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

DISCOVERY

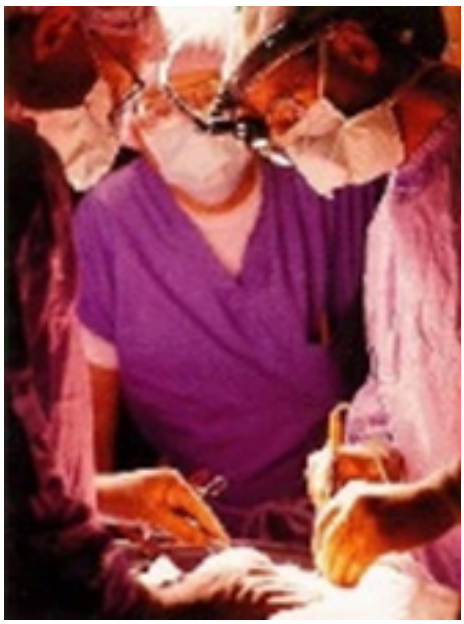
Volume II | Winter 1991

Newsletter Recreated from Historical Document

JOHNS HOPKINS
MEDICINE

hopkinsmedicine.org/urology

Letter to Patients



Once again I have the opportunity to share with you some of our most exciting treatment and research results. In this issue, we report unique and important findings on the inheritance of prostatic cancer, the ability of radical prostatectomy to cure prostate cancer with few side effects, the influence of hormones on growth of benign prostatic hyperplasia, and experimental work on nerve grafts to restore sexual function after wide excision of tumors.

I am grateful for the support I've received from all of you, including your enthusiastic involvement in the study of genetic factors in prostate cancer and the diligent involvement by some of you in the study of hormones and benign prostatic hyperplasia and the use of ultrasound and MRI in the preoperative staging of prostate cancer.

Thank you also for the generous contributions that have made all of this possible. As this goes to press, other new and exciting advances are under way; they will be the subject of our next issue.

Sincerely yours,

Patrick Walsh

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

Family History and the Risk of Prostate Cancer

Prostate cancer is the most common malignancy in American men and the second most common cause of cancer deaths. Because prostate cancer produces no symptoms until it is far advanced, at least 40% of men have metastatic disease - disease that has spread - at the time the tumor is detected. Recognizing the high incidence and mortality of this disease, early detection of prostate cancer is of vital importance.

Most women in the United States are aware of the close association between a family history of breast cancer and their risk of developing the disease and recognize that if their mother or sister has the disease they are twice as likely to be affected. Up to this point, however, important information such as this has not been available for men with prostate cancer.

Thanks to the participation of many of you, we have just completed a study comparing the family history of prostate cancer in 690 men with prostate cancer and 640 spouses who were used as controls. Fifteen percent of the men with prostate cancer had a brother or father affected with the disease as opposed to only 8% of the spouses. Men with father or brother affected with the disease were twice as likely to develop prostate cancer as men with no affected relatives. In addition, with increasing numbers of affected family members the risk increased, e.g. men with 2 or 3 first degree affected relatives had a five- and 11-fold increased risk of developing prostate cancer (Table 1).

Recognizing that 9-10% of men in the United States will develop prostate cancer in their lifetime, men with a

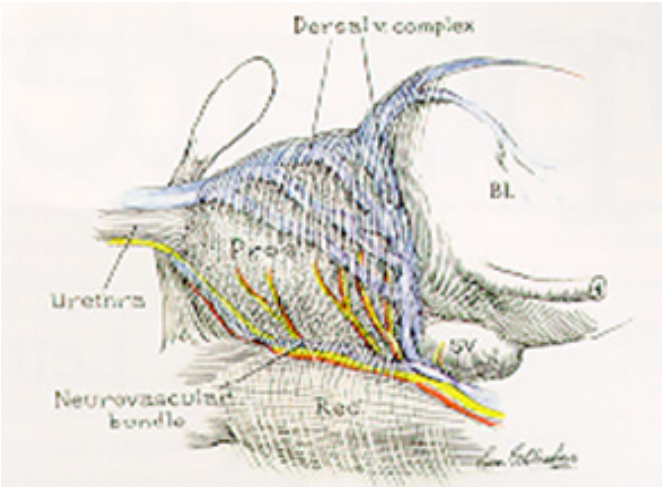
family history of prostate cancer should be advised of their significantly increased prostate cancer risk and after age 40 should undergo yearly digital rectal examinations. In the future, other screening measures may prove useful, e.g. serial prostate specific antigen (PSA) determinations, transrectal ultrasound, or magnetic resonance imaging of the prostate. This is important information for your brothers and sons. We are actively searching for genetic probes that may help us identify individuals at the greatest risk for developing the disease.

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

	Number of Affected Relatives	Relative Risk
Father and/or Brothers	One	Twofold
	Two	Fivefold
	Three or more	11-fold
Father/brother or grandfather/uncle	One	1.5-fold
	Two	2.3-fold
	Three or more	3.6-fold

Radical Prostatectomy and the Control of Cancer

The approach to radical prostatectomy developed here at Johns Hopkins Hospital was based on better visualization and sound anatomical and pathologic principles. With this technique, we have been able to remove tumors with wider margins than was previously possible. All of us have been looking forward to long-term results on cancer control. Although a follow-up of 15 years is ideal to evaluate the efficacy of any form of treatment for prostate cancer, local recurrence of tumor is one measure that is meaningful sooner. Because two-thirds to three-quarters of all local recurrences occur in the first five years after radical prostatectomy, they are an especially useful yardstick.



We have just finished evaluating the first 600 men who underwent this procedure one and a half to eight years ago. The local recurrence rate at five years was only 4%, distant metastases occurred in 7% of patients, and 3% of men died of the disease. When this low rate of local recurrence is compared to previously published results of operations for similar stages of disease we find that our radical prostatectomy offers local control of tumor equal to or greater than any past operations. This confirms our impressions that better visualization enables the surgeon to perform a more precise operation with wider excision of tissue when necessary. Follow-up evaluations at 10 and 15 years will be carried out to confirm these findings.

Preservation of Sexual Function

The anatomical approach to radical prostatectomy has two important goals--the total removal of all tumor and the preservation of quality of life. At the time of surgery, it is often necessary to remove a wide margin of tissue on the side of the tumor, wider than previously possible. We have previously shown that it is possible to preserve sexual

function even when the nerves (neurovascular bundle) are excised on that side.

Recently we evaluated the return of sexual function in 503 men who were potent before the operation. Overall, 68% were potent following surgery. Three factors were linked with the return of sexual function: age, pathologic extent of the tumor, and surgical technique (preservation or excision of the neurovascular bundle). In men under age 50 years, potency was similar in patients who had both neurovascular bundles preserved (90%) and in patients who had one neurovascular bundle widely excised (91%) (Table 2). With advancing age over 50 years, sexual function was better in patients in whom both neurovascular bundles were preserved than in patients in whom one neurovascular bundle was excised.

These results indicated that the return of sexual function after surgery in men over age 50 years is measurably related to preservation of nerve function. That is very exciting news and suggests possibilities for treatment that have never been considered before. For example, in men where it is necessary to excise the neurovascular bundle on one side, in the future consideration should be given to techniques that may restore autonomic function through nerve regeneration, e.g. partial excision of the bundle, where possible, or nerve grafts.

TABLE 2. INFLUENCE OF AGE AND PRESERVATION OR EXCISION OF NEUROVASCULAR BUNDLE(S) ON RETURN OF POSTOPERATIVE SEXUAL FUNCTION IN 503 MEN

	PERCENT POTENT			
	Age (years)			
Surgical Technique	**< 50**	**50-59**	**60-69**	**70 >**
Both nerves intact	90%	82%	69%	22%
One nerve partially excised	100%	73%	50%	50%
One nerve widely excised	91%	58%	47%	--
TOTAL	91%	75%	58%	25%

Value of Ultrasound and MRI in Staging

Improved techniques for evaluating the local extent of prostate cancer are needed. We have recently completed a cooperative study evaluating ultrasonography and magnetic resonance imaging (MRI) in the preoperative evaluation of men prior to radical prostatectomy. Although these two techniques represent the best technology available today, neither technique was of sufficient precision to accurately stage early prostate cancer. It is hoped that with improvement in technology accuracy these techniques will increase. We are currently testing an intrarectal surface coil as a means to improve the sensitivity and accuracy of MRI. Early results look very encouraging

Importance of Follow-up Examinations

At least once a year, you should undergo the following simple evaluations: digital rectal examination and measurement of serum acid phosphatase and prostatic specific antigen (PSA). A small percentage of patients will develop local recurrence of their disease because cells escaped the prostate locally prior to the radical prostatectomy. It is often difficult to predict this event and thus it is important for patients to be surveyed at least annually with these simple tests. If one of these tests is abnormal, we then proceed to examinations that exclude the possibility

that the cancer has spread elsewhere: chest X-ray, bone scan, pelvic CT scan. If these are normal, radiation to the prostatic bed may be useful in eliminating the tumor, especially if it is detected early. For this reason it is wise to be evaluated at least yearly.

Vascular Factors are Important in Recovery of Sexual Function

Erectile function in men is the end result of a series of tightly coupled events: nerve stimulation, dilatation of arteries, and constrictions of veins. Therefore, during radical prostatectomy it is important to preserve nerve function where possible. However, despite nerve preservation, some patients are still impotent following radical prostatectomy. This may be secondary to arterial or venous problems. Men who are older or who have a history of vascular disease, diabetes, or hypertension are more likely to have a restrictions in the arterial blood supply to the penis. Potency in these patients may be maintained by small accessory blood vessels that surround the prostate. Interruption of these blood vessels may be responsible for impotence. (We can test for this; these patients will not respond to injections with papaverine, a drug that relaxes smooth muscle).

Another important cause of impotence is a condition known as venous leak. In these patients, although the nerves and arteries are intact, the blood does not collect in the spongy tissues of the penis because the veins no longer constrict normally. These men note that they may start to have an erection but loose it. Fortunately, there is a simple treatment that helps most patients. By placing a soft tourniquet at the base of the penis, e.g. a "ponytail holder" or rubber band, the blood is held in the penis and the erection is not lost.

The recovery of sexual function following radical prostatectomy may take up to two years and patients report that sexual function often improves for two or more years thereafter. During this interval, vacuum constriction devices and injections with pharmacologically active agents such as papaverine, phentolamine, or prostaglandin-E1 should provide erections sufficient for intercourse.

Progress in Prostate Cancer through Research – The Brady Tradition Continues

The Brady Research Laboratories have focused the major part of their research on understanding the cause of abnormal growth of the prostate and developing improved methods for growth control. Any abnormal growth that forms a tumor is the result of an abnormal accumulation of cells. This increase in total cell number is similar to the increase in a population--it results from an imbalance between the birth rate minus the death rate. As cells turn over in normal organs of our body, the processes of cell replication and cell death are held in strict balance so that the organ does not increase in size. However, in prostate tumors there is an imbalance caused by both an increase in cell replication and a decrease in the rate of cell death so that the net effect is an abnormal accumulation of cells. Natural substances in the prostate that cause cells to replicate are called growth factors and there are a variety of these factors that appear to work in tandem and in sequence that signal the cells to replicate and divide. In addition to changes in replication, it is now apparent that a decrease in the rate of cell death is also of importance and this is also driven by natural factors that cause the cells to self-destruct. These two opposing pathways of cell growth and cell death are under intensive study in the laboratory, and new pathways of cell growth and self-destruction are being delineated.

Work in the laboratory by Dr. John Isaacs shows that prostate cell death involves a programmed series of timed events including the controlled influx of calcium ions into the cell which activates a calcium-dependent enzyme that destroys the DNA genetic tape of the cell. One of the natural factors involved in cell death is tumor necrosis factor (TNF), a protein which can now be produced synthetically for drug use by applying recombinant DNA techniques. We have shown that TNF used alone is not very effective, but when combined with certain cancer chemotherapeutic agents, can greatly enhance therapeutic potential. At present, this approach is in its very early phases of study but appears to hold great potential promise for our future understanding of how cell death may be regulated.

In addition to knowing the rate of growth of the tumor, it is also important to determine the metastatic potential of the cells. As the cells spread through the tissue, they can dislodge and travel through the blood stream or the lymph fluid to distant organs and start growing in inappropriate sites, which are called metastatic lesions. Our laboratory has observed tumor cells with different malignant and metastatic potential by making time-lapse movies of their movements when grown in culture dishes. It appears that cells with increased cell motility have the ability to migrate and therefore invade adjacent tissues. In animal models, we have shown that we can quantitate this cell motility with a new mathematical analysis of cell shape that measures the malignant potential of the cells in a quantitative manner.

We are now busy trying to determine molecular mechanisms that cause cancer cells to move. It appears that these cancer cells have a protein system containing acting and myosin molecules which are very similar to the types of proteins that are involved in our muscles that enable us to walk. We are now studying several drugs that are capable of blocking this type of cell motility and we are determining how they may be used in preventing metastatic spread of cancer cells.

Many patients, who have had localized prostate cancer and have been surgically treated by Dr. Walsh, have cooperated in a large study to determine if there is a genetic basis that might dispose on to prostate cancer. It appears that there are some families that have a higher probability of developing prostate cancer than would be expected on a random basis. Meanwhile in the laboratory, Dr. William Isaacs has been studying the DNA of prostate cancer to determine how this genetic tape has been altered. He has shown that certain chromosomes have a higher probability of being altered in specific locations in prostate cancer. He is now busy identifying the genetic information that has been altered in these areas. This is a large, long-term study requiring the most tedious and modern molecular biological techniques. His work has been recognized as being in the forefront of these types of studies. We are all enthusiastic about the information that is becoming available through these powerful new molecular techniques.

These and other studies continue to provide exciting information on prostate cancer. The four basic scientists working full time in the laboratory in close collaboration with our clinical investigators are producing important new insights and inroads into the understanding and control of prostate cancer. Their continued efforts will require constant dedication and cooperation. There is much to be done and the search continues as new young investigators are being trained to join this important mission.

Experimental use of Nerve Grafts to Restore Erections

Although potency can be preserved in most men following radical prostatectomy, in some patients one or both nerves must be sacrificed to remove all tumor. For these patients, we have considered nerve reconstruction at the time of surgery using a nerve graft. We have recently tested this possibility in a laboratory rat model. Using a nerve graft obtained from the genitofemoral nerve (a nerve conveniently located in the pelvis that can be removed with few side effects) we were able to restore sexual function after excision of both nerves. Furthermore, we were able to show that nerve growth factor - a biologically active chemical - enhanced nerve regeneration in this animal model. It is still too early to consider the possibility of performing this procedure after surgery in patients who have not

regained sexual function. But these results are promising and suggest that it might be possible in the future to place a nerve graft in patients at the time of surgery when the neurovascular bundle requires excision.

Hopkins Urology - Number One

In April 1990, U.S. News & World Report published a survey of the best hospitals and best departments within hospitals in the United States. The magazine contacted 30 experts in 12 different fields and asked them to list, in no particular order, the 10 leading hospitals nationwide in his or her own specialty. Hopkins' Department of Urology was listed more often (71% of the time) than any other urology department in the country. Moreover, the publication highlighted shock-wave treatment for kidney stones and the Hopkins technique for radical prostatectomy as the two top advances in the field in recent years. Overall, the Johns Hopkins Hospital was mentioned as one of the top hospitals in 10 of the 12 areas studied. I'm pleased that U.S. News and World Report confirms the decision that you made before coming to us for your care.

Hormones and BPH

With aging, men are subject to two distinctly different prostatic diseases: cancer of the prostate and benign prostatic hyperplasia (BPH). It is estimated that 75% of men over the age of 50 years have symptoms arising from BPH, that more than 350,000 prostatectomies are performed each year in the United States, and that 20-30% of men who live to age 80 require surgical intervention for the management of BPH. If the cause of this common disorder were determined, it might be possible to develop effective treatments to prevent the progression of the disease and reduce the need for surgery. Because prostate growth is regulated principally by hormones, it has been assumed for years that BPH may be under endocrine (hormone) control. In an effort to determine whether there is an endocrine effect on BPH, 70 patients agreed to extensive blood tests prior to radical prostatectomy. We were able to link 23 hormonal factors in the serum obtained from these patients with the extent of BPH. We learned that patients with larger volume of BPH had higher serum androgen (male hormone) and estrogen (female hormone) levels, suggesting that these hormones may be factors in the persistent advance of BPH with age. If so, attempts at lowering androgen levels, reducing estrogen levels, or blocking androgen stimulation through other mechanisms may interfere with the progression of BPH with age. We are currently testing some important compounds that appear to show activity.

Urology Outpatient Diagnostic Facility

A new 80,000-square-foot urology diagnostic outpatient's facility is currently under construction. It will be located in the new Outpatient Center on the west side of Broadway directly across from the dome of the hospital. This center will provide comprehensive outpatient consultative and diagnostic facilities for the Medical Institutions and

should be an enormous resource for patient care. For years, we have had inadequate space and now at last we will have a comfortable well-equipped unit to provide efficient care and the latest in modern imaging.

Although the Outpatient Center will be subsidized by both the hospital and the medical school, the expense of this new clinic will place a major burden on the department. Furthermore, these increased expenses are occurring at a time when federal reimbursement from Medicare for outpatient diagnostic care is being markedly reduced. Faced with the forecast of increased expenses to support the outpatient clinic along with reduced revenue, I am struggling to find a way to maintain the quality of our care without compromise. For this reason, I have decided to look for endowment to support this clinic so that we can continue placing the patient first and reimbursement second. The additional revenues necessary to fund this clinic will be in excess of $250,000 per year.

BIBLIOGRAPHY

1. Oesterling, J.E., Chan, D.W., Epstein, J.I., Kimball Jr., A.W., Bruzek, D.J., Rock, R.C., Brendler, C.B., and Walsh, P.C.: Prostate specific antigen in the preoperative and postoperative evaluation of localized prostatic cancer treated with radical prostatectomy. J. Urol. 139: 766-772, 1988.
2. Epstein, J.I., Oesterling, J.E., and Walsh, P.C.: Tumor volume versus percentage of specimen involved by tumor correlated with progression in stage A prostatic cancer. J. Urol. 139:980-984,1988.
3. Epstein, J.I., Oesterling, J.E., and Walsh, P.C.: The volume and anatomical location of residual tumor in radical prostatectomy specimens removed for stage A1 prostate cancer. J. Urol. 139:975-979, 1988.
4. Walsh, P.C., Schlegel, P.N.: Radical pelvic surgery with preservation of sexual function. Ann. Surg. and Transactions of the American Surgical Association, 106:145-154, Oct. 1988.
5. Walsh, P.C.: Nerve-Sparing Radical Prostatectomy for Early Stage Prostate Cancer. In Seminars in Oncology, Vol. 15, (ed) Marc B. Garnick, Grune & Stratton, 1988, pp. 351-358.
6. Walsh, P.C.: Radical retropubic prostatectomy with reduced morbidity: An anatomic approach. NCI Monographs, #7:133-137, 1988.
7. Lepor, H. and Walsh, P.C.: Longterm results of radical prostatectomy in clinically localized prostate cancer: experience at The Johns Hopkins Hospital. NCI Monograph #7:117-122, 1988.
8. Lepor, H., Kimball, A.W., and Walsh, P.C.: Cause-specific actuarial survival analysis: A useful method for reporting survival data in men with clinically localized carcinoma of the prostate. J. Urol. 141:82-84, 1989.
9. Partin, A.W., Epstein, J.I., Cho, K.R., Gittelsohn, A.M. and Walsh, P.C.: Morphometric measurement of tumor volume and percent of gland involvement as predictors of pathological stage in clinical stage B prostate cancer. J. Urol. 141:34 1 345, 1989.
10. Quinlan, D.M., Nelson, R.J., Partin, A.W., Mostwin, J.L. and Walsh, P.C.: The rat as a model for the study of penile erection. J. Urol. 141:656-661, 1989.
11. Weber, J.P., Oesterling, J.E., Peters, C.A., Partin, A.W., Chan, D.W., and Walsh, P.C.: The influence of reversible androgen deprivation on serum prostate-specific antigen levels in men with benign prostatic hyperplasia. J. Urol. 141:987-992, 1989.
12. Walsh, P.C., Oesterling, J.E., Epstein, J.I., Bruzek, D.J., Rock R.C., and Chan, D.W.: The value of prostate-specific antigen in the management of localized prostatic cancer. In Therapeutic Progress in Urological Cancers, (eds) Gerald P. Murphy and Saad Khoury, Alan R. Liss, Inc., New York, 1989, pp. 27-33.
13. Alexander, R.B., Maguire, M.G., Epstein, J.I., and Walsh, P.C.: Pathological stage is higher in older men with clinical stage B1 adenocarcinoma of the prostate. J. Urol. 141:880-882, 1989.
14. Schlegel, P.N. and Walsh, P.C.: The use of the preperitoneal approach for the simultaneous repair of inguinal hernia during surgery on the bladder and prostate. World J. Surg. 13:555-559, 1989.

15. Carter, H.B., Hamper, U.M., Sheth, S., Sanders, R.C., Epstein, J.I., and Walsh, P.C.: Evaluation of transrectal ultrasound in the early detection of prostate cancer. J. Urol. 142:1008-1010, 1989.

16. Christensen, W.N., Partin, A.W., Walsh, P.C., and Epstein, J.I.: Pathologic findings in clinical stage A2 prostate cancer. Relation of tumor volume, grade, and location to pathologic stage. Cancer 65:1021-1027, 1990.

17. Walsh, P.C., Brendler, C.B., Chang, T., Marshall, F.F., Mostwin, J.1., Stutzman, R., and Schlegel, P.N.: Preservation of sexual function in men during radical pelvic surgery. MMJ 39:389-393, April 1990

18. Partin, A.W., Carter, H.B., Chan, D.W., Epstein, J.I., Oesterling, J.E., Rock, R.C., Weber, J. P., and Walsh, P.C.: Prostate specific antigen in the staging of localized prostate cancer: Influence of tumor differentiation, tumor volume and benign hyperplasia. J. Urol. 143:747752, 1990.

19. Steinberg, G.D., Epstein, J.I., Piantadosi, S., & Walsh, P.C.: Management of stage D1 adenocarcinoma of the prostate: The Johns Hopkins Experience 1974-1987. J. Urol. (in press).

20. Partin, A.W., Oesterling, J.E., Epstein, J.I., Horton, R., & Walsh, P.C.; Influence of age and endocrine factors on the volume of benign prostatic hyperplasia. J. Urol. (in press).

21. Walsh, P.C., Quinlan, DM., Mortoti, R.A., and Steiner, M.S.: Radical retropubic prostatectomy: Improved anastomosis and urinary continence. Urol. Clin. N. Amer. 17:679-684, 1990.

22. Steiner, M.S., Morton, R.A., and Walsh, P.C.: Impact of anatomical radical prostatectomy on urinary continence. J. Urol. (in press). 23. Quinlan, D.M., Epstein, J.I., Carter, B.S., and Walsh, P.C.: Sexual function following radical prostatectomy: Influence of preservation of neurovascular bundles. J. Urol. (in press)

23. Morton, R.A., Steiner, M.S., and Walsh, P.C.: Cancer control following anatomical radical prostatectomy: An interim report. J. Urol. (in press).

24. Brendler, C.B., Steinberg, G.D., Marshall, F.F., Mostwin, J.I., and Walsh, P.C.: Local recurrence and survival following nerve-sparing radical cystoprostatectcomy. J. Urol. (in press).

25. Marshall, F.F., Mostwin, J.I., Radebaugh, L., Walsh, P.C., and Brendier, C.B.: Ileocolic neobladder postcystectomy: continence and potency. (Submitted for publication).

26. Rifkin, M.D., Zerhouni, E.A., Gatsonis, C.A., Quint, L.E., Paushter, DM., Epstein, J.I., Hamper, U., Walsh, P.C., and McNeil, B.J.: Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer. NEJM 323:2- 7, 1990.