Subtype Progression and Pathophysiologic Deterioration in Early Schizophrenia

by Thomas H. McGlashan and Wayne S. Fenton

Abstract

It is important to elaborate what we know about the symptomatic, syndromal, and functional course of schizophrenia in order to test models for this illness. The sample of schizophrenic patients from the Chestnut Lodge followup study was subtyped using classical (modified DSM-III-R) criteria and deficit/nondeficit (Schedule for the Deficit Syndrome) criteria. During the first 5 years of manifest illness, the subtype phenomenologies were moderately stable. Instability consisted of a drift toward disorganization (hebephrenia) and nonspecificity (undifferentiated) among the classical subtypes, and toward the deficit subtype within that categorization. Over the same time, positive symptoms were relatively stable, but negative symptoms became significantly worse. Such changes probably reflect “deterioration” because they were associated with poorer functional outcome an average of 15 years later. These data dovetail with other reports in the literature and suggest a hierarchy of symptomatic/syndromal progression in early manifest schizophrenia that may reflect active deterioration processes at work. We suggest that any theory of schizophrenic pathophysiology must account for these patterns of symptom course.

The course and progression of symptoms and the functional capacities in schizophrenia have been considered characteristic of the illness since the time of Emil Kraepelin. In fact, he elevated the vicissitudes of longitudinal course to the level of definition; schizophrenia as dementia praecox was a disorder with a long-term, deteriorative course (Kraepelin 1919/1971). Although many contend that the form and depth of the deterioration in the schizophrenia of today may not be as devastating as that of dementia praecox, few will argue that nothing is “lost” or that the changes wrought by this disease are easily and completely reversible. While today’s average case of schizophrenia may be milder than its counterpart at the beginning of the century, schizophrenia remains one of the most common and devastating mental illnesses. The course of schizophrenia remains distinct enough so that any purported pathophysiologic model of this illness, in order to be considered valid, should be able to explain the patterns of its expression over time.

For purposes of model testing, then, it is important to elaborate what we know about the symptomatic and functional course of schizophrenia so that we can articulate the natural history data that our model must explain. Are there any patterns of symptom and syndrome expression or progressions of functional capabilities that occur with any regularity? What are the symptoms of schizophrenia, and how do they progress over the long term? Can phenomenological subtypes be discerned, and do they evolve with time? How does functional capacity covary with the ebb and flow of these symptoms? Is there any loss of mental capac-

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ity, emotional alertness, or behavioral responsiveness? If so, what is lost, and what is the time course of this loss? Does it happen early or late in the course of the disease? Is there a pattern to this loss? Drawing on observations from the Chestnut Lodge followup study (McGlashan 1984a, 1984b) and on data from the literature, we propose tentative answers to these questions.

Relevant Literature

Symptom Progression in Early Course of Schizophrenia. The symptom picture in the early course of schizophrenia has been the subject of several recent comparative and longitudinal investigations. Shtasel and colleagues (1991) studied symptom differences between first-episode and later episode patients. The former scored higher on ratings of delusions and hostility, while the latter were higher on poor attention, flat affect, and thought disorder. King and colleagues (1990) examined the language of schizophrenic subjects at two periods separated by 3 years and found a deterioration in the complexity and integrity of speech, especially mean length of utterance and percentage of sentences with imbedding. Harrow and Marengo (1986) found that thought disorder that persisted after the acute phase predicted subsequent poor outcome over 4 years of followup. Comparing first-episode schizophrenic patients and patients in later stages of illness (≥5 years), Haas and colleagues (1991) found greater deficits in male patients on cognitive measures (verbal recognition, fluency, and coding and recall memory) and on negative symptoms (alogia and affect flattening). In a 3-year longitudinal study of recent-onset schizophrenic patients, Ventura and colleagues (1991) found that positive symptoms increased over time, but negative symptoms showed no trend in either direction. Overall, the data suggest that early, highly charged affects and positive symptoms may become less conspicuous with time as thought disorder, attention disorder, and negative symptoms advance. The data of Ventura and colleagues (1991) stand in contrast to this and suggest that earlier patterns may remain quite heterogeneous and difficult to predict.

Symptom Progression in Schizophrenia Over Many Years. Frohlich and Winokur (1982) studied hebephrenic schizophrenic patients from the Iowa 500 who had comprehensive documentation of mental status for a minimum of 12 consecutive years. They rated these records for the presence of 28 signs and symptoms, which they categorized into positive and negative types by the Schedule for the Assessment of Negative Symptoms (SANS; Andreasen 1984a) and the Schedule for the Assessment of Positive Symptoms (SAPS; Andreasen 1984b). They found many more positive than negative symptoms within 1 year of illness onset. After 5 years this pattern reversed to a significant degree, and negative symptoms predominated. They also found that negative symptoms were significantly more likely than positive symptoms to persist over many years. Winokur and colleagues (1985) followed the patterns of depression, mania, thought disorder, incongruous affect, delusions, and hallucinations across many years and hundreds of episodes in patients with schizophrenia, schizoaffective disorder, unipolar disorder, and bipolar disorder. The most striking finding was a decrease in the prevalence of positive psychotic symptoms (hallucinations and delusions) in all diagnostic groups, especially among the schizoaffective, unipolar, and bipolar patients. These changes often evolved only after many years and many episodes of illness; from episode to episode individual symptom profiles tended to be more similar than different.

Ciompi’s (1980) long-term followup study of schizophrenia found a gradual accrual of deficit symptoms or states over time. Summarizing an average of 37 years of followup observation, he wrote:

The prominent symptom pictures that had originally suggested the patient’s inclusion in one of the classic schizophrenic subgroupings were almost totally or nearly flattened out beyond recognition at the time of the final catamnestic follow-up examinations. This far-reaching despecification and flattening, along with a general tendency toward calming and improving, seemed to be the most characteristic influence in advancing age on the schizophrenic manifestations. [p. 611]

Finally, McGlashan and Fenton (1992) summarized their review of the natural history of positive and negative symptoms in schizophrenia as follows:

The course of positive and negative symptoms in schizophrenia is variable depending on phase of disorder. In first or early episodes, positive symptoms are frequent, negative symptoms are infrequent, and both types are unstable, fluctuating, and usually treatment responsive. In subacute/subchronic stages of the illness, negative symptoms...
increase in prevalence, are at least as common as positive symptoms, and fluctuate less. In the latter stages of the illness, negative symptoms are quite stable and usually dominate the clinical picture. The different character and course of negative symptoms in early versus mid-to later-phases of schizophrenia strongly suggest they may be generated by different underlying mechanisms. [p. 68]

Subtype Stability and Progression in Schizophrenia. Kendler et al. (1985) subtyped 132 schizophrenic patients from the Iowa 500 into paranoid, hebephrenic, undifferentiated, and catatonic subtypes using Tsuang/Winokur (1974) criteria; Research Diagnostic Criteria (RDC; Spitzer et al. 1978); International Classification of Diseases (ICD-9; World Health Organization 1978); and DSM-III (American Psychiatric Association 1980). They rated patients at index admission and followup; the mean interim interval was 25 years. They found modest subtype stability. The most and least stable subtypes were the paranoid and undifferentiated, respectively. The stability of the paranoid subtype tended to diminish over time. The same was true for the hebephrenic subtype though less so. Overall, the more specific subtypes of schizophrenia (paranoid, hebephrenic) evolved into less specific syndromes (undifferentiated). The most and least stable subtypes (paranoid, hebephrenic) based on modified DSM-III-R criteria suggest that the classical subtypes of schizophrenia are somewhat stable entities, but that time tends to erode syndromal patterns in the direction of greater disorganization (hebephrenia) or nonspecificity (undifferentiated).

The Study
To compare the validity of different approaches to subtyping schizophrenia, we applied several operational criteria to the schizophrenic cohort of the Chestnut Lodge followup study (McGlashan 1984a, 1984b). Initial findings have upheld the validity of the classical subtypes (Fenton and McGlashan 1991a) and of the positive/negative symptom construct (Fenton and McGlashan 1991b). For this study the schizophrenic cohort has been subtyped by the classical system (paranoid, undifferentiated, hebephrenic) based on modified DSM-III-R criteria and by the deficit/nondeficit criteria of Carpenter and colleagues (1988). These data are used to address the following questions: (1) Are the classical and deficit subtypes related in this population and if so, how? (2) Are these subtypes stable over time and if not, how do they vary?

Method: Data Sources and Population. The followup sample consisted of all patients discharged from Chestnut Lodge between 1950 and 1975 and a smaller cohort of nondischarged inpatients from a comparable period of time. Patients without organic brain syndrome who were between 16 and 55 years of age at admission and who had been treated at Chestnut Lodge for at least 90 days were selected. The majority of patients were single. All were white and from upper socioeconomic brackets. The baseline sample of schizophrenic patients (n = 187) included 98 males and 89 females (60% males). The mean age at illness onset for the schizophrenic group was 20 years, the mean age at first hospitalization was 23 years, the mean age at index hospitalization was 28 years, and the mean age of those who received followup evaluation (n = 162) was 47 years.

For the original followup study (McGlashan 1984b), two categories of data were collected: demographic, premorbid, sign, symptom, and diagnostic data rated from abstracts of index admission medical records; and long-term followup data independently collected by interviews with subjects and/or significant others an average of 19 years after index admission (range = 2-32). The reliability of the measures used for these assessments has been reported (McGlashan 1984a).

For the present study, subtype ratings were generated for the index hospitalization for 187 patients from the followup who received a research diagnosis (mostly DSM-III) of schizophrenia. As outlined previously (Fenton and McGlashan 1991a, 1991b), index admission rat-
ings were based on extensive archival records (not abstracts), including written observations of multiple informants and verbatim transcripts of clinical case conferences. This information was sufficient to allow the formation of index admission subtype ratings.

In addition to the above, records from an earlier (usually first) psychiatric hospitalization were also available for a significant subset of this cohort ($n = 125$ for classical subtypes, $n = 120$ for deficit/nondeficit subtypes). These records were less detailed and missing ratings were coded for between 1 and 7 percent of patients, depending on the particular scale employed. Additional historical, manifest illness, and illness course variables were also collected. The reliability of these assessments has been detailed previously using data on the natural history of the classical schizophrenia subtypes (Fenton and McGlashan 1991a).

Schizophrenia Subtype Systems: Classical Subtypes. The most commonly used classical subtypes in DSM-III-R nosology include the paranoid, disorganized (hebephrenic), and undifferentiated. Criteria for these subtypes were applied reliably to the Chestnut Lodge followup study schizophrenic cohort using RDC, DSM-III, ICD-9, and Tsuang/Winokur criteria. To approximate DSM-III-R, which was not available when this study began, research subtype criteria were rated based on items from the Tsuang/Winokur and DSM-III as follows:

Paranoid schizophrenia: Meets A and B

A. Either 1 or 2:
   1. A type of schizophrenia dominated by persecutory, grandiose delusions, delusions of jealousy, or hallucinations with persecutory or jealous content, or
   2. Preoccupations with extensive, well-organized delusions or hallucinations (any theme) without marked inappropriate or flat affect or bizarre behavior.

B. Does not meet criteria for hebephrenic subtype.

Hebephrenic schizophrenia: A, B, and C required

A. Disorganized thought.
B. Bizarre behavior or hebephrenic/catatonic traits.
C. Flat or inappropriate affect.

Undifferentiated schizophrenia

A. Does not meet criteria for paranoid or hebephrenic type.

Like those in DSM-III-R, these criteria are hierarchical. Hebephrenic patients can meet symptom criteria for paranoid schizophrenia, but paranoid patients cannot meet symptom criteria for hebephrenia.

Undifferentiated patients do not meet criteria for either subtype. Unlike DSM-III-R, which excludes patients with any significant thought disorder, blunted or inappropriate affect, or bizarre behavior from the paranoid category, we excluded patients with these symptoms only if they meet criteria for hebephrenia. This broader criteria for paranoid schizophrenia was used to maximize the number of patients receiving a specific (rather than undifferentiated) subtype diagnosis. Our criteria for hebephrenia were also unlike DSM-III-R, which requires only two of the three listed symptom domains. Our definition narrows the category but increases its specificity and discrimination from the undifferentiated subtype (Fenton and McGlashan 1991a).
putatively linked to the underlying defect from those which are secondary to other processes such as drug side effects, depression, or institutionalization. These primary negative symptoms are also enduring and in Carpenter and colleagues' scheme must be present for at least 1 year.

The criteria for the deficit and nondeficit subtypes are as follows (Wagman et al. 1987):

1. Meets DSM-III criteria for schizophrenia.
2. At least two of the following symptoms present:
   (a) flattened or restricted affect
   (b) anhedonia
   (c) poverty of speech with curbing of ideational field
   (d) lack of sense of purpose
   (e) lack of social drive
3. Negative symptoms not fully accounted for by depression or anxiety, drug effect, or environmental deprivation.
4. Two or more of negative symptoms always present for the preceding 12 months and always present during periods of clinical stability, including chronic psychotic states or during recovery from psychotic exacerbations. These symptoms may not be detectable during transient episodes of acute psychotic disorganization or decompensation.

These criteria were also applied reliably to the records of our followup study schizophrenic patients (Fenton and McGlashan 1990).

Results

Subtype Prevalence and Overlap.
Table 1 contains a crosstabulation of the two subtyping schemes for the index admission (baseline) sample of schizophrenic patients. It is clear that of the deficit patients, very few were paranoid, many were hebephrenic, and most were undifferentiated. Of the nondeficit patients, very few were hebephrenic, many more were undifferentiated, and most were paranoid. These differences were highly significant ($\chi^2 = 44.7; p < 0.00001$).

Comparative Validity of Subtypes vis-a-vis Long-Term Outcome.
The ultimate utility of any subtyping scheme rests upon its ability to define subgroups with distinctive profiles on a variety of independent validators. Table 2 presents a crosstabulation of the classical versus the deficit/nondeficit schemes versus global outcome dichotomized as good and poor. A sample of 162 patients received followup evaluation and global outcome assessment. Global outcome ranged from 0 to 4 (0 = continuous incapacitation and 4 = complete recovery; McGlashan 1984b). Overall, 35 percent had a good outcome (global outcome score = 2, 3, 4) and 65 percent had a poor outcome (global outcome score = 0, 1). The ratios of good to poor outcomes varied considerably across subtypes. In the classical scheme, for example, 91 percent of the hebephrenic patients had a poor outcome, and 45 percent of the paranoid patients had a good outcome. For the deficit subtype 80 percent had a poor outcome, and

Table 1. Classical versus deficit/nondeficit subtypes: Subtype crosstabulation at index admission

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Par n (%)</th>
<th>Heb n (%)</th>
<th>Und n (%)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficit</td>
<td>4 (9)</td>
<td>18 (39)</td>
<td>24 (52)</td>
<td>46 (25)</td>
</tr>
<tr>
<td></td>
<td>0 (0)</td>
<td>6 (13)</td>
<td>28 (58)</td>
<td>34 (19)</td>
</tr>
<tr>
<td>Nondeficit</td>
<td>74 (52)</td>
<td>8 (6)</td>
<td>59 (42)</td>
<td>141 (75)</td>
</tr>
<tr>
<td></td>
<td>8 (6)</td>
<td>26 (19)</td>
<td>34 (24)</td>
<td>68 (35)</td>
</tr>
<tr>
<td>Total</td>
<td>78 (42)</td>
<td>26 (14)</td>
<td>83 (44)</td>
<td>187</td>
</tr>
</tbody>
</table>

Note.—$\chi^2 = 44.7, p < 0.00001$. Par = paranoid, Heb = hebephrenic (disorganized), Und = undifferentiated.

Table 2. Classical versus deficit/nondeficit subtypes: Subtype crosstabulations and dichotomized global outcome

<table>
<thead>
<tr>
<th>Global Outcome</th>
<th>Par n</th>
<th>Heb n</th>
<th>Und n</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficit (n = 41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>4</td>
<td>13</td>
<td>16</td>
<td>33 (80)</td>
</tr>
<tr>
<td>Good</td>
<td>0</td>
<td>2</td>
<td>6</td>
<td>8 (20)</td>
</tr>
<tr>
<td>Nondeficit (n = 121)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>31</td>
<td>8</td>
<td>33</td>
<td>72 (60)</td>
</tr>
<tr>
<td>Good</td>
<td>29</td>
<td>0</td>
<td>20</td>
<td>49 (40)</td>
</tr>
<tr>
<td>Total sample (n = 162)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor</td>
<td>35 (55)</td>
<td>21 (91)</td>
<td>49 (65)</td>
<td>105 (65)</td>
</tr>
<tr>
<td>Good</td>
<td>22 (45)</td>
<td>2 (9)</td>
<td>26 (35)</td>
<td>57 (35)</td>
</tr>
<tr>
<td>Total</td>
<td>64</td>
<td>23</td>
<td>75</td>
<td>162</td>
</tr>
</tbody>
</table>

Note.—Par = paranoid, Heb = hebephrenic (disorganized), Und = undifferentiated.
for the nondeficit subtype 40 percent had a good outcome score. Thus, the hebephrenic subtype was more robustly associated with or predictive of poor outcome than the deficit subtype, and the paranoid subtype was more indicative of good outcome than the nondeficit subtype, even though the actual differences were small. It is also clear that with this sample it was easier to predict poor outcome than it was to predict good outcome, no matter which subtyping scheme was used.

Subtype Progression Over Early Course of Schizophrenia. As noted, a substantial subpopulation of patients from the followup schizophrenic cohort had records from their initial treatment contact (usually hospitalization) that were sufficiently detailed to allow subtype classification. This made it possible to evaluate subtype stability between first hospitalization and index admission. The average time between these two points was approximately 5 years. Table 3 presents this cross-tabulation of subtype assignment for each of the subtype systems. As can be seen, the classical subtypes were moderately stable between first and index admission (top left to bottom right diagonal). Changes, when they occurred, were generally in the direction of undifferentiated and hebephrenic subtypes. The deficit/nondeficit distinctions were even more stable between the first and index admission. Of 12 deficit patients at first admission, 10 or 83 percent were still deficit by index admission. When change occurred, it was in the direction of the nondeficit to deficit. The classical subtype progression but not the deficit/nondeficit subtype progression has been reported elsewhere (Fenton and McGlashan 1991a).

Symptom Progression Over Early Course of Schizophrenia. Some of the SANS and SAPS symptoms used to construct subtypes were assessed and rated independently. Eight of these symptoms (four negative and four positive) are presented in table 4. Over the 5 years between first and index treatment three of the four negative symptoms became significantly worse. Among the positive symptoms, hallucinations and delusions were unchanged or slightly better, and thought disorder and bizarre behavior were slightly worse, but none of these changes reached significance.

Prototypic Case. A prototypic case illustrates some of these vicissitudes of course in schizophrenia.

Gary S. was a 40-year-old, white, Protestant, married male and father of one when admitted to Chestnut Lodge in the 1950s. He came in transfer from another psychiatric hospital, where he had resided for about 5 years. Gary’s first signs of difficulty were periods of withdrawal beginning around age 16. These receded when he became interested in literature and dramatics later in high school. He pursued instruction in dramatic arts and earned a masters degree at age 25. During this time he was more active socially and experienced one or more homosexual encounters after heavy drinking at parties. After earning his degree, Gary moved to a small New England town where he secured a job as director of a community theater.

For the next 3 years Gary worked diligently but did not accomplish much. Despite periods of loneliness, he turned down most social invitations. Around age 28 he became paranoid about the townspeople, feeling they were “out to get him.” He saw a psychiatrist for 8 to 10 sessions but became discouraged and stopped. At age 30 he married after a 2-week courtship. Dissatisfied with the financial hardships of theater life, he entered school for training

<table>
<thead>
<tr>
<th>Subtype Progression Over Early Course of Schizophrenia.</th>
<th>Note. Par = paranoid, Heb = hebephrenic (disorganized), Und = undifferentiated.</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 3. Classical versus deficit/nondeficit subtypes: Subtype assignment at first and index admission, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Admission</td>
<td>Par</td>
<td>Heb</td>
</tr>
<tr>
<td>Classical, n = 125</td>
<td>62 (49)</td>
<td>12 (10)</td>
</tr>
<tr>
<td>Index admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Par 44 (35)</td>
<td>38 (61)</td>
<td>0</td>
</tr>
<tr>
<td>Heb 22 (18)</td>
<td>5 (8)</td>
<td>8 (67)</td>
</tr>
<tr>
<td>Und 59 (47)</td>
<td>19 (31)</td>
<td>4 (33)</td>
</tr>
<tr>
<td>First Admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficit/nondeficit, n = 120</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deficit 12 (10)</td>
<td>108 (90)</td>
<td></td>
</tr>
<tr>
<td>Nondeficit 85 (71)</td>
<td>2 (17)</td>
<td>83 (77)</td>
</tr>
</tbody>
</table>
Table 4. Negative and positive symptom progression between first and index admissions, paired t test

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>First admission mean (SD)</th>
<th>Index admission mean (SD)</th>
<th>t</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flat affect</td>
<td>2.0 ± (1.6)</td>
<td>2.0 ± (1.5)</td>
<td>0.0</td>
<td>119</td>
<td>1.000</td>
</tr>
<tr>
<td>Alogia</td>
<td>1.1 ± (1.4)</td>
<td>1.5 ± (1.6)</td>
<td>3.0</td>
<td>118</td>
<td>0.003</td>
</tr>
<tr>
<td>Apathy/avolition</td>
<td>1.7 ± (1.4)</td>
<td>2.2 ± (1.7)</td>
<td>3.5</td>
<td>119</td>
<td>0.001</td>
</tr>
<tr>
<td>Anhedonia/asociality</td>
<td>1.8 ± (1.6)</td>
<td>2.3 ± (1.6)</td>
<td>3.0</td>
<td>119</td>
<td>0.003</td>
</tr>
<tr>
<td>Positive</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>1.9 ± (1.7)</td>
<td>1.9 ± (1.8)</td>
<td>-0.3</td>
<td>124</td>
<td>0.748</td>
</tr>
<tr>
<td>Delusions</td>
<td>3.2 ± (1.4)</td>
<td>3.0 ± (1.4)</td>
<td>-1.8</td>
<td>124</td>
<td>0.081</td>
</tr>
<tr>
<td>Bizarre behavior</td>
<td>2.7 ± (1.4)</td>
<td>2.8 ± (1.5)</td>
<td>0.7</td>
<td>123</td>
<td>0.510</td>
</tr>
<tr>
<td>Thought disorder</td>
<td>1.4 ± (1.5)</td>
<td>1.5 ± (1.4)</td>
<td>0.9</td>
<td>124</td>
<td>0.368</td>
</tr>
</tbody>
</table>

Note.—df = degrees of freedom.

1From the Scale for the Assessment of Negative Symptoms (Andreasen 1984a).

2From the Scale for the Assessment of Positive Symptoms (Andreasen 1984b).

in naval combustion mechanics. When he was 32, the family moved to the Southwest after the birth of a daughter. Gary secured work in the shipbuilding industry (naval destroyers). Over the next 2½ years, according to his wife, Gary was "excessively nervous." He lived in terror of being assassinated for participating in sensitive defense work and he tried to purchase a revolver to "protect" his wife. When Gary was 35 years old, his wife and daughter left the Southwest for an extended visit with her family in the East and never returned. Later, his wife recalled that following the birth of their child Gary's demeanor became more worrisome. He could be a "veritable Hitler" with her—cruel, quarrelsome, and irritable. He found their sexual encounters repulsive and avoided intercourse, yet he became excessively demanding and developed an intense clinging dependency upon her.

Shortly after Gary's wife and daughter left, he became increasingly tense and began to feel people were following him on the street and were making fun of him. He began to hear voices, some of which told him he was homosexual. While in a restaurant, Gary suddenly felt the walls were going to fall in. He became very disturbed but burst into laughter, causing the proprietor to call an ambulance. Gary was hospitalized but released the next day. Two days later he had a similar "attack" and had to leave work. He became unable to function at work and was fired. He moved into his father's house and complained of being weak, tired, and sleepless. Within 2 weeks he was hospitalized voluntarily.

Upon admission to this hospital, Gary cried readily, but his thoughts did not connect with what he felt. In the intake interview he would slip off the chair, crawl under the table, and rub his face in the rug. He acknowledged hearing voices and complained about having "upset ideas" concerning his relationship with God. He occasionally burst into laughter that was irrelevant in context. During this prolonged hospitalization Gary was committed and received numerous insulin shock and electroconvulsive therapy (ECT) treatments. He never made a good adjustment to the institution, and during the last 2 years Gary was described as depressed, silent, confused, and withdrawn. At the age of 40 Gary was transferred to Chestnut Lodge.

Upon admission to Chestnut Lodge the patient was wearing a raincoat, rubber boots, and carrying an umbrella despite a cloudless sky. He presented in a passive, compliant fashion and allowed others to decide his activity schedule. He talked very slowly in a blase tone of voice. His speech was generally coherent but he would occasionally block, that is, he would seem to plunge into the contemplation of a word from which he could not be aroused for several minutes. Then he would snap out of it but be confused and disoriented to rime for several more minutes. He occasionally had outbursts of inappropriate laughter, acknowledged auditory hallucinations, and displayed extensive paranoid ideation.

Gary remained at Chestnut Lodge for 3 years, essentially un-
improved, and was then transferred to a State hospital near his home. He remained there for 20 years until his followup.

The followup interview was conducted over the phone with the patient and with his doctor. At the time of the interview the patient was 71 years old. He was medicated with Haldol and Mellaril and had been for many years. He was oriented to person and place but not to time. He said he had gone to the State hospital straight from Chestnut Lodge, which was correct, but that he had only been there for 5 years. His affect fluctuated between flatness and agitation. He was impatient with the questioning and ended the conversation abruptly by yelling, “I’m tired of talking to you!” and hanging up. He had marked poverty of speech and answered in monosyllables wherever possible. The interviewer more than once had to ask Gary if he was still there. When he spoke, his stream of thought was frequently tangential and occasionally loose. His ideation was paranoid and he asked several times, “Why are you so curious about me; are you representing my wife?” Insight was limited; Gary asserted he was in the State hospital for financial reasons and because he was physically debilitated, not because of mental or emotional problems.

Gary’s doctor confirmed that this mental status was quite typical. He added that there was no evidence of hallucinations at this time but that Gary heard voices frequently. He also reported that Gary, despite being very slight, frail, and stooped over in a Parkinsonian-like stance, was frequently physically violent. He had been discharged to a nursing home on only one occasion, approximately 10 years before the followup. He was readmitted to the State hospital shortly thereafter when he became increasingly assaultive, hostile, and uncontrollable. Gary had a guardian with whom he had not conversed in years. His doctor reported that Gary had no contact with his family for many years and that they were not even sure if his wife was still alive. His daughter lived across the country but never made contact.

Discussion

Syndromal Stability and Progression. These data indicate that over the first years of manifest schizophrenic illness, subtype phenomenologies, whether classical or deficit/nondeficit, remained only moderately stable. In unstable cases, the general drift was toward undifferentiated and hebephrenic constellations among the classical subtypes and toward deficit constellations among the deficit/nondeficit subtypes. Furthermore, our data indicated that some form of deterioration was taking place because these transformations were associated over the long term with poor outcome (see table 2). Our data can say very little about the time course of these changes because we were usually privy to only the first 5 years of manifest illness. It is clear, however, that these changes can occur for at least some patients within this period of time. As will be discussed, the literature suggests that these transformations occur earlier rather than later in the overall course of schizophrenic illness.

These findings indicate that for some schizophrenic patients, subtype aggregations are syndromal constellations subject to dynamic transformation. Table 5 attempts to integrate these data into a heuristic progression of subtypes (using both schemes) that may characterize many patients with schizophrenia in the early phase of their disorder, when deteriorative pathophysiologies are hypothetically most active. The progression as outlined was observed, either wholly or in part, in many of our schizophrenic patients from the time they first entered treatment to the time they were referred to Chestnut Lodge. Of course, the majority of patients did not run the entire gauntlet to deterioration. Sometimes patients presented at middle to lower “levels,” for example, deficit state or active hebephrenia at first break. Sometimes the deterioration occurred rapidly within a single episode, for example, acute catastrophic schizophrenia. Most of the time patients stabilized at a level above severe deterioration.

Schizophrenic Deterioration.

For some patients, perhaps 10 to 20 percent, the evidence for deterioration was strong. Review of their records indicated that, like Gary S., they had regressed through the entire sequence. The prototypic case began with an initial episode loaded with positive symptoms, often well organized in a paranoid structure. Negative symptoms, when present, covaried with active psychosis. The initial hospitalization and treatment were usually successful in bringing the patient around to an apparent full remission without any positive or negative symptoms.

In the prototype situation, this state lasted from a few months to a few years, but eventually psychosis returned, this time precipitated by less stress and charac-
Table 5. Subtype progression and pathophysioligic deterioration

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Likely State</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Hi</td>
<td>Low</td>
<td>Acute break treatment</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>Remitted state time and stress</td>
</tr>
<tr>
<td>Hi</td>
<td>Moderate</td>
<td>Acute exacerbation treatment</td>
</tr>
<tr>
<td>Low</td>
<td>Low</td>
<td>Residual state time and stress</td>
</tr>
<tr>
<td>Hi</td>
<td>Hi</td>
<td>Exacerbation treatment</td>
</tr>
<tr>
<td>Low</td>
<td>Moderate</td>
<td>Deficit state time and stress</td>
</tr>
<tr>
<td>Hi</td>
<td>Hi</td>
<td>Exacerbation treatment</td>
</tr>
<tr>
<td>Low</td>
<td>Hi</td>
<td>Either: Deteriorated deficit state or Deteriorated active and deficit state</td>
</tr>
<tr>
<td>Hi</td>
<td>Hi</td>
<td></td>
</tr>
</tbody>
</table>

This residual state was more fragile and interrupted by yet another exacerbation of psychosis, this time precipitated by trivial stress and characterized by severe negative and positiv symptoms. Treatment was relatively successful for the positive symptoms but less so for the negative, which remained moderately intense and marked the patients entry into a deficit state. The latter could be quite disabling and render the patient unable to work or socialize effectively.

Noninstitutional living was possible, however, until the next exacerbation, which usually came rapidly because the patient's stress tolerance was now minimal. This time the psychosis was disorganized or hebephrenic in nature and severity and proved unresponsive to treatment so that the pa-
tient required transfer to a tertiary care facility offering long-term residential attention. With time and institutional treatment, the patient might respond with an attenuation of acutely disorganizing positive symptoms, but he or she remained in a deteriorated deficit state, described elsewhere as “aphanisis” (McGlashan 1982). The patient could make a reasonable institutional adjustment but was unable to function outside of a structured setting. Other patients suffered unremitting active positive and negative symptoms, that is, a deteriorated actively psychotic state that was difficult to handle even with the resources of an institution.

Comparison With Literature.
Over the first 5 years of manifest illness in our population, positive symptoms were relatively stable but negative symptoms became significantly worse. These findings appear to agree with more recent prospective studies that find an initial heavy presentation of positive symptoms followed by gradual predominance of negative symptoms and signs of disorganization (Harrow and Marengo 1986; Haas et al. 1991; Shtasel et al. 1991). A similar symptom progression appears to characterize illnesses that are continuously or intermittently active over many years (Ciompi 1980; Pfohl and Winokur 1982; Winokur et al. 1985; McGlashan and Fenton 1992). Because we assessed functional capacity but not symptom profile at long-term (15-year) followup, our data cannot offer a lifetime perspective on our sample’s syndromal psychopathology. From other analyses of this sample (Fenton and McGlashan 1991b), however, it was clear that those who deteriorated the farthest were those whose negative symptoms increased the most within the first few years of active illness.

Our finding of modest classical subtype stability over time is in agreement with the two other studies in this area (Kendler et al. 1985; Leboyer et al. 1990). We noted no predominant hierarchy of stability among the subtypes, but over time we did see an accumulation of undifferentiated and hebephrenic cases at the expense of cases with the paranoid subtype. This suggests that when subtypes are unstable they evolve to more nonspecific or disorganized types; these findings are in agreement with both Leboyer and coworkers (1990) and Kendler and coworkers (1985).

To our knowledge, this is the first study tracking schizophrenic psychopathology using the deficit/nondeficit subtyping scheme. Our findings suggest that when instability occurs over time, the evolution is in the direction of the deficit subtype.

Time Course of Deterioration.
Failure to collect detailed signs and symptom information at followup also made it impossible for us to learn about the time course of symptom progression over decades of illness. On the other hand, strong evidence indicates that whatever deteriorative or regressive process occurs in schizophrenia occurs earlier rather than later in the disorder’s natural history and is not relentlessly progressive. Kraepelin (1919/1971) suggested that dementia can appear within the first year and that “weak-mindedness” can develop over the initial 2 to 3 years of manifest illness, after which changes occur slowly if at all. Bleuler (1972/1978) stated that when deterioration occurs it is seen over the first decade of illness and over shorter periods of time in the majority of cases. Harrow and coworkers (1985) and Carone and coworkers (1991) found that a strikingly high percentage of young schizophrenic patients had stable poor outcomes within 2½ years of index hospitalization, which was the first hospitalization for about half the sample. In fact, as detailed by McGlashan in his comparison of schizophrenia followup studies across North America (McGlashan 1988), it may take only 6 months to 1 year of active illness for deterioration or a “threshold of chronicity” to be reached. That is, the long-term outcomes of patients from studies who had been ill for less than this amount of time were superior to the long-term outcomes of patients from studies who had been ill for approximately this amount of time. Periods of illness longer than this, however, were not associated with further deterioration in long-term outcome.

Overall, it appears that the disease process in schizophrenia (whatever that may be) is most active at onset and early in its manifest course. Certainly the risk of relapse and rehospitalization appears to be highest within 5 years of the onset of the disorder (Engelhardt et al. 1982; Eaton et al. 1992a, 1992b). Long-term followup studies also suggest that after 5 to 10 years there appears to be a plateau, if not a gradual amelioration, of illness activity (Ciompì 1980; McGlashan 1988). Thus, our symptom data collected over the first 5 years of illness may well be an accurate reflection of the pathophysiological process of deterioration in schizophrenia. That is, for many of the patients in our
sample, by the time they reached their Chestnut Lodge admission the illness had already wreaked most of its damage.

**Methodology Caveats and Sampling Perspectives.** Several sampling and methodology shortcomings render any conclusions tentative at best. This study was retrospective and relied upon rating medical records. While these documents were voluminous, the clinical data they held were not collected in any systematic fashion. Furthermore, virtually all of the psychopathologic data were based on records. While patients were assessed directly at long-term follow-up by interview, no attempt was made at that time to conduct a structured interview reviewing signs and symptoms in a thorough or comprehensive way. Our primary aim at this time was to assess functional capacity.

It is perhaps most difficult to know how representative these data are to current samples of schizophrenic patients. Our patients were white, well-to-do, and hospitalized in the 1940s, 1950s, and 1960s. Many became ill before neuroleptics were available, and most received care that was institution based. Whether these findings have any relevance to the neuroleptic-treated and community-treated schizophrenic patient of today remains a question. Do we still see, for example, cases as sick as those profiled here? Several clinicians have noted that schizophrenia has become less severe in this century (Odegard 1967; Grinker 1973; Romano 1977; Saugstad 1989), especially in the post-neuroleptic era (Wyatt 1991). On the other hand, Bleuler noted “although modern treatment has caused the disappearance of severe, permanent states immediately following a first acute attack, it has not succeeded in reducing the number of severely deteriorated cases from the level of 10%” (Bleuler 1983, p. 78). Our sample may well characterize that 10 percent at the bottom, with the deteriorated deficit state (see table 5) corresponding to Kraepelin’s terminal state of weak-mindedness and the deteriorated active state corresponding to his terminal state of dementia (Kraepelin 1919/1971).

While catatonia and hebephrenia may be disappearing (Hogarty and Gross 1966; Morrison 1974; Romano 1977; Mahendra 1981), chronic, unremitting schizophrenia still exists. Today it is labeled “Kraepelinian schizophrenia” and is characterized by severe negative symptoms, formal thought disorder (Frecska et al. 1991), increased family loading for schizophrenia-related disorders (Silverman et al. 1991), and evidence of cerebral structural pathology (Kirch 1991).

**Theoretical Afterthoughts.** The grim progression elaborated in table 5 was not too common but unfortunately common enough. Much is contained, and even more unexplained, in that table. It highlights that the course of schizophrenia is characterized by some or all of the following: (1) state changes in which the illness and its symptoms can be more or less intense; (2) productive or negative symptoms (hallucinations, delusions), which can persist but usually become less severe with time; (3) deficit or negative symptoms (alogia, avolition), which usually get worse and more stable with time; and (4) disorganization, which over time gets worse and may be seen symptomatically (as thought disorder, incongruous affect) and syndromally (as progression of subtype to undifferentiated or hebephrenic). These observations were collected by many different investigators from different sites over different time periods.

At a more theoretical level, these observations suggest that several pathophysiologic processes may be at work. The state changes, for example, may be largely biochemical and relate to fluctuations in neural network dopamine tone. The symptomatic and syndromal changes may be more structural and relate to alterations in neural network richness and synaptic density or to the psychological and/or iatrogenic responses to such alterations. Many of these possibilities are discussed in other articles in this issue.

While some of these changes observed in the course of schizophrenia may reflect processes that are homeostatic or compensatory, they also reflect processes that interact destructively. Symptom formation, for example, may require a certain threshold of neural network pruning. At the same time, symptom formation may itself be toxic to network richness. We do not know whether any of these processes involve anatomic changes, some kind of functional deprogramming of neurocircuits, or both. The term deterioration, starting with Kraepelin, is linked with assumptions about neuronal tissue loss or injury, and such processes may indeed be involved. However, the rare but remarkable reversal of profoundly chronic and severe psychotic/deficit states after years of illness (either spontaneously or more recently with clozapine) should make us cautious about believing in processes that cannot be reversed.
Whatever may drive such a course and whether it involves tissue deterioration, it is clear that a process of functional deterioration or behavioral regression takes place in schizophrenia. It may be one, but more likely it involves several, pathophysiological processes. We do not know when these processes start but conjecture that some begin with the prodrome, which is often impossible to pinpoint at the phenomenological level. We also do not know when these processes stop but guess that all begin to slow or plateau after 1 to 5 years of illness. We do suggest, however, that some of the processes are most active during late prodrome and early manifest illness, and that their consequences may be observed and tracked during manifest illness via the progression of symptom and subtype phenomenologies such as we have outlined here. We also suggest that any theory of schizophrenic pathophysiology needs to account for these patterns of symptom course.

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