Genetic Epidemiology of Schizophrenia: Phenotypes, Risk Factors, and Reproductive Behavior

To the best of present knowledge, schizophrenia is a disorder with variable phenotypic expression and a poorly understood complex etiology, involving a major genetic contribution as well as environmental factors interacting with the genetic susceptibility. Multiple genes and alleles in different combinations may contribute to the genetic background, with a proportion of the transmitted genotypes remaining clinically unexpressed (1). Schizophrenia occurs in diverse populations at comparable rates (2), which is consistent with an ancient origin of its genetic basis, and—as far as records go—its incidence has not changed much for the past two centuries. Genetic epidemiology provides an integrating framework for research tackling this complexity. A quartet of articles in this issue addresses several of its many facets.

"The question about the factors that sustain the incidence of schizophrenia…has continued to exercise epidemiologists and geneticists."

Evidence for the salience of alternative, or "spectrum," phenotypes sharing a common genetic etiology with "core" schizophrenia is provided by Nicolson and colleagues, who report new findings from the National Institute of Mental Health study of childhood-onset schizophrenia in this issue of the *Journal*. Previous reports from this study (3, 4) have confirmed the syndromal continuity between early- and adult-onset schizophrenia, as well as the presence of neurocognitive, neurological, and neuroanatomical abnormalities common to both. However, childhood-onset schizophrenia is characterized by a greater clinical severity than the adult form and by a paucity of environmental correlates, such as maternal obstetric complications. These features, together with the higher concordance rate for monozygotic twins in childhood-onset schizophrenia (5), suggest a higher genetic load for the disorder in those families. Nicolson and colleagues compared the diagnostic assessments of parents of patients with childhood-onset schizophrenia, parents of patients with adult-onset cases, and parents of unaffected comparison subjects. Both sets of parents of schizophrenia patients had higher rates of schizophrenia spectrum disorders than the comparison set of parents, but the prevalence of such disorders was significantly higher in the parents of the childhood-onset patients, providing further evidence of an "enrichment" of susceptibility genes in childhood-onset schizophrenia. The findings are also consistent with the conjecture, first formulated by Bleuler (6), that the "latent" forms of schizophrenia (Meehl's "schizotypes" [7]) may be the more common phenotypic expression of the susceptibility genes underlying schizophrenia. However, the finding in the study by Nicolson et al. of equally low lifetime risks of overt schizophrenia in both groups of parents of schizophrenia patients is puzzling since the "gene enrichment" model would predict a higher risk for the childhood-onset group. Could it be that a higher lifetime risk in the parents of the childhood-onset patients remained undetected because of the small number of subjects or a selective recruitment bias? As childhood-onset schizophrenia is rare, pooled groups of affected individuals and family members ascertained by different research groups may provide the requisite power for a more stringent test of the hypothesis of a greater genetic vulnerability in these families.

In schizophrenia of adult onset, obstetric complications remain a prime candidate environmental factor contributing to the risk of the disorder. Compared to earlier studies, recent research into obstetric complications tends to be based on larger and better-defined population samples; to use prospectively recorded evidence of obstetric complications (e.g., from structured obstetric charts); and to explore putative pathogenetic pathways linked to specific obstetric complications, such as hippocampal volume reduction resulting from perinatal hypoxic damage (8). Although the evidence is not entirely consistent and some studies have not shown a relative excess of obstetric complications in patients with adult schizophrenia, the majority of the recent investigations go beyond simple counts of obstetric complications and explore the joint effects of genetic vulnerability and complications of pregnancy and birth (9). In this issue of the *Journal,* Sørensen and colleagues propose two novel pregnancy-related risk factors, based on findings from the Copenhagen Perinatal Cohort of 1959–1961 (7,866 individuals at risk). Both maternal hypertension during pregnancy (apart from the preeclampsia syndrome) and its treatment with diuretics in the third trimester of pregnancy were independently associated with schizophrenia in the offspring, and the association remained significant after adjustment for a maternal diagnosis of schizophrenia (but no paternal diagnoses are reported). Since hypertension in pregnancy and prescription of diuretics are not uncommon (19% of women in the Copenhagen cohort had hypertension, and 5% were treated with diuretics), further investigation of these risk factors and the mechanism through which they affect neurodevelopment (e.g., maternal plasma volume depletion) may have preventive implications.

In contrast to exposure to risks such as obstetric complications, the impact of which can be ascertained at the level of the individual, "ecological" candidate risk factors, such as urban residence, must be shown to be clear of "ecological fallacy"—an error in inference that may occur because observed associations between variables on an aggregate level do not necessarily represent associations that exist at an individual level (10). The urban environment has been implicated as a risk factor in schizophrenia since the classic studies of Faris and Dunham in Chicago (11), which showed a higher than expected rate of first admissions for schizophrenia in inner-city areas. Such findings led to two competing hypotheses: one of "drift" (urban environments attracting selective migration of preschizophrenic individuals) and another of a "breeder" influence (urban environments precipitating psychosis in genetically vulnerable individuals by the stress of social isolation and complex cognitive demands that characterize inner-city life). Studies in Denmark (12, 13) and the Netherlands (14, 15) have resuscitated the nearly forgotten "breeder" hypothesis by showing a higher risk of schizophrenia among people born in big cities than in people born in rural areas. A similar association has been reported for urban upbringing, regardless of place of birth, and the effects of urban birth or upbringing have been shown to be independent of familial risk for psychosis.

In this issue of the *Journal,* van Os et al. explore the relationship between familial risk of psychosis and urban residence as a risk factor by relating rates of psychosis, inferred from interviews with respondents in a large Dutch community survey (N=7,076), to their familial history of psychosis and to the degree of their exposure to "urbanicity" (defined as current residence, quantified on a scale of density of dwellings). Psychotic symptoms were reported as present in 3.8% of the community sample, and a DSM-III-R diagnosis of psychosis was made in 1.4%. According to the respondents, 3.6% of their first-degree relatives had ever experienced hallucinations or delusions and had received psychiatric treatment for a mental health problem. The relationship between family history of psychotic symptoms and "urbanicity" was then explored by computing the additive (synergistic) effects of the two risk factors. The risk of psychosis in the respondents rose from 1.59% in those exposed to urban environments alone and 3.01% in those exposed to familial risk alone to 9.72% in those exposed to both risk factors. According to the statistical model endorsed by the authors, "biological synergism" be-

tween family risk and the urban environment accounted for 60%–70% of the cases of psychosis in this sample.

An obvious caveat to the interpretation of the results of this study and other similar research is that the nature of the putative exposures subsumed under "urbanicity" remains entirely cryptic. "Urbanicity" could be a proxy for a broad range of heterogeneous physicochemical, biological, and psychosocial exposures, but so far none has been demonstrated to be consistently associated with the incidence of schizophrenia. Unless a direct influence on the incidence of schizophrenia can be shown for a specific factor, results of studies on "urbanicity" remain vulnerable to ecological fallacy. At the same time, the "drift" hypothesis, largely neglected in recent debates about urban birth and the incidence of schizophrenia, harbors plausible clues. Migration is the most potent vehicle for the transfer of genes across populations and geographic regions, and in many parts of the world rural-urban migration has been occurring during much of the last century, increasing greatly in scale in more recent generations. The urban birth phenomenon in schizophrenia must be of a relatively recent origin since a study by Astrup and Ødegaard, published in 1961 (16), showed only a weak effect of birthplace, and there is evidence that the effect of urban birth on the risk of schizophrenia is stronger in the more recent birth cohorts (14). Demographic data from the Netherlands (17) indicate that a large-scale rural-urban and urban-suburban migration, culminating in the early 1970s, involved a large number of young people moving to urban agglomerations. Among the rural-urban "movers," 44.5% were unmarried and 58.4% had no children yet (compared to 15.4% and 23.7% among the "stayers"). If we assume 1) that a proportion of the population (which may be as high as 10%) carry vulnerability genotypes that are either unexpressed or expressed only partially as "spectrum" personality traits and 2) that for people with "spectrum" traits the chances of finding a partner and bearing children are higher in urban environments than in rural areas, the expected proportion of offspring (per 1,000 births) inheriting vulnerability alleles from one or both parents would be higher in urban areas than in rural areas. The net effect would be a relative excess of persons at high risk for schizophrenia among the city-born, even without the assumption of an overrepresentation of individuals with "spectrum" traits in the flow of migrants to the cities. Thus modified, a "drift" hypothesis postulating that the fertility of individuals with "spectrum" traits is higher in urban areas than in rural areas merits consideration and may account for the observed association between urban birth and the incidence of schizophrenia.

The related issue of fertility among patients with schizophrenia and their siblings is discussed in this issue of the *Journal* by Haukka and colleagues, who report findings from a large (N=870,093) Finnish cohort, comprising all births during 1950–1959 and followed up through the national hospital discharge register for hospitalizations between 1969 and 1992. Since the first epidemiological study on the reproduction of people with psychoses by Essen-Möller in 1935 (18), diminished fertility among individuals with schizophrenia has been documented by numerous investigators. Coupled with the evidence that the lifetime risk of the disorder (about 1%) is similar across populations and stable over time, the question about the factors that sustain the incidence of schizophrenia despite a clearly reduced reproductive fitness of the affected individuals has continued to exercise epidemiologists and geneticists.

Haukka and colleagues found, unsurprisingly, that fertility (the mean number of offspring) in both male and female patients with schizophrenia was markedly lower than in the general population and that the difference was more pronounced in men. Among the unaffected siblings of the patients, fertility was moderately lower than average in the brothers but mildly higher in the sisters. The authors show that the minor degree of greater fertility in the sisters, although statistically significant, cannot compensate for, on the population level, the lower fertility of the patients. They consider alternative explanations that might resolve the seeming discrepancy between the population rates of

schizophrenia and the lack of a compensatory higher fertility rate among relatives. The hypotheses considered include de novo germ-line mutations, greater fertility among individuals with schizophrenia spectrum disorders and/or their relatives, and selectively greater neonatal survival of carriers of schizophrenia susceptibility genes in regions with high neonatal mortality (such regions are no longer present in Finland, but if selective neonatal survival exists at all, it must still be operating in many parts of the world). Each one of the proposed mechanisms can claim some degree of support from the reported findings. However, a question to address first is whether the uncompensated low fertility in patients with manifest schizophrenia indeed constitutes a demographic anomaly that is difficult to reconcile with current knowledge about the genetic epidemiology of the disorder. An early hypothesis about the issue was proposed in *Nature* in 1964 by Huxley et al. (19), who argued that the high frequency of schizophrenia was evidence of a balanced polymorphism whereby the low fertility rate of affected individuals was compensated for by a higher than average fertility rate of "cryptoschizophrenic carriers." Such carriers were thought to possess some selective advantage, e.g., high resistance to shock, autoimmune disease, or infection that increased their reproductive fitness. The hypothesis bore obvious similarities to the "malaria resistance trait" proposed earlier by Haldane (20) to explain the maintenance, in parts of Africa and the Mediterranean, of recessive hemoglobinopathies such as sickle cell anemia and thalassemia through the protective effect of heterozygosity for hemoglobin variants against endemic malaria. Attempts to demonstrate a comparable advantage for schizophrenia or the related spectrum phenotypes, e.g., in disease resistance, abilities and creativity, or adaptability to extreme environments, have been unsuccessful. It is unlikely that if any such advantage exists, it would be difficult to detect. Huxley et al. assumed that schizophrenia was a single-gene disorder with a low penetrance. Today, most geneticists assume multiple genes, incomplete or variable expression of the genotype, and locus heterogeneity, both across and within populations. The multiple-genes model implies that the loss of susceptibility alleles resulting from the lower reproductive fitness of affected individuals would have a negligible effect on the overall gene pool in the population. A simplified illustration is provided by cystic fibrosis, a common autosomal recessive disorder in which only 1%–2% of the disease-causing alleles are subject to selection because of the low fertility of affected individuals, whereas the remaining 98%–99% of alleles remain latent within clinically unaffected carriers. As regards the hypothesis of de novo mutations, it is now known that mutation rates for most genes fall within the range of 10^{-6} to 10^{-5} per generation (21); therefore, the contribution of new mutations to the maintenance of the incidence of schizophrenia would be insignificant. Unless schizophrenia is exempt from the general laws governing genetic diseases, it is here to stay. The question is how to mitigate its devastating effects on individuals and communities.

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