PATHOLOGY OF THE UROPOIETIC SYSTEM
Tubulointerstitial diseases
Pathology of urinary bladder
Congenital and developmental disorders

• **Bilateral agenesis of kidneys**: kidneys and ureters absent, combined with other disorders - oligohydramnion, *Potter’s syndrome* (beak-like nose, low set ears, abnormally bent lower extremity.)
• **Unilateral agenesis**: boys, compensatory hyperplasia
• **Fixed dystopy**: caudal position of kidney, short ureter, renal a. from iliac artery
• **Ren migrans**: normal development, secondary descent, long („folded“) ureter, renal a. in normal position
• **Malformations**: merge of poles (e.g. horseshoe K.)
Renal cysts

• Acquired: due to scarring, mostly in adults
  – Simple: solitary or multiple; cortex - a few mm to 5-10 cm, flat epithelium, clear fluid, simulate tumor; innocent, may cause hypertension
  – Acquired polycystosis in hemodialysis: 0,5-2 cm
Solitary cysts of the kidney

Large thin-walled cyst. Midportion of right kidney

Renal cyst. Injected with contrast medium by percutaneous needle puncture (arrow)

Thick-walled cyst with calcification

Renal angiogram. Revealing evidence of solitary cyst in lower pole of kidney
Renal cysts

• Autosomal recessive polycystic kidney disease ("Infantile polycystosis"): ARPKD - autosomal rec. inheritance

Grossly: large kidneys (bilateral) with multiple tiny cysts (1-2 mm) - huge abdomen, pulmonary hypoplasia, oligohydramnion = Potter’s syndrome

Histology: elongated cysts from collecting tubules

Clinical course: - stillborn or die very soon (pulmonary or renal failure)

who survive infancy - disordered concentration ability, uremia, congenital hepatic fibrosis,
Renal cysts

- Autosomal dominant polycystic kidney disease ("adult polycystic disease"): autosomal dominant inheritance
  - PKD1 gene (chr. 16): mechanism of cysts formation unclear
  - Grossly: huge kidneys (1-3 kg), cysts up to 40 mm
  - Micro: cysts from all parts of nephron (flat epithelium), atrophy of renal parenchyma
  - Clinical course: 4th decade, flank pain, hypertension, hematuria, renal failure (end stage kidney)
  - Intracystic bleeding, inflammation, tumor
  - Accompanied by liver & pancreatic cysts, aneurysms of cerebral arteries, (mitral valve prolapse)
Polycystic kidney.
Surface aspect

Cysts

Polycystic kidney sectioned

Intravenous pyelogram. Bilateral polycystic disease
Tubulointerstitial diseases

*Tubules and interstitium - „intimal relation“ = tubular injury can also involve the interstitium and vice versa*

- Diseases affecting predominantly tubuli and interstitium.
- Different etiopathogenesis, but similar morphological changes.
- Glomeruli - relatively unaffected
Tubulointerstitial nephritis - pathogenesis

1. Direct damage
   - infections
   - drugs, toxins, heavy metals

2. Immune mediated (infections, drugs)
   - Hypersensitive reaction
   - Immune complexes
   - Antibody against TBM
   - T lymphocytes (local and circulating lymphokines)

3. Metabolic
4. Congenital tubular diseases
5. Mechanical
6. Hemodynamic
Infectious tubulointerstitial nephritis

The commonest type of tubulointerstitial diseases.

Etiology: bacterias, viruses, parazites, fungi

-bacterial tubulointerstitial nephritis (TIN) - *(pyelonephritis)*

Course:

• acute

• chronic
Acute pyelonephritis

*bacterial suppurative inflammation of the K and the pelvis*

important manifestation of urinary tract infection (UTI)
- almost always assoc. with infection of the lower UT  !!!
ETI: Escherichia coli, Proteus, Enterobacter, Klebsiella

2 routes of inf:

**ascending** (from lower UT) *most common*
**hematogenous** (far less common) by bloodstream (sepsis, endocarditis)
Acute pyelonephritis

**Ascending**: bacteria from rectum/perineum into the urethra = **urethritis** (F:M = 10:1), after instrumentation (F:M-same) Bact. - bladder. Normally is B cleared by micturition

**Retention of urine** = conditions for ↑ bact growth in B

- cong. disorders, stones, gravidity, prostate, B dysfunction, uterine prolapse, DIA, tumors → urocystitis

- From bladder into the ureter- **vesicoureteral reflux** (due to incompetence of the vesicoureteral orifice)

  **Children** congenital incompetence - short intravesical portion

  **Adults** after inflammation, stone passage, flaccid bladder

- Infected urine → ureter → pelvis (pyelitis)

  B. to renal parenchyma through collecting ducts (**intrarenal reflux**) or by ruptured calyces into the interstitium
Acute pyelonephritis

**Grossly (ascending):** unilateral x bilateral K (edema), raised
long cortical and medullar yellow abscesses, reddish pelvis

**Grossly (hem.):** bilateral af., small cortical abscesses
• **Histology (asc.):** LEU in interstitium and in tubules = tubules melted by inflammation – abscesses

• **Histology (hemat):** bacteria in G - abscesses in interstitium

• **Complications:** - necrotizing papillitis (DIA)
  - pyonephros (pyonephrosis) - pelvis, calyces filled by pus
  - perinephritic abscess (subcapsular)
  - paranephritic abscess (pus in perinephric fat tissue)
  - urosepticemia (renal failure + septicemia) bilateral pyelon.

• **Clinical course:** sudden onset, costovertebral angle pain, fever, chills, dysuria, bacteriuria, pyuria, urosepsis
Possible routes of kidney infection

A. Hematogenous
B. Ascending (ureteral reflux)

Predisposing factors in acute pyelonephritis

- Anomalies of kidney and/or ureter
- Calculi
- Obstruction at any level (mechanical or functional)
- Diabetes mellitus
- Pregnancy
- Instrumentation
- Neurogenic bladder

Acute pyelonephritis.
Radiating yellowish-gray streaks in pyramids and abscesses in cortex; moderate hydronephrosis with infection; blunting of calyces (ascending infection)

Acute pyelonephritis. With exudate chiefly of polymorphonuclear leukocytes in interstitium and collecting tubules

Chronic pyelonephritis.
Thinning of renal parenchyma. With wedge-shaped subcapsular scars; blurring of corticomedullary junction; dilated, fibrosed pelvis and calyces seen in many but not all cases of chronic pyelonephritis

Chronic pyelonephritis. Areas of lymphocytic infiltration alternating with areas of relatively normal parenchyma
Light microskopy

Interstitial edema
Infiltration by PMN
Abscesses
Renal carbuncle and perirenal abscess

- Staphylococcus species
- Confluence of smaller abscesses
Chronic pyelonephritis and reflux nephropathy

- interstitial inflammation + scarring of the renal parenchyma + scarring and deformity of the pelvicalyceal system
- chron. obstructive P (reccurent ac inflammations -stones, ureteral obstruction, prostate, obstruction of the urethra)
- chronic reflux-associated P (vesicoureteral reflux) - infection?
- Grossly: unilateral x bilateral /// diffusely x in patches
diffusely = small, contracted K, in patches = cortical flat scars („U-shaped“) + blunted calyces
- scarring of the pelvicalyceal system = deformation
  Obstructive = whole K, reflux = polar scarring
• **Histology:** - uneven interstitial fibrosis + inflammation
  - tubular dilation, epithelial atrophy (thyreoidisation)
  - arteriosclerosis (hypertension)
  - inflammation and fibrosis of calyceal mucosa and wall
  - periglomerular fibrosis, glomerulosclerosis

• **C. course:** - progressive deterioration of renal functions
  - loss of concentrating ability
  - arterial hypertension
  - US = changes of size and shape

*Chronic pyelonephritis is important cause of chronic renal failure!!!*
Chronic pyelonephritis

Flat scars
Dilatation of pelvis
Deformation of calyces
Microscopy

Interstitial fibrosis
Atrophy of tubuli and casts (thyroid-like)
Periglomerular fibrosis
Vascular nephrosclerosis
TBC of kidney

Route: **Hematogenous**

Forms:

- Milliary
- Chronic kaseous
TBC of the kidney
Viral nefritis

- herpes simplex
- cytomegalovirus
- arbovirus
- Hanta virus
Non-infectious tubulointerstitial nephritis-nephropathy

- metabolic
- toxic
- ischemic (acute tubular necrosis)
- immune
- irradiation
Toxic tubulointerstitial nephritis

Mostly direct damage by toxins

1. Acute tubular necrosis (ATB, cytostatics, heavy metals, mushrooms – phaloidin)
2. Prolonged exposure, less toxic agents - chronic tubulointerstitial nephritis
Acute tubular necrosis (ATN)

- Destruction of tubular cells = ARF + oliguria < 400 ml
- 2 causes: **ISCHEMIC** and **TOXIC**
- **Ischemic** hypoperfusion (shock), septicemia, pancreatitis trauma - similar - crush sy (myoglobinuria), mismatched transfusion
- **Toxic**: heavy metals (mercury), ethyleneglycol, herbicids, solvents, ATB (gentamicin)

**Patogenesis**: similar - **tubular necrosis = oliguria** (blockage by necrotic debris, vasoconstriction (renin-ang, endothelin), tubular fluid leakage into the interstitium - edema = tubul. collapse, inflammation (leukocytes)
After a week = regeneration of tubular cells - tubules with undestroyed basement membranes (complete regeneration)

Clinical course: 3 stages
- initiating phase lasting 36 hrs. (inciting event = ischemia) decline in urine output, increased blood urea nitrogen
- maintenance phase (2.- 6. day) urine 50-400 ml/24 hrs. = Threat of uremia, water overload - DIALYSIS !!!
- recovery (regeneration) urine volume 3 litres /24 hrs. Threat of dehydration, mineral dysbalance, infection

Finally: - GF normalize in 2-3 months, concentrating ability in 6 months

Survival 90 - 95 %
• Grossly: pale cortex, dark medulla

• Histology: ischemic - necrosis of segments of proximal and distal tubules. Histologically difficult to discern !!!

Rupture of tubular basement membranes = tubulorrhexis.

- necrotic material (myoglobin, Hb) + TH protein = casts in the distal and collecting tubules
- interstitial edema, inflammation (lymphocytes, leukocytes)

Toxic - similar necrosis of proximal tubules, Tubular basement membranes are spared !!!

- sometimes calcification of necrotic cells
Microscopy
Chronic toxic
tubulointerstitial nephritis

Analgesic nephropathy

a few years lasting hyperconsumption of analgesics (2-3 kg in 2-3yrs - phenacetin, aspirin, acetaminophen...) = *chron. TIN + papillary necrosis*

- metabolits are inhibiting vasodilation = papillary ischemia

**Histology:** necrotic papillae **without** leukocytic reaction, interstitial scarring, tubular atrophy, inflammation and fibrosis
• Analgesic nephropathy

**Grossly**: contracted kidneys with yellowish brown necrotic papillae (into the pelvis = hydronephrosis)

**Clinical course**: chronic renal failure, hypertension, increased incidence of urothelial carcinoma (pelvis, bladder)
Papillary necrosis
Immune mediated TIN

• Acute TIN
  – Drugs - penicillin, sulfonamids, analgesics
  – Parainfectious
  – Idiopathic

Clinically: begins after 2 weeks, fever, exantema, eosinophilia, hematuria, proteinuria, oligouria, renal failure
Clinical and laboratory features

- History of drug exposure
- Fever
- Eosinophilia
- BUN elevation
- Renal enlargement
- Oliguria
- Hematuria

Ureter, low power. Extensive edema resulting in marked narrowing of lumen; cellular infiltration in submucosa and in musculature (H and E stain)

Kidney, low power. Prominence of interstitial tissue due to clusters of cells; necrotic tubules in upper right corner (H and E stain)

Kidney, medium power. Uniform interstitial edema and cellular infiltration, chiefly of lymphocytes; tubules relatively normal except necrotic tubules at upper left (H and E stain)

Ureter, high power. Cluster of eosinophils in submucosa adjacent to band of smooth muscle (H and E stain)
Microscopy

- Interstitial edema
- Lymphocytic infiltration
- May be eosinophilism PMN
- Tubular cell dystrophic, necrotic, tubulitis
- Glomeruli normal
Metabolic TIN

A. Urate nephropaty – gout kidney
   hyperurikemia

B. Hyperkalcemic nephropathy – nephrocalcinosis
   Metastatic and dystrophic

C. Hypokalemic nephropathy
Hypokalemic (potassium-depletion) nephropathy

Etiologic conditions
- Gastrointestinal loss of K
  - Vomiting
  - Anorexia nervosa
  - Diarrhea
  - Islet cell adenoma
- Excessive catharsis
- Frequent enemas
- Fistulas
- Malabsorption syndrome
- Sprue
- Ureterosigmoidostomy
- Villous adenoma of colon
- Excessive steroids
  - Primary hyperaldosteronism
  - Cushing syndrome
  - Steroid therapy
- Urinary loss of K
  - Renal tubular acidosis
  - Fanconi syndrome
  - Cystinosis
  - Chronic pyelonephritis
  - Other chronic renal disease
- Diabetes mellitus
- Excessive diuretic therapy; some weight reduction pills

Associated clinical conditions
- Focal myocarditis
- Muscular weakness or paralysis
- Ileus, gastric secretory alterations
- Impaired urinary concentrating ability
  - Polyuria
  - Polydipsia
  - Mild proteinuria and cylindruria may be present
  - Impaired bicarbonate excretion; alkalosis
  - Paradoxic aciduria
  - Sodium retention (urinary ammonia may be increased)

Extensive vacuolization of renal tubules in hypokalemic nephropathy (H and E stain, X250)
**Calcium nephropathy**

**Etiologic or associated conditions**
- Hypervitaminosis D
- Milk-alkali syndrome
- Hyperparathyroidism
- Hyperthyroidism
- Sarcoidosis
- Malignancies, with or without bone involvement
- Bone dissolution; disuse atrophy; Paget disease
- Idiopathic (in infants)

**Clinical findings**
- Decreased urinary concentrating ability
- Polyuria Polydipsia
- Increased sodium and chloride excretion
- Potassium reabsorption and acid excretion may be impaired
- Hematuria and pyuria may occur
- Mild proteinuria often present
- In severe cases, azotemia
- Anorexia
- Vomiting
- Stupor
- Coma

**Calcium nephropathy**, Periglomerular fibrosis and varying degrees of glomerular hyalization; multifocal calcium deposits (arrows); intratubular protein material simulating thyroidization of pyelonephritis (H and E stain, ×100)

**Renal tubule**, Intraluminal accumulation of calcium and cellular debris (PAS stain, ×400, enlarged)
Myelomatosis with renal involvement

Bone marrow biopsy. Characteristic malignant myeloma cells (may also be found occasionally in circulation)

Presence of abnormal proteins in serum (y spike); also hypercalcemia

Globulins Albumin

Bence Jones protein in urine in 60% of cases (precipitates at 45 to 60°C, redissolves at boiling, and reprecipitates on cooling to 60 to 55°C)

55°C  100°C  55°C

Anemia. Rouleau formation; increased blood viscosity

Myeloma kidney. Many dilated tubules containing eosinophilic amorphous casts; atrophy of epithelium; giant cell formation

Diagram of electron microscopic findings in glomeruli. Epithelial (Ep) and endothelial (En) cells and mesangium (M) show changes often seen in other proteinuric conditions; focal loss or fusion of foot processes; basement membrane (Bm) thickened but free of deposits; occasional cell on luminal side suggestive of plasma cell transformation with Russell bodies (R)
Congenital tubulopathias

rare diseases
Manifested from childhood

A. systemic metabolic changes
   enzymopathy
   - oxalosis
   - cystinosis
   - glykogenosis

B. primáry renal diseases
   - Renal glykosuria
   - aminoaciduria
   - cystinuria
Diabetic nephropathy

- **Vessels:** - accelerated ARTS (plaques reach aa. arcuatae)  
  - hyalinne arteriolar sclerosis of the affer. and effer. aa.
- **Glomerular lesion:** - *thickened BM* (electron microscopy)  
  - *diffuse glomerulosclerosis* (th. BM + inc. mesang. matrix)  
  - *nodular Gsclerosis* (Kimmelstiel-Wilson lesion) ball-like nodules of laminated matrix arising within the mesangium
- Glomerulosclerosis - proteinuria, NS, later renal failure  
  - glomerulosclerosis = ischem =scarring=cortex granulation
- **Tubulointerstitial lesion:** - incr. disposition to repeated inflammations (pyelonephritis) + necrosis of the papillae  
  - storage of glykogen in proximal tubules - *Armani cells*
Diffuse intercapillary glomerulosclerosis. PAS stain

Diffuse intercapillary glomerulosclerosis. H and E stain

Nodular intercapillary glomerulosclerosis. PAS stain

Capsular deposits. H and E stain

Arteriolsclerosis. Hyalinization of efferent and afferent arteriole; aniline blue stain

Armanni-Ebstein cells in renal tubules. H and E stain
Diseases involving blood vessels

- **Renal artery stenosis**: - elderly (ARTS), younger patients fibromuscular hyperplasia (dysplasia) = hypertension
  Long term stenosis = atrophy
- **Kidney infarction**: trombotic embolism (from heart), atheroma plaque material from aorta, trombosis (PAN)
- **Arteriosclerotic nephrosclerosis**: ARTS aorta = branches ren. artery in parenchyma = „V“ shaped scars
- **Benign nephrosclerosis**: benign hypertension
  Grossly: symmetrical atrophy, finely granulated surface
  Histology: hyalinne thickening of small arteries, arterioles
  = **hyalinne arteriolarosclerosis** (insudation of plasma proteins into the wall = production of hyalinne matrix)
thickening = stenosis = ischemia = atrophy (collapse and obliteration G) = granulated surface, tubular atrophy, interstitial fibrosis

**Clinical course:** slight functional impairment, NO uremia

- **Malignant nephrosclerosis:** malignant hypertension (diastolic BP 110)
  fibrinogen into the wall = endoth. injury = *fibrinoid necrosis*
  intimal hyperplasia = stenosis (ischemia)
  Ischemia (renin-ang.-aldos) = elev BP= mal. hypertension

**Grossly:** petechial hemorrhages, granulated K, shrunken K

**Histol:** - larger aa - concentric proliferation of intimal smooth m. cells (onion skin app.) = **hyperplastic arteriolar sclerosis**
  - **arterioles** - fibrinoid necrosis (inflammation= arteriolitis)
  - **glomeruli** - segmental necrosis, crescents, obsolete G
• **Clinical course:**

- papilledema (visual impairments)
- encephalopathy (headaches, nausea, vomiting)
- renal failure (inc. proteinuria, hematuria)
Normal size kidney.
Only slight granulation, in hypertension of relatively short duration

Markedly contracted, granular kidney. In long-standing essential hypertension

Cut surface of kidney in advanced nephrosclerosis

Fibrosis and hyalinization of preglomerular arteriole.
Stenosis of lumen (wall cut on bias); glomerulus still unaltered (×160)

Obliterative fibrosis and hyalinization (sclerosis). Of small intrarenal artery (×160)

Obliterative fibrosis and hyalinization (sclerosis). Of intrarenal artery of moderate size (×160)
Onset of malignant phase after relatively short benign phase. Kidney of normal or large size, with little granulation and multiple small hemorrhages.

Malignant phase superimposed on long-standing benign phase.

Obliterative, endarterial fibroelastosis. Of intrarenal artery of moderate size, usually associated with chronic pyelonephritis but more commonly with malignant phase of hypertension (×160). "Onion-skinning".

Early stage of malignant hypertension. Subendothelial deposit of fibrin in preglomerular arteriole (×160).

Later stage. Necrosis of wall of preglomerular arteriole (×160).
Systemic vasculitis

- **Polyarteritis nodosa**: aa interlobulares, aa. arcuatae
  - fibrinoid necrosis, inflammation, trombosis = infarctions
  Glomeruli are not affected
- **Polyangiitis microscopica**: interlobular arteries, affer. art.,
  glomerular capilaries - necrosis, **ANCA +**
  Focal segmental necrotizing glomerulonephritis (crescents)
- **Wegener granulomatosis**: morphology - see above
  periglomerular granulomas in addition, **ANCA +**
- **Alergic granulomatosis (Churg-Strauss syndrome)**
- focal segm. necrotizing glomerulonephritis + eosinophils
Renal stones (nephrolothiasis)

- **Urolithiasis**: calculus in urinary coll. syst. (*nephro-*-, ....)
  - 75% calcium oxalate (calcium phosphate) - hard, dark
  - 15% magnesium ammonium phosphate - white
  - 10% uric acid or cystine - round, smooth-surfaced, brown

- **Causes**: often unclear, most important (*calcium stones*)
  1. increased urine concentration of the stones constituents = exceeding their solubility in urine (*hypersaturation*) (e.g., idiopathic hypercalciuria, hypercalcemia...).
  2. Persistent alkaline urine due to UTI (*Proteus vulgaris*) - magnesium ammonium phosphate stones
  3. High uric acid level in urine (gout, cell break up...) or excretion of acid urine (pH under 5.5) - uric acid stones
  - defective renal transport of cystine - cystine stones
Renal stones (nephrololothiasis)

- Supporting effects of stones formation: dehydratation, bacteria colonies, epithelial desquamation, calcification = nidi for stones formation
- Morphology: - 80 % unilateral (r. pelves, calyces, bladder)
  - 20 % bilateral
Number, shape and size varies (solitary x multiple), mm - cm, smooth, jagged, „staghorn“
- Clinical course: - large stones often asymptomatic or disordered outflow of urine
  - small stones into the ureter = hydronephrosis (dilation and infection), = renal/ureteral colic
  = hematuria
Hydronephrosis

- **Hydronephrosis** = *dilation of renal pelvis and calyces + atrophy of the renal parenchyma due to obstruction to the outflow of urine* (obs. insidious x sudden, complete x incom)

Obstruction at any level of the UT (renal pelvis - urethra)
- obstruction below pelvis = **hydroureter** (dilation of the ureter)

- **C**: Congenital - atresia of the uretra, - valve formations in either urethra or ureter, aberrant r.art. compressing ureter, renal ptosis with torsion or kinking of the ureter

- **Acquired** - „*foreign bodies*“ (stones, necrotic papila, blood coagulum), - *tumors* (prostate, bladder, ureter, uter.cervix, retroperit, rectum), - *inflammation* (prostate, retroperitoneal fibrosis, postinflammatory stricture of the ureter)
- neurogenic (bladder paralysis), - pregnancy (mild, rev.)

- **Bilateral HN** (obstruction below the level of the ureters)
- **Unilateral HN** (obstruction at the ureter or above)

**Clinical c.:** - *sudden bilateral obstr* = ARF without dilation
  - *rapid unilateral obs* = GF declined (in aff. K), fce normal
  - *incomplete (intermitent) obs* = dilation

After obstruction GF persists some time = urine increases pressure in pelvis

**Grossly:** long term obstr. = dilation of pelvis +(ureter), flat papilae, atrophied K parenchyma

**Micro:** tubular dilation, interstitial edema, later atrophy of tubular epithelia, interstitial fibrosis, glomerulosclerosis

HN incr. disposition to kidney infection = pyelonephritis !!!!
Etiology

Spinal cord
- Syphilis (tabes dorsalis)
- Pernicious anemia (subacute combined sclerosis)
- Tumors
- Trauma (transection)
- Hematoma
- Syringomyelia
- Multiple sclerosis
- Arteriosclerosis
- Poliomyelitis
- Transverse myelitis
- Paralysis agitans
- Disc herniation

Cauda equina
- Tumors
- Trauma
- Spina bifida

Nerves and/or nerve plexus
- Trauma
- Accidental
- Surgical
- Diabetes
- Neuropathy
- Infections
- Scarlet fever, etc.
- External pressure
- Fetal head
- Neoplasms

Sympathetic trunk

Key
- Red: Sympathetics
- Blue: Parasymp.
- Black: Sensory
- Green: Somatic

Aortic (intermesenteric) plexus

Spastic ("Christmas tree") bladder with sacculation

Pelvic splanchnic nerves (nervi erigentes)

Inferior hypogastric and vesical plexuses

Pudendal nerves

Flaccid, distended, atonic bladder with fine trabeculation
The urinary bladder

- Inflammations
  - Infectious (enterobacteria) (hemorrhagic, ulcerative, suppurative, pseudomembranous)
  - Granulomatosus
  - Eosinophilic
  - Interstitial chronic (Hunner’s ulcer)
  - Malakoplakia

- Reactive changes
  - Squamous metaplasia
  - Intestinal m.
  - hyperplasie
Cystitis
Diverticula of the bladder
Tumors of the ureter and urinary bladder

Similar histological type like in pelvis (urothelial Ca)

- **Ureter** = hematuria, obstruction (HN)
- **Bladder**: 6.-7. decade, increased risk = smoking, industrial exposure to azo dye, exposure to **beta-naphtylamine**, chronic cystitis, drugs (cyclophosphamide, analgesics), radilation therapy
- **Grossly**: flat or papillary (exophytic growth), later invasion into the wall of the bladder
- **Clinical course**: hematuria, later obstruction of the ureters, metastases

*Prognosis depends on histologic grade and depth of invasion !!!*
Tumours

Flat urothelial lesions with atypia (Dysplasia, CIS)
Papillary urothelial neoplasma
  papilloma, inverted papilloma, PUNLMP,
  noninvasive carcinoma (Low grade, high grade)
Invasive urothelial neoplasma
Tumours

- Squamous ca
- Adenocarcinoma
- Neuroendocrine neoplasma
- Mesenchymal (rhabdomyosarcoma)
Glomerulonephritis
glomerulopathy
Glomerular diseases- glomerulopathy

• Glomerular damage of whatever etiology
• As a result of
  a. Inflammation
  b. Vascular changes
  c. Metabolic diseases
  d. Hereditary diseases
Classification

1. Primary glomerulonephritis and glomerulopathy
2. Glomerulonephritis in systemic disease (SLE, IgA glomerulonefphritis, bacterial and parasititis diseases)
3. Glomerulopathy in vascular diseases (vaskulitis and non-inflammatory vasculopathy – vascular nephrosclerosis, HUS)
4. Glomerulopathy in metabolic diseases (diabetes, amyloidosis, dysproteinemia)
5. Hereditary glomerulopathy
6. Others
7. Chronic sklerosing glomerulonephritis
8. Glomerulopathy in transplant kidney
Kidney biopsy

• Since 1951

Indication:
  a. Clinically unknown diseases
  b. Clinically suspicious diseases
  c. Clinically known diseases
Kidney biopsy – evaluation

Representative samples - minimum of 10 glomeruli.

A. Light microscopy
   - glomeruli
   - tubuli and interstitium
   - vessels

B. Immunofluorescence
   - type of positivity (IgA, IgG, IgM, C3, C1q, fibrinogen, kappa, lambda
   - localization (mesangial, loop, combined)
   - type of positivity (linear, granular)

C. Electron microscopy
Morphologic patterns og glomerular damage

- Alteration (necrosis, rupture of GBM)
- Exsudation (PMN, lymphocytes, macrophages)
- Proliferation (epithelium, endothelium, mesangial cells)
- Hyalization (insudation of plasma proteins)
- Sclerosis (increase collagenous matrix)
- Fibrosis
- Thickening of capillary loops
Mechanisms of glomerular damage

A. *Immune damage*
- Circulating immune complexes
- in situ immune complexes
- Antibodies against GBM
- Anti-neutrophil autoantibodies (ANCA)
- antibodies against glomerular cells

B. *Non–immune damage*
- ischemia
- hyperfiltration
- Congenital alteration of glomerular tissues
- Damage of podocytes and a loss of GBM integrity
Glomerulonephritis

*Immune related non-suppurative inflammation of glomeruli*

Mechanisms:

1. Immune complexes formation
2. Inflammatory cells
   - PMN, macrophages, lymphocytes, platelets destičky
3. Inflammatory mediators
Classification according damage extent

- Focal X segmental
- Global X Diffuse
Clinical signs of glomerular diseases

- Asymptomatic proteinuria
- Nephrotic syndrome
- Asymptomatic hematuria
- Recurrent and persistent hematuria: (long term macro or micro hematuria without proteinuria (or mild), no other symptoms of nephrit syndrome
- Acute nephritic syndrome
- Rapidly progressive syndrome (hematuria, proteinuria and rapid progressive loss of renal functions (renal failure)
- Chronic nephritic syndrome **Slowly developing uremia:** chronic G injury = sclerosis and hyalinization of G
Nephrotic syndrome

- Heavy proteinuria (more than 3.5 g/24h)
- Hypoalbuminemia
- Edema
- Hyperlipidemia
- Lipiduria
Nephrotic syndrome

• Minimal change disease („lipoid nephrosis“) 15%
• Membranous GN 30%
• Focal segmental glomerulosclerosis 30%
• Membranoproliferative GN (type I-III) 5%
• Systemic disorders (amyloidosis, SLE, DM...) 20%
Nephritic syndrome

- Hematuria
- Oliguria, anuria
- Water+ natrium retention
- Edema
- Hypertension
- Hyperkalemia
Uremia (chronic renal failure)

• Pericarditis
• Pleuritis
• Gastroenteritis (vomitus, diarrhea)
• Treitz colitis (pseudomembranous)
• Pancreatitis
• Brain edema
• Anemia
• Metabolic acidosis
• Renal osteopathy
Primary glomerulonephritis and glomerulopathy
Acute diffuse proliferative glomerulonephritis (postinfectious)

- Mesangial and endocapillary cellularity, narrowed capillary lumens, mostly infiltration of PMN
- Postinfestious etiology (beta-hemolytic streptococci, rarely staphylococci, viruses, parazites, infective endocarditis, SLE

- **Macro:** large, pale kidneys with punctuate bleeding
- **Micro:** large, hypercellular G (mes, end, leu...)
- **Immuno:** granular posit (IgG and C3 in mes and BM)
- **EM:** GBM - subepithelial deposits („humps“)
Clinical sy

- Begins 1-2 weeks after infection
- Acute nephritic sy
- Rarely asymptomatic
- Serologic evidence: ASLO, a decrease of complement - C3 C2,C4
- Prognosis resolves after several weeks, rarely progressive renal failure
Light microscopy

- Enlarged glomeruli
- Narrowed capillaries
- Increased cellularity
Immunofluorescence

- Granular C3 deposits in capillaries, mesangium
- Granular IgG, less frequently IgM, IgA
Electron microscopy
Membranoproliferative GN (I-III)

- Thickening of BM, proliferation of mesangial cells, incr. matrix

- **MPGN I**
  - All ages
  - Proteinuria, hematuria
  - **micro:** lobular pattern of G, thickening of BM
  - **immuno:** C3, IgG
  - **EM:** subendothelial deposits, interposition of mesangium into BM, (prognosis bad – in 10 yrs renal failure)

- **MPGN II (dense deposit disease)** C3NeF in serum - autoAb × C3 convertase = activation of C by alternative pathway
  - **EM:** BM „false“ ribbon-like deposits of unknown composition, prognosis bad (100% recurrence after transplant.)

- **(MPGN III deposits variably in BM)**
• Primary - idiopathic
• Secondary
  – Subacute bacterial endocarditis
  – Osteomyelitis
  – Hepatitis C
  – Cryoglobulinemia
  – Neoplasia
Light microscopy

- Enlarged glomeruli
- Mesangial enlargement
- GBM thickening
- Double GBM contours (tram-tracking)
Immunofluorescence

- C3 v BM, mesangium
- IgG, less IgM
Rapidly progressive (crescentic, extracapillary) GN

- RPGN is syndrome and not a specific etiologic form of GN
  common feature = crescents in most of G (at least 50%)
- crescents-fibrous, fibrocellular, cellular
- Rapid \(\downarrow\) renal functions, hematuria, proteinuria
- In 1-2 M – loss of all G
- ETI: 1. AutoAb IgG × BM- 20% (lungs–Goodpasture sy)
  linear positivity IgG
  2. Immune complex GN-40% (SLE, Henoch-S. purpura...)
  3. ANCA associated-40% (m. polyang., Wegener, Ch-S)
- micro: severe injury of G (BM) -necrosis, perforation of cap. - fibrin into Bow. capsule, prolif of parietal cells, migration of monocytes (cellular Cr.), later fibrosis and sclerosis of G
Clinical sy

• Young adults, middle age
• Acute nephritic sy
• Renal failure in few weeks
• Prognosis:

  depends on the etiology and extend – better in postinfectious and pauciimmune than anti GBN Ab
Light microscopy
Immunofluorescence

IF reflects different etiology

linear  negative  granular
Mesangial proliferative glomerulonephritis

- Mesangial hypercellularity (more than 3 cells per mesangial segment together with an increase in mesangial matrix. Basal membranes normal.
- Only when mesangial deposits of Ig (not ischemic, hereditary, or metabolic) mesangial proliferation
Clinical sy

Depending on the basic disease

- No signs
- Microscopic hematuria
- Nephritic sy
- Nephrotic sy
Immunofluorescence

2 basic types:
- IgA mesangioproliferative GN
- non – IgA mesangioproliferative GN
Minimal change disease (lipoid nephrosis)

- in 75% preschool children, selective albuminuria, edema
- Sudden onset or in association with infection
- causes? (T lymphocytes - cytokines increasing permeability of BM, alteration of adhesion molecules - integrins, food allergy, probably immune complexes, loos of polyanion,)
- Micro: minimal G changes, (lipids in proximal tubules - reabsorption)
- EM: loss (effacement) of epithelial foot processes
- Therapy: Corticosteroids - sensitive, dependent, resistant
- prognosis good, rarely sclerosis of G
Light microscopy
Immunofluorescence

- Usually negative, or IgM in mesangium
Focal segmental glomerulosclerosis

• FSG- sclerosis affecting some but not all G and involving only segments of G

• Primary (idiopathic) x secondary (IgA, SLE, HIV...)
• Adults and children, NS with nonselective proteinuria
• causes? Circulating cytokines ↑ permeability of BM
• micro: segm. sclerosis of some G (incr. matrix, collapsed GBM, hyalinosis
• Immunofluorescence : IgM (granular)
• EM: effacement of the foot processes, podocyte detachment
• Prognosis: bad - 50 % renal failure after 10 years
Clinical sy

- Proteinuria – nephrotic sy
- Microscopic hematuria
- Hypertension
- Renal failure
- Bad response to corticotherapy

Prognosis: bad - 50% renal failure after 10 years

*Malignant variant of FSGS – collapsing glomerulopathy*
Light microscopy
Immunofluorescence

- Often negative.
- mesangial IgM and C3
Membranous GN (glomerulopathy)

- Immunoglobulin-containing deposits along BM, mostly adults (In situ complexes)
- 80% idiopathic, 20% (SLE, drugs, hepatitis B, tumors)
- micro: thickening BM, (Jones spikes)
- Immunofluorescence: granular positivity in BM (IgG)
- EM: subepithelial deposits
Clinical sy

• The most common between 40-60 yrs
• Proteinuria, nephrotic sy
• May be microscopic hematuria
• Rarely – hypertension or changes of renal function
• Prognosis: in 20 % (G sclerosis) - end stage kidney
Light microscopy
Immunofluorescence

- Granular deposits
- IgG a C3
Chronic sclerosing GN

• 30-50% patients requiring HD
• **CrGN:** End stage of a variety entities (RPGN, IgA, memb. GN, MPGN, DIA, SLE, FSG,)
• **Usually is impossible ascertain primary disease !!!**
• **Grossly:** small, contracted kidneys (weight under 100 g), granulated surface
• **Histology:** G sclerotic replaced by hyaline „targets“, secondary fibrosis of interstitium, atrophy of tubules („thyroid-like“), sclerosis of vessels (hypertension), chronic interstitial inflammation
• **Clinical course:** slowly progressive renal insuff. - dialysis
• **END STAGE KIDNEY**
Renal involvement in systemic disorders

- Systemic lupus erythematoses
- GN with IgA deposits
- GN in systemic infections
- GN in infectious endocarditis
- GN in parasitic diseases
Renal involvement in systemic disorders

- **Systemic lupus erythematoses:** females, kidney – one of affected organs
- **AutoAb × nuclear DNA,** kidneys almost always involved
  variable intensity: hematuria, proteinuria, nephrot. sy, nephrit.sy

**WHO - 6 types:**

- I  normal G
- II mesangial GN (↑mes cells, deposits)
- III FSGN (proliferation, karryorhesis)
- IV diffuse lupus GN (prolif, necrosis, crescents, wire loop) – worst prognosis
- V membranous GN
- VI sclerosing GN – terminal stage
Light microscopy
• **IgA nephropathy** (Berger disease) – the most common GN
  young adults, children,
hematuria (often gross), after inflamm. of respiratory tract, sometimes proteinuria. **Micro:** ↑ mes. cells, later sclerosis of G

**Immunofluorescence:** IgA in mesangium **EM:** deposits in mesangium

**Prognosis:** variable (20-40% in 20 years = renal failure)

• **GN in Henoch-Schönlein purpura** children. skin (purpuric rash), joints (arthritis), GIT (abdominal pain). Kidneys variably affected
  micro: similar IgA nephropathy, focal-segm involvement, necrosis, crescents

• **(IgM nephropathy)**
Light microscopy

Variable
May be all types including crescent
Mesangioproliferative – the most common
Immunofluorescence

IgA in mesangium, less C3, IgM, IgG.
Renal involvement in systemic disorders

- **GN in inf. endocarditis**: ImmCpx – focal GN with necrosis of parts of glomeruli

- **Amyloidosis**: in AA amyloidosis – kidney always involved, in AL in majority of cases
  - micro: amorphous material in glomeruli (also arterioles, capillaries, peritubular stroma) Congo red
  - EM: fibrils in mesangium and BM
  - clinically: proteinuria → nephrotic syndrome, deterioration of renal functions = renal failure
Renal tumors
Classification (WHO)

Renal cell tumors
• Metanephric tumors (metanephric adenoma, adenofibroma)
• Nephroblastic tumors
• Mesenchymal tumors
• Mixed mesenchymal and epithelial tumors (cystic nephroma)
• Neuroendocrine tumors (carcinoid, neuroendocrine ca, PNET, neuroblastoma, paraganglioma)
• Hematopoietic and lymphoid tumors (primary lymphoma-transplanted kidney, EBV infection)
• Germ cell tumors
• Metastatic tumors
Malignant epithelial tumors – risk factors

- Tobacco smoking
- Obesity
- Hypertension
- Exposure to arsenic, asbestos, cadmium, organic solvents, pesticides, fungal toxins
- Tuberous sclerosis
- Chronic renal failure
- Acquired cystic diseases
Inherited syndromas

• Von Hippel-Lindau (VHL) disease
  – AD
  – Hemangioblastoma in cerebellum and retina
  – Pheochromocytoma
  – Pancreatic cysts
  – RCC (clear cell) typically multiple and bilateral
Inherited syndromas

- Hereditary papillary ca
  - AD, mutation of MET oncogene
- Hereditary leiomyomatosis and renal cell cancer
  - AD, leiomyomas in skin and uterus+uterine leiomyosarcoma+papillary ca
- Birt-Hogg-Dubé sy (AD)
  - Cutaneous fibrofolliculoma, trichodiscoma+chromophobich ca
- Constitutional chromosome 3 translocation
  - RCC clear cell type
Tuberous sclerosis complex (TCS)

• is a rare multi-system **genetic disease** that causes non-malignant tumors to grow in the **brain** (sunependymal nodules, astrocytomas, hydrocephalus, autism, aggression, seizures, developmental delay) and on other vital organs such as the **kidneys, heart** (rhabdomyomas), **lungs** (lymphangioleiomyomatosis), and **skin** (angiofibroma, hypomelanotic malules).

• TSC is caused by a **mutation** of either of two **genes**, **TSC1** and **TSC2**, which code for the **proteins** hamartin and tuberin respectively. These proteins act as **tumor growth suppressors**, agents that regulate cell proliferation and differentiation
Clinical diagnosis

• Classic triad: hematuria, flank pain, abdominal mass in 10%
• Single hematuria
• Others:
  – Paraneoplastic sy (hyperparathyroidism, erythropoetin production – erythrocytosis, renin - hypertension,
  – weight loss, anorexia, fever, hypercalcemia, anemia
Epithelial tumors
Benign epithelial tumors

- Papillary adenoma
- Oncocytoma
Papillary adenoma

• Mostly incidental findings in bioptic or necroptic material, often associated with nephrosclerosis
• Closely under renal capsula
• Solitary or multiple
• Measure less than 5 mm

Cytogenetics:
  Trizomy 7 and 17 chromosomes, loss of Y chromosome
Microscopy

- Small cells with uniform nuclei
- Structure: tubular, tubulopapillary.
Oncocytoma

- 5% of renal epithelial tu
- Well circumscribed, brown color with a central scar.
- Mostly solitary, when multiple - oncocytomatosis).
Microscopy

- Eosinophilic granular cytoplasm – mitochondrias.
- Round usually small nuclei, may be hyperchromatic cells
Malignant epithelial tumors

- Clear cell (conventional) carcinoma
- Multilocular clear cell carcinoma
- Papillary renal cell carcinoma
- Chromophobe renal cell carcinoma
- Carcinoma of the collecting duct of Bellini
- Renal medullary carcinoma
- Xp11 translocation carcinoma
- Mucinous tubular and spindle cell carcinoma

- Sarcomatoid carcinoma
Conventional (clear cell) renal carcinoma

- Cler cell renal carcinoma - 70-80% of all renal carcinomas.
- Mostly solitary, may be multiple, bilateral
- Grossly: pale, often necroses, cystic changes
- Behaviour:
  - Progression to renal vein and vena cava
  - Progression to perinephric tissue
  - Metastases via blood vessels – lungs, skeleton, liver, even after years after primary dg
  - Paraneoplastic symptomas: production of hormones, AA amyloidosis.
- Prognosis: depending on grade (1-4 according Fuhrmann) and stage
  stage I – 5 let survival 80% , (tumor not beyond renal capsula)
  stage IV – 5 let survival 5%
Clear cell carcinoma

- Clear cells - glykogen
Chromophobe renal cell carcinoma

- 5% of RCC
- Polygonal cells with prominent cell borders
- Wrinkled nuclear membranes, perinuclear halos
- Much better prognosis than clear cell RCC, rarely metastasizes, may transform to sarcomatoid ca
Papillary renal cell carcinoma

- Comprises about 10-15% RCC
- Genetically: Trisomy of chromosomes 7 and 17
- Associated with end stage kidney
- *Prognosis*: depends on grading and staging
  - Low grade better outcome than clear cell RCC
Papillary renal cell carcinoma
Collecting duct carcinoma

- Arise from collecting duct
- 1% of RCC
- Mostly in medula
- Tubular- tubulopapillary architecture
- High grade nuclear grade
- **Prognosis:** poor
  - 40% of patients have meta at the time of dg
Renal medullary carcinoma

• Rare

• Highly malignant, only with sickle cell trait

Sickle cell trait (or sicklemia) describes a condition in which a person has one abnormal allele of the hemoglobin beta gene (is heterozygous), but does not display the severe symptoms of sickle cell disease that occur in a person who has two copies of that allele (is homozygous). Those who are heterozygous for the sickle cell allele produce both normal and abnormal hemoglobin (the two alleles are co-dominant). Sickle cell disease is a blood disorder in which the body produces an abnormal type of the oxygen-carrying substance hemoglobin in the red blood cells. Sickling and sickle cell disease also confer some resistance to malaria parasitization of red blood cells, so that individuals with sickle-cell trait (heterozygotes) have a selective advantage in some environments.)
Sarcomatoid carcinoma

- Dedifferentiation of clear cell or chromophobe ca
- *Prognosis*: poor
• Metanephric adenoma
  (kids, adults, 50% incidental)

• Cystic nephroma
  (benign, women after 30)
Mesenchymal tumors

- Angiomyolipoma
- Medullary fibroma
- Reninoma (juxtaglomerular cell tumor): severe hypertension and hypokalemia
- Leiomyoma
- Hemangioma
Angiomyolipoma

- The commonest mezenchymal renal tu
- Originates from perivascular spindle cells (PEComa)
- Solitary, multiple, bilateral
- Multiple tumors are associated with tuberous sclerosis of brain
- **Specific features:**
  Tumor location in lymph nodes or other organs (liver, vagina,) not a sign of metastases!!!!
Microscopy

- Fatty tissue
- Spindle cells SMA a HMB-45 pozitive
- Thick-wall vessels with irregular elastic fibres
• Medullary fibroma: Small demarcated nodules in renal medula
• Reninoma: from juxtaglomerular cell, clinically may be hypertension
Tumors of renal blastema

• Nephroblastoma (Wilms tumor)
Nephroblastoma (Wilms tumor)

- Malignant tu of embryonal nephrogenic elements composed of mixtures of blastemal, stromal and epithelial elements.
- Childhood (mostly between 1-3 yrs, 98% before 10yrs), rarely in adults
- Sporadic (90%, unilateral) X inherited (6% familiar, bilateral, mutations of WT1, WT2)
- Highly malignant, rapid growth
- Metastases-lungs, liver
- Prognosis: chemotherapy. Radiotherapy – survival rate 90%
  - Depends on the age better before 2 yrs of age, anaplasia
Clinical features

• Abdominal pain
• Intestinal obstruction
• Hypertension, hematuria, symptoms of traumatic tumor rupture
Other pediatric neoplasms

- Mesoblastic nephroma 1-3%
- Malignant rhabdoid tu 2%
- Clear cell sarcoma 4%
- Metanephric stromal tu – rare
- Ewing sarcoma/PNET- rare
- Translocation carcinoma
- Clear cell ca (VHL)
- Papillary ca
- Medullary ca
- Synovial sarcoma
- Metanephric adenoma
Tumors of renal pelvis and calyces

• *Transitional cell papilloma*

• *Transitional cell carcinoma*