

The Neglected Sex Gland

A protein in the blood forecasts cancer of the prostate

By KATHY A. FACKELMANN

Tucked away under the bladder in a man's body is the walnut-size prostate gland that often labors away under a cloak of anonymity. Many men don't know they have this male sex gland. Others don't know where the prostate is located or what it does. And when something goes wrong with the prostate, even doctors can't always tell whether the condition is a life-threatening cancer or a relatively harmless enlargement.

For much of a man's life, the prostate gland produces some of the fluid, or semen, that carries sperm through the urethra during sexual climax. But after age 50, the prostate can begin causing trouble.

For reasons not well understood, the prostate gland often gets larger as a man ages. Indeed, more than half of all men in their 60s suffer from an enlarged prostate, a condition called benign prostatic hyperplasia (BPH). If the gland gets too big, it can squeeze the urethra, the tube that also carries urine from the bladder. This pressure can cause a weakened or hesitant urine stream or an increased need to urinate, especially at night.

While the symptoms of BPH can be annoying, a second, more serious threat involving the prostate gland plagues older men: cancer. Men with BPH are not at increased risk for prostate cancer; however, symptoms of prostate cancer and BPH are often identical. Even worse, doctors don't have a foolproof diagnostic test to distinguish between BPH and cancer of the prostate, a disease that will kill an estimated 34,000 men in the United States in 1992 alone.

Until recently, doctors looking for prostate cancer had to rely on a test known as the digital rectal exam. After pulling on gloves, the physician inserts a finger into the rectum and probes for any hard lumps that may indicate the presence of cancer. While this time-honored test does reveal some malignancies, it misses a large number of prostate tumors. Furthermore, the rectal exam often turns up only advanced cancers — those that have spread beyond the prostate wall and thus are more deadly.

Within the last few years, a protein known as prostate-specific antigen (PSA) has taken center stage in the fight against this potentially lethal cancer. For some

time after PSA's discovery more than 20 years ago, the molecule attracted little attention. Then, during the 1980s, a slew of researchers began to take another look at PSA. The scientific community's renewed interest in PSA accelerated about a year ago, when William J. Catalona of the Washington University School of Medicine in St. Louis and his colleagues published a pioneering report on PSA and prostate cancer.

By measuring the concentration of PSA in the bloodstream, Catalona's team found they could detect more prostate cancers than they could by relying on the rectal exam alone.

"We found that PSA was the most powerful test we had," Catalona says about the study, reported in the April 25, 1991 *NEW ENGLAND JOURNAL OF MEDICINE*. The findings fueled a virtual boom in PSA blood tests ordered by doctors around the country.

More than a year later, most scientists would agree that, although a powerful predictor of prostate cancer, PSA has shortcomings. Still, "PSA may be better than anything we have, even though it's not perfect," Catalona says. His group and several other research teams are now searching for ways to refine PSA's ability to flag prostate cancer and distinguish it from a harmlessly enlarged prostate.

The key to curing prostate cancer is finding the malignancy very early in the disease process — well before the cancer spreads. Catalona's team now has evidence that the PSA blood test can detect prostate cancer before it travels to the bone or other body sites. That finding sparks the hope that early detection will lead to longer lives for men afflicted with this disease, Catalona told *SCIENCE NEWS*.

His team began their study by looking at a group of 274 men being evaluated for possible prostate cancer. All had gone to their doctor prior to 1991 and had received the traditional rectal exam, which discovered suspicious lumps in the prostate. A biopsy, in which a physician takes a needle and withdraws a small number of cells from the suspect tissue, showed that 36 of the 274 men had cancer of the prostate. Furthermore, 24 of the 36 (67

percent) had advanced cancer at the time of their diagnosis.

Because doctors had to rely on the rectal exam, most of the cancers they detected had already metastasized. Such cancer is much harder to cure because it has spread beyond the prostate, Catalona notes. To see if they could detect prostate cancer before it runs amok, the team began to use the PSA blood test as a screening test for outwardly healthy men. They recruited more than 10,000 men age 50 and over. None had reported trouble with his prostate prior to entering the study. These recruits all had an initial PSA blood test, followed by a biopsy if their PSA values were at least 4 micrograms per liter of blood — concentrations that can indicate a malignancy.

That initial screening identified 244 men with prostate cancer. However, just 86 (35 percent) of those men had prostate cancer that had spread at the time of their diagnosis.

Men who passed the initial PSA test came back for additional blood tests later in the study. The team discovered another 46 men with prostate cancer during this process, but just 13 of them (29 percent) had advanced cancer.

Taken together, these results indicate that widespread PSA screening could stop many prostate cancers before they can kill, Catalona says. He presented his group's data in May at the American Urological Association meeting in Washington, D.C.

Nearly 70 percent of prostate cancers discovered by means of a rectal exam have already reached a potentially deadly stage. PSA screening reverses that lethal trend, enabling doctors to find cancers still confined to the prostate gland. At that stage, surgeons can remove the diseased gland or radiologists can kill the cancerous tissue with radiation therapy. In most cases, such therapy can cure prostate cancer. Anticancer drugs are not as effective.

Men appear more willing to have their blood drawn for a PSA test than to undergo a rectal exam, Catalona notes. While most men are used to getting their blood tested for cholesterol and other markers of disease, they often balk when doctors suggest an uncomfortable rectal exam, he says.

Nonetheless, men have the best chance of finding prostate cancer early if they allow doctors not only to take blood for a PSA reading, but also to do the rectal exam, which sometimes finds very small tumors that won't markedly elevate PSA readings, Catalona adds.

"The most complete evaluation of the prostate gland is when you use both PSA and the rectal exam," agrees PSA researcher Joseph E. Oesterling of the Mayo Clinic in Rochester, Minn. "That allows you to detect the greatest number of prostate cancers."

What is PSA anyway? Like cholesterol, which the body manufactures to help keep cell membranes strong, PSA serves a much-needed function in the healthy man. The protein is manufactured by the epithelial cells that line the prostate gland. When a man ejaculates, his semen is initially very thick. To help the sperm swim to their destination, PSA liquefies the semen.

While young men have a low concentration of PSA in their bloodstream, that concentration tends to rise as they age. Scientists believe the increase occurs because the prostate expands as a man gets older. More prostate cells simply mean more PSA in the blood, explains Jay D. Pearson of the National Institute on Aging's Gerontology Research Center in Baltimore.

If PSA concentrations in the blood simply reflected the size of a man's prostate, however, oncologists wouldn't be able to home in on cancers. Researchers also know that malignant tumors secrete far more PSA than would be expected based on volume alone. Pearson and H. Ballentine Carter of the Johns Hopkins University School of Medicine in Baltimore and their colleagues used that knowledge to devise another method of investigating prostate tumors.

The team relied on the Baltimore Longitudinal Study of Aging, a long-term project funded by the National Institute on Aging. Participants in the study, which began in 1958, undergo several days of medical tests every two years. For their particular project, the researchers searched study records to find 20 men who had developed benign prostatic hyperplasia and 18 who had received the bad news of prostate cancer at some point during their participation. For purposes of comparison, they also identified 16 men with no sign of prostate trouble. All of the men had participated in the aging study for at least seven years.

Next, the researchers analyzed each volunteer's blood samples, which had been frozen and stored at two-year intervals. The investigators wanted to get a picture of how PSA changes over time, especially among men eventually stricken with prostate cancer.

Their findings proved intriguing: Five

to 10 years before a diagnosis of prostate cancer, PSA concentration in the blood starts to rise rapidly and exponentially. In men who eventually developed BPH, PSA also increased, but at a much slower rate. The team detailed their findings in the April 22/29 JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION.

By tracking the rate of change, the researchers could differentiate between men who would eventually develop BPH and those who would suffer prostate cancer. About 40 percent of men with BPH will have a PSA blood level of 4 micrograms per liter or higher. Right now, doctors often err on the side of caution and recommend that such men get a

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— William J. Catalona

biopsy to look for malignant cells.

However, Carter and Pearson suggest that the rate of change in PSA concentration could help distinguish between patients who have cancer and those with BPH. If further study confirms this hypothesis, doctors could advise a man with a PSA of 4 and no other risk factors to get another PSA blood test in six months.

Why not send all men on for a biopsy? Pearson says such a strategy is unnecessary and puts an emotional strain on the men, who are told they might have cancer. On the other hand, doctors are understandably cautious when it comes to metastatic prostate cancer—a disease for which there is no cure.

Today, prostate cancer is the second leading cause of cancer deaths in U.S. men. According to a June 12 report in the Centers for Disease Control's MORBIDITY AND MORTALITY WEEKLY REPORT, age-adjusted incidence

rates of prostate cancer rose steadily for both black and white men during the 1980s.

Why the increase? It may be that men simply are living longer and are thus giving tiny prostate tumors the time to grow and cause problems. Many men age 50 and older have tiny prostate tumors that go undetected and never cause harm.

Indeed, some scientists discount the value of massive screening tests for a condition that afflicts huge numbers of men—in most cases with no ill effects. Not every man over the age of 50 should get an annual PSA, Carter says. He believes that doctors should test for prostate cancer only when men complain of symptoms or have a family history of the disease. On the other hand, Catalona takes a more aggressive approach, advising men to obtain a PSA blood test once a year, regardless of whether they notice signs of a swollen prostate.

One key question lies at the heart of that scientific debate: Would men live longer if physicians adopted a widespread PSA screening program? Nobody really knows the answer.

To determine whether the PSA screening test will catch cancers early enough to boost longevity, the National Cancer Institute (NCI) plans a trial of 74,000 men age 60 to 74 who have no symptoms of prostate cancer, says NCI's Barnett Kramer. Some will get an annual PSA blood test and a rectal exam; others will get just the rectal exam. The study will take up to 16 years.

"The question is, Do we wait years before we start using this powerful new test?" asks Catalona. "With all these men dying of prostate cancer, at the end of 16 years half a million men would be dead of prostate cancer."

Similar reasoning led the American Urological Association to recommend that men age 50 and over get an annual rectal exam and blood test for PSA. For men who are at risk because of a family history of prostate cancer, the group advises the same strategy starting at age 40. The American Cancer Society is considering a similar recommendation.

The public health debate about PSA can be viewed as a personal dilemma. Should men age 50 and over ask for this experimental test at their regular check-up? Men should talk about the risks and benefits of a PSA blood test with their doctor, Kramer advises. The down side of the test is that it may detect slow-growing cancers and thus may lead to unnecessary and risky treatments such as chemotherapy, he says. On the other hand, PSA may identify potentially lethal tumors that are on the verge of spreading, Kramer notes.

Until researchers get some definitive answers about PSA's ability to save lives, "it boils down to an individual decision," Kramer says. □