Informed Consent in Early Psychosis Research: National Institute of Mental Health Workshop, November 15, 2000

by Robert K. Heinssen, Diana O. Perkins, Paul S. Appelbaum, and Wayne S. Fenton

Abstract

Recent research on the early detection and treatment of schizophrenia has generated significant scientific interest along with considerable controversy and debate. Because our ability to alleviate fully the symptoms and deficits of established schizophrenia is limited, the prospect of interrupting disease progression early is compelling. At the same time, in the absence of an infallible marker of disease risk, there are serious questions about the safety, feasibility, and ethics of intervention research on "at-risk" or putatively prodromal individuals. A workshop, Informed Consent in Early Psychosis Research, was convened by the National Institute of Mental Health (NIMH) on November 15, 2000, to review the results of recent research on early detection and intervention in schizophrenia. Beginning with the assumptions that (1) treatment of asymptomatic individuals with antipsychotic medication is not appropriate in research or clinical care, and (2) neither data nor clinical consensus defines optimal intervention for symptomatic at-risk individuals, workshop participants—including clinical researchers, mental health consumers and family members, bioethicists, community health care providers, and NIMH staff—systematically reviewed available data on the potential risks and benefits of alternate approaches to the management of prodromal states. Ethical issues involved in early detection and intervention studies were discussed. Workshop participants summarized information presented during the meeting into informed consent "bullets" that must be communicated to, and understood and appreciated by, potential research participants.

Keywords: Schizophrenia, psychotic disorders, informed consent, risk factors, prediction, early intervention.

***Schizophrenia Bulletin*, 27(4):571–584, 2001.**

More than ten studies conducted throughout the world in the past decade have described a delay averaging 1 to 2 years between the onset of psychosis and accurate detection, diagnosis, and initiation of treatment (McGlashan 1999). Reported associations between treatment delay and longer time to medication response (Loebel et al. 1992) and earlier relapse (Crow et al. 1986) have focused attention on duration of untreated psychosis as a potentially modifiable determinant of illness course. The provocative hypothesis that delayed treatment allows disease progression that affects long-term morbidity (Wyatt 1991), along with intriguing descriptions of catchment-based detection and prevention efforts (Falloon 1992; McGorry et al. 1996), has catalyzed a surge of scientific interest in the early detection, treatment, and prevention of schizophrenia. This interest has grown alongside recognition that despite progress in developing medications with fewer side effects, the treatment of established schizophrenia is very often inadequate to alleviate the morbidity and disability associated with chronic forms of the illness. Deficit symptoms and cognitive impairments, which appear to be the greatest determinants of disability in this disorder, remain largely beyond the reach of current treatments (Fenton and McGlashan 1994). Cures are rare, and permanent disability is still alarmingly frequent (Hegarty et al. 1994).

Scientific interest in the possibility of altering the course of schizophrenia through early intervention has generated both enthusiasm and controversy. While there is little disagreement that timely detection and treatment of those already ill with schizophrenia are important public health priorities (Lieberman and Fenton 2000), the identification and treatment of patients prior to full-blown disease onset—treatment of prodromal states—has generated significant debate (Cornblatt et al. 2001; McGlashan et al. 2001*a*; Warner 2001). Because of the relative nonspecificity of prodromal symptoms (McGorry et al. 1995), the possibility of exposing young persons who would never

Send reprint requests to Dr. R. Heinssen, Division of Mental Disorders, Behavioral Research, and AIDS, National Institute of Mental Health, 6001 Executive Boulevard, Room 6181, MSC 9625, Bethesda, MD 20892–9625; e-mail: rheinsse@mail.nih.gov.

develop schizophrenia to unnecessary and potentially harmful medications has received particular attention in both scientific (Yung and McGorry 1997; Schaffner and McGorry 2001) and popular (Goode 1999; Zimmerman 2000) press reports. Furthermore, neither empirical data nor clinical consensus defines the optimal treatment strategy for putatively at-risk patients demonstrating prodromal symptoms.

The absence of a clear-cut standard of care for at-risk patients makes further research necessary, but also creates ambiguity regarding appropriate and ethical study design. In this context, NIMH convened the Informed Consent in Early Psychosis Research workshop on November 15, 2000, to review the results of recent research on early detection and intervention in schizophrenia. Workshop participants—clinical researchers, mental health consumers and family members, bioethicists, community health care providers, and NIMH staff—were charged with reviewing available data on the potential risks and benefits of alternate approaches to the management of prodromal states. Two prime assumptions guided these deliberations. First, treatment of asymptomatic individuals through antipsychotic pharmacotherapy is not clinically appropriate. Second, in the absence of empirical guidelines or clinical consensus, the prospective participant in early psychosis research must possess the best current knowledge regarding the risks and benefits of alternative management options. Workshop participants evaluated data regarding prodromal schizophrenia definitions, psychosis risk markers, and secondary intervention efforts. For comparison, studies and approaches for early detection and intervention in other medical disorders were also reviewed. The workshop goal was to discern elements of informed consent that must be communicated to, and understood and appreciated by, potential research participants.

Characterizing Prodromal Schizophrenia

The search for at-risk variables begins by specifying the cardinal features of the disease or syndrome in question, demarcating the boundary between normal and abnormal functioning, and developing objective and reliable methods for establishing the presence of illness. Defining core clinical features using the statistical principles of sensitivity, specificity, and predictive power (Baldessarini et al. 1983) establishes a diagnostic target that anchors subsequent efforts to validate risk markers. Of equal importance are efforts to chronicle the natural history of the clinical condition, including variations in modes of onset, course, and outcome. In combination, data from diagnostic and longitudinal studies underpin the consent process in prediction research, providing answers to research participants' typical questions, such as "What do I have?" "How certain is the diagnosis?" and "What will happen if I just wait and see?"

Compared with predictive research in medical disorders such as type 1 diabetes mellitus or breast cancer, predictive research in schizophrenia is at an early stage of development. The presymptomatic pathways that lead to clinical illness are largely unknown, and definitive genetic markers await discovery. These conditions dictate a "close-in" investigative strategy that focuses on proximal determinants of the disorder. Accordingly, acute psychosis has emerged as the target of prediction efforts, as psychosis defines an important stage in the development of schizophrenia and is considered a pivotal juncture and cardinal component of active illness. An initial step in characterizing the prodromal stage of schizophrenia has been, therefore, to establish the boundary separating nonpsychotic and psychotic states.

Current definitions of psychosis emphasize disordered perception, thought, and communicatioh as characteristic features, taking into account the intensity, frequency, and duration of these phenomena. There are currently no biological, neurocognitive, or psychological tests that confirm psychotic disturbance objectively. The diagnosis is based on clinical judgments concerning unusual thought content, hallucinations, unintelligible speech, and conceptual disorganization. Various criteria have been used in early detection studies to set the psychosis threshold, including *DSM-IV* definitions of hallucinations and delusions; Brief Psychiatric Rating Scale hallucination, unusual thought content, and formal thought disorder scales; and the Comprehensive Assessment of Symptoms and History (CASH) rating scale for delusions (Andreasen et al. 1992; Yung et al. 1996; Yung et al. 1998). Recently, structured symptom assessment methods have moved toward operational definitions and rating anchors for prodromal and psychotic states, further specifying frequency and duration criteria in the process (Miller et al. 1999; Yung et al. 2000; McGlashan et al. 2001*b*). Using these revised criteria, raters have been able to reliably distinguish prodromal and nonprodromal conditions among persons seeking treatment for nonspecific forms of psychological distress (McGorry et al., submitted for publication; Miller et al., submitted for publication).

Initial efforts to chart the prepsychosis pathway have followed a retrospective research strategy. In this approach, patients diagnosed with a first episode of psychosis, or their relatives, are asked to describe any changes in behavior or mental state that preceded overt illness (Klosterkotter 1992; Hafner and Nowotney 1995; Yung and McGorry 1996*a*, 1996*b*; Hafner et al. 1999; Moller and Husby 2000). About 80 percent of patients with schizophrenia recall changes in mental status and functioning in the weeks and months preceding psychosis; on average, this transformation starts between 2 and 3 years before the onset of overt symptoms (Hafner et al. 1992; Yung et al. 1996). According to psychotic patients' reports, precursors of illness include general distress (i.e., dysphoric mood, sleep disturbance, suicidal thoughts), deficit features (i.e., social withdrawal, reduced drive, diminished emotions, deterioration in role functioning), and attenuated positive symptoms (i.e., ideas of reference, suspiciousness, thought disturbance, impaired attention/concentration, perceptual abnormalities). In perhaps 10 percent of patients, transient hallucinations precede the development of persistent psychotic symptoms by 2–3 years. Retrospective studies suggest that the earliest prodromal symptoms include negative and cognitive symptoms and that attenuated positive symptoms are later manifestations of the emerging illness (Maurer and Hafner 1995).

Risk Markers for Psychosis. Yung and colleagues (1996) were the first researchers to define putative risk criteria for psychosis. These criteria, which reflect the influence of retrospective patient reports, basic schizophrenia symptom research, and genetic risk studies, are a mixture of attenuated positive symptoms, brief intermittent psychotic states, and genetic risk for psychosis coupled with recent and dramatic loss of social and instrumental capacities. Two diagnostic interview and rating systems have been developed to assess the Australian at-risk criteria prospectively: the Comprehensive Assessment of At-Risk Mental State (Yung et al. 2000) and the Structured Interview for Prodromal Symptoms (Miller et al. 1999).

Data regarding the predictive validity of the Australian at-risk criteria are slowly emerging. In an initial sample of 33 individuals who displayed one or more risk features, 21 percent demonstrated conversion to psychosis over a 20-month observation period (Yung et al. 1996). Revised criteria were applied in a subsequent study of 49 at-risk individuals. Psychosis conversion in this cohort was 41 percent at 12 months and 50 percent at 2-year followup (Yung et al. 1998). McGorry and colleagues (2001) recently adjusted downward the latter estimate of annual conversion to psychosis, based on results from a sample of 104 prospectively followed patients. Within this sample, 35 percent developed a psychotic disorder within 1 year of the initial at-risk diagnosis. Other centers in the United States and Scandinavia are currently evaluating the Australian criteria longitudinally; preliminary results from these studies support initial findings obtained by McGorry and colleagues (see McGlashan et al. 2001*a*).

Conversion to psychosis is not the sole adverse outcome associated with the at-risk mental state. Approximately 30 percent of individuals so characterized in the Australian investigations either developed or maintained a nonpsychotic *DSM–IV* Axis I disorder in the year following initial assessment, most often in the areas of mood disturbance or disabling anxiety (Yung et al., submitted for publication). Taken together, available longitudinal data suggest that approximately two-thirds of the individuals displaying at-risk features are at imminent risk for developing a diagnosable psychiatric condition. Conversely, 29 percent do not meet criteria for a major mental illness by the end of 1 year. Ongoing research will clarify whether the conversion rates reported thus far change as a function of longer followup intervals.

Taken as a whole, these initial research efforts are encouraging and suggest that a risk state can be defined that is moderately predictive of subsequent psychotic illness. However, methodological refinements might improve the predictive power of existing diagnostic tests, such as concurrent longitudinal study of prodromal negative patients. Adding this type of clinical sample would allow researchers to calculate the sensitivity and specificity of existing risk criteria, as well as to estimate negative predictive power and the rate of incorrect classification. The value of this approach is illustrated by a recent German study of prodromal psychosis (Klosterkotter et al. 2001). In this investigation, the presence of one or more prodromal symptoms at baseline (assessed by the Bonn Scale for the Assessment of Basic Symptoms) differentiated clinic patients who did and did not subsequently develop schizophrenia (sensitivity = 0.97, specificity = 0.59, positive predictive power = 0.70, negative predictive power = 0.96). While false negative cases were rare (3%), a sizable number of supposedly prodromal positive patients did not go on to develop schizophrenia in the ensuing 10 years (false positive rate = 41%). Data such as these, generated by studies that evaluate psychosis conversion for at-risk and comparison samples simultaneously, should hasten the search for markers capable of increasing predictive power.

In all likelihood, relying solely on clinical sign and symptom assessment of prodromal symptoms will prove to be a suboptimal strategy for identifying individuals at high risk for psychosis. As with other illnesses, measurable developmental, neurocognitive, biological, familial, and epidemiological factors are likely to add to diagnostic specificity. For psychotic disorders, family and high-risk studies suggest a variety of candidate variables, including environmental risk factors such as pre- or perinatal birth complications (Verdoux et al. 1997; Geddes et al. 1999), premorbid clinical features such as poor social functioning and low IQ (Amminger et al. 1997; Davidson et al. 1999), and disturbed antisaccade performance (Thaker et al. 1998). Additional biological markers may help to distinguish persons experiencing prodromal symptoms from individuals already in the early stages of psychosis. Potential measures for this task include electrophysiological abnormalities detected by electroencephalogram, such as lack of P50 suppression (Freedman et al. 2000) and auditory P300 (Frangou et al. 1997; Blackwood 2000; Niznikiewicz et al. 2000), that indicate alterations in the processing of sensory inputs. How subjects' gender, race, ethnic, or socioeconomic status might affect the expression of early psychosis symptoms has yet to be explored, but studies of established psychiatric illness suggest that these variables account for systematic differences in phenomenology and treatment response (Adebimpe 1981; Lawson 1986; Strakowski et al. 1993). Consequently, these factors should be evaluated as further refinements of risk criteria.

Cornblatt (2001) has suggested that increased accuracy in prodromal risk assessment may be achieved by adding neurocognitive tests, as well as measures of nonspecific behavioral disturbance, to the evaluation battery. Findings from genetic high-risk studies suggest a number of neurocognitive variables that hold promise as psychosis vulnerability markers, including deficits in sustained attention, executive functioning, and working memory (Cornblatt et al. 1999; Erlenmeyer-Kimling et al. 2000). Potential behavioral markers derived from schizophrenia patients' retrospective accounts of illness progression include negative features such as depressed mood, social withdrawal, deterioration in functioning, reduced motivation, sleep disturbance, anxiety, and suspiciousness. Cornblatt and colleagues are now testing the predictive power of an expanded risk assessment battery (Australian criteria + neurocognitive measures + behavioral indicators) in the Recognition and Prevention Program (RAP) of Hillside Hospital, a longitudinal study that follows clinical samples of prodromal positive and negative adolescents, as well as normal controls. By virtue of its multivariable, multiple sample design, the RAP project embodies several methodological advances that should increase our ability to ascertain prodromal cases with greater certainty.

Early Psychosis Intervention Strategies

For any medical disorder, treatment decisions depend on multiple factors, including the severity of distress and disability from symptoms, the certainty of diagnostic tests, the empirical knowledge of the illness course, and the nature of proposed interventions, including known benefits and risks. When diagnosis is certain and the condition is known to be devastating, aggressive interventions are justified, even if discomforting side effects are a possibility. For this reason, few debate the ethics of early antipsychotic drug therapy for individuals with active psychosis: the diagnosis can be made reliably, psychotic symptoms are usually distressing and disabling, persistent psychosis is known to contribute to poorer outcome, and first episode patients typically respond well to treatment, with remission of symptoms in approximately 80 percent of cases (Robinson et al. 1999). Indeed, current practice standards advocate integrated biobehavioral treatment for first episode psychosis, an approach organized around the goal of secondary prevention.

There is less consensus regarding appropriate treatment strategies for nonpsychotic persons who meet at-risk criteria. This uncertainty relates to the early stage of prodromal psychosis research, specifically our limited ability to identify true positive cases with accuracy, or to describe the evolution of the prodrome over time. Clearly, further empirical research is needed to increase the precision of diagnostic tests, to illuminate the range of potential at-risk trajectories, and to deepen our understanding of the pathological mechanisms that produce active psychosis. These efforts are likely to increase our understanding of the clinical course and developmental processes that confer vulnerability to schizophrenia, and ultimately to lead to targeted treatment interventions that may prevent the development of this disabling disorder. In the meantime, persons with prodromal features continue to seek professional help, asking clinicians "What are my treatment options?" Data pertaining to current practice standards in the United States, coupled with results from two small-scale clinical trials from Australia, provide preliminary answers to this query.

Cornblatt reported on the treatment experience of 38 adolescents who sought help at the Hillside Hospital RAP Clinic for problems such as depression, academic decline and school refusal, social phobia, social isolation, unusual thoughts, disorganization, and bizarre behavior. Subsequent diagnostic evaluation determined that 22 of these adolescents met criteria for the psychosis at-risk mental state, although this condition was not specifically targeted for treatment. Clinic psychiatrists, who treated patients' presenting problems through conventional symptomatic approaches, prescribed a broad array of medications and psychosocial interventions, including antidepressants; anxiolytics; atypical antipsychotic agents; and individual, group, and family therapies. Six months after initial assessment, only 14 percent of the putatively prodromal patients had developed psychotic symptoms; 41 percent had achieved noticeable clinical improvement and 45 percent were stabilized and moderately improved. Although these results were obtained from a relatively short-term, unblinded, nonrandomized, and uncontrolled observational study, they raise intriguing questions about the range of interventions that should be considered in future clinical trials of preventive treatment approaches (Cornblatt 2000).

In an early prospective intervention study, Yung and colleagues (1998) evaluated the treatment response of 49 young adults who met the Australian at-risk criteria. Each individual received supportive psychological therapy for 1 year, with adjunctive antidepressant therapy for individuals who displayed depressive symptoms. Forty percent of patients converted to psychosis within 12 months of recruitment, suggesting limited efficacy for this nonspecific preventive strategy. In a subsequent controlled but unblinded trial (McGorry et al., submitted for publication), 59 at-risk individuals were randomly assigned to either supportive therapy or an enhanced treatment package that included supportive interventions, cognitive-behavioral approaches, and low-dose risperidone therapy. Treatment was provided for 6 months; outcomes were evaluated immediately following therapy and at 6-month followup. Both treatment groups registered moderate improvements on measures of anxiety, depression, and quality of life over 12 months, but short-term differences were observed in psychosis transition. Significantly fewer recipients of enhanced therapy became psychotic during the treatment period (9.7%; transition rate for supportive therapy = 35.7%), but this advantage was reduced at 6-month followup (enhanced therapy = 19.3%, supportive therapy = 35.7%). Medication adherence, however, may have influenced psychiatric outcome among patients in the enhanced therapy condition. Patients who took medication for ≥ 50 percent of the treatment period ($n = 17$) experienced fewer conversions than members of any other cohort.

Risks and Benefits of Early Identification and Treatment

Human subject issues increase in complexity as the research agenda shifts from characterization of overt illness to assessment of risk in individuals who do not exhibit cardinal features of a disease. For example, genetic testing and screening programs in Huntington's disease, breast cancer, and sickle cell disease suggest that learning one's risk status can have a powerful impact on patients and family members, causing acute anxiety, depression, and interpersonal strain (Jenkins and Conneally 1989; Croyle et al. 1997; Kash et al. 2000). Misunderstanding the implications of a positive diagnostic test can also lead to negative outcomes, including inappropriate stigmatization, discrimination in employment, and difficulties in obtaining life insurance (Motulsky 1989). Accordingly, key components of informed consent in risk assessment studies include (1) the accuracy of testing procedures, (2) the probabilistic nature of risk estimates, (3) the efficacy and availability of preventive interventions, and (4) possible psychosocial consequences for persons undergoing testing, as well as their relatives (Lerman and Croyle 1994; Nayfield 1996). In genetic testing programs, pre- and posttesting counseling sessions are recommended to communicate risk information to subjects and family members, with the goal of preserving participants' autonomy, defusing subjective distress, and using risk status data to plan lifestyle- and health-related behaviors (Marteau 1999).

By and large, the anticipated risks and benefits of research participation for persons experiencing prodromal symptoms mirror those identified in other biomedical prediction research programs (see tables 1 and 2). For example, anecdotal evidence from the Australian Personal Assessment and Crisis Evaluation (PACE) Clinics suggests

Table 1. Potential risks and benefits of identification in the putatively prodromal phase of schizophrenia

Identification risks	Identification benefits
Unnecessary anxiety or dysphoria, or both	Close monitoring of symptoms
Stigmatization or discrimination, or both, by others	Early identification of psychotic disorder
Self-stigmatization	Reduced treatment delay
Avoidance of developmentally appropriate challenges	Reduced risk of hospitalization
	Reduced risk of behaviors that are harmful or stigmatizing, or both (e.g., suicide attempts, violence, strange or bizarre responses)

Table 2. Potential risks and benefits of treatment in the putatively prodromal phase of schizophrenia

Treatment risks	Treatment benefits
Unnecessary monitoring	Reduced distress from presenting symptoms
Unnecessary medication exposure	Reduced distress from prodromal symptoms
Medication side effects	Attenuation of full-blown psychosis

that at-risk patients and their relatives exhibit a broad range of emotions following risk assessment debriefing, ranging from relief in some cases to shock and distress in others. Once learned, communicating one's risk status to others can impact social and occupational opportunities in several ways, including overt discrimination (by teachers, employers, or providers of medical insurance) as well as changed relationships with family members and friends. Self-stigma, a condition common among individuals with severe mental disorders (Corrigan and Watson, in press), presents another potential hazard to the subject's psychological and social development. Self-stigma has been related to low self-esteem, diminished self-efficacy, and abandonment of occupational goals in established schizophrenia (Link et al. 1989), and augurs poorer long-term adaptation. Avoiding or delaying normal developmental activities such as going to college, getting a job, or dating because of illness concerns can further limit the supposedly prodromal subject's psychosocial and economic opportunities.

Several strategies may mitigate the risks of anxiety, stigmatization, and lost developmental opportunities that can accompany prevention research participation. McGorry and colleagues, for example, intentionally selected the name and location of the PACE Clinics to minimize associations with serious mental illness and psychiatric treatment (Yung et al. 1996). Anecdotal evidence suggests that adolescent subjects respond positively to the low-key PACE assessment and counseling services and appreciate the anonymity provided by the nondescript clinic settings (i.e., inside an adolescent outpatient medical service or within a large shopping mall). Equally important have been assurances of subjects' confidentiality vis-à-vis schools, employers, insurance providers, and significant others. With modification, similar stigma-management strategies have been adopted at the Hillside Hospital RAP program and Yale University's Prevention through Risk Identification, Management, and Education (PRIME) Research Clinic.

Supportive, nonjudgmental interventions that combine educational, problem-solving, and relationship-building strategies are crucial in managing subjects' and relatives' adjustment to risk status information. Current at-risk investigations emphasize to potential participants and family members that prodromal features do not necessarily foreshadow serious and persistent mental illness but may relate to any number of conditions, including self-limiting stress or adjustment reactions, anxiety disorders (including posttraumatic stress disorder and obsessive-compulsive disorder), substance use, major depression, bipolar disorder, and schizophrenia. Providing sufficient time for subjects and relatives to ask questions, express concerns, and absorb information may reduce apprehension and encourage productive decision making regarding disclosure of risk status and the application of prophylactic stress management approaches, particularly those that involve curtailing normal developmental activities. In protecting minors, investigators must be wary of parents' potential overzealousness to enroll children and adolescents in clinical treatment trials, particularly if other siblings have already developed a psychotic disorder.

Foremost among the potential benefits for participating in a prodromal research study is the provision of active treatment for presenting problems and some form of ongoing monitoring of patients' prodromal symptoms. Longitudinal clinical assessment increases the probability of early detection if a psychotic disorder does emerge and ensures timely initiation of proven therapies. If other disorders develop, these are also more likely to be detected and treated expeditiously. A variety of benefits accrue from early and aggressive treatment of psychotic illness, including rapid improvement of symptoms; minimization of time lost from school or work; and minimization of aversive events such as suicide attempts, violence, and socially embarrassing behavior (McGlashan et al. 2001*a*; McGorry et al., submitted for publication). Early psychosis researchers in Australia and the United States report additional advantages to treatment at the point of psychosis transition, including increased collaboration between patients and clinicians, a diminished need for hospital-based services, and less progressive damage to peer and family networks.

Treatment Side Effects. All therapeutic interventions, whether psychosocial or pharmacological, present potential risks that must be disclosed to prospective patients. In the case of prodromal psychosis research, it has been proposed that low doses of atypical antipsychotic drugs may delay or prevent transition to psychosis among individuals meeting at-risk criteria. However, there is a dearth of empirical research concerning the safety and tolerability of atypical antipsychotics in adolescents and young adults, who are most likely to present with symptoms that meet the at-risk criteria. There are also too few data concerning the long-term effects of antipsychotic medications on the developing brain. Together, these gaps in knowledge argue in favor of conservative risk calculations.

Some evidence suggests that young people may be particularly vulnerable to neuroleptic side effects such as extrapyramidal symptoms (Keepers et al. 1983; Kumra et al. 1998; Lewis 1998), prolactin elevations (Wudarsky et al. 1999), and substantial weight gain (Kelly et al. 1998; Martin et al. 2000). Prolactin elevations are frequently associated with gynecomastia, galactorrhea, and amenorrhea. In addition, there are concerns that the decreases in estrogen and testosterone associated with elevated prolactin may lead to sexual dysfuntion (e.g., reduced libido, erectile dysfunction, anorgasmia) and loss of bone mass. The short-term consequences of weight gain may include decreased compliance (Gitlin et al. 1989), lowered self-esteem (Stunkard and Burt 1967), increased depression, and an elevated suicide risk. Obesity also has a variety of long-term health consequences, including diabetes and cardiovascular morbidity (Troiana et al. 1996). Further, the health consequences of obesity appear to increase in the young (DiPietro et al. 1994; Dietz 1998; Stevens et al. 1998). Finally, obesity is associated with considerable stigma and social costs (Wadden and Stunkard 1985) that are likely to be exacerbated during adolescence, given the importance of peer acceptance during this developmental period.

At present, we are unable to predict which neuroleptic side effects will occur for which individuals, or the time course of health or metabolic changes. There is some evidence from adult studies, however, that African Americans and members of other ethnic minority groups are at increased risk for extrapyramidal neuroleptic side effects (Lin and Finder 1983; Glazer et al. 1994; Lindamer et al. 1999). Insofar as knowledge about direct benefits of medication interventions to potential prodromal research subjects is unknown, a complete disclosure of these risks is particularly critical.

Prodromal Detection and Early Intervention Studies: Considerations for Ensuring Subjects' Informed Consent

Workshop participants summarized the empirical and clinical data presented during the meeting into informed consent "bullets." It was agreed that each of the following concepts must be understood and appreciated by individuals who are considering participation in prodromal psychosis research investigations, as well as the clinical researchers conducting the study:

1. Treatment of asymptomatic and nondistressed persons with psychotropic drugs is not warranted in clinical care or research.
2. Using structured instruments administered by trained personnel, a diagnosis of "psychosis at-risk mental state" can be made with acceptable interrater reliability. Among people who meet at-risk criteria, we are currently unable to predict who will develop a psychotic disorder and who will not.
3. Transition to psychosis is not inevitable or predetermined for individuals who meet current at-risk criteria. Data from the Australian PACE Clinic suggest that subjects meeting these criteria have an approximately 35 percent chance of developing psychosis over a 12-month period. They appear to have a 30 percent chance of developing a different psychiatric disorder and a 29 percent chance of having no diagnosable condition after 1 year.
4. At present, we do not have enough research to identify the best care or treatment for persons meeting criteria for the psychosis at-risk mental state. Investigations employing both atypical neuroleptics and cognitive-behavioral therapies are being conducted, and prospective studies of selective serotonin reuptake inhibitors are being planned. All of these options, as well as other reasonable drug and psychosocial interventions for treating subjects' presenting problems, need to be disclosed to potential subjects as potential alternative treatment options (Schaffner and McGorry 2001).
5. Participation in a research study involves specific risks and benefits for the person who meets criteria for an at-risk state. Risks include those associated with being identified as vulnerable for a disorder that may never develop (unnecessary anxiety, discrimination from others, self-imposed limitations) and, if treatment is a possibility, the risk of receiving unnecessary counseling, medications that may cause unwanted side effects, or both.
6. Consent forms should acknowledge that there are many unanswered questions regarding antipsychotic therapy for persons under the age of 25. Potential risks include the possibility of extrapyramidal symptoms, tardive dyskinesia, sexual dysfunction, significant weight gain, and long-term medical complications such as diabetes or cardiovascular morbidity.
7. Major potential benefits of research participation include the possibility of receiving early and effective treatment should a disorder develop, and the possibility that treatment could reduce distress from the prodromal or at-risk symptoms per se.
8. We do not have good data to indicate how long a person with prodromal symptoms and distress should remain in treatment. The usefulness of prescribed medications or psychosocial therapies, or both, should be reviewed at predefined intervals, with reevaluation of the cost/benefit ratio at each assessment. Medication discontinuation should likely be attempted under the supervision of a physician able to monitor for the emergence of any adverse events.

As is true for all biomedical research, informed consent for prodromal research participation is based on the assumption of subjects' competence, or the requirement that a prospective research participant be able to (1) understand relevant information, (2) appreciate the nature and consequences of participation options, (3) manipulate information rationally while making decisions, and (4) communicate a choice (Berg and Appelbaum 1999). Anecdotal evidence from Australia and the United States indicates that most at-risk subjects are competent according to these standards. There is reason to believe, however, that at least some candidates for prodromal research may not meet standards of competence because of cognitive deficits, unusual thought processes, or denial of psychiatric illness. The fact that many of the participants in prodromal psychosis research are adolescents introduces additional complexities. Some hypothesized differences between adolescent and adult decision making include responsiveness to peer pressure, altered risk perception, and a disproportionate focus on short-term risks and benefits (Scott et al. 1995). In combination, these cognitive, clinical, and developmental features call into question whether some potential participants will comprehend the probabilistic and uncertain information that relates to the at-risk diagnosis, the course of illness, and current treatment options. An important area of future investigation will be to determine the characteristics of those at-risk individuals who are competent to provide informed consent—and of those who are not.

It is important that those designing prodromal research investigations include educational methods that ensure research candidates' understanding of the study's design, the risks and benefits of participation, the differences between research participation and a personally structured plan of care, and the likely consequences of accepting or declining recruitment. Recently, Carpenter and colleagues (2000) described an informed-consent educational intervention that was designed to offset decisional capacity limitations in adults with schizophrenia. When offered extended opportunities to learn necessary information about protocol, random assignment, and placebo conditions, most subjects were able to master these concepts. Similar results have been obtained in studies using learning-based interventions to improve schizophrenia subjects' comprehension of research study information (Wirshing et al. 1998; Dunn and Jeste 2001; Dunn et al., in press). In combination, these findings suggest that consenting procedures that (1) engage potential subjects over time, (2) are sensitive to the negative impact of cognitive impairments, and (3) employ supportive instructional methods are relevant to the presumed limitations of some prodromal psychosis research participants.

Conclusions

Schizophrenia often represents a personal tragedy for those afflicted, a source of sorrow for family members, and a costly public health concern. Available interventions cannot cure this devastating disorder, but early intervention may help shift the illness trajectory from chronic disability to recovery of function. Consequently, scientific efforts to discern the earliest developmental stages of schizophrenia must move forward. The studies conducted to date represent a laudable step toward the identification of illness onset markers and the design of treatments that may prevent or delay the transition to active psychosis. Future investigations are expected to chart presymptomatic pathways with greater precision, hopefully uncovering pathogenic mechanisms that will be targeted in the coming generation of prevention studies. These studies will continue to rely on the participation of competent research subjects who must understand, appreciate, and act on the elements of informed consent presented in this report.

References

Adebimpe, V.R. Overview: White norms and psychiatric diagnosis of black patients. *American Journal of Psychiatry,* 138:279–285, 1981.

Amminger, G.P.; Resch, F.; Mutschlechner, R.; Friedrich, M.H.; and Ernst, E. Premorbid adjustment and remission of positive symptoms in first-episode psychosis. *European Child and Adolescent Psychiatry,* 6(4):212–218, 1997.

Andreasen, N.; Flaum, M.; and Arndt, S. The comprehensive assessment of schizophrenia symptoms and history (CASH): An instrument for assessing psychopathology and diagnosis. *Archives of General Psychiatry,* 49:615–623, 1992.

Baldessarini, R.J.; Finklestein, M.D.; and Arana, G.W. The predictive power of diagnostic tests and the effect of prevalence of illness. *Archives of General Psychiatry,* 40:569–573, 1983.

Berg, J.W., and Appelbaum, P.S. Subjects' capacity to consent to neurobiological research. In: Pinkus, H.A.; Lieberman, J.A.; and Ferris, S., eds. *Ethics in Psychiatric Research: A Resource Manual for Human Subjects Protection.* Washington, DC: American Psychiatric Association, 1999. pp. 81–106.

Blackwood, D. P300, a state and a trait marker in schizophrenia. *Lancet,* 355(9206):771–772, 2000.

Carpenter, W.T.; Gold, J.M.; Lahti, A.C.; Queern, C.A.; Conley, R.R.; Bartko, J.J.; Kovnick, J.; and Appelbaum, P.S. Decisional capacity for informed consent in schizophrenia research. *Archives of General Psychiatry,* 57:533–538, 2000.

Cornblatt, B. Early pharmacotherpeutic intervention in the prodromal phase of schizophrenia: Is this a good idea? *Journal of Psychotic Disorders,* 4(2):3–15, 2000.

Cornblatt, B. Predictors of schizophrenia and preventive intervention. In: Breier, A.; Tran, P.V.; Herrera, J.M.; Tollefson, G.; and Bymaster, F., eds. *Current Issues in the Psychopharmacology of Schizophrenia.* Philadelphia, PA: Lippincott, Williams & Wilkins, 2001. pp. 389–406.

Cornblatt, B.A.; Lencz, T.; and Kane, J.M. Treatment of the schizophrenia prodrome: Is it presently ethical? *Schizophrenia Research,* 51:31–38, 2001.

Cornblatt, B.; Obuchowski, M.; Roberts, S.; Pollack, S.; and Erlenmeyer-Kimling, L. Cognitive and behavioral precursors of schizophrenia. *Development and Psychopathology,* 11:487–508, 1999.

Corrigan, P.W., and Watson, A.C. The paradox of self-stigma and mental illness. *Clinical Psychology: Science and Practice,* in press.

Crow, T.J.; MacMillan, J.F.; Johnson, A.L.; and Johnstone, E.C. A randomized controlled trial of prophylactic neuroleptic treatment. *British Journal of Psychiatry,* 148:120–127, 1986.

Croyle, R.T.; Achilles, J.S.; and Lerman, C. Psychological aspects of cancer genetic testing: A research update for clinicians. *Cancer,* 80:569–575, 1997.

Davidson, M.; Reichenberg, A.; Rabinowitz, J.; Weiser, M.; Kaplan, Z.; and Mark, M. Behavioral and intellectual markers for schizophrenia in apparently healthy male adolescents. *American Journal of Psychiatry,* 156(9):1328–1335, 1999.

Dietz, W.H. Health consequences of obesity in youth: Childhood predictors of adult disease. *Pediatrics,* 101:518–525, 1998.

DiPietro, L.; Mossberg, H.O.; and Stunkard, A.J. A 40-year history of overweight children in Stockholm: Lifetime overweight, morbidity, and mortality. *International Journal of Obesity and Related Metabolic Disorders,* 18(9):585–590, 1994.

Dunn, L.B., and Jeste, D.V. Enhancing informed consent for research and treatment. *Neuropsychopharmacology,* 24(6):595–607, 2001.

Dunn, L.B.; Lindamer, L.A.; Palmer, B.W.; Schneiderman, L.J.; and Jeste, D.V. Enhancing comprehension of consent for research in older patients with psychosis: A randomized study of a novel educational strategy. *American Journal of Psychiatry,* in press.

Erlenmeyer-Kimling, L.; Rock, D.; Roberts, S.A.; Janal, M.; Kestenbaum, C.; Cornblatt, B.; Adamo, U.H.; and Gottesman, I.I. Attention, memory, and motor skills as childhood predictors of schizophrenia-related psychoses: The New York High-Risk Project. *American Journal of Psychiatry,* 157(9):1416–1422, 2000.

Falloon, I.R.H. Early intervention for first episodes of schizophrenia: A preliminary exploration. *Psychiatry,* 55:4–15, 1992.

Fenton,W.S., and McGlashan, T.H. Antecedants, symptom progression, and long-term outcome of the deficit syndrome in schizophrenia. *American Journal of Psychiatry,* 151:351–356, 1994.

Frangou, S.; Sharma, T.; Alarcon, G.; Sigmudsson, T.; Takei, N.; Binnie, C.; and Murray, R.M. The Maudsley Family Study: II. Endogenous event-related potentials in familial schizophrenia. *Schizophrenia Research,* 23(1):45–53, 1997.

Freedman, R.; Adams, C.E.; Adler, L.E.; Bickford, P.C.; Gault, J.; Harris, J.G.; Nagamoto, H.T.; Olincy, A.; Ross, R.G.; Stevens, K.E.; Waldo, M.; and Leonard, S. Inhibitory neurophysiological deficit as a phenotype for genetic investigation of schizophrenia. *American Journal of Medical Genetics,* 97(1):58–64, 2000.

Geddes, J.R.; Verdoux, H.; Takei, N.; Lawrie, S.M.; Bovet, P.; Eagles, J.M.; Heun, R.; McCreadie, R.G.; McNeil, T.F.; O'Callaghan, E.; Stober, G.; Willinger, U.; and Murray, R.M. Schizophrenia and complications of pregnancy and labor: An individual patient data meta-analysis. *Schizophrenia Bulletin,* 25(3):413–423, 1999.

Gitlin, M.J.; Cochran, S.D.; and Jamison, K.R. Maintenance lithium treatment: Side effects and compliance. *Journal of Clinical Psychiatry,* 50:127–131, 1989.

Glazer, W.M.; Morgenstern, H.; and Doucette, J. Race and tardive dyskinesia among outpatients at a CMHC. *Hospital and Community Psychiatry,* 45:38–42, 1994.

Goode, E. Doctors try a bold move against schizophrenia. *New York Times,* December 7, 1999. Section F, p. 1.

Hafner, H.; Loffler, W.; Maurer, K.; Hambrecht, M.; and an der Heiden, W. Depression, negative symptoms, social stagnation, and social decline in the early course of schizophrenia. *Acta Psychiatrica Scandinavica,* 100:105–118, 1999.

Hafner, H., and Nowotny, B. Epidemiology of early-onset schizophrenia. *European Archives of Psychiatry and Clinical Neuroscience,* 245:80–92, 1995.

Hafner, H.; Riecher-Rossler, A.; Maurer, K.; Fatkenheuer, B.; and Loffler, W. First onset and early symptomatology of schizophrenia: A chapter of epidemiological and neurobiological research into age and sex differences. *European Archives of Psychiatry and Clinical Neuroscience,* 242:109–118, 1992.

Hegarty, J.D.; Baldessarini, R.J.; Tohen, M.; Waternaux, C.; and Oepen, G. One hundred years of schizophrenia: A meta-analysis of the outcome literature. *American Journal of Psychiatry,* 151:1409–1416, 1994.

Jenkins, J.B., and Conneally, P.M. The paradigm of Huntington's disease. *American Journal of Human Genetics,* 45:169–175, 1989.

Kash, K.M.; Ortega-Verdejo, K.; Dabney, M.K.; Holland, J.C.; Miller, D.G.; and Osborne, M.P. Psychosocial aspects of cancer genetics: Women at high risk for breast and ovarian cancer. *Seminars in Surgical Oncology,* 18:333–338, 2000.

Keepers, G.A.; Clappison, V.J.; and Casey, D.E. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Archives of General Psychiatry,* 40:1113–1117, 1983.

Kelly, D.L.; Conley, R.R.; Love, R.C.; Horn, D.S.; and Ushchak, C.M. Weight gain in adolescents treated with risperdone and conventional antipsychotics over six months. *Journal of Child and Adolescent Psychopharmacology,* 8:151–159, 1998.

Klosterkotter, J. The meaning of basic symptoms for the development of schizophrenic psychoses. *Neurological Psychiatry and Brain Research,* 1:30–41, 1992.

Klosterkotter, J.; Hellmich, M.; Steinmeyer, E.M.; and Schultze-Lutter, F. Diagnosing schizophrenia in the initial prodromal phase. *Archives of General Psychiatry,* 58:158–164, 2001.

Kumra, S.; Jacobsen, L.K.; Lenane, M.; Smith, A.; Lee, P.; Malanga, C.J.; Karp, B.I.; Hamburger, S.; and Rapoport, J.L. Case series: Spectrum of neuroleptic-induced movement disorders and extrapyramidal side effects in childhood-onset schizophrenia. *Journal of the American Academy of Child and Adolescent Psychiatry,* 37(2):221–227, 1998.

Lawson, W.B. Clinical issues in the pharmacotherapy of African-Americans. *Psychopharmacology Bulletin,* 32:275–281, 1986.

Lerman, C., and Croyle, R. Psychological issues in genetic testing for breast cancer susceptibility. *Archives of Internal Medicine,* 154:609–616, 1994.

Lewis, R. Typical and atypical antipsychotics in adolescent schizophrenia: Efficacy, tolerability and differential sensitivity to extrapyramidal symptoms. *Canadian Journal of Psychiatry,* 43:596–604, 1998.

Lieberman, J.A., and Fenton, W.S. Delayed detection of psychosis: Causes, consequences and effect on public health. *American Journal of Psychiatry,* 157:1727–1730, 2000.

Lin, K.M., and Finder, E. Neuroleptic dosage for Asians. *American Journal of Psychiatry,* 140: 490–491, 1983.

Lindamer, L.; Lacro, J.P.; and Jeste, D.V. Relationship of ethnicity to the effects of antipsychotic medication. In: Herrera, J.M.; Lawson, W.B.; and Sramek, J.J., eds. *Cross Cultural Psychiatry.* West Sussex, U.K.: John Wiley and Sons, 1999. pp. 193–203.

Link, B.G.; Cullen, F.T.; Struening, E.L.; Shrout, P.E.; and Dohrenwend, B.P. A modified labeling theory approach to mental disorders: An empirical assessment. *American Sociological Review,* 54:400–423, 1989.

Loebel, A.D.; Lieberman, J.A.; Alvir, J.M.; Mayerhoff, D.I.; Geisler, S.H.; and Szmanski, S.R. Duration of psychosis and outcome in first episode schizophrenia. *American Journal of Psychiatry,* 149:1183–1188, 1992.

Marteau, T.M. Communicating genetic risk information. *British Medical Bulletin,* 55:414–428, 1999.

Martin, A.; Landan, J.; Leebens, P.; Ulizio, K.; Cicchetti, D.; Scahill, L.; and Leckman, J.F. Risperidone-associated weight gain in children and adolescents: A retrospective chart review. *Journal of Child and Adolescent Psychopharmacology,* 10:259–268, 2000.

Maurer, K., and Hafner, H. Methodological aspects of onset assessment in schizophrenia. *Schizophrenia Research,* 15(3):265–276, 1995.

McGlashan, T.H. Duration of untreated psychosis in first episode schizophrenia: Marker or determinant of course. *Biological Psychiatry,* 46:899–907, 1999.

McGlashan, T.H.; Miller, T.J.; and Woods, S.W. Pre-onset detection and intervention research in schizophrenic psychoses: Current estimates of benefit and risk. *Schizophrenia Bulletin,* 27(4):563–570, 2001*a*.

McGlashan, T.H.; Miller, T.J.; Woods, S.W.; Hoffman, R.E.; and Davidson, L. Instrument for the assessment of prodromal symptoms and states. In: Miller, T.; Mednick, S.A.; McGlashan, T.H.; Libiger, J.; and Johannessen, J.O., eds. *Early Intervention in Psychotic Disorders.* Dordrecht, Netherlands: Kluwer Academic Publishers, 2001*b*. pp. 135–149.

McGorry, P.D.; Edwards, J.; Mihalopolous, C.; Harrigan, S.M.; and Jackson, H.J. EPPIC: An evolving system of early detection and optimal management. *Schizophrenia Bulletin,* 22(2):305–326, 1996.

McGorry, P.D.; McFarlane, C.; Patton, G.C.; Bell, R.; Hibbert, M.E.; Jackson, H.J.; and Bowes, G. The prevalence of prodromal features of schizophrenia in adolescence: A preliminary survey. *Acta Psychiatrica Scandinavica,* 92:241–249, 1995.

McGorry, P.D.; Phillips, L.J.; Yung, A.R.; and Yuen, H.P. Predictors of psychosis: Identifying young people at risk. *Schizophrenia Research,* 49(Suppl 1):6, 2001.

McGorry, P.D.; Yung, A.R.; Phillips, L.J.; Yuen, H.P.; Francey, S.; Cosgrave, E.M.; Germano, D.; Bravin, J.; Adlard, S.; McDonald, A.; Blair, A.; and Jackson, H.J. Can first episode psychosis be delayed or prevented? A randomized controlled trial of interventions during the prepsychotic phase of schizophrenia and related psychoses. Submitted for publication.

Miller, T.J.; McGlashan, T.H.; Rosen, J.L.; Somjee, L.; Markovich, P.J.; Stein, K.; and Woods, S.W. Prospective diagnosis of the prodrome for schizophrenia: Preliminary evidence of interrater reliability and predictive validity using the Structured Interview for Prodromal States (SIPS). Submitted for publication.

Miller, T.J.; McGlashan, T.H.; Woods, S.W.; Stein, K.; Driesen, N.; Corcoran, C.M.; Hoffman, R.; and Davidson, L. Symptom assessment in schizophrenic prodromal states. *Psychiatric Quarterly*, 70:273–287, 1999.

Moller, P., and Husby, R. The initial prodrome in schizophrenia: Searching for naturalistic core dimensions of experience and behavior. *Schizophrenia Bulletin*, 26(1):217–232, 2000.

Motulsky, G. Societal problems in human and medical genetics. *Genome*, 31:870–875, 1989.

Nayfield, S.G. Ethical and scientific considerations for chemoprevention research in cohorts at genetic risk for breast cancer. *Journal of Cellular Biochemistry*, 25(Suppl):123–130, 1996.

Niznikiewicz, M.A.; Voglmaier, M.M.; Shenton, M.E.; Dickey, C.C.; Seidman, L.J.; Teh, E.; Van Rhoads, R.; and McCarley, R.W. Lateralized P3 deficit in schizotypal personality disorder. *Biological Psychiatry*, 48(7):702–705, 2000.

Robinson, D.G.; Woerner, M.G.; Alvir, J.M.; Geisler, S.; Koreen, A.; Sheitman, B.; Chakos, M.; Mayerhoff, D.; Bilder, R.; Goldman, R.; and Lieberman, J.A. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, 156(4):544–549, 1999.

Schaffner, K.F., and McGorry, P.D. Preventing severe mental illness: New prospects and ethical challenges. *Schizophrenia Research*, 51:3–15, 2001.

Scott, E.S.; Reppucci, N.D.; and Woolard, J.L. Evaluating adolescent decision making in legal contexts. *Law and Human Behavior*, 19:221–244, 1995.

Stevens, J.; Cai, J.; Pamuk, E.R.; Williamson, D.F.; Thun, M.J.; and Wood, J.L. The effect of age on the association between body-mass index and mortality. *New England Journal of Medicine*, 338(1):1–7, 1998.

Strakowski, S.M; Shelton, R.C.; and Kolbrener, M.L. The effects of race and comorbidity on clinical diagnosis in patients with psychosis. *Journal of Clinical Psychiatry*, 54:96–102, 1993.

Stunkard, A., and Burt, V. Obesity and the body image: II. Age at onset of disturbances in the body image. *American Journal of Psychiatry*, 123(11):1443–1447, 1967.

Thaker, G.K.; Ross, D.E.; Cassady, S.L.; Adami, H.M.; LaPorte, D.; Medoff, D.R.; and Lahti, A. Smooth pursuit eye movements to extraretinal motion signals: Deficits in relatives of patients with schizophrenia. *Archives of General Psychiatry*, 55(9):830–836, 1998.

Troiana, R.D.; Frongello, E.A.J.; Sobal, J.; and Levitsky, D.A. The relationship between body weight and mortality: A quantitative analysis of combined information from existing studies. *International Journal of Obesity and Related Metabolic Disorders*, 20:63–65, 1996.

Verdoux, H.; Geddes, J.R.; Takei, N.; Lawrie, S.M.; Bovet, P.; Eagles, J.M.; Heun, R.; McCreadie, R.G.; McNeil, T.F.; O'Callaghan, E.; Stober, G.; Willinger, M.U.; Wright, P.; and Murray, R.M. Obstetric complications and age at onset in schizophrenia: An international collaborative meta-analysis of individual patient data. *American Journal of Psychiatry*, 154(9):1220–1227, 1997.

Wadden, T.A., and Stunkard, A.J. Social and psychological consequences of obesity. *Annals of Internal Medicine*, 103(6):1062–1067, 1985.

Warner, R. The prevention of schizophrenia: What interventions are safe and effective? *Schizophrenia Bulletin*, 27(4):551–562, 2001.

Wirshing, D.A.; Wirshing, W.C.; Marder, S.R.; Liberman, R.P.; and Mintz, J. Informed consent: Assessment of comprehension. *American Journal of Psychiatry*, 155:1508–1511, 1998.

Wudarsky, M.; Nicolson, R.; Hamburger, S.D.; Spechler, L.; Gochman, P.; Bedwell, J.; Lenane, M.C.; and Rapoport, J.L. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *Journal of Child and Adolescent Psychopharmacology*, 9(4):239–245, 1999.

Wyatt, R.J. Neuroleptics and the natural course of schizophrenia. *Schizophrenia Bulletin*, 17(2):325–351, 1991.

Yung, A.R., and McGorry, P.D. The initial prodrome in psychosis: Descriptive and qualitative aspects. *Australian and New Zealand Journal of Psychiatry*, 30(5):587–599, 1996*a*.

Yung, A.R., and McGorry, P.D. The prodromal phase of first-episode psychosis: Past and current conceptualizations. *Schizophrenia Bulletin*, 22(2):353–370, 1996*b*.

Yung, A.R., and McGorry, P.D. Is pre-psychotic intervention realistic in schizophrenia and related disorders? *Australian and New Zealand Journal of Psychiatry*, 31:806–807, 1997.

Yung, A.R.; McGorry, P.D.; McFarlane, C.A.; Jackson, H.J.; Patton, G.C.; and Rakkar, A. Monitoring and care of young people at incipient risk of psychosis. *Schizophrenia Bulletin*, 22(2):283–303, 1996.

Yung, A.R.; Phillips, L.J.; McGorry, P.D.; Hallgren, M.A.; McFarlane, C.A.; Jackson, H.J.; Francey, S.; and Patton, G.C. Can we predict onset of first episode psychosis in a high risk group? *International Clinical Psychopharmacology*, 13(Suppl 1):S23–S30, 1998.

Yung, A.R.; Phillips, L.J.; McGorry, P.D.; Ward, J.L.; Pitman, K.; and Thompson, K. *Comprehensive Assessment of At-Risk Mental States (CAARMS).* Melbourne, Australia: University of Melbourne, 2000.

Yung, A.R.; Phillips, L.J.; Yuen, H.P.; and McGorry, P.D. Risk factors for psychosis: I. Psychopathology and clinical features. Submitted for publication.

Zimmerman, R. Radical study on schizophrenia may be expanded: Tests would seek to find out if drugs can prevent illness. *Wall Street Journal, Europe,* July 27, 2000. p. 13

The Authors

Robert K. Heinssen, Ph.D., is Chief, Psychotic Disorders Research Program, and Wayne S. Fenton, M.D., is Deputy Director of Clinical Affairs, Division of Mental Disorders, Behavioral Research, and AIDS, National Institute of Mental Health, Bethesda, MD. Diana O. Perkins, M.D., M.P.H., is Director, Schizophrenia Treatment and Evaluation Program, University of North Carolina (UNC), Chapel Hill, NC; and Associate Professor of Psychiatry, UNC School of Medicine. Paul S. Appelbaum, M.D., is A.F. Zeleznik Professor and Chair, Department of Psychiatry, and Director, Law and Psychiatry Program, University of Massachusetts Medical School, Worcester, MA.

Appendix 1
NIMH Workshop on Informed Consent In Early Psychosis Research, 11/15/2000

PARTICIPANTS

Victor Adebimpe, M.D.
Mercy Providence Hospital
Pittsburgh, PA

Robin Alise Bhaerman-Dillner
George Washington University
Washington, DC

Patrick Corrigan, Psy.D.
University of Chicago
Tinley Park, IL

Barbara Cornblatt, Ph.D.
Hillside Hospital/RAP Clinic
New Hyde Park, NY

Rex W. Cowdry, M.D.
National Alliance for the Mentally Ill
Arlington, VA

Bruce N. Cuthbert, Ph.D.
DMDBA/NIMH
Bethesda, MD

Steven DeKosky, M.D.
University of Pittsburgh
Pittsburgh, PA

Laura Lee Hall, Ph.D.
Office of the Director/NIMH
Bethesda, MD

Kimberly Hoagwood, Ph.D.
DSIR/NIMH
Bethesda, MD

John Hsiao, M.D.
DSIR/NIMH
Bethesda, MD

Dilip V. Jeste, M.D.
VA Medical Center
San Diego, CA

Kathryn Kash, Ph.D.
Beth Israel Cancer Center
New York, NY

William B. Lawson, M.D.
Howard University College of Medicine
Washington, DC

Jeffrey Lieberman, M.D.
National Advisory Mental Health Council
University of North Carolina at Chapel Hill
Chapel Hill, NC

Thomas H. McGlashan, M.D.
Yale University School of Medicine
New Haven, CT

James McNulty
National Advisory Mental Health Council
National Alliance for the Mentally Ill
Arlington, VA

Susan G. Nayfield, M.D., M.Sc.
National Cancer Institute
Bethesda, MD

Libby Pedrazzani
University of Maryland IRB
Cockeysville, MD

Lisa Phillips, Ph.D.
PACE Clinic
Parkville, Victoria, Australia

Kenneth Schaffner, M.D., Ph.D.
George Washington University
Washington, DC

David Shore, M.D.
OD/NIMH
Bethesda, MD

Lin Sikich, M.D.
University of North Carolina at Chapel Hill
Chapel Hill, NC

Susan Vogel-Scibilia, M.D.
Beaver County Psychiatric Services
Beaver, PA

Richard J. Wyatt, M.D.
Neuropsychiatry Branch/NIMH
Bethesda, MD

OBSERVERS

Paul J. Andreason, M.D.
Food and Drug Administration
Rockville, MD

Alan Breier, M.D.
Lilly Corporate Center
Indianapolis, IN

Albert Derivan, M.D.
Janssen Research Foundation
Titusville, NJ

Diane Gooding, Ph.D.
University of Wisconsin
Madison, WI

Professor Gerald Hogarty
University of Pittsburgh
Pittsburgh, PA

Michael Kozak, Ph.D.
Center for Scientific Review
Bethesda, MD

Todd Lencz, Ph.D.
Hillside Hospital/RAP Clinic
New Hyde Park, NY

Stephen Lopez, Ph.D.
University of California at Los Angeles
Los Angeles, CA

Franklin G. Miller, Ph.D.
NIH Department of Clinical Bioethics
Bethesda, MD

Tandy Miller, Ph.D.
Yale University School of Medicine
New Haven, CT

Margaret Moline, Ph.D.
NY Presbyterian/Cornell Medical Center
White Plains, NY

Richard L. O'Sullivan, M.D.
Pfizer Inc.
New York, NY

Elyse I. Summers, J.D.
Office for Human Research Protections
Rockville, MD 20892

Scott Woods, M.D.
Yale University School of Medicine
New Haven, CT