Pain In Renal Patients….

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Fresenius

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Western Sussex Hospitals NHS
NHS Trust

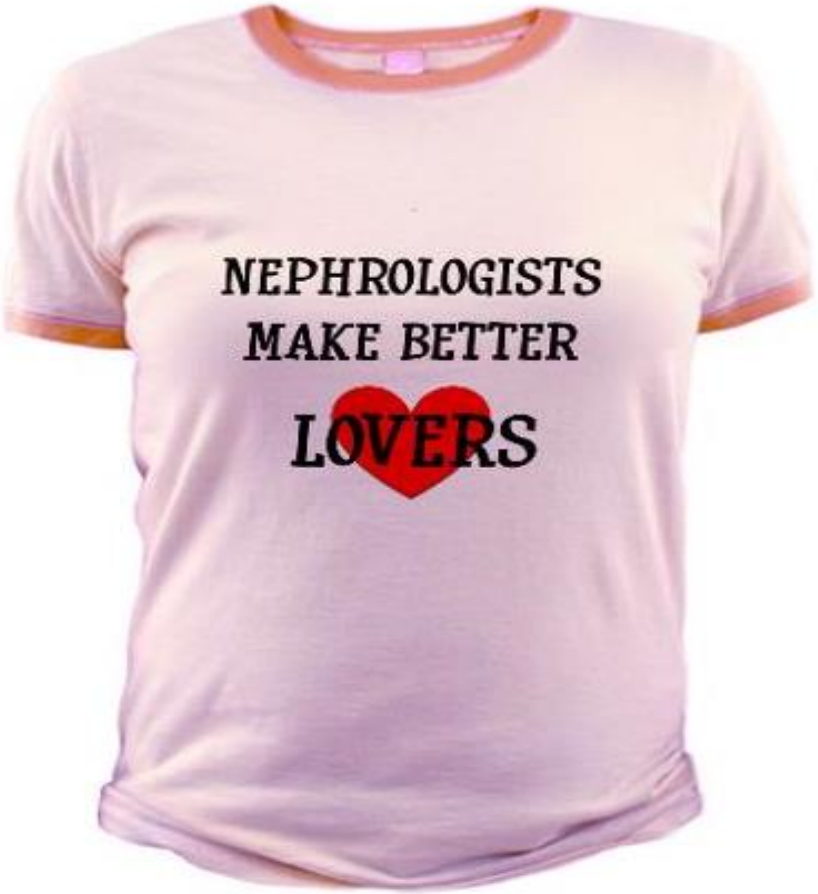

Worthing
Home of the Birdman

What Is A Nephrologist?

A Doctor specialising in diseases of the kidney
A physician board specialised in non-surgical kidney disease
Meat & Potatoes diseases
Salary £275 K + 10% bonus

Alternative Definitions?

Alternative (Favourite) Definitions?



Pain in Renal Patients?

What Shall we Talk About?

How Kidneys Work

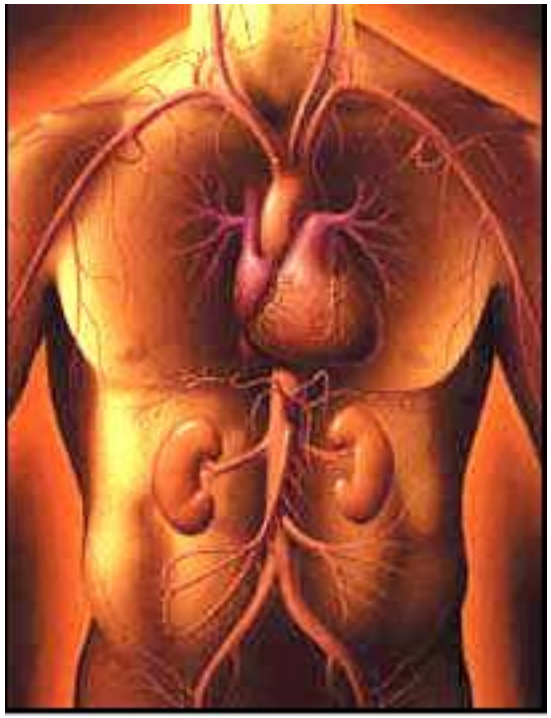
- Structure etc
- What they do
- How they do it

Some Renal Conditions

- LPHS
- ADPCKD
- The Old Favourite

Questions…

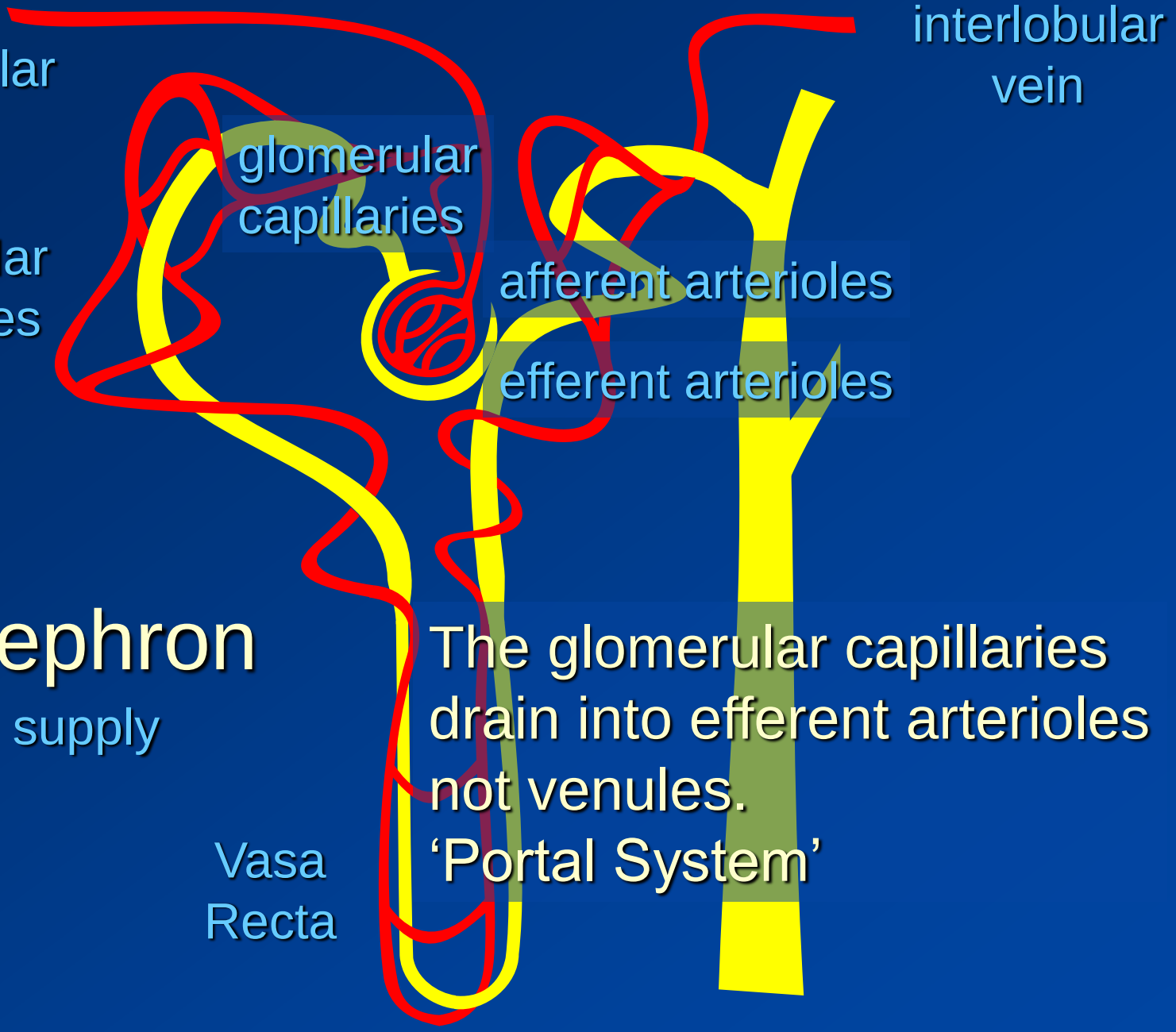
Role of the Kidneys…



Blood flow : 1000-1200 ml/min
Filters the circulating volume about 350 times/day…
0.1% of the blood filtered becomes urine
Acid Base Balance
Vit D metabolism
Ca/PO_4 metabolism etc etc

The nephron

1.5 million per kidney



The nephron

blood supply

The glomerular capillaries drain into efferent arterioles not venules.
'Portal System'

The nephron

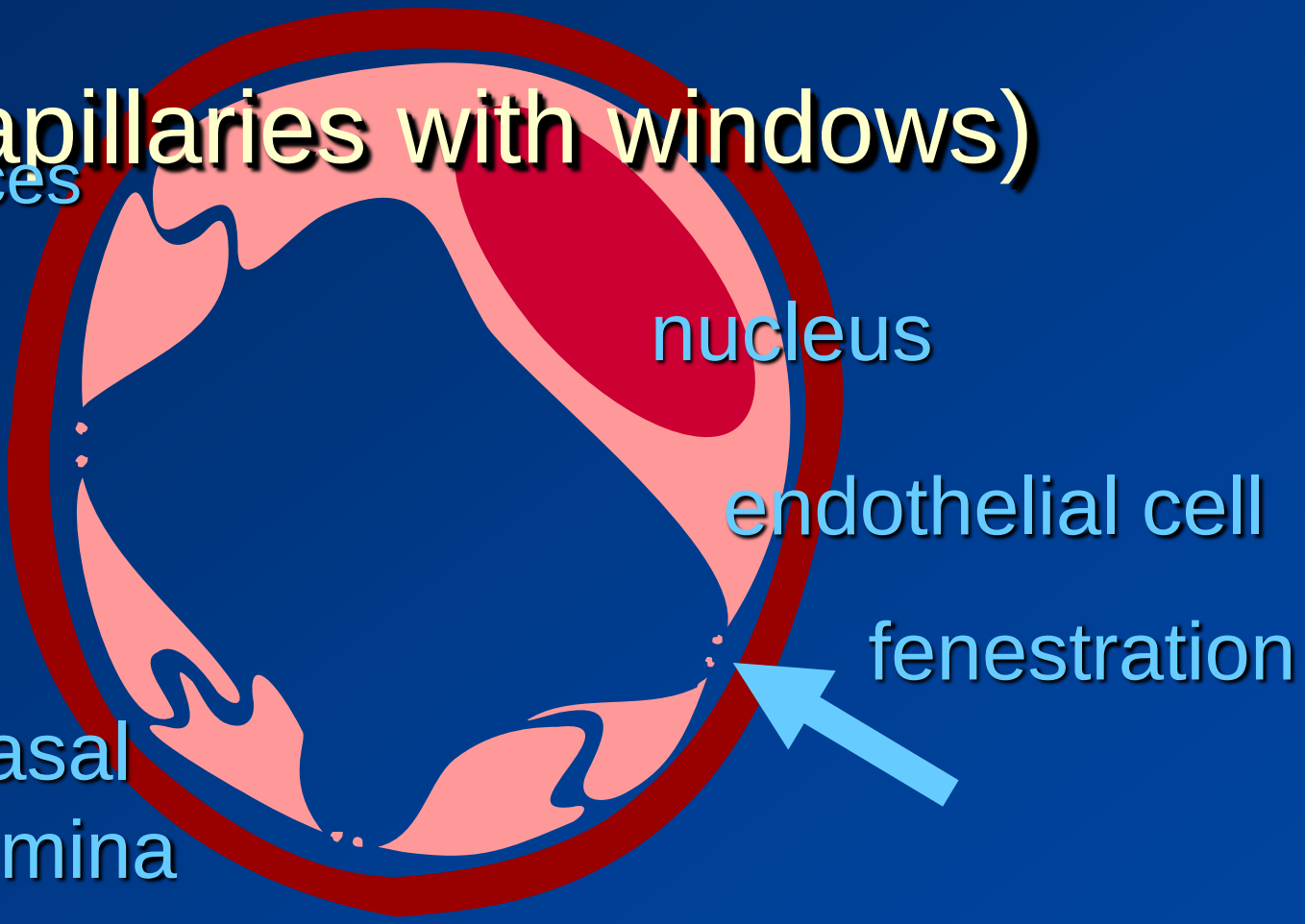
15% juxtamedullary

Fenestrated Capillaries

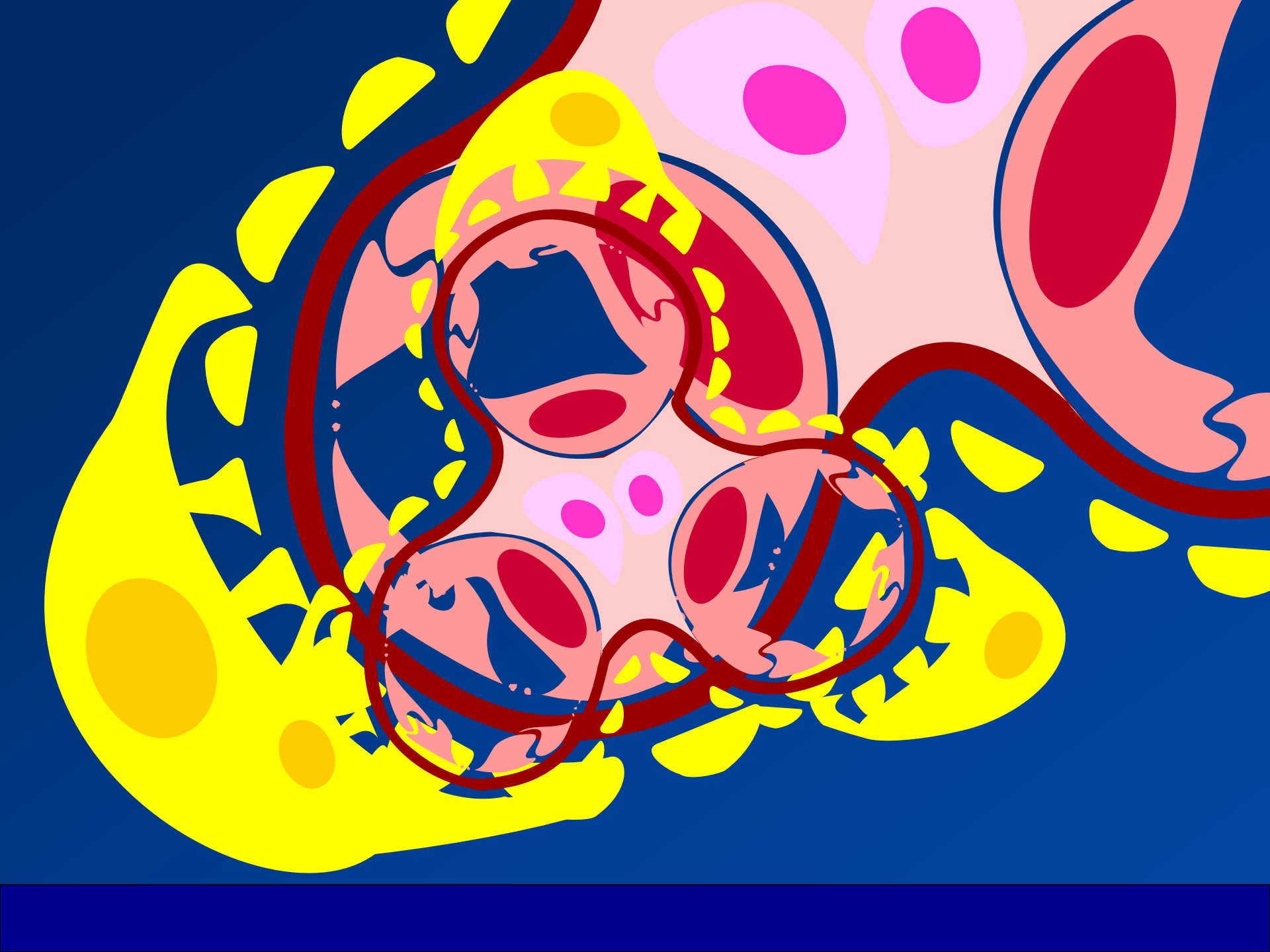
Filtration Barrier

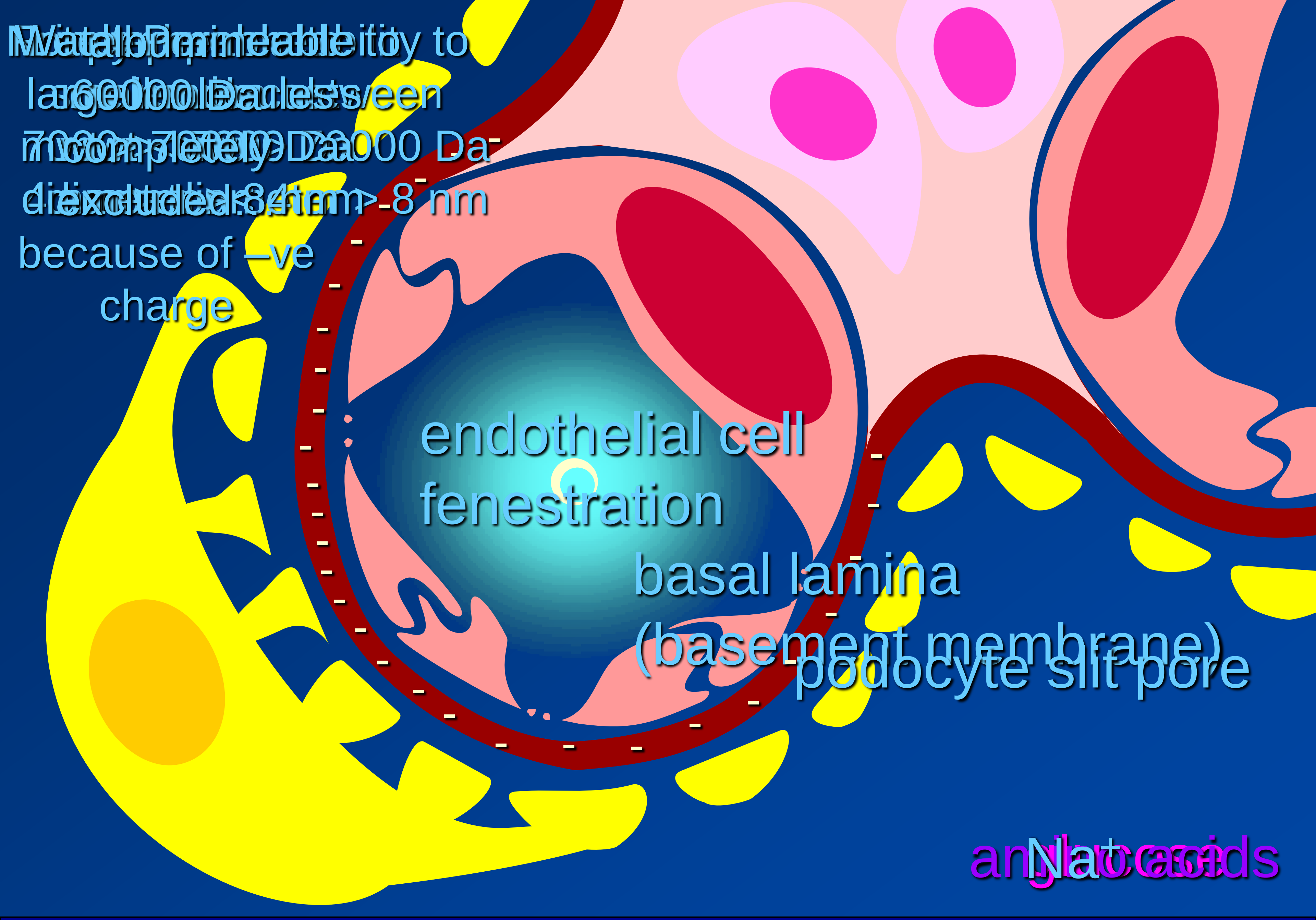
(capillaries with windows)

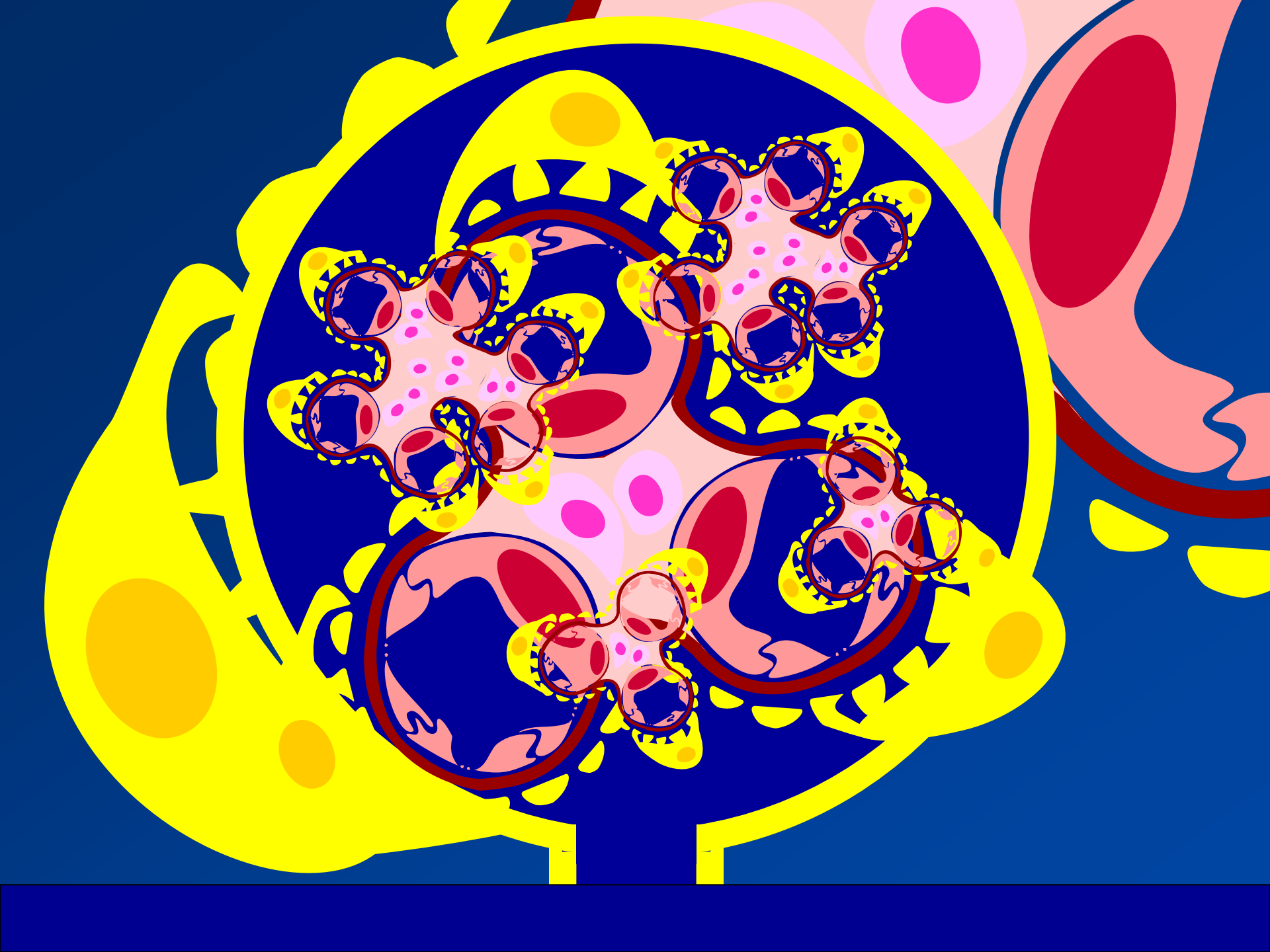
Permeable
to substances
< 100 nm

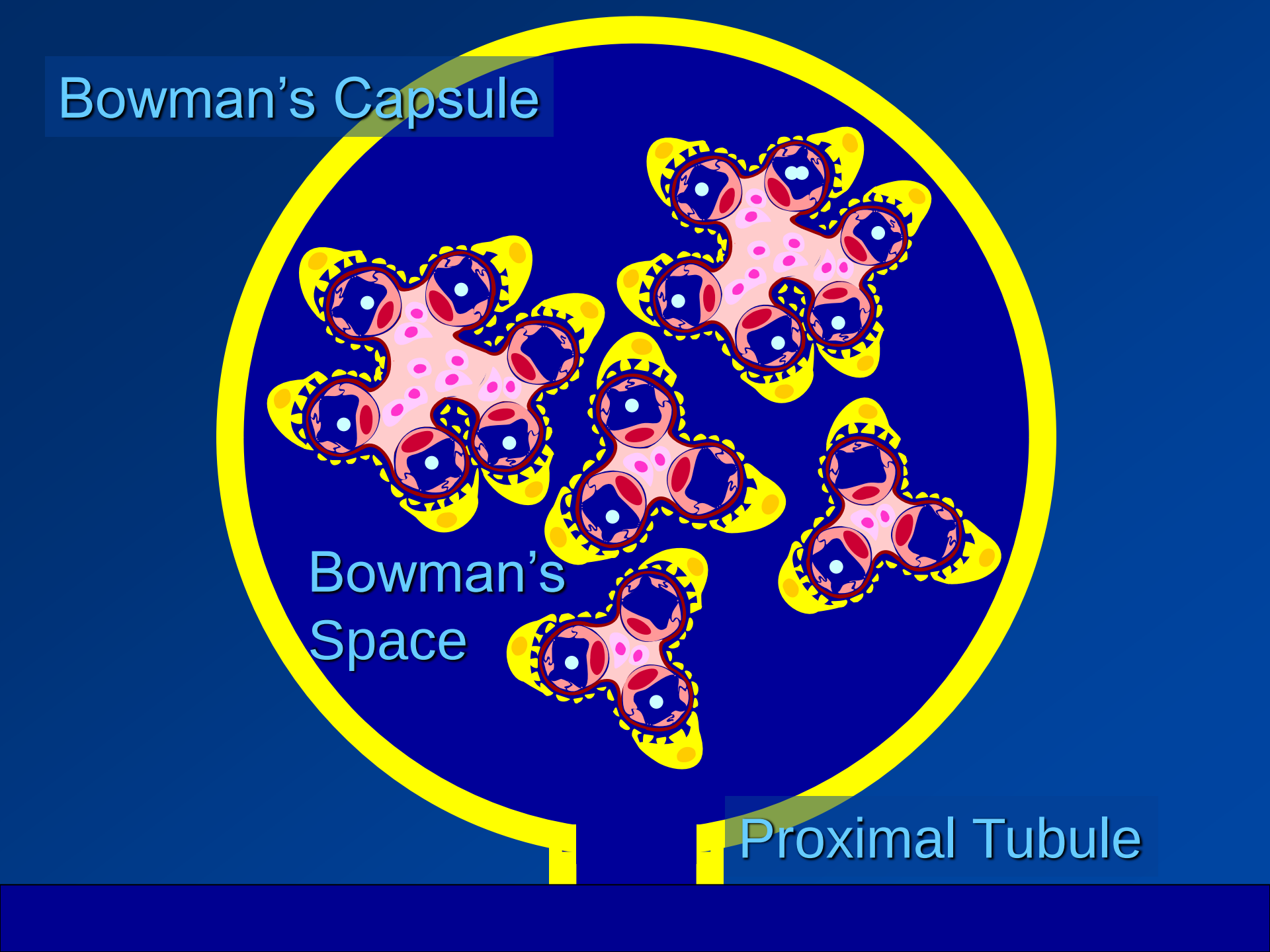



podocyte
ore
gial cells

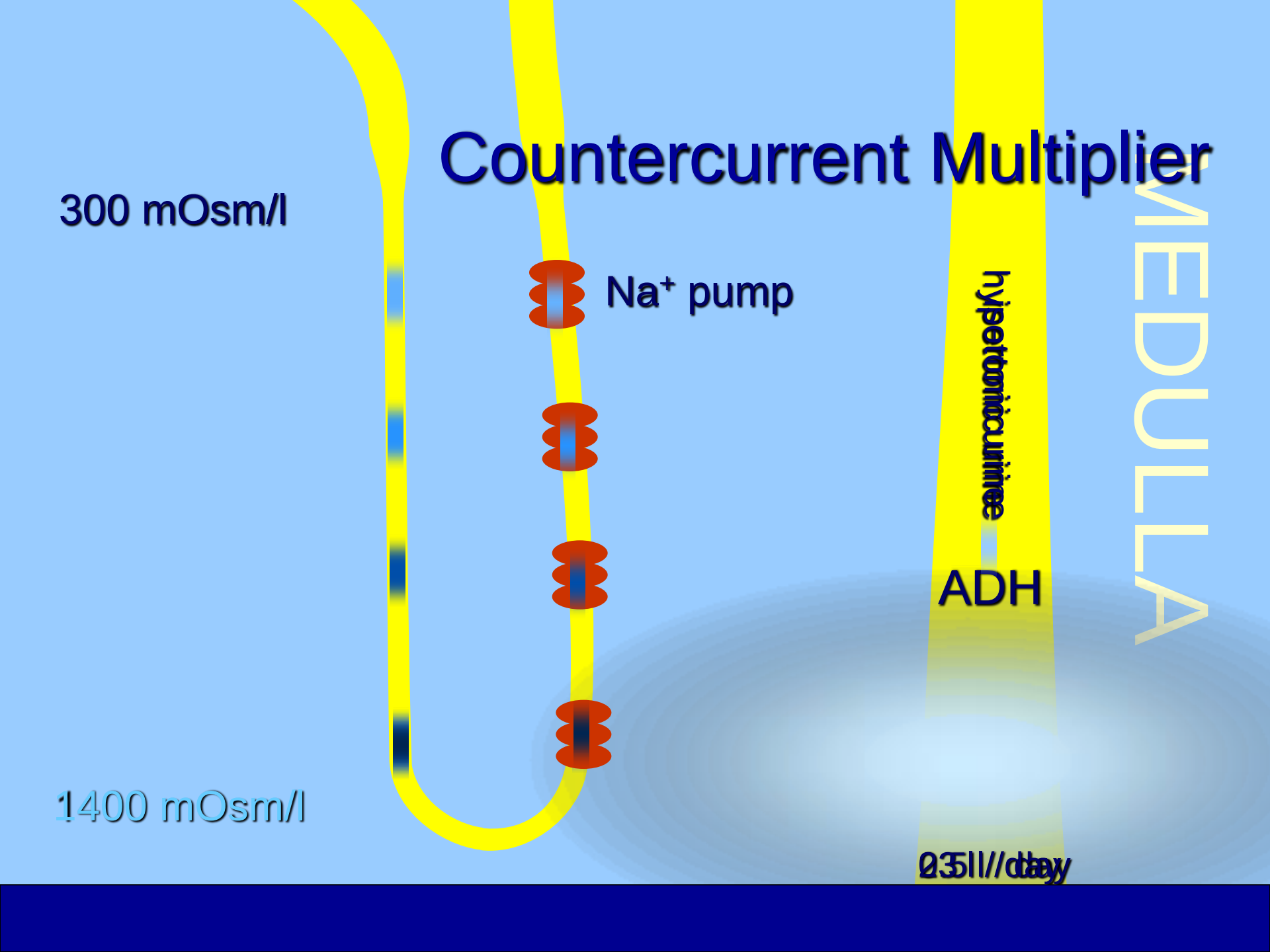



because of –ve charge
endothelial cell fenestration
basal lamina (basement membrane)
podocyte slit pore

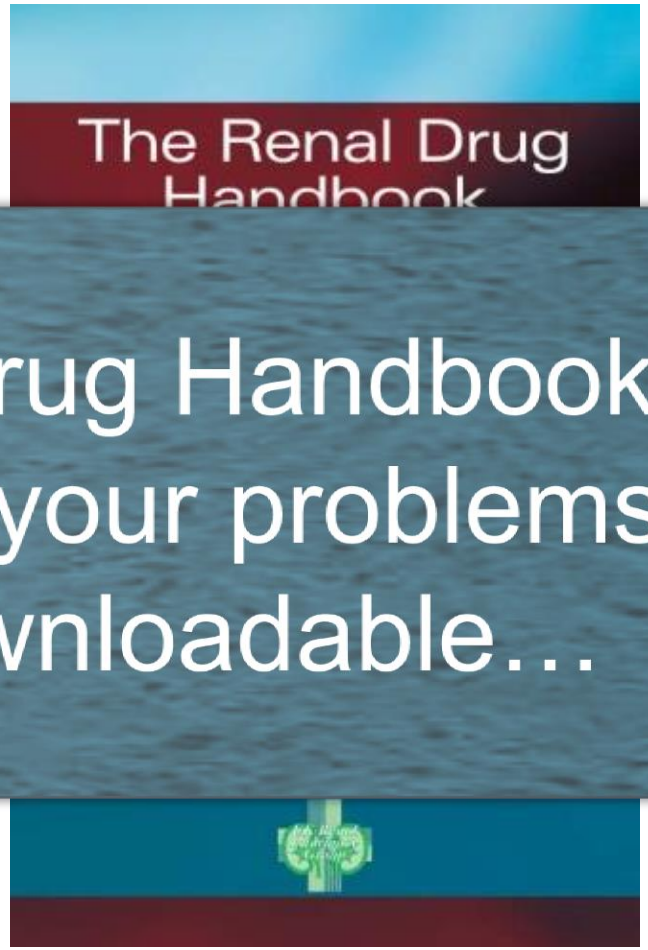



Bowman's Capsule
Bowman's Space
Proximal Tubule

The nephron


Countercurrent Multiplier
300 mOsm/l
Na+ pump
MEDULLA
ADH
1400 mOsm/l

Now we know how they work...



Get the Renal Drug Handbook
It will answer all your problems
Its free and downloadable…

Renal Pain Syndromes

- The kidneys and ureters are densely innervated by:
  - Sympathetic
  - Parasympathetic
  - Sensory afferent fibers
  - Innervation extensively cross-connected with nerve fibers to other visceral structures
- Pain related to the kidney poorly localized and can be associated with nausea due to the proximity of the sensory fibers to the vagus

Renal Pain Syndromes

- Eg: stimulation of the renal pelvis produces pain at the costovertebral angle and may cause referred pain in the testicle or ovary
- Kidney pain may be precipitated by:
  - Ischaemia
  - Inflammation
  - Torsion
  - Traction of the renal pedicle/distension of the capsule

Loin Pain Haematuria Syndrome

LPHS was first described in 1967

3 young women (20 to 28 years of age) who had:

Recurrent episodes of severe unilateral or bilateral loin (flank) pain

Accompanied by gross or microscopic hematuria

Loin Pain Haematuria Syndrome

- Major causes of flank pain and hematuria absent
- Renal arteriography ? focally impaired cortical perfusion
- Renal biopsy showed interstitial fibrosis and arterial sclerosis

Loin Pain Haematuria Syndrome

- Primary :
  - In the absence of an underlying acquired glomerular disease
- Secondary :
  - When it occurs with an acquired glomerular disease (eg, IgA nephropathy)

Loin Pain Haematuria Syndrome

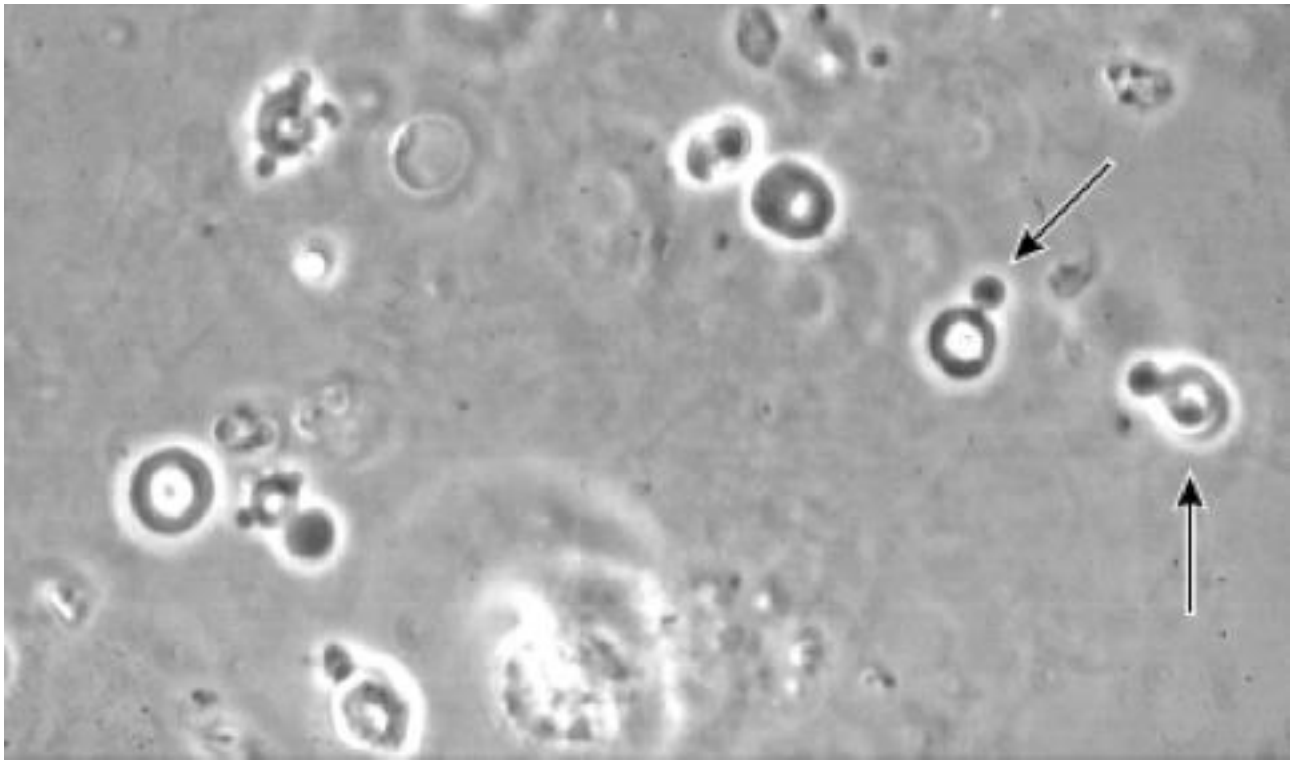
- Affected patients are :
  - Young (mean age 31 years in one review)
  - Predominantly female (70 to 80%)
  - Almost all white
- 50% have nephrolithiasis either a history of passing stones or renal calcifications typical of stones on imaging studies

LPHS : Haematuria

- Characterised by dysmorphic red cells
- Indicate a glomerular origin
- But of acanthocytes does not exclude LPHS
- ? Intratubular crystal deposition may be primarily responsible for the hematuria

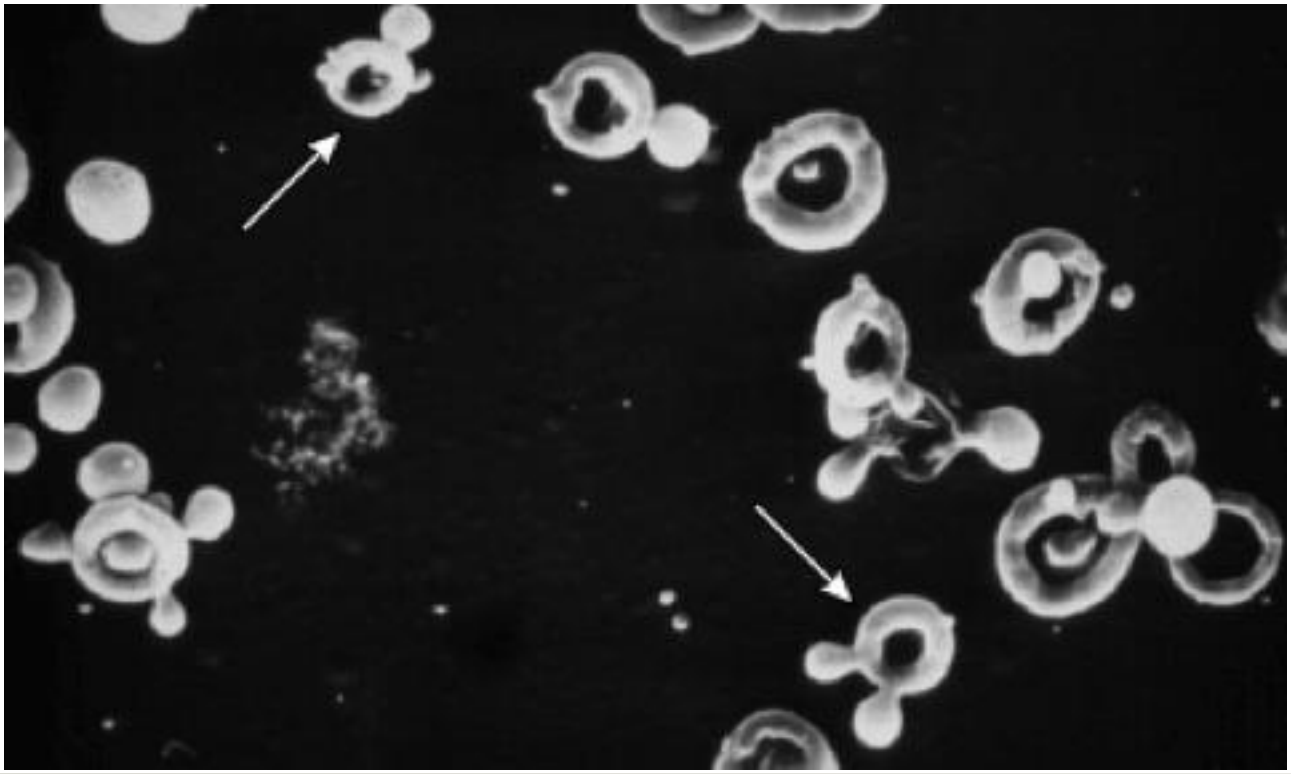
LPHS : Haematuria

Phase contrast micrograph showing dysmorphic red cells in urine sediment



LPHS : Haematuria

Scanning electron micrograph showing dysmorphic red cells in urine sediment

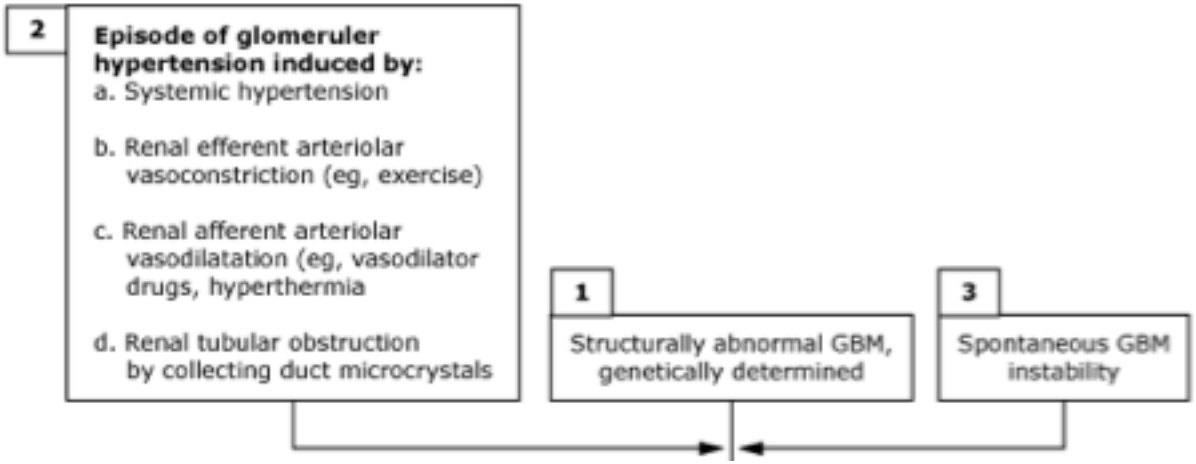


LPHS : Pain

- Described as burning or throbbing
  - Localized at the costovertebral angles (made worse by a gentle punch)
  - May radiate to the abdomen, inguinal area, or medial thigh
  - Can be unilateral or less often bilateral
  - Induced or exacerbated by exercise in 50%
- The pain is typically Severe

Mechanism of Pain in LPHS

Proposed pathogenesis of pain in patients with primary LPHS



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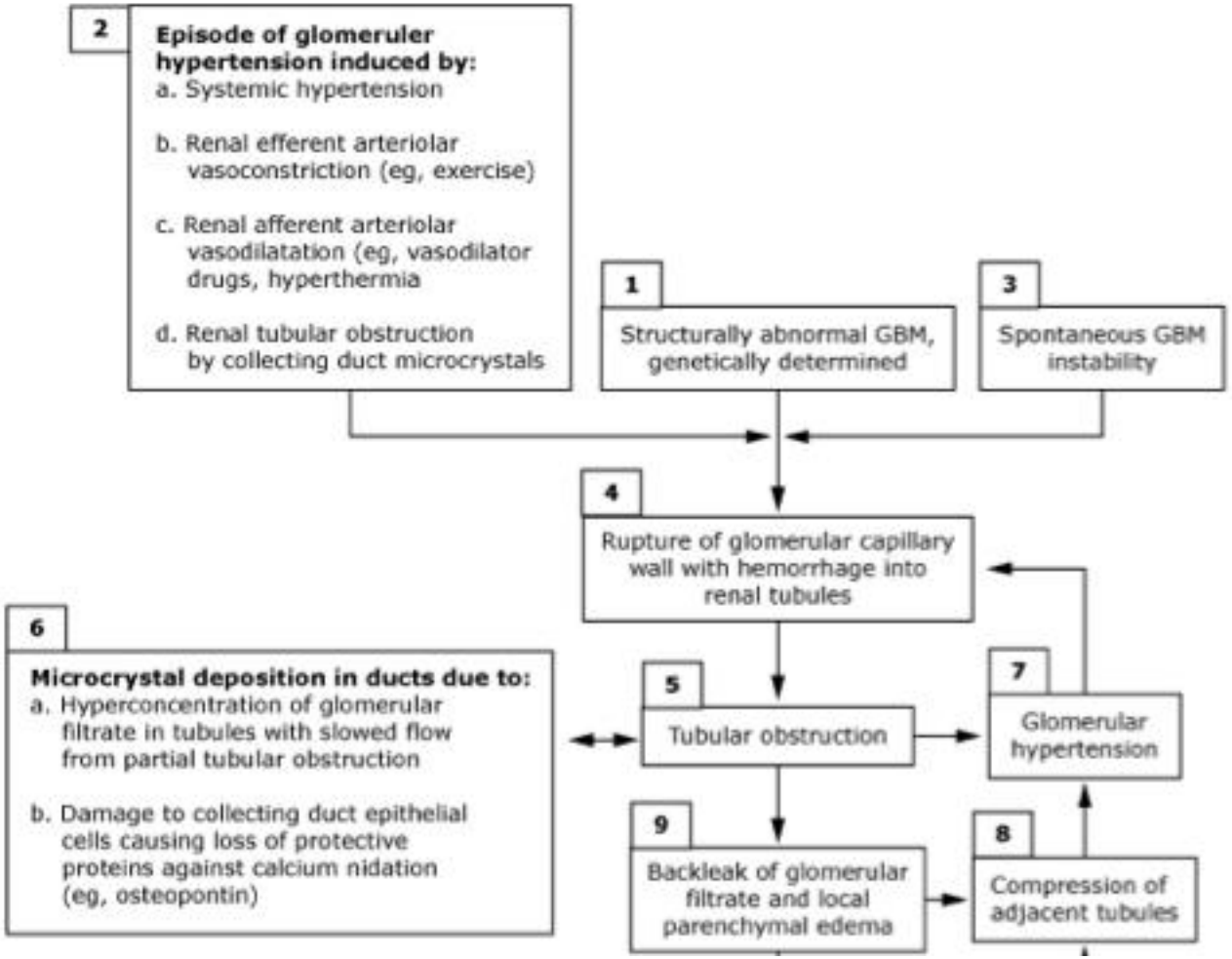

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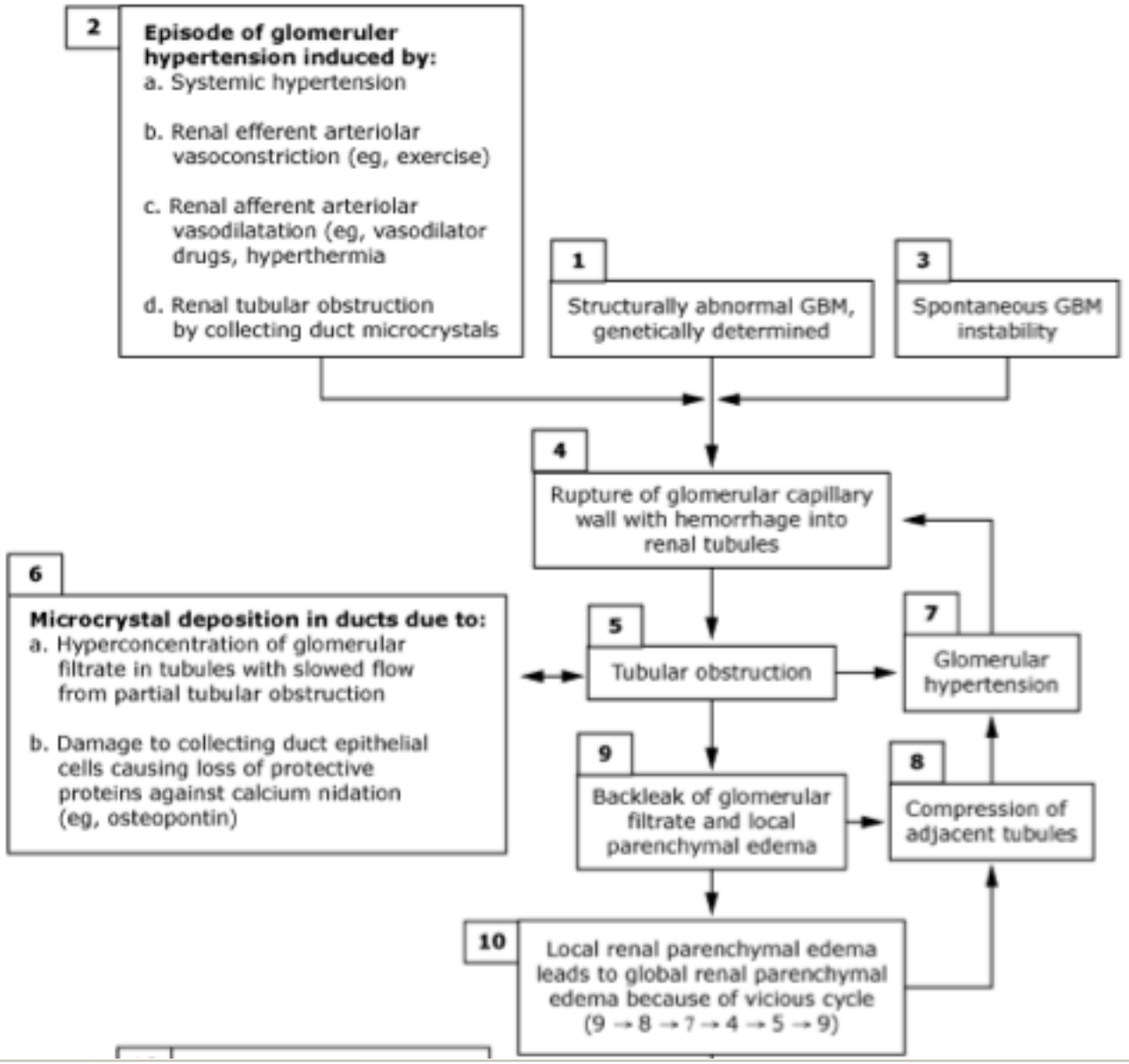
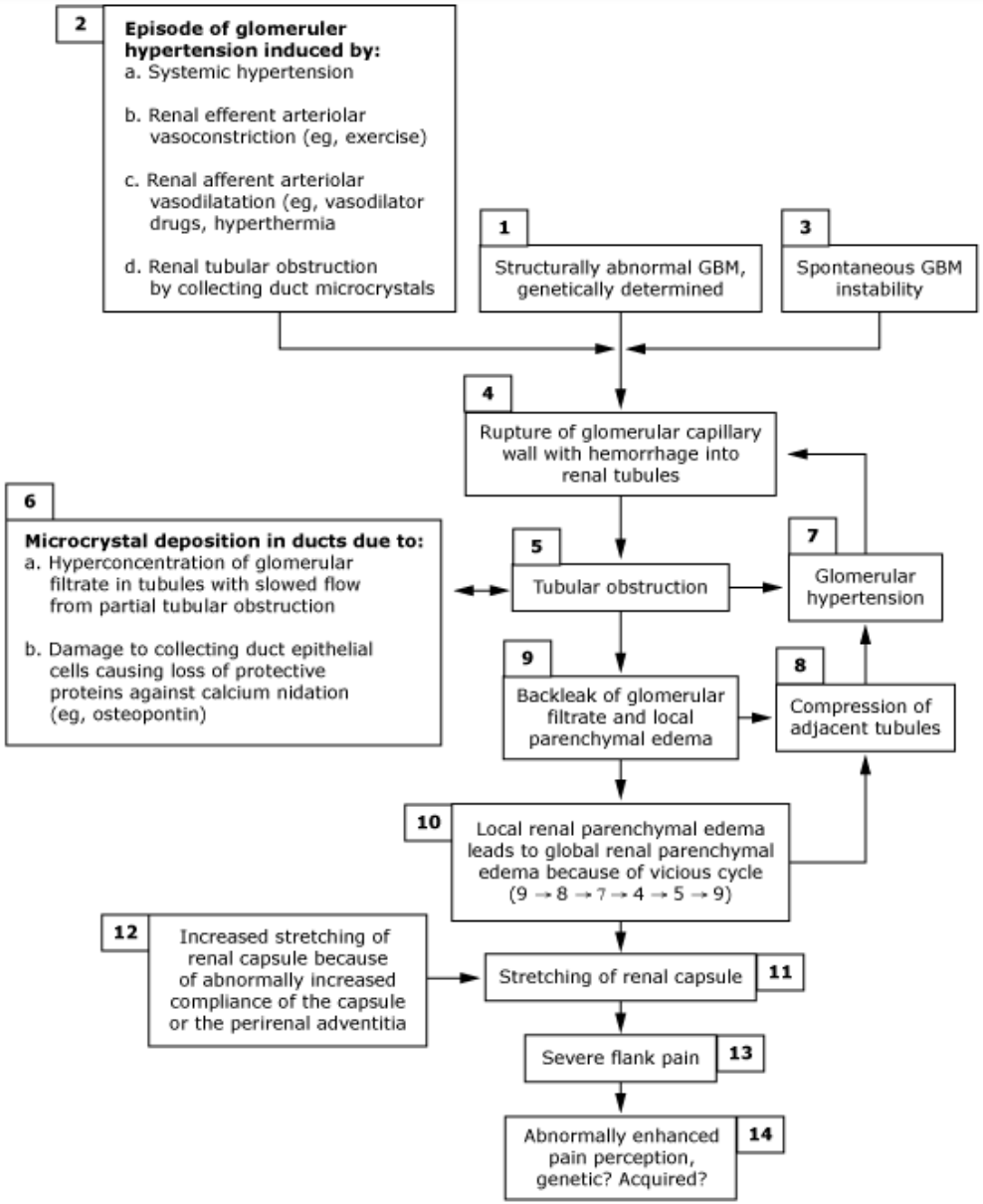


Proposed pathogenesis of pain in patients with primary LPHS



LPHS : ? Somatoform Pain Disorder

- A psychiatric component has been described in LPHS
- ? type of somatoform pain disorder and possible drug-seeking behavior
- 15 patients with LPHS compared to 10 patients with renal stone disease
  - More likely to have unexplained somatic symptoms
  - Adverse psychologic event preceding the onset of pain
  - History of greater analgesic ingestion

LPHS : Natural History

- Poorly defined
  - ? resolves in most patients
  - Unusual in persons > 60
  - Neither ESRF nor premature death is a feature of LPHS
- ? Possible explanation for spontaneous resolution
  - glomeruli that bleed eventually become nonfunctional
  - LPHS will resolve and the patient is left with near normal kidney function

LPHS : How To Make A Diagnosis?

Diagnosis of Exclusion !!

Obstructing urolithiasis, polycystic kidney disease, renal cell carcinoma, recurrent renal papillary necrosis with obstruction, recurrent renal thromboembolism, recurrent renal artery dissection (usually associated with fibromuscular dysplasia), endometriosis, and left renal vein entrapment (nutcracker syndrome)

Diagnostic Criteria

LPHS : Diagnostic Criteria

- Haematuria (> 5 RBC per high power field) should be present in almost all urinalyses
- Recurrent or persistent pain (present for > 6 months) should be severe, localized in the costovertebral angles and be associated with tenderness
- Nonglomerular bleeding must be excluded
- Obstruction of the urinary tract should not be present

LPHS : Treatment

- **General Measures:**
- Patients have normal renal function
- Should be reassured that their kidneys are functioning well and should continue to do so
- Patients should be advised to avoid activities that induce LPHS pain such as exercise or driving

LPHS : Treatment

ACE/ARB Inhibition

Limited Evidence

? Mechanism

Efferent arteriolar dilation induced by ↓ Ang II activity reduces intraglomerular pressure and therefore the likelihood of glomerular rupture and hematuria

LPHS : Treatment

- Nephrolithiasis Treatment
  - Increased Fluids
  - Decreased Salt
  - Potassium Citrate
  - ? Allopurinol
- Chronic Pain Control
- Seek Specialist Advice!!

LPHS : Treatment

- Nausea is often a dominant symptom during exacerbations
- 3-5 days of iv opioids is usually sufficient to break the pain cycle
- Typical intravenous regimen involves opioid administration using PCA
- About 50% of the opioid hourly dose is given as a constant infusion

LPHS : Treatment

All With Limited Success…

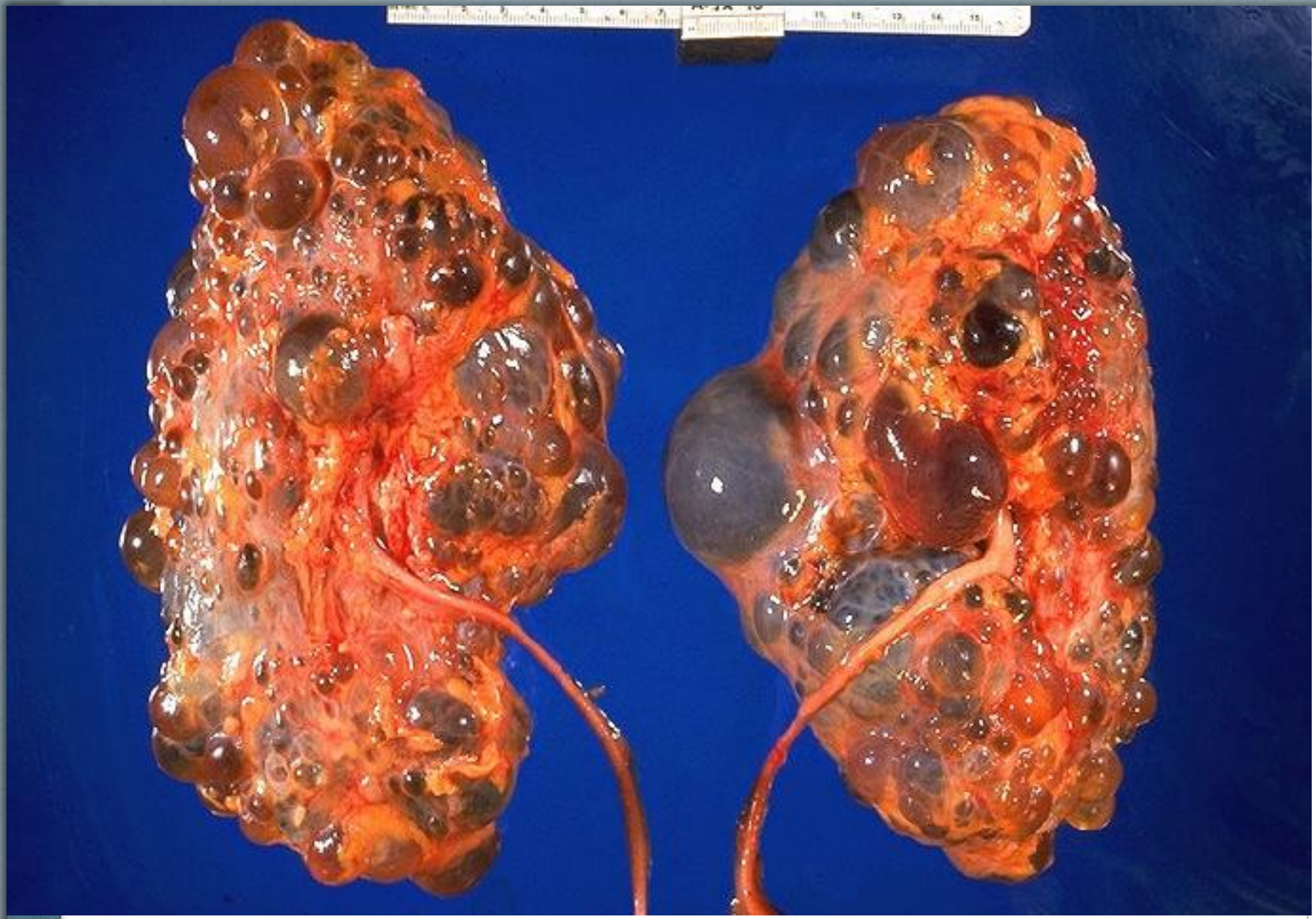
LPHS : Summary

Rare

Extremely challenging

Requires Multidisciplinary Approach

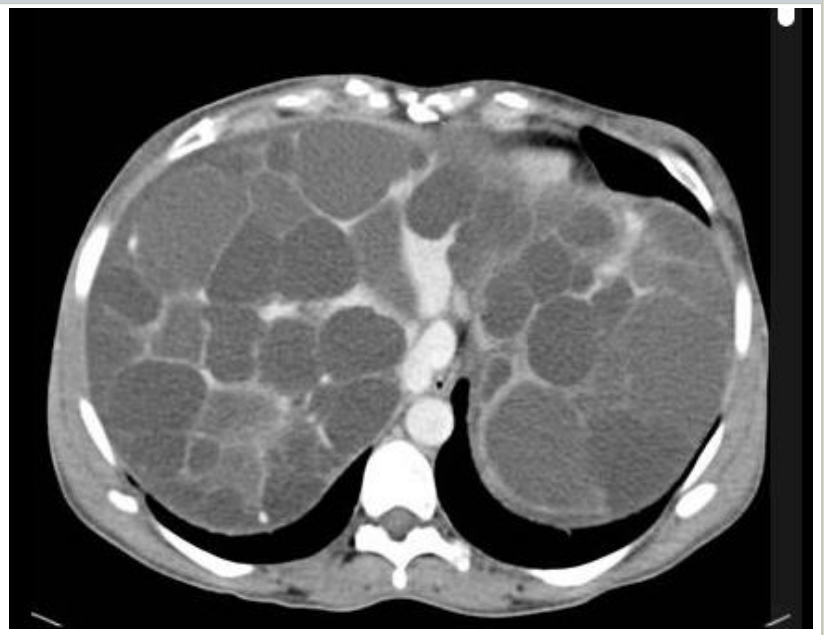
Some Nephrologists Deny It Exists….



ADPKD

- Autosomal dominant polycystic kidney disease (ADPKD) is common
- Occurs in 1 in every 400-1000 live births
- < 50% will be diagnosed during the patient's lifetime
- 85% of families have an abnormality on chromosome 16 (PKD1 locus)
- 15% have a defect that involves a gene on chromosome 4 (the PKD2 locus)

ADPKD : Extrarenal Manifestations



- Cerebral Aneurysms
- Hepatic/Pancreatic Cysts
- Cardiac Valve Disease
- Colonic Diverticula
- Abdominal Wall & Inguinal Hernia
- Seminal Vesicle Cysts

ADPKD : Risk Factors For ESRF

- Genetic factors (PKD1 versus PKD2)
- HT
- Early onset of symptoms
- Male gender
- Increased kidney size (kidney size is greater with PKD1 mutations)
- Increased left ventricular mass index
- Dipstick detectable proteinuria
- Low birth weight
- Decreased renal blood flow
- Increased urinary sodium excretion
- Increased LDL cholesterol
- Increased plasma copeptin (surrogate marker for vasopressin)

Pain Syndromes in ADPKD

- 60% patients with ADPKD have abdo & flank pain
- Abdominal pain is typically related to:
  - kidney cysts
  - liver cysts
- Pain is often not well managed
- Due to problems understanding the aetiology

Pain syndromes in ADPKD

Acute pain

The most common causes of acute pain:

- Cyst infection
- Cyst rupture/hemorrhage
- Nephrolithiasis

ADPKD : Cyst Infection

Sudden

Radiatic

Not relie

Fever, r y be present

If the infected cyst is walled off and does not communicate with the urinary tract the urine sediment may be bland and the urine culture negative

ADPKD : Cyst Rupture

Sudden onset of pain

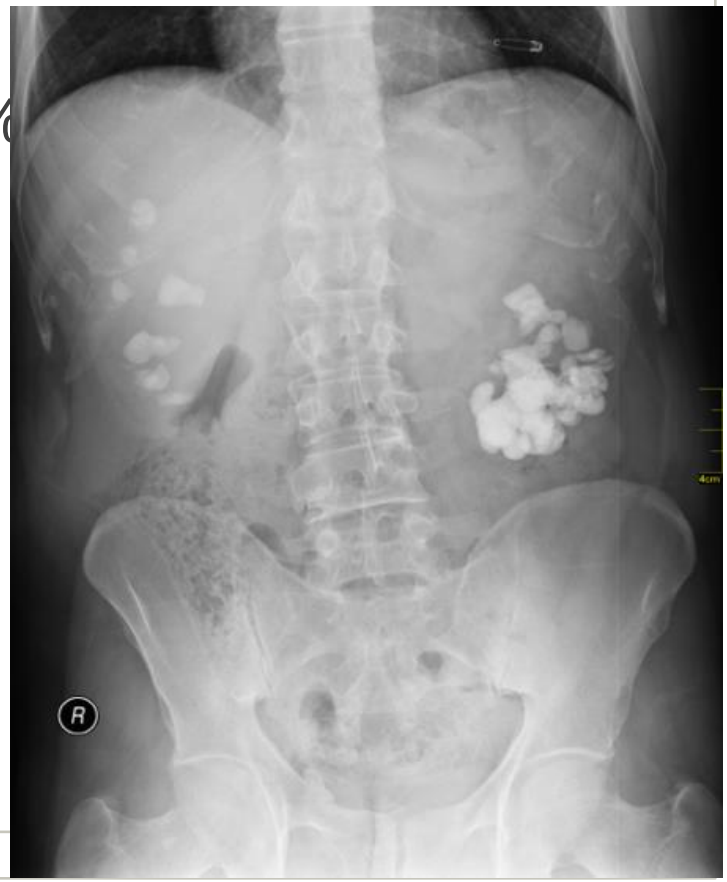
? due to an acute increase in cyst size with distention of the renal capsule

Often have point tenderness

Mild diffuse flank pain may occur when a superficial cyst ruptures and causes a subcapsular hematoma

ADPKD : Nephrolithiasis

- Kidney stones
- Occur in approximately 20-35%
- About 65% are symptomatic
- Treat just like anyone else!



ADPKD : Nephrolithiasis

"Paul is part of an experiment. Instead of giving him morphine for his kidney stone, they are testing the healing power of laughter."

ADPKD : Chronic Pain Syndromes

- Chronic pain is common among ADPKD
- 171 patients with ADPKD
  - low back pain 71%
  - abdominal pain 61%

Chronic pain is generally caused by cyst enlargement stretching of the capsule, traction on the renal pedicle

ADPKD : Assessment

- Location and radiation of pain
- Rapidity of onset
- Frequency, intensity and duration of pain
- Associated symptoms and abnormalities (eg, hematuria, fever)
- Precipitating and relieving factors
- Effect of activity or position on pain

Pain in Renal Patients

NSAID's & AKI

The Devil's Medicine

- Huerta etal AJKD 2005
- Nested case-control study using the GP Research Database
- 386,916 patients aged 50-84 years
- Free of known cancer, renal disorder, cirrhosis, or systemic CTD

Nonsteroidal Anti-Inflammatory Drugs and Risk of ARF in the General Population

Consuelo Huerta, MD, Jordi Castellsague, MD, Cristina Varas-Lorenzo, MD, PhD, and Luis Alberto García Rodríguez, MD

American Journal of Kidney Diseases, Vol 45, No 3 (March), 2005: pp 531-539

The Devil's Medicine

- RR for ARF of 3.2 (95% CI 1.8 to 5.8)
- Risk declined after treatment was discontinued
- Increased risk was present with both short- and long-term therapy
- Slightly greater among users of high doses

The Devil's Medicine : Higher Risk Groups?

- History of
  - Heart Failure
  - HT
  - DM
  - Hospitalizations & Consultant visits in the previous year

Table 4. Effect of NSAID Use in Patients With HF

	Cases (n = 103)	Controls (n = 5,000)	Adjusted RR* (95% CI)
No use of NSAIDs and no HF	19	1,924	1
No use of NSAIDs and HF	6	101	2.82 (1.05-7.57)
Current use of NSAIDs and no HF	21	481	3.34 (1.73-6.42)
Current use of NSAIDs and HF	6	33	7.63 (2.7-21.56)

*Adjusted for sex, age, calendar year, body mass index, diabetes, antihypertensive use, oral steroid use, and consultant visits and hospitalizations in the previous year.

American Journal of Kidney Diseases, Vol 45, No 3 (March), 2005: pp 531-539

Table 5. Effect of NSAID Use in Patients With Hypertension

	Cases (n = 103)	Controls (n = 5,000)	Adjusted RR* (95% CI)
No use of NSAIDs and no hypertension	9	1,459	1
No use of NSAIDs and hypertension	16	566	2.09 (0.87-5.02)
Current use of NSAIDs and no hypertension	9	329	3.69 (1.4-9.75)
Current use of NSAIDs and hypertension	18	185	6.12 (2.54-14.78)

*Adjusted for sex, age, calendar year, body mass index, HF, diabetes, antihypertensive use, oral steroid use, and consultant visits and hospitalizations in the previous year.

American Journal of Kidney Diseases, Vol 45, No 3 (March), 2005: pp 531-539

The Devil's Medicine

- RR increased with concomitant use of:
- NSAID's & Diuretics
  - RR 11.6
- NSAID's & Calcium Channel Blockers
  - RR 7.8

Pain in Renal Patients

BMJ

BMJ 2013;346:e8525 doi: 10.1136/bmj.e8525 (Published 8 January 2013)

Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study

Francesco Lapi *pharmacoepidemiology fellow*[1 2 3], Laurent Azoulay *assistant professor*[1 4], Hui Yin *statistician*[1], Sharon J Nessim *assistant professor and nephrologist specialist*[5], Samy Suissa *professor and director*[1 2]

[1]Centre for Clinical Epidemiology, Lady Davis Institute, Jewish General Hospital, 3755 Côte Sainte-Catherine Montreal, Quebec, Canada, H3T 1E2; [2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Quebec, Canada, H3A 1A2; [3]Department of Preclinical and Clinical Pharmacology, University of Florence, 50139 Florence, Italy; [4]Department of Oncology, McGill University, Montreal, Quebec, Canada, H3G 1A4; [5]Department of Medicine, Division of Nephrology, Jewish General Hospital, Montreal, Quebec, Canada, H3T 1E2

Table 2| **Rate ratio of acute kidney injury associated with exposure to current double or triple therapy combination. Values are numbers (percentages) unless stated otherwise**

Current use*	Cases (n=2215)	Controls (n=21 993)	Rate ratio (95% CI)	
			Crude	Adjusted†
Diuretics only	209 (9.4)	2632 (12.0)	Reference	Reference
Diuretics plus NSAIDs	156 (7.0)	1739 (7.9)	1.16 (0.93 to 1.44)	1.02 (0.81 to 1.28)
ACE inhibitors or angiotensin receptor blockers only	148 (6.7)	1889 (8.6)	Reference	Reference
ACE inhibitors or angiotensin receptor blockers plus NSAIDs	138 (6.2)	1907 (8.7)	0.96 (0.75 to 1.22)	0.89 (0.69 to 1.15)
Diuretics plus ACE inhibitors or angiotensin receptor blockers	414 (18.7)	2432 (11.1)	Reference	Reference
Diuretics plus ACE inhibitors or angiotensin receptor blockers plus NSAIDs	544 (24.6)	2424 (11.0)	1.34 (1.17 to 1.54)	1.31 (1.12 to 1.53)

ACE=angiotensin converting enzyme; NSAID=non-steroidal anti-inflammatory drug.

*Within 90 days before index date; current users of other antihypertensive drugs and past users (>90 days before index date) of double and triple therapy combinations are not shown but were considered in regression model.

†Adjusted for covariates listed in table 1.

What is already known about this topic

Acute kidney injury is a major drug related concern

The combination of one or two antihypertensive drugs (angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and diuretics) with non-steroidal anti-inflammatory drugs (NSAIDs) can theoretically increase the risk of acute kidney injury

Little is known about the risk of acute kidney injury associated with the use of these double or triple therapy combinations in practice

What this paper adds

Double therapy combinations consisting of addition of NSAIDs to diuretics, ACE inhibitors, or ARBs did not generally increase the risk of acute kidney injury

A triple therapy combination consisting of addition of NSAIDs to diuretics and ACE inhibitors or ARBs was associated with an increased risk of acute kidney injury

The risk of acute kidney injury with triple therapy was particularly elevated during the first 30 days of use

BMJ 2013;346:e8525 doi: 10.1136/bmj.e8525 (Published 8 January 2013)

Devil's Medicine

NSAID users : 3 fold greater risk for AKI

Should be used with caution in certain patient groups

Diuretics/ACE/NSAID = Asking for Trouble

Conclusions

- Your Kidneys are fascinating
- In 30 minutes I have only scratched the surface!
- Prescribing in CKD should follow the Renal Drug Handbook
- Certain Renal conditions pose different Challenges
- If you must give NSAID’s THINK FIRST!

Thank You For Listening