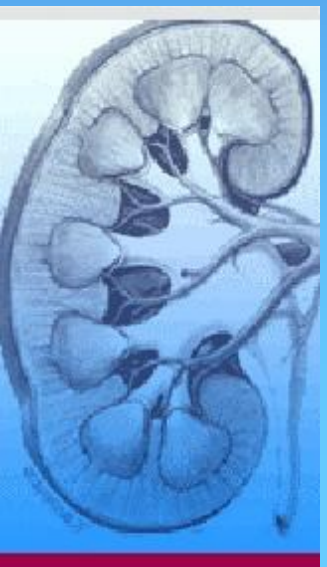
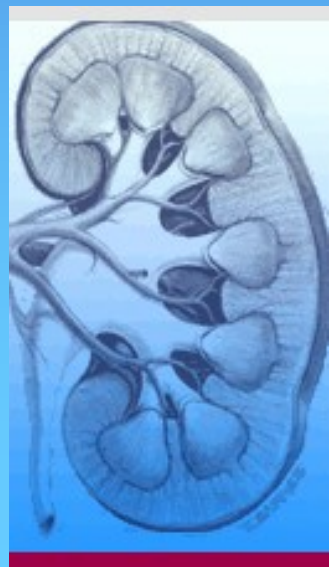
PATHOPHYSIOLOGY OF RENAL DISORDERS (II)

Dr. Pavel Maruna

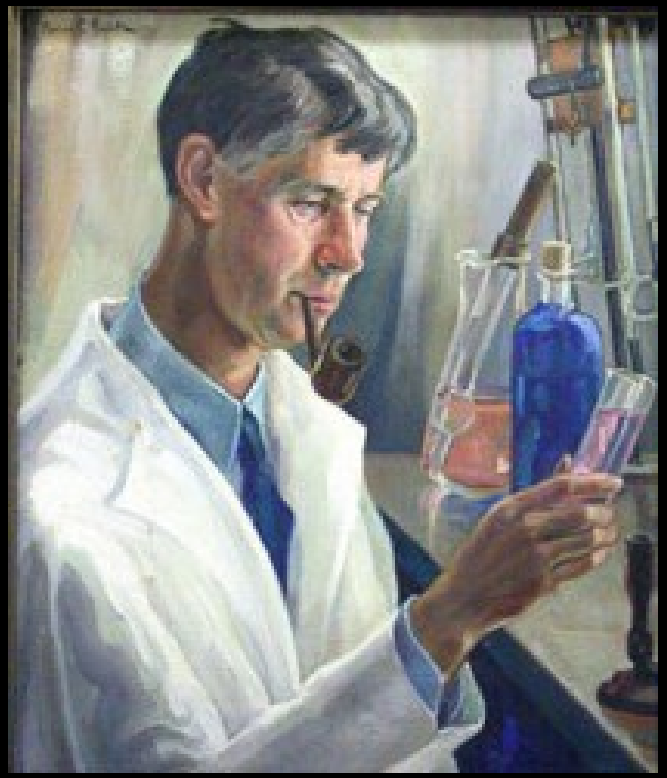




History

„... All we know for certain about the Kidney is that it makes urine.“

Thomas Addis **(1881 – 1949)**

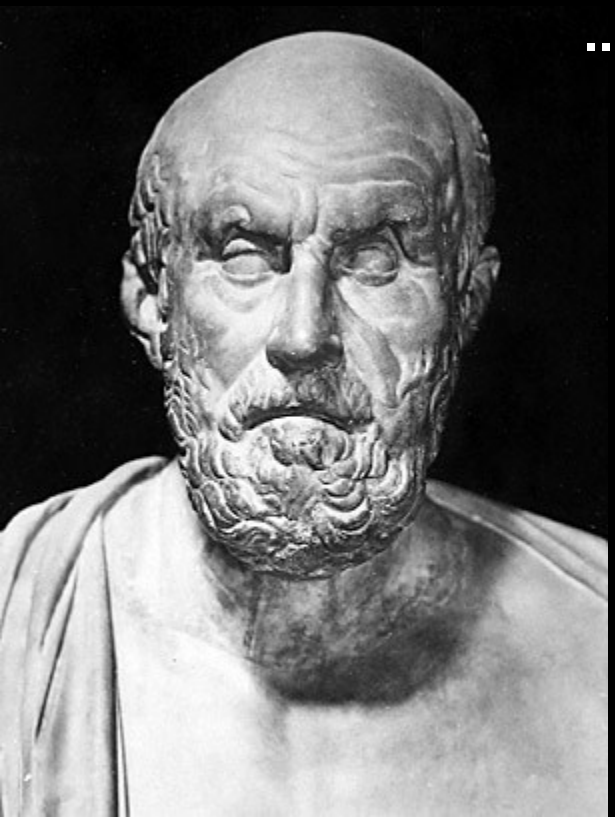


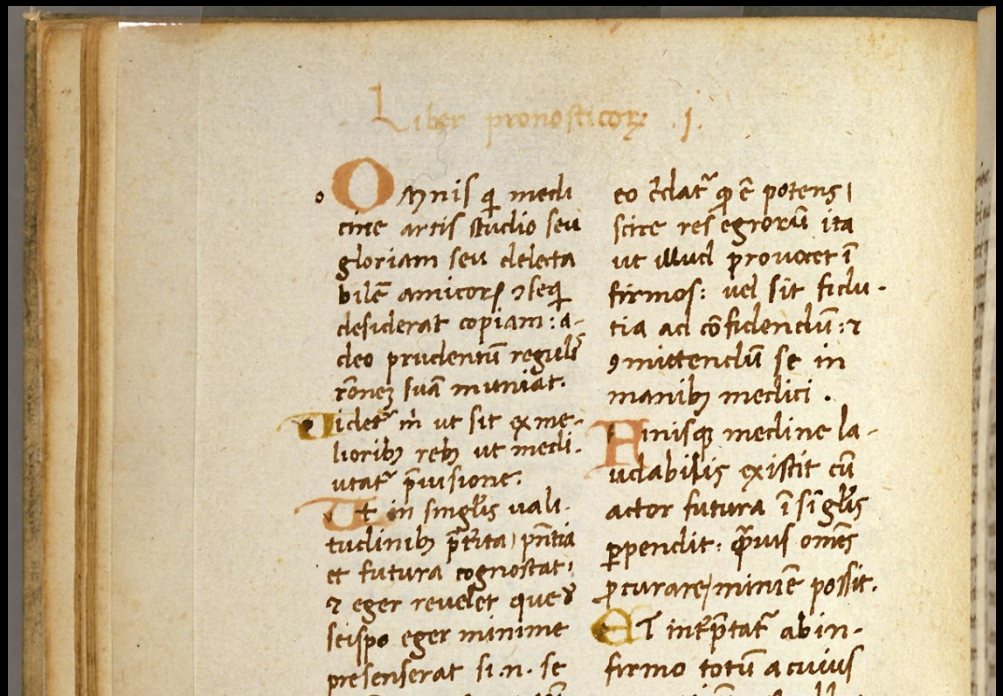
History

Hippocrates of Kos (460 – 370 B.C.)

„Bubbles appearing on the surface of the urine indicate disease of the kidneys and a prolonged illnes.“

... The first description of a chronic renal disease





History

1st Century A.D.

Rufus of Ephesus:

Disease of the kidneys and bladder which is not painful
„Sclerosis of the kidneys“

For treatment he recommended rest, clysters, cupping of the loins, baths and sedative medicaments

„...Diseases of the kidneys are difficult to cure in old age“

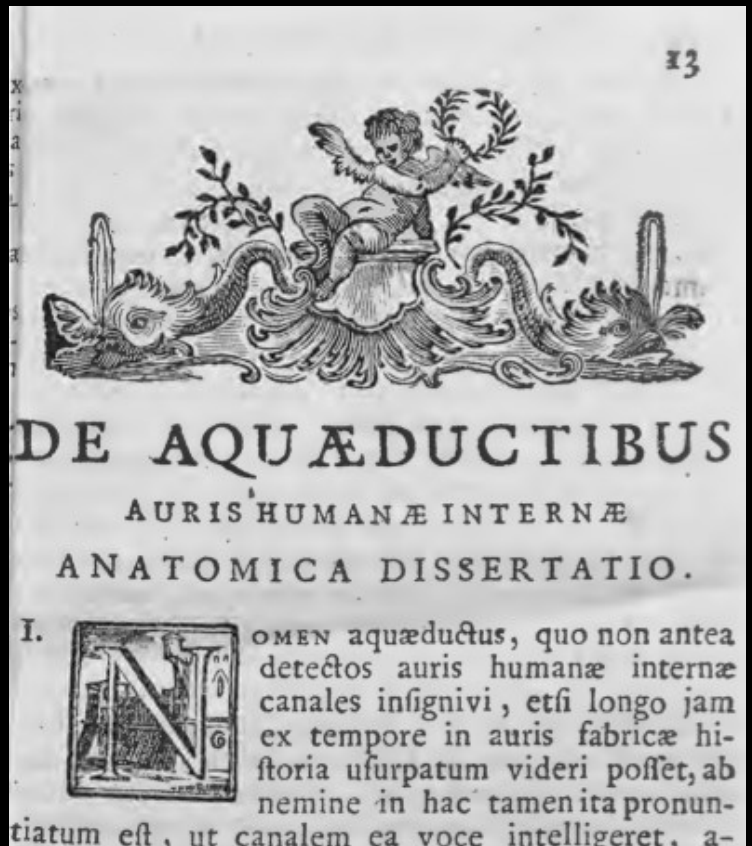
History

1765

Domenico Cotugno:

„Protein-losing disease“

Soldier of 28, suffering from oedema. Cotugno boiled 2 pints of patient's urine over the fire. After evaporation, there was „...a white mass coagulated like egg albumin“.



x3

DE AQUÆDUCTIBUS

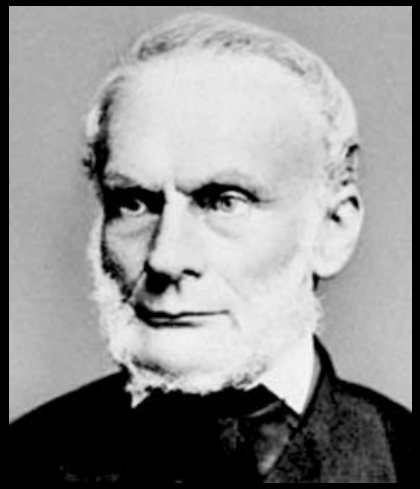
AURIS HUMANÆ INTERNÆ

ANATOMICA DISSERTATIO.

I. NOMEN aquæductus, quo non antea detectos auris humanæ internæ canales insignivi, etsi longo jam ex tempore in auris fabricæ historia usurpatum videri posset, ab nemine in hac tamen ita pronun-

tiatum est, ut canalem ea voce intelligeret, a-

History

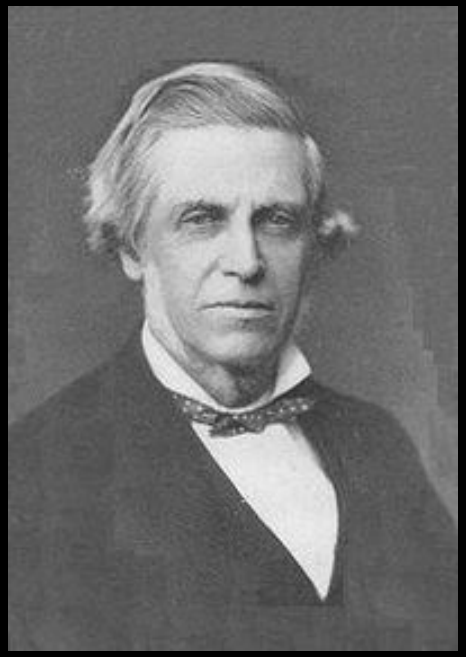


1811 William Charles Wells
„Serum“ in the urine in patients after scarlatina

1813 John Blackall
Described association between edemas, coagulable urine and kidneys

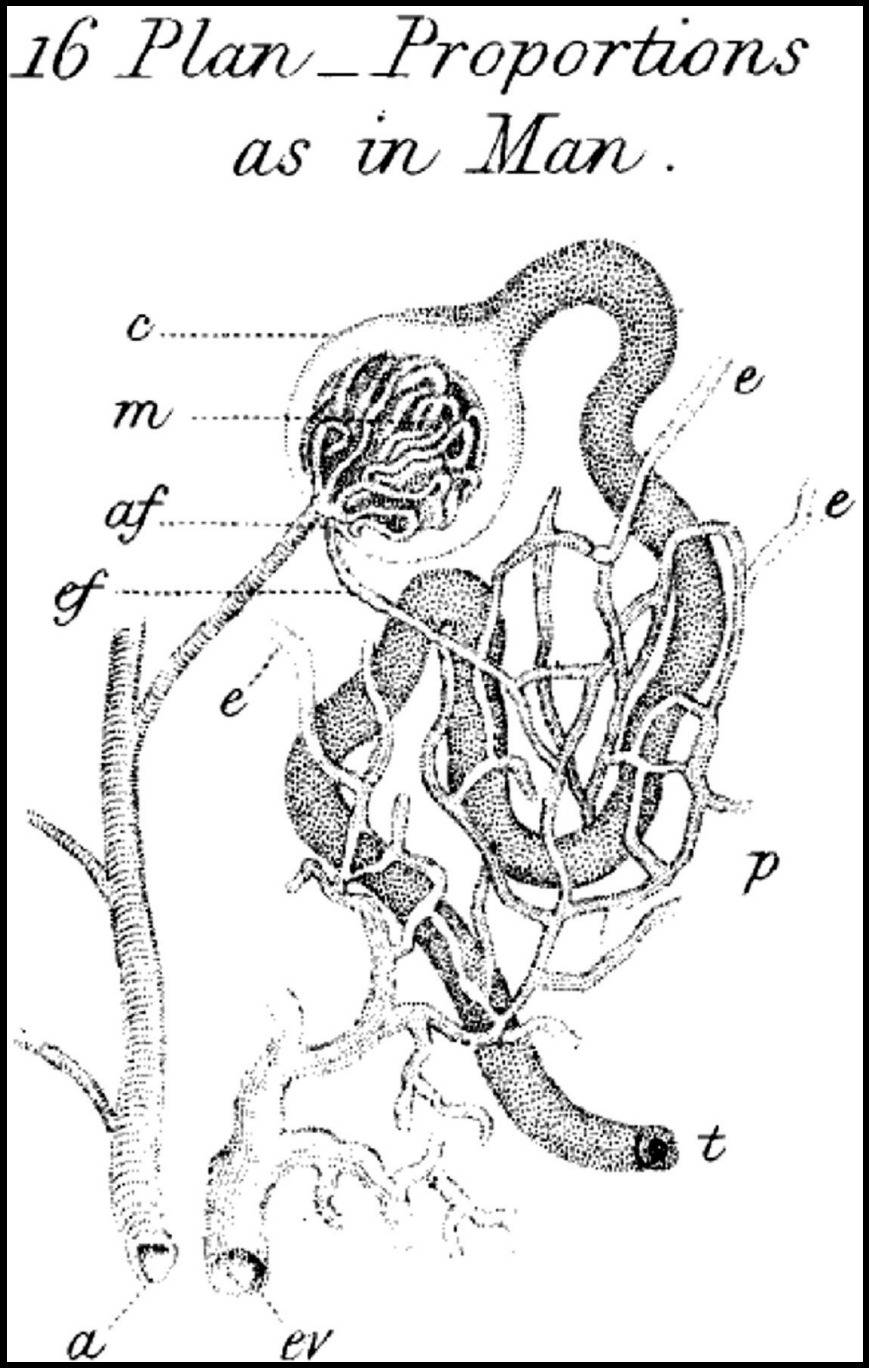
1827 Richard Bright
Clinical-pathological studies of nephrology. An accurate description of **nephrotic syndrome**

History



1842 **William Bowman**

Anatomy of glomerulus and its function as a secretory structure



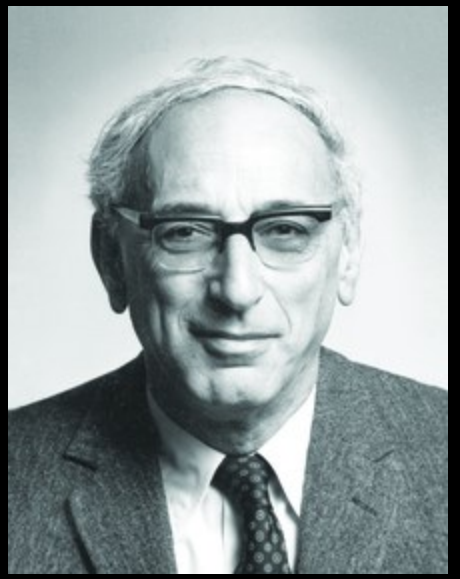
History

R. A. McCance, H. L. Marriott, E. B. Verney
Renal clearance functions

$$R.C. = \frac{\text{Amt Ex } (mg/min)}{\text{Plas Con } (mg/ml)}$$

$$= \frac{(50\,mg/10\,ml)\cdot(80\,ml/20\,min)}{400\,mg/100\,ml}$$

$$= 5\,ml/min$$



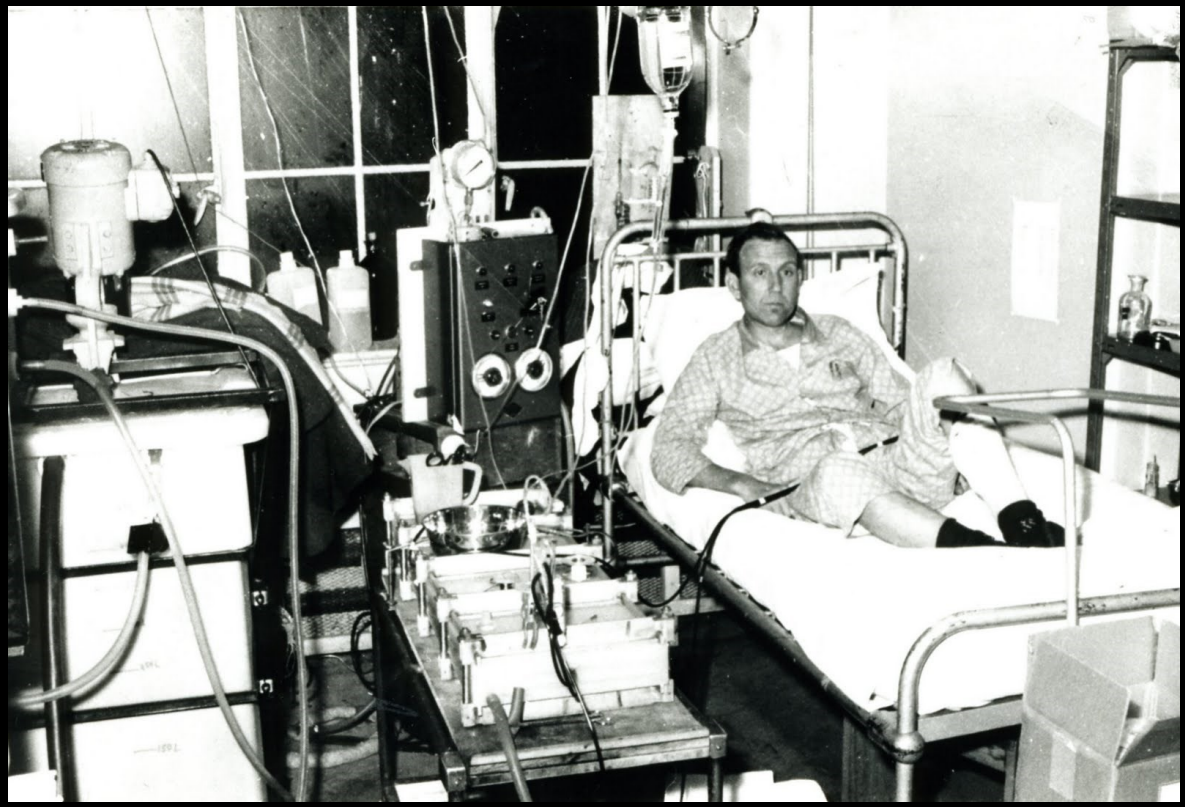
E. B. Verney (1894 – 1967)

History

1943 - **Hemodialysis**

Willem Johan Kolff, Netherlands

W. J. Kolff (1911 – 2009)



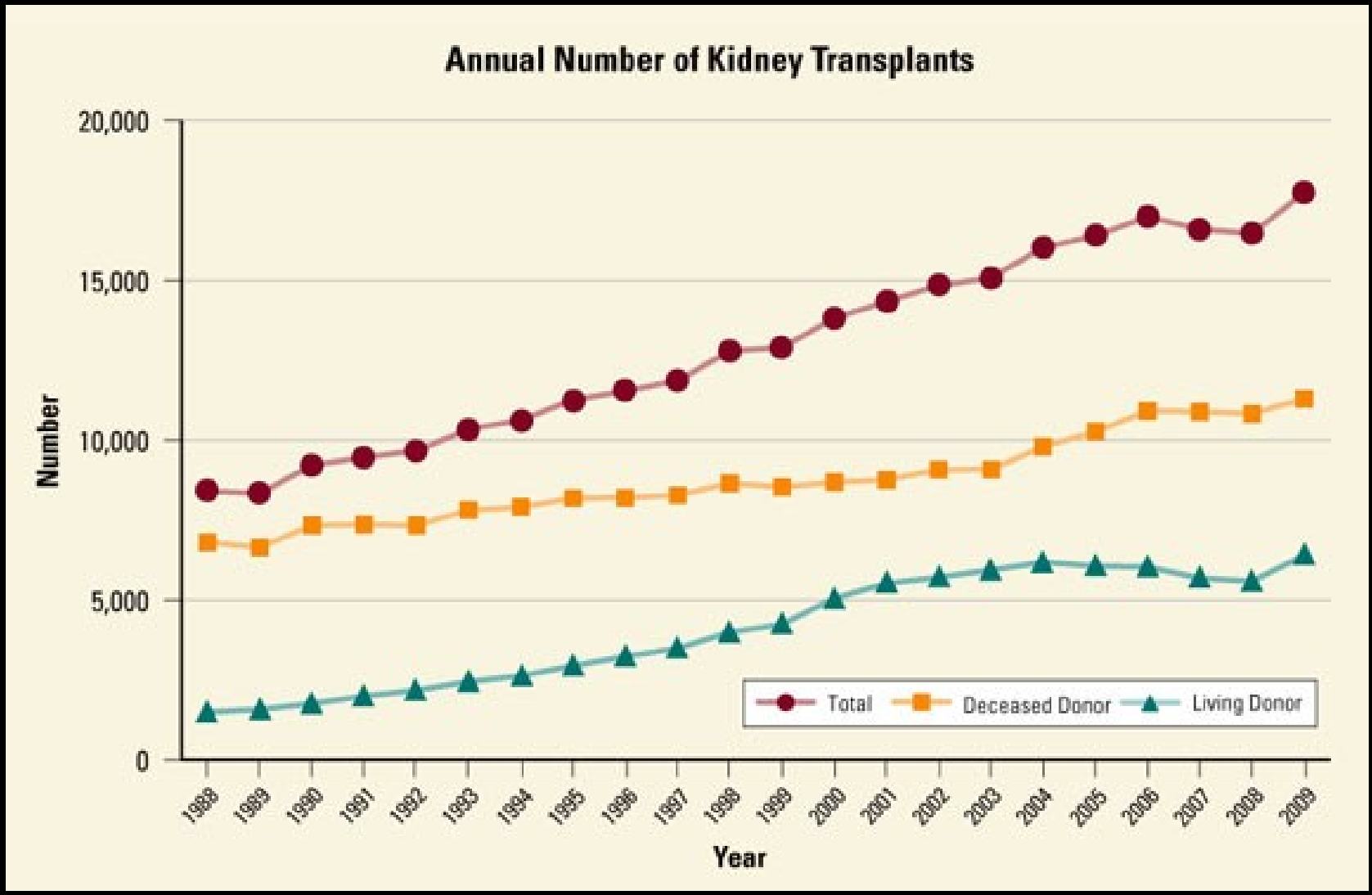
History

1950 - first succesfull kidney transplantation
Mary Hospital, Illinois

44-year-old woman with polycystic kidney disease

The donated kidney was rejected 10 months later because no immunosuppressive therapy was available

History


Annual Number of Kidney Transplants
20,000
15,000
10,000
5,000
0
Number
Total
Deceased Donor
Living Donor
1988
1989
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
Year

Diuresis - basic terms

- Dysuria
- Strangury
- Polakisuria
- Ischuria
- Nocturia
- Incontinence
- Polyuria
- Oliguria
- Anuria
- Isostenuria

Diuresis - basic terms

Dysuria = difficult, painful urination (infection, stones, tumors, prostate...)

Strangury = symptom of painful, frequent urination

Polakisuria = frequent urination of small volumes, expelled slowly only by straining, usually with the residual feeling of incomplete emptying

Ischuria = (pathological) urinary retention, lack of ability to urinate

Paradoxical ischuria = incontinence from overflow of urinary bladder

Diuresis - basic terms

Nocturia

(no exact definition)

= annoying night urinate, more than 1x at night
= night urinate for than 35% of daily diuresis

Nocturia

Causes

1) Defects of the "3rd space"

a) congestive heart failure
b) venous insufficiency
c) excessive salt intake
d) nephrotic syndrome

2) Polydipsia

a) resulting from polyuria – DM, diabetes insipidus
b) excessive liquid intake in evening hours

3) Misbalance between daily and night urine production

a) lack of circadian rhythm in ADH secretion
b) excess of ANP in sleep apnoe syndrome resulting to osmotic diuresis

4) Other

a) diuretic therapy
b) subvesical obstruction
c) anxiety
d) alcohol, caffeine
e) neurogenic urinary bladder
f) status post ictus, spinal lession

Diuresis - basic terms

Urinary incontinence

= Involuntary excretion of urine

Heterogeneous group of disorders, different etiology and pathophysiology

Diuresis - basic terms

Urinary incontinence

1. Stress incontinence	49 %
2. Urge incontinence – motoric and sensoric form	22 %
3. Combined incontinence	29 %
4. Paradoxical ischuria (= overflow incontinence)	rare
5. Extraanatomic ickontinence (fistula, congenital abn.)	rare
6. Reflective incontinence	

Stress type ... Higher intraabdominal pressure without current detrusor contraction (we can objectively verify it)

Urge type: ... With compulsive, intensive impulse to urination

Neurogenous (reflective) type: ... Abnormal reflective activity of spinal centre

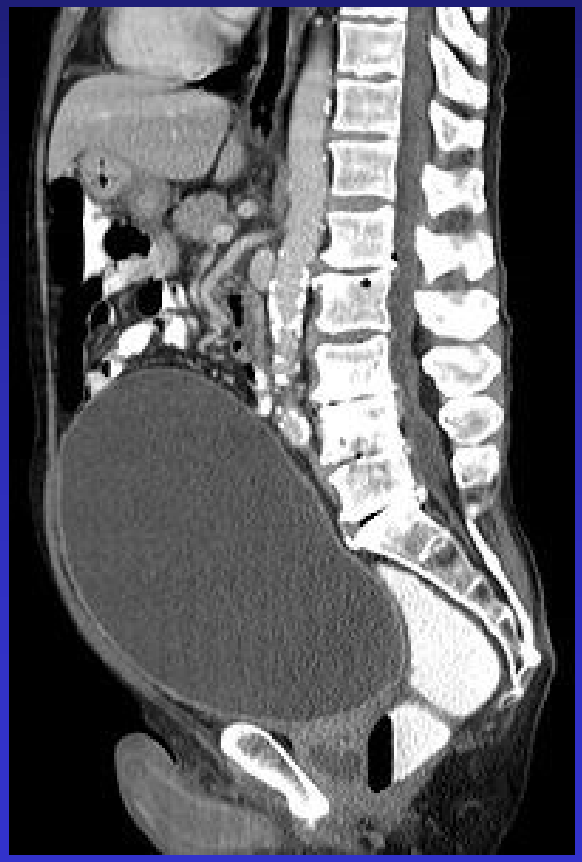
Extraanatomic type: ... Variable causes (congenital or acquired)

Diuresis - basic terms

Paradoxical ischuria

= Spontaneous outflow of urine from overflowing urinary bladder

(subvesical obstruction – prosthetic hyperplasia, stricture of urethra, tumor, lying patient)



Diuresis - basic terms

Polyuria = frequent large urination (> 2500 ml / 24 h)

Oliguria = diuresis < 500 ml / 24 h (20 ml / h)

Anuria = diuresis < 100 ml / 24 h (4 ml / h)

Isosthenuria = U-concentration is equal to P-concentration

(**Concentrated urine** ... U-concentration > P-concentration)

Diuresis - basic terms

Polyuria

= diuresis > 2500 ml / 24 h

Polydipsia

= excessive thirst

Diuresis - basic terms

Polyuria

Water diuresis (polyuria)

- diabetes insipidus centralis
- diabetes insipidus renalis
- psychogen. polydipsia

Osmotic diuresis (polyuria)

- glykosuria (decomp. DM)
- calciurie (hyper-PTH, bone metastases, sarcoidosis)
- natriuria (osmotic diuretics, Addison dis.)

Principal concepts

Renal insufficiency:

The condition in which the kidneys fail to function properly. The kidneys still allows a normal homeostasis during auspicious situation, but not in stress circumstances (infection, surgery, water or electrolyte overload).

Renal failure:

The kidneys are incapable of keeping homeostasis in basal conditions.

Uremia

Syndrome resulting from the renal failure, most often chronic.

Functions of kidneys and urinary tract

1. Selective excretion / elimination
   - water
   - electrolytes
   - catabolites (small compounds, middle-size compounds 500 - 3000 D)

2. Selective retention of filtrated molecules
   - aminoacids
   - proteins
   - vitamins

   ...

3. Endocrine activity
   - Epo
   - 1,25-OH-D3 vitamin

Factors of uremia evolvement

1. Retention

- water
- electrolytes (K)
- small molecules
- middle size molecules (500 - 3000 D)

2. Raised loss

- water, electrolytes (Na, Ca, Mg)
- aminoacids, proteins, vitamins

3. Low production

- Epo
- 1,25-OH-D3 vitamin

4. Compensation (Trade off hypothesis)

= changes resulting from systemic compensatory activity

Renal osteopathy

Acute renal failure

Causes

1. Prerenal → **hemodynamic changes shock circulation**

- **Hypovolemia** — Large bleeding, water and solute loss, 3rd space
- **↓ Cardiac output** — Ischem. heart dis., myocarditis, valvular dis. ...
- **Syst. vasodilation** — Anaphylaxis, sepsis, drugs, hepatic failure
- **↓ Ren. autoregulation** — Drugs (ACEI, NSAID, ...)

Acute renal failure

Causes

2. Renal (parenchymal) - mainly damage of tubular cells

- **TIN (infectious /non-infectious), allergic reaction**
- **glomerulonephritis (poststreptococcus, SLE, Goodpast. sy)**
- **nephrotoxins (CCl4, ethylene glycol, propylene glycol, Hg, Au,Bi, amanita phal...)**
- **nephrotoxic drugs (SFA, gentamycine, cefaloridine)**
- **hemolysis (incompatible TRF)**
- **crush syndrome**
- **burns (dehydration, sepsis, toxemia)**
- **„malignant“ hypertension**
- **acute pancreatitis**
- **ischemia (occlusion of renal artery, thrombosis of renal vena)**

Acute renal failure

Causes

2. Renal (parenchymal) - mainly damage of tubular cells

- TIN, allergic reaction
- glomerulonephritis (SLE, Goodpast. sy)
- nephrotoxins (CCl_4, ethylene glycol, propylene glycol, Hg, Au,Bi, amanita phal...)
- nephrotoxic drugs (SFA, gentamycine, cefaloridine)
- hemo (TRF)
- crush syndrome
- burns (dehydration, sepsis, toxemia)
- „malignant“ hyper
- acute pancreatitis
- ischemia (occlusion of renal artery, thrombosis of renal vena)

Toxins

Glomerular dis.

Interstitial dis.

Renal hypoperfusion

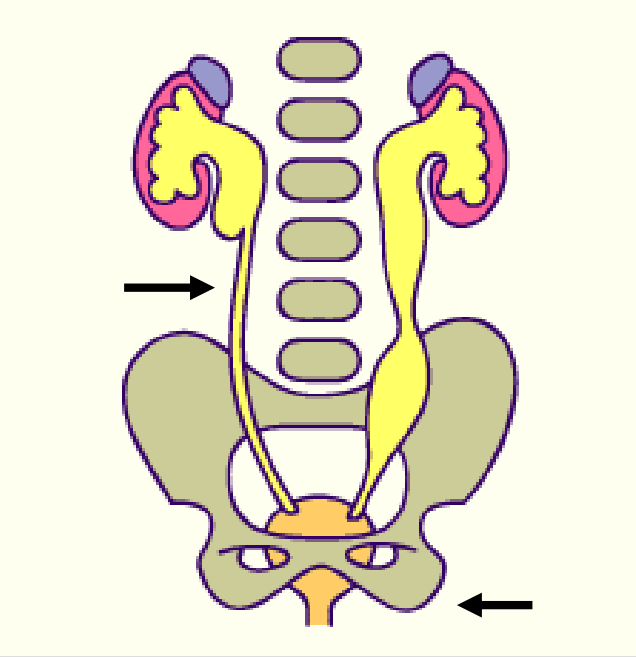
Acute renal failure

Causes

obstructions

3. Postrenal →

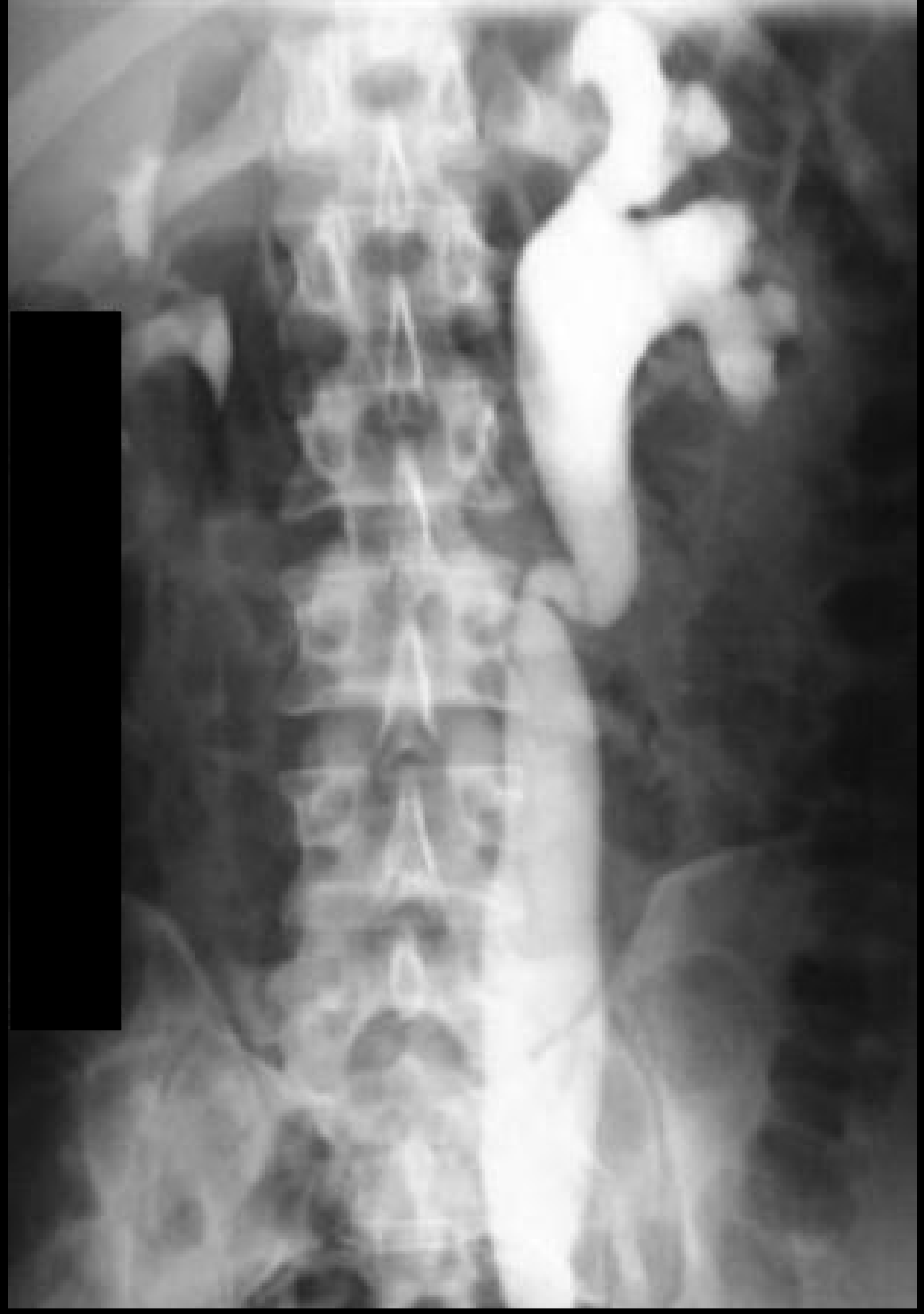
urolithiasis, blood coagula
tumors
prosthetic hyperplasia
retroperitoneal fibrosis
ligature of ureter
atonia of urinary bladder



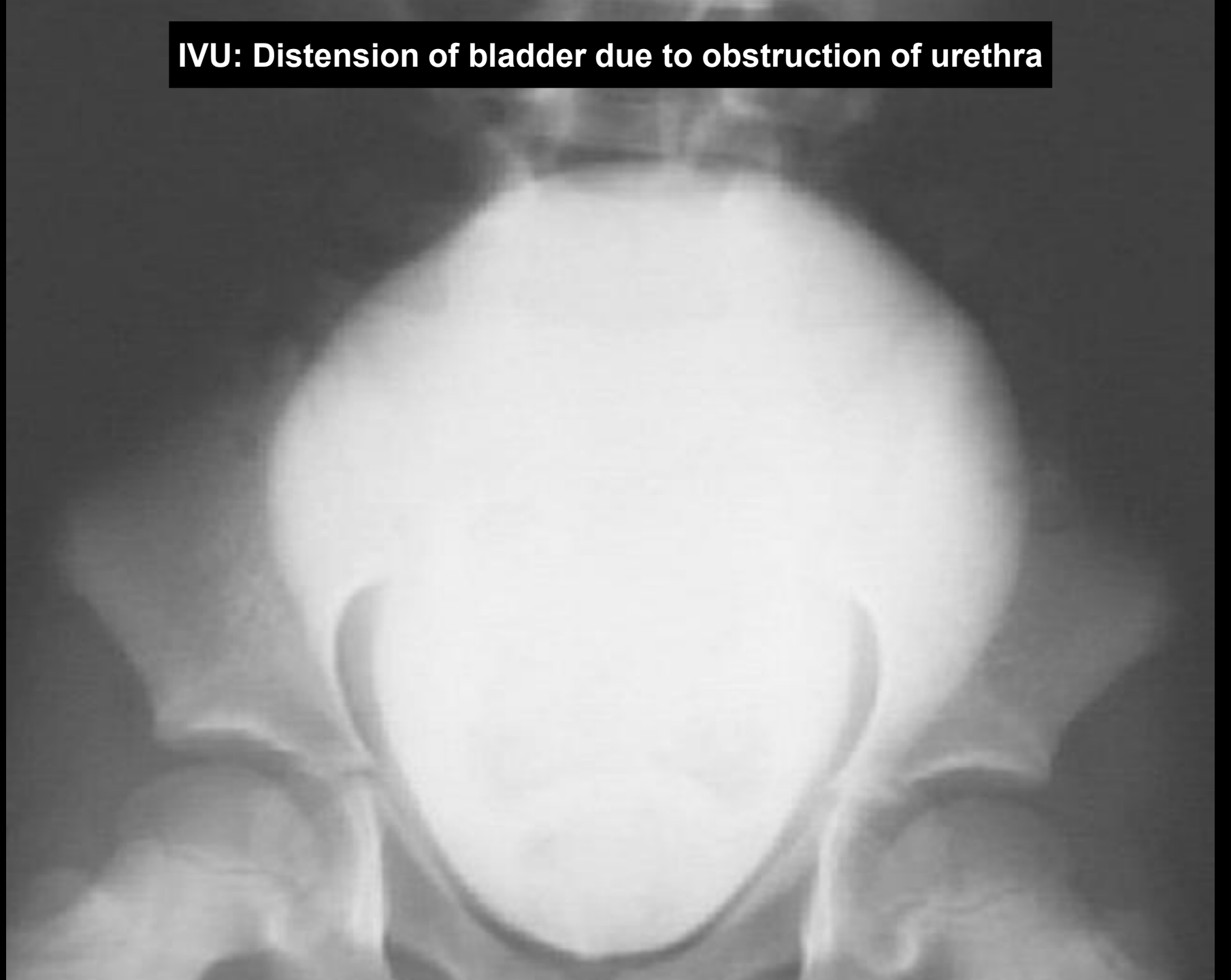
suprapubic pain or renal colic,

palpation of distend urinary bladder

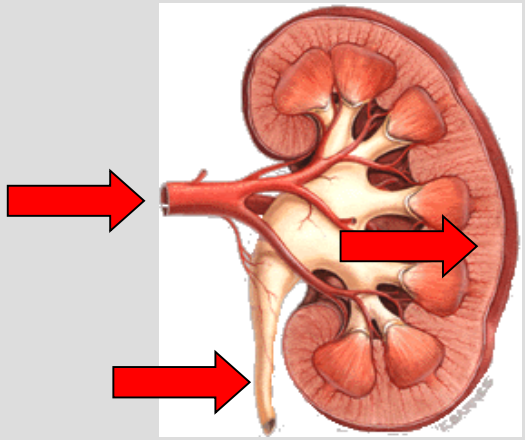
USG, CT



IVU: Distal obstruction of urether


IVU: Distension of bladder due to obstruction of urethra

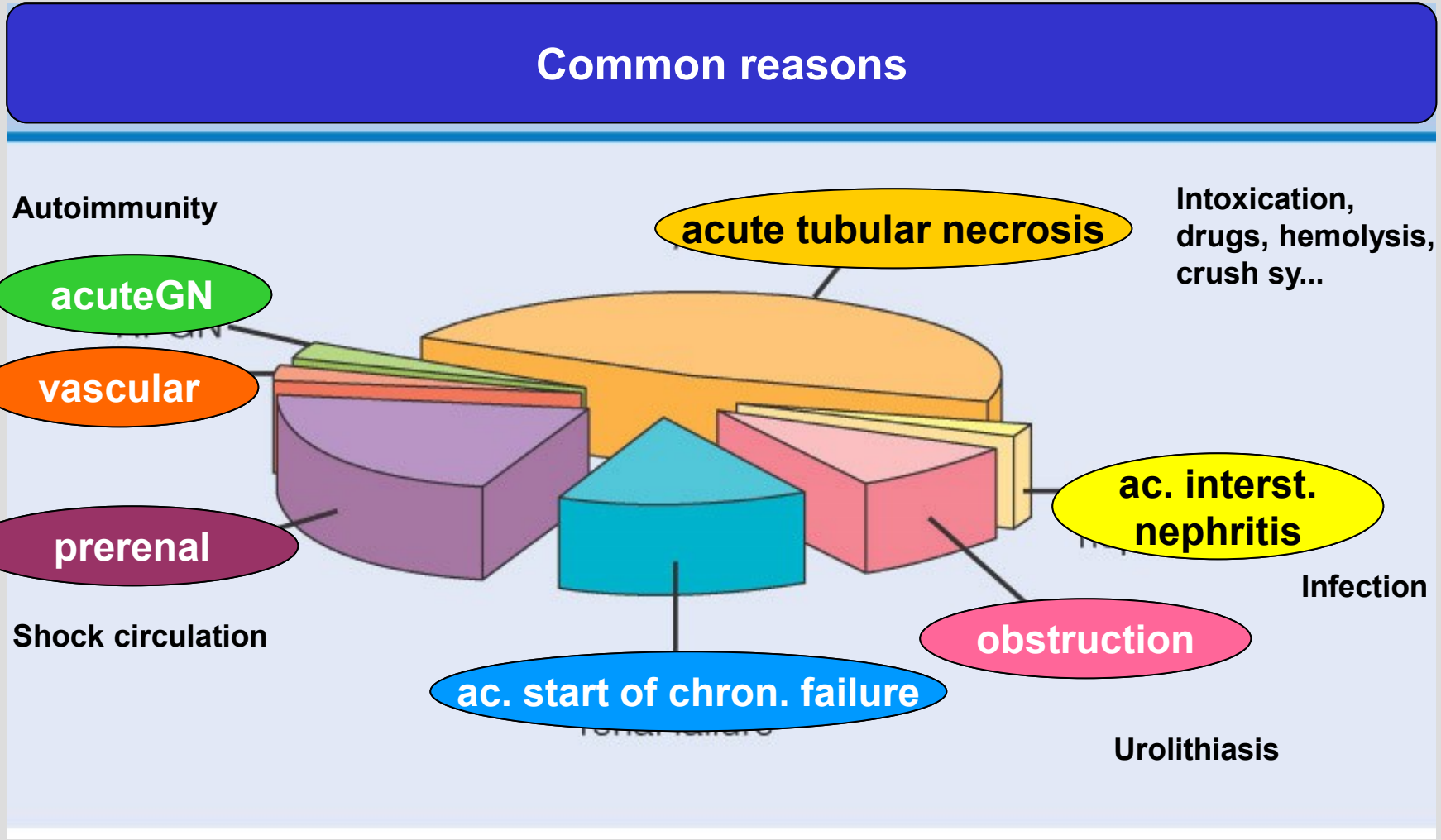
Acute renal failure



Causes

1. **Prerenal** — Physiological response to renal hypoperfusion in case of normal kidney function
2. **Renal** — Functional insufficiency of renal parenchyma
3. **Postrenal** — Acute obstruction

Acute renal failure



Acute renal failure

Most considerable nephrotoxins

Heme pigments

- Myoglobin – rhabdomyolysis
  - Crush syndrome, ethanol, peripheral ischemia, drugs (statins)
  - dg.: ↑CK, myoglobin in plasma
- Hemoglobin – hemolysis
  - Incompatible transfusion, hemolytic anemia, malaria, G6PDH deficiency, PNH

Nephrotoxic drugs

- NSAID, ACEI
- Aminoglykosids, Amfotericine B, Pentamidin, Acyclovirum
- Cyclosporine
- Cisplatin, Ifosfamide

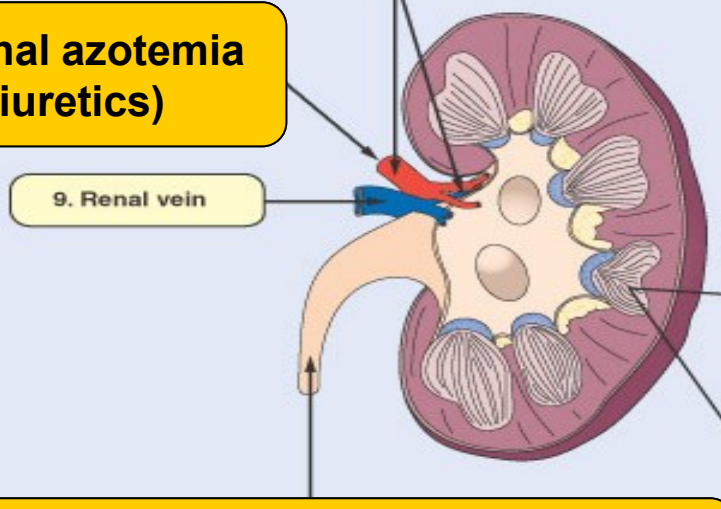
Ethylene glycol

Heavy metals

Vegetable and fungal poisons

Drugs, poisons and nephrotoxicity

Prerenal azotemia (diuretics)



Mikroangiopaty (thrombotic or vasoconstrictory) (ACEI, NSAID, cyklosporin, cocaine, oestrogen contraception)

Rapidly progressive GN (penicilamin, hydralazin)

Papillary necrosis → postren. obstruction (NSAID)

Acute tubular necrosis (amfotericin, cisplatina, heavy metals, vegetable poisons)

Production of crystals → tubular obstruction (acyclovirum, methotrexate, ethylenglycol)

Ac. interst. nephritis (PNC, cephalosporins, NSAID, allopurinol, omeprazol, phenytoin)

Acute renal failure

Parameter	Prerenal	Renal
natriurie	< 20	> 40 mM
U-osmol.	> 500	< 350 mosm / kg
konc. index kreat.	> 40	< 20 (U-kr / P – kr)
konc. index urey	> 8	< 3 (U-urea / P-urea)
frakční exkrece Na	< 1	> 2

Is valid before diuretic or infusion treatment only.

Acute renal failure

1. Initial
2. Anuria / oliguria
3. Diuretic phase
4. Recovery

Commonly reversible process with recovery ad integrum

Acute renal failure

1. Initial
2. Anuria / oliguria
3. Diuretic phase
4. Recovery

1 - 2 days
↑ urea, ↑ creatinine
↓ diuresis

Acute renal failure

1. Initial
2. Anuria / oliguria
3. Diuretic phase
4. Recovery

Duration from 2 days to 6 weeks
Loss of nephrons
Azotemia
Electrolyte split
Oliguria < 500 ml / 24 h
Anuria < 100 ml / 24 h

Acute renal failure

1. Initial
2. Anuria / oliguria
3. Diuretic phase
4. Recovery

Tubuli proliferate,
their enzymatic activity is insufficient

Acute renal failure

1. Initial
2. Anuria / oliguria
3. Diuretic phase
4. Recovery

Restitution of renal function may take till 1 year

Acute renal failure

water + mineral disorganisation

metab. acidosis

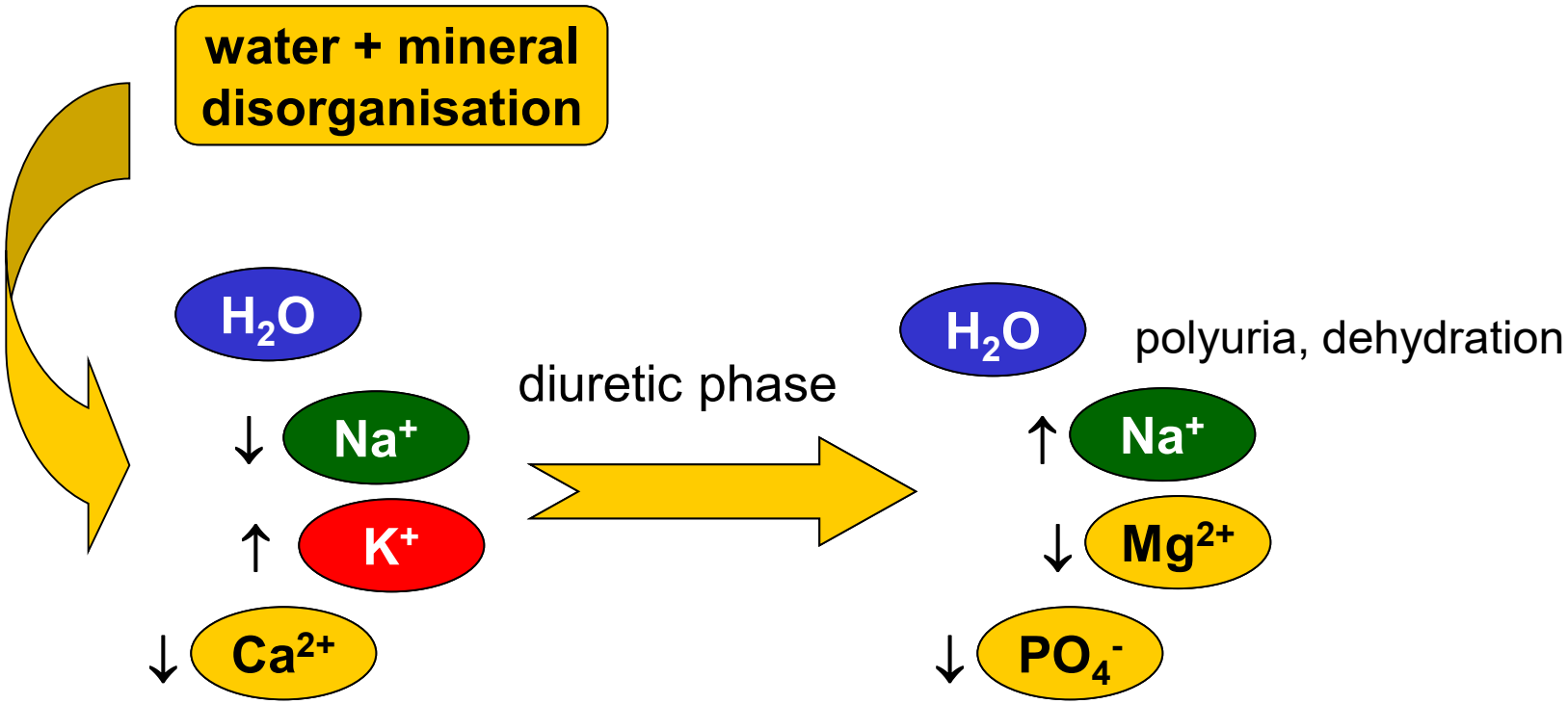
H_2O

↓ Na^+

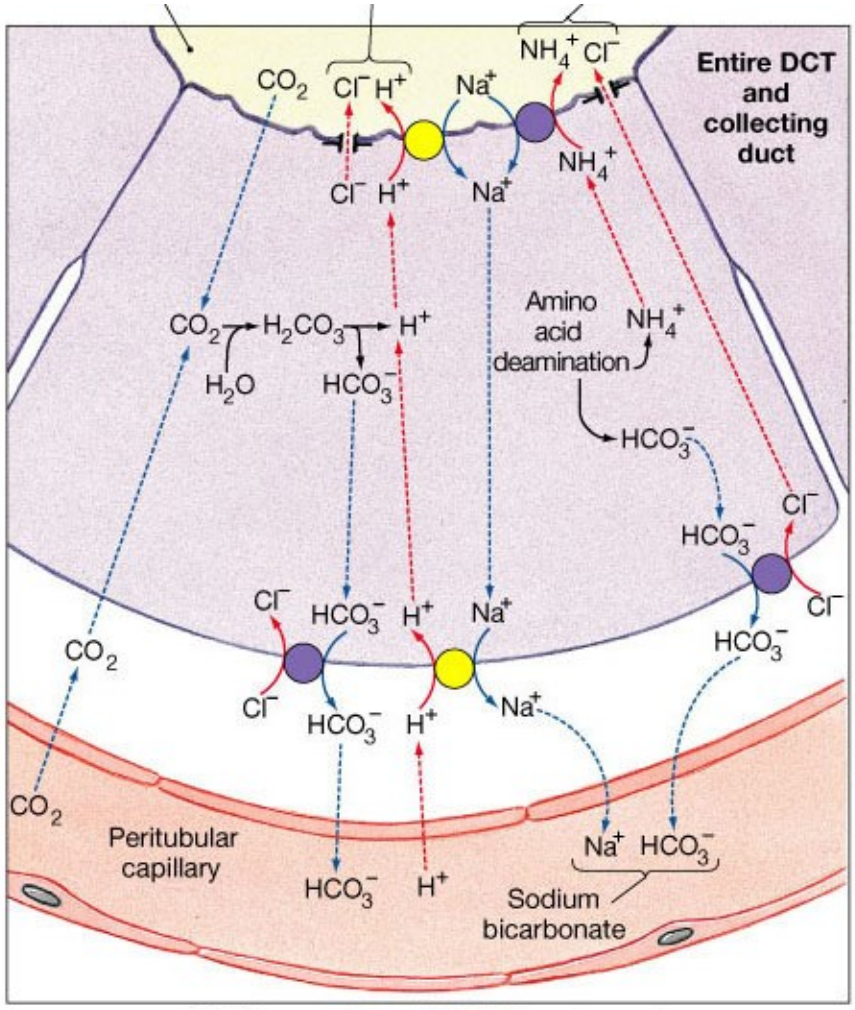
↑ K^+

↓ Ca^{2+}

Acute renal failure



Acute renal failure



metab. acidosis

HCO_3^-

NH4$^-$

PO4$^-$

Case report (1)

45-year-old female patient presented to a hospital with complaints of

- muscle pain, weakness, fatigue,
- decreased urine outflow, and a dark brown urine color

...for the previous 3 weeks.

Case report (1)

Past history:
Type 2 diabetes, 12 yrs.
Hypertriglyceridemia for about 2 years
Hypertension 2 yrs.

Drugs: glimepiride (3 mg daily) and metformin (2 x 1 g daily).

About 3 weeks before presentation, she was prescribed **fenofibrate** (Lipanthyl M267 mg) daily for hypertriglyceridemia, and she had used it regularly.

Case report (1)

No family history of liver, muscle, or kidney disease,
had not traveled recently,
no history of abuse - alcohol, tobacco, or drug.

Case report (1)

Clinical examination:

- **decreased urine output**
- **generalized weakness (3/5 of muscle strength)**
- **muscular tenderness**

Case report (1)

Laboratory:

CK (serum creatine kinase)	56 ukat / L
AST	19 ukat / L
ALT	24 ukat / L
creatinine	467 umol / L
urea	37 mmol / L
LDH	97 ukat / L
glucose	14 mmol / L
HbA1C	7.85 %
triglyceride	4,6 mmol / L
total cholesterol	5,4 mmol / L
myoglobulin	>100,000 cg / L

Case report (1)

Laboratory:

Her liver and renal functions tests were normal before the fenofibrate therapy.

urea	37 mmol / L
LDH	97 ukat / L
glucose	14 mmol / L
HbA1C	7.85 %
triglyceride	4,6 mmol / L
total cholesterol	5,4 mmol / L
myoglobin	>100,000 cg / L

Case report (1)

Laboratory:

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Rhabdomyolysis

Case report (1)

Laboratory:

CK (serum creatine kinase)	56 ukat / L
AST	19 ukat / L
ALT	24 ukat / L
creatinine	467 umol / L
urea	37 mmol / L
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Renal failure

Case report (1)

Laboratory:

CK (serum creatine kinase)	56 ukat / L
AST	19 ukat / L
ALT	24 ukat / L
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glucose	14 mmol / L
HbA1C	7.85 %
triglyceride	4,6 mmol / L
total cholesterol	5,4 mmol / L
myoglobin	>100,000 cg / L

Decompens. DM

Case report (1)

Rhabdomyolysis + **Renal failure**

She had no

- recent viral illness,
- history of trauma,
- epilepsy,
- hypothyroidism,
- or over-the-counter medication use and had not taken any other medication known to induce rhabdomyolysis.

Case report (1)

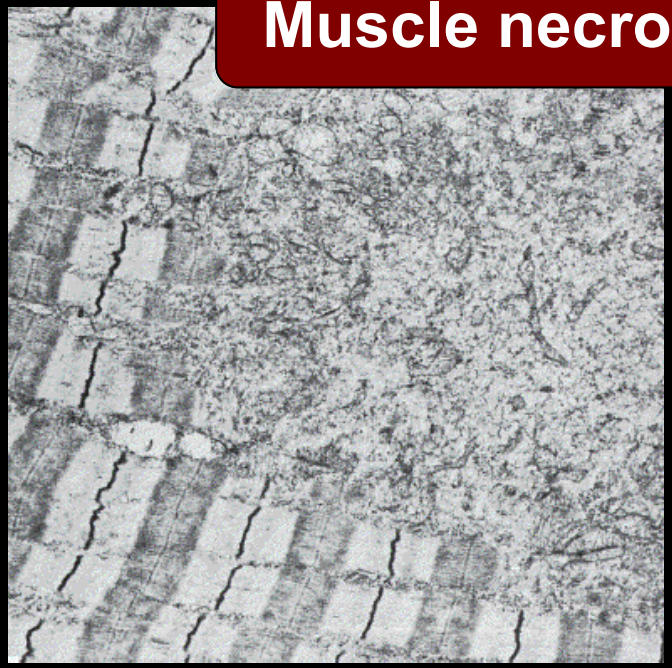
The fenofibrate was discontinued, and intravenous fluid replacement with bicarbonate therapy was started. The myalgia resolved, urine output was normalized, and serum urea and creatinine decreased to normal values on the second day of treatment.

Case report (1)

Serum	Day 1	Day 2	Day 3
Urea (mmol/l)	37.5	8.3	8.2
Creatinine (umol/l)	467	136	112
ALT (ukat/l)	24.3	18.3	12.0
AST (ukat/l)	19.6	16.1	8.2
CK (ukat/l)	56.1	28.7	19.9
LDH (ukat/l)	96.9	23.1	17.1
Na (mmol/l)	128.5	122.5	119.5
Ca (mmol/l)	2.01	2.07	2.19
K (mmol/l)	3.9	3.6	3.8
P (mmol/l)	1.34	1.26	1.21

Case report (1)

Fenofibrate



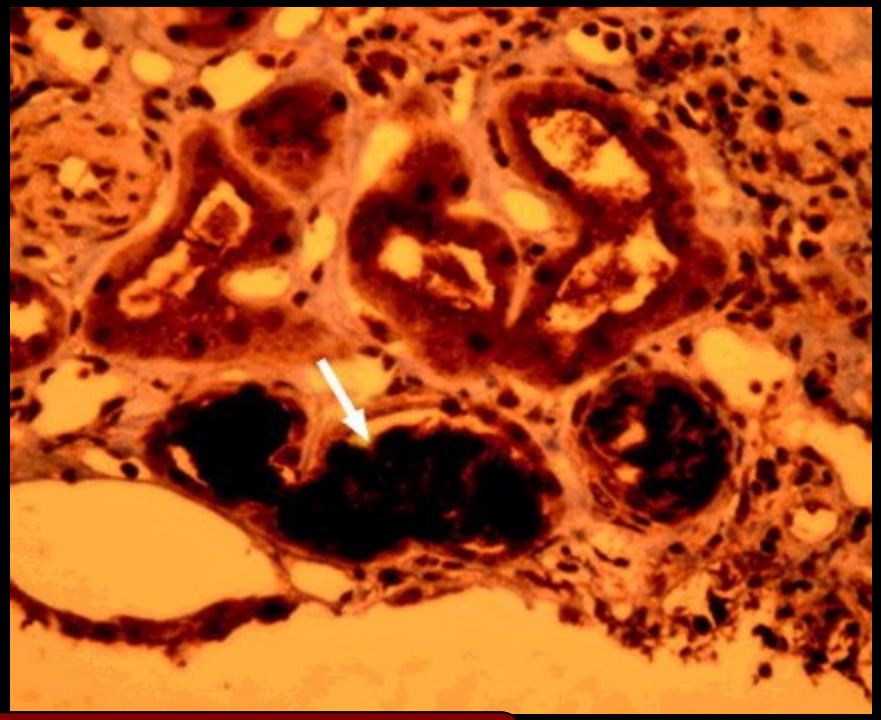
Muscle necrosis

Release of myoglobin into circulation

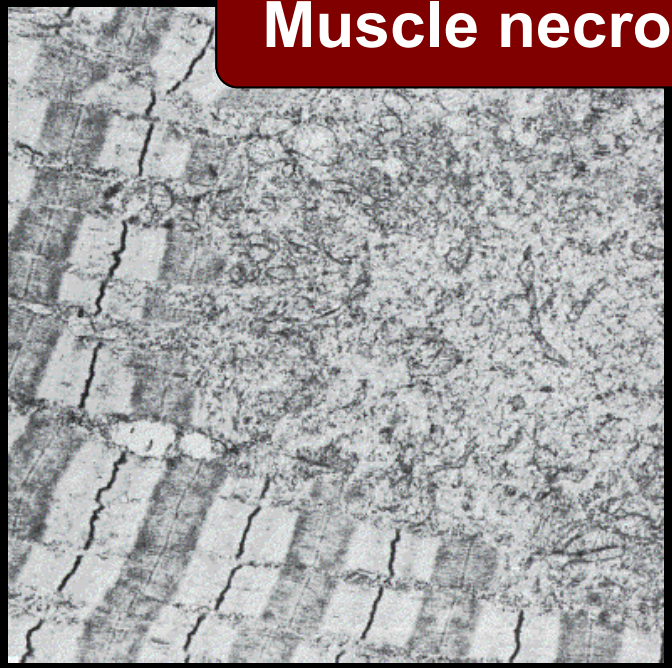
Renal failure

Case report (1)

Fenofibrate



Muscle necrosis



Renal failure

Chronic renal insufficiency

Terminal phase of various chronic renal disorders

44 %	glomerulonephritis, glomerulopathies
25 %	TIN
10 %	renal polycystosis

Phases

I. Full compensation (creat. < 300)

II. Compensated retention (creat. = 300-700)

III. Decompensated retention (creat. > 700) ... dialysis

IV. Uremia

Uremia

= systemic manifestation of renal failure (mainly chronic failure)

Syndrome.

Considerably changed after dialysis for imposed into standard therapy.

Uremia

water + mineral misbalance

metab. acidosis

bleeding

hypertension

secondary gout

osteopathy

polyneuropathy

infections

anemia

Water and mineral changes

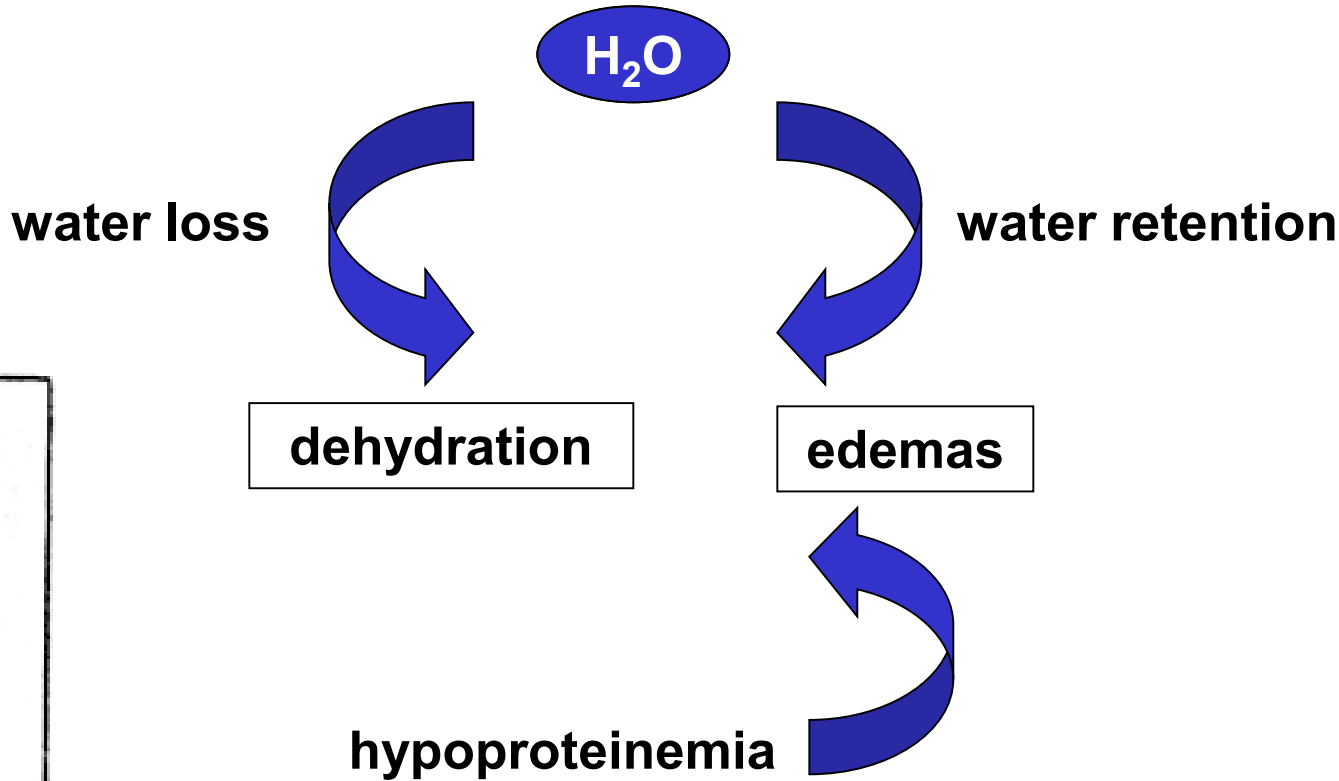
water loss

H_2O

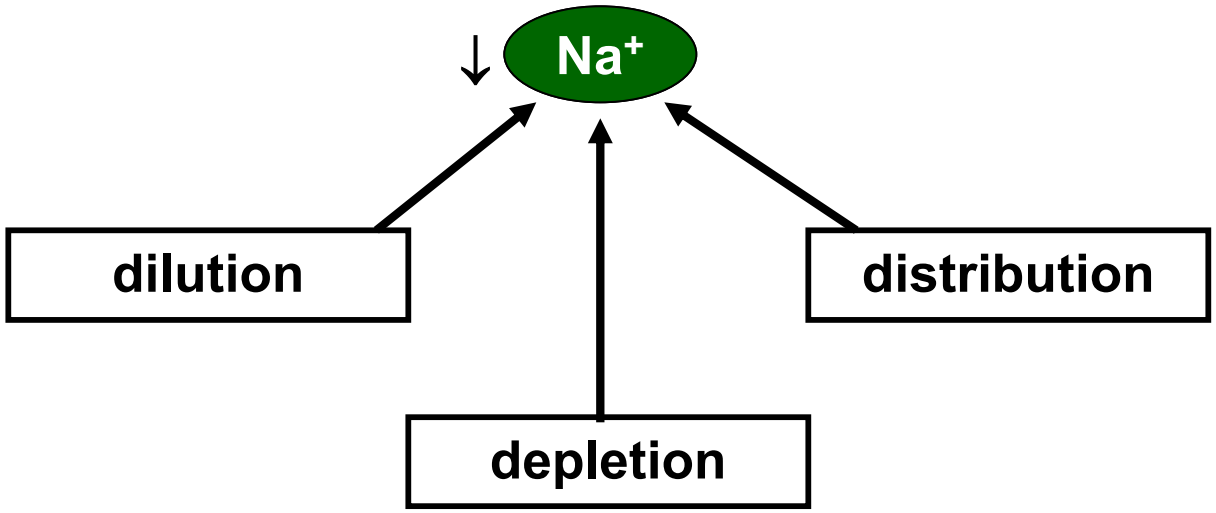
polyuria
diabetes insipidus ren.

dehydration

Water and mineral changes

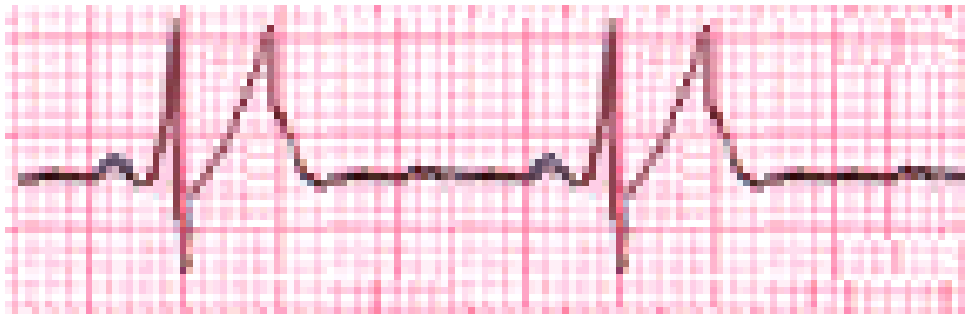


Water and mineral changes



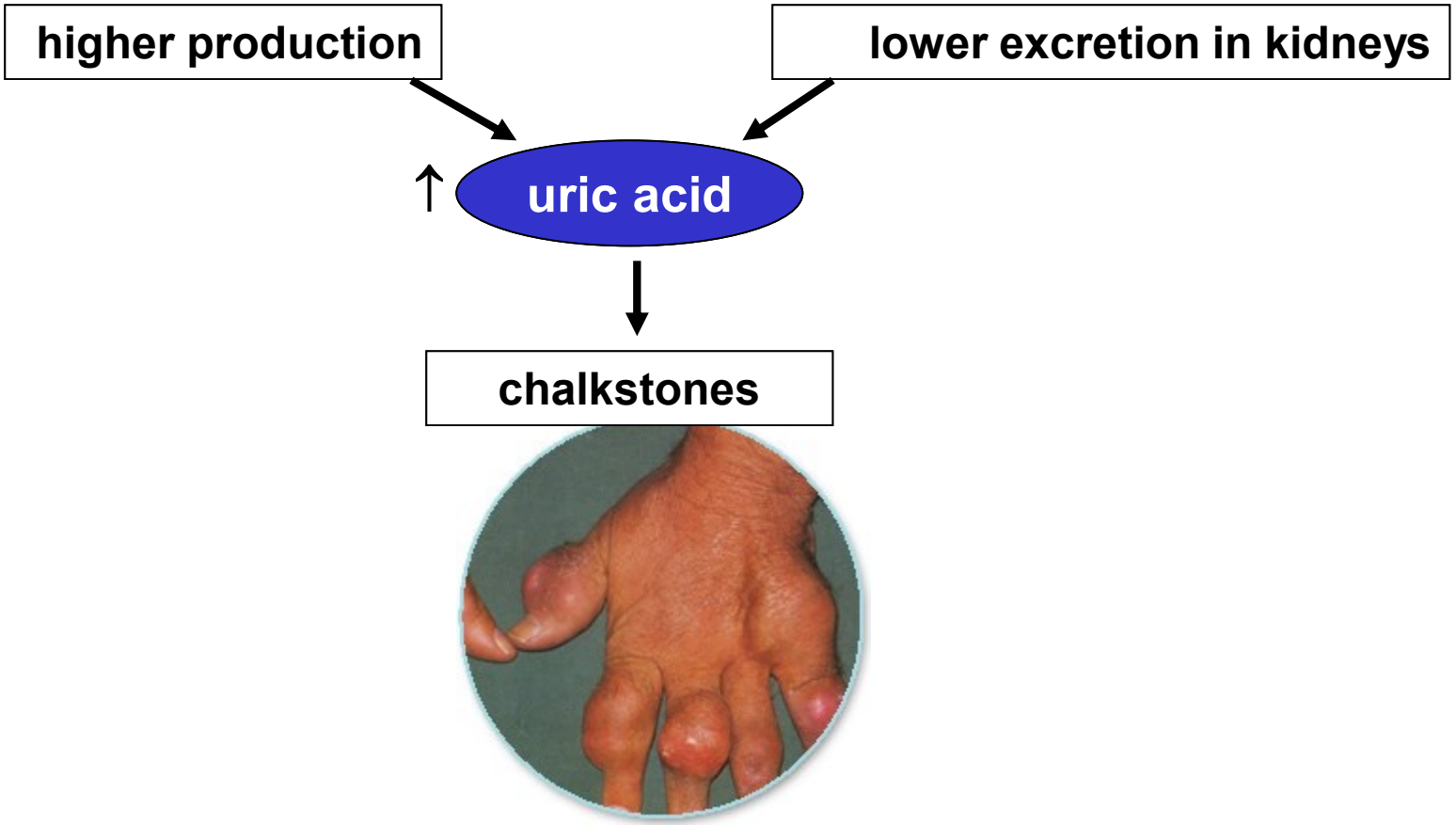
Water and mineral changes

weakness, fatigue
dyspepsia (anorexia, morning nausea, vomiting, diarrhea)
arrhythmia, pericarditis



Secondary goat

= Goat based on extraneous causes



Renal (renoparenchymal) hypertension

Factors:

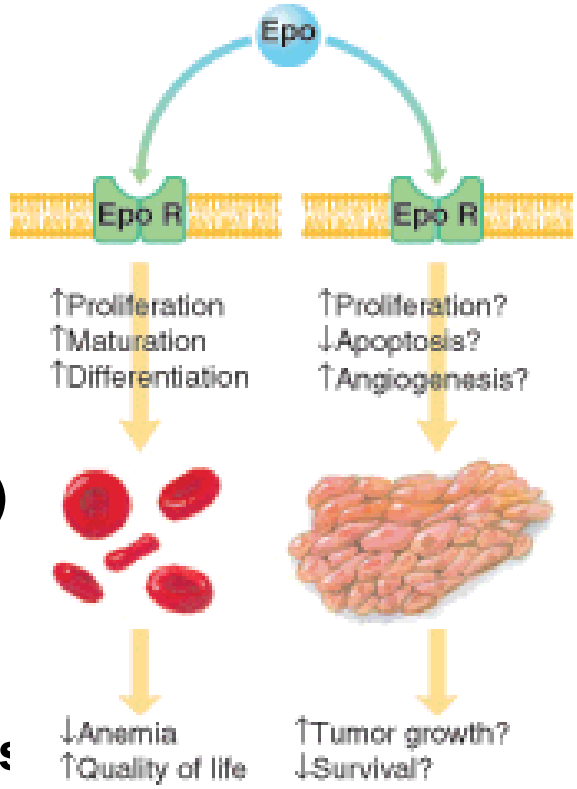
- **pressoric (renal hypoperfussion → renin)**
- **depressoric (kallikrein / kinins, PG E)**
- **Na, H_2O excretion**

x

Renovascular hypertension

Reaction of renal pressoric mechanisms (renin) to hypoperfussion in case of renal artery stenosis

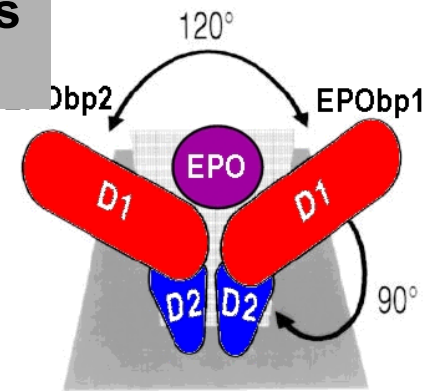
Anemia



Factors:

- **Epo**
- **loss of vitamins, proteins (proteinuria)**
- **blood loss (hematuria)**
- **lack of iron (inflammation, ↓ Trf)**
- **toxic inhibition of bone marrow**
- **inflammatory inhibition of erythropoies**

Chronic normocytyc normochromic anemia,
Patients adapted well even when Hb concentrations are very low



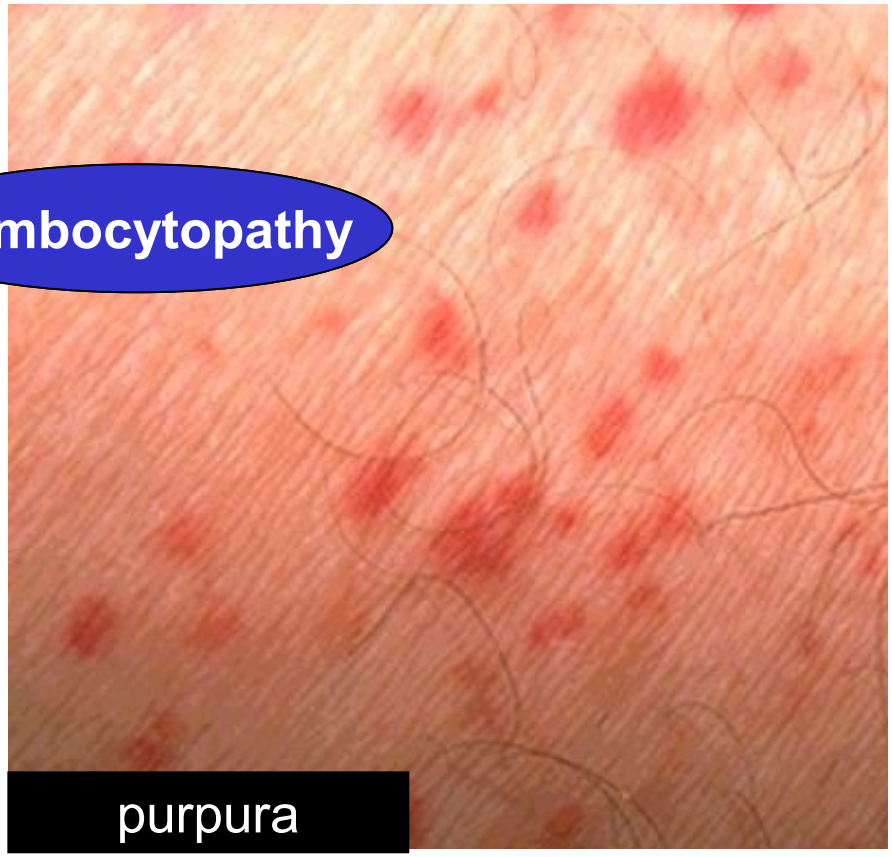
Uremic thrombocytopathy

↑ urea

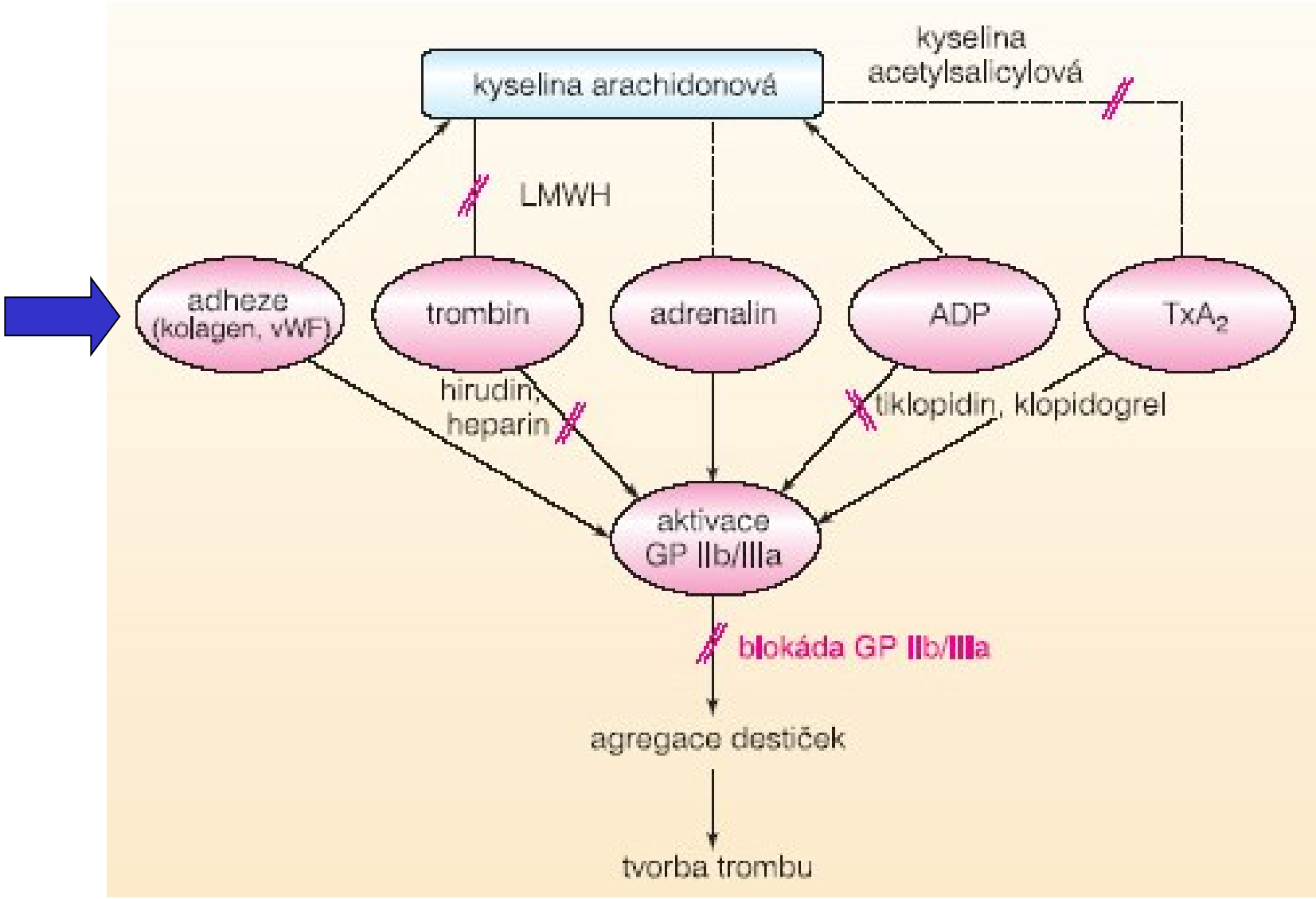
↑ arginine succinate

↓ highly molecul. vWf

} trombocytopathy



Uremic thrombocytopathy

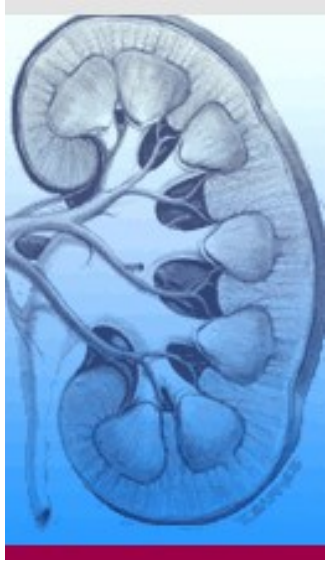


Renal osteodystrophy

Factors:

- **↑ PO_4**
- **↓ 1,25-0H-vit. D3 ... low production**
- **↓ Ca ... renal loss, ↓ absorption in gut**
- **secondary ↑ PTH ... bone absorption**

impaired hydroxylation in proximal tubule



retention

↓ 1,25-0H-vit. D3

↑ PO_4

↓ Ca absorption in gut

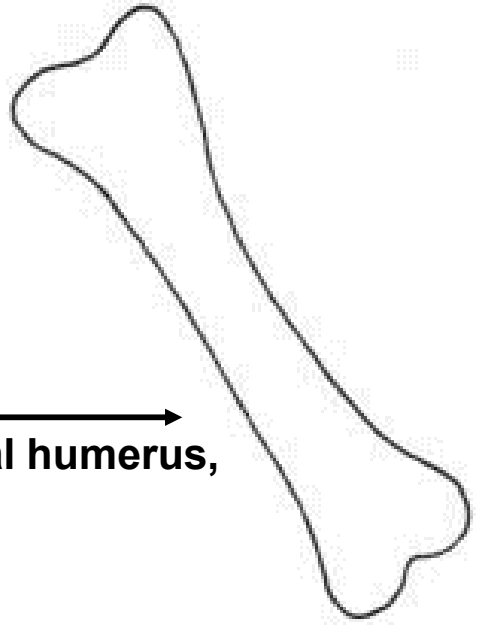
renal loss

binding of serum Ca

↓ Ca

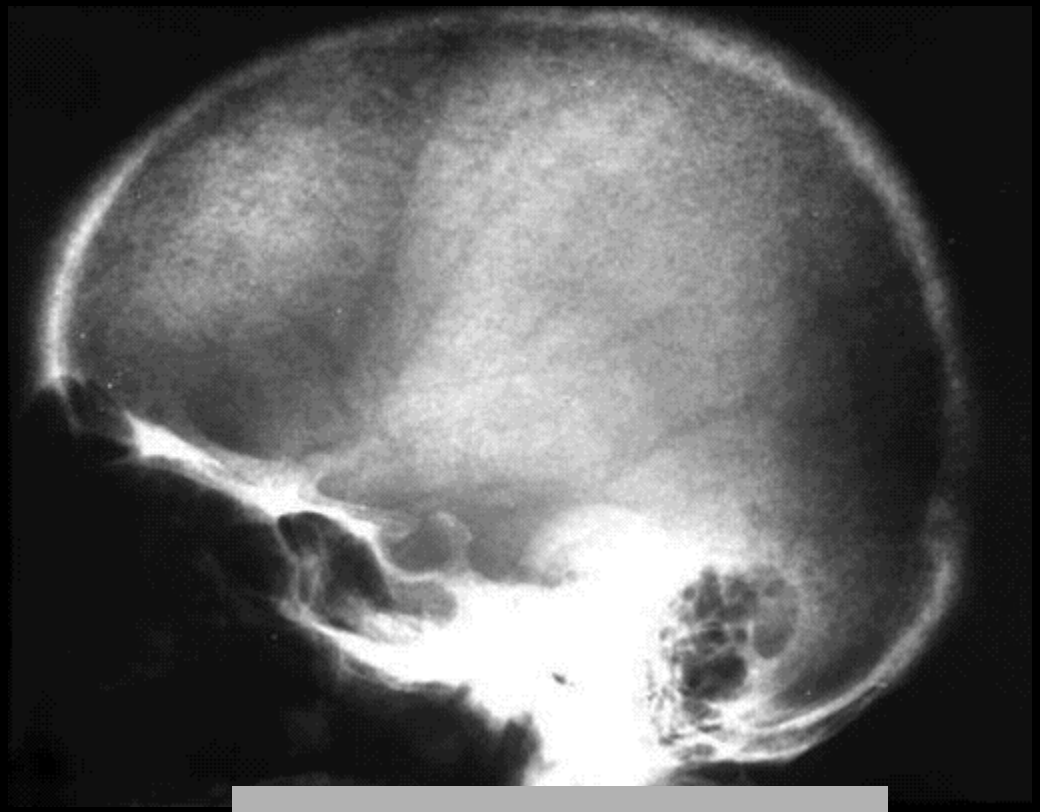
secondary hyper-PTH

↑ PTH

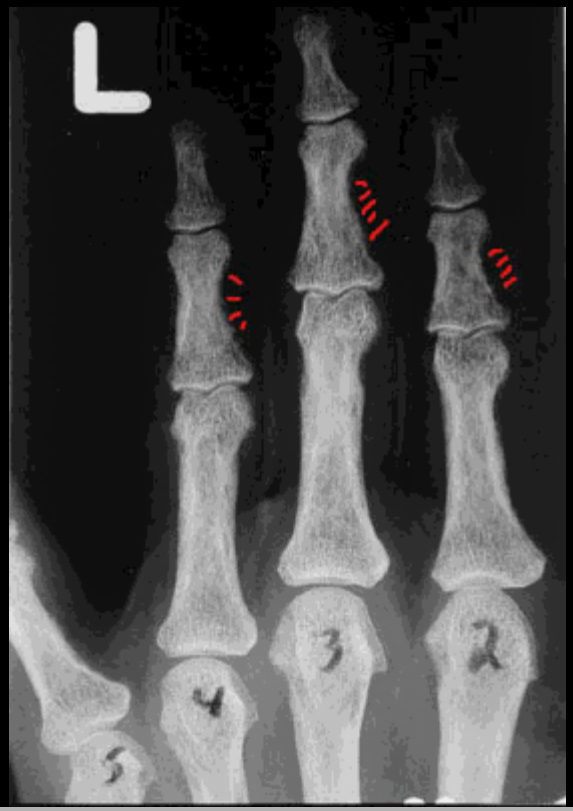


Bone absorption, mainly subperiostal - phalanges, proximal humerus, tibia, femur, scull.

Renal osteodystrophy

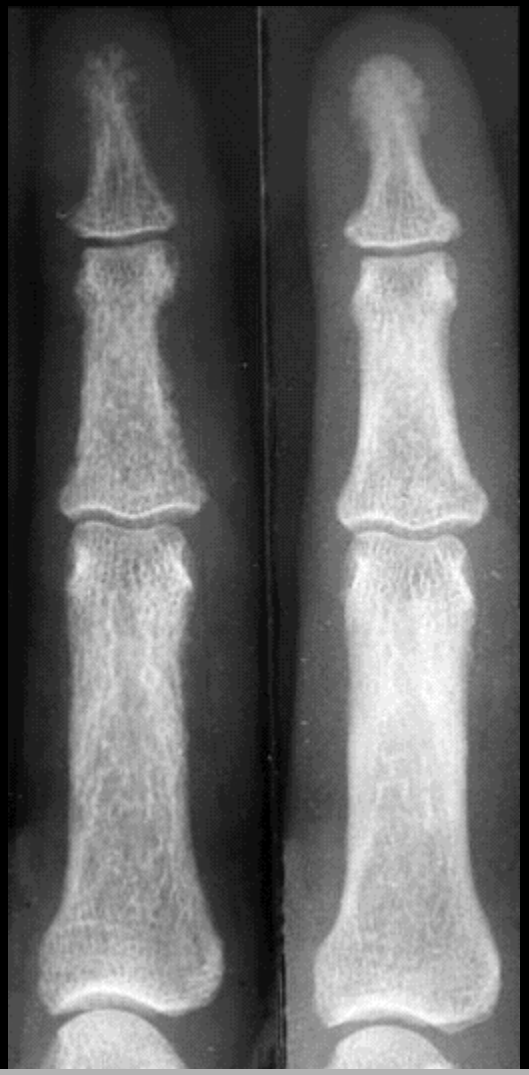


Scull „salt and pepper“



Hyper-PTH resulting to characteristic subperiostal absorption

Renal osteodystrophy



Bone changes are partially reversible:
The same finger before treatment and 6 months after.

Infectious complications

Bronchitis, bronchopneumonia
Hepatitis
Sepsis

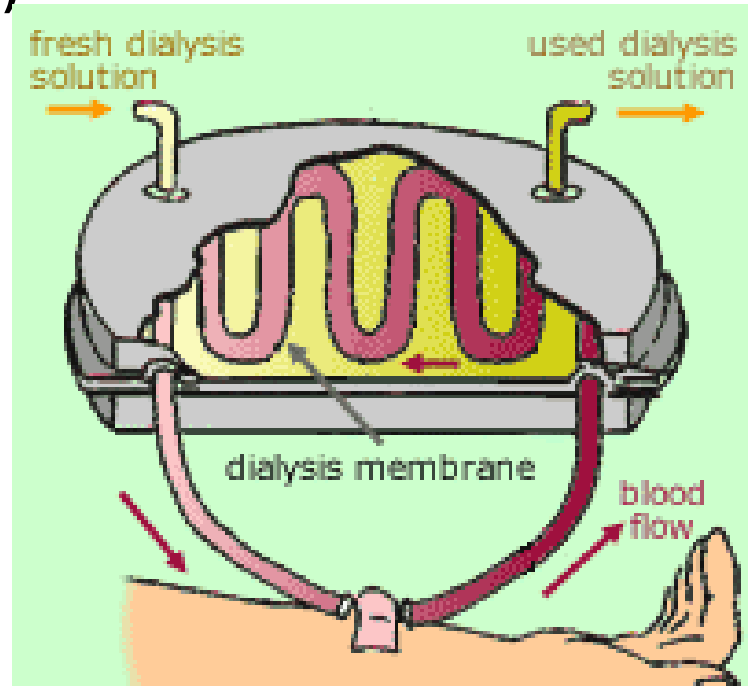
Cheyne - Stokes breathing

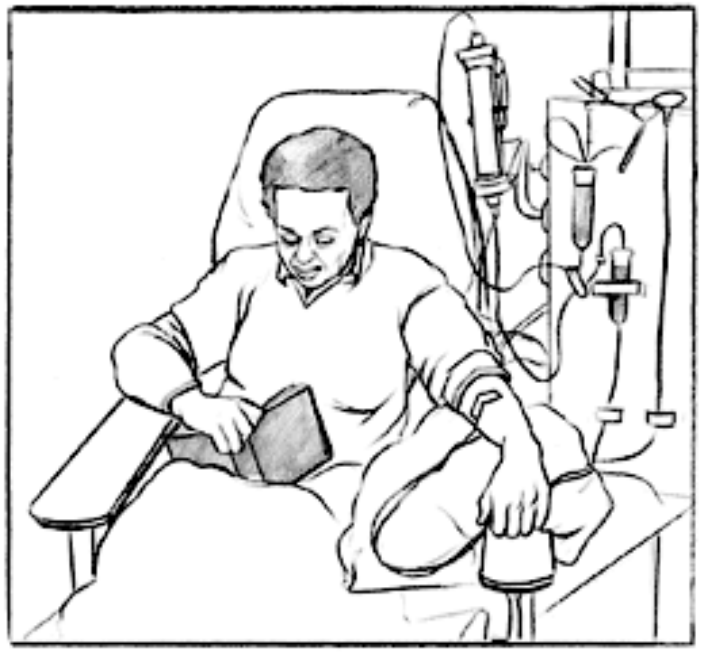
Acute dialysis

Artificial replacement for lost kidney function

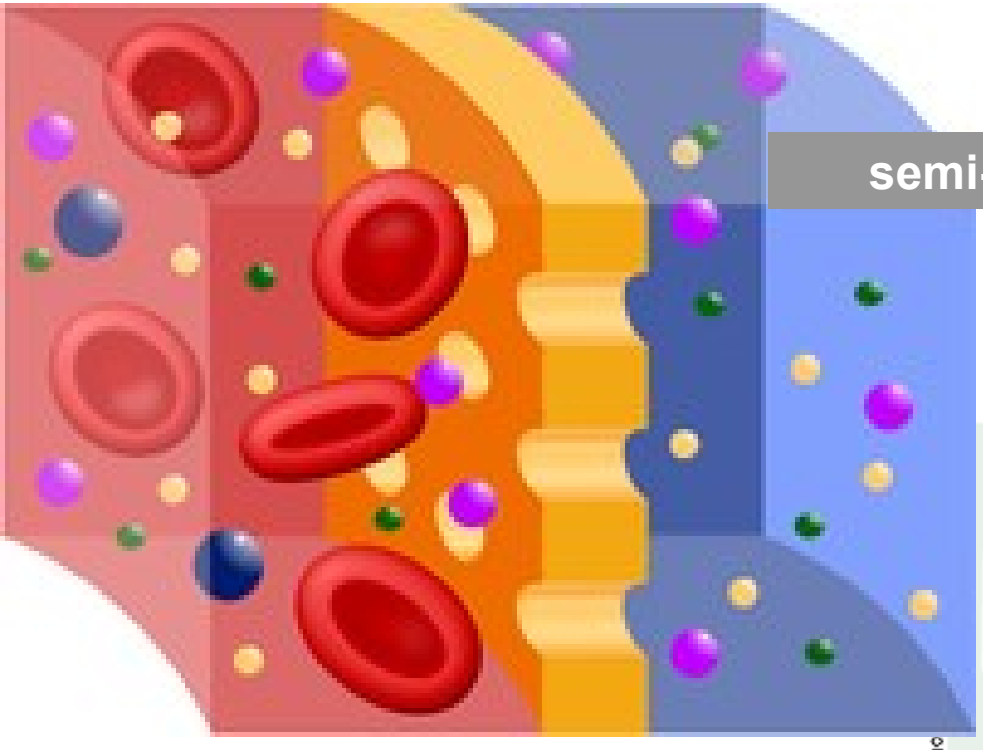
Dialysis works on the principles of the diffusion of solutes and ultrafiltration of fluid across a semi-permeable membrane.

Elimination of low molecular solutes (which are not protein-bound)

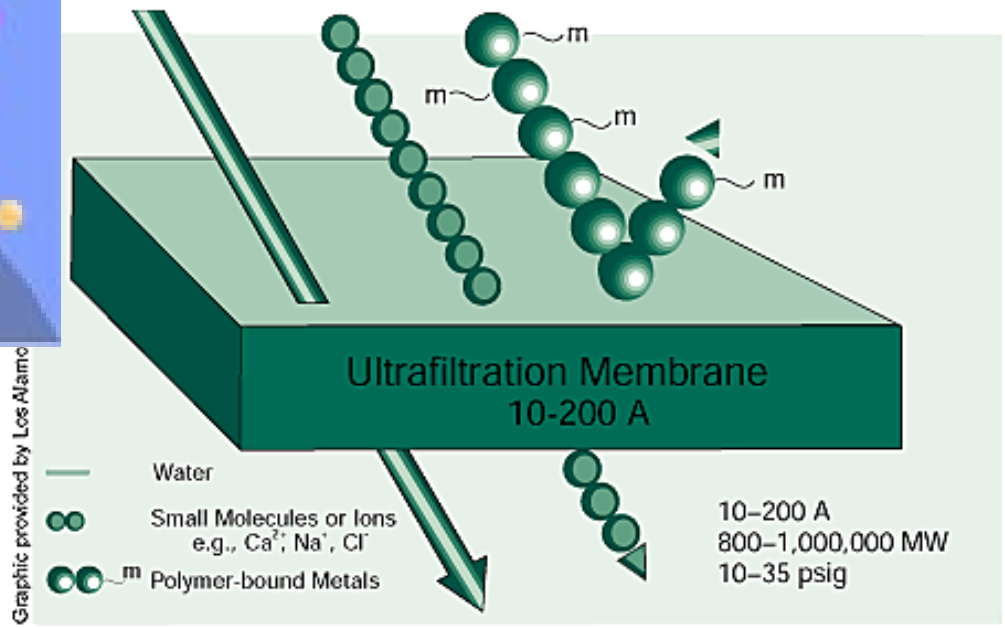




Acute dialysis



semi-permeable membrane

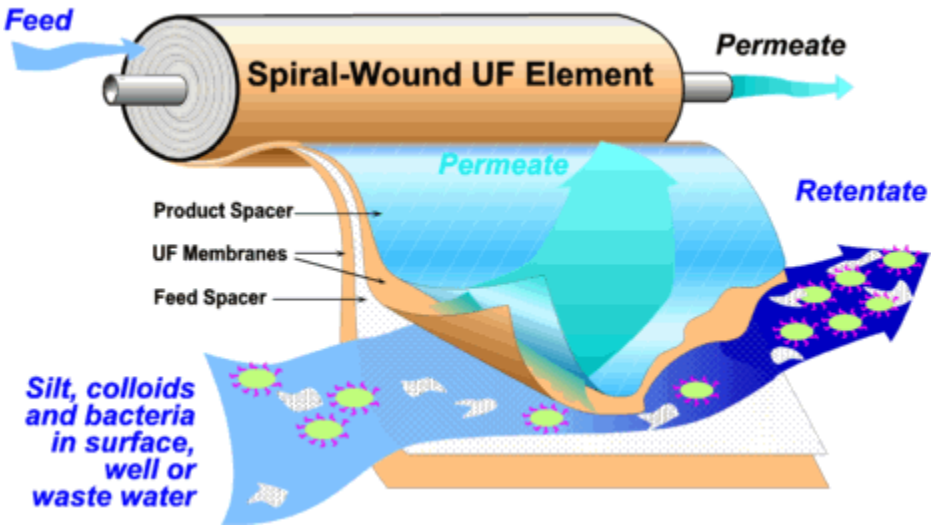


Polymer Filtration is a membrane-based technology for metal-ion recovery. This separations technology uses specially designed, water soluble polymers that selectively bind metal ions to prevent metals from entering waste water streams and to prevent sludge formation.

Acute dialysis

Possible combination with ultrafiltration

(hyperhydratation, pulmonary edema)



Ultrafiltration

Variety of membrane filtration. Hydrostatic pressure forces a liquid against a semi-permeable membrane.

Acute dialysis

Indications

1. Renal failure

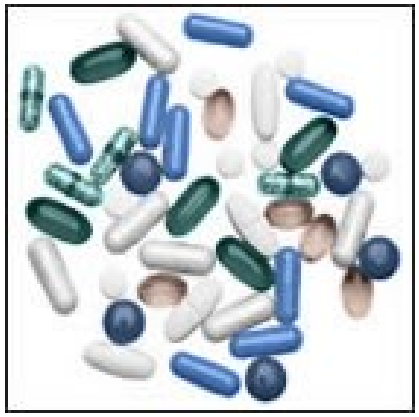
- **uremia**
- **anuria / oliguria > 3 days**
- **creatinine > 700 umol / L**
- **urea > 30 mmol / L**
- **↑ urea > 10 mmol / L / den**
- **K > 6,5 mmol / L**
- **acidosis**
- **hyperhydration**

Acute dialysis

Indications

1. Renal failure
2. Intoxication ... poisons non-bound on proteins

psychiatric drugs



Acute dialysis

Indications

1. Renal failure
2. Intoxication
3. ↑ Ca
4. ↑ uricemia ... e.g., after cytostatic therapy of leukemia
5. Hypotermia
6. Alkalosis ... rarely, not in CZ

Acute dialysis

Contraindications

Terminal phase of malignancy only

x Age, diagnosis

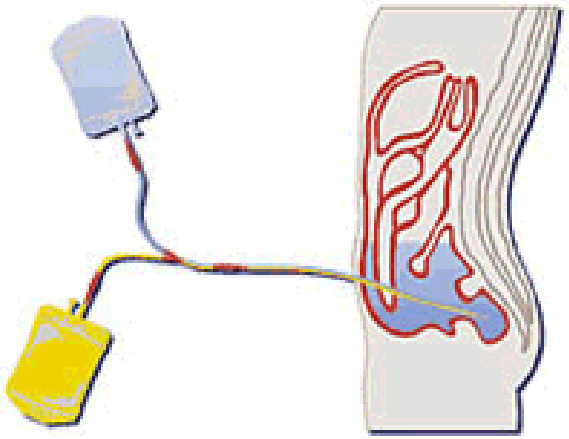
Creatinin > 300 nmol / L ... Following of patient in nephrology dept.

Peritoneal dialysis

Principle

A sterile solution containing minerals and glucose is run through a tube into the peritoneal cavity, where the peritoneal membrane acts as a semi-permeable membrane. The dialysate is left there for a period of time to absorb waste products, and then it is drained out through the tube and discarded. This cycle is repeated 4-5 times during the day,

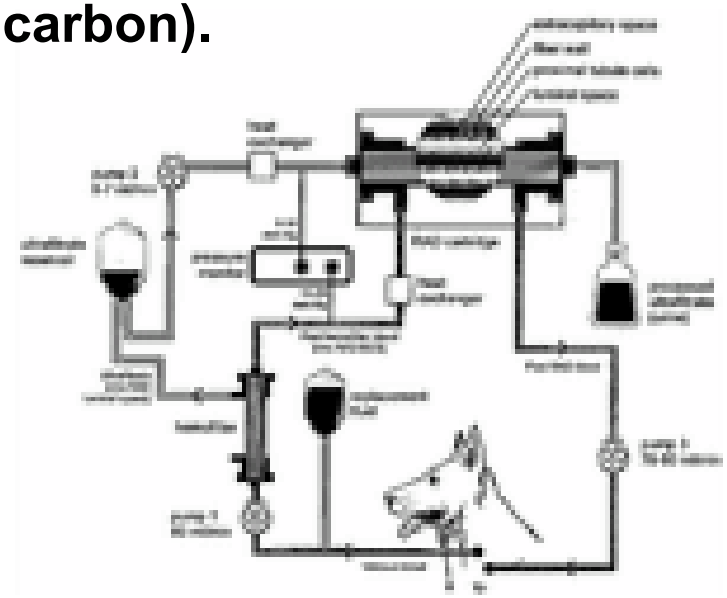
CAPD = Continual peritoneal dialysis



Hemoperfusion

Principle

Extracorporal treatment. Elimination methods of toxins bound on plasma proteins.
Technique involves passing large volumes of blood over an adsorbent substance (most commonly resins and activated carbon).



hemoperfuzní kapsle