Does obesity trigger chronic inflammation?

Overweight people show symptoms of chronic, low-grade inflammation—perhaps indicating early atherosclerosis, a major government study finds.

Dutch epidemiologist Marjolein Visser of the Free University in Amsterdam collaborated with scientists at the National Institute on Aging in Bethesda, Md., to analyze health data from 16,600 U.S. adults. These people had been studied between 1988 and 1994 as part of the third National Health and Nutrition Survey (NHANES III), a massive federal program to measure health indicators in a cross section of the U.S. population.

Visser's new analysis shows that overweight people are far more likely than lean ones to have excess concentrations of c-reactive protein (CRP) in their blood. Though no one knows what this compound does, it's generally used as a gauge of inflammation because the body produces it while fighting infections or experiencing other types of inflammation, such as muscle soreness. Moreover, people who show even moderately elevated concentrations of CRP face a high risk of developing heart disease (SN: 6/14/97, p. 374).

At the Experimental Biology '99 meeting in Washington, D.C., last week, Visser reported that obese women were far more likely than equally overweight men to produce elevated concentrations of CRP. Moreover, obese but otherwise healthy women under age 40 were 13 times as likely as lean women to have elevated CRP concentrations.

Comparably healthy though obese men of the same age were five times as likely as lean men to have high concentrations of CRP, defined as 0.2 milligrams per deciliter of blood or higher. Such concentrations fall well below those usually associated with overt infections or inflammation but within the range that, in other studies, put apparently healthy people at high risk of heart attacks or strokes.

Cardiologist Paul M. Ridker of Brigham and Women's Hospital in Boston has assayed CRP in middle-age people. Like Visser, he sees higher CRP concentrations in women than in men. In his work, the women most likely to have elevations in this protein are those taking postmenopausal hormone-replacement drugs to restore their hormone concentrations to those typical of premenopausal women. He also finds that obesity seems to increase CRP concentrations.

Over the past year, Ridker has published four studies showing that moderately elevated CRP is a strong predictor of heart attacks and strokes, even when he takes into account known risk factors such as smoking or elevated cholesterol concentrations. In those studies of middle-age men and women, CRP often proved most predictive of impending disease in people lacking any other known heart risks, including obesity.

"I'm a little underwhelmed by the NHANES data," Ridker told SCIENCE NEWS. His data indicate that "any traditional coronary risk factor that you pick—smoking, obesity, hypertension, elevated cholesterol—all correlate with [high] CRP levels. Why? Because they all correlate with atherosclerosis, which itself may be inflammatory." In other words, they all may just reflect the process underlying cardiovascular disease.

Others are less certain that CRP is simply a marker of inflammation. Among such skeptics is Susan K. Fried of Rutgers University in New Brunswick, N.J. She points out that CRP is usually made by the liver in response to a chemical called interleukin-6 (IL-6), which is made by the immune system. Fat cells also produce IL-6, and Fried's test-tube data show that abdominal fat cells from obese people make more of it than do abdominal fat cells from lean individuals.

Because IL-6 can limit the uptake of fat by fat cells, she says, the excess production of the chemical in obesity may represent the body's feeble attempt to prevent itself from getting fatter. However, when the IL-6 spills into the blood, she speculates, the liver "may misread the message"—thinking that infection is present somewhere—and begin generating CRP.

Samuel Klein of Washington University in St. Louis, who has studied fat's IL-6 production in people, also argues that the excess CRP in obese individuals "may stem from their having more fat tissue, not inflammation." Alternatively, he says, "maybe the IL-6 and CRP are also causing inflammation. It's possible there is some kind of vicious cycle in this."

All the researchers agree, however, that CRP elevations are probably not healthy and may point out people who should be targeted for risk intervention. This could start with a recommendation of weight loss or healthier diets and then, if appropriate, of aspirin or cholesterol-lowering drugs. *—J. Raloff*

More than one way to mutate a cell's DNA

High-energy particles that zip through a cell can cause dangerous mutations—even if they don't hit the DNA directly, new research shows. These alpha particles spawn chemicals called free radicals, which in turn damage DNA. This newly discovered mechanism may change how experts estimate people's risks from exposure to radioactivity.

Radon gas, a breakdown product of uranium that seeps naturally from the ground, accounts for most of the alpha particles that bombard people. Second only to cigarette smoking in causing lung cancer, radon gas results in as many as 22,000 cases, or 12 percent of lung cancers, in the United States each year (SN: 3/7/98, p. 159).

Until recently, scientists attributed the cellular havoc wreaked by alpha particles to their direct effects on DNA. The relatively large, high-energy particles, consisting of two neutrons and two protons, "come barreling through the nucleus, breaking things left and right," says Noelle F. Metting of the Pacific Northwest National Laboratory (PNNL) in Richland, Wash. The alpha particles batter the nuclear DNA, knocking out chunks of chromosomes.

To test how alpha particles damage a cell even when they miss its DNA, Tom K. Hei of Columbia University and his colleagues shot the particles through the body of the cell, or the cytoplasm, while carefully avoiding the nucleus. They report their results in the April 27 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES.

The exposed cells still suffered mutations, but the damage was more subtle than that caused by direct hits to the DNA. The small mutations resembled damage from naturally occurring free radicals, chemicals that are highly reactive because they either hold an extra electron or are missing one. When the researchers added compounds that scavenge free radicals, the rates of mutation dropped. When they interrupted the cells' natural defense against free radicals, the mutation rate climbed.

Cells naturally make free radicals, particularly when generating energy. Enzymes continually repair the damage that free radicals cause when they chip away at DNA, Metting says. "[Alpha particles] greatly enhance the background damage that just happens when you're alive," she says.

Although free radicals created by alpha particles make only small mutations, they ultimately could do more harm than alpha particles blasting directly through a cell's nucleus, comments PNNL's Michael K. Bowman. The reason is that alpha particles hitting the cytoplasm are less likely to kill a cell, so the mutated cell may proliferate into a cancerous tumor.

The research by Hei's team showed that twice as many cells survived when the alpha particles bombarded the cytoplasm compared with when they hit the nucleus.

The new findings will allow researchers to refine models of how alpha particles cause cancer, study collaborator Gerhard Randers-Pehrson of Columbia University says. If both the cytoplasm and the nucleus are sensitive to the particles' energy, current models may underestimate the effects of low doses of alpha radiation, he says. *—L. Helmuth*

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