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# Research

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# in Progress

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What causes many cancer patients to die of tumor-related problems—such as a respiratory tract infection, a urinary obstruction, or malnutrition—rather than of the tumor itself? Scientists at BUSM are conducting research they hope will answer this question. See story on page 3.

## BUSM researchers study benefits of exercise in treating diabetes

Studies by researchers at Boston University School of Medicine could lead many individuals with the maturity onset form (Type II) of diabetes mellitus literally to run for their lives.

While most everyone feels better after exercise—whether it's riding a bicycle to work, swimming a few laps at the pool or just going for a walk—BUSM researchers, working in conjunction with researchers at New Jersey College of Medicine, are gathering new information about how exercise can help control this common impairment of the body's ability to control blood sugar.

Eighty-five percent of all diabetics in the United States have Type II diabetes, and most of them are treated with oral drugs and special diets. The remaining 15 percent have the more severe juvenile-onset (Type I) form of diabetes, and must control the disease with injections of insulin, the body's own sugar-regulating hormone.

Type II diabetics, who do not require insulin injections, usually are able to live normal lives by controlling their diet and keeping their weight down. However, they are at high risk for developing premature atherosclerosis in coronary, peripheral and cerebral arteries, which can *continued on page 2*



Neil B. Ruderman, M.D., D.Phil., conducts research on a rat as part of his studies on the effects of exercises on diabetics. (Photo by Lewis Glass, Educational Media, BUSM)

## Scientists explore cells' inner workings to determine causes of abnormalities

From the moment of conception to the birth of a child, billions of cells are created in the womb. Early in development, these cells multiply at a tremendous rate while moving in the embryo. At a certain point, the nuclei of these cells "decide" what type of cells they will be (nerve cells, blood cells, etc.), and where in the body they will be located.

What triggers this "decision?" Why, for instance, do two seemingly simi-

lar cells formed at the same instant in the embryonic nervous system develop differently and move in separate directions—one to become a neuron in the brain, another to become one of thousands of cells that form nerve endings in the tongue?

Researchers at Boston University School of Medicine are working to answer such questions about cell *continued on page 5*

### Exercise in diabetes...

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lead to heart attacks, strokes and gangrene. For example, diabetic men and women are two to three times more likely to have a stroke, and diabetic women are seven to eight times more likely to have a heart attack, than comparable people in the general population.

Results from early investigations conducted by researchers under the direction of Neil B. Ruderman, M.D., D.Phil., a professor of medicine and chief of the Division of Diabetes and Metabolism of the Department of Medicine at BUSM, suggest that a simple program of regular exercise may be useful in preventing some of the complications experienced by Type II diabetics.

"While we don't really know if exercise slows the development of cardiovascular disease in the diabetic, we do know there are risk factors for atherosclerotic disease that change in the right direction when a non-diabetic exercises. These factors include raised plasma cholesterol, insulin, and triglycerides, and high blood pressure," explained Ruderman. They also include low fibrinolytic activity—a reduced ability to break down blood clots in the circulatory system—which often is a problem in diabetics.

Ruderman began his studies on the role of exercise in diabetes about four years ago, when animal studies suggested that the ability of muscle to metabolize glucose—the form of sugar used by the body for energy—is temporarily improved following bouts of exercise. Because impaired glucose tolerance is a fundamental problem that could contribute to the vascular complications in diabetics, and because physical exertion helps maintain a healthy cardiovascular system, Ruderman and his colleague, former BUSM researcher Stephen H. Schneider, M.D., now at the New Jersey College of Medicine,



Subjects in study conducted by Neil B. Ruderman, M.D., D.Phil., exercise 30 minutes a day, three times a week for six weeks. (Photo by Lewis Glass, Educational Media, BUSM)

set up a three-year study to test their hypothesis that exercise would be beneficial in treating Type II diabetes in humans. The research is funded by grants from the National Institute of Arthritis, Diabetes and Digestive and Kidney Diseases.

In the study, patients exercise 30 minutes a day, three times a week for six weeks. The patients, mostly Type II diabetic males between 40 and 60 years old (the diabetic group most at risk for coronary disease), maintain their normal diet and keep a diary of the foods they eat. In this way the researchers can detect any dietary changes that might influence the results. Patients above the age of 40 with diabetes for more than 10 years or with a family history of heart disease are required to take an exercise electrocardiogram before starting the program. Those found to have existing heart disease are care-

fully supervised.

Patients in the study engage in such endurance exercises as running, cycling and swimming. In the early stages of the investigation, however, patients worked out on a bicycle ergometer, a standing bicycle with a device that measures the amount of work performed. At selected intervals the research staff analyzes the patients' blood.

"Our first clue that the exercise was improving glucose tolerance was the measure of the patients' hemoglobin A-1, hemoglobin that has sugar bound to it. We found that it went down," explained Ruderman, "suggesting that the patients' average blood sugar level during the six weeks of exercise was lower than it had been previously."

Guided by this initial evidence, the researchers administered glucose tolerance tests at 12 hours and at 72 hours following exercise. They discovered that in every patient, tolerance was better at 12 hours. "And, in about half of the patients, it was much better," noted Ruderman.

"We reasoned that the improvement in glucose tolerance after exercise is a result of an increase in use of sugar by the muscle as it repletes its stores of glycogen, the carbohydrate form in which muscles store sugar," explained Ruderman. "Exercising muscles use their glycogen for energy, and for reasons we do not yet understand, following exercise there is an increase in insulin sensitivity as muscle uses blood sugar to rebuild its glycogen. This results in an improvement in glucose tolerance," said the investigator.

"Another finding is that exercise lowers plasma triglycerides and increases fibrinolytic activity. In some patients blood pressure, plasma cholesterol and insulin also may decrease. By virtue of these many effects on risk factors, we hope exercise will retard the development of atherosclerosis in diabetics," said the investigator.

About 60 patients currently are in

the study, and a total of 120 patients have been entered since its beginning. Data has been analyzed on about 25 patients.

Ruderman said future research will be aimed at identifying potential diabetics and those most likely to benefit from an exercise program, because diabetes and its vascular complications may be easier to prevent than to treat. "Hopefully, genetic markers will soon be available to allow us to do this," he said.

While Ruderman's research still is under way, he recommends that previously inactive Type II diabetics undertake exercise programs only after consulting a physician. He feels that substantial benefit may result from exercise three to five times a week, for about half an hour a day. Swimming, cycling, running, tennis and similar activities are among the best exercises for such a program, he noted. "Even walking or gardening might be suitable, although not as good," he said.

"You don't have to be a marathon runner who does 100 miles a week. Indeed, beyond seven to 10 miles a week we find an increasing incidence of orthopedic problems of the ankles, knees and hips," the researcher said.

"There's a lot to be learned," said Ruderman. "Which people will benefit, how much they will benefit, what the precise exercise regimen should be and which factors we should look for to determine progress all are questions that remain to be answered."

—Steve Stiles

#### Suggested Further Readings

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2. Richter, E.A., et al: Diabetes and exercise. *Amer. J. Med.* 70: 201-208, January 1981.
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## Researchers eye metabolic factors causing death in cancer patients

One of the questions that has long perplexed researchers and clinicians alike is how cancer actually harms the patient. In many cases, the patient dies of a tumor-related problem—a respiratory tract infection, or urinary- or gastrointestinal-tract obstruction. Many patients eventually suffer from cachexia, the malnutrition and physical wasting usually associated with chronic disease. This problem is the result of changes within the patient's metabolic system, caused by the uncontrollable growth of cancer cells.

A team of researchers headed by Dennis F. Devereux, M.D., director of the Surgical Oncology Research Laboratory at Boston University School of Medicine, is working to identify possible biochemical factors in tumors that contribute to these metabolic defects.

"The tumor itself often isn't large enough to kill a patient. It's all the metabolic changes the tumor causes within the host that eventually cause death," said Devereux, who also is director of surgical oncology at Boston City Hospital, an assistant professor of surgery at BUSM, and a member of the School's Hubert H. Humphrey Cancer Research Center.

Devereux began studying the problem of the host (or body's) response to tumors in 1976 while working at the National Cancer Institute in Bethesda, Md. He recently discovered that the blood of rats bearing fibro-sarcomas—small tumors found in soft tissue, muscles, connective tissue and blood vessels—had larger-than-normal amounts of triglycerides, a type of lipid (fat). The amount of lipids present directly corresponded to the size of the tumors the rats were carrying. He found that this condition, called hypertriglyceridemia, could be reversed only partially with injections of glucose and insulin.

According to Devereux, these tests also have shown that fibro-sarcoma cells use large quantities of glucose for growth. As a result, the host's blood has lower-than-normal levels of the glucose and insulin, which are necessary for host-cell maintenance.

In an effort to combat these problems, Devereux and his research team—Trevor Redgrave, M.D., an associate research professor of medicine and an associate professor of physiology at BUSM; David Hollander, M.D., BUSM '81, a teaching fellow in medicine; and Henry Hoppe, Ph.D., a research associate in the Medical Oncology Group at University Hospital—planned a diet high in additional fats and found that tumor-bearing rats could not metabolize the exogenous (added) fats.

"For years, cancer patients have been hyperalimmented, that is, given additional lipids and proteins to combat cachexia. Now we're learning that it may not be the best combination for cancer patients," Devereux explained.

Hypertriglyceridemia also has been shown in previous studies to suppress the function of lymphocytes, Devereux said. Lymphocytes are white blood cells that are important to the host immune system in fighting infection and recognizing disease. However, when excess lipids are present in the bloodstream, the lymphocytes are unable to recognize the antigens they normally should recognize and, therefore, are unable to respond appropriately. This information may explain why cancer patients often become more susceptible to other types of illness and succumb to infection, according to Devereux.

Devereux and his co-investigators, whose work is funded by the Humphrey Cancer Research Center, have been working on ways to identify a possible factor in the blood serum of

tumor-bearing rats that might account for the system's inability to return blood-lipid levels to normal.

The basic problem is that cachexia in cancer patients is a wasting-away syndrome in which the patients become malnourished, the researcher said. Because the body contains only three *major* energy sources—sugars, lipids and proteins—losing more of one than of the others may deplete the host of fuel for energy.

Since the tumor is using up excessive amounts of carbohydrates for growth, the host has no available carbohydrates to use. Therefore, the host apparently mobilizes all of its fat for energy supplementation. Once the host runs out of fat, it begins using protein, thereby eventually causing cachexia, tissue-wasting, and ultimately, death.

"We have identified a factor in the sera of tumor-bearing animals that is responsible for this massive fat mobilization," Devereux said. This factor may be responsible for the irreversible fat-losing state noted in cancer patients. This, in turn, compounds cachexia.

"We haven't characterized the factor yet and we don't know what its exact components and constituents are, but we have identified its presence," he said.

In addition to these studies, Devereux and his research associates are working to develop new methods to treat cancer patients without worsening the already malfunctioning metabolism. They also are studying the mechanisms of glucose and tumor growth. Though their work in these areas still is in the early stages, the researchers said it looks promising.

As part of the tumor-growth studies, the researchers work with 2-millimeter fibro-sarcomas that have been surgically implanted in rats. They have found that they have been able to temporarily slow down tumor growth, both within the rat and in a tissue-culture setting, by injecting anti-neoplastic (anti-tumor) agents that suppress cell division.

The agents the researchers have been using are 2-deoxy-glucose, a non-energy yielding glucose analogue (an inactive compound similar to glucose but that has the opposite

metabolic effects), and a drug called Ara-C, a sugar-like anti-neoplastic agent that the tumor is unable to metabolize. "While we have not been able to prevent tumor growth completely," said Devereux, "the agents have been relatively effective in slowing down the usually rapid growth of the tumor."

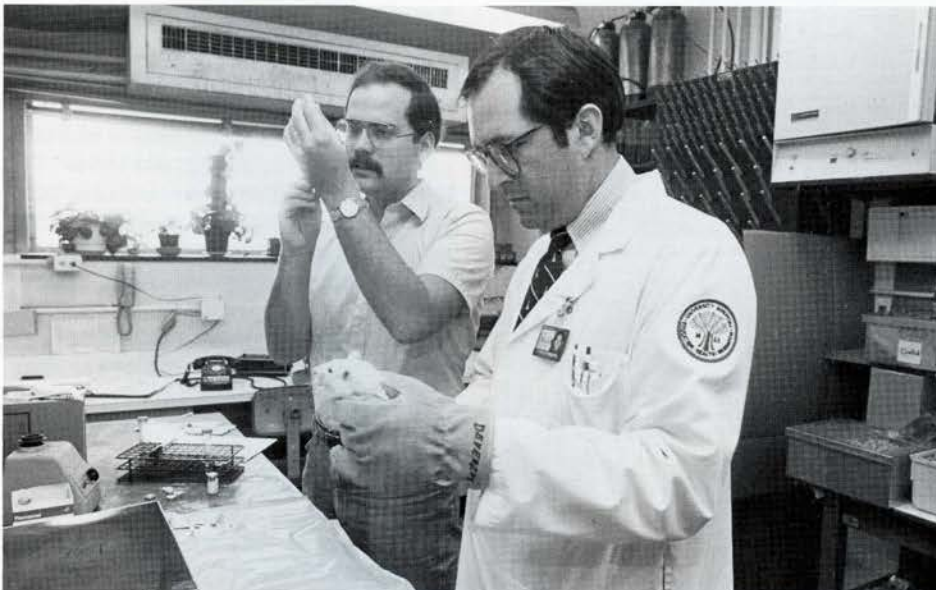
These agents are effective because the tumor cells use such large amounts of glucose that they "mistakenly" pick up these non-energy yielding compounds. The tumor cells, therefore, are not able to reproduce themselves as rapidly.

"All of this relates to the metabolic activity of the tumor itself," Devereux explained. "If the tumor were not this metabolically active—for example, picking up the sugar—then we couldn't 'confuse' it by giving it a 'poison' sugar. But it just happens that the sarcoma cell lives off the sugar and subsequently can be tricked into trying to metabolize sugar-like anti-neoplastic compounds, like 2-deoxy-glucose and Ara-C."

The decrease in the tumor growth rate, however, is only temporary. Therefore, Devereux said, the next step in the research effort is to use combinations of the 2-deoxy-glucose and Ara-C to see if the combined effects are great enough to prevent growth entirely.

"We're not dealing with a 'miracle cure' for cancer," Devereux said with cautious optimism. "But perhaps in time, we can use this as a treatment method in conjunction with other forms of treatment—like chemotherapy, radiation and surgery—and wipe out these tumors altogether."

—Heidi Paul



Dennis F. Devereux, M.D., right, and research associate David A. Hollander, M.D., conduct laboratory animal research. (Photo by Lewis Glass, Educational Media, BUSM)

#### Suggested Further Readings

1. Devereux, D., et al: The effect of tumor bearing and removal on lipid metabolism in the rat. *Surg. Forum* 33: 406-408, 1982.
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**Inner workings of cells...**  
*continued from page 1*

development, specifically those surrounding the development of the cells in the nervous system. The answers someday may help scientists solve the mysteries of such conditions as Alzheimer's disease, Parkinson's disease and cancer, and to better treat—and perhaps cure—patients with spinal-cord injuries.

"The more we learn about the nervous system through this basic research, the better chance we're going to have of understanding what goes wrong with this system," said Stephen R. Farmer, Ph.D., who has been studying cell development in the nervous system for the past seven years.

"The next milestone, or level of complexity, that scientists want to understand is the brain. There are many, many disorders that exist

within the nervous system that we don't understand," said Farmer, an assistant professor of biochemistry who is working in the Hubert H. Humphrey Cancer Research Center. The Humphrey Center is located in the School's new Centers for Advancement in Health and Medicine.

A cell is made up of a semi-permeable membrane surrounding the intracellular matrix, or the cell's skeleton. Inside of this structure is the nucleus, where the cell's genetic material is located. This genetic-coding material in the developing cell has the capability of making that cell any one of several different types.

Developing cells in the womb that eventually will make up the nervous system are located in a particular region of the embryo called the neural crest. Researchers are relatively sure that the way the cells of the neural crest develop is dependent upon the surfaces to which the

cells find themselves attached, according to Farmer.

"The cell responds to the 'signals' of its physical environment by 'turning on' particular sets of genes. This eventually determines the particular cell-type that arises," said Farmer.

Farmer is working on several levels to understand this development phenomenon. On one level, he is studying the specific effects of these external signals on the genes nestled in the developing cell nucleus.

On another level, using experiments performed on cells grown in lab cultures, Farmer is altering the surfaces on which the cells rest to determine what effect this has on the development of the cells.

"We can develop cell-culture experiments where we can isolate nerve cells and grow them in cultures," explained Farmer. "We can change their physical environment (what the cell "sits on") and then, using molecular biology and recombinant DNA techniques (measuring the activity of specific genes), we can analyze the effect that change has on the gene coding for nerve-specific functions."

Farmer also is trying to determine exactly how the cells' nuclei receive the signals from the surfaces to which they are attached.

"The cell knows what it's sitting on, but we don't know how it knows that," said Farmer.

The signals probably are transmitted physically from the extracellular matrix (the surface on which the cell rests) to the nucleus of the cell through the intracellular matrix, said Farmer.

In an effort to prove whether or not this is the case, he is working to alter with drugs the skeleton of the cells themselves to stimulate changes in the cell's development without changing the surfaces on which the cells sit. He will determine if this will elicit the same responses in the cell that occur when the surfaces are changed.

"This will enable us to see if the



Stephen R. Farmer, Ph.D., hopes his cell development studies will help solve the mysteries of such conditions as Alzheimer's disease, Parkinson's disease and cancer. (Photo by Lewis Glass, Educational Media, BUSM)

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internal skeleton is in fact the means of transmitting those signals to the nucleus," he said.

Farmer's research already has enabled him to define the genes that activate specific types of nerve-cell proteins. "We've been able to clone those genes using recombinant DNA technology and show that the production of proteins coded for by one of those genes does in fact respond to specific drug-induced changes in the cell skeleton," he said.

"Now, I'm trying to show that the gene also responds to changes in the shape of the nerve cell, brought about by growth on different surfaces," said Farmer.

Farmer hopes his basic research someday will aid in the treatment of several different types of disorders. One of the more interesting possible results of his work would be in the area of treatment of spinal-cord injuries.

"The problem with nerve tissue is that it doesn't regenerate itself as easily as other tissues," said Farmer. "There are many situations in which spinal-cord injuries and other types of lesions in the nervous system could be corrected with transplanted regions of nervous tissue."

"If we can understand more about what controls the growth of nerve cells, and if we could somehow control the growth of nerve cells, then there may be a chance that we will someday be able to do transplantation-type experiments on the nervous system," he explained.

Noting that such experiments prob-

ably will not be undertaken for many years, Farmer said if scientists can transplant early embryonic nerve cells that still have the potential to develop, and if they know what is required in that environment to stimulate that growth, then "it is not unrealistic to think that we will be able to do that sort of experiment."

Other areas in which this type of research may be able to help in the future include the understanding and treatment of such nervous system diseases as Parkinson's, Huntington's and Alzheimer's diseases.

"Cell development and cancer are very much related," said Farmer. "The more we understand about normal development and what these particular cells depend upon to bring about that normal development, the more we will understand about what goes wrong during malignant transformation."

He said that a prevalent idea among cancer researchers is that cancer cells are merely cells that revert back to an earlier developmental stage, a stage of very active growth and mobility.

"Cancers within the nervous system, neuroblastomas (tumors in the nerve cells), are quite a problem in very young children...By understand-

ing normal growth, we hope to be able to understand more about the production of cells in the nervous system that become malignant," said Farmer.

To this end, Farmer is working with co-researchers Richard M. Niles, Ph.D., an associate professor of biochemistry, and Ellen Berkowitz, Ph.D., an assistant professor of biochemistry. Their work is funded by the National Institutes of Health, and they currently are seeking more funds to expand their work.

"The more we understand basic mechanisms of growth and development of nerve cells, the better chance we will have of being able to do these new types of experiments and understand and treat the many diseases of the nervous system," said Farmer.

—Paul D. Vaskas

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