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NIDDK New Research Directions in Urinary Incontinence Symposium

January 7 – 9, 2009
Bethesda, MD

Summary Report

WEDNESDAY, JANUARY 7, 2009

WELCOME

Debuene Chang, M.D., National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institutes of Health (NIH), Bethesda, MD

Dr. Chang welcomed the participants and thanked Planning Committee members for their work in organizing the meeting. The meeting was planned to provide an opportunity for brainstorming and networking to help determine future directions for research in urinary incontinence (UI).

INTRODUCTION: NEW RESEARCH DIRECTIONS

Deborah Lightner, M.D., Mayo Clinic Graduate School of Medicine, Rochester, MN

Dr. Lightner, the Chair of the meeting, thanked the Planning Committee, the abstract reviewers, and NIDDK for their contributions to organizing the meeting.

Excellence in education, research, and clinical practice related to UI must be maintained, but competition for scarce research resources is increasing. Nevertheless, exciting progress has been made in the past 10 years. Federally funded prospective randomized clinical trials have produced meaningful outcomes; evidence-based clinical practice guidelines have improved; transparency with regard to conflicts of interest is increasing; and there has been a significant push for open access, open registration of trials, and for the open sharing of ideas.

New research directions in UI should: (1) focus on important questions, (2) be rapidly translational, (3) have broad clinical application, and (4) be efficient. Efficient research implies not only the use of large rigorously designed prospective and randomized trial designs that will involve increased collaboration among talented and productive researchers from diverse geography and across specialties to achieve unassailable results. This occurs in a time where sharing of facilities and the efficient use of constrained resources are necessary. This occurs in a time where the comparative effectiveness of therapies must be considered. So together we will discuss how shall we best design, prioritize and carry out the UI research that will lead to the development of better clinical outcomes for the population.

NIDDK INSTITUTE DIRECTOR'S WELCOME

Griffin Rodgers, M.D., Director, NIDDK

Dr. Rodgers welcomed meeting participants and thanked members of the Planning Committee, especially Dr. Lightner, for their work in putting together the meeting. He also thanked the NIDDK staff, especially Dr. Chang, for their efforts.

Urinary incontinence is a common and costly problem that affects both women and men in the United States. The estimated frequency is between 20 and 50 percent in women and 17 percent in men, although these may be underestimates. Direct and indirect costs have been estimated at $12.4 billion in women and $3.9 billion in men; these are data from 2005, current estimates are higher.

Because of the enormous burden facing the American public as a result of UI, it is important for NIDDK to facilitate collaborative research in this field to better understand the complexity of this disorder. Some collaborative efforts already exist, including NIDDK's UITN and the Eunice Kennedy Shriver National Institute for Child Health and Human Development's PFDN. These network2+2 bring together investigators from multiple disciplines, including urologists, urogynecologists, geriatricians, and clinicians involved in primary care, as well as physical therapists.

It is important to energize and attract young investigators to the UI field; this is a major reason for holding this forum. This meeting also provides opportunities to exchange scientific ideas, bring people together, begin to network, and "think out of the box" to develop new ideas, which will help NIDDK to consider new approaches and set priorities as the Institute looks forward toward additional programs.

CURRENT NIH-SUPPORTED RESEARCH

Moderator: *Dr. Chang*

Review of NIDDK's UITN

E. Ann Gormley, M.D., Dartmouth-Hitchcock Medical Center, Lebanon, NH

In the mid-1990s, multiple reviews and guideline panels concluded that the literature did not focus on generalizable or comparable outcomes of the various UI treatments. In response, NIDDK issued Requests for Applications (RFAs) in 1999 and 2000 to establish the Urinary Incontinence Treatment Network (UITN), a multidisciplinary clinical research network that would design and perform clinical trials to evaluate the efficacy and safety of UI treatments.

The first trial completed was the Stress Incontinence Surgical Treatments Efficacy Trial (SISTEr), which compared two surgical procedures—the autologous fascial sling and the Burch procedure—chosen because they were considered "gold-standard procedures" with similar cure and improved rates. The trial included 651 patients; randomization was conducted in the operating room. The study included a strict definition of treatment success. The sling procedure proved superior for treating both stress-specific UI and overall incontinence, although sling

patients had higher rates of urinary tract infection (UTI) and voiding dysfunction. A longitudinal followup of participants in this trial is in progress.

A second study, Behavior Enhances Drug Reduction of Incontinence (BE-DRI), evaluated the impact of adding behavioral treatment to drug therapy. In summary, the combined drug and behavioral therapy did not produce a greater reduction in incontinence episodes over that achieved with drug therapy alone, and the addition of behavioral treatment did not enhance patients' ability to withdraw successfully from drug therapy. Combined therapy did, however, enhance patients' satisfaction with progress and perceptions of improvement relieving in part, stress UI symptoms and irritative bladder symptoms.

At the time of this meeting, another surgical trial that compared retropubic midurethral slings (RMUS) and transobturator midurethral slings (TMUS), was completed, but results were not yet available. A fourth trial comparing medical and surgical approaches for mixed incontinence had just begun; a trial assessing the value of urodynamics in uncomplicated patients (conducted in collaboration with the Pelvic Floor Disorders Network [PFDN]) was about to start; and a fitness trial was being planned.

The productivity of UITN included 30 papers published, in press and three under review. The studies underscored that multicenter collaborative clinical and surgical trials can produce high recruitment, quality data, standarized urodynamic studies and operative care across multiple sites.

Review of NICHD's PFDN

Holly Richter, M.D., Ph.D., University of Alabama at Birmingham, Birmingham, AL

The PFDN is a multicenter network established in 2001, also in response to the need for well-designed clinical research studies of female pelvic floor disorders. During its 7½ years, its multidisciplinary investigators have successfully completed prospective randomized trials for the treatment of all major areas of female pelvic floor disorders, performing credible, robust cohort studies which will influence the design of future randomized trials. The results of PFDN trials have changed the clinical paradigm in counseling and treating women with pelvic floor disorders.

PFDN trials include the Colpopexy And Urinary Reduction Efforts (CARE) trial, a randomized controlled trial designed to optimize the management of incontinence at the time of surgery for those stress-incontinent women undergoing surgery (sacrocolpopexy) for pelvic organ prolapse (POP). Participants were randomly assigned either to undergo or not undergo a Burch procedure at the time of sacrocolpopexy. The Burch procedure proved beneficial, resulting in a 20-percent absolute risk reduction for postoperative stress urinary incontinence 3 months after surgery, without increased irritative or voiding dysfunction symptoms.

Studies in progress include: (1) a trial to compare the effectiveness of an intravaginal continence pessary with behavioral therapy for stress UI; (2) a trial in (PLEASE CLARIFY_ I THOUGHT THIS WAS FOR CONTINENT WOMEN) continent women undergoing vaginal surgery for POP to assess whether treatment with tension-free vaginal tape (TVT) is superior to no

intervention in the prevention of postoperative stress UI; (3) a trial for apical prolapse comparing sacrospinous ligament fixation and uterosacral vaginal vault suspension; this trial will also compare the efficacy of perioperative behavioral therapy/pelvic muscle training in addition to surgery with that of surgery alone; and (4) an observational study of women with fecal incontinence to describe their adaptive behaviors and changes in these behaviors with effective treatment.

NEW RESEARCH ON WHOM?

Moderator: *Jennifer Anger, M.D., University of California, Los Angeles, Santa Monica, CA*

The Urologic Diseases in America (UDA) project was designed and funded by NIDDK to create a synthesis of the published data concerning the burden of urologic disease. The first national compendium was published in 2007; it presented the epidemiology of practice patterns and the economic and health impact of urologic disease on the American public in both women and men. This work provided the necessary evidence base to identify variations in care and variations in the disease prevalence. These practice variations have served as one foundation for planning strategic and evidence-based research funding. Essential in this strategic planning is determining the target populations for prevention and intervention, a key focus also of this workshop session.

Epidemiology/Natural History

Steinar Hunskår, Ph.D., Department of Public Health and Primary Health Care, University of Bergen, Bergen, Norway

While epidemiologic studies have contributed much to our understanding of UI prevention and treatment, the quality of epidemiologic research needs to improve. Many published epidemiologic studies of UI have been small and underpowered, many suffered from poor design, biased recruitment, or analytical flaws. Longitudinal study design is needed with, multivariate analysis and other advanced statistical analyses. Studies should concentrate on populations with higher UI burden; the elderly person with severe comorbidities is one such example.

An epidemiologic understanding of UI will be improved by conducting smaller numbers of large, collaborative studies not many small or parallel studies. Large longitudinal studies using defined risk classifications and linked to national registries are crucial to establish individual risk profiles. These studies have the potential for large scale prevention as well as personalized treatment. Natural history studies are still needed to identify incidence, progression, and remission, but these studies must be of high quality to give us better understanding and to enhance future trial design. More research is needed, even in areas where the current published data is substantial, such as the role of pregnancy and childbirth. The associations between UI and specific diseases such as stroke, diabetes, psychiatric disease, and genital prolapse remain poorly understood. Study designs should include blood sample collection to investigate biological factors and possible markers. Since epidemiologic studies are costly, a more cost-efficient UI study will likely involve broader community studies or the conduct of UI investigations as trailer studies in cohort studies, in randomized controlled trials on other topics.

Continence Promotion: What the Whole Population Needs to Know: Vulnerable Populations, Older Adults, Women Having Babies, Men Post Prostatectomy (PPI)
Diane Newman, M.S.N., Penn Center for Continence and Pelvic Health, University of Pennsylvania, Philadelphia, PA

UI is a prevalent and costly problem, but underreported. Health-seeking behavior is very poor; nearly two-thirds of patients are symptomatic for 2 years before seeking treatment. Many manage their problems on their own by voiding frequently, reducing fluid intake, and wearing absorbent products. UI is also undertreated. Primary care providers may perceive the problem to be a low priority: fewer than half question their patients about it. Only 40 percent of patients who ask for help receive treatment suggestions. Barriers to seeking help include associated embarrassment, a misconception that incontinence is a normal part of childbirth or of aging, a lack of knowledge of the condition and its treatments, and in the face of possible physician disinterest, a desire to not bother the physician.

Research on bladder health educational needs in older adults indicates that this population is actually confused by terms such as "overactive bladder," "bladder control issues," and "urinary incontinence." While older adults tend to attribute incontinence to the aging process, but they also are eager for ways to improve their health and daily lives, hence many older adults will discuss the problem with family members and friends. Incontinence, causing embarrassment and isolation, lowers quality of life (QOL). Because older adults are dissatisfied with the amount of time that physicians have to discuss health issues, other information sources are needed.

Evidence-based research on community continence awareness is lacking. Assessment of the impact health-promotion initiatives is difficult as individuals obtain information from many sources producing many interacting variables. Continence promotion may be enhanced by adopting evidence-based methods from other areas of health promotion, such as smoking cessation. The first annual World Continence Week, scheduled for late June, is a step in this direction.

Incontinence is a public health issue and should be regarded as such. Public education should focus on normal urinary functioning, on dispelling myths regarding the diagnosis and treatment of incontinence and thereby eliminating the stigma. Research on the most effective educational opportunities for the public and professionals on continence issues is needed.

Prevention
Ananias Diokno, M.D., William Beaumont Hospital, Royal Oak, MI

Among women age 60 and older, 2 of 10 who currently are continent will become incontinent during the next year; among men, the ratio is 1 in 10. Thus, prevention of incontinence could benefit large numbers of people.

Prevention occurs at three levels: primary, secondary, and tertiary. The term "tertiary prevention" refers to the prevention of complications and side effects in those who already have UI, for example, by improving super absorbent technology. "Secondary prevention" refers to efforts to prevent mild incontinence from worsening, for example, through behavior

modification. "Primary prevention" refers to reducing the incidence or onset of incontinence in people who do not yet have the condition.

The focus of primary and secondary prevention efforts should be on high-risk groups, which include pre- and postpartum women, pre- and postmenopausal women, community-dwelling elderly men and women, residents of nursing homes and assisted living centers, men with prostate cancer who have undergone or will undergo therapy, and neurologically or physically impaired individuals.

Comparative effectiveness studies should be performed to establish the most effective, safest, and least expensive prevention program. Such a program must be standardized in order to reach the public successfully.

Several examples were discussed: a randomized controlled primary prevention trial in postmenopausal women involved a group behavior modification program (2 hours of classroom sessions with one followup visit), the treated group scored significantly better than the control group after 12 months in terms of continence status, pelvic floor muscle strength, improved voiding frequency, and improved inter-void interval. In a secondary prevention pilot study, incontinent women treated with behavior modification showed significant reductions in incontinence severity and voiding frequency and significantly improved pelvic floor muscle strength after 6 to 8 weeks, but control women did not.

Barriers to prevention include apathy from caregivers and consumers, a lack of funded support and of standardized prevention strategies. These barriers can be reduced: a funding campaign, educational efforts to increase awareness and understanding of UI, rallying professional organizations, identifying and supporting lay champions for UI prevention, including incentives for caregivers, and establishment of standarized prevention strategies.

The Genetics of the At-Risk Population
Bertha Chen, M.D., Stanford University School of Medicine, Stanford, CA

Abnormal connective tissues are found in those with female pelvic floor disorders, but determining whether this is a cause or an effect is complicated by the multifactorial origin of pelvic floor disorders, including but not limited to age, parity, vaginal delivery, menopause, obesity, and smoking. Despite the importance of environmental factors, they do not account for all individual differences in susceptibility to stress UI and other pelvic floor disorders; genetic differences also play a role.

Epidemiologic evidence, including racial differences in prevalence and evidence from twin studies, supports a genetic role in POP. Case-control studies show a higher prevalence of stress UI among first-degree relatives of women who also have the condition. These genetic associations may be due at least in part to connective tissue differences; women with genetic connective tissue disorders, such as Marfan syndrome and Ehlers-Danlos syndrome, have higher-than-expected rates of stress UI and POP.

Molecular evidence suggests that polymorphisms in genes associated with increases in proteolytic/degradation activity of both collagen and elastin, driven by downregulation of inhibitors of the proteases, is associated with higher risk of pelvic floor disorders. Animal models also support the concept that abnormal elastin deposition is associated with POP. Differences in the activity of proapoptotic and antiapoptotic proteins also have been associated with stress UI, with susceptible animals having higher ratios of proapoptotic to antiapoptotic activity.

Genetic differences therefore determine in part the variations in: (1) growth and development of the pelvic floor, (2) response to cyclic reproductive hormonal fluctuations throughout life, (3) response to aging, and (4) wound repair and tissue regeneration. Investigations of these genetic differences should continue to identify the specific families of genes responsible for these variations. The use of blood bank libraries would be helpful in such studies. Existing evidence suggests that these associations are applicable to translational research, and lead to effective clinical treatments. For example, it may be possible to use hormonal manipulation to overcome an identified genetically increased risk of pelvic floor disorders or to use pharmacogenetic agents to block or slow the process of apoptosis, overcoming the genetic differences in wound repair and tissue regeneration.

Pregnancy/Partuition

Carolyn Sampselle, Ph.D., R.N.C., The Carolyne K. Davis Collegiate Professor of Nursing, University of Michigan, Ann Arbor, MI

The 2007 NIH State-of-the-Science Conference on the Prevention of Fecal Incontinence and Urinary Incontinence in Adults concluded that pelvic floor muscle training (PFMT) and biofeedback are effective in preventing and reversing UI in women in the first postpartum year.

Results from the PERL Project (Promoting Effective Recovery from Labor), a trial of self-directed pushing in second-stage labor to prevent UI, showed that women with the greatest degree of objectively measured urinary leakage at 35 weeks gestation were most likely to have UI at 6 weeks, 6 months, and 12 months postpartum; the method of delivery also was a consistent predictor of incontinence. The findings imply that a test of leakage at 35 weeks gestation can provide a "teachable moment" for targeted, conservative self-management interventions.

Findings from this and other studies suggest that the "Knack Maneuver," a volitional pelvic floor muscle contraction to preempt expected stress UI, could: (1) be a valuable stand-alone brief intervention for urinary incontinence, (2) improve adherence to PFMT, and (3) be the basis for a widely disseminated media-based public health initiative on preventing incontinence (e.g., a "squeeze before you sneeze" campaign). Pelvic floor muscle training could be promoted for its potential beneficial effects on sexual pleasure as well as its preventive effects against urinary incontinence.

New research directions suggested by this work include: (1) the possibility of screening for objective UI in late pregnancy, (2) introducing conservative interventions for those women who demonstrate incontinence in late pregnancy, (3) considering Knack instruction as a stand-alone

intervention and a method to promote adherence to PFMT, and (4) investigating the motivating effect of the potential sexual benefits of PFMT.

Discussion

Dr. Anger noted that the use of absorbent pads is a self-management strategy that helps women with UI maintain their QOL. She asked Ms. Newman whether and how health professionals can help older women who use these products. Ms. Newman replied that because absorbent products are available in retail stores, consumers get the message that they may be the only solution to UI. Consumers often are surprised to learn that other approaches exist. Ms. Newman also noted that it is unlikely that absorbent products will ever be reimbursable in the United States, and that their cost is a problem for some users.

Dr. Anger asked each speaker to highlight one area of research that he or she thought deserved funding from NIDDK. Dr. Hunskår called for more emphasis on elderly women with comorbidities. Dr. Diokno called for investigations into the best preventive measures and further study of noninvasive behavioral preventive methods, especially for the vulnerable geriatric population. Dr. Sampselle said that research on primary prevention would be most cost-effective. Dr. Chen said that she would like to see a risk-factor calculator developed, including both environmental and genetic factors, to allow better identification of the population at risk. Ms. Newman called for increased teamwork and joint funding with agencies that deal with the aging population.

In response to a question from Dr. Anger about whether there should be different expectations of outcomes in the elderly population, one participant said that the data suggest that the answer should be no. Ms. Newman noted, however, that the treatment goals and expectations of elderly people with incontinence often are different from those of younger patients, with the younger group wanting total dryness, and the older patients having more modest goals. A participant responded that as older people are a heterogeneous population, their individual expectations also vary. Differences in expectations also may be linked to society's stereotypic expectations, to ageism. Both elderly patients and their doctors may have limited expectations because they are accustomed to thinking that incontinence cannot be completely controlled in older people.

Dr. Bradley Kropp recommended that studies on aging include questions about childhood voiding history. He noted that, currently, there is an epidemic of childhood dysfunctional voiding. Whether affected children are more likely than others to have incontinence problems as adults has not been established.

BASIC RESEARCH

Moderator: *Margot Damaser, Ph.D., The Cleveland Clinic, Cleveland, OH*

Animal Model of OAB and CRH

Rita Valentino, Ph.D., The Children's Hospital of Philadelphia, Philadelphia, PA

Corticotropin-releasing factor (CRF), which orchestrates the stress response, affects urinary function in experimental animals. When animals are stressed, CRF is released, initiating an endocrine cascade that is the hallmark of the stress response. CRF release during stress causes adrenocorticotrophic hormone to be secreted from the anterior pituitary. This in turn leads to corticosteroid release, the endocrine part of the stress response. CRF also has been shown to act as a neurotransmitter in other brain regions to mediate autonomic and behavioral aspects of stress. While there are just a few CRF-containing nuclei in the brain, including Barrington's nucleus, which receives information from the bladder and colon, CRF has been shown to have an inhibitory effect on bladder contractions.

Subjecting animals to social stress results in bladder hypertrophy and changes in bladder function generally similar to those observed in the early stages of partial bladder obstruction. Restraint, another type of stress, did not cause the same effects. The effects of social stress on the bladder are associated with an upregulation of CRF at the level of transcription.

These findings illustrate the principle that brain regulation of urinary function is a potential contributor to pathophysiologic processes in incontinence and may be a target for treatment. Social stress may indeed be a risk factor for bladder disorders. This relationship may be particularly relevant for pediatric dysfunctional voiding characterized by voiding postponement. Adult bladder disorders may be a consequence of adverse social events that occurred either in childhood or adulthood, and CRF may be a potential target for treatment of certain bladder disorders.

Mechanisms of Childbirth Injury Leading to SUI

Dr. Damaser

Vaginal childbirth—particularly with a long second stage of labor, a large infant, or increased parity—is a known risk factor for stress UI. Animal models can more precisely clarify who is at risk for stress UI and how to treat them. While the models do not exactly replicate human childbirth, they can provide insight into the mechanisms of injury.

Both muscle injury and nerve injury occur during childbirth; this dual injury may contribute to the prolonged impairment of bladder function sometimes seen in postpartum women. When nerve injury occurs, neurotrophins are upregulated in the muscle. These neurotrophins, particularly BDNF and NT-4, help regenerate the injured axon. Of note, the nerve cell body does not upregulate the neurotrophin production as much as muscle. However, when muscle is injured, these same neurotrophins are downregulated as they inhibit neuromuscular junction re-formation. What happens when both the muscle and the nerve are injured at the same time is not fully understood.

Pudendal nerve regeneration after vaginal delivery, therefore, may be impeded by injury to the associated innervated muscles, such as external urethral sphincter, during vaginal delivery. Evidence from animal experiments, including both neurophysiological testing and neuroanatomical evidence, support the hypothesis that nerve regeneration or restoration of nerve function occurs more slowly after a dual injury to both the pudendal nerve and the external urethral sphincter than after either type of injury alone. Clinical evidence suggests that pudendal nerve function remains diminished years after vaginal delivery and that diminution of function is associated with the clinical development of stress UI. Insufficient regeneration after injury, in combination with other effects of aging, may be sufficient in the development of stress UI symptoms over time.

These studies suggest that electrical stimulation may be clinically useful. Electrical stimulation for as little as 1 hour can increase the neurotrophin content of a nerve cell. Thus, electrical stimulation may be useful for facilitating nerve regeneration in women with nerve injury and might facilitate innervation after stem cell or other biologically based treatment.

OAB/Urge Incontinence

Toby Chai, M.D., University of Maryland School of Medicine, Baltimore, MD

Two types of overactive bladder (OAB)/urge urinary incontinence (UUI) exist: neurogenic (in which bladder symptoms are associated with a neurologic diagnosis) and nonneurogenic or idiopathic (in which bladder symptoms are present but have no identifiable etiologies). Treatment for neurogenic OAB ideally is directed at reducing the impact of the neurologic disorder; control of bladder symptoms us secondarily important. For idiopathic OAB, treatment is directed at controlling bladder symptoms; addressing the associated pathophysiology is less important.

The definition of OAB/UUI requires "urgency," which is defined as a "sudden, compelling desire to pass urine that is difficult to defer." This definition poses some problems: first, because it is the sensation that is considered to be pathological, it remains unclear where in the afferent pathway that pathology resides. Also, the sensation of urgency is not always succeeded by the objective finding of detrusor overactivity (DO) on UDS. Furthermore, some patients do not associate this definition of urgency with their symptoms but report rather that they have frequent desires to urinate that are not necessarily compelling. At present, urgency should be regarded as a symptom rather than a readily measurable biological phenomenon, making research on OAB more difficult to design.

Basic research on OAB/UUI focuses, therefore, on the neural, detrusor smooth muscle, urothelial, and inflammatory aspects of the condition. Knockout mice and cell culture are useful models to study DO triggers; investigations focus on the BK-channel, the β3-adrenoreceptor, the m2/m3 receptor ratio, and gap junctions between smooth muscle cells. Several urothelial cell phenotypes are being assessed in culture—evaluating ATP-stimulated ATP release, carbachol-stimulated acetylcholine release, intracellular calcium changes in response to neurotransmitters, stretch-induced ATP release, and cytokine release—to determine whether differences between these phenotypically disordered cells and control cells can be demonstrated.

OAB/UUI research should aim at improving pathologic understanding of this condition. This will improve objective diagnostic criteria, disease stratification, and prognosis. It may become possible to treat OAB/UUI based on its pathobiology rather than merely attempting to control its associated symptoms.

Panel Discussion

Dr. Werner Schaefer commented that the terminology for OAB/UUI is unclear and potentially misleading because it emphasizes the bladder even though the scientific evidence has not clearly shown that the problem resides in this organ. He also stated that there is a need for research on the role of the sphincter in urge UI. Dr. Chai agreed, emphasizing that the urethra and the sphincter also are difficult to study.

Dr. Gerald Timm asked whether the rat model of childbirth injury used in Dr. Damaser's studies had been validated in humans. Dr. Damaser said that she and her colleagues had not validated the model in women although clinical evidence on the effects of delivery on the nerves is consistent and encouraged them to proceed with this model. Childbirth involves injury to a variety of tissues; the animal model is more target specific, involving just nerve and muscle injuries. Dr. Damaser further noted that these neural structures do remain intact in this model as shown by stimulus-evoked response and other signal-tracing methods.

A participant asked Dr. Valentino how her studies with CRF might relate to the observation of an association between depression and incontinence. Dr. Valentino replied the psychiatry literature suggests that that CRF may be upregulated in depression and that this association could be explored in bladder disorders. For example, this may be a mechanism by which antidepressants that downregulate CRF might also be of value in the treatment of some bladder disorders.

A participant noted that clinicians have observed that anxiety affects the pelvic floor in humans. He asked whether the pelvic floor is involved in voiding in rodents and whether it might play a role in the abnormal patterns of urination observed in rodents under stress. Dr. Damaser stated that the pelvic floor muscles in rodents primarily control the tail and do not play the same role as they do in humans.

Dr. Schaefer and Dr. Damaser discussed the possible inadequacy of the terms "resistance" and "urethra closure," and Dr. Damaser noted that as new animal models are developed, there is a need to develop new or modified terminology as well.

Dr. Damaser asked Dr. Valentino to comment on her experience as an investigator from another field who developed an interest in research on UI. Dr. Valentino responded that because it historically has been difficult to obtain funding for multidisciplinary work, obtaining adequate funding for it was challenging until she began working with a large urology research group.

THURSDAY JANUARY 8, 2008

ANNOUNCEMENTS: AWARDS FROM THE POSTER SESSION

Bold in the list of authors indicates the individual who was the primary author and recipient of the award.

Basic Science Honorable Mention

Association of MMP1 Promoter Variant with Stress Urinary Incontinence and Pelvic Organ Prolapse in Women

*Gopal H. Badlani, M.D., F.A.C.S.[1], **Sonia Vishwajit, M.B.B.S.**[2], Jan Rohozinski, Ph.D.[2], Karl-Erik Andersson, M.D.[2]*

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Introduction and Objective:
Our previous studies have shown increased levels of Matrix Metallo Proteinase-1 (MMP-1) activity in the serum and pelvic support tissues of women diagnosed with Stress Urinary Incontinence (SUI) and Pelvic Organ Prolapse (POP). There is a well recognized variation within the promoter of the MMP-1 gene where the insertion of an extra base (G), 1607 bases upstream of the transcriptional start site, creates an Ets transcriptional enhancer that upregulates MMP-1 expression. The aim of this study is to determine if the GG promoter genotype of MMP-1 is associated with the increased MMP-1 activity observed in patients with SUI and POP. The expected frequencies of the alleles based on their occurrence within the general population are GG/GG 0.248, GG/G- 0.475 and G-/G- 0.277.

Methods:
A total of 20 patients with and without SUI and POP were enrolled in an IRB approved pilot study. The presence of SUI and POP was established by history, physical examination, and completion of a validated questionnaire (Urinary distress inventory and incontinence impact questionnaire). Blood samples were taken, DNA extracted and the promoter region was sequenced. Three primer pair combinations spanning the promoter were used to generate amplicons by PCR. Amplicons for sequencing were recovered from the PCR mixtures and sequenced using the Applied Biosystems big dye Terminator V3.1 cycle sequencing kit. Sequence data were generated using an Applied Biosystems 3130 genetic analyzer. Polymorphisms within the MMP-1 promoter were subsequently identified and recorded.

Results:
Of the 20 patients,12 had SUI with various degrees of POP. All of these patients possessed the GG genotype. Of the 12, 9 were heterozygous, possessing both the GG and G- alleles (0.75) The other 3 were homozygous for the GG allele (0.25). The control group of 8 patients showed the expected allele frequency as in the general population.

Conclusions:
Our preliminary data suggest that the frequency of the GG allele in the patient population with both SUI and POP significantly exceeds that of the general population and may explain the

increased level of MMP-1 activity previously observed in this patient population.

Augmented Polyamine Signaling Blocks the Large Conductance Calcium Activated Potassium (BK) Channel in Bladder Urothelial Cells from Patients with Overactive Bladder Syndrome

***Mingkai Li*[1]*, Yan Sun*[1]*, J. Marc Simard*[2]*, Jian-Ying Wang*[3]*, Toby C. Chai*[1]
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Purpose:
To determine how polyamine signaling affects BK channel activity in bladder urothelial cells (BUC) and whether this is altered in OAB using cell culture and tissue from human controls and OAB subjects.

Materials and Methods:
BUC were cultured from biopsies of OAB and control subjects. Electrophysiologic techniques were utilized to study outward currents mediated by BK in cells. Exogenous spermine was used to augment and DFMO was used to block polyamine signaling. Immunohistofluorescence was utilized to measure expression of ODC, the rate limiting enzyme in polyamine synthesis, in bladder urothelial biopsies.

Results:
OAB BUC had significantly reduced outward currents compared to control BUC (6.31 ± 2.76 pA/pF vs 11.83 ± 2.76, respectively, $p < 0.05$). When OAB BUC inside-out patches were used, we detected a significant increase in outward currents. The outward current in normal BUC was mediated by the BK channel because of block by both Ba2+ charybdotoxin and iberiotoxin. Spermine blocked ($p < 0.05$) the outward current in normal BUC in both the whole cell and inside-out patch configurations. Conversely, DFMO increased ($p < 0.05$) outward current in OAB BUC. The outward current in DFMO-treated-OAB BUC could be reduced ($p < 0.05$) by adding back spermine. Immuno-histofluorescence for ODC from bladder urothelial biopsies from 3 OAB syndrome and 3 control subjects showed increased ODC expression in OAB urothelium.

Conclusions:
These data suggest that polyamine signaling is upregulated in OAB urothelium and OAB BUC. Furthermore, polyamines in BUC block the BK channel. Targeting of bladder urothelium polyamine signaling may represent a novel approach for OAB treatment based on pathophysiologic mechanism.

Basic Science Poster Winners

Urine Inflammatory Chemokines Are Novel Biomarkers for the Diagnosis of the Overactive Bladder—Pilot Study

***Pradeep Tyagi, Ph.D.*[1]*,** *Bruce Jacobs, M.D.*[2]*, Xianggui Qu, Ph.D.*[3]*, Derek Barclay, B.S.*[4]*, Yoram Vodovotz, Ph.D.*[4]*, Wendy Leng, M.D.*[2]*, Dmitriy Nikolavsky, M.D.*[1]*,*

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Chemokine expression precedes inflammatory cell infiltration and cytokine production and inflammation is suspected to be a causative factor for OAB. Urinary chemokines were assayed to determine if they could be used to noninvasively monitor OAB and response to therapy. Urine samples from 17 patients with OAB (9 dry and 8 wet), along with nine controls, were assayed for 32 proteins using a microsphere antibody-based assay. OAB was associated with a 10-fold increase in MIP-1β, IL-12p70/p40, MCP-1, IL-8, GRO-α, and EGF; a 5-fold increase in sIL-2Rα, IL-5, and sCD40L was observed. Increased levels of IL-10 and sIL-2Rα also were observed, suggesting a compensatory response to elevation of proinflammatory chemokines/cytokines. These chemokines were elevated in the absence of UTI, suggesting a different etiologic pathway for OAB. Urine chemokines may be useful as surrogate, noninvasive biomarkers for diagnosis, progression monitoring, and outcome monitoring of OAB.

Drug Delivery Device for Urological Disorders
*Heejin Lee, Ph.D.[1], **Michael J. Cima, Ph.D.**[2,3]*
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Continuous low exposure of the bladder to a drug results in a higher net exposure than bolus delivery. Two devices made of silicone with a retentive feature and drug reservoir (drug in solid phase) were used to deliver the drug over 3- or 6-day periods. Systemic and local tissue exposure were examined and compared to bolus delivery. Bolus delivery resulted in high concentrations of the drug that persisted for a short time. The devices delivered lower concentrations that were sustained for longer periods. Local tissue (urothelium) concentrations were approximately 1 ug/ml using the devices, which were significantly higher than local tissue concentrations detected when the drug was delivered as a bolus. The urine and tissue concentrations also were similar when the devices were used for delivery.

AGING

Moderator: *Patricia Goode, M.D., University of Alabama at Birmingham, Birmingham, AL*

Nocturia
Mary Pat FitzGerald, M.D., Loyola University Medical Center, Maywood, IL

Nocturia (defined as waking from sleep to void during the night) arises when there is an imbalance between nocturnal urine production and nocturnal bladder capacity. The prevalence of nocturia increases with age and nocturia is more common in women than men. Nocturia also occurs more frequently in African Americans. Most people who suffer from nocturia consider it

to be highly bothersome. Nocturia is not well studied or understood; validated clinical algorithms for evaluation and treatment and evidence that evaluation and treatment change outcomes are lacking.

Epidemiological studies confirm a link between nocturia and chronic medical illness, which reinforces the broader idea of nocturia and other lower urinary tract (LUT) symptoms being markers for poor health, and also suggests causative factors outside the LUT. Nocturia is common among people with chronic diseases such as type 2 diabetes, cardiac disease, hypertension, and depression. Nocturia may be a sign of early chronic kidney disease (CKD); one in nine National Health and Nutrition Examination Survey (NHANES) respondents who voided three times per night had decreased estimated glomerular filtration rates (eGFR). Nocturia also appears to predict mortality; 30 percent of older men who void three or more times per night are likely to die within 5 years (Asplund R. BJU Int 1999;84:297-301). Nocturia is also a significant independent predictor of mortality in older patients with known cardiac disease.

Since nocturia often arises outside the lower urinary tract, it is not reliably relieved by LUT treatments. For example, a trial to treat nocturia in men with benign prostatic hyperplasia (BPH) found that LUT treatments resulted in little improvement over that seen with placebo. Clinically there is little improvement in nocturia after treatment with anticholinergic medications.

The International Continence Society (ICS) diagnostic algorithm is not clinically useful because it does not suggest an efficient way to determine the cause(s) of nocturia in a given patient, looking at polyuric states versus bladder storage problems alone. It ignores the interactions that may exist between several causes of nocturia. She recommends that the ICS algorithm be revised to include more attention to the interactions among urine production disorders occurring with medical conditions, such as hypertension, primary sleep disorders, and bladder storage problems and

Future areas for nocturia research include development of a useful clinical classification system, evidence-based clinical investigative algorithms , validation of treatment paradigms, the benefit of treatment. , including whether treatment results in either improved QOL or increased survival.

Incontinence in the Aging Woman
Holly E. Richter, PhD, MD

Urinary incontinence (UI) prevalence in women older than 60 years of age is between 35 and 45 percent. UI prevalence increases progressively up to middle age, levels off until approximately age 70, and then increases steadily once more. Among community-dwelling women, 1-year incidence rates are 1 to 11 percent for women under 60 and 5 to 29 percent for women over 60. As women age, there also is an increase in severity and a change in the type of symptoms; in younger women, stress symptoms predominate, whereas as women age, urge and mixed UI predominate..

Currently, more than 200,000 in- and outpatient surgeries are performed each year for UI and pelvic organ prolapse (POP). Demand for these surgeries is expected to increase by

approximately 45 percent over the next 30 to 55 years, paralleling the aging American population. In addition, the numbers of these surgeries performed in women over 50 years of age is increasing.

Factors associated with UI include race (higher reported incidence in whites than blacks), obesity and weight gain, menopause status, hormone therapy, hysterectomy, and smoking. Genetic components might contribute to risk, although data are lacking. Cognitive, functional, sensory, and mobility impairments contribute to the worsening of UI symptoms, even in healthy aging women who do not reside in nursing homes. Diseases and comorbidities such as congestive heart failure, diabetes, stroke, Parkinson disease, and chronic obstructive pulmonary disease also are associated with UI.

Data on the outcomes of treatment are needed to more effectively counsel patients. For example, there is a theoretical concern that successful outcomes from operative intervention in older women can be reduced by increasing degrees of pelvic muscle attenuation and atrophy; ischemic and inflammatory changes that occur with aging may impact innervation, blood supply, and bladder contractility. Urodynamic changes observed in the aging woman, include smaller voided volumes, increased residual volumes, smaller functional bladder capacities, increased prevalence of DO, decreased urethral closure pressures, decreased urinary flow rates, and increased storage symptoms.

Synthetic mid-urethral slings procedures are the most common surgery performed to alleviate UI. Existing data show similar cure rates for older and younger women, although complications tend to arise more frequently in older women. Similar short- and long-term outcomes have been demonstrated with the midurethral sling, and pubovaginal sling in older women. There are challenges with the literature however. Most studies are small, retrospective, often without comprehensive baseline data, validated outcome measures or control for comorbidities. One example is the Urinary Incontinence Treatment Network (UITN) SISTEr trial which analyzed if outcomes from synthetic mid-urethral sling surgery differed between older (mean age 69.7 years) and younger (mean age 49.4 years) women. The study found that older women were more likely to undergo surgical retreatment but had less improvement in subjective stress and urge incontinence symptoms; however, there was no difference in satisfaction between the two age groups.

Her recommendations for further research include extensive comprehensive baseline data, prospective trial design and standardized evaluation of outcomes using validated questionnaires, including those designed to characterize age-related outcomes and controls for medical comorbidities. Barriers to recruitment of older women into clinical trials also must be overcome.

Incontinence in Aging Men

Tomas L. Griebling, M.D., M.P.H., The University of Kansas Medical Center, Kansas City, KS

Nearly 13 percent of the U.S. population is older than 65; this will increase to more than 20 percent by 2030. Thus, the prevalence of urinary incontinence (UI) will increase. Epidemiological studies of UI in men, however, are comparatively limited. Community prevalence of UI in men is 5 percent for men under 45 years and approximately 21 percent for

men older than 65 years. Urge UI constitutes between 40 and 80 percent of UI in men and mixed UI accounts for 10 to 30 percent. NHANES found an overall prevalence of UI in men of 17 percent, and 31 percent in those over 85 years of age. Poorer physical performance is associated with an increased risk of incident UI over a three year follow-up, for an overall incidence rate of approximately 4% per year. Studies of race/ethnicity differences in men are lacking.

Risk factors for UI include comorbid conditions such as diabetes, hypertension, and heart disease; neurological/neuropsychiatric disorders such as stroke, depression, Alzheimer disease, and Parkinson disease; urological disorders such as prostate diseases, urological malignancies, and urinary tract infections; and other conditions such as bowel disease and functional impairments. Frailty, defined as a syndrome of changes associated with increased impairment in the elderly as measured by3 or more components of decreased gait speed, diminished grip strength, exhaustion, and weight loss, also appears to be associated with UI risk. The impact of frailty on longevity, functional reserve capacity, surgical healing, and other factors requires further investigation. Several biomarkers also are being investigated as markers of frailty; for example, increases in c-reactive protein, D-dimer, fibrinogen, IL6 and WBC are observed in the frail, as are decreases in insulin-like growth factor (ILG-1), growth hormone, DHEA, and glucose tolerance as seen in the metabolic syndrome and in diabetes mellitus.

A shift in UI evaluation and treatment in older adults is occurring, as we shift from maximally invasive, high-risk, painful treatments with poorer outcomes to minimally invasive, lower risk, less painful treatments with better outcomes. Elderly patients once considered inappropriate candidates now are receiving therapy. However, clinical outcomes research for UI, particularly in men, is limited by its heterogeneous causes , diverse populations, variations in health care practice and by small studies with, unclear definitions and terminology, with limited follow-up. . UI has on large impact on health care utilization and costs, as an example, the annual health care expenditures for men with UI are $7,702, compared to $3,204 for men without UI. . Despite a 17 percent UI prevalence in men over 65 years of age, health care utilization rates for these men are less than 1 percent. Compared to men, women are more likely to receive active therapy for UI;

Future directions for research include expansion of gender-related epidemiological research to include incidence, risk factors, and an improved understanding of the natural history of UI in men. Translational research also should be expanded to include analysis of genetic risks, biomarkers, and the impact of the hormonal milieu. Prevention efforts should include identification of and targeted strategies for those at risk. Continence promotion, which should destigmatize UI for men and increase public awareness and education, also is needed. Lastly, analysis of health care utilization and costs is needed to understand health disparities, economic and psychosocial issues, and the impact of UI on men's sexual health.

Discussion

The panelists discussed whether nocturia was part of the LUT syndrome. Nighttime frequency is one parameter by which to define nocturia, but other aspects such as nocturnal polyuria versus global polyuria should be taken into account.

The panelists discussed that pelvic floor muscle therapy (PFMT) can be effective for many patients with UI and should receive more focus. Studies of urge and stress incontinence in older patients have shown that PFMT can be effective. . Surgeons can work with physical therapists and nursing specialists to offer minimally invasive techniques.

ECONOMICS

Moderator: *Tomas L. Griebling, M.D., M.P.H., The University of Kansas, Kansas City, KS*

Costs of Urinary Incontinence for Women

Leslee L. Subak, M.D., University of California, San Francisco, CA

Incontinence costs more than $20 billion per year in the United States, more than the annual cost of all cancer care. More than 80 percent of this spending is associated with care for women, underscoring the treatment disparities between men and women with incontinence. Per person costs for incontinence are $600 for community-dwelling persons but $3,500 for institutionalized persons. A majority of this money is spent on UI management and routine care (absorbent supplies, laundry, dry cleaning) and represents out-of-pocket costs paid by the patient. Costs of diagnostic evaluation, drug treatments, and surgery his also increasing. Associated complications such as UTIs and skin breakdown also account for a substantial proportion of UI-associated costs; lastly, the burden of UI often is the impetus for institutionalization. Spending associated with UI represents 0.5 to 1.5 percent of median annual household income, similar to out-of-pocket spending on prescription drugs. Factors independently associated with increased costs include more frequent UI episodes, type of incontinence (mixed or urge are more costly than stress UI), race (costs are higher for African American women), and having a lower UI-specific QOL score. Effective treatment reduces costs associated with UI. As UI frequency decreases by approximately 50%, costs decrease by 37 percent at 6 months and by 60 percent at 18 months post treatment.

Incontinence also is associated with psychological costs, causing a profound adverse effect on QOL. The Health Utilities Index (HUI3) quantifies health status and health-related QOL. People with incontinence have HUI3 scores similar to or lower than people with stroke, cancer, diabetes, and heart disease.

Cost studies of UI are limited by inaccurate assumptions, poor generalizability, a dearth of sensitivity analyses, and an over-representation of descriptive rather than quantitative analyses. Given the high economic and QOL costs associated with UI, better research is needed; cost-utility analyses will impact health policy. Future UI trials should collect primary cost data for UI management and interventions, assess change in costs with treatment, and estimate the incremental cost-utility of treatments. Information also should be collected on health-related QOL and patients' preferences for outcomes.

Natural History: Complication of Untreated Urinary Incontinence. Translating Research to Improved Patient Care

Jeanette S. Brown, M.D., University of California, San Francisco, CA

Because obesity and diabetes are known risk factors for incontinence, decreasing incidence of obesity and diabetes should improve UI rates. Being overweight is associated with a 20 to 60 percent increase in risk for UI; being obese is associated with a two- to four-fold increase. Diabetes is associated with a 10 to 70 percent increase in UI risk. Because of the inter-relationship among these conditions, obesity and diabetes research activities also may help improve understanding of UI and could be used to model ways to improve health care delivery and ultimately health. One important question is whether weight reduction leads to decreased risk and severity of UI. The Program to Reduce Incontinence by Diet & Exercise (PRIDE) trial tests the impact of weight reduction on UI frequency. Early results show that reducing weight can reduce UI frequency by approximately 50 percent. Thus, the avoidance of UI could be another healthy incentive for weight reduction.

Independent of BMI, diabetes is also associated with an increase in urge UI incidence and severity. . Similar increases in risk for UI are found among women with prediabetes. It is estimated that the prevention of diabetes would eliminate 17 percent of UI and 50 percent of severe UI. The Diabetes Prevention Program compared lifestyle modifications to drug treatment (metformin) or placebo in the prevention of UI. The study found that lifestyle activities, such as weight reduction and increased physical activity resulted in the largest statistically significant decrease in UI rates. The Action for Health in Diabetes trial (Look AHEAD) is currently recruiting women with type 2 diabetes to a trial which will address whether weight loss and increased physical activity affects cardiovascular disease risk and incidence and severity of UI. It is important to determine if **the benefit of weight loss on UI is mediated by improvement in diabetes.**

UI research in the obese and diabetic patients should include investigation of possible mechanisms. Various hypotheses include that increased body weight increases abdominal and bladder pressure leading to UI, or that the oxidative stress associated with excess body weight leads to vascular damage secondarily causing pelvic floor and/or detrusor injury. Hyperglycemia, polyuria and the oxidative stress arising from poor glycemic control may also increase the risk of UI Lastly, increased awareness of UI as a possible complication of diabetes is needed for both patients and caregivers.

Discussion

A participant stated that collection of cost data for UI is complicated. Effective instruments for data collection are needed, but once cost and utilization information have been included in a study design, collection and use of such data can be fairly straightforward.

A participant noted that in the DPP study, increased physical activity did not increase UI, in contrast to what one might intuitively expect, and asked about the sort of physical activity performed by these trial participants. Dr. Brown answered that any message that physical activity increases UI is counterproductive. The Diabetes Prevention Program called for

moderate activity, primarily walking, but also swimming, low impact aerobics, and Pilates. Dr. Subak said that some data also suggests that exercise can be protective against UI, and that protective effect is independent of weight loss.

HOW CLOSE ARE WE TO THE OUTCOMES PATIENTS WANT?

Moderator: *Kimberly Kenton, M.D., Loyola University Medical Center, Maywood, IL*

Role of Urodynamics

Charles W. Nager, M.D., University of California-San Diego Medical Center, San Diego, CA

Urodynamic studies (UDS) used to investigate LUT function include assessments of bladder, urethral, detrusor, and abdominal pressure during storage and micturition. UDS are used to help confirm the lower urinary tract symptoms reported by patients and inform possible treatment or management strategies. UDS are expensive, time consuming, invasive, and uncomfortable.

How useful are UDS studies at predicting outcome of an intervention? In the SISTEr study, a randomized trial of rectus fascial sling and Burch colposuspension, none of the pre-operative UDS parameters were predictive of postoperative treatment success, suggesting, perhaps, that there is a limited value of UDS in predicting surgical outcomes. MUCP were not measured during the SISTEr study, however. Future studies will assess whether MUCP is associated with surgical outcomes. MUCP were measured in TOMUS, a randomized trial of retropubic and transobturator midurethral slings, but were not associated with any measures of UI severity pre-operatively. A Cochrane review found no consensus concerning whether or not UDS need to be performed to guide management.

Therefore, current evidence is insufficient to determine whether physicians alter clinical decisions based on results of UDS or whether having UDS results improves clinical outcomes. The ValUE (Value of Urodynamic Evaluation) study will assess whether preoperative UDS result in better outcomes for women desiring surgery for stress UI compared to basic office evaluation (a full bladder stress test) and determine how often physicians alter treatment decisions based on UDS, and compare the incremental cost of performing UDS.

Quality of Life Assessment

Lior Lowenstein, M.D., M.S., Rambam Health Care Campus, Haifa, Israel

QOL assessment should include not only physical health, perceived health but also mental, emotional, sexual and social well-being. QOL assessment has now been mandated for outcome studies. For example, the U.S. Food and Drug Administration has stated that efficacy with respect not only to overall survival but in improvements in QOL might provide the basis for drug approval. However, measuring QOL is challenging because it is context-dependent. Furthermore, QOL measures can be general or disease-specific. Standardized measures and definitions also are lacking. Measureable factors that influence QOL include not only the interventions or treatments, but also the disease process, labeling (diagnosis may bring on change), concomitant care, and nonrelated life events such as a death in the family. QOL is

assessed in trials to determine if treatments improve QOL and the impact of side effects may miss these important confounding issues.

UI and OAB reduce QOL because they cause embarrassment, social isolation, depression, and avoidance of sexual contact and/or intimacy. The effect is large. A European survey found that OAB adversely affected the life of more 60 percent of respondents. People with OAB scored worse than people with diabetes on QOL assessment tools. The coping mechanisms that people with UI or OAB employ, such as limiting daily travel, reducing fluid intake, or carrying extra clothes, also adversely impact QOL. Among women with urge UI, 19 percent reported avoiding at least one social activity, 3 percent reported avoiding visiting a friend, and 1 percent reported abstaining from work. For these women, worsening QOL is correlated with increased frequency, nocturia, and pad usage. Women with OAB reported worse QOL than women with stress UI. Judging the severity of OAB has been difficult because objective clinical measurements provide little information on the impact of OAB on patients' lives. In addition, UDS are not diagnostic for OAB in general. Efforts are under way to determine if specific tests correlate with OAB severity or QOL.

To accurately assess QOL, the objective must be defined and an instrument that is reliable, valid, responsive, and feasible must be chosen. The use of global versus disease-specific measures also must be considered. The most effective means of data collection and analysis must be defined, and the validity of the overall score must cover the domains of interest. Several generic QOL tools are available, but because they are insensitive to the specific condition, they do not address many of the disease-relevant issues. More specific tools, including the OAB-q, Nocturia Quality of Life Questionnaire, Patient Perception of Bladder Condition, and Urge Incontinence Impact Questionnaire will provide a closer focus on the impact of the condition on the patient. Selection of a QOL tool to use in a trial should take into consideration whether the tool has adequate psychometric properties, is adequate for a relevant domain, and is valid for the patient population in question.

Outcome and Expectations in Post-Prostatectomy Incontinence (PPI): Review of the Literature

Ajay K. Singla, M.D., F.A.C.S., Wayne State University, Detroit, MI

Treatment options for men with PPI include pelvic floor exercises, bulking agents, and the artificial urinary sphincter (AUS). Minimally invasive procedures may be non-adjustable (bone-anchored male sling, TOT, bulbourethral sling) and adjustable (ProACT, Remeex, and Argus); these adjustable procedures are currently not available in the United States.

Pelvic floor exercise, bulking agents, and AUS can be considered for mild to moderate PPI. A study of pelvic floor exercise for PPI treatment found that only 16 percent of men who participated remained incontinent after 12 months of this intervention. In contrast, bulking agents in PPI had only a 10 percent cure rate. Countariwise, a study of the AUS reported that 60 percent of men had a good outcome, and 4 percent reported a very good outcome. A number of studies have found generally high satisfaction with AUS; most men were nearly completely cured of incontinence.

The ProACT device features two small balloons that are placed periurethrally; saline is injected to compress the bladder neck and stop leakage. Adjustments can be made percutaneously and post-procedurally as necessary. One study of 177 patients found that 67 percent of men were dry (0-1 pad per day), and 92 percent reported improvement (2-5 pads). The Argus device uses a thick silicone pad to compresses the urethra. A study of 48 men found that 73 percent of patients were cured (no pads), and 10 percent reported improvement (1-2 pads). The Remeex prosthesis features an adjustable sling. In a study of 51 patients, 64.7 percent were cured and 19.6 percent improved; patient satisfaction was 84.3 percent. A study of 71 patients receiving the bulbourethral sling found a 36 percent cure rate (0 pads) and patient satisfaction of 69 percent. The bone-anchored male sling was assessed in a study of 92 men, most of whom had PPI. Patient satisfaction was greater than 70 percent. A number of studies of the bone-anchored male sling found satisfaction rates in properly selected patients at greater than 70 percent, an overall cure rate of approximately 58 percent, and a 13 percent improvement rate. A recent study of the male TOT study found an 86 percent success rate at short term 6 month followup.

The patient's degree of leakage helps guide the choice of therapy. Mild leakage may be treated with bulking agents (noting that most have poor outcomes), slings, or an AUS but poor urethral function associated with higher grade of leakage indicates the need for circumferential as provided by an AUS. AUS remains the "gold standard" for treatment of PPI and has the highest patient satisfaction rate.

Population Measures: Using Secondary Datasets To Understand Outcomes of Incontinence Surgery on a National Level
Dr. Anger

Use of minimally invasive procedures is increasing. Analysis of 147,473 patients who had surgery for stress UI between 1988 and 2000 found that a substantial number of women who underwent sling procedures suffered complications.

To determine the impact of surgeon volume (e.g., number of procedures performed) and specialty on outcomes, as well as the impact of patient variables such as age, race, and comorbidities such as prolapse, Medicare claims were used to identify women who underwent sling procedures. The analysis found that the majority of surgeons involved performed only a few such procedures each year (average 3.9 over a 2-year period). Analysis of complications arising after surgery found a significant rate of urologic complications (22.9% for local urologic complications), infectious complications (49.7%), and repeat incontinence procedures (8.3%); 23 percent of patients underwent subsequent prolapse surgery within one year of the sling. There were no significant differences in rates of urologic, nonurologic, or infectious complications; diagnosis or management of outlet obstruction; or repeat incontinence procedures between high- and low-volume providers. However, high-volume providers tended to perform concomitant prolapse repair at the time of sling surgery. Similarly, gynecologists were more likely than urologists to perform concomitant prolapse repair at the time of the sling procedure. Patients receiving concurrent surgeries were less likely to require a repeat incontinence procedure (4.7% versus 10.2%).

Analysis of patient variables found that older women had worse outcomes and suffered higher rates of urologic and nonurologic complications. Older women also had higher rates of repeat incontinence procedures. Analysis of comorbidities found that women undergoing simultaneous sling and prolapse repair had nearly three times the risk of deep vein thrombosis/pulmonary embolism as women undergoing only a sling procedure. These analyses found that complications after sling surgery are higher than reported in the clinical literature and that outcomes are affected by provider volume, specialty, and prolapse management techniques, as well as by patient age and comorbidities.

What Outcomes Matter?

Linda Brubaker, M.D., M.S., Loyola University Medical Center, Maywood, IL

The importance of outcomes varies among patients and physicians. Physicians tend to prefer quantitative outcomes, but these may not take into account patient perspective; even if the procedure was "successful," the patient may not be satisfied. To determine if the treatment goal was met, patient and provider must agree on the goal. Patients must consider if the procedure was "worth it"; i.e., if the outcome outweighs complications. In addition, complications may not be medically serious, but nonetheless may be seriously disruptive to patients, changing their impressions of the success of the procedure. In other cases, the treatment goal may not be met, but if there are no serious offsets, patients still may be satisfied that they tried to treat their condition.

Numerous instruments exist for assessing outcomes and QOL, but few are optimal. The instruments tend to overmeasure "good" and undermeasure "bad," and few allow patients to indicate a worsening of their condition as an outcome. In addition, few instruments allow patients to weigh tradeoffs—for example, minor urge incontinence might be more bothersome than moderate stress incontinence because stress incontinence is more predictable and tends to have less of an impact on life activities. The instruments also do not assess the usually significant gap between patient and physician assessments of complications and do not take into account the degree to which treatment complications may impact the patient's daily activities. Research on outcome measures is needed to clarify the balance between conflicting outcome measures, i.e., a painful but well-supported vagina or cured stress incontinence but significant voiding difficulties or urge incontinence. Investigators should report multiple outcome measures to allow other investigators to compare results in subsequent systematic reviews.

Panel Discussion

The panelists agreed that patient satisfaction should be part of procedure outcome assessments because satisfaction generally is related to outcome. High-quality research is needed to determine and document what success means to patients. Identifying baseline characteristics also could help explain differences in subjective outcomes. Understanding patient-centered outcomes and impact on QOL is important, but data also should be collected to better understand the mechanism of these conditions and how treatments affect them. Failure analysis, i.e., determining why adverse outcomes occur based on assessment of both the procedure itself and any related patient conditions, is needed.

Center for Medicare and Medicaid Services (CMS) records appear to indicate gaps between the best medical option and what is done in practice; for example, complete kidney removal continues to be performed when partial nephrectomy would suffice. Outreach to the practitioner community is needed to encourage best practice use, particularly among older providers.

DEGENERATIVE DISEASE: PARKINSONISM, MS

Lower Urinary Tract Symptoms in Multiple Sclerosis and Parkinson's Disease

Gary E. Lemack, M.D., University of Texas Southwestern Medical Center, Dallas, TX

LUT symptoms eventually occur in up to 90 percent of multiple sclerosis (MS) patients over the course of their disease. LUT symptoms occur in most men and women with MS at a fairly young age (mean 32.9 years). Disease duration and overall disability predict the likelihood of LUT symptoms but are not predictive of the urodynamic findings; thus, urodynamic assessment of MS patients is of questionable value. The presence of LUT symptoms increases risk of upper tract infections, but predicting the long-term risk of upper tract infection is difficult and is not influenced by patient demographics, including MS subtype. Baseline renal sonogram abnormalities generally are minor and their value in predicting risk is poor.

Because LUT symptoms are not predicted of the UDS findings and few patients develop abnormalities of bladder compliance, patients initially are assessed by questionnaire, physical examination (neurological and pelvic for females), urinalysis, and a simple PVR. OAB is managed initially by dietary and behavioral changes with alpha blockers in some cases. Catheterization is avoided, as this does not appear to be helpful for the patient with a low PVR. Botulinum toxin has been used in some cases of refractory OAB. Neuromodulation also has substantially reduced LUT symptoms in appropriately selected patients, although whether benefits are maintained in a progressive disease remains to be determined. Pelvic floor exercises appear to be helpful for MS patients,. Cannabis has been shown to be beneficial for treatment of urge UI in MS patients.

LUT symptoms in PD are a significant clinical problem, particularly DO, and occurs early in the onset of this disease. Because PD tends to occur in aging patients, it can be difficult to determine if the severity of symptoms is determined primarily by the disease or by frailty. Treatment with higher doses of l-dopa in more severely affected patients results in lower capacity and higher DO amplitude, and treatment with moderate doses in patients with less severe disease results in increased capacity. Positron emission tomography scanning during DO found more activity in specific areas of the brain, some of which overlap with sites active during idiopathic DO (pons and anterior cingulate gyrus). PD treatments such as subthalamic stimulation and deep brain stimulation appear to alleviate LUT symptoms slightly, although predicting success remains difficult.

Research is needed to determine the longitudinal risk of renal disease in PD and MS patients, the cost effective use of LUT evaluations. Efforts also are needed to understand the extent to which systemic therapies impact incontinence, the effectiveness of botulinum toxin, and the role of neuromodulation (sacral and peripheral) for these patients. The safety of conventional stress UI therapies in these populations also must be determined.

COMPLICATIONS OF TREATMENT

Moderator: *Kathleen Kobashi, M.D., Virginia Mason Medical Center, Seattle, WA*

Complications of Implants: Synthetics

Jan Deprest, M.D., Ph.D., University Hospitals Leuven, Leuven, Belgium

Synthetic implants are increasingly used to treat conditions such as stress UI, POP, rectal prolapse, and hernia repair. However, increased use is associated with increased incidence of side effects, including vaginal dysfunction. Understanding and treating these complications is hindered by a lack of clear definitions for many complications. Therefore, specific definitions were proposed for exposure (loss of tissue continuity over an implant with no symptoms), erosion (loss of continuity over an implant with symptoms), extrusions (migration of material away from implant site toward the lumen of an organ or the skin), and fistulization (formation of a non-natural connection between the implant and the skin or a lumen). A clearer definition is also needed for deformation because altering physical features of the implant as well as the local anatomy will lead to functional side effects. However, the manner in which patients complain about a particular problem will continue to vary. Loss of epithelial integrity can present as bleeding, discharge, or pain, or may be asymptomatic.

Possible mechanisms for erosion include lack of normal healing in the covering epithelium, subclinical infection of the mesh, or inappropriate integration of the implant into the host. Infections may play a more significant role when erosions present early after surgery, but long-term complications probably arise because of abnormalities in the host inflammatory response. Migration of implant material and contraction of the tissues around the implant also tend to occur later.

Because patients present with a wide variety of functional problems and loss of tissue integrity, and because these complications are described using different definitions, reviewing the data to develop a better understanding of why complications occur and how to manage them is difficult. Several European centers have developed local registries of patients presenting with complications, especially erosion and exposure. The data will be used to try to recognize patterns associated with the development of complications. Explant banks also have been established to assess clinical pathological correlations. Analysis of data from the local registries suggests that tape complications present earlier than those associated with mesh used in sacropexies. In general, mesh complications were not diagnosed for as long as 20 weeks for most many patients, and management took another 3 months. In 30 percent of cases, the complication was discovered by the doctor rather than reported by the patient. At present, management has been conservative, focusing primarily on treatment with estrogen and antibiotics; this is beneficial for small exposures but does not help most patients. Suggestions for preventing complications associated with the use of implants include choosing implants that do not cause local side effects, researching modification of host inflammatory processes, and educating surgeons to place implants correctly using good surgical techniques.

Complications of Autologous Pubovaginal Slings
Fred E. Govier, M.D., Virginia Mason Medical Center, Seattle, WA

The primary procedure performed using autologous tissue is the pubovaginal sling (PVS). Compared with synthetic implants, use of autologous tissue generally results in fewer complications. Initial PVS procedures resulted in high rates of obstruction, erosion, infection, and retention. However, in the late 1970s and early 1980s, the procedure was improved and simplified, and surgeons realized the importance of ensuring low tension on the sling to avoid complications. PVS became the "gold standard" treatment for complex incontinence, particularly for patients for whom previous procedures had failed. It also became apparent that PVS was preferable to other procedures for incontinence, including the Burch procedure and various types of needle suspension. By the late 1990s, PVS also was used for patients with simpler forms of incontinence. One study of 251 patients, with a median followup of 3 years, found that stress UI resolved in 73 percent of patients; unexpected urinary retention occurred in only four patients. Stress UI did not recur in any of the patients in which it initially resolved. This procedure has been refined further to use smaller lengths of fascia ("sling on a string"), avoiding long, painful incisions in the leg to harvest the fascia. Additionally. the surgery to place the sling has been simplified.

The primary complications arising from the PVS procedure are obstruction, urinary retention, *de novo* urge UI, presumptively due to excess sling tension. Other complications are associated with the harvesting site, which increases operative time and may be associated with incisional hernias, wound infections, hematomas, and increased post-operative discomfort. Muscle relaxants, intra-operative positioning of the patient and autologous fascia contraction over time affect sling tension, such that the determination of sling tension can be difficult to ascertain. However, unique advantages of autologous PVS include low rates of both early and late failures, the virtual absence of erosions, and extrusions making it ideally suited for the complex patient requiring adjunctive tissue for urethral reconstruction.

Trials are underway to comparing anti-incontinence methods and materials. One trial has already reported results: the SISTEr trial compares autologous rectus PVS with Burch colposuspension for stress UI. At 24 months, the success rate for correction of incontinence was 47 percent in the sling group versus 38 percent in the Burch group. Overall satisfaction was 86 percent in the sling group versus 78 percent in the Burch group. There were no differences in serious complications other than voiding dysfunction which led to surgical revision in 6.13 percent of the sling patients versus none of the patients in the Burch group. Rates of voiding dysfunction rates were 14 percent in the sling group versus 2 percent in the Burch group.

Safety of Bulking Agents
Jacques Corcos M.D., McGill University, Montreal, Canada

The ideal bulking agent should be biodegradable, biocompatible, nonmigratory, nonallergenic, and efficacious; the efficacy and patient satisfaction with these agents should be defined very clearly as dry rates are low.

The history of bulking agent use shows the limited success of this therapy. PFTE (polytetrafluoroethylene) Teflon was used extensively in the 1960s to 1970s, but it tended to migrate and was found in the brain and lungs. Its use was associated with granuloma formation with complete urethral obstruction, inflammation, periurethral abscess, and urethral diverticulum; PFTE Teflon also was suspected of being carcinogenic. Collagen was considered safe, but the overall incidence of complications (*de novo* urgency, allergic reaction, urinary retention, bladder obstruction, and UTI) associated with this agent was 20 percent. Some of these issues were related to the technique used to inject the collagen and the large amounts used. Fat injections are no longer in use because of risk of fat embolism leading to death, infection, urethral lipoma, retention, and DO. Carbon-coated zirconium beads (Durasphere®) use has been associated with periurethral mass formation (abscess, pseudocyst, or granuloma), migration into lymph nodes or the urethral mucosa, urinary retention, and urethral prolapse.

The story of Zuidex represents one of the problems with clinical trials. This agent was the subject of a large international trial wherein women with mild incontinence might find that their stress UI was alleviated, but developed a large obstructing periurethral pseudocysts in over 10% of patients. Despite cyst drainage, several patients developed complete incontinence requiring much more invasive procedures. Patients and investigators do not understand the true risk of many of the procedures we purport as minimally invasive, and naively, therefore, as minimal risk.

Bulking agents cure only approximately 25 percent of treated patients and have an average 50 percent complication rate, approximately 10 percent of which are severe. Well-conducted animal and human tissue response studies are needed, as well as strong pilot studies, before these products are launched for general use. Well-conducted randomized controlled trials also are needed to better determine the role of these treatments in place of surgery. Industry, investigators, ethics committees, and government agencies must work together to ensure safe and effective use of these products.

Complications of Male Stress Incontinence Surgery
Victor W. Nitti, M.D., F.A.C.S., New York University Langone Medical Center, New York, NY

Outcomes on the use of AUS in males and male sling procedures to treat stress UI come primarily from case series and some prospective studies, not from randomized controlled trials. Because bulking agents are no longer recommended for male stress UI, slings and AUS are the predominant treatments for this condition. Significant intra-operative complications are rare and not significant if recognized and treated appropriately. Early postoperative complications include urinary retention if the cuff is placed too tightly, swelling and hematoma, pain and paresthesia (most common in bone-anchored slings), infection, and early erosion. Of note, infection is unusual, occurring more commonly in immune-compromised or diabetic patients, and early erosions usually occur because of an unrecognized urethral injury. Secondary urethral injury from atrophy or erosion is somewhat more common. The incidence of urethral atrophy will increase over time, and mechanical failure of the AUS, while rare, may occur.

A meta-analysis of published data on AUS procedures found that 88 percent of patients reported improved incontinence and 73 percent reported achieving full continence. Regarding

complications, 32 percent of men required revision, 11.7 percent suffered urethral erosion, and the infection rate was 4.5 percent. Complication rates and their management are well established for AUS, but less information is available on the sling procedures due to shorter followup times.

Male slings' complication rate for the InVance™ sling was between 2.1 and 7.9 percent; no data were available for the AdVance™ sling. Most patients present with complications at 6 to 9 months after surgery; most are chronic and low-grade (e.g., mild perineal pain or swelling, or a sinus tract with small amounts of intermittent drainage). These complications are managed by removal of the sling; a few salvage attempts were unsuccessful, although one patient has been managed with intermittent antibiotics and fulguration of a chronic sinus tract for more than 3 years due to his refusal to have the sling removed. Obstructions are uncommon and have not been reported for the AdVance™ sling, but can be managed by loosening or removing the sling. Pain and parasthesia are relatively rare, particularly for the AdVance™ sling. Pain usually is minor and resolves; if it does not, the patient should be assessed for possible bone infection.

BEHAVIORAL INTERVENTION

Moderator: *Kathryn L. Burgio, Ph.D., University of Alabama at Birmingham, Birmingham, AL*

Pelvic Floor Muscle Training

Jean Hay-Smith, Ph.D., University of Otago, New Zealand

Randomized trials have shown that PFMT can effectively treat female incontinence. In these trials, PFMT was defined as repeated voluntary pelvic floor muscle contractions, was taught and supervised by a health care professional, and could include education (e.g., anatomy) and behavioral components. There are two distinct bodies of trials; those conducted in pregnant or postpartum women and those in women over 45 years of age with symptoms of UI.

"Intensive" antenatal PFMT (i.e. regular health professional visits and an exercise regimen sufficient to strengthen muscles) appears to effectively reduce the prevalence of UI in late pregnancy and up to a year postpartum in primiparous women who are continent at about 18 weeks gestation. In addition, PFMT is an effective treatment for women with UI symptoms that persist for 3 months or more after childbirth. However, there is little information about long-term outcomes, the effects of parity, and the effectiveness of PFMT given differences in risk for incontinence and continence status. Antenatal PFMT appears to be more effective for reducing postnatal incontinence than postnatal training, but trials are needed to confirm this. Studies also are needed to determine if it is more cost-effective to offer PFMT to all pregnant and postnatal women or only to those at high risk for UI (e.g. women with increased antenatal bladder neck mobility, forceps delivery, or delivery of a baby weighing $\geq$ 4,000 grams). Although women link pregnancy to incontinence and view pregnancy and the postnatal period as a logical time to receive PFMT, many women report that they do not have time to perform the exercises. Innovative approaches to training and adherence with PFMT during the childbearing period are needed. Research is also needed to better understand whether the intensity of health professional contact during PFMT is associated with greater reduction in postpartum UI prevalence.

In women older than 45, PFMT is effective for treating stress UI, urge UI, and mixed UI. As with pregnant women, including more health professional contact increases the success rate. Biofeedback does not appear to affect ultimate incontinence outcomes but may help women learn to perform the exercises properly to affect that outcome. Information is lacking regarding the minimal effective dose and long-term outcomes of PFMT. Research also is needed to better understand the effects of new approaches to PFMT.

Other research priorities for PFMT for all patients (including men) are the effects of periodic refresher PFMT courses; better analyses of baseline variables (age, BMI, race) that likely affect outcomes; information on adherence or lack thereof; and cost effectiveness and utility—although PFMT is inexpensive, the intense supervision required for effectiveness raises costs. Long-term data on PFMT outcomes and information on its use in patients with comorbidities such as neurological disorders also are needed. Finally, the role of PFMT as part of a comprehensive conservative management programs for UI should be examined.

Pelvic Floor Muscle Training and Dose-Response Issues
Kari Bø, Ph.D., Norwegian School of Sport Sciences, Department of Sports Medicine, Norway

Exercise dose, inclusive of exercise type and intensity, repetitions, sets, frequency, volume, and duration, determines the effectiveness of PFMT. Adherence is also a key factor. Muscle training includes motor learning (search, find, learn, control)—which usually involves teaching by physical therapists—and training, which can be done by the patient alone or in groups with other patients.

Analysis of PFMT for stress UI is complicated by the significant variation in exercise dose and training programs used in PFMT studies. Studies vary in the intensity of contractions, number of repetitions, and duration of training, and few studies assess adherence to an exercise regimen. The goal of PFMT is increased strength; if an improvement in strength is not detected, the program has not been effective. The results of PFMT should also include lifting of the levator plate, hypertrophy and stiffness of muscles, and closing of the levator hiatus, all leading to permanent changes and better functioning of the pelvic floor musculature. Recommendations for effective pelvic floor muscle strength training include specificity of contractions, performing 8 to 12 slow velocity maximum contractions (fewer repetitions better optimize strength and power), three sets performed 2 to 4 days per week, and more than 5 months of training.

A randomized trial of women to either home training alone or home training plus intensive training reported significant differences in muscle strength and in outcomes with respect to curing incontinence. The home training program was fairly intense and included individual education in anatomy and physiology; vaginal palpation, observation, and strength measurement; 8 to 12 contractions three times per day, held for 6 to 8 seconds; and seven visits with a physical therapist. The intensive training program included these same activities and also a 45-minute pelvic floor muscle exercise class once per week. This study and numerous others have shown that more training results in increased effectiveness of PFMT for stress UI.

A few studies claim that PFMT is not effective for stress UI. However, many of these studies had inadequate training programs and inadequate exercise dose and intensity. Adherence may

also be low; adherence was only 15 percent of the requested level in one study. A study of PFMT for antenatal UI had equivocal results but had a significant dropout rate, and many women in the study had mixed UI. Meta-analyses that include studies with inadequate training may push the effect size of PFMT toward zero, despite the existence of data showing that intensive PFMT can be effective. Comparing effective and noneffective PFMT studies does not add to the understanding of the role of PFMT in treating UI. High-quality randomized trials are needed, and quality of training and dose-response issues must be addressed.

Devices for the Woman With Pelvic Organ Prolapse/Urinary Incontinence
Ingrid Nygaard, M.D., University of Utah College of Medicine, Salt Lake City, UT

Pessaries have long been used to manage POP, and are currently used for long-term and interim management, and may be useful for predicting surgical results. For example, a pessary can be placed temporarily to determine if it can resolve pelvic floor symptoms purportedly caused by prolapse. A survey of American Urogynecologic Society members found that 77 percent use pessaries as first-line therapy for prolapse whereas 12 percent reserve pessaries only for nonsurgical candidates. Contraindications for pessary use include an inability to care for or receive help with care for the pessary, vaginal ulcerations or lesions, severe atrophy, or recurrent vaginitis.

Two different kinds of pessaries, space-occupying and support, are used to treat POP, and the devices can vary in shape, size, and stiffness. Women with good levator ani muscle tone are candidates for support pessaries, while those with poor muscle tone are better suited to space-occupying pessaries. Vaginal devices can also be used to treat stress incontinence. Devices useful for short-term control of incontinence include the tampon, Hodge pessary, contraceptive diaphragm, cube pessary, and ring- and dish-shaped devices. At the first followup visit after a woman receives a pessary, the vagina is examined and pessary size and type adjusted as needed. The woman also practices insertion and removal and receives a referral for a visiting nurse, if needed. Long-term follow-up is important, particularly for women with space-occupying pessaries as these are more likely to cause ulcerations or granulation tissue in the vagina.

Few studies have examined the number of women who try a pessary when offered. One study found that 63 percent of 190 women with stress/mixed UI tried a pessary; another found that 42 percent of 77 women with POP agreed to try a pessary. Similarly, few studies have examined the success of fitting a pessary. Success rates for fitting for prolapse were 73 and 41 percent in two studies and 89 percent in a study of women with stress UI. Of those successfully fitted, 55 percent of women with stress UI were using the pessary for 3 to 12 months or more. Generally high rates of satisfaction were reported (73% and 92%) amongst women that continued pessary use; these numbers do not reflect the dissatisfied women who discontinued use. Of women successfully fitted with a pessary for POP, 34 percent to 73 percent were still using it 12 months later. Bulge symptoms improved in most women. Symptoms of urge incontinence and voiding difficulty improved in one-quarter to one-half of women, and prolapse and urinary scales also improved. Improvement in anatomy also was observed. Adverse events, primarily erosion, were observed in only a small number of women. There is very scant poor-quality evidence that pessaries may help prevent progression from mild to severe prolapse.

Pessaries are a useful treatment for a minority of women with POP and stress UI. However, data on long-term use and on which patients would benefit from long term-use are lacking.

Bladder Training and Urge Control Techniques

Jean F. Wyman, Ph.D., R.N., F.A.A.N., University of Minnesota, Minneapolis, MN

Bladder training has long been used in urgency syndromes to improve bladder function, specifically by improving urgency control, decreasing frequency, prolonging the voiding interval, increasing bladder capacity, reducing incontinence episodes. More recent studies have found that bladder training also is useful for improving stress UI in women. Bladder training is believed to work by improving the brain's ability to inhibit bladder contractions and facilitate urethral closure during bladder filling. Bladder training also improves central modulation of afferent sensory impulses, increases individual awareness, and changes behavior related to the circumstances that trigger LUT symptoms.

Bladder training involves patient education regarding bladder function, causes of incontinence and urge control strategies. Patients are also provided with a scheduled voiding regimen and asked to self-monitor and keep diaries to help set voiding intervals. Reinforcement in the form of clinician support and encouragement to adhere to the training regimen is critical. Urge control strategies involve a variety of relaxation or distraction techniques, including breathing exercises and self-affirmation, by which the patient distracts herself from the sense of urgency, permitting longer intervals between voiding. Relaxation activities help the detrusor to relax. More recently, patients have been instructed to perform five quick, strong muscle contractions as part of urge control; there is some evidence that this aids detrusor muscle relaxation.

Some older studies of bladder training found that this approach was effective for reducing UI in women older than 55 years of age. In a definitive randomized trial, older women achieved an average 57 percent reduction of incontinence episodes, with 75 percent realizing a 50 percent or greater improvement. This study included women diagnosed as having stress UI or DO (with or without stress UI); no significant differences were found in outcomes for these two groups. Bladder training also resulted in significant improvements in QOL scores for these women.

Bladder training has been compared to PFMT and to a combination of bladder training plus PFMT for treatment of stress UI. Initially, the group receiving combination therapy had better outcomes, but by 6 months after treatment there were no significant differences in outcomes among the groups. Relapse was observed at 12 weeks for the PFMT group and at 6 weeks for the bladder training groups, which might provide information on when booster interventions would be needed. In one study, bladder training in conjunction with antimuscarinic drug therapy appeared to provide no additional improvement in UI symptoms over drug therapy alone, but patients were provided with only minimal bladder training instruction.

A Cochrane review of 12 trials found that patients who received bladder training had greater perceptions of cure immediately and 6 months after treatment and demonstrable QOL improvements. However, the data are limited and provide only a tentative conclusion about bladder training's effectiveness. Larger clinical trials are needed to examine short-term and long-term outcomes; analyze age, gender, and racial/ethnic differences; and examine the effect of

bladder training in specific subpopulations (such as UI subtypes, the frail elderly, or people with stroke or diabetes). Research on bladder training parameters such as urge control strategies, supervisory intensity, adherence strategies, and delivery methods also is needed.

Behavioral Training and Urge Suppression Techniques for Urinary Incontinence
Dr. Burgio

Bladder training focuses on modifying voiding habits and includes urge control techniques. Behavioral training for incontinence focuses on teaching continence skills, new responses to urgency, and includes using pelvic floor muscles to suppress urgency and detrusor contraction. Urge control strategies include avoiding rushing to the toilet, squeezing the pelvic floor muscles and relaxing the rest of the body, concentrating on suppressing the urge and waiting until the urge subsides, walking to the toilet at a normal pace, and delaying voiding. Biofeedback can be used to help the patient learn what a detrusor contraction feels like and to teach the patient how to use pelvic floor muscle contraction to abort detrusor contraction. Verbal feedback based on vaginal palpation can be as effective as biofeedback for reducing episodes of UI. Behavioral training for urge UI can result in a 60 to 80 percent reduction in the frequency of incontinence episodes. Changes in bladder capacity can also occur, although this is not necessary for achieving symptom improvement.

Because behavioral training and drug therapy appear to work by different mechanisms, combining the two have been hypothesized to improve incontinence more than either therapy alone. A conditional crossover of patients whose incontinence was not adequately improved in a trial comparing behavior and drug treatment found that combining the two approaches improved outcomes. The BE-DRI trial is a two-stage clinical trial in which patients were randomized to 10 weeks of drug therapy alone or drug therapy combined with behavioral training. At least 70 percent reduction in incontinence episodes was observed in 69 percent of those receiving combined therapy; this was not significantly different than the results observed for those who received drug therapy alone. However, greater benefits on secondary outcomes, such as patient satisfaction and perceptions of improvement, were realized in the combination therapy group compared to those who received a single therapy. Further work is needed to determine if it is better to combine therapies initially or to implement them in a stepped fashion.

Research is needed to study the effectiveness of behavioral training in understudied populations (e.g., men and people with neurological conditions) and to determine which patients are the best candidates for behavioral training. The mechanisms of therapeutic change related to behavioral training also remain to be determined. There are few good studies of long-term outcomes or of how patients can be helped to adhere to training. Studies on implementation and dissemination of behavioral training, along with novel models of delivery, are needed.

UPDATES ON CURRENT TREATMENTS AND TRIALS

Moderator: *Christian Winters, M.D., Louisiana State University, New Orleans, LA*

An Argument for the Use of Slings To Treat Male Stress Urinary Incontinence

Dr. Nitti

PPI is a significant and increasing problem in the United States. Although the AUS is the "gold standard" of treatment for men with stress UI, not all men are interested in mechanical devices and an AUS may not be appropriate for a man with minimal but bothersome incontinence. A sling procedure offers appropriately selected men an effective treatment with acceptable complications in the short to intermediate term, although long-term safety and efficacy are not known. Comparing published AUS and male sling series is not appropriate because of large differences in patients, selection criteria, the differing degrees of their baseline incontinence and outcome measures, including the definitions of "success" and "satisfaction."

The two primary types of male slings used currently are the bone-anchored perineal sling and the transobturator sling. The bone-anchored perineal sling provides direct compression of the urethra against the pubic bone using synthetic materials. Determining the success of sling procedures, again, is difficult because no definition of success has been established; "cure" or "dry" rates are too high an expectation. Thus, reported success rates range from 40 to 92 percent depending on the definition of success, length of followup, and patient selection. Patients' impressions of improvement also were difficult to evaluate; Patient Global Impression of Improvement scores were worse in patients with minimal incontinence because these patients have a lower tolerance for any residual leakage or complications. There was no association of radiation or previous bladder neck contracture with failure of the procedure. Only preoperative pad weight predicted success; the odds of a successful surgery were six times greater for patients with a pad weight of less than 423 grams versus those with higher pad weights. Although extensive data on long-term outcomes are lacking, one study found good durability of the slings 4 years after surgery.

The transobturator sling avoids bone anchor and thus should be less painful, but outcome data are minimal. Transobturator slings most likely work by allowing the dorsal sponge to compress the urethral lumen. Nonpeer-reviewed results of the AdVance™ sling claim that 52 percent of 67 men in one study were cured (no pads) and 38 percent improved (1 to 2 pads versus 4). Eleven patients had temporary urinary retention, and five underwent repeat procedures. This sling appears to work well in appropriately chosen patients, but the criteria for selection are vague.

Sling procedures for men have become popular for a number of reasons, despite a lack of clinical trial data. They are comparable in efficacy to AUS and the surgery is easier to perform. Many patients also wish to avoid a mechanical device. Slings are most useful for treatment of men with mild to moderate stress UI, or for men with uncontrolled stricture disease. Slings also are useful for men who are unwilling or unable to operate an AUS.

"Surround" with Artificial Genito-Urinary Sphincter (AGUS)
Stephen R. Kraus, M.D., F.A.C.S., The University of Texas Health Science Center at San Antonio

Artificial genitor-urinary sphincters (AGUS) traditionally were placed using perineal and suprapubic incisions, but a transscrotal approach was popularized in 2003. This greatly simplified surgery, although cuff placement may not be as accurate. Although there is a significant amount of research on AGUS outcomes, many studies rely on patient-reported outcomes; thus, definitions of success vary widely. Most studies did find significant reductions in pad use by men who were treated with an AGUS. QOL scores also improved for most patients. Risks associated with AGUS include device malfunction (6 - 25%), erosion (4 - 7%), infection (1 - 5.5%), and atrophy (0 - 10%). Between 19 and 30 percent of men required a repeat procedure. The rates of these complications varied due to different definitions and outcome parameters, variations in surgeons and surgical technique, and the length of followup.

Pre-operative urodynamic findings such as abdominal leak point pressure, presence of DO, and voiding patterns did not predict outcome. Good candidates for AGUS include men with PPI both with and without radiation, men who have undergone salvage prostatectomy, and men who have undergone a transurethral resection of the prostate. Incontinence in appropriate candidates for AGUS can range from mild to severe, although the procedure typically is reserved for men with moderate to severe incontinence. Previous AGUS failure or complications are not contraindications for a subsequent AGUS; tandem or alternative cuff placement can be used in these patients. Poor candidates for AGUS include men with poor bladder storage parameters, poor dexterity, poor mental aptitude, nonstable bladder neck contracture, or unrealistic expectations.

Better assessment of PPI is needed; current incidence estimates range from 2 to 87 percent; between 8 and 12 percent of PPI patients are estimated to have stress UI severe enough to seek treatment. Standardization of outcome parameters is needed, as well as outcome predictors, for both success and failure. Parameters also are needed to help guide treatment selection. NIDDK could provide guidance for a cross-Institute effort to assess incontinence outcomes after prostate cancer treatment.

Conservative Treatment of Post-Prostatectomy Urinary Incontinence
Dr. Goode

Although four randomized controlled trials have demonstrated that perioperative pelvic floor muscle exercises and bladder control training reduce post-prostatectomy incontinence (PPI), there are few data assessing the value of these treatments for persistent PPI.

In a study of 300 men who underwent radical prostatectomy, one group was taught pelvic floor muscle exercises during their hospital stay and provided with a home exercise program and two postoperative reinforcement visits. The other group received no formal exercise training. At 3 months, continence rates were 74 percent in the group that received treatment compared to 30 percent in the no-treatment group. By 1 year, the treatment group had a continence rate of 99 percent versus 88 percent for the untreated group (continence was defined as daily use of one "precautionary" pad or no pads). A second trial similarly randomized 102 men to perioperative

pelvic floor exercise or to the control group, which received "placebo" treatment, i.e., weekly false transdermal electrical stimulation of abdominal and thigh adductor muscles. Continence rates were 88 percent in the treatment group versus 56 percent in the control group after 3 months, and 95 percent and 81 percent, respectively, after 1 year; continence was defined as 2- and 24-hour pad tests < 2 grams and no report of leakage for the prior 3 days. A third trial randomized 152 men to pelvic floor muscle exercises or usual care. Continence rates (< 2 grams on 24-hour pad test) were 46 percent in the treatment group and 22 percent in the untreated group at 3 months and 83 percent and 47 percent at 1 year. The fourth study examined the effect of a less intensive intervention (a single session of preoperative, biofeedback-assisted PFMT, and instructions for home exercises) in a group of 125 men after radical prostatectomy. Continence rates were similar to those in the other three trials (continence was defined as no accidents on three weekly 1-day bladder diaries in a row or on one 7-day bladder diary); this study also found that the number needed to treat to have one additional man pad-free by 6 months was five men.

There are no randomized trials testing the use of PFMT for men who remain incontinent 1 year after prostatectomy. Three case series appear promising. One study found that biofeedback-assisted behavioral training in a series of 20 men resulted in a 78-percent decrease in stress UI episodes and that 38 percent of the men were cured; for urge UI, there was an 81 percent decrease in incontinence episodes and 25 percent were cured. A second case series of 27 men found a 57-percent decrease in incontinence episodes for men who received behavioral training, and a third found that training cured 48 percent of the men and improved incontinence in 26 percent. A randomized controlled trial is under way to test PFMT with and without biofeedback and electrical stimulation in men who are incontinent 1 year after prostatectomy; initial results appear promising.

These results show that perioperative behavioral training can aid in recovery of bladder control and reduce the severity of incontinence following radical prostatectomy. Implementation studies are needed to determine the optimal components and timing of visits for perioperative PFMT and to develop selection criteria for patients needing more intensive programs. Efforts also are needed to encourage urologists to refer radical prostatectomy patients for perioperative training or develop the expertise in their own practices. Studies also are needed to determine whether PFMT can improve continence when combined with sling/AUS procedures or medication.

ACQUIRED LUTS: PELVIC FLOOR/PATHOPHYSIOLOGY/COMBINED INCONTINENCE

Moderator: *Dr. Fenner*

Combined/Dual Urinary and Fecal Incontinence

Dr. Fenner

Incontinence patients often present with multiple complaints, and for women, fecal incontinence (FI) often is the most bothersome. FI has serious functional and psychosocial impacts on QOL; there is an additive effect on QOL for women suffering from both UI and FI. Dual incontinence affects approximately one-third of women with UI and/or POP. FI is defined as involuntary loss of liquid or solid stool; anal incontinence (AI) includes involuntary loss of flatus and either

liquid or solid stool. Common causes of FI include functional or inflammatory bowel disease, weak sphincters/nerves, poor rectal reservoir, or loss of sensation. Fecal continence depends on having normal stool consistency and frequency, a "functional" bowel and compliant rectum, a neurologically intact anal-sphincter complex, and a "functional" pelvic floor. An article published in 2005 found an overall prevalence of FI, defined as any stool loss that occurred at least monthly, of 7.2 percent. FI prevalence increases with age, ranging from 3.6 percent of women in their 30s to 14.8 percent of women in their 80s. UI is highly associated with FI; there also are significant associations of FI with major depression and an operative vaginal delivery (not including lacerations).

The association of FI with injuries occurring during childbirth is complicated. The prevalence of recognized obstetric anal sphincter injuries (OASIS) is between 0.6 and 20 percent; occult tears have a prevalence of 1 to 20 percent. Risk factors for OASIS include forceps delivery, macrosomic infant, midline episiotomy, prolonged second-stage labor, and sphincter laceration. A study of 407 women with OASIS at 6 months post delivery found that 17 percent had FI compared to 8.2 percent of women with no tears; there were no differences in UI. The study also assessed continence in women who underwent Cesarean sections and found that 23 percent had UI and 7 percent had FI at 6 months post delivery, indicating that pregnancy itself likely is a risk factor for incontinence. A longitudinal study of injury after delivery found that women with lacerations developed more incontinence symptoms as they aged, despite having no symptoms earlier in their lives.

Because pelvic floor dysfunction plays a significant role in incontinence in older women, analysis of the anal sphincter and pelvic floor muscles as women age was performed. The internal anal sphincter thickens secondary to fibrosis as women age. In continent and incontinent older women, the diameter of the internal sphincter increases; in older incontinent women, the external sphincter thins. Analysis of sphincter function found a decrease in resting pressure with age, and incontinence status was related to a decreased ability to squeeze the sphincter. When rectal sensation was tested using balloon distention, the older incontinent women felt the urge to defecate at a much lower volume than the young and the old continent groups. These studies showed that thickening of the internal anal sphincter occurs with aging (likely a result of fibrosis), but that thinning of the external anal sphincter and the corresponding drop in squeeze pressure was correlated with FI but not aging. Rectal hypersensitivity also was associated with FI rather than aging and may play a role in the mechanism of FI.

Standard definitions are needed to improve studies of FI. Prospective studies documenting labor are needed, as is information on possible modifiable risk factors, including operative vaginal delivery, length of second-stage labor, and midline episiotomy. The long-term impact of OASIS, nonsurgical vaginal delivery, and Cesarean section on the pelvic floor should be assessed. The impact of aging on smooth and striated muscle also requires study. Finally, new therapies such as nerve stimulation, tissue engineering, and sphincter replacement should be evaluated.

The Role of the Pelvic Floor and Birth Injury in the Pathophysiology of Urinary Incontinence in Women: Mechanisms of Disease

John Delancey, M.D., University of Michigan, Ann Arbor, MI

The small physical area involved in incontinence has only four or five different types of tissues; thus, determining mechanisms involved in incontinence and gathering data to help understand the physiological causes of incontinence symptoms should be relatively straightforward.

Stress UI appears to involve both loss of support (urethral hypermobility) and sphincter function (sphincter deficiency). Continence relies on interactions among the sphincteric system, endopelvic fascial support, and the levator ani, which contributes to urethral support. The Hammock Hypothesis, which states that abdominal pressure compresses the urethra closed against the urethral support, describes one way in which urethral support influences continence. The relative contribution of the sphincter, urethral support, and other unknown factors to continence remains to be determined. To determine the relative contributions of sphincter function and urethral support to incontinence, the Research On Stress incontinence Etiology (ROSE) study measured urethral function (MUCP) and urethrovaginal support (POP-Q, Q-tip test, vaginal closure force, and levator defects) in 103 women with daily stress UI and 108 asymptomatic controls, matched for age, parity, race, and hysterectomy. The study found that MUCP had a strong effect on continence, but urethral support appeared less important. MUCP was better for predicting continence than ultrasounds to assess urethral mobility (cough test). Predictive models for stress UI found relative contributions of 50 percent for sphincter function, 9 percent for support, 2 percent for the cough test, and 30 percent for "other factors" to stress UI.

The Establishing the Prevalence of Incontinence (EPI) study, a population-based study of racial differences in incontinence, found that urinary incontinence was less prevalent in black women (14.6%) than white women (33.1%). There was no difference by race in the frequency of incontinence, but black women reported more urine loss per episode. A larger proportion of white women also reported symptoms of pure stress UI (39.2%), whereas a larger proportion of black women reported symptoms of pure urge UI (23.8%). Risk factors for both groups generally were similar. However, racial differences in MUCP and differences with respect to type of incontinence were observed. Black women generally had stronger urethras, but both white and black women with stress UI had lower MUCPs. White but not black women with urge UI had looser MUCPs. This work found that MUCP accounts for approximately 50 percent of stress UI and urethral support accounts for an additional 9 percent. Thus, stress UI may arise from both poor urethral sphincter function and hypermobility; urge UI may arise from poor urethral function despite good support.

Analysis of stress UI after first vaginal birth in 80 primiparous women with stress UI and 80 primiparous continent women found that both sphincter function (MUCP) and support (vesical neck movement when coughing) were important. However, the relative contributions of sphincter function and support appear to change as women age. Analyzing MUCP and support (levator ani defects) in women with stress incontinence early in life and/or shortly after first birth (28 years) and at midlife (47 years) found variability in MUCP over time in women who had not given birth, as well as those who had. Levator ani defects were found more frequently in young women with stress incontinence, whereas rates were similar in women with and without stress UI

in midlife. Stress UI in older women appears to be associated more with MUCP than support. Young women giving birth have relatively strong urethras and thus require a significant support defect to cause stress UI. In contrast, older women have weaker urethras; thus, MUCP is more important than support.

Comparison of the histology of the urethra in older and younger women found a decline over time in the number of striated muscle cells. Because 50 percent of stress UI is attributable to loss of urethral function, the urethral sphincter presents a potential therapeutic target, and developing ways to grow new muscle may be a therapeutic approach to consider. Urethral support also may play a role in continence and is affected by vaginal birth. Although vaginal birth has little effect on MUCP, in 10 to 12 percent of first births the levator ani muscles are displaced. Levator ani defects are twice as likely to be found in women with stress UI as in continent women, and levator ani injury also may contribute to POP.

Although factors controlling urethral function are poorly understood in humans, the urethra is a relevant therapeutic target for stress UI and better understanding of its function (and dysfunction) should lead to new treatment options. Urge UI also may be associated with poor sphincter function and may benefit from this line of research as well. Analysis of MUCP and dynamic urethral function, including analyses of striated muscle, smooth muscle, vascular factors, and neural control mechanisms, also is needed. Because vaginal birth injures the levator ani muscle and affects urethral mobility, urethral support injury at vaginal delivery should be investigated and may represent a prevention opportunity. Research also is needed to determine how these factors interact to cause incontinence.

Synthetic Mid-Urethral Slings: Present and Future
Pamela Moalli, M.D., Ph.D., University of Pittsburgh, Pittsburgh, PA

Synthetic meshes are distinguished by textile properties (porosity/pore size), host tolerability, and mechanical properties. A pore size greater than 75 mm^2 allows access of key immune cells and fibroblasts; smaller pore sizes can harbor bacteria that cannot be eliminated by immune cells because the pores are too small to permit passage of these cells. Increased pore size and porosity decreases the amount of mesh in contact with the host tissue, improves mechanical properties (decreased stiffness), and improves host tolerability, thus decreasing complication rates. Filament type also is important, with monofilaments preferred because multifilament meshes were associated with higher rates of infection. Knitted meshes provide high tissue conformability and larger pore size and are preferable to woven meshes. Host tolerability can be a significant problem with synthetic meshes. Older meshes were associated with high complication rates, particularly exposure, erosion, infection, and encapsulation. In general, large pore size, high porosity, low density, and low stiffness meshes are associated with increased host tolerability and thus a decreased rate of complications.

Tension-free Vaginal Tape™ (TVT™) represents the new generation of incontinence mesh. It is made of lightweight polypropylene, macroporous (1,300 mm), low density (100g/m^2), knitted, has tanged edges, and is covered in a translucent polyethylene sheath. It is designed to be used as a midurethral sling. TVT™ has been associated with a relatively low rate of vaginal

exposures or erosions. Dependent on outcome definitions ,the success rate for use of this mesh to treat uncomplicated stress UI is around 80 percent.

Recently, numerous other slings have entered the market. These devices have required little premarket testing because of their similarities to the TVT™. However, all have been significantly modified based on clinicians' reports of deficiencies with the TVT™. The main complaint about TVT™ was difficulty handling it, because it permanently deformed with minimal manipulation. Companies modified their products to make them easier to handle during surgery, and although manufacturers claimed that these modifications did not change the behavior of the mesh, this has not been fully tested. A number of these meshes were subjected to a series of tests to determine the impact of modifications on sling behavior. The mechanical behaviors of the slings were different, with some slings deforming under low loads and exhibiting high stiffness at high loads. The behavior of the TVT™ mesh also differed from the other meshes in its response to cyclical loads that mimic loads occurring as a result of daily activities (coughing, sneezing, light lifting, and sitting to standing). The results of these tests showed that the TVT™ mesh is uniquely characterized by its very low stiffness and is easily deformable at very low loads.

To fully address urethral sphincter problems, future sling materials should include composite meshes with both permanent and biodegradable components. The permanent component would restore urethral support, while the biodegradable component could be biochemically active or bioinductive, helping to restore urethral function by regenerating damaged or physiologically deficient structures. Meshes with biodegradable scaffolds also could be developed. The scaffold could be used to deliver growth factors or other molecules that could induce differentiation and regeneration of functional urethral tissue. *In vivo* studies are needed to determine whether the increases in stiffness observed in the newer meshes correlate with decreased host tolerability. NIH should consider funding independent interdisciplinary research teams to objectively test current meshes.

Discussion

A participant asked Dr. DeLancey to explain the effects of menopause on continence status. Dr. DeLancey replied that the data were equivocal and that estrogen likely has little effect on the muscularis of the urethra. A participant asked about the contribution of the sphincter and levator ani to continence. Dr. DeLancey answered that, in a study of women with bilateral loss of the levator ani, women with complete levator defects often could not raise their intraurethral pressure, but if they could, they could raise the pressure to the same extent as an uninjured woman. A participant noted that urethral closure pressure is variable and thus is not adequate as a sole measure of urethral function. Dr. DeLancey agreed, and said that better understanding of the relationship between motion changes and pressure changes is needed. Understanding the relationship of these changes to symptoms will improve understanding of incontinence.

FRIDAY, JANUARY 9, 2009

ANNOUNCEMENTS: AWARDS FROM POSTER SESSION

Bold in the list of authors indicates the individual who was the primary author and recipient of the award.

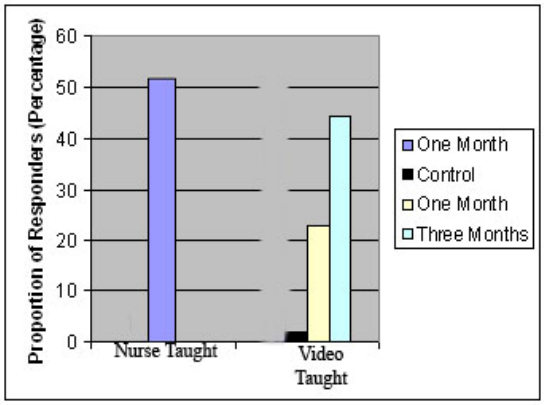
Clinical Science Honorable Mention

Short Term Response to Knack Therapy (No Dedicated Muscle Strengthening) for Treatment of Incontinence

***Janis Miller, Ph.D., R.N.**, Lee Park, M.S., Meg Tolbert, M.S., James Ashton-Miller, Ph.D., John DeLancey, M.D., University of Michigan, Ann Arbor, MI*

Introduction and Objectives:
The Knack treatment for urinary incontinence involves teaching women to contract their muscles in anticipation of expected leakage. It does not include dedicated muscle strengthening exercises. The Knack "quick therapy" has demonstrated effectiveness in reducing leakage on standing stress test when evaluated in the clinic but is untested in daily life. This abstract summarizes three phases of a project designed to evaluate Knack effect: Phase 1) demonstrating short-term efficacy with personalized instruction, Phase 2) a randomized controlled trial of video instruction, and Phase 3) long-term efficacy at 1-year post-intervention.

Methods:
In Phase 1, 64 incontinent women completed a pre- and post-test trial in which Knack instruction was provided individually by a nurse practitioner as part of a prospective clinical trial. The nurse taught how and when to use the Knack and provided feedback on the technique through digital palpation and by demonstrating the woman's own pelvic muscle contraction when coughing on perineal ultrasound. In Phase 2, 111 incontinent women completed a single-blinded randomized controlled trial of Knack instruction as provided by video. All women had a pelvic examination during which a nurse asked them to contract their pelvic muscles, including on ultrasound, but did not provide instruction in using them to reduce urine leakage. The treatment group watched a video about Knack therapy while the control group watched a video on food pyramid instruction. Both videos were approximately 10 minutes long. The Knack video included actresses portraying when to use the Knack in situations such as sneezing, coughing, on arising, and to suppress urge sensations triggered by running water or arriving home. The video also included an ultrasound showing use of the Knack to stabilize the bladder during a cough maneuver. Phase 3 recycles the control group women back into the study to receive the Knack intervention after their 1-month visit. Responders from all three phases will be followed to 1 year.



Outcomes:
Strict *a priori* criteria were used to determine response. Positive response required 50 percent

improvement on at least 2 of 3 measures: incontinence episodes on diary, leakage volume on quantified standing stress test, and self-reported improvement using a scale of 0 to 100 percent.

Results:
In Phase 1, Knack instruction provided by a nurse resulted in 51 percent of the sample being categorized as a positive responder at 1-month f/u. In the RCT (Phase 2), at 1 month the control group (diet video) showed a 2 percent response rate, whereas the treatment group (Knack video) showed 23 percent (p = .007). This initial response rate to the Knack video improved to 44 percent at 3 months, without any additional intervention. Phase 3 is in analysis phase.

Conclusion:
Using stringent objective outcome criteria, half of women who learned the Knack from the nurse have a 50 percent reduction in their incontinence episodes during normal activities at 1 month. When Knack instruction is provided by video the response rate is lower at 1 month (23%), but similar at 3 months (44%) compared to a 2 percent response rate in control women at 1 month. *Comment:* These improvements occur without dedicated muscle strengthening exercises as part of the intervention, demonstrating that skill and habit development in using a muscle contraction to stop incontinence is effective at rates that are similar to those reported from muscle strengthening trials. Although personalized instruction in the Knack elicits a quicker response than video instruction, the exciting potential is that a brief video could be viewed, for instance on YouTube, with remarkable potential as a wide-scale public health intervention.

Funding:
NIH/NICHD #P50 HD044406.

Racial Differences in Bother for Women with Urinary Incontinence

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Introduction and Objectives:
It is well known that UI has a significant impact on quality of life. However, little is known about the impact of UI or degree of bother in different races. It was our objective to compare differences in degree of bother in women with urinary incontinence (UI) in a sample of black and white women. Specifically, we were interested how UI frequency episodes, amount of urine loss, and type of UI would affect bother (as measured by the Incontinence Impact Questionnaire short form- IIQ-7) in black and white women and if there were differences between racial groups.

Methods:
A population-based study was conducted investigating the prevalence, impact, and structural mechanisms of UI in women of southeastern Michigan. Women aged 35-64 who self-identified as black or white, completed a telephone interview and the Incontinence Impact Questionnaire short form (IIQ-7). Statistical analysis included 2-way ANOVA for post-hoc comparisons of IIQ-7 scores between the two races at different levels of frequency, amount, and type of UI.

Results:
In women with mild and severe UI, no racial differences in IIQ-7 scores were seen. However, black women who reported moderate UI had significantly higher IIQ-7 scores than white women with UI of similar severity (31.4 ± 3.5 vs. 23.7 ± 1.9, p = .03). Overall, black women with urge incontinence had higher scores than white women as well (30.5 ± 4.0 vs. 21.0 ± 3.0, p = .05). When adjusting for significant covariates as well as for severity, black women with urge and mixed incontinence tended to be more bothered by their UI than white women (p = .06).

Conclusion:
In women with moderately severe UI, black women are more bothered than their white counterparts. At this discriminatory level of UI severity, these racial differences are important, as they may dictate care-seeking behavior among black versus white women.

Funding:
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Urodynamic Trends in the Female Aging Population: Detrusor Hyperactivity with Impaired Contractility, Two Conditions or One?

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Introduction and Objectives:
Lower urinary tract (LUT) dysfunction is a major cause of morbidity and decreased quality of life in the elderly. Studies have shown that symptoms of LUT disease increase with age, vary by gender, and may be related to detrusor hyperactivity with impaired contractility (DHIC).

Methods:
1,231 patients underwent multichannel video urodynamics (UDS) between November 2006 and September 2008. 274 patients were 75 years of age and older and 176 of these patients were female. UDS parameters in older females were compared to the 737 female patients in this sample who were under 75 years of age. Stratification of the data to exclude diagnoses likely to affect voiding parameters allowed for comparison of variables that may be influenced by age alone. Student's t-test was used to determine statistical significance.

Results:
The older population voided with lower noninvasive flow rates (nonQmax), lower invasive flow rates (Qmax), lower voiding pressures at peak flow (PdetQmax), higher post void residuals (PVR), and experienced more detrusor overactivity (DO) than the younger population (Table 1). Stratification of data to exclude likely confounding causes of obstruction (pelvic organ prolapse, urethral stricture, prior bladder augmentation, and neurogenic bladder dysfunction) continued to show statistically significant differences in these parameters. Furthermore, exclusion of patients with stress incontinence (which may decrease PdetQmax by decreasing outlet resistance) did not nullify the effect. Within the older group (Table 2), patients with DO voided with higher PdetQmax than those without DO (opposite of what is suggested in DHIC), and patients with PVR > 100 also had higher PdetQmax than those with PVR < 100. Within the older group, we

also compared PdetQmax > 20 cmH20 and < 20 cmH20 and showed no difference in voiding parameters with a trend toward less DO in the PdetQmax < 20cmH20 group (opposite of what is suggested in DHIC).

Table 1. Urodynamic parameters in women ≥ 75 and < 75 with exclusion of confounding diagnoses, *n* = 913

	Age ≥ 75 *n* = 176	**Age < 75** *n* = 737	p value	**Age ≥ 75*** *n* = 114	**Age < 75*** *n* = 494	p value	**Age ≥ 75**** *n* = 73	**Age < 75**** *n* = 350	p value
NonQmax (mL/s)	14.0	19.7	**< 0.01**	13.8	20.7	**< 0.01**	12.3	19.6	**0.02**
PVR (mL)	114.6	87.7	**< 0.01**	102.2	77.7	**0.04**	128.3	83.0	**0.02**
Qmax (mL/s)	13.3	16.7	**< 0.01**	14.1	17.7	**0.02**	11.9	16.3	**< 0.01**
PdetQmax (cmH_2O)	33.4	38.2	**0.03**	34.1	38.4	**0.05**	34.3	42.7	**0.03**
% with DO	43.1%	26.5%	**< 0.01**	44.7%	26.7%	**< 0.01**	43.8%	28.5%	**< 0.01**
DLPP (cmH_20)	32.1	38.5	**< 0.01**	31.9	38.9	0.06	33.7	36.5	0.54

* Excluding pelvic organ prolapse ≥ Baden-Walker Grade 2, urethral stricture, bladder augmentation, and neurogenic bladder.
** Also excluding stress incontinence.
Qmax, maximum flow rate; PVR, post void residual; PdetQmax, detrusor pressure at maximum flow rate; DO, detrusor overactivity; DLPP, Detrusor Leak Point Pressure.

Table 2. Urodynamic parameters in women ≥ 75 stratified by detrusor overactivity, post void residual and detrusor pressure at maximum flow rate.

	+ DO *n* = 76	**No DO** *n* = 100	p value	**PVR > 100** *n* = 73	**PVR < 100** *n* =103	p value	**PdetQmax < 20** *n* = 7*	**PdetQmax > 20** *n* = 42*	p value
NonQmax (mL/s)	13.7	14.2	0.79	12.5	15.1	0.15	14.2	10.8	0.22
PVR (mL)	100.9	124.8	0.30	230.6	31.0	n/a	85.0	103.2	0.69
Qmax (mL/s)	10.9	16.5	**<0.01**	10.8	14.6	**0.02**	12.8	12.4	0.90
PdetQmax (cmH_2O)	38.1	27.4	**<0.01**	38.1	31.1	**0.05**	12.2	37.0	n/a
% with DO	100%	0	n/a	40.9%	46.0%	0.20	42.9%	61.9%	0.50

* Small *n* secondary to large number of patients who could not void during the study with the urodynamic catheter in place.
Qmax, maximum flow rate; PVR, post void residual; Pdet, detrusor pressure; PdetQmax, detrusor pressure at maximum flow rate; DO, detrusor overactivity; DLPP, Detrusor Leak Point Pressure.

Conclusions:

Aging appears to have significant impact on LUT function. Our results challenge the concept of DHIC in the aging population. We present evidence that the two conditions (DH and IC) occur in the older population at greater rate than in the younger population, but these conditions are not linked. Matched stratification of the younger group was performed for comparison and bivariate analysis suggests age is a significant predictor of decreased Qmax, decreased noninvasive flow, decreased PdetQmax, increased PVR and increased DO.

Clinical Science Poster Winners

Brain Responses to Bladder Filling Reflect Clinical Severity of Urge Incontinence
Stasa D. Tadic, M.D., M.S.[1]*, Derek Griffiths, Ph.D.*[1]*, Werner Schaefer, D.I.*[1]*,*
Cathy I.Cheng, B.A.[2]*, Neil M. Resnick, M.D.*[1]
[1]*Division of Geriatric Medicine and Gerontology;* [2]*School of Medicine,*
University of Pittsburgh, Pittsburgh, PA

Urinary incontinence is diagnosed based on patient reports of episodes of urgency or leakage, although "urgency" is not measurable. In addition, the role of the brain in bladder control is not well understood. Functional magnetic resonance imaging (fMRI) and urodynamics were used to simultaneously measure brain and bladder response to bladder filling. This approach showed that urgency (without detectable DO or leakage) was accompanied by activation of specific regions of the brain, including the right insula (RI), anterior cingulate cortex (ACG), and orbitofrontal cortex (OFC). These three regions are involved in mapping bladder sensations (RI), emotional processing of fear or pain (ACG), and decisionmaking/control of voiding (OFC).

To determine whether this brain activity is related to clinical measures of urge UI, 14 older women (65 years) with urge UI underwent fMRI with urodynamics during repeated cycles of bladder filling and emptying. Analysis using brain imaging software found that brain activity during bladder filling or urgency correlated with incontinence frequency and leakage. The regions that correlated with urge UI severity are involved in neural processing of bladder afferents and working memory. This work may help identify a reliable neural correlate of urgency and in the future could be used to evaluate therapy.

One Year Clinical Outcomes with Lumbar to Sacral Nerve Rerouting In Spinal Bifida
Kenneth M. Peters, M.D.*, Benjamin J. Girdler, M.D., Cindy Turzewski,R.N., Kevin Feber, M.D., William Nantau, Jose Gonzalez, M.D., Juan de Benito, M.D., Evan J. Kass, M.D., Ananias C. Diokno, M.D., Gary Trock, M.D., Brian Bush, Beaumont Hospital, Royal Oak, MI*

In cases of spina bifida or spinal cord injury (SCI), signaling from the urinary tract does not reach the brain. One approach to creating continence in patients with these injuries involves creating a new reflex arc in which motor nerve roots from the leg (L5) are rerouted to the bladder. This permits patients to void voluntarily by scratching the corresponding L5 leg dermatome. Information travels to the spinal cord via the L5 motor route, but rather than traveling back down the leg, it sends information to the bladder, causing sphincter relaxation and bladder contractions.

At Beaumont Hospital, nine spina bifida patients were treated using nerve rerouting. Surgery takes approximately 3 hours, and there is little blood loss and few complications. Continence initially worsens, and then improves. The patients experienced lower leg weakness postoperatively, but this resolved completely in eight of the nine patients; the ninth had foot drop 1 year after surgery. Seven of the patients were able to cause urination by scratching their legs,

and two no longer required catheterization. The ability to return bladder and bowel function to patients with spina bifida using nerve rerouting may have a major impact on QOL for these patients.

THE ROLE OF INTERNATIONAL ORGANIZATIONS IN THE FUTURE OF RESEARCH

Dr. Corcos

Dr. Lightner welcomed Dr. Corcos in his role as General Secretary of the ICS to address the NIDDK conference. The International Continence Society (ICS) has developed a strong statement supporting research. ICS proposes to support urological research by funding grants to award creativity, creating fellowships at premier urology centers worldwide, establishing international and national networks, creating research protocol committees to review and assess protocols for young investigators, providing free online access to ICS's main journal, and providing free translation and editorial assistance. Beneficiaries of these activities must be ICS members.

ACQUIRED LUTS: NEUROLOGIC

Moderator: *Dr. Peters*

Overactive Bladder: Central Nervous System Aspects

Karl-Eric Andersson, M.D., Ph.D., Institute for Regenerative Medicine, Wake Forest University School of Medicine, Winston-Salem, NC

The pathophysiology of OAB is multifactorial, involving a decreased capacity to handle afferent information, decreased suprapontine inhibition, increased afferent and myogenic activity, and increased sensitivity to contraction-mediating transmitters and mediators. Most targets for OAB therapy are directed at the detrusor, to inhibit its activity; these have not been highly effective. Another approach is to modulate the afferent activity generated by the detrusor.

Afferent activity signals through two pathways: (1) the myogenic pathway, in which smooth muscle distension creates the signal, and (2) the mucosal pathway, which involves urothelial and suburothelial structures. The myogenic pathway signals through small contractions of the smooth muscle, which can generate a signal through the C5 fibers and perhaps also A-delta (Aδ) fibers. Initiation of the micturition reflex occurs when the bladder is distended and is mediated by Aδ fibers. Distension also initiates events in the urothelium or mucosa, such as release of transmitters that act on interstitial cells and afferent nerves. The urothelium, suburothelium, interstitial cells, and afferent nerves constitute a signaling unit and a target for therapies. The sympathetic storage reflex (pelvic to hypogastric reflex) is initiated as the bladder distends, and the afferent activity generated travels through the pelvic nerves to the spinal cord. The somatic storage reflex (pelvic-to-pudendal reflex or guarding reflex) is initiated by sudden increases in bladder pressure (e.g., cough, laugh, or sneeze), and the afferent activity travels through the pelvic nerves. Introducing capsaicin into the bladder in rats causes DO, pain, and leakage. However, treatment with a nitric oxide synthase inhibitor results in motor activity but no pain or

leakage, demonstrating that at the spinal level, it is possible to differentiate between various types of afferent information.

Information travels through the spinal cord to specific structures in the brain, including the periaqueductal gray (PAG), which receive afferents from the bladder; the insula, which maps sensation; the anterior cingulate gyrus (ACG), a site for emotional/autonomic motor controls; and the prefrontal cortex (PFC), which is involved in voluntary control. The pontine micturition center (PMC) connects with the PAG. The PMC has two components (micturition and storage) that can be functionally separated. Afferent signals from the bladder go first to the PAG, are processed in the ACG, go through the thalamus and hypothalamus, and then to the PMC. If PMC activity is uncontrolled, urge UI results.

Uncomfortably filling the bladder results in increased activity in the anterior insula. In micturition dysfunction, there brain activity switches toward the anterior insula, resulting in a stronger, more unpleasant sensation related to voiding. In patients with poor control and a strong desire to void but no DO, changes in activity in the insula, ACG, and PMC are observed. Abnormal activity from the PFC, which normally inhibits activity during bladder filling, may indicate impaired voluntary control or involvement of different neural pathways; this suggests that incontinence may be a pathological phenomenon. In OAB patients, inhibition occurs during filling; however, the PMC is active and there is abnormal activity in the pelvic nerve and the detrusor. This work suggests that dysfunctions involved in OAB and urge UI occur at the level of the PAG, PMC, and their connections. These results also indicate that in cases of poor bladder control, afferent information is processed abnormally in the brain. The activation of the ACG indicates that emotions also are involved.

Targeting abnormal activity in the brain may represent a therapeutic approach for urge UI and OAB, but there are few effective drugs for this. Tramadol is a receptor agonist that inhibits reuptake of noradrenalin and serotonin. It reduces incontinence episodes and number of voids and increases capacity, but it is not an ideal drug for OAB. Gabapentin, used in the treatment of epilepsy, may have therapeutic activity in neurogenic and non-neurogenic DO. Neurokinin-1 receptor antagonism may represent a therapeutic approach to treating OAB. To fully explore targeting brain activity to treat urge UI and OAB, systematic preclinical studies of targets, mechanisms, and transmitters are needed, as well as systematic preclinical studies of the effects of these interventions, both behavioral and pharmacological.

Spinal Cord Injury
Michael B. Chancellor, M.D., William Beaumont Hospital, Royal Oak, MI

Approximately 10,000 SCIs occur each year, primarily in males. The life expectancy of SCI patients is determined by the severity of the injury, but paraplegics injured at age 20 can expect to live another 46 years. Thus, a high health-cost burden is associated with SCI patients.

Genitourinary issues account for 30 percent of rehospitalizations in the first year after SCI and continue to account for approximately one-third of rehospitalizations throughout the patient's life. Neurogenic bladder associated with SCI can arise from neurogenic DO (NDO), NDO plus detrusor-sphincter dyssynergia (DSD), or detrusor areflexia and impaired contractility.

Approximately 10 percent of male SCI patients are discharged with an indwelling or suprapubic catheter; by 20 years postinjury, approximately 30 percent have a suprapubic catheter. More than one-quarter of female SCI patients are discharged with an indwelling catheter.

The Center of Urology Research Excellence-Spinal Cord Injury (CURE-SCI) has a number of projects under way. Dr. William de Groat's project, "Mechanisms of Detrusor Hyperactivity after SCI," uses a cat SCI model to trace afferent pathways in SCI and determine the key receptors in the Aδ fibers that may play a role in SCI. This project also found increased ATP release in SCI cat urothelium. Possible therapeutics such as potassium channel openers, pudendal nerve stimulation, and 5HT1A receptor agonists are being explored. Dr. Michael Sacks's project, "Alterations in Bladder Mechanics," uses a bioengineering approach to explore the effects of SCI on bladder structure in a rat SCI model. This work has detected a 50 percent increase in circular stretch versus longitudinal stretch in the injured bladder, along with smooth muscle hypertrophy and connective tissue changes. Dr. Robert Getzenberg's project, "Biomarkers of Bladder Cancer in SCI", seeks to mitigate the 460-fold increase in bladder cancer risk suffered by SCI patients; this risk arises largely because of the use of indwelling catheters, and yearly cystoscopy is recommended beginning 8 to 10 years after SCI. Preliminary results indicate that BLCA-4, which appears to be a novel member of the ETS transcription factor family, can identify individuals with bladder cancer who do not have positive cytologies. Drs. Chancellor's and Naoki Yoshimura's projects, "Mechanisms of Detrusor Overactivity" and "Novel Intervention Strategies for Neurogenic Bladder," are testing potassium channel openers and other neuromodulators for treatment of DO and neurogenic bladder. This work has found that manipulating pudendal nerve stimulation frequency can inhibit the micturition reflex, resulting in better storage capacity. Higher frequencies of stimulation also can provoke an erection response. CURE-SCI also is sponsoring a clinical trial testing botulinum toxin injections of the sphincter and introduction of botulinum toxin into the bladder itself to promote bladder relaxation and better storage.

Neuromodulation for the Treatment of Voiding Dysfunction
Dr. Peters

Sacral nerve stimulation (SNS) has been approved for treatment of urinary urgency and frequency, urge incontinence, and nonobstructive urinary retention. Improvements in surgical techniques have simplified placement of these devices. Placing a permanent lead is now relatively simple, and the settings on the device can be manipulated by the patient. Long-term, multicenter studies of sacral neuromodulator implants have found a greater than 50 percent improvement in symptoms of urgency, frequency, and incomplete bladder emptying that is maintained for at least 5 years. SNS also may be useful for treatment of FI, pelvic pain, vulvodynia, and interstitial cystitis.

Pudendal nerve stimulation (PNS) represents an alternative approach that may help relieve symptoms in those not helped by SNS. The pudendal nerve is a distal branch of sacral nerves S2, S3, and S4; PNS potentially may increase afferent stimulation through the sacral nerve roots. Animal studies show that PNS can inhibit bladder contraction in SCI cats and dogs. PNS also has been tested in humans with urgency, frequency, or urge incontinence. First Sensation of Fullness increased 98 percent in these patients and maximal cystometric capacity increased 66

percent. In another trial, patients were randomized to PNS or SNS. Overall improvement in symptoms was 44 percent for SNS and 59 percent for PNS. PNS was superior to SNS for relieving pelvic pain, urgency, frequency, and improving bowel function. Stimulating at different frequencies had different effects on symptoms, which may allow targeting of PNS treatment to specific symptoms. Patients also preferred PNS to SNS. Multicenter trials of PNS are needed, as is assessment of optimal stimulation parameters.

Tibial nerve stimulation also may be a way to alleviate UI symptoms and voiding dysfunctions. Percutaneous tibial nerve stimulation (PTNS) showed some success in treating OAB, but daily stimulation was needed and maintenance therapy may be necessary for sustained symptom reduction. Urodynamic studies of 90 patients with OAB found that PTNS increased bladder capacity and also increased the volume at which the first unstable detrusor contraction occurred. PTNS has been approved by the FDA, but reimbursement issues exist.

Other approaches to treating incontinence include botulinum toxin injection to treat a number of symptoms, including OAB, urge UI, interstitial cystitis, and sphincter dyssynergia. Nerve rerouting to create a skin-to-bladder reflex also is being tested for treatment of voiding dysfunction associated with SCI and spina bifida. Initial results from small trials in spina bifida patients have been promising, with improvements in both urinary and bowel continence observed. Because a partial connection to the brain is maintained in some cases, some spina bifida patients have begun to sense when the bladder is full.

Well-controlled trials are needed to determine the effects of various neuromodulation techniques on different disease states and to determine the best neuromodulation technique, timing of introduction, long-term efficacy, risks and benefits, and ideal stimulation parameters. A multicenter trial of nerve rerouting is needed to understand its impact on SCI, spina bifida, and other voiding dysfunctions. Other issues to address include preventing lower extremity complications that may occur during nerve rerouting and finding ways to enhance nerve growth (e.g., stem cells or nerve growth factors).

Discussion

Dr. Chancellor explained that improvements in PNS and SNS have occurred because of improved understanding of muscle and nerve physiology, including the different properties of nerve fibers. For example, pudendal sensory upstream stimulation at low frequency can inhibit the bladder, whereas efferent, downstream high-frequency stimulation can fatigue the external sphincter. Participants also discussed using fMRI to analyze changes in brain activity in response to behavioral or physical therapy that has a cognitive basis to determine which patients benefit from these interventions.

TREATMENTS MOVING FORWARD

Moderator: *J. Quentin Clemens, M.D., University of Michigan, Ann Arbor, MI*

Medications: Why Do We Need New Ones?

Dr. Clemens

Subject to the inherent weaknesses of meta-analyses, the effectiveness of antimuscarinic medications vs. placebo in such studies has found only small differences in reduction of symptoms (leakage, number of voids) between the drug and placebo; some of these were of questionable clinical significance. Only modest improvements in QOL were realized. Another meta-analysis found no clear difference in efficacy between the various antimuscarinic agents, but longer-acting preparations did result in fewer side effects. Finally, medication adherence is a significant problem. Seventy to 90 percent of patients discontinue drug therapy within the first year of treatment, primarily because of unmet treatment expectations. Drugs developed more recently have slightly better adherence than older drugs such as oral oxybutynin. New treatment options include triple-drug therapy (maximal dose of an antimuscarinic, plus imipramine and terazosin). In a study of 16 patients with SCI, three-drug therapy had better compliance and helped reduce symptoms of reflux, incontinence, and DO. The pilot data suggest that combination therapy will be more effective than treatment with a single drug.

Industry funding is a factor in the development of pharmacologic treatments for incontinence, in part because most randomized controlled trials in this area are supported by pharmaceutical companies. Few studies have directly compared 'modern' antimuscarinic agents, and all such studies have been sponsored by industry. Perhaps not surprisingly, all of these studies reported results that were in favor of the sponsor's medication. These results may reflect real findings, but the possibility of bias exists. Research has shown that pharmaceutical company support of a trial is strongly associated with results in the sponsor's interest.

Analysis of comparative effectiveness is increasingly important because of the unsustainable increase in U.S. medical spending, due in part to widespread use of treatments and procedures even when evidence about their relative effectiveness is lacking. Trials required by FDA for new drugs or devices typically focus on efficacy relative to placebo rather than to existing therapies; pharmaceutical companies rarely conduct head-to-head trials of new and existing therapies. Comparative effectiveness analysis calls for a rigorous evaluation of the impact of different options that are available for treating a given medical condition in a particular set of patients, and includes analyses of both clinical effectiveness and cost-effectiveness. Current major health policy proposals call for establishing a federal institute to study comparative effectiveness. Since there are currently multiple therapies that are available for the treatment of urge incontinence, it is clear that non-industry sponsored comparative effectiveness research is needed in order to determine the relative efficacy of these various agents.

Medical Device Regulation

Janine M. Morris, Office of Device Evaluation, Center for Devices and Radiological Health, FDA, Rockville, MD

FDA was granted authority to regulate medical devices by passage of the Medical Device Amendments in 1976. FDA's role in medical device regulation is to ensure that safe and

effective products are available to the patient, a product does what it claims to do, and claims of clinically significant results are supported by valid scientific evidence. Medical devices are regulated through three mechanisms: 510k, Premarket Agreement (PMA), and investigational device exemption (IDE). Medical devices are distinguished from drugs by having a primary action that is not chemical and is not dependent on being metabolized.

Currently, 1,700 generic types of devices exist and there are 16 classification regulations. The classification of the device determines the extent of regulatory control. Class I covers simple, low-risk devices and comprises approximately 782 different product types (approximately 46% of all medical devices). These are subject to general controls for assurance of safety and efficacy, and most are exempt from premarket submission. Class II devices are more complex and are associated with higher risk. These are subject to general and special controls, such as premarket notification (510k), substantial equivalence, clinical data (10 to 15% of Class II devices), performance testing, postmarket surveillance, patient registries, special labeling, and mandatory performance standards. Approximately 46 percent of medical devices are considered to be Class II; surgical meshes used for slings and tapes are reviewed as Class II devices. The remaining 8 percent of devices are Class III. These devices are complex and pose the highest risk to users. Extensive data (laboratory, animal, and human) on these devices are required to establish safety and effectiveness, as well as a PMA; post-approval study requirements also may apply.

The PMA mechanism applies to high-risk or first-of-its-kind devices. The applicant must demonstrate reasonable assurance of safety and effectiveness, and each PMA must stand on its own. The 510k mechanism allows devices to reach the market by demonstrating "substantial equivalence," given similar intended use and existing technology on which to base the application. Post-market surveillance is required if a product begins to fail or causes adverse effects; however, FDA's post-market authority is weaker than that for premarket devices. For example, FDA cannot act until it has received reports about malfunction or harm. The Medical Device Reporting Program states that manufacturers must (by law) report deaths and serious injuries if a medical device may have caused or contributed to the event, as well as malfunction. All user facilities (hospitals, nursing homes, etc.) must report deaths to FDA and serious injuries to the manufacturers. Physicians and facilities can voluntarily report to manufacturers and to FDA through MEDWATCH. Surgical mesh used to repair POP and stress UI received 1,000 reports of complications (erosion through vaginal epithelium; infection; urinary problems; and bowel, bladder, and blood vessel perforation) over 3 years. This prompted FDA to issue a Public Health Notification and begin an epidemiologic study to assess the safety and effectiveness of mesh by analyses of data from the Los Angeles Medical Center Kaiser Permanente database.

Discussion

Ms. Morris explained that a single device can be chosen as a predicate device after the sponsor has determined substantial equivalence and comparability of intended use; the sponsor also must determine if any new characteristics impact safety and effectiveness. If a predicate device is removed, the devices related to it are not banned and can continue to be marketed legally unless

FDA decides to issue a class action to recall all related devices. A participant noted that most slings and meshes are 510k devices based on devices developed before the 1976 amendment and, thus, extensive premarket clinical testing of new slings and meshes has not been required. Ms. Morris explained that FDA cannot ask for more information until it receives notices of clinical issues.

Components of Good Clinical Trial Design for SUI Surgeries
Dr. Nygaard

A number of issues complicate randomized controlled trials for stress UI. Generalizability of participants can be a problem that can be solved by minimizing exclusion criteria; including elderly, obese women and others at risk for SUI; and, in general, recruiting all eligible potential participants. Surgical trials also must consider the generalizability of the abilities of the surgeons involved; outcomes may be different if a surgeon is more or less skilled in a procedure. Trial designers must consider learning curves and decide whether to exclude learners and low-volume surgeons (to test efficacy) or inventors and high-volume surgeons (to test effectiveness). Randomization to a surgeon, rather than the procedure, also could be considered, but noting the inherent difficulties of generalizability with that schema. Masking is also a particular problem for surgical trials. Staff measuring outcomes always should be masked, as should the participant, when possible; sham bandages or incisions could be used to mask participants.

Comorbidities, particularly POP, which often coexist with stress UI, also complicate stress UI trials. To circumvent this problem, trials could assess only stress UI surgery, although this would decrease generalizability and result in a longer recruitment period. Both stress UI surgery and POP surgery could be performed, requiring stratification of randomization and power adequate to analyze both groups. Determining followup intervals also can be difficult. Short-term followup might be sufficient for describing adverse events, medium-term for describing early failures, and long-term (more than 2 years) for describing success. Long-term registries and electronic databases could be used to help determine how the surgery assessed in a trial affects future bladder function, retreatment ability, and other related issues.

Defining success also can be complicated, given a lack of clear outcome definitions related to incontinence. This can be addressed by always defining, in advance of the trial, outcome measures, whether the outcome is incontinence or specifically stress UI, how to analyze re-treatments, and a success rate relevant to patients. Randomized controlled trials also rarely address societal perspectives; cost studies therefore should be incorporated into the trials and reported with the primary outcome.

What Are the Components Necessary To Design Good Clinical Trials: Male SUI
Brian Flynn, M.D., University of Colorado, Denver, CO

Trials for male UI, as for others, are complicated by the lack of a clear definition of continence. Some trials define continence as using zero pads per day, others as using zero to one pad per day, and others one pad per day. Estimates of PPI incidence also vary widely, ranging from 2.5 to 87 percent among various epidemiological studies. This wide variation in reported outcomes is attributable to the variability and methodology used in defining continence.

Approximately 200,000 men in the United States are diagnosed with prostate cancer each year, and about one-third undergo radical prostatectomy. A significant proportion of these men have moderate to severe UI, leading to an increase in AUS implantation, which has improved continence successfully in at least 80 percent of recipients. In 2005, 4,426 AUS units were placed; based on PPI rates, more than 5,000 should be placed each year, indicating that PPI is vastly undertreated. Despite high cure rates and high patient satisfaction, all AUS carry the risk for possible future revision. Male slings have become popular for treatment of male UI for physician and patient reasons. Surgery to place slings generally is minimally invasive and restores continence immediately; revision are less likely. Choosing the best procedure for each PPI patient relies on a paradigm that has not changed in 20 years—patients with low-volume leakage receive slings, and patients with-high volume leakage receive an AUS. Other issues, such as a lack of dexterity or mental capacity to operate the AUS, or refusal to have an mechanical device, lead to some patients with high-volume leakage receiving slings. No clinical trials support this decision-making process.

Clinical trials to determine the most effective procedure, i.e., sling or AUS, for treating PPI are complicated by several issues. The ideal index patient for such trials would be under 65 years of age, with good cognition and dexterity, and no prior x-ray therapy or recurrent cancer; incontinence duration of less than 1 year requiring use of more than one pad per day; no prior surgical treatment for stress UI; and normal bladder compliance. However, most men referred for these trials are older, have received x-ray therapy, are obese, and have strictures or erosion risk factors; a number are still receiving treatment for their cancer. Objective disease assessment measures also are needed, such as pad weight, as well as global assessment. The roles of urodynamics and cystoscopy in assessing PPI patients also need to be clarified. The placement of slings is changing from bone-anchored to transobturator approaches; transobturator slings are easier and faster to place, but there are no data to indicate that such slings are more effective than bone-anchored slings. AUS placement also has changed from perineally placed cuffs to penal-scrotal placement. Although one study showed that perineally placed cuffs result in better continence rates and less need for revision, the majority of AUS are placed penal-scrotally because the surgery is simpler. Another parameter to test is whether antibacterial coating, such as that used for penile implants, should be used on AUS. Randomization also is an issue, specifically whether an individual surgeon should perform both sling and AUS surgeries or whether patients should be randomized to surgeons, how to randomize patients while taking into account patient preferences, and whether patients can be blinded to the type of device they receive. Followup would be needed for 3 months to detect infection (90 percent occur within 3 months of surgery) to 10 years to assess mechanical durability of an AUS.
Future efforts for improving male stress UI clinical trials should focus on developing validated research tools, agreement on outcome measures, and indentifying risk factors for failure. A national database should be created to track results and complications such as urethral and bladder erosions, infection, and mechanical failure.

Components Necessary To Develop Good Clinical Trial Designs: Urge Urinary Incontinence (and Urinary Frequency/Urgency)
Roger Dmochowski, M.D., Vanderbilt Medical Center, Nashville, TN

The urge/OAB population is difficult to define because OAB is a nonspecific syndrome with numerous causes. OAB trials tend to enroll people with dissimilar OAB symptoms and histories; thus, results of some trials may be misleading. Trials also tend to enroll patients based on self-report of symptoms; complicating this is the lack of straightforward, understandable terms for various symptoms and conditions.

Defining the population for a trial is critical for general utilization of a drug or device. Precedents set by regulatory authorities influence definition of the population for OAB trials; to change the indication for a drug for OAB, regulations for changing the label must be met. However, although many urologists consider inclusion of QOL and patient-reported outcomes in trials to be valuable, the FDA does not mandate their inclusion. The primary criteria for selection of patients in trials remain diary-based variables. A number of diary-measured symptoms exist, such as incontinence episodes and type, number of volitional voids, urgency episodes (with or without magnitude), and volume voided.

Assessing outcomes of OAB trials also is complicated. Many trials rely on patient-reported outcomes, despite a lack of clarity and agreement on terms describing these outcomes. QOL is increasing in importance for understanding the impact of therapies, although harmonization of QOL metrics is needed. How patients assess "bother" also usually is considered, but level of bother experienced varies from patient to patient and does not correlate directly with symptom severity. Outcomes must be meaningful to the patient; recent FDA guidelines stress criteria for patient-reported outcomes.

Other issues to consider include trial design and use of appropriate controls, methods of monitoring results, and trial length. Use of control groups is critical, given behavioral responses to an intervention. Electronic record keeping may aid diary reporting, but some studies have shown higher placebo rates when electronic diaries are kept. In many OAB trials, an effect is seen early, but the duration of the effect is unknown. This is of particular importance for OAB because persistence is poor for both drugs and devices. Short-term persistence also may be responsible for missed safety signals.

The use of UDS in these studies has been questioned. Urodynamics can help show that a drug or device has an LUT benefit, but not all trials or all patients need urodynamic assessment. The reproducibility of these tests has been questioned in the past, but recent results have found good reproducibility. A detriment to including UDS is that they may dissuade patients from enrolling in a trial. Urodynamic assessment also may complicate enrollment; for example, discordance between urge UI symptoms and DO findings are common.

Defining urgency also is complicated. Urge is an important symptom, but the best criteria for assessing urge have yet to be determined. Urgency effect appraisal may include magnitude of discomfort and time criteria. A number of specific measures for urgency exist, such as the Overactive Bladder Symptom Score or Urgency Perception Score, and urologists must reach an agreement on one best measure to ensure that multiple studies do not rely on different outcome measures. Although urgency is important, it is only a subcomponent of the entire OAB syndrome. Nonetheless, urgency should be applicable across medical specialties, symptoms

should be described in a standardized fashion, normal urge should be distinguished from pathologic urgency, and the definition of urgency should be straightforward.

Better OAB trials will result from better understanding of OAB pathophysiology. Agreement regarding study outcomes and designs will permit better comparability across trials. Designing trials to enroll the "real population" also will aid in identifying meaningful interventions and therapies.

Issues in Design of Clinical Trials: Physical Therapy
Dr. FitzGerald

Chronic pelvic pain is accompanied by points on skin, fascia, and muscle that are tender to the touch. Although it is known that work on somatic tissues can affect visceral function, no clinical trials have methodically assessed the impact of physical therapy on chronic pelvic pain. A randomized, multicenter trial to test myofascial treatment of chronic pelvic pain therefore was initiated. A planned total of 48 patients were randomized to manual physical therapy with targeted internal and external connective tissue manipulation, including work on the levator ani, performed transanally or transvaginally, or to global therapeutic massage, which was a nonspecific somatic treatment with full-body Western massage and no internal touching. Patients were asked if their overall pelvic symptoms had worsened, improved, or stayed the same. Fifty-seven percent of the group receiving physical therapy reported improvement, compared to 21 percent receiving massage. The response rate to massage in women was 0 percent, but was 45 percent in men. No serious adverse events were reported (pain was the most common); 21 percent of people receiving global massage therapy reported pain, compared to 52 percent of the physical therapy group.

This study achieved its major objectives: first, it is important to note that the patients were willing to be randomized; 37 percent of those eligible were enrolled and randomized; treatment approaches were standardized; and rates of study withdrawal and severe adverse events were low, suggesting that patients found the treatments acceptable. The overall response rate of 57 percent suggests that physical therapy represents a clinically meaningful treatment option.

A number of issues arose in designing the trial. Novelty represented an immediate roadblock; participating physicians did not have experience with massage therapy, and therapists did not have experience with trials. No literature on acceptable placebos or possible adverse events existed. Standardization of treatments was complicated, but the participating therapists agreed to choose one approach for the trial. Possible confounding of treatment with therapist also needed to be addressed. Certification of therapists was an issue, as there is no subspecialty certification for pelvic floor therapy. The study did not train the therapists but rather had them attest to routinely performing these therapies for at least 2 years prior to the study. Many of the participating centers had specialized therapists, but the results would not be generalizable if only patients seeing these therapists saw improvement. Determining that therapists maintained the same approach throughout the trial also was difficult, because video recordings of the treatment sessions were not made. Determining an appropriate placebo was complicated because the magnitude of the placebo effect likely varies with treatment modality. In addition, the

appropriateness of touching patients internally without intent to treat had to be considered (although this ultimately was not done).

Physical therapists must lead the design of physical therapy trials, which should become easier as the field matures and more therapists receive doctoral-level training. Treatments must be standardized and high-quality control measures maintained to avoid jeopardizing further testing of these seemingly effective treatments.

What Would Ten Years From Now Look Like?
Dr. Dmochowski

Comparative effectiveness is becoming an increasingly important standard by which the impact and effectiveness of medical therapies are assessed. The field of urology must standardize terms and outcome measures and use uniform reporting to enable comparability across trials. Outcomes in effectiveness studies should be defined using standardized and generally accepted measures that are non-specialty specific. Outcome measures should have specific efficacy, objective, and patient-oriented components; clearly identify adverse events; and incorporate a time component. An evaluation mechanism for interventions should be developed that includes comparison to a "therapeutic standard" and is applicable to devices, drugs, or other types of interventions. The goal of comparative effectiveness studies is to balance effect with side effects and costs and can be important for identifying novel outcomes to distinguish an intervention from competing therapeutic approaches.

Interest in developing comparative effectiveness information is increasing in the United States, with an emphasis on pharmaceutical reimbursement but applicability for all aspects of health care delivery. Health care spending in the United States was $5,267 per person in 2002, compared with $3,446 for the next highest spending country (Switzerland). If sustained at this level, health care spending in 2045 will exceed the current federal budget. Federal agencies such as FDA, NIH, and CMS, along with third-party entities, need to interact to address this issue.

Creation of national registries will help foster better understanding of the impact of interventions. The experience of other countries in this area could be used as a model, but most such registries are voluntary and established in small countries. Analysis of data in a national registry in Finland found that high volume centers and surgeons had better results and fewer complications for sling procedures. A Dutch registry found that mode of anesthesia may impact sling success rates. Registries should not pose a burden to clinicians and providers, should have defined stakeholders and funding, should be highly accessible, and should reflect generic practice rather than practice only at academic centers.

FUTURE DIRECTIONS IN RESEARCH

Moderator: *Tom F. Lue, M.D., F.A.C.S., University of California, San Francisco, CA*

Tissue Engineering in Skeletal Muscle

Herman Vandenburgh, Ph.D., Brown University, Providence, RI

Skeletal muscle progenitor cells are isolated easily; so-called "satellite" cells re-enter the cell cycle upon muscle injury and give rise to more muscle fibers. Growth factors, morphogens, and cytokines can be incorporated into synthetic scaffold material to create different patterns of activity and recapitulate *in vivo* muscle cell growth control mechanisms. Attractant factors also can be placed on the scaffolds to recruit appropriate cell types. Natural scaffolds (e.g., collagen) can be mixed with cells to create bioartificial muscles that have contractile properties. Bioartificial muscles have typical twitch reactions, generate force, and are excitable under normal conditions. However, they generate a normalized force only 2 to 3 percent of that of native tissue because of lower packing density and lack of innervation and vasculature. Bioartificial muscles could be used for drug screening, structural repair, as a therapeutic protein delivery system, and in basic research.

Bioartificial muscle can be used to deliver therapeutic proteins by biopsying the patient's muscle, inserting bioactive protein genes into the cells, expanding the cells, and developing a retrievable implant to deliver the cells. Muscle stem cells are ideal for protein delivery because they are reproducible but non-tumorigenic, non-dividing, non-migratory, long-lived, have high protein output pre-implantation to permit monitoring for predictive dosing, produce bioactive proteins, and can deliver proteins systemically or locally from a non-muscle site. Bioartificial muscles have been used to deliver proteins such as growth hormone, insulin-like growth factor 1, and erythropoietin. Challenges to this approach include improving cell transplant survival; scaling up to deliver therapeutic doses in humans; and determining appropriate doses to limit side effects; along with cost, regulatory, and manufacturing issues.

Bioengineered contractile tissue can be used in functional assays, toxicology studies, and in disease models to facilitate drug discovery. Drugs would be screened based on tissue physiology, for example by monitoring changes in active force generation by the tissue-engineered muscle; changes would represent an effect on multiple biochemical pathways.

The MyoForce Analysis System (MFAS™) represents a quicker, cheaper, and faster alternative to animal testing. It can be used in secondary screening to find drugs that increase skeletal muscle strength (e.g., to treat some forms of urinary incontinence), drugs with adverse effects on muscle strength (e.g., statins), or to find compounds that regulate smooth muscle cell activity, which might be useful for treatment of OAB. MFAS™ also may help determine the tissue selectivity of a compound (e.g., skeletal versus cardiac versus smooth muscle), and could represent an approach for engineering bladder tissue for drug screening.

Why Does It Take So Long To Grow a Bladder?
Bradley P. Kropp, M.D., F.A.A.P., Children's Hospital of Oklahoma, Oklahoma City, OK

Currently, bowel tissue is used for bladder augmentation. This results in increased bladder capacity but is associated with significant complications. Tissue engineering could be used to avoid these complications. The two primary techniques used to engineer tissue are the "seeded" and "unseeded" techniques. In the unseeded technique, a biomatrix, such as small intestine submucosa (SIS) or bladder acellular matrix, is used to augment existing tissue and promotes regeneration directly. Using this technique, functional bladder regeneration is possible, depending on the size and amount of regenerated tissue needed. The unseeded technique may be useful for simple augmentation alone. For the seeded technique, biomaterial acts as a cellular transport vehicle; cells from the host are seeded onto the biomaterial. Human studies have shown that bladder regeneration can be used clinically. Improved methods to bioengineer a functional bladder will require better understanding of the mechanisms of regeneration, improved biomaterials and methodology, improved angiogenesis for revascularization of the grafts, and better understanding of abnormal host cells that prevent reliable regeneration. The urinary bladder actually has an innate ability to regenerate, and, if given the proper scaffold or environment, partial enlargement or augmentation will not require cell seeding.

Porcine SIS has been used as a scaffold for bladder regeneration. The SIS consists of collagen with intrinsic growth factors and promotes regeneration of blood vessels, ligaments, and genitourinary organs. Early work with SIS had inconsistent and unreliable results. However, closer investigation found that the age of the donating sow and the location of the SIS were important; better results were achieved with distal SIS than proximal SIS. The distal SIS was less permeable and had better elastic properties than the proximal SIS. SIS also was superior to other biomaterials in stimulating angiogenesis.

Commercializing distal SIS for bladder augmentation alone is hampered by high costs and potentially low sales volume. An alternative approach would be to standardize commercially available SIS (SurgiSIS, Cook Biotech) using nanoparticles to create an "off-the-shelf" biomaterial for bladder augmentation. The regenerative potential and angiogenesis activity of SIS could be enhanced further by using nanoparticles to alter SIS permeability and deliver growth factors, angiogenesis promoters, and pro-regenerative compounds such as hyaluronic acid. Initial studies found that commercial SIS can be modified, standardized, and improved. Work also is under way to better understand the inflammatory process that develops in SIS-augmented bladder and to determine if abnormal bladder cells from a patient will revert to a normal state when placed into culture and thus be usable for tissue engineering.

Experimental Studies With Implants
Dr. Deprest

Animal models are used for preclinical evaluation of meshes for fascial reconstruction, including examination of immune response and visco-elastic properties. Rats are most commonly used for experimental reconstruction of the abdominal wall. Rabbits have been proposed as a model for vaginal surgery, but rabbits have different life events and different collagen metabolism than

humans. There is increasing interest in using sheep as a model for vaginal surgery, but financial challenges exist.

Subcutaneous implantation can be used to analyze the local and systemic immune response to an implant. To examine the surgical consequences of using meshes, they are used in experimental surgeries that mimic those performed in the clinic. A defect is created in the tissue and the implant is placed. After 90 to 100 days (for rats) explants are taken that are composed of the implant, interface, and native tissue to be used for histologic studies and studies of tensiometric strength. Side effects (such as adhesion), inflammatory processes, and visco-elastic properties can be examined using explants. For example, microscopic analysis of an explant found macrophages deep in the interstices between the fibers of a multifilament mesh. Making pores larger and reducing the amount of material present in a mesh is believed to generate a weaker inflammatory response, because increasing the pore size and using small fibers prevents inflammatory reactions around the filaments from forming a continuum across the filaments. Thus, the mesh should not behave as a stiff material, but this remains to be demonstrated.

Elasticity usually is measured by subjecting the explanted material to stressing, and elongation and amount of force used are measured and graphed; the area under the curve represents the energy needed to disrupt the implant. As the constructs are stretched, changes reported as a function of the cross-section of the implant occur, which is relevant because thickness plays a role in elastic properties. Digital measuring techniques can measure changes in dimensions that occur during the experiment and allow the investigator to adjust for these changes. Many of these experiments report on disruptive forces that happen beyond the physiological force range and therefore may be less clinically relevant.

Rat experiments have shown that the implants are relatively weak within the first 30 days after implantation (tensile forces of less than 60 newtons per cm, which is the limit calculated for abdominal wall hernia repair). After 90 days, synthetics appear to be stronger, but many of the other materials, including biodegradable materials, are not resistant to forces of more than 60 newtons. Further analyses found that many of the implants ruptured within themselves rather than at the interface between host and implant. Clinical data for the use of SIS and Pelvicol for sacropexy found a failure rate of 10 percent and a significant number of graft-related complications.

This work suggests that more preclinical testing is needed in animal models that more closely mimic patients requiring reconstructive surgery (i.e., older, obese, smokers). Testing materials along only one axis also is not sufficient because materials have different visco-elastic properties in different orientations. Noninvasive measurements of elasticity *in vivo* also would be useful. Ultrasound elastography cannot be used in rats but has been used to measure displacement in sheep vagina. These experiments remain an important step in evaluating new materials for use in fascial reconstruction, but better models are needed—particularly for vagina—as are better ways to perform visco-elasticity testing and bidirectional measurements.

Regenerative Medicine for Incontinence: Bladder Replacement

Anthony Atala, M.D., Wake Forest University School of Medicine, Winston-Salem, NC

An initial challenge to developing an engineered bladder was identifying a cell population that could be expanded in culture and that would develop the properties of urothelial cells. Experiments on bladder injury identified a population of targeted committed progenitor cells that could be expanded and would give rise to urothelial cells. A second challenge was developing appropriate delivery vehicles; scaffold should replicate the mechanical and structural properties of the tissues being replaced. A third challenge was to promote vascularization in the implanted tissue. The discovery of vascular endothelial growth factor (VEGF) and other experiments determined that using muscle cells, endothelial cells, and VEGF resulted in the best vascularization and good muscle formation. Subsequent experiments found that implanting biomaterials alone allowed regeneration sufficient to span a 1-cm defect. Unseeded scaffolds could be used to treat urethral stricture if healthy urethral bed is still available.

Efforts to develop an artificial bladder included analyzing different types of matrices, including collagen (bladder submucosa), biodegradable polyglycolic acid (PGA) scaffolds, and SIS. Preclinical experiments in dogs found that using scaffold alone and suturing the neobladder at the bladder neck resulted in increased capacity but a poorly compliant bladder. Seeding the scaffold with muscle cells on the outside and urothelial cells on the inside resulted in good tissue formation and less scarring and fibrosis at the bladder neck. Compliance for the seeded scaffold decreases initially, but then returns to normal levels.

Because bladder regeneration is needed by people suffering from pathological conditions, experiments were performed to determine if cells from functionally abnormal organs could be engineered to create functionally normal tissues. Although cells from patients with conditions such as spina bifida showed different properties in culture than cells from unaffected patients, the progenitor cell population was not influenced by the environment and could regain functionality in culture. Recent work found that although muscle cells may have epigenetic changes associated with a pathological condition, many of these are reversible. The expanded cell populations could be used with a scaffold to regenerate a bladder with three complete tissue layers, each with normal thickness. Studies in animals found that use of these neobladders resulted in increased compliance, and the bladders had physiological properties (resting potential, calcium mobilization) similar to that of native bladders. This work also found that bladder cycling was required for good capacity and compliance.

Intestinal tissue currently is used for bladder regeneration in humans but has major complications, including a significant increase in neoplasia. Studies in a small number of children with spina bifida and neurogenic bladder found that use of a cell-seeded PGA collagen scaffold with omentum was optimal, resulting in decreased bladder pressures and increased capacity and compliance. The need for bladder cycling also was confirmed. Urodynamic parameters improved over time, and all patients reported improvements in QOL. This work shows the utility of the bioengineered bladder in patients with compromised bladder function. Developing inductive biomaterials will be useful for larger regeneration needs. Further research also is needed to define the patient population in which use of a bioengineered bladder is most likely to be successful.

Adipose Derived Stem Cells in a Rat Model of Stress Incontinence
Dr. Lue

Adult stem cells represent a way to circumvent some of the difficulties associated with working with embryonic stem cells. Adipose-derived stem cells (ADSCs) are being tested for use in treating stress incontinence. ADSCs can be isolated from adipose tissue, which is available in large quantities; thus, sufficient ADSCs can be isolated such that expansion in culture, with its attendant changes in gene expression and karyotype, is not needed. ADSCs are mesenchymal perivascular progenitor cells in different stages of differentiation.

These cells were tested in a rat model in which a balloon was inserted into the vagina of rats shortly after delivery, followed by ovariectomy, to mimic pregnancy, prolonged labor, and menopause—three events that are believed to contribute to the development of stress incontinence in women. The bladder neck/urethra of these rats was injected with approximately 1 million ADSCs, and functional studies (conscious cystometry) and histological analyses were performed. Cystometry results (voiding, incontinence, detrusor overactivity) were normal in 72.7 percent of rats who received stem cells but in only 20 percent of control animals. Microscopic visualization found that the transplanted ADSCs survived for at least 4 weeks, remained primarily in the bladder neck, and some underwent cell differentiation. To understand how the ADSCs improved continence, staining was used to determine if any of the cells differentiated into smooth muscle cells; very few ADSCs differentiated. Because the urethral wall is 70 percent extracellular matrix (ECM), and elastic fibers in the ECM are important for urethral function, the ECM of the transplanted rats was examined. A significant increase in elastic fibers was observed in the transplanted animals. In addition, changes in relative amounts of collagen 1 and collagen 3 were observed. Sham-operated rats had mostly collagen 1 fibers, control animals had lower levels of collagen 1 and increased amounts of collagen 3, and the treated animals had higher levels of collagen 1, similar to what was observed in the sham-operated animals.

Adipose tissue is abundant, renewable, and readily available. This work shows that ADSCs hold promise for treating incontinence. ADSCs also present an opportunity to perform autologous transplants and thereby avoid immunologic and ethical concerns.

Discussion

The panelists discussed new technologies for bladder regeneration, including new forms of bladder matrix and SIS from knockout animals that do not express the marker that elicits an inflammatory response. Decellularized urinary bladder submucosa has some growth factors associated with it, although not as many as SIS. The submucosa also is thinner and more difficult to work with, but Dr. Atala has used it with some success. Dr. Kropp explained that hyaluronic acid (included in some of his bladder matrix materials) has angiogenic activity, but whether it acts directly or recruits other angiogenic factors is not clear. Hyaluronic acid also is important in the scarless wound healing that occurs in the fetus. Dr. Lue added that stem cells also have angiogenic and neurotrophic effects. In response to a question about trials in which stem cells and bovine collagen were used to improve continence, Dr. Lue said that because

bovine collagen is degraded in human tissue, it is unlikely that collagen alone would be sufficient for improving continence.

BEHAVIORAL THERAPY—FUTURE RESEARCH DIRECTIONS

Kari Bo, Ph.D., Linda Brubaker, M.D., Dee Fenner, M.D., J. Christian Winters, M.D., and Ingrid Nygaard, M.D.

The panelists discussed future needs for behavioral therapy research. Lifestyle interventions, such as fluid restriction or weight loss, should be tested in randomized controlled trials. Effective intervention parameters (e.g., duration, intensity) need to be defined. Treatment failures could be examined using ultrasound or other physiological approaches to learn why some patients do not respond to PFMT. Additionally, cohort studies are needed to determine which patients adhere to and which drop out of PFMT. Studies to determine the effects of PFMT in men and multiparous women are needed, as is research to determine the efficacy of PFMT for stress UI and FI. NIDDK could sponsor creation of a multidisciplinary (primary care, nursing, physical therapy, and geriatrics) behavioral treatment and prevention network that would include behavioral scientists and address UI and FI issues in men and women. Efforts to determine the best way to translate this research to the clinic also are needed.

The panelists also considered whether behavioral arms could be included in surgery or drug trials, although ethical issues may arise; the panelists agreed that most women should be offered PFMT as an option before surgery, because surgery sometimes can worsen existing problems. PFMT could be taught pre-operatively or as a followup to surgery to determine if it improves outcomes. Pre-operative PFMT might optimize muscle strength and structural integrity before surgery.

Motivating patients to adhere to PFMT regimens is difficult. Teaching patients that chronic pelvic pain or interstitial cystitis originates in the muscle might serve as motivation. Qualitative research has shown that speaking to women about PFMT can evoke feelings of guilt about their incontinence, especially if they believe they did not perform adequate pelvic floor exercise after a pregnancy. Behavioral and health psychologists can provide counseling to these women to help them overcome their guilt and potential reluctance to undertake PFMT. One barrier to PFMT has been a lack of trained continence nurse specialists. A lack of data regarding the characteristics of those who are most likely to benefit from PFMT also hampers communication with these women; compliance and motivation cannot be predicted. Patients could be counseled by a nurse specialist regarding their feelings about PFMT, learn about PFMT, and learn how to perform the exercises. Group training also can be motivating. Creation of easily disseminated videos (e.g., YouTube) could help to promote PFMT and serve as a first-level public health intervention.

ADJOURNMENT

Dr. Lightner thanked the speakers for their work in preparing for this meeting and thanked attendees for their participation.

SESSION SUMMARIES

Below are session summaries provided to highlight critical areas of current and future research as determined from presentations during each session of the symposium. These summaries were compiled by the session moderators.

NEW RESEARCH ON WHOM?

Jennifer Anger, M.D., Session Moderator

Epidemiology and Natural History of UI

- Design large trials that are linked to nationwide registries to establish risk factors, evaluate interventions, and support genetic/molecular studies.
- Develop a better understanding of the associations between UI and pregnancy/delivery, stroke, diabetes, psychiatric disease, and pelvic prolapse.

Continence Promotion

- Increase bladder health education efforts among older adults.
- Develop behavioral interventions using a public health model.
- Increase public awareness of and destigmatize incontinence.
- Determine patient preferences for treatment and management.
- Include biobehavioral factors in theory development.
- Develop a lifespan approach, gender-specific interventions, and ethnically sensitive interventions.

Incontinence Prevention

- Definitions:
  - Primary prevention: Reduce the incidence or onset of UI.
  - Secondary prevention: Promote early identification through screening to prevent worsening of UI.
  - Tertiary prevention: Prevent or eliminate complications of established UI (such as through safe and effective medical or surgical intervention, improved absorbent pads).
- Identify groups at increased risk of UI and target prevention measures to them.
- Increase efforts to educate people about healthy habits and behavior, including diet and exercise.

Genetics of the At-Risk Population

- Evidence supports a genetic component for DO and stress UI.
- Genetic differences affect variation in tissue growth, response to hormones and aging, wound repair and regeneration, and fibroblast-to-myofibroblast transformation.
- Differences in apoptosis: Higher rates of apoptosis occur in vaginal wall tissues of premenopausal women with stress UI/POP and in women with severe stress UI/POP versus milder forms.

Pregnancy and Parturition

- New Research Directions
  - Screen for objective UI in late pregnancy.
  - Promote conservative interventions for late pregnancy UI.
  - Determine the effect of Knack instruction PFMT adherence.
  - Determine the effect of PFMT on sexual pleasure.

- Research Questions
  - Is Knack maneuver instruction an efficacious stand-alone brief intervention?
  - Could immediate benefits from the Knack maneuver improve adherence to PFMT?
  - Could Knack maneuver instruction be disseminated widely in a media-based public health initiative?

BASIC RESEARCH

Margot Damaser, Ph.D., Session Moderator

Animal Models of Social Stress

- New animal models of social stress develop signs of urinary retention and/or functional obstruction (increased bladder weight, increased capacity, increased nonvoiding contractions, increased CRF in brain voiding centers).
- Animal models can be used to study bladder dysfunction due to social stress and novel treatments.

Mechanism of Childbirth Injuries

- Simultaneous injury to both the pudendal nerve and the muscle it innervates may lead to long-term pudendal nerve dysfunction after delivery.
- Rat models show slowed nerve and urethral recovery after vaginal distension and pudendal nerve crush occurring during childbirth.
- A neurotrophin-based treatment (i.e., electrical stimulation) may facilitate nerve recovery after childbirth injury.

Mechanisms of OAB/Urge Incontinence

- Triggers of overactivity: reduction of urothelial cells current output via the polymaine synthetic pathway, inflammation arising from dysregulation of urinary cytokines
- Possible stress/neuroimmune connection in OAB
- Information on mechanisms could help stratify patients and individualize treatments.

Tissue Characterization

- Structural characterization of urethra and bladder tissue using imaging techniques
- Role of the brain (functional MRI) in LUT function
- Tissue engineering – better characterization will promote progress in this area

Future Funding

- Provide opportunities for young investigators (funding, mentoring).
- Support collaboration, particularly for translation.

- Support creative thinking that is translatable (may require accepting grants with limited preliminary data, development of novel techniques, and less conservative NIH study sections).

INCONTINENCE AND LOWER URINARY TRACT SYMPTOMS IN OLDER ADULTS
Patricia Goode, M.D., Session Moderator

Clinical research: Nocturia

- Validation of a clinically useful classification system
- Validation of clinical evaluation paradigms
  – Tools for cost-efficient screening
  – Ensure cost-efficient, accurate evaluation of LUT and other potential causes of nocturia
- Validation of treatment paradigms
  – Consider effectiveness (e.g. QOL, Falls, Survival) and safety
  - Define useful outcomes including those clinically meaningful to the patients.
- Improve understanding of natural history
  – Increase translational research, support research on genetic risk, biomarkers, and hormonal milieu.

Future Directions for UI Research in Older Men and Women

- Prevention
  – Identify and target those at risk.
- Continence promotion
  – Increase public awareness and education; educate professionals about screening and effective treatments.
- Treatment
  - Include older patients in all clinical trials.
  - No upper age exclusions for clinical trials.
- Overcome recruitment barriers.
- Include geriatric appropriate outcomes, e.g., cognition, functional status.
- Perform robust pre-operative characterization of older patients.
- Include prospective evaluations of outcomes and complications (low burden registries).
- Perform research on older adults in different settings: nursing homes and assisted living facilities.

Future Directions for UI Research in Older Men

- Treatment
  - Improve volume and quality of research.
  - Develop network models for men's UI.
- Health care utilization/costs
  - Health disparities (including frail elderly)
  - Economic/Psychosocial (nested qualitative studies in RCTs)
  - Influence of UI on sexual health

AGING: RESEARCH PRIORITIES
Patricia Goode, M..D, Session Moderator

- Role of the central nervous system in control of LUT with age as well as in geriatric UI
- Pathogenesis of and effective treatment for geriatric nocturia
- Pathogenesis of and effective treatment for overactive bladder (OAB) in the elderly
- Assess the burden of LUT dysfunction for older adults: the patient (values/goals change with age), caregiver stress, risk of nursing home placement, psychosocial impact, costs, etc.
- Cost-effective management strategies for frail, community-dwelling elderly (more frail older adults live in the community than in nursing homes)
- Cost-effective diagnostic and management strategies for older men with LUT dysfunction (for use by specialists and primary care physicians)
- Prevention of geriatric UI and its secondary complications
- Development of appropriate screening and evaluation protocols for enrolling older adults in LUT trials
- Further studies on the etiology and improved therapeutic approach to fecal and dual incontinence

Cross-Cutting Suggestions

- Establish a network to increase the diversity of enrolled patients, procedures evaluated, speed of accrual, and ways to account for comorbidity.
- Develop appropriate outcomes for older patients (e.g., falls, confusion, and function) that also incorporate patient values and include impacts on the caregiver.
- Require that all NIH-funded research on UI include commensurate representation of older adults whenever relevant, particularly no upper age limit on inclusion criteria.
- Require that all NIH-funded research display data and stratify analyses by age whenever relevant.

Establish closer partnerships between NIDDK and other relevant NIH Institutes, especially NIA, NINR, NIMH, NCI, and NIDRR, as well as AHRQ.

ECONOMICS AND COST
Tomas L. Griebling, M.D., M.P.H., Session Moderator

Incontinence represents more than $20 billion in health care spending in the United States each year, more than the total annual cost of all cancer care for women.

- Sources of financial costs: diagnosis/evaluation; treatment/management; education/training; outreach/promotion
- Types of cost analyses: cost-comparison, cost-efficacy, cost-utility, cost-benefit, cost-minimization, cost-change
- Other analyses: health resource utilization, reimbursement, financing, public health promotion, health care access, policy

Other Costs of Incontinence

- Psychosocial costs
- Patient /providers/caregivers
- Health-related and general QOL
- Social engagement and productivity
- Environmental costs

Natural History and Assorted Conditions

- Interactions between comorbidities and UI and FI (diabetes, neurological disorders, trauma)
- Opportunities for significant new and creative research– emphasis on translational work
- Potential for prevention/public health initiatives

Research Recommendations

- Include assessment of economics and/or costs in all research on incontinence (design phase).
- Determine costs for inclusion of cost analyses (usually low).
- Identify variables /measurements that will have relevance for patients, providers, funders, and health care delivery systems.
- Develop rigorous scientific techniques.
- Promote generalizability and dissemination.

HOW CLOSE ARE WE TO THE OUTCOMES PATIENTS WANT?
Lior Lowenstein, M.D., Session Moderator

Future Research:

- Patient-Centered Global Measures
  - Health care providers and patients differ in interpretation of success and complications.
  - Innovative ways to measure the "worth it" factor and help patients weigh tradeoffs, such as benefit/harms, are needed.
- Place strong emphasis in all NIH trials on UI/POP/FI on reporting multiple subjective and objective outcomes to better understand the disease process and permit comparison between trials/studies.
- Promote NIH-funded meetings or contracts to expert groups capable of recommending minimum data sets that would include bother, QOL, and objective measures such as UDS.
  - PROMISE – NIH Roadmap Initiative
- Expand the currently limited understanding of patient's treatment goals and expectations.
- Initiate research on the effects of treatment "offsets" (complications, life disruptions, etc.) to guide discussions regarding balance/tradeoffs.
- No need to develop new questionnaires— promote more effective use of existing questionnaires.

COMPLICATIONS OF TREATMENT: FUTURE DIRECTIONS
Kathleen Kobashi, M.D., Session Moderator

- Standardization
  - Develop clear definitions of complications.
  - Use consistent terminology when describing conditions.
  - Develop similar clarity for outcome reporting.

- Risk/Benefit Ratios
  - Develop multicenter trials to assess risks and benefits.

- How to Decrease Risk
  - Define mechanisms of complications.
  - Optimize what can be optimized.
  - Factors contributing to risk:
    - Material (synthetic, biomaterial)
    - Host factors (comorbidities, age, lifestyle, estrogen status)
    - Techniques (injection, interpositions, use of antibiotics, dissection plane and thickness)

SURGICAL: UPDATES ON CURRENT TREATMENTS AND TRIALS
Chris Winters, M.D., Session Moderator

- Establish a working group to develop a consensus for outcomes assessment before beginning another trial.
- Develop methods of trial alteration to save time and money and include more investigators and "real life" patients. Develop Internet registries to obtain information more quickly and consider creating a protocol development workgroup to design protocols for incontinence studies that sites can "bid" to perform.
- Support stem cell, pelvic floor tissue, and tissue engineering research to improve understanding of incontinence and surgical outcomes.
- Trials:
  - Neural rerouting trials
  - Compare slings and AUS for male PPI
  - Compare Botox to neuromodulation for OAB
  - Pudendal versus sacral neuromodulation trial

DUAL INCONTINENCE
Dee Fenner, M.D., Session Moderator

- Assess LUTS, POP, and FI, and consider use of all possible therapies.
- Develop standard definitions/validated questionnaires/QOL assessments, particularly for bowel continence.
- Understand mechanisms of aging on smooth and striated muscle.
- Evaluate novel therapies, including nerve stimulation, tissue engineering, and sphincter replacement.

- Plan prospective studies documenting labor to determine long term impact of OASIS, NSVD, and CS on the pelvic floor.
- Educate generalists, family practitioners, and nurses on modifiable risk factors, including operative vaginal delivery, length of second stage labor, and midline episiotomy.

Urethral Function

- Conduct research to better understand the mechanisms that create and modulate normal urethral closure.
- Identify pathologic alterations that reduce sphincteric competence.
- Conduct research on smooth and striated muscle, vascular factors and connective tissue and the mechanical factors that create pressure.
- Develop better techniques to measure urethral function.

Synthetic Incontinence Meshes

- Understand the pathophysiology of stress UI, including problems occurring in the urethral support system and the urethral sphincter system.
- Develop new diagnostic techniques to specifically define deficiencies in the components of these systems to target therapy (current treatment is empiric).
- Develop biochemically active bioinductive scaffolds that are designed to restore and regenerate the function of a deficient tissue.
- Fund an interdisciplinary group of investigators to objectively test existing and future meshes.

ACQUIRED LUTS: NEUROLOGIC
Ken Peters, M.D., Session Moderator

Multiple Sclerosis/Parkinson Disease
- Improvement in QOL/Bladder function
- Botox
- Neuromodulation
- Behavioral therapy
- Centrally acting drugs
- Deep brain stimulation

OAB/Central Nervous System
- Provocative studies on central effects of OAB and micturition centers
- Centrally acting drugs
- Behavioral therapy and its central effect
- Neuromodulation, effects on the brain, different rates, disease states, etc.

Spinal Cord Injury
- Cost, QOL, protecting upper tracks
- Role of Botox in patient management

- New neuromodulation techniques (Tai)
  - Developing method to stimulate bladder and relax sphincter
- Nerve rerouting

Research Needs – Neuromodulation

- Conduct well-controlled trials to determine the effect of various neuromodulation techniques on different disease states: chronic pelvic pain, neurogenic bladder, irritable bowel syndrome, vulvodynia, partial spinal cord injury, chronic constipation, dysfunctional elimination syndrome in childhood.
- Determine the best neuromodulation technique—Assess PNE vs. Stage, timing of introducing neuromodulation, long-term efficacy, risk/benefits, ideal stimulation parameters, and reprogramming.

Research Needs – Nerve Rerouting

- Multicenter trial: spinal cord injury, spina bifida, TM, other voiding dysfunctions
- Novel Micturition Centers: functional MRI
- Preventing lower extremity complications: end-to-side anastamosis
- Enhance Nerve Growth: nerve growth factor, electrical stimulation

FUTURE DIRECTIONS IN RESEARCH
Tom Lue, M.D., Session Moderator

Stem cells

- Can be used to engineer contracting muscles, kidney, and liver.
- Can be used to screen medications before human trials.
- Can be used to produce beneficial substances, e.g., angiogenesis promoters.
- Adult stem cells may be preferable for ethical and technical reasons (less likely to be tumorigenic than embryonic stem cells).