The Heterogeneity of the Long-Term Course of Schizophrenia

by William T. Carpenter, Jr., and Brian Kirkpatrick

Abstract

Research has demonstrated considerable heterogeneity in the long-term course of schizophrenia. In the period preceding the onset of frank psychosis (onset), patients vary relative to the rapidity of onset, the presence or absence of asociality, and the presence or absence of semipsychotic symptoms. Following the onset of psychosis (middle course), patients may suffer from episodic or unremitting psychosis, and may or may not exhibit the deficit syndrome. In late adult life (late course), patients vary relative to the presence or absence of an improvement in psychosis and social capability.

The usual approach to the study of putative course subtypes is to define a subtype by a number of features; they may include features of more than one epoch. In addition, the course of psychosis has not been distinguished from enduring personality impairments in these subtypes. Another approach to defining putative course subtypes would be based on dichotomizing patients according to the presence or absence of a particular feature of a single epoch. This second approach has important advantages: the availability of larger study populations and a diminished liability for confounding due to the correlates of features other than those under scrutiny.

It is very likely that schizophrenia is a clinical syndrome rather than a single disease entity (Kendell 1975; McHugh and Slavney 1983; Carpenter 1987). Clinical observation has documented the marked variation among cases in all aspects of psychopathology. Factors such as age of onset, rate of onset, early morbid or premorbid picture, symptoms and signs, interepisode residual impairments, long-term outcome, late course improvement, treatment response, and distribution of risk factors show much difference among patients that each may prove useful as a categorical variable for the purpose of subdividing the syndrome of schizophrenia. Furthermore, many other variables (e.g., pattern of familial interaction, performance on cognitive or neuropsychological tests, biochemical assessments, and brain imaging) reveal such a range of values as to question the concept of schizophrenia as a single disease entity.

Relative homogeneity in long-term course has been the prevailing concept of schizophrenia, although it has been frequently refuted; and alternative diagnostic classes have been defined for patients with more benign course and outcome. In DSM-III and DSM-III-R (American Psychiatric Association 1980, 1987), this approach has given way to the tautology of distinguishing putative disease entities by their duration, per se, and by an accompanying acceptance of a greatly increased heterogeneity of affective disorders; the latter include many forms of atypical psychoses and cases with mood-incongruent psychotic features. Other DSM-III and DSM-III-R psychoses, such as brief reactive psychosis, atypical psychosis, schizoaffective disorder, and schizophréniform psychosis, have doubtful validity and clinical utility. However, even in the relatively chronic category of DSM-III schizophrenia, considerable variability of

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course is observed. Angst (1988) and McGlashan (1988) document this in their reviews of European and North American followup studies, and Harding (1988) describes interesting variability observed during the course of illness. Taken together, these studies belie a single disease construct to the extent that the construct is dependent on a relatively homogeneous long-term course. Since the pathophysiology of psychoses is enigmatic, similarities in onset, symptoms, and course have been used to define disease entities. Clinical heterogeneity does not exclude the possibility of etiological homogeneity; general paresis of the insane is such an example.

This variability in clinical course is of relevance for the design of future studies. It is important to devise methods to reduce the apparent heterogeneity of schizophrenia to define the most appropriate study cohorts and to provide optimal circumstances for replication studies. Too often, when a study fails to confirm a hypothesis or replicate a previous study, it cannot be ascertained whether the failure is due to a lack of validity of the hypothesis or to an inability to construct a suitable study population for testing. In this regard, the course of schizophrenia (i.e., the nature of onset of episodes and remissions, and the nature of the illness late in its course) provides a promising criterion for reducing the heterogeneity of study populations.

As is documented in this issue, the research on the long-term course of schizophrenia leads to a number of conclusions that can be stated with confidence. This body of research also suggests important reconceptualizations of how to conduct research on schizophrenia, some of which we discuss here.

**The Concept of Course of Schizophrenia**

There have been several attempts to define subtypes of schizophrenia based on long-term course. Huber et al. (1975, 1980) described 12 patterns of course of illness, while Bleuler (1968, 1978) described 7 patterns and Ciompi (1980a, 1980b) described 8 patterns. There is extensive overlap in these descriptions, encouraging the view that a relatively small number of patterns may characterize the onset and course of illness for the vast majority of patients. In addition, Harding (1988) was able to categorize the patients in the Vermont study into the eight course patterns of Ciompi. These patterns incorporate observations about the nature of onset, the pattern of psychotic episodes, psychopathology between episodes, and the presence or absence of recovery late in the illness. There is a body of followup literature suggesting that even the progressive forms of illness tend to plateau within 5–10 years, making it feasible to classify most cases without waiting for long-term followup or ultimate outcome of illness (Bleuler 1978; Ciompi 1980a, 1980b; Huber et al. 1980; Engelhardt et al. 1982; Pfahl and Winokur 1982, 1983; Dube et al. 1984; McGlashan 1984; Achte et al. 1986).

Relative to reducing the heterogeneity of schizophrenia, one can delineate two approaches to using pattern of course. The first is to regard each distinctive pattern as a putative disease entity. Eight patterns are generated by the dichotomization of onset (insidious and acute), psychotic episodes (chronic or episodic), and late course pattern (deteriorated or improving) (Bleuler 1968, 1978; Flekkøy et al. 1975; Huber et al. 1975, 1980; Ciompi 1980a, 1980b; Harding et al. 1987a, 1987b; McGlashan 1987). This approach, depicted in figure 1 and table 1, has been useful in summarizing descriptive course data. However, the approach is difficult to implement in defining putative disease entities, because each epoch embraces multiple factors. Insidious onset may, for instance, refer to a gradually emerging psychosis or a persevering deficit syndrome to be classified? If these psychopathological domains are to be separated, the dichotomization within each epoch of onset, middle and late course, results in four or more subgroups, not two. Rather than eight resultant patterns defining putative disease entities, two dichotomizations per epoch would result in dozens of patterns. An alternative approach is therefore more practical.

The second approach is similar but is based on a dichotomization of patients according to the particular period of clinical course, or course epoch, of interest. These three epochs are onset, middle course, and late course. Within this approach, instead of presuming that, for instance, the combination of insidious onset, prolonged psychosis, and personality deterioration defines a disease entity, one could view each of these factors as an important dichotomizing tool that may represent a lesion or disease process; one would make no a priori assumption about the relationship of each feature to those of other epochs. This approach has the practical advantage for most investigators of dividing a study cohort into two groups (e.g., acute
This figure summarizes the course subtypes found in the classic long-term studies of Ciompi, Huber, and M. Bleuler and replicated by Harding (see this issue). It is adapted from Ciompi (1980). Although derived from these studies, the subtypes also represent the 8 possible combinations of dichotomizing the 3 course epochs. The subtypes are presented in the same order as those in table 1. Within each of the 8 course subtypes, the X axis represents time and the Y axis represents severity.

onset vs. insidious onset of psychotic symptoms) rather than the large number of groups (see table 1) required by combining observations from the three course epochs. A definition of these epochs requires clarification of an issue relating to long-term course and the definition of putative subtypes that has frequently not been clear in previous research. Too often, psychotic and nonpsychotic impairments have not been clearly distinguished. The first epoch (onset) includes both the beginning of psychotic symptoms (e.g., hallucinations and delusions) and the nonpsychotic personality abnormalities such as childhood asociality that often precede the clearcut appearance of psychotic symptoms. The second epoch (middle course) includes periods of active (episodic or unremitting) psychosis and the nonpsychotic (personality) impairments present between episodes such as sustained inappropriate affect or the deficit syndrome. The third epoch refers to late course and outcome. A pattern of improvement or recovery in psychosis is observed in some patients, and a pattern of persistence or worsening is seen in others. The same variability may be found in nonpsychotic impairments such as the deficit syndrome (Bleuler 1968, 1978; Ciompi 1980, 1980/; Harding et al. 1987a, 1987b; McGlashan 1987). Table 2 summarizes this approach to the definition of study groups.

The Onset Epoch. There is a long tradition of dividing the schizophrenic syndrome according to premorbid, early morbid, and onset characteristics. The dichotomies of good versus poor premorbid, reactive versus process schizophrenia, and acute versus insidious onset are examples of putative entities defined by the features of the epoch of onset. These dichotomies have been validated by assessing short- and long-term outcome, association with precipitating stressors, prediction of treatment response,
Table 1. A summary of patterns of course in schizophrenia

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Onset</th>
<th>Nature of psychotic episodes</th>
<th>Improvement late in life</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Insidious</td>
<td>Chronic</td>
<td>Present</td>
</tr>
<tr>
<td>2</td>
<td>Insidious</td>
<td>Chronic</td>
<td>Absent</td>
</tr>
<tr>
<td>3</td>
<td>Insidious</td>
<td>Episodic</td>
<td>Present</td>
</tr>
<tr>
<td>4</td>
<td>Insidious</td>
<td>Episodic</td>
<td>Absent</td>
</tr>
<tr>
<td>5</td>
<td>Acute</td>
<td>Chronic</td>
<td>Present</td>
</tr>
<tr>
<td>6</td>
<td>Acute</td>
<td>Chronic</td>
<td>Absent</td>
</tr>
<tr>
<td>7</td>
<td>Acute</td>
<td>Episodic</td>
<td>Present</td>
</tr>
<tr>
<td>8</td>
<td>Acute</td>
<td>Episodic</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Note — This table summarizes the patterns of course of illness found in the classic long-term followup studies. Compare these patterns to those of Ciompi in figure 1.

Table 2. Dichotomization of research populations on the basis of epochs

<table>
<thead>
<tr>
<th>Epoch</th>
<th>Basis of dichotomization</th>
<th>Study group 1</th>
<th>Study group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>A. Psychotic symptoms</td>
<td>Insidious onset</td>
<td>Acute onset</td>
</tr>
<tr>
<td></td>
<td>B. Nonpsychotic impairments</td>
<td>Present before onset of psychosis</td>
<td>Absent</td>
</tr>
<tr>
<td>Middle course</td>
<td>A. Psychotic symptoms</td>
<td>Chronic</td>
<td>Episodic</td>
</tr>
<tr>
<td></td>
<td>B. Nonpsychotic impairments</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Late course</td>
<td>A. Psychotic symptoms</td>
<td>Persistent</td>
<td>Improved</td>
</tr>
<tr>
<td></td>
<td>B. Nonpsychotic impairments</td>
<td>Persistent</td>
<td>Improved</td>
</tr>
</tbody>
</table>

Note — This table summarizes an approach to research into the heterogeneity of schizophrenia. One would categorize patients in a study population into 2 groups, based on 1 of the features above, and then contrast the groups relative to correlates such as neuroendocrinological or genetic variables. Within each epoch, there may be many bases for dichotomization. Each such dichotomization should be based on either a psychotic or nonpsychotic impairment, but not on both. Future research would help determine which are the most fruitful variables for dichotomization.

The Epoch of Middle Course. All currently accepted diagnostic criteria for schizophrenia include positive symptoms of psychosis (e.g., hallucinations and delusions); the course of this psychosis is quite variable. Terms in the literature such as “chronic,” “treatment-refractory,” “residual symptoms,” and “poor functioning” usually fail to make clear the extent to which the relevant dichotomization is based on interepisode personality pathology or on the persistence of psychosis per se. At our present state of knowledge, it is important to allow for the possibility that factors involved in the pathogenesis of psychotic symptoms (hallucinations, delusions, and marked formal thought disorder) may be different from factors involved in the pathogenesis of longstanding interepisode impairments of personality. Family aggregation studies confirm this view (Heston 1966; Kendler et al. 1986).

The Late Course Epoch. Those who...
have viewed schizophrenia as a chronic, deteriorating illness have sometimes proposed long-term outcome as a definitive diagnostic and dichotomizing tool. Recovery or very substantial improvement disallowed the diagnosis of schizophrenia, and diagnoses such as schizophreniform psychosis were introduced for the nonprogressive cases (Kleist 1960; Leonhard 1966; Langfeldt 1969).

Work from around the world has now documented variability in course, regardless of diagnostic criteria (Bleuler 1968, 1978; Flekkøy et al. 1975; Hawk et al. 1975; Brockington et al. 1978; Kendell et al. 1979; Ciompi 1980a, 1980b; Angst 1988; Harding 1988; McGlashan 1988). A substantial number of patients with schizophrenia show sustained and substantial improvement in psychopathology late in the course of illness, the proportion of such cases depending on diagnostic criteria and perhaps on treatment and cultural/environmental circumstances as well (Lin and Kleinman 1988). This improvement can apparently involve decreased intensity of psychosis or improvement in nonpsychotic impairments. Predictors of late course improvement have not yet been well validated, but McGlashan (1987) examined 100 clinical and demographic variables from patients' distant past and found only five variables predictive of late improvement at the p = .05 level. All five may be chance findings, but family closeness (p = 0.1) and schizotypal personality (p = .02) merit further study.

Some conceptual distinctions will assist in the investigation of late course processes: (1) We suggest that study groups should be differentiated according to whether improvements occur in psychotic or nonpsychotic aspects of illness, or both. (2) Of those patients with the deficit syndrome (one form of nonpsychotic impairment), it may prove very interesting to differentiate between early onset (i.e., early deficit morbidity before psychosis) cases and those cases in which the deficit syndrome developed only after the appearance of psychosis.

**Using Epochs for Research: The Domains Approach**

We have argued elsewhere that schizophrenia is a clinical syndrome defined by combining quite divergent aspects of psychopathology (Carpenter et al. 1985). In the absence of valid disease entities, it is useful conceptually to identify domains of psychopathology, such as positive symptoms or the deficit syndrome, for independent scrutiny (Carpenter and Buchanan, in press). Course patterns may also depend on distinct pathophysiological processes and, thus, are also candidates for this approach. For each epoch, we give below an example of a hypothesis relating to a dichotomy within that epoch.

Concerning the first epoch (onset), there is evidence that chronic schizophrenia is genetically linked to the schizophrenia spectrum and that acute schizophrenia is not (Kety et al. 1968). The clinical features that define chronicity have not been teased apart, so the basis for the excess of the schizophrenia spectrum in biological relatives of chronic schizophrenic probands is not known. Defining cohorts using first epoch patterns may clarify this important issue. One could replicate the finding that a high prevalence of schizophrenia spectrum relatives is associated with childhood asociality in schizophrenic probands (Kendler et al. 1982) by subdividing a cohort of schizophrenic probands according to the presence or absence of this feature and determining the prevalence of the schizophrenia spectrum among biological relatives of the two schizophrenic cohorts (and appropriate controls). Such a design would be strengthened if the two proband cohorts were similar in rate of onset of psychosis and the features of the other epochs, thus increasing the likelihood that a nonpsychotic childhood impairment would be the crucial variable.

Concerning the second epoch (middle course), a question of prime importance is the pathophysiological mechanism that underlies persistent as opposed to remitting psychosis. To help isolate this factor in a study design, patients with schizophrenia could be dichotomously categorized on the basis of persistent and remitting psychoses. To avoid a confounding effect, the two study cohorts must be similar relative to the features of the first epoch. We would hypothesize that the pathophysiological difference in these two patterns of psychosis is based on a failure of a homeostatic mechanism in mesocortical or mesolimbic dopaminergic systems in patients with persistent psychosis. Studying the responses of various dopaminergic systems to pharmacologic probes, using variables such as prolactin, homovanillic acid, and in vivo dopamine receptor imaging, could be informative if the comparative cohorts were similar in onset and psychotic state at time of study but differed relative to persistence or remission of psychosis. Again, more specific conclusions can be achieved by shifting from the acute/chronic dichotomy to a discrete pattern of pathology within a specified epoch.
Concerning the third epoch (late course), it will be important to discover the mechanisms that lead to late improvement in a subgroup of patients. Here one might hypothesize that an amelioration of psychosis is associated with an age-related decrease in the number of neurons in dopaminergic systems, and that patients vary considerably in the age of occurrence and in the rate and extent of these neuronal changes. Using variables that permit inferences about this neuronal mechanism hypothesis, the investigator would define cohorts distinguished by late improvement versus nonimprovement in psychosis, but which are otherwise comparable.

Discussion

Certain assumptions underlie the epoch-based research strategy outlined above: (1) there are a variety of psychopathological domains within schizophrenia; (2) these domains differ in their pathophysiology and associated risk factors; and (3) these pathological processes can occur independently and can be observed in attenuated form (e.g., schizoid traits and subtle thought disorder). Although an underlying biological heterogeneity of schizophrenia is not unequivocally established, it is certainly heuristic to hypothesize etiological and pathogenetic heterogeneity (Carpenter and Buchanan, in press). If schizophrenic patients suffer from diverse pathophysiological processes, studying heterogeneous groups will obscure these processes, whereas if there is a unitary pathophysiology underlying schizophrenia, studying more homogeneous subgroups will not undermine the elucidation of that single process.

Dichotomizing study populations on the basis of individual epochs as described here has important advantages relative to the "disease entity" approach which was summarized earlier. There is first the practical advantage that the researcher needs only to contrast two groups, rather than to define a number of putative disease entities. If the psychopathological domains model is a valid one, then there is another important advantage having to do with the interpretation of study results. For instance, suppose a biological marker distinguished classic "process" schizophrenic patients (with an insidious onset and unremitting psychotic symptoms) from classic "good prognosis" patients (with an acute onset and an episodic course of psychotic symptoms). It would be difficult to interpret such a finding, as the marker could be associated with the prepsychotic abnormality or with the pattern of course of the psychotic symptoms. However, if the two study groups differed in the nature of their onset but not relative to the course of their psychotic symptoms, a correlation with a marker would have a more specific interpretation. The latter design would be clearly mandated by the epochs approach.

There is already extensive evidence supporting the value of subdividing the schizophrenia syndrome by course pattern or domain of pathology. Distinctions such as acute/chronic, Kraepelinian/non-Kraepelinian, or type I/II have already been productive (Kety et al. 1968; Crow 1985; Lesonczy et al. 1986). The power of such dichotomies will be increased by explicit attention to the domain of pathology and phase of illness upon which the subtypes are being delineated. Long-term followup studies provide a strong basis for examining these three epochs, and Harding (1988) and McGlashan (personal communication) have demonstrated an ability to apply similar criteria to new study cohorts.

This conceptual approach may guide the investigator in several crucial tasks:

- The elucidation of the many pathological processes which, in various combinations, lead to the heterogeneous clinical syndromes which currently define schizophrenia.
- The clarification of those pathological processes which are shared across nosological classes and those which are specific to schizophrenia.
- The identification of areas neglected by previous research (e.g., neuroleptic effects in the third epoch).

It is to be anticipated that new data generated within this conceptual framework will provide the scientific basis for advances in nosology of relevance to DSM-IV and ICD-10. Application of the course typology in psychosis other than schizophrenia may even provide a basis for a new division of the psychoses. For instance, almost 20 percent of major affective disorder patients have a chronic course (Rennie 1942; Keller and Shapiro 1982; Keller et al. 1983). Do many of these patients have insidious onset or late course deficits? If so, does this subgroup share a pathophysiologcal process with some chronic schizophrenic patients? A focus on epochs may clarify whether similar causal mechanisms are involved in discrete aspects of several entities we now consider independent diseases.
References


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