Clues to preventing schizophrenia

One of science's most enamoring qualities is its propensity for unexpectedly discovering one thing when it is in hot pursuit of something else. Psychiatry's latest version of this phenomenon may be developing in the laboratories of New York University's Medical School, where researchers Arnold J. Friedhoff and Helen Rosengarten are testing the effects of antipsychotic drugs on rats.

The actions of such drugs — called neuroleptics — have been fairly well documented since their first clinical use with human psychiatric patients in the mid-1950s. Neuroleptics have been applauded as a major factor in reducing mental hospital populations over the past two decades. On the other hand, they have fallen short of some expectations by failing to significantly improve many severe, chronic schizophrenics.

Most antipsychotic drugs work by blocking either the brain's production or reception of the neurotransmitter dopamine, scientists have learned over the years. If all this is known about effects on humans, why study rats? In this case because in research efforts to develop such drugs to help emotionally disturbed persons, relatively little attention has been paid to neuroleptics' long-term effects on the offspring of female users who take antipsychotics while pregnant.

Friedhoff and Rosengarten have tested two dopamine-blocking drugs — haloperidol and AMPT (the latter still in the experimental stage) — on pregnant rats, and compared their offspring with those of rats given a placebo salt solution. The results, reported in the March 16 SCIENCE, have sent a ripple of intrigue through Friedhoff's lab and, undoubtedly, beyond.

Examined 60 days after birth, the brains of the offspring of neuroleptic-taking mother rats contained significantly fewer dopamine receptor cells than those of the control group of pup rats. This indicates that less dopamine activity is going on in the brains of the rat pups of neuroleptic-taking mothers. And theoretically, since schizophrenia is believed to be associated with an overproduction or overactivity of dopamine, the offspring may actually have a better chance of avoiding schizophrenia than if their mothers were not on antipsychotic drugs.

Friedhoff concedes this is very preliminary but suggests the results indicate "there might well be a beneficial effect" for human babies of mothers who took antipsychotic drugs during their pregnancy. Many forms of schizophrenia are thought to have a hereditary component, and if administration of neuroleptics to the mother during pregnancy could act as a preventive measure by reducing dopamine receptors in offspring, then "it ought to be looked into," Friedhoff told SCIENCE NEWS.

Previous studies indicate that dopamine-containing neurons in the brain gradually develop during fetal life and the first four weeks of life after birth. "We don't know the critical period [for taking neuroleptics during pregnancy]," Friedhoff says, "but we suspect it may be a relatively short time during the middle trimester." He says the pregnant rats were given relatively high doses of the drugs, but other data indicate that dopamine reduction in offspring could probably be achieved with lower-level, human-equivalent dosages. On the other hand, "normal" women who take such drugs for nausea might possibly increase the chances of their offspring developing Parkinson's disease, which appears to involve too little dopamine.

And although just two drugs were tested in the experiment, Friedhoff says he believes that "all neuroleptics" — including the widely used chlorpromazine and compazine, which is used sometimes by nonpsychotic pregnant women as an anti-nausea agent — would have similar consequences for offspring.

Retrospectively, Friedhoff acknowledges that the phenomenon may already have helped cut down on the incidence of schizophrenia over the last 20 years. "Millions of people, including a lot of pregnant women, have taken these drugs, and they are still used extensively," he says. Friedhoff and his colleagues are planning a long-term study of the babies of human mothers who take antipsychotics while pregnant. While they won't be able to observe receptor formation directly in human brains, the researchers plan to follow the physiological and behavioral progress of such youngsters over a period of years. □

Diabetes therapy to match the cause

Diabetes used to be thought a simple disease: The pancreas didn't make enough insulin. But that was in the days when insulin couldn't be measured in the blood. With the advent of sensitive detection techniques in the early 1960s, complexities arose. Investigators learned that only 20 percent of diabetics are insulin deficient. The problem in the rest has to do with the specific receptor molecules that recognize insulin and that trigger the biochemical steps leading to uptake of glucose from the blood. Drawing an analogy with a mother who calls but whose children don't respond, Jesse Roth of the National Institutes of Health explains that the cells seem to be hard of hearing.

Appropriate therapy should be influenced by the underlying characteristics of each case of the disease. For those patients who are truly deficient in insulin, hormone injections are necessary. Those patients are the thin, "juvenile-type" diabetics. A device recently developed at Yale University may make insulin use more effective and convenient for them.

Seven teenage diabetics successfully wore a 14-ounce insulin pump for several days, Philip Felig and his associates reported in the March 15 NEW ENGLAND JOURNAL OF MEDICINE. The pump, which is attached to a belt, continuously injects insulin just beneath the skin. The pump is programed to the individual patient (for example, providing larger doses of insulin just before meals), but it does not monitor glucose in the blood. The Yale scientists report patients' blood sugar levels were more constant with the pump than when identical amounts of insulin were injected conventionally once or twice a day.

However, most diabetics, the "maturity-onset" group, have normal or raised intrinsic blood levels of biologically active insulin but their receptors do not adequately respond, Roth told a science writers' seminar sponsored by the Endocrine Society. Some people can be satisfactorily treated with large doses of insulin, as if the receptors are only partially deaf and respond to shouting. Treatments, such as weight reduction, that increase the patients' response to insulin, also increase the number of receptors.

A novel treatment has been reported for one subgroup of extremely insulin-resistant patients. These patients, who may receive 1,000 times the usual dose of insulin and still respond inadequately, produce antibodies that bind to the receptors, making them less likely to bind insulin. In this instance diabetes must be considered an autoimmune disease. Michele Muggeo, C. Ronald Kahn and colleagues reported in the March 1 NEW ENGLAND JOURNAL OF MEDICINE that a technique for removing antibodies from the blood is useful therapy for these diabetics. For long-term benefit they suggest combining that plasma exchange with drugs that suppress the immune system. Together these therapies should deplete existing antibodies and inhibit new antibody synthesis.

Future therapies for diabetics may also be far removed from insulin injection. Roth says study of the receptor antibody has opened a new approach. While antibody binding makes the receptor less likely to bind insulin, it also stimulates the receptor somewhat. Thus the program that leads to glucose uptake is all in the receptor and can be triggered by a number of molecules that bind there. "Insulin is not essential in the bioengineering," Roth says. "We can bypass the hormone."

Because the insulin receptor is a molecular complex with a multiplicity of regulatory sites, diabetes can result from a variety of defects. Only in the last several years have scientists had the tools to work comfortably with receptors, Roth says. But that work can help discover appropriate treatments for diabetes, now known to be a complex, heterogeneous disease. □