Cholesterol and Cancer

Do cholesterol-lowering drugs lead to tumors?

By KATHLEEN FACKELMANN

Millions of people in the United States take cholesterol-lowering drugs to reduce their risk of heart attack. They know that a high concentration of this waxy substance in the bloodstream increases their risk of developing clogged arteries.

Now, a controversial scientific report highlights evidence that such drugs cause cancer in rats and mice. The finding raises the question of whether cholesterol-lowering drugs pose a risk of cancer to humans.

During the past 10 years, prescriptions for cholesterol-lowering medication have increased 10-fold, according to Thomas B. Newman and Stephen B. Hulley of the University of California, San Francisco. They expect those sales will continue to soar because of aggressive marketing by drug companies.

Are such drugs safe, especially when taken by people for 30 years in order to reduce their risk of heart disease? In view of the animal studies, Newman and Hulley think caution is in order. They present their view in the Jan. 3 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION (JAMA).

"We, along with everyone else, are strong advocates of the appropriate use of cholesterol-lowering drugs," Hulley says. Yet the researchers contend that the cancer-causing potential of the drugs outweighs the advantages for many people.

Not surprisingly, the duo has drawn criticism from a bevy of medical experts.

James I. Cleeman, director of the National Cholesterol Education Program of the National Heart, Lung, and Blood Institute in Bethesda, Md., calls the Newman-Hulley report "much ado about nothing." He goes on to say that "there is just no evidence of a cancer risk in humans."

William S. Dalton, a cancer specialist at the University of Arizona in Tucson, agrees that it's very difficult to draw conclusions from rodent studies. "The bottom line is, Do you tell people with heart disease who you know are at higher risk of heart attacks to stop a known effective drug? My answer is no."

This isn't the first time that cholesterol-lowering drugs have drawn fire. Journalist Thomas J. Moore attacked them as unnecessary and sometimes dangerous in a provocative article in the September 1989 ATLANTIC MONTHLY. He detailed what he called the myths surrounding the link between cholesterol and heart disease.

Newman, a pediatrician, got started down this research track somewhat reluctantly. A few years ago, he noticed something odd while looking up information on lovastatin (Mevacor), a popular cholesterol-lowering drug, in the *Physicians' Desk Reference* (PDR), a directory of federally approved prescription drugs.

"The last time I had looked, it said that lovastatin caused liver cancer in mice at 312 times the human dose," Newman says. Two years later, it said three to four times—"that's a big difference."

Newman thought other physicians should take note of that modification. He sent a letter to the NEW ENGLAND JOURNAL OF MEDICINE. It was rejected. He sent a letter to JAMA. It was rejected. And so went things with a handful of other prestigious medical journals.

Eventually, Newman teamed up with epidemiologist Hulley, and together they began a project that culminated in the JAMA article.

Newman and Hulley began by taking a close look at the information from animal studies that the Food and Drug Administration requires as part of its drug approval process. After a drug wins the agency's approval, the PDR summarizes those data. The scientists homed in on two classes of cholesterol-lowering drugs, the fibric acid derivatives and the statins.

"The product information for [cholesterol-lowering] drugs indicates that all the fibric acid derivatives and statins caused cancer in rodents," they say. "In most cases, the rodent exposure at which carcinogenicity was observed was of the same order of magnitude as that observed with the maximum dose recommended for humans."

By comparing the 1992 and 1994 editions of the PDR, the researchers discovered the reason for the discrepancy in cancer risk that had piqued Newman's interest. In 1992, drug companies presented cancer risk in terms of milligrams of drug per kilogram of body weight.

In 1994, however, the companies presented the information in terms of the drug concentration produced in the bloodstream by a given dose.

Comparing concentrations of drugs in the blood produces a more accurate view of cancer risk, according to Elizabeth Barbehenn, a pharmacologist at FDA's Division of Metabolism and Endocrine Drug Products. In 1993, the agency started requiring certain companies to report such drug concentration data.

That change in policy led to the discrepancy in cancer risk for lovastatin.

Another cholesterol-lowering drug, gemfibrozil (Lopid), showed a similar difference when measured in the two ways. The 1992 PDR says this drug causes liver cancer in rats at 10 times the human dose. The 1994 version says cancer can occur at 1.3 times the human dose.

For comparison, Newman and Hulley looked at PDR data on drugs used to combat high blood pressure. These drugs, like the cholesterol-lowering medications, are prescribed to large numbers of healthy people, most of whom take them for many years in order to reduce the risk of stroke

and heart attack. The researchers wondered if such drugs also pose a cancer risk. Most appeared to be a safer bet, however—causing no tumors when given to rodents, the authors report.

Yet critics say that rodent studies can't predict human response to a drug. "To extrapolate from the rodent experience to the everyday experience in humans is fraught with major problems," says Dalton, who, with James E. Dalen, also at Arizona, wrote a commentary accompanying the report in JAMA.

Cleeman agrees that going from rodent cancer to human cancer is a stretch. "We're talking about a species that's not comparable. We're talking about a dose that's not comparable."

Rodents metabolize drugs more rapidly than people do, so to achieve drug concentrations in rat blood similar to those seen in humans, researchers have to give very large doses, Dalton says. That exposes the gastrointestinal tract and the liver, the organ responsible for detoxifying chemicals, to a heavy chemical load. Since rodent tumors usually arise in the liver and gastrointestinal tract, Dalton contends that they're an artifact of the research method.

Dalton and Dalen point out that if one believes in the applicability of rodent studies, a cup of coffee carries a cancer danger. Of the 26 compounds in coffee that have been examined, 19 have caused cancer in at least one rodent test. Yet Dalton and Dalen say people in the United States drink, on average, three cups of the brew per day. "It is unlikely that there is any increased risk of cancer with this use," they conclude.

Hulley calls that comparison misleading. He says that the cancer-causing substances in coffee are present in minute quantities, whereas people take large doses of the cholesterol-lowering drugs. "You'd have to drink 400 cups of coffee a day to get up to the same level of [drug] exposure," he says.

Barbehenn is the first to admit that rodent toxicity studies have limitations. She says scientists must give high doses of drugs to rats and mice or they'd never see a cancer—an otherwise rare event. Barbehenn says rodent tumors simply raise a warning flag for other mammals, including humans.

Although far from perfect, rodents represent the best models that scientists have for studying drug-induced cancers, adds Larry Sasich, a research analyst for Public Citizen's Health Research Group, a consumer group based in Washington, D.C. "Human cancer-causing agents, almost all of them, have been shown to cause cancer in rats and mice," he points out.

Newman, Hulley, and others assert that the evidence so far supports a cautious approach to the cholesterol-lowering drugs. The fibric acid drugs, in particular, carry a lot of negatives on the risk-benefit balance sheet.

These drugs, which include gemfibrozil, belong to a class of chemicals known as peroxisome proliferators. Some scientists believe they cause liver cancer in rodents by spurring the production of peroxisomes, organelles in liver cells. According to this hypothesis, the proliferation of peroxisomes leads to the generation of free radicals, which can result in damage to the cell's DNA and, eventually, cancer.

At least two groups have reported some peroxisome proliferation in people on therapeutic doses of fibric acid drugs. However, Russell C. Cattley, a scientist at the Chemical Industry Institute of Toxicology in Research Triangle Park, N.C., says the evidence suggests that the peroxisomes in human liver cells don't proliferate markedly in response to the drugs. He says the weight of the evidence on fibric acid drugs argues against a cancer risk for

Cholesterol testing under fire

The debate on cholesterol testing started to sizzle this week.

The Philadelphia-based American College of Physicians (ACP) kicked off an unusually acrimonious fray with a policy statement that recommends testing only for people in certain age groups—men age 35 to 65 and women age 45 to 65.

The statement, published in the March 1 ANNALS OF INTERNAL MEDICINE, runs counter to guidelines put forth by the federal government's National Cholesterol Education Program (NCEP). Those guidelines advise that testing of cholesterol concentrations in the blood be started at age 20.

The ACP proposal would, in effect, ration cholesterol screening, says the Dallas-based American Heart Association, which endorses the NCEP guidelines. A heart association task force called the new policy "flawed and misguided."

In a commentary that also appears in the journal, John C. LaRosa of the Tulane University Medical Center in New Orleans says that the policy is "in error and should be rejected."

What did the policy statement contain that provoked such ire?

- ACP proposes no routine cholesterol testing in men under age 35 and women under age 45. "Because the short-term risk for developing coronary heart disease is low in [these groups], even among persons with an elevated blood cholesterol level, the potential benefits of cholesterol reduction are small," the college states. There are some exceptions, however. Among them are people with a family history of extremely high cholesterol and those with at least two characteristics that boost the risk of heart disease, such as high blood pressure or cigarette smoking.
- There is insufficient scientific evidence to advise or discourage cholesterol testing among men and women age 65 to 75, ACP says. Moreover, there is no proof that cholesterol-lowering drugs reduce the incidence of heart disease among people in this age group.
- High cholesterol is unlikely to pose a danger for people over age 75, ACP says, in part because heart disease takes decades to develop. The college therefore advises against routine screening of such men and women.

The ACP makes the same recommendations as the other groups for people who already have heart disease. Such people should request a laboratory analysis of their cholesterol concentrations. The tests can help guide the choice of cholesterol-lowering treatment, ACP says.

The college based its recommendations on a review of published clinical trials. That review, by Alan M. Garber of Stanford University School of Medicine and Warren S. Browner and Stephen B. Hulley, both at the University of California, San Francisco, appears in the same issue of the ANNALS OF INTERNAL MEDICINE. It suggests that cholesterol screening confers benefits primarily on people with a high short-term risk of dying from heart disease—survivors of a heart attack and middle-aged men with multiple risk factors.

The American Heart Association task force states that, if physicians follow the ACP's advice on screening, they may drive many people to buy cholesterol-measuring kits sold in drugstores. Without a physician's counseling, the results might create unnecessary anxiety, the task force says. The 14-member heart association panel plans to publish a rebuttal to the guidelines in the March 15 CIRCULATION.

The ACP proposal is built on the "false premise" that physicians prescribe cholesterol-lowering drug therapy to people who don't need it, LaRosa told SCIENCE NEWS. Even people with established heart disease are not getting life-saving treatment to reduce the high concentrations of cholesterol in their bloodstream, he says. He calls the move to limit cholesterol screening "bad public policy." □

humans. The institute is funded in part by the chemical industry.

Cancer isn't the only problem with gemfibrozil. The fine print in the 1994 PDR indicates that middle-aged men with heart disease who took the drug actually increased their risk of dying, both from another heart attack and from all causes.

That evidence, along with the potential threat of cancer, has spurred Public Citizen to call for a ban on gemfibrozil. The group's book, *Worst Pills, Best Pills II* (1993), advises consumers not to use Lopid. "There is no proof that gemfibrozil has any health benefit," the book says. Instead, authors Sidney M. Wolfe and Rose-Ellen Hope suggest alternative ways to lower cholesterol concentrations in the blood, such as exercise and a diet low in saturated fat.

In contrast to the fibric acid durgs, the statin drugs have seen their reputation enhanced in recent months. In the Nov. 16, 1995 NEW ENGLAND JOURNAL OF MEDICINE, James Shepherd at the University of Glasgow and his colleagues report that pravastatin (Pravachol) reduced the risks of experiencing and dying from a heart attack in middle-aged men with high cholesterol concentrations. The results of this trial suggest that there are "massive benefits" to the use of a cholesterol-lowering drug like the statins, Cleeman says.

Newman and Hulley concede that the statins offer advantages to a narrow group of people at high risk of heart disease. For middle-aged men who cannot lower their cholesterol with diet or exercise, such drugs may be lifesavers, they say.

However, they are concerned about the cancer-causing potential of the drugs for most people in their twenties and thirties. Cancers take many years to develop; a person popping such pills every day for decades might run a cancer risk, they worry.

Moreover, cholesterol-lowering drugs have never been proved to benefit the very old, the very young, or women, they say.

Cleeman counters that women and the elderly are not different from middle-aged men when it comes to heart disease. "Based on what we know from trials to date . . . the prudent approach is to treat women and the elderly in the same fashion," he says. If a low-fat diet fails, they should then consider medication to lower their cholesterol, he adds.

Although most experts advise against the use of cholesterol-lowering drugs in children and young adults, there's one exception: those with a genetic predisposition to sky-high cholesterol. Without drug treatment, such young people face an extremely high risk of heart attack, Cleeman notes.

The federal government's drive to screen people age 20 and older for high cholesterol (see sidebar) may fuel the sales of cholesterol-lowering pills, Newman and Hulley argue. They say such programs turn healthy people into patients and spur the inappropriate use of drugs. Many people have no symptoms of heart disease but have a cholesterol reading that puts them in a "risk" category. Newman and Hulley are concerned that for millions of people, the potential cancer risk of the medication overshadows any heart benefits.

Cleeman counters by saying that asymptomatic people with high cholesterol concentrations are indeed at risk.

"It's not appropriate from a public health point of view to throw up one's hands and say, Gosh, who knows what might happen in 40 years? We do know what will happen on the cardiovascular death side," he says.

Newman and Hulley are quick to agree that there are no data proving conclusively that the statin or fibric acid drugs cause human cancer. However, they contend that further study is needed before ruling out the cancer threat. "The best thing that could happen is that this is a false alarm," Hulley says. □

Technology

Safer water for poorer nations

In the world's developing nations, more than 400 children die every hour from diseases such as cholera, typhoid fever, dysentery, and hepatitis, which they contract by drinking contaminated water.

To stem this threat, Ashok J. Gadgil, a physicist at the Lawrence Berkeley (Calif.) National Laboratory, and his colleagues have built a simple device that uses ultraviolet light to rid water of pathogens. The tabletop system takes in water from a well or hand pump, for example, bathes it with ultraviolet radiation from a mercury-vapor lamp, and sends it out free of germs. Ultraviolet light has the "highest germicidal efficiency" at a wavelength of 254 nanometers, he says.

The current model can disinfect 15 gallons per minute at a cost of 2 cents per metric ton of water. It weighs 15 pounds, costs $300, draws only 40 watts of power supplied by solar cells, and can run unsupervised in remote locations.

Serving a community of 1,000 in the developing world, one unit could prevent 15 infant deaths and 150 cases of stunted growth during its service life of 15 years, Gadgil estimates.

Virtual crash-test dummy

Automobile manufacturers seeking to build safer cars have traditionally relied on one procedure for safety-testing their new models: Build 'em and crash 'em.

Such tests involve placing humanlike models—known as crash-test dummies—behind the wheel and in the passenger seats of a vehicle, then propelling it into a brick wall. Scientists gather data on potential injuries from sensors in the dummies.

William O. Wray, an aerospace engineer at the Los Alamos (N.M.) National Laboratory, and his colleagues are now designing a computer system to simulate crash tests.

"We're developing a human body model for use in crashworthiness calculations," he says. Simulations are less expensive than crash tests and can be performed earlier in the design process, considerations that he expects will prove attractive to auto manufacturers.

"The goal is to identify areas of the body that might be injured," Wray adds. Auto designers would first run a model of the entire human body in a simulated crash to get a sense of where injuries might occur. A second round would focus on detailed models of the head, spine, or other area of the body to observe subtle damage. Wray believes the simulations would enable automobile companies to fine-tune new designs, making cars safer for people of different body types and sizes.

The computerized crashes could also reduce design-to-production time by 3 months, Wray estimates. "We think the number of crashed vehicles can be cut by 15 to 20 percent," he says. "There will still be crash tests, but the better the computer models are, the fewer cars you have to destroy." Each crash tests costs roughly $750,000.

Computerized wheelchair lessens sores

People confined to wheelchairs often develop pressure sores because of poor blood circulation.

A research team led by A. Keith Miller at Sandia National Laboratory in Albuquerque has designed a specially contoured wheelchair to lessen this problem. The new Generic Total Contact Seat, to be manufactured by Numotech of Sun Valley, Calif., contains four air bladders that inflate periodically, redistributing the person's weight.