A Publication of the **Patrick C. Walsh Prostate Cancer Research Fund** | The Brady Urological Institute | Johns Hopkins Medicine

DISCOVERY

Volume III | Spring 1994

Newsletter Recreated from Historical Document

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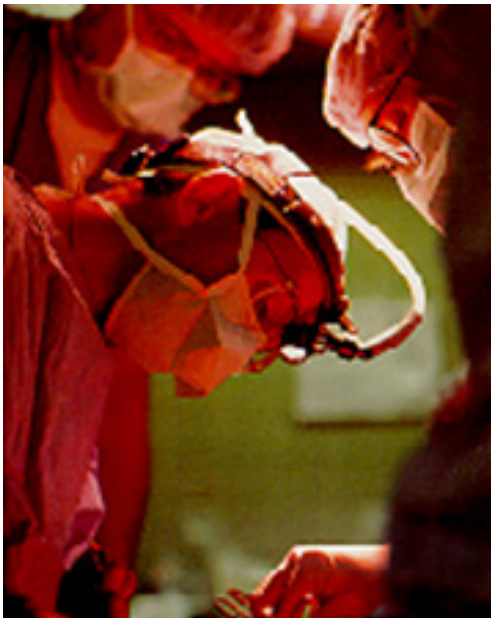
Letter to Patients

Once again, it is a pleasure to share with you the exciting results of our discoveries over the past several years. Since the last Update we have characterized a new syndrome of hereditary prostate cancer, improved the use of PSA in screening for prostate cancer, demonstrated that the anatomical approach to radical prostatectomy provides superior cancer control, and have embarked upon a host of new and exciting research endeavors. I share these results with you as my patients who are partners in this process of discovery. Thank you for your participation and support.



Sincerely yours,

Patrick Walsh

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

Hereditary Prostate Cancer: A New Discovery

We have known for many years that some cancers were hereditary, e.g. breast cancer and colon cancer. However, based upon studies from Johns Hopkins, it is now clear that prostate cancer should also be included in this list. With help from the first 700 patients who underwent radical prostatectomy at Johns Hopkins, we were able to establish a strong association between a family history of prostate cancer and the risk for developing the disease.

Since that original observation we have identified a new variant of prostate cancer, hereditary prostate cancer (HPC). Families with hereditary prostate cancer are characterized by an early age at onset of the disease and/or the presence of cancer in multiple family members. We derived the following operational definition for such families: 1) prostate cancer in 3 or more first degree relatives (father or brothers) or 2 first degree relatives if both developed the disease before the age of 55 years; or 2) prostate cancer in 3 generations, e.g. grandfather, father, son.

The mode of inheritance is characterized as autosomal dominant. Autosomal means that it can be transmitted by either your father or mother. Therefore, when examining your family history it is important to ask both your father and your mother about the presence of prostate cancer in their brothers and father. The fact that this disease is inherited as a dominant trait means that 50% of the male offspring in these families are at risk for developing the disease.

Because the disease is characterized by early age at onset, male members of these families should begin screening measures (digital rectal examination and serum PSA measurements) at age 40 rather than 50. We estimate that 88% of offspring who inherit the gene will develop prostate cancer by age 85. We have established a hereditary prostate cancer registry at Johns Hopkins and have evaluated the pedigrees of over 100 patients from around the country. We have not yet identified any strong association between prostate cancer and other cancers in these families. This suggests that the mutated gene may be specific for prostate cancer. DNA samples from multiple members of 60 families with HPC have been assembled and we are proceeding rapidly with linkage studies to identify the mutated gene. This gene appears to be responsible for an early rate limiting step in the development of prostate cancer. The

isolation of this gene someday will help identify affected members in HPC families. Also, it will provide major insight into the cause of the disease and hopefully, new approaches to prevention and treatment.

References:

1. Carter, B.S., Bova, G.S., Beaty, T.H., Steinberg, G.D,, Childs, B., Isaacs, W.B., and Walsh, P.C.: Hereditary prostate cancer: Epidemiologic and clinical features. J. Urol. 150:797-802, 1993. (Review Article).
2. Carter, B.S., Beaty, T.H., Steinberg, G.D., Childs, B., and Walsh, P.C.: Mendelian inheritance if familial prostate cancer. Proc. Natl. Acad. Sci. 89:3367-3371, 1992.
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Excellent Cancer Control at 10 Years

The technique of anatomical radical prostatectomy has been perfected over the past 15 years. It is often incorrectly referred to as a "nerve-sparing" procedure. This term, however, does not tell the entire story and indeed sends the wrong message. Based upon anatomical studies, the technique of radical prostatectomy was modified in the following ways:

1. Accurate control of bleeding to enable the operation to be performed in a bloodless field
2. Intraoperative assessment of tumor extent and preservation or wide excision of the nerves where necessary (prior to the advent of this technique the nerves were never widely excised but merely cut and left in place)
3. Precise preservation of the external sphincter mechanism with functional reconstruction of the urinary tract to preserve urinary control.

Over the past decade we have been able to demonstrate that this technique is associated with less blood loss, improved rates of urinary continence, and preservation of sexual function in many patients.

At last, enough time has elapsed to evaluate the influence of this technique on cancer control. We recently analyzed the results on 955 men who underwent surgery between April 1982 and March 1991. At 10 years 70% of all patients had an undetectable serum PSA, 7% developed distant metastases, and 4% were found to have local recurrence of their cancer. These are the best results ever reported for radical prostatectomy. It is now clear that an anatomical approach to radical prostatectomy provides excellent cancer control while preserving quality of life.

References:

1. Partin, A.W., Pound, C.R., Clemens, J.Q, Epstein, J.I., and Walsh, P.C.: Serum PSA after anatomic radical prostatectomy: The Johns Hopkins Experience After 10 Years. Urol. Clinics N. Amer. 20:713-725, 1993.

Do I Need Treatment?

The lifetime risk of developing prostate cancer for a man in the United States is 13%. However, up to 50% of men are found to have microscopic cancers in their prostate at autopsy. These observations have led some to criticize PSA testing because it may identify cancers that are incidental and would never trouble the patient during his lifetime. This has been a popular theme in the lay press recently. What are the facts?

If you can feel a cancer (stage B or T2-T3), it is almost always a significant tumor that requires treatment. If your cancer cannot be felt but is detected only by a serum PSA, it is possible that you could harbor a small cancer. In a study of 150 men with cancers that could not be felt (stage Tlc) who underwent radical prostatectomy at Johns Hopkins Hospital, 11 % of men with PSA levels greater than 4 had very small cancers (.2 cc and confined to the prostate).

We subsequently identified some criteria to help identify those patients prospectively so that they can be cautioned about the need for aggressive therapy. If the cancer was present in 3 cores of tissue, or involved more than half of 1 core, or was Gleason 7 or greater, the amount of tumor found at radical prostatectomy was always significant. These patients should be strongly encouraged to undergo therapy. However, if the patient has none of these findings and if his PSA density (serum PSA divided by the prostate weight estimated from transrectal ultrasound) is in the range of 0.1 to 0.15 then there is a good chance that the patient harbors a small cancer. Based upon the age and desire of the patient, it may be wise for these patients to be followed expectantly. If they elect to do so, they should undergo a digital rectal examination and serum PSA every six months and needle biopsies once a year. We cannot rely upon serum PSA alone because it is known that approximately 25% of patients with cancers that progress in size do not have a concomitant increase in their serum PSA.

References:

1. Epstein, J.I., Walsh, P.C., Carmichael, M., & Brendler, C.B.: Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA 271:368-374, 1994.

Why Make An Early Diagnosis of Prostate Cancer?

Why would anyone want to be treated for prostate cancer if he believed one of the following "facts"?:

1. It has never been proven that an early diagnosis of prostate cancer increases survival;
2. There is no need to treat men who have prostate cancer because they do just as well when left alone;
3. Screening for prostate cancer will detect the tiny microscopic cancers that are found in 30% to 50% of men at autopsy, thus resulting in more deaths from treatment than cure.

However, I like Don Coffey's quote "There is a difference between a fact and a true fact". What are the true facts?

In the United States a man is diagnosed with prostate cancer every 3 minutes and dies from the disease every 15 minutes. In 1994, 38,000 men in the U.S. will die from prostate cancer, approximately 1 out of every 5 who develops the disease; this is similar to the 25% death rate in women who develop breast cancer. And deaths from prostate cancer are on the rise by 2% to 3% per year, because older men are dying less frequently from cardiovascular disease.

To reduce the number of deaths from prostate cancer there are 4 approaches: prevention, early diagnosis, effective treatment of curable disease, and improved management of advanced disease. In the foreseeable future it is unlikely that we will be able to prevent the disease by manipulating environmental or genetic factors or to cure patients with advanced disease while keeping side effects at an acceptable level. Therefore, in order to reduce the number of deaths from prostate cancer we need to diagnose the disease more often when it is still localized to the prostate and treat it effectively.

"FACT" NUMBER 1.

Indeed, no study has demonstrated that an early diagnosis of prostate cancer increases survival. But the true fact is that this issue has never been studied and no one has ever shown that an early diagnosis of prostate cancer does not prolong survival. It has been shown that an early diagnosis of breast cancer is associated with increased survival

rates. Breast cancer, like prostate cancer, is an adenocarcinoma that cannot be cured once the disease has escaped the primary organ and it has a natural history not dissimilar from prostate cancer. Today, with serial PSA screening, 70% of men detected with prostate cancer have cancers that are confined to the prostate that can be cured. Thus, it is reasonable to assume that if a proper study is ever performed it is likely that screening studies in prostate cancer will demonstrate improved survival as they have in breast cancer.

"FACT" NUMBER 2.
If prostate cancer is undetected before it has metastasized and is left untreated, it usually takes longer than 10 years to kill the patient. This concept has 3 important implications: 1) the progression of prostate cancer is relatively slow, thus providing a reasonable window wherein the diagnosis can be made and the disease cured before it has spread; 2) if treatment is delayed too long the disease progresses beyond the prostate, undergoes more malignant transformation, and cure is no longer possible; and, 3) efforts at screening for early localized prostate cancer and aggressive therapy should be concentrated only in those men who have a projected life-span longer than 1O years.

There is a series from Sweden which is frequently quoted. In this carefully selected series of patients (average age 72 with small well differentiated tumors) in whom watchful waiting was undertaken, at 10 years 13% of the patients were dead and 50% of the patients had progression of cancer to bone or adjacent structures. Thus, although prostate cancer does not kill many men during the first ten years, it does progress in most men causing bone pain or urinary obstruction that requires treatment with castration or hormones. Most patients who experience progression will die during the next 5 years. This may explain why Sweden has one of the highest death rates from prostate cancer in the world.

"FACT" NUMBER 3.
Although small microscopic foci of prostate cancer can be found in 30% to 50% of autopsies performed on men older than 50 years of age, it is unreasonable to assume that today's diagnostic techniques are sensitive enough to detect all of these small foci of tumor. However, in a small minority of men these cancers are detected.

To reduce deaths from prostate cancer we need to diagnose the cancer earlier and treat it effectively. With improvements in the use of PSA testing this should be possible. Today, 70% of men who are identified through sequential PSA screening are found to have localized prostate cancer. In the past, most men with early localized prostate cancer were not identified and the window of curability silently closed before treatment could be instituted. Most of these patients presented late with advanced disease at a time when they were not curable. In the future, this should not occur.

References:

1. Walsh, P.C.: Using prostate-specific antigen to diagnose prostate cancer: Sailing in Uncharted waters. Annals of Int. Med. 119:948-949, 1993.
2. Walsh, P.C.: Why make an early diagnosis of prostate cancer. J. Urol. 147:853-854, 1992.

Results of Clinical Studies

Many of you signed up for participation in studies that were overseen by the joint Committee on Clinical Investigation at The Johns Hopkins Hospital. I am most grateful for your participation and would like to share with you a brief summary of some of the results.

MRI STUDY
In an effort to identify spread of cancer beyond the prostate, some of you participated in our study of MRI using

the endorectal coil. Although this technique provides excellent images of the prostate, it did not improve the ability of the radiologist to detect spread of cancer beyond the prostate. The reason for this is becoming increasingly clear. When prostate cancer cells escape the prostate, they creep along the edges of the gland just millimeters away from the edge as they progress toward the seminal vesicles. Unfortunately, it is almost impossible to detect this microscopic spread.

HEMODILUTION STUDY

In an effort to reduce the need for auto transfusion of blood, we evaluated a technique known as hemodilution. At the time of surgery, just after the epidural anesthetic is placed, 3 units of blood were drawn acutely from the patient and the blood volume was restored using solutions containing salt and starch. At the end of the case all 3 units were readministered to the patient. We learned that this technique was as safe and as effective as the donation of 3 units of blood prior to surgery However, this technique can only be used in patients who have an excellent cardiovascular status.

References:

1. Ness, P.M., Bourke, D.L., and Walsh, P.C.: A randomized trial of perioperative hemodilution versus transfusion of preoperatively deposited autologous blood in elective surgery. Transfusion 32:226-230, 1992.

EPIDURAL STUDY

In an attempt to improve the techniques of pain control, we evaluated the use of ketorolac, a non--steroidal anti-inflammatory agent similar to Motrin or Advil that can be given intravenously. We learned that ketorolac not only improved pain control but also permitted bowel function to recover more rapidly. As a result of this study, and studies at other institutions, ketorolac is now playing a major role in the postoperative management of patients. We now understand that most of the nausea which occurred following surgery was caused by the narcotic pain medications and that by eliminating narcotics from postoperative pain control we can now discharge patients on their 4th or 5th postoperative day.

References:

1. Grass, J.A. et. al.: Assessment of ketorllacasan adjustment to fentanyl patient-controlled epidural analgesia after radical retropubic prostatcctomy. Anesthesiology 78:642-648, 1993.

NERVE-GRAFT STUDY

Experimentally we demonstrated that nerve grafts restored sexual function in rats. We then embarked upon a study to determine whether or not nerve grafts would improve the recovery of sexual function in men who underwent wide excision of one nerve. Many of you had 18 months of suspense waiting to find out whether or not you underwent a nerve graft. By now that suspense is over. Unfortunately, we were not able to answer the question about whether nerve grafts worked because too few patients required wide excision of their nerves. This actually is good news because it demonstrates how prostate cancer today is being detected at an earlier more curable stage. Unfortunately, we may never know the answer to this question.

What if PSA Goes Up After Surgery?

At 10 years, 70% of the patients who underwent an anatomical approach to radical prostatectomy at The Johns Hopkins Hospital have an undetectable serum PSA. What about the rest of the patients and what does an elevated serum PSA mean following surgery?

Because PSA is prostate specific, it means that some prostate cells must be present. Although it is possible in rare instances that some benign prostate cells may be responsible for the elevated serum PSA, it usually means that some residual cancer cells are present. But where are they and what do they mean? We recently evaluated 51 men who had an elevated serum PSA following radical prostatectomy. These patients were followed expectantly until the source for the PSA elevation was detected: in 30% the disease recurred locally and in 70% the cancer recurred in lymph nodes or in bone. We determined that if the PSA elevation occurred during the first postoperative year, or if the patient had involvement of his seminal vesicles or lymph nodes, or if the patient had high-grade disease (Gleason 8-10) the cancer almost always recurred through distant metastasis. Using information from this study we have created a nomogram which enables us to identify those patients who are most likely to have local recurrences of cancer that may benefit from radiation therapy to the prostatic bed.

References:

1. Partin, A.W., Pearson, J.D., Landis, P.K., Carter, H.B., Pound, C.R., Clemens, J.Q, Epstein, J., and Walsh, P.C.: Evaluation of serum prostatic specific antigen velocity after radical prostatectomy to distinguish local recurrence versus distant metastases. Urology: in press, 1994.

Improving PSA for Diagnosis

PSA (Prostate Specific Antigen) is extremely valuable in detecting prostate cancer at earlier more curable stages. However, PSA is only prostate specific, not cancer specific. That means that there are other prostate problems that can cause your PSA to increase, e.g. infections, benign prostatic hyperplasia (BPH), and instrumentation. To solve this problem we recently demonstrated a simple means to improve the specificity of PSA in distinguishing cancer from these other causes by measuring the rate of change in serum PSA levels from one year to the next.

This discovery was based upon some very simple principles. First, the amount of PSA in the serum produced by 1 gram of cancer is 10 times higher than the amount of serum PSA produced by a similar amount of benign disease. Second, the growth rate of prostate cancer is much more rapid than the growth rate of BPH. We therefore reasoned that yearly changes in serum PSA should be much greater in men with cancer than in men with BPH. This theory was tested using the large group of men who are enrolled in the Baltimore Longitudinal Study of Aging. Since 1958, 1500 men have returned every other year to undergo an extensive examination and storage of blood samples.

We were able to obtain blood samples from age matched men with prostate cancer, BPH, and no prostate disease, who had blood samples stored for almost 20 years prior to diagnosis. We were able to demonstrate that 5 years prior to standard diagnosis, the yearly increases in serum PSA in men with prostate cancer were greater than in men with BPH or no prostate disease. Based upon these findings, we feel that any man who has a consistent increase (over 3 determinations) in his serum PSA of greater than 0.75 ng/ml per year runs a strong likelihood of having prostate cancer. Using this formula we were able to identify 75% of the men with cancer and only falsely classified 10% of the men with BPH and none of the men with no prostate disease. We feel that this concept will make it possible to identify prostate cancer with greater specificity and at lower levels of serum PSA than using the current established upper limit of normal of 4.0 ng/ml. It is possible that this technique may also make it possible to identify those cancers that are growing and require treatment.

References:

1. Carter, H.B., Pearson, J.D., Metter, J., Brant, L.J., Chan, D.W., Andres, R., Fozard, J.L., and Walsh, P.C.: Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA 267:2215-2220, 1992.

Improved Preoperative Staging of Prostate Cancer: Predicting How Far it's Spread

Three factors independently help to predict the extent of prostate cancer in any individual patient: PSA, Gleason score, clinical stage. Recently, we demonstrated that all 3 of these factors are inter-related. For example, there is more PSA produced pet gram of well differentiated cancer (Gleason score 2-6) than by poorly differentiated cancer (Gleason 7 or greater). Therefore, to evaluate the significance of a serum PSA level in any one patient, you also need to know his Gleason score. Furthermore, there is a strong association between the extent of the tumor, the serum PSA, and the clinical stage of the disease, e.g. stage A-D in the old classification or stage T I -T4 in the new TNM classification.

We have recently developed nomograms that correlate the level of serum PSA with the Gleason score and clinical stage in individual patients. These nomograms are very useful in predicting the extent of the cancer and therefore the type of treatment best suited for individual patients.

References:

1. Partin, A.W., Yoo, J., Carter, H.B., Pearson, J.D., Chan, D.W., Epstein, J.1., and Walih, P.C.: The use of prostate specific antigen, clinical stage and Gleason score to predict pathological stage in men with localized prostate cancer. J. Urol. 150:110-114, 1993.

Medical Oncologists Join Faculty

Today, once prostate cancer cells spread to other sites, it is impossible to destroy them completely with medical therapy. Therefore, improved techniques for the management of advanced disease are a major priority. To address this important aspect of prostate cancer, we have recently appointed 3 medical oncologists to the faculty of The Brady Urological Institute.

Dr. Mario Eisenberger is an Associate Professor of Oncology & Urology. He is one of the world's experts on Suramin, a potent inhibitor of growth factors which induces a dramatic response in some patients with advanced prostate cancer. Dr. Eisenberger has established a major clinic for the management of men with advanced prostate cancer.

In addition, two young medical oncologists have established their laboratories on the 4th floor of The Brady Urological Institute. Dr. Jonathan Simons and Dr. William Nelson will dedicate 90% of their time and effort to laboratory investigations directed at developing new pathways for the control and cure of advanced prostate cancer. We are thrilled to have these talented members as part of our team.

Experimental Approaches to Improved Drug Therapy of Advanced Prostate Cancer

Hormone therapy kills prostate cancer cells through a process known as "programmed cell death". Although hormonal therapy can be effective for a long period of time, eventually hormone independent metastatic prostate

cancer cells grow and become dominant. Although these hormone independent cancer cells do not develop programmed cell death when hormone levels are lowered, they do retain the ability to be "tricked" into activating this death pathway by exposure to a natural compound, termed Thapsigargin. This is a compound isolated from the Thapsia Gargancia plant. In order to target the killing effect of this agent specifically to metastatic prostate cancer cells and not to other normal cells, Dr. John Isaacs is chemically modifying Thapsigargin to a "pro drug" form. This pro drug form is designed to be inactive until specifically converted to the active drug by proteins present only in normal and cancerous prostate cells. Thus, even though the pro drug would circulate throughout the entire body of the patient, it would only be converted to active drug in the metastatic cancer cells, thus greatly minimizing non-tumor cell side effects. Presently, this pro drug concept is being tested in pre-clinical animal models.

Dr. William G. Nelson has approached this problem in a slightly different way. p53 is a tumor suppressor gene that plays a major role in activating programmed cell death. When cancer cells are injured by exposure to chemotherapeutic drugs, they often die as a result of this process. However, cancer cells with a mutated form of the p53 gene fail to activate these cell suicide pathways in response to chemotherapy. Dr. Nelson, working in collaboration with Dr. Michael Kastan, has identified the major intracellular signal that activates the p53 dependent cell suicide pathways in prostate cancer cells when they are exposed to chemotherapy. By understanding these pathways, they hope to design new treatment strategies targeted at other preserved cell suicide pathways in cancer cells that contain p53 mutations. Hopefully, such new treatment strategies may prove to benefit men with advanced prostate cancer.

Nuclear Matrix Proteins May Improved Prostate Cancer Detection

Through the use of PSA has been very helpful in the earlier detection of prostate cancer, PSA is only prostate specific and not prostate cancer specific. For this reason, research in the laboratories of Dr. Donald S. Coffey and Dr. Alan Partin has focused on characterizing unique proteins that make up the structural network of the cancer cells nucleus, proteins that are prostate cancer specific which might improve early cancer detection. Recently, Drs. Coffey and Partin have identified one protein (PC-1) which has been identified in all prostate cancer tissues examined and not in any normal or benign prostatic hyperplasia specimens. They are currently in the process of purifying and characterizing this protein to determine its usefulness as a new and potentially more specific serum marker for prostate cancer.

Awards

The Johns Hopkins Hospital and The James Buchanan Brady Urological Institute are consistently rated among the best hospitals and medical specialties in the United States by US News & World Report.

Also, in recognition of his contributions, Dr. Walsh received the Distinguished Alumnus Award from Case Western Reserve University School of Medicine, his alma mater, the Medal of Grand Officer of the Order of Leopold from his late patient, King Baudoin, the King of Belgium, the 1994 Dornier Innovative Research Award from the American Foundation for Urologic Disease and the Ellen Browning Scripps Society Medal.

He gave the keynote lecture on hereditary prostate cancer at the annual meeting of the American Urological Association in May 1993 on strategy to reduce death from prostate cancer in 1994.

Molecular Genetics of Prostate Cancer

Molecular genetics is a powerful tool which enables investigators to understand the basis for cancer. Dr. William Isaacs has made some extraordinary observations on defects in molecular mechanisms that may be responsible for the development of prostate cancer.

There are a variety of proteins that act like glue holding normal cells together. When these adhesion molecules disappear, prostate cells become disorganized and are less able to carry out their normal activities. This also makes them better able to grow, to move around, and to invade surrounding tissues and vessels. Dr. Isaacs is investigating two protein adhesion systems (catenin and E-cadherin). When these adhesion molecules are absent, prostate cancer cells act more aggressively.

In an experimental setting he has been able to restore this adhesion system to cancer cells that are deficient and in this process block their ability to form tumors. The identification of this deficiency in prostate cancer cells may be a useful marker for identifying cancers that are highly aggressive.
In another line of experiments, he has identified a relatively small area on chromosome 8 that is consistently deleted when prostate cells become cancerous. This region is likely to contain a gene that normally plays a role in preventing the uncontrolled growth of prostate cancer cells. The identification and characterization of this gene should provide important insight into the critical, perhaps initial steps, in the formation of prostate cancers.

References:

1. Bova, G.S., Carter, B.S., Bussemakers, M.J.G., E. Mitsuru, Fujiwara, Y, Kyprianou, N., Jacobs, S.C., Robinson, J.C., Epstein, J.1., Walsh, P.C. and Isaacs, W. B.: Homozygous deletion and frequent allelic loss of chromosome 8p22 Loci in human prostate cancer. Cancer Res. 53:3869-3873, 1993.

Mutations of Receptor for Androgens

Androgens are the major hormones that stimulate the prostate to grow. Their action in the cell is mediated by a specific protein called a receptor. When androgens enter the prostatic cell, they bind to this receptor, like a key in a lock, and this steroid -receptor complex activates cellular growth and function. Thus, androgen receptors are very important for hormone action.

Dr. Evelyn Barrack has recently demonstrated that as prostate cancer progresses, the receptor for androgens may undergo mutations. Recently, Dr. Schoenberg and Dr. Barrack have demonstrated that a specific mutation in the receptor is associated with a paradoxical response to hormones. Flutamide is an antiandrogen that blocks the binding of androgens to the receptor. It is frequently used in combination with castration or treatment with an LHRH agonist. Some people believe that flutamide may be useful in providing total androgen ablation. However, in some patients flutamide actually stimulates cancer growth and PSA levels paradoxically fall when flutamide is discontinued. They demonstrated that in one patient who had this paradoxical stimulation by flutamide, there was a mutation in the androgen receptor. Further elucidation of androgen receptor mechanisms may make it possible to improve hormonal therapy for prostate cancer.

References:

1. Schoenberg, M.P., Hakimi, J.M., Wang, S., Bova. G.S., Epstein, J.1., Fishbeck, K.H., Isaacs, W.B., Walsh, P.C. & Barrack, E.R.: Microsatellite mutation (CAG24-18) in the androgen receptor gene in human prostate cancer. BBRC 198:74-80, 1994.

Human Gene Therapy

A new approach to immunological therapy of advanced cancer has been developed in a collaborative effort between The Brady Urological Institute and the Oncology Center. The initial clinical trials are being undertaken in men with advanced kidney cancer. The principle is simple although the technology is advanced. The cancer containing kidney is removed at surgery and the cells are grown in tissue culture. The cells are then infected with a genetically engineered virus that contains a gene which stimulates the immune system. These cancer cells, which are armed with genes that will enhance the immune response, are then radiated so they cannot grow and are reinjected as a vaccine under the skin of the patient at regular intervals. This technique has been worked out and documented in experimental animals and clinical trials in human kidney cancer began in January 1994. The investigators responsible for this major advance are Drs. Jonathan Simons, Fray Marshall, Drew Pardoll, Elizabeth Jaffey and Dr. Richard Mulligan.

Experimentally, the application of this technique to prostate cancer is also well on its way. Dr. Martin Sanda and Dr. Jonathan Simons have been able to show that prostate cancer cells can be grown in culture, infected with the virus, and that these immunologically activated cells can produce an immune response in animals. These studies have paved the way for similar trials in human prostate cancer in similar trials in human prostate cancer in the future.

References:

1. Sanda, G.A., Ayyagari, S.J., Jaffee, F,.M., Epstein, J.I., Clift, S.L., Cohen, L.K., Dranoff, G., Pardoll, D.M., Mulligan, R.C., & Simons, J.W.: Demostration of a rational strategy for human prostate cancer gene therapy. J. Urol- 151:622-628, 1994.

Fund For Research & Progress in Urology

The Brady Urological Institute has always been a center for the discovery of new pathways for patient care. Two and a half floors of the historic Marburg building are dedicated to research on prostate cancer. This space houses the laboratories of six full-time Ph.D. faculty members and 60 support staff. Support for this mission has been provided by grants from the National Institutes of Health, fund-raising, and income from patient care. However I am worried about the changes in health care financing that could have a profound impact on our ability to maintain this mission of discovery.

Recognizing that reductions in Medicare reimbursement and income through managed care contracts will reduce this major source of funding, a campaign to raise endowment was established by a group of my patients who collectively are termed “The Friends of Patrick Walsh.” A goal was set to raise $5 million over 5 years to supplement the endowment of The Brady Urological Institute. Without this support, the rapid progress of research in the field of prostate cancer will falter.

Recognizing that prostate cancer kills one man in the United States every 15 minutes, we must do something soon. To reduce deaths from prostate cancer, four approaches are necessary: prevention, early detection, effective and acceptable treatment of localized disease, and new approaches to advanced disease. In our laboratories and in our clinic we are aggressively exploring all of these avenues.