Accelerating New Knowledge in Schizophrenia

A perusal of the contents of this issue—which features new research in schizophrenia and accompanying scientific editorials—supports an optimism that important knowledge about neural mechanisms in schizophrenia is really accruing. Knowledge about the brain pertinent to schizophrenia (indeed, to brain diseases in general) has grown over the last several decades in distinct but complementary tracts, with each benefiting the other. First, the field of fundamental neuroscience has greatly expanded, providing a framework of knowledge for exploring pathophysiology. Based on the extensive understanding of mammalian brain anatomy, neurochemistry, physiology, and systems function, firm knowledge can be translated to human systems to form the basis for fundamental discoveries in brain diseases. Because the brain is a protected organ and because its function is not intuitively obvious from its gross structure and cannot be observed without sophisticated instruments, understanding "how the brain works" was delayed until specialized technologies were developed. However, the field of neuroscience is now one of the most active among the basic sciences, capturing the attention of the public and the imagination of students and generating critical discoveries for understanding mental illness (1). Each one of the articles on schizophrenia in this issue uses constructs, knowledge, and models from fundamental neuroscience to model experiments and interpret findings. For example, the molecular discoveries and characterization of neurotransmitter receptors in the brain and their drug affinities make possible the study of in vivo receptor occupancy in the Gründer et al. article (2). Development in human brain anatomy underlies the Ellison-Wright et al. (3) and Friedman et al. (4) studies; advances in systems neuroscience provides the basis for the EEG and functional imaging studies by Ferrarelli et al. (5) and Yoon et al. (6); and basic cholinergic pharmacology provides the basis for the Shekhar et al. (7) and Freedman et al. (8) studies on cholinergic agonists in schizophrenia cognition. Fundamental neuroscience is still a young field and will continue to grow and contribute much to our understanding of diseases of the brain over time. Moreover, it is important to keep in mind that the path between basic neuroscience and clinical research travels in both directions, with fundamental neuroscience being guided and stimulated by clinical observation and concepts.

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Second, the studies in this issue used sophisticated clinical research methodologies to tap unique clinical outcomes. Human brain methodologies have advanced considerably since the early days when, for example, plasma prolactin levels were measured as a "window" into the brain. Now, in vivo brain imaging (2–4, 6), scalp electrophysiology (5), and advanced clinical assessments (7–9), among others, all provide a knowledge base supporting scientific discovery in diseases in which using animal models is difficult. Translational neuroscience has emerged with favorable methodologies and models and is now generating results to inform schizophrenia research. The extent of the productivity of translational clinical research is impressive, as seen in this issue, and suggests that a mechanistic understanding of the schizophrenia syndrome is believable. It is only from sophisticated human clinical data, interpreted in the context of fundamental neuroscience, that significant gains can be made in understanding a psychiatric illness like schizophrenia, ensuring progress in the field. A shared understanding

or current model of the illness does not yet exist; yet there is a willingness to hypothesize, collect, and interpret clinical data experimentally using the most advanced clinical research methodologies while seeking plausible targets. We have moved the dialogue regarding the pathophysiology of schizophrenia from theoretical psychological constructs to concrete brain mechanisms.

Third, there is an ongoing reformulation of illness categories in psychiatry, especially in schizophrenia (10). This is not for the practical purpose of establishing formal diagnoses but for research purposes, to see which illness characteristics provide the most homogeneous groups for defining genetic and biological characteristics. The current research approach pursues dimensional constructs instead of applying traditional diagnostic criteria when examining pathophysiology, etiology, and treatment of diagnoses like schizophrenia. Attempts to identify a single mechanism that might explain all aspects of the illness have met with practically no success. The explanation most often given is that the illness is a syndrome that encompasses multiple distinct pathophysiologically and etiologically driven diseases; schizophrenia could be a diagnosis more like congestive heart failure than like Parkinson's disease. The current response to this kind of thinking has been to suggest novel illness categories, new "bins" for phenomenology with a focus on intermediate phenotypes. Whereas schizophrenia was once conceptualized as a single illness with one diagnosis, one treatment, and an explanatory pathophysiology, it is now conceived of as a syndrome with multiple domains of dysfunction or "component symptom complexes" (11). These components are thought to be separable and independent and to command different mechanisms and treatments. Therefore, when the clinical studies published in this issue set out to define a mechanism, etiological factor, or treatment for schizophrenia, the factor the authors proposed no longer had to wholly explain the full illness. Rather, it could identify an intermediate phenotype for study. While the number of components within schizophrenia can be debated, they would certainly include psychosis and cognitive dysfunction. Although each of these categories in itself might still be a complex construct, the idea of being able to model and examine a more homogeneous phenomenological entity may well be heuristically useful. This also means that treatments need no longer treat the whole of schizophrenia but can be specifically directed to the pathophysiology that underlies one of the component complexes, like psychosis or cognitive dysfunction. The National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project headed by Wayne Fenton, Ellen Stover, and Steve Marder has most visibly depended on this framework. A basic contribution that MATRICS made to this field was to involve the U.S. Food and Drug Administration in the process of demonstrating that distinct pathophysiologies (and hence treatments) are likely to exist for psychosis and cognitive dysfunction, opening up drug development in disease components and generating tremendous activity in identifying drugs rationally for cognitive dysfunction; two articles in this issue represent that effort (7, 8). The process of compartmentalizing phenomenology is still new, and we will likely encounter surprises and have to remodel concepts. But the idea that schizophrenia is not a single illness, while previously hypothesized, is now being actualized by directed research. Just as the development of distinct treatments for component symptom complexes is rational, so too our hypotheses for pathophysiology, intermediate phenotypes, and even etiology need to become component-specific, as well as our animal models.

Where do we have to go? The realistic answer is: a long way. It is the underlying disease constructs of mechanism and etiology that have resisted articulation in schizophrenia. How does the brain create a delusion, a hallucination, a psychotic memory, or inadequate or misdirected attention? Given the wealth of fundamental neuroscientific knowledge, the powerful clinical research methodologies available, and the new conceptual constructs in defining components of schizophrenia, the field should be able to

make solid advances in identifying components of mechanisms and etiologies, as represented by the articles in this issue.

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Disclosures of the American Journal of Psychiatry *editors are published in each January issue. Dr. Freedman has reviewed this editorial and found no evidence of influence from these relationships.*