SI PUO' VINCERE LA CISTITE RICORRENTE?



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Recurrent Urinary Tract Infections
R-UTI's

DEFINITION

3> episodes of cystitis in the last 12 months

2> episodes in the last 6 months

PREVALENCE

1 out of 3 adult women experiences a cystitis

1 out of 4 of these will develop R-UTI's

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CISTITI SEMPLICI?

CISTITI SEMPLICI = *UNCOMPLICATED UTI's*

***COMPLICATED UTI's*: calcoli, pielonefriti, stents**

TAKE HOME MESSAGE

CISTITI RICORRENTI

Situazioni complesse

Epifenomeno di multiple disfunzioni in più apparati

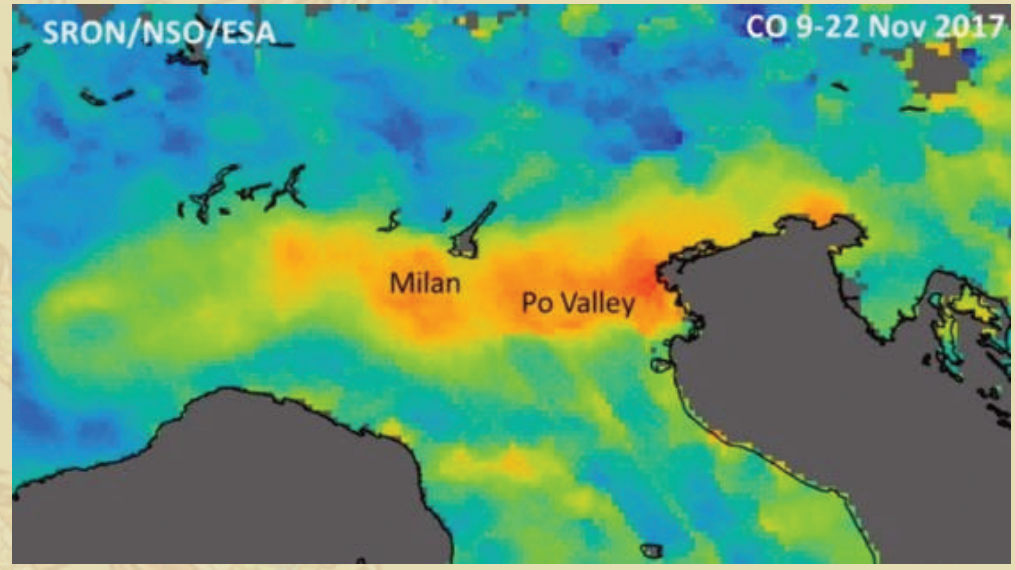
Associate a plurime comorbilità

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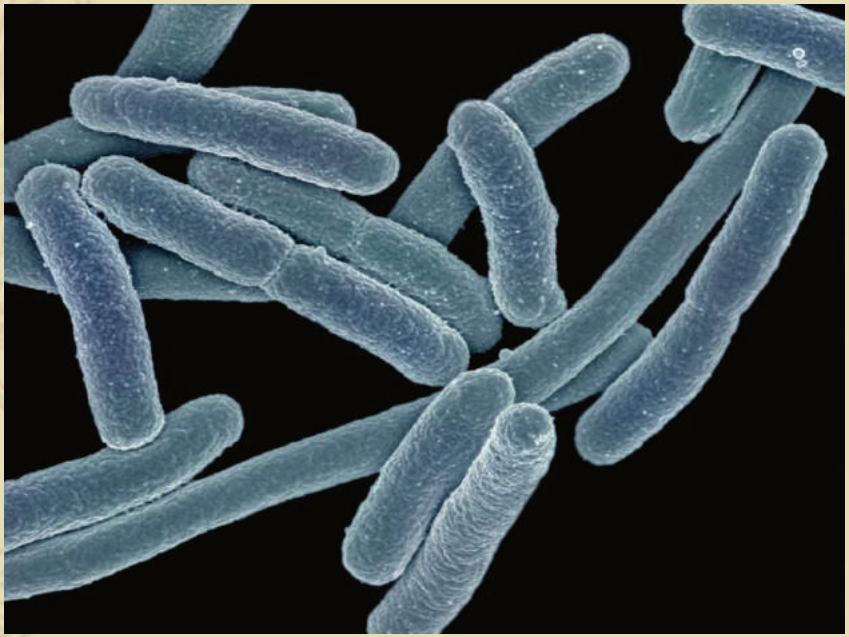
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SVIZZERA
ALPI LEPONTINE
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FRANCIA
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Dora Riparia
Torino
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Stura di Demonte
Cuneo
ALPI MARITTIME
Mar Ligure
Po
Pavia
Alessandria
Tanaro
Bormida
Scrivia
APPENNINO LIGURE
Sondrio
ALPI OROBIE
Varese
Como
Lecco
Adda
Lambro
Olona
Sesia
Milano
Serio
Oglio
Mella
ORTLES
Bolzano
Trento
Isarco
Belluno
Piave
Treviso
Adige
Verona
Venezia
ITALIA
Mincio
Mantova
POLESINE
Cremona
Piacenza
Trebbia
Taro
Parma
Enza
Parmaj
Panaro
Modena
Secchia
Ferrara
Po di Volano
Mare Adriatico
APPENNINO TOSCO-EMILIANO
40 km

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FATTORI PREDISPONENTI ALLE RUTI's

1. BATTERI
2. URINE
3. VESCICA
4. URETRA
5. VAGINA
6. PAVIMENTO PELVICO
7. INTESTINO
8. VIE DI DIFFUSIONE BATTERICHE

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I BATTERI NELLE RUTI's

1. Fattori di virulenza batterica
2. Antibioticoresistenze multiple
3. Biofilm batterici
4. Comunità batteriche intracellulari

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Recurrent Urinary Tract Infections
R-UTI's Species

85% ***Escherichia Coli***

15% ***Proteus Mirabilis, Enterococcus Fecalis***

KES (Urea-splitting bacteria): ***Klebsiella, Enterobacter, Serratia, Pseudomonas Aeruginosa, Staphylococcus Saprophyticus, Staphylococcus Aureus, Chlamydia Trachomatis, Mycoplasma, Candida Spp***

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UPEC: Uropathogenic *Escherichia Coli* Virulence Factors

Type 1 pili: FimH adhesin molecule binds mannose-containing glycoprotein receptors of urothelial cells

Type 2 pili: secretion systems (T2SS) binds galactose-containing receptors



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Agenzia sanitaria e sociale regionale

RegioneEmiliaRomagna
SERVIZIO SANITARIO REGIONALE EMILIA-ROMAGNA

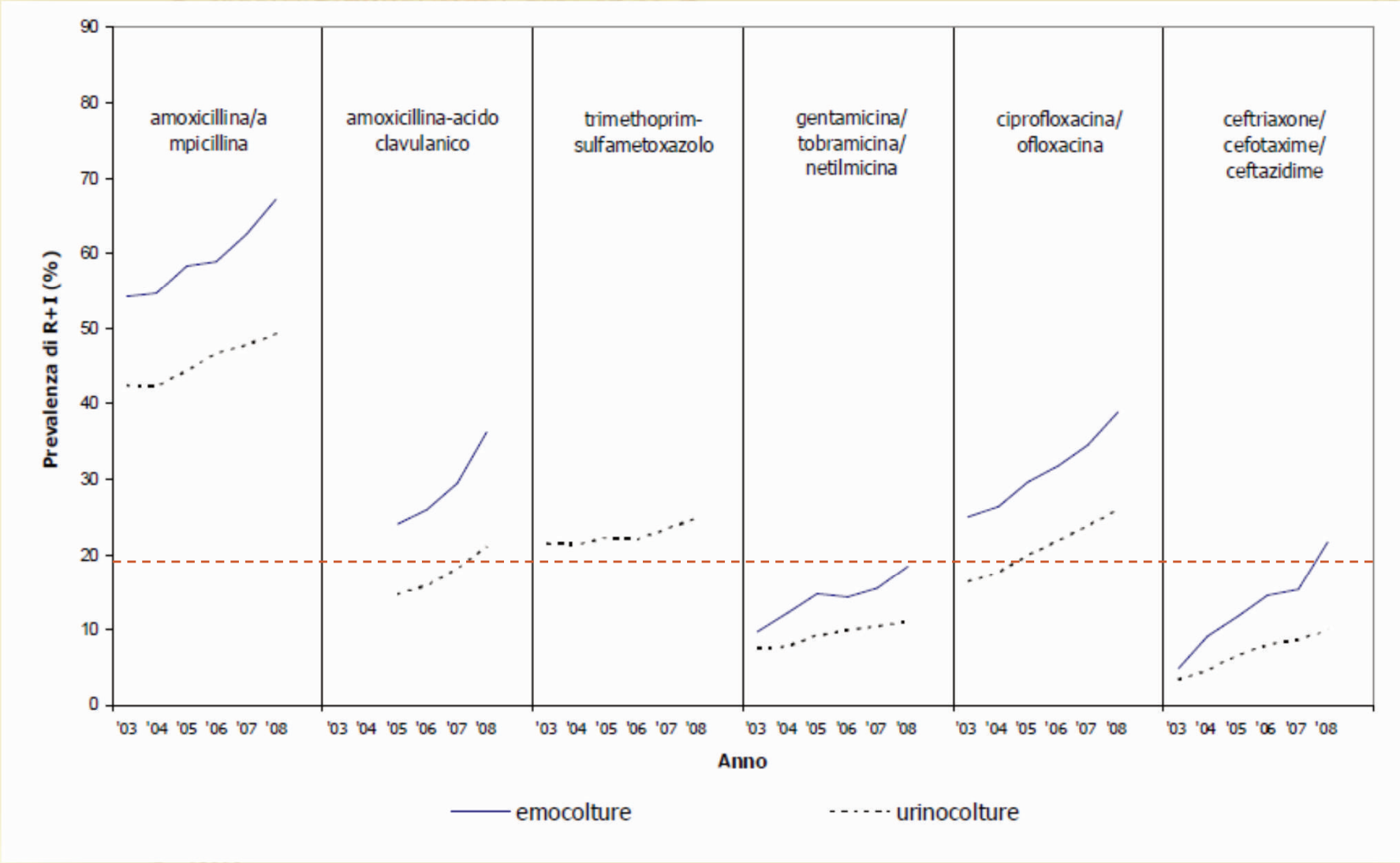
Sorveglianza dell'antibioticoresistenza e uso di antibiotici sistemici in Emilia-Romagna

Rapporto 2008

Redazione a cura di

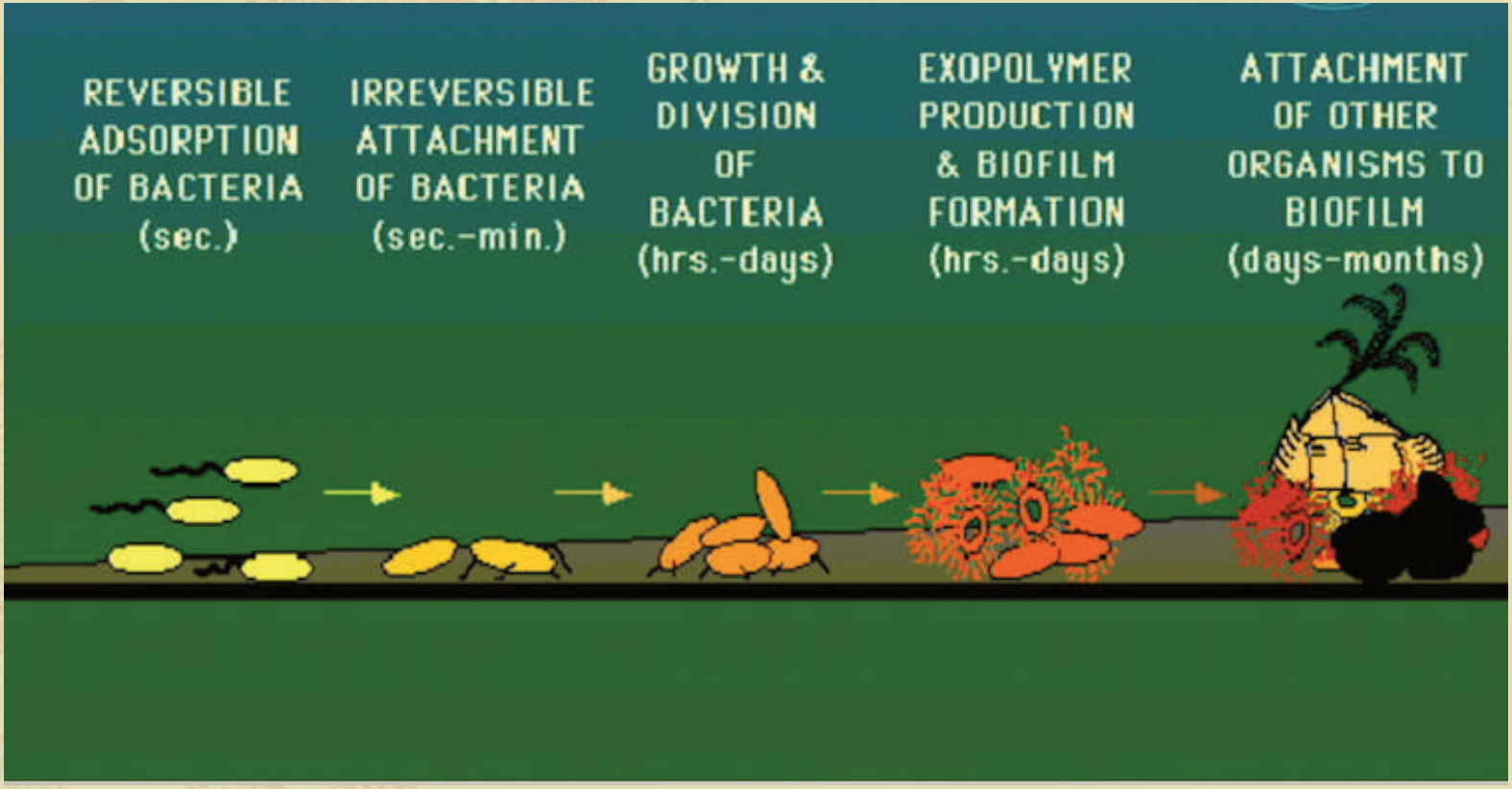
Angelo Pan	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Rossella Buttazzi	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Carlo Capatti	Azienda ospedaliera di Reggio Emilia
Federica Pedna	Azienda USL di Ravenna
Davide Resi	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna
Mario Sarti	Azienda USL di Modena
Claudia Venturelli	Azienda ospedaliero-universitaria di Modena
Maria Luisa Moro	Agenzia sanitaria e sociale regionale dell'Emilia-Romagna

Antibioticoresistenza di E. coli - emo ed urinocolture (Regione Emilia-Romagna, 2003-2008)



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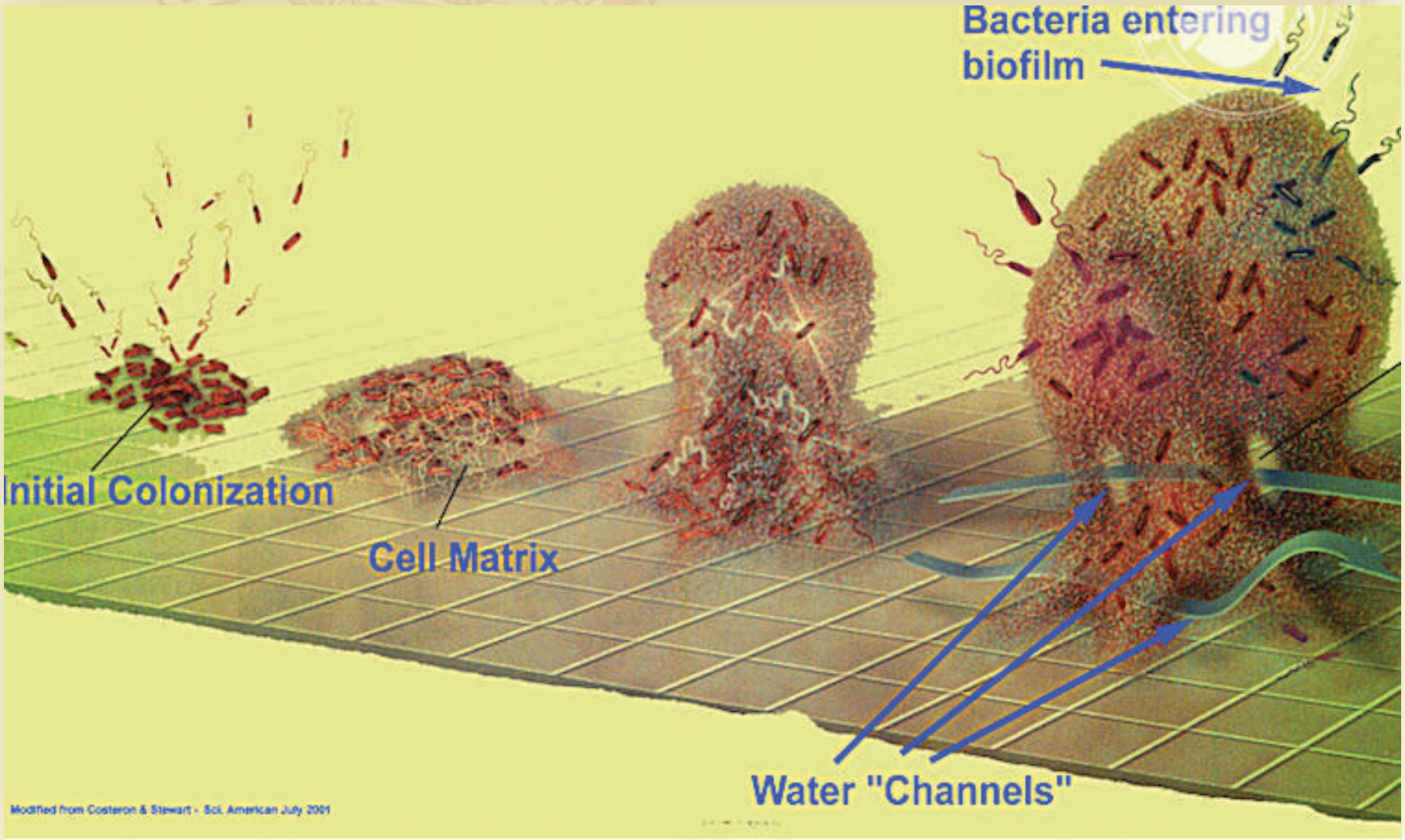
BIOFILM BATTERICI EXTRACELLULARI



Comunità strutturate di cellule batteriche spesso di specie diverse anche di natura fungina racchiuse in una matrice polimerica autoprodotta attesa alla superficie mucosa

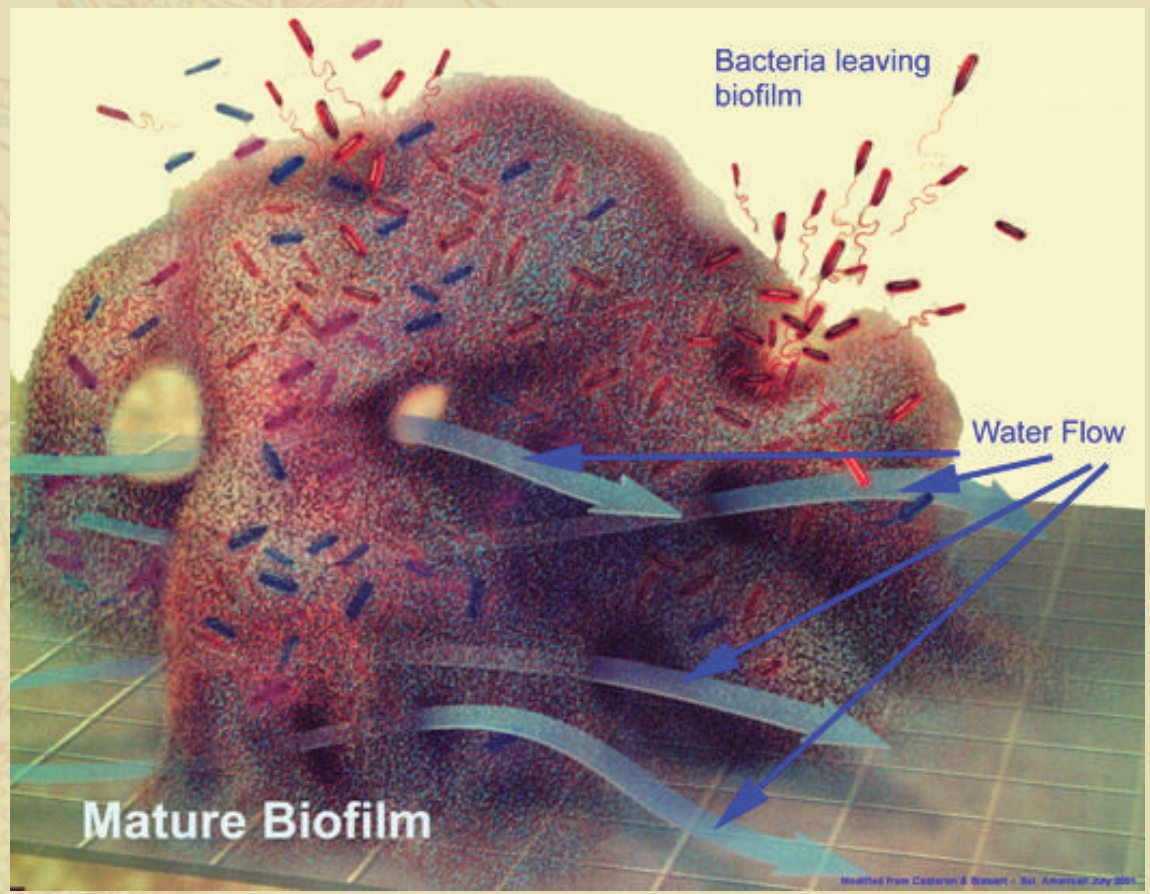
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BIOFILM BATTERICI EXTRACELLULARI



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BIOFILM BATTERICI EXTRACELLULARI



***Persister Cells*: parte più profonda del Bíofilm, sottopopolazione (1%) di cellule batteriche quiescenti, completamente resistenti agli antibiotici e alle difese immunitarie, pronte a ripristinare la carica batterica una volta completata la terapia antibiotica**

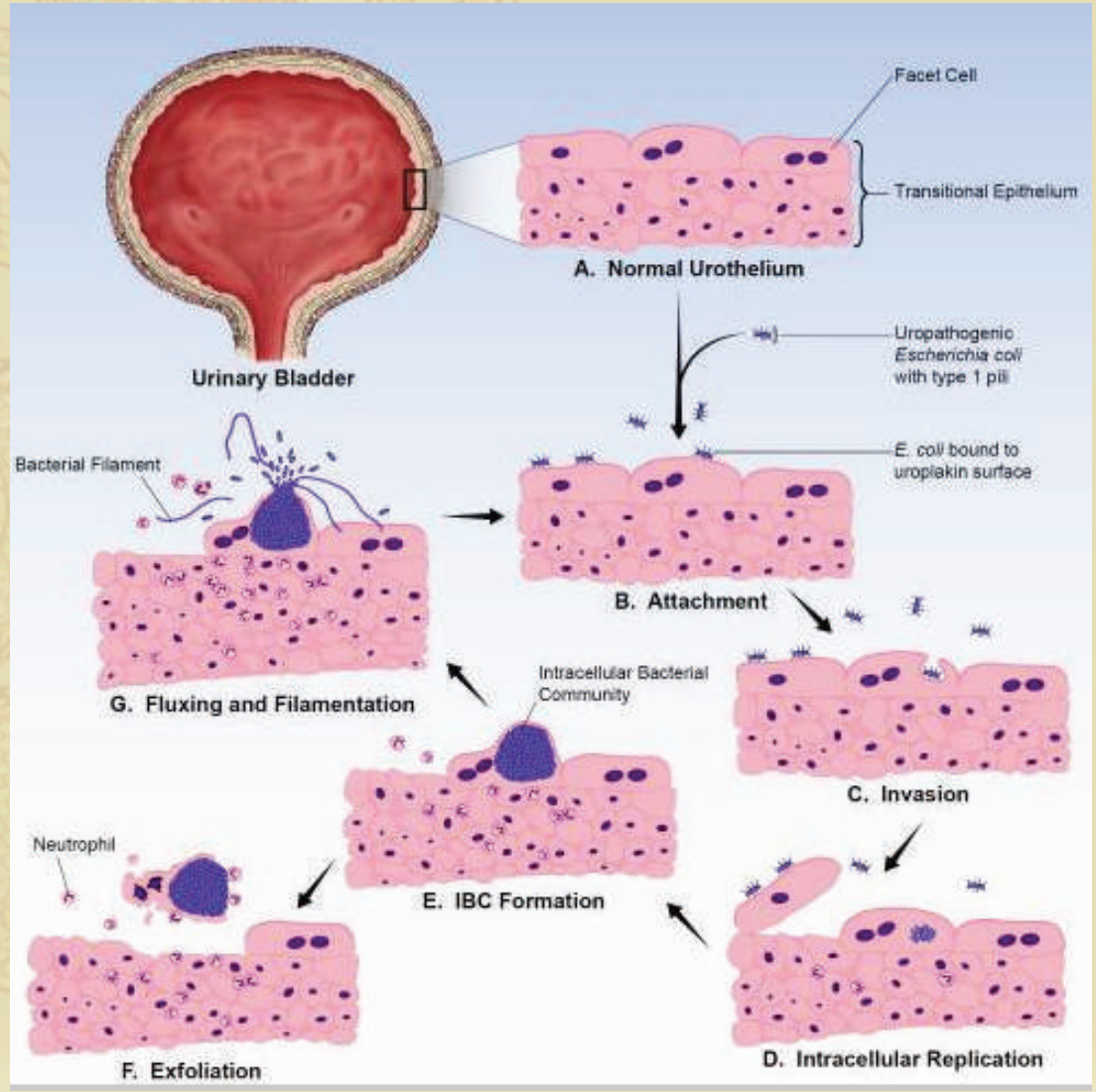
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PLoS Med. 2007 Dec;4(12):e329.

Detection of intracellular bacterial communities in human urinary tract infection.

Rosen DA, Hooton TM, Stamm WE, Humphrey PA, Hultgren SJ.

Department of Molecular Microbiology and Microbial Pathogenesis, Washington University School of Medicine, St. Louis, Missouri, United States of America.



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I BATTERI NELLE RUTI's
PRINCIPI DI TERAPIA

1. Ridurre la pressione degli antibiotici
2. Profilassi continuativa (6 mesi): linee guida
3. Profilassi pulsatile (post-coitale): linee guida
4. Strategie antiadesive: Cranberry, D-Mannosio, Ellirose da Hybiscus sabdariffa o Carcadé o rosa dell'Abissinia
5. Trattamento dei Biofilm

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I BATTERI NELLE RUTI's
PRINCIPI DI TERAPIA

Ridurre la pressione degli antibiotici

Profilassi continuativa (6 mesi): linee guida

Profilassi pulsatile (post-coitale): linee guida

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Guidelines on

Urological Infections

European Association of Urology

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Table 2.3: Continuous antimicrobial prophylaxis regimens for women with recurrent UTIs (33).

Regimens	Expected UTIs per year
TMP-SMX* 40/200 mg once daily	0–0.2
TMP-SMX 40/200 mg thrice weekly	0.1
Trimethoprim 100 mg once daily	0–1.5**
Nitrofurantoin 50 mg once daily	0–0.6
Nitrofurantoin 100 mg once daily	0–0.7
Cefaclor 250 mg once daily	0.0
Cephalexin 125 mg once daily	0.1
Cephalexin 250 mg once daily	0.2
Norfloxacin 200 mg once daily	0.0
Ciprofloxacin 125 mg once daily	0.0
Fosfomycin 3 g every 10 days	0.14

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European Association of Urology

Table 2.4: Postcoital antimicrobial prophylaxis regimens for women with recurrent UTIs (33).

Regimens	Expected UTIs per year
TMP–SMX* 40/200 mg	0.30
TMP–SMX 80/400 mg	0.00
Nitrofurantoin 50 or 100 mg	0.10
Cephalexin 250 mg	0.03
Ciprofloxacin 125 mg	0.00
Norfloxacin 200 mg	0.00
Ofloxacin 100 mg	0.06

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I BATTERI NELLE RUTI's
PRINCIPI DI TERAPIA

Strategie antiadesive: Cranberry, D-Mannosio, Ellirose da Hybiscus sabdariffa o Carcadé o rosa dell'Abissinia

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I BATTERI NELLE RUTI's
PRINCIPI DI TERAPIA

Trattamento dei biofilm:

- Fitoterapici: Ac Ellagico, Galium aparine, Tarassaco, Betulla, Frassino, Aloe, Uva ursi,)
- Micoterapici: Polyporus umbrellatus (Zu Ling), Shiitake (lentinula edodes, xianggu)
- Olii essenziali: Origano, Solidago, Ginepro, Bergamotto
- Quintessenze Spagyriche: Thuia, Pino, Origano
- NAC

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LE URINE NELLE RUTI's

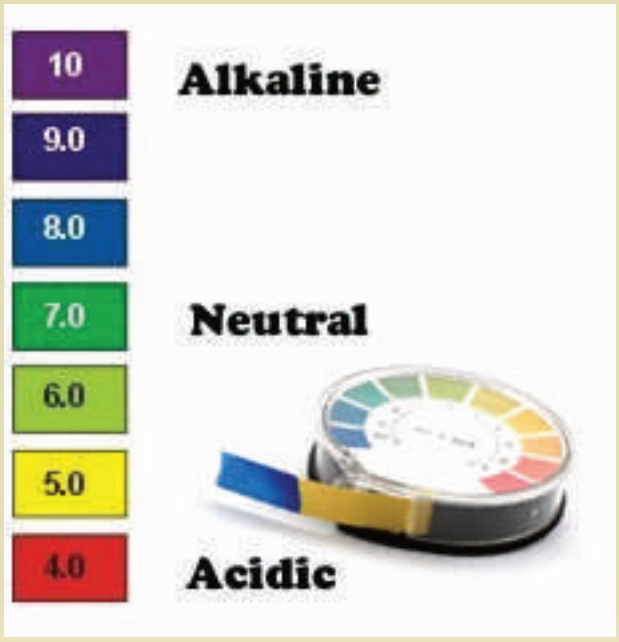
1. **Volume urinario:** quanto bere?
2. **pH:** Acidificare? Basificare?

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LE URINE NELLE RUTI's

1. **Volume urinario:** quanto bere?
2. **pH:** Acidificare? Basificare?





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LE URINE NELLE RUTI's
PRINCIPI DI TERAPIA

1. **Liquidi introdotti:** i trucchi per bere, soluzioni acquose di fitoterapici (EIE), associazioni drenanti
2. **pH -** verificare caso per caso
3. **Batteri gruppo KES: *Klebsiella, Enterobacter, Serratia.*** Batteri ureasi positivi (*urea-splitting*): scindono per idrolisi 1 molecola di urea in 2 atomi di ammoniaca (base forte)

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LA VESCICA NELLE RUTI's

1. Ostruzione, *Dysfunctional Voiding*
2. Residuo Post-Minzionale (RPM)
3. Leaky Urothelium: tight junctions
4. Difetto del coating
5. Violazione dell'Interstizio
6. Attivazione mastocitaria
7. Dolore Neurogenico
8. Leaky Barrier Syndrome: RUTI's, IC

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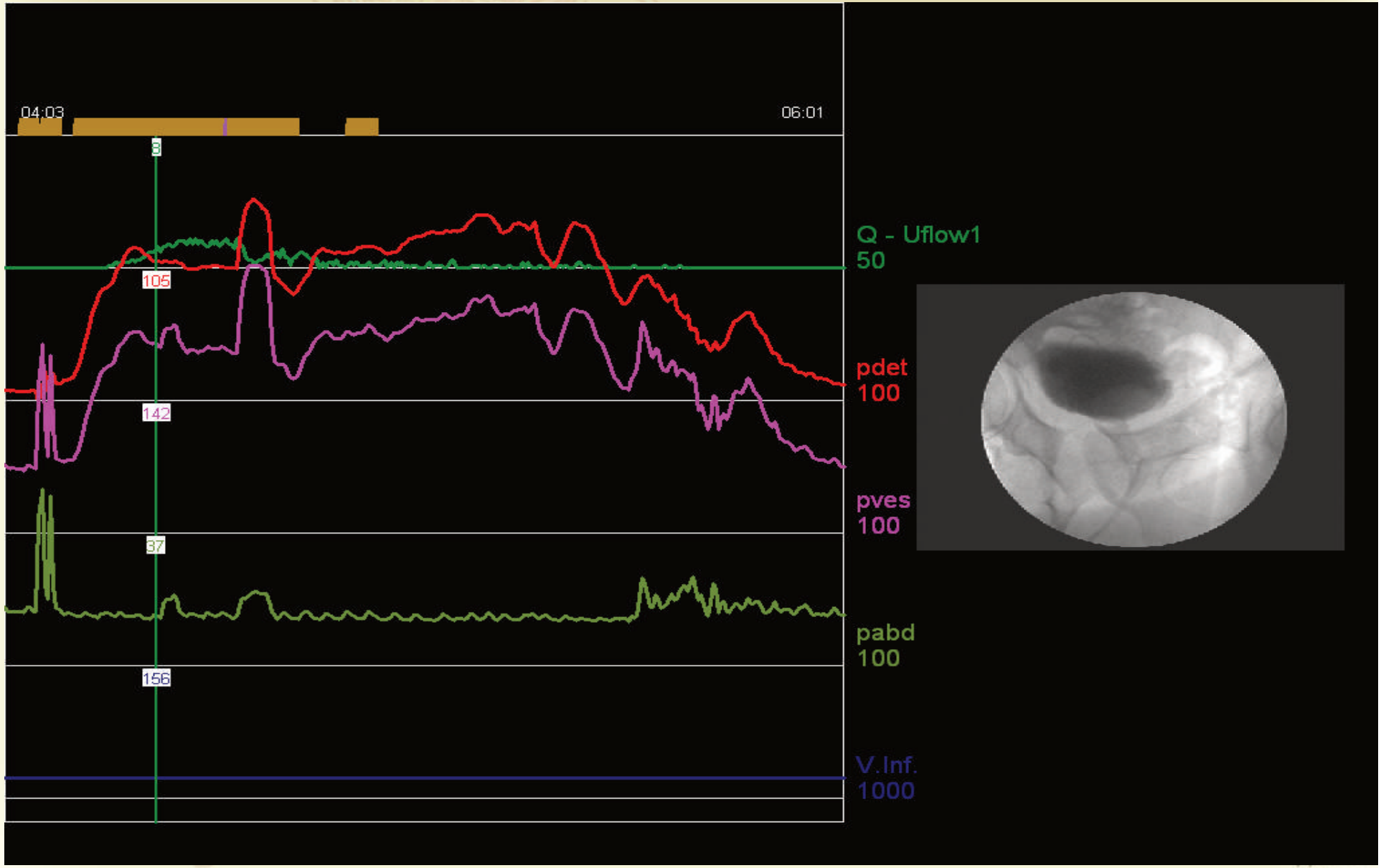
LA VESCICA NELLE RUTI's

Ostruzione, *Dysfunctional Voiding*

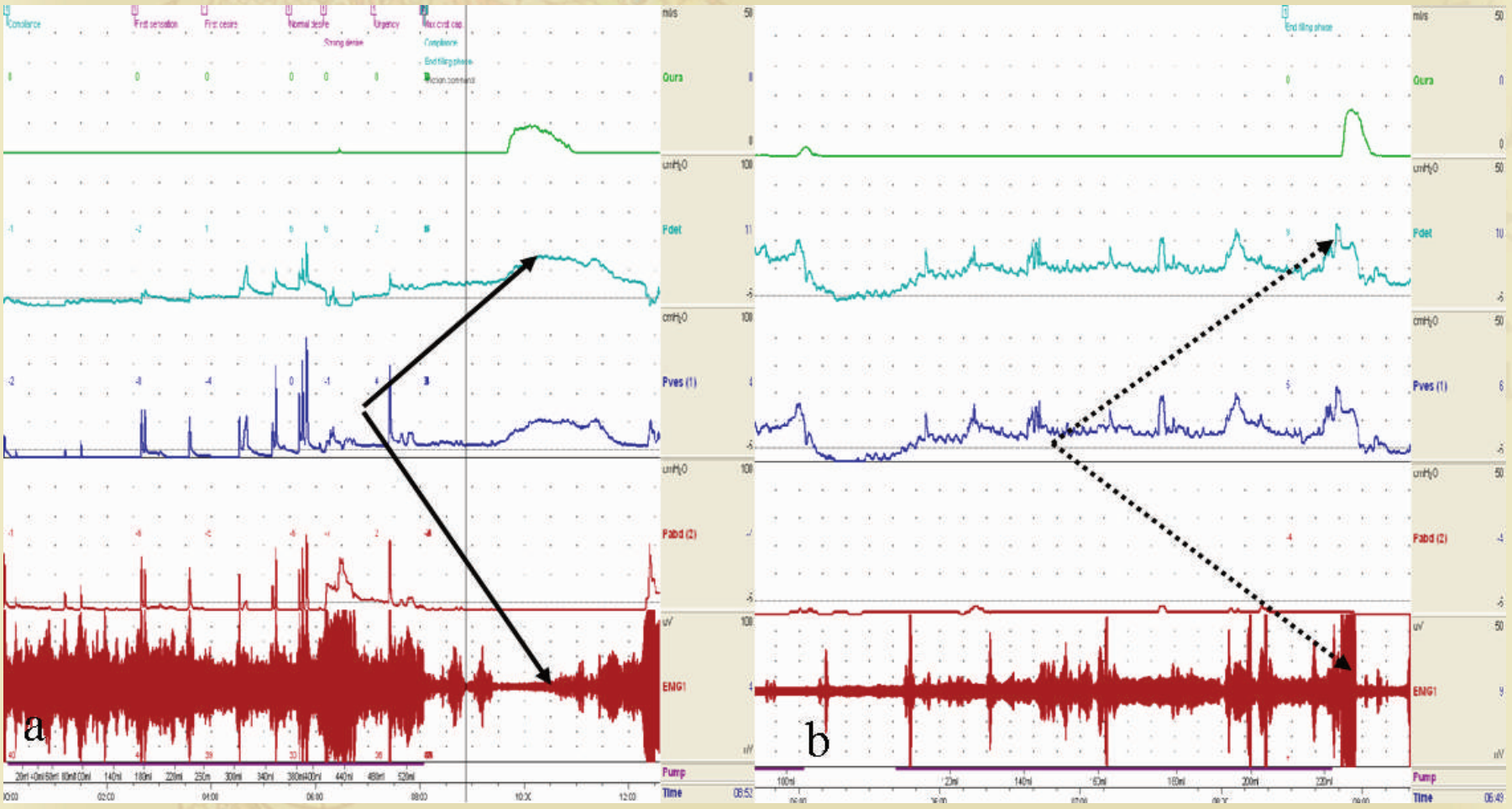
Residuo Post-Minzionale (RPM)

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Ostruzione

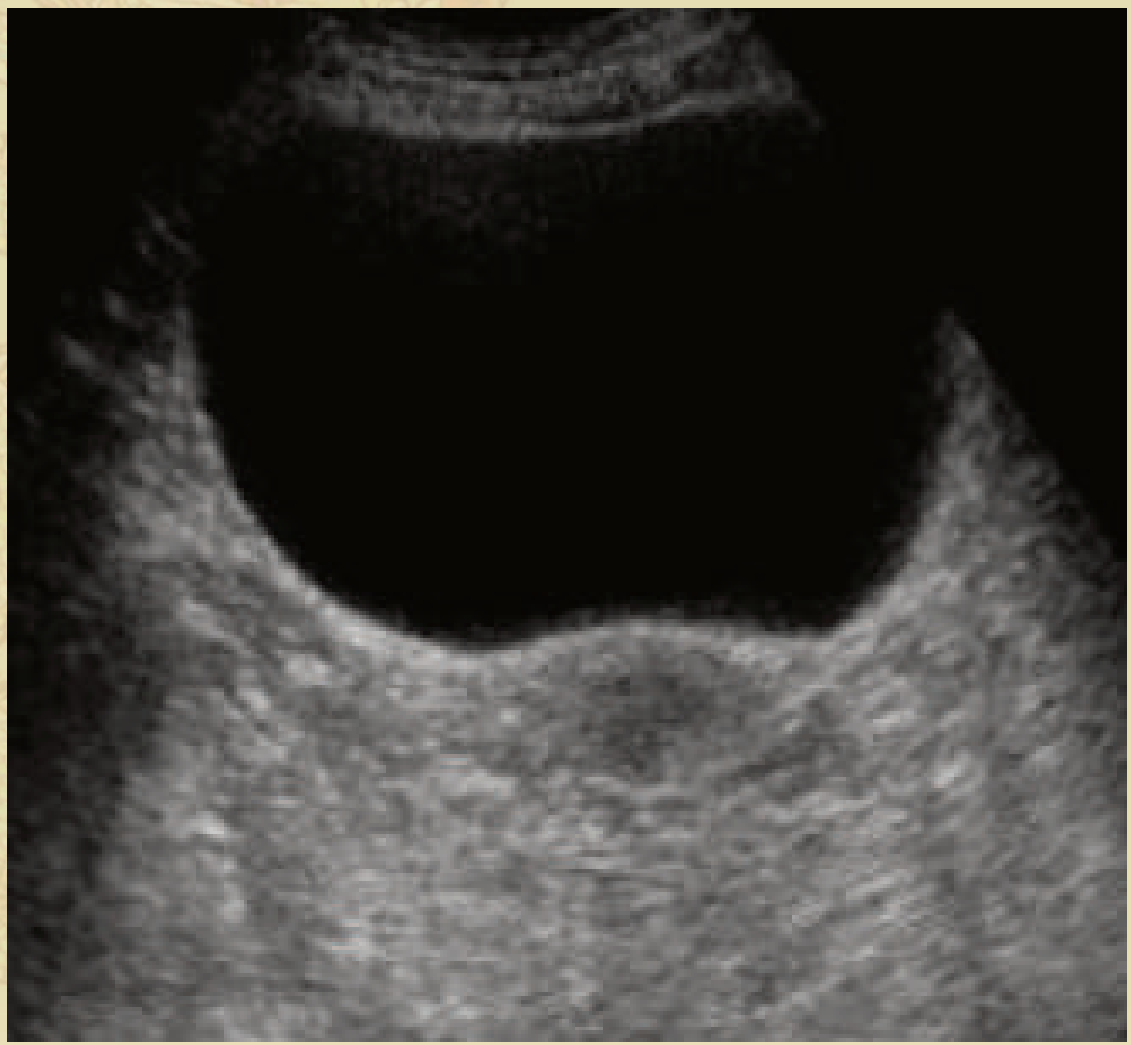

04:03
06:01
8
105
142
37
156
Q - Uflow1
50
pdet
100
pves
100
pabd
100
V.Inf.
1000

Dysfunctional Voiding



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Residuo vescicale post-minzionale (RPM)



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LA VESCICA NELLE RUTI's

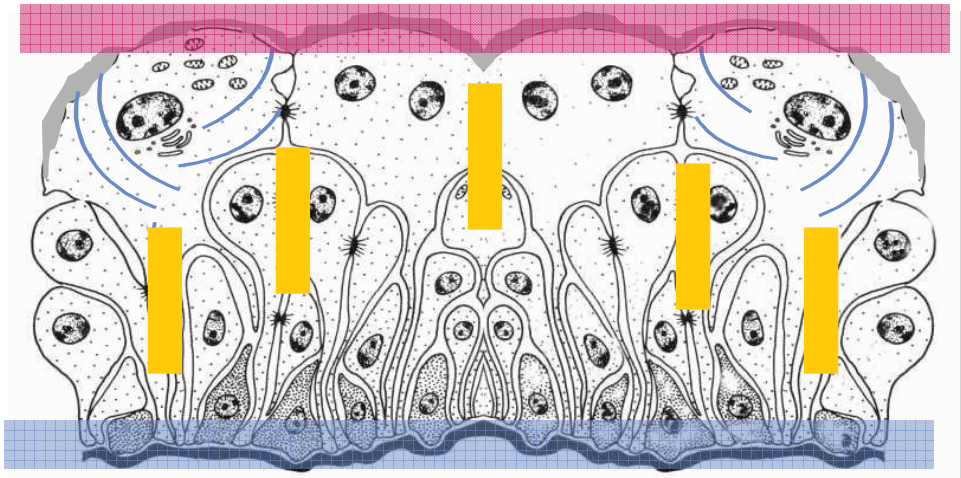
Leaky Urothelium: tight junctions

Difetto del coating

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Barriera apicale

Barriere laterali

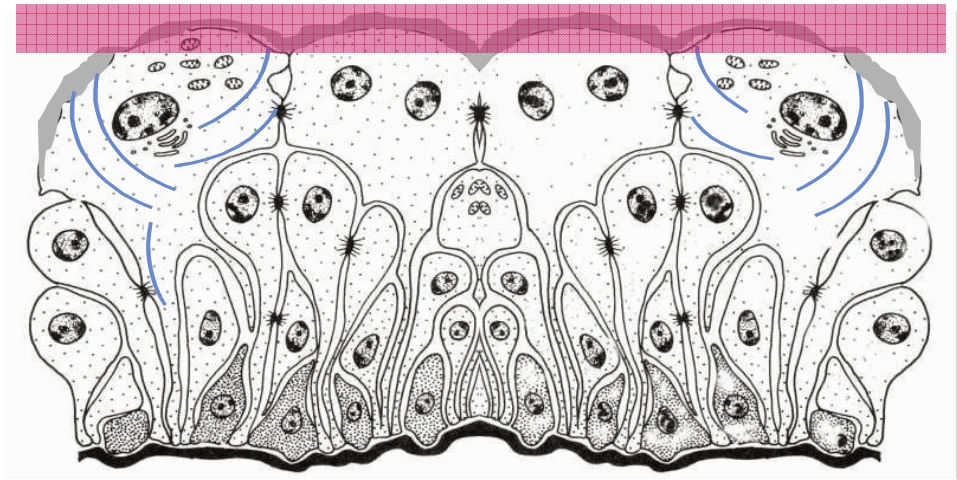


Barriere laterali

Barriera basale

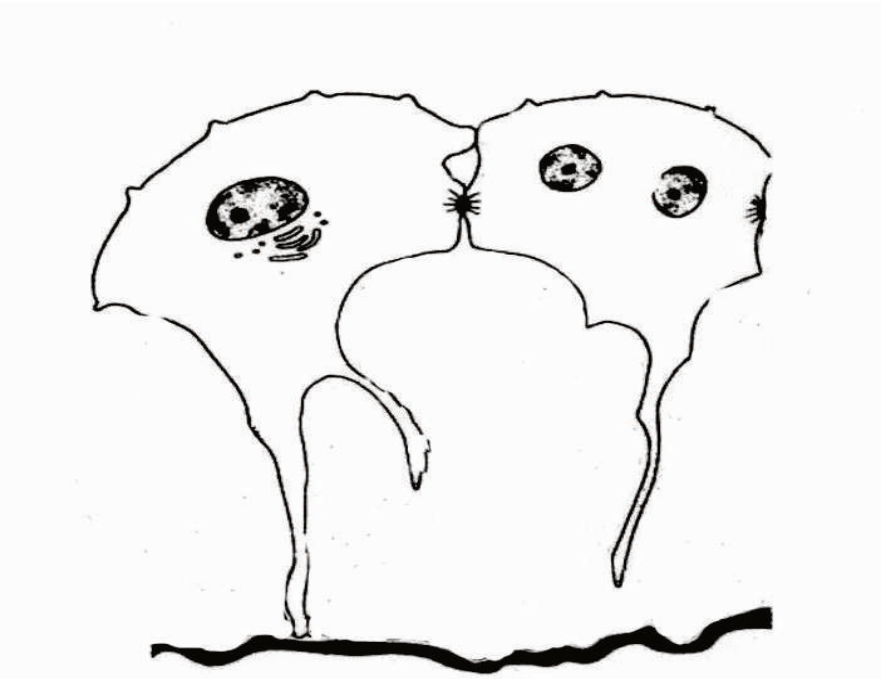
Courtesy of Tajana

Barriera apicale



Courtesy of Tajana

Barriera apicale

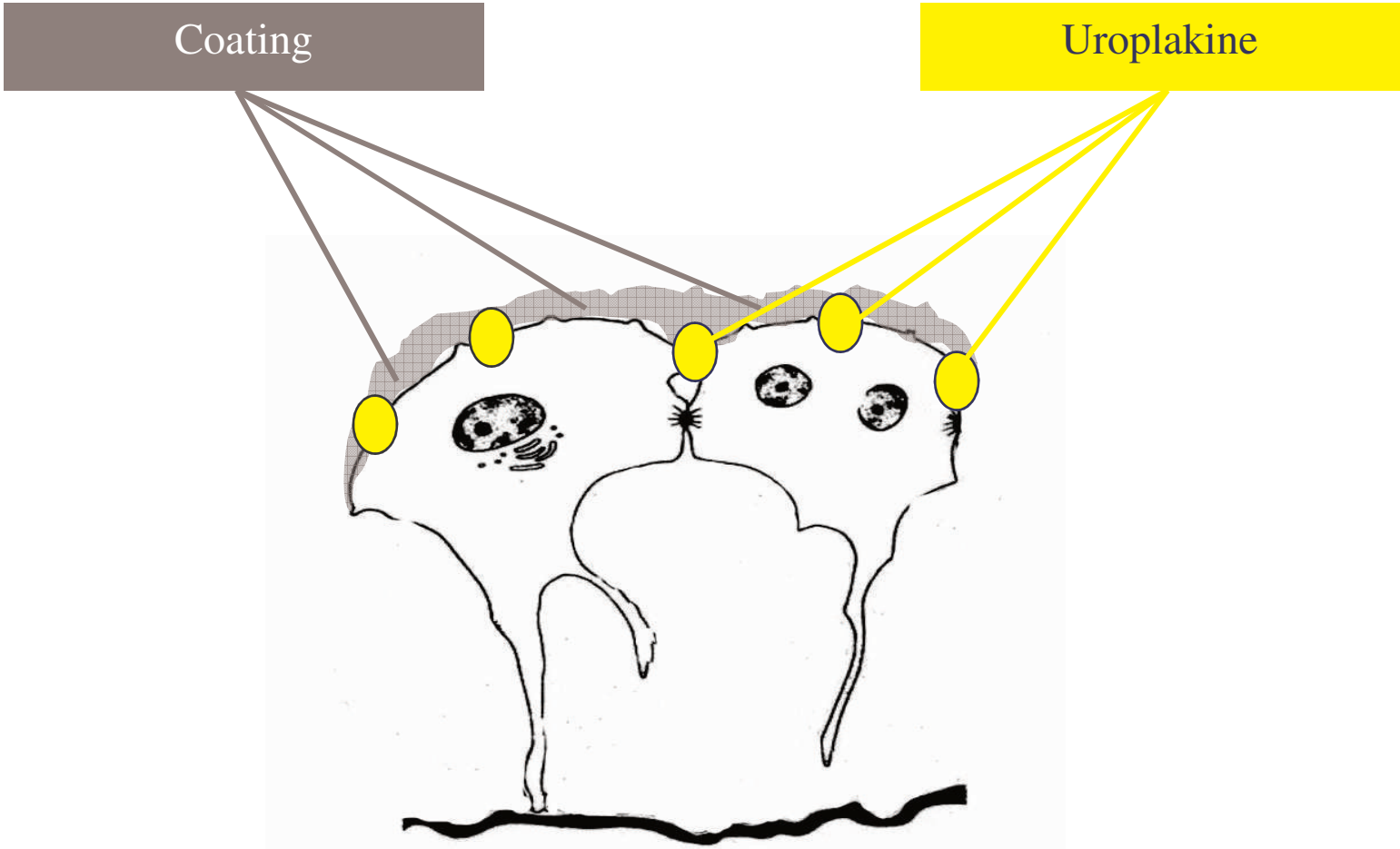


Cellule “ombrello”

Courtesy of Tajana

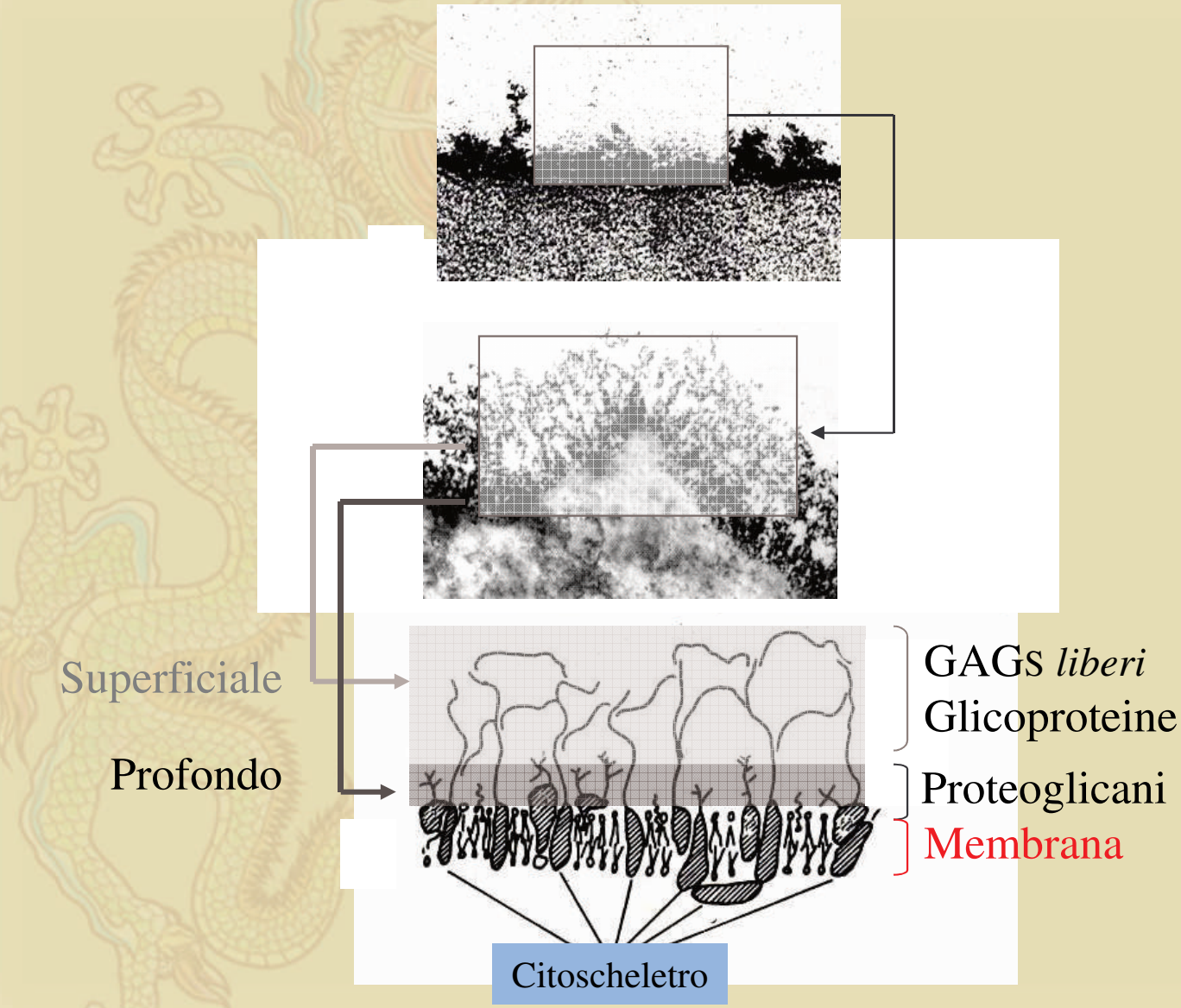
Barriera apicale

Il Coating



Cellule “ombrello”

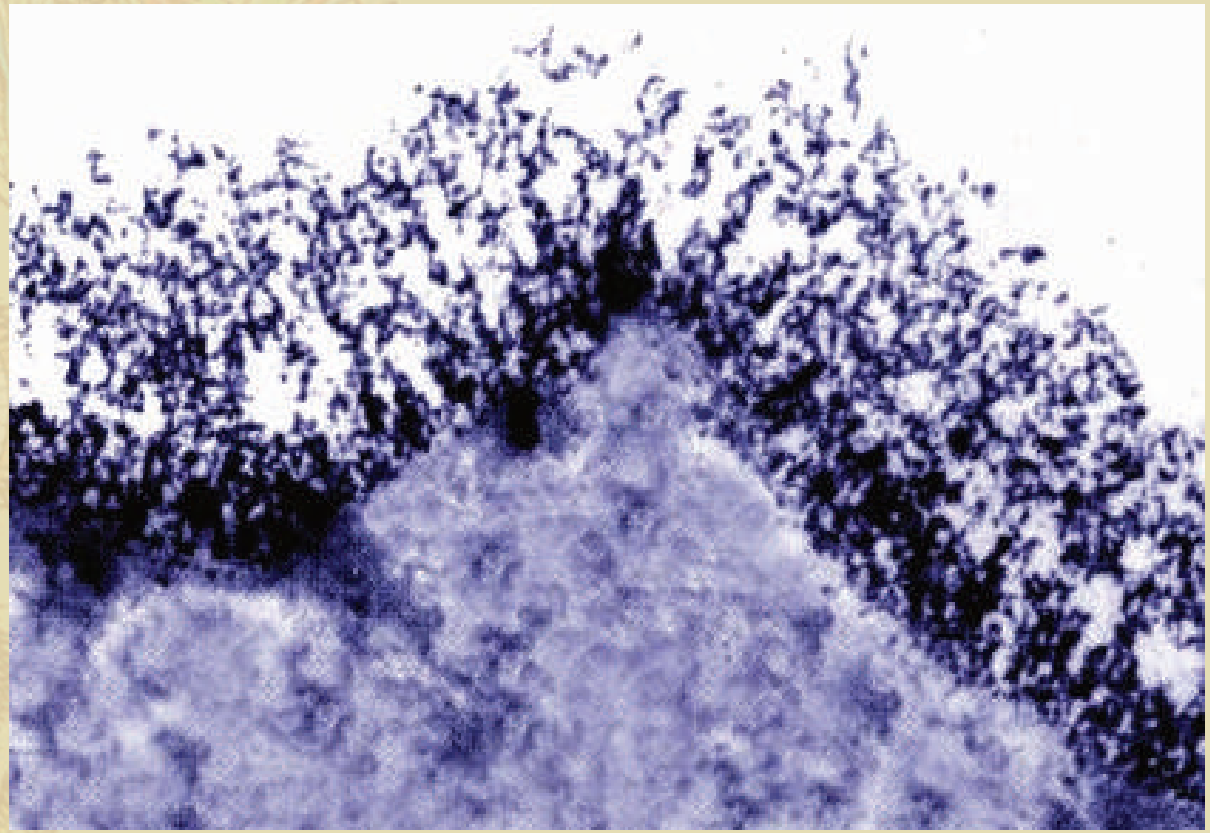
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COATING



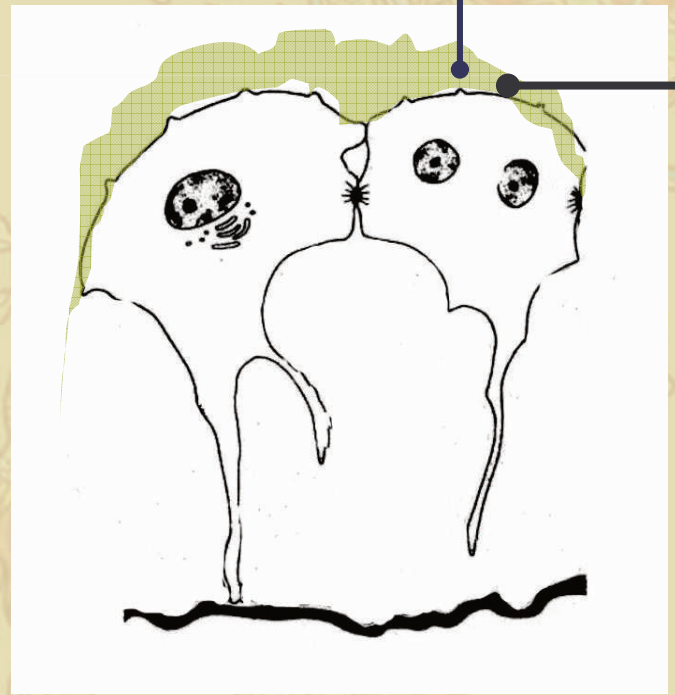
Peixoto EB 2005

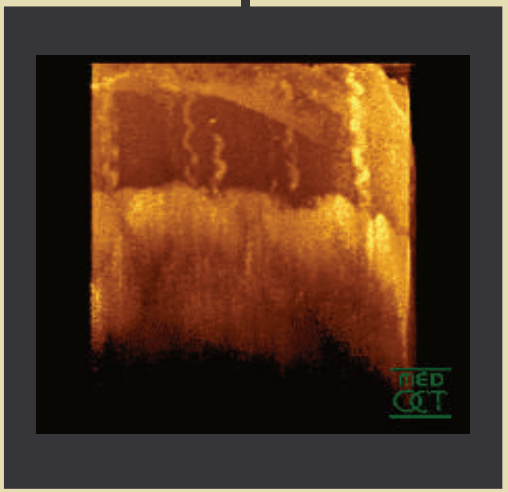
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COATING *in vivo*

Laser Confocal Endomycroscopy (*Sonn GA 2009*)





Ultrahigh resolution optical coherence tomography
(Hermes B 2008)

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Barriera apicale

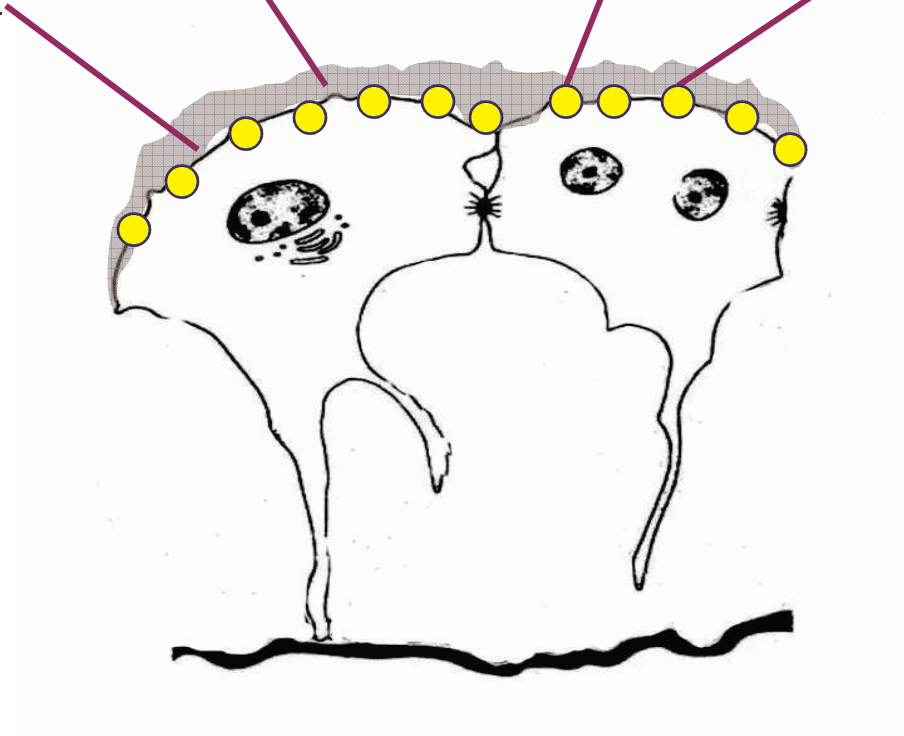
Il Coating

Neutralizza sostanze tossiche

Ostacola l'adesione di uropatogeni

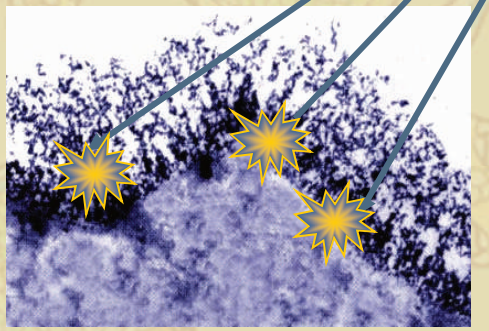
Impedisce il passaggio di piccole molecole

Inibisce la formazione di microcristalli



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“Attacco al Coating”

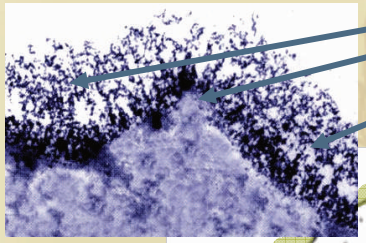


Coating

Peixoto EB 2005

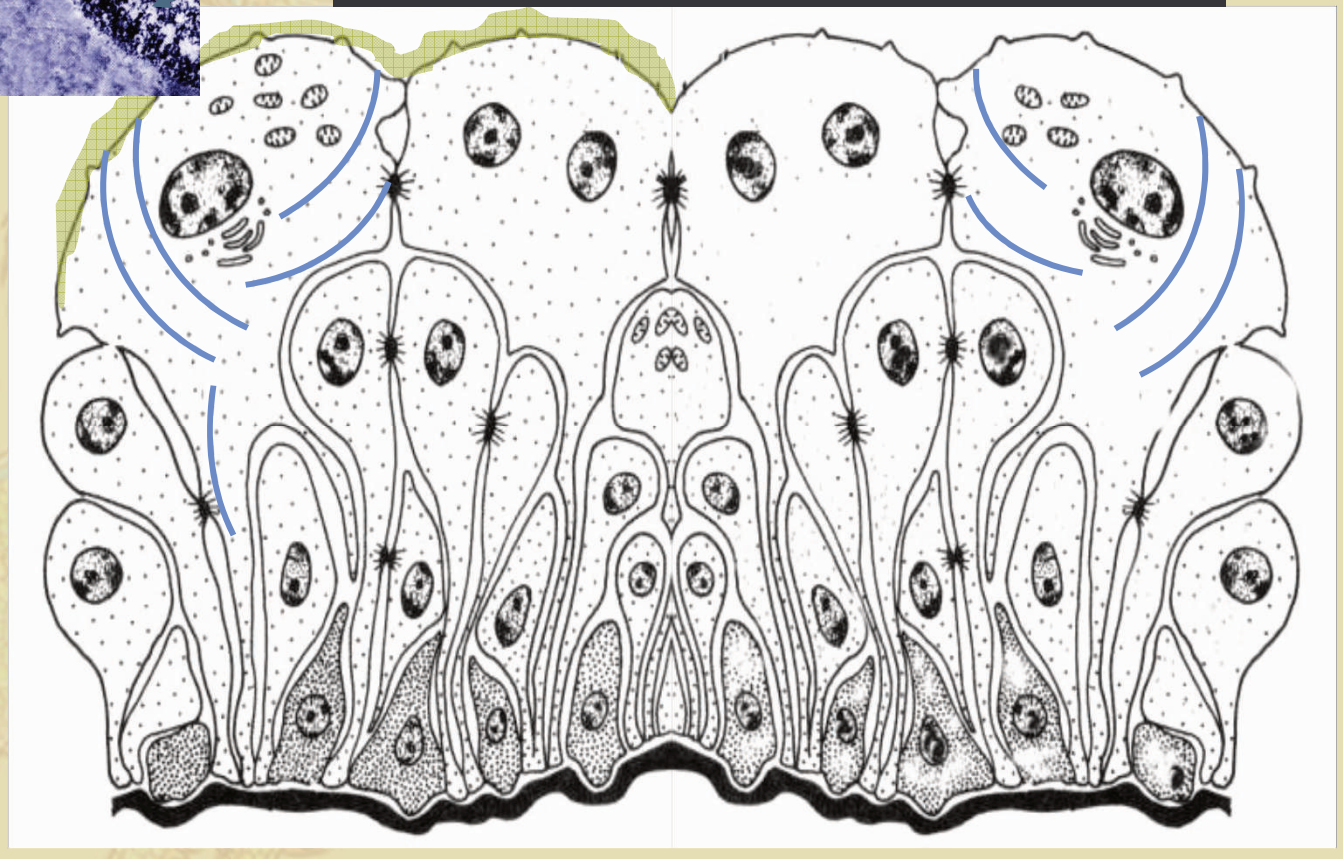
Courtesy of Tajana

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"Attacco al Coating"

Scomparsa del Coating

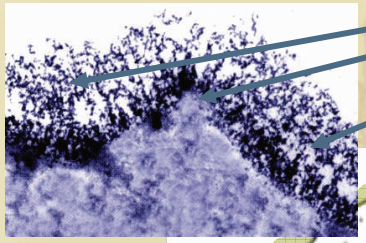


Peixoto EB 2005

Courtesy of Tajana

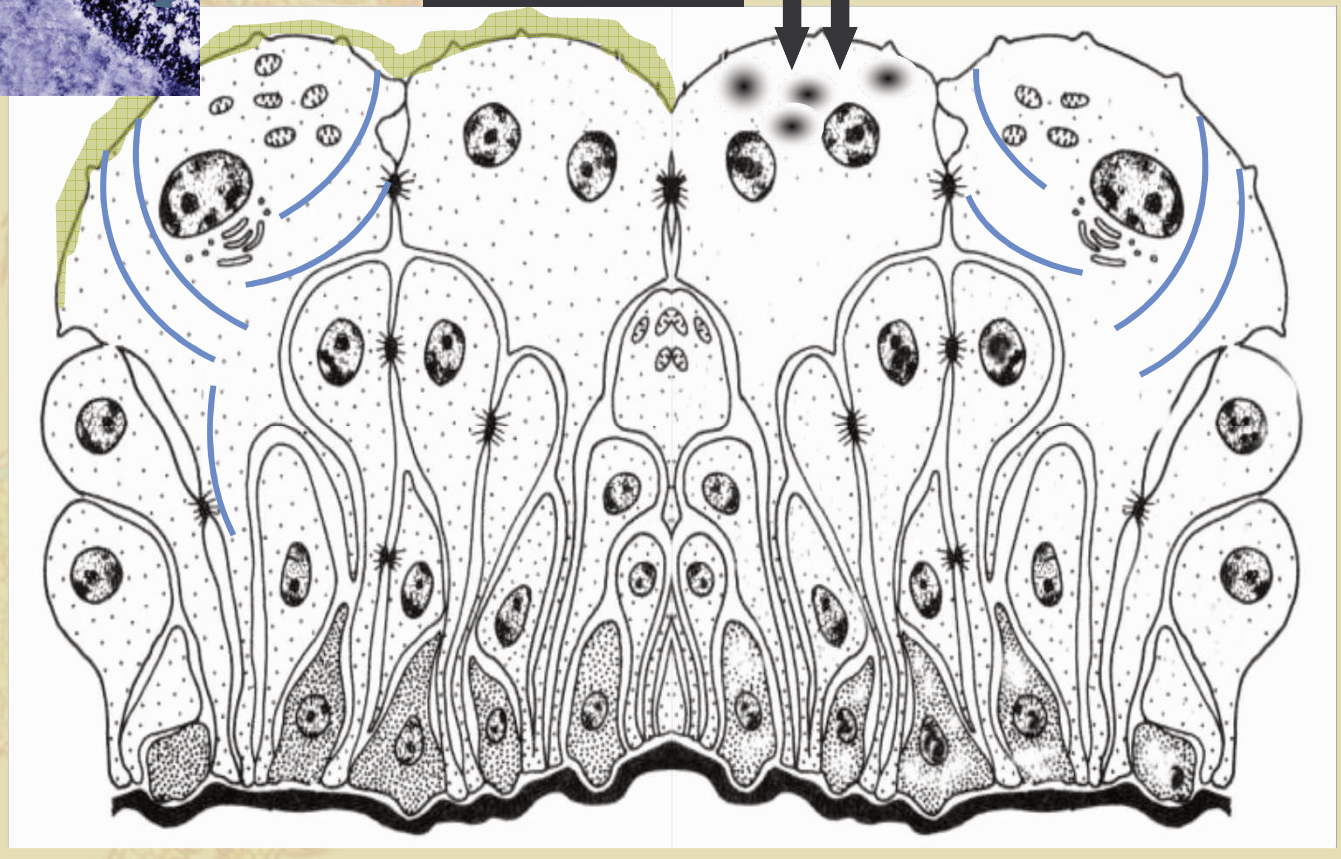
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“Attacco al Coating”



Permeabilità

Scomparsa del Coating

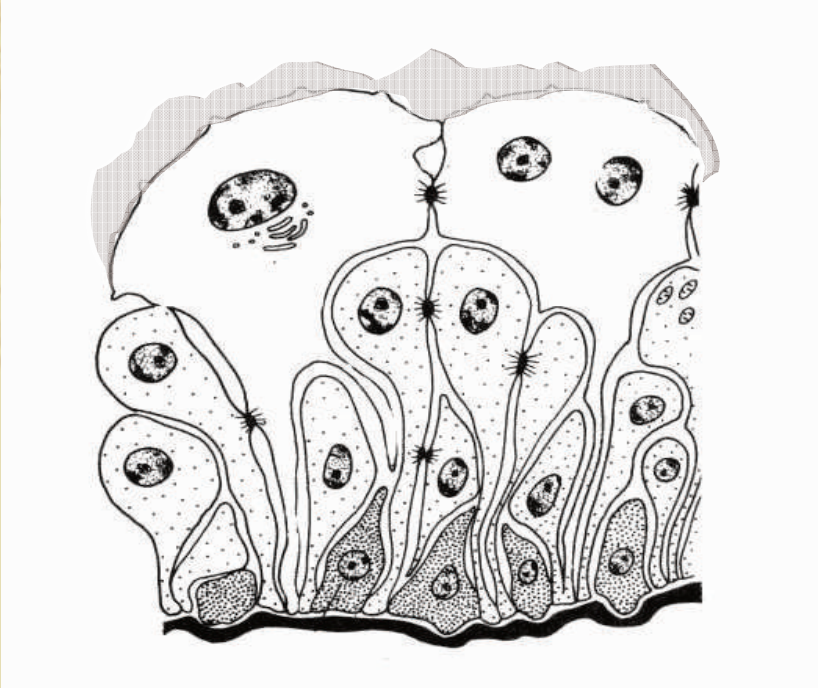


Peixoto EB 2005

Courtesy of Tajana

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Involuzione del *coating*



Interstizio

Courtesy of Tajana

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LA VESCICA NELLE RUTI's

Violazione dell'Interstizio

Attivazione mastocitaria

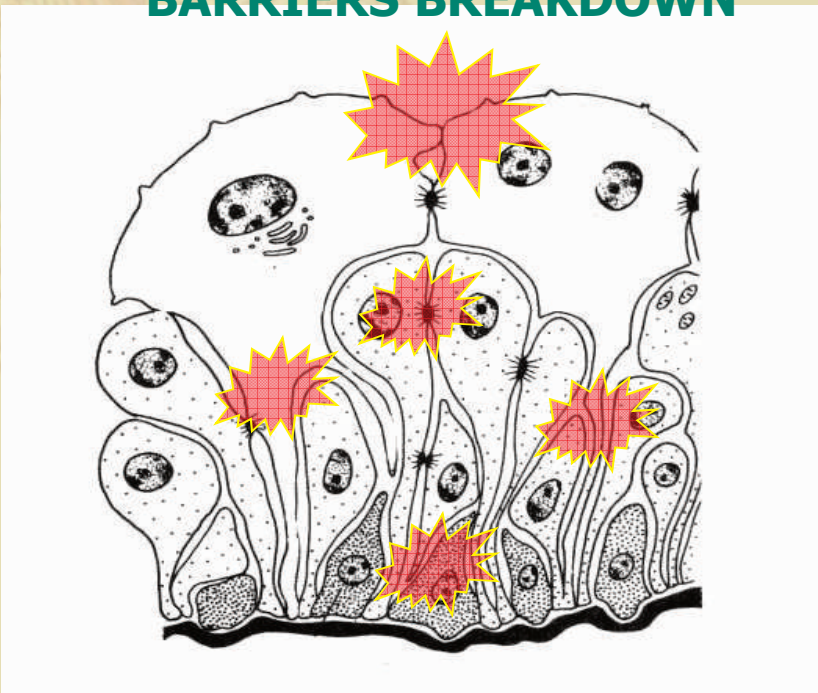
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Urothelial Barriers Break-Down

“cedimento strutturale”

VIOLAZIONE DELLE BARRIERE

BARRIERS BREAKDOWN

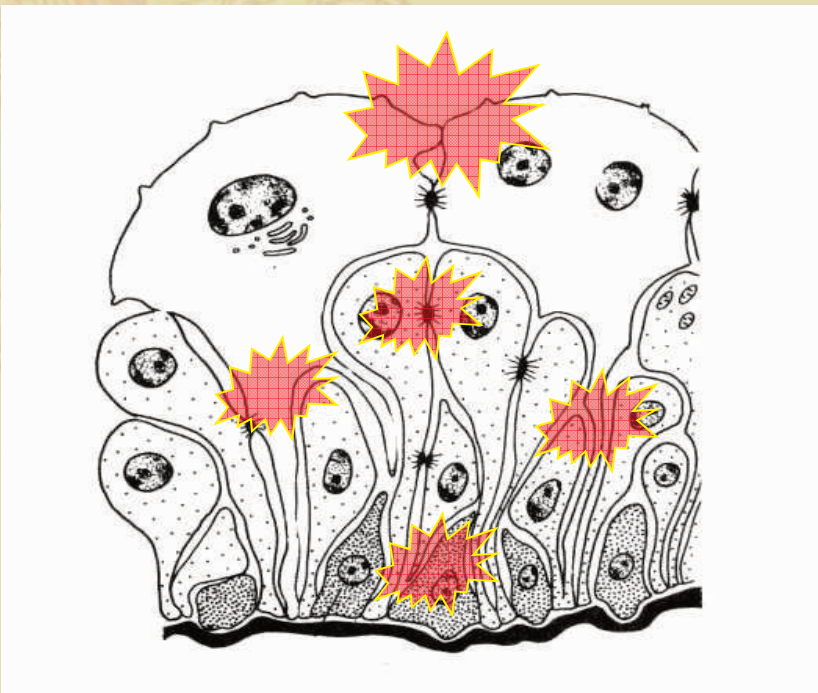


Interstizio

Courtesy of Tajana

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"**Structural Breaking Down**" of the ***Barriers***

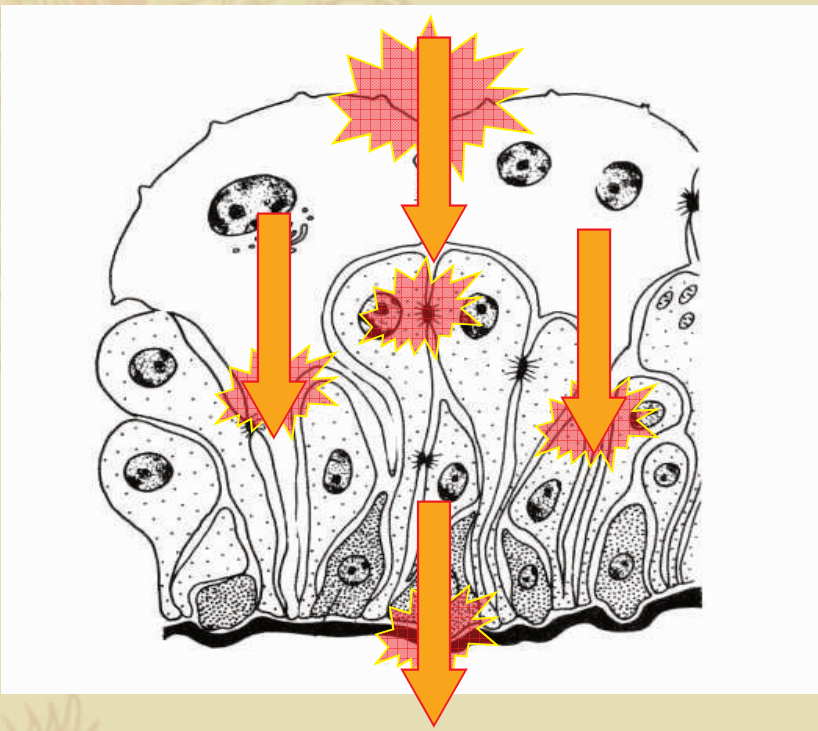


Interstice

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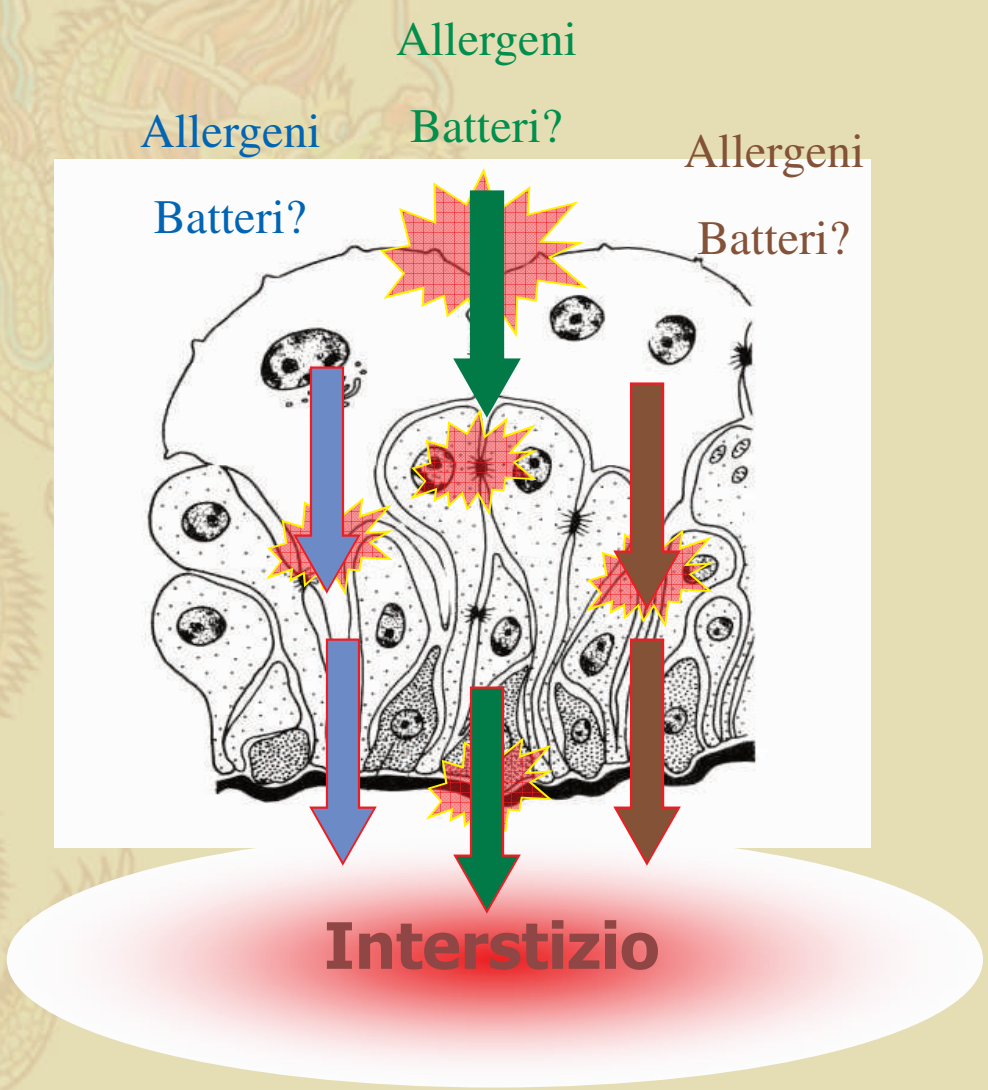
Percolazione intercellulare



Interstizio

Courtesy of Tajana

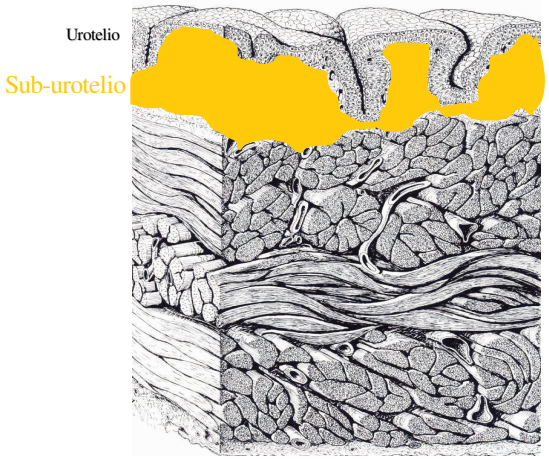
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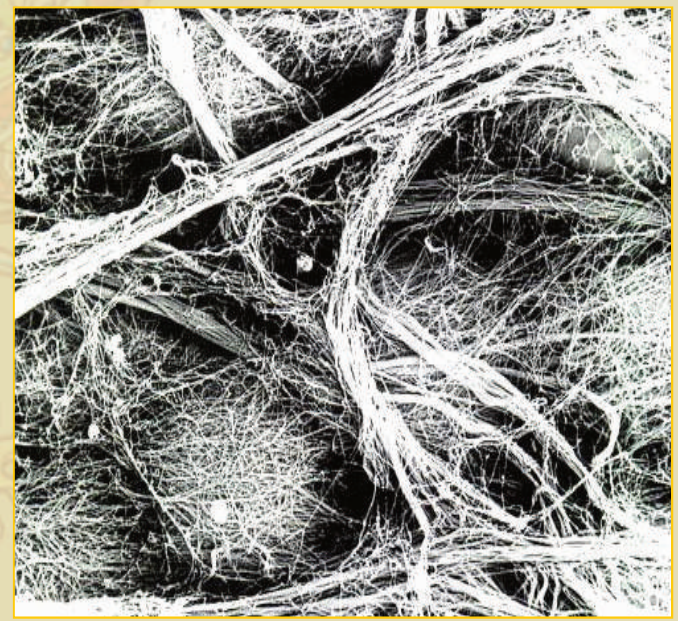
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Sub-urotelio

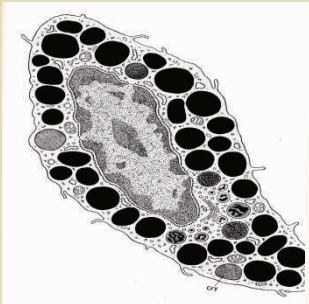


INTERSTIZIO

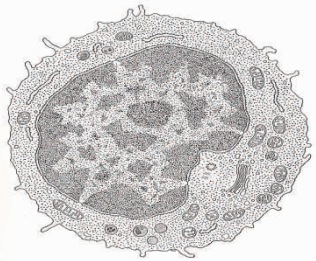




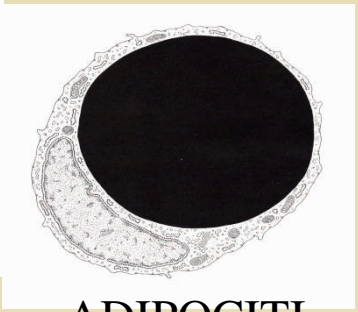
FIBRE NERVOSE



MASTOCITI



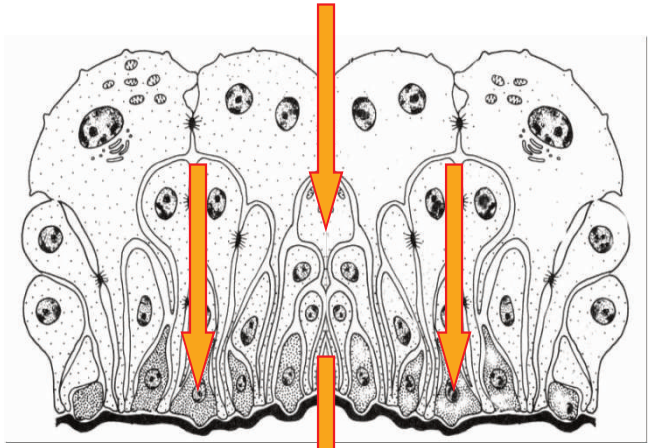
LINFOCITI



ADIPOCITI

Courtesy of Tajana

fppt.com





Attivazione MASTOCITA

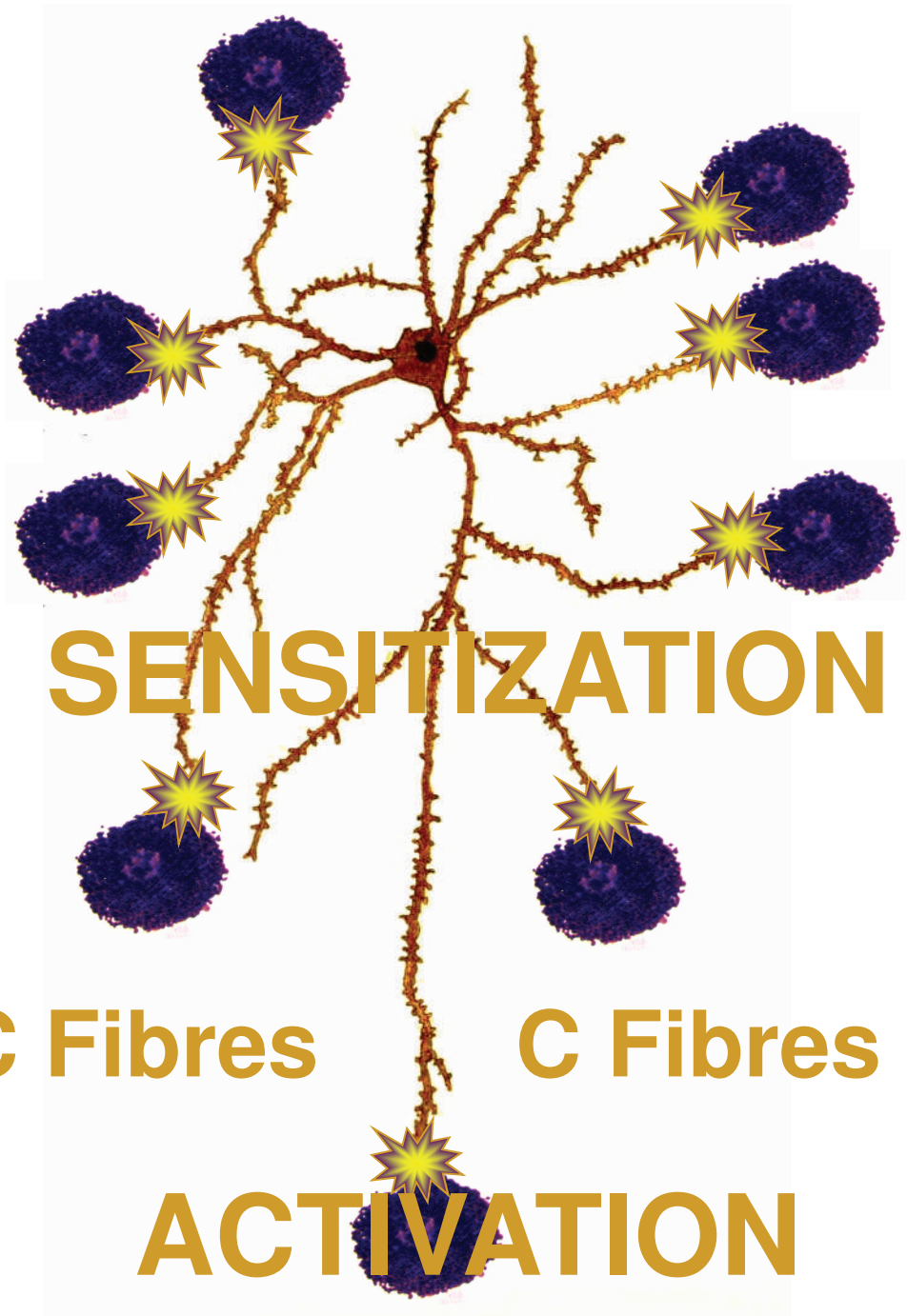
Courtesy of Tajana

LA VESCICA NELLE RUTI's

Dolore Neurogenico

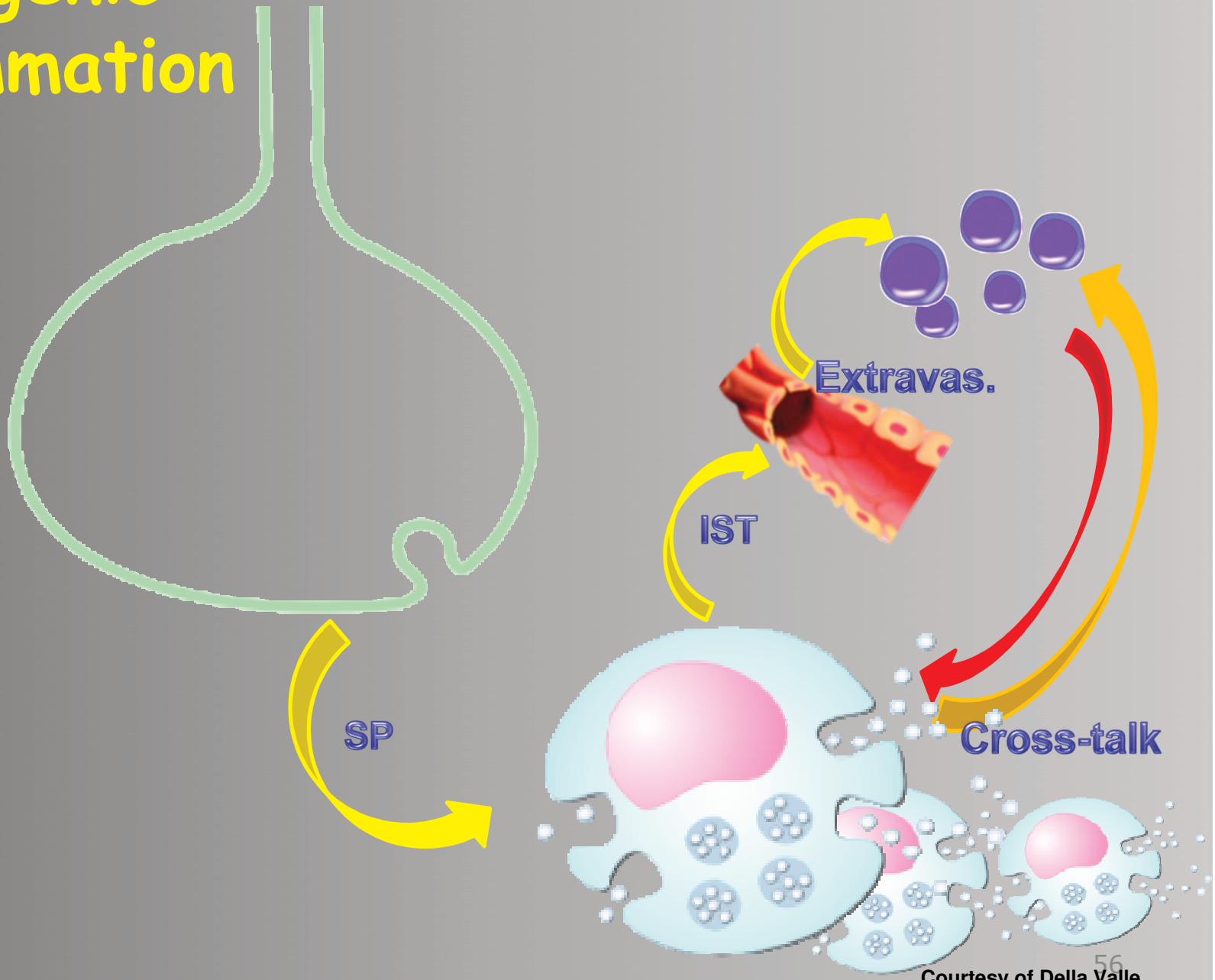
Leaky Barrier Syndrome: RUTI's, IC

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Courtesy of Tajana

Neurogenic Inflammation

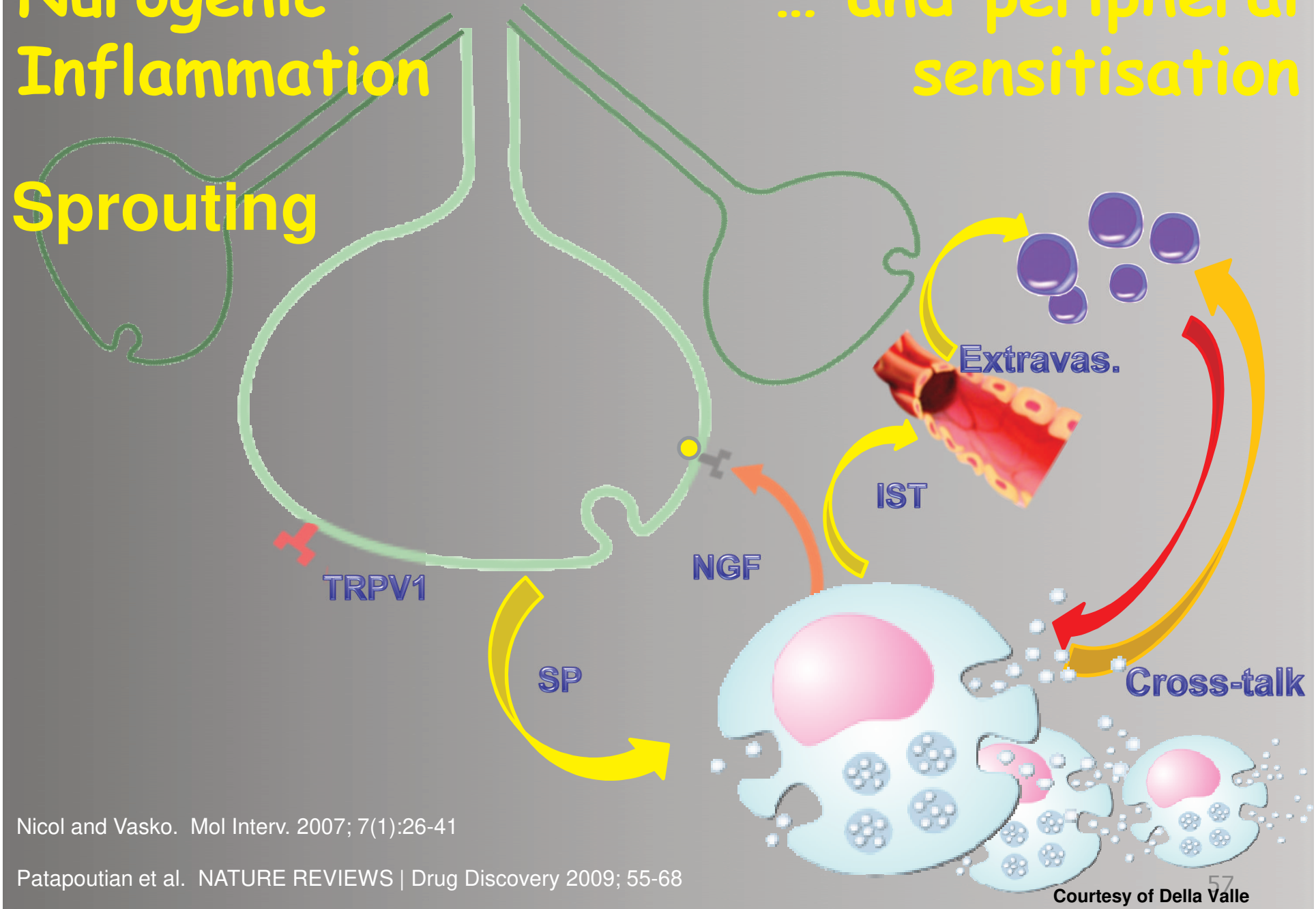


Courtesy of Della Valle

Nurogenic Inflammation

… and peripheral sensitisation

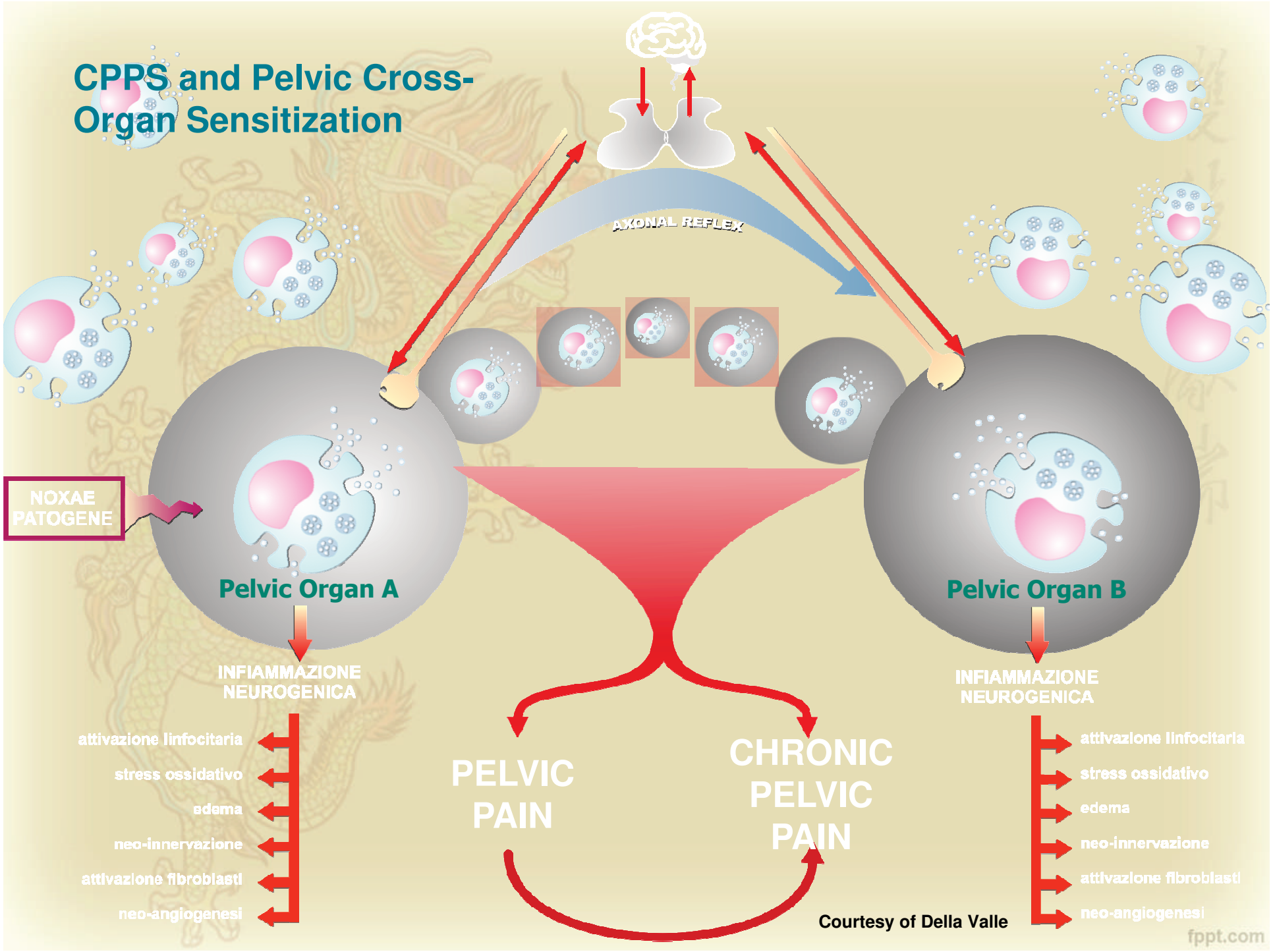
Sprouting



Nicol and Vasko. Mol Interv. 2007; 7(1):26-41

Patapoutian et al. NATURE REVIEWS | Drug Discovery 2009; 55-68

Courtesy of Della Valle


CPPS and Pelvic Cross-Organ Sensitization
AXONAL REFLEX
NOXAE PATOGENE
Pelvic Organ A
Pelvic Organ B
INFIAMMAZIONE NEUROGENICA
INFIAMMAZIONE NEUROGENICA
attivazione linfocitaria
stress ossidativo
edema
neo-innervazione
attivazione fibroblasti
neo-angiogenesi
PELVIC PAIN
CHRONIC PELVIC PAIN
attivazione linfocitaria
stress ossidativo
edema
neo-innervazione
attivazione fibroblasti
neo-angiogenesi
Courtesy of Della Valle
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LA VESCICA NELLE RUTI's

Leaky Barrier Syndrome: RUTI's, IC

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Sindrome del Dolore Vescicale
Bladder Pain Syndrome BPS
Cistite Interstiziale
Interstitial Cystitis - IC

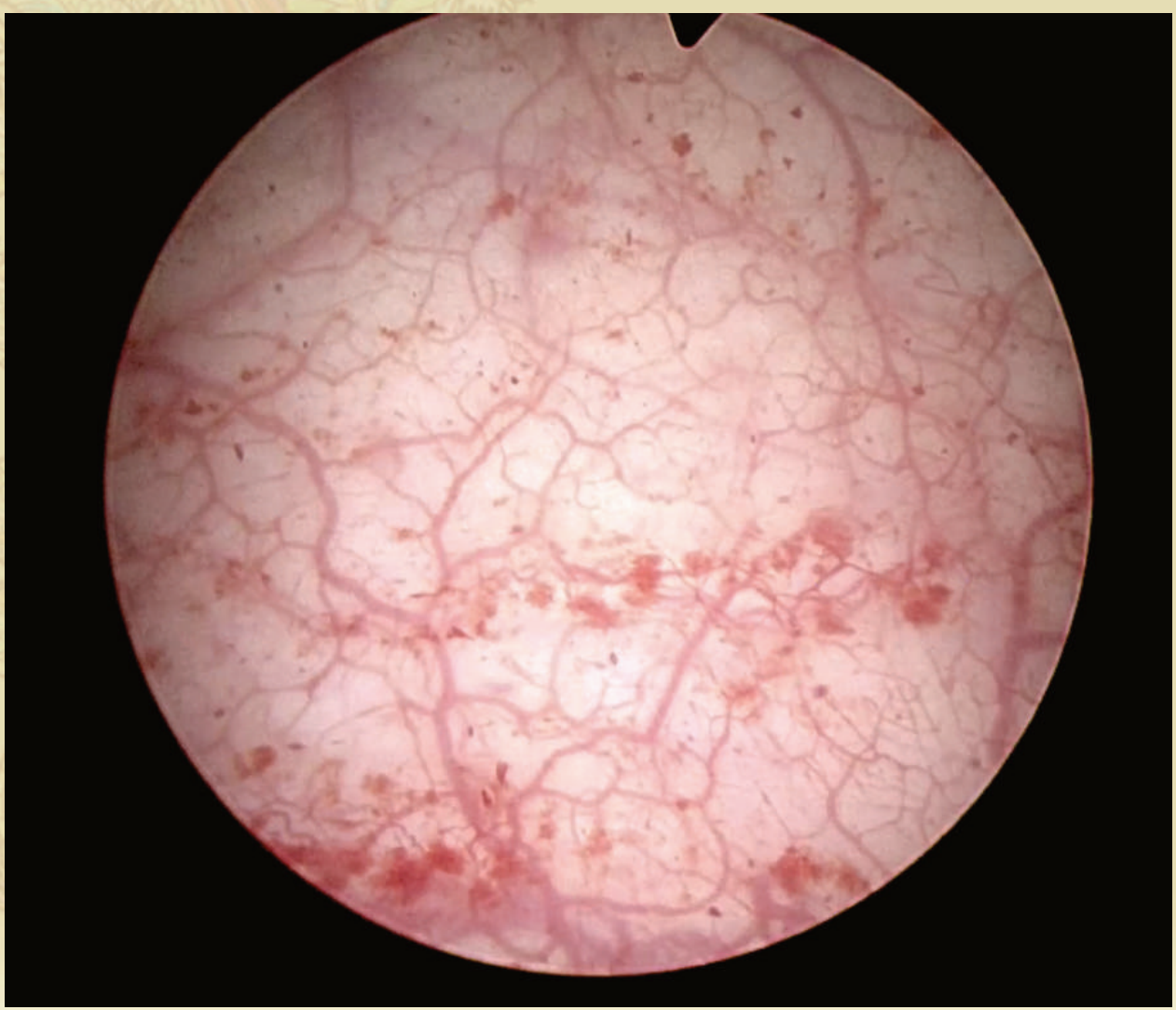
Violazione delle Barriere Uroteliali

Urothelial Barriers Break Down

Urothelium Leakage Syndrome

CISTITE INTERSTIZIALE

INTERSTITIAL CYSTITIS



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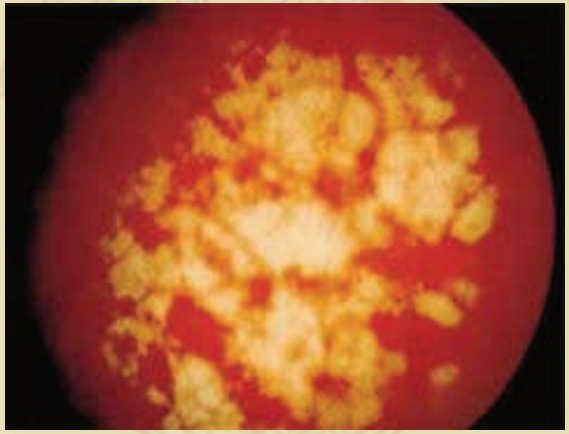
CISTITE INTERSTIZIALE

INTERSTITIAL CYSTITIS

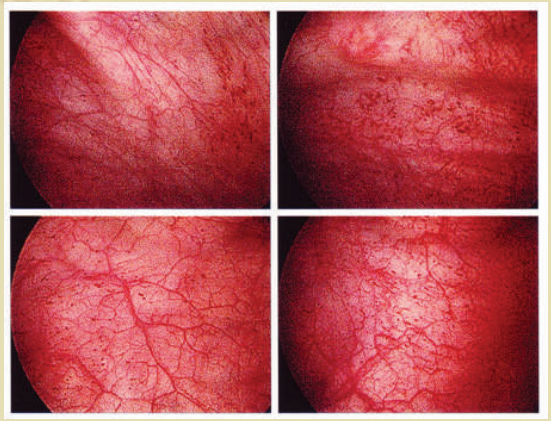
a Cystoscopy: glomerulatios grade 2 – 3

b With or without glomerulations

c Histology showing inflammatory infiltrates and/or detrusor mastocytosis (mast cell count > 28 mast cells/mm^2) and/or granulation tissue and/or intrafascicular fibrosis



Glomerulations Grade 2



Glomerulations Grade 3



Hunner's Ulcer

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LA VESCICA NELLE RUTI's
PRINCIPI DI TERAPIA

Ostruzione e Dyfunctional Voiding: modulazione farmacologica (alfa-litici off label, benzodiazepine), FKT

Leaky Urothelium, Difetto del coating: Acido Ialuronico, Condroitinsolfato, Adelmidrol

Violazione dell'Interstizio, Attivazione mastocitaria: PEA

Dolore Neurogenico: modulazione farmacologica (amitriptilina, pregabalin, gabapentin, duloxetina, clonazepam, diazepam, PEA ultramicronizzata, Ac alfa-lipoico)

Leaky Barrier Syndrome: RUTI's, IC, Vulvodinia, IBS: multi/transdisciplinarietà

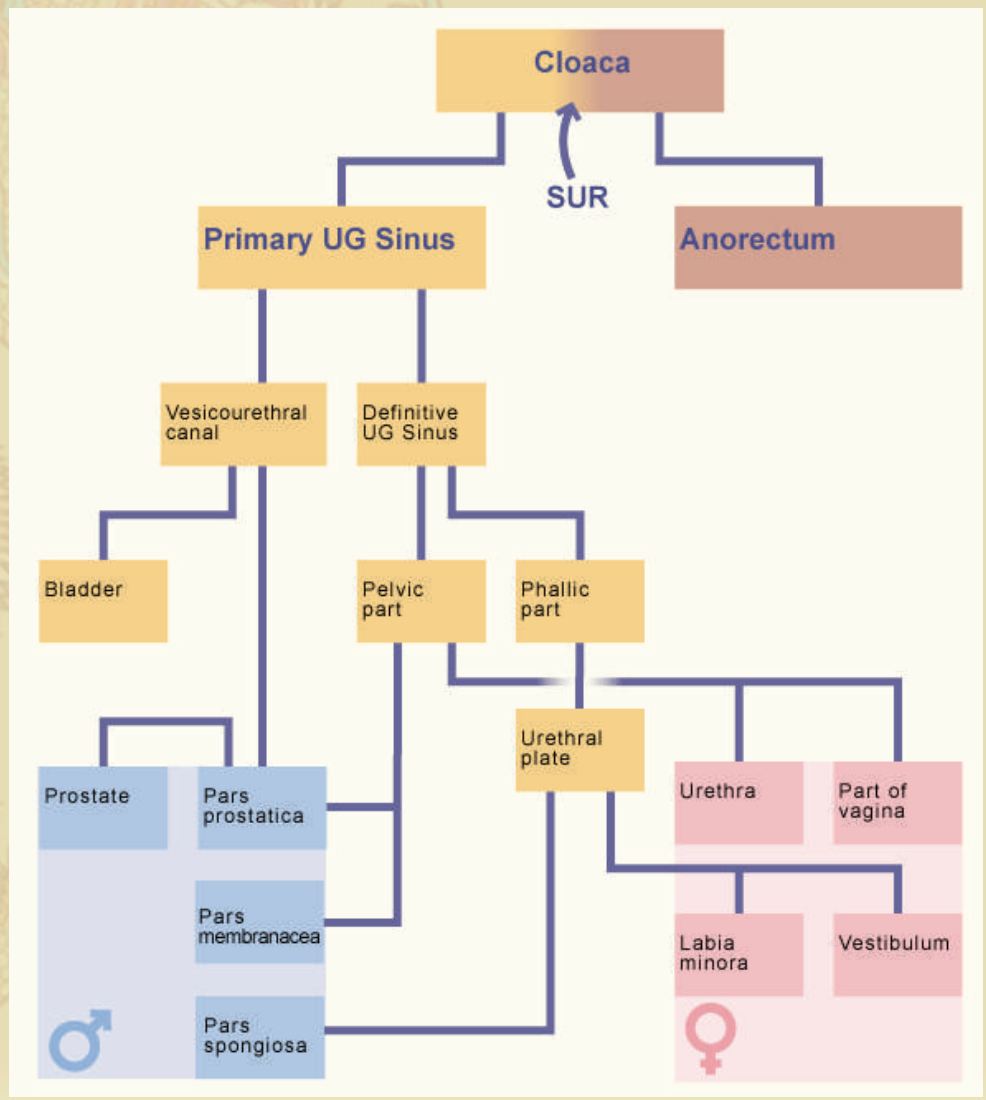
fppt.com

L'URETRA NELLE RUTI's

1. Brevità anatomica?
2. Embriogenesi comune con vestibolo
3. Mucosa: azione di sigillo (*Sealing Effect*)
4. Sottomucosa: componente vascolare (*engorgement*), muscolare, nervosa
5. Influenza Ormonale
6. Compressione ad opera del mm pubococcigeo (ipertono) durante i rapporti (cistiti post-coitali)

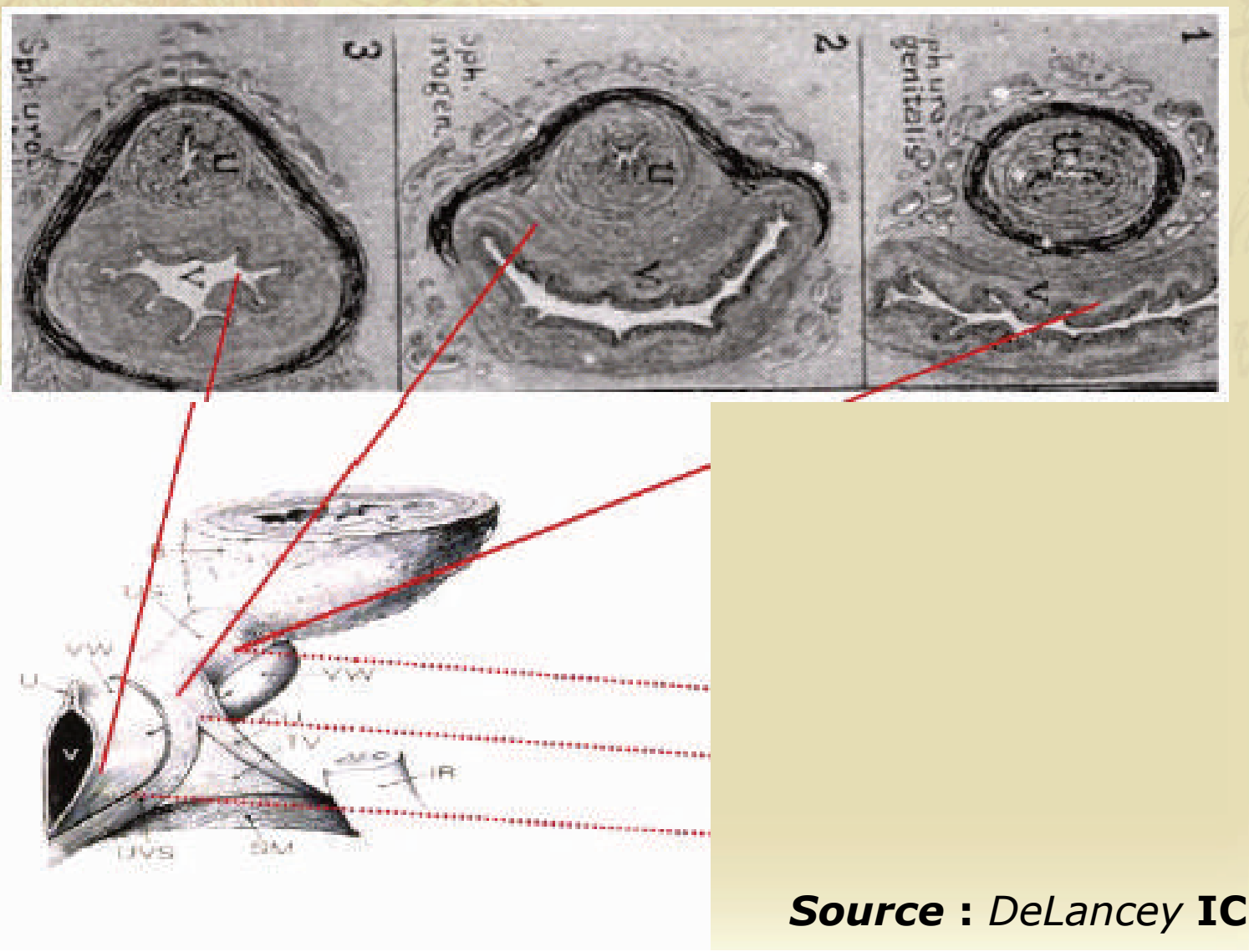
fppt.com

URETRA & VESTIBOLO: COMUNE ORIGINE EMBRIONALE



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Urethral Lumen

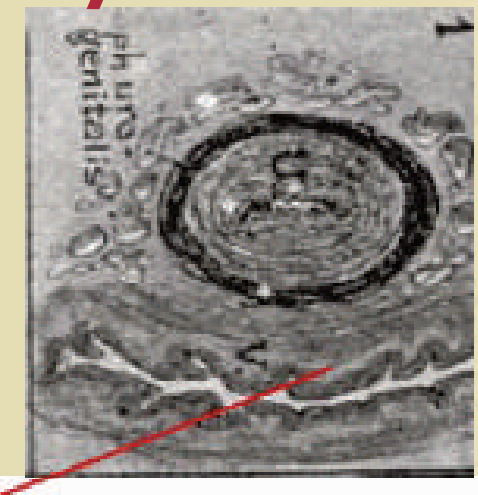


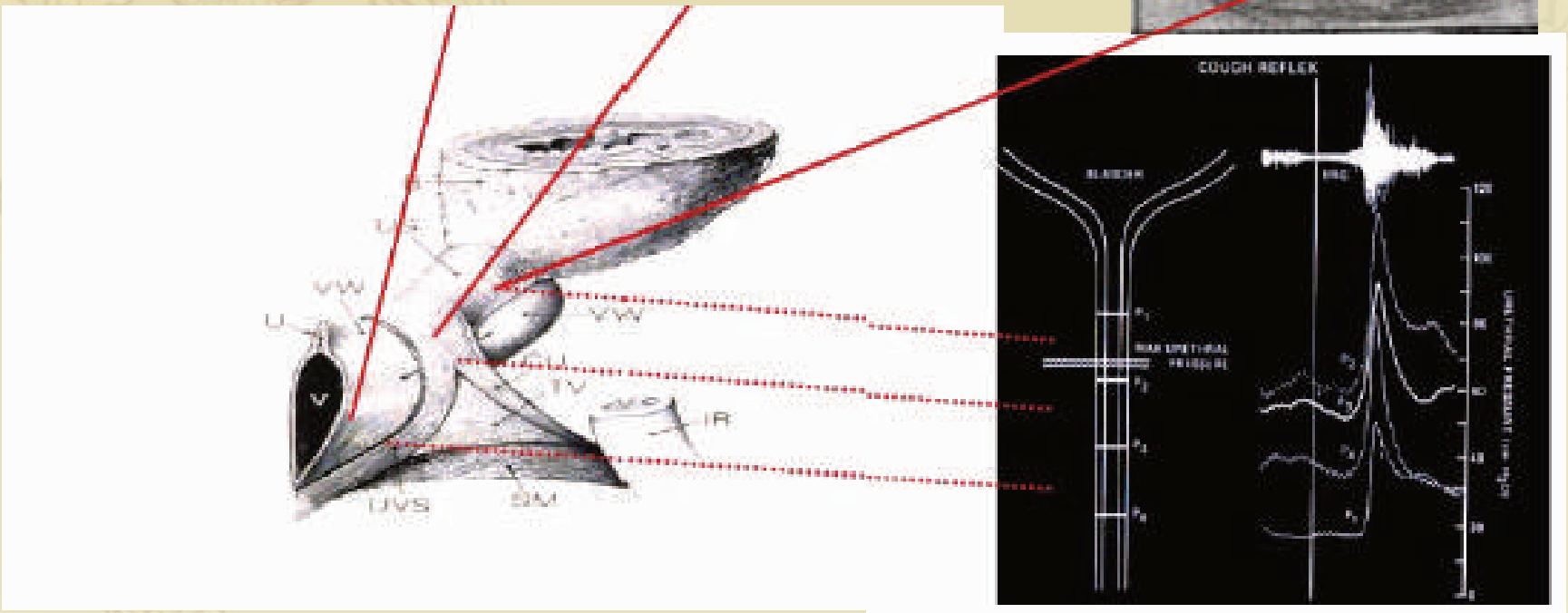
Source **:** *DeLancey* **ICI**

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Urethral Lumen Prox 1/3

The broadest muscular structure
The richest vascular component
The highest MUCP
The highest EMG Activity
The narrowest lumen

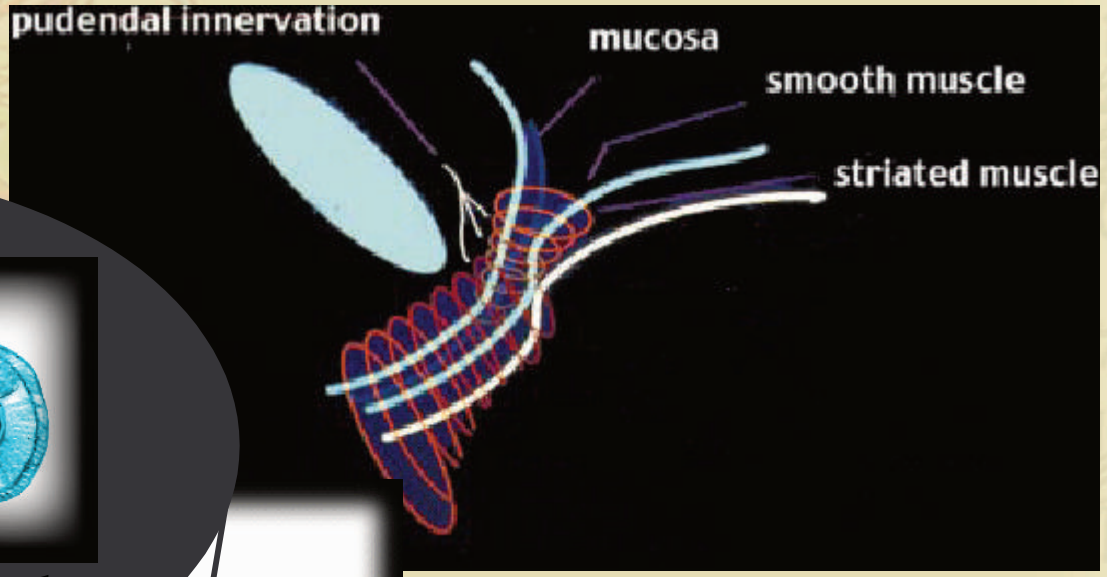


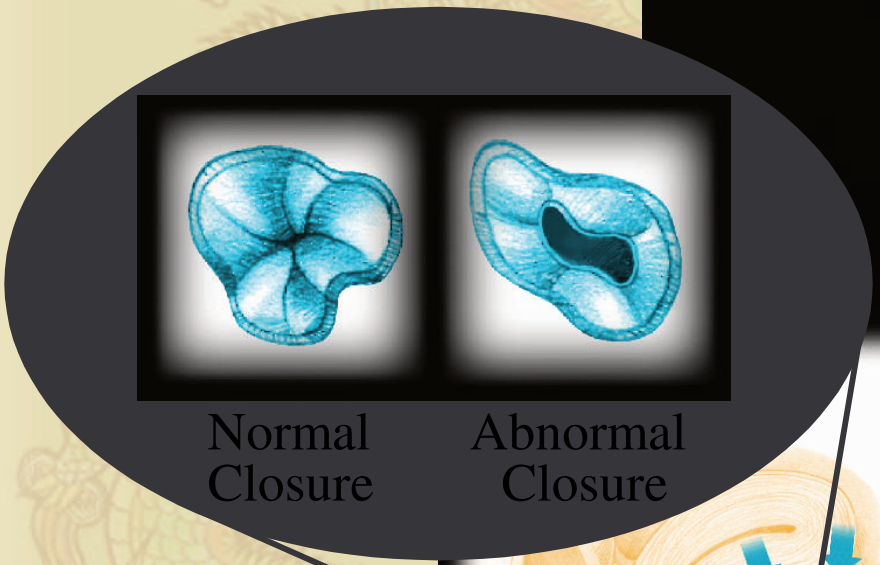


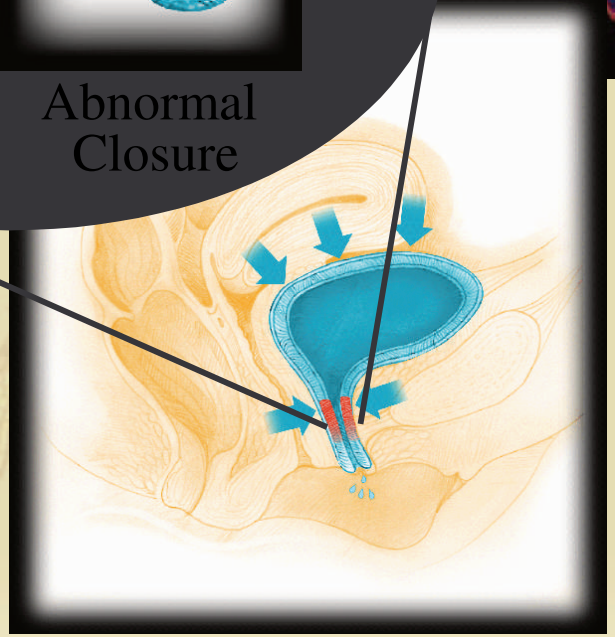
Source **:** *DeLancey* **ICI**

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Urethral Sealing

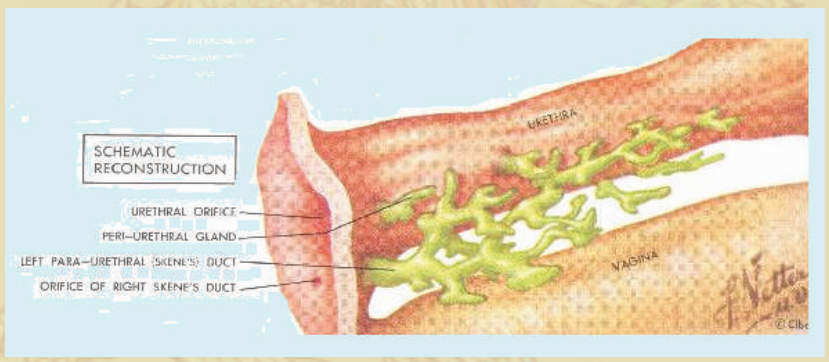


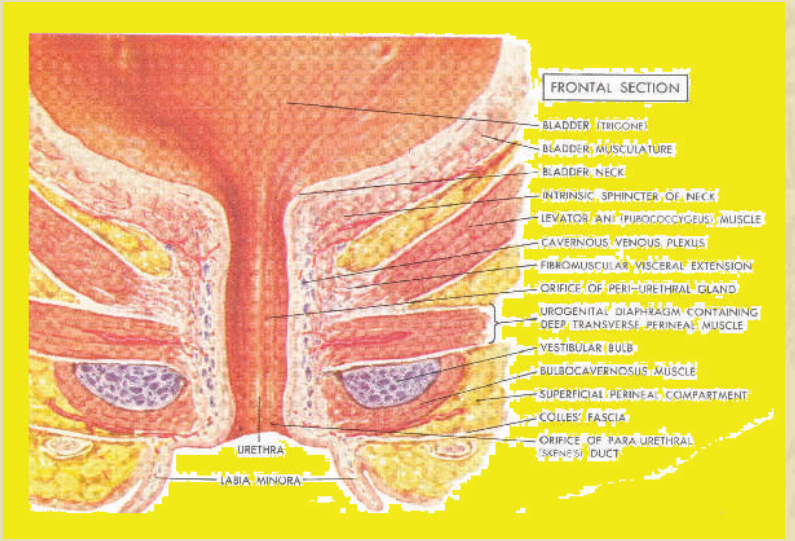




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dyspareunia & bladder symptoms





Coital pain causes:

1) tightened defensive myalgic pelvic floor

2) reflex inhibition of periurethral vascular arousal

3) mechanical urethral trauma

O'Connell et Al.Anatomical relationship between urethra and clitoris, J.Urol. 159; 1892-7,1998

D'Amati et Al Type 5 phosphodiesterase expression in the human vagina J.Urol.60 (1)191-195 2002

Courtesy of A. GRAZIOTTIN

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LA VAGINA NELLE RUTI's

1. Vaginosi e Vaginiti
2. pH Vaginale
3. Eubiosi e Disbiosi Vaginale
4. Età fertile, pillola, climaterio, menopausa e GSM

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IL PAVIMENTO PELVICO NELLE RUTI's

1. Ipertono e Iperattività
2. Sinergia e Dissinergia (minzionale, defecatoria, coitale)
3. Incoordinazione
4. POP (Pelvic Organ Prolapse)

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IL PAVIMENTO PELVICO NELLE RUTI's
Riabilitazione Funzionale





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IL PAVIMENTO PELVICO NELLE RUTI's
Tono Perineale



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European Association of Urology

Guidelines on
Chronic
Pelvic Pain

M. Fall (chair), A.P. Baranowski, S. Elneil, D. Engeler, J. Hughes, E.J. Messelink, F. Oberpenning, A.C. de C. Williams

Pelvic Floor Muscles Pain Syndrome

Persistent or recurrent, episodic, pelvic floor pain with associated trigger points, which is either related to the micturition cycle or associated with symptoms suggestive of urinary tract, bowel or sexual dysfunction. No proven infection or other obvious pathology (5,6)





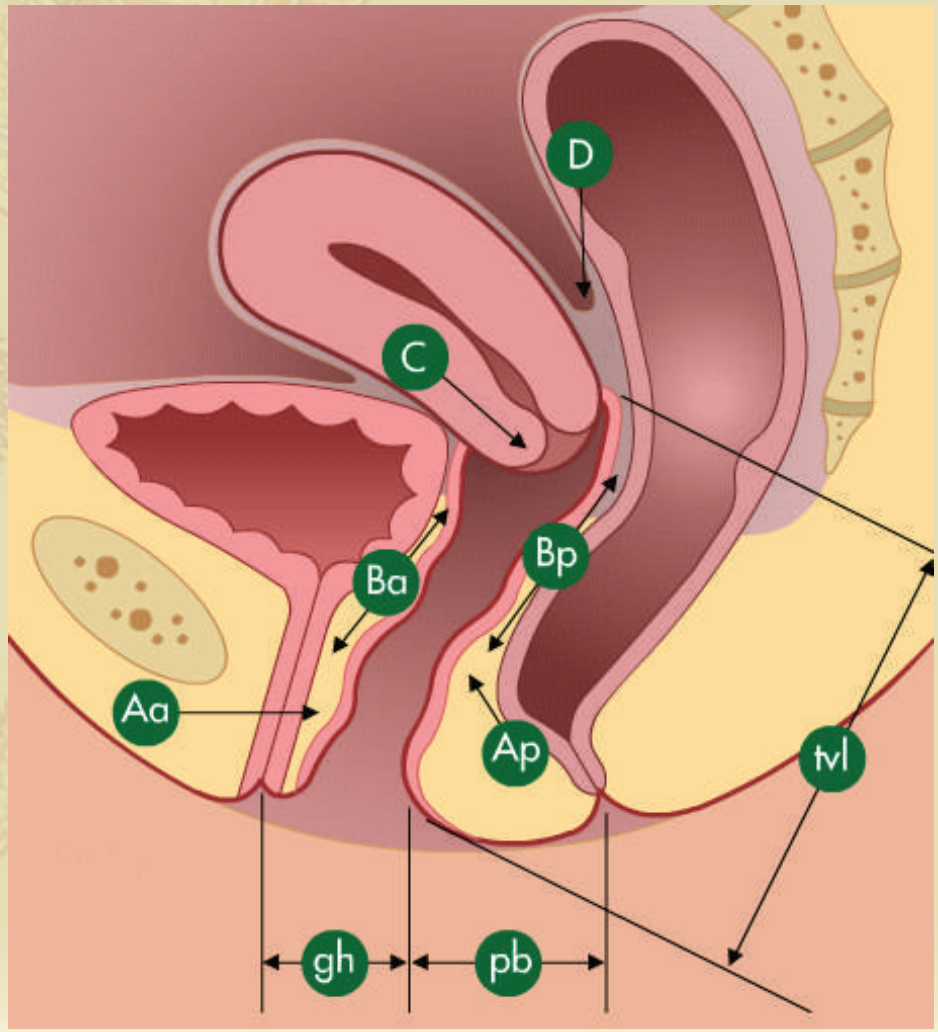


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Prolasso Degli Organi Pelvici

Pelvic Organ Prolapse - POP

ICS POP-Quantification System



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L'INTESTINO NELLE RUTI's

1. Eubiosi e Disbiosi (fermentativa, putrefattiva)
2. Sovracrescita batterica (tenue, colon)
3. Sovracrescita fungina (Candida)
4. Leaky Gut Barrier Syndrome
5. Violazione dell'Interstizio, attivazione dei mastociti
6. Brain Gut Axys
7. Gut Brain Axys

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L'INTESTINO NELLE RUTI's
PRINCIPI DI TERAPIA

1. Dietoterapia e sani stili di vita
2. Prebiotici e Probiotici
3. Colostro
4. Enteroadsorbenti, glutamina, melissa, camomilla
5. Fitoterapici, Micoterapici, Olii Essenziali, Quintessenze Spagyriche
6. SANUM
7. Idrocoloterapia
8. Trapianto di feci

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VIE DI DIFFUSIONE BATTERICHE NELLE RUTI's

1. ANTEROGRADA: diretta per trasmigrazione batterica dall'intestino
2. RETROGRADA: per via uretrale

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TAKE HOME MESSAGE

CISTITI RICORRENTI

NO APPROCCIO MINIMALISTA

SI' APPROCCIO MULTIDISCIPLINARE

SI' APPROCCIO TRANSDISCIPLINARE

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MEDICINA TRADIZIONALE CINESE



TERAPIA INTEGRATA

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GRAZIE DELLA

VOSTRA PREZIOSA ATTENZIONE

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