

Current Research into Prenatal Causes of Schizophrenia

Summarized by Thomas T. Thomas

For years psychiatrists accused parents and their child-raising of being the probable cause of schizophrenia. More recent findings, however, imply a physical basis for such brain disorders. For example, Dr. E. Fuller Torrey, author of *Surviving Schizophrenia*, writes that a virus may produce some forms of this disease.

Another researcher currently at work in this area, **Catherine Schaefer, PhD**, an epidemiologist with Kaiser Permanente's Division of Research in Oakland, spoke at our July 23 meeting. Kaiser is one of the nation's oldest HMOs and holds a unique set of birth records, from prenatal care through delivery and pediatrics, on more than 19,000 patients from the 1960s.

Schaefer reported on a study of these records that Kaiser has under way in collaboration with colleagues from Columbia University in New York and the National Institutes of Mental Health. The study is funded in part by a grant from the National Alliance for Research on Schizophrenia and Depression (NARSAD), which our members support with their contributions and purchases of note cards. The aim of Schaefer's work is to determine what prenatal factors may contribute to schizophrenia.

As background, she cited a general suspicion in the medical community that schizophrenia may be a neuro-developmental disorder, resulting from some kind of disease or injury to the brain during pregnancy, delivery, or early infancy. An insult at this stage might not be a direct cause of schizophrenia, she said, but could be a co-factor or work on a genetic susceptibility to the disorder.

The reason for this widespread belief is that imaging studies have shown anatomical differences between the brains of schizophrenics and control patients, especially differences that were present before the onset of the disorder. Metabolic scans of brain function also show differences between the brains of patients and controls.

Some of the prenatal factors of concern include a prospective mother's:

- Viral infections. German measles, rubella, cytomegalovirus, and HIV all are known to have neurological consequences for the baby. For instance, children born during or shortly after the flu epidemic of 1957 grew up with a significantly higher rate of schizophrenia than those born in the previous and following years.
- Nutrition immediately before and during pregnancy. Studies of babies born during the "Hunger Winter" of 1944-45, when the Nazis starved Holland in reprisal for its support of the Allies, found much higher rates of schizophrenia in those children when they grew up. For some reason, this was especially true for girls. Other studies have shown that a folic-acid deficiency in the mother's diet can lead to neural-tube defects such as anencephaly and spina bifida.

These results are so strong that the FDA is planning to add folic acid—or folate, the vitamin in green, leafy vegetables—to commercially baked bread, so that at-risk mothers can be assured of receiving adequate amounts of this substance.

- Exposure to toxins. Alcohol, nicotine, cocaine, and other poisons are known to influence brain development.
- Hormone levels. Thyroid deficiency, for example, can also affect the infant's brain.

Schaefer's study, which is still in the early stages of identifying individuals and conducting interviews, is based on data that were gathered during the Child Health and Development Study (CHDS) conducted by Kaiser Permanente from 1959 to 1966. This was one of a group of studies performed nationwide in the wake of the thalidomide crisis of the late '50s, when women in Europe who were given this drug for morning sickness bore children with horrendous anomalies, such as missing arms and legs. This dramatic effect prompted many studies of prenatal influences and birth defects.

The Kaiser CHDS study collected detailed records of 19,044 births over the eight-year period, following them from conception to an age of between 9 and 11 years. The data gathered back then included:

- Interviews with the mother during her pregnancy.
- The mother's medical records.
- Stored, frozen samples of the mother's blood serum during pregnancy. Having the actual serum now—not just laboratory analyses dating from 1959—can show, for example, the presence of viral antibodies and other factors which might not have been considered at the time.
- Records from the admission for labor and delivery.
- Standard measures, called APGARs, of the newborn's physical condition and activity levels. These measure things like skin color (pink or blue), the time at which the newborn begins breathing on its own, and muscle tension and limb movement.
- Medical records from the first year of the infant's life.
- Developmental examinations made at 5 years and again at 9 to 11 years.

Of the original 19,000 study participants, 62 percent were still members of the Kaiser system in 1981, when this group of babies would have reached between 15 and 22 years of age—the usual time for the onset of schizophrenia. Using this subgroup of 11,800 patients, Schaefer and her colleagues performed a computer study of Kaiser's admissions records, looking for symptoms of mental disorders that could indicate a diagnosis of schizophrenia. This analysis identified approximately 200 people who were suitable for follow-up interviews.

The design of the study, Schaefer said, is to match these patients having signs of mental disorder with other members of the CHDS study who exhibited no mental problems. The latter group becomes a control, because the same kind of in-depth prenatal data are available for them from the 1959-66 study.

Schaefer's team can then identify factors and exposures that differ between the patients and the controls. The goal is to reduce these data to statements such as

“mothers in the patient group were twice as likely to have suffered influenza during pregnancy than mothers in the control group.”

The factors Schaefer and her team are focusing on include the parents’ ages at the time of conception and circumstances of the mother’s life, such as:

- History of smoking and alcohol consumption, and use of these substances during pregnancy.
- Reproductive history, including previous births and miscarriages, if any.
- Place of birth and where she grew up, to check for possible developmental influences in her own early life.
- Medical history and any health problems, especially a history of viral infections.
- Any prescriptions for diet pills and amphetamines, which are known to induce psychoses and can influence brain development. (It is suspected that about 10 percent of mothers were taking them during the CHDS study period.)
- Records of weight gain during pregnancy.
- Any complications during labor and delivery.

The study will also note any subtle anomalies, called dysmorphologies, that the doctors may have described after delivery. These might include things like an unusual shape to the baby’s ear lobes, eyelid folds, hair whorls, or palm creases. These minor defects, which are indistinguishable to the average person, can be used to link *in utero* insults to precise stages of the baby’s development. From the frozen serum samples, which were taken during each trimester of the pregnancy in 4 milliliter amounts, the study team will check for:

- Exposure to the influenza virus during the second trimester.
- Nutritional factors, such as folic acid levels.
- Other analyses that may be suggested by the interview process.

At present, Schaefer and her team have contacted and interviewed only ten of the 200 potential study members identified by the computer matching. The slow pace is due in part to the fact that they only have two interviewers, who must be trained psychological social workers, and the interview process takes more than three hours. Still, she hopes to have preliminary results in another 18 months.

“This study is important,” Schaefer said, “because the data are unique. Detailed birth records—independent of people’s recollections, which can be fallible—just don’t exist anywhere else for such a large base population. The data are very high quality, especially the prenatal serum samples, and we have a powerful study design. This work could lead to the discovery of measures that will prevent future cases of schizophrenia, and that’s very exciting.”