Pathophysiology of kidneys – part II

GFR determinant and measurement

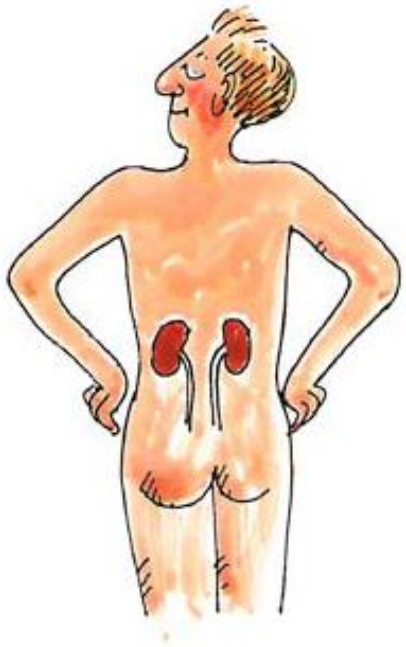
Acute renal failure (acute kidney injury)

Acute tubular necrosis

Chronic kidney disease (CKD)

End stage renal disease

Mineral bone disease in CKD



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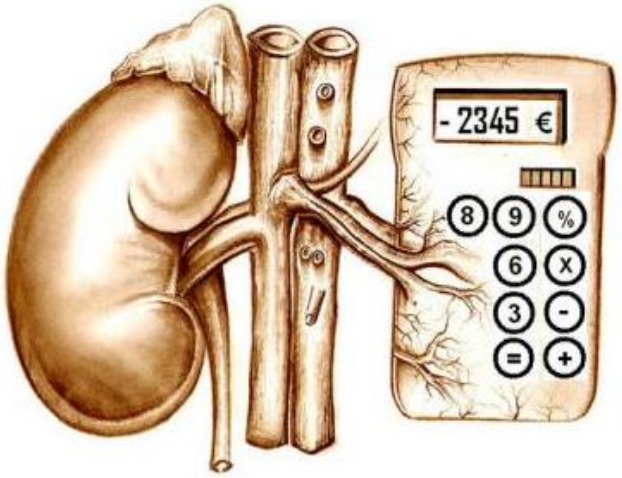

GLOMERULAR FILTRATION RATE (GFR) AS A PARAMETER

ESTIMATING KIDNEY FUNCTION

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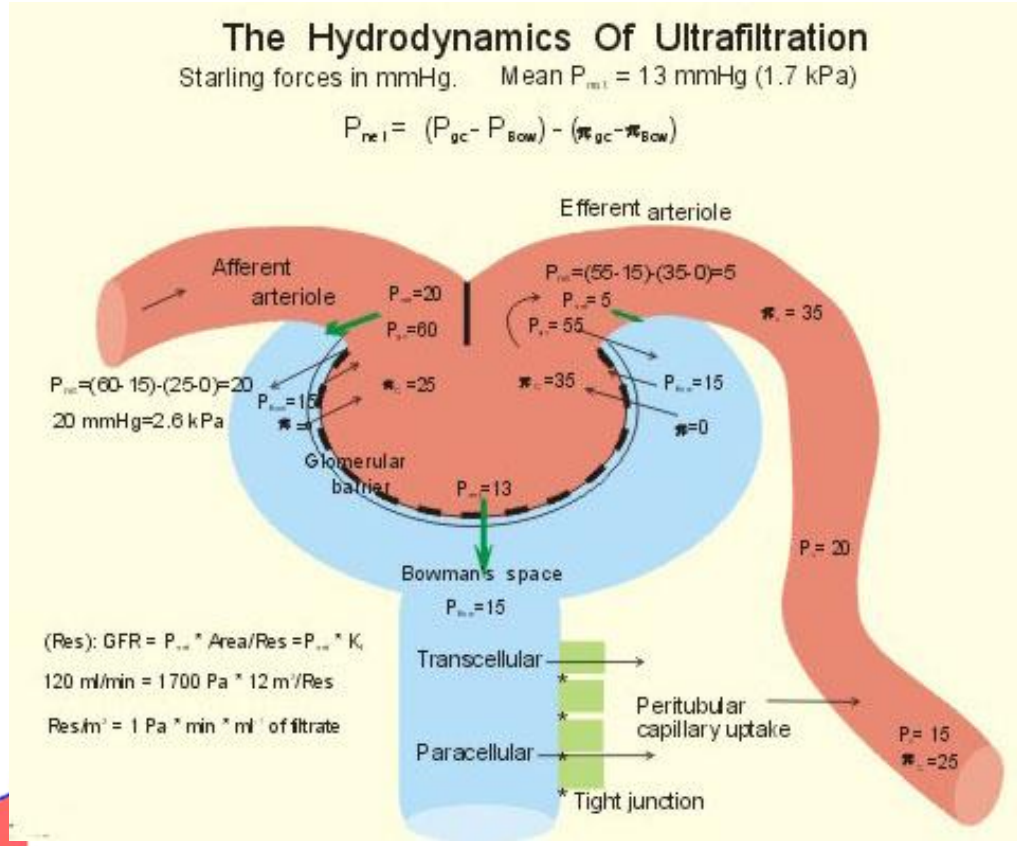
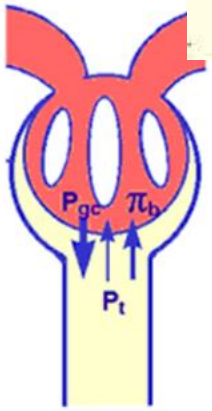
Determinants of GFR

- rate of ultrafiltration of plasma to Bowman capsule is determined:
  - **GFR = A × K × P_f**
- depends on:
  - **A** = a total area available for filtration (~100m^2)
    - number of glomeruli (approx. 500,000 – 1,000,000 per kidney)
      - changes with loss of functional glomeruli
    - effect of mesangial cells
      - capable of contraction (a thus ↓ A)
  - **K** = permeability of filtration membrane
    - changed by diseases affecting structure of glom. filtr. membrane (see glomerular diseases)
  - **P_f** = effective ultrafiltration pressure
    - Starling forces (see further)





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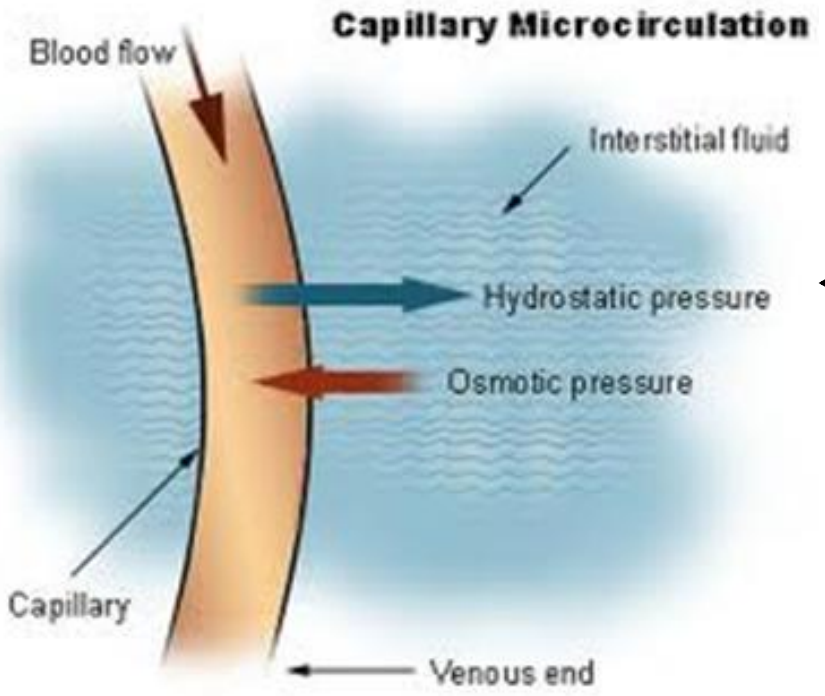
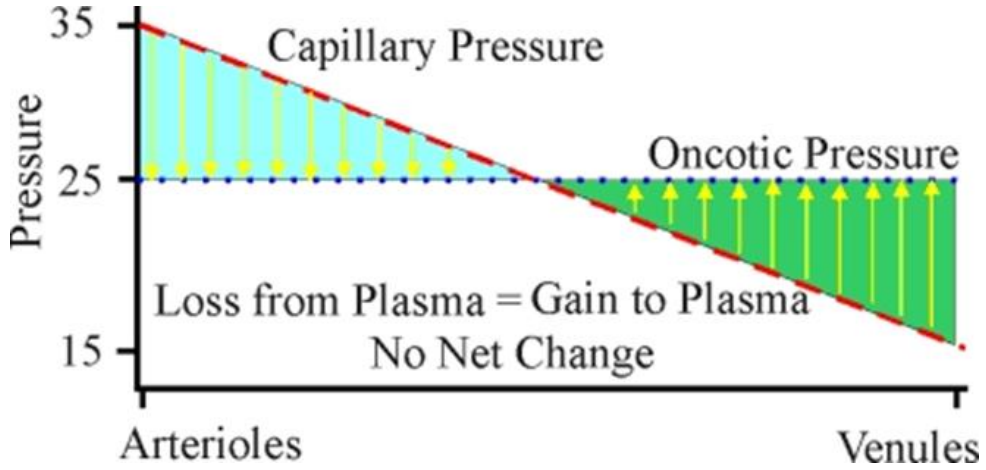
Microcirculation – Starling forces



situation elsewhere in capillary beds/microcirculation is quite different compared to glomerulus



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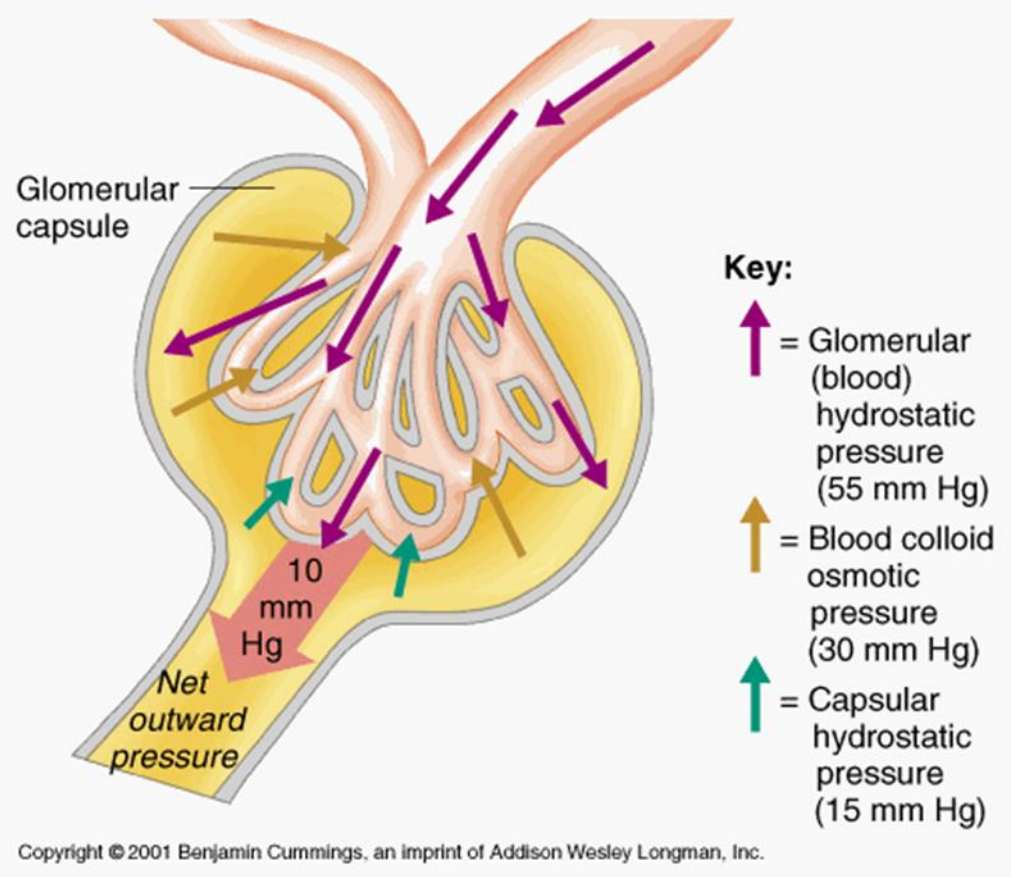
P_f = effective glomerular (ultra)filtration pressure



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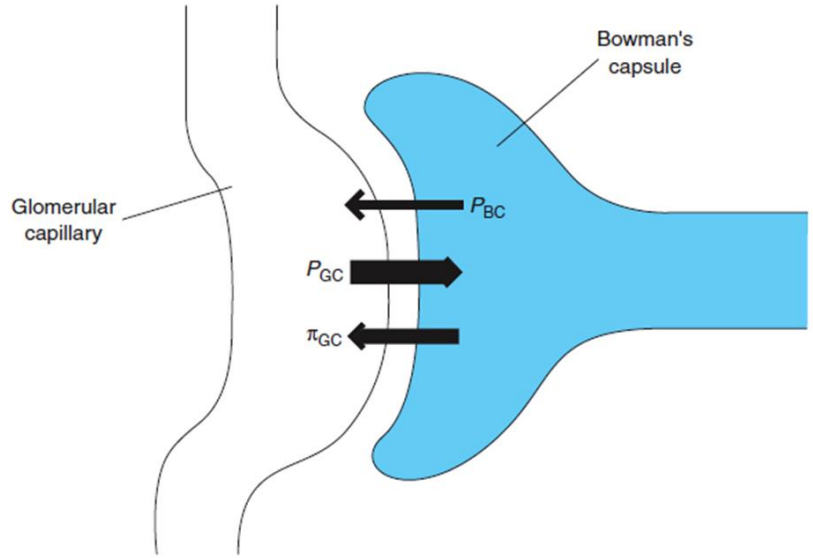
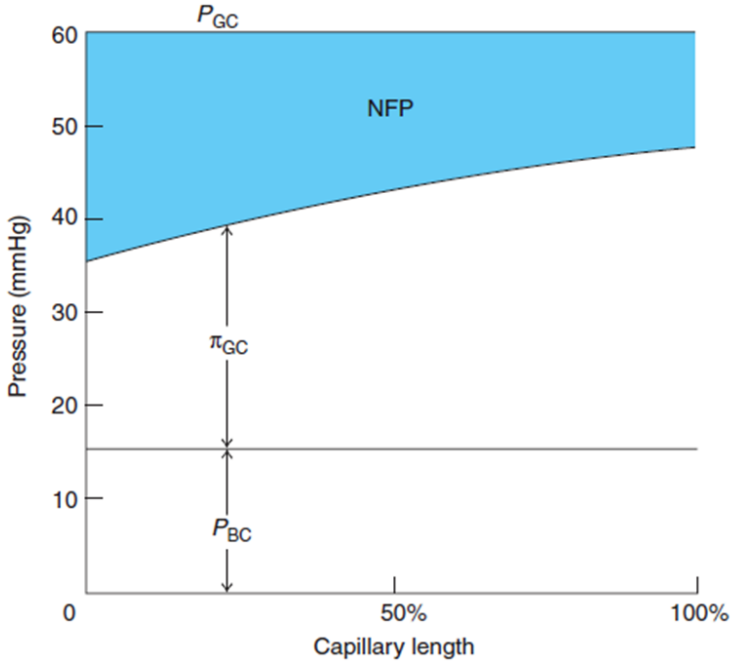
Glomerular capillaries – Starling forces





- net filtration pressure (P_f) in the renal corpuscle equals glomerular-capillary hydraulic pressure (P_{GC}) minus Bowman's capsule hydraulic pressure (P_{BC}) minus glomerular capillary oncotic pressure (π_{GC})
- contrary to other capillary beds **hydrost. pressure in the whole length of glom. capillary decreases minimally** (due to autoregulation), therefore filtration is about 100-times higher compared to other capillaries
- hydrostatic pressures
  - P_{GC} is high and constant ~45 - 55mmHg
  - P_{BC} ~10 - 15mmHg

  } **net filtration pressure P_f ~35 mm Hg**
- osmotic pressures
  - π_{GC}~25 - 30mm Hg
  - thanks to large filtration π_{GC} increases along the capillary up to ~35 mm Hg at which point pressures reach equilibrium

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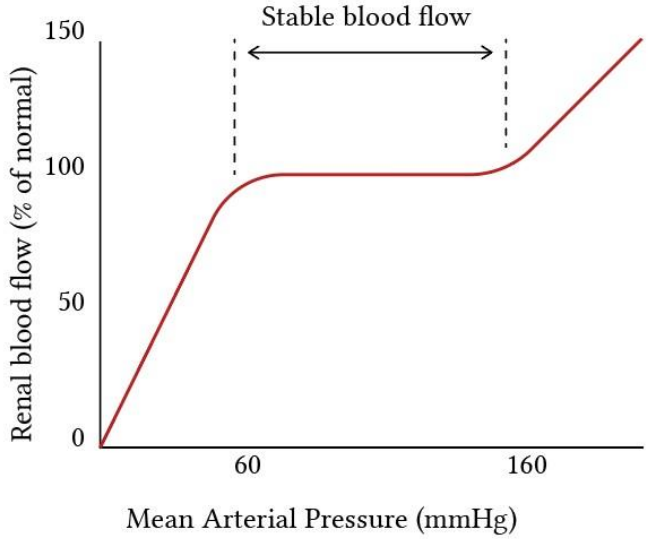
Renal blood flow (RBF) and GFR

- RBF in a healthy man (and GFR too) are thanks to the autoregulation quite stable
  - all plasma volume circulate through kidney in approx. 20 min
  - systemic pressure typically fluctuates
  - however, RBF stays rather constant in the range of 80 – 180 mmHg due to the autoregulation
  - only after significant drop of syst. BP RBF falls
    - → risk of ischemia and subsequent tubular necrosis
- RBF vs. renal plasma flow (RPF)
  - RBF ~ 20-25% of CO (cortex >>> medulla)
    - i.e. ~1000 - 1200 ml/min
    - rather high considering the weight of kidneys (~350 g)
  - RPF (hematocrit 0.45) ~600 - 700 ml/min
- glom. filtration
  - GFR ~20 - 25% RPF → **GFR ~ 120 – 140 ml/min**
  - ratio GFR/RPF = filtration fraction (~ 120/600 = ~ 0.2)
  - daily filtered ~ 180 l, but 99% reabsorption → 1.5–1.8 l of urine/day
- GFR and RPF can be assessed by various methods based on **clearance**
  - RPF (RBF) – PAH
  - GFR – creatinin, inulin (experimental) etc.



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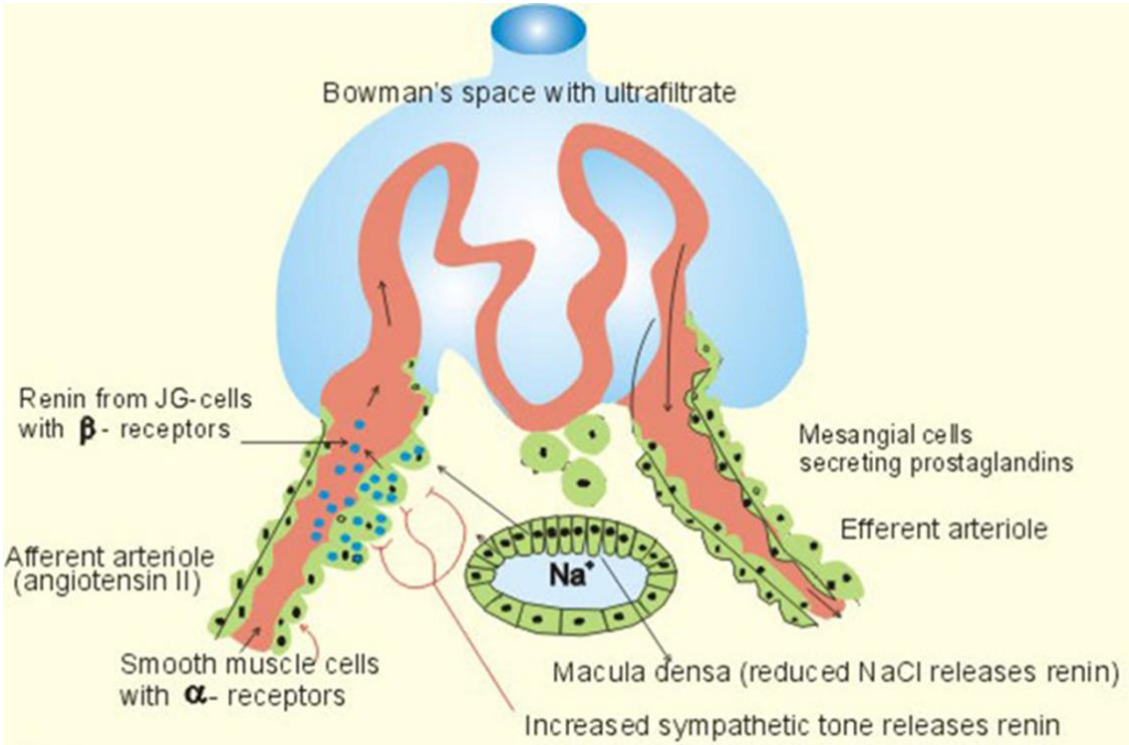
Regulation of RBF

- **autoregulation** of RBF
  - (1) **myogenic reflex**
    - SMC of the aff. and eff. arterioles detect wall tension and modify their resistance
  - (2) **tubuloglomerular negative feedback**
    - juxtaglomerular apparatus – macula densa - changes of NaCl – renin release – local RAS (dose-dependent effect)
- other **paracrine factors**
  - prostaglandins, adenosine and NO
- **sympathetic** nervous system
  - NE from adrenergic nerve endings and circulating E from adrenal medulla mediate constriction of afferent and efferent arterioles (α1-receptors)
    - drop of RBF and GFR
  - NE stimulates release of renin from granular JG-cells (via β1-receptors) and thus activation of systemic RAAS
  - NE ↑Na^+-reabs.in prox. tubule
- systemic RAAS



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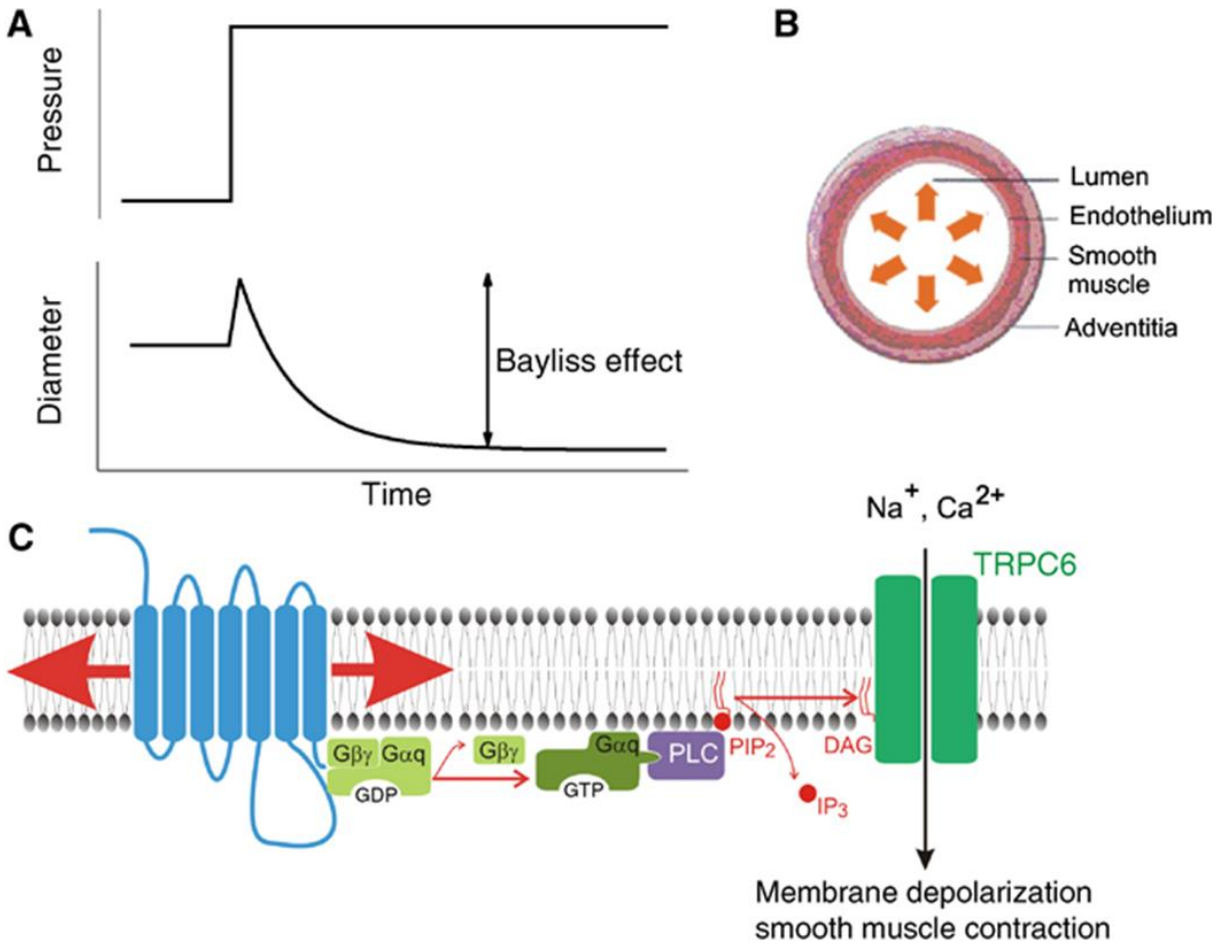
(1) Myogenic regulation (Bayliss effect)



- (A) Increasing pressure/stretch causes vasoconstriction
- (B) The BE is mediated by the smooth muscle layer, independent of the inner layer of endothelial cells
- (C) Proposed mechanism for stretch-induced activation of stretch-activated receptors in vascular smooth muscle membranes

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(2) Tubulo-glomerular feedback

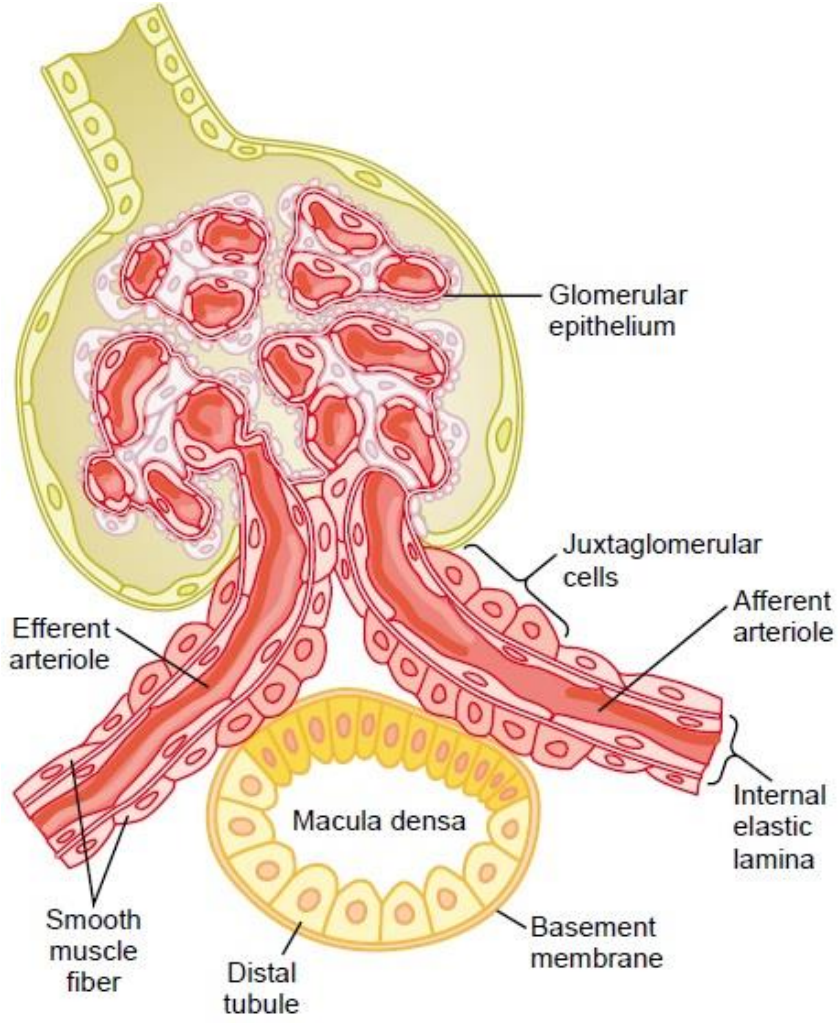

Figure 26–17

Structure of the juxtaglomerular apparatus, demonstrating its possible feedback role in the control of nephron function.

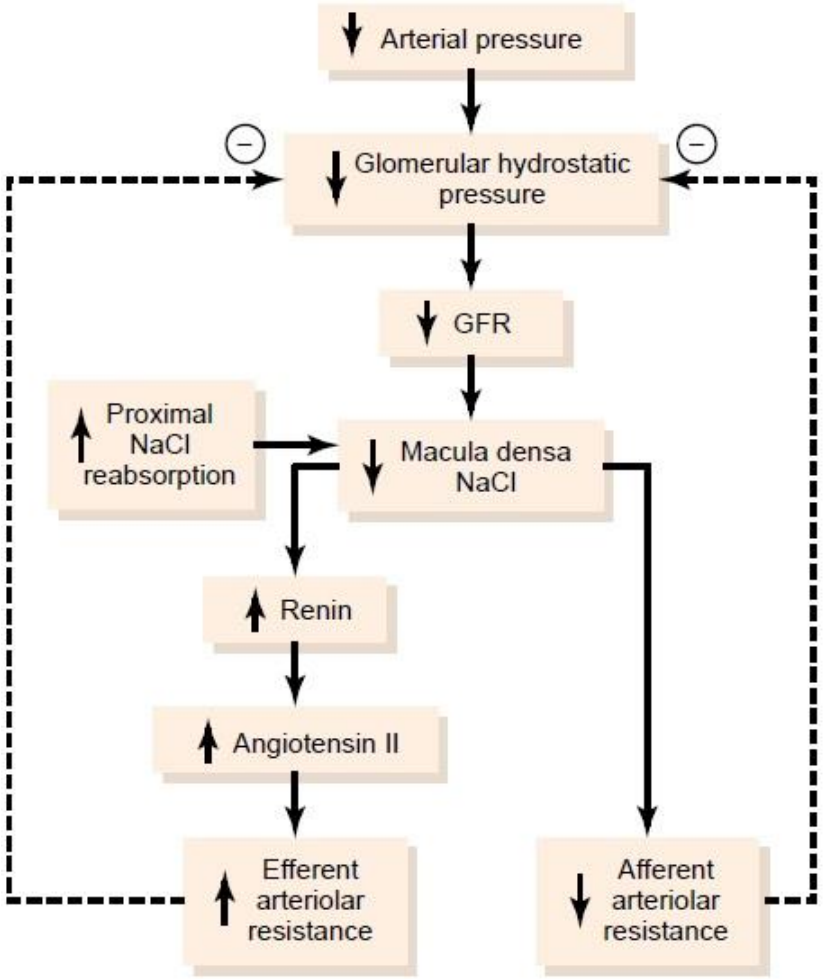

Figure 26–18

Macula densa feedback mechanism for autoregulation of glomerular hydrostatic pressure and glomerular filtration rate (GFR) during decreased renal arterial pressure.

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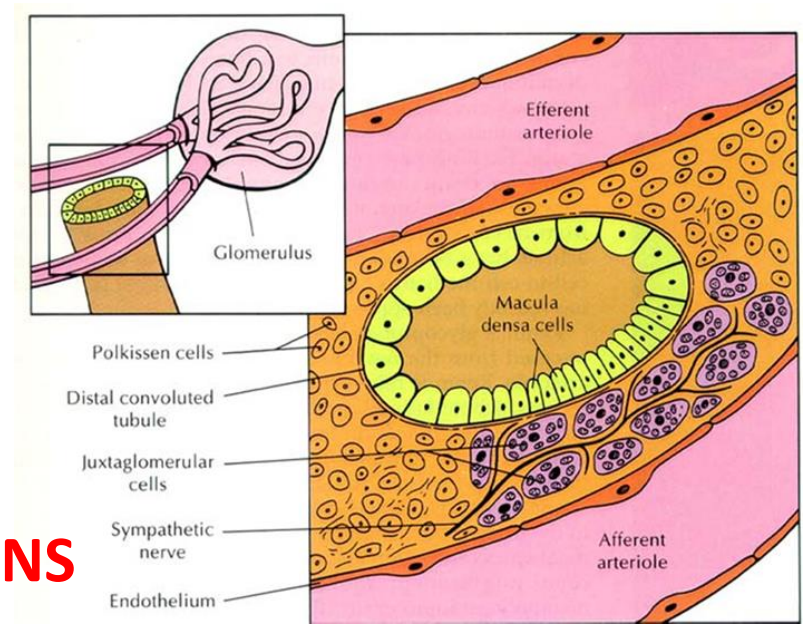
Juxtaglomerular apparatus (JGA)

- tubular and vascular component
  - (1) tubular component
    - specialized parts of distal tubule near afferent and efferent arterioles (**macula densa**)
    - cells of macula densa are sensitive to NaCl and control production of renin in **granular cells** of JGA
      - ecreased GFR slows the flow rate in the loop of Henle, causing increased reabsorption of sodium and chloride ions in the ascending loop of Henle, thereby reducing the concentration of sodium chloride at the macula densa cells
  - (2) vascular component
    - **afferent and efferent arterioles**
    - extra-glomerular **mesangium**
- JGA granular cells are specialized SMC producing and storing **renin**
  - cells of macula densa do not have a basal membrane to ensure tight contacts with granular cells
- both vascular and tubular components are **innervated by SNS**
  - renal nerve stimulation increases renin secretion by NE-induced stimulation of beta-adrenergic receptors



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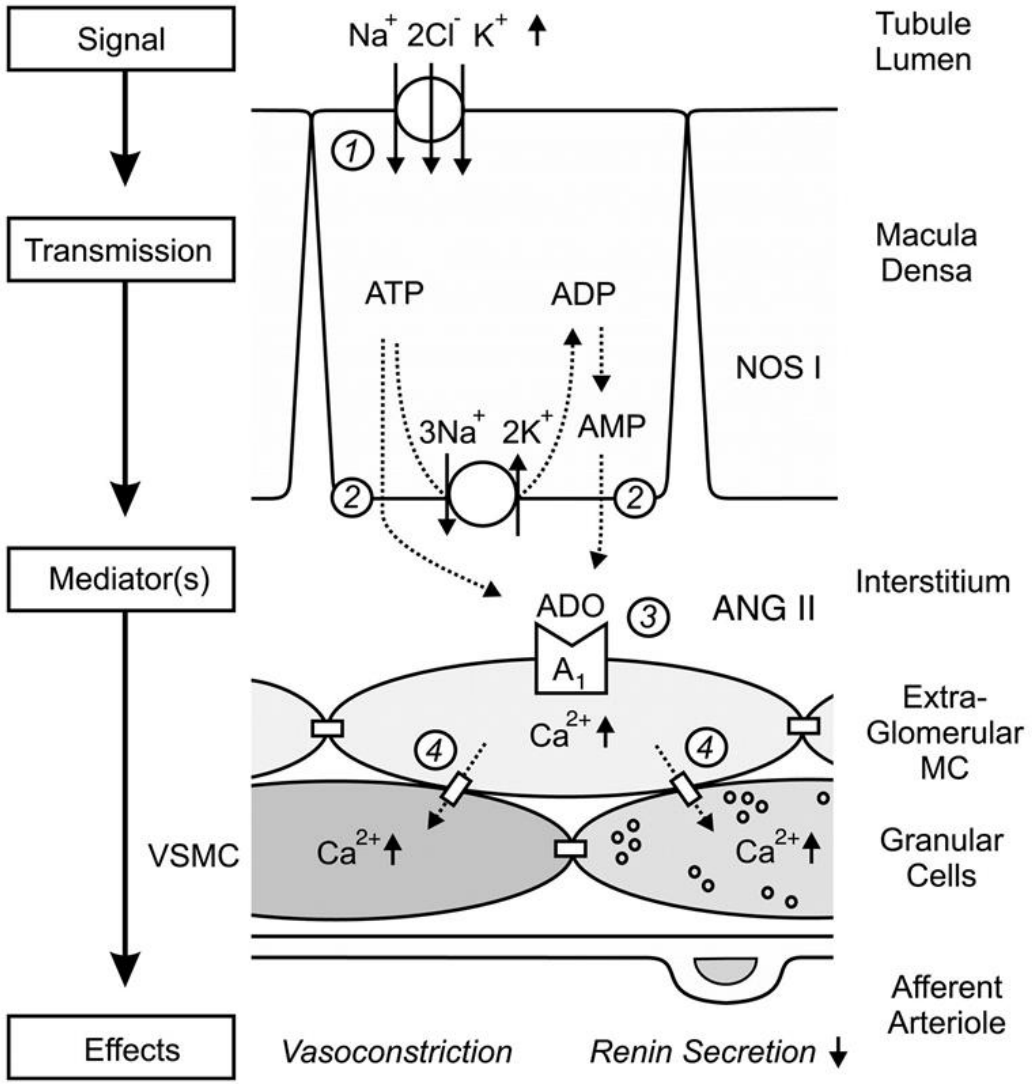
Detail mechanisms of TGF



Vallon V Physiology 2003;18:169-174

- macula densa cells (at the junction of ascending limb of loop of Henle and distal convoluted tubules)
  - presence of Na-K-2Cl symporter
    - when ↑ NaCl content at macula densa cells →- ↑ NaCl uptake → swelling of macula densa cells → release of ATP
      - stimulation of purinergic P2 receptors on mesangial cells and afferent arteriole smooth muscles
      - alternatively ATP may be metabolized to adenosine, which also causes vasoconstriction here
        - adenosine normally causes vasodilation in other tissues !!!
- effect of increased NaCl content
  - contraction of mesangial cells and contraction of glom. arterioles
    - reduction in effective filtration area
    - decreases GFR and RBF
  - NaCl content at macula densa also ↓ renin release
- effect of decreased NaCl content
  - opposite

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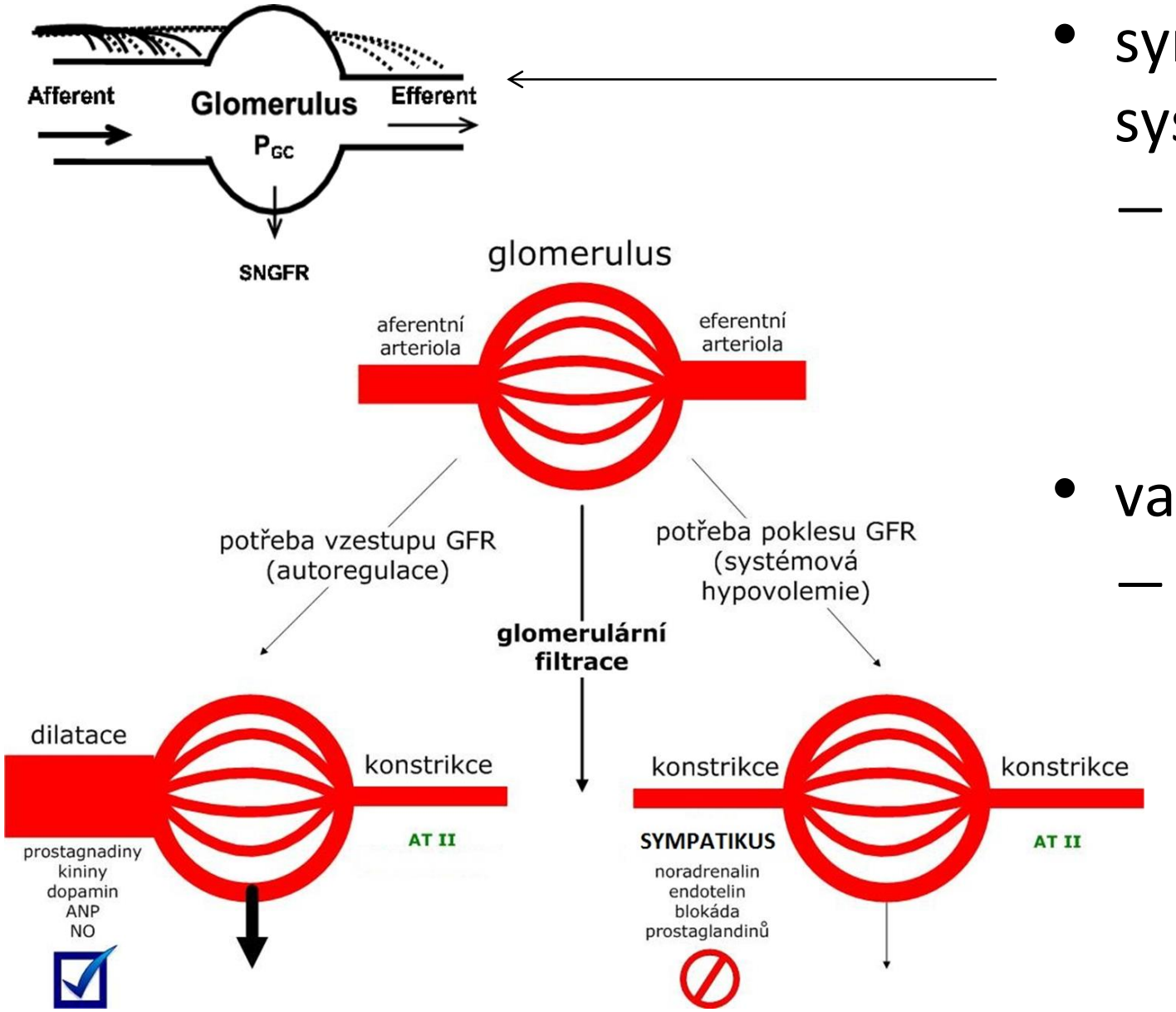
Other regulators of glom. hemodynamics



- sympathetic nervous system
  - sympathetic innervation of glom. arterioles
    - 3-time denser in afferent arteriole
- vasoactive peptides
  - receptors for vasodilators mainly in AA
    - their pharmacological blockade (e.g. by COX1 inhibitors) can decrease GFR without BP change

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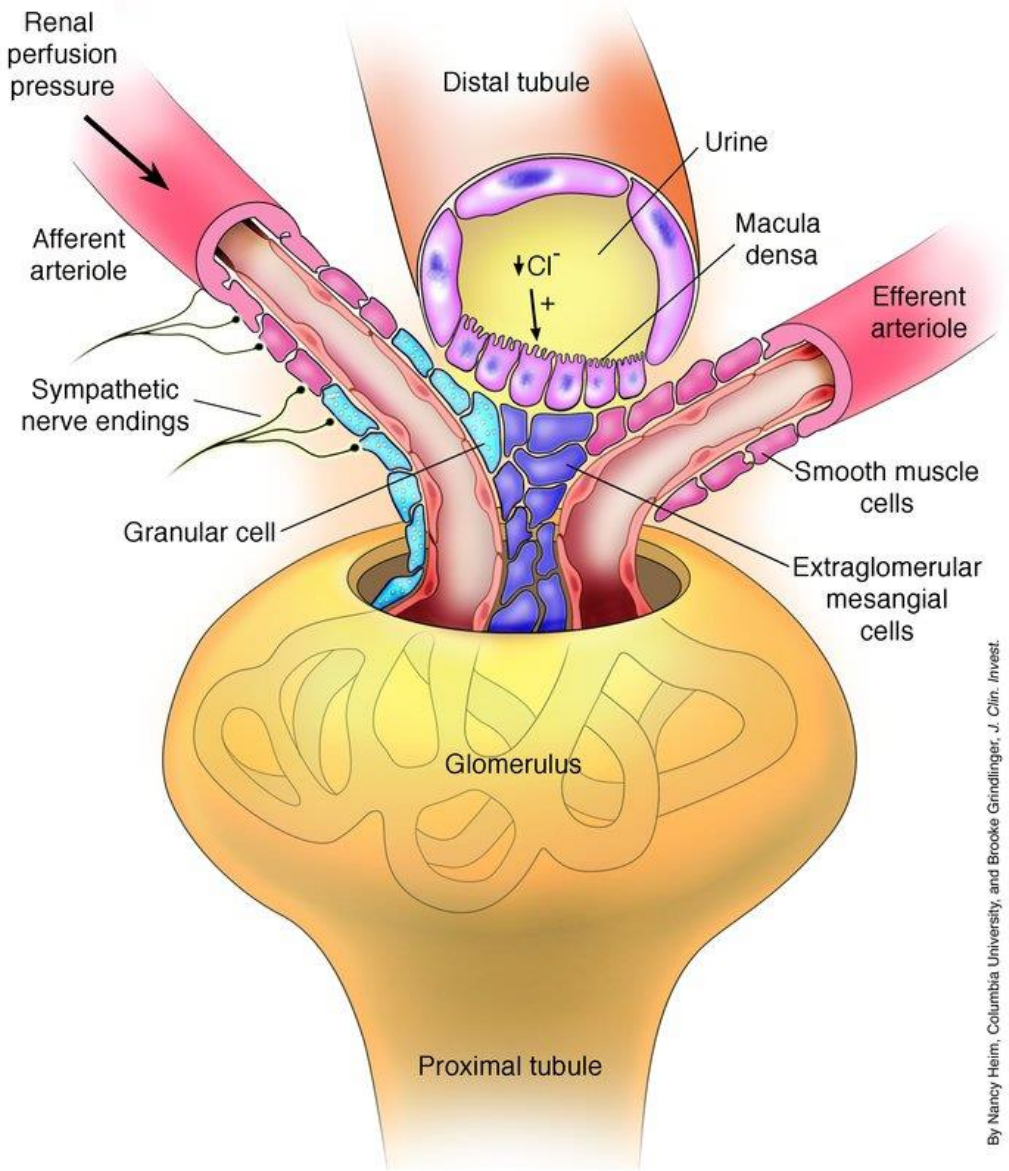
Three major mechanisms governing renin release and its effect



- (1) signals at the individual nephron
  - decreased NaCl load at the macula densa
  - decreased afferent arteriolar pressure
    - probably mediated by a cellular stretch mechanism (baroreceptors)
- (2) signals involving the entire kidney (systemic)
  - sympathetic activity
    - beta1-adrenergic receptor stimulation at the juxtaglomerular cells
  - at the same time, negative-feedback inhibition by AT II at the JG cells
  - other hormonal factors
- (3) local effectors – usually antagonists
  - prostaglandins E2 and I2
  - nitric oxide
  - adenosine
  - dopamine
  - arginine vasopressin

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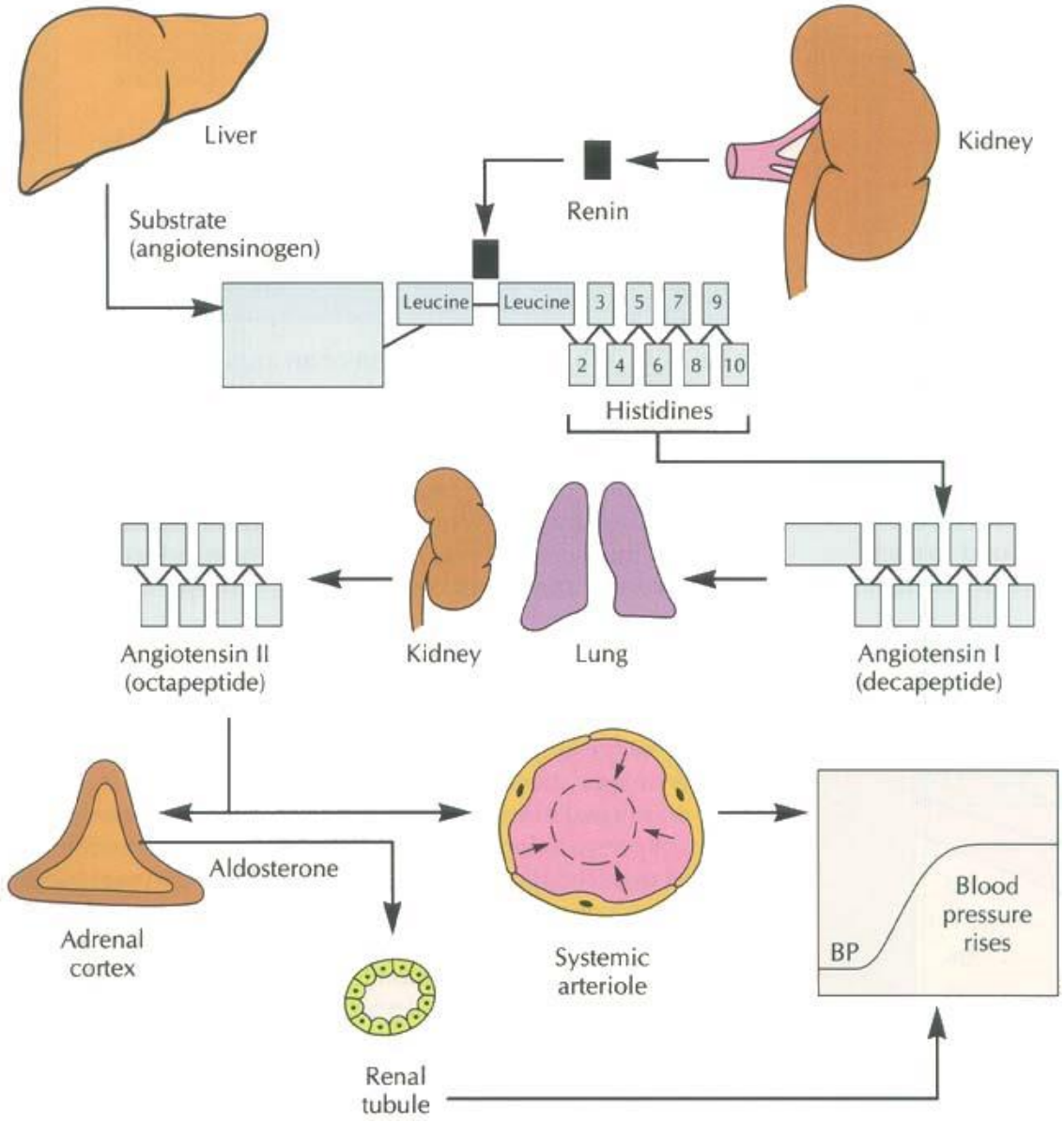
Systemic RAAS



- prorenin is converted to active renin by a trypsin-like activating enzyme
- renin enzymatically cleaves AGT to form the decapeptide AT I
  - this step can be blocked by renin inhibitors
- AT I is hydrolyzed to the octapeptide AT II by angiotensin- converting enzyme (ACE)
  - this step is blocked by ACE inhibitors
- AT II acts at a specific receptor
  - this interaction can be blocked by a variety of peptide or non-peptide AT II antagonists

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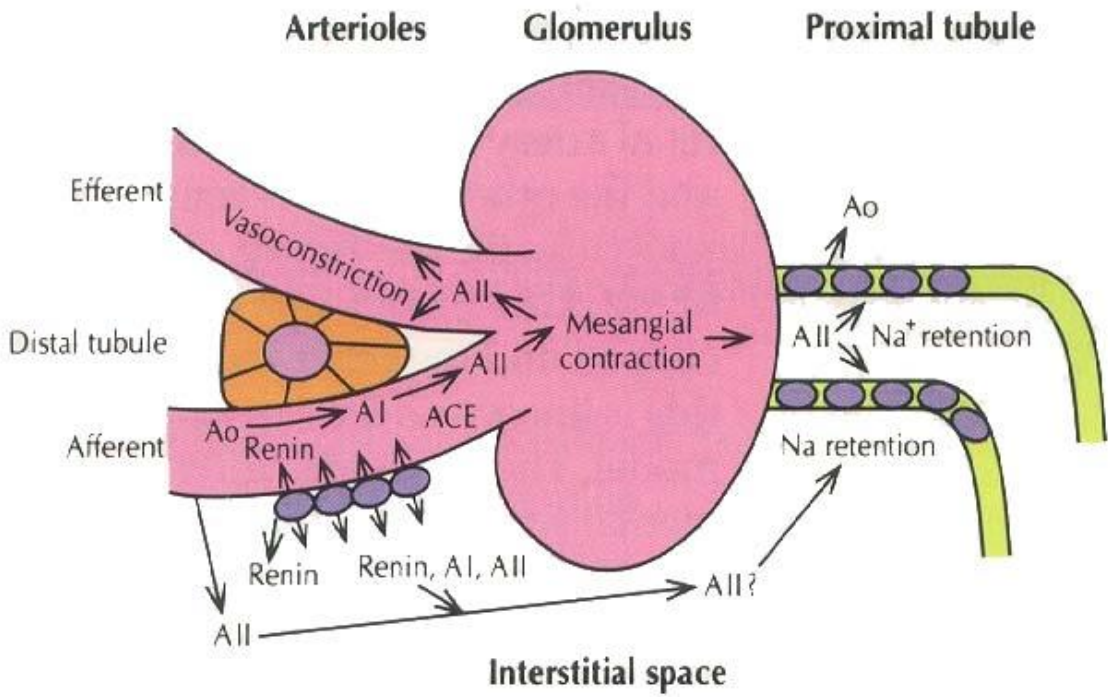
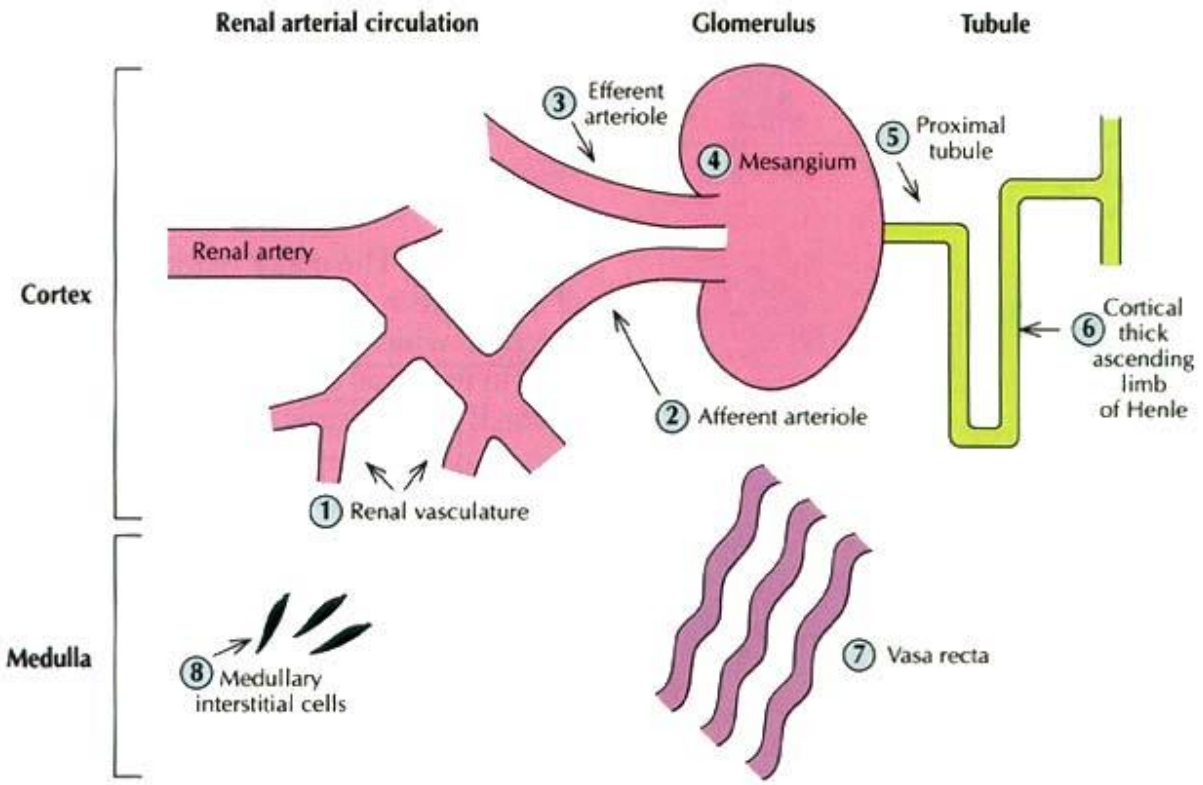
Paracrine effects of AT II in the kidney

- AGT either circulates to the kidney from the site of production in the liver or is synthesized locally in proximal tubular cells in the kidney
- renin is synthesized and released from the JG cells into the afferent arteriolar lumen or into the renal interstitium
- AT I is generated in the afferent arteriole and is converted to AT II by ACE and acts on efferent arteriole
- AT II can also be filtered at the glomerulus and may subsequently act at the proximal tubular cells to increase sodium reabsorption
- in the renal interstitium renin can cleave AGT to produce angiotensin peptides
  - these peptides may act at vascular and tubular structures



The renal tissue localization of AT II receptors and their physiologic action



- vasoconstriction occurs when AT II acts at receptors in the arcuate and interlobular arteries **[1]**, the afferent **[2]** and efferent **[3]** arterioles and the medullary vasa recta **[7]**
  - AT II preferentially constricts the efferent arteriole, thereby increasing glomerular filtration pressure
- AT II also acts on mesangial cell receptors [4] to produce cellular contraction and reduce glomerular filtration
- AT II receptors also are localized to the proximal tubule **[5]** and the cortical thick ascending LH cells **[6]** which cause sodium reabsorption
- AT II receptors are expressed also elsewhere in kidney - medullary interstitial cells **[8]** - but the physiologic significance of these receptors is still unknown
- in summary, AT II has three major effects all of which result in sodium retention
  - 1) arteriolar vasoconstriction
  - 2) renal sodium retention
  - 3) increased aldosterone biosynthesis
- these effects work together to maintain arterial blood pressure as well as blood volume
- AT II also stimulates the sympathetic nervous system, particularly the thirst center in the hypothalamus

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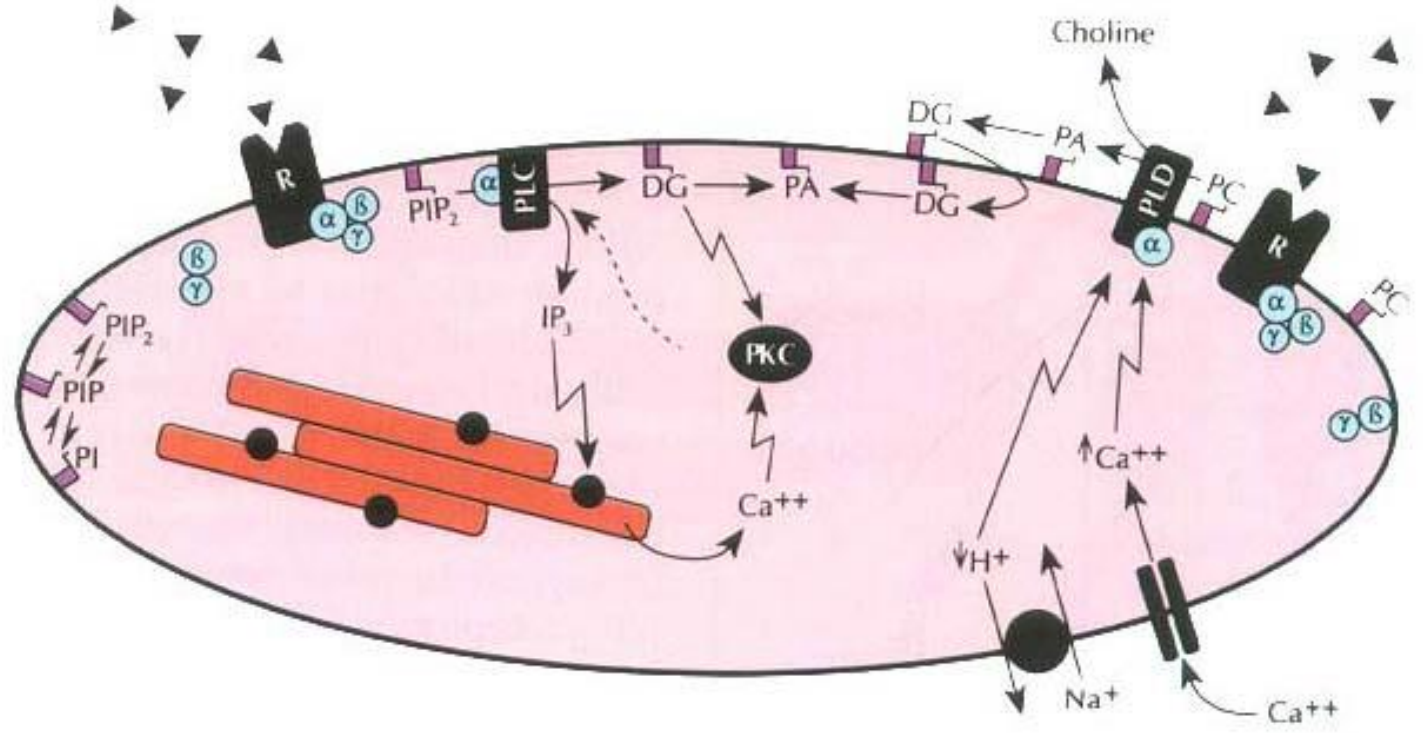
Cellular action of AT II



- when ATII activates AT1 receptors in vascular cells the peptide initiates a biphasic signalling response
  - the initial phase comprises PLC-mediated break-down of the inositol polyphospholipids to generate IP3 and DAG as well as to mobilize intracellular calcium
  - the second phase is characterized by a sustained accumulation of DAG, activation of PKC, hydrolysis of phosphatidylcholine-mediated by PLD, and intracellular alkalinization

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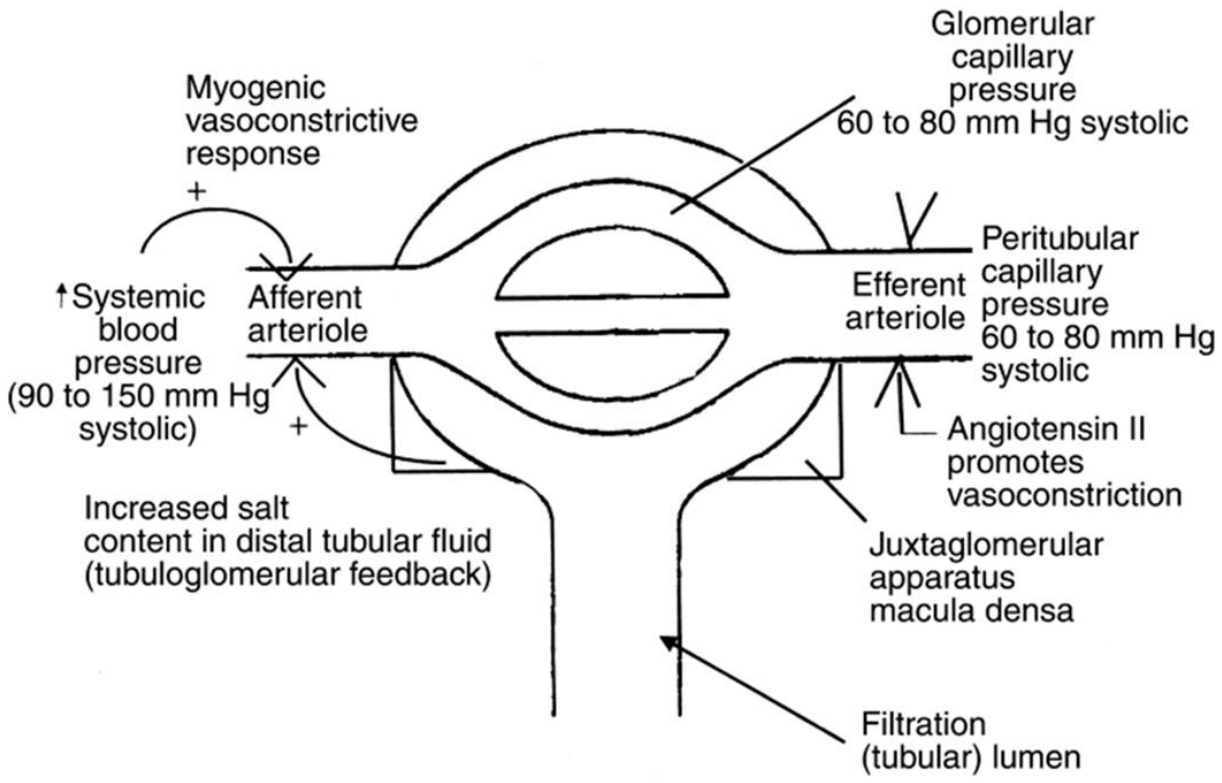
RBF is regulated in conflicting manner



- during light to moderate decrease of systemic pressure by autoregulation
  - the aim is to maintain stable renal perfusion, GFR a homeostasis
  - BUT! there are pathologic situation arising from this, for example **pressure diuresis** in
    - **high protein intake** – increased reabsorption of AA (together with Na^+) in PCT will deplete Na^+ in DCT and increase filtration pressure
    - **hyperglycemia** – increased reabsorption of glucose (together with Na^+) in PCT will deplete Na^+ in DCT and increase filtration pressure
      - in this case also osmotic pressure of filtrate with incompletely reabsorbed glucose (renal threshold) will potentiate **osmotic diuresis**
- during significant decrease (circulation emergency) perfusion of kidney drops in "systemic interest"
  - **pre-renal azotemia**
  - eventually with morphological consequences (**acute tubular necrosis**)

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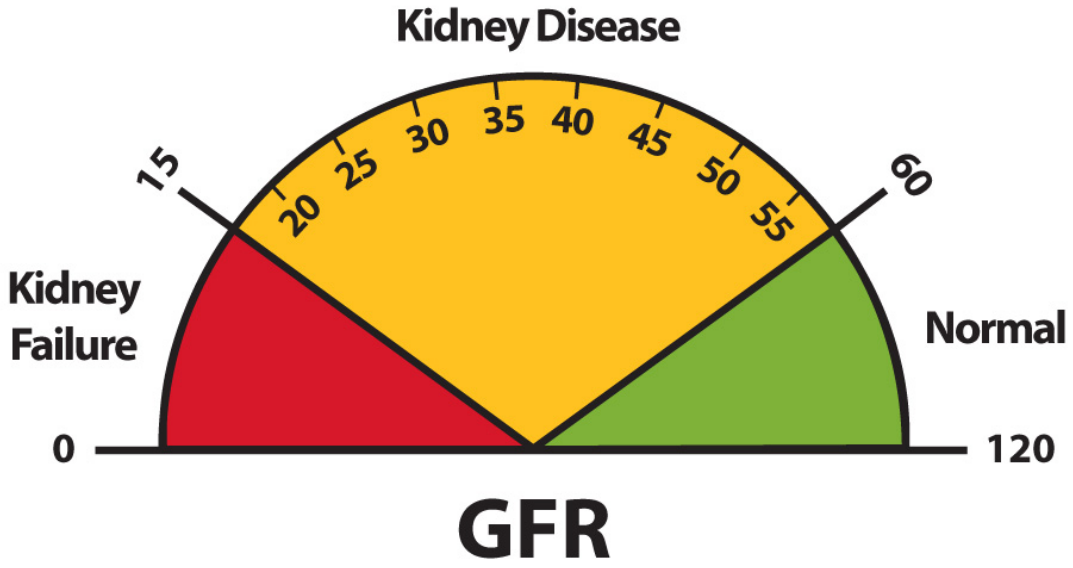

GFR MEASUREMENT / ESTIMATION SINCE IT CANNOT BE MEASURED DIRECTLY

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Measurement of GFR

- GFR is a main parameter characterizing kidney function
  - — however the volume of glomerular filtrate produced per time unit is **not directly measurable**
- it can be assessed precisely enough by
  - — (1) determining **clearance** of certain substances fulfilling certain criteria (see further)
    - endogenous substances – creatinine, urea
    - exogenous
      - — unlabeled tracer – inulin,
      - — radio-contrast - iohexol
      - — radioactive isotope – [^{51}Cr] EDTA, [^{125}I] iothalamate, [^{99}Tcm] DTPA
  - — (2) **estimation** of GFR based on plasma levels of endogenous substances by **formula**
    - creatinine - Cockroft-Gault, MDRD, CKD-EPI, …
    - other endogenous markers (freely filtered and completely degraded by tubular cells)
      - — β2-microglobulin, cystatin C

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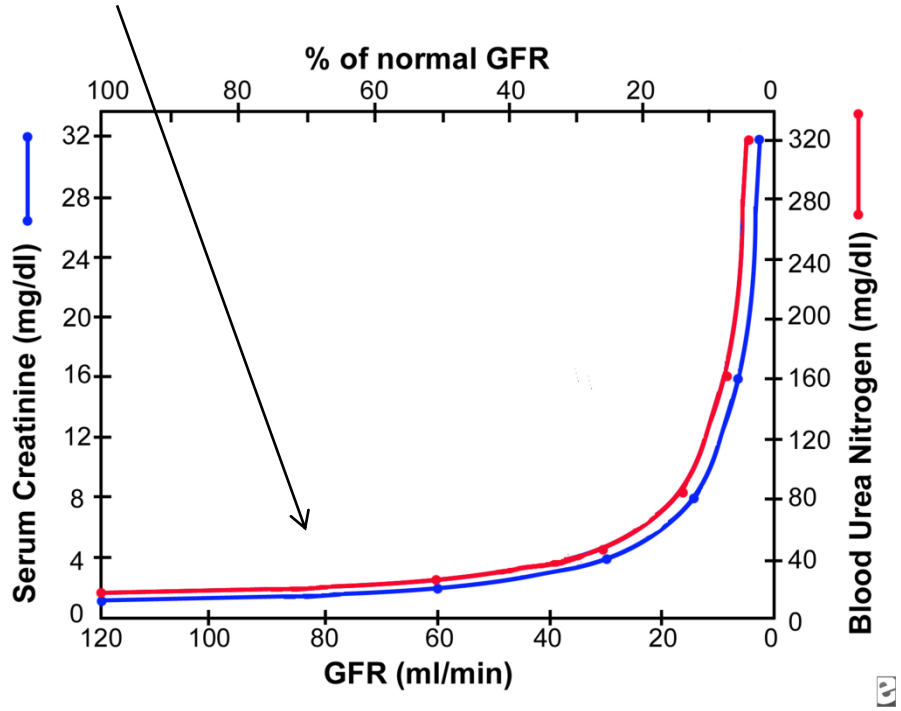
Clearance

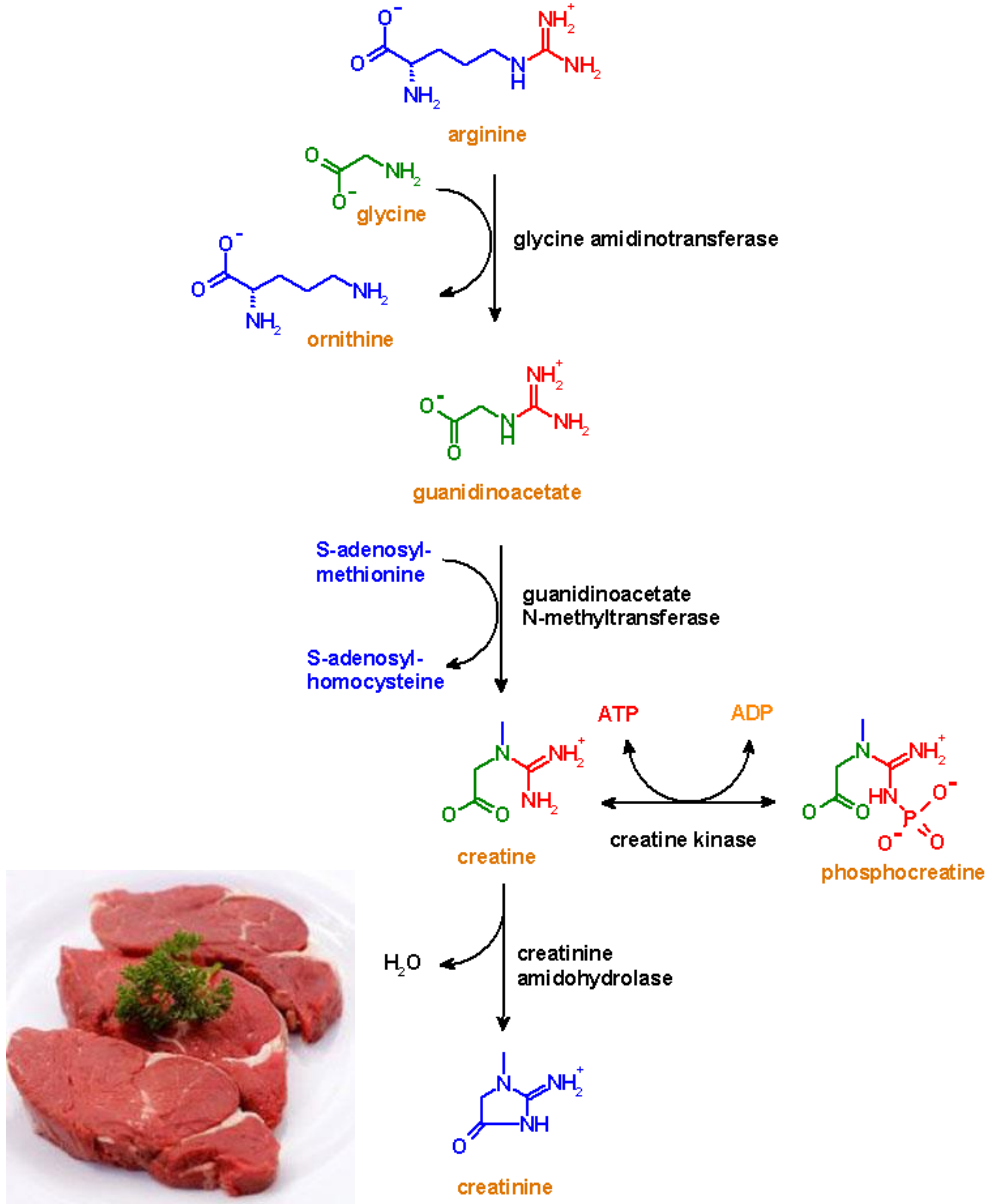
- substances must fulfill following criteria
  - LMW, freely filtered to urine, unbound to plasma carriers
  - not undergoing further degradation
  - no tub. reabsorption nor secretion
  - concentration in plasma and analogic volume of glom. filtrate is stable
  - detection method is simple, cheap and standardized
- concentration in urine is proportional to changes of GFR:
  - **$[P] \times GF = V \times [U]$**
- clearance of substance X = volume of plasma that is cleared of substance X per unit time
  - units: volume/time
  - timed urine collection is necessary
    - ideally 24 hrs, often shorter

hyperbolic relationship is clinically very important



Creatinin

- produced in muscles from creatin
- in kidneys 90% filtered, z 10% secreted to urine by tubules
  - the contribution of tubular secretion rises with ↓ filtration (↓ number of functional nephrons)
  - i.e. the lower the GFR the less precise assessment of GFR by Cr, but still the best endogenous marker of GFR
- there are possible technical problems with timed urine collection
  - suboptimal cooperation of patient
- concentration of S-creatinine directly related to muscle mass (therefore depends on age and gender)
  - plasma creatinine = 35 – 100 µmol/l, production 1.2mg/min
  - usually corrected for body surface area (1.73m^2), but still there are discrepancies due to body composition
    - 25-yrs old athlete vs. 60-yrs old obese man with the same weight and body surface
- intra-individual fluctuation not more than 10 - 15%
  - concentration rises after the strenuous physical exercise and after intake of exogenous creatinine (meat)
    - especially fried



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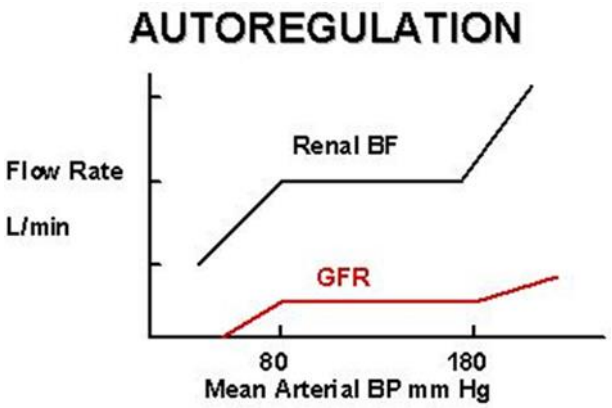
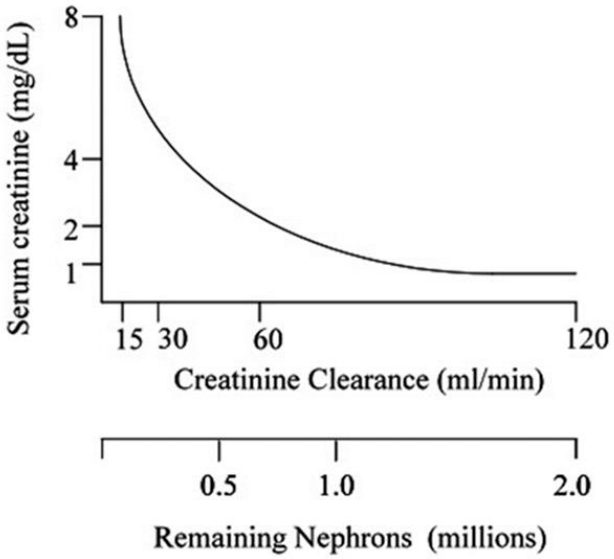
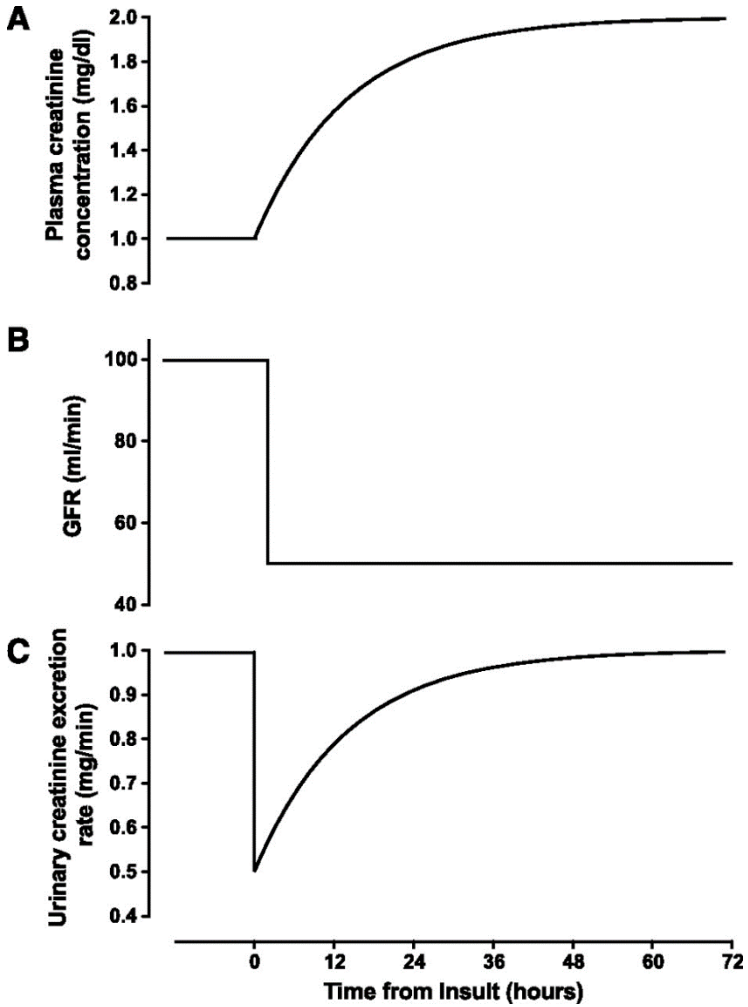
Relationship between GFR and serum creatinine!!!

GFR ~120ml/min/1.73m²





- no significant changes of GFR with loss of up to 50% of functional glomeruli
  - non-linear relationship of [Cr] and GFR
- with progressive renal disease (e.g. another ~50% of the remaining capacity) initial GFR decline is not accompanied by rise of [Cr]
  - with more pronounced GFR decline serum Cr levels rise more steeply
  - only then have Cr serum levels diagnostic value
  - at the same time, tubular secretion of Cr starts to rise
- estimated GFR (eGFR)
  - calculation of GFR using serum Cr, age and body weight
    - Cockroft-Gault and other formulas → mathematical expression of hyperbolic



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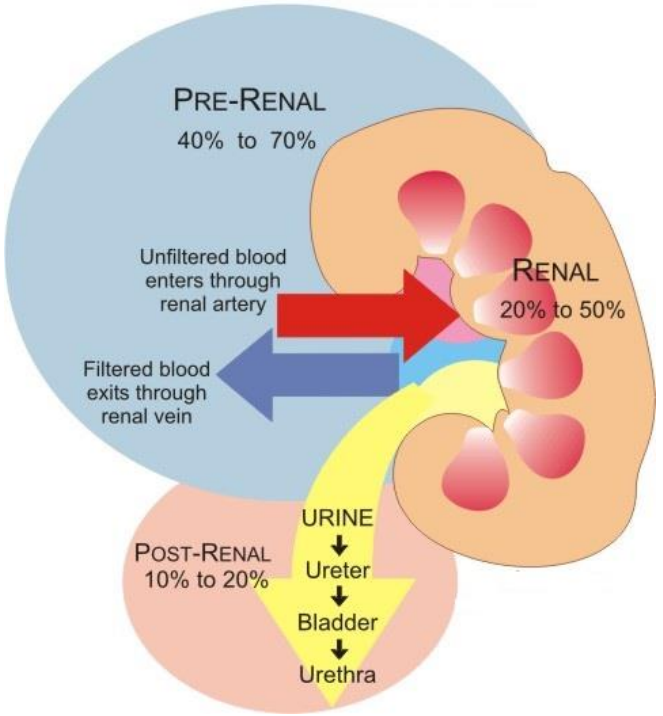

ACUTE KIDNEY INJURY (AKI)
[FORMERLY ACUTE RENAL FAILURE (ARF)]

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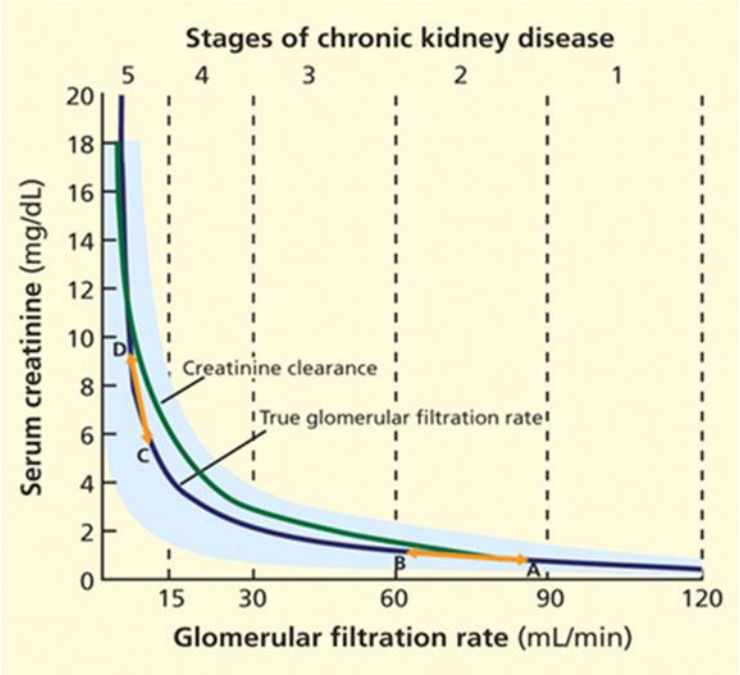
Terminology – renal insufficiency

- situation when kidneys are able to maintain homeostasis under the basal conditions, but not under the stress, e.g.:
  - infection
  - surgery
  - excess intake of protein, fluid or electrolytes
- typically a product of **chronic kidney disease** (CKD)
  - CKD (stages 1 - 5) defined (disregard of etiology) solely based on GFR (see table)
  - degree of albuminuria can be taken into account
    - renal insufficiency corresponds to stages 3 - 4
    - renal failure to stage 5

Stage	Description	GFR (ml/min/1.73m^2)
1	Kidney damage with normal or ↑GFR	≥ 90
2	Kidney damage with mild ↓GFR	60 - 89
3	Moderate ↓GFR	30 - 59
4	Severe ↓GFR	15 – 29
5	Kidney failure	< 15 (or dialysis)



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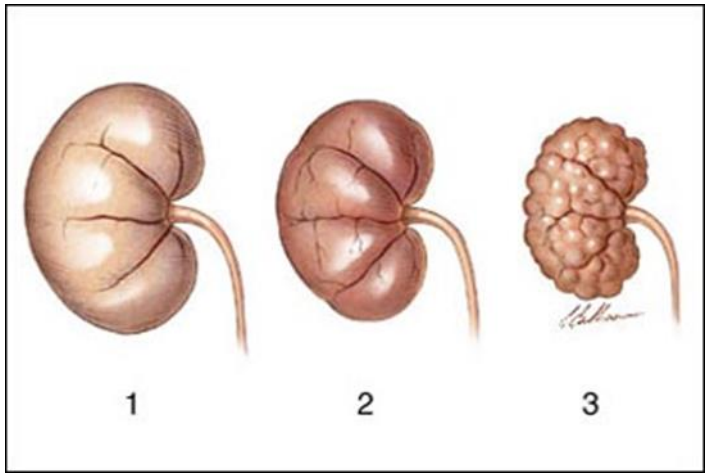
Terminology – renal failure (RF)

- situation when kidneys are not able to
  - a) excrete waste products of protein catabolism (nitrogen-containing compounds) metabolism
  - b) maintain volume and electrolyte homeostasis and AB balance
- under the basal conditions with normal protein (min 0.5g/kg/day) and energy intake
- **azotemia** = increased concentration of non-protein nitrogen-containing compounds
  - creatinine, blood urea nitrogen (BUN)
  - accompanies RF (diagnostic sign) and is a feature of uremic syndrome
- **uremia** („urine in blood“) = cluster of clinical abnormalities (uremic syndrome) due to RF
- causes of RF:
  - suddenly in subject without pre-existing renal pathology = **acute RF** (ARF, situation 1 in figure below)
    - **acute kidney injury** (AKI) is a synonym
  - as a consequence of a chronic renal disease with progressive loss of renal function = **chronic RF** (situation 3 in figure below)
    - **end-stage renal disease** (ESRD) is a synonym
- etiology
  - 1) pre-renal
  - 2) renal
  - 3) post-renal
- 70% patients with ARF/AKI develop **acute tubular necrosis**



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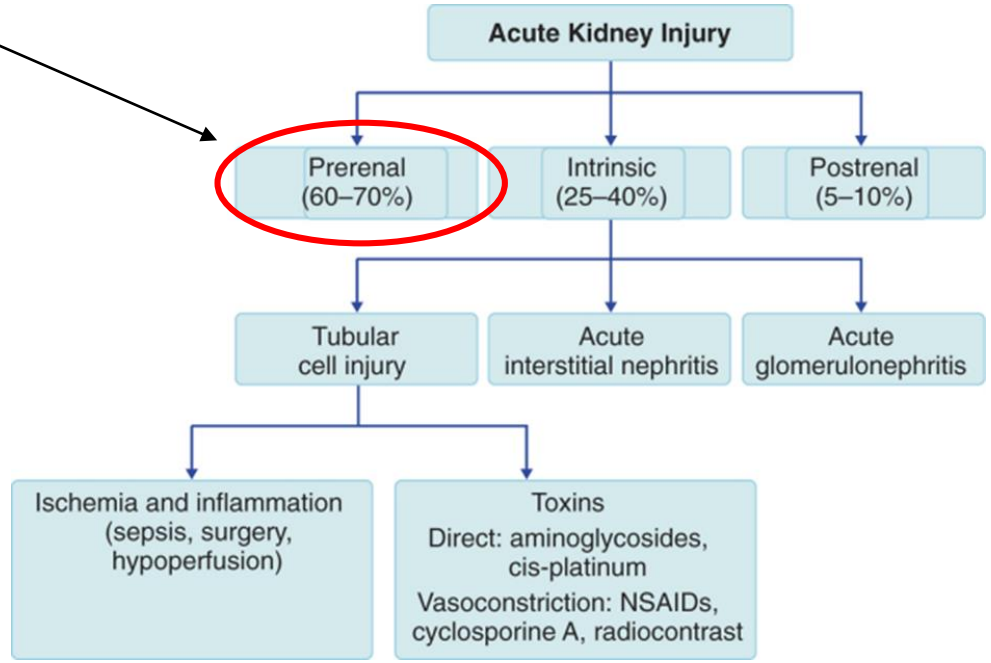
Who is in immediate risk of AKI

- most episodes of AKI occur in the hospital !!!
  - mortality rates ranging from 36% to as high as 86% (depends on the setting in which AKI is acquired, the age of the patient, and the acuity of the illness)
- **5–20% of critically ill patients** experience an episode of acute renal failure during the course of their illness, in many cases accompanied by **multi-organ dysfunction syndrome** (MODS)
- recognition of risk patients – blood loss, vasodilation, ↓ effective circulating volume (systemic edema)
  - patients after extensive surgery
  - heart operations (extracorporeal circulation)
  - septic shock
  - but also less critically ill patients with
    - **pre-existing kidney disease** (serum creatinine >180 µmol/l)
    - **multiple comorbidities** (heart and liver!)
      - renovascular disease has been found in 34% of elderly people with heart failure!
    - those treated with **NSAID, ACEI or ARBs**
- risk of progression of pre-renal AKI into the renal form
  - **acute tubular necrosis**
- maintenance of sufficient renal perfusion
  - isovolemia, cardiac output, normal BP
  - attention to administering potential nephrotoxins



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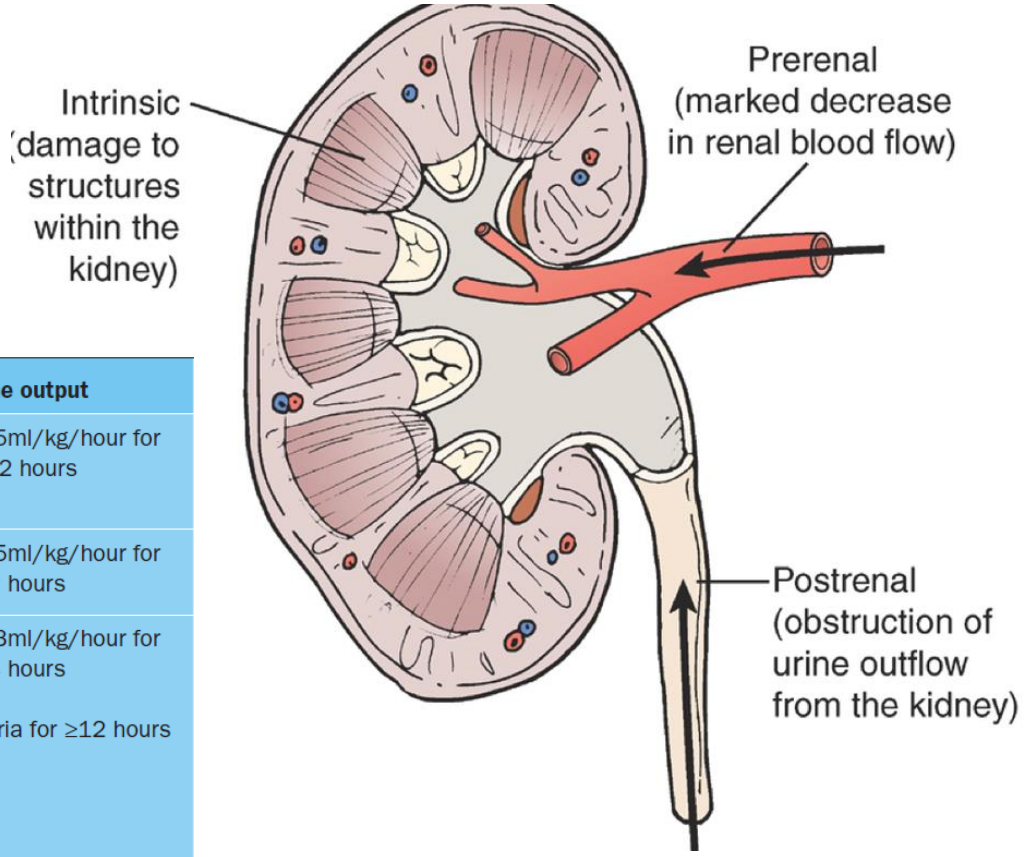
Etiology and pathogenesis of AKI

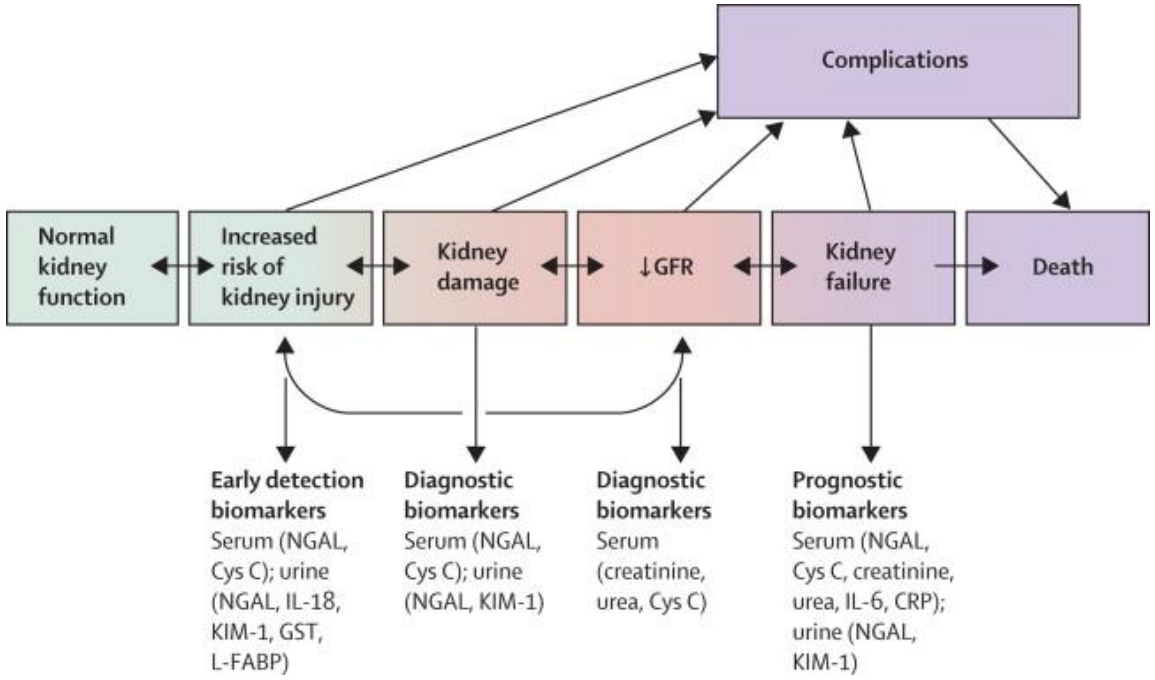
- acute and rapidly progressive (**within hours to days**) **decrease of GFR** and excretion in both kidneys
- classification stages AKI into three levels of severity on the basis of acute increases in serum creatinine level, decreased urine output or need for renal replacement therapies
  - oliguria < 500 ml/day
  - anuria < 100 ml/day
- etiology
  - (A) pre-renal azotemia
  - (B) renal (intrinsic) azotemia
  - (C) post-renal azotemia
- pathogenesis
  - volume depletion
    - decreased blood flow through glomeruli
  - loss of filtration area or change of glomerular filtration barrier permeability
  - increased pressure in tubules or Bowman capsule
- Although the process may be reversible, **full recovery of kidney function is uncommon**
  - each episode of AKI is associated with considerable mortality and long-term adverse outcomes, including cardiovascular complications, chronic kidney disease and end-stage renal disease

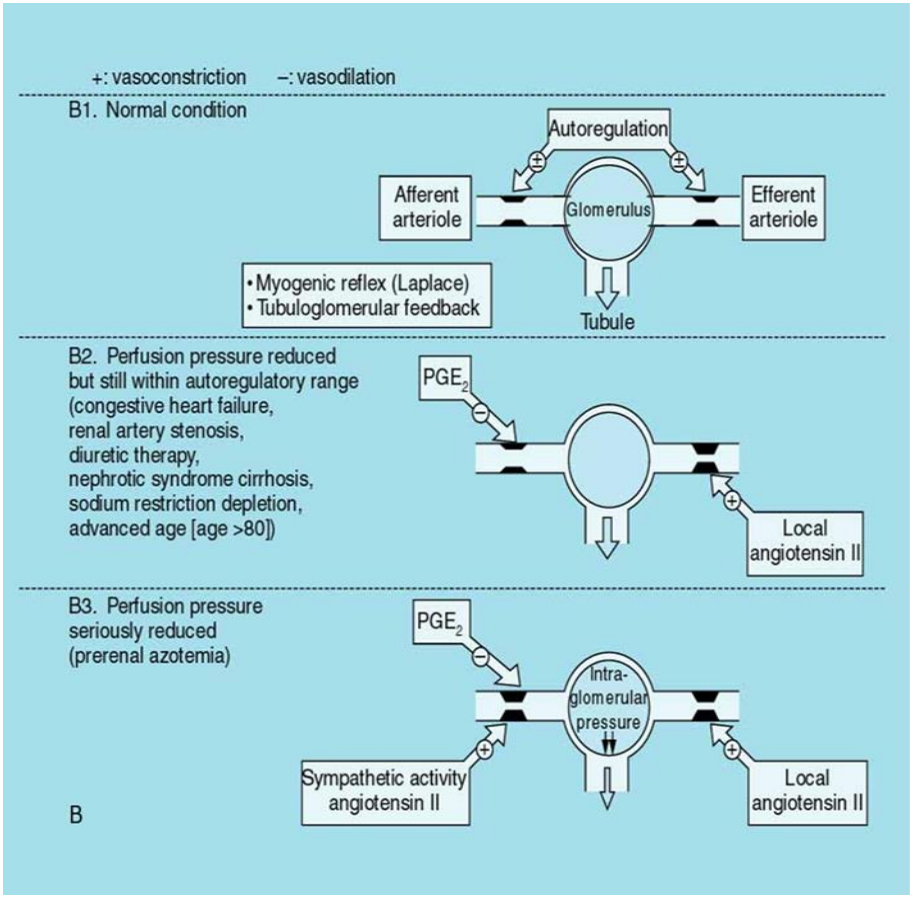
Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ≥26.5μmol/L increase	<0.5ml/kg/hour for 6–12 hours
2	2.0–2.9 times baseline	<0.5ml/kg/hour for ≥12 hours
3	3.0 times baseline OR Increase in serum creatinine to ≥353.6μmol/L OR Initiation of renal replacement therapy	<0.3ml/kg/hour for ≥24 hours OR Anuria for ≥12 hours



(A) pre-renal AKI

- most common type of AKI caused by **impaired renal blood** flow below the range of autoregulation
  - GFR declines because of the decrease in filtration pressure
    - massive activation of RAAS
    - systemic sympathetic activity
  - AKI may superimpose on chronic renal condition under the sudden stress
- failure to restore normal blood perfusion through kidneys may cause **acute tubular necrosis** (ATN)
  - therefore progress to a renal form of ARF
- **biomarkers** are being used to monitor the dynamics of AKI





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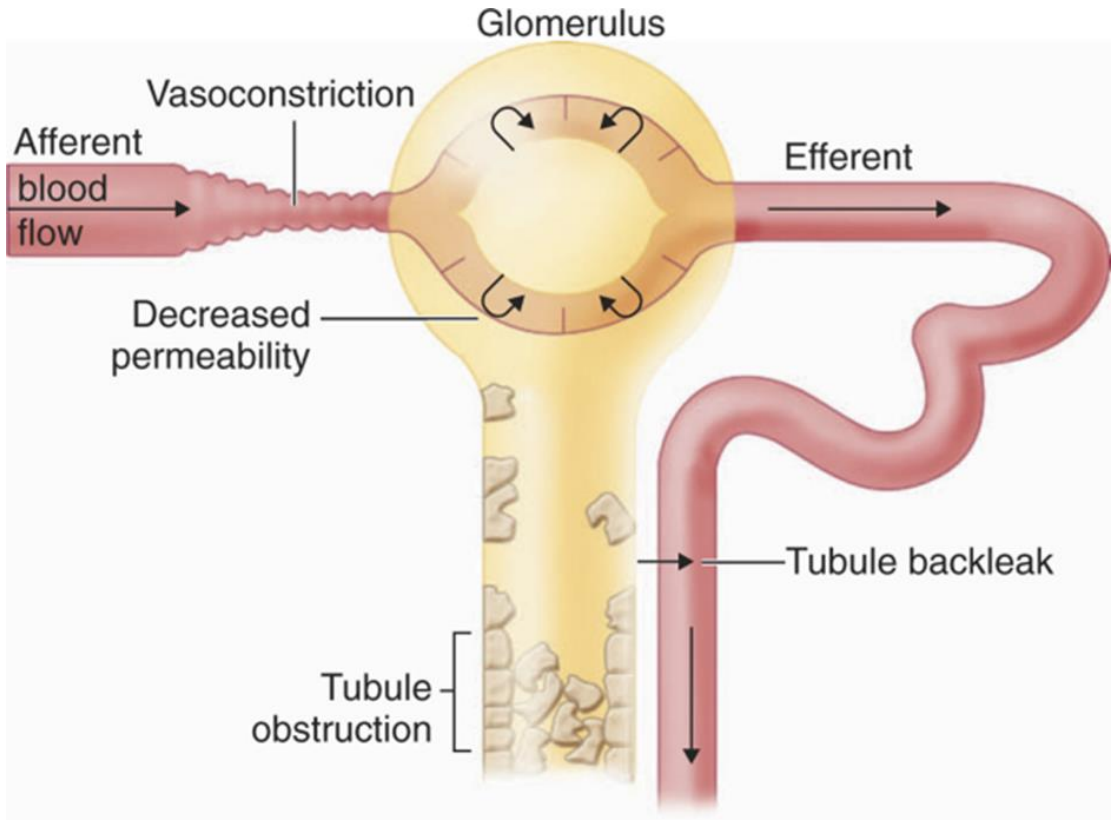
Examples – selected etiologies of pre-renal AKI

- acute heart failure & cardiogenic shock
  - acute myocardial infarction
  - arrhythmias with low cardiac output
  - pericardial tamponade
- intravascular volume depletion and hypotension
  - hemorrhage
  - gastrointestinal, renal, and dermal losses (burns)
- decreased effective intravascular volume
  - congestive heart failure
  - cirrhosis (ascites)
  - peritonitis
- systemic vasodilation/renal vasoconstriction
  - sepsis
  - hepatorenal syndrome
  - inappropriate anti-hypertensive therapy



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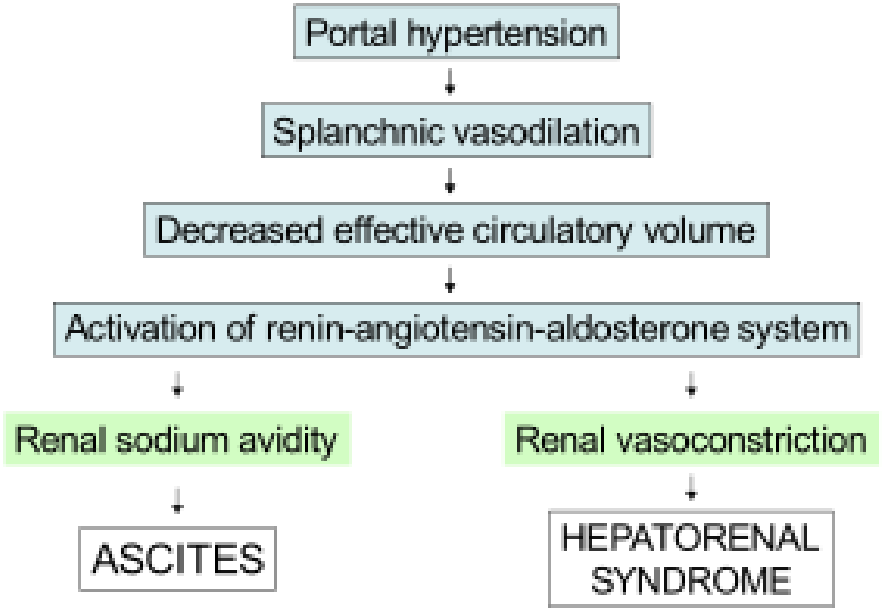
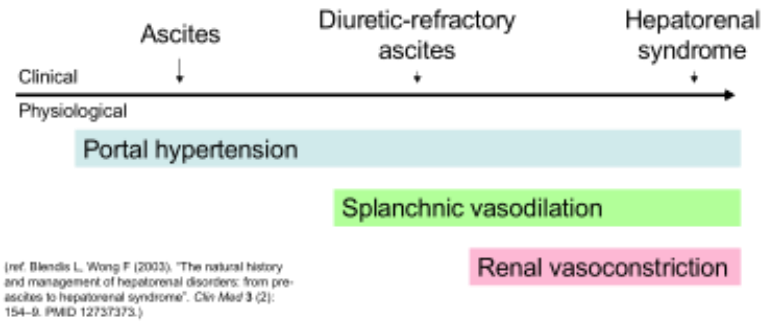
Typical pre-renal AKI: hepatorenal syndrome

- developing in patients with advanced chronic liver disease who have portal hypertension and ascites
  - at least 40% of patients with cirrhosis will develop HRS during the natural history of their disease
- pathogenesis
  - hypovolemia
    - congestion in GIT due to portal hypertension
    - ascites
    - bleeding
  - decreased RBF in generally hyperkinetic circulation (typical liver failure)
    - drop of BP due to peripheral vasodilation lead to constriction of afferent arterioles (mediated by sympathetic innervation) and subsequent ischemia of renal cortex





(ref. Blendis L, Wong F (2003). "The natural history and management of hepatorenal disorders: from pre-ascites to hepatorenal syndrome". *Clin Med* 3 (2): 154–9. PMID 12737373.)

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Circulation abnormalities in liver cirrhosis

Liver cirrhosis

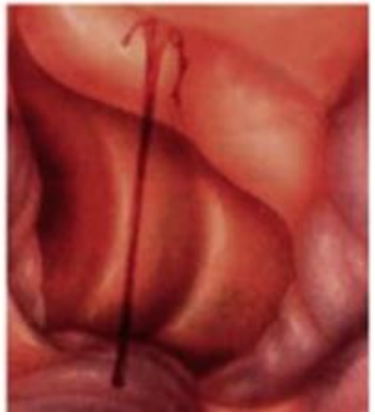
↓

Increase in intrahepatic resistance

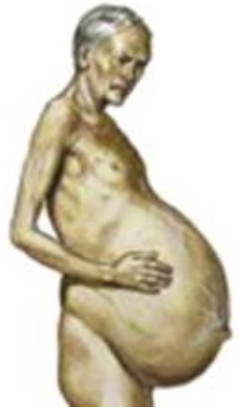
↓

Portal (sinosoidal) hypertension

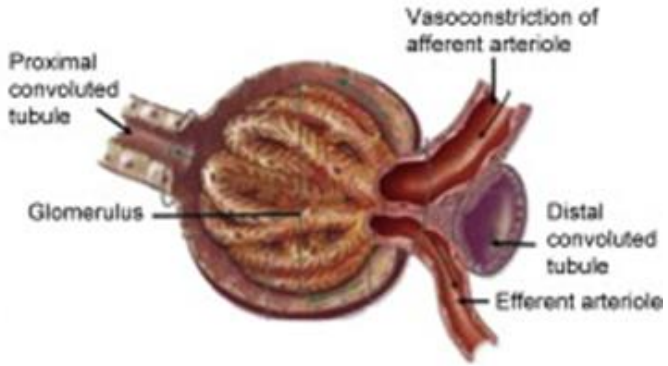
- development of collateral porto-systemic shunts
  - ↓
  - development of varices in the oesophagus
    - ↓
    - **Variceal Bleeding**



- Splanchnic/systemic vasodilation
  - ↓
  - Reduction in effective arterial blood volume
    - ↓
    - Activation of vasoconstrictive neurohumoral systems
      - ↓
      - Water and sodium retention
        - ↓
        - **Ascites**



      - ↓
      - Renal vasoconstriction
        - ↓
        - **Hepatorenal Syndrome**



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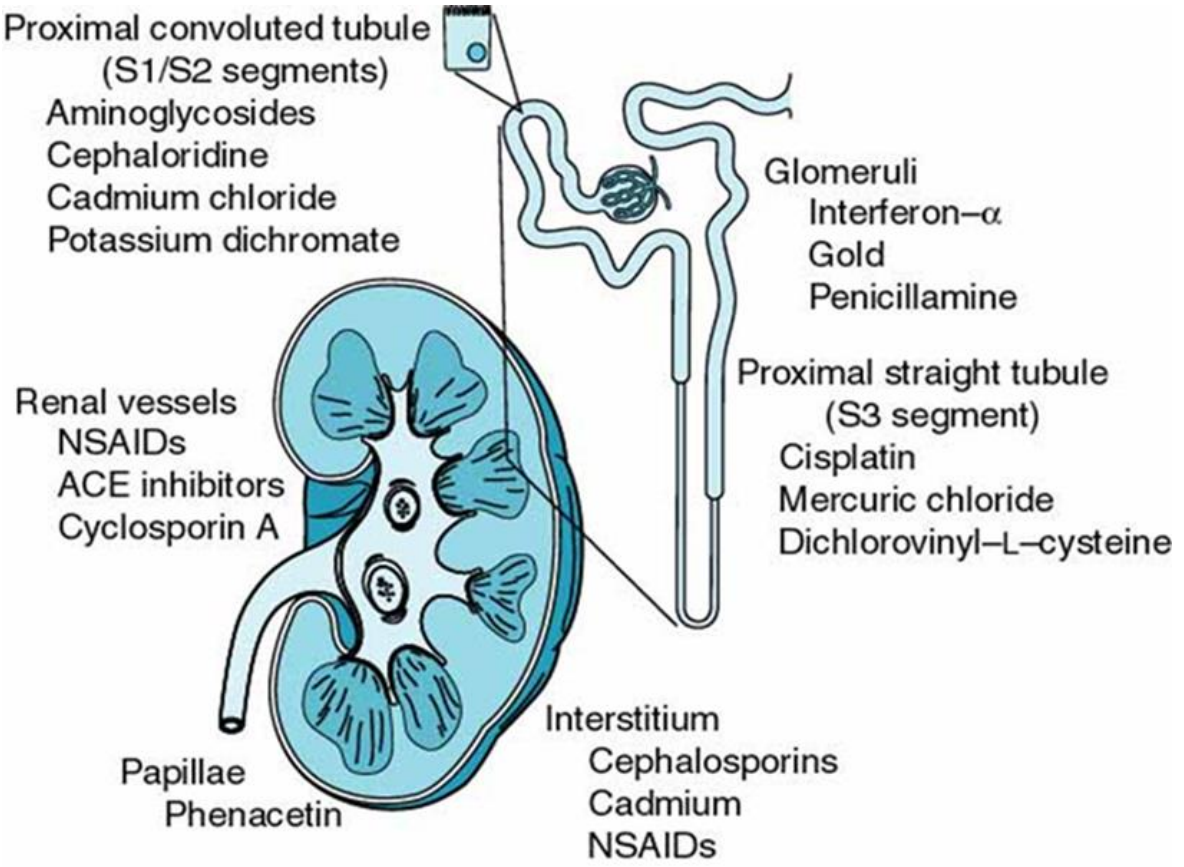
(B) renal (intrinsic) AKI

- large-vessel renal vascular disease
  - renal artery thrombosis or embolism
  - renal artery stenosis
  - thrombosis of renal veins
- small-vessel renal vascular disease
  - vasculitis
  - hemolytic-uremic syndrome
  - others
    - malignant hypertension, scleroderma, preeclampsia, sickle cell anemia, hypercalcemia, transplant rejection
- impaired renal blood flow
  - ↓ post-glomerular resistance (**ACEs, ARBs**)
  - ↑ pre-glomerular resistance (**NSAIDs**)
  - **radiocontrast agents**
- glomerular diseases
  - acute glomerulonephritis, esp. rapidly progressing GN
- acute tubular necrosis
  - ischemia
  - **toxins/drugs**
  - obstruction (hemolysis, rhabdomyolysis, paraprotein)
- acute interstitial diseases
  - **toxo-allergic (drugs)**
  - infection
  - idiopathic



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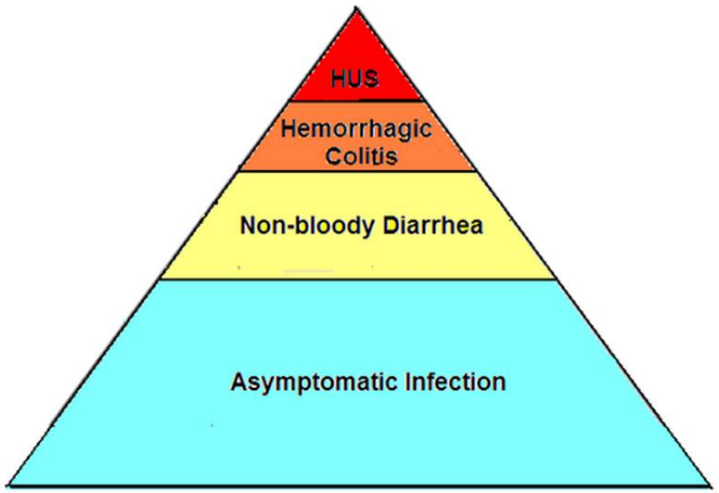
Typical renal AKI: hemolytic-uremic syndrome



Spectrum of Disease Caused by E. Coli

- HUS is a disorder that usually occurs when an infection in the digestive system (but also other causes) produces toxic substances that destroy red blood cells
  - hemolytic anemia → hemoglobinuria → precipitation of hemoglobin in tubules causes AKI
  - also thrombocytopenia → bleeding
- etiology
  - gastrointestinal infections
    - E. coli
    - Shigellosis dysentery
    - Salmonellosis
  - non-gastrointestinal infections
    - Pneumococcus infection
  - iatrogenic (drugs)
- HUS is most common in children
  - the most common cause of AKI/ARF in children
- HUS is more complicated in adults
  - similar to thrombotic thrombocytopenic purpura (TTP)

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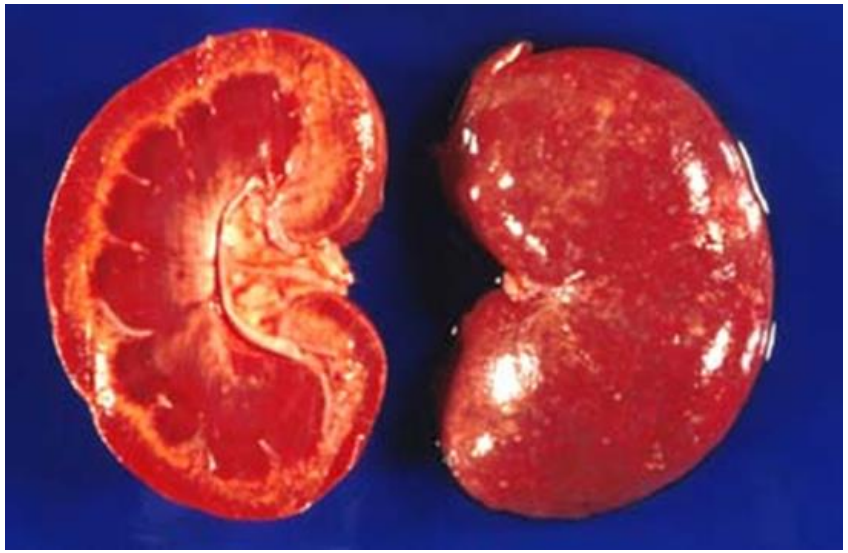
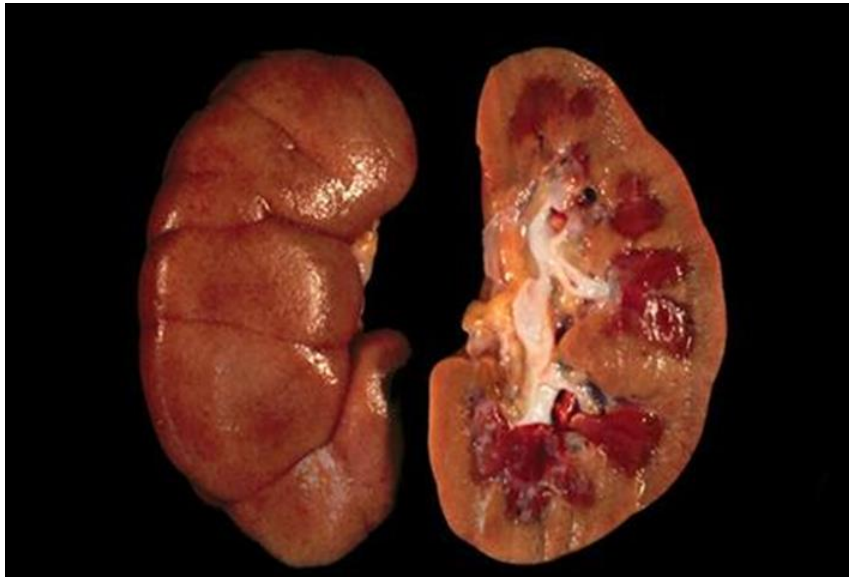
Acute tubular necrosis (ATN)





- clinical-pathological entity, not a disease
- abrupt and sustained drop of GFR due to ischemic od nephrotoxic insult to tubules
  - but tubular pathology also affects kidney intersticium
- etiology
  - (1) ischemia
    - generates toxic oxygen free radicals and inflammatory mediators that cause swelling, injury, and necrosis
  - (2) toxic
    - drugs
      - antibiotics, antiviral, antifungal, cytostatics
    - toxins (bacterial), myoglobin, haemoglobin,
    - radiocontrast nephropathy
    - environmental toxins (heavy metals such as mercury, arsenic)
- reasons for high vulnerability of tubules to ischemia and toxins
  - lower perfusion of medulla compared to cortex, worse energetics
  - local increase of concentration of toxins during reabsorption of water
  - additional increase of concentration of toxins by their secretion
  - intracellular toxicity due to their reabsorption
  - change of toxicity in low urine pH
- final effect mediated not only by necrosis but also by apoptosis

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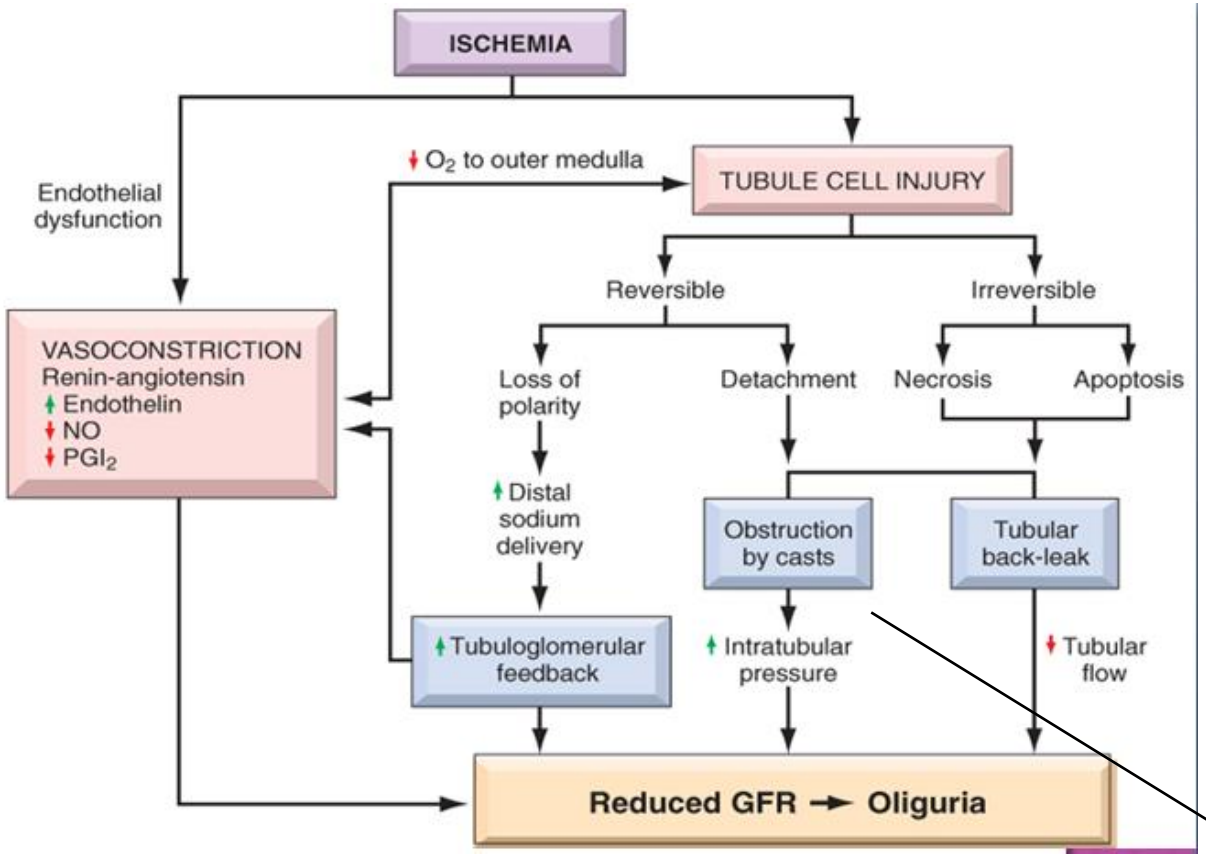
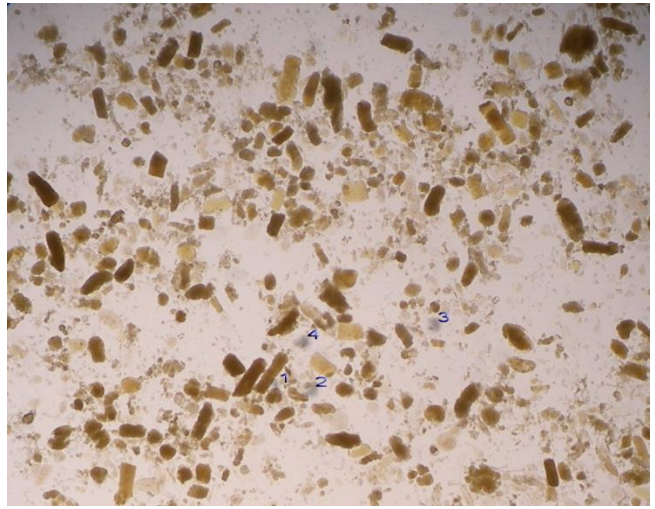
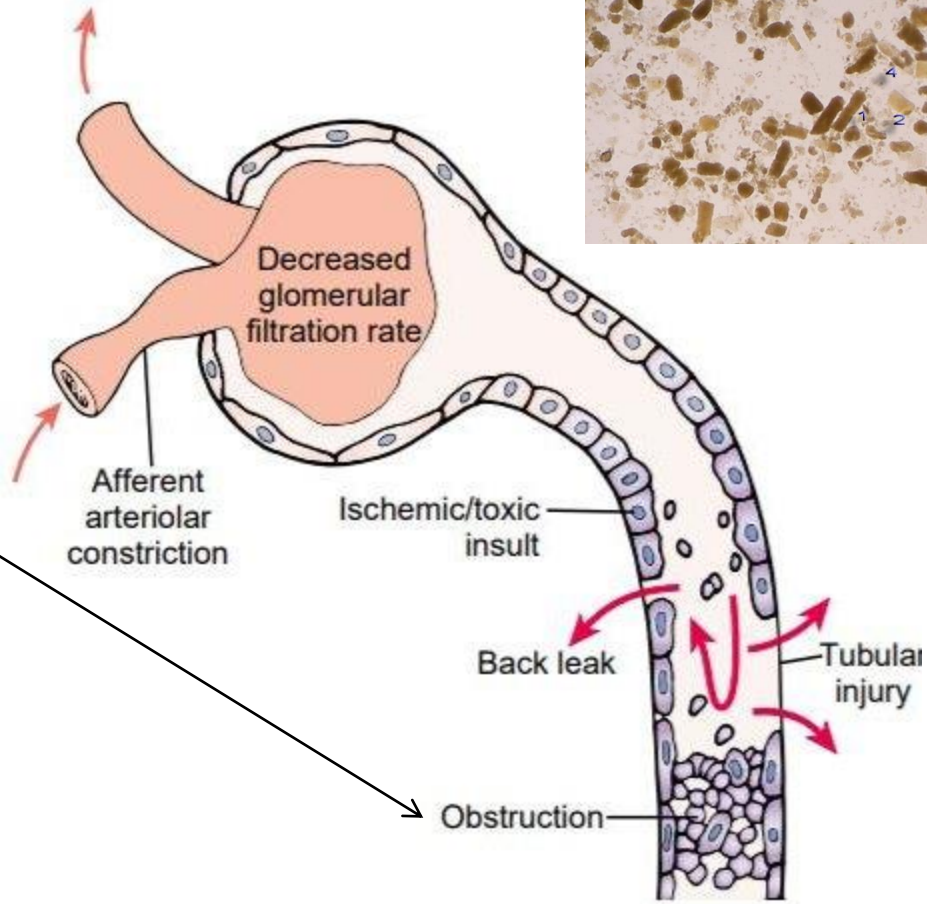
Pathogenesis and mechanisms of oliguria in ATN



pigmented granular ("muddy brown") casts in urinary sediment





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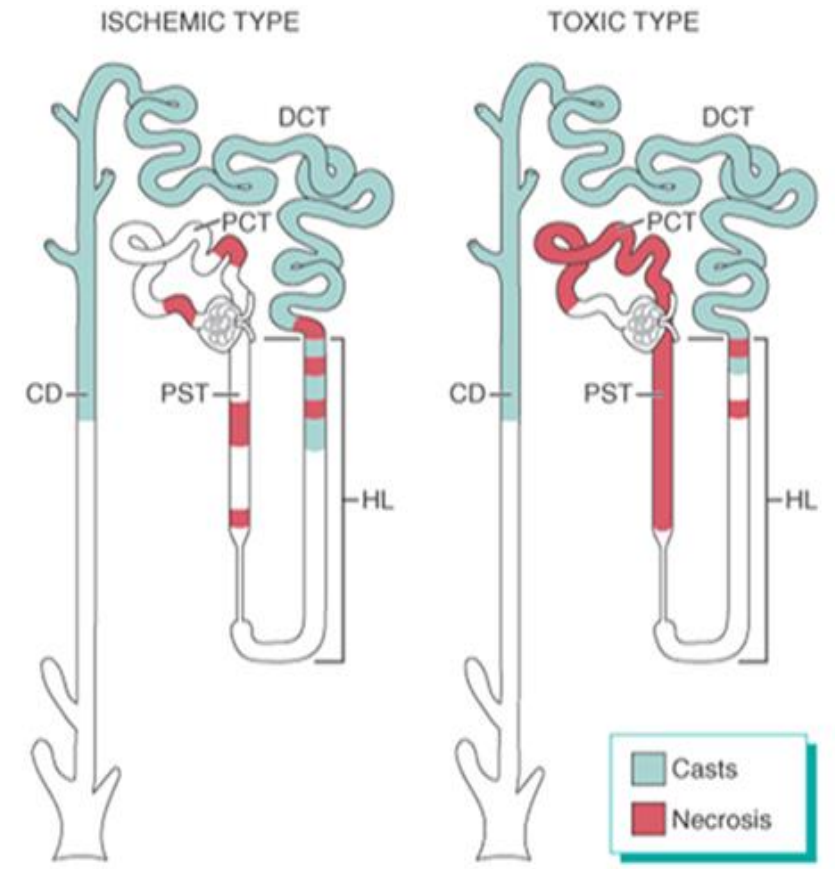
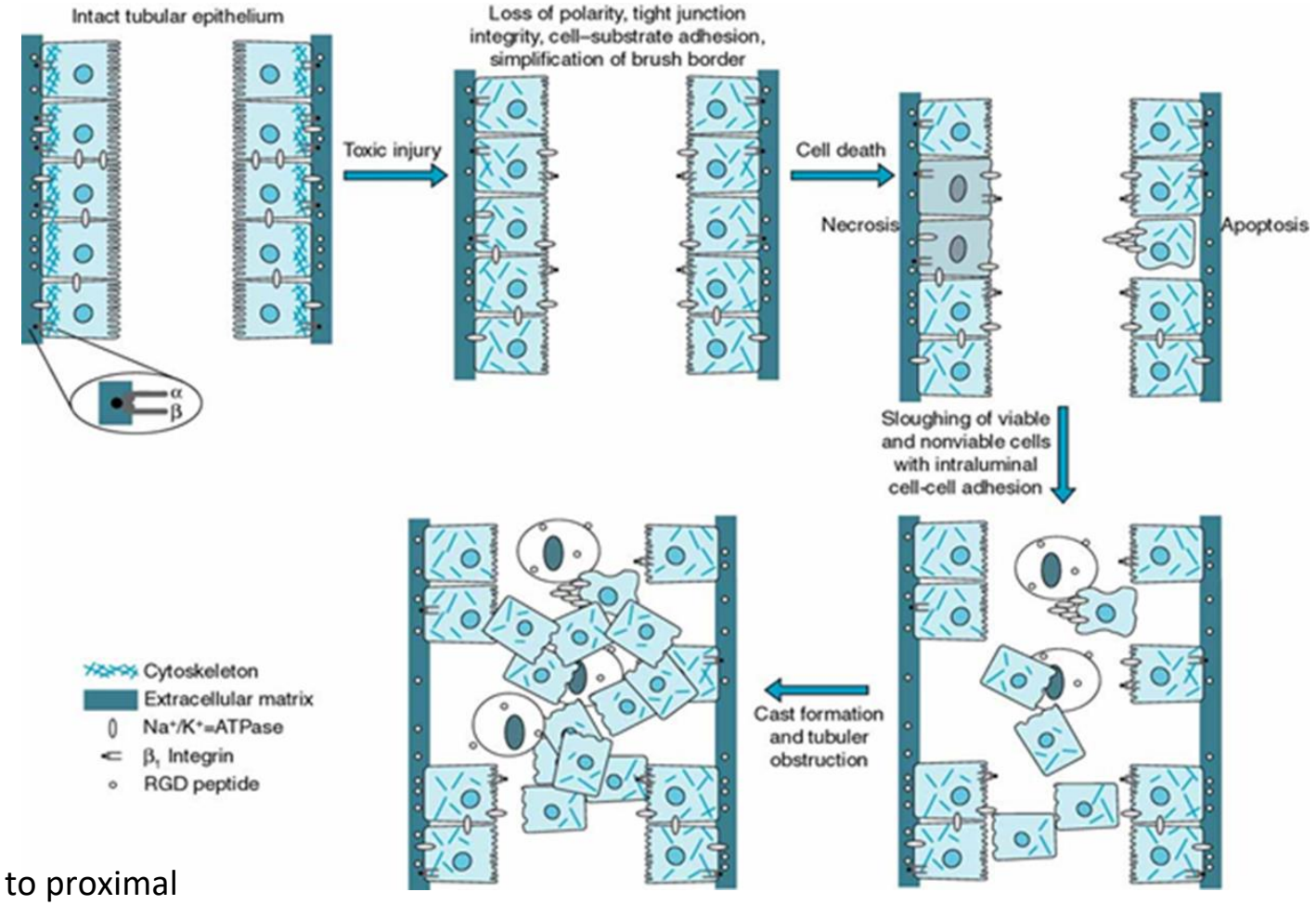
Patterns of tub. damage and formation of casts in ATN





- ATN caused by nephrotoxins is usually uniform and limited to proximal tubules
- ischemic ATN tends to be patchy and may be distributed along any part of the nephron

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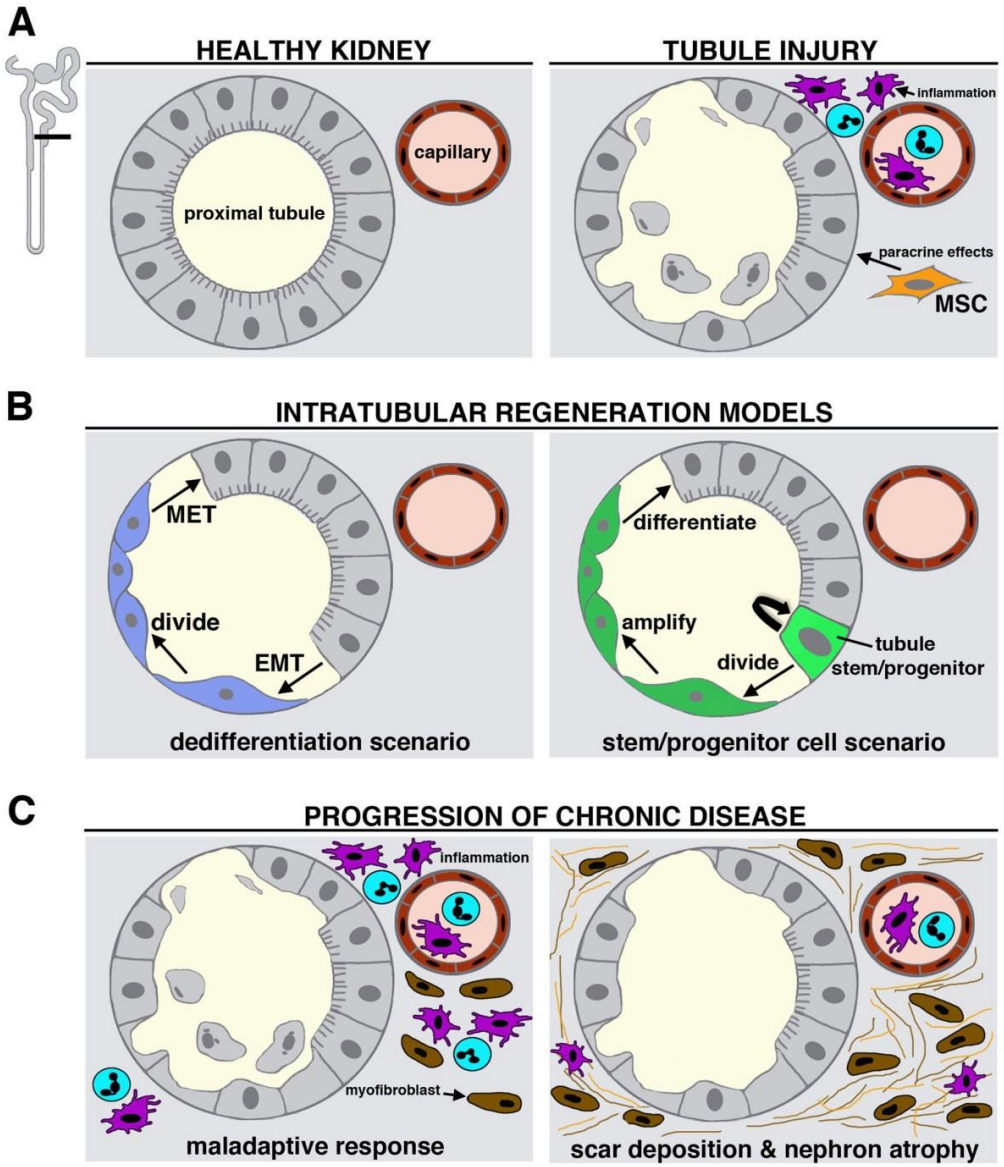
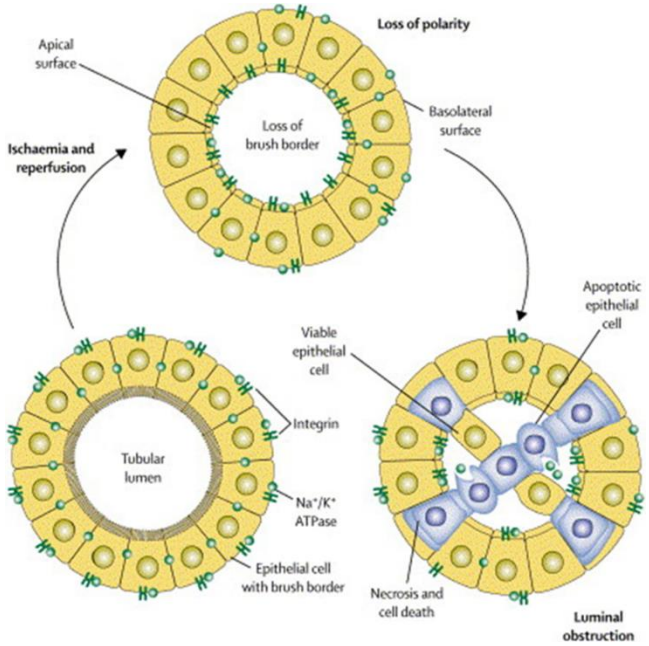
Tubular changes in ATN pathophysiology and reversibility of ATN





- morphological changes occur in the proximal tubules, including loss of polarity, loss of the brush border, and redistribution of integrins and sodium/potassium ATPase to the apical surface. Calcium and reactive oxygen species also have roles in these morphological changes, in addition to subsequent cell death resulting from necrosis and apoptosis. Both viable and non-viable cells are shed into the tubular lumen, resulting in the formation of casts and luminal obstruction and contributing to the reduction in the GFR
- tubular epithelia regenerates but it takes time and additional damage can be caused by reperfusion injury
- long term consequences of uncompleted regeneration
  - interstitial fibrosis and scaring

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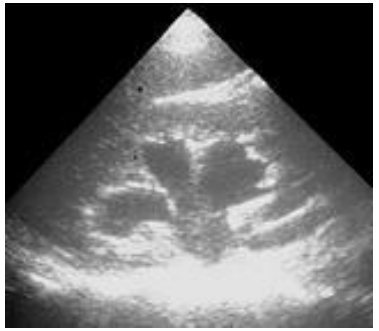
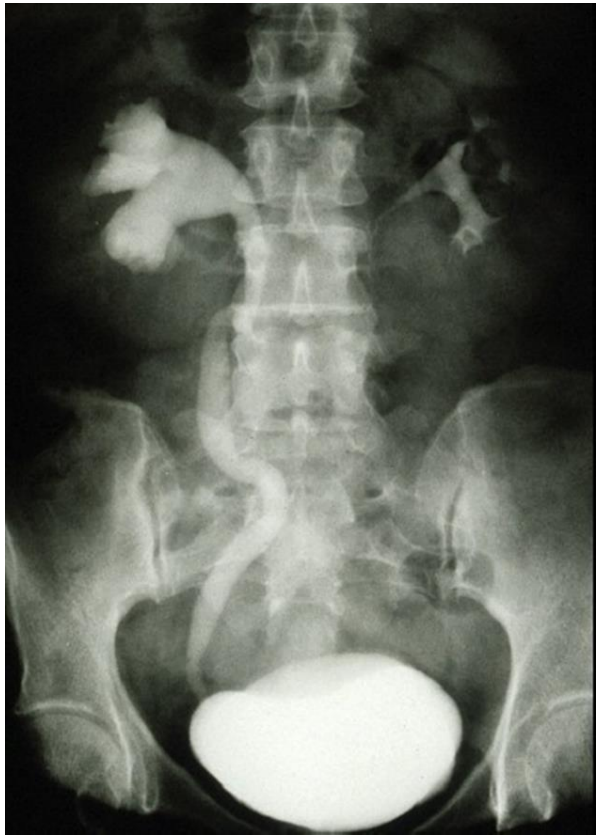
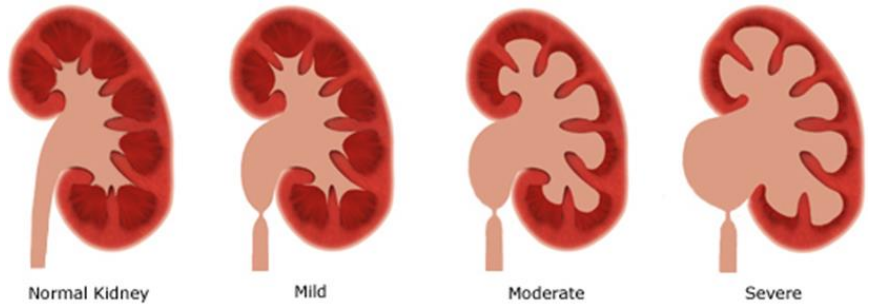
Specific etiology of AKI – (C) post-renal

- obstruction of the urinary tract below the kidneys for fluid outflow leading to waste product accumulation
  - bilateral
  - unilateral in solitary kidney or with reflex anuria in contralateral unaffected kidney
    - due to the pain during the renal colic
  - nephrolithiasis
  - benign prostate hypertrophy
  - tumors (prostate, urinary bladder, intestine, ovary…)
  - retroperitoneal fibrosis or hematoma
  - neurogenic dysfunction of bladder
- consequences (apart from AKI)
  - already after the relatively short obstruction → ↑pressure above obstruction → dilation of renal pelvis and calices → **hydronephrosis** → reflux nephropathy → infection → kidney atrophy
  - post-obstructive **profuse diuresis** (>4l/day)
  - hyperkalemic hyperchloremic renal tubular **acidosis**







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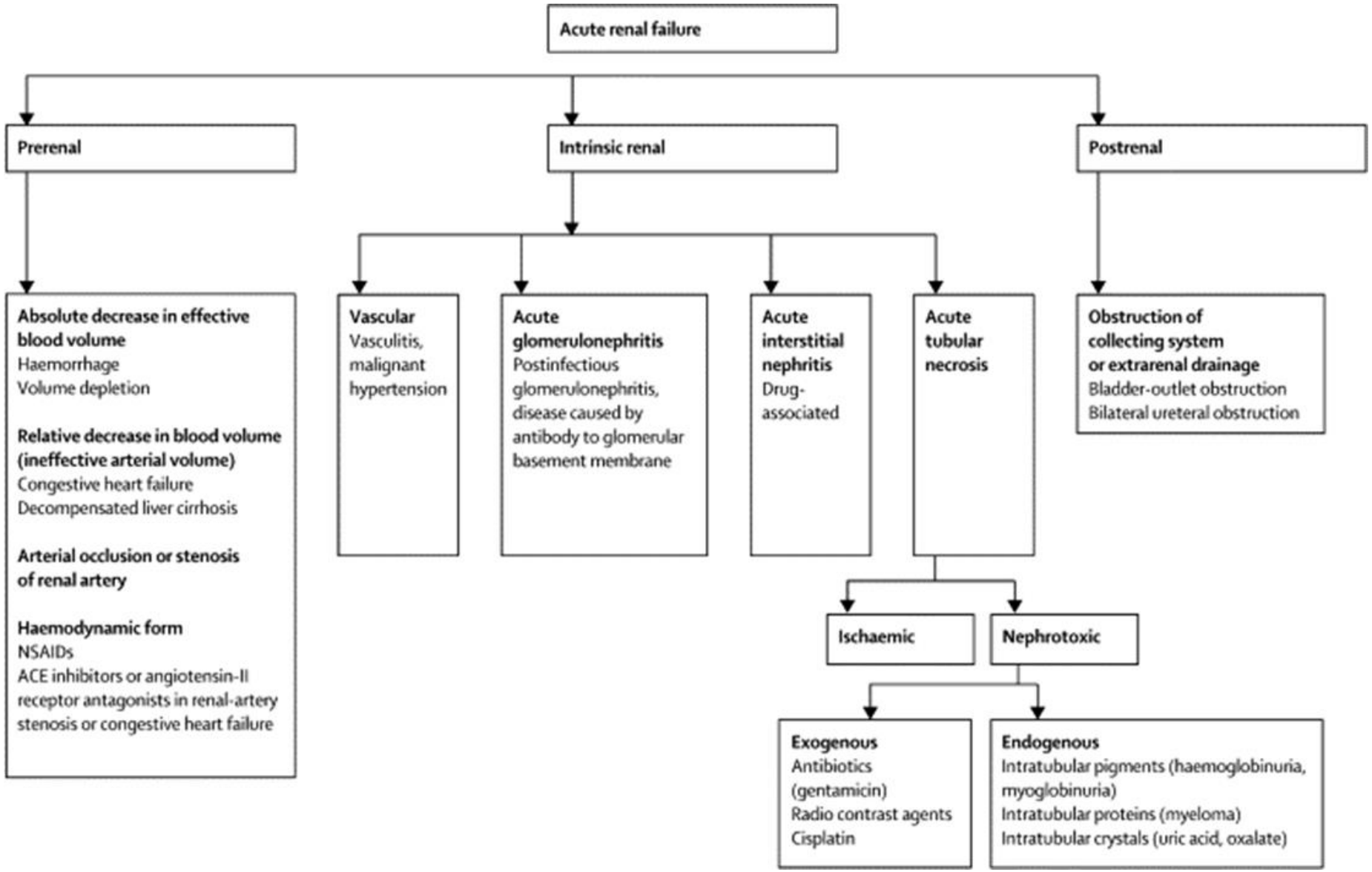
Summary of etiology of AKI



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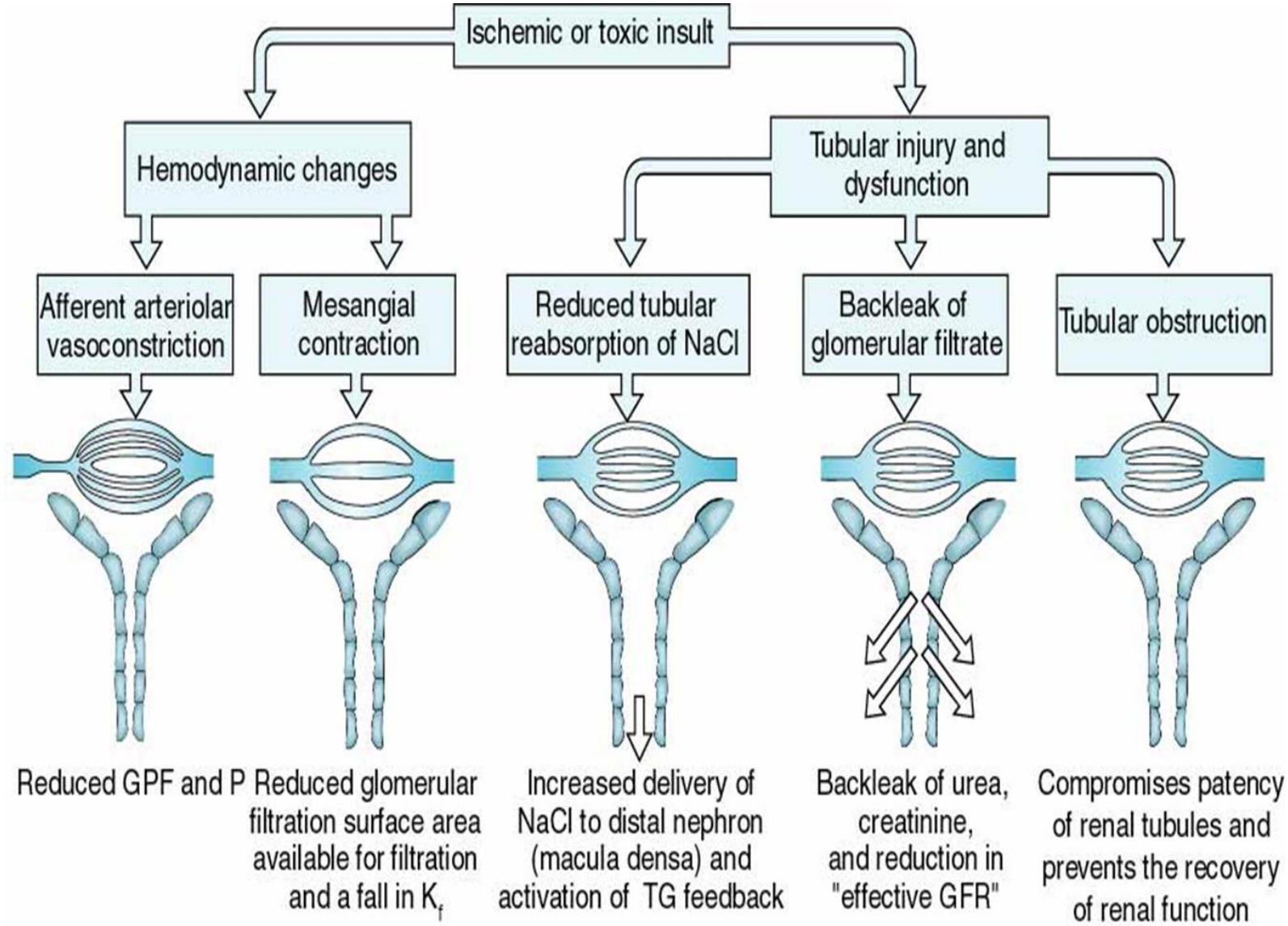
Summary of pathogenic mechanisms of AKI



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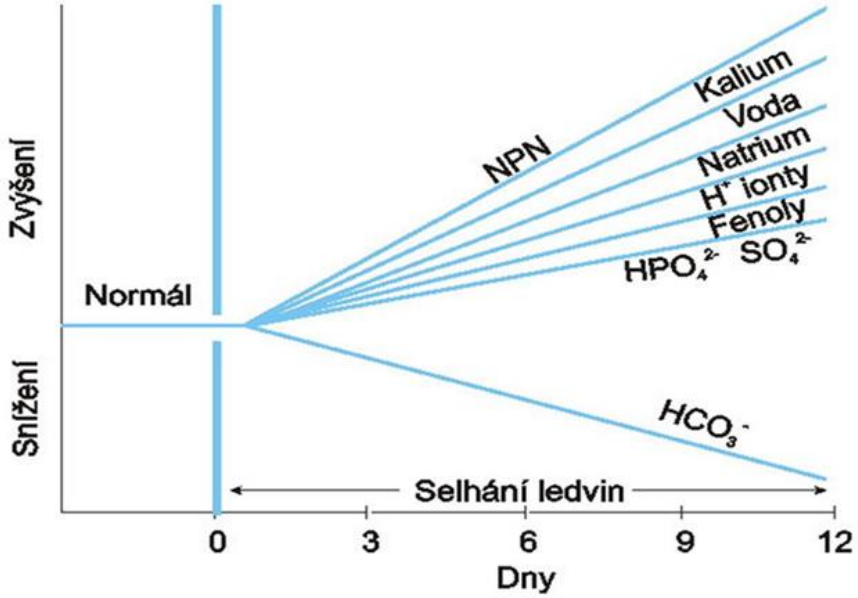
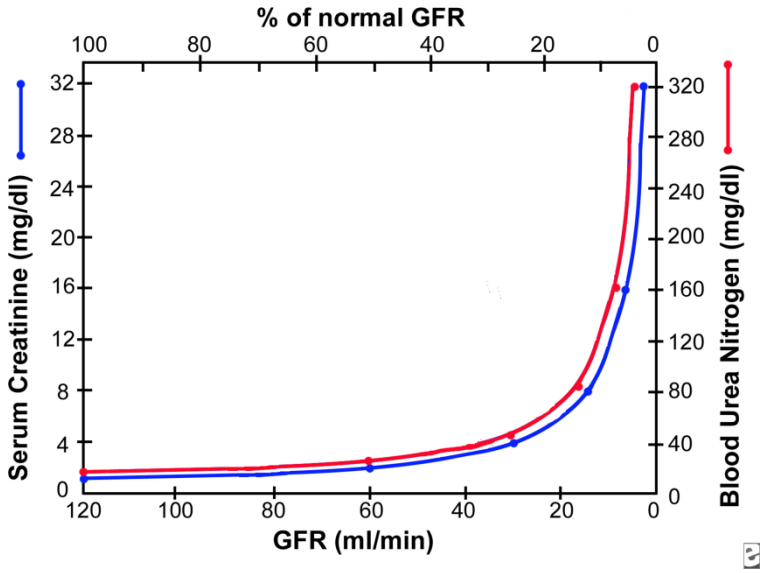
Homeostatic abnormalities during AKI

- development during several days but generally quite fast!
- ↑ serum creatinine and BUN
  - however BUN reflects more factors (GFR , protein catabolism, nutrition) than creatinine
- changes of P_{urea}/P_{creat} ratio
  - normally ~40-100:1
    - urea reabsorbed in prox. tubule while creatinine is not
    - can be normal in post-renal ARF
  - in pre-renal ARF often >100:1
    - increased reabsorption in hypovolemia
  - in renal ARF often <40:1
    - tubule damage and decreased reabsorption
- plasma concentration of K^+
    - see later for more detail
  - ↑ during oliguria phase
  - ↓ during polyuria phase
- conc. of Na^+
  - normal, ↑ or ↓ = depends on volume
- metabolic acidosis (high anion gap)
- water retention (+ metabolic water ~500ml/day)





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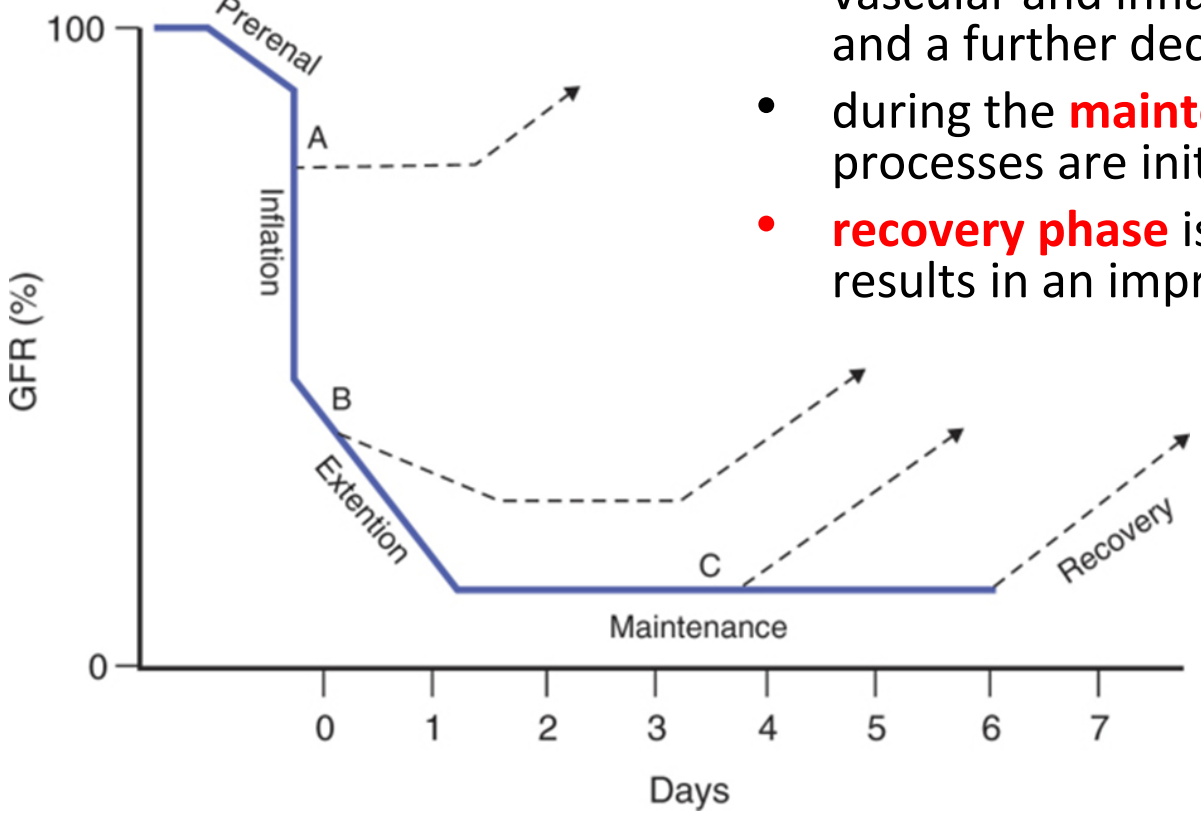
Clinical phases of AKI



- reduction in renal blood flow causes a reduction in GFR
  - variety of cellular and vascular adaptations maintain renal epithelial cell integrity during this phase
- **initiation phase** occurs when a further reduction in renal blood flow results in cellular injury, particularly the renal tubular epithelial cells, and a continued decline in GFR
- vascular and inflammatory processes that contribute to further cell injury and a further decline in GFR usher in the proposed **extension phase**
- during the **maintenance phase**, GFR reaches a stable nadir as cellular repair processes are initiated in order to maintain and re-establish organ integrity
- **recovery phase** is marked by a return of normal cell and organ function that results in an improvement in GFR

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Risks associated with AKI

- major risks during the oliguric stage of AKI
  - **hyperkalemiaa** (>7mmol/l)
    - arrhythmias, heart arrest
  - **hypervolemia** (hyperhydration)
    - isoosmolar
    - later hypoosmolar due to dilution
      - hyponatremia → **brain edema** → increased intracranial pressure → brain ischemia and hypoxia → subjective symptoms (head pain, nausea, vomiting) → disorder of consciousness
    - volume and pressure overload of the **heart**
    - congestion or even **pulmonary edema**
- indication to **renal replacement therapy** (mainly an **acute hemodialysis**)
  - absolute
    - hyperkalemia (>6.5mmol/l)
    - metabolic acidosis
    - hypervolemia
    - uremia
      - see in more detail later
  - relative
    - progressive hyperazotemia (creatinine >500 µmol/l, urea >35mmol/l)
    - hypercalcemia (> 4mmol/l), hyperuricemia
    - prolonged oliguria (>3 days)

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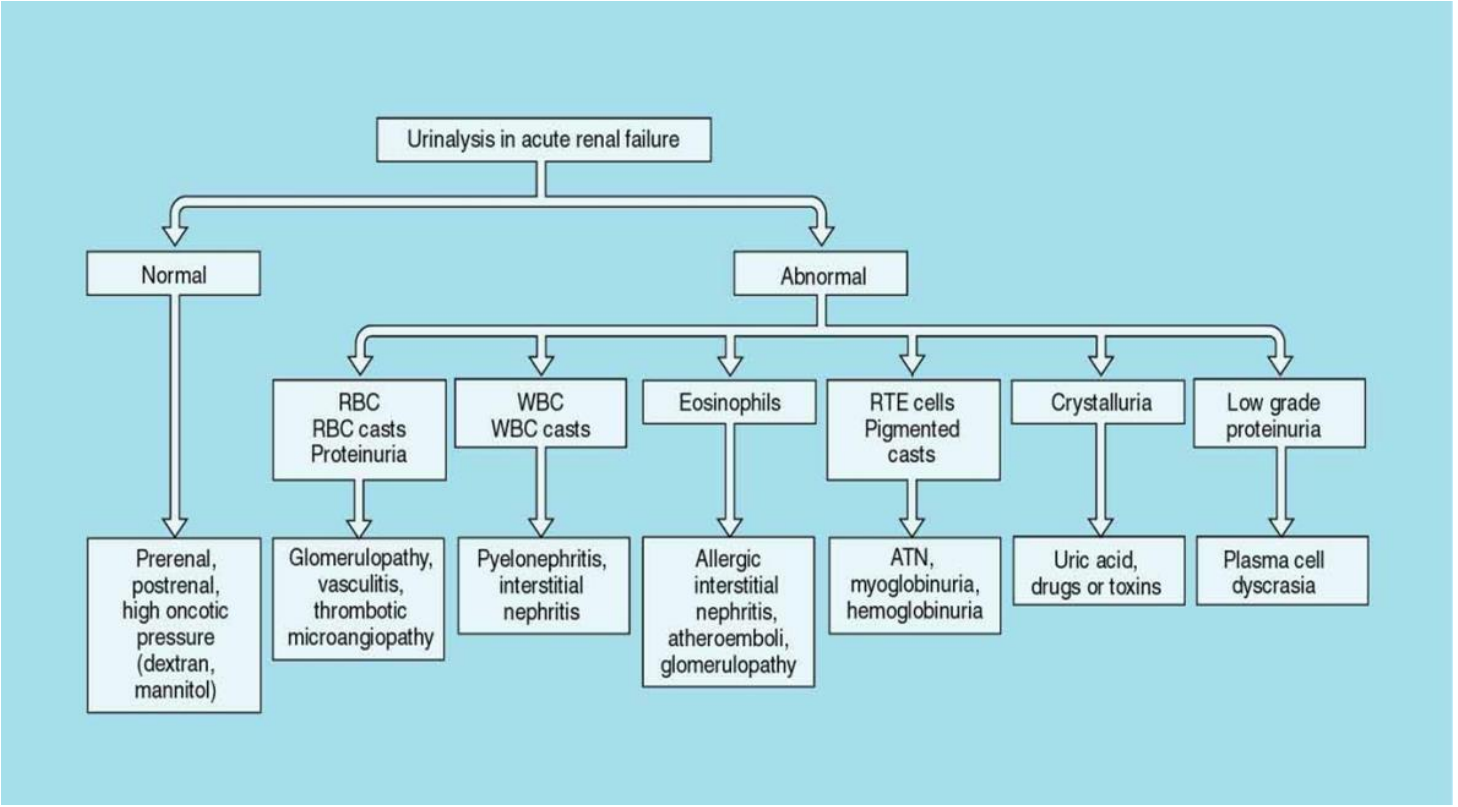
Urine analysis in AKI



- concentration of Na+ in urine:
  - pre-renal azotemia, acute GN or altered vascular resistance - tubules functioning and reabsorb Na+ from lower amount of filtrate (Na+ in urine < 20 mmol/l)
  - damage of tubules and post-renal azotemia: Na+ in urine > 40 mmol/l)
- fractional excretion of Na+
  - FE-Na+ = U-Na/S-Na, normally < 1 %
- osmotic concentration of urine
  - pre-renal azotemia: > 500 mOsm/kg
  - tubular damage: < 350 mOsm/kg

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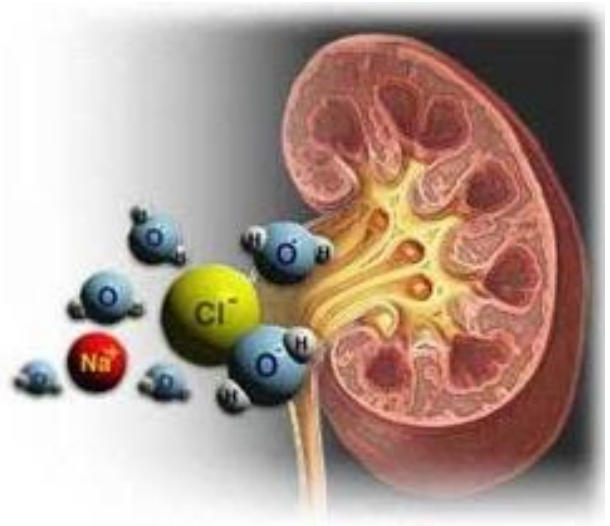

CHRONIC KIDNEY DISEASE (CKD) AND END STAGE RENAL DISEASE (ESRD)

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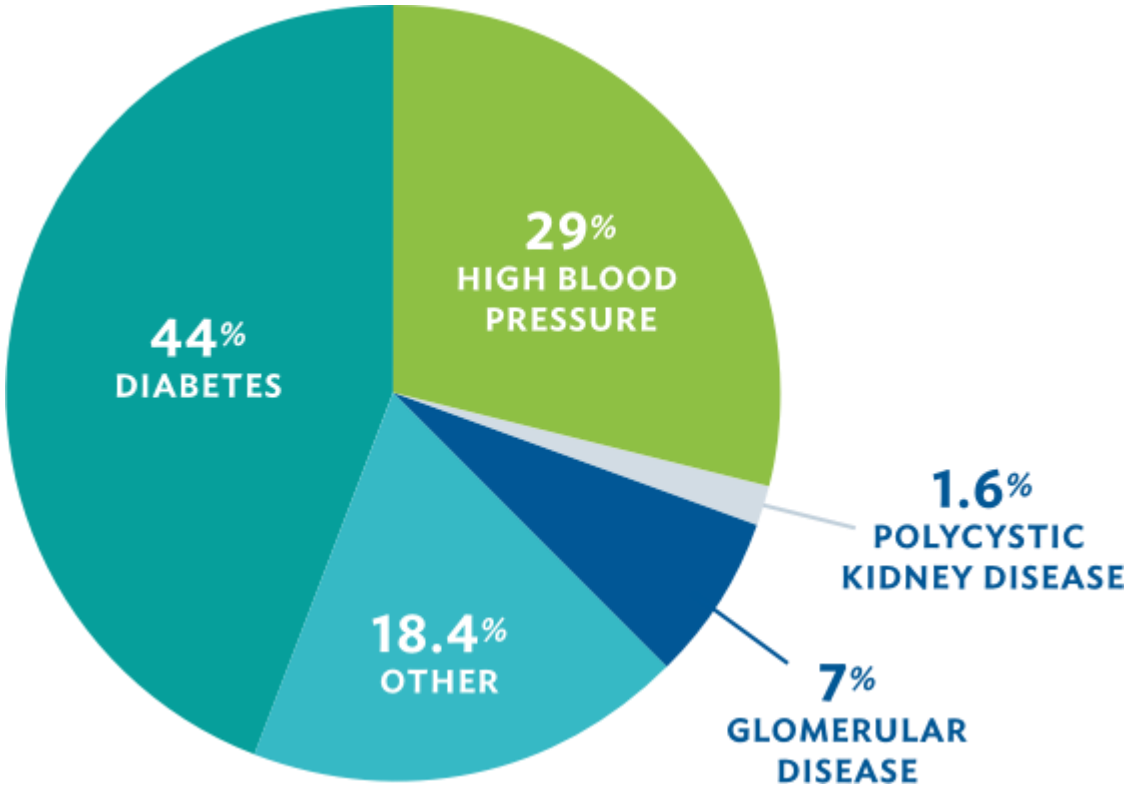
Chronic kidney disease (CKD)

- progressive, typically many months to years lasting decline of renal function
  - no matter of the etiology CKD defined solely based on degree of GFR decline
- basically any kind of progressive kidney disease can by the cause
  - up to 50% - diabetic nephropathy
  - up to 30% - hypertensive nephropathy
  - 10 - 20% - any form of GN
  - other causes
    - polycystic kidney disease
    - tubulointerstitial nephritis (drugs, toxins, urate)
    - myeloma
    - hereditary kidnez diseases
    - vascular nephrosclerosis
    - others



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Progressive nature of CKD

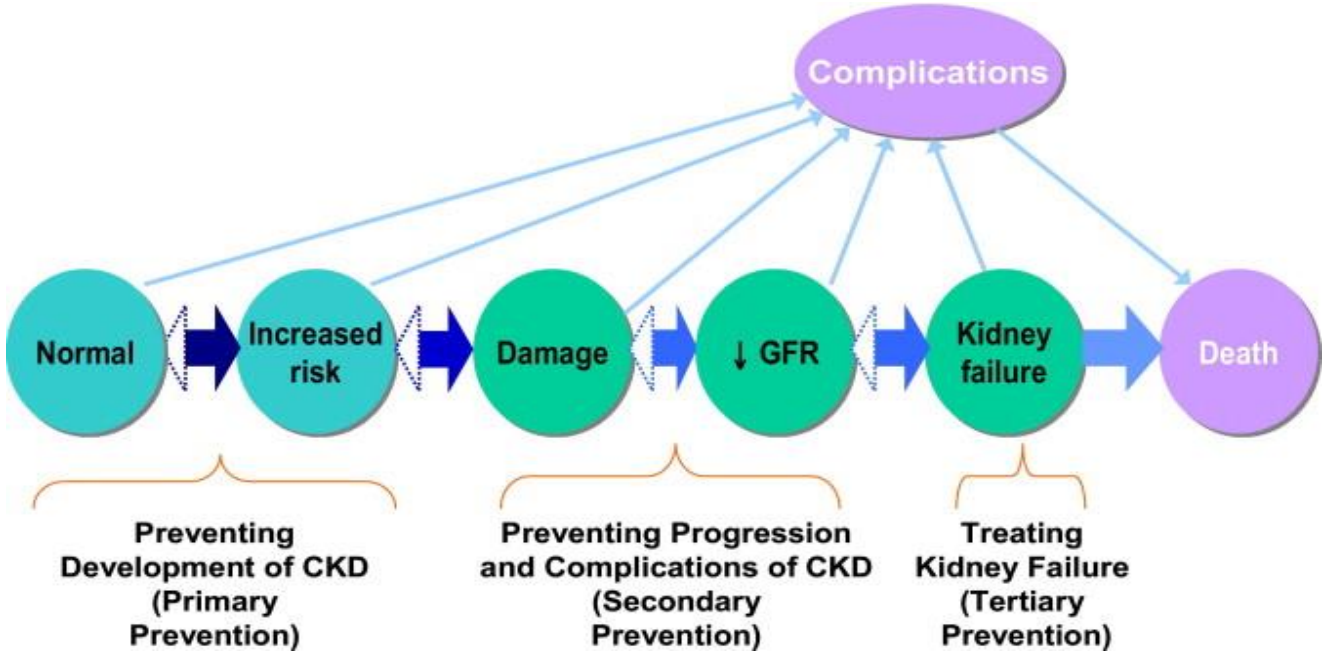
- damage and loss of nephrons caused by **initial specific process**

↓

- damage and loss of nephrons caused by **overload of residual nephrons** (a further non-specific process)

↓

- damage and loss of nephrons caused by **reno-parenchymal secondary arterial hypertension**
  - i.e. after the loss of critical number of nephrons caused by initial disease, further progression of CKD becomes independent in the primary pathological process
- factors determining the rate of progression
  - non-modifiable risk factors
    - primary disease
    - age, gender, ethnicity, genetics
  - modifiable risk factors
    - proteinuria
    - art. hypertension
    - obesity
    - glycemic
    - hyperuricemia
    - smoking?
    - hyperlipidemia?



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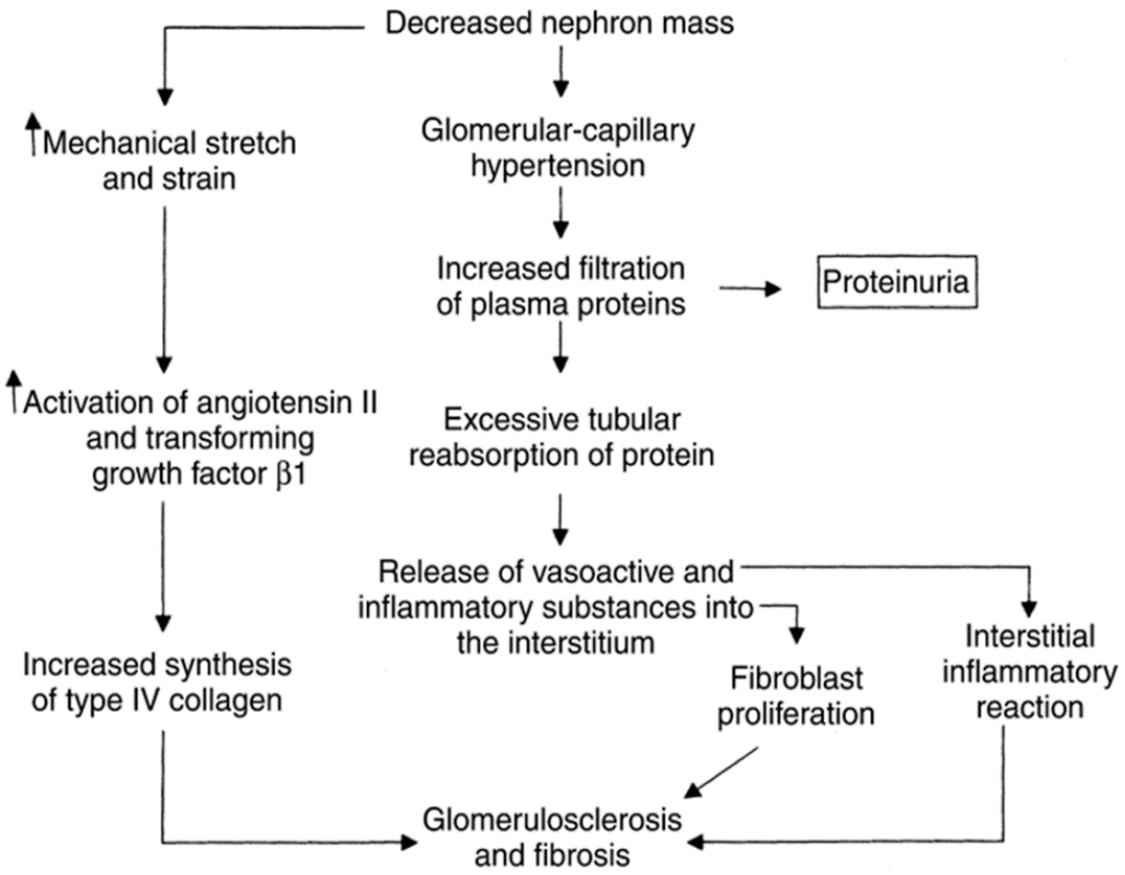
Pathogenesis of CKD – perpetual damage

- an **initial glomerular insult** is responsible for alterations of glomerular cell functions, leading to glomerulosclerosis and thus **reduction in nephron number**
  - however, symptoms appear only after the loss >75% nephrons
- this induces an increase in glomerular capillary pressure and/or glomerular volume in residual nephrons, which have to adapt (functionally and morphologically) to sustain higher workload and became damaged later, i.e. **further glomerular damage**
  - higher glomerular pressure favours **proteinuria**
- reduced nephron number is also associated with **tubular dysfunction**
  - tubular dysfunction is responsible for interstitial fibrosis and destruction of peritubular capillaries (capillary rarefaction), which leads to tubular destruction
  - destruction of interstitial capillaries may also increase glomerular capillary pressure and thus enhance glomerular damage
  - similarly, **glomerulosclerosis** damages glomerular capillaries and enhances tubular hypoxia
  - proteinuria enhances tubular dysfunction and thus **interstitial fibrosis**
- along this process GFR decreases, later on renal insufficiency and event. failure develop
- CKD is associated with **high cardiovascular mortality**
  - several times higher of that in non-CKD population



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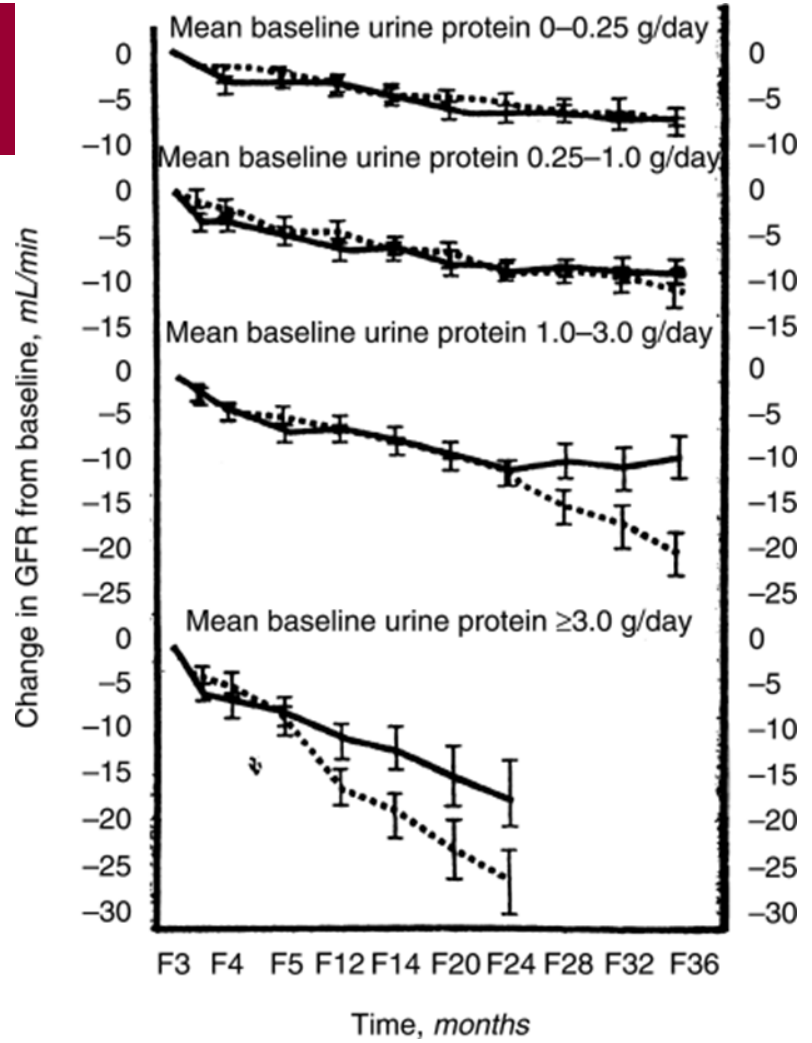
CKD staging

Prognosis of CKD by GFR and Albuminuria Categories

GFR categories (ml/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	**A2**	**A3**
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90			
	G2	Mildly decreased	60-90			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
KDIGO 2012



- Mean decline in GFR depends on proteinuria
  - mean decline in GFR (mL/min) over a 36-month period in groups with four different mean baseline 24-hour urine protein levels in non-diabetic patients with chronic renal failure in the MDRD study
  - compared in each of these four groups are the
    - normal blood pressure group (dashed line; 140/90 mm Hg; 102-107 mm Hg MAP)
    - intensive control group (solid line; 125/75 mm Hg; 92 mm Hg MAP)

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CKD example 1: diabetic nephropathy/diabetic kidney disease (DKD)

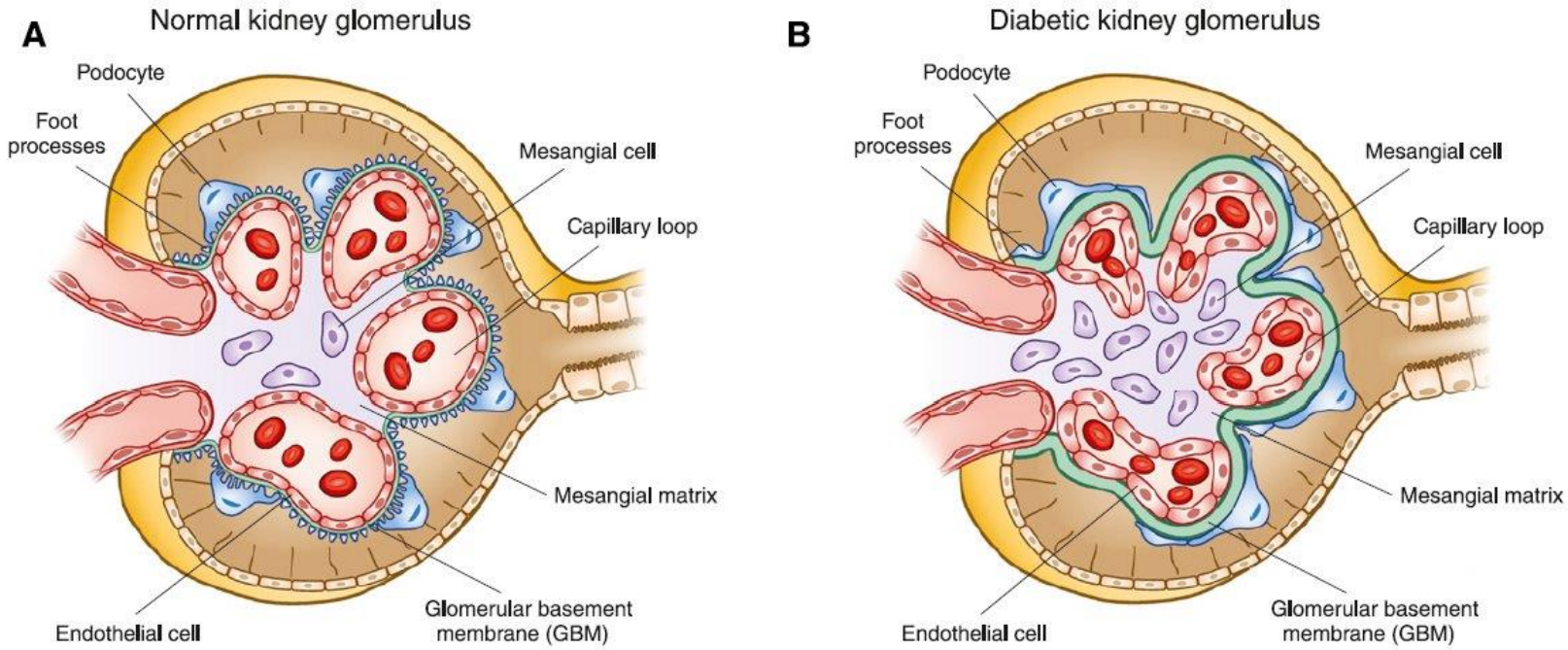

Figure 2. | Normal kidney morphology and structural changes in diabetes mellitus. Diabetic kidney disease induces structural changes, including thickening of the glomerular basement membrane, fusion of foot processes, loss of podocytes with denuding of the glomerular basement membrane, and mesangial matrix expansion.

- DKD progresses in stages:
  - clinical presentation usually starts with kidney hypertrophy, urinary protein excretion (microalbuminuria), and glomerular hyperfiltration
  - DKD can progress to higher levels of urinary protein excretion (macroalbuminuria) and diminished glomerular filtration rate (GFR)
  - both of these conditions are dynamic and can improve or deteriorate depending on treatment.

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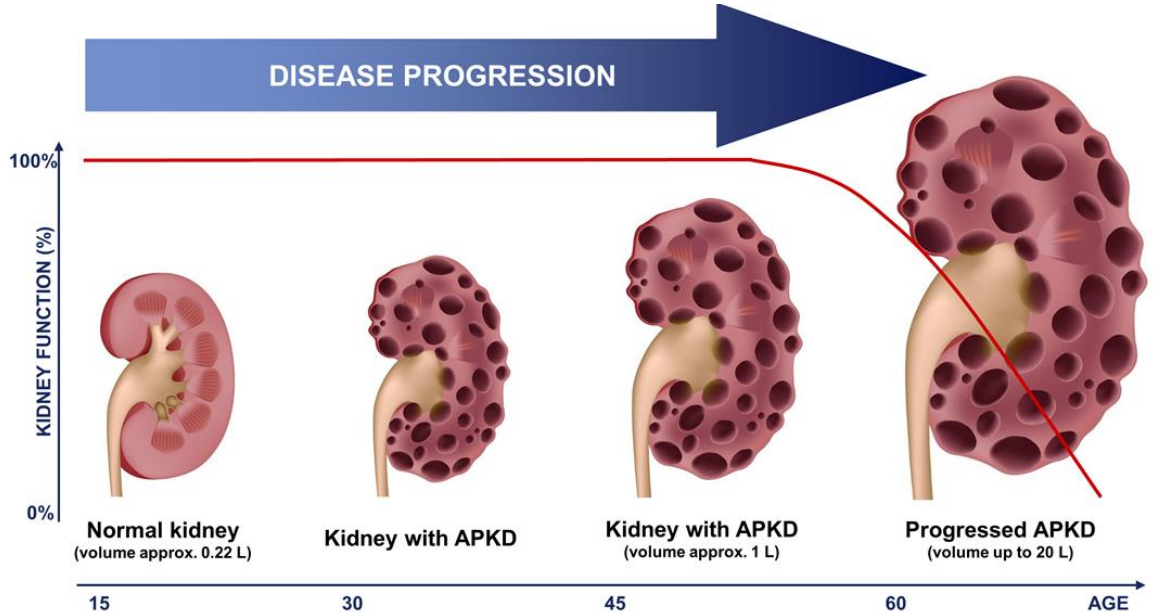
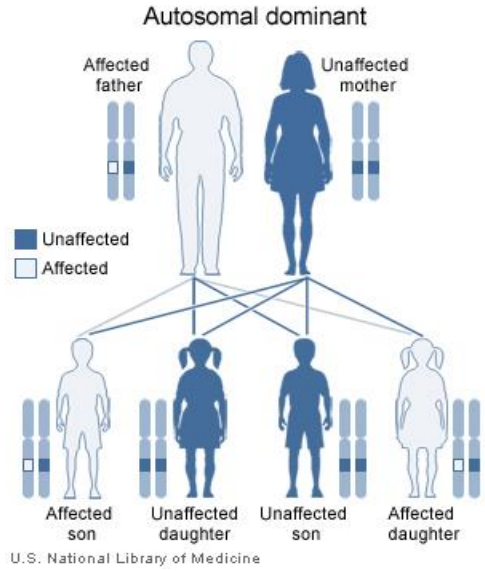
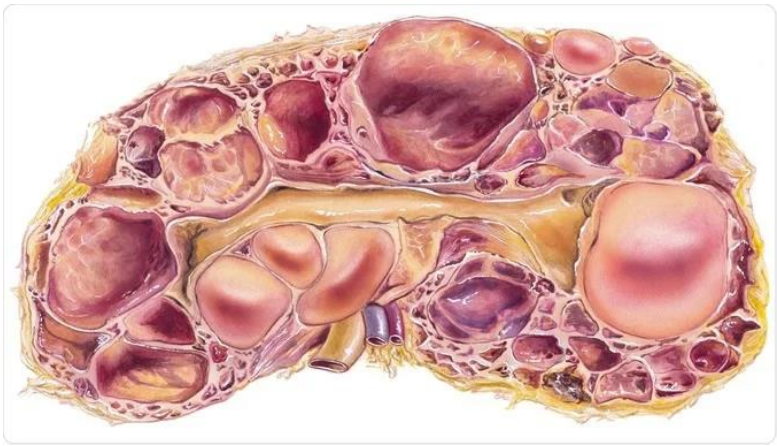
CKD example 2: polycystic kidney disease (PKD)

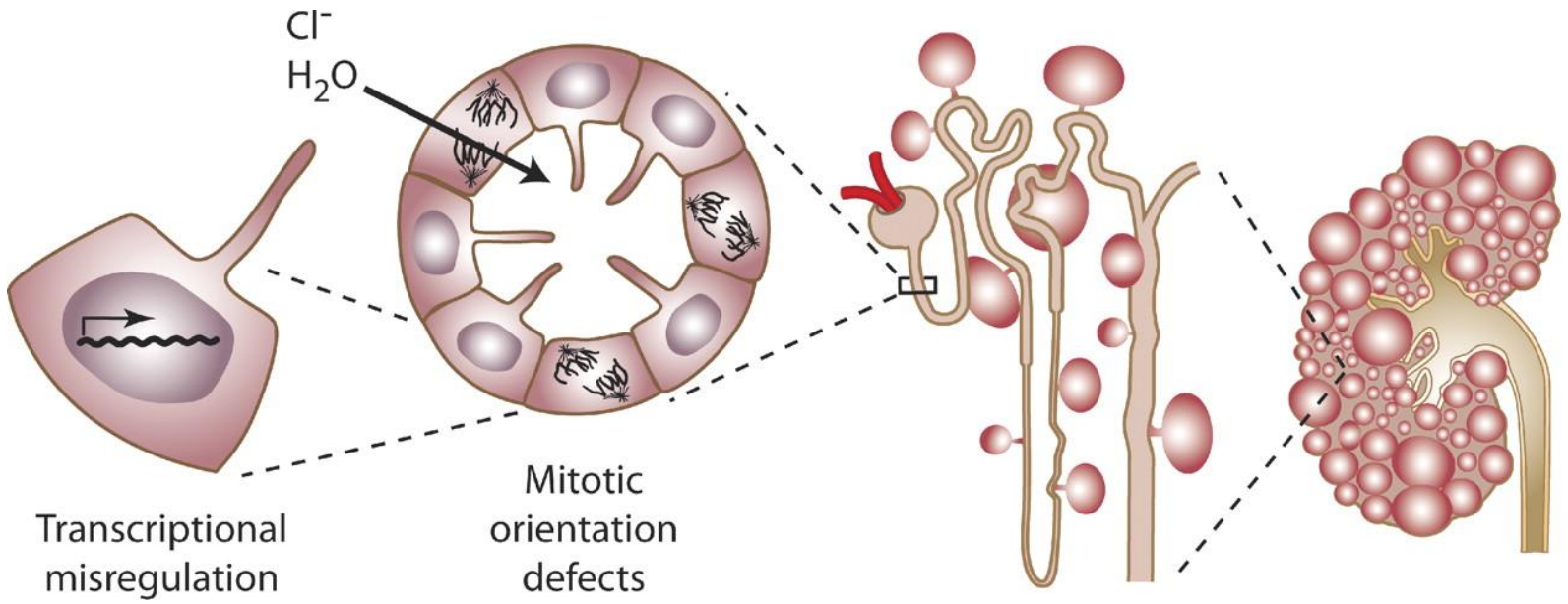
- autosomal dominant (ADPKD)
  - mutations in genes encoding for transmembrane protein
    - polycystin 1 (PKD1, ch. 16) ~85%
    - polycystin 2 (PKD2, ch. 4) ~15% cases
  - progressive development of multiple cysts bilaterally in kidneys
  - hypertension
  - CKD
    - typically not apparent until 4th decade of life
    - enlargement of kidneys leads to flank pain
    - haemorrhage to cysts can lead to haematuria or infection (pyelonephritis)
    - kidney stone (urate) formation
    - extra renal manifestations
      - cysts in liver (often women - estrogen)
      - ovaries/testes
      - diverticulosis
      - thyroid cysts
    - in ~50% cases leads to ESRD (more often in males)
- recessive form is very rare but more serious

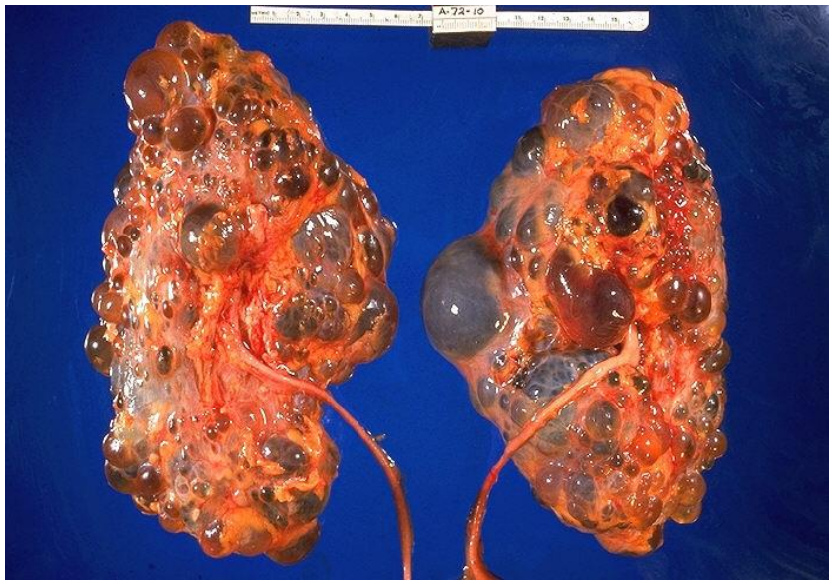






CKD example 2: polycystic kidney disease (PKD)





- Defects in the genes encoding PC1 or PC2 lead to aberrant gene transcription, cell proliferation, and ion secretion, which in turn result in the formation of fluid-filled cysts.
- As cysts balloon out from individual nephrons, their collective effect leads to the displacement of the normal renal parenchyma and the formation of a cyst-filled kidney with reduced functional capacity.

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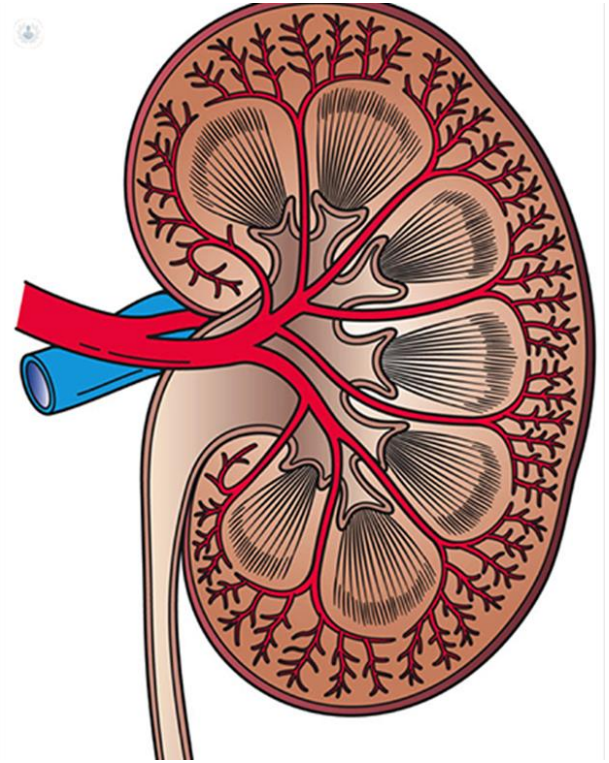
Functional adaptation of residual nephrons

- allows to maintain homeostasis even if GFR is substantially decreased
  - **modification of intensity of tubular transport processes**, mainly maintenance of normal sodium, potassium and water balance (↓ tubular reabsorption or ↑ tubular secretion)
    - it is useful to measure fractional excretion (FE) of compounds (i.e. percentage of the given compound filtered by the kidney which is excreted in the urine)
- ↓ tubular reabsorption of **sodium and water**
  - normal reabsorption of Na ~99%
  - when ↓ GFR then ↓ reabsorption from filtered volume
    - although for normal excretion of Na GFR 4ml/min would be sufficient
  - mechanisms ???
    - ANP, prostaglandins
- ↓ tubular reabsorption of **phosphate**
  - normal renal excretion of phosphates ~10-20% of filtered amount
  - when ↓ GFR then ↓ reabsorption from filtered volume, i.e. excretion ~40% - 100%
  - requires compensatory ↑ PTH release
    - if not sufficient → hyperphosphatemia
- ↑ secretion of **potassium**
  - mechanisms maintaining homeostasis of K+ until very low GFR
    - hyperkalaemia develops only after extreme fall of renal function
  - secretion via extra-renal ways (GIT) contributes to the potassium balance



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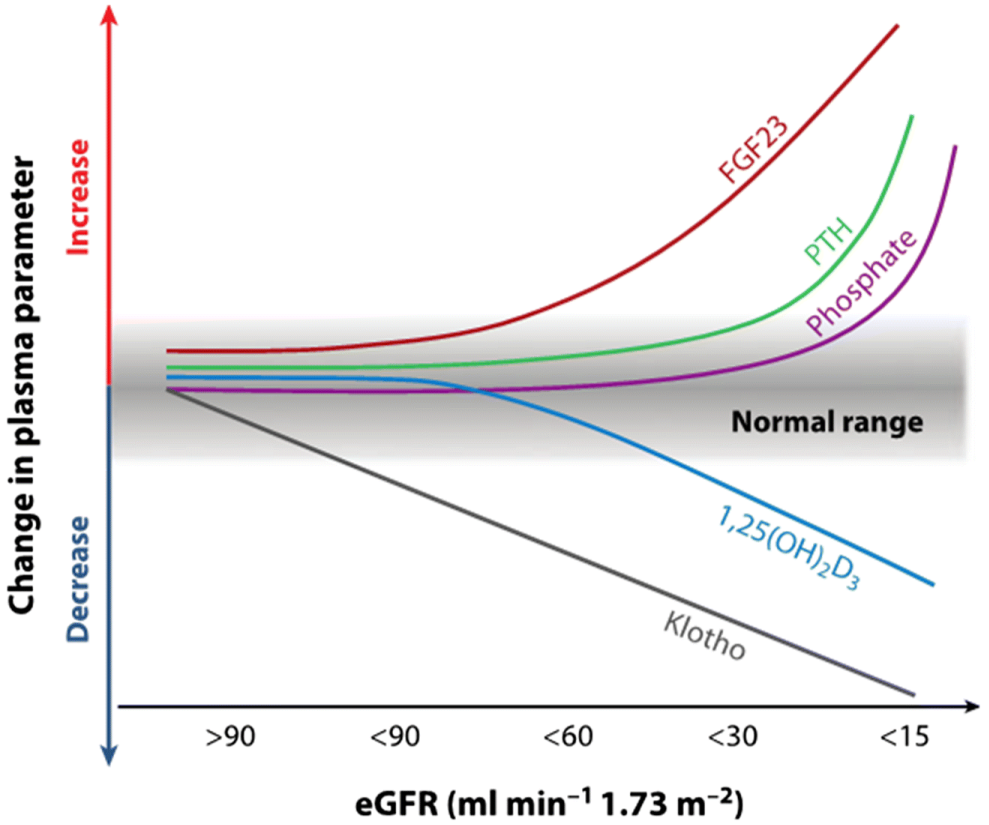
Time profile/dynamics of CKD associated abnormalities and their relationship to GFR

- ↓ of GFR by ~¼ - ½ (CKD stage 2) do not causes changes of internal environment of the body (**renal functional reserve**)
  - functional adaptation of tubules to decreased GFR
- in the stage of ½ - ¾ decrease of physiological GFR (late CKD stage 3 – early 4) = **renal insufficiency**
  - gradual failure of tubular adaptation to ↓GFR and rise of plasma concentration of waste products
    - creatinine, BUN
    - uric acid
    - uremic toxins ?
- in the stage < ¾ of initial GFR (late CKD 4 – 5) **kidney failure** with full blown symptoms of **uremia**
  - changes similar to ARF
    - azotemia
    - hyperkalemia
    - hypervolemia/hypertension
    - hyperphosphatemia
  - and on top of that
    - anemia
    - uremic toxins
    - bone disease
    - polyneuropathies



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Abnormalities of hormones and metabolism

- altered concentrations of many hormones in CKD influence function of many systems
  - ↓ formation/activity
    - **1, 25-dihydroxycholecalcipherol**
      - contributes to MBD (esp. osteomalacia)
    - **erythropoietin**
      - untreated anemia places patients at risk for
        - cardiovascular events (hypoxia)
        - more rapid progression of CKD
        - significantly decreased quality of life
    - prostaglandins
  - ↑ formation/activity
    - **angiotensinogen**
      - contributes to CVD morbidity and mortality
    - **parathormone**
      - contributes to MBD (esp. renal osteodystrophy)
- metabolic abnormalities in CKD/CHRI
  - metabolism of **proteins** and **amino acids**
    - malnutrition in proteinuria and decreased dietary intake of protein (necessary though)
    - increased protein catabolism in muscle
    - changes of intracellular AA concentrations in tissues as well as in plasma (↓essential, ↑non-essential)
  - saccharide metabolism (**insulin resistance**)
    - fasting hyperglycemia in 30 % h of CKD patients
    - impaired glucose tolerance in oGTT in 60%
    - ↑ plasma insulin due to peripheral resistance (post-receptor defect)
      - moreover secretion of insulin stimulated also by ↑K+ (insulin promotes transport of K+ into cells)
  - lipid metabolism - **hyperlipidemias**
    - present in ~70% of CKD patients
    - pathogenesis of secondary hyperlipidemia is complex
      - ↓ catabolism (↓LPL) and ↑ liver synthesis of lipoproteins
    - ↑ VLDL, LDL and TAG, ↓ HDL

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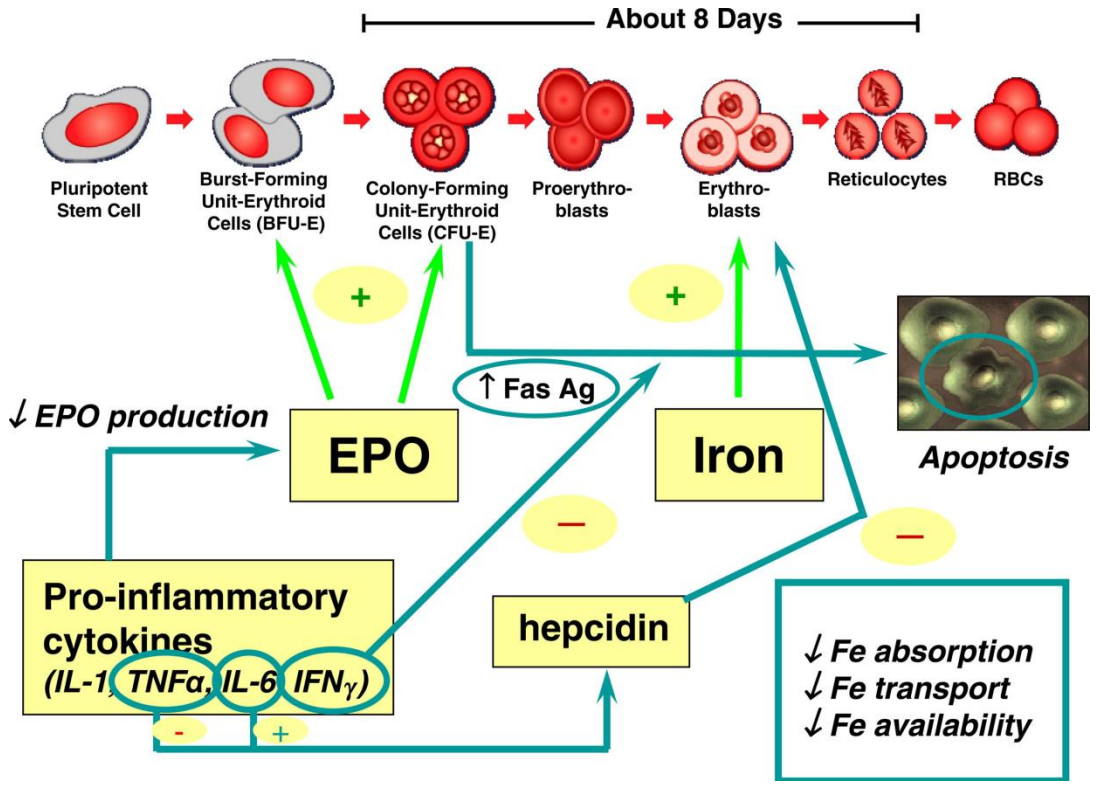
Anemia in CKD



- The cause of anemia in patients with CKD is **multifactorial**
- The most well-known cause is inadequate **erythropoietin** (EPO) production
  - EPO is produced in the peritubular capillary endothelial cells in the kidney relying on a feed-back mechanism measuring total oxygen carrying capacity
    - subsequent production of hypoxia inducible factor (HIF)
  - EPO then binds to receptors on erythroid progenitor cells in the bone marrow(BFU-E and CFU-E). With EPO present, these erythroid progenitors differentiate into reticulocytes and red blood cells (RBCs)
  - The absence of EPO leads to pre-programmed apoptosis mediated by the Fas antigen
- There are other factors in chronic kidney disease which contribute to anemia
  - **pro-inflammatory cytokines** decreasing EPO production and inducing apoptosis in CFU-E
  - inflammatory cytokines have also been found to induce the production of **hepcidin**, a recently discovered peptide generated in the liver, which interferes with RBC production by decreasing iron availability for incorporation into erythroblasts.
- **Red blood cells** also have a **decreased life span** in patients with CKD
- **Uremic toxins** have been implicated as contributing to apoptosis as the anemia will often improve after initiation of dialysis

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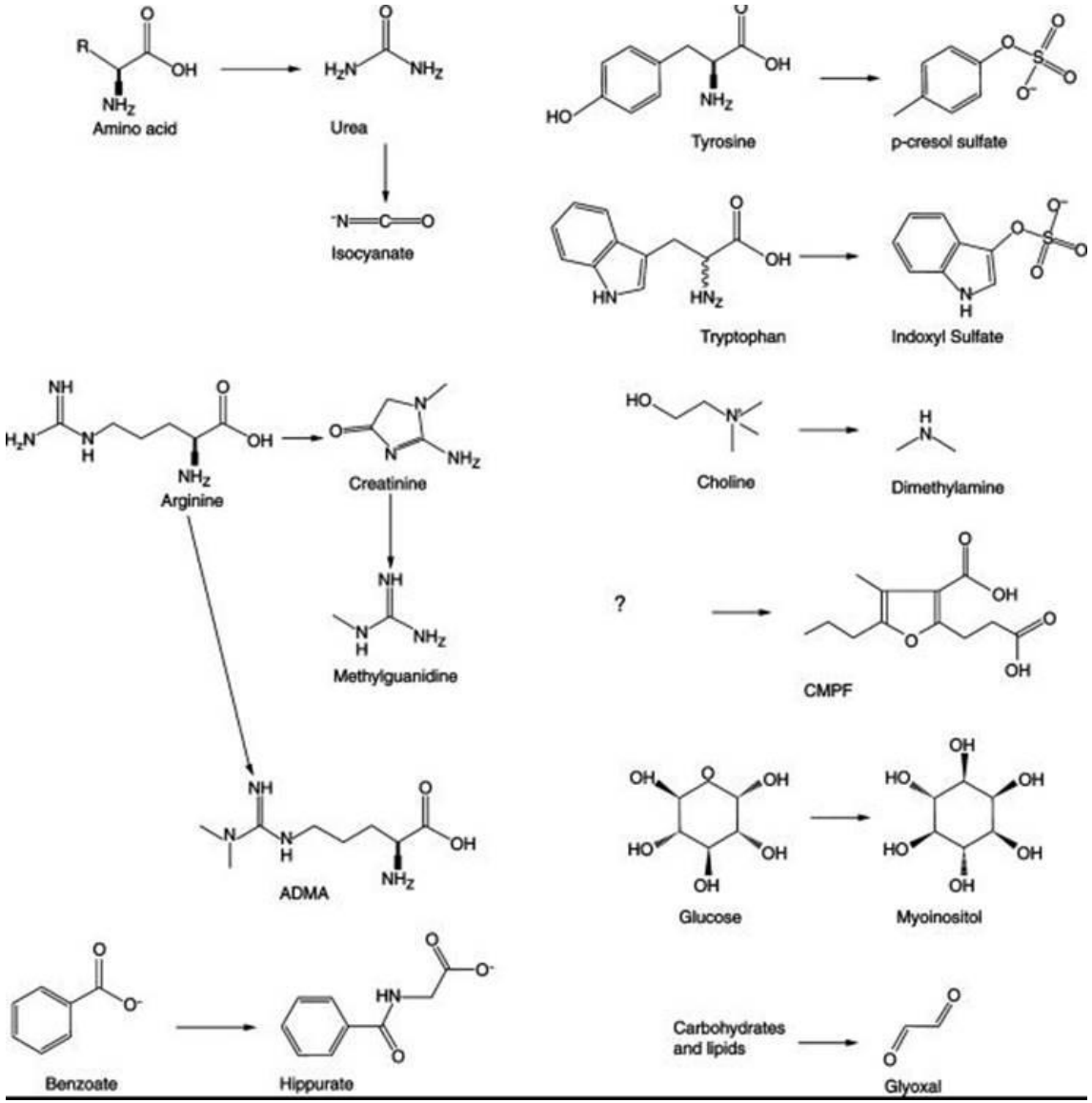
Uremic toxins



Small Water-Soluble Compounds (<500 Da)	Middle Molecule (≥500 Da)	Protein Bound Compounds (Mostly < 500 Da)
ADMA	ANP	AGEs
Carbamylated compounds	β_2-microglobulin	Homocysteine
Creatinine	Endothelin	Indoxyl sulfate
SDMA	FGF23	Indole acetic acid
TMAO	Ghrelin	Kynurenines
Urea	Immunoglobulin light chains	*p*-cresylsulfate
Uric acid	Interleukin-6	Phenyl acetic acid
	Interleukin-8	
	Interleukin-18	
	Lipids and lipoproteins	
	Neuropeptide Y	
	PTH	
	Retinol binding protein	
	TNF-α	

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MINERAL BONE DISEASE (MBD) IN CKD [FORMERLY RENAL OSTEODYSTROPHY]

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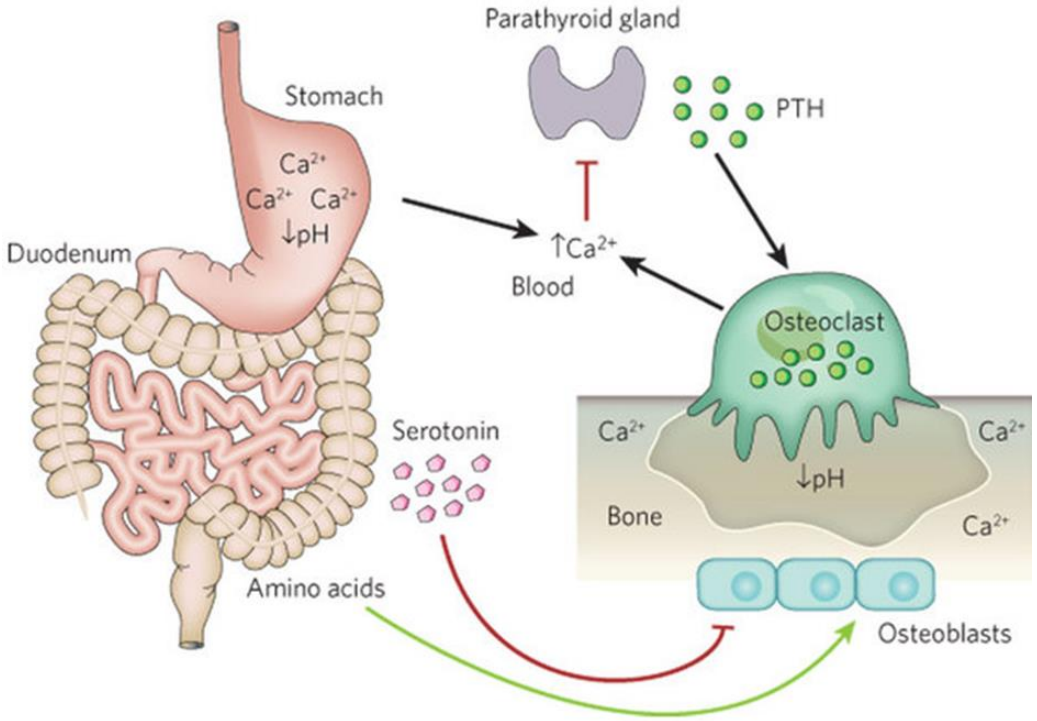
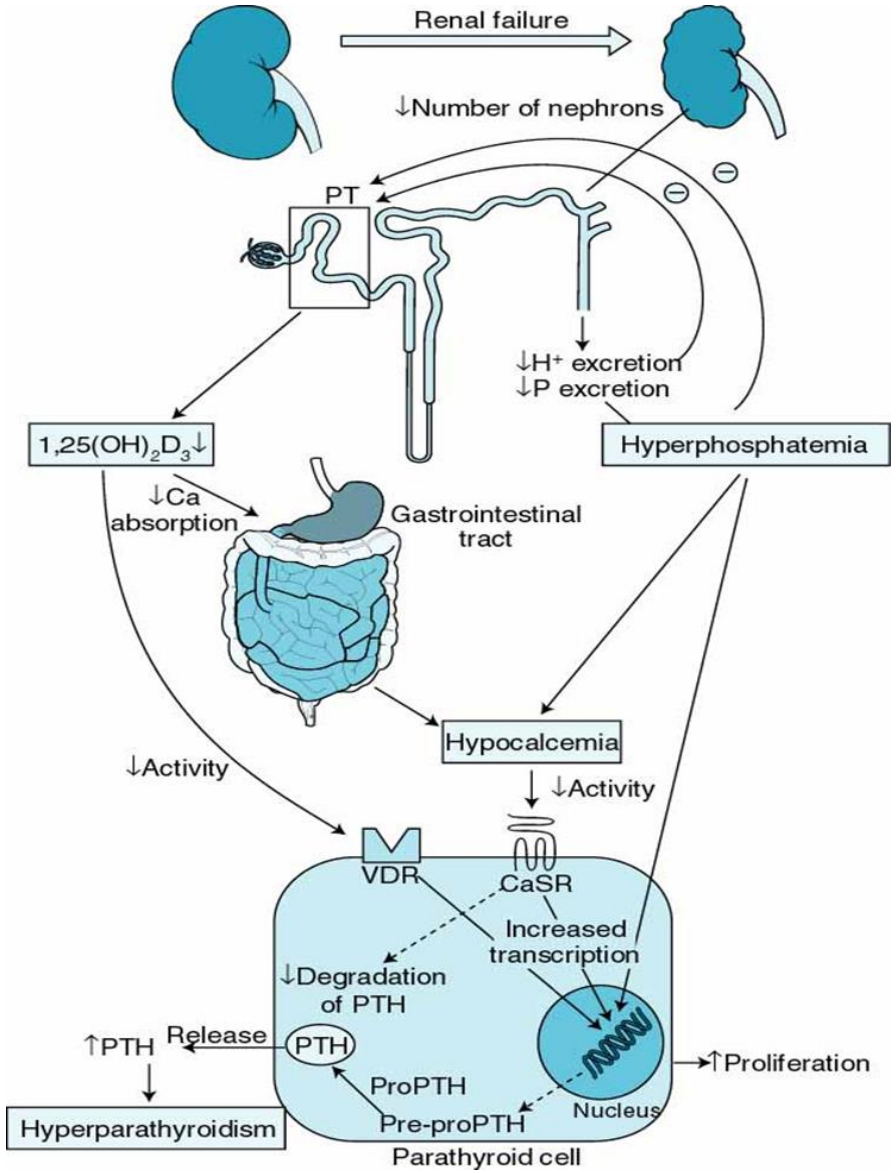
Terminology

- **osteoporosis** ("porous bones“)
  - the bone mineral density (BMD) is reduced, bone microarchitecture deteriorates, and the amount and variety of proteins in bone are altered
  - an increased risk of fracture
  - causes: old age, inactivity, menopause
    - ↓ sex steroids (esp. estrogens) → ↓synthesis of collagen (prevent mineralization)
- **osteomalacia**
  - softening of the bones caused by defective bone mineralization secondary to inadequate amounts of available phosphorus and/or calcium
  - causes: hypovitaminosis D or hypophosphatemia
    - lack of calcium or phosphate in the body
      - calcium : phosphate ratio prevents mineralization
    - ↓vitamin D → hypocalcaemia → ↑ PTH → ↑ calcaemia but ↓ phosphataemia
- **osteodystrophy**
  - bone mineralization deficiency associated with either high or low bone turnover as a consequence of hyperparathyroidism
    - primary HPTH: ↑ PTH → ↑ calcemia but ↓ phosphatemia
    - secondary (renal osteodystrophy): ↑ phosfatemia → ↓calcemia → ↑ PTH
  - in advanced stage accompanied by **osteitis fibrosa**



Hyperphosphatemia/hypocalcemia in CKD



- abnormal metabolisms of Ca, phosphorus, PTH and vitamin D in CKD
- ↓ excretion of phosphorus in kidney when ↓ GFR leads to **hyperphosphatemia** and
  - a) ↓ ionized Ca, **hypocalcaemia** stimulate production of PTH
    - altered calcium : phosphate product leads to calcium phospate precipitation and extraosseal calcifications
  - b) inhibition of 1α-hydroxylase in proximal tubular cells and ↓production of active D vit.
    - impaired intestinal absorption of Ca in GIT aggravates hypocalcaemia and this way to another ↑ of PTH
  - c) blockade of inhibitory action of vit. D on parathyroid bodies
    - less vit. D binds to VDR receptors in parathyroid bodies , ↓ inhibition of transcription of the PTH gene and ↑secretion of PTH
  - d) direct stimulatory effect on parathyroid bodies
- development of **secondary hyperparathyroidism**

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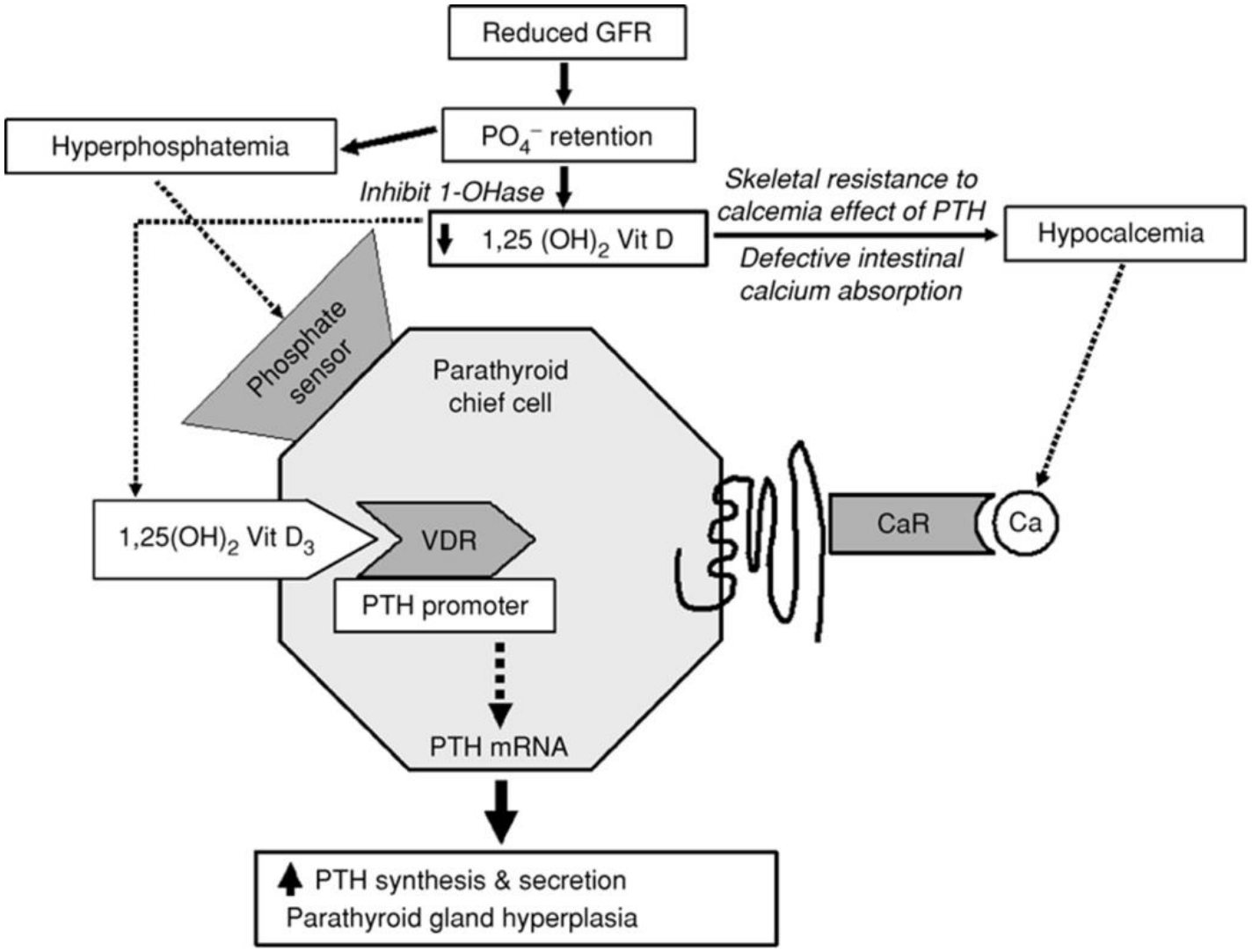
Pathophysiology of secondary hyperparathyroidism in CKD



- consequence of phosphate retention and reduced renal production of active vitamin D, resulting in hyperphosphatemia and hypocalcemia. With GFR <70 mL/min, renal excretion of phosphate can no longer keep pace with GIT absorption, and phosphorus retention occurs. Hyperphosphatemia inhibits the renal 1–alpha-hydroxylase, so that production of active 1,25 dihydroxy vitamin D_3 by the kidney is reduced. Vitamin D deficiency then leads to hypocalcemia as a consequence of defective gastrointestinal calcium absorption and skeletal resistance to the calcemic effect of PTH. The serum-ionized calcium is the most important factor regulating PTH secretion. The effects of calcium on parathyroid cells are mediated by a membrane-bound calcium-sensing receptor (CaR). Low serum calcium leads to an increase in PTH . In contrast, active vitamin D modulates PTH production in the parathyroid by binding to the cytoplasmic vitamin D receptor (VDR). The vitamin D-VDR complex binds to the PTH promoter and inhibits the transcription of PTH mRNA. Thus, vitamin D deficiency will lead to increased production of PTH message. A chronic decrease in vitamin D levels also leads to parathyroid cell proliferation and gland hyperplasia.

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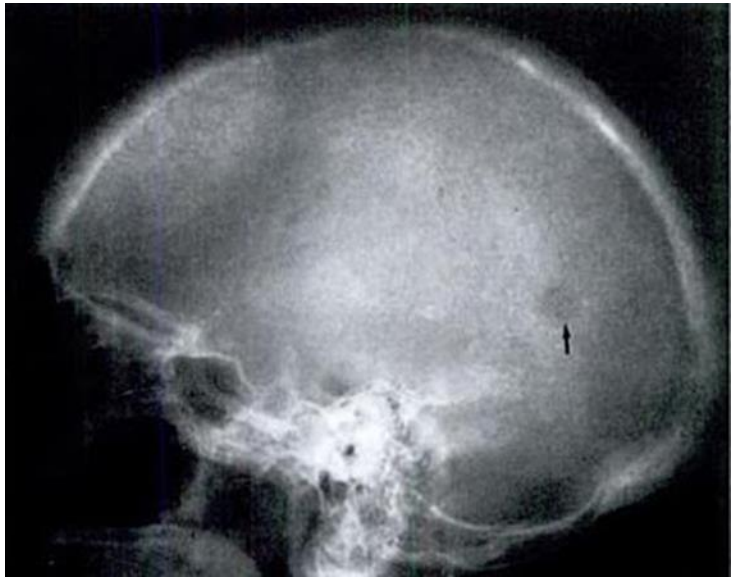
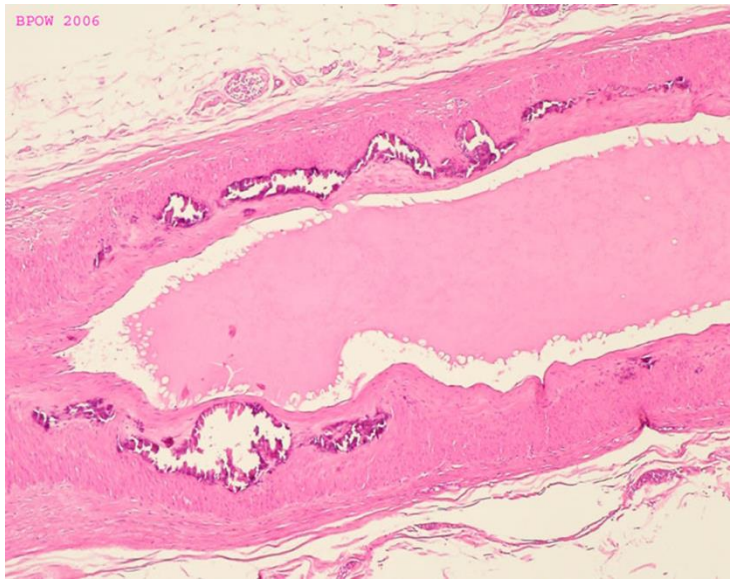
Renal osteopathy (synonym mineral bone disease, MBD)

- adverse complication of advanced CKD
- main features
  - — abnormal mineral metabolism
  - — increased bone fragility and impaired linear bone growth
    - fractures, pain, limited mobility
  - — soft tissue, vascular and valvular calcification
    - arterial calcification is an active process similar to bone formation with participation of multiple factors (osteopontin, osteoprotegerin, RANKL, RANK, FGF23 and fetuin A)
- MBD consists of a mixture of bone abnormalities
  - — osteodystrophy (+ osteitis fibrosa cystica)
  - — osteomalacia
  - — osteoporosis





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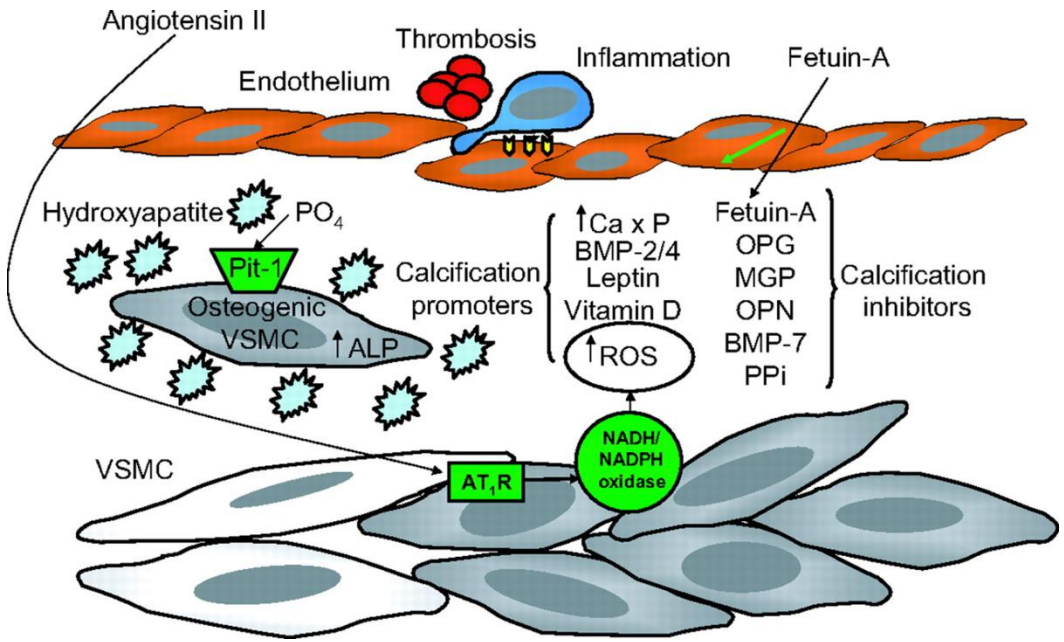
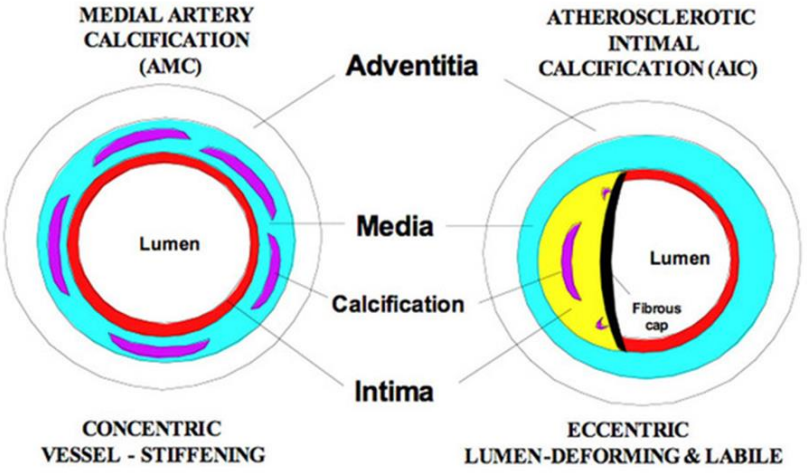
CV consequences of CKD-MBD

- causal abnormalities
  - arterial hypertension (90%)
  - hyperlipidemia, diabetes
  - sec. anemia (anemic hypoxia)
  - hyperhydration (volume overload)
  - calcification (arteries and valves)
  - uremic toxins
  - others
    - oxidative stress, hypofibrinolysis (= thrombophilia), homocystein
- manifestation
  - **LV hypertrophy**
  - **CAD**
    - compared to non-CKD patients ↑ media thickness, ↓ lumen diametr and more calcification, due to uremic neuropathy quite often „silent ischemia“
  - **arrhythmias**
    - due to hyperhydration and electrolyte dysbalances , event. pericarditis and CAD (+ myocardial ischemia during hypotension in dialysis)
- consequences
  - cardio-renal resp. reno-cardiac syndrome
    - pre-existing heart disease worsens CKD prognosis and vice versa





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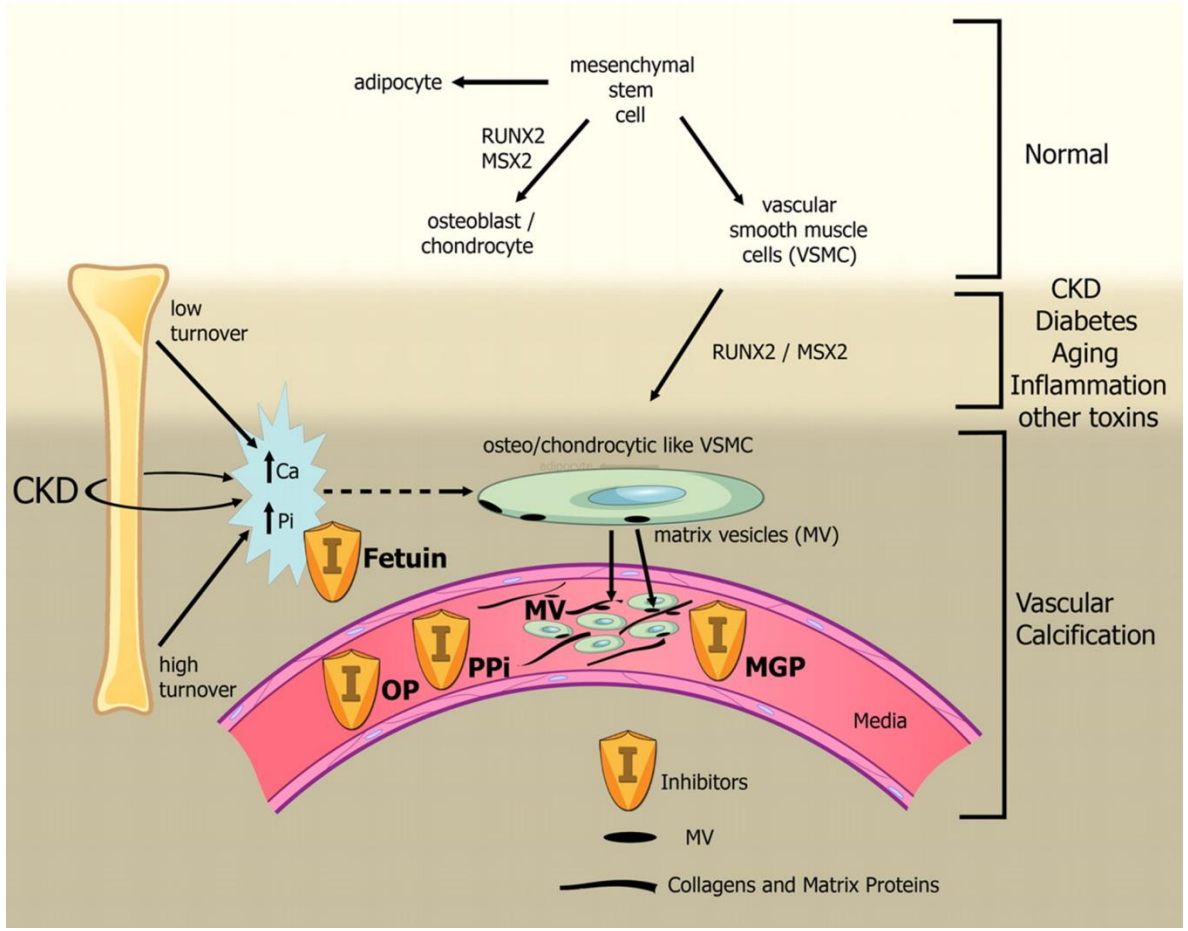
Pathogenesis of vascular calcification



- Normally, mesenchymal stem cells differentiate into adipocytes, osteoblasts, chondrocytes, and vascular smooth muscle cells (VSMCs). In the setting of chronic kidney disease (CKD), diabetes, aging, inflammation and multiple other toxins, these VSMCs can de-differentiate or transform into chondrocyte/osteoblast-like cells by upregulation of transcription factors such as Runx2 and Msx2. These transcription factors are critical for normal bone development and thus their upregulation in VSMCs is indicative of a phenotypic switch. These osteo/chondrocytic-like VSMCs then become calcified in a process similar to bone formation. These cells lay down collagen and non-collagenous proteins in the intima or media and incorporate calcium and phosphorus into matrix vesicles to initiate mineralization and further grow the mineral into hydroxyapatite. Ultimately, whether an artery calcifies or not depends on the strength of the army of inhibitors standing by in the circulation (fetuin-A) and in the arteries
- MGP = matrix gla protein; OP = osteopontin; PPi = pyrophosphate

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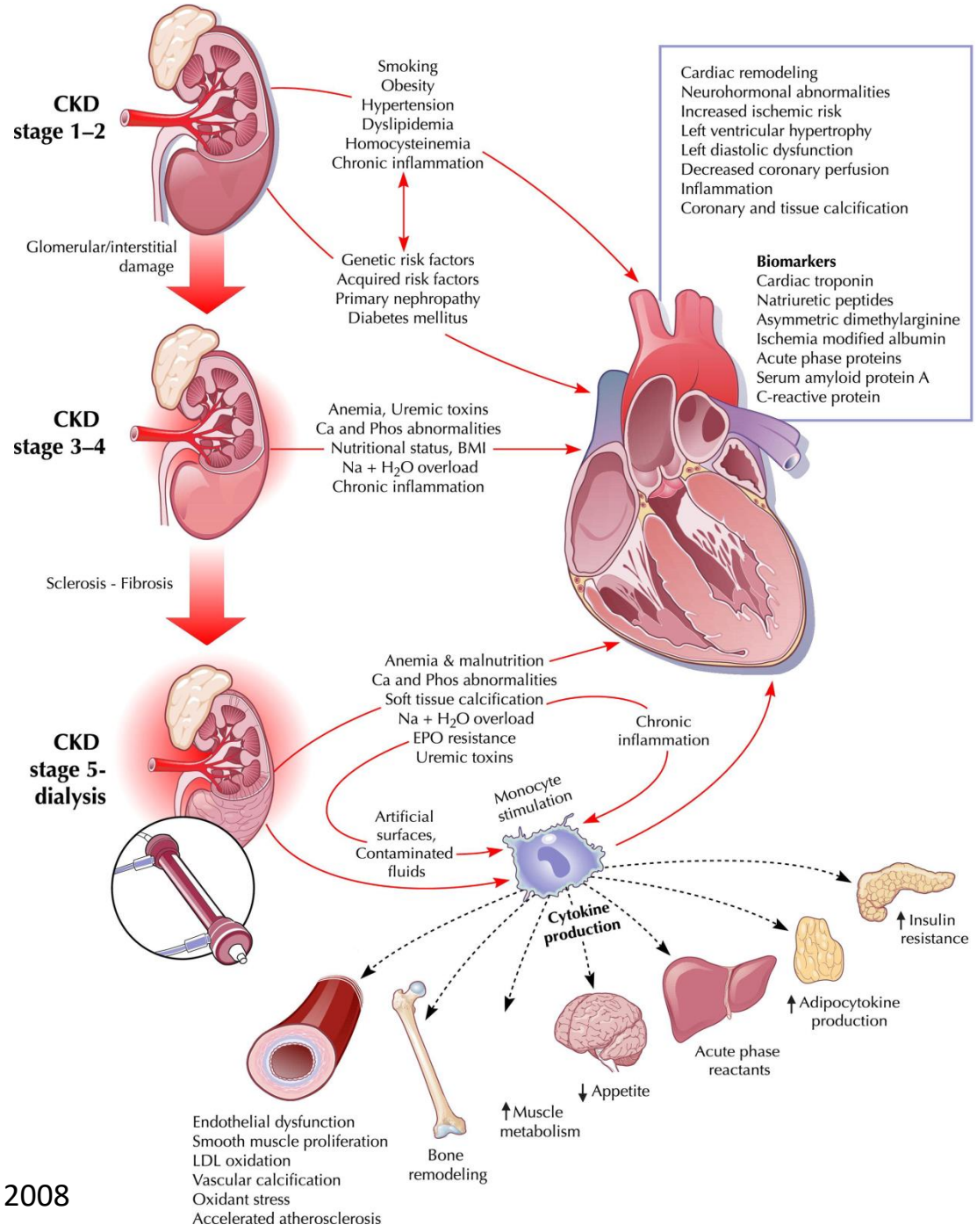
Pathophysiological interactions between heart and kidney (= reno-cardiac syndrome)

CKD contributing to decreased cardiac function, cardiac hypertrophy, or increased risk of adverse cardiovascular events)

BMI = body mass index; EPO = erythropoietin; LDL = low-density lipoprotein



Ronco C et al, JACC 2008

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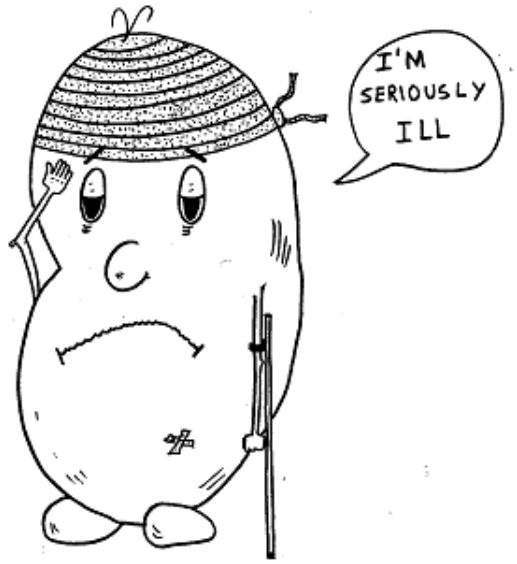

CHRONIC KIDNEY FAILURE

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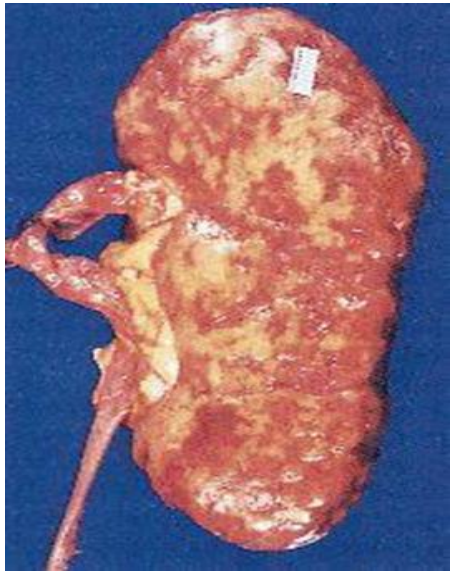
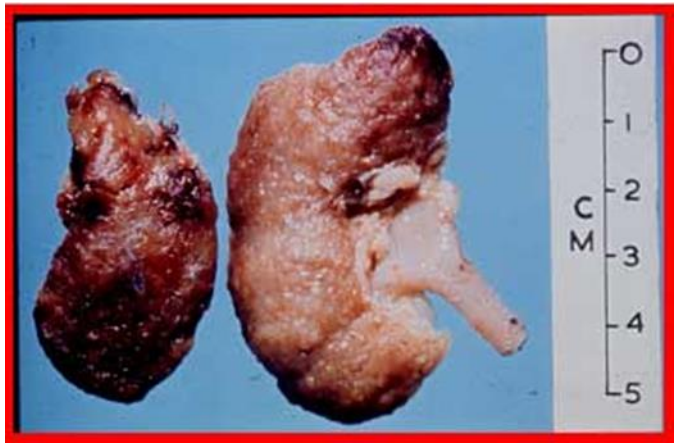
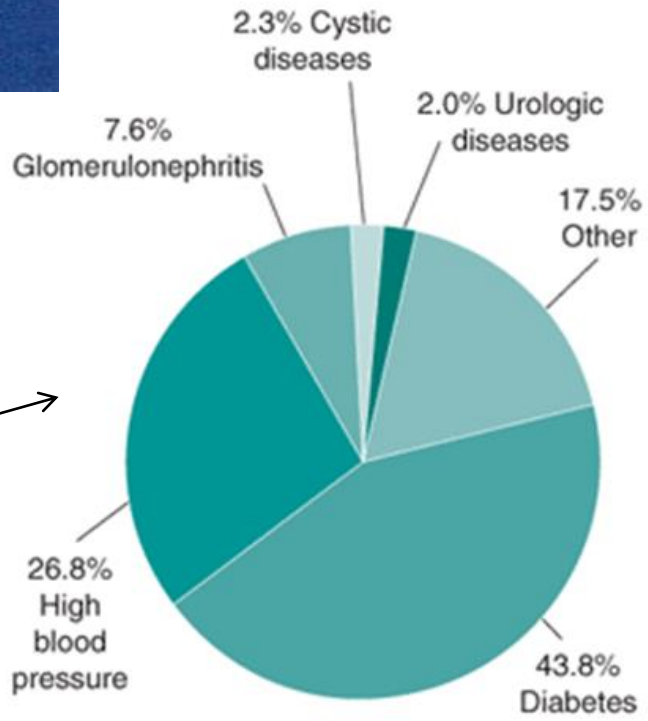
Chron. renal failure = CKD stage 5 = ESRD

- appearance of small, irregular shape, scarred, **shrunken kidney** with granular surface
- full blown symptoms of **uremia**
- it is necessary to
  - treat conservatively but aggressively (only symptomatic though)
    - ↓ fluid intake
    - ↓ Na+, K+ intake
    - ↓ protein intake
    - complications
      - anemia, MBD, hypertension, infections, …
    - modification of drug dosage!!
  - kidney replacement therapy
    - dialysis
    - transplantation
  - etiology of the most common CKD causes progressing to ESRD







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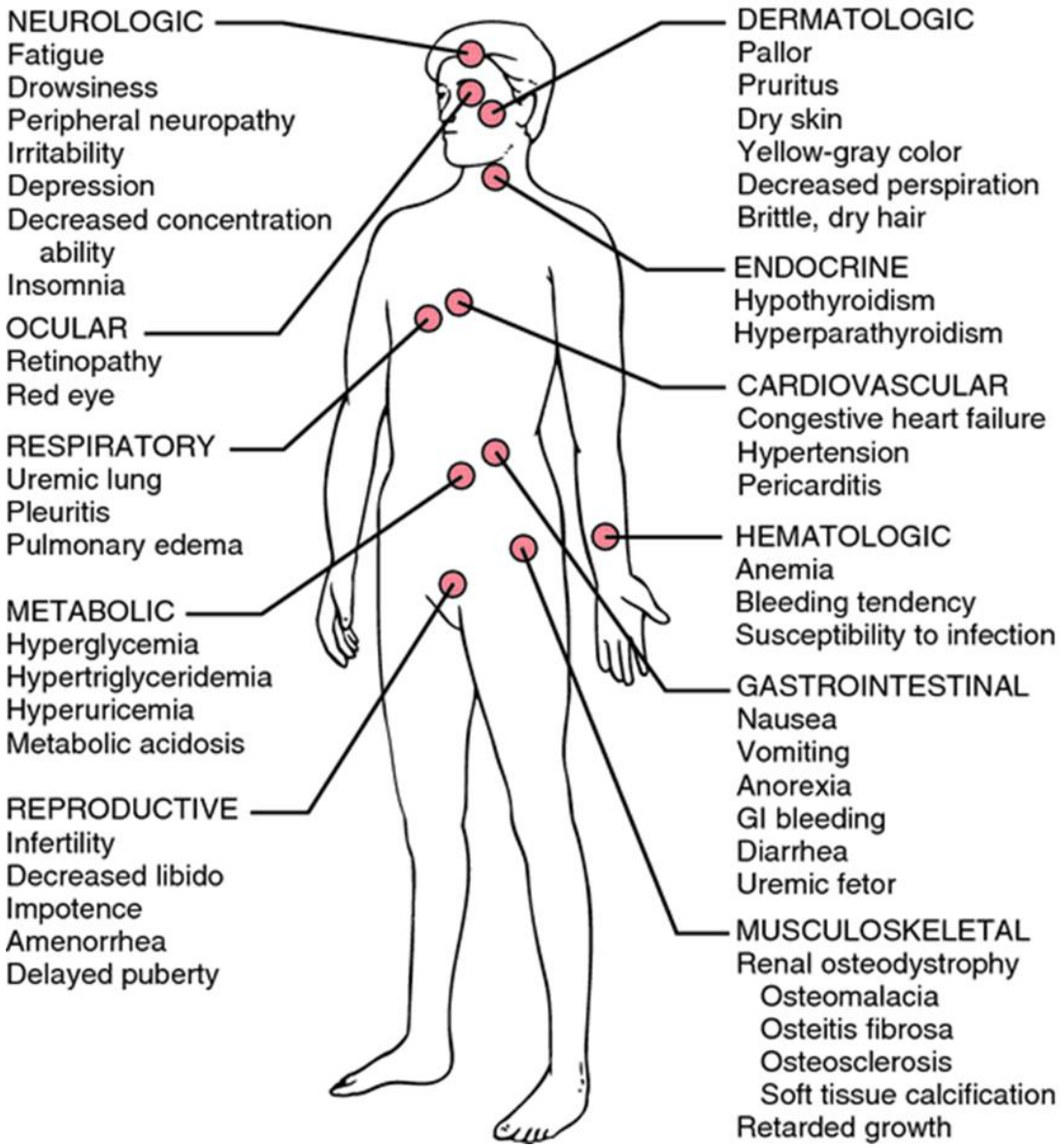
Uremic symptoms



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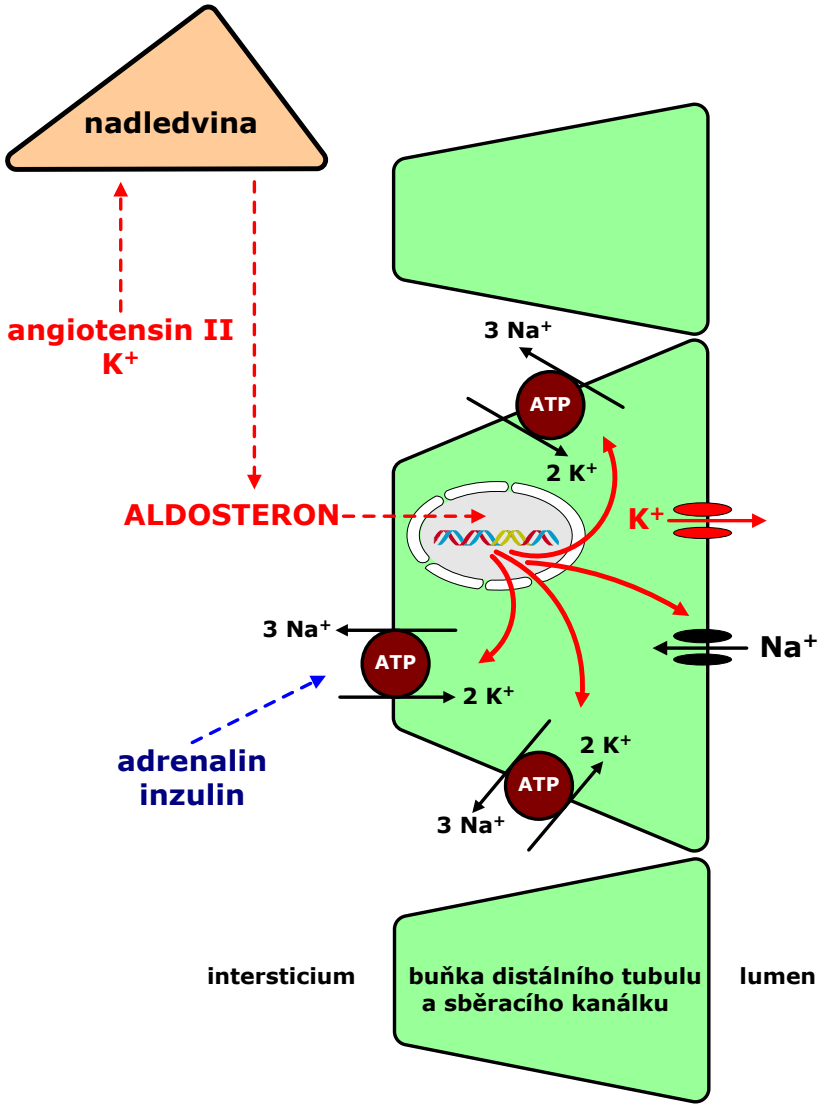
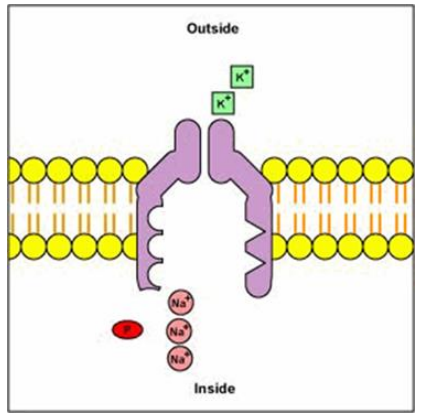
Hypercalemia

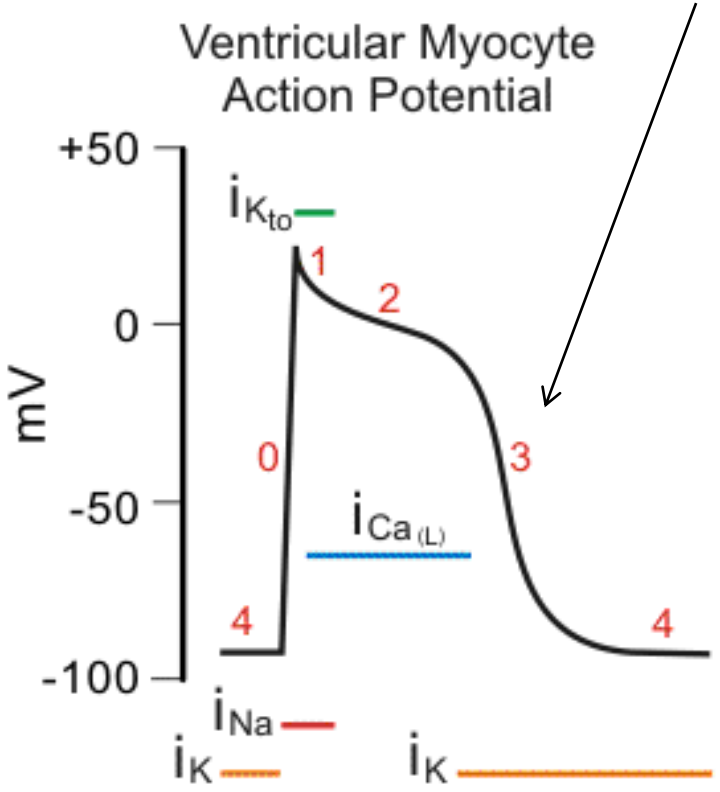
- 98% K+ in ICF
  - 35-50x more than in ECF (3.8 – 5.5 mmol/l)
  - Na+/K+ ATPase
- higher permeability of membrane for K+ that other cations
  - contribution to the resting membrane potential
    - passive K flow from the cell along the conc. gradient limited by intracellular anoints
  - changes of kalemia in ECF are slowly reflected in ICF too
- disorders of K balance in organism:
    - ↑ dietary intake with intact kidneys is not a problem
    - decreased K excretion in renal insufficiency and ESRD
- disorders of distribution – multiple factors influence K distribution between ECF and ICF:
  - disruption of cells/ hemolysis
  - osmolality
  - acidosis
- regulation of [K+] in ECF
  - (1) redistribution of K+ (from ECF to ICF)
    - pH, insulin, adrenalin
  - (2) renal excretion
    - aldosterone, [K+]



Effect of hyperkalemia on heart

- **effect depends on the magnitude of change (= how much) and speed of change (= how fast)!!!!**
  - therefore there are significant differences between acute and chronic renal failure
- hyperkalemia
  - ↑ excitability by moving the resting membrane potential closer to the threshold
    - passive K flow from the cell along the conc. gradient limited by intracellular anoints is diminished by ↑[K+] in ECF, retention of K+ in ICF and depolarisation
  - initially also quicker repolarization (phase 3)
    - activating substrate effect on Na+/K+ ATP-ase (↑ availability of K+ for exchange)
  - later when ↑↑ [K+] inhibition of repolarization
    - too low concentration gradient
  - finally when ↑↑↑ [K+] cardiac arrest
    - inhibitory effect on Na+/K+ ATP-ase (it cannot pump against extremely high concentration of K+ in ICT)
    - too close shift of resting m. potential to threshold disables opening (voltage gated) of Na+ channels





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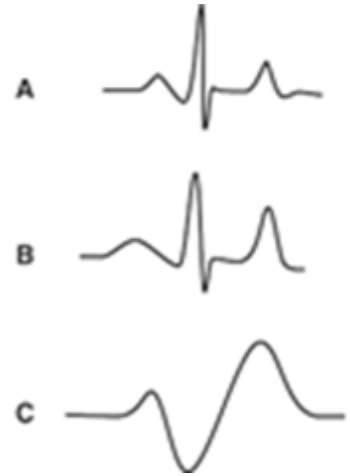
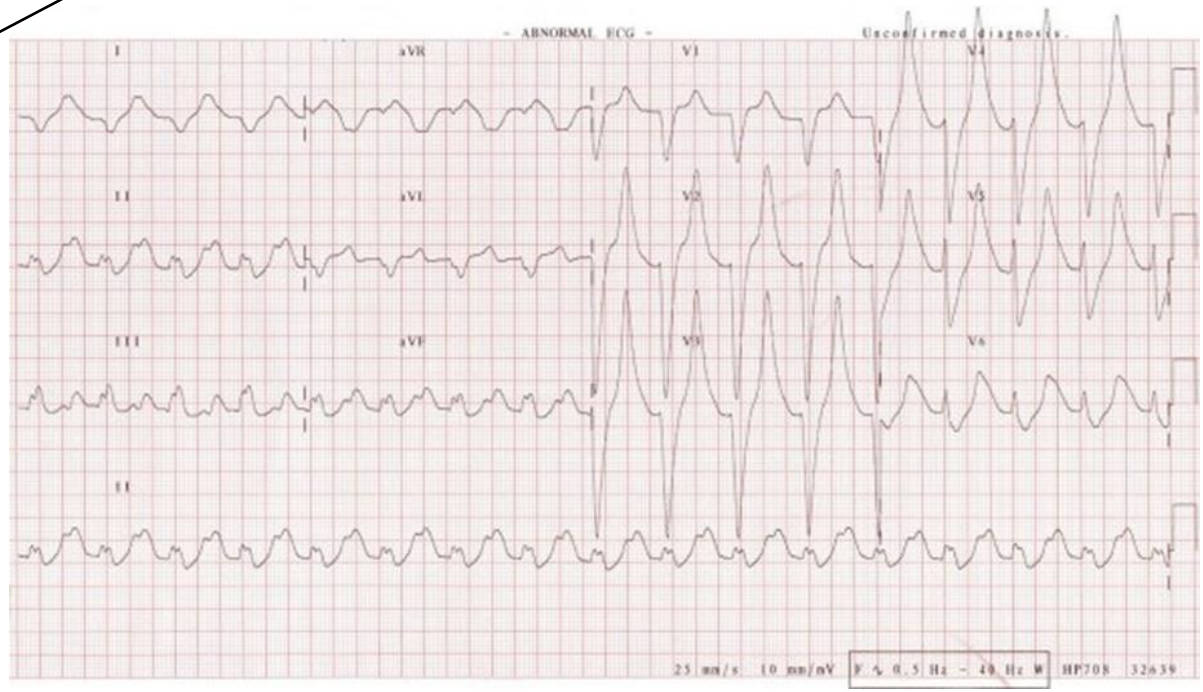
Hyperkalemia (K+ >5.5 mmol/l)

- affected all types of muscles
  - skeletal
  - smooth
  - myocardium
- signs
  - arrhythmia (ECG):
    - < 7 mmol/l
      - spiked T waves
      - widened QRS
      - prolonged PR interval
      - flattened P waves
    - > 7 mmol/l
      - lowered voltage
      - bradycardia
    - > 8 mmol/l
      - „sinusoidal“ shape of QRS
      - idioventricular rhythm
      - ventricular fibrillation, arrest
  - paresthesias, weak reflexes, paresis and obstipation





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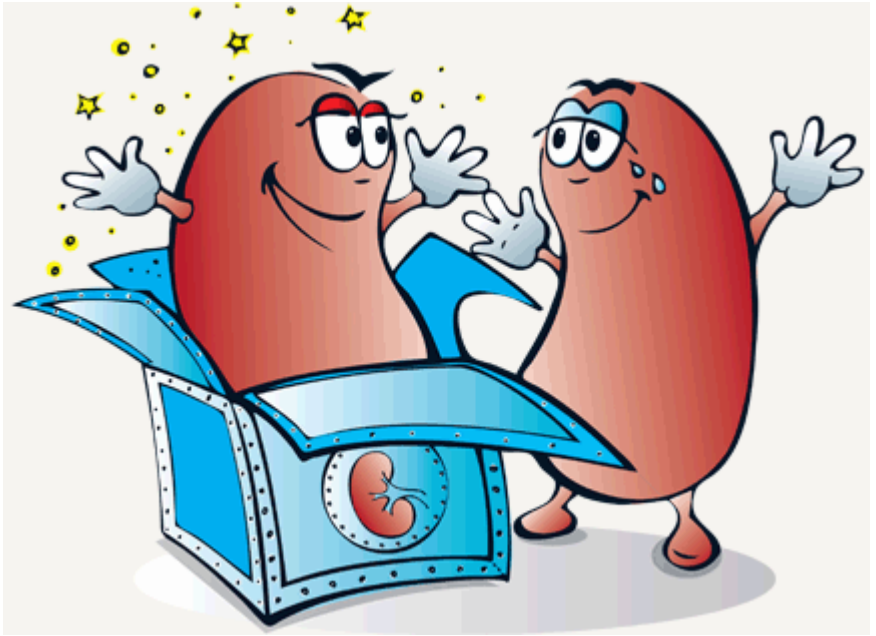

RENAL REPLACEMENT THERAPY - METHODS

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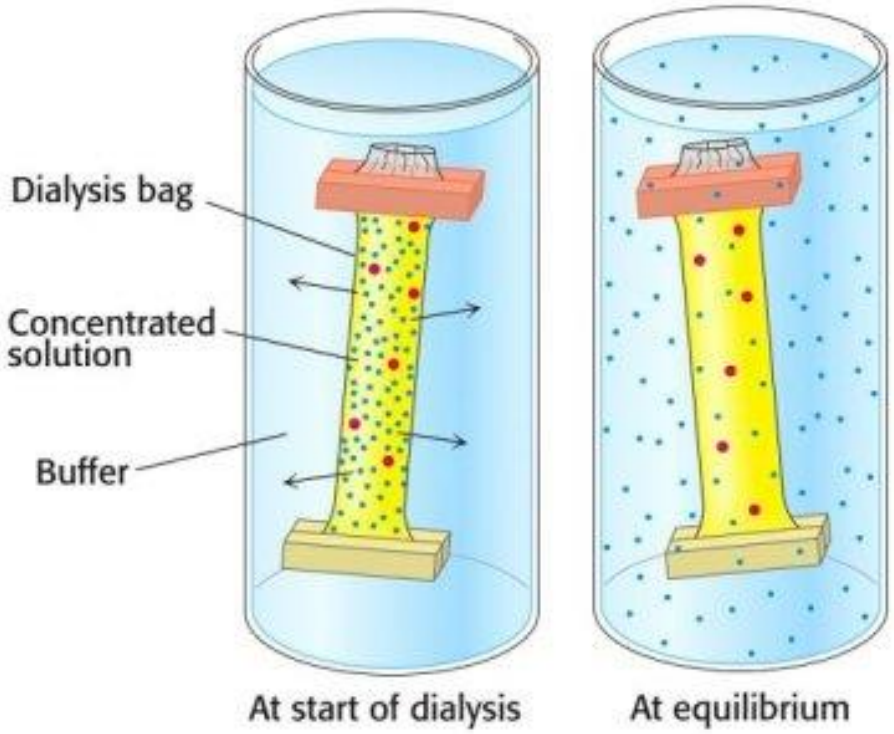
Principle of hemodialysis



- for the first time in 1943 in Netherlands
- 3 main physical principles
  - **diffusion** and **ultrafiltration** of solutes across a semipermeable membrane
  - **counter current flow** where the dialysate is flowing in the opposite direction to blood flow in the extracorporeal circuit
- standard regimen
  - three times a week, 3–4 hours per treatment schedule
- dialysis solution
  - **urea, creatinin, potassium** and **phosphate** diffuse into the dialysis solution (high in blood, low in solution)
  - concentrations of **sodium** and **chloride** are similar to those in plasma to prevent loss
  - **sodium bicarbonate** is added in a higher concentration than plasma to correct blood acidity
  - **glucose** is also added to balance glycaemia and prevent hypoglycemia

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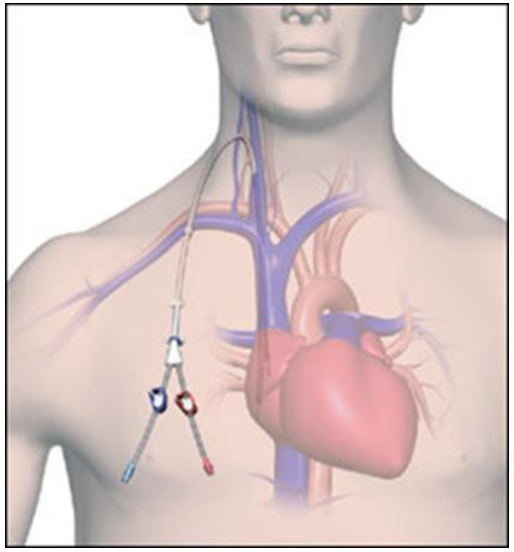
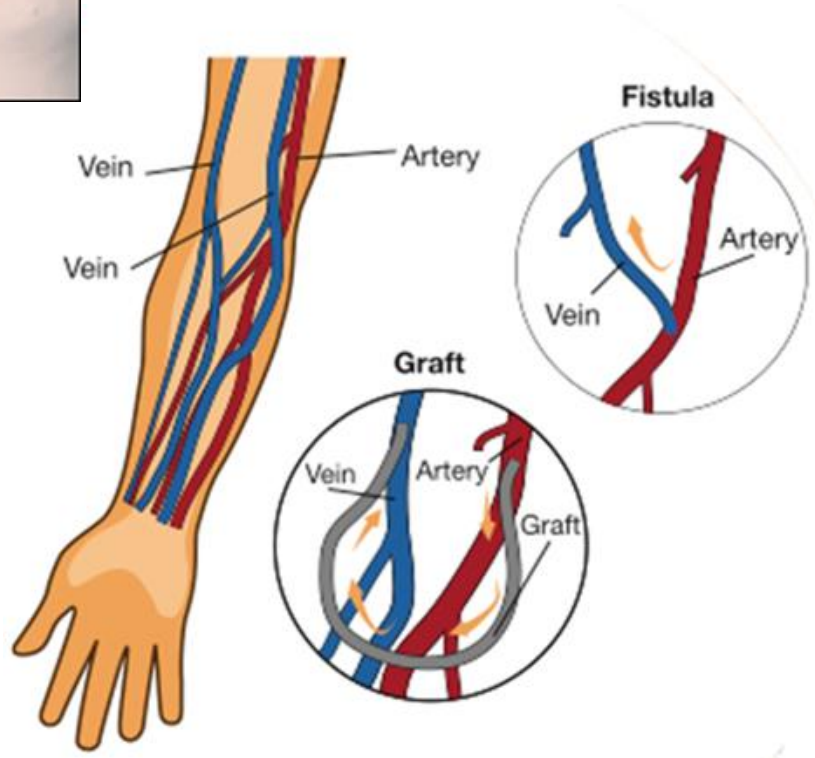
Blood stream access





- temporary – useful for limited number of procedures
  - —two-way catheter
    - v. subclavia, v. jugularis, v. femoralis
  - —risks: bleeding, thrombosis, stenosis, infection
- permanent – in patients in regular HD program
  - —arterio-venous fistule
    - between a. radialis and v. cephalica
  - —synthetic graft

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HD side-effects and complications

- **hypotension**
  - — most often, nearly 30% of dialyses
- **leg-cramps, nausea** and **headaches**
  - — second most common complication
  - — due to volume depletion during ultrafiltration or ion dysbalance
- **disequilibrium syndrome**
  - — u acute HD with high pre-dialysis BUN and too fast HD
    - sudden drop of BUN is not reflected with urea decrees in CSF
    - ↑ CSF osmolality causes intracranial hypertension and brain edema
  - — metabolic acidosis also contributes
    - during HD plasma bicarbonate (HCO_3^-) level rapidly increases, but bicarbonate cannot readily pass across the BBB, whereas carbon dioxide (CO_2) diffuses rapidly. The initial increased passage of carbon dioxide into the CSF and brain leads to a reduction in pH (Henderson-Hasselbach equation), and intracellular acidosis results in the breakdown of intracellular proteins to create idiogenic osmoles that create an osmotic gradient for water movement into the brain
  - — stop of HD and anti-edematous therapy
- **infection** (esp. endocarditis and osteomyelitis)
- long term (neuropathies, amyloidosis)

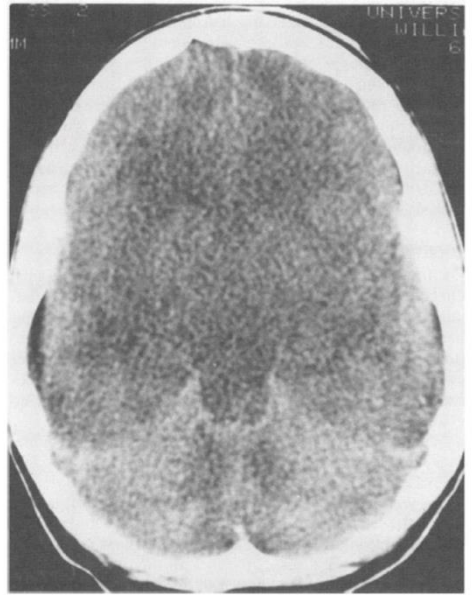

Figure 1.—An enhanced computed tomographic scan of the head shows diffuse cerebral edema.

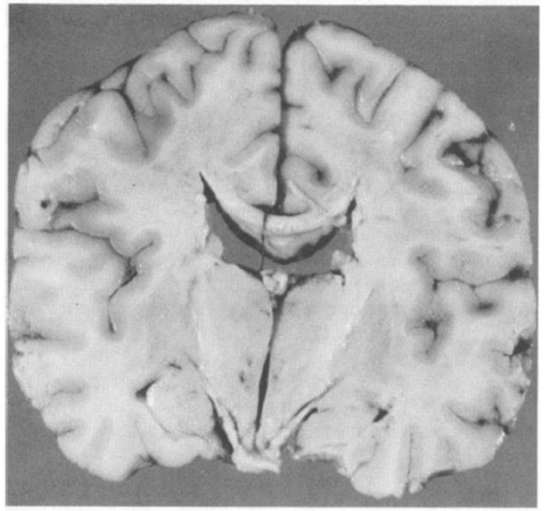

Figure 2.—A coronal section of the brain shows severe cerebral edema.

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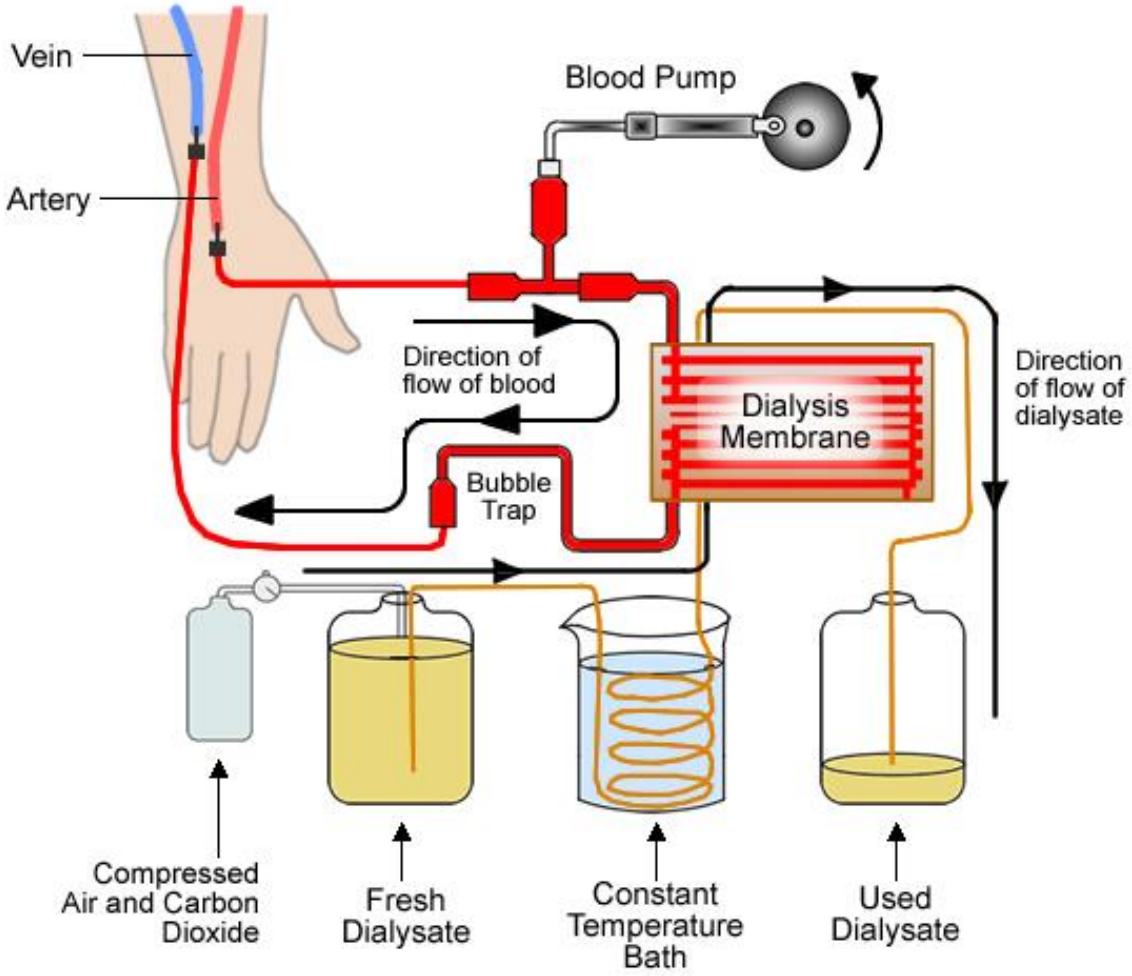
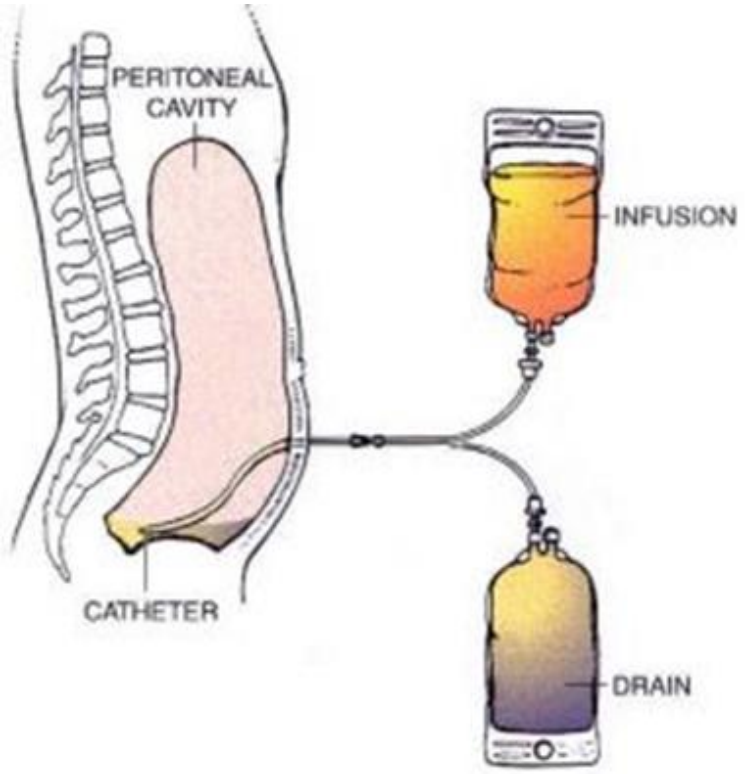
HD vs. peritoneal dialysis





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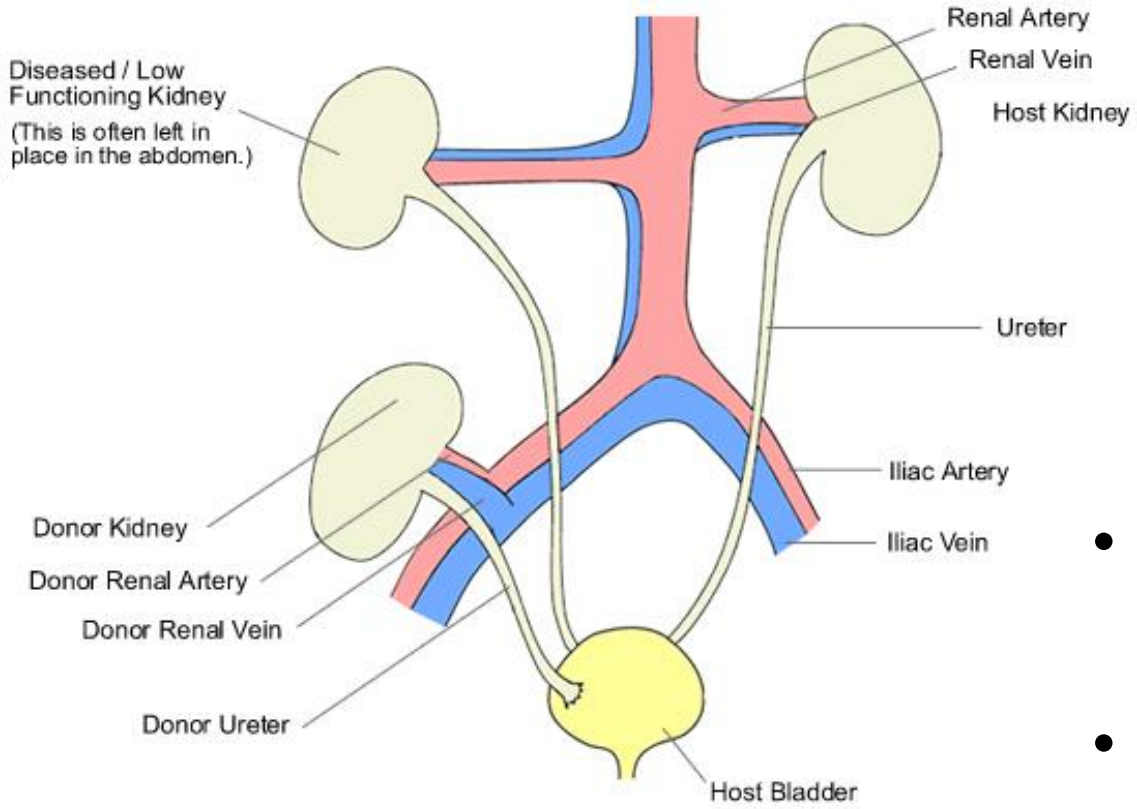
Kidney transplantation



- necessity to obtain donor kidney
  - cadaverous
  - from living donor (often relative)
- immunological compatibility
  - risk of rejection
    - hyper-acute
    - acute
    - chronic
  - risks associated with immunosuppressive therapy

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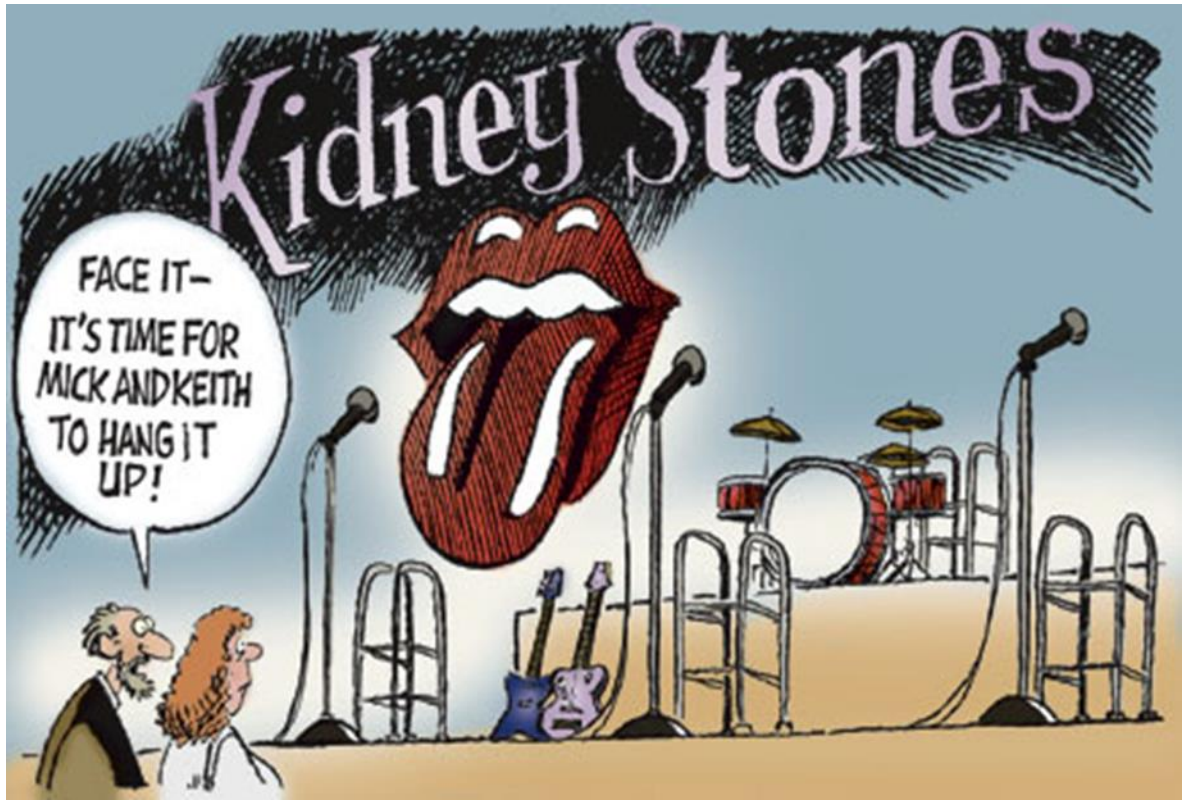
Kidney Stones
FACE IT–
IT'S TIME FOR
MICK AND KEITH
TO HANG IT
UP!

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