Viral Exposure Boosts Schizophrenia Risk

For about a month in the fall of 1957, Helsinki, Finland, was swept by a serious Type A2 influenza virus epidemic that is estimated to have infected two-thirds of the population. Thanks to the meticulous record-keeping of the Finnish government, researchers now have established that people who were exposed to the worldwide epidemic while in their second trimester of fetal development have an increased risk of hospitalization for schizophrenia.

"A basic risk for schizophrenia seems to occur when there is some kind of fetal trauma during the second trimester," says psychologist and research director Sarnoff A. Mednick of the University of Southern California in Los Angeles. "It is not so much the type of stress as it is the timing of stress during gestation which is critical in determining the risk."

But, importantly, he and his colleagues report they have found a link between second-trimester exposure to a specific virus and the adult diagnosis of schizophrenia. Longstanding theories of an "infection connection" in some cases of schizophrenia have generated more debate than data (SN: 11/30/85, p.346). The Finnish study, which will appear later this year in ARCHIVES OF GENERAL PSYCHIATRY, was generated by the researchers' ongoing, 24-year study of Danish children with schizophrenic mothers. Children who developed schizophrenia in adulthood and had an excess of birth complications also tended to have been born during periods of increased viral infections (January, February and March) in crowded Copenhagen.

For the county encompassing Helsinki, the investigators tracked all children born in the nine months immediately following the 1957 epidemic who were hospitalized before the age of 26 in one or more of the county's eight psychiatric facilities. These 216 "index" individuals were compared with 1,565 "control" children born in the same county in the corresponding months of the previous six years, and who were hospitalized for psychiatric disorders before 26 years of age.

Nearly 36 percent of the index patients exposed to the epidemic during their second trimester of fetal development were diagnosed as schizophrenic by Finnish psychiatrists. In contrast, about 22 percent of both control patients and index subjects exposed to the epidemic in the first or third trimester of fetal development received diagnoses of schizophrenia; the rest had a variety of psychiatric diagnoses. The "second-trimester effect" held for both males and females, and independently in each of several of the psychiatric hospitals.

Moreover, for the entire Helsinki population, the rate of hospital diagnoses of schizophrenia per 1,000 Helsinki live births for second-trimester exposures was around 1 percent, twice the rate for first- and third-trimester exposures.

There is no direct evidence that pregnant women actually sufferred a viral infection during the epidemic, notes Mednick, and psychiatric admissions beyond 26 years of age have not been examined. Nevertheless, he says, the study adds to "sparse evidence" implicating other second-trimester disturbances with an increased risk of adult schizophrenia. For instance, Finnish researchers previously found that when pregnant women learned of their fathers' deaths during the second trimester, the offspring later showed an elevation in psychotic disorders including schizophrenia.

Infections and other disturbances during the second trimester may interfere with the migration of brain cells to structures in the cortex, the brain's outermost layer, says Mednick. A combination of these influences and a genetic predisposition may produce different forms of schizophrenia, he adds. The Danish study has identified birth complications, poor parental supervision and placement in public institutions as additional risk factors.

Further work needs to examine whether second-trimester vulnerability occurs over a limited period of perhaps a few days, says Mednick. He plans to repeat the influenza study in Denmark, where extensive population data are also available. *– B. Bower*

New class of antibiotics confirmed

It was quite by chance that Alexander Fleming in 1928 discovered penicillin. Since then, many antibiotics have been developed, but the serendipitous route of discovery has changed very little. Antibiotics are to this day being patiently sought in naturally occurring substances such as tropical plant extracts and soil molds.

In recent years, however, as molecular biologists have become more proficient at making customized biochemical compounds, interest in "rational drug design" has increased. Rather than looking for naturally occurring drugs – or modifying already-discovered ones – scientists are attempting to craft extremely specific molecules that are capable of killing pathogens without harming the human host.

The first successful synthesis of a rationally designed antibiotic was reported by Swedish researchers in late June of this year. Now scientists working independently at Abbott Laboratories in Abbott Park, Ill., report success with a similar "designer" drug. Tests have so far been restricted to laboratory cultures of disease-causing bacteria. But the research confirms the potential of this new class of antibiotics and provides some encouraging details about how effective the drugs are apt to be.

Robert Goldman and his co-workers report in the Sept. 10 NATURE the synthesis of a potent antibiotic that is effective against an important class of disease-causing microbes – the gram-negative bacteria. Gram-negative bacteria cause a large number of diseases, including gonorrhea, cholera, meningitis and a variety of dysenteries.

"Even penicillin-resistant, erythromycin-resistant and tetracycline-resistant organisms are still sensitive to this compound because it's an entirely different metabolic pathway that's being affected," Goldman told SCIENCE NEWS. The compound inhibits an enzyme inside the bacterial cell that is crucial for the production of lipopolysaccharide – an important component of the bacterial cell membrane. The resulting defective membrane leaves the bacteria unable to reproduce, while rendering them up to 10 times more susceptible to standard antibiotics.

The synthesis of such a specific inhibitor is the culmination of years of research in which the critical bacterial enzyme – CMP-KDO synthetase – was identified, isolated and eventually cloned. Using nuclear magnetic resonance, scientists determined its structure in 1985. On the basis of that information, they designed an inhibitor to mimic the enzyme's natural target, or substrate.

"It's a very straightforward competitive inhibitor of the enzyme," Goldman says. "When the inhibitor [drug] binds to the active site of the enzyme, the enzyme has no access to the real substrate. But the enzyme can't do anything with the inhibitor, so it just sits there, dead."

Moreover, he says, the targeted enzyme "is unique to gram-negative bacteria, so you don't have to worry about inhibiting some analogous pathway in the human."

Encouraging as the research is, work remains to be done before the drug will be ready for clinical trials. Most impor-