the symptoms defined as prodromal in subjects of the same age with no disorder are unknown (Yung et al. 1996); (3) several prodromal symptoms cannot be reliably measured and are too nonspecific (Keith and Matthews 1991); and (4) it is not always possible to differentiate between a prodromal symptom and the true onset of psychosis (Keshavan and Schooler 1992).

There are several studies focusing on prodromal symptoms appearing before a relapse of psychosis (Herz and Melville 1980; Herz et al. 1982; Heinrichs and Carpenter 1985; Subotnik and Nuechterlein 1988; Malla and Norman 1994). However, little research has been con-

Send reprint requests to Dr. S. Beratis, University of Patras Medical School, Department of Psychiatry, 265 00 Rion-Patras, Greece; e-mail: psychdpt@med.upatras.gr.

ducted into the initial prodromal symptomatology—that is, the prodromal symptoms of the first schizophrenic episode. The symptoms of this phase of the disease—in which various factors, such as chronicity, long-term medication, and institutionalization, are not involved—may differ from the prodromal symptoms of relapse.

Häfner et al. (1992, 1993) reported on the early symptomatology of schizophrenia and observed that in the vast majority of cases the disease started solely with negative symptoms. Subsequently, symptoms accumulated exponentially, with positive symptoms appearing later in the disease. A limitation of the study is that the transition from the prodromal to the frank psychotic phase is not evident. Huber et al. (1980) followed for 6 years patients who had been hospitalized for schizophrenia some years earlier and, in comparing patients in the prodromal state to those same patients at relapse, concluded that phenomenologically the initial prodromes are, to a great extent, identical to the pure residues. The study contributes to the understanding of the clinical phenomenology and the course of schizophrenia, but the long time interval of 8 to 28 years between the initial hospital admission and the initiation of the study raises questions about the accuracy of the description of the initial prodromal symptoms.

The symptoms most commonly said to precede a first psychotic episode are reduced concentration and attention, reduced drive and motivation, anergia, depressive mood, sleep disturbance, anxiety, social withdrawal, suspiciousnêss, deterioration in role functioning, and irritability (Yung et al. 1996; Yung and McGorry 1996). These symptoms are characterized by their lack of specificity. Another group of prodromal features is closer to the psychotic state and includes cenesthetic symptoms (Huber et al. 1980), obsessional perseveration of thought and intrusion of thought (Gross and Huber 1985; Gross 1989), magical ideation (Chapman and Chapman 1987), increased acuity (De Lisi et al. 1986), and perceptual aberration that primarily manifests itself as distortion in the perception of one's own body and of other objects (De Lisi et al. 1986; Chapman and Chapman 1987).

A number of studies have emphasized the subjective experiences of the patients' reports of initial prodromes. Conrad (1958) described in detail the onset of schizophrenia in 117 patients. During the initial period he found a longstanding elevation of tension that was experienced as an unavoidable future event coming to the present. Also, he observed in preschizophrenia subjects a feeling of being put in an unknown test situation, which might indicate the future theme of delusion. Gross and Huber (1985) reported on subjective cognitive thought disorders, the most common of which was disturbance of concentration. Also, Cutting and Dunne (1986) reported that there were early qualitative changes in visual perception, particularly affecting the way colors, people, space, and facial expression were viewed, and a sense of indefinable strangeness.

DSM–III (American Psychiatric Association 1980) and *DSM–III–R* (American Psychiatric Association 1987) provided a list of symptoms, mainly observable behavioral changes, that appear in the prodromal phase of schizophrenia. Two or more of the listed symptoms were necessary to establish the presence of the schizophrenia prodromal period. However, criticism has been raised related to the lack of specificity of these symptoms and to the omission from the list of several other features observed before the official onset of the schizophrenia disorder (McGorry et al. 1995; Yung et al. 1996). Because of these concerns, the list of prodromal symptoms was dropped from *DSM–IV* (American Psychiatric Association 1994), in spite of the well-recognized value in identifying the prodromal phase of schizophrenia.

First episode psychotic patients were investigated in a study of the prodromal symptoms listed in *DSM–III*, and it was found that the levels of reliability in the diagnosis of the symptoms were generally acceptable (Jackson et al. 1994). In another study of 313 first episode psychotic patients, it was found that the frequency of *DSM–III–R* schizophrenia prodromal symptoms was significantly higher in schizophrenia than in other psychotic disorders. Individual prodromal symptoms, however, were relatively poor at distinguishing between diagnoses, and they cannot be considered as pathognomonic of schizophrenia. According to this study, the most frequently reported prodromal symptom for schizophrenia was social isolation or withdrawal (Jackson et al. 1995).

In a community survey of 657 Australian high school students based on questionnaires administered to the youngsters on a computer, 50 percent of them reported the presence of two or more prodromal symptoms (McGorry et al. 1995). However, because of methodological weaknesses, these findings should be interpreted with caution. In two recent reports, initial prodromal symptoms of schizophrenia have been explored. McGorry et al. (2000) studied 61 schizophrenia patients and found that prediction of schizophrenia was likely when from the list of *DSM–III–R* prodromal symptoms the individual exhibited either marked impairment in role functioning or odd-bizarre behavior/magical thinking in conjunction with socially isolative behavior/withdrawal. Møller and Husby (2000) studied 19 first episode patients and observed that, during the initial prodromal phase, the three most frequent experiential dimensions were disturbances of perception of self, withdrawal from the external world, and extreme preoccupation by overvalued ideas. The most common behavioral dimensions were quitting studies or jobs, major shift of interest, marked social passivity/withdrawal/isolation, and marked change in appearance or behavior.

Focusing on the onset of the first episode of schizophrenia, the present study investigates (1) the constellation of symptoms appearing during the initial prodromal phase of the schizophrenia subtypes and the existing quantitative and qualitative differences in the symptomatology between patients and control subjects from the general population; (2) the frequency and diagnostic power of each symptom; (3) the course of symptoms from the initial prodromal phase into the psychotic state; and (4) the relationship between the symptomatology of the initial prodromal state and the symptomatology of the psychotic state.

Methods

Subjects and Procedure. Subjects in this study consisted of 100 patients (64 of them male) hospitalized for schizophrenia in the Department of Psychiatry of the University of Patras Medical School, Patras, Greece, from December 1992 through May 1997. Patras is located in southwestern Greece and is the center of a larger administrative area of approximately 1 million people. The Department of Psychiatry is the only inpatient service in the area and admits acute cases for a 3-month maximum hospitalization period. Of the 100 patients studied, 50 (37 of them male) had the paranoid, 26 (13 males) the disorganized, 20 (11 males) the undifferentiated, and 4 (3 males) the catatonic subtype. The mean age of the patients was 25.6 (standard deviation [SD] = 5.2), with a range from 15 to 39 years. Ninety-one of the patients were unmarried, 5 married, 3 divorced, and 1 separated. In urban areas were living 63 patients, in semiurban 10, and in rural 27. Eleven of the patients had completed university education, 68 high school education, and 20 elementary school education; 1 was uneducated. All patients investigated were in their first psychotic episode or had disease onset within the preceding 2 years. Specifically, 75 patients were in their first psychotic episode, 14 had had two episodes, 8 had had three episodes, and 3 had had four episodes. In all patients the number of hospital admissions was the same as the number of psychotic episodes. The mean length of the index episode (psychotic state) was 2.2 (SD = 0.87) months, with a range from 1 to 5.1 months. The original diagnosis of schizophrenia according to *DSM–III–R* (American Psychiatric Association 1987) and *DSM–IV* (American Psychiatric Association 1994) criteria was made by staff psychiatrists during the patients' hospital stay, after assessment of their history, clinical symptomatology, and overall behavior.

In addition, all patients underwent two independent diagnostic interviews with the Structured Clinical Interview for *DSM–III–R*-Patient Edition (Spitzer et al. 1990), given by two of the authors (P.G. and A.K.). The patients were interviewed during symptomatically stable periods of their hospitalization. Supplemental information was obtained from family members by the same interviewers (Keshavan and Schooler 1992). In the patient assessment the initial prodromal symptoms investigated were those included in *DSM–III–R* as well as additional less specific prodromal symptoms that have been described in the literature on the prodromal phase of schizophrenia (DeLisi et al. 1986; Yung et al. 1996; Yung and McGorry 1996). Subsequently, the data of each case were reviewed by the third project psychiatrist (S.B.), who was unaware of the conclusions of the two interviewers. For each case a consensus conference was carried out in which there was agreement by at least two of the authors on the diagnosis of the schizophrenia subtype, the nature of the initial prodromal symptoms, and the time of the prodromal phase onset and its duration. The onset of the prodromal phase was defined by the appearance of the first noticeable symptom or symptoms considered to indicate the appearance of the disease. The onset of the psychotic phase was defined as the appearance of active phase symptoms (American Psychiatric Association 1994).

The Global Assessment of Functioning (GAF) Scale (American Psychiatric Association 1987) was used to describe general functioning at the time of the hospital admission, as well as retrospectively, for a 1-month period with the highest level of functioning during the prodromal phase. The mean of the two examiners' scores was used in the study. The mean overall difference between the examiners' scores in the GAF for the psychotic state was 2.0 (SD = 1.3), range 0 to 6, and for the prodromal phase 2.1 (SD = 1.0), range 0 to 4.

All patients included in the study were free of any neuroleptic medications during the prodromal phase.

In addition, 100 control subjects closely matched with the patients for age (24.4 [SD = 5.1], range 16 to 34), gender (64 of them were male), residence (urban 63, semiurban 10, rural 27), and educational level (university education 12, high school 70, elementary school 18) were interviewed by two of the authors (P.G. and A.K.) for the presence of any of the prodromal symptoms investigated in the patients. The data were examined by the third project psychiatrist (S.B.) as described for the patients.

Prodromal Symptoms. The prodromal symptoms investigated were those reported in *DSM–III–R*. Also, in keeping with the previous literature, the following additional symptoms and types of behavior were chosen as representing less specific initial prodromal symptoms: impairment in concentration, depressive mood, sleep disturbance, anxiety, irritability/anger, suspiciousness, quarrels, aggressiveness, hyperacousia, restlessness, suicidal ideas,

mood swings, preoccupation, somatic/cenesthetic symptoms, lack of appetite, and compulsive behavior.

We have classified the *DSM–III–R* prodromal symptoms into categories of negative, positive-prepsychotic, and positive-disorganization symptoms, similar to the three dimensions described for the symptomatology of schizophrenia (Andreasen and Olsen 1982; Bilder et al. 1985; Liddle 1987*a*, 1987*b*; Arndt et al. 1991; McGlashan and Fenton 1992; Häfner et al. 1993; American Psychiatric Association 1994; Liddle et al. 1994; Andreasen et al. 1995; Arndt et al. 1995; McGorry et al. 1995). To those have been added suspiciousness and impairment in concentration, classified with the positive and negative symptoms, respectively. The latter was classified with the negative symptoms because it correlates more strongly with the negative factor (Andreasen et al. 1995). Table 1 lists the categories of prodromal symptoms studied.

Statistical Analyses. Data were analyzed with the FASTAT for the Macintosh, Version 2 (Systat, Inc., Evanston, IL). For numerical data the 2-tailed t test was applied. Differences in the GAF score between two groups (prodromal and psychotic phase) were compared by paired t test. Differences in the frequency of symptoms between groups were compared by unpaired t test. For determining the diagnostic power of the symptoms, the sensitivity (the proportion of patients who had the particular symptom), specificity (the proportion of patients who did not have the particular symptom), positive predictive value (the possibility that a patient with a particular symptom will develop the disease), and negative predictive value (the possibility that a patient without a particular symptom will not develop the disease) were estimated. One-way analysis of variance (ANOVA), with Tukey's post hoc tests, was applied to analyze the differences in the number of prodromal symptoms among the subtypes observed in the patients, as well as in the GAF score among the subtypes in the prodromal or the psychotic phase. ANOVA with repeated measures with two grouping factors was used to compare the GAF score of the subtypes between the prodromal phase and the psychotic state. The Kruskal-Wallis H nonparametric equivalent to one-way ANOVA, with Mann-Whitney U comparisons, was applied to compare the frequencies of prodromal symptoms among the subtypes (Statistical Package for the Social Sciences for Windows, version 10). To test reliability among the three diagnosticians, the unweighted κ for three raters was used (Bartko and Carpenter 1976). Because of the small number of cases with the catatonic subtype studied, the nature, frequencies, and course of symptoms are reported but with the exception of the GAF scores no other statistical analyses were made for this subtype.

Results

Interrater Agreement. The unweighted κ for interrater agreement among the three diagnosticians was highly significant for the identification of the schizophrenia subtypes ($\kappa = 0.99$, $z = 13.227$, $p < 0.0001$). Among the three diagnosticians, there was complete agreement in 24 of the 39 prodromal symptoms, one discordance in 11 of the symptoms ($\kappa = 0.98$, $z = 8.219$, $p < 0.0001$), two discordances in 3 of the symptoms ($\kappa = 0.97$, $z = 6.624$, $p < 0.0001$), and three discordances in 1 of the symptoms ($\kappa = 0.84$, $z = 1.367$, $p = 0.087$). Regarding the length of the prodromal phase, there was agreement among the three diagnosticians for the month of the prodromal phase onset in 92 patients, for 6 patients there was disagreement of 1 month (one diagnostician), and for 2 patients there was

Table 1. Prodromal symptoms of schizophrenia subtypes characterized as negative, positive-prepsychotic, and positive-disorganization

Negative symptoms	Positive-prepsychotic	Positive-disorganization
Marked isolation	Odd beliefs/magical thinking	Marked peculiar behavior
Marked withdrawal	Suspiciousness	Inappropriate affect
Marked impairment in role functioning	Belief in clairvoyance	Digressive speech
Marked impairment in personal hygiene and grooming	Telepathy	Vague speech
Blunted affect	Sixth sense	Overelaborate speech
Flat affect	Belief that others can feel one's feelings	Circumstantial speech
Poverty of speech	Overvalued ideas	Poverty of content of speech
Marked lack of initiative, interests, or energy	Ideas of reference	
Impairment in concentration	Unusual perceptual experiences/ perceptual aberration/body image aberration	

disagreement of 2 months (one diagnostician). For the onset of the psychotic phase there was agreement among the three diagnosticians in 97 cases; for 3 patients there was disagreement of 1, 1.5, and 2 months by one of the diagnosticians. Among the three diagnosticians there was agreement in all 76 control subjects in which no prodromal symptoms were identified. Of the 46 symptoms found in 24 subjects, there was disagreement by one of the diagnosticians in 6 symptoms.

Frequency of Prodromal Symptoms in Patients and Controls. In the 100 patients studied, the median number of initial prodromal symptoms was 8, with a range from 2 to 13. Of the 100 control subjects, 24 had one or more of the prodromal symptoms identified in the patients: 1 control had five symptoms, 1 had four symptoms, 5 had three symptoms, 14 had two symptoms, and 3 had one symptom. The median number of symptoms in the control subjects was 0. The difference between patients and controls was significant ($U = 67.5$, $p < 0.0001$). The symptoms most commonly recorded in the control subjects were odd beliefs/magical thinking, belief in clairvoyance, and depressive mood (in five individuals each). These symptoms were followed by impairment in concentration, telepathy, sixth sense, and anxiety, which were found in four subjects; suspiciousness, found in three subjects; marked isolation, marked impairment in role functioning, ideas of reference, irritability/anger, sleep disturbance, and lack of appetite, each found in two individuals; and poverty of speech, marked lack of initiative, interests, or energy, overvalued ideas, marked peculiar behavior, overelaborate speech, circumstantial speech, suicidal ideas, restlessness, and quarrels, each found in one individual.

Individual Symptoms in Subtypes. Table 2 lists the initial prodromal symptoms of paranoid, disorganized, and undifferentiated subtypes, with a frequency greater than or equal to 10 percent in any of the subtypes. The two most common symptoms in the paranoid subtype were marked isolation and suspiciousness; in the disorganized subtype, marked impairment in role functioning and marked lack of initiative, interests, or energy; and in the undifferentiated subtype, marked impairment in role functioning and blunted affect. The frequency of these symptoms ranged from 64 percent to 92 percent. Among the four patients with the catatonic subtype studied, all of them in the prodromal phase manifested impairment in role functioning; three showed marked isolation, irritability/anger, blunted affect, and marked impairment in personal hygiene and grooming; and two had quarrels, marked withdrawal, marked lack of initiative, interests, or energy, and sleep disturbance. Thirteen other symptoms were recorded only once in the group of catatonic patients.

The statistical differences among the initial prodromal symptoms of the three most common schizophrenia subtypes are listed in table 2. The symptoms that better differentiated the paranoid from the disorganized and the undifferentiated subtypes were suspiciousness (more common in the paranoid subtype) and marked impairment in role functioning, marked lack of initiative, interests, or energy, blunted affect, and poverty of content of speech (all more common in the disorganized and undifferentiated subtypes). The disorganized and the undifferentiated subtypes exhibited greater similarity in the symptomatology of the prodromal phase. Symptoms that showed the greatest differences between these subtypes were impairment in concentration, aggressiveness, and marked impairment in personal hygiene and grooming (all more common in the disorganized subtype) and digressive speech (more common in the undifferentiated subtype).

Diagnostic Power of Initial Prodromal Symptoms. The sensitivity, specificity, positive predictive value, and negative predictive value of the 10 most common initial prodromal symptoms for each of the three most common schizophrenia subtypes are listed in table 3. Prodromal symptoms with a sensitivity of 0.90 or greater were marked isolation for the paranoid subtype, and marked impairment in role functioning and marked lack of initiative, interests, or energy for the disorganized subtype. Blunted affect and marked impairment in role functioning had the greatest sensitivity (0.80) for the undifferentiated subtype. Symptoms with a specificity of 0.90 or greater were suspiciousness and odd beliefs/magical thinking for the paranoid subtype, and poverty of content of speech, and marked impairment in personal hygiene and grooming for the disorganized subtype. For the undifferentiated subtype, the greatest specificity was shown by sleep disturbance (0.82) and poverty of content of speech (0.81). Initial prodromal symptoms with the greatest positive predictive value were suspiciousness for the paranoid subtype, poverty of content of speech for the disorganized subtype, and blunted affect for the undifferentiated subtype. Several initial prodromal symptoms displayed a high negative predictive value, particularly for the disorganized and the undifferentiated subtype.

Negative and Positive Initial Prodromal Symptoms. The relative frequency of the negative and positive initial prodromal symptoms varied significantly among the subtypes, whereas the less specific symptoms constituted approximately one-third of the total number of symptoms in each subtype. In the paranoid, the disorganized, the undifferentiated, and the catatonic subtypes, the mean

Table 2. Kruskal-Wallis H ANOVA with Mann-Whitney *U* comparisons of prodromal symptoms with a frequency ≥ 10 percent among schizophrenia patients with different subtypes

Symptom	Frequency (%)					Mann Whitney, *p* Value		
	All patients	P (*n* = 50)	D (*n* = 26)	U (*n* = 20)	ANOVA	P vs D	P vs U	D vs U
Marked isolation	71	92	31	60	< 0.0001	< 0.0001(P)	0.001(P)	0.050(U)
Marked impairment in role functioning	59	30	92	80	< 0.0001	< 0.0001(D)	< 0.0001(U)	0.224
Preoccupation	44	32	62	55	0.030	0.014(D)	0.076	0.659
Marked lack of initiative, interests, or energy	43	12	92	65	< 0.0001	< 0.0001(D)	< 0.0001(U)	0.022(D)
Irritability/anger	39	48	23	45	0.102	0.036(P)	0.822	0.120
Blunted affect	38	2	65	80	< 0.0001	< 0.0001(D)	< 0.0001(U)	0.280
Poverty of speech	36	24	62	35	0.006	0.001(D)	0.353	0.078
Impairment in concentration	35	14	73	35	< 0.0001	< 0.0001(D)	0.049(U)	0.011(D)
Marked withdrawal	35	14	69	40	< 0.0001	< 0.0001(D)	0.017(U)	0.050(D)
Unusual perceptual experiences/perceptual aberration/body image aberration	35	28	31	60	0.036	0.802	0.013(U)	0.050(U)
Ideas of reference	34	50	8	35	0.001	< 0.0001(P)	0.259	0.022(U)
Suspiciousness	34	64	0	5	< 0.0001	< 0.0001(P)	< 0.0001(P)	0.254
Anxiety	32	22	31	60	0.009	0.405	0.002(U)	0.050(U)
Quarrels	21	32	8	15	0.038	0.019(P)	0.151	0.435
Sleep disturbance	21	10	27	35	0.035	0.057	0.013(U)	0.559
Poverty of content of speech	20	0	58	25	< 0.0001	< 0.0001(D)	< 0.0001(U)	0.028(D)
Aggressiveness	18	16	35	5	0.031	0.066	0.218	0.017(D)
Odd beliefs/magical thinking	18	28	0	15	0.010	0.003(P)	0.255	0.043(U)
Restlessness	16	10	23	25	0.189	0.127	0.108	0.881
Depressive mood	14	10	23	15	0.312	0.127	0.555	0.498
Somatic/cenesthetic symptoms	14	12	23	10	0.352	0.212	0.814	0.251
Marked impairment in personal hygiene and grooming	12	8	35	5	0.003	0.004(D)	0.662	0.017(D)
Marked peculiar behavior	9	4	19	10	0.099	0.030(D)	0.332	0.393
Mood swings	9	2	12	20	0.039	0.079	0.009(U)	0.433
Overvalued ideas	8	14	0	5	0.095	0.047(P)	0.288	0.254
Suicidal ideas	7	2	15	5	0.001	0.001(D)	1.000	0.040(D)
Vague speech	7	2	8	25	0.003	0.636	0.002(U)	0.037(U)
Digressive speech	6	4	0	20	0.014	0.305	0.032(U)	0.018(U)
Flat affect	6	0	23	0	< 0.0001	< 0.0001(D)	1.000	0.023(D)
Compulsiveness	5	0	19	0	0.001	0.001(D)	1.000	0.040(D)

Note.—ANOVA = analysis of variance; D = disorganized; P = paranoid; U = undifferentiated. Letters in parentheses indicate subtypes with the greater frequency of the symptoms.

Table 3. Sensitivity, specificity, positive predictive value, and negative predictive value of the 10 most frequent prodromal symptoms for different schizophrenia subtypes

Symptom	Sn	Sp	PPV	NPV
Marked isolation				
Paranoid	0.92	0.54	0.67	0.87
Disorganized	0.30	0.33	0.12	0.63
Undifferentiated	0.60	0.28	0.17	0.74
Marked impairment in role functioning				
Paranoid	0.30	0.12	0.25	0.14
Disorganized	0.92	0.53	0.41	0.95
Undifferentiated	0.80	0.46	0.27	0.90
Preoccupation				
Paranoid	0.32	0.44	0.36	0.39
Disorganized	0.61	0.63	0.36	0.82
Undifferentiated	0.55	0.58	0.25	0.84
Marked lack of initiative, interests, or energy				
Paranoid	0.12	0.22	0.13	0.20
Disorganized	0.92	0.72	0.53	0.96
Undifferentiated	0.65	0.60	0.29	0.87
Irritability/anger				
Paranoid	0.48	0.64	0.57	0.55
Disorganized	0.23	0.51	0.14	0.65
Undifferentiated	0.45	0.58	0.21	0.81
Blunted affect				
Paranoid	0.02	0.30	0.03	0.22
Disorganized	0.65	0.73	0.46	0.96
Undifferentiated	0.80	0.74	0.43	0.94
Poverty of speech				
Paranoid	0.24	0.52	0.33	0.41
Disorganized	0.62	0.73	0.44	0.84
Undifferentiated	0.35	0.64	0.19	0.79
Impairment in concentration				
Paranoid	0.14	0.48	0.21	0.64
Disorganized	0.73	0.81	0.58	0.90
Undifferentiated	0.35	0.68	0.21	0.80
Marked withdrawal				
Paranoid	0.12	0.44	0.18	0.33
Disorganized	0.69	0.78	0.52	0.87
Undifferentiated	0.40	0.67	0.24	0.82
Unusual perceptual experiences/ perceptual aberration/body image aberration				
Paranoid	0.28	0.58	0.40	0.45
Disorganized	0.30	0.63	0.23	0.72
Undifferentiated	0.60	0.71	0.34	0.87
Ideas of reference				
Paranoid	0.50	0.82	0.74	0.62
Disorganized	0.08	0.65	0.05	0.63
Undifferentiated	0.35	0.66	0.20	0.80
Suspiciousness				
Paranoid	0.64	0.96	0.94	0.73
Disorganized	0.00	0.54	0.00	0.60
Undifferentiated	0.05	0.58	0.03	0.71
Anxiety				
Paranoid	0.22	0.58	0.34	0.43
Disorganized	0.30	0.67	0.25	0.73
Undifferentiated	0.60	0.75	0.38	0.88
Quarrels				
Paranoid	0.32	0.86	0.69	0.55
Disorganized	0.08	0.71	0.09	0.67
Undifferentiated	0.15	0.75	0.13	0.77
Sleep disturbance				
Paranoid	0.10	0.68	0.24	0.43
Disorganized	0.27	0.81	0.33	0.76
Undifferentiated	0.35	0.82	0.33	0.83
Poverty of content of speech				
Paranoid	0.00	0.60	0.00	0.38
Disorganized	0.58	0.93	0.75	0.86
Undifferentiated	0.25	0.81	0.25	0.81
Aggressiveness				
Paranoid	0.16	0.80	0.42	0.48
Disorganized	0.35	0.86	0.47	0.80
Undifferentiated	0.05	0.77	0.05	0.76
Odd beliefs/magical thinking				
Paranoid	0.28	0.92	0.78	0.56
Disorganized	0.00	0.64	0.00	0.39
Undifferentiated	0.15	0.81	0.17	0.79
Marked impairment in personal hygiene and grooming				
Paranoid	0.08	0.07	0.24	0.45
Disorganized	0.35	0.90	0.53	0.81
Undifferentiated	0.05	0.80	0.06	0.77

Note.—NPV = negative predictive value; PPV = positive predictive value; Sn = sensitivity; Sp = specificity.

number of negative symptoms per patient was 2.0 (SD = 1.2), 5.4 (SD = 1.2), 4.0 (SD = 1.3), and 4.3 (SD = 1.3), respectively; of positive symptoms, 2.1 (SD = 1.0) (2.0 [SD = 1.1] prepsychotic, 0.1 [SD = 0.4] disorganization), 1.2 (SD = 0.9) (0.4 [SD = 0.6] prepsychotic, 0.9 [SD = 0.8] disorganization), 2.0 (SD = 1.1) (1.2 [SD = 0.9] prepsychotic, 0.8 [SD = 0.8] disorganization), and 1.0 (SD = 0.8) (0.8 [SD = 0.9] prepsychotic, 0.3 [SD = 0.5] disorganization), respectively. A significant difference between the frequencies of the negative and the positive symptoms was observed in the disorganized ($t = 13.814$, $df = 25$, $p < 0.0001$) and the undifferentiated subtype ($t = 5.305$, $df = 19$, $p < 0.0001$). Although there was no significant difference between negative and positive symptoms in the paranoid subtype, the positive-prepsychotic symptoms were significantly more common than the positive-disorganization symptoms ($t = 11.980$, $df = 49$, $p < 0.0001$). Conversely, in the disorganized subtype the positive-disorganization symptoms were significantly more common than the positive-prepsychotic symptoms ($t = 2.328$, $df = 25$, $p = 0.02$). In the undifferentiated subtype, the positive-prepsychotic symptoms were more common than the positive-disorganization symptoms, but the difference was not significant.

One-way ANOVA showed that there was a significant difference in the frequency of the negative symptoms across the three most common subtypes ($F = 71.58$, $p < 0.0001$). Tukey's post hoc comparisons showed that the negative symptoms were significantly more common in the disorganized and undifferentiated subtypes than in the paranoid subtype ($p = 0.001$). Also, negative symptoms were significantly more common in the disorganized subtype than in the undifferentiated subtype ($p = 0.0008$). One-way ANOVA of all positive symptoms showed that there was a significant difference across the three most common subtypes ($F = 6.353$, $p = 0.006$). Tukey's post hoc tests showed that the positive symptoms were more common in the paranoid and undifferentiated subtypes than in the disorganized subtype ($p = 0.002$ and 0.04, respectively). There was no significant difference between the paranoid and the undifferentiated subtype. Also, there was a significant difference across the subtypes in the frequency of the positive-prepsychotic symptoms ($F = 24.48$, $p < 0.0001$). Post hoc comparisons showed that the frequency of the positive-prepsychotic symptoms was significantly greater in the paranoid subtype than in the disorganized ($p = 0.0001$) or the undifferentiated ($p = 0.007$) subtype; also, it was significantly greater in the undifferentiated than in the disorganized subtype ($p = 0.01$). A significant difference across the subtypes was also present in the frequency of the positive-disorganization symptoms ($F = 15.52$, $p < 0.0001$). These symptoms were significantly more common in the disorganized and undifferentiated subtypes than in the paranoid subtype ($p = 0.001$ and 0.01, respectively).

The frequency of the less specific symptoms in the paranoid, the disorganized, the undifferentiated, and the catatonic subtypes was 33 percent, 31 percent, 33 percent, and 40 percent, respectively.

Duration of Prodromal Phase and Appearance of Symptoms. The mean duration of the prodromal phase in the paranoid subtype was 14.6 (SD = 11.8), with a range from 1 to 48 months; in the disorganized it was 18.2 (SD = 11.8), range 0.5 to 30 months; in the undifferentiated it was 12.7 (SD = 10.7), range 0.5 to 36 months; and in the catatonic it was 13.8 (SD = 7.5), range 6 to 24 months. One-way ANOVA of the duration of the prodromal phase across the three most common subtypes did not show a significant difference among the subtypes.

In the paranoid subtype, initially only one first prodromal symptom appeared in 17 (34%) patients, and a combination of two first symptoms appeared in 16 (32%), of three first symptoms in 11 (22%), and of more than three symptoms in 6 (12%). In the disorganized subtype there was no patient in which the prodromal phase started with one symptom, whereas a combination of two, three, or more than three symptoms appeared in 1 (4%), 4 (15%), and 21 (81%) patients, respectively. The corresponding numbers in the undifferentiated subtype were 1 (5%), 0 (0%), 3 (15%), and 16 (80%) patients, respectively.

The prodromal symptom that most often appeared first, as the only symptom, in the paranoid subtype was marked isolation, followed by irritability/anger, which was recorded in nine and three of the patients, respectively. Marked isolation was also the most common first prodromal symptom, appearing alone or in combination with other symptoms, among patients with the paranoid subtype. Of the 47 patients with the paranoid subtype, 35 developed this symptom at some time during the prodromal phase. This symptom was followed by irritability/anger (13/24), poverty of speech (9/12), and ideas of reference (9/25). In the disorganized subtype, the prodromal symptoms that most often appeared first, although always in combination with other symptoms, were marked lack of initiative, interests, or energy (20/25), impairment in concentration (18/20), marked withdrawal (17/18), and marked impairment in role functioning (17/25). In the undifferentiated subtype, the most common first prodromal symptoms were marked impairment in role functioning (13/16), blunted affect (13/17), and marked isolation (12/12). In the catatonic subtype, the initial prodromal symptom that most often appeared first, always combined with other symptoms, was marked impairment in role functioning (4/4).

The mean number of initial prodromal symptoms found in the paranoid, the disorganized, and the undiffer-

entiated subtypes was 6.0 (SD = 2.6), 9.6 (SD = 1.8), and 8.9 (SD = 2.0), respectively. One-way ANOVA showed that the three subtypes differed significantly in the total number of symptoms that appeared during the prodromal phase ($F = 24.68$, $p < 0.0001$). Tukey's post hoc tests showed that there was a significantly lower number of symptoms in the paranoid than in the disorganized or the undifferentiated subtype ($p < 0.0001$). The difference between the disorganized and the undifferentiated subtypes was not significant.

Course of Prodromal Symptoms. The course of the recorded symptoms from the prodromal phase to the development of the psychotic state of the disease in the paranoid, the disorganized, and the undifferentiated subtype is listed in tables 4–6. In the 50 patients with the paranoid subtype, the intensity increased in 148 symptoms, decreased in 17, and remained unchanged in 59, and 11 symptoms disappeared. Also, 46 symptoms developed into delusions when the patients became psychotic. In the 26 patients with the disorganized subtype, increase was found in 144 symptoms, decrease in 5, the same intensity in 59, disappearance in 5, and evolution into another symptom in 23. Of these 23 symptoms, in 6 patients flat affect evolved into grossly inappropriate affect, whereas in 17 patients blunted affect evolved on 12 occasions into grossly inappropriate affect and in 5 into flat affect. In addition, 5 symptoms progressed into delusions and 4 into hallucinations. In the 20 patients with the undifferentiated subtype, increase was found in 107 symptoms, decrease in 12, no change in 30, disappearance in 8, and progress into delusions or hallucinations in 14 and 2, respectively. In the four patients with the catatonic subtype, there was increase in 20 symptoms, no change in 5, evolution into another affective difficulty in 2, and progress into delusions or hallucinations in 2 and 1, respectively. The symp-

Table 4. Course of symptoms with a frequency ≥ 10 percent from prodromal to psychotic phase in 50 patients with the paranoid subtype

	Intensity of Symptoms				
Symptom	Increase	Stay same	Decrease	Disappear	Delusions
Marked isolation	26	11	9	—	—
Suspiciousness	27	5	—	—	—
Ideas of reference	—	2	—	—	23
Irritability/anger	21	2	1	—	—
Quarrels	15	1	—	—	—
Preoccupation	7	7	1	1	—
Marked impairment in role functioning	14	1	—	—	—
Odd beliefs/magical thinking	—	2	—	—	12
Unusual perceptual experiences/ perceptual aberration/ body image aberration	1	5	—	6	2
Poverty of speech	2	7	—	—	3
Anxiety	9	1	1	—	—
Aggressiveness	6	1	1	—	—
Impairment in concentration	4	3	—	—	—
Marked withdrawal	4	2	1	—	—
Overvalued ideas	—	3	—	—	4
Marked lack of initiative, interests, or energy	3	1	2	—	—
Somatic/cenesthetic symptoms	—	1	—	3	2
Sleep disturbance	4	1	—	—	—
Restlessness	4	1	—	—	—
Depressive mood	1	2	1	1	—

Table 5. Course of symptoms with a frequency ≥ 10 percent from prodromal to psychotic phase in 26 patients with the disorganized subtype

	Intensity of Symptoms				
Symptom	**Increase**	**Stay same**	**Decrease**	**Evolve/ disappear**	**Delusions/ hallucinations**
Marked impairment in role functioning	22	2	—	—	—
Marked lack of initiative, interests, or energy	20	4	—	—	—
Impairment in concentration	13	6	—	—	—
Marked withdrawal	14	2	2	—	—
Blunted affect	—	—	—	17[1]	—
Poverty of speech	5	11	—	—	—
Preoccupation	9	7	—	—	—
Poverty of content of speech	5	9	1	—	—
Marked impairment in personal hygiene and grooming	9	—	—	—	—
Aggressiveness	9	—	—	—	—
Marked isolation	7	1	—	—	—
Unusual perceptual experiences/ perceptual aberration/body image aberration	—	2	—	1	4/1
Anxiety	5	3	—	—	—
Sleep disturbance	6	1	—	—	—
Flat affect	—	—	—	6[2]	—
Restlessness	5	1	—	—	—
Depressive mood	—	3	—	3	—
Irritability/anger	5	1	—	—	—
Somatic/cenesthetic symptoms	—	2	—	—	1/3
Marked peculiar behavior	5	—	—	—	—
Compulsiveness	1	3	1	—	—
Suicidal ideas	3	—	—	1	—
Mood swings	1	1	1	—	—

[1] In 12 cases replaced by grossly inappropriate affect and in 5 by flat affect.
[2] Replaced by inappropriate affect.

tom that evolved was blunted affect; it was replaced by inappropriate affect in one patient and by flat affect in the other. Specifically, in the total sample of the 100 patients studied, ideas of reference observed in 34 patients during the prodromal phase evolved into delusions of reference in 32 of them during the psychotic phase. Of the 18 patients with odd beliefs/magical thinking during the prodromal phase, 7 developed delusions of magical influence, 7 bizarre delusions, 1 delusions of control, and 1 delusions of both magical influence and thought withdrawal during the psychotic state. Of the 35 patients with prodromal unusual perceptual experiences, 2 developed auditory hallucinations and 13 developed delusions (6 bizarre, 6 of body image change, and 1 of control). Of the 15 patients with initial prodromal somatic/cenesthetic symptoms, 6 developed cenesthetic hallucinations, 3 delusions of body image change, and 1 delusions of control. Of the nine patients with overvalued ideas in the prodromal phase, six developed delusions, all of which were grandiose. Of the four patients with belief in clairvoyance, one developed bizarre delusions and one delusions of control. The initial prodromal symptom "others can feel my feelings" observed in one patient evolved into delusions of control during the psychotic phase.

Table 6. Course of symptoms with a frequency ≥ 10 percent from prodromal to psychotic phase in 20 patients with the undifferentiated subtype

Symptom	Intensity of Symptoms				Delusions/ hallucinations
	Increase	Stay same	Decrease	Disappear	
Marked impairment in role functioning	15	1	—	—	—
Blunted affect	9	7	—	—	—
Marked lack of initiative, interests, or energy	12	1	—	—	—
Marked isolation	11	1	—	—	—
Unusual perceptual experiences/ perceptual aberration/body image aberration	—	3	—	5	4/0
Anxiety	7	4	1	—	—
Preoccupation	8	3	—	—	—
Irritability/anger	8	—	1	—	—
Marked withdrawal	6	2	—	—	—
Poverty of speech	1	1	5	—	—
Ideas of reference	—	—	—	—	7/0
Impairment in concentration	7	—	—	—	—
Sleep disturbance	7	—	—	—	—
Vague speech	1	3	1	—	—
Poverty of content of speech	2	3	—	—	—
Restlessness	5	—	—	—	—
Digressive speech	2	1	1	—	—
Mood swings	1	—	3	—	—
Odd beliefs/magical thinking	—	—	—	—	3/0
Depressive mood	—	—	—	3	—
Quarrels	3	—	—	—	—
Marked peculiar behavior	2	—	—	—	—
Somatic/cenesthetic symptoms	—	—	—	—	0/2

GAF Score. In the patients with the paranoid, the disorganized, the undifferentiated, and the catatonic subtypes, the mean GAF score at the time of examination, during the psychotic state, was 40.4 (SD = 9.5), 29.4 (SD = 7.6), 35.7 (SD = 6.2), and 16.3 (SD = 4.3), respectively. One-way ANOVA with Tukey's post hoc tests showed a significant difference in the GAF score among the subtypes ($F = 17.735$, $p < 0.0001$). The difference was significant between paranoid and disorganized ($p < 0.0001$), paranoid and catatonic ($p < 0.0001$), undifferentiated and catatonic ($p < 0.0001$), and disorganized and catatonic ($p = 0.021$). The difference just failed to reach the level of significance between the disorganized and undifferentiated subtypes ($p = 0.06$).

The mean retrospective GAF score in the same patients for the 1-month period with the highest level of functioning during the prodromal phase was 56.9 (SD = 8.9), 46.3 (SD = 8.4), 51.8 (SD = 8.4), and 28.3 (SD = 5.4), respectively. The difference among the subtypes was significant ($F = 19.402$, $p < 0.0001$). Post hoc tests showed a significant difference between the paranoid and disorganized subtypes ($p < 0.0001$), the paranoid and catatonic subtypes ($p < 0.0001$), the undifferentiated and catatonic subtypes ($p < 0.0001$), and the disorganized and catatonic subtypes ($p = 0.001$).

ANOVA with repeated measures, with two grouping factors applied to the GAF scores, obtained in the four schizophrenia subtypes, showed a significant difference

between the prodromal phase and the psychotic state of the disease ($F = 15.784$, $p < 0.0001$). Paired t tests showed a significant difference between the GAF scores of the prodromal and the psychotic phase in the paranoid ($t = 19.297$, $df = 49$, $p < 0.0001$), the disorganized ($t = 10.491$, $df = 25$, $p < 0.0001$), the undifferentiated ($t = 16.455$, $df = 19$, $p < 0.0001$), and the catatonic subtypes ($t = 14.697$, $df = 3$, $p = 0.001$).

Psychotic and Other Symptoms of Index Episode. During the index episode (active phase) of the 100 patients, 97 experienced at least one delusion, organized or fragmentary. The median number of delusions was two, with a range from one to six. Also, 62 of the patients had hallucinations: 51 had only auditory, 4 had only visual, and 7 had both auditory and visual. Disorganized speech was observed in 36 patients, significantly disorganized or catatonic behavior in 50 patients, and negative symptoms in all patients. The mean number of negative symptoms was 3.4 (SD = 1.6), with a range from 1 to 8.

Discussion

This study investigates the initial prodromal phase of schizophrenia, with particular emphasis on the subtypes as well as the positive and negative dimensions of the initial prodromal symptoms. Clearly, schizophrenia patients during the prodromal phase were different from control subjects derived from the general population. The patients had a significantly greater number of prodromal symptoms than did the controls. Actually, the frequency of the prodromal symptoms in the patients was 14-fold greater than in the controls. Also, patients and control subjects differed in the nature of the most common symptoms. In the patients, marked isolation, marked impairment in role functioning, preoccupation, marked lack of initiative, interests, or energy, irritability/anger, and blunted affect were the most common symptoms. In the control subjects, the most frequently recorded symptoms were odd beliefs/magical thinking, belief in clairvoyance, depressive mood, impairment in concentration, telepathy, sixth sense, and anxiety. Thus, it appears that schizophrenia patients during the initial prodromal phase tended to develop symptoms indicating social, occupational, and affective dysfunction, whereas in the control subjects, symptoms involving magical content and disturbance in mood predominated. These observations appear to be of clinical importance because they may lead to the development of quantitative and qualitative criteria that could identify schizophrenia patients before the development of florid psychosis. Future studies with a combined behavioral-phenomenological and subjective-experiential approach may provide an even more refined approach to early diagnosis of schizophrenia.

In the paranoid subtype, 20 prodromal symptoms were identified with a frequency of 10 percent or greater. The most common symptom was marked isolation, appearing in 92 percent of the patients; it was followed by suspiciousness and ideas of reference in 64 percent and 50 percent of the patients, respectively. On the other hand, the specificity was high for suspiciousness (0.96) and odd beliefs/magical thinking (0.92). However, odd beliefs/magical thinking had a low sensitivity, and, therefore, its diagnostic usefulness is limited. Suspiciousness, when present, has a significant diagnostic power, because this symptom has a high specificity, high positive predictive value, and high negative predictive value. Also, marked isolation appears to be a useful prodromal symptom for early diagnosis because it combines high sensitivity with helpful, for diagnostic purposes, values of specificity, positive predictive value, and negative predictive value.

The disorganized subtype had 23 initial prodromal symptoms with a frequency greater than 10 percent. Both marked impairment in role functioning and marked lack of initiative, interests, or energy were recorded with a frequency of 92 percent among the patients who developed this subtype. Impairment in concentration and marked withdrawal followed with a frequency of 73 percent and 69 percent, respectively. However, marked lack of initiative, interests, or energy appears to have a better prognostic value than marked impairment in role functioning because it has a greater specificity, positive predictive value, and negative predictive value. Nonetheless, the prodromal symptoms with the greater specificity for the disorganized subtype were poverty of content of speech and marked impairment in personal hygiene and grooming.

In patients who later developed the undifferentiated subtype, 23 initial prodromal symptoms were observed with a frequency of 10 percent or greater. The most common symptoms were marked impairment in role functioning and blunted affect, both appearing with a frequency of 80 percent, followed by marked lack of initiative, interests, or energy. However, blunted affect seems to have a greater diagnostic value than marked impairment in role functioning because it had a greater specificity, positive predictive value, and negative predictive value. The prodromal symptoms with the greater specificity for the undifferentiated subtype were sleep disturbance, poverty of content of speech, and odd beliefs/magical thinking, which symptoms, however, had a low sensitivity.

It is noteworthy that during the initial prodromal phase, similar to the psychotic state (American Psychiatric Association 1994), the negative symptoms were more common in the disorganized and the undifferentiated subtypes

than in the paranoid subtype. On the contrary, the frequency of the positive symptoms was greater in the paranoid than in the disorganized and the undifferentiated subtypes. This finding indicates that the development of a subtype is already programmed from the prodromal phase of the psychosis. Additional support for this concept is provided by the observations that (1) the frequency of the various initial prodromal symptoms differs significantly among the three most common subtypes; and (2) the total number of the initial prodromal symptoms as well as the combinations of the first prodromal symptoms differs significantly between the paranoid subtype on the one hand and the disorganized and undifferentiated subtypes on the other.

Certain initial prodromal symptoms frequently developed to related delusions when the patients became psychotic. The fact that in these patients the specific delusions substituted for the particular prodromal symptoms is indicated by the observation that in all cases in which these delusions developed in the psychotic state, the corresponding prodromal symptoms disappeared. Similarly, earlier reports proposed that nearly all single cognitive and cenesthetic symptoms appearing earlier in the disease evolve into hallucinations and delusions (Huber 1966; Gross 1989).

It is of interest that the GAF score of the prodromal phase was already reduced in the subtypes in a degree parallel to that of the psychotic state. Thus, the order of the subtypes, from the lowest to the highest GAF score, in both the prodromal and the psychotic phase, was catatonic, disorganized, undifferentiated, and paranoid. In the three most common subtypes, the decrease of the GAF score from the prodromal phase to the psychotic state was unexpectedly stable, ranging between 16.1 and 16.9. These findings indicate that the functioning of the patients in the subtypes differs even when the patients are still in the prodromal phase.

A limitation of the present study is the difficulties inherent in obtaining retrospective data from patients (distortion or incomplete reporting because of cognitive deterioration) and family members (emphasis on negative symptoms). To minimize the introduction of possible errors into the results, we took a number of precautions: (1) assessment was based on personal interviews and not on medical chart information or questionnaires; (2) only patients with a recent onset of the disease were studied, and 75 percent of them were in their first psychotic episode; (3) patients and family members were interviewed by two independent interviewers, and the data were reviewed by the third author, who was unaware of the conclusions of the interviewers; and (4) the κ statistics for interrater agreement were applied on the results, and highly significant agreement among the reviewers was observed.

Although transition from one subtype to another may occur (Fenton and McGlashan 1991), it appears that the subtypes are more distinct than is frequently thought. In addition to previous reports from our group indicating differences in the age at onset among the subtypes (Beratis et al. 1994) and gender differences in the frequency of the schizophrenia subtypes (Beratis et al. 1997), the findings of this study extend the differences in the clinical phenomenology of the subtypes into the prodromal phase of the disease.

The type and the constellation of the prodromal symptoms provide clues to the schizophrenia subtype that will develop, in cases where prodromal symptoms evolve into a psychotic state. Of particular clinical importance is the observation that the GAF score of the psychotic phase is related to the GAF score of the prodromal state, regardless of the subtype. Thus, a reasonable prediction of the patients' subsequent functioning can be made from the prodromal phase. Also, the information provided improves our understanding of the prodromal state of schizophrenia, the onset of the disease, the signs and symptoms that best define it, and their prognostic significance. Such systematic characterization of the earliest manifestation of schizophrenia may aid other studies in identifying individuals at risk for the disease and raises the possibility of developing a clearer rationale for stage-appropriate treatment.

References

American Psychiatric Association. *DSM–III: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed. Washington, DC: APA, 1980.

American Psychiatric Association. *DSM–III–R: Diagnostic and Statistical Manual of Mental Disorders.* 3rd ed., revised. Washington, DC: APA, 1987.

American Psychiatric Association. *DSM–IV: Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: APA, 1994.

Andreasen, N.C.; Arndt, S.; Alliger, R.; Miller, D.; and Flaum, M. Symptoms of schizophrenia: Methods, meanings and mechanisms. *Archives of General Psychiatry,* 52:341–351, 1995.

Andreasen, N.C., and Olsen, S. Negative vs. positive schizophrenia: Definition and validation. *Archives of General Psychiatry,* 39:789–794, 1982.

Arndt, S.; Alliger, R.J.; and Andreasen, N.C. The distinction of positive and negative symptoms: The failure of a two-dimensional model. *British Journal of Psychiatry,* 158:317–322, 1991.

Arndt, S.; Andreasen, N.C.; Flaum, M.; Miller, D.; and Nopoulos, P. A longitudinal study of symptom dimensions

in schizophrenia. *Archives of General Psychiatry,* 52:352–360, 1995.

Bartko, J.J., and Carpenter, W.T. On the methods and theory of reliability. *Journal of Nervous and Mental Diseases,* 163:307–317, 1976.

Beratis, S.; Gabriel, J.; and Hoidas, S. Age at onset in subtypes of schizophrenic disorders. *Schizophrenia Bulletin,* 20(2):287–296, 1994.

Beratis, S.; Gabriel, J.; and Hoidas, S. Gender differences in the frequency of schizophrenic subtypes in unselected hospitalized patients. *Schizophrenia Research,* 23:239–244, 1997.

Bilder, R.M.; Mukherjee, S.; Rieder, R.O.; and Pandurangi, A.K. Symptomatic and neuropsychological components of defect states. *Schizophrenia Bulletin,* 11(3):409–419, 1985.

Chapman, L.J., and Chapman, J.P. The search for symptoms predictive of schizophrenia. *Schizophrenia Bulletin,* 13(3):497–503, 1987.

Conrad, K. *Die beginnende Schizophrenie: Versuch einer Gestaltanalyse des Wahns.* Stuttgart, Germany: Thieme, 1958.

Cutting, J., and Dunne, F. The nature of the abnormal perceptual experiences at the onset of schizophrenia. *Psychopathology,* 19:347–352, 1986.

DeLisi, L.E.; Crow, T.J.; and Hirsch, S.R. The third biannual winter workshop on schizophrenia. *Archives of General Psychiatry,* 43:706–711, 1986.

Eaton, W.W.; Badawi, M.; and Melton, B. Prodromes and precursors: Epidemiologic data for primary prevention of disorders with slow onset. *American Journal of Psychiatry,* 152:967–972, 1995.

Fenton, W.S., and McGlashan, T.H. Natural history of schizophrenia subtypes: I. Longitudinal study of paranoid, hebephrenic, and undifferentiated schizophrenia. *Archives of General Psychiatry,* 48:969–977, 1991.

Gross, G. The "basic" symptoms of schizophrenia. *British Journal of Psychiatry,* 155(Suppl 7):21–25, 1989.

Gross, G., and Huber, G. Psychopathology of basic stages in schizophrenia in view of formal thought disturbances. *Psychopathology,* 18:115–125, 1985.

Häfner, H.; Maurer, K.; Löffler, W.; and Riecher-Rössler, A. The influence of age and sex on the onset and early course of schizophrenia. *British Journal of Psychiatry,* 162:80–86, 1993.

Häfner, H.; Riecher-Rössler, A.; Maurer, K.; Fätkenheuer, B.; and Löffler, W. First onset and early symptomatology of schizophrenia: A chapter of epidemiological and neurobiological research into age and sex differences. *European Archives of Psychiatry and Clinical Neurosciences,* 242:109–118, 1992.

Heinrichs, D.W., and Carpenter, W.T. Prospective study of prodromal symptoms in schizophrenic relapse. *American Journal of Psychiatry,* 142:371–373, 1985.

Herz, M.I. Prodromal symptoms and the prevention of relapse in schizophrenia. *Journal of Clinical Psychiatry,* 46:22–25, 1985.

Herz, M.I., and Melville, C. Relapse in schizophrenia. *American Journal of Psychiatry,* 137:801–807, 1980.

Herz, M.I.; Szymaski, M.V.; and Simon, J.C. Intermittent medication of stable schizophrenic outpatients: An alternative to maintenance medication. *American Journal of Psychiatry,* 139:918–922, 1982.

Huber, G. Reine defektsyndrome und basisstadien endogener psychosen. *Fortschritte der Neurologie-Psychiatrie,* 34:409–426, 1966.

Huber, G.; Gross, G.; Schuettler, R.; and Linz, M. Longitudinal studies of schizophrenic patients. *Schizophrenia Bulletin,* 6(4):592–605, 1980.

Jackson, H.J.; McGorry, P.D.; and Dudgeon P. Prodromal symptoms of schizophrenia in first-episode psychosis: Prevalence and specificity. *Comprehensive Psychiatry,* 36:241–250, 1995.

Jackson, H.J.; McGorry, P.D.; and McKenzie, D. The reliability of *DSM–III* prodromal symptoms in first-episode psychotic patients. *Acta Psychiatrica Scandinavica,* 90:375–378, 1994.

Keith, S.J., and Matthews, S.M. The diagnosis of schizophrenia: A review of onset and duration issues. *Schizophrenia Bulletin,* 17(1):51–67, 1991.

Keshavan, M.S., and Schooler, N.R. First-episode studies in schizophrenia: Criteria and characterization. *Schizophrenia Bulletin,* 18(3):491–513, 1992.

Liddle, P.F. Schizophrenic syndromes, cognitive performance and neurological dysfunction. *Psychological Medicine,* 17:49–57, 1987*a*.

Liddle, P.F. The symptoms of chronic schizophrenia: A reexamination of the positive-negative dichotomy. *British Journal of Psychiatry,* 151:145–151, 1987*b*.

Liddle, P.; Carpenter, W.T.; and Crow, T. Syndromes of schizophrenia: Classic literature. *British Journal of Psychiatry,* 165:721–727, 1994.

Lipton, A.L., and Cancro, R. Schizophrenia: Clinical features. In: Kaplan, H.I., and Sadock, B.J., eds. *Comprehensive Textbook of Psychiatry/VI.* Vol. 1. Baltimore, MD: Williams and Wilkins, 1995. pp. 968–987.

Malla, A.K., and Norman, R.M.G. Prodromal symptoms in schizophrenia. *British Journal of Psychiatry,* 164:487–493, 1994.

McGlashan, T.H., and Fenton, W.S. The positive-negative distinction in schizophrenia: Review of natural history

validators. *Archives of General Psychiatry,* 49:63–72, 1992.

McGorry, P.D.; McFarlane, C.; Patton, G.C.; Bell, R.; Hibbert, M.E.; Jackson, H.J.; and Bowes, G. The prevalence of prodromal features of schizophrenia in adolescence: A preliminary survey. *Acta Psychiatrica Scandinavica,* 92:241–249, 1995.

McGorry, P.D.; McKenzie, D.; Jackson, H.J.; Waddell, F.; and Curry, C. Can we improve the diagnostic efficiency and predictive power of prodromal symptoms for schizophrenia? *Schizophrenia Research,* 42:91–100, 2000.

Møller, P., and Husby, R. The initial prodrome in schizophrenia: Searching for naturalistic core dimensions of experience and behavior. *Schizophrenia Bulletin,* 26(1):217–232, 2000.

Spitzer, R.L.; Williams, J.B.W.; Gibbon, M.; and First, M.B. *Structured Clinical Interview for DSM–III–R-Patient Version (SCID-P).* Washington, DC: American Psychiatric Press, 1990.

Subotnik, K.L., and Nuechterlein, K.H. Prodromal signs and symptoms of schizophrenic relapse. *Journal of Abnormal Psychology,* 97:405–412, 1988.

Yung, A.R., and McGorry, P.D. The prodromal phase of first episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin,* 22(2):353–370, 1996.

Yung, A.R.; McGorry, P.D.; McFarlane, C.A.; Jackson, H.J.; Patton, G.C.; and Rakkar, A. Monitoring and care of young people at incipient risk for psychosis. *Schizophrenia Bulletin,* 22(2):283–303, 1996.

The Authors

Philippos Gourzis, M.D., is Lecturer in Psychiatry; Aggeliki Katrivanou, M.D., is Assistant Attending in Psychiatry; and Stavroula Beratis, M.D., is Professor of Psychiatry, Child Psychiatry, and Psychoanalysis. All authors are at the Department of Psychiatry, University of Patras Medical School, General University Hospital, 265 00 Rion Patras, Greece.