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Notes from the Chairman

Challenges in Graduate Urologic Education

The evolution of the specialty of urology during the past 15 years has been unprecedented among surgical disciplines. Urologists now comprise a heterogeneous group of clinicians and scientists working in diverse areas linked by a global relationship to the genitourinary system. Urologic sub-specialization now exists in distinct areas such as oncology, female urology, pediatrics, infertility, neurourology, endourology/stone disease, and transplantation.

There are several challenges that we face in the field of graduate urologic education today:

- Urologic sub-specialization has increased the challenge of providing a comprehensive core curriculum for trainees.
- Increasing clinical and administrative demands on our faculty are rendering them less available for teaching.
- Fewer open surgical cases are being performed with an increase in the volume of outpatient-based practice and procedures, which has led to a 2-tiered system of practice in the United States.
- New minimally invasive therapies such as laparoscopy pose new challenges to surgical training which are spawning the development of novel approaches to skill acquisition involving virtual reality techniques and tele-mentoring.
- We exist within an increasingly restrictive medical economic environment that has eventuated in shortages of hospital beds, operating time, and nursing support in some centers.
- Funding to support research training is less readily available than in the past.
- Maintenance of accreditation for our graduate training programs now entails compliance with new limitations on resident work hours, and the requirement to objectively assess six measures of competence in our trainees.

Most worrisome, in my view, are recent trends in the United States that have impacted adversely on the training of academic surgeons or surgeon-scientists who have been an important product and lifeblood of our urological training programs. This has occurred in part because of the need for additional postgraduate training in subspecialty areas, which has lengthened the overall duration of clinical training, resulted in more restrictive funding for research training positions, and reduced the number of residency programs that currently offer a fixed period of time devoted exclusively to research.

We must adapt to the challenges of our time to ensure the survival and continued proliferation of academic surgeons. We need to rededicate ourselves to the development and support of those qualities in our trainees that truly characterize an academic surgeon. These characteristics include strong personal motivation, training in the conduct of research, ongoing guidance from scientific mentors, the early acquisition of scholarly habits and socialization to academic values, a network of productive academic colleagues, and the availability of both resources and protected time to carry out investigative work. And, since research is in many ways a social process of communication, interaction and exchange of knowledge and ideas with colleagues, students and mentors, academic surgeons must reside within a research-conducive environment.

The process of medical discovery in general, and certainly within our specialty of urology, is progressing at its most rapid rate ever. We are on the precipice of exciting advances, at both the clinical and molecular levels, that will reshape our current concepts regarding many diseases. It is vitally important that capable and motivated trainees have the opportunity to contribute toward these advances through a career in academic medicine.

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

Derek Raghavan, M.D., Ph.D., Director of the Cleveland Clinic Taussig Cancer Center and chairman of Hematology and Medical Oncology, has a dual appointment in the Glickman Urological Institute. Dr. Raghavan’s specialty interests include prostate cancer, prostatic disease and bladder cancer. Dr. Raghavan received his medical degree from the University of Sydney in Australia. Residency and fellowship training were obtained in Australia, England and the United States. Prior to joining The Cleveland Clinic, Dr. Raghavan was a professor of medicine, professor of urology and chief of the Division of Oncology at the University of Southern California. He also served as associate director for clinical research at USC/Norris Cancer Center.

Steven Campbell, M.D., Ph.D. joins The Cleveland Clinic from Loyola University in Chicago. His specialty interests include bladder, prostate, kidney, testicular and penile cancer. Dr. Campbell received his Ph.D. in biochemistry and molecular biology from the University of Chicago, where he also obtained his medical degree. Residency training in urology was completed at The Cleveland Clinic followed by a clinical and research fellowship at Memorial Sloan Kettering Cancer Center. Dr. Campbell has authored more than 84 publications and is the assistant editor of the Journal of Urology.

Margot Damaser, Ph.D., a prominent researcher in the areas of female pelvic floor disorders and urinary incontinence, has joined the staff of the Center for Female Pelvic Medicine and Reconstructive Surgery. She has a dual appointment in the Department of Biomedical Engineering of the Lerner Research Institute. Dr. Damaser will use principles of bioengineering, physiology, pharmacology, instrumentation and virtual reality to develop and test new models and devices for improvement of diagnosis, treatment and rehabilitation of lower urinary tract dysfunction. Dr. Damaser received her Ph.D. from the University of California at Berkeley and San Francisco. Prior to joining The Cleveland Clinic, she was at Loyola University Stritch School of Medicine, Maywood, Illinois.

This will entail preserving or refashioning the necessary environment and facilities to provide such training. Academic programs that aspire to train the future scientific leaders of our specialty must continue to provide a full year of protected time for research during the residency curriculum. We will need to increasingly share resources and collaborate more in education and research with specialties whose interests overlap with our own, perhaps through the development of multidisciplinary centers of excellence. There is an ever-present need for academic faculty role models who are able to convey the importance, the intellectual stimulation and enormous satisfaction that can be derived from a career in academic medicine. Finally, we need to continue to recognize the academic achievements of our trainees and faculty, and be more creative in developing sources of funding to support their investigative work. An important corollary of this is that faculty who devote a portion of their time to research should be treated the same financially as full-time clinical faculty within an academic urology department.

Recent Developments at the Glickman Urological Institute
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 offer expertise in every urologic subspecialty area, and comprise the largest full-time urology faculty in the United States.

Our 6-year urologic residency training program offers superb clinical and academic training, including a full year of laboratory research, and now comprises 4 residents per year. Postgraduate fellowships are offered in endourologic and laparoscopic surgery, female urology, male infertility, and renal transplantation. The Institute’s faculty contributed 166 scientific publications to peer-reviewed medical journals in 2004. There are currently 124 ongoing prospective clinical research studies and 43 ongoing laboratory research projects, supervised by 10 full-time Ph.D. investigators within the Institute.

Our faculty 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
New Staff
(continued)

Michael Kattan, Ph.D. is chairman of Quantitative Health Sciences in the Glickman Urological Institute. He specializes in prediction, medical decision making, quality of life assessment, patient preferences and decision analysis. Dr. Kattan completed his MBA at the University of Arkansas and his Ph.D. at the University of Houston. He has authored 194 articles in peer-reviewed journals and is a member of the National Association of Cancer Research and the American Urological Association. Prior to joining The Cleveland Clinic, Dr. Kattan was with Memorial Sloan Kettering Cancer Center.

Daniel Shoskes, M.D. specializes in transplantation and prostatitis and interstitial cystitis. Formerly with Cleveland Clinic Florida, Dr. Shoskes received his medical degree from the University of Toronto, where he later completed residency training in urology. A fellowship in renal transplantation and renovascular surgery was completed at the Glickman Urological Institute. Dr. Shoskes is the author of nearly 60 journal articles and is a member of many professional organizations including the Urologic Society for Transplantation and Vascular Surgery and the American Society of Transplant Surgeons.

The Glickman Pavilion, scheduled for completion in 2008, will be the new home of the Glickman Urological Institute.

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. Our program was recently the recipient of a $2.5 million NIH T32 training grant which will provide salary support for our postgraduate research trainees during the next 5 years. We continue to conduct annual national urology resident preceptorship programs in female pelvic medicine/reconstructive surgery and laparoscopic surgery, which are also supported with NIH funding.

A major development within the past year has been the establishment of the Center for Advanced Study within the Glickman Urological Institute, which will coordinate and provide resources for all of our educational and research activities, including expansion of our existing outcomes research program. Our educational and research activities are now also closely linked with the new Cleveland Clinic Lerner College of Medicine whose primary mission is to train graduates with a combination of clinical and research skills and a passion for scientific inquiry.

Finally, the administration of the Cleveland Clinic has recently approved the construction of a new building on our campus which will be named the Glickman Pavilion and which will house the Glickman Urological Institute. This initiative, scheduled for completion in 2008, will provide additional space and resources to enable further development of our clinical and academic 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.
International Recognition

Urological Society of India Honors Andrew C. Novick, M.D.

In recognition of his outstanding contributions to the field of urology, Andrew C. Novick, M.D., has been elected an honorary fellow of the Urological Society of India, the primary scientific organization for urologists in India. Dr. Novick, chairman of the Cleveland Clinic Glickman Urological Institute, is only the second person ever to receive the honor.

Dr. Novick, widely regarded as the premier kidney surgeon in the world, was recognized for his clinical and academic contributions worldwide and in India specifically. Dr. Novick and the Glickman Urological Institute have assisted in furthering urologic research at several medical centers in India.

Inderbir S. Gill, M.D. Receives Prestigious Dr. B.C. Roy Award for Eminent Medical Person

For the first time in its 39-year history, the Medical Council of India bestowed the prestigious Dr. B.C. Roy Award for achievement in medicine to a physician living outside India. Dr. Gill received notice of the award from the Honorable President of India H.E. Dr. A.P.J. Abdul Kalam. The Dr. B.C. Roy awards, established under the aegis of the Medical Council of India, are given every year to honor eminent persons who have achieved distinction in medicine, philosophy, science and arts.

Dr. Gill was also named an honorary member of the Royal College of Surgeons in 2005.

U.S. News

For the sixth 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. The Cleveland Clinic continues to be recognized as one of “America’s Best Hospitals.” In the magazine’s latest survey, The Cleveland Clinic was ranked the nation’s 4th best hospital.

New on the Book Shelf!

The Glickman Urological Institute announces the publication of Operative Urology at The Cleveland Clinic, which will be available from Humana Press in early 2006. Order online at www.humanapress.com.

Surgical repair through abdominal or vaginal approaches has been the mainstay of treatment of pelvic organ prolapse (POP). New advancements in laparoscopic surgery and robotic assisted laparoscopic surgery offer a less invasive approach in the reconstruction and repair of female pelvic floor disorders.

Taking advantage of existing expertise in female pelvic reconstructive surgery and robotic laparoscopic procedures, we have initiated and performed robotic laparoscopic abdominal sacrocolpopexy (RLASC), which is indicated for treatment of women with stages III and IV POP (based on POPQ system).

More than 40 different techniques have been described for the treatment of vaginal vault prolapse including abdominal or vaginal exposures. There has been much controversy over the benefits and the superiority of the more invasive abdominal approach over the vaginal approach. While studies have shown abdominal sacrocolpopexy to be more effective in correcting severe vaginal vault prolapse (Benson 1996), the abdominal exposure has higher morbidity and longer recovery time. With the introduction of laparoscopy and robotic assistance, interest has focused on creating a less invasive and traumatic approach to the repair of severe vault prolapse.

RLASC can be performed in presence (RLASC with uteropexy) or absence of uterus (vaginal vault prolapse). The use of robotic laparoscopic repair alleviates the need for an abdominal incision and accelerates the patient’s recovery. In the past, the uterus was removed as a part of the repair for pelvic organ prolapse. The use of robotic laparoscopic repair allows for a wider range of freedom in preserving the woman’s uterus and other organs, and yet, provides an equally efficacious management of the pelvic organ prolapse.

The surgical steps of RLASC with or without uteropexy are as follows: The patient is placed in the lithotomy position to provide access to both the abdomen and vagina. Five ports, 3 robotic and 2 standard laparoscopic ports are placed transperitoneally. 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 3X15 cm pieces of polypropylene mesh are sutured to the vaginal vault—one anteriorly and one posteriorly—making a cup support of the prolapsed vault (Figure 1). 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. Non-absorbable sutures are used for suspension sutures. The peritoneum is closed using running or interrupted absorbable sutures.

Robotic laparoscopic sacrocolpopexy with or without uteropexy provides a less invasive approach to the repair of vaginal vault prolapse, and also allows preservation of the uterus in the case of uterine prolapse.
Laparoscopic pyeloplasty has gained acceptance over the past decade by mirroring the principles and results of open surgery without the associated morbidity of a flank incision. The primary technical challenge is creating a tension-free, watertight, widely patent, stented anastomosis at a dependent renal pelvic location. Acquiring free-hand suturing skills or using devices such as the Endostitch may be technically demanding and time consuming.

The robotic surgical system offers specific technical advantages in performing intracorporeal suturing and knot tying that include enhanced surgical dexterity. Natural hand tremor is filtrated allowing motion scaling between the robotic control handles and the robotic instruments. The system also provides favorable suturing angles that minimize torque and avoid damage to fragile tissues. The lack of tactile feedback is a drawback, but the improved 3-dimensional visualization with up to 10-fold magnification allows for the visual assessment of tension on suturing material.

Similar to conventional laparoscopic pyeloplasty, the majority of reported robotic pyeloplasty cases utilize the transperitoneal approach. Because the retroperitoneal technique allows a direct approach to the stenotic UPJ area, and limits postoperative urinoma collections to the retroperitoneum, it may allow laparoscopic pyeloplasty to be performed on an outpatient basis.

At The Cleveland Clinic, we modified laparoscopic port placement and robot positioning so we could perform robotic pyeloplasty using the retroperitoneal approach. Between February 2004 and January 2005, 10 adult patients with unilateral ureteropelvic junction (UPJ) obstruction underwent robotic-assisted retroperitoneal dismembered pyeloplasty.

All patients had radiological evidence of UPJ obstruction and/or had symptoms consistent with UPJ obstruction. Seven patients had primary UPJ obstruction and three patients had secondary obstruction after failed endopyelotomy. Retrograde pyelography and stent placement were performed preoperatively.
The surgical procedure involves the placement of four ports in the retroperitoneal space: one for the robot camera, two for the robot arms and a fourth port placed anterior to the iliac crest into the ipsilateral retroperitoneal space without violating the peritoneal cavity. This port is used for retraction, suction, or introduction of sutures. Optimal positioning of the robot is critical to assure adequate range of motion of the robotic arms and mounted laparoscopic instruments (Figure 1).

During robotic surgery, the stented ureter is dissected towards the renal pelvis along with generous periureteral tissue to avoid devascularization injury to the ureter. The upper ureter and lower half of the renal pelvis are dissected using J-hook electrocautery and robotic shears. Crossing vessels at the UPJ area are identified and preserved. The stenotic UPJ is excised, the ureter spatulated, and ureteropelvic anastomosis performed over the ureteral J-stent using two running 4-0 vicryl sutures for the anterior and posterior ureteral walls, respectively (Figure 2). A Jackson-Pratt drain is inserted in the retroperitoneum and removed when drainage is less than 50cc a day. The ureteral stent is removed cystoscopically 4-6 weeks post surgery.

All the cases in our study were successfully completed using the robot without conversion to conventional laparoscopic or open technique. Total surgical time ranged from 90 to 200 minutes. Most patients went home after 48 hours and resumed oral diet the day after surgery. Median estimated blood loss was 50 cc, and there were no peri-operative complications. Early results revealed all patients had subjective resolution of flank pain and objective improvement in renal drainage by post-operative IVP and MAG III renal scan followup.

Our study established that retroperitoneal robotic pyeloplasty can be performed safely and effectively. Our initial outcome results are comparable to previously published open and pure laparoscopy results. The technique combines the advantages of high precision suturing using the robot with decreased patient recovery time using a retroperitoneal laparoscopic approach.
Robotic Laparoscopic Radical Prostatectomy
Outcomes similar to open and laparoscopic approach
Jihad Kaouk, M.D., Sijo J. Parekattil, M.D., and Inderbir S Gill, M.D.

Since the first laparoscopic radical prostatectomy in 1992, great strides have been made in refining techniques, reducing operative time and enhancing outcomes. We have performed over 650 laparoscopic radical prostatectomies at The Cleveland Clinic. In addition, we have performed over 70 robotic laparoscopic prostatectomies (RLRP), the most recent extension of the laparoscopic approach.

Robotic assisted surgery provides 3-dimensional magnified visualization, and articulating laparoscopic instruments that facilitate suturing, allow motion scaling, filter tremor, and decrease surgeon fatigue. These technical advantages allow microsurgical applications such as sural nerve grafting after radical prostatectomy. An analysis of our first 50 RLPRPs reveal that this technique can be performed in a safe and effective manner, and outcomes appear similar to open and laparoscopic radical prostatectomy.

Technique
The patient is positioned in modified dorsal lithotomy (Figure 1a). A transperitoneal 6 port technique is used, and port placement is illustrated in Figure 1b.

The bladder is dissected off the anterior pelvis and pubic bone; the endopelvic fascia is incised laterally, and the dorsal vein is sutured. The bladder is separated from the prostate by dissecting the bladder neck completely from the base of the prostate. The seminal vesicles and vas are then dissected to create the posterior plane between the prostate and the rectum. At this point, the lateral vascular blood supply to the prostate is controlled and the neurovascular bundles are dissected carefully and, at the same time, all prostate tissue is removed (Figure 2).

With the prostate base completely dissected and the dorsal venous complex already ligated and cut, the urethra is incised and the apex of the prostate is carefully dis-
sected until the specimen is completely free of the pelvis. The prostate is removed later by enlarging the umbilical port incision to 3-4cm in length. The bladder neck is then anastomosed to the urethral stump using a continuous running suture (Figure 3).

A Foley catheter is placed in the bladder just prior to completing the anastomosis; after which, a JP drain is placed in the lower pelvis. The prostate is now removed, as well as the ports, and the small skin incisions are closed.

Robotic Sural Nerve Grafting

All attempts are made to preserve the NB that are involved in achieving penile erections, but in some cases they may need to be excised to remove all the cancer. We now offer the option of performing a robotic sural nerve graft procedure to create new NB in the pelvis. (Figure 4). The procedure is performed with a plastic surgical team, adding about two hours to the overall procedure.

We have successfully performed the procedure in three potent men. In patient 1, the entire procedure was performed robotically. In patients 2 and 3, the robot was used only for sural nerve grafting and the urethro-vesical anastomosis, while radical prostatectomy was performed by conventional laparoscopy.

After the completion of radical prostatectomy with deliberate wide resection of the NB, the plastic surgery team harvested 10 to 15 cm of sural nerve from the left calf. Sural nerve grafts were interposed robotically by placing 4 to 6 interrupted perineural stitches of 6 or 7-zero polypropylene sutures.

After one year, patient 1 reported penile engorgement with sildenafil not sufficient for penetration; patient 2 with unilateral nerve preservation was potent without any medication; and patient 3 did not achieve any degree of erection.

Long-term oncological and erectile function outcomes are currently being evaluated, but the early results appear to be consistent with open and laparoscopic techniques.
Open Partial Nephrectomy for Tumor in a Solitary Kidney: Experience with 400 Cases

Andrew C. Novick, M.D.

After two decades and an extensive worldwide experience, partial nephrectomy, has become an accepted modality for surgical treatment of renal cell carcinoma (RCC) with oncologic outcome similar to traditional radical nephrectomy in appropriately selected cases. Although oncologic outcome parameters have been extensively evaluated, the long-term effect of partial nephrectomy on renal function has not been as carefully studied.

Patients with a localized tumor involving a solitary kidney constitute a mandatory indication for partial nephrectomy. Such patients present an ideal clinical situation for studying the effect of the surgical technique on renal function without any confounding functional input from a contralateral kidney. As far as renal function is concerned, these patients are considered high-risk surgical candidates by most urologists, and are referred with regularity to tertiary care centers.

From January 1980 to December 2002, 400 patients with sporadic renal tumors in a solitary kidney were treated with open surgical partial nephrectomy. All operations were performed by the author using in-situ surgical techniques. In 323 patients (81%) the contralateral kidney was surgically removed, while the remaining 77 patients (19%) had a congenital solitary kidney. Mean follow-up was 44 months.

A number of adverse risk factors were present in this patient population: All patients had surgery for an imperative indication, preoperative renal insufficiency was present in 46% of patients, 43% of the tumors were more than 4 cm in size, 36% were multifocal tumors, 44% were in a central location, and 30% were pathologic stage T3. All these factors contributed to increasing the degree of technical difficulty as well as the surgical and functional risk associated with these cases.

In the overall series, 5-year and 10-year cancer-specific survival was 89% and 82%, respectively. Fourteen patients (13.5%) required hemodialysis in the immediate postoperative period. Only two of these patients remained on permanent dialysis. Therefore, early postoperative renal function was achieved in 398 patients (99.5%). Satisfactory long-term renal function was achieved in 382 patients (95.5%). Eighteen patients (5%) progressed to renal failure requiring dialysis over a mean period of 3.6 years after surgery.

Several factors were found to have a statistically significant effect on postoperative creatinine in the first 3 months after surgery. These factors were: length of renal ischemia time (p=.001), use of surface hypothermia (p=.002), percentage of renal parenchyma resected (p=.001), patient age (p=.001), congenital solitary kidney; and timing of contralateral nephrectomy (p=.002) had a statistically significant impact on the percentage of creatinine change. When the same analysis was done for renal function more than 4 months postoperatively, renal ischemia time and surface hypothermia were found to be of no statistically significant impact. The percentage of parenchyma resection (p=.1), patient age (p=.001), and congenital solitary kidney, time of contralateral nephrectomy (p=.03) were the only statistically significant factors affecting long-term renal function.

We found that the status of the contralateral kidney significantly affected the renal function outcome in both short- and long-term analyses. Of note, patients with congenital atrophic or absent contralateral kidneys had the least degree of renal function impairment after NSS. This probably results from a long period of time for compensatory hypertrophy to develop. For patients with a congenital solitary kidney, this hypertrophy will occur at the optimum time, during development and childhood. This seems to justify our clinical impression that congenital solitary kidneys are most resistant to renal ischemic injury. The same mechanism (time for compensatory hypertrophy to develop) would explain our finding that patients who had a contralateral nephrectomy more than one year before partial nephrectomy suffered less renal function impairment than patients who had a contralateral nephrectomy within the same year as partial nephrectomy.

In conclusion, our results demonstrate that open partial nephrectomy is a safe and effective procedure for patients with tumor in a solitary kidney. Surgical complications are minimal, and long-term cancer-free survival with preservation of renal function can be expected in the majority of patients.
Emerging Renal Cell Carcinoma Therapies Show Promise by Targeting Receptors Influencing Angiogenesis

Ronald Bukowski, M.D., Head, Experimental Therapeutics, Cleveland Clinic Taussig Cancer Center

For a decade or longer, advances in the treatment of renal cell carcinoma (RCC) have been modest. Now three new oral agents, all targeting receptors in the pathway to angiogenesis, hold the promise of becoming a major advance. Although all three remain as experimental treatments, they may well change the way advanced kidney cancer is treated.

The agents are AG-013736, Sutent (SU-011248) and Sorafenib (BA 43-9006). The first, AG-013736, has recently completed a Phase II trial. Sutent completed a Phase II trial and has entered a 700-patient Phase III trial. Sorafenib has completed a Phase III trial and will likely be considered by the FDA as a therapy for metastatic RCC. The Cleveland Clinic played a prominent role in the study of all three agents, and has been one of the principal institutions conducting the Phase III study of Sorafenib.

All three agents are known as multifunctional tyrosine kinase inhibitors. Most kidney cancers are highly vascularized tumors. One of the principal pathways to angiogenesis is keyed by growth factor (VEGF) interaction with a class of cellular membrane receptors called protein tyrosine kinase (PTK) receptors. Among the genes that are known to be up-regulated in RCC are those that code for vascular endothelial growth factor and platelet derived growth factor (PDGF), both of which promote angiogenesis in addition to other responses. These agents bind to the cytokine receptors, inhibit signal transduction and thus inhibit angiogenesis.

In the Phase II trial of AG-013736, 52 patients with metastatic cytokine refractory clear cell carcinoma were treated with 4-week cycles of the agent at 5 mg twice daily. Responses were evaluated by Response Evaluation Criteria in Solid Tumors (RECIST), an international criteria that uses X-ray, CT, and MRI. Twenty-four patients (46%) evidenced a partial response to the treatment and another 21 (40%) showed stable disease. Only seven (14%) showed no reduction in tumor burden. At a median one-year followup, one patient with a partial response has relapsed, 16 (31%) evidenced progressive disease, and seven have been withdrawn due to adverse events. More than half (56%) remain on the therapy.

Sutent (SU-011248) was studied in two sequential single-arm trials at The Cleveland Clinic and other institutions. Sixty-three patients with RCC enrolled in the first trial whose data were reported last year, and 106 patients were enrolled in the more recent Phase II trial. The majority of patients had cytokine refractory disease. Although each trial was independent of the other, outcome data from each is remarkably consistent. In the first trial 40% of patients evidenced an overall response compared to 39% in the second. Eighteen (28%) showed stable disease at three months follow up or longer, compared to 23% (25) in the second trial. An international, multicenter Phase III trial involving 700 or more patients with RCC who had prior treatment with interferon or interleukin 2 at the time data were presented to the annual meeting of the American Society of Clinical Oncology this year, 769 patients were eligible for evaluation. The median progression free survival was 24 weeks in patients receiving Sorafenib compared to 12 weeks in those on placebo ( p = <0.000001).

Although none of these drugs is yet approved, the studies permit a number of important clinical observations. All three agents are oral drugs that achieve their effects by inhibiting cellular receptors involved in angiogenesis. All three have low, adverse event profiles. Responses to date with the agents indicate that these and other angiogenesis mechanisms are promising targets. All trials involved the drugs as single-agent therapies in patients with advanced disease refractory to almost all therapy. It is reasonable to suspect that these agents may have a significant role in combination therapies and in less advanced disease. It is likely that these agents will change the nature of kidney cancer treatment.
As modern imaging techniques have increased the detection of small incidental renal tumors, the trend has shifted from radical nephrectomy to nephron-sparing techniques, which include partial nephrectomy, cryoablation and radiofrequency ablation (RFA).

Radiofrequency electrocautery has been used for more than 70 years to achieve hemostasis during surgical procedures. Today, the technology has advanced, allowing large volumes of tissue to be ablated by thermal energy. RFA has been applied to various solid organs including prostate, liver, and recently, kidney. Experimental and clinical data in the literature confirm the feasibility of using RFA for treatment of localized RCC. Currently, more powerful RFA devices, new RFA probe designs, and accurate features of temperature control make this technology even more reliable and promising. Technology now available includes new powerful generators that have the ability to redistribute the electric current from high impedance to low impedance areas. Continuous redistribution of electric current allows homogeneous lesions to be produced, overcoming the problem of impedance rise due to tissue charring. This capability gives a high level of confidence that a reproducible coagulative necrosis is taking place in the targeted site.

To deploy radiofrequency energy, the interstitial needle electrode must be placed precisely using visual guidance during open or laparoscopic surgery. Alternate deployment may be performed with ultrasound, CT or MRI guidance during percutaneous approach. Newer electrode probe designs now consist of nine evenly spaced wire electrodes arranged in a constant radius of curvature around a metal insertion cannula, which houses the electrode array. This umbrella pattern:

- Creates a uniform spherical lesion and, therefore, is suited to ablate most cases of RCC < 4cm.
- Serves to secure the electrode in the tissue during treatment, which is critical because it prevents the electrode from moving with respect to the kidney during respiration. Any movement during respiration would result in incomplete tumor ablation and undesired ablation of surrounding normal tissues.
- Allows placement of the extremities of the wire electrodes at the edge of the tumor under real time ultrasound guidance.
Since most percutaneous radiofrequency treatment of kidney masses is performed with the patient under local anesthesia with intravenous sedation, it is an attractive treatment option for poor surgical risk patients who are at advanced age or have significant medical comorbidities. Also, the percutaneous approach can be useful for managing patients with prior kidney surgery or other unfavorable anatomical conditions such as abdominal aortic aneurysm. Studies suggest that this less invasive treatment is well tolerated and can be performed on an outpatient basis.

Since August 2003, a total of 66 patients underwent 76 percutaneous RFAs for localized RCC at The Cleveland Clinic. Of the total, 35 patients with only one kidney and 18 patients with only part of one kidney had undergone prior ipsilateral partial nephrectomy and contralateral radical nephrectomy for RCC.

Under light sedation and local anesthesia, the RFA needle was placed in the center of the targeted tumor under CT guidance. A 150-watt generator was used to achieve a target temperature of 105°C. Total RFA time was 30 min. per session. Several overlapping needle deployments were performed to confirm complete tumor ablation. Patients were observed for a few hours then discharged the same day. Mean tumor size was 2.5cm (range, 0.9 to 4.5). Four patients had multiple renal tumors that required two-three RFA sessions. Post-RFA residual enhancement was noted in three patients who required RFA retreatment with no residual enhancement. With a mean follow-up of six months (range, 1.5 to 10), five patients were retreated for local recurrence or persistence of kidney tumor. Success rate after first attempt of treatment was 89.2%. Patients who had residual tumor were re-treated successfully with percutaneous RFA. Complications were limited to one patient, who required blood transfusion and one patient who required percutaneous drainage of retroperitoneal abscess. Kidney function was preserved in all patients with no significant difference in pre RFA creatinine (1.44mg/dl) compared to post RFA creatinine (1.59 mg/dl).

Although percutaneous RFA for localized RCC in solitary renal remnants seems to be safe and effective for select patients, additional experience and longer follow-up is needed to evaluate the oncological efficacy of this approach.
Immune Evasion by Renal Cancer Involves Apoptosis of T cells by Gangliosides

James H. Finke, Ph.D., and Charles S. Tannenbaum, Ph.D.

Although recent studies demonstrate cancer patients have an immune response to tumors, these responses are generally ineffective, evidenced by continued tumor growth and disease progression. Interleukin-2 based immunotherapy and vaccine strategies to induce tumor regression in patients with metastatic renal cell carcinoma (RCC) have met with modest results—about 15%.

The microenvironment of malignant tumors is highly complex and can regulate not only the growth of tumors but also the development of a local immune response. Recent studies at The Cleveland Clinic suggest that the tumor microenvironment can cause destruction of T lymphocytes infiltrating human tumors, such as RCC. Approximately 10%–20% of tumor-infiltrating T lymphocytes were found to be apoptotic in RCC. Data from our group and others have now confirmed that it is the tumor cells themselves that mediate these effects, because when co-cultured in vitro, cancer cell lines can be clearly shown to induce apoptosis of T lymphocytes.

Studies reveal that gangliosides, structurally diverse acidic glycosphingolipids that are present in the outer leaflet of the plasma membranes, promote tumor-associated angiogenesis and regulate cell adhesion/motility, thereby initiating tumor metastasis. Enhanced production of gangliosides has been observed in different tumor types, and in many cases the changes in individual ganglioside expression has been identified. The role that different gangliosides play in promoting tumor growth is not well defined, however, GM2 specifically has been implicated in promoting tumor growth and metastasis. Indeed, GM2/GD2 synthase mRNA expression is increased in human gastrointestinal cancers, suggesting a role for GM2 in this disease. GM2 expression has been directly related to the tumorigenicity and metastatic potential of human melanoma.

Current investigations by researchers at The Cleveland Clinic have focused on defining the gangliosides that are expressed by clear cell renal tumors, the most common type of kidney cancer. Their findings show that GM2 along with other gangliosides, such as GD1a are overexpressed by RCC tissue and that RCC-associated GM2 can induce apoptosis in T cells. High performance liquid chromatography (HPLC) demonstrated that GM2 expression is significantly increased in clear cell RCC tissue compared to unaffected adjacent kidney tissue (9/16), which was supported by mass spectrometry analyses (LC/ESI/MS/MS). Immunostaining with anti-GM2 antibody confirmed increased expression of GM2 in freshly cultured tumor cells versus uninvolved adjacent cells, while real time PCR demonstrated increased expression of GM2 synthase mRNA in tumor over normal tissue. Furthermore, gangliosides isolated from RCC tissue induced apoptosis in T cells from normal volunteers that was partially blocked by an anti-GM2 antibody but not by an isotype control IgG, suggesting that GM2 expressed by RCC is immunosuppressive.

The conclusion that GM2 is expressed by RCC tumors and is apoptogenic is further supported by the demonstration that established RCC lines expressing GM2, as well as gangliosides isolated from these tumors, induced T cell death. The ability of anti-GM2 antibody to partially block T cell apoptosis initiated by GM2 expressing RCC lines further supports the role of this ganglioside in RCC immune dysfunction.

Additional studies by Cleveland Clinic investigators suggest that TNF-α a cytokine present in the tumor microenvironment, can significantly enhance the ability of RCC lines to induce T cell apoptosis. This conclusion is supported by the observation that incubating RCC lines with either recombinant TNF-α or transfecting tumor lines with the TNF-α transgene significantly promoted T cell apoptosis in lymphocyte-tumor co-culture experiments. HPLC analysis and immunostaining revealed that exposure of renal tumor lines to TNF-α promoted their production of gangliosides, including GM2, while PCR analysis demonstrated TNF-α increased mRNA expression of the enzyme that regulates GM2 production (ie GM2 synthase). It also appears that GM2 induced on RCC by TNF-α is partly responsible for tumor-induced T cell apoptosis since a temporal relationship was established between TNF-α-induced GM2 expression and TNF-α-dependent killing of T cells by RCC lines. Furthermore, anti-GM2 antibody significantly blocked T cell apoptosis induced by tumor cells pretreated with either rTNF-α or transfected with the TNF-α gene. These findings support the notion that TNF-α can promote tumor immune escape by stimulating the production of immunosuppressive gangliosides on renal tumors.
Removing organs from a supply of oxygen followed by rapid reoxygenation are inherent events in transplantation that lead to an almost immediate inflammatory response. The response often induces graft cells that produce proteins and attract neutrophils.

Our renal transplant team recently completed a study demonstrating that the induction of neutrophil chemoattractants in renal grafts was higher in deceased donor grafts when compared with grafts from living donors, and the levels induced correlated with the time of ischemia.

We have used laboratory models of renal ischemia/reperfusion injury and vascularized cardiac allograft to demonstrate that the inflammatory response is accompanied by the infiltration of neutrophils into the ischemic tissue or allograft, resulting in clearly discernible foci of tissue necrosis.

Recently, two important aspects of neutrophil infiltration and activation have been revealed in our laboratory: The first is: neutrophil infiltration is increased in allografts when compared to isografts. This increase is mediated by circulating memory CD8 T cells that are rapidly recruited and activated at the graft site, within 12 hours post-transplant. Although these memory CD8 T cells were not originally activated to the allograft antigens, they express reactivity (or cross-reactivity) to these antigens. This concept is now known as “heterologous immunity” where CD8 T cells primed to viruses, bacteria or other agents develop into memory T cells that may have reactivity to allogeneic MHC molecules and promote rejection of grafts in sensitized recipients.

The mechanisms by which such cells undermine the survival of transplanted organs have remained unclear. Results from our studies indicate that one mechanism is through induction of neutrophil infiltration and activation. The more alloantigen-reactive memory CD8 T cells present, the more intense the neutrophil infiltration observed and the more rapid the rejection of the allograft. Studies are now under way to test functions expressed by the memory CD8 T cells that induce this neutrophil response.

The second important aspect of these studies is: neutrophil mediated damage to the allograft serves to “mark” the allograft. Consequently, interruption of alloreactive T cell priming may not be an effective form of immunosuppression if T cells resistant or escaping the immunosuppression can eventually find the allograft. To test this concept, we utilized a cardiac allograft model in a lab model. When recipients were treated with reagents to either block the neutrophil mediated allograft damage or delay priming of alloreactive T cells, survival of the heart allografts was significantly extended when compared to control treated recipients. However, the combination of the two treatments resulted in the long-term survival of the allografts with little to no evidence of cellular infiltration into the grafts.

These results suggest that intervention at the point of graft ischemia/reperfusion should improve the function and survival of solid organ transplants.
In the Section of Laparoscopic and Robotic Surgery, we continue to refine our approach to laparoscopic radical prostatectomy (LRP) through advances in instrumentation and imaging. Our goals are to prevent trauma to the neurovascular bundle (NVB) and to preserve its integrity so that we can preserve sexual function while fully eradicating disease.

In this article, we will describe a lateral pedicle ligation technique that we have developed as well as our exploration of real-time transrectal ultrasound (TRUS) as a guide to intraoperative decision-making. We believe that the substantial benefits these modifications appear to produce in LRP will translate into similar benefits for open procedures.

The introduction of nerve-sparing radical prostatectomy techniques has made the preservation of sexual function a primary consideration for both surgeons and patients in appropriately selected cases. Even in optimal clinical circumstances, the procedure is challenging; attempts to preserve the integrity and function of the NVB may fail for reasons that have yet to be defined.

We hypothesize that instrumentation, and not necessarily technique, can be a source of neural trauma that impedes or prohibits recovery of sexual function postoperatively. This hypothesis rests on the following observations:

- Controlling bleeding from a transected lateral pedicle artery with standard clips is difficult to accomplish without incorporating adjacent NVB tissue within the jaws of the clamp. This significantly raises the risk of inducing trauma to the NVB.
- Electrocautery instruments (monopolar or bipolar) and those using thermal energy, such as harmonic scissors, are standard means of providing hemostatic dissection in a variety of laparoscopic procedures, including prostatectomies. However, the cellular damage wrought by these instruments is not confined to the line of dissection, but may extend one or more millimeters on either side of the line. This creates a path of collateral damage that poses a significant threat to delicate neural fibers. Laboratory studies have shown that these instruments, when used to release the NVB, are associated with a significantly decreased response to cavernous nerve stimulation.
- Bioadhesives and biologic hemostatic agents do not work well in this particular setting. They may increase the risk of local toxicity and local inflammatory response. The effect of these compounds and responses on the restoration of nerve function is unknown, but is unlikely to be beneficial.

Lateral pedicle ligation during LRP eliminates all electrocautery, ultrasound thermal energy, clips and bioadhesives. Precise cold-cutting with Endoshears, monitored by real time transrectal ultrasound (rtTRUS) as described below, minimizes collateral damage. Delicate hemostatic suturing with 4-0 Vicryl eliminates the need for cauterizing instruments. Bulldog clamp placement on the lateral prostate pedicles allows the operation to proceed without significantly interrupting blood flow within the NVB.

To date, we have used the procedure in 25 men, 22 of whom underwent a bilateral nerve-sparing procedure and three of whom underwent a unilateral procedure. The mean age of the cohort was 58.8 years and mean preoperative PSA level was 6.2. Twenty men had T1c disease, four had T2a disease and one had T1b disease.

Laparoscopic transection of the lateral pedicles and release of the NVB was monitored in real time by transrectal power Doppler as well as gray-scale ultrasonography. Mean Bulldog clamping time ranged from 11.1 to 11.2 minutes. The mean arterial blood flow resistive index changed little during the
procedure. It was 0.86 before clamping, 0.85 during clamping and 0.85 at the conclusion of the procedure.

All 25 procedures were successfully conducted with an average operating time of 254 minutes. Final pathologic evaluation showed pT2a disease in three men, pT2b disease in 19 men, and pT3a disease in three men. The average hospital stay was 1.6 days.

The study is too recent to provide the long-term follow up data necessary to evaluate the technique’s impact on sexual function and to compare results to those achieved in open procedures. The reduction in trauma resulting from the elimination of clamps and replacement of electro- and harmonic instruments with cold cutting shears should be beneficial, but raises the issue of whether Bulldog clamping of the prostate pedicle causes trauma to the NVB.

Ultrasound demonstration of continued pulsatile blood flow within the NVB throughout the procedure is encouraging and suggests that minimal pressure is being applied to the NVB. We continue to refine this technique with the goal of duplicating results seen with current open procedures.

Our exploration of the full potential of transrectal ultrasound (TRUS) in laparoscopic prostatectomy has helped in this regard. Surgeons in our section have been using real-time rectal ultrasound (rtTRUS) imagery to assist in intraoperative decision-making and guide instruments for a little over a year. Our initial experience suggests that (rtTRUS):
- identifies extracapsular extensions more frequently and accurately
- significantly improves the incidence of negative margins
- minimizes the amount of tissue removed, and
- offers substantial value in preserving the integrity of the NVB.

Modern TRUS can produce accurate images of prostate contours and depict important but subtle aspects of periprostatic anatomy, such as the course, dimensions and vascularity of the NVB. It can also visualize a substantial percentage of nonpalpable prostate cancers. Without the information provided by rtTRUS, such cancers would be all but invisible, regardless of whether prostatectomy was conducted openly or laparoscopically.

To evaluate the potential of rtTRUS, we identified 294 patients with clinically organ-confined prostate cancer who had undergone laparoscopic radical prostatectomy (LRP) since March 2001 and divided them into two groups. Group 1 consisted of 217 patients who had LRP with rtTRUS (n = 217). Group 2 consisted of those who had LRP with rtTRUS (n = 77). The two groups were similar in PSA values, biopsy and final specimen Gleason scores, and distribution of clinical and pathologic stages.

Initial data from this study indicate that rtTRUS contributed to improvements in several parameters. The overall rate of positive surgical margins was significantly reduced from 29 percent in those without rtTRUS to 9 percent in those with rtTRUS. Intraoperative TRUS correctly predicted pT2 disease in 85 percent of the patients, and pT3 disease in 86 percent of patients in the series. Importantly, rtTRUS appeared to reduce positive surgical margins in pT2 disease from 21 percent to 5 percent, and in pT3 disease from 57 percent to 18 percent.

Accurate real-time intraoperative images of the potential location and extent of extracapsular extension disease (pT3) appear to produce substantial benefits in laparoscopic procedures.

Earlier studies of our data have shown that the TRUS-determined length of the tumor nodule that is in direct contact with the prostate correlates with the likelihood of extracapsular extension (ECE). This knowledge offers three real-time options for the surgeon.

When the tumor image suggested organ-confined cancer, a complete nerve-sparing procedure was conducted. When the image suggested limited ECE, a calibrated, lobe-specific, slightly wider (1- to 2-mm) dissection was conducted. When the image suggested advanced ECE, an ipsilateral wide-excision, non-nerve-sparing procedure was conducted.

The accuracy and clarity of the images produced by TRUS have significantly improved in recent years with the combination of biplanar probes and sophisticated software. This initial study suggests that rtTRUS can produce accurate information on the location and extent of hypoechoic prostate cancer nodules. This visual information can guide the surgeon during NVB release and apical dissection around cancer nodules with suspected extracapsular extension.

As with the use of lateral pedicle ligation to eliminate electrocautery, thermal energy, clips and bioadhesives, the use of rtTRUS to perform a monitored, individualized, precise dissection tailored to individual presentation and anatomy should minimize collateral damage. There is no reason to doubt that these benefits would not be duplicated in open procedures.
Although rare, the most severe complication following radiation therapy (RT) for prostate cancer is a rectourethral fistula (RUF). As more men are treated with radiation we have seen an increase in the incidence of this problem (Figure 1). Because conservative measures and local surgical treatment are suboptimal, we recently reviewed our experience.

Between Jan. 1, 2000 and Dec. 31, 2003, 22 patients with a radiation induced RUF were referred. Twenty-one received RT as initial definitive treatment; 6 received brachytherapy (BT) alone, 4 received external beam (EBRT) alone, 10 received a combination, and 1 underwent EBRT followed by cryotherapy. One patient received EBRT for biochemical failure.

Severe rectal and pelvic pain were documented in 10 patients, and rectal bleeding in 6. Six had more severe complications attributable to RUF at or shortly after presentation including life-threatening bleeding requiring ICU admission in 5 individuals, and intra-abdominal abscess, sepsis, and/or necrotizing fasciitis in 4. Only 1 of the patients was found to have biochemical failure.

All patients underwent imaging with CT and VCUG (Figure 2). Cystoscopy and proctoscopy were performed in order to define the extent of the radiation damage and to generate a surgical plan. Factors assessed included: condition of the external urethral and rectal sphincters, size and location of the fistula, presence of associated urethral stricture, condition of the adjacent tissues and degree of necrosis of the tissues adjacent to the fistula. The size of the fistula in these patients ranged from 1 to 7 cm (mean: 2.8 cm).

Initial fecal and urinary diversion and a course of antibiotics were the only means of therapy in three of the 21 treatable patients in this series. Two had large defects involving the sphincters and were poor candidates for reconstruction due to comorbidities. Both of these patients died within three months. The third patient underwent fecal and urinary diversion with a SP catheter after initial diagnosis and has been doing well. Two patients received initial bowel and urinary diversion by SP catheter and later underwent urinary diversion by ileal conduit. Pelvic surgery was avoided in both because of the extensive radiation damage.

Seventeen patients underwent a more formal surgical procedure. Only 1 of 3 transanal repairs succeeded. Four patients underwent surgical management of RUF with permanent fecal and urinary diversion. Abdominoperineal
Resection (APR) was performed with end colostomy along with cystectomy and urinary diversion. The procedure was successful in all with adequate postoperative stoma function.

In 5 patients, repair was performed with preservation of one sphincter. Two patients underwent APR and end colostomy in conjunction with omental pedicle flap. Another underwent APR and end colostomy in conjunction with buccal mucosa onlay graft repair of the prostatic urethral defect. One patient with a contracted bladder underwent cystectomy with ileal conduit and primary closure of the rectum. The final patient underwent cystectomy and ileal conduit formation, along with rectal resection and Turnbull-Cutait colonic pull-through.

Six patients underwent RUF repair with preservation of both fecal and urinary sphincter function. In 5 patients, APR with colonic pull-through and staged colo-anal anastomosis were performed in conjunction with buccal mucosa onlay graft repair of the prostatic urethral defect. A sixth patient was repaired through a trans-perineal approach with primary closure of the rectum and buccal graft closure of the prostatic urethral defect. A gracilis muscle interposition flap was then placed between the rectum and urethra. All 6 of these patients are free of recurrence, are voiding without catheters, and have had stoma closures. Overall, of the 9 patients who underwent restoration of urinary function, success was achieved in each case. Of 8 patients having rectal reconstruction, all patients demonstrated radiological and clinical bowel integrity with 2 still pending final diverting stoma closure.

We believe that with the increasing use of radiation, the number of patients developing severe rectal injury will likely continue to rise over time. Radiation-induced RUF carries significant morbidity, and most patients are managed initially with fecal and urinary diversion. We have developed an algorithm for the subsequent evaluation and management of this problem (Figure 3). In properly selected patients, good outcomes can be expected following repair using buccal mucosa for the urethral defect along with colo-anal pull-through, or primary rectal repair and gracilis muscle interposition.
Cryosurgical Ablation of the Prostate: Finally Ready for Primetime?

J. Stephen Jones, MD, FACS

No doubt ever existed that freezing kills cancer. The problem has always been damage control, which led to unacceptable complications during initial attempts at cryosurgical ablation of the prostate.

After years relegated to the role of an “alternative therapy”, cryotechnology has caught up with cryobiology. Ultrasound monitoring allows accurate visualization of the freeze zone. Smaller (3-mm or less diameter) cryoprobes allow atraumatic placement. Using the Joule-Thompson effect, extreme temperature changes occur when argon gas is expanded rapidly into the outer of two chambers. Thermocouples give notice when freezing approaches important structures such as the external sphincter or rectum, and switching to helium gas and its opposite (warming) reaction to the Joule-Thompson effect thaws tissue quickly. Finally, warming catheters protect the urethra. Based on these advances, we are finally achieving success with complication rates comparable to radiation options.

The freeze zone created by the 3-mm probe systems we currently use is approximately 4 cm in diameter and 4-5 cm in length. Their flame-shaped iceball correlates with the quasi-conical shape of the prostate. Cell death occurs at 20-40 degrees below zero Celsius, and is assured by double freezing. Using 4-8 probes (usually 6), we can sculpt the prostate with tolerable damage to extraprostatic tissues. Men with prostates greater than 50-75 grams are treated following six months’ LHRH therapy to optimize the prostate volume.

Protective thermocouple probes are placed in the external urinary sphincter and between rectum and prostate. Others are placed into the neurovascular bundles and prostatic apex to ensure that freezing reaches these vital areas. The urethral warming catheter is in place only during the procedure in previously untreated patients, but is left in place for an hour in the recovery room in patients undergoing salvage therapy following radiation failure.

Although men with locally persistent cancer following radiation therapy are obvious candidates due to the high complication rates of salvage prostatectomy, two-thirds of our patients present for primary therapy. Complication rates for salvage cryotherapy are higher than they are with primary treatment, but still appear to be lower than the rates with salvage prostatectomy. Finally, cryotherapy at present is appropriate only for men who understand they will probably not have spontaneous erections following treatment. Although some centers report that occasional men have normal erections following cryotherapy, we currently treat only men who are willing to accept the likelihood of erectile dysfunction.

We do not currently perform “focal” or “nerve-sparing” cryotherapy. However, we will spare the lateral aspects at the location of the NVB in carefully selected men with unilateral cancer who have undergone negative office-based saturation biopsy of the contralateral prostate. This experience is too limited to make definitive statements regarding success. We regard this as investigational at present.

Like radiation, cryotherapy leaves a small amount of residual prostate tissue so PSA remains detectable in most men. Fortunately, tissue remaining after cryotherapy is typically near the urethra due to its preservation courtesy of the warming catheter. This minimizes urethral slough and incontinence, but also leaves a source of detectable PSA. It also leaves a potential source of cancer recurrence in the uncommon situation where the tumor is near the urethra.

There is no universally accepted PSA level confirming cure, but using ASTRO criteria we have found that >90% of both primary and salvage patients have successful cancer control in early follow-up. All are enrolled in an ongoing database of localized prostate cancer patients, and survival curves are being generated. Cryotherapy provides disease control and survival through five to seven year follow-up, rivaling surgery and radiation in the published literature.

Penile or rectal pain occurs in about 10% of patients, and has resolved in 6 weeks to 6 months. We have experienced urethral sloughing and incontinence in less than 5%, and have observed no urethrostomy or fistulæ.
Radical retropubic prostatectomy has historically included complete removal of the seminal vesicles (SV) because of their relatively common involvement by cancer in the pre-PSA and early PSA eras, with reported rates of 19% to 26%. More recently, several studies have demonstrated that SV invasion is rare in men with lower Gleason grades and PSA levels, suggesting that the tips of the SV may be left in place to facilitate ease of prostatectomy without compromising the chance for cure. Some have also suggested that sparing the SV minimizes injury to the trigonal nerves that subservice micturitional sensation and minimizes traction injury to the pelvic plexus and neurovascular bundles, improving postoperative return of continence and potency.

The involvement of the SV by prostate cancer is a well-defined adverse prognostic factor that often dictates the use of adjuvant therapy. For that reason, we undertook a retrospective review of a large, multi-institutional database to determine the pretreatment factors that are associated with tumor involvement of the SV and the likelihood of long-term cure by surgery alone in those with SV invasion.

A retrospective analysis was undertaken of 6,740 patients (treated between 1983 and 2004) who underwent a radical prostatectomy without neoadjuvant or adjuvant therapy and complete removal of the SV. Pathological analysis was performed by serial step-sectioning, which included examination of the SVs according to standardized techniques. Five hundred sixty-six patients (8.4%) had SV invasion. The 5 and 10-year bRFS rates were 85.7% and 77.2% for those with negative SV, and 38.0% and 25.6%, respectively for those with positive SV (Figure). In multivariate analysis, age, margins, extracapsular extension, SV invasion, LN positivity, Gleason score, and PSA were significant predictors of SV involvement. Continence and potency were similar to those reported by other centers of excellence, and equal or better than those reported in series where the SVs were spared.

This study documents the therapeutic efficacy of complete removal of the SV at the time of prostatectomy, demonstrating that at 5 and 10 years after surgery, 38% and 26% of patients with SV invasion, respectively, are disease free without adjuvant therapy. These findings are important because:

- SV invasion is often occult and difficult to predict for an individual patient even at the time of surgery.
- The best chance for cure is complete SV removal.
- More patients than previously thought are cured by complete removal even if they have SV invasion.
- Even if adjuvant therapy is given for positive SV, their removal diminishes the chance for local recurrence and decreases tumor burden.
- While SV sparing is unlikely to compromise the chance for cure in lowest risk patients, it leaves some patients at risk for recurrence with no functional advantages.

The findings strongly support that complete removal of SV is indicated at the time of radical prostatectomy.
The total number of TURPs in the United States continues to fall. In order to ensure that our current and future residents are well trained in the art of resection, we must continue to do these resections in some form.

At The Cleveland Clinic, we have critically evaluated the Gyrus device (both from a resection and a vaporization aspect) as an alternative to traditional electrocautery TURP in large prostate glands (>80 grams). The Gyrus device was evaluated for treatment of large prostates (80-117 grams) between September 2004 and March 2005.

Both the larger resection loop as well as the plasma V vaporization loop were evaluated. Operative times were greater than one hour in 90% of patients. No blood transfusions were required.

There were no abnormal electrolyte findings appreciated in any of the cases performed. All patients were admitted after the procedure, but none required more than one night of hospitalization. No re-operations have been performed to date. Because of the safety benefits of saline irrigation, residents are able to resect prostatic tissue for longer periods of time.

Under appropriate supervision, this may lessen the total number of cases required in the learning curve for residents to become acceptable resectionists in this era of declining TURP procedures. We also have begun a clinical trial using a new and improved vaporization loop known as the Gyrus Super V. Initial results have been promising with all patients undergoing the procedure on an outpatient basis.
Increased PSMA Expression — Cause of Disease or an Innocent Bystander?

Warren Heston, Ph.D.

The Urological Oncology Research Laboratory continues to investigate the role of PSMA function in the normal and abnormal prostate. All of the literature suggests that PSMA expression is associated with aggressive disease. It is also considered an excellent target for therapy and imaging because it is expressed on nearly 100% of metastatic tumors. The question is whether this increased expression is a cause of aggressive disease or whether PSMA is merely an innocent bystander.

We observed that if we inserted PSMA into non-expressing prostate tumor cells that it reduced, but did not eliminate their invasive properties. When we reduced PSMA expression in prostate tumor cells that normally express PSMA, it increased their invasive properties when examined using a Boyden Chamber assay and matrigel-coated plates as an in vitro test of invasiveness.

Because the situation in vivo as in laboratory models or patients can be different from in vitro tests, we are currently investigating the impact of PSMA expression in vivo. Since PSMA is a target for imaging and therapy, we also are exploring how different imaging and therapeutic agents impact a cell’s invasive characteristics. Early results suggest substantial differences between different PSMA ligands.

PSMA is expressed on nearly 100% of metastatic prostate tumors and is expressed in all solid tumor-associated neovasculature, making it an excellent target for imaging and therapy. Antibodies are being used for targeting, and in the near future The Cleveland Clinic will begin a clinical trial using second generation anti-PSMA antibodies linked to cytotoxins.

To determine whether we could target these analogs to the prostate, we linked them to an antagonist of PSMA enzymatic activity and were surprised to find that the new molecule had much better binding affinity than the original antagonist. We are currently performing structure activity relationships to optimize this type of analog and create better therapeutic targeting agents and imaging agents. The recent definition of 3-D structure of PSMA will aid in these studies. In a lab model, we have knocked out the lab model’s equivalent of human PSMA. The models continue to provide insight into the function of PSMA, as well as provide a laboratory model to design small molecules as PSMA imaging and targeting agents.
Bladder Cancer: Well past time to move beyond “superficial” and “invasive”

In an era of high technology medical care, urothelial cancer surveillance and treatment have stagnated. Mortality rates are steady despite the emergence of digital optics, bladder tumor markers, intravesical therapy and chemotherapy.

Even though cytology series fail to detect most tumors, cystoscopy and conventional urinary cytology remain the primary diagnostic tools. Likewise urologists can suspect malignancy on endoscopy based only on the presence of visible changes such as tumors or “red spots.” But fluorescence cystoscopy demonstrates that many malignant areas can be completely indiscernible by even highly experienced cystoscopists. Both small papillary tumors and almost one-third more cases of CIS are overlooked by cystoscopy.

Underestimating disease extent is also common. Many patients diagnosed with high-grade “superficial” disease actually have invasive, extravesical, or even metastatic disease. Patients may progress dangerously further into their disease course before definitive treatment is instituted. A recent survey found that 81% of urologists were reluctant to recommend cystectomy for patients with high-grade persistent Ta-T1 disease after two courses of intravesical immunotherapy. This reticence should end. Studies document that patients on surveillance protocols actually may have mortality rates almost double those whose tumors are muscle invasive at the time of diagnosis.

Like other malignancies, bladder cancer is a genetic disease caused by oxidative DNA damage. Two separate genetic pathways occur. One leads to noninvasive, papillary tumors, which usually follow an indolent course except in the <5% of cases that convert to the second pathway leading to high-grade or invasive cancer.

Unlike noninvasive papillary tumors, high-grade tumors (whether CIS, T1, or invasive) tend to have numerous and greatly variable chromosomal gains and losses regardless of whether they are “superficial” or “invasive.” Because of their different genetic imprint, some have suggested that papillary pTa tumors might be effectively benign or a completely different disease than high-grade tumors.

Using in-situ hybridization of fluorescently labeled DNA probes (FISH) allows detection of chromosomal abnormalities in urothelial cells and offers an objective measurement of the cells’ genetic profile. The degree of aneuploidy is related to the likelihood of tumor progression regardless of histological grade or stage. This allows early categorization into low-grade (genetically almost normal) vs. high-grade (genetically chaotic and aggressive).

We recently reported such testing on patients with known malignancy whose cytology had failed to detect the tumor. To determine how many of these cases could be identified, we stained archived cytology slides and found that FISH detected 85% of the cancers that had been missed by cytology, including 23 of 24 high-grade tumors, and all cases of CIS. We subsequently confirmed the conclusions prospectively in 250 patients. In addition to the positive predictive value of molecular testing, we found that of patients clinically free of cancer at the time of FISH testing, 26% were FISH positive. Only 38% of such patients remained disease free through the study period, compared with 95% of those FISH negative. Moreover, almost two-thirds of these “anticipatory positive” findings identified recurrence of high-grade cancer a mean of four months prior to cytological or cystoscopic evidence of recurrence.

These studies here and at other institutions demonstrate that the traditional categories of “superficial” and “invasive” are not only inadequate, but can mislead the patient and physician into potentially dangerous reassurance. It is time for our categorization to marginalize stage and emphasize the grade and molecular aspects of TCC in order to appropriately guide patient management and minimize the risk of progression to incurable stages.
Managing Iatrogenic Foreign Bodies Within the Bladder

Howard B. Goldman, M.D.

Iatrogenic foreign bodies can be a frustrating complication of incontinence surgery. When patients present with recurrent UTI, pain, or hematuria, (even years after surgery) a cystoscopy should be performed. A 70° angle lens should be used to inspect the areas near the bladder neck, and either a 0° or 30° angle lens should be used to inspect the urethra.

Prior to laparoscopic procedures, most foreign bodies were sutures. Endoscopic techniques are usually sufficient for suture removal. After the stitch is grasped with a device or stone basket, it should be placed on tension. Using endoscopic scissors or a laser, the stitch can be cut at the level of the bladder mucosa at which point the rest of the stitch “bounces back” and is free of the bladder. In some cases, open removal is necessary depending on the location of the stitch or excessive stone formation on it.

With the advent of laparoscopic techniques used in performing a Burch retropubic suspension, other foreign bodies such as eroded staple lines, screws and various anchors are now found. Our protocol is to use an endoscope if one or two staples/screws are noted. If an entire row of staples has eroded through, it is usually easier to remove them through a small abdominal incision.

Recently, a number of synthetic mesh slings have been detected within the bladder. Some may have been placed at the time of surgery and missed during cystoscopy; while others were likely placed within the detrusor or placed under tension and eroded into the bladder. Because of the tissue in-growth within the interstices of the polypropylene slings, they cannot be placed on tension, cut, and then have the cut edges “bounce” out of the bladder wall. If the sling is cut at the bladder wall, the sling ends are left protruding through the mucosa. Some have reported success with laser excision of these slings at the level of the bladder mucosa, but we have found an open procedure is usually necessary to remove all the exposed portions. Even with maximal open exposure and the mesh isolated both within and outside of the bladder wall, it is nearly impossible to simply pull the mesh out. Typically a small portion of the surrounding bladder wall has to be removed with the mesh.

Our technique is as follows: Through a Pfannenstiel or lower midline, extraperitoneal incision, expose the bladder and open it to identify the mesh. Locate both the entry and exit points. Put tension on the portion within the bladder and find the mesh outside the bladder. If one arm of the mesh is near the bladder incision, extend the incision to that point. Core a small portion of bladder wall around the mesh perforation site and cut the mesh outside of the bladder so that the mesh can be removed entirely. Close the small holes in the bladder with a figure-eight absorbable suture. Close the bladder. Leave a Foley catheter in for one week. The mesh not involving the bladder can be left in place. With this technique, most patients are managed successfully after one procedure and an overnight hospital stay.

Algorithm For Iatrogenic Foreign Bodies in the Bladder

| History of recurrent UTI’s, pelvic pain, or hematuria + History of anti-incontinence surgery |
| Careful cystoscopy with 70° angle lens for bladder and 0° or 30° angle lens for urethra |
| Suture or one or two staples/screws identified in accessible position |
| Multiple staples/screws or synthetic mesh |
| Attempt endoscopic removal |
| Successful Failed → Open removal |

Laparoscopic tack inadvertently placed within the bladder during a laparoscopic Burch. It was removed endoscopically.

Polypropylene mesh loop within the bladder. Removed via open approach.
Pelvic organ prolapse (POP) is a major health care problem and will increase as the population ages. Estimates of the annual number of POP procedures performed in the United States range up to 500,000.

In many cases, the predominant problem is loss of apical support. Procedures to restore apical support have evolved from uterine fixation to anterior abdominal wall; to sacral hysteropexy; and then to abdominal sacrocolpopexy (ASC). A recent review of the literature showed that 39 out of 46 studies of ASC had success rates of at least 90%.

However, the desire for less invasive approaches led to the development of the transvaginal sacrospinous colpopexy (SSLF). While this leaves no visible scar and provides a quicker return to normal activities, it requires an adequate vaginal length, specialized instruments, and a high degree of training and skill.

No large, multicenter study compares open ASC and SSLF, but the impression from the literature review and clinical experience is that open ASC has a success rate around 95%, while that of SSLF is around 75%-80%.

We have investigated and applied laparoscopic approaches in an effort to obtain the results of open ASC while avoiding the morbidity of an abdominal incision. These include a traditional laparoscopic sacrocolpopexy (LSC) with and without robotic assistance, and our latest innovation, the laparoscopic-assisted percutaneous vaginal vault suspension (Figure 1).

Laparoscopic-Assisted Percutaneous Vaginal Vault Suspension: Technique

After the peritoneum over the vaginal apex has been incised, the prolapse is reduced with a bivalve speculum. Two small stab incisions are made in the labial folds just lateral to the vagina at the 4 and 8 o’clock positions (Figure 2).

Strips of polypropylene mesh cut 1.5 x 30 cm are passed using Stamey needles with a suture tied to the mesh. Care is taken to pass these in the subvaginal wall plane. The laparoscopic view helps direct the mesh just lateral to the vaginal apex, where the needles are passed into the abdomen. The mesh is then grasped laparoscopically and pulled into the field. The mesh strips are left along the entire length of the vagina, and trimmed at the level of the labial skin. Each strip then requires only one stitch to hold it in place. A third stitch is thrown near the apex, joining both mesh strips to each other and to the vaginal wall.

No large, multicenter study compares open ASC and SSLF, but the impression from the literature review and clinical experience is that open ASC has a success rate around 95%, while that of SSLF is around 75%-80%.
**Uterine Prolapse Repair Without Hysterectomy**

Our innovative procedure for vaginal vault suspensions after hysterectomy may also be applied to cases of uterine prolapse repair. The technique replaces the uterosacral ligaments to support the vagina and uterus. It is easier and safer than open or conventional laparoscopic techniques (Figure 4).

![Figure 4. Percutaneous placement of bilateral prolene mesh through the perineal body, along the lateral recto-vaginal fascia (RVF) and through to the vaginal apex in (A) vaginal vault suspension after hysterectomy, or (B) for uterine suspension for uterine prolapse.](image)

**International Registry for Laparoscopic Cystectomy Established**

14 centers from around the world have already joined L

aparoscopic radical cystectomy for bladder cancer is a relatively new approach to the disease. During the past five to seven years, approximately 300 such procedures have been conducted worldwide.

The Cleveland Clinic has assumed the responsibility for ensuring that the new procedure is developed efficiently to its maximum potential by establishing an International Registry for Laparoscopic Radical Cystectomy for Bladder Cancer. Inderbir S. Gill, M.D., laparoscopic urologic surgeon and Derek Raghavan, M.D., Ph.D., director of the Cleveland Clinic Taussig Cancer Center, are co-directors of the registry.

The goal of the registry is to draw upon worldwide experience to create uniform surgical techniques, standardize peri-operative data collection, and create a long-term oncologic and functional follow-up database. Computerization makes the acquisition and exchange of data exceedingly efficient and allows the creation of a far larger database than would otherwise be obtainable. The registry will allow investigators to evaluate and draw conclusions from hundreds of such procedures, enable refinements to the procedure and allow evaluation of outcomes to rest on a far broader foundation of experience.

To date, 14 centers of excellence around the world have agreed to contribute to the registry. Representatives from these institutions will discuss the design and potential of the registry at the 23rd World Congress on Endourology this year in Amsterdam, the Netherlands.
Urinary incontinence affects 40% of adult women, with stress urinary incontinence (SUI) accounting for a large portion. Over 165,000 surgical procedures are performed for SUI, with slings offering both the highest success rate as well as the highest rate of morbidity and complications.

The introduction of transvaginal tape (TVT) has led to a new generation of minimally invasive procedures. The TVT utilizes synthetic prolene mesh placed through vaginal incisions with trocars that are passed retropubically through the abdominal wall. The sling is placed at the level of the mid urethra under no tension. Many products utilize a similar technique.

To reduce morbidity, the mid-urethral sling has undergone multiple modifications, including suprapubic, prepubic and transobturator approaches. No modification has addressed the question of “how loose the sling should be?” Currently, there is no evidence that the new generation of slings has changed the complications associated with this procedure, which include voiding dysfunction such as urinary retention.

In a review of 800 cases of slings, the percentage of women who had at least one complication was a minimum of 18% and a maximum of 62.9%. The cause of most sling complications is thought to be due to excessive pressure applied to the bladder outlet causing obstruction (BOO). The clinical evidence for this explanation comes from BOO seen in men due to BPH and from the mechanical obstruction seen in women after obstructive anti-incontinence procedures. The experimental data for effects of induced BOO have followed that clinical paradigm—demonstrating changes in the in-vivo and in-vitro function of the bladder and the detrusor muscle in urethral obstruction models.

Despite some validity of the BOO theory, unresolved issues include: a) no experimental study has specifically addressed how a sling as only a hammock support without a complete circular obstructive effect on the urethral could cause BOO; b) why have none of the sling modifications in which no tension is applied to the hammock support still continue to create identical complication rates?

To address the unresolved research questions, we developed and validated a new murine model of a vaginal sling procedure built upon a previously validated lab model of SUI, in which reproducible changes in the Leak Point Pressure (LPP) measurement were reported. This lab model replicates all the principles of mid-urethral sling in the female murine model.

We have used our lab model to test the research question of whether the hammock support of sling at its suburethral section is required for the sling’s anti-incontinence effect. We hypothesized that cutting the sling at its suburethral section does not cancel its anti-incontinence effect.

In a randomized trial, SUI was created in 60 female murine models by the previously established method of bilateral pudendal nerve transection. Under anesthesia, the lab models underwent either vaginal sling (n=20); vaginal sling in which the suburethral portion of sling was cut immediately after its placement (n=20); or sham vaginal sling (n=20). Six weeks after the procedures, the LPP and anesthetized CMG were examined via a previously implanted suprapubic catheter.

Our results showed that both cut and intact sling increased the LPP levels six weeks after placement (24.9 and 27.9 cm H2O respectively) which were significantly higher than the sham sling (20.7 cm H2O) (p<0.0001). The peak micturition pressure was not significantly different among the three groups indicating absence of bladder outlet obstruction in the sling groups. Bladder compliance was significantly reduced six weeks after placement of cut or intact sling compared to the sham sling (p= 0.007 and 0.05 respectively).

This study suggests that an intact suburethral portion is not a requirement for effectiveness of the sling in the murine model of SUI. However, the sling reduces bladder compliance and may explain the observed voiding dysfunction associated with sling procedures. The results also indicate that this model can be used in addressing open and unresolved clinical questions related to sling, sling material or SUI.
Various neuromodulation devices have been implanted in more than 500 patients for the treatment of urge incontinence, urinary frequency, idiopathic retention, interstitial cystitis, pelvic pain and bowel dysfunction. This milestone represents one of the world’s largest and diverse clinical experiences with neuromodulation therapy and serves as a clinical resource in tracking long-term outcomes associated with specific treatment indications.

Interstim, which is implanted in two stages, is the currently available FDA approved device for voiding dysfunction. A test stage determines if the therapy is effective. This entails percutaneous implantation of a specially-designed lead through an appropriate sacral foramina and stimulation of the sacral nerves with an electrical impulse. Proper location of the lead is verified via appropriate sacral responses in the patient and by fluoroscopic localization of the lead. The outpatient procedure is performed under IV sedation and local anesthesia. The patient wears a small generator externally during the trial period. If patients note a greater than 50% improvement in their condition, implantation of a permanent pulse generator in the upper buttock is performed within a few weeks.

Initially, this therapy was reserved for patients with overactive bladder symptoms (urge incontinence and urinary frequency and urgency). However, it has been found to be effective in patients with idiopathic retention and other pelvic organ and muscle diseases. Currently, neuromodulation is also being used for those with interstitial cystitis and some bowel dysfunctions.

Outcomes were reported recently at a number of national and international urology meetings. Overall, 75% of patients in whom a Stage 1 procedure is performed will have a good response and go on to have the permanent implant placed. Of those patients, the vast majority maintain a persistent response, though occasionally a revision is necessary.

We have even found success in patients with challenging disorders. For example, treatment has been successful in 67% of patients with bladder dysfunction, secondary to neurologic disease. Sustained success has been more of a challenge in patients with interstitial cystitis, where only 52% of those who had implants reported sustained success 10 months post treatment.

We are currently involved in research studies helping to design and test the next generation of neuromodulation devices as well as evaluating approaches to the nerves of the pelvis. Current research focuses on accessing the pudendal nerve and its branches at different sites and using stimulators with unique characteristics such as the Bion device. Using this extensive experience, we will continue to seek innovative ways to provide better patient care for those with challenging voiding and pelvic disorders.

During the first stage of neuromodulation therapy, a small lead wire is inserted through the sacrum.
Pelvic Organ Prolapse Research Focuses on Urothelial and Autologous Stem Cells

Raymond Rackley, M.D., Margot Damaser, Ph.D., Adonis Hijaz, M.D., Joe DiDonato, Ph.D., and Steven Campbell, M.D.

Physician scientists within the Section of Female Urology have created two new programs in the Urothelial and Stem Cell Biology Laboratory of the Lerner Research Institute: the immortalization of urothelial cells of the bladder; and the use of autologous stem cell and tissue regeneration to restore pelvic organ dysfunction.

The GU tract is composed of heterogeneous organs consisting of a large variety of cell types that interact in physiological and cellular processes responsible for maintaining health and preventing disease. Obtaining an abundant supply of individual somatic cell types is key to accelerating research studies, biotechnology applications and translational therapeutics.

Somatic cells have limited proliferative potential as these cells lose telomeric DNA each time they divide. This occurs as a function of age in vivo or in cell culture before the cells enter a nondividing state called replicative senescence.

There is an urgent need to develop methods that allow the immortalization of GU somatic cells in culture to avoid the replicative senescence barrier without losing other normal cellular properties. Recently, a novel way has been achieved that bypasses replicative senescence by retroviral mediated expression of the human telomerase reverse transcriptase (hTERT) gene.

This imparts immortality to somatic cells grown in culture without causing neoplastic transformation, karyotype instability, or phenotypic changes when compared to their parental cells. We have established a successful retroviral system for telomerase transfection in bladder urothelium, and we expect to be able to produce and share immortalized urothelial cell lines. In the near future, we hope to share other GU somatic cell-types to researchers who need an unlimited supply of standardized GU cell-types from healthy organs as well as cells from organs with diseases such as interstitial cystitis and bladder cancer.

We believe this work will accelerate molecular studies on the GU tract that require unlimited somatic cell-types needed for cellular comparisons of unique differences in gene and protein expression, as well as, the cellular function of individual cell types within GU organs.

The second program addresses stress urinary incontinence (SUI), one of the most common symptoms of pelvic organ dysfunction, common after vaginal delivery and with advancing age.

These causes were the basis for the development of the vaginal distention laboratory model for SUI in a murine model, which allows study of the continence mechanism as measured functionally by leak point pressure (LPP) and histologically by degeneration of the urethral sphincter. Interestingly, this dysfunction is transient; it reaches a nadir 4 days after the distention and recovers by day 10-14.

Moreover, our recent research has revealed that there is concomitant ischemia to the lower urinary tract with vaginal distention. Translational findings in an ischemic cardiac myopathy murine model reveals that the ischemic event triggers the transient appearance of homing molecules that invite the model’s own bone marrow stem cells to migrate to the area of ischemia for repair, resulting in improvement in cardiac function.

Following the cardiology model, we hypothesize that the recovery in urethral sphincter after vaginal distention induced ischemia may be secondary to transient expression of these homing molecules and subsequent migration of stem cells to the injured area. In our new program, we will investigate if particular homing molecules are expressed in the lower urinary tract with vaginal distention and whether this expression results in migration of bone marrow stem cells.

Future work will focus on whether injections of these homing molecules will induce functional and histological recovery of the sphincter mediated through the migration of bone marrow stem cells. The results of this study will help us better understand the mechanism of injury and recovery in the lower urinary tract with vaginal delivery. It will also provide us with a potentially new therapy for medical intervention using recruitment of autologous stem cells as a treatment modality for SUI and other pelvic organ dysfunctions.
Successful Urethral Reconstruction in Patients Undergoing Excision of a Urethral Stent

Kenneth W. Angermeier, MD

In 1996, the FDA approved the Urolume stent. While the device has a reported success rate of approximately 80%, a subset of those treated will require ex-plantation due to recurrent stenosis or poor tolerance, such as perineal pain or urinary incontinence.

Complete removal of the stent endoscopically can be difficult and, if successful, always results in a recurrent stricture that is often refractory to conservative treatment. Definitive treatment in older patients or those who are poor candidates for anesthesia would usually consist of perineal urethrostomy at the time of open stent excision. However, this may not be an acceptable solution to younger patients or those who are medically and physically fit.

Definitive urethral reconstruction at the time of open stent excision is the preferred method of treatment, but this is often difficult due to the presence of full thickness spongiofibrosis and, at times, a full thickness urethral defect after the stent is excised. There are few published reports addressing this issue.

To date, we have surgically treated four patients with Urolume stent excision and simultaneous urethral reconstruction. The patients’ ages were 21, 32, 44 and 77 years. The oldest patient presented with severe obstructive voiding symptoms, whereas the youngest patient complained of severe perineal pain and significant urinary incontinence without recurrent stricture. The two other patients also described perineal pain and incontinence, and were found to have recurrent stricture disease. In each case, the stent was excised completely, with the oldest patient undergoing reconstruction via primary urethral anastomosis and the others using buccal mucosa. In one of the buccal graft patients, we were able to mobilize the urethra sufficiently to perform a dorsal urethral anastomosis with placement of a ventral buccal mucosa graft (augmented anastomotic repair).

Urethral mobilization in the other two patients did not allow urethral anastomosis, and we were left with a full thickness defect. Reconstruction in each case was accomplished using a 3 cm dorsal buccal mucosa graft that was spread fixed onto the corporal bodies to recreate the urethral plate, followed by a 5 cm buccal graft placed ventrally.

Spongioplasty was completed over the ventral graft using corpus spongiosum that was preserved with its proximal blood supply intact during stent excision. These patients have been followed closely with flexible cystoscopy and symptom assessment. All four patients have done well to date with no recurrent strictures and complete resolution of perineal pain and incontinence.

This small series re-emphasizes the importance of patient selection when using a Urolume stent. Younger patients may be more likely to develop local symptoms with this device, and reconstruction is more difficult if it has to be removed with the patient having many years at risk. Early results after stent excision and urethral reconstruction seem to indicate that stent-related perineal pain and incontinence can be reliably improved with a low incidence of recurrent stricture.
Persistent Lower Urinary Tract Symptoms and Complex Urethral Diverticula

Sandip P. Vasavada, M.D., Raymond R. Rackley, M.D., Howard Goldman, M.D., Firouz Daneshgari, M.D., and J. Stephen Jones, M.D.

Urethral diverticulum is among the most challenging pathologies to diagnose and treat. It should be considered in a patient with LUTS refractory to standard therapy. Patients may experience urgency, frequency, dysuria, pelvic pain, dribbling or obstruction.

Pelvic MRI is the gold standard for diagnosis, offering high sensitivity without radiation. At The Cleveland Clinic, we use an external coil 1.5 T magnet with a study sequence requiring no intravenous gadolinium contrast. Patients void a small amount immediately prior to the exam while maintaining the rest of the urine in the bladder. Mid, sagittal, axial and coronal reconstructions yield the presence or absence of a diverticulum, as well as its extent, loculations, size and location. We have had an extensive experience with complex diverticulae.

During the procedure, a flap of the anterior vaginal wall is carefully dissected with scissors, taking care to keep this dissection superficial over the periurethral fascia, to avoid entrance into the diverticulum. The periurethral fascia is opened transversely. The dissection must be carried out precisely, and each layer should be identified and preserved to assist in later reconstruction. This dissection is easier while the diverticulum is still full of fluid, as a full sac aids in identification of the edge of the sac and its subsequent mobilization off the urethra and surrounding tissues. Inflating a pediatric Foley in the diverticulum can also be helpful.

In an intact urethral diverticulum, the wall is opened transversely and a collection of pus and fluid is drained. The lumen is typically seen, and the thick wall of the sac is dissected free from the spongy tissue of the urethral wall. The Foley balloon is then taken down and the catheter is brought into the urethral lumen. Irrigation of the urethra should demonstrate the diverticular ostium. The urethral communication site is identified and closed.
Urethral disruption managed with buccal mucosa

BLADDER

Urethral disruption managed with buccal mucosa

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Strategies for Preventing Oxidative Stress-Induced Injury to Human Spermatozoa
Ashok Agarwal, Ph.D., HCLD

Oxidative stress (OS) due to excessive generation of reactive oxygen species (ROS) has been implicated as a major cause of sperm dysfunction. Spermatozoa are susceptible to OS-induced damage because their plasma membranes are rich in polyunsaturated fatty acids. Factors increasing the production of ROS include lifestyle habits, infections, intrinsic defects in spermatozoa, and many methods of sperm handling, processing, and storage, which have evolved with the advent of assisted reproductive techniques (ART).

It is difficult to block OS-induced injury to cells or tissues because ROS are continuously produced by the aerobic metabolism of cells. Spermatozoa contain very limited cytoplasmic enzymes, which are required for the repair of peroxidative damage. With the aim of preventing OS-induced injury, several clinical trials are under way at The Cleveland Clinic to determine how OS damage can be minimized.

There are two types of antioxidants: prevention and scavenger. Prevention antioxidants include metal chelators and metal binding proteins, which block the formation of new ROS, whereas scavenger antioxidants remove the ROS that have already formed. Both prevent the action of ROS on spermatozoa.

**Prevention Antioxidants**
Transition metal ions such as iron, lead and cadmium adversely affect the male reproductive system either by directly acting on the sperm plasma membrane or by catalyzing ROS formation (Fenton’s reaction). Metal chelators control lipid peroxidation of the sperm plasma membrane and protect the integrity of the spermatozoon, and also prevent DNA damage. Metal chelators such as DL-penicillamine, 2,3-dimercaptopropan-1-sulphonate, and meso-2,3-dimercapto-succinic acid are being used to improve the quality of sperm in ART. albumin, ceruloplasmin, and metallothionein are proteins that interact with iron and copper and decrease ROS formation.

**Scavenger Antioxidants**
OS may also be limited by using chain-breaking antioxidants such as vitamin E and vitamin C. Vitamin C neutralizes hydroxyl, superoxide, and hydrogen peroxide radicals and prevents sperm agglutination. In addition, it also helps recycle vitamin E, which neutralizes H2O2 and protects the plasma membrane from lipid peroxidation.

Other important antioxidant components include carotenoids such as beta-carotene and lycopene. Glutathione plays an important role in protecting lipids, proteins, and nucleic acids against oxidative damage, and selenium is a necessary component for the synthesis of glutathione peroxidase and works synergistically with vitamin E. Other antioxidants may also protect against OS.

Modifying lifestyle habits such as smoking cessation, reducing alcohol intake, and avoiding exposure to environmental pollution can reduce the occurrence of OS. The use of specific sperm separation techniques, such as migration-sedimentation, density gradient centrifugation, and glass-wool filtration significantly reduce the level of ROS by removing leukocytes, which are the major source of ROS. In vitro supplements used during sperm preparation and ART also help protect spermatozoa against ROS. Moreover, adding antioxidants to the culture media neutralizes ROS produced by the leukocytes and immature spermatozoa and improves sperm-oocyte fusion. Similarly, it has been found that adding N-acetyl-L-cysteine, glutathione and hypotaurine protects spermatozoa against oxidative damage induced by H2O2. Pentoxifylline – a methylxanthine derivative that inhibits phosphodiesterase – has been approved by the FDA. It has a beneficial effect on sperm motility and acrosome reaction and reduced the O2− release by the human spermatozoon. The use of vitamin E in vitro has been also documented to improve sperm motility and viability.

**Summary**
Studies are under way at The Cleveland Clinic to determine the safe dose of antioxidants for human consumption.

Development of new antioxidants that target specific types of ROS and various measures that can be used to protect spermatozoa against the OS-induced injury are the areas of future research.
Combining Magnetic Cell Sorting Technique with Sperm Preparation for Assisted Reproduction

Ashok Agarwal, Ph.D., HCLD

The low fertilization and implantation rates in assisted reproduction may be related to programmed cell death (apoptosis), which decreases sperm quality after cryopreservation. A classic feature of apoptosis is the externalization of phospholipid phosphatidylserine (PS) residues, normally present on the inner leaflet of the sperm plasma membrane. Annexin-V has a high affinity for PS but cannot pass through an intact sperm membrane. Therefore, when annexin-V binds to spermatozoa, it signifies that the integrity of the membrane has been disturbed.

Colloidal super-paramagnetic microbeads (~50 nm in diameter) conjugated with annexin-V may be used to separate dead and apoptotic spermatozoa by magnetic cell sorting (MACS). Cells with externalized PS and deteriorated plasma membranes will bind to these microbeads. When placed into a separation column containing super-paramagnetic annexin V conjugated microbeads and passed through a strong magnetic field, the apoptotic and dead spermatozoa (annexin-positive) are retained in the column. On the other hand, non-apoptotic cells with intact membranes (annexin-negative) do not attach to super-paramagnetic annexin V conjugated microbeads and pass freely through the column (Figure 1).

To determine if MACS technology can improve rates of ART, we conducted a study to evaluate the quality of the non-apoptotic sperm prepared by MACS while examining its tolerance to cryopreservation-thawing (cryosurvival rate) as well as its oocyte penetration potential.

Semen specimens collected from healthy donors were prepared by double density gradient centrifugation (DGC) followed by MACS or DGC only (controls). The sperm quality was monitored in terms of motility and the presence of apoptotic markers: caspase-3 activation (CP-3), disruption of mitochondrial membrane potential (MMP) and externalized phosphatidylserine residues. The percentage of sperm that survived the cryopreservation process (percentage CSR) was calculated using the following formula: 100 \( \times \) post-thaw total motile sperm/pre-freeze total motile sperm. The sperm-oocyte penetration potential was assessed using the zona-free hamster oocyte penetration assay (SPA). Results of the SPA were evaluated as the percentage of oocytes penetrated by sperm (percentage penetrated) and the average number of sperm per oocytes penetrated (sperm capacitation index, SCI). For results of the study, see Table 1.

Our results clearly indicate that the selection of non-apoptotic spermatozoa by MACS should be considered to enhance success rates of assisted reproduction.

The cryosurvival rate (%CSR) was highest in the annexin-negative spermatozoa that were separated by MACS prior to freezing when compared with the annexin-positive spermatozoa.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Controls</th>
<th>Annexin-negative</th>
<th>Annexin-positive</th>
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</thead>
<tbody>
<tr>
<td>Motility (%)</td>
<td>76.2 ± 8.6</td>
<td>83.2 ± 8.1**</td>
<td>19.2 ± 9.7**</td>
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<tr>
<td>Caspase-3 (% active)</td>
<td>8.9 ± 8.1</td>
<td>3.7 ± 1.2*</td>
<td>57.6 ± 16.1**</td>
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<td>MMP (% intact)</td>
<td>87.9 ± 11.1</td>
<td>92.2 ± 8.4**</td>
<td>39.1 ± 15.7**</td>
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<td>Externalized PS (% positive)</td>
<td>5.8 ± 3.2</td>
<td>3.4 ± 1.7</td>
<td>54.9 ± 18.1**</td>
</tr>
<tr>
<td>Percentage penetrated oocytes</td>
<td>33.8 ± 6.9</td>
<td>44.5 ± 12.6**</td>
<td>20.8 ± 5.3**</td>
</tr>
<tr>
<td>SCI</td>
<td>1.5 ± 0.6</td>
<td>1.8 ± 0.3*</td>
<td>1.2 ± 0.4*</td>
</tr>
</tbody>
</table>

Values are expressed as mean ± standard deviation. **p < 0.01; *p < 0.05 in comparison to controls. Controls = separation by double density gradient; MACS = magnetic cell sorting; MMP = mitochondrial membrane potential; PS = phosphatidylserine; SCI = sperm capacitation index, average number of sperm penetrated per oocyte.

Figure 1
On April 27, 2005, during National Minority Health Month, the Glickman Urological Institute Minority Men’s Health Center (MMHC) held its 3rd Annual Minority Men’s Health Fair.

Cleveland Browns football legends Jim Brown and Reggie Rucker lent their support by promoting the event and then being on hand to meet and greet health fair participants. Several current Cleveland Browns football players also attended.

Over 700 minority men attended this free event, which included screenings for prostate cancer, blood pressure, lipid disorders (cholesterol and triglyceride), diabetes, glaucoma, colorectal cancer, head and neck cancer, body fat composition, lung disease and heart disease. Participants had the chance to attend various health talks on topics including prostate cancer, diabetes, hypertension and heart disease.

A host of volunteers from the Glickman Urological Institute, and other departments including Primary Care Medicine, Laboratory Medicine, Cardiology and Endocrinology collaborated to make the health fair a great success. Several agencies from Northeast Ohio also participated at the health fair including LifeBanc of Ohio, Minority Organ Tissue Education Program, the Cleveland YMCA, Cleveland Public Library, 100 Black Men of Cleveland, American Cancer Society, American Red Cross and the Cleveland NAACP.

Minority men are plagued with a significantly higher risk of developing urological diseases, such as prostate cancer and kidney disease, as well as hypertension and diabetes. The MMHC’s mission is to inform and educate the minority community in a culturally competent fashion about the merits of healthy lifestyle patterns. The MMHC has also developed a dedicated community outreach program designed to promote wellness and improve health literacy in the minority community.

With a focus on prevention, the MMHC encourages minority men to access early screenings for detection and subsequent treatment of diseases. Several men who attended the health fair were found to have previously undiagnosed elevated blood pressures, cholesterols, blood sugars and abnormal PSAs.

To further basic science, members of the MMHC staff are involved in research with colleagues from the Cleveland Clinic Lerner Research Institute. Studies are focusing on why minority men develop prostate cancer on average three years earlier than Caucasian men, and why minority kidney transplant recipients develop higher rates of transplant rejection.
New Non-academic Mentoring Program Eases the Stress of Residency

Residency is difficult; no one argues otherwise. A new nonacademic mentoring program started in 2001 for 20 residents in the Cleveland Clinic Glickman Urological Institute has successfully taken some of the strain off those turbulent years.

J. Stephen Jones, M.D., FACS, Associate Professor of Surgery (Urology), founded the one-of-a-kind nonacademic mentoring program. He recalls how the idea came to him: “The residents had had a particularly bad week, and I realized that many of these young professionals had moved away from family and friends to do their urological residency at the Clinic. We provide good academic, clinical, and surgical mentoring, but residents were without a social infrastructure.”

Dr. Jones created the nonacademic mentoring program to provide that missing piece. Many of the Institute’s professional staff of 62 physicians and researchers volunteer to mentor and befriend one or more residents.

“Physicians are high stress people,” Dr. Jones says. “We want to ensure that our residents’ mental and physical well being are every bit as protected and mentored as their academic well being.”

Mentor and resident meet several times a year outside the hospital. Dr. Jones explains his mentoring style: “We talk. I ask questions such as: ‘How are things at home? Were you able to replace your car? Do you still have a houseguest? How are you getting along with so and so?’”

Residents choose mentors or are assigned mentors on a mutually-agreed basis. A resident can change mentors if needed, without any negative ramifications, but that has happened only once in the nearly four years of the program, due to timing not personalities.

Ryan Hedgepeth, M.D., a fifth year resident in urology who was introduced to the program in July 2001, calls the mentors “global role models.”

“Residency is such a radical experience,” Dr. Hedgepeth says. “It is really difficult to find balance in your life. The nonacademic mentoring program provides social and professional support to develop a successful professional career and maintain a personal life.”

A second benefit Dr. Hedgepeth sees is that the program opens up lines of communication between staff and residents. “There is a lot of pressure, politics and personalities to deal with in a large academic program,” he says. “Open communication is essential to dealing with those issues, and this program provides the outlet.”

The nonacademic mentoring program has spawned an offshoot called the Top Doc Series started by residents in July 2004. Each month, a professional staff member lectures on his or her specialty, gives a short biographical overview, followed by a Q&A. “Residents are always interested in how these world-renowned surgeons make decisions and how they balance professional goals with their personal life,” Dr. Hedgepeth says.

Jonathan Ross, M.D., vice chairman of the Institute and assistant director of the residency program, helps organize the residency program and assign mentors. “This is a great program,” Dr. Ross says, “because it officially recognizes that personal issues can impact physician well-being and ultimately affect patient care.”

Ja-Hong Kim, M.D., a fifth year urology resident and one of six women in the residency program, said that the purpose of the mentoring program is that “there is one person who is going to be my ally.” She credits her mentor, Eric Klein, M.D., with having “an open door approach” that frees her to ask him for career advice or help with a specific problem.

Dr. Hedgepeth insists the program is more effective than reading a self-help book on balance. “It is much more beneficial for me to see how Dr. Jones sets aside time to have coffee with his wife and how my mentor, Dr. Jim Ulchaker, always makes time to attend his children’s events.”

Dr. Jones is pleased that the program has achieved its intended outcome and recognizes an additional benefit from the mentor’s perspective: “There is tremendous satisfaction in helping these bright young people achieve their potential.”
As medical school enrollments have hovered in recent years at 50 percent female, women have begun entering fields long dominated by men. The Cleveland Clinic’s traditional male-oriented urology residency program, which has graduated one female urologist in the past 60 years, has undergone a dramatic shift with the arrival of six female residents.

According to Kristene E. Whitmore, M.D., past president of the Society for Women in Urology, “women now comprise 20 percent of residents in urology residency programs in the United States.” At The Cleveland Clinic, women have exceeded the average, comprising one-quarter of the 24 urology residents.

In 1988, Dr. Whitmore became only the thirteenth board certified female urologist in the country, but the trend is changing. The number of board certified women has steadily increased, Dr. Whitmore says, from less than 200 in 2000 to 277 in 2005.

“Urology has been one of the last surgical specialties to attract women,” says Drogo Montague, M.D., program director of the Clinic’s Urology Residency Program. “These six women are not going exclusively into pediatric urology or female urology, like the few women urologists of the past,” Dr. Montague says. “They are choosing erectile dysfunction, cancer, kidney stones, reconstructive surgery and transplantation. This is a very good thing. And it is changing our specialty.”

Why They Were a Match
The Clinic’s urology residency program is one of 121 accredited residency programs in urology in the United States. “The criteria for matching is not different for women than for men,” Dr. Montague insists. “We want to train academic urologists, and we look for evidence of very high scholastic standing, evidence of previous research, and scholarly goals.”

He noted that the six female residents “all were academically accomplished as medical students and they have continued being academically productive during their residencies.”

The Clinic’s rigorous program appealed to the current female residents for various reasons. “I chose the Clinic for my residency because it offers a very technical program and a broad range of complex cases,” says Connie Marks, M.D., a fifth year resident.

The guaranteed year of research appealed to second year resident Hadley Wood, M.D. “That feature was very attractive in terms of my career choices,” says Dr. Wood.

With the exception of their final year as Chief, residents spend much of their clinical training in outpatient clinics, seeing patients, doing outpatient procedures, and learning to treat medical problems. “Male and female residents take the same calls, operate the same hours and have the same issues with the intensity of the program,” Dr. Montague says.

Women in a Male Specialty
Although women are outnumbered by men 4 to 1, it is not an issue. “If I had a real problem with being outnumbered, I wouldn’t have chosen this field,” Dr. Wood says frankly.

“Most women in this specialty are pretty confident of their abilities to relate to both men and women.”

Dr. Marks agrees. “I don’t feel like one of the guys but that has never been my objective. I am certainly one of their colleagues, and I have the full support of the staff. That is what interests me.”

As an African American, Dr. Marks says she is sensitive to long-held perceptions that are slow to change. “If there are any issues at all, they are social adjustment issues, and frankly, in the 21st century, it is time for the adjustments to be made.”

Patient Response
While staff and male residents have welcomed women, on occasion, male patients are surprised when a woman enters the examination room.

“Male objections to a female urologist occur far less than you might think,” Dr. Montague says. “In general, women spend more time with patients and show more compassion. Urologic care has improved because of this.”

“We are in the midst of a micro revolution,” Dr. Marks says. “If there is a story, it is that it is not that big of a story. Women are doing the same work as our male counterparts. We are transitioning just fine. We are progressing along the evolutionary pathway.”
**Preceptorship Programs**

**Preceptorship Program in Laparoscopic Surgery**

The National Urology Resident Preceptorship (NURP) in Laparoscopic Surgery is an invitation-only preceptorship. Residents must be nominated by their program directors of accredited national urology residency programs.

Held during the past three years at the Glickman Urological Institute, the symposium includes live laparoscopic surgical demonstrations with two-way real-time interaction with the surgeon, didactic lectures, discussed video sessions, inanimate trainer session, and “hands-on” laboratory sessions in live models.

Program directors are invited to nominate one resident (PGY-3 or higher) who displays a keen interest in and potential for laparoscopic and/or academic urology. The program is free to the accepted applicants who are responsible only for airfare and ground transportation. The preceptorship is limited to 60 residents. For information about the 2006 preceptorship, contact 216/444-8043.

**Fourth Annual Preceptorship Program in Female Pelvic Medicine & Reconstructive Surgery**

The 4th National Urology Resident Preceptorship Program in Female Pelvic Medicine & Reconstructive Surgery (NURPP in FPM&RS) was held February 21-24, 2005, in Weston, Florida. Over 70 PGY3-4 residents from more than 70 urology residency programs from the United States, Canada and Latin America participated in the four-day program.

The curriculum included didactic lectures on clinical and research topics, live surgery broadcast and group discussion of translational research. Dr. Gamal Ghoniem hosted the program in the Weston Campus of The Cleveland Clinic. Drs. Shlomo Raz and William Steers were guest faculty. In addition, Dr. Chris Winters represented the Board of Directors of the Society for Urodynamics and Female Urology (SUFU) at the NURPP.

The meeting was held in conjunction with annual scientific meeting of the SUFU, which waived the registration fee for the residents. In addition, the Board of Directors of SUFU approved up to 10 travel awards per year for future participants of the NURPP. The travel award will allow the residents who participate in NURPP to also attend the annual scientific meeting of SUFU.

The NURPP continues to be supported by a grant from National Institutes of Health and an unrestricted educational grant from Pfizer, Inc.

For more information about future meetings, call 216/444-3677 or email daneshf@ccf.org.
Upcoming Conferences

Don’t Miss This Conference!

Ambulatory Urology
April 7–8, 2006
An update on the most current, state-of-the-art practice and medical issues of ambulatory urology. The presentations will focus on the two-track system in urology, recognizing that more urologists practice the ambulatory track, than the surgical track. The conference will feature noted urologists from around the country. Confirmed faculty include Mark Soloway, M.D., Miami; Neil Baum, M.D., New Orleans; and Richard Kerr, M.D., editor in chief of Urology Times. For more information or to register, e-mail keppc@ccf.org.

World Congress of Endourology Convenes in Cleveland in 2006
The 24th World Congress of Endourology (WCE) will be held at the InterContinental Hotel and MBNA Conference Center August 8–12, 2006. WCE is the official annual meeting of the Endourology Society, founded in 1983 to advance the field of endourology, laparoscopic surgery and minimally invasive urology worldwide. The scientific program will include live surgical modules; “hands-on” live laboratory sessions; robotics and virtual reality simulation programs, breakout sessions; postgraduate courses; state-of-the-art lectures; debates; panel discussions; meet-the-professor events and sponsored symposia. The program will cover endourology, laparoscopic surgery, extra-corporeal shock wave lithotripsy, female urology, being prostatic hyperplasia, transurethral surgery, and robotic surgery. It is anticipated that 1,500 to 2,000 delegates from 60 countries will participate in the conference. Dr. Inderbir S. Gill is chairman of the 24th World Congress.

For more information or to register, visit www.2006wce.com. Registration deadline is December 15, 2005.

Residents and Fellows Receive Recognition

Courtney Moore, M.D., a fellow in Female Pelvic Medicine and Reconstructive Surgery, was named a Research Scholar by the American Foundation for Urologic Disease, which was recently made a part of the American Urological Association (AUA).

Ja-Hong Kim, M.D., received the 2004 American Urogynecological Society’s Scholarship Award. Dr. Kim also won 3rd prize at Ohio Urological Society resident essay contest, March 2005.

John C. Thomas, M.D., was awarded the North Central Section’s John D. Silbar Award.

Ryan Hedgepeth, M.D., won 2nd prize at the Ohio Urological Society resident essay contest March, 2005.

Brian Lane, M.D., received the Crile Research Fellowship Award for July 1, 2005 through June 30, 2006.

Ryan K. Berglund, M.D., received the 2005 SLS Outstanding Laproendoscopic Resident Surgeon Award.

David S. Sharp, M.D., was awarded the Bruce Hubbard Stewart Memorial Award for Humanistic Medicine, June 2005.

How to Refer

Appointments with Cleveland Clinic Glickman Urological Institute physicians can be made by calling the numbers listed below.

From outside the Cleveland area, call: 800/553-5056, request Ext. 45600
From within the Cleveland area, call: 216/444-5600

For your convenience, offices are located in Beachwood, Elyria, Euclid, Independence, Lakewood, Mayfield Heights, Strongsville, Warrensville Heights, Westlake, Wooster and Charleston, WV. Please ask the appointment secretary how to schedule at these locations.

Visit Us on the Web

Please visit the Glickman Urological Institute Website at www.clevelandclinic.org/urology.
Professional Staff

Andrew C. Novick, M.D.
Chairman, Glickman Urological Institute
Specialty Interests: urologic oncology, renal vascular disease, adrenal disease, transplantation
Joint appointment with Transplant Center, Cancer Center

Matthew D. Barber, M.D.
Specialty Interests: urogynecology, pelvic organ prolapse, incontinence
Joint appointment with Obstetrics and Gynecology

George V. Coseriu, M.D.
Specialty Interests: general urology, benign prostatic hyperplasia, incontinence, erectile dysfunction, urologic oncology

Gerard A. DeOreo Jr., M.D.
Specialty Interests: diseases of the prostate, prostatic ultrasound, female incontinence, general urology

Ashok Agarwal, Ph.D., HCLD
Director, Andrology Laboratory and Reproductive Tissue Bank
Specialty Interests: andrology and male infertility, sperm cryopreservation in cancer patients, reactive oxygen species, and sperm DNA damage
Joint appointment with Obstetrics and Gynecology, Clinical Pathology and Immunology

Jonathan C. Boyd, M.D.
Specialty Interests: Stone management, prostate and bladder cancer, incontinence, general urology

Louis D’Amico, M.D.
Specialty Interests: general urology
Joint appointment with ENH Medical Center

Mihir Desai, M.D.
Specialty Interests: endourology and stone disease, laparoscopic and minimally invasive surgery

Kenneth W. Angermieier, M.D.
Specialty Interests: lower urinary tract reconstructive surgery, urethral stricture disease, genitourinary prosthesis, Peyronie’s disease, urologic oncology

Robert Fairchild, Ph.D.
Director, Transplant Immunology Laboratory
Specialty Interests: T-lymphocyte tolerance, transplantation immunology
Joint appointment with Immunology, Transplant Center

Margot Damaser, Ph.D.
Specialty Interests: female incontinence, pelvic floor dysfunction, urodynamics

Robert Dreicer, M.D.
Specialty Interests: genitourinary medical oncology, experimental therapeutics, cancer pain management
Joint appointment with Hematology/Medical Oncology, Cancer Center

Ronald M. Bukowski, M.D.
Specialty Interests: medical oncology, biologic response modifiers, genitourinary cancer
Joint appointment with Hematology and Medical Oncology, Immunology, Cancer Center

Steven C. Campbell, M.D., Ph.D.
Specialty Interests: bladder, prostate, kidney, testicular and penile cancer
Joint appointment with Obstetrics and Gynecology

Firouz Daneshgari, M.D.
Co-Director, Center for Female Pelvic Medicine and Reconstrcutive Surgery
Specialty Interests: female urology, voiding dysfunction, neurourolgy, pelvic organ prolapse
Joint appointment with Obstetrics and Gynecology

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Professional Staff

Amr Fergany, M.D.
Specialty Interests: Bladder, prostate and renal oncology

James H. Finke, Ph.D.
Specialty Interests: Tumor immunology, lymphokines/monokines, immunotherapy
Joint appointment with Cancer Center, Immunology

Stuart M. Flechner, M.D.
Specialty Interests: Renal transplantation, vascular disease, general urology, prostate cancer
Joint appointment with Transplant Center

Jihed Kaouk, M.D.
Co-Director, Robotic Urologic Surgery
Specialty Interests: Laparoscopic and robotic urologic oncology and reconstructive surgery

Inderbir S. Gill, M.D.
Head, Section of Laparoscopic and Robotic Surgery
Specialty Interests: Laparoscopic urologic surgery, adrenal disease, kidney-pancreas transplantation, renal vascular disease
Joint appointment with Transplant Center

Peter S. Heeger, M.D.
Co-Director, Program in Transplantation Immunology Research
Specialty Interests: Transplantation research, kidney transplantation, nephrology, immunology
Joint appointment with Immunology

David A. Goldfarb, M.D.
Specialty Interests: Adrenal disease, renal physiology, renal vascular disease, renal transplantation, prostate cancer
Joint appointment with Transplant Center

Michael Kattan, Ph.D.
Specialty Interests: Prediction, medical decision making, quality of life assessment, patient preferences, decision analysis

Warren Heston, Ph.D.
Specialty Interests: Prostate cancer, gene therapy
Joint appointment with Cancer Center, Pediatrics

Brian R. Herts, M.D.
Specialty Interests: Genitourinary radiology, imaging of renal tumors, 3D imaging
Joint appointment with Radiology

Robert Kay, M.D.
Chief of Staff
Specialty Interests: Pediatric urology
Joint appointment with Cancer Center, Pediatrics

Eric A. Klein, M.D.
Head, Section of Urologic Oncology
Specialty Interests: Urologic oncology, continent urinary diversion, prostate cancer, bladder cancer, testicular cancer
Joint appointment with Cancer Center

Julian A. Gordon, M.D.
Division Chief, Urology and Co-chief of Medical Staff, South Pointe Hospital
Specialty Interests: General urology, prostate disease, incontinence, erectile dysfunction

Inderbir S. Gill, M.D.
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Specialty Interests: Laparoscopic urologic surgery, adrenal disease, kidney-pancreas transplantation, renal vascular disease
Joint appointment with Transplant Center

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Head, Section of Urologic Oncology
Specialty Interests: Urologic oncology, continent urinary diversion, prostate cancer, bladder cancer, testicular cancer
Joint appointment with Cancer Center
Professional Staff

Venkatesh Krishnamurthi, M.D.
Specialty Interests: renal and pancreas transplantation
Joint appointment with Transplant Center

Elroy D. Kursh, M.D.
Specialty Interests: management of prostate disease, including benign enlargement

Milton M. Lakin, M.D.
Head, Section of Medical Urology
Specialty Interests: evaluation of male sexual dysfunction, prostate diseases, hematology
Joint appointment with General Internal Medicine

William A. Larchian, M.D.
Specialty Interests: urologic oncology, prostate disease, gene therapy for urologic tumors

Sanford S. Luria, M.D.
Specialty Interests: general urology, infertility

Christina Magi-Galluzzi, M.D., Ph.D.
Specialty Interests: genitourinary pathology, surgical pathology, molecular pathology

Stephen A. Mahoney, M.D.
Specialty Interests: general urology, female urology, prostate cancer, benign prostatic hypertrophy, incontinence

Charles S. Modlin Jr., M.D.
Co-Director, Minority Men’s Health Center
Specialty Interests: renal transplantation
Joint appointment with Transplant Center

Drogo K. Montague, M.D.
Head, Section of Prosthetic Surgery and Genitourthral Reconstruction
Specialty Interests: genitourinary prosthetics, impotence, urinary incontinence

Mark J. Noble, M.D.
Specialty Interests: general urology, female urology, incontinence, microsurgery

Jerome O’Hara Jr., M.D.
Specialty Interests: genitourinary and gynecologic anesthesia
Joint appointment with General Anesthesiology

Marie Fidela R. Paraiso, M.D.
Specialty Interests: urogynecology, pelvic organ prolapse, advanced laparoscopic surgery, incontinence
Joint appointment with OB/GYN

Arthur Porter, M.D.
Division Chief, Urology, Hillcrest Hospital
Specialty Interests: general urology, impotence, minimally invasive treatment of prostate, prostate cancer, kidney and bladder tumors

Jeannette M. Potts, M.D.
Specialty Interests: medical urology, infectious diseases

C. Thomas Powell, Ph.D.
Specialty Interests: basic science research

Raymond R. Rackley, M.D.
Co-Director, Section of Voiding Dysfunction and Female Urology
Specialty Interests: female urology, male and female voiding dysfunction, pelvic organ prolapse, urothelial cell biology
Joint appointment with Cancer Biology
Professional Staff

Derek Raghavan, M.D., Ph.D.
Chairman, Taussig Cancer Center
Specialty Interests: prostate cancer and prostatic disease, bladder cancer
Joint appointment with Cancer Center

Jonathan H. Ross, M.D.
Vice-Chairman, Glickman Urological Institute
Head, Section of Pediatric Urology
Specialty Interest: pediatric urology
Joint appointment with Cancer Center, Pediatric Surgery

Bashir Riad Sankari, M.D.
Specialty Interests: renal transplantation, renal vascular surgery
Joint appointment with Charleston Area Medical Center

Robert A. Shapiro, M.D.
Specialty Interests: general urology, laser surgery and stone management

Rakesh K. Sharma, Ph.D.
Specialty Interests: male and female infertility, free radicals in infertility, sperm cryopreservation, endometriosis associated infertility
Joint appointment with Obstetrics and Gynecology

Daniel Shoskes, M.D.
Specialty Interests: transplantation, prostatitis, interstitial cystitis

James C. Ulchaker, M.D.
Specialty Interests: BPH, prostate cancer, bladder cancer, general urology

Sandip P. Vasavada, M.D.
Co-Head, Section of Voiding Dysfunction and Female Urology
Specialty Interests: female urology, male and female voiding dysfunction, pelvic organ prolapse, reconstruction, neurology

Mark Walters, M.D.
Co-Director, Center for Female Pelvic Medicine and Reconstructive Surgery
Specialty Interests: urogynecology, vaginal reconstructive surgery
Joint appointment with Obstetrics and Gynecology

Anthony J. Thomas Jr., M.D.
Head, Section of Male Infertility
Specialty Interests: male infertility, microsurgery
Joint appointment with Obstetrics and Gynecology

Thomas Weimbs, Ph.D.
Specialty Interests: membrane traffic in renal epithelial cells, renal cell carcinoma polycystic kidney disease

Lawrence M. Wyner, M.D.
Specialty Interests: renal transplantation
Joint appointment with Charleston Area Medical Center

Ming Zhou, M.D., Ph.D.
Specialty Interests: genitourinary pathology

Craig D. Zippe, M.D.
Specialty Interests: urologic oncology, bladder cancer, continent urinary diversion, prostate cancer, testis cancer, benign prostatic hyperplasia
Cleveland Clinic Urology Staff National Committees and Visiting Professorships
September 2004 – September 2005

Andrew C. Novick, M.D.
Visiting Professorships:
- Confederacion Americana de Urologia, Dominican Republic, Dec. 8-9, 2004
- Indian Urological Association, Ahmedabad, India, Jan. 6-8, 2005
- European Association of Urology, Istanbul, Turkey, March 16-18, 2005
- Baylor Hospital, Dallas, March 25, 2005
- Japanese Urological Association, Tokyo, Japan, April 13-15, 2005
- International Kidney and Bladder Cancer Symposium, Orlando, Florida, July 15, 2005

National Committees:
- Editorial Board, AUA Update Series
- Chairman, Kidney Advisory Council, AFUD
- Oral examiner, Campbell’s Urology
- Medical Advisory Board, Kidney Cancer Association

Ashok Agarwal, Ph.D., HCLD
Visiting Professorships:
- International Seminar on Reproductive Medicine & ART, Beijing, Sept. 2004
- American Society of Reproductive Medicine, Philadelphia, Oct. 2004
- Lucknow University, Lucknow, India, Feb. 2005
- Banaras Hindu University, Varanasi, India, Feb. 2005
- Urological Society of Pondicherry, India, Feb. 2005
- Ramachandra Medical College and Research Institute, Chennai, India, Feb. 2005

National Committees:
- Editorial Board Member, Reproductive BioMedicine Online

J. Stephen Jones, M.D.
Visiting Professorships:
- Maimonides Medical Center, Brooklyn, NY, Dec. 2004
- Hackensack University Medical Center, Hackensack, NJ, Sept. 2004
- San Francisco General Hospital (UCSF), Jan. 2005
- Cedars-Sinai Medical Center, Los Angeles, March 2005
- Hubert Humphrey Comprehensive Medical Center, Los Angeles, March 2005
- Milwaukee Urological Society Meeting, Milwaukee, April 2005
- American Urological Association, course director, May 2005

Drogo K. Montague, M.D.
Visiting Professorships:
- University of Tennessee Health Sciences Center, Memphis, TN
- University of Chang Mai, School of Medicine
- Grand Rounds:
  - Department of Urology, Brooke Army Base, San Antonio, TX

Jeannette Potts, M.D.
National Committees:
- Investigator NIH prostate/study
- Investigator NIH Radzi and Prostate Cancer Study

Raymond Rackley, M.D.
National Committees:
- American Urological Association Advisory Council
- Visiting Professorships:
  - Medical College of Georgia
  - Medical College of Wisconsin
  - University of Colorado
  - University of Florida
  - University of Hospedetta, Ankara, TR
Award:
- AUA/Nid Travel Award
- Preparing for a Career in Clinical Research in Kidney and Urothelial Diseases

James Ulchaker, M.D.
Indian Urological Society: 2004
American Urological Association, Young Leadership Committee

Sandip P. Vasavada, MD
Visiting Professorships:
- Philadelphia Urology Society, Nov. 2004
- World Congress of Endourology, Mumbai, India, Nov. 2004
- Wayne State University Department of Urology, Jan. 2005
- Pittsburgh Urologic Society, Jan. 2005
National Committees:
- University of Chicago Board Review Course, April 2005

Urology News is a publication of the Cleveland Clinic Glickman Urological Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195. Urology News is written for physicians and should be relied upon for medical education purposes only.

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The Cleveland Clinic is an independent, not-for-profit, multispecialty academic medical center. Founded in 1921, it is dedicated to providing quality specialized care and includes an outpatient clinic, a hospital with more than 1,000 beds, an education division and a research institute.

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