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Changes in Schizophrenia Across Time

Paradoxes, Patterns, and Predictors

Courtenay M. Harding, Ph.D.

There exist two polar, yet accurate, views about the outcome of schizophrenia. Huber et al. (1979), after studying the outcome of schizophrenia in 502 patients for more than two decades, wrote: "Schizophrenia does not seem to be a disease of slow progressive deterioration. Even in the second and third decades of illness, there is still a potential for full or partial recovery" (p. 595). Nine other such studies agree. Yet today, we have dayrooms, shelters, and public mental health caseloads consistently overcrowded with persons chronically languishing with the diagnosis of schizophrenia. Furthermore, DSM-IV (American Psychiatric Association 1994) indicates that complete remission is likely uncommon, and they go on to describe a variable course of exacerbations and remissions for some patients and a chronic one for most persons. Although this is an improvement from earlier, more

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I thank Dr. Zlatka Russinova of Boston University for quickly translating the Lithuanian article.

dire, predictions of a deteriorating course for all patients (e.g., American Psychiatric Association 1980, 1987; Kraepelin 1902), a significant discrepancy remains between the prognostic expectations of official psychiatry and the findings of 10 long-term studies completed during the last three decades of the twentieth century. Arguments against this paradox have often centered around the use of other diagnostic systems in these studies, although most are similar to the DSM-IV. This chapter shows that regardless how wide or narrow such systems are, patients still persist in improving across time and thus have much to teach us.

Some of the 10 catamnestic (or longitudinal follow-up) studies of schizophrenia analyzed particular areas of functioning, whereas others did not. Some of these reports were published in the authors' native languages and were only translated roughly by the author and colleagues. The end of the chapter will target a few implications for treatment and research. Other key factors that shape the long-term course of schizophrenia (but are not yet mentioned in DSM-IV) are discussed in more detail by other chapter authors. Other key factors that also shape the long-term course of schizophrenia (and that are not yet mentioned in the official diagnostic manual) are discussed in more detail by other chapter authors. These modifiers include 1) the neural plasticity and recalibration of the aging brain, 2) gender differences and the effects of hormones, 3) cognitive decline in the face of a nonstimulating environments, 4) medical comorbidities, and 5) misdiagnosis and other iatrogenic effects of treatment. Such crucial ingredients, which help or hinder forward progress in persons with schizophrenia, contribute further pieces of the puzzle inherent in the paradox.

Brief Overview of 10 Contemporary Follow-Up Studies of Two to Three Decades in Length

The common practice in psychiatric research is to follow samples of convenience for only those subjects who remain in treatment. However, the following longitudinal studies investigating schizophrenia and other serious mental illnesses followed intact cohorts across a period of two to three decades, regardless of whether the subjects were still in treatment. By not following samples of convenience and by maintaining follow-up for such a long time, these studies provide a new view of schizophrenia. They also give evidence that challenges our preconceptions about chronicity and allows us to rethink models and treatment. Each of these projects was reported within the past 30 years or so, during an era of keen interest and funding of such studies. Each provides significant evidence confirming the

wide heterogeneity of outcome, and each finds that approximately one-half to two-thirds of people with schizophrenia can achieve a state of significant improvement or even recovery (M. Bleuler 1972/1978; Ciompi and Müller 1976; DeSisto et al. 1995a, 1995b; Harding et al. 1987b, 1987c; Hinterhuber 1973; Huber et al. 1979; Kreditor 1977; Marinow 1974; Ogawa et al. 1987; Tsuang et al. 1979). Table 2–1 summarizes data from these studies.

As can be seen in the table, the studies were conducted in seven countries. Studies outside the United States consisted of primarily urban samples, whereas the American studies examined rural samples. Altogether, a total of 2,429 patients (sample range 115–502) were followed for an average of approximately 28 years (range 20–37 years). The percentage of patients showing significant clinical improvement ranged from 46% to 84% (median value 53%), and the percentage of patients who were considered socially recovered ranged from 21% to 77% (median value 49%). Thus, a wider range among studies was found for social response than for clinical response. Together, these studies help to rebalance the picture of schizophrenia.

Switzerland #1—The Burghölzli Hospital Studies

The first of these studies was conducted in Zurich, Switzerland. Manfred Bleuler (1972/1978) began following a sample of patients admitted to the Burghölzli Hospital between April 1942 and December 1943 and maintained follow-up over the next two decades, regardless of whether the patients remained in treatment—something his father did not do. His sample consisted of 100 males and 108 females with diagnoses of schizophrenic psychoses. The diagnostic criteria used were a combination of those from his father, Eugen Bleuler, and Emil Kraepelin and were considered to be narrower than those of the American DSM-II (American Psychiatric Association 1968) and wider than the DSM-III (American Psychiatric Association 1980). M. Bleuler excluded patients with brain disease, endocrine disorders, poisoning, latent schizophrenia, neurosis, mixed psychosis (schizoaffective), or a previous course. This strategy had been unavailable to Kraepelin. Sixty-eight of the 208 (33%) probands studied were considered first admissions. Their ages ranged from 16.0 to 67.5 years, with an average age of 40 years. After considerable research, M. Bleuler (1972/1978) concluded that these subjects came from "the same sectors of the population as do all schizophrenics hospitalized in the Canton of Zürich during the period in question" (p. 12). None of the probands in this study died of brain disease during the follow-up period.

The Burghölzli Hospital Study was conducted in a systematic and comprehensive manner using structured instruments as well as clinical in-

TABLE 2–1. Long-term studies of schizophrenia

Study	Sample size, *n*	Average length, years	Percentage of subjects recovered and/or significantly improved*	Percentage of subjects socially recovered
M. Bleuler 1972/1978, Switzerland	208	23	53–68	46–59[a]
Hinterhuber 1973, Austria	157	30 (approx.)	75	77
Huber et al. 1975, Germany	502	22	57	56
Ciompi and Müller 1976, Switzerland	289	37	53	57
Kreditor 1977, Lithuania	115	20+	84	NI
Tsuang et al. 1979, United States	200	35	46	21[b]
Marinow 1986, Bulgaria	280	20	75	NI
Harding et al. 1987b, 1987c, United States	269	32	62–68	68[c]
Ogawa et al. 1987, Japan	140	22.5	56[d]	47
DeSisto et al. 1995a, 1995b, United States	269	35	49	[e]

Note. *Recovered = no further symptoms, no use of psychotropic drugs, living independently in the community, working, and relating well to others, with no behaviors that are considered to be odd or unusual; significantly improved = all of the above, but one domain of functioning. NI= not enough information to rate.
[a]Multiple admissions vs. first admissions.
[b]Marital status only recorded.
[c]Live interviewed DSM-III schizophrenia group—the hardest data.
[d]Derived by adding 33% recovered with a conservative 23% as improved (from 43% listed).
[e]When variables not chosen for matching criteria were covaried out of the Maine–Vermont comparison, differences in social functioning lost statistical significance.
Source. Adapted from Harding and Keller 1998.

terviews. M. Bleuler (1972/1978) found that 68% of the first-admission patients and 53% of the multiple-admission patients significantly improved or recovered. Among the many findings reported were that 1) life histories revealed that most patients had experienced "disturbances in their home life," but no one particular type stood out and no direct causal linkages could be established; 2) genetics appeared to play a role, but only a partial one (citing discordant monozygotic twins and other family data); 3) therapy may or may not have played a key role in the recovery process; 4) E. Bleuler's (1911/1950) "group of schizophrenias," which implied different etiologies, was still elusive; and 5) gender differences played a role. Bleuler focused on getting to know these patients and their relatives personally, and further social functioning was determined from criteria of work, independence from care, and living in a nonsheltered environment. No social impairment was observed for 46% of the overall cohort and for 59% of members of the first-admission subsample. With regard to sex differences, Bleuler found a 6:1 female-to-male ratio of improvement, and females showed a slight edge over the males in the recovered and mild impairment categories. He said, "I have found the prognosis of schizophrenia to be more hopeful than it has long been considered to be" (M. Bleuler 1984).

Austria—Hinterhuber's Study

Between 1930 and 1940, 157 people with schizophrenia were first admitted to the Innsbruck Psychiatric Clinic in Austria (Hinterhuber 1973). At follow-up, 99 (63%) of these patients had died or were presumed dead, and 58 (37%) were still alive. Data were extracted from several sources, including structured questionnaires, interviews with relatives, and biographies. Hinterhuber (1973) used diagnostic criteria from Bleuler, Kraepelin, and Schneider to study the sample, which was composed of 87 women and 70 men considered to have "obvious schizophrenia." Using data from all sources, the results, which were published primarily in German, revealed that 50% of these patients were "released from treatment," but 33% remained enrolled in continued full-time care. In measures of psychopathology, 29.2% of the sample were reportedly "cured" of their schizophrenia, with another 45.6% improved and 30.5% still ill. Work functioning had remarkably resumed, with 77% working full-time, 20% working part-time, and the remaining 8% in family care. Subjects who had incurred injuries prior to illness (34.6%) remained mostly in the "severe final stages" of illness, with only 21% falling into the "cured" category. Course modifiers leading to poorer outcomes included psychological trauma, genetic loadings, and interestingly, later onset (after age 40 years).

Switzerland #2—The Lausanne Investigations

The "Lausanne Investigations" were conducted by Ciompi and Müller (1976), who undertook the longest follow-up study reported in the world literature. They conducted assessments of 92 men and 197 women across a median length of 36.9 years (SD = 13.3 years), with a range of up to 64 years after first admission to the University Psychiatric Clinic. Of the sample, 20% had catamnestic histories of more than 50 years' duration. Thus, Ciompi and Müller's findings might be considered closer to E. Bleuler's concept of *Reichtung Prognose* ("final prognosis"). The average age of males at follow-up was 75.2 years; females averaged 75.8 years. This sample was considered to be representative of the 1,642 patients admitted to the clinic who were 64 years of age or younger at their first admission and who were 65 years of age or older at the beginning of the study in 1963 (Ciompi and Müller 1976). The initial large group (N=1,642) was targeted to study mortality and causes of death.

These investigators used a combination of Kraepelinian and Bleulerian criteria. Inclusion symptoms for schizophrenia included "disturbance of psychotic proportions...marked by manifold and alternating combinations of the so-called primary disorders of thought and emotion, autism, ambivalence, loss of contact, and experience of depersonalization or derealization" (Ciompi 1980, p. 607). Patients with questionable diagnoses of schizophrenia were excluded. The research team conducted 2-hour semi-structured interviews in the probands' homes, and more data were collected through records, correspondence, and interviews of family, friends, and others in care systems (agencies and clinicians). Because of the complexities of human beings and schizophrenia, outcome domains were measured separately before being combined into a "recovered," "improved," or "deteriorated" status.

Results were quite varied. Highlights revealed that the average mortality rate for those in the sample was 173%, versus 100% for the Swiss population (Ciompi 1980), with women suffering the most, at 185% (vs. males at 161%). Twenty percent of subjects had been hospitalized for more than 20 years. Ciompi pointed out that hospitalization rates were also influenced by many social and economic factors (e.g., system, family, social structures).

Symptoms among the patients changed considerably over time. For example, 62% of all individual symptom profiles had "'vanished' in old age,...and [an] additional 11% were clearly improved, with just 20% who remained unchanged in old age or had intensified" (Ciompi 1980, p. 611). However, only about a third of these patients were doing exceptionally well in social relationships. Classical predictors, including "good premorbid social, familial, and professional adaptation, few premorbid personality disorders; a marriage, completion of vocational training, and a higher premorbid occupational level," held into old age. Furthermore, it was found that "the disease tends to run a more favorable course, the more acute, the more lively, and the more mobile the onset of the illness." Finally, Ciompi (1980) noted that "treatment factors were much less important for the long-term course than the above-described personality and disease factors" (p. 615).

Sex similarities were found, with 66.3% of the women in the "recovered" or "mild" categories compared with 61% of the men; whereas 7.1% of the men became worse, only 3.3% of the women did so (Ciompi 1980). Five patients demonstrated very late improvement. Using composite ratings, the team found "59% recovered or mild end states" (p. 616). Ciompi (1980) later concluded that "the long-term evolution of schizophrenia is much better than hitherto admitted," which was in keeping with the conclusions of "Bleuler and Huber, [who] both concluded that schizophrenia is in no way 'basically' or even 'predominately' [an] unfavorable 'disease process' running an inexorably deteriorating course" (Ciompi 1980, p. 616).

United States #1—The Iowa 500 Study

In the first American study, the Iowa 500 Study assessed 100 patients with mania, 225 patients with depression, and 200 patients with schizophrenia who had been part of the annual admissions to Iowa State Psychopathic Hospital during the 1930s and 1940s. An additional group of 160 nonpsychiatric surgical patients (appendectomy or herniorrhaphy) was selected for a control group (Tsuang et al. 1979). These investigators applied the narrow Feighner criteria and clinical judgment to the comprehensive records available of that era (Feighner et al. 1972). The study concluded that these diagnosis were validated by follow-up information (à la Kraepelin) as well as family studies. Of 3,800 admissions, 874 charts were initially reviewed, with 20%–63% of records rejected depending on the chart diagnosis for schizophrenia (i.e., 63% of those diagnosed with schizophrenia were rejected) (Winokur and Tsuang 1996).

In the schizophrenia sample, 48.5% were females; 20% were married; 50% had poor premorbid psychosocial adjustment; 28% were high school graduates; median age at onset was 25 years; age at admission was 27 years; and only 26% had been discharged to the community (this was an era of custodial care with essentially no treatment [Winokur and Tsuang 1996]). Follow-up data were extracted from letters sent by social workers to the families for several of the early years. No information was available on 4%, only 17% of patients were interviewed, and 25% had information supplied by family or friends, with 53% supplied by physicians or other hospital

admissions (Winokur and Tsuang 1996). The fieldwork of the very-long-term follow-up period (average=37 years) consisted of interviewing those patients still living who could be found (n=86 of 200, or 43%) and first-degree relatives and evaluating all available records. The Iowa Structured Psychiatric Interview (ISPI; Tsuang et al. 1980) was administered by non-medical interviewers. Current diagnosis was based on data from the ISPI and on medical records through a consensus of three clinicians. Patients or first-degree relatives who had died or who refused to participate were given an "approximate" diagnosis based on medical records. Twenty screening questions were used for both reliability and validity of all diagnoses with little data reported.

Only four major outcome domains were measured: marital, residential, and occupational status and psychiatric symptoms. The criteria for good outcome were married or widowed, living in one's own home or with a relative, employed, retired, homemaker or student, and no symptoms. A fair rating was defined as divorced or separated, living in a nursing or county home, incapacitated due to physical illness, and some symptoms. A poor rating was considered if the patient was single or never married, living in a mental hospital, not working due to mental illness, and experiencing incapacitating symptoms. At long-term follow-up 30–40 years after the index hospitalization, 39 of 186 (21%) had a good marital outcome and 22 of 186 (12%) were rated as fair. For occupational status, 65 of 186 (35%) had good outcome, with an additional 14 of 186 (8%) with fair levels. For residential status, outcomes for 64 of 186 (34%) were good and another 89 (48%) were fair. For psychiatric status, 38 of 186 (20%) were rated as good, with 48 of 186 (26%) at fair levels. Winokur and Tsuang (1996) noted that disorientation and memory deficit at admission seemed to predict poorer outcome. Sex differences (men=102; women=98) were not reported in the overall outcome variables. Although these investigators focused on the 54% of patients who were rated as doing poorly, they neglected to point out that 46% of the cohort were actually doing much better. Nonetheless, the findings showed that outcomes for schizophrenia were at the end of a sequence ranging from affective disorders having the best outcome to schizoaffective disorders to paranoid-type schizophrenia to disorganized type having the worst outcome.

Lithuania—"Late Catamnesis of Recurrent Schizophrenia With Prolonged Remissions"

In an observational study, Kreditor (1977) studied patients with episodic schizophrenia (N=115) over a period of 20 years in five regions of Riga at the National Dispensary. The sample consisted of 38 men and 77 women

with an age range of 35–82 years. Approximately 54% were 50 years or older. Diagnostic criteria for schizophrenia were fairly broad. Ninety-seven (84%) of these patients had long-term remissions that extended 8–40 years. Kreditor identified two types of episodic courses, one with occasional episodes and the other with multiple episodes. Ninety-seven subjects had prolonged remissions (including 39% with 20–40 years remitted), and only 18 became worse. Predictors of long-term remission were "harmony of premorbid personality," lack of or low occurrence of character pathology, late onset (ages 30–40 years), and affective stability. The two course-type groups differed in premorbid personality, age at onset, and illness course. "The data give ground to eliminate the prognostic criteria of the probability of long-term remissions" (Kreditor 1977, pp. 110–113).

Germany—The Bonn Investigations

Huber et al. (1979) followed 502 of 758 admissions to the University Psychiatric Clinic of Bonn, Germany, between 1945 and 1959. Of these patients, 142 died before follow-up (including 7 [4.9%] who were suicides). Of those probands still living, 209 males and 293 females were assessed for 22.4 catamnestic years with personal interviews by the clinical team between 1967 and 1973. This part of the sample was believed to be representative of the usual admission profile for the clinic. Relatives reported on the status of an additional 26 probands (4%); 34 (7%) more were lost to follow-up, and 6 (1%) had brain diseases. Forty-eight (10%) refused interviews; however, the investigators found that this group consisted mainly of persons with good prognostic factors such as above-average intelligence and upper-class status. The investigators used the combination criteria of Schneider (based primarily on Kraepelin) and Eugen Bleuler, which had also been used by Manfred Bleuler (1972/1978). Like Bleuler, Ciompi, Harding, and others, they did not use outcome to define the diagnosis. Furthermore, "no symptoms or syndromes at the time of onset could be used to predict with any certainty whatever, the differentiation between malignant or benign, process or nonprocess,...schizophrenic...psychoses" (Huber et al. 1980, p. 593). Sixty-seven percent became cohort members at first admission.

The authors reported that 57% of their subjects were improved and/or recovered. Other instruments found that 22.1% had achieved complete remission, with an additional 40.2% demonstrating "noncharacteristic residual syndromes." Thirty-five percent were considered to have "characteristic residual syndromes." Fifty-six percent of the cohort were judged to be socially recovered (meaning that they had returned to their premorbid fully employed status)—"all the more remarkable when only 13% had participated in any outpatient rehabilitation program" (p. 595). Social func-

tioning was highly correlated with outcome of psychopathology (Huber et al. 1980). Sex differences were found in better outcome for females in general and specifically in social outcome. Schizophrenia in first-degree relatives tended to differentiate men with poorer outcomes. Females were more likely to have better outcomes if they had multiple episodes with clear-cut precipitating factors. Females also tended to have more florid symptoms but a later illness onset. Complete remission, more favorable outcomes, and social recovery tended to occur in females. Cerebral atrophies occurred more often in males, who also had more psycho-organic disorders of the elderly. Course was described as "phasic" in 22%, "surges" in 48%, and "sluggish" in 21%. The authors identified 76 course types, which they reduced to 12 categories. They also noted that outcome shifted among some cohort members no matter how long a certain status was in effect. However, they found that "no reasonably reliable prognosis for the individual patient is possible" (p. 604).

Bulgaria—Marinow's Long-Term Follow-Up Study

A two-decade study (mean=20.2 years) conducted in Bulgaria by Marinow (1986) followed 280 male schizophrenia patients who had been discharged from hospitalization between 1946 and 1950. The cross-sectional outcomes for members of this cohort were measured every 5 years. Subjects were assessed on variables such as psychopathology and social and work functioning. Each factor was then combined into a summed total outcome or "prognostic" score. Findings revealed that at least 50% of subjects had a "favorable" outcome, with approximately 25% improved and another 25% with a poor outcome. Marinow found the course picture to be one of mixed signals with conflicting indicators of long-term outcome and concluded that it was impossible to predict future status for individuals. In a later study of persons with schizophrenia (N=634) whose illness duration ranged from 2 to 20 years, Marinow (1988) found that long-term outcome had greater correlation with the patient's marital status, ability to work, and with neuroleptic treatment than with illness history, number of readmissions, and length of hospitalizations, but he was unable to "predict prognosis." The diagnostic criteria used in this study appear to have been wider than those used in American, Swiss, and German studies.

United States #2—The Vermont Longitudinal Research Study

A second American long-term catamnestic study was conducted in Vermont for which base reports were published in the 1980s (Harding et al. 1987b, 1987c). This study is the longest study of deinstitutionalized patients to be conducted in the United States (ranging up to 62 years after first admission) and one of the longest studies of schizophrenia. The sample of 269 patients (144 females and 125 males) with severe and persistent mental illness was selected from the back wards of Vermont State Hospital in the mid-1950s.

Probands were provided with a "rehabilitation unit" after 2 years of only modest responses to long trials of clinically therapeutic dosages of phenothiazine. The patients and their multidisciplinary clinicians jointly created a federally funded, comprehensive model demonstration, biopsychosocial rehabilitation program that targeted self-sufficiency and community integration (Chittick et al. 1961). Their combined effort in the hospital provided training in activities of daily living and social skills; continued medication; vocational assessment, training, placement, and continued supports; patient government; peer support groups; case management; and careful deinstitutionalization.

A substudy of the parametric characteristics of the entire hospital census (N=1,300) revealed that the back-ward patients in the cohort had the most chronic course and were the most severely ill and disabled (especially the males) patients compared with the hospital population at large (Harding et al. 1987b). The study cohort had an average of 16 years of illness and 10 years of total disability. Furthermore, these patients were shown to be among 19% who remained in the hospital during the previous 5 years or longer while other patients were admitted and discharged (G.W. Brooks, unpublished study ["Retained Patients With Schizophrenia From 1920s to 1970s"], October 1975). This group is considered to be the most chronic cohort ever studied in the world literature and therefore should have had the worst long-term outcome.

Members of the cohort were carefully deinstitutionalized in the late 1950s into a pioneering community mental health system and were provided rehabilitation for 10 years, until 1965, by the same team from the hospital (Chittick et al. 1961). In the community, all aspects of community care were established, including a range of residential and occupational placements and supports, outpatient clinics, inclusion in natural community organizations, and continuity of care long before community mental health centers were established (Chittick et al. 1961). They were followed for an average of 32 catamnestic years, with a range of 22–62 years after first admission. A major follow-up study funded by the National Institute of Mental Health was initiated in the early 1980s, at which time 97% of the Vermont cohort was located (262 of 269). The average age of the surviving interviewed cohort at follow-up was 61 years. A comprehensive and structured instrument battery was implemented, with all the interrater and interitem concordance testing reported (Harding et al. 1987b, 1987c). The

field interviewers were blinded to the patients' records, and the record abstractors were blinded to outcome. Both cross-sectional and longitudinal measures were assessed. Prospectively gathered records and retrospective data were used to fill in the longitudinal picture, along with vocational rehabilitation records and structured interviews of family, friends, and clinicians. Recalibration of the index-admission diagnosis from the 1950s to the then-new DSM-III (American Psychiatric Association 1980) was performed with interrater trials that achieved a kappa level of .78 ($P<.0007$) (Harding et al. 1987c).

The original cohort was recorded to have 213 of 269 (79%) members with schizophrenia. The rediagnostic effort, done without the previous diagnosis assigned and according to DSM-III criteria, reduced that number to 118 (55%). Although the investigators followed 97% of the total sample of 269 subjects, only the hardest data were reported for outcome of schizophrenia, unlike in other studies. Those probands who were rediagnosed, primarily with schizoaffective disorders, psychosis not otherwise specified, and atypical psychosis, were excluded from the analysis of schizophrenia and outcome, as were those who were deceased.

In a review of North American follow-up studies, McGlashan (1988) mistakenly reported that these patients had very late average onsets, in their 30s. He later corrected that report to a mean onset of 24.2 years for males and of 27.1 years for females (Childers and Harding 1990; McGlashan 1991). McGlashan also originally thought that these patients were the workers of the hospital and were retained by the staff until the rehabilitation study, another misconception that he subsequently corrected (McGlashan 1991).

With 24% of the cohort deceased, an important methodological balance was introduced. Instead of simply comparing the demographic and illness variables with the surviving cohort, a special protocol was introduced that systematically interviewed the family, friends, and clinicians connected to these patients in one room in order to piece together the life lived by the patients until their deaths. This strategy revealed that instead of the most seriously ill cohort members dying first, leaving the less ill members reporting better outcomes, the subjects mirrored the same proportions of recovered, improved, or unimproved persons found in the live cohort (Harding et al. 1987b). Other long-term studies have combined information for the living and deceased subjects.

The interview instrument battery used in the follow-up study consisted of 15 standard scales and schedules (Harding et al. 1987a, 1987b). Much to their surprise, the Vermont investigators found that nearly two-thirds of the subjects from this chronic, severely ill cohort met stringent objective criteria for recovery and/or significant improvement. Of the

whole, 62%–68% achieved significant improvement or recovery across multiple domains of function, increased work (40%), reestablished social relationships (68%), and self-care (81%) (Harding et al. 1987c). Sixty-eight percent showed no further signs or symptoms of schizophrenia, with 45% of that group having no symptoms at all. All of these areas were predicted in the DSM-III to deteriorate or remain at marginal levels (American Psychiatric Association 1980). Instead, the domains not only reconstituted and improved but also developed further in two-thirds of the cohort.

Recovery criteria included no psychiatric medications, no symptoms, no behaviors that could be construed as those of a "mental patient," being employed, relating well with others, and living outside the hospital. Significant improvement meant that the person had achieved recovery in all but one of these domains. Social functioning was measured by several widely used and standard structured assessments and was another area that showed reconstitution and further development in 62%–68% of subjects (Harding et al. 1987c). Sex differences were also examined in the surviving DSM-III schizophrenia sample, which had 41 men and 41 women. Females, who had had the better premorbid functioning scores (Childers and Harding 1990), were shown to have lost their competitive advantage and ended up at only a trend level better than their male counterparts, who had consistently performed more poorly on all subscales and overall score of the Premorbid Adjustment Scale (PAS). Harding and Hall (1997) suggested that the explanation for the performance decrement seen in women might be the loss of estrogen protection at midlife (see also Seeman 1995). Furthermore, the men appeared to have slowly gained in strength across time (Harding 1994; Harding and Hall 1997; Harding et al. 1987c). Nevertheless, women's scores on the Community Adjustment Scale (Consalvo et al. 1984, cited in Harding 1994) remained slightly higher than those of men, despite the fact that they had longer lengths of stay in the hospital. Women also demonstrated more productivity, had less evidence of psychotic symptomatology, and evidenced higher levels of functioning in social relationships (Harding and Hall 1997).

During the initial data analyses, Strauss and Harding wrote, "we have gathered some evidence that the course of schizophrenia is a more complex, dynamic, and heterogeneous process than has been heretofore appreciated or predicted by diagnostic specificity" (Strauss and Harding 1984, p. 349).

Japan—Gumma University Hospital Study

Ogawa et al. (1987) conducted a 21- to 27-year follow-up of 140 consecutive patients (67 males and 73 females) discharged from the Department of Neuropsychiatry at the Gumma University Hospital in Japan between

1958 and 1962. At entry to the cohort, 81% of these patients were younger than 30 years; 79% were first admissions and resided primarily in the provincial town of Maebashi, northwest of Tokyo. These patients were provided with a program of "neuroleptic drugs, the open-door system, and intensive aftercare" (Ogawa et al. 1987, p. 758). The hospital's rehabilitation model was called *Seikatasu-rinsko* and was described as "clinical work in a patient's everyday life" (p. 750), which was reported as a combination of case management and individual counseling techniques.

At follow-up, 93% of the 140 members of this cohort were assessed, with 105 still living an average of 23.6 years after index hospitalization (range=21–27 years). One hundred subjects were alive and interviewed. In addition to the *International Statistical Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM; World Health Organization 1978) rediagnosis, subjects were also evaluated on social functioning indices with Eguma's Social Adjustment Scale (ESAS; Eguma 1962; Ogawa et al. 1987). Information was acquired from multiple data sources. The data were not analyzed with regard to sex differences.

The results revealed that 57% of the subjects were considered to be "fully self-supportive" (i.e., fully productive, living in own home and often also married, psychologically recovered, with a return to premorbid levels of functioning and independent social life without clinical interventions as well as maintenance of a normal family life). "Semi-self-supportive" ratings were given to another 19%, and 34% were considered to be "hospitalized and maladjusted cases." The Japanese team concluded that social recovery was greater than improvement in psychiatric status. They conducted monthly assessments of social adjustment and reported patterns of adjustment across time. These patterns showed multiple fluctuations early in the illness course, with later differentiation between the self-supporting and chronically institutionalized groups (Ogawa et al. 1987).

United States #3—The Maine–Vermont Longitudinal Comparison Study

The most recent American study was conducted in Maine (DeSisto et al. 1995a, 1995b) and, to my knowledge, is the only matched comparison study of very long outcome ever reported in the world literature. In this study, patients from the Vermont Longitudinal Research Study (N=269) were matched by age, sex, diagnosis, and length of hospitalization with patients in Augusta State Hospital who were treated during the same era and in similar catchment areas as defined by health and census data. The Maine study employed the same research protocols as the earlier Vermont study and incorporated the careful rediagnostic workups that the Vermont Longitudinal Project had used (DeSisto et al. 1995a, 1995b). The study also used the same treatment era and intraproject reliability testing. Of the Vermont patients, 97% were tracked for an average of 32 years after first admission; 94% of Maine patients were tracked across an average of 36 years. The major difference between the two study cohorts was that whereas subjects in the Vermont cohort had been part of a comprehensive model rehabilitation demonstration program, the Maine patients had experienced primarily traditional custodial care.

The Maine–Vermont study had an average of 36 catamnestic (time since first admission) years. Following the rediagnostic work, the sample comprised 102 subjects with DSM-III schizophrenia (57 males and 45 females). Comparisons of the two matched cohorts revealed significant differences. After covarying out several variables that could not be matched (e.g., urban vs. rural residence, level of education), three very strong findings held: Vermont patients 1) had much stronger community functioning ($P<.001$), 2) much stronger work functioning ($P<.009$), and 3) substantially reduced symptoms ($P<.002$). Overall, global functioning results found Vermont patients at 68% and Maine patients at 49% ($P<.0001$). Sex differences were found in the Maine cohort, with women rated better in premorbid social functioning.

What Have We Learned From These Studies?

In the following sections I assess the combined findings described above to determine what we might learn about the domains of diagnosis and time, symptom course, social functioning, ability to work again, psychopharmacology and side effects, predictors of long-term outcome, and reconstitution of lives.

Diagnosis and Time: Not as Strong a Predictor as Once Thought

In the field of psychiatry, diagnosis has long been reified and conceived of as a "lifetime" label (American Psychiatric Association 1980, 1994). In the United States, psychiatry tended to be ethnocentric, especially after an analysis showed that American clinicians overdiagnosed schizophrenia based on DSM-II criteria (American Psychiatric Association 1968) in comparison with clinicians in the United Kingdom (Cooper et al. 1972). Thus, although the Swiss and German studies used criteria narrower than those of Eugen Bleuler but wider than the Kraepelinian-based DSM-III (American Psychiatric Association 1980), American investigators discounted the European findings and proceeded to make criteria narrower and narrower.

However, the narrowness of the criteria used does not predict uniformly poor outcome, as was once thought (Harding et al. 1979, 1987c). The narrow Feighner criteria employed by the Iowa 500 study identified such a poor-outcome group with more efficiency (Tsuang et al. 1979, 1981). This approach was a trade-off, because it made the cohort findings less generalizable to the entire population with schizophrenia. However, much to everyone's surprise, even the sample identified in this manner has found heterogeneity in outcome. With one exception, these long-term studies revealed that diagnoses could be reconceived as "cross-sectional working hypotheses" (Harding 1998, p. 321) that need to be reviewed and revised over time and in many cases eventually discarded. There is evidence that patients with schizophrenia have more difficulty in achieving good long-term outcome than do many patients coping with affective and schizoaffective disorders, as found by the Iowa 500 group and others. However, the Vermont sample and others have demonstrated that even this effect is reduced to a trend level across decades. In an opposite approach, Vaillant (1975) also found heterogeneity when he attempted to follow up the other end of the continuum, the so-called good-prognosis patients. Discovering heterogeneity after 10 years, he concluded that "prognosis and diagnosis are two different dimensions of psychosis," in direct contradiction to Kraepelin (1902).

Symptom Course—Ever-Widening Heterogeneity With Early Fluctuations and Later Decrease of Virulence

Eugen Bleuler (1911/1950) called the disorder "a group of schizophrenias," and follow-up investigators are aware of the wide variation of individual histories, which supports Kendler's complex model of gene–person–environment interaction (Kendler and Eaves 1986). Huber et al. (1975) suggested 76 course types, indicating the wide heterogeneity found, but eventually reduced these to 12. Ciompi (1980) also published a diagram of 8 course types. His chart, with accompanying percentages, has been perceived as *the* standard by which course and outcome regularly proceed. However, Childers and Harding (1990) found evidence in the Burghölzli Hospital reports and the Vermont findings that these percentages are not written in stone but rather depend on the composition of the cohort. This observation means that predicting a probable long-term course for individuals is difficult if not impossible.

Predictors of Long-Term Outcome Weaken Over Time

Although some studies, such as the Lausanne Investigations, found that the classical predictors held across time, an unpublished manuscript by Harding and colleagues showed that the classical predictors of outcome in schizophrenia research can also fade in power to trend levels across decades. Such predictors include gender, type of onset, early versus late onset, symptom profile, and age at onset. The predictive power of sex, which has classically shown strong evidence in favor of females, weakens across time, perhaps as the protective effects of estrogen wear off with menopause (see Seeman [Chapter 8] in this volume). Menopausal women in the Vermont cohort lost their edge to the trend level, whereas the men grew increasingly stronger (improved in functioning and had fewer symptoms) across time. The only predictors that showed resistance to weakening over time were certain types of negative symptoms.

Restoration of Social Functioning

Harding et al. (1987a) and Harding and Keller (1998) analyzed the literature on social functioning and schizophrenia, which describes poor premorbid adjustment, deterioration during illness, feelings of isolation and estrangement, disordered emotional responsivity, bizarre behavior and speech that can drive friends and family away, and the symptom of blunted affect, which increases social isolation. The long-term studies revealed that social functioning most often is restored and even undergoes further development after a schizophrenic psychosis. Many of the studies found that this effect happened with greater frequency or was highly correlated with improvement in psychological functioning.

Regaining the Ability to Work Again

The assumption that once-psychotic persons are unable to work has been challenged repeatedly by a number of investigators (e.g., Anthony et al. 1984; Drake et al. 1999). Strauss and Carpenter (1974) showed that the best predictor of working is past work experience. Furthermore, diagnosis and symptoms did not predict work or social functioning or outcome across 5 years of follow-up. Previous social functioning did cross over to help predict work functioning. In the Maine–Vermont comparison, the subjects were matched and also happened to have had similar work histories prior to being hospitalized. The Vermont patients, who had participated in an intensive vocational rehabilitation program, continued working throughout the follow-up period at a rate of 30%–40%, with an additional 20% engaging in volunteer work within their communities. The Maine patients who did not receive vocational rehabilitation struggled to regain their employment status. The Vermont model focused on rehabilitation, self-sufficiency, and community integration; by contrast, the Maine model emphasized stabilization, maintenance, and entitlements (DeSisto et al. 1995a; 1995b).

Psychopharmacology and the Assumption of Lifetime Use Not Supported

There is an assumption—albeit one not supported in the literature—that most persons with schizophrenia need to remain on antipsychotic medication all of their lives. However, the Vermont study revealed that 20% were no longer receiving prescriptions for medication; 30% had drawers full of medications never taken; 25% had invented targeted strategies before Herz et al. (1991) and Carpenter et al. (1988); and the remaining 25% were taking their medications religiously, having been so threatened with recurring psychosis by past clinicians that their current clinicians were unable to taper their dosage. Harding (1998) concluded that perhaps only a small group of patients really needed continuing medications across a lifetime and recommended that the findings be investigated further. The idea of lifetime use of antipsychotics has been assumed because of the myth "once a schizophrenic, always a schizophrenic" or nowadays reframed as "once a broken brain, always a broken brain."

Many Pathways to Improvement and Recovery

M. Bleuler (1972/1978) observed that "the long-term experience gleaned from my probands revealed one fact most impressively, namely that successful results can be achieved through totally different methods" (p. 441). Furthermore, in the Vermont–Maine comparison, the investigators were startled to find that although significant outcome differences were found between the samples (which may have been attributable to the rehabilitation program in Vermont versus the custodial care in Maine), 49% of Maine patients continued forward toward improvement. At first, DeSisto et al. (1991) thought that the greater forward progress of the Vermont patients was due to decisions made at the top of the system—that is, Vermont appeared clear and consistent in its mission and comprehensive in its programs whereas Maine did not. Although some of this environmental impact may have been operative, Maine patients continued to improve despite the vagaries of their system of care.

After looking at all of the long-term studies across many treatment eras and finding that patients persisted toward recovery and/or improvement, new thoughts began to emerge about the power of human relationships, no matter what services are being delivered. The Vermont patients reported that they received the greatest benefit when they were told that someone believed in them: "Someone believed in me, someone told me I had a chance to get better." To Harding, this illustrated the importance of hope and showed that hope was connected to the natural self-healing capacities

of people. She began to write about neural plasticity (e.g., Harding 1998). Andreasen (2001, p. 31) stated recently, "brain plasticity...stresses that our brains are in constant dynamic change, which occurs as a consequence of the impact of experience on our mental functions and states." Strauss and Harding (1990) suggested that treatment providers and research investigations need to target developmental issues and course of disorder as "two interacting systems," especially in this era of biological psychiatry. They described both positive (amplifying) and negative (limiting) feedback loops within this interaction. Given the arguments of schools fighting for certain models of treatment as more effective than other models, one wonders whether clinicians may need to rethink this stance. An alternative plan calls for clinicians to collaborate with one another and with their patients by employing a range of treatment options—depending on the ever-changing needs of patients—with warmth, encouragement, optimism, and persistence.

Rebalancing the Picture for Schizophrenia

The long-term course of schizophrenia is vastly different than what has been extrapolated from short-term studies as well as from older cohorts of convenience formed by patients still in systems of care for a wide variety of reasons. Such reasons include lack of incentives to get better, self-fulfilling prophesies derived from pessimistic attitudes and continuing severity of symptoms, and the expectation of lifetime diagnostic specificity and need for psychopharmacology.

In regard to treatment, M. Bleuler (1972/1978) suggested that "The inner life of the schizophrenic is never 'burnt out.' It always continues on its way. When ceaseless attempts are made to establish contact with him as with a normal person, and he is not left to stand aside like an outsider, a communal relationship is established that means a great deal to both the patient and the doctor" (p. 442). In fact, Bleuler taught us to see "the person behind the disorder" with comments such as "seriously 'demented' schizophrenics have not lost touch with a healthy psychic life,...in their case, healthy perception, memory, recall, judgment, and feeling are merely concealed behind their pathological behavior" (M. Bleuler 1972/1978, p. 191).

Summary of Findings

For the past century, the course of schizophrenia has been thought to be a downward course for most if not all patients. In this chapter I presented ev-

idence from the long-term literature that revealed a very different outcome. These studies found wide heterogeneity of course and social and work functioning, significant weakening of traditional predictors, and an interaction of adult development with symptom course. The discussion detailed the possibilities for a more positive outcome emerging from such studies. Explanatory models were proposed of neural plasticity, the change from extreme anxiety and fear arising from the experience of schizophrenia itself, to "active coping" through rehabilitation, hope and optimism, recalibration of neurobiological mechanisms during the aging process, and human endurance and resilience.

The most remarkable finding of these long-term studies is the confluence of results showing that at least 50%–60% of each intact cohort studied across two to three decades significantly reclaimed their lives, even in the face of persisting beliefs that this would be impossible. Reconstructed lives have begun to erode the old beliefs, and new strategies with a recovery vision are beginning to be employed.

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