



THE WAR



A nationally prominent OU researcher offers a status report and a wake-up call for Oklahomans.

BY JUDITH WALL
OU Health Sciences Center
Public Affairs

photos by TERRI JENNINGS

Survival rates for cancer in this country would dramatically improve if all patients received the best standard treatment for their disease, says prominent cancer geneticist John J. Mulvihill.

Mulvihill points to childhood leukemia as a shining example of what can be accomplished with medicine's current cancer-fighting arsenal—surgery, radiation therapy and chemotherapy. He believes that childhood leukemia is being managed in the United States the way all cancers should be.

"It is absolutely astonishing that over the past three decades, the survival rate for childhood leukemia has increased from 30 percent to about 70 percent with no new agents for treat-

cancers how doctors and hospitals can cooperate and make a difference in survival rates," says Mulvihill, who was featured last summer in an ABC presentation on cancer.

"As we continue to search for better cancer treatments, we need to be sure that the most up-to-date cancer treatment is truly available to every citizen in Oklahoma," he insists. "Just doing that would make an enormous difference in survival rates."

Mulvihill's concern is well taken. Cancer is overtaking heart disease as the biggest killer of Americans. While many victims are elderly, cancer is the second largest killer of children and a major cause of premature death in younger adults.

AGAINST CANCER

OPPOSITE, top left: The arrival last year of John J. Mulvihill to occupy the Kimberly V. Talley/Children's Medical Research Institute Chair in Genetics and to head the genetics section at Children's Hospital of Oklahoma signals OUHSC's intention to become a major contributor in the research and treatment of cancer and genetic disorders.

OPPOSITE, top right: John Mulvihill, right, stops to talk with Ruprecht Nitschke, former chief of the hematology/oncology section at Children's Hospital, who was instrumental in the creation of the Jimmy Everest Center for Cancer and Blood Disorders in Children.

OPPOSITE, bottom: OU pediatric oncologist William Meyer, director of the Children's Hospital of Oklahoma's Jimmy Everest Center, examines 5-year-old Zachary Cruse, whose medulloblastoma was diagnosed in February 1998 and is now in remission. The cure rate for his stage of medulloblastoma is at least 70 percent.

ment being introduced," says Mulvihill, who holds OU's Kimberly V. Talley/Children's Medical Research Institute Chair in Genetics and heads the genetics section at Children's Hospital of Oklahoma.

This amazing turnaround in survival rates occurred because nearly every child with leukemia is treated with the nationally recognized treatment plan—or *protocol*—usually at specialty centers of excellence, such as the Children's Hospital of Oklahoma Jimmy Everest Center for Cancer and Blood Disorders in Children, directed by OU pediatric oncologist William Meyer. In addition, national protocols also are used for the treatment of other childhood cancers, including neuroblastoma, sarcoma and Wilms' tumor of the kidney.

The situation is quite different for adults, whose care frequently does not follow a nationally recognized protocol, Mulvihill points out. Nationwide, only 6 percent of cancer patients are on a research protocol, and he believes the rate is even lower in Oklahoma.

"Yet, over and over again, we have shown with the treatment of childhood

"When compared to other diseases, the burden of cancer is huge, both in lost years of healthy life and the cost of diagnosis and treatment," he says.

As a nationally respected cancer geneticist, Mulvihill is striving to clarify the genetic origins and genetic changes that lead to the first cancer cell and the progression of those cells into a full-blown disease. His arrival last year at the Health Sciences Center is an indication that OU intends to become a major contributor in the research and treatment of cancer and genetic disorders.

"Dr. Mulvihill brings great knowledge and experience to the OU Health Sciences Center in the areas of genetics and cancer," says Joseph J. Ferretti, senior vice president and provost. "He will be a key player in advancing both of these areas as we further develop strong clinical and research programs in the state of Oklahoma."

Both a researcher and practicing physician, Mulvihill is board-certified in pediatrics and medical genetics. A former director of the medical genetics program at the National Institutes of Health, he came to OU from the Univer-

“The vast majority of adult cancer patients are denied the option of contributing to science and perhaps making a difference in the outcome of their own cancer.”

sity of Pittsburgh Graduate School of Public Health, where he founded the human genetics department.

Mulvihill is adamant in his belief that those who suffer from cancer should make certain the treatment they receive is the best available one for their disease.

Great strides have been made in care, he points out. For example, the gamma knife offers a highly focused energy beam to target cancer cells and spare the surrounding tissue.

“It is never wrong for a cancer patient to ask for a second opinion at a recognized cancer center,” he says emphatically.

His statement begs the question: What is a recognized cancer center?

“Any institution can put the words ‘cancer center’ over its door, but the moniker has gained empowerment by the federal government’s National Cancer Institute,” he responds. “It has become almost a trademark term for NCI-designated cancer institutes, which are usually located at academic medical centers.”

Mulvihill explains that such centers must meet rigorous NCI standards by offering the most advanced care possible and have an ongoing body of research.

Oklahoma does not have an NCI-designated cancer center. In fact, a vast area in the American heartland does not have one. Oklahoma adults with cancer often have to leave the state to access nationally recognized protocols or take advantage of experimental protocols.

“The vast majority of adult cancer patients are denied the option of contributing to science and perhaps making a difference in the outcome of their own cancer,” Mulvihill says.

“At the OU Health

Sciences Center, we don’t meet the whole definition of an NCI cancer center,” Mulvihill says. “Only the element for treating childhood and adolescent cancers is well established in Oklahoma. Our children are being offered the best standard of care and the option of participating in research that may exceed the standard of care.”

The OU Health Sciences Center is initiating the arduous process of establishing an NCI-designated cancer center in Oklahoma. Many at the University and throughout the state believe that striving for an NCI cancer center would be an excellent use for some of the money that will be coming to Oklahoma from the multi-state settlement with tobacco companies.

Mulvihill believes that a truly comprehensive cancer center can be created at the OU Health Sciences Center. Such a center would provide the most up-to-date care, launch further cancer research at OU and make experimental protocols more readily available to people in Oklahoma and beyond.

It also would be a source of knowledge and continuing education for Oklahoma physicians and play a leadership role in making the standard of care more uniformly applied across the state and region.

An NCI center would assure that promising new therapies would be available to Oklahomans as soon as they are approved for clinical trials. Some of these therapies are just around the corner; others, on the distant horizon. In two areas—immunology and angiogenesis—pilot work is already under way, but the science is not yet included in the standard of care.

Tremendous advances have been made in understanding the immunology of cancer, Mulvihill says. This knowledge is leading to the development of therapies that augment and build on the body’s immune system. One avenue of research involves altering existing antibodies through laboratory methods to target peculiar characteristics of cancer cells with the hope that these antibodies can overcome cancer cells and eliminate the tumor. Another approach involves introducing radioactive agents along with the antibodies, allowing them to concentrate at the cancer cell and spare normal cells.

Angiogenesis research is based on the body’s ability to form new blood vessels.



Elaine Reeves, left, clinical research associate at Children’s Hospital, delivers to pharmacist Gene Early a supply of investigational drugs from the National Cancer Institute, ordered for a research chemotherapeutic study.

Cancer tumors must have a blood supply to survive, grow, spread and kill. Mulvihill explains that laboratory investigation with mice has shown the feasibility of attacking the growth of blood vessels to eradicate cancer. "The translation of that concept into human cells and human beings is proceeding at a quickened rate," he says.

The more distant future of cancer treatment involves the exciting realm of gene therapy. One strategy involves understanding cancers that are caused by the loss of a tumor suppressor gene.

"Tumors in the back of the eye, some childhood cancers and some breast cancers seem to arise from the loss of the tumor suppressor gene, whose normal job is to put the brake on the little clusters of cancer cells that occur in everyone's body," he explains. "If the origin of that cancer is the loss of a gene, it's very tempting to say, 'Let's just replace it.'"

In theory, this is a great idea and has been carried out in tissue cultures. Mulvihill admits, however, that it is a long way from human trials.

Another perhaps more achievable goal for gene therapy involves targeting genes that can recognize changes in a cell's surface and enter only those cells. Brain tumors, for example, have acquired genetic changes that alter the surface of their cells. In theory, genes can be put into a virus that causes brain infection. When these genes are transferred into the cancer cell, that cell becomes susceptible to antiviral agents.

"Antiviral agents kill the cancer cells because they have been fooled into thinking they are a virus," Mulvihill explains. "This type of research uses what we know about virus genetics to contribute to curing a brain tumor. This represents an enormous confluence of biological information that is very, very clever and has, in principle, been shown to work.

"The practicality of applying it to the general population has yet to be demonstrated, however, and will be the subject of a great deal of additional research," he adds.

Mulvihill warns that there will not be a magic bullet to cure all cancer. "There will be helpful bullets, better

bullets and instruments that don't require bullets but rather arrows or some other agent to destroy cancer cells."

The complexity of treatment options arises, due in part to the complex origins of cancers, he says. "Every person's cancer probably arises uniquely from a complex mix of their inborn susceptibility in combination with their lifelong story of environmental exposures. What might look like an identical cancer under the microscope could very well call for two very different treatment protocols."

He foresees a time when patholo-

John J. Mulvihill recently completed A Catalog of Human Cancer Genes: McKusick's Mendelian Inheritance in Man for Clinical and Research Oncologists, an upcoming publication of the Johns Hopkins University Press. (Victor McKusick's Mendelian Inheritance in Man, now in its 12th edition, is the standard reference for geneticists needing information about inheritable conditions and diseases.)

In his book, Mulvihill offers a collection of the 635 print and online entries of MIM that relate to oncology. Complete with notations about the disorders of greatest interest to oncologists, the book groups the disorders according to the human body organ system where the disease occurs.

gists, in addition to doing the microscopic work needed to recognize a pattern of cells and identify it as a cancer, also will identify the molecular signature of the cancer. One breast cancer, for example, might need a totally different strategy with a totally different recipe of chemotherapy, immunotherapy or other biological therapies than another breast cancer.

Many cancers have molecules on their surface that distinguish them one from another and determine how signals from outside the cells control the nucleus of the cells. One example of surface receptors—HER2—is found in

breast and many other cancers. An antibody against HER2 has been released for treating some breast cancers.

No discussion of the future of cancer would be complete without mentioning prevention, Mulvihill says. If humankind is ever to rid itself of cancer, prevention would have to play a major role.

"We already know how to prevent many cancers. If everyone would stop smoking, the majority of lung and some other cancers would be prevented. We already know that avoiding the sun prevents some melanomas and other skin cancers, that eating a healthy diet and avoiding unnecessary medication may contribute to decreasing the frequency of other cancers.

"We also can look forward to a time when we recognize cancers very early—before they are a problem and still can be cured by standard treatment."

During Mulvihill's tenure at the NIH, a study was begun of 13 families with high rates of melanoma. Through education, family members have become experts at identifying problem moles early enough to permit a cure through surgical intervention. Over a three-decade period, there have been no deaths from melanoma in these families.

"Can we apply the principles of patient education and early detection to the general population?" Mulvihill ponders.

He believes that cure rates would soar if people understood their own family history and individuals highly disposed to cancer received the best screening available, either through mammography, molecular testing, gene testing or whatever technology is available.

Not so many years ago, cancer was spoken of in whispers, if at all, he recalls. Patients often were not told they had the disease. Such attitudes worked against early detection. Even though the veil of secrecy has been removed from cancer, all too often people continue to ignore early warning signals and wait too long to seek medical care.

A major objective of medical research and practice is the prevention of premature death. It would suit Mulvihill just fine if no one ever died of cancer. There are better ways for life to end, he contends.

"Our goal," he says, "is to die well at an old age."