Preface

The Developing Field of Schizophrenia Research

There are developmental milestones in the life of a disorder – the moments that it is defined (or redefined) at a diagnostic level, the moments that it is understood (or better understood) at a scientific level, and the moments that it is effectively treated (or more effectively treated) at a clinical level. Deciding when to pause and take stock of these milestones is a matter of choice, particularly in the absence of a transformative event like the identification of a definitive gene (e.g., BRCA or the Huntington's gene), causative agent (e.g., HIV), enzyme (e.g., Lesch–Nyhan syndrome), or intervention (e.g., the polio vaccine). We do not have such clear transformative milestones to mark our understanding or treatment of schizophrenia; smaller milestones are either part of the distant past (e.g., Bleuler's diagnostic reformulation, or the advent of modern antipsychotics and resulting "deinstitutionalization" of schizophrenia) or perhaps our evolving present (e.g., the growing list of candidate genes).

But just as our field aspires to reject biological determinism in the etiology of schizophrenia, we should hold that the path toward understanding this disorder is not predetermined. For this reason, pausing to assess the field's milestones, even (especially) in the absence of transformative events, affords us the opportunity to better nurture it: to willfully make (or not make) midcourse corrections and thereby alter (or sustain) its developmental trajectory. To do so is not an admission of failure, but to not do so would be a serious omission, and in my opinion, an act of scientific arrogance.

Where on this developmental path do we find ourselves? As the chapters in this volume suggest, we are still in a "learning stage." Diagnostically, the boundaries of the schizophrenias are less clearly marked than we once believed, expanding in some directions toward the bipolar disorders, in others toward the "Cluster A" personality spectrum, and in still others toward "pure" genetic disorders such as Velo-Cardio-Facial Syndrome. In its pathogenesis, we are recognizing a multiplying number of candidate "risk" genes, as well as epigenetic "risk" factors. In its pathophysiology, we have a growing array of increasingly sophisticated experimental tools to characterize its aberrant neural substrates at nano-, micro-, and macro-systems levels, neural

information at millisecond–microvolt resolution, and gene networks and neural signaling pathways that seem to interact within two-, three-, and four-dimensions.

Where is this "learning stage" taking our field? As boundaries expand and lists of genes, neural elements, and signal molecules grow, and as the temporal and spatial resolution of our measures increase to reveal more and more about less and less, it can appear that this "learning stage" of schizophreniology is teetering toward a state of fixation, more than of growth. This conclusion would be bolstered by the fact that developments in antipsychotic efficacy, so highly touted by our commercial counterparts, have not withstood the light of data, bringing us full circle, more or less, to where we started 50 years ago, though many pounds heavier. So, are we "fixated" in this learning stage? A closer inspection of our developmental path, described in the chapters in this text, may suggest otherwise.

As Bromley and Brekke describe, our field now has tools to assess and target not merely psychosis but also real-life function and functional outcome in the schizophrenias. This seemingly simple recognition of the importance of "real-life function" in the study of any disorder, but particularly schizophrenia, charts a path away from "learning for learning's sake," and toward a next developmental stage. These real-life metrics will become new benchmarks for assessing the efficacy of current "next generation" interventions, delivered toward different clinical (Barch; Kaur and Cadenhead) or receptor targets (Kim and Stahl), or via different technologies (Rabin and Siegel), even as we better understand and address the failings of the "former generation" interventions (Meyer).

These chapters on schizophrenia neuroimaging (Brown and Thompson; Urban and Abi-Dargham; Levitt et al.), neurophysiology (Rissling and Light; Levy et al.; Braff), neurocognition (Kalkstein et al.), and preclinical models (Young et al; Powell) report that our field has developed a highly advanced ability to submit the neurobiology of the schizophrenias to rigorous experimental analysis. While some of these developments might appear fixated within nitty-gritty experimental issues – finding the most informative ligand, evoked waveform, stimulus condition, scanning state, or neurocognitive domain – they are actually the grist for healthy scientific development: for testing hypotheses under controlled conditions to generate interpretable data and conclusions. And such inquiry across multiple levels of analysis, and across species, creates the opportunity for converging lines of evidence – scientific triangulation – so essential for establishing new knowledge about disorders of brain, mind, and behavior.

At this developmental stage, convergent information has focused our attention on abnormalities in specific brain regions and circuits, including systems within and interconnecting the prefrontal cortex (Volk and Lewis), specific thalamic nuclei (Cronenwett and Csernansky), and mesial temporal lobe (Heckers and Conradi), as causative events in the pathophysiology of the schizophrenias. These abnormalities have been identified and characterized using strategies of volumetric, neurochemical, and functional neuroimaging described in earlier chapters in this volume, and extend to detailed neuropathological studies, and studies of altered developmental and molecular processes. In fact, where the schizophrenias were once characterized pejoratively as "functional" based on the paucity of clear neuropathological

findings, it is now characterized pejoratively as "heterogeneous," based on the long list and multiple combinations of such findings across studies. Nobody said development was easy.

Perhaps the most studied (at least in terms of sheer "N") and rapidly evolving facet of our developing field is schizophrenia genetics. Some candidates have emerged as prime "risk gene" suspects (e.g., COMT, NRG1, and DISC1, among others), yet perhaps the bigger developmental advancement is the growing awareness that traditional strategies for identifying disorder genes – even with heroically (and some might say excessively) powered samples – may not be most informative for schizophrenia. Rather, the key to genetic risk in schizophrenia may lie in aberrant patterns of copy number variants (Mantripagada et al.), rare mutations, or DNA methylation (Akbarian) that characterize this disorder. The wide range of different possible genetic disturbances in this disorder might gain coherence via their action within a smaller number of critical molecular signaling pathways (Kvajo et al.) that might ultimately be responsible for downstream disturbances in the development and function of neurons and the limbic-cortical circuits that they populate.

With this pause to assess the developmental trajectory of our field comes the opportunity – and I would say, the obligation – to consider and discuss what lies ahead in our understanding of the neurobiology and treatment of the schizophrenias. Does our "growth chart" suggest that we will ultimately be able to use a molecular toolbox to "fix" this disorder? Or, projecting out some years, will our trajectory make us amenable to other therapeutic approaches? Which paradigms – scientific or therapeutic – once viewed with promise have we now outgrown? And with what will they be replaced? As I note in my chapter, should "midcourse changes" be necessary, this is a sign of growth and not of failure. There can be no question that, with countless dedicated lifetimes of work, our field has learned great amounts about an exquisitely complex biology of schizophrenia; but, I suggest, an equally important question is whether, given all that we know, we can hope to predictably and effectively manipulate this biology within our lifetimes, in a way that will fundamentally change the course of this disorder. If the consensus is "no," or even "who knows?" then our field might consider other approaches (and I raise the speculative example of pharmacologically augmented cognitive therapies), for which the biological and clinical complexity of the intervention is developmentally suited to our ability to deliver it.

The key milestones in schizophrenia research and treatment will be reached only if we maintain a healthy developmental course, and this means that we cannot tolerate fixation. Knowing what we know, and having developed such a rich scientific and clinical knowledge base, to pause and consider whether we are approaching this disorder correctly, is perhaps the best way that we can help our field and the families that we serve.

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