Commentary:
The Schizophrenia Prodrome:
A High-Risk Concept

by Alison R. Yung

The past decade has seen the beginning and subsequent burgeoning of "prodromal" or "prepsychotic" research in schizophrenia and related disorders. The idea was originally formulated and trialed in a population-based manner by Falloon, with a project that encouraged general practitioners in the English county of Buckinghamshire to refer patients suspected of having a "schizophrenic prodrome" to a mental health service for treatment. A reduction in incidence of first episode schizophrenia compared with historical figures was found and cited as possible evidence for the effectiveness of such targeted preventive intervention (Falloon 1992, 2000). Falloon acknowledged methodological difficulties with this approach and the fact that some people not actually at risk of schizophrenia would have been unnecessarily labeled and treated. However, this study opened the way for early intervention strategies in psychosis to consider the prodromal phase as a potential focus for treatment. The first "prepsychosis" clinical and research center, the Personal Assessment and Crisis Evaluation (PACE) Clinic, was established in Melbourne, Australia, in 1994 (Yung et al. 1995, 1996). Its history and development are described in this issue (McGorry et al., this issue). There are now similar services worldwide (McGorry et al., this issue). This issue of Schizophrenia Bulletin highlights the level of interest in the area. There are contributions from a diverse range of backgrounds: clinical psychiatry and psychology, neuroimaging, neurochemistry, neuropyschology, and epidemiology. Most focus on the prediction of onset of schizophrenia and related psychotic disorders for one of two, or possibly both, purposes: (1) understanding the process of onset and (2) intervening prior to psychosis onset during the putatively prodromal phase. This latter aim is termed "indicated prevention" (Mrazek and Haggerty 1994), as it involves treatment of a person prior to a full threshold syndrome developing (see McGorry et al. [this issue] for detailed explanation of indicated prevention as it applies to "Ultra High-Risk" [UHR] or "prodromal" research). Thus, this field of research is highly significant from both a scientific and practical clinical perspective.

There is now some evidence that suggests that the prevention of, or at least the ability to delay or ameliorate, the onset of a full-blown psychotic disorder is becoming possible, as is the aim of indicated prevention. The role of late neurobiological changes, around the time of onset of the prodrome and its transition to frank psychosis, is discussed by Cannon et al. (this issue) and the literature around medial temporal lobe dysfunction as a vulnerability indicator for schizophrenia is extensively reviewed by Seidman et al. (this issue). Wood et al. (this issue) examine the issue of brain chemistry changes in those at high risk of schizophrenia. One important finding from neurosciences research is that the process of onset of psychotic disorder seems to be associated with brain changes. A sample of individuals meeting UHR criteria (McGorry et al., this issue; Yung et al. 2003, in press) (i.e., who were considered to be at high risk for first onset of psychosis within a brief time period or "putatively prodromal") underwent structural MRI brain scans. A subsample of these young people became psychotic during the 12-month followup period. Reduced gray matter in right temporal areas at baseline was found in those who did develop psychosis compared with those who did not. In addition, subjects with psychosis who were rescanned after psychosis onset had evidence of ongoing neurobiological changes. Thus, it appears that at some point in transition from prodromal state to psychotic disorder, alterations in brain structure (and presumably function) occur (Pantelis et al. 2003).

Further evidence for the importance of the prodromal phase and its relevance to outcome comes from the work of Keshavan et al. (this issue). They studied the relationship between duration of untreated illness, including the prodromal phase, and outcome in a sample of 104 first episode psychosis patients. They found that illness duration was significantly associated with 2-year outcome. This measure of illness duration, which included the prodrome, was a more robust predictor than duration of untreated psychosis alone, thus the duration of prodromal

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phase may contribute to prognosis. The authors cautiously suggest that this may be a causal relationship. It is unclear whether this might occur through a neurobiological or psychosocial mechanism or both. (However, the alternative or possibly additional explanation is that the relationship may be due to psychoses of insidious onset—and therefore associated with prolonged prodromes—being intrinsically linked to poor prognosis).

A number of issues linking clinical status and brain structure and function remain unclear. When do the brain changes occur during the process of psychosis onset? Are they irreversible, or can they be arrested or modified with intervention? Is there a point prior to which these brain changes can be averted, but a critical time after which it is too late and full-blown psychotic disorder inevitable? Or are the changes on a continuum? What is the underlying cause or causes of the brain changes? Do the brain changes cause the symptomatic worsening, particularly of positive symptoms, or vice versa, or is there an interaction effect—worsening positive symptoms result in brain abnormalities, which result in increased positive symptoms, and so on. Could this “vicious circle” be interrupted by interventions? And if so, what interventions?

To date, the only published clinical trials conducted in the UHR population have used antipsychotic medication. The first, by McGorry et al. (2002), was a randomized controlled trial of combined intensive cognitive therapy plus low-dose risperidone compared with a treatment as usual (supportive case management) arm. At the end of the 6-month treatment phase, significantly more subjects in the treatment as usual group had developed an acute psychosis than in the intervention group \( (p = 0.026) \). This difference was no longer significant at the end of a posttreatment 6-month followup period \( (p = 0.16) \), although it did remain significant for the risperidone-adherent subgroup of cases. This result suggests that it is possible to delay the onset of acute psychosis with intervention. Both groups experienced a decrease in symptoms and improved functioning over the treatment and followup phases compared with entry levels. There is currently a further intervention trial underway at PACE, which is attempting to distill out the active ingredient from the first study by separating the psychological and pharmacological treatment components. A double-blind randomized control of olanzapine in the active ingredient from the first study by separating the trial underway at PACE, which is attempting to distill out with entry levels. There is currently a further intervention.

The above discussion refers to the indicated prevention model aimed at high-risk individuals. This is contrasted with universal and selective prevention strategies, which target the whole population. These different preventive approaches are elegantly described in the article by Mojtabai et al. (this issue). This article discusses the prospect of primary prevention in schizophrenia by use of population-based interventions, such as improved prenatal care, and contrasts this with the approach of targeting high-risk or putatively prodromal individuals. Of importance, the authors of this article state that primary population-based interventions and indicated interventions are not mutually exclusive. As they conclude, preschizophrenic research such as is the subject of many of the articles in this Special Issue of Schizophrenia Bulletin is crucial in determining the place of indicated prevention within the broader context of schizophrenia prevention as a whole.

However, one disagreement I have with Mojtabai et al. (this issue) highlights some conceptual issues that need to be resolved in the area. These authors suggest that the presence of early prodromal symptoms means that an illness is already established. In fact this is not the case, and many individuals who experience what appear to be early prodromal symptoms, such as attenuated psychotic symptoms, do not develop psychotic disorders but instead have symptoms which remit or remain stable without signifi-
significant decline in function (Yung et al. 2003, in press; Miller et al., this issue). This underlines the importance of semantics in this debate: calling such symptoms “prodromal” implies inevitable progression to psychosis, but, as has been argued previously (Yung et al. 1996), psychosis is not an invariable outcome of such symptoms, and a more appropriate term is ARMS (McGorry and Singh 1995).

And hence to the focus of this commentary, which is to underline some unresolved and possibly controversial issues facing investigators in the field at present. First, the use of terminology and its implications, and second, the meaning of the UHR criteria.

**Terminology and Its Implications**

The article by McGorry et al. (this issue) discusses our use of terminology at the PACE Clinic. Young people belonging to one of three groups are said to be at Ultra High Risk (UHR) of developing full-blown psychosis within a short followup period: (1) Attenuated Psychotic Symptoms Group have experienced subthreshold, attenuated positive psychotic symptoms during the past year; (2) Brief Limited Intermittent Psychotic Symptoms Group (BLIPS) have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have been spontaneously abated; or (3) Trait and State Risk Factor Group have a first degree relative with a psychotic disorder or the identified client has a schizotypal personality disorder, and they have experienced a significant decrease in functioning during the previous year.

The UHR criteria, as the name suggests, imply that a person is at risk of developing a psychotic disorder. They define a research sample, in contrast to the term At Risk Mental State (ARMS), which defines a syndrome that may or may not develop into psychosis. A person can be experiencing an ARMS (for example, by having depressed mood, anxiety, and social isolation) but not meet UHR criteria. This is because UHR criteria are set at a high threshold in an attempt to reduce false positives. All syndromes that could possibly develop into psychosis cannot be included as UHR criteria as most precursor features for psychosis are very nonspecific (Yung and McGorry 1996). The above person may well develop schizophrenia, but he or she could also get better, develop major depression or another psychiatric disorder. The term ARMS was originally coined to counter the notion of a prospective prodrome. Such a term is an oxymoron. Prodrome is a retrospective term, which can only be used once a full-blown disorder has evolved. One cannot “diagnose” a psychotic prodrome with any certainty based on the presence of any particular symptom or combination of symptoms.

A first episode of psychosis cannot even be predicted from the presence of attenuated psychotic symptoms. Not only have these been observed to resolve or persist without deterioration, but they have also been found to be not uncommon in the general population (Eaton et al. 1991; Peters et al. 1999a, 1999b; Tien 1991; van Os et al. 2000, 2001). In the study by van Os et al. (2001), the majority of people found to have such “psychotic-like symptoms” (which consisted probably of both attenuated and frank psychotic symptoms, but the methodology was not fine-grained enough to make this distinction) in the community were not distressed by them and did not seek help. It may be that attenuated psychotic symptoms may occur and then resolve spontaneously without any treatment-seeking, may occur intermittently, perhaps in response to some stressor, or may be present chronically but without resulting in distress or help-seeking, in addition to the possibility that they may worsen and develop into a full-blown psychotic disorder. These attenuated psychotic symptoms make up a clinical syndrome that may have multiple underlying etiologies, all with different likelihoods of causing functional impairment, distress, and help-seeking. This is an area that needs ongoing investigation.

The finding of substantial numbers of people with attenuated and even frank psychotic symptoms in the general population who were seemingly not in need of care (Eaton et al. 1991; Peters et al. 1999a, 1999b; Tien 1991; van Os et al. 2000, 2001) also has implications for how we think of and define “psychosis” and “psychotic disorder.” Does the mere presence of a psychotic symptom mean that the person has a psychotic disorder? Should people with psychotic symptoms who are not disabled or distressed by their symptoms be considered to have a disorder? Or should disorder only be diagnosed in the presence of impaired functioning, disability, help-seeking, and/or distress? The level of intensity of psychotic symptoms, their frequency, and duration also need to be factored into the definition. Is there an absolute level of intensity, frequency, and duration of symptoms considered to be at a psychotic threshold? Or should different levels of symptoms be applied depending on variables such as distress and disability? Other parameters that could be included in a definition of “psychotic disorder” include presence or absence of and degree of comorbidity with other psychiatric syndromes such as depression, and level of suicidality, and dangerousness. Such lack of clarity around basic questions is reflected in the differing end points used by a number of “UHR,” “prepsychotic,” and “prodromal” clinics. (My liberal use of quotation marks is intended to emphasize the problems with terminology in this field.) The articles by McGorry et al., Miller et al., and Lencz et al. (all this issue) illustrate this, and table 2 in Miller et al. (this issue) demonstrates some of the differences between the PRIME group definition of psychosis and our definition in the PACE Clinic. At this stage, at the PACE Clinic, we have chosen to operationalize a definition of psychosis based on...
the presence of clear-cut threshold level psychotic symptoms (delusions, hallucinations, and formal thought disorder) occurring several times per week for at least 1 week in a help-seeking population. This threshold is essentially that which neuroleptic medication would be commenced in common clinical practice and was developed via local consensus of PACE and Early Psychosis Prevention and Intervention Centre (EPPIC, Melbourne, Australia) psychiatrists (McGorry et al. 1996). This definition of onset of psychosis is of course somewhat arbitrary, but it does at least have clear treatment implications and applies equally well to substance-related symptoms, symptoms that have a mood component—either depression or mania—and schizophrenia spectrum disorders. However, it does not include a requirement of functional impairment or decline. This is an area currently under consideration in our Clinic. This highlights the arbitrariness of any operational definition, which is inherently open to error, and emphasizes that all such definitions must continually be reviewed.

Another area of unclear semantics is in reference to “psychosis,” “psychotic disorder,” and “schizophrenia,” none of which are synonymous for each other. Many centers, PACE and PRIME included, have chosen a first onset of “psychosis” as a meaningful end point, without the requirement of threshold criteria for schizophrenia being met. This is because the first episode of positive symptoms is an important stage in the development of schizophrenia (Heinssen et al. 2001). It also represents a broad and proximal target. Some patients with a first episode of psychosis will develop schizophrenia, but it is often unclear at the time of the first psychotic episode whether this will eventually or not (McGorry, this issue). This does create some problems in the area, however, as some patients will have vulnerability markers for schizophrenia, but not make the transition to psychosis within a study’s followup time frame, while others will not have the markers but will develop a first episode.

The Meaning of the Ultra High-Risk Criteria

The UHR criteria were developed empirically. From our clinical features and patterns of the prodrome and onset phase prior to a first psychotic episode (Hafner et al. 1992, 1993; Yung and McGorry 1996), as well as the high-risk literature in schizophrenia (Chapman and Chapman 1987; Mednick et al. 1987; Asarnow 1988; Comblatt et al. 1998; Erlenmeyer-Kimling et al. 2000), we constructed three heterogenous groups that we suspected would show high transition rates to frank psychosis within a brief time period. This hypothesis was tested in a prospective followup study (Yung et al. 2003). A high transition rate to full-blown psychosis of nearly 41 percent of a sample of 49 subjects was found. However, this first study was undertaken in a small sample, and we welcomed the criteria being adopted and adapted at other sites for further investigation. Similar transition rates have been found in other sites, as reported in this issue of Schizophrenia Bulletin. For example, 7 of 14 (50%) patients meeting the SIPS criteria in the PRIME study developed psychosis within 1 year (Miller et al, this issue). However, the population from which subjects are drawn is likely to affect the predictive validity of the criteria. As Mojtabai et al. (this issue) and Maier et al. (this issue) emphasize in their articles, as the prevalence of a disorder decreases, the positive predictive value decreases also. This is a basic epidemiological fact, the importance of which must be stressed when debating the use of the UHR criteria. Thus, if the same criteria were applied to a general population or school setting and those defined as UHR followed up for a year, the transition rate to full-blown psychosis would be much less than 41 percent. Thus, the criteria need to be continually evaluated, and the population from which subjects are drawn taken into consideration.

Additionally, the UHR criterion of help-seeking must be highlighted. The UHR criteria in the original study, and all subsequent studies in the PACE Clinic, were applied to a help-seeking population. That is, the young people, or others close to them, recognized that they were having problems and referred them to a service for care. They were sufficiently disturbed or distressed to warrant some kind of clinical attention, for example from a general practitioner or family doctor, a counseling service, or even a mental health service, from whence they were referred to the PACE Clinic. The UHR criteria have not been evaluated in a non-help-seeking population. We do not know what the transition rate to psychosis would be in non-help seekers who otherwise meet the criteria. This is particularly pertinent in the light of the population studies cited above (Eaton et al. 1991; Peters et al. 1999a, 1999b; Tien 1991; van Os et al. 2000, 2001), which found large numbers of people with attenuated psychotic symptoms and “psychotic like experiences.”

Finally, the UHR criteria and other “prodromal” concepts should not be reified into a new clinical entity. There is a possibility that this will occur, and that a disease model will be applied to what is essentially a heterogeneous group of people with variable degrees of risk of developing psychotic symptoms of arbitrarily defined duration, frequency, and intensity with variable degrees of associated disability and comorbidity. The danger is that whenever the particular UHR syndromes are seen in a young person (no matter how and where they are noticed), well-meaning clinicians will “diagnose” an “at risk mental
state” or “prodrome” and start some form of intervention. Although treatment may be indicated on clinical grounds at an individual patient’s level, the codifying of such a syndrome, for example into a system like the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association 1987, 1994) is not justified at our present state of knowledge. The UHR criteria should be seen as a “work in progress” in need of continual evaluation and reflection.

Conclusion

As several of the articles in this Special Issue point out (Maier et al.; Kane et al.; Heinssen et al.), there is much still to be learned in the ultra high-risk area, and research is proceeding slowly, hampered by small sample sizes and lack of multisite studies (Maier et al., this issue; Heinssen et al., this issue). As Heinssen (this issue) opines, there is a case for linking prodromal and early psychosis studies and for broadening the scope of prodromal research beyond schizophrenia to other major mental disorders as well, as is occurring in Melbourne via a broad youth mental health strategy. There is also the need to link targeted UHR studies with epidemiological studies that can examine both endophenotypic markers for a range of disorders and clinical indicators such as subthreshold syndromes, including attenuated psychotic symptoms. There is clearly now momentum behind the idea of UHR or “prodromal” research, which we hope can be matched with appropriate funding for furthering the research agenda. This Special Issue of Schizophrenia Bulletin has made a valuable contribution to summarizing the present knowledge in the field and laying the groundwork for further projects. I thank the Editors for inviting me to submit this commentary.

References


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