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FROM THE DIRECTOR: Preserving Lives, Improving Lives, Teaching Others

In this issue of Prostate Cancer Update, we report two milestones that I believe are related:

1. The 20th anniversary of the first nerve-sparing operation, and
2. The first concrete evidence that aggressive treatment of localized disease saves lives.

Twenty years ago, the first anatomic radical prostatectomy was performed. The new procedure overcame many obstacles that had kept urologists and their patients from accepting surgery as the best form of treatment for localized prostate cancer.

Before 1982, radical prostatectomy was often associated with excessive, life-threatening bleeding; as a result, 2 percent of men who underwent the operation died from it. However, with less blood loss, the operation became safer, and the mortality rate fell tenfold to where it is today, at 0.2 percent. Before 1982, all men who underwent radical prostatectomy were warned that they would be impotent afterward, and between 10 and 25 percent would have severe incontinence. It's easy to understand why many men felt the treatment for prostate cancer was worse than having the disease itself.

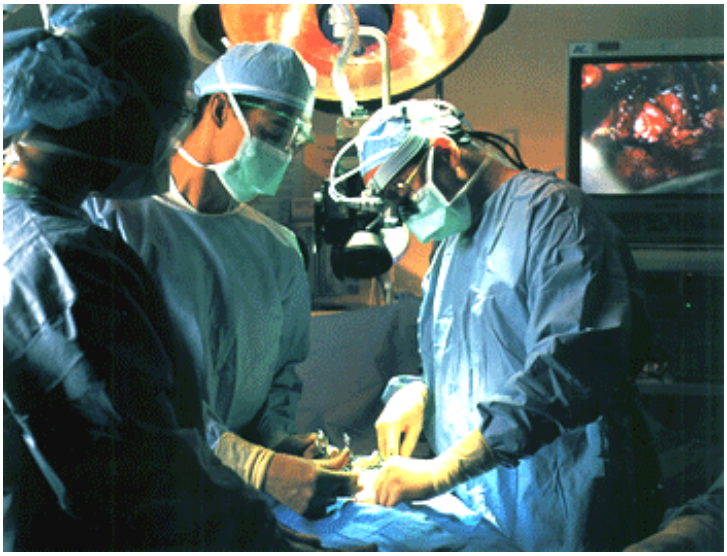
With the development of this new anatomical approach, more men accepted radical prostatectomy. In 1983, only 7 percent of men with localized prostate cancer underwent surgery. By 1993, the number had reached 35 percent. Indeed, in that year, 104,000 men underwent radical prostatectomy. Within a decade, prostate cancer deaths in the United States plummeted. In 1993, 43,000 American men died of the disease.

By 2002, the number was down to 30,200. Is there any cause-and-effect relationship between the rise in radical prostatectomy and a reduction in prostate cancer deaths by 13,000 a year a decade later? The Scandinavian story provides some insight.

In this landmark study from Scandinavia, men who underwent radical prostatectomy were half as likely to die of prostate cancer as men who were treated with watchful waiting. This raises the intriguing possibility that the major cause for the reduction in deaths from prostate cancer now is the rise in radical prostatectomies a decade ago, simply because an operation was made safer.

Sharing what we know

Men who invested in having a radical prostatectomy over the last 20 years have made a wise decision. Unfortunately, it is not yet an "equal-opportunity" operation: Not all men have the availability of a surgeon who is skilled in performing the surgery, and either are not offered an operation, or suffer needless side effects. Over the last 20 years, I have worked to perfect this procedure—by studying videotapes of my own operations, by following my patients carefully, and understanding their true side effects, by developing new techniques, and by identifying anatomical variations in men that might affect their long-term urinary continence and potency.



Patrick Walsh, seen videotaping a "nerve-sparing" procedure for worldwide distribution to urologists

Now, I have put everything I know about this operation on a DVD, which I plan to distribute around the world free of charge, to any urologist who wants to view it. My dream is that no man with prostate cancer will miss the opportunity to be cured, and to live a long, happy life free from devastating side effects.

Patrick C. Walsh, M.D.

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"Nerve-sparing" Surgery Turns 20

FLASHBACK: The bad old days, the late 1970s. Doctors who treated prostate cancer had few weapons in their arsenal. One was radical prostatectomy, developed by Johns Hopkins urologist Hugh Hampton Young in 1904; another was the retropubic approach, first described in the 1940s.
Both procedures were known to cure cancer, if it was still contained within the prostate, but at a terrible price. Every man was impotent after surgery, and 25 percent had severe problems with urinary control. Worse, the retropubic procedure itself was life-threatening, because of the horrendous bleeding that went along with it.

Another option was external-beam radiation treatment, introduced in the 1960s. Radiation did not cure prostate cancer as well as surgery, but at least it had fewer side effects—and to many men, this presented a more attractive alternative. Hormonal therapy, a stopgap measure, was also bleak—castration, which immediately shut off the production of testosterone, and temporarily slowed the growth of cancer.

Urologist-in-chief Patrick C. Walsh, M.D., began devising the procedure that would later bear his name with the simple goal of finding surgical methods to lessen the bleeding so we could actually see what we were doing, instead of blindly feeling our way," he recalls. "Like many urologic surgeons, I was appalled by the blood loss in these men."

Walsh spent years studying the anatomy of the blood vessels (particularly, the large veins) surrounding the prostate, and developed new techniques, which did two things: First, with the bleeding under control, the operation became much safer. And with the now "bloodless field," for the first time, critical structures "which previously had been unrecognized and damaged, simply because they were swimming in blood and invisible" could be looked for and saved. More precise dissection and reconstruction reduced the likelihood of significant urinary incontinence to 2 percent, and of those 2 percent, incontinence is generally mild.

Breakthrough In Understanding How Potency Works
But what about impotence? "Everybody believed that penile nerves were automatically damaged by the radical prostatectomy," says Walsh. The assumption was that the nerves that controlled erection ran through the

prostate, and were destroyed when the prostate was removed. This was considered an unavoidable hazard, the price of curing cancer.

"Even the textbooks said that this was the case," Walsh says. "One highly respected anatomy textbook stated merely that the nerves that enable erection were "extremely small, difficult to follow in the adult cadaver," and that their location was known "merely through experimental studies." But it didn't make sense to me that the nerves from one organ would run through another organ."

"If we could just figure out where these nerves were" and then find a way to save them but still cure prostate cancer" then men would no longer be faced with an either-or situation. They could be cured of cancer, and remain potent."

Around this time, "something unbelievable" happened to Walsh. In 1977, one of my patients returned for a follow-up visit three months after surgery and reported that he was potent. To me, this news was staggering how could this man be potent, if the nerves that control potency were inside the prostate that I had removed? Furthermore, if this could happen to one man, then why only this one? Why weren't all men potent after radical prostatectomy? The key was finding these elusive nerves. If we could just figure out where they were and then find a way to save them but still cure prostate cancer then men would no longer be faced with an either-or situation. They could be cured of cancer, and remain potent.

In 1981, Walsh went to the Netherlands for a conference, and met Pieter Donker, a urology professor, recently retired, who was studying anatomy and tackling unanswered questions. "No one had successfully dissected the nerves to the bladder, because they were difficult to identify in adults" says Walsh. "However, these nerves are not nearly so obscured in infants." At the laboratory where Donker was working to trace these nerves in the cadaver of a stillborn male infant, Walsh asked the Dutch urologist if he knew what happened to the other end of this plexus of nerves the ones that controlled penile erection. "I've never looked," he said. We got to work. Four hours later, we were jubilant. We could see clearly that the nerves were outside the capsule of the prostate and that, indeed, it was possible to completely remove the prostate and preserve sexual function!

The next step was to apply what Walsh and Donker had found in infant cadavers (where nerves are easier to see for many reasons, including the fact that infants have less fatty fibrous tissue than adults), and locate these tiny structures in the deep, complicated recesses of the pelvis in adult men. Over the next months, Walsh made another important discovery: He noticed a jumble of arteries and veins that traveled along the edge of the prostate in the exact location where these nerves were found in the infant cadaver. Perhaps, he thought, these blood vessels acted as they do elsewhere in the body maybe they provided a scaffolding for these microscopic nerves. And maybe he could use the bundles instead of pinpointing the microscopic nerves themselves as landmarks. Donker agreed. Walsh tested this theory while performing an operation called a radical cystectomy, removal of the prostate and bladder, in a 67-year-old man. "I had never seen or heard of a patient who had been potent after this operation. But 10 days after surgery, this man stated that he awoke in the morning with a normal erection."

A month later, on April 26, 1982, Walsh performed the first purposeful nerve-sparing radical prostatectomy, on a 52-year-old professor of psychology. This man regained his sexual function within a year, and has remained complication-free "and cancer-free" ever since. Over the years, Walsh has made many modifications in his original operation. "Now that we've learned exactly where the scalpel can and cannot go, depending on the extent of a man's cancer, it has become possible either to save these nerves deliberately, or to remove more tissue by cutting these bundles away than we previously had believed possible." It used to be that surgeons never excised these nerves, because they were adherent to the rectum; instead, surgeons just cut the nerves and unknowingly left them in place.

With these anatomical techniques, "we now have a better chance of removing all the cancer," says Walsh. "Many people call this a nerve-sparing operation, but a more accurate description is that it's an anatomic radical prostatectomy, because there are actually two things going on. One is preserving the nerves; the other is creating wider margins, by excising them when necessary, removing as much tissue as possible around the cancer, and making this a better cancer operation."

Impotence was considered an unavoidable hazard, the price of curing cancer.

Of Walsh's patients, 86 percent of men under age 65 who undergo radical prostatectomy are potent, only 2 percent wear a pad that they change more than once a day, and the cancer control rates are used as the "gold standard," to which all other forms of treatment are compared.

Scandinavian Study Shows Surgery Saves Lives

Some of the most exciting news in prostate cancer treatment has come from Scandinavia, where so many men die of this disease. A groundbreaking study, conducted by the Scandinavian Cancer Group and published in the September 12, 2002, issue of the New England Journal of Medicine, provides the first concrete evidence that treating localized disease reduces deaths from prostate cancer.

In the study, involving hospitals from Sweden, Finland, and Iceland, nearly 700 men with localized prostate cancer were randomly assigned to radical prostatectomy or to watchful waiting, the most common form of treatment in those countries. During the average follow-up of six years a surprisingly short time twice as many men in the watchful waiting group died of prostate cancer. This means, the scientists concluded, that radical prostatectomy may reduce prostate cancer deaths by about half.

A man's risk of dying from prostate cancer exists for 20 to 25 years after he is diagnosed. In another study from Sweden, 63 percent of men who were treated with watchful waiting, who lived longer than 10 years, eventually died of prostate cancer. In the Scandinavian study, at 8 years, there was an absolute reduction of 14 percent in the number of men whose cancer had progressed to distant metastases (27 percent of men in the watchful waiting group developed metastases, compared to 13 percent in the surgery group). The scientists, noting that the average survival of men with distant metastases is only about two to three years, anticipate that with longer follow-up, the differences in cancer deaths between these two groups will become even more distinct.

What about quality of life? The men who had surgery experienced more erectile dysfunction and urinary leakage, and less urinary obstruction than the men in the watchful waiting group. However, in the Scandinavian trial, nerve-sparing surgery was not routinely performed. Also, many men in the trial were over age 65, and thus more likely to experience problems with incontinence and impotence. And 20 percent of these men had received hormonal therapy within five years after being diagnosed with cancer.

Any of these three factors, the lack of a standardized, nerve-sparing procedure, older age, and the use of hormonal therapy could explain why there were more complications with radical prostatectomy in this study than if the operation had been performed uniformly, at a center where many of these procedures are done each year.

The men in the watchful waiting group experienced erectile dysfunction and urinary leakage, as well, either from progression of the cancer which occurred in 60 percent of these men or from the treatment of it. As a result, at

four years, there was no significant difference in quality of life in the two groups.

And finally, in this study, 75 percent of the Scandinavian men were diagnosed with cancer advanced enough to be felt during a physical exam, and only 10 percent were diagnosed with non-palpable cancer, because of an elevated PSA. This is in sharp contrast to the United States, where 75 percent of men are diagnosed on average five years earlier, and at a much more curable stage with non-palpable cancer, detected because of a change in PSA.

"How should the results of this study influence the advice we are giving patients?" asks Urologist-in-Chief Patrick C. Walsh, M.D., in an accompanying editorial in the New England Journal. "Should no one have watchful waiting? Should all patients undergo radical prostatectomy? The answer to both of these questions is a categorical 'no.'" There have always been, and "always will be," men who are best served with watchful waiting, Walsh continues. Many of them are "men who are too old or too ill to survive longer than 10 years. If their cancer progresses to the point where it causes symptoms, there are many ways to palliate the disease." Other men who are good candidates for watchful waiting are men with slow-growing, low-volume cancer, he adds.

For men with more significant cancer that needs to be treated, there are two good options, Walsh says. "For young, healthy men, there is no better way to cure prostate cancer than surgery. And if this operation is performed by experienced surgeons, their quality of life should be excellent."

For men who are older, or who have other health problems that may preclude surgery, radiation therapy is the best option, and offers the fewest side effects, he adds. "Over the last decade, radiation therapy has been improved, providing higher-dose delivery targeted more specifically to the prostate." Walsh notes that although the Scandinavian trial shows that surgery reduces deaths from prostate cancer, no similar trial of radiation therapy has been carried out, although several studies comparing radical prostatectomy to external-beam radiation and brachytherapy are in the works.

Mixing Apples and Oranges: Using Two Standards to Determine Cure with Surgery and Radiation Therapy

"Did the treatment work?" For men with prostate cancer, this is the million-dollar question. And yet, this is the one question that remains elusive for many men who undergo radiation treatment for prostate cancer, because depending on how a man's follow-up results are interpreted, he may never formally fail treatment, even if all evidence suggests that his cancer is back, and growing.

For men who undergo radical prostatectomy, the definition for success is simple "an undetectable level of PSA, of 0.1 ng/ml or lower. With radiation, however, there is no such "line in the sand" no definitive PSA cutoff point between success and failure.

In 1997, the American Society for Therapeutic Radiology and Oncology (ASTRO) defined relapse, or "biochemical failure," as three consecutive rises in PSA after it reaches its nadir. One difficulty with this is that the PSA increases are not always consecutive. A man's rise in PSA with one test might be followed by a transient decrease in the next, followed by another increase.

Under the ASTRO guidelines, even though there is still what in a radical prostatectomy patient would be

considered evidence that cancer may be present, the treatment would be considered a success.
The ASTRO guidelines suggest that a man should have a PSA test every three or four months during the first two years after treatment, and every six months after that.

The theoretical date of failure is then backdated to the midpoint between the PSA nadir and the first of the three consecutive rises. But it may take years for PSA to fall to its lowest point, and then if the treatment didn't work several more years before failure is declared. During that time, the cancer may be growing, and the opportunity to kill it while it's still localized may slip away.

What would happen if the ASTRO criteria were applied to radical prostatectomy patients?
In a recent study, published in the Journal of Urology, Hopkins scientists did just this: They applied a double standard, using the surgical criteria, the cut-and-dried PSA level of 0.2 or above, as a sign of cancer recurrence, and then interpreting those same results using the ASTRO criteria.

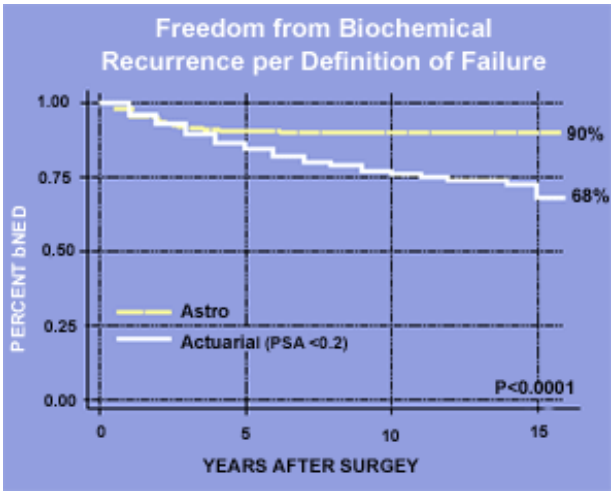
In this study, the scientists retrospectively evaluated 2,691 men who underwent radical prostatectomy at the Brady Urological Institute between 1985 and 2000, and who were followed with PSA tests and rectal exams every three months for the first year, every six months for the second year, and then annually. The average follow-up time was six years; none of the men in the study underwent radiation therapy or hormonal therapy, unless cancer recurred.

Using the surgical criteria for failure, at five years after surgery, 85 percent of the men were cancer-free; at 10 years, 77 percent were, and at 15 years, 68 percent were cancer-free (see graph).

But using ASTRO criteria" requiring three consecutive rises in PSA, and backdating failure to the midpoint between nadir and the first PSA"90 percent of those same men were cancer-free at five, 10, and 15 years.

"Applying the ASTRO criteria artificially improved the patients" probability of being free from cancer at 15 years from 68 percent to 90 percent," says Urologist-in- Chief Patrick C. Walsh, M.D., lead author on the study. "Because most men with prostate cancer are being diagnosed when the disease is curable, and because there are more choices for treatment than ever, it is essential that they make the best decision they can about treatment. Should he have his cancer surgically removed, treated with external-beam radiation or brachytherapy (implanted radiation seeds), or left alone and followed closely?

"Today, many men are told that radiation therapy cures everyone, that 90 percent of men are cured, and no one fails after five years. But unfortunately, these results are based on the ASTRO guidelines, which grossly overestimate the probability of cure. Thus, men must be cautious in interpreting any comparison of these therapies based on ASTRO criteria, because they may be misleading."



These lines show the same men.
How many are cancer-free?
According to the ASTRO criteria, nearly all of them—90 percent—are. But the surgical criteria tell a more sobering story—68 percent are cancer-free—giving the men whose PSA has started to climb a chance to seek further treatment as soon as possible.

The Double Standard
Why is the PSA cutoff used to define success or failure after radical prostatectomy?
The reasoning is this: If all the prostate cells are removed from the body, then there should be no PSA in the body. Zero PSA, technically, less than 0.1 nanograms per milliliter, equals cure.

Conversely, the presence of PSA, detectable levels over 0.1 ng/ml, means that there are still some PSA-making prostate cells somewhere in the body. After radical prostatectomy, a PSA of 0.2 signals a recurrence of cancer. The great benefit of this cut-and-dried rule is that, if the treatment did not get all the cancer, the doctor and patient can know about it as soon as possible and plan further treatment accordingly.

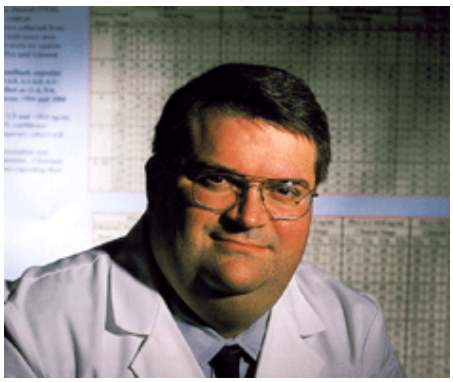
Why is the PSA nadir so important after radiation therapy?

This is because radiation"' effect is gradual; it generally takes two or even three years for PSA to hit rock bottom. Some men reach this nadir quickly, as soon as three months. Rarely, it can take much longer, as long as 10 years. Ideally, once PSA has reached its lowest level, it should stay there.
Some doctors consider a man cured if he has a PSA between 1.0 and 1.5; others even assume that a man has been cured if his PSA after radiation is in the "normal" range" lower than 4.0. But a PSA of 1.0 to 1.5 means that 10 to 15 grams or more of viable prostate tissue could still be there in the body (because the PSA level in the blood is about 10 percent of the weight of the prostate).

Theoretically, even if there is no cancer in this tissue, it could still become cancerous in the future. Thus, after any form of radiation, the PSA level should eventually fall to less than 0.5, and ideally, to less than 0.2.

The Partin Tables: Bigger and Better Than Ever

For men with prostate cancer, urologist Alan Partin is a household name, right up there with Donald Gleason, the pathologist for whom the grading system for prostate cancer is named. Partin's ability to make sense out of numbers specifically, a man's PSA, Gleason score, and estimated clinical stage" has allowed thousands of men worldwide to benefit from "virtual surgery," by predicting what would be found if the prostate were removed surgically, and examined by a pathologist.



Alan Partin: The latest tables reflect the good news in prostate cancer diagnosis, and the huge improvement in cancer control.

The Partin Tables were developed at the Brady Urological Institute in 1993 by Partin and urologist-in-chief Patrick Walsh, after Partin studied the course of prostate cancer in hundreds of Walsh's radical prostatectomy patients. The tables correlate those three key pieces of the prostate cancer puzzle with the actual pathologic stage, determined when pathologist Jonathan Epstein, M.D., examined the surgically removed prostate specimens. With 95-percent accuracy, they predict a man's likelihood of being cured by treatment. In the span of a few years, these tables have become indispensable for many patients as well as doctors trying to chart the right course of treatment in a sea of confusing choices. To give you an idea of their importance as a layman's tool, a recent Google search on "Partin Tables" turned up 1,220 entries on the Internet in English alone. (For this and other work, Partin recently was awarded the prestigious Golden Cystoscope Award by the American Urological Association.)

Now, the tables are bigger and better than ever. The 2001 Partin Tables are based on the results of 5,079 men who underwent surgery at the Johns Hopkins Hospital between 1994 and 2000, and they reflect the huge improvement in cancer control that has come with increasingly early diagnosis. They're also more consistent; while earlier Partin Tables had included patients from other hospitals, these don't. Now, "the numbers are sufficient at Johns Hopkins alone to create and validate the results."

The 2001 tables are broader, too, reflecting the good news in prostate cancer diagnosis. Earlier versions of the Partin Tables divided PSA into broad ranges: 0-4, 4-10, 10-20, and higher than 20. "But because of early detection, the disease is changing," says Partin, M.D,. Ph.D., Bernard Schwartz Distinguished Professor of Urologic Oncology. "More men are coming in with cancer still confined to the prostate, and over 80 percent of them have a PSA score that is between 4 and 10. We had to offer a better breakdown with respect to PSA points." The 2001 tables also include two categories for Gleason 7. This is because, Partin explains, "we've learned that not all Gleason 7 cancers are alike."

Briefly, the Gleason score is an equation involving five specific patterns of cancer-cell architecture, called grades. Pathologists add the number of the most common pattern to the second most common pattern and use this score, such as 3 + 3 = 6, to assess the aggressiveness of prostate cancer cells. When a man has Gleason 7 cancer, one part of the equation is a 3 and the other is a 4, which means it's more aggressive. But there is a difference between Gleason 3 + 4, where most of the tumor is Gleason grade 3, and Gleason 4 + 3, where more of the tumor is Gleason 4. "We now know that Gleason 4 + 3 tends to act more like a Gleason 8, but Gleason 3 + 4 tends to act more like a Gleason 6," says Partin.

On the Horizon: PSA Profiling

If the Partin Tables are the next best thing to having surgery and knowing the result, the wonders Partin and colleagues are performing with the prostate-made enzyme PSA may make this simple blood test the next best thing to a crystal ball.

Imagine you got the ultimate Swiss Army knife for Christmas, with more blades and gizmos than you could count, and all day long you kept saying, "Wow, it does this! And this! And this!" That's what PSA (prostate-specific antigen) has been for scientists studying prostate cancer" the gift that keeps on giving. The more they study it, the more they learn about the chemistry of the prostate, and the many sophisticated biochemical signals it sends out all the time.

"We're getting to understand PSA a lot better," says Partin. "It used to be, all we knew was that if your PSA was above 4, your chances were one out of four that you had cancer. We were performing biopsies on everybody with a PSA over 4, but that was acceptable, because we needed to find those cancers. Then, along came free PSA."

Chemically speaking, a PSA molecule is like a tiny pair of sharp scissors, and its main job is to break down coagulated semen after intercourse, chomping "like a little Pac Man," as Partin describes it. But PSA also appears in the bloodstream "and it would be disastrous to have millions of these tiny scissors clanking around in the blood, each pointed blade slicing tissue to ribbons. Fortunately, the body is smarter than that: PSA is usually packed in a protective case" a chemical straitjacket, which keeps it from harming innocent tissue. In this form, PSA is "bound", tied to other proteins, rendered harmless. But sometimes, PSA inactivates itself. In this case, it's like a pair of scissors with one broken blade. These scissors don't fit into the case anymore, but that's okay because they don't need it; they are chemically passive. This form of PSA is called "free." With its wings clipped, it flutters freely in the bloodstream, causing no harm.

When a man gets a regular, or "total PSA" blood test, both of these forms are lumped together, the dangerous scissors in the case, and the ones with the broken blade. But in recent years, scientists have developed assays sensitive enough to isolate and quantify both bound and free forms of the PSA molecule, and this separation of PSA can help men in two important ways. It can make the PSA test more specific, and it can help determine how aggressive a man's cancer

is. Patrick Walsh explains it this way: "The higher the free PSA, the more likely that you are free of cancer." Men with prostate cancer are more likely to have low levels of free PSA.

"The free PSA test allowed us to spare 20 percent of unnecessary biopsies in men with PSA between 4 and 10," says Partin, "but then the plot thickened. We found that 18 percent of men with PSA between 2.5 and 4 had cancer. So we had to come up with a better test, or better ways to use PSA to predict prostate cancer," in men with low PSA readings, because "it's just not fathomable to biopsy every man."

Partin has been studying two newly discovered subgroups of free PSA, which he believes will become part of the prostate cancer-diagnosing arsenal within the next few years. One of them is called BPSA, for benign PSA "because it's primarily made by the cells in the center (called the "transition zone") of the prostate, where benign enlargement occurs, and where cancer rarely begins. BPSA is strongly linked to BPH (benign prostatic hyperplasia, commonly called enlargement of the prostate). The other is called pPSA, for "pro-PSA," because it's been identified as the proenzyme, or precursor form of PSA. This pro- PSA, which appears truncated, like a sawed-off shotgun, is a storm cloud, an early warning signal associated with cancer. "When any cell in the body makes a protein, it generally gets a tag, or flag, put on it," Partin explains. In this case, the chemical pennant that should be attached to the pPSA molecule is a piece of peptide. "When this flag gets put on PSA, you have an active, good working form of PSA." But without it, "the molecule is inactive. It won't work as PSA, but it also won't be bound up by other proteins." As a result, these little pieces of pPSA flotsam are left adrift in the bloodstream, and learning how to read them, as Partin has been doing over the last few years, may give more specific evidence that a man with low PSA and no other signs of cancer needs to have a biopsy.

"Free PSA is important, but knowing how it's further fractionated, how much of it is benign, how much of it is not" means we can better detect who does and does not have cancer, especially in the low ranges of PSA," says Partin. "By itself, the serum BPSA is unlikely to tell us whether a man has BPH instead of cancer, because prostate cancer and BPH frequently coexist. However, in combination with pPSA immunoassays, BPSA may give us additional discrimination.
"PSA should not get into your bloodstream," Partin continues, "and when it does, it should be in low concentrations. If you have too much of it floating around, is it the good or the bad, and that's where we start breaking it down. Is it benign free PSA, or pro free PSA?" Partin envisions one day being able to give each man a specific PSA breakdown, "like a bar code on a can of baked beans, or a PSA profile, like a cholesterol profile, of good and bad PSA."

Partin has developed blood tests to measure these new forms of PSA, working with Hybritech-Beckman, and about 300 men have been tested so far. He gives credit to the many Brady patients who have helped this research by donating their blood. "Without them, we couldn't have done what we've done. The blood they donated has gone to the development of new tests. Our patients helped us do this."

Radical Prostatectomy and the Probability of Cure
As the new Partin tables show, prostate cancer is being diagnosed earlier than ever. The detection of advanced cancers has gone down 18 percent since 1991, to the point where today, only about 8 percent of men who are diagnosed with prostate cancer are found to have distant metastases.

The great gift of PSA testing is that it has bought us time. On average, prostate cancer is now diagnosed five years earlier than it used to be, when it had to be large enough for a doctor to feel in a rectal exam, or worse, when it caused symptoms such as urinary retention, because it had grown big enough to interfere with the urethra, or back pain, because it had already spread to the bone.

This five-year lead time, plus the increasing success of radical prostatectomy has dramatically shifted the window of curability for most men. The good news is that today, most men diagnosed with prostate cancer can be cured with surgery.

We can now divide men who undergo radical prostatectomy into four risk groups, based on their pathologic stage:
Group I. These men have an excellent chance of having an undetectable PSA at 10 years. They have a Gleason score of 6 or lower, organ- or specimen confined disease, with or without capsular penetration (there is no difference), and negative surgical margins. At 10 years, the likelihood of having an undetectable PSA is 95 percent.
Group II. These men have a good probability of having an undetectable PSA at 10 years. They have a Gleason score of 6, with positive surgical margins, or a Gleason 7 with organ- or specimen-confined disease. At 10 years, the likelihood of having an undetectable PSA is 72 percent.
Group III. These men have a moderate probability of having an undetectable PSA at 10 years. They have a Gleason score of 7 with capsular penetration and positive margins, or Gleason 8-10 disease or positive seminal vesicles. The probability of an undetectable PSA at 10 years is 41 percent.
Group IV. These men have a low probability of having an undetectable PSA at 10 years. They have cancer in the lymph nodes. Yet, at 10 years without any treatment other than surgery, 13 percent have an undetectable PSA.
Of the men who underwent radical prostatectomy at Johns Hopkins in 2000, 70 percent were in Group I, 20 percent were in Group II, 5 percent were in Group III, and fewer than 1 percent were in Group IV.

Racemase: A New Marker for Cancer, and More

Men who consume large amounts of dairy products or red meat are more likely to develop metastatic prostate cancer and to die of the disease. What De Marzo (left), Issacs and colleagues are learning about racemase may help explain why.

Have you ever seen an operator's switchboard? If it's "prime time" and many people are talking on the telephone at once, it can be a dazzling array of lights; after hours, the lights may be few and far between. This is the general concept of a gene chip, except the "lights," or lack of them, are really fluorescent-dyed copies of RNA, the switchboard is a glass slide that's half the size of a credit card, and the super-fast operator can handle more than 10,000 calls-in this case, each dyed- RNA dot represents a separate gene-at a time. All the information is then read on a scanner about the size of a laser printer.

The microarray technology was a gift from the Peter Sharp Foundation, and Brady molecular geneticist William Isaacs, Ph.D., and colleagues are using it to troll through the human genome, looking to see which genes are expressed differently in men with prostate cancer. (Note: This is different from Isaacs' other search for genes linked to inherited prostate cancer). With Jeffrey Trent, Ph.D., and colleagues at the National Institutes of Health, Jun Luo, Ph.D., a Brady research scientist, and technician Tom Dun, Isaacs set up the microarray-like a telemarketer making random "cold calls" to look for "hits," genes that are expressed differently in normal and cancerous prostate cells.

And bingo-out of these studies came a gene from nowhere, one nobody even thought of in connection with prostate cancer, called a methylacyl CoA racemase (AMACR, or racemase for short). Next Isaacs turned to

pathologist Angelo De Marzo, M.D., Ph.D., who also has expertise in molecular genetics, to figure out what racemase may have to do with prostate cancer.
In an elegant series of studies, De Marzo demonstrated that production of racemase is turned up in both prostate cancer and in high-grade PIN (abnormal cells that are not yet cancerous, but considered a pre-curser to cancer)-but not in normal prostate tissue. As a result of this work, De Marzo says, "we think we have a new marker for prostate cancer. This is one of the most consistently upregulated genes in prostate cancer. It gets turned up early in the process of cancer formation, and it stays up even in men who are failing hormonal therapy. This might be something we could start using right away, to help us diagnose prostate cancer in difficult cases." He is working with pathologist Jonathan Epstein, M.D., to see whether looking for higher-than-normal levels of racemase can improve the diagnosis of prostate cancer on a needle biopsy.

"We have every indication that this is going to work," says Isaacs. "There is going to be a gene expression profile which correlates with high Gleason grade." He and De Marzo also are working to create a "molecular definition" that will help predict what a man's cancer will do. For example, says Isaacs, "with men who have a Gleason 6 or 7 prostate cancer, some are going to progress, and some aren't."

Bingo. Out of these studies came a gene from nowhere, one nobody even thought of in connection with prostate cancer.
Racemase and Diet
But using racemase as a marker for cancer is just the proverbial tip of the iceberg, say De Marzo and Isaacs.

Racemase itself is not a "new" gene; scientists have known for years that it plays a key role in the body's metabolism of fatty acids. It makes an enzyme that "takes branch-chain fatty acids, which are found in dairy products and red meat, and converts them to a form that we can burn as energy," says De Marzo. But the fatty acids in question are very specific, adds Isaacs. "You don't need this enzyme for most fatty acids. However, you do need it to metabolize a type of fatty acid that's particularly prominent in dairy products." This acid, called phytanic acid, comes from phytol, which in turn is derived from chlorophyll. Which means, Isaacs explains, "that animals that eat a lot of grass end up incorporating a lot of phytanic acid into their milk and meat." Think cows, and think-as De Marzo and Isaacs are thinking, with growing excitement-of the known links between red meat and dairy products and prostate cancer.

Scientists have known for several years that men who consume large amounts of dairy products or red meat are more likely to develop metastatic prostate cancer, and to die of the disease.

"This may be the best scientific evidence to support the concept that dietary factors influence the growth of prostate cancer."

What De Marzo, Isaacs, and colleagues are learning about racemase may help explain why. Racemase is expressed nine times higher in prostate cancer than in normal tissue. This means that when men with prostate cancer eat red meat or dairy products, the cancer cells have the potential to gain and use more energy from these foods than normal cells can. And something else happens, too: When the body metabolizes phytanic acid, it makes a toxic byproduct-hydrogen peroxide. "Right now it's complete speculation, but this may turn out to increase oxidative stress in the cell," says Isaacs. Oxidative damage is incremental harm, caused over many years, as free radicals-a harmful result of everyday metabolism- attack the DNA in cells, causing mutations that lead to cancer, or cause it to progress.

For years, there has been increasing scientific speculation on the role diet may play in preventing progression of prostate cancer. Says Urologist-in-chief Patrick C. Walsh, M.D.: "This may be the best scientific evidence to support the concept that dietary factors influence the growth of prostate cancer. I am impressed enough by these data to use them in making recommendations to patients. I tell men who are considering watchful waiting, or

who have PSA progression after surgery or radiation therapy that they should markedly limit their intake of red meat and dairy products." (Fat-free milk is fine, Walsh adds.)

And the microarrays launched it all. "Here's a gene that we never would have thought about ordinarily," says Isaacs. "We were not even aware of this pathway, or phytanic acid, or what any of these things were, and here's this gene that comes screaming up on our arrays. This not only gives us a new marker for prostate cancer it may give us some insight into the mechanisms by which normal prostate cells convert to cancer cells. And perhaps it could prove this idea that reducing dairy products in the diet may be an important way to prevent or slow the progression of prostate cancer."

Giving Prostate Cancer a Killer Cold

Most of us just want to get rid of the common cold. It takes vision to look at the common cold virus and think: Aha, opportunity! But that's exactly what radiation oncologist Ted DeWeese, M.D., and urologist Ron Rodriguez, M.D., Ph.D., have done, and their vision is paying off in exciting new therapeutic approaches for killing prostate cancer.

Ron Rodriguez: "A few years ago, we figured out how to make the bomb. Now we've learned how to control it, so it's more specific."

The common cold in question is a genetically revved-up adenovirus, called CG706, programmed by Rodriguez to detonate only in cells where it finds PSA. Its potency was tested in the first gene therapy trial for this type of virus, in 20 men who had a local recurrence of prostate cancer (detected when their PSA levels started going up) after radiation treatment.

In this trial, recently completed, DeWeese administered droplets of the virus using a system he designed several years ago, similar to the system used to administer brachytherapy seeds-a highly precise computer program that places tiny doses of virus at exact intervals within the prostate, guided by transrectal ultrasound and CT imaging.

"Giving external radiation to these cells, and then adding the virus, killed about seven times more effectively than either the virus alone or the radiation alone. The radiation makes the virus replicate even better."

DeWeese, who is also on the faculty of the Kimmel Cancer Center, is a master in "dosimetry"-the scientific way of knowing exactly how much ground each tiny bit of virus will cover. He has plotted these doses in minute detail, using CT scanning and laser microscopy techniques, and has found that each drop of virus spreads in a sphere, about 10 millimeters in diameter, the size of a small grape.

The trial was a Phase I study, designed to make sure a drug is safe for patients to take, and the researchers found-just as they had expected-that side effects were minimal. "It was quite easily tolerated, which we and the FDA were happy about," DeWeese reports. "However, what we were really interested in was what happened to the prostate." Would the virus kill cancer cells? Would it do what cold viruses normally do-replicate, and cause a lot of trouble to the cells in its target-or would the body's immune system recognize the invader as an old adversary, and fight it off? "We've all had colds before," says DeWeese.

"We all walk around with antibodies to these common cold viruses. About half of us have a special kind of

antibody, called a neutralizing antibody, that is ready to attack. When we started our first study, about half the patients had neutralizing antibodies to the adenovirus, and over the subsequent months, all the patients developed these antibodies. But here's the good news: The presence of those antibodies didn't seem to correlate with how well they responded to the virus treatment."

DeWeese, Rodriguez, and colleagues tracked the virus's progress through biopsies and changes in the PSA level in the blood, and found that the virus was doing its job beautifully-it killed prostate cancer cells. "We could see that on the biopsies," says DeWeese. And the patients who received the highest doses of virus had the best response. "At the top two dose levels, half of the patients had their PSAs drop by more than 50 percent. We gave the highest dose that we could make, and we probably could give even more, because the virus is so well controlled, and because it only kills prostate cancer cells." The limiting factor is a technical one; at this moment, it's scientifically impossible for the researchers to pack a more concentrated viral punch into CG706.

Rodriguez, who is studying even more potent viruses, including one laced with diphtheria (read "Looking for the Ultimate Search-and-Destroy Cancer Weapons), is amazed by how far the team's research has come in a very short time. "A few years ago, we figured out how to make the bomb, but we didn't know how to control it. Now we've learned how to control it, to make it more active, and we've learned how to aim it better, so it's more specific. It's really come along very nicely."

What DeWeese calls the "Achilles heel" of any adenovirus-based treatment is the idea that the body's immune system will cut off the virus at the knees, and stop it from taking hold and killing the cancer. He and Rodriguez have a different take on this idea, which they hope to prove one day soon: "We believe that this is part of the reason why it works-that we induce an immune response to the virus. The virus is replicating and killing cells, but also your own body is trying to get rid of that virus-and that, in and of itself, will also be anti-cancer."

Next: Combining the Virus with Radiation

What could the scientists do to make the virus even more effective? DeWeese has a couple of ideas: One, it might have more "oomph" if given even earlier, in men with less cancer-ideally, in men with what DeWeese calls "intermediate risk" prostate cancer, "patients with T2b cancer, that you can feel on both sides of the prostate, or men with a Gleason 7, or men with a PSA between 10 and 20." But these men are also candidates for radiation therapy, or for surgery. "Because we know that radiation alone or surgery could be standard therapy for this group of patients, and we believe that radiation alone could be improved upon for that group, that's why we're going to target these men."

DeWeese and Rodriguez tracked the virus's progress through biopsies and changes in the PSA level in the blood, and found that the virus was doing its job beautifully-it killed prostate cancer cells.

DeWeese believes the combination will be synergistic: "In classic science terms, you can mathematically prove that when you give the two together, they kill far more than either individually." He has proven this theory in the laboratory, in culture dish experiments, and then in animals with prostate cancer. "We were able to show that giving external radiation to these cells, and then adding the virus, killed about seven times more effectively than either the virus alone or the radiation alone. The radiation makes the virus replicate even better. We haven't figured out exactly why that's happening. But when we took the tumors out of these animals, it was very clear that the combination treatment caused considerably more widespread cell death than either one individually. And the animals actually were gaining weight during the treatment-so they didn't seem to have any toxicity from this more effective cancer-killing combination."

An added bonus: It may even be that because of the virus's effectiveness, the doctors can lower the dose of radiation needed, and minimize some of that treatment's side effects, such as rectal or urethral injury.

The FDA has approved another Phase I study-again, designed to make sure the combined treatment is safe-for DeWeese and Rodriguez, to try the virus and radiation together in patients. After the initial treatment, the patients will undergo follow- up PSA tests every three months, and a prostate biopsy after 18 months. If the treatment, as DeWeese and Rodriguez expect, proves safe, the next step will be to study the combined treatment in a larger, multicenter study.

Looking for the Ultimate Search-and-Destroy Cancer Weapons

What's worse than the common cold? Diphtheria. Ron Rodriguez, M.D., Ph.D., who genetically harnessed the adenovirus and taught it to kill prostate cells, has not put all his viral cancer-killing eggs in one basket. Instead, he's working with a handful of serious weapons, trying to determine which will prove most lethal to-and thus, most likely to cure-prostate cancer.

These cancer-killing viruses, called oncolytic viruses, have achieved spectacular results in his laboratory experiments. One of them, a virus that contains the bacterial toxin diphtheria, for example, has proven even more effective than the adenovirus at killing prostate cancer tumors in animals. "Eighty percent of our animals with prostate cancer have been completely cured when we treat them with a single injection, over a year after treatment. The cancer has never come back. We've never had that happen with any of our other vectors," says Rodriguez. "That's pretty impressive, and we're very excited."

But diphtheria is not, as they say in Hollywood, quite ready for prime time yet. Rodriguez and colleagues are working to fine-tune the virus that packages it-to keep its potency, but limit its toxicity to other cells. Dealing with diphtheria is like holding the proverbial hot potato, and this has proved a great challenge to Rodriguez. The toxin is so deadly that even the cells that make up its delivery system-if diphtheria were a letter, these cells would be the mailbox-have proven susceptible to it. "We've gotten around that problem by designing new packaging cell lines"-cast-iron vessels that remain impervious to the toxin.

Diphtheria's other big challenge has been its risk of what military strategists call collateral damage-harm to the innocent bystanders, cells that have nothing to do with prostate cancer, but happen to be situated next to PSA-containing cells. "If we use the hand-grenade analogy," explains Rodriguez, "right now, we throw the bomb into a lot of cells, and prostate cells will pull the pin very easily.

Other cells will not, but there are still some non-prostate cells that are pulling the pin, and they die." Rodriguez has worked out this problem by making the diphtheria-containing virus still more specific, so the other cells can't "pull the pin" and activate the toxin.

Based on this work, and on other viruses he's investigating, Rodriguez is already planning the next generation of cancer vaccines, which he believes will be more cancer-specific, more powerful, more stimulating to the body's immune system- which means the body's own weapons will be more adept at fighting the cancer, too-and even able to target and kill metastatic disease. "We've come a long way," he says. "When we first started this work, we achieved a proof of concept; we could get some stimulation of the immune system, so the body would recognize prostate cancer cells and start to work against them, but not in any significant way.

Then we got a response in a few patients-we're talking single-digit responses. Then, in our most recent trial, one-fourth of the patients had a partial response, meaning more than a 50-percent drop in the PSA that's sustained. We've done that in about a five-year period. The way I see it, this is growing exponentially. We're getting better at this very quickly."

"Insignificant" Cancer? What Should You Do?

"For which men is surgery necessary, and which men can safely forego treatment?"

Twenty years ago, most men diagnosed with prostate cancer had advanced disease. Only about 25 percent of men were diagnosed with cancer that appeared to be confined within the prostate-and of those, only about half actually had curable disease. Today, the story is nearly reversed: 75 percent of men diagnosed with prostate cancer have clinically localized disease, and at least 80 percent of them are curable.

PSA testing has been a godsend for men with prostate cancer. It's been hugely successful at spotting cancer in its earliest, most curable stages. However, as with every other screening test (with breast cancer, for example), as cancers are detected earlier than ever, some are detected at such an early stage, and are so small and slow-growing, that they don't need to be treated.
Today, some men are found to have minuscule amounts of cancer-smaller than 0.2 cubic centimeters, about the size of a pinpoint, captured by sheer chance during a biopsy. For some men, these are cancers that will never cause harm, and ideally, should never have been diagnosed. Which leads to a treatment dilemma: If this kind of small-volume cancer is diagnosed, what should happen? To treat, or not to treat? What should a man do?

For some men, these are cancers that will never cause harm, and ideally, should never have been diagnosed.

This is the kind of problem urologists -who, for so many years, could only diagnose prostate cancer when the chance of cure had become uncertain-have always dreamed of having. It's also, increasingly, a clinical challenge. Exactly which kind of cancer is it-the "good" kind, that seems content to remain in the prostate and never causes harm, or the kind that will be less indolent over time, and needs to be nipped in the bud? "To what extent are we diagnosing and treating a disease that would progress very slowly, and never threaten a man's life?" asks urologist H. Ballentine Carter, M.D., who is also a professor of oncology at the Kimmel Cancer Center. "For which men is surgery necessary, and which men can safely forego treatment?"

Fortunately, there are guidelines, developed by Jonathan Epstein, M.D., Rose-Lee and Keith Reinhard Professor of Urologic Pathology (see Epstein's criteria). There's also the matter of a man's age, Carter notes. "In a very young man (in his thirties, forties or fifties), a very small tumor might be significant. But in an older man, a very small tumor probably isn't significant, because of the time it takes for that tumor to grow and become dangerous." Even without treatment, cancer that is fairly well-differentiated (to the pathologist, this kind of cancer cell looks fairly normal, or not terribly abnormal) Gleason 6 or below, and localized to the prostate, takes more than 10 years to spread and cause harm.

Thus, "for men who are in their sixties or older, we feel that if we can identify who has low-volume disease, then expectant management may well be a rational approach." For the last few years, Carter and Epstein have been studying this strategy in men with stage T1c disease. Their results, published in the Journal of Urology with Patrick C. Walsh, M.D., and Patricia Landis, were so encouraging that a larger trial, involving several institutions, is in the works.

In this study, 81 men who fulfilled the criteria for low-volume disease were followed. At an average of two years' follow-up, 25 (31 percent) had progression of disease. In 22 of these men, every follow-up biopsy showed cancer. In the men who had progression of cancer, PSA density was significantly higher, and free PSA was lower. Thirteen of these men underwent radical prostatectomy, and 12 (92 percent) had curable disease

Most importantly, Epstein says, the Hopkins research shows that "there is no evidence that prostate cancer grade worsens significantly during a one and a half-to two-year period after biopsy. If a tumor grade changes relatively

soon after biopsy, it's most likely not because the tumor evolved, but because the higher grade component of the cancer was missed." Based on this study, what should men do? "If a man is interested in this approach, the first thing we do is have his pathology slides re-read here at Hopkins (by Epstein), and if we think he is still a candidate, we repeat the biopsy, taking at least 12 samples," says Carter.

Then, if the repeat biopsy confirms that the cancer is low-volume, the man returns to Hopkins every six months for a PSA test and rectal exam, and undergoes a follow- up biopsy once a year. Epstein has found that if the repeat biopsy is negative, it almost certainly means that the cancer truly tiny, and the initial biopsy just happened to hit some of its few cells. "An important message of this paper is that as we accumulate biopsy history on these men, and the biopsies continue to be negative, it's more evidence that what was found initially was small-volume disease," he says. The study has now expanded to include more than 200 men. "Another thing we've learned," notes Carter, "is that there's a lot of variability in men's comfort levels. Some men end up getting treated, even though there is no evidence of serious cancer, because they learn something about themselves-they don't like the uncertainty. They worry, and that decreases their quality of life. Then there are other men who appear to be incredibly comfortable with this approach, and for them, it's the best decision."

Carter and Epstein point out that these results are short-term, because the entity of T1c cancer has been recognized for less than a decade. "Because the follow-up is short-term, we can't say that this is an absolutely safe approach," says Carter. "We think it is, but we're still trying to learn. What we do know is that the potential here is very exciting, because we may save a lot of men from surgery that they don't need."

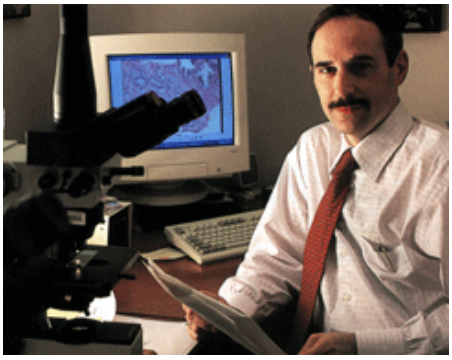
Significant or Not? Epstein's Criteria for Stage T1c Treatment
If you're a healthy man under the age of 60, you should strongly consider curative treatment for low-volume stage T1c cancer. But if, for reasons of age or health, your projected life expectancy is not more than 15 years and there is evidence of small-volume stage T1c prostate cancer, your cancer may never become significant, and may never need to be treated. Pathologist Jonathan Epstein, M.D., has developed criteria that can help predict which men should consider the option of expectant management.

Stage T1c cancer is significant if:
- It's found in three biopsy needle cores, OR
- It's present in greater than half of any one biopsy needle core, OR
- If the Gleason score is 7 or higher, OR
- If the PSA density is greater than 0.1-0.15, OR
- If the free PSA is less than 15 percent.

Stage T1c cancer is probably NOT significant if:
- It's found in only one or two needle cores, AND
- It makes up less than half of each needle core, AND
- The Gleason score is 6 or lower, AND
- The PSA density is less than 0.1-0.15, AND
- The free PSA is greater than 15 percent.

The Pathologists' Troubleshooter

Detecting prostate cancer in a biopsy is, on a much smaller scale, about as easy as finding a needle in a haystack. With a needle. Consider this: The prostate gland is roughly the size of a large strawberry and in it, a patch of cancer-the average cancerous prostate has about seven-is about the size of a strawberry seed. To make diagnosis even more challenging, the cancer cells that are found generally tend to be hard to interpret; thus, biopsy is often a hit-and-miss affair. And yet, the pathologist's judgment is a major part of the treatment decision-making. Is it cancer? Sometimes, the answer is clear. But sometimes, the best the pathologist can say is that it's "atypical."



Jonathan Epstein "wrote the books on the diagnosis and prognosis of prostate cancer. He's one of the reasons our work in prostate cancer is so well respected."

Enter pathologist Jonathan Epstein, M.D., who is world-renowned for his expertise and accuracy in judging prostate cells. A pioneer in the budding specialty of urologic pathology, Epstein also has the distinction of holding the world's only endowed chair in this field. This year, he became the Rose-Lee and Keith Reinhard Professor of Urologic Pathology. "He's unsurpassed in what he does," says Patrick C. Walsh, M.D., director of the Brady Urological Institute. The idea of a chair for urologic pathology was his-a way to honor and support Epstein's considerable research contributions. "In general, pathologists are the unsung heroes," he explains. "Patients sit in their doctor's office and receive some of the most important information they'll ever hear in their lives-the verdict on whether or not they have cancer-and it comes from the pathologist, a person they'll never know." Walsh wants Epstein to be-well, sung. "Jonathan Epstein wrote the books on the diagnosis and prognosis of prostate cancer. He's one of the reasons our work in prostate cancer is so well respected: Our patients start with the scientific opinion of the best pathologist in the world." It is Epstein's pathology work, for example, that gives remarkable continuity to the Partin tables, developed at Hopkins by urologists Alan Partin and Walsh as a means of estimating the exact extent of prostate cancer.

Epstein discovered that he had a knack for deciphering prostate cancer cells in 1982, during his pathology internship at Hopkins. Fresh out of the Boston University School of Medicine, Epstein was tapped by Joseph Eggleston, then head of surgical pathology, to work with urology. "They had a project, a very tedious project, where you actually had to circle cancer cells under the microscope. It would take hours." Epstein recalls it vividly-mainly because he had a case of shingles at the time. "I was in tortuous pain, and I was sitting there without a shirt on, because I couldn't have a shirt touch the shingles, circling these cancer cells forever."

For hundreds of pathologists and urologists, and thousands of their patients, Epstein remains the fallback position-a rock in the unsteady world of hollow-core needle biopsies.

The study was published in Cancer, and the Brady urologists, impressed with his stoicism as well as his work, kept right on collaborating with Epstein. He finished his residency at Hopkins, did a fellowship at Memorial Sloan-Kettering, came back to Hopkins to serve as Chief Resident in pathology, joined the faculty, and now is a professor in pathology, urology, and oncology.

Epstein was a full-time urological pathologist before there was such a thing. "When I started out, there was absolutely no such specialty," he says. At national pathology meetings, "there would maybe be three talks and a handful of posters on prostate cancer," and Epstein's own work would account for at least two of those. "Last year, there were 150 posters and talks. There were no fellowships back then; now there are seven or eight in the country. There's a Urological Pathology Society, there's now the Journal of Urological Pathology-so it's really coming into its own." Epstein gets calls from around the country from hospitals looking for urological pathologists, and as yet, "there are not enough of us around."

For hundreds of pathologists and urologists, and thousands of their patients, Epstein remains the fallback position-a rock in the unsteady world of hollow-core needle biopsies. Which begs the question: What is it about prostate cancer that makes it so tough for pathologists to interpret? "Of all biopsies," explains Epstein, "prostate biopsies are probably the hardest. You're dealing with such a limited amount of tissue." Until very recently, a prostate biopsy consisted of just six needle cores of tissue, taken from throughout the gland; at Hopkins and many other centers, it's now routine to take 12 samples, more if a prostate is particularly enlarged. Even so, the cancer is often wafer-thin, a veneer over healthy tissue. (Using the strawberry image, it's not only a tiny dot, it's a flimsy one.) And the veneer itself is often maddeningly ambiguous-so, not only can the biopsy needle overshoot and miss the cancer, the cancer cells it does get don't always match the pictures in the textbook.

Under the microscope, prostate cancer looks a bad work of modern art. Imagine countless shades of gray, some nearly white, some nearly black, most subtle variations of indeterminate shades somewhere in between, spilled onto a canvas. It's a mess, a jumble of cells that run the gamut from the almost ordinary-looking to cells that are so poorly differentiated and obviously diseased that they could never be considered normal. Worse, cells taken from one part of the prostate may look one way, and those from another part may look completely different.

When a biopsy is labeled "atypical" this happens in about 5 percent of biopsies at most institutions, says Epstein-it means that a pathologist sees "something that could be cancer, but isn't sure that it's definitely cancer." For many patients, the next step is having a repeat biopsy-and the value of this is often questionable, he says. "The problem is, in about 20 percent of cases, the biopsy can miss cancer-so even if it's negative, it doesn't mean the patient doesn't have cancer. In fact, the cancer can be extensive."

Compounding the diagnosis are cells that are not cancerous, but not normal, either. Epstein has shed considerable light on these "funny-looking cells"-called PIN, or prostatic intraepithelial neoplasia. PIN cells, found in the tissue lining the prostate, are abnormal, and they are strongly linked to prostate cancer. Like cancer, PIN has its own distinct patterns, and high-grade PIN, Epstein believes, is a marker for prostate cancer. "We'll often find high-grade PIN next to cancer." If high-grade PIN is found but cancer is not, instead of indicating that a man's prostate is cancer-free, the more likely scenario is that cancer may have been missed, and a man should have another biopsy. Epstein's research continues to define these not-quite-cancerous cells; in fact, he just discovered a new form of high-grade PIN, which he named after its resemblance to a hobnail.

The other end of this vexing spectrum, Epstein has found, is that many pathologists seem just as likely to over-diagnose cancer. "There are many mimickers of prostate cancer under the microscope, and people not as familiar with prostate biopsies can diagnose cancer when it's not." About six to eight men who come to the Brady Urological Institute each year with a diagnosis of prostate cancer are found to have been misdiagnosed. But even biopsies that seem straightforward deserve another look; Epstein and colleagues have shown this in studies looking at the reproducibility of Gleason scores in the general pathology community, comparing the biopsy's Gleason grade to the actual prostate specimen removed during surgery.

Another issue is that at most hospitals, pathologists don't have the luxury of specializing in prostate cancer. "Even in academic centers, maybe five percent would have somebody whom I would say is a urological pathologist." Epstein recommends that any man about to undergo treatment for prostate cancer get a second opinion from a pathologist. "It's just as important as getting a second opinion for surgery or radiation," he notes. In a recent six-month period, Epstein and colleagues looked at 3,000 consults, "almost 700 of which were sent at the request of either the patient or the urologist. Overall, we changed the diagnosis about 35 percent of the time-which to me was quite striking, because these were not cases where the pathologist even had a problem."

"The key to getting better diagnoses is education," he says; thus, he also teaches pathologists, urologists, oncologists, doctors-in-training, and even patient groups worldwide.

So far, more than 2,000 pathologists have taken his short course. Epstein is encouraged by this, and by a change he has noticed in the kinds of biopsies he's receiving. Now, the consult cases that he is getting are more difficult. And this, he believes, is a good sign.

The Next Frontier in Surgery: Preserving and Protecting the Nerves

"What happens with the FK506 solution is nerve regeneration -these nerves start to come back over time. They just start to reawaken, regrow, re-sprout, reconnect."

Say you're planning a grueling trip, an iron-man endurance trek through the tropics. Your goals are fairly simple: To make it out alive, of course-but more than that, to avoid illness, injury, and dehydration. Because your best hope for staying healthy is prevention, you do everything you can think of to prepare: Load up on vitamins, water, and electrolyte-boosters, pump iron to get your muscles in shape, and get yourself injected with a battery of disease-preventing shots. Now, as much as possible, you've evened the odds.

To the tiny, frail nerves involved in erection, radical prostatectomy is just such an endurance test. The first trick is simply surviving the surgery-which, for about seventy years, didn't happen, because the surgeons performing the radical prostatectomy routinely cut right through these microscopic nerves, never realizing they existed. Then came the "nerve-sparing" procedure developed by Patrick Walsh, and the knowledge that if even one of the two bundles of nerves-one on either side of the prostate-that are responsible for erection can be preserved during the surgery, is still possible for a man to recover potency. Now, thanks to prostate cancer screening, more men are being diagnosed with early-stage, curable cancer-which means it's increasingly common that both nerve bundles are preserved in surgery.

Burnett's pioneering work in rats with nerve injury and erectile dysfunction has had such promising results-stronger erections, recovered earlier-that he and colleagues are patenting the technology, and the drug industry is very interested in developing it.

And yet, for reasons that no one yet understands, even when the radical prostatectomy is flawless and the scalpel stays well away from the nerves, the recovery of potency-the ability to have and maintain an erection-is not always immediate. For some men, it can take up to two years for potency to return; for some men, potency doesn't return at all. The kicker is that nobody can predict which men will recover potency fairly quickly, and which men will have trouble. Indeed, two men the same age, with the same degree of cancer, can have exactly the same operation, performed with the same skill by the same surgeon-and the time to the return of erections can vary greatly.
"We know that despite the very best surgical techniques, nerves still will be injured," says urologist Arthur L. Burnett, M.D., "and this can occur apart from any direct nerve-cutting or trauma. It could happen by stretching the nerves, or by dissecting in the area where the blood supply to the nerves is diminished." Whatever the reason, "nerve function is depressed." The nerves take a beating. Which brings us to what Burnett and others are calling the next frontier of radical prostatectomy-a solution using special proteins called immunophilins, administered nerves take a beating.
Which brings us to what Burnett and others are calling the next frontier of radical prostatectomy-a solution using special proteins called immunophilins, administered during or shortly after surgery, that soothes, protects, and even invigorates these nerves. Burnett's pioneering work in rats with nerve injury and erectile dysfunction (similar to that found in men after radical prostatectomy) has had such promising results-stronger erections, recovered earlier-

that he and colleagues are patenting the technology, and the drug industry is very interested in developing it. The rats treated with immunophilins-the particular drug is known as FK506-had dramatically less nerve damage, and much greater recovery of function.

How does it work? The short answer is, nobody knows exactly. Immunophilins are proteins made by nerve tissue. When a nerve is injured, they respond like a local rescue squad, dispatched to the scene, that helps the injured nerve repair itself. "We're really talking about the ligands for the immunophilins," says Burnett. "Ligands like FK506 are very specific stimulants for immunophilins, and apparently enhance nerve recovery after injury by acting on specific receptors." Future generations of these nerve-recovering agents may work even better, and be even more targeted. Immunophilins are abundant in brain as well as nerve tissue, and these proteins now are being studied for their potential to help many people-organ transplant recipients, for example, or sufferers of trauma, stroke, or neurological ailments. And, as scientists learn more about what immunophilins do, they're also hoping to pinpoint exactly how these proteins work their magic. Do they somehow shield the nerves from inflammation and an immune reaction to injury? Is their action directly on the nerves, or on one of the processes that affect them? Going back to our iron-man image, are they the Gatorade, the vitamins, or the shots? And how do they protect, and also, as Burnett describes it, "vivify?"

"We use the word neurotrophic. They're nerve-protective and regenerative, and that's the key, really," Burnett says. "We think there's more to it than just preventing immune cells from doing damage.

Usually, once nerves are injured, they undergo degeneration. If you crush or cut a nerve at one focal point, over time, the tissue shrivels up. But what happens with the FK506 solution is nerve regeneration. These nerves start to come back over time. They just start to reawaken, regrow, resprout, reconnect."

Before an immunophilin solution can be used routinely on men who undergo radical prostatectomy-and Burnett expects clinical trials to begin in the near future- many logistics, such as dosage and side effects, need to be worked out. But Burnett envisions it this way: "One of the nice things here is that we can plan ahead. We know a man's going to have surgery, and that he's probably going to sustain at least some nerve injury, and we can start treating him in an immediately preventive way. We've got the pelvis open, and we can see the nerves. We put in the drug-maybe in a time-released wafer-and maybe also give the man some oral agents for about a week, and maybe that's all we need to do." And maybe the man will recover erections in three to six months after surgery, instead of longer. It sounds like science fiction now, but that's where we're headed."

What About Nerve Grafts to Restore Potency?

Surgeons at some hospitals are offering nerve grafts as a means of restoring a man's potential for erection. Although it's getting some publicity now, the idea of nerve grafts in radical prostatectomy patients is not that new. The first experimental work on nerve grafts to restore sexual function was reported from the Brady Urological Institute in 1989, by Patrick Walsh and colleagues. Walsh's studies in rats were encouraging, and in the early 1990s, collaborating with a neurosurgeon, he carried out a study of nerve grafts in patients who underwent wide excision of the neurovascular bundle. He followed the patients for more than five years, and found no difference in the recovery of sexual function in men who received a nerve graft and those who did not. At the same time, another trend was emerging: With the widespread use of PSA testing, more men were being diagnosed with early-stage, localized cancer, and as a result, fewer men needed to have a nerve bundle removed.

Recently, some urologists elsewhere have reported that in men who had both neurovascular bundles removed and received nerve grafts (using small nerves taken from the side of the foot), 30 percent had recovery of sexual function. However, a review of these surgeons' results found that 58 percent of the men who underwent nerve grafts had no evidence of capsular penetration on either side-which means they didn't need to have either nerve bundle removed in the first place.

What about nerve grafts in men who have one bundle removed? This same group of surgeons stated that when they removed one neurovascular bundle, only 25 percent of their patients were potent. These results, frankly, are not as good as they are at other hospitals. At Johns Hopkins, for example, without a nerve graft, 64 percent of our patients who have one neurovascular bundle removed are potent. Would a nerve graft improve these results even further? The argument is not terribly convincing. In a study done here several years ago, Walsh and colleagues analyzed the factors that influenced a man's recovery of potency after surgery. It turned out that men who had more extensive disease-capsular penetration, or cancer involving the seminal vesicles-were less likely to have recovery of sexual function, even if both neurovascular bundles were preserved.

Also, nerve grafts are not without their own risks. Potential side effects include the development of numbness or nerve damage on the side of the foot (at the site where the to-be-grafted nerve is removed), and the possibility of a delay in walking after surgery. Also, removing a nerve, closing that site, and then grafting the nerve in the pelvis prolongs the surgery, and may cause men to lose more blood. Before nerve grafts become an added component to many radical prostatectomies, they need to be studied in many men, in a randomized, controlled investigation. For now, a man's best chance to recover sexual function, if one neurovascular bundle must be removed, is to find a surgeon who is an expert at preserving the other bundle (the one on the opposite side).

Prostate Cancer is worse in Men Who Smoke

The good news: If a man stops smoking before he is diagnosed with prostate cancer, he may slow the development of the disease, or may have a less severe- and more likely curable- form of it.

To everything else you know about how smoking cigarettes can hurt you, add this: It contributes to prostate cancer, in ways scientists are just beginning to understand. At the very least, it makes cancer worse, and men who smoke are more likely to die from their prostate cancer than men who don't smoke. But it may turn out to be far more than this-it may be that cigarettes weaken a man's ability to fight off daily damage to his DNA, leaving him unprotected, and unable to prevent cancer from developing.

The more a man smokes, the higher his odds of being diagnosed with cancer that is more aggressive, and that has already spread beyond the prostate. The relationship is "dose-dependent"- which means that each cigarette raises the risk just a little bit, like the fabled straws on the camel's back.

We already knew that each puff of a cigarette injects nicotine and a toxic chemical cocktail into every cell of the body- so even if smoking didn't cause prostate cancer directly, it probably didn't help prevent it, either. Now, thanks to a new study of younger men with prostate cancer, done by Johns Hopkins scientists Patrick C. Walsh, M.D., William Roberts, M.D., and Elizabeth Platz, ScD., M.P.H., we know much more: The more a man smokes, the higher his odds of being diagnosed with cancer that is more aggressive, and that has already spread beyond the prostate. The relationship is "dose-dependent" -which means that each cigarette raises the risk just a little bit, like the fabled straws on the camel's back.
But the opposite is true, too, and this is exciting news: If a man stops smoking before he is diagnosed with prostate cancer, he may slow the development of the disease, or may have a less severe-and more likely curable-form of it.

Why did the scientists focus on younger men for this study? "One reason is that prostate cancer is so rare in these men," says Walsh. "Only 3 percent of men with prostate cancer are younger than 55, and we have been very interested in finding out why these men get prostate cancer. But we also wanted to see how cigarette smoking

affects men who have prostate cancer."

We know that men who have a family history of prostate cancer are more likely to develop the disease at a younger age. But until this study, no other risk factors stuck out as obvious red warning flags for cancer in younger men. "Previous studies had shown that although the risk for being diagnosed with prostate cancer appears to be the same in men who smoke cigarettes and men who do not, men who smoke are more likely to develop metastatic disease, and to die from it. We wanted to find out whether men who smoked were more likely to have more aggressive disease."

For consistency's sake, the men in this study all underwent radical prostatectomy performed by the same surgeon, Walsh. Between 1992 and 1999, Walsh performed the procedure on 1,544 consecutive men; about one-third of these-498 men-were under age 55 at the time of surgery. The researchers sent a detailed questionnaire to these younger men, asking them about a variety of aspects of their life, and then divided them into two groups: Men with aggressive cancers-high-grade disease, with a Gleason score of 7 or greater, and/or cancer that had spread beyond the prostate-and men who did not have aggressive disease.

In comparing these two groups, the scientists found one risk factor that stuck out like the proverbial sore thumb: Cigarette smoking. Not only were men who smoked cigarettes more likely to have more aggressive disease than nonsmokers, but men who smoked more cigarettes in the 10 years before surgery had an increased risk of high-grade disease, or cancer that quickly spread beyond the prostate. And the men who smoked the most (more than 40 pack-years; this could mean 2 packs a day for 20 years, one pack a day for 40 years, etc.) had greater than three times the risk of high-grade cancer, or more advanced disease. The risks were highest for men who still smoked, and lower for former smokers.

Now, the question is, why? Why are men who smoke at high risk of developing the worst kind of prostate cancer, and of dying from it because they're diagnosed when the disease has already advanced? One possibility might be that men who smoke are less concerned about their health generally, less likely to have regular check-ups, and thus less likely to have any health problem caught early. But the Brady scientists don't believe this is the case.

Instead, "we believe that cigarette smoking affects prostate cancer cells directly, resulting in aggressive tumor behavior," says Walsh. And the key to this is in understanding a concept called oxidative damage. Briefly: In oxidative damage, cells are injured by free radicals-volatile molecules that cause a buildup of toxic byproducts in cells. Normally, free radicals are helpful things-rushing like crime- fighters to a scene of unrest, fighting bacteria and other foreign invaders. And normally, the body makes substances that are able to control free radicals and limit their damage. The most important of these substances is an enzyme with the difficult name of glutathione-S -transferase p, called GS T-p, which provides toxic cleanup in cells. (Note: Brady scientist Bill Nelson, M.D., Ph.D., who also is part of the Kimmel Cancer Center, was the first to figure out GS T-p's role in prostate cancer. He showed that in all cancers, and even in PIN cells, which are not yet cancerous, but well on their way, GS T-p is knocked out-it is simply not there to prevent oxidative damage.) If cancer is a disastrous chain reaction-one genetic mistake, or mutation, that leads to another, and so on, then what happens to this enzyme is probably among the very earliest events.

Cigarettes are known to contain many carcinogenic (cancer-causing) chemicals. One of the worst is benzopyrene. "And here's the really interesting thing," says Walsh: "Benzopyrene is also detoxified by GS T-p. So when a man starts down the pathway to developing prostate cancer and loses GS T-p, not only is he more vulnerable to oxidative damage-he's also more susceptible to the benzopyrene carcinogens produced by cigarette smoking, and this is a double whammy. He's in twice as much trouble."

Could Blocking Inflammation Stop Cancer from Forming?

The Holy Grail, for scientists studying evolution, is the idea of a "missing link," a creature somewhere between man and ape, to explain how humans came to be. Scientists studying prostate cancer are also looking for missing links-more than one, certainly-to explain the complicated journey through which a normal cell evolves into a cancerous one. What lies between Point A and Point B?

One step before prostate cancer is PIN, prostatic intraepithelial neoplasia, or "funny-looking" cells that aren't normal, but aren't quite cancerous. One likely step before that, as pathologist Angelo De Marzo, M.D., Ph.D., discovered a couple of years ago, is PIA, proliferative inflammatory atrophy-cells that appear to be shut down, or atrophied, and are surrounded with inflammation. PIA cells, despite their appearance, are actually volatile, with wildly fluctuating levels of glutathione-S -transferase p, which protects against prostate cancer. Is early inflammation of the prostate an important step-even a missing link- to cancer? And is this inflammation a "done deal," or is it reversible?

Oncologists Michael A. Carducci, M.D., and Theodore DeWeese, M.D., of the Brady Urological Institute and the Kimmel Cancer Center, interested in the idea of reversing the steps leading to cancer through "chemoprevention," are hoping to find out.

They have started a clinical trial, funded by the National Cancer Institute, of anti-inflammatory drugs called COX (cyclooxygenase) inhibitors-a class of drugs that includes NSAIDS (nonsteroidal anti-inflammatory drugs) and even plain old aspirin. The particular drug in this trial, a selective COX-2 inhibitor (which has fewer side effects than aspirin and other drugs in this class) called celecoxib, was developed as a treatment for arthritis. "But it turns out," says Carducci, "that the COX-2 inhibitors also interact heavily with the pathways that are important for cancer progression. The idea, bolstered by research from Angelo De Marzo, Bill Nelson, Ted DeWeese, and others, is that early inflammatory injury-and whether or not the body's able to repair it-may be the next step to forming cancer. And new evidence suggests that when there's inflammation, growth factors are produced that promote blood vessel growth, and this also may increase the likelihood that cancer will develop. So it's becoming increasingly clear that maybe just blocking this pathway could delay disease. "

COX inhibitors are known to lower someone's risk of developing colon cancer; they also may help prevent esophageal cancer, and some recent studies suggest that men who regularly take aspirin and other COX inhibitors are less likely to develop prostate cancer.

"Our research (done in collaboration with Brady molecular geneticist Bill Isaacs) suggests that if these inhibitors do work, they don't seem to be working by directly affecting the cancer cells themselves," says De Marzo, "because the target protein of the inhibitor is not present in prostate cancer cells. It's only present in some of the inflammatory cells, the white blood cells, and in the PIA cells themselves. So it suggests that if these drugs really do inhibit prostate cancer-if these are little fires burning in the prostate-this might put them out." These early cells, De Marzo notes, are a different kettle of fish altogether from advanced cancer cells.

"We want to see whether this is something we should be giving very early in the disease, to someone who's at high risk, or if taking this could help prevent prostate cancer, like an aspirin a day for your heart."

"When we examine a prostate that's been removed for cancer-even in the ones where there is not a lot of cancer-we see several little, separate cancers," says De Marzo. "If we could decrease the rate of formation of these little cancers-prevent new lesions from forming-we might stop the big cancers."

In Carducci's new study, which is "double- blind"-meaning the doctors don't know who is getting the drug, and who is getting a placebo-men who are scheduled to undergo radical prostatectomy will be given celecoxib for about six weeks, from the time their cancer is diagnosed until the time of surgery. De Marzo, explaining the need to make the study "blind," quotes Brady scientist Don Coffey, Ph.D. "As Dr. Coffey says, you don't see with your eyes, you see with your mind, what you expect to see. If you can't possibly see it, that's the only way to make it really valid."

"The idea," says Carducci, "is to look a short-term exposure, and see what the effect of the drug is on inflammation, angiogenesis (growth of new blood vessels to feed the cancer), DNA damage, and cell proliferation." After the men undergo surgery, De Marzo will examine the removed prostate tissue.

If the COX inhibitor shows promise, the study will be expanded. "We want to see whether this is something we should be giving very early in the disease, to someone who's at high risk, or if taking this could help prevent prostate cancer, like an aspirin a day for your heart," says Carducci.
De Marzo is conducting longer-term laboratory studies to see whether giving COX inhibitors can prevent prostate cancer in rats. "It would be nice one day," he envisions, "to give this to younger men, in their 30s and 40s, and say, you don't have cancer yet, but you have a high risk. Start taking these fairly nontoxic drugs, and they may prevent your prostate cancer, and incidentally, prevent colon cancer. We're not there yet, but that's the real potential payoff. "

New Drugs for Prostate Cancer: Chemotherapy Transformed

New drugs, smarter drugs, safer drugs, just plain better drugs. The world of chemotherapy for prostate cancer is experiencing an earthquake, and Hopkins is at the epicenter, with a wealth of clinical trials, many of compounds and drug regimens developed at the Kimmel Cancer Center by Mario Eisenberger, M.D., Michael A. Carducci, M.D., Ted DeWeese, M.D., Roberto Pili, M.D., and Samuel Denmeade, M.D.-aimed at an unprecedented spectrum of men.

Gone are the days of last-ditch efforts- waiting to start conventional chemotherapy until everything else had failed, often when men were too sick to tolerate the drugs' harsh side effects, and the cancer had become too aggressive and widespread. Over the last several years, these oncologists, building on a solid basic science foundation of molecular insights into how prostate cancer works, have transformed the "traditional" chemotherapy mindset. They're attacking the disease earlier, and developing an elite cadre of selective drugs aimed at controlling - if not necessarily curing - prostate cancer, and prolonging life for years. "We're using smart' drugs," says Eisenberger. "They work at very specific molecular steps of cancer cell growth. Some of these drugs interfere with those steps; many of them will not cause a response in a traditional way-that is, the PSA may not always drop immediately; it will just remain stable." Because the drugs work differently, their effects must be measured differently, and the newest clinical trials are designed for long-term follow-up.

"We're taking advantage of the current patterns of prostate cancer patients coming to the clinic," Eisenberger continues. "We're seeing more men with early disease, and we believe these are the men who are most likely to benefit from our new compounds. Say a man has a probable lifetime survival, without further treatment, of eight to 10 years. If we could double this time, that man may never die of prostate cancer. So we may not be able to cure the disease, but we may be able to stabilize it-delay the progression in a big way. Because these smart compounds either don't have side effects, or have far fewer side effects than conventional chemotherapy and hormone therapy, they're perfect for men with early disease, and we'll have achieved a benefit that is comparable to a cure."

Clinical trials are available for patients at every stage of prostate cancer. The ever-evolving range of clinical trials is so big that we can only hit a few highlights here.

For men with locally confined cancer awaiting radical prostatectomy: Most men have a "limbo" period between the time their cancer is diagnosed by biopsy, and the time surgery is scheduled. Although it can seem like an interminable stretch of time, in the world of clinical trials, it's actually quite brief. Could taking a drug or dietary supplement for a few weeks make a difference in the prostate, on the cancer cells and their rate of growth, and on the growth of nearby blood vessels? Two trials aim to find out. One of them involves the anti-inflammatory drug celecoxib. The other will study the effects of the antioxidant vitamin E and a drug called Sulindac, alone and in combination. For men after radical prostatectomy, whose cancer is likely to recur:
These are men who have no evidence of disease, but a risk (based on Gleason score and pathological stage) that the prostate cancer may come back. In one multicenter study, led by Hopkins, men receive adjuvant chemotherapy with docetaxel (Taxotere) - a drug in the taxol family, used for women with breast cancer. Treatment, given weekly, starts at two months after surgery, three out of every four weeks for six months. In prostate cancer, some cells are driven by male hormones, and some are impervious to them. (This is why hormonal therapy is very effective at killing some prostate cancer cells, but it can't kill all of them.) "The idea is that the docetaxel would potentially kill both the hormone-independent and the hormone-dependent cells." There are a few mild, reversible side effects, including fatigue, a risk of a lowered blood count, a risk of tingling or numbness, some swelling in the legs and ankles, and modest hair loss. "This is an aggressive treatment," says Eisenberger. "We're trying to see whether we can prolong the time to PSA relapse," a point when the blood's PSA level starts to climb. "Our objective is to double that time."

Eisenberger and colleagues have just finished taking part in a massive, 40-country study of docetaxel in men with "hormone-refractory" cancer-men with metastatic disease after months or years of being on hormonal therapy. "This study is going to define a new standard for chemotherapy treatments for prostate cancer," says Eisenberger. "Over the last five years, docetaxel has shown reproducible evidence of cancer- fighting activity. In at least 50 percent of our patients, we get a remission." Building on this study, the Hopkins oncologists are launching new studies to test docetaxel in combination with other drugs, including exisulind, which is related to the antiinflammatory drug sulindac.

For men with a rising PSA after surgery or radiation: One trial for these men features the drug Gleevec. Although the trial is currently full, if early results are successful, "we will build on it," Eisenberger promises. "Gleevec is a smart drug. It blocks the signal for overproduction of a growth factor called PDGF. About 60 percent of the patients in our prior trials appear to overproduce PDGF." In laboratory studies, Eisenberger and colleagues have found that Gleevec appears to stunt the growth of prostate cancer. The drug is already approved by the Food and Drug Administration for use in a form of leukemia, and in a rare intestinal tumor. "With these two diseases, the majority of patients can enter a very remarkable, very impressive remission," Eisenberger says. In another trial, he is also studying Gleevec's effectiveness in men with a rising PSA who are taking hormonal therapy.

Another trial for men with a rising PSA, who have not begun hormonal therapy, features the drug atrasentan, which was developed at Hopkins several years ago by urologist Joel Nelson and Carducci. It blocks a chemical called endothelin, made by the endothelial cells that line blood vessels. Endothelin is linked to both the excruciating, debilitating pain that comes when cancer invades the bone, and the unique bone damage found in some men with prostate cancer, in which the bone becomes unnaturally thick and rock-hard. But it also may have something to do with the progression of prostate cancer-and blocking it, in addition to preventing or easing bone pain and damage, may also slow or halt progression of the disease.

In this trial, led by Carducci, men with a PSA of 0.6 to 5 are given either atrasentan or a placebo. "The goal is to see whether atrasentan delays the progression of PSA's rise," Eisenberger explains. Carducci's research,

conducted on men with more advanced cancer, suggests that it can. "In studies of men with metastatic bone disease, without symptoms, who had a rising PSA after hormonal therapy, we found that the men who were treated with atrasentan had a significant delay in the time to progression. What we also showed fairly dramatically, was that the drug seemed to target bone tissue and be protective against damage and pain, while the men in the placebo group continued to progress." That work has led to an expanded Phase III study, under way in the U.S. and Europe.

There are many more drugs being studied, including one that has no name yet- for men with advanced cancer. This drug, called MLN-2704, is genetically engineered to target cells that make PMSA (prostate-membrane specific antigen, an enzyme that's made on the surface of prostate cells). "A monoclonal antibody is hooked up to a chemotherapeutic agent that kills cells," explains Eisenberger, "so it's a smart bomb."

Assassinating Cancer Cells, or Just Stopping Them in their Tracks?

The challenge isn't killing cancer cells, says cancer biologist John Isaacs, Ph.D. "That's actually not as difficult as you would imagine." The real trick, he adds, is figuring out how to kill cancer cells selectively-so that normal cells, particularly those in the kidneys, liver, and brain, remain untouched.

Over the last decade or so, Isaacs has come up with some ingenious ways of doing this. One of them, under Phase I clinical development, is made from a parsley- like plant called thapsigargin. Long a staple of medicine in the Mediterranean, where it's used to ease the pain of rheumatism, thapsigargin is a natural irritant, easily absorbed through the skin. It weasels its way into a cell and starts causing trouble, targeting a protein that acts as a calcium pump. This pump-like someone baling water out of a leaky rowboat- keeps calcium from rising above a certain level inside a cell. Why is this important? Because calcium also happens to be a key that turns the engine of a genetic process called programmed cell death, or apoptosis. When too much calcium comes into a cell, it activates a cell's self-destruct button. "It causes the cell to pull the trigger on its own suicide pathway," says Isaacs.

Which is great-by activating this pathway, Isaacs can kill any cell within hours. "The thapsigargin analogues we have developed were able to cause the death of prostate cancer cells," he says. "But they had no specificity." So how to teach a drug to discriminate? How to focus the thapsigargin so it leaves "innocent bystander" cells-normal body cells minding their own business, causing no harm-alone, but assassinates the deadly prostate cancer cells that have defied hormone therapy and are headed toward metastasis?

Two words: Molecular engineering. Isaacs and colleagues have taken the thapsigargin molecules and reconfigured them, "made them essentially a smart bomb, so they are unable to get inside of cells, so they can't activate this death pathway. We changed it from being an active drug, when it gets inside a cell, to an inactive drug that's kept outside the cell." They did this by hooking the thapsigargin to a molecular peptide, a particular string of amino acids that targets PSA. "PSA is an enzyme that works like a pair of molecular scissors," explains Isaacs, "It can hydrolyze, or clip, certain linkages between molecules." If the prodrug were a letter bomb, the PSA would be the knife that slices it open, and boom-out comes the poison. Interestingly, although the bomb is activated immediately outside the PSA-making cell, the prodrug detonates when it moves inside- like the "bunker-busting" daisy-cutter bombs recently used against terrorists. "The molecular scissors clip the prodrug, liberate the toxin, and the thapsigargin molecule is so chemically sticky that it goes right into the cell, hits the target and kills it."

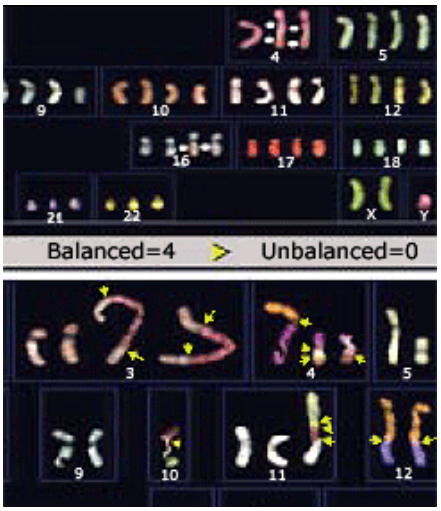
If the prodrug were a letter bomb, the PSA would be the knife that slices it open, and boom-out comes the poison.

Men with prostate cancer have PSA floating around in their bloodstream; some men with advanced cancer have extremely high PSA levels, of several thousand nanograms per milliliter, instead of the usual one- or even two-digit numbers. But the prodrug would ignore the PSA in the bloodstream, Isaacs explains, "because it is not chemically active. The PSA is bound to other proteins." In other words, the scissors are sheathed, and unable to cut anything -and the bloodstream becomes a safe delivery system for the prodrug. "The only enzymatically active PSA is the one right outside the cells, in either the primary or metastatic sites. Prostate cancers have very leaky blood vessels; the compound leaks into the fluid that surrounds these cancer cells. And the nice part here is that its inherent chemistry makes it want to get into the cell-so we don't need to help it get there with any specific energy-dependent protein or transport machinery." The prodrug, which Isaacs has developed in collaboration with the National Cancer Institute, is undergoing animal toxicity studies required for clinical testing.

Stopping the Cancer's Blood Supply

But as promising as thapsigargin is, Isaacs is hedging his bets. For years, he has also been working on a different strategy- starving prostate cancer by shutting off its blood supply, or its ability to create new blood vessels to feed itself. Drugs that do this are called angiogenesis inhibitors, and Isaacs has been working with a particular one called Linomide; over the years, he's developed "sons of Linomide" that are 100- to 500-fold more potent, with even fewer side effects, in collaboration with a company called Active Biotech, Inc. Preclinical studies of the drug's safety are under way, and Isaacs anticipates that clinical trials will begin in a year.

Chaos in the Chromosomes, and New Keys to Advanced Cancer



The more vicious the prostate cancer, the crazier this chromosomal mix-up becomes.

Of all the bizarre things that can happen in the genetic structure of men with prostate cancer, this may be one of the most bizarre-unstable chromosomes, which break apart and patch themselves together with completely different chromosomes. Groundbreaking genetic work at the Brady Urological Institute, building on decades of pioneering research by a handful of scientists including Don Coffey, William Isaacs, William Nelson, Alan Partin and others, has shown that the more vicious the prostate cancer, the crazier this chromosomal mix-up becomes.

Coffey, whose legendary work on the architecture of cancer cells laid the foundation for this most recent discovery, thinks he knows what makes this happen, and he even has two key culprits-and maybe, two new pathways for blocking the very worst kinds of prostate cancer.

In this case, the architecture of cancer cells is a bit different from the structural landmarks pathologists use to determine the Gleason grade and stage of cancer. If we were talking about buildings-say, a medieval cathedral-what the pathologists make note of would be things like apses, arches, naves, and buttresses. What Coffey and colleagues are investigating would be the stones and mortar.

Like a Funhouse Mirror

To backtrack two and a half decades: Coffey helped create a new subspecialty of cell biology when he discovered how DNA- the body's genetic material-is organized within a cell's nucleus. Scientists had long known that the nucleus of a cancer cell is odd-looking; it's distorted, like someone's reflection in a funhouse mirror. When this happens, the chromosomes often lose their normal shapes, as well. Coffey discovered that there is a scaffolding inside each nucleus, a skeleton that determines its shape. He called this the nuclear matrix. He found that the DNA was attached to this matrix in countless loops (actually, about 50,000 little loops), each locked at its base to the scaffolding. Coffey and colleagues also showed that those loops are a genetic hot spot, where DNA replicates itself. They named the loops "replicons," and found that DNA reproduces itself in little pieces-the loops-instead of as one very long string of information.

Several years ago, William Nelson discovered a key enzyme, called topoisomerase II (topo II for short) at the base of those loops, and Alan Partin found that the composition of the nuclear matrix was different in normal and in cancer cells. Then Coffey and colleagues noticed that in cancer cells, the loops were unwinding -because topo II was unwinding them. Another strange thing: The composition of the proteins in the nucleus was changing-and another scientific subspecialty, called proteomics, the study of proteins expressed by various genes, was born.

Coffey likens what's happening here to the working of an audio cassette player. "The tape is the DNA, the cassette is the nucleus, and the cell is the whole tape recorder," he explains. "The messenger RNA is the electricity coming off the tape, and the protein is the sound the tape recorder is making. The transient material is the electricity, and the product is sound. What we want to know is the sound that's coming off the tape recorder-what protein is the cell making? That pattern is proteomics." There's also plenty of static. "About 95 percent of the DNA in a chromosome never makes sound, or protein. We used to call it junk DNA,' but now we find it's this silent, repetitive DNA that makes up the distance between letters, words, and paragraphs." (Some of these spaces are now called introns.)

A Bad Patchwork Quilt

At the ends of the chromosomes are little pieces of repetitive DNA-small caps, like the aglet at the tip of a shoelace-called telomeres. "If you look at your shoe lace, as long as the aglet's there, it's pretty stable," says Coffey. "But when the aglet wears away, the lace starts fraying, and the chromosome starts getting in trouble. When that happens, the cell is unhappy; the DNA is not doing well."

Losing the telomeres is one cause of the spooky chromosomal rearrangement. Another culprit is a protein at the base of those loops on the matrix, with the alphabet- soup name of HMGI(Y). "It's like a railroad switch that can make the train go down a different track," says Coffey. "The train is attached to the matrix, the railroad track, but this little protein can flip the switch, and get the trains mixed up." HMGI(Y)'s close buddy, genetically speaking, is topo II, and they work together. HMGI(Y) puts the railroad tracks in a dangerous situation, and topo II is the miscreant hammering the boards together.

One suspicious fact about HMGI(Y) is that it's not found in normal adult cells. It's usually a part of embryonic cells, but as we mature, it disappears. It reappears in cancer. "So cancer is a lot like developmental tissue," notes Coffey, "and it picks up a lot of embryonic properties-like a stem cell for the cancer." Coincidentally, telomerase (which makes telomeres) is also in stem cells, and in cancer cells, too.

When HMGI(Y) is added to DNA, it causes it to form four-way junctions (think of any awful exit of I-95)-and makes "a perfect place for DNA rearrangement to occur," says Coffey. "HMGI(Y) is in the right position at the base of those loops, it can form a four-way junction, and we know that topo II is sitting there, flipping the DNA open and closed. It's the ideal place to mess it up, especially if the matrix isn't normal. So rather than two train tracks going left and right, they now cross over, and the cars begin to pile up."

Coffey and colleagues have a way of painting the chromosomes to make each appear as a different color under a microscope. "Imagine yourself standing in front of a white wall, and you pick up a brush and paint the first

chromosome as a red stripe, all the way down the wall," explains Coffey. "The longest by size is chromosome 1; the smallest is number 22. Next, you paint the 2 chromosome blue, and make it a little shorter. By the time you get to the end of the wall, you have a picket fence that goes down, and gets shorter and shorter, 22 different colors." When the scientists painted the chromosomes of prostate cancer cells in this way, they were shocked at the result. "Holy mackerel! There's a piece of red on top of a piece of blue, with a piece of green at the bottom. Or a piece of yellow, a piece of blue, and a piece of green. Then two that look okay, but the fence has too many pickets-instead of 22, it's got 37. This thing is messed up."

The scientists looked for this crazy patchwork effect in three well-known strains of prostate cancer. Like the porridge that Goldilocks taste-tested, two are extreme- one notoriously vicious, (Coffey calls it a "mean sucker that grows like crazy"), one pretty mild, and one right in the middle. In rat tumors, the worse the cancer, the more metastatic and aggressive it is-the more HMGI(Y) it has. In humans, the higher the Gleason grade, the more HMGI(Y) there is. In Coffey's recent experiments to study chromosomal rearrangement, the most benign cell line had some rearrangement, but-this is important-it was balanced rearrangement. "If you took a deck of cards, and put the top half of the two red queens on the bottom half of the two black jacks, you would see two other new cards made, with the bottom half of the red queens and the top half of the black jacks." This is called a "reciprocal translocation," and it is balanced.

Coffey thinks he knows what makes this happen, and he even has two key culprits-and maybe, two new pathways for blocking the very worst kinds of prostate cancer.

But the very worst cell line resembled a train wreck-"31 unbalanced chromosomes. It looked like a trash dump, all parts combined in unbalanced translocations, colors mixed up in every way you could imagine."

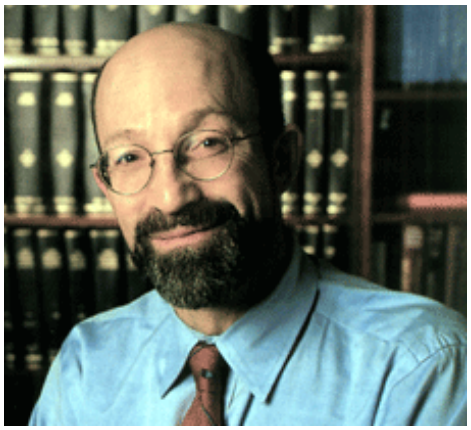
When the Brady scientists inserted a piece of HMGI(Y) into the tamest cancer, the one with the balanced rearrangements, it became unhinged-and made the unbalanced matches found in the worst form of cancer. The extent of the damage matched the level of HMGI(Y).

Now, what to make of all this? "We can cure some cancers-such as leukemias, lymphomas-easily," says Coffey. "They are the kinds of cancers that have balanced rearrangements of chromosomes." One such cancer, Burkett's lymphoma, has an "8-14 translocation", an even mix-and-match of chromosomes 8 and 14. This form of cancer affects children in Africa, and it's horrible: "The whole face is distorted, like the most severe mumps ever," says Coffey. "It looks like the person has elephantitis of the face; the lymph glands are growing like a house afire. But if you treat this person with cytoxan, he goes home. He's cured!" Another example is advanced testicular cancer, which struck American cyclist Lance Armstrong. "Some of these men have so many metastases in their lungs, it looks like they're drowning in tumor; they're spitting up blood, they can't get enough oxygen. Lance Armstrong had three metastases in his brain the size of golf balls. But he was treated, his cancer went away, and he wins the Tour de France. I want to know why that's so."

Coffey's latest research has found that the cancers most difficult to cure are the kinds-like prostate cancer-prone to unbalanced rearrangements. "We know that the reason it's so hard to cure advanced prostate cancer is because of its genetic instability. It spins off such a variety of cells that it's almost impossible to beat it." The latest piece of the puzzle, the subject of some of the cutting-edge research at the Brady right now, is the telomeres- the tips of the shoelaces, or chromosomes. Knocking out telomerase-getting rid of the telomeres-causes unbalanced chromosomal rearrangement, too. "So we've got two ways to cause unbalanced rearrangement-HMGI(Y), and losing telomerase. Both of these can happen in a man with prostate cancer. Can we make a target out of this? Maybe we can go after HMGI(Y) and telomerase, and somehow stop this mismatched rearrangement. Currently, we're trying to figure out the best way to take this to the patient."

An Epidemiologist Comes to the Brady

Like fingerprints, cases of prostate cancer differ from man to man, depending on many particulars - his age, for instance, or PSA, or even the ratio of cancer cells that are nourished by male hormones, compared to those that aren't. It's a terribly individual disease. So why is Bruce Trock, Ph.D., so interested in looking at the bigger picture?



Bruce Trock: "How do variations in treatment affect a man's quality of life? How do the symptoms that he experiences afterward affect it?"

Because he's an epidemiologist. Actually, he's the first of a first-the new director of the Brady Urological Institute's brand new division of Epidemiology, the first of its kind in any urology department in the country; the division was launched by a gift from philanthropists Helen and Peter Bing. And epidemiology, Trock explains, is the connection between basic science and the clinic. "A scientist like Bill Nelson or John Isaacs might be looking at something in the lab-a new marker for detection, or a preventive agent, or a risk factor-or examining 30 specimens of prostate tumor and measuring something. We examine it in 300, or 500, or 1,000 people, so we can find out whether it works differently in older men than younger men, in black men versus white men, in men who have a family history versus those who don't. All of these aspects are important in how the disease actually manifests itself in the population."

Men who die from prostate cancer have more cadmium in their prostate than other men. And of all the body's organs, guess which one has the highest concentration of cadmium? The prostate. Apparently, once cadmium enters the body, it stays put.

So many variables, and so many different groups of men-who make up the word epidemiologists love to use, "populations." "That's part of the challenge," says Trock. "It's like a puzzle, a detective story. How do the pieces fit together?"

Trock, who came to Hopkins from Georgetown University, "brings unique strengths that enhance our translational research efforts," says Urologist-in-Chief Patrick C. Walsh, M.D. Trock's distinguished research-in cancer of the breast as well as the prostate-has made important contributions to the understanding of diet and breast cancer. Trock also made the first comprehensive assessment of a particular gene, called the multi-drug resistance gene, to show that it is commonly expressed in breast cancer, and is a strong predictor of resistance to chemotherapy. "It's unusual to find someone with strong credentials in epidemiology and biostatistics who can successfully bridge his work with clinical and basic science," says Alan Partin, M.D., Ph.D., Bernard Schwartz Distinguished Professor of Urologic Oncology, who recruited Trock to Hopkins, and who will be working with him on many projects.

Trock's research at Hopkins is focused on four major areas:
Causes. What sparks prostate cancer? How do environmental or dietary exposures cross-pollinate with the body's basic gene makeup? "We're looking at oxidative damage, at diet, at what normal processes of the body, normal function of the prostate, and normal aging of the prostate make it susceptible to cancer," says Trock.

He's also zeroing in on exposure to cadmium. "Some studies have shown that men in certain occupations, with higher levels of exposure to cadmium, have a higher risk of prostate cancer." Laboratory rats that are given cadmium are known to develop prostate cancer, and cadmium has been shown to mimic some effects of male

and female hormones. "Cadmium interacts with the hormone receptors in a way that's similar to estrogen or testosterone," says Trock. "So it's possible that it can stimulate growth of the prostate in an abnormal way." Cadmium also may push beneficial zinc out of the prostate. Autopsy studies have shown that men who die from prostate cancer have more cadmium in their prostate than other men. And of all the body's organs, guess which one has the highest concentration of cadmium? The prostate. Apparently, once cadmium enters the body, it stays put. "It's very metabolically inert," Trock explains. "You can get cadmium in your body, and it will stay there for 20 years."

Baltimore is a natural for studying cadmium exposure-it's an issue for men who build and repair ships, welders, men who work in canning factories, men who are exposed to paints, and a risk of soldering, galvanizing, and electroplating. "We're mapping the city for areas that potentially had higher cadmium exposure. Then we'll take the highest-exposure zip codes, and whenever a man comes here to be biopsied for prostate cancer, if he's from one of those zip codes, we'll take a sample of his biopsy. With the men who turn out to have cancer, we'll see whether they have more cadmium in their prostates than the men who didn't."

Clinical biomarkers. Trock is interested in tapping (literally) a largely unexplored area in prostate cancer research-prostatic fluid. In the past, it was difficult to obtain prostatic fluid for examination. However, today it is easily collected from surgical specimens.

One of the prostate's main jobs is to contribute a bit of fluid to the mixture that makes up semen. "Prior to ejaculation, the sperm are kept in an inactive form," explains Trock, "they don't have much movement. But when they mix with the prostatic fluid, that seems to activate them and make them move around a lot, so they are ready to seek out the egg." There's an abundance of reactive oxygen in semen and prostatic fluid, and "a lot of research in fertility that's looking at the effects of oxidative stress on the viability of sperm. So we know that oxidative stress is being generated in that process. Is any of that affecting the prostate? Does this over time lead to some sort of irritation or inflammation? Are certain groups of men more susceptible to this, perhaps men with lower levels of a protective enzyme, or lower levels of dietary antioxidants?" Trock also believes that studying the prostatic fluid can shed light on normal aging of the prostate.

Chemoprevention. Does eating spaghetti several times a week somehow help prevent prostate cancer? Does broccoli make your body more cancer-proof? Trock is ready and able to investigate, taking advantage of the many compounds being identified and studied in Brady laboratories. "There's the potential to do relatively quick studies with these," says Trock. One easy, short-term period for testing a chemo-preventive agent is the time between a man's diagnosis with prostate cancer and radical prostatectomy. The removed prostate is then compared to the "before" snapshots of the needle biopsy, to see if anything's changed, "if something is altered in a way that suggests there would be a lower risk if the man didn't already have the disease," Trock explains. "Are we decreasing the growth rate of the cells, decreasing PSA, enhancing the level of normal cell death? All of these can be measured with what we call surrogate endpoint biomarkers.' They tell us if we're altering the biology in a beneficial way, and provide insight into what we really want to know, which is, Does it change the risk?"

Quality of life. Ideally, a man's cancer is diagnosed early, he's treated at a "high-volume" center-a place like Hopkins, where radical prostatectomy is done every day- by an experienced surgeon. He has minimal side effects, then it's over. He gets his life back, and the whole thing, from biopsy to recovery, is just a "blip" on the radar screen of his life. But for many men, this doesn't happen. "How do variations in treatment affect a man's quality of life? How do the symptoms that he experiences afterward affect it?" It's hard enough comparing surgery patients to surgery patients, harder still comparing these men to men who have undergone radiation therapy. "There are many papers that compare results in men who've had radiation to men who've had prostatectomy," says Trock, "but in fact, those are not comparable. There are many differences that come into play-particularly, different ways to compute survival rates in one group compared to another. So how can you get a valid comparison, short of doing a trial where you randomly assign some men to radiation, and some to prostatectomy?" Lars Ellison, a Robert Wood Johnson research scientist, will collaborate with Trock on a study of men who receive treatment at nationally recognized "centers of excellence"

for radiation or radical prostatectomy.

In the most ambitious project so far, Trock is one of several scientists planning a super-sized study, involving possibly 100,000 Baltimore-area men and women. One major focus would be prostate cancer risk, side effects, progression, and prognosis. "There are a number of these very large-scale cohort studies, but none with a heavy urban component. We're going to be looking at a population that's representative of Baltimore-a high representation of African American men, men in other ethnic groups who have different levels of prostate cancer risk. This will encompass Brady, the Kimmel Cancer Center, the School of Hygiene and Public Health, and it will be going on for 10 to 20 years."

Prevailing in our War on Prostate Cancer

Prostate cancer is a formidable enemy. From the very beginning, it is "multifocal" -that is, it springs up in many places inside the prostate. A man with localized prostate cancer has an average of seven separate tumors growing all at once. Worse, that growth is silent. Symptoms for prostate cancer don't appear until the disease has advanced beyond our ability to cure it. And unless it is caught early, prostate cancer is difficult to cure.

It is also way too common. This year, an estimated 180,000 American men will be diagnosed with prostate cancer, and 30,200 will die from it. We find those statistics unacceptable. Every scientist and physician here at the Brady Urological Institute is dedicated to eliminating the scourge of prostate cancer. We have declared war against it.

How do you fight a war? We are waging our investigative attack on prostate cancer from many fronts: Preventing cancer from developing, improving early diagnosis, reducing side effects of treatment, and discovering new ways to manage advanced disease. Our full-scale assault hinges on strong collaboration among urologists, basic scientists, medical and radiation oncologists from the Kimmel Cancer Center, and pathologists-our version of the Army, Navy, Air Force and Marines-and it has been unparalleled in its success.

Maybe the language of war sounds dramatic -until you talk to a patient with fear in his eyes, newly diagnosed with high-grade cancer, who holds his wife's hand for strength and comfort as they both think about the future. Or, as a doctor, you close your own eyes at the memory of how it often used to be, not so long ago-when you watched helplessly as one of your patients slipped away despite your best efforts, in agonizing pain because his disease was caught too late to be cured.
The great news at the Brady Urological Institute-it's in this issue, it's in the halls, laboratories, clinics, operating rooms and at the patient's bedside-is that, in the language of war, we are winning skirmishes and battles, pushing back the enemy's front lines, and changing the course of this disease.

But wars are expensive. In the past, we have relied upon grants from the National Institutes of Health, our main source of funding, and the revenue generated by professional fees. Our urologists at the Brady Urological Institute work for a salary, and for years, we have reinvested all of the extra money from professional fees into our mission of research. However, this fine luxury-this auxiliary "cushion" of research money from professional fees-has disappeared. Over the last decade, reimbursements have dwindled due to sharp cutbacks in Medicare reimbursements, and the increasing pervasiveness of HMOs. Fortunately, when our patients learned about this need, they responded with generous support and helped us build an endowment to provide the research income that has kept our mission going. Because of the philanthropy of our patients, we have been able to make progress

faster than we ever could have using our resources alone. Thank you.
Urologist-in-chief Patrick C. Walsh, M.D., has always believed that the best way to tackle the multifaceted problem of prostate cancer is to hit it hard from every possible angle, by achieving a critical mass of brilliant minds-scientists and clinicians. It is through Dr. Walsh's vision that income from the Brady's endowment has supported scientists throughout Johns Hopkins who are working on prostate cancer.

Over the next several years, Dr. Walsh-after serving 30 years as chairman of the Brady Urological Institute-will relinquish his administrative duties to devote more time to seeing patients, operating, and teaching. In formal recognition of the winning philosophy that he has pursued for so many years-and to make certain that Dr. Walsh's vision continues -Johns Hopkins is developing the Patrick C. Walsh Prostate Cancer Research Fund. The change in leadership will not diminish the vigor of our war on prostate cancer. Indeed, we hope to raise $20 million for this fund by the time Dr. Walsh steps down as chairman. We invite all of Dr. Walsh's patients to participate in this initiative to honor him, and to further Hopkins' tremendous effort to defeat prostate cancer.

This research fund will support the work of scientists from all disciplines at Johns Hopkins who want to join our fight against prostate cancer. Although the fund will be held in the Brady Urological Institute, it will be overseen and administered by a scientific advisory board, composed of Hopkins medical and radiation oncologists, basic scientists, pathologists, and urologists. Each year, the fund will send out requests for research applications to scientists throughout Johns Hopkins. This fund will enable us to continue attracting the best scientific minds from basic sciences, and from other departments we have not yet tapped-scientists who may see an opportunity to apply some of their most recent findings to this field. In this way, we'll make the cure that we are all working so hard to attain happen even faster.