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obtained, although John Cowley of Arizona State University complained in a 1979 Nobel Symposium on direct imaging of atoms and molecules that this approach had not been terribly effective. For the most part, achievable resolution of interpretable structural detail remains at 2.5 angstroms or worse. Reducing this figure to 1.7 angstroms, as called for in the ARM design specifications, would usher in the era of single-atom resolution, since many chemical bonds are longer than this.

High electron accelerating voltages have two effects on resolution, one good and one bad. The good effect is that the mathematically achievable resolution improves as the electron energy increases, although not linearly. This is what makes cracking the 2-angstrom barrier possible. The bad effect is the inability to keep the electron accelerating voltage absolutely constant. Slight fluctuations in the voltage give rise to the equivalent of chromatic aberrations in light optics because the electron wavelength depends on its energy. In general, it is harder to keep the accelerating voltage stable as the voltage increases. Gronsky says that the choice of 1 MeV for the ARM was a kind of compromise between the two contrasting consequences of high voltages. By means of a very precise feedback system, JEOL will be able to keep its 1 million volts steady to within 0.1 volt. It will also be necessary to make the lens system to very precise specifications in order to reduce spherical aberrations.

With atomic resolution, any number of investigations in materials science, chemistry, geology, and biology would become feasible. One that is especially interesting to Gronsky and to his DOE sponsors is the study of the atomic structure of the boundary regions between crystalline regions in metals. These grain boundaries are often the weakest link in those features that determine the mechanical properties of structural materials. From the biologists' point of view, studying cell membranes might represent a problem of comparable interest.

Credit for establishment of the electron microscope center at LBL, says DOE's Stevens, should go to Gareth Thomas, who is its director. Thomas arrived at Berkeley in the early 1960's when a 200-keV microscope was the state of the art. By the end of the decade, Thomas had garnered a 650-keV machine for the laboratory. In the early 1970's, he teamed with biologist Robert Glaeser of Berkeley and physicist Cowley to propose a national center for electron optics centered around an atomic resolution instrument. An initial approach to the National Science Foundation was rebuffed. The turning point seemed to come after a 1976 workshop on high resolution electron microscopy that was held at LBL. The workshop successfully unified community support for the idea. Just as important, adds Gronsky, was that the technology had by then advanced to the point where an instrument with atomic resolution could be more seriously considered. The center later received considerable support in Congress when a budget balancing exercise initiated by former President Carter almost brought the project to a premature end.

Last year, JEOL won out in a three-way contest with another Japanese company, Hitachi, and Kratos for the right to develop the ARM. JEOL will build the instrument in Japan and test it there. Then, the ARM will be disassembled and shipped to LBL, where it will be put back together in a silo similar to that housing the HVEM. Final acceptance testing should be completed by March 1983. The LBL microscopists can hardly wait.—ARTHUR L. ROBINSON

Data Sought on Low Cholesterol and Cancer

Low cholesterol levels seem associated with cancer, but it is not yet clear how strong the association is or what it means

Accumulating evidence for a connection between low serum cholesterol concentrations and an increased risk of cancer has led researchers to pursue the question more vigorously, especially in light of other data that point to a clear relationship between high cholesterol levels and heart disease. Jeremiah Stamler of Northwestern University Medical School, who strongly supports cholesterol-lowering diets, says "there certainly seems to be something there but the relationship between low serum cholesterol and cancer is by no means clear, consistent, and unequivocal."

In an attempt to resolve the issue, the National Heart, Lung, and Blood Institute (NHLBI) contacted about 100 researchers who have been studying cholesterol and heart disease and asked them to reevaluate their data to see if they show an association between low cholesterol concentrations and cancer. Many of these investigators are expected to attend an NHLBI meeting in May.

As long as 10 years ago, evidence suggesting a low cholesterol–cancer connection was reported by M. L. Pearce and S. Dayton of Veterans Administration Hospital in Los Angeles, who noted an increased incidence of cancer in men on a cholesterol-lowering diet. But Frederick Ederer, now at the National Eye Institute, and his associates could not confirm this result when they looked at data from four similar studies.

About 5 years ago, Geoffrey Rose of the London School of Hygiene and Tropical Medicine accidentally came across a relation between low cholesterol and colon cancer. Rose hypothesized that colon cancer might be associated with high cholesterol concentrations, reasoning that the populations with high rates of colon cancer were those with high rates of heart disease and high average cholesterol concentrations. He reviewed data from a number of large, prospective studies of heart disease and found, unexpectedly, that those who got colon cancer tended to be those whose cholesterol was low—less than 190 milligrams of cholesterol per 100 milliliters of serum. The serum cholesterol concentration of the average American is 215 mg per 100 ml, and until recently it was 230 mg per 100 ml. Only 10 percent of Americans have cholesterol concentrations below 190 mg per 100 ml.

But Rose's study was retrospective. One of the first prospective studies was that of Robert Beaglehole and his associates at the University of Auckland, New Zealand, who reported last year that in their 11-year study of 630 New Zealand Maoris, men and women with serum cholesterol concentrations below 190 mg per 100 ml had a higher rate of cancer. Similar results were then reported by

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Curtis Hames, director of the Cardiovascular Epidemiology Study in Claxton County, Georgia. Hames's group studied 3102 people for 12 to 14 years.

In the meantime, researchers with the Framingham study, a prospective NHLBI-supported study of 5200 residents of Framingham, Massachusetts, were looking at their data, which go back to 1948. Manning Feinleib, an NHLBI epidemiologist in charge of analyzing Framingham results says, "We found to our surprise and chagrin that people who were at the lowest end of the cholesterol spectrum had an increased cancer mortality." The association, however, held only for Framingham men, not women. It was especially strong for colon cancer but also held for all cancer combined. Men with cholesterol concentrations below 190 mg per 100 ml had three times the incidence of colon cancer of men with higher cholesterol concentrations.

Data from two other NHLBI prospective studies that involve only men—the Puerto Rico Heart Health Study and the Honolulu Heart Study—also show an association between low cholesterol and cancer. In Honolulu, the association was with stomach, colon, liver, and lung cancers. In Puerto Rico, it was with stomach and esophageal cancers.

However, four other prospective studies do not show any such association. These include the Chicago Peoples Gas Company Study and the Chicago Western Electric Company Study, with 15- and 17-year follow-ups, respectively. These studies included deaths from all types of cancer.

Two other groups have found an association between low blood cholesterol concentrations and cancer, but the association disappeared with time. Rose and M. J. Shipley of the London School of Hygiene and Tropical Medicine followed nearly 18,000 men for 7½ years. In the first 2 years of follow-up, but not subsequent years, those who had low cholesterol concentrations on entering the study had higher cancer death rates. This finding led Rose and Shipley to propose that the men who died of cancer in the first 2 years of the study may have had undetected cancer when they entered the study. This cancer may have caused their cholesterol concentration to drop. Thus the low cholesterol concentrations in those who died of cancer in the first 2 years may have been a manifestation of the cancer, not a cause.

F. Cambien and J. Richard of Equipe de Recherche de Cardiologie INSERM in Paris together with P. Ducimetiere of Unité 169, INSERM in Villejuif, France, came to a similar conclusion after noting that an association between low cholesterol and cancer in their population of 7603 middle-aged men disappeared after 7 years of follow-up.

About 1 year ago, the NHLBI held a conference to review the available data on low cholesterol and cancer. "We agreed that there is weak but suggestive evidence that low cholesterol may be in some way associated with cancer risk," NHLBI director Robert Levy says. "But the association still seemed inconsistent."

One reason why existing data are inadequate to determine whether there is a relation between low cholesterol and cancer is that heart disease is much more common than cancer. Therefore, even the largest of the studies of cholesterol and heart disease have relatively few cancer deaths. And when it comes to breaking down the data into cancers of specific types, there are even fewer deaths. It remains possible that low cholesterol may be associated with cancers in general, yet, says Stamler, "Everything we know about cancer tells us you must be very careful about treating all cancers as a group."

The heart institute plans to hold a meeting in May for a review of new data.

Several explanations have been considered for the association, if any, between low cholesterol and cancer. First is the possibility, raised by the French and British studies, that low cholesterol results from, rather than causes, cancer. Levy is a bit doubtful of this, because if it were true, the Framingham cases would have had low cholesterol concentrations for more than 10 years before their cancers were detected. "It would be strange, although not impossible, for low cholesterol to be a marker for cancer so long ahead of time," he says.

It also may be that low cholesterol levels are linked to another factor that makes people susceptible to cancer. One possibility is that some people absorb less fat, and so absorb less of the fat-soluble vitamins, especially vitamin A. A deficiency in vitamin A has been associated with an increased risk of cancer. Hames finds that those people in his study who had low cholesterol concentrations and cancer also had lower blood concentrations of vitamin A.

Stamler suggests that people whose serum cholesterol is naturally low may either absorb dietary cholesterol inefficiently or excrete it efficiently. In either case, they would tend to have more sterols in their intestines than do people who eat the same diet but have higher cholesterol levels. Intestinal bacteria can convert sterols to carcinogens, which may explain why those people with low cholesterol are at a higher risk at least for colon cancer—if indeed they are. "If this hypothesis is true," says Stamler, "the way for people with naturally low cholesterol concentrations to protect themselves against cancer may be to eat a diet low in total fat and cholesterol and also to eat plenty of fiber to move the cholesterol out of their intestines."

It is not yet clear what this information means to anyone who is concerned about diet. Levy says that the NHLBI still recommends that those whose cholesterol concentrations are high try to lower them by dieting. But, he says, "To those who have suggested that the lower the [serum] cholesterol the better, the data on low cholesterol and cancer doesn't silence them but it should make them a little more cautious."

Although the American Heart Association recommends diets low in saturated fats and cholesterol, Scott Grundy of the Veterans Administration Hospital in San Diego, who heads the Heart Association's nutrition committee, says he thinks that for those whose serum cholesterol is below 200 mg "the reasons for changing the diet are not as compelling as for those whose cholesterol is 250, where the risk of heart disease is 4 to 5 times as high. There is no proof yet that lowering your cholesterol from 200 to 160 is beneficial. I'm not advocating that people push their cholesterol as low as possible." But, he explains, since diet can lower cholesterol concentrations by only 10 to 15 percent, no one with elevated cholesterol is likely to lower his cholesterol to anywhere near the range that may be associated with cancer.

At present, the NHLBI and the Heart Association are awaiting additional information on low cholesterol concentrations and cancer. The data to be presented at the NHLBI meeting in May, says Levy, "should enable us to see whether the association is real, how strong it is, and whether other factors impinge on it."—GINA BARI KOLATA

Additional Reading

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