Does yo-yo dieting pose cancer threat?

Several studies have linked obesity to a heightened risk of breast cancer. Though the mechanism has remained elusive, some scientists have suggested that excess body fat may spur this and other hormone-sensitive tumors because fat produces its own estrogen.

A provocative new animal study now finds that this old theory may be right—but for a different reason.

Robert M. Bigsby of the Indiana University School of Medicine in Indianapolis and his colleagues have focused on estrogen and two estrogen-mimicking compounds that the body stores in fat: beta-hexachlorocyclohexane (β-HCH) and DDT. β-HCH, a variant of the active ingredient in the pesticide lindane, occurs in commercial preparations. Widespread use has made DDT and β-HCH ubiquitous in nature, including the fat of most people.

In experiments described in the March 1 CANCER RESEARCH, scientists removed the ovaries from female mice and injected the animals on three successive days with estrogen, β-HCH, or DDT. Without ovaries, the mice could not make their own estrogen. All three chemicals stimulated temporary growth of the uterus, which soon returned to normal size.

Two weeks later, the researchers put such mice on a 3-day fast, which triggered a burning of stored body fat. During the fast, DDT stayed in the fat, but animals treated with β-HCH released the compound into their bodies. This release again spurred dramatic uterine growth—a hallmark of estrogen's presence. Had seeds of a tumor been present, this pollutant probably would have spurred their growth too, observes Bigsby.

After the fast, the uteruses of mice that had been treated with β-HCH were "nearly as large as immediately after the 3-day chemical treatment," Bigsby notes.

Though he acknowledges that the doses he administered seem large, he also notes that the concentrations which probably developed in fat "should be comparable" to those reported in a 1990 study of Finnish women.

Earlier, the Indiana-based team had shown that β-HCH spurs the growth of breast cancer cells, but in an unusual way. "It didn't do the normal thing that estrogens and DDT do," notes physiologist Rosemary Steinmetz, who led that study.

Not only did β-HCH not bind to the estrogen receptor—at least, not at the usual site—it also didn't turn on the normal switches for estrogen-responsive genes. Steinmetz's follow-up studies with bisphenol-A, another environmental estrogen (SN: 4/6/96, p. 214), suggest that it, too, works without binding to that receptor.

The two Indiana reports "provide empirical confirmation of a theory that we've been developing," says toxicologist Devra Lee Davis of the World Resources Institute in Washington, D.C., referring to three papers that she and Michael Osborne of the Strang Cancer Prevention Center in New York are about to publish. They argue that not all estrogen mimics work through the estrogen receptor to increase cancer risk. Some may instead alter DNA to produce effects similar to those of estrogen.

The Indiana data also could be important for people who repeatedly lose and gain weight, contends endocrinologist H. Leon Bradlow of the Strang Center: Every time such yo-yo dieters drop in weight, they risk releasing substances stored in fat, thus exposing their organs to toxic chemicals.

Helena Mussalo-Rauhamaa of Helsinki University Hospital agrees, saying epidemiologists should begin surveying for yo-yo dieting when they probe cancer links to pollutants. In 1990, she found that breast cancer patients had more β-HCH in their fat than women without cancer. Clearly, she argues, β-HCH does not appear as benign as most chemistry handbooks allege.

Indeed, contends Davis, the fact that lindane is still used on children to kill head lice "is appalling." —*J. Raloff*

Shape, not bonds, may drive DNA synthesis

The enzyme that fashions the double helix of DNA works like a reliable, predictable matchmaker, lining up the molecular units of the two strands on the basis of the hydrogen bonds between them—or so scientists have long thought. New research suggests, however, that the enzyme arranges this marriage by recognizing the shape of those units rather than the bonds between them.

The four bases that make up DNA pair off depending on how well they form hydrogen bonds with each other: Adenine sticks to thymine, and cytosine fastens to guanine. Those pairings hold complementary strands of DNA together in a double helix.

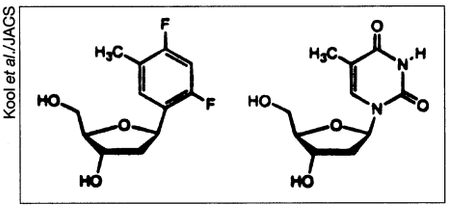
"Clearly, [the bases] form those hydrogen bonds once the DNA is made," says Eric T. Kool of the University of Rochester in New York, but he asks how the enzyme, DNA polymerase, recognizes which bases go together.

To test hydrogen bonding's role, Kool and his colleagues looked at how a molecule impersonating thymine affected DNA polymerase's ability to make DNA. They synthesized difluorotoluene, a molecule that has the same size and shape as thymine but that is "terrible" at forming hydrogen bonds with adenine, says Kool. When incorporated into DNA, difluorotoluene makes the double helix unstable.

The researchers substituted the molecule for thymine in single strands of DNA, which serve as templates for the synthesis. DNA polymerase moves along the template, selecting the appropriate bases and linking them together to form the second strand of the double helix.

To the group's surprise, the enzyme matched adenine to difluorotoluene without problems. "The molecule by itself is really bad at base pairing, yet the enzyme very faithfully puts adenine opposite it," Kool says. "I expected it to be a bad substrate, but the reverse was true." The synthesis proceeded at about the same rate as if thymine had been in the template, Kool and his colleagues report in the Feb. 26 JOURNAL OF THE AMERICAN CHEMICAL SOCIETY.

Kool *et al.*/JACS



The synthesized compound difluorotoluene (left, upper ring) has the same shape as the base thymine (right, upper ring). Both molecules are attached to sugar rings to form precursors to the building blocks of DNA.

Moreover, the rate was about 100 times better than that for templates with sites that contain no base. Previous studies had shown that DNA polymerase tends to select adenine for empty spots.

Other researchers have tested base mimics that don't form hydrogen bonds, Kool says, but those molecules also had different shapes and sizes. "Size effects can be easily as large as hydrogen-bonding effects."

One unanswered question, says Ronald Breslow, a chemist at Columbia University, is whether the fluorine atoms in the impostor form some kind of bond with adenine. Synthesizing a compound without fluorine would clear up that issue, he adds. Kool says that difluorotoluene is the closest possible analog to thymine; other compounds would introduce differences in size or shape once again.

The Rochester team now plans a complementary experiment, testing whether, in the absence of free thymine, the enzyme will choose difluorotoluene to insert opposite adenine in the template. They've synthesized mimics for other bases as well, so testing those should provide further information about the role that hydrogen bonds play. —*C. Wu*