

# Men, Cancer & Hope

For decades, prostate cancer was the silent scourge of men, neglected by scientists. Now a research revolution is yielding a potent new arsenal of weapons to quell this killer | **By Robert Langreth**

ALAN SCHEIN / CORNELL

**I**F YOU ARE A MAN—OR A WOMAN WHO LOVES ONE—READ THIS and reap. The longer a man lives, the greater his chances of getting prostate cancer. But the buoyant new truth is that scientists and medical companies are closer than ever before to taming this threat, reducing prostate cancer to a chronic, manageable—and utterly survivable—disease. For most of 60 years men with advanced cases have had a dearth of treatments other than crude hormone therapy adopted in the 1940s, which essentially was a form of chemical castration. Now researchers are on the brink of a revolution in prostate care, deploying an arsenal of new weapons that were all but unimaginable 20 years ago.

A hundred experimental drugs are now in human efficacy trials, targeted at crucial “lethality” genes that help some tumors spread and kill. State-of-the-art robotic surgery can remove the prostate while preserving the delicate nerves needed for sexual function. New computer-guided systems for pinpoint radiation can zap tumors at far higher doses than previously possible, without destroying healthy tissue. And futuristic genetic tests will single out which men are most likely to get the most virulent forms of the disease, letting preemptive treatment begin years before cancer turns deadly.

“The science is starting to connect,” says Emory University oncologist Jonathan Simons, who leads a consortium of 13 universities developing new prostate drugs. “It is like a huge circuit board, and we are starting to figure out the master circuits.” A few years ago Memorial Sloan-Kettering oncologist Howard Scher had little to offer men with advanced cases. “Now I can talk to them about eight or ten different options,” he says. “I’m successfully treating patients with advanced disease for four, five, six, eight or even nine years. That just didn’t happen before.”

of surgery to block these hormones. Eventually, most hormone therapy ends up failing.

But breakthroughs in targeting suspect genes in prostate cancer have yielded a tsunami of new drugs, with 100 now in mid- to late-stage human trials, almost triple the number in 1997. They include compounds that block bad genes responsible for spreading cancer into the bones, chemicals that prompt prostate cancer cells to destroy themselves and vaccines that train the body's killer T-cells to seek and destroy tumor cells.

The promise of new chemo drugs got a boost in the spring when studies found that the cancer drug Taxotere, made by Sanofi-Aventis, extended survival in prostate cases from 16 months to 18 months, the first time any chemo agent had been found to extend the life of prostate patients. Now others are working on a raft of vaccines that stimulate the immune system to attack cancerous prostate cells. Firms now in human trials of this approach include Dendreon of Seattle, Cell Genesys in South San Francisco, England's Onyx and Therion Biologics near Boston.

So far Cell Genesys and Dendreon are in the lead, with final-stage trials under way. Dendreon contends its vaccine, Provenge, boosted survival by 8 months (to 31 months total) in a trial of 127 patients who had failed hormone therapy. Detractors argue the results are overstated because the drug worked well in only a subset of patients. Results from a final-stage trial on 275 patients are due next year.

Of the new gene-targeted therapies, the one furthest along may be Xinlay from Abbott Laboratories. It blocks a protein called endothelin, which is secreted by prostate tumors in large amounts and helps them metastasize. The drug aims to shut down this process by gumming up an endothelin receptor found on bone cells; it also may act directly on prostate cancer cells to inhibit their growth. In advanced cases Xinlay staves off miserable bone pain by an additional three months but has minimal side effects, according to two studies of almost 1,100 patients.

Abbott plans to apply for approval by year-end, and Wall Street analysts foresee a billion-dollar bestseller. Says University

of Pittsburgh urologist Joel Nelson, who first discovered endothelin's prostate role: "If you can delay cancer progression with a drug that causes virtually no side effects, that is going to give patients a lot of quality of life. It would be a huge advance."

Another approach, now being tested by Millennium Pharmaceuticals and, separately, by Medarex, is to develop smart antibodies that help destroy prostate cancer cells. Millennium's drug, now in early human trials, homes in on prostate cancer cells and aims to obliterate them with a precise dose of toxic chemotherapy while leaving surrounding tissue untouched. In animal tests the drug shrank advanced tumors by 90%. The drug consists of a bioengineered antibody linked to toxic chemotherapeutics; the antibody targets a prostate-specific membrane antigen, a protein found only on prostate cells. When the drug is injected into the body, the antibody clamps onto molecules on the surface of cancer cells; the toxin is then sucked into the cancer cell, killing it.

Medarex's competing drug is similar but doesn't contain a toxin; instead, it gloms onto prostate cancer cells and stimulates the body's own immune system to attack. Results of early human tests are due next year.

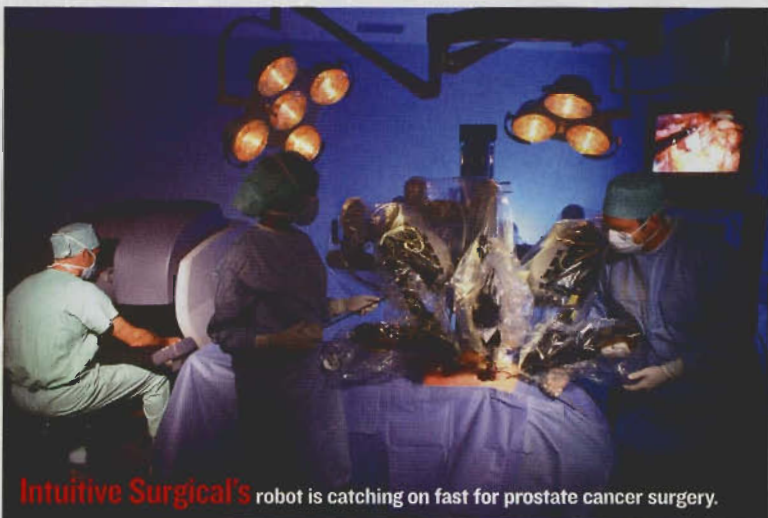
## Robosurgery

**I**N EARLY-STAGE PROSTATE CANCER, THE GOLD STANDARD of treatment for the past 25 years has been the surgical removal of the prostate. Prostatectomy vanquishes the tumor 80% of the time. But it requires a five-inch-long slash across the abdomen and often results in urinary incontinence and erectile dysfunction. Sixty percent of men were rendered impotent by the operation, according to one study.

But a new surgical procedure eliminates the surgeon's big incision and possibly reduces side effects. It aims to have patients fixed and back to work in as little as a week—with their sexual function intact. In one of the biggest shifts in two decades, dozens of hospitals have started offering the new approach, a less invasive procedure that entails making five or six keyhole incisions through which instruments and a tiny camera are inserted.

Many doctors now do this with the help of a \$1.3 million robot from Intuitive Surgical in Sunnyvale, Calif. The surgeon, instead of wielding a scalpel and cutting away, sits at a 3-D monitor across the room from the patient and controls three robotic arms with two joysticks. "Robotic surgery is going to go down as one of the landmark developments in prostate cancer treatment," says City of Hope Cancer Center urologist Mark Kawachi. "In the right hands it produces fantastic results." Kawachi says his colleagues were able to preserve potency in 80% of 175 patients operated on by the robot.

Of the 70,000 prostate removals done this year, only 6,000 or so used the new robot technology, but



Intuitive Surgical's robot is catching on fast for prostate cancer surgery.

that is up threefold in a year, Intuitive estimates. As sales of the equipment surged in the past year, Intuitive shares have risen 60% to \$26. Skeptics, and there are many, contend it is an expensive fad with no major advantage. "It has been hyped by the instrument makers," says Johns Hopkins University urologist Patrick Walsh, renowned for inventing a nerve-sparing prostatectomy procedure that preserves sexual function. "I don't think there is any solid evidence you get better results."

Prostatectomy often reduces sexual function because of collateral damage to nearby nerves; the prostate sits less than a millimeter away from bundles of nerves and blood vessels involved in maintaining erections. Complicating matters further: The urethra passes through the center of the prostate and must be reconnected back to the bladder once the prostate is removed.

Little hard data exists comparing the minimally invasive operation with the old "open" version. But proponents argue that the better visualization provided by the 3-D camera will boost doctors' ability to spare the delicate nerve bundles.

Minimally invasive prostate removal was pioneered in the late 1990s by two French surgeons, Guy Vallancien and Bertrand Guillonneau. They did the operation manually, maneuvering chopstick-like instruments through small incisions while watching via a laparoscope, a tube with a tiny camera at the end. But the operation was so demanding technically that most urologists were afraid to try it. (One doctor likens it to backing up a tractor trailer around a curve by looking through the rearview mirror.)

The robot, first approved in 2000 for gallbladder and heartburn surgery, started catching on for prostate surgery in 2002 after urologist Mani Menon at Detroit's Henry Ford Hospital reported that it was a far easier way to learn the new technique.

The robot "has leveled the playing field," says Duke University urologist David Albala, who has done many robot-assisted prostate removals. But some surgeons who perform traditional open surgery warn that the rush to offer the minimally invasive operation may compromise patients' health.

"People think it is a highly refined procedure," says Peter Scardino, chairman of urology at Memorial Sloan-Kettering Cancer Center. But because so few doctors have mastered the operation, "in reality, it is almost certain to give you worse continence and worse potency."



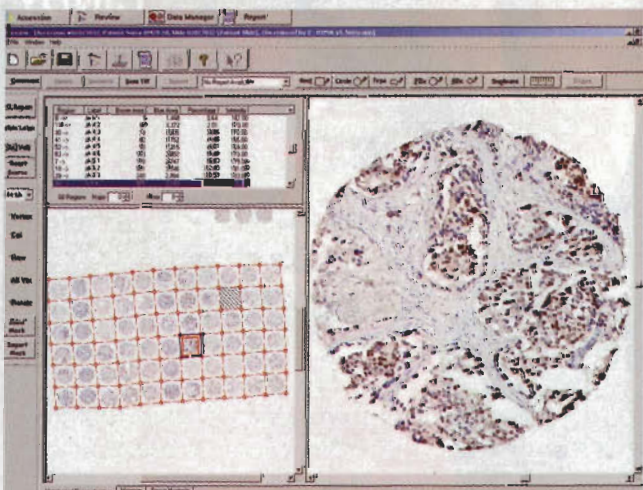
**Precise Plan** Treatment plan for IMRT radiation ensures that high doses (red) hit only the prostate.

## Tumor Zappers

**T**HE ADVANCES IN SURGERY MIGHT HAVE ECLIPSED the other main treatment choice—radiation—but startling developments on this front have created a kind of engineering arms race between the two rival approaches. In the past radiation was a clumsy and indiscriminating weapon, killing cancer cells and healthy cells in one sweep. Now new computer-guided systems cut down on collateral damage by molding the radiation beam to the precise contours of the prostate, reducing side effects and boosting cure rates. "Radiation is now as good as surgery, and that wasn't the case 15 years ago," says Daniel Shasha, a radiation oncologist at Beth Israel Medical Center in New York.

External beam radiation involves zapping a patient with high-dose X rays generated by a machine called a linear accelerator. The trick here is to blast all the cancer while frying as little healthy tissue as possible. Until the 1980s radiation oncologists could only crudely estimate where to aim based on the position of nearby bones in 2-D X rays. In the late 1980s computer-aided techniques used data from CT scans to mold the radiation beams to the shape of the prostate. This allowed for slightly higher doses, but it still caused significant rectal damage.

In recent years instrument makers have refined the therapy further with a technique called Intensity Modulated Radiation Therapy. IMRT systems contain computer-controlled metal fingers that move in and out to vary the shape and intensity of the radiation beam during treatment. This allows doctors to boost the dose at the core of the tumor while giving lower doses at the edges, preserving healthy tissue. Roughly 40% of hospitals now have the \$1.5 million systems, which are sold by Varian Medical Systems, Siemens and Elekta. Researchers at Memorial Sloan-Kettering reported in 2002 that a mere 4% of 698 prostate cancer patients who underwent IMRT suffered significant rectal bleeding, less than one-third the rate for older technology. In a separate study they found that IMRT's higher doses let 90% of



**Gene Hunters** Researchers are analyzing hundreds of prostate samples to search for the genes that make some prostate tumors lethal.

early-stage patients remain cancer free for five years, up from 77% of patients treated with older methods.

Another option that has taken hold in recent years, radioactive seeds, aims to minimize side effects by placing the radiation source directly inside the prostate. Doctors implant 100 or so tiny radioactive pellets into the prostate during a short operation. The seeds must be evenly spread out to cover the cancer fully, but at first doctors had no way of knowing whether they had all the seeds in the right place until afterward, when it was harder to fix mistakes. Now they can get an earlier peek with software that has been tested by oncologists at several institutions across the country. It takes real-time ultrasound data during the seed operation to confirm that the right dose is going to the right place; doctors can adjust on the fly if needed. West Virginia-based Schiffler Cancer Center radiation oncologist Gregory Merrick says it will revolutionize how radio seed therapy is done.

## Killer Genes

**F**OR ALL THE ADVANCES SOME DOCTORS LAMENT that they are unnecessarily treating thousands of men who would have survived without any intervention at all. One study found that among elderly prostate patients who shunned treatment after diagnosis, only 16% died from their cancer in the next 20 years; 75% died of other causes. The study, though it covered only 223

patients, pointed up a painful choice: Because doctors have no way of telling which cases are benign, they err on the side of treatment, despite the side effects.

But scientists are gaining a peek into this cancer's future. Tiny strands of DNA hidden inside prostate tumors offer clues, studied via DNA chips and other exotic new technologies. The goal: a gene-based prognostic test, one that could predict years in advance which tumor will metastasize and kill you. Harvard pathologist Mark Rubin says such a genetic fingerprint would have far more predictive power than current methods. The clumsy prognoses available today center on changes in PSA levels in blood and on the so-called Gleason score, a pathology grading system.

Rubin's team at Harvard, along with colleagues at the University of Michigan, has identified three genes that may be involved, including one that appears to remove the normal brakes on cellular growth, allowing prostate cells to spread like wildfire. Meanwhile, Todd Golub at MIT and Harvard's Broad Institute has found a group of five genes involved in prostate cancer progression. The two have joined forces, and they plan to combine a dozen or more gene markers into one test; they hope to confirm the results in a study of 2,000 doctors with prostate cancer.

Elsewhere, Celera Diagnostics, Abbott Labs and closely held Genomic Health also are pursuing prognostic gene tests for prostate cancer (and for other tumors, as well). The efforts are in tacit recognition of a medical inevitability: Even the most sluggish cancer can't be stopped if you don't see it coming at you early enough. **F**

## Disease and Redemption

PROSTATE CANCER, ONCE A RESEARCH BACKWATER, is suddenly sexy thanks to the work of one patient: Michael Milken, the Wall Street wizard who fell from grace in the late Eighties and found redemption in a medical miracle.

Milken was diagnosed with prostate cancer in early 1993 and was told he had 11 months to live. He underwent hormone therapy and radiation, and vastly altered his diet to beat the disease. The same year he founded the Prostate Cancer Foundation, committing \$25 million. He figured the research effort needed new blood.

The Milken foundation acted like a venture capital firm, funding high-risk projects un-

likely to win government grants and wooing young researchers into the field. Milken doled out small grants to get upstart scientists established; they could then leverage preliminary results to snag bigger bucks from more cautious government agencies.

The Milken group required only a five-page application and cut checks within 90 days; government grants run on for scores of pages and can take up to a year to go through. One catch: normally secretive researchers were required to share their results at an annual conference.

"Milken is probably the single most effective layperson ad-



vocate for cancer research," says former National Cancer Institute director Samuel Broder, now an officer at Celera Genomics. Back in the early 1990s "the word on the street was that prostate cancer wasn't being funded," so the best scientists and their protégés

were uninterested, Broder says.

"Milken primed the pump. He started funding young investigators and suddenly the quality of grant applications got better." Milken also cofounded the National Prostate Cancer Coalition in 1996. It successfully lobbied Congress to create a prostate program at the Department of Defense, which now spends \$85 million a year on it.

The Milken foundation had a crucial early role in numerous prostate drugs now in late-stage trials. Among others, in 1995 it funded a young Johns Hopkins researcher to test a new concept for a prostate cancer vaccine on 20 patients. The trial was successful, and now the vaccine, called GVAX, has begun a final-stage trial on 600 patients at biotech firm Cell Genesys. —R.L.