Editors’ Introduction: New Frontiers in Prodromal Research

by Barbara A. Cornblatt, Robert K. Heinssen, Tyrone D. Cannon, and Todd Lencz

This special issue emerged indirectly from discussions that took place on a train ride from Bonn to Berlin after an international conference held in Germany in 2000. At that time, a handful of research programs had been started to investigate the period preceding the onset of full-blown psychosis in individuals displaying attenuated (i.e., subsympathetic intensity) positive symptoms. One of us (B.A.C.) was interested in starting a collaborative project with other prodromal researchers on that train. But after a lunch, a few beers, and a slight detour to look at castles, it became quite clear that many issues had to be resolved before an international, multisite collaboration on this topic would be feasible. For example, some consensus was needed on issues such as how to define risk, how to define the prodrome, and how to quantify prevention. Furthermore, because most prodromal projects were quite new, few had had time to publish their early findings, and communication among researchers about shared problems, experiences, and discoveries had been limited. And so the idea of a small interactive working group to overcome some of these problems was born. The First Annual Workshop on the Schizophrenia Prodrome was held at the SoHo Grand Hotel in New York City from April 4 to 6, 2002. Made possible by an educational grant from Janssen Pharmaceutica Products, L.P., the workshop focused on methodological issues unique to the study of risk states.

Initially, it was hoped that, if successful, the workshop might result in a short article that would announce the emergence of the prodromal research area and provide a rudimentary methodological framework for researchers seeking to establish new programs in this field. What emerged was three days of intense scientific discussion, a very definite spirit of collegiality, and enough new data and theory to justify an entire special issue. John Hsaio, the editor-in-chief of Schizophrenia Bulletin, recognized the potential contribution of such a volume, and Robert Heinssen, a major contributor to the workshop, agreed to serve along with Barbara Cornblatt as primary co-editors. Tyrone Cannon and Todd Lencz also agreed to join the editorial board of the special issue. It was apparent to all that the field of prodromal research was no longer in its infancy but was experiencing an exciting spurt of growth, with all of the accompanying growing pains.

This special issue cannot solve all the problems that cropped up that day on the train, but we believe that it will provide a major push in the right direction. While most of the contributors to this issue participated in the 2002 workshop, there are also several invited articles and commentaries by researchers who were unable to attend. To maximize the potential impact of this issue on the field, the editors and authors agreed to an unusually stringent review process. Articles were sent to as many as four internationally recognized opinion leaders in the field of schizophrenia research, in addition to review by the editors themselves. Our thanks are extended not only to the authors, who returned very strong contributions with relatively short deadlines, but also to the reviewers, who provided extensive comments on even tighter deadlines.

This meeting also led to the formation of the International Prodromal Research Network (IPRN), which is co-directed by Barbara Cornblatt and Tyrone Cannon. The goal of the network is to provide a forum for researchers to form collaborations and to pool resources and data in pursuing goals related to the prediction and prevention of schizophrenia and other forms of psychosis. IPRN activities are expected to generate a set of common assessment instruments and to pave the way for the multisite trials critical for amassing large samples, currently not available to any one site or study. The network will also coordinate future workshops and smaller working group meetings. The first of these was the Second Annual Workshop, held in Santa Monica, CA, from May 1 to 3, 2003, which was hosted by Tyrone Cannon and co-sponsored by Janssen Pharmaceutica Products, L.P., and by Garen and Shari Staglin. The Staglins have pledged ongoing support of the network through funds raised at the Music Festival for Mental Health, held annually at the Staglin Family Vineyard in Rutherford, CA. The sec-

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ond workshop focused on clinical assessment instruments and the application of neuroimaging techniques to the study of the prodrome, and led to ongoing working groups in these two areas. A third workshop is planned for Vancouver, BC, in 2004, to be hosted by Patrick McGorry, in conjunction with the International Early Psychosis Association.

As discussed in greater detail in the summary of the First Annual Workshop (Auther et al. 2003), one surprising aspect of the SoHo meeting was the amount of discussion generated by issues of terminology. Over the course of the weekend, it became clear that these discussions were far more substantive than semantic. Specifically, while everyone agreed that prediction and prevention were the goals of prodromal research, there was much debate as to what it was we were seeking to predict (e.g., schizophrenia vs. psychosis vs. a more diffuse vulnerability) and what we were seeking to prevent (e.g., psychotic illness vs. symptoms vs. long-term disability). Similarly, there was broad consensus that the neurodevelopmental model of schizophrenia provided the framework for commonly used terms such as "vulnerability" and "risk factor," but the exact nature and details of the model were still open to discussion.

The first set of papers in this issue follow from those discussions, attempting to put meat on the bones of the neurodevelopmental model and to specify the targets for prediction and prevention. Cornblatt et al. employ the neurodevelopmental model to identify two dimensions of vulnerability: an underlying substrate of enduring negative symptoms and an evolving domain of increasing positive symptoms. Emphasizing the developmental aspect of the model, these authors hypothesize that specific phases of the clinical illness unfold in a longitudinal sequence over the course of adolescence, leading to predictions that can be tested in future prospective research. Furthermore, the two clinical dimensions are suggested to have cognitive and functional correlates, a view supported by data presented from the Hillside Recognition and Prevention (RAP) Program.

Similarly, Cannon et al. attempt to parse two dimensions of abnormality at the neural systems level and to relate these dimensions to both early (i.e., prenatal/perinatal) and later (i.e., adolescence/early adulthood) neurodevelopmental processes that may play a role in the etiology and pathophysiology of schizophrenia. Drawing on their extensive experience with structural and functional brain imaging in genetic high-risk samples, these authors identify brain deficits that are shared by relatives of patients with schizophrenia and that are not sufficient in themselves to cause the fully expressed illness. These putative markers of an early genetic abnormality are contrasted with other neuroanatomical and functional abnormalities specific to affected patients, which may represent late-emerging changes accompanying onset of psychotic illness. These late changes in the brain, and their possible precipitants, are further explored by Corcoran et al. in their discussion of the stress cascade. These latter authors focus primarily on the possible role of the hypothalamic-pituitary-adrenal axis in mediating the too-often-neglected stress component of the diathesis-stress model.

Maier et al. build upon these contributions to the neurodevelopmental model of vulnerability to schizophrenia by calling for a new taxonomy of risk, to supplement the traditional taxonomy of clinical end states. Initial responses to this call are provided by the subsequent three articles, which examine current, and possible future, clinical assessments of the prodromal state. Miller et al. demonstrate how far the field has come in developing reliable and valid clinical assessment tools for defining prodromal symptoms and syndromes. Lencz et al. then examine these tools in detail, focusing on how they might be refined to more accurately capture the dimensionality and heterogeneity of the prodrome. This approach might lead to changes in the as-yet-unsettled definition of inclusion criteria for prodromal states. Ross et al. end this section by extending the process further down the age spectrum, to examine the applicability of prodromal concepts and assessment techniques to pre-adolescent children, a group thus far not studied in the context of the prodrome. These authors highlight the fundamentally developmental nature of the prodrome.

Despite controversies on many issues, a major point of consensus throughout the SoHo workshop was the need for collaboration among multiple research sites in order to maximize power and sample sizes. As noted above, this is a goal of the working groups established as part of the IPRN. In addition, in recognition of the need for high-risk and early illness research to move in this direction, Robert Heinsen and his colleagues at the National Institutes of Health have proposed a series of guiding principles and a formal structure for such collaborations in their contribution to this special issue. In their discussion, these authors methodically lay out a plan for the creation of multisite networks that can examine not only the schizophrenia prodrome but a broader range of "early serious mental illness" from both a pathophysiological and a clinical/treatment perspective. They suggest that the key to such networks is the use of a common core of clinical and neurobiological assessments that is broad enough to capture the full range of phenotypic expression and is flexible enough to follow an iterative longitudinal approach.

The appropriate balance between broad and narrow definitions of the prodrome has been actively debated in the workshop and in several articles in this issue. Casting a broad net will increase the sensitivity of the findings and their generalizability in the real world. It will also lead to a higher false positive rate, although such subjects may, in turn, be the optimal controls. By contrast, a more narrow definition of the prodrome will maximize specificity and may be preferred for randomized clinical trials.

A similar balancing act characterizes discussion of treatment strategies. Long-term goals of prevention must be tem-
The last two articles take us back from the societal level to the neuronal level, using one of the most exciting modern research tools, neuroimaging, to begin the empirical exploration of the neuroanatomical basis of the prodrome. Seidman et al. focus on the medial temporal lobe, a region that has become a key source of data in schizophrenia and high-risk studies. Continuing the theme of Cannon et al., these authors use a genetic high-risk approach to point toward promising directions for the initial application of neuroimaging to prodromal research. Wood et al. report the first application of magnetic resonance spectroscopy (MRS) to the study of a prodromal sample. As these authors note, MRS has the potential to complement other neuroimaging techniques by providing direct evidence of changes in brain chemistry and metabolism over different stages of the illness. While their study is cross-sectional, comparing high-risk patients with already-psychotic patients and unaffected volunteers, it incorporates longitudinal data on outcome and points toward the possibility of future longitudinal neuroimaging studies of the transition to psychosis, which have begun in their laboratory as well as others.

This special issue concludes with four commentaries on the current state of prodromal research, as reflected in the contributions to this volume. These commentaries provide both an “inside view,” derived from two experts within the field of prodromal research, and an “outside view,” solicited from two experts in schizophrenia whose work does not primarily focus on the prodrome. As editors of this special issue and organizers of the prodromal workshops, we have attempted to turn a critical lens on our own approaches, so that the assumptions and methodologies that have guided the field in its early phases do not automatically become the entrenched standards. In the selection of the outside commentaries, the invitation of several independent consultants to the workshop, and the use of a very rigorous external review process for this special issue, we hope to have built in the kind of objective and constructive criticism that will help to move the field forward over the next five to ten years.

Just over a decade ago, in the spring of 1992, this journal published a two-part special issue on the study of first episode schizophrenia edited by Jeffrey Lieberman et al., which encouraged a major shift in focus to the early phases of schizophrenia. Hundreds of studies later, the field is now much richer in knowledge concerning this critical period. In turn, it has appeared increasingly likely that a push to even earlier phases of illness will benefit the field still further. The initial set of such very early illness studies was first introduced in a 1996 special issue of Schizophrenia Bulletin that was edited by Thomas McGlashan. Since then, there have been many new developments and many new prodromal studies launched. It is our hope that the articles in the current issue will provide the foundation for the next generation of research concerned with prevention.

The authors open up an as-yet-undereexplored avenue for current, ongoing clinical research, as well as guidelines for future trials that emphasize potential methodological pitfalls such as selection of patients, trial duration, and outcome measures.

McGorry et al. follow the Kane et al. discussion of rigorous clinical trial methodology with a novel and well-defined service model for the delivery of such treatment to at-risk populations. The approach outlined by McGorry et al. is designed to bridge several gaps that exist in conventional service structures: between prevention and early treatment, between adolescents and adults, and between the desire to help and the need not to harm. The contribution by Keshavan et al. bridges another type of gap: that between retrospective studies of the prodromal phase in schizophrenia patients, and prospective studies of prodromal populations. Their study combined a prospective assessment of long-term outcome in schizophrenia with a retrospective examination of the role of duration of untreated psychosis (DUP) and untreated illness, broadly defined (i.e., the prodrome). Clarifying the somewhat murky role of DUP, these authors report a strong association between the duration of the prodromal phase and long-term functioning in patients with diagnosed schizophrenia. This relationship is stronger than the relationship with DUP and is independent of premorbid adjustment. While not able to determine causality from this study, the authors encourage further study of the long-term effects of intervention during the often quite long prodromal period.

While these last several articles examine issues related to the prevention of poor outcomes in affected and at-risk individuals in the clinic, Mojtabai et al. provide a complementary, epidemiological approach to population prevention. Drawing on historical precedent in the field of hypertension, the details of which may be unfamiliar to many readers, this article provides a useful broadening of perspective for the study of prevention of schizophrenia. The authors open up an as-yet-undereexplored avenue for research in the prodrome, with potential political and social, as well as clinical, ramifications. Although several groups in Europe, Canada, and Australia have attempted to broaden community outreach and awareness of schizophrenia, psychosis, and mental health services, such approaches have begun only recently and have not yet spread to the United States.

pered by the need to improve the immediate clinical needs of treatment-seeking adolescents and young adults. Furthermore, there is a widespread recognition that it is critical to prevent the functional decline and lifelong disability typically associated with chronic mental illness. Thus, the target of treatment is now considerably broader than the prevention of psychosis. Within this context, Kane et al. provide a framework for considering key issues in the design of prodromal clinical trials. They provide a much-needed overview of current, ongoing clinical research, as well as guidelines for future trials that emphasize potential methodological pitfalls such as selection of patients, trial duration, and outcome measures.

Editors' Introduction
Minority Research Training in Psychiatry

Through a five-year, $2.5 million grant from the National Institute of Mental Health, the American Psychiatric Institute for Research and Education (APIRE) is seeking through the Program for Minority Research Training in Psychiatry (PMRTP) to increase the number of minority psychiatrists entering the field of psychiatric research.

The program provides medical students with funding for stipends, travel expenses, and tuition for an elective or summer experience in a research environment, with special attention paid to trainees’ career development in research. In addition, stipends are available for a limited number of one- or two-year postresidency fellowships for minority psychiatrists. Residents may engage in full-year research training during the last year of psychiatric residency or in “year off” research training.

Training takes place at research-oriented departments of psychiatry in major U.S. medical schools and other appropriate sites throughout the country. An individual at the site (the research “mentor”) is responsible for overseeing the research training experience.

Administered by the American Psychiatric Institute for Research and Education, the program includes outreach efforts to identify minority medical students and residents who are potential researchers and to put them in touch with advisors who counsel them about careers in psychiatric research. Additional activities assist fellows and alumni in their research career development.

The director of the PMRTP is James Thompson, M.D., M.P.H.; the project manager is Ernesto Guerra. An advisory committee of senior researchers and minority psychiatrists developed guidelines for applicants and criteria for selection. The members of this committee evaluate and select trainees, oversee the research training experiences, and play a role in evaluating the effectiveness of the program.

December 1 is the deadline for applications for residents seeking a year or more of training and for postresidency fellows. For medical students, applications are due three months before training is to begin. Summer medical students who will start their training by June 30 should submit their applications by April 1.

For more information about the PMRTP, call the toll-free number for the PMRTP, 1-800-852-1390, or 202-682-6225, e-mail eguerra@psych.org, or write to PMRTP at the American Psychiatric Institute for Research and Education, 1400 K Street, NW, Washington, DC 20005.