PROSTATE CANCER
DISCOVERY
THE BRADY UROLOGICAL INSTITUTE • JOHNS HOPKINS MEDICINE
VOLUME 2 • AUTUMN 2005
A PUBLICATION OF THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Getzenberg: Recruiting worldwide, seeking fresh viewpoints, and speeding up the pace.

Getzenberg Takes Helm of Brady's Research Program

Armed with energy, enthusiasm, a love of the Brady — where, trained by legendary scientist Don Coffey, he launched his own impressive career — and a host of questions about prostate cancer that he wants answered, Robert Getzenberg, Ph.D., is the Brady's new Director of Research.

For Getzenberg, this is a homecoming — and the chance of a lifetime, to step into the formidable shoes of his former mentor, Donald S. Coffey, Ph.D., whose 30-year tenure as Director of the Research Laboratories put Hopkins at the forefront of urologic research worldwide. "It's great to be back," he says. "I cannot overstate how excited I am to be here."

Hiring Getzenberg as the successor to Coffey — whose research at Hopkins is still going strong — was one of the first things Alan W. Partin, M.D, Ph.D., did when he succeeded Patrick C. Walsh, M.D., as the Brady's new director. "Dr. Getzenberg brings a fresh new approach to discovery that combines critical thinking, state-of-the-art research methods and quality leadership," says Partin. "We are extremely fortunate to have him."

Getzenberg, professor of urology, earned his Ph.D. from Hopkins in 1992, then completed a postdoctoral fellowship at the Yale University School of Medicine. He returns to Baltimore after spending 11 years at the University of Pittsburgh, where he directed urological research in the Department of Urology, co-directed the Prostate and Urologic Cancer *[continued on page 2]*

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

FOUNDERS' CIRCLE

ANONYMOUS (3)
MR. AND MRS. ROBERT B. AIKENS
MR. AND MRS. ROBERT C. BAKER FAMILY FOUNDATION
MARY ANN AND BILL BECKER
DR. AND MRS. PETER S. BING
JENNIFER A. CHALSTY
JOHN S. CHALSTY
THE DEEKS FAMILY FOUNDATION
R. CHRISTIAN B. EVENSEN
PHYLLIS AND BRIAN L. HARVEY
HEATHER C. AND PATRICK HENRY
CHARLTON C. AND F. PATRICK HUGHES
BEVERLY A. AND GARY L. MCDONALD
BETH W. AND A. ROSS MYERS
NANCY AND JIM O'NEAL
MR. AND MRS. PAUL W. SANDMAN
THE PETER JAY SHARP FOUNDATION
IRENE AND BERNARD L. SCHWARTZ
VIRGINIA AND WARREN SCHWERIN
CAROLYN AND BILL STUTT
MR. AND MRS. CHARLES B. THORNTON JR.
LUCIANA AND JOE VITTORIA

Critical Mass, and Creative Momentum

So close, we can feel it. Breakthroughs every day. Hope is all around us at the Brady, and in this issue of *Discovery*, we've tried to convey some of the excitement to you. The phrase "thinking outside the box" means thinking innovatively, and if I had to sum up the way we approach our work here, I would say that's what we're doing — thinking creatively. The Brady has always been a bit outside the traditional academic mold — for one thing, we never pigeonhole people, limiting their field of study. Instead, our approach has been to bring together a lot of very smart scientists and physicians, and let them help each other to make life better for our patients. The result is an atmosphere that's stimulating, productive, and inventive, with scientists from many disciplines — urologists, molecular biologists, geneticists, radiation oncologists, pathologists, epidemiologists, medical oncologists — achieving "critical mass," and awesome momentum.

The Patrick C. Walsh Prostate Cancer Research Fund is an ideal example *[continued on page 2]*

[continued from page 1]

Patrick C. Walsh

of this: We didn't go looking for "prostate cancer scientists." Instead, we opened the door to scientists in any field with good ideas, and the results have been just as exciting as we'd hoped (see pages 4 to 7). All of you who have helped, and are continuing to help, make this possible, should be very proud of what you have set in motion. Our new research director, Robert Getzenberg, sets another good example of the Brady approach — his mission, with our patients always in mind, is to speed up the process of bringing research advances to those whose lives are depending on them.

On a personal note, it is wonderful having Alan Partin as my successor. Dr. Partin is doing a great job, and without having to spend so much time on administration duties, I have been able to concentrate fully on my patients and my own work, operating as often as always, and traveling a little more than usual as a guest speaker, to Austria, China, Korea and India. Once again, I enjoyed a "working vacation" this summer, reviewing videotapes of recent cases, and formulating some new surgical concepts for my next chapter in the Ninth Edition of the *Campbell-Walsh Textbook of Urology*. Everything I learn, and all of the advancements happening here at the Brady every day — particularly, new advancements in radiation oncology, brachytherapy, and chemotherapy, as reflected in the work of Ted DeWeese, Danny Song, Mario Eisenberger and Michael Carducci, will be reflected in the revised version of *Dr. Patrick Walsh's Guide to Surviving Prostate Cancer*, which I am currently writing with Janet Farrar Worthington. And all of this, as always, is dedicated to our patients and their families.

Patrick C. Walsh, M.D.
University Distinguished Service Professor of Urology

PROSTATE CANCER DISCOVERY
is published by The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, MD 21287-2101.

Patrick C. Walsh, M.D, *University Distinguished Service Professor of Urology*
Janet Farrar Worthington, *Writer/Editor*
Claude Skelton, *Designer*

[continued from page 1]

Center of the University of Pittsburgh Cancer Institute, and served as professor of urology, pathology, and pharmacology at the University of Pittsburgh School of Medicine. In his distinguished career so far,

"We can circle the wagons around prostate cancer," attacking it from all sides.

Getzenberg has earned many awards, is the recipient of grants from the National Institutes of Health and other agencies and foundations, and was a member of the Board of Directors of the American Foundation for Urologic Diseases.

The Brady is "in the driver's seat" of urology research, says Getzenberg, and he intends to keep it there. "We are clearly at an exciting time in scientific research. There are many new technologies, and large projects like the human genome effort have been completed. Our task now is convert these as quickly as possible to discoveries that will help our patients." In addition to continuing his own exciting research (see side story), he has several plans in mind for making this happen:

Recruiting worldwide. "For the first time in the Brady's history, we have an international search going on, to identify the best investigators in the world," he notes. He and Partin are thinking big, looking for scientists who will bring "new ideas, new expertise, and new approaches," to prostate cancer research.

Looking for Markers

Besides being the Brady's new research director, Robert Getzenberg, Ph.D., professor of urology, is searching for better, smarter tests and biomarkers for prostate cancer and other diseases.

Is it cancer, or another prostate problem? **One of his first targets is PSA. A major drawback to using PSA (prostate-specific antigen) to detect cancer is that it doesn't show only cancer, Getzenberg says. "PSA is a normal product of the prostate that is found at high levels even within the normal prostate." Men who have a PSA of between 4 and 10 ng/ml have roughly a 25 percent chance of having prostate cancer, he continues, "which means that more than 75 percent of the men biopsied do not have the disease."**

So Getzenberg has been wondering: What does prostate cancer make, that normal prostate tissue doesn't? And he's found what may be a good answer: "We have developed a novel biomarker for prostate cancer called early prostate cancer antigen (EPCA)," he says. "One interesting characteristic is that this marker is elevated not only in the prostate cancer itself, but in the entire prostate of men with the disease." However, he adds, men who don't have prostate cancer — even men with other prostate problems, such as BPH and prostatitis — don't show any EPCA within their prostate.

EPCA, which is already available as a test for pathologists to use, could be particularly useful in evaluating negative prostate biopsies: If a stain of prostate cells shows elevated EPCA levels, this would indicate that prostate cancer exists — even if the needle samples didn't find it. "But the absence of EPCA staining would

"Which men have prostate cancer with the potential to kill them, and which men have prostate cancer that is more like a pussycat?"

reveal that there is no prostate cancer within the gland," Getzenberg continues, and the patient can relax, knowing he doesn't need to have another biopsy right away.

Getzenberg and colleagues have also developed an EPCA blood test, to go along with the PSA test, that can help doctors figure out what's causing the PSA to rise — namely, whether it's cancer, or another prostate problem. The EPCA blood test is "highly specific for prostate

Assembling multidisciplinary teams. By bringing together scientists from different disciplines to focus on specific problems, "we can circle the wagons around prostate cancer," attacking it from all sides. A key part of this endeavor, Getzenberg notes, is The Patrick C. Walsh Prostate Cancer Research Fund, which "allows us to make certain that any scientist at Johns Hopkins who is interested in working on prostate cancer is able to. We are also seeking out scientists who may never have considered working on prostate cancer, explaining to them how their work may be applicable to the disease and allowing them to refocus their minds on this problem. This is an amazing opportunity to bring so many fantastic scientists to the field."

Speeding up the pace from bench to bedside. "We have many exciting ideas, but we need to move them much more rapidly to the point where they have an impact on patients' lives," Getzenberg says. One way to do this is to make the most of the massive sources of patient information already on hand at the Brady. Help is needed in the form of people — epidemiologists, bioinformationists, computer programmers and others — who can make sense of of all of this information, so Brady scientists can "carefully focus on which of it is clinically meaningful."

"We have many exciting ideas, but we need to move them much more rapidly to the point where they have an impact on patients' lives."

cancer," he says. "Men with elevated EPCA levels have about a 90- to 95-percent chance of having prostate cancer." Clinical trials for this EPCA blood test have already been conducted, and a larger study is now under way.

Is the cancer slow-growing, or aggressive? **"Which men have prostate cancer with the potential to kill them, and which men have prostate cancer that is more like a pussycat?" Getzenberg has developed a test to help determine this, using a new, blood-based prostate cancer marker (one of several he's testing) called EPCA-2. "We have evidence that EPCA-2 appears to be elevated at its highest levels in men with most aggressive forms of the disease." However, EPCA-2 shows up at much lower levels in men with less aggressive cancer. EPCA-2 is now being tested in clinical trials.**

BPH, like cancer, can be "good" or "bad." **Benign enlargement of the prostate (BPH), doesn't just affect the prostate, and it isn't always benign. It affects the bladder, and in severe form, its symptoms can be debilitating. "Until recently, all BPH was considered to be a single disease," notes Getzenberg. But his research group has found a genetic marker, called JM-27, that's associated with the most aggressive type of BPH. Further, Getzenberg and colleagues have developed a blood test that can determine whether a man has the most severe form of BPH, or whether his case is mild. They hope that this test will even be able to predict how a man will respond to various treatments of BPH. "This is the first BPH-specific marker that has been identified, and we hope it will play a role in how men are treated for the disease," he says.**

Markers for bladder cancer: **Getzenberg's search for markers has extended to bladder cancer. "Bladder cancer is the second leading urologic cancer, and it has increased significantly over the past couple of years," he explains. He and colleagues have identified several novel markers for bladder cancer, and have developed a simple urine test for one of these, called BLCA-4. BLCA-4 may have other uses, as well: It appears to regulate gene expression within the bladder, and also to affect certain proteins that may be important in the development of the disease. Getzenberg and colleagues have developed a similar urine test for another marker, called BLCA-1, and hope to combine these two assays in clinical studies. These markers are being tested in a large clinical trial of more than 3,000 patients.**

BPH and cancer — any connection? **BPH and prostate cancer affect different regions of the prostate, but they're both associated with aging. They may have other things in common, as well, says Getzenberg. "We have identified a series of genes that appear to be altered in both BPH and prostate cancer. There may be much more connection between BPH and prostate cancer than we originally envisioned. Understanding more about the development of each of these diseases will help us develop better tools with which to attack them both."**

After Cancer Diagnosis, Is it Okay to Wait a Few Months Before Having Surgery?

Alan W. Partin

Most men, when they find out that they have prostate cancer, and that it's clinically localized — confined to the prostate, and curable with surgery — want it out yesterday. Understandably, "they are anxious to get something done right away, and most men have surgery within just a few months of their initial diagnosis," notes Alan W. Partin, M.D., Ph.D., David Hall McConnell Professor of Urology and director of the Brady Urological Institute. Although any hold-up can seem too long for a worried patient, the good news is that a modest delay of several months is okay. "There is little evidence to suggest that it affects the man's outcome, or our ability to control the cancer."

Partin has long known this anecdotally, but recently studied this question of a few months' delay between diagnosis and surgery in response to a study in the *Canadian Journal of Urology*, which "cast unfounded doubt on the safety of such a delay with respect to cancer control," and needlessly worried patients, Partin says.

Partin and colleagues analyzed the medical records of 926 men who underwent surgery between January 1989 and December 1994. All of them had the same surgeon — Patrick C. Walsh, M.D. Some of these men were treated early — within two months — and others had surgery at three, six, nine months or even more than a year after diagnosis. The investigators found no significant difference in the long-term cancer control rates of these men. These findings were published in the *Journal of Urology*.

"Patients can be reassured," says Partin, "that there is no immediate urgency to perform surgery after a prostate cancer diagnosis, especially in men with stage T1c disease and biopsy Gleason scores less than 7."

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

Scientists Named in First Round of Funding

From its start a year ago, The Patrick C. Walsh Prostate Cancer Research Fund has been something different. Its goal is understanding and curing prostate cancer, but its support isn't limited to scientists specializing in urologic research. "We've thrown open the doors to any scientist, in any department at Johns Hopkins who has a promising idea worth pursuing," says urologist Patrick C. Walsh, M.D, whose lifetime work inspired the idea, and whose generous patients made it possible.

The Patrick C. Walsh Prostate Cancer Research Fund hit the ground running, and in its inaugural round of funding received applications from more than 40 Hopkins scientists. "The review panel spent significant effort reviewing each of the applications," Walsh reports. "Although we did not have the funds to support all of the work that the panel thought was worthy, we were able to fund individuals and research projects from diverse backgrounds." The panel is "greatly anticipating the exciting applications that will be submitted for the next round later this year. Everyone is encouraged to apply."

The work of the first awardees is covered on the next four pages of *Discovery*. These scientists are:

Joshi Alumkal, M.D.,
Fellow, Oncology
Dmitri Artemov, Ph.D.,
Assistant Professor, Radiology
David Berman, M.D., Ph.D.,
Assistant Professor, Pathology, Urology, Oncology
Angelo DeMarzo, M.D., Ph.D.,
Associate Professor, Pathology, Urology, Oncology
Charles Drake, M.D., Ph.D.,
Assistant Professor, Oncology
Barry Nelkin, Ph.D.,
Professor, Oncology
Roberto Pili, M.D.,
Assistant Professor, Oncology

As part of this same review process, the panel also awarded career developmental and pilot project grants to individuals from the Prostate Cancer SPORE grant. These awardees are:

Charles Foster, M.D.,
Assistant Professor, Pediatrics
John Isaacs, Ph.D.,
Professor, Oncology, Urology
William Isaacs, Ph.D.,
Professor of Urology, Oncology
Alan Meeker, Ph.D.,
Fellow, Urology, Oncology

Unleashing Good Genes to Reform Cancer Cells

Imagine a garden hose, neatly wrapped around a coil. It may be the greatest hose in the world, but while it's all rolled up like that, it can't do much to help your flowers.

A similar situation exists in prostate cancer, and oncologist Roberto Pili, M.D., assistant professor of oncology, believes unwrapping a specific piece of DNA — the garden hose, on a molecular level — can stop the transformation of a normal cell into a cancerous one. In fact, it may even cause a cancerous cell to revert back to its harmless state.

Pili has been named The Peter Jay Sharp Foundation scholar from The Patrick C. Walsh Prostate Cancer Research Fund. He is focusing on a tiny site, found in every cell that has a nucleus, called chromatin. Chromatin contains spool-shaped proteins called histones. But here's the interesting twist: In this peculiarly structured area, DNA wraps itself in a big bear hug around the histones — think of filet mignon, bundled in two strips of bacon — and keeps them tightly coiled. This wrapping silences the proteins, keeping these particular genes turned off, or asleep.

Sometimes this is a bad thing — particularly when there's trouble afoot, when normal cells are changing, and encouraging cancer. When good cells go bad, they lose their well-differentiated (distinct, or clearly defined) structure and normal regulation routines, and melt together. They encourage the growth of blood vessels that can supply new life to a tumor. Pili believes that waking up the sleeping genes — in this case, in epithelial cells, which make up the prostate's glandular tissue — will counteract the loss of certain key proteins that can help cancer thrive.

"If we can reactivate these specific proteins in the tumor," Pili says, "we can push cancer cells to differentiate — to turn back into regular cells — and eventually, to die." Pili is testing drugs known to act on the chromatin, called histone deacetylase inhibitors, and he's hoping for a double impact: He wants to wake up some good genes, and cause some cancer-promoting genes to be repressed.

If these drugs pack the punch Pili believes they will — if they teach a cancer cell to change its ways — he envisions one day using them in combination with other therapies for men with metastatic prostate cancer. "This study represents a novel and exciting approach toward conquering prostate cancer," he says, "by using agents that push tumor cells to return to normal epithelium."

Immunotherapy: Making it Better

The idea of using a man's own immune system to fight cancer has intrigued scientists for years. It makes perfect sense: The body is supposed to attack harmful invaders, and it does a great job protecting us from most of the germs, viruses, and disease-causing agents we encounter throughout our lives. It even fends off most cancer for decades.

But this idea, called cancer immunotherapy, has not progressed as successfully as scientists had hoped it would. One major hindrance may be a well-meaning but misguided group of cells called regulatory T cells, which shut off the body's immune response.

Prostate cancer is not the only disease enabled by these cells: "The presence of regulatory T cells has been clearly shown in breast and ovarian cancer," says Charles Drake, M.D., Ph.D., assistant professor of oncology. Drake has been named the Phyllis and Brian L. Harvey scholar from The Patrick C. Walsh Prostate Cancer Research Fund to figure out "how common regulatory T cells are in prostate cancer, and whether the presence of these cells predicts how well, or how poorly, a man with prostate cancer will do.

Drake and colleagues, using a mouse model of prostate cancer, have been able to isolate regulatory T cells from prostate tumors. His next step will be to characterize these cells, "with the eventual goal of blocking their function so that immunotherapy for prostate cancer will be more successful." Earlier experiments have provided some clues about how these regulatory cells work,

he adds. "They seem to depend on a substance known as transforming growth factor beta (TGF-β)." Drake will determine whether blocking TGF-β will help immunotherapy for prostate cancer work more effectively. All of this work, in turn, "should provide new insights into the role of regulatory T cells in prostate cancer, and help us to design combination immunotherapy strategies that will be more successful in treating patients."

New Tests Look for "Silenced" Genes

What is it with methylation, anyway? Why does this word keep popping up in some of the Brady's most exciting research? Chemically speaking, methylation is like taking a zipper and adding an extra tooth, so it doesn't work properly — or changing the tumblers on a lock ever so slightly, so the key doesn't fit it anymore. What does this have to do with prostate cancer?

Quite a lot, says William G. Nelson, M.D., Ph.D., professor of oncology, medicine, pathology, pharmacology and molecular sciences, and urology. When a gene is methylated, it's silenced, rendered useless. In more than 90 percent of men with prostate cancer, Nelson has discovered, the major gene that's supposed to defend the

Methylation is like taking a zipper and adding an extra tooth, so it doesn't work properly. What does this have to do with prostate cancer?

prostate against oxidative damage to DNA — incremental harm that occurs over years or even decades, as carcinogens repeatedly attack our genes — is silenced, or methylated, early on. This gene is called GSTP1 (pronounced "GST pie"), and what happens here — this targeted "hit," an assassination on the genetic level — allows cancer to develop much more easily.

Exploring the role of methylation as a cause of prostate cancer has helped Nelson and colleagues look for new genetic markers to help detect it. Nelson is working to develop tests that can detect abnormal GSTP1 methylation changes in DNA from cancer cells; specifically, the tests look for altered clumps of DNA, called "hypermethylated CpG islands," that aren't supposed to be there. "Exactly how such tests might be used has not been established yet," says Nelson. But, he speculates, "they could be used in prostate biopsies or even urine specimens, to help identify men who harbor prostate cancers that have been missed by prostate biopsy." Also, such tests targeting CpG islands of other genes, such as the endothelin B receptor or cyclooxygenase-2 (COX-2), in DNA in prostate cancer cells and tissues, might one day help doctors predict outcomes from radical prostatectomy or radiation therapy.

Methylation and inflammation: Methylation helps cause cancer. Now, can we somehow backtrack — retrace the steps of cancer — and catch methylation in the act? Pathologist Angelo De Marzo, M.D., Ph.D., has been named the Dr. and Mrs. Peter S. Bing scholar from The Patrick C. Walsh Prostate Cancer Research Fund. He believes that prostate cancer is driven by a bad combination of forces from within and without. From inside the prostate comes inflammation; from without come attacks by cancer-causing elements in the diet. Together, they cause damage that results in regions of "proliferative inflammatory atrophy," or PIA.

De Marzo believes these PIA spots, or lesions, represent evidence of a "field effect" change, "indicating that a very large region of the prostate has been exposed to something that causes cancer," and that these PIA lesions somehow pave the way for cancer. It may be that the next step a pathologist could detect in the tissue is high-grade PIN (prostatic intraepithelial neoplasia), and from there, the next step is cancer.

To prove that PIA lesions are early precursors on the way towards cancer, De Marzo is looking for intermediate changes in the DNA between normal cells and cancer cells. The most common of these changes, which he expects to find in abundance, is our old friend — the hypermethylated "CpG island" in GSTP1. "We suspect that PIA will contain intermediate levels of CpG island methylation, greater than normal, but less than high grade PIN and carcinoma," he says. He will also look for some of the other genes with DNA methylation changes that Bill Nelson and colleagues have discovered. If his work is able to connect the dots from PIA to PIN to cancer, he hopes to use these results as pilot data for a larger, externally funded grant to investigate the order of events in early prostate cancer.

Better biomarkers to predict recurrence: Oncologist Joshi Alumkal has been named the Irene and Bernard L. Schwartz scholar from The Patrick C. Walsh Prostate Cancer Research Fund. He is studying methylation in a different gene, with the alphabet-soup name of NKX3.1. Although the genetic players are different, the basic script is the same: Whatever causes the DNA to methylate in this gene — or, as Alumkal believes, several genes — knocks out the body's ability to prevent cancer's development, growth, and spread. In this case, the kind of cancer that results is particularly unpleasant, and most likely to defy treatment.

The gene NKX3.1 is important in normal prostate development, and its loss can mean not only that prostate cancer develops, but that it's an aggressive form. "Loss of this gene in animal models leads to pre-cancerous and cancerous prostates — many of which appear very primitive, much like high Gleason score tumors," Alumkal explains. In this case, figuring out a way to screen for these DNA methylation changes "may help us identify those at highest risk of recurrent and potentially lethal prostate cancer."

Stopping Cancer's Blood Supply

When cancer reaches a certain point, it somehow learns how to make its own blood supply. The blood nourishes the tumor, and the blood vessels help pave the way for future growth. This process is called angiogenesis. Treatment designed to fight it — to curb the blood vessel growth, and keep the cancer from spreading — is called antiangiogenic therapy.

In prostate cancer, angiogenesis is an issue with advanced disease that has defied hormonal therapy. For antiangiogenic therapy to be successful, scientists need to understand more about how prostate cancer cells make these new blood vessels, says Dmitri Artemov, Ph.D., assistant professor of radiology, who has been named the Beth W. and A. Ross Myers scholar from The Patrick C. Walsh Prostate Cancer Research Fund to learn more about this process.

"There is evidence that tumor blood capillaries do not simply grow from existing blood vessels," Artemov says. Instead, the growing cancer may somehow attract formative cells from the bone marrow, called endothelial precursor, *[continued on page 6]*

[continued from page 5]

or progenitor, cells to join its bandwagon. "These cells can divide and change their shape and function to become new endothelial cells, which line the newly formed tumor blood vessels." Because they're important in laying down the cancer-nourishing blood vessels, these cells are also an important target of future cancer-fighting drugs, he adds.

Artemov is hoping to develop a new way to see these progenitor cells, using MRI scans and special contrast agents specifically designed to target them. Then he hopes to watch these cells in action, as they join growing prostate cancers in animal models — and to see how they are affected by various antiangiogenic drugs. The results of this study, he believes, will lead to better angiogenesis-fighting drugs, and better control of prostate cancer.

Blocking Metastasis, Protecting Bone

Metastasis, the spread of cancer past the point of treatment, is what kills men with prostate cancer. Somehow, scientists must learn how to block metastasis, which is a complicated process, with many steps. But if metastasis is a railroad track for cancer, maybe scientists don't need to dismantle the entire track to derail the train. Maybe just blocking one section will be enough.

This is what Barry D. Nelkin, Ph.D., professor of oncology, believes, and he has found a highly promising target — an enzyme called CDK5. He has been named the Nancy and Jim O'Neal scholar from The Patrick C. Walsh Prostate Cancer Research Fund to see whether stopping CDK5 will put metastasis on hold. Nelkin's work on this began with a startling observation: There are "striking similarities" between the way neurons migrate during normal brain development, and the way cancer cells travel in metastasis. "We reasoned that the underlying mechanisms of these processes might be similar," he says. In brain development, the enzyme CDK5 controls cell migration and invasion. But he has found that CDK5 is active in the vast majority — 28 of 32 — of strains of metastatic prostate cancer he has studied.

"Genetic inhibition of CDK5 activity blocked cell motility, invasion, and, in an animal model, reduced metastases by 79 percent," he continues, "suggesting CDK5 as a potential therapeutic target to limit metastasis in prostate cancer."

There's good news already in this story — some CDK5-blocking drugs already exist, for treatment of neurodegenerative disease. This means that Nelkin and colleagues have hit the ground running, and are testing these drugs in laboratory animals with metastatic prostate cancer. They are also looking to develop laboratory tests to monitor CDK5 activity in prostate cancer cells.

What this means for bone: "Bone is the most significant metastatic site for prostate cancer," notes Nelkin. "Blocking CDK5, in addition to inhibiting metastasis, may also inhibit the ability of prostate cancer to survive and grow in bone." Nelkin and colleagues will be exploring this, using an animal model of prostate cancer metastasis in bone. They will also see whether blocking CDK5 makes other chemotherapeutic drugs more effective. "We envision that this could provide a therapeutic benefit, especially for patients with limited disease," he says. For example, blocking CDK5 in a man with prostate cancer that has spread only to the lymph nodes, "could prevent further progression — potentially allowing effective therapy or even cure by other forms of treatment. We speculate that clinical trials could begin within one to two years of the successful completion of this project."

Hedgehog Blockers: Can They Stop Advanced Prostate Cancer?

Scientists One Step Closer To Finding Out

There's a "point of no return" in prostate cancer, a moment when it grows too big to be killed by surgery or radiation, when it is able to spread far beyond the prostate, when it is considered unstoppable. *Or is there?* For the first time, scientists at Hopkins believe they may have found a way to turn back the clock on cancer — to thwart metastasis by blocking every possible escape route the cancer cells can create.

Their key to stopping metastasis is a protein pathway so common, so routine, that it's involved in embryonic development of the lung, pancreas, prostate, part of the brain, and other organs. But in prostate cancer — and, it turns out, in many other cancers — this pathway has been commandeered for harmful purposes. It's called the Hedgehog pathway, and in exciting research (published in the journal *Nature*, and described in the Winter 2005 issue of *Discovery*), Hopkins scientists learned that this pathway serves as a lifeline that enables cancer cells to live and spread outside their original home tumor. They also proved that they can block this pathway, and stop cancer from spreading.

How does the Hedgehog pathway work? Patrick C. Walsh, M.D., describes it to his patients like this: "It's like soil and seeds. The soil is the stroma of the prostate — the connective tissue that serves as its framework — and the cancer cells are the seeds." And the Hedgehog protein is compost, sunlight and water — everything the seeds need to grow. "If these cells spread but try to grow in poor soil, they can't survive. But if they can manufacture the Hedgehog signal, they can make the soil that they need — they can pack their lunch and take it with them."

"We believe this may in time offer a completely new way to treat metastatic prostate cancer."

In laboratory research, "we found that we could shrink human prostate tumors growing in animals, and prolong their lives with a drug that blocks signaling by the Hedgehog pathway," says David Berman, M.D., Ph.D., assistant professor of pathology, urology and oncology. "We believe this may in time offer a completely new way to treat metastatic prostate cancer." Berman has been named the R. Christian B. Evensen scholar from The Patrick C. Walsh Prostate Cancer Research Fund.

Berman and colleagues Sunil Kahadkar, M.D., and Philip Beachy, Ph.D., professor of molecular biology and genetics and a Howard Hughes Medical Institute investigator, also believe that this and similar drugs, called Hedgehog blockers, can be useful for cancers in the brain, skin, lung, breast, and upper digestive tract.

But, except for testing a Hedgehog blocker on a common skin cancer — performed by dermatologists in Turkey, who found that the drug, given as a skin cream, had therapeutic benefit — researchers have not yet studied these agents in humans. There's a good reason for that: The government is extremely cautious about allowing drugs to make the

transition from pure laboratory studies to clinical trials in patients. "When a drug does get this far," explains Berman, "the first step, and the most risky one, is the Phase I trials — testing whether humans can tolerate the drug. We are excited to report that Hedgehog blockers are now entering this stage."

However, Berman points out, it's possible that the drug might pose significant risks, at least to some people: "The pathway is absolutely critical for normal embryonic development, so it couldn't be given to pregnant or nursing patients," he explains. "In adult mice, Hedgehog blockers appear to be tolerated at therapeutic doses, but Hedgehog signaling appears to be active in a smattering of adult tissues, including the brain, and its function in adults is not understood."

A Massachusetts biotechnology firm, Curis, has licensed cyclopamine, a naturally occurring compound, extracted and purified from plants, from Johns Hopkins University, and is also developing other forms of Hedgehog blockers with another company, Genentech, Inc. The Hedgehog blocker to be used in the upcoming trials will be given in topical form to people with certain skin cancers. If the tests prove safe, the next step will be to administer a Hedgehog-blocking drug systemically — in pill form, or as an injection. "We are very hopeful that the project will progress to this stage," says Berman, "and that the drugs show some benefit for patients. But more importantly, we hope that these agents do no harm."

And as these trials are being carried out, Berman and colleagues at Hopkins will keep plugging away, in hopes of identifying new diagnostic, prognostic, and therapeutic strategies for prostate cancer. Are there any other "Hedgehogs" out there? Are there other embryonic signaling pathways that might also regulate prostate growth? The Hopkins scientists are exploring this lead. They are also investigating whether Hedgehog signaling — like PSA levels — can be used as a crystal ball, to identify men whose prostate cancer warrants more aggressive treatment.

Note: *Under a licensing agreement between Curis Inc. and the Johns Hopkins University, Berman and Beachy are entitled to a share of royalty received by the University on sales of products described in this article. JHU owns Curis Inc. stock, which is subject to certain restrictions under University policy. Berman and Beachy are paid consultants to Genentech and Curis. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict-of-interest policies.*

Scandinavian Study Shows Prostatectomy Patients Do Better, Live Longer

When men with curable prostate cancer — disease that has not spread widely beyond the prostate — undergo radical prostatectomy, they are much less likely to have the cancer come back, and much less likely to die of the disease than men who don't have surgery.

This has been illustrated dramatically by a large Scandinavian trial published three years ago, and by a follow-up report, published recently in the *New England Journal of Medicine*. The results of both publications have rocked the way prostate cancer is perceived in Sweden, Finland, and Iceland — where the mainstay of treatment traditionally has been watchful waiting and where, sadly, most men with prostate cancer in those countries eventually die of it. In the first report, nearly 700 men were randomly assigned either to radical prostatectomy or to watchful waiting. The results provided the first concrete evidence of something American doctors had known anecdotally for years — that treating localized disease reduces deaths from prostate cancer. During the average follow-up of six years, twice as many men in the watchful waiting group died of prostate cancer — which meant, the scientists concluded, that radical prostatectomy can reduce prostate cancer deaths by about half. That study brought hope that treatment can make a difference, and the elated scientists anticipated that with a longer follow-up, the differences in cancer deaths between these two groups would become even more clear.

They were right. At 10 years after the study began (the results published in the second paper), half of the men in the watchful waiting group had died from prostate cancer. Radical prostatectomy reduced the likelihood of dying from prostate cancer by 40 percent. And the overall survival (including all causes) was significantly better in the men who underwent radical prostatectomy. Surgery was of greatest benefit to men who were younger than age 65 at the time their cancer was diagnosed. In that age group, after 10 years, 19 percent of the watchful waiting patients had *[continued on page 8]*

Radical prostatectomy reduced the likelihood of dying from prostate cancer by 40 percent.

A Verdict in the Great Treatment Debate

What's the best course of action — to treat prostate cancer, or to follow it carefully, treating specific symptoms? Many doctors, for many years, believed the question was moot, that either way, the results were about the same — that most men who were treated would die of the disease anyway, that many men who were not treated would die *with* their cancer, but not *of* it and ultimately, that prostate cancer was not really treatable.

This may have been true years ago, when men died at an earlier age from cardiovascular disease and when it was rarely possible to detect prostate cancer at a curable stage. But it's not true today. Many striking advances have occurred over the last two decades, dramatically changing the picture. Among them:

- **Better management of cardiovascular disease has prolonged the lives of men, so that they now live long enough to potentially die from prostate cancer;**
- **The development and widespread application of a surgical technique has made it possible to cure prostate cancer; and**
- **The ability to detect it sooner with more widespread screening, using the PSA test and the digital rectal exam, has made it possible to identify more men at a curable stage**

For these reasons, *men who are curable and who are going to live long enough to need to be cured are ideal candidates for surgical intervention.* This doesn't mean surgery is the only option; men should also consider watchful waiting and radiation therapy. But it does mean, says Walsh, "that men with prostate cancer should not put their heads in the sand and believe the old saying that everyone has it and no one dies from it."

[continued from page 7]

died of prostate cancer, but fewer than 9 percent of the men who underwent surgery had died. Also, surgery reduced the risk of local recurrence of cancer by 67 percent, and of the cancer's spread to distant sites by 40 percent. "The impact on distant metastasis is all the more impressive here," notes Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology, "because hormonal therapy was given more often to the men in the watchful waiting group than to the men who underwent radical prostatectomy." The study's authors concluded: "We expect the benefits of this surgery will increase during longer periods of follow-up."

One important note about this study: Most — 75 percent — of the Scandinavian men were diagnosed with cancer advanced enough to be felt during a physical exam, with an average PSA of 13 ng/ml. This is in sharp contrast to the United States today, where 75 percent of men are diagnosed, on average, five years earlier, and at a much more curable stage – with non-palpable cancer, detected because of a change in PSA. However, says Walsh, "Although these men had more advanced disease than we commonly see today in the United States, they are very similar to the men who underwent surgery in the early 1990s, before the widespread use of PSA screening."

In 1992, 104,000 men underwent a radical prostatectomy in the United States, Walsh continues. "If we apply the outcome from the recent Scandinavian trial to these figures, we would expect that there would be at least 5,000 fewer men dying of prostate cancer 10 years later, which is close to what we have experienced." In applying the findings of the Scandinavian study to today's patients, who are diagnosed with smaller cancers, detected much earlier, the authors note that it may take much longer to see the difference in survival and quality of life, "but the removal of small tumors may facilitate surgery and result in fewer side effects."

Just before the *New England Journal Of Medicine* study was published, an investigation by researchers at the University of Connecticut and McGill University in Canada appeared in the *Journal of the American Medical Association*. The article made headlines with its authors' conclusion that their findings do "not support aggressive treatment for localized low-grade prostate cancer." However, the *JAMA* study's patient population was limited in several ways: First, 60 percent of the patients were diagnosed with low-grade tumors found during transurethral resection of the prostate, a treatment for benign prostate enlargement. "Today these low-grade (Gleason 2-4) tumors are rare," notes Walsh, "because with the availability of medical therapy, fewer men are undergoing surgery for an enlarged prostate. I haven't operated on a patient with Gleason 2-4 disease in the last 10 years. What the authors' data supported, and what they should have stated in their conclusion, was that men with Gleason scores greater than 4 — the vast majority of all men diagnosed today — have a significant risk of dying from prostate cancer, and may benefit from treatment." Also, this paper did not accurately describe the natural history of untreated prostate cancer, because 42 percent of the patients received hormonal therapy within six months of diagnosis. And finally, because many of the study's patients also had serious, chronic health problems — when the paper was written, only 6 percent of the patients in the study were still alive, and most had died from other causes — the results aren't helpful to an otherwise healthy man trying to decide on the best course of treatment for cancer.

Obesity and Prostate Cancer: Does Being Overweight Make it Worse?

America is becoming a heftier nation. Take three American adults, and current statistics show that one of them is likely to be overweight, and another one out of the three is frankly obese. The health consequences here are serious; some illnesses, such as diabetes, hypertension, and coronary artery disease, have long been linked to obesity. But it turns out that obesity plays a role in cancer, too. In 2003, a landmark study by the American Cancer Society showed that obese people are at increased risk for death from several kinds of cancer, including prostate cancer.

What does this mean for a man being diagnosed today, with early-stage disease that is considered curable by surgery or radiation therapy? Did obesity somehow affect his development of prostate cancer — and more significantly, does it change his odds of surviving it? Hopkins investigators, led by urologist Stephen Freedland, M.D., have been trying to answer these questions, and they have made some important discoveries.

First, Freedland and his team noted that obese men treated by radical prostatectomy at several Veterans Affairs Hospitals were more likely to have their cancer come back after surgery. In two further studies, they have extended these findings to more than 5,000 men treated by radical prostatectomy at Johns Hopkins Hospital. "These studies provide strong evidence that obese men undergoing radical prostatectomy are more likely to have aggressive prostate cancer," says Freedland. However, he notes, the exact reason for the more aggressive cancers remains unclear.

"These studies provide strong evidence that obese men undergoing radical prostatectomy are more likely to have aggressive prostate cancer."

One problem with studying obesity is simply defining the term "obese." Men can be very muscular and weigh a lot without being obese. In addition, recent evidence suggests that obesity may lower levels of PSA in the blood — perhaps masking cancer when it is less aggressive.

Because both of these factors make it challenging to study how obesity affects prostate cancer, Freedland and his team are also exploring potential molecular links that would explain why obese men may be at greater risk for aggressive cancer. For example, along with Alan Partin, M.D., David Hall McConnell Professor and Director of Urology, they examined the expression of two hormones made by fat cells: leptin and adiponectin. It turns out that obese men produce more leptin but less adiponectin in the blood than thinner men.

The scientists did not find any association between leptin and aggressive prostate cancer. However, they may have struck gold with adiponectin: Overweight and obese men who had lower adiponectin levels tended to have higher-grade cancers.

"Though the data for adiponectin look exciting, we continue to search for new molecular links between obesity and

prostate cancer," Freedland says. In exciting new research, Freedland, William Isaacs, Ph.D, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology, and Jun Luo, Ph.D., assistant professor of urology, have begun to examine genetic differences in the cancers of men who are obese and men who are not. In their preliminary studies, they've found that cancers from obese men have a "molecular fingerprint," and can be distinguished from cancers from trimmer men. They are currently investigating some of these genetic differences. Notes Freedland: "We hope that the differences we have found may give us some insight into why obesity causes more aggressive prostate cancer — which, in turn, will give us greater insight into prostate cancer biology in general."

High-Tech Seed Placement Making Brachytherapy Even More Precise

Brachytherapy — implanting radioactive seeds into the prostate to kill cancer — has come a long way since the 1970s, when doctors made an incision in the prostate and tried to space the seeds evenly, with a "free-hand" approach. Over the last decade, with the use of CT scans and ultrasound guidance to place the seeds through the perineum, and the development of dosimetry — precise placement of the seeds to kill prostate tissue, but avoid harming nearby organs, such as the bladder and rectum — brachytherapy has become much more effective. This is particularly true as more men, with the help of regular PSA screening, are diagnosed with early-stage prostate cancer, where the cancer is still confined within the prostate.

However, the goal is perfection — curing prostate cancer with minimal side effects — and as good as brachytherapy has become, radiation oncologists and colleagues at Hopkins are working to improve it. One challenge is that there is no "regulation" prostate — no standard in size, shape, or tissue consistency. Every man's prostate is different. This means that "the highest level of precision is sometimes difficult to achieve, even for the most experienced physicians," says Danny Y. Song, M.D., assistant professor of radiation oncology. Sometimes, for example, dense prostate tissue slightly bends the needles used to place the seeds, and the implanted seeds don't always end up exactly where they are supposed to be. "In addition, although we use ultrasound to view the prostate during the procedure, seeds cannot readily be seen on the ultrasound image once they have been placed. This means that the results of the implant are not always exactly what was intended — and yet, when it occurs, this cannot always be identified and corrected in the operating room."

Treating a moving target

Even with "pre-plan" (a map and radiation dosage guide drawn up before the procedure) and intraoperative "real time" dosimetry, "the treatment plans are based on a fixed organ," says Chan. "In reality, the prostate gland is mobile. As it is pierced with needles, the prostate gland can move, rotate, and swell. The radioactive seeds can also move, shift and migrate during the procedure. This can make perfect implants difficult." (This frustrating movement of the prostate, by the way, can also happen during a needle biopsy to look for cancer, and is why doctors now take a dozen samples instead of just a handful.)

What's needed, continues Chan, is "a better mouse trap" — improved dosimetry. "We are currently evaluating two different approaches to help solve this issue." One potential solution involves Dan Stoianovici, Ph.D., Director of Uro-Robotics Laboratory at the Brady Urological Institute. Stoianovici has been developing an automated method of performing brachytherapy, using a computer-driven, robotically automated brachytherapy seed implant device, which can be coupled with continuous real-time MRI imaging. Another benefit: "The automatic implant device will make the success of treatment independent from the operator," says Chan. "Dr. Stoianovici's work is revolutionary, and will change the face of prostate brachytherapy."

What does this mean? The ability to see in the dark, to know what's happening to the ever-changing prostate during the procedure.

Chan and Song: Looking to revolutionize brachytherapy by designing a "better mousetrap."

Another approach involves a device created by Gabor Fichtinger, Ph.D., and colleagues in the Hopkins School of Engineering. "This device links an x-ray machine, which is capable of viewing the seeds but not the prostate, to an ultrasound, which can view the prostate but not the seeds," says Song. Computer software then spots the seeds on the x-ray and projects their location onto the ultrasound, showing exactly where the seeds are. What does this mean? The ability to see in the dark — to know what's happening to the ever-changing prostate during the procedure. "The concept," explains Chan, "is that as the seeds are placed, the prostate gland is constantly reimaged and revaluated for adequate dosimetry. If a seed shifts, a 'cold spot' would be recognized and treated. This is not possible with current techniques." The result: "An ideal seed distribution," says Song.

The next step is to prove that these "better mousetraps" work as well as the Hopkins scientists expect. "We have recently been awarded funding through the Prostate Cancer Research Program of the Department of Defense to carry this out this study," says Song. He and colleagues will conduct a randomized study, comparing men treated with standard brachytherapy techniques to men treated with the new technology. If shown to be effective, this technology will rapidly be made available to all physicians, and their patients, who are using brachytherapy to treat prostate cancer.

Platz: Long-term inflammation may create an environment that leads to cancer.

Could Fighting Chronic Prostate Inflammation Help Prevent Cancer?

Imagine going around with chronic sunburn on your face: Your muscles hurt from being tense all the time; it hurts to smile. Your pulse is higher, too, from the strain. Even though you are able to function, the discomfort is always there, wearing away at your body, making you vulnerable.

This is what it's like, on a much smaller scale, for the prostate, which is prone to inflammation (even though this doesn't always cause noticeable symptoms). Cells called inflammatory infiltrates are immune-system cells that migrate into inflamed tissue. Their job is to clean up infection, and generally make sure it doesn't happen again. "These infiltrates may be there as a response to prostate infection, chemical or physical damage to the prostate's epithelium (lining), and even changing hormone levels within the prostate," explains Elizabeth Platz, Sc.D., M.P.H., associate professor of epidemiology, urology and oncology. But sometimes, these cells can outstay their welcome. "If the inflammatory response persists unnecessarily" — creating a situation of chronic stress — "it may create an environment that is conducive to cancer," she adds. For the last few years, this possibility has intrigued scientists, who are actively looking to answer this question: "If we can inhibit chronic inflammation, can we reduce the future risk of prostate cancer?"

Scientists have a ready-made population in which to start looking — men taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDS). These drugs block chemicals called cyclo-oxygenase enzymes, which play a key role in the body's inflammatory response. One large study of these men found that men taking NSAIDS had a 15 percent lower risk of developing prostate cancer than men who weren't taking them.

Platz, with colleagues at Hopkins and at the National Institute of Aging, recently studied 1,244 men participating in the Baltimore Longitudinal Study of Aging, a study begun more than 40 years ago and involving about 1,500 men, who return every other year for physical examinations and medical tests — including an assessment of their use of prescription and over-the-counter drugs. The researchers found that men who used aspirin or other NSAIDS had a 29 percent lower risk of prostate cancer than men who did not use these drugs; this work was published in the journal *Cancer Epidemiology, Biomarkers & Prevention*.

One concern with this study, Platz says, was the possibility that inflammation damages the epithelial cells, and causes PSA to leak out of the prostate and into the bloodstream. Did some of these men have falsely lowered PSA scores because they were taking NSAIDS — in other words, did treating inflammation actually mask a man's true PSA level, and were some cancers not detected because the PSA wasn't getting out of the prostate at levels high enough to be considered significant? To address this issue, Platz and colleagues studied 933 of the men who did not have prostate cancer and who, over the years, had undergone a combined total of 3,749 PSA tests. In these men, there was no difference between those who used NSAIDS and those who didn't. "Thus, the lower risk of prostate cancer in the users of aspirin and non-aspirin suggests a modest, but possibly genuine benefit of these anti-inflammatory drugs."

"If we can inhibit chronic inflammation, can we reduce the future risk of prostate cancer?"

Need A Radical Prostatectomy? Find a Hospital Where They Do Many of Them

When it comes to finding a hospital for radical prostatectomy, a Brady study has found a simple rule for potential patients to keep in mind: Experience counts — especially if you want the best chance to be cured.

"Radical prostatectomy is a complex, notoriously difficult surgical procedure," says Bruce J. Trock, Ph.D., associate professor of urology, epidemiology, and oncology, and director of the Brady's Division of Epidemiology. A new study from Brady scientists shows what many in the medical community have known for years: That the best results — fewest side effects, and greatest control of cancer — are found at academic medical centers, where the urologists specialize in this complicated operation.

The study, headed by Robert Wood Johnson Scholar and urology fellow Lars Ellison, M.D., compares the recurrence of prostate cancer at a hospital to the number, or volume, of prostatectomies performed at that hospital. What does hospital volume have to do with the results of surgery? A lot, explains Trock, who also took part in the study — particularly when the procedure is a hard one for surgeons to master. For radical prostatectomy, he says, several studies have examined the link between hospital volume and short-term problems, such as surgical complications, and death up to one year after surgery. But this study, published in the *Journal of Urology*, is the first to examine whether hospital volume is related to cancer control — the likelihood of that cancer will come back — after prostatectomy.

Ellison and colleagues evaluated 12,635 men aged 65 or older — patients from hospitals in Arizona, California, Connecticut, Iowa, Utah, and Washington State — who underwent radical prostatectomy between 1990 and 1994, and who were followed through 1999. The researchers determined hospital volume based on the number of prostatectomies performed in men aged 65 or older during 1990-1994 — low (1-33), medium (34-61), high (62-107) or very high (108 or more). Then they looked for evidence of prostate cancer recurrence in these men — the start of hormonal therapy or radiation therapy more than six months after radical prostatectomy.

They found that the low-volume hospitals had more patients with low-grade disease and local tumor stage, both of which indicate a better prognosis. This suggests that hospitals with less experience prefer to operate on the men most likely to do better, explains Trock. Even so, low- and medium-volume institutions had significantly higher rates of treatment for cancer recurrence — 25 percent and 11 percent higher, respectively — than did very high-volume institutions. However, hospital volume did not seem to affect the number of deaths, from prostate cancer or otherwise; Trock believes this is due to the study's relatively short follow-up time of five to nine years, and the low rate in general of death from prostate cancer after radical prostatectomy.

"Surgeons at high-volume institutions encounter the full range of this diversity, and are prepared to deal with it."

The higher recurrence rates at lower-volume institutions could be because the surgeons' experience — and also their techniques — vary widely. Ellison and colleagues found as much as a 25-percent difference in cancer control between low- and very high-volume hospitals. "The anatomy of the prostate and biology of a tumor can vary tremendously among patients," concludes Trock. "Surgeons at high-volume institutions encounter the full range of this diversity, and are prepared to deal with it."

For Men at Risk, Radiation Combined With Temporary Hormonal Therapy

Here's a statistic: About half of American men with prostate cancer are treated with some form of radiation therapy. But after that, it's a bit harder to generalize — and more complicated to determine which men will need additional treatments in combination with the radiation. For most men — those diagnosed with early-stage, low-risk cancer — radiation therapy alone is enough, says Theodore L. DeWeese, M.D,. Chairman of the Department of Radiation Oncology and Molecular Radiation Science, and professor of radiation oncology, oncology and urology. "These men rarely experience a clinical recurrence of cancer after treatment. But some men are diagnosed with more aggressive disease, and are at greater risk for recurrence."

Which men, then, are at extra risk? The Partin Tables (discussed in the Winter 2005 issue of *Discovery*, and the Winter 2003 issue of *Prostate Cancer Update*, both Brady publications), based on the course of prostate cancer in thousands of men, can predict the likelihood of cancer recurrence with 95-percent accuracy. One surprising revelation of such tables, says DeWeese, is that "a substantially greater number of patients than we previously believed actually have cancer that is already outside the prostate at diagnosis — even though it is not able to be detected by physical examination or scans." With the help of such data, "we can group patients into low-risk, intermediate-risk and high-risk groups for tumor recurrence," he adds. This is very important, because at five years after treatment, men with intermediate-risk disease have a likelihood of biochemical recurrence — the return of PSA — of about 40 to 50 percent. The odds of recurrence for men with high-risk disease: 65 to 75 percent. "Clearly, for patients with intermediate and high-risk disease, we need better therapeutic approaches."

What about the men with intermediate risk of recurrence? Can the combined treatment help them, as well? The latest evidence signals a hearty "yes."

One approach that immediately suggests itself is based on prostate cancer's sensitivity to hormonal therapy (suppressing the male hormones, or androgens). Can hormonal therapy make radiation treatment more effective for men with localized prostate cancer? For men at high risk of recurrence, "a number of studies have been conducted to test the benefit of this combined treatment," comments DeWeese, "and each trial has shown a significant advantage in improving cancer outcome." This includes controlling the cancer in the pelvis, limiting the risk of developing metastatic disease, and in one trial, prolonging life. These studies "strongly argue" for the combined approach in high-risk men.

But what about the men with intermediate risk of recurrence? These men have stage T1b-T2b disease, with a Gleason score of 7 or a PSA between 10 and 20 ng/ml. Can the combined treatment help them, as well? The latest evidence signals a hearty "yes" to temporary androgen suppression for these men, too. In a recent study, reported in the *Journal of the American Medical Association*, men with primarily intermediate-risk cancer were treated with either a short course (six months) of androgen suppression in addition to radiation therapy or with radiation therapy alone. "This study is very important," says DeWeese, "because it is the first trial to demonstrate that men with intermediate-risk disease who receive a short course of androgen suppressive therapy plus radiation achieve a significant increase in overall survival when compared to men treated with radiation therapy alone."

However, DeWeese notes, "the radiation doses used in this study were relatively low by today's standards. At Johns Hopkins, we routinely administer higher radiation doses to the prostate and areas around it," using techniques such as intensity modulated radiation therapy (IMRT) to deliver these higher doses safely. "This is more likely to eradicate prostate cancer cells, and to improve control of cancer. So it might be that the low radiation dose used in this study could have resulted in lesser control of cancer than if *[continued on page 12]*

[continued from page 11]

higher doses had been used." It is not clear how higher doses of radiation affect the hormonal therapy. Could this also mean that the hormonal therapy is only helpful with lower doses of radiation? "While this is a possibility, it cannot be easily answered with one or even several studies," says DeWeese. "We will continue to use higher radiation doses along with androgen suppression in men with intermediate-risk disease, because it has been shown to be beneficial and to increase survival."

However, DeWeese adds, the field of radiation therapy is constantly evolving. "As we are able to deliver significantly increasing doses of radiation with unprecedented accuracy and precision, whether all patients will ultimately require hormonal therapy is not clear."

The Changing Picture of High-Grade PIN

Not As Sharp a Pointer as it Used To Be

On the spectrum of prostate cells, high-grade PIN cells are closer to being cancerous than they are to being normal. But just because a man has high-grade PIN cells in his prostate, it doesn't necessarily mean that he has cancer there, too. "High-grade PIN is known to be strongly associated with prostate cancer, and is, indeed, probably a precursor to it," says pathologist Jonathan Epstein, M.D., Rose-Lee and Keith Reinhard Professor of Urologic Pathology, whose work over the last decade has helped define these cells. However, because biopsies are so much more accurate than they used to be, a finding of high-grade PIN cells isn't nearly as worrisome as it was a few years ago.

In the 1990s, when high-grade PIN turned up on a needle biopsy, men were told that they needed an immediate repeat biopsy, because cancer was hiding there somewhere — and indeed, on repeat biopsies, cancer was often found. Today, however, evidence from a large Hopkins-led study of thousands of men with prostate cancer shows that this is no longer the case: When men with high-grade PIN undergo a repeat biopsy, they are no more likely to have cancer than other men.

Why is that? The reason is better biopsies, says Epstein. "A decade ago, only four or six biopsies were taken, and if cancer was present it was often missed. Today, however, most men undergo 12 or more biopsies, which gives us a much greater opportunity to detect cancer."

Because biopsies are so much more accurate these days, a finding of high-grade PIN cells isn't nearly as worrisome as it used to be.

Epstein's advice: "If your biopsy has not been read by a pathologist who specializes in prostate cancer, the first thing you should do is get a second opinion." If there are no other clinical indicators of prostate cancer, "I recommend that men do not need a repeat needle biopsy within the first year." Further studies are needed, he adds, to confirm whether repeat biopsies should be performed several years after high-grade PIN is found on a needle biopsy and, if so, how often and when.

Prostate Cancer and Men with Very Low PSA Levels

The Key to Screening is Getting a Baseline Level, and Watching It Closely

Recently, a well-publicized study, which appeared in the *New England Journal of Medicine*, sent shockwaves through much of the medical community, and raised many questions about screening for prostate cancer. The study showed that in men with very low PSA levels (less than 4.0 ng/ml) who underwent needle biopsies of the prostate, 15 percent had prostate cancer — and of these men, 15 percent had worrisome Gleason scores of 7 or higher. "Basically, this study showed that for men with a PSA greater than 1.0 ng/ml, there is no threshold PSA," explains Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. "There is no magic cutoff number to guarantee that a man does not have cancer — and most specifically, a life-threatening cancer."

So, what's the best way to screen for prostate cancer? The key is to look beyond cutoff numbers, says H. Ballentine Carter, M.D., professor of urology and oncology, and one of the world's top experts in the study and understanding of PSA. "Today, it is impossible to base any recommendations for screening on scientific outcomes, because they simply don't exist." The trouble, he adds, is that PSA is *prostate-specific and not cancer-specific*, and so *any* prostate disease — including infection and benign enlargement, as well as cancer — can cause PSA levels to rise.

PSA is most valuable as a marker for cancer when the slate is relatively clean — "when the other confounding, benign conditions do not exist." With this in mind, the best time for a man to have his first PSA test is when he's young and not even terribly worried about prostate cancer, "about 35 to 40 years of age, when he is unlikely to have benign prostatic enlargement. This will provide a valuable baseline upon which other measurements of PSA can be compared for the rest of his life."

For men with low PSA levels (between 1 and 3), any increase is alarming," warns Carter. Increases *as small as 0.2 ng/ml a year* were a predictor of death from prostate cancer.

After this first test, Carter recommends that a man have follow-up PSA measurements every two to five years. Just how far apart to space these subsequent tests depends on the baseline level: "If the initial PSA is greater than the median for his age, then PSA levels should probably be checked every two years." For men in their forties, the median PSA is 0.6 ng/ml, and for men in their fifties, it is 0.7 ng/ml. "At present," Carter says, "this seems to be the most reasonable approach for *all* men based on

available data, whether they're high-risk (if prostate cancer runs in their family, or if they are of African descent) or not. From this baseline, the rate of increase in PSA every year can be calculated." This concept, called PSA velocity, was pioneered by Carter in 1992, in a landmark article in the *Journal of the American Medical Association*.

"For men with low PSA levels (between 1 and 3), any increase is alarming," warns Carter. In a study presented this year at the American Urological Association, Carter found that increases *as small as 0.2 ng/ml a year* were a predictor of death from prostate cancer.

In his 1992 article, Carter reported that for men with PSA levels between 4 and 10, a PSA velocity of 0.75ng/ml per year suggested that cancer was present, and for men with these PSA levels, this remains a critical guideline. "Change in PSA over time is the most valuable tool we have for interpreting the PSA — for predicting both the presence of cancer, and whether or not it is life-threatening."

What if it's my first PSA test? I don't have a baseline. How do I know I don't have cancer? "For men in this situation, given the prevalence of life-threatening cancers at very low PSA levels, the guidelines commonly being used are of questionable help," says Carter. His recommendation: "If you are in your fifties or sixties, have never before had a PSA test, and have a PSA level greater than 3.0 per ng/ml — and you are otherwise healthy, and could expect to live 15 or 20 years — a biopsy is indicated. If you are in your forties, a biopsy is a good idea if your PSA exceeds 2 to 2.5ng/ml."

As long as PSA testing has been used as a screen for prostate cancer, "there have been naysayers who have said it is not valuable," notes Walsh, "and many of them spoke up when the *New England Journal of Medicine* article came out. But nothing could be further from the truth. PSA testing is valuable. But you need to know how to test, how often to test, and how to interpret the results. There is no question, however, that we could also use a new marker."

(*For an exciting breakthrough in this area, see the article on Robert Getzenberg's work on EPCA, on Page 2.*)

Sparing Potency, Sparing Nerves with Laparoscopic Prostatectomy

The Brady's Laparoscopic Radical Prostatectomy (LRP) Program is the new kid on the block, and it's coming on strong. In just four years, there's been a 15-fold increase in the number of operations performed by the program's two surgeons, Li-Ming Su, M.D., associate professor of urology and director of Pelvic Laparoscopy and Stone Disease at the Johns Hopkins Bayview Medical Center, and Christian Pavlovich, M.D., associate professor of urology and director of Urologic Oncology at Bayview. "So far, we've performed more than 500 successful LRPs," says Su, "and we anticipate that we will be performing more than 200 a year."

In a recent study of the return of sexual function in their LRP patients, Su and Pavlovich found that — as is the case with the "nerve-sparing" retropubic procedure pioneered by Patrick C. Walsh, M.D. — men who had both of the nerve bundles (one on either side of the prostate, these bundles contain the nerves responsible for erection) spared had better potency results than men who had only one nerve bundle spared. "At one year after surgery, 72 percent of our patients who underwent bilateral (both sides) nerve-sparing surgery reported the ability to engage in intercourse," with or without the use of drugs such as Viagra, reports Su. However, when only one nerve was spared, 35 percent were potent at one year.

Younger men, too — men in their fifties — were more likely to recover potency than older men. Su found that younger men who received nerve-sparing LRP reported a higher potency rate of 74 percent, as compared to 41 percent of older men at one year after surgery. And of the men younger than 58 who had both nerve bundles spared, 82 percent reported successful intercourse at one year.

Su and Pavlovich are continually working to improve their results in this still-new area of surgery. From laboratory work with animals this year, they have found that the delicate nerve bundles are sensitive even to heat. "We have modified our technique to avoid the use of thermal energy sources when dissecting the fine cavernous nerve bundles, just like in open surgery," explains Su.

Su and Pavlovich: Continually refining their techniques and improving their results.

Su has specially designed fine-tipped laparoscopic instruments that allow him to "meticulously dissect and preserve the fragile nerve fibers, while removing the cancerous prostate. We clearly have learned a great deal from the surgical principles defined by the anatomic nerve-sparing radical retropubic prostatectomy approach described by Dr. Patrick Walsh," he adds, "and we're simply applying these principles to our laparoscopic technique."

"In our last 50 patients, more than 90 percent of men received successful nerve-sparing surgery, with both nerves preserved in 72 percent of men."

Preserving the nerves — and potency — during LRP is a skill that comes with experience, says Su, and with their vigilant efforts to improve the procedure, the results are getting better all the time. "In our last 50 patients, more than 90 percent of men received successful nerve-sparing surgery, with both nerves preserved in 72 percent of men. This is in contrast to the first 50 LRPs, where only 50 percent of men received successful bilateral nerve-sparing surgery."

Isaacs: Prostate cancer likely requires many different mutations, and involves many different genes.

Prostate Cancer Runs in Some Families; World's Largest Study Aims to Find out Why

Message to men: One of the strongest risk factors for developing prostate cancer is your family history. This means that if your brother or father had prostate cancer, then your risk for developing the disease is two and a half-fold higher than for a man without family history of the disease. And if you have two affected relatives, your risk is three and a half times higher. Scientists also know from studies carried out in twins (where it is sometimes easier to rule out environmental causes, and focus on genetic factors), that prostate cancer is more heritable than either colon cancer or breast cancer. Genetically speaking, it's the gift that keeps on giving.

"These are powerful facts," says molecular geneticist William B. Isaacs, Ph.D., one of the world's foremost authorities on hereditary prostate cancer, "and they have given us great hope that we can identify one or more genes to explain why prostate cancer runs in families." Isaacs, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology, is a pioneer in this field. In 1996, he and colleagues from Hopkins, the National Human Genome Research Institute, and Umeä University in Sweden reported that there appeared to be a gene or genes located on the long arm of chromosome 1 that increased susceptibility to prostate cancer. Since that time, at least 8 other sites on different chromosomes have similarly been identified.

But the goal of pinpointing these locations exactly hovers tantalizingly out of reach — due, Isaacs believes, to "the very nature of prostate cancer itself." Because it tends to strike older men, he continues, many different mutations are probably needed to convert a normal cell to a cancer cell — which suggests that there may be many genes involved. "Some of these genes are important in the initiation of the disease," he continues, "while some are more important in determining which prostate cancers will progress. Also, because the disease occurs in older men, it's difficult to collect genetic material from multiple generations in a single family." Another difficulty is that PSA testing — while a godsend for detecting the disease early — may muddy the waters: "It's often difficult to know which men with prostate cancer truly carry a major cancer susceptibility gene, and which men were detected because of intensive screening."

To circumvent these roadblocks, Isaacs is aiming big — launching the largest study of hereditary prostate cancer families ever amassed in the world. The study, headed by Isaacs, combines data from 10 research groups (called the International Consortium for Prostate Cancer Genetics), and involves investigators from the United States, Canada, Norway, Australia, Finland, Germany, and Sweden, and 1,233 prostate cancer families. In a recent study based on these patients, published in the American Journal of Human Genetics, they identified the presence of a significant area of linkage (evidence that a cancer gene is present at this site) on chromosome 22. They also identified five other likely sites of linkage, and are focusing on families in whom multiple men have aggressive prostate cancer.

Prostate cancer is more heritable than either colon cancer or breast cancer. Genetically speaking, it's the gift that keeps on giving.

Why so big? Isaacs reasons that by putting together many families, and by breaking these families down into the ones most likely to harbor a mutated gene (families with large number of affected men who developed prostate cancer at an early age), "we'll have our best shot at determining where these elusive genes are most likely located."

Killing Prostate Cancer with PSA-Detonated "Smart Bombs"

PSA has long been used as a monitor, a marker, and a detector. Now, thanks to two Brady researchers, PSA has a new job — as a trigger, a detonator of a "smart bomb" designed to kill locally advanced prostate cancer.

This work takes advantage of PSA's normal role in the body as an enzyme that, like a pair of "molecular scissors," cuts other proteins into small pieces, says John Isaacs, Ph.D., professor of urology, who developed this new therapy with Samuel R. Denmeade, M.D., associate professor of oncology.

Working together with scientist Thomas Buckley, from the University of Victoria in British Columbia, Isaacs and Denmeade have modified a highly potent bacterial toxin called aerolysin — which comes from a Mediterranean plant called Thapsia garganica (known as the "death carrot"). In its altered form, however, aerolysin's killing powers are severely limited: It's only toxic in the presence of PSA. "The treatment is highly focused," Isaacs explains. "PSA is only made by normal prostate and prostate cancer cells, and it only functions as molecular scissors within cancerous tissue — not in the bloodstream. This means that it will only target and kill prostate cancer cells, and leave normal tissues alone."

PSA detonates aerolysin by snipping off its tail — which allows the toxin to drill large holes in the cell membrane. These holes cause the cell to swell, and then

explode. Isaacs and Denmeade have tested their PSA-detonated bomb in mice that have human prostate cancer, with exciting results: Just one injection of the toxin into the center of the tumor leads to a dramatic reduction in tumor size. In one recently completed study, 60 percent of mice receiving a single injection had no detectable tumor 15 days after the treatment.

Denmeade and Isaacs are developing this therapy with Protox Therapeutics, Inc., for injection into the prostate gland in men with prostate cancer that has returned after radiation therapy. In toxicology studies required by the FDA before the drug can be tested in humans, a single injection of the PSA-detonated toxin into the prostate of monkeys (the only other species besides humans that makes PSA) produced widespread destruction of prostate tissue without any significant side effects. Once these toxicology studies are completed, the first clinical studies in men with recurrent localized prostate cancer will be performed at Johns Hopkins by Ted Deweese, M.D., chairman of radiation oncology and molecular radiation science. These clinical trials are expected to begin in early 2006.

Nerve-Protecting Drugs May Help Men Recover Potency Sooner

Two men have "ideal" prostate cancer scenarios: Both are fairly young, in their late fifties, both have cancer that's detected early, when it is well within the prostate, and both undergo radical prostatectomy. And yet — one man recovers potency within six months; the other takes more than a year. Why?

Nobody knows for sure. The nerves that are responsible for erection have three strikes against them with any form of treatment for prostate cancer: They're tiny, very frail, and unless the surgery to preserve them, while removing the cancer, is performed flawlessly, they're right in the line of fire — they run in microscopic bundles along both sides of the prostate.

In pioneering laboratory research several years ago, Arthur L. Burnett II, M.D., professor of urology, discovered that solutions using special proteins called immunophilin ligands helped rats with nerve injury and erectile dysfunction (similar to that found in men after radical prostatectomy) recover penile nerve function. The immunophilin ligands, and eventually, a prototype drug called GPI1485, seemed to soothe, protect, invigorate these nerves — and even to help them repair themselves — resulting in stronger erections, recovered earlier, and dramatically less nerve damage. The results were so promising that GPI1485 was tested

One man recovers potency within six months; the other takes more than a year. Why?

in clinical trials, given orally to men undergoing radical prostatectomy who had both nerve bundles spared.

The latest Hopkins-led trial, involving 196 men in 23 hospitals, is nearing completion, says Burnett. "This is a Phase II investigation. Our overall objective is to determine whether the drugs can speed up and improve the process — whether erectile function recovery is achieved faster and better with treatment than with nerve preservation alone." Men in the study are monitored up to a year, not only for erectile function, but for health-related quality of life issues, and to make certain that the drug is safe. "Our early impressions are that the treatment has been well tolerated, without major side effects," says Burnett. "We will determine how successful this has been, and report on it by early 2006."

STRICTURE-FREE AND CONTINENT

Help for Severe Bladder Neck Contracture

One infrequent but troublesome complication of radical prostatectomy is bladder neck contracture. This happens when dense scar tissue forms in the bladder neck, the area where the bladder and urethra are joined together after the prostate is removed. The thickened scar tissue narrows the inside of the urethra, causing a slowdown — or sometimes even an outright blockage — of urine flow. Exactly why this scar tissue forms is unknown, but it may be due to poor healing at the surgical site.

Mild cases are fairly simple to treat; a urologist dilates the area, using instruments passed through the urethra. Or, if the contracture is more significant, the urologist uses a cystoscope, passed through the penis, to make cuts in the scar tissue and break its stranglehold on the urethra. Rarely, however, severe contracture can cause the urethra to become completely obstructed.

"In the past, the only option when the opening was completely blocked was major surgery," says Thomas W. Jarrett, M.D., associate professor of urology, and chief of the Division of Endourology and Laparoscopy. This was especially tough on men who had just undergone major surgery, radical prostatectomy. Recovering from this procedure could take months, and involved the long-term use of a catheter (placed either in the urethra or directly into the bladder, through the skin in the lower abdomen). Worse, men faced a high risk of impotence and long-term incontinence from the extra surgical trauma.

Jarrett has developed a new technique that avoids a second open surgical procedure, and all of the complications that go with it. "In this technique, we place small telescopes simultaneously through the penis and through a tiny incision above the pubic bone," Jarrett explains. "We have been able to successfully reestablish the channel between the bladder and urethra in a minimally invasive fashion in all patients." Once the urethra is reopened, Jarrett cuts the scar tissue, using a laser beam to minimize trauma to the tissues. Then, very gently and gradually, over the next few months, he enlarges the urinary tract until it is stable. The theme of this approach, borrowing from Aesop, is "Slow and steady wins the race." The process may require several minor surgical revisions to treat additional scar tissue. Also, during this time of healing, "the patient must catheterize himself on a regular basis to prevent the opening from closing."

However, the results are worth the wait, Jarrett concludes: "Using this technique, we have been able to successfully treat most patients without major surgery and the devastating side effects of impotence and incontinence."

Which Drug is the Real Hero of Vaccine Trial?

It's the "Holy Grail" of prostate cancer, or any cancer, for that matter. A vaccine — perhaps one highly personalized, made from your own cells — that works the way nature intended, only better. There are no side effects; like a bodybuilder, the vaccine adds heft to your immune system. One day such a vaccine may even prevent prostate cancer altogether.

We're not there yet, but we're getting closer. Over the last decade, scientists at the Brady Urological Institute, led by Ronald Rodriguez, M.D., Ph.D., have made remarkable progress in this area, diligently overcoming obstacles that at first seemed impossible (for more on his work, see story on Page 17).

Mario Eisenberger

In the news recently has been widespread coverage of a vaccine called Provenge, given to men with advanced prostate cancer, and reported to prolong their lives. Provenge is made up of a patient's own blood cells, enriched by immune system cells specially engineered to kill cells that make an enzyme called acid phosphatase. "This is an earlier vaccine," comments Mario Eisenberger, M.D., R. Dale Hughes Professor of Oncology and Urology, who has designed and tested many prostate cancer drugs, and who recently reviewed this study. More recent vaccines have been targeted to more specific targets, such as PSA or PMSA (prostate membrane-specific antigen, a protein that's made on the surface of prostate cells). Unfortunately, he notes, acid phosphatase is expressed ubiquitously in tissues throughout the body. "We would not expect a vaccine generated against a generalized protein to be so powerful."

As it turns out, Eisenberger adds, the key to these results has much to do with the study itself. "The study was originally designed to look at men who had metastatic prostate cancer and who had failed hormonal therapy, to determine whether treatment delayed progression of the disease. Unfortunately," he says, "it didn't cause a delay. There was no significant difference in the time it took cancer to progress — which means that the primary endpoint of the study was negative."

Is Prostate Cancer Likely to Return? Global Study Launches Preemptive Strike

Imagine you are looking at two boxes. Both contain weapons. One box reads, "To be used as a last resort only. Open if all else fails, and hope for the best." The other says, "Open at the first sign of trouble. Strike early, strike hard, and set your sights on victory."

Such is the transformation of chemotherapy for prostate cancer in recent years. Energized by scientists such as Mario Eisenberger — unsinkable, creative, stubborn, and above all, confident that they can find the winning formulas — the field has undergone nothing less than a revolution.

One key to the change is the philosophical evolution in chemotherapy's role. Today's drugs — many of them developed by Eisenberger and colleagues — are more targeted, with far fewer side effects than the devastating, "scorched earth" drugs of old. And this means that instead of being stuck on the sidelines — waiting to be needed in case the "A" team treatments (radical prostatectomy and radiation therapy) and "B" team treatments (hormonal therapy) were not successful — chemotherapy is getting into the game sooner than ever.

"Radical prostatectomy cures many men with prostate cancer," says Eisenberger. "However, the disease comes back in about one-third of men, and many, unfortunately, will suffer from the symptoms caused by metastasis and die of their disease." The good news is that instead of waiting for this to happen, "we now have many factors to help us predict which men are more likely to have cancer recur after surgery." These factors include:

- **The presence of tumor in the lymph nodes adjacent to the prostate**
- **The presence of cancer in the seminal vesicles**
- **The presence of cancer in the surgical margins**
- **Gleason scores higher than 9, and**
- **A very high PSA before surgery.**

Success in other cancers: **Doctors treating cancer of the breast and colon have found, in patients at high risk of having a recurrence, that adjuvant treatment — starting chemotherapy and, in breast cancer, starting hormonal therapy as well, immediately after surgery — can delay the onset of metastasis and even prolong survival. "In fact," notes Eisenberger, "in these two tumor types, if the surgical specimen shows that the adjacent lymph nodes are positive, the use of chemotherapy is standard." In breast cancer, too, researchers have identified certain molecular markers that not only predict higher risk of recurrence, but have led to more specific ways of controlling the cancer.**

Adjuvant therapy: "The time has come for prostate cancer."

"The time has come for prostate cancer," says Eisenberger. He is heading a massive study to determine whether adjuvant treatment can delay the return of prostate cancer in men at high risk. This investigation, called the ATLAS study (Adjuvant Taxotere and Leuprolide Acetate Study), will involve more than 2,000 patients from more than 20 countries worldwide. It will test whether immediate hormonal therapy using leuprolide acetate (which stops the production of testosterone) with or without taxotere, started right after surgery, works better than treatment with the same drugs given months or years later, when the cancer shows the first sign of recurrence (when the PSA starts climbing). "Taxotere is the best chemotherapy for prostate cancer that kills both cancer cells, which respond to testosterone, and those that do not respond to hormonal therapy," says Eisenberger. Researchers in the ATLAS study also will collect patients' tumor tissue and blood samples, in an attempt to discover, as in breast cancer, whether there are molecular markers to help define the biology of the cancer and even the design of new treatments.

However, surprisingly, the men who had randomly been assigned to the vaccine group survived four months longer than men who were treated with placebo. "How could that be? How could there be a survival advantage, if the vaccine failed to prevent progression of the disease?" The answer to the question may be in understanding what else these men received. In all of the men — those who received the vaccine, and those in the placebo group — cancer progressed. When this happened, the men in the placebo group were treated with the vaccine. The men who had already taken the vaccine were immediately given the chemotherapy drug taxotere — "a drug of great promise," says Eisenberger, who has studied taxotere extensively, by itself and in numerous combinations with other drugs, and who will be leading a global study of the drug (see side story). Eisenberger and other scientists have reported that giving taxotere plus prednisone prolongs life in men with advanced prostate cancer. Thus, what helped these men the most — getting the vaccine, or receiving effective chemotherapy as soon as the cancer progressed?

What helped these men the most? Getting the vaccine, or receiving effective chemotherapy as soon as the cancer progressed?

Finally, this study was limited by its small number of participants — only 127 men. With this type of study, the larger the number, the more helpful the results, notes Eisenberger. For example, in one study of taxotere plus prednisone, published in the *New England Journal of Medicine*, 1,006 patients were required to show the effect on survival. The company that makes provenge has now embarked on a larger study in an attempt to confirm these results, and clarify the value of this vaccine.

Gene Warfare: The Latest from the Front

For the last several years, Ron Rodriguez, M.D., Ph.D., has tried to do what nobody else has ever done — kill prostate cancer with gene therapy. And there's a reason nobody's ever done it — because it's really hard. Rodriguez assistant professor of urology, medical oncology, cellular and molecular medicine, and viral oncology, and director of the Urology residency program, has labored valiantly over several Herculean projects, each taking aim at prostate cancer in a unique way.

One approach involves changing a common virus, called the adenovirus, into a cancer-killing machine. Rodriguez and colleagues have developed several generations of these adenoviral gene therapy drugs, each better than the last. "We are generating new technology to allow adenoviruses to attach themselves only to prostate cancer cells," Rodriguez reports. "This has never been accomplished before, and is the most ambitious project taken by a gene therapy group to date. We have overcome some of the initial obstacles, which at one point were thought to be insurmountable." One breakthrough came in the form of new technologies that allowed the scientists to rebuild genes by exchanging bits of DNA, like shuffling a deck of cards. Another breakthrough was the discovery of certain peptides that specifically bind to PSMA, prostate-membrane specific antigen, a protein that is made on the surface of prostate cells. "We have published the new peptides and are in the process of incorporating them into the adenoviruses," he says. "It has been far more complicated than we had originally anticipated. However, we have been able to identify each obstacle and systematically engineer a solution to the problem. We are gaining confidence that the approach will pay off in the long run."

All of these challenges have produced a nice bonus, Rodriguez notes. "The tools that we needed to perform this genetic engineering work did not exist." So Rodriguez and colleagues had to develop them — a series of powerful methods to perform complex viral manipulations. The good news here is that these same tools can now be applied to other research problems that were once thought unapproachable — which Rodriguez hopes to do, with more funding.

Another molecular approach involves drugs called differentiating agents. Normally, cells appear well differentiated — they have distinct, clearly defined borders, and their growth is fairly slow and orderly. The opposite of this is cells that are poorly differentiated. Highly malignant and aggressive, these are the cells that are given high Gleason grades by a pathologist (Gleason 8, 9, or 10). In physical appearance they are not well defined; instead, they seem to melt together. The good news is that it's possible, at least in the laboratory, to slow down this growth, and to make poorly differentiated cells more distinct — to make them less dangerous, and more like normal cells.

"In the past, clinical trials devoted to this approach have not worked," says Rodriguez. But in recent research, he and colleagues have found that the best way to turn a cell away from cancer and back toward normal is to do it gradually, and continually. "We've found that the optimal activity requires prolonged, chronic exposure to the drug — not short-term exposure, as given in previous clinical trials." Rodriguez believes that administering a differentiating agent continuously — and starting well before any symptoms of advanced cancer, most likely at the first rise in PSA after a man's initial treatment — will slow the progression of the cancer cells significantly. "The hope is that such an approach would turn a terminal disease into a manageable chronic illness, like HIV."

The good news is that it's possible, at least in the laboratory, to slow down the growth of the most aggressive cancer cells — to make them less dangerous, and more like normal cells.

If Prostate Cancer Comes Back, Who Needs Aggressive Treatment?

If a man develops an elevated PSA level (more than 0.2) after surgery, he is considered to have recurrent disease — and "recurrence" is a dreaded word for men who have undergone treatment for prostate cancer. But a new Brady study shows that not all recurrence, like not all cancer, is equal, and that not all men need aggressive treatment — or any treatment right away — if cancer comes back.

Brady investigators have developed reference tables for physicians and patients that help determine which men are going to be in trouble and in need of more aggressive treatment, and which men have a slow-growing cancer that may not cause trouble for years, are relatively safe and can be carefully watched. The tables estimate the risk of prostate cancer-specific survival at five, ten, and 15 years after biochemical recurrence (the return of detectable levels of PSA in the blood, even if there are no other symptoms of cancer).

The difference between high- and low-risk recurrence can mean a matter of years. Some men in the low-risk group lived more than 16 years after their cancer returned, with no sign that the cancer had spread to bone.

The difference between high- and low-risk recurrence can mean a matter of years, says urologist Stephen J. Freedland, first author of the study, which was published in the *Journal of the American Medical Association*. Some men in the low-risk group lived more than 16 years after their cancer returned, with no sign that the cancer had spread to bone.

If caught early enough, prostate cancer can be cured by radical prostatectomy. However, as many as one-third of those who undergo surgery will eventually show signs that the cancer has recurred, Freedland explains. This investigation — an update of another Brady study, published in 1999 by Charles R. Pound, M.D., and colleagues — studied 379 men who underwent a radical prostatectomy at Hopkins between 1982 and 2000 and developed a rising PSA after surgery. (The study did not include men who received radiation treatment before surgery or hormonal therapy.) "We looked at the long-term outcomes of these men over five, ten, and 15 years," Freedland explains, "to see who died from the cancer and who was alive and well." The scientists found that the severity of recurrence depended on three risk factors:

PSA doubling time. Based only on the PSA values during the first two years after PSA reappeared, how long did it take for the PSA level in the blood to double? Less than three months, between three and nine months, from nine to 15 months, or greater than 15 months?

Gleason score: Is it 7 or lower, or Gleason 8 to 10? and

Time from surgery to the return of PSA. Was it within three years, or afterward?

If a man's PSA doubled in less than three months, his risk of dying from prostate cancer was much higher than that of a man whose PSA doubling time was more than a year. The same holds true for the time from surgery to the return of PSA: If PSA appeared on a blood test within three years after surgery, that man is at higher risk than is a man whose PSA returns in five years.

The differences in risk turned out to be great, Freedland says. "It is amazing to me that for a man who has all the low-risk features — if his PSA doubling time is greater than 15 months, his Gleason score is below 8, his PSA comes back after three years — his odds of being alive 15 years later are 94 percent." These men do not need treatment, he adds. "If we know that 94 percent of these men are alive and well 15 years after surgery with no further treatment, anything we do to treat them is unlikely to improve on that, and probably would only affect the quality of life."

In contrast, for a man at highest risk — a man whose doubling time is less than three months, whose PSA returns within three years, and whose Gleason score is 8 or higher — the odds of being alive 15 years after surgery were less than one percent. These are the men who are candidates for further treatment, says Freedland, "including clinical trials and starting more aggressive therapy."

Estimate of the Risk of Survival After PSA Recurrence Following Radical Prostatectomy

PSA Doubling Time (in months)	Recurrence >3 Years After Surgery: Gleason Score <8	Recurrence >3 Years After Surgery: Gleason Score ≥8	Recurrence <3 Years After Surgery: Gleason Score <8	Recurrence <3 Years After Surgery: Gleason Score ≥8
5-year Estimate:				
≥15.0	100 (98–100)	99 (98–99)	99 (96–100)	98 (90–100)
9.0–14.9	99 (70–100)	98 (75–100)	97 (76–100)	94 (63–99)
3.0–8.9	97 (81–100)	94 (74–99)	91 (67–98)	81 (46–95)
<3.0	92 (70–98)	83 (52–96)	74 (37–93)	51 (19–82)
10-year Estimate:				
≥15.0	98 (96–100)	96 (93–98)	93 (80–98)	86 (61–96)
9.0–14.9	95 (75–99)	90 (58–98)	85 (49–97)	69 (30–92)
3.0–8.9	84 (62–94)	68 (37–89)	55 (25–82)	26 (7–62)
<3.0	59 (29–83)	30 (10–63)	15 (3–53)	1 (<1–55)
15-year Estimate:				
≥15.0	94 (87–100)	87 (79–92)	81 (57–93)	62 (32–85)
9.0–14.9	86 (57–97)	72 (35–92)	59 (24–87)	31 (7–72)
3.0–8.9	59 (32–81)	30 (10–63)	16 (4–49)	1 (<1–51)
<3.0	19 (5–51)	2 (<1–38)	<1 (<1–26)	<1 (<1–2)

Other authors of the study include Brady scientists Alan Partin, Patrick Walsh, Mario Eisenberger, Leslie Mangold and Elizabeth Humphreys, and from the University of Southern California, Frederick J. Dorey.

Could a Simple Urine Test Detect Prostate Cancer?

Right now, there are two keys to detecting prostate cancer early: The digital rectal examination, and the blood test for prostate-specific antigen, or PSA. The use of both of these, plus safer surgical treatment of early-stage disease, has led to five-year survival rates for localized prostate cancer now approaching 100 percent, says Christian Pavlovich, M.D., associate professor of urology, and Director of Urologic Oncology at the Johns Hopkins Bayview Medical Center. But early detection is still far from perfect, he adds. "There are still many men who undergo biopsy needlessly, and others in whom these tests fail to detect early disease. We still miss quite a few cancers."

The challenge, then, is to come up with better tests. One approach is to look for ways to get more out of PSA. Heading this school of thought are pioneering scientists such as Alan Partin, M.D., David Hall McConnell Professor and Director of Urology, and colleagues at the Brady, who are exploring different forms of PSA — such as "percent free PSA," and "complexed PSA" — in hopes of developing more specific tests.

Another approach is to look for a different biomarker, or substance made by the cancer that can be measured. With this in mind, Pavlovich and colleagues have zeroed in on a highly promising candidate — a protein that's been found in prostate cancer, and in the urine of men with prostate cancer. This molecule, called AMACR (for alpha methylacyl CoA racemase; rhymes with "eraser") is involved in fatty acid metabolism, and it was first linked to prostate cancer by Jun Luo, Ph.D., Angelo M. DeMarzo, M.D., William Isaacs, Ph.D., and colleagues at the Brady Urological Institute.

Although it's not yet clear exactly what the connection is between fatty acids and prostate cancer, Pavlovich's group has found that urinary AMACR is tightly linked to prostate cancer. In a small study, they found that the presence or absence of urinary AMACR accurately predicted whether a man had prostate cancer 86 percent of the time. "Most exciting for us is that AMACR was found in the urine of all of the men who had prostate cancer," says Pavlovich. "The sensitivity was one hundred percent."

With funding from the National Institutes of Health, Pavlovich is attempting to develop a quantitative assay for urinary AMACR that will make testing easier and even more reliable. He is also searching for other urinary biomarkers for prostate cancer, "with the hope that noninvasive urinary testing for prostate cancer can soon become a reality for all men."

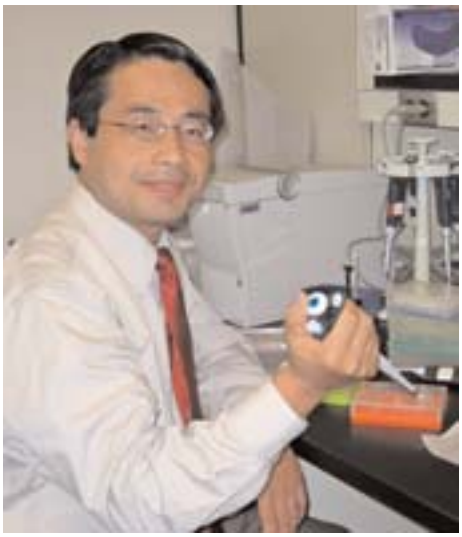
How Some Cancer Survives Deadly Attack

What is prostate cancer's secret weapon? What allows it to survive an onslaught of the most lethal chemotherapy drugs known to science? Why, if such drugs are akin to a mini-nuclear blast, do a few cells manage to stagger out of the mushroom cloud, and start growing again?

This is called "therapeutic resistance," and it's one of the biggest challenges facing men with advanced prostate cancer, and the doctors working to treat it. Prostate cancer succeeds, in large part, by sheer diversity, Its cells are notoriously heterogeneous — which means that each cell can respond differently to the same type of therapy. This differential response is the ultimate culprit that causes cancer to turn aggressive, as the milder cancer cells are killed, and the tougher ones — the ones resistant to further therapy — survive.

The most lethal drugs are like a mini-nuclear blast to cancer. And yet, a few cells manage to stagger out of the mushroom cloud, and start growing again.

Jun Luo, Ph.D., assistant professor of urology, wants to figure out what's in the hardiest cells' survival kits. What do they need, or what do they do, so they can survive in the cytotoxic environment created by the cell-killing drugs? As a basic scientist, he is particularly interested in how cancer cells sense the danger, make last-minute adjustments, repopulate, and thrive. With funding help from The Peter Jay Sharp Foundation, he is focusing on a particular part of the cell, called the endoplamic reticulum (ER), which is responsible for the folding and maturation of proteins that will eventually be secreted outside the cell.



Luo: How do cancer cells sense danger, make last-minute changes, bounce back, and thrive?

"The ER is very sensitive to environmental changes," Luo explains, "and may be the sensor that determines the survivability of the cancer cells." Like a military bunker in wartime, the ER is chock-full of sensors, and functions to keep the cell alive even when it's under attack. "Characterizing the key molecular sensors will give us new targets for advanced therapeutics that can disrupt the adaptive strategies that cancer cells use to survive treatment." Luo believes that these sensors may be moving targets — that, like emergency batteries, they switch on and off, and probably provide just the immediate and transient relief that cancer cells need to survive the therapy. His challenge now is to catch them in the act.

Working on a molecular level, Luo is using cutting-edge technologies such as microarray to investigate the machinery that enables cancer cells to respond and adapt to stress. His results are promising: Already, Luo has found a molecule, named AGR2, that is massively over-produced *[continued on page 20]*

[continued from page 19]

in cancer cells subjected to the toxic stress that happens in chemotherapy. This molecule is quickly sensed by the ER. Luo has also found that this molecule is over-produced in human prostate cancer tissues.

Luo's work, says Patrick C. Walsh, M.D., University Distinguished Professor of Urology, "proves that cancer cells have acquired the readiness to respond and adapt to stress conditions caused by the therapeutic drugs. While there is much work to do to follow this important lead, the basic concept is starting to bear fruit." The next step is to design with this "secret weapon" in mind — to target and disable the adaptive response pathway that cancer cells use to evade primary therapy.

The Battles We Fight

At the Brady, we're doing our utmost to beat prostate cancer every day, using all of the weapons we can think of. The challenge is that, in addition to fighting prostate cancer, we're also fighting cuts in funding.

Why are we here? Our whole reason for being is to save lives from prostate cancer, to preserve quality of life, and one day, to prevent this disease altogether. As you can see, from all of the research we've covered in this issue of *Discovery*, we're doing our utmost to beat this disease every day, using all of the weapons we can think of. What you may not be able to see is that it's always a challenge, and sometimes even a struggle, to maintain our great momentum — because in addition to fighting prostate cancer, we are fighting cuts in funding.

At the Brady, long recognized by *U.S. News & World Report* and others as the country's finest urological institute, our world-class physicians and scientists are battling prostate cancer in the clinic, the operating room, and the laboratory. For decades, we have advanced the field of prostate cancer research despite decreases in federal support. Even current grants from the National Institutes of Health, the National Cancer Institute, and the Department of Defense, are being funded at much lower levels than originally anticipated.

Such uncertainty can have serious consequences. Recently, one scientist, on the verge of tackling a novel treatment for advanced prostate cancer using gene therapy, was forced to hire his research fellow for six months as opposed to a full year — when, in fact, he needed three years to complete the work. Fortunately, this scientist didn't have to make some of the choices he was dreading, and he didn't lose his essential staff. His dreams and program were rescued by the kindness of a generous donor.

The fact is, working for a cure for prostate cancer is an expensive endeavor. We cannot do it without you. Our new chairman, Dr. Alan Partin, in the great tradition started by Dr. Patrick Walsh, is forging ahead boldly with new drives to help us achieve important objectives. Among the most vital of these are:

- Finding the genes. We are dedicated to unraveling the genetic puzzle that causes prostate cancer, and using this information to develop novel ways to cure and prevent the disease in the sons and grandsons of our patients.
- Improving diagnosis. For the last decade, we have led the fight for early diagnosis, and worked to refine PSA. But many cancers are still missed, and many men still undergo biopsies they don't need. We are committed to research that will make diagnosis more accurate — finding more reliable biomarkers for prostate cancer.
- Learning from our patients. We are grateful stewards of a tremendous asset — the data archive of the 15,000 men who have been treated for prostate cancer at the Brady. Our scientists have discovered so much from the demographic information, pathological records, and follow-up data of these patients, but there is much more to learn from this unparalleled resource.
- Recruiting and keeping the best and brightest faculty. This is the only way we will continue to lead the world in groundbreaking prostate cancer research.
- Bringing our scattered scientists and faculty under one roof. Our faculty is spread out, sprinkled among three buildings on a sprawling campus — which makes seamless collaboration more challenging than it should be.

In this difficult battle against a powerful enemy, we cannot afford to miss any opportunity. With your help, we will remain in steadfast pursuit of our goal of defeating prostate cancer. For more information on how you can help win this war by making a gift to the Brady Urological Institute, please call (410) 516-6160.

WANT TO LEARN MORE? To find earlier issues of *Discovery* and *Prostate Cancer Update* — and much more — check out our website: http://urology.jhu.edu

If you do not wish to receive this newsletter, please write to us at The James Buchanan Brady Urological Institute, The Johns Hopkins Medical Institutions, Baltimore, MD 21287-2101.