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Culprit in Heart Disease Goes Beyond Meat's Fat

By GINA KOLATA

It was breakfast time and the people participating in a study of red meat and its consequences had hot, sizzling sirloin steaks plopped down in front of them. The researcher himself bought a George Foreman grill for the occasion, and the nurse assisting him did the cooking.

For the sake of science, these six men and women ate every last juicy bite of the 8-ounce steaks. Then they waited to have their blood drawn.

Dr. Stanley Hazen of the [Cleveland Clinic](#), who led the study, and his colleagues had accumulated evidence for a surprising new explanation of why red meat may contribute to heart disease. And they were testing it with this early morning experiment.

The researchers had come to believe that what damaged hearts was not just the thick edge of fat on steaks, or the delectable marbling of their tender interiors. In fact, these scientists suspected that [saturated fat](#) and [cholesterol](#) made only a minor contribution to the increased amount of heart disease seen in red-meat eaters. The real culprit, they proposed, was a little-studied chemical that is burped out by bacteria in the intestines after people eat red meat. It is quickly converted by the liver into yet another little-studied chemical called TMAO that gets into the blood and increases the risk of heart disease.

That, at least, was the theory. So the question that morning was: Would a burst of TMAO show up in people's blood after they ate steak? And would the same thing happen to a vegan who had not eaten meat for at least a year and who consumed the same meal?

The answers were: yes, there was a TMAO burst in the five meat eaters; and no, the vegan did not have it. And TMAO levels turned out to predict heart attack risk in humans, the researchers found. The researchers also found that TMAO actually caused heart disease in mice. Additional studies with 23 vegetarians and vegans and 51 meat eaters showed that meat eaters normally had more TMAO in their blood and that they, unlike those who spurned meat, readily made TMAO after swallowing pills with carnitine.

"It's really a beautiful combination of mouse studies and human studies to tell a story I find quite plausible," said [Dr. Daniel J. Rader](#), a heart disease researcher at the University of Pennsylvania

School of Medicine, who was not involved in the research.

Researchers say the work could lead to new treatments for heart disease — perhaps even an [antibiotic](#) to specifically wipe out the bacterial culprit — and also to a new way to assess heart disease risk by looking for TMAO in the blood.

Of course, critical questions remain. Would people reduce their heart attack risk if they lowered their blood TMAO levels? An association between TMAO levels in the blood and heart disease risk does not necessarily mean that one causes the other. And which gut bacteria in particular are the culprits?

There also are questions about the safety of supplements, like [energy drinks](#) and those used in body building. Such supplements often contain carnitine, a substance found mostly in red meat.

But the investigators' extensive experiments in both humans and animals, published Sunday in [Nature Medicine](#), have persuaded scientists not connected with the study to seriously consider this new theory of why red meat eaten too often might be bad for people.

[Dr. Frank Sacks](#), a professor of cardiovascular disease prevention at the Harvard School of Public Health, called the findings impressive. “I don't have any reason to doubt it,” he said, “but it is kind of amazing.”

[Lora Hooper](#), an associate professor of immunology and microbiology at the University of Texas Southwestern Medical Center, who follows the [Paleo diet](#), heavy on meat, exclaimed, “Yikes!”

The study does not mean that red meat is entirely bad or that it is best to avoid it entirely, said Dr. Hazen, the lead researcher. Dr. Hazen is the chairman of the department of cellular and molecular medicine at the Lerner Research Institute of the Cleveland Clinic, a nonprofit academic medical center. Meat contains protein, for example, and [B vitamins](#), which are both essential for health. But the study's findings indicated that the often-noticed association between red meat consumption and heart disease risk might be related to more than just the saturated fat and cholesterol in red meats like beef and pork.

Dr. Hazen began his research five years ago with a scientific fishing expedition. He directs a study of patients who come to the Cleveland Clinic for evaluations. Over the years, there have been 10,000. All were at risk for heart disease and agreed to provide blood samples and to be followed so the researchers would know if any patient had a heart attack or died of heart disease in the three years after the first visit. Those samples enabled him to look for small molecules in the blood to see whether any were associated with heart attacks or deaths.

That study and a series of additional experiments led to the discovery that a red meat substance no

one had suspected — carnitine — seemed to be a culprit. Carnitine is found in red meat and gets its name from the Latin word *carnis*, the root of *carnivore*, Dr. Hazen said. It is also found in other foods, he noted, including fish and chicken and even dairy products, but in smaller amounts. Red meat, he said, is the major source, and for many people who eat a lot of red meat, it may be a concern.

The researchers found that carnitine was not dangerous by itself. Instead, the problem arose when it was metabolized by bacteria in the intestines and ended up as TMAO in the blood.

That led to the steak-eating study. It turned out that within a couple of hours of a regular meat-eater having a steak, TMAO levels in the blood soared.

But the outcome was quite different when a vegan ate a steak. Researchers had hypothesized that vegans would not have as many of the gut bacteria needed to make TMAO, and indeed virtually no TMAO appeared in the vegan's blood after he consumed a steak.

“We did not expect to see such a dramatic difference,” Dr. Hazen said.

Then researchers gave meat eaters doses of antibiotics to wipe out almost all of their gut bacteria. After that, they no longer had TMAO in their blood either after consuming red meat or carnitine pills. That meant, he said, that the effect really was because of gut bacteria.

Researchers then tried to determine whether people with high blood carnitine or TMAO levels were at higher heart disease risk. They analyzed blood from more than 2,500 people, asking if carnitine or TMAO levels predicted heart attacks independently of traditional risk factors like smoking, high cholesterol and **blood pressure**. Both carnitine and TMAO did. But upon further analysis, they discovered that the effect was solely because of TMAO.

The researchers' theory, based on their laboratory studies, is that TMAO enables cholesterol to get into artery walls and also prevents the body from excreting excess cholesterol.

But what is it about carnitine that bacteria like? The answer, Dr. Hazen said, is that bacteria use it as a fuel.

He said he worries about carnitine-containing energy drinks. Carnitine often is added to the drinks on the assumption that it will speed fat metabolism and increase a person's energy level, Dr. Hazen said.

Dr. Robert H. Eckel, a professor of medicine at the University of Colorado and a past president of the American Heart Association, worried about how carnitine might be affecting body builders and athletes who often take it because they believe it builds muscle.

Those supplements, Dr. Hazen said, “are scary, especially for our kids.”

Dr. Hazen, though, has taken his findings to heart. He used to eat red meat several times a week, about 12 ounces at a time. Now, he said, he eats it once every two weeks and has no more than 4 to 6 ounces at a time.

“I am not a vegan,” Dr. Hazen said. “I like a good steak.”

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