BETTER UNDERSTANDING OF ATHEROSCLEROSIS—THE INFLAMMATION AND BUILDUP OF FATTY DEPOSITS IN BLOOD VESSELS—HAS TRIGGERED NEW APPROACHES TO TREATING THE NATION'S LEADING CAUSE OF DEATH

saving hearts that grow old

BY DELIA K. CABE

BAD BUGS: Common bacteria—*Chlamydia pneumoniae* (*left*), *Helicobacter pylori* (*right*) and other microorganisms—may cause infections that lead to heart disease.

A. B. DOWSETT SPL/Photo Researchers, Inc. (left); KARI LOUNATMAA SPL/Photo Researchers, Inc. (right)

Blood vessels are built to last. Up to about 100 years, some experts say, under normal wear and tear. For that to happen, you not only have to abide by a heart-healthy lifestyle—low-fat diet, weight in check, exercise, stress management, blood pressure control, good cholesterol numbers, moderate alcohol use, no smoking—but you also should be a woman, have the right genes and age slowly.

Cut to reality: we're not perfect. Our blood vessels endure various assaults because of factors only some of which we can control. We get heart disease—some 14 million Americans have it, and 500,000 die from heart attacks annually. The older we get, the more likely it is we'll end up with it. The proof is in the numbers: heart disease affects an estimated 15 percent of adults in their late 30s to early 40s, about 50 percent of 55- to 64-year-olds, and 65 percent of those in the next decade. Obviously, many of us slept through Heart Disease Prevention 101.

Yet the heart cognoscenti say only half to three fourths of heart disease cases result from the established risk factors. The

rest come about from infection and other factors that may promote atherosclerosis, the buildup of fatty deposits in blood vessels. Indeed, current research indicates that all of us are in jeopardy from the leading cause of death in the U.S. "Everyone needs to maintain a healthy lifestyle," says endocrinologist Joanne Manson, chief of the division of preventive medicine at Brigham and Women's Hospital in Boston. "Everyone's at risk."

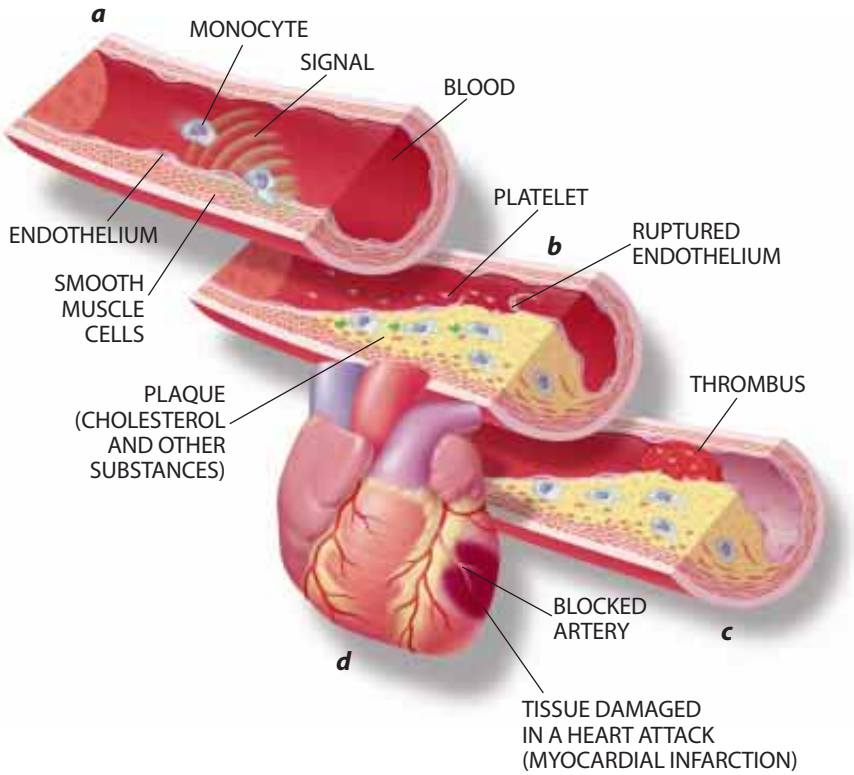
Efforts to find additional means of preventing heart disease have led to the unearthing of about 300 predictors, including bad relatives of the trouble-maker cholesterol as well as bacteria and baldness. Yes, baldness.

Manson and her colleagues at Harvard Medical School, which is affiliated with Brigham and Women's Hospital, published a study this year that found that hair loss, specifically on the crown of the head rather than at the front, is linked to a threefold greater risk of heart disease in men. Blame it on male hormones. The connection may be elevated androgen levels, which are associated with baldness and have been linked to atherosclerosis and a higher risk of blood clotting.

Such a marker as baldness may seem an unlikely place to look for risk factors. But in 1988 Manson's group also found a correlation between height and heart disease. Let's just say that taller people are better off—perhaps because they have wider blood vessels. Such information may help identify people who are more prone to heart disease and may lead to better means for prevention and interruption of disease progression tailored to an individual's physiology. The discovery of many of these markers arose from a closer examination of the cycle of inflammation, plaque formation and injury that causes atherosclerosis, the forerunner to angina and to heart attack and stroke, the major causes of death and disability as we move into later life.

The broadened understanding of the underlying causes of heart disease has paved the way to potential therapies, including antibiotics and ACE (angiotensin converting enzyme) inhibitors. ACE inhibitors were developed to control high blood pressure, but they have recently been found to have therapeutic effects in preventing heart disease.

a primer on vascular disease



OBSTRUCTIONS: The events that precipitate plaque-clogged blood vessels—the disease called atherosclerosis—begin when smooth muscle cells underneath the inner cell lining, the endothelium, release a signal that attracts monocytes (*a*). These white blood cells migrate into and under the endothelium, where they amass cholesterol and other substances. The swollen endothelium may rupture, drawing clot-forming platelets (*b*). The platelets may aggregate red blood cells and form a blood clot, or thrombus (*c*). The narrowed artery may cause chest pain (angina) or, if completely obstructed, a heart attack (*d*).

JOHN W. KARAPELOU

Read My Lipids

Atherosclerosis, which begins in our teenage years and builds up as we age, starts when the smooth muscle cells underneath the endothelium, or inner lining, of blood vessels release a signal in response to high cholesterol levels. This signal attracts monocytes—white blood cells that fight infection and amass cholesterol, calcium and other substances. The resulting cheesy mass, or plaque, bulges like a pimple. Over time, the endothelium loses its elasticity and may rupture. This injury to the lining summons clot-forming platelets, which further restrict blood flow through the already narrowed artery. An inadequate supply of oxygen-rich blood to heart muscle may cause temporary chest pain, or angina, and if blood flow is completely cut off, a heart attack—in clinical terminology, a myocardial infarction. All this from the best-known harbinger of

heart trouble, the lipid cholesterol. But only to a degree.

Cholesterol has been the cause célèbre in heart disease prevention. Fifty percent of Americans have elevated cholesterol levels. And the increase occurs naturally as we age—mostly after about age 45 for men and age 55 for women. Women in their reproductive years tend to have lower levels than men of the same age. After menopause, their cholesterol levels rise. But we also should fault our lifestyles. Without a doubt, lowering dietary intake of cholesterol and saturated fats does wonders for the heart. The goal is to keep down blood levels of the bad cholesterol (low-density lipoprotein, or LDL), behavior that can produce a 25 to 35 percent reduction in what the pros term "cardiovascular events"—that is, heart attacks, strokes and the like. At the same time, don't forget about raising your levels of good cholesterol (high-density lipoprotein, or HDL), which mops up LDL.

But the picture's more complex. Some people develop heart disease in spite of attaining ideal lipoprotein levels. For them, an approach that goes beyond controlling cholesterol and other lipids may be in their future.

Six years ago researchers with the Framingham Heart Study (the decades-long study that brought us the term "risk factor") identified a relative of LDL called lipoprotein(a) as an independent risk factor for heart disease. Lp(a) fosters the deposition of cholesterol on artery walls and interferes with the body's means of dissolving clots. Lp(a) also enhances oxidation of LDL.

Oxidation is nature's way of spoiling things like food. But old food gets thrown out, whereas oxidized LDL stays in the bloodstream and penetrates the endothelium. Elevated levels of Lp(a), which are most likely genetic, place people in the "high risk" category, as would a total cholesterol level greater than 240 milligrams per deciliter of blood (mg/dl) or an HDL level less than 35 mg/dl. Blood tests to measure Lp(a) have become available, but Lp(a) is difficult to lower. Two therapies that show promise include the vitamin niacin at prescription doses that are 100 times higher than the recommended daily allowance and the hormone estrogen. In addition, a few studies suggest that reduction in LDLs may help.

But it now seems that some LDL particles are worse than others. In the few studies done to date, people with predominantly small LDL particles have a risk of heart disease between three and four and a half times greater than those with large LDL particles. Why does size matter? Small particles are more prone to oxidizing, damaging blood vessel walls and invading them 50 percent faster than larger particles to initiate cholesterol accumulation.

Looking for Little Stuff

A blood test to measure LDL particles is useful in determining which drugs would be most effective in individuals with heart disease or in those who have a strong family history of it. Fortunately, current heart disease interventions cut down small-particle LDL levels. These include exercising, taking niacin (but only under a doctor's supervision) or some cholesterol-lowering drugs. Diet can also help lower triglycerides (another type of fat in the blood).

Even the good cholesterol, HDL, turns into a traitor in certain environments, much like a chameleon changes its colors in different surroundings, says cardiologist Alan M. Fogelman, executive chairman of the department of medicine at the University of California at Los Angeles School of Medicine.

Normally, HDL prevents LDL oxidation. But he and other researchers have observed HDL in its other guise. After surgery or during infections, atherosclerotic plaques burst more easily. These ruptures may occur because the immune system has geared up to fight infection. In this environment, HDL changes into a molecule that promotes LDL oxidation. If studies bear out this model, researchers could develop medications to thwart HDL's metamorphosis.

The possibility that the inflammation within the blood vessel walls and the immune system's response might be triggered by an infection led investigators to two bacteria—*Chlamydia pneumoniae* and *Helicobacter pylori* (the latter was recently deemed the culprit in stomach ulcers)—and herpesvirus. Of these three, *C. pneumoniae,* which causes respiratory infections, has received the most attention. The burning question is whether this bacterium, which has been found in 70 to 80 percent of plaques taken from heart disease patients, is an innocent bystander or an accomplice.

Cardiologists Jeffrey L. Anderson and J. Brent Muhlestein of the University of Utah are among several researchers looking for the answer. But these two col-

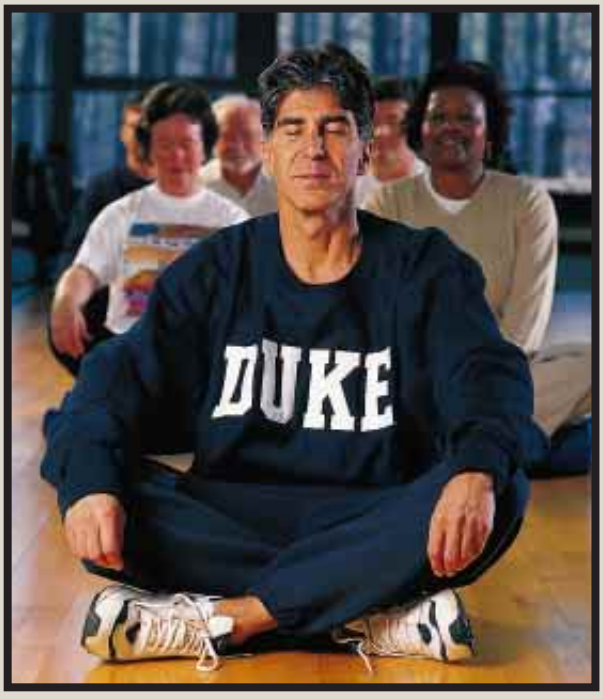
ticked off:
anger can knock you dead

A Barnes and Noble or Borders bookstore carries many of the 1,000 or so stress management guides, primers and tomes all intent on revitalizing, detoxing and streamlining the lives of road ragers and drivers in the fast lane, idiots and dummies, managers and underlings, and a host of others based on the principles of Zen or the habits of zebras. The promise is inner peace and healing, emotional wellness and self-renewal in six seconds, one minute, 16 minutes or a day. Or you could avoid sweating the small stuff altogether.

Why the fervor to calm down? The most important reason can be found in the title of a book, *Anger Kills,* written by psychiatrist Redford B. Williams, one of the pioneers in the research linking heart disease to Type A behavior. Type A people are those who are driven, tense, competitive and hostile, and his work showed that these folks are on the road to cardiac ruin. Stress may age their hearts faster than a New York minute—and it only gets worse as they get older. A study conducted by psychologist James A. Blumenthal of Duke University Medical Center, where Williams is director of behavioral research, found that a group of physicians from the University of North Carolina at Chapel Hill who scored in the upper half of a hostility questionnaire administered at age 25 had a four to five times greater chance than those with lower scores of developing heart disease by the time they were 50.

Williams and others have since sifted through Type A characteristics and found that some of the traits are worse for your health. Overt anger has dire consequences, as Williams writes. One study found that an episode of anger doubles heart attack risk up to two hours later. But no increased risk occurred in people who took aspirin, which prevents the blood clots that could cause a heart attack. Such research hinted at a connection between clotting tendencies and anger.

Now stress researchers are focusing on blood flow to the heart to try to uncover a direct relation between stress and heart disease. Ischemia, a lack of blood flow to the heart caused by narrowed or blocked arteries, may produce transient chest pain called angina and may lead to a heart attack. In the 1990s several studies showed that ischemia can be induced by mental stress in the laboratory and by negative emotions in daily life. Hostility and anger were usually the culprits.



HOT UNDER THE BREAST POCKET: James A. Blumenthal of Duke University Medical Center uses meditation and other techniques to teach students strategies to quell anger and hostility.

LES TODD

Results of the largest study to date to measure the heart's physiological response to stress—which combined blood tests and pressure measurements along with radionuclide angiography to view blood flow through the heart—reached publication in the *Journal of Health Psychology* early this year. Headed by psychologist Mark Ketterer of Henry Ford Hospital in Detroit, the study showed that laboratory-induced stress—especially anger and irritability—in heart disease patients caused ischemia more than half the time. Women, who more readily acknowledge their anger, fared better. Williams's

leagues were not about to take their cue from the scientist who gave himself an ulcer by ingesting *H. pylori*. Instead of hardening their arteries in the name of medicine, Anderson and Muhlestein opted for studies on other animals. They set about infecting rabbits, which normally do not develop atherosclerosis, with *C. pneumoniae*. Plaques did indeed appear, and antibiotics reduced the number of these thickenings.

Having shown cause and effect, the researchers set their sights on humans with heart disease who had evidence of past infection with *C. pneumoniae*. After six months on the antibiotic azithromycin, the human subjects had a modest but significant reduction in key markers of blood vessel inflammation: C-reactive protein, tumor necrosis factor, and the interleukins IL-1 and IL-6, all of which are released by the immune system. At the end of two years, Anderson and his colleagues hope to see at least a 50 percent reduction among those treated with the antibiotic in the frequency of heart attacks, angina, stroke, and procedures such as angioplasty and bypass surgery.

Anderson is among the investigators taking part in long-term trials now under way at several medical institutions with large numbers of human subjects. If antibiotics do significantly reduce the incidence, physicians say this would be a major advance in heart disease treat-

book is required reading in Ketterer's stress management classes, in hopes that the students recognize these tendencies in themselves.

Blumenthal has also published several studies showing that stress serves as a trigger for ischemia. He has found that stress management graduates experienced fewer ischemic episodes. But getting in touch with one's angry side is a gradual process among heart disease patients in his classes. "It's not as if a lightbulb goes off in their heads," Blumenthal says. In addition to observing other people, his relaxation wannabes learn to recognize the physiological reactions to stress and anger, such as increased heart rate and muscle tension.

Once enlightened, the students learn strategies to deal with their anger and hostility. Altering one's thought patterns is vital. Easily angered people engage in all-or-nothing thinking, producing exaggerated reactions to ordinary life events and taking everything personally. Blumenthal teaches them these ABCs in anger management and illustrates with a familiar situation:

Recognize Antecedents: You are driving, and a car cuts you off.
Assess Your Beliefs: He's out to get me.
Know the Consequences: I feel angry.
Dispute the Thoughts: The person was rude, but it wasn't directed at me.

Notice that there's no E for yelling Epithets. Maybe if those ABCs appear on bumper stickers, road rage will diminish. And those bad drivers won't give you a heart attack. —*D.K.C.*

ment. Heart patients who show these inflammatory markers might be prescribed medication to combat the bacteria. "Until that time, though, I think we shouldn't be giving antibiotics to our patients," Anderson says, because studies are still ongoing.

Meanwhile cardiologists are assessing whether taking folate and other B vitamins might lower heart disease rates. Accumulating evidence from the Physicians Health Study, the Framingham Heart Study and others seems to point to a direct relationship. And homocysteine levels in blood could be the smoking gun. Homocysteine, an amino acid that results from the body's metabolism of food, may contribute to atherosclerosis and increase clotting because it makes platelets stickier. In addition, homocysteine may lessen the flexibility of blood vessels, slowing blood flow. In people such as older adults and postmenopausal women, who typically have high levels of homocysteine in their blood, the risk of heart attack and stroke increases. Folate and other B vitamins may bring about a decrease in heart disease risk because they break down homocysteine.

Folate in Your Diet

Randomized, controlled trials are needed to determine if managing homocysteine levels, as is done with cholesterol, could join the list of heart safeguards. Nevertheless, the American Heart Association currently advocates that people who are at high risk for heart disease include more folate and other B vitamins in their diet—at least 400 micrograms' worth. That deed is accomplished simply by eating a balanced diet that includes the already recommended five daily servings of fruits and vegetables.

High blood pressure, or hypertension, was long ago shown to predispose people to atherosclerosis, heart attack and stroke. Hypertension is indeed an affliction of aging. The number of men and women with high blood pressure rapidly escalates in older age groups. More than 50 percent of Americans over age 65 have high blood pressure. First-line treatment to control hypertension involves a healthy diet, exercise and weight loss. If that fails, physicians prescribe antihypertensives such as ACE inhibitors. Until the 1980s, the presumed and only benefit of ACE inhibitors was the foiling of the body's production of angiotensin, a chemical that constricts arteries, so that blood can flow through vessels easier. But new research indicates that ACE inhibitors do more. So much more that the HOPE study evaluating the effects of the ACE inhibitor ramipril in 9,541 heart disease patients at multiple medical institutions was stopped six months early and its results released last November, before publication, so that study participants receiving a placebo could also reap the drug's benefits.

"We got stunning results—more than we expected," says study chairman and cardiologist Salim Yusuf of McMaster University in Ontario. "It is like the discovery that cholesterol drugs lower risks of heart attacks." The data showed a 22 percent overall reduction of heart attacks, stroke or death from other cardiovascular causes. The benefit was independent of ramipril's small reduction in blood pressure. In fact, most of the participants did not have hypertension when they enrolled in the study. Ramipril, Yusuf adds, may have an important effect within blood vessel walls, but it is unknown if other ACE inhibitors work in a similar fashion. Now physicians can offer one more preventive approach to their patients.

But these pills and other advances are meant for those of us who have flaunted time-tested heart-saving advice or the few who have only their genes to blame for abnormal lipid levels and such. As for waiting for that quick fix, researchers promise none. You can hope and pray. Take it from the grand poohbah of heart health, American Heart Association president Lynn A. Smaha: New research findings hold promise but no certainty of licking heart disease, so "in the meantime, take care of yourself."

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Further Information

Saving the Heart: The Battle to Conquer Coronary Disease. Stephen Klaidman. Oxford University Press, 2000.

The Michigan Electronic Library, a project of the University of Michigan and the Library of Michigan, maintains a **Heart and Cardiovascular System site:** http://mel.org/health/health-disease-heart.html

Research projects on heart disease can be surveyed at the Web site of the **National Heart, Lung and Blood Institute** of the National Institutes of Health: www.nhlbi.nih.gov/