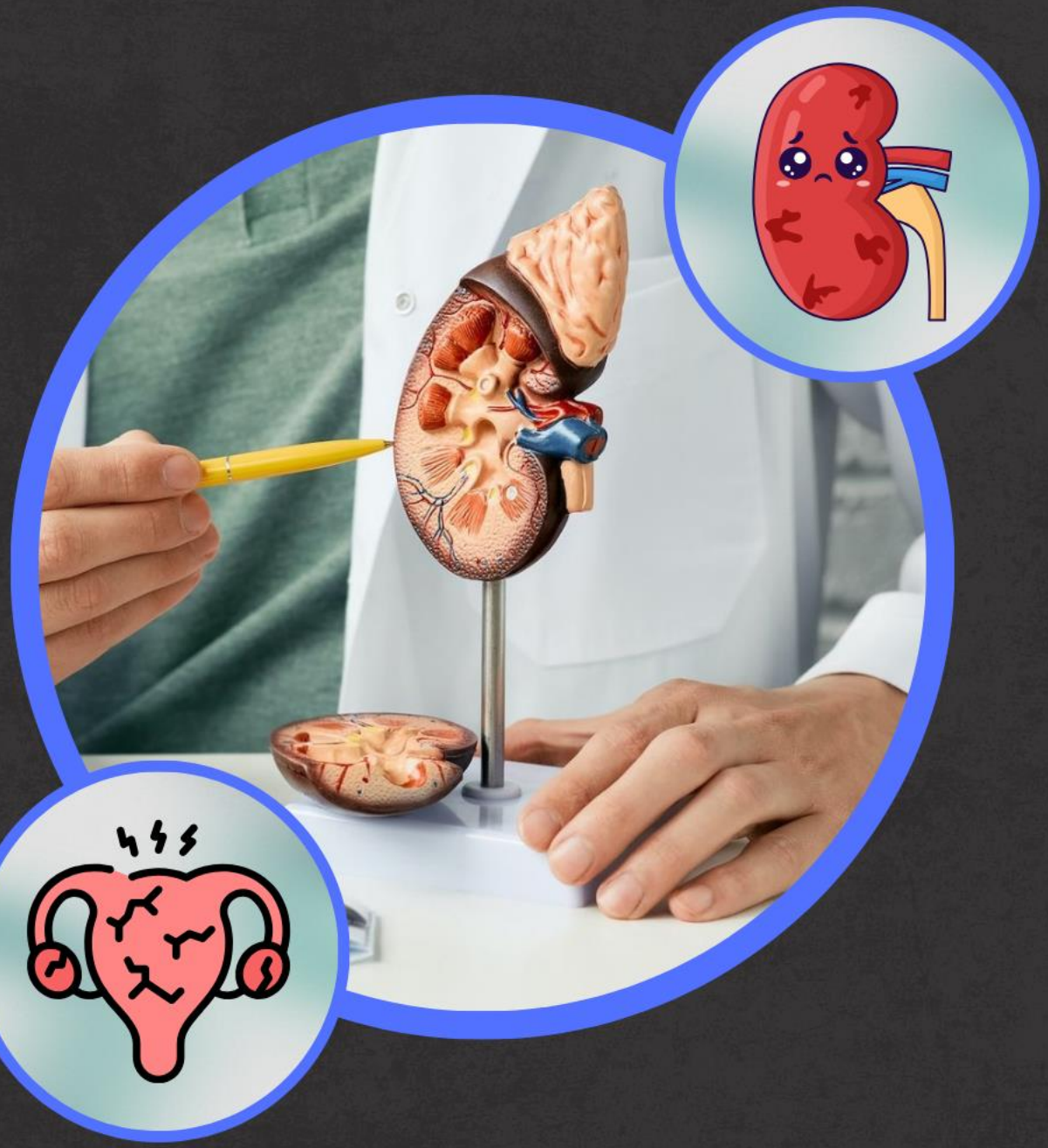

PATHO

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الكُتّاب: إسماعيل العارضة و علاء خضر

المدققين: عمر الصمادي

الدكتور/ة: د. نسرين

DISEASES AFFECTING TUBULES, INTERSTITIUM, and collecting system

1

Color code
Slides
Doctor
Additional info
Important

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Topics covered in lecture:

Urinary Outflow Obstruction: - Renal Stones
- Hydronephrosis

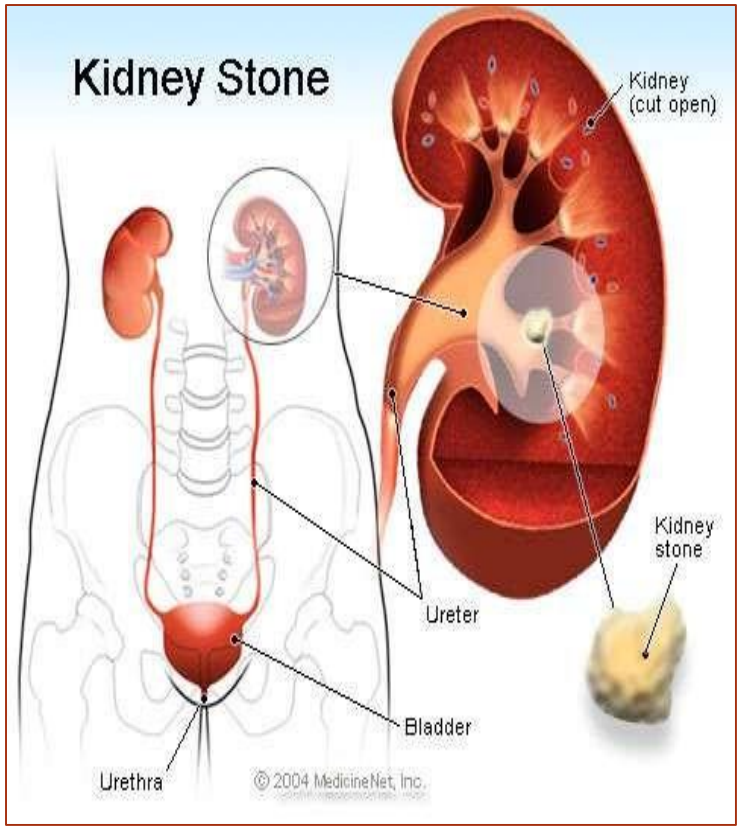
Tubulointerstitial Nephritis (TIN)

Acute Tubular Injury (ATN)

URINARY OUTFLOW OBSTRUCTION

Renal Stones (*Urolithiasis*) (Nephrolithaiasis)

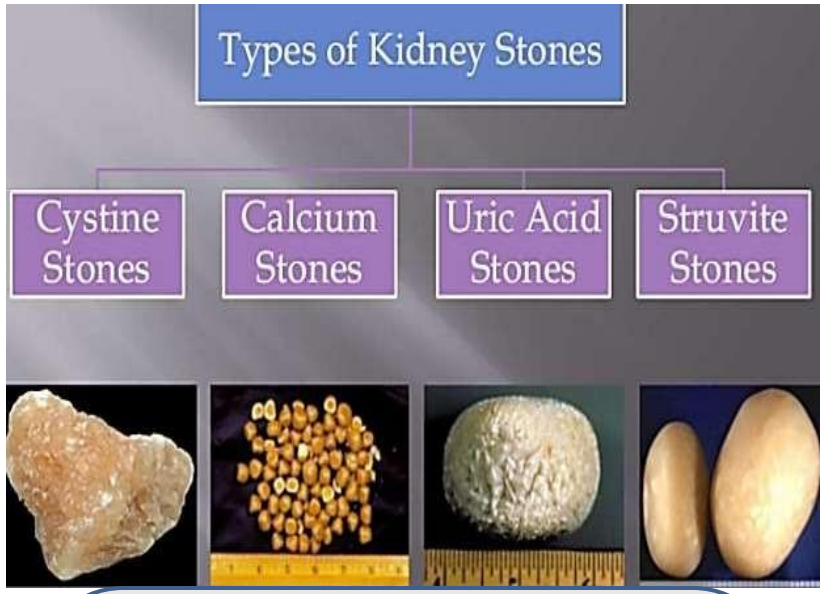
- Presence of stone at any level in urinary collecting system (starting from renal calyces and ending down inside the urethra).
- Most common in kidney.
- (1%) of all autopsies.
- Symptomatic OR asymptomatic.
- Familial tendency (can be caused by a specific and nonspecific genetic defect).
- unilateral in 80%.
- Variable size.
- Symptoms: painful hematuria, renal colic.



- Stone= inorganic salt (98%)+ organic matrix (2%)

❖Types are according to inorganic salt:

1) **calcium oxalate/ calcium oxalate+ calcium phosphate--** (80%) (the most common).
2) Struvite **(magnesium ammonium phosphate)** (<10%)
3) **uric acid** (6-7%)
4) **cystine stones** (the least common) (2%)



- This picture represent different sizes, shapes and textures of renal stones.
- Some of them can attain large sizes, some of them are very small, they can be radio opaque or radio lucent according to the composition.

- The renal stone is composed of two distinct parts; a center and then something that surrounds the center.
- The core of the stone is called the nidus, this nidus is organic matrix representing only 2% of the stone. Surrounding this organic matrix, we will have precipitation of salts (inorganic salts) and with time this precipitation will lead to initiation of the stone and then enlargement of the stone.

Causes of Renal Stones

1-increased urine concentration of stone's constituents exceeds solubility in urine (supersaturation).

- 50% of *calcium stones* pts have hypercalciuria with no hypercalcemia.
- 5% to 10% → hypercalcemia and hypercalciuria.

- As we know from chemistry, in order to precipitate a salt in a solvent, you need to reach and then get more or beyond the saturation point of concentration, so when we reach a high concentration of the salt inside it's solvent, in our case it's urine, so any further concentration can lead to precipitation of that salt.
- The high concentration of calcium in urine was the initiating factor for the production of renal stones.

- Check next slide

2-The presence of a nidus

- Urates provide a nidus for calcium deposition.
- Desquamated epithelial cells (an example of organic matrix)
- Bacterial colonies

3-urine pH

- *Magnesium ammonium phosphate (struvite) stones* occur with **alkaline urine** due to UTIs.
- Uric acid stones form in **acidic** urine (under pH 5.5).

- The core of the renal stone is organic matrix. This organic matrix can be for example desquamated epithelial cells. A patient is having some sort of defect or metaplasia inside his urinary tract and the squamous epithelium will have desquamation and those epithelial cells get into the tract and there they can be regarded as a nidus for the stone formation.
- Also patient who have urinary tract infection, the bacterial colonies together with the necrotic tissue can represent a good nidus for the production of stone.
- A third important pathogenic mechanism to consider is the urine PH. Again from chemistry, we already know that the PH of a solvent determines whether a certain salt will precipitate or it can favor the precipitation of a certain salt. for example, certain inorganic salts their precipitation is favored in acidic PH of urine while other inorganic sources their precipitation would be favored in alkaline urine.
- For example, strauvite stones which are composed of magnesium ammonium phosphate, they usually developed in alkaline urine in cases of UTI (urinary tract infection) and the offending microorganism is a urea splitting bacteria, it has the capacity to produce urease and ammonium which is a base ,so the PH of the urine increase and the presence of alkaline urine will be in favor of production of magnesium ammonium phosphate stones or struvite stones.
- A different example is uric acid stones which favor acidic urine to precipitate.

4-infections

- e.g. urea-splitting bacteria (*Proteus vulgaris* and staph).

- 5- disorders causing hyperuricemia/ high cell turnover and:
- e.g. gout; leukemia; tumor cell lysis following chemotherapy; etc

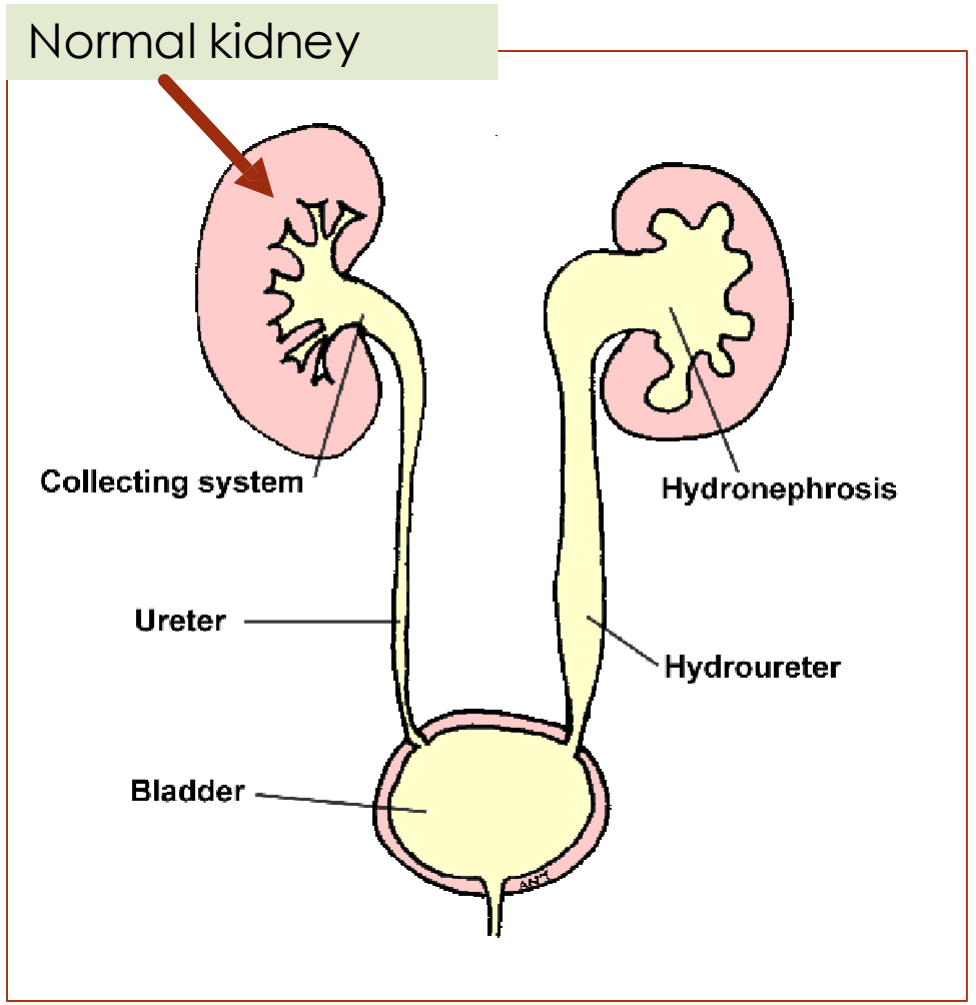
- 6- certain genetic/ metabolic abnormalities:
- e.g. cystine stones…

- The rapid cell turnover leads to lysis or destruction of many cells at the same time ,so the content of the cell will be spilled into the blood and an important metabolite will be produced is uric acid which is in high concentrations will go to the urine and cause stone.
- Cystine stone are related to a defect in the transport and reabsorption of an amino acid called cystine ,so they will have hypercystineuria (high concentration of this amino acid) which get precipitated in urine with the formation of cystine stones.

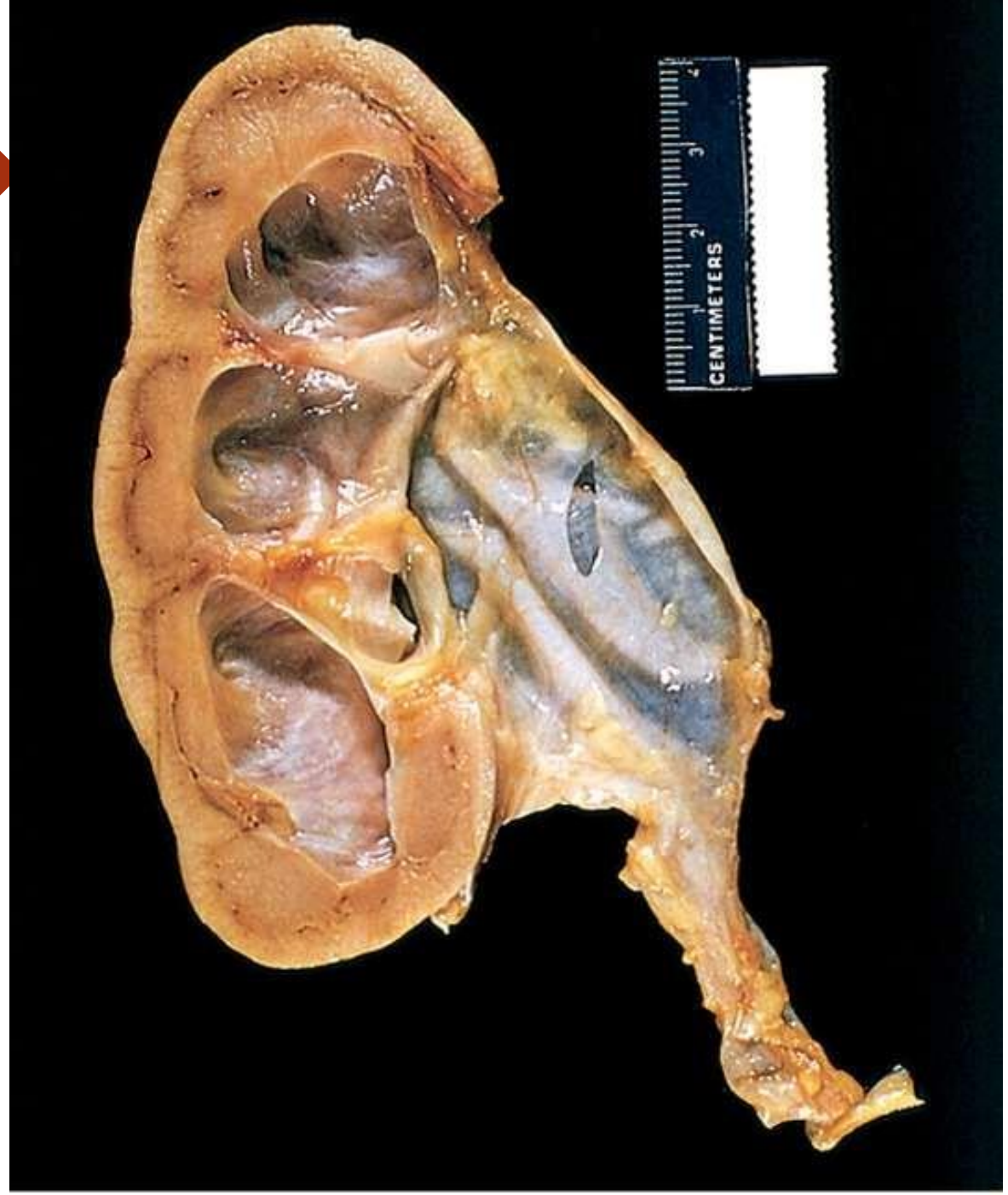
- Now, we will go into an important consequence of urinary outflow obstruction:

Hydronephrosis

- dilation of the renal pelvis and calyces due to obstruction, with accompanying atrophy of kidney parenchyma.
- sudden or insidious
- Obstruction at any level from the urethra to the renal pelvis. (By stone or tumor).
- Significance: if untreated, leads to renal parynchemal damage and dysfunction



- In the picture, we have the right and left kidneys of a patient.
- On the left side, this is the normal kidney and on the right side, this is the abnormal kidney which has the hydronephrosis.
- They differ in between each other in the right side we have dilated renal calyces and renal pelvis as well as there is a dilated ureter (hydroureter) in the right side ,the size of the kidney is smaller in the right side (atrophy in cortex (functional part)) which make impairment in the function.
- This condition can be acute or chronic, unilateral or bilateral according to the underlying cause.



Hydronephrosis of the kidney, with marked dilation of the pelvis and calyces and thinning of renal parenchyma.

The most common causes are

1- Congenital:

- There are anatomical causes of hydronephrosis that can be seen during childhood and they are related to anatomical aberrations ,this causes are called congenital.

examples

- Atresia of urethra
- Valve formations in ureter or urethra
- Aberrant renal artery compressing ureter
- Renal ptosis with torsion or kinking of ureter

2-Acquired:

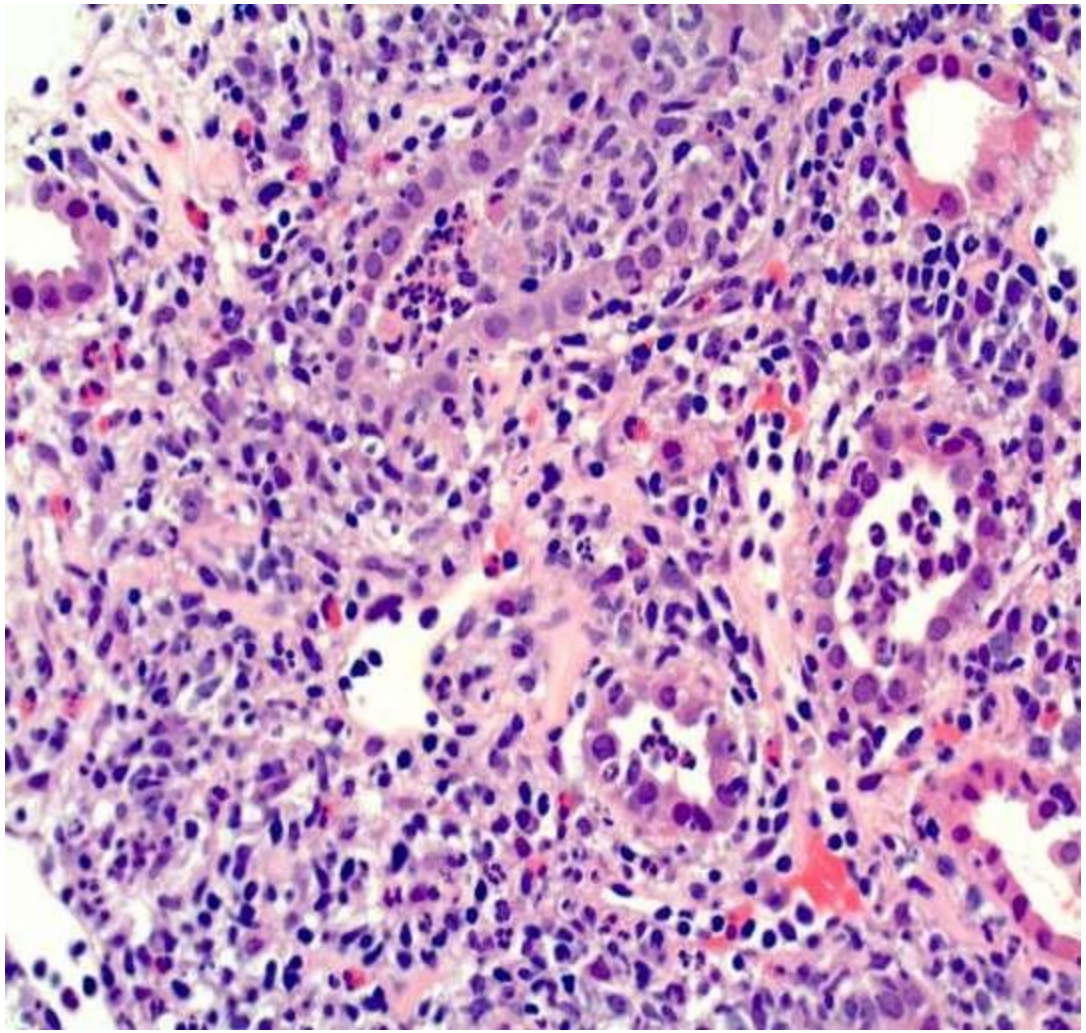
- On the other hand, we have acquired causes of hydronephrosis like foreign bodies, stones, tumors inside or outside the urinary tract, inflammation and neurogenic bladder which is related to spinal cord damage and loss of control over the neuromuscular coordination in the bladder.

- ***Examples:***
- **Foreign bodies**: Calculi, necrotic papillae
- **Tumors**: prostatic hyperplasia, prostate cancer, bladder tumors, cervix or uterus cancer.
- **Inflammation**: Prostatitis, ureteritis, urethritis,
- **Neurogenic**: Spinal cord damage

- The most common consequence of hydronephrosis is the damage or dysfunction that will develop due to atrophy of the affected kidney.

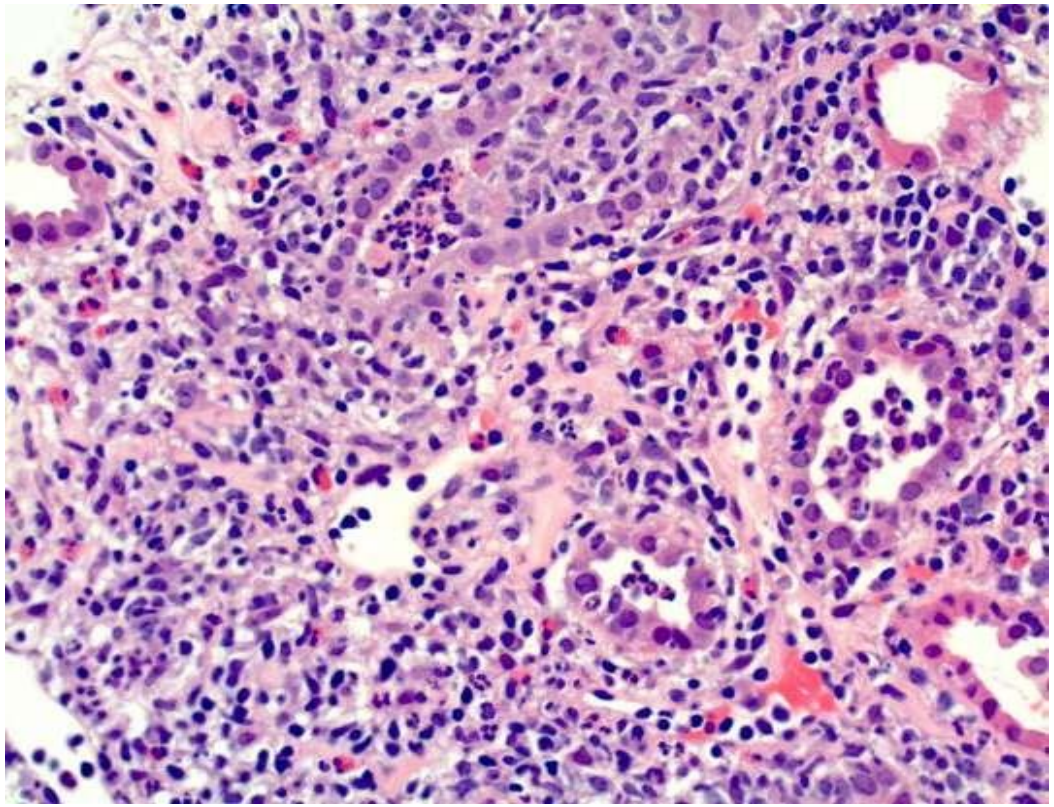
Tubulointerstitial Nephritis (TIN)

- Inflammation of tubules and interstitium
- Causes :
- 1- bacterial infection.
- 2- drugs.
- 3- metabolic disorders
- 4- physical injury (irradiation).
- 5- auto-immune reactions.
- duration can be divided into :
- 1-acute (days to months)
- 2-chronic (longer duration)



- Moving on to the second topic of the lecture, we will discuss Tubulointerstitial Nephritis (TIN). As always, keep in mind that the name can provide clues about the condition. "Nephritis" refers to the inflammation of the kidneys, and "tubulointerstitial" specifies the sites of inflammation, which are the tubules and the interstitium.
- In this lecture, we will focus on drug-induced TIN, as it is a very common cause of this condition.

- In this picture represents an area of tubules and interstitium, and we have large amounts of leukocytes, WBCs infiltrating and attacking the interstitium. Those leukocytes include lymphocytes, eosinophils, macrophages, and neutrophils, leading to functional abnormalities.



Drug-Induced Interstitial Nephritis

- Two forms:

1 Acute Drug-Induced Interstitial Nephritis

2 Chronic Drug-Induced (Analgesic Nephropathy)

They have different underlying pathogenetic mechanisms.

- **Acute form of drug- induced TIN**
- Most common drugs: synthetic penicillins (methicillin, ampicillin)
- Others: synthetic antibiotics; diuretics; NSAIDs; other drugs

Pathogenesis of Acute Interstitial nephritis:

- immune mechanisms:
  - IgE –mediated(type I hypersensitivity).
  - T cell-mediated (type IV) hypersensitivity reaction.

- The immune system produces a hypersensitivity reaction to the drug, which involves mechanisms shared by both type 1 (IgE-mediated) and type 4 hypersensitivity reactions.

Morphology

- interstitium : lymphocytes, plasma cells, macrophages, eosinophils and neutrophils

- glomeruli are normal

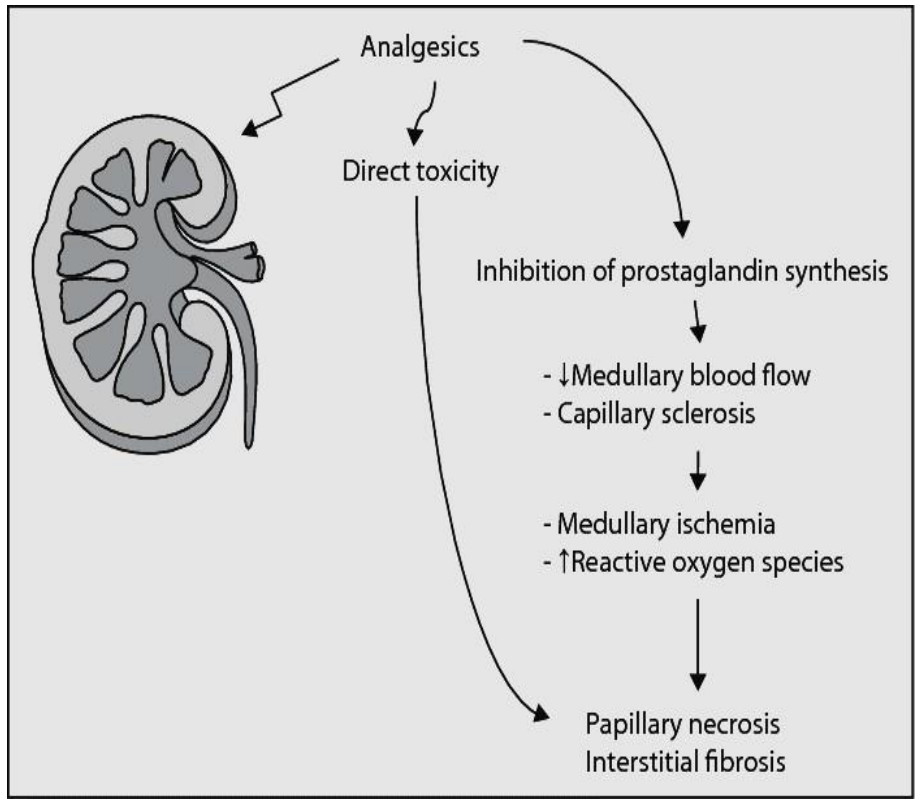
Clinical Course

- 2-40 days after exposure to drug. (like methicillin)
- *fever*, *eosinophilia* (eosinophils in blood) & *rash* (25%) & discoloration of urine
- *renal abnormalities:* hematuria, minimal or no proteinuria, and leukocyturia

Management:

- withdrawal of the offending drug is followed by recovery

Analgesic Nephropathy: chronic drug-induced TIN



- Consumption of **large** quantities of analgesics (pain killers) over **long** periods may cause **chronic interstitial nephritis** *often with* ***renal papillary necrosis***.

Typical scenario:

- **taking Aspirin and acetaminophen for long duration are common causes.**

- **Pathogenesis** not entirely clear.
  - ***covalent binding* and *oxidative damage***
  - **inhibition of prostaglandin synthesis**

- The pathogenesis is not completely understood, but it involves the formation of oxygen free radicals.
- ❑ For example, COX-2 inhibitors may lead to vasoconstriction, which can result in medullary ischemia and an increase in free radical production.
- ❑ This sequence of events can lead to tissue injury and subsequently cause interstitial fibrosis.
- ❑ As a result, the deterioration of renal function occurs in an insidious and progressive manner.

Clinical Course of chronic Interstitial Nephritis

Outcome:

- Progressive renal impairment, chronic renal failure, hypertension….

- A RARE complication of analgesic abuse is: **increased incidence of *transitional-cell carcinoma*** of the renal pelvis

Acute Tubular Necrosis/Injury (ATN/ ATI)

- characterized :

1. morphologically by damaged tubular epithelial cells
2. clinically by acute suppression of renal function.

- ***It is the most common cause of acute renal failure.***
- **ATN is a reversible condition if treated properly and quickly.**

Because of tubular epithelial cells capacity to regenerate

- Clinical manifestations: **electrolyte abnormalities, acidosis, uremia, signs of fluid overload, often oliguria.**
- Proximal tubular epithelial cells are particularly sensitive to hypoxemia and toxins

Acute Tubular Necrosis/ Injury (ATN/ ATI)

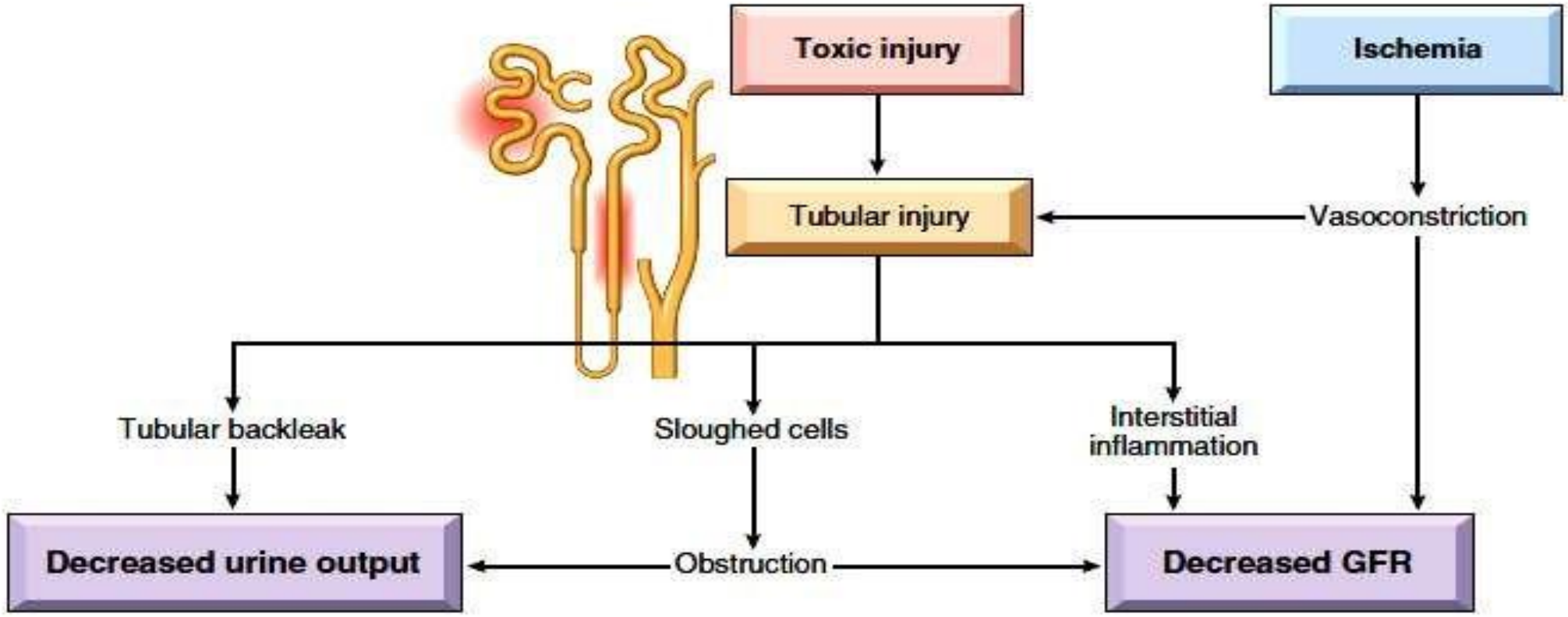


Fig. 14.16 Postulated sequence in ischemic or toxic tubular injury.

The two important mechanisms involved in Acute Tubular Necrosis (ATN) and Acute Tubular Injury (ATI) are:

1. **Ischemic mechanism:** This leads to vasoconstriction, which reduces ↓ the glomerular filtration rate (GFR) and can result in tubular injury.
2. **Toxic mechanism**

The injury can cause:

- **Sloughing of epithelial cells** into the lumen of the tubules, leading to obstruction.
- **Inflammation.**
- **Tubular backleak**, which results in decreased urine output, giving a picture of acute renal failure.

Types:

1- ischemic ATI :

- most common type
- associated with hypovolemia or shock (e.g. hypotensive shock, severe trauma; acute pancreatitis; septicemia; mismatched blood transfusion, hemolytic crises, myoglobinuria, etc…)

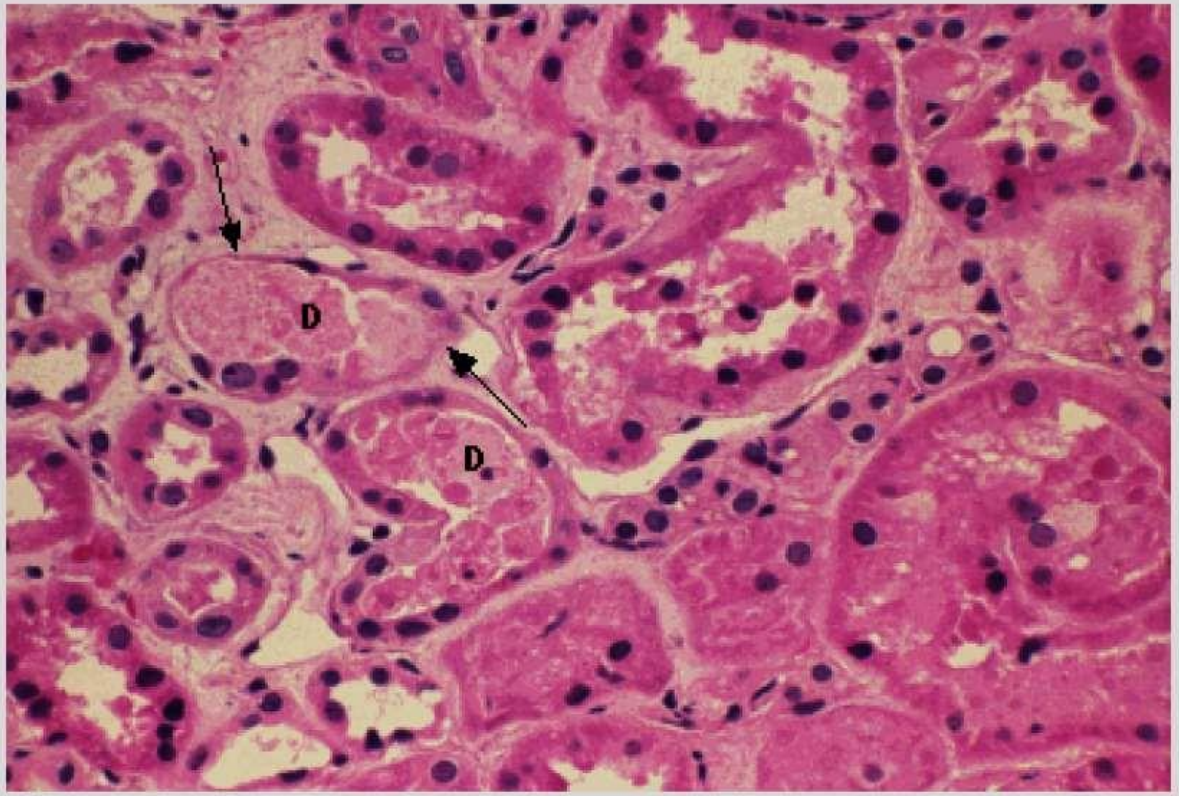
2- nephrotoxic ATI

- poisons including heavy metals (e.g., mercury)
- organic solvents (e.g., carbon tetrachloride, CCL4)
- drugs (e.g., gentamicin, other antibiotics, radiographic contrast agents)

Acute tubular epithelial cell injury with blebbing at the luminal pole, detachment of tubular cells from their underlying basement membranes, and granular casts

- Morphology: necrosis of tubular epithelium; we will have sloughed epithelial cells, and cells will accumulate in the lumen. Inside the lumen, we would have necrotic debris that can cause **partial obstruction** of tubules.

ATN



Acute tubular necrosis Light micrograph in acute tubular necrosis showing focal loss of tubular epithelial cells (arrows) and partial occlusion of tubular lumens by cellular debris (D). Courtesy of Helmut Rennke, MD.

ATI- management

- ➡repair and tubular regeneration → gradual clinical improvement
- ➡With supportive care, patients who survive have a good chance of recovering renal function
- ➡In those with preexisting chronic kidney disease, complete recovery is less frequent. Patients who already have chronic renal disease are less probably going to recover their renal function.

قال النبي صلى الله عليه وسلم يومًا لأصحابه: من أصابته فاقةٌ فأنزلها بالناس، لم تُسدَّ فاقته، ومن أنزلها بالله أوشك الله له بالغنى، إما بموت عاجل أو غنىً آجل.
خذ بالاسباب ما استطعت ولكن لا تنس أنها مجرد أسباب، لا تنفع الا من بعد أن يأذن الله بذلك، الطبيب لا يشفي ولكنه سبب، والعمل لا يرزق ولكنه سبب، والأسباب تجري على الناس ولا تجرى على الله سبحانه، فانه ان شاء أعطى بالسبب وبدون السبب وبخلاف السبب، النار لم تحرق إبراهيم، والسكين لم تذبح إسماعيل، والحوت لم يأكل يونس ،العصا لا تشق البحر عادة ولكن عندما شاء الله ذلك شقته.
أنزل حاجتك بالله أولاً، ليكن بابه قبل كل الأبواب، أره أنك تؤمن أنه لا يكون شيءٌ في كونه ال بأمره، ثم اعمد الى الأسباب وخذ منها ما شئت.

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!