happened for 10 years. But if Chu hadn't done what he did, somebody else might have done it the next week."

Be that as it may, a great deal still needs to be done before high-temperature superconductivity becomes a practical tool. For example, what is the mechanism?

"The community has yet to converge on an appropriate model," says Bell Laboratories' Cava. "The only one that is definitely *not* true is the standard model." In that picture, named the BCS theory after its creators, John Bardeen, Leon Cooper, and Robert Schrieffer, the supercurrent is carried by pairs of electrons bound together by their interactions with the crystal lattice. The model works quite well for conventional superconductors—and indeed, won a Nobel Prize for its inventors in 1972—but it seems to fail for the 90 K class of ceramics. It predicts that a substitution of oxygen-18 for oxygen-16 in the compound should subtly change the transition temperature, when in fact no such change is seen.

The one common theme in all the alternative models is that the crystals contain long chains of copper and oxygen atoms that have a fortuitous overlap in their electron orbitals. This overlap in turn seems to produce a metallic bond. "That's very unusual," says Cava. But at this point, no one can say for sure what it means.

Meanwhile, a major obstacle to practical use of the 90 K class of superconductors is that the superconductivity ceases in the bulk material when the current density exceeds about 1000 amperes per square centimeter. And yet for large-scale applications such as power transmission, the materials will need to support currents up to one million amperes per square centimeter. "It could take several years to do better," says Cava. On the other hand, thin films of the material have already displayed current densities in the latter range, which means that small-scale applications in microprocessors and data transmission may be much closer.

And finally, what about superconductivity at even higher temperatures? There have been innumerable reports of very high transition temperatures, says Cava, "but the results are almost universally not reproducible in other labs." Many of the materials that people are trying are unstable when exposed to air or water. Their crystalline structure is very sensitive to how they are prepared. And yes, many of the experiments have been sloppy. "The community is hopeful, but skeptical," says Cava.

"The Nobel Prize closes the door on the first chapter, the first hectic year," he adds. "Now it's time to take a few days off, catch our breath, and see what happens." ■

**M. MITCHELL WALDROP**

# Measuring Cholesterol Is as Tricky as Lowering It

*A federal panel has issued precise recommendations on how and when to treat elevated cholesterol levels, but determining those levels is trickier than generally acknowledged*

THE federal government, in combination with more than 20 health organizations, has launched an aggressive campaign, through the National Cholesterol Education Program, to convince physicians and the population at large of the dangers of high cholesterol. The first salvo is a new report, issued earlier this month, that provides physicians with the most precise guidelines to date on how and when to treat elevated cholesterol.*

At a press conference releasing the report, Claude Lenfant, director of the National Heart, Lung, and Blood Institute, speculated that, if adopted, these recommendations could result in 300,000 fewer heart attacks each year. About half a million Americans die of heart attacks each year.

This new report is one of a slew of studies on the subject released over the past few years. In 1984 the National Institutes of Health (NIH) consensus conference attempted to lay to rest any doubts about the role of cholesterol in heart disease. The consensus panel urged the entire nation, including children over age 2, to adopt a low-fat diet to reduce cholesterol and recommended diet and, in some cases, drug therapy for individuals with moderate to high cholesterol.

Despite widespread publicity, the nation's physicians have been slow to follow these guidelines. A recent survey by the Heart Institute revealed that only 50% of the nation's physicians use dietary therapy to treat patients with cholesterol levels of 240 milligrams per deciliter, and more than 75% do not use drugs to treat patients with levels of 260, as the consensus panel recommended. Hence the new initiative.

Just how much to reduce cholesterol—especially among the "normal" population with moderate levels and no other risk factors—is still the subject of considerable debate. Some of the more sweeping recommendations of the past few years, such as putting the entire nation on a low-fat diet, have been criticized for exaggerating the benefits and ignoring possible risks.

But with its more limited purview—it addresses cholesterol levels that most experts agree constitute high risk—this report largely escapes those criticisms. Rather, the problem several people have with the general approach outlined in this report is that it underestimates the difficulty of determining cholesterol levels with any accuracy, given the substantial variation in cholesterol tests from both biological causes and from testing inaccuracies.

The panel urges all Americans to have their cholesterol checked and then ties treatment to precise cholesterol levels. In keeping with earlier reports, the panel defines total blood cholesterol levels below 200 milligrams per deciliter of blood as desirable, levels from 200 to 239 as "borderline" high, and levels above 240 as high. What distinguishes this report from earlier ones is that the aggressiveness of treatment depends on the presence of other risk factors, at least for the borderline group. Also, in an effort to simplify the guidelines, the cutoff points are the same for adults of all ages.

Intensive medical intervention—diet and, if necessary, drug therapy—is urged only for individuals at high risk, that is, those with cholesterol levels above 240 or those in the borderline group who have two or more additional risk factors. Risk factors include being of the male sex, hypertension, cigarette smoking, diabetes mellitus, severe obesity, low levels of high-density lipoprotein (HDL) cholesterol (the "good" cholesterol), and a family history of premature coronary heart disease. If patients in the borderline category do not have additional risk factors, then the panel recommends that they simply be given general dietary advice and rechecked in 1 year.

For high-risk patients, treatment should be based on their levels of low-density lipoprotein (LDL) cholesterol, not total cholesterol, the panel says. LDL cholesterol, the "bad" cholesterol, appears to be the major cause of clogged arteries, whereas HDL cholesterol seems to aid in removing cholesterol deposits. A separate and more expen-

**National Cholesterol Education Program: Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*, draft (NIH, Bethesda, MD 1987.)

sive test is required to determine the level of LDL cholesterol, but once it is determined, total cholesterol can serve as a surrogate. The panel sets the cutoff for initiating treatment at 160 milligrams of LDL cholesterol per deciliter, or 130 for borderline patients with two additional risk factors. These levels roughly correspond to total cholesterol levels of 240 and 200.

The first course of action is a moderately stringent diet, similar to that recommended by the American Heart Association, that restricts total fat intake to less than 30% of calories (down from a U.S. average of about 40%), and saturated fat intake to less than 10% of total calories. Cholesterol consumption should be held at less than 300 milligrams per day. One egg, for instance, contains about 274 milligrams of cholesterol; 6 ounces of lean beef, about 156.

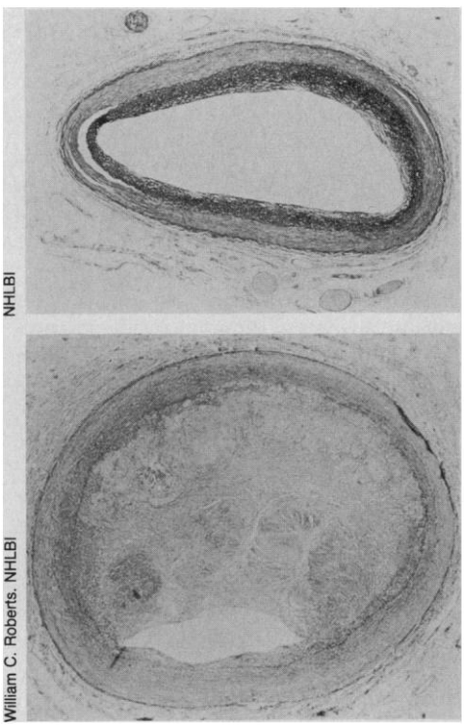
If LDL levels are still above target at the end of 3 months of restricted intake, a very stringent diet is in order, the panel says, that limits saturated fat intake to less than 7% of total calories and cholesterol intake to less than 200 milligrams per day. Only if that diet fails should drug therapy be considered.

Although diet should be the cornerstone of cholesterol-lowering therapy, getting physicians to prescribe and monitor it will be tricky, panel chairman DeWitt S. Goodman acknowledges. "Busy doctors in practice are often inclined to use drugs." For that reason, the panel set the initiation levels for drug therapy at LDL levels of 190 or 160 milligrams per deciliter, so as to provide "a protective barrier to the inappropriate overuse" of cholesterol-lowering drugs, Goodman says.

Because these drugs may be required for a lifetime, safety is paramount, the panel says. For that reason, it urges caution in the use of lovastatin, the widely heralded new drug, one of the HMG-CoA reductase inhibitors, approved by the Food and Drug Administration a couple of months ago. While these drugs are "extremely powerful" in reducing cholesterol, Goodman says, they are also relatively new and data on their long-term safety are lacking. Older drugs, like cholestyramine, colestipol, and nicotinic acid, may not be as effective at lowering cholesterol levels, the panel says, but they remain the drugs of first choice because of their proven clinical efficacy and long-term safety.

But all of this assumes that cholesterol levels can be readily determined, which D. Mark Hegsted of Harvard University, for one, says is trickier than generally acknowledged. Hegsted and others say that the variation in cholesterol tests, from both biological and analytical causes, is so large as to render a single test virtually meaningless, and that even the repeat tests that the panel recommends for some individuals may not sort out the true cholesterol level.

Hegsted, a nutrition professor, and Robert J. Nicolosi of the University of Lowell, Massachusetts, recently reported that an individual's cholesterol level varies substantially from test to test, even when diet is controlled.† "It seems clear that data obtained from occasional blood samples will, inevitably, result in misclassification of large numbers of individuals," they write. LDL tests appear to be just as variable, Hegsted says.




**Clogged arteries:** *At top, an unobstructed artery; at bottom, one clogged by fatty buildups.*

No one knows the cause of this biological variation, Hegsted says, but it is large. He and Nicolosi found a coefficient of variation of 5 to 10%, which means that if one test shows a level of 250 milligrams per deciliter, the next test might be 25 to 50 points off in either direction. "If you have your cholesterol checked and it's OK, they just send you home. If it's high, they tell you to come back for another. But the first test might show your level as 200 when it is really 250, and you won't know you are at high risk. Or it can happen the other way around."

"I'm not opposed to people learning their cholesterol levels," Hegsted says. "What irks me is the complacency of the experts, who don't seem to recognize that it is difficult to determine what an individual's cholesterol level is."

Repeat tests will help, but at least several are needed to ensure accuracy, Hegsted says. The new National Cholesterol Education Program report recommends that individuals whose cholesterol levels are below 200 milligrams per deciliter on the first test need not be rechecked for up to 5 years. Those individuals with cholesterol levels above 200 should be given a repeat, confirmatory test, the report says. If the two vary by more than 30 milligrams per deciliter, a third test should be conducted.

It is "wishful thinking" to say that one test will reveal the actual cholesterol level, agrees Ancel Keys, professor emeritus of epidemiology at the University of Minnesota and a leader in cholesterol studies. "If you want to be sure within 5%, the test would need to be repeated five to ten times."

And that is just for biological variation, given carefully controlled analytical techniques. Even among high-quality laboratories, test results can vary dramatically because of analytical errors, says Herbert Naito of the Cleveland Clinic Foundation, who chairs another National Cholesterol Education Panel on laboratory standardization.

A 1985 survey of 5000 testing laboratories, conducted by the College of American Pathologists, found that 47% did not meet the desired goal of being within 5% of the "true" cholesterol value. And these are not your "Mom and Pop" shops, says Naito, but motivated laboratories that volunteered to participate in the survey. About 85% were within 10% of the true value, and 15% were "unacceptable." Repeat tests will do little to help, Naito says, because the laboratories are usually quite consistent in their performance, whether or not they are accurate.

Naito's panel, which will issue its report in the coming months, recommends that all manufacturers adopt uniform methods to calibrate their instruments. Despite the expense involved, manufacturers have been quite receptive, according to Naito, who is "extremely optimistic" that there will soon be a "dramatic improvement" in accuracy.

"But even if we get all the labs to run perfectly," he says, there will still be variation resulting from the way the samples are taken and stored. Whether a patient is standing or sitting when blood is taken and how long the tourniquet is left on both affect the cholesterol measurement. That can be controlled too, he says, but "it will take a lot of education." And once that is done, physicians and patients alike will still have to contend with biological variation, which can result in substantial imprecision. ■

LESLIE ROBERTS

†D. M. Hegsted and Robert J. Nicolosi, "Individual variation in serum cholesterol levels," *Proc. Natl. Acad. Sci. U.S.A.* **84**, 6259 (1987).