



# CYSTISTAT

Hyaluronan Training



# HISTORICAL ASPECTS

- In 1934, Karl Meyer and his assistant, John Palmer, described for the first time the process to isolate a new Glucosa- Amino-Glycan (GAG) from the cows vitreous humor.
- The composition was initially defined as Uronic acid + an aminosugar, being the first described GAG without a sulphate group.
- It was named as Hyaluronic acid:

Hyaloid (vitreous) + Uronic acid



# CHEMICAL STRUCTURE

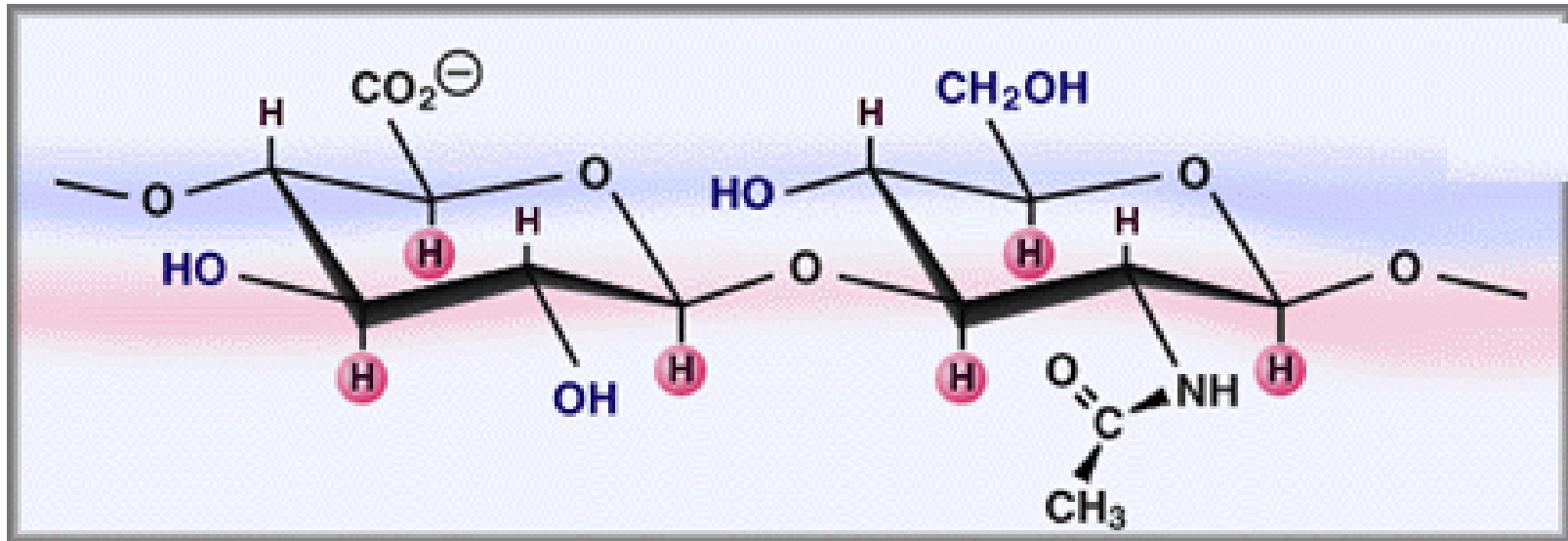
- The definitive and precise chemical structure was not published since 1954.

- Uronic acid ----- D-Glucuronic acid  
Aminosugar ----- N-Acetylglucosamine



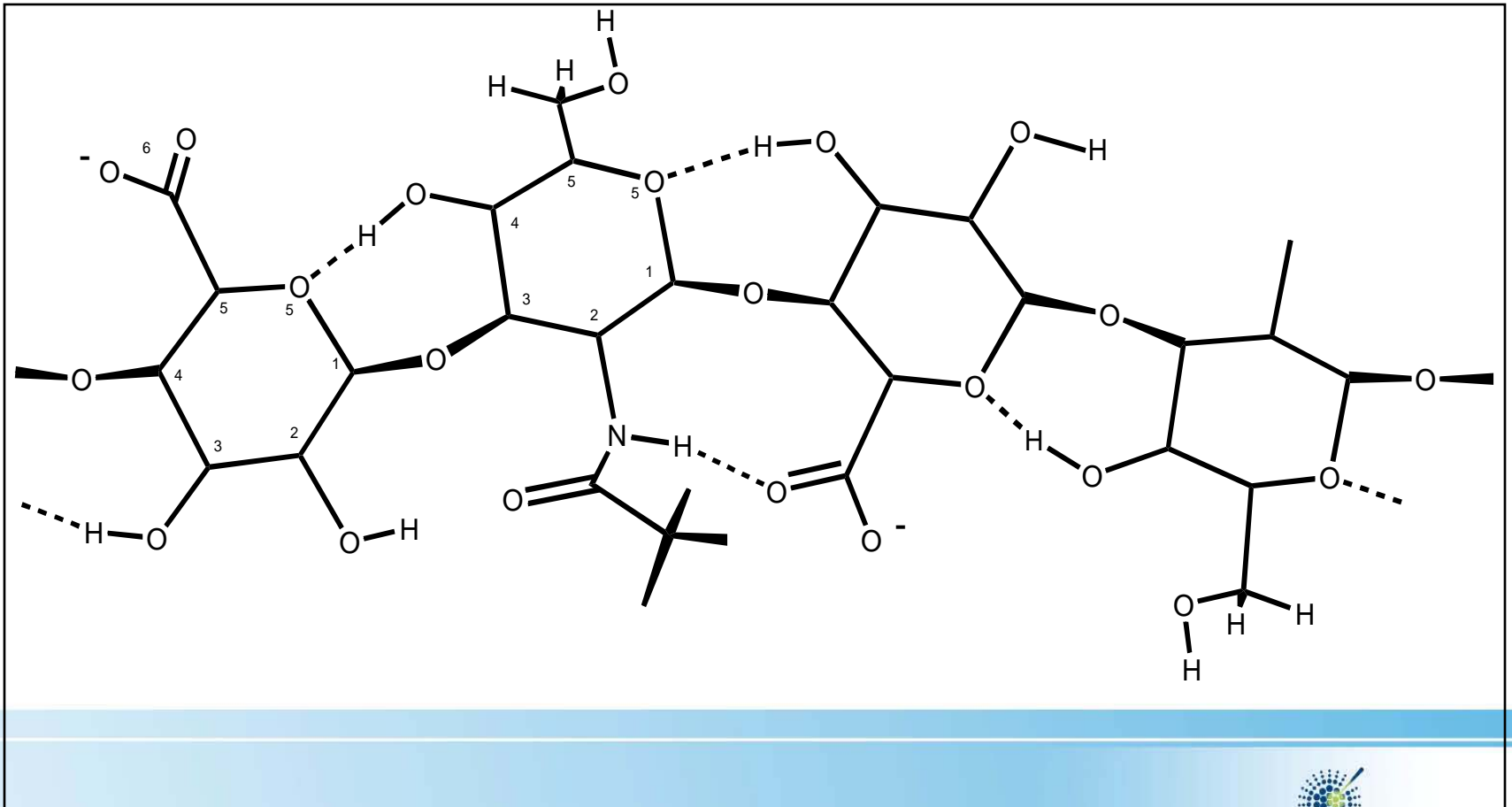
# HYALURONIC ACID

## Glucosaminoglycan (GAG)



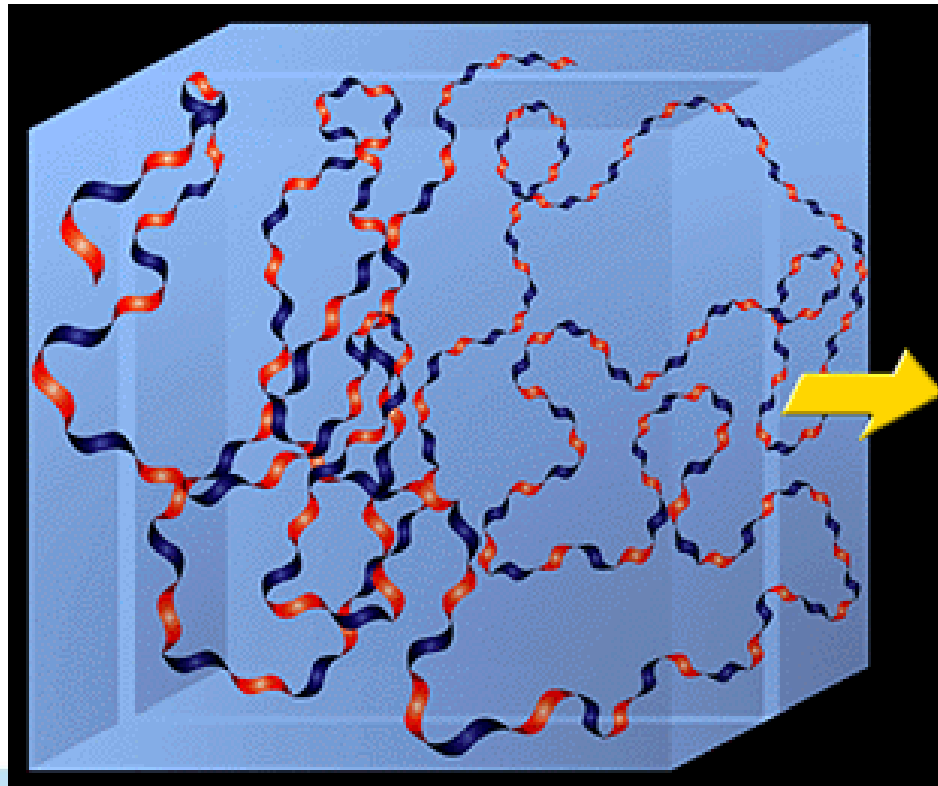


# HYALURONIC ACID





# 3 D Hyaluronan Structure





# HYALURONIC ACID

# SODIUM HYALURONATE

# HYALURONAN



# Sodium Hyaluronate

- Hyaluronic Acid is in nature always linked to sodium molecules.
- The concept Hyaluronan or Hyaluronate reflects much better what it really is. In vivo, it exists as a polyanion and not in the protonated acid form.
- Cystistat is manufactured as a solution with HA and Sodium (40 mg in 50 mL solution).



# Cystistat

## ***What is it ?***

Cystistat is a new form of treatment for Interstitial Cystitis in which the main active ingredient is Sodium Hyaluronate (Na-HA), a natural occurring polysaccharide.

It is presented in a 50 ml vial containing 40 mg of Na-HA.





# Hyaluronate properties

- Mechanical effect: Barrier/Lubrication
- Moisturising properties: High water binding properties
- Healing properties: Normalization of cell migration and proliferation
- Nutrient effect: Transport of essential molecules from the bloodstream to the epithelial cells
- Pharmacological effect: Cell signaling (CD44 Receptor)  
Antiinflammatory



# Hyaluronate properties

- Mechanical effect: **Barrier**
- Healing properties: **Proliferation of epithelial cells**



# BLADDER INDICATIONS

Restoration of the GAG layer:

- BPS/IC
- RBC
- RIC
- UTI Prevention
- Hemorrhagic Cystitis





# BPS / IC

## Bladder Painful Syndrome / Interstitial Cystitis



# Consensus?

Difficult to

Find the Cause (Etiology)

Diagnose (Prevalence)

Cure (Treatment)

“The disease remains an enigma in Urology” Kirsten Bouchelouche (DK)



# REASONS FOR UNDERDIAGNOSIS

- Unknown origin
- No definitive diagnostic test
- Individual development of the disease
- Different medical approaches

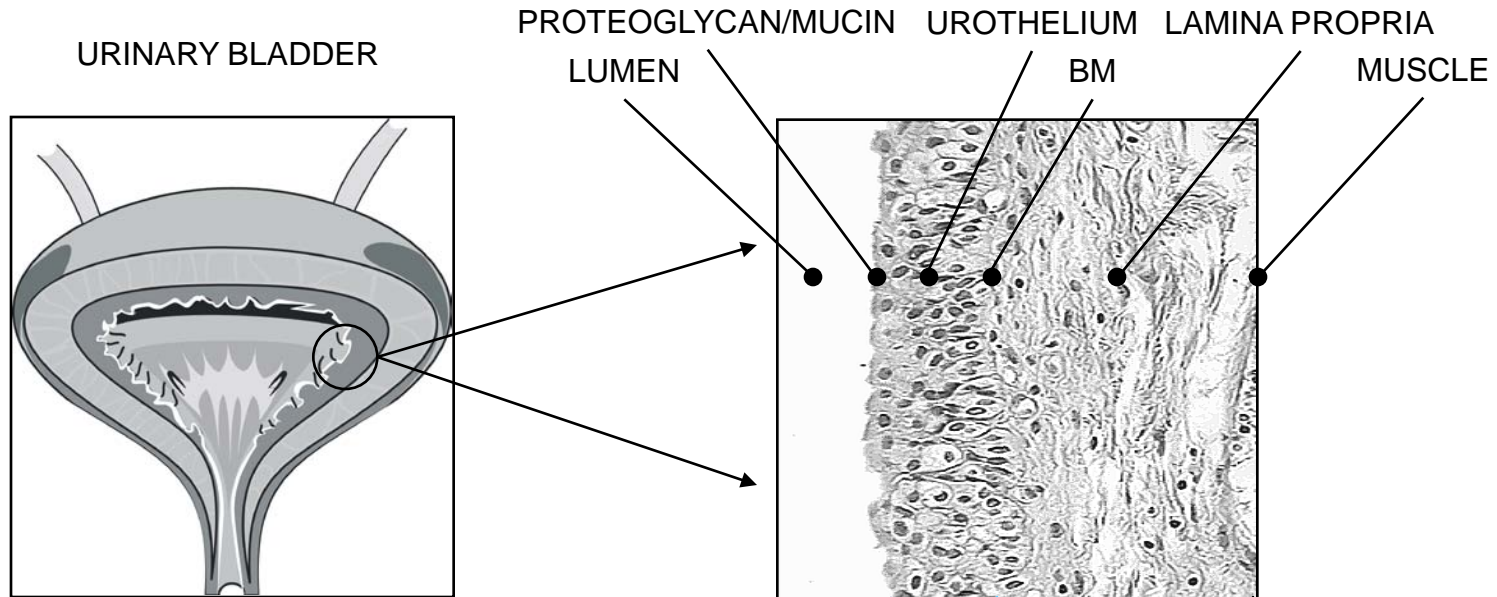


# Etiological hypothesis

- Urothelium disorders
- Detrusor disorders
- Mediators
- Neurological disorders
- Autoimmune disorders

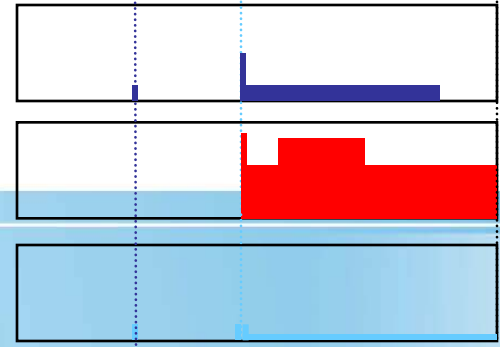


# Glycosaminoglycans and the GAG layer



ELEVATED URINARY LEVELS IN INTERSTITIAL CYSTITIS – LOSS OF URINARY BLADDER WALL PERMEABILITY BARRIER

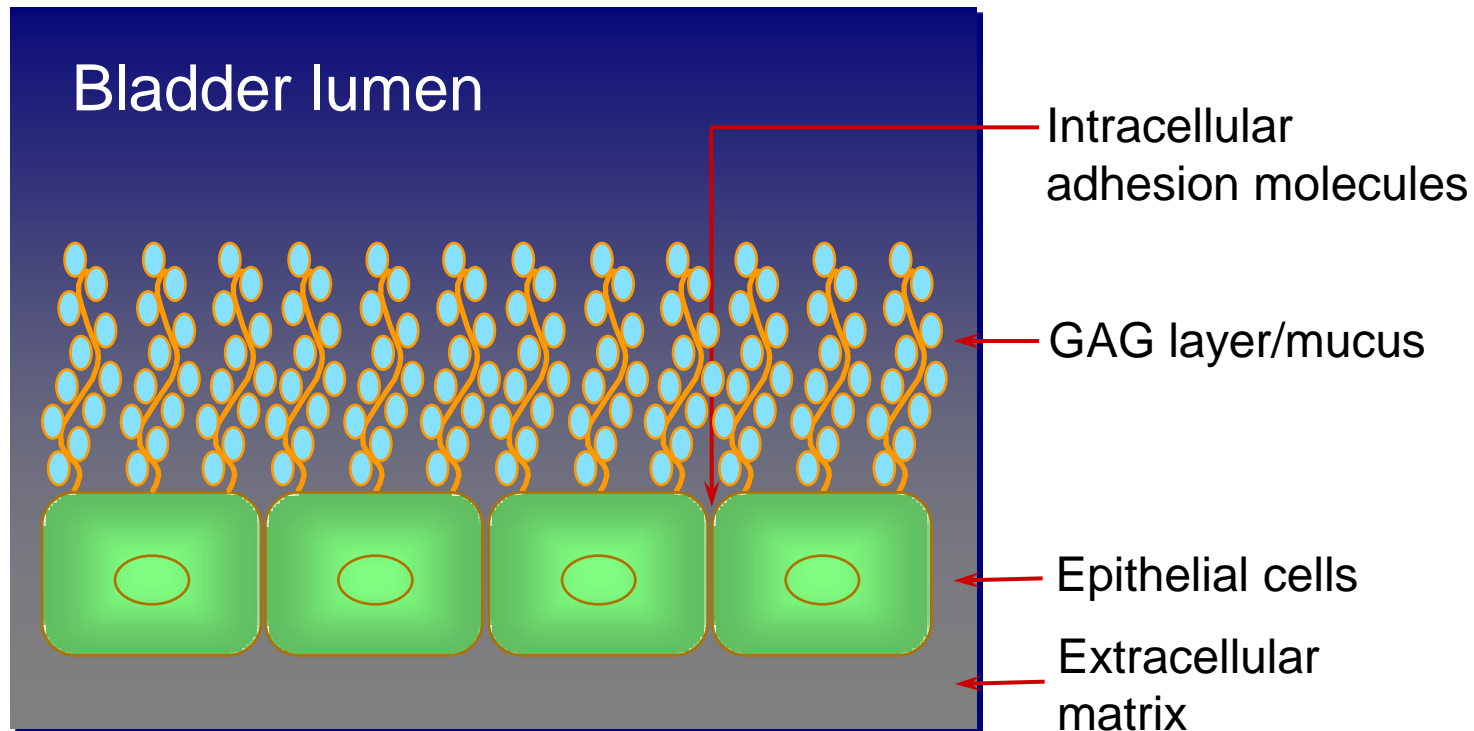
- CHONDROITIN SULPHATE (AS PROTEOGLYCAN)
- HYALURONAN
- HEPARAN SULPHATE (AS PROTEOGLYCAN)



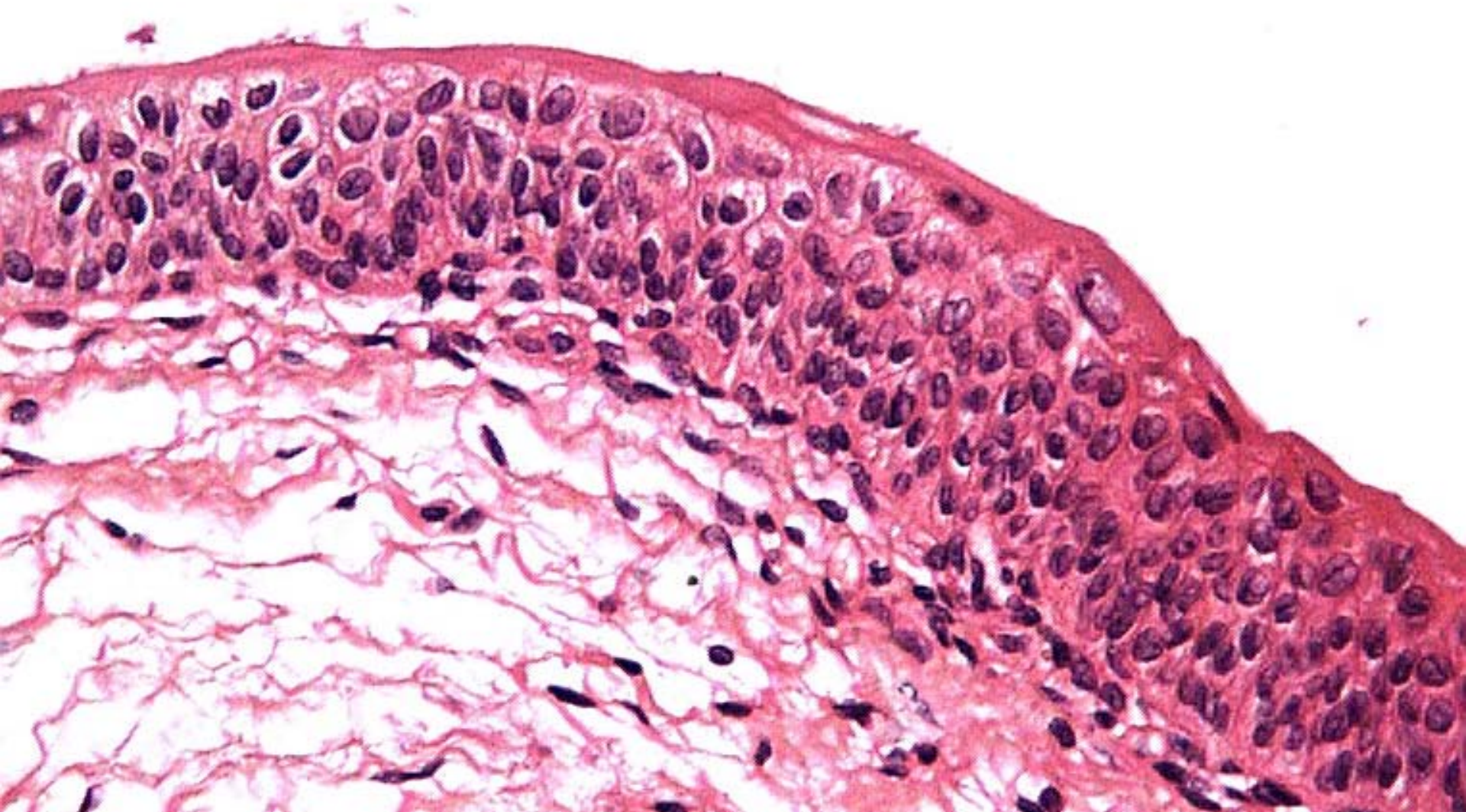
↑  
RELATIVE INTENSITY OF DISTRIBUTION



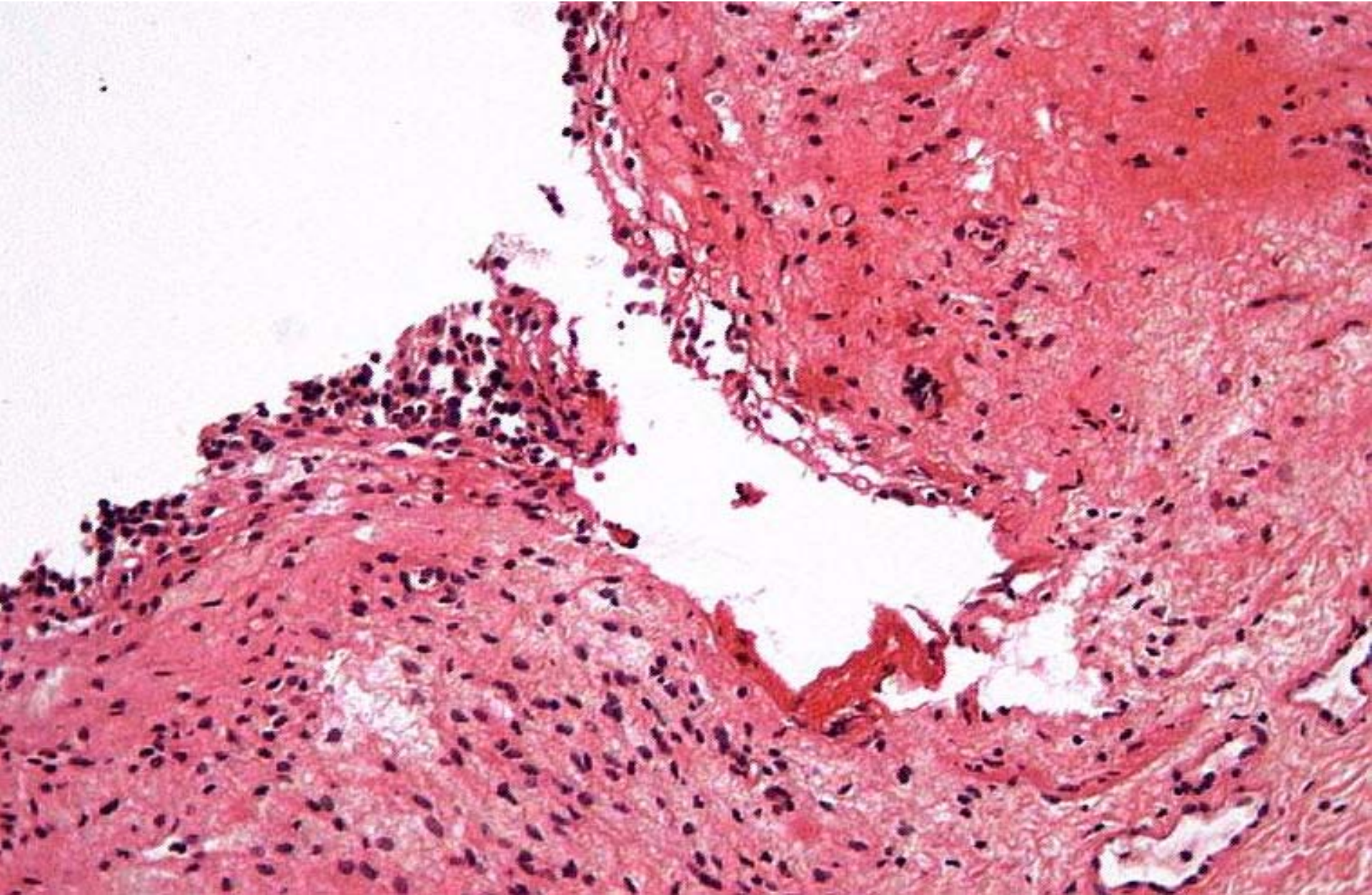
# Normal Epithelium



# Bladder Mucosa-Epithelium



# Interstitial cystitis





# Uroepithelium

Impermeable barrier / Part of a sensory web

Changes in permeability

- Passage of irritant substances

- Release of neuroactive chemical mediators

Excitability of afferent receptors in the mucosa



# Uroepithelium

## Weakness of urothelium in BPS patients

### Histological Findings

Evidence of disruption on the bladder epithelial cell tight junctions

Glomerulations / Ulcers

### Functional Findings:

After intravesical instillation of Urea:

Increased concentrations in plasma

Decreased concentration into the bladder

Increased sensitivity to intravesical Potassium instillation



# Uroepithelium

## Changes in urothelium in BPS patients

- Production of APF (specific Antiproliferative Factor)
- Decrease in the ratio of cellular proliferation
- Decrease tight function proteins (occludins)
- Increased ATP-stimulated ATP release



# Neurological Disorders

Hypersensitivity – Hyperexcitability C Fibers

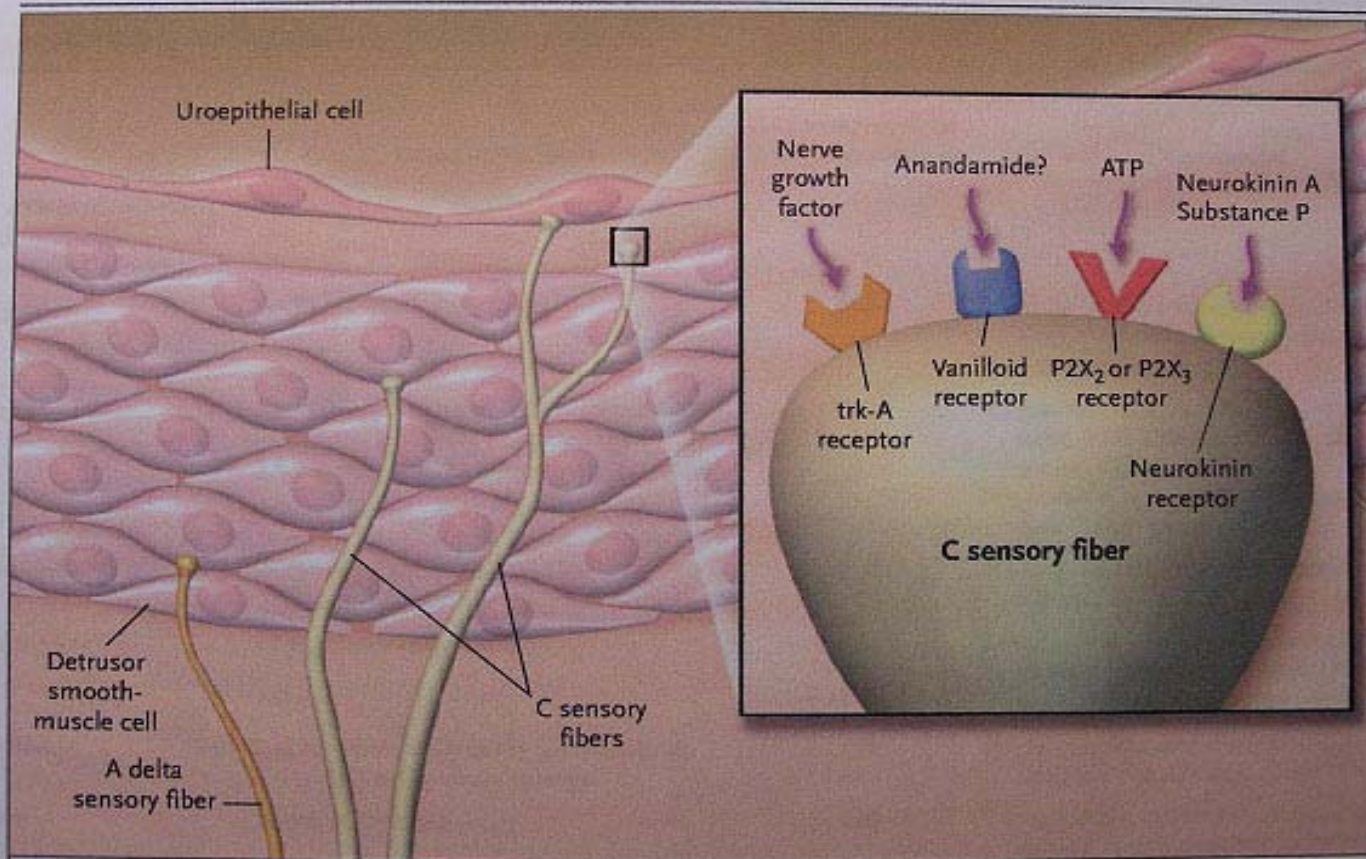
Autonomic function disorders

# Autoimmune Disorders

Sjögren Syndrome, Fibromyalgia, RA



The NEW ENGLAND JOURNAL of MEDICINE





# Concomitant diseases

BPS/IC has been related with many other conditions:

- Irritable Bowel Syndrome (IBS)
- Inflammatory Bowel Disease (IBD)
- Fibromyalgia & Chronique Fatigue Syndrome
- Endometriosis
- Migraine
- Allergies
- Lupus
- Sjögren Syndrome



# Food & Beverages

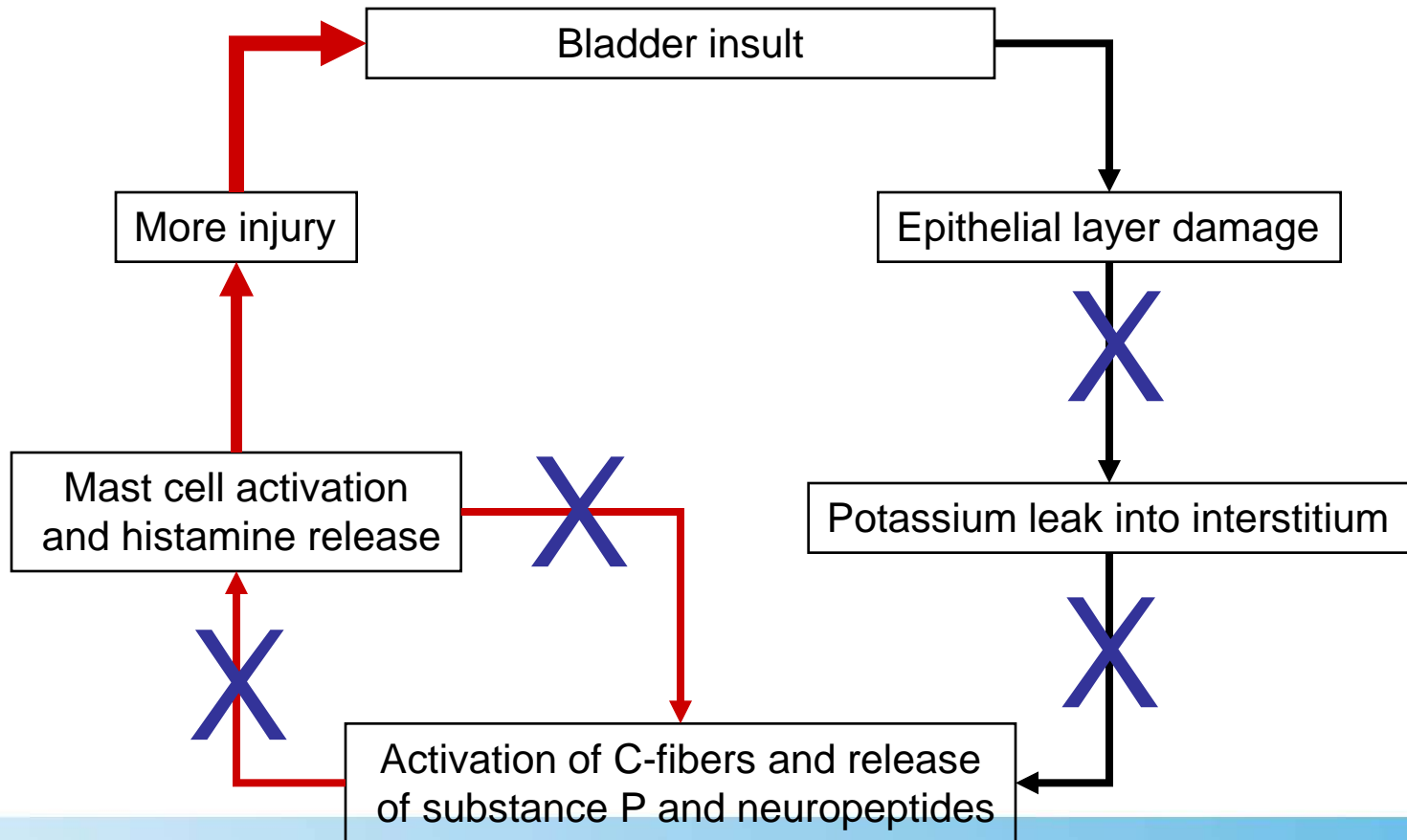
Many BPS/IC patients report a relationship between what they eat or drink and how they feel

BPS patients have to avoid:

- Foods & Beverages that are rich in acid content (citrus fruits, vinegar, tomatoes, pineapples, vitamins,...)
- Hot or spicy foods and seasonings
- Potassium rich foods (Bananas, Coke,...)
- Caffeine
- Alcohol



# Pathological amplification in IC



X = Potential GAG interaction sites



# ESSIC Proposal for new definition

## Bladder Pain Syndrome (BPS):

The diagnosis of BPS will be made on the basis of the symptom of pain related to the urinary bladder, accompanied by at least one other urinary symptom such as day-time and night-time frequency, and exclusion of confusable diseases as the cause of the symptoms and cystoscopy with hydrodistension and biopsy if indicated



# BPS/IC Symptoms

- Suprapubic Pain
- Urgency (Day & Night)
- Frequency

Symptoms very similar to other kind of cystitis (unespecifics).



# Pain

Pain is a sensitive experience, and also emotional (generally negative) associated with tissue damage, current or potential.

New definition recognizes pain as the main factor, previous to the final diagnosis.



# Incidence

Similar incidence than:

- Parkinson's disease
- Type 1 Diabetes
- Inflammatory bowel disease

25% of women with BPS/IC are below 30 years old



# PBS

IC

10% Hunner's Ulcers

90% Glomerulations on cystoscopy

What about patients without ulcers or glomerulations?



# BPS/IC Diagnosis

## ESSIC recommendations 2004:

- Medical History
- Physical Examination
- Laboratory Tests
- Symptoms Evaluation
- Urodynamics
- Potassium Sensitivity Testing
- Cystoscopy and Morphological Findings
- Morphology



# Suggestive symptoms identification

## KPNW Study:

IC symptoms were defined in 2 ways:

- Pelvic pain for at least 3 months, plus either urgency or frequency for at least 3 months
- Same criteria plus pain increasing as the bladder fills and/or pain relieved by urination

Prevalence:

11,2 %	Women	-	4,6%	Men	Definition 1
6,2 %	Women	-	2,3%	Men	Definition 2

Clemens et al. Prevalence of interstitial cystitis symptoms in a managed care population. J Urol  
2005;174:576-580



# Costs

## KPNW Study

2,4-fold greater yearly costs in cases than controls

(7.100 \$ vs 2.994 \$)

These cost differences were predominantly due to outpatient and pharmacy expenses



# Future

At the end, the treatment will most probably be a combination of different agents to be optimally effective

For sure, restoring the GAG layer will be one of them.



# GAG layer

Interstitial Cystitis (PBS/IC)

Radiation induced Cystitis

Recurrent Bacterial Cystitis

Overactive Bladder (OAB)

Chronic Non Bacterial Prostatitis (NBP)

Haemorrhagic Cystitis



# Cystistat

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# Cystistat

## ***Dosage and administration***

4-12 weekly instillations, and then monthly instillations until symptoms resolve.

Instill the entire volume of the solution into the bladder after any residual urine has been removed.

Cystistat should be retained in the bladder for as long as possible, with a minimum of 30 minutes.



# Cystistat

## *Minimal side effects*

With route of administration as intra-vesical instillation, Cystistat® causes very few, if any, systemic side effects. Cystistat® has been used in the treatment of interstitial cystitis with an **excellent safety profile**, which allows patients to return to normal life.

## *Cystistat® is prescribed in more than 40 countries*

Cystistat® has been approved for use in over twenty countries around the world including most of the countries of Western Europe, and Canada.

**Over 450,000** patients have benefited of the treatment.



# Cystistat

## ***Extended Indications***

By temporarily replacing and then restoring the protective layer in a patient's bladder wall, Cystistat® has proven successful in relieving pain and discomfort in not only interstitial cystitis, but also effective in other forms of cystitis, like:

- prevention of **recurrent bacterial cystitis**.
- management of **radiation-induced cystitis**,
- prevention of catheter-acquired **UTI (Urinary Tract Infection)**
- **Haemorrhagic cystitis**



# Target-Groups

- Urologists
- Gynecologists
- Radiotherapists
- Oncologists



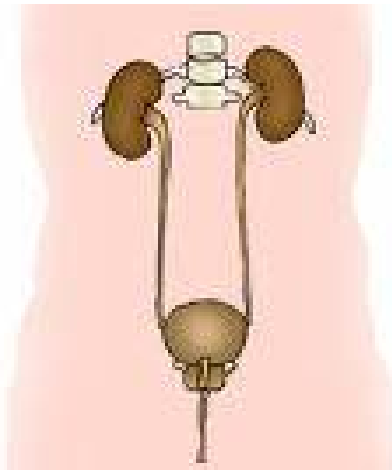
# Clinical References

- ***In total, there are around 50 published studies on Cystistat ® involving more than 900 patients.***
  - ***32 studies on Interstitial Cystitis***
  - ***6 on RIC***
  - ***4 on RBC***
  - ***3 on UTI***
- ***Studies under evaluation: in RBC, RIC, CYST vs DMSO***



# UTI

Bacterial invasion of the urinary tract,  
between the Urethra and the Kidney



Bladder

Kidney

Urine

Cystitis

Pyelonephritis

Bacteriuria



# UTI

Second most common infectious complaint in outpatient primary care clinics overall.

Most common outpatient complaint caused by bacteria.



# UTI: Risk Factors

- Sexual activity (Premenopausal)
- Oestrogen deficiency (Post-Menopausal)
- Genito-urinary Surgery
- Incontinence
- Diabetes
- Genetic Factors
- Contraception (Diaphragms, Spermicides)
- Number of Sexual Partners
- Previous use of Antibiotics





# UTI

By far, the most common mechanism by which bacteria enter the urinary tract is by ascending from the periurethral area:

More common in women (95%) because:

- Shorter urethra
- Closer proximity to the anus
- Habits



# BACTERIURIA

Presence of bacteria in the urine

Asymptomatic bacteriuria should only be treated in the pregnant female.



# UTI

## Symptomatic infection:

- Frequency
- Burning
- Straining
- Urgency
- Pain with voiding

## Other possible symptoms:

- Hematuria
- Suprapubic Pain
- Tenderness
- Change in odor of urine



# RBC vs UTI Prevention

RBC = 3 or more clinical UTI per year  
(Gynecology)

UTI Prevention:

Oncologic patients with high risk of UTI may receive Cystistat instillations to decrease or avoid this risk.

(Oncology)

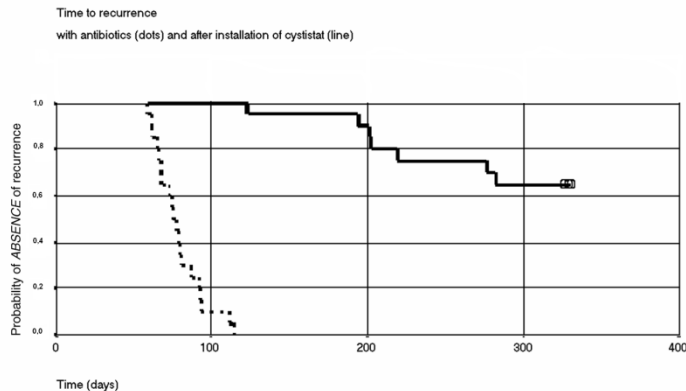


# In the treatment of RBC

## Study of *C. Constantinides*:

- a) 5-fold increase of the time to recurrence
- b) 92.4% decrease in the number of recurrences per year (0.33 vs 4.32 pre-treatment).<sup>13</sup>

Median time to recurrence in pre and post hyaluronic acid treatment		
Pre-treatment	Post-treatment	P value
96 days	498 days	<0.0001



## Study of *M. Lipovac* & *M. Imhof*:

- a) The number of urinary tract infections per year per patient was reduced from  $4.99 \pm 0.92$  to  $0.56 \pm 0.82$  ( $p < 0.001$ )
- b) Time to recurrence post-HA treatment was  $178.3 \pm 25.5$  days compared with  $76.7 \pm 24.6$  days before treatment.



# In the treatment of RIC

## ***Perez et al., 2003:***

90 patients receiving combined external and brachyradiotherapy for cervix/uterine cancer were divided into 2 groups: 45 patients treated in a standard fashion vs. 45 patients receiving 40 mg of Cystistat<sup>®</sup> during the weekly brachytherapy planning. Radiation-induced toxicity was reduced by 46 % in the Cystistat<sup>®</sup> group, as was the risk of bacterial cystitis throughout the radiation period, allowing for treatment completion in the scheduled time in the majority of patients.

	Usual Care	Usual Care + Cystistat <sup>®</sup>	P-value
Week 4	1.33	0.71	P<0.0001
End Radiotherapy	1.24	0.71	P<0.0001

## ***Diamantopoulos et al., 2004:***

20 patients suffering from post-radiation cystitis were treated with intravesical Cystistat<sup>®</sup> once a week for 4 – 6 weeks, and then monthly for up to one year. **80%** of patients were **significantly improved** at the end of therapy, and clinical improvement was in accordance with the endoscopic appearance of the bladder.



# Hyaluronan treatment of IC/BPS

Riedl, 2008



# Efficacy of HA Therapy

121 Patients

with Average symptoms duration: 6,1 years

received Cystistat

When were diagnosed by:

- Modified Potassium Test
- VAS Questionnaire
- QoL impact



# Results

## Symptoms Improvement

85% (103 patients)

## VAS Score

BT: 8'5

AT: 3'5

SS. Statistically significant



# Results

## Long Term Results

64,5% of patients free of symptoms after 5 years

## Quality of Life

84% Significant improvement of their QoL



# Results

34,5% of patients received new intravesical therapy in less than 5 years

1'521 instillations

No adverse reactions were reported

Mild irritative symptoms



# Results

Selection of patients for Hyaluronan therapy by Potassium testing improves the outcome of intravesical therapy with a response rate > 80%



# Treatment of Post-hematopoietic Stem Cell Transplantation Hemorrhagic Cystitis with Intravesical Sodium Hyaluronate

Miodosky, 2006



# HC Definition

## Hemorrhagic Cystitis:

Presence of macroscopic hematuria in the absence of other conditions such as gynecological-related bleeding, nephrolithiasis and/or bacterial or fungal infection of the lower urinary tract



# Hemorrhagic Cystitis

Complication observed after high-dose of chemoradiotherapy, mainly in hematopoietic stem cell transplantation (HSCT).

Early-onset < 1w.

Direct toxicity to the uroepithelium

Late-onset > 1 w.

Viral reactivation + Difuse bladder mucosa inflammation



# HC Severity

I: Microscopic Hematuria

II: Macroscopic Hematuria

III: Macro Hem + Presence of clots and/or necessity of blood transfusions

IV: Life-threatening bleeding requiring surgical intervention



# Study

123 patients who underwent HSCT, 7 developed clinically significant HC (6%)

Median Time: 30 d. after transplantation

7

1 Early transplantation

6 Late-onset

Grade III



# HC Treatment

Cystistat 1 Vial

Slow instillation through a Foley catheter

Minimum time in bladder: 20 min

When no response 7 d. later, another instillation

All patients received hyperhydration and transfusion support



# Results

4 patients improved W1

2 patients improved W2

1 patient did not improve

Treatment with Cystistat initiated 3 d. after  
the development of symptoms



# HA Action

- Inhibition of immune complexes
- Adherence to polymorphonuclear cells
- Inhibition of leukocyte migration
- Regulation of fibroblast and endothelial cells proliferation
- Enhancement of connective tissue healing



# Cystistat: Roadmap to leadership

## Core strategy:

- Continue building robust clinical evidence
- Be creative/perseverant in obtaining reimbursement
- Enter into new indications (RBC)
- Expand distribution network
- Ensure strong field force: « adequate in quantity / top in quality »
- Build opinion leader network
- Develop innovative application forms



# Positioning

- Development of GAG ethiological hypothesis for bladder disorders
- Promoting Key Opinion Leaders  
(Riedl, Imhoff, Mañas, Nordling, Van Ophoven, Pontari, Constantinides,...)
- Main Scientific Conferences attendance



# Reaction to something new

15%	Immediate acceptance
70%	Delayed acceptance
10%	Late acceptance
5%	Resistant to change



# Promotion

**I<sup>st</sup>** phase : To be conscious

**II<sup>nd</sup>** phase : Active implication

**III<sup>rd</sup>** phase : Testing

**IV<sup>th</sup>** phase : Assumption



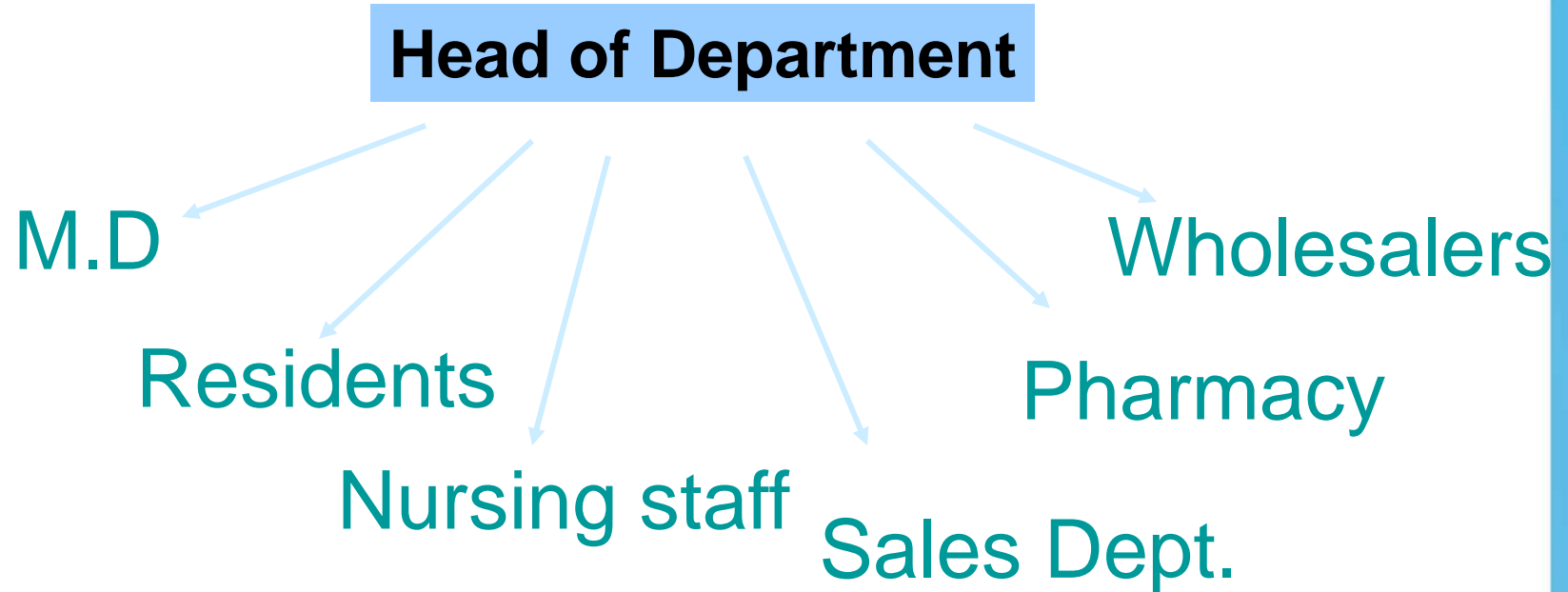


# Promotion

- ↖ Medical Visit
- ↖ Samples
- ↖ Bibliography
- ↖ Advertising
- ↖ Congresses
- ↖ Others



# Promotion





# Samples

**High cost / Fewer future treatments**

**Restrictive use**

**Objective**

**Special attention to the sceptics**

Control by Area Manager



# Leadership

183 different therapies have been used in PBS/IC

## CYSTISTAT

Leadership

- GAGs layer
- Clinical studies
- Few competitors
- Worldwide distribution
- Experience
- Possibility of expanding indications