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.

Webster Cavenee of the Ludwig Institute for Cancer Research in Montreal, who with colleagues determined several years ago that retinoblastomas resulted from the absence of a normal copy of the gene, says the current work may influence more than just retinoblastoma research. While much cancer research has focused on dominant genes whose presence causes cancer, his laboratory and others have found many tumors that, like retinoblastoma, are linked to recessive genes whose absence leads to cancer.

Says Cavenee, "I think the answers that will come out of [the retinoblastoma work] are going to be expandable to a wide range of human cancers, and maybe most of them." —*J. Silberner*

Muscular dystrophy gene cornered

After years of chasing down the exact location of the gene responsible for Duchenne muscular dystrophy (DMD), a devastating muscle-wasting disease afflicting thousands of U.S. males, medical researchers have it cornered. A team of six scientists from the Harvard Medical School in Boston report in the Oct. 16 NATURE that they now know about 10 percent of the DNA code associated with this gene. If all goes well, they say, they will decode the entire gene by the end of next summer. The scientists then will be able to predict what biological molecules are missing or defective in DMD patients, brightening the outlook for developing effective treatments.

Researchers have known for decades that among the 46 chromosomes in the nuclei of human cells, the X chromosome would be the one on which they would find the DMD gene. DMD is a sex-linked disease that affects half the sons of the female carriers. While the carriers themselves usually show no symptoms because they have a second, normal X chromosome, affected sons rarely live beyond their early 20s.

But the X chromosome is like a city with thousands of streets. To find the street on which the genetic trouble spot resides, scientists have used several clues. By comparing DNA from normal populations with DNA from DMD carriers and affected males, researchers found genetic markers that are in the vicinity of, and passed on with, the DMD gene (SN: 9/7/85, p.151). These markers are on the shorter of the X chromosome's two short arms. Another clue comes from microscope observations of the X chromosome of a boy suffering from three X-linked diseases, including Duchenne muscular dystrophy. A chunk in the middle of the same chromosomal arm was missing. Also, research done at several laboratories showed that all of the 13 women known to suffer from the disease had "breakpoints" in their second X chromosomes in the same location, designated by geneticists as Xp21 (SN: 11/10/84, p.293).

Still more evidence that Xp21 is the correct genetic street comes from single-stranded DNA probes that attach to and flag only those RNA or DNA sequences that are complementary with the probe. With the help of more than 20 laboratories worldwide, Louis M. Kunkel, leader of the Harvard research team, was able to report in the July 3 NATURE that probes made from specific DNA sequences within the Xp21 sector do *not* attach to the X chromosomes from a number of DMD-affected boys. This means these boys are missing DNA within that same sector of the X chromosome.

Now the six Boston researchers report for the first time about a tenth of the exact street addresses on Xp21 that together make up the DMD gene. They found that the same probes used to detect DNA deletions in DMD boys bind to parts of specific RNA isolated from fetal muscle tissue. The scientists are presently busy doing the laborious "door-to-door" search of Xp21 to find more probes that do the same. Anthony P. Monaco, one of the researchers, says the RNA sequence probably codes for a protein important in muscle structures that are absent or defective in DMD. Those DNA probes that bind with the muscle-derived RNA will divulge the addresses that make up the remaining 90 percent of the gene's code.

Monaco says that spelling out the entire code should enable him and his colleagues to predict what protein the gene codes for. Specifically how this achievement might bear on potential treatments for muscular dystrophy is unknown, he adds. First, researchers will have to learn just how the protein fits into the complex biochemical fiasco that underlies muscular dystrophy.

But the more scientists know about the molecular events that orchestrate muscular dystrophy, the more rationally they can design therapies, says Donald Wood, associate director of research for the New York-based Muscular Dystrophy Association of America, which helped fund the research. He says the short-term possibility for treatment would be to supply the muscle cells of DMD patients with the specific protein coded for by the gene. Wood speculates that such a treatment might halt the progress of the disease, which otherwise would be invariable and relentless. Farther down the road, he says, it might even be possible to substitute a normal gene for the one deficient in DMD. —*I. Amato*

Pole's ozone hole: Who NOZE?

"We suspect that a chemical process is fundamentally responsible for the formation of the [Antarctic ozone] hole," said atmospheric chemist Susan Solomon at an Oct. 20 press conference beamed to Washington, D.C., from McMurdo Station in Antarctica. Solomon is the leader of the National Ozone Expedition (NOZE), which went to Antarctica in August to study the stratospheric ozone hole that has worsened each Antarctic spring during the last decade (SN: 3/1/86, p.133).

NOZE researchers have not determined how the hole is created. But Solomon says they have "strong evidence" against two proposed theories that don't lean primarily on chemistry: a dynamic model involving the upward movement of ozone-poor air from the troposphere into the stratosphere, and the "odd-nitrogen" theory, which holds that the highly active sun during the last solar cycle generated large levels of ozone-destroying nitric oxide (SN: 10/11/86, p.239).

Several scientists involved with these two theories dispute the NOZE conclusion. Mark Schoeberl at NASA Goddard Space Flight Center in Greenbelt, Md., says that NOZE evidence, based on only one station at the edge of the hole, cannot be used to dismiss dynamic vertical motion. Adds Richard Stolarski, also at Goddard, "I don't believe the dynamic theories are dead."

Part of the evidence against the odd-nitrogen idea, developed by Linwood B. Callis at NASA Langley Research Center in Hampton, Va., is that Antarctic nitrogen dioxide levels during the expedition have been low — the lowest ever observed in the world. Callis says low levels are to be expected, since solar activity is on the wane. "Their suggestion that the solar cycle is not playing a role in this thing is wrong," he says. "And even if it is not wrong, it's certainly premature."

NOZE measurements of 15 kinds of atmospheric molecules should help scientists establish whether the hole is a result of natural processes or of human activities such as the emission of chlorofluorocarbons (CFCs). Some researchers have worried that the chlorine in CFCs, which are used in car air conditioners and many industrial practices, is destroying the ozone layer. The NOZE evidence for chlorine theories is not overwhelming: While the observed nitrogen dioxide concentrations are consistent with chlorine models, chlorine monoxide levels are lower than some theories predict. Solomon, however, says this finding doesn't exonerate chlorine.

Whatever the hole's cause, Solomon says it is more complex than anyone had imagined and "may well be something not yet thought of." —*S. Weisburd*