# Biomedicine

## AIDS drug passes preliminaries

The two most recent tests of the experimental AIDS drug dideoxyinosine (DDI) have provided a more revealing peek at a potentially powerful weapon against AIDS.

The studies, detailed in the May 10 NEW ENGLAND JOURNAL OF MEDICINE, involved a combined total of 71 AIDS patients and were conducted to determine safe DDI doses. Although the higher doses brought serious side effects, including inflammation of the pancreas and painful aching in the legs and feet, smaller doses nonetheless combated the disease. Within two weeks, levels of the p24 antigen – a gauge of AIDS virus replication – dropped significantly in patients receiving high or low doses of the drug, while CD4 lymphocytes – infection-fighting white blood cells usually ravaged by the AIDS virus – increased significantly. After six weeks, many of the patients had gained weight and said they felt more energetic.

Pancreatitis, DDI's most dangerous side effect, diminished with lower doses. Since last October, 34 AIDS patients receiving DDI have died from pancreatitis, says Susan Yarin, public relations officer for DDI manufacturer Bristol-Meyers Co. of New York City. Only two of these victims, however, had been enrolled in a clinical study; the rest had obtained the drug through an expanded-access program available to patients who are already too sick to qualify for clinical research programs.

Unlike zidovudine (AZT) – the only AIDS drug so far approved by the FDA – DDI did not cause anemia. Hastened by these preliminary successes, large-scale clinical studies involving more than 900 patients are now underway to compare DDI's long-term effectiveness with that of AZT.

## Antibodies shield some infants from AIDS

Scientists have known since 1981 that the AIDS virus can be transmitted from mother to fetus. But not all babies born to infected mothers develop the disease, and among those who do, symptoms may not appear until the infants reach 6 months to 1 year of age. The diagnostic uncertainty forces physicians to delay experimental AIDS treatments that might otherwise begin soon after birth.

Researchers now report that a new antibody test, given to pregnant women infected with the AIDS virus, may indicate whether the newborn will be infected. Such knowledge could allow earlier diagnosis and treatment for diseased infants.

Yair Devash of Ortho Diagnostics in Raritan, N.J., with colleagues at the Albert Einstein College of Medicine in New York City, examined blood serum from 15 infected mothers and their newborns. The four infants who did not develop AIDS had antibodies that bind tightly to a key surface protein of the virus at a region known as the principal neutralizing domain (PND). Three of the four mothers of these babies also had the tightly binding antibodies. In contrast, none of the infected infants or their mothers had these antibodies.

Although the antibodies appear to prevent transmission of the virus from mother to infant, they do not protect mothers from infection, the investigators note in the May PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (Vol.87, No.9).

Underpinning the study was an assay developed by Devash to detect antibodies that bind most strongly to the PND region of an AIDS viral strain common in patients. Devash says other research groups had previously found a significant but smaller correlation between infant protection and maternal antibodies to the PND region of a laboratory strain of the virus. He suspects those studies yielded less dramatic results because they could not distinguish between tightly binding antibodies and weakly binding ones, which may not protect infants against infection. The new assay, he adds, could rapidly screen the effectiveness of potential AIDS vaccines by measuring the concentration of tightly binding antibodies they stimulate.

# Chemistry

*Janet Raloff reports from Boston at a meeting of the American Chemical Society*

## Sweet and bitter: Common origins?

The tongue senses at least four discrete tastes: sweet, sour, salty and bitter. Scientists have assumed that taste buds discriminate among these using highly specific receptors, each sensing only one of the basic four. In fact, many studies have indicated that sweetness may involve multiple receptors that discriminate among various sugary flavors, notes Grant E. DuBois of NutraSweet Co. in Mt. Prospect, Ill. But his group's new research suggests that a single receptor responds to all sweet compounds – *and* to bitter ones.

The NutraSweet researchers anesthetized rhesus monkeys and placed electrodes on a nerve behind the ear to "wiretap" electrical communications relayed to the brain from the tongue's sensory cells. To ensure that the wiretap was working and to establish a profile of typical responses, they presented the monkeys with each of the four tastes. Then they presented a solution containing either of two sweet-taste inhibitors. These newly developed inhibitors are chemical analogs of potent sweet compounds – one based on a guanidine structure, the other on a structure of aryl urea.

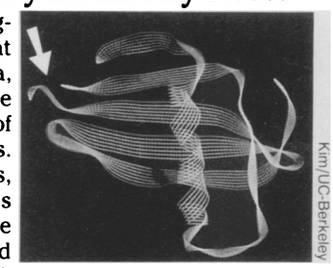
Shining ultraviolet light on the monkeys' tongues after exposure to the guanidine-based inhibitor stimulated the formation of highly reactive compounds, which then permanently bonded to the nearest receptive chemical on the tongue. Because the inhibitor resembles a sweetener in chemical structure, the researchers expected it to bind to a sweetness receptor. And indeed, for several hours (the time it takes for a natural turnover in taste cells), any sweet compound passing over the tongue elicited only about half the original electrical response, DuBois reports.

Bitter compounds, however, triggered the same depressed response. This indicates the inhibitor had "deactivated" not only many of the sweet receptors but also those sensing bitterness, he says. The aryl-urea-based inhibitor similarly depressed both sweet and bitter recognition, though in this case the bond was temporary.

Within a few years, DuBois says, researchers should be able to radioactively tag the guanidine-based inhibitor to unmask the specific receptors responsive to sweet and bitter tastes, and then clone the receptors to identify their chemical structure.

## 'Marriage' makes sugary bands stay sweet

Over the last five years, Sung-Hou Kim and his co-workers at the University of California, Berkeley, have identified the three-dimensional structure of a pair of sugary compounds. Derived from African berries, each is about 100,000 times sweeter than sucrose. The larger compound, called thaumatin-1 (SN: 3/23/85, p.186), recently won FDA approval for use in chewing gum.




*Computer image of monellin's natural structure.*

But Kim says thaumatin's unwieldy size complicates genetic tinkering to overcome certain drawbacks, such as its permanent loss of sweetness when heated.

Monellin, its far smaller chemical cousin, has proved more adaptable. In its natural form, monellin loses sweetness during heating because its two interlacing strings of amino acids are unbound and tend to separate at high temperatures. But Kim's team has inserted genes for a mutant version of monellin – in which the two adjacent loose ends (see arrow) are bound – into microbes. He now reports that the microbially produced, single-stranded monellin has a three-dimensional structure that allows it to recover its shape and sweetness after heating.