Moving toward a future without cancer.

momentum

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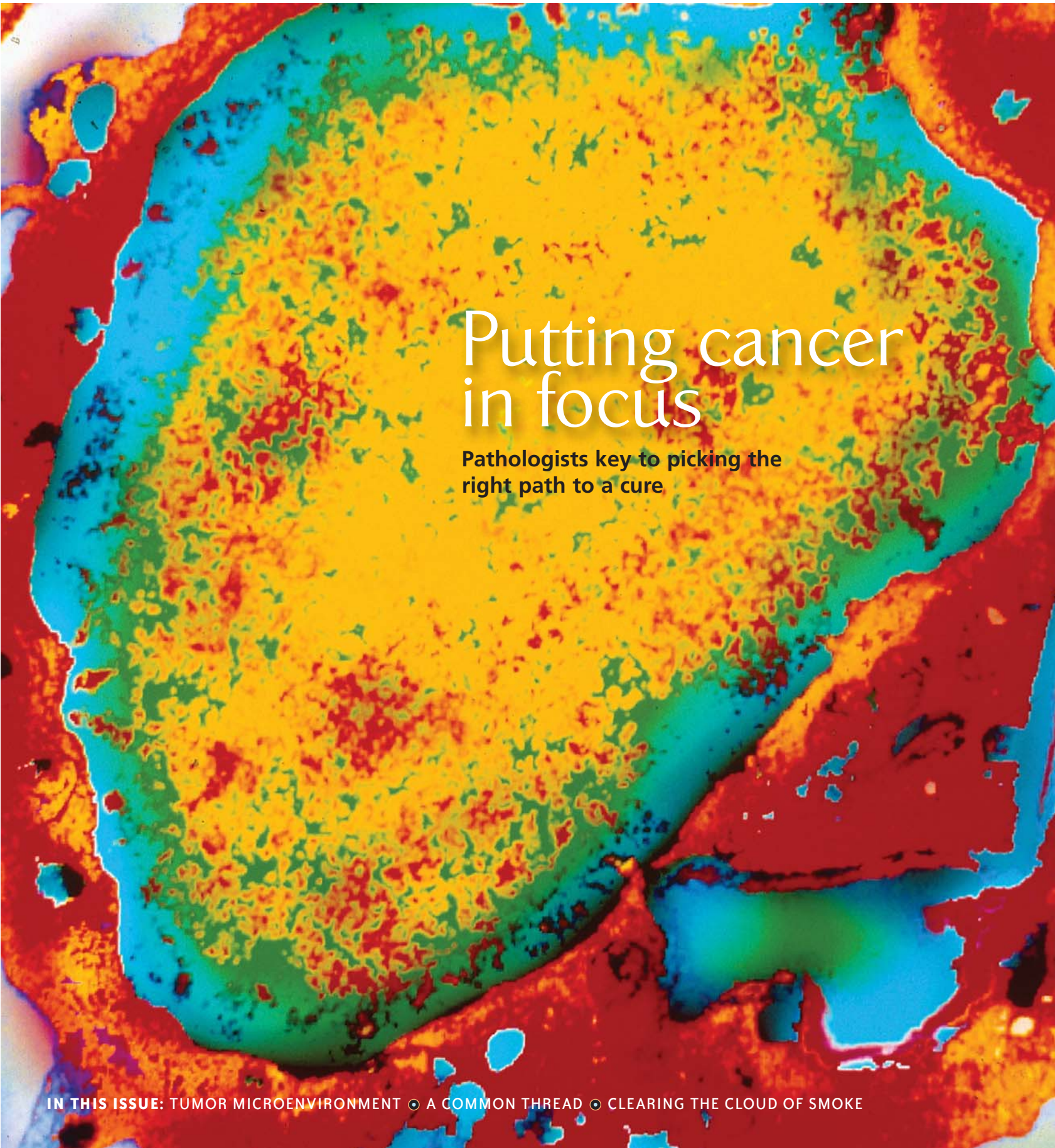


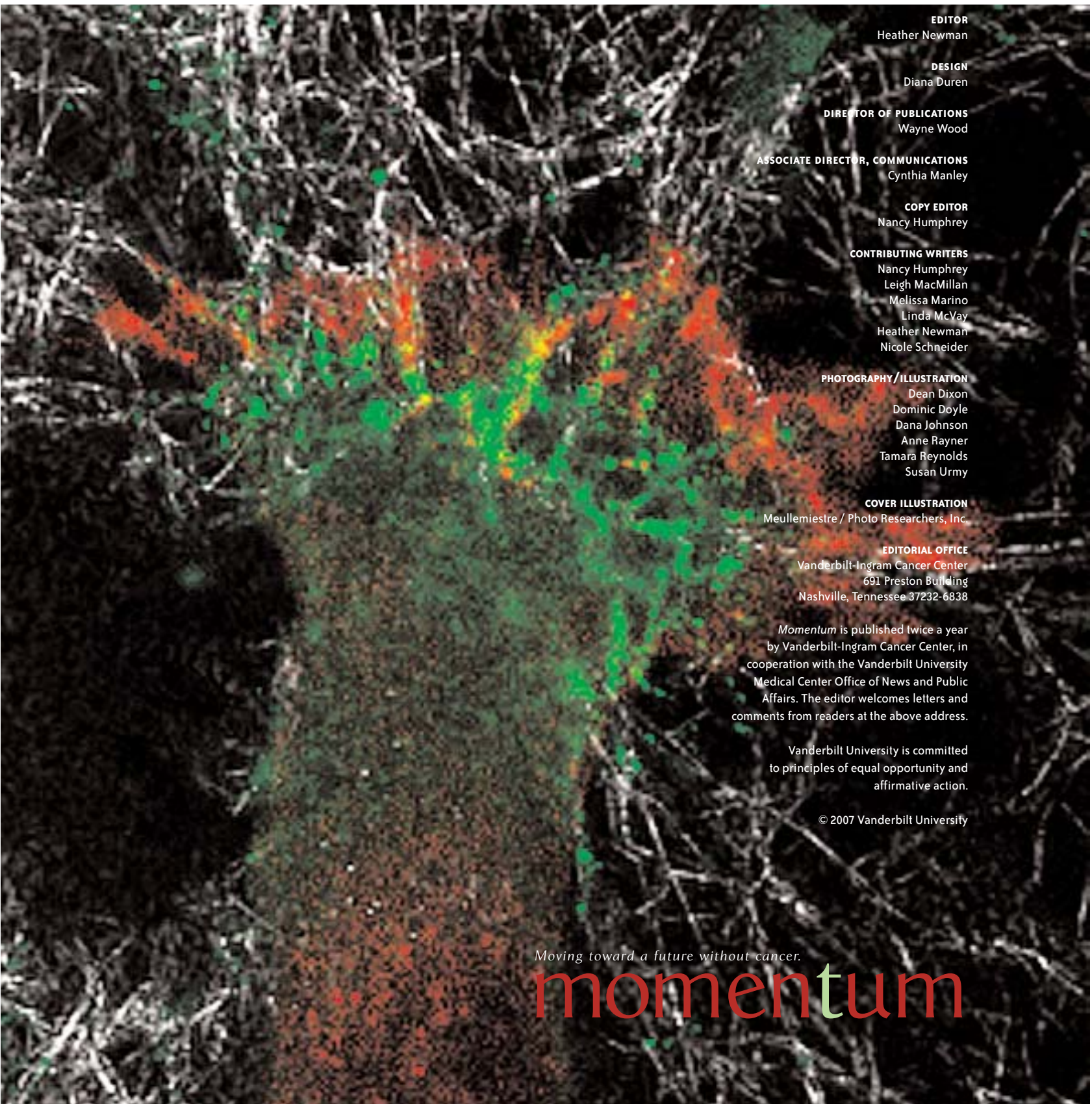
Putting cancer in focus

Pathologists key to picking the right path to a cure

On the cover:
Acute promyelocytic leukemia (see story page 8)

Pictured below:
Cancer cell invasion through three-dimensional tissue

Reproduced from: Wolf., K. and Friedl., P. 2006. Molecular mechanisms of cancer cell invasion and plasticity. Br. J. Dermatol. 154 (Suppl. 1): 11-15. (see story page 14)



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Moving toward a future without cancer.

momentum

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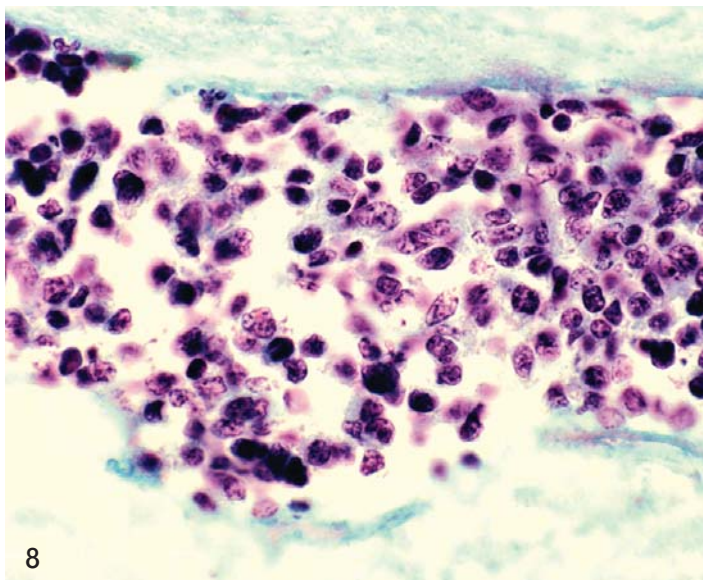

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departments

EDITOR'S NOTE: *Jennifer Pietenpol, Ph.D., Ingram Professor of Cancer Research and professor of Biochemistry, was selected earlier this year to lead the Vanderbilt-Ingram Cancer Center as interim director while a national search is under way.*

PHOTO BY DEAN DIXON

Director's letter

One of my goals as interim director is to maintain the momentum of the Vanderbilt-Ingram Cancer Center. I'm honored to have this opportunity to guide the Cancer Center through a time of change and transition. The Cancer Center is a team of committed, talented clinicians and scientists who are dedicated to working together to provide the highest quality patient care and to pursue cutting-edge cancer research that will have the greatest impact on preventing cancer and treating patients with the disease.

In this, our second issue of *Momentum*, we continue to highlight the expert level of patient care and scientific excellence here at Vanderbilt-Ingram. In Tennessee, and across the country, we're seeing debate and legislation over smoking in public places and the serious health consequences of secondhand smoke. You'll meet a courageous patient with end-stage lung cancer who found hope at Vanderbilt-Ingram.

You'll learn about Vanderbilt-Ingram's role in a national effort to investigate the tumor microenvironment. We're taking a closer look at just how important the non-tumor cells surrounding a tumor are when we determine how to treat a tumor. The research is funded through a new type of grant awarded to Vanderbilt-Ingram by the National Cancer Institute (NCI) for $1.3 million a year for the next five years.

We'll share research progress from several laboratories in our NCI-designated Comprehensive Cancer Center. It is in these laboratories where some of the brightest minds in cancer research spend their days, and often nights, studying tumor samples, proteins, and the delicate connections that play a role in how cancer begins, grows and spreads. We'll introduce you to a researcher who has been hard at work for three decades.

The Cancer Center is a team of committed, talented clinicians and scientists who are dedicated to working together to provide the highest quality patient care and to pursue cutting-edge cancer research that will have the greatest impact on preventing cancer and treating patients with the disease.

You'll also learn more about the vital role of a pathologist – the medical doctor tasked with diagnosing disease from blood, tissue and body fluid. A pathologist's diagnosis is one of the first steps in cancer care. Their initial report will set in motion a plan of attack, yet patients typically never meet these behind-the-scenes members of the treatment team.

One of our own staff members, Linda McVay, will share her personal story of becoming a stem cell donor and meeting her recipient for the first time, after spending years coordinating the donor program for Vanderbilt-Ingram. She'll explain how you can become a donor and offer a cancer patient a second chance at life.

You'll also meet a few volunteers that make the Henry-Joyce Cancer Clinic a more welcoming and comforting place for our patients and their loved ones – from the college student serenading patients and healing tired souls with a song from the piano, to the longtime community member who sits and talks with patients who know him by name and look forward to his warm smile. These people give of themselves to offer some simple comforts that help ease the burden of a difficult time in our patients' lives.

We hope these stories inspire you, spark dialogue about cancer-relevant issues, and motivate you to get involved in the fight against the disease.

ACLOSERLOOK

MARY AAKRE | Lab Manager, Vanderbilt-Ingram

PHOTO BY TAMARA REYNOLDS

TWO DECADES AGO, MARY AAKRE WAS DOING WHAT SHE HAD BEEN DOING EVERY day for 12 years as a research specialist, when the lab in which she worked made cancer history.

She was working alongside Harold (Hal) Moses, M.D., emeritus director of Vanderbilt-Ingram Cancer Center, when his team and others across the country identified TGF-beta, transforming growth factor beta. This protein, which stimulates growth in some cells while inhibiting growth is others, is a key player in cancer development and progression. It is the Moses Lab's primary focus to this day.

"It was a crazy time," she recalled. "The media were all over and that was a first-time experience."

Today, most days are quieter, but Aakre said no two are ever the same. A self-described morning person, Aakre starts her day as manager of the Moses Lab at 6 a.m. Her work to assist others and order supplies is instrumental for the lab's study of cancerous tissues, mostly breast and pancreas.

Aakre has been working for Moses her entire career. She followed him to Vanderbilt in 1985 after working as part of his team for 12 years at the Mayo Clinic in Rochester, Minn.

Having such longtime technicians and other support personnel in the laboratory is key to the success of the research, Moses said. Post-doctoral fellows and students move through for shorter periods, but people like Aakre are the backbone. She, in particular, has been instrumental, he said.

"When she goes on vacation everyone at the lab realizes how much she really does," Moses said.

Anna Chytil, senior research specialist in the Moses Lab, agrees. "Without her, the lab would collapse," said Chytil. "She is one of the most enthusiastic people I've ever met when it comes to getting work done."

In the years she's spent as a researcher, Aakre has seen great changes in technology. "The tools have improved. There was no micro-pipetting 30 years ago," she said, describing a tube-and-mouth technique to transfer cells onto a Petri dish that would make today's safety officials cringe. Due to advances in equipment and technology, researchers can now get more results with smaller amounts of material.

When she's not at work in the lab on the sixth floor of Vanderbilt-Ingram's Preston Research Building, Aakre enjoys spending time with her husband and 22-year-old son, volunteering in her church nursery, and cooking. She is also an avid biker, and longs for the day when Nashville will have plentiful bike paths.

Aakre takes pride in the work she and her colleagues are doing to make cancer advancements and in the history that she has helped build under Moses' direction.

"In the long run," she said, "it's good to think that something we're doing will help people with cancer. Curing cancer won't happen overnight, but we've made progress. Cancer deaths are on the decline.

"I like to think that we're making a difference."

– by Nicole Schneider

SPOTLIGHT: RARE CANCER

CHUCK CAGLE | Esophageal Cancer

FACING A NEW CASE OUT OF THE COURTROOM

A Tennessee lawyer shares his personal fight against cancer

When 50-year-old Chuck Cagle learned he had stage IV esophageal cancer he had one thought – "I'm a dead man." He had a fever that wouldn't go away. Concerned, he made an appointment to see his doctor. Several tests revealed no clues, but then an MRI picked up a cyst on his pancreas.

Doctors assured Cagle it was nothing serious, but they wanted to do some more tests to get a closer look. A tube placed down Cagle's throat revealed a tumor blocking the way. It was esophageal cancer. And had it not been for the unrelated cyst on his pancreas, it might not have been found quickly enough. "I don't think my wife or I will ever get over hearing that. I had to sit down. That's the last thing I expected to hear. There is no cancer in my family. I was just in a stupor," Cagle said.

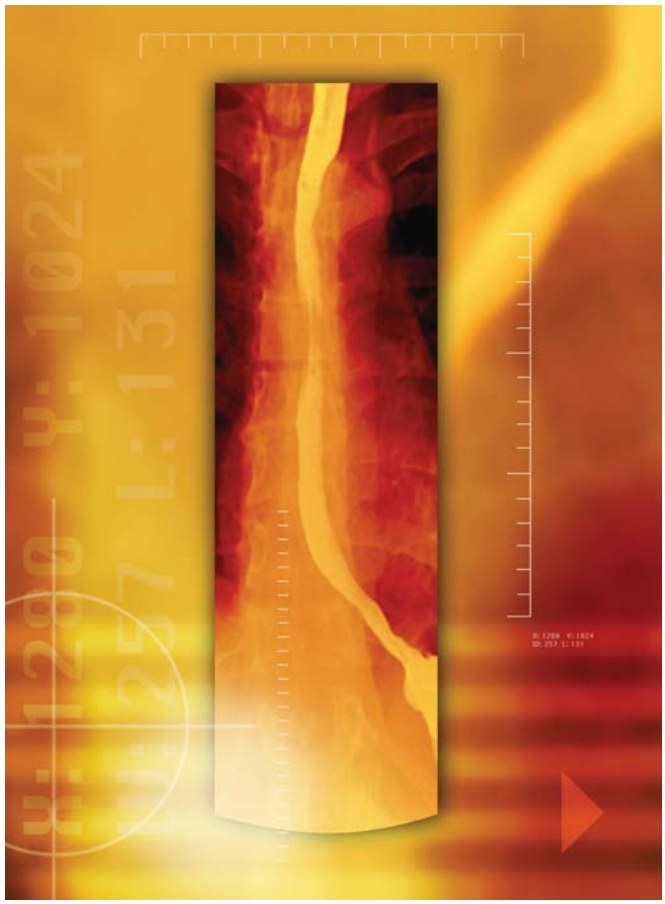
Cagle didn't have the majority of problems that typically put people at risk for esophageal cancer. He is not a regular smoker, although he admits to smoking an occasional cigar. He's not a big drinker, and he doesn't recall any problems with acid reflux. "We know it relates to acid reflux, but the connection is not 100 percent certain," said Bill Putnam, M.D., chair of Thoracic Surgery and Vanderbilt-Ingram member.

An estimated 20 million Americans experience chronic heartburn, and about 2 million of those people have Barrett's esophagus. Barrett's esophagus is a precancerous condition of the esophagus that is typically found in white men over 50. The condition, which affects the lining of the lower esophagus, is often associated with long-term acid reflux.

By Heather Newman | Photography by Dean Dixon

WE HAVE ESSENTIALLY AN EPIDEMIC OF ESOPHAGEAL CANCERS, SPECIFICALLY ADENOCARCINOMA.

PHOTO BY MIRIAM MASLO/PHOTO RESEARCHERS, INC.



PICTURED HERE:
The esophagus (orange) is the tube that carries food and drink from the mouth to the stomach. It has been visualized here using a barium swallow, a radio-opaque liquid swallowed by the subject that highlights the esophagus on X-rays.

Barrett's esophagus is another warning sign for esophageal cancer, but Putnam said not all people who have the condition will develop esophageal cancer, which remains a mystery. "It probably results from chronic, repetitive chemical trauma to the esophagus," Putnam said. "The treatments for acid reflux might play a role in causing the esophageal cancer."

Adenocarcinoma is the type of esophageal cancer connected to Barrett's esophagus, and it's seen in roughly 10,000 Americans a year, with numbers rising faster than any other cancer in the U.S. "We have essentially an epidemic of esophageal cancers, specifically adenocarcinoma," Putnam said.

Adenocarcinoma is the kind of esophageal cancer Cagle was diagnosed with, but he hadn't experienced any of the textbook signs or symptoms. Putnam said it was only a matter of time, because patients typically won't notice warning signs until the cancer is very advanced. Esophageal adenocarcinoma is also on the rise in women and African-Americans. "In the past it used to be primarily squamous cell esophageal cancer, but we rarely see that these days," Putnam explained.

Cagle has refused to let his diagnosis slow him down. He's a lawyer, chairs his law firm's educational law practice group, and lobbies the Tennessee General Assembly on behalf of the organization representing school superintendents.

Treatment of cancer of the esophagus requires close interactions between surgeons, medical oncologists and radiation oncologists. For his first step in treatment, Cagle needed to start chemotherapy and radiation immediately. He spent six weeks on the radiation table and two weeks receiving chemo, but missed only one day of work from the fatigue. "I tell everybody this without hesitation, I am a blessed guy. I was not sick one minute," Cagle said. "I worked the whole time. I had some sores in my mouth after the second round of chemo, but only one day was I not able to drive myself home."

The next step was surgery. Putnam, his surgeon, removed his entire esophagus. "We use the stomach and fashion it into a tube and move the stomach up where the esophagus used to be," Putnam said.

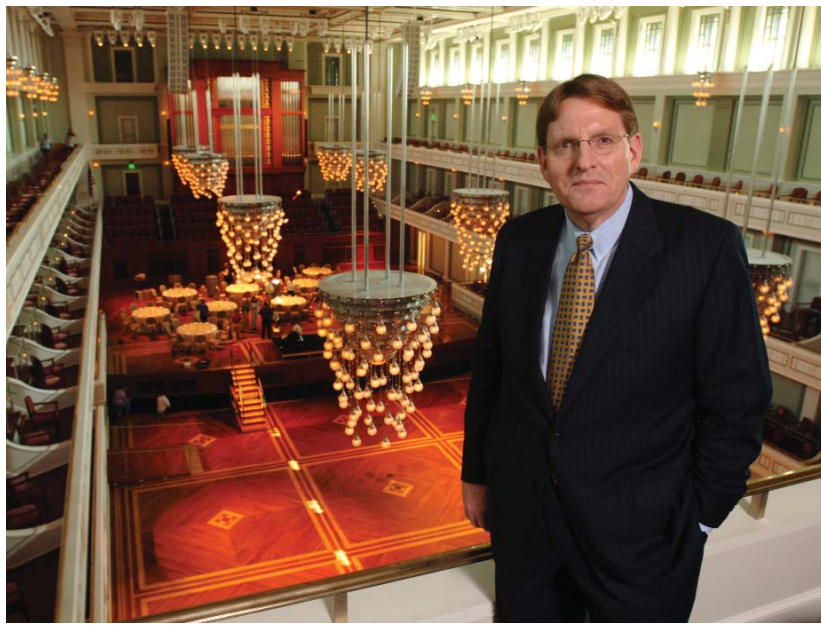
After surgery, Cagle was able to eat and swallow normally, but he had to make some big adjustments. "Your lifestyle changes – things like sleeping and eating. I was a pretty big guy. He said I would lose 100 pounds," said Cagle.

He can't sleep flat on his back any more, because he could choke, and he has had to learn to eat several smaller meals. But for Cagle, good food is one of the joys of being alive, and he has continued to cultivate that pleasure. "I'm a cook. I like to grow food, cook food, harvest food and eat food," he said, although he now enjoys those pleasures in a different way. "That's a small price to pay for being here," he said.

Now, Cagle is watched closely by a team of Vanderbilt-Ingram physicians and nurses, who monitor for the cancer's possible return. "The risk of recurrence for patients with esophageal cancer is over 50 percent and the percentage of patients alive at five years after proper treatment is about 30 percent, so we have a lot of progress to make in the treatment of this disease that is unfortunately becoming more common," said Craig Lockhart, M.D., Cagle's medical oncologist. He sees Cagle every three months for blood tests and periodic CT scans. "Mr. Cagle is doing very well and we will continue to see each other regularly over the next five years," said Lockhart.

The tests are nerve-racking, but Cagle said he stays positive. "I still hold my breath a little," Cagle said. "But I'm not going to let this defeat me. I feel good. I am blessed."

PHOTO BY ANNE RAYNER



PICTURED HERE: A reflection of one of two away-from-work loves – cooking and music – Cagle stands in the new Schermerhorn Symphony Center, home to the Nashville Symphony. A musician (tuba player in bands, ensembles, brass choirs and quintets), Cagle is president-elect of the Nashville Symphony Orchestra League and a member of the Symphony's board of directors.

ESOPHAGEAL CANCER

Esophageal cancer grows in tissue lining the esophagus, the 10-inch-long, muscular tube that allows food to move from your throat to your stomach. The National Cancer Institute projects about 15,560 new cases of esophageal cancer in the U.S. in 2007, and approximately 14,000 deaths from the disease.

There are two types of esophageal cancer. Squamous cell carcinoma begins in flat cells lining the esophagus, and adenocarcinoma begins in cells that make and release mucus and other fluids.

The risk factors for squamous cell esophageal cancer are:

- Being male
- Tobacco use
- Alcohol abuse
- African-Americans at higher risk than white men
- Ingesting very hot liquids

The risk factors for adenocarcinoma are:

- Obesity
- Acid reflux
- Barrett's esophagus

Diagnosis of esophageal cancer usually involves endoscopy (a tube in the throat to view changes), CT scanning, PET scanning, and endoscopic ultrasound.

Lockhart, a specialist in esophageal cancer, said treatment requires a multidisciplinary team with surgeons, radiation oncologists and medical oncologists. "Depending on the size and stage of the tumor, patients either have surgery only for small tumors, or chemotherapy and radiation first if they have larger tumors," Lockhart said. Surgery is usually the next step.

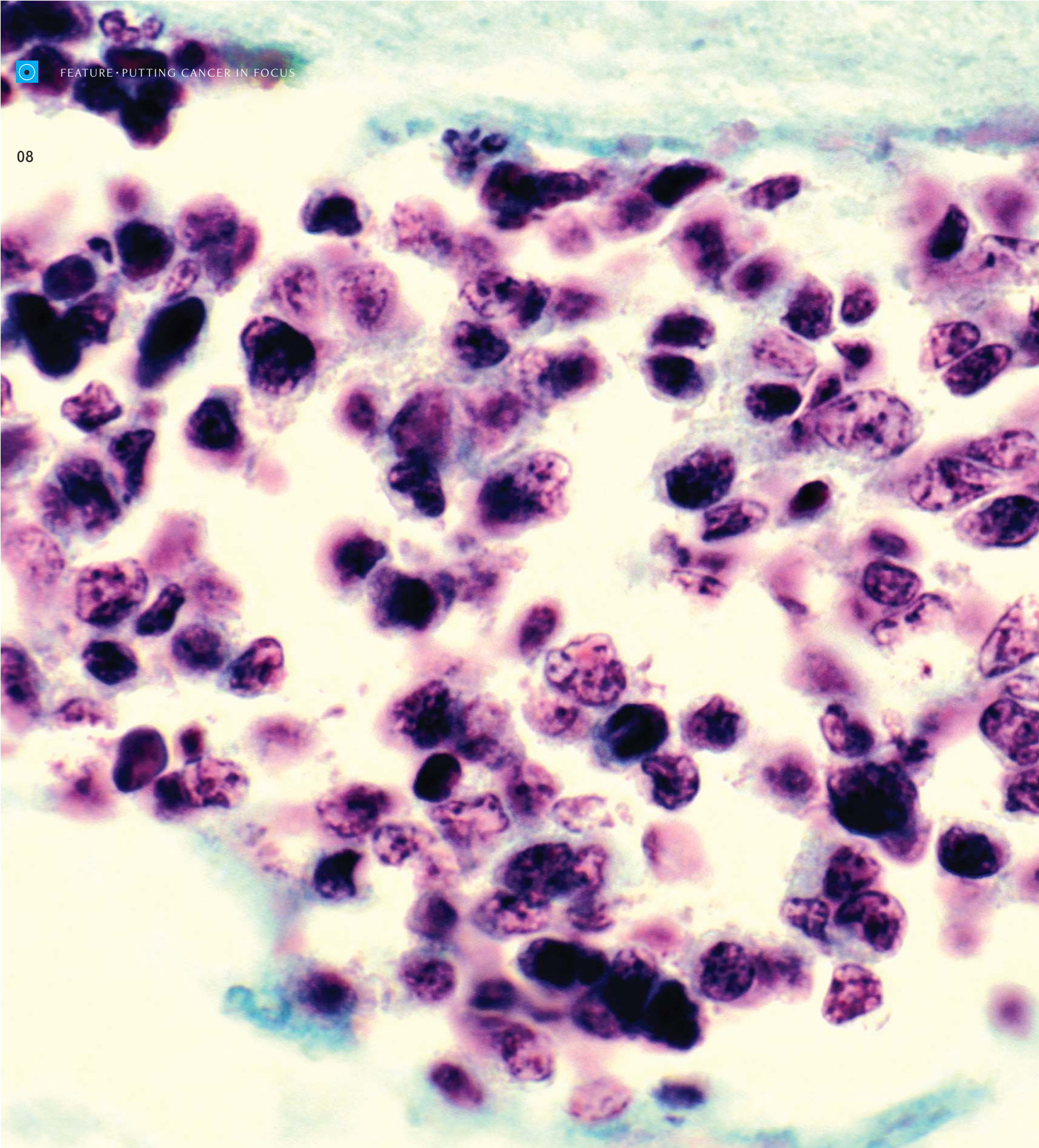
Lockhart said when looking for a doctor or facility to treat esophageal cancer, experience is the key. "Especially for the surgery," Lockhart said. "A number of studies have shown that outcomes are better when patients have surgery at a center where more surgeries for this kind of cancer are performed. For the oncologists, experience is important too, to help manage treatment complications and design a treatment regimen that fits the patient's clinical presentation."

As far as prevention, Lockhart said if you have chronic reflux you need to be followed by a gastroenterologist. If you are diagnosed with Barrett's esophagus, you need close and regular follow-up with biopsies, in order to try to diagnose cancer at the earliest stages, he said.

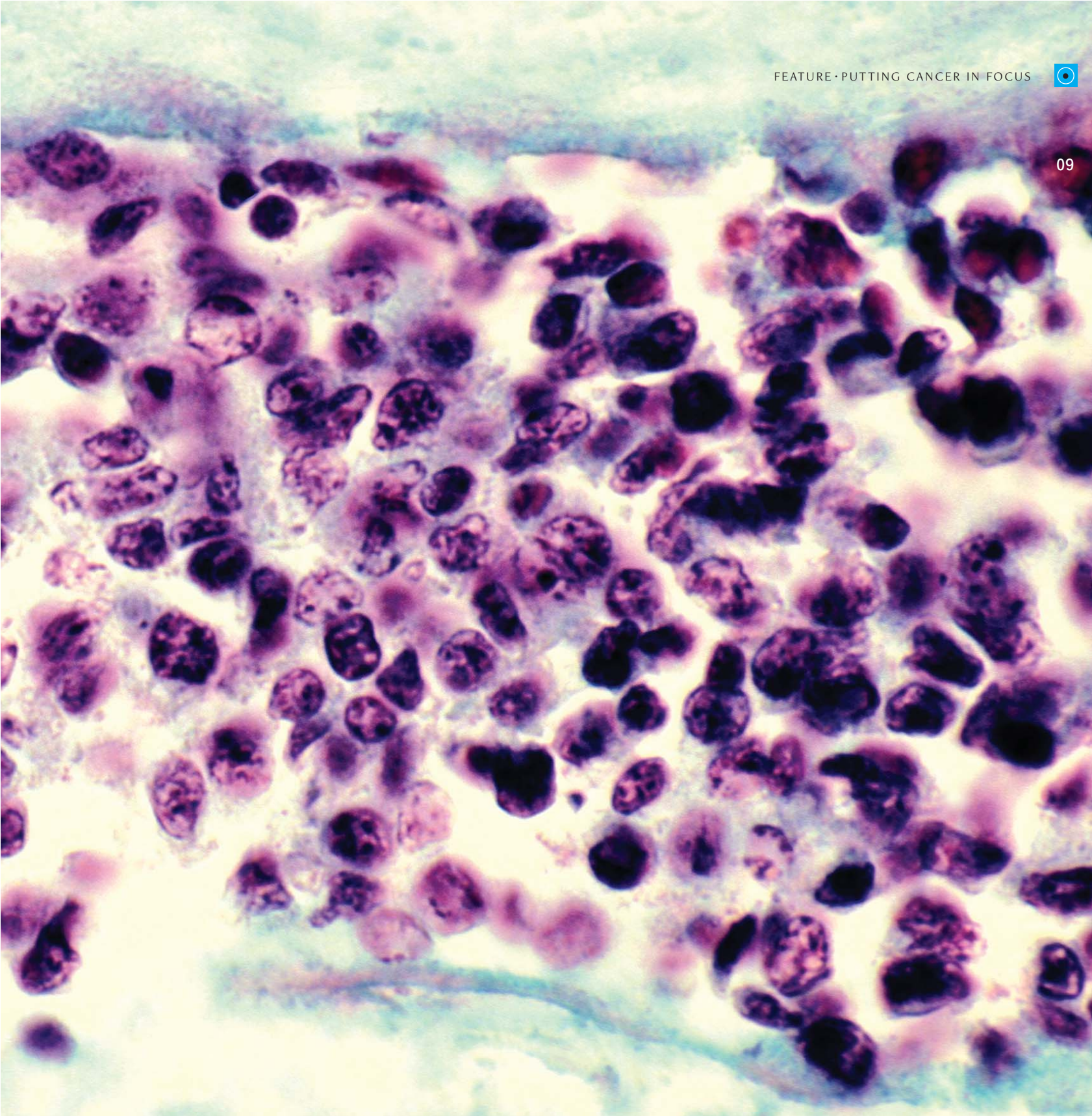
WARNING SIGNS TO WATCH FOR:

- Trouble swallowing or a feeling of food stuck in your throat or chest
- Pain in your throat, mid-chest, or between your shoulder blades
- Hoarseness
- Chronic cough or coughing blood
- Vomiting blood

For more information about the Vanderbilt-Ingram Esophageal Cancer Program, log on to: www.vicc.org, and click on cancer types. Or call our Information Program at: 1-800-811-8480.



PICTURED HERE: Pap stain of small cell lung cancer cells



Putting Cancer in Focus

PATHOLOGISTS KEY TO GUIDING CANCER CARE

By Melissa Marino
Photography by Dr. Gladden Willis / Visuals Unlimited

Marcy Thomas thought it might be an infection. Low-grade fevers, swollen lymph nodes, and malaise had been troubling her for months. But antibiotics weren't working. Her physician in her hometown of Dalton, Ga., suggested that it was time for a biopsy of her lymph nodes.

It was late 1991 – just three years after Burkitt's lymphoma had claimed her husband's life.

"When I started having these peculiar sorts of symptoms, the last thing I wanted to think about was cancer," says Thomas, now a chaplain at Vanderbilt University Medical Center.

But it was a reality she would soon have to face. The surgeon who performed the biopsy in Chattanooga told her that the preliminary pathology report suggested a malignancy, but they weren't sure what type of cancer it was. She would need to see an oncologist.

During a tense two weeks of waiting for the appointment with the oncologist, Thomas did everything she could think of to make herself better.

"I was grasping at anything. I was terrified. I was fasting with juices, doing all these alternative therapies," she says. "And, of course, I was praying…A LOT!"

And by the time of her appointment with the oncologist, her symptoms seemed to have "miraculously" disappeared. Because he had never seen a lymphoma with symptoms that would come and go, the oncologist quelled her fear with guarded optimism.

"He said, 'I don't think you have it,'" Thomas recalls. "So, we were just rejoicing, thinking 'Thank God, we don't have to deal with this again,' especially my children."

But when she walked into his office in January for a follow-up, Thomas knew from the look on the oncologist's face that something was wrong. They finally had an answer to what was causing her unusual and erratic symptoms.

"He said that my slide had been sent all over the country…and in the end, it had come to Vanderbilt."

Robert Collins, M.D., the John L. Shapiro Professor of Pathology, had identified the disease as Ki-1 anaplastic large cell lymphoma – a rare type of T-cell lymphoma that can cause symptoms that wax and wane, just as Thomas' had.

After the rollercoaster of emotion over the preceding months, she at least had a definitive answer. Her oncologist referred her to Vanderbilt's John Greer, M.D., professor of Medicine and Pediatrics, who suggested she go ahead with treatment because of the fairly aggressive nature of the cancer.

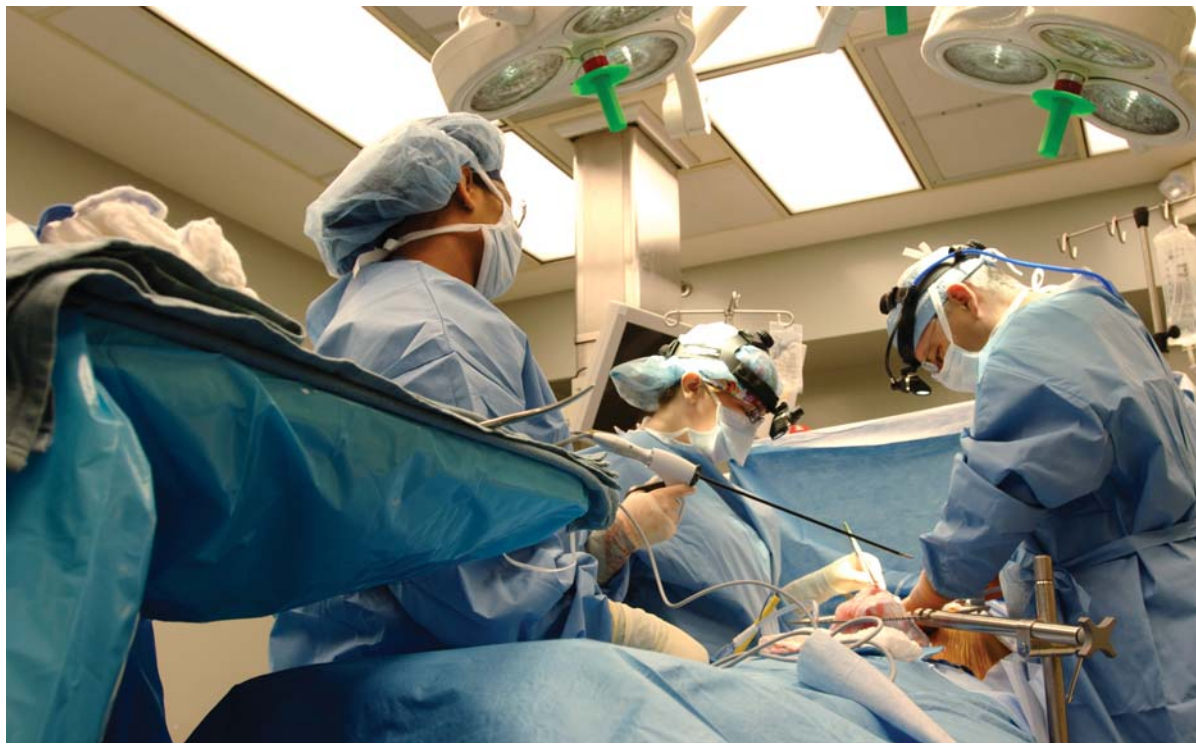
Having watched her husband go through treatment and die, Thomas felt uneasy and, at first, declined chemotherapy since she had no symptoms.

But the symptoms returned virulently, and, after Greer confirmed the original diagnosis with another biopsy, Thomas decided to go ahead with the treatment.

The story of a biopsy

How pathologists provide critical information from surgery to diagnosis

PHOTOS BY ANNE RAYNER



Behind the microscope

Getting that answer – even when it is not an answer you want or expect – is the single most important moment in cancer care. Those answers come from people rarely seen by the patient, the pathologists.

Pathologists are medical doctors with extensive training in diagnosing disease from blood, tissue and body fluid samples. Many pathologists specialize in particular areas – for example, hematopathologists focus on diseases of the blood and bone marrow (e.g., leukemias and lymphomas).

"We are largely unknown, behind the scenes," says Mary Kay Washington, M.D., Ph.D., professor of Pathology and director of Surgical Pathology at Vanderbilt. "But we are very invested in patient care."

From a sample of the patient's tissue or blood, pathologists make the initial diagnosis based on what they see under the microscope.

The first, most important question is: is it cancer? Pathologists can usually, but not always, tell this by the appearance of the cells under the microscope. To their trained eyes, cancerous cells and tissues look very different from healthy tissue cells, with abnormal shapes and organization.

"The first step for the pathologist is to characterize the tissue – examining its architecture and the appearance of individual cells," says Mary Zutter, M.D., professor of Pathology and Cancer Biology and director of the Division of Hematopathology.

After determining that the cells are malignant, the pathologist identifies other attributes of the cancer, including the type of cancer, how aggressive the cancer appears, and the size of the tumor.

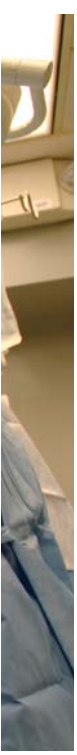
In the case of solid tumors, this usually requires that the tissue be surgically removed, or "resected." During the surgery, pathologists are on standby to provide the surgeon with rapid feedback to help guide the removal of the tumor.

"We are in the surgical pathology lab during the operation, so if the surgeon has a question that can be answered by an immediate consultation with a pathologist, we are there to perform that," explains Washington.

The surgeon may send some tissue samples to the lab, where a pathologist can perform a quick "frozen section" to help identify the edges, or "margins," of the tumor. This tells the surgeon if they have removed the entire tumor, or if more tissue should be removed.

After the tumor is resected, the pathologist examines the characteristics of the tumor that are visible to the naked eye. In this "gross examination," the pathologist notes the tumor's size, weight, color and texture. They also take a closer look at the margins to confirm whether the entire tumor was removed.

To look inside the tumor, the pathologist cuts thin slices, or "sections," from the tumor, stains them, and examines the appearance of the cells under a microscope. This process, called histology, has traditionally been the technique at the core of pathology.



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STEP 1: As surgeons remove tissue from a suspected tumor, pathologists and their staff are standing by to provide rapid feedback.

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STEP 2: The pathologist takes the tissue sample to the pathology lab

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STEP 3: The pathologist chooses a piece of tissue and prepares it for microscopic examination.

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STEP 4: After a histology technician freezes the tissue, cuts thin slices and stains them on slides, pathologists carefully review the tissue under a microscope.

●●●●●

STEP 5: While the patient is still on the table, the results are delivered to the surgery suite.

Cancer staging

Cancer staging provides important information for the patient, the physician, and agencies that track cancer statistics and patterns.

The traditional staging systems, however, are undergoing an evolution in response to the increasing cellular and molecular markers used in cancer diagnosis.

"There have actually been three separate staging systems used in the United States," says Stephen Edge, M.D., chair of the Department of Breast Surgery and medical director of the Breast Center at Roswell Park Cancer Institute in Buffalo, N.Y.

The systems used by the National Cancer Institute and the Centers for Disease Control and Prevention to evaluate cancer incidence and deaths collect different data than the system used in medical settings to help guide therapy.

"This leads to confusion and duplication of effort on the part of the people who collect the information," says Edge, who is leading the ongoing overhaul of staging systems by American Joint Committee on Cancer (AJCC).

The new system, called Collaborative Staging (CS), aims to integrate the three different systems so that everyone – from local physicians to cancer registrars tracking national cancer statistics – is on the same page.

The system most familiar to doctors and patients – the TNM system of the AJCC and the International Union Against Cancer – is central to Collaborative Staging and is also undergoing significant changes to incorporate new molecular and cellular markers that predict the patient's outcome or how they might respond to therapy.

"The TNM system is still the anatomic basis," says David Page, M.D., a member of the executive committee of the AJCC. "What we're now trying to do is to add to that and integrate other factors."

"The ongoing revision of TNM is going to incorporate, wherever possible, factors beyond anatomy, including molecular tumor characteristics that affect prognosis," Edge says. "This will provide patients and physicians with a more robust system to help treatment planning."

"The Collaborative Staging System that allows for the integration of new factors associated with cancer prognosis and with response to treatment into the same data collection system will be the key element that supports these improvements," he says. "We think that the Collaborative Staging will provide doctors in the future with better means to collect and use information – molecular factors and factors associated with cancer outcome rather than the purely anatomic information previously used."

Mary Kay Washington, M.D., Ph.D., who is also involved in the AJCC's efforts, predicts this will have a major impact. "The better our data are, the more we can refine our staging system, and, ultimately, the better we can take care of the individual patient."

– by Melissa Marino

But in recent years, research has led to the development of tests that can identify specific genes and proteins involved in the tumor's growth. These specific tests can help to more accurately identify the type of cancer and may provide clues to the best treatment for that cancer type.

"Research over the last 20 years has moved us from simple microscopic examination to the identification of specific genetic defects that contribute to cancer initiation and progression," says Zutter, who conducts research on the role of proteins called "integrins" in cancer progression and metastasis.

One of the first major steps in this new era of pathology came with the development of antibodies that recognize specific cell markers in the patient's tissue, Zutter notes. The techniques that utilize antibodies for diagnosis, immunohistochemistry and flow cytometric analysis, are particularly critical in the field of hematopathology for categorizing lymphomas as either "T" or "B" cell types, which is an important factor in selecting the appropriate treatment.

More recently, as specific genetic and chromosomal abnormalities have been identified, genetic markers have been incorporated into the diagnostic process. Certain lymphomas and leukemias can now be identified by looking for chromosomal translocations or rearrangments between pieces of two different chromosomes.

Because of their usefulness as diagnostic and prognostic factors, both immunohistochemistry and genetic techniques are now part of the set of pathology tools and have become "routine, standard of care" for many cancers, Zutter says.

In addition to identifying the type of cancer a patient has, pathologists also determine the tumor's "grade," which indicates how aggressive the tumor might be. To do this, pathologists examine the size and shape of the cell's nucleus, the number of cells that appear to be dividing, and the patterns the cells form.

"We look at the growth rate of the tumor in several manners," says David Page, M.D., professor of Pathology and Preventive Medicine. "We look at the atypicality of the nuclei (of the cells), and that gives us extra information about the possibility of metastasis and malignant outcome."

If the cancer cells appear relatively normal and are dividing slowly, the cancer is considered "low grade," "well differentiated," or "grade 1." If many of the cells appear to be dividing, which indicates that the cancer may be more aggressive, the cancer is called "high grade," "poorly differentiated," or "grade 3 or 4."

The grading systems are different for different types of cancer. Some, like prostate cancer, are graded on a wider scale ranging from 2 to 10. Generally, the lower the grade, the less aggressive the cancer.

Pathologists also play an important role in cancer "staging," which describes the extent of the cancer and provides clues about the appropriate treatment and the individual's prognosis.

Like the grading systems, systems for staging cancer also vary for different types of cancer. However, most systems take into account the location of the tumor, tumor size and number of tumors, lymph node involvement, cell type and tumor grade, and presence or absence of metastasis (spread to distant tissues).

The most well-known staging system is the TNM system. The "T" refers to the size and extent of the primary tumor; the "N" signifies lymph node involvement; and the "M" indicates spread to distant parts of the body. A number is added to each letter to indicate the extent of disease.

"The pathologist is usually involved in evaluating the 'T' and the 'N,'" says Page, "while the 'M' is more and more determined with clinical imaging, like CT and MRI scans," features added in the recent Collaborative Staging System (see sidebar).

These factors are then combined to determine an overall "stage," which can range from "0" to "IV" with "0" being an early stage cancer (carcinoma in situ) and "IV" being advanced cancer that has spread to distant areas of the body.

Staging provides information about the patient's prognosis and helps guide treatment. And as new diagnostic and predictive markers are discovered, staging systems will evolve to incorporate that new knowledge.

Accurately staging a cancer involves input from many areas – clinicians, radiologists and pathologists.

"The pathologist provides the basic diagnosis, but it needs to fit into the clinical setting. It's not made in a total vacuum," says Page. "Therefore, we work carefully with clinicians about how the information intersects."

This interaction between clinician and pathologist is critical, especially when the diagnosis is not straightforward, as in Marcy Thomas' case.

"A clinician is only as good as their pathologist," says Greer, who has continued to care for Thomas since her initial diagnosis. "The oncologist may be on the 'front lines'…but everything hinges on the pathology."

Since there are over 30 types of lymphoma, determining the specific type was key to deciding how to treat Thomas. Fortunately, Greer says, Vanderbilt has one of the world's experts in lymphoma classification in Collins – one of the originators of the "Lukes-Collins" classification system for lymphoma, an important component of the evolution of lymphoma classification systems.

And it was that answer from the behind-the-scenes player that gave her the information she needed to go forward.

"It was the only way I could make an informed decision," Thomas says. "I think this is important for people who are diagnosed and may have something that doesn't present forthrightly, as mine didn't. You have to have all the information at your disposal."

PICTURED HERE: Marcy Thomas owes her life to the expertise of a pathologist who identified her rare and aggressive cancer, making an effective treatment possible.

PHOTO BY TAMARA REYNOLDS

"A clinician is only as good as their pathologist," says Greer, who has continued to care for Thomas since her initial diagnosis. "The oncologist may be on the 'front lines'…but everything hinges on the pathology."

Playing by the neighborhood rules

Tumor's environment may offer new options for making cancer cells "behave"

Cancer cells are the new neighbors who turn their noses up at the "rules." They're the ones who never mow the yard, install an oversized plastic play structure, paint their home an unapproved color, and plan an addition that will surely encroach on the property lines. It's up to the neighborhood association to flex its muscles and force these rabble-rousing homeowners to fit in. Or else. Like a neighborhood, the "microenvironment" around a tumor may be able to push cancer cells to behave, suggesting new therapeutic possibilities.

By Leigh MacMillan

Illustration by Howard Berman / Getty Images

"Our approach to cancer therapy for many years has been to kill the proliferating cancer cells," says Lynn Matrisian, Ph.D., professor and chair of Cancer Biology. "With the growing recognition of the microenvironment's role in cancer, there has been a change in thinking. Can we find ways to 'trick' the microenvironment into having a suppressive function, so the tumor cells don't do anything – they just sit there, and cancer becomes a chronic disease."

The way forward, Matrisian says, is to fully understand the molecules and signaling pathways that govern interactions between tumor cells and their surroundings. This area of research got a boost this year with the launch of the Tumor Microenvironment Network (TMEN), a National Cancer Institute-supported initiative. Ten groups, including a team at Vanderbilt, will be working to define the interactions of tumor cells with their environments.

"These are some very extraordinary laboratories that are participating," says Suresh Mohla, Ph.D., chief of the Tumor Biology and Metastasis Branch in the NCI Division of Cancer Biology and program director for the TMEN. "They're working on human cancers that range from breast to colon to glioblastoma, and other cancer sites as well, and they bring state-of-the-art technologies to the network. We are very pleased."

Fertile ground

The idea that the microenvironment plays an important role in a cancer's progression is not new.

In the late 19th century, Stephen Paget, assistant surgeon to the West London Hospital and the Metropolitan Hospital, proposed the now famous "seed and soil" hypothesis of metastasis.

"When a plant goes to seed," he wrote in an 1889 paper in *The Lancet*, "its seeds are carried in all directions; but they can only live and grow if they fall on congenial soil."

Paget was trying to understand the distribution of metastases in breast cancer – if all organs were equally receptive, he reasoned, then secondary tumors should be randomly distributed. But his examination of 735 case histories of fatal breast cancer revealed that metastases formed more often in certain organs, suggesting that those organs provide more fertile ground for tumor growth.

"The best work in the pathology of cancer is now done by those who … are studying the nature of the seed," he concluded. "They are like scientific botanists; and he who turns over the records of cases of cancer is only a ploughman, but his observation of the properties of the soil may also be useful."

How right he was.

The "soil" in which a tumor develops is a complex system of many cell types, diffusible growth factors, and the structural components of the extracellular matrix. Cells in the tumor microenvironment include vascular cells (endothelial cells, pericytes and smooth muscle cells), cells that respond to infection and injury (lymphocytes, macrophages and mast cells), and fibroblasts. Taken together, these components are called the "stroma," and it is the tumor-stroma interactions that ongoing research efforts seek to understand.

"There has been a growing appreciation that a tumor really is like an organ," Mohla says. "Tumors are not masses of autonomous cells; they are more like organs with their own vascular supplies, immune cells, structural matrix … and both the tumor and the stroma are co-evolving.

"To understand the continuum of cancer biology from initiation all the way to metastasis, we must focus on the tumor microenvironment."

This long-recognized concept of a tumor as an organ – a concept pathologists have "always known," Matrisian says – was overlooked in the hubbub that accompanied discovery of the first oncogene in 1970.

"We got very involved, for 30 years, on what happens inside the cancer cell, on the genetic changes that occur and cause tumorigenesis," Matrisian says.

This focus wasn't all bad; it contributed enormously to our understanding of oncogenes, tumor suppressor genes and signaling pathways, and to the development of successful targeted anti-cancer therapies like Gleevec and Herceptin.

Microenvironment trumps genetics

While most of the cancer research community focused on defining genetic mutations in the fast-growing cancer cells, some investigators

PHOTO BY TAMARA REYNOLDS

PICTURED ABOVE: Lynn Matrisian, Ph.D., helped organize an NCI workshop on epithelial-stromal interactions – an event that sparked collaborations that have blossomed into a promising network of tumor microenvironment research.

continued to probe the interactions of the tumor with its stroma.

The potential of a normal microenvironment to suppress tumorigenic potential was first reported in the 1970s. In a series of publications, investigators at the University of Pennsylvania and at the Fox Chase Cancer Center in Philadelphia showed that mouse teratocarcinoma cells – highly malignant cells that form tumors composed of varied tissue types – could develop normal tissues and generate normal mice when they were injected into early stage mouse embryos.

The studies "provided a striking exposition of the power of tissue context to modify the malignant potential of cancer cells," wrote Mina Bissell, Ph.D., Distinguished Scientist at Lawrence Berkeley National Laboratory, in a 2003 review. But "the implications of these experiments, that genetic alterations could be trumped by the microenvironment, were not widely appreciated as the oncogene paradigm and the importance of genetic changes in cancer rapidly took hold."

Bissell and her colleagues were undeterred. The group, now part of the NCI TMEN, pursued its interest in how tissue context contributes to tumorigenesis.

Focusing on the mammary gland as an experimental system, Bissell and colleagues developed a three-dimensional cell culture model. In this culture system, normal breast epithelial cells form growth-arrested multi-cellular structures that resemble mammary lobules *in vivo*, but breast carcinoma cells fail to "mature" into such structures and instead continuously grow in a disorganized fashion.

Blocking a single cell surface molecule, an integrin, on the surface of the tumor cells caused these cells to undergo a "striking morphological reversion," Bissell wrote, "becoming visually indistinguishable from the acinus-like structures formed by the nonmalignant cells." The findings, published in 1997, made other investigators take notice.

"For a lot of us, that was a very dramatic demonstration that you can override the genetics with the microenvironment," Matrisian says.

Matrisian was no stranger to thinking about the tumor microenvironment. Her own laboratory was exploring the roles of enzymes called matrix metalloproteinases (MMPs), molecular "scissors" that cut up proteins in the extracellular matrix. MMPs are now known to be present at high levels in tumors and inflammation, but not in normal tissues, and to participate throughout the processes of tumor progression, from initiation to metastasis.

At the request of the NCI's Tumor Biology and Metastasis Branch, Matrisian co-organized a 2001 workshop on epithelial-

stromal interactions and tumor progression. More than 90 percent of human cancers – the "carcinomas" – originate in epithelial cells. The 2001 meeting was the first of a series of workshops and then NCI-sponsored think-tanks from which a common theme emerged, recalls NCI's Mohla. "We kept coming back to the idea that if we knew more about the stromal cells, we would benefit more."

From the recommendations of the small group meetings, the division of Cancer Biology developed the concept of the Tumor Microenvironment Network. Matrisian is the principal investigator for Vanderbilt's program, called the VUTMEN. The overall network has broad goals, Mohla says, that emphasize understanding the host characteristics in normal tissues and studying human cancers.

Cancer's bad influence

The tumor microenvironment is awash in "conversations" between tumor cells and the cells that surround them. Cancer cells produce a variety of growth factors that "activate" the stroma to secrete additional growth factors and proteases, promote the growth of new blood vessels (angiogenesis), and induce an inflammatory-like response. These changes make the stroma supportive of cancer progression. Tumor cells also produce enzymes including MMPs that contribute to a pro-migratory, pro-invasive microenvironment.

The activating effects of the tumor on surrounding fibroblasts were first demonstrated by Gerald Cunha, Ph.D., and colleagues at the University of California, San Francisco. Cunha's group, including

Tumor forecast

Math modeling and computerized simulations predict tumor cell behavior

Vito Quaranta, M.D., clicks on a small black dot on his computer screen. The dot – which represents about a thousand cancer cells – begins to "grow," morphing into a mass with finger-like projections that looks like an invasive tumor.

Quaranta, professor of Cancer Biology, envisions a future when computer simulations like this will be used to predict a tumor's clinical progression and formulate individualized treatment plans.

This kind of approach is similar to forecasting the weather.

"Today we can know pretty well that for the next few days we're going to expect good weather or that there's a storm on the way," Quaranta says. "That's the kind of predictive power we want to generate with our model for cancer invasion.

"When a patient comes in with a tumor, we'd like to understand for that particular tumor, what are the chances that metastasis is going to occur? Does that patient need to be treated very aggressively, or not so aggressively?"

Quaranta and colleagues at Vanderbilt University and the University of Dundee in Scotland described a mathematical model for cancer invasion last December in the journal *Cell*. The model – a series of mathematical equations that drive computer simulations of tumor growth – suggests that the microenvironment around tumor cells determines the tumor's ultimate cellular makeup and invasive potential.

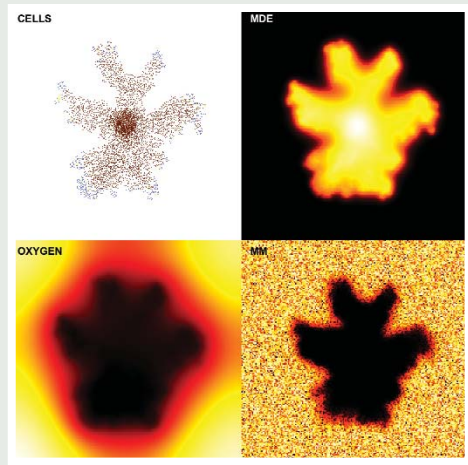
In mild microenvironments – imagine a lush tropical rainforest, Quaranta says – many cell types co-exist and the tumor shape is round with smooth edges, characteristic of a non-invasive tumor. Under harsh microenvironmental conditions – imagine a desert – the most aggressive cell types dominate and the tumor shape has fingering, invasive projections. In particular, the investigators found that they can modulate the tumor's degree of invasiveness by changing a single condition, oxygen concentration.

"That's what the mathematical modeling teaches you – tumor growth patterns may be very sensitive to outside input," Quaranta says. "By changing just one condition in the microenvironment, we can change a tumor from non-invasive to invasive."

The findings suggest that current chemotherapy approaches which create a harsh microenvironment in the tumor may leave behind the most aggressive and invasive tumor cells.

"In the immediate term we may be diminishing tumor burden, but the long-term effect is to have a much nastier tumor than there was to begin with," Quaranta says.

The math modeling team includes core members Alexander Anderson, Ph.D., associate professor of Mathematics at the University of Dundee; Peter Cummings, Ph.D., John R. Hall Professor of Chemical Engineering at Vanderbilt; and Alissa Weaver, M.D., Ph.D., assistant professor of Cancer Biology at Vanderbilt, working with a highly interactive and interdisciplinary group of cancer biologists, bioengineers, imaging scientists, computational biologists and mathematicians. The research is supported by the National Cancer Institute's Integrative Cancer Biology Program.



PICTURED ABOVE: A computer simulation of cancer cells (upper left) "growing" into the many-fingered shape characteristic of invasive tumors. MDE: matrix-degrading enzymes, MM: matrix macromolecules.

The application of mathematical modeling to cancer invasion reflects a broader theme, a sea change in "how biology is being done," Quaranta says. "We have mathematics driving experimentation."

VUTMEN and other efforts will test, validate, refine and add to the model.

"You go back and forth, and every time you get a new result, you correct the model, and you're a little bit closer to reality," he says. "This is a paradigm that is new to experimental biology."

– by Leigh MacMillan

PICTURED RIGHT: Tumor cells and cells in the microenvironment use molecular signals to have a back-and-forth "conversation." The tumor activates the microenvironment to produce growth factors and build new blood vessels that bring in supplies and provide a route for metastatic growth.

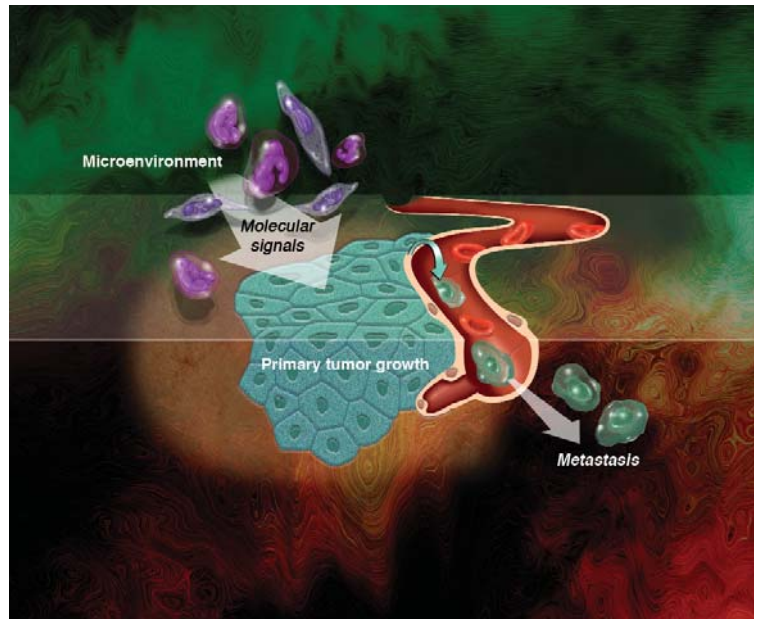


ILLUSTRATION BY DOMINIC DOYLE

Simon Hayward, Ph.D., now associate professor of Urologic Surgery and Cancer Biology at Vanderbilt and one of the VUTMEN project leaders, developed an *in vivo* "recombination model" to study interactions between human prostate epithelial cells and fibroblasts. In short, they combined the two types of cells, mixed them together with collagen – a structural Jello-like substance – and put the mixture under the kidney capsule in mice, an environment whose ample blood supply is able to support cell growth.

Combining normal prostate fibroblasts with normal or "immortalized" (able to grow continuously in culture) prostate epithelial cells did not generate cancer. But combining fibroblasts from prostate cancer – "carcinoma-associated fibroblasts" – with the immortalized epithelial cells generated malignant tumors. The studies showed that cancer changed the fibroblasts and made them capable of promoting tumorigenesis of nonmalignant cells, Hayward explains.

How do the fibroblasts promote tumorigenesis? What are the molecules that convey this particular message? Hayward and Neil Bhowmick, Ph.D., assistant professor of Urologic Surgery and Cancer Biology, are using the prostate tissue recombination model to probe these questions in one of the VUTMEN projects.

"We have the tools now to put specific genes into a tissue, or inhibit specific genes in a tissue, so we can really mix and match and see the effects of those manipulations," Hayward says. "Ultimately we're looking for the really key molecular pathways that are involved in the stroma acting to promote tumor progression, and which ones of those need to be taken out to prevent that progression."

In the case of prostate cancer, specifically, knowing the pathways that push progression will open up possibilities for moving the window of "active surveillance," Hayward says, so that the patient's cancer doesn't progress in his lifetime.

"Obviously we want to identify the disease early on and stop it progressing any further," Hayward says, "and if we have to intervene, we need to know the critical timepoint markers for intervention."

Focusing on a key growth factor

The VUTMEN has as its unifying theme a focus on transforming growth factor-beta (TGF-beta), a protein that is near and dear to its co-discoverer, Harold Moses, M.D., the Hortense B. Ingram Professor of Molecular Oncology and director emeritus of the Vanderbilt-Ingram Cancer Center.

TGF-beta is a "molecular Jekyll and Hyde" in cancer, Moses says; it can both suppress and promote cancer growth. It functions in normal cells as a tumor suppressor, and its loss is critical to tumorigenesis.

"If you look at the whole signaling pathway, most cancers have some aberration in one of the molecules necessary for TGF-beta growth inhibition," says Moses, who is leading another of the VUTMEN projects.

Once a carcinoma is present, TGF-beta switches personalities and promotes cancer progression. TGF-beta levels go up in the tumor microenvironment, and it acts to inhibit immune surveillance – mechanisms that fight against the cancer – and to promote the angiogenesis necessary to build tumor blood supply lines.

The tumor microenvironment is awash in "conversations" between tumor cells and the cells that surround them.

PICTURED RIGHT:
Leading the projects in Vanderbilt's Tumor Microenvironment Network are (left to right) Gregory Mundy, M.D., Harold Moses, M.D., and Simon Hayward, Ph.D.

PHOTO BY TAMARA REYNOLDS

In their quest to understand the complex nature of TGF-beta signaling in the tumor microenvironment, Moses and colleagues including Bhowmick generated mouse models in which the TGF-beta receptor (type 2) was eliminated only in certain types of cells. When they eliminated the receptor in fibroblasts, the mice developed prostate and forestomach cancers and died by eight weeks of age.

"To my knowledge, this is the first demonstration of the development of a carcinoma with the initiating genetic lesion in stromal cells," Moses says.

The findings suggested that TGF-beta normally acts in the stromal cells to suppress the development of cancer in the neighboring epithelial cells. So, not only can the microenvironment put pressure on existing cancer cells to "behave," it can directly contribute to tumor initiation.

Moses' VUTMEN team will extend their studies of the tissue-specific TGF-beta receptor knockouts – they are generating mice in which they can eliminate the receptor in an acute way, rather than from the beginning of its expression during development. The group also will explore TGF-beta signaling using breast tissue recombination models.

To probe the "conundrum" that both blocking and enhancing TGF-beta signaling promote cancer progression, Moses and colleagues are studying bone marrow-derived cells they call Myeloid Immune Suppressor Cells (MISCs). The investigators propose that blocking TGF-beta signaling enhances the expression of chemokines – signaling factors that influence immune system cells – which then recruit MISCs to the tumor. The MISCs, in turn, pump out more TGF-beta, other tumor-promoting factors, and MMPs to remodel the extracellular matrix.

"I think we're really just beginning to scratch the surface of understanding how important the microenvironment is in terms of how tumors behave."

"I'm pretty convinced that in many model systems, in many human cancers, the immature bone marrow-derived cells play a key role," Moses says. "So if we can figure out which chemokines and which chemokine receptors are involved in recruiting those cells … those molecules might offer good targets."

TGF-beta signaling is also a target of interest for cancer therapy, and small molecule inhibitors are already in clinical trials, Moses says, adding that caution is warranted given that inhibition of TGF-beta signaling in the stroma can promote carcinoma development.

The vicious cycle in bone

Another VUTMEN project, led by Gregory Mundy, M.D., will focus on a third microenvironment: bone. Both breast cancer – Moses' focus – and prostate cancer – Hayward's focus – metastasize preferentially to bone.

"When patients with breast or prostate cancer die, it's most often because the cancer has spread to bone, and in fact the bulk of the tumor burden is likely to be in bone," says Mundy, Oates Professor of Medicine and Pharmacology and director of the Vanderbilt Center for Bone Biology.

Bone offers fertile "soil" for breast and prostate cancer metastases, and Mundy and colleagues propose that TGF-beta is one key nutrient.

TGF-beta is stored in the bone matrix and released in its activated form when bone tissue turns over. It is likely important in normal bone remodeling and normal injury repair, Mundy says.

When tumor cells metastasize to bone, Mundy's group proposes that a "vicious cycle" begins to spin: the tumor cells stimulate bone resorption (bone-dissolving activity of osteoclast cells), active TGF-beta is released, and tumor cells behave aggressively to promote bone resorption.

The investigators are teasing apart the mechanisms by which TGF-beta causes this aggressive tumor cell behavior. In one model, they inject human breast cancer cells into the heart of immunodeficient mice, which develop bone metastases. The investigators examine those metastases – the tumor burden and the bone lesions, taking advantage of small animal imaging technologies available through the Vanderbilt University Institute of Imaging Science.

"When we follow these tumors, we're always looking at the effects on bone in parallel with the effects on the tumor," Mundy says. "That's going to be really important for patients, because if we can block this vicious cycle, we'll have effects not only on reducing the bone lesions, but also on relieving tumor burden.

"I think we're really just beginning to scratch the surface of understanding how important the microenvironment is in terms of how tumors behave."

NATIONAL CANCER INSTITUTE TUMOR MICROENVIRONMENT NETWORK

Bioengineering 3-D Models for Breast Cancer Therapy
Mina Bissell, Ph.D.
Ernest O. Lawrence Berkeley National Laboratory

Molecular and Functional Characterization of Colon Tumor Cancer Stem Cells and Stroma
Michael F. Clarke, M.D.
Stanford University School of Medicine

Novel Methods for Detecting Cell Interactions in the Tumor Microenvironment
John S. Condeelis, Ph.D.
Albert Einstein College of Medicine of Yeshiva University

Tumor Microenvironment Interactions in Brain Tumors
Eric C. Holland, Ph.D., M.D.
Memorial Sloan-Kettering Cancer Center

Tumor-Stroma Interactions in the Tumor Microenvironment
Richard Hynes, Ph.D.
Massachusetts Institute of Technology

Paracrine TGF-Beta Signaling in Tumor Initiation and Progression
Lynn M. Matrisian, Ph.D.
Vanderbilt University Medical Center

Significance of Microenvironment for Prostate Cancer Initiation and Progression
Stephen R. Plymate, M.D.
University of Washington School of Medicine

The Role of Inflammation and Stroma in Digestive Cancers
Timothy C. Wang, M.D.
Columbia University Medical Center, Irving Cancer Center

Co-evolution of the Reactive Microenvironment in Prostate Cancer Progression
David R. Rowley, Ph.D.
Baylor College of Medicine

TMEN Genomics and Bioinformatics Core
Lynda Chin, M.D.
Dana-Farber Cancer Institute

clearing the cloud of smoke

By Heather Newman | Photograph by Anne Rayner

Pam Collins was 21 and fresh out of college, when she heard about interviews for airline stewardesses. She had a college degree and her parents had different plans for their daughter, but Collins liked the prestige that came with the airline job, and the money sealed the deal. "They paid more than anyone else – $400 a month," Collins said.

But now she is the one paying. Collins is living with inoperable lung cancer. "They think it's a good likelihood that I got this from secondhand smoke exposure," she said. "Nobody smoked in my family. There was high blood pressure and heart disease, and I thought that would be my nemesis. Never in a million years did I think it would be cancer."

During Collins' three decades as a stewardess, smoking on planes was commonplace – practically encouraged, she recalls. "They put these little five-pack cigarettes on their trays. We gave them away. They sat by me and blew smoke in my face for hours while I sat in the jump seat," said Collins, 60. "It was awful. There was no designated smoking and non-smoking area. I just don't think we thought about the impact. We didn't have all the information."

Today, the cloud of smoke is clearing and more people are beginning to see the dangers of smoking and secondhand smoke, including here in Tennessee, where the General Assembly just passed a historic ban on smoking in most – but not all – public places and voted to raise the cigarette tax by 42 cents. Efforts by groups like SmokeFree Nashville and the Campaign for a Healthy and Responsible Tennessee (CHART) are making headway in the historically tobacco-driven state and legislature.

The movement in Tennessee and other states has gained ground, in part, due to a recent scientific report from the U.S. Surgeon General Richard Carmona. The report found that even brief secondhand smoke exposure can cause immediate harm. "The scientific evidence is now indisputable: secondhand smoke is not a mere annoyance. It is a serious health hazard that can lead to disease and premature death in children and nonsmoking adults," said Carmona when the 2006 report was released. William Blot, Ph.D., professor and cancer epidemiologist with Vanderbilt-Ingram and the International Epidemiology Institute, contributed to the report.

Secondhand smoke is the combination of smoke from the burning end of the cigarette and the smoke exhaled by smokers. There is no safe amount of secondhand smoke, according to the Centers for Disease Control and Prevention (CDC). Breathing even a little secondhand smoke can be dangerous. "Tobacco smoke dramatically affects virtually every part of the body," said Terry Pechacek, Ph.D., associate director for Science for the CDC's Office on Smoking and Health. "It has a powerful ability to impact the whole structure of DNA."

You are what you inhale

Why is smoking and exposure to secondhand smoke so dangerous? Secondhand smoke contains more than 4,000 chemicals, many of them toxic. "There are over 60 carcinogens in tobacco smoke," said Pechacek. They include things like arsenic, commonly used in pesticides; hydrogen cyanide, used in chemical weapons; polomium-210, a radioactive and highly toxic chemical; and formaldehyde, used to embalm dead bodies.

Exposure to these chemicals through secondhand smoke makes the platelets in your blood behave as if you were a regular smoker. Even after a short time in a smoky room, the chemicals seep into your bloodstream and cause the platelets in your blood to stick together. Tobacco smoke also damages the inner lining of your blood vessels. The carbon monoxide found in cigarettes binds to hemoglobin in red blood cells and prevents affected cells from carrying a full load of oxygen. Adults who breathe five hours of secondhand smoke a day have higher, artery-clogging bad cholesterol. Nonsmokers who breathe secondhand smoke are more likely to develop lung cancer, heart disease and other serious diseases. If you inhale secondhand smoke at home or work, your chances of getting lung cancer are increased by 20 percent to 30 percent.

Children are even more vulnerable. They are more likely to have lung problems, asthma, ear infections, sudden infant death syndrome (SIDS), and other serious health problems from secondhand smoke exposure. The city of Bangor, Maine, has made it illegal to smoke in vehicles when children are present. Similar measures have been adopted in Arkansas and Louisiana and are being considered in several other states.

Tobacco states lag behind

Much of the United States is getting this message, with 22 other states passing laws to ban smoking in public places. Tennessee lagged behind. Smoking was only recently banned in Tennessee's government buildings, where this kind of legislation would be determined.

The tobacco-growing state faces an uphill battle against the cash and the culture that came with the crop for so many years.

Pam Collins, at 21, just beginning her career as a flight attendant, and years later before knowing what would lie ahead.

"Nobody smoked in my family. There was high blood pressure and heart disease, and I thought that would be my nemesis. Never in a million years did I think it would be cancer."

"Traditionally we have been a tobacco growing state with a very big tobacco lobby. For many years they have had a lot of power and say-so in the government," said Jason Stamm, Tobacco Control Coordinator with the Metro Public Health Department in Nashville. "We are definitely behind the curve."

Tennessee has one of the lowest tobacco taxes in the nation, at just 20 cents per pack, and there are no smoke-free workplace laws on the books. Stamm said 22 states have some kind of protection in place. In Tennessee, local communities don't have the authority to ban smoking in public places, as has occurred in New York City, for instance. A growing number of restaurants in Tennessee have voluntarily eliminated smoking, but a city government can't decide to ban smoking in all restaurants and similar businesses. That, too, is something advocates like Stamm are trying to change.

Donna Henry, M.P.H., R.D., director of the Health Promotion Division in the Tennessee Department of Health's Community Services Section, said 1 million Tennesseans, or about 26 percent of adults in the state, smoke cigarettes and another 4 percent use snuff or chewing tobacco. These people are at greatest risk for oral, head and neck cancers. In addition, 14 percent of public high school students in Tennessee reported using smokeless tobacco products and about 27 percent reported they smoke cigarettes. All that smoking, chewing and dipping takes a toll; Tennessee ranks fourth in the nation for lung and bronchus cancer deaths.

Funding for tobacco prevention programs in Tennessee is also one of the lowest in the country, Henry said. "It makes it harder to counteract the marketing and advertising efforts that are being used in Tennessee by manufacturers of tobacco products," she said. Tobacco companies spend $227.2 million a year to advertise in Tennessee.

Funds received by each state from a multi-state lawsuit settlement against tobacco manufacturers have been put to use for tobacco prevention programs in most states, but Henry said Tennessee elected to place the settlement money into a general fund, allowing for a limited amount of state funds for her programs targeting tobacco. Tennessee receives in excess of $250 million a year in settlement funds, yet Henry said most funding for programs in Tennessee comes from the federal level by the CDC.

Changes on the horizon

But the tide is slowly beginning to turn in Tennessee and other states. Tobacco is not the cash crop it once was. "It used to be one of the top crops in Tennessee, but it's struggling to be in the top 10 now," Stamm said. Tennessee production of burley tobacco, which is chopped up and used to make cigarettes, has dropped by 111 million pounds since its peak in 1982, according to the state Department of Agriculture.

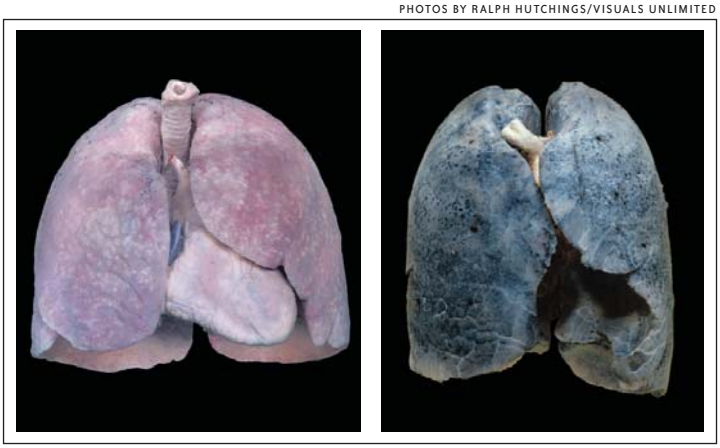
Income from tobacco totals less than what tobacco cost Tennessee in health care dollars. In 2002, an estimated 50 percent of smokers in Tennessee were Medicaid or TennCare recipients. The cost to the state for smoking-related Medicaid costs per capita was $142.6 million. The economic toll of tobacco use is staggering, with about $1.69 billion spent each year on smoking-related health costs in the Volunteer State.

With the cost, the new data from the Surgeon General's report and the consistent efforts of several state organizations in mind, Tennessee Gov. Phil Bredesen weighed in on the fight against the dangers of tobacco use. He proposed a ban on smoking in

According to the National Cancer Institute (NCI), cigarette smoking causes 87 percent of lung cancer deaths and is responsible for other cancers such as cancer of the larynx, oral cavity, pharynx, esophagus, bladder and more. Secondhand smoke is also responsible for about 3,000 lung cancer deaths each year among nonsmokers. Tobacco use, particularly smoking cigarettes, is the single most preventable cause of death in the U.S. Cigarette smoking alone accounts for about 30 percent of all cancer deaths in the country.

The American Cancer Society said cigarettes kill more Americans than alcohol, car accidents, suicide, AIDS, homicide and illegal drugs combined.

PHOTOS BY RALPH HUTCHINGS/VISUALS UNLIMITED



A look inside the body at a set of pink, healthy lungs, compared to the blackened lungs of a smoker.

workplaces, as well as increasing tobacco taxes by 40 cents, bringing the total to 60 cents, which would still be well below the national average.

As the legislative session neared an end, the General Assembly approved, and sent to Bredesen for his signature, bills to ban smoking in enclosed businesses with more than three employees, effective Oct. 1, and a 42-cent hike in the cigarette tax, raising it on July 1 to 60 cents per pack, still below the national average of 80 cents. The smoking ban has exemptions, including bars that serve only patrons over age 21 and up to a quarter of the state's hotel rooms, but anti-tobacco advocates called it a break with Tennessee's tobacco ties and smokers railed against the perceived infringement on personal rights.

Nationally, the latest American Cancer Society figures show fewer Americans are dying from cancer for a second straight year, and this time by a greater number. Officials say this drop shows prevention and treatment efforts, including anti-smoking efforts, are paying off. However, lung cancer deaths, which dropped among men, increased among women. Health officials say that is due, in part, to the fact that women traditionally begin smoking at a later age than men.

The Speaker of the U.S. House of Representatives, Rep. Nancy Pelosi, made banning smoking a top priority after taking her seat as the first female house speaker by stamping out smoking near the house floor.

The advocacy group Americans for Non-smokers' Rights says for the first time in the nation's history more than half of Americans live in a city or state with laws mandating workplaces restaurants or bars be smoke-free, and they think all of Americans will live in smoke-free places in a few years. Seven states and 116 communities enacted tough smoke-free laws in 2006, bringing the numbers to 22 states and 577 municipalities across the country, and making last year the most successful year for anti-smoking advocates.

> "I just want to have a good quality of life while I'm living. As long as I can stay the same or get better, I'll continue."

Until the last breath

It's all good news to Pam Collins, as she continues chemotherapy to try to keep her lung cancer from spreading. She has three tumors in her liver, one in her right kidney, and the one in her lung that can't be removed because it is too close to her heart.

So the Atlanta resident makes the three-hour trip each month to Vanderbilt-Ingram Cancer Center for treatment and tests. It's a routine she'll continue until she takes her last breath. She compares her situation with that of a recent high-profile lung cancer patient, Christopher Reeve's widow, Dana. "I've been alive for a year and a half with this diagnosis and I have the same lung cancer that Dana Reeve had and she lasted six months," said Collins.

She went to several other cancer centers and saw several other physicians, some much closer to her home, but Collins said Vanderbilt is the only place that offered her hope. "I came here to see Dr. [David] Johnson and felt very connected to him."

For now, her tumors aren't growing and doctors haven't discovered any new ones. So Collins tries to keep a positive attitude while she's in for, literally, the fight of her life. "I just want to have a good quality of life while I'm living. As long as I can stay the same or get better, I'll continue. I know I will know when enough is enough," she said. "I look at it this way, if it's not cancer it will be something else that will come to test you. I just decided that I couldn't dwell on it."

PHOTO BY SUSAN URMY

LUNG CANCER RESEARCHER GETS BOOST FROM FLIGHT ATTENDANTS' GROUP

PHOTO BY DEAN DIXON

Datta has a three-year grant from FAMRI for $100,000 a year to continue his work looking for clues in lung cancer.

Pran Datta, Ph.D., a Vanderbilt-Ingram member who is currently studying an important protein in cancer research, transforming growth factor beta (TGF-β), has received funding from the Flight Attendant Medical Research Institute (FAMRI) to look for clues in the fight against lung cancer.

"We are looking for how TGF-β signaling is lost in lung cancer," Datta said. "In more than 77 percent of cases TGF-β type-2 reception is lost or very reduced and we're trying to understand why the receptor is lost." Datta has a three-year grant from FAMRI for $100,000 a year to continue his work.

Patty Young, a trustee with FAMRI, said supporting research like Datta's, that could help former flight attendants like her, is key to the organization's mission. The group was established as a result of a class action lawsuit brought against the tobacco companies on behalf of non-smoking flight attendants in Miami-Dade, Fla. Among other considerations, $300 million was awarded to form a scientific and medical research institute. "We're committed to funding research worldwide to cure diseases caused by exposure to tobacco smoke," Young said.

Young has made the fight against secondhand smoke exposure her life's mission. She flew for nearly 30 years on smoky planes. "We were the canaries in the coal mines," Young said. "When I started flying, I was as Pollyanna as you can get. I thought everything was just fabulous," she added. Then she started watching her friends die, all former flight attendants. "We were all non-smokers being murdered by secondhand smoke."

Lung cancer took the lives of both of her parents, but Young herself has been spared a diagnosis with the deadly disease, so far. She has been told by her physicians that she has the lungs of a long-term smoker. "I worry all the time. I never stop coughing. I have severe allergic reactions to tobacco smoke," Young said.

The advocate said she has strong words for tobacco smokers. "I say they have a profound responsibility first to those around them and then to themselves. Your tobacco addiction comes with great responsibility," Young said.

Until the war on tobacco has been won and cures for the diseases linked to tobacco smoke have been found, Young said her work and FAMRI's will continue. And Datta's research could unlock the answers Young and her colleagues, and so many others, have been waiting to hear. "We're trying to take this research from the lab or the bench to the bedside for the clinical benefit to patients," said Datta.

If you need help to quit smoking in Tennessee, call: 1-800-QUIT-NOW (1-800-784-8669). The help line will connect you to a free quit coach who specializes in tobacco addiction and dependency. For hearing impaired call: 1-877-559-3816. Outside of Tennessee, call the National Cancer Institute's Smoking Quitline: 1-877-44U-QUIT (1-877-448-7848).

Information about the SmokeFree Tennessee Campaign can be found online at: www.smokefreetn.org.

Campaign for a Healthy and Responsible Tennessee or CHART, is a membership-based, grassroots coalition focused on educating and motivating Tennesseans to take a stand on key health issues, including tobacco. To get involved log on to: www.tnchart.org.

the common thread

By Nancy Humphrey | Photography by Dana Johnson and Susan Urmy

Volunteers at the Vanderbilt-Ingram Cancer Center come from all walks of life – a retired minister who offers snacks and a kind, sympathetic ear; a Vanderbilt undergraduate whose calming piano music provides a temporary distraction in the waiting room; an aging golden retriever therapy dog who's always game for a scratch behind the ears; a retired Hendersonville English teacher who makes brightly colored quilts to keep patients warm.

Different talents from different personalities, but all with the same goal: making the day better for patients and their families at Vanderbilt-Ingram.

There are 26 dedicated volunteers who visit the Vanderbilt-Ingram Cancer Center on a weekly basis. From July 2006-March 2007, they had provided more than 700 hours of service to Vanderbilt-Ingram patients and visitors.

The number doesn't include countless others from Nashville and surrounding communities who help out in other ways, such as church groups who collect and donate bottled water and snacks or make hats and blankets to keep patients warm and comfortable.

"We have lots of opportunities for people in the community to be involved," says Greg Martin, manager of Patient and Family Support Services for Vanderbilt-Ingram. "A lot of people can't come down here two hours a week, but they can do something that makes a difference, where everybody feels good about it in the end."

Cancer Center volunteers must go through an application and approval process that involves a background check, health record check and the administration of vaccinations if required. Volunteers must be at least 18 and must be able to commit a minimum of two hours a week to volunteer, Martin said.

National events might have contributed to a rise in volunteers, a federal study shows. From 2002 to 2005, basically right after 9/11 through the devastation of Hurricane Katrina, the number of volunteers nationwide increased by about 5.6 million. The study, released in 2006 by the Corporation for National and Community Service, shows that 65.4 million – 28.8 percent of American adults – volunteered in 2005, compared to 59.5 million in 2002.

In 2005, most volunteers were between 35 and 44, there were more women volunteers than men, and more were married than not.

The greatest percentage of volunteers in the U.S. volunteered through religious organizations (34.8 percent) with only 7.7 percent reported volunteering at hospitals or other health facilities.

Breaking the information down by state, Utah has the highest volunteer rate with 48 percent. Tennessee ranks very low – 41st – in the ranking with only 25.9 percent volunteer rate. However, when you look at median hours spent on volunteer activities, Tennessee does better. The state median volunteering hours ranged from 36 to 96, and Tennessee is in between, with 52.

Another recent study by the corporation shows that baby boomers are volunteering at higher rates than their predecessors, the Greatest Generation and the Silent Generation, did at their age. Baby boomers were volunteering at lower rates than their predecessors while in their 30s, but that trend has reversed as they've grown older. The report also shows that the more often baby boomers volunteer, the more likely they are to volunteer again, and those who volunteer 12 weeks or more annually are most likely to serve year after year.

Six Vanderbilt-Ingram volunteers recently talked to *Momentum* about the gifts they give and receive by volunteering.

Ministering to many needs

Bob Richardson speaks softly as he walks down the halls of Vanderbilt Ingram's Henry-Joyce Cancer Clinic. Wearing neatly pressed khaki pants and a vest with a Vanderbilt-Ingram pin, the gray-haired, 80-year-old retired Presbyterian minister greets a patient who is pulling an IV down the hall. "Mornin', you OK?"

He pushes a steel cart with three carafes of coffee, cups, a nearly empty plate of donuts donated by a Nashville donut shop, and a basket of bananas. It's nearly time to replenish the donuts, as he goes from room to room offering snacks. As he leaves each room, he tells the patients and visitors to "have a nice day."

For two hours nearly every Thursday morning for nearly the past decade, Richardson has pushed the cart and visited with patients. Some haven't had breakfast. They welcome the donuts and fruit. Others want to talk. "The food isn't as important as the visit in my judgment," Richardson says. "Many of our patients have friends or family members who come in with them. We're serving their needs as well as the patient's." Richardson never forces a patient to talk, but many welcome the opportunity. With years of pastoral experience behind him, he's a good listener.

"I saw a guy in here today who had gone into remission, but now has a breakout of tumors in his abdomen. He's back here for another round of chemo," Richardson says. "I sat down with him and talked to him to find out how he's doing. He was not prepared for this recurrence of cancer, and was pretty upset about it, trying to deal with it. I let him know I was thinking about him and that I care about him."

Richardson isn't one to leave his volunteer job behind at Vanderbilt-Ingram. It's with him every hour of the day. "I have a prayer list at home, and a number of the people I meet here are on it. I think it helps people when they know they're being prayed for."

Speaking words of wisdom

It's a quiet afternoon in the Cancer Clinic; not many patients waiting to be seen, but the ones who were there listen quietly as **Anju Mammen** plays the piano. The Vanderbilt University senior visits the clinic each Friday afternoon, playing by ear an assortment of Christian hymns, and easy-listening and contemporary music for the patients.

A male patient approaches Mammen quietly with a request, The Beatles' "Let it Be." "Will you just keep playing that over and over again?" he asks. And she does.

> *"When I find myself in times of trouble, mother Mary comes to me,*
> *speaking words of wisdom, let it be.*
> *And in my hour of darkness she is standing right in front of me,*
> *speaking words of wisdom, let it be.*
> *Let it be, let it be, let it be, let it be.*
> *Whisper words of wisdom, let it be."*

"Patients ask me to play songs all the time," says the Augusta, Ga., native. "Sometimes you just need to get your mind off things. It's soothing music and it relaxes me. I hope it does the same thing for the patients and their families."

Mammen started volunteering at Vanderbilt-Ingram after she heard about the Cancer Center's music program. Before she sits down at the piano in the clinic's waiting room, she makes sure that coffee is made and the snack supply is stocked. She plans to be a doctor, and feels that her volunteer time at the Cancer Center has prepared her well. "It's a great opportunity to get to know patients, to get used to patient interaction," she says. "These are the sweetest patients. The staff is amazing. They make every day I volunteer easy. I've loved it."

Mammen says that although she is a busy college student, it hasn't been hard to find the time to come to the Cancer Center every week. "It's only two hours in my week."

Showing her appreciation

When **Peggy Wood's** husband, Harry Joyce, died of cancer in 1981, the Cancer Center was basically three infusion chairs in a dark corridor of Medical Center North. "It was little and dark, but they cared," said Wood.

She saw such dedication there that she and her family became involved with the Cancer Clinic, which is dedicated to the staff for their care and dedication to meeting the needs of patients. Her interest has helped with faculty recruitment and training of the next generation of scientists. Wood is also a member of the Clinic Expansion Advisory Committee, which has provided input on the design of the ongoing renovation and expansion of the clinic. She

"A lot of people can't come down here two hours a week, but they can do something that makes a difference."

Bob Richardson

Anju Mammen

Peggy Wood

has served for many years as a volunteer on the Cancer Center's Board of Overseers, and is now an emeritus member.

But Wood's dedication to the Cancer Center doesn't end with committee meetings. She's at the Cancer Clinic every Tuesday morning, pushing the refreshment cart and talking to patients and their families if they want to talk. She hands out pillows if they need them, and gets them something to read if they need reading material. If a patient has to bring a child with them to the infusion area, she gets crayons and a coloring book to help keep the child occupied. "I just love and enjoy the patients and enjoy helping make them more comfortable," she says. "I get a great deal of satisfaction going down there and doing what I can."

Wood says she believes the community is fortunate to have a National Cancer Institute-designated Comprehensive Cancer Center at its own back door.

"We are so fortunate to have this cancer center here. We don't have to take an airplane and stay in a hotel to get excellent care. People can stay in their own homes with their own support systems. That's important."

Grief didn't keep her away

Nancy Webb and cancer are not strangers. She lost her 21-year-old son, Vann, nearly four years ago to cancer.

"Our second home was Vanderbilt. It became like family to us. He felt comfortable there, and we did too," she said.

Webb said she waited a while after her son's death to volunteer. "I had to wait long enough, just to get through a certain grieving process," she said. "Time went by, and I felt like I wanted to give back because of how Vanderbilt helped us."

So beginning this past fall, Webb began volunteering at lunchtime on Mondays. She hands out refreshments, but is also there if patients want to talk. "I feel like in some ways it's easier for me than for someone who hasn't been through the cancer experience," she said. "I'm not shocked when I see people who are really sick while they're in the infusion area. It doesn't faze me. I've lived it."

Webb said she's established relationships with patients who have their regular visits on Mondays.

"I see a lot of the same people week after week. There's one

Nancy Webb

Sarah-Jane Mitchell and QBert

Janice Slaughter

couple who drives in from somewhere outside the Nashville area. I was sick one Monday, had a cold, and the Cancer Center was the last place I needed to be. I didn't want to get any of the patients sick. But when I came in the next week, they told me they had missed me. That meant a lot to me."

A four-legged volunteer

The Vanderbilt-Ingram volunteer makes her way cautiously into a patient's infusion room. She sits down slowly by the patient, not making a sound, a welcome diversion from the cancer-killing chemicals that pour into the patient's body. The patient smiles. The volunteer wags her tail.

QBert is a 12-year-old golden retriever who has been a certified therapy dog for the past 11 years. She has been volunteering at the Cancer Clinic with her owner, **Sarah-Jane Mitchell**, almost every Wednesday for the past eight years. QBert wears a green vest, identifying her as a therapy dog. A message on the vest reads, "Ask to pet me. I'm friendly."

Mitchell takes QBert room to room on a leash, asking before she enters if the patient wants a visit. Most do. "It's such a hopeful place to come," Mitchell says.

QBert has reddish fur and a snout that is mostly gray. She's clean and neatly trimmed. She sits quietly once she enters an infusion room, or if she feels like the patient wants her to, she will lie on the floor near the infusion chair. She runs only once during a recent two-hour stay at the clinic – making a beeline toward the nurse's station where her favorite nurse, Linda Bates (favorite only because she is the keeper of the dog treats) greets her with squeals. "I love you. I love you," Bates says. "Let me rub your belly because I don't have any

"The staff is amazing. They make every day I volunteer special."

biscuits today." QBert, named for a 1980s Atari game, willingly accepts the belly rub.

"QBert loves people," Mitchell says. "She's never met a stranger. Everywhere we go, we see somebody we know. Once we were hiking in East Tennessee, and someone came around the corner and said, 'there's QBert.' My husband just couldn't believe it."

Mitchell says that she tries to avoid discussing the patient's illness when she and QBert visit the infusion area. "I don't mind talking about it, but if people don't want to, we don't. It's none of my business why they're here. We mostly just talk about their pets.

"I remember one patient who didn't know anybody when she came here from out of state," Mitchell says. "She said when QBert stuck her head around the door, she felt like she had come to the right place, that any place that had a pet therapy program was a good spot for her," Mitchell recalls. "I think that QBert is primarily a diversion for patients here, a good opportunity to think about something else. She also probably brings a touch of home and helps bring some happiness here. But I know I've gained way more than I've given."

Warm quilts for cold times

Janice Slaughter (pronounced Ja-neese) started making quilts soon after she retired from teaching English in Hendersonville. She made one for each member of her family, made them a second one, started making them for friends of friends, then turned her focus to church members at Good Shepherd United Methodist Church who had cancer, and family members of church members with cancer.

A friend suggested she call Vanderbilt, and Slaughter contacted Greg Martin at Vanderbilt-Ingram's Patient and Family Support Services, who enthusiastically welcomed her donation of several brightly colored lap-size quilts and small teddy bears that she also makes. To date, she's donated 15 of her quilts – each takes 40 to 60 hours of hand and sewing machine work and costs about $50-$75 to make. Each is unique, although a few have had a pink ribbon fabric to give to patients with breast cancer.

Some of the materials have been donated. She has been given leftover fabric scraps from a mother who was making a dress for her daughter, and fabric from sewing friends who have died. "There's an awareness out there that 'Janice uses anything' and people can pass it on if they're cleaning out their house and find some fabric, batting or spools of thread," she says.

Slaughter has received handwritten thank-you notes from some of Vanderbilt-Ingram's patients who have received her quilts. "One woman wrote me and said she understood the work involved because her mother quilted. She said she understood the value, the work, the purpose. She said she'd treasure it."

The quilts are made of 100 percent cotton and are intended for heavy use, not to be put in a closet and saved for someone, Slaughter says. "One of my quilts is like Linus' blanket. It's something that people can hang onto because it's small. If it gets stained, that's good. That means they're using it, loving it, it's theirs."

Gifts of Time, Talent Key to Team Effort Against Cancer

Cancer and the devastation it causes is too daunting a health challenge to be conquered without a true team effort. Volunteering is one important way you can be a part of that team. Your gifts of time, talent or financial support can make a huge difference in the lives of cancer patients and their families, today and in the future. Among ways to help:

Volunteering with patients undergoing treatment
There are many volunteer opportunities at Vanderbilt Medical Center, many of them at the Cancer Center. To volunteer with patients undergoing treatment, you must be 18 years old a high school graduate, and available at least two hours a week (or four hours every other week). For more information, contact Greg Martin at (615) 343-7776 or e-mail gregory.r.martin@vanderbilt.edu.

Service opportunities with Vanderbilt-Ingram's Patient and Family Support Services
For those who are unable to volunteer in this way, other opportunities exist to get involved, including making hats, turbans or scarves for patients or providing items on the Patient and Family Support Services Wish List. For more information, contact Greg Martin at (615) 343-7776 or e-mail gregory.r.martin@vanderbilt.edu.

Current wish list items include:

- Bottled water
- Canned soft drinks
- Peanut butter crackers
- Hot chocolate
- Apple cider
- Tea
- Hard candy
- Coloring books
- Puzzles
- Board games/word games

STORIESOFSURVIVAL

LINDA MCVAY

In Her Own Words

By Linda McVay | Photograph by Anne Rayner

Linda's "blood brother" sent her a framed poem before they ever met. She treasures the words and the special gift:

Just think, you're here not by chance
but by God's choosing.
His hand formed you and made you
The person you are.
He compares you to no one else –
you are one of a kind.
You lack nothing that His grace can't give you.
He has allowed you
to be here at this time
in history to fulfill
His special purpose
for this generation.

– By Roy Lessin, "Just Think."

Have you ever wondered why you are here? What your purpose is? Can you imagine being given the opportunity to potentially save someone's life?

On Dec. 30, 1996, I started working for Vanderbilt's Bone Marrow Transplant Program. I knew nothing about bone marrow transplant, but I was very eager to learn. I knew it meant helping people with potentially fatal diseases, and that was enough for me to know I would love the job.

Soon after my training began, I learned I would be working with a network called the National Marrow Donor Program (NMDP). The network consists of transplant centers, donor centers and collection centers from all around the world. This makes it possible for a patient in the United States to be transplanted using a donor from as far away as London, England, but neither the patient nor the donor has to leave the country. I was tasked with helping these donors and potential recipients connect from around the globe.

It was early in my new role that I learned about the ever-increasing need for more volunteer donors on the NMDP registry. I was very intrigued at the thought of being a donor. The one question that kept racing through my head was how do I sign up?

About a decade later, I learned the answer to my burning question and got my chance at saving a life. It had been years since I was "typed" and entered in the National Marrow Donor Program database, and not a day went by that I wondered when my time would come. I just wanted to be sure I didn't miss the opportunity to donate.

I finally got that call on April 19, 2000. I got word that I had potentially matched with a recipient, a baby girl, not quite a year old, who had leukemia and who was in desperate need of a stem cell transplant. There is no way to put into words how excited I was to be receiving that call. Was this precious baby going to be my recipient?

It was not to be. I was not a match to this baby. But I wasn't ready to give up. The years passed and although many times I wondered if a second chance to be an unrelated donor would arise, I knew my recipient was out there.

May 26, 2005, started out as just another day, but quickly there was a life-changing turn in my quest to be a donor. In the early afternoon hours, I received a request for more testing for another potential recipient. I knew this might be it. All I could do was wait. I am not a patient person, and I had been waiting to give the gift of life for seven years.

My phone finally rang on July 14, 2005, at 6:30 p.m. I was asked to undergo the more extensive testing required of donors to determine if they are a suitable match. I was ready. I knew barring any unforeseen abnormalities in my tests, this was it. Per NMDP guidelines, all I could be told about my recipient was he was a 61-year-old man with refractory acute myelogenous leukemia. I knew, due to his age, he would have to undergo a reduced intensity transplant. For a man of his age, with his type of disease and that type of planned transplant, the outcome wasn't too promising.

All of my testing went very well and things looked very promising. I was finally able to breathe a sigh of relief when a date was set. I would become a donor on August 4, 2005. In preparation for my stem cell donation, I had to undergo five consecutive days of injections. The injections would mobilize (or multiply) my blood stem cells, so there would be an adequate number of cells for transplant to my recipient. I prayed hard and often that the injections would be successful and there would be more than enough cells to cure this man of his potentially fatal disease.

The process is fairly simple and relatively painless. The injections didn't hurt, but I did take a little Tylenol to help the minor aches and pains. I know my minor aches were nothing compared with the pain that the man that I was to be a donor for and his family had endured.

My stem cell collection was set for the early morning on Aug. 4, 2005. The day I had hoped and dreamed about had finally arrived.

PHOTO BY NEIL BRAKE

PHOTO BY NEIL BRAKE

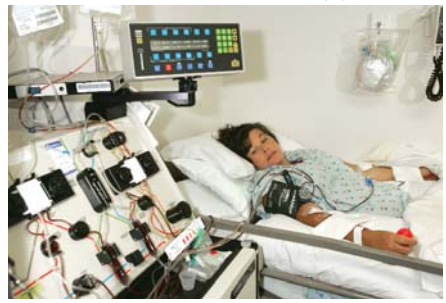


PHOTO COURTESY OF NATIONAL MARROW DONOR PROGRAM

PHOTO COURTESY OF NATIONAL MARROW DONOR PROGRAM

PICTURED HERE: (top left) Linda looks on as nurses show off her life-saving stem cells and a special gift she sent with them to her recipient. (top right) Linda lies in wait as her stem cells are removed through an IV in her arm using this special machine. (bottom) Linda and her "blood brother," Jim Caygle, after their first meeting.

I did not need 1,200 people cheering for us, I only cared to meet him, and see for myself that my cells had done their job.

Here is how stem cell donation works: Your blood is removed through an IV line in one arm, just like a blood test. A special machine sorts out the life-saving stem cells and funnels them into a bag to be sent to the recipient. Then your blood, minus the stem cells taken out for transplant, is sent back into your body through an IV in the other arm. It felt just like getting a blood test, except in this case, you have to lie very still for several hours while the entire process takes place.

The transplant was behind us and I now had a new name for the man that until now I referred to as my recipient. I called him my "blood brother," and his wife became my "blood sister-in-law." NMDP guidelines dictated that we were not permitted to have direct correspondence for one year. I didn't even know if they shared the desire to have direct contact with me, so I would have to wait and see.

Fifteen months after I donated stem cells for my blood brother, my husband and I traveled to Minneapolis, Minn., where I met Jim Caygle and his wonderful wife, Pat. Our first meeting was at the NMDP council meeting, in front of approximately 1,200 people. I never dreamed that our meeting would be that exciting. I could have met Jim on a dirt road in the backwoods of Alabama, with not a single soul around but us, and I would have been just as excited. I did not need 1,200 people cheering for us, I only cared to meet him, and see for myself that my cells had done their job.

Since our meeting, we have kept in very close contact. Not more than a few days go by before Pat is calling with either an update on Jim or just to check in and see how we are doing. The Caygle family and the McVay family share something that will always make us feel like family, something we cannot quite explain, something that is in the blood.

INTERESTED IN BECOMING A DONOR?

In Tennessee, contact:
Blood Assurance
1-800-962-0628
or
Cooperative Appalachian Marrow Program (CAMP)
(423) 854-5658

Outside Tennessee, contact:
National Marrow Donor Program
1-800-MARROW2
Or online at: www.marrow.org

For information about umbilical cord blood donation contact:
Cryobanks International
1-800-869-8608

quicktakes

Vanderbilt-Ingram becomes member of prestigious cancer alliance

Vanderbilt-Ingram Cancer Center has been named a member of the National Comprehensive Cancer Network (NCCN), an alliance of the world's leading cancer centers.

The NCCN includes centers dedicated to improving the quality, effectiveness and efficiency of oncology practice so patients can live better lives. Vanderbilt-Ingram is now the organization's 21st member.

"We welcome Vanderbilt-Ingram Cancer Center to the NCCN. Vanderbilt-Ingram is one of the nation's leading cancer centers, with more than $150 million in annual research funding," said William T. McGivney, Ph.D., Chief Executive Officer of NCCN. "Through their interdisciplinary collaborative methods, VICC is highly regarded as a leader in the development and delivery of high-quality cancer care."

"Vanderbilt-Ingram is very pleased to join the NCCN," said Jennifer Pietenpol, Ph.D., interim director of Vanderbilt-Ingram. "Promising discoveries in cancer research are being made every day, but our work is not finished until those findings are translated into advances in patient care. We are excited to join this group of cancer centers to help make that happen."

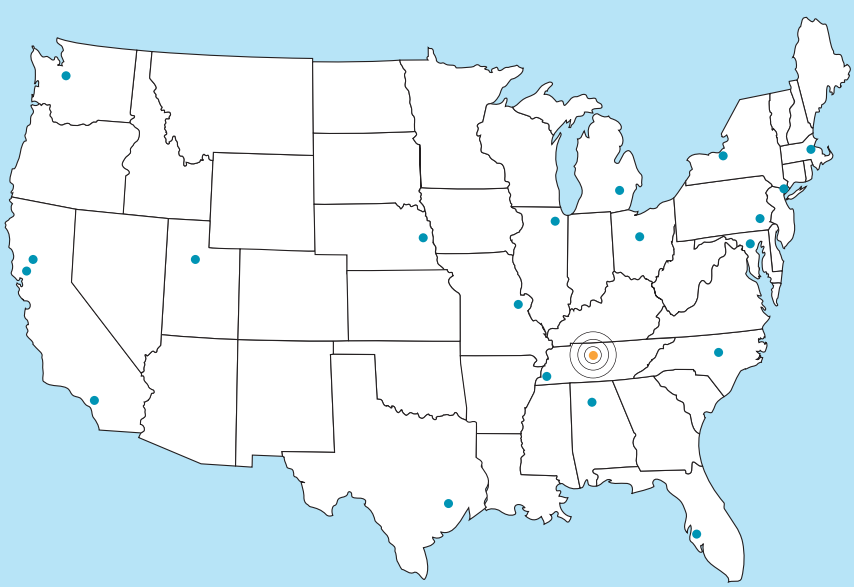
Harold L. Moses, M.D., Vanderbilt-Ingram's founding director and director emeritus, noted that joining NCCN had been a longtime goal of the cancer center. "I am very pleased that we have achieved this goal and we look forward to collaborating with our colleagues to improve cancer care for patients across the country."

Vanderbilt-Ingram cares for nearly 4,000 new cancer patients each year. A National Cancer Institute-designated Comprehensive Cancer Center, Vanderbilt-Ingram is consistently ranked among the best places for cancer care by *U.S. News & World Report* and is among the top 10 nationally in competitively awarded NCI grant support.

The NCCN, a not-for-profit alliance of 21 of the world's leading cancer centers, is dedicated to improving the quality and effectiveness of care provided to patients with cancer.

> "Promising discoveries in cancer research are being made every day, but our work is not finished until those findings are translated into advances in patient care. We are excited to join this group of cancer centers to help make that happen."
>
> – JENNIFER PIETENPOL, PH.D., INTERIM DIRECTOR OF VANDERBILT-INGRAM.

THE NCCN MEMBER INSTITUTIONS ARE:



The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 21 of the world's leading cancer centers, is dedicated to improving the quality and effectiveness of care provided to patients with cancer. For more information, visit www.nccn.org.

City of Hope Cancer Center, Los Angeles, CA; **Dana-Farber/Brigham and Women's Cancer Center / Massachusetts General Hospital Cancer Center**, Boston, MA; **Duke Comprehensive Cancer Center**, Durham, NC; **Fox Chase Cancer Center**, Philadelphia, PA; **Huntsman Cancer Institute at the University of Utah**, Salt Lake City, UT; **Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance**, Seattle, WA; **Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University**, Columbus, OH; **The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins**, Baltimore, MD; **Robert H. Lurie Comprehensive Cancer Center of Northwestern University**, Chicago, IL; **Memorial Sloan-Kettering Cancer Center**, New York, NY; **H. Lee Moffitt Cancer Center & Research Institute at the University of South Florida**, Tampa, FL; **Roswell Park Cancer Institute**, Buffalo, NY; **Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine**, St. Louis, MO; **St. Jude Children's Research Hospital/University of Tennessee Cancer Institute**, Memphis, TN; **Stanford Comprehensive Cancer Center**, Stanford, CA; **University of Alabama at Birmingham Comprehensive Cancer Center**, Birmingham, AL; **UCSF Comprehensive Cancer Center**, San Francisco, CA; **University of Michigan Comprehensive Cancer Center**, Ann Arbor, MI; **UNMC Eppley Cancer Center at The Nebraska Medical Center**, Omaha, NE; **The University of Texas M. D. Anderson Cancer Center**, Houston, TX; and **Vanderbilt-Ingram Cancer Center**, Nashville, TN.

Clinic renovations set to begin

When the dust settles on a new renovation project involving Vanderbilt-Ingram's Henry-Joyce Cancer Clinic, waiting room space and exam rooms will nearly double to help meet the needs of an ever-increasing number of cancer patients in Middle Tennessee and beyond.

With approximately 52,000 outpatient visits in the last fiscal year, adding more space to handle the influx was inevitable. "The numbers have skyrocketed by about 60 percent since 2002," said David Johnson, M.D., deputy director of Vanderbilt-Ingram. "They have leveled off a bit, but only because there is a limit to what we can physically do. We can't fit in any more people."

The estimated $15 million renovation plan began this summer and will take about 18 months to complete. The current space of 58,000 square feet will double to 116,000 square feet once the work is done. The changes will take place in several stages, so the business of seeing and treating patients can continue through the renovation process.

In the first phase, the second floor of The Vanderbilt Clinic, where Otolaryngology was once located, will be slightly redesigned to be used for cancer exam rooms. The current exam rooms in the Cancer Clinic will move up to that second-floor space for an interim period. Once vacated, the current Cancer Clinic space will be gutted and re-designed.

In the second phase of the project, cancer care will move back down to a newly designed clinic, and the old space on the second floor will be renovated to become the new infusion area for cancer treatment.

The old infusion area will become the new main clinic lobby and waiting area. So patients will walk right from the Preston Lobby to the check-in area of the new clinic and waiting area. The existing skylights will stay in place to brighten the entrance and waiting room. In addition, the new space will have about 100 chairs for patients and loved ones in the waiting area. "Our patients frequently come with two to three family members or friends who provide support during the cancer treatment journey," said Carol Eck, R.N., M.B.A. "We want for them to be able to wait in a comfortable and inviting area."

A Family Resource room will be conveniently located off the waiting area where patients and family members will be able to access many types of information regarding cancer care and resources available for before, during and after treatment.

The new infusion area on the second floor will include 46 rooms with a mixture of chairs and stretchers and 40 chairs in the waiting room. In addition, many of the treatment rooms will have windows. The new space will include some private rooms, a family break and dining area, and an IV pharmacy in the center of the unit. The infusion area will also feature a team concept, grouping patients in clusters based on their diagnosis or treatment needs.

Beth Franklin, a former Vanderbilt-Ingram patient, is now a donor and member of the Board of Overseers. She still visits the clinic for her regular cancer checkups, but she's here most often now as a caregiver for her mother, who is being treated for lung cancer. Franklin said the plans to expand will make the experience calmer and more efficient for patients and their providers alike. "I think the plans are great. They are probably overdue. I think it's a great beginning," said Franklin, a seven-year cancer survivor.

More growth is already on the horizon to keep up with the number of people seeking care. Johnson said outpatient visits are up 35 percent since 2002, more than 90 percent of the care delivered at Vanderbilt-Ingram is on an outpatient basis, and up to half of all cancer patients here come from more than 100 miles away.

Eck added that despite the volume, Vanderbilt-Ingram's outcomes remain strong. "Our survival rates are better regionally and nationally as well. We consistently exceed the national benchmarks," Eck said. Johnson added, "Our numbers are not just a little better, they are a lot better than the national average."

– by Heather Newman

The Preston building lobby (left) will become the main patient entrance. When renovations are complete, the infusion area (right) will double in size and move to the second floor.

PHOTOS BY DANA JOHNSON

New colorectal cancer registry tracks serious, inherited form of the disease

Despite a healthy lifestyle and youth on her side, 47-year-old Jane Sentner has spent the better part of a decade fighting cancer, thanks to what she calls bad genes.

"I'm unfortunately the winner of the gene pool jackpot," said the four-time cancer survivor. "All of my aunts and uncles died before they were 60 of stomach or colon cancer." Her mother had breast and colon cancer and died at 59. Her father had a heart attack that claimed his life at 44.

Sentner has something called Lynch syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC). It's a rare disorder, but having this inherited syndrome means you have more than an 80 percent chance of developing colorectal cancer and are at high risk for developing several other types of cancer. HNPCC causes cancer to grow and spread more quickly than typical colon or other cancers.

Sentner was first diagnosed with ovarian cancer when she was 38, before she called Nashville home. During the surgery, her doctors also discovered a very early endometrial cancer and removed the area of concern. After a hysterectomy and six months of chemotherapy, a routine CT scan lit up an area of concern in her rectum. It was stage III colorectal cancer.

"I didn't even know it was there," she said. Surgeons removed about eight inches of her colon and managed to spare Sentner a colostomy bag. She went back on chemotherapy for another six months, followed by five weeks of radiation.

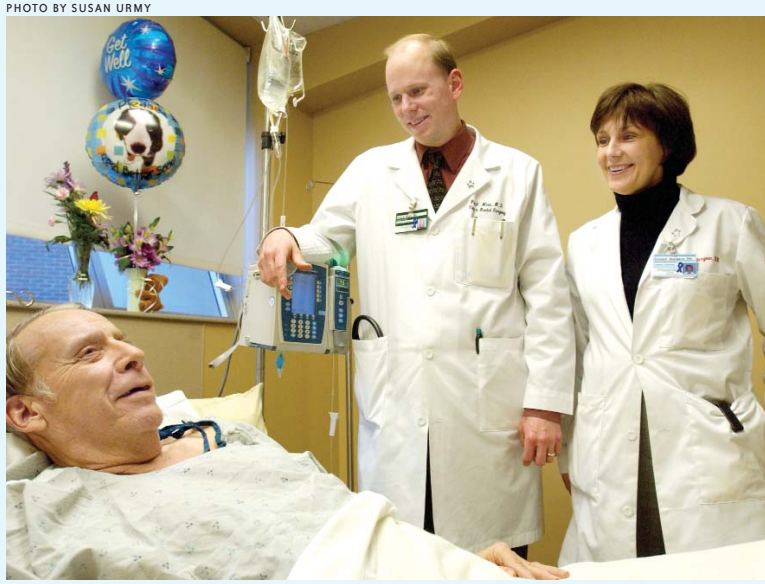
She went for about six years with a clean slate, and in the meantime moved to Nashville. But a routine colonoscopy found another colon cancer. It was caught early and Sentner's new surgeon, Vanderbilt's Alan Herline, M.D., only needed to remove a few inches of her colon.

Though several doctors had mentioned the idea of genetic testing, Sentner didn't think too much about it. Four cancers later, she was ready to be tested, but in the back of her mind she already knew the outcome. "This just doesn't happen — four separate primary cancers?"

That's exactly what Herline thought when he began caring for Sentner. "We used to think colorectal cancer was greater than 90 percent sporadic, but now we think it's only about a 60 percent range with 30-40 percent being familial. More and more we're seeing it is largely familial," said Herline.

Tests revealed the expected and Sentner soon began doing her part by informing younger relatives they may be at risk, too, and should be screened for colon and other cancers at an earlier age than traditional guidelines recommend. "If one family member tests positive for this mutation they need to start colonoscopies between 20 to 25 years of age, when it's preventable," said Duveen Sturgeon, R.N.

PHOTO BY SUSAN URMY



Duveen Sturgeon, R.N., (right) and Paul Wise, M.D., talk with patient Charles Wilson about the new Hereditary Colorectoral Cancer Registry.

Sturgeon is the program coordinator for a new Hereditary Colorectal Cancer Registry at Vanderbilt-Ingram Cancer Center. She'll be on the lookout for patients like Sentner, to help reach out to their loved ones for early screening and prevention. She said it is the first registry of its kind for colorectal cancer in Tennessee. "We want to start here at Vanderbilt, but eventually we want to go out into the community, to talk to other community physicians. Right now Tennessee has no hereditary colorectal cancer registry and neither does Southern Kentucky," said Sturgeon.

There will be a monthly clinic for patients identified at high-risk for having HNPCC, and a multidisciplinary team will evaluate each case before the patient's visit. Sturgeon will work with the patient to schedule necessary screening tests for colorectal and other related cancers. "We're hoping for one-stop shopping, so people can come in, have colonoscopies, biopsies, and appointments with all the people that they really need to see," said Sturgeon.

Paul Wise, M.D., a colorectal surgeon, is heading up the new Vanderbilt Hereditary Colorectal Cancer Registry with Sturgeon and said it will be a win-win situation for patients and providers. "We are in the process of creating a tissue and serum repository from the patients in the registry, both to support current research efforts as well as potential future research down the line. "We hope to find out if there is a protein signature to help diagnose the family members that are at risk for cancer. This could be in the form of a blood test that would be easier than biopsies and cheaper than genetic testing," said Wise.

Sentner said people should not be afraid to be screened for colorectal cancer. "It is not a big deal. How could one day of your life — a little inconvenience — possibly compete with the confidence of knowing you've been checked?"

– by Heather Newman

TO FIND OUT MORE ABOUT SCREENING GUIDELINES FOR COLORECTAL CANCER AND THE HEREDITARY COLORECTAL CANCER REGISTRY AT VANDERBILT-INGRAM, GO TO: WWW.VANDERBILTCOLORECTAL.COM.

JOURNAL WATCH

Vanderbilt-Ingram Cancer Center's mission is to conduct the innovative, high-impact basic, translational and clinical research with the greatest potential to make a difference for cancer patients. Here's a sampling of recent work published by center members:

Study Finds Treatment Paradox
A team led by Carlos Arteaga, M.D., reported a paradox in the treatment of advanced cancer – the link between a treatment-induced growth factor and the cancer's future spread. The findings may help explain why anti-tumor therapies often work only partially or not at all in advanced cancers and tumors progress after treatment. The investigators reported that radiation and chemotherapy increase circulating levels of the growth factor TGF-beta, circulating cancer cells, and tumor metastases in a mouse model of metastatic breast cancer. Blocking TGF-beta in the model prevented tumor metastases, suggesting that TGF-beta inhibitors – some of which are currently in early stage clinical trials – may be useful in combination with primary therapies. The work appeared in the *Journal of Clinical Investigation.*

Team Identifies Culprit in Metastasis
Researchers at Vanderbilt have identified a molecular mechanism at the hub of numerous cell behaviors — and possibly at the root of metastasis. Albert Reynolds, Ph.D., and colleagues have identified a protein at the center of it all, p120-catenin, and described the mechanism it uses to coordinate cell growth, motility and adhesion. Reynolds first discovered p120 in 1989 and found that the protein is a key regulator of cadherin function and plays a critical role in cell-cell adhesion. The current study continues to build the case that p120 participates in processes that govern whether a cancer cell becomes metastatic, and provides a mechanistic link between the behaviors that are disrupted in metastatic cells — something that has been suspected since p120's discovery. The work appeared in *Cell.*

Model Could Help Doctors Pick Best Treatment for Lung Cancer
Some patients with non-small cell lung cancer (NSCLC) respond to treatment with a class of drugs that block cell communication and growth (tyrosine kinase inhibitors). However, physicians don't have a good way to predict just who will respond well. Now David Carbone, M.D., Ph.D., and colleagues have developed a model that predicts survival of patients with NSCLC after treatment with gefitinib or erlotinib, two of these drugs. The model uses mass spectrometry "signatures" of proteins found in the bloodstream of patients before their treatment to categorize patients by "good" and "poor" outcomes. In one of the validation groups, the "good" outcome patients had a median survival of 306 days, compared to 107 days for the "poor" group. This work, which appeared in the *Journal of the National Cancer Institute,* suggests that these so-called biomarkers could be used to select the most effective therapy.

Animal Model May Shed Light on Deadly Pancreas Cancer
Vanderbilt-Ingram Cancer Center researchers have developed a new animal model for pancreatic cancer that exhibits a high degree of similarity to human tumors. Results from a study of genetically engineered mice, published in the journal *Genes and Development,* suggest that the mice could provide new opportunities to investigate targeted chemotherapeutics and screening methods for one of the most deadly cancers. "Most cases are diagnosed at a late stage when it is incurable," said Hal Moses, M.D., professor of Cancer Biology and senior author on the study. Developing an animal model of pancreatic cancer is essential to identifying new treatment and screening options.

Trial Shows Promising Option for Advanced Cancer
Results of a multi-center clinical trial of the drug bevacizumab (Avastin) in patients with advanced, non-squamous, non-small cell lung cancer show it may help extend the lives of some patients. Alan Sandler, M.D., David Johnson, M.D., and colleagues reported in the *New England Journal of Medicine* data from a trial of nearly 900 patients with metastatic, non-squamous, non-small cell lung cancer (NSCLC). The patients had not received prior chemotherapy. Half received Avastin in addition to chemotherapy, and half got standard chemotherapy alone. Patients who received Avastin combined with chemotherapy lived, on average, about two months longer (12.3 months) than the group who only received chemotherapy (10.3 months). The findings show the first promising option in years for treating patients with this advanced and often deadly form of lung cancer.

Structure Identification Sheds Light on DNA Repair Enzyme
A team led by Brandt Eichman, Ph.D., has identified the structure of an enzyme that removes certain damaged DNA bases, the single "letters" that make up a strand of DNA. Having the structure reveals clues about how this enzyme works and could be helpful in understanding cancer because exposure to carcinogens can cause this kind of damage. This enzyme, part of the cell's DNA repair system, reverses the damage and returns the DNA to its "undamaged" state. In addition, agents that produce this type of DNA damage are used in some chemotherapy. So, understanding this type of damage could help protect against carcinogens, and might help improve anti-cancer drugs that use these agents. The work was reported in *The EMBO Journal.*

New role for DNA-binding proteins
In the April 15 issue of *Genes & Development*, Stephen Brandt, M.D., and colleagues report that single-stranded DNA-binding proteins (SSBPs), which normally act to keep DNA "unraveled" during transcription, also regulate the abundance of protein components of DNA-binding complexes that drive red blood cell differentiation. The results also suggest that altered expression of SSBPs, which has been observed in several cancer types including certain leukemias, may contribute to tumorigenesis by disrupting the normal balance of these DNA-binding complexes.

onefinalnote

PHOTO BY DANIEL DUBOIS

Teresa Knoop, Pam Carney and Gloria Cherry (left to right) are nurses who answer your calls and e-mails as part of Vanderbilt-Ingram's Cancer Information Program. Since the hotline and program launched in 1997, the volume of new contacts has more than tripled to nearly 3,000 a year.

To reach the nurses for questions about new cancer therapies, clinical trials and general cancer information, toll-free, call: 1-800-811-8480.

Facing a new case out of the courtroom

A Tennessee lawyer shares his personal fight against cancer

PHOTO BY DEAN DIXON

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