The Phylogeny of Medicine

William See, MD, Professor of Urology, Chairman, Department of Urology

Words are powerful tools. Contingent upon the context, the media by which they are deployed, the author and no doubt other variables, words can serve as sharp instruments through which to divide, or powerful adhesives which function to bind. The field of medicine exemplifies this concept. For example, it is possible to parse our profession into ever smaller fragments. Academic or community based, part-time or full time, employed or independent, clinician or researcher, office or hospital based, osteopathic or allopathic, physician or non-physician provider are some of the labels applied to health care professionals.

If we consider practice focus, it is possible to put an “ever finer” point on the categorization. First, there are clinical fields of practice encompassing generalist or specialist, cognitive or procedural, etc. Within each of these, further specialty distinctions are possible. Adult or pediatric, benign or malignant, male or female, reconstructive or extirpative, minimally or maximally invasive, micro or macro surgeon – the list goes on! While potentially important to our personal identity, what function do these distinctions serve for continued on page 8

Envisioning a Bright Future in Pediatric Urology

John V. Kryger, MD, Professor, Urology; Chief, Division of Pediatric Urology; Medical Director, Children’s Hospital of Wisconsin Pediatric Urology Program

I am very pleased and proud to assume the position of new medical director of Pediatric Urology at Children’s Hospital of Wisconsin, and chief of the Division of Pediatric Urology at The Medical College of Wisconsin. It is an exciting opportunity to have a leadership position in a successful, nationally recognized pediatric urology program with the support of one of the top children’s hospitals in the nation.

In addition to this role, I am also actively involved in leadership of urologic societies on a state and national level. I am currently the incoming president of the Society for Fetal Urology and a member of the Board of Directors for the North Central Section of the American Urological Association (AUA).

I am the immediate past president of the Wisconsin Medical Alumni Association and continued on page 2
What’s New in the Department of Urology?

- U.S. News & World Report has recognized Froedtert Hospital as one of the top 50 hospitals in the country for urology specialty care. See page 6 for details.

- Two of our residents graduated in June. Daniel Flewelling, MD, entered private practice in Traverse City, Mich. Anand Shridharani, MD, stayed with the Department to complete an andrology fellowship, training under Jay Sandlow, MD.

- Anas Ghousheh, MD, completed a fellowship in pediatric urology in June. Dr. Ghousheh will return to practice in his home country of Jordan.

- As a result of a generous gift from a former resident and fellow and her husband, the Department has established a new resident award. The Anna and Dickie Smither Award for Neuurology will foster resident education and research in the field of neuromurology.

- William Annesley, MD, joined the Department this spring as a staff physician and will practice at Froedtert & The Medical College of Wisconsin clinics in suburban Milwaukee. Dr. Annesley comes to us with 30 years of private practice urology experience in Milwaukee.

- The Department welcomed two new advanced practice providers in the first half of 2012. Karen Henrichs, PA-C, comes to us with more than 20 years experience as a physicians assistant. She will assist with robotic surgery procedures. Morgan Meier, CNS, APNP, joined us after recently completing her CNS training. She will work with our general urology and urologic oncology patients.

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the Wisconsin Urologic Society. My special interests include complex reconstructive surgery for children with neurogenic bladder disorders, congenital birth defects and disorders of sexual development. I am also passionate about enhancing the quality and style of surgical training for medical students, residents and fellows.

I was previously the director of pediatric urology for the past 12 years at the University of Wisconsin in Madison, Wis. and the program director of the residency training program there. Our Pediatric Urology Program is fortunate to have the ongoing involvement of many of the faculty that have made this program a great success. These include Hrair Mesrobian, MD, Charles Durkee, MD, and Anthony Balcom, MD, with more than 70 years of combined experience in treating advanced complex pediatric urologic conditions. Further, we are strengthened by the infusion of the newer energy and insight of our finest fellowship graduate Travis Groth, MD, and the ongoing participation of Michael Mitchell, MD, as Emeritus Professor of Urology.

I anticipate the future success of Pediatric Urology at Children’s Hospital will thrive on a balance of many assets. First and foremost, we will continue to maintain first-rate attention to patient care. Children’s Hospital was recently ranked among the top three in the nation by Parents Magazine. Second, our faculty are able to offer the most advanced and innovative surgical techniques, especially in all areas of complex reconstructive pediatric urology. We have, and will continue to provide the care for certain complex conditions that is only offered at some of the best pediatric urology programs in the country. Our program is listed among the top 30 in the country by US News and World Report. We also benefit from a robust system to monitor and assess outcomes that will continue to help us improve our care.

Thirdly, we will stimulate and support clinical basic science research in pediatric urology that will improve the health of children throughout Wisconsin and the nation. We will do this with outcomes-based research, participating in multi-institutional clinical trials and exploring basic science and translational research in obstructive uropathies. Fourthly, we will focus on innovation and quality education in the surgical training programs for urology. Our pediatric urology fellowship and residency training programs remain a mainstay of the mission of our academic medical center to properly train the next generation of urologists. Lastly, we will continue to actively participate in international healthcare missions, performing surgery throughout the world in collaboration with well recognized non-profit organizations.

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Our research has focused on urinary biomarker discovery utilizing research technology available at The Medical College of Wisconsin Department of Biochemistry and Biotechnology and Bioengineering Center. We are analyzing the urinary proteome (PROTEin complement of the genOMe). Proteomics is the study of the composition, structure, function and interactions of proteins directing the activities of cells or found in an environment or special condition (UPJO). Urinary proteome analysis has been a rapidly growing discipline with applications in biomedical research aimed at discovery of disease biomarkers, better understanding of physiology and biology, and discovery of new therapeutic modalities. More than 2,000 proteins have been identified in normal urine. Individual proteins, which are increased or decreased in their level of abundance in disease compared to normal, are valuable biomarkers. Analysis of the urinary proteome as a whole can identify underlying pathologic processes taking place in a diseased kidney. Biomarker-linked functions of interest include inflammation, cell death, oxidative stress, tubular or glomerular damage and interstitial fibrosis. In addition, 30 percent of the urinary proteome is derived from the general circulation. Therefore, the urinary proteome has been interrogated for early markers of coronary heart disease, hepatic carcinoma, diabetes and neurologic disorders, in addition to urinary tract malignancies in adults. In contrast to other body fluids or tissues, urinary proteins have been shown to remain stable up to six months at -80° C and to allow the performance of reliable analyses. Two milliliters of urine is sufficient to run an experiment. The specimen is subjected to trypsin, which cuts the proteins into peptides. The latter are ionized and injected in a mass analyzer. Each peptide or fragment has a specific mass to charge ratio, which is detected by the mass spectrometer. It is analogous to sorting and counting pocket change (the mixture of peptides in the urine). The identity of the proteins is derived from matching the output data to known fragmentation patterns of proteins/peptides based on the genome.

**CASE 1:** A two-month-old boy presents with a history of prenatally detected left hydronephrosis. This is confirmed postnatally to be secondary to ureteropelvic junction obstruction (UPJO), the most common of all genitourinary (GU) anomalies detected by virtue of prenatal sonography. Despite the high grade of the hydronephrosis, the patient was asymptomatic and the diseased kidney had good function by diuresis renography (Figure 1). Therefore, he was placed on a protocol of watchful waiting. Over the following three years, the natural course of the disease unfolded, and by 27 months of age, the percentage function of the diseased kidney decreased by 11 percent and the AP diameter of the renal pelvis increased by 30 percent. The toddler remained asymptomatic throughout this period. He underwent a left dismembered pyeloplasty. This case underscores the need to discover **prognostic urinary biomarkers** that portend progression at presentation.

**CASE 2:** This baby girl presents with a similar history. She now has been followed for three years by imaging. Neither the degree of hydronephrosis nor the percentage function of the diseased kidney has changed (Figure 2). She remains asymptomatic, and our plan is to follow her indefinitely until the kidney declares itself (increasing hydronephrosis, decreasing percentage function or both). This case underscores the need to discover **diagnostic biomarkers** for early renal functional deterioration in the presence of apparent stable disease by imaging criteria alone.
Intersex and VENUS Clinic (Vaginal Enhancement in Unique Situations)

Anthony Balcom, MD, Assistant Professor, Pediatric Urology

While the terminology has changed, the emergency situation of a newborn with an indeterminate (or ambiguous) gender still exists and is a very stressful circumstance for the family. The current terminology for intersex and ambiguous genitalia is now “disorder of sexual differentiation.” This classification system was introduced in 2006 by the European Society of Pediatric Endocrinology and the Lawson Wilkins Pediatric Endocrine Society. Spearheaded by Pediatric Urology, a newly formed working group at Children’s Hospital of Wisconsin is dedicated to the evaluation and management of children (especially infants) with disorders of sexual differentiation. The working group includes representatives from Pediatric Urology, Endocrinology, Psychiatry, Psychology, Social Work, Ethics Committee, Pathology and Pediatric Radiology. This group of individuals meets to discuss children who have a disorder of sexual differentiation. The group carefully considers evaluation of the neonate or child, including a complete physical and biochemical evaluation and a targeted radiographic evaluation. Gender identity and assignment, surgical management, including masculinizing genitoplasty and feminizing genitoplasty, as well as future fertility issues for each patient are discussed, and a conference is held with the parents. Grandparents are also typically invited, and the families may choose to have a spiritual advisor involved. Our goal is to establish as precise a diagnosis of the disorders of sexual differentiation as possible to ensure appropriate treatment, and to address potential chronic medical, psychological and social issues that have lifelong consequences to help the patient and family through a stressful time. This will form the basis of a healthy long-term relationship with the family for years to come.

Another new program recently started by Pediatric Urology is the Vaginal Enhancement in Unique Situations, or VENUS Clinic for vaginal inadequacy. There are many different diagnoses that can result in vaginal inadequacy, such as Complete Androgen Insensitivity Syndrome, Mayer Rokitansky Kuster Hauser Syndrome and cloacal anomaly/exstrophy situations, to mention a few. There is also multidisciplinary representation in this clinic, including Pediatric Gynecology. These patients can present as neonates or as older adolescents. A targeted physical exam, biochemical evaluation, radiographic evaluation and counseling process are undertaken. Our goal is to treat patients with vaginal inadequacy in a very sensitive, individualized, age-appropriate, patient-directed manner. We offer the complete range of treatments including the no treatment/delayed treatment approach, nonsurgical treatments such as progressive pressure techniques, and surgically constructed/enhanced neo-vaginas that may be performed using laparoscopic techniques. The patients treated in the newly formed Disorders of Sexual Differentiation Clinic will benefit from the multidisciplinary approach to disorder of sexual differentiation, and ultimately may also need the expertise of the new VENUS Clinic.

Our studies have focused uniquely on patients with SFU grade 4 hydronephrosis and confirm the presence of statistically significant differential levels of abundance of a number of urinary proteins and polypeptides between normal and UPJO. Our results strongly point to the presence of inflammation, apoptosis, tubular fibrosis and oxidative stress in the hydronephrotic kidney even prior to the emergence of increasing hydronephrosis and or decreasing function by imaging. We are now in the process of validating these results in a prospective fashion. Our ultimate goal is to design a point of care urinary test, which identifies early glomerular or cellular injury, inflammation, oxidative stress and cell death before the onset of fibrosis and irreversible injury. An appropriate analogy is the treatment of acute myocardial infarction since 1960, which has evolved over time in major part because of the discovery of more specific and sensitive markers of injury. This has resulted in a reduction in mortality by 50 percent during this time period. The evolution from serum LDH to troponins in this decade is remarkable. Current modalities (serum creatinine) for assessing renal function are inadequate or too invasive (renal biopsy). The urinary proteome contains information equivalent to a renal biopsy. Our treatment paradigms for UPJO and other GU diseases including malignancies in adults may change.

Anthony Balcom, MD
Laparoscopic surgery has been used in pediatric surgery since the 1970’s. However, these procedures were solely used for diagnostic purposes. The first laparoscopic cholecystectomy was performed in 1985, and the first laparoscopic nephrectomy was performed in 1990. These procedures demonstrated the feasibility of laparoscopic surgery, along with the great promise it held to decrease patients’ morbidity of certain operations. In a short period of time, laparoscopic surgery, also referred to as minimally invasive surgery, has become the standard of care for the treatment for various surgical conditions in pediatric and adult patients. This has been made possible because of advancements in technology of endoscopic optics and miniaturization of instruments.

Currently, our department offers various minimally invasive surgery (MIS) procedures for children, including robotic assisted laparoscopic surgery for various conditions. Numerious studies have demonstrated that MIS is as effective and as safe as open surgery in children. Laparoscopic surgery involves making only a couple of incisions that are under 1cm in size to allow for the endoscope (camera) and a couple of ports for instruments to perform the entire procedure. Since the surgery can be performed through small incisions, MIS offers several benefits to patients, including decreased post-operative pain, improved cosmetics, shorter hospital stay and quicker return to full activity when compared to open surgery. Because of these advantages, MIS has become more prevalent in the treatment of pediatric urologic surgical conditions.

In 1998, Intuitive Surgical, Inc. developed and released the first da Vinci Surgical System® (e.g., robotic assisted laparoscopic surgery). Although the da Vinci Surgical System is referred to as a “robotic system” or “robotic assisted laparoscopic surgery,” it is not truly a robot, because it cannot function independently and is controlled solely by the surgeon. Robotic surgery or tele-operator surgery was first conceived by the United States Department of Defense for possible remote surgery for injured soldiers. Computer enhanced surgery (robotic surgical systems) was developed to overcome limitations of conventional laparoscopy which include two-dimensional visualization and instrumentation with very limited articulation, making intracorporal suturing and knot tying difficult.

The da Vinci Surgical System has quickly gained prominence nationally because of the benefits the system provides for adult and pediatric surgical laparoscopic cases. The robotic system provides three-dimensional visualization, visual magnification, filtration and removal of any physiologic tremor. Also, the surgeon has improved dexterity from the EndoWrist laparoscopic instruments that allow for 90-degree articulation, much like a human wrist. These benefits allow for easier intracorporal suturing and knot tying, making the technology ideal for pediatric reconstructive urologic surgery. Surgery that used to be performed solely as an open surgical repair can now be performed as robotic assisted laparoscopic surgery with similar results, along with providing the global benefits of MIS to these patients.

The most common robotic assisted laparoscopic surgeries in pediatric urology include: pyeloplasty for ureteropelvic junction obstruction, ureteral re-implantation for vesicoureteral reflux, nephrectomy, nephroureterectomy, bladder surgery and genitourinary reconstructive surgery.

Recently, the first robotic assisted laparoscopic procedure was performed at Children’s Hospital of Wisconsin for the treatment of an ureteropelvic junction obstruction.
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Robotic assisted laparoscopic surgery has now become close to the standard in adult urology for prostatectomies and other laparoscopic surgeries. Nationally, close to 80 percent of all prostatectomies are performed robotically. However, robotic laparoscopic surgery has been less available for children.

Recently, the first robotic assisted laparoscopic procedure was performed at Children’s Hospital of Wisconsin for the treatment of an ureteropelvic junction obstruction. Children’s Hospital has the only dedicated pediatric robotic surgery program in Wisconsin and is one of only a handful of pediatric free-standing hospitals in the nation with its own robotic system. We also have a robotic training simulator helping to train future physicians in this new technology.

We are very excited about the future and the opportunity to provide our patients with the access and benefits of this technology at a pediatric hospital dedicated to treating children’s unique needs.

REFERENCES


Medical College of Wisconsin Urologists Among Best Doctors in America®

Thousands of physicians across the country are surveyed each year to identify the most skilled specialists treating complex medical conditions. A total of 318 Medical College of Wisconsin physicians who practice at Froedtert were nominated by their peers as the Best Doctors in America® 2012-2013. In Urology, these include:

- Anthony Balcom, MD
- Carley Davis, MD
- Robert Donnell, MD
- Michael Guralnick, MD
- Kenneth Jacobsohn, MD
- Peter Langenstroer, MD, MS
- R. Corey O’Connor, MD
- Jay Sandlow, MD
- William See, MD

To learn more about these physicians, visit froedtert.com/bestdoctors.

Recognized for Urology Expertise in U.S. News & World Report

Froedtert Hospital is recognized in a total of 12 specialty areas - including Urology - in U.S. News & World Report’s 2012-13 “Best Hospitals” list, released last year. Froedtert received national ranking in urology, diabetes/endocrinology, gastroenterology and nephrology. This places Froedtert Hospital among the top 50 U.S. hospitals in these areas. In addition, the following Medical College of Wisconsin urologists were recognized by U.S. News & World Report as Top Doctors:

- Peter Langenstroer, MD, MS
- Jay Sandlow, MD
- Hrair-George Mesrobian, MD
- William See, MD
- Michael Ernst Mitchell, MD

To learn more about these physicians, visit froedtert.com.
Clinical Trials Update

Female Urinary Incontinence

InTone: A Revolutionary Device for Home Pelvic Floor Electrical Stimulation and Biofeedback for Urinary Incontinence

The purpose of this study is to assess whether or not InTone improves urinary incontinence in women. Other objectives are to determine improvement in pelvic floor muscle strength (as measured by InTone device), to determine any improvement in sexual function based on a sexual function questionnaire, and to determine usability and tolerability of the InTone device. A somewhat similar device has been studied by others and found to offer benefit in women with stress urinary incontinence or mixed urinary incontinence. However, in that study, the device was used to provide biofeedback or electrical stimulation, combined with pelvic floor muscle training, but not all three therapies together. In the study being conducted at Froedtert & The Medical College of Wisconsin, InTone is used to provide biofeedback and electrical stimulation with pelvic floor muscle exercises in patients with stress, urge or mixed urinary incontinence.

A new device for the conservative management of urinary incontinence has been developed that combines pelvic floor muscle training, biofeedback and electrical stimulation. InTone is a non-implanted cylindrical device that is inserted into the vagina. Its diameter is adjustable to the size of the vaginal opening. It uses surface electrodes to provide pelvic floor muscle electrical stimulation, as well as sensors that detect pelvic floor muscle contraction force, and provides visual biofeedback to the patient regarding pelvic muscle contraction/relaxation. It also provides verbal cues to the patient regarding the timing of each pelvic muscle contraction, thereby taking patients through a full pelvic floor muscle training session. It is able to record and store data regarding usage and strength parameters, providing a mechanism to track progress.

The trial will enroll 30 to 50 women. All participants will receive an InTone device, which they may keep after participation in the study is completed.

This study is sponsored by InControl Medical.  510(k) K110179

Bright Future continued from page 2

Highlights of this year’s pediatric urology program include:

1) Acquisition of a pediatric surgical robot dedicated to Children’s Hospital. This will enhance opportunities to explore minimally invasive surgery and improve surgical outcomes. Dr. Groth was named the first director of Pediatric Robotics Surgery at Children’s Hospital in February of 2012.

2) Multidisciplinary specialty clinics and programs will continue to build upon the expertise of faculty throughout the system to improve the care and outcomes for children and their families. In addition to a strong multidisciplinary spina bifida clinic, which cares for children with complex neurologic bladder and bowel disorders, we are actively developing additional programs. We will actively participate in development of the Fetal Concerns Center of Wisconsin (chw.org/fetalconcerns).

As the new president for the Society for Fetal Urology, I hope to bridge a relationship with other nationally recognized centers of expertise in fetal urology. We will also continue to develop a specialty program for the care of children and families with disorders of sexual development.

3) Pediatric Urology research has had a significant boost since joining collaboration with the Pediatric Surgery Clinical Research Program. With these additional resources, our program can now utilize the expertise of a dedicated pediatric research team led by Melissa Christensen and Ruth Swedler.

This will greatly facilitate faculty, fellow, resident and medical student research support. In addition, Dr. Mesrobian recently submitted an National Institutes
of Health grant to continue his basic research studies on proteomics at the molecular level of obstructive urologic disorders.

4) The Voiding Improvement Program remains a successful element in the care of children throughout the community and the state with bladder control and dysfunctional voiding disorders. This family-centered program is spearheaded by our dedicated, skilled and compassionate nurse practitioners with extensive experience in treatment of bladder and bowel conditions that can plague children throughout childhood. Our program offers advanced opportunities to incorporate medical therapy with biofeedback, complimentary medication and motivational support.

5) Our current pediatric urology fellow, Anas Ghousheh, MD, completed his two year fellowship in June of 2012. We are actively recruiting for his successor. We look forward to utilizing more surgical simulation techniques in minimally invasive surgical training in collaboration with the development of the pediatric robot surgery program.

I am proud to be part of such an accomplished program. We continue to grow with an upward trajectory and the future of Pediatric Urology at Children’s Hospital is bright. This program will continue to have major impact on local, national and international pediatric urologic care of children and their families.

My wife Lynn and I look forward to new friends and adventures in the Milwaukee area. We currently live in Brookfield and enjoy raising our two dogs, and spending time outdoors and participating in the community.

Politics and a sharply divided electorate, we must not fall prey to this risk. Within specialties and across the broader landscape of medicine, we will be far better positioned to argue in the interest of our patients and our profession given a unified voice. In the words of Patrick Henry, “Let us not split into factions which must destroy that union upon which our existence hangs.”

This issue of Urology News focuses on pediatric urology, a subspecialty area that represents an important facet of our field. Within The Medical College of Wisconsin Department of Urology, fully one fourth of the faculty focuses their energies on this area. Despite issues that are unique to their profession, the pediatric faculty’s commitment to the Department of Urology and its missions exemplifies what medicine must do to survive into the future. It is the contributions of our entire faculty, including pediatric, oncologic, robotic, reconstructive, and general that have brought us to be recognized by U.S. News & World Report as one of the top 50 hospitals in the country for urology specialty care. As you read the following exciting pages about the field of pediatric urology, and are perhaps prompted to consider your own niche area, please remember that as urologists and health care providers, our common interests far outweigh our parochial concerns.
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