AZT Falls Short for Kids with HIV

Preliminary — and unexpected — results of a new study raise questions about using AZT, a standard anti-AIDS drug, to treat children with the disease.

In 1990, the Food and Drug Administration approved AZT (zidovudine) for use in youngsters who exhibit symptoms of infection with HIV, the virus leading to AIDS. Yet a government-sponsored clinical trial now indicates that the drug fails to halt the progression of HIV infection in children.

Investigators at 62 medical centers across the country recruited 839 children between the ages of 3 months and 18 years who had experienced symptoms of HIV infection. They gave one-third of the children AZT in the form of a strawberry-flavored syrup provided by the Burroughs Wellcome Co. in Research Triangle Park, N.C. Another third took a different antiviral drug called didanosine (ddI) from Bristol-Myers Squibb Co. in Princeton, N.J. The remainder received both AZT and ddI.

Neither the investigators nor the children and their parents knew which group was getting which of the three regimens. Furthermore, the children had received little or no treatment with anti-AIDS drugs in the past.

The National Institutes of Health in Bethesda, Md., which sponsored the study, assigned an independent board of scientists to check on the trial's progress. That panel's review of the interim data revealed that the group receiving only AZT fared much worse than the other two groups. On Feb. 8, NIH halted the AZT-only arm of the study. Kids who had been getting AZT alone were offered the option of switching to one of the other ongoing treatments.

"[The AZT portion of the] study was stopped over 6 months early because of the results," says study cochair Janet Englund of Baylor College of Medicine in Houston. "The finding that AZT was the least effective among the three options was quite a startling surprise," adds team member Ross E. McKinney Jr. of Duke University School of Medicine in Durham, N.C.

The data revealed that AIDS progressed more rapidly in youngsters getting just AZT, compared to children receiving ddI or the combination therapy. Children on AZT alone faced a higher risk of failure to grow, cognitive problems, the development of new opportunistic infections, and death.

In addition, kids getting the solo AZT treatment developed more side effects, such as low white blood cell counts, which can leave people with AIDS prey to infections.

"In the long run, AZT is not the best of the three choices [for children]," says James F. Balsley, chief of the pediatric medicine branch of NIH's National Institute of Allergy and Infectious Diseases. AZT remains a recommended drug treatment for adults with HIV infection.

Researchers don't know why kids on AZT alone fared so poorly. McKinney speculates that the children simply developed resistance to this drug. On average, kids in this study took AZT for 2 years, enough time for resistance to surface, Balsley notes.

NIH will not be able to tell physicians whether ddI or the combination approach is better until all the data in the ongoing trial have been collected and analyzed, a process that could take until the end of the year. However, many researchers believe that a combination of chemical weapons will ultimately prove most effective against this wily virus. — *K. Fackelmann*

Additional genes may affect color vision

Whether human beings can enjoy wisteria or lilac's gentle hues rests on their genetic inheritance of color vision.

The standard model of color vision, proposed more than 200 years ago, postulates three kinds of photopigments in cone cells on the retina. Sensitive to red, green, and blue light, the three enable one to perceive a rainbow's colors.

This trichromatic theory of vision assumes that people inherit a separate gene for each of the three photopigments. In color blindness, which affects as many as 8 to 10 percent of men, a person may lose the ability to see all colors or merely the capacity to discriminate between certain hues. Standard theory holds that such people lack the gene for one or more pigments or that those genes have failed to work properly.

Now, new evidence suggests a more complex genetic model of color vision.

Molecular geneticist Maureen Neitz and neuroscientist Jay Neitz, both at the Medical College of Wisconsin in Milwaukee, report in the Feb. 17 SCIENCE that many men with normal color vision have more pigment genes on their X chromosomes than previously realized.

"It was long assumed that people with normal color vision all have three stereotyped cone pigment genes in common," they say. Recently, scientists have shown that the number of pigment genes in red-green color vision can vary. Now, their results reveal that individual differences in the number of pigment genes "are much larger than have been appreciated," the Neitzes say.

Examining the DNA of 30 men, some normal and some color-blind, they found that men with normal color vision "had as few as two and as many as nine [different] X-linked pigment genes." In fact many men had multiple "long-wavelength" genes for detecting red light — "often two and as many as four."

These findings have implications for understanding color vision as well as color blindness. "The fact that individuals with multiple long-wave [red light] genes tend to make more intermediate color matches hints that some may be expressing more than one long-wave pigment," they explain. "If that is true, in total they would [make] at least four different cone pigments: two long-wave, a middle-wave, and a short-wave pigment."

This finding contradicts the standard model of color vision "that has held sway for more than 2 centuries, in which the presence of three pigments is proposed to explain human trichromatic color vision," the Neitzes conclude.

"This is an important new finding," says Gerald H. Jacobs, a neuroscientist at the University of California, Santa Barbara. "Their work may lead to a reexamination of the roles of various pigment genes in color vision."

Another set of findings casts new light on the long-accepted explanation of red-green color blindness in British chemist John Dalton (1766–1844).

Dalton, to whom the pink flower *Geranium zonale* appeared sky blue, decreed that upon his death, his eyes be removed and studied to uncover the defect. His eyes were indeed examined, and scientists concluded that Dalton lacked the retinal pigment for red vision.

However, molecular geneticist David M. Hunt of the University of London and his colleagues recently subjected a tissue sample they obtained from the remains of Dalton's retina to DNA analysis. As it turns out, Hunt's team reports in the Feb. 17 SCIENCE, Dalton lacked the gene for pigment sensitive to middle wavelengths, not long wavelengths of light. This deficiency, known as deuteranopia, has a different genetic profile from protanopia, which scientists had blamed for Dalton's problem.

"Molecular biology has finally set history straight," says Hunt. — *R. Lipkin.*