

Diet, drugs slow heart-felt 'insults'

Another piece of the cholesterol puzzle fell into place last week with the announcement that cholesterol-reducing drugs and decreased dietary fat together not only significantly lower blood cholesterol, but also slow the spread of fatty buildup in blood vessels. Based on a study of patients who had had coronary bypass surgery, the findings are expected to alter the standard treatment of patients after heart surgery. But they also raise questions about which of several groups considered at increased risk for heart disease — including asymptomatic individuals with moderate to high cholesterol levels — should follow the time-consuming and potentially expensive therapy regimen as a preventive measure.

Although elevated cholesterol levels have been tied to increased risk of heart disease for several years, the latest study is one of the first to lower blood cholesterol in patients who have had previous coronary bypass surgery. During a briefing at the National Heart, Lung, and Blood Institute (NHLBI) in Bethesda, Md., institute director Claude Lenfant said this "very important" study, conducted at the University of Southern California (USC) in Los Angeles, also is the first designed to determine whether controlling cholesterol can regulate existing atherosclerotic lesions.

Called the Cholesterol-Lowering Atherosclerosis Study, the two-year test included 162 men — nonsmokers and ex-smokers aged 40 to 59 years — who at the beginning of the study had blood cholesterol levels ranging from relatively low (185 milligrams per deciliter) to high (350 mg/dl) levels. Placed on similar low-cholesterol diets, half received a placebo, while the remainder were given a combination of colestipol hydrochloride and niacin.

In the drug-treated group, there was a 26 percent reduction in total cholesterol, a 43 percent reduction in low-density lipoprotein (LDL) cholesterol and a 37 percent increase in high-density lipoprotein (HDL) cholesterol. HDL cholesterol, the "good" kind, helps block the adverse effects of LDL cholesterol.

In contrast, parallel changes in the placebo group varied between 2 percent and 5 percent, said USC researcher David H. Blankenhorn at last week's briefing. Because of their history of heart disease, the men had been following a variety of low-cholesterol diets prior to beginning the study.

By injecting special dyes, the researchers also studied the size of atherosclerotic lesions in both native and "foreign" blood vessels, the latter added during bypass surgery to replace damaged vessels. Lesion changes, described

in the June 19 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA), showed either stabilization or shrinkage of lesions in the drug-treated group. According to Blankenhorn, actual regression of the lesions "as judged by perceptible improvement" occurred in 16.2 percent of the treated group, as opposed to 2.4 percent of the placebo group.

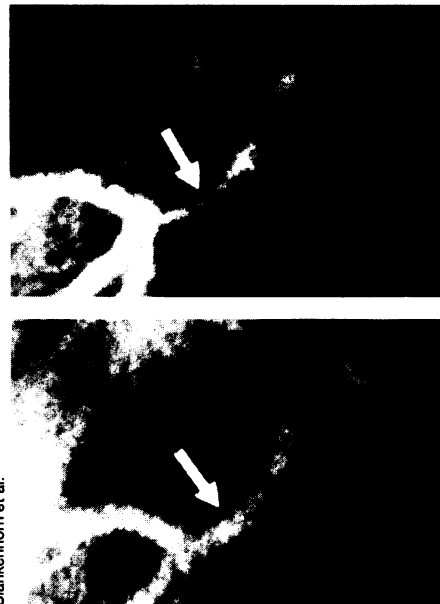
"We have the tools at hand to begin reducing the mortality of heart disease," says Blankenhorn, referring to various cholesterol-lowering drugs being tested. When given in large doses, niacin, which is one of the B complex vitamins, lowers total blood cholesterol and LDL cholesterol, while raising HDL cholesterol. Colestipol, a bile-acid binding resin, carries bile acids out through the intestine, forcing removal of cholesterol from the blood to help form new bile acids.

However, Blankenhorn and others emphasize that physician-mandated diet changes must precede drug use, and that the public should not begin taking large doses of the commercially available niacin. In the amounts used in the study, both niacin and colestipol can cause unpleasant side effects, including hot flashes, intestinal discomfort and joint pain. Scientists are hopeful that another drug group, which inhibits an enzyme important in cholesterol synthesis, will be better tolerated by the body. One of those drugs, called CS-514, reduced total average cholesterol levels between 11 percent and 25 percent (depending on dosage) in a clinical study at Japan's Tokai University Tokyo Hospital, according to a report in the June 12 JAMA.

In an editorial accompanying the USC report, NHLBI's Eugene R. Passamani writes that, although it suffers from flaws common in clinical trials, the study makes "a most persuasive argument for the aggressive use of lipid-lowering diet and drugs as important adjuncts to coronary artery bypass graft surgery," despite the "substantial effort" necessary to change diets and use the often-expensive drugs. Such treatment could benefit the estimated 220,000 patients undergoing coronary bypass surgery each year in the United States, and many of the 1.7 million who have had the procedure since it was first performed.

But what of the one out of four Americans who, according to NHLBI scientists, have elevated cholesterol levels yet may have no symptoms of heart disease? And what of the more than 6 million who do have symptoms? The study's data are drawn from too few subjects to determine whether there would be differences between the drug- and placebo-treated groups in the development of symptomatic heart disease, says Blankenhorn. But, he says, "the entire range of blood cholesterol levels between 185 and 350 mg/dl should be considered for vigorous treatment."

"The big issue facing us in the cho-



Drug treatment has visibly increased blood flow in this patient's coronary arteries, say scientists. Taken in 1982, the top picture shows an artery narrowed by fatty accumulation; two years of drug therapy resulted in regression of the same lesion. Researchers say another angiogram taken in 1986 showed that blood-flow improvement was maintained.

lesterol study ... is the question of at what point does the benefit outweigh the risk," says Basil M. Rifkind of NHLBI, adding that a change in diet remains "by far the preferred approach" for most people with higher-than-healthy cholesterol levels.

— D.D. Edwards

New drugs with that enzymatic touch

Serendipity was key in the discovery nearly 60 years ago that a common mold produced a substance fatal to bacteria — leading to the broad availability of penicillin. But the present-day search for new drugs, combining computers with chemical acumen, is a far more premeditated pursuit. Two studies reported this week, which target specific enzymes essential to disease-causing microorganisms, show just how calculating drug design has become.

At Astra Alab in Södertälje, in Sweden, scientists have made finely tuned inhibitors of an enzyme needed in the synthesis of lipopolysaccharide (LPS). LPS is found exclusively in the cell walls of gram-negative bacteria, a broad classification that includes *Salmonella* species, *Escherichia coli* and many others. Because the inhibitor's target enzyme is not present in mammalian cells, the new class of synthetic drugs will attack certain bacteria and be nontoxic to the host, say the scientists in the June 25 NATURE.

But the group found that making the

inhibitors is not enough, since the "foreign" structures cannot pass through the cytoplasmic membranes of bacteria in large enough amounts to be lethal. The scientists thus used a surprise-attack approach: They linked the inhibitors to protein fragments recognized by several bacterial transport mechanisms, enabling them to be taken into the unsuspecting cells. Once inside, the fragments are degraded and the inhibitors are released, killing the bacteria.

Another study, also reported in *NATURE*, attempts to optimize the effectiveness of azidothymidine (AZT), the only drug thus far approved in the United States for the treatment of AIDS (SN: 3/28/87, p.198). Scientists at the Wellcome Research Laboratories in Kent, England, cloned the gene for reverse transcriptase, the enzyme necessary for replication of the AIDS virus and the target for AZT. Mutations induced in the gene at selected sites can eliminate activity of the enzyme, say the scientists, who are now inserting the mutant genes back into viruses to see whether such mutations will affect virus growth. — *D.D. Edwards*

U.S., Soviets to study Antarctic ozone

In an agreement announced last week, U.S. and Soviet scientists plan to collaborate in an investigation of the seasonal thinning of Antarctic ozone.

The agreement calls for the United States to provide 50 packages of ozone-monitoring equipment and balloons, which the Soviets will fly above their Molodezhnaya station on the Indian Ocean side of Antarctica. The Soviets will exchange data from these flights with the United States, which will, in turn, supply the Soviets with daily ozone profiles measured by satellites.

"We will have much more information — just the basic observations of the distribution of ozone over Antarctica as a function of space and time — than we've ever had before," says James Peterson of the National Oceanic and Atmospheric Administration's Air Resources Lab in Boulder, Colo., who was the senior U.S. official involved in the negotiations.

Currently, one British and two American stations in Antarctica take balloon soundings of the ozone levels. By combining the vertical profiles from balloons with spatial information from satellites, scientists can obtain a detailed, three-dimensional picture of the ozone distribution, says Peterson.

Scientists are concerned about the stratospheric ozone depletions, which appear over Antarctica in September (SN: 5/23/87, p.326) and over the North Pole in February (SN: 10/4/86, p.215), because the ozone layer is needed to filter out harmful ultraviolet radiation from the

sun. Some fear that these holes signal a worldwide drop in ozone levels, possibly caused by chlorofluorocarbons, a class of chemicals used chiefly in refrigerants and aerosols.

Lasers light the way for computer links

Even the most efficient and swift super-market shoppers will get bogged down in their task if they have to stand in long, slow-moving checkout lines. Scientists are facing a similar kind of bottleneck in their race to make faster, higher-capacity computers. While the speeds of the electronic devices that do the actual computing have skyrocketed, the whole enterprise is rapidly being bogged down by the electrical wires that transmit information between these ultrafast devices. Not only are these electrical "interconnects" cumbersome and relatively slow, but over half the power consumed by processors goes into shuttling electrons along them.

Consequently, computer designers have had their eyes on laser diodes as replacements for the electrical links between computer devices, chips and boards. By sending light through fibers, waveguides or free space, these lasers promise to transmit more information faster and in less space, with less power and greater reliability than their electrical counterparts. As evidenced by recently reported work on one kind of laser diode, researchers are now within reach of redeeming that promise.

One of the technical problems involved in making optical interconnects has been to develop solid-state laser diodes that require a low input current. (The input current "pumps" electrons in the laser material up to an excited state, and when electrons fall from this state to a lower energy, laser light is emitted.) A low input current translates to low power consumption and less generated heat (heat can adversely affect the operation and reliability of a laser). All of these reductions are essential if scientists are ever to put hundreds and thousands of these laser devices on single chips.

Most researchers have been aiming for a "threshold current" of 1 milliampere (mA) — for laser diode scientists, this current level has been the psychological equivalent of the 4-minute mile, says Amnon Yariv at Caltech in Pasadena. While scientists have had little trouble making lasers with 10-mA-threshold currents, obtaining lower currents has been tough going. Researchers at the University of Illinois at Urbana-Champaign had achieved the lowest-threshold current with one laboratory device operating at 1.5 mA.

Now Yariv and his colleagues say they have crossed the 1-mA milestone with a gallium arsenide laser that has a threshold current of 0.95 mA. Yariv, Caltech's Pamela L. Derry and Kam Y. Lau, Nadav

The two superpowers also discussed plans for a scientific meeting next year in the Soviet Union concerning computer modeling of ozone and other trace gases.

— *R. Monastersky*

Bar-Chaim, Kevin Lee and Jan Rosenberg of ORTEL Corp. in Alhambra, Calif., report on their laser in the June 22 *APPLIED PHYSICS LETTERS*.

Yariv's group is one of a few working on quantum well lasers, so called because the region doing the lasing is very narrow — in Yariv's laser the active region is about 100 angstroms wide and the entire laser device is about the size of a grain of sand. The narrowness of the active region quantizes, or makes discrete, some of the energy levels of the semiconductor material from which the laser is made. This leads to a much more efficient production of light.

Yariv says the main contribution of his group's paper is to demonstrate that putting even moderately reflective coatings on the facets of a laser has a much more pronounced effect on improving the threshold current of a quantum well laser than of conventional solid state lasers. "If you put coatings on an ordinary laser, you will only improve the threshold by a factor of 10 or 15 percent," he notes. "But [with the quantum well laser], the improvement is 300 to 400 percent."

Yariv says his group passed below the 1-mA mark on its first try with a laser that was made out of materials of mediocre quality. With better materials and higher-reflectivity coatings, Yariv expects to reach a threshold current of 0.1 mA. At this low level, he says, it becomes feasible to use lasers in computer circuits. And, he adds, it opens the door for many other applications such as reliable instrumentation in cars powered by small batteries.

Some other researchers, however, do not share Yariv's enthusiasm. They do feel that his group has done excellent work in making the laser and that, from the standpoint of applications, the lower-threshold current is important. But they don't believe that Yariv's paper constitutes a fundamental advance in laser physics. Yariv's discussion of reflection coatings, says John Epler at Xerox Palo Alto (Calif.) Research Center, merely "points out the obvious. All the important elements of his argument have already been considered . . . The real figure of merit for a device is its threshold current without reflection coatings."

Yariv disagrees, contending that his critics don't fully comprehend the physics of this laser. "We're talking about a generic development here which should make it possible with a given laser to reduce its threshold current by probably more than a factor of 10," he says. ". . . This is a major breakthrough." — *S. Weisburd*