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IN THIS ISSUE:

Making Sense of Cholesterol



**Dr. Robert
Mendelsohn**

The significance of this Newsletter goes far beyond cholesterol: The vagaries, uncertainties and pitfalls of laboratory tests for cholesterol unfortunately are typical of all laboratory tests. And the drug treatments can strike terror into even the healthiest of hearts.

As you read the documentation in this Newsletter, note how doctors frankly admit to one another the problems caused by the tests and the treatments for high cholesterol. Then, see how frank your own doctor is being with you.

Q

I am a 66-year-old female who has had a problem with raised cholesterol since her 30's. Neither of my two brothers has this problem.

My most recent blood test showed a cholesterol reading of 389. Because this is my highest reading ever, I am concerned and am watching my diet even more. For years, I have used skim milk, have eaten no butter or solid shortenings, and have tried to always eat foods low in cholesterol, although this is sometimes very difficult.

Is this reading extremely high? What else should I be doing?--O.W.

A

*Cholesterol
count
worries her*

Enthusiasm for the cholesterol test has waxed and waned over the decades. In his "Patient's Guide to Medical Tests" (Facts on File, \$7.95), Edward R. Pinckney, M.D., points out that cholesterol measurements are not very specific for diagnosing disease: "...and for many years, the test was virtually abandoned; recently it has had a resurgence as a possible predictor of heart problems. Its actual predictive value has not yet been proved, however, and it is not totally accepted as a reliable heart risk measurement by most scientists and many cardiologists. Cardiac surgeons, who usually treat the most severe heart and artery disease, report that 80 percent of their patients have normal blood cholesterol levels. Recently, it has been observed that the lower the blood cholesterol levels, the higher the incidence of cancer."

Q

My cholesterol level varies from blood test to blood test. What could cause this?--D.C.

A
*Cholesterol
levels
may vary*

When your doctor last took blood from you, were you standing up? Sitting down? Lying flat? According to investigators at the Institute for Aerobics Research in Dallas, the Bowman Gray School of Medicine in Winston-Salem, North Carolina, and the University of Texas Health Science Center in Dallas, the body position at the time of blood withdrawal significantly influences cholesterol, lipid and lipo-protein levels. When the body is prone, the blood becomes diluted, and when the person stands, the blood becomes concentrated. This change alters the concentration of fatty substances (lipids) in the blood.

Not only the body's position, but also the duration of time in that position before blood samples are taken must be considered in interpreting the results of serum cholesterol and lipid testing. So, see if your doctor and you can remember the position of your body before and during your various blood tests. If you both need further help in making correlations that will help you accurately interpret the test results, ask your doctor to contact these investigators whose work was reported in the journal American Family Physician in September, 1986.

Q

What is your reaction to the current cholesterol screening and dietary treatment craze? Do you feel that a national campaign to lower cholesterol is premature?--Dean E. Whiteway, M.D., LaCrosse, Wisconsin

A

*Cholesterol
is no
simple matter*

Your questioning letter on cholesterol matches my 35-year-old questioning attitude on this subject.

During my pediatric residency at Michael Reese Hospital in Chicago in the early 1950's, researchers at that medical center--including renowned Louis Katz, M.D., and Jeremiah Stamler, M.D.--were generating a lot of excitement because of their work on cholesterol. Their original experiments, like most scientific work, led to criticism--and counterpublications--from their scientific colleagues in other medical centers. And for the past three and-a-half decades, right up to now, cholesterol has remained a controversial issue.

Some doctors say it is bad for people to eat foods that are rich in cholesterol, while others point out that the body itself manufactures this essential product. Some doctors would have you believe that cholesterol is related to fat, but in reality cholesterol is a solid alcohol called a steroid. (Steroid compounds also include hormones, vitamins and some types of medication.)

Vegetarians know plant foods usually are free of cholesterol, but this substance is found in most foods of animal origin. Even though some doctors have given cholesterol a bad reputation, this substance is indispensable for brain and nervous system growth and development, as well as for the body's manufacture of sex hormones.

Many doctors tell their patients that they must lower their cholesterol level. Yet epidemiological studies repeatedly show that patients who have low blood cholesterol levels have a much higher incidence of cancer, gall bladder problems leading to surgery, and personality disturbances--violent behavior, aggressiveness, homicide and suicide. Low cholesterol levels also have been found to be related to poorly internalized social norms, irresponsibility and poor self-control.

Some doctors pay attention to the total cholesterol level in the blood. Others pay more attention to specific protein-fat complexes to which the cholesterol is attached--high-density lipoprotein (HDL) and low-density lipoprotein (LDL), while other doctors believe in calculating the ratio between these various measures.

Blood cholesterol levels will rise almost instantaneously when an individual is frightened, anxious or in pain--or even when an individual is exposed to an uncomfortable loud noise. Income tax accountants have a great increase in their cholesterol levels during the weeks before

April 15; the levels return to normal by May 1.

There is no agreement on what constitutes "normal" serum cholesterol values, which vary with the technique used and the laboratory. High cholesterol levels may result from plenty of conditions other than heart disease, including pregnancy, fear of the test results at the time the test is performed, tranquilizers, cortisone products, vitamins A and D, diuretic drugs, epilepsy medications, birth control pills, epinephrine products such as those used by asthmatics, and the ingestion of male hormones. Low cholesterol levels may be due to certain antibiotics, aspirin, and female sex hormones. Even changes in posture are important. Values may be completely different when blood is taken when the patient is lying down as opposed to after the patient has been standing for several minutes.

Cholesterol measurements are not very reliable--the average accuracy rate is less than 80 percent. And recent surveys have shown that different laboratories will report a difference of 50 mg per 100 cc (normal ranges often are given as 150 to 350 mg per 100 cc) on the identical blood specimen.

If a person's blood were tested hourly, or even once daily over a month's time, it would not be unusual to find a wide variation in blood cholesterol values. When an HDL test is performed, the serum must be packed in dry ice immediately and kept there until the analysis is undertaken; otherwise false values will be reported.

I don't really care whether or not a national campaign is mounted to lower cholesterol. After all, national campaigns come and go. What does concern me are the eternal responsibilities of the doctor/patient relationship. The doctor has the responsibility to fully inform his patient about the controversies surrounding cholesterol manipulation. The patient has the responsibility to ask the doctor plenty of questions and then to check up on his answers to see whether he received the whole truth. Only by careful adherence to this vital ethical standard can a patient make up his mind about whether or not to pay any attention to the cholesterol issue. National campaigns notwithstanding, every patient stands alone, independent and exclusively responsible for protecting his own life when he decides to roll up his sleeve for a cholesterol blood test.

*Watch
for
lovastatin*

The latest entry in the cholesterol drug market is Merck's Mevacor (lovastatin). If Mevacor finds its way onto your doctor's prescription pad, I hope that he tells you that the FDA Advisory Panel recommended regular monitoring of serum liver enzymes and regular ophthalmological exams. Merck has announced that the company is "about to initiate a very large study of several thousand patients" which will take up to two years to address the safety issues raised by possible effects on the lens and the liver. One might well ask, why not wait until the study is completed before approving the drug? Good question. Especially since Merck speculates that the potential treatment population could total 10 million people.

Regular readers of this Newsletter may remember my long-standing rule that one never learns the dangers of previous treatments until a new treatment comes along. In accordance with this rule, the FDA now tells us that "currently available medications [for high cholesterol values] have two or more of the following side effects: unpalatability, troubling side effects, undefined mechanisms of actions, untoward effects on other lipid fractions and most importantly, only modest efficacies." Unsurprisingly, the FDA assures us that "lovastatin may have less of these problems."

Warnings against lovastatin have been issued by Dr. John Nestor, a retired FDA medical officer, and by Dr. Edward Pinckney, a former associate editor of the Journal of the American Medical Association. According to Washington Post writer Morton Mintz (March 8, 1987), these two giant figures in medicine contend that treatment of cholesterol which relies upon this

drug has risks--including cataracts, liver disease and cancer--which may outweigh the benefits. Dr. Nestor compares Mevacor to MER/29, Merrell Dow's previous anti-cholesterol drug which Nestor helped to force off the market in 1962, after MER/29 was linked to cataracts, skin and hair problems and other afflictions.

Writing in the highly-respected British medical journal, Lancet, Dr. Pinckney, together with researcher Russell L. Smith, attacked the safety of Questran (cholestyramine), the anti-cholesterol drug manufactured by Bristol-Myers' Mead Johnson unit. Pinckney and Smith point out that the drug-treated group suffered more deaths due to gastrointestinal cancers than did the placebo group.

Other adverse reactions of lovastatin include headache, skin rash, gastrointestinal symptoms, myositis (muscle inflammation), peripheral neuropathy (numbness and tingling, etc.), myocardial infarction and other serious cardiovascular conditions, and liver abnormalities.

Writing in the Journal of the American Medical Association (March 27, 1987), Richard Cenedella, Ph.D., also warns against the possible complication of cataract development from the long-term use of lovastatin, giving evidence from experimental studies as well as a human patient.

As the torrent of new anti-cholesterol drugs (Merrell Dow's new entry is named Lorelco) is promoted by the drug detail men to your doctor, you can expect your doctor to grab for his prescription pad. Before he touches pen to paper, ask him if he is aware of the opposition voiced by these prominent U.S. scientists.

*Questran
raises serious
questions*

On Friday, January 13, 1984, headlines across the country heralded the "breakthrough" news about cholesterol: Doctors at the National Heart, Lung and Blood Institute and at the American Heart Association claimed that the drug cholestyramine can cut the cardiac death rate by lowering blood cholesterol. A 10-year study of middle-aged men who took this drug while staying on a certain diet showed 24 percent fewer cardiac deaths than among those who had merely stayed on the diet.

At that time, I suggested a few questions people should ask their doctor about Questran:

The drug-takers appear to have suffered fewer cardiac deaths. But how about deaths that might have been caused by the drug itself? While newspaper reports told about such side effects of the drug as constipation or bloating, they left out bleeding tendencies due to Vitamin K deficiency, osteoporosis, calcification of the gall bladder, biliary colic, hemorrhoidal bleeding, hemorrhage from peptic ulcer, and pancreatitis. Additional side effects may include anemia, asthma, shortness of breath, arthritis, headache, anxiety, dizziness, tinnitus, fainting, numbness and tingling, uveitis (inflammation of the lining of the eye), bloody urine, weight gain, swollen glands, and edema. These are just some of the many adverse reactions listed among the prescribing information for Questran. Ask your doctor if the investigators determined whether the lower death rate from cardiac causes may have been counteracted by a higher death rate from other causes.

Ask whether the researchers carried out any interviews and/or biochemical tests to prove that the drug-treated group actually took the medicine. Many previous studies have shown that the compliance rate among patients may vary from 30 to 80 percent. In other words, lots of people don't follow doctors' orders. There must have been some patients who stopped the drug because of the constipation, flatulence, nausea, diarrhea, heartburn, hiccups, sour taste, skin bruises, hives, wheezing, muscle pains, dizziness, and fatigue listed among Questran's side effects. Did all such patients tell their doctors the truth? Or did some of them, for a variety of reasons, fail to inform the researchers? How many patients were in non-compliance both as far as the drugs and the diet were concerned?

Next, you might ask your doctor about the diet. The scanty details given in newspaper articles I read listed skim milk among the emphasized foods, even though plenty of doctors are skeptical of cows' milk in general --skim milk included--for patients with heart disease.

The evidence on Quesstran was presented in the Journal of the American Medical Association (January 20, 1984). Let's take a look at the almost incredible answers to the above questions.

I had requested details about the nature of the diet that was prescribed. Yet in this one-year, \$150,000,000 study which involved thousands of patients and which was carried out by distinguished doctors and medical centers, the elements of the diet in terms of food are not mentioned. Instead of telling us about milk or sugar or flour or vegetables or meat, the researchers prescribed a "moderate cholesterol-lowering diet." Instead of talking about fruits, butter, vitamins, or trace minerals, the researchers discussed "a polyunsaturated-to-saturated fat ratio...." Why this omission? Did the researchers believe in their cholesterol-lowering diet? The researchers state, "When the [study] began, it was the practice of many physicians to recommend such a diet to hypercholesterolemic patients." In other words, the diet wasn't their own idea. They might well have preferred to tell people to disregard diets prescribed by their own doctors. They might have preferred to tell the experimental subjects to eat whatever they wanted (Twinkies, cream puffs, baked Alaska, whipped cream), but they recognized that people, and their individual doctors, know that diet is important in the prevention and treatment of cardiac disease, and they knew their subjects would not listen to the researchers who told them that any kind of food was o.k.

Not only did the researchers seem to lack commitment to dietary management, but they also used the diet to get subjects for their study. Or as they put it, "...It was hoped that such a diet, along with a nutritional counseling program, would facilitate recruitment of participants." Rather than take the risk of running an elaborate study to which no subjects would come, the investigators bent their study to the wishes of the people. So don't bother looking to this study for any helpful information about diet.

As important as the diet question is, I am even more fascinated by the statistics on the death rates of the participants in this study. Right in the boldface first paragraph which summarized the article, the researchers admit, "The risk of death from all causes was only slightly and not significantly reduced in the cholestyramine group." In other words, the people who were on the drug were just as likely to die as the people who did not take it! While they weren't dying from the nation's number one killer--heart disease--they were nevertheless dying. What was killing them?

The very next sentence states that the cholestyramine group had "a greater number of violent and accidental deaths." There were 11 deaths from accidents and violence in the cholestyramine group compared with four in the placebo (dummy tablet) group. Of these, five in the cholestyramine group were homicides or suicides versus two in the placebo group. Six of the cholestyramine group deaths were due to accidents, mainly automobile, versus two in the placebo group.

How do the researchers explain the excess death rate from violent causes? "Since no plausible connection could be established between cholestyramine treatment and violent or accidental death, it is difficult to conclude that this could be anything but a chance occurrence."

But hold it right there a moment! If these violent and accidental deaths, already shown to be statistically significant, are just a chance occurrence, why isn't the drop in heart disease from the drug also just a chance occurrence? Why hasn't at least one of the hundreds of researchers considered the possibility, even the likelihood, that some of those excess deaths were caused by anxiety, shortness of breath, headache, dizziness, fainting, eye inflammation, fatigue, and the other dozens of listed side effects of cholestyramine? Why didn't newspaper headlines read, "Heart

drug responsible for 40 percent more suicides, homicides, and automobile accidents"?

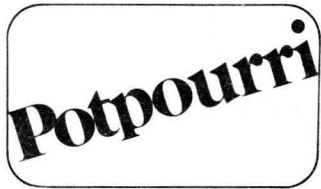
You may wish to write for a reprint of this scientific article--if so, send your requests to Lipid Metabolism-Atherogenesis Branch, National Heart, Lung, and Blood Institute, Bethesda, Md. 20205 (Basil M. Rifkind, M.D.). You then will be able to read other surprising aspects of this study--e.g., the almost double number of operations or procedures involving the nervous system in the cholestyramine group; the almost double number of gastrointestinal cancers, and the higher incidence of gall bladder surgery.

If your doctor prescribes Questran for you, the least you can do is call your insurance agent and make sure your insurance policy carries a double-indemnity clause! (Ed. note: Some of the material on Questran has appeared in previous Newsletters.)

*Low cholesterol
and
cancer*

Another low blow to "low cholesterol" comes from a New Zealand study reported in the British Medical Journal, February 9, 1985. This 17-year study showed an inverse relationship between serum cholesterol and mortality from cancer. In other words, the higher your cholesterol level, the lower your chance of dying from cancer. Conversely, the lower your blood cholesterol level, the better your chance of dying from cancer.

As you might guess, several possible explanations for this startling finding were considered by the study's authors, including the relationship between retinol (Vitamin A) and cholesterol. But regardless of the explanation, you might ask your doctor (before he takes measures to lower your cholesterol) whether he is familiar with this study--or with others showing the same results.



*Death linked
to
sleepy doctor*

Earlier this year, I appeared on a PBS television program which was hosted by the president of Rutgers University and which dealt with the problems of modern medicine. One of the other guests was New York journalist Sidney Zion, whose 18-year-old daughter, Libby, had died in a New York hospital, allegedly a victim of medical malpractice.

Among the serious criticisms that Zion leveled at the hospital and doctors in control of his daughter's questionable treatment was the poor judgment of sleepy hospital residents. In fact, a New York grand jury investigation of Libby Zion's death ended with a series of recommendations, one of which called for limited shifts for interns and residents of not more than 12 hours, followed by at least eight hours off. This recommendation now is in the process of being implemented by the New York State Health Commission. Hopefully, residents who are not suffering from sleep deprivation would not commit the kind of error that may have resulted in Libby Zion's death.

The young woman, who came to the emergency room because of a severe earache after a dental extraction, was injected with Demerol (a narcotic), even though doctors were aware she was taking Nardil (an anti-depressant). In combination, the two drugs may cause a toxic condition known as malignant hyperpyrexia. Miss Zion's temperature rose to 108 degrees, and she died several hours later, although the physicians who were responsible for her treatment diagnosed her as "hysterical."

Motivated by this tragedy, Eugene D. Robin, M.D., professor of medicine and physiology at Stanford University, has written a paper entitled "Libby's Legacy: Sleep Deprivation and Housestaff Training," in which he reviews 80 years of human sleep deprivation studies. (Reprints are available from Dr. Robin at the Anatomy Building, Room 169, Stanford University School of Medicine, Stanford, California 94305.)

As you may know, sleep deprivation leads to impaired performance. In road traffic situations, sleep deprivation leads to impairment of perception, concentration, attention and adaptability to rapidly changing conditions. At critical moments, rapid and sensible reactions cannot be guaranteed, but subjects of studies assess their performance as better than they actually are.

Sleep-deprived subjects show increased irritability, suspicion and intolerance. A number of studies done on sleep-deprived hospital house-staffs over the past 15 years have shown deterioration of cognitive and behavioral performance, including memory loss of recent events. A variety of emotional disturbances including difficulty in thinking, depression, irritability, depersonalization and inappropriate affect also have been documented. Dr. Robin notes that one of the most pernicious reactions is a feeling of anger directed against specific patients!

What meaning does this have for patients? While the spotlight of public opinion has temporarily focused on sleepy house doctors, it may take years to change the outrageous working conditions of hospital doctors.

Furthermore, doctors are crafty fellows. Even if their hospital working hours are legally limited, they may turn to moonlighting elsewhere. Therefore, it is extremely important for every patient to protect himself against sleep-deprived residents or interns. Take special precautions if you are in a research and teaching hospital in which many doctors work long shifts. If the person treating you seems to be acting peculiarly or doesn't appear to like you, ask how much sleep he has had. Better yet, as soon as he walks in, and before he questions you, ask him some questions.

Find out if he is fully awake--or if he is sleep-deprived. Remember that the patterns doctors learn during their training often are carried into their later professional careers. Therefore, whenever a doctor comes near you in an emergency room, a private office, the operating room, delivery room or your hospital room, be suspicious. Find out whether he has unlearned the bad lessons he learned during his training or whether he still is prone to work himself into sleep deprivation.

If any friends or relatives of yours are thinking of becoming doctors, make sure they read Dr. Robin's paper. The same applies to patients who are suing doctors. Lawyers should be particularly aware of the number of hours a doctor who is accused of malpractice may have been on duty.

Add sleepy doctors to the growing list of medical risks, which already includes antibiotic-resistant germs, surgical complications, erroneous laboratory results, withholding of information, etc., etc.

Why should New York State government officials step in to restrict doctors' working hours to the same as those worked by ordinary human beings. Can't doctors discipline themselves?

The answer, of course, is no. God doesn't sleep; why should doctors? God doesn't suffer sleep deprivation; why should doctors? Remember what I have told you about hospital surveillance of handwashing practices? That study revealed that all personnel--nurses, technicians, dietary employees, etc.--washed their hands between patients. But not doctors. Why should doctors wash their hands? God doesn't.

The long hours worked by doctors, particularly those in training, do not result from conventional explanations--a desire to learn more, "hazing" practices of fraternity life, initiation "rites" into maturity, the process of separating the men from the boys and the women from the girls, cheap labor for the hospitals, etc., etc. The basic reason stems from feelings of omniscience and omnipotence inculcated into the doctor from the moment he learns he has been accepted into medical school.

From then on, he is no longer an ordinary mortal, subject to bodily frailties, germs, etc. This identification with God (or rather, the Gods) prevents doctors from facing--or even recognizing--their humanity. At times, however (particularly when caught making a mistake), they may confess sanctimoniously, "I'm only human." But this lip service is designed to mollify, placate and appease the laity, and to get the doctor over bumps in the road.

The carefully nurtured trait of doctors to confuse themselves with the deity makes it vital for government to remind them--with laws, if need be--of their human state. And for ordinary mortals to scrutinize their every move.

Another View

by Marian Thompson



The issue of diet and cholesterol took an interesting turn this year with the report of a cholesterol challenge test in which a group of people who ate triple the recommended amount of cholesterol daily found that, instead of doubling or tripling their cholesterol levels, there was hardly any difference. As explained on national television by Bob Arnot, only eight of the 75 people tested showed an increased cholesterol level. Dr. Arnot explained that, when we eat cholesterol-rich foods, our bodies make less cholesterol, and we absorb less. But why doesn't this response occur in everyone, he asked?

These kinds of unknown factors in the cholesterol debate continue to pit expert against expert. In a New York Times article explaining this dilemma, Philip M. Boffey points out that some experts worry that an anti-cholesterol campaign such as the one being coordinated by the federal government is "racing far ahead of what science can support in favor of lifelong dietary changes that might yield limited benefits for most people and conceivably harm some." Paralleling this national effort, rapid tests to determine cholesterol levels are being offered in shopping centers and at workplaces around the country.

Yet according to Boffey, such levels provide only a rough approximation of actual risk because the total cholesterol level includes both "good" and "bad" cholesterol. The "bad" cholesterol is carried by low density lipoproteins which seem to deposit cholesterol on artery walls, whereas the "good" cholesterol is carried by high-density lipoproteins, which seem to remove cholesterol from body tissues. Obviously, people with high total cholesterol readings should take steps to determine which kind of cholesterol is dominant.

Fearing that a nationwide push to reduce cholesterol levels might cause more harm than good to children and adolescents who need fats and cholesterol for growth and development, the American Academy of Pediatrics has refused to endorse the diet recommended by the Heart Association. Dr. Marshall Becker, chairman of the Department of Health Behavior and Health Education at the University of Michigan School of Public Health, asks why we are driving people nuts about cholesterol when other things, such as smoking, are clearly phenomenally damaging. "Nobody knows," says Dr. Becker, "what will happen in our society if you put them on severely-restricted cholesterol diets. It's never been done for a lifetime. And the drugs you need to take have side effects."

In 1968, G.R. Osborn, a British pathologist published a report on the relationship of infant feeding to the etiology of coronary disease. Examining the arteries of 1500 young people from newborns to 20 years old who were killed in accidents, he found a range of pathological changes from mucopolysaccharide accumulations to fully developed arteriosclerotic plaques. Lesions were more frequent and severe in children who had been formula fed and were uncommon or mild in breastfed children.

Last year, at a conference on the effects of Human Milk Upon the Recipient Infant held in Konstanz, West Germany, Margit and Paul Hamosh reviewed the current status of information on the relationship between early infant feeding practices and health in later life. Although it's been 20 years since Osborn made his observations, no studies have been done on humans which compare the type of feeding in infancy with cholesterol levels after adolescence. The Hamoshes have concluded that animal studies are inadequate in addressing this question.

Because human breast milk contains about 15 mg/dl cholesterol and infant formulas contain only trace amounts, it is felt that the breastfed infant would be better prepared to handle dietary cholesterol than the adult who was bottlefed in infancy. When the day comes that scientists take breastfeeding seriously enough to factor it into epidemiological studies of heart disease, we might begin to get some basic answers to Dr. Arnot's question.

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