



Your Unstoppable Heart

Before you swallow what your doctor prescribes, we suggest you read this article.

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Two laboratory machines have played a role in perhaps the greatest medical misadventure of our time: the indictment of a villain -- LDL [cholesterol](#) -- with the ultimate crime of the heart, coronary artery disease.

One machine delivered the early, misleading evidence of [cholesterol](#)'s guilt, and another may have just nabbed the actual killer. And because the killer's likeliest and earliest targets are men, we'd all better pay attention to the new case being made against it.

The first machine, an early prototype of a device called an analytical ultracentrifuge, was crucial to the 1949 discovery of high-density lipoprotein (HDL) and low-density lipoprotein (LDL). These common blood fats would become cemented in people's minds by their angel/devil personas, "good" and "bad" [cholesterol](#). But now the halo-and-pitchfork images seem a little simplistic. And hardly useful.

These [cholesterol](#) characterizations were spun out of a wall-size contraption that rotated plasma at 40,000 revolutions per minute from the late 1940s until the machine's retirement in 2004. When you consider its role in the powerful beliefs we hold about [heart disease](#), the sprawling, rattling beast should be mounted under flattering light in the Smithsonian.

For decades, a tidy narrative about the [relationship](#) between [LDL cholesterol](#) and [heart disease](#) has affected everything from the food we eat to the drugs we take to the test results we track and the worries we harbor. This over-simplified view of [cholesterol](#) -- that all LDL is the same and that all LDL is bad -- has enabled the adoption of an accompanying oversimplified dietary belief, that all saturated-fat consumption raises your risk of [heart disease](#).

The LDL hypothesis has also encouraged many of us to swallow the most-prescribed class of drugs in recent history. Americans spent more than \$14 billion on LDL-lowering medications in 2008. Whether that money came out of their own pockets -- straight up, or through ever-escalating co-pays -- or out of the hemorrhaging U.S. health-insurance system known as Medicare, it's a huge expenditure. Twenty-four million Americans take statins, and the latest

health directives suggest that those numbers should be higher. And why stop at grown-ups? Some pediatricians want to start feeding Lipitor (and the like) to kids.

As John Abramson, M.D., writes in his book *Overdosed America*, "Largely as a result of these guidelines, [cholesterol](#) control has become the main focus of preventive health care in the United States."

So it's more than a little disconcerting that the other machine in this story, a complex pile of gadgetry quietly clicking away on a countertop in Berkeley, California, is only the most recent breakthrough that has called the entire LDL [cholesterol](#) premise into question.

On a balmy Sunday last August, Ronald M. Krauss, M.D., the director of the department of atherosclerosis research at Children's Hospital Oakland Research Institute, showed me into his workplace to demonstrate a novel new system for tabulating LDL. Using a particle-spitting process known as ion mobility analysis, Dr. Krauss and his colleagues have developed the first device capable of counting LDL and other lipoproteins down to their smallest subcomponents. (Several other ways of analyzing LDL subparticles exist, but they involve indirect methods.)

A New Jersey company, Quest Diagnostics, worked for 7 years with Dr. Krauss -- who is helping to set the new [cholesterol](#) recommendations from the NIH's National [Cholesterol](#) Education Program -- to develop a method of analyzing [cholesterol](#). Borrowing the same processes used for testing air pollution and residue from explosives, the quarter-million-dollar prototype is very sophisticated [technology](#). "It determines the size of the particle based on physics," says Dr. Krauss with nerdy admiration, "on the speed at which it flies through the air."

In other words, this machine won't be coming to your community clinic any time soon. But even if it's not ready for mass production, the information gleaned using technologies like ion mobility means that LDL [cholesterol](#) can no longer be identified as the single source of all heart trouble. Those pamphlets adorning your doctor's waiting room may portray LDL as a kind of lone gunman taking a bead on your heart, but they hide a basic fact of science: "Bad [cholesterol](#)" is at best a poor shorthand for four major types of independently behaving LDL, each with its own implications for [heart disease](#). We ignore the distinctions at our peril.

Some of these forms of LDL are relatively safe and some are dangerous, and treating them all as one and the same -- the way we do every time we pay our clinic for a three-part lipid panel that simplistically says "LDL: 125" -- is telling us little about the LDL cholesterol that matters, all the while sending health costs through the roof. We may be medicating many people who have no clear need for medication, using drugs that don't target the right particles, and replacing foods that are benign with foods that are anything but.

So in the heart-disease world, we've been stalking the devil we know instead of the devils we don't know. But we need to get to know them if we hope to dodge the number one killer of men.

LDL COMES IN FOUR BASIC FORMS: a big, fluffy form known as large LDL, and three increasingly dense forms known as medium, small, and very small LDL. A diet high in [saturated](#)

[fat](#) mainly boosts the numbers of large-LDL particles, while a low-fat diet high in carbohydrates propagates the smaller forms. The big, fluffy particles are largely benign, while the small, dense versions keep lipid-science researchers awake at night.

But here's the problem: The typical LDL test doesn't distinguish between large and small LDL particles -- it can't even spot the difference. And people can have mostly large LDL or mostly small LDL in their overall LDL, depending upon a host of genetic, lifestyle, and environmental factors. Your own personal mix may make all the difference between living to a heart-healthy old age and becoming a Monday-morning casualty at your desk.

Dr. Krauss and collaborators from Harvard and Malmo, Sweden, have helped identify what influences the difference. Working with blood samples from 4,600 healthy Swedish men and women, they used ion mobility analysis to count 11 forms of cholesterol subparticles for each person, and then ran the data through a complex statistical sorting program. After looking for [relationships](#) correlating with the 8 percent of people who went on to develop cardiovascular disease, they found three scenarios that predicted it, from the most powerful predictor to the least:

1. High levels of smaller and medium LDL combined with low HDL (a dreaded diabetes-linked syndrome Dr. Krauss had previously called atherogenic lipoprotein phenotype, or pattern B)
2. Low HDL levels
3. High total LDL levels

According to Dr. Krauss, the three risk factors appear to represent three separate processes that put your cardiovascular health at risk. For men, the first two scenarios are more predictive of [heart disease](#), but the third -- high total LDL -- was only marginally predictive of [heart disease](#) in men. Nowhere to be seen, of course, is the "total cholesterol" number doctors have been bashing us over the head with for decades. Turns out that number is not as useful a predictor for individuals. "LDL cholesterol is used as a marker for heart-disease risk," Dr. Krauss explains. "It's not a perfect marker, and the particle story is part of the reason for that."

In other words, when you tease apart the subsets of LDL that are preferentially involved in [heart disease](#), total LDL is a less reliable bio-marker. It's like the sniffles that could signal allergies, or the onset of swine flu, or nothing at all. This ambiguity works both ways. Just because you have less of the symptom (statin users take note) doesn't mean you'll have less of the disease. A drop in your total LDL cholesterol might mean nothing at all. A higher LDL cholesterol reading, for that matter, could simply mean you are a healthy person who has learned how to build an amazing sauce out of wine, garlic, shallots, butter, and heavy cream.

We currently test for a number that tells us less about our health than we think it does, and then we busily (and expensively) medicate it downward. It would be more effective to test the numbers that do matter, of course, and then to learn how we can keep those meaningful numbers

in check, whether we do it through different meals, more miles on the pedometer, or better-targeted medications.

CHOLESTEROL IS A NATURAL SUBSTANCE your body produces for a variety of uses. It is carried through the body in three containers -- LDL, HDL, and VLDL -- that deliver it to cells along with triglycerides. The average man reasons that the [cholesterol](#) in his scrambled eggs must surely end up in his arteries somehow, and this makes him do things like order egg-white omelets for breakfast.

There is indeed a link between the [cholesterol](#) you eat and the [cholesterol](#) in your arteries. It's just not the "eat more, have more" worry that's been drummed into you for years. In fact, your body's production and uptake of [cholesterol](#) is highly regulated; eat a six-egg omelet and your body simply produces less cholesterol because of the dietary onslaught. "There is a very weak connection between the LDL cholesterol we measure and dietary cholesterol," Dr. Krauss says. "I spend a lot of time talking to reporters and trying to explain that dietary cholesterol is not the same as blood cholesterol." He adds that the 200 milligrams of cholesterol most people eat every day is nothing compared with the 800 milligrams their bodies produce. But you don't have to take his word for it. "It is now acknowledged that the original studies purporting to show a linear relation between cholesterol intake and coronary [heart disease](#) may have contained fundamental study design flaws," wrote the author of a recent review in the *International Journal of Clinical Practice*.

So eggs are off the heart-disease hook. But what about [saturated fat](#)? One of the major types of [saturated fat](#) we eat -- the stearic acid that makes up one-third of the [saturated fat](#) in beef -- has little or no impact on blood cholesterol. And you may well imagine that pizza grease and butter are magically transported from your gut to your arteries, but that's like using sock puppets to explain the workings of a supercomputer. Other types of [saturated fat](#) do increase LDL, it turns out (sometimes HDL, too), and high LDL is modestly associated with [heart disease](#), but the [saturated fat](#) on your plate never goes anywhere near your arteries. Saturated fat increases bad-cholesterol levels by interfering with receptors responsible for removing LDL from the blood. Whether or not that's a health concern is anyone's guess.

"If you substitute polyunsaturated [good] fat for saturated fat, you see a reduction in heart-disease risk," Dr. Krauss says, casting more doubt on four decades of diet advice. "The interpretation of that finding has been that saturated fat is bad. My view, based on the data I have seen, is that it means polyunsaturated fat is good; it doesn't necessarily say anything about saturated fats being bad. . . . Does that mean saturated fat is bad fat? Or just that saturated fat is not a good fat?"

Of course, that isn't the message we're all accustomed to hearing. And for that you can blame the analytical ultracentrifuge -- or, more specifically, the fact that so many heart-disease authorities weren't ready for what it discovered. The first one ever used in the United States arrived in Berkeley thanks to the efforts of John Gofman, Ph.D., M.D., a physicist-turned-physician previously employed by the Manhattan Project. After the war, Dr. Gofman wanted to cure [heart disease](#) in the worst way, and he thought the answer might lie in the newly discovered particles

known as lipoproteins, the fat-protein particles that encircled [cholesterol](#) and triglycerides to shepherd them through the bloodstream. He took plasma samples from people with and without [heart disease](#) and used his new machine to spin the samples like nobody's business. Because of the physical properties of the plasma, the fatty lipoprotein particles separated and floated, with the lightest ones making it to the top first. Thanks to his analytical ultracentrifuge, Dr. Gofman discovered three major classes of lipoproteins. He named the lightest lipoproteins VLDL, for very-low-density lipoproteins (chicken-fat-type globules carrying triglycerides); the next most buoyant came to be known as LDL, and the heaviest were called HDL. Then Dr. Gofman asked people about their health and diet. He learned that having high LDL or high triglycerides correlated with an increased risk of [heart disease](#), high HDL correlated with a low risk of [heart disease](#), and that the two profiles responded entirely differently to foods in the diet. (He also learned that [cholesterol](#) could be packaged either tightly clustered or loosely assembled within LDL; measuring it did little to reflect this risk.) [Saturated fat](#) raised LDL, while carbohydrates raised triglycerides, ultimately lowering HDL. (Dr. Gofman even recognized that LDL was made up of subtypes, although the meaning of the diversity was unclear at first.) It was groundbreaking work, but too advanced for the movement it ultimately spawned. With so few analytical ultracentrifuges available, researchers began using cheaper methods of counting lipoproteins, methods now offered during routine physicals. One form of [cholesterol](#) became "good," the other "bad." "It sort of lost the details," says Dr. Krauss.

By the time Dr. Krauss arrived at Berkeley in 1976, the ideas of Dr. Gofman, who had left for greener pastures, began attracting support. A 1977 NIH study -- an early set of papers from the now legendary Framingham Heart Study -- confirmed that high HDL is associated with a reduced risk of [heart disease](#). It also confirmed that LDL and "total [cholesterol](#)" tells us little about the risk of having a heart attack, language that heart-disease authorities would downplay years later. Given this finding, as Gary Taubes writes in *Good Calories, Bad Calories*, we would have been better off to start testing for HDL -- or even triglycerides -- and nothing else.

Dr. Krauss was working part-time in Dr. Gofman's old lab and flipping through some data cards when he noticed a correlation that would change everything. As he combed through a recently completed study of 80 men and 54 women in Modesto, California, Dr. Krauss noticed that the people with low HDL tended to have high LDL. But not just any LDL was elevated; only the smaller forms observable to Dr. Gofman's analytical ultracentrifuge.

"I started studying these readouts, and what popped out were some amazingly strong inverse correlations," he says, still amazed at his good fortune. "It was just sitting there in the data." Dr. Krauss had found that small, dense LDL particles were the evil twin of good [cholesterol](#). HDL and small LDL tended to move at the same time, he discovered, but in opposite directions. If your smaller forms of LDL were high, your HDL was low; if your smaller forms of LDL were low, your HDL was high. Whether one was the cause and the other was the effect was unclear, but given the newly discovered importance of HDL, the importance of smaller forms of LDL was now real.

This created a practical problem. Lumping all forms of LDL [cholesterol](#) together, as labs currently do when they count it in your basic blood draw, tells us little about how much of that LDL is small and how much is large. "Everyone doesn't necessarily have the same amount of

very small LDL in their LDL," Dr. Krauss explains. Some people have mostly large LDL, a group Dr. Krauss would describe as "pattern A," while others have mostly small LDL (and usually, low HDL and high triglycerides), a group Dr. Krauss would label "pattern B." The second group has an increased risk of [heart disease](#) (a finding suggested again this year through the use of ion mobility). Large LDL, on the other hand -- and large LDL is usually the majority of the LDL that shows up in a standard blood profile -- is mostly benign.

The heart-disease community was not impressed. "It took me 4 years to publish that paper," he says, recalling his early work on subparticles in the late 1970s. "That's beginning to tell you some of the obstacles I was going to face."

The cost of that resistance had become apparent by the mid-1980s and into the 1990s as Dr. Krauss began to test whether changes in diet could change a person's LDL profile from good to bad, or from pattern A to pattern B. Using data from the Framingham Heart Study -- the longest-running study of its kind -- health organizations had begun to roll out the message of "good" and "bad" [cholesterol](#), a message that in turn created the concept of good fats and bad fats. But during experiments, Dr. Krauss discovered that while a diet high in [saturated fat](#) from dairy products would indeed make your LDL levels rise, "[saturated fat](#) intake results in an increase of larger LDL rather than smaller LDL particles," as he wrote in an *American Journal of Clinical Nutrition* review he co authored in 2006. A diet heavy in full-fat cheese and butter -- but not overloaded in calories -- triggered the relatively harmless health profile described as pattern A. (Having demonstrated the benign consequences for [cholesterol](#) from consuming dairy fat, he is currently conducting studies to find out if the same holds true for diets high in [saturated fat](#) from beef.)

Not only is dairy fat unlikely to increase heart-disease risk, Dr. Krauss and others have learned, but reducing [saturated fat](#) in a way that increases carbohydrates in a diet can shift a person's LDL profile from safe to dangerous. That's pretty much what happens whenever some well-meaning person with "high LDL" starts eating "low-fat" frozen dinners filled out with corn-derived additives, all the while engaging in the customary ravaging of a basket filled with dinner rolls.

"I like Ron Krauss and admire his work," says Dean Ornish, M.D., a fellow Bay Area heart-disease researcher and surely the most visible proponent of the idea that a diet low in [saturated fat](#) and high in carbohydrates can help reduce the risk of [heart disease](#). But Dr. Ornish says Dr. Krauss shifted his study participants from pattern A to pattern B by having them eat more of the processed carbohydrates. "The carbohydrates they fed people were predominantly refined, like sugar and white flour," says Dr. Ornish. "That's not what I've been recommending."

Dr. Krauss concedes that it's possible that refined carbohydrates are the problem when it comes to small LDL, but adds that his study used both complex and simple carbohydrates "in a manner consistent with many people's dietary practices when they adopt a low-fat diet." Low-fat diets are old news, you say? Try telling that to the makers of, say, Baked Lays. It will take us years to shake off the damage done by broadly implicating fat in the diet. "Everybody I know in the field -- everybody -- recognized that a simple low-fat message was a mistake," says Dr. Krauss.

DR. KRAUSS LEARNED ABOUT THE SAFETY OF DIETARY FAT from dairy thanks to a grant from -- guess who? -- the dairy industry. He also receives royalties on patents for two of the five methods for measuring small forms of LDL, including ion mobility. These are no small details, of course, and to his credit, he readily places his conflicts of interest on the table when the talk turns to heavy cream or particle-measurement technology. You could raise an eyebrow at these potential biases, but if you did, you'd also have to rethink the guidelines we now follow about healthy LDL. Their authors, nearly to a person, have taken money from a drug industry that's made a lucrative mission out of LDL mythology.

Then there is this: Dr. Krauss is not sure we should all race out to have our small LDL measured just yet. "I have not been an advocate of widespread testing for small LDL to assess heart-attack risk," he says. "It would be hard to justify the added expense for many people." At this point, he sees a role for small-LDL testing primarily in the management of people with [heart disease](#) or people who have a high risk of developing it. More research needs to be conducted before national guidelines make tests routine, he says. Until then, we have to live with the knowledge that the tests most commonly offered tell us only part of the story. (If you fall into either of the categories above, or you want a more detailed test, see "Small LDL, Big Risk".)

But what about statins? Dr. Krauss believes statins probably offer beneficial effects on heart-disease risk beyond those of lowering LDL (anti-inflammatory properties, for example). Interestingly, statins may help men who want to reduce their small-LDL levels. However, because they increase the removal of LDL from the blood (a process partial to larger LDL), "the benefit may be less than what you would expect from the drop in total LDL," he says.

So with small-LDL testing far from standard (your doctor can request an ion mobility analysis from Quest Diagnostics), the surest way you can reduce your numbers of the LDL that matters is to rely on time-tested advice. Eating fewer carbohydrates, losing weight, and engaging in more physical activity have all been shown to reduce small LDL. [Weight loss](#), in fact, has been demonstrated to reverse the dreaded pattern B all by itself. In other words, worry less about eggs or butter and their effect on LDL, and focus more on eating fewer processed foods and staying in motion. "I am very much an advocate of starting with lifestyle first," Dr. Krauss says.

Standing over his ion-spitting device quietly tabulating microscopic blood particles as the weekend wears on, Dr. Krauss invokes his admiration for Dr. Gofman, who died of heart failure at the age of 88. Dr. Gofman spent the second half of his career sounding the alarm about the dangers of low-level ionizing radiation, the type emitted from CT scans. (He was years ahead of his time on that subject, too.)

"Like the analytical ultracentrifuge, this process of ion mobility is based on first principles of physics," says Dr. Krauss. "So it's my attempt to leave a legacy, I hope, having been around to put Dr. Gofman's ultracentrifuge out to pasture."

It's in a warehouse, actually. Next door to a carpet store.