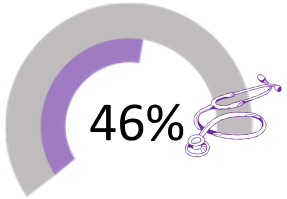

بسم الله الرحمن الرحيم

Tubulointerstitial Diseases

MID | Lecture 2

Written by: Amro Najada
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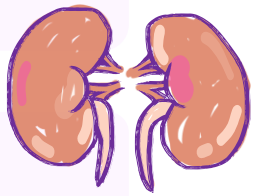
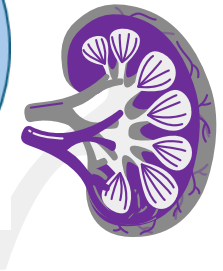


﴿ قُلْ بِفَضْلِ ٱللَّهِ وَبِرَحْمَتِهِۦ فَبِذَٰلِكَ فَلْيَفْرَحُوا۟ هُوَ خَيْرٌ مِّمَّا يَجْمَعُونَ ﴾



DISEASES AFFECTING TUBULES, INTERSTITIUM, and Collecting System

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Pathology Department
University of Jordan

قبل ما نبدأ بالملف, لا تنسوا تصلوا على الرسول
اللهم صلِّ وسلم وبارك على سيدنا محمد

Topics covered in lecture:

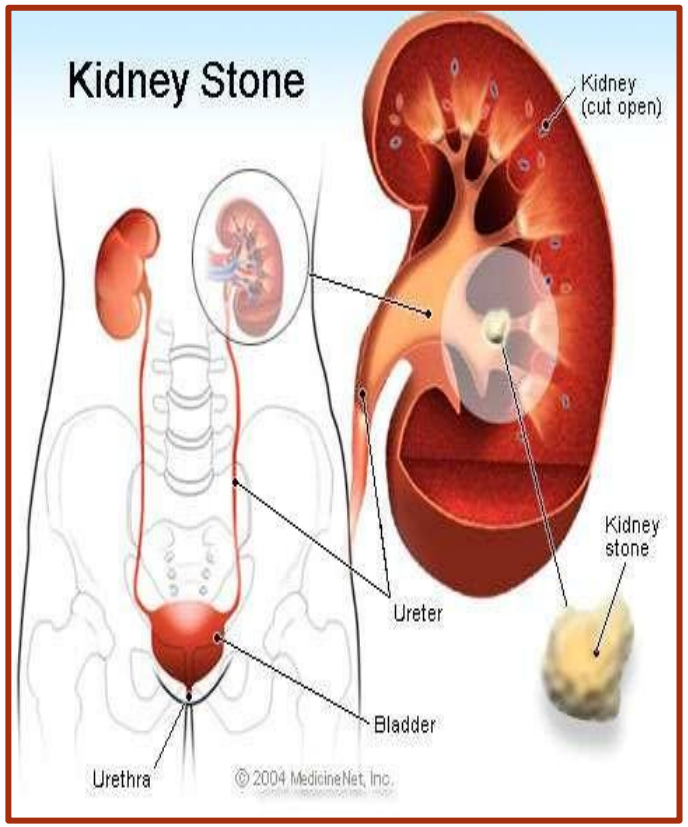
- ❑ **Urinary Outflow Obstruction:**
  - **Renal Stone**
  - **Hydronephrosis**
- ❑ **Tubulointerstitial Nephritis (TIN)**
- ❑ **Acute Tubular Injury (ATN)**

Urinary Outflow Obstruction

❖ Renal Stones (Urolithiasis) Or Nephrolithiasis

- **Definition: formation of stones at any level inside the urinary collecting system (renal calyces/renal pelvis/ureter/bladder/urethra)**
- **Most common in kidney**
- **Can be detected in about (1%) of all autopsies**
- **Symptomatic OR Asymptomatic**

✓ Asymptomatic are often found by accidentally when the patient undergoes radiographical examination for any other reason



Continued…

- **Familial tendency** to develop renal stones (especially the recurrent cases of renal stone formation)
- **Most of cases are unilateral (80%)**
- **Variable size, shade and color**
- **Symptoms: painful hematuria, renal colic**

❑ **Stones are composed of:**

➢ **inorganic salts (98%)** ⟶ A mixture of salts undergoes precipitation around an organic matrix.

➢ **organic matrix (2%)** ⟶ Forms **the center** of the stone and Represents 2% of the stone's weight.

- Types are according to the **predominant** inorganic salt **inside the stone**:

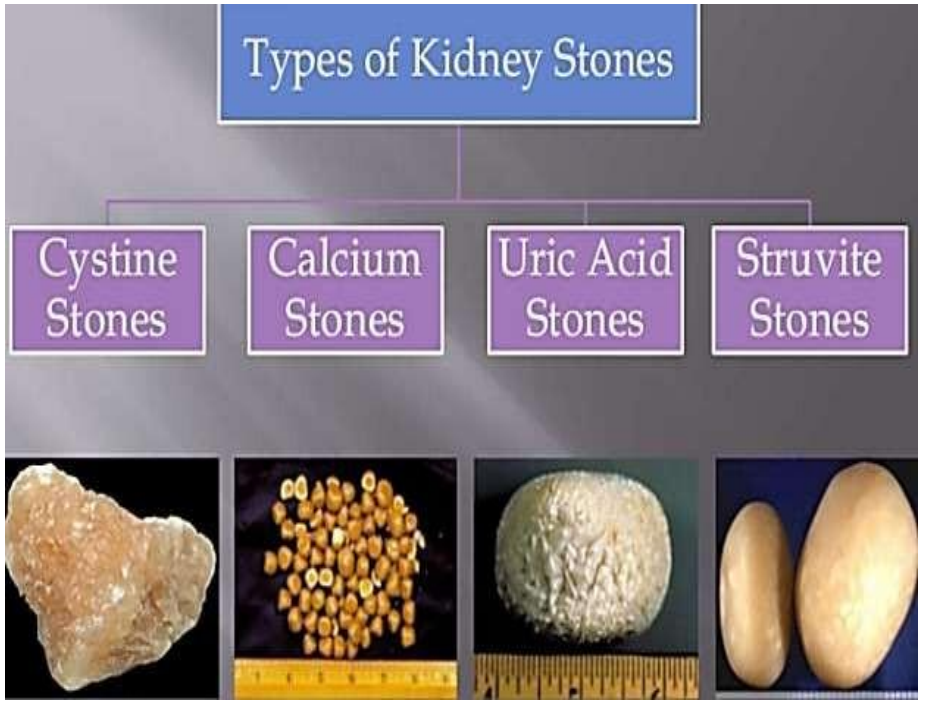
1- calcium oxalate/ calcium oxalate + calcium phosphate (80%) .

2- Struvite (magnesium ammonium phosphate) (<10%)

3- uric acid (6-7%)

4- cystine stones (2%)

The reported percentages reflect the relative probability of occurrence of each stone type. Among these, **calcium oxalate, either alone or in combination with calcium phosphate**, constitutes the most common form.



❑ Causes of Renal Stones

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

- ✓ From a chemical perspective, **urine acts as the solvent**, while **inorganic salts** (such as calcium, oxalate, phosphate, and uric acid salts) act as **the solute**.
- ✓ Under normal conditions, these inorganic salts remain dissolved (soluble) in urine as long as their concentration stays within the solubility limit of the solvent.

- ✓ When the concentration of these **inorganic salts** increases and exceeds the solubility limit, the urine first reaches **saturation** and then **supersaturation**. At this point, any further increase in salt concentration leads to **precipitation**, which is the initial step in **renal stone formation**.
- ✓ Conversely, as long as the concentration of inorganic salts remains below the solubility threshold, they stay dissolved and **no precipitation occurs**.

Continued…

- **50% of calcium stones (calcium oxalate & calcium phosphate) patients have hypercalciuria (high levels of calcium in urine) with no hypercalcemia (high levels of calcium in blood).**

✓ Having the states of hypercalcemia is by itself a risk factor for calcium stones formation

- **5% to 10% of cases have both hypercalcemia and hypercalciuria.**

2- The presence of a nidus

Nidus : an organic substance which forms a center that inorganic salts surround and easily precipitate on.

-Examples of a nidus:

- **Urates → provide a nidus for calcium deposition.**

- **Desquamated epithelial cells → cells from the kidney or the urinary tract that undergo destruction or desquamation it may assemble forming a nidus.**

- **Bacterial colonies → in cases of bacterial infection, necrotic cells and inflammatory cells aggregates to form a nidus that promotes renal stones formation.**

3- urine pH

Certain types of renal stones are pH-dependent, and their formation is influenced by the chemical properties of the constituent salts. Accordingly:

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

4- infections

- **e.g. urea-splitting bacteria – bacteria that produce urease (*Proteus vulgaris* and *Staphylococcus aureus*).**

✓ Urea-splitting bacteria possess **urease enzyme activity**, which hydrolyzes (splits) urea into ammonia. The generated ammonia, being alkaline, **increases urinary pH**, rendering the urine more alkaline. This alkaline environment promotes supersaturation of magnesium and phosphate salts, leading to the formation of **struvite stones.**

5- disorders causing hyperuricemia/ high cell turnover and:

- **e.g. gout; leukemia; tumor cell lysis following chemotherapy; etc**

✓ Blood cancers and anticancer therapy lead to rapid cell turnover and destruction over a short period, resulting in **increased uric acid levels in the blood (hyperuricemia).** Similarly, patients with gout also exhibit hyperuricemia.

✓ This elevated uric acid is reflected by increased urinary uric acid levels, and in the presence of favorable conditions (e.g., supersaturation), it promotes renal stone formation.

6- certain genetic/ metabolic abnormalities:

- **e.g. cystine stones… → 4th type of renal stones (least common)**

✓ They are usually related to genetic abnormalities in the metabolism or reabsorption of **cystine.**

✓ Patients inherit genetic mutations in transport proteins responsible for the reabsorption of cystine in the renal tubules. This leads to increased excretion and accumulation of cystine in the urine. When additional predisposing conditions are present, this results in the formation of cystine stones.

✓ And because this condition is genetic, patients will start to develop these kinds of stones early in their life (during their childhood) and they can have **recurrent cases** of renal stone formation.

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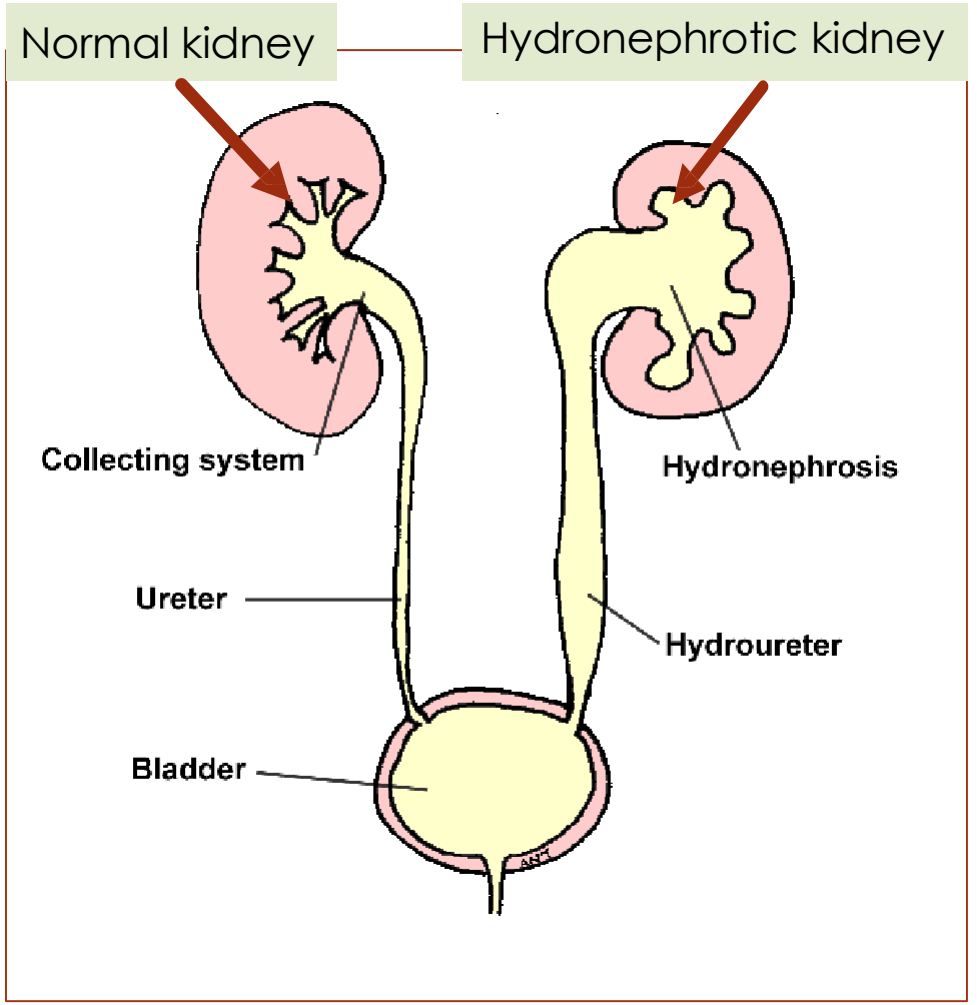
❖ Hydronephrosis

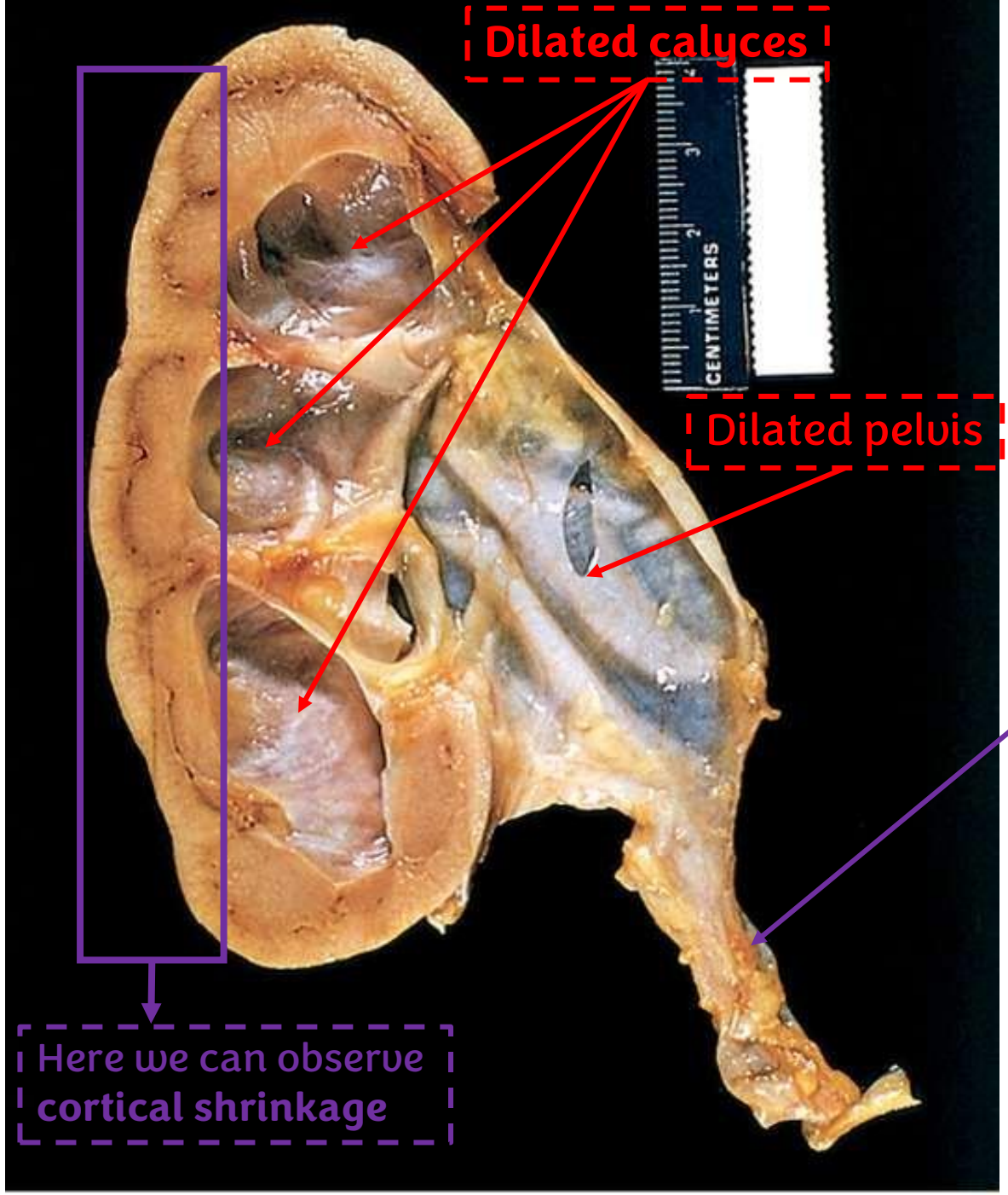
See the next slide...

- 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.
- Significance: if untreated, leads to renal parenchymal damage and dysfunction



❖ Hydronephrosis:

- ✓ **Hydronephrosis** is defined as the collection and accumulation of urine within the renal collecting system, leading to dilation of **the renal pelvis and calyces**. This occurs due to obstruction of urine flow at any level distal to the dilated segment, from the renal pelvis, ureter, ureterovesical junction, bladder, or urethra.
- ✓ The urine accumulation happens because of continued urine production with impaired drainage, resulting in progressive dilation of the collecting system.
- ✓ Over time, **the increased intrapelvic pressure** is transmitted backward to the renal parenchyma, causing compression of renal blood vessels, and it may also directly exert pressure on the renal cortex (parenchyma of the kidney). This leads to ischemia of the renal cortex, resulting **in cortical shrinking (atrophy)** and progressive loss of functional nephrons, which may ultimately impair kidney function.
- ✓ In addition, prolonged urine stasis may lead to **accumulation of toxic substances in the urine**, and their long-term presence can further contribute to damage of the renal parenchyma.
- ✓ **Hydroureter** refers to dilation of the ureter due to obstruction located distal to it, commonly at the level of the bladder or urethra.



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

❑ The most common causes of hydronephrosis are:

1- Congenital:

examples

Urethra = bilateral

- **Atresia of urethra**, which will cause bilateral hydronephrosis
- **Valve formations in ureter or urethra**
- **Aberrant renal artery compressing ureter**
- **Renal ptosis with torsion or kinking of ureter**

2- Acquired:

examples:

- **Foreign bodies**: Calculi (Stones), necrotic papillae
- **Tumors**: prostatic hyperplasia, prostate cancer, bladder tumors, cervix or uterus cancer.
  - ✓ Tumors may arise within or outside the urinary collecting system; those arising externally exert a compressive effect, leading to hydronephrosis.
- **Inflammation**: Prostatitis, ureteritis, urethritis.
- **Neurogenic**: Spinal cord damage, which leads to a **neurogenic bladder**, resulting in loss of normal voiding (تَبوّل) mechanisms. Consequently, the bladder becomes distended and unable to empty urine, which eventually leads to hydronephrosis.

Tubulointerstitial Nephritis (TIN)

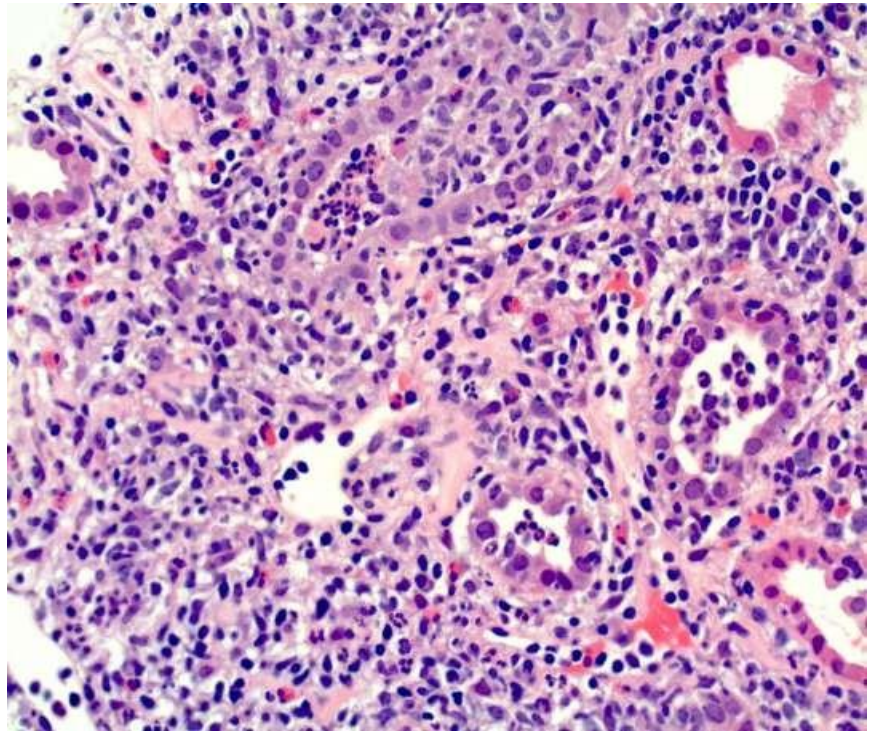
- Inflammation of tubules and interstitium

❑ Causes :

- 1- bacterial infection.
- 2- drugs. (most common)
- 3- metabolic disorders
- 4- physical injury (irradiation).
- 5- auto-immune reactions.

❑ Divided by duration into :

- 1- acute (days to months)
- 2- chronic (longer duration)



✓ The image represents the renal tubules and interstitium of the kidney, showing abnormal findings characterized by inflammation and marked infiltration of white blood cells involving the tubular and interstitial cells.

Drug-induced Interstitial Nephritis

❑ **Two forms:**

1- Acute Drug-Induced Interstitial Nephritis

2- Chronic Drug-Induced (Analgesic Nephropathy)

✓ They differ in their pathogenesis, offending drug, and overall outcome.

➢ Acute drug- induced TIN

- **Most common drugs: synthetic penicillins (methicillin, ampicillin)**
- **Others:** other synthetic antibiotics; diuretics; NSAIDs; other drugs

Acute interstitial nephritis is synonymous with **acute tubulointerstitial nephritis**; both refer to the same condition.

❑ Pathogenesis of Acute Interstitial nephritis:

immune mechanisms involve an allergic reaction against the offending drug and divided into:

- **IgE -mediated (type I hypersensitivity), which associated with eosinophilia**
- **T cell-mediated (type IV hypersensitivity).**

✓ This leads to recruitment of a variety of white blood cells.

❑ Morphology

- **Interstitium and Tubules :** infiltrated by lymphocytes, plasma cells, macrophages, eosinophils and neutrophils**.**
- **glomeruli are normal and spared from this reaction.**

Typical clinical scenario in Acute TIN:

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- A patient typically presents after recent exposure to drugs such as **penicillins (especially methicillin or ampicillin)**, followed by the development of fever, fatigue, and sometimes rash. After a short period, the patient may also notice urinary changes such as hematuria, frothy urine, or change in urine color, which prompts medical evaluation.

- Laboratory investigations usually show:
  - ✓ **eosinophilia** on CBC.
  - ✓ Urine analysis reveals **hematuria, leukocyturia, and pyuria** without any infection, with mild or no proteinuria.
  - ✓ In some cases, kidney function tests demonstrate elevated creatinine and urea, indicating impaired renal function.

- This clinical picture is due to an immune-mediated hypersensitivity reaction directed against the offending drug and initially occur as a **systemic immune response**, which subsequently targets the kidney specifically - **the renal interstitium and tubules**, leading to inflammatory cell infiltration and interstitial injury.

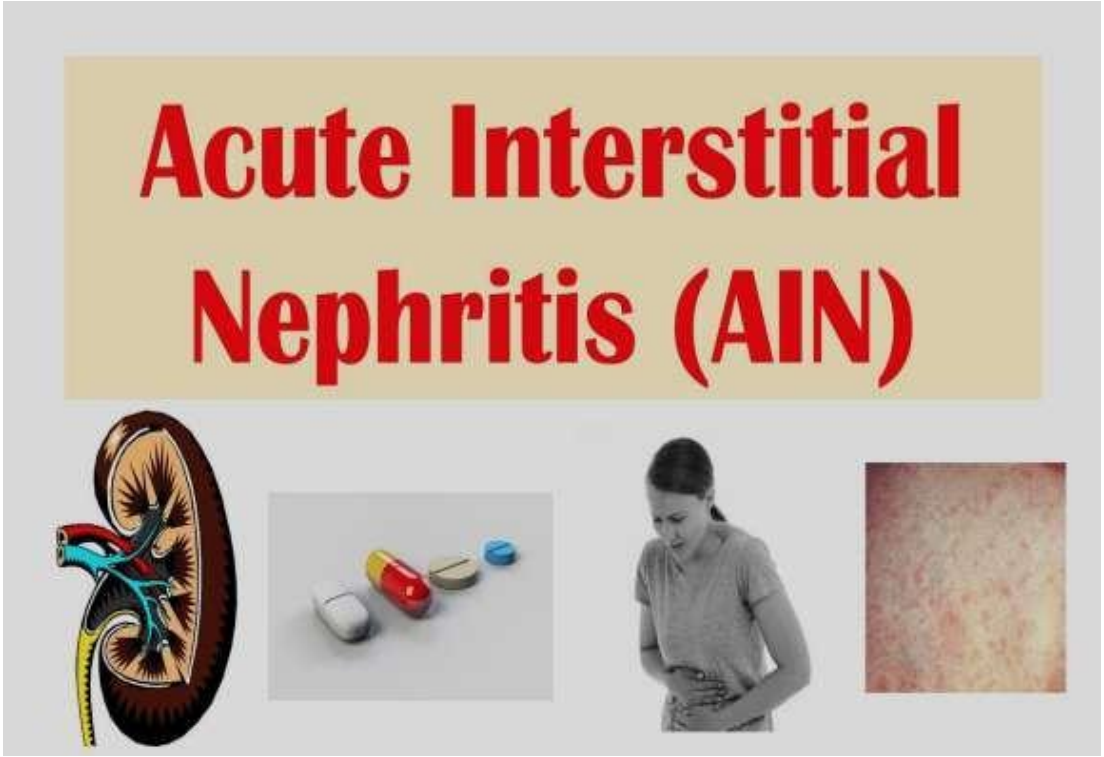
Continued...

- **What is the appropriate management in this situation?**
- ✓ Management is primarily based on **immediate withdrawal of the offending drug**, which typically results in recovery as the immune reaction subsides and inflammatory cells are cleared.

- ✓ In more severe cases, corticosteroids may be considered to reduce inflammation and accelerate recovery.

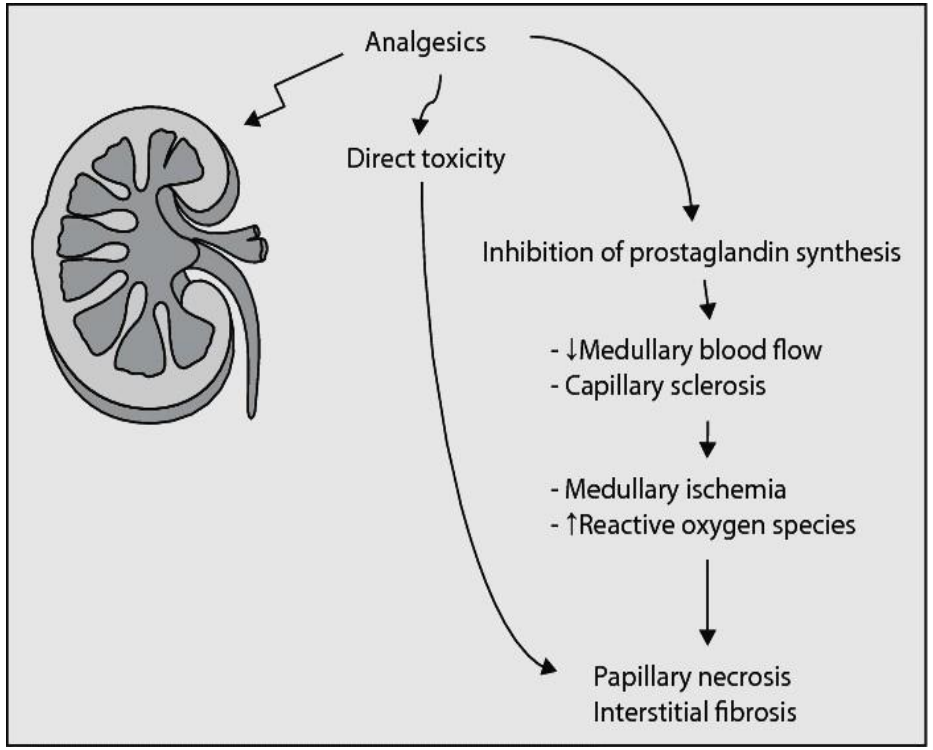
Clinical Course

- 2-40 days after exposure to drug.
- *fever*, *eosinophilia* & *rash* (25%)
- *renal abnormalities:* hematuria, minimal or no proteinuria, and leukocyturia
- withdrawal of the offending drug is followed by recovery



➢ Chronic drug –induced TIN (Analgesic nephropathy)

- Consumption of **large** quantities of analgesics over **long** periods may cause **chronic interstitial nephritis** often with **renal papillary necrosis**.
- **Aspirin (NSAIDS) and acetaminophen are common causes**
- **Pathogenesis** not entirely clear.
  - **covalent binding and oxidative damage**
  - **inhibition of prostaglandin synthesis**



See the next slides...

Further explanation

- Chronic drug-induced tubulointerstitial nephritis differs from the acute form in its pathogenesis, offending agents, and overall outcome. It is classically referred to as **analgesic nephropathy**, reflecting its most common cause.

- It typically develops in patients with prolonged consumption of large quantities of analgesics **(e.g., aspirin, acetaminophen),** over months to years. Accordingly, it is more likely to occur in patients requiring long-term pain control, such as those with chronic (e.g., hematologic diseases) or malignant conditions.

- The pathogenesis is not fully understood but involves two main mechanisms:
- ✓ Direct tubular and interstitial injury through **covalent binding and oxidative damage.**
- ✓ **Prostaglandin inhibition** by NSAIDs. Since prostaglandins normally mediate vasodilation, their inhibition leads to **relative vasoconstriction, resulting in chronic, mild renal ischemia** that progressively damages the renal interstitium and tubules over time.

Further explanation

- Unlike acute interstitial nephritis, this condition is not primarily inflammatory and does not present with acute hypersensitivity features such as rash or marked hematuria. Instead, it develops **insidiously, with cumulative damage that may only become evident after significant renal impairment has occurred.**

- Clinically, it may lead to **azotemia** (elevated creatinine and urea), **progressive renal dysfunction, and hypertension.**

- Management focuses on prevention and early detection, including careful monitoring of analgesic use and regular assessment of kidney function to minimize further renal damage.

Clinical Course of chronic Interstitial Nephritis

- 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 morphologically by damaged tubular epithelial cells (Acute necrosis of the tubular cells) and clinically by acute suppression of renal function (Acute renal failure).**
- **It is the most common cause of acute renal failure.**

Acute renal failure is characterized by an **acute loss of renal function**, associated with **azotemia**, **uremia**, and reduced urine output (**oliguria** or anuria).

- **However, ATN is a reversible condition if treated properly and quickly**
- **Clinical manifestations: electrolyte abnormalities, acidosis, uremia, signs of fluid overload, often oliguria.**
- **Proximal tubular epithelial cells (most affected cells) are particularly sensitive to hypoxemia and toxins**

Acute Tubular Necrosis/Injury (ATN/ ATI)

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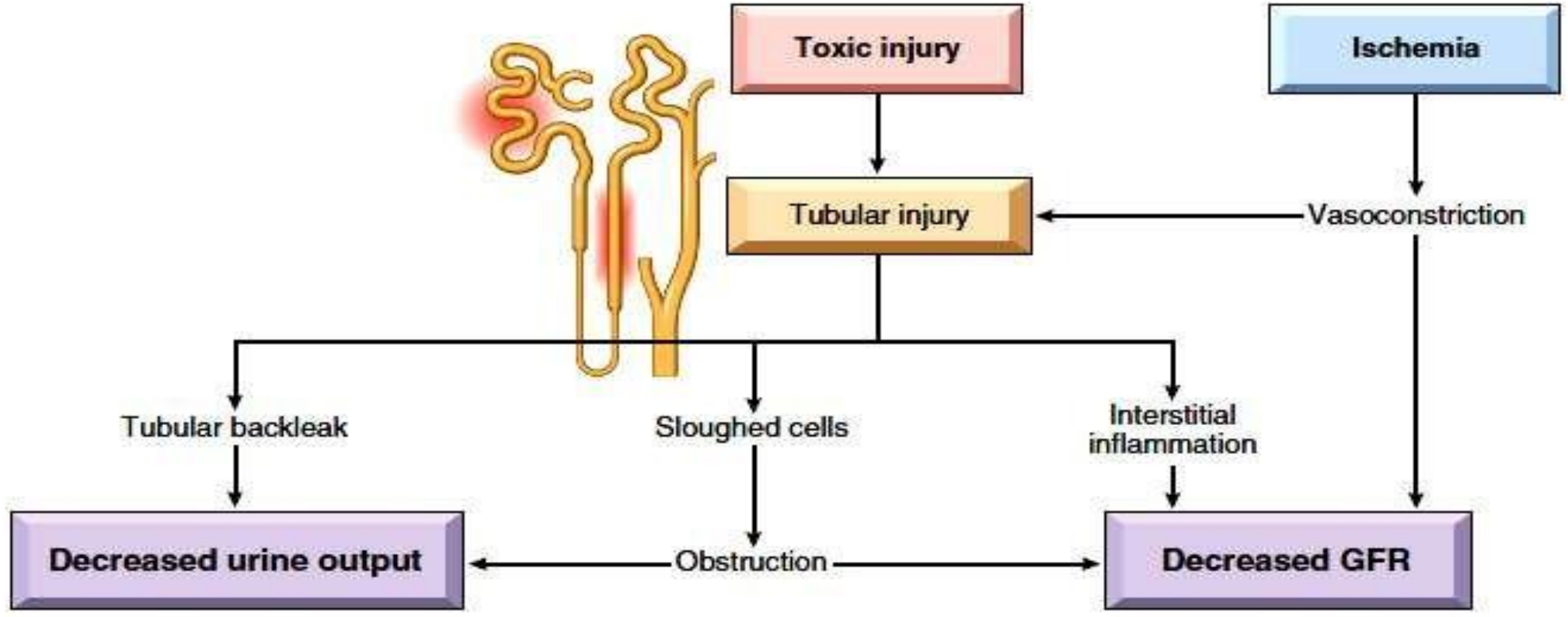


Fig. 14.16 Postulated sequence in ischemic or toxic tubular injury.

Further explanation of the figure

Acute tubular necrosis/injury (ATN/ATI) arises from two main causes: **ischemia** and **toxic injury**.

- **Ischemia** leads to vasoconstriction, resulting in decreased GFR and contributing to tubular injury. Similarly, **toxic injury** directly causes tubular epithelial damage.

- Tubular injury leads to interstitial inflammation, sloughing of necrotic tubular cells into the lumen causing obstruction, and disruption of the tubular basement membrane resulting in tubular backleak of filtrate, whereby urine and toxic substances flow back into the circulation, ultimately leading to decreased urine output.

- These processes collectively result in **decreased urine output and reduced GFR**.
- Accordingly, ATI is classified into **ischemic ATI** and **nephrotoxic ATI**, based on the underlying cause.

❑ Acute Tubular Necrosis/Injury Types:

1- ischemic ATI :

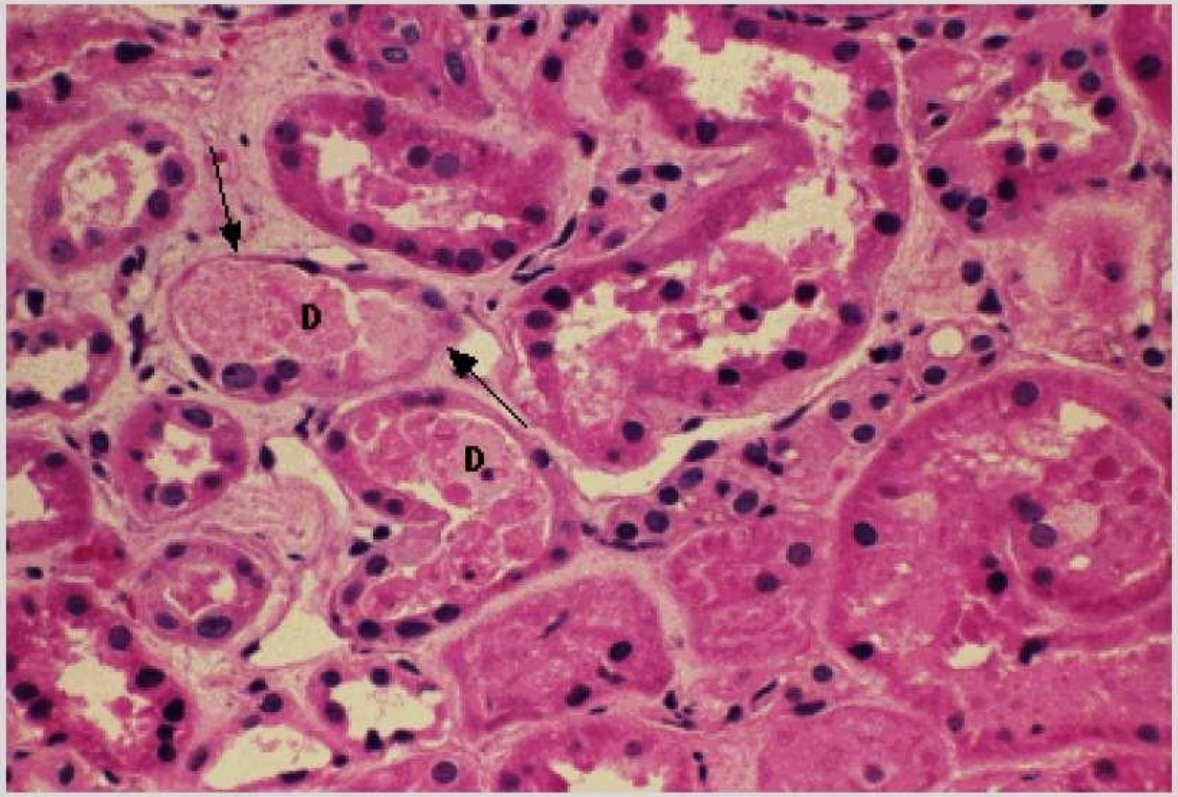
- most common type
- associated with hypovolemia or shock (e.g. hypotensive shock, severe trauma; acute pancreatitis; septicemia; mismatched blood transfusion, hemolytic crises, myoglobinuria, etc…)

2- nephrotoxic ATI: (Causes)

- poisons including heavy metals (e.g., mercury)
- organic solvents (e.g., carbon tetrachloride)
- 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

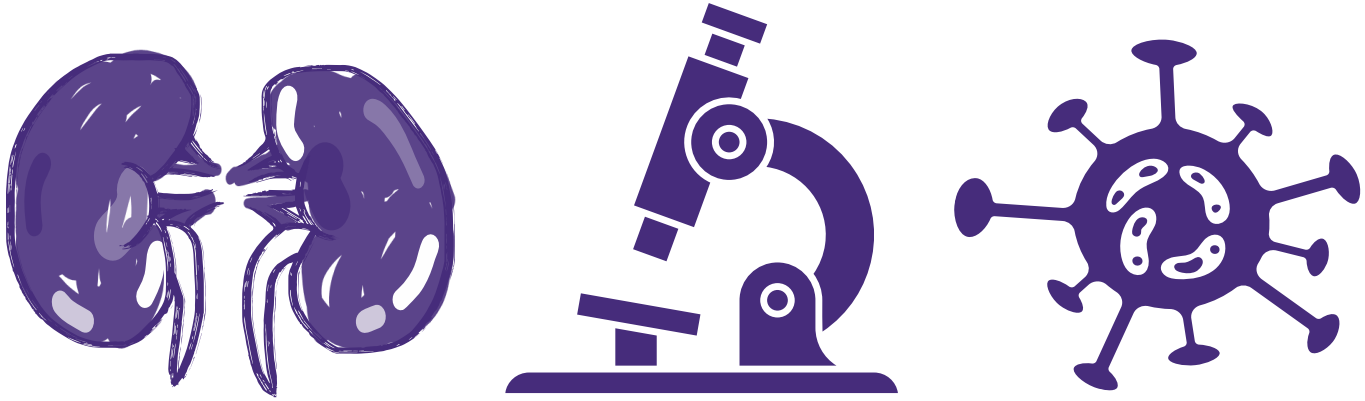
ATN



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:

- **Treat the underlying cause**
- **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

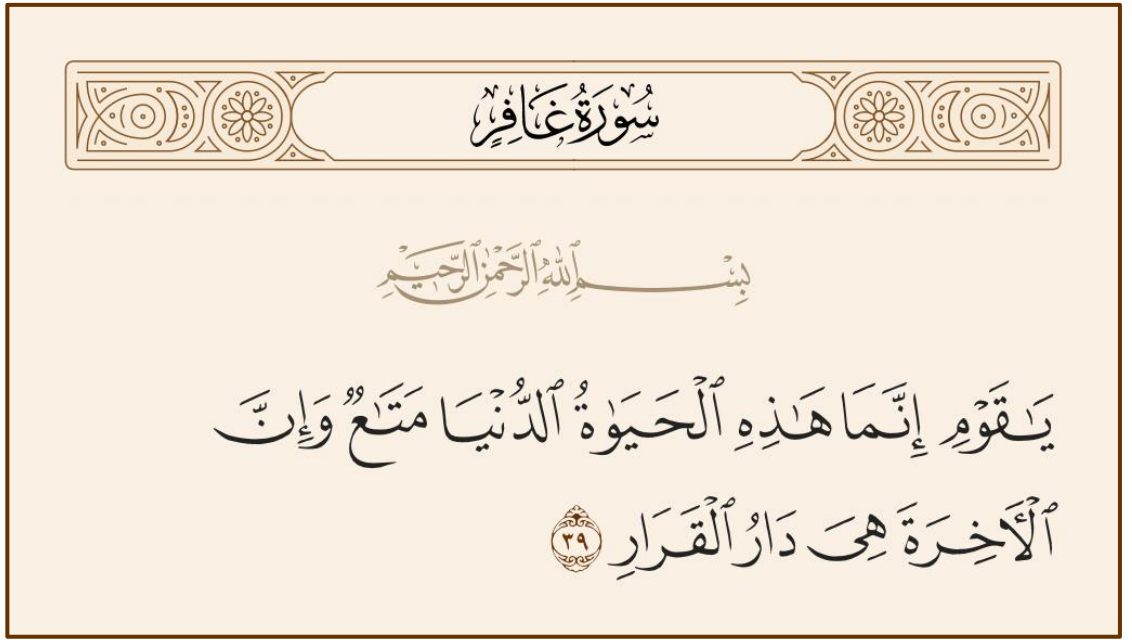


PATHOLOGY QUIZ LECTURE 2

External Resources

رسالة من الفريق العلمي

اللهم إن عمر عطية في ذمتك وحبل جوارك، فقِه من فتنة القبر وعذاب النار، أنت أهل الوفاء والحق، فاغفر له وارحمه إنك أنت الغفور الرحيم.



هذه الحقيقة، وصدق رحمه الله، إنما هذه الحياة الدنيا متاع، كما قال جلَّ وعلا: أَرَضِيتُمْ بِالْحَيَاةِ الدُّنْيَا مِنَ الْآخِرَةِ فَمَا مَتَاعُ الْحَيَاةِ الدُّنْيَا فِي الْآخِرَةِ إِلَّا قَلِيلٌ [التوبة:38]، هذه متاعٌ قليلٌ زائلٌ، فلو..... من الأموال، ومن القصور، ومن الخدم، وغيرذلك كله متاعٌ قليلٌ، كله يزول، وإنما الآخرة هي دارالقرار، وهي دار النَّعيم، وهي دارالخلد، فلا يُؤْثِروا عليها العاجل الزائل الذي .....؛ ولهذا أرشدهم هذا المؤمن ونصحهم: اتَّبِعُونِ أَهْدِكُمْ سَبِيلَ الرَّشَادِ ۝ يَا قَوْمِ إِنَّمَا هَذِهِ الْحَيَاةُ الدُّنْيَا مَتَاعٌ [غافر:38- 39]، مثلما يتمتع المسافرفي السفربطعامه الذي معه، أومركوبه الذي معه، أوما أشبه ذلك، ثم ينتهي، كلها متاعٌ، وإن عمَّرفيها ألف عامٍ، وإن عمَّرفيها آلاف الأعوام، كلها متاعٌ زائلٌ، ولكن الآخرة دارالنَّعيم الباقي الذي لا ينتهي أبدًا ولا يزول، بل نعيمها دائمٌ أبد الآباد، وحياتها مستمرةٌ أبد الآباد، كما قال جلَّ وعلا: إِنَّ الْمُتَّقِينَ فِي جَنَّاتٍ وَعُيُونٍ ۝ ادْخُلُوهَا بِسَلَامٍ آمِنِينَ [الحجر:45- 46] يعني: آمنين من الموت، وآمنين من المرض، وآمنين من الخوف، وآمنين من الجوع، وآمنين من كل بلاءٍ.

~ الشيخ عبد العزيزابن باز-رحمه الله-

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			