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Introduction

At age 55, I underwent a routine PSA (prostate-specific antigen) blood test. I'd spent the previous five years living in remote parts of Asia where this screening test for prostate disease was unavailable. A visiting doctor friend of mine (general practitioner) had done a digital rectal exam (the dreaded "finger wave") three years prior, and he found that my prostate was generally enlarged, but there were no areas of hardness. The prostate border was smooth and regular. I'd had minor urinary symptoms for years, getting up two to three times each night to urinate. This was compatible with my age and the moderately enlarged prostate my doctor friend felt when he examined me, but it was certainly no cause for concern. Benign prostatic hypertrophy (BPH), as this condition is called, is quite common in men over 50 and usually responds to medicinal treatment.

I started taking a remedy containing saw palmetto oil to shrink the prostate gland. I also started taking a new over-the-counter "wonder drug" called DHEA. I really liked the effects of DHEA. I felt much more energetic and focused. As you'll read later, however, DHEA and prostate cancer don't mix.

When my PSA (prostate specific antigen) came back at 11.2 (normal is less than 4.0), I was shocked, to put it mildly. I had been extremely health conscious since graduating from medical school nearly 30 years earlier. I ate very little red

meat, used only "good" oils, exercised regularly, and took antioxidant-rich vitamin supplements. Surely this was a lab error. I repeated the test and the result was the same. From my medical training, I knew that at my age a PSA of this magnitude meant that the probability of prostate cancer was high.

I sought out a top-notch urologist who did another digital rectal exam (DRE). Unlike the one three years earlier, this test revealed an area of hardness in the right base of the prostate. A few more blood tests and a prostate biopsy later and the diagnosis was confirmed—prostate cancer.

I felt scared and confused. What to do? As I had done so often in medical school, I decided to find out as much as possible about this disease and its treatment. What I discovered was one of the most muddled areas in modern medicine.

Recognized experts in the field diametrically disagreed with each other as to the preferred treatment. To be sure, there were many options, but none was a clear-cut magic bullet. And there were many nasty potential side-effects to consider. Despite my medical training, given my level of confusion, I found it hard to imagine how someone who was not a doctor could successfully navigate the maze of options.

Indeed, most don't. They simply put themselves in the hands of their local urologist, do what he says, and hope for the best.

My purpose in writing Prostate Cancer—Prevention and Cure is to familiarize as many readers as possible with the current state of the art in the diagnosis and treatment of prostate cancer. This book is not only for someone who's been diagnosed with prostate cancer, but also for anyone who's a potential candidate for it—in other words, all men. It's also for women whose partners are either prostate cancer patients or who simply want to understand the disease in the event that it enters their lives.

In writing this book I reviewed more than 2,000 papers in the medical literature. Armed with this background information, I then spoke with many of the top doctors in the field of prostate cancer—urologists, medical oncologists, and radia-

tion oncologists. Each expert has his own view of the disease: which treatment to use, how to evaluate side-effects, and an overall approach, or philosophy, for dealing with prostate cancer at different stages.

However, this book has been written with the best interests of the patient as the overriding paradigm. I've tried to demystify the way doctors think in order to provide you with clearer insights, allowing you to take control of your illness. Then, once you've gotten rid of the cancer cells, I teach you the most optimal course for staying healthy.

The fact is, there's only one person whom you can rely upon to significantly improve your chances of cure from prostate cancer: You! Your active involvement in managing your disease is likely to increase your chances of success.

From this book and other sources, learn all you can. Ask questions, even if you think they might be dumb or embarrassing (such as those that concern sexual implications, incontinence, or bowel problems). Do not blindly accept medical pronouncements.

Optimistic and informed action is likely to improve your overall health and outlook.

Cancer is usually a defining event in someone's life. It can be viewed as a curse or a wake-up call. If you choose to behave as a passive victim, you are less likely to survive, and the quality of your life may erode. However, if you choose to view it as a catalyst for change in lifestyle and thinking, it can become a blessing in disguise. The course you set now will shape the balance of your life. It's up to you.

SECTION I:

WHAT IS PROSTATE CANCER?

Prostate Cancer Basics

In the year 2000, roughly 500,000 American men died of cancer. If you're between the ages of 45 and 64 your chances of dying from cancer are greater than from any other cause; if you are older than 65, cancer deaths are surpassed only by deaths from heart disease.

The two most common cancers for men are skin cancer and prostate cancer. Cancer of the prostate is second only to lung cancer as the leading cause of male cancer deaths. According to the American Cancer Society, in 1998 about 184,000 American men were newly diagnosed with prostate cancer and 39,000 died from it. In 2002, new cases were estimated to be 189,000, with 30,200 deaths. While new cases have increased slightly during the past four years, deaths from prostate cancer have decreased by about 23%. This dramatic decrease in death rate is probably attributable to both earlier detection and better treatment. If you're over 50, statistically you have a 50% chance of getting prostate cancer at some point in your life.

The prostate (not prostrate) gland is about the size and shape of a plump chestnut. The gland is surrounded by a protective sheath called the prostate capsule. The gland/capsule is located in the space between the bladder and the rectum.

The urethra, through which both urine and semen flow, passes through the middle of the prostate. When the size of the prostate increases due to either benign or malignant growth, it can compress the urethra, producing symptoms. These symptoms may include frequent urination, especially at night, start-and-stop urination, difficulty in starting the stream of urine, and reduction in the rate of flow.

The prostate is an expendable gland. You can live quite nicely without it. Its limited functions include providing fluid that may help transport sperm and protecting the urinary system against bacterial infections. It's not required for erections or fertility. As men age, the prostate becomes a liability.

Most aging men are well aware of the annoying symptoms of an enlarged prostate, which is caused by cell proliferation, whether benign (non-cancerous) or malignant. Benign prostatic hypertrophy (BPH), as it's called, is a common problem. Fortunately, the symptoms of BPH can usually be controlled by medicines or herbal formulas.

Another common prostate problem is prostatitis, or inflammation of the prostate. It's usually caused by bacteria. Often the invading bacteria are difficult to identify. Symptoms of prostatitis can mimic those of BPH or prostate cancer. Prostatitis can also dramatically raise blood levels of PSA (prostate specific antigen). Measuring the PSA is a screening test for prostate cancer (see "Screening and Diagnosis"). Prostatitis can sometimes be mistaken for prostate cancer; when the two occur together, prostatitis can make the cancer seem more advanced than it really is.

Prostate cancer may produce symptoms identical to BPH or prostatitis. But it can also grow for years without causing any symptoms at all. The cause of prostate cancer is unknown. About 9%-15% of the cases are hereditary. Inflammation from hit-and-run infections, hormone levels, and lifestyle factors like diet and exercise are thought to play a role in the development, growth, and spread of prostate cancer.

What all these possible causes have in common is that they damage the DNA, or the genetic blueprint, of prostate

cells. The DNA of our cells is perpetually being damaged by internal and external factors, and our cells are constantly repairing DNA damage. A delicate balance exists between factors that stimulate cell growth and agents that trigger cell death. This balance is controlled by proteins. The production of these proteins is controlled by the DNA of genes. One gene produces one specific protein.

Some of these proteins turn cells "on," some turn cells "off." If the DNA in particular genes is damaged, this fine on-off balance is disrupted. Genes that stimulate prostate cell growth may act unimpeded by genes that suppress cell growth, if these "suppressor" genes have been damaged (see "Risk Factors: Age").

For example, some genes control a built-in suicide program in cells. In due course they program cells to die. This process of programmed cell death is called "apoptosis." You will see this term often when you read about prostate cancer. When genes that control apoptosis are damaged, cells continue to live longer than normal. Much longer. New cells continue to be formed, but old cells don't die. This leads to clumps of cells growing out of control: cancer.

As these clumps of aberrant cells continue to grow, they require more nutrients. When a clump of cancer cells reaches no more than one cubic millimeter, about the size of the head of a pencil, it requires new blood vessels to provide nutrients for continued growth. The cancer cells secrete proteins that stimulate cells lining small adjacent blood vessels to grow, thereby creating new minute vessels. This process is called "angiogenesis" (blood-vessel development). It's important to understand that no cancer, no matter which kind, can grow without new blood vessels. In fact, one of the most fertile fields of anti-cancer research is the development of "anti-angiogenesis" agents, drugs that interfere with the ability of cancer cells to form new blood vessels. Prostate cancer is no exception. Anti-angiogenesis is discussed in detail in the chapter titled "New and Future Developments."

As prostate cancer cells continue to grow, cells can break

off from the clump and be carried away in either the blood or lymph systems. Most of these cells are killed by the body's immune system. Special lymphocytes (white blood cells) called T-cells, and other lymphocytes called natural killer (NK) cells, attack and kill these circulating cancer cells. But as their number increases, some cancer cells may slip through the body's defenses. They may wind up establishing themselves far away from their original source. Here they grow, forming new clumps and stimulating the formation of new blood vessels. These distant groups of cancer cells are called "metastases." These cells grow faster than the surrounding normal cells and don't die. Like weeds in a garden, they eventually crowd out the cells in the organs where they settle, compromising their function.

Prostate cancer has a particular affinity for bone. Most prostate cancer cells that break off of a clump wind up in the bone or bone marrow. In fact, the cause of death for most men who die from prostate cancer is complications from bone metastases. One of the most important goals in the treatment of prostate cancer, as you will read in the chapter on bisphosphonates, is to prevent it from getting established in bones. Accomplishing this goes a long way toward improving your chances of recovery.

Prostate cancer is not a single disease. In other words, it exhibits different characteristics in different individuals. This makes intuitive sense, since there are undoubtedly multiple causes. It's not surprising, therefore, that some men have very slow growing cancers and other men have aggressive cancers. Actually, the two are probably different diseases entirely. As such, it makes sense to treat them differently. We will discuss treatment options later. For now, suffice it to say that men who have slow-growing cancers have more treatment options and generally less disease than men with aggressive cancers. Determining whether you're dealing with a tortoise or a hare is a major role of the tests your doctor will order for you.

Prostate cancer usually develops in more than one location in the gland (multi-focal). By age 90, virtually all men

have microscopic pockets of prostate cancer. This has been confirmed by autopsy results. But most men die with their prostate cancer, rather than from their cancer. As you will read, there are things you can do, steps totally within your control, to delay the development and growth of this cancer. Understanding the risk factors and lifestyle factors that affect your chances is a good start.

1

RISK FACTORS

Who gets prostate cancer? Who's at risk? Some risk factors, like age, race, and family history, are well-established. Recent studies also present strong evidence for dietary factors, hormonal influences, lack of exposure to sunlight, and environmental contaminants as significant influences on the incidence of prostate cancer. Some medical conditions, like diabetes and obesity, appear to predispose men to prostate cancer. Other potential risk factors, including vasectomy, baldness, and body type, are more controversial.

If you have known risk factors, you can increase your level of vigilance to reduce your risk. Annual PSA blood testing and digital rectal exam (DRE) from as early as age 40 can help in early detection and treatment of prostate cancer. Dietary and lifestyle changes may slow a developing cancer. Thus, there are steps you can take if you are at increased risk. Let's look at each risk factor.

Age

Not much you can do about this one. The older you are, the greater your risk of getting prostate cancer. You may have heard this truism: "All men will die from prostate cancer if they don't die of something else first." This indicates how common prostate cancer is in aging men. And it is common. Upwards of 20% of all American men will get clinically signifi-

cant prostate cancer sometime in their lives. Many more will have microscopic pockets of prostate cancer found at autopsy that caused them no trouble in life. In fact, virtually 100% of men lucky enough to make it to 90 have evidence of cancer in their prostate tissue. No other cancer is so prevalent. Yet most men die from other causes.

It's generally believed that these microscopic cancer foci are precursors (forerunners) of clinical prostate cancer. Interestingly, these small pockets of cancer occur pan-culturally—Japanese, Chinese, and Thai men are just as likely to harbor them as Swedes, Frenchmen, or African-Americans. But clinical prostate cancer is a far different matter. Here, other factors seem to come into play changing insignificant microscopic lesions into a potentially life-threatening disease. Both hereditary and environmental forces may influence this unwanted metamorphosis.

That brings us back to age. The chance of a man 39 years old or younger developing this active clinical form of prostate cancer is less than 1 in 10,000. From 40 to 59 the odds dramatically plummet, to 1 in 78. Between 60 and 79 they drop again, to 1 in 6!

Why does age make such a difference? A big part of the reason seems to be the increased tendency for DNA to be damaged over time. DNA controls all cell processes. It's the stuff that genes are made of—the building blocks of life. Destructive environmental forces, such as radiation, pesticides, heavy metals, and free radicals, damage DNA. As we've seen, our bodies are constantly repairing damaged DNA. But if destructive elements overwhelm our ability to mend DNA, cells become abnormal. Over time, this can lead to cancer. As we age, it appears, there may be a build-up of damaged DNA. Our bodies may not be as efficient repairmen.

One class of genes that's pivotal in keeping prostate cancer at bay is the tumor suppressors briefly mentioned earlier. There are at least several of these. As the mysteries of the human genome are unraveled (the complete genome has now been mapped), more of these tumor-suppressing genes are likely

to be discovered. The proteins produced by these genes are a large family of natural proteins that block numerous pathways involved in progression to malignancy.

One key suppressor gene is called p53; this gene is crucial for DNA repair. When it's altered, damaged DNA can't be mended. About half of the men with advanced prostate cancer have mutations (alterations) in p53. By special testing, changes in p53 can be detected in a prostate biopsy specimen. If p53 has mutated, the chance of the cancer recurring after treatment is higher. For this reason, some oncologists (cancer specialists) will treat patients who have altered p53 at the time of diagnosis more aggressively. So it may be worthwhile requesting this test when you have a biopsy that shows prostate cancer.

It's likely that advancing age increases the chances of gene mutations. A probable example of this phenomenon comes from a potential risk factor reported in the American Journal of Epidemiology in late 1999. Investigators from Boston University Medical School found that a father's age (not the mother's) at the time of conception affected the chances of his sons developing prostate cancer. Men who have male children early in life impart far less risk of prostate cancer to their offspring than men who reproduce later in life. Men aged 38 or more had about a 70% greater chance of having an affected son than men under age 27. Fathers between 27 and 38 had less risk of having an affected son than older men, but their risk was still 20%-30% higher than men whose age was less than 27 years old. The researchers postulated that the reason for this previously undiscovered risk factor might be genetic changes (mutations) to sperm cells due to advancing age.

Age may also predict the ability to cure prostate cancer. A recent study out of Johns Hopkins University discovered that older men who underwent radical prostatectomy (removal of the prostate by surgery) had less chance than younger men of being cured of their disease. In fact, the researchers were surprised to discover that age was a better predictor of disease outcome than the highly informative PSA levels. PSA is the global blood test used to screen men for prostate cancer.

Although controversial, it's generally agreed that PSA levels above 4.0 nanograms per milliliter (ng/ml) are abnormal. In men with prostate cancer aged 40 to 50 with PSA levels greater than 10 ng/ml and who had no detectable lump in the prostate on rectal examination, the chance of surgical cure was 73%. This compared with only a 49% chance of cure in men 61 to 73 years of age with comparable PSA levels, rectal exam status, and identical surgery. So advancing age seems not only to predispose men to the development of clinically significant prostate cancer, it also appears to reduce the chances of cure.

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Race

Race significantly influences the incidence of prostate cancer. Asians have very low rates, Caucasians intermediate rates, and African-Americans very high rates of prostate cancer development. The difference in death rates between African-Americans and American whites is surprisingly large. As a report from the National Institutes for Health (NIH) puts it, "The disparity in mortality rates from prostate cancer is greater between white and black men than for any other type of cancer in the U.S. and possibly the world." Several studies confirm that African-Americans have a 35% higher chance of developing prostate cancer, and a more than 220% chance of dying from it, than white men.

If the gap between African-Americans and western Caucasians is large, the disparity between African-Americans and Asians is cavernous. African-Americans are between 50 and

200 times as likely to die of prostate cancer than their various Asian counterparts.

Meanwhile, Asian men living in the United States have more chance of getting prostate cancer than men who remain in Asia. Put it all together and it's highly probable that both environmental and hereditary forces are at work in determining the racial make-up of who gets prostate cancer and who doesn't.

Why are African-Americans more prone to develop prostate cancer and much more likely to die from it than American whites? This is a hotly debated topic in the corridors of a number of centers for prostate cancer. The definitive answer remains elusive. A combination of factors seems to be involved.

One element that has received a lot of attention in medical publications of late is that African-Americans are less likely to be screened for prostate cancer. This may be due both to a lack of awareness and a lack of access to PSA blood testing and digital rectal exams. Without proper screening, black men often have significantly more advanced and aggressive disease at the time they first seek medical attention. Often they will have troublesome symptoms that lead them to seek medical help.

One multi-institutional study from North Carolina showed a statistically significant inverse correlation between income level and health-insurance status and advanced prostate cancer in black men. The study found that black men with lower income levels and/or no health insurance were more likely to have advanced cancer than those with higher income and health insurance. No such correlation was observed in white men in North Carolina.

Another study showed significantly lower levels of literacy in black men showing up at the doctor's office with prostate cancer than in whites. In a study of 212 lower-income-level men diagnosed with prostate cancer in Louisiana and Illinois, only 48% of African-Americans possessed at least a sixth-grade literacy level; 91% of Caucasian men of comparable income

had achieved at least sixth-grade literacy. Interestingly, in this study, when adjustments were made for literacy, age, and geographic location, race was no longer a predictor of advanced disease. The authors postulate that low literacy rates in African-Americans may lower their awareness to the availability of screening. They suggest that literature designed specifically to literacy level might go a long way toward rectifying the increased risk among black men.

Although screening is getting the lion's share of racial attention lately, it's unlikely to be the whole story. For one thing, African-Americans had higher incidence and mortality before screening became popular. Also, researchers at Wayne State University's Harper Hospital led by Dr. Powell found that black men have a greater risk of recurrent cancer than white men if the cancer has spread beyond the prostate. These investigators observed that African-American men and Caucasians develop prostate cancer at similar ages. But across all age groups, black men have metastatic cancer much more often than whites. They concluded that the reason black men have worse outcomes is due to more aggressive cancers in black men under 70 years of age. Why? See below.

These findings were confirmed by research from the Southwest Oncology Group (SWOG). At the May 2000 meeting of the American Urological Association (AUA), Dr. Thompson revealed that in the SWOG data black men had more extensive disease and more bone pain than whites. Additionally, race independently predicted survival outcome when variables like age, bone pain, etc. were factored out.

Besides race, other considerations that might affect risk in African-American men include diet, hormonal influence, infections, and response to sunlight.

There is now considerable evidence, though not yet conclusive, that consuming fat may stimulate changes from dormant to active prostate cancer. Some investigators have noted that African-Americans have more fat in their diets than whites. Similarly, whites take in more fat than Asians. Mortality from prostate cancer correlates with fat intake.

Not only the amount of fat in a man's diet may predispose him to prostate cancer, but how much its cooked also seems to make a difference. Cancer-causing compounds, called heterocyclic amines (HAs), are formed when meat is cooked. According to a recent study, meat type, intake rate, cooking method, and meat doneness all influence the amount of carcinogenic HAs that are formed. Pan-fried meats produce the most HAs. Surprisingly, chicken (with skin) is the largest source of HAs among the different types of meat.

This study showed that African-American men over age 30 consume about three times as much HAs as whites. A national survey showed a preference amongst African-American men for well-done meat, which increases the HA content. About $^{2}/_{3}$ of HA content is comprised of a compound that causes prostate DNA to mutate and induces prostate cancer in rats.

A recent study by the National Cancer Institute (NCI) showed that increased amounts of animal-fat intake doubled the risk of blacks getting prostate cancer, but did not significantly increase the risk in whites. This lends support to the idea that cooking with its increased HA content is a significant risk for prostate cancer and predominately affects black men.

The risk of prostate cancer progressing to advanced disease is also increased by animal-fat intake, but in this case both blacks and whites with comparable fat intake are equally affected. Since HAs have been implicated in the initiation of prostate cancer and the amount of animal fat consumed has been associated with the cancer progressing and spreading, this NCI finding makes sense.

Young black men have been found to have a higher level of circulating testosterone than white men of equivalent age—about 15% higher. Testosterone levels also appear to decrease more slowly in aging black men. Although these hormonal differences may account for some of the black-white difference, this has not been proven.

African-American men have a higher incidence of a known prostate cancer risk factor called prostatic intra-epithelial hyperplasia (PIN). Thought to be a precursor to cancer,

PIN is an area of inflammation and cellular growth within the prostate. It may be part of a process that starts with an infection in the prostate and becomes an area of smoldering inflammation. Then, under hormonal influences primarily from DHT and estrogens, DNA changes may occur. A study by Dr. Sakr at Wayne State University noted that blacks had more areas of PIN in their prostates and that the PIN tended to be of higher grade (more abnormal) than in a comparable group of white men. This difference started when men were in their twenties.

The researchers compared the prostates of black and white men in several ways. At autopsy they found that extensive higher-grade PIN was present in 7% (25/364) of black men less than 50 years of age compared to 2% (4/208) of white men. When they examined prostates removed surgically in a group of 1,200 men, they consistently found more extensive and higher grade PIN in African-Americans, especially in those under 50. In men with disease discovered by PSA testing and no evidence of cancer upon digital rectal exam, 33% of blacks had extensive high-grade PIN compared with only 12% of whites, a highly significant difference.

Dr. Sakr concludes: "Our findings suggest an important role for high-grade PIN in the development of clinically significant, potentially aggressive prostate cancer in African-American men."

Yet another ingredient that may influence African-American susceptibility is response to sunlight. Here, there is some conflicting data. While blacks seem to have reduced ability to convert sunlight into vitamin D, recent data show that vitamin D levels are equivalent in black men whether or not they have prostate cancer. Vitamin D is thought to play a protective role in halting the growth of prostate cancer. What significance, if any, it has in relation to the higher death rate from prostate cancer in African-Americans is unclear. It seems prudent, however, for all men with prostate cancer to periodically check their vitamin D blood levels. If low, whether the man is black

or white, he'll probably benefit from supplemental vitamin D. The active form of vitamin D, known as calcitriol (Rocaltrol), is available only by prescription and must be taken under doctor's care (see "Sun Exposure" later in this chapter and the section on vitamin D in the "Nutrition" chapter).

A great deal of work is being done to reduce the risk of death from prostate cancer in African-American men. One technique that shows great promise is interactive screening. Dr. Myers and colleagues report in a recent issue of the journal Cancer that understandable printed material, combined with telephone follow-up, lead to a far greater turnout for a screening examination and PSA blood test when compared with men who only received a letter inviting them to be screened. Undoubtedly better screening will help close the gap between black and white men.

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Heredity

Regardless of race, the risk of prostate cancer escalates for a man when his immediate male relatives (father, son, or brother) are diagnosed with this disease. If your father (or son) is affected, your risk doubles. If your brother is affected, your risk triples. One study reported that if your brother or father got prostate cancer at 50 or younger and another first-degree relative (brother, father, son) is also diagnosed, your chances of developing prostate cancer increase seven-fold!

Overall genetic factors are believed to account for about 9%-15% of all cases of prostate cancer. However, for men under age 55, the chance of genetically determined disease skyrockets. In this group 43% of all instances of prostate cancer are thought to be due to genetic factors.

Due to the increased risk, for men in families with known prostate cancer, especially when the onset in a close relative occurs early in life (age 50 or less) or if more than one first-degree relative is involved, initial screening for prostate cancer should begin at age 35. Normally, screening is not recommended until age 50.

Generally, although hereditary prostate cancer starts earlier

than non-hereditary prostate cancer, it does not appear to differ significantly in its characteristics or survival patterns.

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Obesity and Fat Consumption

Besides being at greater risk for heart disease and diabetes, obese men appear to be more vulnerable to aggressive prostate cancer than men who are overweight, or of normal weight. Dr. Amling and associates reported at the AUA meeting in May 2000 that 20% of a group of 860 men who had surgery for prostate cancer were obese. These men had significantly more aggressive prostate cancers on average, they got cancer much earlier in life, and they had more advanced cancer than slimmer men. Dietary factors are an obvious place to begin in accounting for these differences.

Obese men have high levels of insulin-like growth factor-1, a hormone that has been associated with markedly increased chances of developing prostate cancer (discussed in depth later in this section). If the increased risks of heart disease, diabetes, and other debilitating conditions are not persuasive enough to compel obese men to lose weight, perhaps the increased risk of dying from prostate cancer added to the list will help provide sufficient motivation.

One popular theory floating around the halls of prostate cancer academic centers is that various kinds of fat might stimulate the change of dormant prostate cancer to the more

dangerous clinically significant form. Since microscopic prostate cancer is essentially equally prevalent for all cultures, diet, specifically fat consumption, is one element that might make a difference. A 2002 study from the Fred Hutchison Cancer Research Institute in Seattle, Washington, shows an association between fat intake and total caloric intake, not with the initiation of prostate cancer, but rather with its spread (see "Nutrition").

Fat intake is discussed in detail in the chapter "Nutrition." Suffice it to say here that animal fat (saturated fat) and polyunsaturated oils containing either linoleic acid (corn oil, soybean oil, safflower oil, etc.) or linolenic acid (flax oil) are potential contributors to the promotion of prostate cancer. Char-broiling or frying animal or fish fat produces cancer-causing substances known as heterocyclic amines that cling to the surface of fat molecules. Heavy ingestion of these carcinogens may increase risk.

In addition, nutrients that have medical evidence to support a protective effect against damage from fat ingestion include selenium, vitamin E, soy protein (but not soybean oil), green tea, cruciferous vegetables and sprouts, silymarin, and curcumin (see "Nutrition"). Olive oil and oil from fish appear to be helpful. However, since olive oil is high in calories, it's probably best to use only the necessary amounts for cooking and salad dressing. Olive oil should be the predominant oil consumed. Other beneficial oils are macadamia nut, avocado, and walnut oils.

HELPFUL HINT

Avoid eating animal fat. If you eat fish, eat it raw (sushi and sashimi), steamed, or poached, to minimize heterocyclic amines consumption.

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Environmental Hazards

More and more evidence is now coming out on the link between environmental contaminants and cancer. In mid-2000, the Washington Post published a summary of a report yet to be released from the Environmental Protection Agency (EPA) on dioxin. Dioxin is a bi-product of waste incineration, as well as paper-pulp production and other industrial sources. You may be aware that Agent Orange, the defoliant used in the Vietnam War, has been shown to significantly increase the risk of a variety of cancers. Dioxin is the prime active ingredient of Agent Orange. The EPA now concedes, according to the Post, that dioxin is a "human carcinogen."

Accumulating in animal fats, fish fats, and dairy products, dioxin is ubiquitous—people worldwide have measurable blood-dioxin levels. This toxin accumulates over time and the effects are cumulative. The EPA now estimates the risk of cancer from dioxin consumption to be 10 times as high as previous estimates. Cancer of the lung and lymphoma are increased by dioxin exposure. Since toxin exposure is usually not organ-specific, it's likely that dioxin increases the chances of getting a variety of cancers. I would not be at all surprised to ultimately discover that prostate cancer is one of these.

Another risk factor for cancer is traffic pollution. Two recent Scandinavian studies showed a clear-cut increase in lung cancer in people exposed to prolonged periods of heavy traffic. In a Swedish study, 30-year exposure resulted in a 40% increase in the chances of getting lung cancer for both smokers and non-smokers. Ten years of exposure increased lung cancer probabilities by 20%.

One contaminant in auto-exhaust fumes is cadmium, a heavy metal. Although cadmium in polluted air has not been directly linked to prostate cancer, prostate cancer is an

occupational hazard for workers exposed to cadmium in battery manufacturing. Other substances that increase the risk of prostate cancer are pesticides, metallic dust, liquid fuels, lubricating grease and oil, and aromatic hydrocarbons. Dr. Kristan Aronson found that in Montreal, Canada, men working in aircraft manufacture, gas and water utilities, and around jet fuels had an increased risk of prostate cancer. Farmers regularly exposed to pesticides and herbicides also appear to be more vulnerable. Dr. Aronson estimates that about 10% of prostate cancer cases are due to occupational hazards, primarily exposure to environmental toxins.

Lack of Exposure to Sunlight

As you'll read in the Nutrition chapter, there is considerable evidence that vitamin D may retard the growth and spread of prostate cancer. Vitamin D production depends upon the skin's exposure to sunlight—specifically UV-B rays, according to Dr. William Grant. Demographically, the incidence of prostate cancer in the United States increases incrementally as you head south to north. The farther north you live, the greater your chances of getting prostate cancer. This may be due to a deficiency of vitamin D.

Although most studies of cancer and sunlight use average yearly amounts, Dr. Grant believes that lack of winter sun is the key variable. The long northern winter may deprive men of UV-B rays, impairing their ability to make vitamin D. This may account for increases in prostate cancer oc-

HELPFUL HINTS

Avoid walking or jogging in areas with heavy traffic. Select organic produce whenever possible to reduce pesticide ingestion. Thoroughly soak all fruits and vegetables in water before eating. Peel apples, pears, persimmons, and peaches, if not organically grown. Buy organic strawberries whenever possible. Straw-berries, although rich in a nutrient associated with a reduction in prostate cancer, are one of the most highly sprayed fruits.

currence in northern areas. By the way, according to Dr. Grant, winter UV-B exposure also reduces the risk of colon and breast cancer. It appears that those winter vacations to sunny destinations may have even greater benefits than mere stress reduction.

2

SCREENING

More than 10 million Americans who have had cancer are living today. I'm amused when people I know come up to me, look searchingly into my eyes, and ask, "Are you all right?" The clear implication is that they believe, since I have prostate cancer, I must be dying. A female friend who hadn't seen me in more than a year became wide-eyed and blurted out, "Lee, you still have hair!"

Cancer is not a death sentence. The earlier it's discovered, the greater your chances of cure. A simple blood test (PSA) and an annual digital rectal exam (DRE) can pick up most prostate cancers while they're still imminently curable. As you'll read in the "Treatment" section, men with tumors caught early do well regardless of which treatment they select; men with more advanced cancers at the time of diagnosis have fewer treatment choices and tend to do more poorly.

PSA

The PSA blood test has revolutionized the evaluation and treatment of prostate cancer. PSA stands for prostate specific antigen. For practical purposes, significant amounts of PSA are produced only by prostate cells. The antigen's main purpose is thought to be in helping to dissolve a gel that forms after ejaculation (from a little leftover semen). In a normal

prostate, PSA goes directly into seminal fluid, not blood. But small amounts "leak" out and diffuse into the circulation. These minute amounts can be measured by sensitive assays in nanograms per milliliter (ng/ml). When prostate cells become cancerous, however, their normal orientation and structure change. Instead of "leaking" into circulation, cancer cells actively release PSA into the fluid that surrounds them. The result is that cancer cells elevate blood PSA levels 30 times more than normal cells!

PSA blood tests to screen men for prostate cancer started being used in the mid-1980s. Even today, there is considerable debate in the medical literature as to whether PSA screening is worthwhile. Against PSA screening are the following arguments:

• PSA may be elevated by diseases other than prostate cancer: specifically, BPH and prostatitis. Elevated PSA levels may lead to unwarranted prostate biopsies, causing patients needless anxiety and discomfort.

• Even if an elevated PSA results in the ultimate discovery of prostate cancer, unnecessary treatment with potentially serious side effects may be inflicted on a man who has no symptoms. This may seriously, and unnecessarily, compromise his quality of life.

Although there is some credence to these positions, they are overwhelmed, in my opinion and in the opinion of most top prostate academicians, by the fact that PSA testing saves lives. Although screening impugners argue that this has not been firmly established, I disagree. I believe the evidence is far too strong to be denied. Consider this:

• After consistently rising for 20 years, the death rate from prostate cancer has been falling since the early 1990s. The National Cancer Institute reported a reduction in the number of deaths from prostate cancer from 25 per 100,000 men in 1990 to 17 per 100,000 men in 1995. This dovetails perfectly with the effects of PSA testing. During this five-year period, death rates in younger Caucasian males declined nearly 12%. Although the decline in death rate was not as dramatic in

African-Americans, it still went down along the entire age spectrum. The smallest decrease in mortality rate was seen in elderly black men—a 3% decrease.

• Deaths from prostate cancer continue to fall. From 1997 to 2002 they fell by an additional 27% in American men, according to the American Cancer Society.

• A massive study of 65,123 men was conducted in Tyrol, Austria. Here it's standard operating procedure to aggressively treat virtually all men diagnosed with prostate cancer. Ninety-six percent of the men with prostate cancer had a radical prostatectomy (prostate removed by surgery). In a study begun in 1993 Dr. Bartsch and associates compared the death rate of Tyrolean men who had been screened (and treated) with mortality statistics from the rest of Austria. They found a 48% decrease in deaths from prostate cancer in the men from Tyrol.

• In the area around the Mayo Clinic in Rochester, Minn., where testing is prevalent, death rates have also dropped considerably more than the national average.

• A Finnish study randomized men in two groups. One received screening, the other didn't. Of the men in the group to be screened, about 10,300 men took a PSA test, while 23,400 men didn't. The investigators found that 86% of cancers found in the screened group were confined to the prostate at the time of diagnosis. This compared with only 67% in the unscreened group, a highly significant difference. What this study strongly shows is that screening allows prostate cancer to be picked up at an earlier, less dangerous stage in the screened group.

Estimates from prostate cancer experts are that PSA testing allows prostate cancer to be picked up as much as five years earlier than by standard examination (DRE).

Decreasing death rates in all age groups and races in the United States sharply reduced death rates in screened men in Tyrol, Austria, and clinically less advanced prostate cancer in PSA-screened men in Finland—all potent evidence in support of screening.

It now appears that there are three different forms of prostate cancer: those that are aggressive, fast-growing, and

potentially lethal; those that are very slow-growing and far less likely to be fatal; and those in between whose behavior may mimic either fast- or slow-growing types. This intermediate type is often lumped in with aggressive tumors.

One of the most important aspects of screening is that aggressive cancers can be picked up while they're still curable in men with 20-30 years of life left. In my case, for example, I had a moderately aggressive cancer that showed signs it was about to spread, if it hadn't already done so. I had no symptoms. The PSA test was part of a routine check-up. Had I waited even one more year, my cancer would almost surely have spread. The PSA screening test probably saved my life.

And I'm not alone. There are more, many more, men I know personally, all with one thing in common. They were in great health, but a routine PSA showed they had prostate cancer that was at a very dangerous stage. There is no doubt that, left undiscovered, many of these cancers would likely have been fatal.

Twenty-five percent of all prostate cancers are found in men under age 65. It's in this group, men who have 20 or more years to live, that PSA testing is most beneficial. Make no mistake. PSA testing saves lives. If you're 50 years of age or older, you should have an annual PSA blood test and a DRE. (As you'll read shortly, less frequent testing may be possible if your PSA is 2.0 or less.) If you have a brother or father who has prostate cancer, you should start annual screening at age 40. African-Americans should also consider starting screening at age 40. An initial PSA test at age 35 for men at very high risk (like a father and brother with prostate cancer) is probably warranted. If less than 1.0, it would not need to be repeated for five years.

At the May 2002 annual meeting of the American Society of Clinical Oncology (ASCO), Dr. E. David Crawford of the University of Colorado made a provocative presentation.

He and his associates reviewed the medical records of 27,863 men between the ages of 55 and 74 who had annual PSA tests. Fifty-five percent of these men had initial PSAs of

2.0 or less. The generally accepted upper limit of normal for PSA testing is 4.0.

In the nearly 15,000 men whose first PSA was 2.0 or less, Dr. Crawford's group found the following:

• 98.8% of men whose initial PSA was 1.0, or less, had a PSA less than 4.0 five years later.

• 98.8% of those whose initial PSA was 1.0 to 2.0 had a PSA less than 4.0 two years later.

Based on these findings, Dr. Crawford recommends that men with PSAs of less than 1.0 be tested every five years; men with PSAs 1.0 to 2.0 be tested every two years; men with PSAs higher than 2.0 be tested annually.

If these recommendations are accepted and the American Cancer Society is giving them a hard look, it would save the health system $500 million to $1 billion annually in PSA testing costs, according to Dr. Crawford.

Key Reference

Proceedings of the 38th Annual American Society of Clinical Oncology meeting notes. May 18-21, 2002.

Why is the issue of PSA testing still hotly debated? First, medical insurers are still trying to determine the economics of screening. And second, the results of a prospective, randomized study, the sine qua non of indisputable proof in the medical world, are not yet in. Dr. Crawford's findings, if accepted as standard, may help bridge these gaps.

HELPFUL HINT

PSA screening has been shown to help detect prostate cancer at an earlier stage when it's still confined to the prostate. Prostate-confined tumors have very high cure rates. PSA screening saves lives.

The National Cancer Institute (NCI) mounted just such a study in 1994. But it could take another 10 years before the definitive results

are fully known. This issue has such wide-ranging ramifications that it's rumored the NCI may take a look at the accumulated results as early as next year. While we wait for the definitive answer, I strongly urge you to get tested.

DRE (Digital Rectal Exam)

Part of the screening process for prostate cancer involves a DRE. Although not the most pleasant experience for most of us, it's generally more embarrassing than uncomfortable. It should be done by a urologist, a doctor who specializes in diseases of the urinary system (including the prostate gland). The doctor inserts a single, gloved, well-lubricated finger (digit) into your rectum. Then gently (some are more gentle than others) he, or she, will thoroughly examine your prostate. The prostate should feel soft, with a regular outline. Both sides of the gland should be about equal in size and shape. Areas of hardness, irregularity, or asymmetry are warning signs that often point to cancer.

Dr. Jacobsen and his associates studied a large group of men in Minnesota, comparing those who had screening with DREs with those who hadn't. They found that having a DRE during the prior 10 years reduced a man's chance of dying from prostate cancer by 50%. In men who had no symptoms that caused them to seek medical attention, but were in for a DRE as a precaution, the results were even more dramatic. In this group a screening DRE reduced the risk of death from prostate cancer by a whopping 69%!

In the PSA era, the majority of prostate cancers are not identified by the DRE. This is a positive event. I have a close friend who was diagnosed with a moderately aggressive cancer and had a PSA of 22.0. His urologist could not feel any sign of the cancer in this man's prostate. Although generally a PSA of 22 might be considered too high for surgery, my friend "wanted the damn thing out." At surgery, his disease was totally confined to his prostate and his outlook is excellent.

A DRE is an important part of the prostate cancer work-

up, especially the process called "staging," which helps determine risk level. Grin and bare it.

Elevated PSA—Now What?

The "official" normal range for PSA is 0.0 ng/ml to 4.0 ng/ml. For men under 60, PSA readings of between 2.5 and 4.0 are also suspect, especially for younger men. Some urologists do not believe men over 75 should be screened because, even if they have prostate cancer, treatment may not be advisable. Many men of this age will die of other causes long before their prostate cancer kills them. Whether a 75-plus-year-old man should be screened, in my mind, should depend on his overall health. If he is in generally poor health with a myriad of medical problems, I agree that checking for prostate cancer may not be warranted. But if he's healthy, I think he should be tested. Since people are now living longer, he could have 15-20 years left. (With genetic medicine just around the corner, it could be even longer.) He may want to be treated, although surgery might not be his treatment of choice.

Within the "normal" PSA range of 0.0-4.0, there can be big differences in the chances of contracting prostate cancer. Dr. Gann and colleagues found that men with PSAs between 2.01 and 4.0 were five to eight times as likely to develop aggressive prostate cancer over a 10-year period than men with PSAs of less than 1.0.

For this reason, some top urologists, such as Dr. Catalona at Washington University Medical School in St. Louis, believe that all men with PSAs above 2.5 ng/ml should be further evaluated. Twenty-two percent of these men have been found to have cancer when biopsied, and 14% of these were considered to be aggressive cancers (Gleason score of 7 or higher—see "Staging"). Since 81% were found to be contained within the prostate at the time of surgery, Dr. Catalona argues that lowering the upper limit of the screening threshold from 4.0 to 2.6 ng/ml may cure more cancers, by catching them before they spread. At surgery, men with PSAs of 4.0 or less

have about an 83% chance of having the tumor limited to the prostate. This compares to about 70% organ-confined cancers for PSAs 4.0-10.0, and 53% for PSAs above 10.0.

In any event, if your PSA is above 4.0 (or 2.5 to play it safer), additional tests should be done. Often these will show that the increased PSA is not due to cancer. Remember, an elevated PSA can come from benign causes, like BPH and prostatitis. Even with a PSA as high as 10.0 ng/ml, there is only a 50% chance of cancer; with PSAs between 4.0 and 10.0, 70% will be traced to benign causes.

But how do you distinguish between benign and malignant etiologies? The most definitive way is by biopsy (a surgical procedure by which bits of living prostate tissue are removed from different areas of the prostate gland and examined by a pathologist, a doctor trained to identify normal and abnormal cells). But since much of the time biopsies don't turn up any cancer, researchers have (mercifully) looked for less invasive tests that help distinguish between benign disease and cancer.

Just such a test has now been developed that spares men from needless biopsies. The free PSA test is especially useful in the PSA 2.6-10.0 group. Men with PSAs above 10 have such a high risk of cancer that virtually all are biopsied. But PSAs between 2.6 and 10.0 are in a gray area.

PSA travels in the blood either in free form or bound to protein. With prostate cancer the percentage of free PSA tends to be lower than with BPH. The higher the percentage of free PSA, the less likely you are to have cancer.

A number of studies have been done to determine a reasonable cutoff point that will detect the most cancers, while sparing as many men as possible the unpleasantness of a biopsy. A recent (June 2000) study from the University of Washington in Seattle demonstrated that not doing biopsies on men with free PSA percentages of 26.4% or more in men with total PSAs of 4.0-10.0 would have detected 96% of cancers, while eliminating 27% of the biopsies. By lowering the cutoff point for biopsy to 20% free PSA, Dr. Gann and his group,

using a database of 15,000 men from the Physicians' Health Study, determined that 50% of unnecessary biopsies would be avoided, although a few more cancers (11% vs. 4%) would be missed. Like Dr. Catalona, Dr. Gann believes that if free PSA levels are used as a guideline for biopsy, men with PSAs of 3.0 ng/ml and above should be tested. This is not much different from Dr. Catalona's 2.6 ng/ml level. Of note is this fact: 25% of all prostate cancers have PSAs of less than 4.0.

Dr. Roehl, Dr. Catalona, and their colleagues found that out of 132 men who had surgery for prostate cancer at Washington University in St. Louis and whose PSAs were 2.6 ng/ml to 4.0 ng/ml, 80% had no sign of cancer beyond the removed prostate. Yet they determined that in their view, most of the removed cancers were clinically significant and 14% were considered to be aggressive.

What happens if this combination of tests misses a cancer? All is not lost. Since the PSA is already elevated, it will be closely monitored. Dr. Gann observed in his study that cancers missed by combined PSA and free PSA testing probably developed more slowly than detected cancers and were likely to be diagnosed later with the cancer still confined to the prostate. In other words, the missed cancers were unlikely to be the aggressive type.

If the PSA continues rising, a biopsy will undoubtedly be suggested. If you're in this position, you should be aware that free PSA testing is only now starting to become more widely used. If your doctor is not associated with an academic center, he may not be familiar with this test. If you have a PSA of less than 10.0 and your doctor is unfamiliar with a free PSA and wants to do a biopsy, I suggest you educate him. Failing this, it might behoove you to seek help at a university cancer center.

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3

DIAGNOSIS

Prostate Biopsy

Let's say your PSA is 6.0 (too high) and your free PSA comes back at 15% (too low). What's next? Since your free PSA is less than 20%, it's prudent to have a biopsy. This is usually done in the urologist's office. The procedure involves the insertion of an ultrasound device, a plastic instrument about one inch in diameter, into the rectum. The perineum, the area between the scrotum and the anus, is then anesthetized with a local anesthetic. Under guidance from the ultrasound, a special needle is inserted through the now-deadened perineum. The needle has a small nipper attached that can take a snip of the prostate. If done properly, at least six snips from six separate areas should be taken (known as a "sextant" biopsy). Some urologists recommend up to 11 snips (the upper snip limit) from different parts of the prostate. Doctors from M.D. Anderson Cancer Center in Houston, Texas, claim that a greater number of samples is more likely to find cancer, if any is there. I recommend insisting on at least a sextant biopsy. Current thinking is that eight snips is optimal. Biopsies aren't fun, so they should be done correctly the first time.

The reason that an 8-snip biopsy is probably best is revealed by the results of two studies reported in the June 2002 edition of the Journal of Urology, both from excellent

academic institutions. The first, from Dr. Catalona's group at Washington University in St. Louis, Missouri, showed that in 2,526 volunteers who underwent prostate biopsy at this institution using either a 4-snip biopsy (prior to May 1, 1995) or a 6-snip biopsy thereafter, only 75% of cancers were discovered on the first biopsy. Ninety-one percent were uncovered by two biopsies; 97% by three biopsies; 99% by four biopsies. Note that 73% of cancers missed by the first biopsy were discovered by a second 6-snip (sextant) biopsy.

A group at Stanford University studied 185 men whose cancer was missed on the first biopsy using an 8-snip biopsy for the repeat, rather than a sextant biopsy. The 8-core biopsy detected 95% of all prostate cancers, compared to only 73% with 6-cores. Had the 8-snip biopsy been done originally, many of these men would not have to have been subjected to a second biopsy.

How much pain is involved? Depends who you ask. Most urologists will tell you, "It's a little uncomfortable." But when I asked a nurse who had observed many of them, she vouchsafed, "They look pretty bad to me." I decided I didn't want to find out, so I insisted on intravenous Versed, a fast-acting drug similar in effect to Valium. With Versed you don't remember a thing. However, I came out of it a little early—just in time to get the full flavor of the last snip. I practically jumped off the table! The pain was quite sharp; thankfully, it only lasted a couple of seconds. Personally, I wouldn't have wanted to have to endure six bites without good drugs. But some men I talk to say it's no big deal.

This may depend on age. Men over age 65, one study reports, seem to experience less pain than younger men. Whether this is because younger men are more squeamish or the nerve plexus in the area is more sensitive in younger men remains to be established. Whatever the reason, it does seem that, in general, younger men have more discomfort from biopsies.

Dr. Mark Soloway from the University of Miami Medical School has come up with an elegant solution. In the January 2000 issue of the Journal of Urology, he concedes that many

men complain of pain during prostate biopsies. He then details a procedure using local anesthesia to deaden the nerves in the area surrounding the prostate, much as a dentist uses a nerve block to deaden your mouth before drilling. Dr. Soloway concludes: "Many patients have pain during transrectal ultrasound-guided biopsies of the prostate and few clinicians provide a periprostatic nerve block before this procedure. A periprostatic nerve block administered before the biopsies dramatically decreases discomfort. We urge all urologists to attempt this procedure, and we are confident they will adopt it as part of their practice." Amen, Dr. Soloway!

Nitrous oxide (laughing gas) provides another effective form of pain relief during prostate biopsies. In a British study of 110 patients that was randomized, double-blind, and placebo-controlled, men who received nitrous oxide gas instead of air reported a highly significant reduction in pain. In a double-blind study, neither the patient nor the doctor knows which treatment is being administered. Nitrous oxide is safe and seems effective for pain relief from a prostate biopsy.

Forty-nine out of the 51 men who received nitrous oxide said they would have a repeat biopsy (with nitrous oxide) if needed. Of the 45 men who got the air placebo, 2 had to withdraw from the biopsy due to pain; 19 would prefer more anesthesia if the procedure had to be repeated, and two men would prefer general anesthesia.

The study's authors recommend that use of nitrous oxide be widely adopted by others and that it should become the "analgesia (pain reliever) of choice for this procedure."

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Evaluating The Biopsy

It's extremely important that a skilled pathologist examine the prostate biopsy. If the results come back positive for cancer, a second expert opinion is probably warranted. You'll be making consequential decisions based on the biopsy, so you want to be certain of its accuracy. Although I'm sure there are a number of highly competent pathologists at local hospitals across the country (I personally know several), I recommend that you choose a "pathological prostate specialist" for this task. Fortunately, this is easier than it sounds.

Two labs routinely evaluate biopsy specimens from urologists all over the country: UroCor, Inc. in Oklahoma City, Okla., and Dianon Laboratories in Boston, Massachusetts. Either of these is an excellent place to send your biopsy specimens. To accomplish this, simply instruct your urologist on where you want your biopsy sent. Although he may argue that the pathologists at his hospital are "just as good," I think it's better to go with a "known dog." If you insist, your urologist will comply. After all, you're the one paying the bill.

If the diagnosis comes back cancer, a second opinion should be sought from one of these expert pathologists:

Jon Epstein at Johns Hopkins Medical School in Baltimore, Maryland.

David Bostwick at University of Virginia Medical School.

John McNeal at Stanford University Medical School, Palo Alto, California.

Michael Becich at University of Pittsburgh Medical School, Pittsburgh, Pennsylvania.

What Can Be Learned From the Biopsy

Several items of information include the Gleason score, the PIN grade, perineural invasion, p53 and bcl-2, and the number of positive cores. Let's examine them one at a time.

The Gleason Score

The biopsy can provide some very useful information that will help determine the probable extent of your disease and thus the treatment options. First, it will "grade" the cancer. This helps determine how aggressive it's likely to be. Grading uses a scoring system known as the "Gleason score." Named after its creator, Dr. Gleason at Johns Hopkins, the Gleason score determines the extent to which the cancer cells are differentiated (in other words, how close they are to normal cells) and how well the borders of the tumor are defined. The more the differentiation and margin definition, the less aggressive the cancer; the poorer the differentiation and less distinct the cancer margins, the more aggressive the tumor.

In determining the Gleason score, both a primary and a secondary cancer pattern are determined by the pathologist. The Gleason score is expressed as a single number, which is determined by adding the primary pattern and secondary pattern scores together. Tumors are graded from 1 to 5: 1 is the most differentiated (best), 5 the least differentiated (worst). The higher the Gleason score, the worse the prognosis. The best Gleason score possible is a primary pattern of 1 and a secondary pattern of 1. This results in a Gleason score of 2 (1+1). The worst possible Gleason score is 10 (5+5).

A Gleason score of 6 (3+3) or less is a favorable sign. The majority of newly diagnosed cases in the PSA era fall into this category. A Gleason score of 6 or less on biopsy, combined with a PSA of 10 or less and a DRE where the doctor could either not feel a lump or feels a lump comprising half or less of only one side of the prostate, is considered to be low-risk pros-

tate cancer. Men with this profile have about an 80% chance of being cured by either surgery, radiation, or radioactive seed implants. In fact, these types of cancers are generally so slow growing that some experts are now beginning to recommend significant life-style changes as treatment for men willing to commit to changing their eating habits, exercise programs, and stress levels, while closely monitoring their PSA. A conservative approach like this may be particularly suited for men with normal-feeling prostates on digital rectal exam (see "Watchful Waiting"), in whom the size of the tumor is likely to be small.

Not only is the total Gleason score an important prognostic indicator, but the primary and secondary patterns are also significant. This important point is often overlooked by both patient and clinician. A Gleason score of 3+4 and 4+3 are both Gleason 7s, but the probable outcomes are different. The chances of cure for a man with a Gleason 3+4 is greater than for a man with Gleason 4+3, even though they are both classified as Gleason 7s.

Dr. Anthony D'Amico, a brilliant researcher, and his colleagues at Harvard Medical School, have studied this difference. They found that in a group of men with PSAs of 10 or less who had radical prostatectomies (surgery), men with Gleason 3+4 in their biopsies had a better outlook than men with Gleason 4+3. Estimates of the five-year outcome without a rise in PSA were about the same for the 3+4 group as for men with biopsy Gleason scores of 2 to 6. About 80% of both groups were free from cancer five years out, as determined by PSA testing. But only 62% of men with Gleason 4+3 were biochemically free from disease (no measurable PSA) after 5 years. Additionally, at the time of surgery 17% of men with Gleason 4+3 had cancer in their seminal vesicles; only 4% of the 3+4 group had seminal vesicle invasion. (Cancer in the seminal vesicles significantly increases the chance of recurrence.) If you have a Gleason 7 tumor, be sure to ask your doctor whether it's a Gleason 3+4 or a Gleason 4+3.

Another top group of doctors from Stanford University Medical School, led by urologist Dr. Stamey and pathologist

Dr. McNeal, made an interesting related discovery. They found that measuring the actual percentage of Gleason grade 4 or 5 in the tumor removed at surgery was highly predictive of outcome—another indication that the amount of grade 4 (or 5) in the tumor makes a difference. Obviously, 4+3, where 4 is the primary pattern, has a higher percentage of grade 4 than does 3+4.

Another study, this one from Johns Hopkins Hospital, showed that even small percentages of grade 4 or 5 patterns in prostate cancer removed by surgery significantly raised the odds of the cancer returning. In a large number of patients, this team found small pockets of Gleason grade 4 or 5 in tumors from men with Gleason scores of 6 or less. Though these pockets generally comprised less than 5% of the total tumor (designated as "tertiary" patterns), the consequences of this finding was sufficiently significant for the investigators to suggest a modification in the Gleason scoring system, which recognizes primary and secondary, but not tertiary, patterns. Since this research group includes acclaimed doctors like urologist Alan Partin (of Partin tables fame; see "Prognosis") and first-rate pathologist Jon Epstein, there's a good chance this recommendation may be heeded.

The authors of this study noticed that some men have a tiny tertiary (third most common) tumor pattern of Gleason grade 4 or 5. If a man has a total Gleason score of 5 (3+2 or 2+3), or 6 (3+3), but has a small area of grade 4 as well, even though this grade-4 tumor is not a primary or secondary pattern, in this study it still has prognostic significance. Men with this tertiary grade 4 pattern did not ultimately fare as well as a group, compared to the pure Gleason 5s and 6s. They did better, however, than the Gleason 7s. So they formed a group that was intermediate in its outcome prediction between Gleason 5-6 and Gleason 7.

Men with Gleason 7 tumors who had small tertiary pockets of Gleason grade 5 in their tumors also had significantly higher rates of cancer progression than men with Gleason 7s and no tertiary grade 5 areas. In fact, just this small amount of

grade 5 made their predicted outcome statistically no different from men with Gleason 8 cancers. Based on Dr. D'Amico's work, these Gleason 7 tumors that behave much like Gleason 8s are more likely to be 4+3 than 3+4. Researchers at Johns Hopkins confirm that men with Gleason 4+3 tumors tend to have more extensive disease than men with Gleason 3+4 at the time of surgery.

In fact, Dr. Partin, who participated in this study, subsequently changed the Partin tables to reflect the difference in Gleason 7 cancers. The latest edition divides Gleason 7s into two groups: those whose primary tumor pattern is 3 and those whose primary pattern is 4.

Keep in mind that after surgery, the pathologist re-examines the surgical specimen and re-evaluates the Gleason score. The scores sometimes differ; perhaps the tumor changed between the time of the biopsy and surgery, or the biopsy didn't tell the whole story. The Gleason score based on the pathologist's examination of the removed prostate after surgery is used from this point forward in evaluating risk, as it is the most current and accurate information available. Of course, for men selecting radiation or seeds, the biopsy Gleason score is used to determine risk.

Note that Dr. D'Amico, a radiation oncologist, used biopsy Gleason score in his study, while the Hopkins surgeons used post-surgical (tertiary) findings to fine-tune prognosis. Though not specifically stated, the tertiary findings would be less frequently identified in biopsy specimens, if at all.

You may be wondering why I'm spending so much time on this subject. The reason is that these pathological subtleties play a huge role in determining the appropriate treatment. The higher the risk the cancer will come back, the more aggressive the treatment choice. Selecting the treatment that offers the best chance of cure starts with the pathology report from the biopsy. This is why it's critical to have your biopsy slides reviewed by a highly experienced pathologist whose special area of interest is the prostate. What he finds, or doesn't find, is likely to have significant impact on your approach to this

cancer (see Appendix II).

Want a practical example? Okay. Let's look at the difference as described above between a Gleason 7 (3+4) and a Gleason 7 (4+3). In Dr. D'Amico's recent paper he concludes, "Patients with biopsy Gleason 3+4 disease and PSA less than or equal to 10 ng/ml may be suitable candidates for radiation therapy directed at the prostate only." Men with 4+3 disease would likely be treated more aggressively with wider field radiation and hormonal therapy.

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Prostatic Intra-Epithelial Hyperplasia (PIN)

This medical mouthful is thought to be a "pre-cancerous" condition. Commonly seen in biopsy specimens, it consists of areas of proliferation (growth) and changes in the shape of prostate cells. These areas are not "normal," but they're also not cancerous (at least not yet). There are three grades of PIN. The one called "high-grade PIN" is the one that should concern you. High-grade PIN is the only form of PIN believed to be able to develop into cancer. PIN is not an indication for aggressive therapy, but it must be closely monitored. I recommend PSA testing every six months and an annual DRE. The presence of PIN, especially the high-grade variety, is also an

excellent time to initiate lifestyle changes, such as nutrition and exercise.

Clinical Staging

Once cancer has been diagnosed in the prostate biopsy, the next step is to establish its stage, or how far it has progressed. Everyone undergoes the first staging, called "clinical staging," prior to treatment. Men who have surgery reap the benefits of a second staging, called "pathologic staging." This is done by a pathologist with surgically removed specimens of cancerous prostate glands.

The system by far most widely used for clinical staging is called "TNM," short for "tumor, lymph node, and metastasis." The first piece of staging evidence comes from the DRE. Can the tumor be felt by a DRE? If so, is it located on one side of the prostate or both? If localized to one side, does it comprise more or less than half the volume? An ultrasound is used to assist in making the "T" rating. Newer techniques improve accuracy: erMRI (endorectal magnetic resonance imaging) and spectroscopic MRI (magnetic resonance imaging). These new tests were not available when the original TNM system was devised.

The "N" or lymph-node portion of the clinical staging has been classically evaluated by CT-scan and MRI, but both have low sensitivity for picking up involved (cancerous) nodes. A recent development, the ProstaScint Scan, has improved sensitivity. It's limited to some extent, by false positives.

The "M" stands for metastasis to bone. The test used to determine this is the bone scan.

If cancer is present, but the urologist can't feel it upon rectal examination, the stage is said to be T1c. In the current era of PSA screening, this is the most common stage.

If the urologist finds an area of hardness, or a nodule, this is T2 disease. If the area of hardness is only on one side of the

prostate and comprises up to half the volume, this is called T2a; if more than 50% of one side is involved, it's a T2b. If both sides of the prostate are involved, it's a T2c.

If the cancer has spread beyond the prostate, its clinical stage is referred to as T3 (for complete TNM staging, see "Appendix I").

Even though the tumor may appear to be well-defined within the prostate on DRE (stage T2), the cancer may be more extensive. This has been repeatedly shown at surgery.

As mentioned, in men who elect to have surgery a "re-staging," or pathologic staging, will be done by a pathologist on a specimen of the removed prostate. There is no guesswork here. This is the true stage of the disease. If the pathological stage is worse than the clinical stage, there will be an "up-staging" done to reflect this.

When you read medical articles that refer to staging, try to determine if the authors are talking about clinical or pathologic staging. Remember that clinical staging may be under staged. Even men who have no palpable tumor on DRE can have cancer that has spread beyond the prostate, but this may not become known prior to surgery.

Tests to Help Determine Stage

A number of tests are used to help doctors distinguish between organ-confined disease and cancer that has escaped beyond the prostate. Here are some of the most used and most useful.

Prostatic Acid Phosphatase (PAP)

A simple blood test, the PAP should be a part of every prostate cancer work-up. If the PAP is elevated, concerted effort should be made attempting to find metastatic disease.

Even when metastases are too small to be found by imaging techniques, such as those described below, the PAP may pick-up "micro-metastatic" disease. In most men when the PAP is elevated, systemic therapy, like hormones, is added to local therapy (surgery or radiation). Systemic therapy goes all over the body. It's designed to kill cancer cells that may have escaped the prostate. Hormonal therapy and chemotherapy are examples of systemic treatments.

CAT Scan and MRI

I'm not going to spend a lot of time on these frequently prescribed tests. I think they're generally overrated and over-used. Their purpose is to try to ascertain whether the cancer has spread to the lymph nodes. The problem is that when lymph-node metastases are known to have occurred (found at surgery), these two tests pick them up only 20% of the time. In my opinion, they're often not worth the time, money, discomfort, and anxiety. This is especially true for men with Gleason scores of 6 or less, clinical stage T2a or less, and PSAs of 10 or less. Men with this profile have a mere 2%-3% chance of having lymph-node involvement. Combining the low 20% identification rate with the low 2%-3% chance, CAT scans and MRIs reveal lymph-node metastases, on average, in one out of every 200 men tested.

In a study of 861 men with newly diagnosed prostate cancer, only 13 (1.5%) had a positive scan and all 13 had PSAs higher than 20 ng/ml. This is a solid indication that CAT scans are often being used unnecessarily. I should know. I had one and didn't need it. I could have spared myself the unwanted radiation and expense.

Unless the PAP is elevated, using MRI and/or CAT scans in this group is unwarranted. However, in men with an elevated PAP, regardless of PSA, Gleason, and clinical-staging status, an MRI and/or CAT scan should be considered. As you now know, an elevated PAP shifts the odds in favor of

metastatic disease. In this case, I think all the stops should be pulled out in an effort to discover cancer that has spread.

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Endorectal MRI (erMRI)

HELPFUL HINT

To get an accurate fix on whether your disease is organ-confined, have the endorectal MRI done *before* starting hormones. Hormones are likely to shrink the tumor, making it difficult to determine whether it has penetrated the prostate capsule.

As overused as the MRI and CAT scan appear to be, that's how underused is the erMRI. This is a superb test to help determine if the tumor is organ-confined. Unfortunately, this test is not yet widely available. Perhaps by the time you read this book, it will be available in your area. On the west coast it's available at the University of California Hospital in San Francisco. On the east coast this test is available at Sloan Kettering in New York and Dana Farber in Boston. If it's not available in your area, you might try one of these.

This test involves the insertion of a small coil into the rectum adjacent to the prostate. You are then placed inside a long plastic cylinder that contains powerful magnets. The combination of the wave emissions from the coil and the magnetic fields allows the prostate to be clearly viewed on radiographic film. The radiologist can distinguish normal prostate tissue from cancer.

More importantly, this test can distinguish cancer contained within the prostate from cancer that has penetrated the prostate capsule, the thin sheath that encloses and protects the

gland. When the cancer penetrates the capsule, it has now, by definition, "escaped" from the prostate, even if only by a few millimeters; this is known as "extracapsular extension." From this point, the cancer may spread into the soft tissue and fat that surrounds the prostate gland. Once in the surrounding tissues, the cancer has a tendency toward faster growth and metastasis. This is important in selecting the appropriate treatment. Surgery, for example, is not generally the treatment of choice if capsular penetration is confirmed. Capsular penetration appears as a blurred, or irregular, margin on the film. The erMRI is far and away the best test for helping to determine this critical variable. According to a French group that has considerable experience with erMRI, it can predict spread to the surrounding tissues with 95% accuracy.

Another use of the erMRI is in helping to detect prostate cancer in men who have had negative prostate biopsies, but the doctor still suspects undetected cancer. In a pilot study, Perrotti and his colleagues found cancer in five of seven men with highly suspicious erMRIs by repeating the biopsy in the area that appeared suspicious on the erMRI. I think an erMRI can be very useful in helping to locate tumors in men where prostate cancer is strongly suspected, but prior biopsies were normal.

Dr. D'Amico at Harvard has come up with an ingenious way of using the erMRI to help determine whether a tumor is prostate-confined. He found that after an initial erMRI, if the patient is given a complete hormone treatment, the response of the tumor helps predict organ confinement. In a 1998 pilot study of 21 men, Dr. D'Amico and colleagues found that hormones shrunk the overall size of the prostates of all 21 men. However, only 10 of 21 (48%) had a reduction in their tumor volume as determined by erMRI, after hormone treatment for an average of three months. These 10 men were far more likely to have organ-confined disease than men whose tumor volume remained unchanged after hormones.

If confirmed in a larger study still in progress as this book is being written, quantifying tumor volume has practical value.

In men considering surgery versus radiation, if the tumor volume shrinks in response to hormones (as seen in an erMRI), increasing the likelihood that the disease has not escaped the prostate, surgery may be the way to go. But if the tumor volume doesn't shrink in response to hormones on erMRI, radiation might be the wiser choice. (See the "Treatment" section for a complete description of both.)

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ProstaScint Scan

While the erMRI can often identify cancer that extends immediately beyond the prostate capsule, the ProstaScint scan is used to help determine if prostate cancer has spread to lymph nodes. Although this test is not always accurate, it's the best test currently available for identifying lymph-node metastases.

Here's how it's done. There is a substance on the surface of prostate cancer cells called prostate specific membrane antigen (PSMA). The test uses an antibody to PSMA that has a radioactive isotope attached. This PSMA antibody, injected via IV, now travels through the bloodstream. If it encounters its complementary antigen, PSMA, on a prostate cancer cell, it attaches to it. Then, the radiologic image (like an x-ray image) is taken with a ProstaScint scan and these antigen-antibody combinations become visible (the attached radioactive marker leaves bright spots on the radiographic film).

The ProstaScint scan identifies up to 80% of lymph-node metastases. Unfortunately, 20%-30% of the time, this test

indicates cancer in the lymph nodes when none exists. This is called a "false-positive" result. It can cause needless added anxiety in men already on pins and needles, worrying if their cancer has spread.

For this reason, I think it's helpful to discuss the risk of a potential false positive with men before they get this test. Then a positive reading won't automatically be interpreted as disastrous. Factors that support a positive reading are PSAs over 20 ng/ml, elevated PAP blood test, and high Gleason scores (7-10). If one or more of these factors are present and the scan indicates cancer cells in the pelvic nodes, or nodes along the aorta where prostate cancer is most likely to spread, further tests, such as a biopsy of the suspected lymph nodes, should be done.

An interesting innovation has recently been developed by a group at the University Hospitals of Cleveland, the hospital associated with Western Reserve University. By combining the ProstaScint scan with a CT-scan, they've developed a technique to fuse the images from these two tests to more clearly view the location of the cancer within the prostate gland. This new technology dramatically improves the clarity of the imaging, giving a far clearer view of the location of the cancer.

This novel imaging technique can be quite helpful in guiding the urologist doing a prostate biopsy by identifying the areas where the biopsy needle is likely to find cancer. It can also help show whether the cancer has spread to the seminal vesicles.

This innovation allows for better targeting when radioactive seeds or external beam radiation is used, insuring that adequate treatment is delivered to areas of the prostate likely to be affected with cancer. If you have intermediate or high-risk prostate cancer and can get to Cleveland, I think it's well worth the trip. Don't have a CT-scan before going; get it done there. Hopefully, this technology will become more widespread.

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If the ProstaScint scan, along with PAP, PSA, and Gleason score, indicate a significant risk of lymph-node metastases, the nodes that appear to be involved should be removed and examined by a pathologist to determine if they harbor cancer.

Recently, a surgical procedure has been developed to remove suspicious lymph nodes with minimal invasiveness. Using a technique known as laparoscopy, the surgeon is able to view the nodes through a tube. This tube is inserted through a very small incision in the skin. Although it does require general anesthesia (being put to sleep), it results in little post-operative pain. As Dr. Charles (Snuffy) Myers at the American Institute for Diseases of the Prostate in Charlottsville, Virginia, who had 25 lymph nodes removed by this procedure, put it: "I didn't even need to take the Tylenol!"

Like so many of the new procedures in prostate cancer, laporoscopic lymphadenectomy (lymph-node removal through a tube) must be done by a skilled hand. Dr. Myers used Dr. Kavoussi at Johns Hopkins, who has authored scores of papers on all sorts of laparoscopic procedures. He is an acknowledged expert in the field of laparoscopic surgery. Once again, choosing the best person you can find pays dividends.

HELPFUL HINT

A laparoscopic lymphadenectomy is only indicated if the ProstaScint scan shows suspicious nodes and a man is at high risk for lymph-node metastases (Gleason 7 or more, or PSA 20 or more), or has an elevated PAP blood test.

Besides being helpful in

detecting lymph-node involvement in the initial prostate cancer evaluation, the ProstaScint scan has also proved useful in locating cancer in men when the cancer recurs after surgery or radiation (see "Advanced Disease").

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Spectroscopic MRI

Another high-tech, state-of-the-art, staging test is the spectroscopic MRI. Developed by Dr. Kurhanewicz at the University of California-San Francisco, this test greatly enhances the accuracy of the erMRI. Used together they make a dynamite diagnostic combination, providing a highly accurate assessment of the location, extent, and aggressiveness of the tumor. Studies have consistently attested to their accuracy, and proven that they're considerably more powerful when used in tandem than when used separately.

At the time of this writing, the only institutions I know of that use both of these fine tests are the University of California-San Francisco and Sloan Kettering in New York. In the South, try M.D. Anderson in Houston. If you can't find a hospital that offers both these tests, San Francisco is a lovely city to visit. But beware. Both tests are expensive and may not be covered by insurance. You'll want to check if your insurance covers them before jumping on a plane. But if you can arrange to have both these tests, you'll have the best tests currently available for determining tumor location and capsular penetration.

Spectroscopic MRI is currently being evaluated as a way to get more accurate seed placement for brachytherapy, and as a guide for the new intensity-modulated radiation therapy, IMRT. (see "Radiation").

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Bone Scan

One of the most important items to determine on the prostate cancer agenda is whether the cancer has spread to bone. Fortunately, now that PSA testing is becoming progressively more common, bone metsatases in newly diagnosed men are becoming rarer.

In the event that a test is necessary, the one used to pick up prostate cancer in bone is the bone scan. In this test, a radioactive substance is injected into the bloodstream, then tumor cells in bone pick up this marker and "light up," forming small bright spots on the x-ray film where cancer has lodged. Injuries and arthritis will also light up, but these are usually readily distinguishable from tumor. Questions about whether an area of activity on the scan is tumor-related can be answered with an MRI of the area in question.

Like the CAT scan, the bone scan is overused by many doctors. In one study, in men with an initial PSA of less than 20, the chances of the bone scan being normal was 99.7%. Only one out of 306 men with PSAs in this range had a positive bone scan. Yet many good doctors still prescribe bone scans for men with far lower PSAs, "just to be sure."

In my case, I had a bone scan, with a starting PSA of 11.2. Like my CAT scan and standard MRI, the bone test showed nothing, was expensive, and exposed me to needless radiation, discomfort, and anxiety. But you know more now than I did then. If diagnosed today, I'd skip the CAT, MRI, and bone scan, but would definitely have a PAP blood test, endorectal MRI, and spectroscopic MRI. If I lived in the Midwest, I'd go to Cleveland for the CT-scan-ProstaScint diagnostic tandem. (Note: The terms CAT scan and CT-scan are identi-

cal.) If either the erMRI/spectroscopic MRI combo or the CT-scan-ProstaScint tandem were inconclusive, I'd have the other done. This way I'd learn far more about the extent of my cancer than I knew at the time I had to make a treatment decision. This information is vital for men faced with treatment decisions for intermediate or high-risk prostate cancer. For low-risk cases, the inconvenience and expense of these sophisticated tests are probably unnecessary.

4

PROGNOSIS

How to Quantify Risk

The burning question in the minds of most men with prostate cancer is, "Has it spread?" Even if all the sophisticated tests indicate that the cancer is well-contained within the prostate, there's still a chance that it has escaped. It may not have grown large enough to be detected. But prostate surgery has taught us that when the surgeon gets in there, he frequently finds more extensive disease than the tests have indicated.

Dr. Alan Partin, a urologist at Johns Hopkins, observed the surgical findings in more than 700 patients. Although the clinical tests estimate the severity of the tumor, the actual surgical findings provide an exact measure. After noting the surgical findings, Dr. Partin went back and looked at the PSAs, Gleason scores, and clinical stages for these men, and correlated them with what he found from surgery. He then prepared a set of tables that predicts the risk of extension of the tumor past the capsule of the prostate, seminal vesicle involvement, and lymph-node metastases.

The Partin Tables, as these risk tabulations are called, provide men with critical information. They can be of great help in determining the choice of treatment. For example, in my own case, with PSA 11, Gleason 7, and stage T2a, my chance of organ-confined disease was only 36% according to the Partin Tables. In other words, there was a 64% chance

that the prostate capsule had already been penetrated by invading cancer.

Delving deeper into the tables, I was able to determine that the chance of seminal vesicle involvement in my case was 19%, and the chance of the cancer having spread to my lymph nodes was 9%. I also had another poor prognostic sign from the biopsy that I'll discuss later in this section, referred to as "perineural invasion." For now, let's just say that this biopsy finding increased my chances of capsular penetration from 64% to 77%. That means there were roughly three chances out of four that my tumor had escaped the confines of the prostate. There were also significant risks of seminal vesicle and/or lymph-node metastases.

Knowing these risks, I shied away from surgery, which might not have been able to get all of the tumor. I opted for hormones combined with external beam radiation. Without the Partin Tables I would not have been able to clearly understand these risks and would have had a far more difficult time making an intelligent treatment decision.

The Partin Tables were updated in 2002 to include initial PSA ranges starting with 0.0-2.5 and separating Gleason 7 tumors into two groups (3+4; 4+3). See "Appendix II" for Web site details.

Number of Positive Biopsy Cores Predicts Outcome

Dr. Anthony D'Amico and his group at Harvard found that the percentage of positive biopsy cores, as each snip in a prostate biopsy is called, made a highly significant difference in predicting progression of cancer after surgery. He also found that erMRI was also independently useful in predicting outcome.

He studied 977 men with T2 disease (positive DRE) and found that men with the following profiles were at high risk of having their cancer recur after surgery.

• Men with erMRI that shows T3 (instead of T2 by DRE),

three of six or more positive cores on biopsy, Gleason score 6 or higher, and a pre-surgery PSA of more than 10 but less than 20 ng/ml.

• Any Gleason score when the pre-surgery PSA is over 20, and erMRI shows T3 disease.

• ErMRI shows T2 disease, but three out of six biopsy cores have cancer, while the Gleason score is 8 or higher and the pre-surgery PSA is greater than 20 ng/ml.

Men in these high-risk categories should strongly consider adjuvant androgen blockade (hormones), combined with either surgery or radiation.

The importance of the percentage of positive biopsy cores has been confirmed by at least three other high-powered groups: Johns Hopkins, the Mayo Clinic, and the University of California Medical School in San Francisco. In the Hopkins study, researchers compared pre-surgical data like Gleason score, PSA, number of positive cores, and a slew of other variables. Their objective was to evaluate the significance of these factors in predicting whether or not the tumor would be organ-confined at surgery. They found that of all the variables they looked at, the two that were most predictive of organ-confined disease were the number of positive cores and the Gleason score. Here are the interesting results of 113 sextant (six core) biopsies, after which all men had a radical prostatectomy.

• Gleason score 6 or less and two or fewer positive cores and PSA 0-4ng/ml: Chance of tumor being confined to the prostate proven by surgery, 89%.

• Gleason score 6 or less and with two positive cores on one side of prostate only (unilateral): Chance of tumor being confined to the prostate, 87%. (Note that PSA was not considered in this calculation.)

• Gleason score of 7 or more and more than one positive core: Chance of tumor being confined to the prostate, 10%. (Note: I had two positive cores and a Gleason score of 7. Combining this risk assessment with other data, the chance

that my disease had already escaped the prostate capsule was 80%-90%.)

The third and most recent study on the predictive value of the percentage of biopsy cores that show cancer (positive biopsy cores) comes from the evaluation of 1,265 men, all of whom had surgery for their prostate cancer. Investigators led by Dr. Gary Grossfeld determined the risk of recurrence in this group of men. They asked this seminal question: Does the risk of cancer coming back increase as the percentage of positive cores found at the time of prostate biopsy increases? If so, how can this information be used to help make an optimal treatment decision?

They divided the men into three groups:

• Low risk: PSA at diagnosis of 10 or less and biopsy Gleason score of 6 or less and clinical staging of T1-c or T2-a (note: need all three).

• Intermediate risk: PSA at diagnosis of 10.1 to 20.0 or biopsy Gleason score of 7 or stage T2b.

• High risk: PSA greater than 20 or biopsy Gleason score 8-10, or clinical stage T2-c or T-3.

These men had a median follow-up period of 3.3 years from the time of surgery. As groups, without considering the number of positive biopsy cores, these investigators calculated the probability of recurrence at five years to be:

Low risk: 18%
Intermediate risk: 28%
High risk: 36%

The number of cancer-effected biopsy cores was then taken into account. They were stratified into three groups: 0%-33% positive biopsy cores; 34%-66% positive cores; 67% and higher positive cores.

The percentage of positive biopsies proved to be a significant predictor of recurrence in all three risk categories.

For low-risk patients the risk of recurrence 5 years after surgery more than doubled when the percentage of positive cores increased to 34% to 66%. Only 12% of low-risk men who had 0% to 33% positive cores had a recurrence within five

years; 28% of patients with 34% to 66% positive cores had a return of their cancer. Only seven out of 427 men at low-risk had greater than 66%, too few to draw accurate conclusions.

For men at intermediate risk, the probability of disease recurrence five years after surgery varies widely depending on the percentage of positive biopsy cores:

0% to 33%: 17%
34% to 66%: 37%
above 66%: 47%

Again, the risk of recurrence more than doubles when the percentage of positive biopsy cores increases to 34%-66%, as opposed to 0%-33%, and nearly triples in the greater than 66% group.

For high-risk men, the relevant 5-year recurrence risks were:

0% to 33%: 24%
34% to 66%: 34%
above 66%: 59%

As you can see, the percentage of positive biopsy cores makes a big difference when considering the risk of the cancer returning after surgery. The researchers believe that this is especially important for the intermediate-and high-risk groups. Local therapy, either surgery or radiation, is probably enough for men with 0% to 33% positive cores; men with a greater percentage of positive cores than this will probably do better if they add a systemic therapy, like hormones, to their treatment plan (see Chapter 11). Additionally, these men would be well-advised to consider making significant changes regarding diet, exercise, and stress-reduction.

HELPFUL HINT

Establish whether your prostate cancer is low-risk, intermediate-risk, or high-risk. Then take the percentage of positive biopsy cores into account to further assess your risk of recurrence when working with your doctors to obtain optimal treatment.

Accurately assessing risk prior to selecting a treatment plan will provide you with an objective basis for making a tough decision. Don't be

surprised if your doctor doesn't try to establish this kind of rational risk assessment. Few private practitioners do. Most make treatment recommendations by "feel" or "experience." For me, knowing the probabilities of treatment failure formed a foundation to discuss treatment options with my doctors in a meaningful way. The facts are always friendly.

A number of university medical centers are now setting up comprehensive multi-discipline cancer centers. At these, you're more likely to get a better handle on both the risks and treatment options.

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Other Prognostic Factors in a Nutshell

Perineural Invasion (PNI)—At biopsy, when the cancer is seen to be spreading along nerves, it's a poor prognostic sign. Studies show that when PNI is present in the biopsy specimen, 77% of prostates removed by radical prostatectomy have cancer that has penetrated the prostate capsule. In addition, 51% of these cases had positive margins, microscopic evidence of cancer right up to the edge of surgically removed prostate, another poor prognostic sign, according to a Johns Hopkins study; a third had either seminal-vesicle or lymph-node involvement. It seems that prostate cancer spreads faster along nerve sheaths. I had PNI present in my biopsy—another reason I chose radiation and hormones over surgery.

Just because the cancer has penetrated the prostate capsule doesn't mean that it will recur after treatment. As you'll read later, quite often the penetration is only by a few millimeters and the cancer can still be completely removed by surgery or

killed by radiation or radioactive palladium seeds.

Two studies done after my radiation treatment showed that PNI does not significantly increase the risks of recurrence.

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Ploidy Status—Ploidy status refers to the microscopic appearance of the cancer cells. Diploid is considered the most favorable, because it's closer in appearance to normal prostate cells; aneuploid is considered to be the least favorable configuration. Although it's debatable whether ploidy status is an independent predictor of outcome, if your tumor is diploid, this should be considered as a plus. Diploid tumors are generally slower growing and less aggressive.

p53 Mutations—As previously discussed, p53 is a cancer-suppressing gene. When it mutates, it loses its ability to inhibit cancer growth. A number of studies have shown a strong correlation between p53 mutations and advanced prostate cancer. A recent study released from the Mayo Clinic showed that if 10% or more of the cells of specimens removed by radical prostatectomy stain positive for mutated p53, the chance of cancer recurrence triples. p53 status can be tested in the biopsy. I advise you to do so. If more than 10% of the cells in the

biopsy show altered p53 genes, you might want to consider being more aggressive in treatment.

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Bcl-2—This is an oncogene (cancer-causing gene) for prostate cancer. The prostate biopsy can test for it. Positive bcl-2 testing is a poor prognostic indicator. The combination of a p53 abnormality and bcl-2 positivity is a particularly bad prognostic sign. Most men with this profile will eventually have a recurrence.

Formula for Estimating the Probability of Lymph Node Involvement

Dr. Roach at the University of California Medical Center in San Francisco, California, has come up with a formula to give a rough approximation of the risk of lymph-node metastases. Here is the formula. It's not as complicated as it may appear at first glance:

2/3 x initial PSA + 10 (Gleason score—6) = risk of lymph-node metastases.

In my case, the initial PSA was 11.2 and the Gleason score 7. Using Dr. Roach's formula: 2/3 x 11.2 + 10 (7-6) = 17.5%. According to the Partin Table, my chance of lymph-node involvement was 9%. Combining the two, I rate my chance at about 13%.

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NUTRITION

The role of diet in preserving health is becoming progressively more established in the medical community. Food selection and total caloric intake are now recognized as key ingredients to a longer higher-quality life. The incidence of some of the major killers—heart disease, cancer, and Alzheimer's—are all influenced by diet. Obesity in America has increased rapidly over the past 15 years. Diabetes, a disease highly correlated with obesity, has also increased proportionately. Annual deaths from diabetes-related causes increased 40% from 1985 to 1999. Deaths from diabetes are now nearly equal to deaths from breast cancer!

At this point, it has been well-established that a reduced animal-fat diet with increased consumption of fruits and vegetables will protect you from heart disease. Soy protein, as you will read later in this chapter, seems to be particularly effective at reducing the risks of heart disease, so much so that the stringently controlling FDA has allowed soy-protein manufacturers to add this statement to their products: "Diets low in saturated fat and cholesterol that include 25 grams of soy protein (per day) may reduce the risk of heart disease." Permission such as this is not given lightly by the FDA.

Can diet and supplements really do anything to prevent prostate cancer? Can changes in nutritional habits retard its spread in men that already have the disease? I'm convinced

they can. But there is no scientific proof that this is so. Scientific proof would require prospective (not retrospective), controlled, randomized studies of large patient populations for long periods of time. It would require hard evidence that the dietary products or supplements were faithfully being consumed in the specified quantities over the entire time of the study. Short of very regular urine and blood samples, a researcher could not be certain that a study participant was following the prescribed regimen. Such studies are difficult and expensive to mount. They would cost millions of dollars and take at least 10 years to start producing meaningful data. As one top researcher in the field put it: "I'd be dead before I got results from this kind of study."

In light of the lack of medical proof that dietary factors make a significant difference in the incidence or progression of prostate cancer, why am I convinced that they're useful? To understand my conviction, it's helpful to compare science with the justice system in the United States. At a criminal trial, the burden of proof is "beyond a reasonable doubt." At a civil trial, the standard is "a preponderance of the evidence." Scientific proof is analogous to "beyond a reasonable doubt." With diet and supplements, we're not yet there.

But "a preponderance of the evidence" is a standard that's more easily met. I think the evidence of the benefits of nutrition meets this measure. Here's why.

Epidemiologic Studies

The term "epidemiology" as used in the title of this section refers to population comparisons, not the study of widespread disease (epidemics). When prostate cancer is compared in different countries, interesting details emerge. In Asian populations, for example, the incidence of microscopically detectable prostate cancer is similar to that of Western cultures, but these cancers become clinically significant much less frequently than those in Western nations. The extent of this difference is striking. African-Americans have 100 times

as much *clinical* prostate cancer as Chinese men. A hundred times! American Caucasians have about 20 times as much clinically significant prostate cancer as Japanese men. It's not that these Asian men don't have cancer in their prostates; they do. It just remains dormant until they die of something else and even when Japanese men get clinical prostate cancer, it tends to be less aggressive.

When Asian men migrate to the United States, within one generation the incidence of clinically recognizable prostate cancer approaches that of Western men. Additionally, the rate of clinically observable prostate cancer has been rising in Japan as Japanese eating habits become progressively more Westernized. From 1950 to 1975, the incidence of prostate cancer increased six-fold!

This pattern of disease expression implicates environmental factors as the main reason why prostate cancer becomes a problem for some men, but remains latent for others. If the difference was all due to genetics, then why would a change in environment so dramatically change the development of clinically significant prostate cancer in Japanese men? Investigators around the globe have attempted to identify the environmental differences that account for this markedly altered disease history. Dietary factors appear to be the most important. A high-calorie diet is one culprit.

Fewer Calories Slow Prostate Cancer Growth

It's been well-established that restricting calories in the diet of laboratory animals prolongs life and reduces cancer. Centenarians (people who live to be 100 or more) in Okinawa consume an average of about 1,200 calories daily. While this seems very low, it should be noted that these elderly people are sedentary and burn fewer calories than active adults. This low caloric intake is almost certainly part of their longevity success.

A recent study done at Harvard Medical School showed a dramatic reduction in the growth rate of prostate tumors transplanted into rats that ate a reduced calorie diet. At the

end of the study, a 20% reduction in calories resulted in 62% lower tumor weight, when compared to tumor weight in rats eating a normal diet. Interestingly, this result did not seem to be related to fat content in the respective diets. So long as calories were controlled, increasing the amount of calories coming from fat did not appear to affect tumor growth.

The average Japanese man consumes about 2,000 calories daily; the average American man devours nearly 3,500 calories per day, almost twice as much. Only a small part of this difference can be accounted for by differences in height and weight. The rest is due to dramatically different eating habits. Too many calories lead to obesity. And obesity is associated not only with a significantly increased risk of prostate cancer, but also of other cancers, heart disease, and diabetes. In fact, most experts I've spoken with agree that, aside from not smoking, calorie reduction is the most beneficial step one can take to increase longevity. Prostate cancer is no exception. As calories go down, the risk of prostate cancer goes right down with them.

How does reducing calories slow the growth of prostate cancer? That's not known. One possible mechanism is a reduction in serum insulin and IGF-1 levels. It has been well-established, both in rodents and primates, that calorie restriction lowers insulin levels in the blood. Fewer calories reduce IGF-1 levels in humans. Exercise also helps lower insulin levels. Lower insulin levels lead to an increase in a hormone called sex hormone binding globulin (SHBG). SHBG binds circulating testosterone. One way that calorie restriction might decrease the growth of prostate cancer, then, is by reducing the amount of circulating testosterone.

Insulin and IGF-1 are also known to have a direct effect on prostate cells. They increase the rate of cell division. This "mitogenic effect," as it's called, may speed up the growth of prostate cancer cells in the transplanted tumors in animal studies. Whatever the mechanism of its action, calorie restriction is strongly associated with a slowdown in the growth

and development of prostate cancer. This effect seems to be independent of fat content in the diet.

Calorie restriction is difficult, to put it mildly, for most of us. Researchers are now working on ways to reduce calorie absorption from the digestive tract by perfecting foods that have ingredients that can't be metabolized. When perfected, these will accommodate the joys of eating and satiety without the unwanted calories. Such products may be as near as a year or two away.

What To Eat

Besides putting a lid on calories, a proper diet seems to make a difference in prostate cancer prevention. It also appears to reduce the rate of tumor growth in men that have prostate cancer. Epidemiologic studies indicate that fruits, vegetables, fiber, soy, tomatoes, and green tea are associated with a reduction of prostate cancer. Diets high in fat, especially from red meat and dairy products, correlate with an increase in prostate cancer and prostate cancer mortality. Additionally, cows and chickens are routinely fed hormones to stimulate growth and antibodies to decrease infections. According to CNN, 40% of all antibiotics produced annually go into beef and poultry food. Consuming growth-stimulating hormones can't be good for men with cancer that grows more rapidly when exposed to them.

So what you eat makes a difference. The National Cancer Institute attributes more than one-third of all cancers to dietary factors. It's also something that you can directly control.

Fruits, Vegetables, and Fiber

The National Cancer Institute (NCI) recommends five servings of fruits or vegetables each day to help prevent prostate cancer and to slow its progression. This may sound like a

lot, but an apple or orange counts as a serving. If you eat a fruit salad at breakfast containing an apple, orange, strawberries, and kiwi fruit, as I do, you're well on your way to your five servings. A banana in your soy protein drink, a salad, and a couple of vegetable dishes at lunch or dinner and you've more than eclipsed the NCI recommendation.

As for fiber, the NCI recommends 25-35 grams daily. Eating fruits and vegetables provides fiber, so by eating five or more servings a day, you're well on your way to getting your required fiber. An orange or banana has about three grams of fiber. A cup of raspberries has eight grams. Add to this a high-fiber cereal, such as All-Bran, Grape Nuts, or Shredded Wheat, and you'll get an additional 10 grams of fiber per day. By eating a bowl of one of these cereals with a nice fruit salad, you'll be consuming more dietary fiber than the average American eats in an entire day!

Grain dishes—rice, barley, couscous, and polenta—are high in fiber. Brown rice has more fiber than white rice. So do some of the Japanese noodle products, like soba, which is made out of buckwheat. Nuts and seeds are also rich in fiber, but you'll need to consume them in moderation due to the calories in them. Whole-grain, sprouted-grain, and black breads, along with rye wafers, are also excellent sources of fiber. They can be used for sandwiches or between-meal snacks. Read the package carefully and select only varieties that are low in fat. Bread can be a source of "hidden" fats, if not carefully selected.

Beans, peas, and lentils are particularly high in fiber. Beans (legumes) contain more than 10 grams of fiber per cup, and peas have about nine grams per cup. Due to the way they're metabolized, they're an even better source of fiber than whole-grain breads. These foods are also a rich source of beneficial lignans. If you stop eating meat, you'll have much more room for a variety of fiber-rich foods.

Avoid Fatty Foods

Fiber helps the body remove fats by binding fat that has been ingested. This fiber-bound fat is then eliminated. (As an added benefit, fiber increases the transit time of intestinal wastes. This may reduce the risk of colon cancer by more rapidly removing intestinal toxins that can potentially damage normal colon cells.) You can help this process along by reducing your total intake of fats and oils, especially from red meat, dairy products, and partially hydrogenated oils found in packaged foods. Red-meat and dairy products, such as whole milk, butter, and cheese, are loaded with fats. Population studies have shown that the incidence of prostate cancer is highest in countries where fat consumption is greatest. This association also holds true for deaths from prostate cancer. The United States, Canada, and Western European countries have much higher death rates from prostate cancer than China, Japan, Taiwan, and Thailand. Interestingly, dairy products are rarely consumed in Asian countries. Likewise, portions of red meat, when consumed, are small.

A high consumption of fat may lead to obesity. Eighteen percent of the United States population is now considered to be obese, up from 12% as recently as 1991. This is a 50% increase! As Dr. Jeffrey Koplan, director of the Centers for Disease Control and Prevention (CDC) in Atlanta, puts it: "Obesity has spread with the speed and dispersion characteristic of a communicable disease epidemic." According to Dr. Koplan, more than half of all Americans are overweight.

The typical Japanese diet has about 20% calories from fat; Americans have about 36% fat calories on average, down from 40% ten years ago. Although this may appear to be an improvement, it isn't really, because Americans have increased their calorie intake. The total amount of fat consumed has actually increased. Twenty percent of total calories from fat is a good target for prevention of prostate cancer and heart disease. For men that already have prostate cancer, 10%-15% is a better target.

Note that we're discussing the percentage of calories from fat, not the percentage of fat by weight. Since gram for gram, fat has more than twice the calories of carbohydrates or protein, 20% of calories from fat is equivalent to less than 10% fat based on weight. When reported on food labels, percentage of fat is based on weight, not calories. One-percent-fat soy milk actually contains in excess of 2% fat based on calories.

Fat is deleterious in a number of ways. Fat contains nine calories per gram; protein and carbohydrates have only four calories per gram. Even the so-called "good oils" still have nine calories per gram. It's really difficult, therefore, to control your caloric intake if you eat lots of fats or oils. Although in the laboratory, experimental animals can be maintained on high-fat diets while limiting the number of calories, it's virtually impossible for men to get 40% or more of their calories from fat and still limit their total calories to the point where they don't gain weight.

Fat, especially animal fat, has been implicated in a number of studies as a risk factor for prostate cancer. A study of more than 47,000 men, all health professionals, done in 1993 at Harvard Medical School showed that men eating a high-fat diet, primarily from red meat, had nearly double the risk of getting advanced prostate cancer as those eating a low-fat diet. These findings were confirmed in May 1999 in a study reported in the *British Journal of Cancer*. This case-controlled study compared 175 men with prostate cancer with 233 controls. Men who consumed the most red meat (those in the top 25% of red-meat consumption) had twice the risk of developing prostate cancer as those men in the lowest quartile. The risk for total fat intake, desserts, and calories was similar: The highest quartile had nearly double the risk in each category as the lowest.

This effect appears to be separate from the caloric risk. In several studies a group of men with high consumption of red meat had a greater risk of getting prostate cancer than a group of men with comparable total caloric intake, but less meat.

The relative risk of calories versus fat has not been studied. It's best to control both.

A prospective study on the relationship between dietary fats and prostate cancer survival was conducted at Laval University in Quebec, Canada. Observers studied 384 men diagnosed with prostate cancer for a median time of 5.2 years. Trained nutritionists interviewed the men about their dietary habits, then divided them into three groups, determined by their fat intake. During the study period, 32 men died of prostate cancer, 9% of the men. The investigators found that saturated fat consumption was significantly associated with the risk of dying from prostate cancer. Those in the top third of saturated fat intake had three times the risk of dying from their cancer, when compared with the third who consumed the lowest amount of saturated fat.

Linolenic and Linoleic Acid

Linolenic acid and linoleic acid are essential fatty acids that must be obtained from dietary sources. The body does not make either of them. But most of us consume far more of these fatty acids than our bodies need.

Meat is rich in a fatty acid called alpha-linolenic acid. In animal studies this fatty acid has consistently been found to stimulate prostate cancer growth. Interestingly, another food replete with alpha-linolenic acid is flax. Flax seed and flax oil are common items in most health-food stores and have been lauded as a nutritional panacea. More than once I've seen flax oil recommended in the popular press for prevention of a variety of cancers, including prostate. Medical evidence does not support this. Although flax products may be beneficial in lowering blood-cholesterol levels while boosting high-density lipoproteins (HDLs), the so-called "good cholesterol," I wouldn't put flax oil into the same body with prostate cancer.

In a 1997 study by the American Health Foundation, observers found that a diet rich in flax oil did not protect mice from the growth of injected prostate cancer cells.

In human studies, flax consumption has been associated with a reduction of some forms of cancer, but not of the prostate. Dr. Charles (Snuffy) Myers thinks it's dangerous. More studies need to be done on what role, if any, linolenic acid-rich flax has in a prostate cancer diet. When in doubt, leave it out.

Polyunsaturated vegetable oils, such as safflower, corn, and soybean oils, are rich in a fatty acid called linoleic acid. These linoleic acid-rich oils stimulate prostate cancer cell growth in the lab and in animals in much the same manner as linolenic acid. In fact, they're worse. In mice, prostate tumor growth is enhanced by a diet rich in linoleic acid. One reason for this may be because linoleic acid can be converted in your body into arachidonic acid. As you'll soon read, arachidonic acid is one of the most potent promoters of prostate cancer growth. All polyunsaturated oils should be avoided.

The good news is that most vegetables have low overall fat content. By substituting fruits and vegetables for meat, you'll reduce the saturated fat in your diet. The fat in meat is much denser than the fat in vegetables. This means fewer calories in vegetables.

Soy products like tofu are also high in linoleic acid and are generally not low in fat. But soy seems to have other compensating benefits due to its phytoestrogen content. Look for soy products that have the lowest fat levels—lite tofu, low-fat (or non-fat) soy protein isolates, low-fat (or non-fat) soy milk, etc.

What about the "good oils" like olive and walnut? This is an area of conjecture. Much has been written about the "Mediterranean diet." Men living along the Mediterranean Sea have less heart disease and a lower incidence of some cancers, including prostate. Their food is often swimming in olive oil. Does this mean olive oil is protective? Perhaps. A slew of recent studies put olive-oil consumption in a favorable light. It seems to

HELPFUL HINT

Read the label on soy products carefully. You can reduce the amount of fat (linoleic acid) considerably by judicious selection.

reduce total cholesterol levels, particularly the "bad cholesterol," or LDLs. This may reduce the risk of heart disease, as seen in those people who eat the Mediterranean diet. Diets rich in olive oil have also been reported to do the following:

- reduce inflammation
- reduce the risk of blood clots
- reduce atherosclerosis
- lower blood pressure
- may reduce the risk of colorectal, breast, and prostate cancer
- decrease arachidonic acid mobilization

Recently, the European Union has countenanced olive oil as the oil of choice for its population. You should too.

Substituting olive oil for lard and saturated and polyunsaturated oils is certainly a positive nutritional change. Palm, cottonseed, and coconut oils contain saturated fats similar to lard. Diets containing high amounts of polyunsaturated oils, such as corn and safflower, have been associated with an increased risk of prostate cancer in laboratory experiments. Olives produce a predominately monounsaturated oil, which is better for health than other oils or fats. But 14% of olive oil is still saturated fat. And a tablespoon of olive oil still has 140 calories! Nutritional experts like Dr. Heber and Dr. Myers conclude that it's best to try to reduce all oil and fat intake, but to use olive oil when oil is required in cooking and salad dressings. Other acceptable oils, all predominately mono-unsaturated, are walnut, macademia, and avocado oils. The current consensus is that moderate consumption of olive oil is

HELPFUL HINTS

- Olive oil contains useful nutrients and can be used in moderation, provided that total caloric intake is kept down.
- Macadamia nut oil, walnut oil, or avocado oil can be substituted for olive oil for taste; no other oils should be used either for cooking or in dressings.

probably beneficial, so long as total caloric consumption is kept under control.

Prostate cancer cells seem to have an affinity for fat. At the 1999 Prostate Cancer Foundation prostate cancer retreat, one investigator told me that unpublished experiments have shown that prostate cancer cells are amazingly efficient at trapping fat molecules and metabolizing them. If a prostate tumor is suspended in saline solution and a spurt of oil is run through the tumor, 80% of the fat is removed by the tumor in a single pass! It makes sense to me to reduce fat intake so that any microscopic colonies of cancer cells will be kept on meager fat rations and their growth will, hopefully, be suppressed.

What Is The Best Diet?

The best diet for the prevention of prostate cancer luckily happens to be the most heart-friendly as well. Doctors Heber, Myers, and Ornish all agree—the optimal diet for heart and prostate is a low-fat vegan diet. A vegan diet is composed of vegetables, fruits, beans, legumes, and grains. Milk, milk products (like yogurt and ice cream), and eggs are not included. All meat and fish are eliminated. Use of oil, any kind of oil, should be minimized, but when required limited to the monounsaturated oils discussed above. Although this diet has not been proven to prevent prostate cancer, it has been proven to lower serum cholesterol levels and protect against heart disease. Epidemiologic and animal studies indicate that this diet also reduces the risk of prostate, breast, and colon cancer, but conclusive proof is not yet in hand.

Does this mean a low-fat vegan diet has no validity? No. It means it's the best available alternative based on present evidence. It will make it easier to control your weight; your serum cholesterol will almost certainly decline (mine went from 180 to 135), and you're likely to be reducing your risk of prostate cancer. Recent data show that adding fish to a

vegan diet may provide additional protection against dying from prostate cancer.

Improving on the Low-fat Vegan Diet

Adding soy and green tea to your vegan diet will probably reduce your prostate cancer risk further still. Numerous laboratory, animal, and epidemiologic studies have shown the anti-proliferation potential for these two foods. They are an integral part of the Japanese and Chinese diets.

Cruciferous vegetables should also be eaten regularly. These include broccoli, broccoli sprouts, cauliflower, cabbage, Brussels sprouts, bok choy, kale, chard, radishes, arugula, and watercress. Crucifers contain sulforaphane and indole-3-carbinol. Sulforaphane activates enzymes that have a detoxifying effect on a variety of cancer-causing chemicals. These detoxifying enzymes, called glycosinolates, are potent antioxidants. Sulforaphane is a powerful stimulator for production of glutathione transferases, one of the potent glycosinolates, and other strong detoxifying enzymes.

Indole-3-carbinol has recently been shown to slow down the growth of prostate cancer cells that are no longer sensitive to sex hormones (androgen independent). These are the type of cancer cells that men have when they no longer respond to hormonal therapy. Not only did indole-3-carbinol slow the growth of these aggressive cancer cells, it helped to re-establish the built-in suicide program. This was accomplished by increasing the protein production of the cancer-protective genes p21 and p27 (up-regulation), while down-regulating the expression of the Bcl-2 cancer-promoting gene. Reduction of Bcl-2 is a primary goal in the treatment of prostate cancer.

A gene known as GSTP-1 appears to be lost early in the prostate cancer process. It's inactivated by a process called hypermethylation. Heterocyclicamines from animal fats cooked at high temperatures may accelerate the deactivation of GSTP-1. Loss of GSTP-1 seems to be one of the earliest-observed gene changes in prostate cancer, according to in-

vestigations at Johns Hopkins led by Dr. William Nelson. Its function is lost in 65% of men with PIN and 94% of men with localized prostate cancer. Glycosinolates in crucifers may help protect GSTP-1 from the effects of carcinogens like heterocyclicamines. Antioxidants, such as selenium, may also be protective in men in the lowest 25% of selenium blood levels. Selenium supplements in this group may help preserve GSTP-1 function. Selenium blood levels decrease with age, increasing the risk of GSTP-1 inactivation and raising the risk of prostate cancer.

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It's little wonder that the January 5, 2000, issue of the Journal of the National Cancer Institute reported a 41% reduction in the risk of prostate cancer among men eating three or more servings per week of crucifers, compared to men eating one serving or less weekly. In this study, statistical adjustments were made for total vegetable intake so that the reduced risks were specifically isolated to consumption of crucifers. Interestingly, increasing total vegetable consumption also decreased the risk of prostate cancer in this study. Men who ate 28 or more servings of vegetables (all kinds) per week had 35% less risk of developing clinical prostate cancer than men who ate 14 servings or less. The study's authors, from the Fred Hutchison Cancer Research Institute in Seattle, Washington, concluded, "High consumption of vegetables, particularly cruciferous vegetables, is associated with a reduced risk of prostate cancer."

What if you, like ex-president George Bush, hate broccoli? Researchers at Johns Hopkins University found a solution: broccoli sprouts. Three-day-old broccoli sprouts have 10-100 times as much glucoraphanin, a sulforaphane derivative, as the whole vegetable! What's more, for those of us too lazy to

grow our own sprouts, tablets containing extracts from these 3-day-old sprouts are readily available and not expensive. Fresh sprouts are also available in selected stores, marketed under the name "BroccoSprouts." These are the same sprouts patented by doctors at Johns Hopkins. Look for them in your local market or health-food store.

In experiments in rats, this extract proved highly effective in decreasing the incidence and development of breast cancer. The researchers concluded: "Small quantities of crucifer sprouts may protect against the risk of cancer as effectively as much larger quantities of mature vegetables of the same variety." Although I eat lots of crucifers, I still take broccoli-sprout tablets when I travel. They are not harmful and may reduce the risk of recurrence of my prostate cancer. I routinely add broccoli sprouts to my salads when I'm at home. Broccoli sprouts are readily available in supermarkets throughout New Zealand.

The Case for Fish

If a low-fat vegan diet is optimal for prevention of prostate cancer (and heart disease), where does this leave fish? The answer is controversial. Fish is rich in menhaden oil. Several studies in mice have shown that a diet rich in menhaden oil significantly retards the growth of transplanted prostate tumors when compared with corn oil (linoleic acid) or flax oil (linolenic acid), both of which stimulate tumor growth. Although both fish oil and flax oil are rich in omega-3 fatty acids, they seem to affect tumor growth differently in mice. A study by Connolly, Coleman, and Rose, reported in 1997 in Nutrition and Cancer, showed that genetically identical mice with prostate cancer seemed to benefit from menhaden oil. Mice fed a diet of 18% menhaden oil and 5% corn oil had a 30% reduction in prostate tumor growth, when compared to mice fed 18% flax oil and 5% corn oil, or 18% corn oil and 5% flax oil.

Why the difference, since both flax and fish oils are rich

in omega-3 fatty acids? Flax oil is high in alpha-linolenic acid. The two main fatty acids in fish oil are EPA and DHA. Alpha-linolenic acid can be converted in the body to EPA and DHA, but this isn't an efficient process. In the mice being studied, some of the linolenic acid was metabolized to EPA, although not to the same extent as in fish oil. This was not the case for DHA. In fact, DHA levels were lower in the flax oil-fed mice than in the corn oil-fed group! Other studies have shown that DHA, but not EPA, may inhibit an enzyme called protein kinase C. When this enzyme is deactivated in prostate cancer cells, they die more readily, like a normal prostate cell. Their genetic program to die is switched back on and they undergo apoptosis (programmed cell death). This may be part of the reason why fish oil was so much more effective than flax oil in reducing the tumor mass in these mice. Another reason might be that EPA and DHA reduce inflammation, which has been associated with cancer growth.

What about humans? Does eating fish help reduce the risk of prostate cancer? Here the evidence is far less clear. A 1996 study by Dr. Godley and colleagues showed a positive association (increased risk) between linoleic acid (corn, safflower, soy oils) and prostate cancer, as did the Connolly study. They did not, however, find that increased tissue levels of EPA or DHA reduced the risk of prostate cancer. On the other hand, a 1996 study in England reported reduced risk of prostate cancer from eating fish regularly.

A recent New Zealand study done in Auckland and reported in the *British Journal of Cancer* compared the levels of EPA and DHA in the red blood cells of 317 men with prostate cancer and 480 age-matched normal men. The study revealed that men whose EPA and DHA levels were in the top 25% had 41% and 38% less risk of getting prostate cancer respectively, when compared to men in the lowest quartile of EPA and DHA levels.

Dr. Giovannucci at Harvard showed a relationship between total fat consumption and the risk of prostate cancer. He found that high alpha-linolenic acid, predominately from

animal fat, was the major culprit. Although fish fats contribute to total fat intake, this study found no effect, either positive or negative, on the risk of prostate cancer from high fish consumption.

A recent preliminary study by Dr. June Chan at the University of California-San Francisco, however, shows that fish consumption four or more times a weeks seems to significantly reduce the risk of progression of prostate cancer in men who already have it. Preliminary results show a 50% reduction in death from prostate cancer in the high-fish-consumption group. These results, presented at the 2001 Prostate Cancer Foundation Retreat, have not yet been published and more cases are still being studied. Dr. Chan believes that this work is still too preliminary to draw conclusions and to recommend frequent fish eating for men with prostate cancer.

New data just released by Dr. Giovannucci does show what appears to be protection from prostate cancer by fish consumption (see "New and Future Developments—Nutrition").

Are you confused yet? You may be thinking, "Don't bug me with linolenic acid and DHA. Just tell me what to eat."

Okay. My considered opinion is that including fish in your diet is fine. I am a prostate cancer survivor and eat fish regularly. I concentrate on fish high in the beneficial fatty acids DHA and EPA. These include wild salmon (not farm-grown), sardines, mackerel, anchovies, tuna, cod, swordfish, and halibut. Why do I avoid farm-fed salmon? The DHA and EPA in salmon comes mainly from eating other fish that have fed on DHA- and EPA-rich algae. Farm-raised fish are fed pellets lacking these fatty acids. Although farm-fed fish have plenty of fat, this fat lacks the high concentration of DHA and EPA of wild fish. When eating high-caloric food like fatty fish, it's important to extract full nutritional benefit. Without high levels of DHA and EPA, farm-raised fish aren't worth the caloric investment.

There's no question that whenever you substitute fish for red meat, you're doing your heart and prostate a favor. Substituting white-meat chicken (cooked without its skin—

remember, chicken skin cooked at high temperatures is one of the richest sources of cancer-causing heterocyclic amines) or turkey breast for red meat would also be an improvement. These changes do not necessarily need to be made overnight. Depending on your personality, you may choose to make them gradually, as a process. You may otherwise wish to make a radical dietary change and stick with it. Knowing the operative principles should help.

What should vegans do to obtain adequate amounts of DHA and EPA? The answer, according to nutrition experts like Dr. Myers and Dr. Heber, does not lie in guzzling flax oil. Here a supplement is probably the best answer. If you're a pure vegan (no animal-derived food whatsoever), algae-derived DHA capsules are available, although you'll need about 15 capsules daily to get the anti-inflammatory benefits. DHA can be converted to EPA by the body. If you have no moral problem with consuming fish-oil capsules, these are also readily available and are a less costly way to get active amounts of EPA and DHA. If no fish is eaten, 1,000-mg capsules are available and should be taken twice daily. Men who do eat fish regularly can take less, or none at all, depending on the amount of fish being consumed. (For sources of algae-derived DHA and pure fish oil capsules, see Appendix IV).

By the way, fish consumption has also been associated with a reduction of a variety of degenerative diseases, including heart disease, stroke, arthritis, Alzheimer's, and other cancers. This is, in large part, due to its anti-inflammatory effects. Studies indicate that fish oil inhibits the production of inflammation-causing prostaglandins.

At this time, it's unclear whether a pure low-fat vegan diet or a vegan diet with added fish, is optimal. Either, however, is a highly constructive alternative to what most men currently eat.

More Fat (Not) to Chew On

Besides minimizing (or eliminating) red-meat consumption, you should eliminate the use of polyunsaturated oils and saturated fats. Although red meat is the main source of saturated fats, other sources include egg yolks, butter, coconut oil, and palm oil. Cooking oil should be reduced to minimal levels. The only cooking oil that should be used is olive oil. This is available as a spray, which will help you limit the amount used. Olive oil should also be the main oil used in salad dressings, although macadamia nut, walnut, or avocado oil can be substituted for taste. A delicious salad dressing can be made by mixing soft tofu and a little olive oil with lemon juice, spicy mustard, and fresh garlic. Balsamic vinegar can be substituted for lemon juice, if you prefer the taste.

Reducing oils and red meats will also help you reduce calories. I want to stress that calorie reduction is the single best thing you can do to reduce the risk of degenerative diseases such as cancer, heart disease, stroke, diabetes, and arthritis. Some experts believe that fat intake is not important so long as you're able to keep your calories low (2,000-2,200/day). Animal studies confirm this.

What is the relative value of reducing fats to reducing calories? The answer is not clear. It's probable that both calorie reduction and fat reduction have independent beneficial effects for men with prostate cancer, although fats high in DHA and EPA appear to be protective. Dr. Heber sums it up as follows.

• Fat and oils provide about 140 calories per tablespoon. This means that a mere 15 tablespoons would make up an entire day's diet! Obesity is a major risk factor for cancer and heart disease, so decreasing overall fat intake makes sense. I haven't lost anybody yet to fatty acid deficiency, so 20% (of calories) from fat or less is great, with fat being used to enhance taste where necessary.

• Fruits and vegetables have a natural balance of n-3 (linolenic) and n-6 (linoleic) fatty acids, as well as monounsaturated n-9 fatty acids, so increasing fruit and vegetable intake would be positive.

• Eating low-fat fish rich in n-3 fatty acids is okay, but a vegetarian diet balanced in linolenic and linoleic acid would probably be just as good, and perhaps better.

• Much more research is needed in this area, and [Dr. Heber's group is] planning to include this area as a major emphasis in [its] work at UCLA.

Diet is a complex subject. It's difficult, if not impossible, to isolate one food source from the overall diet. Diet may also be influenced by lifestyle. For example, a man who is 20 pounds overweight may eat lots of red meat, rich desserts, and dairy products. He may drink excessively, hate vegetables, and be under considerable stress. He may exercise infrequently and have a sedentary job. To say that his increased risk of getting prostate, or colon, cancer is from eating red meat is simplistic. A combination of dietary and lifestyle factors is likely involved in his increased risk of cancer. Yet a study looking at red-meat consumption would show an association in this man between his red-meat intake and his risk of developing prostate cancer.

"Epidemiologic studies do not provide cause and effect information," states Dr. Heber. "They indicate a dietary or eating pattern. For example, the associations between red meat and colon cancer say more about the overall diet and lifestyle of the red-meat eater than they do about any chemical contained in the red meat." Practical changes in patterns of eating and exercise are desirable.

HELPFUL HINTS

• Overall fat consumption should be reduced to about 20% of consumed calories.

• Calorie reduction is probably the single most important step you can take to increase longevity and the quality of life in old age.

• Some fats are beneficial, especially those containing the fatty acids DHA and EPA found in deep-water fish. Fat consumption should be limited to these and the monounsaturated oils—olive, walnut, macadamia nut, and avocado.

• Reducing calories should always be the paramount consideration, so that intake of even the beneficial oils, like olive oil, should be controlled for optimal health. Each tablespoon has 140 calories.

How Fats May Stimulate Prostate Cancer Growth

None of the mechanisms by which dietary fat may increase prostate cancer risk have been proven. It's a complex area. Factors that may make a difference include the type and quantity of fat consumed, the interaction of ingested fatty acids with antioxidants, such as vitamins and minerals, changes in fat induced by cooking, and the effects of various fat mixtures on cells in the body.

While these areas are actively being studied, conclusions are hard to come by. We now know that heating saturated fats by cooking animal food, especially at high temperature, produces chemicals called heterocyclic amines, which are directly toxic to cells. This causes damage to cellular DNA. Other theories are more subtle. One that has received a lot of recent attention is the effect of dietary fats on insulin, growth factors, and hormones in the body. Gram for gram, fats have more than twice the calories of protein or carbohydrate and are a significant contributor to obesity, a disease that has reached epidemic levels in the United States.

Obesity and Prostate Cancer

Eating disorders are rampant in the U.S. According to Dr. Heber, half the population doesn't eat a single piece of fruit a day. Only 20% eat the five daily servings of fruits or vegetables recommended by the National Cancer Institute.

Obesity is a much bigger problem than not being able to button your trousers. It causes significant hormonal changes. Insulin levels are increased and diabetes is a common result. Diabetes-related deaths in America have increased 40% over the past 15 years and are now approaching deaths from breast cancer.

Besides diabetes, obese people have a significantly higher risk of heart disease and prostate cancer. They secrete a chemical, called adipocytokine, that leads to inflammation and

oxidative changes that increase the risk of prostate cancer, arthritis, atherosclerosis, and other chronic debilitating diseases.

One hormonal change prevalent in obesity is changes in an insulin-related hormone known as insulin-like growth factor-1 (IGF-1). IGF-1 has received considerable attention in recent years in association with the development and spread of prostate cancer.

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IGF-1, IGFBP-3, and Prostate Cancer

IGF-1 stimulates prostate cancer cell growth. Although obese men tend to have high levels of IGF-1, men of normal weight can also have elevated IGF-1 levels. I know, because I'm one of those. In the bloodstream, IGF-1 can circulate freely or bind to a protein called IGF binding protein-3 (IGFBP-3). The relationship of IGF-1 to IGFBP-3 and their respective effects on prostate and breast cancer are a hot topic in cancer research. IGF-1 is a powerful stimulator of prostate cancer cell growth and also interferes with apoptosis. Elevated IGF-1 levels increase the risk of prostate cancer development and also increase the chances of localized prostate cancer becoming more aggressive and spreading beyond the prostate. In a prospective study, men in the highest quartile of IGF-1 levels had more than 4 times the risk of prostate cancer than men in the lowest 25%.

IGFBP-3, on the other hand, is a highly beneficial protein. Not only does it neutralize circulating IGF-1 by "mopping" it up, new studies show that it also has a direct inhibitory effect on the growth of prostate cancer cells. In fact, it has just been discovered that one of the main ways vitamin D works against prostate cancer is by increasing IGFBP-3 levels.

All evidence now points toward lowering IGF-1 levels and raising IGFBP-3 levels as one of the more important steps a man can take in preventing prostate cancer. For men who already have prostate cancer, this interplay is even more important. Moving toward a plant-based diet, decreasing calories, and increasing exercise levels all reduce IGF-1 levels and raise IGFBP-3 levels. Increasing vitamin D levels appear to raise IGFBP-3 levels. Silymarin or silibinin supplements may also raise IGFBP-3 levels and decrease IGF-1. For a more complete discussion of this important topic, see pages 418-423.

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Sex Hormone Binding Globulin (SHBG)

We men have a hormone circulating in our blood called sex hormone binding globulin (SHBG). SHBG binds testosterone in the blood, reducing the levels of free testosterone. Low dietary fat intake leads to increases in SHBG; high fat intake reduces SHBG levels. In 1996, a study conducted at Harvard Medical School by Gann et al. showed a significant increased risk of prostate cancer as the level of testosterone increased. Men with levels in the top 25% of those tested had a two to six times greater chance of getting prostate cancer than men whose testosterone level was in the lowest 25%.

The opposite effect was observed when SHBG was measured by these investigators. The higher the SHBG level, the lower the risk of prostate cancer. Men whose SHBG levels were in the top 25% had a 54% less chance of getting prostate cancer, compared to men in the lowest 25% for SHBG.

The Gann study was prospective, involving 222 men who subsequently developed prostate cancer and 392 controls matched for age, smoking, length of follow-up, etc. Although this was a seemingly well-designed investigation, not all researchers have reached the same conclusion. It cannot be said with any certainty that increased testosterone levels, or low SHBG levels, cause prostate cancer. But the Gann study shows a strong association between these blood factors and prostate cancer. So, although the evidence is not conclusive, it seems beneficial, as far as prostate health is concerned, to maintain relatively high blood levels of SHBG. That means, once again, a low fat intake.

What factors regulate SHBG levels? Major influences include insulin and insulin-like growth factors. As insulin levels in the blood increase, SHBG levels decrease. Obese men often have high insulin and low SHBG. Diet and exercise can lower insulin levels and raise SHBG levels. A 1998 study done at UCLA Medical School monitored the effects on insulin and SHBG levels produced by a three-week diet and exercise program in 27 obese men. The men exercised by walking 30-45 minutes daily and participating in a supervised exercise class. They ate as much as they wanted, but fat was limited to 10% of calories. Protein comprised 10% -15% of calories and complex carbohydrates provided the balance. Carbohydrates were primarily in the form of vegetables, fruits, legumes, and grains. Animal consumption was limited to 85 grams of chicken or fish per week (about three ounces).

At the end of the three weeks, insulin levels had decreased by 43% and SHBG levels had increased by 39%.

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20

ATTITUDE

Does attitude really make a difference if you have cancer? I posed this question to each clinician I interviewed for this book. Virtually all believe it helps. Frequent responses included, "Men with a positive constructive outlook seem to do better," or, "That's my impression, though I can't prove it." As Dr. Snuffy Myers puts it, "In my clinical practice, I've been impressed that the men who seem to do best are those who fully confront the implications of their disease and take an active part in developing the treatment plan." He referred to a 1999 study on women with breast cancer that characterized this attitude as "realistic optimism." In the words of Dr. Spiegel, the author of this study, "Optimistic women appear to accept more readily the reality of the challenge they face, whereas pessimistic women try to push this reality away."

I first became aware of a possible influence of mental factors in medicine while still a medical student (too many years ago to mention). Part of our training in the final year included clinical experience. While on the surgery wards, a respected surgeon was talking with a patient scheduled for surgery the next day. The surgeon asked the patient, "Are you ready? How do you feel about your operation?"

She responded, "Doctor, I'm really scared. I don't think I'll make it through the surgery. I think I'm going to die," and she burst into tears.

I've never forgotten the surgeon's response: "Well, in that case, I'm canceling your surgery." Additionally, the doctor withdrew from the case!

I was spellbound. Why? I sought out the surgeon and asked him. He said, "This has happened to me several times before and in each case the patient died. I won't operate on patients who are convinced they won't survive."

Wow! I was thunderstruck. Although the surgeon's opinion was clearly based on what researchers refer to as "anecdotal evidence," from then on I began paying close attention to how patients approached their disease and observed their outcome.

Just what is the relationship between mental factors and disease? Is there a mind-body connection? If so, how does it work? It probably won't surprise you that we have only a rough guideline to the interaction between the brain and nervous system and the immune system. How emotions influence this interaction is fuzzier still. But there have been some fascinating observations that have practical implications.

What Is the Immune System?

The immune system is comprised of white blood cells, lymph nodes, the spleen, thymus, and bone marrow. The job of the immune system is to protect the body from "foreign invaders," such as bacteria, viruses, and the body's own damaged cells (cancer).

The "soldiers" of the immune system are the lymphocytes, specialized white blood cells. These circulating cells are armed with receptors on their surface that recognize alien molecules (antigens). When lymphocytes recognize antigens, it triggers the "immune response." Part of this response is the production of an increased number of special lymphocytes, called "natural killer" (NK) cells. These and other specialized lymphocytes defend the body from everything that they recognize as "other

than self." In other words, they're constantly poised to identify and destroy any molecule determined to be foreign to the functioning organism. They behave as if they can "think," constantly re-evaluating an ever-changing interior chemical environment and participating in its response to a multitude of external influences.

Medicine and Information

How does the immune system distinguish "self" from "other?" How does it "think?" The answer to this question is redefining the entire medical paradigm: information.

The DNA sequence that makes a gene is information. Like Morse code, which uses combinations of dots and dashes to form words, the genetic code uses sequences of DNA to form genes. Each gene has the code to produce a single protein. Proteins then become the "biological information superhighway." They form information pathways that interconnect with other streams of information. In this way the nervous, immune, and endocrine systems are perpetually interacting. Chemical signals (messages) are constantly being sent and received, which produces responses.

Chemical signals from proteins are received at sites on the cell surface. Until recently, these were thought to exist only in the brain. We now know that receptors are present on circulating immune-system cells and are capable of responding to messages from hormones produced by the central nervous system. These hormones, called "neuropeptides," affect our mood.

Not only can hormones from the brain affect the immune and endocrine systems, but immune and endocrine hormones can also affect the brain. Communication is not one way. An all-powerful brain is not solely sending out commands to ever-obedient body systems, like a puppeteer pulling the strings of a marionette. Rather, information flows in multiple directions. Each body system is interdependent on other body systems. As Dr. Candace Pert recounts in her excellent book

Molecules of Emotion, immune-system cells not only have surface receptors to receive neuropeptides from the brain, they also make their own neuropeptides that act on the brain and affect our mood. This has opened up a whole new way of looking at the interaction between mind and body. Called by Dr. Pert "psychoimmunoendocrinology," this big word encompasses the effects of thinking and emotions on the immune and endocrine systems.

Geneticist Dr. LeRoy Hood of the University of Washington sums it up, "Medicine is informational science."

Not only are messages generated internally by the body's systems, but external environmental messages also affect the on-going interchange of the body's signals and responses. Laurence Foss, author of *Healing Biological Medicine* and co-author of *The Second Medical Revolution: From Biomedicine to Infomedicine*, points out that the environment includes not only the physical and ecological environments, but the psychological, social, and cultural environments as well. Thoughts and feelings form an integral part of the environment and, as Foss points out, can produce physical responses. Conversely, physical responses can generate thoughts and emotions. This differs from the traditional biomedical model that doesn't account for intercommunication between the body and mind in any significant way. In Foss' words, "In the infomedical but not in the biomedical picture, a thought or emotion can manifest itself bodily; and, conversely, a body process can translate itself into a thought or emotion."

Examples of the two-way communication between the mind and body include:

• An embarrassing thought and feeling (mind) can lead to blushing, a dilation of blood vessels in the face triggered by neuropeptides acting on receptors on these blood vessels (body).

• Turning "white with fear" or "red with anger." Intense fear can cause uncontrollable shaking (quivering with fear). This is a physical response to an emotion.

• Recalling past noxious events can provoke a physical

response. Someone with a fear of snakes may shudder upon hearing a conversation about an encounter with one. A cancer patient may feel nauseous while sitting in the waiting room prior to chemotherapy.

This kind of "conditioned response" has potential therapeutic ramifications. Just as a negative association can lead to an undesired physical response, so too can a positive association produce a desirable physical change. Dr. Spector and associates at the University of Alabama in Birmingham, working together with Italian colleagues, demonstrated a three- to 39-fold increase in natural killer (NK) cells in response to conditioned activity in mice. Typically, this increase is seen in response to an antigen. But when these researchers combined a "conditioner," such as a certain taste, with the introduction of an antigen, they found that mice could be "trained" to dramatically increase their NK cells by experiencing the taste without the antigen. NK cells are one of the key lymphocytes in the fight against cancer. As you'll see, their production can be influenced by thinking and emotions.

All these are physical responses to thoughts and feelings.

Other emotions—joy, depression, and amusement—are also expressed both mentally and physically. Biochemically, it appears that neuropeptides produced by the brain are then received by receptors in the body, resulting in a variety of physical responses. Emotions can, therefore, be the catalysts for physical responses, which, in turn, can evoke emotions. In other words, the body processes are constantly changing in response to the mind's interpretation of external events. This change is reflected in alterations of pulse rate, respiration rate, blood pressure.

When it comes to coping with cancer, perception of events is a critical variable. How we think about events is perhaps more consequential than the events themselves. Cancer itself can be interpreted by one person as punishment for a body-abusive lifestyle, creating feelings of guilt and helplessness, while another regards it as the sternest warning for the necessity of a drastic change in lifestyle. Framing events in

a consistently constructive way not only makes dealing with cancer easier, it also improves the quality of life. The emotions evoked by constructive interpretations of events are also likely to bolster your immune system.

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How Moods Affect the Immune System

What are the effects of neuropeptides produced by our various moods on the immune system? One measure of immune function is immunoglobulin A, or IgA. It's the primary immunoglobulin in tears and saliva. Because saliva IgA is so readily accessible, it's frequently used as a measure of immune strength.

It has been shown in a series of studies by Dr. Arthur Stone, professor of psychiatry at State University of New York at Stony Brook and his associates, that salivary IgA levels are influenced by moods. Debilitating emotions, like anger, depression, anxiety, and despair, lower salivary IgA levels. So do stressful events in daily life. On the other hand, positive emotional states like joy, happiness, and serenity, raise salivary IgA levels. Supportive social interactions, humor, and meditation also raise IgA levels.

Emotions and Natural Killer (NK) Cell Levels

Emotional states have also been correlated with the number of NK cells in the circulation. Stress, anxiety, and depression have been associated with a decrease in the number of

NK cells. Positive moods correlate with an increase in NK cells. Activities like meditation and massage have also been associated with increases in NK cells. There are even suggestions in the literature that intensive meditation and religious or spiritual epiphanies may lead to a spontaneous remission of cancer in some people. While this is conjecture, there is some logic in the premise that if positive moods strengthen the immune system, then extremely positive experiences could conceivably trigger a disease-altering immune response. No studies have been done to verify this hypothesis. The combination of a peak experience and spontaneous remission of cancer occurs so rarely that reports must be anecdotal. Still, the possibility is extremely intriguing.

Emotions and Disease

If the hypothesis that emotions can affect disease is true, then we should be able to identify an association between negative emotions and illness. A number of studies have demonstrated such a connection.

The May 2, 2000, issue of the journal *Circulation* reports that in people with normal blood pressure, anger is associated with heart attacks. The investigators from the University of North Carolina found that people who were most prone to anger had three times the chance of a heart attack, or sudden death due to heart failure, as those least prone to anger.

One of the most interesting and poignant recent studies comes from Dr. Stone at Stony Brook. It's germane for men who have prostate cancer, as well as those trying to prevent it. Dr. Stone found that stressed-out men, or men lacking social support, were two to three times more likely to have an elevated PSA. Men with high stress levels were three times as likely to have a high PSA; men with a poor social-support network were twice as likely to have an elevated PSA as those with good social support. Not surprisingly, the stressed-out men reported frequent feelings of anger and nervousness.

One possible explanation is that stress reduces immune

function, which may make a man more susceptible to prostate cancer. Stress consistently reduces NK cells. Another possibility is that the hormonal response to stress stimulates prostate cancer cell growth. According to Dr. Snuffy Myers, researchers at his former institution, the University of Virginia, led by Dr. Michael Weber have shown that epinephrine (adrenalin) stimulates the growth of prostate cancer cells. It's possible that chronic stress with its associated increased levels of "stress hormones," like epinephrine, stimulates the proliferation of prostate cancer cells and increases PSA levels. Dr. Meyers, in his private clinical practice, has observed a frequent correlation between periods of particularly intense stress and the onset of clinically relevant prostate cancer. Yet another possibility is that high stress promotes an unhealthy lifestyle. Anxious men are likely to have poor eating and exercise habits.

As for social support, a good support network may increase immune function by generating positive emotions that come with a sense of belonging and helping others. Men lacking social interconnections might not receive this immune benefit.

These studies do not prove that stress or lack of social support cause prostate cancer. As with diet there is an association, but an association is not a cause. However, as Dr. Stone points out, it's "not likely" that the cause of the high stress levels was the elevated PSA. The men in the study filled out questionnaires that were used to determine their level of stress. At the time they answered the questions they had no knowledge of their PSA results.

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Can Attitude Influence Outcome

Is there any evidence that attitude makes a difference in the prognosis of cancer patients? Dr. Steven Greer addressed this issue by interviewing women three months after radical mastectomy (breast removal) for breast cancer. He divided the women into four categories.

Group 1

Fighting Spirit—Accepted diagnosis and optimistically approached the disease by learning about it and getting involved in the decision-making process.

Group 2

Positive Avoiders—Denied or diminished the seriousness of their condition.

Group 3

Stoics—Accepted the diagnosis, but did not try to learn more. Accepted their fate submissively.

Group 4

Helpless and Hopeless—Convinced that they were going to die and that there was nothing they could do about it.

Survival Data for Each Group Five Years Later

Group 1	80% survival
Group 2	70% survival
Group 3	32% survival
Group 4	20% survival

After 10 years, "Fighting Spirit" still led in survival benefits. If these data are to be believed, it appears as though attitude may play a role in survival.

Two things particularly stand out in the above study. I found it interesting that denial was nearly as effective as fighting spirit in five-year survival outcome. Other studies have

included denial in their list of positive attitudes. This seems to me to be counterintuitive. Second, women with attitudes characterized as "pessimistic" (helpless, hopeless, fatalistic) were two to four times as likely to die in the first five years, when compared to optimistic women. Denial would have to be classified as optimistic. If you don't have cancer, or believe it's not serious, it certainly can't do you much harm—a strong reason for optimism.

Researchers at Ohio State University conducted a study and found that pessimism may have a stronger negative influence on disease than the positive impact of optimistic thinking. They discovered that pessimistic adults were more likely to report higher levels of stress and anxiety than optimistic people. When they looked at the two groups a year later, the pessimistic group reported poorer overall health.

It seems to me that one role for physicians should be helping patients to maintain hope and optimism. This doesn't mean becoming a Pollyanna. I don't think, however, that physicians should make pronouncements like "You've got three months to live." This can become a curse. Look at it this way. The patient has a great deal of respect and confidence in his doctor. He has developed a deep trust in his doctor, much like the relationship between a religious devotee and his spiritual leader. The doctor's opinion has great importance in this context. A statement like the one above may be tantamount to a death sentence in this setting. If not one before, the patient immediately becomes a member of the "helpless and hopeless" set. This can lead to depression and lassitude. As we've seen, such suppression of emotional response has been linked with a decline in natural killer cell activity. Logically, this may accelerate the tumor's growth, resulting in a downward spiral. The prophecy is fulfilled.

Not only is this unfortunate, it's also inaccurate. The physician has no way of knowing that this particular individual will survive three months. It may be accurate that the median survival for men with comparable disease is three months, but as we've discussed, statistics don't apply to individual cases.

Median survival means that half the men will live longer than three months, some much longer. The truth is that the doctor is extrapolating from a group statistic to an individual case and, in the process, stripping the man of hope. To me, this is not good medicine.

What's a better approach? I'd respond this way, "Survival depends on a complex set of factors and is difficult to predict. I could give you a statistic that would apply to a large group of men with similar levels of disease, but this almost certainly does not apply to your situation. Some studies show that people who keep battling live longer. Let's discuss the available options and determine together the best course for you to take from now on."

A statement like this supports the patient in his battle and reinforces the thinking that's most likely to be helpful in extending survival. Pronouncements, such as the first example, seem to me to have the opposite effect.

In the words of Dr. Keith Block, director of the Block Medical Center in Evanston, Illinois, "Initial coping responses, such as despair and helplessness, may trigger a cascade of neuroendocrine processes that compromise the very immune mechanisms the individual needs to keep malignant tumors and micrometastases in check. Conversely, positive coping behaviors appear to help keep the immune system actively engaged in neoplastic surveillance and cytotoxic activities, thereby discouraging the progression of cancer." One role of a care-giver, according to Dr. Block, is to provide "an unrelenting life-affirming attitude," allowing patients to experience "the optimism of possibility." This way "people feel more whole, more alive, more engaged with life, and inspired to go on living."

Excellent clinicians are careful not to strip patients of hope. Quoting earlier investigators Dufault and Martocchio, Dr. Block provides this excellent definition of hope, "A multidimensional life force characterized by a confident yet uncertain expectation of achieving a good future that, to the hoping person, is realistically possible and personally significant."

Good doctors provide the tools for positive coping. Although this hasn't been conclusively proven to improve outcome, it will certainly provide a better quality of life. As Dr. Block points out, "Quality of life is inseparable from the biological, psychological, and psychosocial context for maintaining sound health." It may also improve immune function.

Bottom line: The patient feels better and may be better equipped to fight the cancer.

Key Reference

Block K. The role of the self in healthy cancer survivorship: A view from the front lines of treating cancer. *Advances: The Journal of Mind-Body Health* 1997; 13: 6-26.

Will Power

I have read about many cases where people with terminal diseases survive far longer than "expectation" when they have a specific target or time goal. This goal is often an important event: a child's wedding, a college graduation, or an anniversary.

Although I found this interesting, I didn't pay much attention to it. Then, one day, events emblazened this phenomenon in my memory.

When my mother was dying of lung cancer, she vowed that she would "make it" to her 79th birthday. Several months prior to her birthday her cancer progressed dramatically. She became totally bedridden, was jaundiced (yellow skin and eyes), and had a large mass of cancer in her abdomen. She was on supportive care only.

She said, "It doesn't look good, but I will make it to my birthday." I lived a great distance from her and she told me to "make travel plans to be here on my birthday."

"I wouldn't miss it for the world," I replied.

She continued to slowly decline until a week before her birthday, when her condition started to rapidly deteriorate. She had trouble breathing and required continuous oxygen.

She flitted in and out of consciousness. In response to an urgent summons, I arrived two days before her birthday. My mother was unconscious. She did not open her eyes and did not acknowledge my presence. Her breathing was heavy and labored. She was severely jaundiced.

The next day, one day before her birthday, she was still alive. It seemed to me that she was struggling to stay alive. Each breath seemed a tremendous effort. Knowing her vow to survive until her birthday and thinking she might still be able to hear me, I decided to ease her burden. I said softly, "Mom, it's your birthday. You can let go now."

To my utter amazement, her eyes opened suddenly and she said, "Not till tomorrow." These were the only three words she had uttered in two days! How she could keep track of the time she needed to fulfill her goal is beyond me. At 4 a.m. the day of her birthday, a scant four hours into the day, her fight ended.

Had I, and others, not witnessed this, I might have been incredulous. The power of will can be marvelous. Just how this works physiologically is a mystery to which I'd love to know the answer.

Helpful Mental Factors

• Learn all you can about prostate cancer.

• Be actively involved in the decision-making process. Take control of your disease.

• Determination to defeat the cancer and maintain an active engaging existence may help improve outcome.

• Adherence is important if you make the decision to change your lifestyle.

• Seek out physicians with whom you can establish a close working rapport. A physician-patient partnership is likely to be more effective than a dominant-submissive doctor-patient relationship.