

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



Bob Hastings, who beat prostate cancer 25 years ago, and the surgeon who helped him, Patrick Walsh.

The Big 25: The Brady Remembers the Procedure That Started It All

It was a celebration of life — of lives saved, of quality of life, of lives changed by hope, in a disease that not too long ago was considered hopeless. It was also a recognition of the greater changes wrought by the operation — on the treatment of prostate cancer worldwide and, closer to home, on the Brady Urological Institute itself.

For many who attended the seminar in April marking the 25th anniversary of the first “nerve-sparing” radical prostatectomy — an operation developed by Patrick C. Walsh, M.D., and known worldwide as the Walsh Procedure — it felt like a family reunion, of patients, doctors, nurses, scientists, and friends. Front and center, and by many accounts stealing the show, was Bob Hastings,

who in 1982 — at age 52 — became the first-ever patient to undergo Walsh’s operation.

Hastings had already had survived one brush with cancer when he was young, of the testis, but he knew that his prospects of coming unscathed through prostate cancer were nowhere near as rosy. Back then, surgery could cure the disease — although the chances of cure were much slimmer than they are today, because so many men were diagnosed after the cancer had already spread beyond the prostate. But the operation itself was devastating, involving major bleeding, and resulting in impotence for every man, and incontinence for 25 percent of men who underwent it. “It’s no exaggeration to say that we used to operate in a sea of blood,” says *[continued on page 2]*

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

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Doing a Great Deal of Good



I want to share with you a letter one of our doctors received from a patient. “I am glad to say that each and every event that takes place in the Institute makes me feel doubly assured that I am doing some little good in this great world and that

you are doing a great deal of good. Again let me say that I never doubted for a moment you were the man for the place, and every day increases my belief. Feel that before you get through you will make the Institute known throughout the world for its work and benefit to mankind.”

That letter was from James Buchanan — better known as “Diamond Jim” — Brady, to his urologist, *[continued on page 2]*

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Hugh Hampton Young, and it was written in 1915. Brady saw the potential of Johns Hopkins Urology, and believed in it so much that he endowed the Urological Institute that bears his name. The Brady, the first center of its kind in North America that placed patient care, laboratory research, and teaching under one roof, honored a tradition of discovery that continues to this day.

The milestones of our institute are the milestones of urology.

Our first benefactor was right. From its inception, the Brady has led the world in research and treatment of urologic diseases. The milestones of our institute are the milestones of urology — from the performance of the first radical prostatectomy by Hugh Hampton Young to the discoveries that led to the first “nerve-sparing” radical prostatectomy 25 years ago (see story on Page 1), to breakthroughs in understanding the molecular biology and genetics of prostate cancer and other diseases. How far we have come! In some ways, the Brady has traveled a long way from its simple beginnings (see the story on our much-needed, state-of-the-art laboratories on Page 4), but in other important ways, we haven’t changed a bit. Patients are still our focus, and helping them remains our great mission. Excellence is, always has been, and will always be, our standard. And the support of our generous patients remains critical to our ability to do all of this. Without your help, in an era of uncertain and diminishing government research funds, the discoveries we are making every day would not happen.

So when you look through these pages, I invite you to share our excitement and to be proud of your part in it. With your help, we are making a huge difference in the lives of men with prostate cancer and their families. We are still — faithful to the wishes of Mr. Brady — “doing a great deal of good.”

**Best wishes,
Alan W. Partin, M.D., Ph.D.
David Hall McConnell Professor and Director
The Brady Urological Institute**

MAKING A GIFT

If you are interested in making a gift to support The Brady Urological Institute, or if you are considering a gift of stock, real estate, IRA, or other asset, please call the Development Office at (410) 516-6160.

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Walsh, University Distinguished Service Professor of Urology. “The complications of radical prostatectomy were so harsh that most men said they’d rather have the disease.” Although radiation was much less powerful than it is today, and was not often able to cure the disease, most men — 93 percent — opted for it instead. And experienced pelvic surgeons — Walsh studied with the best, at Harvard, UCLA, and the University of California, among other places — accepted these side effects as the “price for curing prostate cancer,” and never asked why they occurred, or how they could be avoided, Walsh recalls. (Walsh made this his first mission when he came to Hopkins; see side story.)

Without much hope, Hastings, a college professor from Ohio, met with Walsh, who was the Director of the Brady Urological Institute, to discuss the possibility of surgery. What Walsh had to say stunned him: “He said, with complete modesty, ‘I can cure you.’ I liked that. He said, ‘I don’t think you’ll have any trouble with impotence.’ I really liked that.” Walsh told Hastings that he would be the first patient in his new surgical series. Hastings didn’t realize until years later “that I was the first one — ever.”

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Walsh kept his word and cured Hastings’ cancer. The next month, he presented a scientific paper on his techniques at the 1982 meeting of the American Urological Association, and from that day onward, the Brady Urological Institute was never the same. “The phones started ringing off the wall,” says Cynthia DiFerdinando, the clinic manager. In the clinic, a low-key suite of rooms in a hall to the parking lot, with a few rows of orange plastic chairs for waiting patients — compared to today’s bustling clinic, which takes up an entire floor of the Outpatient Center — the receptionists were caught off guard. “Nerve-sparing? What nerves?” DiFerdinando recalls saying. “Are you sure you want urology? You must want neurology.”

Patients from around the world began coming to Hopkins for the operation; in fact, in June 2007, Walsh performed his 4,000th Walsh procedure. With every patient, Walsh kept meticulous, lifetime follow-up records, so that he could learn from anything that happened to these men over time, and use that knowledge to help other patients. “He single-handedly changed the field of prostate surgery,” says Alan W. Partin, M.D., Ph.D., the David Hall McConnell Professor of Urology, who recently succeeded Walsh as Director.

“Nerve-sparing? What nerves?”

Are you sure you want urology?

You must want neurology.”

“Then he began teaching other surgeons, including me, how to perform this very difficult operation.” For many years, surgeons from around the world came to Hopkins to watch Walsh perform his procedure. Several years ago, with funding from The Mr. and Mrs. Robert C. Baker Foundation, Walsh made a two-hour DVD, and sent 50,000 copies free to surgeons around the world who wanted to learn how to perform the procedure better. (To view excerpts, please go to our website at <http://urology.jhu.edu> and click on “Anatomic Radical Retropubic Prostatectomy.”)

“This is one of the best examples of knowledge being developed at Hopkins and spreading around the world,” says Partin. “The operation has had a fundamental impact on the field of urology, as well, allowing scientists to study the disease in ways — looking at the genetics, for example, or using molecular biology techniques to find ways to stop cancer, or to find new markers that are better than PSA — that were never feasible before.” Partin is, himself, a household name in the field of urology — known worldwide for, among other things, his development, with Walsh, of the Partin Tables. Based on evidence from thousands of men who underwent the Walsh Procedure, the Tables are the next best thing to a crystal ball, allowing men with prostate cancer to predict their likelihood of being cured. (See story on Page 4.)

The Walsh Procedure’s ripple effect has transformed other specialties — especially pathology. “Before Dr. Walsh’s operation, almost all men diagnosed with prostate cancer were treated with either radiation or

How Serendipity Helped

Like most overnight successes, this one took years of hard work. Patrick Walsh took the helm of the Brady in 1974, and spent the next three years figuring out how to reduce the drastic bleeding that had plagued radical prostatectomy ever since it was invented (at Hopkins) in 1904, by surgeon Hugh Hampton Young. Walsh developed surgical techniques that kept bleeding to a minimum and then, with a near-bloodless field, was able to reduce men's likelihood of incontinence, because he could see urinary sphincter muscles and other structures that, previously, had been routinely destroyed. By 1977, Walsh had excellent rates of continence, but still hated the fact that all men were impotent after surgery.

Then, a 58-year-old patient from Philadelphia reported that he was fully potent within a year after surgery — and instantly, Walsh realized that everything surgeons had thought about the nerves that are responsible for erection — that they ran through the prostate, and were inevitably severed when the prostate was removed — was wrong. “Nobody knew where the nerves actually went,” Walsh recalls, “and this is because the only way we learned anatomy was by studying adult cadavers.”

Unfortunately, he adds, when cadavers are preserved, the fixative solution dissolves the fatty tissue that separates tissue planes, and in the postmortem state, the abdominal contents compress the pelvic organs

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into a thick pancake of tissue, making anatomic dissections impossible. Walsh began studying living anatomy — examining the nerves, blood vessels, and tissue surrounding the prostate — in the operating room, as he performed surgery.

“That same year, I attended my first meeting of the American Association of Genitourinary Surgeons,” Walsh recalls. The night before the meeting, he and his wife, Peg, went to a restaurant and saw an older man standing by himself and, Walsh suspected, feeling rather lonely. On the spur of the moment, Walsh asked the man if he were also attending the meeting, and if he would care to join them for dinner. “That night was the first time I met Pieter Donker, the Professor and Chairman of Urology at the University of Leiden.” They became friends. Walsh continued to try to decipher

the anatomy of the pelvic nerves, and in 1981, at a meeting in Leiden, the Netherlands, he met up with Donker again. “Had it not been for that dinner four years earlier, we would never have met, and this opportunity would have been missed.”

Donker had retired as Chairman, and was spending his days dissecting out the nerves to the bladder, which had never been done successfully before. “He was using infant cadavers,” says Walsh, “and when I asked why, he said that this was the best model,” because the nerves were much more visible than in adult cadavers. Walsh studied his drawings, and asked Donker about the location of the nerve branches to the penis. “He said that he had never looked. Three hours later, both of us could see that the nerves were located outside the prostate.” Walsh and Donker continued their anatomical studies, looking for landmarks to identify these nerves in adult men. Back in Baltimore, “in the operating room, I noticed that there was a cluster of vessels, the capsular arteries and veins of the prostate, that traveled in this exact location, the neurovascular bundle, which I concluded could be used during surgery to preserve the nerves.”

By April 26, 1982, Walsh was ready to test his newfound knowledge on a patient. Today, that patient, Bob Hastings, remains cancer-free, with an excellent quality of life.

This happy occasion was featured on National Public Radio's “All Things Considered.” To hear the story, go to <http://www.npr.org> and type “Patrick Walsh” in the search box.

hormone therapy, with no additional tissue removed to verify the presence of cancer,” says Jonathan Epstein, M.D., the Rose-Lee and Keith Reinhard Professor of Urologic Pathology. “Many mimickers of prostate cancer on biopsy were overcalled as cancer. Conversely, limited prostate cancer on biopsy — that today would be readily recognized as malignant — was often diagnosed as ‘atypia.’ But after Dr. Walsh's operation, pathologists had the opportunity to study prostate cancer and all of its variants in large tissue specimens. Previously, the diagnosis of cancer was based on a gestalt ‘it looks like cancer.’ Now, because of the study

of radical prostatectomy specimens fostered by Dr. Walsh's discovery, the diagnosis of prostate cancer is based on a systematic approach — and the pervasive under- and overdiagnosis of prostate cancer that prevailed in the past no longer exists.”

With the development of the PSA test, which made it possible to diagnose prostate cancer at an earlier, curable stage, plus improvements in radiation therapy and proof, recently demonstrated by a large Scandinavian study, that radical prostatectomy saves lives, there has been a dramatic drop in deaths from prostate cancer in the United States. In fact, the number of men

dying from prostate cancer over the last 10 years has fallen by 33 percent — the highest for any cancer in American men or women.

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.

2007 Partin Tables Show the Increasing Curability of Prostate Cancer

Good news: The Partin Tables have changed. Even better news: They *had* to change, to reflect the sharp decrease in men being diagnosed with later-stage, more advanced cancer.

The Tables, which use a man's Gleason score, his PSA, and clinical stage (determined by his prostate biopsy), are used by millions of men worldwide as "virtual surgery" — the next best thing to knowing what would be found if the prostate were removed surgically and examined by a pathologist. They provide an excellent way to predict a man's chances of cure — his chances that treatment will eliminate the disease forever, and that no cancer cells have escaped the prostate.

Originally developed in 1993 by Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D., after Partin studied the course of prostate cancer in hundreds of Walsh's radical prostatectomy patients, the Tables have gotten bigger, better, and increasingly hopeful over the years. The 2007 Tables are based

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on the results of 5,730 men who underwent surgery at The Johns Hopkins Hospital between 2000 and 2005. "There has been a dramatic shift in clinical stage of men being diagnosed with prostate cancer," says Partin, Director of Urology and the David Hall McConnell Professor. "Men are being diagnosed at a younger age — which means that they're starting prostate cancer screening earlier — and the overwhelming majority are now being diagnosed with local or regional disease." The results of the latest study were published in the June 2007 issue of *Urology*. "The original tables were based on our institutional experience from an era when few patients were diagnosed with screen-detected prostate cancer," comments collaborating scientist Dan Makarov. "Therefore, the older versions tended to paint a bleaker prognosis."

In fact, so many of the men studied for these latest Tables had early-stage, organ-confined cancer, that Partin and colleagues

decided to combine stages T2b and T2c (cancer that is big enough to be felt, involving more than half of one or both lobes, respectively). "From our very first Tables to these latest nomograms, there has been a decline in palpable disease from 86 percent to 23 percent," says Partin. Even men with high Gleason scores (Gleason 8 to 10) tended to be diagnosed with more curable cancer, because it's being detected earlier.

Note: The tables only include men who underwent surgery, and for this reason in men with Gleason 8-10 disease, the predictions only apply to a best-case scenario, of a few carefully selected men, with limited high-grade disease on their biopsies.

New Research Labs Will Reunite Spread-Out Faculty

At some institutions, doctors are doctors, and scientists are scientists, and although they may be headed in the same direction, their tracks are parallel, like a railroad line. They don't talk very often, and consequently, they don't help each other very much. It's never been that way at the Brady Urological Institute, where doctors and scientists see each other all the time, and work on different parts of the same problems.

However, in recent years, due to a shortage of research space, some of our faculty have suffered from a campus version of suburban sprawl — tucked away at various buildings on the enormous Johns Hopkins Medical Institutions site, which encompasses several city blocks. Others, who were fortunate enough to remain in the Marburg Building, were cramped, with insufficient laboratory and office space.

Help is on the way — nearly 17,000 square feet of prime laboratory and office space on the second floor of the Park Building, which is right next door to the Marburg Building. "This much-needed new space will give us the opportunity to bring together many different groups, particularly those related to biomarker studies and prostate cancer," says Alan W. Partin, M.D., Ph.D., Director of the Brady, who has been working hard to secure research space for the Brady over the last three years. "It will also allow us to recruit new faculty." The new space was made possible in part through gifts from The Peter Jay Sharp



The new design features lots of glass, and is deliberately open, to facilitate communication and team research.

Foundation, The Patana Fund for Research, The Zickler Family Foundation, and Luciana and Jose-Maria Castro.

In addition to the research laboratories, there will be 13 faculty offices, plus room for support staff. The design is deliberately open. "We did that to facilitate the communication between the research and clinical faculty and staff," says the Brady's Director of Research, Robert H. Getzenberg, Ph.D., the Donald S. Coffey Professor of Urology. "The laboratory has a floor-to-ceiling glass wall, and the faculty offices have glass walls as well, so that all who visit will be able to see team research under way." The architectural design is also flexible, "to accommodate not only our needs today, but to adapt to changing technologies and opportunities."

BPH: New Marker Can Spot the Worst Kind; May Help Prevent Damage

Do you have BPH? If you're a man, chances are, you will. Your risk of BPH (benign prostatic hyperplasia) increases every year after

age 40. It's present in 20 percent of men in their fifties, 60 percent of men in their sixties, and 70 percent of men by age 70. For some men, BPH is not so bad; for others — more than 350,000 a year in the United States alone — the symptoms of urinary obstruction or irritation eventually require treatment; if treatment is delayed, or the symptoms are very severe, the bladder may be damaged.

Scientists used to think all BPH was created equal. Not anymore. On the genetic level, severe BPH is dramatically different from milder forms.

“Not all BPH is created equal,” says Robert H. Getzenberg, Ph.D., the Brady's Research Director, and the Donald S. Coffey Professor of Urology. Although doctors and scientists have long noted the wide variation in men's symptoms, “we considered that all types of BPH were biologically the same thing — a single disease. Now we know that this is not the case.” Getzenberg and colleagues have discovered that men with severe BPH, which can be debilitating, have dramatically different genetic findings from men with few symptoms. Their work has led them to identify a new marker, called JM-27, which is linked to the most aggressive form of BPH.

They first spotted the marker in prostate tissue samples, but recently, in research published in the February 2007 *Journal of Urology*, they found that JM-27 can also be detected in the blood. “This is great news, with the potential to help many men,” says Alan W. Partin, M.D., Ph.D., Director of the Brady, who envisions that one day, men may be screened for BPH just as they are now screened for prostate cancer. “If we can catch this highly symptomatic form of BPH earlier, we can treat these men, and potentially prevent some of the bladder changes that are often difficult to reverse.” Today, however, this test is still under investigation, and is not yet available for use in patients.

Interestingly, Getzenberg has found, JM-27 levels don't seem to be affected by the presence of prostate cancer. “Also, this marker has the potential to serve as a molecular monitor — to show whether medications being given for the treatment of BPH are actually helping.” He reports that a large study is being conducted to learn more about JM-27's effectiveness, as part of the National Institutes of Health MTOPS

(Medical Therapy of Prostatic Symptoms) trial, a multi-institutional study that showed that a combination of Proscar and Cardura is more effective than either drug alone in preventing the complications of BPH.

EPCA-2:

In More Tests, Marker Performs Like a Champ

On the front page of our last issue of *Discovery*, we covered a major breakthrough — a new test for prostate cancer, called EPCA-2, that has proven to be more specific than PSA. The marker was found by a research team led by Robert H. Getzenberg, Ph.D., the Donald S. Coffey Professor of Urology, in work published in the April 2007 *Urology*. In early tests, EPCA-2 did a better job than PSA at distinguishing men with prostate cancer from other men, and of showing which men had organ-confined cancer, and which men had cancer that had spread beyond the prostate.

EPCA-2 proved better than PSA at distinguishing men with prostate cancer from other men, and of showing which men had organ-confined cancer, and which men had cancer that had spread.

In further tests, the marker has been able to distinguish cancer from BPH and prostatitis — two conditions that can elevate PSA, and confuse a diagnosis of cancer. Most recently, Getzenberg and colleagues analyzed blood samples, provided by Children's Hospital in Boston, of men with prostatitis, and “we demonstrated that blood-based EPCA-2 levels are not elevated in these men,” Getzenberg says. “Previously, we found that the levels were not elevated in men with BPH.” In other studies, “the separation between men with organ-confined and non-organ-confined disease continues to be dramatic.” While PSA has some ability

to tell whether a man's prostate cancer is advanced — for example, the risk of having advanced prostate cancer goes up as PSA increases from 4 to 10 to greater than 20 — EPCA-2 is significantly more accurate.

More studies are needed before the test can be approved for clinical use, but the results “continue to support that EPCA-2 is highly specific for prostate cancer, is found in higher levels in men with disease that has spread outside the prostate, and that it may serve as a means to target drugs specifically to prostate cancer. The next year should be an exciting one as many of these studies are completed.”

Zeroing in on Chromosome 8: A Hotspot for Genetic Risk Factors

What is it about chromosome 8 that makes it such a bad neighborhood for prostate cancer? William B. Isaacs, Ph.D., who has been scrutinizing this area, has found many genetic risk

In mice, over-expression of this gene causes prostate cancer.

factors. Mysteriously, “although we have found multiple genetic variants in this region, none of these actually resides within a gene,” says Isaacs, the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology. So how do these factors raise a man's risk of developing prostate cancer? One possibility is that the errant gene may be close, but not right next door, to the trouble spots that have been pinpointed. “We are especially interested in one gene that is nearby — the C-MYC gene — for two reasons,” says Isaacs. “We know that in mice, over-expression of this gene causes prostate cancer. Also, Angelo De Marzo's lab has shown that C-MYC is over-expressed very early in many human prostate cancers, and this may be observed even in some cells that appear normal, but then become cancerous.” Using tissue samples from men who carry the risk variants in one particular region of Chromosome 8, called *[continued on page 6]*

Why Chromosome 8?

Last year, researchers in Iceland reported that a small region on the long arm of chromosome 8 harbored a genetic variant associated with an increased risk for prostate cancer. William Isaacs and colleagues were able to confirm this observation, “which is significant, because results in this field have been notoriously difficult to reproduce,” Isaacs notes. “Also, we discovered multiple independent genetic variants in the 8q24 region (of Chromosome 8), which are associated in an additive fashion with an increased risk for prostate cancer.” Isaacs’ research indicates that trouble spots in this region account for much of the genetic risk for prostate cancer. “One of the variants we identified at 8q24 is particularly important in affecting risk for prostate cancer in African Americans,” a group that is particularly hard-hit by prostate cancer.

[continued from page 5]

8q24, Isaacs and colleagues are looking at the levels of C-MYC in both normal and early prostate cancer cells. “It’s possible that in some men, these variants can increase or otherwise disrupt the expression of C-MYC in prostate cells, and that this can increase their chance of developing cancer.” (For more on C-MYC, see story on Page 6.)

In other news, the National Cancer Institute has awarded an additional five years of support to the International Consortium for Prostate Cancer Genetics Study, which is led by Isaacs. The study involves more than 65 investigators from around the world who are interested in the inherited susceptibility of prostate cancer. “Together, we have collected more than 2,500 families with three or more first-degree relatives affected with prostate cancer,” reports Isaacs. Using linkage analysis to study these families, “we have identified regions of chromosomes 6, 11 and 20 which may harbor genetic variants that increase a man’s risk of developing an aggressive prostate cancer. We are actively pursuing these regions to identify the specific genes responsible for this inherited risk.”

The C-MYC Gene: *If Controlled Early, Could it Stop Cancer?*



Angelo De Marzo

Angelo De Marzo, M.D., Ph.D., a pathologist studying prostate cancer, has spent the last several years trying to go back in time. Studying endless slides of prostate tissue, starting with cancer and working his way back, past PIN (prostatic intraepithelial neoplasia — “funny looking” cells that are precursors for cancer), he discovered PIA — proliferative inflammatory atrophy — a chaotic, volatile mix of cells that seem to be dying, but are actually undergoing rapid change. These cells could be headed toward cancer, but then again, they may be redeemable, with the right environmental changes. De Marzo, the Beth W. and A. Ross Myers Scholar, believes that inflammation plays an important role in PIA, and may be the cellular “last straw” that kicks these cells over into precancer — PIN.

This seems to start at the earliest recognizable stage of prostate cancer development.

Recently, De Marzo and his team have been investigating how a gene called C-MYC (pronounced C-“mick”) fits into this timeline. He got interested in this gene after work by Brady scientists William Isaacs and Jun Luo — who, with technological help, examined more than 10,000 genes in normal and cancerous prostate tissue — implicated C-MYC as a suspicious character. “C-MYC is known to function in many cancers as an oncogene — a cancer-causing gene,” explains De Marzo, “but scientists didn’t know when — or how often — the C-MYC gene became activated during the process of prostate cancer development.”

Now they have a pretty good idea. De Marzo’s research group has discovered that the C-MYC protein is cranked up in prostate cancer. “And, not only is it expressed in more than 80 percent of prostate cancers — previ-

ous estimates were around 25 to 50 percent — but this seems to start at the earliest recognizable stage of prostate cancer development, in PIN.” De Marzo’s work may enable C-MYC to become a biomarker in prostate cancer. “We also hope that it will inspire biomedical researchers to press hard to develop and test new ‘smart’ drug inhibitors of the C-MYC pathway in prostate cancer.”

Robot-Assisted Prostatectomy: Beyond the Flashy Technology

Just how good is robot-assisted radical prostatectomy? Many centers, in aggressive marketing campaigns, proclaim the miracles of the robotic procedure — its minimal invasiveness, its short recovery time, its delicacy and accuracy. At the Brady, Hopkins urologists have been performing minimally invasive radical prostatectomies for several years — first, using the conventional laparoscopic technique, and more recently, using the daVinci Surgical System, a highly sophisticated, four-armed robotic device that allows the prostate to be removed through six keyhole-sized incisions. But this team of surgeons has also been looking past the flashy technology, working hard to evaluate these procedures — subjecting them to rigorous standards, to determine the true impact on cancer cure, urinary continence, preservation of sexual function, and even cost-effectiveness.

“Along with enthusiasm for a new technology comes the responsibility of comparing its success to that of the ‘gold standard’ — the open surgical procedure,” says Li-Ming Su, M.D., Director of Laparoscopic and Robotic Urologic Surgery. There are no long-term results yet, because the technology is too new. But the Brady team is working on it, “collecting and studying data on cancer margins and the rate of recurrence, as well as continence and potency with validated quality-of-life surveys.”

“We established our program for robot-assisted laparoscopic radical prostatectomy in 2005,” says Su, “with more than 375 cases performed so far.” But that number is increasing rapidly: “In just two years, we

have seen a six-fold increase in the number of cases, and for the year 2007, our department is on track to perform over 300 robot-assisted laparoscopic radical prostatectomies” — about one-third of all prostatectomies performed at Hopkins. With the daVinci System, the surgeon operates from a computer console, looking at a three-dimensional image with 10X magnification. “With one of the robotic arms controlling the endoscope, the surgeon actively works with the remaining three robotic arms — each one equipped at the end with sophisticated, multi-jointed instrument tips that allow us to operate and dissect fine tissues with the dexterity of a human wrist.”

There are no long-term results yet, because the technology is too new. But the Brady team is working on it, studying data on cancer margins and the rate of recurrence, as well as continence and potency.

Currently, Su and five other Brady surgeons — Jonathan Jarow, Mark Gonzalgo, Christian Pavlovich, Mohamad Allaf, and Misop Han — offer this technique routinely to patients with organ-confined prostate cancer. There is also a specially trained team of operating room nurses, physician assistants, and anesthesiologists. The short-term results are excellent. “For the patient, blood loss and transfusion rates are minimal, average hospital stays are one to two days, and the urethral catheters are removed in most patients by one week following surgery,” notes Su. He is optimistic that the long-term results will be just as promising.

The Brady Welcomes New Faculty

We are proud to tell you about two new additions to our faculty, welcome reinforcements in our fight against prostate cancer: Mohamad E. Allaf and Edward M. Schaeffer. “Neither of these physician-scientists is a stranger to the Brady,” says Alan W. Partin, M.D., Ph.D.,

Director of the Brady. “Indeed, we felt that their work as residents was so promising, we wanted to give them the best opportunity to flourish clinically and in the laboratory.”



Mohamed Allaf

Engineering and earned a medical degree from the School of Medicine at Johns Hopkins, then went on to complete his residency and advanced training in urology at the Brady Urological Institute.

In a series of laboratory experiments with rats, working with Arthur L. Burnett, M.D. Professor of Urology (whose work appears on Page 12), Allaf recently discovered that erythropoietin (“EPO”) — a drug most commonly used to boost the production of red blood cells in people with kidney failure — appears to speed up the recovery of nerve function and hasten the return of erections. Also, Allaf and colleagues have found a receptor for EPO in the periprostatic neurovascular bundles — the nerves essential for erection — in humans. Based on this exciting work, Allaf and Burnett are planning a clinical trial to evaluate the role of EPO in promoting erectile recovery following radical prostatectomy. Allaf’s other research interests, building on his background in biomedical engineering, include designing and testing novel devices aimed at improving surgical abilities and minimizing the morbidity of surgery.



Edward Schaeffer

the Brady Urological Institute, and now has appointments as an assistant professor in the Departments of Urology, Oncology and Pathology at Johns Hopkins.

Mohamad E. Allaf, M.D., Assistant Professor of Urology and Director of Minimally Invasive and Laparoscopic Surgery at Johns Hopkins Bayview Medical Center, completed his undergraduate studies in Biomedical

Schaeffer, in molecular studies with pathologist David Berman, M.D., Ph.D. (whose research appears on Page 11), has been working on understanding how prostate cancer begins and spreads. Like Berman, he believes clues to cancer’s origins, and its subsequent pathways for growth, lie in the early development of the prostate itself. “During development,” he explains, “the prostate is built from scratch, using processes of cellular invasion, division and differentiation — which is very similar to what we see in the formation of cancer.” Schaeffer hopes that by mapping, on a molecular basis, what happens in androgen-regulated prostate development, his team can also identify — and figure out how to stop — new molecular pathways that become activated in prostate cancer.

When PSA is High, Cancer’s Location Makes a Difference

You can’t judge a man’s cancer by his PSA alone. Men with PSA levels lower than 4 ng/ml can have serious disease, and men with PSA higher than 20 ng/ml can have cancer that is curable with treatment. For these men with high PSA, as in real estate, location is very important.

Some prostate cancers form in the *anterior* part of the prostate gland — an inaccessible area that the urologist’s finger can’t reach in a rectal examination. Other tumors — which can be felt, if they become large enough — are located in the *posterior* portion of the prostate.

In a recent study, of men with a PSA level higher than 20 who underwent radical prostatectomy, Mark L. Gonzalgo, M.D., Ph.D., and urologists Ahmed Magheli, M.D. and Patrick C. Walsh, M.D., investigated the relationship between a tumor’s location and the likelihood that cancer will come back after surgery. The study was published in the October 2007 *Journal of Urology*.

“We found that tumor location was a significant factor,” says Gonzalgo, assistant professor of urology and oncology, and the Nancy and Jim O’Neal Scholar. “About 63 percent of men with anterior tumors had no evidence of PSA recurrence five years after surgery, compared to 40 percent of men

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THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

Read About the Research You Have Helped Make Possible

The Patrick C. Walsh Prostate Cancer Research Fund is the result of great generosity, from many generous patients and friends. It began three years ago, with a novel announcement that said, in effect: "Attention, all Johns Hopkins scientists. We want to find the cure for prostate cancer. We don't care which discipline you're in. If you have a good idea, and our scientific advisory board thinks it's worth pursuing, we will give you some money to help you do it."

So far, with your help, we have raised more than \$28 million, and of more than 100 applications, we have funded proposals from the best and brightest scientist at Hopkins, in many departments. These include: Oncology, Pathology, Medicine, Mechanical Engineering, Radiology, Urology, and the School of Public Health. Our scientific advisory board is made up of distinguished Hopkins scientists and two lay members, Joseph Rascoff, Chairman of the Johns Hopkins Prostate Cancer Advisory Board, and Samuel Himmelrich. This year, we awarded more than \$1 million to 13 recipients. Some of their work and updates of the work of the scientists funded last year are described below.

THE 2007-2008 AWARDEES

Arthur Burnett, M.D.
Department of Urology

H. Ballentine Carter, M.D.
The Peter Jay Sharp Foundation Scholar
Department of Urology

Robert Casero, Ph.D.
Irene and Bernard L. Schwartz Scholar
Department of Oncology

Angelo De Marzo, M.D., Ph.D.
Beth W. and A. Ross Myers Scholar
Department of Pathology

Mark Gonzalgo, M.D., Ph.D.
Nancy and Jim O'Neal Scholar
Department of Urology

Sheila Gonzalgo, M.D., M.P.H.
Carolyn and Bill Stutt Scholar
Department of Medicine, Division of Geriatric Medicine and Gerontology

Jun Luo, Ph.D.
Phyllis and Brian L. Harvey Scholar
Department of Urology

Shawn Lupold, Ph.D.
Virginia and Warren Schwerin Scholar
Department of Urology

Alan Meeker, Ph.D.
Departments of Urology and Oncology

George Netto, M.D.
Department of Pathology

Elizabeth Platz, Sc.D.
Department of Epidemiology
School of Public Health

Dan Stoianovici, Ph.D.
R. Christian B. Evensen Scholar
Departments of Urology and Mechanical Engineering

Srinivasan Yegnasubramanian, M.D., Ph.D.
Dr. and Mrs. Peter S. Bing Scholar
Department of Oncology

THE 2006-2007 AWARDEES

Dimitri Artemov, Ph.D.
Beth W. and A. Ross Myers Scholar
Department of Radiology

David Berman, M.D, Ph.D.
R. Christian B. Evensen Scholar
Department of Pathology

Robert Casero, Ph.D.
Irene and Bernard L. Schwartz Scholar
Department of Oncology

Angelo M. De Marzo, M.D., Ph.D.
Dr. and Mrs. Peter S. Bing Scholar
Department of Pathology

Charles Drake, M.D., Ph.D.
Phyllis and Brian L. Harvey Scholar
Department of Oncology

Mark L. Gonzalgo, M.D., Ph.D.
Nancy and Jim O'Neal Scholar
Department of Urology

Sheila Gonzalgo, M.D., M.P.H.
Carolyn and Bill Stutt Scholar
Department of Medicine, Division of Geriatric Medicine and Gerontology

John T. Isaacs, Ph.D.
Department of Oncology

Jun Liu, Ph.D.
The Peter Jay Sharp Foundation Scholar
Department of Pharmacology

Shawn Lupold, Ph.D.
Virginia and Warren Schwerin Scholar
Department of Urology

William G. Nelson, M.D., Ph.D.
Department of Oncology

Elizabeth Platz, Sc.D.
Department of Epidemiology,
School of Public Health

Martin Pomper, M.D., Ph.D.
Department of Radiology

Spermine Oxidase, Hydrogen Peroxide, Inflammation, and Prostate Cancer

Imagine looking for the first dominos, after a whole line has fallen — retracing the steps of a chain reaction to find the root cause — and you'll have a pretty good idea what molecular pharmacologist Robert Casero, Ph.D., is trying to do. Actually, this is what many Brady researchers are trying to do; but in Casero's case, the particular series of events involves an oxidized molecule called spermine.

His starting platform is pioneering Brady research, well under way in many labs here, showing that inflammation plays a key role in the development of prostate cancer. Inflammation causes oxidative damage — harm to DNA, which can cause one or more genes to mutate — and this, in turn, can lead to cancer. One substance known to cause oxidative damage is hydrogen peroxide, which is produced when there is inflammation. The same stuff that, in a bottle in your medicine cabinet, kills germs can also hurt your cells. It doesn't take much — very tiny amounts, even just one molecule's worth, can cause harm.

Casero, the Irene and Bernard L. Schwartz Scholar, has taken this process back a step further. What, in inflammation, causes hydrogen peroxide to be made? This can happen when an enzyme called spermine oxidase mixes oxygen with spermine, a substance found in high concentrations in the prostate. Previously, Casero and colleagues found that when there is inflammation in the stomach (caused by bacterial infection with *H. pylori*) spermine oxidase makes

hydrogen peroxide, and damages DNA. Casero suspected that this also happens in the prostate — which has the highest concentration of spermine of any human tissue.

The same stuff that, in a bottle in your medicine cabinet, kills germs can also hurt your cells.

As he and colleagues have pursued this, they have built up an incriminating file showing that inflammation — and inflammatory cytokines (regulatory proteins, released by the immune system) — causes more spermine oxidase to be made. “Our data indicate that increased spermine oxidase is associated with prostate cancer,” he says. “As the product of spermine oxidase is hydrogen peroxide, we suspect that this can lead to greater DNA damage, and ultimately, to the initiation and progression of prostate cancer.” Are men with higher levels of spermine oxidase more prone to developing prostate cancer? Do men who don’t have prostate cancer have lower levels of spermine oxidase? These are among the next questions Casero plans to pursue.

Turning Back the Clock on Cancer

In health and beauty products, the big trend now is for skin potions that turn back the clock on aging — that restore damaged cells, and revitalize tissue. This same thing — a genetic “fountain of youth” — needs to happen with prostate tissue that’s headed for cancer, before it’s too late. Mark L. Gonzalzo, M.D., Ph.D., is working on that. Gonzalzo, the Nancy and Jim O’Neal Scholar, is one of several Brady scientists studying a process called methylation, which happens to genes. It’s been compared to taking the bullets out of a gun, or changing a key, so it doesn’t fit its lock anymore — basically, a gene that has been methylated doesn’t work the way it’s supposed to.

In the prostate, when certain cancer-fighting genes are methylated, they don’t do their job, and cancer develops. Gonzalzo, using a mouse model he developed, is looking at methylation in several genes, including GSTPi, Timp3, and IgF2. (GSTPi, which has been studied extensively at Hopkins by

William G. Nelson, M.D., Ph.D., and others, and has been written about in previous issues of *Discovery*, is an important cancer-fighter that is knocked out early in prostate cancer.) In innovative research, he is also looking at “demethylating” agents and other genetic turn-back-the-clock drugs that can reverse the process of methylation. “It will be exciting to see if we can affect not only the development of prostate cancer, but even the development of metastatic disease,” he says.

The Frailty Factor and Prostate Cancer



Sheila Gonzalzo

works the other way, too; some men in their sixties, who have other serious health conditions in addition to cancer, probably won’t benefit from surgery.

Does age discrimination affect prostate cancer treatment? Very often, it does.

The key is frailty — and its reverse condition, general good health, says geriatrician Sheila Gonzalzo, M.D., M.P.H., the Carolyn and Bill Stutt Scholar. “Some people are afflicted with it as they age,” she explains. “For reasons we don’t yet fully understand, frailty is a biological syndrome, characterized by weight loss, weakness, exhaustion, and loss of muscle mass and strength.” She has been working to quantify frailty as a factor in determining how well a man will recover from a serious illness, such as cardiovascular disease, dementia, lung disease, and cancers including prostate cancer. She has also been looking at frailty in data collected from the Cardiovascular Health Study, involving more than 2,200 men, ages 65 to 100, to determine how a man’s general

health affects his chances of being helped by surgery.

“Our preliminary findings appear to support the notion that some men with prostate cancer aged 65 to 74 years, and possibly aged 75 to 84, might be amenable to more aggressive forms of therapy,” she says. Further studies are needed to determine which men would benefit the most — and the least — from prostate cancer screening and surgical intervention.

New Drug May Help Men With Metastatic Cancer

A new drug, able to attack blood vessels within prostate cancer — but so focused on the cancer that it leaves nearby blood vessels in normal tissue unscathed — is about to begin clinical trials. The drug, named Tasquinimod, will be tested in a daily pill form, in a randomized, placebo-controlled trial in men with prostate cancer that has metastasized (spread to other areas beyond the prostate). Testing will begin in 2008 at several centers, including the Brady, under the direction of Roberto Pili, M.D., and Michael Carducci, M.D.

How Tasquinimod reached this point is a long story — featuring the tenacious, patient, and creative work of John Isaacs, Ph.D., professor of oncology and urology, who never gave up on this type of drug, which he has been studying for more than 15 years. “Developing a new drug is not easy,” he comments. “You’ve got to think of the long haul, and not allow yourself to become frustrated by short-term disappointments,” even if some of the roadblocks seem impassable. This journey started when Isaacs discovered that a chemical called linomide had the ability to block the development of tumor blood supply in animal models, and found that it profoundly inhibited the growth of prostate cancer.

Oral linomide entered clinical trials a decade ago, but it produced side effects that prevented its use in prostate cancer patients. Over the last five years, in a collaboration with Active Biotech Inc, a Swedish company, Isaacs and colleagues tested a series of chemical cousins of linomide, hoping to find a drug that produced the same good results without causing harm. Finally, a second-generation linomide compound, Tasquinimod, looked promising in animals,

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THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

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and proved safe in European tests of men with and without prostate cancer. "It's taken a while, but we believe the results will be worth the wait," says Isaacs.

Experimental Therapeutics: Freezing Cancer, Making it Sick, Slowing it Down



Ronald Rodriguez, left, and Shawn Lupold.

At the Brady, cutting-edge work is happening at every level of prostate cancer we can think of — prevention, treating early disease, containing disease that is likely to spread, and finally, attacking cancer that has indeed made the serious leap outside the prostate, to distant sites. The

scientists in the experimental therapeutics group at the Brady, led by Ron Rodriguez, M.D., Ph.D., are in the business of developing new weapons and — this is a tough call, in a scientific think tank abundant in creative investigators — what they're doing is among the Brady's most innovative work.

"The last year has been particularly exciting for the experimental therapeutics group," says Rodriguez. Among their weapons currently in development:

Adenoviral gene therapy "Simply put, we are attempting to give cancer a cold," says Shawn E. Lupold, Ph.D., the Virginia and Warren Schwerin Scholar, "by redirecting a common cold virus called adenovirus to selectively kill prostate cancer cells." One challenge Lupold and Rodriguez have faced is that the androgen receptor, a gene often active in prostate cancer, "actually inhibits our therapeutic viruses, making them less effective," Lupold adds. The team came up with a clever molecular engineering strategy to reverse this — "so the virus can *team up* with the androgen receptor, rather than compete with it." These results were published in *Molecular Therapy*.

Another challenge has been to make the adenovirus more effective. As soon as a virus — even a helpful one — is detected in the body, the immune system begins fighting it. Thus, the best hope is for the virus to be so

targeted that it zooms right to the desired cells (in this case, prostate cancer, wherever it may be hiding throughout the body). The quicker the virus starts to work, the longer the cancer-killing window before the immune system finds the virus and shuts it down. Lupold and Rodriguez have been developing new tools to improve the adenovirus's ability to single out metastatic prostate cancer. "More than 90 percent of

"Simply put, we are trying to give cancer a cold."

adenoviruses are absorbed by the liver and spleen soon after they enter the blood stream," notes Rodriguez, "leaving only a fraction of the desired therapeutic dose for the cancer cells." The current state-of-the-art methods for altering adenovirus are slow and cumbersome, he continues. "But recently, we have made significant inroads by generating a new technology, which allows us to make thousands or even millions of different viruses with various targeting features at the same time." Using a technique known as "biopanning," the scientists can screen these adenoviral libraries to identify viruses with the best ability to target and infect prostate cancer cells, but avoid other cell types, such as liver cells.

New use for an old drug Valproic acid is an anti-seizure drug that has been around for years. But recently, Rodriguez has discovered that valproic acid suppresses more than seizures — it also slows down the growth of prostate cancer. Even better, this happens at doses that have long been proven safe. "We believe that valproic acid causes a subset of cells to become less aggressive," says Rodriguez. "In men who are already on hormonal therapy, this may delay the progression to androgen-independent disease." Rodriguez and colleagues are testing valproic acid in a limited clinical trial, in men with a rise in PSA after hormonal therapy.

Not cryotherapy—immunocryotherapy "Cryo" means freezing. "Immunotherapy" involves strengthening the immune system, to help the body fight off cancer. Put them together, and you have immunocryotherapy. Why freeze prostate cancer? "So far, tumor vaccine therapy (immunizing the body against its own cancer) has met with very limited success," explains Rodriguez. "We believe that one reason for this is that some cancers

promote tolerance. Breaking tolerance has therefore become the 'Holy Grail' of cancer immunotherapeutics." Rodriguez and colleagues including Moshe Levy, M.D., have been working on this for two years. They have developed a protocol for kidney cancer, and hope to start clinical trials soon for men with prostate cancer. "We freeze the prostate cancer at one site, while simultaneously stimulating the immune system with agents thought to inhibit the cells responsible for tolerance. Then we monitor the body's anti-tumor immune response by studying prostate cancer at other sites that we have not treated." This clinical trial will be open to men who have progressive, metastatic prostate cancer and still have an intact prostate.

Rethinking the Very Well-Done Steak



William G. Nelson

Scientist William G. Nelson, M.D., Ph.D., was among the first to discover that eating a lot of fried or otherwise charred meat — particularly red meat — can lead to prostate cancer. Over the last few years, he's been learning more about why this happens, and

his work dovetails beautifully with that of Angelo De Marzo, Elizabeth Platz, and other Brady scientists who are investigating the roles of PIA (proliferative inflammatory atrophy, a precursor to cancer — see story on Page 6) and inflammation in causing prostate cancer.

"The overcooking of meats is now well known to trigger the formation of cancer-causing substances," says Nelson. One of these, called PhIP, causes prostate cancer in rats that eat it. Just as burning wood causes ashes to form, charring meat causes PhIP to form; when you eat meat that's too well-done, you eat PhIP, too. "Over the past year, our new findings have suggested that PhIP consumption may lead to prostate cancer in rats by first causing mutations, and then causing an inflammatory reaction. We suspect that the inflammatory reaction is what drives the mutated cells to become cancerous." In prostate tissue samples studied under the microscope, this mutation and the added stress of inflammation lead to

PIA. Inflammation is the critical factor, and it isn't just caused by food; it can have many causes, including some infections, and other dietary carcinogens. "The implications of this

PhIP causes prostate cancer in rats that eat it. Just as burning wood causes ashes to form, charring meat causes PhIP to form; when you eat meat that's too well-done, you eat PhIP, too.

are really exciting — that anti-inflammatory agents may help prevent prostate cancer." The work of Nelson and colleagues was recently published in *Cancer Research*, and in the *Nature Review of Cancer*.

Infections, Race, and Prostate Cancer

You can't "catch" prostate cancer like a cold. So why is epidemiologist Elizabeth A. Platz, Sc.D., so interested in the fate of men who have sexually transmitted diseases and other infections? Because these infections cause chronic infection in the prostate, and this, in turn, causes chronic inflammation — which can lead to prostate cancer.

In a collaboration with a scientist from the Department of Defense, which has a large medical and blood specimen repository, Siobhan Sutcliffe, Ph.D., the postdoctoral fellow leading the project, and Platz, her mentor, will be studying men who have infections, including sexually transmitted infections, to see if there is any short- or long-term change in PSA.

This study is timely and relevant, the investigators say, because chronic inflammation and cell damage are believed to contribute to the development of prostate cancer precursor lesions — and because young men with elevated PSA concentrations have been found to have a higher risk of prostate cancer later in life. Because of this, it is crucial to address the mechanisms of early prostate cancer formation and PSA elevation, and determine the extent to which infections play a role.

In another study, led by German scientist Sabine Rohrmann, who was a postdoctoral

fellow working with Platz, Platz and colleagues have been looking at hormonal differences and race. "One of our long-standing research interests is identifying factors that explain the notably higher risk of prostate cancer in African American men," Platz says. Several years ago, using data from the Health Professionals Follow-Up Study, Platz found that black men had an 80 percent higher incidence of prostate cancer. This work was published in the *Journal of the National Cancer Institute*. Although some early studies had shown higher levels of blood testosterone in black men than in white men, Platz felt that these studies were not as complete as they could be, and that not enough men had been studied.

In this recent study, published in the *Journal of Clinical Endocrinology & Metabolism*, Platz and colleagues looked at blood levels of the hormones testosterone, estradiol, and a protein called sex hormone binding globulin in more than 1,400 men. The men were participants in the Third National Health and Nutrition Examination Survey. "We took into account factors that may influence hormone concentrations, including age, body fat, physical activity, and whether or not the men drank alcohol or smoked," Platz says.

The results turned up something new: The researchers did not find very significant differences in testosterone levels between black and white men. But black men had more estradiol. More studies are needed, Platz says, looking at estradiol as well as testosterone, in relation to prostate cancer and other diseases where race clearly plays a role.

A Protein Found Only in the Very Worst Prostate Cancers May Lead to New Ways to Treat Them

What happens in cancer is, in many ways, very similar to what happens to our bodies before we're ever born, when our cells are dividing rapidly and we're growing like crazy. Thus, pathologist David Berman, M.D., Ph.D., has spent the last several years trying to understand how cancer spreads by looking back in time, to those embryonic days.

Just as plants and animals were different in prehistoric time — think dinosaurs and lots of giant ferns — in our own far less distant past, our cells were different, too. Before birth is the prime time for stem cells

— tiny chameleons, known for their ability to change and assume the properties of other kinds of cells.

Nestin is a structural protein — part of the scaffolding that cells use to keep their shape — that's widespread in embryos, but not often found in adult cells. Scientists have long used it as a marker of neural stem cells, hibernating cells that wake up in time of need and zoom to the rescue, to replace lost or injured cells. "We still don't exactly understand Nestin's function in stem cells," says Berman, the R. Christian B. Evensen Scholar. But he and fellow pathologist Wolfram Kleeberger, M.D., knew that Nestin was produced by cancer cells, and decided to learn more about it.

Just as plants and animals were different in prehistoric time — think dinosaurs and lots of giant ferns — in our own far less distant past, our cells were different, too.

They looked at cells cultured from several different types of cancer, and found Nestin most often in prostate cancer cell lines. This is significant, because the cultured prostate cells that researchers use are hardened characters — absolute degenerates compared to the far easier-to-cure cancer cells found in most men who are diagnosed today with regular screening for prostate cancer. So advanced are most of these cells that they have passed the crucial point of being able to grow even without the male hormone, testosterone.

And there, in the midst of these worst-case prostate cancer cells, was Nestin. Kleeberger then broadened the search, looking for the protein in tissue samples from a variety of men — ranging from those who were cured by surgery to those who died of widespread metastatic disease. These samples were collected and organized by pathologists G. Steven Bova, Mehshati Herawi, Ai-Ying Chuang, and Jonathan Epstein, and urologist Matthew Nielsen. The team paid particular attention to whether men had been treated with hormone blockade, the most commonly used drug treatment for prostate cancer.

"What we found was surprising and intriguing," says Berman. "Nestin was present exclusively in the most deadly cancers — the ones that had metastasized and failed

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hormone blockade.” Next, he and Kleeberger designed laboratory experiments using a new technology called “short hairpin RNA,” which allowed them to shut down the Nestin gene in prostate cancer. Kleeberger found that silencing Nestin “dramatically reduced the ability of cancer cells to migrate and invade in laboratory cultures, and to metastasize in mice,” Berman continues.

Then they asked a new question: What was it that stimulated cancer cells to start making Nestin in the first place? Kleeberger, looking at cells from a man with testosterone-dependent, metastatic prostate cancer, found that the simple act of *depriving the cells of testosterone* — which is what happens during hormonal therapy for prostate cancer — activated the Nestin gene.

Berman sees these results as both bad news and good news for men with advanced prostate cancer. “The bad news is the startling suggestion that testosterone blockade might actually speed up metastasis by inducing Nestin production,” he says. However, he is quick to caution that more studies are needed to explore this. “The good news is that Nestin now gives us a foothold for tackling metastasis in a new way.” Berman expects that further studies will reveal a whole group of proteins that work alongside Nestin to help cancers spread, and that these would be “prime targets for new or existing drugs that would block metastasis. The fact that Nestin production is limited to cancers and to a few rare cell types in the body suggests great possibilities for this approach.”

Waking Up the Immune System’s Sleeping Soldiers



Charles Drake

Imagine there’s an art museum, and the guard on duty keeps dozing off. Art thieves come in. They step over the guard, who is now snoring, and steal a valuable painting. The guard had a gun, an alarm, and other anti-theft devices at his disposal, but never used them. All that untapped firepower was wasted.

In our bodies, certain white blood cells called lymphocytes are a lot like that guard. They have a great ability to attack and destroy enemies, including bacteria and cancer cells. But when the enemy is prostate cancer, for some reason, these lymphocytes — designed to destroy these cancer cells — don’t do their job.

White blood cells called lymphocytes have a great ability to attack and destroy enemies. But when the enemy is prostate cancer, for some reason, they don’t work.

Oncologist Charles Drake, M.D., Ph.D., the Phyllis and Brian L. Harvey Scholar, has figured out why. “Using a mouse model, we found a protein on the surface of some of these cells that might help explain this lack of function,” he says. This protein is called LAG-3, and “by blocking it, we were able to help lymphocytes move into prostate glands.” Basically, Drake and colleagues put the sleeping soldiers back into action, so they could help fight off prostate cancer. In other experiments, they combined LAG-3 blocking with a specific vaccine against prostate cancer, and this also jump-started the immune system, “causing lymphocytes to move into the prostate gland and destroy their target cells.” This work was published in the *Journal of Clinical Investigation*. Drake hopes to test this strategy in men with prostate cancer, “but first, we need to make a human version of the LAG-3 blocking agent,” called a monoclonal antibody. He and colleagues have teamed up with a leading biotechnology company to do this.

Nerve-Protecting Drugs for Men After Radical Prostatectomy

Arthur L. Burnett, M.D., an excellent surgeon and scientist, wants more for his radical prostatectomy patients. “Even in the best of surgical hands, the nerves coursing around the prostate, which regulate penile erection, can be traumatized during surgery,” he says. Burnett has spent years in the laboratory as well as the operating room, learning more



Arthur L. Burnett

about how these extremely delicate nerves are injured, and seeking new ways to protect them.

Erectile dysfunction after radical prostatectomy remains a major complication of the surgery worldwide, he says. “Many men experience a delay or incomplete recovery of penile erection, even when anatomical nerve-sparing radical prostatectomy is performed.”

Burnett sought to address this problem by carrying out a clinical trial investigating the potential benefit of an oral drug that he helped develop. The drug, called GPII485, has the potential to protect nerves, and help them recover their function more quickly after surgical trauma. The trial was carried out between 2004 and 2006, and men were followed up to a year afterward. About 200 patients from 22 clinical centers participated in the study; men were randomly assigned either to receive the drug or a placebo. In the final analysis, recovery of erections after radical prostatectomy was similar for men who took either the pills or the placebo every day for six months. The treatment was well tolerated, and caused no major side effects. Although Burnett had hoped for more dramatic results, he remains hopeful. “This initial study, the first of its kind, did not prove that the treatment was effective, but it did suggest the feasibility of using ‘neuromodulatory’ drugs for this purpose,” he says. “We remain extremely active in this drug development research effort to facilitate the return of erectile function following radical prostatectomy.” He is now studying the ability of another promising drug, erythropoietin, to do this.

Targeting Metastasis Precursor Cells

Even before there is any evidence of an anthill, there are ants, scurrying around, laying the groundwork. Similarly, for many years before there are any visible signs that prostate cancer has spread to a distant site and started to grow, there are tumor cells, bustling around the bloodstream or bone marrow, doing their work silently. And this,

believes Jun Luo, Ph.D., assistant professor of urology, is the best time to take action against metastasis.

“We call them ‘metastasis precursor cells,’” says Luo, the Phyllis and Brian L. Harvey Scholar, “and they are essential for the development of distant metastasis. Because they are readily accessible to drugs, we believe that if we can target these cells in men at risk of recurrence, or at the time of PSA recurrence, then we can delay or even prevent clinical metastasis.”

Luo has a novel target, called AGR2 (Anterior Gradient 2), a molecule that helps these metastasis precursor cells adapt and survive in foreign conditions (away from the original prostate tumor). It seems to bear the quality of being tenacious. “Its counterpart in the frog embryo is apparently involved in the formation of a structure the embryos use to attach to the rocks, before they become tadpoles,” notes Luo. In humans, AGR2 has not been studied much; however, recent evidence suggests that it is highly expressed in prostate cancer, and more importantly, in prostate cancer that has metastasized. “Animal studies have shown that adding the AGR2 gene to non-metastatic cancer cells turned them into cells that metastasized.”

Luo has made AGR2-blocking antibodies, and is using them on prostate cancer cells in mice. (The cancer cells are stained with a fluorescent protein, which makes them easier to track.) “It is well known that cancer cells don’t do well when they go afloat in the blood,” says Luo. “They are vulnerable and often die, because they do not have the support of their neighboring cancer cells in their original home — the prostate. If AGR2, as we suspect, is essential for these metastasis precursor cells to survive in the harsh new environment, then drugs that block AGR2 may one day be used to prevent and cure prostate cancer metastasis.”

Help For Men Who Need Repeat Biopsies

There is no question that our ability to detect prostate cancer is better than ever. But ask a man who has had an unnecessary biopsy — or two, or three, which probably means at least 36 needle sticks in his prostate, a dozen with each biopsy — and he will tell you that there is still room for improvement.

“Today, the decision to biopsy is driven by abnormal findings on a digital rectal exam, or a PSA test,” says scientist Alan K. Meeker, Ph.D. Unfortunately, both of these can be abnormal even if a man doesn’t have prostate cancer; in scientific terms, they are “lacking in specificity.”

Ask a man who has had an unnecessary biopsy — or three, which probably means at least 36 needle sticks in his prostate — and he’ll tell you that there is still room for improvement.

Worse, although it may feel extremely thorough to the man who undergoes it, “the biopsy only samples a small portion of the prostate,” Meeker adds, “and it can miss cancer.” About one-third of men who turn out to have prostate cancer have a falsely negative result on their first biopsy. “On the other hand, many men who have a negative biopsy truly do not have prostate cancer, despite suspicious physical exam or PSA results.” Thus the biopsy dilemma: “Currently, we lack effective means for distinguishing patients who are at high risk for harboring cancer from those who are unlikely to have it.” Which brings us back to the poor man at the beginning of this story, who has had one or more repeat biopsies. With every procedure, he and his family experience anxiety, wondering if there will be cancer this time — and if so, what should he do — or if it will be another negative result, with still another biopsy looming on the horizon in the near future.

Meeker, with colleagues Christian Pavlovich and Kazutoshi Fujita, is working on a simple urine test that may help. “Prostate cancer cells can be shed into the urine,” he says, “and detecting them would provide a convenient, noninvasive means of improving diagnosis.” In fact, scientists attempted such a test decades ago, but were unsuccessful. Today’s technology — with the discovery of new molecular markers for prostate cancer, and new staining techniques so they can be seen under the microscope — is much better.

The scientists’ plan is to find the most promising markers for cell staining, to



Alan K. Meeker

“combine as many useful markers as possible to provide a robust method for cancer cell identification,” and to test them in the lab with human urine samples, Meeker explains. Once he and colleagues have determined the best way to

do the testing, they will study urine samples collected in the clinic, from men with suspected prostate cancer who are undergoing their first biopsy. Their results will then be compared with the pathology results from this and any subsequent biopsies.

“If we are successful, this noninvasive test will provide valuable additional information to help these men and their doctors,” says Meeker.

When Two Bad Genes Get Together...

An unpleasant genetic fusion happens in prostate cancer. One gene, a nasty, “cancer-inducing” character called ERG1, which is active in prostate cancer, joins up with a gene called TMPRSS2, which is controlled by androgens (male hormones). “This fusion causes the cancer-inducing gene to be constantly turned on by the gene that is normally driven by androgens,” says pathologist George Netto, M.D. “It’s estimated that up to two-thirds of men with prostate cancer may have this fusion, making it by far the most common genetic marker in human cancer.”

Highly dangerous, and very common — two things, Netto believes, that make this genetic duo worth exploring.

Highly dangerous, and very common — two things, Netto believes, that make this genetic duo worth exploring. He is particularly interested in harnessing these fused genes as a way not only to detect which men are at risk of having a return of cancer after treatment for localized disease, but as a potential target for treatment.

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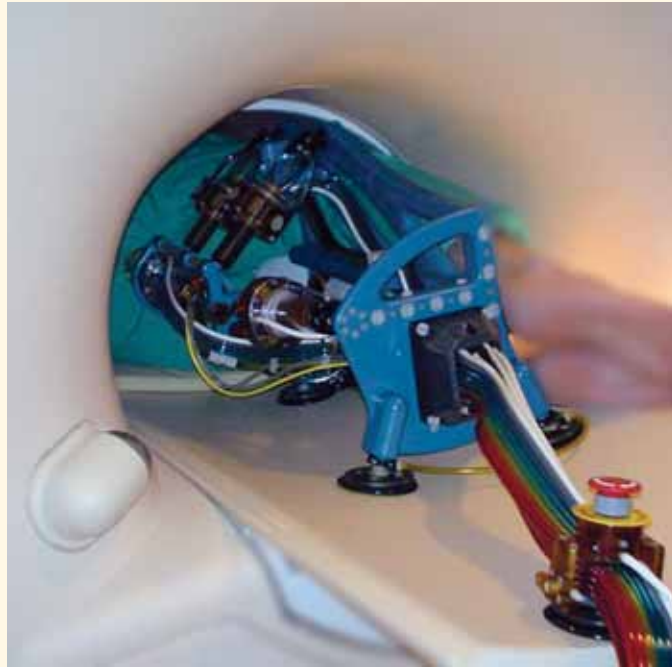
Using a fluorescent technology called FISH (fluorescence in situ hybridization) and another technology called tissue microarrays, which allows hundreds of microscopic tissue samples to be shown on a single glass slide, Netto can look for this fusion in normal and cancerous prostate tissue of hundreds of men with and without prostate cancer. “Studying this fusion may highlight a new target of therapy in prostate cancer patients, in the current era of emerging ‘smart drugs,’ such as those designed specifically to target the HER2 gene in breast cancer patients,” he says.

Robot Uses MRI to Target the Prostate

Meet the MrBot. It’s a robot (not pronounced, as you might think, “Mr. Bot”) designed for making needle biopsies or implanting radiation seeds in the prostate, and it’s done using MRI, not ultrasound. “Needle access of the prostate is routinely performed under ultrasound guidance,” explains scientist Dan Stoianovici, Ph.D., the R. Christian B. Evensen Scholar, “because the ultrasound is widely accessible and economical. But it fails to show exact spots of prostate cancer, and it can’t tell us the extent of the disease.”

Because the doctor’s ability to see what’s happening is not terribly good, Stoianovici says, “prostate biopsies are performed blindly but systematically. Too often, however, biopsy results are false negatives” — and this, he adds, is most likely because the needles miss the spots of tumor, which in the prostate are notoriously hard to predict. “Biopsies are taken from the most probable locations of the gland, where cancer is known to reside according to statistics.” But a needle is not stuck in a particular part of tissue because the urologist sees something suspicious there. “Simply speaking, your biopsy is taken based on someone else’s data, and the needle is placed where a cancer is most likely to be.”

The same image-guiding problem also affects brachytherapy and thermal therapies. “Misplaced probes create recurrence or side effects,” he says. “If biopsies could be more precisely guided, based on cancer imaging” — what can actually be seen — “not only could this increase early detection rates, but



The MrBot works in conjunction with an MRI scanner, and is remotely controlled. “It represents a major technological breakthrough,” says its inventor, Dan Stoianovici, “because no other instrument could precisely, safely, and remotely operate in the high magnetic field of the MRI without interfering with the image.” Early tests have shown promising results, and the robot is nearing clinical trials.

it could provide a way of correlating cancer images with pathology for generating a working map of the disease.”

The MrBot is specifically designed for the prostate. By changing the needle drivers, the robot can be used for different purposes — biopsy, brachytherapy, cryotherapy, or therapeutic injections. Stoianovici is preparing the robot for clinical trials, and he is excited about the possibilities — not only of improving biopsies, but of targeting treatment exactly where the tumor is known, not just suspected, to be.

DNA Microchips: Looking at the Big Picture, for Tiny Clues to Prostate Cancer

Little things matter when it comes to cancer. Very little things — tiny changes to the genes, caused by risk factors in the environment and in a man’s genetic makeup. Some of these are called “epigenetic” changes; they don’t alter the gene’s sequence, but they affect what the gene *does* — making it ineffective, or silencing it altogether. But because the gene itself is basically unchanged, there is hope that what has been locked or otherwise put out of commission can be unlocked, and the damage undone, says Srinivasan

Yegnasubramanian, M.D., Ph.D., the Dr. and Mrs. Peter S. Bing Scholar. He believes that “with the right drug intervention, we may be able to reverse epigenetic alterations.”

Yegnasubramanian’s plan is to tackle these very small changes on a bigger-than-ever scale. “Comprehensively identifying the genetic and epigenetic changes in prostate cancer can not only help us find new targets for prostate cancer diagnosis and therapy, but will also improve our understanding of the pathways involved in cancer development and progression,” he says. “However, so far, because of a lack of appropriate technology, these alterations have largely been identified one at a time, through studies that are mostly limited to well-known genes.” Yegnasubramanian has developed innovative methods to harness the latest technological advancements using “DNA microchips.” And with these, he says, “we can identify genetic and epigenetic changes related to prostate cancer across the entire human genome, in well-known and uncharted genes.”

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with posterior tumors.” Anterior tumors were also more likely to be confined to the prostate, and less likely to involve the lymph nodes than posterior tumors. “The good news is that regardless of tumor location, nearly half of these men with a PSA level higher than 20, treated with radical prostatectomy alone, had no evidence of PSA recurrence five years later,” Gonzalgo says.

“Radical prostatectomy can benefit a large number of men with high PSA levels,” continues Gonzalgo. He adds that men who have a higher risk of having a return of cancer after surgery may benefit from additional treatments such as radiation, hormonal therapy, or chemotherapy. Gonzalgo is working with medical oncologist Mario Eisenberger, M.D., to enroll patients in a clinical trial investigating adjuvant therapy for patients with aggressive prostate cancer.

Brachytherapy Gets More Precise with 3-D Technology

Radiation oncologist Danny Y. Song, M.D., is aiming for utmost precision — making brachytherapy (implanting radioactive seeds to treat prostate cancer) as accurate and effective as possible. Some of the challenges during the procedure itself include tissue swelling and slight movement of the prostate, as the seeds are placed and the needle used to place them is removed. “Unfortunately, current brachytherapy techniques do not allow us to identify these slight but important variations until after the procedure, and this gives us little opportunity to take corrective action,” he says.

To address this, Song and colleagues have developed a “real-time” system of registered ultrasound and fluoroscopy that allows the seeds to be seen inside the prostate, in 3-D, during the procedure. Using standard x-ray images taken from multiple directions, the computer system makes a three-dimensional map showing where the seeds are, Song explains. “Then we can modify our treatment plan, or add seeds before the procedure is completed.” So far, Song and colleagues have tested the new system on six patients in a

pilot study. “We took x-ray images and calculated seed positions three times during each treatment, and modified subsequent seed positions as needed. The x-ray system identified areas of underdosing, and we added extra seeds (between three and 10) to the original treatment plan. Afterward, CT scans showed excellent coverage of the prostate, as well as good sparing of the urethra and rectum.” After the pilot study is completed, Song plans to begin a Phase II clinical trial to compare the results of this three-dimensional system with standard brachytherapy.

PSA Testing: Rate of Change is Better than a Magic Number



H. Ballentine Carter

Urologist H. Ballentine Carter, M.D., is startled by the results of his own research. Carter and Patrick C. Walsh, M.D., together with investigators at the Baltimore Longitudinal Study of Aging (BLSA), pioneered the idea of PSA velocity — the rate at which PSA increases over time — as a way of predicting whether a man has prostate cancer.

For as long as PSA has been in widespread use as an early detection tool for prostate cancer, Carter, The Peter Jay Sharp Foundation Scholar, has worried about the numbers. Nearly two decades ago, he cautioned (and we reported it, in *Prostate Cancer Update*, the predecessor of *Discovery*) that there were risks to locking into specific cutoff numbers. Back then, the general belief was that a prostate biopsy should be performed if a man’s PSA reached the “magic number” of 4 ng/ml.

But there is no such complacency anymore. “We now know that there is virtually no PSA below which a man can be reassured that a lethal prostate cancer does not exist,” Carter says. “Now, the problem of where to set the bar for biopsy is that there should not be one absolute bar.” Instead, Carter believes, “it makes much more sense to pay attention to what *changes in PSA* are telling us about the

presence of a harmful prostate cancer.”

Carter and Walsh, working with colleagues at the BLSA, discovered PSA velocity in 1992. They found that in men with PSA levels between 4 and 10, a PSA velocity above 0.75ng/ml per year was a more accurate predictor of prostate cancer than any absolute level of PSA. Recently, recognizing that about 5 percent of men with PSA levels considered low — between 2 and 3 — have aggressive and potentially lethal cancers, Carter worked with colleagues at the BLSA in hopes of finding more definitive information.

The BLSA is one of the largest studies of aging in the world. Since 1958, scientists have collected and stored blood samples, at two-year-intervals, of approximately 1,500 men. Using these stored blood samples, scientists have measured PSA over decades in men who did and did not develop prostate cancer, and in men who had aggressive and mild cancer. Together with investigators at the BLSA and at the Brady, Carter used PSA velocity to help determine the probability of dying of prostate cancer over three decades. “We found that when PSA levels were below 4 — about 10 to 15 years before men were diagnosed with their prostate cancer — a PSA velocity above 0.35 ng/ml per year was associated with a five-times greater risk of prostate cancer death when compared to a PSA velocity of less than 0.35ng/ml per year.” For example, over a 30-year period, about half of the men with a yearly PSA velocity above 0.35ng/ml died of prostate cancer, compared to only 8 percent of men with a yearly PSA velocity lower than 0.35ng/ml. “I am not aware of another test that can predict the likelihood of prostate cancer death with this accuracy prior to the diagnosis of the disease,” says Carter. He cautions that for the most accurate results using PSA velocity, the interval between tests should be at least six months, and testing should span a period of at least 18 months.

Given this discovery, Carter recommends that *all men* — whether or not they have a family history of prostate cancer, or are at increased risk of developing the disease — should have a baseline PSA test at age 40 — 10 years earlier than many doctors recommend. Then, depending on their baseline level, men should be tested again several times in their forties. “These early PSA tests can be used later, when a man reaches his fifties and sixties, to determine PSA velocity and the likelihood that a lethal prostate cancer is present,” he says.

RECENT HONORS AND AWARDS

Mohamad Allaf, M.D., was named an American Urological Association Foundation Research Scholar, for efforts in the field of sexual medicine.

David Berman, M.D., Ph.D., was the sixth recipient of the annual Jean D. Wilson Distinguished Alumnus Award from the Medical Scientist Training Program at the University of Texas Southwestern School of Medicine.

Arthur Burnett, M.D., who also received a research award from the Patrick C. Walsh Prostate Cancer Research Fund, received the Zorgniotti-Newman Prize, for Best Paper on Clinical Research in Sexual Medicine, at the 12th World Congress of the International Society for Sexual Medicine. He also has been named Co-Editor-in-Chief of the *Journal of Andrology*.

Michael Carducci, M.D., and **Sushant Kachhap**, Ph.D., received a Prostate Cancer Foundation Competitive Research Award for their work on "Determining the Efficacy of Upregulating NDRG1 in Inhibiting Metastasis of Prostate Cancer Cells." Carducci also received the Department of Urology's Teaching Excellence Award.

Daniel W. Chan, Ph.D., received the Outstanding Leadership Award from the National Cancer Institute, for building a strong translational research program on the application of biomarkers in cancer detection and prevention.

Theodore DeWeese, M.D., was appointed Chairman of the Scientific Council of the Radiation Effects Research Foundation (RERF). The RERF, supported by the governments of Japan and the United States, is focused on the study of health effects of radiation in the survivors of the atomic bombings of Hiroshima and Nagasaki, and dedicated to understanding the health effects of radiation for the benefit of mankind.

Jonathan Epstein, M.D., served as President of the International Society of Urological Pathology and was on the Council (the top governing body) of the United States and Canadian Academy of Pathology.

Misop Han, M.D., was named the Dennis W. Jahnigen Career Development Scholar by the American Geriatrics Society. He also

received two research grants from Johns Hopkins Hospital; one, part of the Prostate Cancer SPORE Pilot Project, is to study the effect of antibiotic therapy on PSA variability; the other is the David H. Koch Award, to identify potential biomarkers to stratify a man's risk for lethal prostate cancer.

John Isaacs, Ph.D., who received a research award from the Patrick C. Walsh Prostate Cancer Research Fund, also received a Prostate Cancer Foundation Award.

In addition to receiving a Patrick C. Walsh Prostate Cancer Research Award (see Page 8), **Dan Stoianovici**, Ph.D., has received a Research Award from the Prostate Cancer Foundation, and the David H. Koch Award for Treatments and Cure of Recurrent Prostate Cancer. He also received the Best Paper Award of the Engineering and Urology Society, for "MRI-Guided Robot for Automated Prostate Brachytherapy." Stoianovici is the R. Christian B. Evensen Scholar.

Patrick C. Walsh, M.D., was the co-recipient of the prestigious 2007 King Faisal International Prize in Medicine, was honored as the 2007 National Physician of the Year for Clinical Excellence by *America's Top Doctors*. He also received the Johns Hopkins University Diversity Recognition Award, and was made an Honorary member of the American Urological Association.



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