Recent advances in diagnosis and treatment promise to extend survival time and improve the quality of life for many patients

by Marc B. Garnick and William R. Fair

The death rate from prostate cancer in the U.S. has declined for several of the last few years, but the disease still claims too many lives. It will strike an estimated 179,300 men this year and prove fatal in 37,000, making it the second leading cancer killer of men, behind lung cancer. For such reasons, we and others continue to seek ever better ways to manage this disorder, which is especially prevalent in those older than 65 years. We cannot claim that the ideal solution for every patient is at hand, but a spate of exciting recent discoveries deserves notice.

Some of the newer findings address a vexing flaw in the sole noninvasive screening test for detecting microscopic prostate cancer, the form most amenable to a cure. The test measures the level in the blood of prostate-specific antigen (PSA), a protein released by prostate cells. Both normal and malignant prostate cells secrete this substance, but when cancer is present, the levels in the circulation often rise. Elevated PSA levels can thus warn that the prostate gland harbors cancer even if the tumor is too minute for a doctor to feel. The other main screening test, the digital rectal exam, can identify only tumors that are no longer microscopic. In that procedure, a doctor inserts a finger into the rectum and, through its wall, feels the prostate for hardness or lumps.

Unfortunately, the PSA test is not particularly specific. As many as 25 percent of men with cancer will have normal PSA levels—usually defined as those equal to or below four nanograms per milliliter (ng/mL) of blood. At the same time, more than half of men with higher PSA levels are, in reality, cancer-free.

Before discussing the leading ideas for minimizing that error rate, we should acknowledge that use of PSA testing for mass screening has long been, and remains, controversial. In essence, some physicians, especially in Europe, doubt the need for identifying microscopic prostate cancers, which develop after a once normal prostate cell becomes unresponsive to the usual controls on proliferation and migration. Microscopic tumors, they point out, often grow too slowly to cause symptoms in a man's lifetime or to affect how long he lives. Consequently, doctors may do more harm than good by exposing large numbers of men to PSA testing, to follow-up tests (such as ultrasound imaging and biopsy) in response to elevated scores and then, if a hidden spot of cancer is found, to the side effects of therapy.

Other physicians, we among them, counter that the PSA test generally finds malignancies that will, in fact, affect survival time (become "clinically significant"). Moreover, scientists cannot yet distinguish conclusively between microscopic tumors that will become lethal and those that will not; hence, denying treatment to men with such cancers would certainly doom an unpredictable group of them to a premature death.

Improving Detection

Even investigators who favor PSA screening are unhappy about its lack of specificity. One scheme that may better distinguish patients who have cancer from those who do not relies on a sliding scale of acceptable PSA levels, with the top limits for normal starting low and rising with age. The approach is based on the observation that as men grow older their PSA concentrations tend to climb, even if the prostate contains no cancer. Ideally, such sliding scales should lower the threshold of suspicion for men in their 40s and 50s, in whom prostate cancer tends to be most aggressive. And they should spare more men in their 60s and 70s from unnecessary follow-up tests. Some doctors worry, however, that age-adjusted scales will miss malignancies in the older groups.

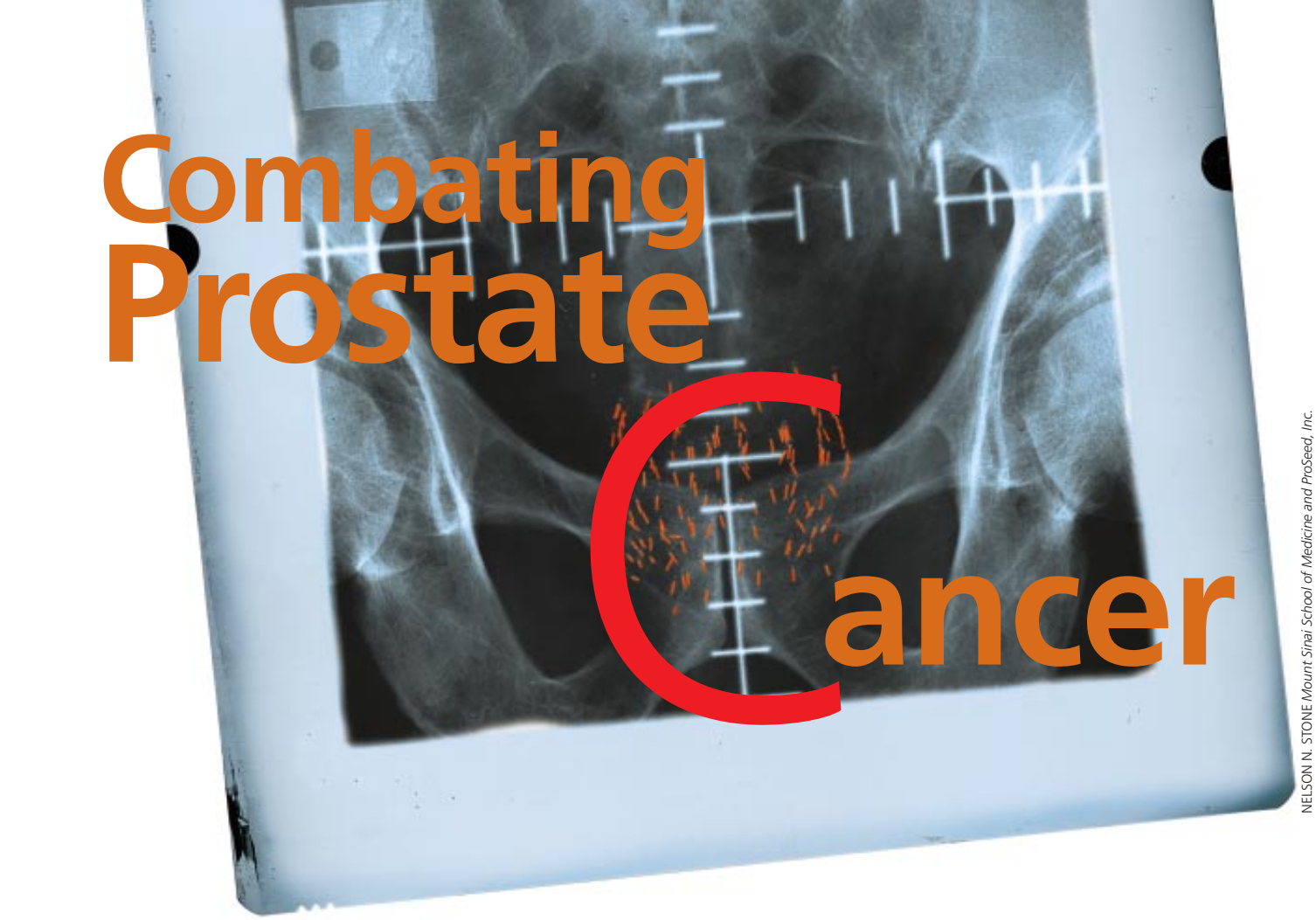
When two or more consecutive PSA results are available, the rate of change from one year to the next, otherwise known as PSA velocity, can help single out patients who have cancer, regardless of whether their raw PSA scores are in the normal range. Increases of greater than 0.75 ng/mL may signify that a biopsy is warranted.

A third manipulation can be especially helpful when a PSA score falls in the gray zone between clearly normal and clearly abnormal, such as between 4 and 10 ng/mL. Along with considering age to decide whether a given patient probably has cancer, physicians can take a blood sample and look at the relative levels of free PSA molecules (those not complexed to other proteins) and protein-bound versions. Men with prostate cancer tend to have an abnormally low ratio of free to bound PSA.

Aside from PSA, other molecules released into the circulation may undergo changes in structure or amount when cancer arises. Scientists are attempting to develop screening tools based on such changes. Certain tests may even identify men who do not yet have prostate cancer but are likely to acquire it; such individuals need extra monitoring and may benefit from promising ideas for prevention. Researchers, for instance, are investigating whether high levels in the blood of a molecule called insulinlike growth factor-1 can serve as a warning that a man has prostate cancer or is at increased risk for its development.

Geneticists, too, are searching for indicators of an increased propensity for prostate cancer. Brothers and sons of women who have breast cancer or who carry a mutant form of genes

Combating Prostate Cancer



NELSON N. STONE *Mount Sinai School of Medicine and ProSeed, Inc.*

RADIOACTIVE PELLETS* (red), *or "seeds," have been inserted into the prostate gland in an attempt to destroy a cancer within it. At one time, seed implantation, also known as brachytherapy, produced disappointing results. The seeds were often distributed unevenly, leaving some parts of the gland untreated. Today templates placed on the patient, combined with real-time ultrasound imaging of the prostate, enable physicians to achieve a uniform distribution and a much improved success rate.

linked to breast cancer and prostate cancer have a somewhat elevated risk. Genetic screening tests for susceptibility to prostate cancer have not yet been perfected, however.

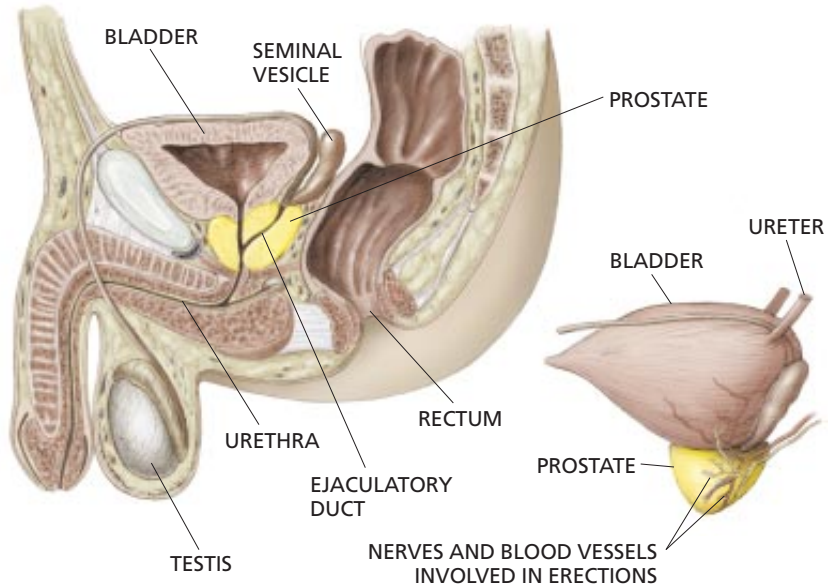
Who Can Be Cured?

If a man is ultimately found to have prostate cancer, doctors will assess its stage, or extent of spread. Accurate evaluations are critical, because the stage determines the type of therapy a patient should receive. Risks of intensive, curative therapies include impotence, incontinence and feminization, among other effects. Unfortunately, existing diagnostic methods often produce an inaccurate picture of tumor stage, but new tools are helping to remedy this serious problem.

Regardless of doctors' best efforts, men are understaged—initially deemed to have less advanced cancer than they actually harbor—with astonishing frequency. This misassessment is true of so-called clinical staging, which is based on tests, such as analysis of prostate tissue, before a patient has therapy. To a lesser extent, it also plagues "surgical," or "pathological," staging, which usually provides a truer picture of a patient's status. In surgical staging, pathologists examine any tissue removed during a prostatectomy, including a margin around the prostate, some lymph nodes and the seminal vesicles. Malignant cells in the margin or in other extraprostatic tissue indicate that a tumor presumed to be confined to the prostate is more extensive than was thought and has a good chance of having spawned undetected metastases (cells proliferating at distant sites).

Tools able to provide more informative images of the primary tumor are beginning to improve the accuracy of clinical diagnosis. In most patients, neither computed tomographic (CT) scanning nor standard ultrasound procedures can provide a clear picture of a tumor or its spread beyond the prostate gland. An experimental ultrasound technique now showing promise applies a signal-processing technology known as spectrum analysis. Sound waves are bounced off the prostate as usual, but the machinery analyzes all the information in the sound echoes instead of the much smaller fraction used by more ordinary ultrasound devices. Then a sophisticated computer program translates the full set of data into a three-dimensional view of the gland.

New approaches to magnetic resonance imaging (MRI) are under study in parallel. MRI devices emit magnetic fields around a patient to produce cross-sectional images of the body. Typical systems do not yield high-resolution maps of a prostate tumor. But when a patient also has a small emitter of electromagnetic waves inserted into his rectum (an "endorectal coil"), the resulting views can often show whether,



VISIBLE PRODUCTIONS, LLC

PROSTATE GLAND **(yellow),** ***which helps to maintain the viability of sperm and participates in semen production, lies close to several structures involved in bladder, bowel and sexual function. As prostate tumors grow, they often impinge on the bladder or urethra, causing such urinary problems as frequency and urgency. Treatments deployed for prostate cancer can likewise affect the surrounding tissues, causing incontinence, rectal inflammation, impotence or other effects.***

and how far, the tumor has grown past the prostate gland. Magnetic resonance spectroscopy, which measures metabolic activity in a viewed area, may further help distinguish between normal and cancerous tissue.

A more mathematical strategy for gauging a cancer's true stage has recently begun to serve as an aid for deciding on a course of treatment. It relies on tabulations of the probability that a patient clinically determined to have organ-confined prostate cancer actually has a more extensive primary mass or metastatic disease.

Other novel approaches to clarifying a tumor's true stage concentrate specifically on assessing signs of aggressiveness—that is, they look for new clues to the growth rate and metastatic potential of the cancer. Before treatment, these tests can help determine which patients need prompt, and possibly systemic, therapy. They might also provide some guidance for deciding which technically curable tumors do not, in fact, need to be cured—because they are so slow-growing that they are unlikely to cause symptoms and turn lethal in a patient's lifetime. Assessments of tumor aggressiveness can also help indicate whether follow-up systemic treatment is advisable for patients who have already undergone surgery or radiation.

Several emerging or experimental approaches to predicting tumor behavior fall under the heading of "molecular" staging tools. They look at genetic alterations or at changes in protein structure or concentration that are more characteristic of metastatic prostate cancer than of localized tumors or normal prostate tissue. If those features appear in biopsied tissue, they suggest the cancer can be fast-growing and prone to metastasizing.

The study of cancer-related molecules is also generating fresh ideas for pinpointing metastases. A promising avenue of research involves molecular "highlighters" (usually radioactively tagged antibodies) that circulate in the body, finding and marking prostate cells in nonprostatic tissues. Normal prostate cells cannot survive outside their original milieu. The presence of prostate cells far from the gland indicates that the wayward cells are cancerous and may well have succeeded in establishing metastases in new sites. A test deploying an antibody able to recognize a protein called prostate-specific membrane antigen is already in clinical use, and others are being investigated.

Making Therapy More Effective

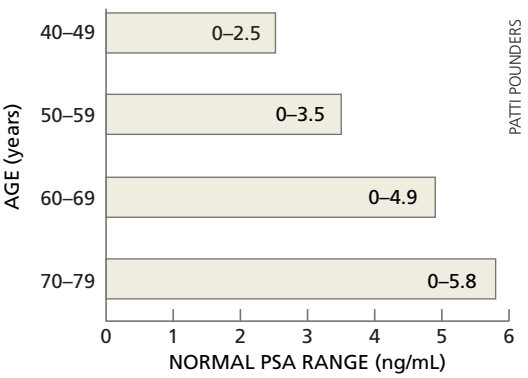
Just as detection and staging methods are undergoing change, so, too, are treatments. Surgery is still considered the "gold standard" for treating organ-confined disease, because it has produced the best survival times in long-term studies. But enhanced approaches to radiation therapy and new applications of hormonal therapy are improving survival prospects.

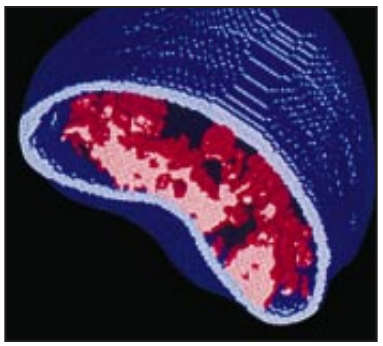
Classical radiation therapy takes the form of external-beam radiation, in which a linear accelerator moves around a patient, shooting intense x-rays or gamma rays at the prostate from several different angles. This rotation aims to limit the radiation hitting healthy tissue in the "line of fire" while still providing a high aggregate dose to the tumor (although normal tissue close to the prostate still receives potentially damaging doses).

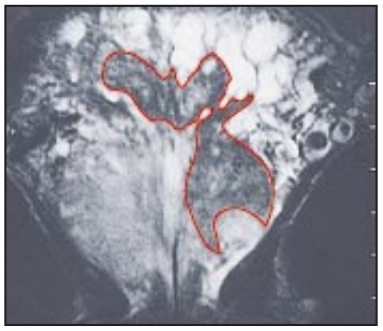
In a recent study that followed patients for five years, this approach appeared to be as successful as prostatectomy in curing relatively small tumors confined to the prostate gland. When a mass in the prostate is large, standard doses of radiation may be too low to erase all cancer cells. And the higher doses that are needed may be too toxic to structures close to the prostate.

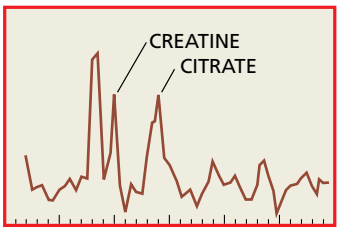
A relatively new technique, known

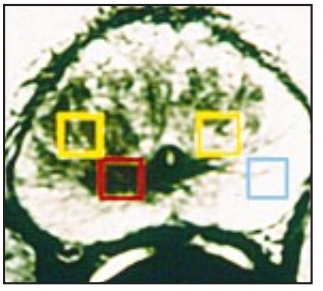
LEVELS OF PSA (prostate-specific antigen) in the blood can indicate whether a man is likely to have prostate cancer and thus needs diagnostic testing. One scale adjusts the definition of an acceptable PSA value as a man ages, instead of using four nanograms per milliliter of blood (ng/mL) as the top normal level for everyone. Doctors are still debating the best cutoffs, however.

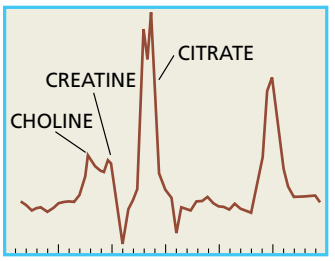












***NEW IMAGING APPROACHES** may help reveal the full extent of a tumor before treatment is attempted. A technique that extracts extra information from ultrasound echoes can generate a three-dimensional picture* (top left) *that distinguishes normal tissue from a tumor* (red). *Combining an "endorectal coil" with standard magnetic resonance imaging (MRI) can also delineate a tumor* (bottom left, outline added). *And MR spectroscopy can add an extra dimension to such results* (below). *By assessing differences in metabolic activity across an imaged gland* (graphs), *it distinguishes cancerous tissue* (red box) *from normal tissue* (blue box). *The yellow boxes highlight noncancerous abnormalities.*

as three-dimensional conformal radiation therapy (3-D CRT), makes it possible to deliver once unheard-of doses to organ-confined tumors without increasing the risk of damage to nearby tissues. In this method, now available at most major medical centers, radiation physicists produce cross-sectional CT scans of the prostate. Then a computer combines the information into three-dimensional images of the gland as it will be "seen" by the rotating accelerator. The computer also directs the accelerator to shape and reshape the radiation beam so that at all times it matches the precise dimensions of the individual's prostate and thus minimizes the amount of radiation striking outside the gland's boundaries.

Although 3-D CRT has not yet been shown conclusively to produce higher cure rates, it appears to be promising and does seem to limit side effects. Proof of greater effectiveness might be needed before the technique, which is more expensive than standard radiation therapy, becomes accepted universally.

Many men choose a rather different form of radiation therapy: brachytherapy. A surgeon puts radioactive, rice-size pellets directly into the prostate, where they emit radiation from within the gland. The seed procedure often proves appealing to patients because implantation is relatively simple, requires minimal hospitalization (lasting perhaps a day or two) and leaves no surgical wound. If a tumor extends past the prostate, brachytherapy may be combined with external-beam radiation to attack the outer reaches of the mass.

When brachytherapy first became available decades ago, it seemed promising, but its long-term results were unsettling. The pellets had to be placed without the aid of imaging technology, and parts of the prostate often ended up with few or no radioactive seeds. These days many brachytherapists perform the procedure with the help of a template placed between the scrotum and rectum. The approach now appears to be about as effective as external-beam radiation or surgery for treating men who have low-stage tumors that seem relatively unaggressive.

A number of medical centers offer another fairly simple way to attack tumors in the prostate: cryosurgery, or freezing the gland with probes containing liquid nitrogen or argon gas. Cryosurgery comes with a high risk of side effects, and its ability to eliminate tumors is not known.

We are impressed by recent findings supporting the value of hormonal therapy as a supplement to classical "definitive" therapies (those intended to achieve a cure). Preliminary reports suggest that such combination therapy often works better than the standard therapy alone. When hormonal therapy is delivered before radiation or surgery, it is known as neoadjuvant hormonal therapy. When it is given with or after those treatments, it is known as adjuvant hormonal therapy.

The idea behind combination treatment is simple. Neoadjuvant therapy aims to shrink bulky tumors so that radiation or surgery can eliminate them more readily. In the case of brachytherapy, for instance, physicians have a hard time inserting the radioactive seeds into glands containing large tumors. Reducing the tumor before insertion can ease the procedure and potentially increase the chance of success; it may also reduce side effects. Adjuvant therapy aims to mop up stray cells left behind at the tumor site after primary treatment and also to destroy cells elsewhere that have broken free and could pose a metastatic threat. Animal studies suggest that hormonal therapy delivered before or with radiotherapy may, in addition, increase the sensitivity of prostate cancers to radiation.

Hormonal therapy usually consists of a combination of two drug classes. One such class includes so-called superagonists of gonadotropin-releasing hormone (GnRH), a substance that is released by the brain and that leads ultimately to testicular secretion of testosterone, the major male hormone that promotes the growth of prostate tumors. GnRH superagonists initially result in increased testosterone secretion, but after a few weeks they inhibit testosterone manufacture and cause prostate tumors to shrink. The other drug class is made up of antiandrogens, which block testosterone from inducing the proliferation of cancerous prostate cells. A permanent means of halting testosterone production—surgical removal of the testes (bilateral orchiechtomy)—is also available.

The most impressive results have

top left: ERNEST J. FELEPPA *Riverside Research Institute, New York City; bottom left:* CLARE TEMPANY *Brigham and Women's Hospital, Boston; right:* HEDVIG HRICAK *University of California, San Francisco*

come from clinical trials of hormonal therapy combined with radiation. For example, in a study of 415 patients treated in Europe, those receiving three years of adjuvant therapy plus radiation survived longer than those who received radiation alone. Estimates projected that 79 percent of the first group but only 62 percent of the second group would still be alive five years after treatment. The study did not include a "hormonal-therapy-only" arm, however, so it cannot address whether combination therapy is superior to hormonal treatment alone.

Long-term investigations of neoadjuvant therapy have yet to be completed, but some studies strongly suggest a benefit from this approach as well. At the Memorial Sloan-Kettering Cancer Center in New York City, one of us (Fair) and his colleagues evaluated the ability of this treatment to ensure that tumors initially believed to be organ-confined were indeed fully within the prostate at the time patients underwent a prostatectomy. They found that three months of presurgical treatment increased the incidence of organ-confined disease at surgery and markedly lowered the frequency of worrisome tumor cells in the outer edges of the excised tissue. Yet to be determined is whether the tumor control achieved in the study will translate into a lower incidence of local recurrence or metastasis in the subjects and, hence, into enhanced survival rates.

Sadly, we have no dramatic news for men who already have metastatic cancer. Hormone therapy usually extends life, but tumors eventually become resistant to the treatment. Investigators are attempting to uncover the molecular basis of this resistance, in the hope of designing drugs able to overcome it.

Scientists are, however, closing in on a way to eliminate a major drawback of hormonal therapy in those with metastatic prostate cancer. Recall that the GnRH superagonists usually prescribed as part of hormonal therapy initially stimulate testosterone production before shutting it down. In that early phase the drugs thereby promote tumor growth and so can exacerbate symptoms. An agent that blocks GnRH activity directly, an antagonist called Abarelix, is being developed by one of us (Garnick) and colleagues at Praecis Pharmaceuticals in Cambridge, Mass., in collaboration with other companies.

As many researchers struggle to improve existing tools for detecting and managing prostate cancer, others are attempting to develop entirely new kinds of therapies. Most of these future treatments would work systemically, preventing cancer cells that escaped first-line attack from establishing metastases. If metastasis could be prevented, death rates from prostate cancer would surely plummet.

Promise of Dietary Intervention

One idea being evaluated is decidedly low-tech: nutritional intervention, especially adoption of a low-fat diet. Conceivably, nutritional interventions might also prevent the development of symptomatic primary tumors.

A suggestive epidemiological finding comes from placing countries on a grid according to death rate from prostate cancer and average fat consumption per person. The U.S. and western European nations, which ingest the most fat, also have the highest prostate cancer mortality rates. Conversely, men in the Pacific Rim nations, who consume the least fat, have a much lower death

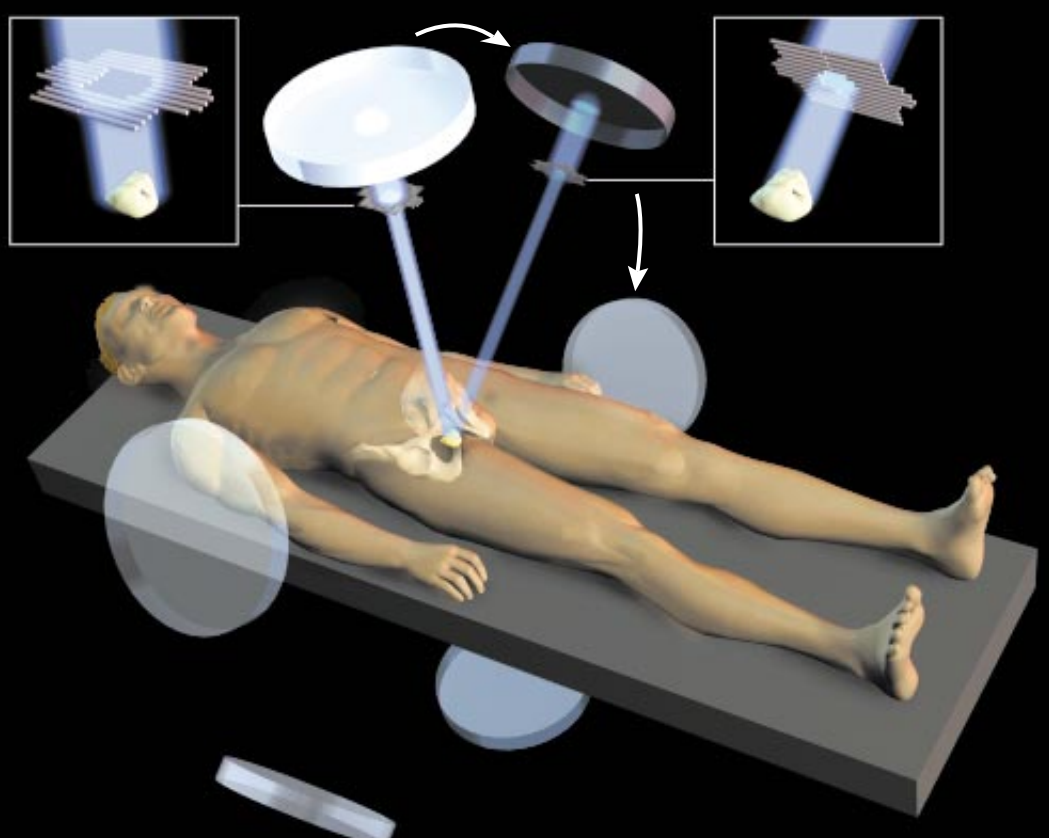
VISIBLE PRODUCTIONS, LLC

A Radiotherapy Advance

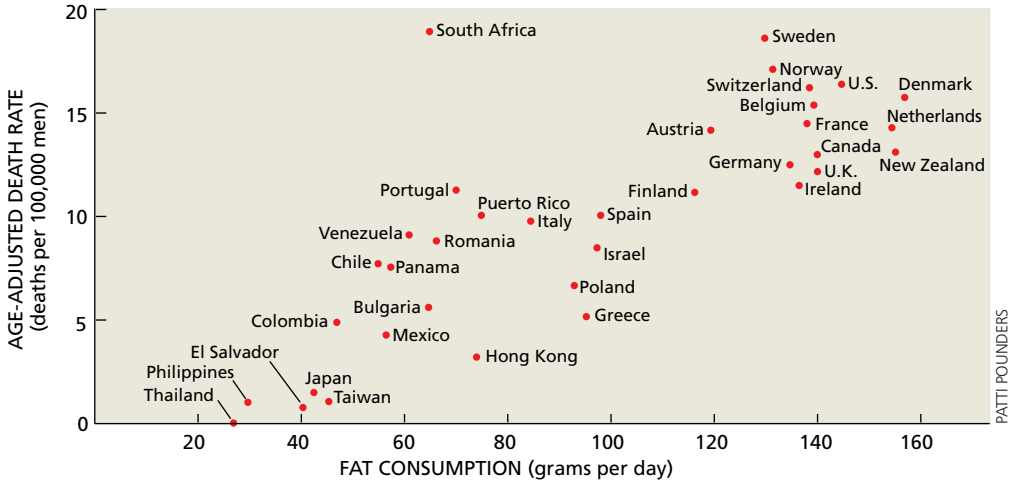
Three-dimensional conformal radiation therapy (3-D CRT) allows doctors to increase the doses of radiation delivered to the prostate gland without increasing damage to nearby tissues. As is true of standard radiation therapy, a linear accelerator rotates around a patient, pointing x-rays or gamma rays toward the prostate. But the conformal technique adds an important twist.

Before treatment is begun, digital images of the individual's prostate are prepared and compiled into virtual 3-D models of how the gland will "look" to the accelerator from all angles. Then the accelerator shapes the beam to match those "beam's-eye views" (*insets*), thus reducing the amount of radiation hitting the bladder, rectum or other unintended targets.

—M.B.G. and W.R.F.



A Link between Diet and Prostate Cancer



SOURCE: K. K. Carroll and H. T. Khor in Progress in Biochemical Pharmacology, *Vol. 10, 1975*

MORTALITY from prostate cancer tends to be highest in those countries that register the most fat consumption. This finding, from 1975, is one of many indicating that consuming fats can serve to promote prostate tumor growth and that a low-fat diet might limit such growth.

rate from prostate cancer. Moreover, a laboratory experiment conducted by Fair and his co-workers at Sloan-Kettering found that human tumors transplanted into mice grew fastest in groups of mice that had diets highest in fat.

Another dietary component that seems to influence prostate cancer—this time as an inhibitor of growth—is soy protein, a substance consumed in abundance in Japan. Soy reduces the amount of testosterone circulating in the blood and also inhibits an enzyme that converts testosterone to its more potent form in prostate cells. Some evidence implies that tomato products, vitamin E and the mineral selenium can inhibit tumor growth as well. Other components of food are also being explored as potential contributors to, or shields against, prostate cancer. Needed now are more human studies assessing the protective value of diet.

Interestingly, animal studies indicate that dietary components can increase or decrease the tendency of a microscopic cancer to grow into a dangerous mass but do not affect the processes that originally cause a normal cell to become malignant. This insight may help explain why the incidence of silent microscopic cancer (as measured by autopsies of men who die from causes unrelated to prostate cancer) is essentially the same worldwide, whereas that of palpable prostate cancers (ones that have managed to grow) varies with geography.

Tomorrow's Therapies

Several other intriguing ideas for systemic therapy derive from an emerging understanding of how prostate cancer develops and becomes increasingly aggressive. These ideas are in very early stages of exploration.

A number of the genes and proteins being evaluated as markers of virulence seem to participate in tumor progression. Some of those substances, therefore, may eventually serve as useful targets of therapy. Similarly, workers are trying to identify agents that will stop fats from stimulating molecular pathways that facilitate tumor growth.

In recent years, scientists have shown that few, if any, cancers can reach large sizes unless they sprout new blood vessels. Drugs that block such tumor blood vessels from arising are already being studied in many cancer patients, including those with prostate cancer.

Gene therapy is another possibility, although scientists will probably need many years to perfect this approach. A particularly intriguing idea would be to deliver genes coding for substances that are toxic to cells. If those genes were engineered to switch on only in prostate cells, they would give rise to the toxin in the prostate and in metastatic deposits but would have no effect on and do no damage to other kinds of cells.

Also in its infancy, but quite tantalizing, is research into vaccines: substances that would incite the immune system to attack cancerous prostate cells anywhere in the body without hurting nonprostatic cells. The immune system is capable of attacking malignant cells but often fails to recognize them on its own. Vaccines could potentially be administered both to prevent prostate cancer in men at high risk and to prevent recurrence in those who have already been treated for the disease.

Such targeted therapies will undoubtedly take many years to develop and evaluate. In the interim, research into improving detection, staging, treatment and prevention is intensifying. Certainly, much work remains to be done before the challenges of combating prostate cancer can be overcome, but we are heartened to see the pace of research quickening. SA

The Authors

MARC B. GARNICK and WILLIAM R. FAIR co-direct a yearly international conference on emerging treatments for prostate cancer. Garnick is clinical professor of medicine at Harvard Medical School and a physician at Beth Israel Deaconess Medical Center. He also serves as the chief medical officer at Praecis Pharmaceuticals in Cambridge, Mass., where he is developing a new hormonal therapy for prostate cancer. Fair is Florence and Theodore Baumritter and Enid Ancell Chair of Urologic Oncology and director of the John and Robert Bendheim Prostate Cancer Research Center at Memorial Sloan-Kettering Cancer Center in New York City. He is also professor of urology at Cornell University Medical Center.

Further Reading

THE DILEMMAS OF PROSTATE CANCER. Marc B. Garnick in *Scientific American,* Vol. 270, No. 4, pages 72–81; April 1994.

THE PATIENT'S GUIDE TO PROSTATE CANCER. Marc B. Garnick. Plume/Penguin Books USA, 1996.

PROSTATE CANCER: EMERGING CONCEPTS, Parts I and II. Marc B. Garnick and William R. Fair in *Annals of Internal Medicine,* Vol. 125, No. 2, pages 118–125; July 15, 1996, and Vol. 125, No. 3, pages 205–212; August 1, 1996.