1980-06

Research in Progress: June 1980 v. 1, no. 1

Boston University School of Medicine

http://hdl.handle.net/2144/17896

Boston University
Scientists at BUSM prove benefits of exercise in primates

For years scientists have been trying to prove in laboratory experiments the generally accepted premise that exercise does help to prevent—and possibly reverse—atherosclerosis, the major cause of heart attack and stroke in humans.

Dieter M. Kramsch, M.D., and his Boston University School of Medicine research team recently completed a four-year study, funded by the National Heart, Lung and Blood Institute, that proved to be a major breakthrough in the research efforts.

The study, believed to offer the first scientific proof that exercise in cynomolgus monkeys does help to prevent atherosclerosis, was the first of its type to utilize primates.

Kramsch and his team of scientists have been conducting research for 13 years to produce atherosclerotic cardiovascular disease in cynomolgus monkeys, which have characteristics very similar to humans.

"The current consensus among leading investigators in the field is that well-regulated exercise may improve the quality of life and may help people feel better, but whether the section of the population that regularly exercises remains healthier or lives longer is not known," said Kramsch, an associate professor of medicine and an assistant professor of biochemistry at the School of Medicine.

continued on page 2

An exercising monkey in researcher Kramsch's BUSM laboratory participates in the breakthrough study. (Photo courtesy of Dieter M. Kramsch, M.D.)

Humphrey Research Center team probes the cell's crucial role in cancer

Although great strides have been made in cancer research in the past two decades, investigators are still faced with countless questions surrounding the cause, prevention, detection and ultimate cure of the disease.

Paul H. Black, M.D., the new director of the School of Medicine's Hubert H. Humphrey Cancer Research Center, has been concerned with research activities in three main areas that may answer many of those questions:

• how a normal cell is transformed into a cancer cell;
• what materials are released from the surface of cancer cells, a question whose answer may provide clues as to how cancer spreads throughout the body;
• how to create cell lines that pro-

continued on page 5
Exercise in primates...
continued from page 1

“The reason for this is that the precise influence of exercise on cardiovascular disease and its basic underlying cause, atherosclerosis (a form of hardening of the arteries), is extremely difficult, if not impossible, to establish in man,” Kramsch said. “Such investigations would require large numbers of participants over many years, the cost would be prohibitive and the outcome uncertain.”

The School of Medicine study showed that a group of monkeys that had been exercise-conditioned on a treadmill had larger hearts and coronary arteries than a group of monkeys that did not take part in the exercise program—even after eating a fat-filled diet known to cause cardiovascular disease.

“There’s no question that after the exercising monkeys ran for one hour every other day for 3½ years, their hearts and arteries definitely became larger,” said Kramsch, who reported on the study at a national meeting of the American Heart Association.

Previous studies in lower animals and birds had produced contradictory results, some even suggesting acceleration of atherosclerosis by exercise,” Kramsch explained. “Studies in primates were an obvious choice because of their closeness to man in cardiovascular anatomy and cardiorespiratory physiology, as well as their propensity to develop similar atherosclerotic cardiovascular disease under experimental conditions,” he added.

Atherosclerosis, with such principal complications as stroke and heart attack—the number one killer in the United States—represents the major cause of death in Western society. The often silent but deadly disease develops when fatty materials in the blood build up in the inner walls of the arteries. The fatty deposits thicken and harden the artery, reducing its elasticity and narrowing the path through which the blood flows. If the blood flow is cut off entirely, the organ of the body dependent on this blood supply dies.

Kramsch and his team used for their experiment 32 young adult male Macaque monkeys, which are naturally prone to developing this disease. The primates were divided into two basic categories: exercising and non-exercising.

Two groups of eight monkeys each were trained to exercise on a treadmill for an hour per day every other day for 18 months while on a low-fat control diet. Over the next 24 months, one of the exercising groups was fed a fat-filled diet known to cause degenerative changes in arterial walls, or atherosclerosis, while both groups continued vigorous exercise. The fat-filled diet contained butter and the approximate cholesterol equivalent of one egg per day.

For comparison, two additional groups of sedentary, or non-exercising, monkeys were fed the low-fat control diet for 12 months, with one group receiving the fat-filled diet for an additional 24 months while the other continued the control diet.

Postmortem studies showed that the monkeys that exercised had larger left ventricles in their hearts and wider coronary arteries than the sedentary groups.

Although both groups fed the fat-filled diet developed some deterioration in all major arteries, fewer changes were evident in the group that exercised.

“The study concluded that, in primates, exercise appears to be highly beneficial, not only for the normal cardiovascular system, but also for the prevention of atherosclerotic cardiovascular disease,” Kramsch concluded.

“The study indicated that the heart as well as the coronary and all other major arteries showed profound adaptive changes in structure, and apparently in metabolism, even with moderate physical training,” he continued.

School of Medicine faculty members working on this study with Kramsch were William B. Hood Jr., M.D., a professor of medicine; Bruce M. Abramowitz, M.D., an instructor in medicine; Anita J. Aspen, Ph.D., a research associate in the Evans Memorial Department of Clinical Research and the Department of Medicine, and Marc A. Abell, M.D., a biomedical engineer who was a research associate in those departments during the project.—Marge Dwyer

Suggested Further Readings

Study team focuses on risk factors for sudden infant death

A Boston University School of Medicine research team working with infants in the newborn nursery of Boston City Hospital has spent the last eight years looking for clues that will lead to lowering the incidence of Sudden Infant Death Syndrome (SIDS), a major cause of death in this country among infants between one week and one year of age.

The syndrome, also known as crib death because it generally strikes infants during sleep, claims approximately 10,000 lives annually and ranks second to accidents as the greatest killer of children.

Sudden infant death has its highest incidence around two to three months of age, and nearly half of SIDS victims have a mild cold at the time of death.

Jeffrey B. Gould, M.D., an associate professor of pediatrics and of obstetrics and gynecology at the School of Medicine and director of newborn services at Boston City Hospital, has studied more than 120 infants during their first three months of life to see how such key vital systems as the brain, heart and respiratory system are maintained and controlled during sleep. Gould and the researchers evaluated the development of these vital systems to see if any specific vulnerabilities in control or function occurred at the period when SIDS was the highest.

The study was one of the largest ever conducted using modern analytic and recording data of what happens physiologically to an infant during sleep. Gould is project coordinator for the Boston Perinatal Center, which is conducted by BUSM and Tufts University in cooperation with Boston City Hospital, the Boston Floating Hospital and St. Margaret's Hospital in Dorchester.

While no specific vulnerabilities in terms of physiologic control were seen at the two- to three-month peak age for SIDS, Gould's group found that during this period, sleeping patterns changed from a series of multiple short naps to a more adult-like prolonged day/night pattern. Gould therefore hypothesizes that failure to maintain accurate control over physiologic processes during prolonged sleep may be important to the pathogenesis of SIDS.

To investigate the relationship between SIDS and respiratory infections, Gould studied sleep in 54 infants who had mild upper respiratory infections.

It was found that normal infants have brief periods—usually less than 10 seconds—when they stop breathing during sleep, and those infants who stop breathing for more than 15 seconds are at risk for SIDS.
"We found that normal infants, or those not considered at high risk for SIDS, decreased their normal amounts of stop-breathing periods when they had a cold. But abnormal infants, those who have had near-miss or aborted SIDS episodes, experienced an increased amount of stop-breathing episodes, or sleep apnea, during mild upper respiratory infections," he said.

Gould and his associates concluded that decreased sleep apnea in a normal infant during a mild cold may serve as a protective mechanism that leaves the child less vulnerable to sudden infant death. "We now have a fairly clear picture of what normal development of sleep in an infant looks like during the first three months of life when the majority of sudden infant deaths occur," Gould said.

"The next stage of the research will be to develop a physiologic risk-assessment technique based on what we know now to see if we can actually predict which infants in the high-risk category are likely to die of SIDS and then monitor them," he explained.

Because of the unique interdisciplinary approach the research team has taken in this study, at times more than 20 scientists from a wide variety of departments within the University have been involved in the project. Gould said that one of his goals is to attract even more people into the research.

In addition to Gould, the basic research team includes Austin Lee, Ph.D., an associate professor of biostatistics in the Department of Pediatrics at the School of Medicine and an associate professor of mathematics at Boston University, and Suzette Morelock, Ed.M., a pediatric research assistant at the School of Medicine, working under a contract from the National Institutes of Health.

Because twins are believed to be at high risk for SIDS, 40 sets of twins were among the infants studied by Gould and the team. "There are many examples of twins, identical as well as fraternal, dying of sudden infant death syndrome on the same day," Gould said.

The twins were matched with other infants to compare and evaluate their breathing patterns during sleep, physiologic characteristics and other pertinent factors by using computer analysis and sophisticated mathematical analysis. The infants were also compared on the basis of economic status, race and sex risk factors for SIDS.

For example, it is known that, in addition to twins, SIDS more often strikes blacks, males and premature infants than singletons, non-blacks, and female term infants.

"Using all these risk factors, we divided the babies into high risk and low risk for SIDS and looked for a difference in brain activity, heart rate and breathing rate. We found that almost every one of these physiologic factors appears to be different in the high-risk and low-risk infants," Gould said.

Gould and the researchers now are trying to develop a way of determining which infants are at risk of developing the syndrome based on such factors as their breathing patterns during sleep, gestational age, weight, family history and relationship to a sibling who has had SIDS.

The goal is to develop a method of screening infants at risk so that they can be monitored during the crucial first months of life, and to devise intervention techniques to prevent the syndrome from occurring.—Linda Lotridge Levin

Suggested Further Readings

Cell’s role in cancer...
continued from page 1

duce specific antibodies in the test tube, a process that could lead to a source of human antibodies that could be used in the diagnosis of cancer.

What causes normal cells to become cancerous? Black, who is chairman of the Department of Microbiology at the School of Medicine, said chemicals in the environment, various types of radiation, and, perhaps, certain viruses can all cause a cancerous change in cells.

"It is also known that these agents affect the hereditary apparatus, or the genes of the cell, and cause changes that affect the cell's behavior and result in cancer," Black explained.

"For example," he continued, "when a person is exposed to a carcinogen in the environment, the normal DNA, or the genetic material, is altered. In other words, a mutation has occurred, and the cell's growth pattern has been permanently changed.

"Unlike the normal cell, the altered cell does not know when to stop multiplying," Black explained. "It will divide continuously, which is the striking characteristic of cancer."

By deregulating the cell's DNA in controlled laboratory experiments, Black and his staff hope to gain insight into how the growth of a normal cell is disturbed and cancer occurs.

When viruses interact with cells, the virus may kill the cell, and disease is the consequence. This occurs with such viruses as poliovirus or the influenza virus. However, the oncogenic, or cancer-inducing, viruses interact with cells and produce cancer cells. Such an interaction can occur in vitro, or in the test tube, a process that the investigators can observe.

"We have been studying the changes in these transformed cells," said Black. "Recently, individual proteins have been identified that are responsible for making the cells cancerous. This is a striking achievement. It immediately suggests that if one knew the identity and function of such a protein, one would gain invaluable insight into the mechanisms of change.

"Recent experiments have disclosed the function of this protein," Black continued. "It is an enzyme that carries out a chemical reaction whereby phosphorus is added to a protein. Thus, the nature and identification of the change in certain cancers, in biochemical terms, is now better understood."

Changes occurring on the surface of cancer cells offer further insight into the cancer puzzle. One such change is called shedding, a phenomenon in which materials are released from the cell surface. Some of these substances are catalytic enzymes that may be involved in the breakdown of tissues when cancer cells separate from the primary tumor mass and spread throughout the body.

Some materials found on the surface of normal cells and in the substance between cells, the matrix, are adhesion molecules. These materials maintain intercellular connections and prevent the random movement of cells. However, when a cell becomes cancerous, the adhesion molecules are released from the surface, enabling the cell to escape from the tumor mass. This is another way in which
cancer cells invade surrounding normal tissues, enter the bloodstream and lymphatic channels, and migrate to distant sites in the body, a phenomenon called metastasis.

The molecules released from the cancer cells may also block the body's natural immune system, which is composed of cells that should destroy the foreign cancerous tissue. This may help to explain why tumors are able to grow despite the fact that there is a natural immunity system or host immunity.

"We are interested in studying these released substances because, if detected early, they would provide a diagnostic test for the presence of cancer," said Black. "Moreover, such tests could also be valuable in determining whether cancer has recurred or the extent to which it has spread."

Black and researchers at the Hubert H. Humphrey Cancer Research Center also are studying drugs and biological materials that prevent the release of the surface components from the cancer cells. "We have found that Interferon and certain drugs can prevent shedding. The same drugs and Interferon also have an anti-cancer effect. The prevention of the release of some proteins or glycoproteins from the cancer cell surface might result in the destruction of the cancer by the host immune system," Black explained.

Creating in the test tube cell lines that can produce a specific antibody is another avenue being investigated by Black and his staff.

Antibodies, which combine with such antigens as bacteria and viruses, protect an individual against those foreign substances. They may also be produced against tumor antigens, which are found on cancer cells and can be used as an early diagnostic test for cancer.

Antibodies against tumor antigens present in human colon cancer have recently been produced by researchers at the Cancer Research Center. By combining antitumor drugs with such antibodies, Black explained, one could deliver specifically to the cancer cell these drugs, thereby sparing the normal cells.

"The creation of cell lines that will grow indefinitely in a test tube, and that produce a human antibody continuously, provides us with a valuable means to fight certain viral diseases as well as cancer," Black said.

"What we at the Hubert H. Humphrey Cancer Research Center hope to do," he continued, "is to be the final common pathway for all of the cancer-related activities at Boston University Medical Center, such as basic and clinical research and clinical cancer care. We hope to bridge the gap between the cause and prevention of cancer and to offer new insight into the treatment of cancer patients."

—Susan B. Saperstein

Suggested Further Readings