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FROM THE DIRECTOR: From Bench to Bedside, and Back Again

Again and again, the Brady Urological Institute has been named number one in the country by U.S. News and World Report magazine.

A great honor -- but it's also just a headline. The ranking alone doesn't tell you anything about why this is such a special place. (We hope to give you a better look at the "big picture" of our work in this issue of Prostate Cancer Update.) One reason, of course, is the people who work here -- bright, dedicated, innovative, and caring surgeons, scientists, nurses, and staff who, to a person, love what they do.

The other reason is our unusual setup -- a one-of-a-kind environment in which scientists and surgeons work side by side under one roof. This juxtaposition of laboratory and clinical setting encourages surgeons to learn science, and scientists to learn medicine. The magic of this facility is our ability to transfer discovery quickly from the "bench to the bedside," so the latest scientific knowledge can be turned into new avenues for patient care.

The process also works in reverse: The discovery of the nerve-sparing radical prostatectomy and the search for the hereditary prostate cancer gene were both inspired by the bedside. Two decades ago, I saw the first patient who was potent after a standard radical prostatectomy -- an operation once notorious for its extreme bleeding and devastating side effects of incontinence and impotence -- and wondered how this could be possible. Ten years ago, I saw a 49-year-old man with prostate cancer who told me that every male member of his family -- his father, his father's three brothers, and his grandfather -- had died of the disease. These people made me ask some basic questions: Why does impotence occur after prostatectomy? Could prostate cancer be inherited? These questions at the bedside were transferred to the research bench for answers.

No matter how our discoveries happen -- whether they begin at the bedside or the bench -- our goal is to understand and eventually conquer prostate cancer. This is our mission; this has been our success. It is our feeling that if this mission does not go forward, the process of discovering new treatments for prostate cancer may be lost.

I am proud and excited to share our latest findings with you as patients who are vital partners in this process of discovery.

Sincerely yours,

Patrick Walsh

Patrick C. Walsh, M.D.
Urologist in Chief

AT LAST, GENETIC PROOF: Prostate Cancer Can be Inherited

In this genetic detective story, involving 91 families from three countries who have been devastated by prostate cancer, the discovery is like finding the first fingerprints at the scene of the crime.

It has been a painstaking quest, and it's far from over. But there has been a major breakthrough in the search to unravel the secrets of prostate cancer: The first conclusive evidence of a genetic defect that predisposes some men to the disease, and causes prostate cancer to run in some families.

The presence of a familial prostate cancer gene (or genes) has long been suspected; in 1992, Johns Hopkins researchers were the first to establish an undeniable link between a family history of prostate cancer and a man's risk of developing the disease, and to characterize the distinct phenomenon of Hereditary Prostate Cancer (HPC). But until now, no proof has ever been found. In this genetic detective story, involving 91 families from three countries who have been devastated by prostate cancer, the discovery is like finding the first fingerprints at the scene of a crime.

Investigators from the Brady Urological Institute, in collaboration with scientists from the National Human Genome Research Institute and from Umeä University in Sweden, recently reported that they've linked the disease to a gene at a specific location -- a site on chromosome 1. The discovery is not an exact "street address," but it's a promising road sign that shows scientists where to look next and narrows the search considerably, says Patrick C. Walsh, M.D., Urologist-in-Chief, who launched this effort 10 years ago. "This study proves that prostate cancer can be inherited like other cancers -- a fact that many people somewhat doubted. Now we know on which chromosome it's located, and armed with that information, we can go after the gene."

This particular gene is probably responsible for about one-third to half of cases of hereditary prostate cancer -- and only about 10 percent of all cases of prostate cancer are thought to be purely hereditary. But many scientists believe that the defective gene or mechanisms involved in hereditary prostate cancer are the same ones that somehow go askew in "sporadic" cancer, disease that just develops over the course of a lifetime -- the kind most men get. (Most scientists believe that cancer happens because of a combination of "hits" -- at least one genetic aberration, plus one or more things environmental, such as a poor diet, or smoking. Think of a genetic slot machine, in which -- in order to develop a disease -- you need to get two, three, or five oranges in a row; having a bad gene is worth at least one orange.)

The next step is to identify the gene, says Walsh, and the ramifications of this will be immense: "First of all, it will enable us to identify the families that carry this mutation -- and in doing so, to identify men who are at high risk for developing the disease," so prostate cancer can be detected in time to cure it. Men with HPC tend to develop the disease far sooner -- even as young as their late thirties or early forties -- than other men.

Unfortunately, by the time these men even start routine screening for prostate cancer, it may already be too late to cure it.

"Next, finding out the function of this gene should enable us to understand what causes prostate cancer in general," Walsh continues. "Once we know what the gene does, this could lead to new strategies of preventing the disease, or treating advanced cancer."

An estimated 250,000 American men may carry the defective gene, named HPC-1, says William B. Isaacs, Ph.D., associate professor of urology and oncology, and the senior author who directed the study, which was published in the journal Science. These men appear to have extremely high odds -- a nearly 90 percent likelihood -- of developing prostate cancer by age 85, he says.

The gene doesn't appear to discriminate: "It may be active over a wide variety of geographic regions and ethnic backgrounds," Isaacs says. In the study, the susceptibility was found in Caucasian and black men scattered throughout the U.S., as well as Caucasians in Canada and Sweden. However, as Walsh points out, this raises still more questions: "We know that prostate cancer is more common in African Americans. Does this increased risk have a genetic basis -- and if so, is this the gene that's involved? We hope to address this and the overall importance of ethnic heritage in the near future. For this reason, we're anxious to find African-American families with strong family histories of prostate cancer."

The difficulty of this task, of looking for a lone defective gene out of the thousands of genes that remain unexplored in the human body, is awesome. Donald Coffey, Ph.D., director of research, likens the quest for HPC-1 to searching for a single misspelled word in 17 sets of the Encyclopedia Britannica -- 323 volumes. Homing in on the gene thus far -- by narrowing it's location down to a small portion of one chromosome -- is the equivalent of reducing the search for the faulty word from 380,490 pages to a mere 400 pages. A monumental step, says Walsh, "but there is still much more to do" -- finding the gene, and looking for other genes that may be involved.

How the Search Began

Prostate cancer is a confoundingly common disease. That's why, for years, scientists downplayed the idea that (just like more conspicuous illnesses such as hemophilia) it could be inherited -- even though it was known to run in families. Thirty years ago, Mormon genealogists in Utah noted that prostate cancer seemed to "cluster" in families -- and that, among familial cancers, this clustering of prostate cancer was actually more common than breast or colon cancer (yet both of these were recognized to have a hereditary predisposition).

But for some reason, prostate cancer got lumped in the category of ailments that simply come with old age, says Walsh. With this perception muddying the water, "these observations went relatively unexplored for a couple of decades -- largely because prostate cancer was so common in older men."

In the 1980s, Walsh began to see increasingly younger men for surgical treatment of prostate cancer, and was struck by how many of them had a family history of the disease. Then, in 1986, he met a 49-year-old patient with a tragic, unforgettable legacy: "He told me that every male member of his family had died of prostate cancer: His father, his father's three brothers, and his grandfather," says Walsh. "At that time, virtually every physician in the United States could tell you that a woman's risk for breast cancer was increased twofold if her mother or sister had it. I wondered why similar information wasn't available about prostate cancer."

So Walsh set out to find some answers, initiating the first of a series of studies, ably led by Bob Carter, an M.D.-Ph.D. student, and Gary Steinberg, a former resident, and aided by pediatric geneticist Barton Childs, M.D., and genetic epidemiologist Terri Beatty. The first question: Would the observations that had been pretty much limited to Utah Mormons hold true with a larger, more diverse group of men? A study of 691 patients, who had come to Hopkins for a radical prostatectomy, confirmed that having a family history of prostate cancer did indeed increase a man's risk of developing the disease. Next, the Hopkins researchers ruled out environmental factors; further, their results strongly suggested that increased susceptibility to prostate cancer could be inherited from either parent. They then went on to define and characterize Hereditary Prostate Cancer, showing the clear link between family history and a man's probability of developing prostate cancer. (Briefly, if your father or brother has prostate cancer, your risk is two times greater than the average American man's which is about 13 percent. It goes up from there: Depending on the number of affected relatives you have and the age at which they develop the disease, your risk could be as high as 50 percent if you are in a family that meets the criteria for HPC -- if you have at least three close relatives, such as father and two brothers affected, or two relatives if both were younger than 55 years old; or if your family has a disease in three generations -- a grandfather, father, or brother.)

Then came this study. Out of a pool of 2,500 families that met the criteria for HPC came an elite group of 91 families -- hand-picked and rigorously screened by Walsh and behavioral scientist Sally Isaacs. Sadly, the families

selected for the study were those hardest-hit be prostate cancer -- so there could be no mistaking hereditary cancer for, as Walsh puts it, "simply bad luck," in which several men in the same family happened to develop the disease. The families filled out detailed questionnaires about their health, occupations and family history, and sent blood samples to Hopkins.

"We had what no one else had," says William Isaacs, "the families. They were our gold mine." It was there DNA that pointed to the marker, or signpost for the gene. It will be their DNA that -- "with a lot of hard work and a little luck," as Isaacs says -- will lead to the gene itself.

Further Reading

"Major Susceptibility Locus for Prostate Cancer on Chromosome 1 Suggested by a Genome-Wide Search," in Science, Vol. 274, pp. 1371-1373, Nov. 22, 1996. Jeffery R. Smith, Diha Freije, John D. Carpten, Henrik Gronberg, Jianfeng Xu, Sarah D. Isaacs, Michael J. Brownstein, G. Steven Bova, Hong Guo, Prioska Bujnovszky, Deborah R. Nusskern, Jan-Erik Damber, Anders Bergh, Monika Emanuelsson, Olli P. Kallioniemi, Jennifer Walker-Daniels, Joan E. Bailey-Wilson, Terri H. Beaty, Deborah A. Meyers, Patrick C. Walsh, Francis S. Collins, Jeffery M. Trent, William B. Isaacs.

Cancer Control After Radical Prostatectomy: Long-Term Results

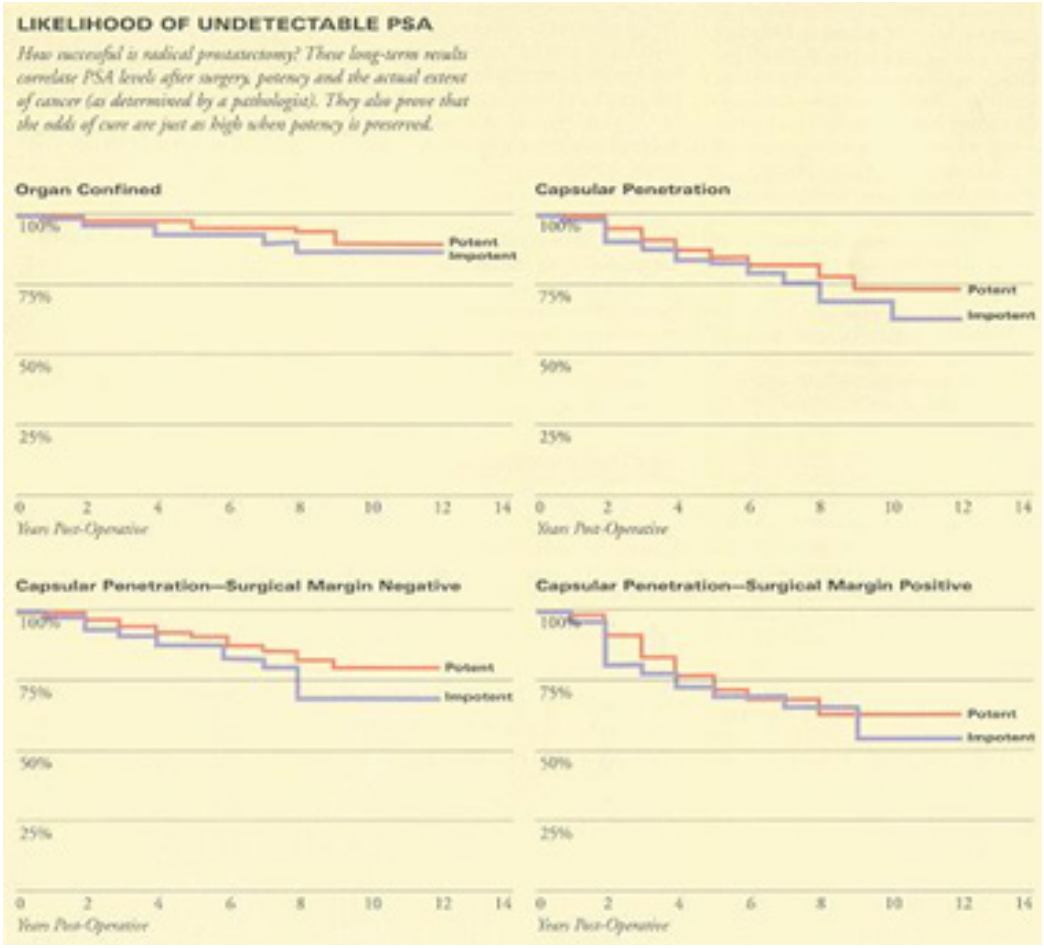
Radical prostatectomy cures the vast majority of men with cancer confined to the prostate. It also cures most men even if cancer has reached or penetrated the prostate wall, if the tumor cells are pretty well differentiated (a Gleason score of 6 or lower), and if surgeons are able to remove all the cancer (if the surgical margins are "clear," or negative). And preserving potency -- by not removing one or both of the nerve bundles adjacent to the prostate, which are responsible for erection -- does not make cure less likely; in fact, the odds of cure are just as high.

However, when a high-grade tumor (Gleason 8 or higher) has penetrated the prostate wall, or when the cancer has reached the seminal vesicles, the chances for a cure are not as certain.

These and other findings have just been confirmed by a massive, long-term study of 1,623 men with clinically localized (estimated before surgery to have stage T1, T2, or T3a) disease. Cure was defined by the "gold standard" -- an undetectable level of PSA after surgery. (PSA, or prostate-specific antigen, an enzyme made by the prostate, is a highly sensitive measure of cancer recurrence; if the prostate is no longer in the body and PSA is being made at detectable levels, then some prostate cancer cells must remain in the body.)

The men, operated on between 1982 and 1995, underwent anatomical radical retropubic prostatectomy and pelvic lymph node dissection; the operations were all done by the same surgeon, Patrick C. Walsh, M.D., who developed this "nerve-sparing" procedure. Five years after surgery, only one percent of these men had died from prostate cancer, and at 10 years, only 7 percent had.
At 10 years after surgery, nearly 70 percent of them remained cancer-free, with no trace of PSA in the bloodstream; 18 percent had experienced a lone elevated PSA level; 8 percent had local recurrence of cancer (some of these men then underwent external-beam radiation treatment, which seemed to work: Their PSA level again dropped to the undetectable range and has stayed there for at least two years); and 9 percent had distant metastases.

The higher a man's clinical stage, Gleason score (particularly, 8 or higher), PSA before surgery (particularly, higher than 20), and pathologic stage (determined when a pathologist examines the actual tissue removed during surgery), the greater this odds of recurrence.



Interestingly, having positive surgical margins didn't dramatically alter the prospects of cure in men with Gleason grades of 6 or lower, even if the cancer had reached the edge where the tumor was removed. However, in men with Gleason grades of 7 or higher, having a positive surgical margin may raise the risk of recurrence. Longer follow-up study of these men is needed to determine this, Walsh says.

Why doesn't radical prostatectomy cure every man? It's probably because the cancer has escaped the prostate before surgery, to the point where surgeons can't remove it all, in the form of invisible, impossible-to-detect, distant metastases -- microscopic, malignant flecks that have already left the main tumor (even before diagnosis), casting themselves into the bloodstream like dandelion seeds in the wind, taking root elsewhere in the body. (Yet, although surgery can't cure prostate cancer in these men, it reduces the many complications of advanced disease and may prolong survival in some men.)

"The bottom line of this long-term study," concludes Walsh, "is that surgery cures the vast majority of men with tumors that are confined to the surgical specimen. Fortunately, today with improved means for early detection, this means that most men diagnosed with prostate cancer can be cured with surgery."

Further Reading

"PSA Following Anatomical Radical Retropubic Prostatectomy: Patterns of Recurrence and Cancer Control." Urologic Clinics of North America, Vol. 24, No. 2, May 1997. Charles R. Pound, Alan W. Partin, Jonathan I. Epstein, and Patrick C. Walsh.

IN BRIEF: Prostate Surgery in Men with Positive Lymph Nodes

Conventional wisdom: Once cancer has escaped the prostate, it can't be cured. Therefore, putting a man with advanced disease through the rigors of surgery is cruel and, more importantly, not helpful.
This belief is why, for years, many physicians have gone to such painstaking lengths to make sure a man has curable disease before performing "curative" treatment -- radical prostatectomy. (Unfortunately, sometimes -- even when

cancer seems entirely curable -- it has already spread invisibly, microscopically into the lymph nodes, and this isn't discovered until well after the operation is over.)

This is the whole purpose of lymph node dissection, the procedure-before-the-procedure in which a man's pelvic lymph nodes are checked for the presence of cancer while he lies sedated on the operating table. If cancer is found, many -- but not all -- surgeons simply sew up the incision they just made, genuinely believing it's kinder to spare the patient the rigors of a tough operation. And the poor patient? Having prepared himself for surgery and its complications, hoping for a cure, he wakes up to a terrible psychological blow: He's got an abdominal incision to recover from -- but his prostate and his cancer are still there. Nothing's changed, except perhaps the hopeful part of the picture for him.

Maybe the conventional wisdom is wrong. Results of a new Johns Hopkins study suggest that in stage D1 prostate cancer, radical prostatectomy not only averts many complications and improves quality of life -- a finding Hopkins surgeons have previously published -- but it may prolong life, as well.

For the study, the investigators looked at 168 men with stage D1 disease diagnosed between 1983 and 1995. Of these, 127 had a lymph node dissection and a radical prostatectomy (most of these men turned out to have microscopic lymph node metastases); 41 underwent the lymph node dissection alone (the situation described above). Reviewing the patients in each group, "we found 19 perfectly matched pairs of men," says urology resident Jeffery A. Cadeddu, M.D., who presented these results at the 1997 annual meeting of the American Urological Association. "Men had the exact same age, PSA score, Gleason grade, clinical stage, follow-up and amount of cancer in the lymph nodes. The only difference was that, in each pair, one man had the surgery, one man didn't."

Many complications in advanced prostate cancer arise from the physical presence of the prostate: As the cancer grows, men often develop such problems as urinary retention and obstruction, blood in the urine, kidney and bowel trouble. Men with advanced cancer who have undergone a radical prostatectomy rarely have these problems; from this standpoint, their quality of life is better.
But do they live longer? This study suggests that they may. Ten years later, only 34 percent of the men who had the lymph node dissection were still alive. But 56 percent of the men who had the radical prostatectomy were still alive -- "a big difference in survival," says Cadeddu.

He hastens to add that this is merely the first salvo -- that a much larger study is needed, that there are too few patients here to make a generalization for all men with lymph-node-positive prostate cancer. But: "I would say it's a strong suggestion that there may be a role for radical prostatectomy even in advanced disease."

Further Reading
"Stage D1 (T1-3, N1-3, M0) Prostate Cancer: A Case-Controlled Comparison of Conservative Treatment Versus Radical Prostatectomy," presented at the 1997 annual meeting of the American Urological Association. Jeffery A. Cadeddu, Alan W. Partin, Jonathan I. Epstein, and Patrick C. Walsh.

IN BRIEF: "Free" PSA is Earliest Marker of Prostate Cancer

As enzymes go, PSA (prostate-specific antigen) is kind of feisty; it actively attacks proteins at every opportunity. In the bloodstream, however, it's usually on its best behavior -- with the help of strong-armed inhibitors that prevent it from breaking down proteins. It's tied up, or "bound." Some PSA molecules, however, are still on the loose: They're "free."

Hopkins scientists are working to characterize the forms of PSA in the bloodstream -- to tell whether it's bound or free, measure each part, and determine what these levels mean over time.
Once study, led by urologist H. Ballentine Carter, M.D., involved a massive data base called the Baltimore Longitudinal Study of Aging. (Since it was begun in 1958, about 1,500 men have participated in this study, returning every other year for physical examination and a battery of medical tests. Their blood samples from every check-up are stored for future studies.)

The investigators looked at men who developed prostate cancer, and those who didn't. "And we found that the percent of free PSA indicated who had prostate cancer long before the (total) PSA level did," says Carter. (Currently, the test doctors use to measure PSA detects all of it -- both the bound and unbound molecules -- without saying which is which.)

Tracking blood samples back two decades before these men ever developed prostate cancer, Carter followed long-term changes in both total PSA and free (also called "percent free," because this is a fraction) PSA. "It turns out that percent free PSA was actually the earliest marker of prostate cancer," says Carter. In linear charts tracing what happened to PSA levels over the years, "the interesting thing is that, as you get closer to the diagnosis of prostate cancer, the percentage of free PSA falls. It's lower in men who have prostate cancer than in men who don't have it." In other words, men who develop prostate cancer have more bound PSA, and fewer of the free molecules.

This finding prompted another question: Do men with more aggressive cancer have a lower percentage of free PSA than men with less aggressive tumors? "We defined aggressive cancers as Gleason scores of 7 or greater, or men who were diagnosed with metastatic disease," says Carter, "and found that percent free PSA could discriminate between aggressive and nonaggressive cancer a decade before these men were ever diagnosed. But total PSA could not."

One day, with more specific PSA tests capable of quantifying different forms of the molecule in the bloodstream, it may be possible to detect aggressive cancers -- ones that will need aggressive treatment -- sooner.

Further Reading
"Longitudinal Analysis of Free and Total PSA," Urology, Vol. 48, pp. 4-9, 1996. H.B. Carter, et al.

Yearly PSA Tests: Do All Men Need Them?

Your level of PSA (prostate-specific antigen) is 1.5 -- just like it was last year, and the year before that. Your yearly rectal exam was normal. Do you need a PSA test next year?

Probably not, says urologist H. Ballentine Carter, M.D. Recently, he looked at the long-term PSA measurements of 312 men who participated in the Baltimore Longitudinal Study of Aging. (Since it was begun in 1958, some 1,500 men have participated in this study, returning every other year for physical examinations and a battery of medical tests. Their blood samples from every check-up are stored for future studies.) With this treasure trove of data, Carter says, "we could go back and look at early PSA levels in men with and without cancer, and then look to see how quickly those men reached a PSA that was abnormal" -- higher than 4.

"Our questions was, for men with really low PSA values, would it be safe to wait more than one year to repeat this test?" If so, some $126 million could be saved every two years in men between ages 50 and 70, Carter estimates.

"We looked at how quickly these men reached the PSA level of 4, depending on what their starting level was. And it

turned out that if you started with a PSA level less than 2, there was no reason to repeat the PSA the following year, because no one reached a PSA of 4 in one year. It took two years, and only a very small percentage of people even did so in two years."

However -- even though men would still receive a yearly rectal examination -- would it be safe to wait an extra year for the PSA measurement? Would any cases of significant prostate cancer be missed? So Carter did a further study, on a data base of 389 Hopkins patients, conservatively defining a curable tumor as Gleason 6 or below, and being confined to the prostate.

His findings: "If you have non-palpable cancer (in other words, a tumor that can't be felt on a digital rectal examination) and a PSA less than 4, there is a 95 percent chance that you have curable cancer. There's also a 50 percent chance you may have an insignificant tumor (which may never need treatment). If you have a non-palpable tumor and your PSA is between 4 and 5, there's still a 90 percent chance that you have a curable tumor -- but only a 19 percent chance that you have insignificant cancer."

In the past, Carter says, "our approach has been, the more cancers we pick up, the better. But this approach is designed to optimize the detection of curable, and at the same time, significant cancers."

Genetic Susceptibility to Prostate Cancer: Are African Americans More Vulnerable?

Prostate cancer hits some groups of men much harder than others. It's much more common in African Americans, for instance, than in Asian men. Could it be that black men in this country are somehow more susceptible genetically than white or Asian men?

Scientific evidence suggests that the development of cancer is like a toppling row of dominos, in that a whole chain of genetic events must occur before a tumor can begin to grow. Inherited mutations in one or more genes (as believed to be the case in hereditary prostate cancer) probably speed up the body's journey toward cancer; presumably, in some men, a few of these dominos are already downed at birth. Environmental variables such as diet -- what men eat and drink and how they live -- may knock over the rest.

Somewhere in between these two is genetic susceptibility: Not exactly a mutation that causes cancer, but a genetic makeup that creates a more hospitable atmosphere -- which makes it easier for cancer to set foot in the door. In the domino analogy, perhaps genetic susceptibility tilts the table slightly, making the dominos more likely to fall, without actually knocking them over.

Evelyn R. Barrack, Ph.D., believes a slight variation she's found in the androgen receptors of men with prostate cancer -- the main switch plate through which the prostate is controlled by hormones -- may make men more susceptible to developing prostate cancer, and particularly to developing more aggressive disease. This variation, a "short repeat" in a sequence of proteins, is more common in African American men -- and may help explain why these men are at higher risk of developing prostate cancer. It's also more common in Caucasian men with clinically localized prostate cancer (cancer that appears to be curable) who are found after surgery to have micromestases -- tiny bits of cancer that have escaped the prostate and taken root elsewhere.

This short repeat may make testosterone more efficient in prostate cells, so that the same amount of testosterone goes further, and has more of an effect than in other man. It may be that men with longer repeats have better cancer-suppressing "brakes," -- better checkpoints for controlling cell division -- and men with the short repeat are

more susceptible to developing prostate cancer -- and to developing a particularly nasty, more aggressive form of the disease.

Further Reading
"Androgen Receptor Gene Structure and Function in Prostate Cancer," World Journal of Urology, Vol. 14, pp. 329-337, 1996. Jeanette M. Hakimi, Rachel H. Rondinelli, Mark P. Schoenberg, Evelyn R. Barrack.

Radical Prostatectomy in Men Younger than 50

Hardly any men -- only around 1 percent -- diagnosed with prostate cancer are younger than 50. Unfortunately, because of their age, prostate cancer is rarely even suspected; because the disease is often advanced by the time it's diagnosed, radical prostatectomy is seldom on option. (However, with increasing recognition of hereditary prostate cancer this is expected to change, as more men at high risk begin prostate cancer screening earlier, in their forties).

Mainly because of sheer lack to numbers, men younger than 50 have been something of a little-known and poorly studied quantity in the world of prostate cancer research. Is the disease more aggressive in younger men? Is it slower-growing? How do these men fare after radical prostatectomy?

Recently, several investigators, led by pathologist Jonathan I. Epstein, M.D., and Urologist-in-Chief Patrick Walsh, M.D., set out to answer some of these questions in a study of 542 radical prostatectomy patients at The Johns Hopkins Hospital. There were 85 men younger than 50 (three of them younger than 40), and 458 men aged 50 or above (the oldest was 76 years old). By far the largest study ever done of men in this age group, this analysis was also the most thorough: The researchers took into account each man's clinical stage, Gleason score, and surgical margins (in other words, they examined the edges of the tissue that was removed during surgery, and looked for the presence of cancer there); they also checked for capsular penetration, seminal vesical and lymph node involvement, and followed PSA tests for at least three years.

Their findings: Younger men who are candidates for radical prostatectomy don't have a worse prognosis after surgery than older men. In fact -- although the nerve bundles, which are responsible for erection, are more often preserved -- they fare even better.

"The operation is more successful because these men have smaller prostates," says Walsh. "There is more tissue surrounding the prostate, so the margins of resection are wider; also, the neurovascular bundles are located farther away from the prostate, and are easier to preserve. This provides a win-win: An excellent chance for cure, with improved quality of life."

Further Reading
"Radical Prostatectomy in Men Less than 50 Years Old," in Urologic Oncology, 1995, pp. 80-83. Maureen A. Riopel, Thomas J. Polascik, Alan W. Partin, Jurgita Sauvageot, Patrick C. Walsh, and Jonathan I. Epstein.

Honors and Awards: Hopkins Receives SPORE Grant

Hopkins is one of only three centers in the U.S. to be awarded a coveted SPORE grant (for Special Projects of Research Excellence) by the National Cancer Institute, for research on prostate cancer. Several dozen medical institutions apply for these esteemed grants, which are given to comprehensive programs adept at translating

research from the laboratory to the bedside, and resolving questions from the bedside in the laboratory. For its work -- judged in competitive review by top experts in prostate cancer research -- the team led by research director Donald S. Coffey, Ph.D., scored highest in the country.

Also, eight of our scientists have been honored with awards for promising new studies in prostate cancer by the Association for the Cure for Cancer of the Prostate (CaPCure), founded by Michael Milken shortly after his own diagnosis with the disease. They are:

- John Isaacs, Ph.D., for his study, "PSA-based Prodrug Therapy for Androgen-Independent Prostatic Cancer."
- William Isaacs, Ph.D., and G. Steven Bova, M.D., for "Identification of the Molecular Determinants of Lethal Disease in Prostate Cancer: A Comprehensive Autopsy Study."
- Hyam Levitksy, M.D., for "Induction of an Immune Response to Normal Prostatic Antigens as an Immunotherapeutic Strategy or Prostate Cancer."
- Joel Nelson, M.D., for "Endothelin-1: A Therapeutic Target for Metastatic Prostate Cancer."
- William Nelson, M.D., Ph.D., for "Combination Chemotherapy and Immunotherapy of Metastatic Prostate Cancer."
- Jonathan Simons, M.D., for a pilot study, "GM-CSF Therapy in Prostate Cancer Patients."
- Patrick C. Walsh, M.D., for "Hereditary Prostate Cancer."
- Donald S. Coffey, Ph.D., Director of Research, has been elected President of the major cancer research organization in the United States, the American Association of Cancer Research.
- Patrick C. Walsh, M.D., David Hall McConnell Professor and Director of the Department of Urology, has been awarded the distinguished Charles F. Kettering Prize for his innovations and contributions to prostate cancer. Sponsored by the General Motors Cancer Research Foundation, this prestigious award is given to people who have made the most outstanding contributions to the treatment of cancer. For his achievements, Walsh has also been awarded the Hugh Hampton Young Award by the American Urological Association, and the Barringer Medal by the American Association of Genitourinary Surgeons.

After Radical Prostatectomy: When Surgical Margins are Positive, or Too Close to Call

In an ideal world, after radical prostatectomy, the pathologist would send a triumphant report to the surgeon: "I've looked at the prostate tissue you removed from Mr. Jones, and all of the edges are clear. Congratulations! You've removed all the cancer!"

Most often, it happens that way. Sometimes, however, the pathologist's report is more ambiguous: Either the margins -- the edges of the removed tumor -- are "positive," meaning they show cancer cells, or they're "close," meaning cancer is just a hair's breadth away from the edge of the specimen.
Hopkins pathologist Jonathan I. Epstein, M.D., who has probably looked at more radical prostatectomy specimens than anyone in the world and is an expert at interpreting how prostate cancer cells look, has good news about margins:

Close margins are almost always negative. Epstein recently finished a study of patients whose tumors were particularly close -- less than two tenths of a millimeter -- from the surgical margin, the edge of the removed tissue. Even though there wasn't a comfortable cushion of tissue between the tumor and the edge of the prostate, "those patients do just as well as if there's more separation between the tumor and the margin."

And, even if the surgical margins are positive, this does not necessarily mean that the cancer is left behind. How can this be? "There are several different explanations why, when the margins are positive, the tumor may still be cure,"

says Epstein. “One is that literally you cut across the last few tumor cells” -- that what appears to be remaining cancer is actually a cross-section of the perimeter of the tumor. “And even though it looks like it’s a positive margin, there’s really nothing left in the patient.”

Another explanation is that the act of surgery itself finishes the job, killing any remaining cells. No cut or injury to tissue happens in a vacuum; the area around the cut is affected, too. (Think of lightning striking a tree; the tree dies, but so does a ring of grass around it). “When the surgeon cuts across tissue the blood supply is cut off, there’s dead tissue, and that can kill off the last few tumor cells that might have been left behind,” Epstein says.

There’s also potential -- “and this probably accounts for a lot of cases” -- that it’s an “artificial” (basically, a fake) positive margin. Sometimes, “since there’s so little tissue next to the prostate, when the surgeon tries to dissect it from the body, and he hands it to the nurse, and then the nurse hands it to the pathologist, and everyone’s kind of touching the gland, and if you’re talking about two tenths of a millimeter of tissue, that tissue can get disrupted very easily. It can appear that the tumor is at the margin -- but in fact, there was some additional tissue there that just got disrupted during all the handling of the specimen.” In other words, a few good “buffer” cells got rubbed off.

And then there’s the “sticky cell” phenomenon. When cancer reaches beyond the prostate to invade nearby tissue, it produces a dense scar tissue that acts, as surgeon Patrick C. Walsh, M.D., describes it, “like Super Glue.” As a surgeon removes the prostate, this thick scar tissue sticks to the surrounding cancer cells -- picking them up like a lint brush. So in some cases, although the pathologist may see cancer cells at the margin -- and make a judgment of “positive surgical margins” -- there are no cancer cells left inside the patient. The sticky scar tissue took them all away.

Epstein recently studied such instances, when Walsh removed the prostate, looked at it, suspected that some cancer cells were present, went back and cut out more of the surrounding tissue. “So in pathology, we got two separate specimens,” says Epstein. “One was the prostate, one was this extra tissue, the neurovascular bundle that he was thinking of leaving in the patient, but decided to remove.” Even when there appeared to be a positive surgical margin at the edge of the prostate, in 40 percent of these patients there turned out to be no cancer left behind in that adjacent tissue.
“So when pathologists call a positive margin, or for that matter, a close margin, it doesn’t necessarily mean that these patients need some other form of therapy, like radiation,” says Epstein “and also that they need not necessarily be tremendously worried.”

But what if a positive margin does mean that there’s still cancer in the area? Many of these men may still be cured with radiation to the prostate bed, the area where the prostate used to be. Here is where other factors come into play. For more on these, and who might benefit from radiation, see the next story.

When PSA Goes Up After Surgery

Is it Local Recurrence? Distant Metastasis? Would Radiation Help?

The return of PSA to the bloodstream after radical prostatectomy is a terrifying prospect for men who have already undergone so much: Stressful diagnosis of prostate cancer, difficult surgery to treat it, and then the big waiting game -- living, as one patient comments, “from one PSA test to the next,” hoping the coast will finally be declared clear.

Perhaps worst of all is the uncertainty created by PSA’s reappearance: If the cancer is indeed back, is it still localized to the prostate, or has it spread elsewhere? Could radiation therapy eradicate the disease -- or would it just cause new

complications by needlessly treating an area already free of cancer?

Two studies by Hopkins researchers have shed much light on these troubling questions. The first, led by urologist Alan W. Partin, M.D., Ph.D., studied rising PSA levels in 51 men after radical prostatectomy. In 30 percent of these men, cancer returned locally, in 70 percent, the cancer showed up in distant metastases. Based on this study, the scientists found they can estimate which course the cancer will take using the combination of Gleason score, pathologic stage (the definitive extent of a man's cancer, determined after surgery, when a pathologist looks at the actual prostate specimen and dissected lymph nodes, if any), and timing -- when the PSA starts to rise, and by how much.

Men most likely to benefit from radiation after prostatectomy:

- Gleason score of 7 or lower and
- Negative seminal vesicles and lymph nodes and
- Recurrence of PSA more than a year after surgery

Men most likely not to benefit:

- Gleason score of 8 or higher or
- Positive seminal vesicles or lymph nodes or
- PSA recurrence within a year after surgery

Men most prone to distant metastases, they found, will have one or more of these conditions: Gleason scores of 8 or higher, cancer found in their seminal vesicles and lymph nodes during surgery, or a rise in PSA within a year after their surgery. On the other hand, men with Gleason scores of 7 of lower, low pathologic stage and/or increases in PSA several years after surgery most likely will have only a local recurrence of cancer -- which means their cancer may still be cured with external-beam radiation treatment to the prostate bed, the area where the prostate used to be, where some residual cancer cells may yet be hiding.

The next study confirmed these findings, and took them one step further: It actually followed the men through radiation therapy: "We found that no man with a Gleason score of greater than 7, positive lymph nodes, or positive seminal vesicles responded favorably to radiation therapy," says urology resident Jeffery Cadeddu, M.D., who presented the results of the second study at the 1997 annual meeting of the American Urological Association. "So in those patients, we do not recommend radiation therapy."

But, even if it couldn't reach a distant metastases -- a chunk of cancer that has broken off from the main tumor and established itself elsewhere -- couldn't radiation do some more good to the prostate bed? Could it buy any time at all? For a man with metastatic disease, irradiating the pelvis -- ironically, an area where the cancer probably is not -- "does not change survival," Cadeddu says. In addition, radiation therapy to the pelvis in a man, who has undergone a radical prostatectomy may cause incontinence and diminish sexual function. Conversely, for men with a Gleason score of 7 or less, and negative seminal vesicles and lymph nodes, the longer the period before PSA starts to rise, the better the odds that radiation therapy will be worthwhile.

This study also had an unexpected finding: If radiation therapy in men with elevated PSA levels was delayed until the local recurrence was palpable (if it was big enough for a doctor to feel), these men appeared to do just as well as those who received radiation earlier. If this finding is confirmed in other studies, it might simplify at least one immediate treatment decision in men with elevated PSA levels: The best course may be simply for doctors to follow these men closely; and then, if they develop local recurrence of cancer, to treat them with radiation therapy, or to begin hormone therapy if distant metastases are found.

Further Reading

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"Long-Term Results of Radiation Therapy for Isolated PSA Elevations Following Radical Prostatectomy," presented at the 1997 annual meeting of the American Urological Association. Patrick C. Walsh, Jeffery A. Cadeddu, Alan W. Partin, Theodore L. DeWeese.

An Enzyme that Holds the Key to Immortality

Hopkins Researchers, searching for an Achilles heel -- for any tiny chink in prostate cancer's impressive armor -- believe they've found a promising candidate in a fascinating enzyme called telomerase.

Prostate cancer is a fearsome foe, whose worst cells are, for all practical purposes, immortal -- ultimately impervious to treatment, once cancer has spread to the lymph nodes or bone.

But Hopkins researchers, searching for an Achilles heel -- for any tiny chink in prostate cancer's impressive armor -- believe they've found a promising candidate in a fascinating enzyme called telomerase. One day, understanding what this enzyme does may unlock riddles far beyond the prostate -- perhaps even expanding our grasp of how the body ages, and why it does.

Donald S. Coffey, Ph.D., Director of Research

And one day, cracking its mysteries may enable scientists to turn prostate cancer into vulnerable -- and killable -- mortals again.

"Every cell in the human body ages, and after a specific number of divisions, dies," says Donald S. Coffey, Ph.D., director of research. "Only the cancer cell has broken through this aging barrier. This means that these cells are capable of dividing on, and sustaining themselves, forever."

Think of a normal cell as a candle with a wick; in this case, the wick is a long strand of DNA. With every cell division, this wick shrinks a little; it loses a small piece of DNA. When this wick becomes too short, the cell dies. "This provides the counting mechanism for the biological clock," Coffey explains.

But in cancer cells, the wick doesn't get any shorter -- because of telomerase: This enzyme keeps replacing the DNA at the end of the strand, so there's not countdown. Like Dorian Gray, the cell never ages.

Coffey and colleagues have shown that telomerase is active in human prostate cancer cells, making them immortal. But it's not switched on in BPH (benign prostatic hyperplasia), and in normal prostate cells.

Say you have a manuscript, says Coffey, "and on the front and back of the manuscript, you have 50 white, blank pages." The blank pages are filler -- meaningless, repetitive chunks of DNA that act as cushions for the really important part, the fragile genes inside. "Each time you go into the xerox room, you lose one of these pages. Every time you make a copy of the manuscript -- in other words, a new cell -- you lose a page. After you lose it down to a certain length, the cell becomes unstable and dies, and that's aging.

"Now, in cancer, somebody stands at the door of that room, and each time you go in, adds a new sheet onto the front and back." So for every sheet lost, one is gained, and the cell remains stable. "The white, blank pages are telomeres, the repetitive DNA at the end of each chromosome, and that person standing at the door is telomerase."

Coffey and colleague Alan Meeker are using a highly sensitive assay that can detect telomerase in as few as 10 cells, and works in needle biopsies of the prostate. Why is this important? Because currently, needle biopsies -- although much improved in recent years -- don't always give definitive answers. Sometimes the needle misses the cancer;

sometimes what's under the microscope is almost impossible to label definitely as cancer. And even if cancer is seen in a few cells, is it the "good kind," so-called "incidental" cancer that, in millions of men, doesn't do much, but just sits in the prostate for decades? (In other words, could a telomerase test help determine if a man can afford to wait on treatment?) Or is the "bad" kind, cancer that needs to be treated as soon as possible? One days, Coffey speculates, a telomerase assay may mark cells that are not only cancerous, but "on the march" -- and potentially headed out of the prostate. Such a test may take much of the confusion out of many treatment decisions.

Even more exciting: If somehow telomerase could be blocked -- so cancer cells age and die like other cells -- then this might even be a way to make even advanced cancer curable one day. Says Coffey: "This could be an important target for future therapy."

Further Reading

"Telomerase Activity, a Prevalent Marker of Malignant Human Prostate Cancer," Cancer Research, Vol. 56, p. 218, 1996. H.J. Sommerfeld, Alan Meeker, Donald S. Coffey, et al.

Can Prostate Cancer be Prevented?

Consider the average American man at middle age, after a lifetime of the typical high-fat, low-fiber, vegetable- and fruit-poor "Western" diet. Throw in a genetic curve ball -- a family history of prostate cancer -- plus advancing age, which also increases risk. If he's ever going to develop prostate cancer, now is probably the time; he's ripe for it. In fact, it may already be percolating away inside him, as it is in so many American men -- more than 300,000 will be diagnosed with prostate cancer this year alone.

Now, say that man is Asian, and he's spent his life there, perhaps in mainland China. His risk of developing prostate cancer is the lowest in the world. Unless, of course, he chooses to immigrate to this country -- in which case, over time, his cancer risk will rise to the level of an American man's.
Clearly, although no one knows all the factors involved in developing prostate cancer, environment -- and this mostly means diet -- is terribly important. Why is this? What do Asians do right -- and what do Americans do wrong? Is the Western diet guilty of sins of commission -- too many french fries and hamburgers -- or omission -- not enough broccoli and carrots? And more importantly: If the Asian diet does, indeed -- as many scientists suspect -- contain cancer-thwarting agents, is it possible to figure out what those are and use them here -- to shore up the body's defenses and perhaps even ward off prostate cancer before it begins?

Oncologist William G. Nelson, M.D., Ph.D., and urologist James D. Brooks, M.D., think that one day, if they can find the right dietary agent, it will be possible to prevent prostate cancer. The key, they believe, lies in bolstering a crucial enzyme that's knocked out early in a man's journey toward prostate cancer.

In the genetic battle that happens years or even decades before prostate cancer even becomes detectable, glutathione-S transferase p -- a scavenger enzyme whose job it is to protect cells by disarming their enemies -- is one of the first casualties. Like Barney Fife, it is a well-meaning but vulnerable hero with a limited arsenal -- as Fife had only one bullet, this enzyme's weakness seems to be the switch that controls it. Unable to withstand the tide of cancerous genetic changes, this switch fails startlingly early (a discovery made by graduate student Wen-Hsiang Lee, Nelson, and Brooks in 1994.)

"This enzyme protects normal cells against bad things," says Brooks, "including things that damage the DNA and cause cancer. It gets turned off very early in the genesis of prostate cancer. It looks like this occurs in PIN" (PIN is prostate intraepithelial neoplasia, "funny- looking" cells that are strongly linked to prostate cancer and considered

by some to be precancerous) -- even though the enzyme is present in normal prostate cells sitting right beside the abnormal ones. "It also looks like this happens in patients who have familial prostate cancer. So this is a change that's germane to prostate cancer: The enzyme has been gone from every single prostate cancer cell we've looked at -- which is the most common genetic change anyone has found yet."

Normally, the enzyme, found in every cell in the body, works by sopping up hazardous materials and neutralizing them -- toxic cleanup, on a cellular level. "It's just a teeny, weeny thing," says Brooks, "a little protein that will take toxins, in whatever form they may be, and inactivate them by hooking another chemical onto them. That chemical is glutathione" -- thus the "transferase" part of the enzyme's name. (Actually, the body's toxin-fighting arsenal includes a host of enzymes, and several different glutathione transferases).

So, how to strengthen glutathione-S transferase pi and its toxin-fighting comrades, so they can stand up to cancer? Nelson and Brooks believe the best "drug" for this may be some dietary agent that's been there all along -- if they can just figure out what that is. They have some good candidates, and they're narrowing their choices for clinical trials that they hope to begin soon. Here's how they got to this point:

How the work began: The search for adjuvant therapy:
In some forms of cancer, a mainstay of treatment is adjuvant therapy, a tough regiment of chemotherapy -- usually, high powered drugs that have shown some success at fighting cancer that's far more advanced -- given at the time of surgery in an effort to keep the tumor from coming back. "The hope is to kill cancer cells that have spread throughout the body, even though you can't see them," says Nelson. Usually, he adds, "when cancer comes back after the initial treatment -- and this is certainly true for prostate cancer -- it's not a failure of the surgical or radiation therapy. It's because the man had small, undetectable deposits of metastatic cancer before he ever shook hands with the surgeon."

There is no good adjuvant treatment for prostate cancer -- no all-powerful drug able to kill these lethal micrometastases while they're still tiny, still invisible. So, several years ago Nelson began looking for one. He was intrigued by a drug called melphalan, which used to be given at the time of surgery for breast cancer. Although, because of it's side effects, it has since been dropped in favor of better drugs, "it was effective, and it did improve the outcome of women undergoing surgery," he says. "The thing that struck me is, if you look at the behavior of melphalan when it's given to women with very advanced breast cancer, it's actually an extremely poor drug. It was not a good advanced treatment, yet it was a good adjuvant treatment."

Could this be because early and advanced cancer -- like the Mississippi as a trickle in Minnesota, versus the raging river that roars past New Orleans -- are two distinct things? "Early cancer may be a different beast entirely," says Nelson. "Or, at least, the way you cure it may be different." So, in a feat of scientific detective work, he began delineating the cell changes they found in early-stage, curable tumors (removed by surgeon Patrick C. Walsh, M.D., during radical prostatectomy) and in late-stage, metastatic disease. One change they noticed was that, as cancer advances, it often develops a "clever and nasty" chemical pump, called p-glycoprotein, which can expel certain cancer-fighting drugs from its cells almost immediately.

"But the cancer cells might not be so clever early on," Nelson notes. Maybe, they thought, if a drug could somehow beat the clock -- and get into the cells before this ejector button develops, it might have a better chance of working. Their search for other "bad" defense mechanisms led them to glutathione-S-transferase pi. Researchers at the National Cancer Institute had discovered the enzyme, and tracked its reactions in cancer cells exposed to low doses of a chemotherapeutic drug; gradually, the cancer cells were exposed to higher levels of the drug until they became completely immune to them. "They were totally resistant," Nelson says. "They could grow even though the drug was around. What those cancer cells did was two things: First, they made a lot of p-glycoprotein, so they pumped the drug out. The other thing they did was, all of a sudden, they made a lot of glutathione-S transferase pi." Was this enzyme a cause of drug resistance? In breast cancer, scientists had learned that when a woman's tumor makes a lot of

glutathione-S transferase pi, adjuvant chemotherapy isn't nearly as effective as in women whose tumors make less of it.

"We decided to check it out, and we found that prostate cancers basically never make it," Nelson says. "The reason this is curious is that most cancers make a ton of it at the earliest stages." When a rat develops liver cancer, "the first thing that happens is that liver cells crank up this enzyme as high as they can. Some people think this is the last-ditch defense -- that the last thing the cell did before it became a cancer was to turn up this enzyme. If the cells become cancerous, most of them still have this enzyme cranked up."

Except in prostate cancer. "So then we thought," Nelson continues, "Is it possible that one of the reasons you get prostate cancer bay be that you can't turn up this enzyme?" Normal prostate cells make glutathione-S transferase pi. So why not prostate cancer cells? "They can't, says Nelson, "because the cancer basically killed the gene, inactivated it so it can't be turned on." If cancer is a series of steps -- or, as Nelson puts it, "genome mistakes, where genes are inactivated and other genes are mutated," this step, eliminating glutathione-S transferase pi, is apparently one of the first -- creating a more hospitable environment for cancer by knocking out one of the bouncers at the door. "You might imagine that a normal prostate cell, if it lost this enzyme, all of a sudden it's vulnerable," says Brooks. "Without this means of protecting itself, now it's susceptible to some carcinogen; it can't detoxify it anymore."

Where diet comes in

So: If a crucial enzyme can be eliminated, can the process work in reverse -- can it be built up, instead?

More than 30 years ago, scientists found that they could stimulate cancer-fighting enzymes in animals by giving them very low doses of carcinogens (cancer-causing agents). "It kind of makes sense," says Brooks. "Here's a toxin that's going in the body at very low doses, and the body's responding to it the way it usually handles toxins -- whether it be from a carcinogen or some charred food, something bad that you eat, the body responds to it by turning on these enzymes."

Recently, Hopkins scientist Paul Talaly, M.D., found that ordinary foods (particularly, broccoli) could also stimulate some cancer-fighting enzymes -- so much so, in fact, that cancer could actually be prevented in animals. For Nelson and Brooks, the puzzle of glutathione-S transferase pi suddenly began making sense: "What that made us wonder," says Nelson, "is, maybe this enzyme was really the critical player all along -- and if we'd had a lifetime of keeping it cranked up, maybe we wouldn't have eliminated it so easily."

Brooks has spent the last two years laboriously seeking dietary compounds that are prostate-specific -- that only stimulate enzymes in the prostate (so they won't be metabolized elsewhere before they ever reach the prostate). The goal is to find a substance that could be taken every day -- like quinine, years ago, to ward off malaria -- as prostate cancer prevention. "You turn on the enzymes by giving the dose over and over again," says Brooks. "And besides, if you think about cancer in general, it's probably a product of long-term exposure to bad things. A number of cancers occur late in life -- so it's probably the accumulation of a number of genetic 'hits' over a lifetime; it's probably a long-term exposure to badness. So if you're thinking about upregulating these enzymes, you probably have to do it over the long term."

The idea has much to recommend it, says Nelson. "If there is something, for instance, in the Asian diet that protects against life-threatening prostate cancer development indirectly, whatever it is that they're eating would be the world's greatest drug: Clearly, they must be able to take it for a lifetime, and without tremendous side effects."

Another bonus is that, traditionally, Americans do a better job of adding to their diet than taking away, Nelson says. "I'm worried that. As a giant public health strategy, if we were to say the problem is eating too many Big Macs, whether that would ever be a truly useful think to know. We already know that smoking cigarettes isn't good for you, and it hasn't helped that much. I think's it's going to be hard to change us into a vegetable-crunching society. But

if I could tell you that eating soybean curd twice a week, or something like that, would keep you from ever getting prostate cancer, I believe people would do it. So I just like the idea of trying to figure out whether there's something in the Asian diet that's protective, because I think it'll be easy to supplement our diet as a preventive maneuver."

Would a man need to take this dietary supplement forever, or just during a crucial decade or two -- so the early stages of prostate cancer would develop when a man was in his eighties, instead of his sixties? Also, when should a man start taking it? High School? In his thirties? These and a host of other questions remain to be answered. Nelson and Brooks may begin the first limited tests of a dietary supplement -- once they have one selected -- within a few months.

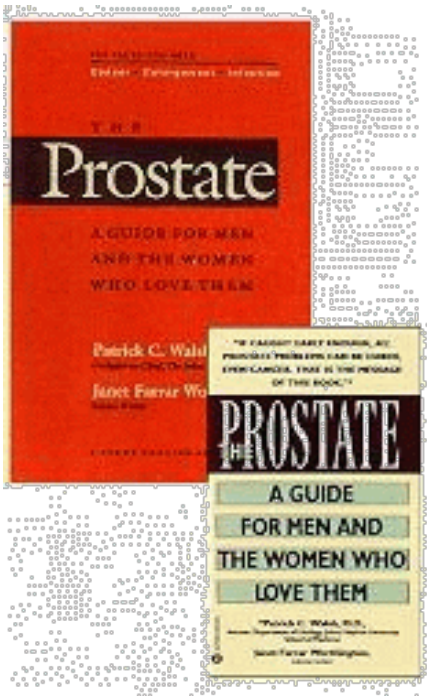
Everything You Wanted to Know About Prostate Cancer, But Couldn't Find in One Place

"Thorough . . . Easy to read. I urge urologists to read this book or risk facing a patient more knowledgeable than you."
--Mitchell Benson, M.D., in a review from the Journal of Urology

"Men wondering where to turn for treatment would do well to start their search by reading this important book, which is not only comprehensive and authoritative, but a model of clarity."
--William Whitworth, editor, The Atlantic Monthly

"Before Dr. Walsh, I wasn't even aware that I had a prostate. Now that I have read this book, I know all about it, and he and Janet Worthington made it so easy for me to understand. This is a book that the prostate did not want the public to see."
--Art Buchwald

"The diagnosis of a prostate problem is a terrifying thing, made worse by misinformation and myth. Men -- and the women who care about them -- will find no better guide than Dr. Patrick Walsh."
--John A. Meyers, Chairman Emeritus, TIME, Inc.



The Prostate: A Guide for Men and the Women Who Love Them, the best-selling health book written by Patrick C. Walsh, M.D., Urologist-in-Chief, and Janet Farrar Worthington, tells you everything you need to know about the prostate and its disorders, including detailed, ground breaking information about every stage of prostate cancer.

Gene Therapy: Fighting Fire With Fire

Hopkins researchers have been learning about prostate cancer cells, cracking their secret code, and developing ingenious ways to change and even fool them.

Prostate cancer cells are cunning: One of their first official functions of advancement is to cloak themselves -- in effect, by knocking out the enemy's radar screen -- so the body won't spot them as foreign invaders.

All warfare is based on deception, wrote the great Chinese general Sun Tzu 2,500 years ago in The Art of War: "if you know the enemy . . . you need not fear the result of a hundred battles." Over the last few years, Johns Hopkins researchers have taken this concept to heart -- learning about prostate cancer cells, cracking their secret codes, and devising ingenious ways to change and even fool them.

Imagine being able to program the body's DNA like a computer chip, sending it on a selective search-and-destroy mission targeted only at prostate cancer cells. This is what oncologist Jonathan Simons, M.D., and urology resident Ron Rodriguez, M.D., Ph.D., have figured out how to do in the laboratory.

Their goal is gene therapy -- using the body's own tools, DNA molecules, to treat cancer that can't be cured by surgery or radiation -- and they're coming at it from two angles: Genetically engineered "vaccines" made from a man's own cancer cells, and doctored viruses that can act as Trojan horses, slipping into the body, attaching themselves to prostate cancer cells and exterminating them before they even suspect anything's amiss.

A cancer "vaccine"

Several years ago, Simons began looking for a way to crank up the body's immune system, and so strengthen its ability to fight off cancer. The sophisticated recipe for his ex-vivo (Latin for "out of the body") work involves culturing a man's own prostate tissue removed during radical prostatectomy, irradiating the cells so they can no longer grow (this is similar to the "dead" vaccines used to treat such diseases as polio and measles), adding a key ingredient -- a gene called GM-CSF, which activates the immune system in unprecedented ways -- and then putting this concoction back into the body as a vaccine.

GM-CSF is a cytokine, in effect an "upper" for the immune system. "We're very enamored of it," says Simons, who, with Fray F. Marshall, M.D., Schwartz Distinguished Professor of Urology, conducted the first gene therapy trials at Hopkins, and was the first to show that it works in kidney cancer. "GM-CSF is the most powerful signal to the immune system known; it says 'Start to recognize me. I am a foreign invader.' So we can teach a patient's immune system to recognize the cancer cells that escaped before the prostate was removed." (Radical prostatectomy can't cure cancer if there are micrometastases -- tiny, invisible bits of cancer that have somehow escaped the prostate and set up shop elsewhere. These are the seeds of lethal cancer, and these are the unseen enemies gene therapy is designed to find and kill.) "In concept, it's a form of adjuvant therapy, with part of the drug being the patient's own cancer."

Why is this needed? Why does the immune system need help to recognize something that's been growing right under its nose? Because prostate cancer cells make it their business to disable GM-CSF as soon as possible. "They don't want to be recognized," Simons says. "Cancers don't make GM; if they did, we probably wouldn't have cancer. They make sure that it gets turned off," one of a series of sneaky maneuvers in a "stealth apparatus" that Simons has identified.

The trick, Simons continues, "is to get a high-enough dose, and have the best ratio of lowest amount of cancer to the maximum amount of immune response."

Although there's some "very exciting early evidence" in the handful of patients participating in early tests of this gene therapy, "it's still very much in its infancy," Simons cautions. "We've gone beyond the Wright brothers -- in the sense that we're sure that it looks interesting, we can fly the thing up and down the coast, but we're not up to Lindburgh yet."

Ron Rodriguez, M.D. (left) and Jonathan Simons, M.D., Ph.D.

One challenge is simply making enough of the drug per patient -- and for now, this depends entirely on who much the tumor scientists are able to extract from the prostate specimen. "Many patients have less than a gram" -- about a thumbnail's worth of tumor. "It's lethal as anything, but that's not a lot, as it turns out," in terms of having enough vaccine-making material to work with. To solve this problem, Simons is working to make a more generic, less patient-specific vaccine.

A "Magic Bullet?"

Which brings us to the in-vivo (for "in the body") work. Ron Rodriguez, who's leading this effort, envisions a "shot" for cancer that would work even in advanced disease. "What can you do now for a man with advanced disease? Well, you can give him hormones, but the effect doesn't always last long enough," he says. "So this is a strategy to try to help those patients who are going to die of their disease, because today there's not cure for it when it's at that stage."

Enter the adenovirus, an upper respiratory virus -- at least, that's what it looks like on the outside. On the inside, it's a souped-up, cancer-killing machine, genetically engineered to deliver its special surprise package only to cells that make PSA (in other words, prostate cancer cells). "What we've done," says Rodriguez, "is to make the virus so that it only replicates in prostate cells, and when it replicates, it lyses (destroys) cells."

In the laboratory, Rodriguez and Simons (using viruses provided by a company called Calydon) remodeled the virus so that it's controlled by the PSA promoter, a small stretch of DNA near the PSA gene in the body. (The PSA promoter acts as a chemical switch that governs how PSA is produced.)

So, unlike chemotherapy, which often tends to have a "buckshot" approach -- killing everything, good and bad, in range, with limited effect in prostate cancer -- the virus acts like a high-powered rifle with only one target in its sights -- PSA-making cells. In other cells, it can't be turned on; with no point of entry, it just brushes past, looking for the next PSA-making cell. "And the effect, at least in animal models so far, is that we've been able to completely cure tumors that are quite large with a single injection," says Rodriguez. "A one-centimeter tumor is a huge amount of tumor, grossly out of proportion to body size for a little mouse, and that's how much we're able to cure." (For this work, Rodriguez won the American Urological Association's 1997 Research Essay Prize.)

Unlike the vaccine, the virus is not patient-specific; theoretically, it will work in any man with PSA-making cells. The elegance of this approach is that it simply doesn't matter whether a cancer cell responds to hormones or is hormone-resistant. "The only thing that matters is whether the tumor cells are capable of producing PSA." Even though, as cancer progresses, some cells become streamlined and lose their ability to make PSA, "the good news for us is, we're pretty convinced that they don't get stripped-down so low that they don't make any," says Simons. ("But they definitely make less," he adds -- and this is another "stealth" technique.)

A virus -- any virus -- works like a terrorist in the body: Like the Trojan horse, it invades an unsuspecting cell, overpowers its defenses, and co-opts its machinery to do the virus's bidding. When it's consumed all the cell's resources -- stripping it clean, like a locust in a wheat field -- and has no more use for the cell, it destroys it and moves on. Normally, when the body realizes that a virus is on the loose, it sends its own powerful home guard -- warrior cells in the immune system -- to fend off the intruder. The body almost always wins (except for a few stark, lethal exceptions, such as HIV, the AIDS virus). So one bonus with engineered adenovirus is that, once the body discovers its presence, "you've activated the immune system to come in and clear the virus, and you may be able to get autoimmunization against your tumor." Although it's still theoretical, the idea here is also to enlist the immune system -- perhaps through techniques learned from the vaccine work described above -- to help the virus on its mission.

Rodriguez envisions the virus as a "one-shot" treatment: "Once you give a single injection and it makes its way to prostate cells and starts replicating, you won't have to give any more, because it continues to propagate itself until it's done the job." In animals, tumors start shrinking (as measured by calipers) in about two weeks; after about six weeks, the tumors are completely gone.

"The fact that we can kill any cell that makes PSA selectively sounds, all of a sudden, a lot like a 'magic bullet' type of approach. And the fact that we can cure laboratory animals of cancers that a lot of patients have -- huge tumors -- is very exciting," says Simons. Even more so is the further promise of DNA-altering technology: "The DNA molecule is a lot like a computer disk," Simons continues, "you can program it, you can manipulate DNA as a drug. Now, we can turn on signals that say, 'Die, you PSA-positive cell.' But what we're trying to do right now is make it even better. If you know the letters of the alphabet and are creative and do experiments, you can literally write in the code of the DNA a kind of special prescription for killing prostate cancer cells specifically."

Cracking the DNA code is, to the world of prostate cancer research, the equivalent of discovering the Rosetta stone -- the key that unlocked Egyptian hieroglyphics. "For the first time, we're really starting to understand the enemy we're trying to kill," says Simons, "and that's very exciting."

It's also rather unique in a field where, often, doctors may know a particular medicine works but not why it does, adds Simons, whose father was one of the first patients to be cure of Hodgkin's disease with a then-experimental form of chemotherapy. "I cannot tell you how that was done; we still don't know how chemotherapy works. But the interesting thing is, I can tell you exactly at the molecular level how this in-vivo gene therapy works."

Simons credits the progress of this work at Hopkins to Patrick Walsh, M.D., urologist-in-chief and Donald S. Coffey, Ph.D., director of research. "Years ago, they saw the future as a molecular medicine -- that you would write prescriptions based on a real molecular understanding of the disease."

Even though this virus work is still experimental, and it hasn't been tested in humans yet, Rodriguez believes the potential in this technology is "unbelievable. For all sorts of tumors, and even for benign disease. I think someday, it may be possible that people with BPH can get a single injection and be cured."

With this work and research in other forms of treatment for advanced disease, particularly angiogenesis inhibitors, "there's a lot of promise now that we're really going to chance survival favorably," says Simons. "And hopefully, really start to cure people. It all comes from a new understanding of the disease."

Simons dreams of prostate cancer, one day, being "sort of a freak thing that occasionally you might see, and you could treat, like tuberculosis today, compared to the way it was in the 1920s -- as this profound epidemic that has been completely controlled by medical and surgical therapy. TB was just as incurable back then."

Would a virus or vaccine ever replace surgery as the definitive treatment? "No, they would all work together. TB was cured by public health prevention; there was a role for surgery always, and then it required four different kinds of drugs to really eradicate it. I think it will be surgery and radiation combined with whole new ways of systematic treatment -- and, of course, prevention -- that's going to do it. Ultimately, the answer will be to try to change our diets, and reduce the predisposing factors. I think it's all of the above."

When Cancer Escapes the Prostate: New Strategies for Prediction, Treatment

Drugs to cut off spreading cancer's blood supply, a molecular grenade that detonates PSA-making cells, and new tests to predict aggressive cancer -- they're all part of an impressive, multi-pronged plan of attack.

Some prostate cancer cells are practically homebodies; their growth is creeping, their advance local. But other cells can't wait to leave the nest -- to hitch a ride on the bloodstream headed for points north. This restlessness has a name -- micrometastasis -- and it can be lethal.

Micrometastatic cells specialize in the quiet exit; these tiny flecks of cancer slip out of the prostate in such small numbers that they're invisible -- and impossible for doctors to detect, even during surgery for what appears to be localized disease.

These cells are the scourge of prostate cancer treatment: Once they've managed this breakout, escaping via the bloodstream to the lymph nodes or spine, prostate cancer can no longer be cured.
But scientist John Isaacs, Ph.D., professor of urology and oncology -- every bit as persistent and determined as the enemy, metastatic cancer -- is undaunted. He's spent his career stalking these cells, working to master their habits and properties, and developing an impressive, multi-pronged plan of attack.
Which Cancers are Likely to Roam?
Pity the meteorologists trying to forecast the weather during tornado season in Kansas: Despite all the technological advances that allow them to track storm patterns, in the end, all they have is probability -- the odds that a tornado will develop, and an informed guess about when and where it might hit.

Scientists studying prostate cancer face a similar predicament. Although landmark tables developed at Hopkins using PSA level, Gleason grade and clinical stage have given men and their doctors an unprecedented ability to predict the extent of cancer, these markers are most helpful "when the cancer looks either terribly aggressive or extremely aggressive," says Isaacs. "The difficulty is, many men fall between those two extremes." Unfortunately, some of these men -- and there's no way to know for certain which ones -- diagnosed with curable disease have cancer that has already left the prostate. "There aren't any techniques now to detect that level of cancer, because it's just so small," says Isaacs. "But it means that local surgery alone isn't going to be curative. What we're trying to do is come up with a molecular mechanism for predicting cancer's aggressiveness."

John Isaacs, Ph.D.

Over the last decade, Isaacs has cultivated what probably is the world's richest nursery of prostate cancer cell lines -- nearly 30 distinct varieties -- which he uses in layers of experiments ranging from tissue cultures to a spectrum of animal models (including mice with no immune systems, in which human tumors can grow). "We've got the full range," he says, human and animal tumors that are "highly metastatic, not metastatic, hormone-independent, hormone-dependent, well-differentiated and poorly differentiated," and everything in between. (In fact, one rat model of prostate cancer, which Isaacs developed when he was a postdoctoral fellow in the lab of Donald S. Coffey, Ph.D., has become the most widely used system for prostate cancer in the world; Hopkins has supplied it to more than 200 research laboratories worldwide.)

Isaacs is using the most aggressive cells in his encyclopedia collection for a sophisticated series of experiments in tissue culture and animals, designed to find genetic restraints for cancer -- molecular fences to keep these cells from roaming. Through painstaking lab work, he and colleagues are adding human chromosomes from normal cells to these nasty, metastatic cancer cells. It's a form of "roll call," in which they're testing, one by one, all 23 pairs of chromosomes in the human body. They're looking for signs of inhibitory effect -- any clue that something (a gene or genes) on one of these chromosomes can either suppress the cancer's growth or its ability to metastasize. So far,

they've earmarked for further study a handful that look promising, including chromosomes 5, 8, 10, 11, and 17. "We've been able to map areas of chromosomes with genes that actually suppress metastatic ability," Isaacs says. Among the most exciting is on chromosome 11, where "we've not only identified the region" (the cancer-suppressing "neighborhood" is on the chromosome's short, or petite arm, called the "P" arm) "but we've cloned and tested the genes. The first gene we identified is called KAI-1."

Like a sandbag that helps keep a hot air balloon on the ground, KAI (pronounced like the Greek "chi")-1 suppresses metastasis. It's product is found in normal cells. But at some point, on a cell's journey from normal to metastatic, it disappears; the cell stops making it. Isaacs and colleagues have developed special antibody stains that recognize KAI-1's distinctive handiwork (telltale proteins that it makes), to search for the gene in prostate cancer biopsy specimens. The idea is that if a cancer is not making enough of it, it may be well on its way to metastasis -- and this stain could help predict aggressive cancer.

Chromosome 11 has proved a fertile field; it's yielded another promising gene, called CD44. Here, too, is a gene, found in the prostate epithelial cells, that makes a metastatic-blocking substance. "When these cells become cancerous, and when they become highly metastatic, they turn off the production of this protein," says Isaacs. "The gene is still there. With both KAI-1 and CD44, the genes are physically still present -- they're just not expressed." Isaacs hopes to find a few more of these genetic markers. Then perhaps one day, if tests (such as the reagent stains his lab has developed) show that a cancer has systematically inactivated several of the genes that could keep it in check, this may be a strong indication for aggressive treatment (However, before this becomes a widely used form of testing, much more study is needed, Isaacs cautions.)

One Way to Stop Cancer: Cut Off the Supply Line

So: After a radical prostatectomy, a man turns out to have micrometastases, invisible offshoots of tumor taking root at satellite locations in the body. His cancer lives; chances are, it will continue to grow. "What are you going to give him? Hormone therapy is very helpful, and in fact, it gives great palliation," says Isaacs.

"But it doesn't cure. It helps people, but it doesn't cure them." This brings us to phase two of Isaacs' cancer-fighting strategy: Putting prostate cancer cells on a leash, with highly-promised drugs called angiogenesis inhibitors.

Like Roman soldiers, advancing cancers pave the way before them, laying down a track of new blood vessels. This guarantees a ready-made supply of nutrients -- nourishing meals for the road -- which, it seems, the cancers absolutely cannot do without. Destroy this infrastructure, cut off the supply line, block these new blood vessels -- and the cancer cells starve.

Cancer cells make new blood vessels grow by subverting a normal process involved in wound healing. "Usually, once you become an adult, your blood supply is pretty stable, and -- except when your body's trying to repair an injury -- you don't really need new blood vessels," says Isaacs. "But in order for a cancer to grow, it has to stimulate its host to do a lot of things for it. A cancer isn't an autonomous machine that can grow anywhere; it's not like an air fern that just needs sunlight and water. It's very dependent on its host, and one of the major reasons why is because it needs vigorous growth of new blood vessels."

This process is called angiogenesis, and drugs to block it, called angiogenesis inhibitors, already exist. The good thing about these drugs, says Isaacs, is "that your other blood vessels -- supplying your heart, lungs, brain and normal tissue -- are already fully developed. Inhibitors of angiogenesis don't really produce any damage to them. They would target the blood vessels only in cancerous areas."

Isaacs and colleagues have been working with an angiogenesis inhibitor called Linomide, which has many qualities of a "dream" drug: It's inexpensive and already available, it can be given in pill form, it has low toxicity and hardly

any side effects -- and it does a beautiful job of stalling tumor growth. Best of all, "there's really no way the cancer cell can become resistant to its requirement for blood vessels." That would be like a lung cells becoming resistant to oxygen.

"The disadvantage is that it's not something you could take only once and then never take again," says Isaacs. "The blood vessels are constantly being stimulated to grow by the tumor, so you'd have to take this chronically -- like someone with high blood pressure who takes medication every day." But many men might find this a tiny price to pay for the potential benefits -- putting a cancer's growth in slow-motion for years, perhaps even decades. "Say a man has very limited, micrometastatic disease," says Isaacs, "we know that, untreated, it might take five or six years for this cancer to produce symptoms. But an anti-angiogenic medication might be able to prevent this happening in 20 years. If the man is 60 years old, that may allow him to not die from prostate cancer. He may still have prostate cancer cells in his body -- this doesn't eliminate all of them -- but it will allow him to survive his cancer."

For Men with Extensive Disease, A Molecular Bomb

But an angiogenesis inhibitor won't do enough to combat more advanced disease. Starting the drug once cancer has become entrenched -- when it starts producing such symptoms as bone pain -- would be like closing the proverbial barn door after the horse has already galloped away: Too little, too late. "What these anti-angiogenic agents do is inhibit the growth of a tumor," Isaacs explains. "If a man has very extensive disease, they won't cause the tumor to regress and melt away."

So how to help these men, who need an effective long-term treatment most of all? This is phase three of Isaacs' research program: A molecular grenade that only detonates in cells that make PSA.

"We're taking advantage of two attributes of prostate cancer here," Isaacs says. "One is that it makes PSA, and the other is that PSA is an enzyme that can -- like a pair of molecular scissors -- clip protein." PSA recognizes certain strings of amino acids, the building blocks of protein, and cuts them up. (The specific proteins are involved in making a sperm-trapping gel, which is part of the semen; the prostate's main job is to contribute part of the fluid for semen.) Isaacs and colleagues are designing a drug by genetically doctoring a potent toxic molecule, hooking it chemically with this protein carrier -- so that's it's activated when PSA goes into its protein-clipping mode. Then the PSA, recognizing this sequence of proteins that it's supposed to cut will, in effect, pull the pin on its own grenade: One clip and boom! Out comes the toxic molecule.

The secret is an unlikely terminator, derived from an innocuous-looking member of the parsley family. "It's a compound called thapsigargin, isolated from the thapsia garganica plant, found in the Mediterranean" says Isaacs. (He is working in collaboration with Soren B. Christensen. the medical chemist from the Royal Danish School of Pharmacy who first isolated, characterized and named thapsigargin.)

For nearly 2,000 years, resin from this plant has been a staple of Arabian medicine; it's a natural irritant, easily absorbed through the skin, which can ease the pain of rheumatism. Thapsigargin works by burrowing its way into a cell and targeting a protein that acts as a calcium pump: Like someone bailing water out of a leaky rowboat, this pump keeps calcium from rising above a certain level inside a cell.

The most interesting thing here is the calcium, which also happens to be a key that turns the engine of a genetic process called programmed cell death; the Greek name for this is apoptosis, which refers to leaves dropping off a tree. "This gives cells very specific signals to activate a process of suicide," says Isaacs. "Normally, calcium is almost 10,000-fold higher outside a cell than within it. If too much of the calcium gets inside it, it causes the cell to reprogram itself and activate this suicide pathway." The effect is like cranking up the gauge on a pressure cooker.

Programmed cell death is certainly not a new concept. It's fundamental to how babies develop -- the way certain cells

in limb buds die, for instance, so that fingers and toes can form. It's the reason a tadpole loses its tail and becomes a frog. "If you look at these developing limb buds (in an embryo), the cells that are going to live are right next to the cells that are going to die. What could control such a tightly orchestrated pattern? For a long time, it was assumed that the microenvironment around the cell basically murdered it -- in other words, that a bad environment killed the cells. But it's now clear that the cells that are dying are in a very happy environment: They've got plenty of nutrients, plenty of oxygen -- they've got everything that they need to live. But they've been given a signal, and that signal says: Don't live. Die." And that pathway to death is apoptosis.

Now imagine a medieval fortress under siege. The enemy is outside; but one soldier scales the walls and opens the mighty gates, and this is all it takes to change the course of battle. By interfering with the crucial pump, thapsigargin allows that calcium outside the cell to sneak inside; it reaches too high a level, disrupts the cell, and activates this pathway of death. "The DNA inside the cell's nucleus gets all chewed up, becomes degraded to the point of not being useful for any information. The nucleus itself becomes fragmented, then the cell becomes fragmented," Says Isaacs. The grand finale is an act of cannibalism: These little fragments, called apoptotic bodies, are then consumed by neighboring cells.

"The great thing about this," says Isaacs, "is that the cell has no way of preventing its own activation of this pathway." Another bonus is that this death pathway -- unlike many chemotherapeutic drugs -- doesn't require rapidly dividing cells. It can kill any cell, within 24 to 72 hours.

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Endothelin: The Key to Bone Pain?

Is it possible that some of the pain . . . is because the cancerous cells are secreting something which is very similar to snake venom?

The bone pain that can come with advanced prostate cancer is particularly horrible -- a nightmare of disabling torment worthy of Dante that, at its worst, defies just about every painkiller except morphine.

Why is it so bad? For years, although there have been many attempts to manage this pain better, no one asked this question; the assumption was that extreme pain was simply an inevitable part of the grim package of "bony metastases," cancer that invades bones.

But urologist Joel Nelson, M.D., has another theory: That this pain is caused by one of the body's own chemicals, called endothelin (made by endothelial cells, which line blood vessels). Endothelin is a vasoconstrictor (a substance that causes blood vessels to contract), "the most potent one ever discovered," says Nelson.

Although it's found in the bloodstream, endothelin's concentrations are highest -- about 500 times greater -- in semen; part of this fluid is contributed by the prostate. The healthy prostate makes endothelin; the cancerous prostate does, too -- even during hormone therapy, when the prostate's supply of male hormones is shut off.

Because endothelin is impervious to hormones -- just like the hormone-insensitive cells in prostate cancer -- "to my way of thinking, it's exactly what we should be studying," says Nelson, "because patients who die of prostate cancer don't die of hormone-sensitive disease."

Endothelin, as it turns out, can be a nasty customer: On a molecular level, it bears an amazing structural resemblance to snake venom. "This particular snake venom is painful," says Nelson, "and so is endothelin when it's given in the right dose to humans. In fact, endothelin has a lot of similarity to a toxin we've all experienced -- apamin, the compound that hurts so much when you get stung by a bee."

Which begs the question: "Is it possible that some of the pain that men experience when they have advanced prostate cancer in their skeleton is because the cancerous cells are secreting something which is very similar to snake venom?"

Even more intriguing: In addition to the terrible pain, men with prostate cancer are often plagued by other bone problems. In some men, the cancer erodes bones, making them riddled and fragile. But in other men, the bones seem to turn to concrete; they get unnaturally thick and hard. Here, the prostate cancer cells apparently secrete something that serves, in effect, as a coat of super-hard lacquer. Endothelin may play a role in this development.

Nelson believes that if endothelin could somehow be blocked, these changes might be prevented. This spring, he will begin the first clinical trial of an endothelin-blocking agent in cancer. Ideally, the study will find that stifling endothelin accomplishes two things -- that it will not only thwart bone damage, but bring desperately needed pain relief.

Endothelin's contributions to pain are complex, Nelson has learned: For one thing, it can act as a neurotransmitter, a chemical signal to the brain, "so it can activate the normal pain pathways," he says. "But the thought is that by releasing endothelin locally, the cancer cells are also stimulating the nerves sitting right next to them, and that is what's causing the (major) pain. Undoubtedly, there's also some pain from the destruction of the bone, as well."

And, local poison aside, don't forget endothelin's impressive credentials as a vasoconstrictor -- one of several chemicals activated in a heart attack, causing the blood vessels to spasm, or clamp shut. It may also be, Nelson speculates, "that some of the pain these men experience is due to ischemia -- just like angina or heart attack." When the supply of blood is suddenly shut off, oxygen-starved tissue immediately reacts with a cry for help -- impossible-to-ignore, severe pain.
Layer after layer of pain.

What's happening here? As in so many aspects of cancer, a switch has gone awry. In molecular studies, Nelson and colleagues have discovered that a crucial "on-off" switch -- a receptor that allows the body to control endothelin -- vanishes when a prostate cell becomes cancerous, leaving behind only an "on" switch. If the on-off switch, like the floorboard of a car, has a gas pedal as well as a brake, this receptor seems to malfunction like a stuck accelerator: It's a switch that turns on and stays on, and only increases the voltage each time it's activated.

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The Tables that Revolutionized Treatment Decision-Making: Now Bigger and Even Better

They call them the Partin tables, and they're everywhere: On several Internet websites, on laminated cards carried by doctors throughout the country, even on home computer programs.

Elegantly simple and meticulously accurate, the tables, developed by urologists Alan W. Partin, M.D., Ph.D., and Patrick C. Walsh, M.D., have quietly revolutionized the way doctors and patients are making decisions about treatment for prostate cancer.

Until these tables, there was no way to predict what urologists might find when they opened up a patients during radical prostatectomy; surgery can only cure prostate cancer if the disease has not spread too far beyond the confines of the prostate. Doctors could guess, but they couldn't be sure -- not until they examined the patient's pelvic lymph nodes (in a procedure called pelvic lymph node dissection), and sometimes not even then, if there were microscopic bits of cancer that had strayed from the prostate but weren't yet big enough to be seen.

Ingeniously correlating the three things that were known about a man's disease -- PSA level, Gleason score, and estimated clinical stage -- the tables produced something that had been desperately needed: An accurate, invaluable means of estimating the exact extent of a man's prostate cancer before surgery.

"We know that if you operated on everybody who came in with these three pieces of information, at best -- at very best -- about 45 to 50 percent would have organ-confined cancer," says Partin. Because surgery is best at curing

cancers that are truly localized to the prostate, it would be better for everyone to know before the operation how extensive the cancer is; this might spare someone unnecessary surgery.

Similarly, radiation won't cure a man who has cancer in his pelvic lymph nodes, and the tables can help spare someone needless side effects of a treatment that won't be helpful.

The tables, first developed after Partin studied the course of prostate cancer in hundreds of Walsh's radical prostatectomy patients, were designed to help men and their doctors predict the definitive pathological stage (determined after surgery, when a pathologist examines the removed prostate for the presence of cancer) and best course of treatment.

Now the tables have been expanded to include data from three institutions -- The University of Michigan and Baylor College of Medicine, as well as Johns Hopkins -- and 4,135 men, operated on by nearly a dozen surgeons. (All three of these institutions have received SPORE grants, for Special Projects of Research Excellence, from the National Cancer Institute).

This latest study, says Partin, "sharpened the tables by having more power, because of the higher numbers. It also provided the capability of testing our hypothesis: We took two-thirds of the patients and recalculated the tables, and then with the third that we had randomly chosen, we tested to see how well we did. We were able to calculate the statistical accuracy of the tables and report that, as well." (Another advantage of tripling the size of patients in the study is that it filled in many of the blanks that had been left on the earlier tables because of a lack of information.)

The four tables predict a man's likelihood of having organ-confined disease; capsular penetration (cancer that has reached the prostate wall); cancer in the seminal vesicles; and cancer in the lymph nodes. For example, a man with a PSA of 3.7, clinical stage T1b, and Gleason score of 6 has a 61-percent chance of having organ-confined disease, with a 23-percent chance of having positive seminal vesicles.

"I think it's really helped the patients and their doctors when they're talking to each other about treatment," says Partin, "so the patient can just say, 'Just what are we looking at, with the information I have right now?'"

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The Fight Against Advanced Cancer: New and Better Drugs

Experimental Treatments show promise in attacking Hormone-resistant prostate cancer. Mario Eisenberger and colleagues are working to develop, test and refine several new drugs, each of which works in a slightly different way

The most frustrating, agonizing aspect of treating prostate cancer is the fact that, when it had advanced past the prostate, invading the lymph nodes or bone, it can no longer be cured; it can only be controlled. The main way to do this is by hormone therapy -- shutting down the hormones that feed the prostate and nourish the cancer. But hormone therapy isn't a long-term solution. Over time, its effectiveness fades. To wage a full-scale ware on advanced cancer, hormone therapy must be combined with something else -- chemotherapy, drugs targeted specifically at these malignant cells.

Unfortunately, this is where the picture gets fuzzy: So far, standard chemotherapy hasn't worked in prostate cancer. Not only does it fail to cure cancer, it doesn't prolong survival to any significant degree, and it sometimes harsh side effects can make an unpleasant situation even worse.
But: Experimental treatments show promise in attacking hormone-resistant prostate cancer, says oncologist Mario Eisenberger, M.D.. He and colleagues are working to develop, test and refine several new drugs, each of which works in a slightly different way. These include:

Suramin. Originally used more than 50 years ago as a drug to kill parasites, suramin has a unique ability to invade cells and rearrange the furniture -- disrupting a cell's most basic business by hooking itself up to substances called growth factors, chemical switches that help promote cell division (some of which are believed to spur prostate cancer's progress). Suramin is known to inhibit growth in certain prostate cancer cells; as a bonus, it also seems to lower the level of adrenal androgens (weak male hormones made by the adrenal gland, which make up a tiny fraction of the total hormone stimulation to the prostate).

Eisenberger and colleagues at Hopkins and Parke-Davis, the company that makes suramin, have just finished a national, randomized clinical trial, in which 455 men with hormone-resistant prostate cancer received either hydrocortisone plus suramin, or hydrocortisone and a placebo. (Hydrocortisone is known to ease bone pain, and also to cause a short-term drop in PSA; it also offsets suramin's temporary disruption of the adrenal gland.) Says Eisenberger: "We should know the results within the next few months. If it's a positive trial, then the FDA will likely approve suramin for prostate cancer."

In another clinical study (currently open for patients -- see below), Eisenberger is giving suramin along with a drug called topotecan. Early research suggests that giving topotecan after suramin causes both drugs to be more effective.

Just how effective is suramin? No one would say it cures prostate cancer, but suramin can chase it into remission from months to -- in a few cases -- even years. "The remission rate worldwide ranges between 20 percent to 65 percent," says Eisenberger. His patients fall in the highest, the 65-percent category. He attributes these good results to when his patients get suramin: At the earliest signs that cancer is worsening (including a rise in PSA in a man who's been on hormone therapy). "That's the ideal time to get started right away -- even though the patient might be feeling very well," he says. "If you wait too long," and miss the window of opportunity, "treatment is unlikely to work."

And how long is remission? Still too short: The average lifespan of men with hormone-resistant cancer (in other words, the point where the PSA starts to rise while the patient is taking hormones, signaling that cancer has defied hormone therapy) is around 11 months. "In our experience with suramin, it was 21 months, so it's almost twice that," says Eisenberger. "We also found that about 30 percent of our patients had been in remission for two years. So it is possible that there's a subset of patients who got helped quite a bit. In fact, I have one patient, a man in his late sixties, who's now been in remission off treatment for six and a half years -- and that's something I had never seen in my previous experience with chemotherapy in prostate cancer."

Differentiating agents. This new class of drugs, also being tested in other forms of cancer, "seems to be particularly active" in prostate cancer, Eisenberger says. Differentiating agents work by slowing down the growth, or proliferation, of cancer.

"Every cancer has cells that are dividing, what we call a cell proliferation subset, and cells that are dying," Eisenberger explains. "If the cells are proliferating very actively -- much more than the rate of dying -- then the cancer's growing." Differentiating agents keep cancer in check by slowing down the booming birth rate, giving the death rate a chance to catch up. "This is not conventional chemotherapy," he adds. "It's not one of those drugs that you give and then you destroy everything, and hope that the healthy things come back very quickly and the cancer cells will not recover. This is more selective." Hopkins oncologist Michael Carducci, M.D., is leading studies of differentiating

agents including phenylbutyrate and another drug called Targretin.

Retinoids. This class of drugs (one of them is the drug Retin-A, derived from vitamin A) has a similar mechanism of action; it slows down cancer growth. The particular drug being tested here is called Targretin, which seems able to hone in selectively on prostate cancer receptors.

Dolostatins. Another new class of drugs, dolostatins are also being studied in other forms of cancer. The mode of action is similar to that of taxol, currently being used to treat ovarian cancer. Eisenberger and colleagues will soon begin enrolling patients in a study of the drug cemadotin.
With so many drugs being studied, how do the researchers decide who gets what? "In general, we try to focus on what we call 'Phase II' agents first," says Eisenberger. "That is, we're treating patients with new regiments using safe doses and schedules. So if a man tries suramin and topotecan, for instance, and these things are not working well, then the next drug we would offer would be phenylbutyrate. If that isn't helping, then the next step would be targretin." (Because much is already known about cemadotin's dosage and side effects, it will probably be given to patients as a first-line treatment when that study begins.)

There is, says Eisenberger, a frustrating phenomenon called drug resistance: "The cancer cells activate a number of molecular and genetic mechanisms by which they become resistant to chemotherapy." If one drug fails, and then another, "by that time, cancer cells are even smarter than they were before, and it becomes even more complicated," plus the drugs each take a toll on the patient. So the ultimate hope, obviously, is to be able to control cancer with the first course of chemotherapy.

Also on the horizon, although not yet near the patient-testing stage, are:

Angiogenesis inhibitors. Yet another group of drugs. "Cancer cells make certain things that make blood vessels," says Eisenberger. "And that's how they spread -- they sort of pave their way through the body. Now, well over 100 drugs are able to inhibit the formation of blood vessels, and we think that prostate cancer's a very good candidate for that."

Immunotherapy. In about 70 percent of patients, as prostate cancer gets worse, there is a substantial drop in lymphocytes -- blood cells that make antibodies, which help the body's immune system fight off disease. "They decrease substantially over time," says Eisenberger, who discovered this during his studies with suramin. "That's something we're studying, and maybe it will be a good rationale for using immunotherapy" -- special drugs and vaccines designed to jump-start the body's flagging immune system.

With so many good prospects in the works, the future of chemotherapy looks brighter than ever before, says Eisenberger: "What I see in cancer, in general, is that we are getting much better in selecting and directing our therapy; and prostate cancer is following that. We understand a lot more about cancer biology -- about the genes, about mechanisms of tumor growth. And we think we understand, in certain circumstances, what's important in making cancer cells grow. And as we begin to understand these steps, we're better able to design treatments that interfere with some of them."

Further Reading
"How Much Can We Rely On The Level Of PSA As An Endpoint for Clinical Trials? A Word of Caution,"Journal of the National Cancer Institute. Vol. 12, June 19, 1996. Mario Eisenberger and William G. Nelson.

Why Hormone Therapy Isn't Enough

In almost every man with advanced disease, hormone therapy prolongs life and eases many symptoms, often bringing a dramatic improvement to quality of life. Sometimes, the cancer can be kept at bay for many years.

When a man starts hormone therapy, the early results are successful: The tumor shrinks, PSA levels drop, and -- most importantly -- the patient feels better. But then, slowly, inevitably, the cancer makes a comeback, and PSA levels, which had fallen so encouragingly before, begin to creep back up.

Why doesn't the effect of hormones last forever? The problem is that prostate cancer is "heterogenous" -- it's made up of many different kinds of cells. Some of them respond brilliantly to hormones; these cells aren't the problem. It's the other kind -- the cells that are hormone-resistant, that continue unfazed despite this treatment -- that ultimately cause hormone therapy to fail. And this is why chemotherapy is needed: To target and kill these ruthless cells.

The PSA-Making Phenomenon

A strange thing happens as prostate cancer becomes very aggressive: Some cells start making less PSA, and some cells stop making it altogether. This probably has a lot to do with cell differentiation: How well-defined and close to "normal-looking" cancer cells are. (On the Gleason scale, the lowest, best grade goes to cancer cells with distinct, clearly defined borders. The highest, worst score is fore poorly differentiated, aggressive cells that seem to melt together into solid, malignant blobs.)

Over time, scientists believe, there's a genetic mutation that uncouples the control of cell growth and PSA; the two are no longer linked. The cell loses its higher-order functions -- in other words, it loses its ability to do prostate-specific things, and oozes down the evolutionary scale, regressing into a primordial dividing machine. All the other things it used to do -- which now get in the way of growth -- become superfluous.

"It's interesting," comments oncologist Mario Eisenberger, M.D. "If you take a drug like phenylbutyrate, which slows the cancer cell: As it slows down, the cancer cell also makes more PSA." Hopkins oncologist Michael Carducci, M.D., decided to study phenylbutyrate because of work done at the National Institutes of Health on phenylacetate, a pharmacological "cousin" of the drug -- and, particularly, because of its spectacular results on one patient. "The man was in a lot of pain, he was not working, almost bedridden," says Eisenberger. "He got phenylacetate, and all of a sudden, his pain went away, his strength came back, he went back to work and he was exercising. And his PSA -- it went from 30 to about 3,000! So you look at the PSA and say, 'He's not going to be around here anymore,' but the gentleman was there."

What happened? It may be that, as the cancer cells slowed down with phenylbutyrate -- which, in effect, took away their main activity -- they also began making more PSA: "Cancer cells that are not growing very much have less to do with their energy and they make PSA," says Eisenberger. "That's a very crude analogy, but it gives you an idea that the cancer cells that don't grow very rapidly tend to make more PSA than those that do."

Much is understood about the relationship between PSA and growth in prostate cancer's earliest stages. "But later on, if your cancer disseminates, that relationship between PSA and tumor burden becomes less well-defined," and much more study is needed. As a consequence, Eisenberger hesitates to over-rely on PSA to monitor his patients with advanced disease: "We need to examine the patient frequently, listen to him carefully, and we probably need to do radiographs and scans a little more often."

Can You Share Your Wisdom?

Do you remember when the words "prostate cancer" became forever part of your life? How, after diagnosis, you and your wife scrambled to learn everything you could about this disease?
As you well know, surviving prostate cancer -- from deciding your best course of treatment to living with the after-effects of radical prostatectomy, radiation therapy, or medication -- is one of the roughest challenges men and their families can face.

We feel that nobody should have to go through this alone. And this is where, we hope, you'll come in: Would you like to be an advisor to new patients? Could you help get them through the rough spots, the uncertainty, doubts and fears?

Among the first questions men often ask me is, "Is there anyone I can talk to?" Often, their wives are equally interested in talking to another woman who has traveled down this same road.

If you or your spouse would be willing to talk to others going through what you've just experienced, please send me a short note with your address, telephone number and fax number, if available. I will put together a directory sorted by zip codes. This directory will be kept strictly confidential. This information will be available only to me. Then, when I see a patient who would like advice from someone who's "been there," I will pick the patient in the closest zip code and will write to you, asking you to contact him and/or his wife.

Sincerely yours,

Patrick C. Walsh, M.D.
Urologist in Chief

How You Can Help?

It takes tremendous resources to do what we do. That's why, in 1991, a group of our patients established The Fund for Research and Progress in Urology, an endowed fund whose sole aim is to help ensure the future of discovery in the field of prostate cancer here at the Brady Urological Institute.

This institute, the world's leading center for research and discovery in prostate cancer, combines the talents of five full-time Ph.D. scientists and world-renowned surgeons and medical oncologists working with a team of postdoctoral fellows, residents in training, and technical support staff. The Brady Urological Institute is a four-story, free-standing institute of the Johns Hopkins Medical Institutions, containing three floors of laboratories dedicated to prostate cancer research. The support necessary to maintain this mission totaled $4 million in fiscal year 1996.

Ideally the government, realizing the significance of what we're trying to do -- and what we've already accomplished -- would provide the funds necessary to continue this mission. However, today more scientists than ever are competing for support from the National Institutes of Health, even as its total available research funds are diminishing. Although the backbone of our funding -- one half ($2 million) -- comes from the NIH, these grants don't provide everything necessary for the research environment. For example, they don't pay for purchases of major

equipment, some salaries, and financial stability between grant periods, so the Brady has the hard money needed to retain the most talented scientists and support personnel in the country.

Another 25 percent of our funding comes from professional fees. Our physicians receive a salary; this enables us to reinvest all extra revenue in discovery. However, with the recent dramatic changes in health care financing, the availability of funds from professional fees is disappearing. Managed-care companies are siphoning off the profit we once used to support this work and providing reimbursements that are less than it costs to provide the kind of care we give. For this reason, we can't depend on third-party reimbursements to support our work in the way they once did.

Currently, the remaining 25 percent of our research budget comes from our endowment, The Fund for Research and Progress in Urology. With the growing demand for NIH support and diminishing availability of funds from professional fees, it's increasingly important that we build this endowment to safeguard the future of our mission of research and discovery.

There is so much hope in prostate cancer -- just take a look at the stories that fill these pages. New discoveries are being made here every day. But we're all too aware that we're fighting the clock. Although the future is brighter than it has ever been, the present is still not ideal for men with advanced prostate cancer. This disease kills one man in the United States every 15 minutes. To reduce deaths from prostate cancer, we need a four-pronged approach: Prevention, early detection, effective treatment of localized disease, and better ways to contain advanced disease. Our laboratories and our clinic are aggressively exploring all of these.

Together, we can save lives. Your gift will help us beat this disease. For more information on how you can make a tax-deductible contribution to The Fund for Research and Progress in Urology of the Johns Hopkins University.