Urinary Incontinence

What We Know
What We Don't Know
What We Would Like To Know

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Picture Two Piles

What We Know

What We Don't Know

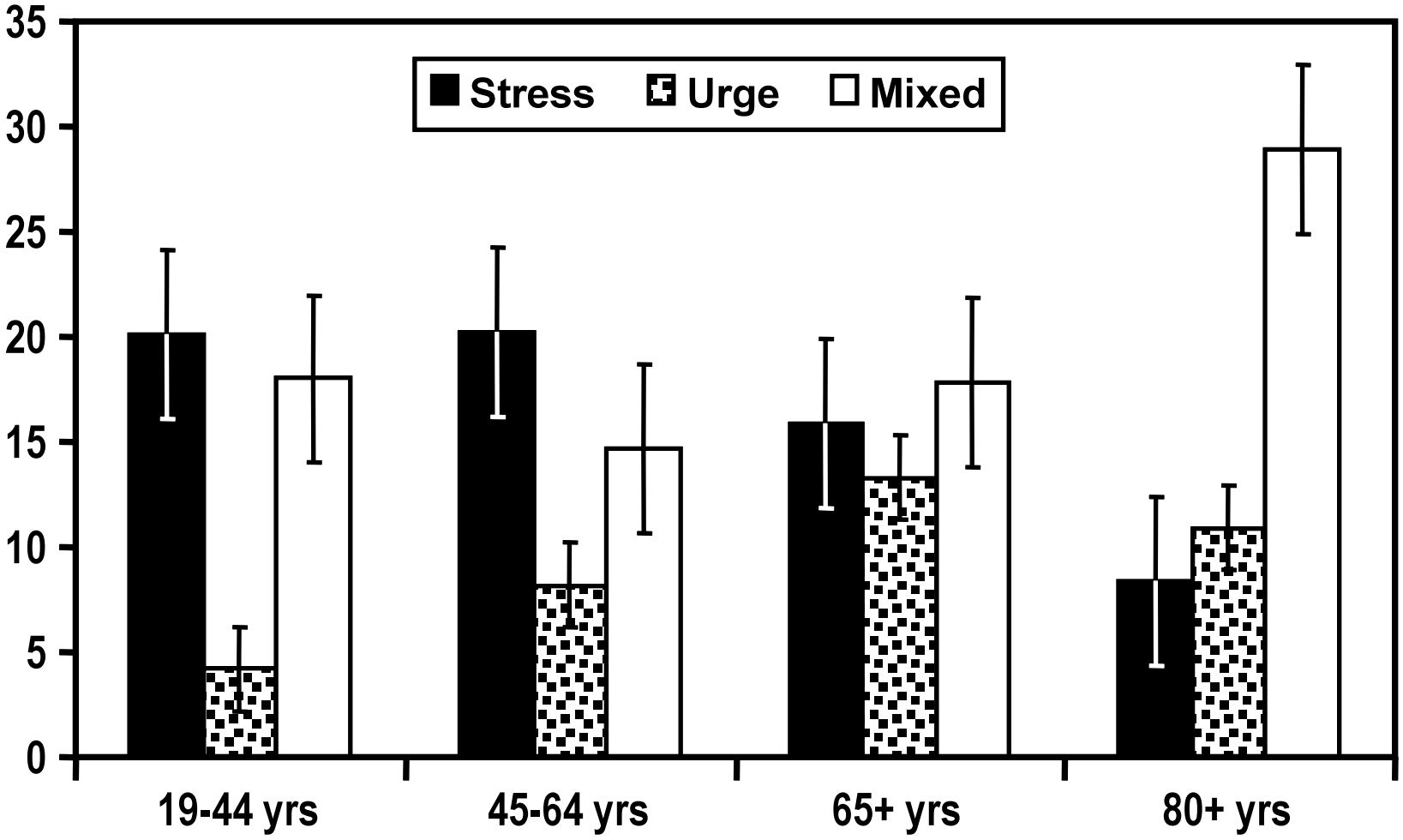
Definitions (Personal)

- What We Know: Reasonable body of factual data, “general” agreement
- What we don’t know: More than 1 “supported” opinion. Could take either side of a debate proposition and support well.
- What we would really like to know now: What we don’t know that affects clinical practice

What We Know: General

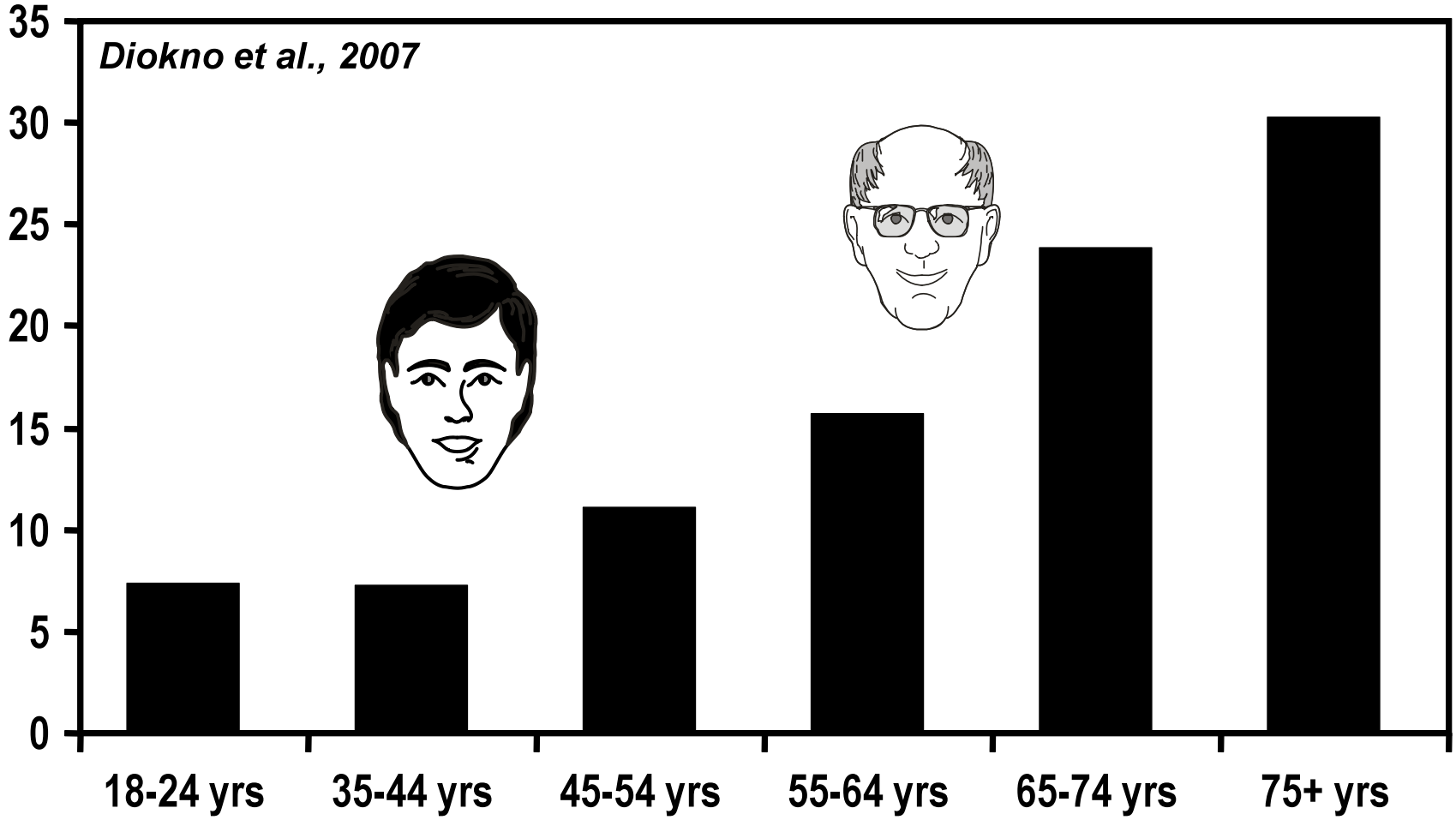
- Prevalence
- Risk Factors (Associations)
- Diagnostic Tools (Diaries, History, Examination, UDS/ VUDS)
- Measurement (Diaries, Pad Tests, UD Parameters, POP-Q)
- Anatomy: The Basics
- Peripheral and Central Neurophysiology, Neuropharmacology: The Basics
- Conservative therapy is “effective”
- Surgical therapy is “effective” for SUI

Prevalence of UI Types in American Women (37 studies)



Prevention of Urinary and Fecal Incontinence in Adults, December 2007; Evidence Report/Technology Assessment, Number 161

Prevalence of UI in American Men by Age (N=21,590)



Possible Risk Factors For Incontinence

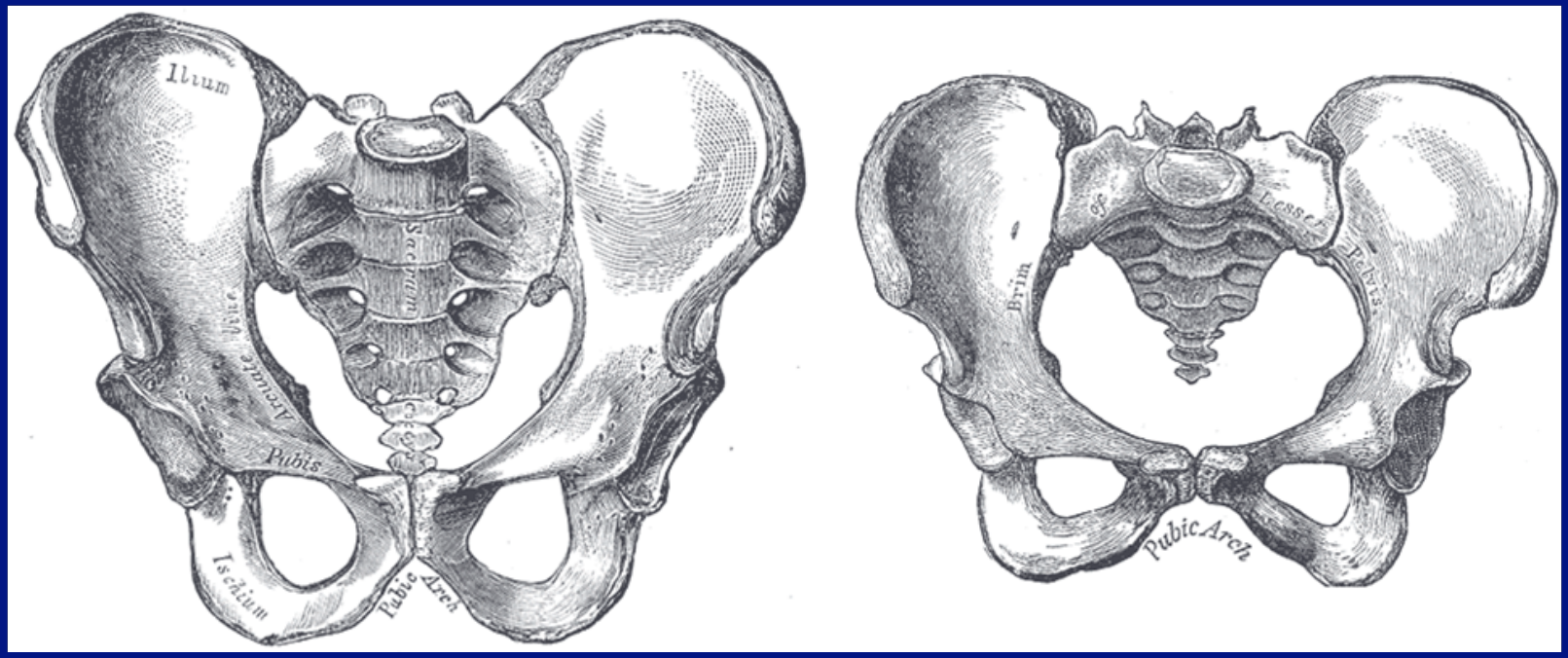
Potential for Improvement/Prevention	
Alcohol	Neurogenic Disease Stroke, Diabetes
Awareness	Obesity
Caffeine	Pelvic Surgery
Childbirth	Pelvic Organ Prolapse
Constipation	Physical Activity
Depression	Prostatic Obstruction
Education	Smoking
Hormonal Change	Stress
Immobility	Urinary Tract Infection
Medications	

Fixed
Age
Sex (M, F)
Genetics

Anatomy

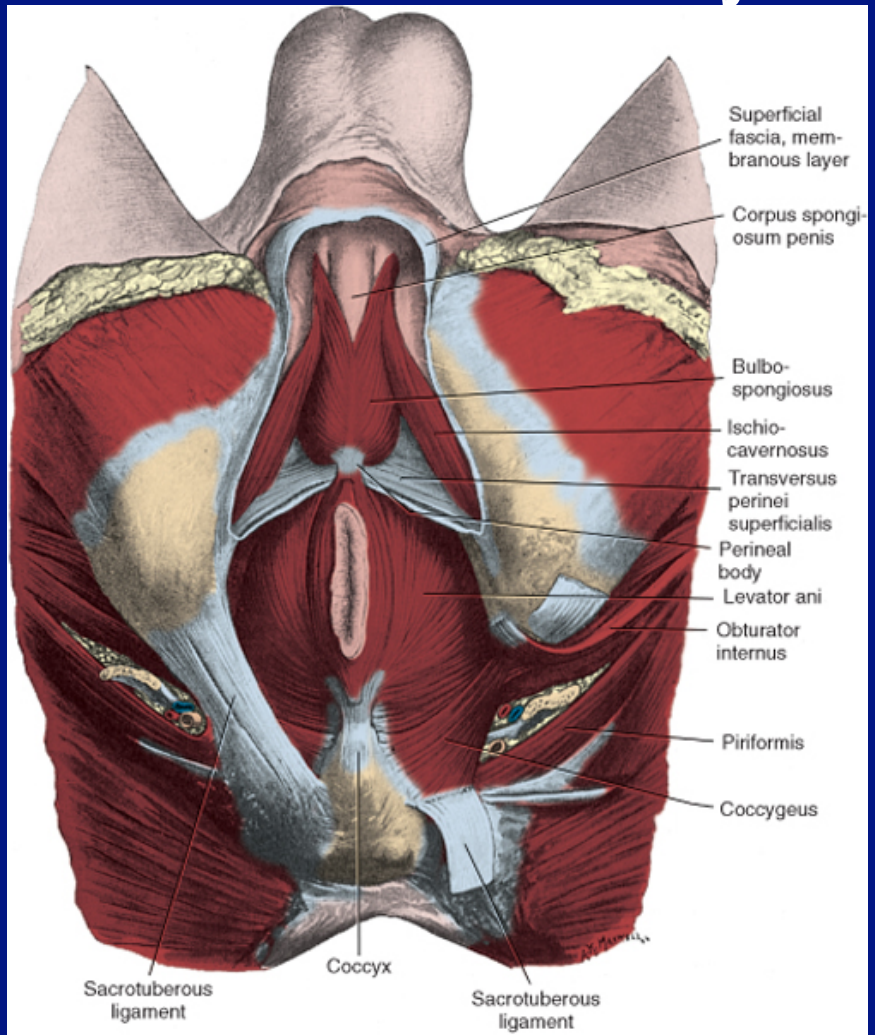
Male Pelvic Anatomy

Female Pelvic Anatomy



Anatomy

Male Pelvic Anatomy



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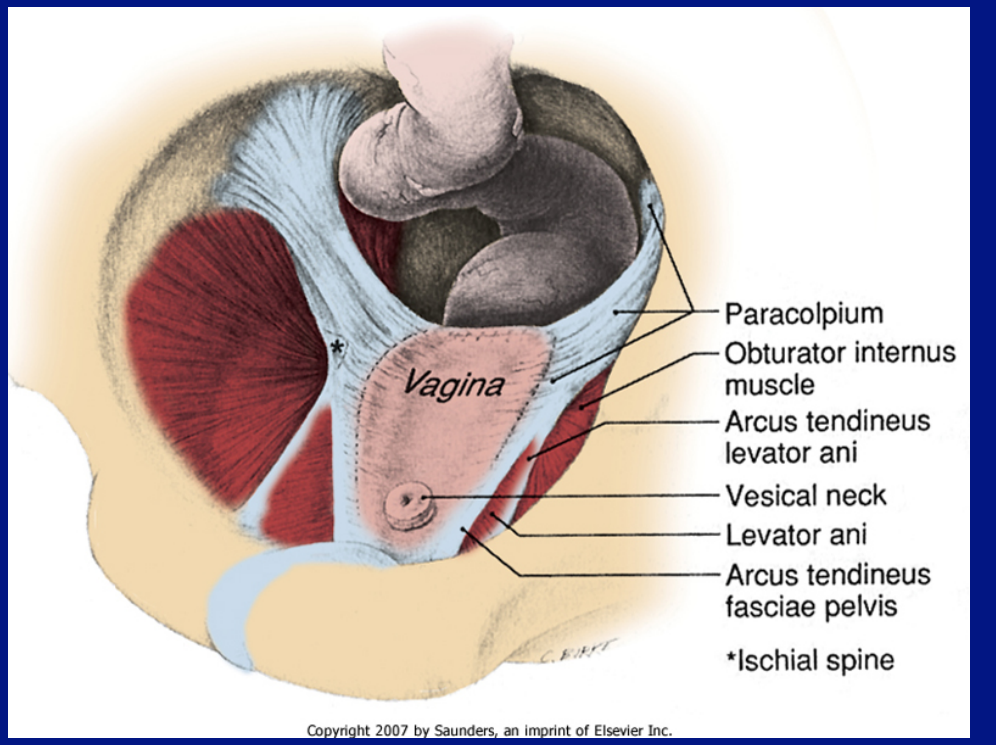
Female Pelvic Anatomy



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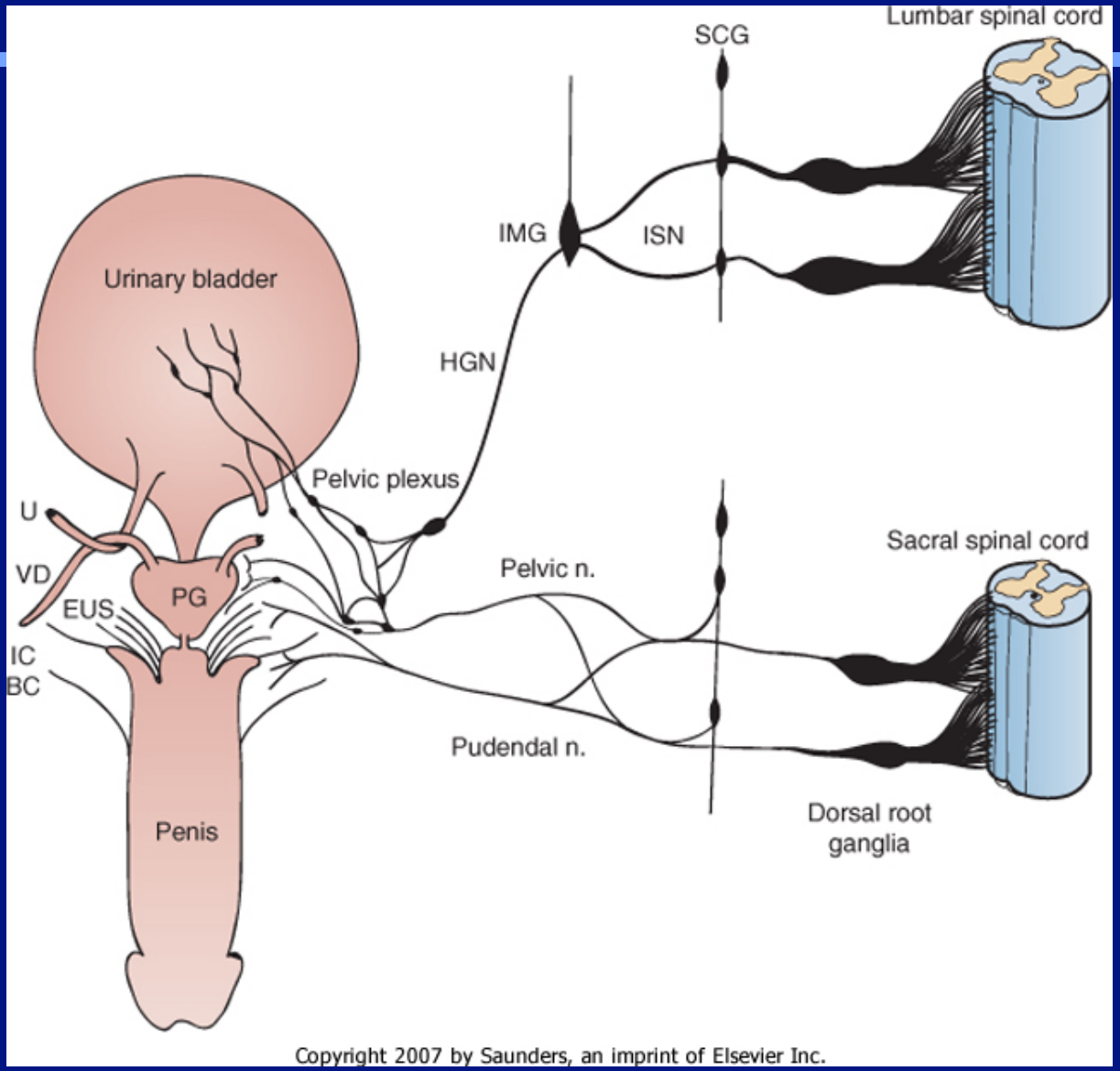
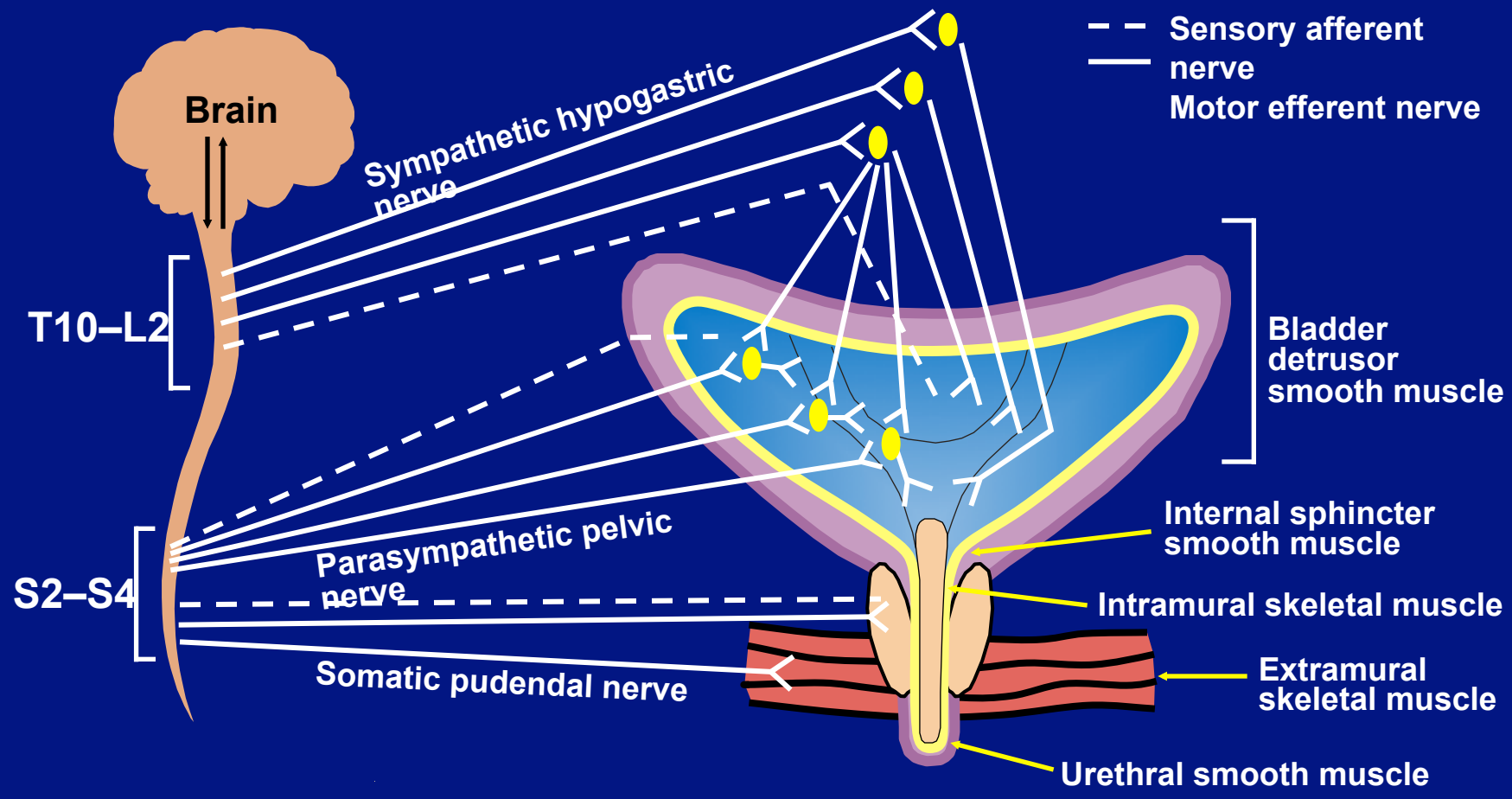
Peripheral Innervation

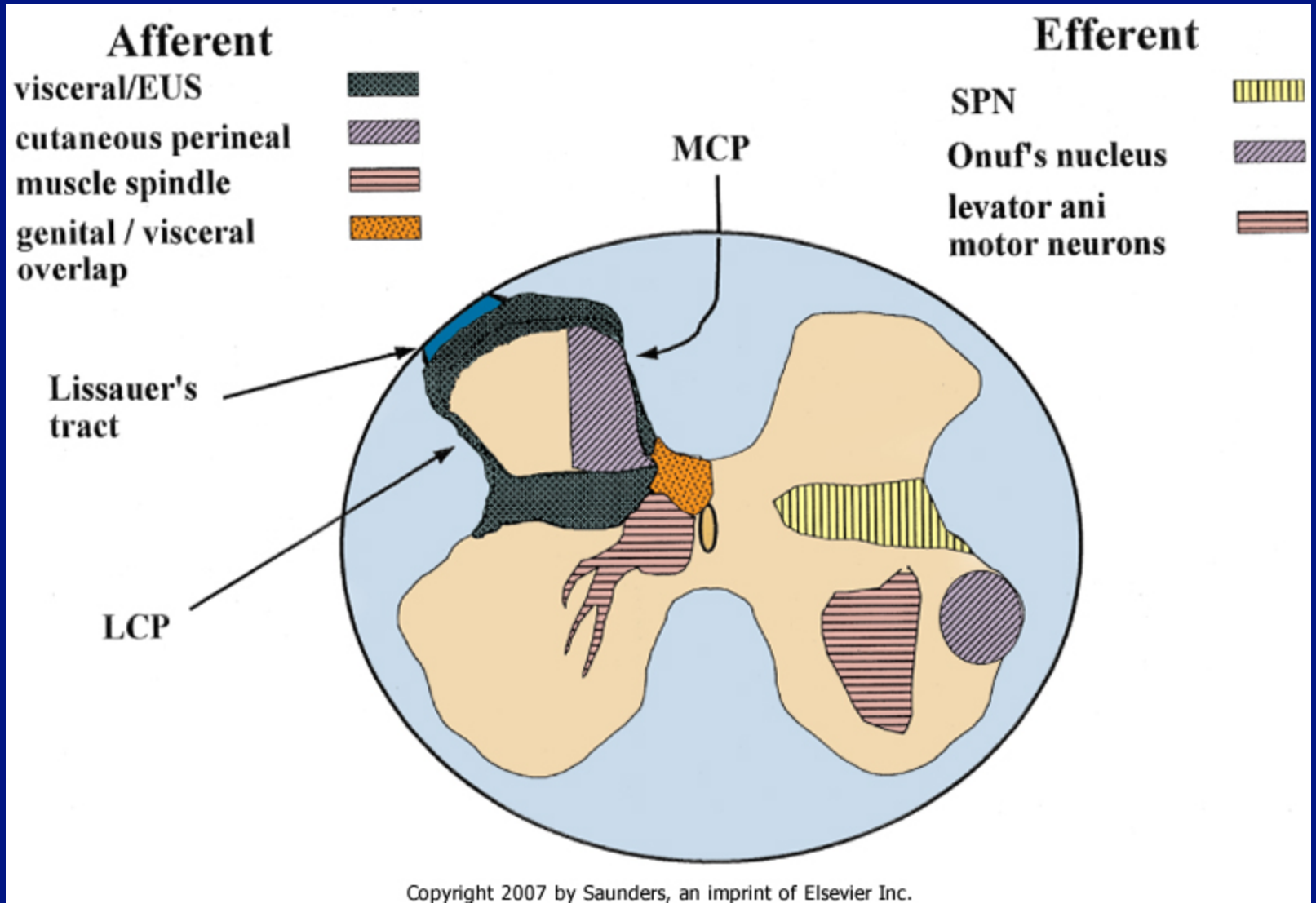


Innervation of the Lower Urinary Tract (LUT)



Adapted from Wein AJ. *Exp Opin Invest Drugs.* 2001:10:65-83.

Sacral Spinal Cord



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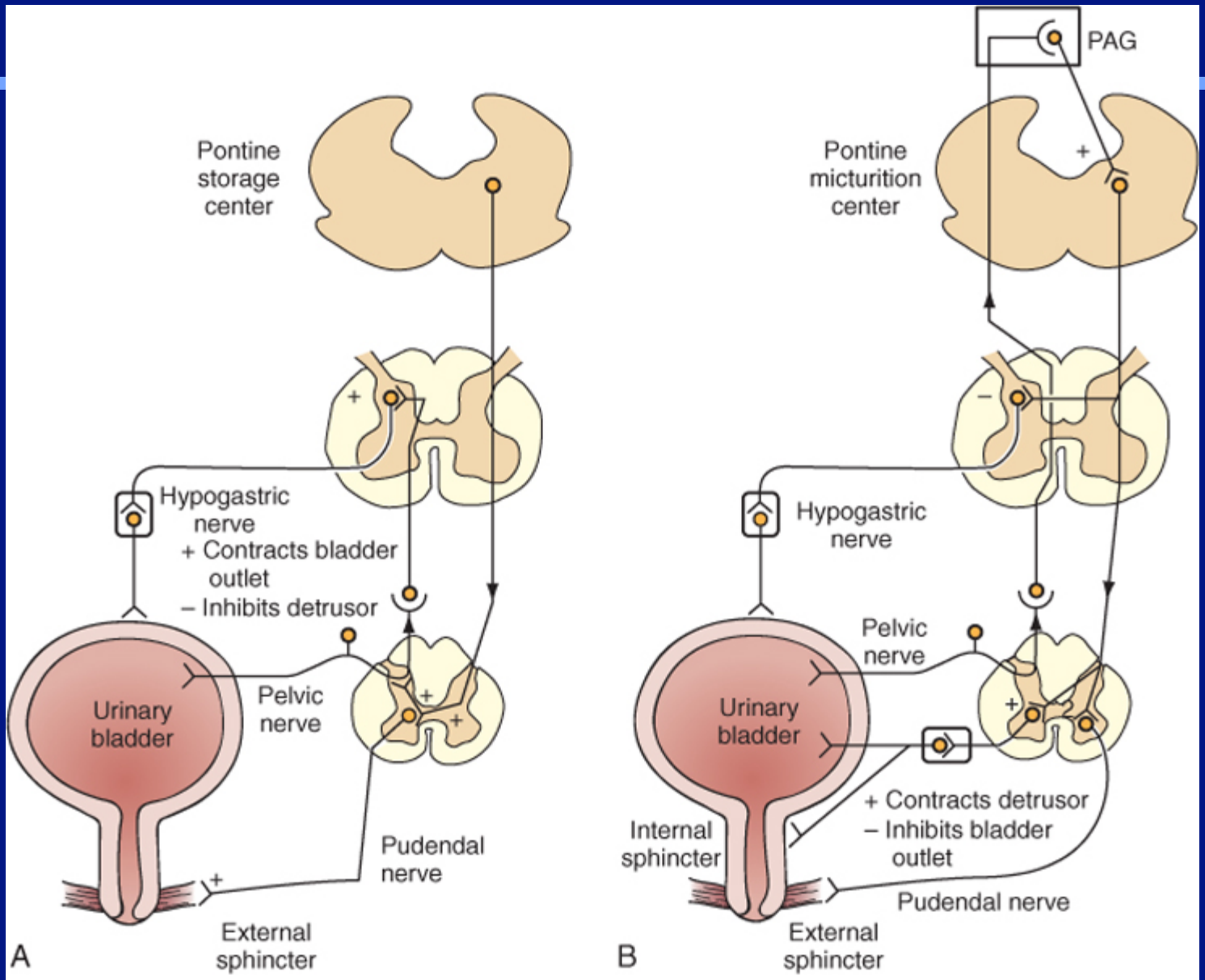
Storage & Voiding Reflex



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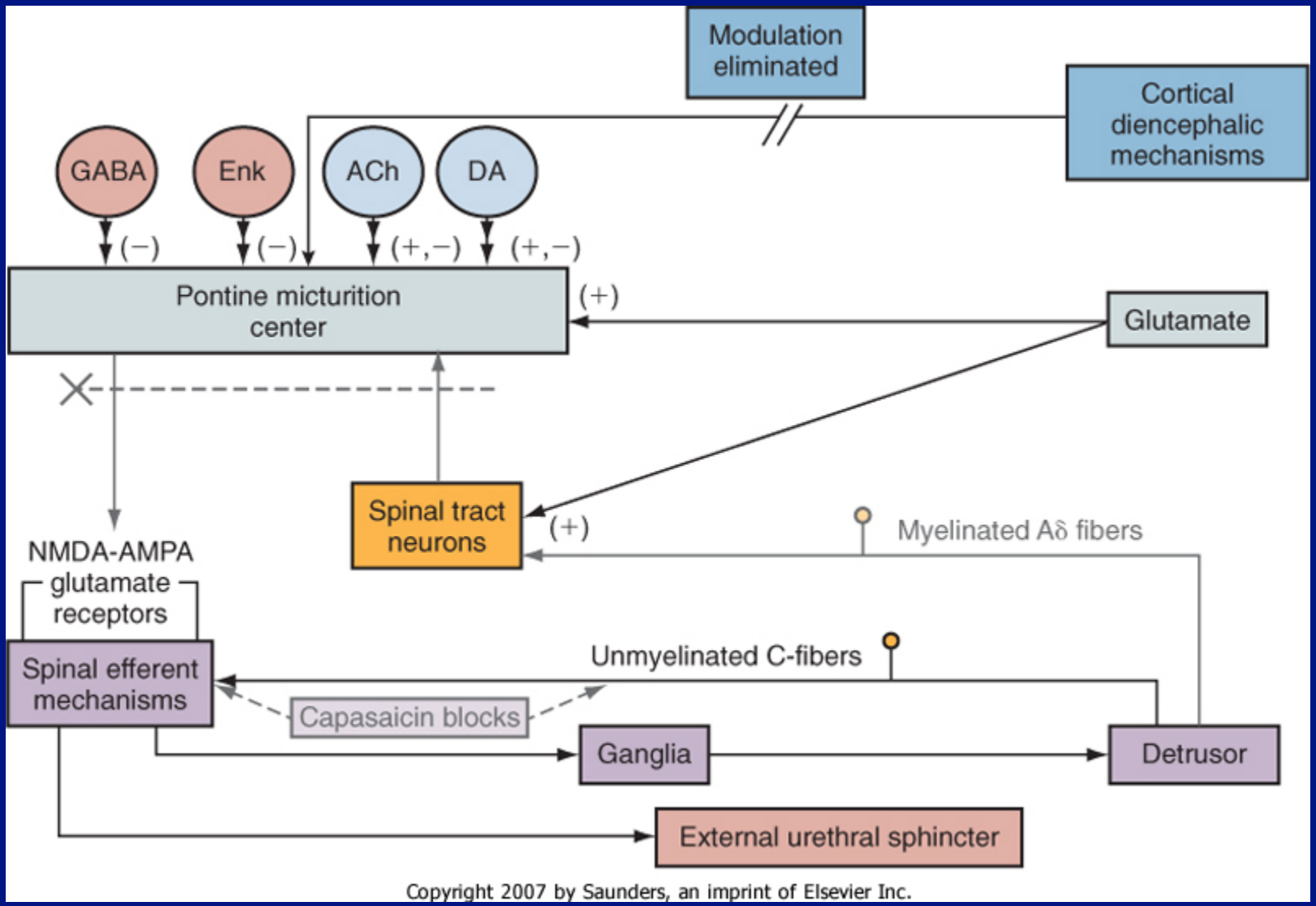
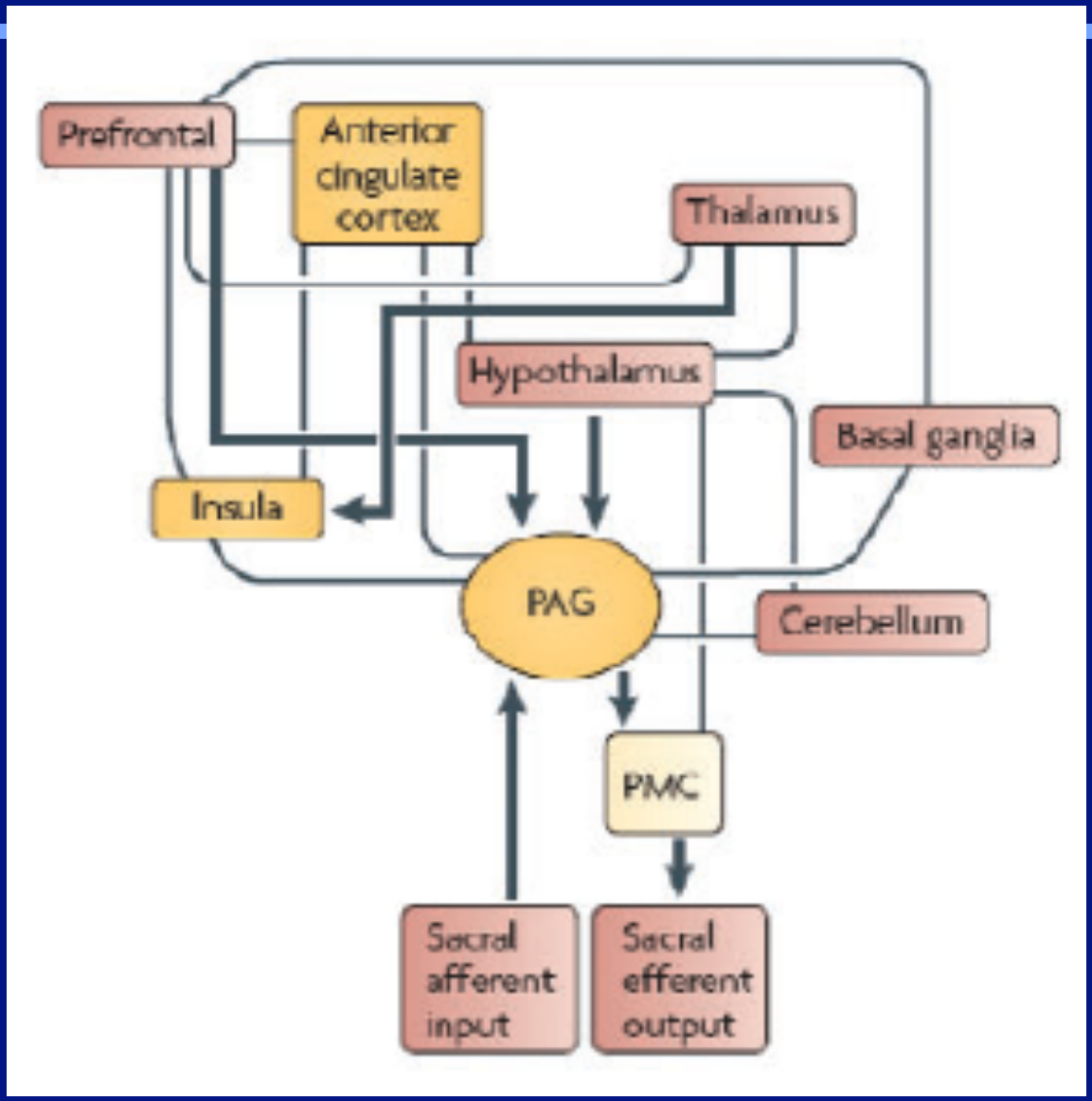
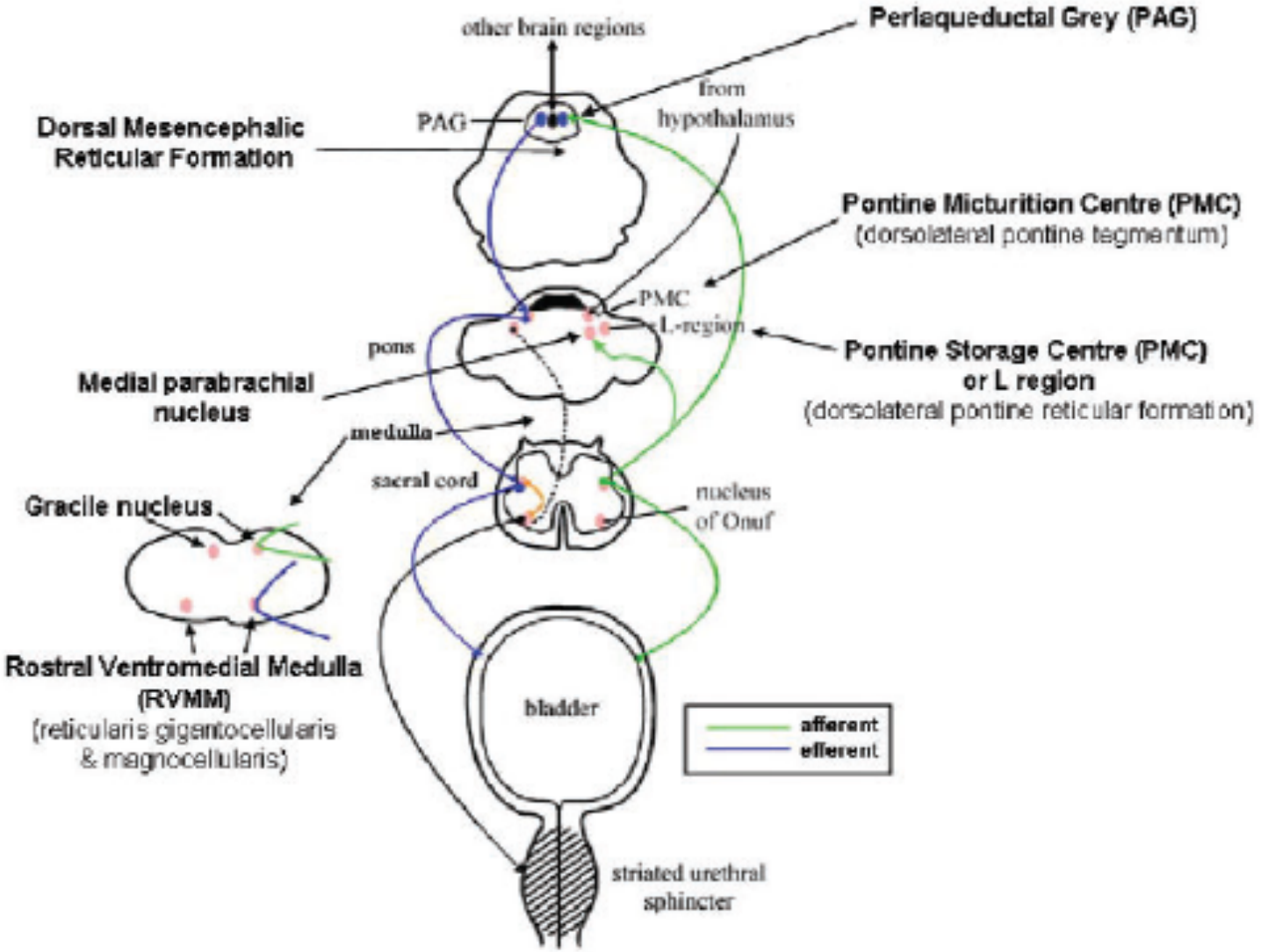
Central Reflex Mechanism of Micturition

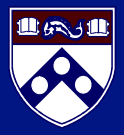


Neural Control - Mechanism

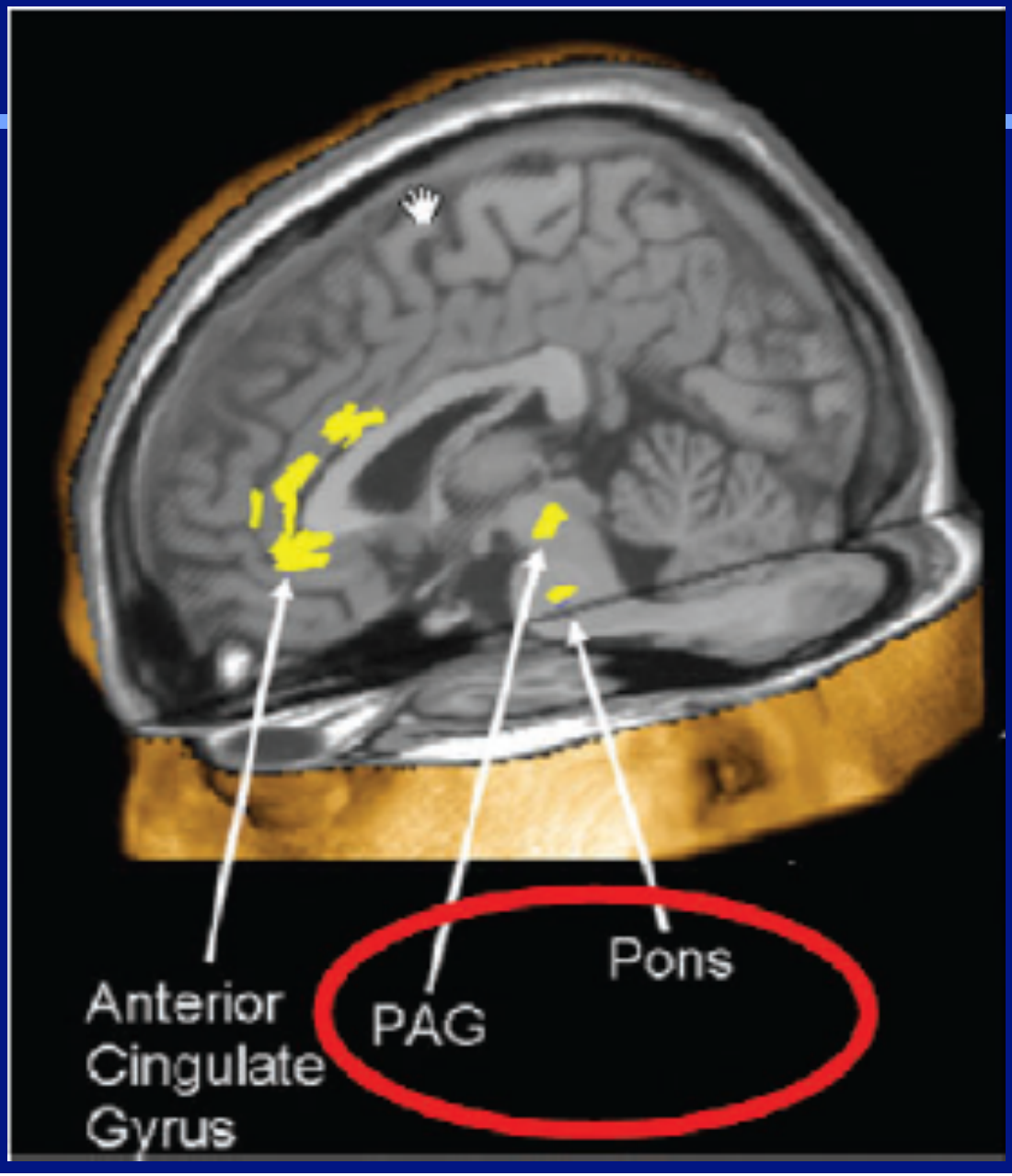


Neural Control

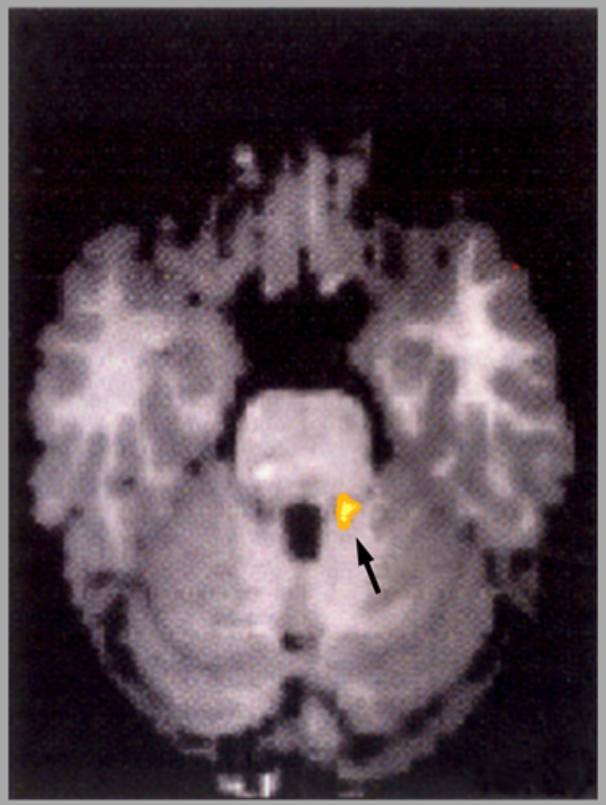




Neural Control - PET Scan



PET scanning in healthy men during micturition & continence



Activation of the ***pontine micturition centre*** during succesful voiding

Activation of the ***pontine storage centre*** during non-successful micturition

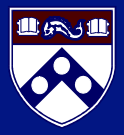
(Blok et al, Brain, 10:111, 1997)

Urodynamics Simplified

	Bladder	Outlet
Filling/storage	$P_{ves}P_{det}$(FCMG) DLPP	UPP VLPP Fluoro
Emptying phase	$P_{ves}P_{det}$(VCMG)	MUPP Fluoro EMG

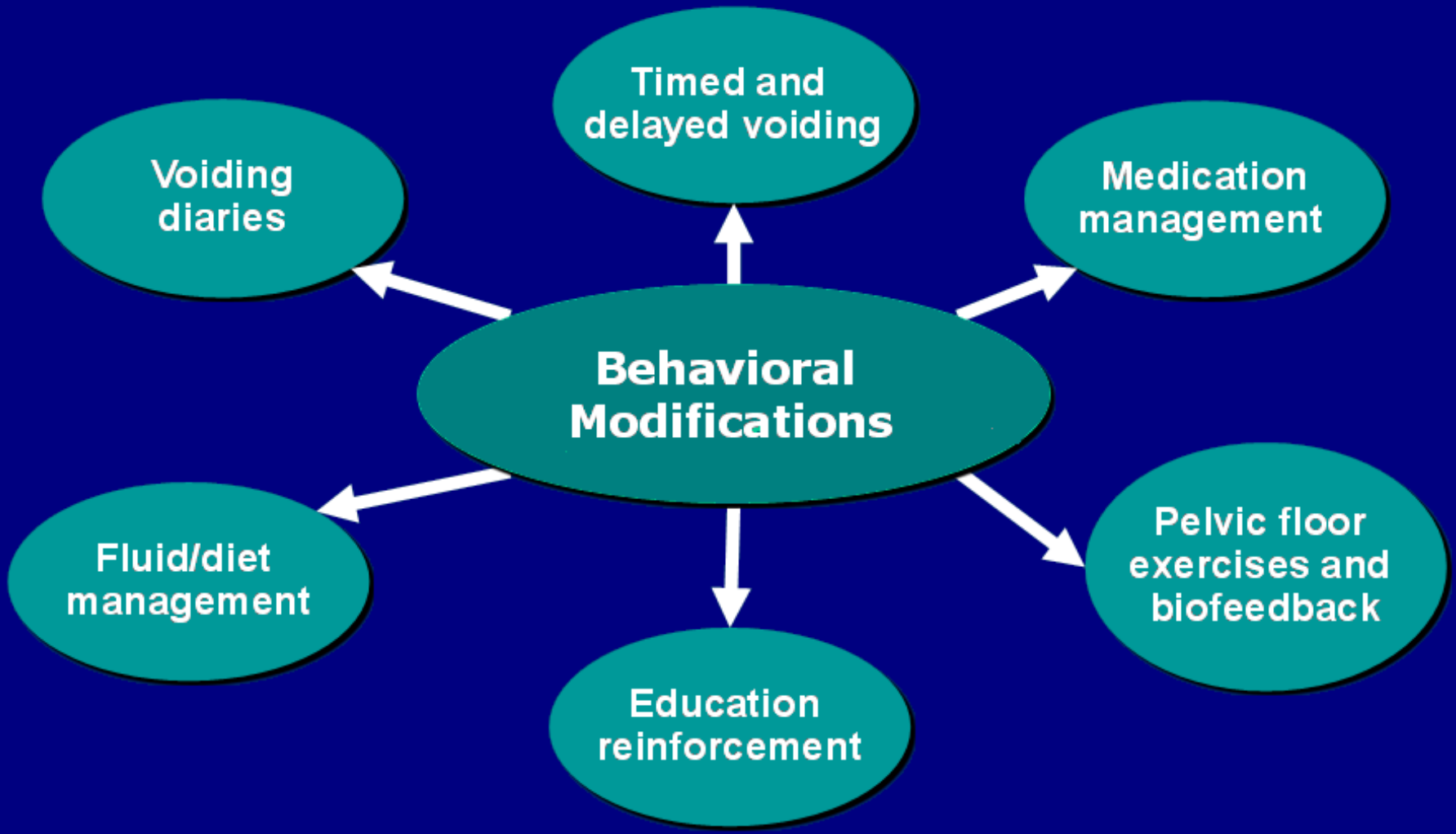
Flow

RU



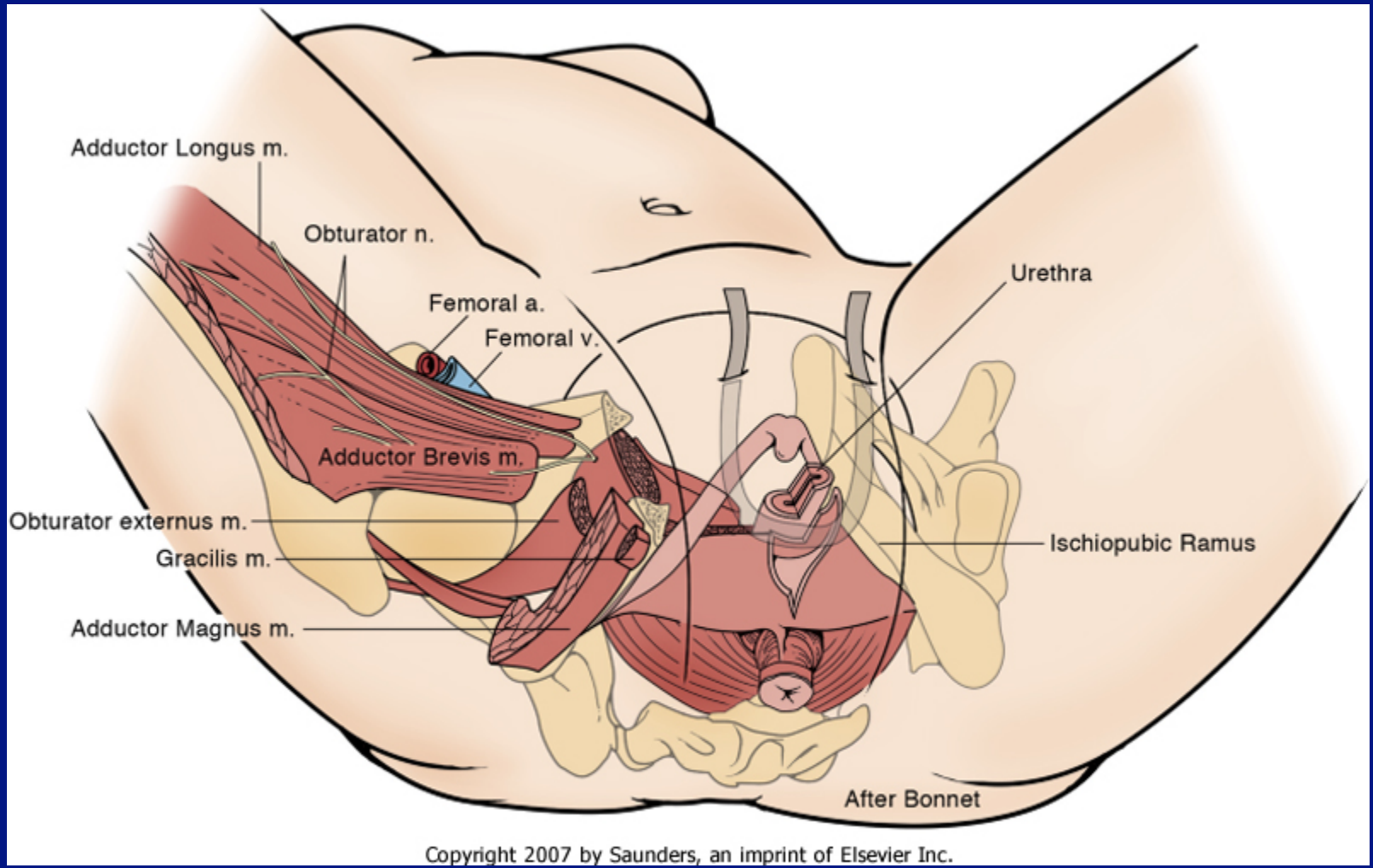

Please try to void normally.

Behavioral Modifications

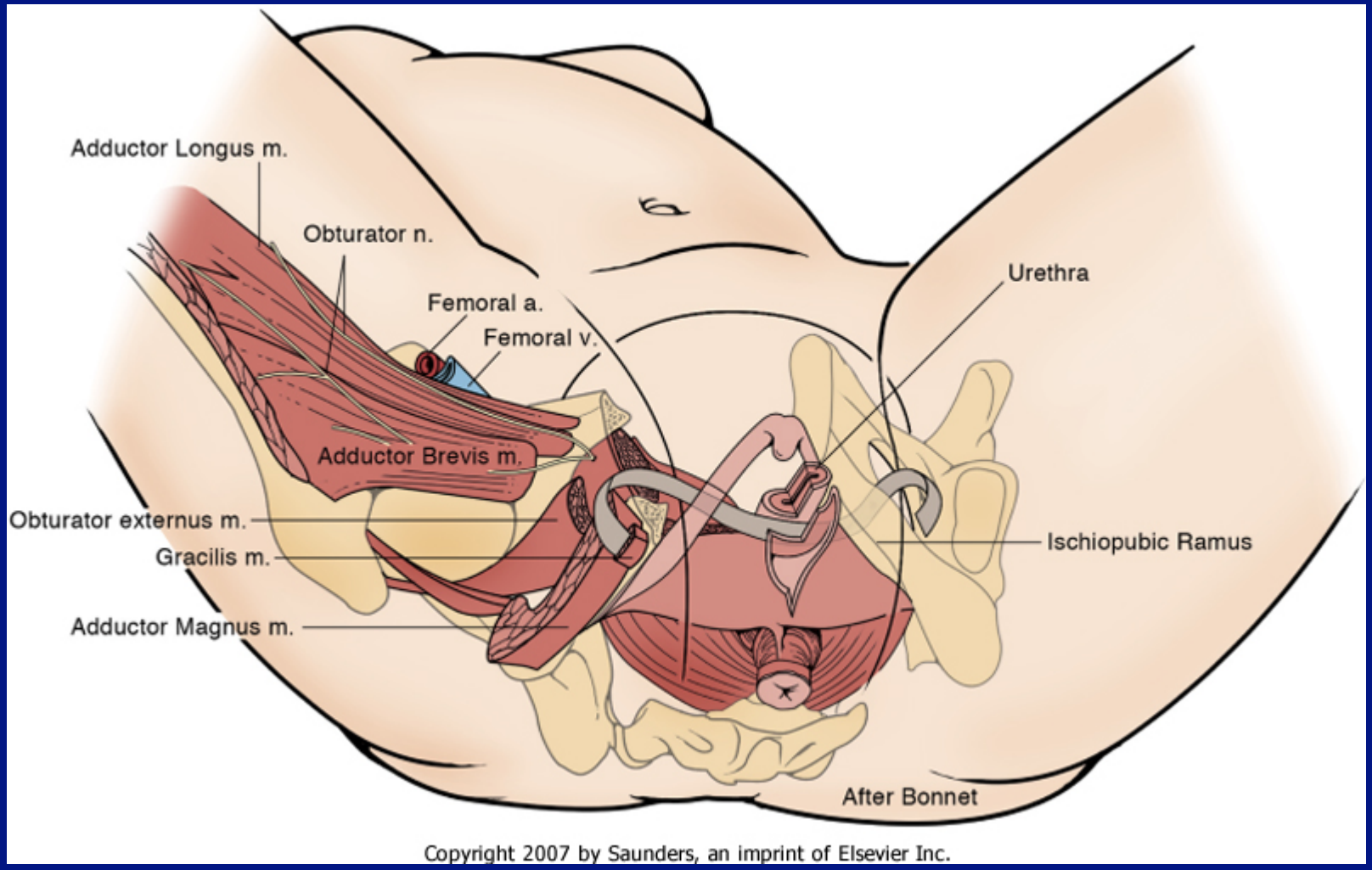


Adapted from Wein AJ. *Urology*. 2003;62:20-27.

Surgical Therapy – Mid-Urethral Sling



Surgical Therapy – Mid-Urethral Sling



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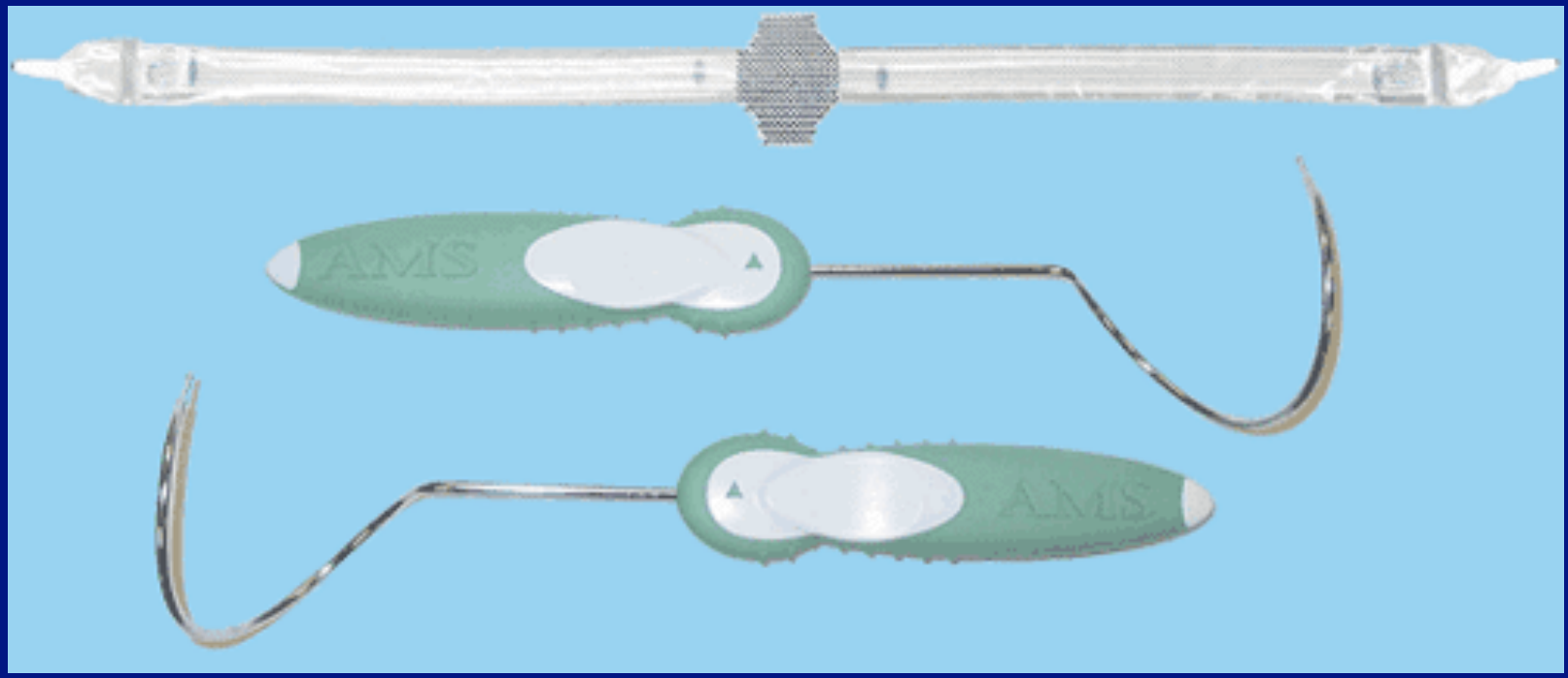
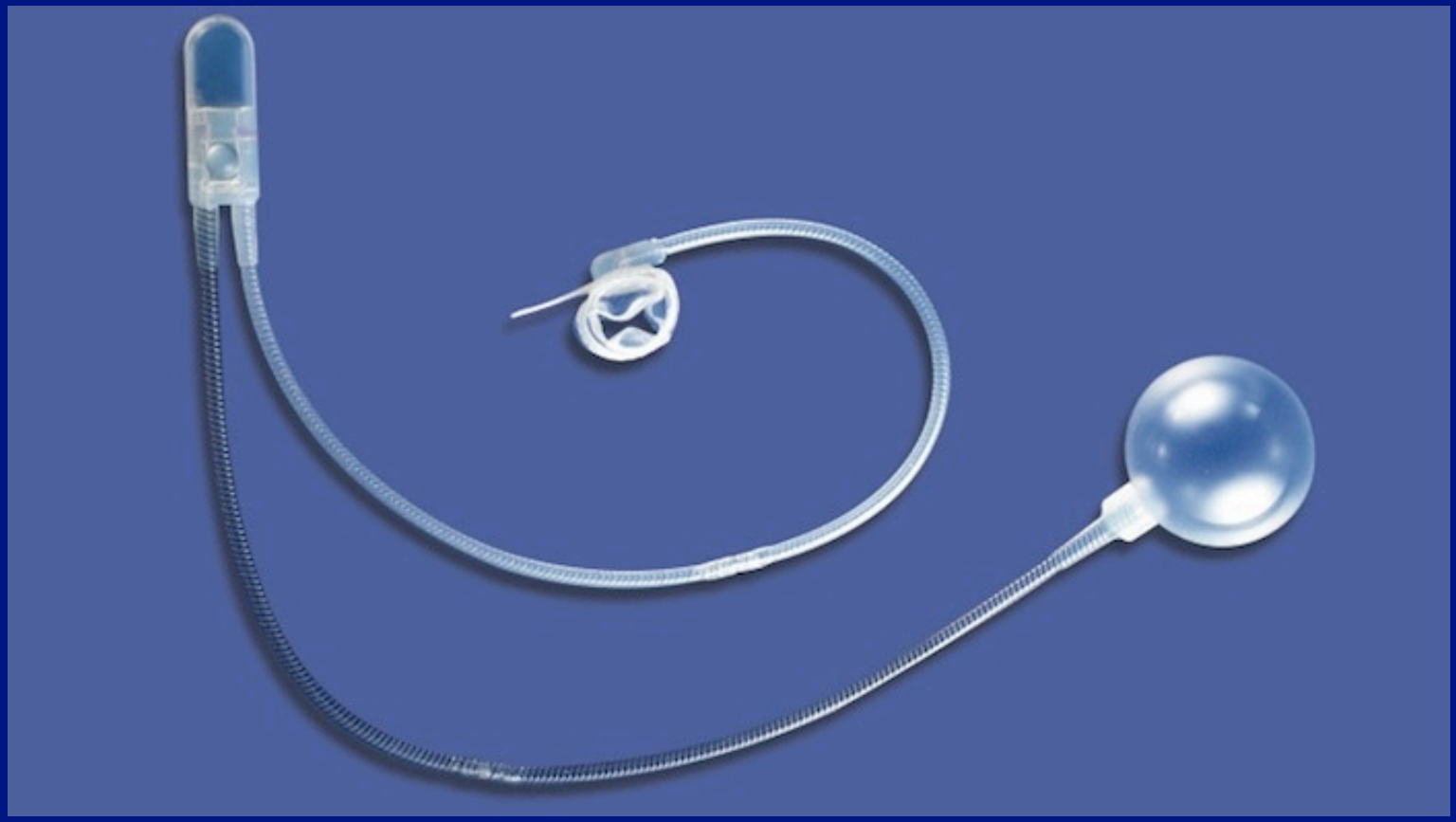
Advance Male Sling



Artificial Urinary Sphincter



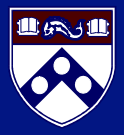
Urinary Incontinence: Accurate Statement

"I am not certain why humans or animals are continent of urine and feces and I am not convinced that anyone knows."

J Berry, 1961

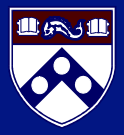
What We Don't Know: General

- **Are the "Risk Factors" Pathophysiologic elements, or just Associations?**
  - If Pathophysiologic, what is (are) the mechanism(s)?
- **Can any be altered as treatment modalities? Or, better yet, as preventative modalities (e.g. weight loss)**



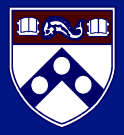
Risk Factors and Prevention / Treatment

- **Either:**
  - Remove causes (risk factors) before symptoms
  - Detect at early stage and remove (alter) causes
  - Intervene after symptoms develop, hope to improve or prevent progression
- **Requires:**
  - Definite proof of cause vs. association and mechanism
  - Identify at risk individuals
    - Ideally before symptoms develop
  - Early Treatment

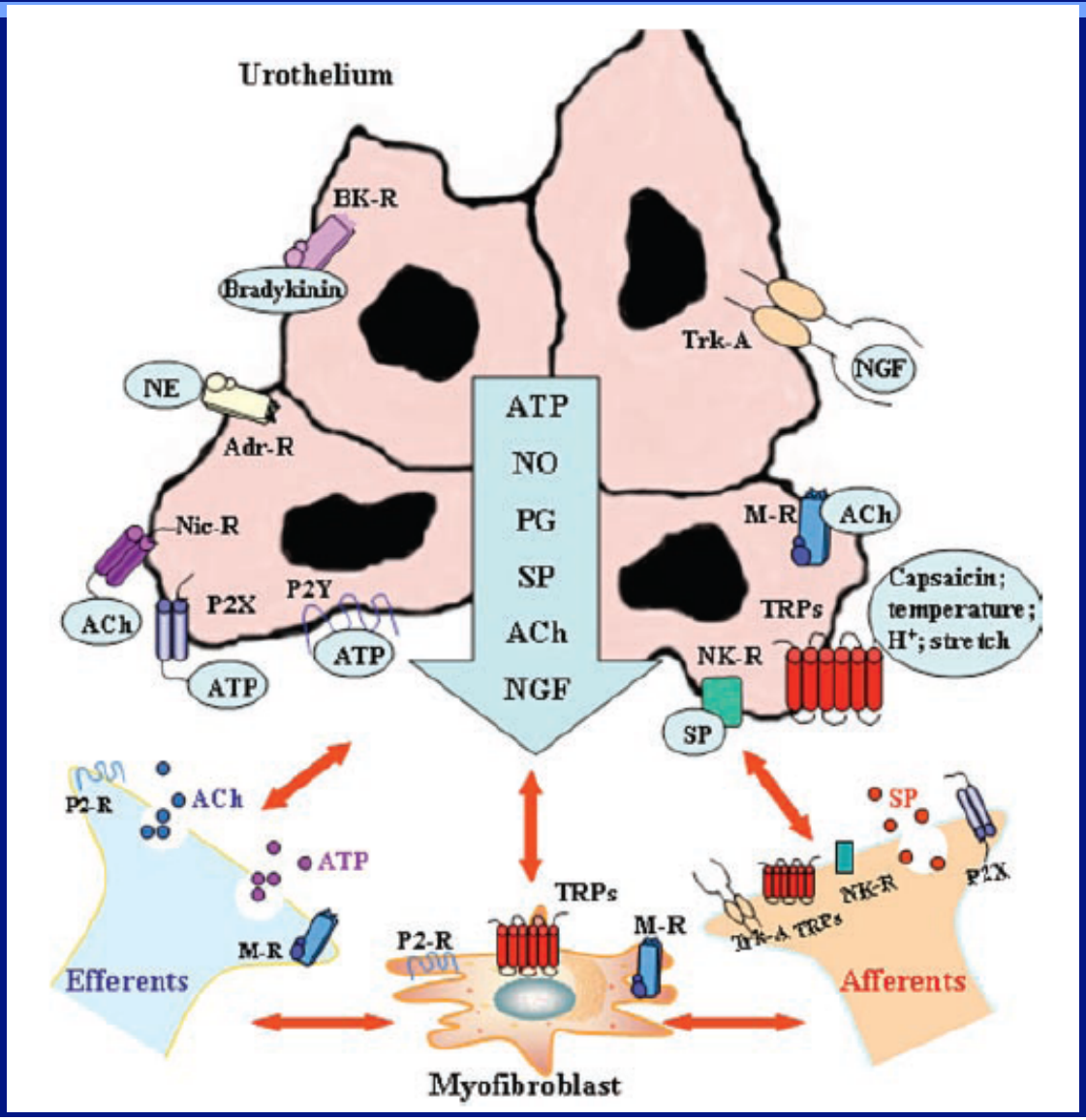


What We Don't Know: Basics (Human)

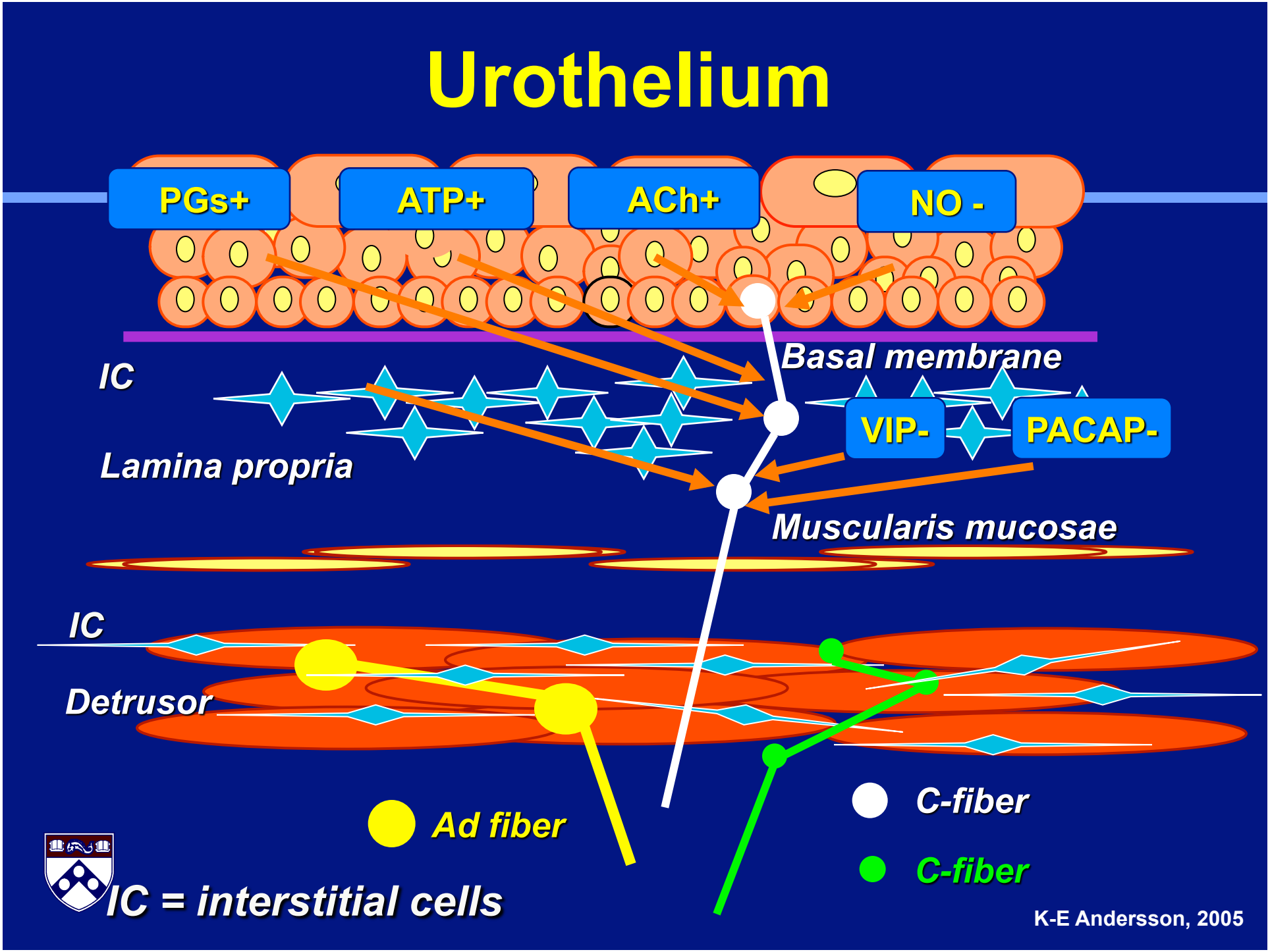
- Peripheral receptors and pathways associated with afferent and efferent innervation and their interaction(s) and the potential for agonist/antagonist therapy.
- The "real" role(s) of the urothelium and the myofibroblast in normal and abnormal filling/storage and the potential for agonist/antagonist therapy.



Birder, et al

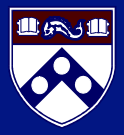

Urothelium
BK-R
Bradykinin
NE
Adr-R
Nic-R
ACh
P2X
ATP
P2Y
ATP
Trk-A
NGF
ATP
NO
PG
SP
ACh
NGF
M-R
ACh
TRPs
Capsaicin;
temperature;
H+; stretch
NK-R
SP
P2-R
ACh
ATP
M-R
Efferents
TRPs
P2-R
M-R
Myofibroblast
SP
NK-R
P2X
Trk-A
TRPs
Afferents

Urothelium


PGs+
ATP+
ACh+
NO -
Basal membrane
IC
Lamina propria
VIP-
PACAP-
Muscularis mucosae
IC
Detrusor
Ad fiber
C-fiber
C-fiber
IC = interstitial cells
K-E Andersson, 2005

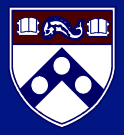
Proposed Neurotransmitters and Neuromodulators in Addition to Acetylcholine and Norepinephrine

	Central	Peripheral
Adenosine triphosphate (ATP)		x
Prostaglandins (F_2, E_1, E_2)		x
Peptides		
Opioids	x	x
Vasoactive intestinal polypeptide (VIP)	x	x
Substance P	x	x
Neuropeptide Y		x
Somatostatin		x
Bradykinin		x



Proposed Neurotransmitters and Neuromodulators in Addition to Acetylcholine and Norepinephrine

	Central	Peripheral
Amines and amino acids		
Dopamine	x	x
Serotonin	x	x
Histamine	x	x
γ-aminobutyric acid (GABA)	x	x
Glycine	x	x
Glutamate	x	x
Taurine	x	
Proline		x
Carnosine		x
Octopamine		x



Nitric Oxide

-major inhibitory NT

-mediates relaxation of urethral SM during micturition

-via a parasympathetic cholinergic pathway

-?role in controlling bladder afferent nerve activity

-role in suppressing detrusor overactivity

Urothelium

Basal membrane

Lamina propria

Muscularis mucosae

Detrusor

Adventitia

Serosa

K-E Andersson, 2005

What We Don't Know: Basics

- Central receptors and pathways associated with afferent and efferent transmission and their interaction(s) and the potential for agonist/antagonist therapy

CNS Transmitters: Numerous

- **NE:**
  - α_1 receptors facilitate some continence reflexes
  - α_2 receptors inhibit some continence reflexes
- **Serotonin:**
  - Depression of micturition reflex
  - Facilitation of "continence reflexes" (striated sphincter) @ spinal and supraspinal levels
- **GABA:**
  - Inhibitory at multiple sites
- **Dopamine:**
  - Facilitates voiding @ level of brain, ? SC
- **Glutamate:**
  - Facilitates bladder contractility at all sites @ brain and SC

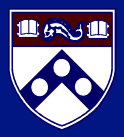
What We Don't Know:
SUI in the Female

Pathophysiology of Female SUI

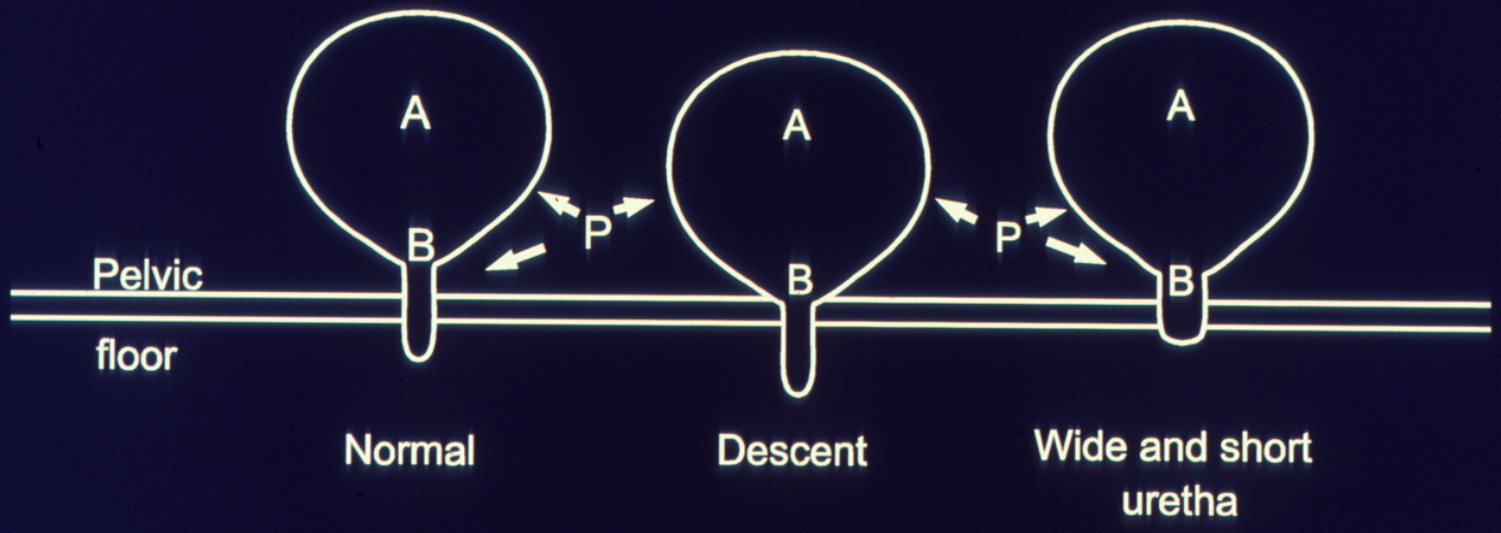
- **Einhorning**
- **Petros-Ulmsten**
- **Delancey**

} ***Does it matter?***

  - **Role of:**
    - Collagen/Elastin synthesis and metabolism
    - Estrogen environment

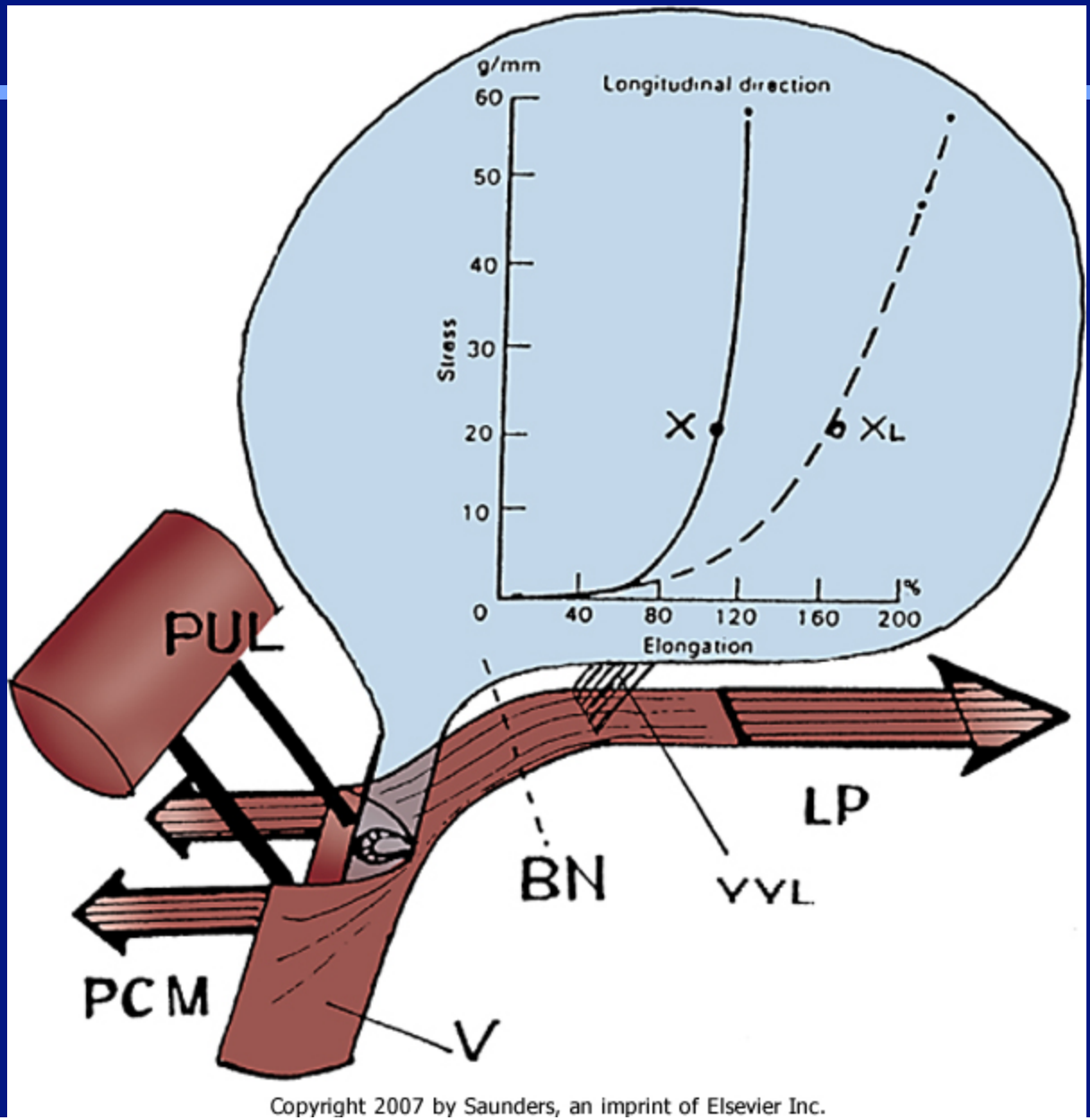


Anatomic localization of the sphincter unit



Einhorning - Stuart Stanton

Petros-Ulmsten: “Integral Theory”



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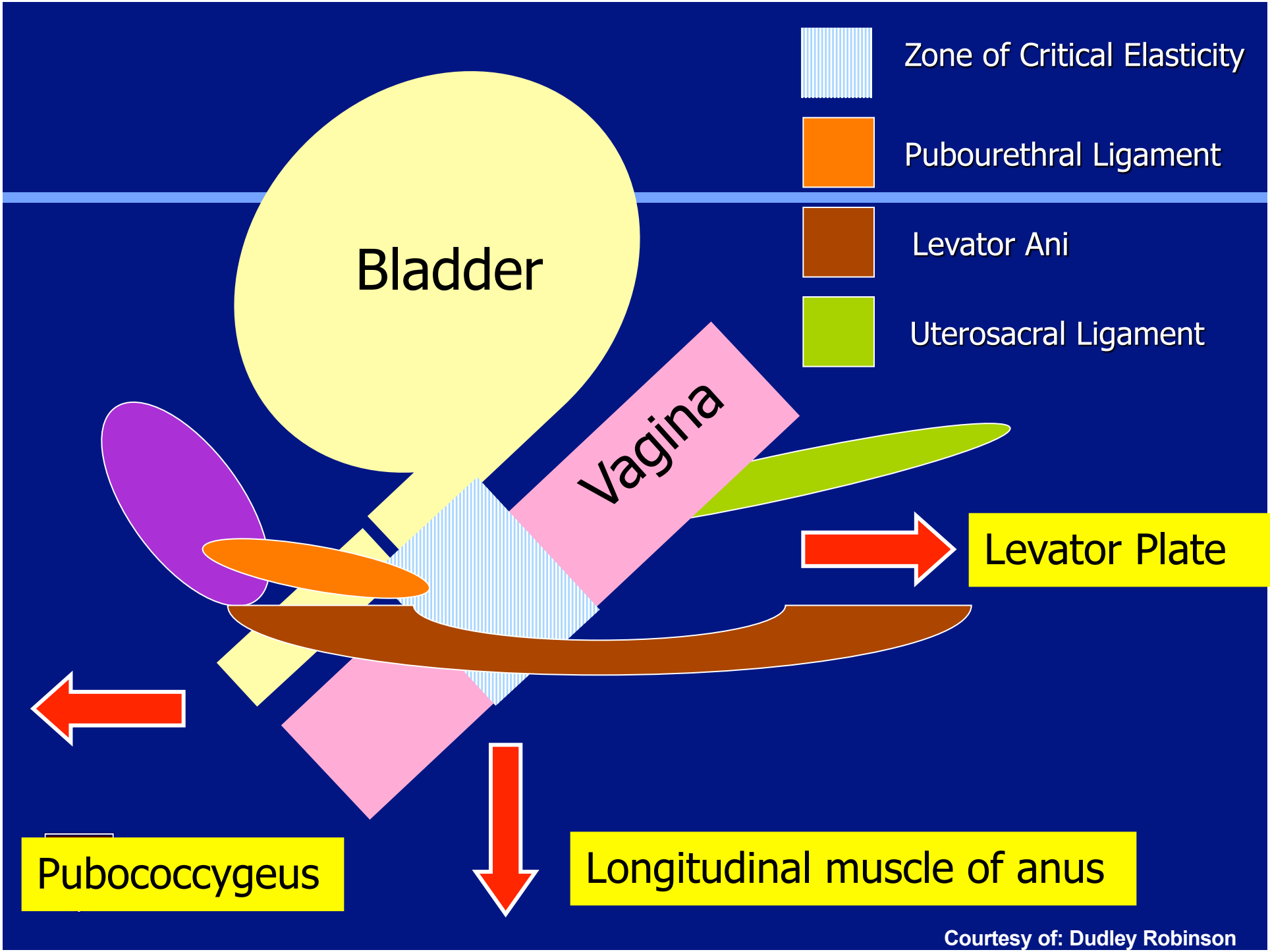
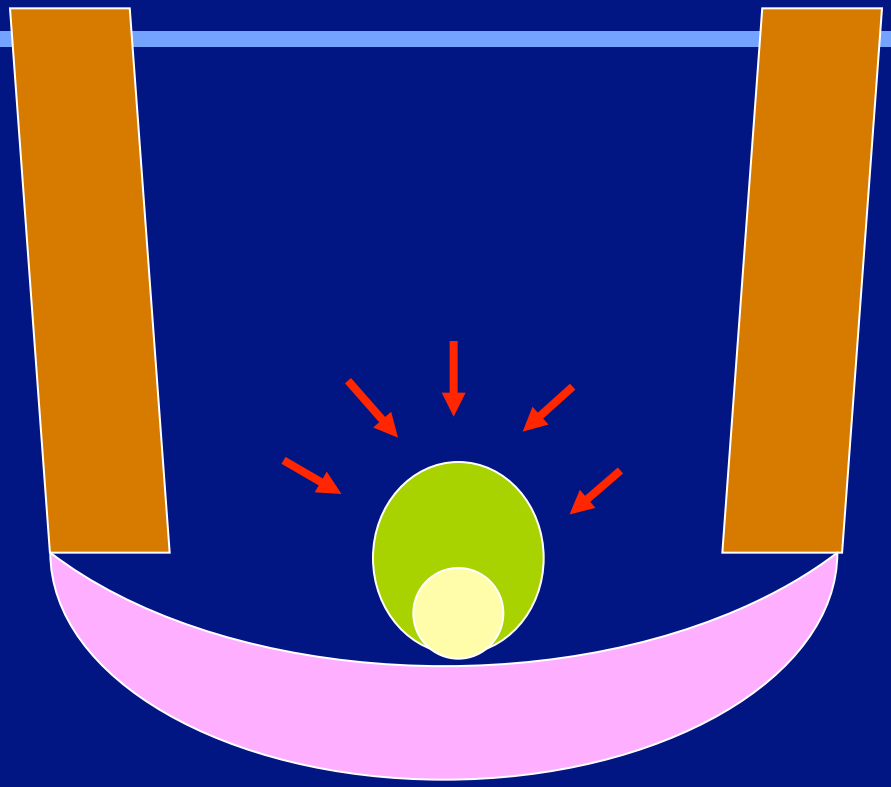
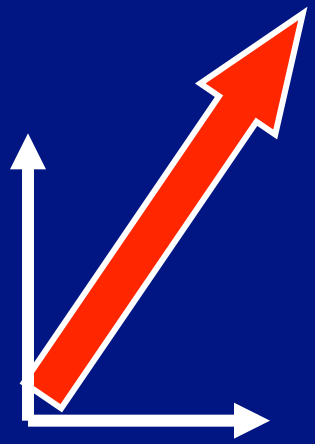

Zone of Critical Elasticity
Pubourethral Ligament
Levator Ani
Uterosacral Ligament
Bladder
Vagina
Levator Plate
Pubococcygeus
Longitudinal muscle of anus
Courtesy of: Dudley Robinson

Urethral Closure Mechanism





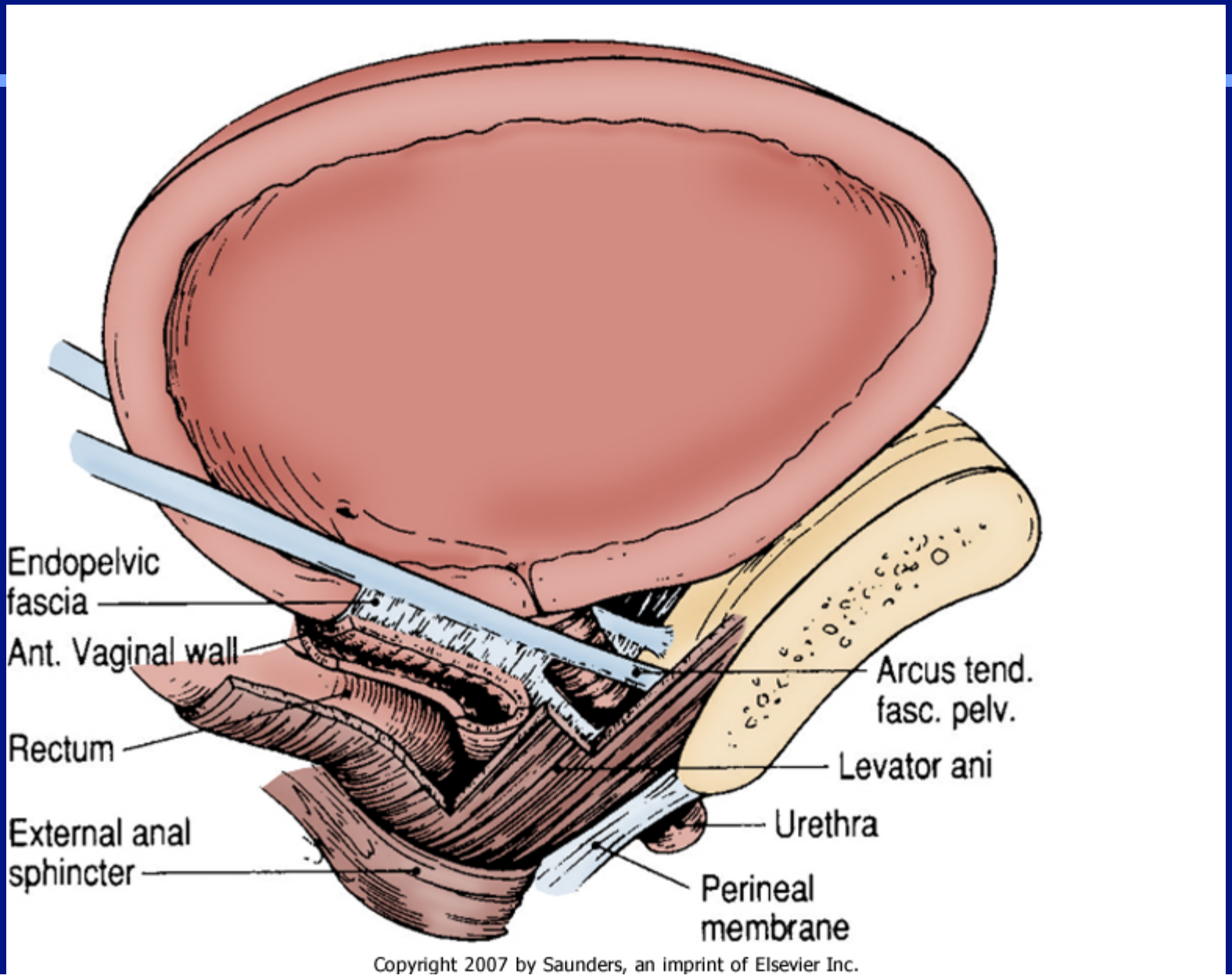
Pubococcygeus

Vagina

Periurethral Striated Muscle

Urethra

Courtesy of: Dudley Robinson



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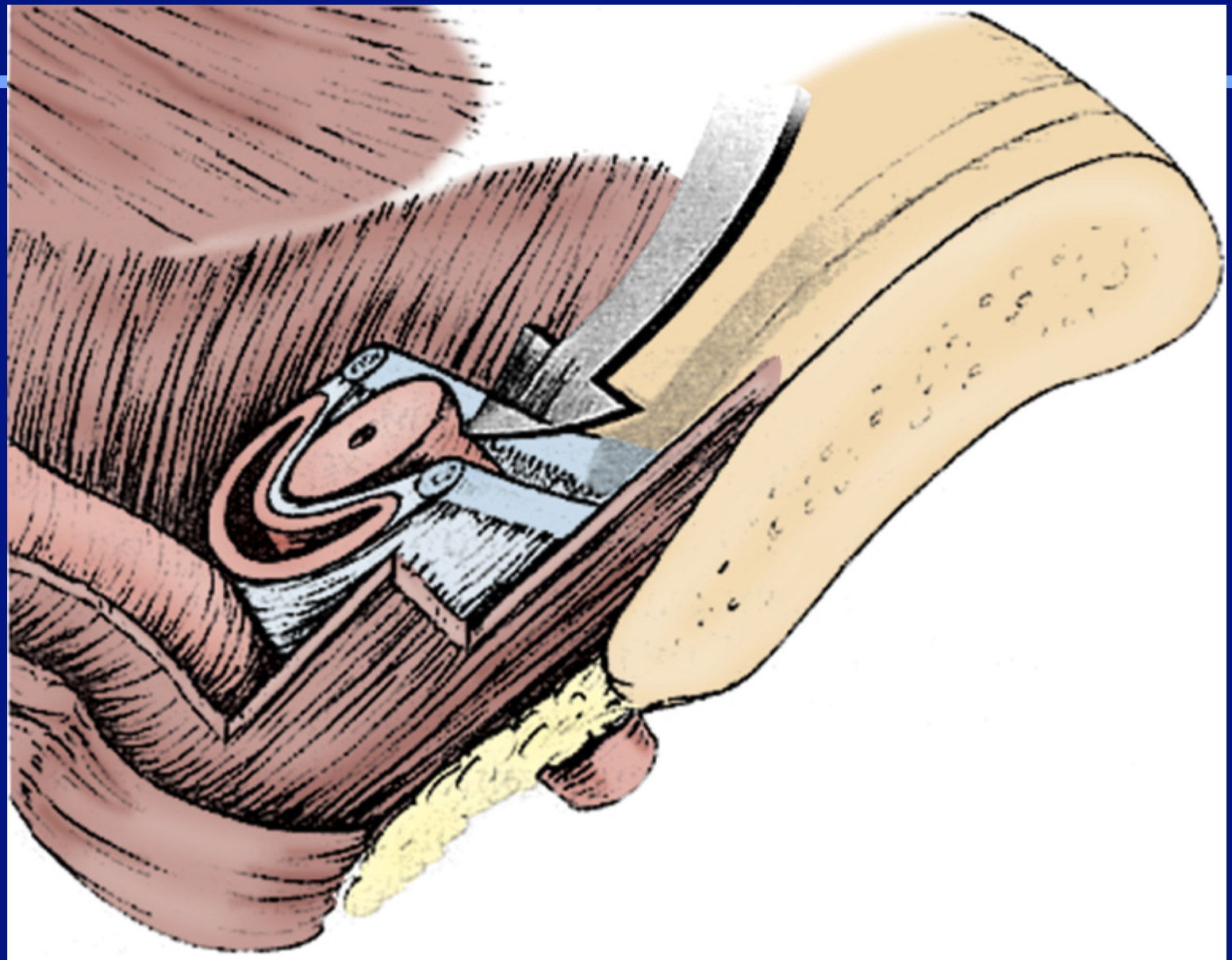
Delancey: Suburethral Hammock



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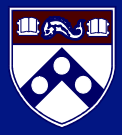
SUI in the Female: Evaluation

- **UDS, PFUDS, VUDS, Ambulatory UDS**
  - Absolute Indications?
  - Is it important to DDx “ISD” vs. Hypermobility?
  - Importance of ALPP and MUCP?
  - Importance of DO?
  - VUDS vs. PFUDS?
  - Ambulatory UDS?
  - What does EMG contribute?

In “Index” case, failed SUI surgery (incontinence, and voiding dysfunction), OAB symptoms, prolapse, neurogenic disease.

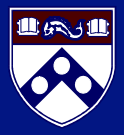


SUI in the Female: Conservative Management

- **Behavioral modification with PFMT**
  - Short and long-term results by grade of incontinence?
  - Contributions of each component?
  - Does PFMT change the characteristics of the “striated” sphincter?
    - If so → How?
  - How much, how long, by whom or what?

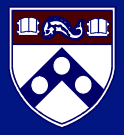
SUI in the Female: Conservative Management

- **Periurethral Bulking**
  - Mechanisms of action?
  - New materials better than old?
  - Results and satisfaction?
  - Stem cell therapy: Promise or Reality?



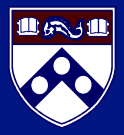
SUI in the Female: Surgical Management

- Colposuspensions (Multiple)
- Traditional Sling
- Mid-Urethral Sling, TVT, TOT
- “Mini”-Sling, Adjustable Sling, or Balloons

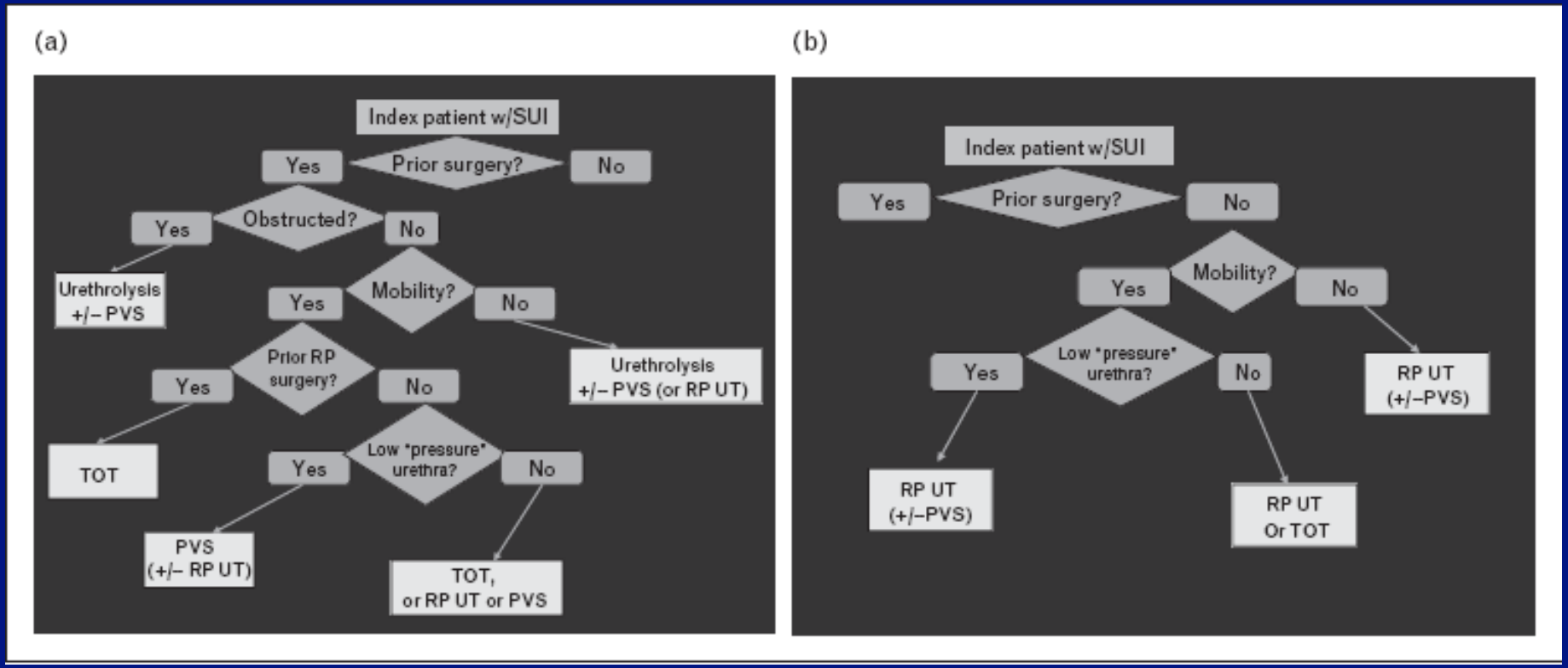


SUI in the Female: Surgical Management

- **Is it possible to construct algorithm for:**
  - Index case
  - SUI + POP
    - POP + (+) Stress Test
    - POP + (-) Stress Test + (+) Reduction Test
    - POP + (-) Stress Test + (-) Reduction Test
  - Failed colposuspension
  - Failed MUS
  - SUI + OAB
  - SUI + concomitant urethral pathology



Rovner's Algorithm



Prior Failed SUI Surgery

Without Prior Surgery

Rovner et al, Current Opinion in Urology. 2009; 19:362-367

SUI in the Female: Pharmacologic Therapy

- **Activation of smooth or striated muscle of the outlet – Possible?**
  - Selectivity
    - Receptors
    - During filling/storage only
    - What happened to Duloxetine?
    - Other SNRI or Selective NRI Compounds?
- **Estrogen**
  - No, Maybe, or Yes?
  - Therapy
    - Sole?
    - Adjunct to drug or surgical therapy
    - Oral or Vaginal

SUI in the Female: Outcomes

- **What is cure, satisfaction, success?**
- **Outcomes**
  - Objective
  - Semi-Objective
  - Subjective
    - Global
  - Adverse
- **Can we establish a common reporting system?**
  - "Truth among friends"

Patient Global Impression of Improvement (PGI-I)

- Very much better
- Much better
- A little better
- No change
- A little worse
- Much worse
- Very much worse

- Validated for treatment of Stress Urinary Incontinence (SUI)

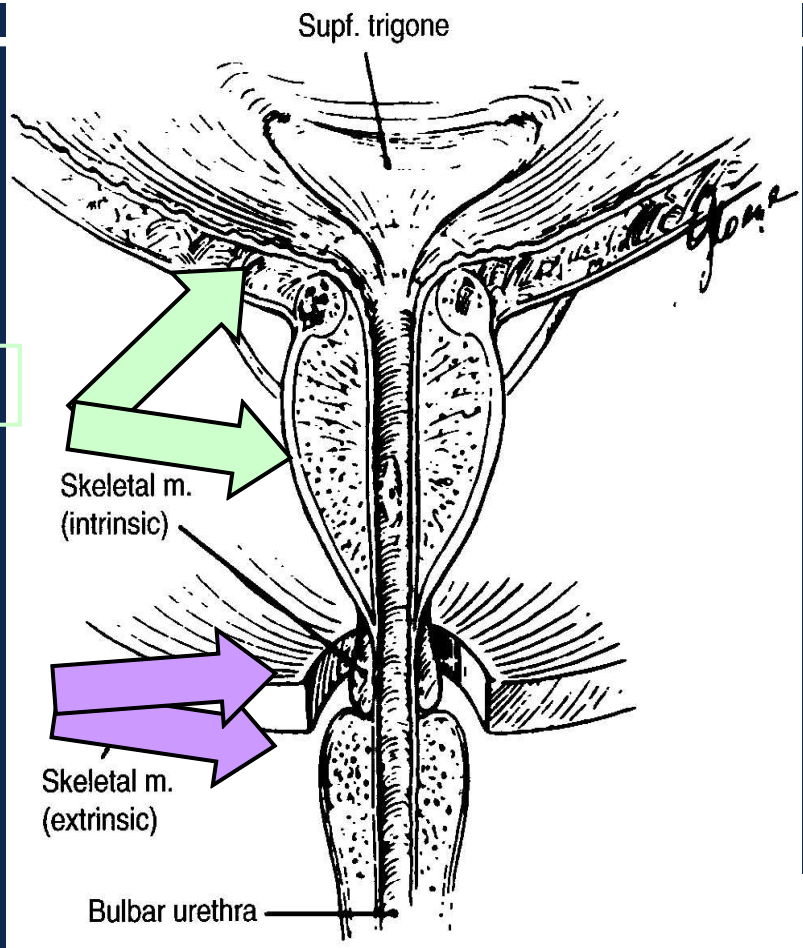
Yalcin I, Bump. RC Am *J Obstet Gynecol.* 2003;189:98-101.

What We Don't Know:
SUI in the Male (Post-Prostatectomy)

Native Sphincters(Male)

Proximal sphincter unit

Distal sphincter unit

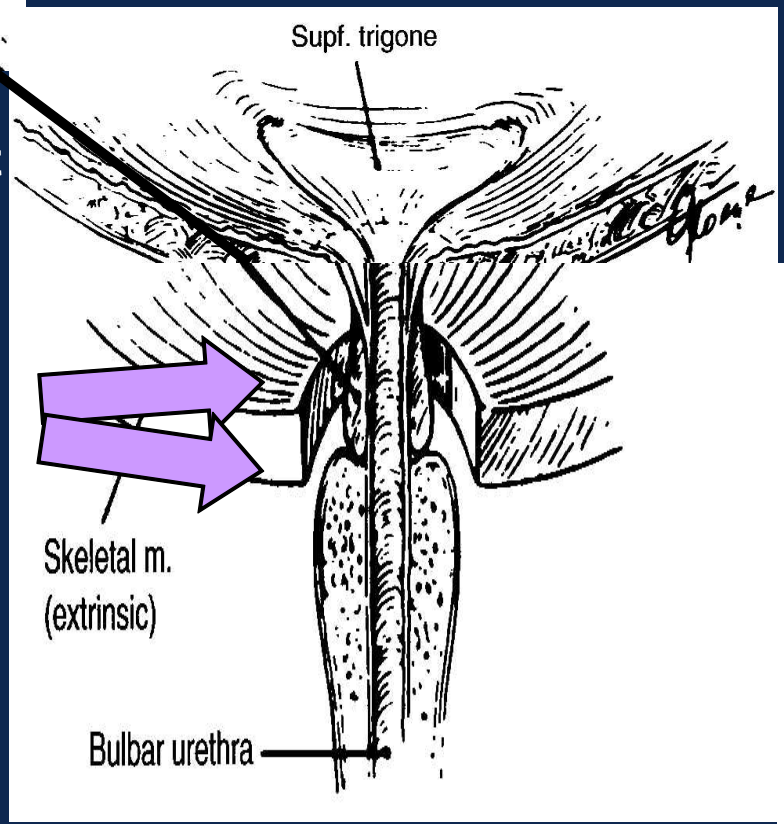


Hadley: Campbell's Urology (1986)

Post Prostatectomy

Proximal sphincter unit

Distal sphincter unit



Hadley: Campbell's Urology (1986)

PPI: Pathophysiology

- **Contributions of:**
  - Neural
  - Vascular
  - Muscular
    - Smooth
    - Striated

} ***Components***

- **Can Knowledge Aid Prevention?**

PPI: Risk Factors

- Age?
- Prostate Size?
- Membranous Urethral Length?
- Diabetes?
- Other Neuromuscular Diseases?
- Can knowledge aid prevention or a better informed choice of therapy?

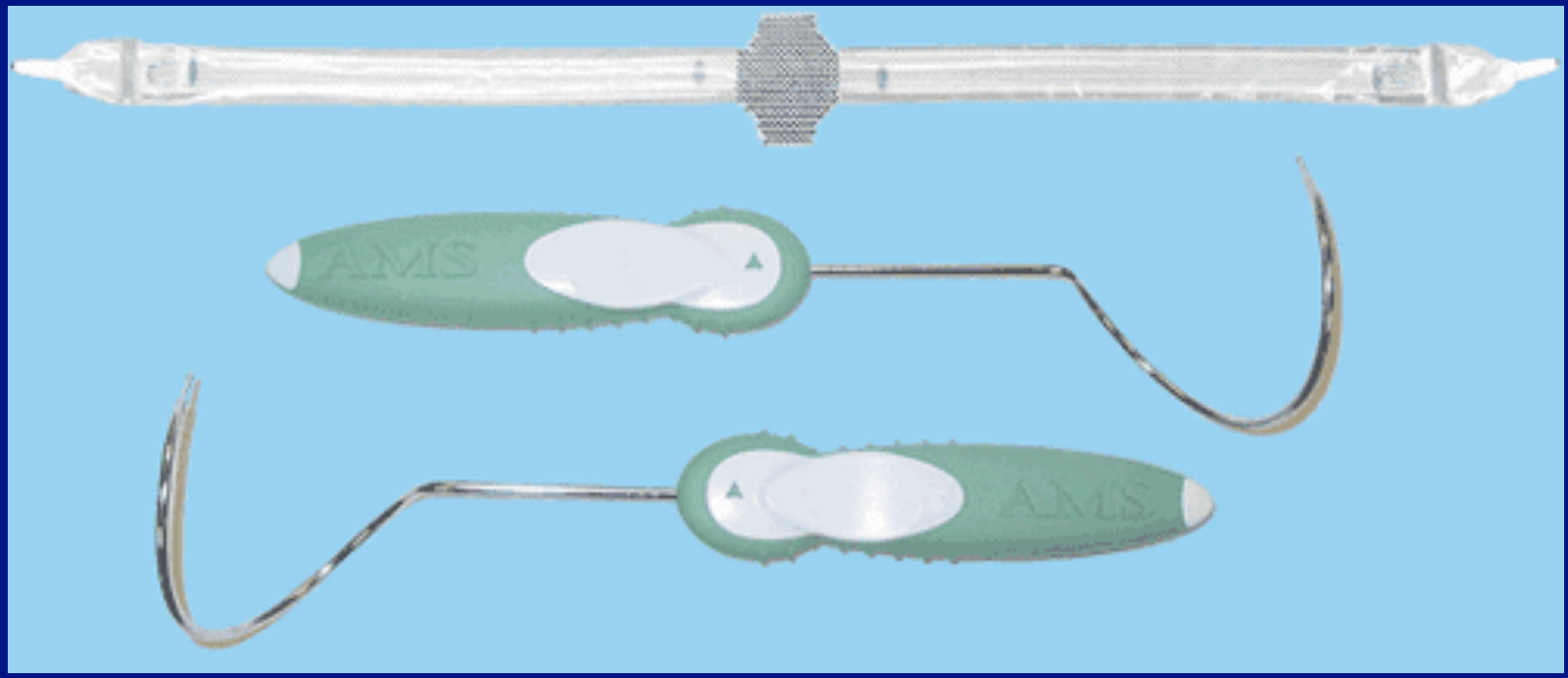
PPI: Evaluation

- **Predictive value of UDS, PFUDS, VUDS?**
- **Significance of DO?**
- **Significance of "DUA"?**
  - How do we diagnose this?
- **Significance of ALPP, MUCP?**
- **What does EMG contribute?**

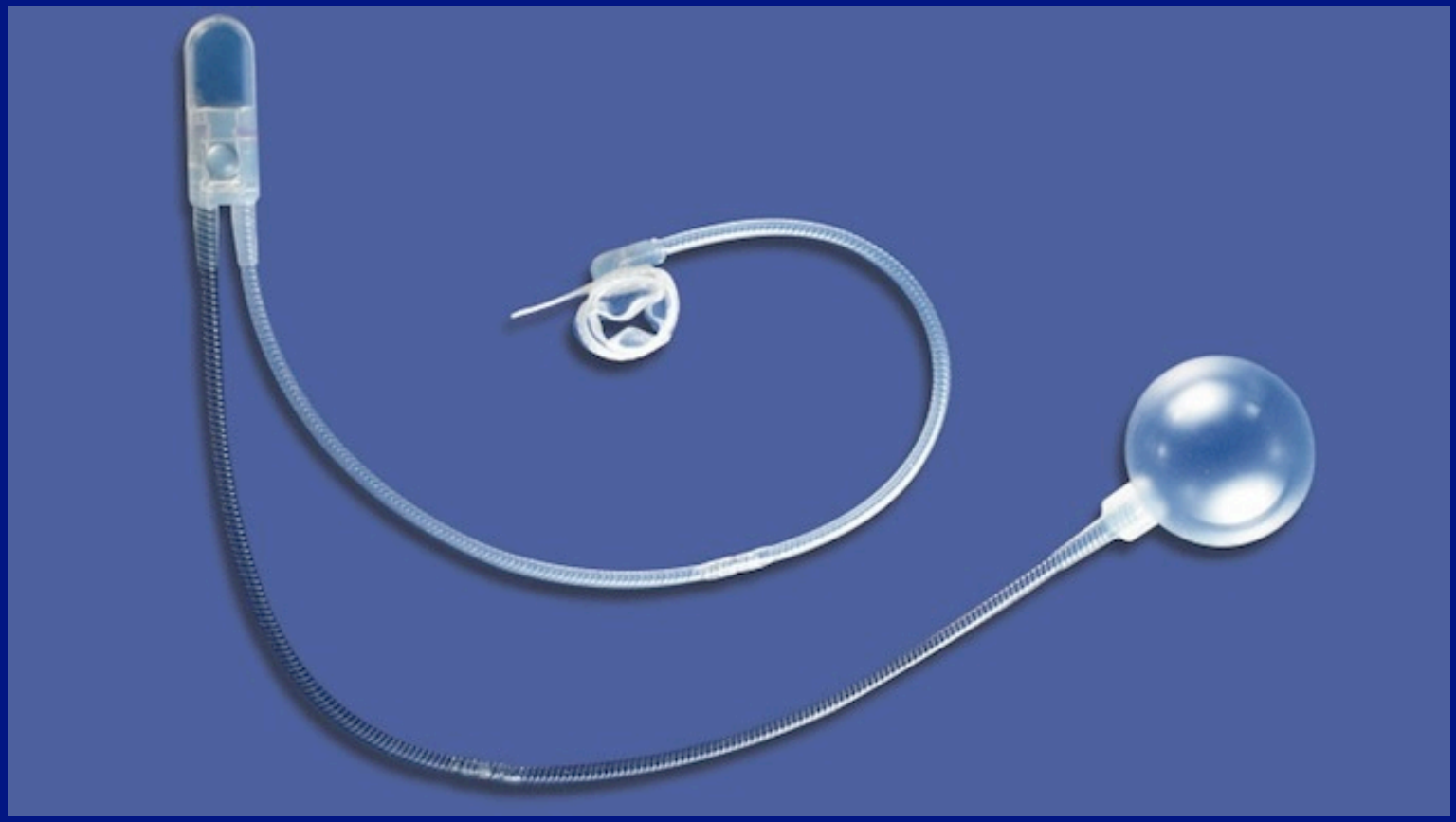
PPI: Treatment

- **Role of Slings vs. AGUS**
  - Mechanism
    - Compressive, “Repositioning”, Both?
  - Durability?
    - Further treatment if failure?
  - Stem Cell Therapy
    - Promise or Reality?

Advance Male Sling



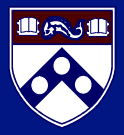
Artificial Urinary Sphincter



What We Don't Know:
OAB Incontinence

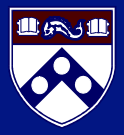
OAB Incontinence: Pathophysiology

- No single set of data or hypothesis explains all IVC (abnormal micturition reflex) or occurrences of urgency/frequency
- 5 concepts seem potentially valid



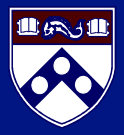
OAB Incontinence: Pathophysiology

1. Faulty central inhibition - true neurogenic (DeGroat and others)
2. Myogenic (combination of Brading-Gillespie concepts)
3. ACh leak – micromotion concept (Andersson)
4. Urothelial Initiation (Birder, Andersson)
5. Pelvic Floor Laxity (Petros-Ulmsten)



OAB Incontinence: Pathophysiology

- **Does this have implications for different types of drug therapy?**
  - Yes
  - What are they?
    - Depends on the transmitters involved and the level of the pathology.



OAB: Pathophysiology as it Relates to Therapy

- If the pathophysiology options are "True", OAB can be due to only one or a combination.
- For #2 (Myogenic) and #5 (Pelvic Floor Laxity) and for non-muscarinic modes of activation in #1 (Neurogenic) and #4 (Urothelial Initiation) antimuscarinics would be minimally or less effective

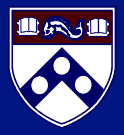
Potential Targets for Pharmacotherapy of OAB

Central

- Cerebral cortex
- Midbrain (pontine micturition center)
- Spinal cord

Peripheral

- Motor (efferent) systems
  - Autonomic
  - Somatic
- Sensory (afferent) systems
  - C-fibers
  - Aδ-fibers



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OAB: Future Pharmacotherapy Ideas

- Potassium Channel Openers (M,S)
- Calcium Channel Blockers (M)
- 5-HT1a Antagonists (M)
- P2X3 Antagonists (M)
- P2X2, P2X, Antagonists (M)
- NK1 Antagonists (S)
- B3 Agonists (M, ?S)

M= Motor S= Sensory

OAB Incontinence: Drug Therapy

- **Beyond Antimuscarinics**
  - Beta Agonists
    - Alone, or In Combination?
    - Drug-Drug Interactions?
  - Which others are possible?

OAB: Future Pharmacotherapy Ideas

- PG Synthesis Inhibitors (?M, S)
- PG Antagonists (EP 1, 3 Receptors) (M)
- Vit D3 Analogues (M)
- Rho Kinase Inhibitors (M)
- Na Channel Blockers (S)
- SNRIs (M,?S)

M= Motor S= Sensory

OAB: Future Pharmacotherapy Ideas

- Vanilloid Receptor Antag/Agonists (S)
- Botulinum Toxin (M,S)
- PDE Inhibitors (M)
- TPRV1 and 8 Antagonists (S)
- Centrally Acting Drugs (M,S)
- Cannabinoids (?)
- Nociceptin/Orphanin FQ (S)
- Gene Therapy (S)

OAB Incontinence: Botulinum Toxin Therapy

- **Does demonstration of DO make a difference?**
- **Mechanism of action?**
  - Afferent, Efferent, or Both
  - Transmitters Involved
- **For Neurogenic and Non-Neurogenic**
  - Location(s)?
    - Relates to sensory locations and spread of impulses.
  - Depth?
  - Dose?

OAB Incontinence: Estrogen

- No, Maybe, or Yes?
- Physiologic Role in sensory and motor function of the LUT in the adult?
- Pharmacologic effects on the sensory and motor function of the LUT?
- Oral or vaginal?

Central Neurotransmitters Involved in LUT Function

- GABA
- Dopamine
- Glutamic acid
- Enkephalins
- Serotonin
- Norepinephrine

Problems: Entry into CNS and specific site of action

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OAB Incontinence: Neuromodulation

- **Mechanism(s) of Action?**
- **Sacral vs. Posterior Tibial vs. Vaginal vs. Magnetic (?). Transcutaneous?**
  - Same MOA, just different effects based on distance from CNS and type(s) of fibers activated?

OAB Incontinence: Surgical Therapy

- **Ingleman – Sundberg (54) ?**
- **Detrusor Myomectomy (63) ?**
- **SUI Surgery and OAB**
  - How much SUI needs to be present?
  - Resolution of OAB symptoms?
  - Worsening? De Novo?
  - Persistence?
  - Mechanism, when effective?

OAB Incontinence: Outcomes

- **What is cure, satisfaction, success?**
- **Outcomes**
  - Objective
  - Semi-Objective
  - Subjective
    - Global
  - Adverse
- **Follow-up: how long is long enough?**
- **Can we establish a common reporting system?**
  - "Truth among friends"

Patient Global Impression of Improvement (PGI-I)

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What We Don't Know:
Pelvic Organ Prolapse as It Relates to Incontinence

POP

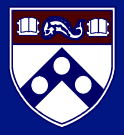
- "Pelvic Medicine and Reconstructive Surgery"
- So, cant ignore it or just "throw a few stitches"

POP: As it relates to incontinence

- **What is the relation (and pathophysiologic mechanism of any effect) to:**
  - OAB?
  - SUI?
- **Could Petros be correct?**
- **POP correction can favorably or unfavorably affect OAB, make manifest or worsen SUI (if no SUI correction).**

POP: Pathophysiology

- **Risk factors**
  - Contributors or Associations?
  - Possible Points of Alteration
- **Common to SUI**
  - Role of Collagen/Elastin synthesis and metabolism?
  - Role of Estrogen?

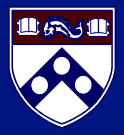


POP: Conservative Therapy

- **Defining outcomes and satisfaction (SUI, OAB)**
- **Conservative Management (Pessaries)**
  - Long term persistence and success?

POP: Surgical Therapy

- **Surgical Management**
  - Anterior
  - Posterior
  - Apical
- **Role of open, vaginal, lap/robotic techniques?**
- **Use of synthetics?**
- **Concomitant SUI procedure?**
  - Colposuspensions (Multiple)
  - Traditional Sling
  - Mid-Urethral Sling, TVT, TOT
  - “Mini”-Sling, Adjustable Sling, or Balloons



Thank You

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