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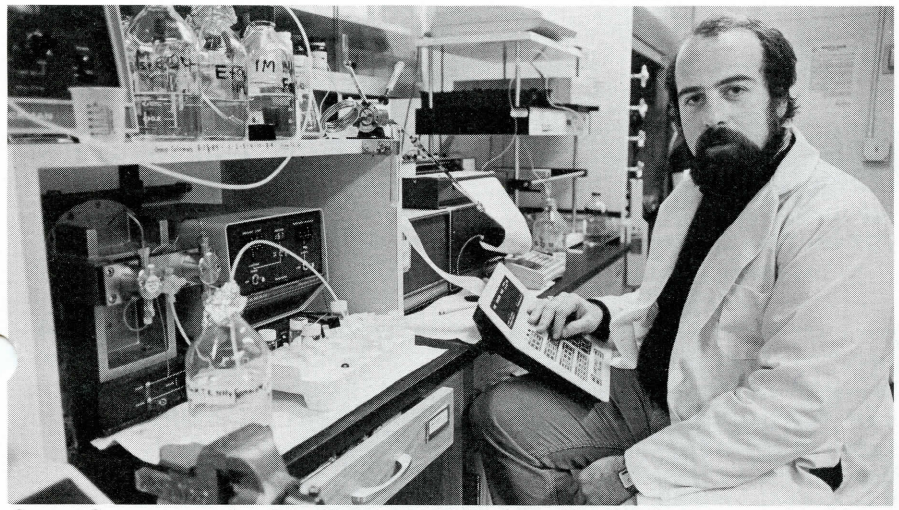


Cancer Center researcher John Groopman, Ph.D., is studying how environmental toxins cause cancer. (Photo by Bradford F. Herzog)

Research on Aflatoxin Yields New Test, Possible Protective Measures Against a Potent Carcinogen

Not all cancer research at the Hubert H. Humphrey Cancer Research Center takes place entirely in the laboratory. An example is the recent work on the agricultural contaminant, aflatoxin, by Cancer Center researcher John Groopman, Ph.D., which has taken him from farms in the United States to remote villages in China and Africa.

A principal focus of Dr. Groopman's studies has been on the role of aflatoxin in the development of liver cancer. Aflatoxin is a potent carcinogen produced by certain molds that commonly contaminate a variety of agricultural crops. Although the incidence of liver cancer is relatively low in this country, it is practically endemic in some areas of the world, perhaps because so much of the grain consumed in those regions is heavily contaminated with aflatoxin. Aflatoxin poisoning of livestock, grain and milk supplies has a deleterious effect on local economies everywhere.

Approximately 100 aflatoxins and related compounds exist in nature and all of them must be distinguished and quantified in order to make a connection between them and cancer. For the past several years, Dr. Groopman and his colleagues have concentrated on developing an accurate, high-speed screening test for the presence of aflatoxin in any sample, including grains, milk and urine. Their efforts led to the development in 1986 of the Aflatest Mycotoxin Testing System, which has been described by Dr. Groopman as a "revolutionary advance" in the field.

"Aflatest is a one-step purification procedure that can detect and measure

continued on page 2

Special Center Facility Provides Essential Services for Cancer Researchers

Successful research at the Hubert H. Humphrey Cancer Research Center depends not only on the inventiveness of its investigators but also on essential support laboratories, such as the Hybridoma Facility, which provide equipment and technical expertise that an individual laboratory may not have.

The Hybridoma Facility of the Cancer Center has been in operation since the Center opened five years ago, and is available to all Center investigators and other researchers at Boston University Medical Center who are interested in producing monoclonal antibodies for their research projects.

"Our people depend on the Facility to support their research. These kinds of specialized laboratories are expensive but absolutely essential to our work," says Herbert Wotiz, Ph.D., director of the Center. Dr. Wotiz' own group, one of several that currently has projects under way at the Facility, is developing monoclonal antibodies for hormone research.

The Facility is directed by Ann Marshak-Rothstein, Ph.D., an assistant professor of microbiology and public health (environmental health), and is staffed by Rachel Ettinger, senior laboratory technician. It is Ms. Ettinger who consults directly with the client laboratories to design the protocols for developing the antibody of choice. Each laboratory using the Facility is respon-

continued on page 3

Research on Aflatoxin
continued from page 1

minute amounts of aflatoxin in five minutes in the field instead of two days in the laboratory, which was the case with the previous existing methods,'' says Dr. Groopman, who also is an associate professor of public health (environmental health) and an assistant professor of microbiology at the School of Medicine. (Aflatest is patented and being manufactured by a Medford, Mass., firm.)

Like so much current research on cancer diagnosis and treatment, the Aflatest approach utilizes monoclonal antibodies, which were developed in the Hybridoma Facility of the Cancer Center (*see related story*). Dr. Groopman and his colleagues were able to develop various monoclonal antibodies—molecular probes that tightly bind to a specific target chemical—for different aflatoxins. ''Aflatest relies on the direct measurement of the inherent physical properties of the aflatoxin molecule, not on an indirect measure as in other tests,'' explains Dr. Groopman.

Dr. Groopman has been testing the new procedure over the last four years in epidemiologically designed studies of aflatoxin exposure in areas of China and Africa in an attempt to link the toxin to liver cancer incidence. He is hoping that the procedure soon can be implemented in this country to test milk supplies at the individual farm level, before they are mixed at collection centers.

A chemoprotective agent?

Using Aflatest to further his studies on aflatoxin, Dr. Groopman now is working on ways to intervene with a variety of chemical compounds to ameliorate the effects of aflatoxin exposure. He believes that aflatoxin may cause cancer by damaging the DNA of cells, which then leads to tumors. Sulfur-containing compounds known as antioxidants may prevent this genetic disruption in the first place and thereby protect against the harmful effects of aflatoxin exposure. Experiments with rats given a variety of antioxidants such as ethoxyquin showed a much lower incidence of tumors after aflatoxin exposure.

The biochemical explanation of this observation, according to Dr. Groopman, is that the antioxidant causes an increase in the level of a particular enzyme important in ridding the body of many toxic substances, including aflatoxins. If the antioxidant is removed, the enzyme level drops again. In addition, in controlled experiments there was a 95-percent reduction in the incidence of original DNA mutations in animals that were treated with the antioxidant before exposure to aflatoxin. And if there is less DNA damage to begin with, there will be fewer tumors, says Dr. Groopman.

Ethoxyquin, and certain other commercial antioxidants often used in packaged foods to preserve freshness, are highly toxic in large doses and are, therefore, impractical to use as therapeutic agents. Instead, Dr. Groopman is concentrating on a synthetic compound known as oltipraz, which has shown some promise.

''Because its toxicity is so much less than other antioxidants and because it also suppresses initial DNA adduct formation (mutation) we have high hopes for it as a chemoprotective agent against aflatoxin exposure,'' said Dr. Groopman at a recent meeting of industry executives held at the School of Medicine.

Dr. Groopman believes in the importance of trying to develop drugs that have chemoprotective qualities, which could have major applications in animals. For example, in developing countries cows that have to eat grains contaminated with aflatoxin could be protected from those contaminants; if the cows don't get sick, not only does milk production increase but the milk supplies are rid of contaminants as well. However, much more work is necessary before such therapies can be put into effect.

ACR Treasurer Carol Epstein, left, ACR member Janet Libin, center, and ACR President Roberta Shlager recently presented Center researchers Richard Miller, M.D., Ph.D., second left, and Thomas Rothstein, M.D., Ph.D., with equipment for lymphocyte research. (Photo by Lucy Milne, Educational Media, BUSM)

Aid for Cancer Research Embarks on 40th Year

The Fall of 1987 marks Aid for Cancer Research's 40th year of raising funds to help support cancer research in the greater Boston area. This small, nonprofit, totally volunteer and completely independent group of 28 women has raised more than $1.5 million for cancer research over the last 39 years.

Aid for Cancer Research was one of the first donors to the Humphrey Center and their seed money, provided to the Center when it first opened, has been followed by gifts every year since. Their primary fundraising activities are an annual luncheon and fashion show (attended by 1,200 to 1,500 people) and an ongoing memorial and other-occasion fund. All monies raised by the group are distributed with the counsel of a volunteer medical advisory board.

The group's gifts include one or two yearly research fellowships, equipment and outright funds, according to ACR spokeswoman Elaine Klubok. In 1986, ACR gave the Humphrey Center more than $12,500 to purchase needed equipment. In 1987, several researchers have benefited from the group's efforts.

A sample of what ACR funds have provided the Center include a Zeiss micromanipulator and microinjector and a Narashige micropipette puller for Judith Campisi, Ph.D., an assistant professor of biochemistry, to facilitate her work on oncogenes. Funds also were given to Richard Niles, Ph.D., a professor of biochemistry and surgery, and Stephen Farmer, Ph.D., an associate professor of biochemistry, for a laser-scanning densitometer to analyze and compare DNA and RNA sequences from normal and cancer cells; for a bacteriological shaker to grow bacterial cultures that contain recombinant DNA that are used in the above analyses; and most recently, for a Zeiss tissue culture microscope with a special optical device that

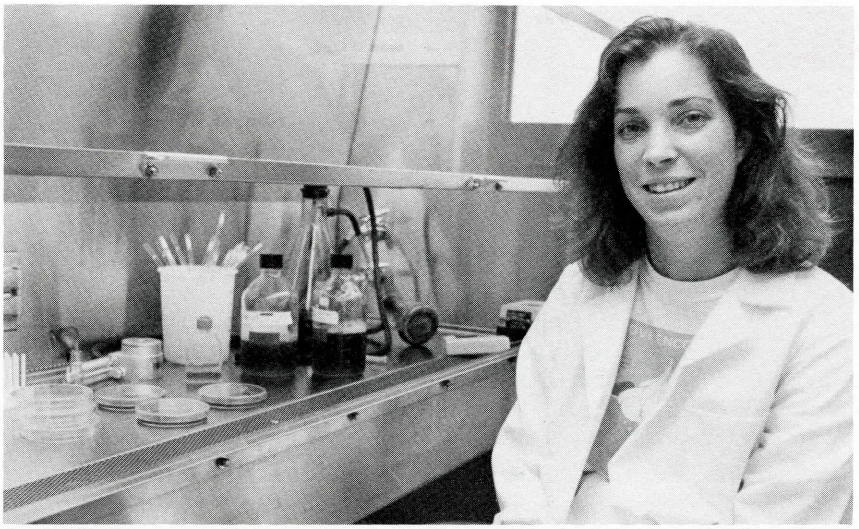
continued on page 3

Special Center Facility
continued from page 1

sible for immunizing mice with the particular antigen they are interested in and for developing a screening procedure to test whether antibodies have been raised against this particular agent. All tissue-culture procedures involved in the production of monoclonal antibodies are then carried out by Ms. Ettinger.

The procedure sounds straightforward: First, researchers immunize a mouse by injection with a particular agent. The mouse then begins to produce antibodies to that antigen. When enough of a response has been observed, cells from the spleen are mixed with a myeloma cell line in culture to form hybridomas. Some of these hybridomas will produce the desired antibody in perpetuity. The best antibody for the particular antigen is selected and cloned to produce the raw material for the investigator's experiment.

"Sometimes an antigen is very immunogenic, that is, you get a response from the mouse in just a couple of months. You can then go ahead and fuse the antibody cells with a tumor cell line and grow the clones for another two months and then you're ready to do whatever experiment the investigator wanted," explains Ms. Ettinger. "Sometimes, though, the animals don't respond to the antigen for six months to a year, or maybe never. All you can do is try a different animal species or protein carrier."



Rachel Ettinger, senior laboratory technician, at work in the Hybridoma Facility of the Humphrey Cancer Center. (Photo by Domenic Screnci, Educational Media, BUSM)

Ms. Ettinger is adept at dealing with setbacks of this sort and often employs a variety of biomolecular tricks to obtain the desired antibody. One of the most successful tasks she has had so far was in helping to produce monoclonal antibodies for research on chemical carcinogenicity being conducted by John Groopman, Ph.D. (*see related story*). In this project, antibodies to many forms of aflatoxin were produced and the result has been a highly successful new test for the presence of this dangerous contaminant. And recently, Ms. Ettinger has carried out work for Cancer Center member Paul Pilch, Ph.D., an associate professor of biochemistry at the School of Medicine, to produce antibodies that can recognize cell vesicles that have been stimulated by insulin as opposed to non-stimulated ones.

The usefulness of the Hybridoma Facility to the work of the Cancer Center can be seen in the steadily growing number of projects that are awaiting Ms. Ettinger's attention. Typically she has as many as five procedures going at any one time, all at different stages of progress.

"Without such a facility," remarks Dr. Wotiz, "it would be much more difficult to get on with a lot of our work here."

Aid for Cancer
continued from page 2

allows cells to be viewed in three dimensions rather than just flat sections. In addition, the group purchased a BioGuard Laminar Flow Hood for Se-Kyung Oh, Ph.D., an assistant professor of microbiology.

"We cannot underestimate the importance of this sort of volunteer effort," says Center Director Herbert Wotiz, Ph.D. "Aid for Cancer Research's consistent support of our work means a great deal to us and the fight against cancer, and we are very grateful."

Aid for Cancer Research has announced a new two-year fellowship available for cancer investigators. The fellowship, to be awarded in the spring of 1988, will be for $22,000 to $22,500, according to ACR. Deadline for applications is Dec. 31. For information, write to ACR at 25 Liberty Street, Natick, MA, 01760.

QUESTIONS...

Answer to question on back panel.

A. The good news is that some cancers, which only a few decades ago had a very poor outlook, today are being cured: acute lymphocytic leukemia in children, Hodgkin's disease, Burkitt's lymphoma, Ewing's sarcoma (a form of bone cancer), Wilms' tumor (a kidney cancer in children), rhabdomyosarcoma (a cancer in certain muscle tissue), choriocarcinoma (placental cancer), testicular cancer, ovarian cancer and osteogenic sarcoma. Other cancers, however, have not yet yielded to effective treatment and are the focus of continuing research.

The diagnosis and treatment of cancer has become increasingly individualized. Early detection is followed by a more precise description of stages and the use of more than one kind of therapy, often in combination. An outstanding example of progress is the improvement in the management of testicular cancer in young men. More precise diagnostic tools and staging allow a better selection of treatment. The use of combinations of cancer drugs has resulted in remarkably improved survival. In 20 years, the five-year survival rate of testicular cancer rose from 63 percent to 88 percent.

Q. ***Can Cancer be prevented?***

A. Some cancers can be prevented but not all. Most lung cancers are caused by cigarette smoking and most skin cancers by frequent over-exposure 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 NOTES

CANCER NOTE: Research has shown there is no such thing as a "safe" cigarette, but that those who are not yet able to quit are well advised to switch to brands with the lowest possible tar and nicotine content. Moreover, low T/N smokers find it easier to quit altogether than high T/N smokers. Remember that in addition to harmful tar and nicotine, cigarette smoke contains a number of poisonous gases such as hydrogen cyanide and carbon monoxide—possibly a critical factor in coronary heart disease and fetal growth retardation.

CANCER NOTE: The incidence of uterine cancer in 1987 was estimated to be 48,000 new cases, including 13,000 cases of cervical cancer and 35,000 cases of endometrial cancer, or cancer of the uterus. Overall, the death rate from uterine cancer has decreased 70 percent during the last 40 years, due mainly to Pap tests and regular checkups.

CANCER NOTE: Oral cancer can affect any part of the oral cavity from lip and tongue to mouth and throat. Incidence is more than twice as high in men as in women, and is most frequent in men over age 40. Cigarette, cigar and pipe smoking, use of smokeless tobacco, and excess use of alcohol are all risk factors for the disease.

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What is the good news about cancer today?

ANSWER ON PAGE 3

Address Correction Requested

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