





STUCK SWITCH:

Inflammation kills bacteria // and heals wounds // But what if your body kept fixing something that wasn't broken? // That's the problem of an immune system that's...

Always On

■ BY RACHAEL MOELLER GORMAN // PHOTOGRAPHS BY JOSEPH CULTICE

When scientists decry the sharp decline in the number of autopsies, they talk about what medical science may lose by not having the chance, after a patient's death, to explore the body in a way that wouldn't have been possible when the patient was alive. One of medicine's earliest diagnostic tools, autopsies have helped solve myriad medical mysteries—including the link between Alzheimer's disease and heart disease, and the discovery of the West Nile Virus—and in the 1980s, evidence uncovered during postmortems began solidifying the case for a risk factor that may have a profound role in the development of heart attacks, strokes and a laundry list of other plagues.

During the first half of the twentieth century, the prevailing view of heart disease considered arteries to be simple pipes, and cholesterol the gunk accumulating in those pipes until blood could no longer reach the heart or brain. But research in lab animals during the 1970s began to suggest that there was much more to it than grungy hardware. In 1973, University of Washington researcher Russell Ross proposed that arteries react to cholesterol and other environmental influences. This set the stage for a new view of atherosclerosis, and, in 1979, pathologist Ross Gerrity, then at the Cleveland Clinic Foundation, found some of the first evidence that atherosclerosis emerges in part because our own immune system attacks our arteries. When he examined the arteries of pigs that ate a high-cholesterol diet, he found inflammatory cells called monocytes packing the



This long-term inflammatory response was very different from acute short-term inflammation, which is a vital part of the so-called innate immune system, the body's first-line defense against bacteria and viruses. When you slice your finger on a jagged can, vessels dilate to allow more blood into the area. The finger becomes red and hot (from the extra blood), and white blood cells ooze into the wound to combat bacteria. The process accelerates until the site is clear, then stops. Inflammatory cells and proteins go back to their normal patrol in the bloodstream, and the finger heals.

Long-term inflammation, on the other hand, is never-ending, and it may be happening inside two of every three Americans, according to the Centers for Disease Control and Prevention and the American

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regions that developed atherosclerotic plaques. In two landmark 1981 papers, he made the case that these inflammatory cells are in fact the most important factors for plaque development: They not only absorb the low-density lipoprotein (LDL, or “bad” cholesterol) that trespasses into the blood vessel wall, but they also become foam cells, which researchers knew to form the core of a plaque.

And when pathologists autopsied patients who had suffered from atherosclerosis, it seemed the disease in humans followed a similar trajectory. Autopsied blood vessels revealed clots, like scabs on cuts, as well as monocytes and macrophages, which are cells that monocytes mature into once they're in the artery wall.

Soon, Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital in Boston, along with many other scientists across the country, was researching the details of this phenomenon in lab animals. The emerging consensus was that it's not just cholesterol that causes problems in the bloodstream; it's also the chronic low-level inflammation that responds to the cholesterol—and to elevated blood sugar, smoking and a diet high in saturated fat, among other “injuries.”

Heart Association. Always on, it attacks things that aren't foreign—abnormally high cholesterol levels, for instance—and damages not only the blood vessels but also the brain, the liver, other organs and even fat. There's a growing consensus that modern lifestyles—fatty, processed foods; a dearth of physical exercise; smoking—are sparking this immune response that's contributing to heart disease and other conditions, including type 2 diabetes, Alzheimer's disease and inflammatory bowel disease. It's as if today's environment were invading us, with our body doing all it can to fend off the onslaught. But we keep shooting ourselves in the foot.

When there's a lot of cholesterol in the bloodstream, it builds up in the artery walls, where destructive free radicals (highly reactive molecules with unpaired electrons) modify it into an odd shape. Sensing the cholesterol as a foreign object, endothelial cells in the walls deploy a molecule called VCAM-1 (vascular cell adhesion molecule-1), a protein that attracts inflammatory cells such as monocytes so they can repair the “injury.” Monocytes then burrow into the artery lining, beginning

an inflammatory reaction that attacks the modified cholesterol. But because the assault by cholesterol and other insults (such as carbon monoxide in smokers) is constant, so is the inflammatory reaction. The monocytes mature into macrophages that live inside the tissue, multiply and release inflammatory-signaling proteins called cytokines; those recruit more cells that may in turn produce their own signaling cytokines. The resulting level of inflammation is common in Americans, with one study that showed a sixth of U.S. teenagers already displaying signs of atherosclerosis in the heart.

Often, such accumulations of cholesterol and the accompanying inflammation don't form a clump large enough to block an artery. Instead, increasing inflammation weakens the top of the plaque by breaking down existing collagen and preventing new collagen fibers from forming. Then, if this tenuous cap ruptures, blood may come into contact with the plaque's lipid core. When the inside of the blood vessel is exposed, a clot will rapidly form to heal the injury, and that can block the flow of blood and cause a heart attack or stroke.

When Paul Ridker began practicing medicine in the mid-1980s, many of these details of the progression of atherosclerosis were unknown, and even now, scientists don't understand why atherosclerosis happens to people with low cholesterol or other risk factors. "Fifty percent of all heart attacks and strokes in the United States every year occur in people with normal or even low levels of cholesterol," says Ridker, director of the Center for Cardiovascular Disease Prevention at Brigham and Women's Hospital and the Eugene Braunwald professor of medicine at Harvard Medical School. "Fifteen to twenty percent of heart attacks and strokes happen to people with no recognized cardiovascular risk factors—no high blood pressure, high cholesterol or diabetes, and they don't smoke." Could inflammation be the real problem?

In 1995 Ridker began examining 1,086 men in the Physicians' Health Study to see whether future heart attack and stroke



victims could be identified in advance by testing baseline levels of inflammation. He zeroed in on CRP (C-reactive protein), a blood protein that acts as a marker for generalized inflammation in the body. Attempting to correlate high-sensitivity CRP (hsCRP) with future risk of disease, he found that in healthy men with no indication of heart disease, even slightly elevated hsCRP predicted who was likely to suffer a stroke or heart attack eight years later. It was as good a predictor as cholesterol levels.

The following year, Ridker discovered that adding a test for hsCRP to cholesterol screenings in men helped determine who would have his first heart attack much more precisely than cholesterol readings alone. And in 2000 he found that in healthy postmenopausal women, hsCRP was a more accurate predictor of risk for heart attack and stroke than 11 other indicators, including total cholesterol and LDL.

Finally, in 2002, a test for hsCRP became available in doctors' offices, and physicians learned that patients with levels higher than three milligrams per liter have twice the risk of heart disease as those with readings below one. "There have been probably 20 major studies, all of which demonstrate that if your hsCRP levels are elevated, this inflammation marker alone means you're at higher future risk of suffering a heart attack or stroke, independent of all other risk factors," Ridker says.

As important as it has been to identify a new, pervasive cardiovascular risk factor, there remains the question of what to do about it. For now, there are no widely accepted answers. That could change, with “every pharmaceutical company pouring money into finding ways to inhibit vascular inflammation,” Ridker says. But he and others have come to think that an old way to treat cardiovascular disease might work better. Statins dramatically cut cholesterol levels, but although they decrease the risk of heart attacks and strokes by as much as 38%, they limit blood vessel narrowing by only a few percentage points. That shouldn’t be enough to cause such a large reduction in heart attacks, and recent studies suggest statins may have another trick up their sleeve: soothing inflammation.

In 1998 Ridker and his colleagues published the results of a clinical trial showing that when inflammation levels were high, statins reduced not just cholesterol but also hsCRP—dramatically. Ridker found similar results in a 2005 trial, in which the chance of survival after a heart attack was highest when both cholesterol and hsCRP levels were reduced. A study by Scott Kinlay at the Boston VA Hospital and Brigham and Women’s Hospital found that statins also helped reduce the risk of stroke.

What is it about statins that soothes chronic inflammation? “There’s a huge debate,” Kinlay says. “It’s possible that statins are directly affecting the inflammatory cells—somehow muting their response—or working indirectly by sucking cholesterol out of the artery wall. Both effects would reduce inflammation.”

Ridker is most interested in preventing heart attacks in people who have normal cholesterol and blood pressure. He thinks some or most of the people who go on to suffer heart attacks or strokes have slightly elevated hsCRP, and he wants to know whether statins, by calming inflammation, could help prevent such individuals from suffering a first heart attack. For the past five years, he has led a trial known as JUPITER—Justification for the Use of statins in Primary prevention: an Intervention Trial

Evaluating Rosuvastatin—a randomized, placebo-controlled test of almost 18,000 people, to see whether putting those with high hsCRP levels but average cholesterol on a statin will lower their risk of having a heart attack or stroke. Depending on the trial results, which are expected to be presented this November, measuring and monitoring inflammation could be as important as tracking cholesterol. “The JUPITER study could revolutionize the way people approach cardiovascular risk reduction and evaluation,” says Roger Blumenthal, director of the Johns Hopkins Ciccarone Center for the Prevention of Heart Disease. “This is a tremendous step forward.”

Not everyone is so optimistic, however. Some, such as Kinlay and Mason Freeman, director of the lipid clinic at the Massachusetts General Hospital, think positive results from the JUPITER trial would need to be interpreted cautiously. Freeman believes statins indirectly treat inflammation by reducing cholesterol; he also contends that what JUPITER defines as “average” LDL is now being shown to be too high—and that if statins help those whose levels are average by JUPITER’s standards, it will be because the drugs primarily reduce LDL.

Other drugs being tested target the inflammatory pathway itself. One pathway component, an enzyme called lipoprotein-associated phospholipase A2 (Lp-PLA2), is produced by



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inflammatory cells involved in plaque development. The same enzyme also binds to LDL, triggers the release of pro-inflammatory molecules and accumulates in human atherosclerotic lesions. Because people with high Lp-PLA2 are more likely to have cardiovascular problems such as heart attacks, in 2002 GlaxoSmithKline began testing darapladib, a drug that inhibits Lp-PLA2. In 959 people with coronary heart disease, darapladib decreased levels of Lp-PLA2 by as much as 66%, and after 12 weeks on the drug, the subjects' levels of hsCRP and interleukin (another marker of inflammation) were both lower. Researchers hope further trials will determine whether the drug actually reduces heart attacks and strokes.

Like other immune responses, inflammation is intended to protect the body, not harm it. But in addition to contributing to heart attacks and strokes, chronic inflammation has been implicated in the development of many cancers, Alzheimer's disease and type 2 diabetes. Recent research on breast cancer, for example, suggests that a cytokine known as colony-stimulating factor 1 (CSF-1) may attract macrophages, which produce enzymes that encourage tumor development. In Alzheimer's disease, atheronals, a newly discovered by-product of inflammation, could be part of a process that results in the misfolding of amyloid beta proteins in the brain.

Inflammation's link to type 2 diabetes began in 1993, when Gökhan Hotamisligil, then a researcher at the Dana-Farber Cancer Institute in Boston and now at the Harvard School of Public Health, discovered that the fat tissue of obese mice showed heightened levels of an inflammation-promoting cytokine called TNF-alpha, and that TNF-alpha caused insulin resistance in the mice, whose cells could no longer efficiently use the glucose they needed for energy (such resistance is a precursor to type 2 diabetes). Hotamisligil then found that the inflammatory response actually originated in the fat cells themselves. "Obesity is like an injury to fat tissue," he says. When fat cells are continually bombarded with nutrients,

they seem to lose the ability to distinguish bad from good. Sensing they're under attack, the cells produce inflammatory cytokines and activate whole inflammatory networks.

Another connection between inflammation and type 2 diabetes was forged in 2001, when Aruna Pradhan, then working in Ridker's laboratory at Brigham and Women's Hospital, and her colleagues sought to discover whether hsCRP was as accurate a predictor of type 2 diabetes as it was of cardiovascular disease. Pradhan tested hsCRP levels in 550 healthy women and found that those with high CRP levels had a fourfold greater risk of developing type 2 diabetes than people with low levels.

That chronic inflammation has taken on such a negative role in diabetes and other diseases seems to be a matter of evolution gone awry. Tens of thousands of years ago, people evolved immune defenses against otherwise deadly diseases and infections, and the people with the best defenses survived to pass on their genes. Now, Ridker says, that process is fighting our modern environment of unhealthy foods, smoking and lack of exercise, causing chronic disease. The solution may be accepting inflammation's new role as a risk factor, testing for the condition and responding with statins, newer drugs, more exercise and better nutrition.

And though there are many who argue against widespread testing (contending that screening for hsCRP is difficult because a cold or other infection can temporarily raise its value, and that if only a few people will be helped, it doesn't make sense to screen everyone), Ridker is hopeful that JUPITER's results may help establish the value of knowing hsCRP levels as a way to reduce the chance of "surprise" heart attacks in people who otherwise seem to be at low risk. "If the JUPITER trial shows that patients with high hsCRP live longer with statins," he says, "as many as 100,000 heart attacks a year could be prevented." ■

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1. "Inflammation, Aspirin and the Risk of Cardiovascular Disease in Apparently Healthy Men," by Paul M. Ridker et al., *The New England Journal of Medicine*, April 3, 1997. The first paper to show that otherwise healthy people with slightly elevated inflammatory markers are more likely to have heart attacks years later.
2. "Statins for Atherosclerosis—As Good as It Gets?" by Michael R. Ehrenstein, Elizabeth C. Jury and Claudia Mauri, *The New England Journal of Medicine*, Jan. 6, 2005. This editorial explains the possible reasons why statins reduce inflammation.
3. "Dietary Factors That Promote or Retard Inflammation," by Arpita Basu, Sridevi Devaraj and Ishwarlal Jialal, *Arteriosclerosis, Thrombosis and Vascular Biology*, May 2006. A comprehensive analysis of studies examining which foods (antioxidants) soothe and which foods (saturated and trans fats) stoke our internal inflammation.