

IN SESSION with Dolores Malaspina, MD, MSPH

Impact of Childhood Trauma on Psychiatric Illness



Dr. Malaspina is professor of psychiatry at Columbia University College of Physicians and Surgeons, and director of the Medical Genetics Division of Clinical Neurobiology at New York State Psychiatric Institute in New York City. Her research concerns the neurobiology and heterogeneity of schizophrenia. She has published more than 150 scientific contributions and is a reviewer for research grants and numerous psychiatric journals. Dr. Malaspina has received the Exemplary Psychiatrist Award from the National Alliance for the Mentally Ill, the NARSAD Ritter Award, and the Research Award from the New York State Office of Mental Health. She is a fellow of the American College of Neuropsychopharmacology and is a distinguished fellow of the American Psychiatric Association.

How did you get interested in researching the relationship between early stress and subsequent psychiatric disorder?

I became interested in stress sensitivity before I went to medical school while I was working in the pharmaceutical industry. At that time, we were culturing rat pituitary cells to use for dopamine receptor studies. I had the unpleasant job of picking up and handling the adult rats the day before the study. We thought that this handling would reduce their stress responses on the study day. Petting the adult rats probably did very little to reduce their stress response. Years later, Meaney and colleagues¹ showed that it is the vigorous licking of a rat pup by its mother after a brief separation, and not the human handling, that lowers

its stress response. Maternal licking during critical early periods can reprogram the genes in the hippocampal-hypothalamic-pituitary-adrenal axis to permanently lower stress reactivity and reduce glucocorticoid responses to stressors.

Nonetheless, I became interested in how experiences could lead to later changes in stress sensitivity. I was able to incorporate that interest into schizophrenia research by probing the common idea that schizophrenia results from an interaction between a genetic diathesis and a “stressor.” My approach to schizophrenia is that it is not one single disease, but rather that it is a group of different disorders, and that one pathway to schizophrenia may involve a sensitivity to stress. For a number of years my group has studied the hypothesis that early life events and stress sensitization could trigger the illness in some individuals.

This interview took place on April 26, 2006, and was conducted by Norman Sussman, MD.

Does stress explain why identical twins do not have the same rates of schizophrenia?

Identical twins share their entire DNA, but if one twin develops schizophrenia, the other is only 50% likely to develop the disease. This data shows that epigenetic and environmental events also contribute to the risk for schizophrenia. The predisposing events may be considered to be the stressors. They probably include pregnancy adversities, obstetric complications, and certain events in childhood and adolescence. These exposures may change the way that genes are expressed, which may be a risk factor for the disease.

Can prenatal stress lead to the development of schizophrenia?

Severe prenatal adversity could cause schizophrenia, even though the disease does not present until late adolescence or early adulthood. Perhaps the best known evidence for this is the much higher risk for schizophrenia among the Dutch population who were exposed to severe nutritional deprivation in early pregnancy during the Dutch Famine Winter of 1944–1945, compared to those who were not exposed to the famine.² During the Nazi blockade of Holland, the genetically homogeneous Dutch population was divided because part of Holland was under Allied control and was well-fed, while the other side was starved. A very limited period of severe famine resulted in a doubling or even tripling of the risk for schizophrenia for individuals who were prenatally exposed. This was one of the first direct demonstrations that an environmental stressor occurring during early gestation could increase the risk for schizophrenia.

Famine is one kind of adversity, but many other fetal exposures are also linked to schizophrenia. These include maternal infections, medical conditions, maternal obesity, and maternal malnutrition. Pregnant women who are obese, starved, or have severe prenatal stress exposure all have an elevation of their glucocorticoids. It may be that elevated stress hormones are a final common pathway for schizophrenia from an array of different prenatal problems. The stress hormones of the mother in early pregnancy can determine gestation length. If it is an adverse time for a mother to be pregnant, it benefits the fetus and the mother if the birth occurs sooner. In an effort to have the baby develop as quickly as possible, fewer cells may be generated in the fetus, resulting in perhaps fewer neurons.

The stress also can program fetal gene expression in the hypothalamic pituitary adrenal axis to increase life-long stress sensitivity. Another view of these events is that the developing fetus receives a signal from the mother that the world

into which it will be born is likely to be adverse, and it adapts accordingly. For humans, having a high stress response is not particularly beneficial in our world where most stress is psychosocial and it never ends. But in other mammals, and perhaps at other times in human evolution, if an offspring was born into a dangerous world, increased stress sensitivity might enhance its ability to survive. For contemporary humans, that stress sensitivity also increases the risk for cardiovascular disease, diabetes, hypertension, and abdominal obesity. While we see these as signs of disease risk, those same physiologic adaptations may have helped early humans survive a time of famine, adversity, predation, or other hardships.

What are the effects of chronic stress exposure on a fetus?

This is an important question. Sadly, there are high levels of chronic stress in many parts of the world, yet we know little about which offspring are susceptible to stress effects or how to protect them. My colleagues and I have been studying the effects of the 1967 Six Day War in Israel. We are examining data collected on 100,000 pregnancies in Jerusalem between 1966–1974. At that time, Israel was a young nation trying to understand its health needs. Information was collected in early pregnancy and ratings were done of each baby's health at delivery and during the first few years of life.³ Many years later, without revealing any individual identifying information, researchers in the Ministry of Health linked the birth cohort to the psychiatric registry. The results for the Six Day War showed a very strong risk for schizophrenia for offspring who were exposed to the war stress in the first trimester. The risk was up to four times as high for female babies, and was dramatically increased for babies of mothers who lived in the areas that received direct shelling.⁴

The Six Day War data is so interesting because there was no accompanying malnutrition or illness, so the stress was predominantly psychosocial. It was also time limited, so that we could look at the effects based on gestational age. It is important to note that the first trimester of pregnancy is a time when most women are not even aware that they are pregnant. One important health question is to determine the implications of lesser amounts of stress on the health of offspring. Schizophrenia may be one extreme end. However, what probably happens far more commonly is the effects of prenatal stress on those who do not have schizophrenia vulnerability genes. The prenatal stress exposure increases one's sensitivity to stress and that may or may not lead to the development of a psychiatric disease, depending upon the environment that someone is exposed to during his or her lifetime.

Were studies conducted on rates of schizophrenia among children who were in utero during September 2001?

It is far too soon to answer this question, since the disease does not have its onset until late adolescence or early adulthood. However, there are ongoing studies. It has already been found that pregnant women who lived near the World Trade Center in the month after September 11 were more likely to have low birth weight babies and to have had shorter pregnancies.⁵ Some of the hallmarks of fetal adversity are a slightly smaller birth weight and being a few weeks early—that is, a pre-term birth, not babies that are commonly considered to be premature. The study is important, especially at this time in history when there is exposure to so much news of trauma. It may be that the world is more chaotic and dangerous now, but also because of news and communication we do not have periods of time where a culture may have many decades of apparent stability.

Previously, populations may have had at least a few generations that were uninterrupted by natural disasters or war. The stress effects on a developing fetus probably occur through epigenetic mechanisms like methylation, which change gene expression without changing their sequences. Methylation patterns set during fetal development can last for the life of the human, but some epigenetic changes that arise because of an adverse pregnancy can also persist for a few generations. Thus, the grandchild of someone who had been exposed to severe prenatal stress can have a low birth weight, even if their intrauterine environment was favorable.

Were there any false starts in your research?

In light of the fact that schizophrenia often follows a stressor, my colleague Cheryl Corcoran, MD, and I hypothesized that an excess of severe life stress might be related to symptoms in individuals with prodromal psychosis. These patients are 12–25 years of age and have signs of deterioration in function and a family history of schizophrenia, or they have transient positive symptoms and impaired functioning. We did not find that the patients had more stresses than other teenagers, but rather that they had an increase in their sensitivity to the stresses.⁶ Even mundane things can cause a problem in someone who copes poorly. So it may not be the amount of stressors for some people, but rather their sensitivity to that stress that affects their neural functioning.

What is the most irrefutable finding that you and your colleagues have made?

The most irrefutable finding is our demonstration that a father's age is a major risk factor for schizophrenia. We were the first group to show that schizophrenia is linearly related to

paternal age and that the risk is tripled for the offspring of the oldest groups of fathers.⁷ This finding has been born out in every single cohort study that has looked at paternal age and the risk for schizophrenia. The only other finding that has been as consistently replicated in schizophrenia research is that there is an increased risk associated with a family history of schizophrenia. Since only 10% to 15% of schizophrenia cases have a family history, family history does not explain much of the population risk for schizophrenia. However, we think that approximately one third or one quarter of all schizophrenia cases may be attributable to paternal age. Paternal age is the major source of *de novo* genetic diseases in the human population, which was first described by Penrose⁸ in the 1950s. He hypothesized that this was due to copy errors that arose in the male germ line over the many cycles of sperm cell replications. These mutations accumulate as paternal age advances. After the Penrose report, medical researchers identified scores of sporadic diseases in the offspring of older fathers, suggesting that these could occur from gene mutations. Particular attention was paid to conditions in last-born children. In the 1960s, an excess of schizophrenia in last-born children was also reported. However, rather than entertaining the main medical hypothesis being explored at that time, the finding of more schizophrenia in later-born children nourished the idea that schizophrenia could be caused by an unavailable mother, soon to be called a schizophrenogenic mother, rather than showing its genetic nature. This perception was a result of the unfortunate idea that psychiatric disorders did not have the same types of biologic underpinnings as other chronic diseases prevalent in the United States from the 1940s through the 1970s. Another rationale for those ideas, which I do not fault, was that if schizophrenia was caused by dysfunctional families, perhaps it could be cured with good treatment. Genetic conditions were seen as being too hopeless and off limits in the years following the Nazi genocide.

What kinds of intervention are useful?

It appears that biologically intervening early and effectively might improve the course and long-term outcome of schizophrenia. This approach is common in the treatment of cardiovascular diseases, where intervening to lower lipids; treat hypertension; and modify weight, smoking, and lifestyle behaviors is clearly linked to a better outcome. Perhaps depression and schizophrenia need to be considered similarly, with an understanding that with thorough treatment and early interventions we may really improve people's long-term outcomes.

In my opinion, the field has not demonstrated that using antipsychotic medications in people who are not yet psychotic improves their outcome. However, it is clearly a good idea to thoroughly treat psychosis with medication when it is present.

My colleagues and I are also looking at cannabis as a trigger of psychosis. Hopefully we can better understand what moves someone from simply being vulnerable to actually having psychosis. Then we might be able to offer some lifestyle changes and other interventions that can benefit individuals at risk for psychosis, rather than using potent antipsychotic medications.

Aside from adversity, is there evidence that changes in the status quo can cause stress?

There are physical and psychologic sequelae, costs, or repercussions involved in the adaptation to significant stress, which McEwen⁹ called the allostatic load of stress. However, changes in the status quo are not necessarily damaging to us. Healthy humans seek out novelty and challenges. Perhaps we need to distinguish between the usual stress of change and stimulation in our lives, and stimuli that is perceived to be threatening.

For a while, there was a diminished interest in the role of stress in human psychiatric diseases, since stress was considered to be too ubiquitous to explain these conditions. Now, we understand that the programming of the stress response system and expo-

sure to stressors can interact with other disease risk factors. I recall a grant critique not that many years ago that commented to me that looking at a role for stress in explaining some of the deterioration of schizophrenia was old fashioned. We had lost our way for a while by thinking that stress is so common that it could not possibly be linked to human psychiatric disorders. **PP**

REFERENCES

1. Meaney MJ, Tannenbaum B, Francis D, et al. Early environmental programming hypothalamic-pituitary-adrenal responses to stress. *Semin Neurosci.* 1994;6:247-259.
2. Susser E, Neugebauer R, Hoek HW, et al. Schizophrenia after prenatal famine. *Arch Gen Psychiatry.* 1996;53(1):25-31.
3. Harlap S, Davies AM, Grover NB, Prywes R. The Jerusalem perinatal study: the first decade 1964--73. *Isr J Med Sci.* 1977;13(11):1073-1091.
4. Malaspina D, Harlap S, Fennig S, Corcoran C, Susser E. Maternal stress and offspring schizophrenia risk. *Biol Psychiatry.* 2003;53(suppl):168S.
5. Berkowitz GS, Wolff MS, Janevic TM, Holzman IR, Yehuda R, Landrigan PJ. The World Trade Center disaster and intrauterine growth restriction. *JAMA.* 2003 6;290(5):595-596.
6. Corcoran C, Cornblatt B, Malaspina D, Goetz R. Stress reactivity and positive symptoms during the prodrome. *Biol Psychiatry.* 2004;55(suppl):26S.
7. Malaspina D, Harlap S, Fennig S, et al. Advancing paternal age and the risk of schizophrenia. *Arch Gen Psychiatry.* 2001;58(4):361-367.
8. Penrose LS. Parental age and mutation. *Lancet.* 1955;269(6885):312-313.
9. McEwen BS. Allostasis and allostatic load: implications for neuropsychopharmacology. *Neuropsychopharmacology.* 2000;22(2):108-124.