Progress on NIMH Initiatives (Memorial Theme for Wayne Fenton, MD)

Ellen Stover, Steve Marder, and William Carpenter

The articles in this special issue demonstrate the extraordinary breadth of Wayne Fenton’s career. His work touched the lives of the patients he was treating, their families, and the larger community of researchers. Fenton combined vision with leadership to jump-start the field on a uniquely broad collaboration for therapeutic discovery. Although his tenure at National Institute of Mental Health (NIMH) was brief (from December 1999 until his tragic death on September 3, 2006), he created a national focus on the unmet therapeutic needs in schizophrenia. He became a central figure because NIMH established new programs to address these needs. He was instrumental in developing a unique collaboration among leaders from industry, academia, the Food and Drug Administration, and NIMH. This collaboration has led to rapid and substantial progress. The articles in this theme issue of the Schizophrenia Bulletin provide an update on this progress and commentaries to provide perspective.

Wayne Fenton would have felt most strongly about the importance of mental health research being energized by the needs of individuals who live with serious mental illnesses. Fenton’s professional life was divided into 2 passions. First, he was dedicated to helping individuals who were suffering from illnesses such as schizophrenia and their families. The contributions by Heinssen and McGlashan and Carpenter describe his experiences as a clinician at Chestnut Lodge and how they formed his views of serious mental illnesses. During his 18 years at Chestnut Lodge as clinician, investigator, and later medical director, he made significant contributions. It was during these years that Wayne developed the view that treatment of just the psychosis in schizophrenia was a limited approach, and other domains of pathology defined critical unmet needs. This history, and Wayne’s research contributions are set forward in the article by McGlashan and Carpenter. His second interest was the potential of research to alter the course of these illnesses on a much larger scale. His impact on research at NIMH is described in the contribution by Insel and Hyman, the current and immediate past directors of NIMH. We believe that Fenton was unique in his ability to integrate his view of schizophrenia as a clinician with his view of research opportunities. That is, he was keenly aware that research could derive benefit from the presence of a well-grounded clinician who continually questioned whether research priorities were on track and its research relevant.

Stover, Brady, and Marder review how new paradigms for treatment development were implemented in the NIMH research portfolio and detail specific accomplishments that have resulted from these initiatives. It is now widely accepted that drugs with novel mechanisms will be required to advance pharmacotherapy of cognition and negative symptom pathology. The Measurement And Treatment Research to Improve Cognition in Schizophrenia (MATRICS) program provided impetus in this area. The article by Stover, Brady, and Marder describes how the MATRICS initiative brought individuals from industry, government, and academia together to address these obstacles to the development of agents to improve cognition in schizophrenia. One of the important outcomes of MATRICS was that it revealed an enormous interest among these different sectors to reach out to address important clinical needs. This interest has led to other initiatives to address issues such as negative symptoms in schizophrenia, the development of better animal models for cognitive impairment in schizophrenia, and the development of more innovative methods for measuring functioning in clinical trials. As noted in the contributions by Carter and Barch, Velligan and Harvey, and Geyer and Tamminga, NIMH has developed better methods for tapping the willingness of clinical and basic scientists to work together to improve their ability to translate findings between divergent research areas. In addition, individuals from the pharmaceutical industry have understood the wisdom of working together with academic scientists to address important issues that have the potential for facilitating research. Fenton’s sensitivity to the varying needs of each of these sectors was critical in facilitating the development of these collaborations.

The Fenton vision was based, in the first place, on poor functional outcomes observed in persons with schizophrenia despite intensive application of therapeutic knowledge.
The MATRICS focus, first on cognition and then on negative symptoms, was in recognition of the robust association of these 2 pathological domains with poor functional outcomes. However, missing from clinical trials methodology are assessments for functional skills. This is a critical issue in drug development because simply showing improvement on tests of cognition will not establish clinical meaningfulness. Harvey, Velligan, and Bellack review progress in performance-based measures of function.

Roth and Gray review the large number of molecular targets with potential relevance for the treatment of impaired cognition in schizophrenia. Moving from potential molecular targets to testing compounds designed to affect these targets is a critical step. NIMH initiated the Treatment Units for Research on Neurocognition in Schizophrenia (TURNS) process to support the first steps in this complex activity. Buchanan, Freedman, Javitt, Abi-Dargham, and Lieberman review the advances in the development of novel pharmacological agents for cognition.

In order to relate imaging biomarkers directly to the neuroanatomy and neurobiology of cognitive processes, new assessment methodologies are needed. Barch and Carter review approaches drawn from cognitive neuroscience. These paradigms have the potential to map the neural substrate for cognitive processes more directly than neurocognitive tests such as the ones selected for the MATRICS battery. The former may prove heuristic in early detection of a compound’s effect while the latter are used to establish efficacy in clinical trials.

The final article in the series is an appreciation of Wayne’s devotion to the well-being of his patients and his extraordinary work as clinician. Heinssen worked with Wayne at Chestnut Lodge and NIMH and provides a compelling picture of an expert and caring doctor. (See also in this Issue, the Editorial, and the First-Person Account).

Brief commentaries are provided by the NIMH Directors, Hyman and Insel, who were influenced by Wayne, and supported many of his insightful research initiatives. Laughren notes the unusual success of these initiatives from the FDA perspective. Breier, Alphs, and Binneman provide an industry perspective, and Geyer and Tamminga provide the academic scientists’ perspective. The final commentary, by Bellack and Frese, places the Fenton vision in the context of recovery.

As guest editors, we have an opportunity to use this collection of substantive articles and commentary to express our admiration for Wayne Fenton’s vision and research accomplishments, our appreciation for his leadership, and our confidence that accelerated progress on therapeutic discovery will be a lasting tribute.

References
2. Geyer M, Heinssen R. New approaches to measurement and treatment research to improve cognition in schizophrenia. Schizophr Bull. 2005;31:806–809.