



Pathophysiology of the Lower Urinary Tract: Continence and Incontinence

TRACY WASHINGTON CANNON, MD* and MARGOT DAMASER, PhD†

**Department of Urology, University of Pittsburgh, Pittsburgh, Pennsylvania*

†Research Service, Hines VA Hospital, Hines, Illinois; Department of Urology, Loyola University Medical School, Maywood, Illinois; Department of Bioengineering, University of Illinois, Chicago, Illinois

Introduction

To better understand the pathophysiologic mechanisms occurring in incontinence, we begin with a brief review of the normal mechanisms of continence. We subsequently review how incontinence can occur when these systems do not function normally. Both anatomic and neurologic hypotheses for the causes of stress urinary incontinence (SUI) are discussed. Pathophysiology of overactive detrusor is discussed in terms of its neurogenic and non-neurogenic causes. The chapter finishes with a review of the relationship between urinary symptoms and pelvic organ prolapse.

Correspondence: Margot S. Damaser, PhD, Research Biomedical Engineer and Associate Professor, Research Service (151), Hines VA Hospital, 5th Avenue and Roosevelt Road, Hines, IL, 60141. E-mail: margot.Damasar@med.va.gov

Normal Mechanisms of Continence

In the normal adult, urinary control can be subdivided into a bladder filling and urine storage phase, and a bladder emptying and voiding phase. Therefore, normal lower urinary tract function requires the ability to store urine at low pressure while the detrusor muscle is quiescent, as well as the ability to completely empty the bladder voluntarily with low resistance urine passage. The bladder and urethra are the most important structures for proper storage and emptying. Other important components include pelvic floor musculature, ligaments, and neural control. Anatomy has been discussed in previous sections and bladder filling, emptying, and neural control has been discussed in previous sections and therefore these topics will not be reviewed here.

During transient increases in abdominal pressure (eg, during coughing, sneezing, or lifting), there is not only an increase in pressure delivered to the bladder but also to the proximal urethra.¹ Normal position of the organs ensures that abdominal pressure is transmitted equally to both the bladder and urethra, decreasing the chances of urine leakage. However, the increase in urethral closure pressure seen with transient increases in abdominal pressure normally exceeds the intra-abdominal pressure. This suggests active muscle contraction from a reflex increase in striated sphincter activity via somatic innervation, which further helps to prevent urine leakage.^{2,3}

In addition to contraction of the external urethral sphincter, levator ani contraction may contribute to this active muscular response to increased abdominal pressure. The following passive anatomic support mechanisms also contribute to maintaining continence. The endopelvic fascia supporting the urethra in a hammock provides a passive mechanism of continence. When abdominal pressure increases, the urethra is forced inferiorly and compressed against the anterior vagina, providing physical closure of the urethral lumen.^{3a}

Pathophysiology of Stress Urinary Incontinence

ETIOLOGY OF STRESS URINARY INCONTINENCE

Vaginal Delivery and Aging

Vaginal delivery is implicated as an etiological factor in the development of SUI.⁴ However, the exact mechanisms are unknown. In addition to crush and traction injury to the pudendal nerve, mechanical trauma can cause disruption of the intrapelvic attachments of the vagina, stretching and tearing of the cardinal and uterosacral ligaments, and stretching, tearing, and avulsion of the levator muscles, resulting in a wider

and longer levator hiatus and poor support of the pelvic organs.⁵⁻⁷ These injuries can cause a rotational descent of the proximal urethra from a retropubic position. Multiple vaginal deliveries can result in multiple injuries,⁴ although the greatest damage appears to come from the first delivery.⁸ Other obstetrical factors associated with incontinence development include large baby birth-weight and long active second stage of labor, both of which may increase trauma and ischemia to the structures of the pelvic floor.⁵

Non-obstetric factors associated with incontinence development include obesity,^{9,10} increased age,^{10,11} and menopause.¹² Decreased estrogen levels may cause decreased urethra mucosal coaptation after menopause since estrogen replacement therapy increases coaptation and can reduce symptoms of mild SUI.^{13,14} Estrogen increases the amount of collagen in the skin¹⁵ and possibly the urethra as well. Despite these non-trivial effects of estrogen, there is little consensus among clinicians about the value of estrogen for postmenopausal SUI.¹⁶ It is likely that estrogen replacement therapy does not reliably lead to recovery from SUI in postmenopausal women since, by that time, nerves, muscles, and other tissues are long past injury and have atrophied beyond their ability to recover well.

Clinical Evidence for Pudendal Nerve Injury

The perineal branch of the pudendal nerve courses in Alcock's canal, lateral and anterior to the vagina,¹⁷ making it vulnerable to damage during childbirth. Pudendal nerve damage has been observed during vaginal delivery¹⁸ and correlates both with recent vaginal delivery^{19,20} and with SUI.²¹ Women with postpartum urinary incontinence have significantly more pudendal nerve damage than continent postpartum women, as measured by slowed pudendal nerve conduction.²¹ Both pudendal nerve damage and damage to pelvic floor muscles

are correlated with multiparity,^{19,20} birth-weight greater than 4 kilograms and active second stage of labor greater than 30 minutes.²² Electromyography (EMG) data indicate that nerve damage and subsequent re-innervation of pelvic floor muscles occurs in 80% of women who deliver vaginally. The damage is greater in women with heavier babies or longer active second stage of labor.⁵

In one study, 60% of women with increased nerve damage immediately after vaginal delivery had normal conduction rates 2 months later.²⁰ This result was recently confirmed in a study on a different group of subjects.¹⁹ However, nerve conduction slowed 5 years after vaginal delivery in the same women of the original study, compared with nulliparous controls.²¹ This suggests that the pudendal nerve is damaged during delivery and recovers initially but that nerve function may deteriorate with age. Recent studies using vaginal distension in the rat to mimic childbirth injury support the hypothesis that nerve damage occurs during vaginal delivery.^{23–25}

ANATOMIC HYPOTHESES FOR THE DEVELOPMENT OF STRESS URINARY INCONTINENCE

Urethral Hypermobility and Loss of Structural Support

When pelvic floor weakness results from childbirth injury or aging, the urethra is shifted to a lower, more dependent position. Increased abdominal pressure is then transmitted unequally to the bladder and urethra, with more transmitted to the bladder. When bladder pressure exceeds urethral pressure, urine leakage occurs, resulting in SUI.²⁶ However, many women are continent despite urethral hypermobility. Thus, new concepts have been developed in addition to urethral hypermobility to explain the possible anatomic basis of SUI.

The Hammock Hypothesis

In the hammock hypothesis, the strength with which the urethra is compressed

against the anterior vaginal wall decreases, leading to SUI. The position of the urethra may remain the same but the strength of pelvic muscles and fascia supporting and compressing the urethra have decreased.⁴ If this layer is intact but in a lower position, continence may still be maintained.²⁸ Normal support relies on proper function of muscle, nerves, and connective tissue. Injury to or deterioration of any of these components can result in incontinence.

Contributions of Imaging

Magnetic resonance imaging (MRI) and real-time ultrasonography demonstrate the relationship of the proximal urethra to vaginal wall movement. Based on MRI and ultrasound studies of the pelvic floor, the anterior and posterior walls of the bladder neck and the proximal urethra move unequally with sudden increases in abdominal pressure, pulling open the urethral lumen and, resulting in SUI.^{29,30}

NEURAL HYPOTHESIS FOR THE DEVELOPMENT OF STRESS URINARY INCONTINENCE: PUDENDAL NERVE INJURY

Effects of Pudendal Nerve Injury

Since the pudendal nerve innervates the external urethral sphincter, pudendal nerve injury presumably causes denervation and dysfunction of the urethra, resulting in decreased urethral resistance and symptoms of SUI. However, a direct causative relationship has been difficult to obtain from clinical data because pudendal nerve injury occurs in women in association with vaginal delivery, when other pelvic tissues are also injured. Therefore, animal studies have been used to establish a direct causative relationship between pudendal nerve injury and symptoms consistent with SUI.^{24,31,32}

A variety of behavioral and functional outcomes have been used to demonstrate urethral dysfunction after vaginal distension or pudendal nerve injury, since animals cannot sneeze or cough on command. Voiding

behavior studies,^{31,32} sneeze tests,²⁵ leak point pressure (LPP) tests,²³ modified LPP tests,³³ maximum urethral closure pressure (MUCP),³⁴ and vertical tilt table test²⁰ have been used to demonstrate urinary function or behavior in animal studies. Overall, the results are consistent with decreased urethral resistance and symptoms of SUI after pudendal nerve injury or vaginal distension.

Neuroregenerative Response

The precise nature of the nerve injury induced in vaginal childbirth is not clear, but it probably involves partial injury, compression, stretching, and hypoxia.¹⁸ In contrast to a more proximal injury, this type of injury tends not to kill a neuron, but also tends not to produce as strong a neuroregenerative response.³⁶ Therefore, distal pudendal nerve fascicles may be injured during vaginal distension but little neuroregenerative response may occur. Consistent with this theory, only 50% of pudendal motoneurons successfully regenerated to the external urethral sphincter 3 months after a pudendal nerve injury in female rats.³¹ Incomplete pudendal nerve regeneration after vaginal delivery may explain why signs of pudendal nerve injury are observed years after the initial injury. In addition, partial pudendal nerve regeneration may help explain why, in some studies, multiparous women have a higher risk of SUI than primiparous women. Each vaginal birth may cause nerve injury that does not fully regenerate each time.¹¹

SUMMARY

All of the various components that contribute to continence may be injured during vaginal delivery and can be detrimentally affected by aging. Both anatomic and neurologic factors contribute to incontinence. With increased intra-abdominal pressure, the proximal urethra can be forced open by shearing forces that separate the anterior and posterior urethral walls, or by the unequal transmission of intra-abdominal force to the bladder more than the urethra. If these forces can be resisted by the active closure of the

striated sphincter (mediated by the pudendal nerve), by urethral compression against the anterior vagina bolstered by levator ani contraction, and by urethra mucosal coaptation, then continence is maintained. Eventually, via multiple injuries and the effects of aging, a threshold level of dysfunction is reached, resulting in symptoms of SUI.

Pathophysiology of Detrusor Overactivity

The term “overactive detrusor” refers to a range of clinical symptoms, including urgency with or without urge incontinence, as well as frequency and nocturia. Urodynamically, an overactive detrusor can be characterized by involuntary detrusor contractions during the filling phase. This can be further classified as neurogenic if there is a known neurologic condition such as stroke, Parkinson’s disease, multiple sclerosis, or spinal injury. Non-neurogenic causes of detrusor overactivity include infection, interstitial cystitis, urolithiasis, bladder outlet obstruction, aging, or neoplasia. Nonetheless, many cases are idiopathic. Regardless of the etiology, the overactive detrusor is characterized by poor accommodation to bladder filling.

NON-NEUROGENIC CAUSES OF DETRUSOR OVERACTIVITY

Age

The prevalence of urgency symptoms increases with age, independent of the presence of outflow obstruction or neurologic disease. In a study of incontinent elderly women and men without outflow obstruction, 61% of women and 59% of men had detrusor overactivity demonstrated urodynamically.³⁷ With aging, the prevalence of neurologic disease increases, potentially providing an etiology for overactive detrusor symptoms. Many cases of detrusor overactivity in the elderly may have an unrecognized neurologic etiology. In addition, the detrusor undergoes structural changes with age that may contribute to overactivity.³⁸

Outlet Obstruction

Detrusor overactivity associated with outflow obstruction in men has long been recognized. In women, the mechanical effect of advanced prolapse or increased outflow resistance following continence surgery can also cause bladder outlet obstruction. The development of detrusor overactivity following outlet obstruction may have a neurologic basis. Outlet obstruction is associated with pathologic patterns of neurologic activity characterized by supersensitivity of the detrusor muscle to acetylcholine, which electrically couples the muscle cells. This places the detrusor in a highly excitable state, resulting in involuntary detrusor contractions and overactive bladder symptoms.^{37a}

Exactly how outlet obstruction alters neurologic activity of the bladder is unclear. One possibility is that either the increased intravesical pressure during voiding or the increased pressure of a hypertrophied bladder wall during filling decreases blood flow and causes detrusor ischemia.³⁹ Another possibility is reorganization of the spinal micturition reflex (mediated by C-fibers) with outlet obstruction.⁴⁰ Hypertrophy of bladder neurons is associated with increased nerve growth factor expression in the bladder and sacral autonomic centers, facilitating the spinal micturition reflex.⁴¹ Nerve growth factor production is also increased in patients with detrusor overactivity.⁴² This suggests that obstruction can create a hyperexcitable state of bladder innervation and of the detrusor muscle itself.

Pelvic Floor Disorders

The detrusor and pelvic floor musculature maintain a reciprocal reflex relationship. Afferent activity from the pelvic floor and urethra contributes to detrusor inhibition during bladder filling. Therefore, when afferent activity is decreased secondary to pelvic floor laxity, involuntary detrusor contractions may result. With this pathophysiology in mind, it is not surprising that detrusor overactivity is associated with SUI in

women.⁴³ Symptoms of detrusor overactivity improve in two-thirds of patients after surgery for SUI.⁴⁴ Electrical stimulation of the pudendal nerve can be used to treat detrusor overactivity.⁴⁵

NEUROGENIC CAUSES OF DETRUSOR OVERACTIVITY***Diseases Above the Brainstem***

Neurologic disease can cause detrusor overactivity by interfering with the normal tonic inhibition of parasympathetic pathways.⁴⁶ Since suprapontine areas generally exert a tonic inhibitory influence on the pontine micturition center, cerebral infarction can alter the balance between facilitatory and inhibitory mechanisms of innervation, causing up-regulation of excitatory pathways and down-regulation of tonic inhibitory pathways and resulting in detrusor overactivity.^{46a} In addition to cerebral infarction, other neurologic diseases that may interfere with these pathways include: Parkinson's disease, brain tumors, traumatic brain injuries, multiple sclerosis, Alzheimer's dementia, cerebellar ataxia, normal pressure hydrocephalus, and cerebral palsy.

Diseases Below the Brainstem

Neurologic lesions below the pons but above the lumbosacral level also interfere with the normal supraspinal control of micturition, causing detrusor overactivity. However, in this case, detrusor overactivity is associated with uncoordinated sphincter overactivity, resulting in detrusor sphincter dyssynergia (DSD). Spinal cord injuries and multiple sclerosis are two of the most common diseases in which DSD is seen. The detrusor overactivity demonstrated in these patients may be modulated by C-fiber afferents, which are normally silent during bladder filling.^{47a} In addition, the functional obstruction caused by DSD could alter the properties of bladder afferent neurons.⁴⁷

IDIOPATHIC DETRUSOR OVERACTIVITY

The diagnosis of idiopathic detrusor overactivity requires the exclusion of all known

causes. Some research suggests that myogenic changes, regardless of the etiology, lie at the root of detrusor overactivity. Muscle denervation is consistently found in detrusor biopsies in patients with detrusor overactivity.^{49a} This theory proposes that partial denervation of the detrusor alters the smooth muscle properties leading to increased excitability and coupling between muscle cells. When this happens, a local contraction in the detrusor will spread throughout the entire bladder. The trigger for this local contraction is unknown. Evidence to support this theory comes from a partially obstructed pig model in which bladder instability could not be eliminated by transection of the spinal roots.^{50a} In addition, when nerve transmission was blocked at the ganglionic level with hexamethonium and globally with tetrodotoxin in a rat model, involuntary bladder contractions could still be observed.

Relationship Between Urinary Symptoms and Pelvic Organ Prolapse

Urinary symptoms commonly coexist with pelvic organ prolapse and vice versa. Prolapse may cause stress incontinence by pulling open the posterior urethral wall; conversely, prolapse may cause mechanical obstruction of the urethra. Over time, urethral obstruction due to prolapse can result in detrusor muscle changes, leading to overactive detrusor and incontinence. Women with anterior vaginal prolapse often have bladder neck hypermobility and SUI, along with uterine and posterior vaginal prolapse. However, with worsening degrees of anterior vaginal prolapse (Stages III and IV), symptoms of SUI decrease⁴⁸ as urethral obstruction is more likely to occur. When the prolapse is reduced (with a speculum, vaginal pack, or pessary), occult SUI can be revealed.⁴⁹ Up to 70% of clinically continent women with severe prolapse are incontinent with prolapse reduction.⁵⁰

Acknowledgments:

The authors gratefully acknowledge support from the Office of Research and Development, Rehabilitation R&D Service of the Department of Veterans Affairs and NIH Grant RO1 HD38679.

REFERENCES

1. Enhorning G. Simultaneous recording of intravesical and intraurethral pressure. *Acta Chir Scand.* 1961;276(Suppl):1–68.
2. Tanagho EA. The anatomy and physiology of micturition. *Clin Obstet Gynecol.* 1978;5:3–9.
3. Kamo I, Cannon TW, Chancellor MB, et al. Active urethral closure mechanisms under sneeze induce stress condition is impaired in a rat model of birth trauma. *J Urol.* 169(4):270.
- 3a. DeLancey JOL. Structural support of the urethra as it relates to Stress Urinary Incontinence: The hammock hypothesis. *Am J OB Gynecol.* 1994;170:1713–1720.
4. Pregazzi R, Sartore A, Troiano L, et al. Postpartum urinary symptoms: prevalence and risk factors. *Obstet Gynecol.* 2002;103:179–182.
5. Allen RE, Hosker GL, Smith ARB, et al. Pelvic floor damage and childbirth: a neurophysiological study. *Br J Obstet & Gynaecol.* 1990;97:770–779.
6. Sultan AH, Monga AK, Stanton SL. The pelvic floor sequelae of childbirth. *Br J Hosp Med.* 1996;55:575–579.
7. Meyer S, Schreyer A, De Grandi P, et al. The effects of birth on urinary continence mechanisms and other pelvic floor characteristics. *Obstet Gynecol.* 1998;92:613–618.
8. Arya LA, Jackson ND, Myers DL, et al. Risk of new onset urinary incontinence after forceps and vacuum delivery in primiparous women. *Am J Obstet Gynecol.* 2001;185:1318–1323.
9. Mommsen S, Foldspang A. Body mass index and adult female urinary incontinence. *World J Urol.* 1994;12:319–322.
10. Brown JS, Seeley DG, Fong J, et al. Urinary incontinence in older women: Who is at risk? *Obstet Gynecol.* 1996;87:715–721.
11. MacLennan A, Taylor AN, Wilson D, et al. The prevalence of pelvic floor disorders and

- their relationship to gender, age, parity and mode of delivery. *Br J Obstet Gynaecol.* 2000;107:1460–1470.
12. Karram M, Partoll L, Bilotta V, et al. Factors affecting detrusor contraction strength during voiding in women. *Obstet Gynecol.* 1997;90:723–726.
 13. Bhatia NN, Bergman A, Karram MM. Effects of estrogen on urethral function in women with urinary incontinence. *Obstet Gynecol.* 1989;160:176.
 14. Bergman A, Karram MM, Bhatia NN. Changes in urethral cytology following estrogen administration. *Gynecol Obstet Invest.* 1990;29:211.
 15. Black MM, Shuster S, Bottoms E. Osteoporosis, skin collagen, androgen. *Br Med J.* 1970;26:773.
 16. Cardozo L. Role of estrogens in the treatment of female urinary incontinence. *J Am Geriatr Soc.* 1990;38:326.
 17. Swash M. The neurogenic hypothesis of stress incontinence. Ciba Foundation Symposium, 1990; 151:156–175.
 18. Clark MH, Scott M, Vogt V. et al. Monitoring pudendal nerve function during labor. *Obstet Gynecol.* 2001;97:637–639.
 19. Lee JY, Cannon TW, Pruchnic R, et al. The effects of periurethral muscle-derived stem cell injection on leak point pressure in a rat model of stress urinary incontinence. *In Urogynecol.* 2003;14:31–37.
 20. Snooks SJ, Swash M, Mathers SE. et al. Effect of vaginal delivery on the pelvic floor: a 5-year follow-up. *Br J Surg.* 1990;77:1358–1360.
 21. Snooks SJ, Barnes PRH, Swash M. Damage to the innervation of the voluntary anal and periurethral sphincter musculature in incontinence: an electrophysiological study. *J Neurol Neurosurg Psychiatry.* 1984;47:1269–1273.
 22. Sultan AH, Kamm MA, Hudson CN. Pudendal nerve damage during labour: prospective study before and after childbirth. *Br J Obstet & Gynaecol.* 1994;101:22–28.
 23. Damaser MS, Ferguson CL, Broxton-King C, et al. Functional and neuroanatomical effects of vaginal distension and pudendal nerve crush in the female rat. *J Urol.* 2003;170:1027–1031.
 24. Kuo HC. Effects of vaginal trauma and oophorectomy on the continence mechanism in rats. *Urol Int.* 2002;69:36–41.
 25. Lin AS, Carrier S, Morgan DM, et al. The effect of simulated birth trauma on the urinary continence mechanism in the rat. *Urology.* 1998;52:143–151.
 26. McGuire EJ, Herlihy EL. Bladder and urethral responses to isolated sacral motor root stimulation. *Invest Urol.* 1978;16:219–223.
 27. Deleted in proof.
 28. DeLancey JOL. Stress urinary incontinence: Where are we now, where should we go? *Am J Obstet Gynecol.* 1996;175:311–319.
 29. Yang A, Mostwin JL, Rosenshein N, et al. Pelvic floor descent in women: Dynamic evaluation with fast MR imaging and cinematic display. *Radiology.* 1991;179:25–33.
 30. Mostwin JL, Yang A, Sanders R, et al. Radiography, sonography, and MRI for SUI. *Urol Clin North Am.* 1995;22:539–549.
 31. Kerns JM, Damaser MS, Kane JM, et al. Effects of pudendal nerve injury in the female rat. *Neurourol. Urodynam.* 2000;19:53–69.
 32. Sakamoto K, Smith GM, Storer PD, et al. Neuroregeneration and voiding behavior patterns after pudendal nerve crush in female rats. *Neurourol. Urodynam.* 2000;19:311–321.
 33. Bakircioglu ME, Sievert K-D, Lau A, et al. The effect of pregnancy and delivery on the function and ultrastructure of the rat bladder and urethra. *BJU Int.* 2000;85:350–361.
 34. Resplande JS, Gholami S, Graziottin TM, et al. Long-term effect of ovariectomy and simulated birth trauma on the lower urinary tract of female rats. *J Urol.* 2002;168:323–330.
 35. Deleted in proof.
 36. Herdegen T, Skene P, Bähr M. The c-Jun transcription factor: bipotential mediator of neuronal death, survival and regeneration. *Trends Neurosci.* 1997;20:227–231.
 37. McGuire EJ. Detrusor response to outlet obstruction. *World J Urol.* 1984;2:208–210.
 - 37a.
 38. Elbadawi A, Yalla SV, Resnick NM. Structural Basis of Geriatric Voiding Dysfunction. VII. Prospective ultrastructural/urodynamic evaluation of its natural evolution. *J Urol.* 1997;157:1814–1822.
 39. Ghafar MA, Anastasiadia AG, Olsson LE, et al. Hypoxia and an angiogenic response in

- the partially obstructed rat bladder. *Lab Invest.* 2002;82:903–909.
40. Steers WD, Ciambotti J, Etzel B, et al. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction. *J Comp Neurol.* 1991; 310:401–410.
 41. Steers WD, Kolbeck S, Creedon D, et al. Nerve growth factor in the urinary bladder of the adult regulates neuronal form and function. *J Clin Invest.* 1991;88:1709–1715.
 42. Tanner R, Chambers P, Khadra MH, et al. The production of nerve growth factor by human bladder smooth muscle cells in vivo and in vitro. *BJU Int.* 2000;85:1115–1119.
 43. Black NA, Griffiths JM, Pope C, et al. Sociodemographic and symptomatic characteristics of women undergoing stress incontinence surgery in the UK. *Br J Urol.* 1996; 78:847–855.
 44. Sand PK. The effect of retropubic urethropexy on detrusor instability. *Obstet Gynecol.* 1988;(part I):71:818–822.
 45. Ohlsson BL, Fall M, Frankenberg-Sommar S. Effects of external and direct pudendal nerve maximal electrical stimulation in the treatment of the uninhibited overactive bladder. *Br J Urol.* 1989;64:374–380.
 46. Yoshimura N, Mizuta E, Yoshida O, et al. Therapeutic effects of dopamine D₁/D₂ receptor agonists on detrusor hyperreflexia in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-lesioned parkinsonian cynomolgus monkeys. *J Pharmacol Exp Ther.* 1998;286: 228–233.
 - 46a. Yokoyama O. Glutamatergic and dopaminergic contributions to rat bladder hyperactivity after cerebral artery occlusion. *Am J Physiol.* 1999;276:R935–942.
 47. Kruse MN, Bray LA, de Groat WC. Influence of spinal cord injury on the morphology of bladder afferent and efferent neurons. *J Auton Nervous Syst.* 1995;54:215–223.
 - 47a. Fowler C, Jewkes D, McDonald W, et al. Intravesical capsaicin for neurogenic bladder dysfunction. *Lancet.* 1992;339:1239.
 48. Richardson DA, Bent AE, Ostergard DR. The effect of uterovaginal prolapse on urethrovesical pressure dynamics. *Am J Obstet Gynecol.* 1983;146:901–905.
 49. Mattox TG, Bhatia NN. Urodynamic effects of reducing devices in women with genital prolapse. *Int Urogynecol J.* 1994;5:283–286.
 - 49a. Mills IW, Greenland JE, McMurray G, et al. Studies of the Pathophysiology of Idiopathic detrusor instability: the physiological properties of the detrusor smooth muscle and its pattern of innervation. *J Urol.* 2000;163:646–651.
 50. Bergman A, Kooning PP, Ballard CA. Predicting postoperative urinary incontinence development in women undergoing operation for genitourinary prolapse. *Am J Obstet Gynecol.* 1988;158:1171–1175.
 51. Igawa Y, Mattiasson A, Andersson K E. Micturition and pre-micturition contractions in unanesthetized rats with bladder outlet obstruction. *J Urol* 1994;151:244–249.