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Boston University
A revolution has occurred over the past five years regarding scientists' understanding of how the delicate inner ear functions. A team of BUSM scientists has been conducting studies that have been in the vanguard of this revolution. See story on page 3.

Diet and cancer: Researchers at BUSM investigate this complex connection

Food—especially delicious, fattening food—has long been a prime suspect in scientists' search for the causes of cancer. Conversely, praise for certain fruits and vegetables as cancer "inhibitors" has grown in recent years. Yet the precise connection between specific nutritional components of food (vitamins, fats, proteins and sugars, for example) and different types of cancer has not been easy to establish.

Adrienne E. Rogers, M.D., a professor and associate chairman of the Department of Pathology at BUSM, has been working to identify how different diets affect the way chemicals are handled by the body and, in particular, how nutrients enhance or inhibit the carcinogenicity of certain chemicals. continued on page 5

Team aims to realize laser's potential as cardiology tool

Many scientists involved in heart-disease treatment and research see tremendous potential in the laser as an instrument for eliminating atherosclerotic buildups in the arteries. Its pinpoint accuracy, its power and its ability to vaporize tissues with little if any bleeding all add to the laser's attractiveness as a tool for attacking the buildups. So, too, does the fact that a laser beam can be transmitted via optic fibers, which means that the beam can be conveyed through a catheter over a course full of twists and turns.

The laser also has drawbacks, however. Its key deficiency as a tool for eliminating arterial plaque is the unintended damage it can do. A laser instrument may do harm when its tip comes in contact with the delicate walls of a blood vessel. Or, the laser beam itself may burn a hole through the vessel wall.

These problems have prevented the laser from finding a significant place in the treatment of narrowed arteries. Now, though, a Boston University School of Medicine research team headed by Timothy A. Sanborn, M.D., may be on its way to surmounting the laser's limitations in treating atherosclerosis. The team is experimenting with a laser design that permits the cardiologist to have a direct view of the continued on page 2
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buildup being treated. They also are testing new catheter tips which, by diffusing the laser beam, minimize the risk of perforating the artery's wall.

For more than a decade, bypass surgery has been the standard way to treat atherosclerotic buildups in the arteries. The surgeon may remove the diseased part of the artery or bypass it with a vein or a prosthetic vessel, allowing the blood to flow freely once again.

Bypasses have helped many thousands of patients avoid the potentially dire consequences of blood-vessel blockages. They are lengthy and costly operations, however, and cannot readily be repeated if plaque builds up in the replacement vessels.

Balloon angioplasty is an alternative way to treat arterial plaque. The technique involves use of a specially designed balloon mounted on the end of a catheter. The implement is inserted until the balloon is centered within the buildup, and then the balloon is repeatedly inflated. (See the November 1981 Research in Progress for more about balloon angioplasty.)

However, balloon angioplasty, although less expensive and generally less risky than bypass surgery, also has its disadvantages. For one thing, buildups often recur in the treated vessels, a process called restenosis. Furthermore, the device will not fit into arterial openings of 1 millimeter or less.

The laser may offer an alternative to both of the more traditional treatments in a wide variety of situations, said Sanborn, an assistant professor of medicine at BUSM and associate director of the Cardiovascular Research Laboratory. In fact, he said, it may even allow treatment of plaque within the coronary arteries. These vessels, whose role is delivering blood to the heart muscle, may be too small for balloon-angioplasty treatment.

Before laser angioplasty can realize its apparent promise, however, the problem of the unintended harm that a laser may do must be solved.

"A great many animal experiments have shown that when you introduce a laser into a blood vessel, there's a very high risk—somewhere between 40 and 80 percent—that you'll perforate the vessel," noted Sanborn, also a staff cardiologist at University Hospital.

The damage rate could be cut dramatically if there were better ways to control the laser, said Sanborn, and investigators are experimenting with a variety of means for accomplishing this.

One solution, for example, is to mount an imaging capability in the same catheter that carries the laser. This can be done, said Sanborn, but it involves more than simply including an additional optic fiber to convey a TV image of the plaque site back through the catheter.

"You basically need four channels in the catheter," he explained. "One for the laser fiber, one for the imaging fiber, one for an illumination fiber to see the interior of the artery and one for a saline solution to flush blood away from the site of the lesion, so that you can see it."

Sanborn, who has experimented with a four-channel catheter, said it is a technology that has promise for treating blockages in larger blood vessels, like the major vessels of the abdomen and the upper leg. On the other hand, since present day four-channel catheters are at least 2.5 millimeters in diameter, they are not suitable for treating coronary arteries.

While engineers strive to develop smaller four-channel systems, Sanborn's group is pursuing another approach to the size and control problems associated with laser angioplasty.

"What we've been working on is modifying the fiber tip so that the laser energy, instead of being focused on a point, is distributed circumferentially," he explained. One of the experimental tips, for example, is designed to transform the light energy of the laser into heat and to distribute it laterally.

By eliminating the pinpoint beam that emanates from a traditional laser tip, this new device minimizes the risk of perforating a vessel's wall. And by letting the cardiologist center the laser tip in a vessel rather than having to train the single beam over each section of the plaque in turn, it greatly simplifies the problem of controlling the laser. In fact, noted Sanborn, his experiments show that the tip can be adequately controlled using just a fluoroscopic image—a finding that means the new technology may be suited for use within the narrow confines of the coronary arteries.

"We've done a lot of animal experiments with the tip, and we've demonstrated that this technology will remove plaque without perforating the artery," said Sanborn. "Now we're studying the long-term consequences of the procedure. So far, we've found that we do get some closing up of the arteries that we've treated, but our numbers are equal to, if not better than, the restenosis rate with balloon angioplasty in this atherogenic model."

The cardiologist said that he and his associates are moving toward use of the procedure to treat arterial...
plaque in patients, but that the first arteries to be treated will be large vessels of the mid-section or the upper leg, not coronary arteries.

Meanwhile, other research ventures that Sanborn's group plans to pursue include experimenting with different types of lasers, and altering the laser's pulse duration—that is, the length of the individual bursts of light—to minimize the damage that can affect tissues heated by laser light delivered in pulses of one second or more.

Before moving on to experiments with different pulse settings, however, Sanborn and his associates want to explore more fully the potential of new kinds of fiber tips. "There are a lot of different ways to modify these tips," he noted, "and it's possible that several of them will provide safer ways of using the laser in angioplasty procedures. That's the issue we're really pursuing now, and once we have a better idea of how much we can accomplish through tip modification, we'll start more detailed studies of issues like the laser's wavelength and its pulse duration."

Another area that Sanborn and his team recognize they will have to pursue is the development of better ways to localize the laser tip to the desired point in the arterial wall. "We're finding that the most promising localized heating effects are with laser tips that are a few millimeters in diameter, but there are some problems to overcome," he said.

Other BUSM researchers working with Sanborn on the laser are Christian Haudenschild, M.D., a professor of pathology, and David P. Faxon, M.D., an associate professor of medicine and head of University Hospital's Cardiac Catheterization Laboratory. Funding for the project comes from a Grant-in-Aid from the American Heart Association and from Trimedyne, Inc., in Santa Ana, Calif.

—Richard P. Anthony

Suggested Further Readings


Scientists explore hearing mechanisms through studies utilizing computers

A small, but significant, revolution has occurred over the past five years regarding scientists' understanding of how the delicate cochlea, or inner ear, functions.

A team of five neurophysiologists and engineers, who hold joint appointments in the Department of Otolaryngology at Boston University School of Medicine and at Boston University's College of Engineering, has been conducting studies that have been in the vanguard of this revolution.

By improved understanding of the hearing process, the scientists hope one day to be better able to help the 16 million Americans who are profoundly deaf or hard-of-hearing. Such information also could be useful for those who have tinnitus, or head noise.

"It has become apparent that the auditory system is a lot more complicated than scientists had thought," said David C. Mountain, Ph.D., who, along with Allyn E. Hubbard, Ph.D., who is also an associate professor of electrical, systems, and computer engineering, has been conducting computerized measurements of the electromechanical processes in the cochleas of laboratory animals for more than a decade. Funding for their work is provided by the National Institutes of Health.

Using an elaborate computer system developed by the group in their lab in BUSM's Housman Medical Research Building, the researchers, all assistant research professors of otolaryngology at BUSM, have been able to monitor responses of the auditory system to acoustical and electrical stimuli in laboratory animal experiments.

"It used to be thought that the cochlea passively separated sound into its different components, and that the hair cells, or receptor cells, simply detected the vibration of the basilar membrane on which they were located. Some parts of the membrane vibrated best in response to high frequencies and others responded best to low frequencies. So the thought was that the different receptor cells, and the nerve fibers associated with them, were responding to a mechanical filtering process, enabling us to discriminate between frequencies or pitches," explained Mountain, who also is an associate professor of biomedical engineering.

He has demonstrated that the brain is capable of controlling the mechanical properties of the inner ear. "This is the first direct evidence of the brain influencing the mechanics of hearing. Much of the work in the past has aimed at exploring a related new hypothesis: that the receptor cells themselves are part of the mechanical process—they're not just passive little microphones detecting vibration—but they're actively amplifying the sound."

The team has come up with the first evidence that a combination of electrical and mechanical processes may bring about this amplification process. "The receptor cells may detect movement and push back," Mountain said. The researchers have shown that electrical current flowing through the hair cells stimulates the cells to generate a force. The cells are known to respond electrically to movement so the electrical response could create another mechanical response that feeds back on the system and results in amplification. "If that hypothesis is correct, that means the force generation has to keep up with the sound vibration," Mountain said.

"We've been trying to characterize and measure the speed of that process. It operates at a higher speed than any comparable biomechanical process we know of," he said. "It's much faster than, say, a mus-
Computerized Hearing Research

core contraction."

Hubbard and Mountain, along with Teresa A. McMullen, Ph.D., an assistant professor of biomedical engineering, have also been conducting computer simulation studies to test this hypothesis of cochlear function. They hope that their computer studies will help them refine the theory to the point where it will be possible to predict the response to sound of both normal and pathological ears. The modeling also may aid in the development of cochlear prosthetics using microcircuit technology.

The vibrations of the basilar membrane, which are crucial to the understanding of the amplification process and of the coding of auditory information that goes to the brain, are the subject of research by Eric L. LePage, Ph.D., an assistant professor of biomedical engineering. He has conducted direct mechanical measurements of the submicroscopic movements of the basilar membrane. His data suggest that the traditional description of the motion is incomplete. In addition to vibrations of the membrane caused by sound, the mean position of the basilar membrane is altered as well. Other studies conducted by LePage have shown that loss of hair cells changes the mechanical properties of the basilar membrane, a result which fits in well with those of Hubbard and Mountain. "Deaf animals do not show the kind of behavior which we now associate with the position shift," LePage said.

Part of the significance of the finding is that it may help explain how nerve fibers respond to high frequencies. "The sensory hair cells do not respond well to high frequencies but they do respond to a shift in the position of the basilar membrane," LePage explained. "Secondly, since other experiments have shown that hearing sensitivity is strongly influenced by similar shifts produced by low tones, we hope that further study of the internally-generated shift will reveal more about how the hearing organ achieves its high sensitivity, and why hair cell loss leads to deafness." To do this, LePage and Hubbard are working on a new series of experiments using the latest optical fiber techniques.

What the brain does with the auditory information it receives from the cochlea is the focus of work by Herbert F. Voigt, Ph.D., an assistant professor of biomedical engineering, who together with McMullen, has been studying the role of the cochlear nucleus in hearing.

"The cochlear nucleus in humans is not one, but at least three interconnected nerve centers, located in the brain near the cochlea, forming a gateway to an incredibly complex auditory system," Voigt explained. "While all of the acoustic information necessary for understanding speech or for listening to music must be encoded in the activity of the nerve that connects the cochlea to the cochlear nucleus, the initial processing of that information is apparently performed simultaneously by these three nerve centers."

Much of Voigt's work focuses on the intricate circuitry of the dorsal cochlear nucleus (DCN). The anatomy, physiology and circuitry of the DCN is much more complicated than that of the auditory nerve. It's an extremely complicated neural system that we are only beginning to understand.

In their studies, which are supported by grants from the Deafness Research Foundation, the National Institutes of Health and the National Science Foundation, Voigt and McMullen are categorizing DCN neurons by their acoustic response properties. They have found that DCN neurons of gerbils behave in a manner similar to those neurons of cats, and that the neurons can be classified into essentially three physiological types. "We have now begun intracellular recording and marking experiments," Voigt said, "and hope to gain a more fundamental understanding of the structure/function relationships that exist in the DCN."

In addition to the experimental side of their work, Voigt and McMullen have developed computer models of hypothesized DCN circuitry. "With our computer simulations, we've been able to mimic various aspects of the physiological results," Voigt said. "This is an indication that we are on the right track."

—Marjorie H. Dwyer

Suggested Further Readings

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One such study currently under way is examining how different types of fat influence the development of breast cancer. A related project is aimed at determining the relationship of diets deficient in certain amino acids and vitamins to cancer of the liver and pancreas. In both cases, it appears these diets interact with exposure to certain known cancer-causing chemicals to produce or enhance cancer development in laboratory animals.

"One of the strongest associations known between diet and cancer is that increased dietary fat appears to increase the incidence or development of breast cancer," said Rogers.

Next to lung cancer, breast cancer is the most common cause of death from cancer among women in North America, according to the American Cancer Society. The ACS estimates that as many as one out of every 11 women may develop breast cancer during her lifetime.

According to Rogers, fat may affect the metabolism of foreign chemicals and their clearance from the blood. Fat also is an important component of cell membranes, which are largely layers of fat molecules with protein sandwiched in between. Because of this structure, the ability of membranes to selectively distinguish what goes in and out of cells, and so protect the cell against potentially harmful agents, could be jeopardized by changes in diet.

"When you feed an animal more fat, the composition of its cell membranes changes depending on the type of fat you feed. Consequently, cellular metabolism may be changed," explained Rogers.

Membranes also are important in interactions with hormones, a factor that may be of particular importance in the development of breast cancer.

Rogers and others have determined that polyunsaturated fats—corn, safflower and soybean oils—have the most marked cancer-enhancing effect in animal models. Highly saturated fats, such as beef tallow, don't seem to produce this effect, while such monounsaturated or mixed fats as lard and olive oil produce an intermediate effect.

When studies were first done on the relationship between fat and breast cancer, investigators suspected that high-fat diets changed the level of hormones in the blood, thereby causing tumors. Rogers has conducted careful studies of blood hormones in rats over the entire reproductive cycle, however, and has not found any effect of high-fat diets on serum endocrine status. But, said Rogers, "there still may be something about the mammary gland itself and its response to hormones in animals fed a high-fat diet that increases tumors."

Just as important to Rogers as the effect of a high-fat diet on tumor production is whether diet exerts its influence before or after exposure to a carcinogen. "When does dietary-fat change make a difference? Does it serve any purpose in adults to lower fat intake? Our rat studies suggest it may, particularly in breast-tumor development," said Rogers.

She and her colleagues at BUSM are comparing mammary glands of rats fed a high-fat diet with those fed a control diet to see whether cell division, and consequently the growth and differentiation of the gland, is different in the two dietary groups with or without exposure to the carcinogen dimethylbenzanthracene (DMBA).

Her studies, and those of other investigators, show that the promotion of tumor growth by a high-fat diet occurs largely after exposure to a carcinogen, suggesting that fat somehow alters the ability of carcinogen-altered cells to develop into tumors. However, certain high-fat diets have an effect on breast tumor development only when fed before the initiation stage, according to Rogers.

A report on "Diet, Nutrition and Cancer," prepared by the Committee on Diet, Nutrition and Cancer, Assembly of Life Sciences, National Academy of Sciences, recommends that Americans lower their fat intake from the current 40 percent of their daily caloric intake to 30 percent. While this may be a manageable goal, it is still not clear that this limited decrease would have any noticeable effect on the development of breast tumors, according to Rogers.

Concurrently, Rogers is pursuing investigations into the effects of a choline-methionine deficient diet on the development of primary liver cancer. Methionine is an amino acid; choline is a B vitamin that prevents the deposition of fat in the liver. Rats that are fed a diet deficient in methionine and choline tend to develop...
fatty livers that eventually become cirrhotic. When exposed to a potent carcinogen, such as aflatoxin, which is produced by a mold that commonly contaminates several types of grains, the rats develop liver cancer. Epidemiologic studies show that people who eat grains containing high levels of aflatoxin, primarily in Asia and Africa, also have a higher incidence of primary liver cancer. The question Rogers has posed is, does a methionine-choline deficient diet lead to an increased susceptibility to aflatoxin and the development of primary liver cancer?

“We used the rat model with a methionine-choline deficient diet and gave them aflatoxin to see if they were more susceptible to cancer and found they were—tremendously,” Rogers explained. “It turns out you don’t even have to make the rats cirrhotic; even with a less deficient diet, they still are much more susceptible to liver cancer.”

In contrast to the breast-cancer studies, said Rogers, “it appears that, in the liver studies, the dietary effect occurs during the time you are administering the carcinogen rather than afterwards. It may be that diet continues to exert some effect and to enhance tumor yield as well, but it appears as if most of the effect is in the initiation stages. We don’t know exactly what’s happening, but we do know that a methionine-choline deficient diet changes the metabolism of carcinogens and increases liver-cell division.”

According to Rogers, whatever methionine and choline do is central to the process of carcinogenesis in the liver. For instance, rats fed a deficient diet but not administered a carcinogen will develop liver tumors anyway whereas the control animals do not. “The deficiency itself could be carcinogenic,” said Rogers. “More likely, however, we have all sorts of carcinogens both in and around us and, because the diet sensitizes the rat so much to carcinogenesis, what we are seeing is a reaction to one or more unrecognized or low-level carcinogens.”

Other BUSM researchers involved in these studies are Carol Walsh, Ph.D., an assistant professor of pharmacology; Michael Conner, D.V.M., an assistant professor of pathology; and pathology graduate students David Malarkey and Henry Nields. Funding for this research is supplied through the National Institutes of Health and the American Institute for Cancer Research, a private foundation in Washington, D.C.

—Caroline H. Lupfer

Suggested Further Readings