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Left: Characterization of XMRV-infected prostatic cells by FISH and FISH/immunofluorescence. The H & E section shows a stromal fibroblast adjacent to tumor, which is shown by immunofluorescence (inset) to contain virus (green dots) located in the nucleus (blue).

Right: Robotic instruments provide surgeons with optimal precision during radical prostatectomy.
Dear Colleague,

The Glickman Urological Institute’s paramount objective remains to provide the highest quality of care for adult and pediatric patients with routine or complex urological disorders. Our activities comprise a unique combination of high-volume and challenging clinical material, extensive clinical scientific activities, and credible laboratory research within an environment that is nurturing the future leaders of our specialty. The institute’s professional staff of 62 physicians and scientists offers expertise in every urologic subspecialty area and comprises the largest full-time urology faculty in the United States.

The demand for clinical services offered by the Glickman Urological Institute continues to increase, reflecting the strong regional and national reputation of our physician staff. During 2005, we performed more than 15,000 operations and recorded more than 80,000 outpatient visits. In addition to our main campus activities, our clinical staff provides medical and surgical care at 14 satellite locations in northeastern Ohio. Our programmatic development remains a collaborative effort between our core group of subspecialty-based, academically oriented faculty and high-quality general urologists practicing in the community. This model has enabled growth of our regional and national tertiary care referral base while simultaneously expanding the local general urologic component of our practice.

During the past year, several outstanding individuals were recruited to join the faculty of the Glickman Urological Institute. Dr. Andrew Stephenson, a specialist in prostate cancer, joined our faculty in January after completing postgraduate fellowship training at Memorial Sloan-Kettering Cancer Center. Dr. Ed Sabanegh, a male infertility specialist at Wilford Hall Medical Center at Lackland Air Force Base, is joining our faculty this month. Dr. Courtenay Moore, a specialist in female urology, is also joining our faculty this month. Dr. Jeffrey Palmer, a pediatric urologist at University Hospitals in Cleveland, is joining our faculty in October.

Our six-year urologic residency program offers superb clinical and academic training, including a full year of laboratory research, and now comprises four residents per year. Postgraduate fellowships are offered in endourologic and laparoscopic surgery, urologic oncology, female urology, male infertility and renal transplantation. The institute’s faculty contributed 206 scientific publications to peer-reviewed medical journals in 2005. There are currently 106 ongoing prospective clinical research studies and 29 ongoing laboratory research projects, supervised by 10 full-time Ph.D. investigators within the institute.

Our faculty members share a passion for discovery and a deep commitment to providing the best possible clinical and investigative training for our residents and postgraduate fellows. We are supporting our academic mission through all available funding sources, including peer-reviewed grants, philanthropy and industry. Faculty of the institute currently serve as principal investigators of NIH or NCI grants totaling more than $20 million.

We are eager to share our knowledge and experience with colleagues in the field and to learn from them as well. Our faculty members have contributed a new major text to the literature, Operative Urology at the Cleveland Clinic (Humana Press, 2006). This is a unique compendium in that it encompasses the entire spectrum of contemporary continued
urologic surgery and is authored exclusively by faculty from a single program. We also remain actively involved in graduate and postgraduate educational programs at both the national and international levels. During the past year, we hosted innovative national urology resident preceptorship programs in female pelvic medicine and reconstructive surgery, laparoscopic urologic surgery, and reconstructive urologic surgery.

Finally, on June 28 we witnessed the groundbreaking for a new building on our main Cleveland Clinic campus. The building will be named the Glickman Tower and will house the Glickman Urological Institute. This initiative, scheduled for completion in the fall of 2008, will double the amount of space that we currently have for our clinical programs while also enabling further development of our educational and research activities.

This is indeed an exciting time for the faculty and trainees of the Glickman Urological Institute. We are proud of our past, energized by our ongoing activities and passionate about our future. We are pleased to share current activities with our colleagues and friends in this issue of Urology News.

Sincerely,

Andrew C. Novick, M.D.
Chairman, Cleveland Clinic
Glickman Urological Institute
Professor of Surgery
Associate Dean for Faculty Affairs,
Cleveland Clinic Lerner College of Medicine
of Case Western Reserve University

CLEVELAND CLINIC PAYS TRIBUTE TO THE GLICKMANS

Cleveland Clinic honored more than 500 of its donors in 2005 at its annual Partners in Philanthropy celebration on June 28, thanking them for their generous support and steadfast commitment to Cleveland Clinic.

At the event, Delos M. “Toby” Cosgrove, M.D., CEO and President of Cleveland Clinic, also recognized Carl and Babs Glickman of Shaker Heights, Ohio, for their lifelong contributions to Cleveland Clinic, while celebrating the start of construction on the Glickman Tower.

New Staff

The Glickman Urological Institute welcomes the following new staff members.

Courtenay K. Moore, M.D., a specialist in female urology, completed a fellowship in female pelvic medicine and reconstructive surgery here. Dr. Moore received her medical degree from Albany Medical College in Albany, N.Y. She completed her residency training in urological surgery at Albany Medical Center in Albany, N.Y. Dr. Moore received several honors and awards during her training. She will direct the Female Sexual Dysfunction Initiative.

Jeffrey S. Palmer, M.D., a pediatric urologist, received his medical degree from Albert Einstein College of Medicine in Bronx, N.Y. He completed his surgical training at Montefiore Medical Center/Albert Einstein College of Medicine. Dr. Palmer completed a residency in urology at The University of Chicago Medical Center/Pritzker School of Medicine. He completed research and clinical fellowships in pediatric urology at Children’s Memorial Hospital of Northwestern University Medical School in Chicago. Dr. Palmer was Director of Minimally Invasive Pediatric Urology at Rainbow Babies and Children’s Hospital in Cleveland.

Edmund S. Sabanegh, M.D., a male infertility specialist, joins us from Wilford Hall Medical Center at Lackland Air Force Base in Texas. Dr. Sabanegh received his medical degree from the University of Virginia in Charlottesville. He also received a bachelor’s degree in chemical engineering from Princeton University. Dr. Sabanegh completed his urology residency at the Wilford Hall Medical Center. He completed his fellowship in male infertility and microsurgery at Cleveland Clinic. He was the Urology Consultant to the Air Force Surgeon General and an assistant professor of urology at the Uniformed Services University of the Health Sciences in Bethesda, MD.
Malcolm Gladwell’s book *The Tipping Point* is an exploration of the mechanism by which new concepts become widely accepted. He notes that while many great ideas go largely unnoticed, others become cultural or business phenomena. The principle extends from such disparate events as the acceptance of “cool” shoes by teens to the slow adoption of hybrid corn seeds as an economically advantageous move by farmers in the twentieth century. Under his theory, not only must an innovation be a good idea, but it must be embraced by mavens (those known for expertise or knowledge) and connectors (individuals who are well-known by large numbers of colleagues) who are responsible for its ultimate success or failure. For example, hybrid seeds languished in their early years although they yield significantly more corn that is less susceptible to wastage. Only when the farmers who were considered by their peers to be the community’s intellectual leaders began extolling the value of hybrids did their use become widespread. Likewise, geeky teens failed to influence shoe sales, but when the “cool” teens began wearing a certain type of shoe, the company became a Wall Street darling due to explosive sales. Each event—a “tipping point”—allowed a good idea to become accepted by its target audience.

In urology, the principle of the tipping point also can be observed when enthusiastic embrace of new concepts by mavens and connectors ushers both good and bad ideas into the market; hence, the rapid acceptance of both balloon dilation for BPH and shock-wave lithotripsy for stones. Urological mavens espoused the value of both trends “not to be missed,” and convinced urologists to adopt these technologies before it was too late. Although both were all the rage, only one of these exciting new developments, for obvious reasons, ended up with long-term success.

Laparoscopic prostatectomy failed to reach a tipping point in the 1990s after Schuessler demonstrated feasibility but prohibitive complexity. Investigators at Cleveland Clinic and other institutions completed the painstaking process of identifying the methods that allowed it to be performed on a consistent basis in the hands of highly skilled laparoscopic surgeons. However, the tipping point in the community occurred when robotic assistance became commonplace, allowing entry to surgeons with limited laparoscopic training.

Most businesses can push for widespread adoption of their new concepts considering the fiduciary impact alone. However, medical fields such as urology have a greater duty, and subsequently stricter criteria for success. Economic viability is essential, but we must also strive to assure that the tipping point is based in quality, peer-reviewed evidence. It is often unclear whether the tipping point in urology is due to the technology or its marketing. Perhaps our best hope would be that it is the combination.

The tipping point also explains how innovations can flounder despite undeniable evidence. For example, perioperative intravesical chemotherapy following TURBT remains the exception in the United States. Few mavens have pushed the issue here, whereas many urological oncology leaders in Europe have used indisputable level-one evidence to suggest it has become essentially the standard of care. In contrast, thought leaders in the United States convinced the urological community of the value of PSA screening (an easily recognizable tipping point), while many Europeans remain unconvinced of the concept almost two decades later.

We all share responsibility to assure that both the introduction of a new concept and its tipping point are based on intellectual rigor. *Urology News* presents articles describing new innovations, as well as those describing innovations that are now state-of-the-art. It is our hope that sharing concepts with the urological community at both stages will help optimize the tipping point for urological progress. We hope it will be based on innovations that are well-conceived, tested in the academic setting and ready for widespread adoption.
Cleveland Clinic’s Glickman Urological Institute and Taussig Cancer Center have combined forces and added key staff to expand Cleveland Clinic’s genitourinary oncology program.

The partnership combines the expertise and experience of internationally renowned experts in urologic oncology, medical oncology, radiation oncology, genetics, pathology and biostatistics in a program designed to attack genitourinary cancers on multiple fronts. The management of urological cancer has been one of the strengths of Cleveland Clinic for many years, with major scientific and treatment advances having been created by Drs. Andrew Novick, Eric Klein, Ronald Bukowski, Amr Fergany, Robert Dreicer, Warren Heston and Robert Silverman, among others.

“We offer all forms of therapy in a fair and balanced way,” says Andrew Novick, M.D., a renowned urologic oncologic surgeon and Chairman of the Glickman Urological Institute. “A major strength is that our urologists, radiation oncologists and medical oncologists conduct joint clinics and joint research. By working together in this fashion, we define the state of the art at the same time we are practicing it.”

Derek Raghavan, M.D., Ph.D., Chairman of the Taussig Cancer Center, adds: “Our goal is to improve patient care by providing even more treatment choices, multidisciplinary management, innovations and second opinions. Medical care can often be improved with more than one opinion, as different viewpoints provide a wider understanding of the biology of any cancer. We are fortunate that we can build on the strengths of one of the leading urology programs in the world, adding the experience of leaders in genitourinary chemotherapy and radiotherapy.”

Collaboration between Cleveland Clinic urologists and radiation and medical oncologists has been ongoing for decades. Physicians in each department have expertise in genitourinary cancers and routinely work together when patients need multimodality therapy. The addition of new physicians and researchers and joint protocols simply has strengthened an already formidable program.

New Genitourinary Staff

Specialists within the genitourinary medical oncology program have strong clinical and research interests that cover the spectrum of the major genitourinary neoplasms.

**Steven Campbell, M.D., Ph.D.**
(from Loyola University Medical Center, Chicago)
Clinical/research interests: Bladder cancer, kidney cancer, prostate cancer, testis cancer, penile cancer, adrenal cancer, osteoporosis related to cancer, complex renal cysts

**Andrew J. Stephenson, M.D.**
(from Memorial Sloan-Kettering Cancer Center, New York)
Clinical/research interests: Prostate, bladder, kidney and testicular cancer; nerve-sparing prostatectomy; robotic prostatectomy; urinary diversion

**Michael Kattan, Ph.D.**
Chairman, Quantitative Health Sciences
(from Memorial Sloan-Kettering Cancer Center, New York)
Research interests: Prediction, medical decision making, quality of life assessment, patient preferences, decision analysis

**Brian Rini, M.D.**
(from UCSF Comprehensive Cancer Center, San Francisco)
Clinical/research interests: Genitourinary oncology, renal cell carcinoma, prostate cancer, anti-angiogenic therapy, immunotherapy
New additions to the staff include Steven Campbell, M.D., a urologist with a specialty interest in bladder and renal cell cancer; Andrew Stephenson, M.D., a urologist with a specialty interest in advanced genitourinary cancer; Michael Kattan, Ph.D., a national authority on treatment algorithms and outcomes for cancers of the prostate, who has been appointed head of the new Department of Quantitative Health Sciences; Brian Rini, M.D., who helped develop a new class of anti-angiogenic drugs for renal cell carcinoma; Jorge Garcia, M.D., winner of the American Society of Clinical Oncology’s Young Investigator Award for prostate cancer research; and Timothy Gilligan, M.D., a medical oncologist with an interest in treatment outcomes in genitourinary malignancies and minority health care.

Post World Congress of Endourology
International Live Surgery Program
Held Aug. 21-25

Immediately following the Endourological Society's 24th Annual World Congress of Endourology, held Aug. 17-20 on the Cleveland Clinic main campus in Cleveland, the Glickman Urological Institute held a five-day international live surgery program at Cleveland Clinic. All World Congress participants were invited, and more than 150 urologists from around the world participated. Andrew C. Novick, M.D., Chairman of the Glickman Urological Institute, presided at the event.

This observership program offered approximately 25 full-length, moderated live surgical operations, performed by Glickman Urological Institute staff members. The operations encompassed all urologic subspecialties. The program was designed to show basic and advanced open and minimally invasive surgical techniques. It was offered in response to requests from urologists around the world for this type of program at Cleveland Clinic.
**Glickman Urological Institute Awarded Additional Funding for Pelvic Neuromodulation Research**

**Collaborative Partnership Leads to $16 Million in Grant Award from the State of Ohio**

Neuromodulation is an innovative treatment for lower urinary tract symptoms and dysfunctions secondary to neuromuscular etiologies. Current therapeutic innovations consist of injectable neurotoxins or neurostimulation. The Section of Voiding Dysfunction and Female Urology has developed an infrastructure of support for translational and basic science research partnerships in the area of neuromodulation and pelvic health. In 2003, the Ohio Neurostimulation and Neuromodulation Partnership consisting of the Glickman Urological Institute, University Hospitals and Case Western Reserve University, Cleveland MetroHealth Medical Center, the Cleveland Veterans Association Medical Center and NDI Medical Inc., was awarded $8 million from the State of Ohio to develop translational applications of neuromodulation therapies. For 2006, this multi-institutional collaborative working partnership was awarded another $8 million from the competitive grant competition of the State of Ohio Third Frontier Project to extend the capabilities of our neuromodulation research and developments with specific attention to pelvic organ functions in relation to incontinence and erectile restoration by the members of the Glickman Urological Institute.

Currently, the only implantable device currently FDA-approved for pelvic neuromodulation therapy is a sacral nerve root neuroelectrode for the treatment of refractory urgency/frequency syndrome, urge incontinence and non-obstructive urinary retention. Other U.S. manufacturers have approved FDA clinical trials under way for implantable neuromodulation devices along the course of the pudendal nerve for similar, as well as expanding, clinical applications.

**Cleveland Clinic Excels in Latest U.S. News Rankings**

Glickman Urological Institute named one of the top 2 urology programs in the country

For the seventh consecutive year, the Cleveland Clinic Glickman Urological Institute was ranked among the top two urology programs in the United States by U.S. News & World Report. And Cleveland Clinic has been ranked among the top three hospitals in the country, according to the latest U.S. News annual survey of “America’s Best Hospitals.”

The report ranks Cleveland Clinic among the nation’s best in all 16 specialties it rates, and 11 Cleveland Clinic specialties are ranked among the nation’s top 10. For details, visit clevelandclinic.org.

**Outcomes Data Available**

The latest edition of outcomes data from the Cleveland Clinic Glickman Urological Institute is available. Our outcomes booklet also offers summary reviews of medical and surgical trends and approaches. Charts, graphs and data illustrate the scope and volume of procedures performed in our department each year. To view outcomes booklets for the Cleveland Clinic Glickman Urological Institute, as well as many other Cleveland Clinic medical and surgical disciplines, visit clevelandclinic.org/quality.
indications. In addition to the expansion of technology and clinical indications for pelvic neuromodulation therapy, other forms of transcutaneous and implantable neuromodulation devices using different nerve roots or for different clinical indications, such as erectile restoration, interstitial cystitis, chronic pelvic pain, defecatory disorders and fecal incontinence, are under investigation at the Glickman Urological Institute.

Andrew C. Novick, M.D., Chairman of the Glickman Urological Institute, delivered two distinguished lectures earlier this year at the American Urological Association’s (AUA) annual meeting in Atlanta. As the Willet F. Whitmore, Jr., lecturer, Dr. Novick addressed the Society of Urologic Oncology with a presentation entitled “Kidney Cancer: Past, Present and Future.” Dr. Novick also delivered the 2006 Ramon Guiteras Lecture at the AUA conference. His address, “Ischemic Renal Disease: Implications for the Urologist,” provided an overview of advancements in diagnostic and treatment methods to preserve and restore kidney function in patients with ischemic renal disease.

Operative Urology at the Cleveland Clinic Receives Top National Award

The Glickman Urological Institute’s monumental publication on urologic surgery — Operative Urology at the Cleveland Clinic — is now available. Through informative text and detailed illustrations, the book describes everything from fundamental surgical techniques to minimally invasive procedures and the latest technologies.

The Association of Medical Illustrators recently awarded Operative Urology at the Cleveland Clinic the Illustrated Medical Book Award. This award is given to a publication that meets the highest standard of the profession in communication and artistic skills. A scale is used by the jury to rate accuracy, problem solving, technical execution, communication and overall aesthetics. Medical illustrators from Cleveland Clinic’s Center for Medical Art and Photography provided the more than 700 illustrations for the book.

Andrew Novick, M.D., Chairman of the Glickman Urological Institute, served as senior editor of the publication while J. Stephen Jones, M.D., worked as associate editor. Inderbir Gill, M.D., Eric Klein, M.D., Raymond Rackley, M.D., and Jonathan Ross, M.D., served as assistant editors to this state-of-the-art surgical atlas.

To order Operative Urology at the Cleveland Clinic, please visit humanapress.com.

Coming soon for patients...

A comprehensive guide to prostate cancer prevention and treatment by Eric Klein, M.D., head of urologic oncology at the Glickman Urological Institute.

To reserve a copy of Prostate Cancer: A Cleveland Clinic Guide, visit clevelandclinicpress.org.
Novel Virus Linked to Prostate Cancer in Genetically Susceptible Men

Eric A. Klein, M.D., and Robert Silverman, Ph.D.

While the etiology of prostate cancer is unknown, it is clear that both genetics and environment play a role in its origin and evolution. Recent scientific and clinical evidence suggests a convergence between genetic susceptibility and predisposition to infection as potentially important in the development of prostate cancer. Of the known susceptibility genes, HPC1 is the best characterized. HPC1 encodes for the enzyme RNaseL, an antiviral gene that plays a key role in the innate immune response to viral infections. Activation of RNaseL by viral infection and endogenous interferon inhibits viral spread by degrading single-stranded RNA and by causing the infected host cell to undergo apoptosis. Preclinical studies have shown that mice deficient in RNaseL are more susceptible to viral infection.

In humans, there is evidence that allelic variants of the RNaseL gene may increase the risk of developing prostate cancer. We have previously shown that men who are heterozygous (RQ genotype) for a single amino acid change from arginine to glutamine at position 462 of the RNaseL protein had about a 50% greater risk of prostate cancer, and men homozygous at this locus (QQ genotype) carried double the risk compared to normals (RR genotype). The observation that variants in an antiviral gene predispose men to prostate cancer led to our investigation for a viral etiology.

To test this hypothesis, we used a powerful tool known as the ViroChip, developed by our collaborators Joe DeRisi, Ph.D., and Don Ganem, M.D. The ViroChip contains highly conserved sequences from all known viruses (almost 1000 in total) in the plant, animal and human kingdoms. Hybridizing RNA from biological samples (such as respiratory secretions or tissue) to the chip allows determination of what expressed viral genes are present in the sample, identification of which family of viruses they belong to, and cloning and identification of the exact sequence of the viruses. We hybridized RNA from the peripheral zone of radical prostatectomy specimens from men with prostate cancer who were genotyped for allelic variants of the RNaseL gene. In the initial 19 men, we identified 8 with a novel retrovirus. Remarkably, 7 of the 8 men with the new virus, dubbed XMRV, were found to have the QQ genotype of the RNaseL gene.

We have since screened more than 150 men. Data analysis is not complete, but preliminary findings show that about half of the men with the QQ mutation test positive for...
of chronic prostatitis but without positive bacterial cultures. It represents the largest category in terms of numbers of affected men and also the one having the fewest proven options for therapy.

Other independent clinical trials are also being planned, including a randomized, placebo-controlled study of anti-nanobacterial therapy for men with Category III CP/CPPS who also have prostatic calcifications. Calcifications in the prostate are found in many men with Category III CP/CPPS, although the significance of that finding is unclear considering that prostatic calcification is also common among asymptomatic men. Nevertheless, because nanobacteria have been implicated in the pathogenesis of various calcific diseases in the body, including urinary tract stones, we previously undertook an open-label, pilot study of a novel, anti-nanobacterial suppository. The published results showed that after 12 weeks, this treatment resulted in at least 25% symptomatic improvement in 12 (80%) of 16 men refractory to all other forms of available therapy.

Another study will investigate men with Category IV CP/CPPS. There has been very little research attention directed to this form of prostatitis that is defined by lack of symptoms with the presence of inflammation in the prostate or seminal fluid. However, it deserves a greater focus because it recently has been implicated in progression to prostatic enlargement and as a potential forerunner of prostate cancer. The study will enroll men who are undergoing prostate biopsy and will require that they provide a semen sample. Powerful laboratory techniques will be used to characterize markers of inflammation and oxidative stress and to correlate the findings in the tissue and fluid specimens. That information is expected to provide insight as to whether the current CP/CPPS classification scheme needs to be reevaluated (i.e., whether it is appropriate to lump all of these men together, or if they represent distinct groups with different potential disease associations).

XMRV, compared to only 1 among those who do not have this variant. Complete sequencing of XMRV reveals that it most closely resembles Murine Leukemia Virus (MuLV), a virus that causes leukemia in mice. There are, however, important differences between XMRV and MuLV, including the fact that XMRV does not infect mice and has a deletion in the glyco-GAG leader sequence that helps determine its virulence.

Tissue localization studies have demonstrated that XMRV does not reside in the epithelium but in fibroblasts adjacent to the cancer. There is a substantial body of scientific evidence describing biological “cross-talk” between cancer-associated fibroblasts and epithelial tumors, and the hypothesis is that XMRV is exerting an effect on the tumor by means of paracrine signaling or through an indirect effect by providing an appropriate microenvironment to recruit macrophages and white blood cells that result in oxidative stress. Both of these hypotheses are currently under study. While a direct link between XMRV as a cause of prostate cancer remains to be proven, this work represents an exciting new finding in the possible pathogenesis of prostate cancer.
Neoadjuvant Therapy for High-Risk Prostate Cancer

Despite remarkable advances in surgical and radiotherapy techniques over the past two decades, patients with high-risk prostate cancer are at risk of developing local and systemic disease recurrence, presumably owing to the presence of micrometastatic disease. The identification of novel and chemotherapeutic agents with activity in advanced prostate cancer (PCA) has led many clinical investigators to evaluate the concept of both adjuvant and neoadjuvant therapy in patients with locally advanced disease.

The administration of neoadjuvant systemic therapy has a number of theoretical advantages, including the potential to achieve a complete pathological response at the time of surgery and the delivery of systemic therapy while the burden of micrometastatic disease is minimal. Potential disadvantages of this approach include treating individuals whose disease is over-staged (obviated in the adjuvant setting) and the time delay (3-6 months) to radical prostatectomy if systemic therapy is either ineffective or results in significant therapy-related toxicity. However, multiple phase II studies have demonstrated the feasibility of this approach, and provide evidence of anti-tumor activity with acceptable toxicity.

Several predictive models can be used to better identify patients at significant risk who may benefit from multimodality approaches. These nomograms have been extensively tested, validated and are used daily by clinicians around the world.

Jorge Garcia, M.D.

A - C: Pre-treatment Biopsies

S100 – Activated Dendritic Cell

CD3 – T cell Marker

CD68 – Macrophage Marker
In contrast to its use in the setting of external beam radiation therapy (EB×RT), neoadjuvant androgen deprivation therapy (ADT) prior to radical prostatectomy (RP), although demonstrating a reduction in the rate of positive surgical margins and pathologic organ-confinement, has failed to demonstrate improvement in progression-free and/or overall survival. Until recently, evaluation of neoadjuvant systemic chemotherapy was hampered by the lack of effective chemotherapy regimens in patients with advanced hormone-refractory prostate cancer (HRPC). The results of two recently published phase III trials showing clinical benefit and survival improvement when advanced HRPC patients receive docetaxel-based chemotherapy have allowed us to move this cytotoxic regimen forward in the treatment of patients with locally advanced PCA. Several trials evaluating the addition of neoadjuvant docetaxel-based chemotherapy prior to either surgery or definitive radiation therapy have been completed, with others ongoing.

New approaches using more targeted, and thereby, less toxic drugs in the neoadjuvant setting are in progress. Several of the targeted agents include growth factor inhibitors, angiogenesis inhibitors, antioxidants and inducers of apoptosis.

In addition to testing novel cytotoxic agents in PCA, another of our research interests has been trying to elucidate the role that the immune system plays in PCA development and progression. As such, we have evaluated the role of several immunomodulatory novel agents such as granulocyte macrophage colony-stimulating factor (GM-CSF), a pleiotropic cytokine that stimulates dendritic cells (DCs) and promotes uptake of tumor antigens by DCs leading to T cell cross-priming, and thalidomide, an immunomodulatory agent with antiangiogenic activity. As single agents or in combination, GM-CSF and thalidomide have shown to induce PSA responses in 20-25% of HRPC patients.

To further evaluate the clinical activity and potential immune prostate tissue findings of this novel combination, we recently conducted a phase II trial of GM-CSF and thalidomide in patients with locally advanced PCA undergoing local definitive therapy with RP. Patients with locally advanced PCA undergoing RP were eligible. All patients received GM-CSF administered subcutaneously three times weekly, and thalidomide was escalated to reach the study dose of 200 mg/PO/day. Pre-treatment and post-treatment tissue was also analyzed for changes in selected immune parameters. Overall, therapy was well tolerated and did not appear to affect perioperative morbidity of RP. No pathological complete responses have been observed. Seventy-nine percent of patients have a PSA decline. In addition, it is provocative that post-GM-CSF/thalidomide RP specimens showed significant T cell and activated DC infiltration in PCA tissue when compared with pretreatment biopsies. Although further immune studies are under way to better understand the significance of these initial tissue findings, they support the clinical activity observed when these agents are used in patients with advanced disease.

A phase II neoadjuvant study evaluating the activity of Abraxane, a novel albumin-bound taxane particle, in high-risk PCA patients undergoing RP is currently under way at Cleveland Clinic.

D-F: Corresponding Post-treatment RP Specimens

D
S100 – Activated Dendritic Cell

E
CD3 – T cell Marker

F
CD68 – Macrophage Marker
Energy-Free Nerve-Sparing Laparoscopic Radical Prostatectomy Results in Superior Potency Outcomes

Inderbir S. Gill, M.D., and Osamu Ukimura, M.D.

Current surgical techniques employed in nerve-sparing radical prostatectomy for prostate cancer produce excellent disease-free outcomes. However, varying degrees of erectile dysfunction, a not uncommon sequela, can compromise quality of life in 40% to 60% of men who were potent before the procedure. It has been postulated that corollary trauma wrought by hemostatic instruments using one or another form of thermal energy (ultrasonic, monopolar or bipolar electric) could create incidental injury to nerves, vessels and tissues comprising the neurovascular bundle (NVB) and delay or even prevent the return of erectile function.

We developed an energy-free technique of nerve-sparing laparoscopic radical prostatectomy (LRP) and have recently acquired updated data from a cohort of 126 men who underwent this specific procedure. Our data suggest that the technique results in a 6-month quicker recovery of erectile function compared to those who undergo nerve-sparing techniques that employ electrical or ultrasonic thermal energy. An additional finding is that power Doppler-confirmed preserved pulsatile blood vessels within the NVB correlates with a quicker return to erectile function and overall superior outcomes.

Our athermal technique involves transient bulldog clamping of the lateral pedicle and cold-cut release of the NVB, followed by delicate and precise hemostatic suturing. Between March 2003 and December 2005 a single surgeon performed laparoscopic radical prostatectomy on 349 men. Either a harmonic scalpel-based technique or our athermal technique was used to hemostatically release the NVB. All men had T1c or T2 cancers.

Erectile function was assessed pre-operatively (baseline) and post-operatively at 3, 6, 12 and 18 months by a patient-completed Sexual Health Inventory for Men (SHIM), a validated instrument shown to have a high degree of sensitivity and specificity. One-year paired pre- and post-operative SHIM data are now available in 59 patients. Of these, 19 patients (Group I) underwent nerve-sparing LRP employing a harmonic scalpel, and 40 underwent nerve-sparing LRP utilizing the novel energy-free technique (Group II).

Restored function was defined as the ability to achieve erections sufficient for intercourse with or without medications (phosphodiesterase inhibitors). A SHIM score of ≥22 was interpreted as a complete erectile function, and a score of 17 to 21 was interpreted as mild erectile dysfunction (ED).

At one year, 67% of the patients undergoing traditional thermal-based LRP (Group I) reported satisfactory intercourse (SHIM ≥22) compared with 82% of those undergoing the athermal technique (Group II). In patients with mild erectile dysfunction pre-op, one year intercourse rates in Group I were 33% compared with 73% in Group II. Overall one-year intercourse rates were also superior in Group II, with 65% reporting intercourse compared with 37% in Group I. Our data also indicated that erectile function recovered six months faster in patients undergoing athermal LRP.

Although the numbers involved in this initial trial are small, we believe they indicate that the application of athermal surgical techniques in nerve-sparing laparoscopic radical prostatectomy leads to a faster and superior return of erectile function in a greater number of patients than is seen with the electrical and thermal energy instrumentation now commonly used. In addition, power-Doppler confirmed preserved pulsatile blood vessels within the NVB correlated with superior erectile function recovery. This is a novel observation.

<table>
<thead>
<tr>
<th>Energy-based technique</th>
<th>Energy-free technique</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with SHIM ≥22</td>
<td>71%</td>
</tr>
<tr>
<td>Patients with SHIM 17-21</td>
<td>33%</td>
</tr>
</tbody>
</table>

Fig 1: Atraumatic bulldog used to achieve hemostasis on the lateral pedicle.

Fig 2: Cold-cut transection of the lateral pedicle and NVB release under real-time TRUS navigation.

Fig 3: One-year intercourse outcomes. Intercourse rate recovery after energy-based versus energy-free technique.
Cryobiology studies have shown that the ice ball is not lethal at its edge. The ice ball can approach the rectum or even touch it without necessarily creating a rectourethral fistula. However, the catastrophic nature of this injury precludes the acceptance of any significant risk for the complication. Our modification allows the edge to be extended several millimeters beyond capsule to assure adequate posterior freeze.

From a tumor-control standpoint, the failure to achieve lethal temperatures at the border of the ice ball makes it clear that the failure to advance the ice ball beyond the prostatic capsule risks oncologic concession posteriorly. It is well known that prostate cancers typically occur in the peripheral zone. This is the tissue that is at greatest risk of inadequate cell kill if freezing is limited to the prostatic capsule. This means that when the surgeon is concerned about rectourethral fistula, the site at greatest need for lethal cryoablation is the site that is least likely to receive optimal freezing. We have demonstrated that such concern can be safely reduced. The maneuvers we have described appear to improve the ability to freeze beyond the prostatic capsule while maintaining a safe distance from the rectal wall. We believe that when this maneuver is used, the distance obtainable makes the risk of rectourethral fistula unlikely and, theoretically, will improve tumor control in the posterior aspect of the prostate.
Office-Based Thermotherapy Improves Symptom Scores and Flow Rate in BPH Patients with Medically Refractory Lower Urinary Tract Symptoms (LUTS)

Shikha Sharma, M.D., Luay P. Susan, M.D., and Craig D. Zippe, M.D.

Transurethral microwave thermotherapy (TUMT) uses microwave energy to achieve intra-prostatic temperatures of >45°C to induce coagulation necrosis in the targeted perirethral glandular tissue of the transition zone. TUMT devices decrease the density of alpha 1-adrenoceptors in the smooth muscle of the prostate. The major advantage of TUMT is that treatment can be performed in an office setting under local anesthesia.

This prospective study evaluates the efficacy of TUMT using the TherMatrx TMx-2000 device (American Medical Systems) in patients with LUTS refractory to medical therapy.

### Treatment Details
The TherMatrx device creates a measured temperature of 50°C in the transition zone of the prostate ensuing tissue necrosis. The device includes the RX-200 applicator for heating and monitoring; this consists of a Foley-like catheter with a coiled microwave-radiating antenna. Two thermo-sensor tracks on opposite sides of the surface of the catheter are in contact with the prostatic tissue for temperature monitoring and mapping along its length. The treatment begins when the target maximum temperature (50°C) is recorded by the sensors, which takes 40 minutes and adjusts the wattage to maintain the

### Table 1

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline</th>
<th>3 months</th>
<th>6 months</th>
<th>9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>39</td>
<td>36</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>Mean total AUA Score</td>
<td>18.4 + 6.1</td>
<td>9.5 + 5.8</td>
<td>8.6 + 5.4</td>
<td>7.9 + 5.1</td>
</tr>
<tr>
<td>Mean Irritative Symptom Score</td>
<td>9 + 3.7</td>
<td>5.2 + 3.8</td>
<td>5.0 + 3.5</td>
<td>4.5 + 2.9</td>
</tr>
<tr>
<td>Mean Obstructive Symptom Score</td>
<td>9.6 + 4.5</td>
<td>4.6 + 3.3</td>
<td>3.8 + 3</td>
<td>3.7 + 2.9</td>
</tr>
<tr>
<td>Mean Quality of Life Score</td>
<td>4.2 + 2.4</td>
<td>2.2 + 1.7</td>
<td>2 + 1.4</td>
<td>1.8 + 1.2</td>
</tr>
<tr>
<td>Q Max (m/sec)</td>
<td>9.7 + 4.04</td>
<td>10.6 + 6.1</td>
<td>11.45 + 4.1</td>
<td>12.4 + 5.1</td>
</tr>
<tr>
<td>Mean Voided Volume (ml)</td>
<td>215 + 80</td>
<td>201 + 89</td>
<td>217 + 79</td>
<td>201 + 91</td>
</tr>
<tr>
<td>Mean Time to Void (seconds)</td>
<td>59.3</td>
<td>39.8</td>
<td>40.3</td>
<td>41</td>
</tr>
<tr>
<td>PVR (ml)</td>
<td>84.4 + 80</td>
<td>81.0 + 76</td>
<td>79.3 + 77</td>
<td>80.1 + 79.0</td>
</tr>
</tbody>
</table>

Baseline and Follow-up AUA Symptom Score, Uroflow Parameters and Post-Void Residue

### Apical Injection Site Relieves Pain Effectively During Prostate Biopsies

J. Stephen Jones, M.D., F.A.C.S.

Periprostatic block to prevent pain during prostate biopsy dramatically improves patient experience with pain and is the standard of care. The traditional injection of lidocaine into the hyperechoic pyramidal area between the base of the prostate and the seminal vesicles, termed the Mount Everest sign, has been the most studied option. We sought to determine whether pain control could be improved by apical injection and also sought a deeper understanding of the anatomical principles involved in successful nerve blockade.

Eighty-five patients were randomized to receive injections of 5 cc lidocaine on each side of either the base or into a corresponding hyperechoic area caudal to the apex. Then 12-20 core biopsies were obtained without delay. Patients were asked to report pain on a 100 mm visual analog pain scale (VAS). Scores were obtained after each step (probe placement, injection and biopsy) in order to keep the perception of pain experiences separate in the patient’s mind.

All 39 patients were treated with alpha-blockers with/without 5-alpha reductase inhibitors for at least 6 months. Microwave thermal treatment was given using the TherMatrx device only after patients failed to improve symptomatically on maximal medical therapy. Patients were evaluated by AUA Symptom Score (AUA SS), office uroflowmetry, and by post-void residual (PVR). Prostate gland size and prostatic urethral length were determined in all patients by transrectal ultrasound. Evaluations were done preoperatively, then 3, 6 and 12 months post-procedure. All patients underwent cystoscopic examination to rule out a protruding large median lobe.

Compared to historical VAS scores without periprostatic block, both methods gave significant relief. Patients with traditional basilar injection had VAS scores averaging 25.9 compared with apical injection patients whose VAS scores averaged 16.2 (p=0.01). Pain during injection was comparable in each group (21.4 vs. 21.3, respectively). Placement of the ultrasound probe prior to periprostatic block was reported as being more painful than either the biopsy or injection in each group, VAS 28.5 and 30.2, respectively.

Our study confirms the impression of initial investigators, such as Kaver, whose 2002 study indicated that apical injection gave better pain control. Although the differences were relatively small from a clinical perspective, they achieved statistical significance. The apical injection was more effective at preventing pain but is subjectively more difficult to teach to residents. The space lateral to the apex is much smaller than the Mount Everest area lateral to the base (Figures 1 and 2).
temperature. Several antenna lengths are available to accommodate prostates of different lengths. This device does not use any form of urethral cooling system. The rectal temperature is monitored by a rectal probe. A rectal temperature >42.5°C at any time during treatment will sound an alarm and cause the power delivery to stop. The patient is sent home with a Foley catheter inserted into the bladder. The catheter is to be removed 5-7 days after the procedure.

**Results**

Of the 39 patients enrolled in the study, 25 were followed for at least 9 months. The mean age was 69.58 ± 11.48 years and mean prostate volume was 58.9 gms ± 40.0. Multiple comorbid conditions were noted. All 39 patients were on an alpha-blocker for a mean duration of 23.9 months ± 15.1 before procedure; 23 patients were also using 5-alpha reductase inhibitors in addition to alpha-blockers. The mean duration of use of 5-alpha reductase inhibitors was 23.08 months ± 14.02 before procedure.

The procedure was well tolerated in 39 patients, and pain was managed with oral analgesics. Post-operative complications were seen in 3 patients (1 meatal stricture, 1 urinary tract infection, 1 urinary retention), which were managed on an outpatient basis. Foley catheter was removed in all patients successfully after 3-7 days post-procedure, and all patients resumed normal voiding.

Mean total AUA SS decreased significantly after treatment from baseline score of 18.4 ± 6.1 to 9.5 ± 5.8 at 3 months, to 8.6 ± 5.4 at 6 months and to 7.9 ± 5.1 at 9 months (Table 1). When analyzing the symptom score improvement in regard to obstructive vs. irritative, the mean scores of questions 1, 3, 5 and 6 (the obstructive questions) improved cumulatively from 9.6 ± 4.5 to 3.7 ± 2.9. When analyzing the irritative symptoms (questions 2, 4 and 7), the TherMatrx patients cumulatively improved from a mean of 9 ± 3.7 to 4.5 ± 2.9. Mean quality of life score improved significantly from the baseline score of 4.2 ± 2.4 to 1.8 ± 1.2 at 9 months.

Mean peak flow rate increased significantly after TherMatrx treatment from a baseline of 9.7 ± 4.04 ml/sec to 10.6 ± 6.1 at 3 months; to 11.45 ± 4.1 at 6 months; and to 12.4 ± 5.1 ml/sec at 9 months. The length of time to empty comparable bladder volumes was less, with voided times decreasing from 59.3 to 41 sec. The mean PVR, however, showed no significant change, with volumes of 84.4 ± 80 to 80.1 ± 79.0 cc. Stratification by prostate size (>60 gms) did not alter the efficacy of TherMatrx.

**Conclusion:**

TherMatrx is an effective, office-based procedure for medically refractory BPH patients irrespective of gland size and type of symptoms. Our data suggest that TherMatrx can improve both refractory obstructive and irritative symptoms. It can be performed safely in elderly patients with multiple comorbidities who have high risks for surgery.
Robotic Radical Prostatectomy: The Extraperitoneal Approach

Jihad H. Kaouk, M.D.

Radical prostatectomy is the only prostate cancer treatment that has been shown to reduce mortality from prostate cancer in the setting of a prospective randomized trial. Recent advances in treatment of localized prostate cancer include robotic-assisted technology that enhances surgical precision by providing 3-D visualization and improved surgical dexterity.

Robotic-assisted radical prostatectomy is mostly practiced through a transperitoneal approach, which provides a relatively easy access to the pelvis and allows a large operative field, facilitating mobilization of the bladder and providing access to the prostate.

Open radical prostatectomy surgery has traditionally been performed through an extraperitoneal approach, whereby the retropubic space is accessed through a lower midline incision. This offers a number of advantages to the urologist in that it provides access with a greater familiarity of anatomy, theoretically less risk of bowel injury, less handling of intra-abdominal viscera and confinement of any bleeding, urinary or lymphatic/serous collections to the extraperitoneal space.

At the Glickman Urological Institute, we have performed more than 200 robotic radical prostatectomies using the transperitoneal and extraperitoneal approach. The majority of the patients underwent nerve-sparing technique using harmonic ultrasound shears for the vascular pedicle and only cold dissection without any energy for dissecting the neurovascular bundle.

In a prospective study, we compared a group of 20 consecutive patients who underwent extraperitoneal robotic-assisted laparoscopic prostatectomy with another group of consecutive 20 patients who underwent robotic radical prostatectomy by the traditional transperitoneal route. Both groups were similar in terms of age, PSA and pre-operative clinical stage and grade of cancer on biopsy. Mean operative time was equivalent using both approaches, with mean blood loss of the order of 300 cc or less for both transperitoneal and extraperitoneal radical prostatectomy. Mean hospital stay was less than 2 days in both groups. The early results in terms of cancer control are also extremely encouraging with 90% and 95% of patients having surgical margins free from disease for transperitoneal and extraperitoneal approaches, respectively; these figures compare favorably with the best open, laparoscopic and robotic radical prostatectomy series in the medical literature.

In our initial evaluation we have shown that this novel extraperitoneal approach can be performed with success similar to the conventional transperitoneal approach in terms of duration of surgery, blood loss and early oncological control.

Encouraged by these results, we endeavor to study if the extraperitoneal approach also provides an advantage in terms of reduced gastrointestinal impairment and earlier resumption of diet, a shorter hospital stay and perhaps shorter duration of catheterization.

### Patient Outcomes

<table>
<thead>
<tr>
<th>Patient Outcomes</th>
<th>Extraperitoneal</th>
<th>Transperitoneal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient no.</strong></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td><strong>Mean Age (yrs)</strong></td>
<td>58.8 ± 7.6</td>
<td>58.9 ± 7.0</td>
</tr>
<tr>
<td><strong>Mean PSA</strong></td>
<td>5.4 ± 2.3</td>
<td>5.1 ± 2.8</td>
</tr>
<tr>
<td><strong>OR Time (min)</strong></td>
<td>176 ± 36</td>
<td>162 ± 50</td>
</tr>
<tr>
<td><strong>Estimated Blood Loss (cc)</strong></td>
<td>285 ± 196</td>
<td>304 ± 162</td>
</tr>
<tr>
<td><strong>Length of Stay</strong></td>
<td>1.7 ± 0.8</td>
<td>1.83 ± 1.3</td>
</tr>
<tr>
<td>(1-4)</td>
<td>(1-7)</td>
<td></td>
</tr>
<tr>
<td><strong>Catheter Duration (days)</strong></td>
<td>9.8 ± 5.2</td>
<td>8.7 ± 6.4</td>
</tr>
<tr>
<td><strong>Margin Positivity</strong></td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td><strong>Nerve-Sparing</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Unilateral</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Bilateral</td>
<td>80%</td>
<td>85%</td>
</tr>
</tbody>
</table>

Robotic-assisted radical prostatectomy is mostly practiced through a transperitoneal approach, which provides a relatively easy access to the pelvis and allows a large operative field, facilitating mobilization of the bladder and providing access to the prostate.
Flexible Intraluminal Robotics – Its Initial Use in Urology

Inderbir S. Gill, M.D., Jihad Kaouk, M.D., Monish Aron, M.D., and Mihir Desai, M.D.

Robotic-assisted surgery has made considerable inroads into urologic surgery – specifically radical prostatectomy. The touted advantages of existing systems include 3-D vision, intuitive wristed motion and precise delicate manipulation of instruments within confined areas. Vibration-dampening programs built into the system ensure that fine movements are conducted smoothly without perturbation by either the device or the operator’s hands. It is employed primarily in pelvic surgery, radical prostatectomy and radical cystectomy.

It is a start.

To date, the term “robotics” implies rigid instrumentation applied to the extra-luminal (external) aspects of abdominal viscera.

Herein, we provide the initial description of a novel flexible robotic system, which is employed intra-luminally in endoscopic urologic surgery.

Flexible robotics represent the next step in the evolving technology. In this catheter-based system, the distal ends of flexible instruments have been made capable of a far greater range of position and motion. The sheath can be directed, advanced and manipulated with less force by the operator. Since the sheath is manipulated remotely by a robot, it can be frozen in place to provide a stable, unyielding platform that gives the surgeon freedom to use both hands to manipulate replaceable instruments within the sheath.

This novel robotic system has memory capability. For example, during ureterorenoscopy, the sheath and instrumentation arrive at a specific position and configuration within the anatomy of the renal pelvis, say the difficult-to-access inferior calyx. The location and configuration of instruments can be noted and stored in the device’s memory. Additional locations, such as the middle calyx, superior pole calyx, etc., can be similarly recorded and stored. When the operator wishes to return to the initial position in the inferior calyx, the mere touch of a button restores the effector end to that position. The memory can be programmed to recall any number of positions and configurations of the robotic sheath and instruments.

An extension of this concept is the performance of intraluminal surgery via a single portal of entry. Permit us a metaphorical description. Imagine an operator with both wrists and forearms firmly taped and tied together with rope. He can move his hands, but that range of movement is limited because the hands are more or less parallel with each other. This situation is similar to what would be seen if two instruments were advanced into the anatomy through a single endoscope sheath. Performing actual surgical maneuvers such as retracting and cutting or sewing would be impossible, since an angle of at least 45-60 degrees is necessary to perform the maneuvers.

Flexible robotics can untie the rope and take the tape off. Flexible instruments advanced through a single sheath and remotely manipulated can bend to approach each other from angles of 45 degrees or greater because the distal section of instrumentation is flexible like a snake’s neck. One instrument can grasp and retract an object while the other, say scissors, can cut. A lumen can be completely explored with the sheath and instruments programmed to return automatically to anatomic landmarks of note. Conventional laparoscopic robotic instruments can grasp and manipulate whatever lies in their path. Flexible robotic instruments can reach around anatomic corners.

It is anticipated that full thickness intraluminal surgeries will be permitted within bladders and other hollow organs. The system is expected to find applications in bladder cancer and stone disease. Our initial animal studies in the porcine model have confirmed the feasibility of the flexible robotic approach for ureterorenoscopy, and clinical trials are under way. The results of these initial clinical trials are expected by year end.

The full range of applications of this novel robotic system has yet to be determined. However, it is anticipated that this technology and its flexibility will allow development of an entire new field: intraluminal and transluminal surgery.

And a final observation as to the speed with which this technology is advancing. The first robots were introduced to practical urologic applications less than 6 years ago. They are no longer advanced technology. We now refer to them as “standard.” And we consider this speed of development “slow.”
Robotic Female Pelvic Reconstruction Surgery Allows Preservation of Uterus and Minimally Invasive Treatment of Complex Pelvic Organ Disorders

Firouz Daneshgari, M.D., F.A.C.S.

Pelvic organ prolapse (POP) often involves a combination of support defects involving the anterior, posterior and/or apical vaginal segments. While the anterior vaginal wall is the segment most likely to demonstrate recurrent prolapse after reconstructive surgery, reoperations are highest among those who require apical suspension procedures with or without repair of other vaginal segments (12%-33%).

New advancements in robotic and laparoscopic surgery have made it possible for the surgeon to use robotic assistance in reconstruction and repair of POP.

Taking advantage of existing expertise in female pelvic reconstructive surgery and robotic procedures, the Glickman Urological Institute recently has performed robotic procedures for abdominal sacrocolpopexy (RASC) and anterior and posterior vaginal prolapse (cystocele and rectocele). RASC is indicated for treatment of women with stage III or IV POP. Use of robotic repair allows for a wider range of freedom in preserving the woman’s uterus and other organs, yet providing an equally efficacious management of the pelvic organ prolapse.

Review of 3 months follow-up results in 12 women who underwent RASC with or without uteropexy demonstrates that comparable results to that of open ASC could be obtained with RASC. The mean of the point C (vaginal vault) and point Ba (dependent portion of anterior vaginal wall) in the POP-Q scale improved from a mean of -1 cm from the hymen ring preoperatively to -8 cm; and from +1 to -5 at 3 months postoperatively, respectively.

The technique of robotic ASC is similar to that of laparoscopic and open ASC. The patient is placed in the lithotomy position to provide access to both the abdomen and vagina. Three robotic and 2 standard laparoscopic ports are placed transperitoneally (Figure 1). Exposure to the pelvis is accomplished using Trendelenberg positioning and a laparoscopic retractor to reflect the colon to the left. Incision of the posterior peritoneum is begun at the level of the sacral promontory and continued distally to the cul-de-sac. The posterior vaginal wall is incised to the level of the vaginal cuff. In a sacrocolpouteropexy, the incision is carried to the level of the cervix. Two 3 X 15 cm pieces of polypropylene mesh are sutured to the vaginal vault- one anterior and one

Figure 1: Positions of the ports for RASC.

Figure 2: The soft polypropylene mesh connects the apex of the vagina to the sacrum promontory and then is positioned in retroperitoneal space.

Figure 3: After completion of abdominal sacrocolpopexy, the entire vaginal cuff is suspended in the normal anatomical position.
posterior, making a cup support of the prolapsed vault. In a sacrocolpouteropexy, only one mesh is sutured to the exposed portion of the cervix at two proximal and two distal sites. The single mesh in the sacrocolpouteropexy and both meshes in the sacrocolpopexy are then sutured to the anterior spinous ligament (Figure 2). Non-absorbable sutures are used for suspension sutures. The peritoneum is closed using running or interrupted absorbable sutures (Figure 3).

Further advantage of RASC can be expected in light of results of a recent NIH-sponsored trail in women with advanced POP. CARE trial demonstrated that women who had Burch colposuspension (BCS) in addition to their abdominal sacrocolpopexy benefited by having a 50% lesser chance of postoperative symptoms or signs of stress urinary incontinence in comparison with those who did not have BCS. Robotic repair of POP would easily allow the surgeon to perform BCS in conjunction with ASC.

Laparoscopic Radical Cystectomy: Optimizing Outcomes, Maintaining Surgical Integrity

Jihad H. Kaouk, M.D., Steven C. Campbell, M.D., Ph.D., Amr Fergany, M.D., Craig D. Zippe, M.D., Inderbir Gill, M.D.

In the surgically fit patient, the standard treatment of invasive, organ-confined bladder cancer is radical cystectomy with urinary diversion performed through a 15-18 cm midline incision. This procedure has been associated with a 2% perioperative mortality rate and represents a major metabolic insult – the average cystectomy patient loses 10-20 pounds before turning the corner toward full recovery. Radical cystectomy also can affect sexual function, and recovery of urinary continence with a neobladder is not always complete, particularly at night.

In an effort to minimize the stress and morbidity of radical cystectomy, we have introduced laparoscopic techniques, now having performed 63 such procedures over the past 5-6 years. The potential advantages of this approach are the following: a) reduced blood loss during the cystectomy, as a result of the tamponade effect of the pneumoperitoneum and enhanced visualization; b) the ability to perform precise nerve sparing due to magnified visualization of the posterolateral anatomy; c) precise apical dissection, thus preserving length of the urethral stump and the external sphincter, resulting in improved continence; d) minimal manipulation of the bowel, thus reducing ileus and bowel distension; and e) decreased surgical morbidity due to the smaller incisions that are required.

Our early experience (n = 17) demonstrated that a pure laparoscopic approach was not acceptable, as we observed prolonged operative times and occasional diversion-related complications (bowel obstruction and anastomotic leak) that were prohibitive. Hence a “laparoscopic-assisted” technique was developed (n = 46) in which a small (6-8 cm) midline incision is used to extract the specimen and create the urinary diversion at or near skin level. The neobladder is then dropped back into the pelvis, the incision is closed, and the anastomosis to the urethra is performed laparoscopically, allowing for precise suture placement and a watertight anastomosis. The laparoscopic-assisted procedure has reduced operative times by almost 3 hours, and major complications are now uncommon and on par with traditional open surgery. The mean operative time is 6.3 hours, mean blood loss is 378 cc, and only 3% of patients have required a transfusion, although all of these parameters are improving with further experience. Perioperative narcotic requirements are reduced, and ileus is less common than previously observed. Assessment of other quality-of-life parameters is ongoing.

Positive surgical margins have been observed in only one case, and lymph node yields are similar to those obtained with open surgery as the principles for wide dissection during anterior exenteration have been replicated and the templates for pelvic lymph node dissection extending back to the aortic bifurcation have been maintained. On occasion the cephalad limit of the template can be extended during the open part of the case, but typically this is not required. Oncologic follow-up to date is encouraging but not yet mature.

More recently, 8 of these procedures have been performed robotically, taking advantage of the 3-D visualization and the wristed instruments, which allow complex reconstructive suturing maneuvers to be performed, even at difficult angles deep within the pelvis. Results in this subset of patients have been encouraging, and the robotic approach is now being fully integrated into this program. With this initiative we are benefiting from our extensive experience with robotic procedures (more than 300 in the last 3-4 years), such as robotic prostatectomy, robotic pyeloplasty and robotic sacrocolpopexy. Robotic technology also may eventually facilitate a pure laparoscopic approach to radical cystectomy and urinary diversion, allowing us to come full circle in this field, thereby driving surgical morbidity to a minimum.
Laparoscopic partial nephrectomy (LPN) has been developed recently as a minimally invasive form of nephron-sparing surgery, incorporating the fundamental principles of open partial nephrectomy (OPN). While LPN currently is being offered at an increasing number of centers, few have achieved sufficient experience to permit comparison of a large number of patients undergoing LPN and OPN. We recently compared the outcomes of LPN and OPN performed at the Cleveland Clinic Glickman Urological Institute in 1,049 patients with a single, clinical T1 (≤ 7 cm) renal tumor. The focus of this retrospective study was on perioperative and early renal functional outcomes with the two techniques.

OPN was performed in 595 patients, and LPN was performed in 454 patients. Patients undergoing OPN were a higher risk group as defined by a greater percentage presenting symptomatically with reduced performance status, impaired renal function and tumor in a solitary kidney (P< 0.0001). More tumors in the OPN group were >4 cm and centrally located (P< 0.0001), and more proved to be malignant (84% vs. 73%, P=0.0003).

Based on multivariable analysis, LPN was associated with shorter operative time (206 vs. 266 minutes, P<0.0001) and shorter hospital stay (3.3 vs. 6.1 days, P<0.0001). However, LPN also was associated with longer warm ischemia time (32 vs. 20 minutes, P<0.0001) and more postoperative renal/urologic complications (11.2% vs. 5.9%, P=0.006), particularly postoperative hemorrhage (5.7% vs. 2.0%, P=0.001). More patients in the LPN group required a subsequent procedure compared with the OPN group (7.9% vs. 3.2%, P<0.001). The odds of a postoperative renal/urologic complication, hemorrhage or a subsequent procedure were 2.17, 3.66 and 4.05 times higher after LPN compared to OPN, respectively.

Renal functional outcomes were similar 3 months after LPN and OPN, with 97.9% and 99.6% of renal units retaining function. Loss of function in the operated kidney occurred in 9 patients from the LPN group (2.0%) and 1 patient from the OPN group (0.2%), which was not statistically significant. Three-year cancer-specific survival for patients with a single cT1NoMo renal cell carcinoma was 99.3% and 99.2% after LPN and OPN, respectively; however, the median follow-up interval was only 1.4 years for patients in the LPN group.

We conclude from these data that LPN can achieve early renal functional outcome comparable to OPN when applied to select patients with a single renal tumor ≤7 cm in size. LPN offers the advantages of shorter operative time, reduced hospital stay and more rapid convalescence. However, LPN is associated with longer intraoperative ischemia time, more postoperative renal/urologic complications (particularly hemorrhage) and more frequent need for a subsequent procedure. Open partial nephrectomy remains the preferred approach for more complicated tumors such as those which are larger, hilar/intrarenal in location and multicentric.
Histopathological Follow-Up after Percutaneous Renal Radiofrequency Ablation

Jihad H. Kaouk, M.D., and Andrew C. Novick, M.D.

The diagnosis of renal masses is often made incidentally due to the widespread availability of advanced abdominal imaging. Inherent with incidental diagnosis is earlier detection of small masses that are amenable to partial nephrectomy. However, not all patients are candidates for traditional nephron-sparing techniques due to comorbid conditions. Percutaneous radiofrequency ablation (RFA) is a treatment option for such patients with high anesthetic risk, multiple abdominal surgeries or numerous renal tumors.

Traditionally, success after ablative therapies depends on the lack of follow-up radiographic enhancement of the ablated lesion. However, our data revealed positive biopsy for renal cell carcinoma (RCC) in 6 patients who had no enhancement on CT or MRI at 6 months follow-up. As such, viable residual RCC can indeed reside in an area that does not enhance radiographically.

Even with negative findings on stringent MRI follow-up, a sizeable number of patients will be found to have viable tumor 6 months after RFA for small renal tumors. In view of these results, we have broadened our indications for biopsy and recommend routine biopsy of all patients at 6 months. We recommend that RFA continue to be restricted to highly selected patients and be performed in the setting of an IRB-approved treatment protocol.

At the Glickman Urological Institute, we perform probe ablative treatments including percutaneous RFA and percutaneous cryoablation for select patients with small renal tumors. Since ablated tumors are not excised, stringent radiological follow-up is required to assess treatment success. We also perform percutaneous biopsy of the ablated tumor at 6-month follow-up to obtain histopathological confirmation of complete tumor ablation.

Between April 2002 and April 2006, we performed 114 RFAs in 92 patients for small renal tumors. Patients were followed with MRI on post-op day 1 and at 3, 6 and 12 months and subsequent annual follow-up. Biopsy was scheduled at 6 months in selected cases, excluding patients with anticoagulation and remnant kidneys. Follow-up of 6 months or more post-RFA is available in 82 patients. Of these patients, 8 have been retreated for persistent or recurrent tumor (9.8%). A stable area of non-specific enhancement is under surveillance in 3 patients, with no enhancement in the remaining 71 patients. Follow-up biopsy at 6 months was performed in 38 patients, and 6 of these have been found to have viable tumor on histology.

An important aspect of evolving technology is the continuing refinement of this technology. We are investigating the feasibility of a real-time ultrasound synchronized with 3-D CT scan navigation for more accurate placement of ablation probes percutaneously. We also are comparing different RFA probes to investigate whether residual tumor could result from inadequate RFA energy or different configuration of available RFA probes. Based on our excellent results with laparoscopic cryoablation providing overall 5-year survival of 81% and 5-year cancer-specific survival of 98%, we are comparing percutaneous RFA to percutaneous cryoablation and investigating whether, by using the percutaneous approach, we can duplicate success rate similar to the laparoscopic approach.
Novel Treatments for Renal Cell Carcinoma Continue to Show Promise

Brian I. Rini, M.D.

Renal cell carcinoma (RCC) that has spread to distant organs (metastatic) is an aggressive disease that is associated with a high mortality rate and for which treatment options have historically been limited. However, basic science research has elucidated underlying molecular mechanisms in the pathogenesis of RCC and led to identification of new therapeutic targets. Novel treatment modalities are now demonstrating a positive impact on disease outcomes. The Glickman Urological Institute and Cleveland Clinic Taussig Cancer Center have been active participants in many studies investigating the efficacy and safety of these new agents.

Sunitinib malate (Sutent) is a multitargeted tyrosine kinase inhibitor that blocks receptors for the blood vessel-promoting proteins vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). VEGF and PDGF were identified as therapeutic targets for RCC based on genetic research identifying an association with alterations in the von Hippel Lindau (VHL) gene and demonstrating that loss of VHL function resulted in increased expression of VEGF and PDGF.

In January, the FDA granted approval of sunitinib malate for the treatment of advanced RCC based on data from two studies demonstrating its efficacy as second-line therapy in patients who had failed available treatment for metastatic RCC. We participated in those trials and also in a phase 3 study evaluating sunitinib as first-line treatment for metastatic RCC. Positive results from that trial were reported in June at the 42nd annual meeting of the American Society of Clinical Oncologists (ASCO).

The Phase 3 study of sunitinib as first-line treatment for metastatic RCC randomized 750 patients to oral sunitinib (50 mg daily for 4 weeks on and 2 weeks off) or 9 MU interferon-alpha injected subcutaneously three times per week. The study was designed to investigate whether sunitinib treatment could improve median progression-free survival (PFS) by at least 35%. The results showed the primary endpoint was achieved with the median PFS for patients treated with sunitinib being almost twofold longer than in the interferon-alpha group, 47.3 weeks vs. 24.9 weeks, respectively. There also was a statistically significant difference favoring sunitinib over interferon-alpha in the objective response rate, 31% vs. 6%.

We also have been participants in the phase 3 study evaluating temsirolimus (Torisel) as first-line treatment for RCC patients with aggressive disease features. Temsirolimus acts as an inhibitor of the mammalian target of rapamycin (mTOR) kinase, a signaling protein that is overexpressed in cancer cells and that regulates multiple pathways involved in tumor development and progression, including cell cycle progression, cell proliferation and angiogenesis.

The phase 3 study randomized 626 previously untreated patients to temsirolimus 25 mg IV weekly, temsirolimus 15 mg IV weekly plus interferon-alfa 6 MU three times a week, or interferon-alfa at a dose escalated from 3 MU to 18 MU three times per week. Results from that trial reported at ASCO showed statistically significant benefits of temsirolimus monotherapy for increasing median overall survival compared with interferon-alpha, 10.9 vs. 7.3 months, respectively. Median PFS data also showed a significant benefit of temsirolimus 25 mg compared with interferon-alfa, 3.7 vs. 1.9 months. The objective response rate was slightly higher among patients treated with temsirolimus monotherapy compared with interferon, 9% vs. 7%, but the difference did not achieve statistical significance.

At Cleveland Clinic, we have led a phase 2 study investigating the use of sunitinib in patients who were refractory to the VEGF binding agent bevacizumab (Avastin). Data we presented at the ASCO meeting demonstrated sunitinib continued to show anti-tumor activity despite the fact that all patients had failed prior bevacizumab. The study enrolled 60 patients with metastatic RCC who demonstrated Response Evaluation Criteria in Solid Tumors (RECIST)-defined disease progression within 3 months after bevacizumab-based therapy. Sunitinib 50 mg was administered daily for 4 weeks of a 6-week cycle to 60 patients. Thirty-two patients had sufficient follow-up to be evaluable for response, of whom 26 (81%) demonstrated some degree of tumor shrinkage and four (13%) demonstrated an objective partial response. These outcomes in bevacizumab-refractory patients suggest that therapies targeting VEGF are not all the same and that strategies blocking the effect of VEGF via alternate pathways may still be efficacious when another option has failed.

Cleveland Clinic is leading the way in developing these therapies further, which includes several clinical trials of combination therapy, application of these therapies in earlier stages of disease, and research into the molecular biology of response and resistance to these agents.
Kidney

New Imaging Techniques for Percutaneous Treatment of Kidney Tumors

Jihad H. Kaouk, M.D., Usamu Ukimura, M.D., Inderbir S. Gill, M.D., and Andrew C. Novick, M.D.

Management of small localized renal tumors has evolved from radical nephrectomy toward nephron-sparing surgery during the past decade. Probe ablative therapies include cryoablation and radiofrequency ablation (RFA). The percutaneous approach allows ablative techniques to be performed under intravenous sedation with needle-size skin incisions and minimal postoperative pain. This is particularly attractive for treatment of poor surgical risk patients due to significant medical comorbidities or advanced age. In addition, the percutaneous approach can be useful for management of patients with prior kidney surgery or other unfavorable anatomical conditions. Percutaneous ablation is performed as a same-day procedure, and patients can resume regular activities within a few days.

To perform successful ablation, the cryoablation or RFA probe must be precisely placed into the tumor. Accurate percutaneous placement of RFA or cryoablation probes can be deployed under ultrasound, CT or MRI guidance. Ultrasound provides real-time imaging. However, image resolution is low, and interference from adjacent structures such as ribs can be problematic. CT scan provides excellent image quality. However, sequential CT scans should be done to confirm repositioning of probes with increased radiation. Open abdominal MRI is not widely available, and needle visualization may be challenging.

Real-time virtual sonography (RVS) (Hitachi Medical Corporation) is a novel fusion system of intraoperative real-time ultrasound (US) and pre-operative CT/MRI. At the Glickman Urological Institute, we assessed the feasibility of the RVS-assisted ultrasound-guided needle placement during percutaneous RFA of renal tumor.

Since February 2005, we used the RVS system for percutaneous needle placement into the renal tumor (mean 35 mm) in 11 consecutive patients who underwent RFA under local anesthesia. Preoperative CT or MRI of the kidney was stored in digital format then transferred into the RVS computer software. The RVS system displayed the real-time US image along with the synchronized CT/MRI image that correlated with the imaged area seen on US. The accuracy of needle placement and radiation needed for CT images were studied.

Preoperative CT or MRI were successfully reconstructed and displayed in synchrony with real-time US images in all but one patient (91%) who had significant obesity resulting in a poor US image and inaccurate kidney tumor localization. By synchronized demonstration of reconstructed preoperative CT/MRI, RVS compensated for conventional ultrasound limitations. Moreover, estimated radiation exposure was significantly reduced in patients with RVS-assisted guidance (208 mGy) compared with CT guidance alone (562 mGy) (p=0.01). In the entire series, no major complications occurred by the additional use of RVS for needle guidance.
Th-1 Suppression in Kidney Cancer Patients

J. Finke, Ph.D., W. Storkus, Ph.D., A. Richmond, B.I. Rini, M.D., R. Suppiah, M.D., P. Rayman, P. Elson, Sc.D., and R. Bukowski, M.D.

Once metastasized, renal cell carcinoma has proven to be unresponsive to chemotherapy and radiotherapy. Although metastatic RCC (mRCC) is sensitive to immunotherapy involving interferon-alpha (IFN-α) and interleukin-2 (IL-2), clinical responses are infrequent (10-15%), and most patients fail to derive long-term benefit. Recently, a paradigm shift has occurred in the treatment of mRCC with the demonstration that small molecule inhibitors and antibodies that antagonize vascular endothelial growth factor (VEGF) signaling significantly increased the frequency and duration of clinical responses. To further improve the outcome for RCC patients, future therapies will likely include combining these VEGF antagonists with strategies that promote anti-tumor immune responses. Thus, understanding how the tumor microenvironment can hinder the development of effective T cell immunity to RCC remains an important issue.

A critical event in the development of an immune response to tumors is the activation of Th-1 (Type-1) CD4+ helper T cells, which in many animal models are necessary for tumor rejection. Th-1 cells secrete IFN-γ that promotes cellular immunity, in part by providing helper signals for cytotoxic CD8+ T lymphocytes. In contrast, Th-2 cells secrete IL-4 and IL-5, which, although important for an antibody response, can dampen development of Th-1-type immunity.

Our collaborative studies with Walter Storkus, Ph.D., (University of Pittsburgh) using peripheral blood T cells from patients with active disease demonstrated an impaired Th-1 response to tumor-associated antigens (MAGE-6 and EphA2). An analysis of MAGE-6- and EphA2-specific CD4+ T cells revealed the predominance of a Th-2 response (IL-5) with few Th-1 CD4+ T cells producing IFN-γ. Interestingly, in patients where the tumor had been removed and there was no evidence of disease, the cytokine response was predominately Type-1 (IFN-γ), suggesting that the presence of tumor was responsible for the suppression of a Th-1 response in patients with active disease. These studies support our earlier work showing that within the tumor microenvironment infiltrating T cells also exhibit a predominantly Th-2 response.

One important question to address is whether therapy with the new inhibitors of VEGF signaling that have recently received FDA approval for the treatment of mRCC will further impair the ability of T lymphocytes to mount an anti-tumor immune response. Alternatively, blocking VEGF signaling may, in fact, promote T cell responses since VEGF has been shown to be immunosuppressive. We examined the Th-1/Th-2 response of CD4+ T cells from mRCC patients receiving the recently approved drug sunitinib malate (Sutent), a multitargeted tyrosine kinase inhibitor of VEGF and PDGF receptors that has demonstrated clinically meaningful responses in patients with mRCC and is well tolerated. Interestingly, our preliminary studies that examined the T cell response in mRCC patients (n=22) receiving sunitinib suggest that this drug can reverse the Th-1 suppression and simultaneously decrease the Th-2 type response that is observed in this patient population. Moreover, tumor shrinkage was associated with the proportion of IFN-γ producing T cells at day 28 (p=0.02). Additional findings suggest that sunitinib may also decrease T-regulatory cells that are known to be one of the mechanisms responsible for the suppression of tumor immunity in cancer patients.

Follow-up studies are needed to define the impact that sunitinib and other tyrosine kinase inhibitors have on restoring T cell responsiveness in RCC patients and to explore the mechanism by which this occurs. These findings could have implications for furthering the clinical benefit of such therapies in RCC and other tumors.
Prevalence data suggest that up to half of U.S. women will experience female pelvic floor disorders (FPFD), such as urinary incontinence (UI); pelvic organ prolapse (POP), including uterine and rectal prolapse fecal incontinence (FI); and associated problems and that risk factors for FPFD include aging, vaginal childbirth, obesity and diabetes mellitus. Data also show FPFD entail substantial and cumulative economic costs as well as negative effects on quality of life. The continuing rise in the age-related incidence of obesity and diabetes, together with a demographically aging U.S. population, are factors that lead us to predict a dramatic increase in FPFD in coming decades. However, despite the prevalence of FPFD, little is known about its pathophysiology; nor do we understand why they often coexist and how they are related—almost predictably—to aging, childbirth, diabetes and other conditions.

The investigators at the Cleveland Clinic Center for Female Pelvic Medicine & Reconstructive Surgery (FPM&RS) have been developing several animal models to study various aspects of FPFD. These investigators have created and studied the following models:

1. **Vaginal Birth Trauma Model.** Margot Damaser, Ph.D., has created and extensively studied the mechanisms of vaginal birth trauma and urinary incontinence in a rat model. This model uses two types of injury that are thought to occur during vaginal birth in women: a) pudendal nerve injury; and b) vaginal distension with plausible ischemic and neuropathic injury.

   Collaboration with Drs. Raymond Rackley (urology), Lynn Woo (urology), Adonis Hijaz (urology at Case Western Reserve University), and Marc Penn (molecular cardiology), has enabled us to investigate recruitment of innate stem cells in response to vaginal distension. This could assist in development of novel treatments. Dr. Damaser also recently began investigation of a combination injury in which an animal undergoes both pudendal nerve injury and vaginal distension. It is believed that this will better mimic the pelvic injuries a woman experiences during vaginal childbirth. Dr. Damaser has hypothesized that injury to the urethra during vaginal distension slows and impedes the normal nerve regenerative response to pudendal nerve injury, a mechanism mediated by neurotrophic factors such as brain derived neurotrophic factor (BDNF). This work has been supported by recently renewed grants from the NIH and the U.S. Department of Veterans Affairs.

2. **Vaginal Sling Model.** Investigators at Cleveland Clinic, supported by a grant from NIH-NIDDK, have developed a model in which the steps of the vaginal sling in a rat with stress incontinence are reproduced. This model aims to study the mechanisms underlying complications seen in the clinical sling procedure, as well as the means through which such complications could be avoided. The goal is to discover procedures that might mitigate or reduce morbidity associated with the surgical treatment of urinary incontinence.

3. **Pelvic Organ Prolapse Model.** In collaboration with Dr. Tiansen Li of Harvard University, Drs. Damaser and Firouz Daneshgari are working on a model in which the role of elastin homeostasis on FPFD is investigated. This work is based on the previous ascertainment of the role of lysyl oxidase-like1 (LOXL1) in elastic fiber remodeling in reproductive organs in mice. The female reproductive organs and pelvic floor are rich in elastic fibers and undergo massive remodeling during pregnancy and childbirth. LOXL1 deficiency in mice results in profound FPFD-like manifestations, including POP and abnormal lower urinary tract function following pregnancy and vaginal delivery of pups. Accordingly, this model would potentially allow one of the first genetic models for studies of FPFD.

4. **Neurogenic Bladder Models.** These investigators have been working on two models of neurogenic bladder. In one, the remodeling of the bladder caused by diabetes is studied. Based on previous discovery of time-dependent changes in the bladder under diabetic conditions, the investigators are in the process of creating a knockout mouse (MnSODlox/lox, SM-CreERT2 mice) in which a late decompensation seen in models such as advanced diabetes or bladder outlet

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*continued*
obstruction is reproduced. In this model, superoxide dismutase (SOD) in smooth muscle of adult mice is depleted. This model is among those studied by the NIH-sponsored Animal Models of Diabetic Complications Consortium.

The second model of neurogenic bladder is the mice model of multiple sclerosis. In mice with experimental allergic encephalopathy (EAE), in vivo manifestations of various neurogenic conditions such as detrusor overactivity, detrusor sphincteric dysynergia and atonic bladder are observed. Further characterization of this model would allow us to expand our knowledge of prevalent conditions such as OAB and other neurogenically mediated pathologies of the bladder.

A major breakthrough in assessment of neurogenic bladder models occurred when the investigators here developed a device by which the function of the afferent autonomic innervation of the bladder can be assessed. This would allow understanding of the pathophysiology of common conditions affecting the bladder in both men and women.

5. Urinary Incontinence in Diabetic Female Model. Several reports indicate that among patients with DM, women appear to have a higher prevalence of lower urinary tract complications. Several studies suggest that vaginal delivery and DM are the most important risk factors for incontinence in women among the many risk factors that have been studied, including age, body mass index, number of vaginal deliveries, number of pregnancies, number of episiotomies, smoking, fecal impaction, high-impact physical activities, stroke, estrogen depletion, pelvic muscle weakness, childhood nocturnal enuresis and race. However, the mechanistic relationship of increased risk for incontinence among diabetic women is poorly understood. Drs. Daneshgari and Damaser have developed a model to study the joint mechanism of the relationship between DM and incontinence. The early work indicates that diabetes causes more severe incontinence, and it also delays recovery from vaginal birth trauma. The work on this model investigating Type I diabetes is currently supported by grants from the NIH. The Department of Veterans Affairs recently awarded a grant to enable investigation into the mechanisms of urinary incontinence in Type 2 diabetes using this model.
The Women’s Health Initiative, a 15-year research program focused on postmenopausal women, found that the rate of uterine prolapse was 14.2%, the rate of cystocele was 34.3%, and the rate of rectocele was 32.9%. By age 80, 11% of women will undergo surgery for prolapse or incontinence.

While many women are asymptomatic, many present with a fullness or discomfort in the vagina, a sensation of heaviness or a pulling in the pelvis, difficulty urinating or a visible bulge from the vagina. Difficulty with bowel movements may be seen with a rectocele. Laboratory testing or imaging are seldom needed.

Traditional procedures for cystocele and rectocele are usually successful but suffer a high degree of recurrence, perhaps 30% to 50% depending on the initial presentation and type of repair. It is suspected that the high failure rates are related to the strength of tissues involved. Sewing weak tissue to weak tissue does not bode well for permanent repair. The unacceptable recurrence rate associated with traditional methods has spawned a number of efforts to improve both initial and long-term results. During the past several years, Cleveland Clinic has been pioneering new techniques for prolapse repair, one of which draws from European experience to employ polypropylene mesh. The preconfigured mesh can be placed to support the pubo-cervical fascia of the bladder (central defect) and the torn arcus tendineae fascia pelvis (para-vaginal defect) to repair a cystocele. Another piece can be placed beneath the prerectal fascia and attached superiorly to treat a rectocele and apical prolapse. Cleveland Clinic has completed more than 50 repairs with excellent early results and anticipated good or better long-term results.

Moreover, the procedure is conducted transvaginally, which minimizes patient trauma and hospital stay. Patients are kept for observation overnight after the operation and are discharged in the morning.

The procedure is preceded by 6 weeks of vaginal hormonal cream application to thicken the walls of the vagina. The procedure begins with a vaginal wall incision, deeper than traditional incisions, going through the pubo-cervical fascia, which is left attached to the vaginal mucosa. Once the bladder is freed from beneath the pubo-cervical fascia, four trocars are passed from the inner thigh: two through the anterio-medial border of the obturator foramen directly under the pubis and two from the inner thigh through the obturator foramen to penetrate the pelvic sidewall just above the ischial spine.

The bladder-supporting mesh is placed, and four arms of the mesh are pulled through the inner thigh to stabilize and support the mesh. The procedure for correcting a rectocele is similar, though the mesh arms are brought through the sacrospinous ligaments. It should be noted that this procedure is applicable in women whether or not they have had a hysterectomy. When a uterus is present, the proximal portion of the mesh is sewn to the isthmus of the cervix, and the uterus is suspended. This allows the patient the option of preserving the uterus if she desires.

Experience to date with this procedure has found good success rates and low rates of mesh extrusion and/or dyspareunia. We have had a few patients with symptomatic mesh extrusion referred in for treatment. Simple local excision of the mesh appears to provide good results when this has occurred.

The progress being made with prolapse repair may be compared to the evolution of inguinal hernia surgery, which was initially repaired by suturing relevant tissue together but is now being increasingly repaired with synthetic mesh. Initial outcomes are promising, but it is still relatively early in the development of the procedure. It is anticipated that this new approach will lead to recurrence rates lower than those seen with traditional approaches to the presentations.
Complex Female Vaginal Reconstruction and Fistulæ

Sandip Vasavada, M.D., Raymond Rackley, M.D., Howard Goldman, M.D.

As urologists, we often participate in the surgical correction of genitourinary disorders in women. These disorders may range from the simple treatment of stress urinary incontinence or vaginal prolapse to complex fistulæ involving more than one pelvic organ. Because often one or more urologic structure is involved in the disease process, we need to be cognizant of surgical correction of these problems as many patients manifest difficulties in voiding. In the last decade or so we have seen major advancements in the areas of incontinence and prolapse surgery. Often, this has entailed the use of mesh and other supplementary materials that, while benefiting a great many, may have a negative side effect of an erosion or infection that, in simple cases, can be managed in the office, but in more complex require operative intervention. As a tertiary care referral center, we have managed many of these types of cases with increasing frequency as specialized techniques in vaginal reconstruction are often necessary to treat these patients.

The rates of vaginal mesh erosion from newer mesh-augmented prolapse repairs is approaching 8-12%. In some serious cases, we have had to remove the mesh and reconstruct the vagina with interposition of a fibrofatty labial fat pad graft (Martius flap) for lack of urinary system integrity. Other cases have been managed with simple removal followed by definitive prolapse repair either vaginally or as an open or laparoscopic abdominal sacrocolpopexy, either with mesh or with biological materials in select cases.

More commonly, perhaps, is the management of complications of the urethra. As recently noted by several case reports, a non-woven, non-knitted polypropylene mesh with pore sizes of 50u has had a high propensity to problems. Perhaps just as complex a situation has arisen when otherwise more favorable polypropylene meshes have been placed and either eroded into the urethral wall or bladder or were placed into a urethral diverticulum. These patients were then presented in urinary retention or had recurrent UTIs or hematuria. While it is beyond the scope of this article to describe all the management schemes possible for these types of erosions, we have had several cases that have been managed with endoscopic laser resection. But we tend to favor definitive removal transvaginally with concomitant urethral reconstruction with Martius flap interposition grafts as needed.

Iatrogenic urethrovaginal and vesicovaginal fistula can occur in the setting of other forms of pelvic floor reconstruction. Despite these being rare complications, they can occur and, more importantly, need to be recognized in order to correct them. Our most recent review of our experience with recurrent vesicovaginal fistulas has yielded a 94% success rate, even when managed transvaginally.

Cleveland Clinic Center for Female Pelvic and Reconstructive Surgery is Awarded Membership in the NIH Pelvic Floor Disorders Network

Pelvic Floor Disorders Network (PFDN) is a NIH-sponsored clinical trial network group devoted to conducting clinical studies on female pelvic floor disorders (FPFD). Funded originally in 2002, this network has completed several landmark studies on FPFD, including the recent study of abdominal sacrocolpopexy with Burch colposuspension to reduce urinary stress incontinence (CARE) trial. Matthew Barber, M.D., led the application for Cleveland Clinic to be one of the PFDN’s clinical sites. The application received a high-priority score, and funding subsequently was provided for participation in the PFDN activities.

The other investigators participating in the PFDN include Firouz Daneshgari, M.D., Marie F. Paraiso, M.D., Sandip Vasavada, M.D., and Mark Walters, M.D.

The Center for Female Pelvic Medicine and Reconstructive Surgery was established in 2001 due to the new collaborative work between the American Board of Obstetrics/Gynecology (ABOG) and the American Board of Urology (ABU). The mission of the center is to “enhance the clinical care of women with urinary incontinence, pelvic organ prolapse, fecal incontinence and other pelvic floor disorders (PFD) through interdisciplinary care, education, research, and innovation.”

In addition to a large clinical and surgical volume, the center provides one of the best fellowship training programs in female pelvic medicine and reconstructive surgery. Of the 23 fellowship programs jointly accredited by the ABOG and ABU, two are at Cleveland Clinic. Thus far, 14 fellows have graduated from these programs.

The center’s research efforts are currently supported by more than $2.3 million annually in external (federal and non-federal) funding in more than 27 independent projects.
Mesenchymal stem cells (MSCs) have gained much recent attention owing to their unique characteristics of developmental plasticity and potential therapeutic roles after tissue injury in multiple organ systems. Despite great interest and diverse applications, the molecular signals that regulate MSC trafficking and homing to injured tissues are not fully understood but may better serve as a therapeutic option for stem cell applications.

Vaginal delivery (VD) is a known risk factor for the development of stress urinary incontinence (SUI) in women. The concept of ischemic injury as a contributing factor to the development of stress urinary incontinence was first suggested by rat models of vaginal delivery, in which vaginal distension resulted in measurable dysfunction to the continence mechanism. Following VD, histologic studies also demonstrate extensive disruption and thinning of skeletal muscle associated with the external urethral sphincter. Decreased blood flow and hypoxic damage to the bladder, urethra and vagina were also observed after VD. Interestingly, dysfunction appears transient, suggesting a possible role of an innate reparative process. Based upon these observations, we have been interested in determining whether similar stem cell homing pathways are upregulated following vaginal distension and are responsible for the reparative process of pelvic organ tissue recovery and regeneration.

Chemoattractant cytokines function as “homing molecules” that signal mesenchymal stem cell (MSC) migration to sites of damage, thus promoting subsequent tissue repair. Given the focal hypoxia and tissue damage observed after VD, we hypothesize that the same cytokines are overexpressed after VD and may participate in the reparative pathways. Once fully characterized, this regenerative process could be supplemented to facilitate recovery after childbirth injuries. We have recently characterized the expression of cytokines in pelvic organ tissues after vaginal distension and characterized the time course of their expression.

MCP-3 was clearly significantly overexpressed in both urethral and vaginal tissues immediately following VD as compared to sham and control animals. MCP-3 levels were found to be decreasing yet still elevated from baseline 24 hours after VD. These findings are consistent with perfusion studies in urogenital organs during and after VD, which demonstrate significant decreases in blood flow to both urethra and vagina. The marked upregulation of MCP-3 in the urethra is of particular interest, as it suggests the initiation of an injury-repair pathway similar to that described after myocardial infarction. We also have demonstrated homing of green fluorescent-labeled stem cells to the site of the urethra following vaginal delivery, as well as the subsequent recovery of leak point pressure (see figure). Our study to date demonstrates significant overexpression of MCP-3 in a rat model of urethral and vaginal tissues immediately following vaginal distention with above-normal but decreasing expression 24 hours later. We are currently investigating the association between MCP-3 overexpression and the induction of targeted stem cell migration and tissue regeneration. The successful characterization and control of such a repair mechanism in the lower urinary tract would introduce the potential for novel, non-operative treatments and/or preventive measures for SUI and possibly other pelvic organ dysfunctions and prolapse.
Outcomes Analysis Supports Conservative Management of Prenatally Detected UPJO

Jonathan Ross, M.D.

The majority of cases of ureteropelvic junction obstruction (UPJO) identified on prenatal ultrasound are mild and have a favorable prognosis, but not all cases resolve spontaneously, and there continues to be significant controversy regarding approaches for postnatal evaluation and management.

At the Glickman Urological Institute, we have been following infants with UPJO-associated hydronephrosis using a conservative screening protocol that centers on the use of ultrasonography and aims to minimize performance of the more costly and invasive nuclear renography. In our approach, all children with moderate or severe hydronephrosis are evaluated initially with ultrasound, voiding cystourethrogram and renal flow scan. The renal flow scan is deferred in those with mild hydronephrosis. Patients with obstructive curves on the renal flow scan and decreased relative function (less than 40% of total renal function) are advised to have immediate pyeloplasty. All others are advised to enter the observation protocol. The infants are followed with ultrasound at 3-4 month intervals to monitor for improvement or worsening hydronephrosis. A renal flow scan is repeated selectively only in the latter situation or if there is not ultrasonic evidence of improvement by the time the child reaches 1 year of age.

To investigate the success of this approach, we recently reviewed outcomes for a consecutive series of 143 children. Fifty-five (39%) of the children had bilateral disease so that the total number of RUs analyzed was 198. The results demonstrate that our protocol offers a practical and safe method for managing infants with prenatally detected hydronephrosis.

In our series, more than half of the cases had an initial ultrasound grade of mild or mild-to-moderate (57%), but nearly one-fourth were categorized as moderate-to-marked or marked (24%). Surgery was performed as the initial approach in 20 RUs (10%), while the remaining 178 RUs were followed according to our observation algorithm. Follow-up for the latter children ranges from 1.5 months to almost 12 years (mean ~15 months). Hydronephrosis resolved spontaneously in almost half of the RUs, while another 40% continue to be under ultrasound surveillance and are demonstrating stable or improving hydronephrosis. Open dismembered pyeloplasty was performed in 10 RUs (5.6%), most often because of worsening appearance on ultrasound or function on renal flow scan, and the postoperative outcome has been favorable in all of those cases with improvement in hydronephrosis and/or washout on diuretic renal scintigraphy. No patient suffered irreversible loss of renal function.

Although pyeloplasty may be performed safely in infants when indicated, our experience supports the concept that the vast majority of children with prenatally detected UPJO can be successfully managed in a conservative fashion. Our selective use of renal flow scans has been important for both influencing parental decisions to choose observation versus early surgery and for optimizing their compliance with scheduled follow-up visits, which is essential for assuring a good outcome. However, while ultrasound studies are well-tolerated by patients and parents, careful comparison of serial ultrasound images is critical to avoid significant undetected renal injury. When these criteria are met, patients with prenatally detected hydronephrosis may be safely managed with a protocol that relies primarily on serial ultrasonography with limited exposure to renal scintigraphy.

Case: A male infant presented with prenatally diagnosed bilateral hydronephrosis. An ultrasound in the first weeks of life confirmed bilateral hydronephrosis, greater on the right (Figures 1a and 1b). A VCUG was normal. A diuretic renal flow scan showed normal and equal function. The T1/2 of the washout curves was 22 minutes on the right and 5 minutes on the left. He was followed with periodic ultrasounds and no further renal scans. These were initially stable and then improved over time. His most recent study at 4 years of age shows just residual pyelectasis.
Augmented Anastomotic Repair for Urethral Reconstruction in Patients with Urethral Stricture

Robert Abouassaly, M.D., and Kenneth W. Angermeier, M.D.

Buccal mucosa has emerged as the material of choice for substitution urethroplasty. The characteristics that make buccal mucosa ideal for this purpose are its being accustomed to a wet environment, ability to be easily harvested, its resilience to infection and its robustness in terms of graft take. Traditionally, the approach for a short bulbous urethral stricture (1-2 cm) has been excision and primary anastomosis, whereas longer strictures have been managed with onlay graft or flap repair. Webster and colleagues have coined the phrase “augmented anastomotic urethroplasty” to describe a technique that combines the principles of excision and primary re-anastomosis with those of onlay grafting for long bulbous urethral strictures that contain a 1-2 cm area that is particularly dense with narrow caliber and associated spongiofibrosis. The premise behind this maneuver is that one excises the densest portion of the stricture. There are two benefits of doing this: it shortens the size of the urethrotomy defect and allows for use of a shorter buccal graft, and it results in improvement of the width of the urethral plate and the vascularity of the underlying corpus spongiosum. In theory, this would help optimize urethral caliber and graft take.

The urethra may be initially transected at the site of the dense portion of the stricture if it is located at the distal end as identified by a bougie. Initial transection also may be performed if the narrowest region is at the proximal end of the stricture, as long as its location can be ascertained by antegrade passage of a flexible cystoscope. The 1-2 cm segment is excised, and ventral or dorsal urethrotomy is then carried out through the extent of the remaining stricture at least 1 cm into healthy urethra. Alternatively, if the narrow segment is within the middle of the stricture, the procedure starts with a ventral or dorsal urethrotomy incision through the entire stricture. The severely narrowed 1-2 cm segment

Figure 1

Figure 1a
Augmented Anastomotic Repair  continued from page 33

is then excised. The excision is typically done full-thickness involving the urethral mucosa and the corpus spongiosum (Figure 1). However, if the underlying spongiosum is judged to be healthy, a partial thickness excision of urethral mucosa and associated mild-to-moderate underlying spongiosfibrosis can be used to avoid complete spongiosal transection and the resulting effect on urethral blood flow. For a ventral graft, the dorsal urethral plate is anastomosed in one layer in the midline with conversion to a two-layer closure as one proceeds laterally. The buccal mucosa graft is sutured in place (Figure 2), and the repair is completed by closing the corpus spongiosum over the top of the graft. When dorsal graft placement is selected, the buccal mucosa is spread and fixed onto the underlying tunica albuginea of the corporal bodies before ventral urethral anastomosis to aid exposure (Figure 3). Subsequently, the ventral urethra is re-approximated in two layers followed by closure of the lateral suture lines to complete the repair.

Between October 1997 and April 2005 we performed this procedure on 69 patients with an average age of 39 years. All patients had bulbous urethral strictures, with 7 (10%) having concomitant pendulous stricture. Mean stricture length measured on preoperative retrograde urethrogram was 4.2 cm (range 1-12 cm), requiring a mean buccal graft length of 5.5 cm (range 2-11 cm). In 58 patients (84%) the graft was placed ventrally and dorsally in 11 patients (16%). With a median follow-up of 34 months (range 13-103 months), 62 patients (90%) remained asymptomatic and had no evidence of stricture recurrence cystoscopically.

Of the 7 patients with evidence of restricturing, 6 had focal recurrences and 1 had evidence of diffuse restricturing at follow-up cystoscopy. Three of the patients with visible recurrence remained asymptomatic and have declined further treatment. Of the patients requiring postoperative intervention, 3 were successfully treated with single DVIU.

Based upon these data, we feel that the augmented anastomotic repair is an effective technique that allows use of a shorter buccal graft and may improve overall results due to improvement in the width of the urethral plate and vascularity of the corpus spongiosum. The additional suture line does not seem to be detrimental. We recommend its use in patients undergoing substitution urethroplasty for strictures that contain a particularly narrow or dense area of 1-2 cm in length.

Fig 1: Dorsal urethral anastomosis (arrow) following full thickness excision of narrow segment.
Fig 1a: Retrograde urethrogram demonstrates bulbous stricture with narrow distal segment (arrow).
Fig 2: Ventral buccal mucosa graft sutured into remaining urethrotomy defect.
Fig 3: Long bulbous urethral stricture following excision of narrow distal segment and placement of dorsal buccal mucosa graft (forceps hold remaining distal and proximal urethra).
Fig 3a: Forceps re-approximating urethra ventrally prior to urethral closure.
William A. Larchian, M.D.

Most bladder cancer patients present with low-grade, non-invasive tumors and are candidates for treatment with transurethral tumor resection and adjuvant intravesical immunotherapy. However, tumor recurrence is common, and a significant proportion of patients with recurrence are at risk for progression to invasive and potentially metastatic disease.

In 1997, we initiated a research program at the Glickman Urological Institute to develop immunogene therapy for bladder cancer. At present, that work has progressed to the point where it is ready for testing in a phase I clinical trial.

Our strategy is based on a cytotoxic gene therapy approach that aims to transfect the cancer cells with cytokine genes to increase local expression of those chemical mediators that will attract antigen-presenting cells to the tumor site and, ultimately, stimulate host production of tumor-specific killer T cells. Our method uses a lipoplex (plasma DNA/liposome complex) consisting of liposomes encapsulating the DNA of genes encoding for interleukin-2 (IL-2) and interleukin-12 (IL-12). The liposomes act as the vector and are able to specifically target and efficiently transfect the cancer cells with the genetic material.

The cationic liposomes and the cytokines that are being used for this immunogene therapy have an established record of safety for use in humans. Studies we have conducted so far using cultured animal bladder cell lines and in vivo animal models show that the lipoplex achieves 70% transfection efficiency and results in production of cytokine levels approximately 100-fold greater than those produced naturally by any cells in the body.

In our original studies, we used the lipoplex to transfect resected tumor cells ex vivo and then reinjected those cells as a “tumor vaccine.” Unfortunately, that approach was fraught with mechanical and physiological problems, and while it was effective in extending survival in an orthotopic murine bladder cancer model, it was not successful in achieving true cures.

Intravesical transfection of liposome/DNA complex. Uptake and production are seen up to nine cell layers deep.

Intravesical treatment of murine bladder with liposome/DNA complex.

Left: Normal bladder without uptake of β-gal marker following transfection.

Right: Bladder tumor with β-gal production after 48 hours transfection.

Continued
Bladder Cancer Immunogene Therapy continued from page 35

Subsequently, we began to investigate in situ treatment with a series of intravesical instillations to achieve targeted delivery of the lipoplex to the tumor. Testing in animal models with both localized bladder cancer and metastatic disease has demonstrated this approach is dramatically more efficient and more effective in stimulating the host immune response, and its use has been associated with a cure rate of approximately 70%. Not only was the treatment associated with elimination of pre-established tumors, but the animals achieving cure also were able to reject tumor rechallenge. Those outcomes are encouraging in suggesting this treatment has the potential to provide an anti-tumor vaccine with the potential to provide long-lasting or even lifelong tumor-specific immunologic memory. Current testing is focusing on establishing the efficiency of transfection into human cancer cell lines. Those studies performed with established laboratory cell lines and fresh cells derived from bladder cancer patients indicate that the transfection rate is about 40%. Although the reason for the relatively lower efficiency of gene transfer to these human tumor cells is unknown, we expect it should not significantly mitigate treatment efficacy because complete tumor cell transfection is not critical for eliciting the desired immune system response, and the tumor-specific killer T cells produced will recognize transfected and nontransfected tumor cells alike.

The phase I study will enroll patients with non-invasive bladder cancer that is refractory to standard intravesical therapy. Our hope is that the results will establish our gene therapy model as a new immunotherapy option able to reduce the morbidity and mortality associated with bladder cancer.

A Novel Approach to Treating Bladder Calculi and BPH

James C. Ulchaker, M.D., F.A.C.S., and Mihir Desai, M.D.

The patient who has a combination of both multiple bladder calculi and urinary outflow obstruction is difficult to treat. Many individuals advocate multiple procedures to both remove the stone burden and open the prostatic channel. At the Glickman Urological Institute we now perform both procedures at one operative setting using a novel combination technique.

First, a 24 F nephroscope is passed through the urethra into the bladder to remove many of the bladder calculi. This nephroscope allows excellent visualization as well as the ability to remove moderate stones intact. Grasping alligator forceps are passed through the working channel of the nephroscope, and pieces of stone that are able to be pulled into the scope and out the urethra safely are removed. Next, the larger stones are fragmented by passing the new LithoClast (EMS Corporation) device through the nephroscope using a similar technique as when performing a percutaneous nephrolithotomy. The holmium laser may still be used; however, we have found the LithoClast system to be both faster in operative time and to produce less superficial injury and subsequent bleeding to the bladder wall. Once the stone fragments are of a smaller size that will allow them to be pulled through the nephroscope, the alligator forceps are once again used. When all of the stone debris has been removed from the bladder, a GreenLight PVP is performed to vaporize the obstructing prostatic tissue.

The combination procedure has been performed on an outpatient basis with a Foley catheter in place overnight. Excellent short-term results have been noted with no significant complications to report.
The Continent Neo-Urachus: For Formation of a Continent Catheterizeable Channel to the Bladder or Neobladder

Many patients with neurogenic bladder dysfunction or other causes of lower urinary tract dysfunction may require the need for intermittent bladder catheterization through a continent access other than the native urethra. To this end, we have developed an innovative outpatient surgical technique for accomplishing this goal. The continent neo-urachus is formed simply by making a skin tube from an in situ abdominal skin flap over an 18 F catheter that extends from the umbilicus to the dome of the bladder. Prior to attachment of the skin tube to the bladder, the skin tube is placed through an opening between the braiding or crossing of the overlying rectus muscle fibers for formation of an external compressive continence mechanism (Figure 1). The abdominal skin is reapproximated and the 18 F catheter through the neo-stomal channel is left to heal for 6 weeks while providing bladder drainage to a leg bag. Following removal of the catheter, the patient begins intermittent catheterization on a regular basis. For patients with hair-bearing skin of the midline, epilation of the hair may be performed or, alternatively, a cadaver skin tube or a Biori flap tube of the bladder may be used instead of in situ skin tube described above.

Figure 1: (A) Isolation of the rectus muscle fibers prior to (B) braiding around the catheterizeable channel.

Figure 2: Cutaneous mobilization of the catheterizeable channel through a key-hole incision prior to muscle braiding as shown in Figure 1B.
The Continent Neo-Urachus: continued from page 37

The simple concept of braiding or crossing the rectus muscle for a continence mechanism may be extended to the revisions of non-orthotopic neobladders or diversion channels that have developed incontinent catheterizable stomas due to outlet resistance pressure that falls under the pressure of the neobladder or bladder filling pressure. By cutaneous mobilization of the catheterizable channel down to the level of the fascia, the underlying muscle may be mobilized enough for braiding around the stoma to provide enough external closure or outlet continence pressure (Figure 2). This simple technique obviates more invasive procedures that require peritoneal access.

International Registry Provides Database for 500 Laparoscopic Radical Cystectomies

Inderbir Gill, M.D., and Georges-Pascal Haber, M.D.

We have established an international registry of laparoscopic radical cystectomy wherein 15 international centers in the United States, Europe and Asia are collaborating. The goals of this group are to standardize surgical techniques across borders, standardize data collection instruments, establish critical care pathways, create a continuing long-term reservoir of oncologic and functional data and establish a collaborative network for future studies.

The effort has collected data on 500 laparoscopic radical cystectomies within one year. This comprises virtually the entire worldwide experience in the field. Every center that has done more than 10 such procedures from December 1999 though July 2005 is part of the registry.

The data collected to date for study and analysis are extensive and cover baseline characteristics, intraoperative parameters, postoperative parameters and follow-up. In the initial 200 patients, baseline data confirm these patients to be a high-risk group with 82 percent having significant comorbidities, 31 percent having ASA score ≥ 3, and 51 percent with prior surgery in the area of interest.

Laparoscopic radical cystoprostatectomy was performed in 65% of the patients and female anterior pelvic exenteration in 12%. Orthotopic neobladder was the most commonly performed diversion performed (54%), and 85% of the urinary diversions were performed extracorporeally through open assisted technique. Pelvic lymph node dissection was performed in 82% of patients. Mean blood loss was 550 cc. Mean operative time was 380 minutes. Oral intake and ambulation required 5 days, and convalescence was complete in a mean of 5 weeks.

Intraoperative complications developed in 5%; postoperative complications appeared in 26%; and delayed complications occurred in 8.5% of patients. Specific intraoperative complications included hemorrhage (1.5%) and viscus injury (3.5%). The overall open conversion rate was 2%, all of which were elective.

Postoperative complications included urologic complications in 9%, GI in 8.5% and other types in 21%. This profile is similar to what is seen in open radical cystectomy.

Final pathology included transitional cell carcinoma in 72% and squamous or Bilharzia cancer in 23%. Final pathologic stage was ≥ pT2 in 77% and ≥ Grade III in 82%. The median number of lymph nodes retrieved was 14. More than 10 lymph nodes were retrieved in 67%. Positive nodes were noted in 20%. Surgical margins positive for cancer occurred in 3%, of which 2% were focal and 1% were extensive. Concomitant CIS was seen in 13%.

There was no evidence of recurrence in 85% of the cohort over a median follow-up of 13 months. Local occurrence was seen in 10%, and systemic metastases appeared in 5%. Importantly, port site recurrence was not seen in any patient during this follow-up.

In conclusion, laparoscopic radical cystectomy is becoming more common, and recent complication rates and oncolgic outcomes are approaching those seen with open surgery. Long-term outcome data are pending. This international registry has been created to coordinate and evaluate advances in the field. The initial data set is being prepared for publication.
Interstitial Cystitis Research Reveals Defective NF-κB Signaling as the Cause and Susceptibility of Uroepithelial Apoptosis

Raymond Rackley, M.D.

Interstitial cystitis (IC) is a chronic, painful bladder disorder that affects approximately 1 million Americans whose curable treatment depends on establishing the etiology of this disease. While diverse in symptomatic presentations, the most consistent histological finding of the bladder is the loss or thinning of the bladder uroepithelial layers. These findings suggest that the clinical and pathological presentation of interstitial cystitis may be caused by an inhibition of bladder uroepithelial cell regeneration, proliferation and/or apoptosis with resulting loss of the normal urothelial barrier and functions that leads to the development of pain from underlying sensory nerve dysfunction. Whether or not urothelial cells undergo proliferative repair, survival or apoptosis following a bladder insult in IC patients appears to involve a balance between anti-apoptotic and apoptotic mechanisms regulated by the transcription factor NF-κB signaling activation.

We have identified transcription factor NF-κB activation in bladder biopsy material from IC patients and have further characterized an aberrant loss of sustained NF-κB signaling activation over time in cell cultures of IC urothelium in comparison to normal urothelial controls upon exposure to TNF-κ. Using an in situ apoptotic assay, exposure to TNF-κ produces a dysfunctional activation pattern in IC urothelial cells that leads to cellular apoptosis (red staining) when compared to normal controls (see figure). Furthermore, incubation of normal urothelial cells with conditioned media from IC cell cultures changes its NF-κB activation signaling into a phenotype observed for IC cell cultures when challenged with TNF-κ, suggesting that something may be produced by this dysfunctional signaling such as APF, a newly characterized biomarker of IC.

Aberrant NF-κB signaling activation may be responsible for the imbalance of apoptotic and survival mechanism of the bladder epithelium that gives rise to the pathogenesis of IC. Not only is the aberrant signaling of NF-κB a potential biomarker, but development of therapies to produce sustained functional NF-κB activation in the IC bladder urothelium may produce uroepithelial survival and subsequent remission of this disease. To this end, we are doing two things clinically in response to our basic science findings. First, we are asking all IC patients to avoid aspirin or aspirin-like products such as NSAIDs that block normal NF-κB signaling as many cases of IC may be iatrogenic results of using these classes of medications. Second, we are providing patients with off-labeled use of misoprostol given as oral and/or instillation therapy as a mean to provide rapid uroepithelium healing.
While we have some understanding of the female sexual response cycle, the field of female sexual dysfunction (FSD) still is in need of research and development. At Cleveland Clinic, we have started a Female Sexual Dysfunction Initiative, under the direction of Courtenay Moore, M.D., involving clinical and animal studies to further our knowledge of this common disorder.

FSD is a highly prevalent problem affecting 38% to 76% of women in the United States. Based on the National Health and Social Life Survey, sexual dysfunction was more prevalent in women (43%) than in men (31%). One third of women reported lack of sexual interest, and almost one-fourth of women did not experience orgasm. Twenty percent of women reported lubrication difficulties, and the same percentage found sex not pleasurable. Yet, unlike male sexual dysfunction, our knowledge and treatment of FSD are rudimentary. To date, there are no FDA-approved medications for the treatment of FSD.

Unlike male erectile dysfunction, FSD is more difficult to assess, diagnose and treat. One of the initial barriers in the field of FSD was the lack of consensus of the definition of FSD. In 1998, the American Foundation of Urologic Disease Consensus convened to create a classification system and common terminology. It was at this conference that FSD was divided into four disorders: sexual desire disorder, sexual arousal disorder, orgasmic disorder and sexual pain disorder. In 2000, the panel reconvened and changed the classification schema to add “causing personal distress” as a criterion of the diagnosis.

Heightened interest and research into FSD have brought new insight into the pathophysiology and potential therapies of FSD. FSD is a multifactorial disease, caused not only by physiologic factors but also by psychological, sociocultural and interpersonal factors (Figure 1).

Much of our research regarding FSD has focused on the physiology of the female sexual response cycle. Studies have shown that the female sexual response cycle is initiated by non-adrenergic/non-cholinergic neurotransmitters—mediated vascular and non-vascular smooth muscle relaxation, resulting in increased pelvic blood flow, vaginal lubrication and clitoral and labial engorgement. While the exact neurotransmitters involved remain unknown, studies of human clitoral and vaginal tissue suggest that vasoactive peptide, nitric oxide (NO), acetylcholine, prostaglandin E, substance P and neuropeptide Y are involved in the normal female sexual response cycle.

Another factor involved in normal female sexual functioning is hormonal status. Three sex hormones have been implicated in normal female sexual behavior: estradiol, progestins and testosterone. Estrogen is involved in the synthesis of vaginal and clitoral NO and provides vasoprotective and vasodilatory effects to the pelvic arteries. Androgens and progestins are involved in psychological well-being, affecting libido and sexual desire.

Figure 1
Proving the Value of Varicocelectomy as a Successful Treatment for Male Subfertility

Ashok Agarwal, Ph.D., H.C.L.D., and Anthony J. Thomas, Jr., M.D.

Varicoceles are recognized as a leading cause of male infertility. Although varicocelectomy can successfully treat the anatomic abnormality, whether it improves semen parameters or pregnancy outcomes is still debatable.

In this report, we present a meta-analysis that was performed to determine the efficacy of varicocelectomy on improving male fertility potential. What makes this analysis unique is the new scoring system that we used to quantify bias. We “blinded” the reviewers during the evaluation process and developed a scoring system to quantify bias that was used to evaluate the literature on infertile men who had surgical correction of varicoceles. In addition, we included scores from both prospective randomized controlled trials (RCTs) and observational studies. Several

Continued

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Test for heterogeneity: $\chi^2 = 320.71$, df = 9 (P<0.00001), $I^2 = 97.2%$
Test for overall effect: $Z = 8.02$ (P < 0.00001)

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Test for heterogeneity: $\chi^2 = 2327.48$, df = 9 (P<0.00001), $I^2 = 99.6%$
Test for overall effect: $Z = 3.87$ (P < 0.0001)
B. Study  N  Pre-varicocelectomy Mean (SD)  N  Post-varicocelectomy Mean (SD)  WMD (random) 95% CI  WMD (random) 95% CI
Barballas 1998 22 36.60 (18.00) 22 49.20 (24.10) 12.60 [0.03, 25.17]  
Cayan 2000 236 25.60 (1.16) 236 43.47 (1.55) 17.87 [17.62, 18.12]  
Dhabuwala 1992 38 24.90 (1.80) 38 30.90 (1.80) 6.00 [5.19, 6.81]  
Grasso 2000 34 22.06 (2.83) 34 22.99 (2.70) 0.93 [-0.38, 2.24]  
Hsieh 2003 96 31.86 (18.64) 96 47.62 (21.03) 15.76 [10.14, 21.38]  
Khan 2003 15 23.60 (6.10) 15 39.20 (7.60) 15.60 [10.67, 20.53]  
Sayfan 1992 55 71.00 (51.00) 55 88.00 (54.00) 17.00 [-2.63, 36.63]  
Total (95% CI) 496 496 11.72 [4.33, 19.12]  
Test for heterogeneity: $\chi^2 = 1302.57$, df = 6 (P < 0.00001), $I^2 = 99.5\%$  
Test for overall effect: $Z = 3.11$ (P = 0.002)
CI: [4.90, 14.95], P = 0.0001) (Figure 1B) following surgery. Similarly, sperm concentration increased by 12.03 X 10⁶/mL (95% CI: [5.71, 18.35], P = 0.0002) (Figure 2A) and motility increased by 11.72% (95% CI: [4.33, 19.12], P = 0.002) (Figure 2B) after high ligation. The change in sperm morphology (3.16%) was statistically significant (95% CI: [0.72, 5.60]; P = 0.01) (Figure 3A). The odds of spontaneous pregnancy after surgical varicocelectomy, as compared to no treatment/medical treatment for clinical varicocele, were significantly different at 2.87 (95% CI: [1.33, 6.20], P = 0.007) (Figure 3B) using a random effects model or 2.63 (95% CI: [1.60, 4.33], P = 0.0001) with a fixed effects model.

Contrary to previous meta-analyses (Nieschlag et al, 1998; Evers et al, 2003), our study suggests that varicocelectomy does indeed have beneficial effects on fertility. Surgery appears to improve semen parameters (count, motility and morphology) in infertile males with palpable varicoceles as well as the spontaneous pregnancy outcomes in their female partners.

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<td>0.77, 13.69</td>
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<tr>
<td>Grasso 2000</td>
<td>34</td>
<td>30.06</td>
<td>3.01</td>
<td>34</td>
<td>28.97</td>
<td>2.99</td>
<td>-1.09</td>
<td>-2.52, 0.34</td>
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<tr>
<td>Hsieh 2003</td>
<td>96</td>
<td>62.30</td>
<td>16.17</td>
<td>96</td>
<td>64.68</td>
<td>16.91</td>
<td>2.38</td>
<td>-2.30, 7.06</td>
</tr>
<tr>
<td>Zini 1999</td>
<td>30</td>
<td>46.40</td>
<td>14.70</td>
<td>30</td>
<td>54.40</td>
<td>11.00</td>
<td>8.00</td>
<td>1.43, 14.57</td>
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<tr>
<td>Zini 2005</td>
<td>37</td>
<td>20.90</td>
<td>1.90</td>
<td>37</td>
<td>22.10</td>
<td>2.60</td>
<td>1.20</td>
<td>0.16, 2.24</td>
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<tr>
<td>Total (95% CI)</td>
<td>528</td>
<td>28.40</td>
<td>22.60</td>
<td>528</td>
<td>22.10</td>
<td>2.60</td>
<td>3.16</td>
<td>0.72, 5.60</td>
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</table>

Test for heterogeneity: CH² = 55.85, df = 6 (P < 0.00001), I² = 89.3%
Test for overall effect: Z = 2.53 (P = 0.01)

**Figure 3A:** Postop sperm morphology increased significantly following varicocelectomy.

**Figure 3B:** Effect of varicocelectomy on pregnancy rate using a random effects model showed significant improvement.

OR = odds ratio; n = number of couples achieving pregnancy with male partners diagnosed with clinical varicoceles; N = total number of cases.
Assessing Oxidative Stress Levels in Semen Using Spectroscopy-Based Metabolomic Profiling: Implications in Male Infertility

Ashok Agarwal, Ph.D., H.C.L.D.

Free radicals such as ROS exert their effect at the molecular level in all cell types and play a role in both physiological and pathological functions. Complex interactions between the pro-oxidants and antioxidants are crucial in the maintenance of intracellular homeostasis. An imbalance in these reactions results in oxidative stress (OS). Biomarkers of OS have been found in the male and female reproductive tracts and are known to affect the quality of gametes, early embryo development and implantation, which, in turn, affects pregnancy. Spermatozoa used for insemination in assisted reproduction techniques (ART) are likely to be exposed to ROS, which can cause extensive DNA damage. Thus, OS has been implicated in the etiology of different forms of male factor infertility.

We evaluated a novel technology platform (Molecular Biometrics, LLC, Chester, N.J.) to assess OS based on the confluence of two scientific disciplines: 1) biospectroscopy, or the applications of different forms of spectral analysis to identify, quantify and validate small proteomic and molecular biomarkers; and 2) metabolomics, the science that examines and integrates the dynamic interplay between the inventory of small molecule biomarkers at the cellular level that characterize complex biological processes and functions. Biospectroscopy is used to quantify a sample’s molecular biomarker makeup by producing novel spectra, which appear as highly unique “metabolomic profiles” or “fingerprints.” Each profile is analyzed using proprietary chemometrics and bioinformatics that correlate the data to a clinical condition or outcome. We examined the potential utility of this technology to explore the possible role of OS in the pathophysiology of male factor infertility.

Seminal plasma was collected with informed consent in four groups of patients: varicocele (N=70); idiopathic male infertility (N=15); vasectomy reversal (N=9); female factor infertility (N=9); and healthy donors (N=30). The specimens were individually analyzed using nuclear magnetic resonance, Raman, and near-infrared spectroscopy. The individual spectra obtained from each sample were separately analyzed using a wavelength selective genetic algorithm. Four spectral regions associated with the OS biomarkers were identified for each patient group. Results were further evaluated by a logistic regression of the light attenuation from the wavelength regions analyzed. Compiled results from the leave-one-out cross-validation of the logistic regression from all three spectroscopic measurements resulted in a specificity and sensitivity of >80%. In addition, two-dimensional self-organized maps (SOM) were constructed based on the input data to locate natural clustering or grouping patterns of the patient data. The total analysis time per sample was ~1 minute and required 10µL of SP.

Unique metabolomic profiles describing differences in the OS biomarkers—concentrations of -CH, -NH and -OH—were observed. When each metabolomic profile was quantified using a direct exponential curve resolution algorithm and coupled with logistic regression analysis, the ratio of the -CH to ROH content—which is reflective of OS—was also different between the groups. The female factor infertility, healthy donor and vasectomy reversal patient groups were well-defined within the self-organized map. The profiles of the varicocele patients were more randomly distributed and did not segregate as a separate population with uniquely identifiable biomarker characteristics. The idiopathic patients were defined as two regions in the SOM.

These results suggest that high-speed, non-invasive metabolomic profiling of seminal plasma using biospectroscopy, along with proprietary bioinformatics, can be used to identify different levels of OS in seminal plasma. The ability to quantify differences in the metabolomic profiles observed in different groups of male patients should prove useful as a diagnostic tool to evaluate semen quality and function. Additional studies are planned to further elucidate the role of OS in normal semen function vs. male factor infertility and to determine if metabolomic profiling of biomarkers of OS can be developed as a routine method for assessing sperm function in ART, as well as for other diagnostic applications in the urologic examination of male patients.
Men who are considering implantation of one of these devices should know the likelihood of needing further surgery due to device failure. Contemporary reporting of penile prosthesis results should express probability for survival free of mechanical failure by using Kaplan-Meier projections. We had previously reported 5-year Kaplan-Meier projections for freedom from mechanical failure for the AMS 700 CX/CXM inflatable penile prosthesis of 90.8%. (J Urol 158: 1400, 1997)

We recently updated our experience with this three-piece inflatable device, and this has resulted in the first report for any penile prosthesis of 10-year device survival using Kaplan-Meier projections. Ten-year Kaplan-Meier estimates for overall device survival were 74.9%. This includes revision or removal of the implant for any reason including, but not limited to, infection, erosion or mechanical failure. Ten-year Kaplan-Meier estimates for device survival free of mechanical failure were 81.3%.

For recipients who undergo successful implantation, these figures of 91% for 5 years and 81% for 10 years represent the probability of having a device that has not failed at these two time intervals. Today’s recipients actually may have an even greater likelihood of device survival because of recent improvements in design that were not reflected in the first study and were reflected only minimally in the second study. These improvements include a parylene coating for the inner and outer silicone layers of the cylinders. This coating, introduced to the product line in 2001, has extended cylinder life on bench testing, and this is expected to be reflected in future in vivo studies. Thanks to design improvements as well as advances in implantation techniques, the man who receives one of these penile prostheses today is less likely than ever before to need revision or replacement for mechanical failure.

### Long-term Mechanical Reliability of AMS 700 CX/CXM Inflatable Penile Prosthesis

<table>
<thead>
<tr>
<th>Prosthesis - Products</th>
<th>Five Years</th>
<th>10 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMS 700 CX/CXM</td>
<td>92%</td>
<td>81%</td>
</tr>
<tr>
<td>AMS ULTREX</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td>Mean PSA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Erectile Dysfunction Following Radical Prostatectomy: The Role of Early Intervention

Craig D. Zippe, M.D., and Shikha Sharma, M.D.

Indirect evidence from multiple studies suggest that early intervention strategies can improve sexual activity and the return of natural spontaneous erections and may improve (10-25%) the return of natural erections sufficient for vaginal penetration or vaginal potency (Table 1).

Early Use of Vacuum Constriction Devices (VCD)

Our group completed a prospective, non-randomized study on the use of early VCD after radical retropubic prostatectomy (RRP) at Cleveland Clinic. This study included 109 patients who underwent RRP between August 1999 and October 2001. Seventy-four patients (Group 1) used early VCD daily for 9 months, and 35 were observed without any treatment except the use of oral PDE-5 inhibitors on a prn basis (Group 2). With the minimum follow-up of 9 months, 80% (60/74) in Group 1 successfully used their VCD with a constriction ring for vaginal intercourse with an overall spousal satisfaction rate of 55% (33/60). Nineteen of these patients (32%) reported return of natural erections, with 17% having erections sufficient for sexual intercourse. Interestingly, when assessing the penile length and girth after surgery in the 60 compliant VCD patients, only 14 (23%) reported a decrease in penile length and girth at 9 months versus 12/14 (85%) in the non-compliant VCD patients. In the control group, 22/35 (63%) reported a decrease in penile length and girth.

We concluded that early use of VCD following RRP facilitated early sexual intercourse, early patient/spousal sexual satisfaction, a potentially earlier return of natural erections sufficient for vaginal potency and preservation of penile length and girth.

Early Use of Intraurethral Alprostadil (MUSE)

Recently, we completed a prospective, non-randomized study of 91 patients on the use of early MUSE after RRP at Cleveland Clinic. Fifty-six received early MUSE and 35 (control) did not receive any treatment except for oral PDE-5 inhibitors.

Table 1: Early Treatment Options for Erectile Dysfunction Following Radical Prostatectomy

<table>
<thead>
<tr>
<th>Potential Early Treatment Options</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Pharmacological agents</strong></td>
</tr>
<tr>
<td>Oral (daily/14-20 days/month)</td>
</tr>
<tr>
<td>a. PDE-5 inhibitors (sildenafil, tadalafil and vardenafil)</td>
</tr>
<tr>
<td>Intracavernosal injections (3 times per week)</td>
</tr>
<tr>
<td>a. Prostaglandin E1 (alprostadil)</td>
</tr>
<tr>
<td>b. Low-dose Trimix (alprostadil, papaverine, phentolamine)</td>
</tr>
<tr>
<td>• Bimix (papaverine, phentolamine)</td>
</tr>
<tr>
<td>Intraurethral alprostadil (MUSE)</td>
</tr>
<tr>
<td>(3 times / week, 125 or 250 mcg)</td>
</tr>
<tr>
<td><strong>2. Non-pharmacological agents</strong></td>
</tr>
<tr>
<td>Vacuum constriction device (daily for 5-10 minutes/without ring)</td>
</tr>
<tr>
<td><strong>3. Combination of above treatments</strong></td>
</tr>
</tbody>
</table>

Table 2: Summary of Early Intervention Therapies Following Radical Prostatectomy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Follow-up (months)</th>
<th>Natural erections (partial)</th>
<th>Vaginal potency w/wo PDE-5 inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>VCD-CCF¹</td>
<td>9</td>
<td>37%</td>
<td>17%</td>
</tr>
<tr>
<td>MUSE-CCF²</td>
<td>9</td>
<td>35%</td>
<td>39%</td>
</tr>
<tr>
<td>Injections-CCF³</td>
<td>8</td>
<td>71%</td>
<td>28%</td>
</tr>
<tr>
<td>Control-CCF²</td>
<td>9</td>
<td>39%</td>
<td>11%</td>
</tr>
</tbody>
</table>
inhibitors on a prn basis. Patients in the early MUSE group were started with 125 mcg 3 times/week, and the dose was increased, if tolerated.

In the MUSE group, 38/56 (68%) continued MUSE treatment. At 9 months, 28/38 (74%) of the patients resumed sexual activity, 15/38 (40%) had natural erections sufficient for vaginal potency without MUSE, and 13/38 (34%) continued to use MUSE as an adjuvant treatment for successful vaginal potency. In the control group, 13/35 (37%) regained spontaneous natural erections, but only 4/35 (11%) had natural erections sufficient for vaginal potency.

We concluded that early MUSE therapy (at low doses of 125/25 mcg) shortened the period of neuropraxia, and increased the incidence of spontaneous erections and erections sufficient for vaginal potency.

Early Use of Intracavernosal Penile Injections
We examined the role of intracavernosal injections immediately following RRP. Our decision to begin an early injection program was based on our report that 41% of long-term injection patients could be switched to a PDE-5 inhibitor.

This prospective study included 22 patients who underwent bilateral nerve-sparing RRP. A sildenafil dose of 50 mg/day was started at the time of hospital discharge, 18 were started on intracavernosal alprostadil PG E1 (1-8 mcg) and 4 were started on low-dose Trimix (20–30 U) 2-3 times/week. The compliance rate was sustained to almost 6 months, then 10 of the 22 patients refused to do further injections. These 10 patients were amenable to switching to a VCD/PDE-5 inhibitor combination. With a mean follow-up of 9 months, 15/22 (71%) had a return of spontaneous erections; 21 (96%) are sexually active, 11/21 (52%) with injections and sildenafil, 10/21 (46%) with VCD/sildenafil. Overall 6/21 (28%) achieved vaginal potency with sildenafil alone.

Early conclusions of this pilot study were that combination therapy using intracavernosal injections and sildenafil facilitated early sexual intercourse, patient satisfaction, earlier return of spontaneous erections, and potentially an earlier return of natural erections sufficient for vaginal potency.

Conclusion
Our available clinical data on the early use of PDE-5 inhibitors, VCD, intracavernosal penile injections and combinations of the above would suggest that there is a short-term benefit of 20-40% in the rate of vaginal potency and a 30-70% improvement in the rate of partial erections (Table 2). Thus, we conclude that an early program with one of the erectaids with or without a PDE-5 inhibitor improves erectile physiology and performance following radical prostatectomy.
Evaluation of Expression of PSMA in Tumor-Associated Vasculatures of Renal Neoplasms

Angelo Baccala, M.D., Ming Zhou, M.D., Ph.D., Linda Sercia, and Warren D.W. Heston, Ph.D.

In spite of its name, prostate-specific membrane antigen (PSMA) has been detected in the neovasculature of a variety of tumor types, including renal, bladder, colon, neuroendocrine, pancreatic, lung and most breast cancers and sarcomas. It has not been detected in normal vasculature and may, therefore, be employed as a target for imaging and therapy.

Distinguishing the different types of renal masses by conventional CT is often difficult, and biopsy carries the risk of cancer seeding along the needle tract. However, knowledge of tumor type is important because benign tumors that need not be excised could spare the patient unnecessary surgery if this were known with certainty via imaging alone. In addition, the presence or lack of PSMA expression in the neovasculature of different malignant renal tumor types may help as a biomarker to determine the aggressiveness of particular tumor types and help direct treatment plans. Furthermore, depending on the expression patterns of PSMA in these different renal tumor types, future therapeutics could be designed to inhibit tumor growth specifically in malignant renal tumors. Therefore, we characterized the expression of PSMA in the vasculatures of different primary renal tumors to assess its potential as a radiodiagnostic marker and therapeutic target in different renal tumor types.

We constructed a tissue microarray (TMA) from recently collected renal tissue specimens, including normal kidney, clear cell renal cell carcinoma (CCIRCC), papillary renal cell carcinoma (PRCC), chromophobe renal cell carcinoma (ChRCC), oncocytoma (Onc), transitional cell carcinoma (TCC) and angiomyolipoma (AML). The TMA was then immunostained for CD 34 (a vascular endothelial marker) and PSMA (PM2j004.5, an antibody recognizing an intracellular epitope of PSMA). PSMA staining was evaluated in CD34-positive vasculature based on the staining intensity. A numerical scheme for determining the PSMA intensity was devised depending on histological analysis. Diffuse strong staining was scored 3; diffuse weak staining or focal strong staining was scored 2; weak staining in <5% of vessels was scored 1; and absence of staining was scored 0. Positive PSMA in tumor-associated neovasculature was defined as a staining score >=2 (Figure 1).

Our results show that PSMA was expressed in the brush borders and apical cytoplasm of proximal tubules of normal kidney but not in the capillaries of the glomeruli or other vasculatures (Figure 2). In the renal neoplasms, PSMA was detected only in the tumor-associated vasculatures.

A Neutrophil-Derived Enzyme that Mediates Ischemic Injury and the Development of Interstitial Renal Fibrosis

Robert L. Fairchild, Ph. D.

Transplantation of kidneys and other solid organs includes an initial inflammatory response induced by the surgical tissue trauma and ischemia/reperfusion injury imposed on the graft. This injury has a considerable impact on the initial and long-term function of the graft. Longer ischemia times are associated with increased development of interstitial fibrosis and incidence of delayed renal graft function and loss.

A major focus of studies in this laboratory is on the mechanisms underlying ischemia/reperfusion injury and the impact of this injury on allograft rejection. These studies have utilized a renal ischemia/reperfusion injury model as well as a vascularized heart allograft model in mice. A consistent observation in both models is that chemoattractant cytokines that mediate the recruitment of neutrophils into the ischemic tissue are induced within minutes following reperfusion. The production of these chemoattractants mediates the infiltration of neutrophils into the ischemic kidneys as well as the activation of the neutrophils to degranulate. In a collaborative study with the renal transplant team, we have observed similar induction of these cytokines in biopsies from clinical renal allografts following reperfusion. Importantly, these studies have indicated that the transcription levels of the neutrophil chemoattractant IL-8 appear within 30 minutes of graft reperfusion and are linked to the ischemic time imposed on the kidney graft. The implication of these results is that the intensity of IL-8-directed neutrophil infiltration and activation is predicted to be greater in renal grafts from cadaveric donors vs. grafts from living donors.

The identity of the functions expressed by neutrophils that result in renal dysfunction and the development of intersti-
We also found that although PSMA expression was higher in CCRCC than other types of renal neoplasms, none of the PRCCs or benign AMLs had positive staining (Table 1).

From this we can conclude that indeed PSMA is differentially expressed in different renal neoplasms. Given its higher degree of expression in the neovasculature of CCRCC, it may be useful as a radiodiagnostic tool, a biomarker of disease response to novel therapy for CCRCC, or as a potential anti-angiogenic target for CCRCC. We are continuing our studies by further exploring the association between PSMA staining and clinical outcomes.

The lack of sustained neutrophil infiltration in the ischemic kidneys from cathepsin G knockout mice results in a 75% decrease in tubular epithelial cell apoptosis. In surviving wild-type mice, kidneys subjected to ischemia/reperfusion injury develop severe interstitial collagen deposition by 30 days post-reperfusion, whereas kidneys from cathepsin G deficient mice have virtually no trace of this deposition.

These results identify the enzyme cathepsin G as a major cause of neutrophil-mediated renal tissue injury following ischemia/reperfusion, including tubular epithelial cell apoptosis and the development of interstitial fibrosis. An implication of these studies is that targeted neutralization of cathepsin G is likely to attenuate neutrophil-mediated inflammation and renal tissue injury following transplantation and in other cases of renal ischemic inflammation.
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C. Thomas Powell, Ph.D.  
Office: 216.445.8055  
Fax: 216.445.0610  
Specialty Interest: basic science research  
Joint appointment with Solid Tumor Oncology

Brian I. Rini, M.D.  
Office: 216.444.9567  
Specialty Interests: genitourinary oncology, renal cell carcinoma, prostate cancer, anti-angiogenic therapy, immunotherapy  
Joint appointment with Solid Tumor Oncology
# Glickman Urological Institute Staff

<table>
<thead>
<tr>
<th>Name</th>
<th>Office</th>
<th>Fax</th>
<th>Specialty Interests</th>
<th>Other Offices</th>
<th>Joint Appointment with</th>
<th>Office (City)</th>
<th>Fax (City)</th>
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</thead>
<tbody>
<tr>
<td>Jonathan H. Ross, M.D.</td>
<td>216.444.9190</td>
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<td>Pediatric urology</td>
<td>Elyria, Fairview Hospital, Hillcrest</td>
<td>Cancer Center, Pediatric Surgery</td>
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<td>Rakesh K. Sharma, Ph.D.</td>
<td>216.445.4350</td>
<td>216.445.6049</td>
<td>Male and female infertility, free radicals in infertility, sperm cryopreservation,</td>
<td></td>
<td>Obstetrics and Gynecology</td>
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<tr>
<td>Andrew J. Stephenson, M.D.</td>
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<td>216.445.9628</td>
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<tr>
<td>Sandip P. Vasavada, M.D.</td>
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<tr>
<td>Bashir Riad Sankari, M.D.</td>
<td>304.388.6370</td>
<td>304.388.6376</td>
<td>Renal transplantation, renal vascular surgery</td>
<td>Transplant Center, Charleston Area Medical Center</td>
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<tr>
<td>Daniel Shoskes, M.D.</td>
<td>216.445.4757</td>
<td>216.445.7031</td>
<td>Kidney transplantation, chronic prostatitis, interstitial cystitis</td>
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<tr>
<td>Mark Walters, M.D.</td>
<td>216.445.6586</td>
<td>216.444.8551</td>
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<tr>
<td>Robert A. Shapiro, M.D.</td>
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<td>440.460.2819</td>
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<tr>
<td>Luay P. Susan, M.D.</td>
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<td>440.329.7316</td>
<td>Urological oncology, female urology</td>
<td>Westlake</td>
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<tr>
<td>Lawrence M. Wyner, M.D.</td>
<td>304.388.6370</td>
<td>304.388.6376</td>
<td>Renal transplantation</td>
<td>Transplant Center, Charleston Area Medical Center</td>
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</tbody>
</table>

**Office:** 216.444.4350 | **Fax:** 216.445.6049
Upcoming Conferences and Preceptorships

September 29-30, 2006
Living Donor Summit
Summit Director: David Goldfarb, M.D.

October 16-17, 2006
2nd Annual National Urology Resident Preceptorship (NURP) in Adult and Pediatric Reconstructive and Prosthetic Urologic Surgery
Program Co-directors: Kenneth Angermeyer, M.D., Drogo Montague, M.D., Jonathan Ross, M.D.

April 6-7, 2007
2nd Ambulatory Urology Symposium
Symposium Director: J. Stephen Jones, M.D., F.A.C.S.

All conferences and preceptorships will be held at the InterContinental Hotel and Conference Center on the Cleveland Clinic main campus in Cleveland, Ohio. Watch for more information in the mail.

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Chairman, Glickman Urological Institute

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J. Stephen Jones, M.D.,
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