

# DISCOVERY



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**JOHNS HOPKINS**  
M E D I C I N E

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# From the Director: Preserving Lives, Improving Lives, Teaching Others

## Keep it Simple

We have one mission: To save lives from prostate cancer through diligence and discovery- in the laboratory, in the operating room, and in the clinic. Everything we do is directly inspired by our patients, and the dedication of our physicians and scientists to helping them.

Every day, in our fight against prostate cancer, our surgeons and scientists come to work armed with hope and sustained by these goals: Pushing back the edges of what is known in our field, saving lives and improving quality of life.

We accomplish our mission with the help of three simple beliefs:

**First:** You only make important discoveries by working on important problems. How can we reduce deaths from prostate cancer? By focusing our efforts, on four main avenues of research:

- Preventing cancer from developing
- Improving early diagnosis
- Reducing side effects of treatment, and
- Discovering new ways to manage advanced disease.

**Second,** we live by the motto: “Do one thing well before doing the next thing.” In the operating room, this means that each operation is a piece of art, a time of total concentration so that the patient can have his cancer cured with the fewest side effects. In the laboratory, this means devoting hours, days, long nights, and even years chiseling away at a single problem until we know for sure whether the answer is yes or no.

**Finally,** we believe in the words of great architect Mies van der Rohe, “Less is more.” We don’t have to do everything. Far better, instead, to identify the most important problems, concentrate on each one and do it well, than to do everything less well.

This update summarizes some of our latest findings, many of which would not have been possible without the participation and dedication of our patients. We are grateful to have you as our partners in discovery.

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## What Happens if PSA Comes Back After Surgery?

### Preserving Lives, Improving Lives, Teaching Others

The return of PSA is a possibility that strikes terror in the heart of every radical prostatectomy patient; in fact, for many men, the dreaded follow-up PSA tests after surgery are almost worse than having the operation itself. What will you do if your PSA is no longer undetectable? The good news is, you may not need to do anything for years.

The return of PSA is a possibility that strikes terror in the heart of every radical prostatectomy patient; in fact, for many men, the dreaded follow-up PSA tests after surgery are almost worse than having the operation itself. What will you do if your PSA is no longer undetectable? The good news is, you may not need to do anything for years.

Does the man have a local recurrence of cancer that would respond to radiation, or does this represent micrometastases to lymph nodes and bone? Until now, there has been no way to tell.

In a landmark paper -- the largest, most complete study of the return of PSA after radical prostatectomy -- Hopkins doctors have developed guidelines to help patients and doctors know what to do if PSA comes back. Their remarkable effort -- an elegantly simple chart that accurately predicts a man's risk of developing metastatic cancer -- is the post-operative equivalent of the "Partin tables," developed by urologist Alan W. Partin, M.D., and urologist-in-chief Patrick C. Walsh, M.D. Like those now-indispensable tables, this chart has the potential to revolutionize the way doctors and patients make decisions about what to do next.

"PSA is very sensitive in detecting any recurrence of cancer. That's because only prostate cells make PSA -- so if it goes up after a radical prostatectomy, it means prostate cells are still present somewhere. For all intents and purposes, it means that a few cells escaped the prostate before it was removed, and now have grown to the point where they're producing enough PSA to be detected," explains Walsh.

"Fortunately, for most men with organ-confined cancer, this never happens. However, for men who had more advanced disease at the time of surgery, the return of PSA is extremely frightening." Walsh originated this study to fill what he describes as a "large knowledge gap" for patients and doctors.

- "The first thing many patients want to know is, how long are they going to live?"
- And the first thing many doctors want to know is, when should they begin treatment, and how should they treat these patients?
- Does the man have a local recurrence of cancer that would respond to radiation, or does this represent micrometastases to lymph nodes and bone?"

Until now, there has been no way to tell. The study, published in the *Journal of the American Medical Association*, is based on 10,000 patient-years of follow-up data. Between 1982 and 1997, nearly 2,000 men underwent a radical prostatectomy at Johns Hopkins. Of these, 315 men developed an elevated PSA (defined as being higher than 0.2 nanograms/milliliter). Eleven of these men opted for early hormone therapy, and were not included in the study. The remaining 304 men were followed carefully.

On average, it took eight years from the time a man's PSA first went up until he developed metastatic disease -- which suggests that there is no need to panic at the first sign of a rise in PSA.

"We set out to ask a few questions, says Walsh: "Could we predict how long it would take for patients who had metastases to show them on a bone scan, and then once that happened, how long would they live? The news is actually quite good: Most patients do very well for a long period of time". On average, it took eight years from the time a man's PSA first went up until he developed metastatic disease -- which suggests, Walsh says, that "there is no need to panic" at the first sign of a rise in PSA. Even after developing metastatic cancer (detected by bone scans and other imaging techniques), men still lived an average of five years -- and if the metastases showed up more than seven years after surgery, men had a seventy percent chance of being alive seven years later.

"When men see their PSA levels rise again, they think that means the cancer is back and they need to get treated right away," says oncologist Mario Eisenberger, M.D., a co-author of the study. "But men often live for years without having the cancer spread. This information will better equip doctors and their patients to decide what treatment -- if any -- is most appropriate."

This interval between the reappearance of PSA and the first sign of advanced disease can be predicted, the Hopkins researchers found, using three pieces of information:

- The Gleason score of the pathologic specimen (the removed prostate, evaluated by a pathologist after surgery). Is it Gleason 7 or lower, or Gleason 8 or greater.
- The time it takes for PSA to come back. Is it less than two years after surgery, or greater? And,
- How rapidly is the PSA level doubling? Is it greater or less than 10 months?

Using these criteria, men and their doctors can pinpoint the likelihood of developing metastatic disease. For example: If a man has Gleason 7 disease, has his first PSA recurrence more than two years after surgery, and has a PSA doubling time longer than 10 months, his likelihood of being free of metastasis at seven years is 82 percent. Conversely, if a man has Gleason 7 disease, but his PSA goes up within two years of surgery, and the time it takes PSA to double is less than 10 months, his likelihood of being metastasis-free at seven years is 15 percent. “So the first thing these tables can do is reassure the many patients who are going to have a long-term, symptom-free, metastasis-free interval, that close observation is all that’s really necessary,” says Walsh. On the other hand, says urologist Alan W. Partin, M.D., Ph.D., co-author of the study: “If their chances of progressing rapidly are high, they may wish to start hormonal therapy earlier or get involved in an experimental trial” of more aggressive treatment. “These tables are going to help men who are at low risk and help men at high risk make a more educated decision. We hope it will also decrease the anxiety for some of them.” The tables will also provide invaluable baseline data for future drug research, adds Partin. “Until now, it’s been difficult to know if a drug was helping someone, because you couldn’t be sure what the disease would have done on its own. Now, researchers can compare their treatment groups with our study group and tell if their treatment is improving survival.”

<b>WHAT THE NUMBERS MEAN</b>	
<b>If you have a Gleason score of 5-7</b>	
Your PSA increased more than two years after surgery AND your PSA doubling time was greater than 10 months: Your chance of <i>not developing metastasis</i> (having a bone positive scan) in:	
Three years:	95 percent
Five years:	86 percent
Seven years:	82 percent
OR your PSA doubling time was less than 10 months: Your chance of <i>not developing metastasis</i> in:	
Three years:	82 percent
Five years:	69 percent
Seven years:	60 percent
OR your time to first PSA recurrence was less than two years: AND your PSA doubling time was greater than 10 months:	
Your chance of <i>not developing metastasis</i> in:	
Three years:	79 percent
Five years:	76 percent
Seven years:	59 percent
OR your PSA doubling time was less than 10 months:	
Your chance of <i>not developing metastasis</i> in:	
Three years:	81 percent
Five years:	35 percent
Seven years:	15 percent
<b>If you have a Gleason score of 8-10</b>	
AND your time to first PSA recurrence was greater than two years:	
Your chance of <i>not developing metastasis</i> in:	
Three years:	77 percent
Five years:	60 percent
Seven years:	47 percent
OR your time to first PSA recurrence was less than two years:	
Your chance of <i>not developing metastasis</i> in:	
Three years:	53 percent
Five years:	31 percent
Seven years:	21 percent

## PSA Anxiety: The Downside of Ultra-Sensitive Tests

You've had the radical prostatectomy, but deep down, you're terrified that it didn't work. So here you are, a grown man, living in fear of a simple blood test, scared to death that the PSA- an enzyme made only by prostate cells, but all of your prostate cells are supposed to be gone -- will come back. Six months ago, the number was 0.01. This time, it was 0.02.

You have PSA anxiety. You are not alone.

This is the bane of the hypersensitive PSA test: Sometimes, there is such a thing as too much information. Daniel W Chan, Ph.D., is professor of pathology, oncology, urology and radiology, and Director of Clinical Chemistry at Hopkins. He is also an internationally recognized authority on biochemical tumor markers such as PSA, and on immunoassay tests such as the PSA test. This is some of what he has to say on the subject of PSA anxiety:

The only thing that really matters, he says, is: "At what PSA levels does the concentration indicate that the patient has had a recurrence of cancer?" For Chan, and the scientists and physicians at Hopkins, the number to take seriously is 0.2 nanograms/milliliter. "That's something we call biochemical recurrence. But even this doesn't mean that a man has symptoms yet. People need to understand that it might take months or even years before there is any clinical physical evidence."

On a technical level, in the laboratory, Chan trusts the sensitivity of assays down to 0. 1, or slightly less than that. "You cannot reliably detect such a small amount as 0.01," he explains. "From day to day, the results could vary -- it could be 0.03, or maybe even 0.05" -- and these "analytical" variations may not mean a thing. "It's important that we don't assume anything or take action on a very low level of PSA. In routine practice, because of these analytical variations from day to day, if it's less than 0. 1, we assume it's the same as nondetectable, or zero."

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## Continence and Potency After Radical Prostatectomy

### Hopkins Study Finds Best Rates Ever

When radical prostatectomies are performed by experienced surgeons, "the results can be excellent," says Patrick Walsh. He recently has worked to make a good operation even better.

As surgical procedures go, radical prostatectomy is one of the most delicate, intricate, and flat-out difficult to perform correctly. Proof of this can be found in the widely varying rates of success of surgeons at hospitals throughout the world -- not simply in controlling cancer, but in preserving a man's quality of life in two major areas: Urinary continence and sexual potency.

Postoperative PSA levels give doctors an excellent grasp of a patient's cancer status; they provide a definitive means of knowing whether all of the tumor has been removed. But there aren't such objective ways to tell how a man's doing in the other important areas: Often, it's up to the patient to report his success in continence and potency -- and very often, these are the last things men want to discuss, even with their doctors.

Recently, before they underwent radical prostatectomy at Hopkins, 64 men agreed to participate in a health-related quality of life survey, to be sent to an independent third party, a data analyst who had no access to their patient records. (All of the men reported that they were potent and that they had a sexual partner before the surgery.)

By one year after surgery, 93 percent of the men reported that they were dry -- that during the previous four weeks, they had not needed a pad or adult diaper to control urinary leakage. When the men were asked to say how much their urinary continence bothered them, 98 percent said they had either a small bother, or none at all. In terms of potency, at 18 months after surgery, 86 percent of the men were able to have intercourse. When asked about difficulty with erections, 84 percent of the men said they had either a small bother, or none at all. Looking at the potency rates by age, at 18 months after surgery, 100 percent of men in their thirties were potent; 88 percent of men in their forties, 90 percent of men in their fifties, and 75 percent of men in their sixties were potent.

Urologist-in-chief Patrick C. Walsh, M.D., who led the study, was not surprised at the success with urinary continence; he has reported the same results for many years. "In the long run," he says, "only about 2 percent of patients have significant long-term problems with urinary control" (defined as needing to change a pad more than once a day). "We are currently trying to eliminate that 2 percent." The men's results with sexual potency, however, "are better than we've ever reported," says Walsh. They are also the highest potency rates reported at any academic medical center.

**Urinary Continence and sexual Function After Radical Prostatectomy**

	3 months	6 months	12 months	18 months
<b>Continence</b>				
No pads	54 percent	80 percent	93 percent	93 percent
No/small bother	96 percent	93 percent	98 percent	95 percent
<b>Sexual Function</b>				
Potent	38 percent	54 percent	73 percent	86 percent
No/small bother	49 percent	64 percent	76 percent	84 percent
Used Viagra	7 percent	13 percent	33 percent	33 percent*

*\*Only two men cannot have intercourse without Viagra.*

Walsh credits this to several factors: "One is that patients are being identified with smaller tumors, which permits us to preserve both neurovascular bundles without compromising cancer control." In this study, both neurovascular bundles were preserved in 89 percent of the men; this was accomplished without incurring positive surgical margins. There was only one positive surgical margin (which means that cancer cells were found in the edge of the removed prostate tissue) in this series of patients. (Cancer cells were found at the bladder neck in a man who had extensive disease.)

Also, Walsh adds, "over time the surgical technique has gradually improved, and finally, today Viagra is available." In the study, at 18 months after surgery, one third of the men said they were using Viagra, although only two patients said they could not have intercourse without it.

"I believe that most men who are incontinent or impotent following surgery want help. If the urologist poses these questions with the intention of helping the men overcome these problems and get their lives back to normal, I believe men will tell the truth."

Although the Hopkins radical prostatectomy results are the best in the world, other experienced surgeons at large referral hospitals and academic medical centers have obtained similar rates for urinary continence, and potency rates as high as 68 percent.

Unfortunately, however, the success of radical prostatectomy is not uniform; patients at some centers report much greater trouble with side effects. For example, a study from Harvard recently reported in the *Journal of the National Cancer Institute* that only 50 percent of their patients were continent, and fewer than 20 percent were potent after radical prostatectomy. These authors suggested that the poor results were not because the surgery by urologists in Boston was faulty, but because their outcome studies were -- as opposed to other centers' -- truly objective. They concluded that nerve-sparing surgery doesn't work, dismissing the far better results achieved at Hopkins and at other centers as unreliable, suggesting that because patients were reluctant to disappoint their surgeons, they were not truthful in discussing their side effects.

"There is always a concern," says Walsh, "that patients may try to minimize their problems to their physicians, or alternatively, that there may be an unconscious bias on the part of the surgeon toward minimizing adverse outcomes." But he does not buy the idea that patients would rather spare their surgeons' feelings than regain urinary continence and sexual potency. "I believe that most men who are incontinent or impotent following surgery want help. If the urologist poses these questions with the intention of helping the men overcome these problems and get their lives back to normal, I believe men will tell the truth."

The Hopkins study shows that when radical prostatectomies are performed by experienced surgeons, major side effects are infrequent. Walsh hopes that these findings will encourage urologists to work on improving their technique. "The study from Boston led many urologists who had poor outcomes to believe that no one had good results. I hope those surgeons will now understand that the results of surgery can be excellent, with proper surgical technique."

The message from both of these studies is, says Walsh: "Patients who believe that radical prostatectomy is the best form of treatment for prostate cancer should seek out centers where experienced surgeons perform many of these procedures, and where the results can be documented through validated, independent outcome studies."

#### FURTHER READING:

"Patient-Reported Urinary Continence and Sexual Function Following Anatomic Radical Prostatectomy" Patrick C. Walsh, M.D., Penny Marschke, MSN, Deborah Ricker, Ph.D., and Arthur L. Burnett, M.D., *Urology* Vol. 55 (1): 58- 61, 2000.

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## Perfecting the Radical Prostatectomy

Baseball pitchers use videotape to perfect their fastball; tennis players use it to get a better spin on their serve. The video camera is a staple for most athletes, in fact: No respectable football coach would dare contemplate next week's game without spending hours seeking wisdom from hindsight, going over this week's effort on the gridiron play by play.

So why don't surgeons do the same thing, wondered Urologist-in-chief Patrick C. Walsh, M.D.? "How are we ever going to improve our technique if we don't analyze our own work this way?" An excellent question, yet no one seems to have asked it before.

Over the years, Walsh says, he has come to believe that “very small differences in surgical technique can have a major impact on outcome.” In a groundbreaking study, he put his theory to the test, watching his own operations. Using a high-quality, three-chip video camera, Walsh videotaped the operations on the men discussed in the story

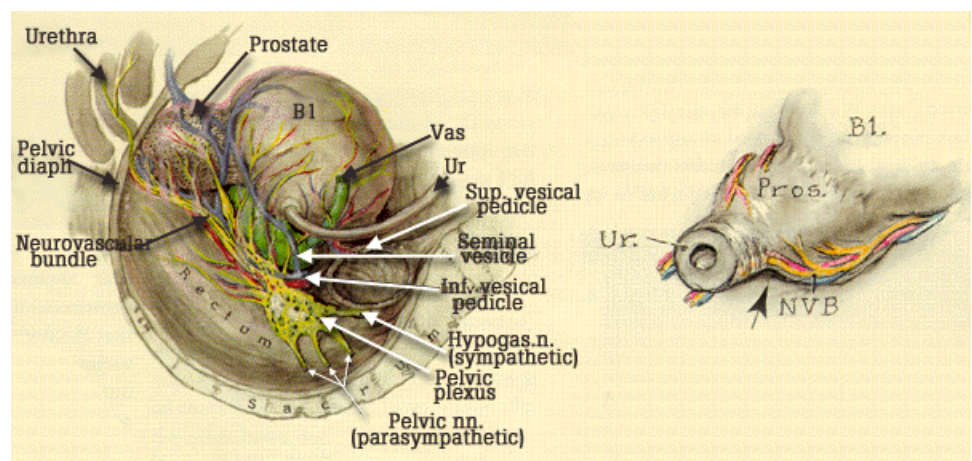
#### “Continence and Potency After

Radical Prostatectomy: Hopkins Study Finds Best Rates Ever”. Then, 18 months after that study began, he reviewed these tapes. His goal was to make a good operation even better, by minimizing the operation’s two major side effect -- incontinence and impotence: “When a patient is continent and potent immediately after surgery, what made the difference in this man?” Walsh spent his summer vacation examining these videotapes, sometimes stopping them frame by frame looking for insight. (Another bonus of the video camera is that it allows a view of the entire operative field, Walsh says, “and not just the small area where you have been working.”) It took hours of intense scrutiny to watch a single two-hour operation, but the hard work paid off: He was able to identify four slight variations in his technique - in controlling bleeding from the dorsal vein and dividing the sphincter-that appeared to make the difference in the men who recovered sexual potency the soonest.

But most exciting was that Walsh -- who discovered the neurovascular bundles years ago -- found that some men had a significant anatomical variation. “Previously, everyone believed that the neurovascular bundle took a rather straight pathway from its origin in the sacrum along the lateral surface of the prostate to the urethra,” explains Walsh. “But I learned that in many patients, the bundle curves around the apex of the prostate, and is tucked just beneath the sphincter and held there by a small group of vessels.

And that, if one attempts in good faith to preserve as much of the sphincter as possible, the neurovascular bundle can be damaged, and recovery of sexual function delayed.” indeed, the eight men who at 18 months had not yet recovered full sexual function all seemed to have this variant curve.

Part two of the Walsh’s self-imposed exercise was to make the study “blind.” He went back over the operations yet again -- this time without identifying the patient or the outcome -- to see if the steps he had identified checked out. They did.



Incontinence is a long-term significant problem for only about two percent of his patients, and Walsh was unable to find evidence that anything he did or did not do during surgery would make a difference there. “Clearly, it had nothing to do with preservation of the sphincter,” he says. “There was one man with perfect preservation of the sphincter who was still wearing a pad one year after the surgery.” For this reason, Walsh is working to refine the procedure for reconstructing the bladder neck during radical prostatectomy.

Walsh believes many surgeons could benefit from regularly reviewing their operations in this way: “Because many surgeons use different techniques, it’s likely that each surgeon may be able to identify other important, arbitrary variations that may help patients.” Also, for surgeons whose patients seem prone to more side effects than usual, “the review of early successful cases may help them identify ways to modify their technique, and improve the outcome of future patients.”



It took hours of intense scrutiny, but surgeon Patrick Walsh examined videotapes of dozens of radical prostatectomies he performed, sometimes stopping the two-hour operations frame by frame. The hard work paid off with a surprising discovery: Walsh -- who discovered the neurovascular bundles years ago -- found that some men have a significant anatomical variation. Until now, it had been widely assumed that the neurovascular bundle traveled in a straight line at the apex (left). But in some men, the nerve bundle makes a detour (arrow, right). - and surgeons, not realizing this, can inadvertently damage the nerves responsible for erection, and delay recovery of sexual function.

#### FURTHER READING

“The Use of Intraoperative Video Documentation to Improve Sexual Function Following Radical Retropubic Prostatectomy,” Patrick C. Walsh, M.D., Penny Marschke, MSN, Deborah Ricker, Ph.D., and Arthur Burnett, M.D., *Urology*, Vol. 55 (1): 62-67, 2000.

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## If PSA is Undetectable After Surgery, No Need for Rectal Exam

Men hate the digital rectal examination -- so much so, in fact, that the desire to avoid it may lead them to put off follow-up visits to the doctor after radical prostatectomy. From a medical standpoint, in turn, the rectal exam is only as good as the physician performing it. Similarly, another test often used in follow-up monitoring of prostate cancer patients after surgery, the radionuclide bone scan, is expensive and also may lead to further tests if the findings are inconclusive.

Is there a better way? A Hopkins study led by urologist Charles R. Pound, M.D., found that PSA is such a sensitive marker of prostate cancer that if the PSA is undetectable, men don't need a digital rectal examination or further imaging studies at that time. In other words, they're off the hook. (However, men still need careful follow-up with a PSA test every year.)

In the investigation, scientists studied the medical histories of nearly 2,000 men who underwent radical prostatectomy at Hopkins over a 15-year period -- a remarkable study of more than 10,000 patient-years of follow-up. Of these men, 56 developed a local recurrence of cancer, and 118 developed distant metastases. For some of these men, it took several years for cancer to return -- which is why men need to keep getting regular PSA tests, even several years after surgery -- but no man with an undetectable PSA had evidence of local recurrence or distant metastasis.

#### FURTHER READING

“Digital Rectal Examination and Imaging Studies are Unnecessary in Men With An Undetectable PSA Following Radical Prostatectomy.” Charles R. Pound, M.D., Owen W. Christens-Barry, Robin T. Gurganus, Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D., *Journal of Urology*, Vol. 162: 1337-1340, 1999.

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“Digital Rectal Examination and Imaging Studies are Unnecessary in Men With An Undetectable PSA Following Radical Prostatectomy.”  
Charles R. Pound, M.D., Owen W. Christens-Barry, Robin T. Gurganus, Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D.,  
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## After Radical Prostatectomy, Men's Testosterone Goes Up

The increase in testosterone is not noticeable, “but it certainly dispels the idea that a loss of male hormones contributes to a loss of the sex drive.”

This story is about testosterone, but it begins in the brain -- in the pituitary gland, which makes a hormone called LH (luteinizing hormone). In the chemical chain of events involved in the production of testosterone, the pituitary is the thermostat, a regulator that controls the testes -- the “furnace” in effect. The furnace cranks out heat -- testosterone -- which, in turn, stimulates the prostate.

The level of testosterone in the blood is constantly monitored by the brain, which regulates how much LH is needed. Hopkins researchers recently were surprised to learn that when the prostate removed, LH goes up--and so, then, testosterone--causing researchers to speculate that the prostate produces a substance that controls LH secretion.

The Hopkins investigators were studying the effect of radical prostatectomy these hormones in 63 men, wondering whether some change in hormonal make-up might explain a loss of libido experienced by some men after surgery. “In normal men, the major factors that influence sexual function are blood flow, nerve supply, and hormones,” explains Urologist-in-chief Patrick C. Walsh, M.D., one of the authors of the study. “A great deal of attention has been placed on studying what disrupts the nerve supply and blood supply during surgery -- but up to this point, there has been little attention as what happens to the hormones.” Some scientists have theorized that perhaps a surgery, there is a decrease in male hormones, “and maybe this is why some men have a diminished libido after surgery.”

The newly discovered information, that the pituitary gland makes more LH after radical prostatectomy, “suggests that the prostate is also making an inhibitor that regulates the release of LH from the pituitary,” says Walsh, “raising the fascinating hypothesis that the prostate itself may influence hormone levels in an effort to modulate its own growth.”

The increase in testosterone is not noticeable, Walsh adds, “but it certainly dispels the idea that a loss of male hormones contributes to a loss of the sex drive.” Instead, Walsh adds, a more like cause of this diminished libido after surgery is depression. In most cases, “treating the depression restores the sex drive back to normal.”

#### FURTHER READING

Leslie R. Miller, Alan W. Partin, Daniel W. Chan, Debra J. Bruzek, Adrian S. Dobs, Jonathan I. Epstein, and Patrick C. Walsh. “Influence of Radical Prostatectomy on Serum Hormone Levels,” *Journal of Urology*, Vol. 1160, 449-453, August 1998.

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## Seeds Vs. Surgery: How Good is Interstitial Brachytherapy?

Part of the problem, is that “prostate cancer is a multi-focal disease. At the time of radical prostatectomy, the average number of individual cancers within the prostate is seven -- seven separate cancers in one prostate. This indicates that in order to cure prostate cancer, you can’t risk leaving any cells behind. You have to eliminate the entire prostate.”

Interstitial radiation seeds are like little grenades, inserted directly into a prostate tumor. In theory, each radioactive seed blasts a targeted area of tissue, ultimately destroying the prostate. In practice, however, it hasn’t been that simple: In the 1960s and 1970s, doctors used a “freehand” technique, placing the seeds during open surgery. The coverage was uneven as some of the target tissue was obliterated, but other tissue was left unscathed -- and the procedure’s ability to control cancer ranked a distant third behind radical prostatectomy and external-beam radiation. At 10 years after seed implantation, overall about 90 percent of men had a detectable PSA level. However, even in the most favorable subset of patients, men with the smallest tumors, the PSA level remained low in only 60 percent of patients. The procedure wasn’t well-suited for men with large or high-grade tumors; also, because most implantation regimens focused only on the tissue within the prostate and ignored the seminal vesicles and tissue outside it, the seeds were unable to reach cancer that had spread locally. Finally, the seeds did cause side effects,

particularly urinary incontinence, in men who needed a TURP (transurethral resection of the prostate) to relieve prostate obstruction following treatment.

The ideal patient for radioactive seeds was (and still is) a man who is also an ideal candidate for radical prostatectomy and external-beam radiation therapy. Because both of these treatments can cure prostate cancer in men with localized disease, doctors faced a question: Is interstitial brachytherapy as good, or better, than either of those treatments? The answer 20 years ago was a definite no. Today, the answer is somewhat more difficult, because the treatment has improved: Instead of the old “free-hand” technique, doctors now use a sophisticated, high-tech approach, guided by ultrasound and CT scans, working from a custom-designed grid, or template, for each patient.

Is it better? Some doctors seem to think so. The most widely quoted data on interstitial brachytherapy come from The Pacific Northwest Cancer Foundation, a small hospital in Seattle. In 1997, doctors at this hospital reported that at seven years after the procedure, 79 percent of their patients (who had small, low-grade tumors and a small prostate) had a PSA of less than 0.5. However, these men had very small tumors.

How can doctors and patients evaluate these results? Are they really remarkable? How well do they really remarkable? How well do they hold up in comparison with the “gold standard” treatment for prostate cancer, radical prostatectomy? Urologist-in-chief Patrick C. Walsh, M.D., wondered how these men would have fared if they had undergone surgery instead.

To answer this question, a recent Johns Hopkins study examined the outcome in 76 comparable patients (matched for Gleason score and clinical stage to the patients in the Seattle study) who underwent radical prostatectomy. At seven years, 98 percent of the men who underwent radical prostatectomy had a PSA of less than 0.2. More recently, the Seattle group reported that at 10 years after the procedure, the number of men with a PSA of less than 0.5 had dropped from 79 percent to 60 percent--the same results as those from the old, “free-hand” approach, which is now nearly universally considered to have been unsuccessful.

Why aren't the results better? Part of the problem, says Walsh, is that “prostate cancer is a multi-focal disease. At the time of radical prostatectomy, the average number of individual cancers within the prostate is seven -- seven separate cancers in one prostate. This indicates that in order to cure prostate cancer, you can't risk leaving any cells behind. You have to eliminate the entire prostate.” Another problem with the Seattle group's reckoning is its standard of “cure.” At Hopkins, men are considered cured only if they have an undetectable PSA -- below 0.1. “The brachytherapy results should be held to the same standard as those for radical prostatectomy. If PSA levels are higher than 0.2, it is clear that prostate tissue remains, which may contain cancer cells, or which may someday turn into cancer. You have to use a precise endpoint, and you have to follow patients over a long period of time, preferably 10 years or longer, to know whether or not you've cured the cancer.”

Also troubling is the higher rate of side effects associated with the radioactive seeds. Investigators from the Pacific Northwest Cancer Foundation reported that following interstitial brachytherapy, 5.1 percent of patients were incontinent, and in 1.7 percent, the incontinence was so severe that the men required a urinary diversion-- attachment of a bag, worn under the clothes, to collect urine. Three other patients also required the urinary diversion procedure because of severe strictures or urinary retention.

What about radioactive seeds combine with external-beam therapy? This approach may prove more successful. Today, however, the jury is still out; this combined approach is still too new for long-term results. Recently, doctors at the Georgia Center for Prostate Cancer Research, using “ProstRcision” (brachytherapy plus external-beam radiotherapy), reported that their 10-year disease-free survival rates were comparable to the 10-year results after radical prostatectomy at Johns Hopkins.

Between 1984 and 1993, most men in this series were treated with open retropubic implantation of radioactive seeds, and all of these men underwent removal of the lymph nodes. But the Center only reported its results on the

patients who had cancer-free lymph nodes; the Hopkins study does not exclude men who turned out to have cancer in the lymph nodes (about 7 percent of the men in this study).

At 10 years, the Georgia Center reported that about 65 percent of patients had PSA less than 0.5, and about 57 percent had a PSA of less than 0.2. Excluding men with positive lymph nodes, the Hopkins results indicate that 77 percent of patients who underwent radical prostatectomy during the same time period had PSA levels less than 0.2 -- a difference of 20 percent.

The Hopkins scientists involved in the study say these results--and the different levels of PSA used as endpoints -- “emphasize the need for caution” in interpreting the ability of radioactive seeds to control prostate cancer.

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## **A Better Biopsy: Twelve Samples Instead of Six**

Despite major breakthroughs in prostate biopsy over the last decade -- development of the tiny, spring-loaded biopsy gun, and the use of transrectal ultrasound as a real-time guide that allows urologists to see the prostate as they're removing small cores of its tissue it's still not perfect. The needle biopsy doesn't always prove, beyond all doubt, whether or not a man has prostate cancer: Sometimes, the sample, when looked at under the microscope, is too ambiguous to label definitively. Sometimes, the needle simply misses the cancerous cells.

Most cancers develop in the prostate's peripheral zone; but cancers here tend to be thin and spread laterally, like a sheet so it's not uncommon for the biopsy needle to plunge in too deep and overshoot the target area. That's why, in an attempt to get a comprehensive sample, urologists have traditionally taken what's called a “sextant” biopsy -- six samples from throughout the prostate, one on the top, middle and bottom of the gland on the right and left sides. But six is not enough, says urologist Ray Stutzman, M.D.

Taking twelve samples -- two each from the same locations -- gives a more accurate picture. “We routinely take 12 cores now,” Stutzman says, although in some cases, when there's strong suspicion that cancer is present, he takes as many as 20. “I've done about the last 1,000 biopsies that way, for the last four years. It doesn't seem to increase the complications” -- there is a minor risk of bleeding or infection -- “and it doesn't seem to cause any greater discomfort.”

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## **For Many Men With Prostate Cancer, It's the Weak Link: The Needle Biopsy**

“It’s just as important as getting a second opinion for surgery or radiation. You could have the best surgeon in the world, but if you don’t have the right pathology, you could have the wrong thing done for you.”

Just a few tiny cores of tissue, and a man’s life may depend on what you have to say about it. You make the call: Your word is, for all practical purposes, the Gleason score, your opinion a huge part of the treatment decision-making. So think, think -- what about those funny looking cells over there? Is it cancer?

The prostate biopsy can be a pathologist’s worst nightmare. “Of all biopsies, prostate biopsies are probably the hardest” explains pathologist Jonathan Epstein, M.D., who is world-renowned for his expertise and accuracy in judging prostate cells, and has probably examined more prostate tissue than any other pathologist. “You’re dealing with such a limited amount of tissue, and cancers tend to creep around the benign gland,” rather than forming as a solid mass. Imagine a Tootsie Roll, wrapped in paper. The cancer is like the paper, a veneer over an expanse of healthy tissue. And the veneer is often maddeningly ambiguous. So not only can the hollow-core biopsy needle overshoot and miss the cancer, the cancer cells it does get don’t always match the pictures in the textbook.

One result of this is the biopsy labeled “atypical” -- a diagnosis that appears in about 5 percent of biopsies at most institutions, says Epstein. “Basically, what that means is that a pathologist will see something that he thinks could be cancer, but is not comfortable calling it cancer.” For many patients, the next step is having a repeat biopsy--and the value of this is often questionable, says Epstein. “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. We’ve seen some missed entirely. They were called totally benign, yet they were cancer.”

A repeat biopsy might be a reasonable option if no cancer is found, he adds, “but if there is already a diagnosis of cancer, or even ‘atypical cells,’ a repeat biopsy may just lead to more confusion.”

Another problem 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 one and a half percent -- 6 to 8 men -- of the patients who come to the Brady Urological Institute each year with a diagnosis of prostate cancer are found to have been misdiagnosed. “We switch the diagnosis. We say, ‘This is not cancer, this is benign.’”

Perhaps the best option in the case of tricky diagnoses, says Epstein, is to have the slides sent to an expert. “About 70 to 80 percent of the time, it can be resolved as being definitively benign, or definitely cancer.” But even biopsies that seem straightforward deserve another look. “We recommend getting a second opinion before anybody undergoes any form of treatment”, says Epstein. “It’s just as important as getting a second opinion for surgery or radiation. You could have the best surgeon in the world, but if you don’t have the right pathology, you could have the wrong thing done for you.”

On this point, Epstein is blunt: “We have done numerous studies showing the reproducibility of Gleason scores in the general pathology community, “ looking at the Gleason grade based on a biopsy, and then comparing it to the actual specimen removed during surgery, “and found that by and large, the Gleason grading that’s performed is disappointing. All across the map, it doesn’t correlate with what you see in a radical prostatectomy. People are having decisions made -- surgery or radiation, or watchful waiting -- based in part on a Gleason grade, when it’s not accurate at all.”

Beware the low-grade Gleason score: Particularly erroneous, Epstein has found, are biopsies given low Gleason scores. “From the standpoint of patient care, the low-grade Gleason (a score of 2, 3, or 4) doesn’t exist, and it gives a false sense of optimism. Even if I call something a 2-4 in a biopsy, when the prostate is removed in a radical prostatectomy, it will turn out to be Gleason 5, 6 or higher.” Low-grade Gleason tumors do exist, Epstein says, “but

where they exist is in the central transition zone of the prostate, not in the peripheral zone where you do biopsies. A low Gleason score is the kind of thing that shows up more in a transurethral resection of the prostate” (TURP), a procedure used to treat prostate enlargement, in which tiny bits of tissue from the center of the prostate are chipped away and removed through the urethra. “If a tiny focus of low-grade cancer shows up on a TURP, it’s not as worrisome as a tiny bit of intermediate tumor found on a biopsy. A low-grade Gleason score is valid on a TURP, but not on a needle.”

An on-line course for pathologists: In an effort to improve prostate cancer diagnosis, Epstein is teaching pathologists in a tutorial he devised for the Internet -- a website for pathologists. “We just did it on our own,” he explains, “because we think pathologists can do better than they have been. The key is education, not just getting frustrated.” Epstein and colleagues have tried other approaches such as articles, he says, but have found that this website is “an amazing tool, because it can reach so many people quickly.” The on-line course -- the first of its kind -- takes about an hour. First, pathologists are asked to grade a set of biopsies. Then, they’re shown some of the telltale signs of various grades-Epstein calls them “tricks of grading”-and taught how to interpret another set of biopsies. Finally, they are asked to re-evaluate the biopsies. “We’ve found that pathologists can make a dramatic improvement, just in this brief tutorial.”

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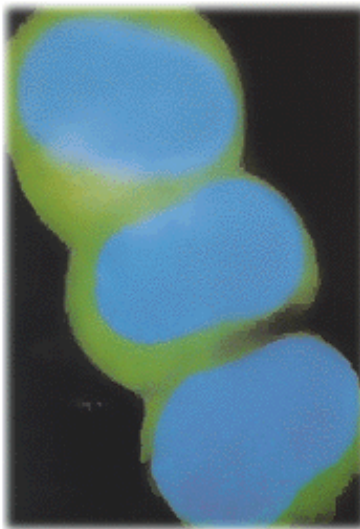
## New Test Can Spot a Single Prostate Cell in Blood

“Are there still prostate cells floating around, and if so, are they cancer cells? That’s what this test allows you to know. We can tell if it’s a prostate cell, we can tell if it’s cancerous.”

Ask scientists which they’d rather try to find--a prostate cell in a blood sample, or a needle in a haystack -- and the answer might have been a toss-up. Until now: A remarkable new technique, developed at Hopkins, allows scientists to isolate a single cell from a milliliter of blood -- a feat indeed, considering that in this dollop (about one-fifth of a teaspoon) of blood are some 6 million cells.

“The whole technology of being able to isolate single cells out of the bloodstream is a major breakthrough,” says urologist Alan Partin, M.D., Ph.D., who helped develop the technique. This research, published in the *Journal of Urology*, used the technique to answer a question that had long worried physicians and patients: Is it possible that the act of removing the prostate, or even removing some tissue in a biopsy, might somehow allow prostate cancer cells to escape into the bloodstream? The answer was reassuring -- most likely, no, “and if some cells do break free, it’s not significant.” (The existence of cancer cells in the blood doesn’t mean that a man’s cancer is not curable, because these cells must also develop aggressive techniques that will permit them to live in a new, hostile environment outside the prostate.)

But the technique can also answer questions in men after surgery: “Are there still prostate cells floating around, and if so, are they cancer cells? That’s what this test allows you to know. We can tell if it’s a prostate cell, we can tell if it’s cancerous.” The test accomplishes what another promising technique has not been able to deliver: That test, called RT-PCR, designed to hone in on PSA, searched for “a piece of DNA that looked like it might have come from a prostate cell,” explains Partin. But RT-PCR tests have not proved terribly reliable; there were many “false positives,” and some scientists worried that the test might be measuring a molecule that bears a striking resemblance to PSA, but isn’t.



Amazing feat: “The whole technology of being able to isolate single cells out of the bloodstream is a major breakthrough,” says urologist Alan Partin. The new test uses tiny magnetic beads, coated with antibodies, that act as flypaper: “They attach to the white blood cells and remove them,” says Partin. “Whatever’s left is stained for PSA, which lights up in a fluorescent field. Everything else is black, and there’s that big prostate cell beacon shining at you.”

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## Neural Networks: Looking at the Bigger Picture

If the neural network can say, “You don’t need that biopsy,” if all the knowledge that we can grasp is saying that a man is probably okay, then that’s where this technology is going to help.

Urologist Alan Partin, M.D., Ph.D., loves statistics, facts, and figures: Rearranging them, making sense out of them, and using what he’s come up with to help patients. A prime example: The “Partin Tables” he developed, along with Urologist-in-chief Patrick C. Walsh, M.D., which filled a great need by correlating three facts about a man’s disease -- PSA level, Gleason score, and clinical stage--and accurately estimating the extent of a man’s prostate cancer to help him make an educated decision about treatment. Now, instead of just three pieces of information, he’s taking more than a dozen, feeding them into a sophisticated neural network -- a “thinking” computer program he has helped develop -- and asking new questions, such as: What will the results of this man’s biopsy be? What will be the pathologic stage of his tumor? Will he have positive lymph nodes?

“Neural networks are not new,” says Partin, “but they’re fairly new to medicine. The stock market uses them all the time: They watch trends; the network tells them what’s going to happen in the next quarter, so they know which stock to buy. Factories use them to measure the temperature of water, steam coming out of the pipes, the noise level in the building about 15 or 20 variables that they continuously monitor -- and they know two days before the machine’s going to go down, because they’ve seen the pattern before. The neural network says, “You’re going to be in trouble, you’d better stop the line and fix something.”

With a neural network program he and colleagues developed with funding from the National Cancer Institute, Partin says, “I can take a man’s PSA, his age, his race, digital rectal examination, free PSA, and I can give him a very good estimate of his probability of having prostate cancer if he were to get a biopsy. Instead of saying “That’s a little high, maybe you should get a biopsy.” I can say, “You’ve got a 48 percent chance of having cancer.”

Neural networks recognize patterns, “just as you can recognize your child 500 yards away just by glancing.” Their answers are educated guesses. The neural networks -- so called because they function like artificial brains, and have the ability to learn from their mistakes -- can see a bigger picture, says Partin: “For the last 15 years, we have been looking at tumor markers, looking at pathologic information, trying to make predictions for prognosis. We look at slides, Gleason scores: we measure PSAs, we have new blood tests. We’ve been doing image analysis -- looking at the shape and texture and organization of the DNA in the nuclei of prostate cancer cells. Some of these tests are good, some are great, and some are okay. No single one of them can tell us the answer, but maybe all of them together would give us more of an idea what the future holds for men.”

But no human, Partin adds, can comprehend so many variables at one time. Enter the neural network, which uses complex mathematical-statistical analysis “to compare variables that aren’t inherently coordinated with each other.” The network doesn’t even try to figure them out. “It simply doesn’t care whether the variables make sense together; it’s just looking for a pattern.”

How, then, does this brainy computer work? Partin gives the example of a kid trying to learn Spanish with flash cards. Hold up a card, the kid looks at the Symbols and takes a guess. “If he’s right, we put that card aside, and pick up the next card. If he’s wrong, we tell him the correct answer, put the card back in the stack, and ask him again in a few minutes. Keep going through the flash cards, and eventually he’ll learn Spanish,” Partin says. “Then you can give him words he’s never seen before, and because he’s learned all the prefixes, suffixes and conjugation he can make a guess, and often he’ll get it right.” The neural network is simply a matter of training a computer to look at complex series of results and determine a pattern -- the possibility of cure, perhaps, or the likelihood that cancer will be aggressive. “The computer does this thousands of times until, like a brain, it gets pretty good at guessing which horse

is going to win the race.”

Compared to standard statistical patterns, the neural networks conclusions, based on retrospective data from prostate cancer patients -- 500 so far -- are “far superior,” says Partin, who is on a committee with the World Health Organization and the International Union of Cancer Control to investigate neural network technology worldwide. He believes the network has the potential to save millions of men from unnecessary biopsies. “Last year, 25 million men in the U.S. had PSA tests; 20 million of them have had a negative prostate biopsy and don’t know what to do next year. We just can’t afford to biopsy 20 million men every year. If the neural network can say, “You don’t need that biopsy,” if all the knowledge that we can grasp is saying that a man is probably okay, then that’s where this technology is going to help.”

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