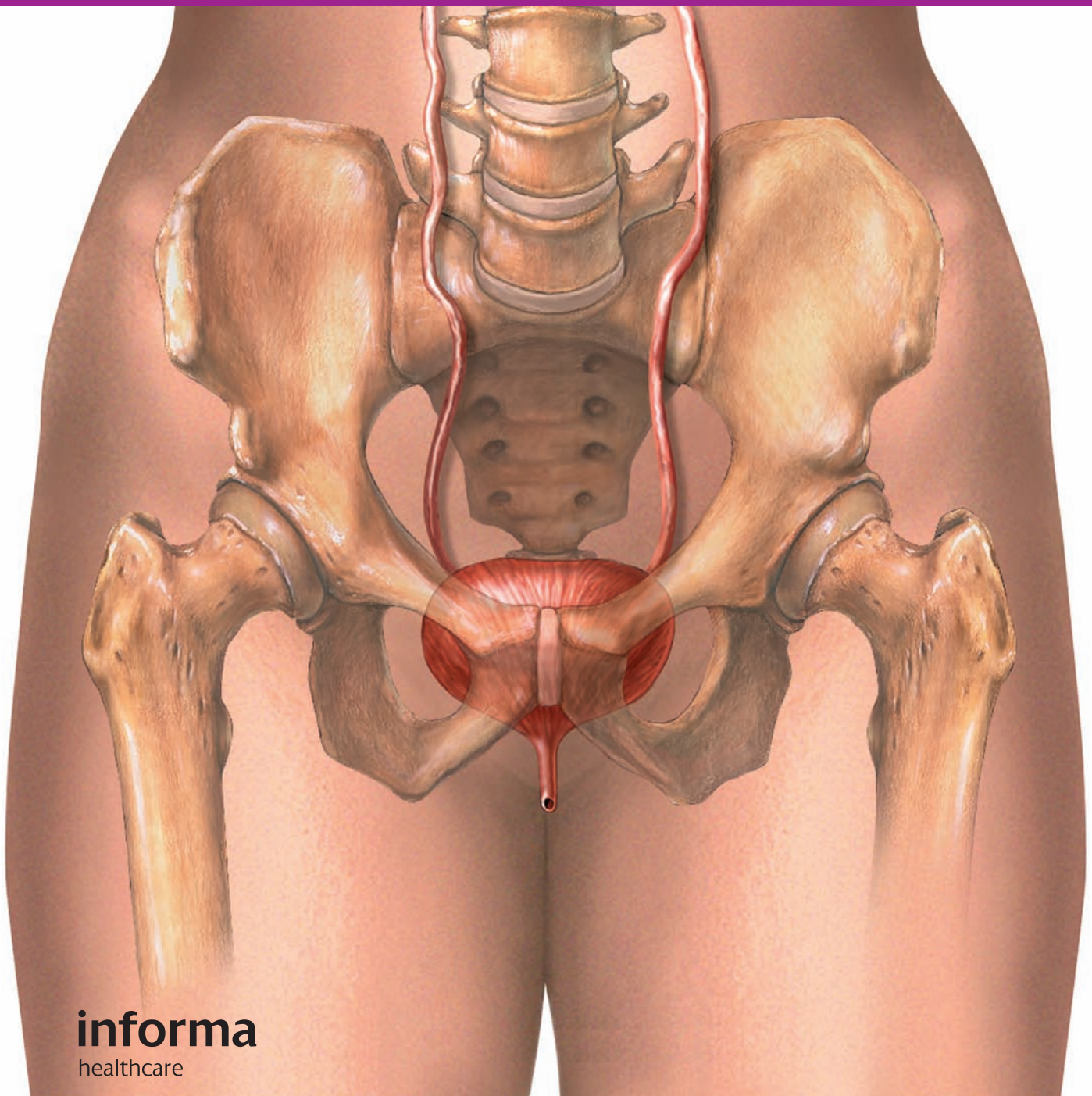
# The Overactive Bladder

## Evaluation and Management

Karl Kreder and Roger Dmochowski

Foreword by Paul Abrams



informa
healthcare

# The Overactive Bladder

# The Overactive Bladder

## Evaluation and Management

**Edited by**

**KARL KREDER** MD
Professor
Department of Urology
University of Iowa Hospitals and Clinics
Iowa City, IA
USA

**ROGER DMOCHOWSKI** MD
Professor
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN
USA

**Foreword by**

**PAUL ABRAMS** MD FRCS
Professor
Bristol Urological Institute
Southmead Hospital
Bristol
UK

informa
healthcare

CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

© 2007 by Taylor & Francis Group, LLC
CRC Press is an imprint of Taylor & Francis Group, an Informa business

No claim to original U.S. Government works
Version Date: 20130129

International Standard Book Number-13: 978-0-203-93162-2 (eBook - PDF)

This book contains information obtained from authentic and highly regarded sources. While all reasonable efforts have been made to publish reliable data and information, neither the author[s] nor the publisher can accept any legal responsibility or liability for any errors or omissions that may be made. The publishers wish to make clear that any views or opinions expressed in this book by individual editors, authors or contributors are personal to them and do not necessarily reflect the views/opinions of the publishers. The information or guidance contained in this book is intended for use by medical, scientific or health-care professionals and is provided strictly as a supplement to the medical or other professional's own judgement, their knowledge of the patient's medical history, relevant manufacturer's instructions and the appropriate best practice guidelines. Because of the rapid advances in medical science, any information or advice on dosages, procedures or diagnoses should be independently verified. The reader is strongly urged to consult the drug companies' printed instructions, and their websites, before administering any of the drugs recommended in this book. This book does not indicate whether a particular treatment is appropriate or suitable for a particular individual. Ultimately it is the sole responsibility of the medical professional to make his or her own professional judgements, so as to advise and treat patients appropriately. The authors and publishers have also attempted to trace the copyright holders of all material reproduced in this publication and apologize to copyright holders if permission to publish in this form has not been obtained. If any copyright material has not been acknowledged please write and let us know so we may rectify in any future reprint.

Except as permitted under U.S. Copyright Law, no part of this book may be reprinted, reproduced, transmitted, or utilized in any form by any electronic, mechanical, or other means, now known or hereafter invented, including photocopying, microfilming, and recording, or in any information storage or retrieval system, without written permission from the publishers.

For permission to photocopy or use material electronically from this work, please access www.copyright.com (http://www.copyright.com/) or contact the Copyright Clearance Center, Inc. (CCC), 222 Rosewood Drive, Danvers, MA 01923, 978-750-8400. CCC is a not-for-profit organization that provides licenses and registration for a variety of users. For organizations that have been granted a photocopy license by the CCC, a separate system of payment has been arranged.

**Trademark Notice:** Product or corporate names may be trademarks or registered trademarks, and are used only for identification and explanation without intent to infringe.

**Visit the Taylor & Francis Web site at**
**http://www.taylorandfrancis.com**

**and the CRC Press Web site at**
**http://www.crcpress.com**

# Contents

**List of contributors** . . . . . vii

**Foreword** . . . . . xi

**Acknowledgments** . . . . . xiii

**Colour plates** . . . . . xv

**Introduction**

1. Nomenclature *Jerry G Blaivas* . . . . . 3
2. The neurophysiology of lower urinary tract function *William C de Groat* . . . . . 11
3. Diagnosis of overactive bladder *Eric S Rovner and Melissa Walls* . . . . . 27
4. Measuring overactive bladder syndrome symptoms *Rufus Cartwright and Linda Cardozo* . . 37
5. Nocturia *Jeffrey P Weiss and Jerry G Blaivas* . . . . . 51
6. Urodynamics *Melissa C Fischer and Victor W Nitti* . . . . . 63
7. Urgency–frequency syndrome and pelvic pain, and interstitial cystitis *Harris E Foster Jr* . . 75
8. Pelvic floor muscle exercises and behavioral therapy *Kathryn L Burgio and Diane F Borello-France* . . . . . 87

**Pharmacology**

9. Overactive bladder: basic pharmacology *Karl-Erik Andersson* . . . . . 97
10. Drug delivery and intravesical instillation *Pradeep Tyagi and Michael B Chancellor* . . . . . 115
11. Pioneering agents: immediate release *Philippe E Zimmern* . . . . . 125
12. Tricyclic antidepressants *Daniel Dugi and Gary E Lemack* . . . . . 139
13. Propiverine hydrochloride in the treatment of idiopathic and neurogenic detrusor overactivity: efficacy, tolerability, and safety profile *Manfred Stöhrer, Gerd Mürtz, Guus Kramer, and Herbert Rübben* . . . . . 145
14. Extended release oral oxybutynin *Rodney A Appell* . . . . . 163
15. Tolterodine in the management of overactive bladder *Jonathan S Starkman, Karl J Kreder, and Roger R Dmochowski* . . . . . 171
16. Trospium chloride *David R Staskin* . . . . . 189
17. Darifenacin *Christopher R Chapple* . . . . . 203
18. Solifenacin succinate *Karl J Kreder and Roger R Dmochowski* . . . . . 219
19. Transdermal oxybutynin (Oxytrol™) *G Willy Davila* . . . . . 229

20. Strategies for data comparison for drugs used in the treatment of overactive bladder
*Alan J Wein and Roger R Dmochowski* . . . . . 239

21. Pharmacotherapy of overactive bladder in bladder outlet obstruction
*Jonathan Sullivan and Paul Abrams* . . . . . 253

22. Botulinum toxin (Botox®) *Christopher P Smith and George T Somogyi* . . . . . 261

23. Acupuncture for treatment of overactive bladder *Mary P FitzGerald* . . . . . 277

24. Fesoterodine *Roger R Dmochowski and Karl J Kreder* . . . . . 283

**Neuromodulation**

25. Neuromodulation: mechanisms of action *Tomas L Griebling* . . . . . 293

26. Sacral nerve stimulation for overactive bladder symptoms
*Suzette E Sutherland and Steven W Siegel* . . . . . 303

27. The bion® microstimulator *Jerome L Buller and Kenneth M Peters* . . . . . 319

28. The Miniaturo™-I device: a new implantable electrostimulation system for the treatment of voiding dysfunction *Ruud Bosch* . . . . . 329

**Surgical therapy**

29. Transvaginal denervation *Jorge Arzola and R Duane Cespedes* . . . . . 339

30. Autoaugmentation *Jerilyn M Latini* . . . . . 345

31. Augmentation cystoplasty for overactive bladder *Anthony R Stone and Dana K Nanigian* . 359

**Special considerations**

32. Overactive bladder in children *Kenneth G Nepple and Christopher S Cooper* . . . . . 373

33. Geriatric population *Pat D O'Donnell* . . . . . 385

34. Late breaking information *Jean Jacques Wyndaele* . . . . . 395

# Contributors

**Paul Abrams** MD FRCS
Professor
Bristol Urological Institute
Southmead Hospital
Bristol
UK

**Karl-Erik Andersson** MD PhD
Professor
Wake Forest Institute for Regenerative Medicine
Wake Forest University School of Medicine
Winston Salem, NC
USA

**Rodney A Appell** MD FACS
Professor
Division of Voiding Dysfunction
Scott Department of Urology
Baylor College of Medicine
Houston, TX
USA

**Jorge Arzola** MD
Resident
Department of Urology (MCSU)
Wilford Hall Medical Center
Lackland AFB, TX
USA

**Jerry G Blaivas** MD
Professor
Weill-Cornell College of Medicine
Urocenter of New York
New York, NY
USA

**Diane F Borello-France** PT PhD
Associate Professor
Department of Physical Therapy
Rangos School of Health Sciences
Duquesne University
Pittsburgh, PA
USA

**Ruud Bosch** MD PhD
Professor and Chairman
Department of Urology
University Medical Center Utrecht
Utrecht
The Netherlands

**Jerome L Buller** MD FACOG
Lieutenant Colonel, Medical Corp, US Army
Division Director and Associate Fellowship Director, Female Pelvic Medicine and Reconstructive Surgery
Department of Obstetrics and Gynecology
Walter Reed Army Medical Center
Washington, DC
USA

**Kathryn L Burgio** PhD
Professor of Medicine
University of Alabama at Birmingham
Department of Medicine
Geriatric Research, Education, and Clinical Center
Birmingham VA Medical Center
Birmingham, AL
USA

**Linda Cardozo** MD FRCOG
Professor and Head
Department of Urogynaecology
King's College Hospital
London
UK

**Rufus Cartwright** MA MBBS
Senior Clinical Fellow
Department of Urogynaecology
King's College Hospital
London
UK

**R Duane Cespedes** MD
Associate Professor and Director
Female Urology and Urodynamics
Department of Urology (MCSU)
Wilford Hall Medical Center
Lackland AFB, TX
USA

**Michael B Chancellor** MD
Professor
Department of Urology
University of Pittsburgh
Pittsburgh, PA
USA

**Christopher R Chapple** MD FRCS (Urol)
Professor
Department of Urology
Royal Hallamshire Hospital
Sheffield
UK

**Christopher S Cooper** MD
Associate Professor
Department of Urology
Children's Hospital of Iowa
University of Iowa Hospitals and Clinics
Iowa City, IA
USA

**G Willy Davila** MD
Chairman
Department of Gynecology
Section of Urogynecology and Reconstructive Pelvic Surgery
Cleveland Clinic
Weston, FL
USA

**Roger R Dmochowski** MD
Professor
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN
USA

**Daniel Dugi** MD
Resident
Department of Urology
University of Texas
Southwestern Medical Center at Dallas
Dallas, TX
USA

**Melissa C Fischer** MD
Clinical Fellow
Department of Urology
New York University School of Medicine
New York, NY
USA

**Mary P FitzGerald** MD
Associate Professor
Division of Female Pelvic Medicine and Reconstructive Surgery
Loyola University Medical Center
Maywood, IL
USA

**Harris E Foster Jr** MD
Professor
Section of Urology
Yale University School of Medicine
New Haven, CT
USA

**Tomas L Griebling** MD FACS FGSA
Associate Professor and Vice-Chair
Department of Urology
The University of Kansas
The Landon Center on Aging
Kansas City, KS
USA

**William C de Groat** PhD
Professor of Pharmacology
Department of Pharmacology
University of Pittsburgh School of Medicine
Pittsburgh, PA
USA

**Guus Kramer**
Biophysicist
Kennemerbeekweg
Bennebroek
Netherlands

**Karl J Kreder** MD
Professor
Department of Urology
University of Iowa Hospitals and Clinics
Iowa City, IA
USA

**Jerilyn M Latini** MD
Assistant Professor
Department of Urology
University of Michigan
Ann Arbor, MI
USA

**Gary E Lemack** MD
Associate Professor
Department of Urology
University of Texas Southwestern
Medical Center at Dallas
Dallas, TX
USA

**Gerd Mürtz** MD
Medical Consultant of Apogepha
Arzneimittel GmbH
Dresden
Germany

**Dana K Narigian** MD
Resident
University of California Davis Medical Center
Sacramento, CA
USA

**Kenneth G Nepple** MD
Resident
Department of Urology
Children's Hospital of Iowa
University of Iowa Hospitals and Clinics
Iowa City, IA
USA

**Victor W Nitti** MD FACS
Associate Professor and Vice Chairman
Department of Urology
New York University School of Medicine
New York, NY
USA

**Pat D O'Donnell** MD
Professor
Division of Urology
Southern Illinois University School of Medicine
Springfield, IL
USA

**Kenneth M Peters** MD
Director of Research
Ministrelli Program for Urologic Research and
Education
Department of Urology
William Beaumont Hospital
Royal Oak, MI
USA

**Eric S Rovner** MD
Associate Professor
Department of Urology
Medical University of South Carolina
Charleston, SC
USA

**Herbert Rübben** MD PhD
Professor and Chairman
Department of Urology
University Hospital Essen
Essen
Germany

**Steven W Siegel** MD
Metro Urology
Centers for Continence Care and Female
Urology
St Paul, MN
USA

**Christopher P Smith** MD
Assistant Professor
Scott Department of Urology
Baylor College of Medicine
Houston, TX
USA

**George T Somogyi** MD PhD
Professor and Director
Neurourology Laboratory
Scott Department of Urology
Baylor College of Medicine
Houston, TX
USA

**Jonathan S Starkman** MD
Clinical Instructor
Department of Urologic Surgery
Vanderbilt University Medical Center
Nashville, TN
USA

**David R Staskin** MD
Associate Professor and Director
Female Urology and Urodynamics
Weill-Cornell Medical College
New York, NY
USA

**Manfred Stöhrer** MD PhD
Professor and Consultant
Department of Urology
University of Essen
Essen
Germany

**Anthony R Stone** MD
Professor
Department of Urology
University of California Davis Medical Center
Sacramento, CA
USA

**Jonathan Sullivan**
Consultant
Department of Urology
Worcestershire Acute Hospitals NHS Trust
Kidderminister
UK

**Suzette E Sutherland** MD
Metro Urology
Centers for Continence Care and Female Urology
St Paul, MN
USA

**Elizabeth B Takacs** MD
Assistant Professor
Department of Urology
University of Iowa Hospitals and Clinics
Iowa City, IA
USA

**Pradeep Tyagi** MSc PhD
Postdoctoral Fellow
Department of Urology
University of Pittsburgh
Pittsburgh, PA
USA

**Melissa Walls** MD
Resident
Department of Urology
Medical University of South Carolina
Charleston, SC
USA

**Alan J Wein** MD PhD (HON)
Professor and Chief
Division of Urology
University of Pennsylvania
Philadelphia, PA
USA

**Jeffrey P Weiss** MD
Weill-Cornell College of Medicine
Urocenter of New York
New York, NY
USA

**Jean Jacques Wyndaele** MD DSci PhD FEBU FISCOS
Professor and Chair
Department of Urology
University of Antwerp
Belgium

**Philippe E Zimmern** MD FACS
Professor
Department of Urology
University of Texas Southwestern Medical Center at Dallas
Dallas, TX
USA

# Foreword

The overactive bladder is *not* a new disease or a term invented for those wishing to sell pills to patients. The term was coined by Alan Wein and myself when we were asked to organize a meeting on "The Unstable Bladder" on an unrestricted educational grant by Pharmacia in 1996.[1] We pointed out that unstable bladder was a urodynamic diagnosis and we usually treated patients with the symptoms of frequency, urgency, urgency incontinence and nocturia without a urodynamics diagnosis, in the first instance. We also pointed out that we wished to include discussion of patients with neurological disease, who would be excluded by the term "unstable bladder", as this only applied to those without an obvious cause for their detrusor overactivity. Pharmacia were most unhappy about our insistence on using the term "overactive bladder" as the title for the meeting. This was because Pharmacia only had "unstable bladder" as an indication for the use of their antimuscarinic drug. Nevertheless, Alan and I insisted and Pharmacia acquiesced. Subsequently, the term has become accepted worldwide and is, of course, used to market all products for the condition. The origin of the term overactive bladder is described in an article in Urology[2].

Once the term was coined it had to be defined, and after several iterations the ICS (2002) Standardisation Report defined the overactive bladder as urgency, with or without urgency incontinence, usually with frequency and nocturia.[3] It was also necessary to exclude other conditions such as urinary infection and inadequately controlled diabetes as causes of the same symptoms. However, despite these definitions which are essentially medical, there is still a need for clarity of thought when looking at these definitions in patient terms. It is confusing to patients to talk about urge and urgency and furthermore, it is unnecessary. The ICS (2002) suggested that urge means need and therefore is easily confused with urgency, and should not be used. There is very little point in asking patients whether they have urgency or urgency incontinence. Of much more use are questions such as "do you have to drop everything and rush to the toilet, otherwise you might leak urine?"

Karl Kreder and Roger Dmochowski are to be complimented on assembling this comprehensive book on Overactive Bladder (OAB) written by a distinguished group of clinicians and scientists. Unusually for a text book, it includes not only accepted treatments but also discusses new treatments, still in the development stage, such as implanted pudendal nerve stimulation and the new antimuscarinic fesoterodine. The inclusion of chapters on particularly problematic patient groups, such as children and the elderly, is most welcome, as the importance and implications of OAB in these two important sections of our society are greater than for independently living young to middle aged adults.

The book is an excellent update on Overactive Bladder, the theories behind its genesis, its assessment and its management from behavioural therapy to augmentation cystoplasty.

Paul Abrams MD FRCS
Professor of Urology
Bristol Urological Institute
Bristol
UK

## REFERENCES

1. Abrams P, Wein AW. The overactive bladder. Urology 50, Suppl. 6A.
2. Abrams P. Describing bladder storage function: overactive bladder syndrome and detrusor overactivity. Urology 2003; 62 (Suppl. 5B): 28–37.
3. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Subcommittee of the International Continence Society. Neurourol Urodynam 2002; 21: 167–178.

# Acknowledgments

The editors would like to thank Kristina K. Greiner for her editorial assitance.

# Introduction

# 1

# Nomenclature

Jerry G Blaivas

**Introduction • Lower urinary tract symptoms**

## INTRODUCTION

There are two basic methods by which the meanings of words are defined – by common usage and by standardizing committee. Usage is the method that was employed in the compilation of the first edition of the *Oxford English Dictionary*. The brainchild of a passionate and indefatiguable Scotsman named James Murray who devoted nearly his entire adult life to it, the *Oxford English Dictionary* was completed in 1928 after an incredible 49 years of research.[1] The scientific methodology employed to develop this dictionary is worth considering. Thousands of volunteer readers were assigned individual words to research. In a systematic way, each reader searched out his word in contemporary and ancient writings. Each time a word was identified in a text, a citation was generated which consisted of the word and the complete sentence in which it was used. Murray and his associates meticulously read each citation and compiled all of the possible definitions for each word, based on the way the words were actually used.

Another approach to defining the meaning of words is to assign a single, very specific, unique definition to each word. In theory, this serves the interest of science so that there can be no ambiguity in experimental observations, studies, and reports. However, contextual differences and subtleties may not be completely captured when definitions are so specific.

The International Continence Society (ICS) has used the latter approach in defining overactive bladder (OAB) and many other terms.[2,3] According to the ICS, lower urinary tract dysfunction is comprised of symptoms, signs, urodynamic observations, and conditions.[3,4] *Signs* are observed by the physician by simple means (e.g. observation of the loss of urine with a cough), or by the use of diaries, pad tests, symptom scores, and validated quality of life instruments. *Urodynamic observations* are made during urodynamic studies and reflect the definitive pathophysiological *condition* that is causing the symptom (e.g. detrusor overactivity or sphincter weakness causing incontinence). When a condition cannot be documented by urodynamic observation, it may be "presumed" by clinical documentation.[4] All definitions cited conform to ICS standards except when specifically stated to be otherwise.

## LOWER URINARY TRACT SYMPTOMS

Lower urinary tract symptoms are composed of three groups: storage, voiding, and postmicturition. *Storage symptoms* include *increased daytime frequency, dysuria* (pollakisuria), *nocturia* (waking one or more times to void at night), *urgency* (a sudden compelling desire to pass urine, which is difficult to defer), and *urinary incontinence* (the involuntary leakage of urine).

Urinary incontinence is further subdivided into the following eight categories:

1. *Stress incontinence*: involuntary leakage on effort or exertion, or on sneezing or coughing. The sign of stress incontinence is the

observation of urine loss from the urethra during coughing or straining. There are two conditions that may cause stress incontinence – sphincteric weakness and stress hyperreflexia. *Stress hyperreflexia* is a term abandoned by the ICS that describes incontinence due to an involuntary detrusor contraction precipitated by a sudden increase in abdominal pressure. *Urodynamic stress incontinence,* as defined by the ICS, is the involuntary leakage of urine during increased abdominal pressure, in the absence of a detrusor contraction. However, we believe the terms *stress hyperreflexia* and *urodynamic sphincteric incontinence* are more appropriate. There are various urodynamic measurements of sphincteric function (see Chapter 6), but the condition stress incontinence can be diagnosed on physical examination alone.

2. *Urge incontinence*: involuntary leakage accompanied by or immediately preceded by urgency.
3. *Mixed urinary incontinence*: involuntary leakage associated with urgency and also with exertion, effort, sneezing, or coughing.
4. *Enuresis*: synonymous with incontinence.
5. *Nocturnal enuresis*: loss of urine occurring during sleep.
6. *Continuous urinary incontinence*: continuous leakage.
7. *Unconscious (unaware) incontinence* is a term not addressed by the ICS, but is the involuntary loss of urine that is unaccompanied by either urge or stress. The patient has no awareness of the actual moment of urinary loss, but rather just finds himself wet.[4]
8. *Overflow incontinence* is not a symptom or condition, but rather a term used to describe leakage of urine associated with urinary retention.

*Voiding symptoms* include the following six symptoms:

- slow stream
- splitting or spraying of the urine stream
- intermittent stream (intermittency)
- hesitancy: difficulty in initiating micturition resulting in a delay in the onset of voiding after the individual is ready to pass urine
- straining to void.
- terminal dribble is the term used when an individual describes a prolonged final part of micturition, when the flow has slowed to a trickle/dribble.

*Post-micturition symptoms* are self-explanatory and include (1) feeling of incomplete emptying; and (2) post-micturition dribble.

*Bladder sensation* can be defined, during history taking, by five categories:

1. *Normal*: the individual is aware of bladder filling and increasing sensation up to a strong desire to void.
2. *Increased*: the individual feels an early and persistent desire to void.
3. *Reduced*: the individual is aware of bladder filling but does not feel a definite desire to void.
4. *Absent*: the individual reports no sensation of bladder filling or desire to void.
5. *Non-specific*: the individual reports no specific bladder sensation, but may perceive bladder filling as abdominal fullness, vegetative symptoms, or spasticity.

*Overactive bladder* (OAB) is defined by the ICS as "urgency, with or without urge incontinence, usually with frequency and nocturia . . . if there is no proven infection or other etiology." More specifically, the ICS refers to this constellation of symptoms as the "overactive bladder syndrome . . . These symptom combinations are suggestive of urodynamically demonstrable detrusor overactivity, but can be due to other forms of urethrovesical dysfunction. These terms can be used if there is no proven infection or other obvious pathology. Urge syndrome or urgency–frequency syndrome are described as synonyms of OAB."[3]

Since urgency (a sudden compelling desire to pass urine, which is difficult to defer) is the sine qua non for a diagnosis of OAB, we shall begin our discussion with its definition. In a position paper, Chapple et al.[5] specifically stated that, "it is important to differentiate between 'urge' which is a normal physiologic sensation, and urgency which we consider pathological. Central to this distinction is the debate over whether urgency is merely an extreme form of 'urge.' If this was a continuum, then normal people could experience urgency, but in the model we propose,

urgency is always abnormal." This distinction between urge and urgency, though, is based on the authors educated opinion, and alternative explanations may also be operational. First, as defined, urgency is an all or none phenomenon; there can be no gradations of "a sudden compelling desire to void". In contradistinction, others believe that there are gradations of urgency and, to this end, a proposed grading system has evolved,[6] the Urge Perception Scale (UPS), which is based on the original work of DeWachter and Wyndaele.[7] The UPS (Table 1.1) describes the reason why a person voids. Grade 4 urgency is identical to the ICS definition, but grade 3 may also be considered under the rubric of urgency and, in some circumstances, grade 2 might also be considered as such. The UPS may be used in a number of ways – to grade the degree of urge that a person usually experiences prior to voiding, as a method of grading each micturition (as part of a bladder diary), or as a nomenclature for describing symptoms, e.g. the patient experiences type 3 urgency. The UPS implies that the sensations that lead to micturition are, in fact, a continuum, and that once the urge to void is felt, if one waits too long, one will experience the same sensation (except for the sudden onset) that is perceived as urgency according to the ICS definition.

Even the ICS standardization document itself recognizes that urgency may be graded. In the discussion of the bladder diary, it states that the "bladder diary . . . records the times of micturitions and voided volumes . . . and other information such as . . . the degree of urgency . . ." At the present time, the only other validated instrument that is designed to grade urgency is the Urgency Severity Score (USS).[8,9] The USS grades urgency, per toilet void, as none, mild, moderate, or severe, and, by implication, supports the contention that the sensations describing the urge to void are a continuum.

**Table 1.1 The Urge Perception Scale**

*What is the reason you usually urinate?*

| | |
|---|---|
| Grade 0: | Out of convenience? (no urge) |
| Grade 1: | Mild urge (can hold > 1 hour) |
| Grade 2: | Moderate urge (can hold > 10–60 min) |
| Grade 3: | Severe urge (can hold < 10 min) |
| Grade 4: | Desperate urge (must go immediately) |

These proposed scales may prove to be more clinically useful than the simple yes/no ICS definition of urgency as "a sudden compelling desire to void", whether or not urgency is on a continuum with the normal desire to void. For example, if a person experiences the gradual onset of a strong desire to void over the course of 1 hour after his last micturition, and the volume of urine in his bladder is 60 ml, it might seem reasonable to propose that that sensation is pathologic and should be considered a severe symptom, yet it does not conform to the current definition of urgency (and there is no other word that conveys this meaning).

The definition of OAB requires that there is "no proven infection or other pathology". This implies that if there is an underlying pathology that causes the symptoms, the condition is not OAB. For example, the majority of men with prostatic obstruction have exactly the same symptoms as described for OAB, but since there is "other pathology", the term OAB does not apply. This is much more than a semantic argument; it has important medical implications. If one considers OAB a syndrome, it presupposes that there is no underlying pathology and no differential diagnosis to consider until such time as empiric treatment has proved ineffective. But there is a differential diagnosis for these symptoms and we believe that a proper evaluation should be undertaken to discover them in a timely fashion. Most algorithms for overactive bladder recommend a basic evaluation to consist of a focused history and examination, bladder diary, and urinalysis. A more detailed diagnostic evaluation is only recommended after treatment failure or if there is microhematuria or an obviously elevated residual urine.[10,11]

Consider the following scenario. A patient presents with OAB and has a normal urinalysis. He or she could be empirically treated with behavior modification for 4–6 weeks followed by each of the six commercially available antimuscarinics for 4–6 weeks each for a total of 7 months of unsuccessful treatment before being considered a treatment failure. Only then would a proper

evaluation be done and a differential diagnosis be considered. There is, in fact, a well known differential diagnosis for OAB symptoms, the most important of which is bladder cancer (even without hematuria) and, in our judgment, 7 months is simply too long to wait to diagnose bladder cancer. For this reason, we believe that OAB should be considered a symptom complex (with a differential diagnosis) and not a syndrome.

The OAB symptom complex can be caused by one or more of the following conditions: detrusor overactivity, sensory urgency, and low bladder compliance. *Sensory urgency* is a term abandoned by the ICS that refers to an uncomfortable need to void that is unassociated with detrusor overactivity (see below). Conditions causing and/or associated with OAB are diverse, as depicted in Table 1.2.[12–21] In patients with OAB, diagnostic evaluation should be directed at early detection of these conditions, because in many instances the symptoms are reversible if the underlying etiology is successfully treated.

*Detrusor overactivity* is a generic term that refers to the presence of involuntary detrusor contractions during cystometry, which may be spontaneous or provoked. The ICS further describes two patterns of detrusor overactivity: terminal and phasic. *Terminal detrusor overactivity* is defined as a single involuntary detrusor contraction occurring at cystometric capacity, which cannot be suppressed, and results in incontinence, usually resulting in bladder emptying (Figure 1.1). *Phasic detrusor overactivity* is defined by a characteristic waveform, and may or may not lead to urinary incontinence (Figure 1.2). Involuntary detrusor contractions are not always accompanied by sensation. Some patients have no symptoms at all. Others void uncontrollably without any awareness. Still others may detect them as a first sensation of bladder filling, or a normal desire to void. The ICS classifies detrusor overactivity as either *idiopathic* or *neurogenic*. In the prior ICS standardization report these were referred to as *detrusor instability and detrusor hyperreflexia* respectively. Further, according to the previous ICS terminology, a bladder that did not exhibit involuntary detrusor contractions could be described as a *stable bladder.* The new terminology offers no word to replace a stable bladder other than "bladder without detrusor overactivity", and therefore this term may still have clinical utility.

**Table 1.2 Causes of detrusor overactivity**

| | |
|---|---|
| I | *Idiopathic detrusor overactivity* |
| II | *Neurogenic detrusor overactivity* |
| | Supraspinal neurological lesions |
| | stroke |
| | Parkinson's disease |
| | hydrocephalus |
| | brain tumor |
| | traumatic brain injury |
| | multiple sclerosis |
| | Suprasacral spinal lesions |
| | spinal cord injury |
| | spinal cord tumor |
| | multiple sclerosis |
| | myelodysplasia |
| | transverse myelitis |
| | Diabetes mellitus |
| III | *Non-neurogenic detrusor overactivity* |
| | Bladder infection |
| | Bladder outlet obstruction |
| | men – prostatic and bladder neck, stricture |
| | women – pelvic organ prolapse, post-surgical, urethral, diverticulum, primary bladder neck, stricture |
| | Bladder tumor |
| | Bladder stones |
| | Foreign body |
| Aging | |

By definition, neurogenic and idiopathic detrusor overactivity are distinguished not by specific symptoms or urodynamic characteristics, but rather by the presence or absence of an identified or previously diagnosed neurological lesion or disorder. For example, a spinal cord injury patient with involuntary bladder contractions is said to have neurogenic detrusor overactivity (detrusor hyperreflexia), whereas an elderly male with such a finding associated with prostatic obstruction is said to have idiopathic detrusor overactivity (detrusor instability). While in some cases the origin of the involuntary detrusor contractions is unknown, in other cases they are caused by, or at least associated with, a variety

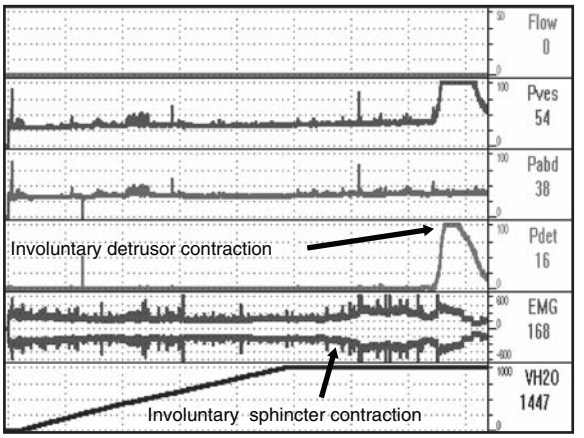



**Figure 1.1** Terminal detrusor overactivity in a man with type 1 detrusor external sphincter dyssynergia (EMG relaxes after onset of detrusor contraction). During this examination he was incontinent and voided to completion, but the examination was performed in the supine position, so uroflow was not measured. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography; VH20, infused bladder volume. (See also color plate section).

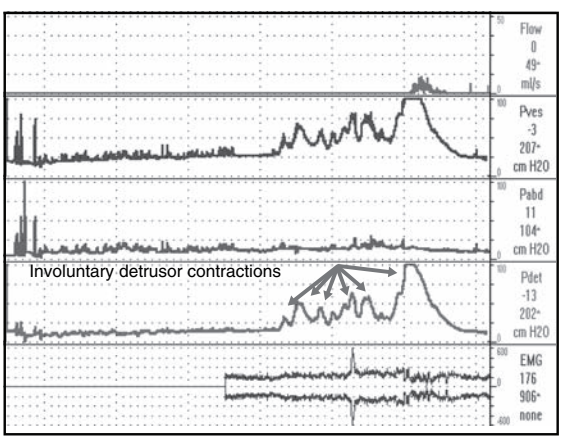



**Figure 1.2** Phasic detrusor overactivity in a 53-year-old man with prostatic obstruction. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography. (See also color plate section).

of non-neurogenic clinical conditions, the same as listed above for overactive bladder.

A *urodynamic OAB classification* based on the presence of detrusor overactivity, patient awareness, and ability to abort the involuntary contraction

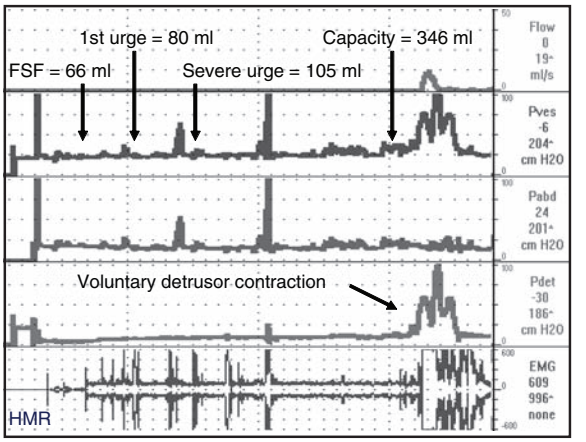



**Figure 1.3** Type 1 overactive bladder (OAB). This is a 54-year-old woman with mild exacerbating–remitting multiple sclerosis who complains of urinary frequency, urgency and urge incontinence. *Urodynamic tracing:* first sensation of bladder filling (FSF) = 66 ml, 1st urge = 80 ml; severe urge = 105 ml; bladder capacity = 346 ml. Although she complains of urge incontinence, there are no involuntary detrusor contractions and she had a voluntary detrusor contraction at 346 ml. The apparent increase in EMG activity during the detrusor contraction is artifact. Unintubated maximum uroflow ($Q_{max}$) = 20 ml/s. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography. (See also color plate section).

was recently proposed.[22] The authors defined four types of OAB. In type 1, the patient complains of OAB symptoms, but no involuntary detrusor contractions are demonstrated (Figure 1.3). In type 2, there are involuntary detrusor contractions, but the patient is aware of them and can voluntarily contract his or her sphincter, prevent incontinence, and abort the detrusor contraction (Figure 1.4). In type 3, there are involuntary detrusor contractions, the patient is aware of them and can voluntarily contract his or her sphincter and momentarily prevent incontinence, but is unable to abort the detrusor contraction, and once the sphincter fatigues, incontinence ensues (Figure 1.5). In type 4, there are involuntary detrusor contractions, but the patient is neither able to voluntarily contract the sphincter nor abort the detrusor contraction and simply voids involuntarily (Figure 1.6). This classification system serves two purposes. First, it is a shorthand method of describing the urodynamic

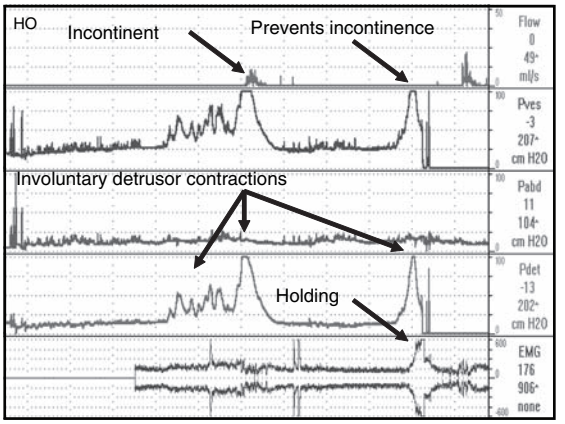



**Figure 1.4** Type 2 overative bladder (OAB) and prostatic obstruction in a 53-year-old man with a 20-year history of refractory urgency, urge incontinence, and enuresis. *Urodynamic tracing*. During bladder filling he is instructed to neither void nor prevent micturition and to report his sensations to the examiner. There are a series of poorly sustained involuntary detrusor contractions (arrows) that he perceives as a severe urge to void and then there is a sustained voiding contraction whence he relaxes his sphincter and is incontinent. The bladder is filled again and there is another involuntary detrusor contraction. This time he is instructed to try to hold. He contracts his sphincter, obstructing the urethra, the detrusor contraction subsides, and he is not incontinent. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography. (See also color plate section).

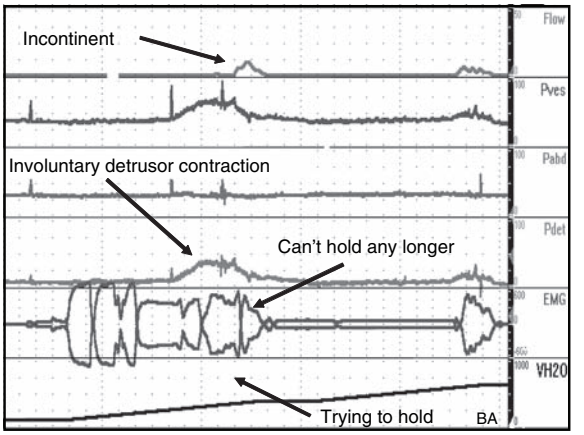



**Figure 1.5** Type 3 overactive bladder (OAB) in a 42-year-old woman with refractory urge incontinence. *Urodynamic study*. A strong urge is felt at a bladder volume of 50 ml and she contracts her sphincter to prevent incontinence. At a volume of 275 ml, she develops an involuntary detrusor contraction and is able to continue contracting her sphincter, preventing incontinence. At 350 ml, she can no longer hold and she voids involuntarily. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography; VH20, infused bladder volume. (See also color plate section).

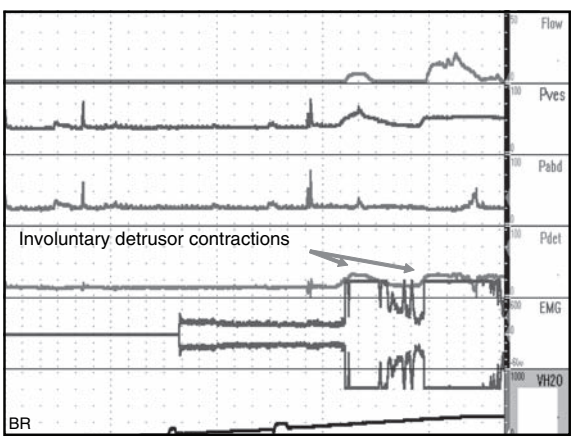



**Figure 1.6** Type 4 overactive bladder (OAB) in an otherwise normal woman with refractory urge incontinence. *Urodynamic tracing*. There are two involuntary detrusor contractions; each time she voids involuntarily without control. The apparent increase in EMG activity is artifact, likely due to poor contact of the EMG electrodes, possibly due to urine leakage. Flow, uroflow; Pves, vesical pressure; Pabd, abdominal pressure; Pdet, detrusor pressure; EMG, sphincter electromyography; VH20, infused bladder volume. (See also color plate section).

characteristics of the OAB patient. Second, it provides a substrate for therapeutic decision making. For example, a patient with type 1 and 2 OAB exhibits normal neural control mechanisms and, at least theoretically, is an excellent candidate for behavioral therapy. It is likely that over time (with or without treatment), an individual patient can change from one type to another. Further, this classification only relates to the storage stage and can coexist with normal voiding, bladder outlet obstruction, and/or impaired detrusor contractility.

*Low bladder compliance* denotes an abnormal volume–pressure relationship, in which there is a high incremental rise in detrusor pressure during bladder filling. It can only be diagnosed by cystometry.

In conclusion, "words are the building blocks of language and the principal means by which

we communicate with one another. Some words convey their meaning with uniform precision and understanding; others lead to confusion and controversy."[23] Choose the words that best fit your needs.

## REFERENCES


1. Winchester S. The Professor and the Madman. New York: Harper Collins, 1998.
2. Abrams P, Blaivas JG, Stanton SL, Andersen JT. Standardisation of terminology of lower urinary tract function. Neurourol Urodyn 1988; 7: 403–26.
3. Abrams P, Cardozo L, Fall M et al. The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002; 21: 167–78.
4. Blaivas JG, Appell RA, Fantl JA et al. Standards of efficacy for evaluation of treatment outcomes in urinary incontinence: recommendations of the Urodynamic Society. Neurourol Urodyn 1997; 16: 145–7.
5. Chapple CR, Artibani W, Cardoza LD et al. The role of urinary urgency and its measurement in the overactive bladder symptom syndrome: current concepts and future prospects. BJU Int 2005; 95: 335–40.
6. Blaivas JG, Panagopoulos G, Weiss JP, Somaroo C, Chaikin DC. The urgency perception score: validation and test re-test. J Urol 2007; 177: 199–202.
7. DeWachter S, Wyndaele JJ. Frequency-volume charts: a tool to evaluate bladder sensation. Neurourol Urodyn 2003; 22: 638–43.
8. Nixon A, Colman S, Sabounjian L et al. A validated patient reported measure of urinary urgency severity in overactive bladder for use in clinical trials. J Urol 2005; 174: 604–07.
9. Zinner N, Harnett M, Sabounjian L et al. The overactive bladder-symptom composite score: a composite symptom score of toilet voids, urgency severity and urge urinary incontinence in patients with overactive bladder. J Urol 2005; 173: 1639–43.
10. Abrams P, Andersson K, Brubaker T et al. Evaluation and treatment of urinary incontinence, pelvic organ prolapse, and faecal incontinence. In: Abrams P, Cardozo L, Khoury S, Wein A. Incontinence. Plymouth, UK: Health Publication Ltd, 2005: 1589–631.
11. Agency for Health Care Policy and Research Urinary Incontinence Guideline Panel. Urinary Incontinence in Adults: Clinical Practice Guidelines (AHCPR publication #92-0038). Rockville, MD: US Department of Health and Human Services, 1992.
12. Awad SA, McGinnis RH. Factors that influence the incidence of detrusor instability in women. J Urol 1983; 130: 114–15.
13. Blaivas JG. The neurophysiology of micturition. J Urol 1982; 127: 958–63.
14. Kaplan SA, Chancellor MB, Blaivas JG. Bladder and sphincter behavior in patients with spinal cord injuries. J Urol 1991; 146: 113–17.
15. Chou ECL, Flisser AJ, Panagopoulos G, Blaivas JG. Effective treatment for mixed incontinence with a pubovaginal sling. J Urol 2003; 170: 494–7.
16. Fusco F, Groutz A, Blaivas JG, Chaikin DC, Weiss JP. Videourodynamic studies in men with lower urinary tract symptoms: a comparison of community based versus referral urological practices. J Urol 2001; 166: 910–13.
17. Groutz A, Blaivas JG, Chaikin DC. Bladder outlet obstruction in women: definition, prevalence and characteristics. Neurourol Urodyn 2000; 19: 213–20.
18. Groutz A, Blaivas JG, Sassone AM. Detrusor pressure – uroflow studies in women: effect of a 7f transurethral catheter. J Urol 2000; 164: 109–14.
19. Hebjorn S, Andersen JT, Walter S, Dam AM. Detrusor hyperreflexia: a survey on its etiology and treatment. Scand J Urol Nephrol 1976; 10: 103–9.
20. Resnick NM, Yalla SV, Laurino E. The pathophysiology of urinary incontinence among institutionalized elderly persons. N Engl J Med 1989; 320: 1–7.
21. Romanzi LJ, Groutz A, Heritz DM, Blaivas JG. Involuntary detrusor contractions: correlation of urodynamic data to clinical categories. Neurourol Urodyn 2001; 20: 249–57.
22. Flisser AJ, Wamsley K, Blaivas JG. Urodynamic classification of patients with symptoms of overactive bladder. J Urol 2003; 169: 529–33.
23. Blaivas JG. Detrusor instability and other "words" [Editorial]. Neurourol Urodyn 1982; 2: 125.

# 2

# The neurophysiology of lower urinary tract function

William C de Groat

**Introduction • Innervation of the lower urinary tract • Urothelium • Anatomy of central nervous pathways controlling the lower urinary tract • Reflex control of the lower urinary tract • Neurotransmitters in central micturition reflex pathways • Conclusions**

## INTRODUCTION

The functions of the lower urinary tract to store and periodically release urine are dependent upon neural circuitry in the brain and spinal cord. This dependence on central nervous control distinguishes the lower urinary tract from many other visceral organs that maintain a certain level of activity even after the elimination of extrinsic neural input. The lower urinary tract is also unusual in regard to the complexity of its neural regulation. For example, micturition depends on the integration of autonomic and somatic efferent mechanisms within the lumbosacral spinal cord. This is necessary to coordinate the activity of visceral organs (the bladder and urethra) with that of urethral striated muscles. In addition, micturition is under voluntary control and depends upon learned behavior that develops during maturation of the nervous system, whereas many other visceral functions are regulated involuntarily. This chapter will review the peripheral and central neural mechanisms controlling the lower urinary tract.

## INNERVATION OF THE LOWER URINARY TRACT

The storage and elimination of urine are dependent upon the coordinated activity of two functional units in the lower urinary tract: (1) a reservoir (the urinary bladder) and (2) an outlet, consisting of bladder neck, urethra, and striated muscles of the urethral sphincter.[1,2] These structures are, in turn, controlled by three sets of peripheral nerves: sacral parasympathetic (pelvic nerves), thoracolumbar sympathetic (hypogastric nerves and sympathetic chain), and sacral somatic nerves (pudendal nerves) (Figure 2.1).

### Sacral parasympathetic pathways

The sacral parasympathetic outflow provides the major excitatory input to the urinary bladder. Cholinergic preganglionic neurons located in the intermediolateral region of the sacral spinal cord send axons via the pelvic nerves to ganglion cells in the pelvic plexus and in the wall of the bladder. Transmission in bladder ganglia is mediated by a nicotinic, cholinergic mechanism, which can be modulated by the activation of various receptors including muscarinic, adrenergic, purinergic, and peptidergic (Table 2.1).[3] The ganglion cells in turn excite bladder smooth muscle via the release of cholinergic (acetylcholine) and non-adrenergic, non-cholinergic transmitters. Cholinergic excitatory transmission in the bladder is mediated by muscarinic receptors,[4–6] whereas non-cholinergic excitatory transmission is mediated by adenosine triphosphate (ATP), acting on P2X purinergic

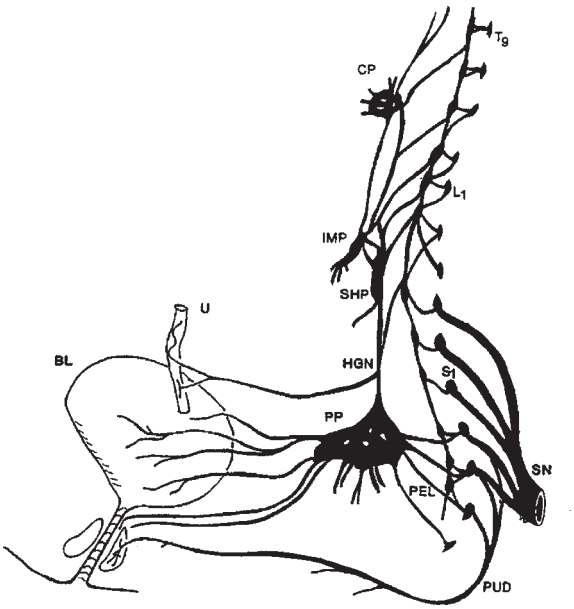



**Figure 2.1** Diagram showing the innervation of the female lower urinary tract. BL, urinary bladder; CP, celiac plexus; HGN, hypogastric nerve; IMP, inferior mesenteric plexus; $L_1$, first lumbar root; PEL, pelvic nerves; PP, pelvic plexus; PUD, pudendal nerve; $S_1$, first sacral root; SN, sciatic nerve; SHP, superior hypogastric plexus; $T_9$, ninth thoracic root; U, ureter.

receptors (Table 2.1).[5,7] Inhibitory input to the urethral smooth muscle is mediated by nitric oxide released by parasympathetic nerves.[2] Both $M_2$ and $M_3$ muscarinic receptor subtypes are expressed in bladder smooth muscle; however, the $M_3$ subtype is the principal receptor involved in excitatory transmission. Muscarinic receptors are also present prejunctionally on parasympathetic nerve terminals.[8] Activation of these receptors by acetylcholine can enhance ($M_1$ receptors) or suppress ($M_4$ receptors) transmitter release, depending upon the intensity of neural firing. Postganglionic neurons innervating the bladder also contain neuropeptides, such as vasoactive intestinal polypeptide (VIP) and neuropeptide Y (NPY). These substances are coreleased with acetylcholine or ATP and may function as modulators of neuroeffector transmission.

### Thoracolumbar sympathetic and sacral somatic efferent pathways

Sympathetic pathways to the lower urinary tract that originate in the lumbosacral sympathetic chain ganglia as well as in the prevertebral inferior mesenteric ganglia pass to the bladder via the hypogastric and pelvic nerves. Sympathetic efferent pathways elicit various effects including: (1) inhibition of detrusor muscle via β-adrenergic receptors; (2) excitation of the bladder base and urethra via $\alpha_1$-adrenergic receptors; and (3) inhibition and facilitation in bladder parasympathetic ganglia via $\alpha_2$- and $\alpha_1$-adrenergic receptors, respectively (Table 2.1).[2,3,5]

The efferent innervation of the urethral striated muscles in various species originates from cells in a circumscribed region of the lateral ventral horn that is termed Onuf's nucleus.[9] Sphincter motoneurons send their axons into the pudendal nerve and excite sphincter muscles via the release of acetylcholine which stimulates postjunctional nicotinic receptors.

### Afferent pathways

Afferent axons innervating the urinary tract originate in the lumbosacral dorsal root ganglia and pass through the three sets of peripheral nerves.[2] The most important afferents for initiating micturition are those passing in the pelvic nerve to the sacral spinal cord. Two types of bladder afferents have been identified: small myelinated (Aδ) and unmyelinated (C) fibers. Aδ bladder afferents in the cat respond in a graded manner to passive distention as well as active contraction of the bladder, and exhibit pressure thresholds in the range of 5–15 mmHg, which are similar to those pressures at which humans report the first sensation of bladder filling.[2] These fibers also code for noxious stimuli in the bladder. On the other hand, C-fiber bladder afferents in the cat have very high thresholds and commonly do not respond to even high levels of intravesical pressure. However, activity in some of these afferents is unmasked or enhanced by chemical irritation of the bladder mucosa. Thus, C-fiber afferents seem to have specialized functions, such as the signaling of inflammatory or noxious events in the lower urinary tract. A large percentage of bladder afferent neurons contain neuropeptides, raising the possibility that these substances may be transmitters in the afferent pathways from the lower urinary tract.[2,10,11] C-fiber afferents are sensitive to the neurotoxins capsaicin and resiniferatoxin as well as to other substances

**Table 2.1 Receptors for putative transmitters in the lower urinary tract**

| *Tissue* | *Cholinergic* | *Adrenergic* | *Other* |
|---|---|---|---|
| Bladder body | + ($M_2$)<br>+ ($M_3$) | − ($\beta_2$)<br>− ($\beta_3$) | + Purinergic ($P2X_1$)<br>− VIP<br>+ Substance P ($NK_2$) |
| Bladder base | + ($M_2$)<br>+ ($M_3$) | + ($\alpha_1$) | − VIP<br>+ Substance P ($NK_2$)<br>+ Purinergic (P2X) |
| Urothelium | + ($M_2$)<br>+ ($M_3$) | + ($\alpha$)<br>+ ($\beta$) | + TRPV1<br>+ TRPM8<br>+ (P2X)<br>+ (P2Y)<br>+ Substance P<br>+ Bradykinin (B2) |
| Urethra | + (M) | + ($\alpha_1$)<br>+ ($\alpha_2$)<br>− ($\beta$) | + Purinergic (P2X)<br>− VIP<br>− Nitric oxide |
| Sphincter striated muscle | + (N) | | |
| Adrenergic nerve terminals | − ($M_4$)<br>+ ($M_1$) | − ($\alpha_2$) | − NPY |
| Cholinergic nerve terminals | − ($M_4$)<br>+ ($M_1$) | + ($\alpha_1$) | − NPY |
| Afferent nerve terminals | | | + Purinergic ($P2X_{2/3}$)<br>+ TRPV1 |
| Ganglia | + (N)<br>+ ($M_1$) | + ($\alpha_1$)<br>− ($\alpha_2$)<br>+ ($\beta$) | − Enkephalinergic ($\delta$)<br>− Purinergic ($P_1$)<br>+ Substance P |

VIP, vasoactive intestinal polypeptide; NPY, neuropeptide Y; TRP, transient receptor potential. Letters in parentheses indicate receptor type, e.g. M (muscarinic) and N (nicotinic). Plus and minus signs indicate excitatory and inhibitory effects.

(tachykinins, nitric oxide, ATP, prostaglandins, and neurotrophic factors) released in the bladder.[10–12] These substances can sensitize the afferent nerves and change their response to mechanical stimuli. Intravesical administration of ATP en-hances the firing of bladder afferent nerves by acting on $P2X_3$ or $P2X_{2/3}$ receptors on afferent terminals within or adjacent to the urothelium.[13,14]

The properties of lumbosacral dorsal root ganglion cells innervating the bladder, urethra, and external urethral sphincter in the rat have been studied with patch clamp recording techniques.[15,16] Based on responsiveness to capsaicin it is estimated that approximately 70% of bladder afferent neurons in the rat are of the C-fiber type. Approximately 90% of the bladder C-fiber afferent neurons are also excited by ATP.[2] C-fiber bladder afferent neurons also express a slowly decaying A-type $K^+$ current that controls spike threshold and firing frequency.[15] Suppression of this $K^+$ current by drugs or chronic bladder inflammation induces hyperexcitability of the afferent neurons.[15]

## UROTHELIUM

The urothelium, which has been traditionally viewed as a passive barrier, also has specialized sensory and signaling properties that allow it to respond to chemical and mechanical stimuli and to engage in reciprocal chemical communication with neighboring nerves in the bladder wall (Figure 2.2).[1,2,17–20] These properties include: (1) expression of nicotinic, muscarinic, tachykinin, adrenergic, and capsaicin (TRPV1) receptors;

(2) responsiveness to transmitters released from sensory nerves; (3) close physical association with afferent nerves; and (4) the ability to release chemical mediators such as ATP and nitric oxide that can regulate the activity of adjacent nerves and thereby trigger local vascular changes and/or reflex bladder contractions.[13,17–22]

The role of ATP in urothelial-afferent communication has attracted considerable attention because bladder distention releases ATP from the urothelium[19] and intravesical administration of ATP induces bladder hyperactivity, an effect blocked by administration of P2X purinergic receptor antagonists that suppress the excitatory action of ATP on bladder afferent neurons.[2] Mice in which the $P2X_3$ receptor was knocked out exhibited hypoactive bladder activity and inefficient voiding, suggesting that activation of $P2X_3$ receptors on bladder afferent nerves by ATP released from the urothelium is essential for normal bladder function.[13] In humans and cats with interstitial cystitis, a painful bladder condition, ATP release from urothelial cells is enhanced.[17] Higher levels of ATP may induce abnormal afferent nerve firing and pain.

Transmitter release mechanisms in the urothelium may also be a target for botulinum toxin A (BTX-A), which is injected into the bladder wall to treat patients with various types of detrusor overactivity. BTX-A can act at multiple sites in the bladder, because it reduces the release of ATP into the bladder lumen in rats with cyclophosphamide-induced cystitis or spinal cord injury and suppresses the release of acetylcholine and norepinephrine from autonomic nerves.[23] BTX-A also blocks the stretch-evoked release of ATP from cultured urothelial cells. Thus, the clinical efficacy of BTX-A in the treatment of bladder dysfunction may be related to its action on urothelial sensory mechanisms as well as to its effects on neurotransmitter release from efferent nerves.

NO release from the urothelium has been implicated in an inhibitory modulatory mechanism.[10,23] Exogenous NO inhibits $Ca^{2+}$ channels in dissociated lumbosacral dorsal ganglion neurons, innervating the urinary bladder. In addition, the intravesical administration of NO donors suppresses bladder hyperactivity in cyclophosphamide-induced cystitis. The intravesical administration of oxyhemoglobin, an NO scavenger, produces bladder hyperactivity in normal rats. These data indicate that NO released from the urothelium can suppress the excitability of adjacent afferent nerves.[23]

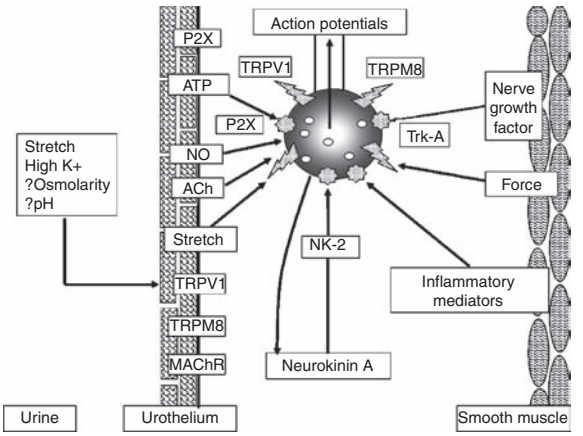



**Figure 2.2** Diagram showing: (1) receptors present in the urothelium and in sensory nerve endings in the bladder mucosa and (2) putative chemical mediators that are released by the urothelium, nerves, or smooth muscle that can modulate the excitability of sensory nerves. Urothelial cells and sensory nerves express common receptors (P2X, TRPV1, and TRPM8). Distention of the bladder activates stretch receptors and triggers the release of urothelial transmitters such as ATP, ACh, and NO that may interact with adjacent nerves. Receptors in afferent nerves or the urothelium can respond to changes in pH, osmolality, high $K^+$ concentration, chemicals in the urine, or inflammatory mediators released in the bladder wall. Neuropeptides (neurokinin A) released from sensory nerves in response to distention or chemical stimulation can act on NK-2 autoreceptors to sensitize the mechanosensitive nerve endings. The smooth muscle can generate force which may influence some mucosal endings. Nerve growth factor released from muscle or urothelium can exert an acute and chronic influence on the excitability of sensory nerves via an action on Trk-A receptors. ATP, adenosine triphosphate; ACh, acetylcholine; MAChR, muscarinic acetylcholine receptor; TRPV1, transient receptor potential vanilloid receptor 1 sensitive to capsaicin; TRPM8, menthol/cold receptor; NO, nitric oxide, Trk-A, tyrosine kinase A receptor.

The presence of muscarinic and nicotinic receptors in the urothelium has focused attention on the role of acetylcholine as a chemical

mediator of neural–urothelial interactions.[17,18,23] Urothelial cells express the various proteins necessary for the synthesis and storage of acetylcholine, including the plasma membrane choline transporter, choline acetyltransferase, and the vesicle acetycholine transporter as well as the enzyme responsible for the metabolism of acetylcholine (acetylcholinesterase). In addition it has been reported that acetylcholine is released from the bladder urothelium in rats and humans by other chemical or mechanical stimuli.[23] Reverse transcriptase polymerase chain reaction (RTPCR) experiments revealed the expression of multiple subtypes of nicotinic ($\alpha_7$, $\alpha_3$, $\beta_4$, and $\beta_5$) and muscarinic receptors ($M_1$–$M_5$) in rat urothelial cells. In addition, exogenous cholinergic muscarinic and nicotinic agonists applied to cultured urothelial cells can elicit an increase in intracellular $Ca^{2+}$ concentration and evoke the release of NO and ATP.[17,18,22] In bladder strips or whole bladder preparations, muscarinic agonists also stimulate the release of a smooth muscle inhibitory factor from the urothelium.[5]

The function of cholinergic receptors in the urothelium has also been evaluated by testing the effects of intravesically administered cholinergic agonists and antagonists on voiding function in cats and rats. The intravesical application of nicotine in the rat elicits two effects: a decrease in the frequency of reflex micturition in low concentrations and an increase in frequency in high concentrations.[22] The inhibitory effect was blocked by methyllycaconitine, an antagonist of $\alpha_7$ nicotinic receptors, whereas the facilitatory effect was blocked by hexamethonium, an antagonist of $\alpha_3$ type nicotinic receptors. Methyllycaconitine alone did not alter reflex bladder activity, whereas hexamethonium alone decreased reflex bladder activity, suggesting the existence of a tonically active nicotinic facilitatory mechanism.

In chronic spinal cord injured cats, intravesical infusion of oxotremorine methiodide, a quaternary ammonium muscarinic agonist that should have a relatively low ability to penetrate the urothelial barrier, or carbachol, a muscarinic–nicotinic agonist, decreased bladder capacity and enhanced the number of premicturition contractions during cystometrograms, but did not alter the amplitude of micturition contractions.[23] These effects were blocked by the intravesical administration of atropine methyl nitrate, indicating that activation of muscarinic receptors in the urothelium or in urothelial afferent nerves facilitates the spinal micturition reflex mediated by C-fiber afferent nerves. Intravesical administration of muscarinic agonists and antagonists elicits similar responses in the rat. Thus, the clinical effect of antimuscarinic agents to decrease sensory symptoms in overactive bladder may be related to the block of muscarinic receptors in the urothelium or afferent nerves.

## ANATOMY OF CENTRAL NERVOUS PATHWAYS CONTROLLING THE LOWER URINARY TRACT

The reflex circuitry controlling micturition consists of four basic components: primary afferent neurons, spinal efferent neurons, spinal interneurons, and neurons in the brain that modulate spinal reflex pathways.

### Pathways in the spinal cord

#### *Afferent projections in the spinal cord*

Afferent pathways from the bladder project into Lissauer's tract at the apex of the dorsal horn and then send collaterals laterally and medially around the dorsal horn into laminae V–VII and X at the base of the dorsal horn (Figure 2.3a).[24] The lateral pathway terminates in the region of the sacral parasympathetic nucleus and also sends some axons to the dorsal commissure (Figure 2.3a). Pudendal afferent pathways from the urethra and urethral sphincter exhibit a similar pattern of termination in the sacral spinal cord.

#### *Efferent neurons*

Parasympathetic preganglionic neurons are located in the intermediolateral gray matter (laminae V–VII) in the sacral segments of the spinal cord whereas sympathetic preganglionic neurons are located in medial (lamina X) and lateral sites (laminae V–VII) in the rostral lumbar spinal cord.[25] External urethral sphincter (EUS) motoneurons are located in lamina IX in Onuf's nucleus.[9]

#### *Spinal interneurons*

As shown in Figure 2.3c, interneurons retrogradely labeled by the injection of pseudorabies

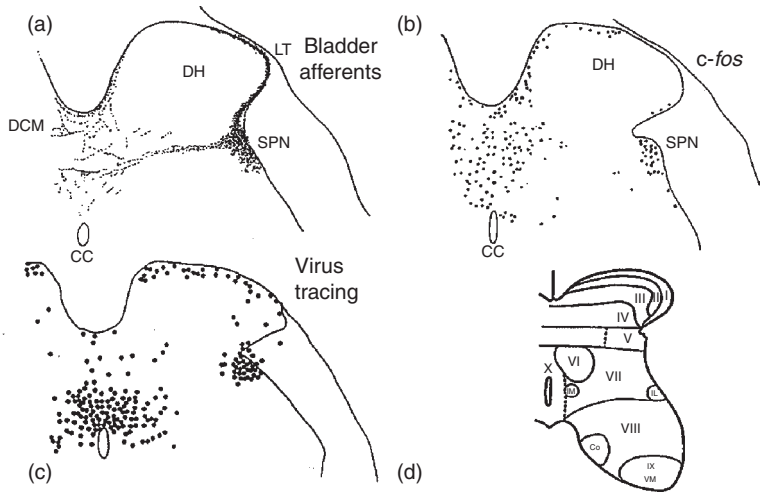



**Figure 2.3** Comparison of the distribution of bladder afferent projections to the $L_6$ spinal cord of the rat (a) with the distribution of c-*fos* positive cells in the $L_6$ spinal segment following chemical irritation of the lower urinary tract of the rat (b) and the distribution of interneurons in the $L_6$ spinal cord labeled by transneuronal transport of pseudorabies virus injected into the urinary bladder (c). Afferents are labeled by wheat germ agglutinin-horseradish peroxidase (WGA-HRP) injected into the urinary bladder. c-*fos* immunoreactivity is present in the nuclei of cells. DH, dorsal horn; SPN, sacral parasympathetic nucleus; CC central canal. (d) This drawing shows the laminar organization of the cat spinal cord.

virus (PRV) into the urinary bladder or urethra of the rat are located in regions of the spinal cord receiving afferent input from the bladder.[26,27] Large populations of interneurons are located just dorsal and medial to the preganglionic neurons as well as in the dorsal commissure and lamina I.

The spinal neurons involved in processing afferent input from the lower urinary tract have been identified by the expression of the immediate early gene, c-*fos* (Figure 2.3b).[28] In the rat, chemical or mechanical stimulation of the bladder and urethra increases the levels of Fos protein primarily in the dorsal commissure, the superficial dorsal horn, and the area of the sacral parasympathetic nucleus (Figure 2.3b). Some of these interneurons make local connections in the spinal cord and participate in segmental spinal reflexes,[29] whereas others send long projections to supraspinal centers, such as the periaqueductal gray (PAG) and nucleus gracilis that are involved in the supraspinal control of micturition.

## Pathways in the brain

In the rat, transneuronal virus tracing methods have identified many populations of neurons in the brain that are involved in control of the bladder, urethra, and the urethral sphincter, including Barrington's nucleus (the pontine micturition center, PMC); medullary raphe nuclei, which contain serotonergic neurons; the locus coeruleus, which contains noradrenergic neurons; periaqueductal gray; and the A5 noradrenergic cell group (Figure 2.4).[26,27] Several regions in the hypothalamus and the cerebral cortex also exhibited virus-infected cells. Neurons in the cortex were located primarily in the medial frontal cortex.

Other anatomical studies in which anterograde tracer substances were injected into brain areas and then identified in terminals in the spinal cord (Figure 2.5) are consistent with the virus tracing data. Tracer injected into the paraventricular nucleus of the hypothalamus labeled terminals in the sacral parasympathetic nucleus as well as the sphincter motor nucleus. On the other hand, neurons in the anterior hypothalamus project to the PMC. Neurons in the PMC in turn project primarily to the sacral parasympathetic nucleus and the lateral edge of the dorsal horn and the dorsal commissure, areas containing dendritic projections from preganglionic neurons, sphincter motoneurons, and afferent inputs from the

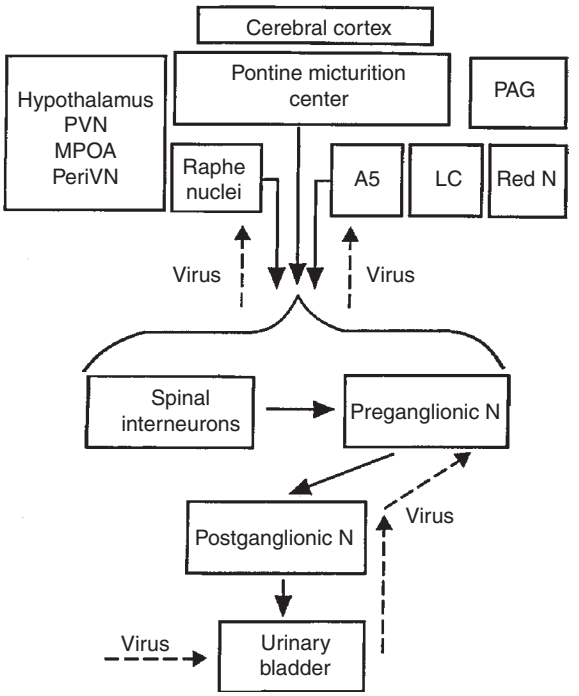



**Figure 2.4** Structures in the brain and spinal cord of the adult and neonatal rat labeled after injection of pseudorabies virus into the urinary bladder or the urethra. Virus is transported transneuronally in a retrograde direction (dashed arrows). Normal synaptic connections are indicated by solid arrows. At long survival times the virus can be detected in neurons at specific sites in the spinal cord and brain, extending to the pontine micturition center in the pons (i.e. Barrington's nucleus) and to the cerebral cortex. Other sites in the brain labeled by the virus are: (1) the paraventricular nucleus (PVN), medial preoptic area (MPOA), and periventricular nucleus (PeriVN) of the hypothalamus; (2) periaqueductal gray (PAG); (3) locus coeruleus (LC) and subcoeruleus; (4) red nucleus (Red N); (5) medullary raphe nuclei; and (6) the noradrenergic cell group designated as A5.

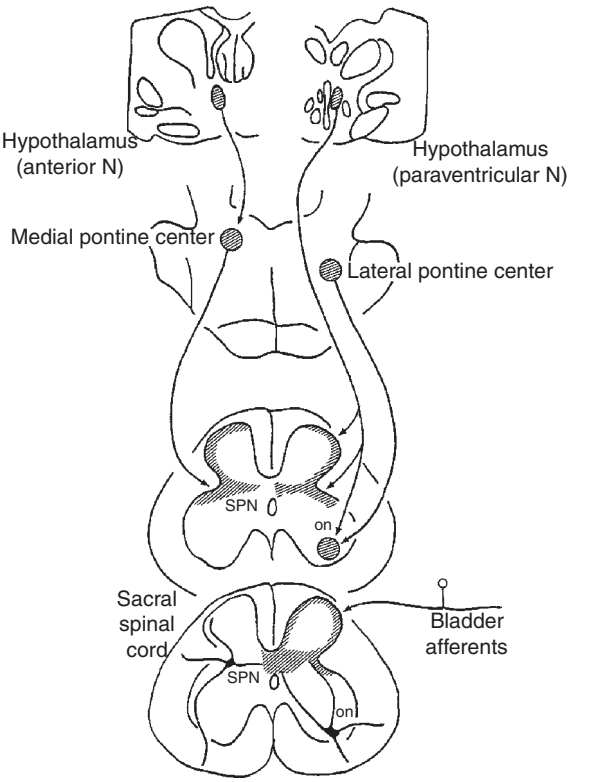



**Figure 2.5** Neural connections between the brain and the sacral spinal cord that may be involved in the regulation of the lower urinary tract in the cat. Lower section of spinal cord shows the location and morphology of a preganglionic neuron in the sacral parasympathetic nucleus (SPN), a sphincter motoneuron in Onuf's nucleus (ON), and the sites of central termination of afferent projections from the urinary bladder. Upper section of the spinal cord shows the sites of termination of descending pathways arising in the medial pontine micturition center (PMC), the lateral pontine sphincter or urine storage center, and the paraventricular nuclei of the hypothalamus. Section through the pons shows the projection from the anterior hypothalamic nuclei to the pontine micturition center.

bladder (Figure 2.5).[2] Conversely, projections from neurons in the lateral pons, an area implicated in the control of urethral sphincter function, terminate rather selectively in the sphincter motor nucleus. Thus, the sites of termination of descending projections from the pontine micturition center are optimally located to regulate reflex mechanisms at the spinal level.

## REFLEX CONTROL OF THE LOWER URINARY TRACT

The neural pathways controlling lower urinary tract function are organized as simple on–off switching circuits (Figures 2.6 and 2.7) that maintain a reciprocal relationship between the urinary bladder and urethral outlet. Intravesical pressure measurements during bladder filling in

both humans and animals reveal low and relatively constant bladder pressures when bladder volume is below the threshold for inducing voiding (Figure 2.6). The accommodation of the bladder to increasing volumes of urine is primarily a passive phenomenon dependent upon the intrinsic properties of the vesical smooth muscle and quiescence of the parasympathetic efferent pathway. In addition, in some species urine storage is also facilitated by sympathetic reflexes that mediate an inhibition of bladder activity, closure of the bladder neck, and contraction of the proximal urethra (Table 2.2, Figure 2.7). During bladder filling the activity of the sphincter electromyogram (EMG) also increases (Figure 2.6), reflecting an increase in efferent firing in the pudendal nerve and an increase in outlet resistance that contributes to the maintenance of urinary continence.

The storage phase of the urinary bladder can be switched to the voiding phase either involuntarily (Figure 2.6a) or voluntarily (Figure 2.6b). The former is readily demonstrated in the human infant (Figure 2.6a) when the volume of urine exceeds the micturition threshold. At this point, increased afferent firing from tension receptors in the bladder produces firing in the sacral parasympathetic pathways and an inhibition of sympathetic and somatic pathways. The expulsion phase consists of an initial relaxation of the urethral sphincter (Figure 2.6a) followed by a contraction of the bladder, an increase in bladder pressure, and flow of urine. Relaxation of the urethral outlet is mediated by the activation of a parasympathetic reflex pathway to the urethra (Table 2.2) that triggers the release of nitric oxide, an inhibitory transmitter, as well as by removal of adrenergic and somatic excitatory inputs to the urethra.

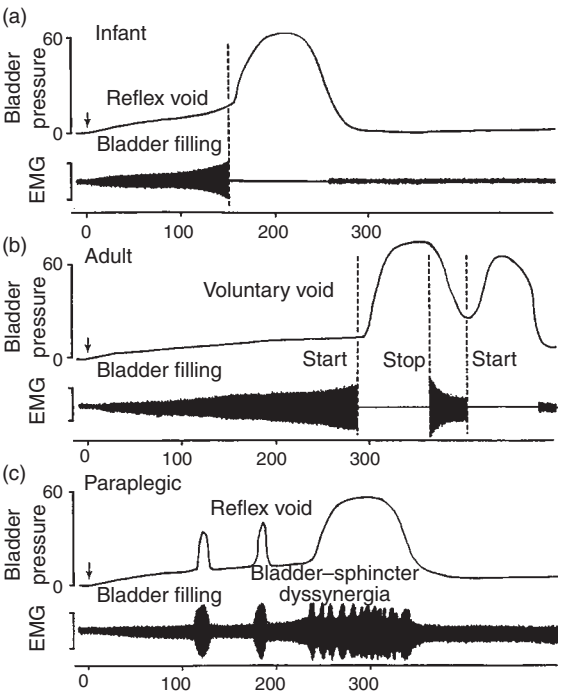



**Figure 2.6** Combined cystometrograms and sphincter electromyograms (EMG) comparing reflex voiding responses in an infant (a) and in a paraplegic patient (c) with a voluntary voiding response in an adult (b). The abscissa in all records represents bladder volume in milliliters and the ordinates represent bladder pressure in $cmH_2O$ and electrical activity of the EMG recording. On the left side of each trace the arrows indicate the start of a slow infusion of fluid into the bladder (bladder filling). Vertical dashed lines indicate the start of sphincter relaxation which precedes by a few seconds the bladder contraction in (a) and (b). In (b) note that a voluntary cessation of voiding (stop) is associated with an initial increase in sphincter EMG followed by a reciprocal relaxation of the bladder. A resumption of voiding is again associated with sphincter relaxation and a delayed increase in bladder pressure. On the other hand, in the paraplegic patient (c) the reciprocal relationship between bladder and sphincter is abolished. During bladder filling, transient uninhibited bladder contractions occur in association with sphincter activity. Further filling leads to more prolonged and simultaneous contractions of the bladder and sphincter (bladder–sphincter dyssynergia). Loss of the reciprocal relationship between bladder and sphincter in paraplegic patients interferes with bladder emptying.

## Organization of urine storage reflexes

### *Sympathetic storage reflex*

Although the integrity of the sympathetic input to the lower urinary tract is not essential for the performance of micturition, it does contribute to the storage function of the bladder. Surgical interruption or pharmacological blockade of the sympathetic innervation can reduce urethral outflow resistance, reduce bladder capacity, and increase the frequency and amplitude of bladder contractions recorded under constant volume conditions.

Sympathetic reflex activity is elicited by a sacrolumbar intersegmental spinal reflex pathway

**Table 2.2 Reflexes to the lower urinary tract**

| *Afferent pathway* | *Efferent pathway* | *Central pathway* |
|---|---|---|
| *Urine storage* | | |
| Low level vesical afferent activity (pelvic nerve) | 1. External sphincter contraction (somatic nerves)<br>2. Internal sphincter contraction (sympathetic nerves)<br>3. Detrusor inhibition (sympathetic nerves)<br>4. Ganglionic inhibition (sympathetic nerves)<br>5. Sacral parasympathetic outflow inactive | Spinal reflexes |
| Afferent activity from the external urethral sphincter | 6. Inhibition of parasympathetic outflow | Spinal reflex |
| *Micturition* | | |
| High level vesical afferent activity (pelvic nerve) | 1. Inhibition of external sphincter activity<br>2. Inhibition of sympathetic outflow<br>3. Activation of parasympathetic outflow to the bladder | Spinobulbospinal reflexes |
| | 4. Activation of parasympathetic outflow to the urethra | Spinal reflex |

that is triggered by vesical afferent activity in the pelvic nerves (Figure 2.7a).[2] The reflex pathway is inhibited when the bladder pressure is raised to the threshold for producing micturition (Figure 2.7b). This inhibitory response is abolished by transection of the spinal cord at the lower thoracic level, indicating that it originates at a supraspinal site, possibly the pontine micturition center. Thus, the vesicosympathetic reflex represents a negative feedback mechanism (Figure 2.7a) that allows the bladder to accommodate larger volumes during bladder filling but is turned off during voiding to allow the bladder to empty completely.

### *Urethral sphincter storage reflex*

Motoneurons innervating the striated muscles of the urethral sphincter exhibit a tonic discharge that increases during bladder filling. This activity is mediated in part by low-level afferent input from the bladder (Figure 2.7a). During micturition the firing of sphincter motoneurons is inhibited. This inhibition is dependent in part on supraspinal mechanisms, since it is less prominent in chronic spinal animals.

Sphincter-to-bladder reflexes may also contribute to urine storage, because afferent activity arising in the striated sphincter muscles during contractions can suppress reflex bladder activity and in turn increase bladder capacity.[9] Studies in cats and monkeys revealed that direct electrical stimulation of the sphincter muscles or electrical stimulation of motor pathways to induce a contraction of the sphincters suppresses reflex bladder activity. Similar inhibitory responses are elicited by electrical stimulation of afferent axons in the pudendal nerve, some of which must arise in the sphincter muscles.

## Organization of voiding reflexes

### *Spinobulbospinal micturition reflex pathway*

Micturition is mediated by activation of the sacral parasympathetic efferent pathway to the bladder and the urethra as well as reciprocal inhibition of the somatic pathway to the urethral sphincter (Table 2.2) (Figure 2.7b). Studies in cats

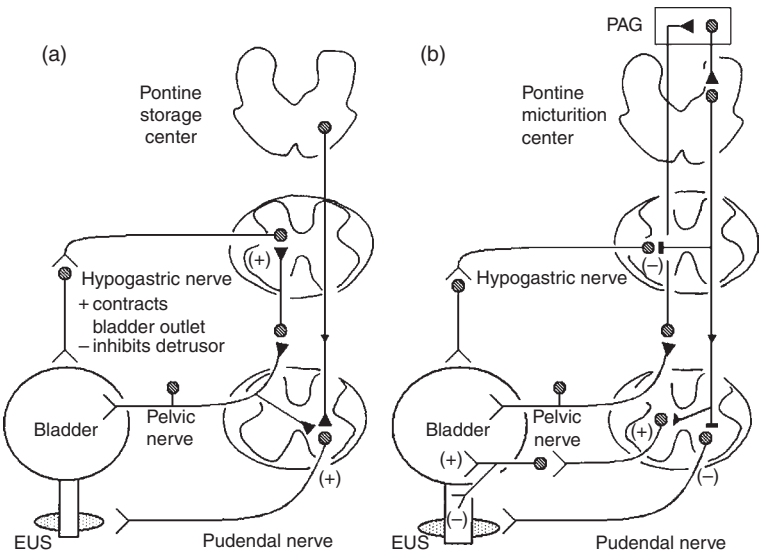



**Figure 2.7** Diagram showing neural circuits controlling continence and micturition. (a) Urine storage reflexes. During the storage of urine, distention of the bladder produces low level vesical afferent firing, which in turn stimulates (1) the sympathetic outflow to the bladder outlet (base and urethra) and (2) pudendal outflow to the external urethral sphincter (EUS). These responses occur by spinal reflex pathways and represent guarding reflexes, which promote continence. Sympathetic firing also inhibits detrusor muscle and modulates transmission in bladder ganglia. A region in the rostral pons (the pontine storage center) increases external urethral sphincter activity. (b) Voiding reflexes. During elimination of urine, intense bladder afferent firing activates spinobulbospinal reflex pathways passing through the pontine micturition center, which stimulate the parasympathetic outflow to the bladder and internal sphincter smooth muscle and inhibit the sympathetic and pudendal outflow to the urethral outlet. Ascending afferent input from the spinal cord may pass through relay neurons in the periaqueductal gray (PAG) before reaching the pontine micturition center.

using brain-lesioning and electrophysiological techniques revealed that the micturition reflex is mediated by a spinobulbospinal pathway that passes through the pontine micturition center in the rostral brain stem (Figures 2.5 and 2.7b).[30] In the cat, afferent input from the bladder reaches the pontine micturition center after passing through a relay station in the periaqueductal gray (PAG).[31] The micturition reflex pathway functions as an "on–off" switch that is activated by a critical level of afferent activity arising from tension receptors in the bladder and is, in turn, modulated by inhibitory and excitatory influences from areas of the brain rostral to the pons (e.g. diencephalon and cerebral cortex) (Figures 2.8 and 2.9).

### *Suprapontine control of micturition*

Lesion and electrical stimulation studies indicate that voluntary control of micturition depends on connections between the frontal cortex, hypothalamus, and other forebrain structures such as the anterior cingulate gyrus, amygdala, bed nucleus of the stria terminalis, and septal nuclei, where electrical stimulation elicits excitatory bladder effects. Damage to the cerebral cortex due to tumors, aneurysms, or cerebrovascular disease appears to remove inhibitory control of the pontine micturition center resulting in bladder overactivity.[32]

Human brain imaging studies (Figure 2.8) using single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) have examined the areas of the brain involved in the control of micturition.[32] Some studies evaluated the brain areas responsible for the perception of bladder fullness and the sensation of the desire to void during bladder filling, whereas others examined brain activity during micturition, and voluntary contractions of the

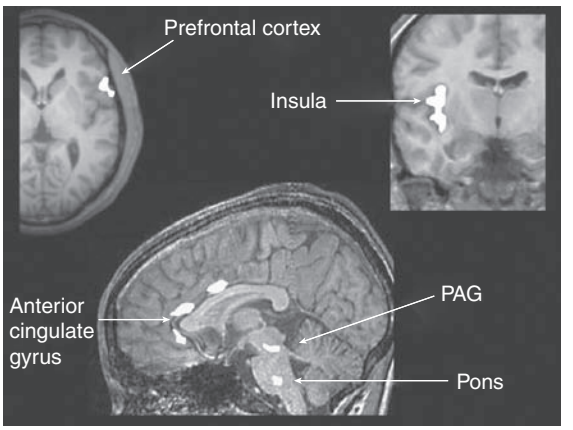



**Figure 2.8** Regions of the human brain identified in positron emission tomography (PET) imaging studies that exhibit differences in activity based on whether the bladder is full or empty. PAG, periaqueductal gray.

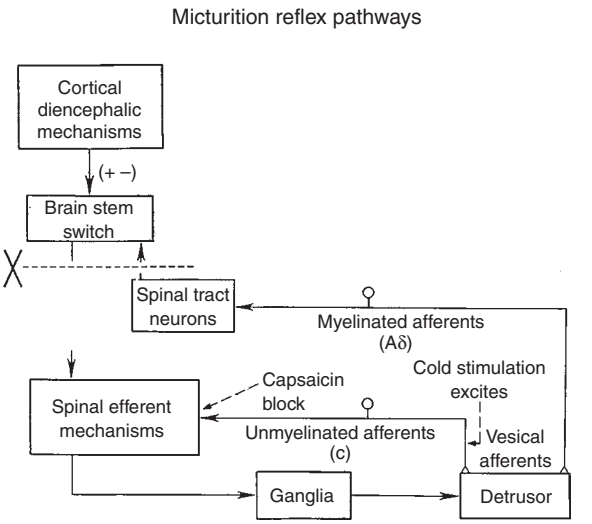



**Figure 2.9** Diagram showing the organization of the parasympathetic excitatory reflex pathway to the detrusor muscle. Scheme is based on electrophysiologic studies in cats. In animals with an intact spinal cord, micturition is initiated by a supraspinal reflex pathway passing through a center in the brain stem. The pathway is triggered by myelinated afferents (Aδ fibers), which are connected to the tension receptors in the bladder wall. Injury to the spinal cord above the sacral segments interrupts the connections between the brain and spinal autonomic centers and initially blocks micturition. However, over a period of several weeks following cord injury, a spinal reflex mechanism emerges, which is triggered by unmyelinated vesical afferents (C fibers); the A-fiber afferent inputs are ineffective. The C-fiber reflex pathway is usually weak or undetectable in animals with an intact nervous system. Stimulation of the C-fiber bladder afferents by instillation of ice water into the bladder (cold stimulation) activates voiding responses in patients with spinal cord injury. Capsaicin (20–30 mg, subcutaneously) blocks the C-fiber reflex in chronic spinal cats, but does not block micturition reflexes in intact cats. Intravesical capsaicin also suppresses detrusor hyperreflexia and cold-evoked reflexes in patients with neurogenic bladder dysfunction.

pelvic floor during urine withholding or during cold stimulation of the bladder. PET scan studies revealed that two cortical areas (dorsolateral prefrontal cortex and the anterior cingulate gyrus) were active (i.e. exhibited increased blood flow) during voiding.[32,33] The hypothalamus, including the preoptic area as well as the pons and the PAG, also showed activity in concert with voluntary micturition. Other PET studies that examined the changes in brain activity during filling of the bladder revealed that increased activity occurred in the PAG, the midline pons, the mid-cingulate gyrus, and bilaterally in the frontal lobes. The results were consistent with the notion that the PAG receives information about bladder fullness and then relays this information to other brain areas involved in the control of bladder storage.

It has been speculated that the role of the prefrontal cortex, which is thought to be the seat of planning of complex behaviors, is to make a decision as to whether or not micturition should take place at a particular time or place.[33] On the other hand, the anterior cingulate, which is a part of the limbic system and which is thought to be involved in cognitive processes involving attention and executive control, may be involved in the integration of afferent input with the control of autonomic efferent outflow to the lower urinary tract. SPECT scanning of patients with urgency incontinence revealed hypoperfusion of the anterior cingulate gyrus as well as other frontal lobe regions such as the prefrontal cortex.

### *Spinal micturition reflex pathway*

Spinal cord injury rostral to the lumbosacral level eliminates voluntary and supraspinal control

of voiding, leading initially to an areflexic bladder and complete urinary retention followed by a slow development of automatic micturition and bladder hyperactivity (Figure 2.6c) mediated by spinal reflex pathways.[2,30] However, voiding is commonly inefficient due to simultaneous contractions of the bladder and urethral sphincter (bladder–sphincter dyssynergia) (Figure 2.6c). Electrophysiologic studies in animals have shown that the micturition reflex pathway changes after spinal cord injury. For example, the afferent limb of the micturition reflex in cats with chronic spinal transection above the lumbar level consists of unmyelinated (C-fiber) axons (Figure 2.9), whereas in cats with an intact spinal cord, myelinated (Aδ) afferents activate the micturition reflex (Figure 2.9).[12,30] In normal cats, capsaicin did not block reflex contractions of the bladder or the Aδ-fiber-evoked bladder reflex. However, in cats with chronic spinal injury, capsaicin, a neurotoxin known to disrupt the function of C-fiber afferents, completely blocked C-fiber-evoked bladder reflexes.[12,30] Evidence of the contribution of C-fiber bladder afferents to bladder hyperactivity and involuntary voiding in humans has been obtained in studies in which capsaicin or resiniferatoxin, another C-fiber afferent neurotoxin, was administered intravesically to patients with neurogenic detrusor overactivity due to multiple sclerosis or spinal cord injuries. In these patients the toxins increased bladder capacity and reduced the frequency of incontinence.[30]

The emergence of C-fiber bladder reflexes seems to be mediated by several mechanisms, including changes in central synaptic connections and alterations in the properties of the peripheral afferent receptors that lead to sensitization of the "silent" C fibers and the unmasking of responses to mechanical stimuli.[2] In rats it has been shown that bladder afferent neurons undergo both morphologic (neuronal hypertrophy) and physiologic changes (upregulation of tetrodotoxin (TTX)-sensitive $Na^+$ channels and downregulation of TTX-resistant $Na^+$ channels) following spinal cord injury.[11,16,30] It has been speculated that this neuroplasticity is mediated by the actions of neurotrophic factors such as nerve growth factor (NGF) released within the spinal cord or the urinary bladder. The production of neurotrophic factors including NGF increases in the bladder after spinal cord injury, whereas chronic administration of NGF into the bladder of rats induces bladder hyperactivity and increases the firing frequency of dissociated bladder afferent neurons.[11,30] On the other hand, intrathecal application of NGF antibodies to neutralize NGF in the spinal cord suppresses detrusor hyperreflexia and detrusor–sphincter dyssynergia in spinal cord injured rats.

## NEUROTRANSMITTERS IN CENTRAL MICTURITION REFLEX PATHWAYS

### Excitatory neurotransmitters

Excitatory transmission in the central pathways to the lower urinary tract depends on several types of neurotransmitters, including: glutamic acid, neuropeptides, nitric oxide, and ATP.[2,10] Pharmacological experiments in rats have revealed that glutamic acid is an essential transmitter in the ascending, pontine, and descending limbs of the spinobulbospinal micturition reflex pathway and in spinal reflex pathways controlling the bladder and external urethral sphincter.[34] *N*-methyl-D-aspartate (NMDA) and non-NMDA glutamatergic synaptic mechanisms appear to interact synergistically to mediate transmission in these pathways.

### Inhibitory neurotransmitters

Several types of inhibitory transmitters, including inhibitory amino acids (γ-aminobutyric acid (GABA), glycine) and opioid peptides (enkephalins) can suppress the micturition reflex when applied to the central nervous system. Experimental evidence in anesthetized animals indicates that GABA and enkephalins exert a tonic inhibitory control in the PMC and regulate bladder capacity. These substances also have inhibitory actions in the spinal cord.[10,35]

### Transmitters with mixed excitatory and inhibitory actions

Some transmitters (dopamine, 5-hydroxytryptamine, norepinephrine, acetylcholine, and non-opioid peptides including vasoactive intestinal polypeptide and corticotropin-releasing factor)

have both inhibitory and excitatory effects on reflex bladder activity. In some instances different effects are mediated by different types of receptors. For example, the inhibitory effects of dopamine are mediated by $D_1$-like ($D_1$ and $D_5$) and the facilitatory effects are mediated by $D_2$-like ($D_2$, $D_3$, and $D_4$) receptor subtypes. Loss of forebrain dopaminergic mechanisms in patients with idiopathic Parkinson's disease is associated with bladder hyperactivity.

Interest in the role of 5-hydroxytryptamine in the central control of micturition has increased following the introduction of duloxetine, a serotonin–norepinephrine reuptake inhibitor, for the treatment of stress urinary incontinence. 5-Hydroxytryptamine (5-HT) has complex effects on the lower urinary tract which vary in different species.[36–40] In the cat, activation of central 5-$HT_{1A}$ receptors inhibits reflex bladder activity,[38] whereas activation of 5-$HT_2$ receptors enhances urethral sphincter activity.[40] On the other hand, activation of central 5-$HT_{1A}$ receptors in the rat enhances bladder and sphincter reflexes.[39] The similarities in the effects of duloxetine in the cat and the human indicate that micturition in the cat may be a useful model for developing centrally acting serotonergic agents for the treatment of lower urinary tract dysfunction.

## CONCLUSIONS

The functions of the lower urinary tract to store and periodically eliminate urine are regulated by a complex neural control system that performs like a simple switching circuit to maintain a reciprocal relationship between the bladder and urethral outlet. The switching circuit is modulated by several neurotransmitter systems and is therefore sensitive to a variety of drugs and neurologic diseases. A more complete understanding of the neural mechanisms involved in bladder and urethral control will no doubt facilitate the development of new diagnostic methods and therapies for lower urinary tract dysfunction.

## REFERENCES


1. Fry CH, Brading AF, Hussain M et al. Cell biology. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. Plymouth, UK: Health Publication Ltd, 2005: 363–432.
2. Morrison J, Birder L, Craggs M et al. Neural control. In: Abrams P, Cardozo L, Khoury S, Wein A, eds. Incontinence. Plymouth, UK: Health Publication Ltd, 2005: 363–432.
3. de Groat WC, Booth AM. Synaptic transmission in pelvic ganglia. In: Maggi CA, ed. The Autonomic Nervous System, Vol. 3, Nervous Control of the Urogenital System. London: Harwood Academic Publisher, 1993: 291–347.
4. Matsui M, Motomura D, Karasawa H et al. Multiple functional defects in peripheral autonomic organs in mice lacking muscarinic acetylcholine receptor gene for the M3 subtype. Proc Natl Acad Sci USA 2000; 97: 9579–84.
5. Andersson KE, Arner A. Urinary bladder contraction and relaxation: physiology and pathophysiology. Physiol Rev 2004; 84: 935–86.
6. Hegde SS. Muscarinic receptors in the bladder: from basic research to therapeutics. Br J Pharmacol 2006; 147 (Suppl 2): S80–7.
7. Burnstock G. Purinergic signaling in the lower urinary tract. In: Abbracchio MP, Williams M, eds. Handbook of Experimental Pharmacology. Berlin: Springer Verlag, 2001: 423–515.
8. Somogyi GT, Tanowitz M, Zernova G, de Groat WC. M1 muscarinic receptor-induced facilitation of ACh and noradrenaline release in the rat bladder is mediated by protein kinase. C. J Physiol 1996; 496: 245–54.
9. de Groat WC, Fraser MO, Yoshiyama M et al. Neural control of the urethra. Scand J Urol Nephrol Suppl 2001; 207: 35–43.
10. de Groat WC, Yoshimura N. Pharmacology of the lower urinary tract. Ann Rev Pharmacol Toxicol 2001; 41: 691–721.
11. Vizzard MA. Neurochemical plasticity and the role of neurotrophic factors in bladder reflex pathways after spinal cord injury. Prog Brain Res 2006; 152: 97–115.
12. Cheng CL, Liu JC, Chang SY, Ma CP, de Groat WC. Effect of capsaicin on the micturition reflex in normal and chronic spinal cord-injured cats. Am J Physiol 1999; 277: R786–94.
13. Cockayne DA, Hamilton SG, Zhu QM et al. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X3-deficient mice. Nature 2000; 407: 1011–15.
14. Rong W, Spyer KM, Burnstock G. Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. J Physiol 2002; 541: 591–600.

15. Yoshimura N, de Groat WC. Increased excitability of afferent neurons innervating rat urinary bladder after chronic bladder inflammation. J Neurosci 1999; 19: 4644–53.
16. Yoshimura N, de Groat WC. Plasticity of $Na^+$ channels in afferent neurones innervating rat urinary bladder following spinal cord injury. J Physiol 1997; 503: 269–76.
17. Birder LA. More than just a barrier: urothelium as a drug target for urinary bladder pain. Am J Physiol Renal Physiol 2005; 289: F489–95.
18. de Groat WC. The urothelium in overactive bladder: passive bystander or active participant? Urology 2004; 64: 7–11.
19. Ferguson DR, Kennedy I, Burton TJ. ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes—a possible sensory mechanism? J Physiol 1997; 505: 503–11.
20. Birder LA, Apodaca G, de Groat WC, Kanai AJ. Adrenergic- and capsaicin-evoked nitric oxide release from urothelium and afferent nerves in urinary bladder. Am J Physiol 1998; 275: F226–9.
21. Birder LA, Nakamura Y, Kiss S et al. Altered urinary bladder function in mice lacking the vanilloid receptor TRPV1. Nat Neurosci 2002; 5: 856–60.
22. Beckel JM, Kanai A, Lee SJ, de Groat WC, Birder LA. Expression of functional nicotinic acetylcholine receptors in rat urinary bladder epithelial cells. Am J Physiol Renal Physiol 2006; 290: F103–10.
23. de Groat WC. Integrative control of the lower urinary tract: preclinical perspective. Br J Pharmacol 2006; 147 (Suppl 2): S25–40.
24. Steers WD, Ciambotti J, Etzel B, Erdman S, de Groat WC. Alterations in afferent pathways from the urinary bladder of the rat in response to partial urethral obstruction. J Comp Neurol 1991; 310: 401–10.
25. Morgan CW, de Groat WC, Felkins LA, Zhang SJ. Intracellular injection of neurobiotin or horseradish peroxidase reveals separate types of preganglionic neurons in the sacral parasympathetic nucleus of the cat. J Comp Neurol 1993; 331: 161–82.
26. Nadelhaft I, Vera PL, Card JP, Miselis RR. Central nervous system neurons labelled following the injection of pseudorabies virus into the rat urinary bladder. Neurosci Lett 1992; 143: 271–4.
27. Vizzard MA, Erickson VL, Card JP, Roppolo JR, de Groat WC. Transneuronal labeling of neurons in the adult rat brainstem and spinal cord after injection of pseudorabies virus into the urethra. J Comp Neurol 1995; 355: 629–40.
28. Birder LA, de Groat WC. Induction of c-fos expression in spinal neurons by nociceptive and non-nociceptive stimulation of LUT. Am J Physiol 1993; 265: R326–33.
29. Araki I, de Groat WC. Unitary excitatory synaptic currents in preganglionic neurons mediated by two distinct groups of interneurons in neonatal rat sacral parasympathetic nucleus. J Neurophysiol 1996; 76: 215–26.
30. de Groat WC, Yoshimura N. Mechanisms underlying the recovery of lower urinary tract function following spinal cord injury. Prog Brain Res 2006; 152: 59–84.
31. Blok BF, De Weerd H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. J Comp Neurol 1995; 359: 300–9.
32. Fowler CJ. Integrated control of lower urinary tract – clinical perspective. Br J Pharmacol 2006; 147 (Suppl 2): S14–24.
33. Kavia RB, Dasgupta R, Fowler CJ. Functional imaging and the central control of the bladder. J Comp Neurol 2005; 493: 27–32.
34. Yoshiyama M, de Groat WC. Supraspinal and spinal alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid and N-methyl-D-aspartate glutamatergic control of the micturition reflex in the urethane-anesthetized rat. Neuroscience 2005; 132: 1017–26.
35. Mallory BS, Roppolo JR, de Groat WC. Pharmacological modulation of the pontine micturition center. Brain Res 1991; 546: 310–20.
36. de Groat WC. Influence of central serotonergic mechanisms on lower urinary tract function. Urology 2002; 59: 30–6.
37. Ramage AG. The role of central 5-hydroxytryptamine (5-HT, serotonin) receptors in the control of micturition. Br J Pharmacol 2006; 147 (Suppl 2): S120–31.
38. Tai C, Miscik CL, Ungerer TD, Roppolo JR, de Groat WC. Suppression of bladder reflex activity in chronic spinal cord injured cats by activation of serotonin 5-HT(1A) receptors. Exp Neurol 2006; 199: 427–37.

39. Chang HY, Cheng CL, Chen JJ, de Groat WC. Roles of glutamatergic and serotonergic mechanisms in reflex control of the external urethral sphincter in urethane-anesthetized female rats. Am J Physiol Regul Integr Comp Physiol 2006; 291: R224–34.

40. Thor KB. Serotonin and norepinephrine involvement in efferent pathways to the urethral rhabdosphincter: implications for treating stress urinary incontinence. Urology 2003; 62 (4 Suppl 1): 3–9.

# 3

# Diagnosis of overactive bladder

Eric S Rovner and Melissa Walls

**History • Physical examination • Urine analysis • Post-void residual urine measurement • Urodynamics • Cystourethroscopy • Imaging • Other laboratory tests • Conclusions**

Overactive bladder (OAB) is a highly prevalent disorder impacting on millions of people's lives throughout the world.[1,2] Despite its high prevalence, many sufferers do not seek medical attention and are not aware that OAB is treatable. Over the past few years, several changes in terminology and advances in therapy for this condition have occurred. Because of these developments, considerable confusion exists within and outside the medical community with respect to the diagnosis of this burdensome condition. In order to optimize the identification and subsequent diagnosis of individuals who may suffer from OAB, it is important to fully understand the current definition of the term.

The exact origin of the term "overactive bladder" is unknown, but nevertheless, it became widely utilized and popularized in the medical lexicon in the latter half of the 1990s. It is interesting that, although much controversy was engendered by the use of the phrase "overactive bladder", this exact term was never actually defined or described by the International Continence Society (ICS) in prior terminology reports until 2001. The term overactive detrusor function (generally shortened to overactive detrusor) does appear[3] in the lexicon as a finding on urodynamic testing. This term is defined by the occurrence of involuntary detrusor contractions during the filling phase of cystometry, which may be spontaneous or provoked.

Thus, overactive detrusor function and the terms which, correctly or incorrectly, have been used as substitutes (overactive detrusor, detrusor overactivity, and, eventually, overactive bladder) were all urodynamic terms, and were utilized to describe abnormalities of detrusor function during filling cystometry. Thus, a urodynamic study was required to describe the finding of detrusor overactivity, which in turn then provided the patient with a de facto diagnosis of overactive bladder despite the fact that the term did not yet exist in the urologic literature. The limitations of this model were recognized by several authors.[4,5] It was apparent that the requirement of urodynamics in making the diagnosis placed an undue burden on the practicing physician, the patient, and the healthcare system in general. In addition, the term overactive bladder would need to be formally defined.

Several important ICS reports with substantial clinical and research implications were subsequently published, including a report on 'The standardisation of terminology of lower urinary tract function'.[3] The definitions and descriptions were meant to restate or update those presented in previous ICS standardization of terminology reports.[6] Among other important changes and updates, this report addressed the definition and use of the term "overactive bladder" and classified it as a type of syndrome. According to this document, syndromes "describe constellations or varying combinations of symptoms but cannot be used for precise diagnosis . . . [syndromes] are functional abnormalities for which a precise cause has not been defined."[3] Overactive bladder

syndrome, urge syndrome, or urgency–frequency syndrome is thus defined as "urgency with or without urge incontinence, usually with frequency and nocturia". Although the document indicates that these symptoms are suggestive of detrusor overactivity (a term later defined in this document as the observation of involuntary detrusor contractions during the filling phase of cystometry), a urodynamic demonstration of detrusor overactivity is not necessary, nor evident, in all cases. Furthermore, the definition allows that a variety of other conditions of urethrovesical dysfunction may result in a similar symptom complex.

Within the framework of this definition of OAB, it is important to emphasize that the use of the term overactive bladder is necessarily restricted to those situations in which local pathology such as infection and malignancy have been excluded. A large number of clinical conditions, both commonly encountered and rarely seen, can present with symptoms suggestive of OAB (Table 3.1).

**Table 3.1 Differential diagnosis of overactive bladder (OAB)**

| |
|---|
| Excessive fluid intake |
| Urinary retention (overflow) |
| Bacterial cystitis |
| Prostatitis |
| Radiation cystitis |
| Sexually transmitted disease (GC, *Chlamydia*, etc.) |
| Interstitial cystitis, sensory urgency syndromes |
| Bladder cancer |
| Bladder stones |
| Pelvic mass (GI, GU, GYN, vascular aneurysm, etc.) |
| Gynecological problem |
| vaginitis, endometriosis, malignancy, etc. |
| postmenopausal atrophic vaginitis |
| vaginal prolapse: cystocele, rectocele, etc. |
| severe stress urinary incontinence |
| Medical illnesses producing fluid shifts: CHF, cirrhosis, etc. |
| Drugs (e.g. diuretics) |
| Other |

GC, *Neisseria gonorrhoeae*; GI, gastrointestinal; GU, genitourinary; GYN, gynecological; CHF, congestive heart failure.

The goal of the practitioner in the evaluation of OAB should be to assess the individual for the presence of symptoms suggestive of OAB, and then be able to comfortably, confidently, and accurately exclude the coexistence of most of these conditions. Fortunately, a well done and complete medical history consistent with OAB, a normal physical examination, and an unremarkable urine analysis will usually be adequate to exclude many of these conditions and arrive at the proper diagnosis. The diagnosis of OAB is usually not difficult; however, in appropriate cases, the use of additional selected, adjunctive studies may be helpful.

In this chapter, we will discuss the usual diagnostic evaluation of the patient with suspected OAB and briefly review some of the adjunctive studies that may be indicated in selected cases. The evaluation of an individual with suspected OAB should be simple, rapid, and accurate, in order to initiate effective therapy and alleviate the symptoms associated with the condition.

## HISTORY

### Symptom assessment

As noted in the definition discussed above, OAB is a symptomatic diagnosis. Therefore, a proper symptom assessment, both qualitatively and quantitively, is of paramount importance. Typical symptoms of the overactive bladder include an increased number of micturitions (urinary frequency, usually greater than 8×/day), a strong and sudden desire to void which is difficult to defer (urinary urgency), and, if the urgency cannot be suppressed, urinary urge incontinence.[7] People suffering from bladder overactivity typically have to empty their bladders frequently, and when they experience a sensation of urgency, they may leak urine if they are unable to reach the toilet quickly. The amount of urine lost may be large, as the bladder may empty completely and involuntarily. Sleep may be disturbed, as the need to void may awaken the patient. Nighttime frequency and nocturnal enuresis (bedwetting) is often particularly disruptive. Urinary incontinence occurring shortly after, or in concert with, the sensation of impending leakage is called urge incontinence. Urinary incontinence of any kind may not be present in up to two-thirds of individuals with OAB.[2] In 2001,