Quieting a Body's Defenses

Researchers are linking inflammation to an ever-wider array of chronic illnesses. But treatments that block the inflammatory response can backfire.

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Illustration by Bryan Christie for Newsweek

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Summer 2005 - A decade ago, the cause of meta Kiss's heart attack might have been written off as a medical mystery. The 59-year-old homemaker had never smoked, weighed in at a slender 119 pounds and had fabulous cholesterol readings, with her good cholesterol actually surpassing the bad. And there was no history of heart disease in her family. So what put her at risk for the heart attack she suffered in 2000? To Eric Matteson, one of her doctors at the Mayo Clinic, the answer leapt right out. "She had rheumatoid arthritis," he says.

If the two conditions sound unrelated, that's because most of us are just now awakening to the risks of chronic inflammation. A decade ago, researchers were blaming oxidative damage for everything from cancer to heart disease. Now chronic, low-grade inflammation is seizing the spotlight. "Inflammation is the evil twin of oxidation," says neuroscientist James Joseph of Tufts University. "Where you find one, you find the other." That would include not only such obvious inflammatory conditions as asthma and rheumatoid arthritis, but also ailments never previously associated with inflammation—such as atherosclerosis, Alzheimer's disease, colon cancer and diabetes. Suddenly medical puzzles seem to be fitting together, such as why hypertension puts patients at increased risk of Alzheimer's, or why rheumatoid-arthritis sufferers have higher rates of sudden cardiac death. They're all connected on some fundamental level—which raises a tantalizing question. If there are common threads in the development of all these diseases, are there common treatments? Drug companies are eager to find out. But it's not as simple as it seems.

If you can't live with inflammation, you can't live without it, either. Inflammation is a key component of the immune system's defenses. If you cut yourself, the body sends in a barrage of microbe-fighting molecules (including oxidants), and the wound becomes red, hot and swollen. When the threat of infection recedes, so does the inflammation. But persistent insults like cigarette smoke, excess cholesterol and lingering infections can

produce a low-grade, chronic inflammation that simmers on, like the low flame on the back burner that we're unaware of until the pot burns.

Diabetes has emerged as a recent example. The correlation between type 2 diabetes and obesity is so well established that some researchers refer to the two collectively as "diabesity." Now we're starting to understand why they're linked. When you gain weight, fat cells grow more biochemically active, churning out inflammatory compounds. As obesity ratchets up inflammation, inflammation in turn promotes insulin resistance, a central feature of diabetes and the so-called metabolic syndrome that precedes it. Just why inflammation leads to insulin resistance is unclear. But Dr. Steven Shoelson, associate director of research at Joslin Diabetes Center, has bred a strain of mice whose fat cells produce exceptional levels of inflammatory compounds like TNF-alpha, IL-1 and resistin (as in insulin resistance). "We reproduced the whole constellation of metabolic syndrome in these mice," he says, "just by inciting inflammation."

In addition to diabetes, heart disease is a risk for people who are overweight. Inflammation may be the common denominator. "Inflammation is the alpha and omega of atherosclerosis," says Dr. Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital in Boston. "It's there at every step of the process." Plaque formation begins when cholesterol gets stuck in arterial walls and oxidizes, prompting the immune system to attempt a cleanup. Although inflammation is the body's attempt to heal, it only encourages the formation of bigger, more complicated plaques. With luck, plaques will remain stable for decades and cause no trouble. But inflammatory chemicals can weaken the fibrous cap that holds a plaque in place. If it ruptures, fat spills into the blood, where it collides with clotting factors, producing a clot that can block an artery and cause a heart attack or stroke.

Even certain cancers are being linked to inflammation. "People with chronic inflammatory bowel diseases have tremendously enhanced risk of colon cancer," says Lisa Coussens, a cancer biologist at the University of California, San Francisco. Other triggers of tumor-inducing inflammation include cigarette smoke in the lungs, persistent infections like hepatitis C in the liver and chronic heartburn, which repeatedly irritates the lining of the esophagus with gastric acid. Whatever the cause, says Coussens, the result is a series of changes that can set a cell on the road to malignancy. These include oxidative damage to DNA, the disabling of suicide mechanisms that should cause an abnormal cell to self-destruct, and the release of growth factors that can make the abnormal cell grow and divide.

This knowledge is beginning to change clinical approaches to treatment. For example, doctors used to use bare wire-mesh frames called stents to hold open clogged arteries, but the blood vessels routinely formed scar tissue over the stents and often narrowed again.

Now doctors are achieving much better success rates with stents that are coated with anti-inflammatory drugs. And they're starting to look beyond cholesterol alone for the keys to reducing heart attacks. Several large trials suggest that those patients who do best reduce both cholesterol and inflammation. Statin drugs help many patients reduce both, but future treatments may target inflammation more directly. Millennium Pharmaceuticals in Cambridge, Mass., is working with an experimental drug that blocks macrophages, a type of inflammatory immune cell, from moving out of the bloodstream and into vessel walls and other tissues.

But taming the immune system isn't as simple as it sounds. As Libby explains, there are three ways to go about it. You can reduce the triggers that cause inflammation. You can hamper the cellular "master switches" that orchestrate the body's inflammatory response. Or you can knock out the inflammatory chemicals—the "foot soldiers," as Libby dubs them—that actually produce the inflammation. Here's the catch. If you turn down the central switches too much, "you run the untoward risk of secondary infections," says Dr. Mark Fishman, president of the Novartis Institutes for BioMedical Research. Tysabri, an immune-modulating drug for multiple sclerosis, was voluntarily withdrawn from the market earlier this year after two patients taking it with another medication called Avonex developed an additional neurodegenerative disease, this one caused by a latent virus most of us harbor. Scientists need a much more detailed knowledge of how the various parts of the immune system interact and overlap, so they can develop key blood tests to tell them just how much they're turning down the system.

As for the foot soldiers, it turns out that many of the body's inflammatory chemicals also have beneficial functions, like protecting the stomach or guarding the lining of blood vessels against clots. If you knock out something that causes harm in one part of the body, you may eliminate positive effects elsewhere. Drugs like Vioxx and Bextra are a case in point. By inhibiting inflammatory Cox-2 enzymes, they relieved pain, but also hampered a compound that helps prevent dangerous blood clots from forming in arteries. A second problem with the foot soldiers is that there are so many with overlapping functions that eliminating a single one doesn't necessarily help you. The drugs Enbrel and Remicade fight rheumatoid arthritis by targeting the inflammatory compound TNF-alpha, but they do nothing for congestive heart failure, which many cardiologists believe is also an inflammatory condition.

Instead of aiming at narrower and narrower targets, some scientists are doing the opposite and striving for broader "immune modulation." One such treatment, called Celecade, is now in advanced testing for congestive heart failure. Doctors withdraw a test tube of the patient's blood and place it in a machine that delivers bursts of UV radiation for 10 to 15 minutes. The radiation kills immune-system white cells by triggering mechanisms of self-destruction. The blood is then reinjected into the patient's hip. As the procedure is repeated during the following weeks and months, the immune system interprets the self- destruction of white cells as a signal that the danger is reduced and responds by turning down systemic

inflammation across the board. "When I first saw this data, I was intrigued but highly skeptical," says cardiologist James Young of the Cleveland Clinic Foundation. Now that he has taken part in trials, he's cautiously optimistic that it will become a useful treatment. W. R. Woofter, 59, of Berea, Ohio, is one patient who's tried it. He's had five heart attacks since 1968 and severe congestive heart failure since 2002. Since last August, he's been going for monthly treatments. "I haven't deteriorated any more," he says. "I've been able to cut back on diuretic drugs by a third and cut another medicine for cardiac dysrhythmia by half." And he's back to golfing. "I'm still taking people's money," he says.

Medicine doesn't provide the only way to beat inflammation. Exercise and weight loss work to reduce inflammation in the fat cells and liver. And a diet rich in fruits, vegetables, whole grains and omega-3 fatty acids tones down inflammation overall.

The omega-3s are particularly important. Found in coldwater fish like salmon, sardines and mackerel, as well as walnuts, flaxseed and dark leafy greens, they form the building blocks of a number of anti-inflammatory compounds in the body. Dozens of studies have shown that the omega-3s can help prevent heart attacks and sudden cardiac death by preventing arrhythmias, making blood less likely to clot in arteries, improving the balance of good and bad cholesterol and limiting inflammation. But the modern diet is generally deficient in them. That's why a growing number of doctors are recommending fish-oil capsules.

A diet rich in fruits and vegetables also helps. One anti-inflammatory compound in food that has been studied extensively is curcumin, the yellow pigment in the curry spice turmeric. Greg Cole, professor of medicine and neurology at UCLA, has found that small doses reduce TNF-alpha and IL-1. Larger doses lead to a decrease in Cox-2 enzymes. But Cole considers curcumin a far safer Cox-2 inhibitor than, say, Vioxx. While drugs usually block a single target molecule and reduce its activity dramatically, he says, natural anti-inflammatories gently tweak a broader range of inflammatory compounds. "You'll get greater safety and efficacy reducing five inflammatory mediators by 30 percent than reducing one by 100 percent," he notes.

The beauty of these lifestyle changes is that they're so low tech, affordable and effective. When patients with a sedentary lifestyle and miserable diets come into the office of cardiologist Herbert Insel at New York University, they invariably ask if he can help them. "Sure," he replies. "But you can help yourself better." We may all have it within our grasp to reduce inflammation—if we can just muster the willpower.

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