Accumulating Evidence for Prenatal Nutritional Origins of Mental Disorders

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The study by St Clair et al1 in this issue of JAMA reports an association between prenatal exposure to severe maternal nutritional deficiency and risk for schizophrenia. Examination of this question was achieved through strategic use of the Chinese famine of 1959 through 1961 as the fulcrum of their study design. In so doing, these authors afford yet another excellent example, frequent among articles in the annual JAMA theme issue on violence and human rights, of epidemiologists extracting otherwise inaccessible scientific knowledge from the harsh soil of human catastrophe.

Susser and Lin2 were the first to demonstrate this link between severe maternal nutritional deficiency and the offspring’s risk for schizophrenia. That earlier study, which served as the scientific impetus and analytic model for the current investigation, examined the association between nutrition and schizophrenia using the unique circumstances created by the Dutch Hunger Winter of 1944-1945. In October 1944, the German Army blockaded food supplies to the Western Netherlands as punishment for Dutch involvement in the planned Allied invasion of Europe. Before the blockade, the food supply had been adequate; in May 1945, following the German retreat, it became quickly plentiful again. In the intervening months, however, the Dutch population, particularly in the larger cities, received increasingly meager food rations, a circumstance rendered especially difficult by an unusually harsh winter. Hence, Dutch women who were pregnant in October 1944 and others who conceived in the following months experienced declining food supplies at varying points in gestation.

This wartime disaster, occurring in a previously well-nourished industrialized nation, created a natural experimental framework for examining the association of prenatal nutritional deficiency of varying intensity imposed at different points in intrauterine development with risk for postnatal psychiatric disorder in offspring. Analyses of rates of schizophrenia based on case data derived from the Dutch national psychiatric registry implicated early severe prenatal nutritional deficiency in a 2-fold increased risk of schizophrenia overall and in men and women offspring separately.3 Parallel studies, drawing on results from the medical examinations conducted on 18-year-old Dutch military recruits, documented a 2- to 3-fold increased risk for schizoid personality disorder and for antisocial personality disorder, respectively, among persons exposed early in gestation to severe maternal nutritional deficiency.4,5

The schizophrenia findings from the Dutch and Chinese famine studies are in remarkable agreement, a consistency that enhances the validity of both investigations. St Clair et al1 also report a 2-fold increased risk for schizophrenia among individuals prenatally exposed to famine both overall and for each sex separately. Furthermore, the profile of both “epidemics” is entirely analogous although on vastly different temporal and population scales—an abrupt rate increase among individuals prenatally exposed to the famine followed by a rapid return to previous background rates at the close of the nutritional crisis. Of equal importance from the perspective of confidence in drawing causal inferences, the Chinese study successfully addresses several competing explanations for the Dutch findings, noted but not remediable in the studies on the Dutch famine.

The nutritional interpretation of the Dutch famine findings was vulnerable to a variety of alternative explanations. Tulip bulbs, consumed at the height of the famine as a food substitute, could have exerted toxic effects on fetal brain development. Hormonal perturbations prompted by the physiological stress of the exceptionally cold winter, some unidentified aspect of urban life under German occupation toward the very end of the war, or the extremely rapid nutritional repletion starting in May 1945—each jointly or separately might have disturbed neuronal maturation. The Chinese replication of the Dutch findings, given the markedly different circumstances, culture, and ethnicity, renders these competing explanations moot or nearly so. During the Chinese famine, food substitutes comprised tree bark and the green algae chlorella, grown at home in vats of urine; the nutritional deprivation did not coincide with unusually harsh winters nor with military occupation by a foreign power.

See also p 557.
The recovery from starvation and return to adequate nutritional levels were gradual. In addition, unlike the Dutch famine, rural not urban areas were the more profoundly affected regions.

Selective reproduction posed a special challenge as a competing explanation for the Dutch findings. The observed association of famine and schizophrenia was compatible with the phenomenon of selective procreation whereby individuals with susceptibility alleles for schizophrenia were overrepresented among people conceiving children during this period of evident physical insecurity and social uncertainty. St Clair and colleagues address this logical loophole in the nutrition argument empirically. Among the cases with schizophrenia, the authors found that the proportion having relatives with mental disorder was the same for those born before, during, or after the famine years. This result reduces the plausibility of selective procreation as a credible explanation for the Dutch or for the Chinese findings. Nevertheless, family history data are generally sufficiently unreliable that appreciable true differences could be present but entirely obscured by measurement error.

In both studies, rates of schizophrenia pertain to persons in treatment, with the Dutch analysis further restricted to psychiatric admissions. This limitation is not trivial. A substantial proportion of individuals meeting criteria for schizophrenia do not come to psychiatric attention. According to one US study, 40% of persons with a lifetime diagnosis of schizophrenia never had a psychiatric admission. Similarly, an Indian survey estimated that one third of persons meeting criteria for schizophrenia were unknown to mental health treatment providers, either as psychiatric inpatients or outpatients. The theoretical possibility exists, therefore, that some factor, coincident with famine exposure, increased case ascertainment and entry into treatment. However, no candidate factor readily presents itself. Additionally, findings of a famine effect for antisocial personality disorder and schizoid personality disorder, based on cases ascertained independently of treatment status, further reduces this threat to the validity of study inferences.

The Dutch famine afforded an opportunity for exquisite precision regarding the timing (early gestation) and degree of nutritional deficiency (average food rations during the first trimester <1000 kcal daily) associated with increased risk for schizophrenia. The association was further refined by using a broad and then a stringent definition of schizophrenia, with the latter, as hypothesized, resulting in a stronger effect size. Similar refinements, rigorously pursued, were infeasible in the Chinese study. Nevertheless, the size of the study population—the number of exposed cases available for analysis being many multiples larger than what was available in the Dutch study—adds appreciably to the strength and credibility of the Chinese investigation and to its successful replication of the basic Dutch findings.

The Chinese study, while providing invaluable confirmation of the earlier Dutch work, unfortunately is not able to directly advance understanding of how nutrition may perturb prenatal neural development so as to influence risk for schizophrenia. The most pressing question from a public health and interventionist perspective is whether the relevant nutritional restriction of interest constitutes a global nutritional deficiency or a specific micronutrient deficiency. If the former, the implications of this work are confined largely to developing countries where severe protein-calorie malnutrition is common—certainly a matter of enormous public health and humanitarian concern in its own right. If the latter, the implications extend to developed and developing countries alike.

The role played by prenatal folate deficiency in risk for neural tube defects serves as a useful model for understanding the possible contribution of micronutrients to brain development more generally. Recent advances in the understanding of DNA methylation now render folic acid a candidate micronutrient, not simply an exemplar, in the search for an understanding of nutrition and schizophrenia. Dietary levels of methyl-donor components, eg, folic acid, influence DNA methylation. In turn DNA methylation at cytosine guanine dinucleotides is capable of producing changes in gene expression and function without disrupting the primary DNA sequence. Diet-triggered DNA methylation may therefore constitute another weapon in the arsenal of environmental agents capable of producing changes in gene activity. Research published within the last 5 years documents a role for such DNA-methylation changes in DNA expression in early development and in several adult-onset disorders. A recent meta-analysis by Lewis and colleagues linked the MTHFR C677T genotype, known to play a role in folate metabolism, with risk for schizophrenia, thereby directly implicating folate metabolism and intracellular availability of folate metabolites for methylation with the development of schizophrenia. Although these results await elucidation, conceptualizing certain cases of schizophrenia as instances of a genetic neurodevelopmental disease, where prenatal-nutrition altered gene expression is an attractive hypothesis. It raises the possibility, a prospect once considered entirely utopian, of primary prevention strategies for this most devastating of psychiatric disorders.

In modern times, famine is not the consequence of failed crops so much as the result of political decisions, backed by military force, or of misguided economic planning and food distribution. The Dutch famine, while exacerbated by an unusually harsh winter, resulted primarily from the punitive, politically driven military tactics of the Third Reich: the artificial restriction of food supplies to the Netherlands by the German Army. By contrast, the Chinese famine resulted in large measure from economic policies adopted during the Great Leap period aimed at transforming China’s agricultural and social systems and by the transfer of grain from stricken rural areas to urban centers and abroad. Today, “state sponsored” starvation is endemic in parts of Africa. And all too familiar forces drives the famine in South
Mental Illness and Violent Death
Major Issues for Public Health

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SUICIDE AND HOMICIDE ARE THE FOURTH AND FIFTH LEADING CAUSES OF DEATH FOR PERSONS AGED 10 TO 60 YEARS IN THE UNITED STATES.1 Suicide completion and homicide perpetration are associated with previous attempts at self-harm2 or violence toward others,3 and both of these predominant causes of violent death are associated with mental illness.

In 2002 there were 31655 suicide deaths in the United States for a rate of 10.99 per 100 000 population.1 Persons who attempt suicide are 38 to 40 times as likely to commit suicide as are persons without previous attempts.4 The population-based National Comorbidity Survey Replication, conducted in 2001-2003,5 reported that 3.3% of US residents aged 18 to 54 years had seriously thought about killing themselves in the past 12 months. Of this group, 28.6% made a plan to kill themselves and 32.8% of those who made a plan carried out a serious attempt to commit suicide. More than 80% of persons reporting these suicide-related behaviors met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria for mental illness, including mood disorders, anxiety disorders, impulse-control disorders, and substance use disorders.

See also pp 563, 598, and 616.

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There were 17638 homicide deaths in the United States in 2002 for a rate of 6.12 per 100 000 population.1 We were unable to identify population-based estimates of mental illness and homicide offending for the United States, but a population-based study of homicide offenders in Sweden who had received multidisciplinary psychiatric evaluations found that 54% had a principal or secondary diagnosis of personality disorder, 47.3% had a principal or secondary diagnosis of substance use disorder, and 25.2% had schizophrenia, bipolar affective disorder, or other psychoses.6 Persons with substance use disorders are 12 to 16 times more likely than persons without substance use disorders to engage in violent behavior:7 This association is strengthened among persons with co-occurring personality disorders (such as antisocial personality disorder) or major mental illness (such as schizophrenia). A review of clinical risk factors for violence identified 4 personality dimensions associated with violent behavior: poor impulse control, problems with affect regulation, threatened egotism or narcissism defined as an inflated sense of self-worth and entitlement, and paranoid cognitive personality style.

It is clear that mental disorders, including substance use disorders, are common among persons who demonstrate suicidal or violent behaviors. These data confirm that some persons with mental illnesses may be at risk of harming themselves or others. However, mental illness is also common...