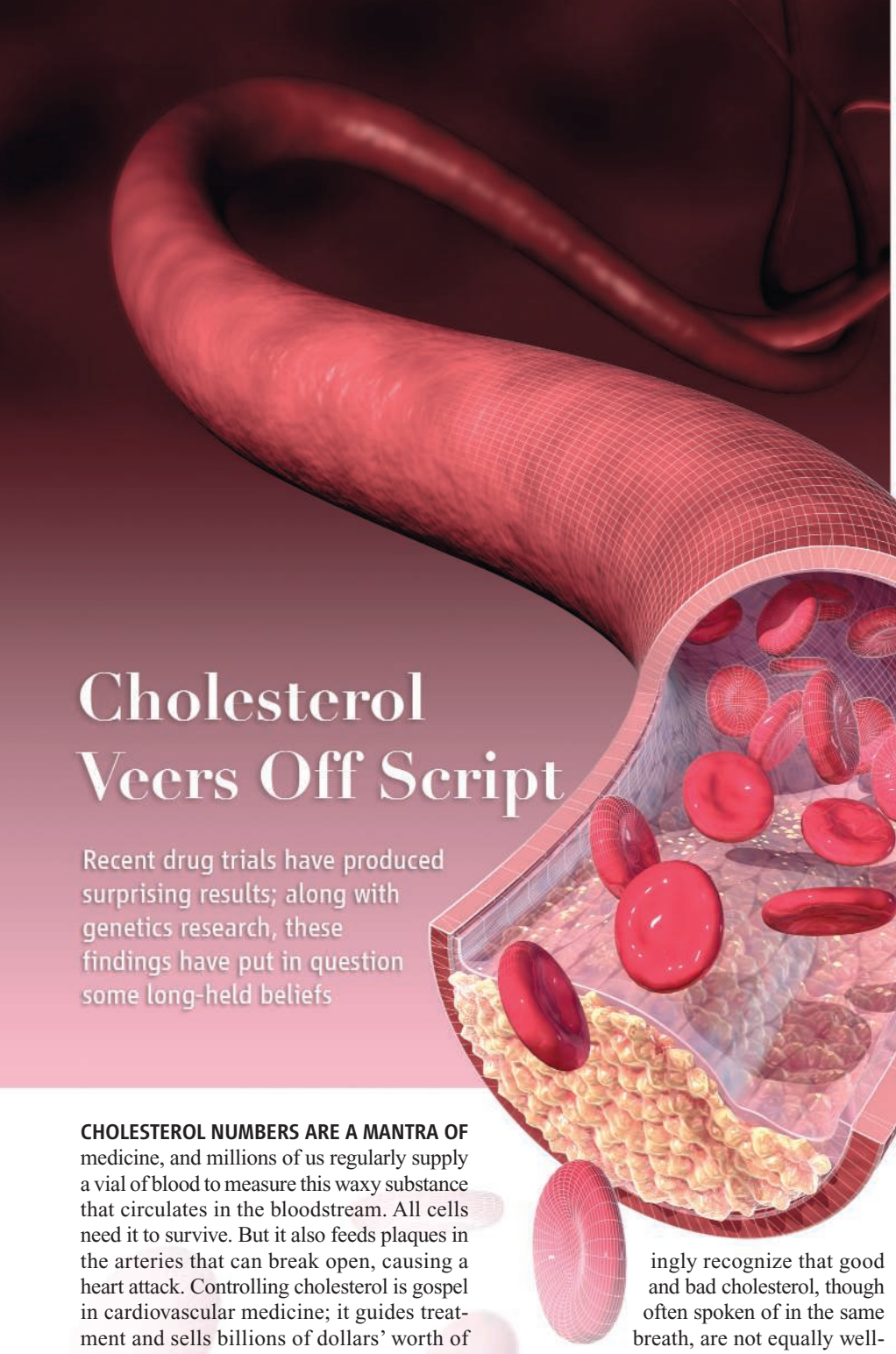

Deadly buildup. High levels of cholesterol in the artery contribute to plaque accumulation (yellow foreground), a precursor of heart disease. But assumed links between cholesterol-control drugs, plaques, and prevention of disease are being challenged.

CREDIT: CHRIS BICKEL/*SCIENCE*

Cholesterol Veers Off Script

Recent drug trials have produced surprising results; along with genetics research, these findings have put in question some long-held beliefs

CHOLESTEROL NUMBERS ARE A MANTRA OF medicine, and millions of us regularly supply a vial of blood to measure this waxy substance that circulates in the bloodstream. All cells need it to survive. But it also feeds plaques in the arteries that can break open, causing a heart attack. Controlling cholesterol is gospel in cardiovascular medicine; it guides treatment and sells billions of dollars' worth of drugs. It has also been reinforced by a Hollywood-like story line: A villainous "bad" cholesterol clogs arteries, and a valiant "good" cholesterol clears them.

The cholesterol hypothesis "is like religion for some people," says Harlan Krumholz, a cardiologist at Yale University. "They've been taught it in medical school. They've been taught it forever."

But Krumholz and some others say that after many decades, the cholesterol story is turning out to be messier and more nuanced than previously believed. Scientists increasingly recognize that good and bad cholesterol, though often spoken of in the same breath, are not equally well-understood. Hundreds of studies have shown that an overabundance of bad cholesterol, known as LDL (low-density lipoprotein), is associated with heart attacks. Good cholesterol, or HDL (high-density lipoprotein), is thought to be protective, but evidence for HDL's benefit is flimsier. Some scientists are now asking whether HDL is even relevant to heart-disease risk at all. Other fundamental questions persist: Why do people with healthy cholesterol levels still suffer heart attacks? Does the mechanism by which drugs tackle cholesterol matter to health? "You ask 20 people, you get 20 opinions," says Edward Fisher, director of preventive cardiology at New York University (NYU) School of Medicine.

That uncertainty is also eroding confidence in long-practiced strategies for drug development. Twenty-one years ago, the U.S. Food and Drug Administration (FDA) approved the first of the so-called statin drugs to lower LDL levels, based on the belief that lowering LDL also prevents heart disease. That proved wildly successful. But subsequent efforts to go after heart disease with a different class of cholesterol drugs produced muddled results. In addition, many people had hoped that a complementary strategy—giving drugs to raise good cholesterol, HDL—would proffer benefits akin to those of statins. But it hasn't worked out that way. A recent clinical trial that pushed up HDL failed to protect the heart.

At the same time, new genetic studies are yielding disparate results that undermine assumptions about cholesterol. This has left scientists puzzled, with some considering whether an altogether different risk factor, inflammation, is a missing link. Next month, a study of a cholesterol-lowering drug that may also reduce inflammation will report a benefit for the heart.

The bad actor

Cholesterol was first tied to heart disease in 1910, when a German chemist found that people with atherosclerosis had a high concentration of cholesterol in their aortas. Feeding rabbits cholesterol dissolved in sunflower oil caused severe atherosclerosis, cementing the connection.

A fatty substance that's both made by the body and ingested in food, cholesterol helps build cell membranes and form hormones, as well as performing many other tasks. It doesn't dissolve in the blood but instead is carted from place to place by bulky complexes called lipoproteins. Two of these travel opposite routes: LDL transports cholesterol from the liver to other tissues, and HDL is thought to carry it from other tissues, such as the arteries, back to the liver.

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For many years, scientists and physicians have recognized that high LDL raises the risk of heart attacks and that lowering it saves lives. This remains the majority view. The first LDL-lowering drug, Merck's lovastatin, was approved in 1987, heralding a new era of blockbuster cholesterol drugs, most of which have reaped billions of dollars in sales every year.

FDA was so confident of the link that, in approving lovastatin and five other statins that followed, it made an unusual departure: Instead of judging efficacy based on the drug's ability to improve health or increase survival, it relied on the therapy's ability to lower LDL. That confidence proved justified: In the 1990s, a trial of 4444 patients in Scandinavia showed that another statin drug, simvastatin, reduced deaths from heart disease by 42%, a number that's held up in subsequent studies. "I have the same position now that I had many years ago," that lowering LDL saves lives, says Terje Pedersen, the cardiologist and clinical trialist at Ullevål University in Oslo who led that early study for Merck.

How low to go?

On the principle that low LDL is good, many favor driving it as far down as possible. What passes for an acceptable LDL level has steadily dropped over time, says Daniel Steinberg of the University of California, San Diego. In the 1960s, he recalls, doctors didn't worry about total cholesterol levels until they topped 280. Today, less than 200 is desirable. For LDL alone, under 100 is considered healthy (and under 130 is "near optimal"). But is that good enough? Helen Hobbs, a human geneticist at the University of Texas Southwestern Medical Center in Dallas, notes that in rural China, LDL levels hover around 60 or 70, and heart disease is about 15 times lower than in the United States.

Hunter-gatherer populations living today have LDL levels of about 70. "That would suggest that's what our species evolved to have," says Thomas Lee, a Harvard physician and the network president for Partners HealthCare System in Boston, which sets cholesterol and other guidelines for doctors.

Steinberg also wishes that treatment with statins started much earlier in life. Autopsies on young men killed in the Korean War found that even at 18 or 20 years old, they already had plaque buildup in their arteries. "We've not gone as far as we can go with LDL," says Steinberg. "The disease starts when you're a kid," and statins "should be started as early as 30."

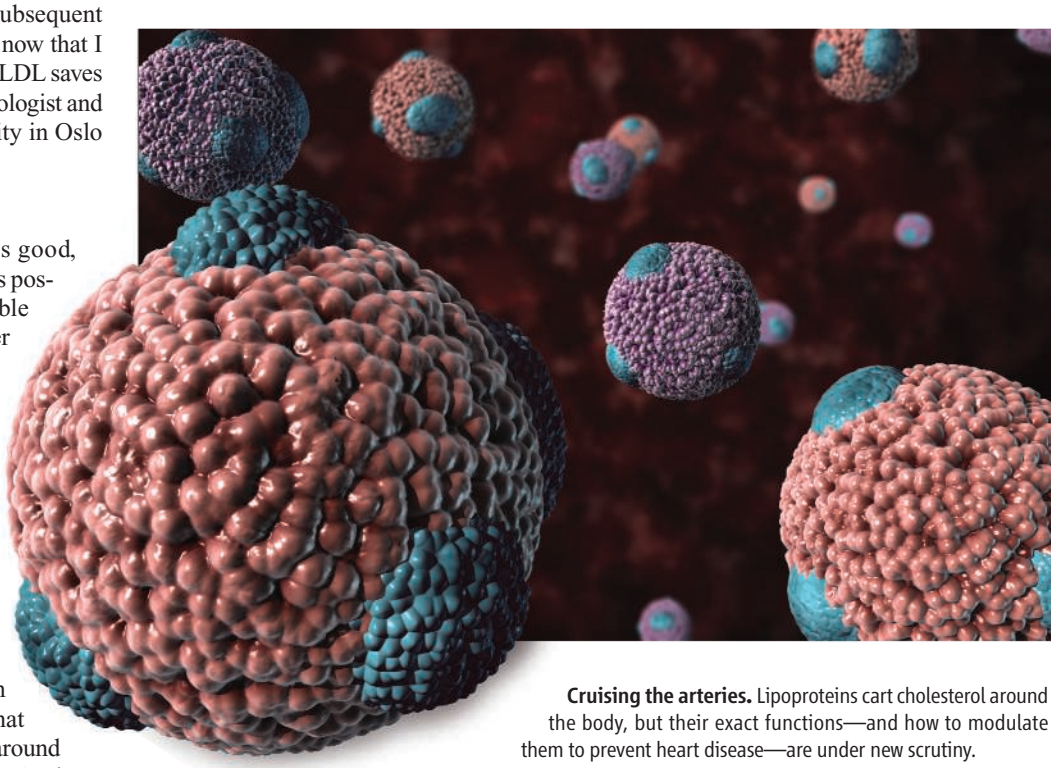
But coaxing LDL down to 70 or so isn't easy, and statins alone often can't achieve this. Pharmaceutical companies, on the lookout for new cholesterol strategies, especially with their statin drugs losing patent protection, in the mid-1990s renewed efforts to find novel ways to lower LDL. Schering-Plough came up with a drug, ezetimibe, which acts in the gut to prevent the body from absorbing cholesterol from food and bile. (Statins work differently, blocking the synthesis of cholesterol in the liver.) Researchers hoped that adding a new cholesterol-control mechanism would make the drug more powerful than statins alone. Like the statins, ezetimibe sailed through FDA approval because it lowers LDL; it was marketed by Merck and Schering-Plough as Zetia and was combined with a statin to be marketed as Vytorin. In 2007, Zetia and Vytorin had combined sales of more than $5 billion.

But after nearly 4 years on the market, Vytorin unexpectedly opened a Pandora's box. In January 2008, Merck announced puzzling results from a closely watched Vytorin trial called ENHANCE, in people genetically predisposed to have very high LDL. In theory, the lower the LDL level, the better off the heart should be—but ENHANCE suggested otherwise.

The study, published in April in *The New England Journal of Medicine* (*NEJM*), found that Vytorin performed no better than a traditional statin in slowing plaque formation in cardiac arteries, a common measure of worsening atherosclerosis. The big shock, however, was that Vytorin's middling artery protection was at odds with its superior LDL-lowering performance. The drug pulled LDL down from 210 or more without treatment to a respectable average of 141, substantially better than 192 for the statin alone. But that didn't translate to healthier arteries.

Vytorin was hammered in a second study called SEAS, which found that even though the drug lowered LDL, it did not help aortic stenosis, a disease that obstructs blood flow from the heart and can lead to heart failure. Results suggested it might also raise the risk of cancer. Aortic stenosis is a different disease than atherosclerosis, but there had been some research suggesting that the two were connected. SEAS, led by Pedersen, was published in September, also in *NEJM*.

Reaction to the disconnect between LDL benefits and heart health in these studies was swift and passionate. Some even questioned the link between LDL and heart disease, wondering whether lowering the first really does prevent the second. Most scientists still agree that it does and that statin drugs reduce



Cruising the arteries. Lipoproteins cart cholesterol around the body, but their exact functions—and how to modulate them to prevent heart disease—are under new scrutiny.

CREDIT: CHRIS BICKEL/*SCIENCE*

the risk of heart disease. But the broader question—whether nonstatin drugs that lower LDL have the same effect—is now up in the air. "For me, it's an epiphany," says Steven Nissen, chair of cardiovascular medicine at the Cleveland Clinic in Ohio, who admits to having been a longtime LDL cheerleader. "It says, 'Let's be careful when you come up with a new class of drugs that lowers LDL by another mechanism.' "

Others say the results have been ridiculously overblown. "I've never seen such herd mentality in my life," especially among cardiologists and the media, says Hobbs, who is convinced that LDL is a reliable indicator of heart-disease risk. The ENHANCE work is "just a terrible paper from beginning to end." She criticizes the study for lasting only 2 years and for relying on an indirect measure of heart disease.

Hobbs points to recent genetic work in LDL that counters the clinical trial data and underscores how potent LDL can be. About 8 years ago, she set about studying the genes of people in the Dallas area with very low LDL cholesterol. She discovered that 1 in 50 African Americans has a genetic mutation that appears to lower LDL by about 30%, and heart-disease risk over 15 years by nearly 90%—far more than statins. This, says Hobbs, is because genetics, unlike drugs begun at age 50, affects an individual over a lifetime.

Hobbs once asked the leaders of the Framingham Heart Study how many participants with an LDL of below 70 throughout life had suffered a heart attack. The answer? One. "It can happen, but it's very, very rare," she says.

> "Knowing what [drugs] do to LDL and HDL doesn't tell you what they'll do to people."
>
> —HARLAN KRUMHOLZ, YALE

The HDL puzzle

If LDL is weathering some controversy, HDL is in a much deeper puddle. Data backing HDL's role in heart disease are much sparser, and HDL's function is much more poorly understood, as underscored by a recent clinical trial disaster.

Unlike LDL, which has one major receptor on the liver and one primary function, HDL appears to have a hand in inflammation, infection, blood clotting, oxidizing molecules, and more. "Nobody has really shown," even in animals, that HDL carries cholesterol out of arteries, as is generally believed, says Anne Tybjærg-Hansen, who studies genetics and heart disease at Copenhagen University Hospital in Denmark.

Still, animal studies have consistently shown that raising HDL prevents heart disease. Researchers, physicians, and drug companies hoped that drugs to raise HDL could become new arrows in their arsenal, making a difference to the many people who lower their LDL levels but go on to have heart attacks.

The first dramatic booster of HDL was Pfizer's drug torcetrapib. That therapy—and other HDL modulators still in development—was inspired partly by a group of families in Japan who have very high HDL and very few heart attacks. They carry mutations in a gene called cholesteryl ester transfer protein (CETP). Torcetrapib goes after this target to increase HDL levels, and by all measures it does so remarkably well. But in the same way that Vytorin lowered LDL but didn't actually help people in ENHANCE and SEAS, torcetrapib raised HDL with no measurable health benefit, and a striking downside. "That drug killed more people than it actually saved," says John Kastelein, a vascular medicine specialist at the Academic Medical Center at the University of Amsterdam in the Netherlands, who participated in the torcetrapib trial.

The 15,000-person trial found that people on torcetrapib were 60% more likely to die than those taking the statin Lipitor. In December 2006, after investing some $800 million in torcetrapib, Pfizer hastily stopped the trial, abandoned the drug, and recommended that trial participants stop taking it immediately. It's still not known why torcetrapib had the effects it did, some of which were head-scratchers, such as deaths from sepsis. More important, no one knows yet whether those effects were a fluke of this particular drug or an ominous hint that boosting HDL is dangerous.

"HDL is a good epidemiologic marker for risk," says Daniel Rader, a preventive cardiologist at the University of Pennsylvania, meaning that people with high HDL levels can rest assured that their chance of suffering heart disease is lower than average. But it's "not the best surrogate for drug development."

Genetics studies are trying to parse a link between HDL and heart disease, examining

CREDIT: TERRY DAGRADI

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whether people have heart-disease risks that track with HDL levels. Some have uncovered a connection, and others have not. Tybjærg-Hansen spent several years trying unsuccessfully to link low HDL to atherosclerosis in humans. An analysis of population studies in Denmark covering roughly 44,000 people, published by her group in June in *The Journal of the American Medical Association*, found no increase in heart disease among those with low HDL caused by a set of genetic mutations. Tybjærg-Hansen admits that her work gives HDL believers "high blood pressure." "I think HDL is a bystander; it's a lipid transporter in the body somehow, but I don't think it has anything to do with risk" of heart disease, she says.

> "I think HDL is a bystander; ... I don't think it has anything to do with risk."
>
> —ANNE TYBJÆRG-HANSEN, COPENHAGEN UNIVERSITY HOSPITAL

Tybjærg-Hansen blames ties between academics and drug companies that she says prevent new paradigms from bubbling up. Yale's Krumholz agrees, noting that markers in the blood may have more complex interactions with disease than thought or may not track as expected if a drug has certain side effects. "This recent group of trials should fundamentally change the way we think," he says. "Knowing what [drugs] do to LDL and HDL doesn't tell you what they'll do to people."

Companies haven't abandoned HDL drugs, however. Rader, who is working on such therapies in concert with drug companies, admits that he and the companies putting up the money are taking a risk, especially in light of torcetrapib's downfall. "But my view is, we need to test this," he says, to determine whether torcetrapib is a fluke or whether it's conveying a broader message.

A handful of large clinical trials are testing whether targeting HDL can help; results won't be available for several more years. "Our one major attempt to increase HDL failed," says Paul Ridker, a cardiologist at Brigham & Women's Hospital in Boston. It's time, he says, to look beyond cholesterol when considering how to stop atherosclerosis.

A new strategy

Ridker is focused on another factor that he thinks is involved in heart disease: c-reactive protein (CRP). High CRP has long been considered a marker of inflammation, often found in people with other risk factors, such as obesity and diabetes. But Ridker goes a step further, arguing that when CRP is lower, plaques are less likely to break open and kill their hosts. And not only that: He and a growing number of others argue that statin drugs can wrestle down CRP levels, just as they reduce LDL.

The theory that statins do more than lower cholesterol is controversial. "It just amazes me that so many people have bought into this idea that statins have all these magical properties," says Rader, who is dubious that the drugs have anti-inflammatory effects that prevent heart disease. A survey published in 2005 of 19 trials with more than 80,000 people found that it didn't matter how LDL was reduced; the effect on heart disease was the same.

Scientists will soon have more hard data to help them assess whether controlling inflammation with statins helps the heart. Ridker is running an unusual clinical trial named JUPITER, which offers statins to people with an LDL of under 130—considered relatively healthy—but high levels of CRP. The trial is enormous, with more than 17,000 people in 26 countries. By comparing a commonly used statin, Crestor, made by the drug company AstraZeneca, with a placebo, it is looking to see if the high-CRP group reaps a benefit. Like nearly all cholesterol drug trials, this one is funded by the drug's maker.

Results haven't been released, but AstraZeneca announced in March that it was halting the trial early because of "unequivocal evidence of benefit." Ridker will elaborate on the results at a cardiology meeting in November. An outspoken CRP proponent, he holds a patent on a method of measuring CRP in the blood. Hobbs, who disagrees with Ridker's perspective, thinks he is picking an easy target by focusing on people with LDL values of up to 130, because he "is talking about LDLs that are still high" compared with "our ancestors," she says. Pushing LDL to lower levels in this group, she believes, may explain why JUPITER succeeded: It cut down LDL, just as earlier statin trials have done.

Meanwhile, cardiologists and others are considering the clouds in their crystal ball, hoping to reach beyond decades-old strategies and more precisely predict an individual's risk of heart disease. Even the biggest proponents of the cholesterol hypothesis admit that there's more to the equation than lowering LDL. "What is causing the rest of that risk?" asks Fisher of NYU. It's the question to tackle next.

–JENNIFER COUZIN

CREDIT: ANNE TYBJÆRG-HANSEN

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