

Early Detection and Intervention With Schizophrenia: Rationale

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Abstract

This article explores the rationale for early detection and intervention in schizophrenia. The most compelling reason is the disorder's severity and chronicity and our knowledge that, while many treatments for schizophrenia are effective, they are also limited and palliative. This state of affairs suggests that researchers pay closer attention to schizophrenia's premorbid and onset phases, when the vulnerability to psychosis becomes expressed and the neurobiological deficit processes driving symptom formation appear to be the most active. We review the evidence that brain plasticity can be retained or reversed despite deficit processes. This evidence includes the putative attenuation of the severity of schizophrenia throughout the 20th century, retrospective and prospective linkage of earlier neuroleptic treatment and better long-term outcome, and data from a program designed to intervene in the prodromal phase of disorder. While the evidence to date does not demonstrate that early intervention with known treatments can change the natural history of schizophrenia, it is suggestive enough (for both biological and psychosocial treatment) to support further investigation. Focusing on the early course of schizophrenia also offers the possibility of identifying potential patients long before onset using vulnerability markers and of making more feasible primary prevention efforts. Finally, studies of untreated psychosis in first-episode cases have revealed that patients are often actively psychotic for a very long time

before they get help. Bringing treatment more rapidly to a person who has been psychotic is in itself enough to justify early detection efforts.

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This article explores the rationale and existing programs for early detection and intervention in schizophrenia. It is based on the conviction that current treatment modalities for schizophrenia are extracting diminishing returns because they do not address the basic neurobiological deterioration or deficit formations associated with the disorder. Therapeutic attention has not targeted these processes because their basic nature remains a mystery. Nevertheless, clinical research findings in recent decades suggest that applying existing schizophrenia treatments as soon as possible in the course of the disorder may slow or stop deterioration. At the very least, the substantial immediate clinical benefits and cost advantages justify careful exploration of the issues and evidence. Sullivan (1927/1994) once wrote of schizophrenia, "The psychiatrist sees too many end states and deals professionally with too few of the pre-psychotic" (p. 135). The question before us is, Do we know enough now, nearly 70 years later, about vulnerability to schizophrenia and the disorder's early course to intervene before the onset of chronicity?

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A Century of Schizophrenia.

Schizophrenia was first defined by Emil Kraepelin at the turn of the century. Kraepelin referred to it as dementia praecox, a progressive mental disorder of unknown organic etiology beginning in adolescence and leading to more or less irreversible deterioration in mental and instrumental capacity (Kraepelin 1919/1971). Schizophrenia is classified among the severe mental illnesses and may be the prototypic form. While only 1 percent of the population may be affected by schizophrenia, its early onset and chronically disabling nature make it costly to all societies.

The "Century of Schizophrenia" has seen a multitude of treatments. Anthony Lehman and his colleagues at the University of Maryland and Johns Hopkins University have recently undertaken a massive review of the data dealing with treatment (Lehman et al. 1995). This Patient Outcome Research Team (PORT) program has concluded that three forms of intervention have demonstrated significant efficacy in clinical trials: (1) antipsychotic medications, (2) family education and support, and (3) programs of assertive community treatment. From a scientific perspective it is clear that certain treatments—which can be vastly different from one another—can make a real difference with schizophrenia. The human brain has proved to be remarkably plastic, responding with comparable strength to interventions that address both chemistry (e.g., medicine) and meaning (e.g., psychoeducation).

Despite our progress in developing and measuring treatments, much work lies ahead. Each successful treatment also has

major limitations. Medications, for example, often fail to remove symptoms, especially negative symptoms. Psychosocial interventions can be limited as well, especially when they are given in doses too intense for processing. Furthermore, and perhaps most important, all effective treatments appear to be effective *only as long as they are actively used*. In most situations, when treatments are stopped, the patients get worse; symptoms increase, relapses become more frequent, and functional capacities begin to erode again. We do not know whether patients regress to what would have been their condition without treatment, and we will never know because studies investigating this issue would be unethical. We do know, however, that patients often get significantly worse, reminding us that all of our treatments, however powerful, are basically palliative. Drugs do not alter the biological vulnerability to schizophrenia but only mute its expression. Nor do psychosocial interventions seem to be internalized or "learned" in any lasting fashion, especially among patients with disorganized and negative symptoms.

We must continue rolling back the limitations of current treatment approaches, but we should also step back and take a longer look at what lies behind this disorder's ultimate treatment resistance. We need to look again at the pathophysiology of schizophrenia to see whether we understand it well enough or can identify it early enough to make a measurable (if not fundamental) difference in its development, presence, or elaboration into manifest illness.

Early-Course Phases and Definitions. The issues discussed here revolve around the early course of schizophrenia. The phases and terminology relevant to this period, illustrated on the left side of figure 1, are generally recognizable phenomenologically and measurable psychometrically. The notions of vulnerability and deficit processes on the right side of figure 1 are mostly theoretical at this point and are discussed in more detail below.

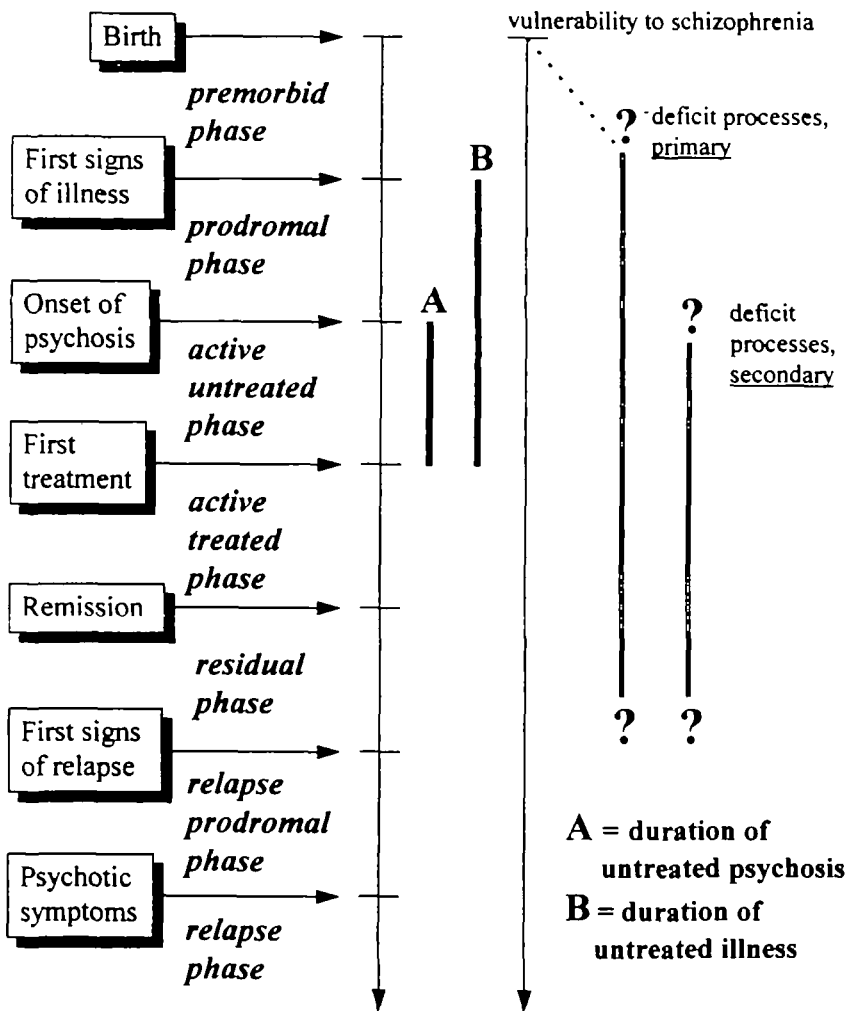
The Pathophysiology of Schizophrenia: Vulnerability to Psychosis

The original notion of vulnerability to schizophrenia is embedded in the schizophrenia spectrum concept that overt psychosis is but the tip of an iceberg of human psychotic proclivity. This notion also goes back to Kraepelin, who believed that far more people have the tendency toward psychosis than ever develop the disorder. It may be seen in milder, subclinical manifestations of the disorder; it may be seen *only upon rigorous testing* of various types; or it may not be seen at all unless psychosis intervenes.

Vulnerability: Biological Contributions.

Genetics and perinatal influence. That genetics plays a role in schizophrenia is no longer an issue. The questions now are how big a role it plays and how the schizophrenic genotype finds expression in overt disorder. One pathway to disorder may be through a genetically linked vulnerability to neurodevelopmental instability during gestation (Lewis

Figure 1. Early course of schizophrenia: Phases and definitions



and Murray 1987). This instability may result in abnormal neuroanatomy. For example, in genetically at-risk probands from the Danish High-Risk Project, computed tomography determined that cortical and cerebellar abnormalities were correlated with degree of genetic risk (Cannon et al. 1993). Instability may also be expressed as heightened risk for

neuronal damage to the developing fetus, especially in the second trimester, from any number of stresses, including influenza (Barr et al. 1990), starvation (Susser and Shang 1992), rhesus hemolytic disease (Rh incompatibility) (Hollister et al. 1996), and winter births (Dalen 1988). Such interaction may play a role in the development of schizotypal conditions as well

(Bakan and Peterson 1994).

Adolescent neurodevelopment. Another question that the genetic hypothesis must answer is why the genotypic vulnerability to schizophrenia usually does not see phenotypic expression before adolescence. Extending the above model of a genetically heightened vulnerability to aberrations of fetal neurodevelopment, the schizophrenic genotype may also result in a heightened vulnerability to aberrations of adolescent neurodevelopment. It is known, for example, that the human brain normally undergoes massive elimination of cortical-cortical synapses in adolescence, known as synaptic pruning (Hüttenlocher 1979). Recent thinking (Feinberg 1982; Hoffman and McGlashan 1993) suggests that this process goes beyond its normal developmental limits, a hypothesis supported by computer modeling of neural network synaptic pruning (Hoffman et al. 1995). Whether or not this proves to be the case, it is highly likely that a major neurobiological alteration accompanies the development of overt psychosis on the threshold of adulthood. The primary hypothesis, starting with Kraepelin, is that this development is a neurologically deteriorative one and is ultimately responsible for the chronic deficits that characterize schizophrenia of many years' duration. The indirect evidence supporting this line of thinking will be highlighted later in the discussion of pathophysiological deterioration in schizophrenia.

While the exact nature of the biological vulnerability to schizophrenia remains a mystery, its presence is certain, and careful investigations of the past two decades have demonstrated clear molecular,

chemical, anatomical, physiological, and other biological abnormalities in patients with schizophrenia and schizophrenia spectrum disorders and their relatives. These findings are reviewed in recent publications (Carpenter and Buchanan 1994), and no attempt will be made to summarize them here; however, specific biological markers of vulnerability to schizophrenia, which are potentially useful for early detection, will be elaborated in a later section.

Vulnerability: Psychosocial Contributions. Biological vulnerability is necessary for the development of psychosis but is seldom sufficient in itself. Environmental stress must usually be present as well for manifest psychosis to emerge. This is most familiar to clinicians and researchers who deal with established schizophrenia, where it is clear that social network strain, stressful life events, or high expressed emotion within the family can precipitate psychotic relapse or aggravate functional incapacity (McGlashan 1986). Likewise, efforts to buffer tensions in the living milieu have been observed to have positive effects on the course of schizophrenia (Falloon et al. 1985). Unusual stress also appears to be necessary for the fundamental development of psychosis. This has been demonstrated most convincingly in the Finnish adoption study (Tienari et al. 1985), in which *both* genetic vulnerability and stressful environment were necessary precursors to the onset of psychosis.

Vulnerability Markers Beyond Genetic Risk. While we can still only guess at the nature of vul-

nerability to schizophrenia, we do have a variety of clues that such a vulnerability is present in addition to genetic risk. Historically, markers initially emerged from (1) concurrent description of behaviors seen in the relatives of identified schizophrenia patients, (2) retrospective descriptions of behaviors displayed by identified schizophrenia patients when they were in the premorbid phase, and (3) prospective linking of candidate markers observed premorbidly and the ultimate development of schizophrenia in subjects at high genetic risk for the disorder. These first-generation markers now serve as concurrent validators for rapidly accumulating new candidates.

The current matrix of markers beyond genetic risk, some of which are listed in table 1, is ex-

tensive. Their order in the table does not imply a hierarchy of importance but reflects the history of their accumulations. Nor do all of the markers fit totally within their assigned category. Extensive reviews are available for details (Erlenmeyer-Kimling 1987; Nuechterlein et al. 1992; Kremen et al. 1994; Moldin and Erlenmeyer-Kimling 1994).

Identifying High Risk at the Population Level. Schizophrenia marker science has advanced enormously in the past two decades under the dual influence of new technology and the maturation of the high-risk studies initiated in the 1960s and 1970s. In fact, so many markers have emerged that it seems reasonable to begin thinking about using them in "normal"

Table 1. Vulnerability markers

Clinical

Cluster A personality disorders
Schizotypy in subjects, families
Psychosis proneness

Behavioral

Early neurointegrative deficits in temperament, arousal, development (pandysmaturation)
Premorbid behavioral problems: perceptual—cognitive, emotional, neuromotor, social, scholastic, functional patterns

Environmental

Perinatal factors: winter births, influenza, starvation, RH incompatibility, pregnancy and birth complications
Psychosocial stress: low socioeconomic status, unstable rearing environment, negative affective climate

Anatomy/neuroanatomy

Minor physical anomalies
Fluctuating anatomic asymmetries
Structural brain abnormalities

Chemistry

HVA in plasma and CSF of SPD
MAO in platelets of SPD

Table 1. Vulnerability markers—Continued

Motor processes
Smooth-pursuit eye movements
Visual scanning/fixation
Grip-induced muscle tension
Perceptual processes
Arousal: psychophysiology
Sustained attention: Continuous Performance Task
Selective attention: Span of Apprehension Task
Discrimination: sensory saltation
Processing: cognitive inhibition, sensory motor gating, startle, prepulse inhibition, backward masking, negative priming, event-related potentials, mismatch negativity, P300 latency
Contextual set: semantic priming, Stroop Test
Hemispheric integration/asymmetry: dichotic listening, covert visual attention
Perceptual-motor speed
Neuropsychology
Intelligence
Abstraction
Mental control/encoding
Verbal, spatial, story memory
Language
Dyslexia

Note—CSF = cerebrospinal fluid, HVA = homovanillic acid, MAO = monoamine oxidase, SPD = schizotypal personality disorder. Continuous Performance Task (Rosvold et al. 1956); Span of Apprehension Test (Asamow et al. 1991); Stroop Test (Stroop 1935).

populations to identify groups that are at heightened risk for psychoses.

Schizophrenia's prevalence is high at 1 percent (and its cost to society even higher because of its severity and chronicity), but first cases are not plentiful. For this reason, preventive technologies have not been feasible up to now. If subpopulations at high risk for schizophrenia can be identified with reasonable sensitivity and specificity, however, then much more in the way of researching prevention may be possible.

We know that a child who has a parent with schizophrenia has 10

times the risk of developing psychosis compared with another person in the population. On the other hand, 85 percent of people who develop schizophrenia have no first-degree relative with the disorder; thus, family history as a marker of risk cannot be applied to the majority of cases. Many of the markers listed in table 1 could be applied and tested over time, however, making it possible to identify a group in the normal population that is behaviorally, if not genetically, at risk for developing schizophrenia. Such a group would have a lifetime prevalence for schizophrenia higher than 1

percent. Theoretically, combining risk markers might create a hierarchical taxonomy of risk, thus maximizing the likelihood of case-ness and minimizing the risk of wasting effort and resources on false positives (Bell 1992). There have been studies looking at multiple markers such as genetic risk and smooth pursuit eye movement (SPEM) (Clementz et al. 1992); at genetic risk, schizotypal personality disorder, SPEM, and attention dysfunction (Grove et al. 1991); and at genetic risk, early neurobehavioral signs, disruptive rearing environment, and poor childhood social adjustment (Hans and Marcus 1987). Studies using multiple markers to aggregate risk for schizophrenia have yet to begin, however. Nevertheless, such a strategy is being applied to predicting behavioral maladjustment in early childhood (Sanson et al. 1991), and given the impressive number of candidate markers now available for schizophrenia, the time to try is ripe.

Finally, population-based testing for behavioral markers of risk would make it possible to study ways of treating vulnerability directly rather than palliatively, as is currently the case. We know that people with the clinical markers of schizophrenia-spectrum personality disorders seldom come to professional attention. Furthermore, when they do, their response to treatment can often be blunted and incomplete (Mehlum et al. 1991). Efforts to identify, collect, and educate subpopulations at high risk for psychotic disorders would enhance the availability of subjects with whom to study the nature of vulnerability to psychosis. Such groups would also provide a pool of potential patients for clinical re-

search in treatment targeted at vulnerability and its early phenotypic manifestations.

The Pathophysiology of Schizophrenia: The Deterioration of Psychosis

The Concept of Deterioration: Brief History. Deterioration was an integral part of Kraepelin's description and diagnosis of dementia praecox (Kraepelin 1919/1971). He wrote, "If no essential improvement intervenes, in at most two or three years after the appearance of the more striking morbid phenomena, a state of weak-mindedness will be developed which usually changes only slowly and insignificantly" (p. 210). Eugen Bleuler did not subscribe to deterioration as a diagnostic criterion of schizophrenia, but he acknowledged the presence of neural deterioration in some cases (Bleuler 1911/1950). Kraepelin, Bleuler, and other clinicians at the turn of the century described cases of deterioration in schizophrenia that were profound and even life threatening. Many feel that we no longer see such severity. Nevertheless, latter-day studies continue to describe clinical patterns in schizophrenia that may be the symptomatic expression of an underlying neurodynamic deficit process. For example, as Manfred Bleuler (1983) wrote, "Although modern treatment has caused the disappearance of severe permanent states immediately following a first acute attack, it has not succeeded in reducing the number of severely deteriorated cases from the level of 10 percent" (p. 78).

Studies of patterns of symptom progression in the early course of

schizophrenia suggest that strong affects and positive psychotic symptoms become less conspicuous with time and are replaced by more thought disorder, attention disorder, and negative symptoms (Harrow and Marengo 1986; King et al. 1990; Shtasel et al. 1992). This progression from positive to negative symptoms has also been reported in studies of schizophrenia covering many years (Ciompi 1980; Pfohl and Winokur 1982; Winokur et al. 1985; Youssef et al. 1993). McGlashan and Fenton (1992) summarized their review of this natural history as follows:

The course of positive and negative symptoms in schizophrenia is variable depending on phase of disorder. In first or early episodes, positive symptoms are frequent, negative symptoms are infrequent, and both types are unstable, fluctuating, and usually treatment responsive. In subacute/subchronic stages of the illness, negative symptoms increase in prevalence, are at least as common as positive symptoms, and fluctuate less. In the latter stages of the illness, negative symptoms are quite stable and usually dominate the clinical picture. [p. 68]

These changes are also seen in the vicissitudes of schizophrenic subtypes over time. Current schizophrenic subtypes include the classical subtypes—paranoid, disorganized, and undifferentiated—of *DSM-IV* (American Psychiatric Association 1994) and the deficit/nondeficit subtype of Carpenter et al. (1988). Recent studies (Kendler et al. 1985; Leboyer et al. 1990; Fenton and McGlashan 1991a, 1991b, 1994; McGlashan and Fenton 1993) indicate that over the early course of manifest illness, schizophrenia subtype phenomenologies remain only moder-

ately stable. When unstable, the classical subtypes tend to drift from paranoid to disorganized and undifferentiated, the deficit/nondeficit subtypes from nondeficit to deficit. Overall the thrust is toward disorganization, non-specificity, and deficit negativity. These changes have also been associated with functional decline (McGlashan and Fenton 1993) and neurological impairment (Merriam et al. 1990; Fenton and McGlashan 1994).

Deficit process changes may also be seen in declining treatment responsiveness over time. Loebel et al. (1993) entered 70 first-episode schizophrenia patients into a standard antipsychotic medication treatment protocol and measured time to remission and degree of remission for the initial episode and for any subsequent episodes. Of the patients achieving remission, 49 percent had one relapse and 13 percent had two or more. The researchers found that the mean time to response and level of outcome worsened with each psychotic episode, suggesting that treatment response deteriorates across successive psychotic episodes in recent-onset patients.

Deficit Process Timing: Endings and Beginnings. Kraepelin wrote that weak-mindedness occurs within 2 to 3 years of onset (see above quote) and that frequently "the unmistakable symptoms of dementia appear already within the first year" (Kraepelin 1919/1971, pp. 210–211). Eugen Bleuler felt that when there is deterioration it occurs within the first decade of illness if not earlier (E. Bleuler 1911/1950). More recently, Harrow and co-workers (1985) and Carone and co-workers (1991)

found that a high percentage of young schizophrenia patients had stable poor outcomes within 2½ years of index hospitalization, which was the first hospitalization for about half the sample. In fact, as McGlashan (1988) detailed in a comparison of schizophrenia followup studies across North America, it may take only 1 year of active illness for deterioration or a "threshold of chronicity" to be reached. That is, the long-term outcomes of patients whose baseline measure of illness was rated less than 1 year from onset were superior to the long-term outcomes of patients whose baseline measure of illness was taken around 1 year. Periods of illness longer than 1 year were not associated with further deterioration in long-term outcome. As schematized in figure 1, this "primary" disease process in schizophrenia (whatever it may be) appears to be most active at onset and early in its manifest course. Certainly, the risk of relapse and rehospitalization appears to be highest within 2 to 3 years of onset (Engelhardt et al. 1982; Eaton et al. 1992a, 1992b). Long-term followup studies also suggest that after 3 to 5 years illness activity reaches a plateau or even begins gradually to ameliorate (Ciompi 1980; Eaton et al. 1992a, 1992b).

Determining when the deficit process begins in schizophrenia may be more difficult. It undoubtedly is present when positive psychotic symptoms emerge at onset and most likely actively contributes to the nonspecific symptoms characteristic of the prodromal phase. If and when the process begins in the premorbid phase is more a matter of conjecture. In cases where the presentation of ill-

ness is slow, insidious, and characterized primarily by loss of function and increasing negative symptoms (Kelley et al. 1992), the process most likely starts quite early and can even evolve into disorder without prodromal or onset stages (simple schizophrenia). In most cases, however, the process probably begins shortly before the first manifest signs and symptoms of distress in the prodromal phase. Clearly, we really do not know and need to focus more research attention and resources on this question.

Deficit Processes: Quantitative Measures and Timing. Our ignorance of the timing of deficit processes in schizophrenia stems in part from a paucity of measures associated with them. Investigations in this area include quantitative measures of neuroanatomy (Woods and Yurgelun-Todd 1991; Nasrallah 1994; Lim et al. 1995; O'Donnell et al. 1995), language complexity (King et al. 1990), eye movements (Sweeney et al. 1992), and electroencephalogram wave forms of attention (P300) (Ford et al. 1995). All suggest changes in the direction of deterioration over time, usually inferred retrospectively by the degree of illness chronicity. Precious few studies have retested the same subjects over time in a progressive fashion. Those that have (King et al. 1990; Lim et al. 1995) found loss occurring over time in samples not far from onset. The pattern, though by no means clear, suggests that deficit processes are actively present early in schizophrenia and that they may be persistent in less active form or render the patient more susceptible to other forms of neuronal loss over the long term

(O'Donnell et al. 1995).

Few if any imaging studies have looked beyond anatomy to reveal or track dynamic changes. Changes in brain anatomy associated with schizophrenia tend to be small when present. Serial volumetric measurements therefore may not be the best way to track neurobiological changes. Magnetic resonance spectroscopy, which provides a window into the ongoing biochemical status of the brain, may prove more useful (Cohen et al. 1995). Changes in the phospholipids of neuronal tissue signaling anabolic versus catabolic processes may provide clues to neurodynamic developments over the periods around prodrome and onset (Keshavan et al. 1991; Hoffman and McGlashan 1993; Petegrew 1993).

Neuropsychological testing of schizophrenia patients has demonstrated significant dysfunction in virtually all cognitive dimensions, especially memory (Saykin et al. 1991, 1994). Before onset, however, schizophrenia patients generally have very mild, focal diminutions in cognitive abilities that do not interfere with functioning (Goldberg et al. 1993). This finding indicates that cognitive deficits are the neuropsychological correlates of deterioration. The decline in cognition seems to occur around onset, although further research is needed to pinpoint timing.

Neuropsychological testing suggests that cognitive decline may not continue for too long into the course of manifest illness. Table 2 summarizes recent studies of neuropsychological functioning that have attempted to track deficits over time, either by correlating neuropsychological functioning in samples of differing chronicity or

Table 2. Neuropsychological measures of deficit processes

Investigators	Samples	Measures	Changes with time
Goldstein et al. (1991)	245 chronic schizophrenia patients	Halstead-Reitan Neuropsychological Test Battery	Static. Stable correlation between cognitive deficits and length of hospitalization
Bilder et al. (1992)	51 first-episode, 50 chronic schizophrenia patients	Tests resistant and sensitive to deterioration	Progressive. Substantial deficits for both, worse for chronic sample
Goldberg et al. (1992)	66 chronic schizophrenia patients in 5 age-related cohorts, 20–70 years old	Neuropsychological battery sensitive to progressive dementia	Static. No progressive deterioration in cognitive functions
Hoff et al. (1992)	32 first-episode, <i>DSM-III-R</i> schizophreniform, 25 chronic schizophrenia patients	Neuropsychological battery, standard	Static. Substantial and similar cognitive deficits in both samples
Sweeney et al. (1992)	60 schizophrenia patients (27 first-episode)	Tests sensitive to prefrontal and left temporal function	Progressive. More severe dysfunction with more prior episodes
Andreasen (1994)	42 new-onset, 46 subchronic, 109 chronic schizophrenia patients	Neuropsychological battery, standard	Static. Dysfunction equivalent across samples
Heaton et al. (1994)	85 early-onset young, 35 early-onset old, 22 late-onset schizophrenia patients	Neuropsychological battery, standard	Static. No differences among groups or with age, age at onset, duration of illness
Davidson et al. (1995)	393 institutionalized schizophrenia patients	PANSS, Mini-Mental State Exam	Progressive. Cognitive impairment correlated with negative symptoms and age
Calev et al. (1995)	First-admission, schizophrenia	Quick Test at index, 6-month and 24-month followup	Progressive. Decline on Quick Test scores
Mockler et al. (1995)	57 chronic schizophrenia patients in 5 age cohorts	WAIS-R	Static. Intellect and memory do not markedly decline with age
Park et al. (1995)	Acutely ill schizophrenia patients	Spatial working memory	Static. Deficits independent of clinical state and comparable to chronic patients

Table 2. Neuropsychological measures of deficit processes—Continued

Investigators	Samples	Measures	Changes with time
Youssef and Waddington (1995)	41 middle-aged schizophrenia patients	Orientation, awareness, immediate recall over 10 years	Progressive. Modest loss of cognitive function later in life, especially associated with emergence of tardive dyskinesia

Note.—PANSS = Positive and Negative Syndrome Scale (Kay 1991); WAIS-R = Wechsler Adult Intelligence Scale—Revised (Wechsler 1955); Mini-Mental State Exam (Folstein et al. 1975); Quick Test (Ammons and Ammons 1962); Halstead-Reitan Neuropsychological Test Battery (Reitan and Wolfson 1985).

by testing the same sample progressively over time. Some studies have found cognitive deterioration to continue long after onset. The bulk of the evidence, however, suggests that cognitive decline halts or slows considerably shortly after onset. Goldberg and colleagues (1993) believe the evidence suggests that cognitive abilities decline at onset but stabilize shortly thereafter. Like the patterns of symptom progression, the patterns of cognitive functioning indicate that deficit processes, whatever they may be, are most active very early in the course of schizophrenia, such that most of the neurological damage is already accomplished by the time it is possible to make a valid *DSM-IV* diagnosis.

We know even less about the commencement of the cognitive decline process. It probably is active during the prodromal phase, perhaps before. If decline predates the prodromal phase, it probably is for only a short period, since cognitive functioning is generally normal in stable premorbid periods. This theory may not hold where there is a deteriorating pattern of premorbid functioning. We simply do not know, and the research to date is sparse because of

many practical limitations. Finding measures that track deterioration in progress depends on identifying cases before they become cases and guessing correctly when this unknown process begins. This constitutes an almost insurmountable challenge in the absence of clues for identifying cases at high risk for psychosis and of detection systems for monitoring prodromal signs in high-risk populations. Such research, in effect, awaits the design of effective systems for early detection and intervention.

Brain Plasticity: Are Deficit Processes Treatable?

Nature of Deficit Processes. The nature of the deficit processes first postulated by Kraepelin has eluded specification for almost a century, starting with the failure to see gross neuroanatomical deviations in the postmortem brains of schizophrenia patients. We still see through the glass darkly despite modern technology, and further basic research is an urgent necessity. Clearly, neuronal tissue or connectivity in the brain is lost. But we do not know if this loss comes from permanent changes in neuromodulatory tone (Wyatt 1995), from endogenous neurotoxic

processes such as the overtransmission of dopamine or excitatory amino acids (Lieberman et al. 1990; Sapolsky 1990), from genetically linked overpruning of cortical synapses in adolescence (Feinberg 1982; Hoffman and McGlashan 1993; Hoffman et al. 1995), or from some other process not yet conceptualized. These are referred to as primary deficit processes in figure 1.

It is also likely that, given brain plasticity, this process is quite complicated and involves not only primary neurodevelopmental/biological components (Weinberger 1987) but also reactive components that are secondary to the brain's hardware changes (illustrated in figure 1 as secondary deficit processes). Highly perseverative neural network activity associated with hallucinations and delusions, for example, could functionally truncate network complexity and result in secondary disuse atrophy of ancillary networks that underlie associative richness and depth (Hoffman and McGlashan 1993). It is also possible that negative symptoms and deficit phenomenologies represent brain changes that in part compensate for more localized pockets of neuronal overactivity associated with productive positive

symptoms. Such secondary changes are theoretically preventable by dampening positive symptoms with medication or by preserving the richness of a patient's environmental and interpersonal experience. In fact, we contend that deficit processes—possibly primary processes and certainly secondary processes—may be prevented by or respond to existing and familiar forms of treatment applied sufficiently early.

Efforts to reverse or reduce some of the cognitive deficits associated with schizophrenia include education, training, reward, and repeated practice (Green 1993; Benedict et al. 1994; Bellack 1995). Changes have been observed and measured, but their strength, persistence, and generalizability have been notably lacking. Treatment resistance appears to be the rule rather than the exception in cases of established (and especially longstanding) deficits. Again, their chronicity argues for the need to focus on the early phases of schizophrenia, either to prevent deficits or to reverse them.

Psychosocial Treatment and Deficit Processes: Historical Evidence of Efficacy. The argument that psychosocial treatments have reduced the deficits associated with schizophrenia is based on historical interpretations of the 20th-century treatment of insanity—namely on the unvalidated observation that schizophrenia has become milder since the turn of the century and that some of this decline in severity dates to the period before the introduction of somatic therapies, when the *only* changes in the care of the insane were psychosocial in nature. The theory also assumes that this change has resulted from

psychosocial manipulation and not to some unknown independent process, such as the elimination of the genetic risk for more severe cases through reduced fertility over time.

Clinicians who have noted progressively milder schizophrenia throughout the 20th century include Ødegård (1967), Grinker (1973), and Romano (1977). Those who have suggested that catatonia and hebephrenia may be disappearing include Hogarty and Gross (1966), Morrison (1974), Romano (1977), and Mahendra (1981). Manfred Bleuler noted that catastrophic schizophrenia seemed to disappear between the time his father described schizophrenia at the turn of the century (E. Bleuler 1911/1950) and the time he started conducting his own longitudinal studies in the 1930s and 1940s (M. Bleuler 1983). Catastrophic schizophrenia was the most severe subtype, characterized by abrupt onset and unremitting positive psychotic course, often ending in early death. According to Eugen Bleuler, it affected roughly 10 percent of patients diagnosed with schizophrenia. Manfred Bleuler considered the changes to be the result of better overall treatment, nursing care, and rehabilitation efforts (M. Bleuler 1983).

Cohorts of patients with progressively milder schizophrenia, or progressively better treated cohorts, were seen, for example, in serial 10-year discharge rates of schizophrenia patients over four decades at Warren State Hospital (Israel and Johnson 1956). For the decade between 1913 and 1923, 55 percent of patients were discharged within a decade of their first admission. The same rate held from 1923 to 1932, but between 1933 and 1942

the rate increased to 61 percent, and between 1943 and 1952 it was 72 percent. These changes were most likely linked to better overall psychosocial care and attention, if they were linked to treatment at all, since they occurred well before the use of neuroleptic medications. They could also have been related to electroconvulsive therapy (ECT) and insulin shock therapy, which were introduced in the middle to late 1930s. Whether or not these technologies “worked,” they were part of a revolutionary change in the concept of mental illnesses as medical disorders potentially responsive to active treatments. This radical departure from an attitude of fatalistic helplessness may have been remarkably therapeutic in itself.

Biological Treatment and Deficit Processes: Historical Evidence of Efficacy. The evidence that biological treatments (e.g., medications) have reduced the deterioration and deficits associated with schizophrenia is also historical, although it is more focused and compelling than the evidence for the success of psychosocial treatments. The data derive from the years immediately before and after the initial use of the neuroleptic chlorpromazine in the mid-1950s for treating hospitalized schizophrenia patients. Several studies were undertaken to compare the course and outcome of inpatients treated before the introduction of chlorpromazine with those treated afterward. In a highly influential paper, Wyatt (1991) reviewed 19 of these studies, focusing on those investigating predominantly first-break populations. He concluded that early intervention with a neuroleptic (i.e., using medication

in the hospital) increased the patients' odds for a better long-term course. He felt this was true even if the patients did not receive maintenance medication after their hospitalization, which was standard practice at the time.

Wyatt termed one form of investigation "mirror-image studies." These compared relapse rates and the functional outcomes of patients in the late preneuroleptic versus the early neuroleptic eras, that is, patients receiving early versus delayed treatment (most patients eventually received medication once its use became widespread). For example, Astrup and Noreik (1966) looked at two cohorts of first-episode schizophrenia admissions to Norway's Gaustad Hospital. The first cohort of 1,102 patients was admitted between 1938 and 1950 and did not receive medication while hospitalized. The second cohort of 706 patients was admitted between 1951 and 1957. Of these, 237 received treatment with neuroleptic as inpatients, but probably did not receive them after discharge. At a 5-year followup patients were rated as to degree of impairment. A rating of severe deterioration usually meant the patient remained actively psychotic with a catatonic or hebephrenic clinical picture. Of the preneuroleptic cohort, 16 percent were judged to be severely deteriorated, compared with 9 percent of the cohort receiving neuroleptic ($p = 0.003$).

A similar study by Huber et al. (1979) from Germany assessed 500 first-admission patients to the Bonn University Hospital between 1945 and 1959. Of these, 287 received neuroleptic or ECT, and 213 received neither. Twenty-year followup between 1967 and 1973

found that 28 percent of the former group had achieved complete remission, compared with 14 percent of the latter group ($p < 0.001$). Furthermore, among the somatically treated cohorts, the patients receiving neuroleptic or ECT within 1 year of onset were doing better than those receiving treatment after they had been ill longer than 1 year.

These studies suggest that Wyatt's conclusions have merit. On the other hand, they have multiple design shortcomings that render any statements tentative, at best. First, randomization was absent. Second, diagnosis was clinical and nonsystematic. Well-defined, operationalized, and reliability-tested diagnosis did not become standard research design until two decades later. Consequently, it is possible—even likely—that the introduction of a powerful new treatment broadened the diagnosis of schizophrenia (Stoll et al. 1993), resulting in postneuroleptic schizophrenia samples that contained a higher rate of milder cases compared with preneuroleptic samples. The samples were seldom described in sufficient detail to make it possible to tell whether they were comparable vis-à-vis key prognostic factors such as premorbid functioning. Third, maintenance drug treatment following discharge may have occurred in the drug-treated inpatients but not have been reported, which would make the followup differences a result of ongoing active medication rather than a lasting positive effect of inpatient medication on the long-term natural history of drug-free disorder. Fourth, one of the most frequent outcome measures was rehospitalization or relapse with rehospitalization. While easy to assess, hospitalization is a poor dependent

measure; too many variables other than clinical condition result in the decision to hospitalize. Finally, all the mirror-image studies suffer from potential cohort effects because they compare samples hospitalized at different times. The differences found between samples could well result from influences other than medication. As noted above, schizophrenia may have become progressively milder over the decades of this century for various reasons. If so, the outcome of the drug-treated groups may have been better simply because they became sick and were treated later, not because they received medication.

Opjordsmoen (1991) conducted a type of mirror-image study in which a sample of *DSM-III* (American Psychiatric Association 1980) schizophrenia and schizophreniform patients received two followups, one 10 years after first admission ($n = 41$) and another 31 years after first admission ($n = 110$). Patients were first-time-admitted delusional cases, about one-half admitted during the preneuroleptic era (1946–48, long-term group) and one-half during the postneuroleptic era (1958–61, short-term group). Roughly 50 percent of the long-term group received ECT; the rest had no somatic therapies. The majority of the short-term group received neuroleptics. Outcome was significantly worse for the long-term patients, who did not receive neuroleptics as their first treatment (most of these patients eventually received antipsychotic pharmacotherapy, but not until 6 to 9 years after index hospitalization).

Overall, the evidence accumulated by Wyatt and Opjordsmoen

suggests that treatments we use now can make a difference in the natural course of schizophrenia if they are applied early. In effect, these findings suggest that treatment can slow or blunt the process of deterioration in schizophrenia, even though we remain ignorant as to its mechanism.

Earlier Treatment and Deficit Processes: Recent Evidence of Efficacy. Considered broadly, history suggests that controlling psychotic symptoms with medication and keeping patients active interpersonally preserve brain plasticity and reduce deterioration. Both of these types of interventions were applied to patients who were clearly psychotic and had been for some time. The natural question to ask is, What if such treatments were given earlier? If deterioration occurs quite early in the course of schizophrenia, as suggested by the evidence reviewed above, earlier application of biological or psychological treatments or both should make a difference in the long-term course and outcome of the disorder. Recent studies that have looked at the duration of untreated psychosis suggest that this may indeed be the case. These studies can be divided into retrospective and prospective investigations.

Duration of untreated psychosis: Retrospective investigations. A heterogeneous collection of retrospective studies and reviews provides indirect evidence that longer duration of untreated psychosis (DUP) is associated with an inferior longitudinal course (or vice versa). Fenton and McGlashan (1987) described a subgroup of *DSM-III* schizophrenia patients ($n = 23$) from the Chestnut Lodge fol-

lowup study who, after a period of inpatient treatment, sustained good outcomes without maintenance neuroleptic medication over an average of 15 years. Compared with the rest of the schizophrenia sample ($n = 140$), the drug-free patients with good outcome had, by the time of their admission to Chestnut Lodge, been continuously psychotic for a shorter time. Coryell and Tsuang (1982) compared the long-term outcome of schizophreniform patients ($n = 83$) and schizophrenia patients ($n = 214$) from the Iowa 500 followup study who were hospitalized between 1934 and 1944. Schizophreniform patients did better than schizophrenia patients, the researchers concluded, because of the subgroup of schizophreniform patients who received somatic treatments (ECT, pentylenetetrazol, and insulin shock). Angrist and Schulz (1990) reviewed 10 studies from the 1950s in which acute and chronic schizophrenia patients received neuroleptics for the first time. In six of the studies the response to medication correlated negatively with chronicity (or duration of illness). Waddington et al. (in press) studied older longstanding schizophrenia inpatients, many of whom were admitted in the preneuroleptic era. They found initial duration of untreated psychosis (average 17 years) to be correlated with muteness at index admission.

Retrospective studies of more recent populations reflect the same bias. Lo and Lo (1977) conducted a retrospective 10-year followup of 133 schizophrenia patients in China and found outcome to be correlated positively with shorter duration of illness before the first treatment. Similar results were

found at 3-year followup for a sample of adolescent schizophrenia and schizophreniform patients ($n = 19$) from Japan (Inoue et al. 1986). Helgason (1990) conducted a 20-year followup of 107 first-treated schizophrenia patients from Iceland. One-third of the sample was admitted within 1 year of onset (early admitted), the rest after 1 year (late admitted). For 18 of the subsequent 20 years of followup, late-admitted (or long-DUP) patients underwent a higher number of readmissions. Moscarelli (1984; Moscarelli et al. 1991) studied 20 schizophrenia patients during the 3 years after treatment and found that the cost of treatment for patients with a DUP greater than 6 months was twice the cost of those with a DUP less than 6 months. Birchwood et al. (1992) examined the early course of first-episode schizophrenia patients using case-note data. The rate of relapse/rehospitalization in the first year after discharge was higher for the Afro-Caribbean patients (49%, $n = 43$) than for the Asian patients (16%, $n = 29$). Further scrutiny revealed that the duration of illness before treatment was significantly different between the two groups: For the Asians the mean was 14.7 weeks, and for the Afro-Caribbeans it was 39 weeks. Finally, Haas and colleagues (1994) studied 150 patients with *DSM-III-R* (American Psychiatric Association 1987) schizophrenia, schizophreniform, and schizoaffective disorders. If the timing of first antipsychotic medication was delayed for 2 years or longer, patients demonstrated delayed treatment response, more severe positive and negative symptoms, and more functional impairment at discharge. Premorbid psychosocial ad-

justment could not account for these findings.

Though suggestive, these studies have methodological limits. The retrospective reviews involve many samples that are quite old and unevenly characterized diagnostically and demographically. The contribution that other well-known prognostic factors make to outcome such as premorbid capacity, age at onset, and type of onset (acute vs. insidious) are frequently not partialled out or even considered. In the Fenton and McGlashan study (1987), for example, better outcomes were seen in samples with briefer prior psychosis but these samples also had better premorbid functioning. Since the latter is known to correlate with better outcome, estimating the unique contribution, if any, of briefer active psychosis is impossible.

DUP: Prospective investigations. Johnstone and colleagues (1986) studied first-episode psychotic patients who met Present State Examination (PSE/CATEGO; Wing et al. 1974) criteria for schizophrenia ($n = 253$). DUP, defined as the time from onset to admission, varied from less than 2 months (32%) to longer than 1 year (30%), despite the presence of overt and often severe symptomatic behaviors in many cases. Relapse rates over the following 2 years were significantly predicted by this duration, with the patients who had been ill longer relapsing most frequently. Furthermore, a subsample of 120 patients entered a randomized placebo-controlled trial of maintenance antipsychotic medication (Crow et al. 1986). The negative effect of longer DUP was seen in both groups. This dimension, in fact, proved to be a stronger predictor of relapse than maintenance

medication status.

Rabiner et al. (1986) assessed 1-year outcome in first-episode hospitalized patients with schizophrenia ($n = 36$) or affective disorder ($n = 19$), as determined by the Research Diagnostic Criteria (RDC; Spitzer et al. 1978a). Outcome was characterized according to standard criteria: in-episode (unremitted), remitted, or relapsed. Duration of illness (DUI) was defined as the time from first signs of noticeable change in behavior to time of baseline behavior. For the schizophrenia group DUI was 14.5 months, compared with 3.6 months for patients with affective disorder. Within the schizophrenia group, longer duration of illness was associated with poorer outcome.

A later study from the same institution (Hillside Hospital) looked at these relationships with even greater precision (Loebel et al. 1992). The study involved 70 first-episode patients diagnosed with schizophrenia or schizoaffective disorder, mostly schizophrenia, according to the RDC. Patients entered a rigorously standardized antipsychotic medication treatment protocol and were followed for 2 years. Independent variables were DUP and DUI (psychosis plus prodrome). Illness onset was ascertained by asking the patient and family members when they first observed behavioral changes that they believed were related to the patient becoming ill. Researchers ascertained psychosis onset by asking when the first psychotic symptoms were observed, after defining and explaining psychosis to all concerned. Dependent variables were time to remission and level of remission. These too were carefully defined and operationalized. Patients were evaluated biweekly

and monthly during the maintenance phase with standard rating scales, for example, The Schedule for Affective Disorders and Schizophrenia—Change Version (SADS-C; Spitzer et al. 1978b), the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), and the Clinical Global Impressions Scale (CGI; National Institute of Mental Health 1985). Remission was defined as treatment response to specified scores on each scale that persisted for at least 8 weeks. Level of remission was trichotomized to full remission (complete response with no residual symptoms), partial remission (substantial improvement but with residual positive or negative symptoms), or no remission (continued active positive symptoms).

The researchers found both independent variables to be quite long. The mean DUI proved to be 151 weeks, the mean DUP 52 weeks. DUP was significantly associated with both dependent variables: longer duration predicted greater time to remission and lower level of remission. DUI was significantly associated with level of remission in the same direction. Other prognostic variables of early course, such as premorbid functioning, age at onset, and type of onset, were tested against time to remission and found not to relate. Better premorbid functioning and later age at onset, however, were related to better levels of remission. Overall, this study demonstrated a significant and relatively unique relationship between DUI/DUP and a carefully monitored response to treatment in early schizophrenia. Additionally, these relationships appeared to be independent of other classic prognostic parameters of early course.

The prospective investigations offer two compelling observations. The first is a relationship between DUP and treatment response that appears robust and less confounded by intercorrelation with other prognostic determinants. The second is the length and consistency of DUP in contemporary clinical samples, which is astonishing given the seriousness and dangerousness of what is transpiring.

Early Detection and Intervention Programs

All the studies reviewed above have involved first-episode patients with widely varying DUPs coming to some prearranged treatment program. The relationship between DUP and treatment response is strictly correlational. In contrast, two programs in the past decade have explicitly incorporated timing in the treatment strategy in an effort to intervene as soon as possible in the course of illness. One ongoing project, (McGorry et al. 1991; McGorry 1992; Edwards et al. 1994; McGorry and Kulkarni 1994) tries to minimize DUP after onset. It is described by the authors in this issue of the *Bulletin*. The other project (Falloon 1992), which was the first to deliver treatment before illness onset, will be described here. The author (Falloon et al. 1996, this issue) offers further details about the operation of this project in a separate contribution in this issue.

Intervention in the Prodrome to Onset. Falloon (1992) designed a public health initiative to detect and treat psychosis in the prodromal phase of onset in Buckingham County, England, between 1984

and 1989. At the time, the county had a population of 35,000 people whose medical and psychiatric needs were almost entirely served by a network of 16 family practitioners organized into four group practices. Mental health teams consisting of psychiatrists, nurse therapists, and other mental health professionals were developed within each of these group practices. Very early detection of potential schizophrenia (i.e., within the prodrome before onset) was based on educating family practitioners to recognize prodromal symptoms and to refer such cases to the mental health team for assessment, early detection, and early intervention, if appropriate. Practitioners were provided with a checklist of the *DSM-III* prodromal symptoms of schizophrenia and trained in their recognition in group seminars or individual consultations.

Family practitioners referred potential cases to the mental health team, which responded within minutes or hours by conducting an immediate evaluation of the patient, usually in the patient's home in the presence of a relative or household member. Patient and caregiver discussed and completed a checklist of prodromal features. If a prodromal state was suggested, further assessment was done, including a structured diagnostic interview (PSE); a psychiatric, medical, drug, and family history; and a differential diagnosis, especially one considering other conditions that could present with the same prodromal symptoms, such as mania, acute anxiety, or atypical depression.

Referrals regarded as being in a prodromal phase were provided with an "educational seminar" within 24 hours about the early

intervention program. As Falloon (1992) wrote:

They were told that the features displayed by the patient *were possible early signs of an impending florid episode of schizophrenia*, and that the application of treatment strategies that had proven highly effective in prevention of major exacerbations in persons with established schizophrenic disorders might ameliorate the current condition. Although it was emphasized that the person's current features might be found in a range of disorders, including benign stress responses, the characteristic symptoms of schizophrenia, theories of etiology, prognosis, and effective integrated drug and psychosocial treatment methods were outlined in an informal discussion in the home . . . The high rates of remission and recovery from long-term application of effective treatment methods was emphasized, as well as the benefits that could be derived from continued support from family/friends backed up around the clock by a well-trained, committed domiciliary mental health service . . . At the completion of this education, informed consent to pursue the early intervention program was sought from patient and key caregivers. In every case this was granted with alacrity. [pp. 7-8]

The intervention then continued with home-based stress management provided by the team and including the patient and key caregiver. Major stressors were identified, and immediate coping strategies were worked out. After crisis intervention, systematic assessments were made of chronic stress and conflict, and more formal methods of problemsolving were introduced, sometimes with daily sessions. Neuroleptic medications in low doses (thioridazine or chlorpromazine, 25-100 mg daily) for short periods (seldom more than 2

weeks) were given for targeted dysfunctional or dysphoric prodromal symptoms such as sleep disturbances, agitation, muddled thinking, or preoccupation with an odd idea.

These more intensive psychosocial and pharmacotherapeutic strategies were continued until the prodromal features had remitted. Thereafter, further problem-solving skills were consolidated in regular weekly meetings "to ensure sustained stress management." Patients and caregivers were also trained to identify specific prodromal signs displayed by the patients and were taught what to do if the signs returned. Patients were assessed regularly by the mental health therapist. If they were found free of psychiatric impairment and associated disability, they were returned to the care of their family practitioner.

During the 4 years of this pilot project, the mental health teams assessed more than 1,000 adults referred for mental health consultation by the family practitioner. In total, 16 cases were observed with symptom patterns suggesting prodromal states. None of these cases had experienced previous episodes of functional psychoses. One person was identified as having an acute first episode of schizophrenia according to PSE/CATEGO criteria. She was treated as an outpatient with low-dose neuroleptic medication and stress management, and her symptoms remitted within 4 weeks. Another person developed bipolar disorder and responded quickly to thymoleptic treatment. A third experienced recurrent episodes of prodromal symptoms "characterized by a feeling that something odd is going on, and by ideas of reference that suggest

that a catastrophic event may be about to occur." This individual responded to family-based stress management, social and vocational skills training, and prophylactic thioridazine 24 mg a day, increased to between 100 and 200 mg with any recurrence of symptoms. The remaining 13 cases with prodromal symptoms "experienced full and usually rapid recovery after brief integrated intervention" (details not provided).

Falloon (1992) regarded the first patient as the only case of schizophrenia, giving an annual incidence rate of 0.75 per 100,000 total population over the study period. In contrast, an epidemiological incidence study of schizophrenia conducted by Falloon 10 years earlier in the same county, using the same diagnostic criteria, yielded an annual incidence of 7.4 per 100,000 total population.

Falloon (1992) notes the striking difference in incidence but is quick to qualify it as highly preliminary. He lists several threats to validity that appear to be relatively minor upon closer inspection: Fewer cases, for example, could result from narrower diagnostic criteria, yet the criteria applied were the same. Cases could migrate or drift out of rural Buckingham County to urban areas, yet this would likely involve established psychosis and prevalence figures rather than potential cases and incidence figures. The author notes that prodromal symptoms are not specific to schizophrenia, yet this is hardly problematic if the intervention works in most cases, including a substantial number that are on the brink of psychosis. Furthermore, while nonspecificity is a "problem," it is probably not one that will change with further naturalis-

tic study, that is, describing and counting prodromal symptoms and seeing which ones predict subsequent caseness the best. More prodromal or predictive symptoms may emerge, but they are unlikely to be any more specific. Finally, while greater specificity would be welcome, it is not a necessary precondition for intervention in the prodrome.

Falloon observes that prodromal detection and intervention programs miss insidious-onset cases that are unlikely to present prodromal symptoms. If this is true one or more such cases should have emerged during the course of this study. That this did not happen may, in turn, suggest that there was an unusual absence of new cases of schizophrenia for that area at that period of time. Such random fluctuations are entirely possible for an uncommon event like the incidence of schizophrenia in a sample such as Buckingham County that, by epidemiological standards, is small. This possibility is readily acknowledged by Falloon, who notes more than once that his findings are preliminary and require further study and replication.

Falloon's landmark study highlights the potential gains of early detection and intervention by focusing on the prodromal phase of schizophrenia. The study has major problems from a public health/epidemiological standpoint, especially Type 1 error. Nevertheless, it has proven to be innovative to the field of schizophrenia treatment by (1) taking prevention seriously and trying to intervene before the development of a full-blown syndrome; (2) demonstrating that potential patients can be identified early in the course of illness

given simple education applied in the context of a comprehensive health care system; and (3) demonstrating that existing treatments can be delivered by such a system with a far greater positive impact than initially believed (i.e., by delaying or actually preventing onset). Ultimately, it suggests that the hypothetical deteriorative process underlying psychosis may be less irreversible and resistant to intervention than has been assumed for almost a century.

The study may fundamentally alter the ethical issue of whether the risks of early detection and intervention justify the benefits. Currently, the most common strategy with early and tentative cases is to "wait and see" in order to avoid unnecessary treatment and iatrogenic stigmatization of false positive cases. Falloon's study strongly suggests that such caution and delay may be deleterious and actively pathogenic. As Falloon (1992) wrote:

Educating persons about schizophrenia and other major mental disorders appears to have considerable benefits, with very rare deleterious effects. Inevitably some persons who would not develop any significant disorder will receive stress management and drugs that they do not need. They may also worry needlessly about the possibility of developing schizophrenia in the future. Promising research on information processing suggests that we may soon be able to differentiate those persons most vulnerable to this disorder, and thereby alleviate the concern of those we have considered vulnerable solely on phenomenological grounds [Nuechterlein 1990]. This future research must estimate the relative costs and benefits of this approach, and consider whether it is an advance over waiting till persons

develop florid episodes to make accurate diagnoses and begin effective treatment. [pp. 13-14]

Early Detection and Intervention: How Compelling Is the Rationale?

Several arguments support initiatives for early detection and intervention. Some of the most compelling are the most obvious. For example, schizophrenia is sometimes severe, often chronic, and always costly. We also know that while many treatments are effective, they are also limited and palliative. The failures of today suggest a shift in perspectives for tomorrow.

We are only beginning to understand the deficit processes of schizophrenia, but they are what make the disorder so difficult to have and to treat. The irreversibilities caused by or associated with these processes provide the strongest argument for exploring prevention and for finding ways of prevention. The evidence that deficit processes are most active around the onset of schizophrenia makes focusing our attention on the early course all the more important.

The evidence that brain plasticity is retained in schizophrenia despite deficit or that deficit processes can be attenuated is promising but soft. Schizophrenia may be milder today as a result of better treatments, but we cannot make any causal connections. The link between earlier medication and better prognosis outlined by Wyatt (1991) and Opjordsmoen (1991) is compelling, but, because of the studies' retrospective focus, lack of controls, and many other meth-

odological lacunae, the data can only be considered preliminary.

Retrospective and prospective studies of first-episode patients provide an association between shorter DUP and better prognosis that is correlational but not causal. Nevertheless, the consistency of findings is striking, as is Loebel et al.'s finding that the DUP effect was not confounded by other prognostic correlates.

Actual preventive early intervention efforts are rare but provocative. Falloon's (1992) study stands out as a pioneering effort demonstrating that early detection and intervention can be done, showing how it can be done, and hinting at what it might promise. While his sample sizes are too small to dictate policy, his results are positive enough to demand replication and certainly support the rationale for early detection and intervention.

Overall, the evidence suggests, but does not demonstrate, that early intervention with known treatments can improve the natural history of schizophrenic disorders. These known treatments appear to include both biological and psychosocial interventions. The studies of untreated psychosis emphasized early treatment with medication, but Falloon's treatment in the prodromal phase was largely psychosocial in nature. Whether or not treatment affects the primary or secondary deteriorative processes in schizophrenia's early courses is unknown because such processes remain hypothetical, but there is reason to wonder and hope. For example, the evidence on timing of treatment and outcome is most tentative in retrospective studies of established schizophrenia cases. In studies of first-onset cases, how-

ever, early treatment, as a predictor of treatment response, appears to be more powerful than other prognostic covariates. If deterioration in schizophrenia is most active around onset, one would expect earlier intervention in first-episode cases to have a greater impact than later interventions in established cases. The evidence supporting early detection and intervention is not yet convincing, but it is certainly compelling enough to justify demonstration projects and further research.

Focusing attention on the early course of schizophrenia also offers the long-term possibility of advances in our understanding of the nature of schizophrenia and how to identify potential patients long before onset. The clinical silence of vulnerability to the disorder in its premorbid phase has, up to now, discouraged enthusiasm for prevention programs. The recent explosion of vulnerability markers provides a very strong argument for early detection and intervention, however, because it offers potential tools for engineering population-based risk testing and early case identification.

Finally, the studies of untreated psychosis in first-episode cases have revealed the important and unfortunate reality that people are often overtly ill with psychosis for very long periods of time before getting help. The study by Loebel et al. (1992), for example, is representative in that it found the mean lengths of untreated psychosis to be 1 year, and the mean length of total illness (prodrome plus psychosis) to be 3 years. Because deficit processes may be active during this time, and because psychosis is a potentially dangerous clinical state, such delay in case identifica-

tion and treatment represents a major public health problem. Bringing treatment more rapidly to a person who has become psychotic is in itself enough to justify early detection efforts.

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