PROSTATE CANCER
DISCOVERY
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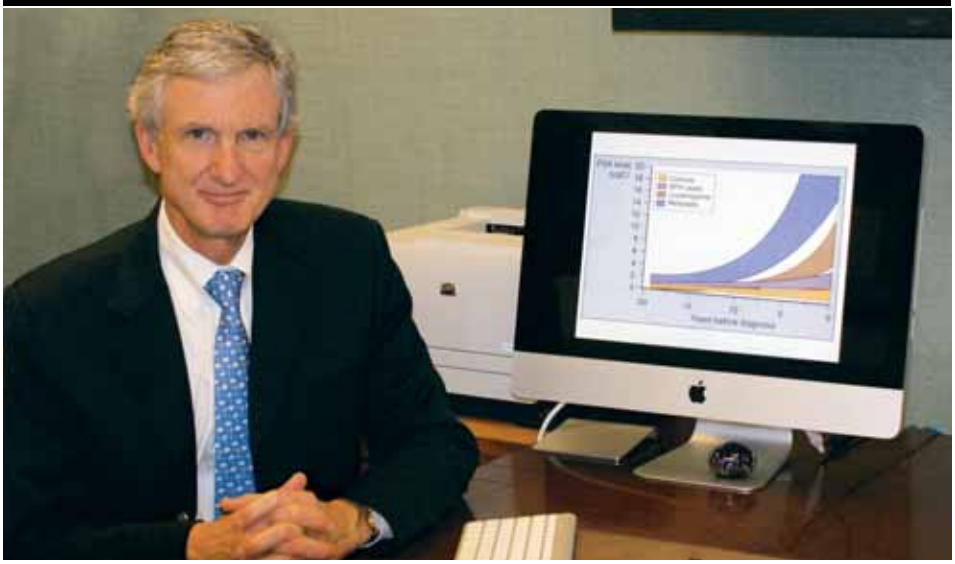

Bal Carter, PSA pioneer. On his computer screen are classic changes in PSA over 20 years, in men with no prostate problems (yellow), BPH (light purple), localized cancer (tan), and metastatic cancer (blue). He published these data in a landmark study 20 years ago. Without the resources of the BLSA, we would still be waiting to know how PSA changes reflect what's happening in the prostate.

How PSA Came to Be Indispensible

Twenty Years of Contributions from the Baltimore Longitudinal Study of Aging

We take it for granted now: PSA, the most versatile weapon in the prostate cancer testing and monitoring arsenal. New uses for PSA show up all the time. It can be parsed — split into "free" and "bound" forms, which tell us different things about the likelihood of BPH and cancer within the prostate. There's PSA velocity — how fast it changes over time — and PSA density, which factors in the weight of a man's prostate. Doctors measure PSA before a man is ever diagnosed with cancer, and for years after he's treated. It's indispensable; one of the "big three" facts (along with the Gleason score and clinical stage) that helps predict how successful treatment will be. Treating prostate cancer today without factoring in PSA is as unthinkable as building anything from Ikea without an Allen wrench.

What most people don't realize is that the vast majority of our understanding of PSA has come from research done over the last 20 years by Hopkins urologist H. Ballentine Carter, M.D., using one remarkable resource — the National Institute on Aging's Baltimore Longitudinal Study of Aging (BLSA). "This work has changed the field," says Patrick C. Walsh, M.D., "When PSA was first discovered, we were facing a thousand unanswered questions, which under normal circumstances would have taken decades to answer. Now, our national guidelines are based on these observations."

What Carter was able to do, using the BLSA data, was like time-lapsed photography. Using decades' worth of blood samples from middle-aged men as they grew older, Carter and colleagues watched what happened to PSA (a protein made by the prostate) over time, in men who developed prostate cancer

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Twenty-One Years and Counting

Partin: Many of the advances in urology are Brady advances.

That's how long the Brady Urological Institute has been ranked the Number One urological center in the country by *U.S. News & World Report Magazine*. Amazing? Should it be surprising that one institution has held this rank for more than a generation? Not to me, because I am privileged to

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see what's happening here every day, in our laboratories, in the clinic, and in the operating room. I also see it in the medical literature — in the journal articles, and in the textbooks that are training doctors in the field worldwide. Many of the advances in urology are Brady advances; some of the most important procedures and reference tools even bear the names of Hopkins doctors.

Our cover story highlights the advances that have come from Bal Carter's work with the Baltimore Longitudinal Study on Aging. I can tell you as a surgeon and as a scientist that the nuts and bolts of what we know about PSA are due to this wonderfully productive collaboration. When I started working on prostate cancer, PSA was an unknown quantity. There were some in the field who thought it would never amount to much — or that, if it did, it would take decades to find out. Dr. Carter short-circuited all those arguments by using the decades of data already available. If you have had your PSA tested, and your doctor thought that your "PSA velocity" was a little high — you should know that this way of tracking PSA exists because of Dr. Carter's work; he even coined the term.

In this issue, we bring you other exciting news: Smart timing may make the combination of radiation and hormonal therapy even more effective for men with high-risk prostate cancer (see Page 8). Through innovative research, scientists are combing through hundreds of drugs that are already available, looking for ones that might help treat or even prevent prostate cancer — and we've found one — the heart drug, Digoxin (see Page 10). Did you know that cancer gets stressed out, just like people do? A multidisciplinary team of scientists is investigating new ways to go after cancer, and to "kick it when it's down" (see Page 12). We also report on a monumental milestone: After 29 years and 4,569 "Walsh Procedures," world-famous surgeon Patrick C. Walsh, M.D., has performed his last operation, with his results at their best ever. He is not retiring — far from it. As he says (see Page 3), "my decision was made easy, because I am confident that patients will have access to a large group of talented surgeons at Hopkins who are skilled in both open and robotic procedures."

Best wishes,

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

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and men who did not. In honor of Carter's 20 years of life saving contributions to our understanding of how to use PSA, we recently asked him how it all started:

Almost a Blank Slate

When you arrived at Hopkins, knowledge of PSA was really still in its infancy. Nobody understood how to use it to diagnose prostate disease.

I remember talking to Pat Walsh (then director of the Brady) about it. The general consensus was that PSA would not be useful for diagnosis because it was elevated by both BPH and prostate cancer. But Dr. Walsh asked me an interesting question: "Do you think PSA rises faster in men with prostate cancer than in those without it?"

How would you go about answering this question?

That's the problem. It would take two to three decades to follow the PSA levels in a group of men, and then see whether or not they developed prostate cancer. But this undertaking seemed worthwhile, given our lack of knowledge about PSA. A few weeks later, Dr. Walsh asked me if I had heard of the Baltimore Longitudinal Study of Aging. I had not. (The BLSA is America's longest-running scientific study of human aging. It was begun in 1958 by the National Institute on Aging, part of the National Institutes of Health as a way to study what happens to our bodies as we get older.) Dr. Walsh believed that the BLSA had a frozen serum bank, and suggested that I might want to find out if PSA could be measured in those samples. If it could, that would allow us to find out quickly what changes occur in PSA with the development of prostate disease and with age.

What a stroke of luck, that you had this conversation at the right time, and you were at the right place to pursue this.

Absolutely. Serendipity and an unanswered question of importance brought me together with investigators at the BLSA, just 15 minutes away. It turned out that the BLSA had been storing blood in freezers since 1958 at two-year intervals, and that men usually entered the study in mid-life and were followed for decades until death. This stored blood could provide us a picture of PSA as men aged — some developing and some dodging prostate disease.

PSA Velocity

One of the great discoveries to come out of this work was PSA velocity. How did this come about?

I had the unique opportunity to work with investigators at the BLSA, James Fozard, Jeff Metter, Jay Pearson, Larry Brant, Reuben Andres. We found that in men without prostate disease, average PSA levels remained around 1 ng/ml. For those who developed prostate enlargement, PSA levels started out around 1, but increased to around 3 over the next two decades. But for the men who developed prostate cancer, the picture was very different: The rise in PSA was much faster for men with prostate cancer compared to men without. Even more exciting: Five years before the diagnosis of prostate cancer was made, the rate of rise in PSA could reliably distinguish men with and without prostate cancer. We coined the term PSA velocity to describe the rate of rise in PSA , and suggested that among men with PSA levels between 4 and 10, a PSA velocity greater than 0.75 ng/ml per year could predict the presence of prostate cancer. Today, the National Comprehensive Cancer Network recommends that physicians use PSA velocity as an indicator of the possible presence of prostate cancer.

Treating prostate cancer today without factoring in PSA is as unthinkable as building anything from Ikea without an Allen wrench. Much of that is due to Bal Carter's longtime work with the BLSA.

PSA Velocity and Lethal Prostate Cancer

PSA velocity gave us a five-year head start on diagnosing prostate cancer, but you were able to refine your results and even predict years ahead of time which men were likely to have more aggressive disease.

By 2006, PSA had become a routine part of clinical practice, and many investigators were concerned about over-detection and over-treatment of cancers picked up through PSA testing — especially when prostate biopsies were performed at PSA levels below 4. On the other hand, we knew that some men with low PSA levels had life-threatening cancers. We wanted to know whether PSA velocity could predict whether a man would develop lethal prostate cancer decades later. If that were true, then PSA velocity could be used to stratify men with low PSA into two categories: Those who should undergo a prostate biopsy, and those who could wait longer to see what happens to their PSA over time. We found that PSA velocity 10 to 15 years before the diagnosis of prostate cancer, when most men had PSA levels below 4, was closely associated with the risk of death from prostate cancer. We concluded that a PSA velocity above 0.35 ng/ml per year could help identify men who might otherwise be overlooked based on a PSA level alone. The NCCN now recommends the use of PSA velocity as one indicator of prostate cancer risk in men with low PSA.

Targeted Screening

Your work has also set the standards for when PSA screening should begin. In the early 1990s, the thinking was that all men should begin screening with a PSA test and digital rectal exam at age 50, and then do it again every year. That has changed.

In reading about screening for breast and cervical cancer, I learned that investigators were using results from prior tests to predict whether or not cancer would be diagnosed later on. So I began to wonder, do all men really need a yearly PSA test? If a man maintained a low PSA level year after year, could he afford to be screened less frequently? Would it be reasonable to perform a baseline PSA test at age 40, and then let the result tell us how frequently to repeat it? Once again, the BLSA helped answer these questions.

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The Last Operation

After 29 years and 4,569 "Walsh Procedures," and with his best results ever, Walsh performs his last operation.

It is very likely that you are reading this now because of an operation that was performed on April 26, 1982. This was the very first "nerve-sparing" operation, the "Walsh procedure," based on painstaking anatomical work and discoveries made by surgeon Patrick C. Walsh, M.D., and the Dutch urologist Pieter Donker. For the first time, a man had his cancerous prostate removed, and did not lose potency. Millions of men have since undergone this life saving operation.

Over the next 29 years, Walsh made 28 major changes to his surgical technique, and has continuously improved his results. On June 29, 2011, he performed his last operation, number 4,569. "I decided to stop operating when I had the best results I have ever had," says Walsh. "I've always believed that as surgeons came close to the end of their career, they should stop operating one or two years too soon and not a second too late. I took my own advice."

"It is an outstanding record by anyone's count," says Ed Miller, M.D., Dean and CEO of Johns Hopkins Medicine. "Pat Walsh is one of the giants in medicine. Although he is best known for his 30 years as the Professor and Director of the Brady Urological Institute (from 1974 to 2004), and for his pioneering work in the development of the nerve-sparing techniques that have dramatically reduced the likelihood of impotence and incontinence with radical prostatectomy, he has also made major contributions to the basic understanding of benign and cancerous growth in the prostate. Along with co-workers, he was the first to describe 5 alpha-reductase enzyme deficiency, to develop an experimental technique to reproduce BPH in the laboratory, to demonstrate the influence of reversible androgen deprivation on BPH, and to characterize hereditary prostate cancer."

Walsh wants everyone to know that he has not retired. Instead, he continues to see patients in consultation, to write and teach. "I will be available to all of my patients at any time when they need my help," he says. "My decision was made easy, because I am confident that patients will have access to a large group of talented surgeons at Hopkins who are skilled in both open and robotic procedures."

This year, Walsh received the Edward Keyes Medal, in recognition of his lifetime contributions to the field, from the American Association of Genitourinary Surgeons. This is considered to be the most distinguished urologic organization in the world, and the Keyes Medal is its highest honor. In his acceptance speech, Walsh made it clear that he owes his successful career to the support and inspiration of his wife, Peg. "In addition, Peg's taste and elegance are reflected throughout the Brady, and around the Johns Hopkins Hospital," he says. "Anyone who has visited has seen her architectural and design contributions in the renovation of the patient, office, and lab spaces in the historic Marburg Building; she has created a wonderful home for patient healing, scientific discovery, and education. What they do not see is her tireless 30 years of dedication in creating and supporting the culture of excellence that has characterized the Brady Urological Institute."

Patrick and Peg Walsh at the meeting of the American Association of Genitourinary Surgeons where he received the Keyes Medal for his lifetime contributions to the field. In his acceptance speech, Walsh thanked his wife for her inspiration and contributions, "without which I wouldn't be here tonight."

PSA [continued from page 3]

Looking at the PSA levels of men in the BLSA, my colleagues and I discovered that if a man has a PSA level below 2, it was very unlikely that over the next two years it would increase to 3 or 4 ng/ml, which would trigger a prostate biopsy. But if the PSA was above 2, it was not uncommon two years later for a man to reach a level that would trigger a prostate biopsy. Combining these findings with surgical data from Johns Hopkins allowed us to recommend that missing a curable prostate cancer would be unlikely if men with a PSA below 2 were to undergo testing every other year.

How did you zero in on the idea of a baseline at age 40?

There were reasons — including evidence that younger men were more likely to have curable cancers — to believe that PSA testing in men younger than 50 would save lives. To explore this, I worked with two epidemiologists, Harry Guess and Kevin Ross. We built a model of prostate cancer development in a simulated population of men. We then tested different screening strategies for preventing prostate cancer death, and found that PSA testing beginning at age 40, again at age 45, then every other year beginning at age 50, not only reduced prostate cancer deaths, but also needed fewer resources (PSA tests and prostate biopsies) to diagnose a prostate cancer.

"It turned out that a single PSA level taken in mid-life was a better predictor of future risk than a family history of prostate cancer."

It turned out that a single PSA level taken in mid-life was a better predictor of future risk than a family history of prostate cancer. For men in their forties with a PSA level above 0.6 ng/ml, and for men in their fifties above 0.7 ng/ml, there was a three- to four-times greater risk of being diagnosed with prostate cancer over the next two decades than for men with lower PSA levels. Results from Europe and Scandinavia are confirming this concept of targeted screening, rather than the "one size fits all" approach.

Screening and Older Men

You have been concerned over the years about older men, diagnosed with small cancers, who might be receiving unnecessary treatment.

Yes, but also the other side of the coin, the older men with prostate cancer that could cause harm without treatment — cancers that would be missed if screening were discontinued in all older men. Some guidelines have recommended that men over 75 stop getting their PSA tested. Edward Schaeffer on our faculty, working with our colleagues at the BLSA, wondered if there was a PSA level that would help identify which older men could safely discontinue screening. Schaeffer and colleagues found that no men in the BLSA who had a PSA below 3 in their mid-seventies went on to develop a lethal prostate cancer. Since two out of three men at age 75 have PSA levels below 3, for the first time it was possible to present an alternative recommendation. Instead of telling all older men, "you don't need a PSA test because you are too old," it was possible to say, "based on your low PSA, you are at minimal risk of dying of prostate cancer, and you don't need to worry about PSA tests anymore." I have found that most men are relieved to hear that news.

BPH Drugs Shown Not Effective in Preventing Prostate Cancer

Everybody would love it if 5-alpha reductase inhibitors – finasteride (Proscar, made by Merck) and Dutasteride (Avodart, made by GlaxoSmithKline) could help prevent prostate cancer. Men would love to be able to lower their risk of cancer by taking a pill. Doctors would love to prescribe something that could help their patients avoid having to get treatment for prostate cancer. Drug companies would love it because they could sell a product that would help thousands of men each year. Sadly, it isn't going to happen.

Although these drugs lower PSA and reduce symptoms in men with benign prostate enlargement (BPH), they do not prevent prostate cancer; in fact, they can make it worse. Two randomized, controlled studies have shown that 5-alpha reductase inhibitors (5-ARIs) can increase a man's odds of developing aggressive, high-grade disease that is difficult to cure. Because of this, the U.S. Food and Drug Administration has turned down a request by pharmaceutical companies to sell these drugs as preventives for prostate cancer, and has notified health care professionals about a change in the Warnings and Precautions for these drugs.

The FDA's decision was based on a re-examination of two studies that initially had seemed promising. "Many urologists were surprised and disappointed by this outcome, because of the encouraging information they had heard regarding these drugs," says Patrick C. Walsh, M.D., who has worked in the field of 5-alpha reductase for 42 years and who was an invited guest speaker at the advisory panel's meeting.

Why were 5-ARIs being studied as possible cancer preventives in the first place? Because they block an enzyme, 5-alpha reductase, that prevents testosterone from changing into another male hormone, DHT, which is active in the prostate. Blocking DHT is helpful in treating BPH because this shrinks prostate tissue, and relieves the urinary symptoms that can be so troublesome when the prostate is enlarged. In the process, these drugs cut a man's PSA levels in half. But the problem here is that cancer is a different disease from BPH, because there is very little 5-alpha reductase enzyme in the malignant tissue. Consequently, prostate cancer is driven by testosterone, not DHT.

In one study, the Prostate Cancer Prevention Trial (PCPT), conducted by the National Cancer Institute, nearly 19,000 men were randomly assigned to take either finasteride or a placebo for seven years. The men underwent a prostate biopsy if they had an abnormal digital rectal exam or change in PSA, and when the study was over, about a third of the men also underwent biopsies. The other study, called Reduction by Dutasteride of Prostate Cancer Events (REDUCE), tested the effect of that drug in 8,000 men over four years. In both studies, there was no significant decrease in cancer in

"If you are worried about dying from prostate cancer, taking a 5-alpha reductase inhibitor is the last thing you should do. These drugs do not prevent the disease, but give a false sense of security because they lower PSA."

men who underwent a biopsy because of an abnormal PSA or rectal exam. But there was a troubling increase in the number of men taking the drugs — not the placebos — who were diagnosed with very aggressive cancer (Gleason 8-10).

Also troubling was that fewer men with an abnormal PSA or examination who were taking these drugs underwent biopsies than actually should have. "This was because their PSA was artificially low, and they did not think it was significant enough to worry about," says Walsh. "The only way finasteride and dutasteride reduce the number of patients with cancer is by fooling men into believing that their PSA is lower than it really is, so that they don't get a biopsy. These agents don't prevent cancer; they merely prevent biopsies."

When the FDA advisory panel met to evaluate two proposals for allowing 5-ARIs to be used as preventive agents to reduce the risk of prostate cancer, Merck did not seek a new indication for the use of Proscar, but instead requested a change in the section on "Adverse Reactions" in the product information — so it would say that the increased prevalence of high-grade disease in men who took Proscar was an artifact caused by improved sensitivity of PSA and/or prostate shrinkage that made it easier to find high-grade cancer on a biopsy. This was rejected by the panel by a vote of 17-0 with one abstention. The application for approval of Avodart as a way to reduce prostate cancer in men at "increased risk" — men who have had a negative biopsy but still had an elevated PSA — was also rejected by a vote of 14-2, with two abstentions.

In March 2011, GlaxoSmithKline announced that it would no longer pursue global marketing of dutasteride for use in the prevention of prostate cancer. Merck's revised product insert concluded that Proscar is not approved to reduce the risk of prostate cancer. "If the pharmaceutical companies that actually make these drugs do not believe that they are safe and effective in preventing prostate cancer, urologists should not be offering them to patients for that purpose," says Walsh. "If you are worried about dying from prostate cancer, taking a 5-alpha reductase inhibitor is the last thing you should do. These drugs do not prevent the disease, but give a false sense of security because they lower PSA. If you take one of these drugs and develop prostate cancer, it may delay your diagnosis until you have aggressive disease that may not be curable." These findings also have potential implications for the use of these drugs in men with BPH and male-pattern baldness, Walsh adds.

"If you take one of these drugs and develop prostate cancer, it may delay your diagnosis until you have aggressive disease that may not be curable."

Still, some interest remains for using 5-ARIs in men diagnosed with very low-risk prostate cancer to lengthen the time that slow-growing disease takes to become significant and need treatment. To investigate this, Hopkins scientists studied 5-ARI use among men with very low-risk prostate cancer in the Active Surveillance Program. Ashley Ross, Walsh, H. Ballentine Carter, Bruce Trock and Ed Schaeffer, found that among these men, 5-ARI use did not decrease the risk of progression of the disease. While the final answer awaits the results of a randomized, controlled trial, these findings suggest that 5-ARIs should not be used to attempt to slow or stop cancer progression in men with low-risk prostate cancer.

What We've Learned From Active Surveillance

Begun 16 years ago, the Hopkins program has helped define national recommendations for men who choose this approach

It's not right for everybody, but new data based on the pioneering Hopkins Active Surveillance program show that for some older men diagnosed with low-grade, low-volume prostate cancer, careful monitoring is a safe approach. In fact, evidence from this program, begun by urologists H. Ballentine Carter, M.D., and Patrick C. Walsh, M.D., in 1995, is so strong that — based largely on the Hopkins results — the National Comprehensive Cancer Network has recommended this as the management of choice for a select group of men with very low-risk prostate cancer. In new guidelines, the Network recommends active surveillance for men with less than a 20-year life expectancy whose PSA, prostate biopsy results, and absence of palpable cancer on the digital rectal exam suggest that they have very low-risk disease.

"We began the active surveillance program at Johns Hopkins as a way of reducing unnecessary treatment for prostate cancer," says Carter. Over more than 16 years, nearly 1,000 men have been accepted into the program. A recent update of the Hopkins results, published in the *Journal of Clinical Oncology*, helps define some of the important considerations for men choosing this approach (see side story).

"Patients who are considering active surveillance are concerned about the longer-term risks of not getting treatment right away," says Carter. The main risk, he says, is that the biopsy has underestimated the true nature of the cancer by missing any higher-grade disease that might be lurking inside the prostate. This is why he places such importance on the yearly follow-up biopsy. "Based on the annual biopsies done in this program, we have now estimated this risk of finding a higher-grade cancer on a surveillance biopsy to be 4 percent per year."

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Further, he explains, "since we know the long-term outcomes of men after treatment for high-grade cancer, and the rate that we will uncover a high-grade cancer among the men in our active surveillance program, we have shown that a 65-year-old man entering our program with very low-risk prostate cancer would have a one- to five-percent risk of dying from prostate cancer over 15 years."

But this information, Carter adds, is only one part of the very personal decision to pursue surveillance rather than immediate treatment — because each man is different, and needs to decide what is best for him and his family. "Men who are considering active surveillance need to weigh their ability to live with an untreated cancer against their preferences for avoiding the side effects of treatment, which can include urinary, bowel, and sexual dysfunction."

The Bottom Line

Eighty percent of the men in this program met all of our criteria for very low-risk disease," says urologist H. Ballentine Carter, M.D., a pioneer who has helped define this area of prostate cancer treatment. Men eligible for the program have:

- Cancer that cannot be palpated on a digital rectal exam (stage T1c);
- A PSA density (PSA divided by prostate volume) of 0.15 or less;
- Gleason score 6 or below;
- No more than 2 biopsy cores with cancer, or more than half of any core with cancer.

Carter is convinced that vigilance is the key to the program's success. "These men undergo twice yearly blood testing and a digital rectal exam, and they get a yearly prostate biopsy to assess their cancer." Any change – if the cancer grows, or if the grade on the biopsy changes – triggers "curative intervention." Half of these men remain untreated after they have been in the program for six to seven years, and no patients in the program have developed distant metastatic disease or died of prostate cancer.

Alan Meeker and Elizabeth Platz: Telomeres, tiny regions at the ends of chromosomes, get a bit shorter every time a cell divides. When they get too short, this can lead to cancer.

How Aggressive is the Cancer? Study of Telomeres May Lead to New Test

Telomeres are kind of like aglets, the little plastic tips on the ends of shoelaces; in fact, their name comes from the Greek words meaning "end" and "part." They are tiny regions of repeated DNA sequences that cap the ends of chromosomes and help protect them from deteriorating. Just as an aglet doesn't last forever — leaving you stuck with a shoelace that's frayed on one end and hard to lace up — telomeres wear out, too, shortening a bit every time a cell divides.

Telomeres can also shrink because of oxidative damage, incremental wear-and-tear at the genetic level caused by diet and other environmental factors. When a telomere gets too short, the chromosome it's supposed to safeguard — think of the poor shoelace — loses its stability, and this eventually can lead to cancer. "Cancer cells tend to have much shorter telomeres than normal cells from the same tissue," notes telomere biologist Alan Meeker, Ph.D., *The Virginia and Warren Schwerin Scholar*. The most dangerous cancers — the ones that metastasize, or spread to distant sites — tend to be those with the most unstable chromosomes. This fact led Meeker, epidemiologist Elizabeth Platz, Sc.D., M.P.H., and pathologist Angelo De Marzo, M.D., Ph.D., along with colleagues at Harvard, to wonder whether the length of telomeres — in cancer cells, or even in normal cells that may be headed for cancer — may foretell how aggressive a man's prostate cancer is likely to be.

"The clinical tools that we currently use to predict the risk of aggressive disease in men with clinically localized prostate cancer are imperfect," De Marzo explains. "Inaccurate predictions make it harder for men and their doctors to determine the best

course of treatment." To address this problem, the scientists recently investigated the link between the length of telomeres and the risk of highly aggressive disease.

The team studied 623 men with clinically localized prostate cancer who underwent radical prostatectomy; the men were participants in a massive, long-term investigation called the Health Professionals Follow-up Study. Of these men, 48 died of prostate cancer. The team analyzed the tissue that was removed during surgery, and measured telomere length using a method developed by the Hopkins investigators, called TELI-FISH, for telomere-specific fluorescence in situ hybridization. After calculating the typical length of the telomeres in these cells, and then looking at the variation in telomere length from cell to cell, the scientists then correlated the length and variability to the men's risk of dying of their prostate cancer over the next 10 years after their surgery. They took into account each man's pathologic stage and Gleason score, as well.

"We found that men with more variable telomere length in their prostate cancer cells had a three-times-higher risk of dying of their prostate cancer," says Platz. "We also found that men with shorter telomeres in their nearby stromal cells (smooth muscle cells and fibroblasts, cells in the connective tissue) had a six-times-higher risk of dying."

Telomeres can shrink because of oxidative damage, incremental wear-and-tear at the genetic level caused by diet and other environmental factors. Cancer cells tend to have much shorter telomeres than normal cells. The most aggressive cancers tend to be those with the most unstable chromosomes. Could telomere length help predict these dangerous cancers?

Next, the investigators combined these two ways of looking at telomeres and found that men who had more variable telomere length in prostate cancer cells, and shorter telomeres in their stromal cells were 41 times more likely to die of their prostate cancer. "Equally importantly, we found that men who did not have this combination rarely died of their prostate cancer over the 10 years."

These results are so promising that the team believes there is strong potential for a new clinical test to predict the aggressiveness of prostate cancer. The next steps are to streamline the process for determining telomere length, to test these findings in other men with prostate cancer, "and to determine the optimal cutpoints for variability and short telomere length," says Platz, "so that we can make this test as helpful as possible."

Prostate Cancer in the Lab: Many Experiments May be Contaminated, Study Shows

In work that has the potential to affect prostate cancer research worldwide, Hopkins scientists have discovered that many prostate cancer cells lines, cultivated and sold to laboratories, may be contaminated with mouse viruses. These viruses are "actively replicating and infectious gammaretroviruses," says pathologist Angelo De Marzo, M.D., Ph.D., who made the discovery with scientist Karen Sfanos, Ph.D. Their work was published in *PLoS ONE*.

"The major implications of this work are that hundreds, if not thousands of biological cancer research-related studies have been carried out with these cell lines," says De Marzo. "It is distinctly possible that some, if not many, of the results of these studies could have been affected in unforeseeable ways by the presence of these heretofore unknown mouse viruses."

The discovery was made while De Marzo and Sfanos (a postdoctoral fellow in De Marzo's lab, who has since joined the faculty), along with investigators from the National Cancer Institute, were hunting for a particular virus called XMRV. In 2006, researchers worldwide became very excited when XMRV, related to the mouse leukemia virus, was isolated in some human prostate tumor tissues. There was good reason to believe that this virus might be a cause of prostate cancer in some men — particularly in light of the landmark finding by geneticist William B. Isaacs, Ph.D. Isaacs, *The William Thomas Gerrard, Mario Anthony Duhon, and Jennifer and John Chalsty Professor of Urology*, discovered that men who inherit a specific mutation in a gene called RNASEL are more prone to prostate cancer. The RNASEL gene's job is to fight off viruses, and when it is mutated, the body is more vulnerable to invading viruses.

Sfanos, then working with Isaacs as a graduate student, began looking for this virus in patient specimens housed at Hopkins. She didn't find it. Sfanos investigated 338 tissue samples from 200 patients, and her study, published in *Prostate*, was the first to report the complete absence of XMRV in prostate cancer. In 2010, De Marzo was approached by Alan Rein, Ph.D., a well-known retrovirus scientist at

De Marzo and Sfanos made the unpleasant discovery that many prostate cancer cell lines, cultivated and sold to laboratories, may be contaminated with mouse viruses that are "actively replicating and infectious."

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the NCI, who wanted to pursue the possible role of XMRV as a cause of prostate cancer. De Marzo, Sfanos, Rein and the NCI's Amanda Aloia, Ph.D., also showed a complete absence of the virus in prostate cancer tissues. The team studied 800 more prostate cancer tissue samples in exhaustive detail, using novel antibodies and a new polymerase chain reaction-based approach. Their work was recently published in *Cancer Research*.

How to explain the team's determination of absolutely no XMRV in the prostate? "A number of recent papers have shown that the presence of XMRV in patient samples is likely the result of laboratory contamination," says De Marzo, "and two papers just published in *Science* refute the plausibility that this virus even circulates in the human population. It appears to have been created by accident in the laboratory during the cultivation of human prostate cancer tumors in certain mouse strains."

De Marzo and Sfanos's discovery of the mouse virus-contaminated prostate cell lines emphasizes the inherent danger of working with human cancer cell lines that have previously been grown in laboratory mice. "It is critical for researchers to test their cell lines for contamination with these viruses," cautions De Marzo, "to avoid the potential confounding of their experimental results as well as the potential to cross-contaminate other cell lines in their labs."

"Hundreds, if not thousands of biological cancer research-related studies have been carried out with these cell lines. It is distinctly possible that some, if not many, of the results of these studies could have been affected in unforeseeable ways."

Timing is Everything: Making Combined Radiation-Hormonal Therapy Better

DeWeese, left, and Hales found that treating prostate cancer cells with hormonal therapy, then testosterone and radiation, worked better.

For men with high-risk prostate cancer, the combination of short-term hormonal therapy and radiation is the standard of care. "This has resulted in better control of cancer in the pelvis, reduced the risk of metastatic disease, and increased survival," says Theodore L. DeWeese, M.D., Ph.D., Chairman of the Department of Radiation Oncology and Molecular Radiation Science. "However, despite this great advance, cancer still recurs in a number of patients with this aggressive type of prostate cancer."

DeWeese and colleague Russell Hales, M.D., have been thinking about this problem for some time. Recently, they reviewed an experiment done years ago by Don Coffey, Ph.D., *The Catherine Iola and J. Smith Michael Distinguished Professor of Urology* and the Brady's former Director of Research, who spent his career studying how cells — normal and cancerous — are structured, and how they behave. One thing Coffey learned was that just like the tide, which changes depending on the phase of the moon, cancer cells vary, too. Depending on where they are in their cycle of making new DNA and dividing in two, they are more or less vulnerable to radiation. "We also knew that hormone therapy kills prostate cancer cells that are hormone-responsive while also putting the other, surviving cells into a non-cycling state, a state in which the cells are thought to be more resistant to radiation," says DeWeese.

Taken together, these two facts led DeWeese and Hales to believe that maybe timing could make a difference in cancer-killing power. "We performed a series of experiments," DeWeese says, and in mice found that "when prostate cancer tumors are treated with hormonal therapy, followed by testosterone and radiation, they are more likely to be controlled" than cancers in mice that received hormonal therapy and then radiation without testosterone. "This is very exciting news."

Next, the team plans to work with Brady scientist Vasan Yegnasubramanian to understand some of the basic science behind this testosterone-radiation interaction, and then to develop novel clinical trials based on this three-part combination.

Good News for Some Men with Positive Margins

What happens when the urologist cannot remove all of a prostate tumor, and the surgical margins are positive? In some men, cancer is more likely to recur, and radiation is the recommended next step. But results from a new Hopkins study, published in *Urology*, suggest that not all men need this extra treatment.

"It turns out that the total length of positive margins was a significant predictor of tumor recurrence after prostatectomy," says Jonathan I. Epstein, M.D., *The Rose-Lee and Keith Reinhard Professor of Urological Pathology*. The study, conducted by Epstein along with Fadi Brimo and Brady Director Alan W. Partin, M.D., Ph.D., also was the first to prove that the grade of cancer at the site of a positive margin influences the long-term outcome.

"Men with Gleason 7 cancer have a mixture of Gleason pattern 3 tumor, which is favorable, and pattern 4, which is more aggressive," explains Epstein. "When there is a Gleason 7 cancer with a positive margin, the remaining tumor could be pure pattern 3, pure pattern 4, or a mix of both. We were able to show that men with pure pattern 3, especially if it's limited, have an 83-percent chance of maintaining an undetectable PSA at two years and a 67-percent likelihood at five years."

The grade of cancer at the site of a positive surgical margin has much to do with the long-term outcome.

Until this study, Epstein says, almost all men with Gleason 7 tumor and a positive margin would have been recommended to receive radiotherapy. "The good news is that now a subset of men with low-grade, low-volume cancer at the margin can be spared extra radiation and the side effects of additional treatment."

Team Seeks Better Ways to Detect High-Grade Disease

Even with advances in screening and early detection, roughly 10 to 20 percent of men are diagnosed with high-grade disease, a Gleason score of 8 to 10. Two Hopkins urologists, Ashley Ross, M.D., Ph.D., and Ed Schaeffer, M.D., Ph.D., are looking for answers on the molecular level, hoping to find markers that will help identify aggressive disease early, and lay the groundwork for new ways to treat it.

"Even if it's localized, prostate cancer has a wide range of aggressiveness," says Ross. "The most powerful predictor of this is the Gleason sum," or score, based on how the cells look to a pathologist under the microscope. "A low Gleason sum, even in the absence of intervention, is often associated with low risk of death, but a high Gleason sum can indicate a poor prognosis."

Ross and Schaeffer began by using laser capture micro-dissection technology to isolate individual cells from the prostates of men who underwent prostatectomy at Johns Hopkins. "We compared the differences between cellular signatures of low- and high-Gleason disease," says Schaeffer, "and then broadened the search to include prostatectomy specimens from other institutions to develop a master list of the genes and signaling pathways that characterize high-Gleason disease."

The scientists are beginning to test candidate markers that could identify aggressive prostate cancer early, and to explore the use of novel therapies targeted against high-grade disease.

New Drug Helps Keep Advanced Cancer in Check

"The idea is not so much to prevent tumors from developing as to stabilize the disease," says John Isaacs, second from right, with Lizamma Anthony, W. Nathaniel Brennan, and Susan Dalrymple.

A new drug called Tasquinimod is the result of years of labor by scientist John Isaacs, Ph.D., *The R. Christian B. Evensen Scholar*, to develop a way to block angiogenesis. Angiogenesis is the creation of new blood vessels, and it is a process that cancers become very good at if they survive long enough. Just as an army can't move forward without supply trucks and roads to carry them, cancers can't spread without their own larder — nutrient-bearing blood vessels. The theory behind drugs that block angiogenesis is that if you cut off the blood supply, you starve the cancer, slow its growth, contain it and maybe, in the process, make it more vulnerable to other drugs designed to kill it.

In an early clinical trial of 200 men with advanced prostate cancer — patients at Hopkins and six other institutions — tasquinimod slowed the rate of disease progression. The men took a pill once a day for four weeks. At six months, 57 percent of the men who took tasquinimod had no disease progression, compared to 33 percent of men in the placebo group. Overall, the drug added about 12 weeks of "progression-free survival" — time that the disease did not get any worse.

"Given these results, we are moving forward with Phase III studies," says oncologist Michael Carducci, M.D., who is leading an international trial of tasquinimod. "After exploring the drug as a single agent, then we may study it in combination with other prostate cancer drugs."

At six months, 57 percent of the men who took tasquinimod had no disease progression, compared to 33 percent of men in the placebo group.

Although tasquinimod shuts off the development of new blood vessels around the tumor, it does not harm the blood vessels that are already there. "The idea for anti-angiogenesis drugs is not so much to prevent tumors from developing as to stabilize the disease," says Isaacs. Tasquinimod is not without side effects, which can include gastrointestinal problems, fatigue and bone pain, and rarely, heart attack, stroke, and deep vein thrombosis. Isaacs is now working to identify the drug's precise cellular target, with hopes of making it more specific and effective.

A Better Biopsy: New Help from an MRI-Guided Robot

The words "overdiagnosis" and "overtreatment" are still big concerns in prostate cancer, even though scientists have made great strides in determining who should be treated right away, and who can afford to wait. Could a more sensitive biopsy help clarify who needs curative treatment? Dan Stoianovici, Ph.D., professor of urology, mechanical engineering, and neurosurgery, hopes to find out. "Our Urology Robotics Laboratory has developed a robot that can be used in MRI-guided prostate biopsy," he says, and a pilot clinical trial is expected to begin soon.

Prostate biopsies are done using a different imaging technology: ultrasound. Stoianovici hopes that MRI will allow for a more precise, systematic approach to sampling the prostate for cancer. The robot, the first of its kind, can operate in the high magnetic field of the MRI without disrupting its imaging ability, and preclinical tests have been promising.

Prostate biopsies today are done using ultrasound. But Stoianovici hopes that a different kind of imaging, MRI, will allow for a more precise, systematic approach. Early tests have been promising.

The device mounts on the MRI table and attaches with suction cups, as the patient lies on his left side. "With robot assistance, primary prostate biopsies would follow true systematic plans," says Stoianovici, "and repeat biopsies would be tailored to target any abnormalities that may be observed, as well as to target any regions not sampled before. Biopsies for men on active surveillance would accurately resample critical regions to make sure that the cancer is not progressing."

Stoianovici, with Doru Petrisor, and their team in the Urology Robotics Laboratory, expects a pilot clinical trial of the new robot to begin soon. They hope MRI will prove more sensitive than ultrasound.

A Faster Way to Find New Drugs for Prostate Cancer: Taking a Close Look at What's Already Out There

Remember the TV show, MacGyver? The main character was a genius at using everyday items to get out of a tight spot. The beauty of his approach was a creative reworking of the materials at hand. Epidemiologist Elizabeth Platz, Sc.D., oncologist Srinivasan Yegnasubramanian, M.D., Ph.D., and colleagues are thinking along those same lines, for a lot of good reasons.

One of them is time. To anyone who could benefit from a better medical treatment than the ones currently out there, it takes an inordinate amount of time for the drug pipeline to do its job. From the time a scientist develops an agent, tests it in the laboratory (in tissue samples, Petri dishes, animal models and any other preclinical tests), gets approval from the government for clinical testing — first, to make sure it is safe and follows the first rule of the Hippocratic oath, which is, "Do No Harm," then to see if it helps, and if so, at what dose — it can take years.

It can also take a whole lot of money. Drug development is "exorbitant," say Platz and Yegnasubramanian, and the cost to bring just one drug through this process, from the laboratory to receiving regulatory approval, is estimated to top $1 billion.

One way to streamline this process is to look at the drugs that are already out there, sitting on the shelves in local pharmacies — drugs whose means of action and potential side effects are already known. "Rapid laboratory screening of these drugs, followed by focusing on the strengths of existing, well-characterized studies could, with relatively little expense, expedite our ability to identify and test drugs for new uses in clinical trials," says Platz.

How much does it cost to bring just one drug through the pipeline, from laboratory development to the pharmacy shelves? $1 billion.

With the goal of finding drugs approved for other diseases that might help treat prostate cancer, Platz, Yegnasubramanian, and a transdisciplinary team used a novel laboratory-epidemiology approach. Their results were published in Cancer Discovery. "It was a two-step program," she says. "First, we did in vitro screening, to see if drugs inhibited the growth of prostate cancer cells." They looked at 3,187 different compounds. "Then, we looked at the link between the most promising drug and the risk of prostate cancer in a large study with long-term follow-up." The result: What the scientists, and colleagues Jun Liu, Curtis Chong, Joong Sup Shim, Stacey Kenfield, Meir Stampfer, Walter Willett, Edward Giovannucci, and Bill Nelson, believe is "compelling evidence" that a drug commonly used to treat heart problems, digoxin, should be considered as a potential drug for prostate cancer.

The team's testing ground in humans was the massive, Harvard-led Health Professionals Follow-up Study, which follows thousands of people for decades, notes which medicines they take, and, among many other functions, documents any illnesses they develop. "Digoxin was highly potent in inhibiting prostate cancer cell growth in the laboratory," says Platz, "and the men who regularly took this drug had a 25 percent lower risk of prostate cancer than other men." Men who took digoxin for a decade or more had the lowest risk. The results offer exciting potential for a new drug to help reduce a man's risk of developing this disease. "Perhaps of equal importance, our study illustrates the power of the transdisciplinary approach in translational cancer research," notes Platz.

PSA: How Low Should It Go?

It may be that we need to rethink "undetectable." After radical prostatectomy, we all focus on the number 0.1 ng/ml — that's undetectable PSA. But recent advances in technology have made it possible to measure PSA at much lower levels. Is it good? Alan W. Partin, M.D., Ph.D., *The David Hall McConnell Professor of Urology* and Director of the Brady, thinks the answer may turn out to be yes.

Partin, Daniel W. Chan, Ph.D., and Lori Sokoll, Ph.D., have been working with a company called Quanterix, in collaboration with New York University urologist Herb Lepor (formerly at Hopkins) to see how well a new, ultrasensitive PSA assay works. "The test, AccuPSA, can accurately measure PSA values at 1,000 times lower than the standard assays we use today," says Partin. In a study to be published in the *British Journal of Urology International*, Partin and colleagues examined blood samples from 31 men whose PSA had been undetectable for at least five years after radical prostatectomy. "All of the men had PSA lower than 0.1 ng/ml after surgery, yet one-third of them later had biochemical recurrence, while the others kept having undetectable PSA for many years after surgery." The men were similar in age, race, and had negative surgical margins after surgery; however, the men whose PSA levels went up had a higher pre-surgical PSA, clinical and pathological stage, and Gleason grade than the men whose levels remained very low.

When the investigators tested the samples with AccuPSA, they found that at three months after surgery, all of the men who ultimately had a rise in PSA had an AccuPSA level of 0.003 ng/ml or greater, "a number that, by standard measures, we would have considered to be really good — undetectable," notes Partin. But among the men whose PSA never went back up, 75 percent had AccuPSA levels lower than 0.003 ng/ml.

This was a small, pilot study, and larger tests are needed to confirm these findings. However, says Partin, "these results suggest that men could have an AccuPSA test at three months after surgery, and if the level is lower than 0.003 ng/ml, they could be better reassured that all of their cancer has been removed. On the other hand, if a man's level is higher than 0.003 ng/ml, he might be monitored more closely for PSA recurrence in the immediate years after his surgery.

Do we need to rethink "undetectable?" Brady Director Partin, with Sokoll and Mangold, believes ultra-sensitive PSA tests may offer peace of mind for many men after surgery.

How Do You Teach the Immune System to Hate Prostate Cancer?

Ideally, the body's immune system would spot prostate cancer, recognize that it's not supposed to be there, and destroy it. Instead, says immunologist Charles Drake, M.D., Ph.D., *The Nancy and Jim O'Neal Scholar*, immune cells — which have the potential to be warriors that could attack and kill very quickly — see prostate cancer, and actually recognize it. Then, frustratingly, they seem to say, "Oh, prostate cancer, I thought that was you. How are you doing?" And nothing else happens.

"Unfortunately," says Drake, "this recognition does not lead to immune attack and eventual rejection of the tumor, as we would hope. One of the most important reasons why this occurs is because immune cells are 'tolerized,' or turned off, when they see cancer cells." This turning off, he adds, is controlled in part by proteins on the surface of immune cells, known as checkpoints.

Immune cells have the potential to attack prostate cancer and kill it very quickly. Unfortunately, they don't do that. Why don't they realize prostate cancer is the enemy? Charles Drake, second from left, with Tina Ceccato, Chris Nirshl, and Nick Durham, is working to find out.

Then, frustratingly, they seem to say, "Oh, prostate cancer, I thought that was you. How are you doing?" And nothing else happens.

In recent clinical studies of people with kidney, lung, and skin cancer, "our group helped to show that a blockade of the immune checkpoint, controlled by a molecule called PD-1, could lead the body's immune system to reject tumors. But this therapy does not work in all patients," says Drake, and this seems to be because a silent partner — another checkpoint protein — is involved. "In the laboratory, we found that many of the immune cells that are not reacting to cancer also express another checkpoint, known as LAG-3. Fascinatingly, we found that blocking both LAG-3 and PD-1 can lead to rejection of tumors that can't be treated by blocking either one alone. Our hope is to translate these findings to prostate cancer, by treating patients with drugs to block both checkpoints at the same time."

Other immunotherapy news:

In a review article for *Clinical Cancer Research*, Drake and James Gulley, a colleague at the National Institutes of Health, recently looked at the progress in therapeutic cancer "vaccines." One of these drugs, sipuleucel-T (Provenge), has been approved by the Food and Drug Administration as the first therapeutic anti-cancer vaccine. The good news is that over the last few years, scientists have learned a lot about timing — when in the tumor's growth it is most vulnerable to immunotherapy and more traditional chemotherapy drugs — and combination, adding a vaccine to other immunotherapy drugs, or to different kinds of drugs.

"Very few metastatic cancers are currently treated with just one chemotherapy drug," says Drake. "Instead, combination chemotherapy can be curative for patients with testicular cancer and other cancers. Thus, it makes sense that combination immunotherapy might also hold clinical promise." Clinical trials are needed to see whether sequencing immunotherapy and hormonal therapy, or conventional chemotherapy, achieves greater effect in prostate cancer, he adds. "Preclinical data overwhelmingly suggest that combination approaches could lead to major advances in clinical benefit."

Even Cancer Gets Stressed Out

The biggest challenge in treating advanced prostate cancer is that it develops resistance to hormonal therapy and cancer-fighting drugs. "In fact, advanced cancers have been shown to be able to become resistant to any therapy that is applied," says Robert Getzenberg, Ph.D., *The Donald S. Coffey Professor of Urology* and the Brady's Director of Research. The answer, he believes, is "not necessarily to keep developing new therapies," but to look for hidden weaknesses. In other words, says Getzenberg, "Does the cancer sacrifice anything in order to become so adept at defying treatment?"

One thing that seems to go out the window, at least in prostate cancer, is tolerance to stresses in the environment. Imagine any movie in which the characters are in a tight spot — say, on a cramped WWII submarine riding out depth charges. What happens? People start snapping at each other; they don't cope well; maybe they make poor decisions. The pressure gets to them.

Imagine any movie in which the characters are in a tight spot. What happens? People start snapping at each other. They don't cope well. Maybe they make poor decisions. The pressure gets to them. This happens to cancer, too.

Apparently, cancer can get stressed out. In studies that were recently published in the *Journal of Cellular Biochemistry*, Youqiang Li, a scientist in Getzenberg's laboratory, compared prostate cancer cells that had become resistant to chemotherapy to those that still responded to it, and found that the resistant cells were sensitive to stresses in their environment. "Stresses such as heat and inadequate food had a much bigger impact on these resistant cells," notes Getzenberg.

Is it possible that we could somehow kick cancer when it's down? These studies point to new avenues of treatment where an environmental stress can be added to make traditional therapy more effective. As it happens, one highly promising example of this type of approach, called TEMT (thermal enhanced metastatic therapy), is being developed here at Hopkins. The idea is to make hidden, metastatic prostate cancer cells more sensitive to treatment with the use of a powerful weapon: Heat.

"Heating cancer cells makes them more vulnerable to radiation, chemotherapy, and immunotherapy," says Getzenberg. The idea for TEMT began with Getzenberg's predecessor as Brady Research Director, legendary scientist Don Coffey, Ph.D., who learned that heating a cell changes the makeup of its DNA, and weakens its internal structure. Hopkins scientists including Shawn Lupold, Robert Ivkov, Prakash Kulkarni, Coffey, Getzenberg, Ted DeWeese and colleagues are working hard to learn how best to exploit this chink in cancer's armor.

In related news from Getzenberg's laboratory:

3-D "Habitats" for Prostate Cancer

Habitat. The name conjures up a glass tank with a hamster wheel in it; and yet, maybe this is what we need, to learn how prostate cancer cells truly operate. Much of what we know about the molecular basis of prostate cancer comes from what scientists have observed in the Petri dish — cells, obtained from prostate cancer specimens, cultured in little, flat containers. "This is certainly not how these cells survive and grow," says Getzenberg, "either within the prostate, or at other sites in the body."

Thus, in hopes of building a more realistic "habitat" that reflects how prostate cancer cells really live and grow, Getzenberg and colleagues here at the Brady have joined forces with Robert Austin, a physicist at Princeton University, and his team. They have studied the behavior of prostate cancer cells — ranging from the less invasive to the most aggressive strains — in specially built microchambers. "These miniature chambers have many small mountains within them, and the ability of the cancer cells to climb these mountains and establish camp at the top appears to correlate with the metastatic

If you want to study a fearsome tiger at the zoo, will you learn more from the one stuck in a cage, or the one that has enough room to roam?

ability of the cells," says Getzenberg. Think about it: If you want to study a fearsome tiger at the zoo, will you learn more from the one stuck in a cage, or the one that has enough room to roam?

"These novel 3-D model systems are unique tools that may give us a better understanding of the molecular mechanisms through which these cells actually grow and invade other cells," Getzenberg adds. This work was published in the *Proceedings of the National Academy of Sciences*, and was supported with a grant from the National Cancer Institute, Physical Sciences and Oncology Center.

A Marker for Aggressive Cancer?

In other work, Getzenberg and colleagues George Netto, Elizabeth Platz, Naoki Terada, Prakash Kulkarni, Alan Partin, and Leslie Mangold, have focused on a protein called Cyr61, which may turn out to be a marker of aggressive cancer. After studies of the protein in tissue samples appeared promising, the scientists demonstrated that Cyr61 could be detected in the blood of men with prostate cancer, "and that it may have some ability to characterize the aggressiveness of prostate tumors," notes Getzenberg. "These studies need to be confirmed with additional samples, but we have shown that Cyr61 represents a unique change found in both tissue and blood. We hope that one day, it will serve as part of a panel of markers that may help us characterize the nature of a man's prostate cancer." Some of this work was published in the journal, *Clinical Cancer Research*.

Research Offers New Potential Target for Chemotherapy

Discoveries about the genetics of prostate cancer may lead to new ways to attack the disease. The new findings, published in two prestigious medical journals, have to do with tiny breakages and repairs to the DNA that happen as cancer develops — and the discovery that the smart use of male hormones and drugs that specifically target this process may allow new, more effective ways to kill the most advanced cancer cells.

The possibility that male hormones cause DNA strands to break raises a new possibility: That high doses of hormones may be able to kill cancer cells.

Previously in *Discovery*, we reported on the work of scientists Bill Nelson, Vasan Yegnasubramanian and Michael Haffner in uncovering a particular problem that develops as prostate cancer advances. It's a mistake that happens in the routine business of DNA, which is always in a state of transition in the body. "The major acquired defects in prostate cancer DNA appear to be rearrangements that occur as a result of accidental breaks in the DNA molecules," says Nelson, M.D., Ph.D., Director of the Sidney Kimmel Comprehensive Cancer Center. "The idea is that if the breaks are repaired incorrectly, the broken DNA segment may be rejoined to the wrong site."

In prostate cancer, a gene found in normal prostate cells, called TMPRSS2, which is regulated by male hormones (testosterone and its kin, dihydrotestosterone), breaks off from where it's supposed to be and fuses with a gene called ERG, which is like a tiny version of the garden product, "Miracle Gro." ERG causes cancer cells to fluorish. Put it together with TMPRSS2, which responds to androgens, and the result can be catastrophic; this rearrangement happens in half of all prostate cancers. "The consequence of this mismatch is that prostate cells — now cancerous — acquire the propensity for invasive growth and dissemination throughout the body," says Nelson. "What we discovered was that the action of the male hormones tended to trigger DNA breaks in specific sites at the TMPRSS2 gene, via some sort of error-prone attempt to initiate production of TMPRSS2." Interestingly, this happens selectively in cells that are found in PIN — cells that are in between normal and cancer.

In an article published in *Nature Genetics*, Nelson, Haffner, and colleagues described their finding that male hormones cause a malfunctioning enzyme, called TOP2B, to become involved in this genetic mismatch. If this enzyme could somehow be blocked, it might offer a new opportunity for attacking prostate cancer. Also involved in this research were scientists Martin Aryeel, Antoun Toubaji, David Esopil, Roula Albadine, Bora Gurel, Bill Isaacs, Steven Bova, Wennuan Liu, Jianfeng Xu, Alan Meeker, George Netto, Angelo De Marzo, and Yegnasubramanian.

In another article, published in *Clinical Cancer Research*, Haffner, De Marzo, Meeker, Nelson and Yegnasubramanian proposed that hormone-cycling therapy, in combination with drugs that poison TOP2B or inhibit some of the other genes involved in DNA repair, could overwhelm cancer cells. An added benefit to this research is that this tactic may find headway where traditional chemotherapy drugs, which target rapidly dividing cells, have had limited success. As lethal as advanced prostate cancer can be, its cells divide fairly slowly compared to other cancer cells, and this has long been a roadblock for doctors trying to treat it.

"This finding has two important implications," says Nelson. "First, the discovery of a male hormone-triggered process leading to gene defects provides a new insight into how such hormones contribute to the development of prostate cancer. Second, the possibility that male hormones trigger DNA breaks might be exploited — so we can kill cancer cells with high doses of the hormones." This idea, he adds, is now under early testing, in clinical trials for men with advanced prostate cancer.

Getting On With His Life

Recently, something happened to Ian MacKechnie that he never would have believed possible a few months ago: He forgot his Gleason score. Just for a minute, then it came back to him: 3 + 4. The "good 7." But it had slipped his mind for the best possible reason. He doesn't have prostate cancer anymore. It's gone, and he is busy thinking about other things. He has his life back.

This is what we hope for, why we do what we do here at the Brady. Until the day comes when we can say, "Follow this list of things to eat and make these lifestyle choices, and you will never get prostate cancer," the next best thing is for a man to be screened regularly — as MacKechnie was, watching his PSA for years, knowing that it was slightly elevated because he had BPH (benign prostate enlargement) — and then, when the PSA made a jump that didn't make sense, getting a biopsy. When the tissue samples came back with a diagnosis of cancer, MacKechnie did what he always does when he tackles a problem: he learned more about it. He started reading up on this disease that had never before been on his radar screen, and he found surgeon Patrick Walsh through his book, *Dr. Patrick Walsh's Guide to Surviving Prostate Cancer*, written with Janet Farrar Worthington.

"I barely knew where Baltimore was. I had heard of Johns Hopkins, but purely as a name."

MacKechnie, a native of Scotland, is a businessman and philanthropist, the founder and CEO of Amscot Financial, a chain of financial services stores based in Florida. "I barely knew where Baltimore was," he says. "I had heard of Johns Hopkins, but purely as a name." Yet "if you look at my copy of the book, it's underlined, every page." This is because as

Jean and Ian MacKechnie: Enjoying life without prostate cancer.

Walsh wrote about the disease that he has dedicated his entire career to preventing, treating, and curing, "he said things that, as a business person, ring true to me. I understand that this focus is the key to success."

MacKechnie liked Walsh's advice to patients to find a medical center where they treat a lot of prostate cancer, every day, and know how to handle highly specific complications — more so, perhaps, than a place where the guy who just got operated on for prostate cancer is in the recovery room next to the lady with the hernia, across the hall from a man recovering from donating his kidney. "I understand, as a layperson, that when you are seeing the numbers that the Urology group at Johns Hopkins are doing, not only are the surgeons extremely skilled, because they're focused on that procedure, but the nursing staff become much better, because they know how to anticipate the issues that patients will have. There is no detail that has not been carefully put together, from the moment you arrive. It kind of makes sense, doesn't it, — it's run the way I've always tried to run my businesses. They get a great result for their patients." MacKechnie's Amscot stores take care of half a million customers a week, "and we try to give them in very much the same way, a very good experience."

In those first few weeks, Mackechnie learned that his older brother, Donald, who lives in England, had also just been diagnosed with prostate cancer. After MacKechnie told his brother about the book, Donald bought one, too. "The book drove me to Dr. Walsh, and to Johns Hopkins," MacKechnie says. He believes that he was able to get treated and recover quickly because he found a doctor he could trust. "Dr. Walsh's commitment comes through in the book, his lifelong commitment to this whole specialty of prostate cancer. In our company, we say, when trust goes up, speed goes up. If you're dealing with someone you don't totally trust, it takes much longer." MacKechnie also was troubled to learn that another friend, back in Scotland, had not fared so well after his treatment for prostate cancer. "He is cancer-free, but his quality of life is totally destroyed," left with debilitating urinary incontinence. "That's what happens if it's not done well."

MacKechnie underwent his radical prostatectomy in the summer of 2011, and regained urinary continence within two to three days. As *Discovery* went to press in the fall, he has started running again. "I'm back to 100 percent. It's wonderful," he says. MacKechnie and his wife, Jean, have given a sizeable gift to the Patrick C. Walsh Prostate Cancer Research Fund, and are the newest members of the Founders' Circle. "We were delighted to do it," he says. "Those who are able to do something should do something, to keep that legacy going. Plus, we have two sons," and MacKechnie knows that their risk of developing prostate cancer is higher, now, because they have two relatives affected — a father and an uncle. Giving back, he adds, is "gratitude. It's a small token. Compared to someone who has spent 30 years, and devoted his life to this disease — this is nothing; it's only money. I am grateful to the research that Dr. Walsh has put into it, and to Johns Hopkins and the commitment to patients."

"In our company, we say, when trust goes up, speed goes up. If you're dealing with someone you don't totally trust, it takes much longer."

MAKING A GIFT

If you are interested in making a gift to support prostate cancer research, please call the Development Office at (410) 955-8434, or send an email to Shabina Bahl at: shabina@jhu.edu

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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THE PATRICK C. WALSH PROSTATE CANCER RESEARCH FUND

Read About the Research You Have Helped Make Possible

For six years now, the Patrick C. Walsh Prostate Cancer Research Fund has been encouraging and rewarding promising scientists who are interested in helping us find the cure for prostate cancer. Anyone, in any discipline, is welcome to apply; if someone has a good idea, and our Scientific Advisory Board thinks it's worth pursuing, we provide $75,000 a year for two years to support pilot projects, to test proof of principle. This provides the investigator with valuable preliminary data to use when applying for continued funding from agencies like the National Institutes of Health. This unique Fund began, is sustained, and continues because of great generosity, from you, our wonderful patients and friends who share our commitment to curing prostate cancer.

So far, your help has allowed us to raise more than $30 million. We have funded proposals from the best and brightest scientists at Johns 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, Christian Evensen and Samuel Himmelrich. Some of the work of the scientists funded this year is described below. Also, because we are so proud of our awardees, we thought you might like to see the names of the scientists who have been awarded grants from our Fund (see below).

The 2011 Awardees

Mohamad E. Allaf, M.D.
The Peter Jay Sharp Foundation Scholar
Departments of Urology, Oncology, and Biomedical Engineering

Trinity Bivalacqua, M.D., Ph.D.
Prostate Cancer Team Scholar
Departments of Urology and Oncology

Gerald W. Hart, Ph.D.
The Beth W. and A. Ross Myers Scholar
Department of Biological Chemistry

John T. Isaacs, Ph.D.
The R. Christian B. Evensen Scholar
Departments of Urology and Oncology

Phuoc Tran, M.D., Ph.D.
The Phyllis and Brian L. Harvey Scholar
Department of Radiation Oncology and Molecular Radiation Sciences

The 2011 Awardees in their Second Year of Funding

Charles Drake, M.D., Ph.D.
The Nancy and Jim O'Neal Scholar
Departments of Oncology, Immunology, and Urology

William B. Isaacs, Ph.D.
The Dr. and Mrs. Peter S. Bing Scholar
Departments of Urology and Oncology

Prakash Kulkarni, Ph.D.
The Irene and Bernard L. Schwartz Scholar
Department of Urology

Jun Luo, Ph.D.
The Carolyn and Bill Stutt Scholar
Department of Urology

Alan Meeker, Ph.D.
The Virginia and Warren Schwerin Scholar
Departments of Pathology and Urology

Which Should a Man Choose: Open or Laparoscopic Prostatectomy?

A new study by Mohamad Allaf, M.D., Director of Minimally Invasive and Robotic Surgery and *The Peter Jay Sharp Foundation Scholar*, aims at answering this question by comparing the results of patients who have received open prostatectomy with those who have undergone robot-assisted laparoscopic radical prostatectomy (RALP). That the question is now being asked signals how far laparoscopic prostatectomy has come over the last 14 years. "Key anatomical discoveries by Patrick Walsh that enabled surgeons to work in a bloodless field, while sparing the nerves responsible for erections, made open radical prostatectomy the gold standard treatment for men with localized prostate cancer." The anatomic discoveries helped pave the way for Johns Hopkins urologists to perform the first laparoscopic radical prostatectomy in 1997 — but the procedure was technically difficult, and the instruments were much less sophisticated than those available today. "It failed to attain widespread use until the advent of the da Vinci robotic platform," Allaf continues. RALP has steadily become more popular. "The principles are the same as those of open radical prostatectomy, and the steps of the robotic procedure largely mimic those of the open technique. So, when a patient is faced with the choice of two types of radical prostatectomy, which one should he choose?"

Allaf is studying outcomes, "specifically, the completeness of cancer removal, in addition to quality-of-life measures such as erectile and urinary function," he says. "Both of these are difficult procedures that require a lot of experience before a surgeon can achieve expert status. Given this, we will analyze the learning curve for these approaches, to shed light on how many procedures are required for a surgeon to achieve competency. We hope our study will set the standard for the results that can be achieved by both open and robotic surgery."

Hormonal Therapy, Diabetes, and the Heart

Many men worldwide are placed on androgen deprivation (AD) therapy, also known as hormonal therapy, as their sole form of treatment for prostate cancer. But AD therapy is not without its side effects, and for some men, particularly those with diabetes, this treatment may put them at higher risk of dying from cardiovascular disease.

Who gets AD therapy? It's complicated, says Trinity Bivalacqua, M.D., Ph.D., *The Prostate Cancer Team Scholar*. "Some men with high-risk prostate cancer (a Gleason score of 8 to 10) are treated with the combination of radiation therapy and AD from the start. Others receive it when their PSA begins to rise after treatment with surgery or radiation."

Although studies have reported improved survival for men with locally advanced cancer who receive AD in addition to radiation therapy, "AD is also frequently used outside of these proven settings," says Bivalacqua, "and for these men, long-term data on the clinical benefits are lacking." Why not just put men on AD?

Because shutting off the male hormones, or androgens, takes a toll on a man over time. It can lead to osteoporosis, loss of libido and erectile dysfunction, memory difficulties, weight gain, and atherosclerosis. "Of particular note," cautions Bivalacqua, "a number of randomized control trials have shown an increased risk of death from cardiovascular disease, and new-onset obesity and diabetes." Loss of testosterone is highly prevalent in men with diabetes and metabolic syndrome, a condition closely linked to the development of diabetes.

Shutting off the male hormones takes a toll on a man over time. It can lead to osteoporosis, memory difficulties, weight gain, atherosclerosis, and diabetes. It can also have a profound effect on the heart.

Further, the loss of testosterone affects the endothelial cells, found in tissue lining organs and blood vessels, and makes the walls of blood vessels more rigid. Tests in heart muscle grown in cell culture suggest that the loss of testosterone directly affects the heart cells' ability to function — a condition that, in the lab, can be reversed by restoring the levels of testosterone — and may contribute to heart failure.

Even though AD has been prescribed for years, "little is known about its effects on the heart problems associated with aging and diabetes. Having more insight into these effects will help us make treatment decisions for older men." Bivalacqua will use mouse models of aging and diabetes to find out more. "We hypothesize that the loss of testosterone will have profound effects on cardiac function by impairing endothelial function in the heart," he says. In early experiments, he has noted impairment in both cardiac muscle and the functioning of blood vessels, as a result of a lack of male hormones.

Men who undergo AD for prostate cancer are often older and have several health problems — particularly diabetes and coronary artery disease. "These experiments have tremendous potential," says Bivalacqua, "because they may help us predict future cardiovascular risk in men undergoing AD for prostate cancer treatment."

Sugar Regulation and Prostate Cancer

How our cells deal with sugar — and there are many forms of it, for highly specific needs — is one of the most basic aspects of our biochemistry. Gerald Hart, Ph.D., should know; he is the DeLamar Professor and Director of Biological Chemistry at The Johns Hopkins University, and has been studying sugar regulation for decades. Now Hart, *The Beth W. and A. Ross Myers Scholar,* is working hard to find out how the regulation of sugar within cells changes in prostate cancer — and whether understanding this could lead to new ways to fight this disease.

"In the early 1980s, we made the surprising discovery that many of the cell's key regulatory proteins are dynamically modified by a sugar that serves to change how they work in response to nutrients and stress," says Hart. Since then, Hart and others have learned that the activity of this particular sugar not only plays a fundamental role in most of the cell's machinery; it also helps oversee nearly all of the cellular processes that go awry in cancer. For example: "This simple sugar modification of proteins regulates the cell's signaling networks, the expression of genes, the structure of the nucleus, and processes controlling cell division." Even though several studies have linked changes in this sugar modification with prognosis in certain cancers, "there have been almost no detailed studies of the roles of this sugar modification in cancer. The resources provided by the Patrick C. Walsh Prostate Cancer Research Fund are allowing us to systematically determine the roles of this important sugar modification of proteins in the properties of prostate cancer cells that contribute to their progression from benign to highly aggressive states."

What does our cells' ability to deal with sugar have to do with prostate cancer? Maybe a lot. No one has really looked, until now.

Hart's first step in his pilot study is to identify which proteins are modified in prostate cancer cells — and more specifically, in all kinds of prostate cancer cells, from benign to the most hormone-resistant. Next, he plans to evaluate how changes in this sugar modification "affect the growth properties, the expression of steroid receptors, and the nuclear structure of prostate cancer cells." This is an area of cell regulation that has been overlooked by cancer researchers. Hart hopes his findings will lead to the development of focused approaches that will create "completely unexpected avenues for diagnosis and treatment."

Targeting Prostate Cancer With Stem Cells

"Prostate cancer will kill more than 32,000 American men this year alone, and the death rate is twice as high in African Americans," says John T. Isaacs, Ph.D., *The R. Christian B. Evensen Scholar.* While early detection and better treatment have saved thousands of lives, science still has far to go in fighting cancer that has been detected at an advanced state, or high-risk cancer that is likely to return after initial treatment. This is the cancer that Isaacs has spent his career working on ways to stop.

"The long-term goal of our lab is to develop effective therapies to prevent death from this devastating disease," says Isaacs, who has developed three drugs that are currently in clinical trials for patients with prostate cancer. One of these is an angiogenesis inhibitor, discussed on Page 9, a drug that slows down cancer by interfering with its ability to make new blood vessels. Now Isaacs is looking at a different way to target cancer that has spread to distant sites in the body: Stem cells. These cells, extracted from bone marrow, have the potential to kill

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lethal cancer cells without touching normal cells just a hairbreadth away.

"This approach is based upon the fact that mesenchymal stem cells, which come from adult bone marrow, travel through the bloodstream and eventually stop at sites of prostate cancer, drawn by the presence of certain chemicals made by the cancer cells," says Isaacs. He takes these cells, found in the bone marrow of healthy donors, and makes more of them in the laboratory. Then, using molecular techniques, "we induce these cells to produce and secrete a protein, which is engineered so that it can only be activated to kill prostate cancer cells." These specially formulated stem cells will then be put back in the patient's blood, where they will travel to areas where prostate cancer has metastasized. "The hope is that they will act as 'Trojan Horses'," says Isaacs, "killing prostate cancer while preventing unwanted side effects in normal tissue."

Using Statins to Target Cancer Therapy

MYC is an oncogene — a gene that's known to cause certain forms of cancer, including prostate cancer. Studies of men with prostate cancer suggest that if MYC is present in a cancer, it is more likely to defy treatment. Mice that have the MYC gene develop prostate cancer. But when the MYC gene has been targeted for treatment in mice that have liver cancer, lung cancer, and lymphoma, the cancer has been cured.

Encouraged by these promising results, Phuoc Tran, M.D., Ph.D., *The Phyllis and Brian L. Harvey Scholar*, is hoping to target MYC in men with intermediate- to high-grade, localized prostate cancer. "In the past, MYC has proven difficult to target directly," he says. But the use of statins — cholesterol-lowering drugs, taken by millions worldwide — may help. "Statins have unintended, yet beneficial, effects on cancer. They inhibit essential processes of cellular growth that include certain oncogenes." Specifically, statins block regulatory genes, called Ras/Rho, which, in turn, control MYC. "In addition, multiple lines of evidence suggest that statins may have a clinical effect on prostate cancer. Studies (including some led by scientists at Hopkins) have consistently shown a lower risk of advanced prostate cancer in men who take statins compared to other men. Also, taking statins seems to improve the likelihood of cure in men with prostate cancer who undergo surgery as well as radiation therapy. But none of these studies focused on how statins affect the MYC gene in prostate cancer.

"Our own laboratory data, with prostate cancer cells grown in a dish, suggest that MYC is the critical target for the cell-killing and radiosensitizing (making cancer cells more vulnerable to radiation) effects of high-dose statins," says Tran. "All of this information suggests that high-dose statins work to kill prostate cancer cells with high MYC levels." The best part is that, compared to other drugs that researchers suspect may help kill prostate cancer, statins are already FDA- approved, and have proven safe in widespread clinical use. "Lovastatin, in particular, is very low-cost," says Tran. "However, it is important to pinpoint the men most likely to benefit from high-dose statin therapy. We hypothesize that MYC levels in prostate cancer can help us determine which patients will benefit from taking statins along with radiation. By using high-dose statin therapy only in men whose prostate cancer has high MYC levels, we hope to make surgery and radiation even better." Tran is working in the laboratory to determine the right dose of lovastatin needed to inhibit MYC. Then, he plans to use his findings as the basis of a clinical study in men with intermediate- to high-grade localized prostate cancer.

What is it about statins and prostate cancer? Why are men who take these drugs less likely to develop advanced prostate cancer? Maybe it has to do with a certain gene, called MYC.

The Patrick C. Walsh Prostate Cancer Research Fund Named Scholars

Open any journal that has to do with prostate cancer, and you will most likely run across one of these names. These scientists are the best at what they do, their work is world-class — and they have all been helped over the last few years by the Patrick C. Walsh Prostate Cancer Research Fund. "I think these grants are pivotal in the careers of many young faculty members," says Charles Drake, M.D., Ph.D., who has had several projects supported by the Fund, "and that their importance can not be overemphasized." We are proud of their achievements, and we thought you might like to see the names of all the scientists whose work you have helped fund.

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You can reach us at (410) 955-8434, or see our website: http://urology.jhu.edu.

Patrick C. Walsh, M.D, University *Distinguished Service Professor of Urology*
Janet Farrar Worthington, *Writer/Editor*
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Bad Science: Late-Breaking News

As *Discovery* went to press, a group of scientists issued a disturbing report. The United States Preventive Services Task Force (USPSTF) recommended against PSA screening for prostate cancer, based on its evaluation of evidence of both benefits and harms. To understand this recommendation, you need to know that the panel is made up of "independent scientists who are better able to objectively evaluate the literature without bias." No urologists were invited to participate.

The panel said that "healthy" men don't need PSA screening. In effect, this decision sets the clock back to before the 1990s, when "healthy" men were diagnosed with cancer that was palpable and often, too late to cure. Is this about progress, or saving money?

Prostate cancer is the most common cancer in American men and the second most common cause of cancer death. Because the cancer begins on the prostate's outer edges, it produces no symptoms until it is far advanced and too late to cure. You can be a "healthy" man and have a steadily climbing PSA, silently trumpeting the danger alarm. Early diagnosis is everything. It is the cornerstone that has dramatically reduced death and suffering.

In 1991, before PSA testing was in place, 20 percent of men were diagnosed with prostate cancer that had already spread to their bone. Today that number is less than 4 percent. It's hard to imagine now, but in 1991, one out of five men had metastases. Today, it's one out of 25.

The effect on deaths is equally dramatic. Between 1994 and 2004, prostate cancer deaths plummeted 40 percent — more than for any other cancer in men or women. But what would have happened if PSA testing and effective treatment had not come along? Using the age-adjusted death rate from 1990 of 39.2 prostate cancer deaths per 100,000 men and applying it to 2007, there would have been 59,000 deaths. Instead, because the death rate fell to 23.5, there were 35,000 deaths. Thus, 24,000 fewer men died from prostate cancer. Because advances in treatment have also played a role, scientists from the National Cancer Institute estimate that 40 to 70 percent of this reduction is the direct result of screening.

Unfortunately, the USPSTF never mentions these figures, and makes no attempt to reconcile them with its recommendations. The scientists did use large, uncontrolled observations to look at the complications of surgery — but not at the number of lives saved since PSA testing was introduced in the United States in the early 1990s. Also, the USPSTF recommendations are based on two trials with only seven and nine years of follow-up — even though it is widely accepted that men with a lifespan of fewer than 10 years should not be screened or treated.

Of course, there can be harm with any intervention. We can reduce the potential risks of PSA testing by: screening frequently the men who are likely to benefit the most

You can be a "healthy" man and have a steadily climbing PSA, silently trumpeting the danger alarm. Early diagnosis is everything. It is the cornerstone that has dramatically reduced death and suffering.

(younger men with higher or rising PSA levels); screening infrequently, or not at all, men who are older, in poor health, or who have lower PSA levels; using surveillance, not immediate treatment, more often for selected men. Finally, PSA testing should continue to be used for monitoring patients after treatment for prostate cancer, to identify progressive disease.

For more information, please visit our website at http://urology.jhu.edu