

## Schizophrenia as A Systemic Disease

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Although in the *Diagnostic and Statistical Manual of Mental Disorders* of the American Psychiatric Association (DSM) schizophrenia is listed as a psychotic disorder, DSM criteria include negative symptoms and psychomotor abnormalities as well as hallucinations, delusions, and disorganization. In recent years, the concept that cognitive impairment—problems in memory, attention, executive function, etc—is also inherent to schizophrenia is gaining acceptance, and cognitive markers are now used as endophenotypes to explore the genetics of schizophrenia.

If the concept of schizophrenia extends beyond psychosis and negative symptoms, how far should it go? What are the boundaries of schizophrenia?

In this theme issue, the authors explore that issue. Three of the articles review neuropsychiatric problems other than psychosis and negative symptoms. Dickinson and Harvey<sup>1</sup> argue that within schizophrenia, cognitive impairment is not confined to a few functions; rather, there is a generalized impairment. They also argue that the severity of this impairment may be related to physiological abnormalities, such as inflammation, that are found outside of the brain. Whitty et al<sup>2</sup> present the evidence that abnormal movements and neurological signs are not only intrinsic to the disease but also have an increased prevalence in the families of people with schizophrenia. Buckley et al<sup>3</sup> review other comorbid neuropsychiatric syndromes that have a high prevalence in schizophrenia, such as anxiety disorders and serious depression; some of these also appear to have a familial relationship to schizophrenia. A fourth article focuses on abnormalities outside of the brain. Compton and Walker<sup>4</sup> review the evidence on minor physical anomalies, which have also been found to have an increased prevalence in the relatives of people with schizophrenia.

There are important limitations to the evidence in each of these areas. Nonetheless, these reviews make a larger point: the boundaries of the heritable schizophrenia spectrum, and the boundaries of schizophrenia itself, are not certain, and may include problems other than psychosis and psychotic-like experiences, negative symptoms, and cognitive impairment.

New evidence that is not reviewed in these articles raises other questions about the boundaries of schizophrenia. Some<sup>5–8</sup> but not all<sup>9</sup> studies have found that compared with matched controls, newly diagnosed, antipsychotic-naive patients with nonaffective psychosis have an increased prevalence of impaired glucose tolerance, diabetes, or increased insulin resistance. This conclusion is far uncertain because some of these studies were weakened by problems in matching or possible confounding by hypercortisolemia. Another problem that may muddy these waters is that abnormal glucose tolerance in patients who are newly diagnosed, antipsychotic naive—and, consequently, usually relatively young—may be apparent only in the face of the physiological challenge of a glucose tolerance test. Another recent study found an increased prevalence of impaired glucose tolerance or diabetes in patients compared with controls: there was no difference in fasting glucose, but a robust difference was found in the results of a glucose tolerance test.<sup>10</sup> In that study, the 2 groups were matched for age, ethnicity, gender, smoking, body mass index, socioeconomic status of the family of origin, aerobic conditioning as measured by resting heart rate, and neighborhood of residence; moreover, the patients did not have increased cortisol concentrations compared with the control group. Inflammation<sup>10</sup>—a risk factor for diabetes—and abnormal immune function<sup>11–14</sup> may also be associated with schizophrenia and not solely because of confounding factors. No doubt medication side effects, poor health habits, poor access to health care, poverty, drug abuse, and other problems increase the risk of diabetes and other medical disorders within schizophrenia. However, the existence of these problems does not exclude the possibility that schizophrenia itself is associated with an increased risk of medical conditions. Findings in schizophrenia of low birth weight, a low body mass index in childhood and adolescence, and short stature<sup>15</sup> support the plausibility of the hypothesis that abnormalities in the periphery cannot be fully explained by confounding factors.

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If the boundaries of schizophrenia are broader than we usually think, why would it matter? Abnormal movements, physical anomalies, diabetes,<sup>16–18</sup> and neuropsychiatric disorders other than psychosis, negative symptoms, or cognitive impairment all may have an increased prevalence in the families of probands with schizophrenia. Should this familial association be confirmed, these disorders might be useful supplementary endophenotypes in genetic studies. There would also be implications for studies of pathophysiology and animal models.

The issue of the boundaries of schizophrenia is also important with regard to clinical care. The concept a clinician has of a disease dictates assessment, and assessment dictates the treatments patients are offered. An exclusive focus on psychotic and negative symptoms shortchanges patients because many people with schizophrenia have significant impairment in their function despite good control of psychotic symptoms. Many of the disorders reviewed in this theme issue are associated with poorer function within schizophrenia, and schizophrenia is associated with a striking increase in mortality rate.<sup>19</sup> Sensitivity to the importance of both the medical conditions and the neuropsychiatric disorders other than psychosis, negative symptoms, and cognitive impairment that have an increased prevalence within schizophrenia makes it more likely that patients will be offered appropriate treatments.

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