Deconstructing and reconstructing illness syndromes associated with psychosis

WILLIAM T. CARPENTER JR.
Department of Psychiatry, University of Maryland School of Medicine, Maryland Psychiatric Research Center, Baltimore, MD 21228, USA

Craddock and Owen summarize evidence supporting a movement away from the Kraepelinian dichotomy. They are correct in the assessment of evidence, but breaking down old boundaries does not establish new boundaries. One approach, however, is well suited for current application: the domains of pathology paradigm. I will briefly illustrate application with work from our group, and suggest where we may be headed with the DSM-V Schizophrenia and Related Disorders Work Group that I will chair.

Schizophrenia is a clinical syndrome. It has not been documented as a single disease entity. Nonetheless, most study designs during the 20th century investigated schizophrenia as a class. This may be analogous to studying dementia rather than specific entities such as Alzheimer's disease. Since specific disease entities had not been identified within the schizophrenia syndrome, we proposed using domains of pathology to reduce syndrome heterogeneity. This was based on the tripartite model that we published in 1974 (1), viewing schizophrenia as comprising positive psychosis, negative symptoms, and impairments observed in interpersonal relations. These domains were found to be rather independent of each other in our studies. Implementation of this model would be a paradigm shift, as we advocated the study of each pathologic domain as the independent variable allowing for differences in etiology, pathophysiology, and treatment between pathologic domains within the syndrome boundaries. However, at that time, the concept of nuclear schizophrenia was dominant and only recently has the domains of pathology paradigm received wide attention.

The 1982 type I/II (2) and positive *vs.* negative (3) proposals attempted to move the domains paradigm forward, but the dominant paradigm held sway. Cognition impairment and negative symptoms are now the focus for drug discovery, with the assumption of relative independence between these pathologies and psychosis (4,5). The failure of the schizophrenia as a disease entity model is seen in the porous boundaries addressed by Craddock and Owen, and is also evident in fifty years of producing antipsychotic drugs and complete failure to develop pharmacotherapy for cognition and negative symptoms.

At our center we focused on negative symptom pathology and advocated application of this domain to reduce heterogeneity in study samples (6,7). We studied schizophrenia, dividing subjects with primary negative symptoms (the deficit schizophrenia group) from subjects with a schizophrenia diagnosis but without primary negative symptoms (8). A series of studies supported the hypothesis that deficit schizophrenia was a separate disease within the syndrome (9). These studies addressed the 100-year challenge of determining whether Bleuler was correct in referring to the "group of schizophrenias".

What is the relevance of this work, which identifies multiple boundaries within schizophrenia, to the breakdown of boundaries between the major diagnostic classes associated with psychosis? I believe that the domains of pathology paradigm provides the best current method for addressing similarities and differences between classes. More importantly, domains of pathology will cut across diagnostic boundaries. Not all cases in any class will have a specific domain unless the domain is a required diagnostic criterion. This will go a long way in the current implementation that Craddock and Owen advocate. Restricted experience and expression of affect may occur in many patients with a schizophrenia diagnosis and few with a bipolar diagnosis. But genes that convey vulnerability to restricted affect pathology may be associated only with those schizophrenia subjects who have this pathologic domain, but also may be found in the few cases of bipolar illness where this pathology is observed between episodes of manic and depressive symptoms. Similarly, etiologic factors associated with hallucinations may be restricted to patients with hallucinations within each class, but be similar across classes. It would be surprising, indeed, if genes associated with vulnerability to depressive episodes in the general population were not also associated with depression in a subgroup of schizophrenia patients.

DSM-V is scheduled for 2011, and the Work Group for Schizophrenia and Related Disorders is being formed at the time of this writing. The DSM process will be a critical opportunity to see how far we can travel along the road outlined by Craddock and Owen. My prediction is that we will retain the major diagnostic classes with extensive similarity to DSM-IV and ICD-10. We simply do not have sufficient new knowledge to radically revise nosology for these illnesses. However, I believe that the shortcomings of the current classification will be substantially addressed by developing a parallel system based on domains of pathology. If a case meets criteria for schizophrenia, for example, it will be essential to also determine if the case meets criteria for certain dimensions. This will include symptomatic domains such as negative symptoms, disorganization, reality distortion, depression and anxiety. It may also include assessment of cognition and, should any have sufficient sensitivity and specificity, biomarkers. General dimensions such as social and occupational function may also be considered. In any case, such a two-step diagnostic approach will address four important problems: a) that domains of pathology cut across syndrome boundaries; b) that developing and applying new knowledge will be more decisive at the level of specific domains; c) that clinicians plan

treatment based on an individual patient's actual pathologies, not a syndrome designation; and d) that our ability to relate pre-clinical models to clinical phenomena is weak at the syndrome level, stronger at the domain level.

The field has much work to do on the roadmap provided by Craddock and Owen.

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