PROSTATE CANCER
DISCOVERY
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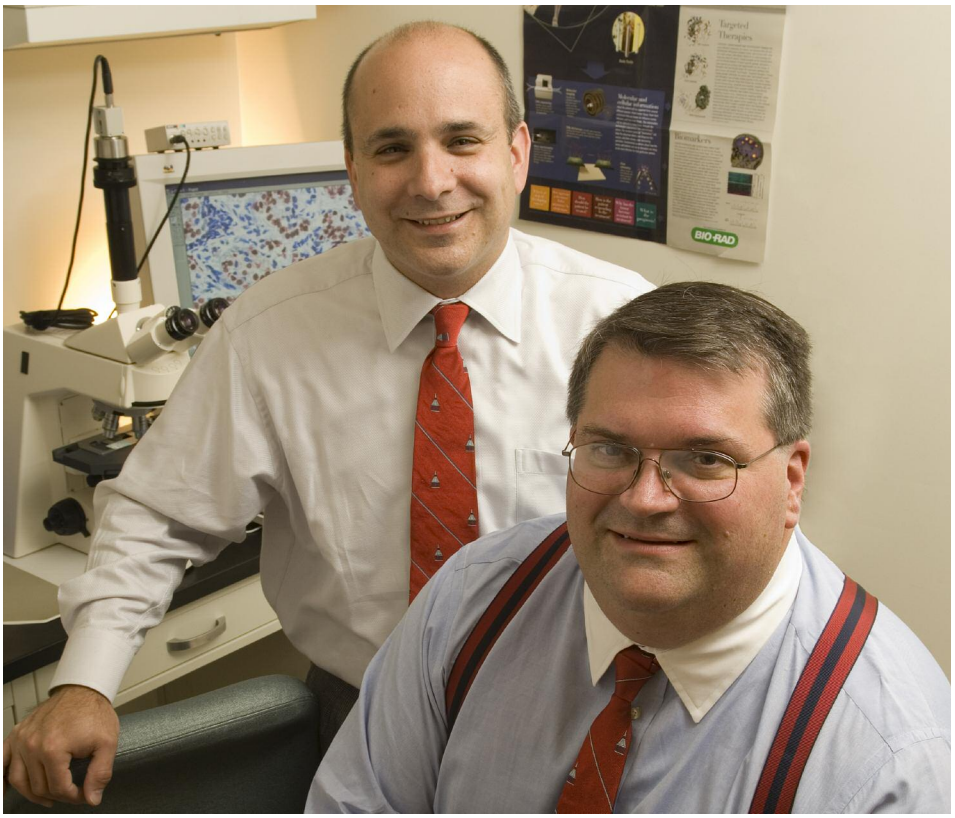

Getzenberg, left, and Partin. The EPCA-2 test can even tell organ-confined cancer from cancer that has spread beyond the prostate.

Breakthrough: New Prostate Cancer Test is More Specific than PSA

As good as PSA is in detecting prostate cancer, there's a lot of room for improvement. "Nobody would call PSA a perfect test," says Robert H. Getzenberg, Ph.D., the Brady's Research Director, and the Donald S. Coffey Professor of Urology. For one thing, "PSA is not specific for prostate cancer. It is often elevated in men with BPH and prostatitis," inflammation of the prostate. Another flaw: "It tells us that a man has cancer, but it doesn't tell us much about what kind of cancer we're dealing with," notes Alan W. Partin, M.D., Ph.D., Director of Urology. "Is it aggressive? Is it a milder, slower-growing cancer? These are very important things a man with prostate cancer would really like to know."

Millions of American men – more than 25 million, says Getzenberg – are waiting from biopsy to biopsy, playing a frustrating form of medical roulette, just looking for an answer: Their PSA test is higher than it should be, but despite many needle sticks, no cancer has been found on biopsy. So why isn't the PSA level lower? The idea of cancer growing, but being repeatedly missed, can be very troubling for these men. For years, Hopkins researchers have been working to find a better, more specific "crystal ball" for prostate cancer.

Now a research team, led by Getzenberg, has found one, called EPCA-2 (early prostate cancer antigen-2), that works in a simple blood test. Their *[continued on page 2]*

What Matters Most to Us

Our driving focus is a simple one — moving our research discoveries to the patient's bedside, and turning our clinical observations into problems to be solved in the laboratory. We used to call this "bench-to-bedside" investigation. Now we call it "translational research."

This issue of *Discovery* shows you some of our translational research in action.

For example:

• *A better cancer predictor:* A new blood test, developed in the laboratory of Robert H. Getzenberg, our Research Director, may not only be better than the PSA test; it also has the potential to help predict how aggressive a man's prostate cancer is. We are very excited about this new blood test, called EPCA-2 (Early Prostate Cancer Antigen), and the great promise it has already shown.

• *Expectant management with curative intent:* Years of research by *[continued on page 2]*

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H. Ballentine Carter have helped define an entire segment of men with prostate cancer — men with low-volume, low-risk disease. Now, Drs. Carter and Christopher Warlick, in a study recently reported in the *Journal of the National Cancer Institute*, have shown that not all of these men need to rush into treatment right away. In fact, when these men are carefully followed, delaying prostate cancer surgery does not appear to compromise their ability to be cured.

• *The "Lance Armstrong" effect:* An intriguing hypothesis, recently published in the *Journal of the American Medical Association* (*JAMA*) by three of our top investigators here at the Brady — Don Coffey, Robert Getzenberg, and Ted DeWeese — suggests that heat treatment may soon make prostate cancer cells more susceptible to treatments that we already have.

• *Genes and prostate cancer:* It is has become very clear, primarily through research performed here by Bill Isaacs and Patrick Walsh, that there are many inherited components that, along with environmental factors, largely determine which men will develop prostate cancer. It is also clear that no single gene or piece of DNA is responsible for this inherited risk. For the first time, Dr. Isaacs' group has demonstrated systematically the identification of many genes which may increase the risk for prostate cancer and could potentially be inherited along family lines. We are extremely excited about the unprecedented insight into the genetic mechanisms responsible for prostate cancer that these efforts will yield.

So much is happening here, every day — much more than we can cover in just these few pages. As always, all of our research is dedicated to you, our patients, and your families.

Alan W. Partin, M.D., Ph.D.
Urologist-In-Chief

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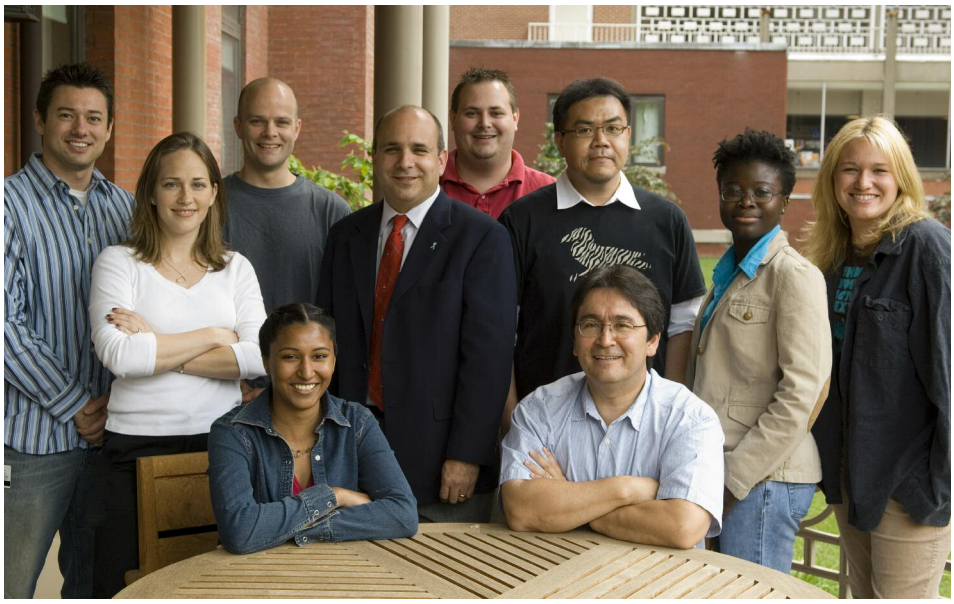

The EPCA-2 test involved years of work and many dedicated scientists, including (Back row): Grant Cannon, Timothy McMurray, David (Brandy) Yeater. (Middle row) Katherine Bright, Robert Getzenberg, Eddy Leman, Elizabeth Dada, Megan Gurganus. (Front row) Simran Jandu, Donald Vindivich.

[continued from page 1]

discovery comes after decades of work by Getzenberg's predecessor, Donald S. Coffey, Ph.D., who noticed something striking about the nuclei of cancer cells: They're funny-looking; they're misshapen. Coffey and Getzenberg then characterized the structural proteins that caused this mess within cancer cells; they're in a part of the nucleus called the nuclear matrix. One of these is EPCA-2. In a series of exciting experiments, using a technique called "focused proteomics," Getzenberg and colleagues were able to show that EPCA-2 was far more specific than any other marker identified so far — even PSA — in distinguishing men with prostate cancer from other men. Further, this test was able to tell which men had organ-confined cancer, and which men had cancer that had spread beyond the prostate.

"Our goal has been to try to identify at the molecular level what the pathologist sees under the microscope," Getzenberg explains, and so far, EPCA-2 has performed like a champ. In tests of more than 600 men, "even in men where PSA has failed, EPCA-2 is almost one hundred percent specific for prostate cancer, and picks up greater than 90 percent of the prostate cancer patients." More good news: EPCA-2 does not appear to be elevated in conditions like BPH and prostatitis. And, EPCA-2 can detect the presence of prostate cancer in men with normal PSA levels. EPCA-2 may even be able to distinguish the deadliest cancers, which quickly develop the ability to spread beyond the prostate, from those that are less aggressive. More tests are needed, and EPCA-2 will soon be studied in a large, multicenter trial, with the goal of obtaining FDA approval for its use.

Many Hopkins scientists were involved in this groundbreaking work, including Partin; Lori Sokoll and Daniel Chan, two internationally recognized experts in the development of cancer biomarkers; and Bruce Trock, a leading epidemiologist and biostatistician in the field of prostate cancer biomarkers. Much of the work on this project was carried out by a young investigator in Getzenberg's laboratory, Eddy Leman, Ph.D., working with Grant Cannon.

"These findings are remarkable, and if they hold up when the marker is tested in a larger group of prostate cancer patients, they may revolutionize the approach to screening for prostate cancer," notes Patrick C. Walsh, M.D. At the very least, adds Partin, "EPCA-2 could help determine which men with abnormal PSA levels have prostate cancer. But it's possible that EPCA-2 may even replace PSA one day as the screening test of choice."

The Search for Better Tests

Why are we so interested in finding new tests for prostate cancer? There are lots of reasons — nearly 35 million of them. That's the number of men — just in the United States — who have a PSA test each year. Of these men, "well over a million undergo a costly, potentially painful, and most certainly anxiety-provoking biopsy," comments Alan W. Partin, M.D., Ph.D., the David Hall McConnell Professor and Director of Urology. "And yet, only 250,000 of these men are found to have prostate cancer. This means that most men undergoing a prostate biopsy do not have cancer."

The PSA test has what scientists call "good sensitivity" — it is good at detecting cancer. But it has "poor specificity" — many men have to get a biopsy before cancer can be ruled out. More numbers: "With all of these men who have no cancer found, yet who have an abnormal PSA test, it's estimated that more than 20 million American men have had at least one negative prostate biopsy."

The biopsy found no cancer. But for most men, the issue doesn't just rest there. The spectre of cancer has been unleashed, and it haunts them — maybe only slightly, or maybe quite a bit. Is cancer there, hiding, and the doctor missed it? Or do some men just have an abnormal PSA? "New tests are urgently needed," says Partin.

Scientists at the Brady Urological Institute are working hard to find them, and we've got three promising candidates. One of them, EPCA-2, is covered in the story on Page 1. Two others — one, called a GSTPi test, used on prostate tissue, and a urine test, which looks for a marker called PCA3 — are being investigated clinically. Partin is heading both of these investigations.

Nearly 35 million American men have a PSA test each year. More than a million of these men undergo a biopsy — but only 250,000 are found to have prostate cancer.

The GSTPi test can detect very small numbers of cancer cells — so small that they may not be visible to a pathologist looking at prostate biopsy samples under a microscope. GSTPi is a gene. Several years ago, Brady scientist William G. Nelson, M.D., Ph.D., discovered that GSTPi helps the body to detoxify harmful chemicals and, in further work, that it is turned off and on by a molecular process called "methylation." Having both copies of this gene methylated within the same cell "is a sure sign that it is cancer," explains Partin. The new test, tried out on archived tissue specimens, "has very good specificity, and would greatly aid pathologists, physicians — and more importantly, men getting biopsied — in understanding whether a negative biopsy is truly "cancer-free." Partin's clinical research group, working closely with investigators from the Cleveland Clinic, the University of North Carolina, and the Walter Reed Army Hospital, has enrolled more than 150 men in a clinical trial of the test. They expect results to be available soon.

PCA3 can look for prostate cancer in a simple urine test. When a man urinates after having a digital rectal exam — which "massages" the prostate — a few prostate cells find their way out of the body, as well. Small amounts of a particular nucleotide, a molecule of RNA, can be detected in these prostate cells if a man has prostate cancer. "With our clinical trials, we hope to find out exactly how accurate this test is," says Partin. "We have great hopes of helping to bring both of these tests into the clinical arena within the next couple of years."

A Chair of Greatness: Don Coffey Honored

Don Coffey is a teacher, a storyteller, a scientist, a scholar, and a Renaissance man who makes the term seem dismally inadequate. He is a fine talker, but an even better listener. He loves his family, is loyal to his friends, is funny, and he's interested in everything. Nothing in the universe is too arcane for Don Coffey, because everything connects, the very big and the incredibly small — it's all part of the wonderful puzzle being worked on, all the time, in his brain. Scientifically speaking, he's a catalyst. He inspires. He charges the air with the electric excitement of ideas. Spend five minutes with Don Coffey, maybe in his office packed with some of the gadgets that fascinate him, or maybe in the halls of Marburg, and you'll likely think, "Wow, that's the smartest guy I've ever met." You may swear your own IQ has risen by a few points, just by osmosis. If you are told that some people have compared Coffey to another famous American scientist, storyteller and scholar, Benjamin Franklin, you may take a half-second to digest this, and then you may think, "I wonder if Ben Franklin was half as bright."

Donald S. Coffey, Ph.D., who is The Catherine Iola and J. Smith Michael Distinguished Professor of Urology, served as Director of the Research Laboratories in the Department of Urology for 30 years, from 1974 to 2004. On October 10, 2006, the Brady Urological Institute dedicated the Donald S. Coffey Professorship in Urology. Its first occupant will be, appropriately, the Coffey-trained and -inspired scientist Robert Getzenberg, whose work is featured on the cover of this issue, and who succeeds Coffey as the Brady's Director of Research.

Spend five minutes with Don Coffey, and you'll likely think, "Wow, that's the smartest guy I've ever met." You may swear your own IQ has risen by a few points, just by osmosis.

"It's very fitting that the first recipient of the Coffey chair should be Rob Getzenberg," says Alan W. Partin, *[continued on page 4]*

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M.D., Ph.D., Director of Urology — and a world-renowned, Coffey-inspired scientist himself. "Like Don Coffey, he is an innovative scientist and teacher, whose exciting work is giving us new ways to think about and tackle prostate cancer."

Look at Coffey's appointments at Hopkins, and see how many departments claim him: He's a professor of urology, oncology, pathology, pharmacology and molecular sciences. He's also a member of the Principal Professional Staff at the Johns Hopkins University's Applied Physics Laboratory. "It's safe to say that the Brady would not be leading the world in understanding the science of prostate cancer without Don Coffey," says Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. "We've worked together for 32 years," most of which time Walsh was the Director of Urology, "and we agreed that the best thing we could do was to get the brightest young people we could, believe in them, teach them all that we could, and then give them the chance to flourish."

Among Coffey's many contributions to urologic research is his groundbreaking work on the "nuclear matrix" — which he identified, isolated, and named — of cells. "The matrix provides the three-dimensional structure of the nucleus," Partin explains, "and organizes the higher order structure of DNA. The nuclear matrix protein composition is tissue-specific, and changes with the development of cancer." These discoveries, Walsh adds, grew out of Coffey's "brilliant ability to simplify. As a non-pathologist, he was able to simplify the pathology of cancer down to one rule: The nucleus is irregular. He then set out to find what makes a nucleus round, and in the process, discovered the nuclear matrix." Coffey's discoveries, according to Getzenberg, "have implications that we're still learning about, and they've set us on whole new courses of scientific exploration."

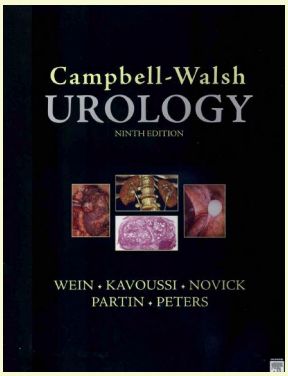
But, Coffey's colleagues agree, even this work isn't his most lasting legacy. "Don is an inspiring teacher," says Walsh, "and the Pied Piper of prostate cancer research. He has attracted more outstanding investigators into the field than anyone who ever lived."

Nothing in the universe is too arcane for Coffey, because everything connects, the very big and the incredibly small. It's all part of the wonderful puzzle being worked on, all the time, in his brain.

One of those is William Isaacs, Ph.D., whose groundbreaking work on the genetics of prostate cancer established conclusive proof that the disease runs in families. His latest research is featured on Page 15 of this issue. "Don has an irresistible way of inspiring students to discover," he says. "He cuts through all the details to reveal the key question, and does it in such a way that you can't help but want to be part of the answer."

Another world-class, Coffey-trained investigator is William G. Nelson, M.D., Ph.D., Because of Coffey's "unique ability to communicate, often by using homespun analogies," Nelson believes, he can explain complex biomedical research to just about anyone. "Watching Don testify in front of Congress on behalf of cancer research, you could almost see the 'now I get it' light bulbs turning on. For an engineer who undertook Ph.D. training in biochemistry, Don has a great sense of cancer not only as disordered biochemistry, but as a disease that threatens life and happiness. I think that he's had as much influence on the thinking and training of great physicians and surgeons as he's had on basic science researchers."

A few other highlights from Coffey's great career: A graduate of the University of East Tennessee, he received his Ph.D. in Biochemistry from the Johns Hopkins University School of Medicine in 1964. He is Past-President of the American Association for Cancer Research, and also of the Society for Basic Urologic Research. He served as a member of the National Prostatic Cancer Program of the National Cancer Institute for 19 years, and served as its national chairperson from 1984 to 1988. He has received the Robert Edwards Award from The Tenovus Institute; both the Fuller Award and Lifetime Achievement Award from the American Urological Association; the highest research award given by the Society of International Urology; and a 2001 American Cancer Society Distinguished Service Award. He is an Honorary Member of Alpha Omega Alpha, the recipient of two Merit Awards from the National Institutes of Health, and the author of more than 250 research publications.



New Edition

It's the "Bible" of urology around the world, the textbook that has helped train urologists for generations. It used to be known as *Campbell's Urology*. But in recognition of its editor-in-chief, Patrick Walsh—who has worked hard over the last 25 years to make this the best textbook in the field—the book's name has changed. The textbook today has grown to four volumes and 4,000 pages, and now is called *Campbell-Walsh Urology*. The Ninth Edition, soon to be released, also features Alan Partin, Director of Urology, as one of the senior editors.

The Gleason Score at 40: Still Making the Grade

The Gleason scoring system — named after the Veterans Administration pathologist who figured out how to crack the code of prostate cancer's highly complicated mix of cells—turns 40 this year. Prostate tissue is notoriously tough to read, and until Donald F. Gleason's innovative formula, many pathologists were stumped by what they saw under the microscope. Gleason's breakthrough system defines cancer cells solely

by their architectural pattern; the two most common patterns are added together, and their sum signals how mild-mannered, or how aggressive, the cancer will likely turn out to be. "It's a testament to the enduring power of Gleason's original ideas that this is still the accepted grading system throughout the world," says Hopkins pathologist Jonathan Epstein, M.D. Epstein, the Rose-Lee and Keith Reinhard Professor of Urologic Pathology, is world-renowned himself, for his expertise and accuracy in judging prostate cells.

Just about everything in the field of prostate cancer has changed dramatically over the last four decades. What about the way we grade cancer?

And yet, just about everything else in the field of prostate cancer has changed dramatically over the last four decades — particularly, how the disease is diagnosed. "In the 1960s, there was no screening for prostate cancer other than by digital rectal exam," says Epstein. There was no PSA test; in fact, nobody knew that PSA was even in the bloodstream. Even in the 1970s, Epstein adds, "the vast majority — 86 percent — of men were diagnosed with advanced disease." Eight percent were diagnosed with a localized spot that could be felt during a rectal exam, and only 6 percent had a tumor that was too small to be felt (these were found by transurethral resection, a procedure to treat benign enlargement of the prostate).

Biopsies were much different then, too — maybe two thick-gauge needles, inserted into a suspicious area of the prostate. Today, urologists use much thinner needles, and do their best to sample the entire prostate — routinely taking a dozen or more cores of tissue. In the 1960s, radical prostatectomy was relatively uncommon. "Prostates were not as often removed intact, and glands were not processed in their entirety, or as extensively and systematically as we do today," Epstein says. The original Gleason system didn't have to deal with grading multiple nodules within the same prostate; it also predated the use of special techniques, such as immunohistochemistry, which can help detect cell changes that mimic prostate cancer. And Gleason probably didn't see too much PIN (prostatic intraepithelial neoplasia, "funny-looking" cells that are likely precancerous), because he didn't get to view much prostate tissue in the early stages of cancer.

To address these and other issues, Epstein recently brought together more than 80 urological pathologists from 16 countries with special expertise in prostate cancer. Among the many decisions they hammered out, the pathologists dealt with some practical issues involving how to grade cancer in surgically removed prostate specimens, in needle biopsies and individual needle cores; and made modifications in some of the Gleason patterns.

"Our conference brought out many differences in how the Gleason system is applied — even within the United States," reports Epstein. "In all but a few areas, clear consensus was reached by the majority of genitourinary pathologists who participated in this meeting. We hope that these guidelines will help pathologists adapt the Gleason grading system to current practice in a more uniform manner, while at the same time fostering collaborative studies to address controversial areas, where we need more data."

Good News for Men Diagnosed with Gleason 7 Cancer

When a man is diagnosed with prostate cancer, his first question is almost always: "How bad is it?" When a man is diagnosed with Gleason 7 disease, the answer is a little tricky. This is because not all Gleason 7 cancers are alike. In fact, the differences can be great.

The Gleason system (see story on this page) is based on a score — the sum of the two most common patterns that the pathologist sees under the microscope. The equation, "2 + 2 = 4," for example, would signal a very mild, slow-growing form of cancer, and one that is rarely diagnosed today. On the other hand, "5 + 5 = 10" would represent much more aggressive disease. The first number in the equation represents the predominant type of cancer. In the case of Gleason 7, this can go two ways: "3 + 4 = 7," or "4 + 3 = 7."

Mark L. Gonzalgo

"Tumors with a Gleason score of 4 + 3 are more aggressive and predictive of advanced disease at the time of surgery, compared to Gleason 3 + 4 tumors," explains Mark L. Gonzalgo, M.D., Ph.D., assistant professor of urology and oncology. In a recent study, published in the journal *Urology*, Gonzalgo and urologists Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D., investigated the relationship between a man's biopsy Gleason score, the Gleason score in the entire prostate (the specimen removed during radical prostatectomy) and the recurrence of PSA among men who were diagnosed with Gleason 7 cancer in a needle biopsy.

"The good news is that the vast majority — 75 percent — of these men turned out to have the less aggressive type of Gleason 7 cancer," Gonzalgo says. "Their Gleason score determined after surgery remained the same, or turned out to be less aggressive." For men diagnosed with the more aggressive form (Gleason 4 + 3), the news was also reassuring: Almost half were found to have less aggressive disease (3 + 4, or less) in their prostates at the time of surgery.

Not all Gleason 7 cancers are alike. Fortunately, most men have the less aggressive type.

"What this means," Gonzalgo continues, "is that nearly half of all men diagnosed with the more aggressive type of prostate cancer on needle biopsy are actually found to have less aggressive disease. These men are also more likely to have more favorable outcomes after surgery. In the majority of cases, prompt diagnosis and treatment will lead to a cure."

In futher laboratory research, Gonzalgo and colleagues are also studying molecular markers that may help identify men who have a higher risk of having more aggressive prostate cancer.

"Lance Armstrong Effect" Gives a New Weapon Against Advanced Cancers—Heat

They call it the "Lance Armstrong Effect," and it's a phenomenon that has fascinated Donald S. Coffey, Ph.D., the Catherine Iola and J. Smith Michael Distinguished Professor of Urology, for years. How is it that a man with very advanced cancer—with pieces of tumor infiltrating his brain, liver, and elsewhere — could be treated with such astounding success that he could go on to win the Tour de France — seven times?

Coffey, with colleagues Theodore L. DeWeese, M.D.,Chairman of Radiation Oncology and Molecular Radiation Science, and Robert Getzenberg, the Donald S. Coffey professor of urology (see story on page 3) believe the key to the "Lance Armstrong effect" has to do with heat—specifically, a concept they call Temperature-Enhanced Metastatic Therapy (TEMT). Their work on this — and how it may be applied to other

"Raising the temperature of cancer cells makes them much more susceptible to all forms of therapy."

diseases, such as prostate cancer — was recently published in the *Journal of the American Medical Association*.

"The testes typically exist at a temperature much cooler than the rest of the body," says Getzenberg. "If normal testicular cells move up into the body, when they reach the normal body temperature, they cease to function." And this may explain why testicular cancers are so sensitive to therapy: Because testicular cancer cells are already more sensitive to the body's normal heat, when they spread from the testicles to the rest of the body, they're more vulnerable to treatment, and more easily killed.

"We have known for years that raising the temperature of cancer cells makes them much more susceptible to all forms of therapy — chemotherapy, radiation therapy and immunotherapy," says Getzenberg. "The organization of the DNA in the cancer cells is altered, and an instability appears to develop in the cells' nuclear structure." The trick now is to apply this concept, using new forms of technology, to other types of cancer. "The goal is to warm the metastatic sites in a tumor-specific manner, to make them more susceptible to chemotherapy or radiation therapy. We are currently doing additional studies to move this treatment into the clinic as quickly as possible. This new way of thinking about treating advanced cancers opens doors into approaches that we've never tried."

Turning Back the Clock on Advanced Cancer

When prostate cancer becomes advanced, its cells change. They go from being "well-differentiated," having clear borders, and well-defined shapes, to being more runny — morphing into little, malignant blobs. Over the last decade, scientists have been studying drugs called "differentiating agents" that can help reverse this process — restoring shape and definition to cancer cells, and slowing down their rate of growth.

"In the past, scientists have focused predominantly on short-term treatment with these agents, looking for rapid changes in tumor regression," explains urologist Ronald Rodriguez, M.D., Ph.D., who is also an expert in molecular biology and viral oncology. But short-term studies of these drugs have been disappointing. He believes that giving differentiating agents to a man who already has advanced cancer, and hoping for a quick turnaround, is not the best way to approach these drugs. "Recently, we have discovered that if these agents are given over long periods of time, the effect on tumor progression can be profound," he says.

Even more exciting: Giving the drugs chronically may even take the most hardened, difficult-to-kill cancer cells — the ones called "androgen-independent," which no longer depend on hormones and can't be killed by hormonal therapy — and make them more vulnerable. "This appears to sensitize certain types of androgen-independent cancer cells, converting them back into androgen-dependent cells," says Rodriguez. "These findings may have the most significant impact on men who develop a PSA recurrence after radical prostatectomy." He and colleagues are now working to develop clinical studies based on their most recent data, published in the journal, *Cancer Research*.

"If these agents are given over long periods of time, the effect can be profound."

Lethal viruses: In 1997, Rodriguez and colleagues were the first to harness a common cold virus, called the adenovirus, as a weapon specifically designed to kill prostate cancer cells. The adenovirus normally kills any cell it invades; the trick of gene therapy was to make this an "oncolytic" virus—to get it to target and invade cancer cells. Working with this virus was one of the toughest challenges Rodriguez has ever wrestled with, but he eventually engineered the adenovirus so that it would only detonate when it came in contact with prostate cells. "This had significant clinical activity when we injected it directly into the prostate of patients who failed radiation therapy," he notes. "But the real need is in men with advanced disease — and for these men, direct injection is not an option." They tried injecting the viruses intravenously, and had to face two enemies — prostate cancer, and the patients' livers. The liver's job is to filter out chemicals that appear harmful. "Despite the fact that greater than 99 percent of the viruses injected this way were sequestered in the liver, we were still able to demonstrate clinical activity." This work was published recently in *Molecular Therapy*. To overcome this obstacle, they worked to make the virus — what little of it could make it past the liver — even more potent. Rodriguez and colleagues also have developed a means to bypass the liver, and "get much more of the virus to the prostate cancer cells." Those efforts are being led by scientist Shawn Lupold, Ph.D. Eventually, Rodriguez believes, "with these new developments, we will be able to have a significant impact on

the patients with the greatest need — men with advanced prostate cancer."

Where's My Best Friend? Loss of Intimacy and Hormonal Therapy

Of all the difficult challenges that happen to a man with prostate cancer, and to his partner, this one is rarely discussed. Hormonal therapy causes personality changes in men, and this — far more than the hormones' effect on sexual function — can be devastating for those who love them.

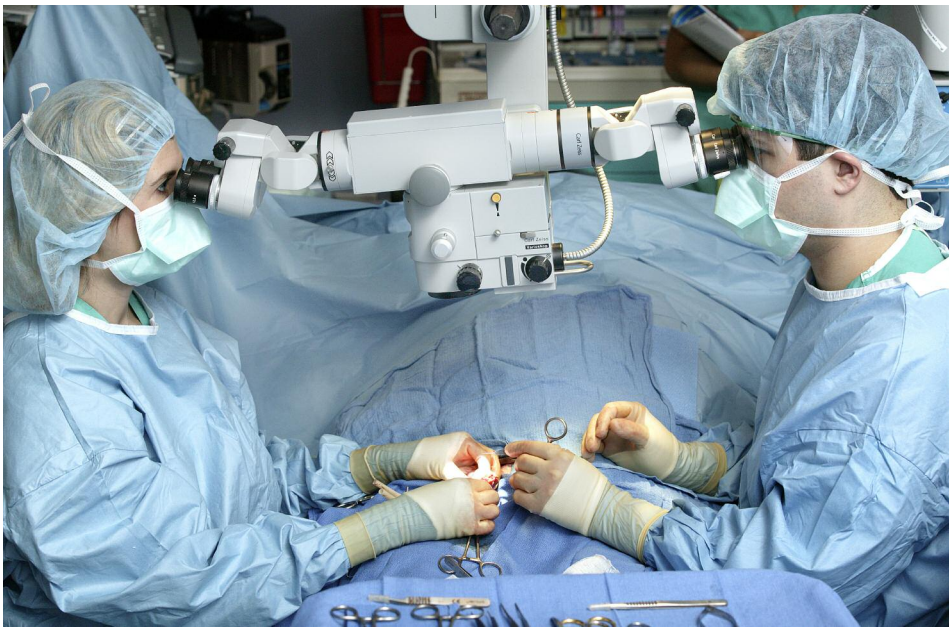
Urologist Karen Boyle, M.D., Director of Reproductive Medicine and Surgery, has seen this many times. She gives an example (although the names have been changed, to protect the couple's privacy): Mr. and Mrs. Taylor, married for half a century. They have always enjoyed an active sex life. Mr. Taylor, who is 78 years old, has advanced prostate cancer, and began hormonal therapy in 2003, when his bone scan became positive.

"Although the couple was aware of the side effects of hormonal therapy, they never anticipated how the most intimate aspect of their marriage would change," says Boyle. "Not only did Mr. Taylor's erections completely disappear, but he became completely

"I feel as if I no longer know him. Not only will he not talk about it, he avoids all discussion of how this makes me feel. It is as if he is a stranger."

indifferent and disinterested in sex, and would not agree to any aspect of sexual intimacy. His lack of affection toward his wife has caused her extreme unhappiness and loneliness."

Mrs. Taylor recently described some of what she is feeling in this way: "It is as if there is a stranger in my bed. I lay in bed at night next to a man whom I have known for over 50 years, but I feel as if I no longer know him. Not only will he not talk about it, he avoids all discussion of how this makes me feel. I'm okay with us not having sex — it's everything else — being physically close, connected — that I miss the most. He is now indifferent. It is as if he is a stranger."



Boyle, seen here performing microsurgery (left), with David Hernandez, a Urology resident, believes couples like the one in this article should confront problems of intimacy before therapy begins.

Mrs. Taylor's experience is "all too familiar to other women whose husbands have had hormone therapy," notes Boyle. But when many physicians talk about the side effects of hormonal therapy, the discussion "does not usually extend to the profound effect it has on the couple's intimacy, and the female partner," she continues. "The thousands of female partners are ignored, silently suffering, and are left emotionally and physically abandoned. Until now, their crying and tears have been very private, often confined to the very bedrooms in which they feel the indifference of 'the stranger' lying next to them at night."

Boyle believes that women like Mrs. Taylor shouldn't have to wait until this happens to them to find out about it. "Confronting this loss of intimacy proactively, before the therapy begins, would be very beneficial." However, "many physicians are unfamiliar with dealing with such complex sexual dysfunction." She recommends "couples counseling" with a medical professional who is familiar with the hormonal and physical effects of medical castration. "The challenge is getting the male partner to recognize the problem and agree to participate in a treatment plan geared not to optimizing sexual intercourse, but optimizing intimacy."

Men with Low-Risk Prostate Cancer:

Expectant Management, with Curative Intent

The downside to prostate cancer screening is that, for some men, it's too good: It finds cancer that probably doesn't need to be found. "There is a tradeoff," says H. Ballentine Carter, M.D., professor of urology and oncology. "Some men are diagnosed and treated unnecessarily." In these men, prostate cancer is very slow-growing. It never spreads beyond the prostate, and never becomes aggressive.

About half of men today are diagnosed with this "low-risk" *[continued on page 8]*

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prostate cancer — cancer that is too small to be felt during a rectal exam, with a Gleason score of 6 or lower, in men with a PSA below 10 nanograms per milliliter. "This is going to be an increasing issue as our population ages, and as more men undergo regular screening for prostate cancer," Carter says.

Some of these men, Carter believes, may be ideal candidates for something new. "Starting with the assumption that men with low-risk prostate cancer can almost always be cured with surgery, and that for younger men, surgery is ideal, there is a subset of older men for whom expectant management with curative intent may be an ideal option, because of the low risk of disease progression."

This is not watchful waiting, it's proactive monitoring. And so far, it does not appear that the window of curability is being lost.

This is not watchful waiting; it's proactive monitoring. Carter, who is leading the research in this new area, started a program at Hopkins in 1995 designed to identify men with low-risk prostate cancer, follow them closely, and intervene with curative intent (surgery or radiation) only if the disease progresses. Over the last decade, about 400 men, with an average age of 67, have entered this program. First, these men undergo at least a 12-core biopsy, to make sure their disease has not been underestimated. Then, they are followed closely, with a PSA and rectal examination every six months, and a yearly biopsy. Progression is defined by what the pathologist sees in the biopsy — cancer present in more than two cores, or in more than half of any one core; or a Gleason score of 7 or greater — or an unusual increase in PSA that prompts another biopsy.

"The trigger for intervention in these men is biopsy evidence that there is more disease, or higher-grade disease," Carter says. But what about the critical "window of curability?" Could men miss their chance of being cured, even with this close monitoring? Carter and colleagues recently addressed this question in a study, published in the *Journal of the National Cancer Institute*. "We compared the surgical outcomes of 38 men who entered the surveillance program and subsequently underwent surgery — on average, two to three years later — with 150 similar men who qualified for the program but chose to undergo surgery immediately after their diagnosis." The scientists found that an equal number of men in both groups turned out to have curable disease.

Carter stresses that this approach is still investigational. However, so far — using this careful plan for enrolling patients and following them — it does not appear that the window of curability is being lost.

LAPAROSCOPIC RADICAL PROSTATECTOMY:

Robot Help or Hype?

Over the last five years, Hopkins urologists Li-Ming Su, M.D., and Christian Pavlovich, M.D., have performed more than 600 laparoscopic radical prostatectomies (LRPs), and their results are excellent: At three years after surgery, 97 percent of their patients remain cancer-free, as defined by an undetectable PSA test; 70 percent of their patients had urinary continence at six months, and 90 percent were continent at one year. Half of the men were potent at six months, and 75 percent of the men who were potent before surgery, and who underwent the bilateral nerve-sparing procedure were potent one year later.

The robot's arms are like ultra high-tech Swiss Army knives, fitted with multi-jointed tips loaded with miniaturized scissors, graspers, dissectors, and needle drivers.

Su, Director of Laparoscopic and Robotic Urologic Surgery at the Johns Hopkins Hospital, and Pavlovich, Director of Urologic Oncology at Johns Hopkins Bayview Medical Center, reported their results this year at the American Urological Association's annual meeting.

Misop Han

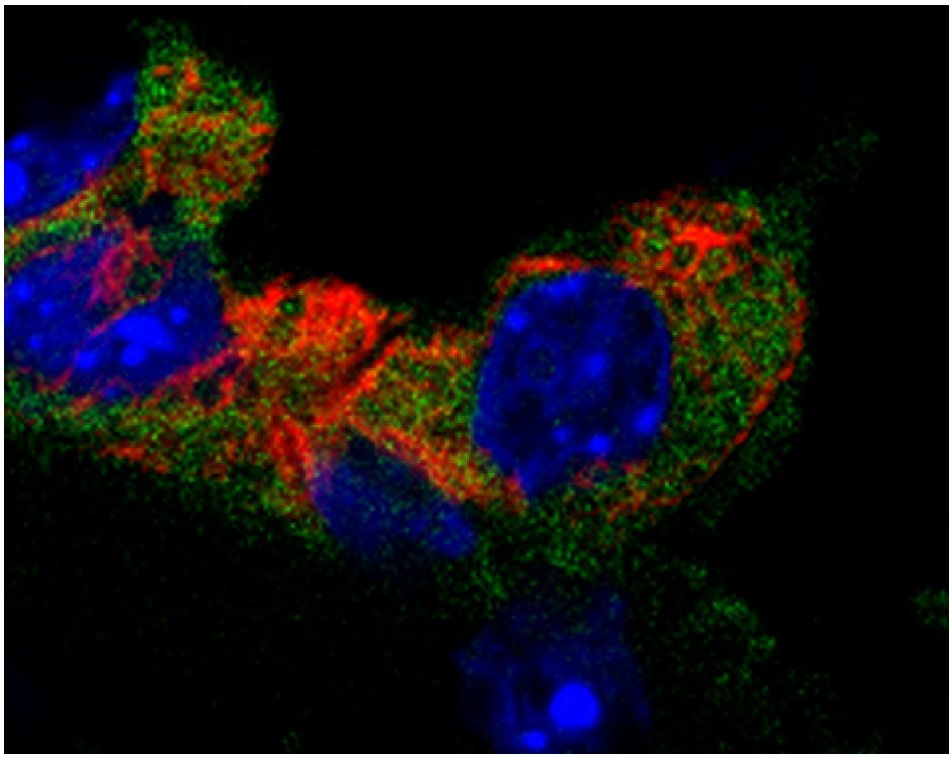
Could the use of a robot make these results even better? Su and Pavlovich, along with fellow surgeons Jonathan Jarow, Misop Han, Mark Gonzalgo, and Alan Partin, Director of Urology, have begun investigating this possibility, using a sophisticated robot with a genius's name—daVinci. Robot-assisted laparoscopic radical prostatectomy (RALP) is the latest minimally-invasive surgical technique to enter into the field of urology, Su explains. With the daVinci technique, "the surgeon sits at a computer console using hand and foot controls to manipulate a highly sophisticated robotic device with three to four instrument arms. These are inserted into keyhole incisions made in the patient's abdomen." The daVinci robot's high-quality telescopic lens "gives us an unprecedented, three-dimensional and magnified view of the operative field," says Pavlovich.

The robot's arms are like ultra high-tech Swiss Army knives, fitted with multi-jointed tips loaded with miniaturized scissors, graspers, dissectors, and needle drivers. The idea is that the more specific tools available, the better the surgeon can — operating within extremely cramped quarters — mimic the versatility and delicacy of the human wrist. Because of its capabilities, the daVinci Surgical System "is considered a device that can help reduce the learning curve of accomplishing complex laparoscopic procedures, suturing and knot-tying," Pavlovich adds. "These are the most significant limiting factors for many surgeons."

Because the technology is making many aspects of laparoscopic surgery relatively easier, the Hopkins surgeons note, RALP has grown in popularity with both urologists and patients, "with an exponential growth of cases performed each year," Su notes. "Much of this growth has been fostered by a combination of aggressive marketing and a peculiar fascination of patients with the use of new technology." However, he cautions, "although RALP has been touted by

some institutions as being superior to open radical retropubic prostatectomy, many of these studies were limited by their short-term outcomes and flawed because they didn't compare the results to those of achieved by experts at open prostatectomy."

The Hopkins surgeons are taking great measures to evaluate RALP objectively. They believe that long-term studies are needed to get past the hype — to determine the true merits of the robot-assisted technique, its impact on cancer cure, urinary continence, preservation of sexual function, as well as its overall cost-effectiveness.



Chameleon cell. *This is a prostate epithelial cell — now. But it began its life as a stem cell in the bone marrow. The green area shows the presence of a protein made only by bone marrow cells. The red shows a protein made by prostate epithelial cells, and the blue shows the cell's nucleus.*

Stem Cells, Inflammation, and Prostate Cancer

Most of us have heard of stem cells. Over the last decade or so, these amazing, changeable cells — among nature's greatest chameleons — have achieved a certain wistful place in medicine. The idea is that if these cells can become, or be turned into, other cells, then maybe one day they could be used to replace vital cells that are tragically missing in such devastating diseases as Alzheimer's.

Stem cells made in the bone marrow apparently make house calls. They travel to the injured organ, and turn into that organ's particular cells. This is not always good.

But new research suggests that stem cells don't always play the hero. Sometimes, when these cells are injured — or maybe even simply inflamed — they can progress to become cancer. "Stem cells are rare, but they're found in each organ in the body," says Ganesh S. Palapattu, M.D., a former postdoctoral fellow in the laboratory of Hopkins scientist William G. Nelson, M.D., Ph.D., and now on the faculty at the University of Rochester. Their main job is to serve as genetic understudies — turning into, and playing the role of, specific cells if needed, so that an organ can keep doing its job. "However, if the stem cells present in an organ suffer genetic damage, these damaged cells may progress to become cancer."

Stem cells made in the bone marrow appear to be even more versatile and generic pinch-hitters. If tissue in certain organs is injured, bone marrow stem cells apparently make house calls — they travel to the injured organ, and turn into that organ's particular cells. Scientists aren't sure how this phenomenon happens — whether the bone marrow stem cells turn into the specialized cells directly, or whether they fuse to other cells in the organ — but it's been seen in several organs.

Can stem cells from the bone marrow form new cells in the prostate? Brady researchers Palapattu, Alan Meeker, Ph.D., Nelson, and colleagues found out that they can. In research published in the *Journal of Urology*, they found that in mice given a virus that causes inflammatory damage and tissue repair in the prostate, bone marrow stem cells appeared. Some of the specific cells they produced were epithelial cells — cells of the tissue that lines the prostate, and protects it from the outside.

What might these findings tell us about how prostate cancer develops? In 2004, a research team reported that bone marrow cells could give rise to epithelial cells in the stomach, in response to infection with Helicobacter, a form of bacteria that leads to stomach cancer. In their experiments, the bone marrow-derived stomach cells were the cells that progressed to become cancerous.

Much of the Brady's research in recent years has turned up increasing evidence that inflammation and infection play a role in prostate cancer. The bone marrow-stem cell link may be another piece in this puzzle. It may be, says Palapattu, "that bone marrow-derived prostate cells appearing in infected or inflamed prostates might be at risk to progress to prostate cancer."

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

Scientists Named in New Round of Funding

It's been two years now since The Patrick C. Walsh Prostate Cancer Research Fund threw open its doors to any scientist at Johns Hopkins — in any discipline — with a good idea worth pursuing, to further our understanding of prostate cancer and help us find the cure. So far, thanks to the tremendous generosity of our patients and friends, we've raised $28.7 million.

In an era of dwindling funding from the National Institutes of Health and the Department of Defense — despite the increasing number of men diagnosed each year with prostate cancer — never has this support, and this kind of research fund, been more vital.

We are now able to provide $1,000,000 a year to fund proposals from the best and brightest Hopkins scientists in many departments, including Oncology, Pathology, Pharmacology, Epidemiology. This year, we received applications from nearly 40 Hopkins scientists, as well as requests for continued funding from last year's awardees. The applications were vetted by a scientific advisory board composed 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 $1,000,000 to thirteen recipients, most of whom are young investigators with new ideas. Some of their work is described below.

The 2006 Awardees

Dimitri Artemov, Ph.D.
Department of Radiology

David Berman, M.D., Ph.D.
Department of Pathology

Robert Casero, Ph.D.
Department of Oncology

Angelo M. DeMarzo, M.D., Ph.D.
Department of Pathology

Charles Drake, M.D., Ph.D.
Department of Oncology

Mark L. Gonzalgo, M.D., Ph.D.
Department of Urology

Sheila Gonzalgo, M.D., M.P.H.
Department of Medicine, Division of Geriatric Medicine and Gerontology

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

Jun Liu, Ph.D.
Department of Pharmacology

Shawn Lupold, Ph.D.
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

New Ways to Block Cancer's Spread

Prostate cancer can't grow without a healthy supply of blood, and prostate tumors seem to have two ways of making sure that they'll have enough blood to flourish. One is a process called angiogenesis — sprouting new blood capillaries from blood vessels that are already there. The other involves formative cells from the bone marrow, called mesenchymal stem cells (MSC). These can become new endothelial cells, which — like tiny paving bricks — line the newly formed blood vessels. Radiologist Dimitri Artemov, Ph.D., the Beth W. and A. Ross Myers Scholar, is using MRI (magnetic resonance imaging) technology to follow the progress of these MSCs. Interestingly, he has found that in slow-growing prostate cancer, MSCs are fairly few and far between. But highly aggressive prostate cancer, in comparison, is chock-full of these cells.

Prostate cancer can't grow without a healthy supply of blood. It has two ways of making this happen.

Artemov is seeking new ways to "light up" these MSCs, using a molecular contrast agent that targets the cells' surface, so that he can monitor them over the long term, as they become incorporated into new blood vessels. "We also plan to study the effects of anti-angiogenic therapy on these cells," he says.

Primitive Pathways and Sophisticated Prostate Cancer

Pathologist David Berman, M.D., Ph.D., the R. Christian B. Evensen Scholar, seeking to stop prostate cancer at its most advanced and sophisticated, is looking at some of the body's simplest, most primitive devices. One of them, discussed in the last two issues of *Discovery*, is called the Hedgehog pathway — a common protein pathway that's involved in embryonic development of several organs, including the prostate. But in prostate and other cancers, it turns out, this pathway serves as a lifeline that enables cancer cells to live and spread outside their original tumor. In exciting work, Berman and colleagues have proved that they can block this pathway, and stop cancer from spreading.

Some of the gene functions that happen early in development are also very important in the earliest beginnings of cancer.

Now, in new research — the first of its kind — Berman is looking at another primitive structure called the urogenital sinus (UGS). Before birth, this structure, stimulated by testosterone, causes the prostate to grow. When this happens, there's also "a burst of proliferation, invasion of surrounding tissue by the growing cells, and the formation of new blood vessels," says Berman. "This is very similar to what happens in cancer." Could it be that learning how to control this process will help stop prostate cancer? In studies using mouse tissue performed with Brady urologist Ted Schaeffer, Berman has launched the first comprehen-

sive analysis of gene activity in early prostate development. He and colleagues have identified several promising cellular pathways and signals that may control prostate growth.

Berman and bioinformatics experts Giovanni Parmigiani and Luigi Marchoni found that some of the gene functions most significantly associated with early prostate development are the ones in charge of cell proliferation, angiogenesis, and movement. Interestingly, these are all very important in early prostate cancer development, as well. Each cell in the body, Berman believes, has a different developmental history that restricts the genes it can activate later in life. "Therefore, each category of cancer — such as prostate, breast, or colon — is likely to use a different assortment of genes and pathways to activate these processes." By identifying the molecular basis for these processes in prostate cells, Berman hopes his research will suggest new, more specific ways to treat prostate cancer while leaving the rest of the body unscathed.

Deadly Chain: Inflammation, Oxidative Damage, and Cancer

Inflammation causes harmful molecules, called "reactive oxygen species" to form. One such molecule is hydrogen peroxide. When the body makes enough of it, hydrogen peroxide can hurt cells, and cause oxidative damage — damage to DNA, which can lead to mutations, and then to cancer.

In the prostate, one molecule, when it reacts with oxygen, can churn out enough hydrogen peroxide to damage DNA. This oxidized molecule is called spermine, and molecular pharmacologist Robert Casero, Ph.D., the Irene and Bernard L. Schwartz Scholar, is very interested in the role this chemical and the enzyme, spermine oxidase, might play in prostate cancer. He and colleagues have recently shown that when stomach tissue is infected by *H. pylori*, a nasty form of bacteria — well-linked to inflammation, it's also known to cause stomach ulcers and, eventually, stomach cancer — spermine oxidase makes hydrogen peroxide. The result is DNA damage. "These findings may provide the link between *H. pylori* infection, inflammation, and gastric cancer," notes Casero. This process in stomach cancer, he continues, is eerily similar to what's happening in cells that are on the brink of becoming prostate cancer. They are in a condition called "proliferative inflammatory atrophy," a wild mix of cells first spotted under the microscope by Hopkins pathologists Angelo De Marzo and Jonathan Epstein — hotspots of inflammation, mixed with cells that appear to be dying, but are actually proliferating very rapidly. "The prostate has the highest concentration of spermine of any human tissue," Casero reports. "We believe that inflammation-caused induction of spermine oxidase, and its resulting damage, has the potential to cause prostate cancer."

These findings may provide the link between *H. pylori* infection, inflammation, and stomach cancer—and this process is eerily similar to what's happening in cells that are on the brink of becoming prostate cancer.

Casero is working to nail down this link between spermine oxidase and the development of prostate cancer, studying tissue samples to see if there's a correlation between spermine oxidase expression and a man's stage and grade of prostate cancer. "We will also try to determine exactly how inflammation regulates spermine oxidase," and figure out whether the oxidative damage spermine oxidase produces is enough to cause prostate cancer. "We hope our results will provide a link between chronic inflammation, hydrogen peroxide production, DNA damage and cancer-causing progression — and at the same time, provide a target for chemo-preventive intervention."

PIA Cells: Cancer in Progress?

Pathologist Angelo M. DeMarzo, M.D., Ph.D., the Dr. and Mrs. Peter S. Bing Scholar, is looking ahead — to a point where he is one or two steps ahead of prostate cancer — and hoping to change the future. In remarkable studies of prostate tissue samples, reported in previous editions of *Discovery*, he has found the equivalent of the chaos that astronomers see in star-forming regions of galaxies. It's a crazy, ever-changing mix of cells called PIA — proliferative inflammatory atrophy. Some of these cells seem to be dying, but are actually undergoing rapid-fire change. DeMarzo believes that PIA is the result of two main problems — a bad diet, which causes oxidative damage, and inflammation within the prostate — and that these PIA lesions are "on their way towards cancer."

But he needs definitive proof that PIA is cancer in progress. Imagine you took a series of snapshots of a building going to ruin. Long before part of the roof falls in, some shingles blow off. A window cracks. Rain gets in. This is the kind of evidence DeMarzo is looking for, on a very tiny scale — intermediate changes in DNA between normal cells and cancer cells. The most common of these are altered clumps called "hypermethylated CpG islands" in a gene called GSTPi, which is disabled early on in prostate cancer. With GSTPi, a protective gene, out of the way, cancer develops much more easily. "We believe that PIA will contain intermediate levels of CpG island methylation," says DeMarzo, "greater than normal, but less than cancer."

Ultimately, their hope is to spot precancerous cells at such an early stage that they can reverse the damage—fix the shingles, in effect, and keep out the rain.

He and colleagues are working to correlate the number of altered CpG islands with the type of atrophy, the extent and pattern of acute and chronic inflammation, and the presence of nearby cancer. They'll also be looking for other DNA abnormalities in PIA cells, searching for methylation changes in other genes that are known to be mutated in prostate cancer. Ultimately, their hope is to spot precancerous cells at such an early stage that they can reverse the damage — fix the shingles, in effect, and keep out the rain.

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

IMMUNOTHERAPY

Helping the Body Help Itself to Fight Cancer

What if a man's own immune system could be beefed up somehow, so it not only recognized prostate cancer cells as the enemy, but destroyed them, as well? This is immunotherapy, and so far, no scientist has been able to pack enough punch into the immune system to change the course of prostate cancer. Oncologist Charles Drake, M.D., Ph.D., the Phyllis and Brian L. Harvey Scholar, suspects that this is because the body — in an attempt to be helpful — is holding itself back.

The goal: Outmaneuver immune system cells that act as overzealous do-gooders—and make immunotherapy much more successful.

The culprit, he believes, is a group of cells known as regulatory T cells. "The presence of these cells has been clearly shown in breast and ovarian cancer," he explains, "and in these cancers, regulatory T cells are associated with a poor outcome." Do these cells — misguided warriors trying to protect the body, but enabling the cancer instead — predict the aggressiveness of a man's prostate cancer? Drake's first job, which he'll accomplish by studying prostate cancer specimens, is to find out whether these cells are indeed at the scene of the crime. Next, he hopes to outmaneuver these overzealous do-gooders. "When regulatory T cells are blocked or deleted, then we suspect that immunotherapy for prostate cancer will be more successful."

MOLECULAR THERAPY

Reactivating Disabled Genes

A gene that has been methylated has been changed ever so slightly. Like a gun with the bullets taken out, it looks much the same — except what was once a powerful weapon is now about as deadly as a doorstop.

Hopkins scientists are hot on the trail of understanding DNA methylation, and how to reverse it in prostate cancer. One of them is urologist Mark L. Gonzalgo, M.D., Ph.D., the Nancy and Jim O'Neal Scholar.

"Methylation is a natural phenomenon," he explains, and most of the time, it serves a useful purpose. For example, "we would not want our prostate to make hemoglobin, the protein required to carry oxygen in our blood cells. But sometimes important genes can become methylated, leading to the development of cancer." Using a mouse model, Gonzalgo is studying drugs called "demethylating agents" — by themselves and in combination with drugs that inhibit tumor growth, called histone deacetylase (HDAC) inhibitors — looking for the right formula to reactivate these silenced genes.

Like a gun with the bullets taken out, the altered gene looks much the same—except what was once a powerful weapon is now about as deadly as a doorstop.

If these demethylating agents prove as effective as Gonzalgo believes they will — if they manage to put the bullets back in the gun — he hopes to use them in clinical trials to help men with recurrent or metastatic prostate cancer.

Frailty and Surviving Prostate Cancer

Age matters in prostate cancer. The vast majority of men diagnosed with prostate cancer, and nearly all of the men who die from it, are over age 65. And yet, despite the recent compelling evidence that surgical intervention for prostate cancer can save lives, "many physicians do not routinely screen their older patients for prostate cancer," notes gerontologist Sheila Gonzalgo, M.D, M.P.H., the Carolyn and Bill Stutt Scholar. Even when they do, many of these men "may not receive potentially curative treatment," because their doctors think they're too old for it.

But general health matters, too, and not all men in their late sixties and over are alike. Some are hearty and vigorous, and some are plagued by health problems and frailty. This makes a huge difference in how men recover from illness, Gonzalgo adds, and it's going to become increasingly important as the Baby Boomer generation ages. There is a "demographic imperative," Gonzalgo believes, to determine which older men would benefit the most from prostate cancer screening and surgical intervention — and which would benefit the least.

"For example, we might expect an active 65-year-old man with no other illnesses to recover fully from the common cold," she explains. But that same cold might be much rougher on a man of the same age who is diabetic, who smokes, has heart disease, and doesn't exercise. "Gerontologists are in the process of defining what it means to age exceptionally. At the other end of the spectrum are the most vulnerable older adults, people afflicted with frailty — a biological syndrome characterized by muscle weakness, lack of stamina, and weight loss."

Some men in their late sixties are vigorous, and some are plagued by health problems. This makes a huge difference in how men recover from illness.

Using information collected from the Cardiovascular Health Study, Gonzalgo is working to see how a man's general health — his likelihood of disability and death from other causes — affects his chances of being helped by surgery.

Speeding Up the Drug Pipeline

To men with advanced prostate cancer who could benefit from antiangiogenic drugs — designed to stop cancer from growing, by thwarting its supply of new blood vessels — the wait for new drugs seems interminable. Scientist John T. Isaacs, Ph.D., is trying to speed up the process. He is studying an antiangiogenic drug (also called an

angiogenesis inhibitor) known simply as ABR-215050, which has just entered the drug pipeline. It's in Phase I trials in prostate cancer patients; these trials are mainly to make certain that the drug can be safely tolerated.

Before these tests can even begin to see whether it works, Isaacs and colleagues are investigating the drug's mechanism of action, trying to figure out how it works — specifically, looking to see whether it stimulates the body to make growth-regulating chemicals. They also want to find ways to measure the drug's progress — perhaps even in skin biopsies. "We hope that we'll be able to predict whether the drug is working in men with prostate cancer without the long time that usually is involved in these types of clinical trials," says Isaacs. In other studies, he and colleagues are combining ABR-215050 with other agents, including interferon gamma, and with hormonal therapy, to see if they can make it even more effective.

The Best New Drug May Be One That's Already Out There

It's an ambitious and ingenious idea, one that has great potential to help men with prostate cancer get new drugs much faster — and it could save millions of dollars, as well. There are an estimated 10,000 drugs already known to medicine and approved for use in patients. Many of them turn out to be helpful for more than one ailment. And yet, there's no centralized reservoir of knowledge about these drugs, says molecular scientist Jun Liu, Ph.D., the Peter Jay Sharp Foundation Scholar.

He is working to change this, and he's got many good reasons — at least 800 million of them. That's how many dollars it takes for just one new drug to be developed and brought, after many tests and clinical trials, to the patients who need it. Even with a host of scientific advances that have speeded up this process, "the average time from discovery to approval has more than doubled since 1964, from 6.5 to 14.8 years," Liu says. Even more sobering, he adds, less than one-quarter of the drugs that advance to Phase I clinical trials ever make it to the market. "Despite an almost thirty-fold increase to $33 billion in research and development from 1977 to 2003, the number of new drugs approved by the FDA remains relatively flat at 15 to 30 each year."

In contrast, the treasury of thousands of already-existing, already-approved drugs has been barely tapped. More than three years ago, Liu and his former graduate student, Curtis Chong, began an effort to systematically collect and screen all available FDA-approved drugs. So far, they have amassed a library that contains about 1,900 FDA-approved drugs and more than 600 that either entered Phase II clinical trials (were shown to be safe and to have few side effects) or were approved abroad for clinical use. From this research, "we have identified several drugs that possess potent and unexpected anti-angiogenic properties," Liu says. "Two of these, an immunosuppressive drug called mycophenolic acid, and an antifungal drug named itraconazole, have been shown to work in animal models of angiogenesis, or tumor growth."

It takes, on average, nearly 15 years for a newly discovered drug to make it to the people who need it most. But there are thousands of already-existing, already-approved drugs out there, waiting to be tapped for new needs.

With support from the Patrick C. Walsh Prostate Cancer Research Fund, he and colleagues continue to expand their library, and to examine the promising drugs they turn up. They are screening the library against prostate cancer cell lines, looking for novel drugs that inhibit the spread of cancer, or that seem to be more effective when combined with other drugs. "When we identify new inhibitors, we try to validate their mechanisms of action and see how well they work in different prostate tumor models in animals," Liu explains. "We are also carrying out follow-up studies on some of the most promising newly identified angiogenesis inhibitors, to facilitate their potential use in people with prostate cancer and other types of cancer."

MicroRNAS: Two Studies

There are so many things that go wrong in prostate cancer, and some of them are tiny. MicroRNAs fall into this category. They're little factory workers — molecules that help regulate cells' production of specific proteins. Their job is small but important; what they do or don't do can affect cell growth, death, and differentiation (how "normal-looking" the cell is; healthy cells are well differentiated; cancer cells are poorly differentiated). Alterations in the work of these microRNAs have been found in several different cancers, including prostate cancer. "Both increased and decreased expression of certain microRNAs are known to affect cancer cells," explains Brady scientist William G. Nelson, M.D, Ph.D. Although nobody knows for sure which particular switch turns microRNAs up or down, Nelson suspects that methylation of certain sections of DNA called cytosine bases may play a big role here. "This type of change has been found to affect many types of genes in prostate cancer," Nelson says. In studies of human prostate cancer cells, Nelson is looking for these changes near 37 microRNA genes, using a new technique developed in his laboratory, called COMPARE-MS.

The next step, Nelson says, is to try to reverse the abnormal cytosine methylation patterns, "and see whether we can restore the normal expression of the microRNAs. We hope our findings can lead to new diagnostic tests, and to new strategies for treating and even for preventing prostate cancer."

"We hope our findings can lead to new diagnostic tests, and to new strategies for treating and even for preventing prostate cancer."

In another series of studies, Shawn Lupold, Ph.D., the Virginia and Warren Schwerin Scholar, is investigating how hormones affect microRNAs — and how this, in turn, affects prostate cancer. Specifically, he wants to find out how male hormones, called androgens, and vitamin D — known to be very important *[continued on page 14]*

[continued from page 13]

in regulating normal and cancerous prostate cells — affect microRNAs in the prostate. He believes that these microRNAs, in turn, significantly affect prostate cell growth, differentiation, and death. "These studies should reveal abnormal microRNAs that exist within prostate cancer, and what we learn may be very important in developing new forms of treatment."

Inflammation, STDs, and Prostate Cancer?

Increasing evidence — much of it discovered and actively being explored by Hopkins scientists — suggests that chronic inflammation may be an important instigator of prostate cancer. One source of chronic inflammation in the prostate is sexually transmitted infections (STIs, more commonly known as STDs). And this begs the question — at least to epidemiologist

Could having a sexually transmitted infection make a man more susceptible to prostate cancer?

Elizabeth A. Platz, Sc.D., one of the pioneers in this area of research, and colleagues including Jonathan M. Zenilman, M.D., Angelo M. De Marzo, M.D., Ph.D., and postdoctoral fellow Siobhan Sutcliffe, Ph.D: Could having a sexually transmitted infection make a man more susceptible to developing prostate cancer?

Before the scientists could answer this question, they had to narrow down the playing field. Which, of the more than 30 known sexually transmitted infections, should they study? First, they looked for an infection known to cause extensive inflammation in the prostate. They also looked for a silent one—one that causes no symptoms, that stays below the radar, in effect. A quiet infection, they reasoned, "would be less likely to be treated and cured, and thus might persist in the man's genitourinary tract."

One infection that fit both criteria was trichomonosis, a sexually transmitted infection caused by the protozoan, *Trichomonas vaginalis*. "About 20 years ago, a pathologist named William A. Gardner Jr. noted that *T. vaginalis* was capable of infecting the prostate and causing a strong inflammatory immune response," explains Platz. "And yet, despite this interesting finding, essentially no work was done on the possible role that *T. vaginalis* might play in the development of prostate cancer."

To investigate this, the scientists selected 691 men with prostate cancer and 691 men without prostate cancer from participants in a large, Harvard-based project called the Health Professionals Follow-up Study. The lead role in the investigation was taken by Sutcliffe. Working with microbiologist John F. Alderete, Ph.D., who developed an assay to detect antibodies against *T. vaginalis* and tested the men's samples, they found that about 11 percent of men had antibodies against *T. vaginalis*. And significantly, "men who had these antibodies were about 40 percent more likely to develop prostate cancer than men who did not have these antibodies," says Sutcliffe. Even more exciting — in research that continues work by Platz and others investigating the use of nonsteroidal anti-inflammatory agents as a preventive measure against prostate cancer— "We then separated men into those who did and did not regularly use aspirin," Platz says. Aspirin reduces inflammation. And in this study, among men who regularly used aspirin, those who had antibodies against this infection had the same risk of prostate cancer as men who had not been exposed to it. "But, among men who did not regularly use aspirin, those who had antibodies against *T. vaginalis* were twice as likely to develop prostate cancer."

Sutcliffe, Platz and colleagues are quick to point out that these results are preliminary, and that much further study is needed. Even so, the Hopkins researchers are excited by these findings and now are looking to see whether young men in the U.S. military with antibodies against *T. vaginalis* have higher blood levels of a marker of prostate inflammation and cell damage than those who don't have antibodies. "This may indicate that *T. vaginalis* infected the prostate and caused cell damage in these men," says Platz.

Taking Molecular Pictures of Prostate Cancer

Based on a rising PSA after treatment, it looks like a man's prostate cancer has come back. Wouldn't it be nice if his doctor could see it — to know where the cancer cells are, to get an idea of what's going on inside him, and what treatment steps, if any, to take next? Right now, we can't do this. But we're getting closer.

Looking at images of tissue and trying to pinpoint the prostate cancer cells hasn't worked, says radiologist Martin Pomper, M.D., Ph.D. However, using a contrast

"We are in dire need of a way to detect small lesions—subtle manifestations of prostate cancer in men with an elevated PSA, but no other obvious symptoms."

chemical that targets something specific to the prostate — a molecule on the surface of prostate cells, for instance — and seeing those tagged cells light up on computer images has great potential. Pomper is leading the first clinical study using positron emission tomography (PET) scans to show probes that are designed to find PMSA, a protein on the surface of the prostate cell membrane. "We are in dire need of a way to detect small lesions — recurrent tumors in the surgical bed, local lymph node invasion, and other subtle manifestations of prostate cancer in men with an elevated PSA, but no other obvious symptoms," he says. "We have achieved the fundamentals of success with several small molecule, PET-based imaging agents for prostate cancer, and now we intend to bring the best of them to the clinic."

Pomper and colleagues are testing the technology on men known to have prostate cancer that is either confined to the prostate, that has come back after surgery in the local area, or that has appeared as distant metastases. If the technology performs as well as Pomper believes it will, he will test it next on men who have a rising PSA after surgery.

Hernias After Radical Prostatectomy

One or two years after radical prostatectomy, about 15 percent of men turn out to have inguinal hernias. Patrick C. Walsh, M.D., has been interested in this phenomenon since he first noticed it several years ago. He believes that many of these hernias may have been present before surgery—but they just weren't diagnosed.

With this idea in mind, he and Matthew E. Nielson, M.D., a resident at the Brady Urological Institute, studied 430 patients who underwent surgery between September 2001 and December 2004. The extra scrutiny paid off: "We found that if one looks very carefully at the time of surgery, about one-third of patients have hernias," he says, "and in 40 percent of these patients, the hernias were on both sides." These hernias were repaired during the radical prostatectomy procedure. Although none of the hernias that were repaired came back, a few of these men — 5 percent — developed another hernia after surgery, at a new site.

This study suggests that at the time of radical prostatectomy, urologists should carefully examine the patient for the presence of a hidden hernia, "and if one is found, it should be repaired," Walsh says. "We hope this will significantly reduce the development of a hernia following surgery."

Inherited Genes that Make Prostate Cancer More Likely

What are your odds of getting prostate cancer? Even if you do everything you can think of to help prevent it — for example, if you load up on fruits and vegetables, avoid red meat, and faithfully drink a glass of red wine several times a week — there's one thing you can't change: Your family history.

"Having prostate cancer in the family is one of the strongest risk factors yet identified for prostate cancer," says William T. Isaacs, Ph.D., the William Thomas Gerrard, Mario Anthony Duhon and Jennifer and John Chalsty Professor of Urology. "Although environmental factors such as diet are also important, it's clear from multiple studies that inherited genetic factors play a critical role in determining prostate cancer risk."

Isaacs and colleagues have been studying familial prostate cancer for more than 14 years, and have scrutinized the genes of more than 200 families. Their intensive genetic work has led them to discover several genes that increase a man's risk for prostate cancer. They've found increasing evidence that inflammation plays an important role, and so do critical variations in the genes involved in developing cancer. And yet, they believe, they've only scratched the surface—that there are many more prostate cancer susceptibility genes out there, waiting to be discovered.

The best way to identify and characterize these new genes is to study the families who, unfortunately, have been hardest-hit by the disease, with multiple relatives affected over several generations. To achieve a "critical mass" of families, and to maximize the information gathered from such families worldwide, Isaacs and colleagues have established a collaborative research network for scientists working in this area, called the ICPCG — International Consortium for Prostate Cancer Genetics. Isaacs is the ICPCG's chairman, and the principal investigator of a federally funded grant supporting this group. Together, the consortium's 14 research teams have obtained a much larger pool of prostate cancer families — more than 2,000 — for genetic analyses.

In one of the largest studies of its kind ever performed, the ICPCG recently combined genetic mapping data from more than 1,200 families with hereditary prostate cancer (with at least three first-degree relatives affected) to pinpoint the regions of the genome most likely to harbor prostate cancer susceptibility genes. The scientists found that a region on chromosome 22 is most likely the home of a gene that raises the inherited risk of prostate cancer in general.

Also, in a separate study, they identified regions on chromosomes 6, 11 and 20 as the locations of genes that make a man more likely to develop aggressive prostate cancer.

"Having prostate cancer in the family is one of the strongest risk factors yet identified."

"This group of families is particularly interesting," notes Isaacs. "Only about 10 percent of all prostate cancer families are in this category, so their study can only be performed by large combined analyses." Because of these studies, he adds, "we now have the critical information necessary to identify these important prostate cancer susceptibility genes." Isaacs and colleagues believe that finding these genes will have a huge impact on our understanding of prostate cancer, how best to treat it, and even how to help prevent it.

Making Life Better for Our Patients and Their Families

What makes Johns Hopkins Urology consistently — for 16 years in a row — ranked the very "Best of The Best" by a national news magazine? It's discovery, the subject of this newsletter, and the heart of the Brady Urological Institute. It's what drives everyone who works here. We're making a difference, and we know it — and we want to keep on

We're making a difference, and we know it—and we want to keep on making life better for our patients and their families.

making life better for our patients and their families. Our unparalleled scientific discoveries have forever changed the way prostate cancer is diagnosed and treated worldwide.

The discoveries written about on these pages show that there is something truly fascinating, even revolutionary going on at the Brady Urological Institute. We specialize in translating scientific discoveries into practical applications. This "translational research" typically begins at "the bench" with basic research, in which scientists study disease at a molecular or cellular level, then progresses to the clinical level — the patient's "bedside."

Translational research, when pursued with vigor, has a profound impact on improving our ability to care for our patients. Led by Alan Partin, Director of Urology, in the great tradition started by Patrick Walsh, we are working to expedite this "bench-to-bedside" process. Now more than ever, our vision is one of collaborative scientific interactions, hastening promising observations and facilitating scientific discoveries. The primary goal of all our research and clinical efforts is meeting our patients' needs. For example:

- Patients need flexible and diverse, custom-made treatment plans. Just as prostate cancer is different in every man, treatment must be, as well. Every man with prostate cancer who comes to Johns Hopkins will find physicians seeking the most appropriate treatment option for him. "One-size-fits-all" care is not an option here.
- Patients need multi-disciplinary clinical trials and the latest breakthroughs — discoveries that can change their lives — as quickly as possible. Our scientists understand that some patients do not have the luxury of time.
- Patients need better and more accurate tests to diagnose disease as early as possible. Currently, PSA is the best tool we have for prostate cancer diagnosis; our scientists are working to change this (see Page 1). We are intensively studying biomarkers that will not miss cancer or subject men to unnecessary biopsies.
- Patients need better treatment options. That's why Hopkins scientists are leading discoveries in new technologies and treatment for prostate cancer.

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.

The greatest challenge we face in bringing the latest research from the laboratory to our patients is finding the resources necessary to support the process. With increased competition for Federal funding and ongoing cuts in these critical funds, we need your support now more than ever. With your help, we can continue our battle to conquer prostate cancer. We hope you will make a gift to support The Brady Urological Institute, using the enclosed envelope. For question about making a gift, or if you are considering a gift of stock, real estate, IRA, or other asset, please call (410) 516-6160.

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

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