Harbinger of a Heart Attack

Does a protein in the blood foretell heart trouble?

By KATHLEEN FACKELMANN

Half of all heart attacks strike people who have no idea they are at risk. These people don't have high concentrations of cholesterol in their bloodstream—the well-known indicator of heart disease.

A surprising report now suggests that a simple blood test may foreshadow heart attacks up to a decade in advance. That knowledge may encourage individuals to adopt a more healthful lifestyle.

The study also adds to evidence that the body's inflammatory response plays a crucial role in the clogging of the heart's vessels. The new findings "may turn out to have great importance in the future," says Charles H. Hennekens of Harvard Medical School in Boston. His team suggests that anti-inflammatory drugs may prevent a heart attack from ever happening.

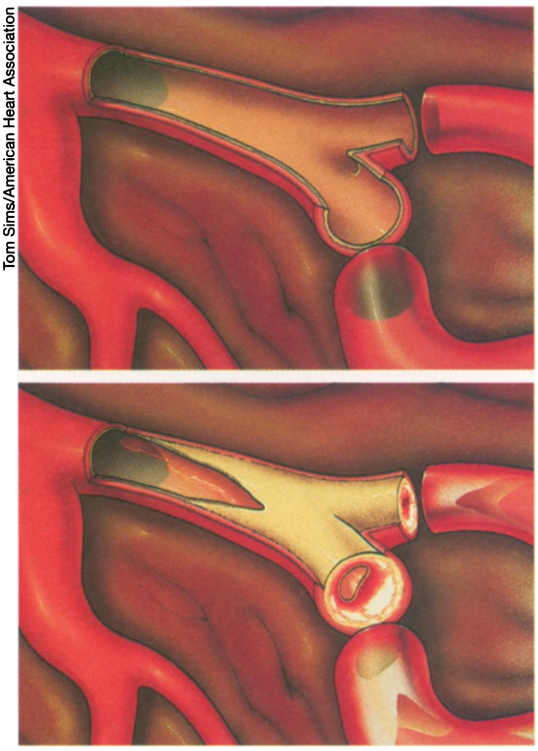
The stakes are high. According to the Dallas-based American Heart Association, heart attacks kill nearly 500,000 people in the United States each year.

Researchers had long suspected that inflammation plays a central role in atherosclerosis, the buildup of the fatlike substance called cholesterol and other debris on the interior surface of the artery wall. However, they lacked supporting evidence from a large epidemiological study.

That's where Paul M. Ridker, a cardiologist at Harvard, comes in. Ridker and his coworkers knew that people who have just suffered a heart attack have a chemical marker of inflammation, called C-reactive protein, in their blood. The researchers wondered whether the protein could serve as an indicator of risk in healthy people.

The team turned to the Physicians' Health Study, an investigation of more than 22,000 male physicians. The group focused on 1,086 of the participants, half of whom had developed heart disease over the course of the 14-year study. All had had blood collected and stored at the beginning of the research effort.

Ridker's group decided to measure concentrations of C-reactive protein in this blood. The protein is a naturally produced inflammatory substance that sends white blood cells to the site of an injury or infection. If prolonged or excessive, however, this response can harm body tissues.



Tom Sims/American Heart Association

Top: A healthy heart artery. Bottom: artery choked with plaque.

Not surprisingly, since all of the men were healthy at the study's onset, the concentrations of C-reactive protein were considered normal. The researchers discovered, however, that men with readings in the top 25 percent of the test group had a much higher risk of heart attack or stroke than men with lower concentrations.

"People with high-normal values ended up over the next 10 years of their lives having three times as many heart attacks and twice as many strokes as did those who had lower levels of this particular protein," Ridker says.

"What that's telling us is that inflammation is present 5, 6, 8, 10 years in advance of the heart attack," he adds.

The correlation between this protein and a future heart attack is independent of known risk factors such as smoking, hypertension, or even high cholesterol, the authors note in the April 3 NEW ENGLAND JOURNAL OF MEDICINE (NEJM).

"It is truly remarkable that they were able to find a correlation between this marker of inflammation and events many years later," comments Peter Libby, an inflammation researcher at Harvard. "That's the real surprise for me."

In an editorial in the same issue of NEJM, Attilio Maseri of the Catholic University of the Sacred Heart in Rome calls the study's findings intriguing. "The time has come to reexamine the pathogenic components of [a heart attack]," he says.

The Harvard team's results hint that researchers may soon have a novel heart attack predictor. By measuring the concentration of C-reactive protein, doctors may flag people who, despite normal cholesterol counts, face a higher-than-average chance of stroke or heart attack in the coming years.

"We may have a new method of detecting risk in this group," Ridker says.

Such a test might add weight to the widespread public health admonitions to eat a low-fat diet, exercise regularly, and stop smoking—habits thought to avert heart and blood vessel disease.

A lot of people ignore such recommendations because they believe a heart attack's not likely to happen to them. "But are they really at low risk?" Ridker asks. "This [test] might change their perception."

The study also suggests that certain people may benefit from drugs to reduce inflammation. At the start of the Physicians' Health Study, the researchers placed participants at random in one of two groups. Volunteers in the first group took an aspirin every other day. The rest took a dummy pill on the same schedule. The researchers designed this part of the study to test aspirin's ability to ward off heart attacks. In 1988, they reported that aspirin dramatically cut the risk of a first heart attack in middle-aged men (SN: 1/30/88, p. 68).

The new analysis elaborates on aspirin's ability to prevent heart attack. Among the men with the highest C-reactive protein concentrations at the beginning of the study, taking aspirin correlated with a large, statistically significant reduction in heart attack rate. For men with the lowest concentrations, the correlation was not statistically significant.

"The very people who were getting the

biggest benefit from aspirin had the most inflammation," Ridker says.

Aspirin is known to discourage the formation of blood clots. Such action helps prevent heart attacks, which strike when a blood clot gets lodged in a plaque-clogged artery. The new findings suggest that aspirin's ability to subdue inflammation is also valuable in fighting heart attacks, Ridker says.

The classic view of atherosclerosis needs an overhaul. For years, cardiologists thought of the artery as a rigid tube with cholesterol and other goo piling up inside, much as a bathroom pipe gets clogged with debris.

Today, increasing evidence shows that atherosclerosis isn't simply a mechanical plugging of the pipes. "It's now clearly recognized that an atherosclerotic plaque is a much more dynamic set of circumstances," inflammation researcher Stephen Prescott of the University of Utah in Salt Lake City told SCIENCE NEWS. Indeed, the data suggest that inflammation is "central to the pathogenesis" of atherosclerosis, he says.

In the 1970s, Russell Ross of the University of Washington School of Medicine in Seattle put forth the theory that an injury to the blood vessel wall kicks off the insidious process of inflammation and plaque formation. Various agents may cause such an injury. People with high cholesterol concentrations also have high concentrations of carrier molecules called lipoproteins, which can oxidize into dangerous compounds known as free radicals. Free radicals also harm the blood vessels of people who smoke cigarettes. Finally, some researchers think that infectious microbes damage the blood vessel wall and trigger atherosclerosis (see sidebar).

In any event, the body mounts an inflammatory response to the injury. If the cause of that injury persists, the protective action of the white blood cells goes awry, says Ross, and inflammation becomes excessive.

The inflammation-causing chemicals released by white cells can further harm the blood vessel wall. White cells congregate at the site of the injury, becoming engorged with fat molecules and forming the first signs of atherosclerosis—the fatty streaks that develop as early as the teenage years (SN: 1/20/90, p. 37).

The body tries to heal that damage by sending in smooth muscle cells to cover the fatty streak and repair the wall. Over the years, layers of fat and cells are deposited on the once-pristine artery surface. By the fifth or sixth decade of life, many people have hardened plaque that significantly narrows the blood vessel.

For years, researchers have been building the basic framework for this view of atherosclerosis. Now, Ridker's team has added epidemiological support.

What's next on the research agenda? The aspirin data hint at a bold new approach to the prevention of heart disease: Quench the chronic inflammation of the blood vessels. This approach "clearly needs to get tested," Ridker says, adding that other drugs may prove more effective than aspirin.

Indeed, a team at Harvard led by Charles N. Serhan has used current knowledge of how aspirin works to design two new anti-inflammatory compounds. Serhan says these agents are much more powerful than aspirin. They stop inflammation by telling white cells to quit migrating to the site of injury, he explains.

Could such research lead to drugs that safely stop inflammation in the arteries of people with atherosclerosis? "That would be my biggest dream come true," Serhan says. So far, however, his team has tested these agents on inflammation only in mouse ears, not the coronary arteries of people. He reports his findings in the May 5 JOURNAL OF EXPERIMENTAL MEDICINE.

The goal of such research is to find a defense against atherosclerosis itself. "Is it possible that taking a particular agent over a period of time would keep the disease at such a low-grade level that it would never prove to be a problem?" Ross asks. "I don't know the answer to that."

Such an antidote could rewrite the future for an estimated 2.2 million people in the United States who harbor plaque-clogged arteries. □

Can You Catch Heart Disease?

Imagine a virus that burrows into the cells of blood vessel walls. The microbe sets off an alarm. The body's immune cells swarm to the scene, beginning a long-term inflammation accompanied by deposits of cholesterol. Over many years, that process results in a plaque-narrowed artery.

That's the radical theory of atherosclerosis favored by some researchers.

For the last several years, they have maintained that infection with a variety of microorganisms, including herpesviruses, plays a central role in the development of atherosclerosis (SN: 4/3/93, p. 216).

It's a theory that has been gaining ground. For example, a study in the August 29, 1996 NEW ENGLAND JOURNAL OF MEDICINE that focused on cytomegalovirus, one of the herpesviruses, added further support.

Stephen E. Epstein of the National Heart, Lung, and Blood Institute in Bethesda, Md., and his colleagues studied people who were undergoing a procedure in which cardiologists ream out the plaque-choked coronary arteries. The researchers found that men and women who had previously been infected with cytomegalovirus had a much higher risk of developing restenosis, a post-treatment narrowing of the vessel. That condition, an accelerated version of atherosclerosis, puts people at high risk of a heart attack, Epstein says.

More recently, a team of researchers demonstrated that a microbe known to cause pneumonia may be linked to a heart valve condition. The disorder, called nonrheumatic heart valve disease, is characterized by inflammation and clogging of the valves of the heart. In the April JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY, the scientists demonstrated that of the 10 people in their study who died of this heart valve disease, 8 were infected with a bug called *Chlamydia pneumoniae*. Of the eight people in the control group, all of whom had died of other causes, only one was infected with this microbe.

"This is quite a provocative finding," says study author Tatu Juvonen of Mount Sinai Medical Center in New York. The clogging material in the heart valves is similar to the plaque that builds up on blood vessel walls, Juvonen notes. Previous research had linked *C. pneumoniae* to atherosclerosis, he adds.

Such evidence has yet to impress most researchers studying inflammation and atherosclerosis. "Viruses are so ubiquitous in humans that you can't prove they're causing disease," says Russell Ross of the University of Washington School of Medicine in Seattle. He insists that the link between atherosclerosis and microbes is, to date, purely circumstantial. Microorganisms have been shown to be at the scene of the crime—the atherosclerotic plaque taken from human blood vessels—but the research proving cause and effect is lacking, he says.

"I can visualize a small percentage of cases where viruses or other microorganisms cause [atherosclerosis] in humans, but I think they represent a small percentage, if any at all," Ross adds.

Epstein disagrees. Findings of cytomegalovirus or other microbes in human plaque are just one piece of the evidence. Researchers also have laboratory data suggesting several molecular mechanisms by which microbes could trigger atherosclerosis. For example, his group has shown that infection with cytomegalovirus spurs smooth muscle cells to proliferate, a key step in the formation of plaque.

"We have not proven that there is an infectious component [to atherosclerosis], but the data are rapidly accumulating," Epstein says. "It's beginning to get very, very interesting." —*K.F.*