Pediatric Incontinence

evaluation and clinical management

Israel Franco • Paul Austin • Stuart Bauer
Alexander von Gontard • Yves Homsy

WILEY Blackwell

Preface

Treatment of children with urinary and bowel problems requires special people who are driven to help them achieve continence and reduce distress. The management of these children has often been neglected in the past although effective therapeutic approaches are available. It takes a very dedicated person to do this work. A group of such like-minded individuals was formed to foster progress in the care of the child with bowel and bladder issues. The end result was the International Children's Continence Society, with its multidisciplinary mentality to address this problem. This organization has brought together specialists from many disciplines including pediatricians, nephrologists, pediatric urologists, urotherapists, nurses, child psychiatrists, and psychologists in order to help establish guidelines and teaching tools so that others interested in taking care of children with incontinence will have a rational and workable blueprint for investigation and care.

Looking at the presently available literature, we saw the need for a book that addressed the issues of bowel and bladder incontinence in a comprehensive manner. Most texts rarely cover more than one or two of the topics that we touch upon in this volume, whether they are urologic, nephrologic pediatric, child psychiatric, or neurologic books. It was the vision of the editors to develop a textbook that covers all aspects of bowel and bladder incontinence in children within one volume and utilize the expertise that is available in the International Children's Continence Society to put together what we feel is a truly comprehensive tome on the topic.

There has been increasing interest in the field and a drive to help these children with more practitioners entering into the discipline daily. A concise and directed document would be beneficial to all of them, whether they are experts or novices in the field. There have been other textbooks on urinary incontinence in children but none cover the breadth of information that is conveyed in this volume. We chose to make this a text that is useful to all who treat children with incontinence, whether it is due to neurogenic causes or functional problems.

The editors asked all the authors to provide the reader with a practical, evidence-based “how I do it” guide to managing problems in children, which should allow the reader to replicate assessment and treatment procedures easily, without having to go to multiple sources. We felt that this should be a guidebook and a complementary compendium to the various ICCS courses that have been and are being given worldwide. We feel that we have accomplished this task and hope that the reader feels the same way so that ultimately children and families will benefit from this book.

The Editors
Israel Franco, MD
Stuart B. Bauer, MD
Paul Austin, MD
Yves Homsy, MD
Alexander von Gontard, MD

SECTION 1
Pathophysiology of bowel and bladder dysfunction

Israel Franco

Introduction

> Francis Bacon wrote, “Knowledge is power.—Nam et ipsa scientia potestas est.”
>
> *Meditationes Sacræ. De Hæresibus.*

To be able to understand the child with urinary and fecal incontinence, it is critical that we have the knowledge on how the systems function individually and interact with each other and the brain. There have been tremendous advances in the fields of neuroscience and neurophysiology that have opened up the doors to new treatments and mechanisms that explain how the systems function.

Without this power, we relied primarily on old models that excluded the higher cortical centers and trusted heavily on vesicocentric models to explain lower urinary tract symptoms as bladder or bowel only problems. These vesicocentric concepts have been proven wrong, and it has become apparent that the system of bowel and bladder control is evermore complex than we imagined. We understand now that the bladder mucosa is a sensory organ in direct communication with the CNS and the bladder and bowel communicate with each other through connections in the spinal cord and other centers. These changes in how we perceive the neurophysiology of bowel and bladder control will help us understand better what is needed to better treat our patients in the future.

In Chapter 1, Drs. Wu and Ogunyemi have condensed decades of work on the neurophysiology of voiding. They help us understand where we are today regarding this topic in a concise and logical manner. Without this foundation, the reader is apt to be at a disadvantage when it comes to managing the treatment of patients with bowel and bladder dysfunction.

In Chapter 2, Drs. Ejerskov and Siggard have gone about the business of explaining bowel physiology and functional anatomy. Again, understandings of these processes are essential for any practitioner who is actively taking care of children with BBD. Most of the readers will not have a background in this topic since the majority of us who take care of these children with BBD are in the fields that are directly related to the urologic and nephrologic management of these children. In this chapter, we see the overlap with the autonomic nervous system and the role that serotonin may play in these children affecting both systems.

In Chapter 3, I (Franco) have put together what we have available on the central control and processing of bladder signals. This is based on work in the field of neuroscience that has expanded in a geometric fashion from its early reports in 1997 to a multitude of publications in the last few years with more publications each year giving us more insight into the process. I have relied heavily on the work of Griffith and Fowler since they have contributed a tremendous amount to the literature helping explain the sensory processes that are taking place during micturition and bladder filling. There are numerous others who have contributed to this field and the synthesis of all these works has given us a better understanding of bladder control and voiding. It was the gastroenterologists who were prescient enough to begin to use functional MRI technology to evaluate functional bowel issues before it was on the

urologic radar and we look at their data as well to better understand children with BBD.

CHAPTER 1
Neurophysiology of voiding

Oreoluwa Ogunyemi and Hsi-Yang Wu
Lucile Packard Children's Hospital, Stanford, CA, USA

Anatomy of the lower urinary tract

The three main components of the bladder are the detrusor smooth muscle, connective tissue, and urothelium. The detrusor constitutes the bulk of the bladder and is arranged into inner longitudinal, middle circular, and outer longitudinal layers [1]. Elastin and collagen make up the connective tissue, which determines passive bladder compliance [2]. Elevated type III collagen and decreased elastin are associated with poorly compliant bladders [2]. Active compliance is determined by the detrusor, which is able to change its length over a wider range than skeletal muscle, allowing for a wide variation in bladder volume while maintaining a low pressure [2]. The detrusor maintains a baseline tension, which is modulated by hormones, local neurotransmitters, and the autonomic nervous system. Impedance studies reveal that compared to other smooth muscles, the detrusor is not electrically well coupled. This decreases the likelihood of detrusor overactivity (DO) during filling [2].

The urothelium has multiple layers, consisting of basal cells, intermediate cells, and luminal umbrella cells. The umbrella cells have tight junction complexes, lipid molecules, and uroplakin proteins that contribute to barrier function. A sulfated polysaccharide glycosaminoglycan layer covers the lumen of the bladder and defends against bacterial infection. Although the urothelium was previously thought to be an inert barrier, we now know that urothelial

cells participate in afferent signaling. Bladder nerves terminate close to, as well as on urothelial cells. Urothelial cells have pain receptors and mechanoreceptors, which can be modulated by ATP to activate or inhibit sensory neurons. Abnormal activation of these channels by inflammation can lead to pain responses to normally nonnoxious stimuli. Urothelial cells release factors such as acetylcholine, ATP, prostaglandins, and nitric oxide that affect sensory nerves [3].

The internal and external urethral sphincters (EUS) are vital for urinary continence. The internal urethral sphincter functions as a unit with the bladder base and trigone to store urine. The EUS is comprised of inner smooth muscle surrounded by outer skeletal muscle. It is omega shaped, with the majority of its muscle anterior to the urethra, and the opening of the omega sitting posteriorly. The smooth muscle is comprised of a thick longitudinal layer and an outer circular layer. The smooth muscle of the female EUS has less sympathetic innervation than that of the male, and the male EUS is larger in size. The skeletal muscle of the EUS has both slow and fast twitch fibers, of which the slow twitch fibers are more important in maintaining tonic force in the urethra. Contraction of the EUS, coaptation of the mucosa, as well as engorgement of blood vessels in the lamina propria contribute to urinary continence [2].

The lower urinary tract (LUT) is innervated by both the autonomic and somatic nervous systems. Sympathetic nervous system control of the LUT travels via the hypogastric nerve (T_{10}-L_2) (Figure 1.1, sympathetic preganglionic nucleus in thoracolumbar spinal cord), while parasympathetic control travels via the pelvic nerve (S_{2-4}) (Figure 1.1, Gert's nucleus in sacral spinal cord) [4, 5]. The somatic motor neurons control the skeletal muscle of the EUS via the pudendal nerve (S_{2-4}) [4]. Its motor neurons

are found in Onuf’s nucleus (Figure 1.1, sacral spinal cord). The sympathetic and somatic nervous systems promote storage, while the parasympathetic system promotes emptying.

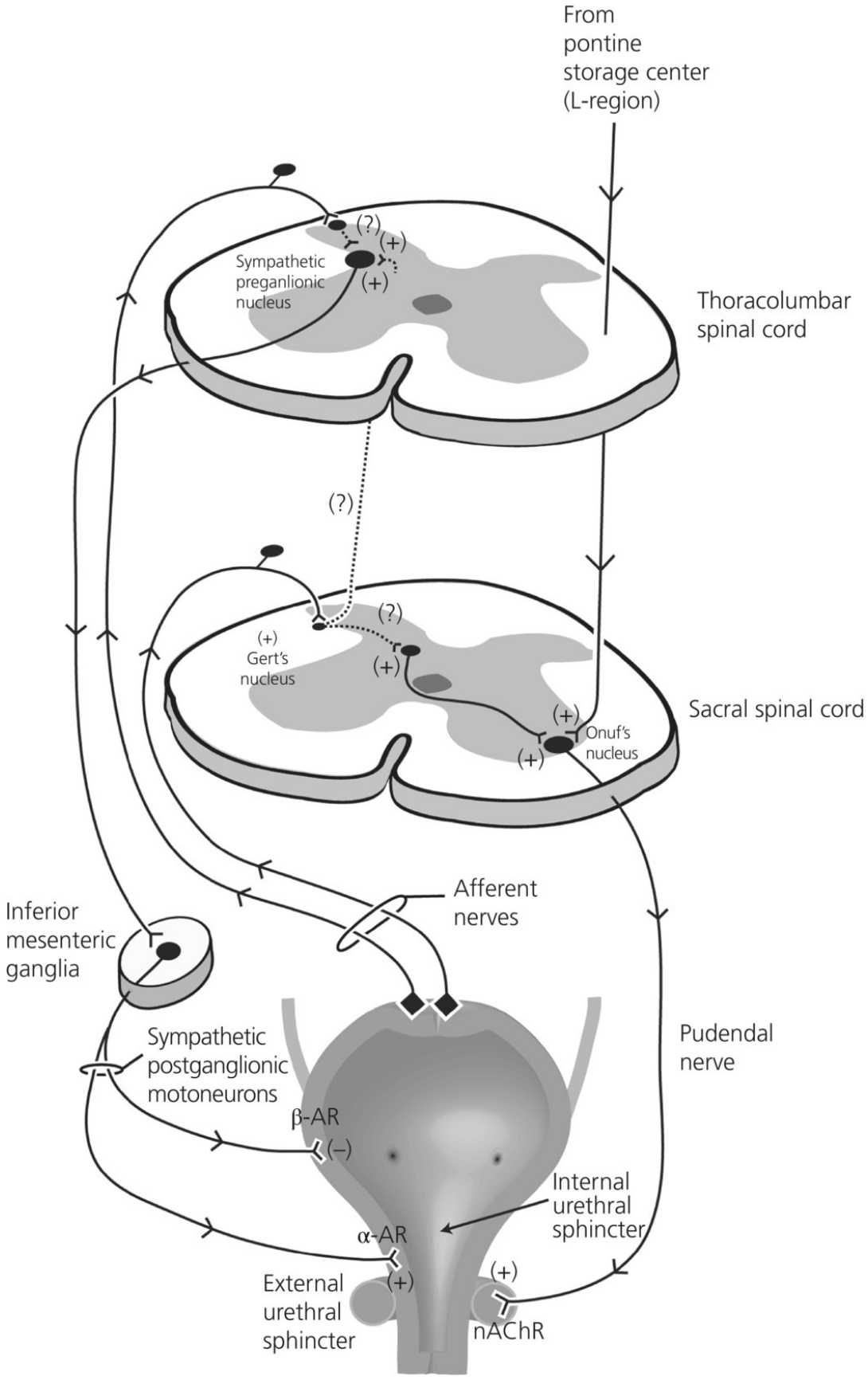

From
pontine
storage center
(L-region)
Thoracolumbar
spinal cord
Sympathetic
preganlionic
nucleus
(?)
(+)
(+)
(?)
(+)
Gert's
nucleus
(?)
(+)
Sacral spinal cord
(+)
Onuf's
nucleus
(+)
Afferent
nerves
Inferior
mesenteric
ganglia
Pudendal
nerve
Sympathetic
postganglionic
motoneurons
β-AR
(–)
Internal
urethral
sphincter
α-AR
External
urethral
sphincter
(+)
(+)
nAChR

Figure 1.1 Storage function. α-AR, α adrenergic receptor; β-AR, β adrenergic receptor; nAChR, nicotinic acetylcholine receptor.

Source: Beckel and Holstege [4]. Reproduced with permission from Springer.

Afferent mechanisms

The sensation of bladder fullness is carried by two types of afferent fibers via the pelvic, hypogastric, and pudendal nerves. A-delta (Aδ) fibers, which are activated at low thresholds, are myelinated large diameter nerves that conduct action potentials quickly [3]. C-fibers are high threshold, unmyelinated nerves that conduct signals more slowly, and usually transmit pain sensations. Normal bladder sensations are carried by Aδ fibers, whereas C-fibers become more important in diseased bladders [3]. In humans, C-fibers are found in the urothelial and suburothelial layers, whereas Aδ fibers are found in the smooth muscle [6]. A certain population of C-fibers is called silent afferents, because they normally respond to chemical or irritative stimuli. While these stimuli are uncommon in the bladder, chemical irritation can sensitize the bladder, to cause abnormal responses to normal stretch [3]. The transient receptor potential vanilloid type 1 ($TRPV_1$) receptor responds to pain, heat and acidity. Vanilloids, such as resiniferatoxin, desensitize C-fibers and suppress painful sensation [7]. Although initial studies suggested that resiniferatoxin may improve neurogenic DO, it is currently being studied as a treatment for cancer related pain [8], rather than as a treatment of DO.

Although we have long known that acetylcholine (muscarinic agonist) and ATP (purinergic agonist) act via the parasympathetic nervous system to cause bladder

contraction, they have been shown to play a role in afferent sensation as well. Muscarinic acetylcholine receptors are found on urothelial cells, suburothelial interstitial cells of Cajal, and on afferent nerves. The urothelium releases acetylcholine and ATP in response to stretch, both of which enhance spontaneous activity in interstitial cells of Cajal, to cause bladder smooth muscle contractions. This enhancement of spontaneous contractions may cause an increase in “afferent noise” that may be interpreted as urgency [9]. In spinalized rats, botulinum toxin lowers ATP release from the urothelium and blocks detrusor contraction [2]. Another mechanism of botulinum toxin’s action is by decreasing afferent firing from the bladder [10].

Adjacent pelvic organs such as the colon and uterus can affect urinary continence [2]. This may be due to a common afferent system via the hypogastric nerve, or intermediary neurons allowing for cross talk between pelvic organs [3]. Distension of the colon from constipation is a well-recognized cause of urinary incontinence in children. This is likely due to changes in bladder afferent signaling arising from a chronically distended colon, which prevents the child from recognizing a full bladder [11].

Spinal cord and brainstem

During bladder storage, afferent signals from the hypogastric nerve and pelvic nerve travel to the thoracolumbar and sacral spinal cord, respectively (Figure 1.1). The hypogastric nerve sends signals via the sympathetic nervous system to block bladder contraction and contact the internal urethral sphincter. Onuf’s nucleus maintains contraction of the EUS, which is coordinated with bladder storage by the pontine micturition center (PMC) in the medial pons (Figure 1.1, L-region).

Once the bladder pressure threshold is exceeded, afferent signals travel via the pelvic nerve to synapse on interneurons in Gert's nucleus in the S_{1-2} spinal cord [4] (Figure 1.2). These interneurons send projections up to the periaqueductal gray (PAG) in the midbrain to initiate voiding, which occurs if the cerebral cortex determines that it is appropriate to void. The PAG sends caudal projections to the PMC, which is the final efferent center of the LUT. The PMC sends projections caudally to the sacral parasympathetic nucleus, activating the neurons, which cause bladder contraction and EUS relaxation [4] (Figure 1.2).

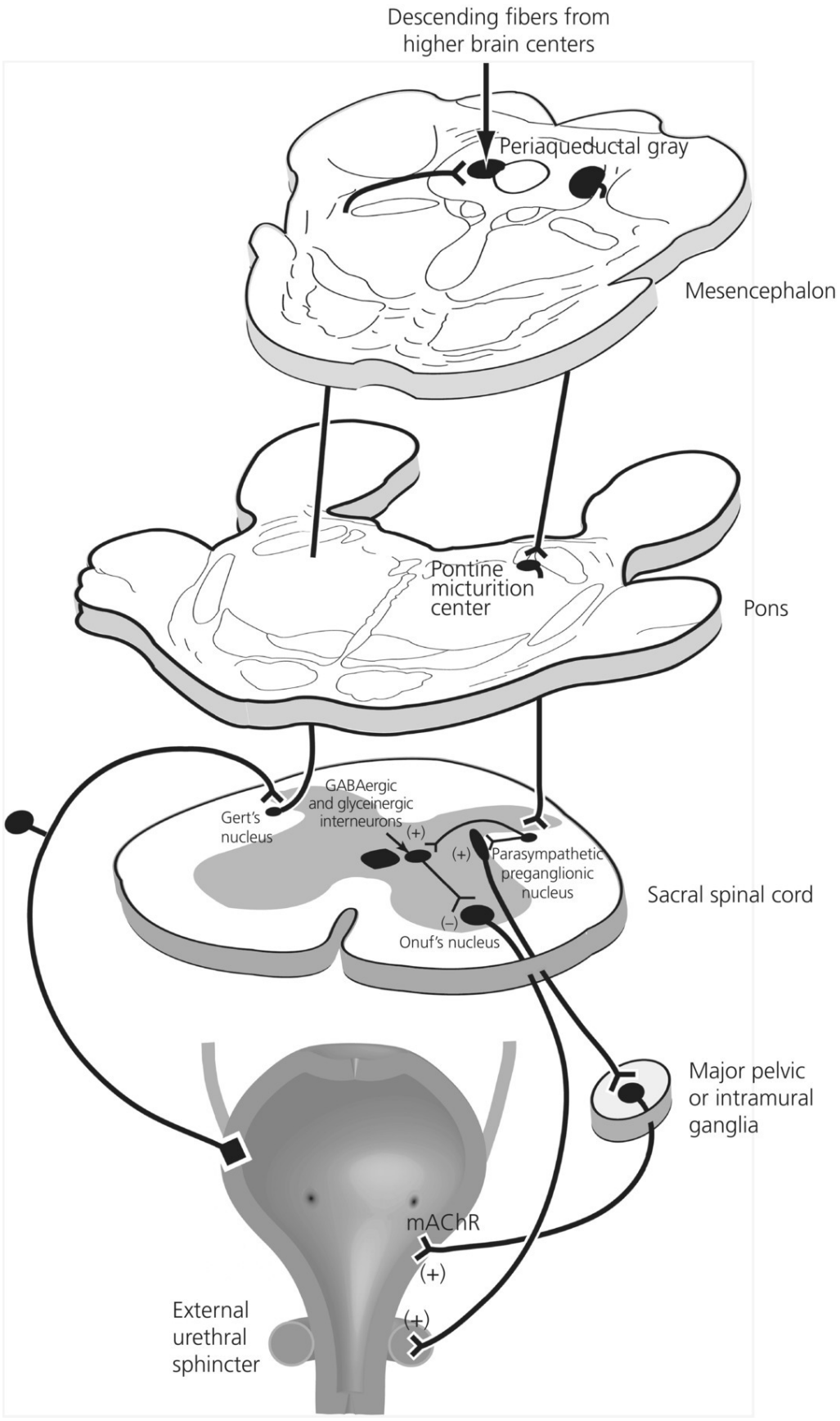

Descending fibers from higher brain centers
Periaqueductal gray
Mesencephalon
Pontine micturition center
Pons
GABAergic and glyceinergic interneurons
Gert's nucleus
(+)
(+)
Parasympathetic preganglionic nucleus
(–)
Onuf's nucleus
Sacral spinal cord
Major pelvic or intramural ganglia
mAChR
(+)
(+)
External urethral sphincter

Figure 1.2 Emptying function. mAChR, muscarinic acetylcholine receptor.

Source: Beckel and Holstege [4]. Reproduced with permission from Springer.

Although the mechanism of sacral or pudendal neuromodulation remains unclear, the two likely locations would be the peripheral nervous system (including the autonomic nervous system efferents) or the brainstem (PAG and PMC) and cortex [12, 13]. Positron emission tomography imaging shows that sacral neuromodulation restores normal afferent midbrain activity in women with Fowler's syndrome, which is characterized by EUS overactivity. Prior to neuromodulation, they exhibit continuous EUS activity and lack of bladder afferent activity reaching the PAG or PMC. After neuromodulation and reestablishment of normal bladder afferent activity, they regain control of EUS activity [14]. Functional MRI evaluation confirms that neuromodulation reduced deactivation in the PAG, suggesting that exaggerated EUS afferent activity is capable of blocking normal bladder afferent sensation from reaching the cortex [15]. Inhibition of DO is also believed to result from inhibition of abnormal afferent activity. Pudendal nerve neuromodulation represents a more peripheral means to stimulate $S_{2–4}$ and inhibit the voiding reflex, decreasing uninhibited detrusor contractions and increasing bladder capacity [12].

Cortex

The role of the cerebral cortex in controlling voiding function has recently been described using PET scanning and functional MRI, to reveal differences in patients with normal LUT function, and those with DO. The PAG gathers information from the median prefrontal cortex, anterior

cingulate gyrus, and insula. It is unclear whether these connections function as a looped relay system to the PAG or if they individually connect to the PAG. The median prefrontal cortex is a decision-making area, taking into account emotions and social context. The anterior cingulate gyrus generates autonomic response to stress and conflict, and the insula processes visceral sensations. Patients with DO show decreased MRI response at small bladder volumes, but have exaggerated responses in the anterior cingulate gyrus at large bladder volumes. When leakage occurs, deactivation of the anterior cingulate gyrus occurs. One hypothesis states that this is a learned response to imminent urinary leakage, which requires increased monitoring by the anterior cingulate gyrus in order to maintain continence [16–18].

Efferent mechanisms, peripheral

The hypogastric nerve causes detrusor relaxation via β-adrenergic receptors and internal urethral sphincter contraction via α-adrenergic receptors [4] (Figure 1.1). Both of these effects enhance storage function. α_1 Antagonists are used off-label to treat children with obstructive voiding patterns. β_3 Adrenergic agonists increase bladder capacity without increasing voiding pressure or post void residual volume [19]. They are approved for treatment of DO in adults, but are not yet approved for children. In male rats, hypogastric nerve stimulation releases norepinephrine and raises urethral pressure, while in female rats the release of nitric oxide predominates over norepinephrine, resulting in a decrease in urethral pressure [20]. If this sex difference is present in humans, this would suggest that electrical stimulation of the hypogastric nerve to enhance internal urethral sphincter contraction would be more effective in males.

The axons of the pelvic nerve travel to two groups of postganglionic neurons in the detrusor and pelvic plexus [2]. The first group causes detrusor contraction by releasing acetylcholine and ATP, while the second group causes internal urethral sphincter relaxation by releasing nitric oxide [2, 4, 7] (Figure 1.2).

Muscarinic antagonists such as oxybutynin block muscarinic receptors. As previously discussed under afferent mechanisms, it is believed that muscarinic antagonists are effective at treating urgency during the storage phase by blocking the enhancement of afferent noise, which may be responsible for spontaneous contractions. M_3 receptors cause detrusor contraction, while M_2 receptors enhance M_3 activity. Despite the relative abundance of $M_2 : M_3$ receptors in the bladder (3 : 1), M_2 receptors play a secondary role in modulating M_3 receptor response. Although there is always a concern with causing urinary retention in patients when using muscarinic antagonists, there is a therapeutic window in which afferent signals can be blocked without affecting bladder contractility [7, 9]. There is one clinical scenario in which completely blocking bladder contractility is useful: neurogenic bladder patients who are already using clean intermittent catheterization to drain their bladders. In these cases, high doses of muscarinic antagonists or botulinum toxin can prevent bladder contractility. Botulinum toxin increases bladder capacity and decreases maximal detrusor pressure by preventing acetylcholine release [21].

ATP stimulates atropine-resistant, noncholinergic, nonadrenergic detrusor contraction, modulates urothelial signaling, and regulates afferent nerve activity. Despite these multiple mechanisms, which would predict that purinergic (P2 × 3) antagonists would be effective in the

treatment of DO, they are currently being developed as treatments for pain. The main obstacle for developing a safe and tolerable purinergic antagonist is the fact that ATP is an important molecule in every organ system in the body, so developing a bladder-specific molecule has been difficult. It is proposed that purinergic signaling becomes more important in obstructed bladders [7, 22].

Prostaglandins facilitate voiding by altering neurotransmitter release or by inhibiting the breakdown of acetylcholine [2]. While there are multiple prostaglandins, it is believed that prostaglandin E2 (PGE2) interacts with EP1 receptors to drive DO [23]. Urinary levels of PGE2 were found to be elevated in both men and women with OAB compared to controls [24, 25]. Nonsteroidal anti-inflammatory drugs, which block prostaglandins, are commonly used after surgery to decrease bladder spasms in children.

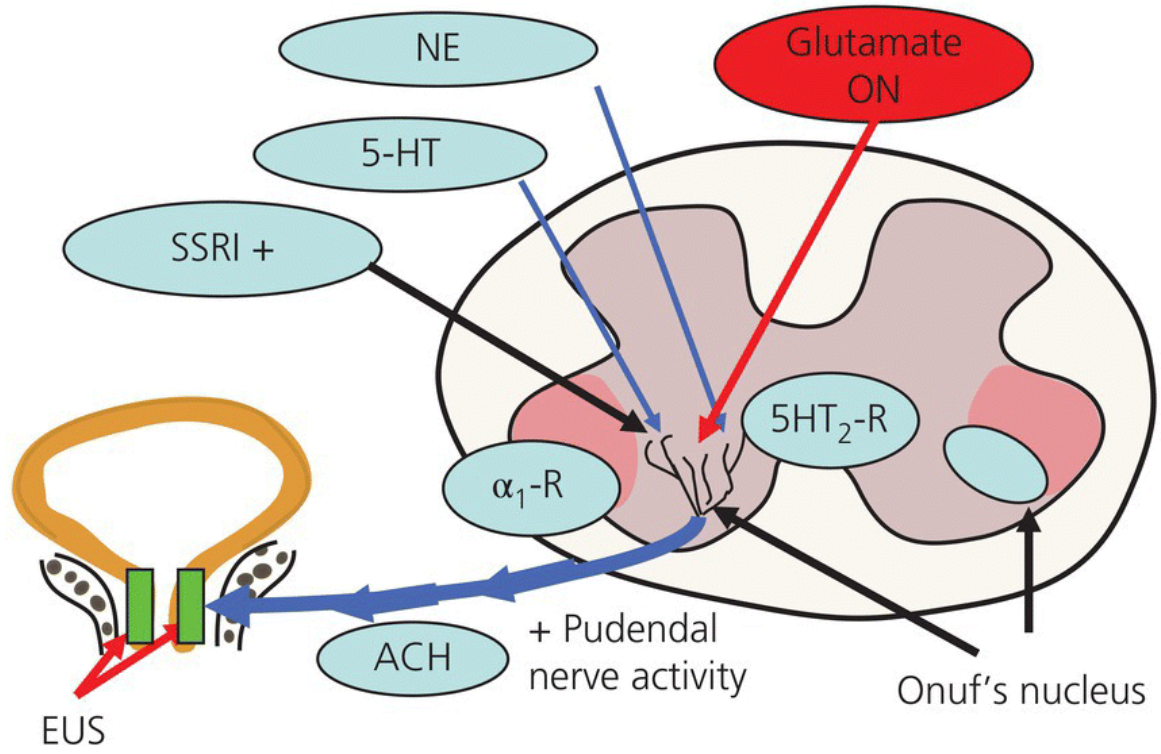
Efferent mechanisms, central

The pudendal nerve has small neurons with both somatic and autonomic components. The skeletal muscle component of the EUS is regulated by GABA, the major inhibitory neurotransmitter in the spinal cord [7]. Baclofen (GABA agonist) can be used to treat detrusor sphincter dyssynergia, although it is more often used to treat limb spasticity via an intrathecal route [7, 26]. Injection of botulinum toxin into the EUS decreases its contractility, and is another means to temporarily block EUS contractility.

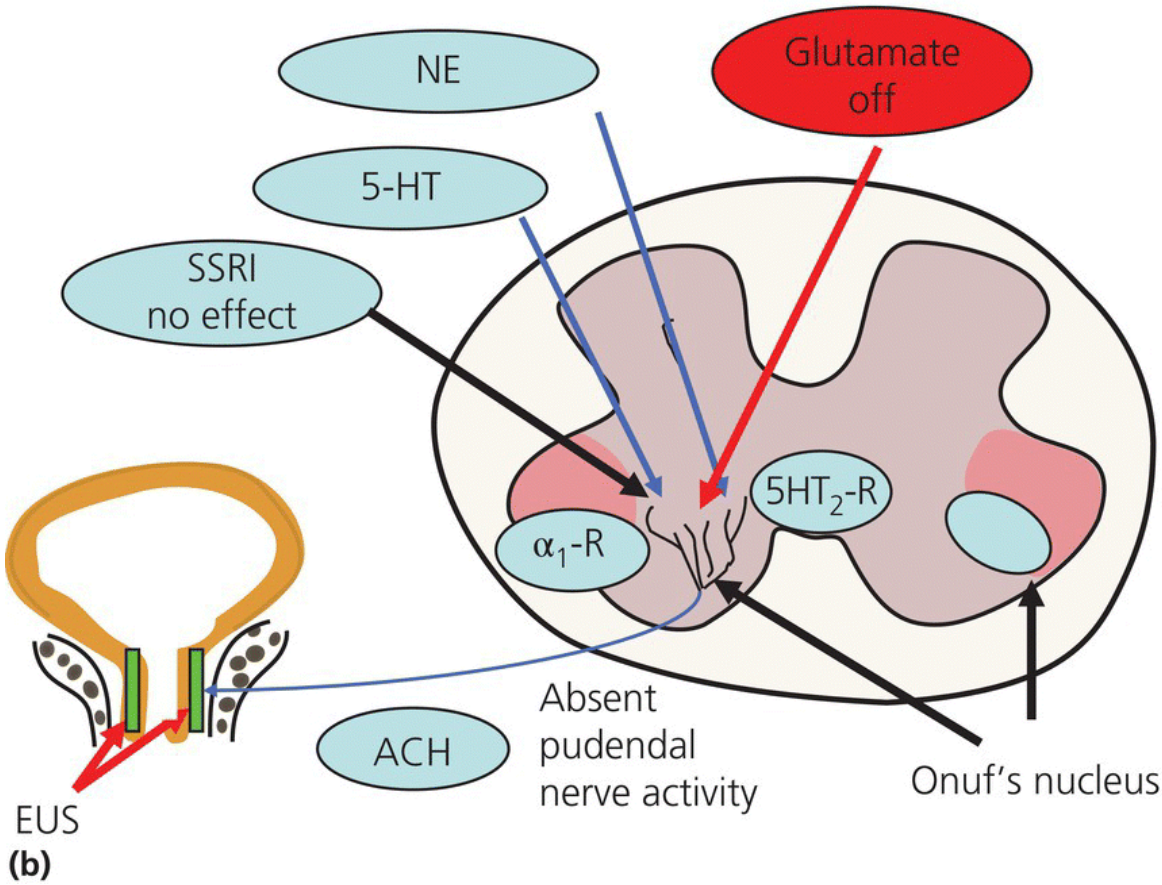
Imipramine, a tricyclic antidepressant drug, has been used for refractory nocturnal enuresis [27]. However, its mechanism of action in treatment of DO remains unclear. It may enhance serotonin and norepinephrine (NE) reuptake

inhibition, directly relax smooth muscle, or increase urethral resistance [5, 28].

Serotonin (5-HT) modulates the afferent system and may affect the bladder and EUS by supraspinal enhancement of bladder storage as well as EUS tonic activity at Onuf's nucleus (Figure 1.3a) [2, 30, 31]. Glutamate is the major spinal cord regulator of the EUS [32] (Figure 1.3a). In the presence of glutamate, both 5-HT and NE can enhance its contraction of the EUS. However, if glutamate is absent, neither 5-HT nor NE can independently cause the EUS to relax (Figure 1.3b). Glutamate can be considered the on/off switch, while 5-HT and NE adjust the gain in the system [31]. The major problem with developing glutamate agonists to enhance continence by increasing EUS activity is that they do not penetrate the blood–brain barrier; therefore, glutamate agonists require intrathecal administration [33]. Duloxetine (a combined serotonin and norepinephrine reuptake inhibitor) decreases voiding frequency and incontinent episodes. Duloxetine reduced the motor threshold for EUS contraction and increased urethral phasic contractions in healthy women without affecting urethral resting pressure, suggesting that it both enhanced the afferent urethral response and increased signaling from the cortex to the EUS [34]. It is approved for stress incontinence in Europe, but not the United States.


NE
Glutamate
ON
5-HT
SSRI +
5HT2-R
α1-R
ACH
+ Pudendal
nerve activity
Onuf's nucleus
EUS

(a)


NE
Glutamate
off
5-HT
SSRI
no effect
5HT2-R
α1-R
ACH
Absent
pudendal
nerve activity
Onuf's nucleus
EUS

(b)

Figure 1.3 **(a)** Serotonin and storage function. **(b)** Serotonin and emptying function. 5-HT, serotonin; $5HT_2$-R, serotonin type 2 receptor; Ach, acetylcholine; NE, norepinephrine; SSRI, selective serotonin reuptake inhibitor; α_1-R, alpha 1 adrenergic receptor.

Source: Adapted from Franco [29]. © Elsevier.

Development of urinary continence

The human neonate initially voids hourly [35], developing an increased bladder capacity in two phases: at birth and then at 3 years of age [36]. Since neonates do not have voluntary control of urination, it was believed that a local sacral reflex was responsible for emptying the bladder without involving the brain. However, electroencephalography suggests that most neonates experience cortical arousal and awaken before voiding, so the brain is always involved with voiding [37]. The interrupted infant voiding pattern results from a lack of coordination between the bladder and the external sphincter, which causes elevated voiding pressures until the child reaches the age of 18 months. One-week-old boys void with detrusor pressures of 117 cm H_2O, and girls with pressures of 75 cm H_2O [36, 38]. Overactive contractions are rarely seen during urodynamic studies carried out in asymptomatic infant [38, 39], indicating that the urinary frequency is due to a small bladder capacity rather than OAB.

Our understanding of neural control and smooth muscle function of the neonatal bladder is derived from animal models. Neonatal rats are unable to void spontaneously [40] and are dependent on their mother to lick the perigenital area to cause bladder emptying. By 3 weeks of

age (the age of weaning), neonatal rats are able to void spontaneously in response to bladder filling [41]. At first glance, this might suggest that the neonatal nervous system is not mature, and additional maturation of the hypogastric, pelvic, or pudendal nerves needs to occur. However, this is not consistent with the fact that human and rat fetuses start to urinate by the second trimester, so the voiding reflex needs to be functional during prenatal life. What actually happens in rats is that the perigenital reflex inhibits the mature bladder emptying reflex at the sacral level, and this inhibition is removed at weaning [42, 43]. Experimental bladder distension does not change the onset of spontaneous voiding at 3 weeks, but prolongs the perigenital reflex for another 2 weeks [44]. Surgical reduction of bladder volume causes the immediate onset of spontaneous voiding in neonatal rats [45]. These findings suggest that maturation from immature and mature voiding reflexes requires central neural control, despite having afferent and efferent connections, which are ready for use at birth.

Animal studies show that the neonatal bladder smooth muscle produces more pressure per gram of tissue and is more dependent on local calcium levels than adult bladder smooth muscle [46–49]. Neonatal bladders also have large-amplitude spontaneous contractions, which are downregulated with maturation [50, 51]. The elevated voiding pressures seen in infants may represent immature smooth muscle function. Once the detrusor becomes more mature and less overactive, it becomes easier for the brain to control. Since the brain makes the decision to void by integrating emotions, social context, stress, and visceral sensation, toilet training can be derailed by multiple factors, resulting in persistent urinary incontinence.

Conclusion

While the neurophysiology of voiding is based on a relatively simple circuit, our ability to improve the treatment of pediatric urinary incontinence will depend on finding more focused methods of regulating bladder sensation and coordinating bladder and EUS function. While there are many possible targets, most of our current therapies are aimed at peripheral efferent systems, and we are only beginning to understand and develop treatments aimed at the afferent system, such as neuromodulation. The challenges of developing treatments aimed at the cerebral cortex and central efferent systems are the next frontier for physicians and researchers treating pediatric urinary incontinence.

References

1 Chung B, Sommer G, Brooks JD. Anatomy of the lower urinary tract and male genitalia. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. *Campbell-Walsh Urology*. 10th ed. Philadelphia: Elsevier Saunders; 2011. p. 33–70.

2 Yoshimura N, Chancellor M. Physiology and pharmacology of the bladder and urethra. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. *Campbell-Walsh Urology*. 10th ed. Philadelphia: Elsevier Saunders; 2011. p. 1786–833.

3 Birder L, de Groat W, Mills I, Morrison J, Thor K, Drake M. Neural control of the lower urinary tract: Peripheral and spinal mechanisms. *Neurourol Urodyn*. 2010;**29**:128–39.

4 Beckel J, Holstege G. Neurophysiology of the lower urinary tract. In: Andersson K, Michel M, editors. *Urinary Tract* (Handbook of Experimental Pharmacology). Vol. **202**. Berlin: Springer; 2011.

5 Yeung CK, Sihoe JD. Non-neuropathic dysfunction of the lower urinary tract in children. In: Wein A, Kavoussi L,

Novick A, Partin A, Peters C, editors. *Campbell-Walsh Urology*. 10th ed. Philadelphia: Elsevier Saunders; 2011. p. 3411–30.
6 Wiseman OJ, Brady CM, Hussain IF, Dasgupta P, Watt H, Fowler CJ, et al. The ultrastructure of bladder lamina propria nerves in healthy subjects and patients with detrusor hyperreflexia. *J Urol*. 2002;**168**:2040–5.
7 de Groat WC, Yoshimura N. Pharmacology of the lower urinary tract. *Annu Rev Pharmacol Toxicol*. 2001;**41**:691–721.
8 http://clinicaltrials.gov/ct2/show/NCT00804154 (accessed February 12, 2015).
9 Andersson KE. Antimuscarinic mechanisms and the overactive detrusor: An update. *Eur Urol*. 2011;**59**:377–86.
10 Ikeda Y, Zabbarova IV, Birder LA, de Groat WC, McCarthy CJ, Hanna-Mitchell AT, et al. Botulinum neurotoxin serotype A suppresses neurotransmitter release from afferent as well as efferent nerves in the urinary bladder. *Eur Urol*. 2012;**62**:1157–64.
11 Wyndaele M, De Wachter S, De Man J, Minagawa T, Wyndaele JJ, Pelckmans PA, et al. Mechanisms of pelvic organ crosstalk: 1. Peripheral modulation of bladder inhibition by colorectal distention in rats. *J Urol*. 2013;**190**:765–71.
12 Vasavada S, Rackley R. Electrical simulation and neuromodulation in storage and emptying failure. In: Wein A, Kavoussi L, Novick A, Partin A, Peters C, editors. *Campbell-Walsh Urology*. 10th ed. Philadelphia: Elsevier Saunders; 2011. p. 2026–46.
13 Amend B, Matzel KE, Abrams P, de Groat WC, Sievert KD. How does neuromodulation work. *Neurourol Urodyn*. 2011;**30**:762–5.
14 Dasgupta R, Critchley HD, Dolan RJ, Fowler CJ. Changes in brain activity following sacral neuromodulation for urinary retention. *J Urol*. 2005;**174**(6):2268–72.

15 Kavia R, DasGupta R, Critchley H, Fowler C, Griffiths D. A functional magnetic resonance imaging study of the effect of sacral neuromodulation on brain responses in women with Fowler's syndrome. *BJU Int*. 2010;**105**:366–72.
16 Griffiths D, Derbyshire S, Stenger A, Resnick N. Brain control of normal and overactive bladder. *J Urol*. 2005;**174**:1862–7.
17 Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: Evidence from functional brain imaging. *Neurourol Urodynam*. 2008;**27**:446–74.
18 Drake MJ, Fowler CJ, Griffiths D, Mayer E, Paton JFR, Birder L. Neural control of the lower urinary and gastrointestinal tracts: Supraspinal CNS mechanisms. *Neurourol Urodyn*. 2010;**29**:119–27.
19 Andersson K, Chapple C, Cardozo L, Cruz F, Hashim H, Michel M, et al. Pharmacological treatment of urinary incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A, editors. *Incontinence*. 4th ed. Paris: Health Publications Ltd; 2009. p. 631–700.
20 Kontani H, Shiraoya C. Sex differences in urethral pressure response to electrical stimulation of the hypogastric nerves in rats. *J Urol*. 2000;**163**:1364–8.
21 Schulte-Baukloh H, Priefert J, Knispel HH, Lawrence GW, Miller K, Neuhaus J. Botulinum toxin A detrusor injections reduce postsynaptic muscular M2, M3, P2X2, and P2X3 receptors in children and adolescents who have neurogenic detrusor overactivity: A single-blind study. *Urology*. 2013;**81**(5):1052–7.
22 Ford APDW, Cockayne DA. ATP and P2x purinoreceptors in urinary tract disorders. In: Andersson K, Michel M, editors. *Urinary Tract* (Handbook of Experimental Pharmacology). Vol. **202**. Berlin: Springer; 2011.
23 Andersson KE. Prostanoid receptor subtypes: New targets for OAB drugs? *J Urol*. 2009;**182**:2099–100.
24 Kim JC, Park EY, Hong SH, Seo SI, Park YH, Hwang TK. Changes in urinary nerve growth factor and prostaglandins

in male patients with overactive bladder symptom. *Int J Urol*. 2005;**12**:875–80.
25 Kim JC, Park EY, Seo SI, Park YH, Hwang TK. Nerve growth factor and prostaglandins in the urine of female patients with overactive bladder. *J Urol*. 2006;**175**:1773–6.
26 Steers WD, Meythaler JM, Haworth C, Herrell D, Park TS. Effects of acute bolus and chronic intrathecal baclofen on genitourinary dysfunction due to spinal cord pathology. *J Urol*. 1992;**148**(6):1849–55.
27 Neveus T, Tullus K. Tolterodine and imipramine in refractory enuresis; a placebo-controlled crossover study. *Pediatr Nephrol*. 2008;**23**:263–7.
28 Hunsballe JM, Djurhuus JC. Clinical options for imipramine in the management of urinary incontinence. *Urol Res*. 2001;**29**:118–25.
29 Franco I. Overactive bladder in children: Part 1. Pathophysiology. *J Urol*. 2007;**178**:761–8.
30 Cheng CL, de Groat WC. Role of 5-HT1A receptors in control of lower urinary function in anesthetized rats. *Am J Physiol Renal Physiol*. 2010;**298**:F771–8.
31 Thor KB. Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: Implications for treating stress urinary incontinence. *Urology*. 2003;**62**(S4A):3–9.
32 Furuta A, Asano K, Egawa S, de Groat WC, Chancellor MB, Yoshimura N. Role of α2-adrenoceptors and glutamate mechanisms in the external urethral sphincter continence reflex in rats. *J Urol*. 2009;**181**:1467–73.
33 Hawkins RA. The blood-brain barrier and glutamate. *Am J Clin Nutr*. 2009;**90**:867S–74.
34 Boy S, Reitz A, Wirth B, Knapp PA, Braun PM, Haferkamp A, et al. Facilitatory neuromodulative effect of duloxetine on pudendal motor neurons controlling the urethral pressure: A functional urodynamic study in healthy women. *Eur Urol*. 2006;**50**:119–25.

35 Gladh G, Persson D, Mattson S, Lindstrom S. Voiding patterns in healthy newborns. *Neurourol Urodyn*. 2000;**19**:177–84.
36 Sillen U. Bladder function in healthy neonates and its development during infancy. *J Urol*. 2001;**166**:2376–81.
37 Yeung CK, Godley ML, Ho CK, Ransley PG, Duffy PG, Chen CN, et al. Some new insights into bladder function in infancy. *Br J Urol*. 1995;**76**:235–40.
38 Yeung CK, Godley ML, Dhillon HK, Duffy PG, Ransley PG. Urodynamic patterns in infants with normal lower urinary tracts of primary vesico-ureteric reflux. *Br J Urol*. 1998;**81**:461–7.
39 Bachelard M, Sillen U, Hansson S, Hermansson G, Jodal U, Jacobsson B. Urodynamic pattern in asymptomatic infants: Siblings of children with vesicoureteral reflux. *J Urol*. 1999;**162**:1733–8.
40 Capek K, Jelinek J. The development of the control of water metabolism: I. The excretion of urine in young rats. *Physiol Bohemoslov*. 1956;**5**:91–6.
41 Maggi CA, Santicioli P, Meli A. Postnatal development of micturition reflux in rats. *Am J Physiol*. 1986;**250**:R926–31.
42 Araki I, de Groat WC. Developmental synaptic depression underlying reorganization of visceral reflex pathways in the spinal cord. *J Neurosci*. 1997;**17**:8402–7.
43 de Groat WC. Plasticity of bladder reflex pathways during postnatal development. *Physiol Behav*. 2002;**77**:689–92.
44 Wu HY, de Groat WC. Maternal separation uncouples reflex from spontaneous voiding in rat pups. *J Urol*. 2006;**175**:1148–51.
45 Ng YK, Wu HY, Lee KH, Yeung CK. Bladder reduction surgery accelerates the appearance of spontaneous voiding in neonatal rats. *J Urol*. 2010;**183**:370–7.
46 Zderic SA, Hypolite J, Duckett JW, Snyder HM 3rd, Wein AJ, Levin RM. Developmental aspects of bladder contractile

function: Sensitivity to extracellular calcium. *Pharmacology*. 1991;**43**:61–8.
47 Zderic SA, Sillen U, Liu GH, Snyder H 3rd, Duckett JW, Wein AJ, et al. Developmental aspects of bladder contractile function: Evidence for an intracellular calcium pool. *J Urol*. 1993;**150**:623–5.
48 Zderic SA, Sillen U, Liu GH, Snyder HM 3rd, Duckett JW, Gong C, et al. Developmental aspects of excitation contraction coupling of rabbit bladder smooth muscle. *J Urol*. 1994;**152**:679–81.
49 Wu HY, Zderic SA, Wein AJ, Chacko S. Decrease in maximal force generation in the neonatal mouse bladder corresponds to shift in myosin heavy chain isoform composition. *J Urol*. 2004;**171**:841–4.
50 Szell EA, Somogyi GT, de Groat WC, Szigeti GP. Developmental changes in spontaneous smooth muscle activity in the neonatal rat urinary bladder. *Am J Physiol Regul Integr Comp Physiol*. 2003;**285**:R809–16.
51 Ng YK, de Groat WC, Wu HY. Smooth muscle and neural mechanisms contributing to the down-regulation of neonatal rat spontaneous bladder contractions during postnatal development. *Am J Physiol Regul Integr Comp Physiol*. 2007;**292**:R2100–12.

CHAPTER 2
Neurophysiology of defecation

Cecilie Ejerskov and Charlotte Siggaard Rittig
Gastroenterology Unit, Department of Pediatrics Aarhus University Hospital, Aarhus, Denmark

Normal defecation patterns

Defecation pattern in childhood differs with age and is determined by the change from breastfeeding to solid foods. At infancy when breast fed, defecation occurs from six to seven times a day to once every seventh day, which is considered the norm, in average three times daily. At 6–12 months, the average defecation rate is just below two times per day, and at 1–3 years, the average defecation rate is one and a half times per day. At 3–12 years, the defecation rate settles at once daily. There is no difference in gender until puberty. During puberty and adulthood, the defecation rate among females is less than among males.

To appreciate colorectal motility of defecation, neurophysiology, and the various pathological changes related hereto, it is important to understand the functional anatomy and neurophysiology of colon, rectum, and anus [1–3].

Functional anatomy of colon, rectum, and anus

The main functions of **the large intestine** are intraluminal bacterial fermentation of nutrients resistant to digestive enzymes (e.g., short-chain fatty acids), to reabsorb water and electrolytes, and to transport and store feces until it

can be discharged from the body. The large intestine is composed of the cecum; the ascending, the transverse, the descending, and the sigmoid segments of the colon; the rectum; and the anus. Main function of the right side of the colon is absorption of water and electrolytes, whereas the main function of the left side of the colon is storage and evacuation of feces.

Histologically, the wall of the large intestine is made up of mucosa, submucosa, tunica muscularis, and serosa. The **mucosa** consists of an inner layer epithelium, underlying lamina propria, and muscularis mucosae. Distributed within the columnar epithelium are absorptive cells, goblet cells, and enteroendocrine cells. The lamina propria is a connective tissue rich in cells. It includes immunocompetent cells, nerve fibers, fibroblasts, lymphatic vessels, and capillaries. The muscularis mucosae is a thin layer of intestinal smooth muscle. The **submucosa** consists of loose connective tissue and substantial fatty tissue and here lies the **submucosal plexus** (**Meissner's plexus**), one of the plexuses of the enteric nerve system (ENS), together with larger nerves, blood and lymph vessels. The **tunica muscularis** consists of the inner complete circular layer, which during contraction divides the colon into segments, the characteristic haustra, and an outer incomplete longitudinal layer, which is made up by three flat longitudinal bands, teniae coli. In the rectum, the teniae disappear and the longitudinal muscle layer becomes complete. Feces is transported as a result of contractions in the muscle layer containing the **myenteric plexus** (**Auerbach's plexus**), the other plexus of the ENS located between the circular and the longitudinal layers. The **serosa** consists of a mesothelial lining resembling the visceral peritoneal surface. Some parts of colon and rectum and the distal one-third part of rectum are located outside the peritoneum, and those parts are adherent to their