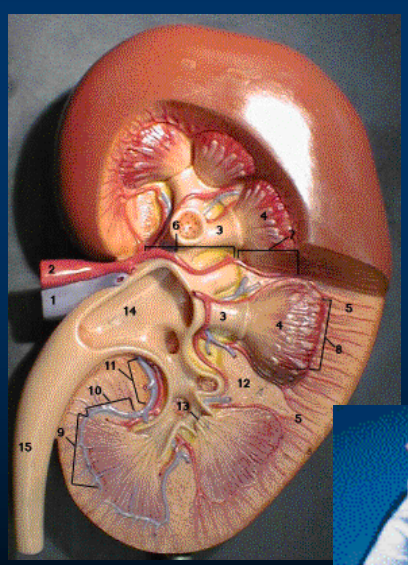
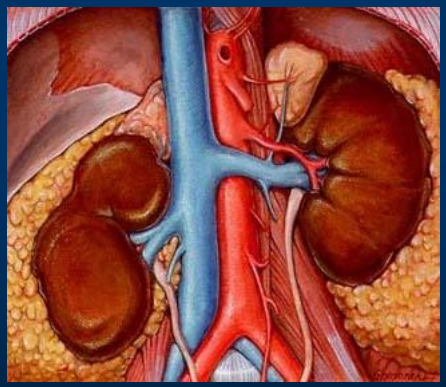
Summer Pathophysiology course 2005

KIDNEY DISORDERS

Dr. R. A. BENACKA
Department of Pathophysiology
P.J. Safarik Univerzity, KOSICE, SK





1

Basic principles

KIDNEY PHYSIOLOGY

1. Excretion of wasting metabolic products

- Pacient with kideny disorder show increased blood nitrogen (creatinin, urea) – azotemia. If the perfusion is normal urea is within normal range.

2. Regulation of water content and concentrations of Na and K

- Hypervolaemia, hypertension, oedema or hyperkalaemia are common findings in progressive stages of renal dysfunction. First manifestations of body cummulation of fluid – periorbital edema.

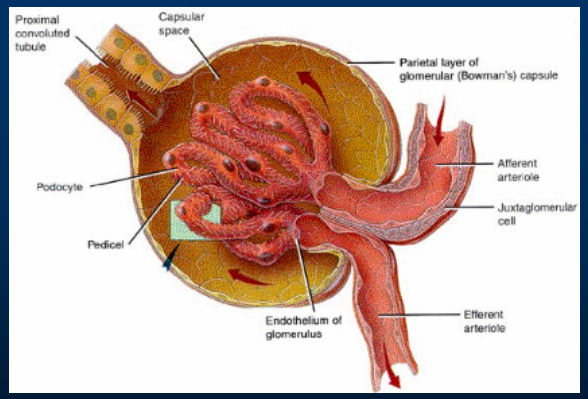
3. Pricipal role in acid- base balance – excretionof acids, regeneration & de novo produtio of bicarbonate

- Severe renal dysfunction is regularly accompanied by metabolic acidosis

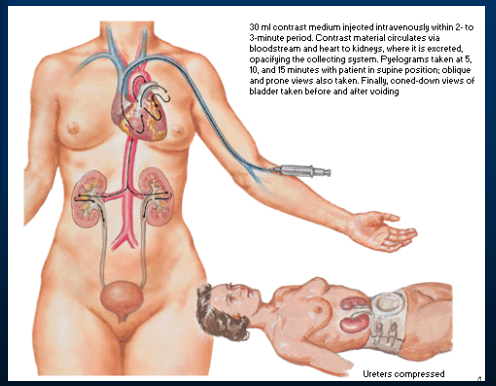
4. Endocrine function of kidney – renín, erytropoetin, PGE, calcitriol

- Manifestations as hypertension, anaemia, bone demineralisation.

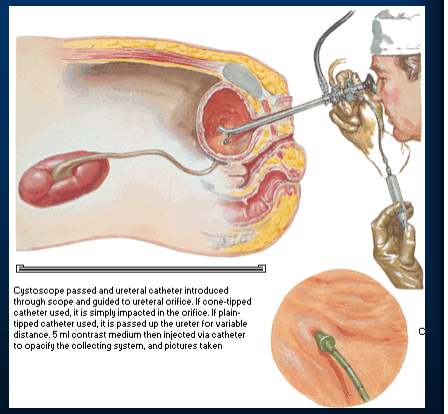
Glomerulárne funkcie



Methods - Pyelography

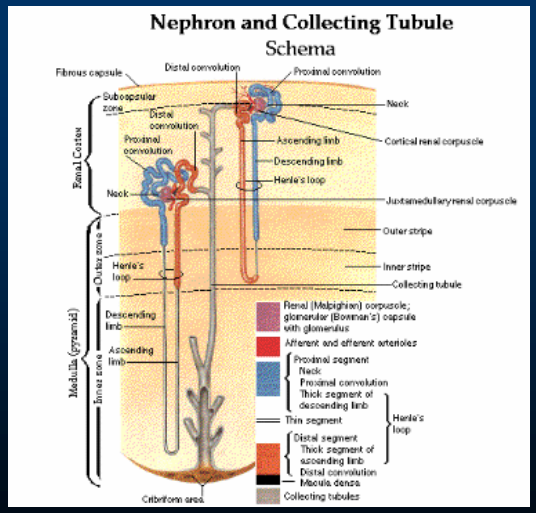


Intravenous pyelography

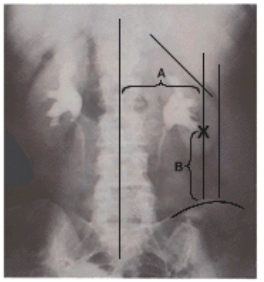


Retrograde pyelography

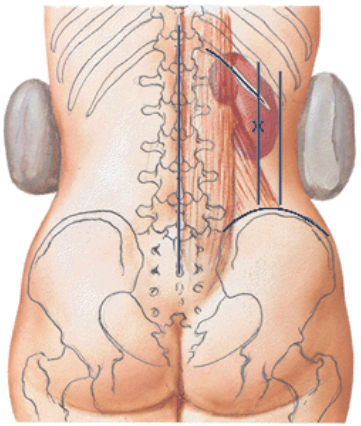
Tubulárne funkcie



Methods - Biopsy

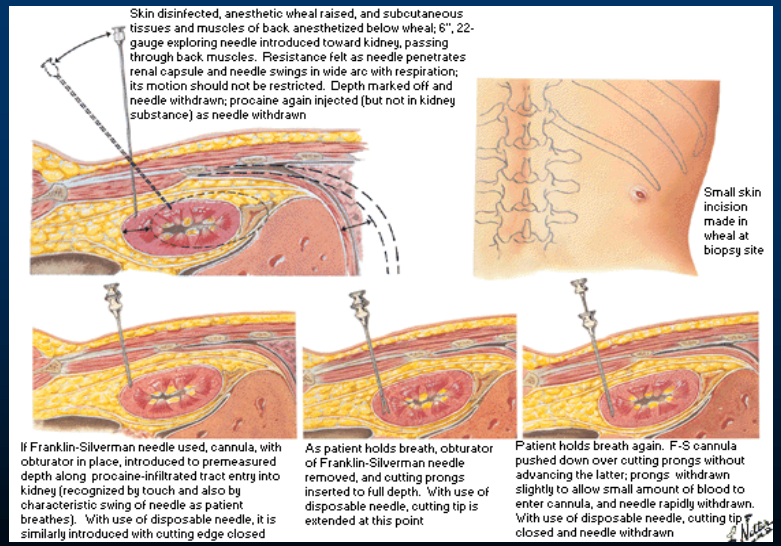


Proposed biopsy site (X) selected on radiograph and its topography defined by measurement from lines of spinous processes, iliac crest, and 12th rib



Site identified on patient's back by identical measurements from same reference lines drawn in 1% crystal violet. Patient lies prone with sandbags under abdomen to fix kidney against back. Blood pressure and pulse monitored

Methods - Biopsy



Acute renal failure

Definition:

sudden state (hours – days) of kidney disability;

Causes:

1. Pre-renal acute renal failure

- decreased blood supply to the kidneys (prerenal ARF)

2. Intra-renal acute renal failure

- abnormalities within the kidney itself; including those that affect the blood vessels, glomeruli or tubules

3. Post-renal acute renal failure

- chronic obstruction of the urinary tract (lasting for several days or weeks)

2

Acute renal failure (ARF)

Causes of ARF

Prerenal causes

(1) Systemic shock, hypotension (70%)

- Hypovolaemia
- Hemorrhage (trauma, surgery, postpartum, gastrointestinal)
- Diarrhea, vomiting, burns,
- Cardiac Failure
- Infarction, valvular damage,
- Peripheral vasodilation
- Anaphylactic shock, Anesthesia
- Septic shock

(2) Primary renal hemodynamic abnormalities

- Renal artery stenosis, embolism, or thrombosis of renal artery or vein

Renal causes

(1) Vascular/Glomerular injury

- Vasculitis (polyarteritis nodosa)
- Cholesterol emboli, Malignant hypertension,
- Acute glomerulonephritis (progressive membranoproliferative nephritis)

(2) Tubular epithelial injury (ATN)

- ATN due to ischemia (shock)
- ATN due to toxins (heavy metals, ethylene glycol, insecticides, poison mushrooms, carbon tetrachloride)

(3) Interstitial injury

- Acute pyelonephritis
- Acute allergic interstitial nephritis

Postrenal causes

(1) Obstruction of kidney pevices urether

- large stones, cysts, tumor

(2) Obstruction of the urether, bladder and urethra

- stones, strictures, tumors, prostatic hyperthophy

Clinical manifestations

(1) Oliguric phase of ARF – day 1-3 little volume of poorly concentrated urine

- ↓↓ GFR + ↓ tubular reabsorption of fluid → anuria or oliguria + hyperhydration with infusion of large volumes of fluid
- ↓↓ renal excretion of wasting/toxic subst. → ↑↑ plasma conc. of BUN (creatinine) = true indicator of function + hyperkalemia (burns, contusions, hemolysis, etc.)

(2) Polyuric phase of ARF – day 4-8 large volumes of urine + salts

- normalisation of GFR + ↓↓ tubular reabsorption of fluid + salts (salt-losing kidney) loss of Na^+, K^+ water, HCO_3^- In the polyuric phase the may be so large as to be life-threatening.
- If the renal tubules are damaged (e.g., by heavy metals) polyuric renal failure occurs as a primary response : ↓↓ GFR + ↓↓ TR

Ischemic injury to kidney - mechanisms

- ***Loss of cell polarity*** due to redistribution of membrane proteins (e.g., the enzyme Na+ K+ - ATPase) from the basolateral to the luminal surface of the tubular cells → abnormal ion transport across the cells
- ***Increased sodium delivery to distal tubules*** →vasoconstriction via tubulo-glomerular feedback, which will be discussed below
- ***Inflammation*** - ischemic tubular cells → cytokines and adhesion molecules (ICAM-1) → leukocytes injury.
- ***Luminal tubule obstruction*** – cells detached from the BM → intratubular pressure → ↓GFR + interstitial edema, increased interstitial pressure → damage to the tubule

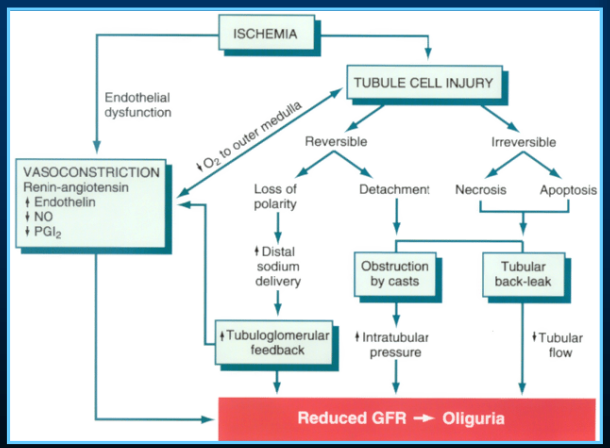
Ischaemic kidney injury

PA:

- reversible injury - cellular swelling, loss of brush border, blebbing, loss of polarity, and cell detach-ment
- lethal injury - necrosis and apoptosis

LA:

- depletion of ATP; accu-mulation of intracellular calcium; activation of proteases (e.g. calpain), cytoskeletal disruption, phospho-lipases damage membranes
- generation of ROS
- activation of caspases (apoptosis)



- *Disturbances in blood flow: intrarenal vasoconstriction* - > reduced glomerular plasma flow and reduced oxygen delivery to the functionally important tubules in the outer medulla (thick ascending limb and straight segment of the proximal tubule) < - the renin-angiotensin mechanism, stimulated by increased distal sodium delivery and *sublethal endothelial injury*, leading to increased release of the vasoconstrictor *endothelin* and decreased production of the vasodilators *nitric oxide* and *PGI2*

- *Direct effect of ischemia or toxins* on the glomerulus, causing a reduced glomerular ultrafiltration coefficient, possibly due to mesangial contraction.

- Re-epithelialization is mediated by a variety of growth factors and cytokines produced locally by the tubular cells themselves (autocrine stimulation) or by inflammatory cells in the vicinity of necrotic foci (paracrine stimulation) -> epidermal growth factor (EGF), TGF-a, insulin-like growth factor type I, and hepatocyte growth factor have been shown to be particularly important in renal tubular repair.

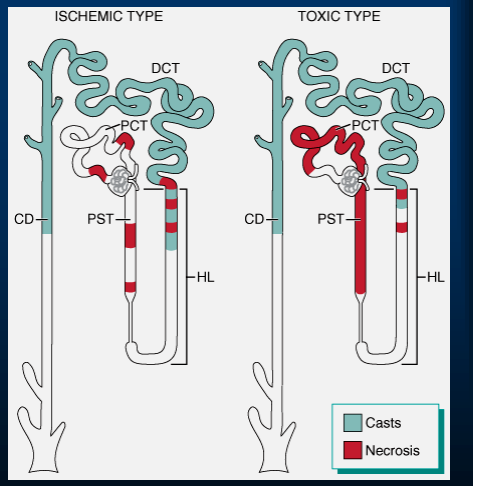
Intrarenal causes – Acute Tubular Necrosis

Tubular necrosis - destruction of epithelial tubular cells, cells "slough off", from the BM and plug the tubules; the basement membrane maybe destroyed

- fail to excrete urine even when renal blood flow is restored
- If the BM remains intact, new tubular epithelia grow along the surface of the membrane within 10 to 20 days.

- **Severe ischemia.**
- circulatory shock - inadequate supply of oxygen and nutrients to the tubular epithel

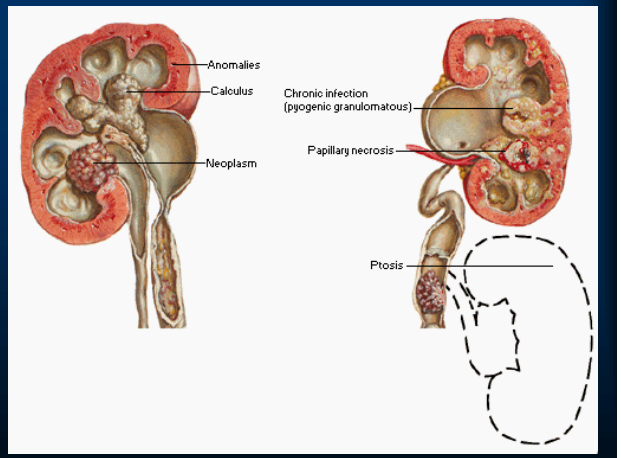
- **Renal poisons** - specific toxins to epithel
- (carbon tetrachloride, mercury and lead ethylene glycol (antifreeze), insecticides, medications (tetracyclines), cis-platinum,



Postrenal causes – Obstructive uropathy

(1) Kidney

- Urinary stones
- Hemolysis, myolysis - hemoglobin or myoglobin precipitated in the acidic tubular lumen
- Neoplasms
- Pyogenic granuloma
- Abscess
- Trauma
- Papillary necrosis



Postrenal causes of ARF

(1) Obstruction of kidney pevices

- large stones, cysts, tumors

(2) Urethereal obstruction

- Intrincis: released calculi, blood clots, sloughed renal tissue,
- Extrinsic: malignancies, retroperitoneal fibrosis

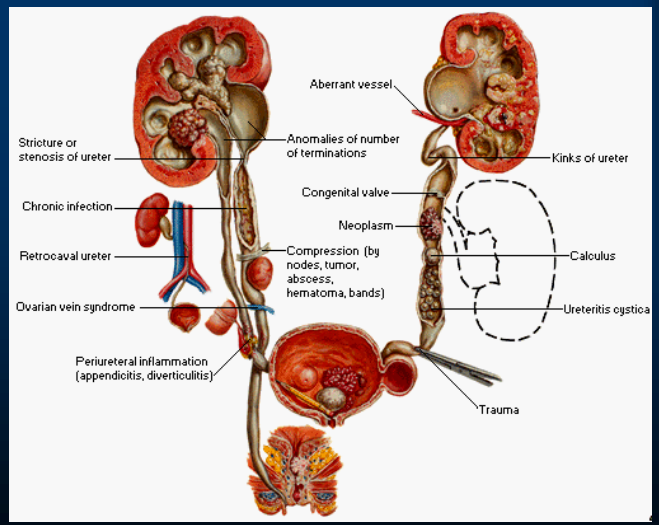
(2) Obstruction of the bladder and urethra

- stones, strictures, tumors, prostatic hyperthophy
- neurogenic bladder – anticholinergics, spinal shock, upper and lower motor neuron syndrome

Postrenal causes – Obstructive uropathy

(2) Urether

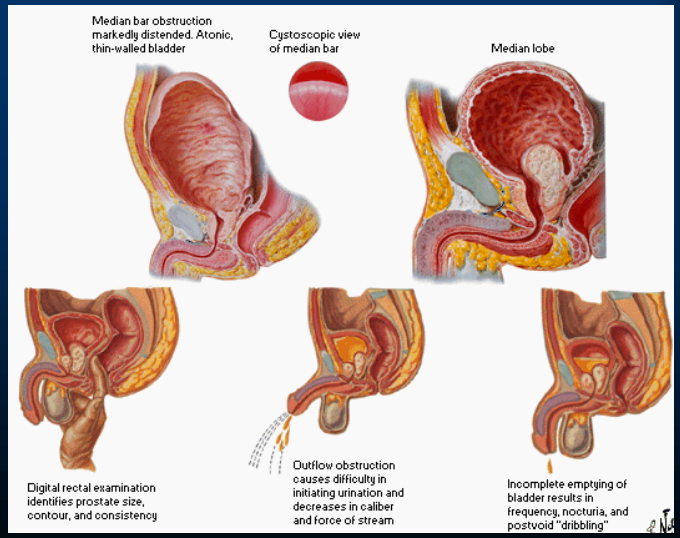
- Strictures, stenosis
- Abnormalities development
- Chronic infections
- Circulatory abnormalities
- Extrincis Neoplasms
- Stones
- Abscess
- Trauma



Postrenal causes – Obstructive uropathy

(3) Prostate

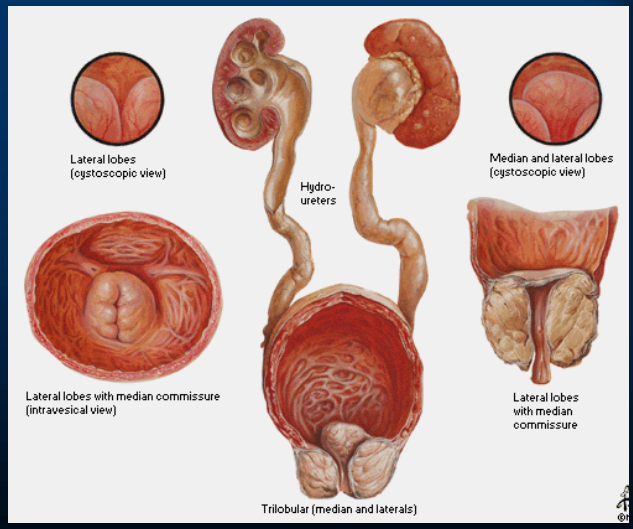
- Benign prostatic hypertrophy
- Ca prostate



Postrenal causes – Obstructive uropathy

Consequences of prolonged obstruction:

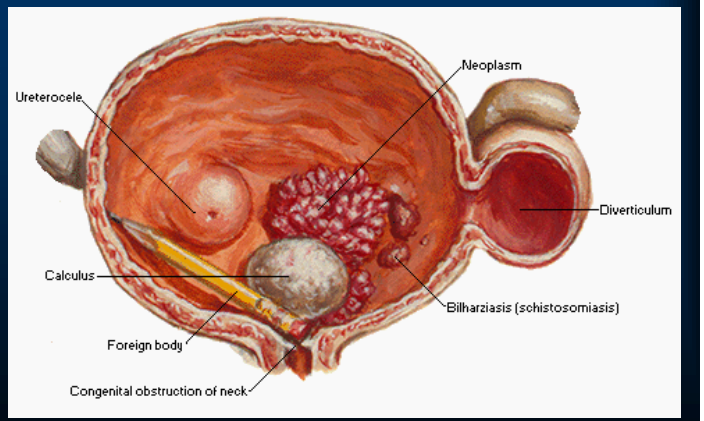
- hydronephrosis
- pyelonephritis



Postrenal causes – Obstructive uropathy

(4) Bladder

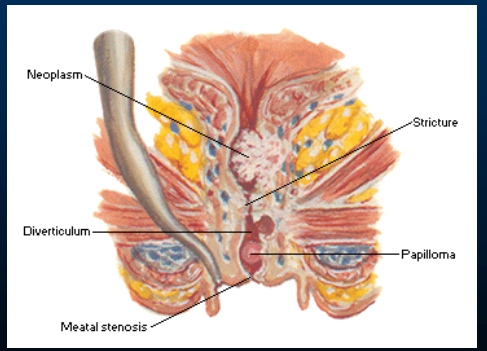
- Benign prostatic hypertrophy
- Ca prostate
- Neoplasms
- Diverticulosis

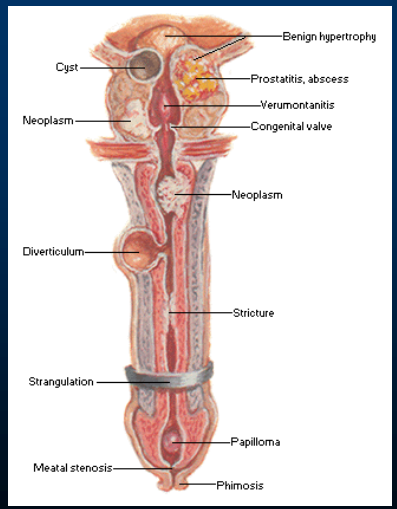


Postrenal causes – Obstructive uropathy

(5) Uretra

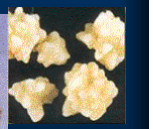
- Tumors (papilloma, adenocarcinomas)
- Postinflammatory strictures, diverticulosis

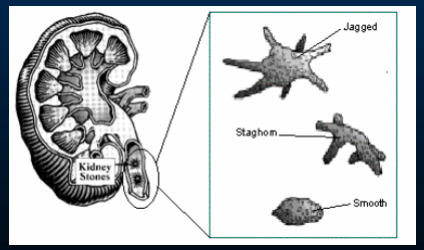




Urinary stones

- WHEWELLIT calciumoxalate (CaC2O4.H2O) – rare in nature; the most common urinary stone, no sharp edges yellow – green
- WEDDELLIT, calciumoxalate CaC2O4.2H2O, very sharp yellow edges causing the pain; relative common
- STRUVITE, Mg(NH4)(PO4).6H2O, non- acidotic environment, bacterial infection





Causes

Renal diseases (e.g., glomerulonephritis, or toxic damage to the kidney.

- **Shock state** (blood loss) - centralization of the circulation → sympathetic α – adrenoceptor renal vasoconstriction → ↓↓ renal perfusion, ↓↓ GFR (acute ischemic renal failure); Kidney ischaemia:
  - § Polonged constriction of the vasa afferentia:
    - Energy deficiency impairs Na+/K+ATPase; increase in intracellular concentration of Na+also causes, via the 3Na+/Ca2+ exchanger, a rise in intracellular Ca2+ concentration and thus vasoconstriction.
    - Release of renin both primarily and via an increased NaCl supply in the macula densa (reduced Na + absorption in the ascending tubules) and thus the intrarenal formation of angiotensin II, which has a vasoconstrictor action.
    - Adenosine is freed from ATP. It acts on the kidney—in contrast to the other organs—as a marked vasoconstrictor.

Manifestations

- retention of water, electrolytes, waste products of metabolism
- hypervolaemia + hypernatriemia → edema (hypoosmolarity), hypertension, hyperosmolarity
- hyperkalemia → heart arrhythmias (> 8mmol/l can be fatal)
- metabolic acidosis → the kidneys are also unable to excrete hydrogen ions + recycle HCO3-, can aggravate the hyperkalemia (letal)
- most severe cases → complete anuria (patient dies in 8 to 14 days unless an artificial kidney is used)

3

Chronic renal failure (CRF - uremia)

1. Characterization

- **Definition:** state charcterized by irreversible and permanent loss of nephrons with progressive decrease in the normal kidney functions in all aspects:
  - regulating fluid, electrolyte balance, acid-base balance
  - controlling blood pressure through fluid volume and the renin-angiotensin system,
  - eliminating nitrogenous and other waste products,
  - governing the red blood cell count through erythropoietin synthesis,
  - directing parathyroid and skeletal function through phosphate elimination and activation of vitamin D
- Typical decrease of GFR, tubular functions
- Untill cost-effective renal replacement therapy (i.e., dialysis therapy and transplantation) 95% of people died (1965)

Causes of Chronic Renal Failure

Metabolic disorders
Diabetes mellitus
Obesity
Amyloidosis

Hypertension
Renal vascular disorders
Atherosclerosis
Nephrosclerosis-hypertension

Immunologic disorders
Glomerulonephritis
Polyarteritis nodosa
Lupus erythematosus

Primary tubular disorders
Nephrotoxins (analgesics, heavy metals)

Urinary tract obstruction
Renal calculi
Hypertrophy of prostate
Urethral constriction

Congenital disorders
Polycystic disease
Congenital absence of kidney tissue (renal hypoplasia)

Infections
Pyelonephritis
Tuberculosis

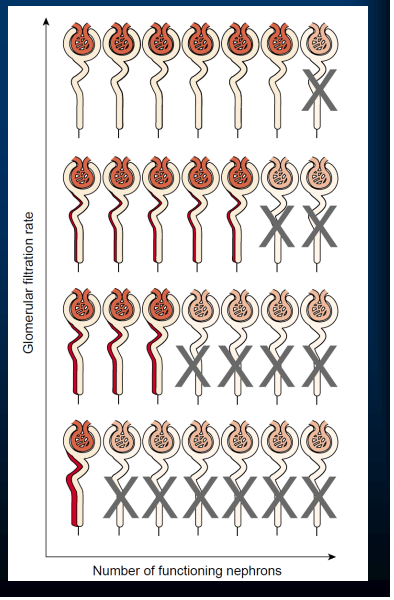
2. Stages

Diminished Renal Reserve (GFR → 50% of normal).
Sy: asymptomatic unless acute imparment occurs drugs (nephrotoxic)
Lab: the serum BUN and creatinine levels are normal,

Renal Insufficiency (GFR 50 → 20% of normal)
Lab: azotemia, anemia, hypertension appear.
Sy: isosthenuria or polyuria (urine that is almost isotonic with plasma)

Renal Failure (GFR 20% → 5% of normal)
Sy: edema, metabolic acidosis, and hyperkalemia neurologic, gastrointestinal, and cardiovascular manifestations.

End-Stage Renal Disease (GFR <5% normal)
PA: reduction in renal capillaries, scarring in the glomeruli. Atrophy and fibrosis are evident in the tubules. The mass of the kidneys usually is reduced.



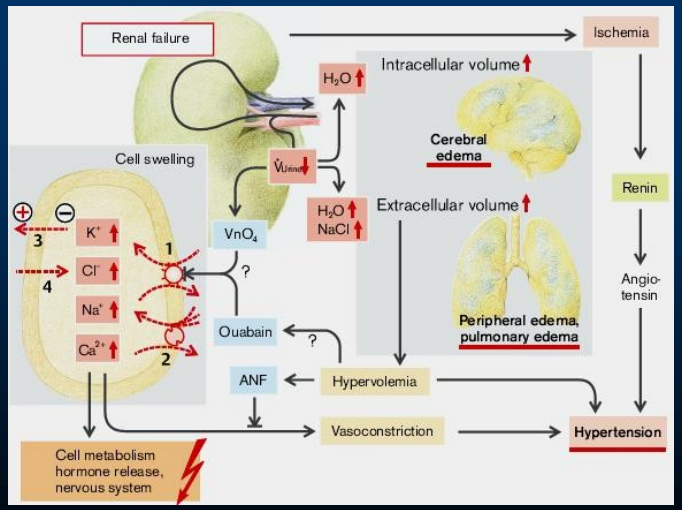
Clinical manifestations

1. Alterations in water, electrolyte
2. Disorder pf acid-base balance
3. Mineral and skeletal disorders
4. Anemia and coagulation disorders
5. Hypertension and alterations in cardiovascular function
6. Gastrointestinal disorders
7. Neurologic complications
8. Skin and integumentum integrity
9. Immunologic disorders

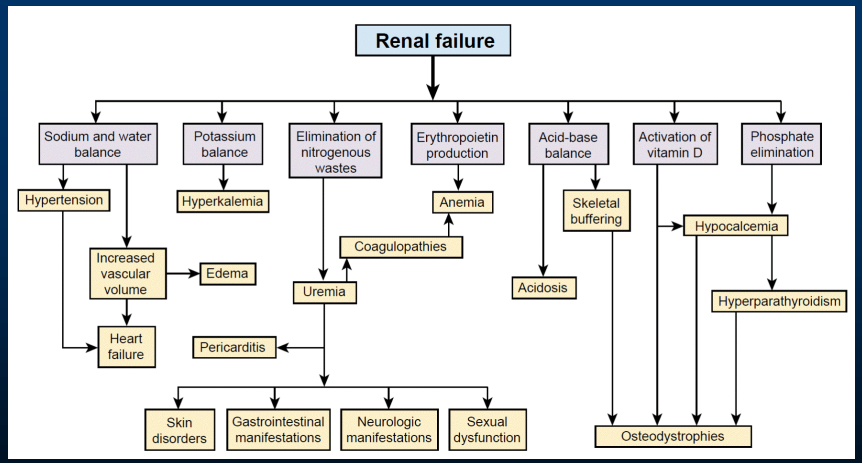
Disorders of Water, Electrolyte, and Acid-Base Balance

- *Isostenuria* - ability of the kidneys to concentrate the urine is diminished
- specific gravity of the urine becomes fixed (1.008 to 1.012) and varies little .
- *Polyuria and nocturia* are common → volume depletion
- *Hypernatriemia* under sodium overload, decrease in the GFR can occur with a restricted sodium intake or excess sodium loss caused by diarrhoea or vomiting.
- *Hyponatriemia* - salt wasting in advanced renal failure (↓tubular reabsorption). ↑ sodium intake improves GFR
- *Metabolic acidosis* - impairment of a) H+ elimination b) HCO3- recycling and de novo production, c) elimination of acids (ammonia buffer)
- acidosis seems to stabilize as the disease progresses,
- (due to buffering capacity of bone → bone resorption, skeletal defects)
- *Hyperkalaemia* - develops only in sever renal damage (GFR < 5 mL/min); or when not fullfilling dietary restrictions (medications that contain potassium; release of K+ from the cells - trauma or infection).

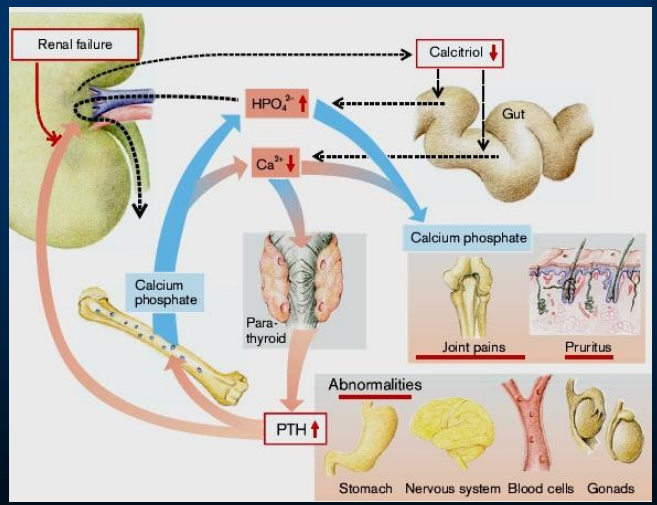
Effects on sodium and water



Mechanisms



Effects on Mineral Balance – Ca^{2+}, HPO_4^-



Cardiovascular Disorders

Hypertension, left ventricular hypertrophy, and pericarditis, are a major cause of morbidity and mortality in patients with ESRD.

Hypertension - an early manifestation of CRF; causes are multifactorial - ↑ volume (water cummulation) + ↑ vascular resistance (↓ renal vasodilator prostaglandin production and ↑ increased activity of RAA)

Left ventricular hypertrophy- ↓ left ventricular ejection fraction, ↓ ventricular filling (systolic + diastolic failure); Anemia, in particular, has been correlated with the presence of left ventricular hypertrophy

Ischemic heart disease, hert failure - increased myocardial work and oxygen demand; contributing conditions (anemia, diabetes mellitus, dyslipidemia, and coagulopathies)

Uremic pericarditis - 20% of persons with uremic state or from dialysis (metabolic toxins) siilar to viral pericarditis (cardiac tamponade)

Gastrointestinal Disorders

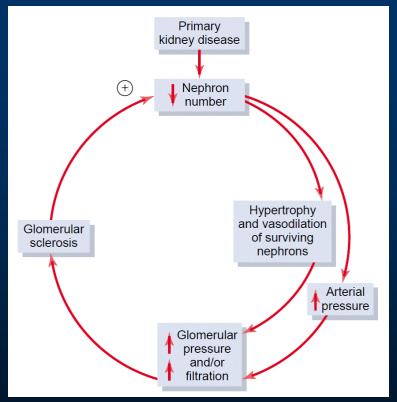
- *Nausea (early-morning), and vomiting* - common in uremia,decomposition of urea by intestinal flora to ammonia.
- *Metallic taste in the mouth* - depresses the appetite (*anorexia)*
- *GIT ulceration and bleeding* - PTH increases gastric acid secretion
- *Hiccups* - are common, improve with restriction of dietary protein, trasplantation

Neurologic symptoms

- ***Peripheral somato-motor neuropathy*** - mainly lower limbs, symmetric
- (atrophy and demyelination of nerve fibers, caused by uremic toxins). *Restless legs syndrome* - 2/3 of dialysed patients; burning, creeping, prickling, and itching sensations more intense at rest; temporary relief is obtained by moving the legs.
- ***Muscle weakness and atrophy*** - uremia.
- ***Uremic encephalopathy*** - (? excess of toxic organic acids, sodium dysbalance) - ↓ alertness and awareness; leaking attention, loss of recent memory, and perceptual errors in identifying persons and objects.
- ***Uraemic delirium, seizures, coma*** - ESRD
- ***Disorders of motor function*** - difficulty in performing fine
- movements of the extremities; the gait becomes unsteady, clumsy with tremulousness of movement.
- ***Asterixis*** (dorsiflexion movements of the hands and feet) - elicited by hyperextending arms at the elbow and wrist with the fingers spread apart (side-to-side flapping movements of the fingers).

Accumulation of Nitrogenous Wastes

- Early sign of renal failure - before other symptoms become evident.
- ***Azotemia*** - accumulation of nitrogenous wastes in the blood and can occur without symptoms
- ***Uremia*** – early sign (norma 20 mg/dL → 800 mg/dL)
- ***BUN*** - elevated as renal failure progresses.
- ***Creatinine*** - index of GFR
- Because creatinine is a by-product of muscle metabolism, serum values vary with age and muscle mass. An increase in serum creatinine to three times its
- normal value suggests that there is a 75% loss of renal function, and with creatinine levels of 10 mg/dL or more, it can be assumed that 90% of renal function has been lost.



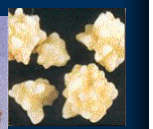
Most Common Causes of End-Stage Renal Disease (ESRD)

Cause	Percentage
Diabetes mellitus	44
Hypertension	26
Glomerulonephritis	8
Polycystic kidney disease	2
Other/unknown	20

Močové kamene

- WHEWELLIT kalciumoxalát (CaC2O4.H2O) – vzácny v prírode; najbežnejší kameň, bez ostrých hrán, žlto-zelený s radiálnymi kryštálmi, často v cebtre s apatitom na papilách

- WEDDELLIT, kalciumoxalát CaC2O4.2H2O ostré žlté kryštály spôsobujúce bolesť. Pomerne hojný.



- STRUVITE, Mg(NH4)(PO4).6H2O, neacidotické prostredie bakteriálne infekcie,