RENAL PATHOLOGY 5

ANALGESIC NEPHROPATHY : CHRONIC DRUG -INDUCED

- Consumption of large quantities of analgesics over long periods may cause **chronic interstitial nephritis** often with **renal papillary necrosis.**
- **Aspirin and acetaminophen are common.**
- While they can cause renal disease in apparently healthy individuals, preexisting renal disease seems to be a necessary precursor to analgesic-induced RF.
- **Pathogenesis not entirely clear.**
- Papillary necrosis is the initial event, followed by the interstitial nephritis in the overlying renal parenchyma.

ANALGESIC NEPHROPATHY: CHRONIC DRUG-INDUCED

- Acetaminophen, a phenacetin metabolite, injures cells by both, covalent binding & oxidative damage.
- The ability of aspirin to inhibit prostaglandin synthesis suggests that aspirin may induce its potentiating effect by inhibiting the vasodilatory effects of prostaglandin & predisposing the papilla to ischemia.
- Clinical Course
- Progressive renal impairment, chronic renal failure, hypertension and anemia....
- A complication of analgesic abuse is: increased incidence of transitional-cell carcinoma of the renal pelvis.

ACUTE TUBULAR NECROSIS (ATN)

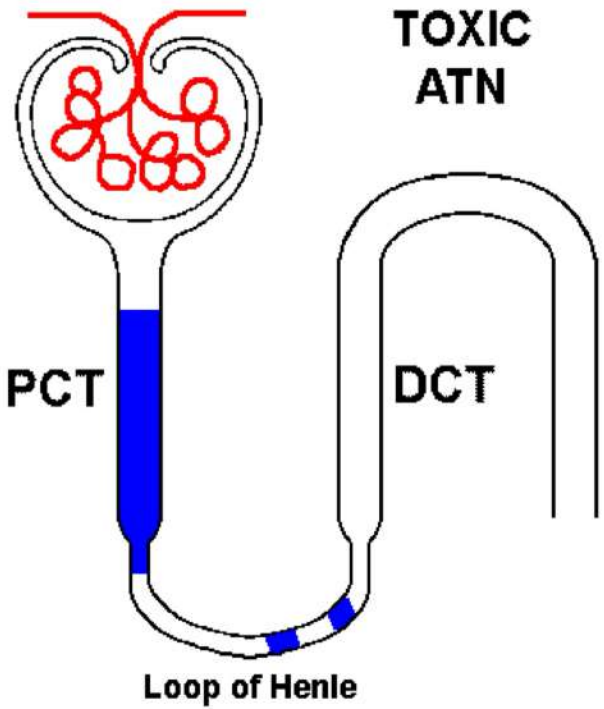
- **characterized morphologically by damaged tubular epithelial cells and clinically by acute suppression of renal function** with oliguria(urine flow of <400 mL/day)..
- **It is the most common cause of acute renal failure (ARF).**
- **Other causes of ARF are:**
- (1)Severe G diseases, manifesting as RPGN,
- (2) Acute papillary necrosis associated with acute PN,
- (3) Acute drug-induced interstitial nephritis (Paracetamol)
- (4) Diffuse cortical necrosis.
- (5) Diffuse renalvascular diseases, e.g., microscopic polyangiitis & thrombotic microangiopathies.

ACUTE TUBULAR NECROSIS (ATN)

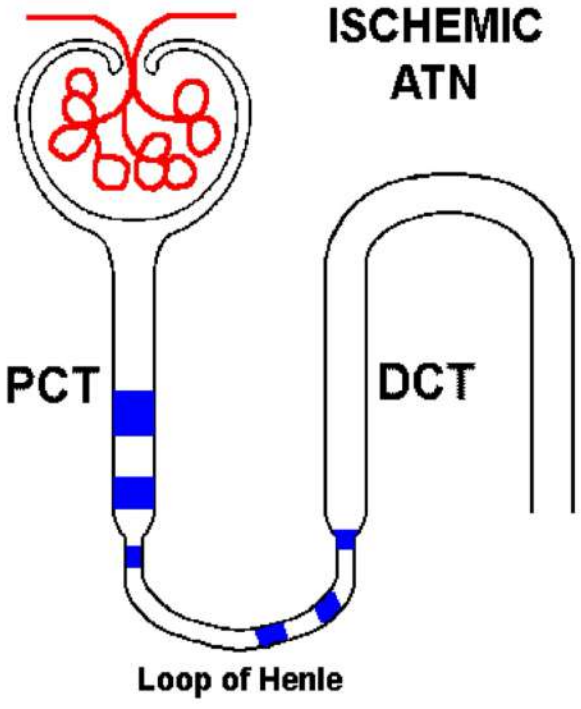
- **is a reversible condition if treated properly and quickly.**
- **Clinical manifestations:**
- **electrolyte abnormalities, acidosis, uremia, signs of fluid overload, often oliguria.**
- **Proximal tubular epithelial cells are particularly sensitive to hypoxemia and toxins.**
- **ATN is quite frequent disorder that can arise in many clinical settings, in one of 2 patterns:**
- **(1st) Ischemic ATN** cause by shock, in which a period of **hypotension & shock is common in most of these settings** (ranging from severe trauma to acute pancreatitis to septicemia) . A similar picture can be produce by mismatched blood transfusions, hemolytic crises, & myoglobinuria.
- **(2nd)Nephrotoxic ATN ,** is caused by a variety of poisons, including heavy metals(e.g., **mercury**); organic solvents(e.g., **CCl4**); & **drugs** such as gentamicin& other antibiotics, & **radiographic** contrast agents e.g., those used for angiogram.

PATHOGENESIS OF ATN

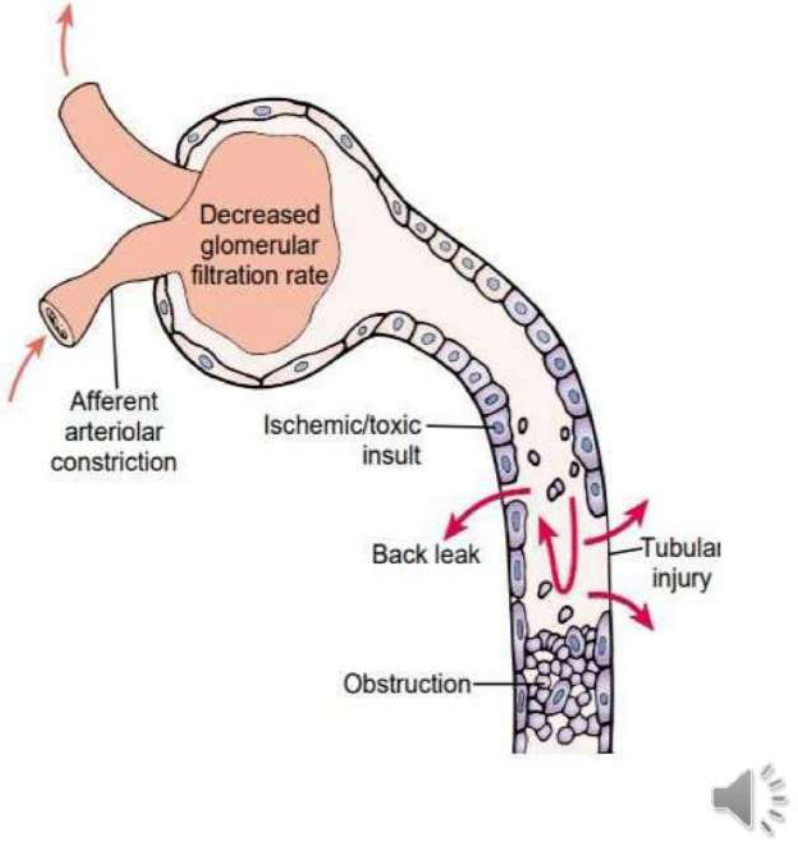
- Tubular epithelial cells are vulnerable to **toxins**& very sensitive to **anoxia**. **Therefore**, the 2 major factors in the pathogenesis of both ischemic & nephrotoxic ATN are:
- **(1) tubular injury.**
- (2) persistent & severe **ischemia** caused by **intrarenal** vasoconstriction, resulting in both: (a) decrease **G** plasma flow, resulting in decrease **GFR**& (b) decrease **O2** delivery to the functionally important tubules in the outer medulla .

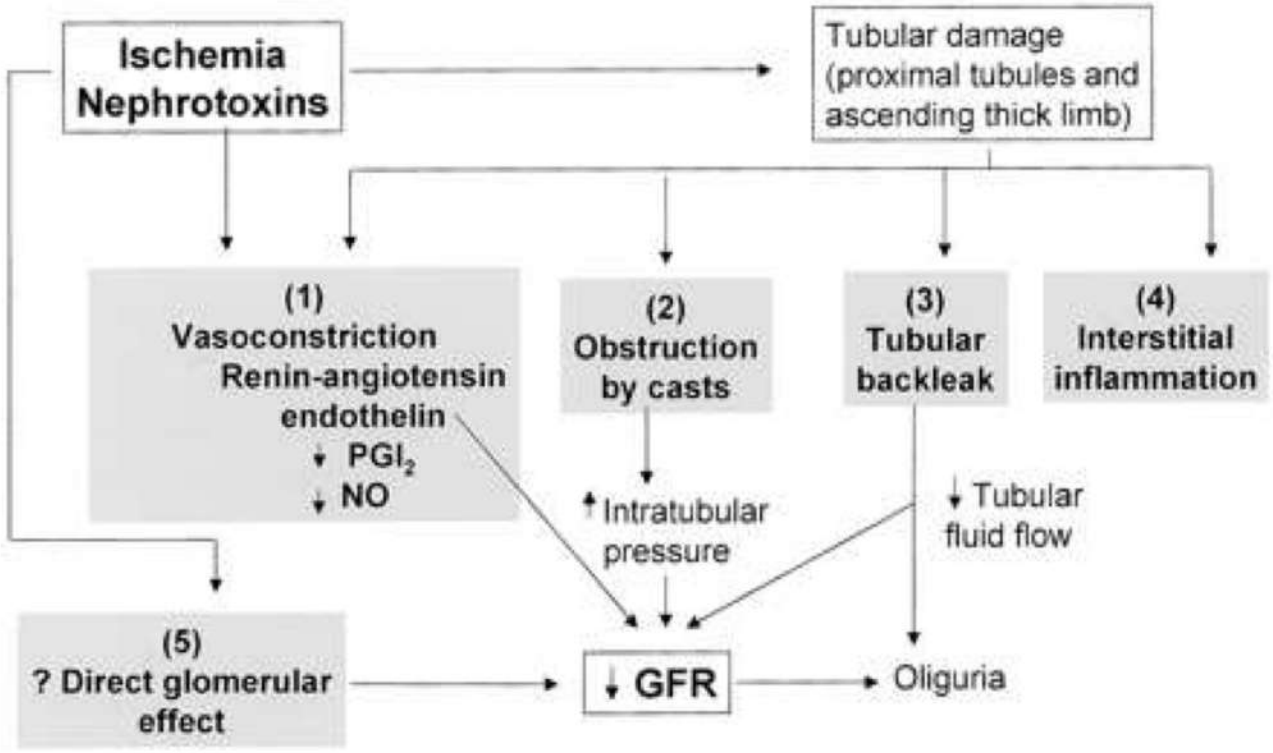


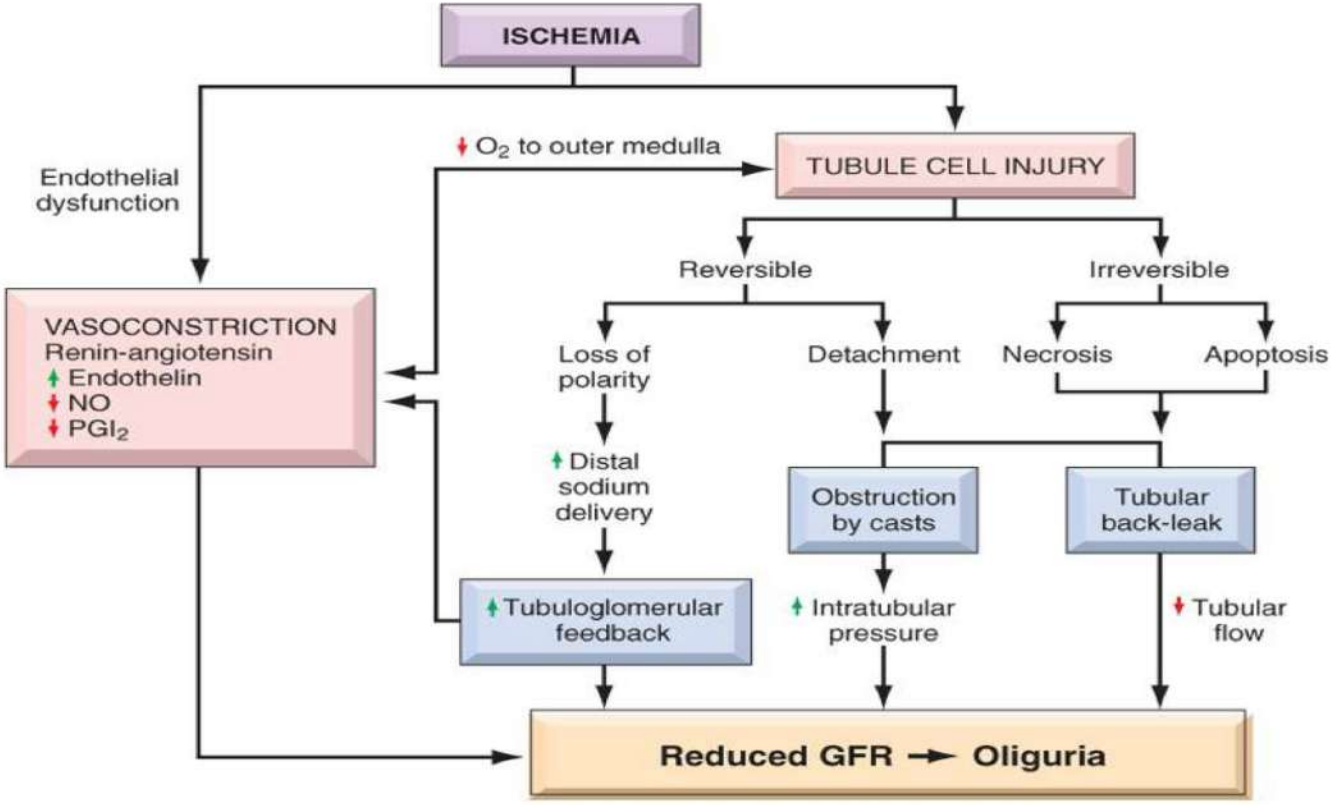
- These diagrams illustrate acute tubular necrosis (ATN).
- The distribution of the areas of necrosis is more segmental with ischemic injuries, while toxic injuries result in more diffuse proximal tubular injury.
- Urine output will drop precipitously.
- If life-threatening uremia can be treated, then recovery of the tubular epithelium can occur.
- As the tubular epithelium is regenerating, urine concentrating ability is impaired, and polyuria occurs.



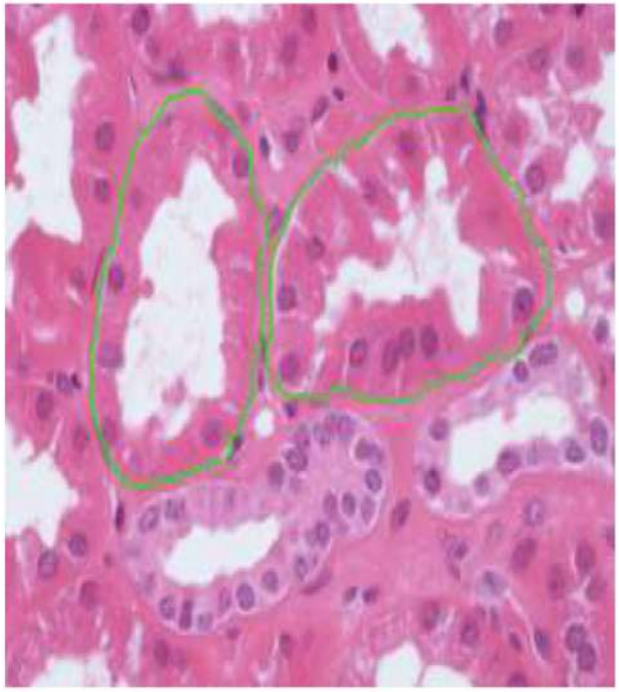
- Pathogenesis of acute tubular necrosis.
- Sloughing and necrosis of tubular epithelial cells leading to obstruction and increased intraluminal pressure, which reduces globular filtration.

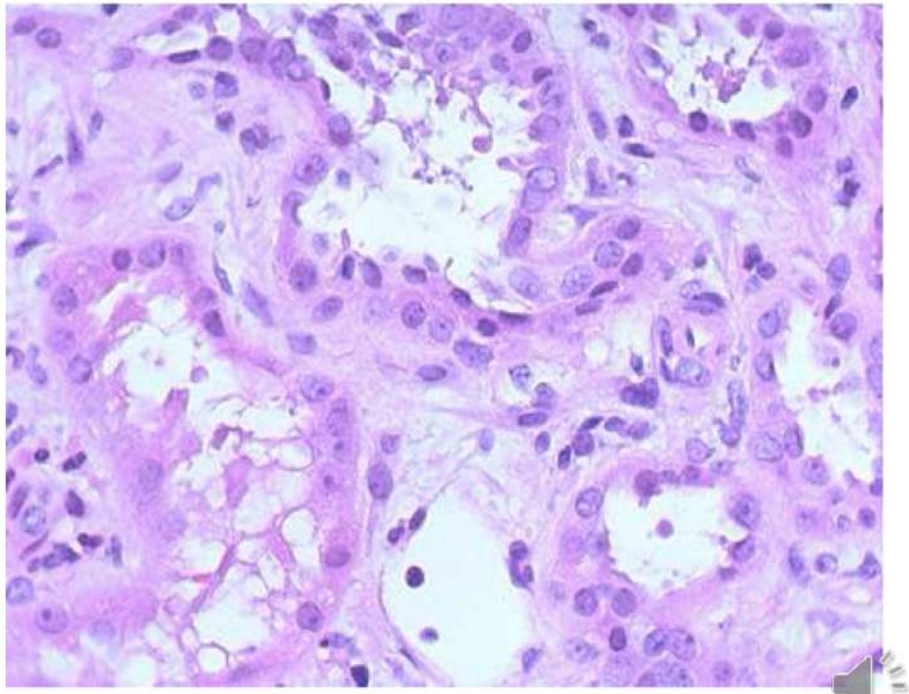



Ischemia
Nephrotoxins
Tubular damage (proximal tubules and ascending thick limb)
(1)
Vasoconstriction
Renin-angiotensin
endothelin
↓ PGI_2
↓ NO
(2)
Obstruction by casts
(3)
Tubular backleak
(4)
Interstitial inflammation
↑ Intratubular pressure
↓ Tubular fluid flow
(5)
? Direct glomerular effect
↓ GFR
Oliguria

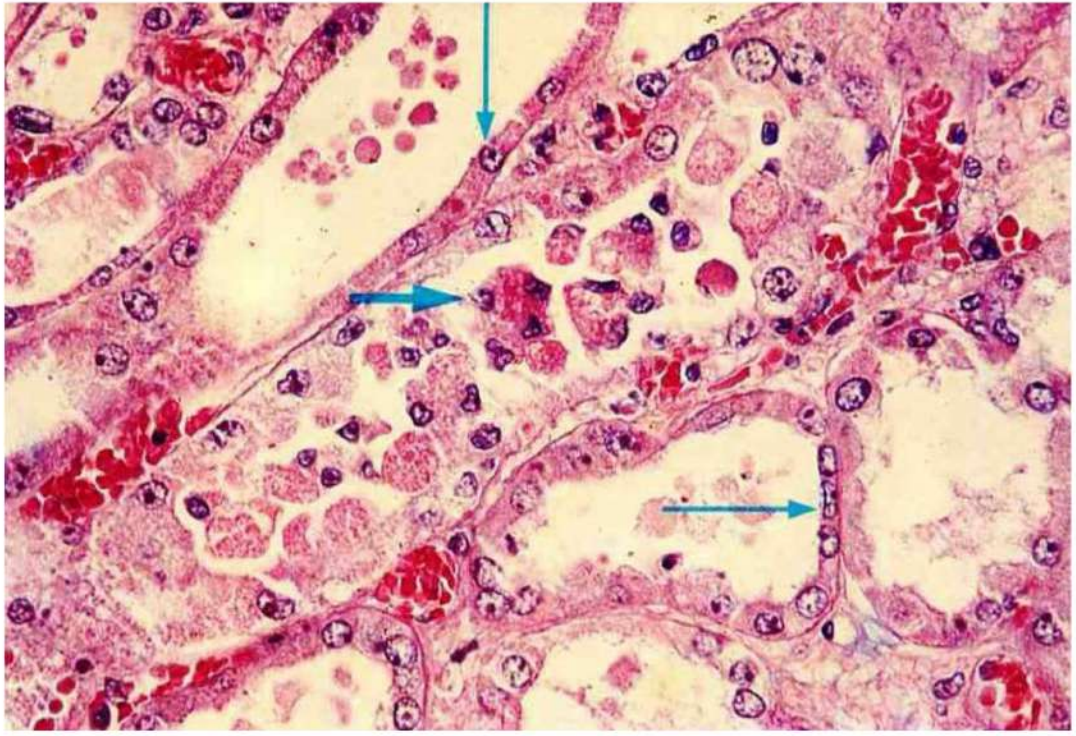


The epithelium of the tubules seen here is ragged from undergoing necrosis with acute tubular necrosis (ATN) from ischemia. In this case, heart failure with hypotension precipitated the ATN. This is one form of acutee kidney injury (AKI) with an abrupt or rapid decline in renal function. (A) left one IS NORMAL TUBULES , (B) right one is Acute tubular necrosis





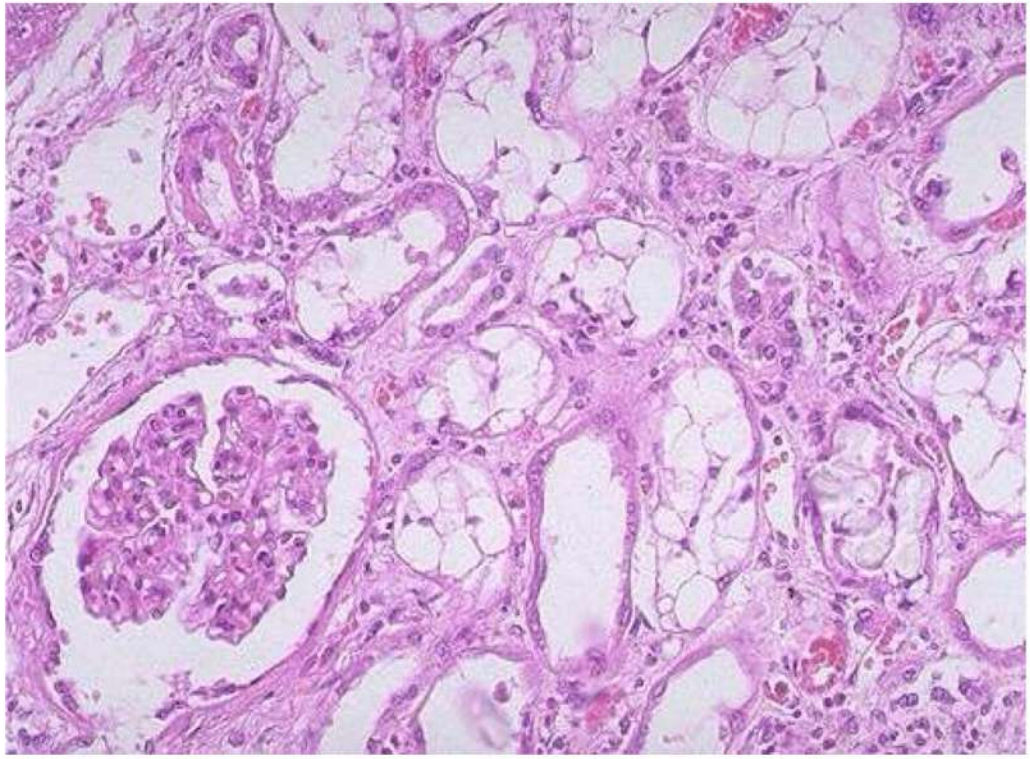
Acute Tubular Necrosis: kidney. Patient died from RF, 7 days following pericardiectomy for constrictive pericarditis (1) Most of the collecting tubules epithelial cells are **died**& the necrotic cells are sloughed into the lumen (**thicken** arrow). (2) The **surviving** cells attempts at **repair**& already the tubules are lined by flat epithelium (**thin** arrow).



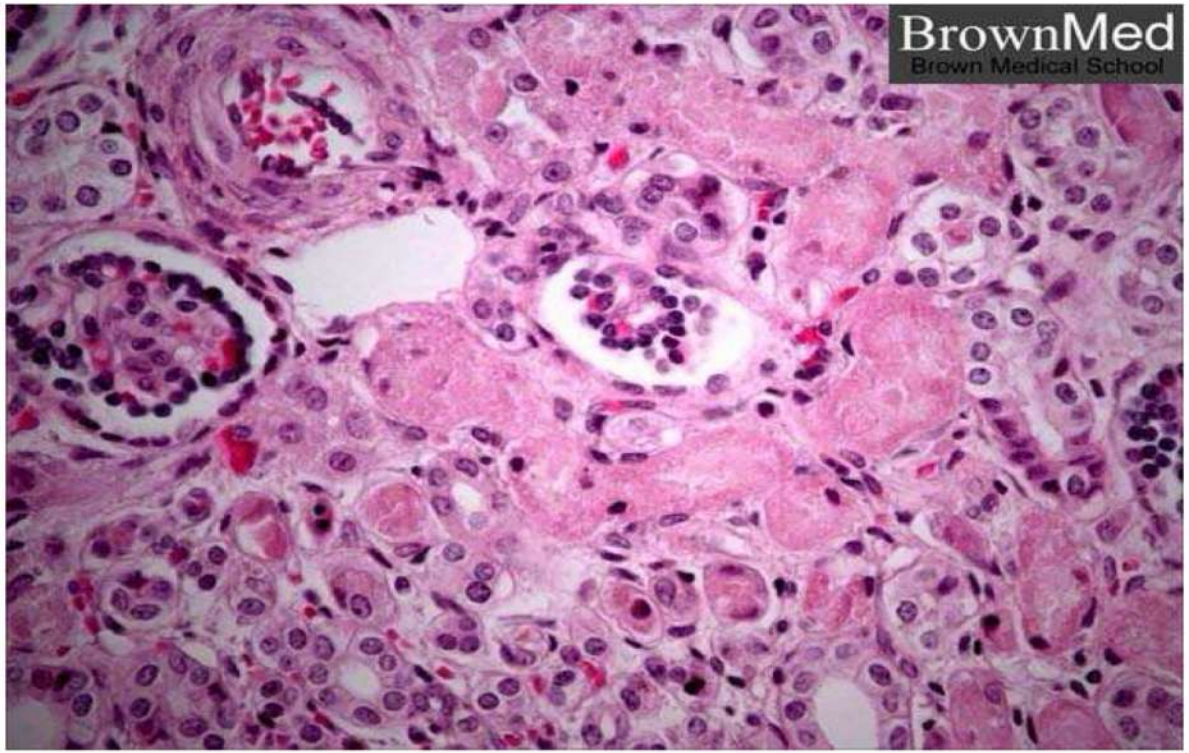
ATN MORPHOLOGY

- **Renal biopsy shows:**
- 1. Blebbing; vacuolization; **necrosis & detachment** of tubular cells from their underlying BM & their **sloughing** in the lumen
- 2. **Proteinaceous casts** in the distal tubules & collecting ducts is a **striking** additional finding. They consist of **Tamm-Horsfall protein (secreted normally by tubular epithelium)** along with hemoglobin & other plasma proteins.
- 3. When **crush injuries** have produced ATN, the casts are composed of **myoglobin**

The tubular vacuolization and tubular dilation here is a result of the toxic effect of ethylene glycol poisoning. This is representative of acute tubular necrosis (ATN), which has many causes. ATN resulting from toxins usually has diffuse tubular involvement, whereas ATN resulting from ischemia (as in profound hypotension from cardiac failure) has patchy tubular involvement.



Note necrosis and sloughing of epithelial cells of the proximal convoluted tubules. The glomeruli and distal convoluted tubules are preserved.



ATI-MANAGEMENT

- repair and tubular regeneration → gradual clinical improvement
- With supportive care, patients who survive have a good chance of recovering renal function
- those with preexisting chronic kidney disease, complete recovery is less frequent

DISEASES INVOLVING BLOOD VESSELS

- All kidney diseases involve the renal BV **secondarily**.
- Systemic vascular diseases, e.g., **arteritis**, also involve renal BV, & often the effects on the kidney are clinically important.
- The kidney is intimately involved in the pathogenesis of both essential & secondary **hypertension(H)**

BENIGN NEPHROSCLEROSIS (HYALINE ARTERIOLOSCLEROSIS)

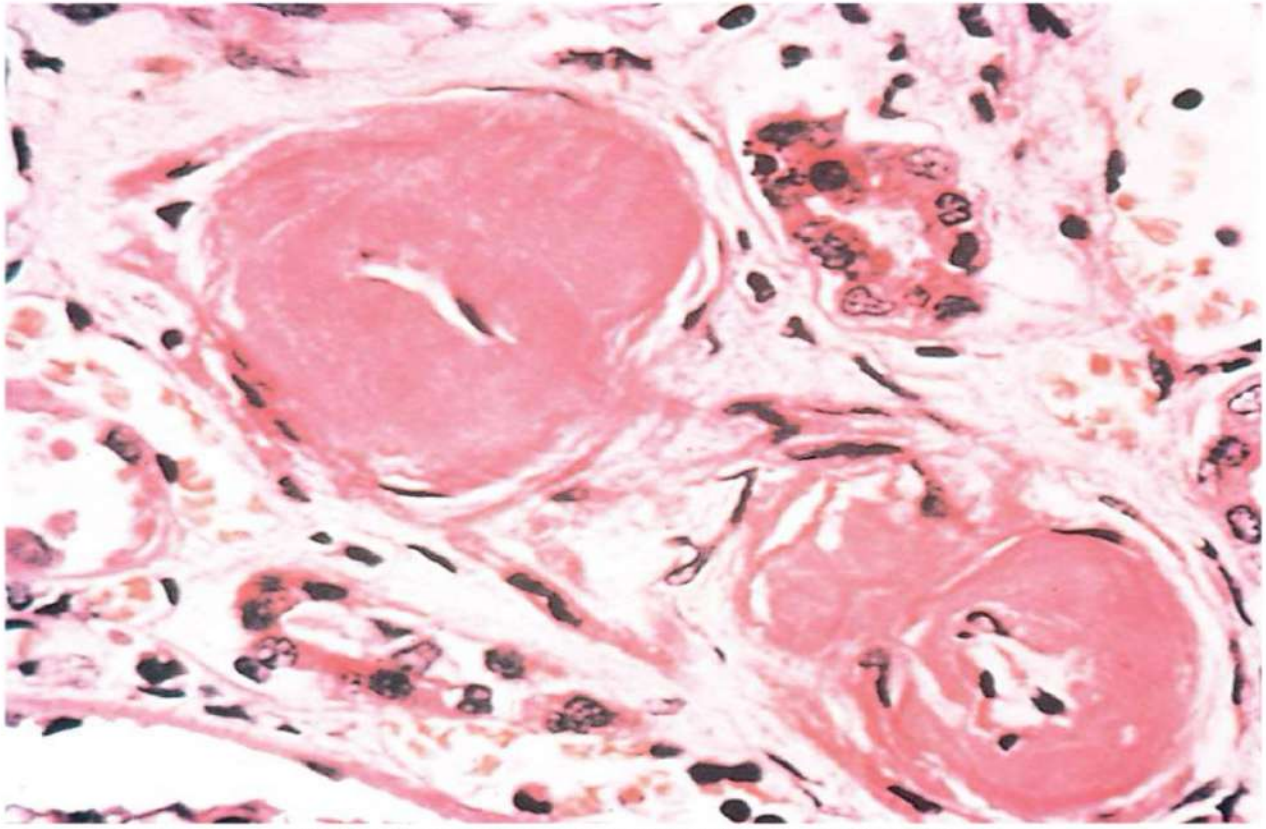
- Term used for the renal changes in benign Hypertention.
- Some degree of benign nephrosclerosis, albeit mild, is present at autopsy in many persons older than 60 years of age.
- But the frequency & severity of the lesions are increase at any age when H or DM are present.
- It is associated with **aging, hypertension, diabetes mellitus and may be seen in response to certain drugs (calcineurin inhibitors).**
- **In malignant hypertension, the vascular damage is acute, and renin release is a very important part of the pressure increase. In benign, essential hypertension, vascular damage is chronic, and its most important pressure-raising influence is sodium retention.**

PATHOGENESIS OF BENIGN NEPHROSCLEROSIS (HYALINE ARTERIOLOSCLEROSIS)

- Many renal diseases cause H, which in turn is associated with benign nephrosclerosis.

Morphology

- Grossly, both kidneys are symmetrically atrophic, each weighing 110 to 130 gm (Normal 300 gm), with a diffusely fine granular surface that resembles grain leather .
- H, there is hyaline arteriolosclerosis, with subendothelial homogeneous, pink hyaline thickening causes narrowing of the BV lumen, resulting in marked decrease blood flow & ischemia through the affected BVs.
- All structures of the kidney show ischemic atrophy.



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Benign nephrosclerosis. HP view of two arterioles with hyaline deposition, resulting in marked thickening of the walls, & narrowing of the lumen

MORPHOLOGY OF BENIGN NEPHROSCLEROSIS, ALONE, RARELY CAUSES SEVERE RENAL DAMAGE. A MILD PROTEINURIA IS A FREQUENT PRESENT

- In advanced cases: the G tufts may become globally sclerosed, with diffuse tubular atrophy & interstitial fibrosis.
- The larger interlobar & arcuate arteries show (fibroelastic hyperplasia) i.e.,reduplication of internal elastic lamina + fibrous thickening of the media & the sub intima.
- Benign Nephrosclerosis, alone, rarely causes severe renal damage. A mild proteinuria is a frequent present

MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

- Malignant **H** is **far less common** in the US **than benign H** & occurs in only about 5% of persons with elevated BP.
- It may arise **de novo**(i.e., from the start, without preexisting **H**), or it may appear suddenly in a person who had mild H .

PATHOGENESIS OF MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

- The **basis for this turn in hypertensives** is unclear, but the following scenario is suggested:
- Long-standing benign **H** eventually → injure the arteriolar walls, resulting in (a) **EC injury,** (b) ↑ **permeability** of the small BVs to fibrinogen & other plasma proteins, (c) **platelet deposition.**
- These 3 changes constitute the... → **Fibrinoid necrosis** of arterioles & small arteries & intravascular thrombosis.
- Mitogenic factors from platelets (e.g., PDGF) & plasma cause intimal SMCs hyperplasia of BVs, resulting in the...
- → Hyperplastic arteriolosclerosis(onion-skin lesion), with further narrowing of the luminae , **typical of malignant H** & of morphologically similar thrombotic microangiopathies.

PATHOGENESIS OF MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

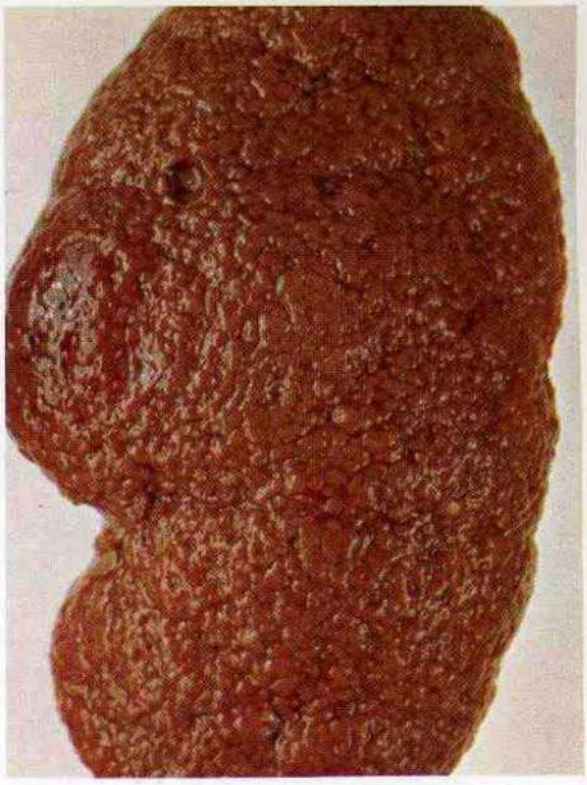
- The kidneys become markedly ischemic & the severe ischemia of the renal afferent arterioles... stimulates the renin-angiotensin system (persons with malignant H have **markedly elevated levels of plasma renin**).
- This then **sets up a vicious cycle O,** in which, angiotensin II causes intrarenal vasoconstriction & the resulting renal ischemia increase renin secretion.
- Aldosterone levels are also elevated& salt retention undoubtedly contributes to the elevation of BP.
- The consequences of the markedly elevated BP on the BVs throughout the body are known as malignant arteriolosclerosis& the renal disorder is referred to as malignant nephrosclerosis.

MORPHOLOGY OF MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

- Grossly:
- the kidneys in malignant H may be normal in size or slightly shrunken.
- Multiple small, pinpoint petechial hemorrhages appear on the cortical surface, from rupture of arterioles or G capillaries, giving the kidney **flea- bitten appearance.**
- Microscopicaly :, there are
- (I) **fibrinoid necrosis of the arterioles** , with homogeneous, granular eosinophilic fibrin deposits. **Necrosis** may also involve **G** with microthrombi within the **G** as well as necrotic arterioles.
- **(II) Hyperplastic arteriolosclerosis** in the interlobular arteries & larger arterioles, in which **concentric** proliferation of intimal SMCs producing an **onion-skin appearance, resulting** in marked narrowing, or obliteration, of arterioles & small arteries.
- Similar lesions are seen in persons with acute thrombotic microangiopathies.

CLINICAL MANIFESTATIONS OF MALIGNANT H & MALIGNANT NEPHROSCLEROSIS

- **malignant H characterize by** ↑ diastolic BP (>120 mm Hg), papilledema, encephalopathy, RF & cardiovascular abnormalities, Most often, the early symptoms are related to ↑intracranial pressure& include headache, nausea, vomiting, & visual impairment.
- Without treatment, malignant H is **fatal**, with 90% of deaths caused by **uremia** & 10% by **cerebral hemorrhage or cardiac failure.**



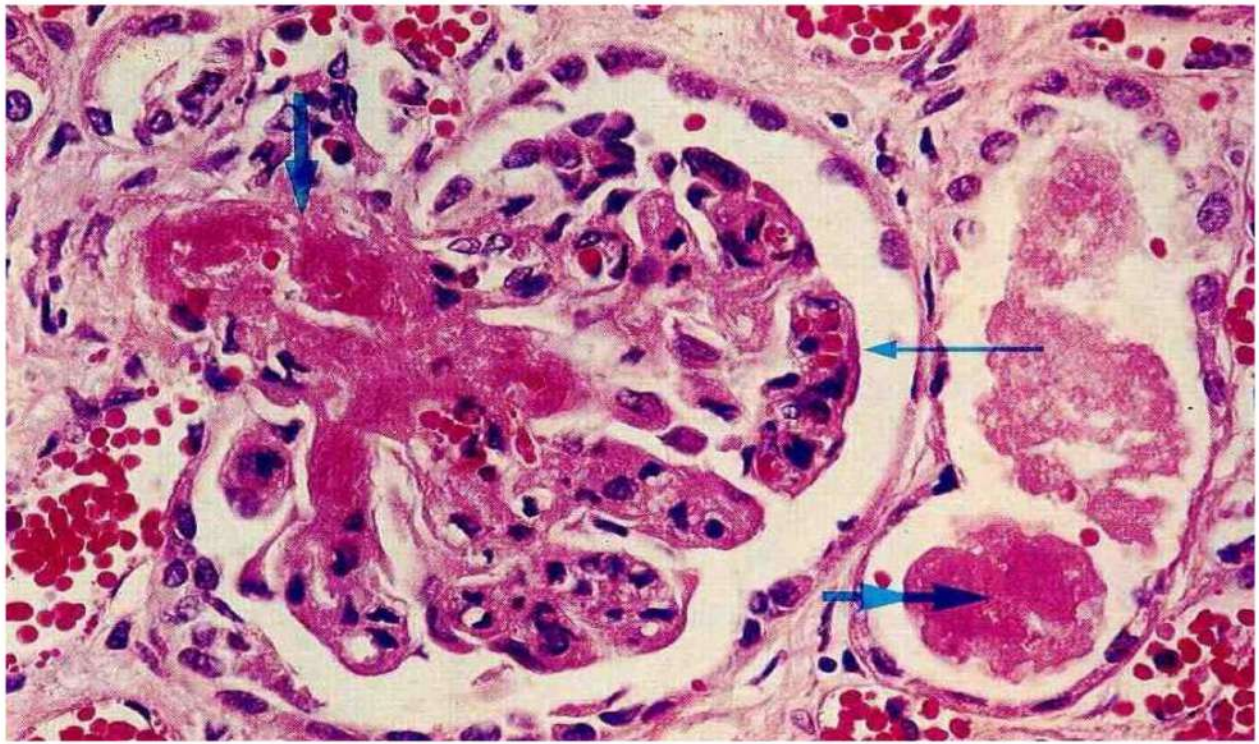
10.39 Hypertensive nephrosclerosis

Benign Nephrosclerosis (Hyaline arteriolosclerosis).

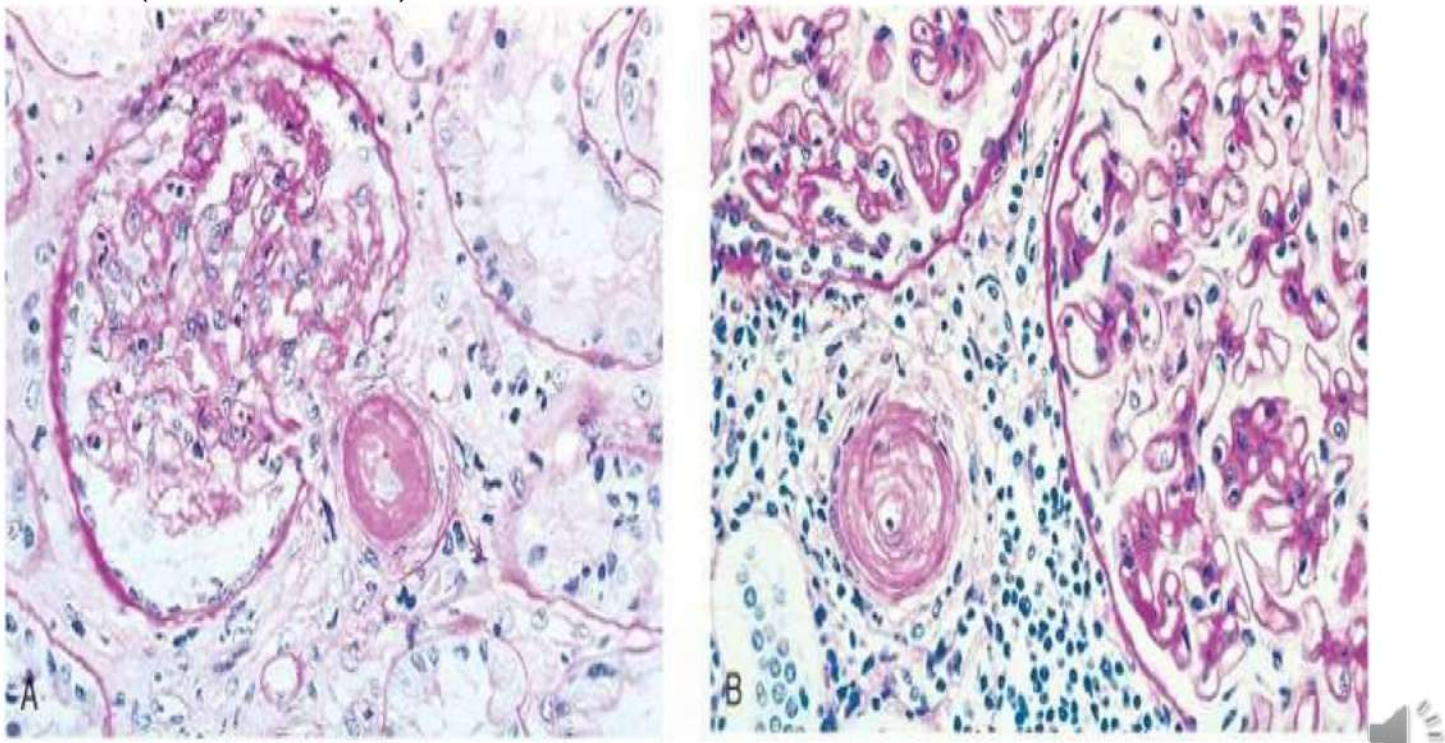
★Diffusely fine granular Kidney surface that resembles **grain leather.**

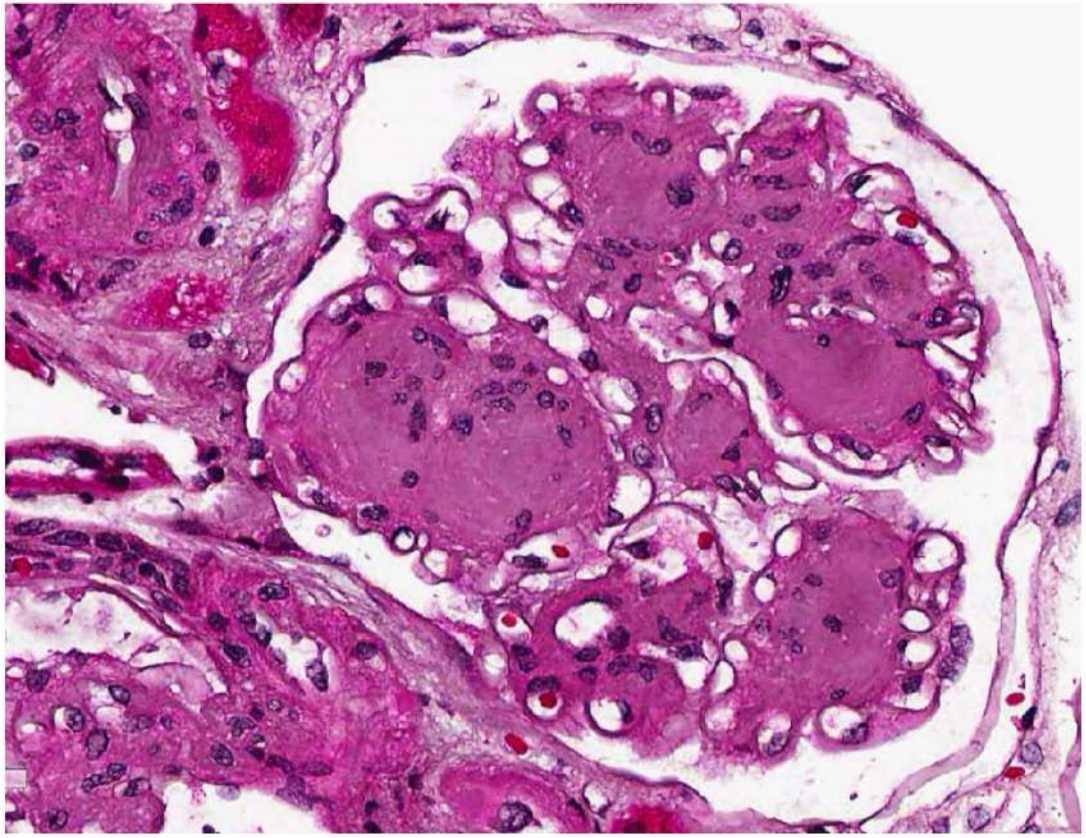
★**Both kidneys** were equally affected ★together weighed 200 grams.

Malignant hypertension: Kidney. ★The afferent arteriole (**thick** arrow) & the adjacent part of the glomerular tuft show **fibrinoid necrosis**, with deposition of homogeneous, granular eosinophilic fibrin. ★Dense protein cast is seen in the tubule (**double** arrow).



Malignant hypertension. A, Fibrinoid necrosis of afferent arteriole (PAS stain). **B,**Hyperplastic arteriolosclerosis (onion-skin lesion).





THROMBOTIC MICROANGIOPATHIES

- This term describes lesions seen in various clinical syndromes, characterized:
- (a) morphologically by widespread thrombosis in the microcirculation(DIVC)
- (b) clinically by microangiopathic hemolytic anemia, thrombocytopenia,&, in certaininstances RF.
- Common diseases that cause these lesions include:
- (1) Childhood Hemolytic Uremic Syndrome (HUS),
- (2) various forms of adult HUS,
- (3) Thrombotic Thrombocytopenic Purpura (TTP).

PATHOGENESIS OF THROMBOTIC MICROANGIOPATHIES

- Although clinically overlapping, HUS & TTP are pathogenically distinct. Central tothe pathogenesis of HUS is endothelial cell (EC) injury & activation, with resultant intravascular thrombosis; while the…
- TTP is now known to be caused by an acquired defect in proteolytic cleavage of von Willebrand factor (vWF) multimers

I. CHILDHOOD HUS

- 75% of childhood HUS cases follow intestinal infection with Shiga toxin- producing E. coli, such as occurs in epidemics caused by ingestion of infected ground meat (e.g., hamburgers) & infections with Shigella dysentery type I.
- **Pathogenesis**
- Shiga toxin is carried by neutrophils in the circulation, targeting the renal G EC , because they express the membrane receptor for the toxin.
- The toxin has multiple effects on the EC, including:
- **I. Cytotoxic, the toxin gains entery to the cells & directly causes cell death.**
- **II. (in the presense of cytokines, such as TNF) EC damage**
- **III. ↑adhesion of WBCs ↑ endothelin production & loss of EC nitric oxide (both favoring vasoconstriction) The resultant EC damage leads to thrombosis, most prominent in → interlobular arteries → afferent arterioles → G capillaries , as well as microangiopathy.**
- 10% of the cases of HUS in children are not preceded by diarrhea caused by Shiga toxin-producing bacteria.

MORPHOLOGY OF CHILDHOOD HUS

- In childhood HUS, there is fibrinoid necrosis, similar to lesions of classic thrombotic microangiopathy, with fibrin thrombi predominantly involving G &extending into arterioles & larger arteries in severe cases.
- Cortical necrosis may be present.

CLINICAL MANIFESTATIONS OF CHILDHOOD HUS

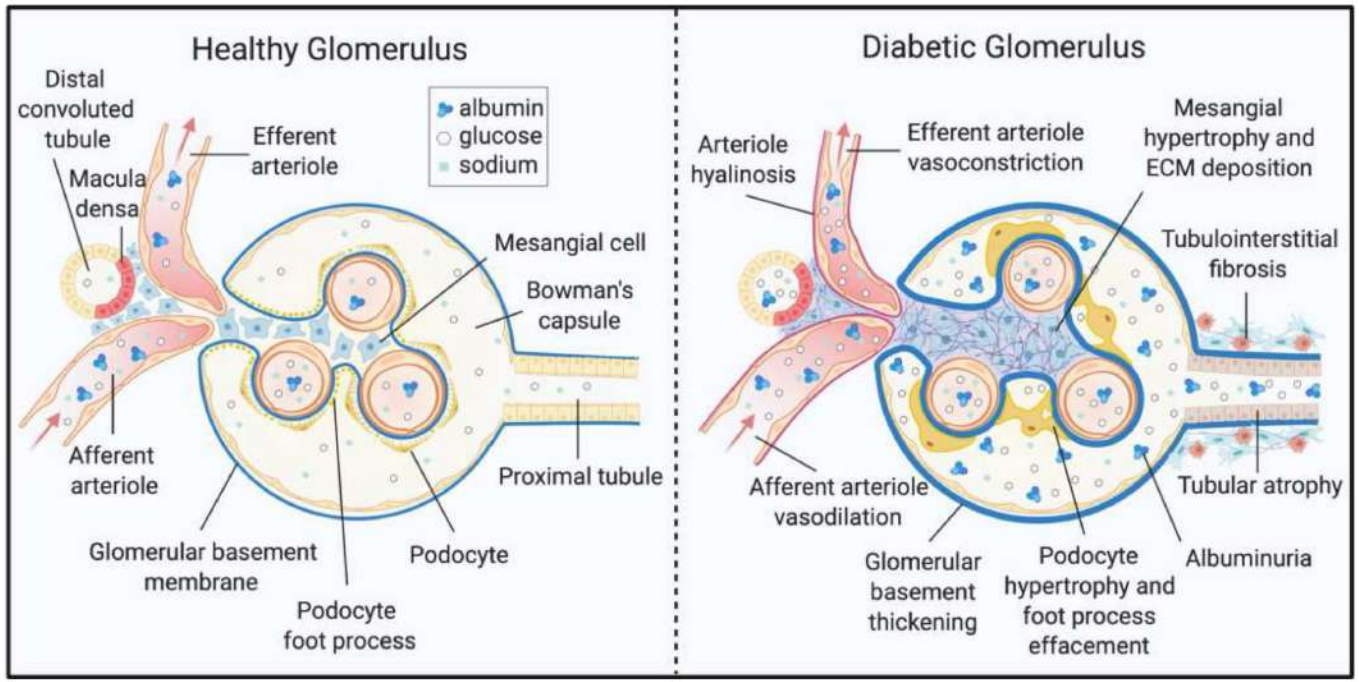
- 1-typical childhood HUS characterized by the sudden onset.
- 2-usually after GIT infection or flulike prodromal episode.
- 3- severe oliguria.
- 4-bleeding manifestations (hematuria) &
- 5- microangiopathic hemolytic anemia (DIC) .
- 6-This disease is one of the main causes of acute RF in children. However,if managed properly with dialysis, most patients with childhood HUS recover in a matter of weeks

DIABETIC NEPHROPATHY

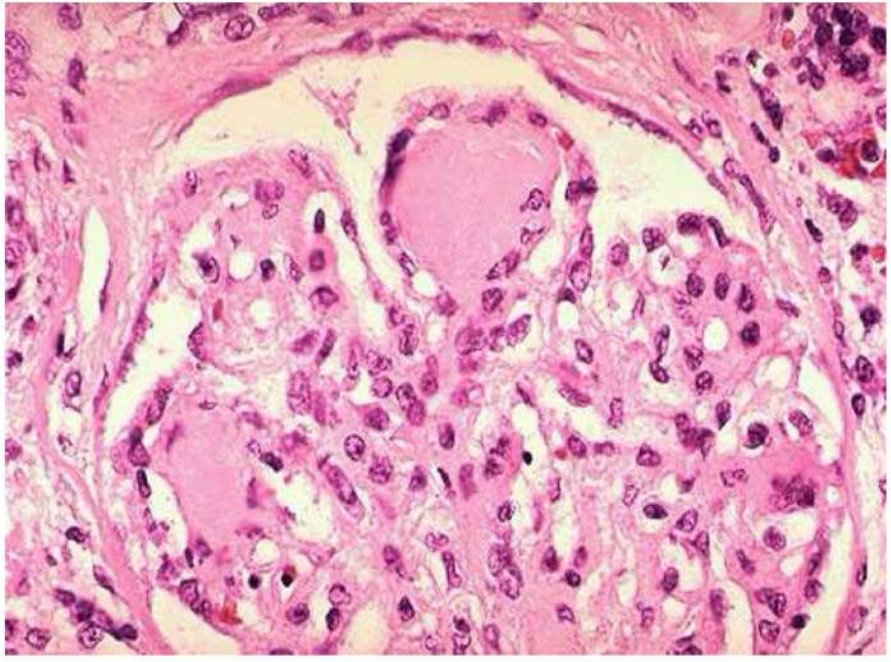
- is a common complication of type 1 and type 2 diabetes.
- Over time, diabetes that isn't well controlled can damage blood vessels in the kidneys that filter waste from the blood. This can lead to kidney damage and cause high blood pressure.
- High blood pressure can cause more kidney damage by raising the pressure in the filtering system of the kidneys.
- **Histopathology :**
- The characteristic histologic changes of DN includes thickening of glomerular and tubular basement membrane
- increase in mesangial matrix, Kimmelstiel-Wilson nodules sometimes combined with microaneurysms, exudative or hyalinosis lesions, capsular drop and afferent and efferent arteriolar hyalinosis.

Risk factors for developing Diabetic Nephropathy

- Poor control of blood glucose,
- Long duration of Diabetes,
- Presence of other diabetic complication,
- Ethnicity (Asian, Pima Indians),
- Pre-existing High BP,
- Family h/o of Diabetic Nephropathy,
- Family h/o Hypertension.


Healthy Glomerulus
Distal convoluted tubule
Macula densa
Efferent arteriole
albumin
glucose
sodium
Mesangial cell
Bowman's capsule
Afferent arteriole
Proximal tubule
Glomerular basement membrane
Podocyte
Podocyte foot process
Diabetic Glomerulus
Arteriole hyalinosis
Efferent arteriole vasoconstriction
Mesangial hypertrophy and ECM deposition
Tubulointerstitial fibrosis
Afferent arteriole vasodilation
Tubular atrophy
Glomerular basement thickening
Podocyte hypertrophy and foot process effacement
Albuminuria

This is nodular glomerulosclerosis (the Kimmelstiel-Wilson lesion) of diabetes mellitus. Nodules of pink hyaline material form in regions of glomerular capillary loops in the glomerulus. This is due to a marked increase in mesangial matrix from damage as a result of non-enzymatic glycosylation of proteins. This is one form of chronic kidney disease (CKD) with loss of renal function over time.



CYSTIC DISEASES OF THE KIDNEY

- Cystic diseases of the kidney are a heterogeneous group, which are important for several reasons: (1) Adult polycystic disease causes 10% of all CRF cases, (2) Cysts are common& often present diagnostic problems for clinicians, radiologists, & pathologists and ,rarely, they can be confused with malignant tumors.
- Types of cysts
- 1-Simple Cysts
- 2-Dialysis-associated acquired cysts
- 3-Autosomal Dominant (Adult) Polycystic Kidney Disease
- 4-Autosomal Recessive (Childhood) Polycystic Kidney Disease
- 5-Medullary Cystic Disease

SIMPLE CYSTS

- **Multiple or single**
- **1-5 cm in diameter**
- **translucent filled with clear fluid & lined by a gray, glistening, smooth membrane** composed of a single layer of cuboidal or flattened epithelium .
- **confined to the cortex.**
- **no clinical significance.**
- **Usually discovered incidentally or because of hemorrhage and pain**
- **Importance: to differentiate from kidney tumors**

CYSTS ASSOCIATED WITH CHRONIC DIALYSIS

- **Dialysis-associated acquired cysts**
- **in patients with renal failure who have prolonged dialysis.**
- **both cortex and medulla**
- **Complications: hematuria; pain**
- **Increased risk of renal carcinomas (100 times greater than in the general population)**
- **Occasionally, renal adenomas or even adenocarcinomas(RCC) arise in the walls of these cysts**

AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

- multiple bilateral cysts
- eventually destroy the renal parenchyma.
- Incidence (1: 500-1000) persons
- 10% of chronic renal failure.

PATHOGENESIS OF AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

- The disease can be caused by inheritance of one of at least two autosomal dominant **genes** of very high penetrance. In 85% to 90% of families, PKD1,the defective gene is on the short arm o chromosome 16. This gene encodes polycystin-1.
- (1)- PKD1: 85-90% (encodes polycystin-1)
- (2)- PKD2 :10-15% (encodes polycystin- 2).

CLINICAL MANIFESTATIONS OF AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

- **Clinical presentation :**
- **asymptomatic until the 4th decade**
- **Symptoms: flank pain , heavy dragging sensation, abdominal mass, hemorrhage, obstruction, Intermittent gross hematuria**

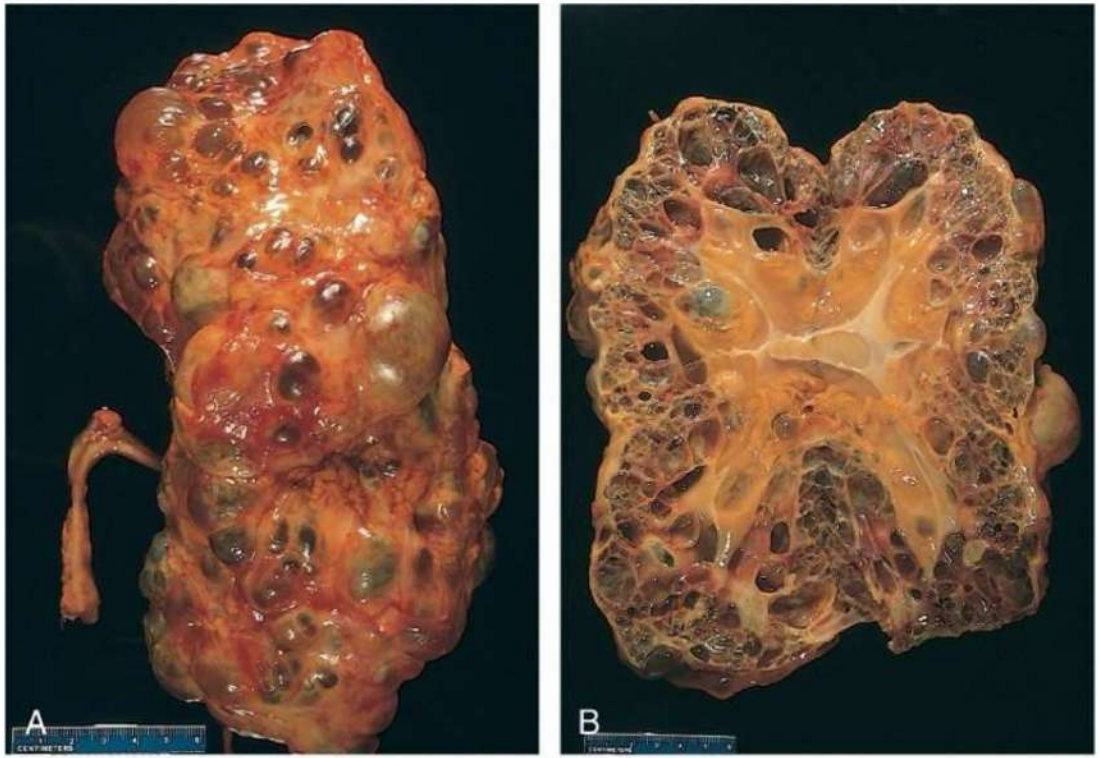
MORPHOLOGY OF AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

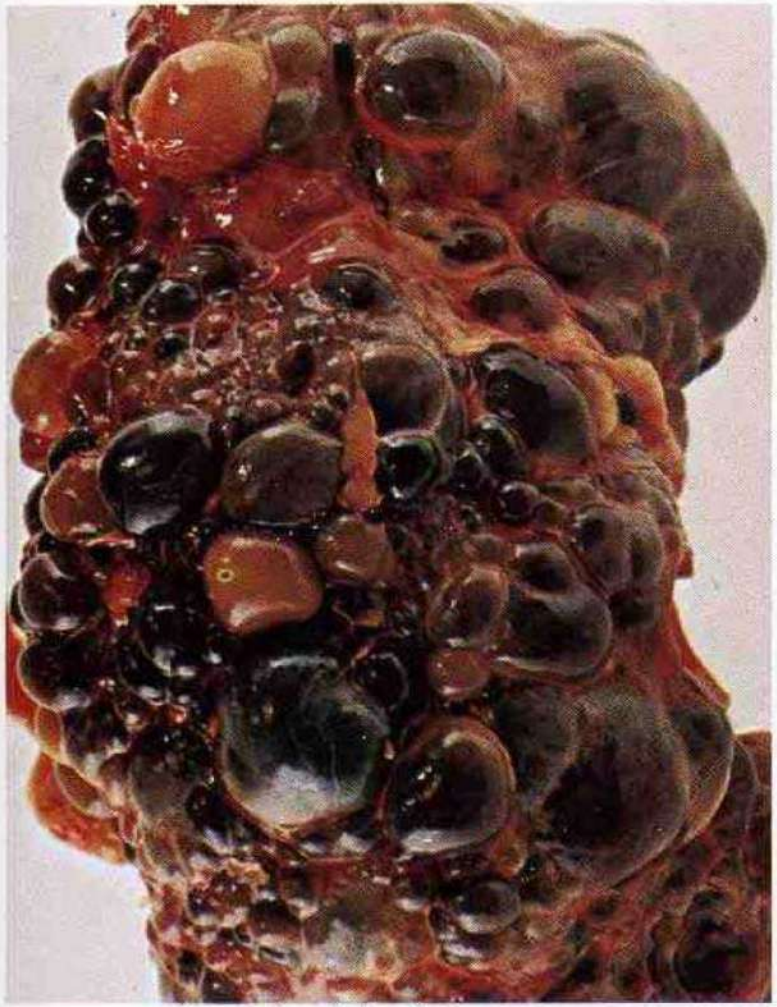
- **Grossly,**
- the **kidneys** may reach enormous size (weights of up to 4 kg for each kidney).
- These **very large kidneys are readily palpable** as abdominally masses.
- Both kidneys composed solely of cysts, up to 4 cm in ∅ with no intervening parenchyma.The cysts are filled with fluid, which may be clear, turbid, or hemorrhagic

COMPLICATIONS OF AUTOSOMAL DOMINANT (ADULT) POLYCYSTIC KIDNEY DISEASE

- 1. Most important complications are **uremia** & hypertension(which develops in 75% of cases)
- 2. **urinary infection.**
- **3. Saccular aneurysms** of the brain circle of Willis are present in **10% to 30% of patients, & these individuals have a high incidence of subarachnoid hemorrhage.**
- 4. Although the disease tends to progresses very slowly, but it is **ultimately fatal from uremia or hypertensive complications.**
- **Treatment is by renal transplantation.**

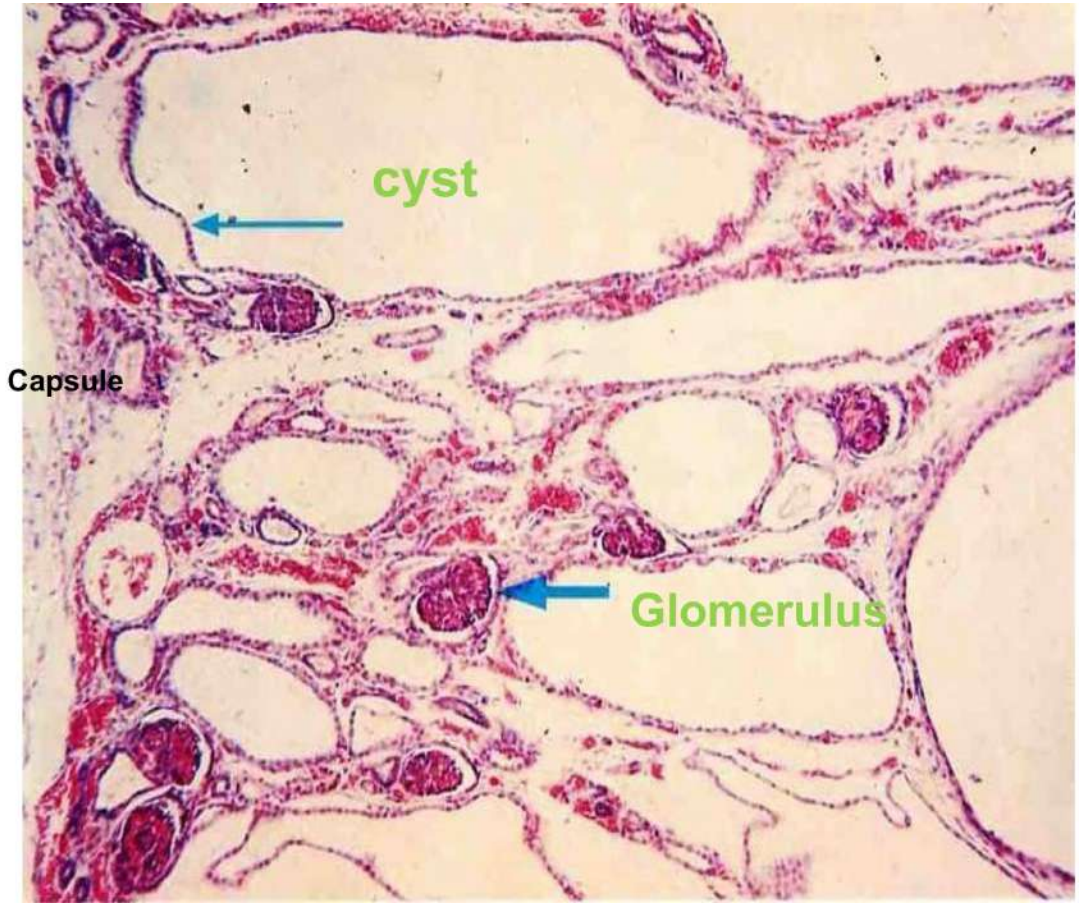
Autosomal Dominant (Adult) Polycystic Kidney Disease





10.4 Polycystic kidneys (adult type)

Polycystic Kidneys (Adult type).
massively enlarged **4000 g** kidney,**(Normal 300g),**consists of numerous small & large cysts bulging through the capsule.
★Some cysts contain clear urine, others are bluish-black from old hemorrhage



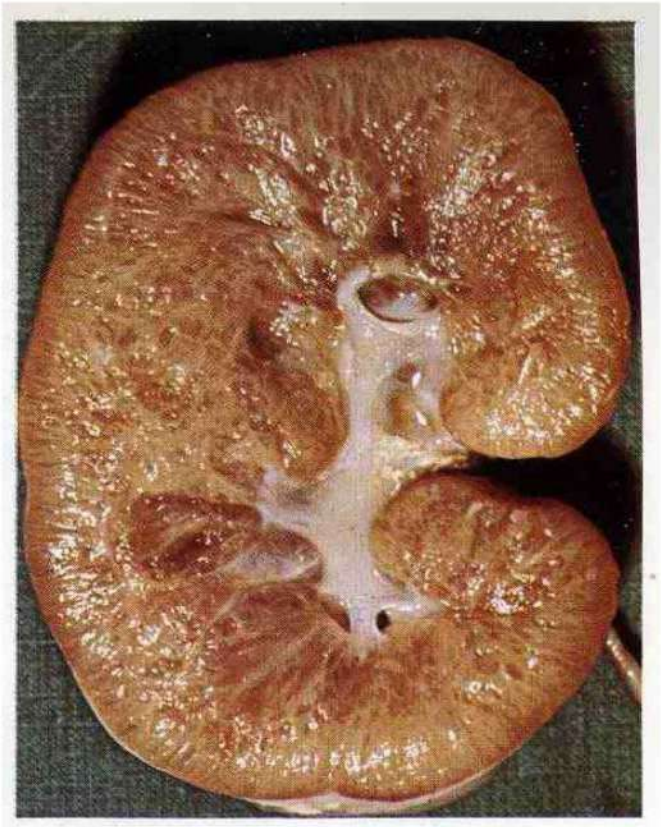
Adultpolycystic Kidneys X55.
Cortex of the kidney, with the capsule on the left.
No normal tubules are present, & instead, the kidney bulk consists of various size **cysts**, lined by flattened epithelium (**thin** arrow).
However, many normal looking **glomeruli (thick** arrow) remain between the cysts.

AUTOSOMAL RECESSIVE (CHILDHOOD) POLYCYSTIC KIDNEY DISEASE

- Autosomal recessive
- Rare ,1:20,000 live births.
- Depending on time of presentation & the presence of associated hepatic lesions, there are perinatal, neonatal,infantile, & juvenile subcategories have been defined;
- **all result** from mutations in a gene PKHD1,coding for a putative membrane receptor protein (fibrocystin)localized to chromosome 6p.
- Fibrocystin may be involved in the function of cilia in tubular epithelial cells .

MORPHOLOGY OF AUTOSOMAL RECESSIVE (CHILDHOOD) POLYCYSTIC KIDNEY DISEASE

- **Grossly**
- the disease is invariably (consistently)bilateral, with numerous small cysts in the cortex & medulla give the kidneys as sponge-like appearance .
- the medulla & cortex are completely replace by dilated & elongated channels & cysts.
- These cysts originating from the collecting tubules & are lined by cuboidal cells.
- **•In all cases (100%),** there are multiple cysts in the liver as well as proliferation of portal bile ducts.



10.3 Infantile polycystic kidneys

Autosomal Recessive (Childhood) Polycystic Kidney Disease.

★A bilateral renal defect which is **incompatible with life.**

★Sponge-like enlarged kidney from the presence of large number of small cysts, in the cortex & medulla which are abnormally, enlarged collecting tubules