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# SCHIZOPHRENIA: COURSE OVER THE LIFETIME

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Among the lifelong remitting and relapsing illnesses, the course of schizophrenia is among the most widely debated. At the core of the debate are the following questions:

1. What is the best way to investigate the course of schizophrenia?
2. What are the manifestations preceding and shortly after the first psychotic episode?
3. How do the manifestations of the illness, both clinical and biological, change over the life span, especially during later life and senescence?
4. Should schizophrenia be conceptualized as the response of a stable encephalopathy to different stages of the life cycle (1), as a progressive, degenerating disease (2), or as a hybrid of the two concepts (3)?

This chapter attempts to provide a critical assessment of these questions in light of the latest empiric data and current conceptualization of this disease.

The results of the major studies on the course of the illness over 20 to 40 years of follow-up are consistent in reporting a chronic, generally persistent course of illness for 50% to 70% of the patients who receive an initial diagnosis of schizophrenia (4–9). However, a more careful examination of the reports reveals marked heterogeneity in course both between and within cohorts (10–12). The reason for this heterogeneity may be that different studies have examined widely diverse samples of subjects and may also be related to the different definitions of what constitutes a good outcome. These definitions range from disease-free for the majority of life to simply not floridly psychotic at the time of last assessment (13). Very few of these studies included elderly patients in their samples or accounted for attrition, and even fewer examined longitudinal biological changes. This is unfortunate because accurate information on the course of schizophrenia is essential to plan the delivery of care, to evaluate treatment effectiveness, to provide information to newly diagnosed patients and their families, and to advance schizophrenia research. The paucity of data on the course of schizophrenia is mostly the result of limitations inherent in studying a relatively low-incidence illness of unknown origin and pathophysiology, with an insidious onset and a course affected by a multitude of personal and social factors.

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## WHAT IS THE BEST WAY TO INVESTIGATE THE COURSE OF SCHIZOPHRENIA?

### Study Design

The ideal way to determine the course of schizophrenia is to follow a randomly sampled birth cohort throughout the entire age of risk for schizophrenia and then continue to follow the incident cases, and appropriately selected controls, through the entire life span. A related but less informative strategy is to follow-up apparently healthy persons hypothesized to be at high-risk of schizophrenia such as first-degree relatives of affected persons (14–17). An alternative strategy is the prospective follow-up of patients from the first time they seek help for psychosis (18–29). Unfortunately, the birth-cohort strategy is impractical because schizophrenia is a very low-incidence disease (.87%) (30), the age of risk spans over more than 4 decades of life, and the age of risk appears different for males and females. Thus, following a birth cohort of 10,000 individuals for 40 years, starting at age 5 years, would detect approximately 90 cases of schizophrenia (not accounting for attrition), a number that is insufficient to make any statement regarding the course of a heterogeneous syndrome such as schizophrenia. Similarly, the high-risk strategy is limited in scope because it excludes most future patients with schizophrenia who do not have affected first-degree relatives, in addition to the problems of investing in a very large research effort for a

relatively small number of persons who will convert into cases.

Therefore, the most often employed strategy to map out the course of schizophrenia has been to start the follow-up only after a diagnosis of psychosis is established (first psychotic episode cohorts). However, these are selected cohorts in that they include only persons who seek help (often in an academic center) and consent to participate in research (31). Furthermore, this strategy does not provide prospectively collected information on events preceding the first psychotic episode. Moreover, it is conceivable that some of the patients recruited for the first-episode studies have been chronically ill for several years but undiagnosed (32,33). This, in turn, could explain the discrepancies between studies finding differences between first-episode patients and patients hospitalized on a long-term basis and other studies that do not find such differences (34).

Regardless of the study design, all prospectively followed schizophrenic cohorts will be characterized by high attrition. There are many reasons for attrition: lack of insight, disappointment with the care received, recovery accompanied by the wish to forget and conceal the experience of illness, and being too sick to maintain contact. Whether following-up 100% of the cohort would find the outcome to be better, worse, or the same (and in which aspect) remains unclear. Even if the debate on the best way to follow patients to describe the course of the illness could be settled, and the attrition rate could be reduced (both of which are unlikely), it still is not clear what defines a case of schizophrenia and therefore who should be followed to elucidate the long-term course of illness.

### What Is a Case of Schizophrenia?

The debate on the nosologic boundaries of schizophrenia is as old as the term itself, and the last hundred years of research have done little to settle this debate (35–39). On the contrary, the pendulum has swung back and forth between a discrete nuclear definition of schizophrenia based mostly on psychotic features and severely impaired functioning and a continuum that includes questionable psychotic manifestations, schizophrenia spectrum personality disorders, and moderate to severe deviations from normality based on psychometric indicators (32,40).

Despite the contribution of the modern diagnostic classifications to the definition of schizophrenia, the abandonment of the continuum-based concept and adoption of the dichotomous model have not occurred, largely because the continuum model has received considerable pathophysiologic support. On the contrary, the schizophrenia-nonschizophrenia distinction is a matter of operational convenience brought about by treatment and economic developments emerging since the 1960s. The emergence in the 1950s of antipsychotic drug treatments that ameliorated psychosis while producing severe adverse effects called on the medical community to distinguish between patients who should and who should not be treated with these medications. Throughout the 1980s, as the accounting between providers of health care and health insurance organizations was becoming more thoughtful, the latter began to demand definitions of which patients were entitled to reimbursement and which were not. Finally, clinical investigators into the biology of schizophrenia also supported a model clearly distinguishing between schizophrenia and nonschizophrenia as more amenable to research. Needless to say, the course of illness of a cohort of schizophrenic patients depends on the definition of the cases enrolled in the cohort (41). Hence, until objective biological markers can be combined with phenomenologic criteria to define a case, the question of the course of "exactly what illness?" will continue to be raised.

It would also be reasonable to assume that regardless of the degree of the cohort's heterogeneity, part of the variability in the course of illness is determined by the interaction between the affected individual and a wide array of societal, familial, and personal interactive influences (42–48). A few of these influences can be captured by careful collection of demographic and treatment information. However, the effects of changes that occur over many decades, such as changes in health care delivery, changes in the public perception of severe mental illness, and the interactions between these changes and aging, may not be amenable to survey and quantification. For example, how will deinstitutionalization, reduction of stigma, intensive community care, managed care, novel neuroleptics, open international borders and resultant migration, and the influence of advocacy groups affect the definition and course of schizophrenia?

In summary, the inherent limitations of studying birth and high-risk cohorts, coupled with the observation that many of the dynamic changes occur over a time span of 3 to 5 years before and immediately after the first diagnosed episode of psychosis, have been the impetus for the proliferation of first-episode studies in the 1990s. These studies can provide some useful information about schizophrenia, particularly because most patients experiencing schizophrenic symptoms in Western societies are likely to be diagnosed and treated at least once by mental health professionals.

## WHAT ARE THE MANIFESTATIONS PRECEDING AND SHORTLY FOLLOWING THE ONSET OF THE FIRST PSYCHOTIC EPISODE?

### Premorbid Phase

The observation that that some schizophrenic patients have premorbid abnormalities dates back to Bleuler (49). History taken on the first contact with a mental health professional

often reveals subtle or flagrant motor, cognitive, emotional, and behavioral deviations during childhood, social withdrawal and mood and personality changes during adolescence, and attenuated psychotic symptoms several months to several years before the first treatment contact and the diagnosis of psychosis (51–62). The period immediately preceding the onset of psychosis, during which behavior and functioning deteriorate from a stable, premorbid level of functioning, as well as the behavioral changes that identify it, is referred to as the *prodrome*. However, the factors that precipitate the transition from prodrome to the first incident of help seeking and the resultant diagnosis are not necessarily distinctly related to the illness itself.

Factors such as the educational level of patients and their families, socioeconomic status, and availability of health care may all determine when the first contact occurs (63–68). Moreover, events such as the sudden unavailability of a caregiver able to maintain a highly symptomatic patient in the community or any change in the threshold of abnormal behavior tolerated by the community can precipitate treatment contact, hospitalization, and diagnosis. Hence, the presence of the premorbid manifestation, the onset of the prodrome, the emergence of the symptoms that define an episode of the illness, and ascertainment of the full syndrome of illness including formal diagnosis do not necessarily coincide and are not always clearly distinct points in time (31). Methods employed to investigate the phenomena preceding the first contact for help and the diagnosis of schizophrenia are the high-risk method, the birth-cohort method, and the historical prospective (or follow-back) method.

The high-risk studies that followed-up children and siblings of patients affected by schizophrenia into adulthood demonstrated that these relatives were more likely than the general population to be affected by emotional and behavioral abnormalities and abnormal psychophysiologic reactions (69–81). For instance, one study compared cognitive and behavioral assessments of twin pairs healthy at the time of testing and discordant for psychoses later on with twin pairs who both remained healthy. The healthy twin from the ill pair performed better than the ill co-twin but worse than the average of the twins from the healthy pair (82) (Fig. 47.1). Thus, abnormalities were found to be associated both with schizophrenia and with being a nonpsychotic identical twin of a schizophrenic patient. Even though the increased risk can be demonstrated in targeted populations, this strategy has not been completely successful in defining the premorbid aspects of schizophrenia. This is because most persons who belong to the high-risk groups represent a small, atypical subgroup of patients with schizophrenia and because of the relatively small number, approximately 10% to 15% at most (30), of high-risk persons who eventually develop schizophrenia.

National health authorities have conducted follow-up studies of persons born in a geographically defined area over a specified period (birth cohort) to study protective and risk factors for healthy development and disease. Among the most publicized and complete studies are two British studies: the Medical Research Council National Survey of Development, covering all births during the week of 3 to 9 March 1946, and the National Child Development Study, covering all births during 3 to 9 March 1958 (83,84). Persons born during these 2 weeks were interviewed and assessed, together with their parents, several times during early childhood and adolescence. Developmental and scholastic achievement data collected on these cohorts were later linked to the data in a registry containing diagnoses of patients discharged from psychiatric hospitals. An overview of these studies indicates that, as a group, persons with future schizophrenia cases had delayed developmental milestones, speech and behavioral difficulties, and lower IQ scores compared with noncases (individuals who did not appear in the psychiatric registry). Although future cases were overrepresented in the lowest third of the IQ scores, these future cases had scores that were distributed over the entire range. The decline in IQ was not limited to a particular test, and the magnitude of decline ranged between 0.25 and 0.75 standard deviations (SD). Thus, the level of performance seen was not necessarily even outside the average range of IQ scores (defined as IQs between 90 and 110, which is 0.67 SD above or below the average score of 100).

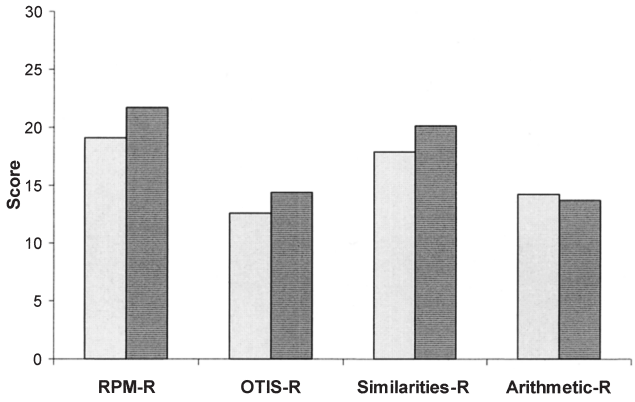


**FIGURE 47.1.** Intellectual functioning in members of twin pairs concordant and discordant for schizophrenia.

Follow-back or historical prospective studies examine the archival premorbid histories of individuals who are already diagnosed as suffering from schizophrenia. They can be based on the linkage of databases containing routine psychometric tests administered by educational or military authorities to large numbers of healthy adolescents with national psychiatric registries. This strategy takes advantage of large-scale, readily available data enabling the testing of hypotheses with high statistical power. The disadvantage of the strategy is that, like birth-cohort studies, the data contained in the archival assessments are not aimed at the detec-

tion of schizophrenia or its premorbid manifestations, which may be responsible for the low predictive specificity found in many of these studies. Several follow-back studies have produced results very similar to the birth-cohort studies, findings confirming, both quantitatively and qualitatively, the cognitive and behavioral abnormalities of future schizophrenic patients (85).

For instance, one study based on a national population of adolescents called by the nonselective Israeli Draft Board revealed that apparently healthy persons who several years later developed schizophrenia had lower mean group scores than their healthy classmates by about 1 SD on items reflecting social adjustment and IQ (53). The differences derived from a ''shift to the left'' of the future patients, one that was clearly more pronounced on social adjustment than on IQ.

Despite the consistency between the studies' results, their interpretation remains uncertain. The premorbid signs of the illness are widely variable, and a single ''typical prodrome'' cannot be identified. For example, for some persons, the premorbid manifestations consist of shyness detectable in elementary school, many years before the manifestation of psychosis. For others, the premorbid manifestations consist of IQ scores 0.67 SD lower than expected, detected in adolescence, or in nonpsychotic paranoid thoughts manifested several years before the first psychotic episode in persons with unimpaired IQ. Yet for others, the premorbid manifestations consist of withdrawn behavior and depressed mood preceding psychosis only by a few months. Furthermore, for some patients, the prodrome is manifested as a crescendo of progressive, continuous deterioration during childhood and adolescence and for others as the barely detectable presence of a few minor cognitive abnormalities. Finally, it is possible that some of the variability in the quality and time of manifestations of premorbid manifestations reflects limitations of the study designs, which are often cross-sectional assessments (34). It is conceivable that a true prospective follow-up study, specifically designed to detect signs of premorbid schizophrenia and conducted from birth through age of risk, would reveal that the same person who manifests mild delay in developmental milestones as a toddler (56), shyness and learning difficulties in elementary school (50,52), restricted peer interaction as a teenager (86), and depressed mood and unusual thoughts in adolescence (87) would have psychosis in early adulthood (30). Alternatively, a particular premorbid manifestation could lead to a particular subtype of schizophrenia (86). It is uncertain whether these various premorbid or prodromal manifestations, which differ in quality, severity, and time of onset, bear the same relation to the first psychotic exacerbation or to the course of the schizophrenic illness.

Despite these uncertainties and even though with current psychometric tools, premorbid abnormalities are detected only in a few persons with future schizophrenia, their presence has opened up both conceptual and practical lines of investigation. Conceptually, it would be interesting to explain the pathophysiologic relationship between the premorbid symptoms and the manifestation of the illness. Practically, it would be helpful if the prodrome could be developed into a reliable predictor of future illness, based on which a secondary prevention strategy could be implemented.

Because the clinical manifestation of schizophrenia could represent an accumulation of genetic and environmental risk factors (or lack of environmental protective factors), the premorbid abnormalities, particularly the early-life ones, could be conceptualized as markers of vulnerability. This is consistent with a ''multiple-hit'' hypothesis by which, in addition to the genetic and environmental factors that have led to the premorbid manifestations, an environmental insult or a gene expressed later in life may be necessary to develop the full syndrome of schizophrenia. A corollary hypothesis would suggest that, depending on the additional, later insults, the same early-life manifestations (e.g., avoidant personality traits) could remain stable through life with no pathologic implication, could evolve into milder mental disorders such as a schizophrenia spectrum personality disorder, or could lead to schizophrenia. If indeed the phenotype of schizophrenia reflects the consequences of an accumulation of genetic and environmental risk factors, studying the course of the disease from birth through the end of the age of risk may be required to identify specific etiologic patterns. Alternatively, it is possible that a subgroup of these persons who manifest certain premorbid abnormalities may be inevitably destined to manifest schizophrenia in the future, and for these, and only these persons, the prodromal manifestations are obligatory precursors of the illness.

## Is Secondary Prevention a Realistic Goal?

From a practical point of view, it would be tempting to use the occurrence of the premorbid and prodromal manifestations of the illness to identify persons at imminent risk of developing schizophrenia and to intervene before the onset of the first psychotic episode, in an attempt to delay or ameliorate it (47,57,88–93). It would be reasonable to hypothesize that any intervention that would delay or attenuate the first psychotic episode would have a major impact on the long-term outcome of the illness. This idea draws support from studies indicating that patients with shorter duration of untreated psychosis have more rapid symptomatic remission and may incur less deterioration in the long run (94–96).

However, the relatively low specificity of the premorbid symptoms such as subtle cognitive deficits, poor social adjustment, changes in personality, and depressed mood has given rise to concerns that an excessive number of persons could be exposed unnecessarily to the stigma of a provisional diagnosis of severe mental illness. Although it is possible to improve the specificity of prediction, for example, by

targeting only persons at very high risk (e.g., first-degree relatives of schizophrenic patients who also manifest putatively prodromal symptoms), this strategy would exclude the 90% of future patients who do not have an affected relative. Furthermore, even if the prediction could be improved, it is not certain that effective prevention exists. Antipsychotic drugs proven to reduce symptoms and to prevent exacerbation in patients who already experienced psychosis may or may not be effective in delaying the onset of psychosis.

Moreover, the notion that psychosis exerts a toxic effect on the brain and that longer duration of untreated psychosis should result in worse outcome has been challenged (20,97). It has been argued that (a) duration of untreated psychosis cannot be accurately assessed, (b) the delay in requesting and obtaining treatment is not the cause of a worse outcome but the result of an insidious-onset illness that is a more severe form, and (c) long duration of persistent untreated psychosis and persistence of psychosis despite treatment both reflect the same psychosis-severity phenomena without proving a causal relationship between the two. Finally, the proof that the duration of untreated psychosis correlates with the more relevant indices of outcome such as quality of life or overall illness outcome is still equivocal.

For all these reasons, the question of treating persons who are not yet floridly psychotic has stirred public debate beyond the professional community. Yet because of the potential benefits of secondary prevention on one hand and the risks and ethical implications associated with it on the other, it is essential to search for rational strategies to assess the risk-to-benefit ratio. Examining such ratios in an area where preventive measurements are already an accepted reality would be such a strategy. For example, even though after remission from the first psychotic episode, only 60% of drug-free patients have an exacerbation of their illness within the first year, 100% of patients are routinely treated with neuroleptics. Hence 40% are exposed to the adverse effects of neuroleptics, although they are not likely to experience a worsening of their symptoms. Similarly, seven families of schizophrenic patients must go through the effort, expense, and potential adverse effects of intensive family therapy for 1 year, to prevent relapse on the part of one of seven recently discharged patients with schizophrenia (98).

The dilemma of preventive treatment is not limited to psychiatry. For instance, approximately 70 elderly patients with moderate hypertension must be treated with antihypertensive drugs for 5 years to save one life, and 100 men with no evidence of coronary heart disease must be treated with aspirin for 5 years to prevent one heart attack (99). In a study using the number needed to treat method, which is the number of persons who need to receive treatment to prevent one bad outcome, it was calculated that one must administer antipsychotics to 35 adolescents with paranoid or schizotypal personality disorder for 1 to 3 years to delay hospitalization for schizophrenia by 6 months to 1 year in a single patient. This calculation assumes that approximately 5% of these adolescents will convert to schizophrenia, and it also assumes a 60% treatment success rate in delaying conversion, which is the same rate by which neuroleptics can induce extended remission in first-episode patients (100).

The early detection and treatment strategy is supported by preliminary results from a community clinic where youths with prodromal symptoms were treated with open-label neuroleptics plus supportive measures or supportive measures alone (101,102). The results indicated that more members of the neuroleptic-treated group were symptom-free for a longer period than similar youths given only supportive therapy or those who refused to enroll in the trial. In a different study, nonpsychotic, first-degree relatives of patients complaining mostly of cognitive deficit also were found to benefit from neuroleptic treatment (103). In summary, although there is much interest in the events leading to the first psychotic episode and a strong appeal for secondary prevention, the information currently available is still tentative. In contrast, much information and a few solid practical implications regarding the first episode of psychosis are known.

## First Episode of Psychosis

Most studies of patients followed for 2 to 5 years after the first episode of illness have provided highly informative data regarding the early course of positive (3,34,105) and negative (19,104,106–108) symptoms, cognitive functioning (109–116), functional status (117–119), and response to treatment (95). Furthermore, some of the studies have described radiologic changes in the brain after the first episode (120–122).

Often, the appearance or worsening of psychotic symptoms constitutes the trigger for the first contact with a mental health professional and subsequent diagnosis and hospitalization. Hence, it is no wonder that what is described as the first episode of schizophrenia is dominated by the presence of positive symptoms, mostly fully formed delusions and hallucinations. Almost 90% of first-episode patients treated with neuroleptics experience a rapid, albeit transient, remission of their psychotic symptoms. Despite the good initial response to treatment, relapse with reoccurrence of psychotic symptoms is common. Predominance of negative symptoms and hebephrenic, catatonic presentations are not part of the characteristic presentation of the first episode. Occasionally, however, negative symptoms of insidious onset are present on the first episode, and the response of these symptoms to treatment is very limited. Cognitive deficits are common and relatively severe at the time of the first episode. Performance on most cognitive tests is approximately 1 SD below age- and education-adjusted expectations, with more that 50% of the first-episode patients performing even worse (123). The impairment affects almost

all aspects of cognition; however, specific areas of impairment are distributed unevenly. For example, deficits in memory, abstraction, and attention are more severe than deficits in verbal or perceptual skills (124). This impairment, measured on remission from the first episode, goes beyond the one-third to two-thirds SD deficit that characterizes the premorbid cognitive performance of the schizophrenic patients, and it raises the question whether it reflects a progressively deteriorating process. In a cross-sectional comparison of Raven Progressive Matrixes scores (a valid measure of IQ), it was found that apparently healthy adolescents closer to their first hospitalization for psychosis performed more poorly than adolescents who were tested several years before their first exacerbation, but better than patients whose disease had already exacerbated (125) (Fig. 47.2). Furthermore, cognitive performance appears to be slightly worse in patients with chronic disease (114) in comparison with first-episode patients, a finding providing indirect evidence of further cognitive deterioration beyond the first episode (110,111). In contrast to psychotic symptoms, cognitive functions are less responsive to the neuroleptic treatment administered for schizophrenia (126).

In contrast to the evidence from studies of conventional antipsychotic treatments that suggest little improvement in cognition with treatment, two separate studies demonstrated modest longitudinal improvements in certain areas of cognitive functioning (111,127). These findings suggest diversity in the course of cognitive deficit even early in the illness, although they also indicate that there is no consistent pattern of specific dimensions of improvement. Furthermore, even though an improvement in cognition was seen in these studies, no research to date has demonstrated that many first-episode patients show evidence of normalization in their cognitive functioning. Thus, although evidence of worsening in cognitive functioning associated with duration of illness was collected from the study of patients with a longer duration of illness (124), patients with multiple psychotic episodes (116), and elderly patients with continuous psychosis (reviewed later), there is still marked heterogeneity of recovery of cognitive functioning immediately after the first episode.

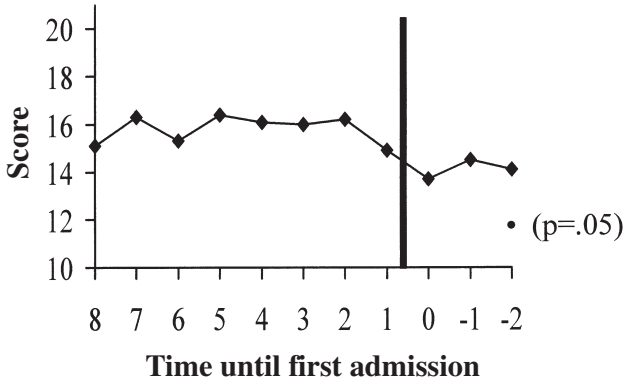


**FIGURE 47.2.** Scores on the Ravens Progressive Matrices as a function of time until first admission for schizophrenia.

Despite the good remission of psychosis achieved by most first-episode patients (95), and even though negative symptoms and cognitive impairments are not very severe at this stage of the illness, most patients are already affected by persistent social and vocational decline in the first psychotic episode. For instance, in a study reported by Ho and colleagues (128), more than half of a sample of first-episode patients with schizophrenia were found to be supported by public funds within 12 months of their first episode of illness, and fewer than 25% of them had a job or went to school. Despite evidence of improvement in cognition on the part of some patients at the time of the first episode, continuing cognitive and functional deficit is the rule.

Taken together, the premorbid and first-episode studies indicate that many of the manifestations of schizophrenia, including psychosis, are present many months to few years before the formal diagnosis, and most, but not all, patients respond well to treatment in terms of their positive symptoms and have a better course of illness in several different domains for the first year or 2 of illness than later. Occupational and cognitive deficits are clearly disproportionate compared with the severity of psychotic symptoms in most cases, despite evidence of improvement on the part of some patients. However, these results may be biased, because most first-episode studies enroll patients who (a) were sufficiently sick to need hospitalization, but (b) became sufficiently well to be able and willing to consent to be followed-up after discharge, yet (c) are not sufficiently recovered to be completely out of the treatment network. More important, most first-episode studies last less than 5 years because of attrition, funding, or other factors.

## HOW DO THE ILLNESS' MANIFESTATIONS CHANGE DURING LATER LIFE AND SENESCENCE?

### Middle Course of Schizophrenia

Until the early 1990s, the characteristics of schizophrenia in patients older than 55 years were largely the subject of speculation. As of 1993, it was estimated that less than 5% of all of the research ever performed on patients with schizophrenia had included any patients older than 55 years (129). It was "common knowledge" that by age 55 to 60 years the illness has run its course, psychotic symptoms had burned out, and most patients did not need or did not benefit from medications. Since the early 1990s, however, a substantial amount of research on this topic has been completed, with this area one of the fastest developing aspects of research on schizophrenia. This research has considered all the topic areas covered by studies on younger pa-

tients and has yielded a considerable amount of information that has helped to refine thinking about schizophrenia in general.

One of the sources of the common knowledge that the course of schizophrenia was established into old age was the consistent findings of symptomatic, cognitive, and functional stability on the part of patients after their first few episodes. Although many patients experience multiple psychotic episodes through middle age and many patients experience continuous psychotic symptoms, there was little evidence of change in cognitive or functional status on the part of these patients. Most research on the course of functional status suggests that the impairments noted at the time of the first episode are rarely reduced. Estimates of the proportion of patients with schizophrenia who are employed are in the range of about 40%, with most patients employed in noncompetitive, sheltered settings (130). Likewise, independent living is the exception for patients with schizophrenia. There is also no significant evidence that functional status in patients with schizophrenia changes markedly over time or is altered by treatment with older antipsychotic medications (131). This large body of data raises issues of importance when older patients are studied, including whether changes seen in later life are part of the natural course of the illness or whether they are the result of additional comorbidities.

## Cognitive and Functional Deficits in Older Patients

It has been consistently reported, however, that many patients older than 65 years who have a lifelong course of schizophrenia, especially those with a history of long-term institutional care, have marked deficits in cognitive and functional status (132–134). Similar findings have been reported at different research sites in the United States and in the United Kingdom (135). Because of the lack of data regarding the lifetime course of functional and cognitive deficits in schizophrenia, it is not clear whether the presence of severe deficits in functioning seen in these elderly institutionalized patients with schizophrenia is the result of deterioration in their cognitive and functional status or is a lifelong feature of their adjustment. There are multiple potential methodologic issues associated with the study of older patients, particularly patients with a history of long-term institutional stay. Among these issues are the difficulty in identifying the patients' "true premorbid status," long-term treatment with antipsychotic medications, extremely invasive somatic treatments, and institutionalization and demoralization, potentially leading to poor motivation to cooperate with testing. There is no question, as would be expected from studies of younger patients, that chronically institutionalized patients have low levels of premorbid functioning, in domains of educational, social, occupational, and independent living skills (132–134). However, the functional history of these institutionalized patients is inconsistent with the idea that their current, grossly impaired status could possibly be their lifelong level of functioning.

Many of these questions are being addressed by a longitudinal cohort study carried out by the Mt. Sinai School of Medicine group since the late 1980s, as well as other investigators who have become increasingly interested in this population. A study of the baseline characteristics of the Mt. Sinai sample demonstrated that these elderly patients manifested moderate to severe negative and positive schizophrenic symptoms not dissimilar to the symptoms present in younger institutionalized patients (133). Many of these patients had cognitive and social performance compatible with dementia (136) that could not be accounted for by somatic treatment, lengthy institutionalization, poor motivation and education, or comorbidity. For example, in the original publication on this population (133), it was demonstrated that psychosurgery, insulin coma, electroconvulsive therapy, and the severity of negative symptoms were not the factors accounting for cognitive deficits. Relevant to the issue of motivational deficits, in a subsample of the patients from that study (137), the average level of education was found to be more than 11 years, and their reading performance was higher than the tenth grade level. In contrast to these indicators of educational achievement, the current average Mini-Mental Status Examination (MMSE) score was 20 (consistent with moderate dementia). Thus, some elderly institutionalized patients with schizophrenia appear to manifest decline in their functioning relative to premorbid functioning.

Studies of the cognitive performance of elderly schizophrenic patients have identified "double dissociation" performance profiles that discriminate them from patients with clearly identified dementia (138–139), and a profile of differential deficits has been identified. Differential deficits cannot be caused by a single constant factor, such as failing to provide adequate effort when assessed. These data suggest that studies of very poor-outcome long-stay patients, although clearly reflecting the most seriously ill subset of the population, are not hugely biased by the obvious factors associated with long institutional stay.

## Longitudinal Course of Cognition and Functional Status in Late-Life Schizophrenia: Patients with Chronic Illness

As noted earlier, some elderly institutionalized patients with schizophrenia appear to manifest decline in their functioning well past premorbid levels at some time in the course of their illness. The time course, prevalence, and correlates of this decline are as yet undiscovered. There is surprisingly little longitudinal research on cognitive functioning and functional skill deficits in schizophrenia. One metaanalysis suggested that indicators of cognitive performance were

largely stable over time in 15 follow-up studies of patients with schizophrenia (140). The total sample size in all these previous studies was only 639, and 225 of those patients were chronically institutionalized patients studied by the Mt. Sinai group in a short-term (1- to 2-year) follow-up study (141). In contrast, in two separate published longitudinal studies of the course of cognitive and functional status in elderly poor-outcome patients with schizophrenia (142, 143), the Mt. Sinai group found that about 15% of these patients per year showed evidence of cognitive and functional worsening. The second study also demonstrated statistically significant cognitive and functional decline over an average of 2.5 years in 57 geriatric schizophrenic patients who entered the study as chronically hospitalized but were reassessed after discharge to nursing home care (143). These data suggest that some proportion of elderly patients with schizophrenia with a history of long-term institutional care experience a notable decline in their functioning over a relatively brief follow-up period. These data suggest the possibility of some adverse effect of aging after a lifetime of poor functional outcome and extensive cognitive deficits.

The Mt. Sinai group completed a larger follow-up study based on 1,102 patients. Some of these patients were unavailable for later study at each of the subsequent reassessments, because they had died or were discharged to nursing home care, where follow-up could not be performed. The primary analyses examined the development of new-onset severe cognitive and functional impairment. Patients were divided on the basis of their baseline Clinical Dementia Rating (CDR) (148) score, such that patients with baseline scores of 1.0 or less were considered less impaired. Worsening in cognitive and functional status was defined as having a CDR score at a subsequent follow-up of 2.0 or greater. At baseline, there were 456 patients with CDR scores of 1.0 or less, whose average MMSE score was 20.8.

The actuarial life-table method, with discrete interval procedures, was used to assess the cumulative risk of cognitive and functional decline over the three intervals between assessments, while considering subject attrition. The cumulative "survival" (i.e., no worsening in cognitive and functional impairment) was then calculated, and survival curves were constructed. At the first follow-up time beginning at 15 months, 17% of patients met criteria for worsening (corrected), and at the second follow-up time beginning at 30 months, 20.4% of the remaining patients met criteria for worsening. At the third follow-up time beginning at 48 months, 25.3% of the remaining patients manifested worsening of their cognitive and functional deficits. Thus, over the entire follow-up period, a corrected rate of cognitive decline of 51% was noted.

The influences of potential risk factors on rates of cognitive and functional decline over the entire follow-up period for the initially higher-functioning patients were examined. The Wilcoxon statistic was used to measure the difference in survival curves as a function of risk factor status. Gender was unassociated with risk for cognitive and functional decline, as were neuroleptic treatment status, age, and age at first psychiatric admission. In contrast, three risk factors were associated with increases in risk for cognitive and functional decline. Patients with more severe positive (Wilcoxon statistic [1df] = 4.28; $p < .05$) and negative (Wilcoxon statistic [1df] = 17.03; $p < .0001$) symptoms were found to be at higher risk for decline. In addition, patients with more education were less likely to experience a cognitive and functional decline than were patients with lower levels of formal education (Wilcoxon statistic [1df] = 8.65; $p < .01$).

In the final analysis, presented in Fig. 47.3, the influences the risk factors previously demonstrated as significant predictors of risk for decline were examined for their influence on the rate of cognitive and functional decline over the entire follow-up period. First, patients were divided at the median level for both baseline severity of symptoms and education levels and were assigned to one of four groups

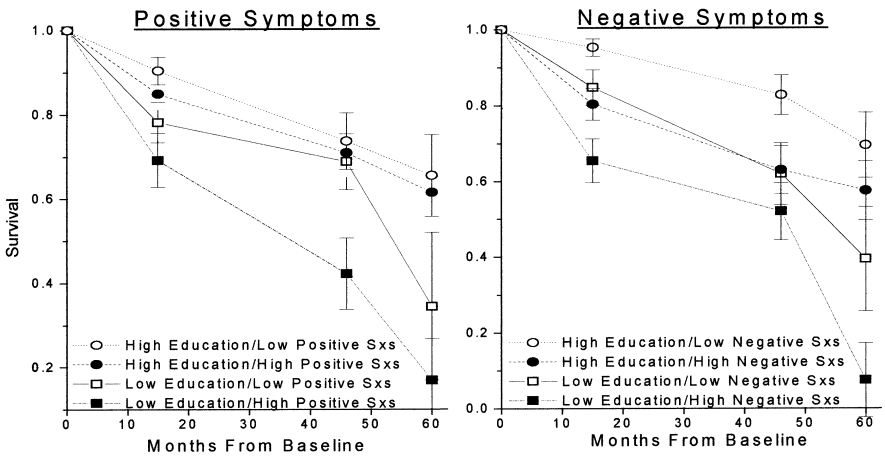


**FIGURE 47.3.** Effects of combined symptom (positive and negative) severity and educational level factors on survival from cognitive and functional decline over a 60-month follow-up period.

on the basis of their status for symptom severity and education level. The Wilcoxon statistic was then used to measure the difference in survival curves as a function of combined risk factor status. Patients below the median level for education and above the median for severity of symptoms were at the highest risk of cognitive and functional decline. This group's level of risk was significantly greater than those with similarly high levels of positive symptoms but higher levels of education (Wilcoxon statistic [1df] = 8.49; $p < .001$) and those with lower levels of positive symptoms and higher levels of education (Wilcoxon statistic [1df] = 15.31; $p < .001$). Similarly, a significant interaction was seen between the influences of negative symptom severity and education level on risk rates for cognitive and functional decline.

Certain potential limitations that must be addressed in the interpretation of these data. No control for institutionalization as a direct risk factor was used in this study. Despite the difficulty in identification of such as a group, there is no other direct way to index institutionalization effects. Similarly, these data do not control specifically for the development of subtle new-onset medical conditions. This is a less difficult question to address in later research. Finally, as noted earlier, multiple additional factors, including subtle environmental changes, may interact with the easily measured risk factors examined in this study.

## Longitudinal Course of Cognition and Functional Status in Late-Life Schizophrenia: Better-Outcome Patients

Although the studies just reviewed indicate that some proportion of poor-outcome patients experience cognitive and functional decline, there is no evidence to date of cognitive decline in patients with a history of better lifetime functional outcome. Cross-sectional comparisons of older and younger better-outcome patients conducted by the University of California at San Diego (UCSD) group found little evidence of relatively poorer cognitive performance on the part of older patients (138,144–145). It is impossible to determine, of course, from cross-sectional data that these older better-outcome patients, with minimal evidence of previous decline in their cognitive and functional status, would never experience a decline at a later date. Furthermore, the proportion of patients in the UCSD samples older than 65 years was only about 15%, a finding suggesting that if the risk of cognitive and functional decline increases with age, these patients may only be entering the period of increased risk. Finally, few of these patients had a history of symptom severity consistent with extended periods of treatment-refractory psychosis, and very few would have met the criteria for kraeplinian status previously demonstrated to be associated with very poor lifetime functional outcome (146–147). These data suggest the need to determine whether long-term institutionalization or the patient characteristics that cause institutionalization are the operant factors in the cognitive decline seen in worse-outcome patients. One of the best possible strategies could be to perform a longitudinal comparison of outpatients with and without a prior history of long-term institutional stay, to separate patient characteristics from current environmental factors.

## Persistent Symptoms Revisited: Duration of Continuous Psychosis

The data from follow-up studies of poor-outcome patients suggest that persistent schizophrenic symptoms, combined with evidence of premorbid educational underachievement, are associated with marked increases in risk for functional decline over relatively short follow-up periods. These data again raise the issue of persistent symptoms as a risk factor for the later course of illness and also suggest that evidence of lifelong intellectual compromise may increase this risk. These data may help to address some of the differences in findings between previous studies of ambulatory patients and these extremely impaired, continuously refractory patients. First, these institutionalized patients have persistent symptoms that have kept them hospitalized for decades and clearly distinguish them from ambulatory samples. As previously demonstrated, functional deficits and negative symptoms do not interfere with discharge to nursing home care in this population, whereas persistent positive symptoms do (149,150). Second, these patients are all older than 65 years. In previous longitudinal studies, even institutionalized patients younger than 65 years old had essentially no risk of cognitive and functional decline over a 6-year follow-up period (151). It would not be a surprising finding that ambulatory patients in this age range who have never been institutionalized would not have elevations in their risk for decline either.

These data may provide a heuristic for understanding the variance in outcome, measured by cognitive performance and ratings of functional status, in older patients with schizophrenia. In institutionalized patients with similar periods of institutional stay, MMSE scores range from 0 to 30, and functional limitations range from moderate deficits in social skills to incontinence and complete dependence on others for feeding and bathing. In addition, better-outcome patients clearly have indications of higher levels of premorbid and current cognitive functioning. These data suggest that the interaction of reduced levels of educational attainment, often referred to as a marker of cognitive reserve (152), and particularly persistent symptoms of illness, may predict functional decline. The previous suggestion that education attainment is an indicator of a cognitive risk-protective factor for dementia (153) appears relevant to schizophrenia. Thus, patients with schizophrenia in late life who have severe and persistent psychotic symptoms, as well as reduced levels of educational attainment, appear to have a much greater risk of worsening in functional status than

patients whose positive symptoms are less treatment refractory and whose cognitive reserve may be greater.

The length of time that some of these patients have experienced continuous psychotic symptoms, despite conventional antipsychotic treatment, is staggering. Some of these patients have been treated since the 1950s with conventional medications, with little relief of their symptoms. The duration of untreated psychosis seen in typical samples of first-episode patients with schizophrenia pales in comparison with these histories of continuous psychosis. This duration of continuous psychosis is much more similar to that typically seen at the time of the initial introduction of antipsychotic medication in the 1950s. At that time, long duration of untreated psychosis was found to be associated with risk for greater functional deficit after initiation of antipsychotic treatment than for patients whose symptoms were treated sooner after the development of illness (96). Much later research will need to address the issues of the impact of continuous psychotic symptoms, in terms influence on the course of illness and whether continuous psychosis despite treatment has the same impact on development as lengthy periods of untreated psychosis at the outset of the illness.

## SCHIZOPHRENIA: STABLE ENCEPHALOPATHY OR PROGRESSIVE DISEASE WITH CORRESPONDING LIFELONG BIOLOGICAL CHANGES?

A most controversial aspect of schizophrenia is whether the few biological and many phenomenologic abnormalities reported are consistent with a degenerative, progressively deteriorating course of the illness (154–158) or a static course for accounted by an early (developmental) insult (1, 159–161). The neurodevelomental models suggest that a perinatal neuronal insult disrupts normal neural maturation and results in disruption of neuronal circuits and thus abnormal neuronal function. It is further postulated that the clinical manifestation of symptoms is triggered by interaction between the initial defect with neuronal maturation processes such as neuronal migration, glial proliferation, and synaptic pruning. This maturation process, in turn, accounts for the gap between the hypothesized early-life insult and later clinical manifestation.

The neurodevelopment concept has prevailed mostly because schizophrenia lacks specific biochemical and histologic changes (gliosis, cellular debris, or amyloid deposits) closely paralleling behavioral abnormalities that define progressive degenerative disorders. Furthermore, because Alzheimer disease has been seen as the prototype of a progressive neurodegenerative disorder, the absence of fast and relentless worsening of illness has been taken as evidence against a degenerative hypothesis in schizophrenia. However, an overview of the data regarding the course and the biology of schizophrenia reveals no sufficient evidence to settle this debate, and the same behavioral evidence can be interpreted to support either of the two hypotheses. For example, subtle cognitive, behavioral, and motor deviation from norms are present in childhood, are amplified in adolescence, and exacerbate shortly before and after the first psychotic episode. This can be interpreted a classic interaction between an early defect and brain maturation or as the behavioral consequence of a slowly progressive degenerative brain process. In addition, lack of consistent worsening of psychosis across episodes argues for the static hypothesis, whereas progressively poorer antipsychotic response after each additional episode could be interpreted as evidence of a slowly progressive degenerative process.

Similarly, biological findings, mostly structural neuroimaging studies, have produced results compatible with both hypotheses (120,121,162,163). Some investigators reported no evidence of progressive brain disease, in either the domains of overall cerebral size (i.e., cortical atrophy) or the size of the cerebral ventricles (i.e., ventricular enlargement) (164,165). However, some cross-sectional and longitudinal studies have produced different results. There are several limitations, of course, in using neuroimaging to make direct inferences about changes in the brain, particularly in reference to whether these changes are degenerative.

### Brain Structure Immediately after the First Episode

One of the interesting recent topics in the area of the course of schizophrenia is that of changes in brain structure after the first episode. Research by DeLisi and colleagues suggested that some patients recovering from the first episode of the illness have evidence of progression in the size of their cerebral ventricles (166,167). This progressive ventricular enlargement is consistent with that seen in patients with more chronic illness, both during adolescence for childhood-onset patients (168) and during middle age for poor-outcome patients with a more typical age of onset (169). These changes are modest, but they are also detected in relatively short follow-up periods. Because the patients in the studies by DeLisi et al. experienced an increase in the ventricular size of about 3.5% in 5 years, the amount of change that would be expected over a lifetime, if this change were continuous, could be substantial.

### Changes in Brain Function in Patients with Established Illness

Changes in cerebral structure have also been noted in patients with an established illness. In a 5- year prospective study (169) comparing middle-aged patients with schizophrenia who varied in their lifetime functional outcome from chronic "kraeplinian" patients with community dwellers, the kraeplinian patients demonstrated progressive ventricular enlargement. These data, consistent with those of

the first-episode and childhood-onset studies, suggest that the cerebral change is dynamic over the life span in patients with schizophrenia. In addition, two separate sets of cross-sectional studies, examining p300 prolongation, suggested that older patients have longer latencies (170,171). The finding of prolonged p300 latency can be associated with the presence of neurodegenerative diseases (172). Finally, cross-sectional studies have also found that older patients show relatively greater atrophic changes in the size of the olfactory bulb (173), and this has been found to correspond to a concurrent deterioration in olfactory sensitivity (174). Because olfactory deficits are also detected with consistency in patients with degenerative conditions, these data are consistent with the p300 data just reviewed. The data to date on the processes of dynamic cortical change in schizophrenia are hardly conclusive. There are, however, multiple, albeit indirect, suggestions that the idea that brain structure and function in schizophrenia are immutably stable over the life span in all patients is open to question. These are important issues that will shape future research in this area.

### Is Integration Possible?

In an attempt to account for the phenomenology, course, and epidemiology of schizophrenia, McGlashan and Hoffman postulated that reduced synaptic connectedness resulting from early, developmental disturbance of synaptogenesis or faulty synaptic pruning is at the root of schizophrenia (3). More specifically, an innately sparse synaptic substrate combined with normal pruning in childhood and adolescence or a normal substrate combined with abnormally accelerated pruning could theoretically reach a critical threshold at which deficient synaptic connectivity manifests as abnormal perceptions and ideas. Because the model incorporates both static and dynamic components, it can account for some of the apparently competing postulations of schizophrenia pathophysiology. Caution is required, however, because integrative models of the development of schizophrenia have been foiled in the past by the remarkable heterogeneity of the illness.

## CONCLUSIONS

From the time schizophrenia was defined, it has been viewed as a chronic, lifelong disease. Yet its specific manifestations along the life cycle have been poorly described, mostly because of inherent methodologic difficulties. Improved medical record keeping and the realization that understanding the course of illness is essential to the understanding the pathophysiology of the illness have been behind the modern long-term follow-up studies. Determining, for example, the earliest manifestations of the illness or the trigger and the length of the window of deterioration has implications for preventive and palliative treatment. Even if otherwise possible, the identification of clinical correlates of progressive cortical atrophy by computed tomography, magnetic resonance imaging, or the biological meaning of spectroscopic abnormalities in synaptic connectivity requires detailed description of the illness course. As more research is focused on these issues, important information about the nature of schizophrenia itself will result.

## DISCLOSURE

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