PROSTATE CANCER
DISCOVERY
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A PUBLICATION OF THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Partin: "I am excited to have the opportunity to guide the ship."

A "Win-Win"

Partin is New Director; Walsh Devotes Time to Surgery

There's good news, and good news. First, although urologist-in-chief Patrick C. Walsh, M.D., is stepping down from his administrative responsibilities as Director of the Brady Urological Institute, he isn't going anywhere: Now he will devote his full time to patient care, surgery and research. The other good news is that the Brady is in excellent hands—the hands of renowned urologist and scientist, Alan W. Partin, M.D., Ph.D., Bernard Schwartz Distinguished Professor of Urologic Oncology.

This is a job, Partin says, that he's dreamed of for years. "I am excited to have the opportunity to guide the ship. We have an excellent group of people here, all doing wonderful things." Partin is a Hopkins-trained doctor and scientist. He learned to perform urologic surgery under Walsh's tutelage, and as he earned his Ph.D., his mentor in molecular pharmacology was Donald S. Coffey, Ph.D., the Catherine Iola and J. Smith Michael Distinguished Professor of Urology. He is the editor of *Urology*, one of the specialty's top two journals, the author or co-author of more than 350 papers, and the recipient of notable honors, including an award by the American Urological Association, given yearly to the urologist who has made the greatest impact within the first 10 years after completing his residency. Partin was the first urologist to receive this honor after only five years of practice, and he was the youngest urologist to be inducted into the prestigious American Association of Genitourinary Surgeons.

The work that has made him famous, and earned him such awards, is the eponymous set of tables that has given thousands of men with prostate cancer worldwide a 95-percent accurate prediction of their likelihood of being cured by treatment. The Partin Tables were developed at the Brady in 1993 by Partin and Walsh, after Partin studied the course of prostate cancer in hundreds of Walsh's radical prostatectomy patients. The tables correlate three key pieces of the prostate cancer puzzle—a man's PSA, Gleason score, and estimated *[continued on page 2]*

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

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The Patrick C. Walsh Prostate Cancer Research Fund: The Winning Vision Continues

This first issue of *Prostate Cancer Discovery* marks the fruition of the Patrick C. Walsh Prostate Cancer Research Fund, spearheaded by the Brady Advisory Council, and made possible by many of Dr. Walsh's patients, their families and friends.

After three decades at the helm of the Brady Urological Institute, Dr. Walsh is stepping down from his administrative responsibilities as Director to devote more time to patient care, surgery and research. In developing the fund that bears his name, the Council has made certain that his winning approach to the prevention, treatment and ultimate cure of prostate cancer will carry on. All of us waging this war against prostate cancer—working to end the havoc of the disease, and to prevent our sons and grandsons from ever developing it—believe that the cure for prostate cancer will be found soon, and it will be found here. The Advisory Council, and all who have given to the Fund, strongly *[continued on page 2]*

[continued from page 1]

clinical stage—with the actual pathologic stage, determined when pathologist Jonathan Epstein, M.D., examined the surgically removed prostate specimens. Revised and expanded over the years, the tables have become an indispensable tool for doctors and patients.

That Partin will continue doing this and other research (one of his studies is featured on page 6), and keep seeing patients and performing surgery, as well as carrying on his editorship of *Urology*, is characteristic; he has a knack for being able to handle many projects simultaneously, and to do them well. He wants the same for the Brady—to keep doing what it's doing at the same standard of excellence, and to do more. "We are going to continue our mission," he says. "We have held our position, of being (ranked by *U.S. News & World Report*) the Number One in urology, 14 years in a row. We're going to continue to foster that in the strongest way." Urologic oncology—especially in prostate cancer—is so strong at the Brady, Partin adds, but he wants to fortify the Institute's efforts in research and clinical care of other cancers, including the bladder, kidney, and testes, by recruiting internationally recognized scientists in those areas. Partin plans to recruit faculty with other research interests, as well, including:

- Female urology, with a focus on such issues as overactive bladder and incontinence.
- Inflammatory and infectious diseases of urology, such as pelvic pain, interstitial cystitis, and prostatitis. In addition to expanding our knowledge of these diseases, Partin says, we need further exploration of the emerging link between inflammation and prostate cancer (see story, page 4).
- Reconstructive surgery, including urethroplasty and pelvic floor reconstruction. "We will strengthen our collaboration with general surgery and gynecology, with our role in the new Pelvic Floor Reconstructive Center" at the Johns Hopkins Bayview Campus.
- Pediatric urology research and clinical care.
- Nonsurgical treatments of prostate cancer. "We are expanding the menu for treatment of men with early-detected, clinically localized prostate cancer, through collaborative efforts with the Department of Radiation Oncology," says Partin, "so men who aren't interested in surgery or external-beam radiation therapy will have an option for treatment here."
- Endourology—stone disease. "We need to focus attention on the art and clinical care of patients with stone disease. For many, it's a lifelong disease, with a lot of issues."

Partin is also determined to increase the Brady's physical size. "The Brady Urological Institute in the Marburg Building has expanded far beyond its walls," he notes, "to include research space in the Cancer Research Building, the Oncology Center, and the Pediatric Building." He is working to acquire enough space within the Hospital "to bring some of this back together, to consolidate it within one area, and continue to grow over the next 20 years."

One of Partin's first challenges will be to replace another longtime Brady legend who seems irreplaceable—his mentor, Don Coffey, who is stepping down as the Institute's research director. Coffey's shoes are so big for one person to fill that Partin isn't even going to try. "We are going to have two research directors," he explains, "one for basic science, and one for translational research—moving those discoveries from the laboratory bench to the patient's bedside, as quickly and as seamlessly as possible."

[continued from page 1]

Patrick C. Walsh

embrace the concept behind the world-class research program that Dr. Walsh has created—one that is unique in its depth, scope, and multidisciplinary approach. Dr. Walsh believes that victory in this war hinges on a many-sided assault—our version of the Army, Navy, Air Force and Marines. Soldiers fighting a battle don't aim to win just a few isolated skirmishes; their goal is "defeat in detail" — winning on every front. With this in mind, Dr. Walsh has enlisted and supported basic scientists, medical and radiation oncologists, and pathologists to work with urologists in finding new pathways, and developing more sophisticated weaponry to penetrate prostate cancer's defenses.

Continuing this vision, the Walsh Fund will make it possible to attract and recruit the brightest scientists from all disciplines at Johns Hopkins to focus their efforts on prostate cancer. Each year, a request for proposals will be sent to every Johns Hopkins scientist; we will cast the net widely, to secure fresh, innovative ideas. Applications will be reviewed by a scientific advisory board, led by Dr. Walsh and made up of Hopkins faculty and two laypeople—patients who are knowledgeable about the management and treatment of the disease, as well as the most current research. Grants, ranging from $50,000 to $100,000, will be awarded each year to the most promising research initiatives.

The Walsh Fund is off to a powerful start, with over $20 million raised to provide critical support for research, equipment, and laboratories. The first grants will be awarded in the Spring of 2005. We will report the latest news from the frontlines of the research supported by the Fund in future issues of *Prostate Cancer Discovery*. On the front page of this newsletter are the names of the Founders' Circle members, donors who have given $500,000 or more in their commitment to defeating prostate cancer. Also inside this issue are the names of all of the people (as of press time, October 15, 2004) who have given so generously to help in this effort. If you are interested in becoming a part of this groundbreaking work, please call (410) 516-6160.

Walsh Wins Top Honors

In recent months, urologist-in-chief Patrick C. Walsh, M.D., has received some of the highest honors in urology the world has to offer. These include:

- **The Ramon Guiteras Award, the highest honor bestowed by the American Urological Association**
- **The Charles Huggins Award, the highest honor given by the Society of Urologic Oncology**
- **Honorary Membership in the Royal College of Surgeons of Ireland**
- **Honorary Membership in the Royal College of Surgeons of England, and**
- **The John Carroll Society Medal**

In addition, the major textbook of urology has been renamed in Walsh's honor. For the last 25 years, Walsh has been the senior editor of *Campbell's Textbook of Urology*, widely considered to be the "bible" of urology worldwide. The textbook, which has expanded over the years to encompass four volumes and 4,000 pages, will now be named the *Campbell-Walsh Textbook of Urology*.

NOW ON DVD, FOR FREE

The "Gold Standard" Treatment for Prostate Cancer

"Nerve-sparing" radical prostatectomy—the operation devised by Patrick C. Walsh, M.D., and continuously refined by him over the last 20 years, in more than 3,000 patients—has been in many ways a double-edged sword. In the hands of Walsh, and the dozens of urologic surgeons he has trained over the years, the operation preserves the delicate, microscopic nerves, which are necessary for erection, that sit on either side of the prostate—but also removes as much tissue as possible around the cancer. At the Brady Urological Institute, the high rates for cancer control and potency, and the very low incidence of incontinence and other side effects, are used as the "gold standard," against which all other forms of treatment are compared worldwide.

This is also the only form of treatment for localized prostate cancer that has been shown to prolong life. In a landmark Scandinavian study, men with localized prostate cancer were randomly assigned either to the Walsh technique of radical prostatectomy or to watchful waiting. Within as little as eight years, twice as many men in the watchful waiting group had metastatic cancer in the bone, and twice as many had died of prostate cancer. In this study, the "Walsh procedure" reduced prostate cancer deaths by about half.

The Walsh procedure is notoriously difficult to perform. "He makes it look easy, but believe me, it's not."

But—and here's the other edge of that sword—the Walsh procedure is notoriously difficult to perform. "He makes it look easy," notes surgeon Alan Woolfenden, of the Royal Liverpool University Hospital, who recently came to Hopkins to watch Walsh perform the operation, "but believe me, it's not." For any surgeon, this procedure—technically, the anatomical radical retropubic prostatectomy—is a bumpy, treacherous road. There can be extreme blood loss. It takes years of training before a surgeon can handle the unexpected bleeding without panicking—and also without inadvertently damaging the fragile nerves. An experienced surgeon, too, can tell much by tactile sensation—literally, feeling the tissue for hardness, adherence, or other signs of cancer, and deciding how best to remove it. A very experienced surgeon has a "Plan B" if one man's anatomical terrain is slightly different from most. For example, in 4 percent of patients, the arteries that supply the penis travel immediately over the prostate. Unless the surgeon knows how to preserve the blood supply in this particular situation—and unfortunately, very few surgeons do—the man will be impotent.

Walsh's "magnum opus," the free, 105-minute DVD for surgeons, was five years in the making.

With Help from a Patient

How do you handle the lightning bolt of discovery—especially when you've seen its great potential to help people? Well, you could guard it jealously, like the proverbial dog in the manger, expressing dismay that other hospitals' results aren't nearly as good as yours. Or, you could do your best to share what you know—and this is what Walsh has done, with the help of a remarkable patient, Robert Baker.

Walsh has put everything he knows about this procedure onto a free, 105-minute DVD for surgeons. On the DVD, which has been five years in the making—and which he calls his "magnum opus"—are detailed descriptions of each step of the operation, including close-up video footage of intricate dissection, suturing and reconstruction, and stunningly detailed illustrations by Hopkins medical artist Juan Garcia. "You won't see this kind of illustrations in Gray's Anatomy," says Garcia. (Many of these illustrations and some video clips from the DVD are available on the Brady website, at http://urology.jhu.edu.)

With the financial help of the Mr. and Mrs. Robert C. Baker Foundation, the DVD was mailed with four major journals to 40,000 urologists around the world. An additional 15,000 copies are available for free, for any urologist who wants one. "I could have gone to a drug company and asked for financing," explains Walsh, "but then they would have control of it, and over who sees it. I wanted to have something I could give to everyone in the world, including doctors in developing countries."

It's worth noting that a century ago, on April 7, 1904, the very first radical prostatectomy was performed by Johns Hopkins urologist Hugh Hampton Young. That operation laid the groundwork for the "nerve-sparing" procedure that Walsh first performed in 1982. And Walsh continues to improve the operation—"I'm at the top of my game," he says. He is sharing what he knows because he believes it's the right thing to do: "If you've been given the privilege of sailing in uncharted waters, you have the responsibility to make those charts."

Nerve-Sparing and Positive Surgical Margins

What happens to the nerves responsible for erection if cancer has escaped the prostate? Can they still be preserved? Sometimes, cancer ventures only slightly beyond the prostate—a distance significant enough for the surgical margins, the edges of the removed tissue, to be considered positive, but really just a matter of a couple of millimeters. If this happens near the neurovascular bundle, one of two tiny packages of blood vessels and nerves adjacent to the prostate that are responsible for erection, is that bundle automatically doomed?

Not necessarily, says urologist-in-chief Patrick C. Walsh, M.D. "When cancer spreads microscopically outside the prostate, the tumor rarely extends more than one or two millimeters into the adjacent soft tissue. This is because cancer cells seem to need the environment of the prostate." Walsh uses the example of seeds and soil: "The soil is the tissue of the prostate, and the seeds are the prostate cancer cells. If they spread without the proper soil, they can't survive."

Prostate cancer cells can eventually learn to make a habitable environment outside the prostate, but this process is complicated and can take years, he adds. (A lot has to do with the Hedgehog pathway—see story, page 12)

In a recent study, urology resident David Hernandez, M.D., along with pathologist Jonathan Epstein and Walsh, reviewed 100

"It takes a great deal of experience, and also tactile sensation, in determining exactly when and where it is possible to preserve the neurovascular bundle, and where it is necessary to remove it".

men who had evidence of extension of cancer outside the prostate, in the area of the neurovascular bundle. During surgery Walsh, who has long respected the use of tactile sensation—what he can feel of the prostate and surrounding tissue—during the operation, determined that it was safe to preserve the nerve bundle in 84 of the men. He excised the bundle and surrounding tissue in the remaining 16 men.

Later, when Epstein examined the removed surgical specimens, he found that the frequency of positive margins was only 5.8 percent—six men. This low rate of positive surgical margins is essentially the same as Walsh achieves in all of his patients. It is also identical to the number of positive surgical margins reported by another urologist—except that urologist widely excises the neurovascular bundle in 65 percent of his patients.

Of the 100 men in this study, 86 percent of the men were potent 18 months or more after surgery. Walsh believes the key to success here is the ability to feel the prostate and surrounding territory during surgery—and the expertise to interpret those findings. "It takes a great deal of experience, and also tactile sensation, in determining exactly when and where it is possible to preserve the neurovascular bundle,and where it is necessary to remove it," he says. This is why he believes that the open radical prostatectomy remains the "gold standard" for treatment. (It's also one of the reasons he produced the DVD of his surgery, so he could teach other surgeons how to do this—see story, page 3.)

Multidisciplinary "Dream Team:" Nelson, De Marzo, and Isaacs, along with a laser capture microscope that was funded by the Peter Jay Sharp Foundation. With this advanced instrument, scientists can collect DNA and RNA from the nuclei of individual cancer cells, and find the genetic fingerprint for prostate cancer.

What Does Inflammation Have to Do With Cancer?

Trio Closes in on "Smoking Gun"

Imagine a movie about a great adventure—a bold jewel heist, a daring escape—and consider the characters. There's the demolitions expert, the safe-cracker, the code-breaker—all specialists, who tackle one facet of a job that looks to be impossible. This kind of multidisciplinary team is the Walsh Fund in a nutshell, and it's happening every day at Johns Hopkins. One of the best examples of it might be called the Brady's own "Dream Team"—a trio of investigators from different scientific backgrounds—oncologist William G. Nelson, M.D., Ph.D., molecular geneticist William B. Isaacs, Ph.D., and pathologist Angelo M. De Marzo, M.D., Ph.D.

Because prostate cancer is so very complicated, and its tapestry of origins seems so intricately woven together, the goal of pinpointing its earliest beginnings has long seemed as formidable as the mountain fortress in the movie, "The Guns of Navarone." But the questions these scientists are asking—and figuring out how to answer—are revealing unexpected cracks in the citadel. Their work so far, recently summed up in a landmark paper in the *New England Journal of Medicine*, has identified a new target—which may, in fact, be the "smoking gun" that causes prostate cancer.

Methylation: Silencing genes

For the last decade, Bill Nelson has been looking at what we eat, what we don't eat, and trying to figure out what we should eat. His pioneering work on the role of diet in prostate cancer has shown that oxidative damage to DNA—incremental damage accrued as carcinogens hammer away at our genes, like invaders with tiny battering rams—is a major factor responsible for the development and progression of the disease. He also discovered that the major gene that defends prostate cells against this damage, called GSTP1 (also known as GSTp)—is knocked out of commission early in the development of cancer. The gene, he learned, is "hypermethylated"—in chemical terms, it picks up an extra building block that changes its shape. This extra baggage has an effect that's akin to changing a lock, so the normal key doesn't fit it any more.

How does this fit in with what we already know about cancer and the genes? "It's an idea that's taking on new importance," says Nelson. "In addition to helping us under-

stand what *causes* cancer, methylation is also being used to help *detect* it, as we identify new tumor markers." This discovery of hypermethylation changes is like finding a set of molecular fingerprints—"which means that we have something new to look for and monitor, to help us detect, diagnose, and predict the course of prostate cancer." (For more, see "Is it Cancer?" at right.)

Scientists have long known that cancer is caused by changes in how our genes work. Tumor suppressor genes, for example, hamper a gene's ability to do its job; in contrast, oncogenes cause a gene's function to be "revved up," and result in out-of-control growth of cells. Methylation falls into a third category of genetic troublemaking, causing what scientists call "epigenetic" change. Here, the genes aren't altered; instead, they're silenced. A gene is methylated and boom—it's useless. In effect, it's put into a chemical straitjacket.

It's chaos on a microscopic level. Some cells atrophic but growing out of control, some cancerous, some inflamed, some funny-looking, and some normal—a primordial breeding ground of cancer.

Nelson has also learned that antioxidants such as vitamin E and selenium, and cruciferous vegetables such as broccoli, which protects GSTP1, can help detoxify cells by preventing oxidative damage.

Epicenter of Cancer: Inflammation?

Meanwhile, pathologist Angelo De Marzo, with the help of his mentor, Jonathan Epstein, the Rose-Lee and Keith Reinhard Professor of Urologic Pathology, has made startling findings in studies of prostate tissue. He has seen cancer cells, and nearby, the suspicious-looking cells called PIN (prostatic intraepithelial neoplasia). PIN cells aren't cancer, but they're not normal, either; the general feeling among pathologists is that they're cancer waiting to happen. And right in the thick of these cancerous and probably precancerous cells, he's seen something else—hotspots of inflammation. And sprinkled around this inflammation were areas of atrophy—cells that appeared to be dying, but actually, under closer inspection, were proliferating very rapidly. Basically, what De Marzo has identified is chaos on a microscopic level—some cells atrophic but growing out of control, some cancerous, some inflamed, some funny-looking, and some normal. A primordial breeding ground of cancer. De Marzo named this inflammation PIA, for proliferative inflammatory atrophy, and identified it as a specific precursor lesion for prostate cancer.

Could it be that inflammation, either in conjunction with other things, such as diet and heredity, or—and this is the concept that has Brady scientists buzzing—by itself, is the cause of the oxidative damage that leads to cancer? There is precedent for this idea. Inflammation is known to cause damage to cells and to DNA; unremitting, long-term inflammation is associated with many kinds of tumors. For example, chronic hepatitis causes cancer of the liver; chronic stomach inflammation, caused by a form of bacteria known as *h. pylori*, causes stomach cancer; reflux esophagitis, over time, can cause cancer of the esophagus.

Do Genes Hold the Answer?

The next question is, what causes this inflammation? Molecular geneticist Bill Isaacs, Ph.D., and colleagues have been asking this question in an entirely different way. They have spent the last decade studying families with hereditary prostate cancer, trying to determine how mutations in certain genes stack the deck toward cancer in some men. They have found two genes that are responsible for the development of prostate cancer in small clusters of families: One, located on chromosome 1, is RNASEL; the other, located on the short arm of chromosome 8, is called MSR1 (macrophage scavenger receptor 1). These genes have something very interesting in common—they're both involved in the body's defense against infection. When animals that lack the MSR1 gene are infected with bacteria, or animals with a defective RNASEL gene catch the herpes simplex virus, 60 percent of the animals die. And this observation, says Bill Isaacs, "raises the intriguing possibility that viral or bacterial infections might be the source of the chronic inflammation in some patients, and that this chronic inflammation might be responsible for the increased risk of prostate cancer." If it's true, he adds, "this will profoundly affect future studies of the causes of prostate cancer, and may ultimately lead to new approaches to prevent it."

"It's a very futuristic approach," says urologist-in-chief Patrick C. Walsh, M.D., "a whole new idea that we're exploring. The idea is that a decreased ability to fight infections could result in chronic inflammation, and chronic inflammation leads to tissue injury and ultimately, to oxidative damage. This, in turn, leads to mutations in DNA, and mutations lead to cancer."

One of the best examples of this is that of stomach cancer, Walsh continues. "For years,

IS IT CANCER?

New Methylation Marker Shows Promise

The doctor suspects cancer—because a man's PSA is higher than it should be, or his digital rectal exam found something abnormal—but the biopsy didn't find any cancer. What happens next? Most likely, another biopsy—at which point, says urologist Mark Gonzalgo, M.D., Ph.D., as many as 36 percent of these men will be found to have cancer.

Here's where a new biomarker, which he and colleagues are working to develop, would be of great help. For one thing, Gonzalgo notes, it could distinguish between cancer and BPH, benign enlargement of the prostate. "Methylation of GSTP1 has been detected in the urine and prostatic fluid of men with prostate cancer, but not in men with BPH, or in normal prostate tissue." Thus, instead of undergoing another biopsy and months of uncertainty, these men could take a simple urine test. In a recent study, published in the journal *Clinical Cancer Research*, Gonzalgo, Christian Pavlovich, and William Nelson analyzed urine specimens of men who underwent prostate biopsies. They found methylation of GSTP1 in about half of the men—in 33 percent of men who had negative biopsies, and in 67 percent of men with either suspicious-looking cells or PIN. "This suggests that there was hidden cancer," says Gonzalgo, "and that the biopsies had a false negative result." He believes that this test could help doctors decide whether a man is at high or low risk for cancer, and whether he needs an early repeat biopsy.

everyone believed that stomach cancer was caused by dietary factors, but we now know it was caused by *h. pylori*, which was an unrecognized pathogen until recently. It would be fascinating to see whether there might be a similar organism that causes prostate cancer."

SURROGATE MARKERS

Saving Years in the Race to Test New Drugs

Good news for men with a rising PSA after treatment for prostate cancer: Fresh insight into how PSA behaves, gleaned at the Brady, may shorten the drug development pipeline by years—which means men will have access to new and possibly better drugs sooner than ever before.

Until now, it has been difficult to study chemotherapy in men with prostate cancer because the Food and Drug Administration (FDA) has historically required that the drugs show a "survival advantage." This stipulation, although well-meaning, has been hard on everybody—on patients, of course, but also on drug companies, because this proof can take up to 15 years.

The irony—for men with metastatic prostate cancer, who need better medicine to contain it, and for the scientists who are trying to get it to them—is that the drug companies are discovering new drugs "at an alarming rate," says urologist Alan W. Partin, M.D., Ph.D., Bernard L. Schwartz Distinguished Professor of Urology. But "very few of the drugs that demonstrate activity against the disease in laboratory testing ever make it to widespread use by patients, due to lack of clinical trials."

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What can PSA dynamics tell us?

There has got to be a better way, and Partin and colleagues believe the key may lie in following the dynamics of PSA—whether it comes back at all after treatment, when it comes back, and how long it takes for the PSA levels to double. They have tracked the course of PSA in nearly 5000 men who underwent radical prostatectomy at the Brady since 1982. Their work, which Partin presented at the recent meeting of the American Urological Association, has produced enough reliably predictive data to demonstrate that PSA can serve as a surrogate marker of survival for these patients. These findings are so impressive that the Food and Drug Administration (FDA) is considering using them, along with data from other institutions, in clinical trials as surrogate markers of survival for the men who might benefit most from novel forms of chemotherapy.

So far, the FDA has considered PSA changes too murky an endpoint for any prostate cancer study, because there was no way to tell which men with an elevated PSA after treatment are at high risk of dying, and which men will live for years before the cancer progresses. As a result, treatment groups are filled with "apples and oranges," says urologist-in-chief Patrick C. Walsh, M.D., "and it takes too long, for too many patients entered into a study, before a result can be determined."

Partin and colleagues believe the key may lie in following the dynamics of PSA—whether it comes back at all after treatment, when it comes back, and how long it takes for the PSA levels to double.

Partin and colleagues have found a way to separate men with a rising PSA after treatment into high-risk and low-risk groups. The high-risk patients tend to be a more homogenous group, with a faster-moving form of cancer—information that can now permit studies of drug efficacy to be carried out on smaller numbers of men in a shorter period of time.

The records of these patients are, in effect, a series of snapshots of cancer. Partin has found two that are the most critical. The first freeze-frame is *the point of a man's first rise in PSA after surgery*. In this study, 19 percent of the men had an elevated PSA after radical prostatectomy; on average, the PSA began to go up 8.4 years after surgery. The next freeze-frame is *the point at which that number doubled*. Partin found that men with the most rapid doubling time—for example, a man whose PSA level goes from 1 to 2 in less than 10 months—had the greatest chance of eventually developing metastatic disease and dying from cancer. Five years after that first PSA rise, 90 percent of the men were alive. Ten years after that first elevation—which means, on average, 18 years after their radical prostatectomy—50 percent of those men had died.

The irony: Scientists and drug companies are discovering new drugs "at an alarming rate." But very few "ever make it to widespread use by patients, due to lack of clinical trials."

To put it into perspective, of these 5,000 men, only a small percentage—2.4 percent—died of prostate cancer. But by using Partin's snapshots, and identifying the men who have a rapid PSA doubling time (of less than 10 months), Partin says, "we can identify men who might benefit from aggressive therapy earlier."

Did You Participate in These Studies?

One of the nicest things about our patients at the Brady is their willingness to help us learn more—so we can do a better job of helping them recover from prostate cancer and get on with their lives. Many of the readers of this publication have been generous partners in our process of discovery—even participating in one or more of our studies. How have those studies turned out?

Earlier recovery of sexual function: This study, led by urologist J. Kellogg Parsons,

M.D., asked a very simple question: Could steroids, which have been helpful in other types of neurological injury, help men recover sexual function after radical prostatectomy? The 70 men in this study received either a short course of high-dose steroids, or a placebo immediately after surgery. The good news is that the steroids did not cause any side effects; however, they didn't improve the recovery of sexual function, either. One year later, 74 percent of the men on steroids, compared to 71 percent of the men on placebo, were potent. These results are not significantly different. However, they do confirm earlier Brady studies that show excellent recovery of sexual function at one year. In earlier studies, 70 to 75 percent of men were potent at one year, and by 18 months, 86 to 90 percent were potent. The results also confirm the excellent recovery of urinary control shown in earlier studies. At one year after surgery, 96 to 100 percent were wearing no pads.

For pain after surgery, continuous local anesthetic: In this study, a small catheter was placed in the incision after radical prostatectomy. The catheter, which was left in place for three days, was attached to an elastic

"Somewhat to our surprise, we learned that men with higher hemoglobin levels did not appear to recover faster, have less fatigue, or improved aerobic capacity."

pump that dispensed either a local anesthetic (0.5 percent bupivacaine) or a harmless saline solution. (The study was "double-blind," which means neither doctors nor patients knew which man was receiving the placebo.) One hundred men were randomized to receive either the local anesthetic or the placebo. "It was a great idea," says urologist-in-chief Patrick C. Walsh, M.D. "Wouldn't it be wonderful if it were possible to give local anesthesia directly to the wound, and avoid the side effects of intravenous and oral narcotics?" Unfortunately, he adds, "that is not the way it worked out." The men who received the anesthetic did not need fewer narcotics for pain relief, and their pain scores did not show any significant improvement. "To all of the men who made this study possible, thank you," says Walsh. He believes that if the catheter were placed more superficially in the subcutaneous tissue, rather than on top of the muscles, it might prove more helpful.

Who needs a transfusion after surgery? A bit of background before we tell this story: The main deciding factor on who needs a transfusion is the concentration of red blood

"This is an important study, because it may result in fewer patients requiring transfusions."

cells in the blood, and there are two ways to determine this. One is the hematocrit, the percentage of red blood cells in the blood; the normal hematocrit is about 45 percent. The other critical measurement is the amount of hemoglobin in the blood. Hemoglobin is the major component of red blood cells, and the normal level is around 15 grams per deciliter (g/dl). It is well known that if a man's hemoglobin falls lower than 6 to 8 g/dl, he has a higher risk of having a heart attack. Traditionally, then, this has been the primary trigger point for transfusions. However, because that hemoglobin count is only half of normal, doctors have worried that men who are anemic at this level might have greater fatigue, and take longer to recover from surgery. Thus, Brady surgeons have traditionally used a hemoglobin cutoff of 10 g/dl as the trigger point for giving patients back their own blood.

In a recent study, 184 men were randomly chosen to receive transfusions either when their hemoglobin was less than 7.5 g/dl, or less than 10 g/dl. The men completed quality-of-life questionnaires after surgery. "Somewhat to our surprise, we learned that men with higher hemoglobin levels did not appear to recover faster, have less fatigue, or improved aerobic capacity," comments Walsh. "This is an important study, because it may result in fewer patients requiring transfusions." These results also may reduce the need for men to donate blood before surgery. "In this modern era of surgery, with our current understanding of the anatomy, only a small number of men would require a blood transfusion if the trigger point were set at 7.5 g/dl."

In Relentless Pursuit of the "Smart Bomb"

In many ways, it's the ultimate weapon—cancer-killers delivered at the molecular level, targeting only cancer cells, leaving the rest of the body unscathed. Gene therapy in the laboratory has been remarkably successful, giving scientists a glimpse at what could be. Gene therapy in humans, however, has turned out to be something of a different animal. The basic concept is to sneak new genes into cancer cells that will stop or disrupt their growth, or to use a specific genetic marker inside a cancer cell to trigger a "smart bomb."

When the cancer-killing bomb is delivered in the form of a virus—viruses are attractive drug-delivery systems, because their one goal is to replicate like mad—the drug has had to contend with the body's own immune system, which (as it's supposed to do) recognizes it as an invader, and starts attacking it. Thus, from the moment it hits the bloodstream, the cancer drug-carrying virus—in effect, a Trojan horse—is racing the clock,

"We can time the bombs to go off all at once, unleashing a tidal wave—instead of several large splashes—of cancer cell death."

trying to get to the cancer before the body's immune system gets to it, and begins creating antibodies. Also, altered viruses haven't proven as lethal as the scientists who doctored them had hoped. Because a virus simply exists to replicate—like kudzu in the South—killing cells is its byproduct, not its number one job.

These are some of the challenges facing Ron Rodriguez, M.D., Ph.D., assistant professor of urology, medical oncology, and cellular and molecular medicine. Lesser scientists might give up; Rodriguez, instead, digs in his heels, doubles and redoubles his efforts, and finds new ways around the problems.

Rodriguez has figured out a means of genetically altering these genes to make them

more potent, and has engineered the ability to switch them on and off by giving specific medications. One drug, bicalutamide, turns the gene on, and geldanomycin turns it off. This way, he says, "we can time the bombs to go off all at once, unleashing a tidal wave—instead of several large splashes—of cancer cell death."

Rodriguez has also developed a series of tiny proteins that specifically target and attach themselves to the prostate-specific membrane antigen (PMSA), the outer husk of the prostate cancer cell. By tucking these tiny proteins into the viruses, he will be able to deliver them intravenously—"which means we can target cancer cells throughout the body."

Rodriguez and colleagues also are exploring other delivery systems. Among the most promising are liposomes. The body doesn't make antibodies to liposomes, little bubbles of fat that coat DNA. Think of two soap bubbles meeting and sticking together—that's how a liposome dissolves through a cell's fatty membrane, and that's how Rodriguez may be able to bypass the body's best efforts to fight off even more effective, cancer-killing medications.

"Progress in gene therapy is slow in coming, but it's being made," says Patrick C. Walsh, M.D., urologist-in-chief. "I'm thankful we have someone like Ron who is working diligently toward this important end."

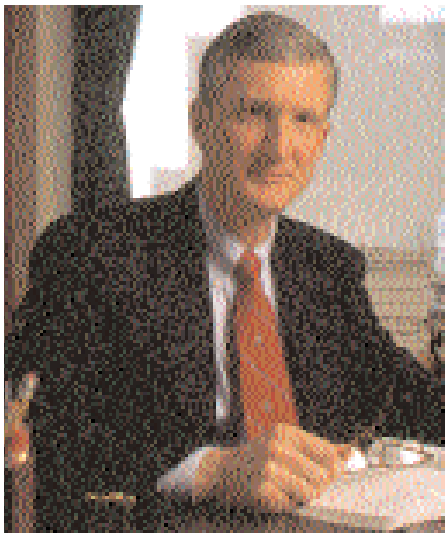
This work was funded in part by Donna and Robert Tompkins.

When the PSA Test Can't Do It All

New Biomarkers To Fill in the Gaps

Low PSA—anything under 4.0—is good, right? The answer is, most of the time, but not always. And this prompts the next question: Would a lower PSA cutoff find more cancer? Yes, undoubtedly. But not all of these cancers would need to be treated, and some men with insignificant, slow-growing disease would wind up getting prostate biopsies they don't need.

And yet, some of these cancers are high-grade (with a Gleason score of 7 to 9), and potentially deadly. In an editorial in the *New England Journal of Medicine*, urologist H. Ballentine Carter, M.D.—who has spent the last decade studying PSA and figuring out how best to use it to diagnose and monitor prostate cancer—discussed the dilemma of low PSA levels and prostate cancer. In the recent Prostate Cancer Prevention Trial, he noted, a small number—2 percent—of a group of nearly 3,000 men with PSA levels below 4 turned out to have serious, high-grade disease.



Carter: PSA doesn't always tell the whole story—so finding one PSA level that's "normal" for every man is impossible.

However, Carter doesn't believe a lower PSA cutoff will solve the problem. One reason, he says, is that PSA doesn't always tell the whole story—so finding one PSA level that's "normal" for every man is impossible. "High-grade cancers actually produce less PSA per gram of tissue than low-grade cancers." For this reason, even though higher-grade cancers are often larger in volume than low-grade cancers, the PSA level does not accurately indicate the volume of the cancer.

Also, as many as 75 percent of men with a PSA higher than 4 who get a biopsy turn out to have BPH, notes Daniel W. Chan, Ph.D., professor of pathology, oncology, urology, and radiology. "PSA is by no means perfect," he concurs. Even with more sophisticated PSA tests—of free or complex PSA—"it gives us some help in deciding who needs a repeat biopsy. However, with free PSA, less than 10 percent is considered high-risk, and greater than 25 percent is considered low-risk. What happens if your free PSA is between 10 and 25 percent? This is another diagnostic gray zone."

Biomarkers to the Rescue

Instead, say Carter and Chan, what's needed are new biomarkers—new ways to detect cancer earlier, and determine the need for biopsy. "A biomarker," explains Robert Veltri, Ph.D., associate professor of urology, "is a cancer property that can be objectively measured, and used to monitor someone's disease. It can also tell us how well a particular therapy is working." Veltri, Chan, and several Brady scientists are exploring many promising new biomarkers, not only as means of improving diagnosis, but of predicting a man's stage of cancer and his risk of recurrence, and of sounding the earliest possible alarm that cancer has spread, so that it can be treated while the disease is most vulnerable.

Chan and colleagues are using a sophisticated computerized proteomic technology—minuscule chips of protein, added to just one drop of a man's blood. The protein chip acts like a tiny magnet, attracting all the proteins in that blood drop to stick to its surface. This process is a bit like dangling a hook into the water, and seeing what bites. In this case, Chan is fishing for proteins. A sophisticated computer technology called Mass Spectrometry allows Chan to see what he caught; each protein has its own characteristic "signature" of peaks and valleys. It also shows Chan what he didn't catch—any proteins that are missing, or mangled, or changed, are of interest, as well.

The protein chip acts like a tiny magnet, attracting all the proteins in the blood drop to stick to its surface. It's a bit like dangling a hook into the water, and seeing what bites.

Chan's next job is to filter out the background noise, to find the real molecular signature of cancer—which may be different in each man, because prostate cancer itself is so complex, and made up of so many different types of cells and genetic configurations. "We want to decide which of these peaks are real proteins, and which have clinical value in terms of early detection of prostate cancer." He and colleagues at Hopkins have developed a set of "bio-informatic" tools—

"High-grade cancers actually produce less PSA per gram of tissue than low-grade cancers."

new ways to analyze all of this information. When he finds likely-looking proteins, he purifies them, sequences them, and determines their molecular fingerprint. Because prostate cancer is so variable from man to man, Chan isn't looking for one key suspect, but a whole gang of them—a panel, or a multiplex, of biomarkers. He then wants to test these biomarkers in as many patients as possible, on patients at Hopkins and centers worldwide. He also believes this technology will produce new tests that can help diagnose early recurrence of cancer.

Some biomarkers under study include:

- Prostate-breast overexpressed gene-1 (PBOV1): Veltri and colleagues discovered that this gene is, as its name suggests, overproduced in prostate and breast cancers. He is working to develop a new blood and biopsy test that can help determine if cancer is present, and whether it is likely to need treatment.
- GSTP1: Veltri and Partin are evaluating a test to measure GSTP1, which helps the body fight oxidative damage to DNA in cells. This test may be useful for men who have what appears to be prostate cancer, based on a rectal exam, but cancer-free biopsies.
- NMP44: Partin and Chan are working on a test to detect NMP44, a protein that binds with Vitamin D.

Protecting the Nerves, Restoring Potency Sooner

Just as a knight heading off to battle needs armor, or a child needs a sweater on a cold day, nerves sometimes need extra protection, too. This is especially true in the case of the fragile nerves involved in erection in men who undergo radical prostatectomy. No matter how meticulous the surgeon, the trauma of surgery—any surgery—is hard on the nearby nerves. Even in the best of cases, says Arthur L. Burnett, M.D., professor of urology, "they sustain some sort of damage, at least temporarily."

The reasons for this damage—and the specific nature of the nerve injury—remain unclear, but the result for many men is a frustrating delay in the recovery of potency, the ability to have and maintain an erection. In breakthrough work with Hopkins neuroscientist Solomon Snyder, M.D., several years ago, Burnett discovered that rats with nerve injury and erectile dysfunction (similar to that found in men after radical prostatectomy) were helped greatly by the use of a solution containing immunophilins. Immunophilins are special healing proteins made by nerve tissue; when a nerve is injured, they rush to its aid, and help repair the damage. The rats treated with an immunophilin ligand—a "jump-starter" that activates these proteins—showed dramatically less nerve damage, and much greater restoration of function. They had stronger erections, and recovered earlier. This and other immunophilin ligands, Burnett says, work by stimulating receptors in nerve tissue "which, in turn, promote healing and recovery in injured nerves."

The rats treated with an immunophilin ligand—a "jump-starter" that activates these proteins—showed dramatically less nerve damage, and much greater restoration of function. They had stronger erections, and recovered earlier.

Burnett's first immunophilin solution was a ligand called FK506, a drug commonly used to suppress the immune system in people who have undergone organ transplants. He and colleagues have since developed even more targeted ligands that don't affect the immune system, and are just as successful in soothing, protecting, and invigorating these delicate nerves.

Now, in what Burnett calls an example of "true translational research," a medical therapy that originated in the laboratory has been developed for a clinical investigation that's currently under way. A new study—the first of its kind—will test this therapy, a neuroimmunophilin compound called GPI 1485, taken in pill form by men after radical prostatectomy. The Brady Urological Institute is one of 13 medical centers in the United States taking part in this clinical trial, sponsored by Guilford Pharmaceuticals, Inc. Men will be randomly assigned either to the drug, or to a placebo; all of the men are required to record their impressions about their functional recovery.

"We hope to be able to report the results from the study within the next year," says Burnett. "So far, we know that the men have tolerated the drug well, with no major side effects. Any evidence that the drug therapy is effective in enhancing the recovery of erectile function after radical prostatectomy will serve as an important advance in the field, and may also help us develop further neuroprotective interventions in the future."

Does Sexual Activity Affect My Risk of Cancer?

What does sex have to do with prostate cancer? Could a man's sexual activity have any repercussions—one way or the other—on his risk of getting prostate cancer?

In the past, scientists considering this question have come up with good but conflicting theories, says epidemiologist Elizabeth A. Platz, Sc.D. Some researchers speculate that men who have sex more often "may be more likely to acquire a sexually transmitted disease, which may infect the prostate, cause inflammation and other damage, and increase the risk of prostate cancer." (For more on the growing link between inflammation and prostate cancer, see story on page 4) Another thought is that men who have sex more often have a higher sex drive, because of a higher level of male hormones—which, in turn, may increase the risk of prostate cancer.

But other researchers believe that sexual activity may actually *decrease* the risk of prostate cancer—that regular ejaculation, if you will, "cleans house" in the prostate, making it a less welcome harbor for cancer-causing agents, infection, and stagnant materials that could lead to inflammation.

Previous studies have been inconclusive, notes Platz, but "taken together, they hint

that men who have more sex, or who have had a sexually transmitted disease, are more likely to have prostate cancer."

Platz and her colleagues at Harvard and the National Cancer Institute were unconvinced. As part of a massive study, led by epidemiologist Michael Leitzmann at Harvard, they recently studied nearly 30,000 men participating in the Health Professionals Follow-up Study. Most of these men were white and middle-aged, and very few had ever had a sexually transmitted disease. "In 1992, we asked the men who did not have prostate cancer to report their typical number of ejaculations per month in their

Could a man's sexual activity have any repercussions—one way or the other—on his risk of getting prostate cancer?

twenties, forties, and during the past year," says Platz. Over the next eight years, nearly 1,500 of these men went on to develop prostate cancer.

The scientists found that men who reported more ejaculations—more than 21 a month, on average across their adult life—had two-thirds the lifetime risk of prostate cancer of men who reported fewer (4 to 7) ejaculations a month. Notes Platz: "Compared with men reporting fewer ejaculations per month at all ages, men who reported 21 or ejaculations per month had one-fourth the risk of prostate cancer."

Certain important features of this study make these observations more credible, she adds. One is the sheer number of men involved; another is "the fact that the men reported their ejaculation frequency well before they were diagnosed with prostate cancer." Also, the scientists were able to rule out such factors as a man's history of sexually transmitted diseases, which could have clouded the results.

Another recent study of many men, with and without prostate cancer, has produced similar findings, says Platz. "Based on these two large, well-conducted studies, men should not be worried that frequent ejaculation will cause prostate cancer." The next step, she adds, is to figure out *why* frequent ejaculation seems to have this protective effect, and the role inflammation plays here.

Study Raises New Hope for Chemotherapy

At last, definitive news: Chemotherapy prolongs life in men with prostate cancer—and it may be most effective when it is started early, and used aggressively. This is the word from a massive, worldwide study of 1006 men with hormone-refractory cancer, led by Mario Eisenberger, M.D., the R. Dale Hughes Professor of Oncology and Urology, published in the *New England Journal of Medicine*.

The results come after years of clinical trials, of dozens of chemotherapy compounds and drug regimens—many of them developed at the Kimmel Cancer Center by Eisenberger and colleagues. Over the last decade, Eisenberger and colleagues have pioneered a new approach to chemotherapy, hitting prostate cancer increasingly harder and earlier—when it is much more vulnerable—and also using "smart" drugs to target specific molecular steps of cancer cell growth. The journey to this point has been hard, often discouraging, and yet Eisenberger has always believed that the secret code of

This shows that "prostate cancer is as sensitive to chemotherapy as other tumor types, such as breast cancer."

cancer was crackable—that it is just a question of finding the right molecular key, or set of keys, and knowing the right lock, or bank of locks.

This 24-country trial is the largest study ever conducted in men with hormone-refractory prostate cancer—men with cancer that has spread after months or years of hormonal therapy. It was chaired by Eisenberger, along with physicians Ian Tannock, from Canada, and Ronald DeWit, from the Netherlands. In the landmark study, men were randomly assigned to receive a combination of prednisone and docetaxel (Taxotere) a drug in the taxol family, used to treat breast cancer—given weekly, or given every three weeks, or to receive a conventional drug regimen of mitoxantrone and prednisone. The men who showed the biggest improvement received

Mario Eisenberger

prednisone and Taxotere every three weeks. Side effects, including a decrease in white blood cells, were moderate and reversible. "In general, treatment was well tolerated," says Eisenberger. "Men receiving Taxotere also were more likely to have a drop in their PSA level, better control of pain, and improvement in quality of life."

Because of the study's results, the Food and Drug Administration has approved the use of Taxotere for prostate cancer, says Eisenberger, who presented these findings at the plenary session of the American Society of Clinical Oncology. "This important study sets a new standard for chemotherapy in prostate cancer," he says. "It also indicates that prostate cancer is a tumor that is as sensitive to chemotherapy as other tumor types, such as breast cancer." Finally, he adds, the results point to further trials aimed at men with less advanced disease—for example, men after radical prostatectomy, whose pathology suggests that some cancer is still present, or men with no symptoms but rapid PSA doubling times (see related story on page 6). "Our clinical trials should now shift to using it even earlier, to delay or prevent the onset of cancer-related symptoms, and to further prolong survival."

BRIDGE-BUILDER:

DeWeese New Head of Radiation Oncology

Imagine looking at something—say, a garden—through two different lenses. One lens zooms in so much that you can focus on a single weed; the other gives you an aerial shot. This is how Theodore L. DeWeese, M.D., works on prostate cancer. He deals with the very small—cancer on a molecular level, in viral gene therapy studies with urologist Ron Rodriguez, and work on oxidative damage with oncologist Bill Nelson—and the bigger picture—pulling together teams of physicians and scientists, tailoring specific therapy for individual patients, and working

with surgeons and oncologists to design new treatment combinations.

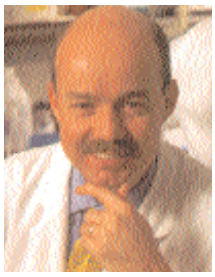
DeWeese is recognized internationally for his expertise in the molecular aspects of radiation's interaction with human cells, particularly prostate cancer cells. He also has designed systems to deliver droplets of cancer-killing viruses—highly precise computer programs that place tiny doses of virus or radiation at exact intervals within the prostate, guided by transrectal ultrasound and CT imaging. But at Hopkins, he is also renowned for his ability to make multidisciplinary collaborations work—so much so, that he has been named the first

"We will be nearly doubling our faculty—from 12 to 23—over the next three years, and tripling our lab space."

director of the new Department of Radiation Oncology and Molecular Radiation Sciences. He is a bridge-builder: Leader of a National Cancer Institute Specialized Program of Research Excellence (SPORE) "translational science" project—turning ideas developed in the laboratory into new forms of treatment for patients, and leader of a Department of Defense Cancer Consortium grant project in adenoviral gene therapy (working with Rodriguez, whose work is discussed on page 7).

"The treatment of prostate cancer has evolved, so that no one specialty has 'ownership' of it any more," says Patrick C. Walsh, M.D., urologist-in-chief. "Because the disease comes in so many different forms, there will never be a single standard way to beat it; we need many options, and many scientific minds from different disciplines turned to the problem. Ted exemplifies this team approach beautifully. Both Hopkins and our patients are very lucky to have him as our leader."

DeWeese is excited about the possibilities of his new job, he says. "We will be nearly doubling our faculty—from 12 to 23—over the next three years, and tripling our lab space." One of those new faculty members is radiation oncologist Danny Y. Song, M.D., who will "re-establish and lead our prostate brachytherapy effort as well as participate in the management of other patients with genitourinary malignancies, and patients



Ted DeWeese

with lung cancer." Song will also lead the prostate cancer clinical research program.

DeWeese is creating a new division of medical physics, bringing in Ph.D. scientists who can apply physics and mathematics expertise to a host of questions. For example: "What does it mean for the patient when a specific gene is functional or not functional, and how can this help us design a better radiation strategy? We tend to treat everybody the same," says DeWeese. "But if you could genetically 'type' a man with prostate cancer, you could individualize that man's therapy far more than we do today."

DeWeese hopes to be able to generate an instantaneous report card that tells him how well radiation is working in a patient, "in a real-time fashion, what this is doing to the tumor. But almost as importantly, can we also monitor the normal tissues that happen to be getting radiation also? Which patients' rectums are more sensitive than others'? If the normal tissue is not being affected, we could give more radiation. If it is being harmed, we could cut back, or come up with another approach."

With the goal of nearly instantaneous feedback from a PET or other nuclear medicine scan, DeWeese and colleagues are testing molecular markers, and working to develop them into a clinical trial—which would be the first of its kind.

In other research, DeWeese and colleagues are studying how cells recover from radiation damage. "We don't want a cancer cell to repair damage; we want to kill it," he explains. Cells have specific sensors that sound the alarm that there has been damage, and call for genetic repair crews. "Those sensors are like the cell's radar," he says. "They constantly scan the cell. If it's injured, the sensor sees it, and starts a whole cascade of events to repair the damage." If those sensors can be disabled—and this can happen, DeWeese found out, by preventing a certain protein from being made—then the damage doesn't get reported. And this means that radiation and chemotherapy can kill more cancer cells at lower doses.

Laparoscopic Radical Prostatectomy: Less is More

In the world of surgery, laparoscopic radical prostatectomy—removing the prostate through tiny keyholes, instead of a larger incision—is the "new kid on the block," but its results are exciting.

Over the last three years, urologists Li-Ming Su, M.D., and Christian Pavlovich, M.D., at the Johns Hopkins Bayview Medical Center, have performed more than 330 of these laparoscopic procedures. Comparing their results with those for the "gold standard" procedure, the nerve-sparing radical prostatectomy, the surgeons have found that their patients need less pain medication after surgery, and have a shorter convalescence—four weeks, instead of six weeks. In a review

Patients need less pain medication after laparoscopic surgery, and have a shorter convalescence—four weeks, instead of six weeks.

of the first 200 laparoscopic radical prostatectomy procedures performed at Hopkins, Su and Pavlovich found that 70 percent of their patients recovered full urinary control at six months, 90 percent were continent at one year; and only a very small percentage (0.6 percent) of men experienced a bladder neck contracture (a treatable condition)—scar tissue that can impede urine flow.

What about cancer cure? Early results, again, are very encouraging, says Su. With an average follow-up time of one year, "98 percent of our patients have shown no recurrence of PSA."

And potency after surgery? The surgeons have worked to modify their procedure to preserve the nerves responsible for erection. "Our goal is to replicate the meticulous dissection achieved during open surgery, in the anatomic nerve-sparing radical prostatectomy," says Su. He and Pavlovich use fine dissecting instruments to ease the fragile nerves from the prostate surface as gently

as possible. Also, the surgeons avoid using any electrical or heat energy, such as cautery, during their dissection of the nerves. This is because animal studies, done by Su and colleagues, have suggested that these energy sources produce a dramatic and immediate detrimental effect on nerve function. "By incorporating these concepts into our nerve-sparing laparoscopic procedure, we've been able to achieve short-term potency results similar to that of open surgery," says Su. He adds that in men who were potent before surgery and who had both nerve bundles spared, 55 percent reported having successful intercourse at 6 months and 75 percent at 12 months. However, they were only able to spare both nerve bundles in about half of the patients. "We are continuing to refine our techniques to make it possible to save both neurovascular bundles more often," says Su.

KEY TO METASTASIS

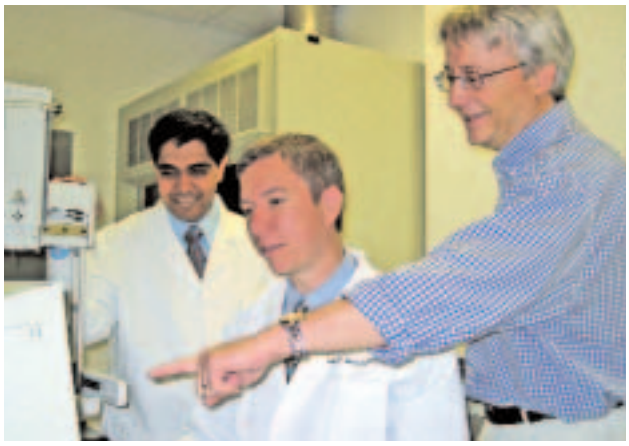
The Hedgehog Pathway

It is the great mystery of prostate cancer: Like people, some cancer cells are better than others, and some are far worse. Some cancer cells don't seem to do much; others quickly become dangerous, spread to sites far away from the original tumor, and eventually, if unchecked, ravage the body. Scientists have long sought to understand the

The Hedgehog pathway is as essential for cancer to live outside its home-base environment as oxygen is to a deep-sea diver.

difference between indolent and overzealous prostate cancer cells. What gives some cells the power to slip away and cause trouble?

Now, they think they've found at least one answer. The secret seems to be a common protein pathway, normally responsible for embryonic development of the lung, pancreas, prostate, part of the brain, and many other organs. The protein in question is called the Hedgehog protein (years ago, scientists discovered that when this protein was mutated in fruit flies, the insects were born with telltale, hedgehog-like prickles).



Karhadkar, Berman, and Beachy have linked Hedgehog activity to prostate cancer's wanderlust. The cancer can spread only if the pathway goes with it.

In breakthrough research, published in the journal *Nature*, Hopkins scientists have shown that the Hedgehog pathway is the key to metastasis—as essential for a cancer cell to live outside its home-base environment as oxygen is to a deep-sea diver. Even more exciting—these scientists have proven that they can block the pathway, and stop metastasis in its tracks.

The implications of this work are far-reaching. "If we can use Hedgehog activity to predict whether a tumor will metastasize, we will have a great diagnostic tool, and we are testing this hypothesis," says David Berman, M.D., Ph.D., assistant professor of pathology, urology and oncology. But 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, are aiming higher. "Manipulating the Hedgehog signaling pathway may also offer a completely new way to treat metastatic prostate cancer," Berman says.

The pathway is not present in normal prostate cells, nor in most low- to middle-grade prostate cancer cells. But it's very active in metastatic deposits; it's also active in cancer cells of men who were thought to have localized prostate cancer, but who later developed metastases.

The investigators looked for detectable activity of the Hedgehog signaling pathway in prostate specimens from men with localized disease, and from men who died of metastatic cancer. They found Hedgehog activity in only three of 12 localized tumors—but in every one of the metastatic cancers, and at levels that were 10 to 100 times higher. In effect, they equated Hedgehog activity with cancer's wanderlust—this suggest that the cancer can spread *only* if the pathway goes with it.

"Think of the soil and seeds," explains urologist-in-chief Patrick C. Walsh, M.D. "The soil is the stroma of the prostate, and the cancer cells are the seeds. If these cells spread but lack the proper soil, they can't survive. But if they can manufacture the Hedgehog protein, they can make the soil that they need—they can pack their lunch and take it with them."

The next part of the story involves one-eyed sheep. In the 1950s and 1960s, several generations of sheep in the western United

"Manipulating the Hedgehog signaling pathway may also offer a completely new way to treat metastatic prostate cancer."

States were born with only one eye—Cyclops sheep. Their birth defect turned out to be caused by something their mothers were grazing on—a plant that was shown to contain a chemical called, appropriately, cyclopamine. When Beachy knocked out the gene that makes the Hedgehog protein in mice, they produced "Cyclops"offspring, as well. From this observation, he deduced and then demonstrated that cyclopamine must block the Hedgehog pathway.

In laboratory experiments on mice with aggressive prostate tumors, from cell lines established by Brady scientist John Isaacs, Ph.D., Kahadkar blocked the Hedgehog signal with daily injections of cyclopamine. Cyclopamine slowed or reversed the cancer's growth, and prolonged the animals' lives.

"It's unbelievable," says Walsh. "This work shows a whole new approach to treating advanced prostate cancer—take away the soil, and the cells die."

The Patrick C. Walsh Prostate Cancer Research Fund

The Patrick C. Walsh Prostate Cancer Research Fund was created to ensure that a multidisciplinary approach to discovery in the field of prostate cancer flourishes at the Johns Hopkins Medical Institutions. The generosity of those listed makes groundbreaking research possible and supports the best and brightest minds working to eradicate prostate cancer.

This list recognizes donors to The Patrick C. Walsh Prostate Cancer Research Fund from April 1, 2002 to October 15, 2004.

We are especially grateful to the Brady Advisory Council for their vision and dedicated support which made this fund possible.

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† *Founders' Circle* ▲ *Brady Advisory Council* * *Deceased*

Discovery happens every day at the Brady Urological Institute – in the laboratory, the operating room, and the clinic. All of it is directly inspired by our patients, and the dedication of our physicians and scientists to helping them beat prostate cancer.

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Every effort has been made to ensure that you have been listed accurately and according to your wishes. If an error has been made, please accept our apologies and notify us directly at (410) 516-6160.