Editorial

Understanding Schizophrenia: A Silent Spring?

This issue of the AJP highlights schizophrenia, one of the most important illnesses that psychiatrists treat. Since we must never forget that we in fact treat **people** who suffer from illnesses, art by a person suffering from schizophrenia is shown on the cover. This man is an excellent photographer and a good graphic artist. The whimsical watercolor was a small "throwaway" that he did for fun when trying a new medium.

Articles in this issue cover many topics at the cutting edge of schizophrenia research, demonstrating the achievements made by many research scientists in recent years in understanding the mechanisms of this important illness. Schizophrenia places an enormous burden of suffering on patients and their families throughout the world. It also creates an enormous economic burden, costing billions of dollars for treatment, disability, and lost productivity. Developing improved treatments and identifying ways to prevent it are at the top of national health priorities, both for psychiatry and for medicine as a whole.

The Special Article by Woods highlights one of the fundamental questions in schizophrenia research. Is this disorder one that leads to progressive deterioration over time in a dementia-like fashion, as was implied in the name "dementia praecox" that Kraepelin originally gave it? Or is it a neurodevelopmental disorder that occurs as a consequence of changes in brain development and maturation, a process that begins in human beings during the first trimester and continues on into at least the early twenties when people become young adults? The synthesis suggested by Woods supports the latter alternative, and this synthesis is consistent with much of the recent data on the longitudinal course of illness in young first-episode patients. As a shocking commentary on the stigma and ignorance associated with this illness, many patients have psychotic symptoms for 1 or 2 years prior to first hospitalization. It is not yet clear whether earlier identification and treatment will improve outcome, but it is certainly clear that more needs to be done to improve public education so that patients will seek treatment when their symptoms begin to occur. Most of the recent longitudinal data suggest that people who develop schizophrenia during the late teens and twenties have a relatively fulminant course during the initial years, but subsequently stabilize and may even improve. Since most patients in these longitudinal studies were ascertained prior to the wide availability of the newer neuroleptics, we do not yet know whether the future course of schizophrenia will be better now that better medications are available, given the reduced side effects, improved compliance, and possible effects on negative symptoms, psychosocial function, and cognition.

Other articles demonstrate additional themes in schizophrenia research. One of these is the importance of cognition, and in particular the importance of identifying the cognitive processes that are fundamental to the disorder. The articles by the NIMH group present one such cognitive hypothesis, while the article from the Harvard group links a cognitive process to a connectionist or network approach, highlighting the fact that contemporary models of schizophrenia are increasingly based on the distributed brain circuits mapped through contemporary neuroscience.

Two papers illustrate important work being done to identify "biological markers" of schizophrenia that may give us a better definition of the underlying phenotype than simply assessing symptoms. These markers are often viewed as potential "vulnerability markers" that may identify a predisposition that requires "multiple hits" in order for the illness to be expressed. The group from the University of California at San Diego (UCSD) examines the P50, an evoked brain wave that reflects the ability to focus attention and suppress unneeded stimuli. The Maudsley group uses the eye tracking methods pioneered in schizophrenia by Holzman and adds to the accumulating evidence that inability to suppress reflexive saccades may be a vulnerability marker for schizophrenia. Both of these use the relatively inexpensive technology of neurophysiology and examine abnormalities that may occur both in the patients who actually have the illness and in their family members who may "carry" the predisposition. The group from Sweden adds to these data by demonstrating that minor physical anomalies are also present in both patients and their family members and may also be a viable candidate as a risk marker. These studies are analogous to the work in Alzheimer's disease or breast cancer that has identified "vulnerability genes" such as ApoE4 or BRCAI. They use the technology of clinical research rather than molecular biology, the latter approach having not yet fulfilled its many promises in more complex illnesses without a visible neuropathology, such as schizophrenia. (Observers in this horse race between molecular and systems-level strategies are welcome to place bets on the likely winner. Most research review committees and governmental funding agencies are wise enough to recognize that the race is not yet over, that the winner is not yet known, and that both horses should therefore be encouraged to continue to run.)

Finally, illustrating both the contributions of imaging technology and the fact that neuroleptic treatment may cause structural changes in the brain, a paper from the University of Pennsylvania group examines subcortical regions in first-episode patients and patients who have been chronically treated. This study used magnetic resonance imaging to conduct *in vivo* measurements of the basal ganglia and the thalamus—essentially doing *in vivo* neuropathology. A mere 10 years ago a study like this was impossible, and no one thought that treatment could produce structural changes in the brain! Now multiple studies have converged to suggest that chronic treatment with typical neuroleptics produces enlargement of basal ganglia regions, while treatment with atypicals has a reverse effect. As the relationship between these findings and tardive dyskinesia is worked out, this work will clearly have an impact on choice of treatment and may suggest that the atypicals are a safer option. Further, this study also adds to the growing database supporting the importance of the thalamus in schizophrenia, a region largely neglected until relatively recently, despite its key role as a "central switchboard" in the brain. It is complemented by a Brief Report indicating that thalamic abnormalities may also occur in patients' relatives.

So what is missing in this picture? What important aspect of schizophrenia research has been left out? What is silent in this exuberant scientific rite of spring?

First, where are the articles on molecular genetics or functional genomics? Other issues of the AJP have addressed this topic, principally with negative studies so far. This is more indicative of the youth of this field than its lack of promise. This area is clearly celebrating the rites of spring with a major growth phase.

Second, however, where is the good old-fashioned clinical research? Where are studies that examine epidemiology, descriptive psychopathology, and course and outcome? Studies in this area are becoming increasingly rare, since they are no longer perceived as "sexy," "cutting edge," "sophisticated," or even "scientific." They are incredibly low tech. They only require having a thinking brain/mind, observing many patients, and recording observations and measurements in a systematic way that can be analyzed by using statistical methods that range from very simple to very complicated. In the United States an older generation of clinical researchers who led the field for many years have died—Eli Robins, Gerry Klerman,

George Winokur—or are dying out. Very few younger investigators are emerging to replace them. The word is out—if you want to succeed as a serious scientist, you need to do something relatively basic. Fortunately, the Europeans still have a proud tradition of clinical research and descriptive psychopathology. Someday in the twenty-first century, after the human genome and the human brain have been mapped, someone may need to organize a reverse Marshall plan so that the Europeans can save American science by helping us figure out who really has schizophrenia or what schizophrenia really is. The fledging American school of descriptive psychopathology will have become extinct. Yet we cannot apply the potentially great fruits of the Human Genome Project to complex mental illnesses if we no longer have clinical investigators who have devoted their research careers to conceptualizing the nature and definitions of symptoms, syndromes, diseases, or diagnoses.

Isn't this problem solved? Isn't DSM sufficient? Unfortunately, no. DSM was developed as a clinical manual to serve as a diagnostic "gatekeeper." Its descriptions of many disorders are intentionally sparse, simple, and incomplete. (This is especially true for schizophrenia.) DSM criteria were not designed for research, and they were certainly not designed for the types of sophisticated studies that examine vulnerability markers, unexpressed or subthreshold cases, or the relationship between subtle cognitive or brain changes and symptoms or outcome. Many people have grown accustomed to thinking of the DSM criteria for schizophrenia as a definition of "what schizophrenia really is." Yet architects of the DSM definitions were well aware of the fact that the descriptions and criteria were the product of a consensus and that the goal was to create reliable definitions, to make criteria "user friendly" for clinicians, and to avoid radical changes that might adversely affect existing databases that might be used for epidemiologic or other research.

Deciding on who has schizophrenia and which patients to include in studies is the **hardest** part of research. High-tech lab work programming workstations or running gels is easy by comparison. Most clinical questions are still open. What are the boundaries? Does the concept include schizoaffective disorder or nonpsychotic spectrum conditions such as schizotypal disorder or simple schizophrenia? Is a schizophrenia-like syndrome occurring in the context of substance abuse "really" schizophrenia? Is this disease a single entity? Is it heterogeneous? If heterogeneous, how do we delineate subtypes? What are the defining symptoms? Are they the psychotic symptoms that DSM emphasizes? Or are they the more fundamental Bleulerian symptoms—i.e., negative/cognitive symptoms? Or should we base the definition on symptoms at all? What is the characteristic course? What can course and outcome tell us about pathophysiology? What does epidemiology teach us about definitions or mechanisms? The questions are annoyingly endless. Ignoring their importance is an easy coping mechanism, albeit a shortsighted one. The optimal ways to answer these questions require deep thought by good minds using sophisticated and integrative approaches. Therefore, we need to make a serious investment in training a new generation of real experts in the science and art of psychopathology. Otherwise, we high-tech scientists may wake up in 10 years and discover that we face a silent spring. Applying technology without the companionship of wise clinicians with specific expertise in psychopathology will be a lonely, sterile, and perhaps fruitless enterprise.

N.C.A.