PATHOPHYSIOLOGY OF THE KIDNEYS
PART II

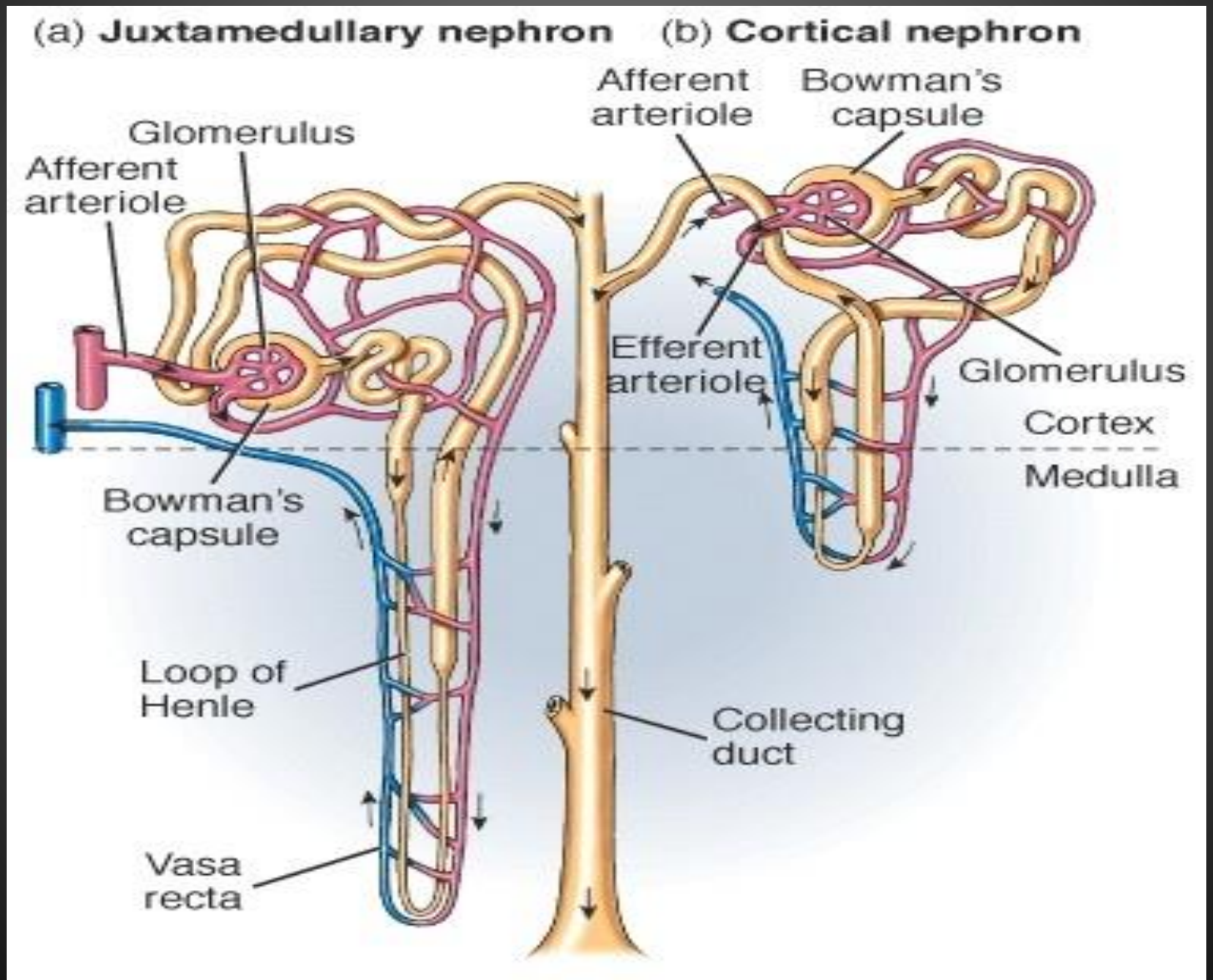
Work for today

Disorders of urine dilution and concentration

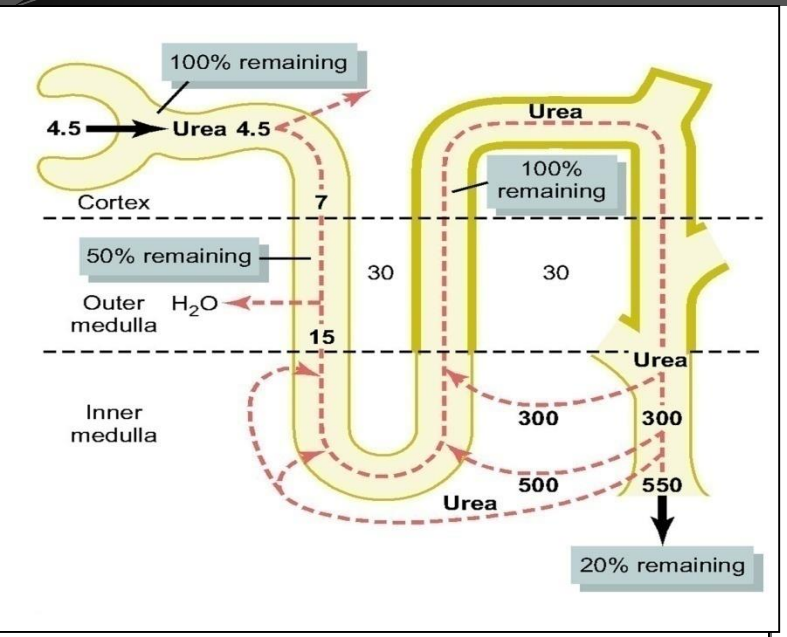
Acute renal failure

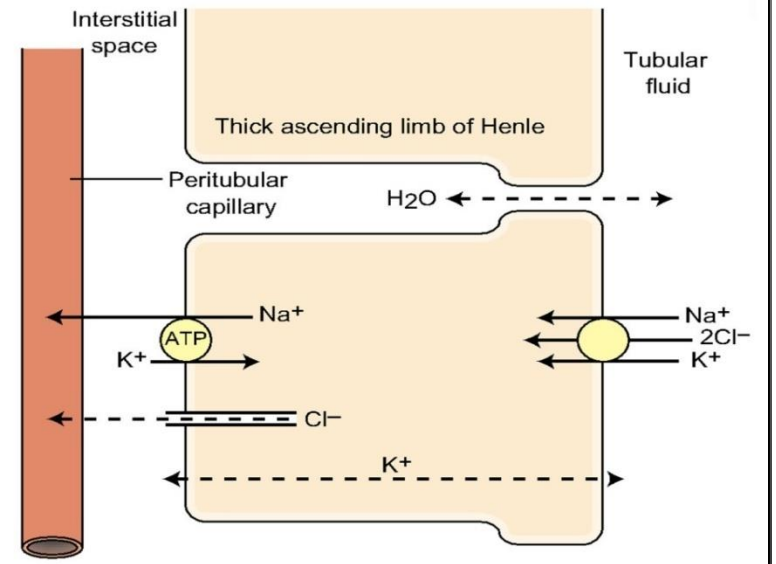
Chronic renal failure

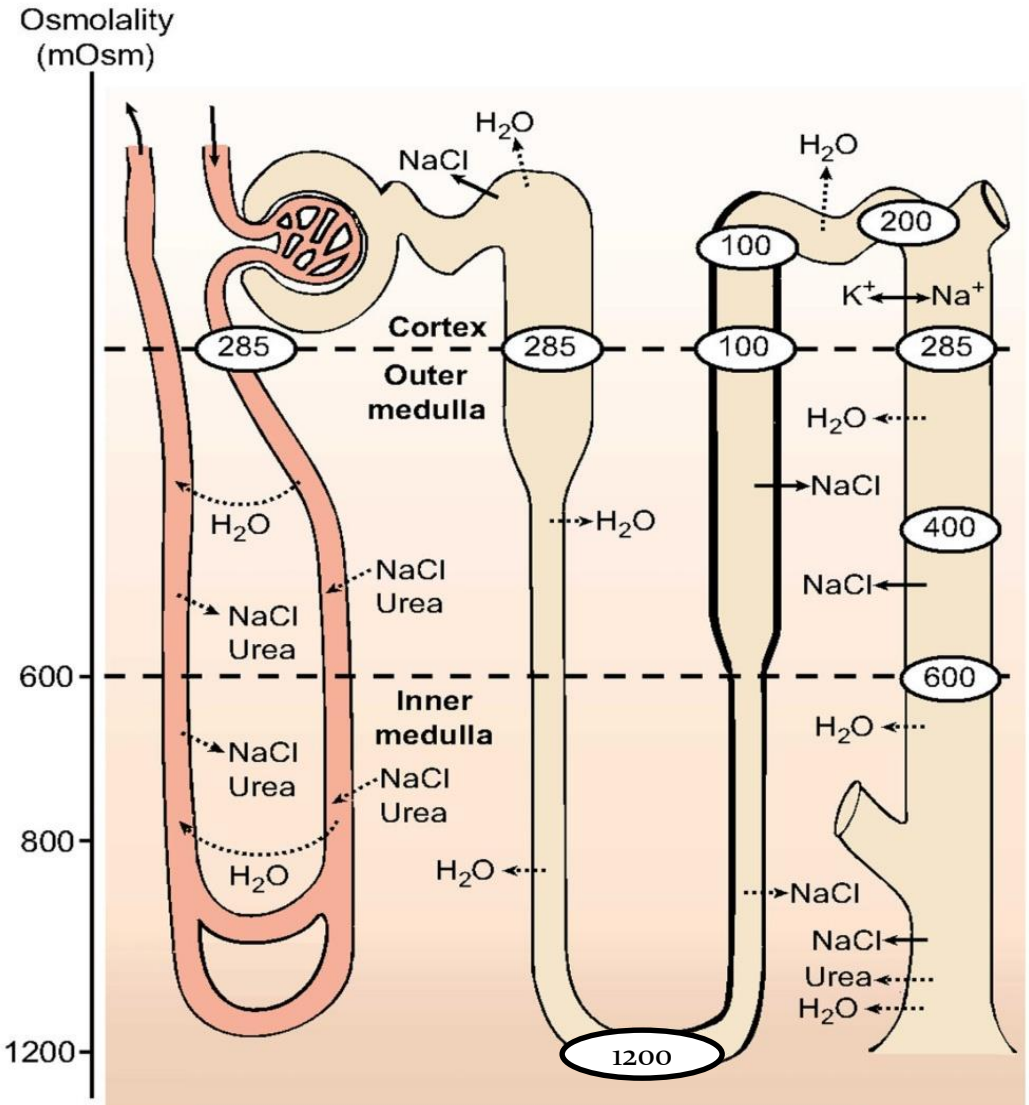
Disorders of mechanisms of urine dilution and concentration



Disorders of mechanisms of urine dilution and concentration







Disorders of mechanisms of urine dilution and concentration

Hypostenuria

Urine osmolarity lower than that of the blood plasma

Diabetus insipidus
Hyperhydration
Inflammation
Loop diuretics

Izostenuria

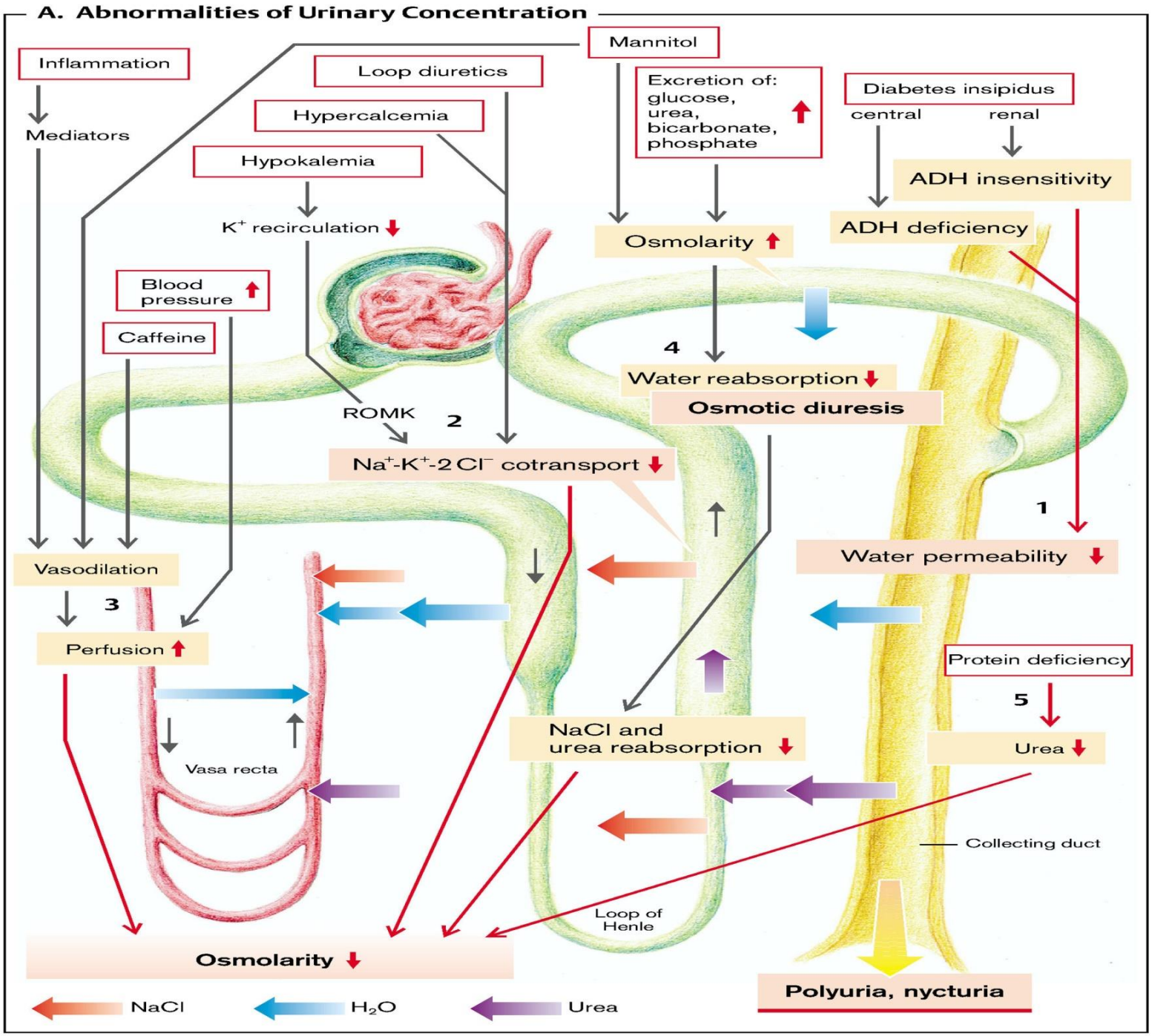
Urine osmolarity is equal with plasma osmolarity

Diffuse injury of renal epithelium at the level of Henle loop, collector tubules

Hyperstenuria

Urine osmolarity is higher than 1035 mOsm/L

Dehydration
Diabetes mellitus


A. Abnormalities of Urinary Concentration
Mannitol
Inflammation
Loop diuretics
Excretion of: glucose, urea, bicarbonate, phosphate
Diabetes insipidus
central
renal
Mediators
Hypercalcemia
Hypokalemia
ADH insensitivity
K+ recirculation
Osmolarity
ADH deficiency
Blood pressure
Caffeine
4
Water reabsorption
Osmotic diuresis
ROMK
2
Na+-K+-2 Cl− cotransport
1
Water permeability
Vasodilation
3
Perfusion
Protein deficiency
5
NaCl and urea reabsorption
Urea
Vasa recta
Collecting duct
Loop of Henle
Osmolarity
Polyuria, nycturia
NaCl
H2O
Urea

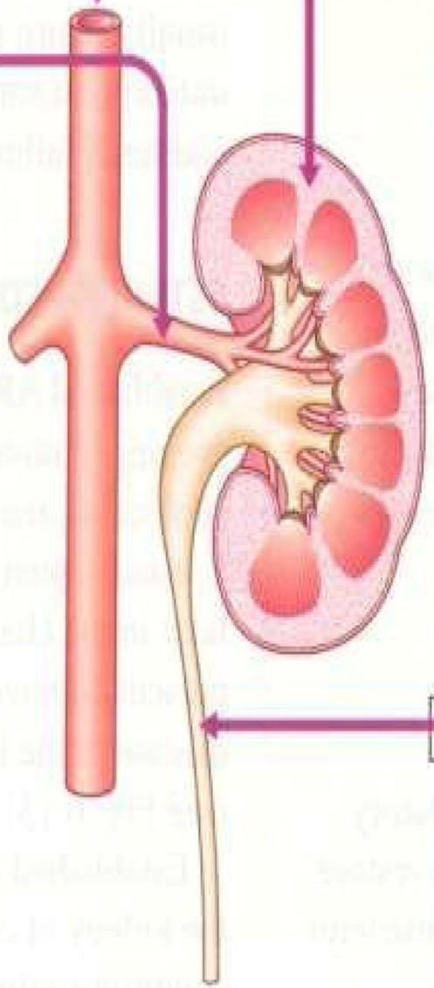
Renal failure

Renal failure is a temporary or persistent decline of kidneys functions and is characterized by general metabolic, hydro-electrolytic, acid-base and circulatory dyshomeostasis

ACUTE

CHRONIC

Acute renal failure



Pre-renal

Systemic
- Heart failure
- Shock

Local
- Renal artery occlusion/stenosis
- Diseases affecting arterioles

Underperfusion initially causes reversible changes. Subsequently 'acute tubular necrosis' or other changes cause longer-lasting, but usually temporary, intrinsic renal failure

Intrinsic renal disease

Acute tubular necrosis/ toxic/septic renal failure	85%	(see p. 430, 447)
Glomerular disease	5%	(see p. 442)
Primary		
Component of systemic disease		
Interstitial disease	10%	(see p. 448)

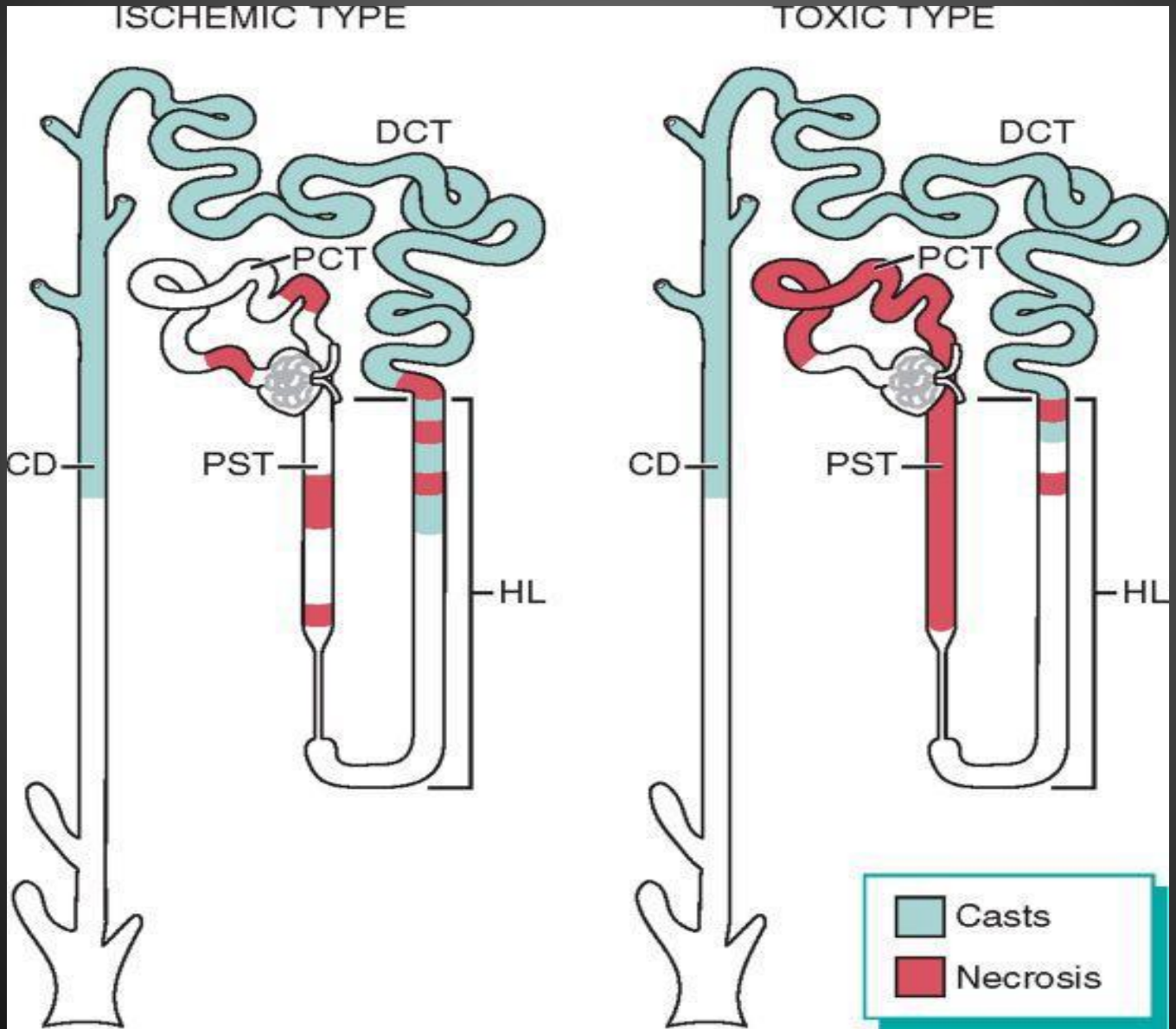
Systemic diseases

Acting via one or more of these three categories

Post-renal

Stones
Inflammation
Tumour
} (see p. 462)

Pathophysiological mechanisms of acute renal failure



General pathophysiological mechanisms of acute renal failure

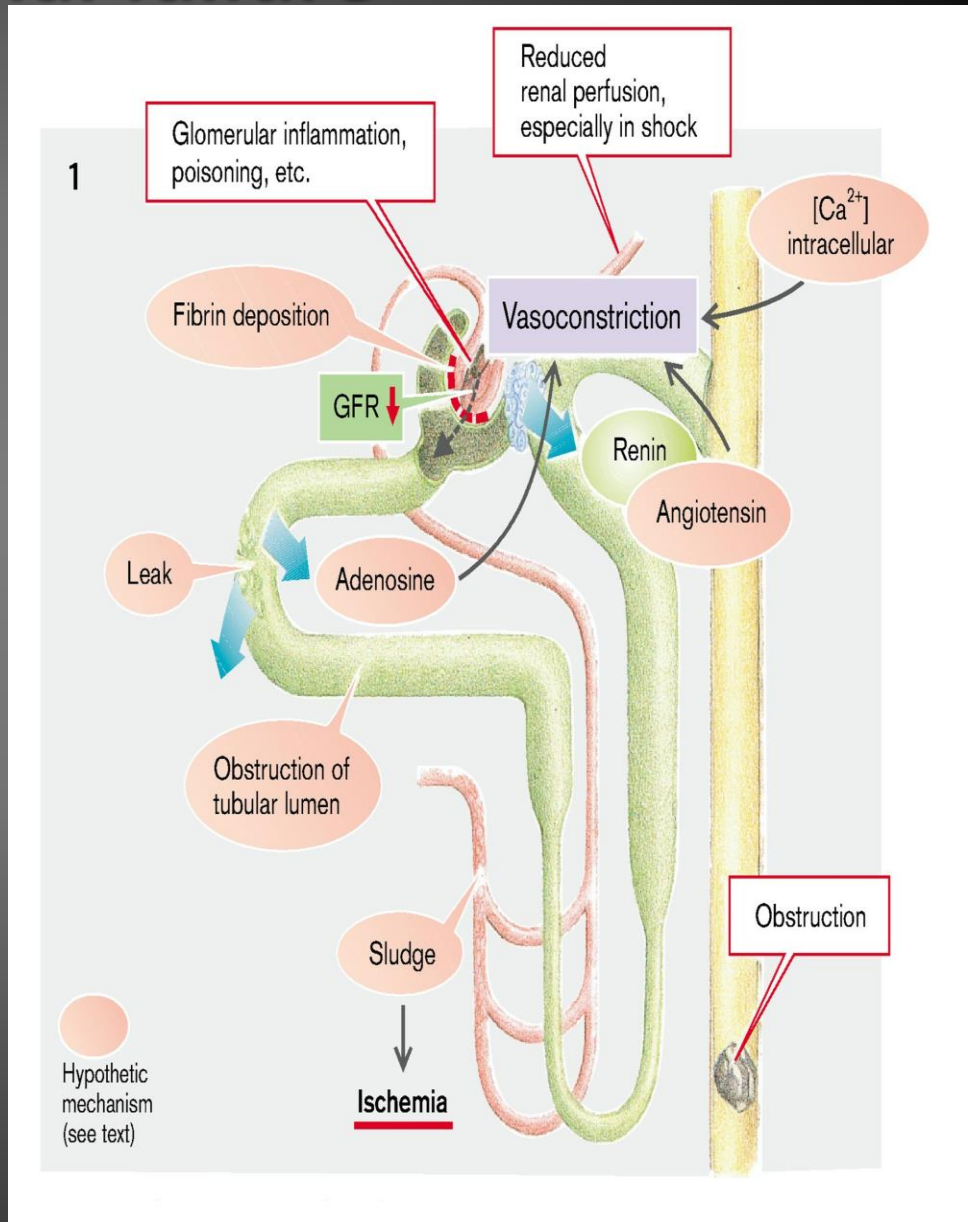
I. Constriction of afferent arteriole with ischemia

- II. Obstruction of renal filter

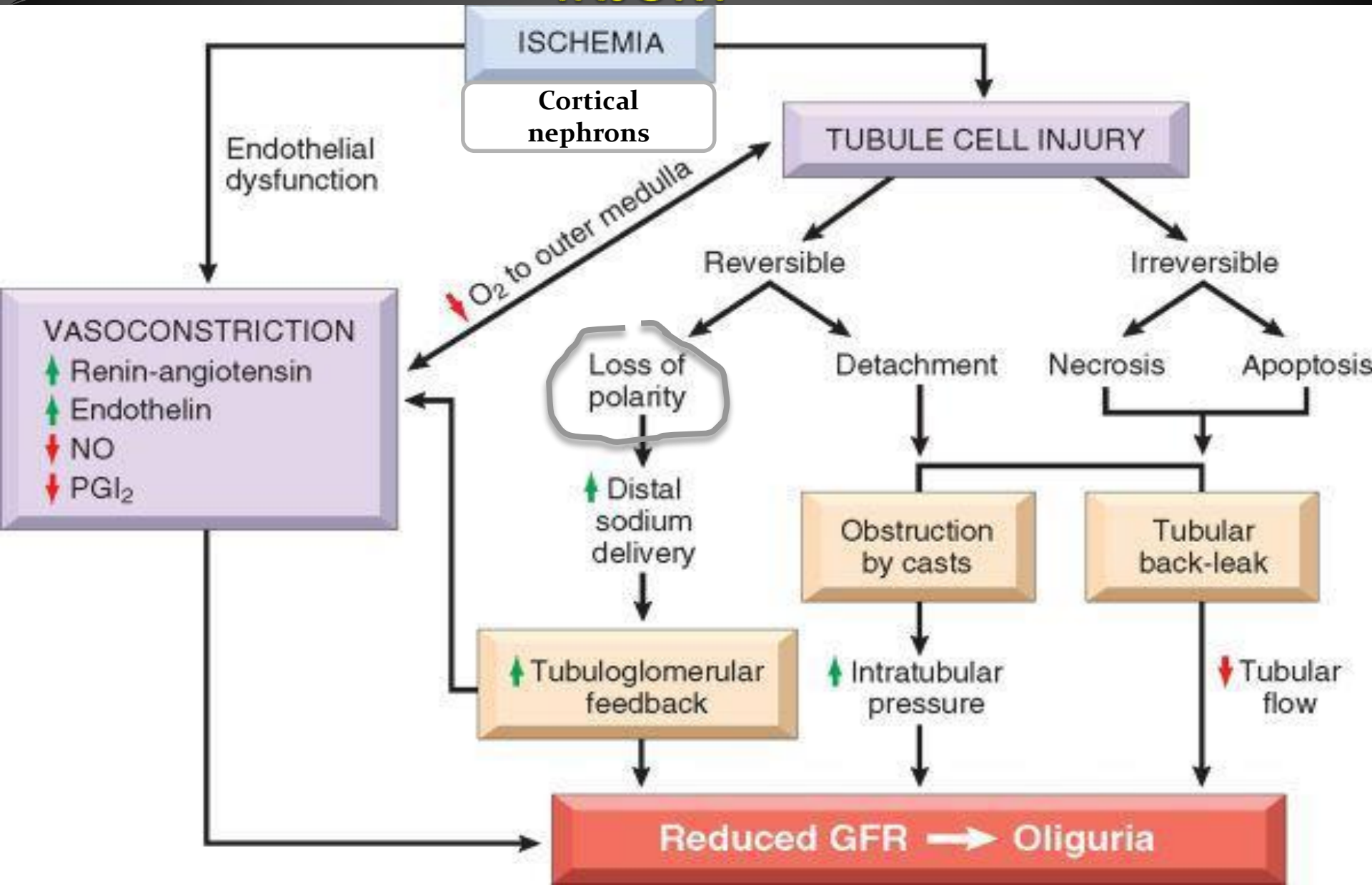
III. Leak of tubular fluid;

IV. Obstruction of tubular lumen

V. Intravascular stasis



MECHANISMS OF ISCHEMIC ACUTE KIDNEY INJURY



CLINICAL EVOLUTION OF ACUTE KIDNEY INJURY

PHASES

Onset
Initiation phase

Maintenance
(oliguric phase)

Recovery
(polyuric phase)

CLINICAL SYNDROMES

URINARY SYNDROME
Changes of urine output and urine osmolarity

HUMORAL SYNDROME
Hydroelectrolytic disorders
Ph disorders
Azotemia

CLINICAL SYNDROME
Disorders of breathing, CVS changes, gastrointestinal, SNS

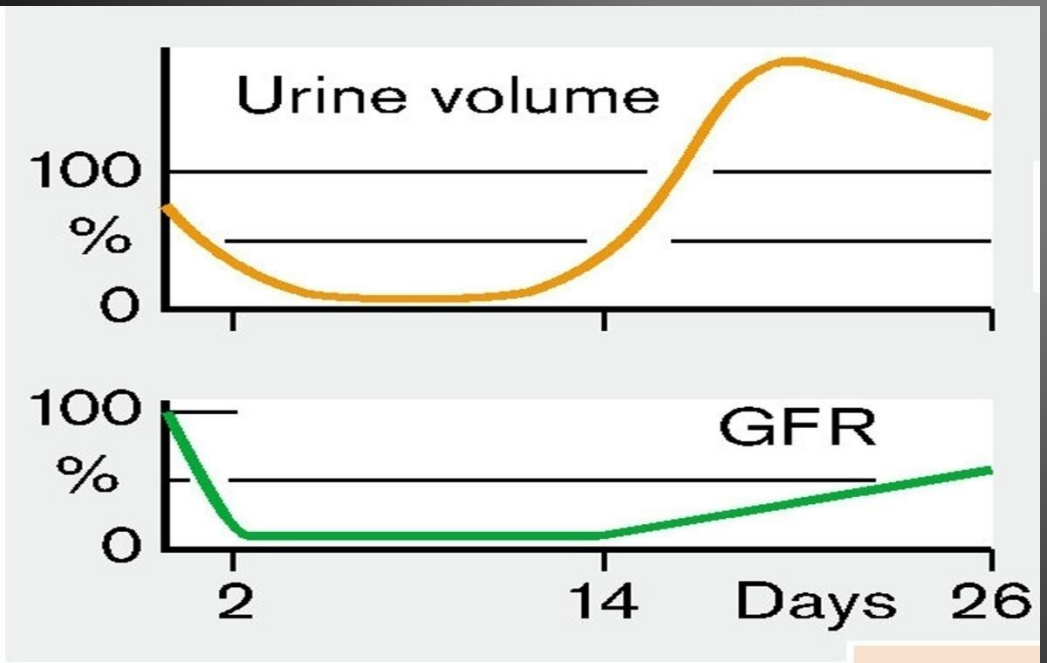
ONSET OR INITIATION PHASE

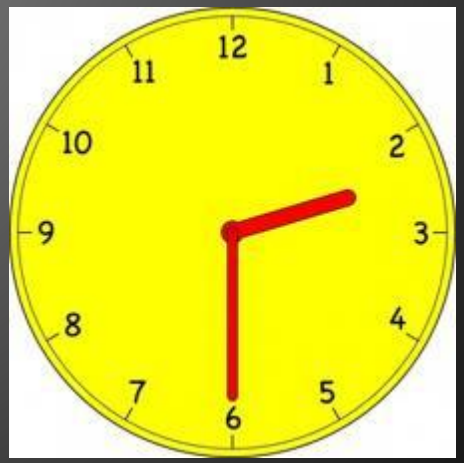
Lasting for about 36 hours;

Is dominated by the inciting medical, surgical, or obstetric event in the ischemic form of AKI;

Indication of renal involvement is a slight decline in urine output with a rise in BUN;

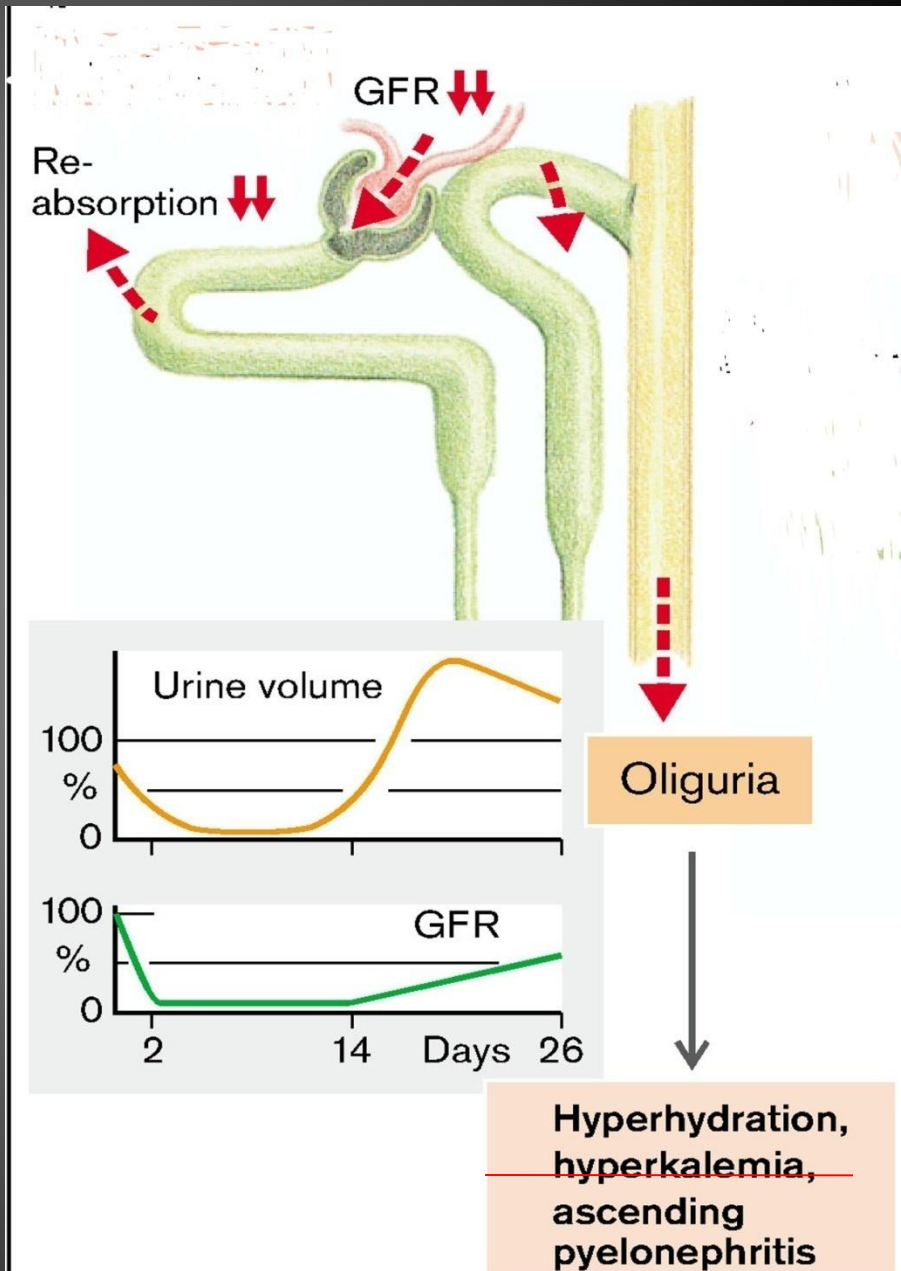
Oliguria could be explained on the basis of a transient decrease in blood flow and declining GFR.





MAINTENANCE PHASE = *OLIGURIC PHASE*

Marked decrease of GFR and tubular reabsorbtion which lead to retention of endogenous metabolites as ***urea, creatinine, potassium, metabolic acidosis, water overload*** and ***decreased urine output*** (between 40 and 400 ml/day – ***oliguria*** and ***anuria***



CLINICAL SYNDROME DURING OLIGURIC PHASE

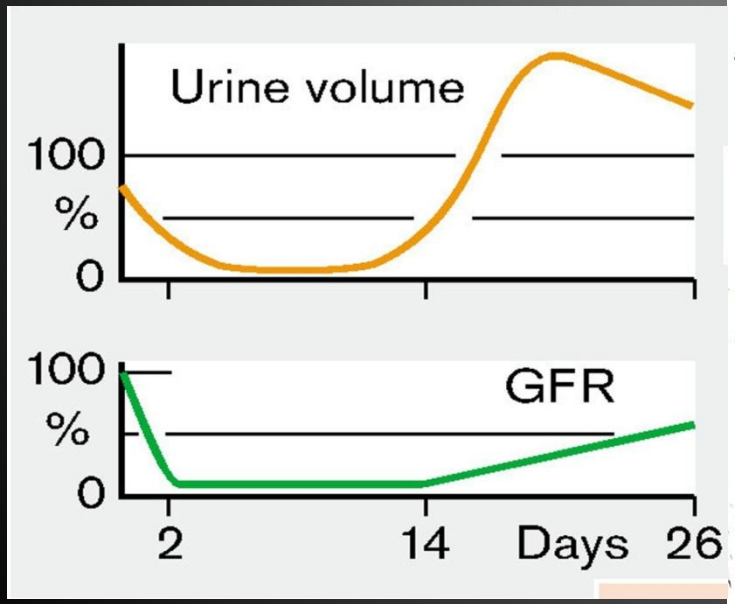
- ***Fluid retention***
- ***Hyperkalemia***
- ***Respiratory disorders***
- ***Cardiovascular disorders***

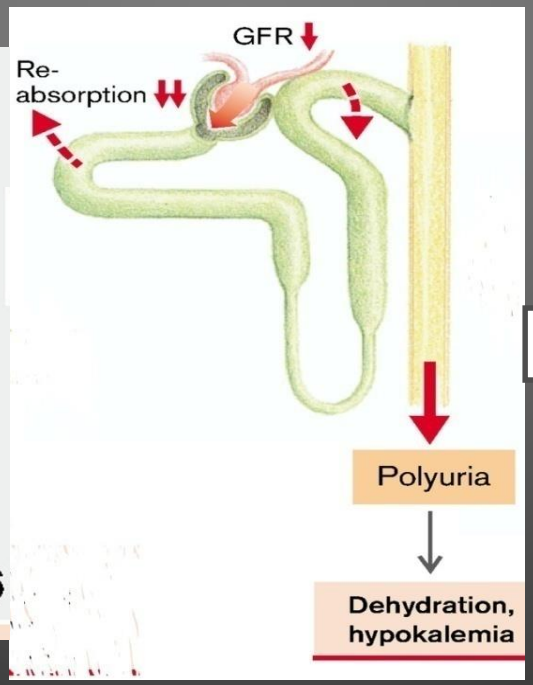
CLINICAL SYNDROME DURING OLIGURIC PHASE

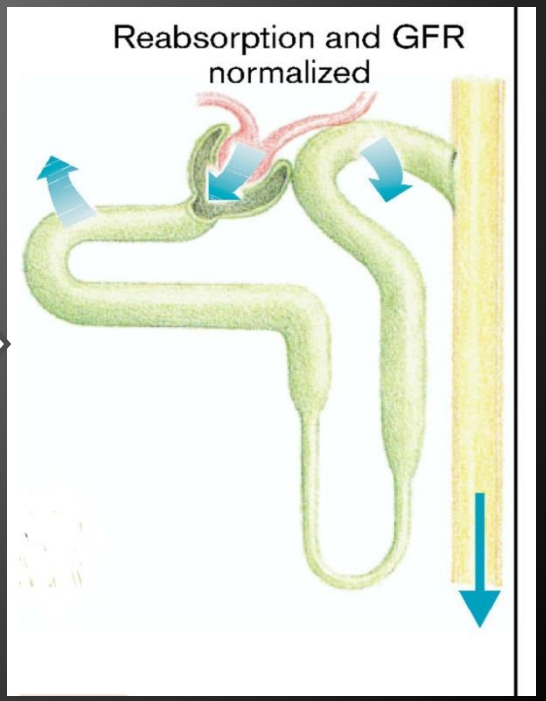
- ***Digestive disturbances***
- ***Blood clotting disorders***
- ***Neurological syndrome***

RECOVERY OR CONVALESCENT PHASE

The *recovery phase* is ushered in by a steady increase in urine volume that may reach up to 3 L/day. The tubules are still damaged, so large amounts of water, sodium, and potassium are lost in the flood of urine.







Chronic kidney disease

CKD represents a loss of functioning kidneys nephrons with progressive deterioration of glomerular filtration, tubular reabsorbtion and endocrine function of the kidneys.

***Primary and secondary glomerulopathies*:**

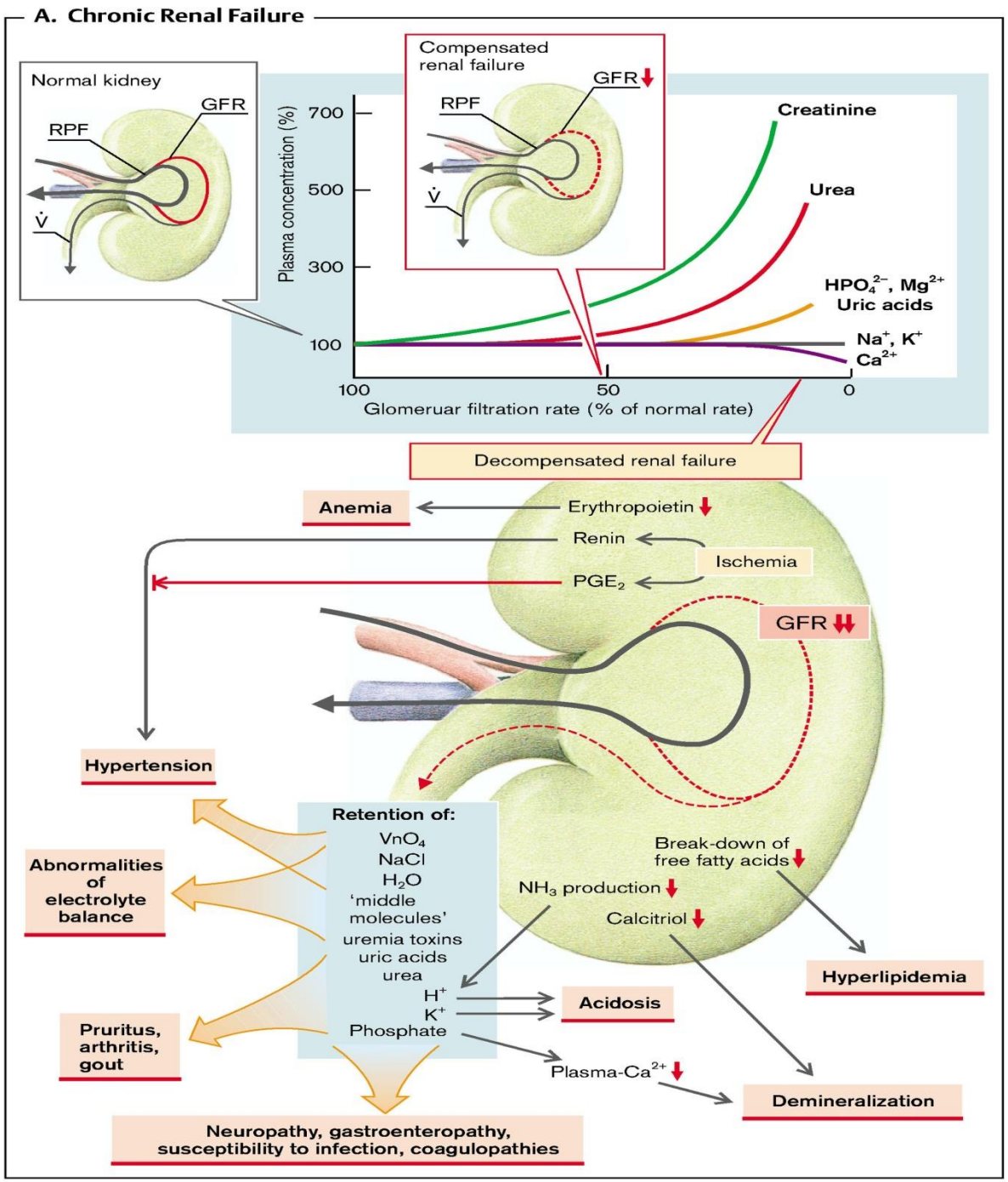
- Tubulo-interstitial disorders

***- Renal vascular disorders*:**

- Extensive destructive processes at the level of renal parenchyma

PHASE	GFR %	% FUNCTIONAL NEPHRONS	MANIFESTATIONS
REDUCED RENAL RESERVE OR FULLY COMPENSATED PHASE	**↑50%**	**50%**	absent
COMPENSATED AZOTEMIA	**25-50**	**25-50%**	**Compensatory polyuria, Isosthenuria.** **Azotemia** (↑Urea and creatinine) **Nocturia** **Anemia, HTA**
CHRONIC RENAL FAILURE (DECOMPENSATE PHASE)	**↓20**	**↓25%**	**Uremia** **Oliguria**
END STAGE KIDNEY DISEASE OR TERMINAL UREMIA	**↓5**	**↓10**	**UREMIA ANURIA DIALISIS TRANSPLANTATION**

Chronic kidney failure (CRF) is defined "as either GFR of less than 15 ml/min/1,73 m^2 usually accompanied by most of the signs and symptoms of uremia or a need to start renal replacement therapy (dialysis or transplantation)"


A. Chronic Renal Failure
Normal kidney
GFR
RPF
V̇
Compensated renal failure
GFR
RPF
V̇
Plasma concentration (%)
700
500
300
100
Creatinine
Urea
HPO4 2–, Mg 2+
Uric acids
Na+, K+
Ca2+
100
50
0
Glomeruar filtration rate (% of normal rate)
Decompensated renal failure
Anemia
Erythropoietin
Renin
Ischemia
PGE2
GFR
Hypertension
Retention of:
VnO4
NaCl
H2O
'middle molecules'
uremia toxins
uric acids
urea
H+
K+
Phosphate
Abnormalities of electrolyte balance
Pruritus, arthritis, gout
Break-down of free fatty acids
NH3 production
Calcitriol
Hyperlipidemia
Acidosis
Plasma-Ca2+
Demineralization
Neuropathy, gastroenteropathy, susceptibility to infection, coagulopathies

Azotemia

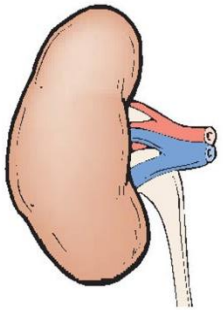
accumulation of nitrogenous wastes products in the blood (creatinine, urea, uric acid), represents an early sign of CRF, usually become evident before other clinical manifestation.

Urea is one of the first nitrogenous products which accumulate in the blood, and BUN level becomes increasingly elevated as CRF progress.

Uremia

in other words means “urine in the blood”, is a term used to describe clinical manifestations of CRF.

The uremic state includes all signs of fluid and electrolyte disbalance, acid-base disorders; alteration in regulatory functions (blood pressure, erythrocythopoiesis, impaired vitamin D synthesis) as well as the effect of uremia on body functions (uremic encephalopathy, pruritus, peripheral neuropathy etc..).



Chronic renal failure

- Sodium and water balance
  - Hypertension
  - Increased vascular volume
    - Edema
    - Heart failure
- Potassium balance
  - Hyperkalemia
- Elimination of nitrogenous wastes
  - Uremia
    - Coagulopathies
    - Pericarditis
    - Skin disorders
    - Gastrointestinal manifestations
    - Neurologic manifestations
    - Sexual dysfunction
- Erythropoietin production
  - Anemia
- Acid-base balance
  - Acidosis
  - Skeletal buffering
- Activation of vitamin D
  - Hypocalcemia
- Phosphate elimination
  - Hyperparathyroidism

Skeletal buffering, Hypocalcemia, and Hyperparathyroidism → Osteodystrophies

URINARY SYNDROME in CKD

COMPENSATORY POLYURIA (II stage)

↓

ISOSTHENURIA (II stage)

↓

OLIGURIA (III stage)

↓

ANURIA

(terminal uremia, dialysis)

Fluid and electrolyte disturbances

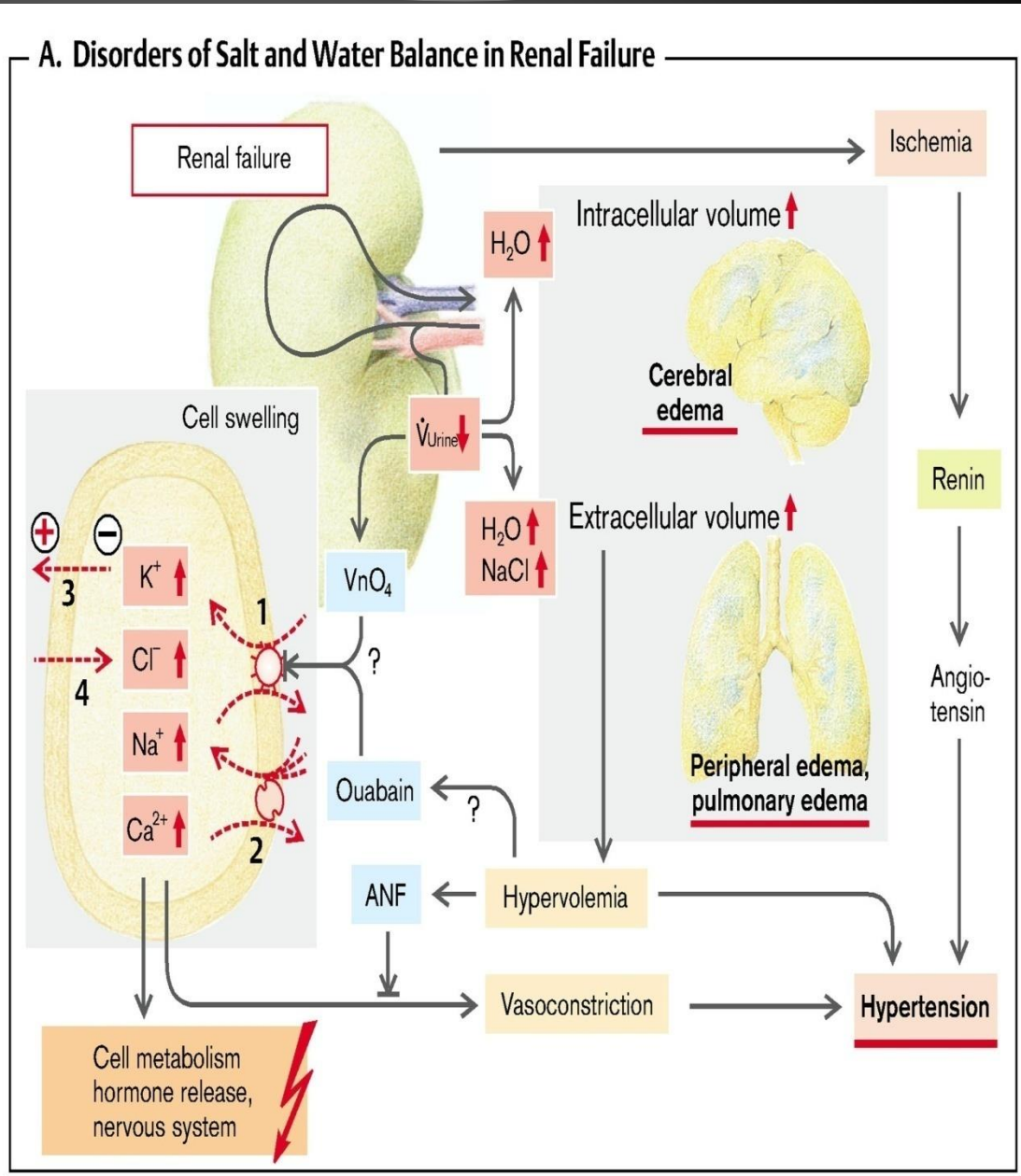
Hypervolemia

Hyper/*Hyponatremia*

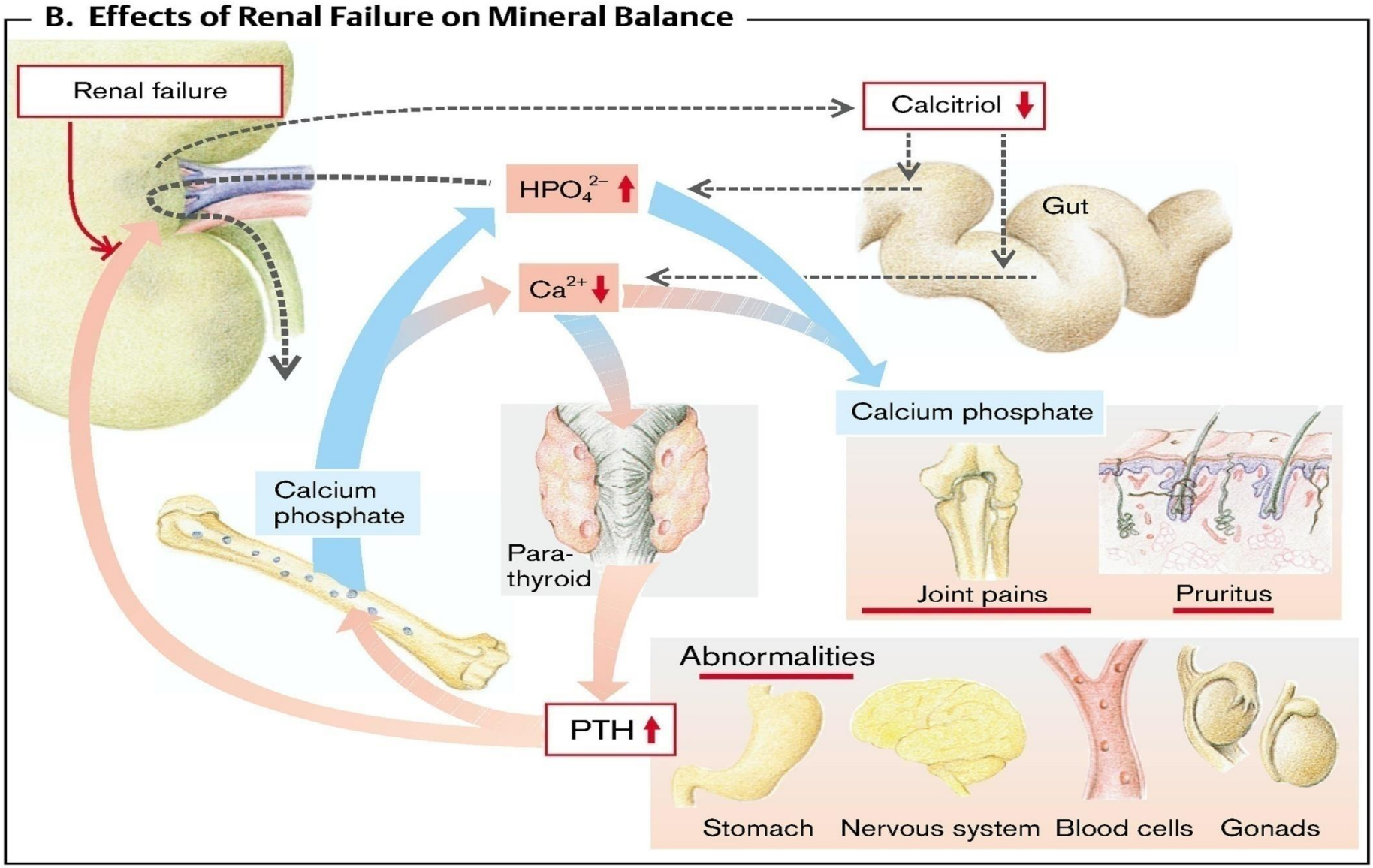
Hyperkalemia

Hyperphosphatemia

Hypocalcemia



Disorders of mineral balance in uremia



UREMIC TOXINS

Renal retention of oxidative substances intensifies oxidative stress injuries and inflammation.

Oxidative stress and decreased GFR lead to increased plasma level of ***uremic toxins*** (ex. ***acetonine, dimethyl-arginine, 2,3-buthylenglycol, hipurate, mehylguanidine, methylglioxal, indols, phenols, aromatic and aliphatic amines, homocysteine*** etc..) as well as other *"average molecules"* (lipids or peptides with molecular mass between 300-2000 Da).

All these uremic toxins exert their injurious effect by different mechanisms. By example, ***dimethyl-arginine*** inhibits synthesis of NO and leads to ischemia and increased blood pressure.

Methylglyoxal lead to cell autolysis (hemolysis, leucocyte dysfunction).

High levels of urea can induce cell shrinkage and protein destabilization.

METABOLIC CHANGES

HYPOGLYCEMIA ⇨ HYPERINSULINISM

↓ GLUCONEOGENESIS

HYPERLIPIDEMIA ⇨ ↓DEGRADATION OF FFA

↓ LYPOPROTEIN LIPASE

⇧ TRIGLICERIDE

CHOLESTEROL

LIPOPROTEINS

⇧ PROTEIN CATABOLISM ⇨ HYPERAMINOACIDURIA

Cardiovascular disorders

- Hypertension

- Hypertrophy of the left ventricle with its dysfunction

- Congestive heart failure

- Pericarditis

Hematologic disorders

Chronic renal anemia:

- chronic blood loss,
- bone marrow suppression due to retained uremic toxins,
- decreased red cell production due to impaired release of erythropoietin and iron deficiency.

Anemia of renal failure contributes to the progression of CRF by subjecting the functional nephrons in the kidneys to increased hypoxic and oxidative stress injuries.

Coagulopathies due to platelet dysfunction. Bleeding disorders are manifested by epistaxis, menorrhagia, gastrointestinal bleeding, bruising of the skin, and subcutaneous tissue.

Gastrointestinal disorders

Anorexia, vomiting, and nausea.

Ulcerations and bleeding of the gastrointestinal mucosa

Disorders in immune function

All aspects of inflammation and immune function can be affected by the high levels of urea and other metabolic wastes:

-Decrease in granulocyte count,

-Impaired humoral and cellular immunity

- Defective phagocyte function.

Neuromuscular disorders

Peripheral neuropathy

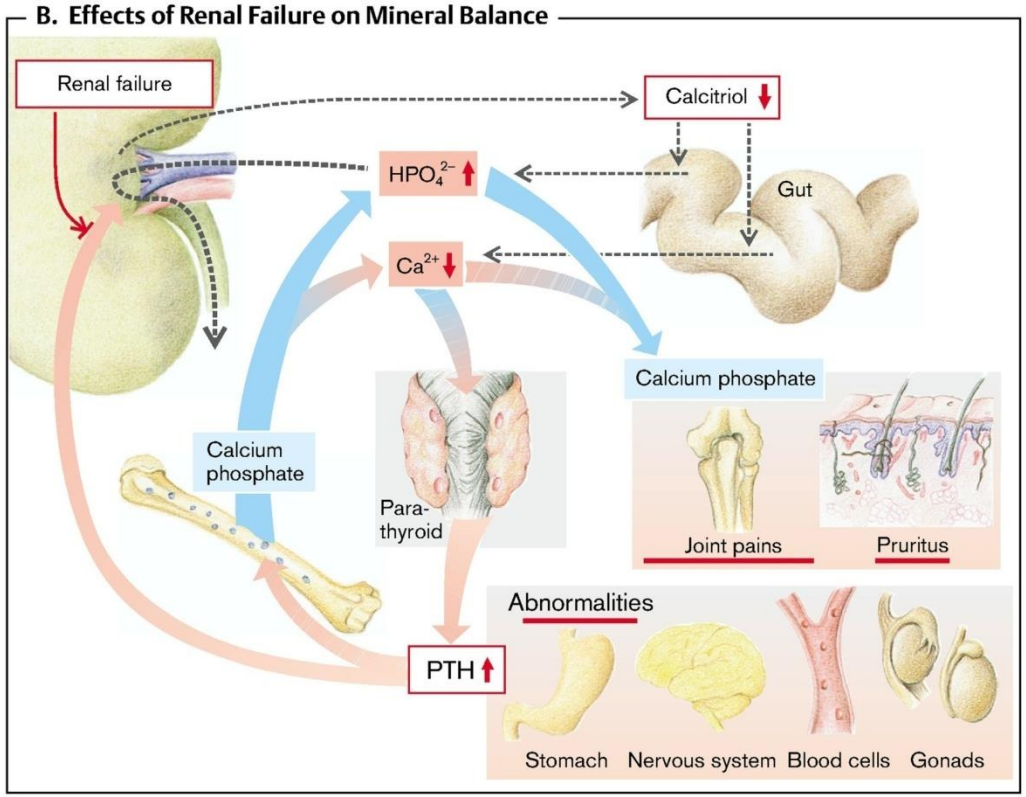
More frequently affect the lower limbs, it is symmetric and affects both motor as well as sensory functions. Is caused by atrophy and demyelination of nerve fibers, possibly caused by uremic toxins.

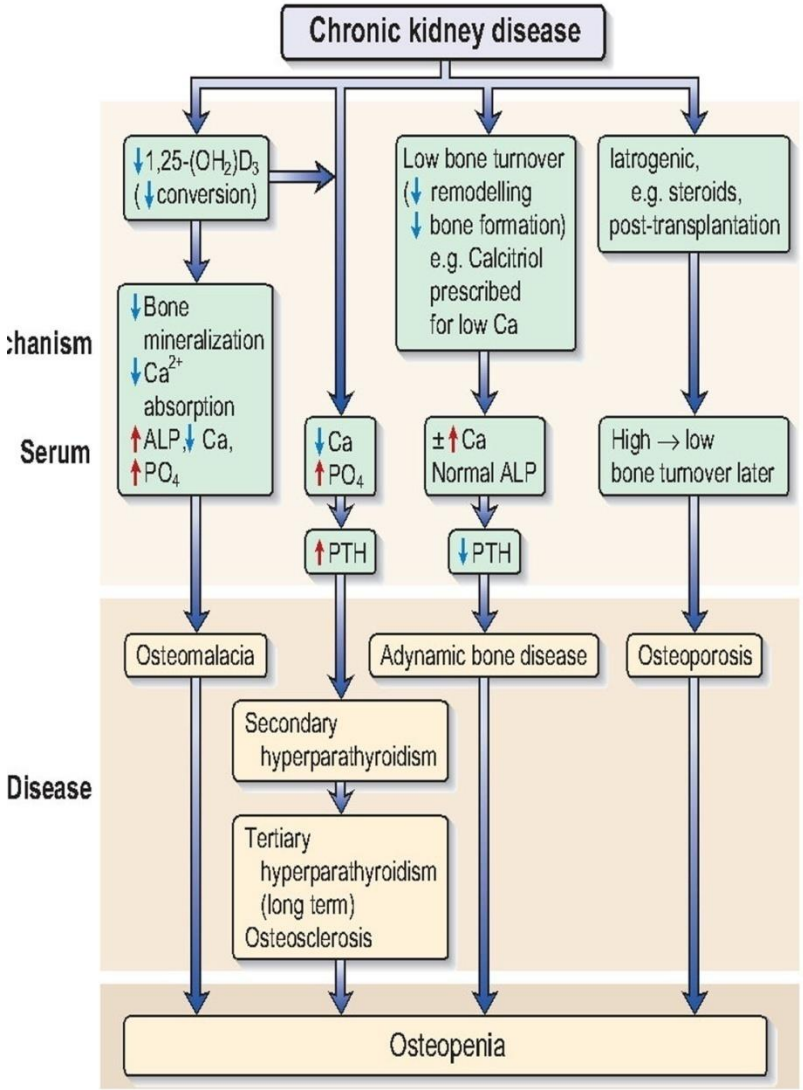
Uremic encephalopathy:

- action of toxic organic acids that alter neural function.
- electrolyte disturbances, such as sodium shift.

RENAL OSTEODYSTROPHY

OSTEITIS FIBROSA
OSTEOMALACIA
ADYNAMIC OSTEODYSTROPHY





Kidney Health is in YOUR hands!