

DISCOVERY



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Letter for Patients

It has been sometime since I've seen most of you and even longer since I've had a chance to review our surgical results. This is the first of a series of updates. I will try to make them informative and personal, with advice that will apply directly to you.

I am grateful to everyone who has come to me for treatment, and I am committed to maintaining contact and involvement with all of you. This update summarizes where we stand after 500 operations. It presents overall results and proposals for long-term follow-up.

If you have suggestions on how this update can be improved in the future or questions, please call or write to me. I love hearing from all of you.

Sincerely yours,



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



Reached 500 Patients with Highly Successful Results

The first patient underwent surgery in April 1982 and since then more than 500 patients have followed. They have come from almost every state in the Union and from Israel, Germany, The Netherlands, Italy, Puerto Rico and Iceland. Moreover, urologists from across the nation and around the world have visited Hopkins to learn the operation and now the procedure is being performed at major medical centers worldwide. The surgical technique has been described in detail in medical literature and has been the subject of two movies, one of which received the coveted Golden Eagle Award the Council on International Non-theatrical Events. Over the last five years, we have learned much about the surgical technique and have made minor modifications in the procedure.

Overall, 74 percent of the patients have retained potency. Of those who actually were potent, approximately 40 percent were able to resume intercourse within three months after surgery, 58 percent by six months, 70 percent by nine months and 95 percent by one year. During the second year of follow-up, 99 percent of the patients who were eventually potent were successful by 18 months and the final patients achieved success at two years. Most patients experience improvement in sexual function over the next several years following surgery. This should encourage patients who are not yet back to normal.

The return of sexual function correlates with both the age of the patient at the time of surgery and the extent of his disease (Table 1). Potency returned in the two patients in their thirties, in 79 percent of men in their forties, 85 percent of men in their fifties, 64 percent of men in their sixties, but in only 14 percent of men in their seventies. Overall, 74 percent of patients are potent. Based on clinical stage, potency returned in 93 percent of patients with stage A1 disease, 72 percent of stage A2, 92 percent of B1 nodules, 72 percent of stage B1 and 56 percent of stage B2 patients. With advancing clinical stage, it is more likely that the tumor extends beyond the prostate, thereby necessitating resection of one or both neurovascular bundles. As a result, one would expect that potency rates would be lower. For example, in virtually all men with stage A1 disease, the cancer is confined to the prostate. This suggests

that almost all men with clinical stage A1 disease should have excellent return of sexual function. Conversely, the reduced rate of potency in men with stage B2 disease indicates that attempts at resection of more advanced tumors result in greater injury to the pelvic nerve plexus.

TABLE 1. INFLUENCE OF AGE AND CLINICAL STAGE ON POSTOPERATIVE POTENCY

Clinical stage*	30-39	40-49	50-59	60-69	70-75	Totals
A1 - found at TUR involving less than 5% of the tissue	-	100%	90%	100%	-	93%
A2 - found at TUR involving more than 5% of the tissue	-	-	90%	57%	0%	72%
B1 nodule - involving one lobe surrounded by normal tissue	100%	80%	97%	92%	0%	92%
B1 - induration involving less than 1 lobe of prostate	-	79%	82%	65%	20%	72%
B2 - induration involving one lobe of prostate or more	-	67%	68%	40%	-	56%
Totals	100%	79%	85%	64%	14%	74%

*All patients have normal tissue and bone scan.

We've learned that it is possible to widely excise one neurovascular bundle and maintain potency. Sixty-nine percent of men who underwent this procedure with wide excision of one neurovascular bundle are potent postoperatively. We now use the information in Table 1 preoperatively in advising patients, based upon their age and stage of their lesion, as to the likelihood for the postoperative return of sexual function.

Success with Preservation of Urinary Control

The most disabling and feared complication following radical prostatectomy is total urinary incontinence (lack of urinary control). Fortunately, it is infrequent. To prevent this complication, there are several important steps in the surgical procedure: the bladder neck must be reconstructed following surgery, the external sphincter must not be damaged during the excision of the tumor, and the bladder neck must be reconnected to the urethra and pelvic floor sphincter with care. If the tumor is located down near the sphincter, it may be necessary to excise muscular tissue in this area to remove all tumor. This is one cause of postoperative urinary incontinence. The other most common cause is variability in the normal anatomy resulting in a short urethral stump. This may create difficulty in placing adequate sutures in the urethra down at the pelvic floor.

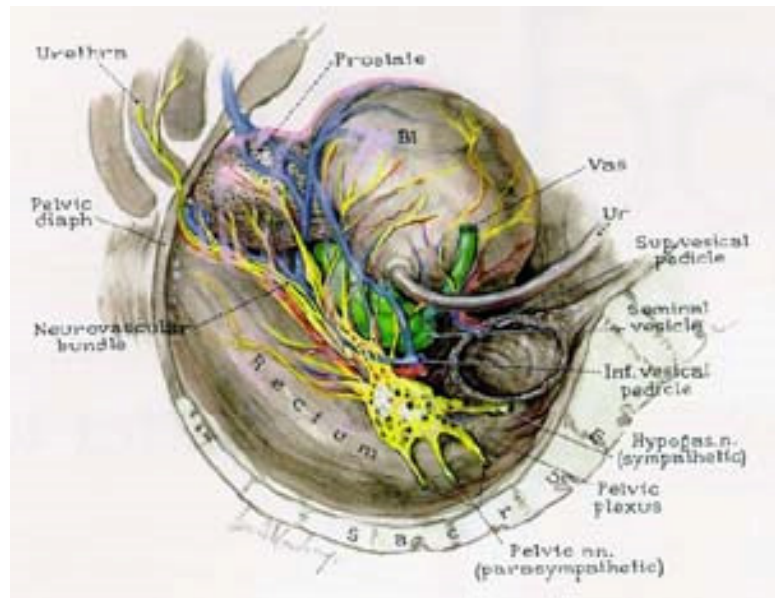
In addition to these surgical considerations, it recently has been suggested that the pelvic nerves which control erection also are important for preservation of urinary control postoperatively. Several authors have suggested that the operation which was developed here also improves urinary control following surgery due to preservation of the nerves which control the external sphincter.

Of 320 patients who have been followed one year or longer, 296 (93 percent) are completely dry and wear no pads. There are 21 patients (7 percent) who have stress incontinence for which they wear a pad. No patient is completely incontinent and so far only one patient has undergone placement of an artificial sphincter. As I mentioned, recently several other authors have noted a marked reduction in the frequency of total incontinence in their series once they've adopted this surgical technique.

Nerve-Sparing Approaches to Bladder Cancer

Men with invasive malignant tumors of the bladder often require complete removal of the bladder and prostate. This has always sentenced the patient to lifelong impotence and the need for an external urinary appliance (a bag). However, the technique that we have perfected for radical prostatectomy is equally applicable to radical removal of the bladder and prostate as well.

In a recent review of the results for 25 men who have undergone this procedure over the last five years, 83 percent are potent. Prior to the development of this surgical advance, all patients were impotent. Furthermore, in the last several years we have been able to fashion an artificial bladder from segments of large and small intestine. Dr. Fray Marshall, professor of urology at Johns Hopkins, has perfected this technique. This artificial bladder can be sutured to the urethra in selected patients, enabling them to have normal urinary and sexual function. Once again, a technique developed at Brady has markedly improved the quality of life for men with bladder cancer.



Anatomy of the adult male pelvis illustrating the relationship of the neurovascular bundles to the rectum, bladder, and prostate (Reprinted with permission from J. Urol. 138:1402-1406, 1987).

Treatment of Sexual and Urinary Incontinence

The goal of radical prostatectomy is the complete elimination of tumor without a major sacrifice in the quality of life. For various reasons this goal may not always be met. However, it is possible to restore quality of life in all patients.

There are three techniques for the treatment of sexual dysfunction. All have major advantages and disadvantages and, for this reason, they can be viewed in a continuum from the least to the most invasive and from the least to the most reversible. These techniques are the use of an external vacuum erection device, the self-injection of papaverine and phentolamine and the placement of a penile prosthesis. If sexual dysfunction persists after a reasonable period of time, you should discuss these options with me or with your local urologist.

The three options mentioned above can be considered sequentially. The least invasive is the use of the external vacuum erection device. This device is temporarily placed on the outside of the penis and a vacuum is created. By reducing atmospheric pressure the penis becomes engorged with blood and a small soft rubber ring is placed at the base of the penis. Although this is a very artificial procedure, patients all agree that it produces satisfactory erections and for some individuals this has been a simple solution to the problem. The next technique involves the self-injection of two pharmacological agents, papaverine and phentolamine, into the penis. A very tiny needle is used. This is successful in about 75% of patients and produces an erection that lasts for two hours. Patients can be taught this technique so that they can self-inject the medication. Although long-term results on large numbers of patients are not yet available, there is some concern that repeated injections may produce some fibrosis in the penis which might interfere with spontaneous recovery. The most dependable means for return of sexual function is the placement of a penile prosthesis. This involves a minor surgical procedure in which one of a variety of prostheses is placed inside the penis. This enables the penis to be erect so that vaginal penetration and orgasm can be achieved.

Sometimes, serious problems with urinary control are unavoidable and require further management. Today, the best form of treatment for patients who have serious problems is the placement of an artificial sphincter which can return urinary control to normal. Most patients regain urinary control spontaneously. This can take up to one year or longer in some patients and in all patients requires strict attention to urinary sphincter exercises when urinating.

Cancer Control Has Been Effective

The goal of any cancer operation is the complete excision of all tumor with the minimum injury possible to surrounding tissue. When this operation was developed over five years ago, it was based upon the anatomical observation that the nerves that control erection are located outside of the prostate and its surrounding fascia. Previously no one knew where these nerves were located. Much to our surprise, when we reviewed old surgical specimens we learned that the nerves were usually not removed previously with the cancer. Instead, they were merely injured and left behind. Thus, in standard radical prostatectomies in the past, these nerves were not resected. However, based upon our anatomical observations, these nerves can now be identified at the time of surgery and either preserved or widely resected with the specimen. These observations have actually made the operation more radical and more complete, where indicated, than previously possible.



Among the large number of patients who have been followed from one to slightly longer than five years, we now have information regarding the success rate for cancer control. Of 320 men followed up to five years, only 10 have developed distant spread of their cancer as the first sign of failure. All 10 had extensive tumor that penetrated into the soft tissue surrounding the prostate and in eight the tumor was so extensive that it was necessary to excise one or both nerve bundles. Three other patients have developed local recurrence of their cancer as the first sign of treatment failure. Thus, only 13 men (4 percent) who have been followed from one to five years have developed progression of the disease. These early results are excellent, but longer follow-up of patients is necessary to confirm this impression.

Based upon our experience with radical prostatectomy prior to the development of the nerve-sparing technique, we know that approximately 10 percent of patients will develop local recurrence as the first sign of failure in the first five years postoperatively and that in the succeeding five years an additional 5 percent may have a similar outcome. Thus, most local failures are seen within the first five years. We are monitoring this closely in our group of patients

and more time must elapse to determine whether the total local recurrence rate will exceed 29 more patients i.e. 10 percent over the next four years. Based upon the trends observed to this point, however, this does not seem likely.

PSA (Prostatic Specific Antigen): A New and Exciting Test for Follow-Up Care

Over the last year, a new test has become available that will be most useful in follow-up evaluations. Prostatic specific antigen (PSA) is a protein that is made only by the prostate. This protein can be measured by a blood test. The protein is not present in women nor should it be present in patients who have undergone removal of the prostate. Following radical prostatectomy, if there is a significant level of PSA in the blood, this suggests that there must be residual cancer cells which may require further treatment. In follow-up evaluations, please have your physician perform this test.

Heredity and Prostatic Cancer: Major Study to Begin

Do you have a close relative who also has prostatic cancer - a brother, father, grandfather, or uncle? Little is known about the heredity of prostatic cancer, and up to now it has been very difficult to study. We do know that roughly 9 or 10 percent of men will develop prostatic cancer. With a disease this common, one would expect to have a relative with the same condition.

However, it has not been uncommon for patients to tell me that their brother, father and uncle have the disease. We also have identical twins with the disease. With this information in mind, we are planning to embark upon a major study of this condition. If you have a family history of prostatic cancer, please let us know. The results of this study will be pertinent for those of you who have sons and grandsons.

Progress in Prostate Cancer Through Research - Brady Tradition Continues

The Brady Urological Institute has always been at the forefront in advancing our understanding of benign and malignant tumors of the prostate. With four Ph.D. faculty members conducting full-time research and a large group of talented young predoctoral and postdoctoral fellows involved in these research projects on the prostate, we have developed many new approaches and concepts that hold promise for new methods to manage localized and advanced prostate cancer.

At present, the research projects in the laboratory range from basic molecular studies to new surgical and medical procedures that are immediately applicable to the benefit of the patient. These contributions have received wide recognition. Dr. Donald Coffey, who is the research director of the laboratories, is also the national chairman charged with developing new concepts and monitoring research on prostate cancer throughout the United States for the National Cancer Institute. The following briefly describes some of the research that we are excited to share with you.

Molecular studies in the laboratory have focused on understanding an enzyme, called topoisomerase, that has the ability to wind and unwind the DNA tape that contains the genetic information for the cell. The control of DNA is important because the inappropriate reading of this genetic tape and the loss of control of its duplication is at the very heart of the cancer process and reflects itself in an abnormal replication and differentiation of the cancer cell. The research team is studying inhibitors of topoisomerases and has learned that when these inhibitors are combined with either standard chemotherapy or biological response modifiers, the end result is a markedly enhanced therapeutic advantage. This is a new and exciting approach for the potential management of advanced tumors and has been tested in an animal system as part of a new drug development program chosen in the five most promising areas of research by the National Cancer Institute. Much knowledge and research will be required before the application can be studied in clinical trials in humans but this team is investigating promising leads.

Prostate cancer cells require hormones for their growth. These hormones come primarily from the testes and are termed androgens. The laboratory has been at the forefront of understanding how prostate cancer cells develop resistance to this requirement for androgens in their growth. The laboratory has traced one possible site for this important resistance to the structure of the nucleus. The nucleus is like a cassette at the center of the cancer cell that contains the DNA tape. It appears that this nucleus is misshapen in the cancer cell and this may be caused by changes in the skeletal framework of the nucleus, a structure that has been discovered in this laboratory and termed the nuclear matrix. Recent interest in this nuclear structure is related to the fact that it contains recording heads that duplicate the DNA tape, as well as the topoisomerase enzyme that must unwind the tape during DNA replication. The research team has also shown that the androgen hormones that are required for tumor growth also reside on this nuclear matrix in the form of specific receptors that bind to the androgens and induce growth. It is hoped that the elucidation of these nuclear structures will reveal mechanisms that may improve our ability to manipulate the growth of prostate tumors.

Through the years the Brady Urological Laboratory has also developed and characterized excellent animal models for the study of prostate cancer which closely mimic the natural disease in man. These models have been ideal for investigating hormonal, chemotherapeutic, immunotherapeutic, and surgical approaches to prostate cancer. Recognizing the importance of these animal models of prostate cancer, the laboratory has supplied these models free to more than 100 research teams around the world.

Over the past five years we have carefully charted the anatomical course of the nerves that control erection and have improved upon the surgical techniques for their preservation. However, in some patients it is necessary to excise these nerves, on one or both sides, because of the location of the tumor or its extensive nature. We have currently embarked upon a series of studies to determine how the nerves could be restored in these patients and potential techniques which may encourage nerve regeneration.

In addition to these basic studies we have a broad variety of clinical programs investigating the pathology of prostate cancer, the usefulness of tumor markers such as prostatic specific antigen, and most importantly, imaging techniques which may improve upon our ability to determine which cancer cells are the most aggressive and have the greatest potential for escaping the prostate gland. In the past, our ability to estimate the aggressive nature of these cancers has been limited mainly to crude estimations of prostatic size based upon physical examination and microscopic examination of the biopsy specimens. However, we have some exciting data using an entirely new approach to the evaluation of cancer cells. Through the work of Dr. Coffey and his students, techniques have been developed for growing prostate cancer cells in tissue culture and observing their cell movement directly under a microscope as they grow. These investigators have learned that specific patterns of cell movement can predict metastatic potential in our animal model series. We hope to extend these studies to human prostate cancer cells.

We are very excited about the future of research and its direct application to patient care. We know we have a responsibility to all men with prostate cancer to improve their care and we will not rest until we have discovered improved approaches for the diagnosis and management of this most common malignancy in man.

BIOGRAPHICAL SKETCH: Donald S. Coffey, Ph.D.

Donald S. Coffey, Ph.D., is director of the Brady Urological Research Laboratories, one of the few triple professors (oncology, pharmacology and urology) in Hopkins history and a major contributor to our understanding of the prostate gland and its disorders. An original thinker whose reputation as a philosopher/lecturer matches his biomedical achievements, the 55-year-old Tennessean is noted for his ability to merge the interests and talents of clinical and basic scientists.



Donald S. Coffey, Ph.D., Director of Research

In recent years, his scientific expertise and leadership led to new discoveries about the shape of cancerous prostate cells and the development of computer software that tracks the distortions and “dances” of these abnormal cells. The cell-tracing technology is expected to add a powerful diagnostic weapon to the

anticancer arsenal. Coffey and his associates also identified a new “core” skeletal structure in the nucleus of cells. His experiments suggest that his nuclear matrix controls the replication of DNA and thus of the cells themselves. And because prostate cancer and other malignancies are diseases of abnormal cell replication, the work is likely to shed important light on how cancer itself begins and on possible ways to control or prevent it.

A noted teacher and adviser to young scientists, Coffey has developed animal models for prostate cancer, used them to assess various treatments and championed urological research among government and other funding agencies.

Urology Research Endowment Fund

Last year, many of you received a letter describing our plans to establish an endowment fund for research in prostatic cancer. As you know, the Brady Urological Institute is a major center for the treatment of prostatic disease with a variety of important programs investigating benign and malignant neoplasms of the prostate. Although these programs are well-funded by federal grants, we feel that the viability of these important projects may be threatened. Already, there has been extensive shifting of research emphasis away from cancer toward other diseases such as AIDS. Furthermore, in an effort to fight the growing national debt, there is constant pressure on Congress to reduce federal spending of all types. We are concerned that, ultimately, research in prostatic diseases may receive less emphasis and we will be unable to continue some of our important studies.

To ensure the future of research in prostatic cancer at the Brady Urological Institute, we have established the Urology Research Endowment Fund. We have set a goal of \$4 million which includes an endowed chair for the director of research and endowed research funds to support programs during hard times. I was thrilled by the response to last year’s letter. Overall, we received \$200,000 toward our goal with the promise of an endowed chair over the next 10 years. As I mentioned at that time, our long-term goal is research endowment. Contributions at any time, either now, in yearly installments, or through mechanisms such as trusts or bequests, will be appreciated. All contributions should be directed to the Urology Research Endowment Fund and mailed directly to Dr. Walsh.

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MOTION PICTURES

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