Biomedicine

AIDS: Building a better inhibitor

Pharmaceutical chemists have developed a compound that, *in vitro,* deactivates an enzyme vital to the maturation and function of the AIDS virus (HIV). The compound's novel structure may allow it to last longer in the body than other potential inhibitors of this enzyme.

Several research groups have been investigating chemicals to disrupt the activity of the AIDS virus by inhibiting one of its key enzymes, HIV protease. However, most of the more promising candidate inhibitors closely resemble peptides — compounds that may be broken down by digestive enzymes long before they can effectively disarm HIV. In hopes of developing longer-lasting antiviral drugs, scientists have begun investigating chemicals tailored to match the structural geometry of the target site (SN: 6/23/90, p.390).

John Erickson and his colleagues at Abbott Laboratories in North Chicago had strong indications that unlike other human proteases, the HIV enzyme has a two-fold symmetry — the left half of its "active site" is virtually a replica of its right half. The fact that peptides lack a two-fold symmetry suggested that some other type of compound might inhibit HIV protease as effectively. Identifuing a bilaterally symmetric compound that roughly matches the shape of the enzyme's active core region, Erickson's team subtly modified its structure until the target enzyme's amino acid side chains could bind this new compound in a tight embrace.

In the Aug. 3 SCIENCE, the Abbott scientists report that this compound — A-74704 — slowed HIV protease activity and infection of human T-lymphocytes by the AIDS virus *in vitro.* The new compound is highly selective, they note. It bound to HIV protease *in vitro* 10,000 times more effectively than to several other human proteases.

In analyzing the crystal structure of the inhibitor-bound enzyme, the team found that a water molecule within the enzyme links atoms on the protease's surface to those on the inhibitor. Erickson speculates that drugs designed to push aside the water molecule and mimic its linking ability may bind protease even more strongly. His group is now developing such drugs, he says.

HIV in the brain and spinal cord

When HIV crosses the blood-brain barrier, it can trigger a host of neuropsychological problems. At least two-thirds of AIDS patients suffer from memory impairment, limb weakness and poor concentration — symptoms collectively known as AIDS dementia. However, despite AIDS' widespread damage to nerve cells, autopsy studies have revealed these cells do not appear to harbor the virus. Instead, scientists have accumulated evidence that HIV in the central nervous system mainly replicates inside two types of related cells: macrophages (scavenger cells that have migrated from the blood) and microglial cells (the resident immune cells of the brain and spinal cord).

Researchers, however, had not directly linked microglial cell death to HIV infection and were uncertain whether the virus could infect other glial cells. To settle these questions, Brynmor A. Watkins and his colleagues at the National Institutes of Health added several HIV strains to a culture of microglial cells and astrocytes — star-shaped glial cells that surround and support nerve cells. In the Aug. 3 SCIENCE, they report that an HIV strain with a preference for macrophages infected only the microglial cells, causing them to fuse and die.

Enzymes and other chemicals released by dying microglial cells may degrade nerve tissue, Watkins now suspects, triggering symptoms related to AIDS dementia. He adds that his team's microglial cell culture may help test drugs targeted at halting HIV infection in the central nervous system.

Food Sciences

How you eat when you drink

Though U.S. adults consume an average of 160 calories in alcohol daily, its effect on dietary patterns "has not received much attention," note John M. de Castro and Sara Orozco of Georgia State University in Atlanta. So these two psychologists paid 92 adults to keep a log of one week's consumption of food and drink, including when they ate, how they felt while eating, and the number of people present. Their findings, reported in the August AMERICAN JOURNAL OF CLINICAL NUTRITION, offer several new insights.

For example, contrary to popular expectations — and observations of alcoholics — the study's social drinkers did not substitute alcohol for more nutritious calorie sources. Though 32 subjects abstained from alcohol, the other 60 recorded either low or moderate alcohol consumption, imbibing an average of 35 and 140 calories of alcohol per day respectively. While the number of calories obtained from carbohydrates, fats and proteins did not differ significantly among the no-, low- and moderate-alcohol groups, the nondrinkers consumed the fewest calories from foods other than alcohol; moderate drinkers consumed the most.

People in the two drinking groups consumed "significantly more" calories on days when they drank — a difference "due solely to the alcohol calories," the researchers note. However, the meals they consumed with alcohol tended to contain about 350 calories more than those consumed without — and about 500 calories more than meals eaten by the abstainers. More than half the caloric increase in meals accompanied by alcohol came from *nonalcoholic* sources: an average of 60 to 80 calories more from carbohydrates, 65 to 100 calories more from fat and 35 to 60 calories more from protein.

Duration may help explain the size of meals consumed with alcohol. Diners spent more than 2.5 times as long on meals with alcohol than on those without. However, meals also got larger as the day wore on, and later meals were more likely to include alcohol. "This suggests that the apparent influence of alcohol on meal size is due to the time of day and is not a direct effect of alcohol on food intake," de Castro and Orozco say. Yet the researchers had found in a previous study — not focusing on alcohol — that the number of people at a meal provided the "single most powerful predictor of food intake." This may also hold for meals served with alcohol, the team notes, since the new study showed an average of 2.44 people present at meals served with alcohol, and 1.37 people at meals served without.

Diet's role in respiratory risks

People with asthma or chronic bronchitis may glean new dietary strategies for moderating their periodic respiratory distress based on the results of a study involving 9,074 adults aged 30 and older. As part of the Second National Health and Nutrition Examination Survey (NHANES II), conducted between 1976 and 1980, researchers asked volunteers to recall what they had eaten the day before. Scott T. Weiss at the Harvard Medical School in Boston and Joel Schwartz of the Environmental Protection Agency in Washington, D.C., have now analyzed the recalled food choices in light of the respondents' respiratory histories, as determined during NHANES II through medical exams and personal interviews.

In the July AMERICAN JOURNAL OF EPIDEMIOLOGY, Schwartz and Weiss report that diets low in vitamin C, fish or their zinc-to-copper ratio, as well as diets with a high sodium-to-potassium ratio, increased the risk of bronchitis and wheezing, regardless of a person's age, gender, smoking history or area of residence. Low niacin levels also correlated with a risk of wheezing. The new findings even suggest that "diet may play a role in the susceptibility of certain smokers to the development of [chronic bronchitis and emphysema]," they say.