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*Boston University*

# Humphrey Center NEWS

A PUBLICATION OF THE HUBERT H. HUMPHREY CANCER RESEARCH CENTER OF BOSTON UNIVERSITY

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## Humphrey Center researcher looks for clues to cancer causes in bacterial DNA

As technology advances and with it the increasing danger of exposure to harmful chemicals, scientists continue to be intrigued by the suspected relationship between environmental toxins and cancer. Members of the Hubert H. Humphrey Cancer Research Center are looking for clues to the cause of cancer in the DNA of bacteria. According to Patricia L. Foster, Ph.D., an assistant professor of environmental health at Boston University School of Public Health, understanding how chemical carcinogens induce mutations may shed light on the origins of cancer.

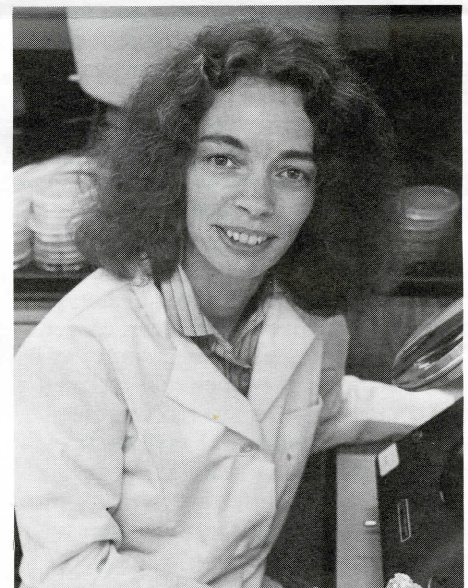
"When animals or cells are exposed to a carcinogen, this carcinogen interacts with and causes damage to the DNA, and is one of the initiating events that eventually leads to cancer," explains Dr. Foster. "I am involved in studying what types of damage occur in bacteria when they are exposed to various chemicals, how the organism responds to them and what the consequences are."

Dr. Foster works primarily with the bacterium *Escherichia coli*. Bacteria act as ideal models to study because they respond to chemical carcinogens by developing mutations, although they do not actually develop cancer. Other advantages of using bacteria as models are that so much knowledge already exists about bacteria, and researchers can manipulate them in various ways. "It's a much simpler system," says Dr. Foster. "We can learn a lot more about what's going on a lot faster."

The research procedure is relatively simple. Dr. Foster generates bacteria that have various defects in their abilities to

repair their DNA, and then exposes them to a particular carcinogenic agent. The endpoint is to document what mutations in the cells result. "Because I know exactly which enzyme is not working, I can figure out step-by-step the entire pathway, from exposure to final mutation," says Dr. Foster. "When this knowledge is put together with the biochemistry of the agent and the biology of other organisms, you can begin to understand the effect of this particular compound. For instance, if human beings have the same enzyme in their livers, they might be able to handle exposure to the same chemical compound."

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Patricia L. Foster, Ph.D., at work in her lab.  
(Photo by Bradford F. Herzog)

## Possible link found between oral contraceptives, breast cancer

Since oral contraceptives became widely available in the 1960s, researchers have conducted numerous studies to explore whether using oral contraceptives increases the risk of breast cancer. A recent study conducted by Hubert H. Humphrey Cancer Research Center investigators at Boston University School of Medicine suggests that women under the age of 45 who use oral contraceptives may be at increased risk.

The senior investigators of the study are Samuel Shapiro, M.B.B.Ch., a research professor of public health (epidemiology) and director of Boston University School of Medicine's Slone Epidemiology Unit, and Lynn Rosenberg, Sc.D., an associate professor of public health (epidemiology) and as-

sistant director of the Unit. Donald Miller, Sc.D., is the first author of the study, which was completed while he served as an epidemiologist with the Slone Unit. The results were made public at a recent federal Food and Drug Administration hearing on breast cancer and oral contraceptives, and were published in the February issue of the *American Journal of Epidemiology*.

"Any study published now on this subject is controversial, because the findings of the different studies not only conflict with each other, but later findings from continuing studies conflict with earlier findings," says Dr. Rosenberg. "Our study has *continued on page 2*

## Contraceptives

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been in progress since 1976. We have published twice before on the data, and in each case, the results were null. Our most recent data are positive. The same thing has happened in an ongoing study conducted in Great Britain, where earlier results were null and recent results were positive."

The case-control study was conducted to assess the relationship between the use of oral contraceptives and the risk of breast cancer in women under the age of 45. The researchers compared cases and controls from hospitals in Boston, New York, Philadelphia and Baltimore. The 407 cases were women aged 25 to 44, with a diagnosis of breast cancer made no more than six months before admission, and with no previous history of cancer. They were compared to 424 controls, women within the same age range, who were admitted for nongynecologic, nonmalignant conditions judged to be unrelated to oral contraceptive use, and with no history of cancer.

To provide information on the relationship between oral contraceptives and the risk of breast cancer, the investigators estimated the relative risk of breast cancer. "We were interested in comparing the risk of breast cancer in women who had used oral contraceptives to the risk in women who have not used them," says Dr. Rosenberg. "If the relative risk equals one, that means there is no difference in risk." In estimating relative risk, the researchers took into account "confounding" variables. These variables, which included age, life-style, geographic area, reproductive history and year of interview, might have distorted a relationship between oral contraceptive use and breast cancer.

In the earlier studies, the researchers found that the histories of oral-contraceptive use of the cases and controls were very similar. In the recent study, the cases were more likely to have used oral contraceptives for longer durations than controls. This translated into an estimated relative risk of 2.0 for women who have used oral contraceptives for less than 10 years, while for those women who had used oral contraceptives for 10 or more years the estimated relative risk was 4.1. The latter estimate was based on small numbers of women, however. "If these results are correct, this implies that the risk of breast cancer is doubled, or more, in oral-contraceptive users as opposed to nonusers," says Dr. Rosenberg.

Dr. Rosenberg adds that the hypothesis that oral contraceptives may cause breast

cancer has become so well known to the general public that researchers must consider so-called "information bias" as an explanation of positive findings. "Since many of the women with breast cancer whom we interview may know the hypothesis, they may be more likely to search their memories and provide more complete information than controls. Even if the hypothesis is not known, cases might remember better or differently than the controls. Medical records of contraceptive use in the distant past do not exist, and we have had to rely on patients' memories of oral contraceptive use. Information bias cannot be ruled out."

Drs. Shapiro and Rosenberg are continuing to pursue additional information by initiating further studies. "We are analyzing a large existing data base on older cases and controls, women aged 45 to 59, to see whether oral contraceptive use and breast cancer are associated in this age group," says Dr. Rosenberg. "We also are continuing the study from which the data on these and younger women were collected. Thus, we will be studying further younger and older cases and controls."

Drs. Shapiro and Rosenberg also hope to conduct a follow-up study of young women who would have had the opportunity to use oral contraceptives at younger



*Lynn Rosenberg, Sc.D., continues to study the relationship between the 'pill' and breast cancer. (Photo by Bradford F. Herzog)*

ages. Dr. Rosenberg believes further studies of breast cancer and contraceptive use are urgently needed. "The positive studies have raised some concern and there is a growing consensus for the need to support further research," she says.

## IN BRIEF

**Ann Aschengau, Sc.D.**, a member of the Hubert H. Humphrey Cancer Research Center and an assistant professor of public health at the School of Public Health, is the principal investigator of a two-year, \$500,000 study on the causes of elevated cancer rates in permanent residents of upper Cape Cod. The study is funded by the Massachusetts Department of Public Health.

According to the most recent statistics, the overall cancer rates in the towns of Barnstable, Bourne, Falmouth, Mashpee and Sandwich are 17 percent higher than the statewide norm. The researchers will study 1,200 cancer cases reported in the area between 1982 and 1985, along with 1,500 controls from the same geographic area. Seven types of cancer will be studied: breast, colon-rectal, lung, bladder, kidney and pancreatic, as well as leukemia.

A number of possible factors will be explored, including exposure to air and water pollution; radio waves generated by a nearby military radar facility; electromagnetic radiation from powerlines and transformers; and such lifestyle factors as smok-

ing and alcohol use. Although data will not be released until the end of the study, public meetings will be held to inform concerned residents of the study's progress.

Humphrey Center member **John R. Murphy, Ph. D.**, a professor of medicine, biochemistry and microbiology and chief of biomolecular medicine at the University Hospital, is the principal investigator of a five-year, \$2.3-million cooperative agreement from the National Cancer Institute (NCI) to continue to study a new class of drugs that attacks specific leukemias and lymphomas. The cooperative agreement award is part of the new NCI-sponsored National Cooperative Drug Discovery Group program, which encourages interaction among academic and commercial interests in partnership with the NCI to discover new strategies for the treatment of cancer.

Also involved in the study is Hubert H. Humphrey Cancer Research Center member **Ronald McCaffrey, M.D.**, a professor of medicine and chief of medical oncology at the University Hospital, as well as researchers at Beth Israel Hospital and Brigham and Women's Hospital in Boston.

## DNA

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Dr. Foster's research involves the use of several chemicals that are known carcinogens, and she is studying their effect on *E. coli* DNA. She chooses the chemicals in her research for two reasons. One is that many serve as good models and are easy to handle in the laboratory; another is that they are important environmental carcinogens. The chemicals under study include aflatoxin and insecticide ethylene dibromide (EDB).

"Aflatoxin is produced by a fungus that grows on rice, corn and peanuts under hot and humid weather conditions," explains Dr. Foster. "Apparently, last summer much of the corn in the Midwest was infected. There now is some concern that the aflatoxin levels in the corn may be too high for human consumption." While until now aflatoxin has not been a major problem in the U.S., it is a major health issue and has been suspected as a primary cause of liver cancer in other parts of the world, including China and Africa.

Dr. Foster was the principal investigator in a recent study published in *Mutation Research* on the mutagenicity of the EDB to *E. coli* DNA and how the bacteria repair the damage. "This pesticide now is banned from use in this country, but we still import fruit that has been treated with EDB," she warns. "We already knew that this chemical is extremely potent. Our recent findings indicate that even though the bacteria do not have the enzymes to metabolize EDB the way that humans do, the compound still is highly mutagenic to the bacteria. Another important aspect of EDB that we have discovered is that under certain circumstances, the bacteria do not readily repair the damage caused by the chemical because the damage stays hidden from the cells. This means that the chemical may be more dangerous than we previously thought. These findings would not have been uncovered if we were working with a higher organism."

Another chemical substance being studied by Dr. Foster is the chemotherapeutic agent cis-diamminedichloroplatinum-II (cis-Pt). Since chemotherapeutic agents themselves are carcinogenic, she is working to uncover how to improve its chemotherapeutic qualities and reduce its carcinogenicity. This would be particularly beneficial for children who receive chemotherapy as treatment for leukemia and may develop cancer later on as a result of this exposure.

Dr. Foster emphasizes that a major focus of her research is the pursuit of basic



*Humphrey Center member Arnold E. Reif, D.Sc., second from left, a research professor of pathology, recently received a \$7,000 grant from Aid for Cancer Research (ACR) to support his research on the immunogenicity of tumors for use in experimental immunotherapy. Shown here with Dr. Reif, from left to right, are ACR members Phyllis Frank, Naomi Wainer, Lois Weinman and Cheryl Bloom, president. ACR is a volunteer group made up of 25 women who raise funds to help support cancer research in the Boston area. (Photo by David Keough, Educational Media, BUSM)*

knowledge about the bacteria, which may shed light on DNA damage and repair systems. "The more we find out about the way these organisms work, the more we will ultimately understand. Basic research is important."

The next step is to apply this information to higher organisms, including humans, in order to learn more about the origins of cancer. "My feeling is that the kinds of damage that arise in DNA are not specific to any particular organism," says Dr. Foster. "There is quite a bit of experimental evidence indicating that the DNA is essentially the same and the kinds of DNA damage you see in bacteria are exactly the same as those in higher organisms. So the research is aimed at understanding what damage there is and how the damage is repaired." This is important, she adds, because much of the DNA repair activity is the same in bacteria as in mammals.

## QUESTIONS...

*Answer to question on back panel.*

**A.** There are over 5,000,000 Americans alive today who have a history of cancer, 3,000,000 of whom were diagnosed five or more years ago. Most of these 3,000,000 can be considered cured, while others still have evidence of cancer. The term "cured" means that a patient has no clinical evidence of the presence of cancer and is considered to have the same life expectancy as a person who never had the disease.

The decision as to when a patient may be considered cured is one that must be made by the physician after examining the individual patient. For most forms of cancer, five years without symptoms following treatment is the accepted time. However, some patients can be considered cured after one year, others after three years, whereas some have to be followed much longer than five years.

**CANCER NOTES**

**CANCER NOTE:** Some cancers, not all, can be prevented. Most lung cancers are caused by cigarette smoking, and most skin cancers by frequent overexposure to direct sunlight. These cancers can be prevented by avoiding their causes. Certain cancers caused by occupational-environmental factors can be prevented by eliminating or reducing contact with carcinogenic agents.

**CANCER NOTE:** More than 500,000 cases of skin cancer are reported each year, the vast majority of which are highly curable basal or squamous cell cancers. The most serious skin cancer is malignant melanoma, which strikes

about 27,000 persons each year. The incidence of melanoma is increasing at the rate of 3.4 percent per year.

**CANCER NOTE:** Improvements in cancer treatment have made more conservative surgical management of some cancers possible. In the early stages of cancer of the larynx, many patients have been able to retain their larynx and their voice; in colorectal cancer, fewer permanent colostomies are needed, and the surgery required in many cases of breast cancer often is more limited.

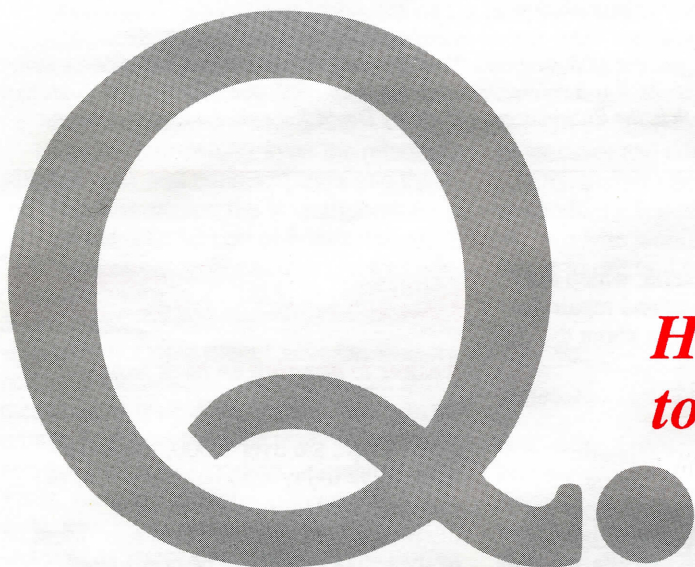
**CANCER NOTE:** The American Cancer Society recommends eating more high-fiber foods, such as whole grain cereals, fruits and vegetables. Studies suggest that diets high in fiber may help

to reduce the risk of colon cancer. Furthermore, foods high in fiber content are a wholesome substitute for foods high in fat.

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*How many people alive today have ever had cancer?*

ANSWER ON PAGE 3

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

