

DISCOVERY

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Each genetic “trouble spot” makes cancer more likely. From left: Kathleen Wiley, William Isaacs, Sarah Isaacs.

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Do the Math: Genetic Risks Add Up

New Findings May Lead to First-Ever Genetic Test for Prostate Cancer

Until about 40 years ago, when genealogists in Utah noticed that prostate cancer seemed to cluster in families, nobody thought that prostate cancer might be hereditary. Unfortunately, the disease is so common — more than 200,000 American men are diagnosed with it each year — that for many years, scientists couldn’t see past the numbers. In 1986, Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology, began to see increasingly younger men with this “old man’s disease.” Many of them had a family history of prostate cancer; one of them had a particularly hard legacy: “Every male in his family had died of prostate cancer — his father, his father’s three brothers, and his grandfather,” says

Walsh. “It seemed odd to me that we knew nothing about the role of family history on a man’s risk of getting prostate cancer.”

So began a series of studies at Hopkins, and the dawn of a genetics powerhouse, built around the work of William B. Isaacs, Ph.D., Don Coffey, Ph.D., and others who set out to answer Walsh’s questions, using data gathered at first from his radical prostatectomy patients, and then from men around the world.

In numerous studies over the last two decades, Isaacs and colleagues kept learning more about prostate cancer genetics — finding genes that seemed to be “prostate cancer genes,” for example — but the idea of a genetic test for prostate cancer seemed like

an idea that would never happen. Now, for the first time, it doesn’t seem so far away.

Risk Factor, Plus Risk Factor, Plus...

Figuring out the genetic risk factors for prostate cancer is like making a highly detailed model of a house. First, you go room by room. In this case, the rooms are chromosomes, and over many years of analyzing volumes of computerized data, certain areas have emerged as trouble spots. Then, you go foot by foot, and then inch by inch. On a much tinier and more precise scale, it’s akin to reporting that the second floorboard from the left in the dining room squeaks, and then, using a magnifying glass,

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finding out that two nails are missing.

This is what Isaacs, the *William Thomas Gerrard, Mario Anthony Dubon and Jennifer and John Chasty Professor of Urology*, has done, except his hard work and achievement are much more difficult to describe adequately. First, looking at blood and tissue samples taken from men and families with a history of prostate cancer, he and colleagues found some chromosomes that appeared to be suspicious. Then they found more specific areas that seemed to be implicated — three of them on the long arm of chromosome 8, and two on the long arm of chromosome 17. Then, in a study recently published in the *New England Journal of Medicine*, Isaacs and colleagues “did the math.” They discovered that while having one of these trouble spots — called single-nucleotide polymorphisms (SNPs, pronounced “snips”) might add just a little to a man’s risk of getting prostate can-

It’s like reporting that the second floorboard from the left in the dining room squeaks, and then, using a magnifying glass, finding out that two nails are missing.

Family History and Prostate Cancer

Hopkins scientists have discovered that having a family history of prostate cancer does indeed increase a man’s risk of developing the disease, and that increased susceptibility to it can be inherited from either parent. They then went on to define and characterize hereditary prostate cancer, showing the clear link between family history and a man’s probability of getting the disease.

Although the percentage of “purely inherited” cases of prostate cancer is low, what happens to the genes in these men is very important, because it may also happen, over time and aided by countless lifestyle and dietary choices, to the vast majority of men who develop prostate cancer.

Having just one of these genetic trouble spots adds just a little to a man’s risk of getting prostate cancer, but the risk is cumulative. It goes up, bit by bit, the more risk factors he has.

cer, the risk is cumulative: It goes up, bit by bit, the more risk factors he has.

“When the SNPs are combined, the association is stronger,” says Isaacs. In this international genetic study, scientists from the U.S. and Sweden studied 2,893 men with prostate cancer, and 1,781 randomly selected men who did not have prostate cancer. They looked at 16 SNPs from five chromosomal regions in these men.

“It turns out that each SNP independently increases a man’s risk of developing prostate cancer slightly,” says Isaacs. “But men who inherit four or five of these have a risk of developing prostate cancer that is 4.5 times higher than men who don’t have these SNPs.”

When a sixth variable — a positive family history of prostate cancer — was added to the mix, a man’s risk of getting prostate cancer was almost ten times higher. “Even though this highest risk group was very small, representing only 1.4 percent of our study population, these results are highly significant,” says Isaacs. “Until now, there has been no genetic test that could be used to guide an individual patient.” Isaacs and colleagues believe that still more individual risk factors will be found in the future — and that one day, based on their findings, they will be able to test for these factors, too, in men at risk of developing prostate cancer.

FROZEN TREASURE:

Biorepository a World Resource for Scientists

For scientists studying prostate cancer, the contents of a certain room on the fourth floor of the Marburg Building hold more riches than Fort Knox. For in here, they believe, lie the answers to curing this disease — if they can

just find the right questions to unlock them.

Welcome to the Biorepository — a treasure trove of freezers, whose contents represent the lives of nearly 4,500 men with all stages of prostate cancer. Neatly categorized, bar-coded, computerized, with demographic information including family history, and readily available to investigators throughout the world, are close to 18,000 samples of blood and urine products. “It is a huge resource,” says Alan W. Partin, M.D., Ph.D., the David Hall McConnell Professor and Director of the Brady. “A scientist can go to our database, and say, ‘I need 300 specimens from African-American men between ages 50 and 60, treated between 2000 and 2004,’ and we can say, ‘Here you go.’ We have distributed nearly 5,400 aliquots (tiny samples) from these specimens to investigators throughout the world.”

The Biorepository is a Clinical Epidemiology and Validation Center for the Early Detection Research Network, funded by the National Cancer Institute for the development of “molecular diagnostics” — bio-

Neatly categorized, bar-coded, computerized, with demographic information including family history, and readily available to investigators throughout the world, are close to 18,000 samples from men with all stages of prostate cancer.

Leslie Mangold, in our own “Fort Knox.”



markers. There are only two other sites like it in the world; one is at Harvard, and the other at the University of Texas-San Antonio. The one here at Hopkins is the flagship, the biggest, the most utilized and comprehensive.

It has provided immense help, says Partin, for scientists working to develop numerous biomarkers for use in blood, urine, and tissue tests, and for scientists (including Partin, whose Partin Tables are used worldwide as a means of calculating a man's prognosis) trying to predict the course of prostate cancer.

"When a new biomarker is being developed, we can test it very rapidly," says Partin. "For instance, EPCA-2 (see Page 10) moved through the system so quickly and efficiently because when Robert Getzenberg needed 700 samples, we opened up the freezers and handed them to him. In the old days, it would have taken us two years to enroll that many patients. This is helping speed discovery, and then getting those advances to the patients faster." Many of his patients, Partin continues, feel proud to have donated samples. "They like to know that they are helping other men with prostate cancer."

The samples date back to the early 1980s, but many of the requests from researchers are for aliquots of more recent vintage. This is because the disease has evolved, Partin notes. "For many men, it is less aggressive, because we are detecting the cancer far earlier than we did 20 years ago."

For Men with High-Risk Cancer, New Clinic Offers One-Stop Shopping

The last thing a man with prostate cancer wants to do is wait to see a physician — particularly if he's worried that his cancer may have spread beyond the prostate. Imagine the frustration, then, of a man diagnosed with "high-risk" disease, which may need more than one form of treatment. He has to talk to a surgeon, a radiation oncologist, and a medical oncologist, just for starters. He may also need to talk to other specialists, such as a nutritionist or an anesthesiologist, and just scheduling these visits can be a nightmare. He's got one appointment set for the beginning of the month with



Answers in a day: The team approach offers multidisciplinary help for men with high-risk disease. From left: Katarzyna Macura, Robin Gurganus, Kelly Cavallio, Danielle Crump, Ted Deweese, Michael Carducci, Melissa Faust, Alan Partin.

one doctor, an appointment four weeks later with a second, and he's hoping for a cancellation at a third doctor's office; otherwise, he can't be seen by that doctor for two more months.

How stressful. And how unnecessary. Men shouldn't have to go through this, says Brady Director Alan W. Partin, M.D., Ph.D. "It takes some men three to six months to make their rounds, see different physicians, and make the decision about the best form of treatment for them. If you have high-risk disease, you often don't have that kind of time. You should be able to make a logical decision, based on good advice."

In May, the Brady Urological Institute began what Partin refers to as "one-stop shopping" — a multidisciplinary clinic for men with high-risk prostate cancer. The clinic meets weekly and between four and six men are evaluated. In the span of just a few hours, a man can meet with a top urologist, medical oncologist, or radiation oncologist. Then those doctors meet and review his case — including his pathology report, MRI, X-rays, and any other relevant materials — together, to come up with the best treatment plan.

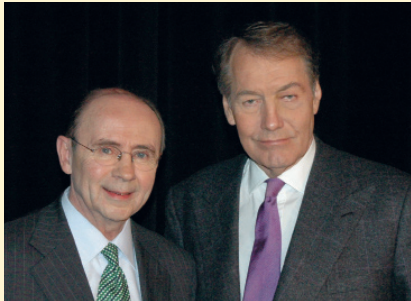
"When there is a high probability that a man's cancer may have gotten to the edge of his prostate, or spread beyond it, finding the right treatment can be a tough decision," says Partin. "This team approach has been

"It takes some men three to six months to make their rounds, see different physicians, and make the decision about the best form of treatment for them. If you have high-risk disease, you often don't have that kind of time."

an awesome experience," and it has been free of any medical turf battles. "We've had no problems coming to a conclusion. It's been very collegial. Then we give the options to the patient and his family, and they're the ones who really make the decision." So far, three urologists, three radiation oncologists, and four medical oncologists are seeing patients together.

Partin anticipates that the multidisciplinary nature of the clinic will foster unique studies and clinical trials involving new treatment combinations — surgery and chemotherapy, for example — and will contribute to ongoing work in understanding the genetics of prostate cancer, and in developing new biomarkers to detect and monitor the disease.

Patrick Walsh and Charlie Rose



Walsh and the PBS host talked about cancer, inspiration, and more.

It wasn't so much an interview as an in-depth conversation. Charlie Rose, whose talk show appears daily on PBS, recently spent half of his hour-long program talking with Patrick C. Walsh, M.D., who was named as the 2007 National Physician of the Year for Clinical Excellence by America's Top Doctors.®

They talked about many things, including the dismal prognosis for prostate cancer until 1982, when Walsh performed his first "nerve-sparing" radical prostatectomy; the dramatic change in prostate cancer survival, with better treatment and early detection; and the qualities that make for a gifted surgeon. In introducing Walsh, Rose said: "His achievements in the world of prostate surgery are remarkable; it has been pioneering, and what he has done has changed the way prostate cancer is treated."

You can watch the interview by going to this link: <http://www.charlierose.com/shows/2008/03/31/1/a-conversation-with-dr-patrick-walsh>. You may also want to look through the comments that appear below the video box on that web page, in which many prostate cancer patients wrote to tell of their own experiences.

MAKING A GIFT

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Good News for Men in Their Thirties

Although screening for prostate cancer is supposed to begin at age 40, many men don't begin thinking about prostate cancer until they're well into their forties; in fact, until a few years ago, most men did not get their first PSA test until age 50 or afterward. The average age of diagnosis is 69. In short — prostate cancer is generally regarded as a disease of older men.

And yet, some men die of prostate cancer in their thirties; others are lucky enough to be diagnosed with it, and to receive curative treatment. Fortunately, men in this age group are fairly rare — but this also means that much less is known about their cancer, and how well they fare after treatment.

"These young men are very curable, and are definitely going to live long enough to be cured."

"There have been few studies of men in their thirties with prostate cancer," says Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. "Most studies of younger men have no men younger than age 40." What sparse medical literature there was suggested that men in their thirties had more aggressive cancer. "We wanted to find out if this was true."

Walsh and colleagues Stacy Loeb, David Hernandez, Leslie Mangold, Elizabeth Humphreys, Marilyn Agro, Alan Partin, and Misop Han recently looked at the records of men who underwent radical prostatectomy at Johns Hopkins from 1975 to 2007. Of these, 42 were in their thirties; 893 were in their forties; 4,085 were in their fifties; 3,766 were in their sixties, and 182 were over age 70.

The news was good for young men: Of the men in their thirties, 81 percent had organ-confined disease, as opposed to 62 percent of men over 40. At an average follow-up period of five years, fewer than 5 percent of the men in their thirties had a detectable PSA, compared to about 16 percent of men over age 40.

"These men had a lower risk of progression of cancer," Walsh notes, "and

these results suggest that early aggressive treatment is ideal, because these young men are very curable, and are definitely going to live long enough to be cured."

STUDY:

Men with Gleason 6 or Lower: Prognosis Is Excellent

Because PSA screening is becoming widespread, many men are diagnosed with prostate cancer years earlier than they would have been 20 years ago — when diagnosis usually depended on a suspicious lump being found in a rectal exam. Most men are diagnosed with organ-confined cancer (stage T2) and a Gleason score of 6 or lower.

"These men have an excellent prognosis," says Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. Recently, Walsh and colleagues David Hernandez, Matthew Nielsen, Misop Han, Bruce Trock, Alan Partin, and Jonathan Epstein looked at 2,526 men who underwent radical prostatectomy at Johns Hopkins between 1983 and 2005, who had organ-confined disease and a Gleason score of 6 or lower.

"If you are a man diagnosed with organ-confined disease and a Gleason grade of 6 or lower, and you undergo radical prostatectomy, your changes of having an undetectable PSA in 10 years are 99.1 percent."

At an average follow-up of five years, fewer than one percent (13 men) had a detectable PSA, and at 15 years after surgery, only 1.3 percent had a detectable PSA. Five patients developed a local recurrence of cancer; four of these underwent salvage radiation therapy, and after this had an undetectable PSA. None of the men had a distant metastasis,

and no one died of prostate cancer.

"If you are a man diagnosed with organ-confined disease and a Gleason grade of 6 or lower, and you undergo radical prostatectomy, your changes of having an undetectable PSA in 10 years are 99.1 percent," says Walsh.

RADICAL PROSTATECTOMY VS. RADIATION:

How to Compare the Results?

Here is one of those situations that prompts annoying phrases like "comparing apples and oranges." There are plenty of answers, but making sense of them is a different proposition altogether. The question seems pretty simple: How can you compare the results of radiation therapy and radical prostatectomy for curing cancer? How can a man trying to make a decision about treatment — or a man who has already had either treatment, and is looking for reassurance that his cancer is gone or going away — know what to look for?

Frankly, it's a lot easier with radical prostatectomy. In the span of a few hours, the prostate is out, gone from his life forever. His PSA should be undetectable, at a level below 0.2 ng/ml., within a few weeks or months, depending on how high it was before the operation (the half-life of PSA in the blood stream is two to three days). That level is the point at which surgeons define "biochemical failure." If that level changes — and even more specifically, when it starts to change, and by how much — there are loads of data, most of it collected and studied meticulously from thousands of patients over the last two and a half decades right here at Hopkins. It is infinitely helpful that a surgeon takes out the diseased prostate, and then a pathologist can pick it up, turn it over, put pieces of it under the microscope, and just generally study the heck out of it. A urologist can tell you, based on your surgical margins and the Gleason score of the prostate specimen, the probability that you will have an undetectable PSA in 10 years. There is even a formula for estimating whether a man is at high risk of an early PSA recurrence, based on factors including

whether cancer was found in his lymph nodes, at the edges of the surgical margin, or in the seminal vesicles. This doesn't mean that PSA will return, but scientists at Hopkins have studied enough men to get a pretty good idea. If the PSA goes up after surgery, doctors also can tell, based on the time it takes for the PSA level to double, which men are most likely to benefit from radiation therapy, and which men should seek more aggressive treatment.

But radiation is different, for several reasons. For one thing, the treatment is ever-more sophisticated. With each impressive technological breakthrough, the long-term results start from scratch; this is nobody's fault — it's just the inevitable price of developing better therapy. So there really aren't long-term results for any of the new forms of radiation therapy for prostate cancer, because it is constantly being refined. We know, easily, that the treatments available now are much better than they were even a decade ago. This is very good news, but it makes it tough if you're looking for a long-term result.

The other problem is the nature of radiation itself. Because of the way radiation kills cancer cells, it is simply impossible for doctors to come up with a PSA cutoff, as they can after surgery. This is because radiation oncologists design their therapy to kill prostate cancer, not to kill normal prostate tissue. The entire prostate is not destroyed;

some tissue remains behind, and continues to make small amounts of PSA.

Radiation oncologists, then, have a real challenge when it comes to interpreting a man's PSA scores after treatment. There is "good" PSA, still being made by the remaining normal tissue. And sometimes there is "bad" PSA, if a few renegade cancer cells somehow managed to survive the treatment. There is currently no way to tell if this PSA is something to worry about. Instead, the thing to do after radiation therapy is to watch what PSA does

**There are plenty of answers,
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different proposition altogether.**

over time. The basic idea is that if the PSA is coming from benign tissue, it should remain stable; if it is coming from cancerous tissue, the PSA will rise.

But first, it falls. When it reaches its lowest point, this number is called the PSA nadir; it's different for every man. Because radiation's effect is so gradual, it may take several years for a man's PSA level to hit rock bottom. However, some men reach this point within a few months. Yet another difficulty is that if a man has had hormonal

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THE BESTSELLING BOOK ON PROSTATE CANCER IS NOW EVEN BETTER:

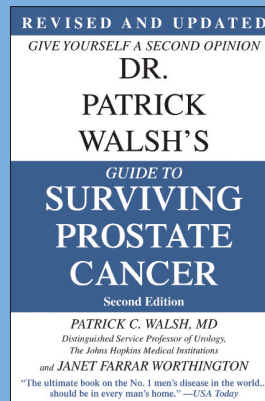
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- Why do I need to have a baseline PSA at age 40? I thought it was age 50!
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therapy before or during radiation, this can artificially lower the PSA level, and when the effect of the hormones goes away, the PSA can rise — because the man's testosterone levels are coming back up, not because of cancer. There is no prostate cancer crystal ball to tell how a man is doing after radiation therapy, but many radiation oncologists use a definition called "nadir + 2." This says that if a man's PSA has risen 2 ng/ml higher than its nadir, his cancer has not been cured. A drawback to this approach is that it may delay a man's knowledge that treatment has failed to cure cancer.

Back to the original question: How to compare radiation and surgery for prostate cancer? In a recent study, Matthew E. Nielsen, M.D., and colleagues Danil Makarov, Elizabeth Humphreys, Leslie Mangold, Alan W. Partin, and Patrick C. Walsh, examined the effect of the nadir + 2 definition on the interpretation of failure after surgery in 2,570 men who underwent radical prostatectomy from 1985 to 2004. Their work was published in the journal, *Urology*. First, they looked at the surgical definition of treatment failure — a PSA higher than 0.2 ng/ml. Of these men, 88.6 percent had an undetectable PSA at five years after surgery; 81.2 percent at 10 years, and 78.1 percent were cancer-free after 15 years. Men with a PSA higher than 0.2ng/ml may have had a nearly undetectable PSA, and no symptoms of cancer, but according to the surgical definition, their cancer was not considered cured. Using the nadir + 2 definition, they found, overestimated the rate of cure: In these same men, 94.6 would be considered cured at five years, 89.4 percent at 10 years, and 84.3 percent at 15 years would be considered cancer-free — even though they clearly had a rising PSA.

"Because patients in this series who experienced a detectable PSA level took more than five years to progress to a PSA level of 2 or greater," notes Walsh, "the five-year biochemical control rates with the definition of 0.2 ng/ml or more following surgery should be compared with the 10-year biochemical control rates for radiation therapy using the nadir + 2 definition. Until we come up with something better, this is the best way to compare the two forms of treatment."

STATINS:

Drugs that Lower Cholesterol May Help Ward Off Lethal Prostate Cancer



Elizabeth Platz

Here's another reason why lowering your cholesterol is good for you: Men on cholesterol-lowering drugs seem less likely to develop the most lethal form of prostate cancer. Platz conducted this investigation working with the massive, long-term Health Professionals Follow-up Study, in which 34,989 men have been followed for many years. As the study began, none of the men had prostate cancer. They answered a host of questions, reported all the medications they were taking, and updated this information every two years; investigators also reviewed their medical and pathology records to confirm their prostate cancer diagnosis. From 1990 to 2002, 2,579 of these men developed prostate cancer; 316 of them had advanced disease.

Platz's study revealed that men who took statin drugs not only were protected against advanced prostate cancer, but that "the longer the men used a statin, the lower their risk of getting advanced and high-grade disease," Platz says. Men who took a statin drug for less than five years had a 40-percent lower risk of developing advanced prostate cancer, and men who used a statin for at least five years had a 70-percent lower risk. This work was published in December 2006 in the *Journal of the National Cancer Institute*.

Why statins? Platz first started looking at these heart-disease drugs because she liked what they do: They have properties that

Platz loves the idea that it might be possible to improve a man's prognosis simply by giving him a statin drug or other means of keeping cholesterol low.

fight inflammation and reduce the likelihood of metastasis, and promote a cellular process called apoptosis, or programmed cell death. (Basically, cells are supposed to die; cancer cells show immortal tendencies, and don't die when they should. This results in uncontrolled growth.) "Statin drugs have exactly the characteristics you would want to find in a drug to prevent and treat cancer," she notes. Her findings were later confirmed in four other studies.

Next, in a groundbreaking study of nearly 1,400 men, Platz and colleagues made another discovery: Low cholesterol itself — whether it was lowered by a statin, or was just a natural blessing — was good news. Men with cholesterol levels under about 190 had a 40-percent lower risk than other men of being diagnosed with high-grade and possibly advanced prostate cancer. Their findings were published in the *International Journal of Cancer*.

In further work, Platz, along with Misop Han, Patrick Walsh and a doctoral student, Alison Mondul, is hoping to answer further questions — investigating, for example, whether statins can influence the pathologic characteristics of prostate cancer in men undergoing radical prostatectomy, and whether these drugs can reduce a man's risk of cancer recurrence after surgery. Platz expects results later this year.

"I am excited about this research," she notes, "because it holds the promise of directly affecting the care of men at high risk for prostate cancer that may be aggressive or even fatal; men with the disease who are at high risk for recurrence after primary treatment; and men whose cancer recurs after treatment."

Platz loves the idea that it might be possible to improve a man's prognosis simply by giving him a statin drug or other means of keeping cholesterol low. If her collaborative work continues to be successful, the next steps likely include clinical trials to investigate the ability of statin drugs to prevent or treat prostate cancer. "Prostate cancer has

been resistant to discoveries that are translatable into clinical interventions for prevention or treatment,” she says. “So, it is fortunate that a commonly prescribed treatment for cardiovascular disease — statin drugs — and its well-recognized target — cholesterol — have emerged possibly as top candidates.”

FINASTERIDE:

Are the Risks Worth it?

Does finasteride prevent prostate cancer? No — it just prevents you from knowing that you have it, says Patrick C. Walsh, M.D., who worries that men taking this drug might be dealing with bad information. Even worse, he adds, taking finasteride might mask the signs of aggressive curable prostate cancer until much later.

“Many of my patients have asked me about an article that was in the *New York Times*,” says Walsh, University Distinguished Service Professor of Urology. The article appeared on the newspaper’s front page on Sunday, June 15, 2008, and the spin on finasteride — that it somehow helps men by preventing them from knowing they have prostate cancer, so they can avoid the potential side effects of treatment — was, in Walsh’s opinion, a disaster.

The trouble with finasteride, he says, actually dates back to 2003, when the original article was published in the *New England Journal of Medicine*. The authors of that article studied 18,000 men who randomly were assigned to receive either 5 mg of finasteride (then used mainly to treat benign enlargement of the prostate; men also use it under the trade name Propecia as a treatment for hair loss) or a placebo. The men in the finasteride group had a 25-percent lower risk of being diagnosed with prostate cancer — but a 68-percent higher risk of being diagnosed with high-grade disease (a Gleason score of 7 to 10; this kind of cancer is generally more difficult to cure). “Since then, the authors have tried to erase these results and encourage urologists to prescribe finasteride for prostate cancer prevention,” says Walsh. “When these attempts failed, they recently decided to approach patients and physicians directly.”

No Decrease in Positive Biopsies

In this study, for the first seven years, men underwent a biopsy if they had an abnormal finding on a digital rectal exam, or if their PSA became elevated. But because this was a double blind study, men on finasteride did not know that their PSA levels were artificially low. For this reason, fewer men on the drug who were told to have a biopsy followed that advice. Were there fewer cancers in these men because finasteride actually prevents cancer, or because fewer men got a biopsy in the first place? “Were they fooled by their low PSA levels into thinking they couldn’t possibly have cancer?” Yes, says Walsh. In this study, 15 percent fewer men on finasteride underwent a biopsy “because they were lulled into a false sense of security by their low PSA,” he continues. “Thus, the major effect of this drug was to keep men from knowing that they even needed a biopsy.” Of the men in the study who actually underwent a biopsy, the frequency of positive biopsies for cancer was statistically the same in the men on placebo and the men on finasteride.

“If men want to prevent prostate cancer, finasteride is the last thing they should take. All it can do is prevent them from knowing that they may have lethal disease, until it may be too late to cure.”

Walsh is very concerned about the increase in high-grade disease, and the possibility, also expressed by others, that this “presents an unacceptable risk for a form of treatment that has little or no value.” Among finasteride’s critics is Stewart Justman, who wrote a book called *Do No Harm — How a Magic Bullet for Prostate Cancer Became a Medical Quandary*, which Walsh recently reviewed for the *New England Journal of Medicine*. “Whether the drug actually causes high-grade disease or merely helps find it,” says Walsh, “the fact remains that when men on finasteride are diagnosed with prostate cancer, they are more likely to have dangerous, high-grade disease.” He believes the “real harm here is that many men will be lulled into a false

Will the Real PSA Number Please Stand Up?

If you are taking finasteride, you need to be able to determine your actual PSA number.

If you have been taking the drug for:

Two years: Multiply your PSA by 2,

Between two and seven years: Multiply your PSA by 2.3

More than seven years: Multiply your PSA by 2.5

If your PSA begins to rise: Get a biopsy immediately. Your risk of having cancer is three times higher than that of men without a rising PSA, and your risk of having high-grade cancer is six times higher.

sense of security. If you are told that you’re on a drug that will prevent cancer, and your PSA falls, you aren’t going to be on your guard.” Walsh wants men taking finasteride to know that if their PSA — no matter how low it is — begins to go up at all, they need to have a biopsy right away, “because their risk of having cancer is three times higher than for men without a rising PSA, and because they are six times more likely to be diagnosed with high-grade disease.”

Risky Business

Recently, Walsh has seen this risk in action twice, in two patients “who thought they were okay,” but weren’t. They had been taking Propecia (a form of finasteride that’s used to restore hair loss) for 10 years. “One man had a PSA of 3.8, and the other had a PSA of 4,” Walsh explains. But because finasteride lowers PSA levels, a little math is needed to figure out the true PSA number (see box), “and these men actually had PSA levels between 9 and 10. Both of them had high-grade prostate cancer, Gleason 8 disease, that had spread outside the prostate. One of them had a positive surgical margin.”

Walsh, who has spent his career working to save lives from prostate cancer, through

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better treatment combined with earlier diagnosis, is greatly troubled by the recent push for men to take finasteride. “I am very concerned about encouraging patients and general physicians to use this drug,” he says. “First, it has no primary effect in reducing the number of men who will have a positive biopsy. Second, men will believe that it prevents cancer, will be pleased that their PSA levels fall, and will not understand the potential danger they’re in — of undiagnosed high-grade disease.”

As a treatment for BPH, finasteride is fine, Walsh says, as long as men who are being screened for prostate cancer understand the guidelines (see box). “If men do not want to know if they have prostate cancer,” he continues, “they should just avoid PSA testing. This will save them \$730 a year (the cost of finasteride), and will avoid the increased risk of high-grade disease. If they want to prevent prostate cancer, finasteride is the last thing they should take. All it can do is prevent them from knowing that they may have lethal disease, until it may be too late to cure.”

Not Just Sparing the Nerves, But Giving Them Extra Protection

Surgeons who perform the “nerve-sparing” radical prostatectomy (developed at Hopkins by Patrick C. Walsh, M.D.) take great pains to preserve the tiny nerves that are responsible for erection. But these nerves are notoriously fragile, easily injured, and — although they recover their function in the vast majority of men who undergo this operation from a skilled, experienced surgeon — sometimes slow to heal. It can take months or even more than a year for some men to recover erectile function after surgery; some men, for reasons no one understands, do not recover this ability on their own (although there are many good treatments, including Viagra and similar drugs, to help with erectile dysfunction).

Surgeon-scientist Arthur L. Burnett, M.D., has spent much of his career working

It’s the same basic idea as taking antibiotics before dental work — except in this case, the goal is to cushion and strengthen the nerves for the ordeal they’re about to endure, and the inflammation that inevitably happens afterward.

to understand how these nerves are injured. Is it possible to protect them — to give them extra armor before, during, and immediately after surgery? It’s the same basic idea as taking antibiotics before dental work — warding off infection before it starts — except in this case, the goal is to cushion and strengthen the nerves for the ordeal they’re about to endure, and the inflammation that inevitably happens afterward.

“Our goal is twofold,” says Burnett: “To improve surgical techniques, for maximal nerve preservation, and also to develop new neuroprotective treatments, to be given at the same time, for the very best chance of erectile function recovery.” What Burnett does falls into the area of neuro-urology, and he is at the forefront of this very small group of scientists and specialists worldwide. Burnett spent years studying at Hopkins in the lab of the great neuroscientist Sol Snyder, whose pioneering work, with Burnett, led to the discovery that nitric oxide is a major chemical responsible for erection. Burnett became convinced years ago that with the right nerve-protecting agent, it might be possible to speed up the nerves’ recovery time after radical prostatectomy — or, ideally, to minimize injury altogether.

He has found a drug that looks highly promising — erythropoietin, also known as EPO. EPO is a natural product, made by the kidneys. “Its ability to improve the blood cell count in people with anemia is well known,” notes Burnett. Recently, scientists have discovered that EPO has other valuable qualities: “It can protect nerves, and facilitate their functional recovery after injury.” In laboratory experiments, Burnett and Mohamad Allaf, assistant professor of urology, found that mice given EPO showed better recovery of erectile function than those who recovered from nerve

injuries (similar to those that happen in radical prostatectomy) on their own.

Based on this progress, in a recent small study, Burnett and colleagues gave erythropoietin to men who underwent radical prostatectomy. Monitoring their progress for at least a year, they found that men who received one dose of EPO before surgery recovered erections better than men who were not given the drug. Although this was a retrospective study, and cannot be considered definitive, Burnett says, “it does give us a strong basis to consider moving forward with a prospective, controlled clinical trial. Such a clinical trial is now awaiting approval.”

The Cancer Seems Small: Is It Safe to Treat Just One Part of the Prostate?



Jonathan I. Epstein

Of all the possible adjectives to describe prostate cancer, two of the most important ones are “bilateral” and “multifocal.” This is true even for a man lucky enough to be diagnosed with potentially insignificant cancer.

Expectant management may be one good option (see side story). But if the man opts for curative treatment, he ought to choose a treatment that eradicates all of the prostate. This, says Jonathan I. Epstein, M.D., would rule out one potential option: Cryosurgery — freezing the tumor — on just one part of the prostate.

The idea there, called unilateral (treatment on just one side of the prostate) cryosurgery, is to treat minimally, just on the area that needs it. This would be “a focal treatment for prostate cancer that, on biopsy, is confined to one prostate lobe,” says Epstein. However, he cautions, “prostate cancer is generally not a focal, unilateral disease.” He should know; Epstein, the *Rose-Lee and Keith Reinhard Professor of Urologic Pathology*, has looked at thousands of prostate cancer specimens, and

Learning More About the Risks of Expectant Management

More men than ever are being diagnosed with prostate cancer when it is very early — with minimal, low-grade cancer. Some of these men choose to have the cancer removed; at Hopkins, about a fourth of men who undergo radical prostatectomy have this kind of “insignificant” disease. But some of these men, with their doctor’s guidance, decide on a course of “expectant management” — active surveillance, with PSA and needle biopsies, until there is evidence that the cancer has progressed.

“A concern for these men is whether their cancer will become worse in grade over time,” says Jonathan I. Epstein, M.D., the *Rose-Lee and Keith Reinhard Professor of Urologic Pathology*. This movement from a nice, harmless, low-grade cancer toward a higher-grade cancer that needs to be treated is called “dedifferentiation.” Differentiated cells have well-defined, or differentiated, walls, and grow slowly. The worst cancer cells are poorly differentiated, and seem to melt with other cells into blobs.

What can these men expect? Until recently, no one knew. In a recent study, led by Epstein and published in the *Journal of Urology*, pathologists moni-

tored grade changes over time in 241 men with cancer considered “good” enough to follow expectantly — too small to be felt, with an initial Gleason score of 6 or lower. For the majority of men, the cancer did not progress right away. “Our results suggest that if dedifferentiation does occur, the risk is low in the short-term,” Epstein says.

But sometimes it did progress, and this seemed to happen fairly quickly. Epstein suspects that these men probably had more advanced cancer cells in the prostate all along — but they had so few of them, they weren’t detected by needle biopsy. About 19 percent (45 men) showed a significant change in grade to a Gleason score of 7 or higher (41 men), and 4 men showed a Gleason score of 8. “About half of the men who moved to a higher grade did so within 24 months of diagnosis,” says Epstein.

Other men showed an increase in Gleason grade after three years, and “this may represent true dedifferentiation,” says Epstein. Many of the men in this study had multiple biopsies over three years of follow-up, and showed no change. “This suggests extremely low volumes of tumor in these patients, and very slow-growing tumors,” says Epstein. “These results should be reassuring to patients suspected of harboring small-volume, low-grade cancer, and they further support the concept of active surveillance as a reasonable alternative to immediate surgery or radiation.”

In work recently published in the *Journal of Urology*, Epstein and colleagues studied 100 consecutive radical prostatectomy specimens of men who would be ideal candidates for the focused cryosurgery — men in whom “the needle biopsy predicted limited disease, and all of the positive needle cores were restricted to one side of the gland,” he notes. On average, each man had about three separate tumor nodules, and the majority of men — 65 percent — turned out to have some cancer on the opposite side of the prostate, the part that had been considered cancer-free. “In most of these men, the tumor opposite to the positive biopsy side was very small.” However, in a fifth of these men, the tumor on the supposedly “good” side of the prostate was worse —

either of a higher grade, or bigger, in some cases extending beyond the prostate or to the surgical margins — than the cancer that had originally been found. “Urologists need to be informed and patients should be told the risks of leaving significant cancer behind prior to undergoing experimental focal therapy,” says Epstein.

INSPIRED BY LANCE ARMSTRONG:

“Turning up the Heat” on Prostate Cancer

Funded by Safeway, its customers, and the Prostate Cancer Foundation, Led by Hopkins

Long before cyclist Lance Armstrong did what many considered impossible — winning the Tour de France race an unprecedented seven times — he did something equally remarkable, by beating devastating cancer that was well on its way to killing him. His amazing recovery has intrigued Hopkins scientists Donald S. Coffey, Ph.D., *The Catherine Iola and J. Smith Michael Distinguished Professor of Urology*, and Robert Getzenberg, Ph.D., for many years, and now it has inspired a whole new form of treatment.

Armstrong had very advanced testicular cancer — cancer so bad that it had spread throughout his body, including to his brain and liver. And yet, he was completely cured. “We had to know,” says Getzenberg, the Brady Research Director and the *Donald S. Coffey Professor of Urology*, “what makes testicular cancer so curable — even when it’s widespread? And how can we apply this to other solid cancers, like prostate cancer?” Getzenberg and Coffey believed that they key to the “Lance Armstrong Effect” had to do with heat, and they called their idea “Temperature Enhanced Metastatic Therapy” (TEMT).

“The reason the testes are outside the rest of the body is that they exist at a much cooler temperature,” Getzenberg explains. If normal testicular cells move up into the body — into an atmosphere that, to them, is a sweltering 98.6 degrees — they stop functioning. “Our idea of why testicular

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In some men, the tumor on the “cancer-free” side of the prostate was worse than the cancer that had originally been found.

has helped define the pathological study and classification of this disease. The cryotherapy idea is like removing a bad spot on an apple — leaving the rest intact. But prostate cancer is typically more like the seeds dotted all over a strawberry. The best way to make sure every tiny seed of cancer is removed is to get rid of the entire fruit.

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cancers are so sensitive to therapy is that once they move from their cooler site, they are more vulnerable, and especially sensitive to heat.” Scientists already knew that raising the temperature of cancer cells makes them much more susceptible to many kinds of treatment — chemotherapy, radiation therapy, and immunotherapy. Getzenberg and Coffey speculated that the heat somehow resulted in the structure of the cell’s nucleus becoming unstable. They figured that they could exploit this by warming — in a highly targeted way — the metastatic sites of a tumor, and then, once the cancer cells were vulnerable, blasting them with other treatments. “This new way of thinking about treating advanced cancer opens doors into new approaches that may help men with advanced prostate cancer.”

This TEMT approach has so much potential that, in a first-time ever project, Safeway Inc., the food and drug retailer, and the nonprofit Prostate Cancer Foundation have donated \$6 million to fund a special program, called S.T.A.R. (for Special Team Amplification of Research), to explore the role of targeted heat and other strategies to treat prostate cancer. Led by Getzenberg, and including Hopkins colleagues Coffey and Theodore L. DeWeese, M.D., head of Radiation Oncology and Molecular Radiation Sciences, the program also puts together an interdisciplinary team of investigators from the University of Michigan Cancer Center and the University of British Columbia.

Safeway’s customers raised \$3 million, in donations made at checkout. The Prostate Cancer Foundation (PCF) developed the collaborative research partnership and matched this money, dollar for dollar. The PCF will also bring in expertise from scientists at the University of Washington, from M.D. Anderson Cancer Center, and from Emory University. “Everyone who has input will be invited to the table,” says Jonathan Simons, M.D. — a Hopkins-trained oncologist and Brady alumnus — CEO and President and *David H. Koch Chair* of the PCF. “We are literally turning up the heat on metastatic prostate cancer.”

“We are pleased and honored to be associated with the S.T.A.R. Program initiative,” says Safeway’s Chairman, President, and CEO, Steve Burd, “and what promises to be pioneering work by some of the world’s top cancer researchers.”



NEW SPACE FOR DISCOVERY, COLLABORATION: Discovery at the Brady has always thrived because surgeons and scientists have worked side by side — except in recent years, when the Institute expanded and space became too cramped. Now, thanks to the generosity of Maria and Andre Jakurski and the Peter Jay Sharp Foundation, collaboration thrives in a new, state-of-the-art, 12,000-square-foot facility. Located on the second floor of the Park Building, immediately adjacent to the Brady inpatient floor, the space is divided into modern laboratory facilities, faculty offices, and expanded workstations for staff.

Armstrong had very advanced testicular cancer. And yet, he was completely cured. How could this happen in prostate cancer?

The program’s goal, says Getzenberg, is to figure out the best way to use heat selectively — aiming at the cancer cells only, but leaving adjacent healthy tissue unscathed. One way to do this may involve ultra-tiny “nanoparticles,” which are attracted to specific proteins on cancer cells. “Once the nanoparticle locates the specific protein, it can enter the cancer cell, heating it from the inside out after exposure to a magnetic field,” Getzenberg continues. “We are actively studying this and other mechanisms for targeted heat delivery to cancer cells. We need new approaches to cancer, and this one has great potential.”

EPCA-2 Update

In other news, Getzenberg and colleagues are moving “aggressively” on EPCA-2, a new biomarker we reported in the last issue of *Discovery*, working hard to make it available to men with prostate cancer, and to men who

are being tested for it. This marker has proven to be more sensitive than PSA, and a more specific test for prostate cancer. In early tests, it also performed better than PSA in showing which men had organ-confined cancer, and which men had cancer that had spread beyond the prostate. “One aspect of our work has been to increase its throughput,” says Getzenberg, so they can “run a large number of samples in a short period of time.” The scientists have conducted several clinical trials, including one in which they were able to correlate a man’s level of EPCA-2 with his likelihood of responding to radiation therapy. “We are also in the final stages of determining the most appropriate large commercial partner to develop the test for patients.” The EPCA-2 test is not yet available.

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.

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 began four years ago, and remains strong today, as the result of the great generosity of many patients and friends. The idea was new: A call to Hopkins scientists of all disciplines, looking for good ideas worth pursuing that might lead us a few steps closer to a cure for prostate cancer.

Since then, we have funded proposals from the best and brightest scientists at Hopkins in many departments, including: 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 (for more on this Board, see page 16), and Samuel Himmelrich. So far, we have raised \$30 million, and received nearly 150 applications. This year, we awarded more than \$1 million to 15 recipients. Some of their work is described below.

THE 2008–2009 AWARDEES

Charles Drake, M.D., Ph.D.

Department of Oncology

William B. Isaacs, Ph.D.

Irene and Bernard L. Schwartz Scholar

Department of Urology

Marikki Laiho, M.D., Ph.D.

*Department of Radiation Oncology
and Molecular Radiation Sciences*

William G. Nelson, M.D., Ph.D.

Nancy and Jim O'Neal Scholar

Department of Oncology

Edward M. Schaeffer, M.D., Ph.D.

Virginia and Warren Schwerin Scholar

Department of Urology

Bruce J. Trock, Ph.D.

Carolyn and Bill Stutt Scholar

Department of Urology

Srinivasan Yegnasubramanian, M.D., Ph.D.

Dr. and Mrs. Peter S. Bing Scholar

Department of Oncology

Hui Zhang, Ph.D.

Department of Pathology

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

Angelo De Marzo, M.D., Ph.D.

Beth W. and A. Ross Myers Scholar

Department of Pathology

Jun Luo, Ph.D.

Phyllis and Brian L. Harvey Scholar

Department of Urology

Alan Meeker, Ph.D.

Departments of Urology and Oncology

George Netto, M.D.

Department of Pathology

Dan Stoianovici, Ph.D.

R. Christian B. Evensen Scholar

Department of Urology

What Does the Prostate's Very Early Development Have To Do With Advanced Cancer?

Edward M. Schaeffer, M.D., Ph.D., the *Virginia and Warren Schwerin Scholar*, has made great strides in understanding how the prostate develops, how hormones affect this, and how what happens before a man is even born has a lot to do with the most dangerous kind of prostate cancer.

In extensive work with pathologist David Berman, M.D., Ph.D., and others, Schaeffer has figured out how male hormones, called androgens, make the prostate develop. He helped create a painstaking roadmap to chart all the genes that get turned on as the prostate grows explosively, turning from a tiny bud into an organ. This same program of growth, he and Berman have found, is reactivated in prostate cancer — especially when the cancers morph into more advanced and invasive types. It's *deja vu* of the worst kind: "In many ways," he says, "it's like a reversion to an earlier state."

If you've ever seen time-elapsed photography, you can imagine what it's like for scientists watching the progress in an embryo. With remarkable speed, the embryo

does its job — moving from one cell to a few primitive tissues, to forming organs. In the developing prostate, this rapid growth is driven and regulated by androgens; this happens in cancer, too — particularly in the most aggressive and malignant tumors. In their research, recently published in the journal, *Oncogene*, Schaeffer and Berman also discovered that some other genes, previously unrecognized, are turned on in both processes, as well. One gene, the transcription factor Sox9, causes growth in the develop-

Instead of reinventing the wheel, prostate cancer is grimly practical; it just recycles.

ing prostate, and is expressed abnormally in early prostate cancers. Another, called Annexin A1, prevents cells from dying — which all cells, normally, are supposed to do.

"These results help us understand better how prostate cancers develop," says Schaeffer. "Prostate cancer is not a random process." Instead of "reinventing the wheel," prostate cancer is grimly practical; it just recycles. "It uses many of the same aggressive growth programs from development." The big difference however, is that one process is not fatal. "The growth programs that stop in development keep going in cancer. Our next key step will be deciphering ways to turn these processes off in cancer."

Chemically Silenced Genes Give Clues to Cancer, Lead to New Tests

Bill Nelson, M.D., Ph.D., the *Nancy and Jim O'Neal Scholar*, has spent much of the last two decades making sense of the subtle, tiny clues that lead to prostate cancer. His pioneering work led to the discovery that a critical gene called GSTP1 (pronounced "GST pie") fails early on in prostate cancer. In recent years, he has learned why this happens: Because of chemical warfare on a very small scale — a genetic process called methylation. Now, with Srinivasan Yegnasubramanian, [continued on page 12]

THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND AWARDEES

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M.D., Ph.D., the *Dr. and Mrs. Peter S. Bing Scholar*, Nelson is discovering new ways to target this process.

GSTP1 is a casualty of methylation. A methylated gene is chemically made useless — like a zipper given an extra tooth, or a ball that's covered with quills like a porcupine. GSTP1 is silenced early on in prostate cancer, for good reason: This gene is one of the good guys. It's a bodyguard, one of the few defenses standing between the prostate and cancer. With GSTP1 out of the way — it is knocked out in more than 90 percent of men with prostate cancer — cancer can proceed much more easily.

Nelson and other Brady scientists, including Don Coffey and Angelo De Marzo, have made many groundbreaking discoveries involving the epigenetics — small but significant changes, such as methylation, in gene expression — of prostate cancer. Looking at methylation changes in genes, they have found other important landmarks for cancer — particularly, abnormal clumps of DNA called “hypermethylated CpG islands.” These appear on GSTP1 before the gene is silenced. On the other hand, *hypomethylated* (undermethylated) DNA is very active, interacting with many different proteins. (Note: Their work has been reported in previous issues of *Discovery*, and is available at our website: <http://urology.jhu.edu>).

In prostate cancer, it seems that methylation is all over the map: “By the time most cancers become life-threatening, there is *increased* methylation in some regions (the hypermethylated CpG islands in GSTP1 and other genes), and *decreased* methylation in others,” says Nelson. He and colleagues recently carried out a definitive analysis of hypomethylation, published in November in *Cancer Research*.

In sophisticated gene-profiling research, Nelson, Yegnasubramanian, and colleagues isolated genes from prostate tissue that were found only in cancer, not in normal cells. Of these, they identified several genes that were undermethylated, which were expressed at high levels in prostate cancer cells. “Some of these genes are already being targeted by anti-cancer vaccines now in clinical trials,” Nelson says.

This research also seems to have given some chronological order to the methylation

changes that can be found in the cells of men with prostate cancer. Hypermethylation happens earlier, and is seen in localized, easily curable cancer. But the presence of hypomethylation is a bad sign, Nelson says. “This appears when cancer is more advanced, and is likely to have spread to distant sites.”

Based on Brady methylation research, a new test looks at cancer-negative prostate biopsies, and predicts the likelihood that a future biopsy might show the presence of cancer.

The “Melting Pot” of Advanced Cancer

As cancer matures, like a good stock portfolio, it diversifies. Instead of one or a few kinds of cells — which are much easier to target and cure — it is a malignant mix of cells, a bad melting pot. “This is called tumor heterogeneity,” explains Yegnasubramanian, “and it makes it very difficult to develop targeted therapies aimed at killing so many different kinds of tumor cells. But now that we have discovered that hypomethylation can be a cause of this heterogeneity, we can develop new weapons to help us control these genes.”

Nelson, Yegnasubramanian, and colleagues including Alan Partin and Bruce Trock are translating what they've learned about DNA methylation changes into clinically useful tests. Based on the Brady research, a company called LabCorp has produced a GSTP1 methylation test that looks at cancer-negative prostate biopsies, and predicts the likelihood that a future biopsy might show the presence of cancer. “For the future,” says Nelson, “we hope to identify DNA methylation changes that can be easily detected in blood or urine. We also hope to be able to stratify a man's risk of prostate cancer into groups, and even to predict which treatments will work best.”

Setting a “Speed Limit” on PSA

All prostate cancer is the same, and all of it needs to be treated. Right? No! But which prostate cancer is bad, and which cancer is slow-growing, not aggressive, and not likely to cause any trouble? Maybe this is not the right question. Instead, says urologist H. Ballentine Carter, M.D., the *Peter Jay Sharp Foundation Scholar*, the answer may lie in setting a “speed limit” for PSA.

“Prostate cancer detection has always focused on finding all cancers, regardless of their potential to cause harm,” says Carter, a pioneer in the study of PSA and the clinical definition of “incidental” prostate cancer (very slow-growing cancer that happens to be in the prostate, but doesn't ever seem inclined to leave it), which is often detected by regular PSA screening and treated needlessly. “Many investigators are looking for methods of preferentially identifying cancers that are destined to cause harm, as an alternative to detecting all prostate cancers.” But Carter has another idea: A new approach, called “risk count assessment,” which doesn't look at the cancer itself as much as what it does. His work, done along with colleagues Anna Kettermann, Luigi Ferrucci, Patricia Landis, and Jeffrey Metter, was published in *Urology*.

Carter's approach doesn't look at good vs. bad cancer, but at what the cancer does.

Using data from the Baltimore Longitudinal Study of Aging (BLSA), Carter, along with investigators in the Brady and the National Institute on Aging, has found that “the number of times a man's PSA exceeds a speed limit is directly related to his risk of having harmful prostate cancer.” This speed limit is also known as PSA velocity — how fast a man's PSA level changes from year to year.

In this study, the PSA levels of 717 men were followed for between 20 and 30 years; 32 of these men had harmful cancers. Carter looked at how the levels changed over time, and also worked to figure out the proper yearly “speed limit.” How much of

a change in PSA is okay? “If the PSA speed limit was 0.4 ng/ml per year,” he reports, “a man who exceeded this limit once had a 15-percent chance of harboring a harmful prostate cancer, and if there were three ‘speeding violations,’ his chance went up to 30 percent. However, if we raised the speed limit to 0.75 ng/ml per year, one violation was associated with about a 20-percent of harmful cancer, and a 60-percent risk of it with three violations.”

The bottom line here, Carter says, is that increases in PSA — no matter how low the actual level is — should be viewed as evidence of the possible presence of a harmful cancer, “especially if the PSA increases occur repeatedly.”

Putting the Brakes on Prostate Cancer: Time for “Peter Pan” to Grow Up

A cancer cell is a lot like Peter Pan: It doesn’t want to grow up. Normally, cells are supposed to divide and generate new cells, and then mature into differentiated cells, with well-defined boundaries — on a very small scale, the equivalent of settling down and having a fenced-in yard in the suburbs. This maturation is called “terminal differentiation,” and cancer cells don’t do it. They do not complete this process, and “there is abundant evidence that this contributes to their unlimited potential to grow, divide and ultimately causes loss of life,” says pathologist Angelo De Marzo, M.D., Ph.D., the *Beth W. and A. Ross Myers Scholar*.

What is wrong with these cells? Why don’t they want what the rest of us are supposed to want — to grow up, do their jobs, have a nice, peaceful life, and not cause any trouble?

Something is missing: A key brake to prevent rampant cell division. De Marzo believes he and colleagues have not only identified an important culprit, but they’ve found out why this is happening in men who get prostate cancer.

More than a decade ago, as a postdoctoral fellow working with legendary Hopkins scientist Donald S. Coffey, Ph.D., De Marzo learned that a protein called p27 was decreased in prostate cancer cells. This

protein is known as a “cell cycle control gene,” which means it helps put the brakes on out-of-control growth. But p27 was even decreased in prostate cells that hadn’t yet become cancerous; these cells, misfits that are not cancer, but not normal, either, are called prostatic intraepithelial neoplasia (PIN), and they are direct precursors to prostate cancer. In the normal prostate, p27 levels were highest in the most mature, “well-adjusted,” terminally differentiated cells.

Scientists have known, from research in mice, that inactivating p27 in the prostate causes the development of early prostate cancer. Men with low levels of p27 tend to have cancer that is more advanced and difficult to cure. But no one has figured out how or why p27 is decreased in prostate cancer.

Cheryl Koh, a Ph.D. student working in De Marzo’s laboratory, may have uncovered a possible explanation: a protein called MYC (pronounced “mick”). This work stemmed

What is wrong with these cells? Why don’t they want what the rest of us are supposed to want — to grow up, do their jobs, have a nice, peaceful life, and not cause any trouble?

from a recent finding just published online by Bora Gurel, M.D. (a postdoctoral fellow working with De Marzo) and others, including De Marzo, William B. Isaacs, Ph.D., and Jun Luo, Ph.D., and Chi Dang, M.D., Ph.D., a renowned expert on MYC, of the McKusick-Nathans Institute of Genetic Medicine at Johns Hopkins.

MYC, which lives in the nucleus of cells, is an administrator type; it regulates cells’ proliferation and growth. In normal cells, MYC makes few public appearances, appearing only briefly, and at low levels. When something goes wrong, when MYC doesn’t function properly and is churned out at abnormally high levels in cells, it can cause cancer; in fact, unregulated MYC has been demonstrated in many types of cancer. This recent work by Gurel and colleagues showed,

for the first time, that MYC protein levels are elevated in most human prostate cancers and in PIN lesions. Thus: When MYC goes up, p27 goes down, and this leads to prostate cancer.

In laboratory experiments, Koh knocked down levels of MYC protein in prostate cancer cells. In four different types of prostate cancer cells, she found that this profoundly inhibited cell division. “These are very exciting results,” says De Marzo, who had worried that advanced cancer cells — such as those tested by Koh — might have figured out how to bypass MYC, and to grow on their own. “These studies suggest that prostate cancer cells remain addicted to MYC, in that they still need it to divide.”

Looking at samples of prostate cancer tissue under the microscope, De Marzo observed that cells which expressed high levels of MYC “appeared to be the identical cells that contained low levels of p27.” Armed with these observations, Koh then discovered that when she decreased the level of MYC in prostate cancer cells, not only did cell proliferation go down, but p27 went up — and this seemed to put the brakes back on cancer cell division. When Koh simultaneously inhibited p27 and MYC, cell proliferation did not go down as much. This revealed that more p27 is required to stop prostate cancer cell proliferation when MYC is reduced.

The next step, De Marzo says, is to determine precisely how MYC is regulating p27. “We will harness the expertise of all our collaborators, including Dr. Dang, to help us uncover these mechanisms.” Even more exciting, he adds: “This new work suggests that methods to decrease the activity of MYC in cancer cells — which are already under development in other laboratories — may be useful in treating prostate cancer in the clinic.”

MRI Robot Is Powered by a Brand-New Kind of Motor

Dan Stoianovici and colleagues have created a new kind of motor — a marvel, made of plastic, ceramic, glass and rubber. It has no metal and uses no electricity; instead, it runs

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Dan Stoianovici: Robot does not affect MRI magnets.

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on puffs of air, with fiber-optic sensors. Just by itself, this motor, which took three years to design, is big news in the engineering world. As complicated as our technology has gotten, everything is still powered by just a handful of different types of motors. But the new motor, called PneuStep, is only half the story: It wasn't created as an academic exercise, but to fill a pressing need — to power a new robot that can work within the magnetic field of MRI.

Why a robot? MRI requires the patient to lie inside a big tube; there's not room for the doctor to be in there, too.

MRI (magnetic resonance imaging) technology is so good these days that it can show the prostate clearly, with great detail. It has the potential to offer the most accurate placement yet of radioactive seeds to kill prostate cancer, except for one big problem: Conventional motors won't work with MRI, because they are made of metal, and they interfere with the strong magnets in the machines. Because the PneuStep motor is metal-free, it can operate inside the scanner. (A robot is necessary because MRI requires the patient to lie inside a big tube; there's

not room for the doctor to be in there, too.) Recently, Stoianovici and colleagues demonstrated that this robot can place seeds with remarkable accuracy. Their work, which was funded by the National Institutes of Health, was published in the journal, *Radiology*.

In animal studies, the scientists made tiny targets, put needles in them, and then inserted dummy seeds through these needles, placing the seeds exactly where they wanted them to go.

These were early tests, and more work is needed before the new robot, and the motor that drives it, can be used to help men with prostate cancer. But it's a highly promising beginning.

"Another exciting aspect of the robot is that we designed it with a modular structure," says Stoianovici, the *R. Christian B. Evensen Scholar*. Like a high-tech LEGO system, its parts can be interchanged. "It is easy to exchange the current seed-placing end with one designed for a different procedure. We can design alternative end pieces to perform biopsies, inject liquid agents, and insert cryotherapy or radiofrequency probes. We believe our robotic system will be able to improve the performance of a number of procedures to treat and diagnose prostate disease."

How Do You Measure a "Smart Bomb?"



John Isaacs

Years ago, John Isaacs, Ph.D., and Samuel Denmeade, M.D. chose as their academic mission undoubtedly the most difficult area of prostate cancer — the one with the greatest need — metastasis. When cancer spreads

The beauty of this approach is that it does not affect healthy tissue, and in laboratory studies using human prostate tumor cells, these "smart bombs" are indeed shrinking the cancer.

beyond the prostate, it is difficult to cure, and when it sows its seeds at far-flung sites in the body, it is impossible to cure. Cancer can be delayed, often for years, but it cannot be killed.

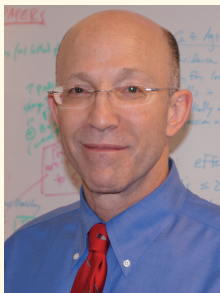
One reason is that it's impossible to know exactly where the cancer is. So Isaacs, professor of urology, and Denmeade, associate professor of oncology, have been making "smart bombs" that — like heat-seeking missiles — follow a trail. In this case, the missiles are designed to track PSA, which, normally, is an enzyme that, as the old commercials used to say, "slices and dices" — except what it cuts are pieces of protein, and this only within cancerous tissue. Once the molecular missile finds its target, it attacks the prostate cancer cells by restarting a normal process that cancerous cells lack — the ability to die; it makes them mortal again. The scientists have identified several new "smart bomb" drugs that cause the cells to kill themselves; this process, which happens all the time in normal cells, is known as apoptosis.

The beauty of this approach is that it does not affect healthy tissue, and in laboratory studies using human prostate tumor cells, Isaacs and Denmeade have found, these "smart bombs" are indeed shrinking the cancer. How well are they working? That's the next question, and the scientists have designed and synthesized some specially tagged molecules — which can be seen through radiologic imaging — to act as little signal flares, to show where the cancer is, and if all goes well, to show that it is being killed.

"These molecules are activated by being cut up, either by PSA (prostate-specific antigen) or by another enzyme on the prostate cell's surface, PSMA (prostate-specific membrane antigen)," says Isaacs. "Since

both of these enzymes are only expressed in high levels by prostate cells, they will only be activated at the metastatic sites where the prostate cancer cells are growing. This way, we can see how well the individual sites of metastasis will respond, and know how well our drugs are working.”

Radiation Therapy Prolongs Life in Men with Recurrent Cancer



Bruce J. Trock

It is a question that dogs every man who undergoes surgery for prostate cancer. Even in the best possible conditions, even if the odds are extremely unlikely, this niggling thought is there. What will I do if my cancer comes back?

There is good news: Radiation therapy. A new study, published in the *Journal of the American Medical Association*, and led by Bruce J. Trock, Ph.D., the *Carolyn and Bill Stutt Scholar*, shows that carefully selected men in this situation are more likely to experience prolonged survival if they undergo “salvage” radiation therapy within two years of the recurrence.

“We were surprised to find that the men who did the best were those whose tumors were growing the fastest,” says Trock, Director of the Brady’s Division of Epidemiology. “Although we knew, from other research, that salvage radiotherapy decreased the progression of disease, this is the first study to show that it significantly prolongs survival — even in men with aggressive disease. It also means that we may be able to give radiation selectively to those who are really likely to benefit from it.”

“I found the results of this study remarkable,” said Patrick C. Walsh, M.D., University Distinguished Service Professor of Urology. “Previously, we believed that these men — who have aggressive disease defined by a rapid doubling of PSA in six months or less — had distant metastases and would not benefit

from any form of local salvage therapy.”

The scientists reviewed records of 635 men who developed recurrent cancer following radical prostatectomy at Hopkins between June 1982 and August 2004. Of these, 397 did not receive salvage radiation therapy, 160 received only salvage radiation, and 78 received both salvage radiation and hormonal therapy. The average follow-up was six years.

Among men who had received salvage radiotherapy, the likelihood of surviving 10 years was 86 percent, compared to 62 percent for those who did not have radiation. Men with particularly aggressive tumors (defined by a PSA doubling time of less than six months) were helped by salvage radiation therapy, regardless of their Gleason score. The survival benefit, however, was limited to men whose PSA decreased to an undetectable level after the radiation, even if it began to rise again later.

“This is the most important news for this group of patients in a long time.”

“This review suggests that even patients with aggressive cancer at the time of surgery may not only benefit from salvage radiation therapy, but also actually live longer without a second prostate cancer recurrence,” said Theodore L. DeWeese, M.D., Chairman of the Department of Radiation Oncology and Molecular Radiation Sciences. “This is the most important news for this group of patients in a long time.”

When Hormones Stop Working: New Receptors May Explain Why

The most confounding aspect of hormonal therapy for prostate cancer — depriving the prostate of testosterone and other androgens (male hormones), that nurture it — is that at first it works very well; in fact, it can keep working for many years. But eventually, in most patients it stops working, and the

cancer becomes what doctors call “hormone-refractory.” The cancer, continually evolving and worsening, somehow develops the ability to survive even in the absence of hormones, and when it reaches this point, cancer is at its deadliest.

This is the last-ditch stage of metastatic cancer, and Jun Luo, Ph.D., the *Phyllis and Brian L. Harvey Scholar*, may have found a crack in its armor — newly discovered androgen receptors. Hormones work in the body as chemical signals, which act as keys for highly specific locks, called receptors. “In order to function properly,” says Luo, “androgens entering the prostate cancer cells need to find and tag the androgen receptor. The tagged androgen receptor then migrates to the cell nucleus, and activates an army of genes that support the growth of prostate cancer.” This is called the androgenic signaling pathway, and “despite decades of effort, there is still much to explore before we will fully understand how this pathway works in hormone-refractory prostate cancer.”

Luo and colleagues discovered sneaky new forms of androgen receptors that somehow manage to keep this pathway going — even without hormones — and relay the androgenic signals without being tagged by androgens. Like stealth planes, they don’t get picked up on the radar. “These new androgen receptors, unlike the androgen receptors previously known to us, can support prostate cancer growth in the complete absence of androgens,” says Luo. “This discovery may help to explain how prostate cancer cells escape hormone treatment and become hormone-refractory.” In normal prostate tissue, Luo and colleagues found, these new receptors are present at low levels. But in hormone-refractory cancer cells, they are “increased by twenty-fold.” The next step, he says, “is to design specific inhibitors for these new androgen receptors, to see whether this will help block the progression to hormone-refractory prostate cancer.” The scientists also hope to develop biomarkers “that may help to monitor the effectiveness of treatment, and also help determine which patients are more likely to benefit from hormone therapy.”



THE BRADY UROLOGICAL INSTITUTE

Not On My Watch



Some people get through cancer, after treatment, by looking at it one way — in the rear-view mirror, as they push the pedal to the floor and race away from it as fast as they can. They don't want to think about it

ever again, and no one can blame them. Others become interested in the disease, especially if there is a risk — as there is in prostate cancer — that their sons or grandsons might one day face this same cancer. They read everything they can about it. They learn about the research, about new developments in prevention, and screening, and the continuing effort to develop new treatments. Many of them — many of you reading this — even help support the work we do here at the Brady Urological Institute, for which we are profoundly grateful.

Despite their varied backgrounds, they all have one thing in common: They are absolutely committed to curing prostate cancer, and they believe the cure will be discovered here.

And some in this group take it a step farther, with an attitude that might be summed up, as the military expression goes, as, "Not on my watch." We are very fortunate to have 28 people like this on our Prostate Cancer Advisory Board. Research funds may dwindle, they realize, but research itself will not dwindle — not on my watch. Opportunities may be missed to recruit and hire promising new faculty — but not on my watch. New technology is available, or is being developed, but we can't afford it. Not on my watch. Discoveries are being made, but it is months or even years before patients can benefit from them. Not on my watch. Not while they have anything to say about it.

These are the people who do a great deal to make things happen at the Brady. They help select recipients for our Patrick C. Walsh Prostate Cancer Research Fund awards, giving scientists with good ideas the help they need to get further



Committed to helping men beat prostate cancer: The Johns Hopkins Prostate Cancer Advisory Board met recently in New York City. Members include, from left: William Stutt, Joseph McCann, Salvatore Bommarito, Joseph Rascoff, Chris Evensen, Norman Peck, Keith Reinhard, and Olin Robison.

funding. Many of their names appear in this publication, in the Founders Circle, and in named scholarships and professorships. Joseph Rascoff is concluding his term as chairman of the Advisory Board, and R. Christian B. Evensen is the new chairman. The leaders on this board come from many different backgrounds — industry, academics, finance, marketing, real estate, to name a few. Twice a year, they meet with Brady scientists and physicians in urology, pathology, radiation oncology, and medical oncology, and are never farther away than a phone call the rest of the year.

Despite their varied backgrounds, they all have one thing in common: They are absolutely committed to curing prostate cancer, and they believe the cure will be discovered here.

As always, in this issue we are bringing you the latest discoveries happening every day at the Brady; and, as always, there is barely room in these few pages to tap the surface of what's going on. As many of you already know, you are playing an invaluable role in our work. Our Biorepository (see Page 2), funded with support from the National Institutes of Health, holds nearly 8,000 samples of blood and urine products from men with every stage of prostate cancer. It is a world-class resource, and it has greatly hastened our ability to develop and test new biomarkers. (One of these, EPCA-2, has proven more specific than PSA in distinguishing men with prostate cancer from other men, and in showing which men have organ-confined cancer, and which men have cancer that has spread beyond the prostate.) Although this resource is precious,

we don't hoard it; instead, we share it freely with scientists from around the world who are working toward our same goal — helping men with prostate cancer.

We have made great strides in learning about the genetics of prostate cancer, and we have taken a huge step toward being able to test men before they ever develop cancer to determine their genetic risk (see Page 1). We are also working on an entirely new form of treatment, inspired by Lance Armstrong, and discovered here at the Brady, using focused heat to treat cancer that has spread beyond the prostate (see Page 9).

I hope, as you read this latest issue of *Discovery*, that you will share in our excitement that great things are happening here to help make lives better for men with prostate cancer and their families.

Best wishes,

Alan W. Partin, M.D., Ph.D.

David Hall McConnell Professor and Director
The Brady Urological Institute

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