Soya-nara, Heart Disease

The United States' top-selling legume gains heartfelt respect

By JANET RALOFF

The United States is experiencing a heart disease epidemic. The medical community, looking for a recipe for prevention, may soon be turning to the kitchen cookbook.

The prevalence of this disease "has gone way up in our population in the last 20 to 30 years," observes Jan L. Breslow, director of the Laboratory of Biochemical Genetics and Metabolism at Rockefeller University Hospital in New York. In part because the U.S. death rate from heart disease has fallen sharply in recent years, the number of people living with heart disease has been rising.

Today, 7.5 percent of U.S. adults have survived a heart attack or experience periodic chest pain caused by heart disease. Still, roughly half of all deaths among both men and women trace to cardiovascular disease, Breslow notes, making this "the number one public health problem."

Such disheartening statistics explain why health researchers are anxious to attack the problem from all angles. One that is attracting increasing interest is foods, sometimes called nutraceuticals, that exhibit pharmacological properties.

Seventy-five percent of cardiovascular deaths stem from atherosclerosis, a buildup of artery-clogging plaque. High concentrations of cholesterol in the blood present a major risk of atherosclerosis. At least half of all adults have cholesterol concentrations above 200 milligrams per deciliter (mg/dl) of blood—the range associated with increased heart disease, Breslow says.

New studies show that several natural constituents of plants, especially soy, can dramatically lower cholesterol concentrations and may improve other measures of vascular health as well.

Seeding the typical, saturated-fat-rich U.S. diet with a little soy won't wipe out heart disease. However, a number of cardiovascular specialists now say, certain soy-laced foods show potential for boosting the cholesterol-lowering benefits of commonly prescribed drugs—and, perhaps, of substituting for them entirely in a portion of the population.

Ever since soy's ability to lower cholesterol in people was first described 30 years ago, scientists have been looking for the specific constituents responsible.

In the late 1970s, Cesare R. Sirtori of the University of Milan and his colleagues narrowed this search to the legume's proteins. Using soy-derived "textured vegetable protein," they were able to lower an individual's cholesterol by as much as 22 percent, but only if the starting concentrations had been especially high. The closer to normal an individual's initial cholesterol, the smaller was soy protein's effect.

Since then, other researchers have homed in on a family of pigments, called isoflavones, as soy protein's most likely heart-sparing constituents. Chief among these proteins are genistein and daidzein.

While efforts to tease out soy's cardiovascular benefits have progressed steadily since the 1960s, they got very little notice from the rest of the medical community until about 8 years ago, recalls Mark Messina, who was working for the National Cancer Institute at the time. Indeed, he notes, "I'd been a nutritionist for 15 years and soy consumer for 25, and even I had no clue that soy lowered cholesterol."

Around 1990, though, a new wave of studies began identifying genistein and its kin as potential anticancer agents. While looking for explanations for soy's anticancer properties, Messina says, medical researchers rediscovered decades of studies on soy's lipid-altering effects.

Even more important, he suspects, the cancer community began referring to these isoflavones as plant estrogens, or phytoestrogens. With this new label, he says, the pharmacology of soy moved from the "folklore" of tofu to discussions of hormones. That transition proved pivotal, he says, because scientists and the public alike recognize that hormones can cause powerful effects in minute doses.

Although considering isoflavones as hormones may have triggered a renaissance in cardiovascular studies with soy, researchers remain divided about whether the weakly estrogenic compounds deliver their heart dividends solely by acting as hormones—that is, triggering activity by binding to specific receptors on a cell's surface. For instance, there's some preliminary evidence that isoflavones can use other means to suppress the activity of growth factors—a group of regulatory proteins—including at least one that fosters the buildup of arterial plaque.

Atherosclerosis "is essentially a chronic form of inflammation," observes Elaine W. Raines, a biochemist at the University of Washington in Seattle. Platelet-derived growth factor (PDGF) is one of the secretions that bind to a receptor on the surface of some cells in arterial plaque. If the receptor is then activated, by a process known as phosphorylation, it can transmit a message into the cell. That message might stoke inflammation, for example. At least in the test tube, genistein "can inhibit PDGF-induced cell growth and receptor phosphorylation," Raines says.

Herman Adlercreutz, a physician and isoflavone chemist at the University of Helsinki, has preliminary evidence of another potentially nonhormonal role of genistein and daidzein—the protection of cholesterol from oxidation.

Much of the body's cholesterol shuttles through the blood inside carriers known as low-density lipoproteins (LDLs), the so-called bad cholesterol. However, LDL cholesterol is harmful only if it becomes oxidized through any of the numerous chemical reactions involving potent molecular fragments known as free radicals. Once oxidized, LDLs can be transformed into the raw ingredients of plaque.

Suspecting that isoflavones might work as antioxidants, Adlercreutz's group asked six healthy adults to avoid antioxidant vitamins and soy products for 6 weeks. During the third and fourth weeks of this experiment, the participants supplemented their diet with three soy-protein snack bars a day. The volunteers then returned to the earlier, no-soy diet. Throughout the 6-week trial, the scientists took samples of the volunteers' LDLs and put them in solutions with a known oxidant.

In the March 17 PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, the researchers report that LDLs extracted from blood during the soy-eating weeks resisted oxidation about 20 minutes longer than did LDLs from the unsupplemented periods. Adlercreutz says that this is about the same lag period seen in LDLs from people who supplement their diet with vitamin E, a well-known antioxidant that also appears to inhibit plaque.

He remains puzzled about why the LDLs were protected, however. A chemical analysis of their contents showed only the barest traces of the isoflavones—too little to defuse the oxidants. His team now suspects that the isoflavones may have been chemically altered by the body. Their latest data

suggest that enough of the altered isoflavones might have been able to enter the LDLs to protect their cholesterol from oxidation.

Regardless of how they work, isoflavones have developed an impressive track record in cardiovascular trials—including a pair of tests by research teams at Wake Forest University School of Medicine in Winston-Salem, N.C. Preliminary data from the new studies were reported in March at the American Heart Association meeting in Santa Fe, N.M.

For one trial, John R. Crouse and his colleagues recruited 62 women and 94 men with moderately elevated cholesterol—typically 240 mg/dl. Each volunteer was asked to drink a daily "milkshake" with 25 grams of soy protein. Some received shakes containing negligible amounts of isoflavones, others were assigned shakes spiked with substantial additions of the compounds (27, 37, or 62 mg). Neither the volunteers nor the researchers knew the isoflavone content of any individual's soy regimen.

After 9 weeks, Crouse's team measured each person's cholesterol again. In the group that consumed soy virtually free of isoflavones, "we saw no change," Crouse says. Among those drinking the other shakes, his group saw a clear decrease in cholesterol that became more pronounced as the isoflavone dose rose.

In those downing the most heavily spiked shakes, the average drop in LDL cholesterol was 5 percent. However, among those with a starting LDL cholesterol of more than 160 mg/dl (and total cholesterol above 260 mg/dl), the drop approached 11 percent. Other studies have shown that each 10 to 15 percent drop in LDL cholesterol can reduce heart attacks and other manifestations of heart disease by 20 to 25 percent.

This test is the first to demonstrate in people that isoflavones are the active cholesterol-lowering constituents in soy, Crouse maintains.

Does this mean that people can soon look forward to isoflavone pills? Not if lowering cholesterol is the aim, says Mary S. Anthony, also at Wake Forest. She notes that Paul J. Nestel of the Baker Medical Research Institute in Melbourne, Australia, and his coworkers published a report in the December 1997 ARTERIOSCLEROSIS, THROMBOSIS AND VASCULAR BIOLOGY showing that when women ate isoflavones in the absence of other soy proteins, even 80 mg daily didn't lower their cholesterol.

Says Anthony, "We, in fact, have now seen the same thing in monkeys. So we believe that there is some necessary component in soy protein that allows the phytoestrogens to act."

However, Nestel points out, the isolated isoflavones weren't useless. For the 5 or 10 weeks that each woman took isoflavone supplements, the elasticity of her arterial vessels improved an average of 26 percent. Stiffening of these vessel walls, which tends to increase with age, contributes to cardiovascular disease.

Soy isoflavones may even substitute someday for hormone replacement therapy in postmenopausal women. Though conducted in monkeys, Anthony's latest, 3-year-long study, reported at the Santa Fe meeting, finds that eating soy protein spiked with isoflavones daily was as effective as the standard postmenopausal hormone treatment in limiting the buildup of atherosclerotic plaque in the carotid artery. Blockage of this artery is a leading cause of stroke.

Anthony recently launched a related 3-year study in women.

Ground soy protein is one of the most concentrated sources of isoflavones. Just 1 ounce of it contains roughly 10 times as much as a cup of soy milk or a half cup of tofu. Though soybean oil is largely devoid of isoflavones, it is naturally low in saturated fats, a major risk factor for heart disease.

Today, only about 20 percent of eligible women take hormone replacement therapy (HRT), Anthony says. "Our goal was to investigate soy with its phytoestrogens as an alternative" for those who don't want to take a conventional drug, those who fear the increased breast cancer risk that HRT can impose, and those who don't like the menstrual bleeding associated with most HRT regimens. The current research is investigating whether soy avoids these side effects.

While a number of manufacturers already market soy protein and other isoflavone-rich foods, U.S. consumers may have to wait the better part of a year before they can buy products containing stanol esters, even newer additions to the list of soy-derived agents for combating cholesterol.

Relative latecomers on the nutraceutical scene, stanol esters are made by modifying sitosterol and other plant sterols, which are essentially the plant equivalents of cholesterol. Forty years ago, researchers discovered that such natural plant sterols can block the absorption of cholesterol from the diet. That finding spawned a host of drugs to treat high cholesterol.

"Even today, after all these years, we don't know exactly how plant sterols work," acknowledges Scott M. Grundy of the University of Texas Southwestern Medical Center in Dallas.

Around 1990, Tatu A. Miettinen of the University of Helsinki suspected that by performing a simple chemical modification on the latest sterol derivatives—stanols—he could improve their effectiveness and allow them to be delivered through the diet. The resulting stanol esters are easily dissolved in fat, which permits them to be incorporated into dietary fats.

Working with a local company, Miettinen developed Benecol, a specialty margarine. In year-long trials with people who have mildly elevated cholesterol (about 235 mg/dl), his group showed major benefits in the 100 people eating 75 grams of Benecol each day. While cholesterol fell an average of 10 percent in these volunteers, it remained unchanged in people who had eaten a comparable margarine without the stanol esters.

On Nov. 16, 1995, the day these findings were published in the NEW ENGLAND JOURNAL OF MEDICINE, Benecol entered the Finnish market. Finland remains the only country in which Benecol is available.

Miettinen's team presented follow-up data in the Dec. 16, 1997 CIRCULATION showing that dietary use of this margarine for 2 to 3 months in women who had suffered a heart attack brought their cholesterol into the normal range. Among those who had been taking cholesterol-lowering drugs, it dramatically reduced the need for a drug.

What's more, Miettinen notes, "we have treated at least 10 individuals with normal cholesterol and achieved a roughly similar reduction in their LDL cholesterol as we saw in those persons who initially had very elevated cholesterol."

That achievement could prove especially significant, says Antonio M. Gotto Jr., dean of Cornell University Medical College in New York and president of the International Atherosclerosis Society. A study that he and his colleagues presented in April at the American College of Cardiology meeting in Atlanta showed that cutting LDL concentrations in healthy men with average cholesterol reduced the risk of a first heart attack by up to 40 percent.

So even "the average population, with average cholesterol levels—both men and women—will benefit from cholesterol and LDL reduction," Gotto says. Taken together with data on the efficacy of the new soy-derived products, such findings present "a strong argument," he says, "for changing the dietary habits of the American population and for changing the approaches that we use to manage cholesterol in the general population." □