1991

Humphrey Center News: Spring 1991 v. 6, no. 1

Humphrey Center NEWS

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

Volume 6, Number 1 Spring 1991

Center's outgoing director believes today's research will yield key strides against cancer

Herbert Wotiz, Ph.D., outgoing director of the Hubert H. Humphrey Cancer Research Center, says his 40 years in cancer research have left him hopeful about ultimate victory but conscious that progress has proven slower than expected.

The research community's record is marked by some major achievements, he notes. Childhood leukemia had a very high rate of mortality until chemotherapeutic treatments for it emerged in the 1960s and 1970s. "Now," says Dr. Wotiz, "70 percent of the kids affected are saved."

In his own area of interest—breast cancer—there have been important advances, too. The drug tamoxifen, which blocks hormone action on cancer cells and so inhibits tumor growth, is another success story.

Dr. Wotiz notes that he has had personal experience of the benefits such agents can bring. "I had a relative with metastatic breast cancer who was one of the early beneficiaries of tamoxifen," he notes. "She was treated with it, and lived a comfortable and productive life for 10 years after being diagnosed with cancer."

Dr. Wotiz concedes that, overall, progress against the disease—especially such common forms of it as lung and colon cancer—has been modest. Yet he's convinced that the major advances being made in laboratories such as those of the Humphrey Cancer Research Center will soon start having a major impact on cancer treatment.

He notes that there have been key steps forward in the study of oncogenes—altered genes thought to be heavily involved in causing tumor growth. Important findings about the immune system and about specialized hormones like tumor necrosis factor (see story at right) also are encouraging, he says. Some of the recent discoveries being made in the laboratory, moreover, are already being put to use in caring for cancer patients, he notes.

Herbert Wotiz, Ph.D., outgoing director of the Cancer Research Center, will remain involved with the Center's research activities.

He believes, however, that some of the work now being done at the Cancer Center and its counterparts around the world will dwarf the contributions that modern biology has made to cancer care up to now. He

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Researcher probes a hormone that destroys tumors

An important achievement of biomedical research in recent years is the discovery of a hormone that can destroy certain tumors.

The hormone, tumor necrosis factor (TNF), is a protein made by specific white blood cells. It was given its name after scientists found that, when added to tumor cells in the test-tube or administered to animals with cancer, it will kill off a variety of tumors.

The discovery of TNF's effects on tumors initially stirred excitement among cancer researchers, says Deborah E. Dobson, Ph.D., a researcher at the Hubert H. Humphrey Cancer Research Center. Efforts to use the hormone as an anti-cancer drug, though, have been impeded by the fact that TNF has multiple activities, some of which cause serious side effects.

One effect is that TNF acts on normal fat and muscle tissue as well as on tumor cells. And that, in turn, reflects the ability of TNF to fight off invasions by tumor cells or microbes by mobilizing the energy that the body stores in the form of lipid (fat) inside fat cells.

While that's obviously a useful role, it can be harmful if carried to extremes. In fact, Dr. Dobson says, it appears that that's what happens to many cancer patients. The body, in response to the continued presence of tumor cells, keeps on making TNF. The hormone, acting

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Dr. Wotiz

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says, for example, that the studies of oncogenes and their counterparts, anti-oncogenes—genes that suppress both normal and abnormal cell growth—should lead to major inroads against the disease. "With any luck, we're going to see meaningful applications of the discoveries about oncogenes and anti-oncogenes within a very few years," he says.

If in fact there is important further progress against cancer in the near future, it would mark a major change from the situation that existed when Dr. Wotiz entered the field.

In 1950, having nearly completed his doctoral work in chemistry at Yale, he joined the Boston University School of Medicine. (The School had not founded the Cancer Center at that point.) He says he was delighted for the chance to conduct research on cancer.

"My dad, though he wasn't a scientist, had read a lot about science, and he encouraged me to work on cancer," recalls Dr. Wotiz. "He recognized even then that biochemistry could have a major impact on our understanding of the disease."

At the time Dr. Wotiz was launching his career, the treatment of cancer was characterized by approaches that had little basis in scientific understanding. Though physicians knew, for example, that there was a connection between certain types of hormones and breast cancer, they didn't know which patients would benefit from what type of hormonal treatment.

And that was not the only problem, says Dr. Wotiz. In the 1950s, many women were afraid to seek treatment. The reason, he says, was that cancer was regarded as a kind of curse or punishment, so that those who contracted the disease were often deeply ashamed of the fact.

Convinced that he could help improve the scientific basis for the treatment of cancer, Dr. Wotiz began what became a lifelong series of studies of the disease and related areas. Over the years, this work led to numerous contributions to our understanding of a range of issues, including how hormones work. His group showed, for example, that hormones such as estrogen and testosterone are not only altered in the liver, as was known, but also in the organs that they act on.

In later studies, the scientists showed that such hormones don't work effectively unless they're acting on a structurally complete cell—a discovery linked with the findings that eventually led to tests showing which breast cancer patients are likely to benefit from hormone-modifying treatments like tamoxifen.

While remaining active in research, Dr. Wotiz found himself increasingly involved in efforts to coordinate cancer research at the School of Medicine. "In the early 1970s, there was an informal group of people involved in cancer work," he recalls. "We'd talk to each other about the problems that needed to be solved, but there was no organized cancer effort."

That group, however, formed the nucleus of what is now the Hubert H. Humphrey Cancer Research Center. Set up in 1974, it has been headed since 1984 by Dr. Wotiz.

High quality scientific work

The outgoing director, who has seen the Cancer Center develop its capabilities in such emerging areas as the study of oncogenes, says it has been an exciting time to head the enterprise. Particularly rewarding, says Dr. Wotiz, has been the chance to work with the Center's young scientists, some of whom joined the Center during his tenure as director. "We've gotten very high marks for the quality of our scientific work," he says, "and the junior people in the Center have had a lot to do with that."

Dr. Wotiz says he's delighted at the choice of his successor, Dr. Douglas Faller. He noted that the new director has the qualities needed to ensure that the Center continues to make important contributions to the struggle against cancer. "The fact that he's both a physician and a scientist is going to help keep the Cancer Center's scientific work closely tied in with patient care," says the outgoing director.

Dr. Wotiz also praises the Center's financial supporters, saying that they have been and will continue to be critical to its success. "Without their backing," he notes, "we wouldn't have been able to make nearly as much progress as we have at this Center."

As for himself, he says he hopes to remain involved in the field. In fact, it's more than a hope. The scientist notes that his former lab, which currently is directed by Dr. Abdul Traish, recently has produced monoclonal antibodies—immune-system molecules that all come from a single type of cell—that show promise of aiding in the diagnosis of breast cancer.

Douglas V. Faller, M.D., Ph.D.

Physician-scientist named new director of Cancer Center

Douglas V. Faller, M.D., Ph.D., a physician-scientist who is deeply experienced in both patient care and research into the nature of cancer, is the new director of the Hubert H. Humphrey Cancer Research Center.

Dr. Faller, previously a faculty member at Harvard Medical School and a senior staff member at Boston's Children's Hospital and the Dana-Farber Cancer Institute, was named to his new post by Aram V. Chobanian, M.D., dean of the Boston University School of Medicine.

Dr. Faller's background includes a long history of treating both child and adult patients with cancer. Named vice chairman of the University Hospital's Division of Medicine as well as head of the Cancer Center, Dr. Faller says he plans to give high priority to enhancing the way cancer care is delivered.

"I hope to simplify and facilitate the continuum of patient care as much as possible, so it is seen by the patient as loving and considerate," he says. The new director also plans to give priority to cancer prevention, with outreach programs for the community neighboring Boston University Medical Center.

As a scientist, Dr. Faller has made numerous contributions to our understanding of how cancer emerges and spreads. Among his key discoveries is the fact that tumor-causing viruses have ways of disarming a cell's own defenses, allowing the virus to reproduce itself more readily.

Dr. Faller earned his Ph.D. in cancer viruses and cell biology at Massachusetts Institute of Technology, and received his medical training at Harvard. A complete profile of the new director will appear in the next issue of *Humphrey Center News*.

TNF protein

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like a traffic light that's always green, keeps signaling fat cells to release energy until all the lipid is used up. Then, TNF causes skeletal muscle cells to break down their proteins in order to continue to keep up with the body's energy demands. The result is a wasting condition called cachexia.

Dr. Dobson says cachexia imposes a terrible burden on those affected. "They become very gaunt due to severe progressive weight loss and they have no energy," she explains.

Exploring effects on genes

Although TNF's effects on healthy cells have limited its potential as a drug, Dr. Dobson says the hormone would still be useful if its activities in the body could be selectively manipulated. "You'd like it to keep on destroying tumor cells," she says, "but not let it attack healthy fat and muscle cells."

Dr. Dobson is exploring the workings of fat and skeletal muscle cells, research that may set the stage for new treatments for both cachexia and cancer. Right now, Dr. Dobson's goal is to find out how TNF acts on these cells. She's doing so by studying its effects on certain genes.

"There's a particular gene that's critical to the manufacture of lipids by fat and muscle cells," she says. "The idea is to figure out how TNF turns off genes like this. Then, we can ask, 'Okay, can we reverse this? Can we start the process of making lipids again?'"

Dr. Dobson and her associates have made progress toward identifying the specific stretch of DNA that serves as the on-off switching point for this gene, glycerophosphate dehydrogenase (GPD). Once that goal is reached, the researchers will move on to studies of the mechanisms that relay the message from the blood-borne TNF to fat and muscle cell genes such as GPD.

One question the reseachers ultimately want to help answer is whether it's possible to custom-design a new form of TNF. "Can we create a form of it," asks Dr. Dobson, "that acts on immune cells—because these cells attack tumors—but not on fat or muscle cells?"

The answer to that question is still a long way off. Still, Dr. Dobson says she feels privileged to be doing some of the work that eventually may provide it. "I really appreciate the Cancer Center's support," she says. "Without that, we simply wouldn't have gotten very far at all."

eborah E. Dobson, Ph.D., is investigating how the protein TNF affects fat and skeletal muscle cells.

Tax Tips

If you itemize your tax deductions, you can claim charitable gifts, like your gift to the Hubert H. Humphrey Cancer Research Center. You may also want to consider supporting the Cancer Center through a planned gift. A planned gift benefits the Cancer Center and usually results in income and a charitable tax deduction for the donor. Planned gifts include:

- **Pooled Income Fund**—similar to a mutual fund. Your gift provides an income, a charitable tax deduction, and avoids capital gains on a gift of appreciated securities.
- **Charitable Gift Annuity**—a contract between the donor and the University that provides a stream of income and a charitable tax deduction. Best for donors age 70 and over.
- **Deferred Gift Annuity**—similar to a charitable gift annuity except that the payments are deferred to a future date. A great idea for donors age 30 to 55. Provides income at retirement and a charitable tax deduction today.
- **Appreciated Securities**—a gift of appreciated securities provides you with a charitable tax deduction and avoids capital gains taxes. Most blue chip stocks pay a return of only two to four percent and if sold create capital gains or consequences. Your gift of securities to a charitable remainder trust or to the pooled income fund enables you to obtain a greater return, avoids capital gains taxes, and provides a charitable tax deduction.

For more information on planned giving, please check off the planned giving box on the enclosed reply card and return it in the self-addressed envelope.

Cancer Center researcher leads studies of new therapy for chemotherapy-linked nausea

Paul J. Hesketh, M.D., has had the pleasure of seeing his research efforts improve the quality of life of many of his own cancer patients. In addition, he can look forward to the prospect of his work benefiting many thousands of such patients around the world.

The experience grew out of Dr. Hesketh's lead role in a patient trial of a new drug, ondansetron, for the nausea caused by chemotherapy. The drug, says the Hubert H. Humphrey Cancer Research Center member, turned out to be highly effective in curbing such side effects.

"We looked at the rate of emesis—vomiting—during the first 24 hours after patients started chemotherapy," he notes. "More than half the patients taking ondansetron had no emesis at all."

Follow-up studies have shown that ondansetron works better and has fewer side effects than another anti-emetic currently in wide use. And Dr. Hesketh is now involved in a major new study to see whether using ondansetron in combination with other drugs—a typical approach in dealing with chemotherapy-linked nausea—will boost the drug's effectiveness still further.

The effort to find better anti-nausea drugs reflects the fact that chemotherapy's benefits often come at a high cost in illness and discomfort. Nausea is one of the most serious of such side effects. "It's the thing that patients have heard about from friends and family members," says Dr. Hesketh, "and it's the thing they ask about the most."

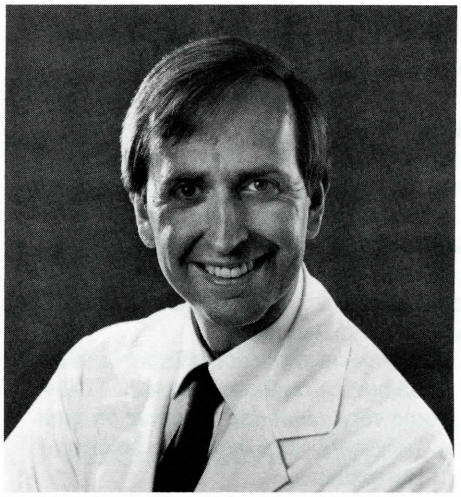
Medical science has developed a range of ways to treat such nausea. The use of combinations of agents has been especially effective. Still, problems remain. For one thing, some of the anti-nausea drugs in use have their own troublesome side effects. More serious is the fact that even combinations of drugs don't work in all cases.

"For at least a third of patients undergoing chemotherapy," notes Dr. Hesketh, "emesis remains completely uncontrolled."

In rare instances, the condition may be so bad that the patient affected drops out of treatment. "It can be a tragedy when that happens," says Dr. Hesketh, "especially when you're dealing with a highly curable condition like cancer of the testes."

Among chemotherapeutic agents, the widely used drug cisplatin is one of the most likely to provoke nausea. Starting four years ago, Dr. Hesketh and his Humphrey Center associates, along with oncologists at other medical centers, began a patient trial of ondansetron's effectiveness in curbing cisplatin-induced illness.

Most of the 85 patients enrolled in the trial had either lung cancer or head-and-neck cancer. They were given ondansetron starting just before they received their first dose of cisplatin. Then, their conditions were monitored over a 24-hour period—the critical span in terms of therapy-related nausea.



Paul J. Hesketh, M.D., led trials of a drug that improves the quality of life for many cancer patients.

Not only did the drug eliminate vomiting for the majority of patients, but it also spared many of them any feelings of nausea. In addition, says Dr. Hesketh, there was less of the drowsiness that often accompanies standard anti-emetics.

"The patients were alert, they were up and around, they were able to eat," he notes. "That could be very useful as we move more and more toward administering chemotherapy on an outpatient basis."

The oncologist says it has been gratifying to do work that is having such visible effects on the lives of many individuals. "This is a small step, but I believe a quite significant one in terms of improving the quality of life for patients undergoing chemotherapy," he notes.

CANCER NOTES

CANCER NOTE: New approaches to drug therapy use combinations of chemotherapeutic drugs, or chemotherapy plus surgery or radiation. New classes of agents are being tested for their effectiveness in treating patients whose disease is resistant to drug therapies now in use.

CANCER NOTE: A genetic fusing of cancer cells with normal cells can produce disease-fighting monoclonal antibodies (specific antibodies tailored to seek out chosen targets on cancer cells). Their potential in the diagnosis and treatment of cancer is under study.

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

CANCER NOTE: Hyperthermia is a way to increase the heat or temperature of the entire body or a part of the body. It is known that heat can kill cancer cells. A cell temperature of 45° centigrade kills cancer cells. A temperature of 42° to 43° centigrade makes the cell more susceptible to damage by ionizing radiation (x-rays). Studies are under way to learn if hyperthermia can increase the effect of radiation chemotherapy.

The Humphrey 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.; *Editor,* Denise Maguire; *Writer,* Richard P. Anthony. Photographs by Kal Zabarsky, David Keough, Bradford Herzog, and Kathy Joyce. "Cancer Notes" information is provided courtesy of the American Cancer Society.