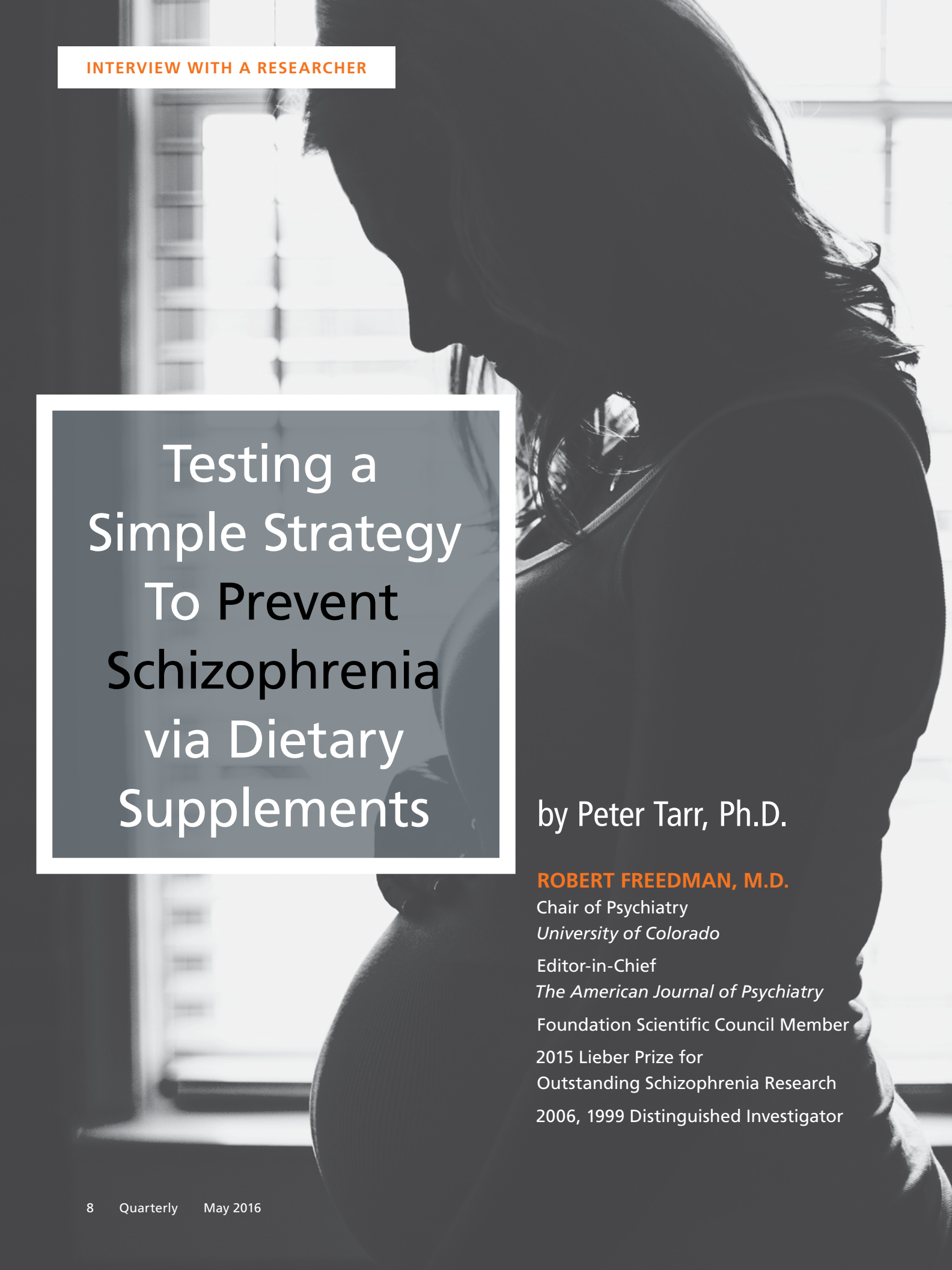

Testing a Simple Strategy To Prevent Schizophrenia via Dietary Supplements

by Peter Tarr, Ph.D.

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2015 Lieber Prize for
Outstanding Schizophrenia Research
2006, 1999 Distinguished Investigator

AT WHAT POINT do the fruits of basic research—the hard-won bits and pieces of knowledge about brain function that the Foundation's grants generate—result in the development of new treatments? There's an exciting example now emerging in the laboratory run by Robert Freedman, M.D.

Dr. Freedman, Chair of Psychiatry at the University of Colorado, editor in chief of *The American Journal of Psychiatry*, and a member of the Foundation's Scientific Council since 2001, has been on a long journey that began in medical school at Harvard in the late 1960s.

The winner of the 2015 Lieber Prize for Outstanding Schizophrenia Research and twice (2006, 1999) a Distinguished Investigator, Dr. Freedman has been on the trail of what neuroscientists call inhibition—specifically, its role in schizophrenia. Inhibition refers to the brain's ability to dial down the strength of signals being exchanged among excitatory nerve cells. In schizophrenia, evidence suggests that an insufficiency in inhibition leads to hyperactivity in key areas involved in cognition and emotional processing.

Much of what Dr. Freedman and his colleagues have learned over decades has been translated into a simple and safe preventive strategy to bolster inhibition in the fetal brain, and thereby lessen the risk and perhaps actually prevent some newborn children from developing schizophrenia—one of the great objectives in all medical research.

The strategy involves providing expecting mothers with supplements of choline, an essential nutrient that plays an outsized role in the fetal brain while it is developing in the womb. The fetal brain is hyperactive as it assembles itself. "It just fires up all of its nerve cells, no inhibition whatsoever," Dr. Freedman says. "Of the 20,000 genes we humans have, more are devoted to building the brain than anything else. And most of them are most active—about tenfold more—before birth compared with after."

Just before birth all this activity needs to quiet down, however. "The brain is settling down," Dr. Freedman explains. "This turns out to be the final step right before delivery, the last of five or six distinct steps which correspond with major changes in brain organization." In each step, he says, "you not only get more memory and more function—as you do each time you upgrade your computer—but you also install a new operating system. In the early brain, each operating system is installed by the one that came before it."

Robert Freedman, M.D.

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Dr. Freedman's research focuses on one of the earliest operating systems, which unlike the others that follow it, "hangs around to do the very last installation." This final step in the pre-birth developmental program makes normal inhibition possible.

Evidence shows that in infants who go on to develop schizophrenia, the brain's inhibitory system does not establish itself as robustly as it should. The results are evident to those who treat and spend time with patients, including Dr. Freedman, still an active clinician.

"You may hear a patient say, 'I vaguely overheard someone talking and I concluded they were talking about me, and that they were saying bad things.' There is often a hypersensitivity to sound. When you investigate, the sound is really there, but misinterpreted. You or I would probably ignore it as noise, if we did hear it. We might say, 'This is a noisy apartment.' But we wouldn't say, 'And they're talking about me.'"

A hypersensitivity to sensory information, accompanied by difficulty discriminating the nature or emotional salience of the information, is characteristic in schizophrenia. It can be traced biologically, at least in part, to a deficiency in inhibition. There is too much excitation, not enough inhibition—as, indeed, Dr. Freedman and colleagues showed in a schizophrenia study of the brain's hippocampus, a vital center for emotional processing. Even in its "resting state," this part of the brain is hyperactive in people with schizophrenia, the study showed.

Several converging lines of evidence have pointed Dr. Freedman to a gene called *CHRNA7* (pronounced "CHUR-na 7"). Very active early in development, the gene quiets down just before birth to a low activity level that continues into adulthood. This is the gene, it turns out, that encodes receptors on nerve cells that become vital at the end of gestation, in the emergence of neural inhibition. The receptors are called alpha-7 nicotinic receptors, or α7 receptors.

CHRNA7 is the gene whose expression is most significantly decreased in the brains of people who have had schizophrenia (as measured in postmortem brain analysis). Genetic studies have also shown that a subset of schizophrenia patients have genomes in which the area on chromosome 15 containing *CHRNA7* is deleted, meaning they do not make enough α7 receptors.

In adults, α7 receptors are activated by a neurotransmitter called acetylcholine. In related research, Dr. Freedman and colleagues have been testing drugs that stimulate the α7 receptor in adults with schizophrenia—who, presumably, have had insufficient inhibitory activity from the time near birth when the system is first activated.

In the fetus, it is choline in the mother's amniotic fluid that activates these receptors. Choline is needed throughout pregnancy in considerable amounts for various purposes, not only to prepare the brain's inhibitory system but also to build the walls of cells throughout the body. Studies show that one expectant mother in five does not get enough choline in her diet. While meat and eggs are rich sources of the nutrient, which is also found in many other foods, poor diets do not supply nearly enough.

These facts led Dr. Freedman and colleagues to an experiment that has taken the last nine years to complete. They wanted to know whether giving expectant mothers extra choline in the second and third trimesters might help their children develop more robust inhibitory capacity. [The accompanying story explains how they conducted the experiment and showed that it works.]

"The larger story is that we've gone from learning ways in which the nervous system doesn't work in schizophrenia to actually doing something to prevent it from happening," says Dr. Freedman. "This is the first group of children that we can point to and say, yes, we can treat earlier and do it effectively."

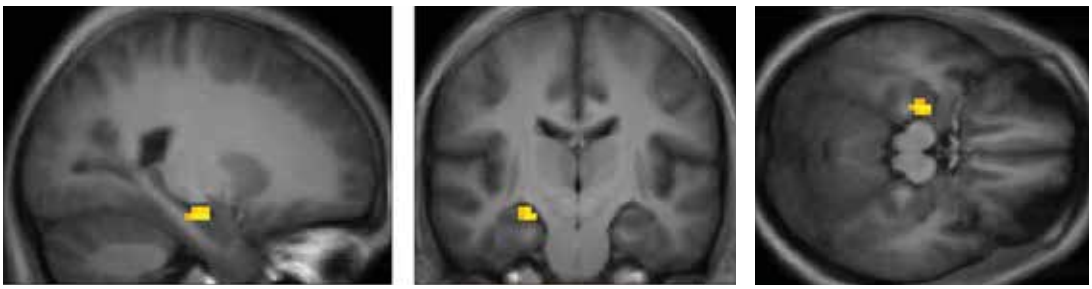
INTERVIEW WITH A RESEARCHER / SIDEBAR

Choline Supplementation in Mothers Has Yielded Positive Results in Children

"We know that babies born to moms who have schizophrenia, as well as babies from other moms who later go on to develop schizophrenia, already have recognizable differences from babies who don't carry that risk," says Dr. Robert Freedman. The problem, he notes, is that detecting these differences in the first years of life is not predictive of schizophrenia. All who develop the illness have biological differences from the beginning; but many infants with these differences don't go on to become ill.

By the time of the first definitive diagnostic symptoms—typically, a first "psychotic break," in the late teens or early 20s—it is already too late to prevent schizophrenia from occurring. Hence, Dr. Freedman decided to focus on reversing or blunting the first step in the multi-step process toward disease onset. "We thought that if we could bolster the brain's inhibitory system even before a child is born, then perhaps we could lessen the risk that the other biological steps toward the illness would occur. We might even prevent the illness in some cases."

His team demonstrated, first in rodents and then in people, that supplying choline in high doses to expectant mothers would suffice to activate the inhibitory system in the developing fetus. They noted that this supplementation would bring the choline level up to levels others had measured in the amniotic fluid of healthy mothers. The team also drew heavily on medicine's past success with another kind of prenatal supplementation—that of folic acid, another vital nutrient that expectant moms must have lest their infants



An experimental drug that targets the A-7 nicotinic receptor reduces hyperactivity in the brain's right hippocampus (yellow), a prime site of emotional processing and affected in schizophrenia.

suffer from neural tube defects and a variety of associated birth defects. Folic acid fortification, ideally begun before conception and continued throughout the perinatal period, especially in women with poor diets, is accepted practice in the U.S. and worldwide.

Dr. Freedman, with critical help from Camille Hoffman, M.D., an assistant professor of maternal-fetal medicine, and Randal Ross, M.D., a professor of child psychiatry, both at the University of Colorado School of Medicine, took a parallel approach with choline. Led by Dr. Hoffman, who was awarded the Foundation's Sidney R. Baer Jr. Prize in 2015, the team recruited 100 healthy women from the Denver area. In a double-blind trial they tested whether giving choline supplements during pregnancy to increase the nutrient's level in the amniotic fluid would enhance the development of inhibition in the fetal brain's cerebral cortex. The supplements (twice normal dietary levels) were given by pill, twice a day throughout the second and third trimesters, and then to mother and newborn through the third postnatal month.

Happily, there were no adverse effects in maternal health, delivery, birth or infant development. But did the supplements make any difference? Dr. Freedman's team gave the newborns a crucial test after five weeks. Each child was exposed to two identical sounds—a succession of clicks. The team measured the activity of the brain during this test. A baby or adult with normal inhibition responds much less robustly to the second sound, which is filtered out as comparatively insignificant. A sharp response to the second sound is what scientists call a "surrogate marker" of a deficiency in inhibition.

This marker, called the P50 response, indicated normal inhibition in 76 percent of the infants whose mothers had been given choline supplements. In babies whose mothers received placebo instead of extra choline, only 43 percent had normal inhibition. That figure would likely have been lower if every mother in the trial, regardless of her treatment, had not received special instructions from visiting nurses to eat a diet rich in choline. (The aim was to compare choline supplementation with normal, not subpar, choline intake by the expecting mother.)

The study showed, too, that choline supplements even benefitted the infants of mothers who carried genetic risk factors for schizophrenia, including variants of *CHRNA7*. But in mothers carrying these risk factors who received placebo, even the benefit of dietary advice (as opposed to supplementation by pill) during pregnancy did not prevent their children from showing diminished P50 inhibition after birth. In 2015, Dr. Freedman's team reported follow-up results when infants in the original trial reached 40 months of age—the time when behavioral patterns become settled and incipient problems are discernable.

"Children who will go on to develop schizophrenia already have recognizable motor problems in the first year of life," Dr. Freedman says, "which are not in themselves diagnostic. But by early childhood they also show clear signs of attention difficulties and social withdrawal, effects that we can trace at least partly to deficits in inhibition."

At 40 months, the team was excited to observe that children of mothers who had received choline supplements had fewer attention problems and less social withdrawal compared with children in the placebo group. It is of course impossible to know the "final" outcome of this experiment until the children reach their 20s. Right now, says Dr. Freedman, "what we know is that the babies exposed to supplemental choline as four year-olds are healthier children than if we had not intervened."

The team will continue to test whether the specific form of choline used in the trial—called phosphatidylcholine—is indeed the best supplement to give. The optimum dose also remains under study. ■

Have A Question?

Send questions for Robert Freedman, M.D. to **asktheresearcher@bbrfoundation.org.**

Select questions and answers will be in the next issue of the *Quarterly*.