

## The Fires Within

Inflammation is the body's first defense against infection, but when it goes awry, it can lead to heart attacks, colon cancer, Alzheimer's and a host of other diseases

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Monday, Feb. 23, 2004



Cover

What does a stubbed toe or a splinter in a finger have to do with your risk of developing Alzheimer's disease, suffering a heart attack or succumbing to colon cancer? More than you might think. As scientists delve deeper into the fundamental causes of those and other illnesses, they are starting to see links to an age-old immunological defense mechanism called inflammation--the same biological process that turns the tissue around a splinter red and causes swelling in an injured toe. If they are right--and the evidence is starting to look pretty good--it could radically change doctors' concept of what makes us sick. It could also prove a bonanza to pharmaceutical companies looking for new ways to keep us well.

Most of the time, inflammation is a lifesaver that enables our bodies to fend off various disease-causing bacteria, viruses and parasites. (Yes, even in the industrialized world, we are constantly bombarded by pathogens.) The instant any of these potentially deadly microbes slips into the body, inflammation marshals a defensive attack that lays waste to both invader and any tissue it may have infected. Then just as quickly, the process subsides and healing begins.

Every once in a while, however, the whole feverish production doesn't shut down on cue. Sometimes the problem is a genetic predisposition; other times something like smoking or high blood pressure keeps the process going. In any event, inflammation becomes chronic rather than transitory. When that occurs, the body turns on itself--like an ornery child who can't resist picking a scab--with aftereffects that seem to underlie a wide variety of diseases.

Suddenly, inflammation has become one of the hottest areas of medical research. Hardly a week goes by without the publication of yet another study uncovering a new way that chronic inflammation does harm to the body. It destabilizes cholesterol deposits in the coronary arteries, leading to heart attacks and potentially even strokes. It chews up nerve cells in the brains of Alzheimer's victims. It may even foster the proliferation of abnormal cells and facilitate their transformation into cancer. In other words, chronic inflammation may be the engine that drives many of the most feared illnesses of middle and old age.

This concept is so intriguing because it suggests a new and possibly much simpler way of warding off disease. Instead of different treatments for, say, heart disease, Alzheimer's and colon cancer, there might be a single, inflammation-reducing remedy that would prevent all three.

Chronic inflammation also fascinates scientists because it indicates that our bodies may have, from an evolutionary perspective, become victims of their own success. "We evolved as a species because of our ability to fight off microbial invaders," says Dr. Peter Libby, chief of cardiovascular medicine at Brigham and Women's Hospital in Boston. "The strategies our bodies used for survival were important in a time when we didn't have processing plants to purify our water, when we didn't have sewers to protect us."

But now that we are living longer, those same inflammatory strategies are more likely to slip beyond our control. Making matters worse, it appears that many of the attributes of a Western lifestyle--such as a diet high in sugars and saturated fats, accompanied by little or no exercise--also make it easier for the body to become inflamed.

At least that's the theory. For now, most of the evidence is circumstantial. (A few researchers think chronic inflammation can in some cases be good for you.) But that hasn't stopped doctors from testing the anti-inflammatory drugs that are already on pharmacy shelves to see if they have any broader benefits. What they've found is encouraging:

--In 2000 researchers concluded that patients who take Celebrex, a prescription drug from Pfizer that was originally designed to treat inflammation in arthritis, are less likely to develop intestinal polyps--abnormal growths that can become cancerous. Now there are dozens of clinical trials of Celebrex, testing, among other things, whether the medication can also prevent breast cancer, delay memory loss or slow the progression of the devastating neurodegenerative disorder known as Lou Gehrig's disease.

--As cardiologists gain more experience prescribing cholesterol-lowering statins, they are discovering that the drugs are more effective at preventing heart attacks than anyone expected. It turns out that statins don't just lower cholesterol levels; they also reduce inflammation. Now statins are being tested for their anti-inflammatory effects on Alzheimer's disease and sickle-cell anemia.

--DeCode Genetics, an Icelandic biotech firm, announced last week that it is launching a pilot study to test whether an anti-inflammatory drug that was under development for use in treating asthma might work to prevent heart attacks.

--Of course the granddaddy of all anti-inflammatories is aspirin, and millions of Americans already take it to prevent heart attacks. But evidence is growing that it may also fight colon cancer and even Alzheimer's by reducing inflammation in the digestive tract and the brain.

This new view of inflammation is changing the way some scientists do medical research. "Virtually our entire R.-and-D. effort is [now] focused on inflammation and cancer," says Dr. Robert Tepper, president of research and development at Millennium Pharmaceuticals in Cambridge, Mass. In medical schools across the U.S., cardiologists, rheumatologists, oncologists, allergists and neurologists are all suddenly talking to one another--and they're discovering that they're looking at the same thing. The speed with which researchers are jumping on the inflammation bandwagon is breathtaking. Just a few years ago, "nobody was interested in this stuff," says Dr. Paul Ridker, a cardiologist at Brigham and Women's Hospital who has done some of the groundbreaking work in the area. "Now the whole field of inflammation research is about to explode."

To understand better what all the excitement is about, it helps to know a little about the basic immunological response, a cascade of events triggered whenever the body is subjected to trauma or injury. As soon as that splinter slices into your finger, for example, specialized sentinel cells prepositioned throughout the body alert the immune system to the presence of any bacteria that might have come along for the ride. Some of those cells, called mast cells, release a chemical called histamine that makes nearby capillaries leaky. This allows small amounts of plasma to pour out, slowing down invading bacteria, and prepares the way for other faraway immune defenders to easily enter the fray. Meanwhile, another group of sentinels, called macrophages, begin an immediate counterattack and release more chemicals, called cytokines, which signal for reinforcements. Soon, wave after wave of immune cells flood the site, destroying pathogens and damaged tissue alike--there's no carrying the wounded off the battlefield in this war. (No wonder the ancient Romans likened inflammation to being on fire.)

Doctors call this generalized response to practically any kind of attack innate immunity. Even the bodies of animals as primitive as starfish defend themselves this way. But higher organisms have also developed a more precision-guided defense system that helps direct and intensify the innate response and creates specialized antibodies, custom-made to target specific kinds of bacteria or viruses. This so-called learned immunity is what enables drug companies to develop vaccines against diseases like smallpox and the flu. Working in tandem, the innate and learned immunological defenses fight pitched battles until all the invading germs are annihilated. In a final flurry of activity, a last wave of cytokines is released, the inflammatory process recedes, and healing begins.

Problems begin when, for one reason or another, the inflammatory process persists and becomes chronic; the final effects are varied and depend a lot on where in the body the runaway reaction takes hold. Among the first to recognize the broader implications were heart doctors who noticed that inflammation seems to play a key role in cardiovascular disease.

IS YOUR HEART ON FIRE?

Not long ago, most doctors thought of heart attacks as primarily a plumbing problem. Over the years, fatty deposits would slowly build up on the insides of major coronary arteries until they grew so big that they cut off the supply of blood to a vital part of the heart. A complex molecule called LDL, the so-called bad cholesterol, provided the raw material for these deposits. Clearly anyone with high LDL levels was at greater risk of developing heart disease.

There's just one problem with that explanation: sometimes it's dead wrong. Indeed, half of all heart attacks occur in people with normal cholesterol levels. Not only that, as imaging techniques improved, doctors found, much to their surprise, that the most dangerous plaques weren't necessarily all that large. Something that hadn't yet been identified was causing those deposits to burst, triggering massive clots that cut off the coronary blood supply. In the 1990s, Ridker became convinced that some sort of inflammatory reaction was responsible for the bursting plaques, and he set about trying to prove it.

To test his hunch, Ridker needed a simple blood test that could serve as a marker for chronic inflammation. He settled on Creactive protein (CRP), a molecule produced by the liver in response to an inflammatory signal. During an acute illness, like a severe bacterial infection, levels of CRP quickly shoot from less than 10 mg/L to 1,000 mg/L or more. But Ridker was more interested in the low levels of CRP--less than 10 mg/L--that he found in otherwise healthy people and that indicated only a slightly elevated inflammation level. Indeed, the difference between normal and elevated is so small that it must be measured by a specially designed assay called a high-sensitivity CRP test.

By 1997, Ridker and his colleagues at Brigham and Women's had shown that healthy middle-aged men with the highest CRP levels were three times as likely to suffer a heart attack in the next six years as were those with the lowest CRP levels. Eventually, inflammation experts determined that having a CRP reading of 3.0 mg/L or higher can triple your risk of heart disease. The danger seems even greater in women than in men. By contrast, folks with extremely low levels of CRP, less than 0.5 mg/L, rarely have heart attacks.

Physicians still don't know for sure how inflammation might cause a plaque to burst. But they have a theory. As the level of LDL cholesterol increases in the blood, they speculate, some of it seeps into the lining of the coronary arteries and gets stuck there. Macrophages, alerted to the presence of something that doesn't belong, come in and try to clean out the cholesterol. If, for whatever reason, the cytokine signals begin ramping up the inflammatory process instead of notching it down, the plaque becomes unstable. "This is not about replacing cholesterol as a risk factor," Ridker says. "Cholesterol deposits, high blood pressure, smoking--all contribute to the development of underlying plaques. What inflammation seems to contribute is the propensity of those plaques to rupture and cause a heart attack. If there is only inflammation but no underlying heart disease, then there is no problem."

At this point, cardiologists are still not ready to recommend that the general population be screened for inflammation levels. But there's a growing consensus that CRP should be measured in those with a

moderately elevated risk of developing cardiovascular disease. At the very least, a high CRP level might tip the balance in favor of more aggressive therapy with treatments--such as aspirin and statins--that are already known to work.

## A NEW VIEW OF DIABETES

Before Dr. Frederick Banting and his colleagues at the University of Toronto isolated insulin in the 1920s, doctors tried to treat diabetes with high doses of salicylates, a group of aspirin-like compounds. (They were desperate and also tried morphine and heroin.) Sure enough, the salicylate approach reduced sugar levels, but at a high price: side effects included a constant ringing in the ears, headaches and dizziness. Today's treatments for diabetes are much safer and generally work by replacing insulin, boosting its production or helping the body make more efficient use of the hormone. But researchers over the past few years have been re-examining the salicylate approach for new clues about how diabetes develops.

What they have discovered is a complex interplay between inflammation, insulin and fat--either in the diet or in large folds under the skin. (Indeed, fat cells behave a lot like immune cells, spewing out inflammatory cytokines, particularly as you gain weight.) Where inflammation fits into this scenario--as either a cause or an effect--remains unclear. But the case for a central role is getting stronger. Dr. Steve Shoelson, a senior investigator at the Joslin Diabetes Center in Boston, has bred a strain of mice whose fat cells are supercharged inflammation factories. The mice become less efficient at using insulin and go on to develop diabetes. "We can reproduce the whole syndrome just by inciting inflammation," Shoelson says.

That suggests that a well-timed intervention in the inflammatory process might reverse some of the effects of diabetes. Some of the drugs that are already used to treat the disorder, like metformin, may work because they also dampen the inflammation response. In addition, preliminary research suggests that high CRP levels may indicate a greater risk of diabetes. But it's too early to say whether reducing CRP levels will actually keep diabetes at bay.

## CANCER: THE WOUND THAT NEVER HEALS

Back in the 1860s, renowned pathologist Rudolf Virchow speculated that cancerous tumors arise at the site of chronic inflammation. A century later, oncologists paid more attention to the role that various genetic mutations play in promoting abnormal growths that eventually become malignant. Now researchers are exploring the possibility that mutation and inflammation are mutually reinforcing processes that, left unchecked, can transform normal cells into potentially deadly tumors.

How might that happen? One of the most potent weapons produced by macrophages and other inflammatory cells are the so-called oxygen free radicals. These highly reactive molecules destroy just about anything that crosses their path--particularly DNA. A glancing blow that damages but doesn't destroy a cell

could lead to a genetic mutation that allows it to keep on growing and dividing. The abnormal growth is still not a tumor, says Lisa Coussens, a cancer biologist at the Comprehensive Cancer Center at the University of California, San Francisco. But to the immune system, it looks very much like a wound that needs to be fixed. "When immune cells get called in, they bring growth factors and a whole slew of proteins that call other inflammatory cells," Coussens explains. "Those things come in and go 'heal, heal, heal.' But instead of healing, you're 'feeding, feeding, feeding.'"

Sometimes the reason for the initial inflammatory cycle is obvious--as with chronic heartburn, which continually bathes the lining of the esophagus with stomach acid, predisposing a person to esophageal cancer. Other times, it's less clear. Scientists are exploring the role of an enzyme called cyclo-oxygenase 2 (COX-2) in the development of colon cancer. COX-2 is yet another protein produced by the body during inflammation.

Over the past few years, researchers have shown that folks who take daily doses of aspirin--which is known to block COX2--are less likely to develop precancerous growths called polyps. The problem with aspirin, however, is that it can also cause internal bleeding. Then in 2000, researchers showed that Celebrex, another COX-2 inhibitor that is less likely than aspirin to cause bleeding, also reduces the number of polyps in the large intestine.

So, should you be taking Celebrex to prevent colon cancer? It's still too early to say. Clearly COX-2 is one of the factors in colon cancer. "But I don't think it's the exclusive answer," says Ray DuBois, director of cancer prevention at the Vanderbilt-Ingram Cancer Center in Nashville, Tenn. "There are a lot of other components that need to be explored."

#### ASPIRIN FOR ALZHEIMER'S DISEASE?

When doctors treating Alzheimer's patients took a closer look at who seemed to be succumbing to the disease, they uncovered a tantalizing clue: those who were already taking anti-inflammatory drugs for arthritis or heart disease tended to develop the disorder later than those who weren't. Perhaps the immune system mistakenly saw the characteristic plaques and tangles that build up in the brains of Alzheimer's patients as damaged tissue that needed to be cleared out. If so, the ensuing inflammatory reaction was doing more harm than good. Blocking it with anti-inflammatories might limit, or at least delay, any damage to cognitive functions.

The most likely culprits this time around are the glial cells, whose job is to nourish and communicate with the neurons. Researchers have discovered that glial cells can also act a lot like the mast cells of the skin, producing inflammatory cytokines that call additional immune cells into action. "The glial cells are trying to return the brain to a normal state," explains Linda Van Eldik, a neurobiologist at Northwestern University Feinberg School of Medicine in Chicago. "But for some reason, in neurodegenerative diseases like

Alzheimer's, the process seems to be out of control. You get chronic glial activation, which results in an inflammatory state."

It appears that some people are more sensitive to plaques and tangles than others. Perhaps they have a genetic predisposition. Or perhaps a long-running bacterial infection, like gum disease, keeps the internal fires burning and tips the balance toward chronic inflammation.

Preliminary research suggests that low-dose aspirin and fish-oil capsules--both of which are known to reduce inflammatory cytokines--seem to reduce a person's risk of Alzheimer's disease. Unfortunately, most of these preventive measures need to be started well before any neurological problems develop. "What we've learned with dementia is that it's very hard to improve people who already have it," says Dr. Ernst Schaefer, a professor of medicine and nutrition at Tuft's Friedman School of Nutrition in Boston. "But it may be possible to stabilize people and to prevent disease."

#### WHEN THE BODY ATTACKS ITSELF

No doctors have more experience treating chronic inflammation than the physicians who specialize in rheumatoid arthritis, multiple sclerosis, lupus and other autoimmune disorders. For decades these diseases have provided the clearest example of a body at war with itself. But the spark that fuels their internal destruction doesn't come from excess cholesterol deposits or a stubborn bacterial infection. Instead, in a bizarre twist of fate, the body's supersophisticated, learned immunological defenses mistakenly direct an inflammatory attack against healthy cells in such places as the joints, nerves and connective tissue.

Over the past few years, powerful drugs like Remicade and Enbrel, which target specific inflammatory cytokines, have worked wonders against rheumatoid arthritis and other autoimmune disorders. But as often happens in medicine, the drugs have also created some problems. Patients who take Remicade, for example, are slightly more likely to develop tuberculosis; the same inflammatory cytokines that attacked their joints, it seems, also protected them against TB.

Inflammation may be more of a problem in the earlier stages of autoimmune diseases like multiple sclerosis. So much tissue is eventually destroyed that nerve damage becomes permanent. "Your initial goal is to keep the immune response in check, but then you have to ask how you encourage regrowth of damaged tissue," says Dr. Stephen Reingold, vice president for research programs at the National Multiple Sclerosis Society. It could take decades to figure that one out.

#### ASTHMA WITHOUT ALLERGIES?

One of the most intriguing questions in immunology today is why everyone doesn't suffer from asthma. After all, the air we breathe is full of germs, viruses and other irritants. Since half of the 17 million Americans with

asthma are hypersensitive to common substances like cat dander or pollen, it stands to reason that their allergic reactions trigger the chronic inflammation in their bodies. Yet the people who develop asthma as adults--one of the most rapidly growing segments of the population--often don't have allergies. Doctors still don't know what's driving their disease, but the signs of inflammation are every bit as present in their lungs.

Many treatments for asthma are designed to control inflammation, although they still don't cure the disease. "It may mean that the inflammatory hypothesis is not entirely correct or the drugs that we use to treat inflammation aren't fully potent," says Dr. Stephen Wasserman, an allergist at the University of California at San Diego. "There are a lot of gaps to fill in."

Everywhere they turn, doctors are finding evidence that inflammation plays a larger role in chronic diseases than they thought. But that doesn't necessarily mean they know what to do about it. "We're in a quandary right now," says Dr. Gailen Marshall, an immunologist at the University of Texas Medical School at Houston. "We're advancing the idea to heighten awareness. But we really can't recommend specific treatments yet."

That may soon change. Researchers are looking beyond aspirin and other multipurpose medications to experimental drugs that block inflammation more precisely. Any day now, Genentech is expecting a decision from the FDA on its colon-cancer drug, Avastin, which targets one of the growth factors released by the body as inflammation gives way to healing. Millennium Pharmaceuticals is testing a different kind of drug, called Velcade, which has already been approved for treating multiple myeloma, against lung cancer and other malignancies. But there is a sense that much more basic research into the nature of inflammation needs to be done before scientists understand how best to limit the damage in chronic diseases.

In the meantime, there are things we all can do to dampen our inflammatory fires. Some of the advice may sound terribly familiar, but we have fresh reasons to follow through. Losing weight induces those fat cells--remember them?--to produce fewer cytokines. So does regular exercise, 30 minutes a day most days of the week. Flossing your teeth combats gum disease, another source of chronic inflammation. Fruits, vegetables and fish are full of substances that disable free radicals.

So if you want to stop inflammation, get off that couch, head to the green market and try not to stub your toe on the way.

--With reporting by Dan Cray/Los Angeles