The BIRTH of S·C·H·I·Z·O·P·H·R·E·N·I·A

A *debilitating mental disorder may take root in the fetal brain*

By BRUCE BOWER

Nearly a century ago, German psychiatrist Emil Kraepelin described healthy young adults who for no apparent reason lose their mental bearings. They cling to shards of lucid thinking but feel compelled to enter an alternate world of disturbing hallucinations, bizarre delusions about themselves and others, incoherent thoughts, and intense emotions seemingly unconnected to daily events or experiences. Kraepelin dubbed this condition "dementia praecox," meaning a premature brain disease that wreaks increasing psychological havoc over time.

Since then, the term schizophrenia (or "fragmented mind," in one translation from the German) has replaced dementia praecox as the favored term for the devastating ailment. But Kraepelin's concept has nonetheless exerted much influence on schizophrenia researchers. It encouraged an intensive and so far frustrating search for specific points in the adult brain that show signs of deterioration or other damage beginning around the time that symptoms of schizophrenia first appear.

Although this approach retains its appeal for many investigators, it faces an increasingly stiff challenge from scientists who maintain that the roots of schizophrenia sprout earlier in brain development — much earlier.

"Considerable evidence points to the importance of fetal brain development in the etiology of schizophrenia," says John L. Waddington, a neuroscientist at the Royal College of Surgeons in Dublin, Ireland. The misplacement or overzealous pruning of disparate groups of fetal brain cells may throw intact and impaired neurons together in ways that set the stage for schizophrenia later in life, Waddington writes in the current SCHIZOPHRENIA BULLETIN (Vol. 19, No. 1).

A few researchers have made similar claims for several decades, but supporting evidence has mounted rapidly only in the last 10 years. Some data implicate viral infections during pregnancy and other prenatal or birth difficulties as early influences on schizophrenia, as well as on disorders ranging from autism to dyslexia (SN: 5/1/93, p.278).

For example, a Finnish study found an increased rate of schizophrenia among the offspring of women exposed to an influenza epidemic during the second trimester of pregnancy (SN: 9/19/87, p.180). Other research has charted frequent prenatal and birth complications in babies who later develop schizophrenia. The disease has also been linked to birth in the winter, when viral infections increase in frequency.

Inheritance may also help produce schizophrenia. Several studies of adult twins suggest that a genetic mechanism — perhaps specific to the disorder, perhaps related to a number of serious mental illnesses — strongly influences about half of all cases. This is an impressive total, considering that an estimated 1 percent of the world's people develop this mental disorder. Yet the same data imply that genes play no major role in a comparable number of cases. In a related study, brain scans of pairs of identical twins — in which only one twin developed schizophrenia — revealed that affected twins display cerebral damage unrelated to inheritance (SN: 3/24/90, p.182).

Researchers who hope to untangle the anatomy of schizophrenia now see promise in microscopic investigations, in which they stain and then magnify swaths of neural tissue from the brains of deceased schizophrenics. Teams employing this approach cite several signs that, among many schizophrenics, fetal brain development goes awry in mid-pregnancy, when large numbers of neurons trek to their final destinations. In parts of the brain's outer layer, or cortex, and within deeper regions associated with emotion and memory, staining reveals disorganized splotches of neurons that contrast with the neat cell arrays achieved before birth in healthy adults.

Staining of schizophrenics' brains also reveals missing or abnormally sized neurons and irregularities in the fatty myelin sheathing that helps neurons transmit messages.

The results of a new brain investigation add another twist to these findings. Thanks to an advanced staining procedure, investigators can now link a topsy-turvy arrangement of neurons bearing a particular enzyme to schizophrenia. These nerve cells migrate to their final location within the brain mainly during the second trimester of pregnancy, and their displacement may point to a more widespread breakdown of fetal brain formation among schizophrenics, assert Schahram Akbarian, a neurobiologist at the University of California, Irvine, and his colleagues.

Akbarian's team studied the brains of seven schizophrenics and seven healthy adults matched for age and sex. All participants died of natural causes, save for one schizophrenic who committed suicide.

The scientists stained neurons containing nicotinamide-adenide dinucleotide phosphate-diaphorase (NADPH-d), an enzyme found in clusters of neurons located in several parts of the brain. NADPH-d appears to help its host cells repel the ravages of Alzheimer's disease and possibly other brain diseases, the researchers say, and any possible schizophrenia-related dementia beginning in adolescence would probably leave these neurons unscathed. Thus these cells are good candidates for looking for evidence of very early brain damage, since they likely don't respond to dementias of later life.

In healthy brains, NADPH-d neurons located at the front of the cortex and in the temporal lobe (in and near the hippocampus, which helps direct memory and learning) cluster in tissue containing the remains of the subplate, a thin layer of cells at the junction of the cortex and deeper brain tissue. The subplate serves as a temporary gateway to the cortex for migrating fetal brain cells. The number of NADPH-d neurons drops off markedly just below the subplate remnants, outside the cortex.

The opposite pattern characterized the same parts of schizophrenics' brains, Akbarian and his associates report in the March ARCHIVES OF GENERAL PSYCHIATRY.

NADPH-d neurons congregate in deeper, noncortical tissue and become sparse in the former subplate regions, indicating the loss occurred during fetal development.

The use of antipsychotic drugs by schizophrenic participants probably did not cause the abnormal distributions of NADPH-d-containing cells. The neurons perform the same chemical functions no matter where they lie and thus should not increase in one spot and decrease in another when exposed to the same medication, the researchers point out.

Moreover, the most severe displacement of neurons appeared in the brain of a schizophrenic woman who had not taken antipsychotic drugs for at least 10 years prior to her death.

◆◆◆◆◆◆◆◆◆◆

Akbarian's group offers two possible explanations for the altered allocation of NADPH-d-containing neurons among schizophrenics. Fewer of these cells may reach the subplate during the second trimester, leaving a surplus below the cortex. Alternatively, the programmed death of selected neurons that occurs closer to birth may malfunction, limiting the number of neurons that reach the cortex.

Individuals with two strikes against them—a genetic predisposition to schizophrenia topped off by second-trimester exposure to viral infection—may face the greatest likelihood of developing this mental disorder as they approach adulthood, the investigators theorize. Minor birth or postnatal complications may boost that risk even further, Akbarian and his co-workers suggest.

In fact, genes may play a pivotal role in facilitating fetal brain damage associated with schizophrenia, asserts Floyd E. Bloom, a neuroscientist at the Scripps Research Institute in La Jolla, Calif. Neurons such as those targeted by Akbarian's group may get misplaced in fetal brains when genes that trigger certain aspects of brain development shut down prematurely, perhaps as a result of fever or famine, Bloom writes in a comment accompanying the new research. And people in some families with high rates of schizophrenia may simply lack one or more genes required to get young cortical neurons where they need to go, Bloom proposes.

However, in the view of Daniel R. Weinberger, a psychiatrist at the National Institute of Mental Health in Bethesda, Md., the new findings suggest only that schizophrenics suffer brain damage in the womb as a result of some environmental factor, not that they harbor defective genes.

"The data from Akbarian's group are quite compelling, but they need to be replicated," advises Weinberger, a staunch proponent of the view that early flaws in brain development underlie schizophrenia. Investigators cannot yet rule out the possibility of a similar misalignment of NADPH-d neurons in other severe mental disorders, such as manic depression, he adds.

Nevertheless, microscopic studies that target the hippocampus support the theory presented by Akbarian and his colleagues, according to two brain researchers writing in the current SCHIZOPHRENIA BULLETIN. At least some instances of schizophrenia spring from an inherited immune disorder that renders the fetal brain more vulnerable to the influenza virus during the second trimester, theorize Arnold B. Scheibel and Andrew S. Conrad, both of the University of California, Los Angeles, Medical Center.

In three studies conducted since 1981, Scheibel and Conrad find that the brains of about half of deceased schizophrenics display haphazardly arranged neurons in specific layers of the hippocampus. The migration of these neurons to their final destinations — like the NADPH-d-containing cells — peaks during the second trimester. And influenza is one of the few viruses that weakens chemical links between neurons and the glial cells that guide them to their assigned positions in the fetal hippocampus, the UCLA researchers note.

◆◆◆◆◆◆◆◆◆◆

Other studies suggest that glitches in brain development during adolescence make their own contributions to schizophrenia, argue Jay W. Pettegrew, a psychiatrist at the University of Pittsburgh, and his colleagues. Signs of either premature aging of neurons at the front of the cortex beginning in the teens, or a quickening of programmed cell death in the frontal cortex timed to occur during adolescence show up in the brains of living schizophrenic patients, they contend in the current SCHIZOPHRENIA BULLETIN.

A technique called phosphorus-31 nuclear magnetic resonance (NMR) generates these clues by directly measuring phosphorus function in cell membranes. Four independent studies published in 1991 and 1992, including one by Pettegrew's team, have obtained phosphorus-31 NMR data from a total of 51 schizophrenics and 30 healthy controls. Results so far reveal decreased production and increased breakdown of membrane phospholipids among schizophrenics, Pettegrew holds. Membrane phospholipids prove crucial for promoting neuron health and the transmission of messages in and out of cells.

Similar changes occur in the course of normal aging, Pettegrew notes. If schizophrenia involves premature aging of selected neuron systems during adolescence, then Kraepelin's concept of dementia praecox may find at least partial support, he remarks.

◆◆◆◆◆◆◆◆◆◆

While accumulating data point to the fetal brain as a major player in schizophrenia, Waddington says researchers still must explain how brain damage forged in the womb stays silent for decades before psychological tumult ensues.

Some provocative clues indicate that unappreciated signs of early cerebral harm often may show up in infants and young children at particular risk for schizophrenia, Waddington holds.

For example, infants of schizophrenic parents, some of whom develop the disorder later in life, and babies not necessarily born to schizophrenic parents but who later develop schizophrenia, exhibit evidence of uneven central nervous system maturation, according to a report in the March 1992 ARCHIVES OF GENERAL PSYCHIATRY. A review of 12 longitudinal studies charting infant development and a further analysis of data from one of those projects, directed by UCLA psychiatrist Barbara Fish, identifies three markers of this problem in infants: a short-lived but noticeable gap in acquiring motor skills and coordination; the appearance of complex motor skills before the accomplishment of simpler feats; and a retardation of skeletal growth.

In another study, Elaine F. Walker and Richard R. J. Lewine, both psychologists at Emory University in Atlanta, directed an analysis of home movies taken of five adult-onset schizophrenics and their nonschizophrenic siblings. The footage covered ages from infancy to 5 years. Youngsters who developed schizophrenia consistently showed reduced emotional responsiveness, lack of eye contact, and poor coordination.

Further research must establish whether these traits herald a vulnerability only to schizophrenia or to other mental disorders as well, Walker and Lewine assert in the August 1990 AMERICAN JOURNAL OF PSYCHIATRY.

Despite the promise of such findings, uncertainty in defining schizophrenia hinders attempts to ferret out its causes, says psychologist R. Walter Heinrichs of York University in Toronto. Investigators typically treat schizophrenia as a single disorder expressed in a number of ways, but they cannot rule out the possibility that the diagnosis encompasses several different illnesses that currently elude definition, Heinrichs notes in the March AMERICAN PSYCHOLOGIST.

"This is not a problem that can be ignored," the Canadian psychologist argues. "It is the major obstacle to scientific progress." □