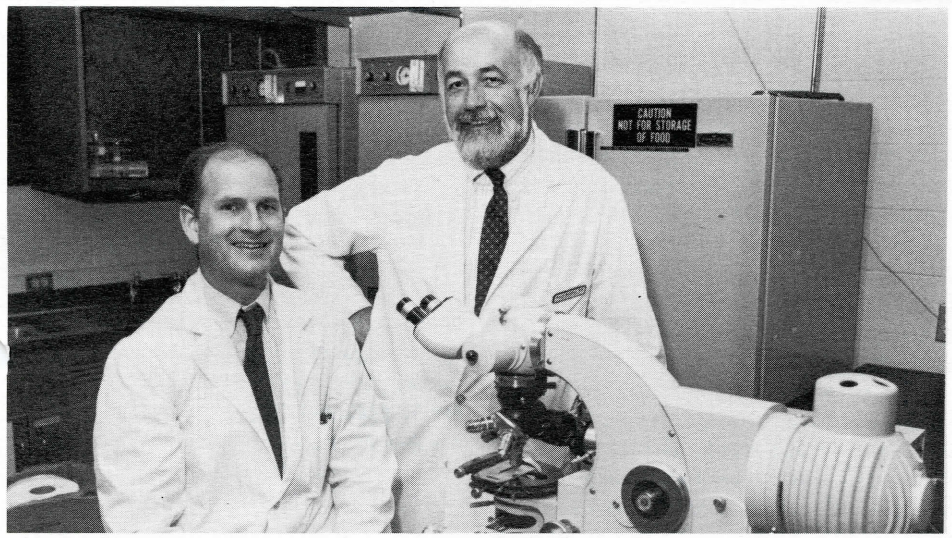
1988

Humphrey Center News: Fall 1988 v. 3, no. 2

Humphrey Center
NEWS
A PUBLICATION OF THE HUBERT H. HUMPHREY CANCER RESEARCH CENTER OF BOSTON UNIVERSITY
Volume 3, Number 2 Fall 1988



Ronald McCaffrey, M.D., right, and Zachary Spigelman, M.D., have discovered that a drug used to combat AIDS also appears to kill certain leukemia cells. (Photo by David Keough)

Humphrey Center researcher finds anti-AIDS drug may benefit some leukemia patients

A new way to combat a deadly form of leukemia—acute lymphoblastic leukemia—may be emerging from studies of an experimental drug to combat acquired immune deficiency syndrome (AIDS). The studies are being conducted by Humphrey Cancer Research Center member Ronald McCaffrey, M.D., and his associates at the University Hospital, a principal teaching affiliate of Boston University School of Medicine.

During research on the anti-AIDS agent dideoxyadenosine (ddA), a medical resident working with Dr. McCaffrey observed that the drug killed cultures of certain types of acute leukemia cells.

"This killing effect of ddA potentially holds great promise for leukemia patients," says Dr. McCaffrey, who heads the UH Section of Medical Oncology and is a professor of medicine at the School. "However, its effect on leukemia cells is distinct from its anti-AIDS action."

Such compounds as ddA and AZT (the only anti-AIDS drug currently approved by the federal Food and Drug Administration) are chemical variants (analogues) of natural substances used by cells to build DNA, the genetic material needed for cells to reproduce, explains Dr. McCaffrey. In the case of AIDS, the virus mistakes AZT for the natural substance thymidine. The use of AZT instead of thymidine stops the synthesis of DNA and the virus is unable to reproduce.

"Our question was: Are there any other enzymes that can be fooled in the

continued on page 3

Cholesterol: A new weapon against cancer?

For years, physicians have advised patients to cut down on cholesterol in their diets in order to lower their blood cholesterol levels and, consequently, their risk of clogged coronary arteries.

However, studies have shown that low cholesterol levels sometimes are associated with the development of bowel cancer, according to Selwyn A. Broitman, Ph.D., a researcher at the Hubert Humphrey Cancer Research Center and a professor of microbiology at Boston University School of Medicine. In studying this dilemma, Dr. Broitman and his associates may have discovered a way to use the tumor cells' need for cholesterol to control the spread of this prevalent form of cancer.

Ten years ago, Dr. Broitman noticed that when laboratory animals with high cholesterol levels were put on low-cholesterol diets, their cholesterol levels fell, but they also developed many more bowel tumors than animals fed normal diets. Similarly, epidemiologists at the Boston University-Framingham Heart Study found that people with cholesterol levels below what is considered normal (below 180 milligrams percent in the blood) were four to five times as likely to develop bowel cancer as people with above-normal cholesterol levels (above 220 milligrams percent).

According to the researcher, people from countries with diets rich in fat and cholesterol show a high incidence of both coronary artery disease and bowel cancer.

"However, an analysis of these

continued on page 2

Cholesterol

continued from page 1

populations reveals that a certain number of people with high cholesterol levels develop heart disease, while another proportion, who do not have high cholesterol levels, develop bowel cancer," says Dr. Broitman. "Instead, their cholesterol somehow gets shunted out through the large bowel and contributes to the development of bowel cancer."

He is quick to point out that an increased risk of bowel cancer is associated only with abnormally low levels of cholesterol—in other words, under the 180mg percent in the blood.

"Reducing cholesterol levels from 250 to 200mgs, for example, by a combination of diet and drugs, probably is good for your heart and is not likely to increase the risk of colon cancer," he explains.

Still the question remains: Why would low levels of cholesterol be associated with bowel cancer at all?

Dr. Broitman and his associates have worked with bowel tumors in rats and found that these tumors actively absorb cholesterol from the blood, much more than normal, noncancerous tissue. When these experiments were repeated with human bowel cancer cells, however, the researchers found that none of the cancer cells picked up cholesterol.

Dr. Broitman and postdoctoral student Michelle Fabricant, Ph.D., reasoned that possibly the human tumor cells did not pick up cholesterol because they lacked low density lipoprotein (LDL) receptors on their surfaces. (LDL is the form in which cholesterol gets ferried from the blood into cells.)

"Many types of cells and tissues—liver, adrenal glands, ovaries, fibroblasts (the cells that cause scars)—have LDL receptors that can trap cholesterol for their use. These cells do not have to make cholesterol themselves but can extract it ready-made from the bloodstream," explains Dr. Broitman.

In fact, Dr. Fabricant was able to show that none of the human tumor cell lines studied had LDL receptors. This led to the conclusion that if tumors were unable to use cholesterol from the blood, and therefore had to manufacture it themselves, it might be possible to destroy tumor cells by cutting off their internal synthesis of cholesterol.

"This was a very important finding for us," says Dr. Broitman. "All cells have to make some cholesterol, as structural components for their membranes and other cell products, and there now is available a variety of drugs that can stop this synthesis. One is Lovastatin, recently licensed by the Food and Drug Administration to lower blood cholesterol levels." Lovastatin causes the liver to stop making cholesterol and begin using cholesterol available in the bloodstream.

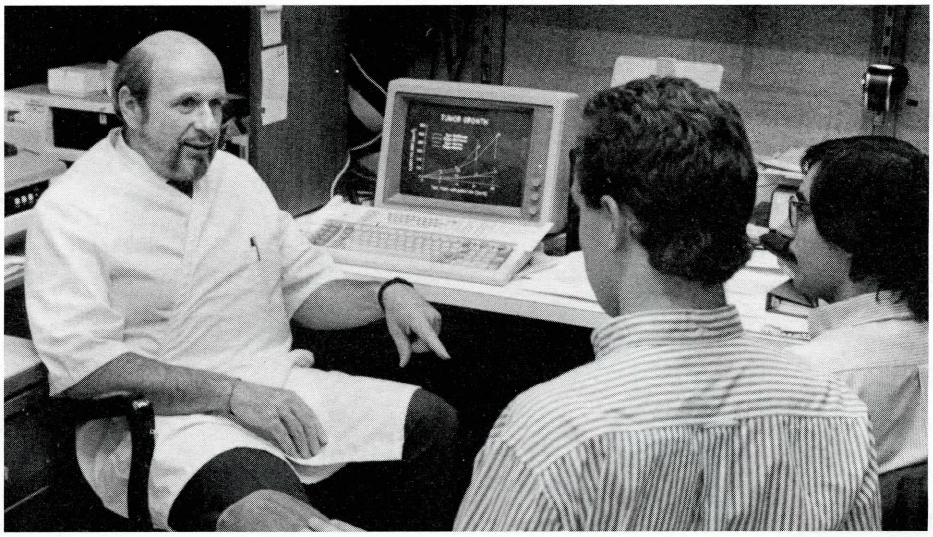
Drs. Broitman and Fabricant have shown that tumor cells given Lovastatin do indeed die as a result. On the other hand, when Lovastatin was given to normal, noncancerous cells, these cells sprouted LDL receptors and started to take it in from the blood to get around the drug block.

According to Dr. Broitman, if a bowel tumor has spread (metastasized) to the liver, where the drug is concentrated, the new tumor might be controlled by giving the patient Lovastatin. The drug would prevent the new tumor from growing but not injure the healthy liver cells.

"This could be a relatively benign procedure for controlling metastatic lesions," he says. Fifty percent or more of people who undergo surgery for bowel cancer ultimately have metastatic lesions.

Dr. Broitman, hopes to begin patient trials of Lovastatin soon. He and his research group also are looking at other types of tumors for the presence or absence of LDL receptors, which might render the cancers susceptible to similar control.

"It is not yet known whether other tumors, such as breast tumors, also lack LDL receptors. We are just beginning to look into it," he says.



Selwyn Broitman, Ph.D., left, is studying how a number of fats, including cholesterol, affect the development of bowel cancer. He discusses his research with technician Wells Wilkinson and M.D. - Ph.D. student Frank Cannizzo. (Photo by Bradford F. Herzog)

QUESTIONS...

Answer to question on back panel.

A. Studies have shown that the chances of developing colon, breast, prostate, gallbladder, ovarian and uterine cancers all are increased for people who are 40 percent or more overweight. But the cancer risks associated with obesity are really an extension of the cancer risks of high-fat, high-cholesterol diets in general.

Fat acts as a cancer promoter, shortening the amount of time it takes a carcinogen (such as cigarette smoke) to transform a normal cell into a cancerous one. All of us may have some cells transformed by a carcinogen, but the process is so slow we are more likely to die of old age or other causes before the cancer becomes evident. In the presence of a promoter, this cancerous transformation of cells is accelerated and the tumor manifests itself much sooner.

It is not yet clear how fat acts as a promoter. Some researchers suggest it is a nutrient for cancer cells, others believe it acts as an oxidative agent that interferes with normal cell functioning. While research in this area has a long way to go, it is clear that by reducing the total amount of fat in your diet, you can reduce your risk of developing certain cancers.

Leukemia

continued from page 1

same way," says Dr. McCaffrey, whose laboratory does research on the enzymes that put together and take apart DNA.

As part of an AIDS research project, the National Cancer Institute (NCI) in Washington, D.C., asked Dr. McCaffrey and medical resident Zachary Spigelman, M.D., to test a number of analogues against a variety of DNA-making enzymes and assess how readily an enzyme accepted an analogue in place of the natural substance.

"To do a comprehensive study we included an enzyme called TdT, which is found in some acute leukemia cells," says Dr. McCaffrey, who discovered TdT some 17 years earlier while working at the Massachusetts Institute of Technology. For years, scientists have been puzzled as to the function of this enzyme and, until now, did not know whether it controlled any vital process in leukemia cells.

The researchers were surprised to find that TdT could and did use ddA instead of natural DNA building blocks. As a result, all DNA building was stopped. According to Dr. McCaffrey, when ddA was introduced into cultures of leukemia cells, those cells that contained the TdT enzyme were killed within 72 hours. The same killing effect was seen in fresh leukemia cells taken from newly diagnosed patients, he says.

Drs. McCaffrey and Spigelman determined that the killing of leukemia cells by ddA was due to the presence of TdT within the cells. The analogue interacts with TdT in such a way that the DNA of the cells is broken into fragments and the cells die. "Essentially, TdT is fooled by ddA in the same way a different enzyme in the AIDS virus is fooled by AZT," explains Dr. McCaffrey.

TdT is found in acute lymphoblastic leukemia cells; the other form of acute leukemia, called acute myeloblastic leukemia, does not contain TdT. As a result, ddA had no effect on cells of this form of leukemia. Acute lymphoblastic leukemia accounts for nearly 90 percent of childhood leukemia and about 25 percent of adult leukemia.

According to Dr. McCaffrey, although nearly 70 percent of childhood cases of acute lymphoblastic leukemia can be cured with existing therapies, these treatments are toxic and very painful.

"There is a genuine need for a new therapy that is more gentle," he says. "And there is still the 30 percent of children with the disease who die, not to mention the adult cases, which, although less common, nearly always are fatal. We think ddA, or a derivative, ultimately may be a new way to treat these patients."

The hitch to using ddA as therapy for acute lymphoblastic leukemia immediately is the amount needed to kill the leukemia cells, which is about 25 times higher than the amount of ddA needed to stop the AIDS virus.

"We think the amount of ddA needed is much too high for clinical use. We have been trying to find a derivative that would be effective at smaller concentrations," says Dr. McCaffrey.

In fact, the researcher has designed a compound that works at one-hundredth the dose of ddA. "Although the data are still preliminary, the results look promising and the NCI is fast-tracking its development. The intent is to get this into clinical patient trials as soon as possible," he says.

Dr. McCaffrey credits the intensive AIDS research effort as a significant factor contributing to the observations on ddA and TdT. In fact, he says, the anti-leukemia effect could be a major "spinoff" of AIDS research.

"When the public demand for intensified AIDS research first began," says Dr. McCaffrey, "it was predicted that findings would result that could lead to the treatment of other diseases, especially in the area of cancer. This anti-leukemia effect of ddA is the first instance of that happening."

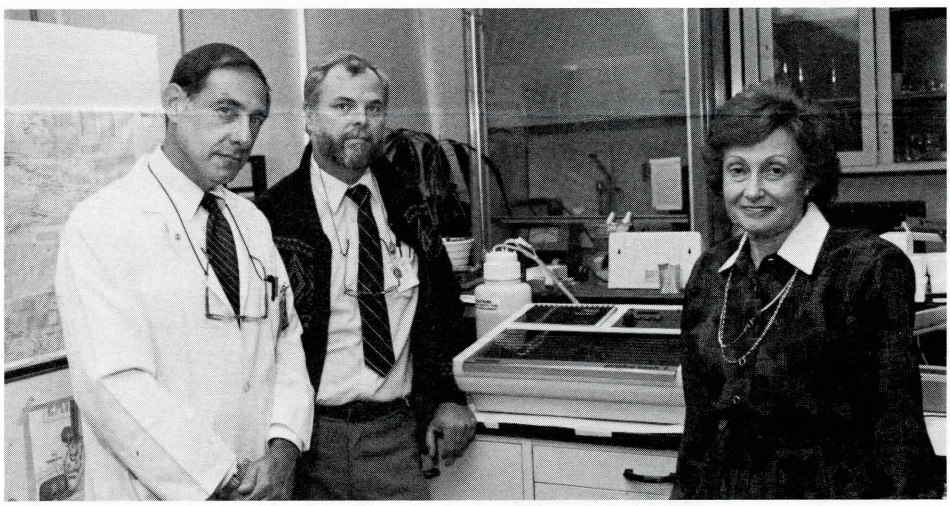
IN BRIEF

Howard Koh, M.D., an assistant professor of dermatology and medicine at BUSM and an assistant professor of public health at the School of Public Health, recently received a five-year, $350,000 Preventive Oncology Academic Award from the National Cancer Institute. He will use the funds to continue his research on the early detection and prevention of skin cancer, especially malignant melanoma.

In addition, Dr. Koh is the co-author of a new American Cancer Society brochure called "Living with Cancer: A Multicultural Experience." The booklet was produced in five languages and presents general cancer information and stories of people from various ethnic groups who have survived cancer.

Elinor Levy, Ph.D., an associate professor of microbiology, recently received a new incubator and flow hood to be used in her research on the suppression of the immune system by retroviruses, such as the ones that cause AIDS and certain leukemias, and on how these viruses interact with the central nervous system.

The equipment was purchased for Levy by Aid for Cancer Research, an organization of women from the greater Boston area who raise funds to support the fight against cancer.



Humphrey Center member Richard Neiman, M.D., far left, chief of the Hematopathology Section of the Mallory Institute of Pathology, was among cancer researchers at Boston University Medical Center who recently received new laboratory equipment donated by Aid for Cancer Research. Dr. Neiman and his associates will use the Probe-Tek Automated Southern Blot Analyzer to detect molecular changes in cancer cells before they can be recognized by routine immunologic or microscopic methods. Shown with Dr. Neiman are hematopathology fellow George Wade, M.D., Ph.D., and Florence Litchman, chairman of the ACR presentation committee. (Photo by David Keough)

CANCER NOTES

CANCER NOTE: Cancer of the colon and rectum is the second most prevalent type of cancer in this country after lung cancer. Three quarters of colorectal cancer cases can be cured if the disease is discovered before it spreads to other areas of the body.

The American Cancer Society recommends three tests for the early detection of colorectal cancer: an annual digital rectal examination after age 40; an annual stool blood test after age 50; and a sigmoidoscopic examination every three to five years after age 50, once you have had two annual sigmoid exams with negative results.

CANCER NOTE: It is estimated that one in 10 women eventually will develop breast cancer. The majority of breast cancers initially are found by women examining themselves. Although all lumps should be checked by a physician, a breast lump does not necessarily mean cancer. Roughly four-fifths of breast lumps biopsied turn out to be benign.

CANCER NOTE: Fifty percent of all human cancers are curable today by surgery, radiation therapy, chemotherapy or a combination of these treatments.

CANCER NOTE: People who smoke have a 10-times greater chance of developing cancer than people who do not smoke. Roughly 30 percent of cancer deaths are related to smoking.

The Humphrey Cancer Center News is published for the Hubert H. Humphrey Cancer Research Center of Boston University School of Medicine by the Office of Publication Services, Boston University Medical Center. *Humphrey Center Director,* Herbert H. Wotiz, Ph.D.; *Editors,* Denise Maguire and Michael Rabin; *Writer,* Caroline H. Lupfer. "Cancer Notes" information is provided courtesy of the American Cancer Society.

Are obesity and cancer related?

ANSWER ON PAGE 2

Address Correction Requested

HUBERT H. HUMPHREY CANCER RESEARCH CENTER
BOSTON UNIVERSITY SCHOOL OF MEDICINE
80 EAST CONCORD STREET
BOSTON, MASS. 02118

Nonprofit Org.
U.S. Postage
PAID
Boston, MA
Permit No. 56031