When Antipsychotic Drugs Can Be Lethal

Neuroleptic drugs, also known as antipsychotic agents, are among the most commonly prescribed medications in the United States, used by up to 3 million people annually. Although in some cases neuroleptics lead to severe movement disorders and other side effects (SN: 7/20/85, p.45), psychiatrists have found that the drugs are often effective at moderating psychotic symptoms.

Yet, according to a report in the October AMERICAN JOURNAL OF PSYCHIATRY, a dangerous but little-known complication of antipsychotic drug use appears to be more common than previously thought. It often goes unrecognized in its early stages, add psychiatrist Harrison G. Pope Jr. and his colleagues of McLean Hospital in Belmont, Mass.

The complication is referred to as neuroleptic malignant syndrome, or NMS. Its cardinal signs are a fever, severe muscle rigidity, elevated blood pressure, elevated heart rate and clouded consciousness. The last feature can include delirium, stupor, mutism or coma. In some cases, a patient takes only a few hours to go from symptoms without serious illness to an inability to swallow, coma, kidney failure or brain damage. It is estimated that about 20 percent of the time, NMS is fatal. Death can result from respiratory, cardiovascular or kidney failure.

The researchers who first described the syndrome in 1968 estimated that it occurs among 0.5 to 1 percent of those taking neuroleptics, which are, among other things, powerful tranquilizers. Case reports of NMS have been published since then, but clinicians have considered the condition to be rare.

Pope and his co-workers, however, found seven definite or probable cases of NMS among an estimated 483 patients who received several types of neuroleptics at McLean Hospital over a recent one-year period. Another patient admitted during the study did not receive antipsychotic drugs because she had twice developed NMS during a previous admission. This prevalence rate of 1.4 percent is a conservative estimate, say the researchers; mild cases may have been missed, and some patients develop NMS years after going on the medication.

"In an extrapolation of our results," note the psychiatrists, "even a conservative estimate would place the annual prevalence of [NMS] in the United States in the thousands of cases, a significant number of which may have fatal consequences."

The good news, they say, is that many patients displaying symptoms of NMS recover fully when neuroleptic treatment is stopped. In addition, the muscle relaxant dantrolene and several medications that increase the transmission of the neurochemical dopamine in the brain (believed to be impeded by neuroleptics) have recently been shown to ease NMS. Low-dose neuroleptic treatment can begin again for some successfully treated patients.

Another encouraging trend is noted by Chester Pearlman of the Boston Veterans Administration Medical Center in the October JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY. He reviewed 320 reported cases of NMS since 1968 and found that "with wider recognition, mortality [from NMS] has decreased from about 22 percent of cases reported through 1980 to 4 percent of the last 50."

But much is still unknown about the syndrome's underlying causes, frequency and possible treatments. Even with the McLean study, it is hard to draw a conclusion about the true prevalence of NMS, according to Shervert Frazier, director of the National Institute of Mental Health (NIMH). Diagnostic changes in only a few of the subjects would have significantly altered the final percentage, he points out.

NMS "has been more recognized in the past few years, but I don't think it's occurring more often than the originally estimated rate of about 1 percent," Frazier told SCIENCE NEWS.

A problem with any piece of research on NMS, says psychiatrist Darrell Kirch of St. Elizabeths Hospital in Washington, D.C., is that the condition's early signs are still unclear. At first, a fever or muscle rigidity cannot be exclusively linked to neuroleptic use. Frazier says an NIMH research team is beginning to look for reliable early signs of NMS.

For the time being, says psychiatrist David E. Sternberg in an editorial accompanying the McLean report, regular monitoring of blood pressure and muscle tone may lead to early recognition of NMS. Furthermore, he says, the syndrome appears to be more common among those under 40 years of age, males and patients with psychiatric disorders that do not include schizophrenia. Sternberg, of Falkirk Hospital in Central Valley, N.Y., concurs with the researchers that the lifetime risk of NMS will probably prove to be higher than the 1.4 percent one-year rate uncovered at McLean Hospital.

—B. Bower

First cancer-protecting gene characterized

Boston-area researchers have identified a gene whose disruption leads to retinoblastoma, a rare eye cancer. They have also developed a way to test for the presence of the normal gene, which is expected to help in prenatal diagnosis.

Human genes analogous to genes known to cause cancer in animals have been identified, and these same human genes cause cancerous changes when transferred to cultured cells or to rodents. But the current work is the first to characterize a genetic *deletion* that causes cancer in humans. The retinoblastoma defect, localized by researchers from the Whitehead Institute for Biomedical Research, Harvard Medical School and Massachusetts Eye and Ear Infirmary, has been the object of a search by several other groups as well.

Retinoblastomas develop in the retinas of young children and can, if caught in time, be treated by removing affected eyes. Previous research has traced the tumors to the absence of a section of chromosome 13. Since developed cells have two copies of each chromosome, initiation of the tumor requires either a mutation in both genes or an inherited problem in one chromosome 13 plus the loss or mutation of the other (SN: 1/5/85, p.10).

In the Oct. 16 NATURE the researchers describe isolating a piece of chromosome 13 DNA that they then used as a probe. The DNA probe matched up with genetic material from normal retinal cells and cells from other tumors, but not retinoblastoma cells. They also determined the size and location of the corresponding segment in the normal gene.

The probe can be used to determine if a person has inherited the retinoblastoma potential and thus could pass it on, or if it resulted from a chance mutation, says Massachusetts Eye and Ear's Thaddeus P. Dryja. The presence of the matching section on only one of the chromosome 13s in cells from other body parts means that the person probably inherited a defective gene and developed retinoblastoma when the remaining normal gene in a retinal cell mutated. If other cells have two normal copies, the retinoblastoma arose from chance mutations in both chromosomes of a retinal cell, and is not in the germ line and thus not inheritable.

The probe can also be used for early or prenatal detection of the defect, allowing early, possibly eye-saving treatment. Next in line, says Dryja, will be determining the structure and function of the protein engineered by the gene.

Retinoblastoma affects only 200 or so children in the United States a year.