HIV-2 Case Found, AIDS Drug Tested

Recent reports of the first U.S. AIDS case caused by a second virus and results from human tests of a potential AIDS treatment illustrate how likely it is that 1988, like recent years, will be riddled with both optimism and pessimism in the now-global war against AIDS.

Physicians at the University of Medicine and Dentistry in Newark, N.J., said last week that they have diagnosed the first known U.S. case of AIDS caused by the virus called HIV-2. Although HIV-2 infection is frequently found in parts of West Africa, HIV-1 has been the cause of AIDS in the United States. Since HIV-2's discovery more than two years ago, scientists have debated whether this second virus actually causes full-blown cases of AIDS (SN: 3/7/87, p.151). Officials have been saying for months that it was inevitable that HIV-2-caused AIDS would be found in North America, with the virus already detected in Europe and Brazil.

Emphasizing that it is too early to assess the threat of HIV-2 in the United States, federal officials say there currently are no plans to specifically test the nation's blood supply for the virus. Peter J. Fischinger, AIDS coordinator for the U.S. Public Health Service, said last week at a Washington, D.C., briefing that existing HIV-1 screening tests cross-react with HIV-2 enough to handle the remote possibility of an HIV-2 blood donor. At the same briefing, Food and Drug Administration (FDA) Commissioner Frank E. Young said that prior screening of blood from more than 22,600 individuals in the United States had not detected infection with HIV-2. In anticipation of future HIV-2 spread, however, Young says the FDA is evaluating a rapid HIV-2 test in a "fast track" review process. He also says the FDA recommended last week that West Africans, like other high-risk groups, voluntarily exclude themselves from donating blood.

Young admits that potential treatments and tests for diseases other than AIDS have suffered under the FDA's concerted effort to rapidly review AIDS-related medical products. "We're running with bloody feet to try to keep up" with the many AIDS-related requests for FDA approval, he says.

Early last year, when zidovudine (AZT) became the first AIDS treatment approved by the FDA, human testing of other drugs was already underway. Among those candidate treatments was 2′,3′-dideoxycytidine (ddC), a more potent relative of AZT that inhibits HIV-1 infection of cells (SN: 3/28/87, p.198). Last month, researchers published the results from the phase I clinical trials of ddC, which were designed to evaluate the drug's toxicity and potential curative effects.

The multicenter study — led by scientists at the National Cancer Institute in Bethesda, Md. — included 20 AIDS or AIDS-related complex (ARC) patients given ddC, plus another six patients given zidovudine alternating with ddC. Length of treatment depended on the individual's response to the drugs.

Whether given intravenously or orally, ddC effectively crossed the blood-brain barrier, which is important because the virus can infect brain cells and cause dementia. Both sets of patients also showed an increase in the total number of certain immune cells called T4 lymphocytes, which can be drastically reduced during HIV infection. But like zidovudine, which has adverse effects on the bone marrow, ddC given alone is not without its problems. In addition to the rashes, mouth sores and fever of some ddC-treated patients, several patients developed reversible neurological symptoms, ranging from dizziness to dementia, after about three months of treatment.

More encouraging, say the scientists, are results from the smaller group of patients given ddC *and* zidovudine. At the time of the report, five of the six were without neurological symptoms after seven months of treatment.

Reporting in the Jan. 16 LANCET, the researchers note that "it is too early to say whether such a [combination] regimen will be better than AZT alone." But they conclude that the different toxicity profiles of ddC and zidovudine suggest that alternating the two therapies might help reduce adverse effects in patients.

— D.D. Edwards

Aspirin/heart issue, cont.

One day after last week's announcement by U.S. scientists that an aspirin every other day can reduce the risk of a first heart attack by 47 percent, British scientists reported that their study of 5,000 British physicians failed to find any similar benefits from daily aspirin intake. Published in the Jan. 30 BRITISH MEDICAL JOURNAL, the second study included data from a six-year study by researchers from Oxford University's Radcliffe Infirmary, who say the U.S. results are overly optimistic.

Both U.S. and British scientists involved in the conflicting research projects, however, agree that the British results do not entirely negate the positive findings of the Harvard Medical School/Brigham and Women's Hospital study (SN: 1/30/88, p.68). Authors of the British report point out that the U.S. study, with its larger numbers (more than 22,000 test subjects and three times as many heart attacks), is more statistically sound. It is because of these statistical differences, Harvard's Meir J. Stampfer said in an interview, that the Boston group feels the British study "is not especially informative. . . .Where they are is where we were in 1983 or so." Charles H. Hennekens, chairman of the U.S. study, also participated in the British project during a year-long appointment in London and is a coauthor of the report.

Despite the British study's smaller size, Stampfer acknowledges that its outcome could alter the final conclusions drawn from the larger study. He says the actual aspirin-related decrease in heart disease risk may not be "quite as extreme" as 47 percent. Authors of the British report suggest that the decrease in risk may be closer to 30 percent.

— D.D. Edwards

FDA to evaluate fat substitute

Two days after announcing its new fat substitute, the NutraSweet Co. agreed last week to file a petition with the Food and Drug Administration to seek "generally recognized as safe" (GRAS) status for the substance, which it calls Simplesse.

At first, company officials said at a news conference that they did not require FDA approval before giving GRAS status to Simplesse because it is made by merely changing the physical form of proteins from common foods.

But they agreed to file a petition after meeting with FDA Commissioner Frank E. Young, who said he was "perplexed" by their decision to announce the product without consulting FDA. Young, in a letter to NutraSweet Chairman Robert B. Shapiro, said the company had not provided "any information about the product to the FDA, leaving the agency unable to evaluate the company's unilateral judgment that the product is safe."

One of the key questions concerning Simplesse will be whether extracting the protein and altering it will change its toxicity and nutritional value, says Theodore Labuza, incoming president of the Institute of Food Technologists and professor of food science and technology at the University of Minnesota in St. Paul.

Labuza says NutraSweet was within legal limits when it commissioned an expert panel to determine whether Sim-

plesse was GRAS. The Flavor Extracts Manufacturers Association (FEMA), for example, also has an expert panel to determine the GRAS status of artificial flavors made from natural products.

But Gerard McCowin, director of FDA's division of food and color additives, says the FEMA situation is different because it deals with minute amounts, compared with the potentially large Simplesse market.

Although NutraSweet, a division of the St. Louis-based Monsanto Co., has done nothing illegal, some believe the company made a public relations blunder. "It is not a legal question, but it is an issue of good regulatory sense," says Richard Merrill, chief counsel at FDA from 1975 to 1977.

"If you want to market a blockbuster product, then you better tell the regulatory agency that gets paid by the American public," says Merrill, now dean of the University of Virginia Law School in Charlottesville.

A spokeswoman for NutraSweet told SCIENCE NEWS the company went through proper legal channels, and would not comment further on the Simplesse issue. According to FDA Deputy Commissioner John A. Norris, company officials told him the whole thing was "a miscalculation on their part."

Some people believe NutraSweet officials may have wanted to avoid a long FDA review process and that they wanted to get a jump on their competition, namely Procter and Gamble's fat substitute Olestra, which is derived from sugar and edible oils and which FDA has been reviewing since June. Unlike Simplesse, Olestra has no calories, is not metabolized and can be used for cooking.

Simplesse, however, still would have broad applications. It can be used in dairy products and in oil-based products, such as salad dressings, mayonnaise and margarine, and it has 1.3 calories per gram, compared with fat's 9 calories per gram. Four ounces of traditional ice cream, for example, contains 283 calories while the same amount of Simplesse ice cream would contain 130 calories.

To simulate fat, NutraSweet scientists used a patented heating and blending process that shapes milk or egg protein into tiny round particles that roll over the tongue, creating a smooth and creamy sensation.

Once NutraSweet submits a GRAS petition, FDA's review process should take about 12 to 18 months, Norris says, which would coincide with NutraSweet's marketing goal. *— S. Eisenberg*

Priming for a lucky strike

Mersenne primes hold a special place in the never-ending pursuit of larger and larger prime numbers — numbers divisible only by themselves and 1. Expressed in the form $2^p - 1$, where the exponent p itself is a prime number, Mersenne numbers have a structure that makes it relatively easy to check whether even enormous numbers truly can't be factored. The largest prime yet found — the 30th Mersenne prime — has 65,050 digits when $p = 216{,}091$ (SN: 9/28/85, p.199).

This week, two computer experts found the 31st Mersenne prime. But to their surprise, the newly discovered prime number falls between two previously known Mersenne primes. It occurs when $p = 110{,}503$, making it the third-largest Mersenne prime known.

"To tell the truth," says Walter N. Colquitt of the Houston Area Research Center in The Woodlands, Tex., "I didn't expect to find anything." Colquitt, working with computer consultant Luther Welsh Jr. of El Toro, Calif., had written a computer program and organized a systematic search of Mersenne numbers in the hope of finding a record-breaking prime.

This time, because he had only a limited amount of time available on an NEC SX-2 supercomputer, Colquitt decided to run some smaller candidates to be sure that nothing had been missed in previous searches. Only Mersenne numbers with exponents up to 103,000 had been exhaustively searched in the past, says Colquitt. Later efforts had been "shotgun" affairs that covered only narrow ranges of large numbers. The new Mersenne prime falls within one of the gaps.

The supercomputer, running a program written completely in FORTRAN, took only about 11 minutes to confirm that $2^{110{,}503} - 1$ is a prime number. "That's an incredibly fast time," says David Slowinski, formerly with Cray Research, Inc., in Minneapolis and now a student at Carnegie-Mellon University in Pittsburgh. "They [must] have some very good trick to get such a fast time." Slowinski himself has discovered several Mersenne primes and plans to check Colquitt and Welsh's result.

"We tried different multiplication algorithms," says Welsh. "The program, as it stands now, is fairly decent, although it's not as fast as it could be."

"If you're going to look for prime numbers," says Colquitt, "you're probably going to learn more about multiplication than you want to know. You also have to be systematic — and you have to be lucky and pray a little bit."

Are there more Mersenne primes lurking in the gaps? "I have absolutely no idea," says Colquitt. "Thousands of them are untested yet." *— I. Peterson*

Good-deed viruses stop mouse diabetes

Apparently not all viral infections are bad news. A California researcher reported last week that injecting a specific virus into mice predisposed to diabetes seems to prevent the disease. Using nonobese diabetic mice and the lymphocytic choriomeningitis virus (LCMV), Michael B.A. Oldstone of the Research Institute of Scripps Clinic in La Jolla found that the virus interacts with certain immune cells to stop the destruction of insulin-producing cells in the mice.

Because of autoimmune reactions against their own pancreatic cells, nonobese diabetic mice develop life-threatening diabetes, usually by the age of 6 months. Prompted by his earlier findings that viruses may alter the autoimmune response, Oldstone injected mice with LCMV, which can infect a range of animals that includes humans. Of the mice injected when newborn, none developed diabetes within 9 months. Of those injected at age 6 weeks, only 6 percent became diabetic within the same period of time, compared with 95 percent of the untreated mice. About 20 mice were in each of the three treatment groups.

Oldstone writes in the Jan. 29 SCIENCE that probably only a small subset of cells is involved in this type of diabetes and that the animal's immune system is still generally intact. He says evidence suggests that the helper T lymphocytes are the culprits, and that they are incapacitated by LCMV through an undetermined mechanism. "We presume the virus gets into a small subset of these helper cells. . .and the virus alters their function or kills them," Oldstone said in an interview.

Although the virus causes chronic infection in mice, its injurious effects on the animals are "subtle and minimal," says Oldstone. Emphasizing that he does not advocate injecting whole viruses as potential therapy, Oldstone says he is searching for a component of the virus that can give the same protection, with possible applications as a treatment for human diabetics.

Aldo A. Rossini, from the University of Massachusetts Medical Center in Worcester, told SCIENCE NEWS that the new results are "an exciting observation. But one has to be very cautious . . . there are a lot more studies that have to be done." Nevertheless, Rossini says the new research direction taken by the La Jolla study could have significant implications for diabetes. "For a long time, it's been suggested that a virus plays a role in the pathogenesis of diabetes," he says. "Now, all of a sudden, we're saying a virus is important in *protection* from diabetes, that there are good viruses and bad viruses." *— D.D. Edwards*