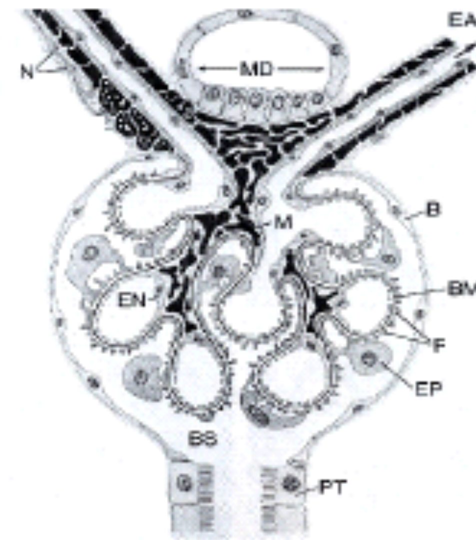
The Kidney in Health and Disease

Frankfurt/Main

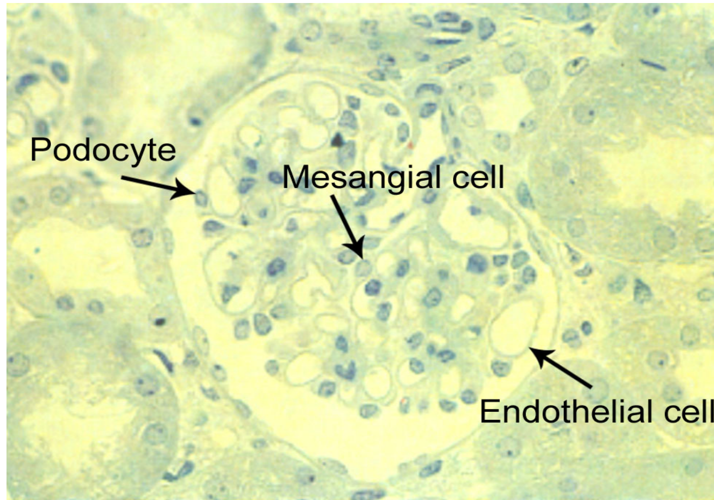
November 07, 2011

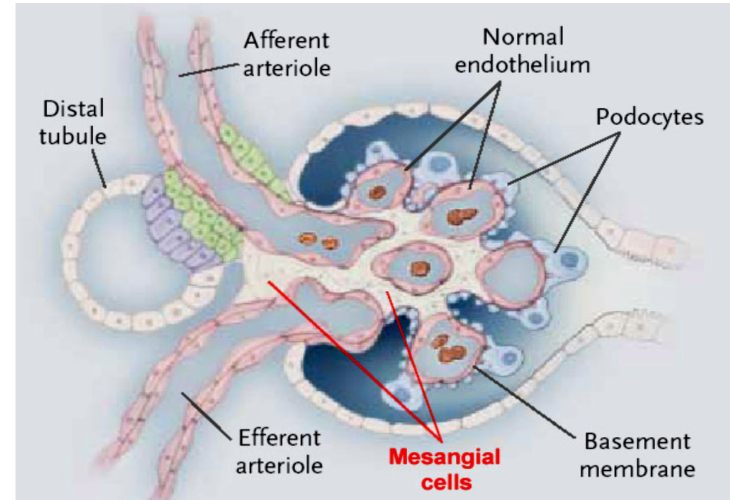


Prof. Liliana Schaefer
Institute for Pharmacology
University of Frankfurt

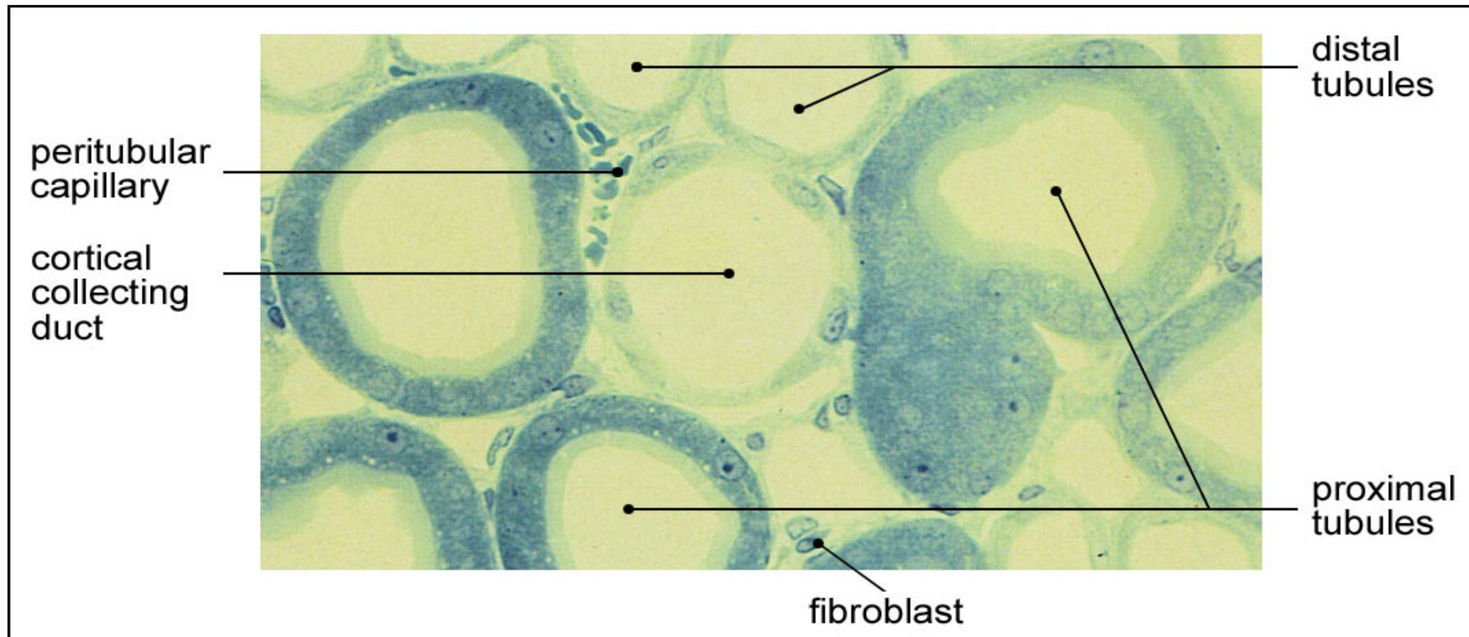
Morphology of the normal glomerulus and tubulointerstitium

Glomerulus - 1% of kidney volume

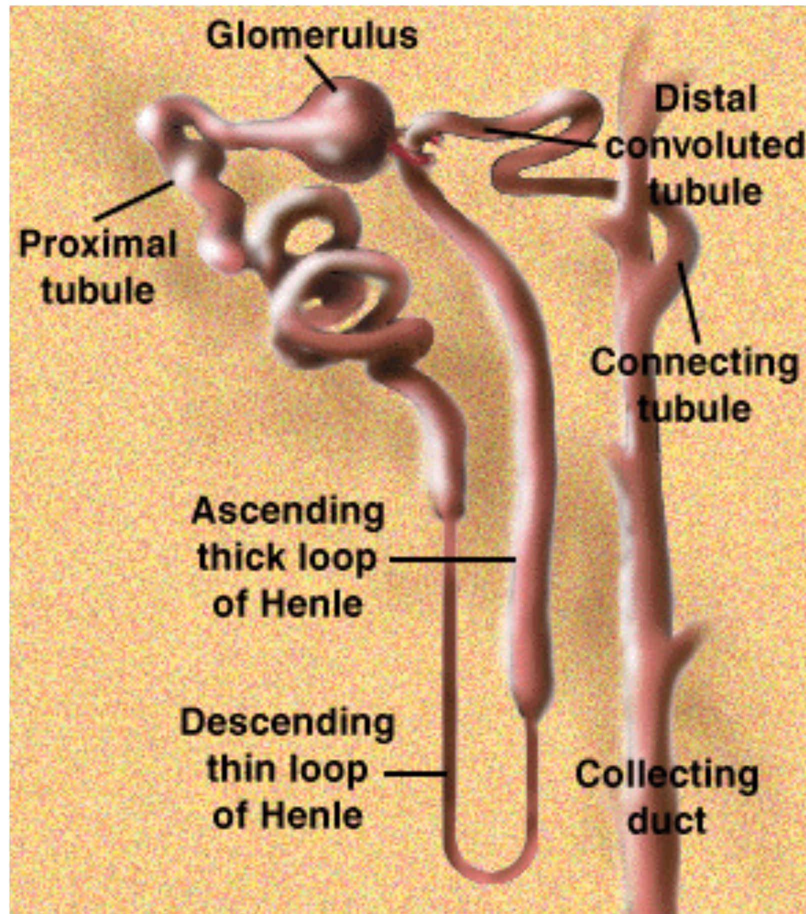


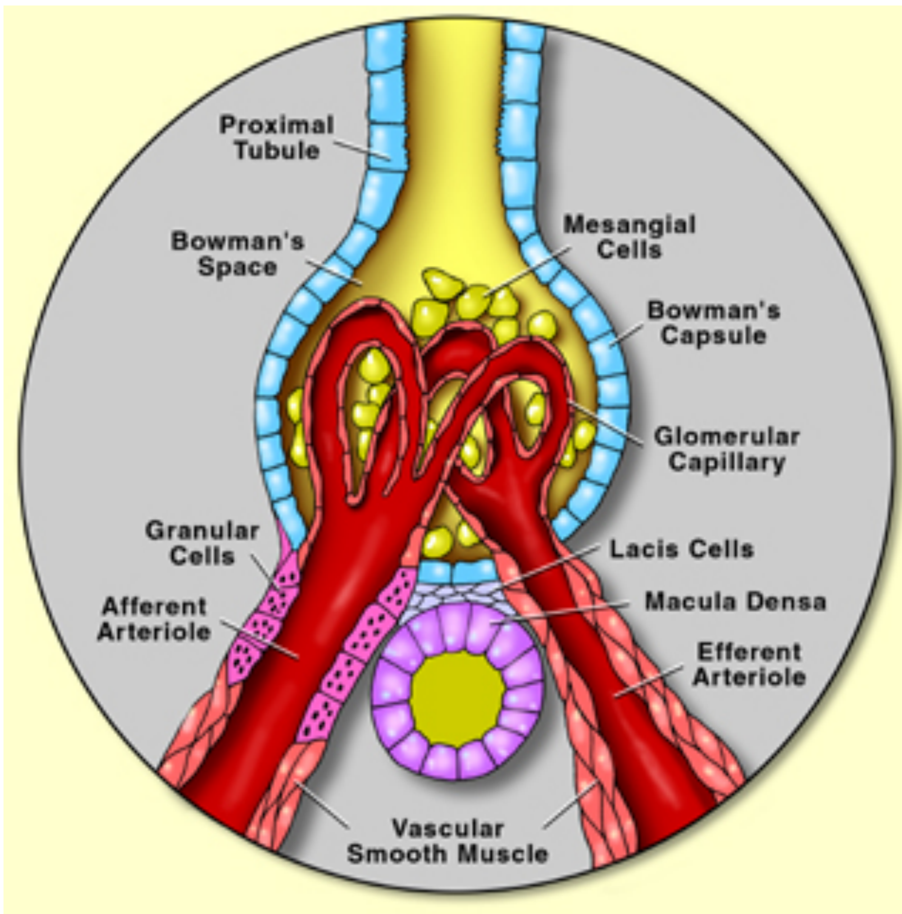


Tubulointerstitium - 99% of kidney volume



Morphology of the normal glomerulus and tubulointerstitium





Physiologic Functions of the Kidney

Exocrine Functions

- Excretion of waste products (urea, creatinine, etc)
- Control of acid/base balance
- Regulation of water and electrolyte metabolism

- **Control of extracellular volume status (blood pressure control)**

Maintaining extracellular volume is the overriding goal of the kidney. During massive volume loss (i.e. blood loss, diarrhea) the kidney will sacrifice excretory function (oligo/anuria) to minimize fluid loss.

Physiologic Functions of the Kidney

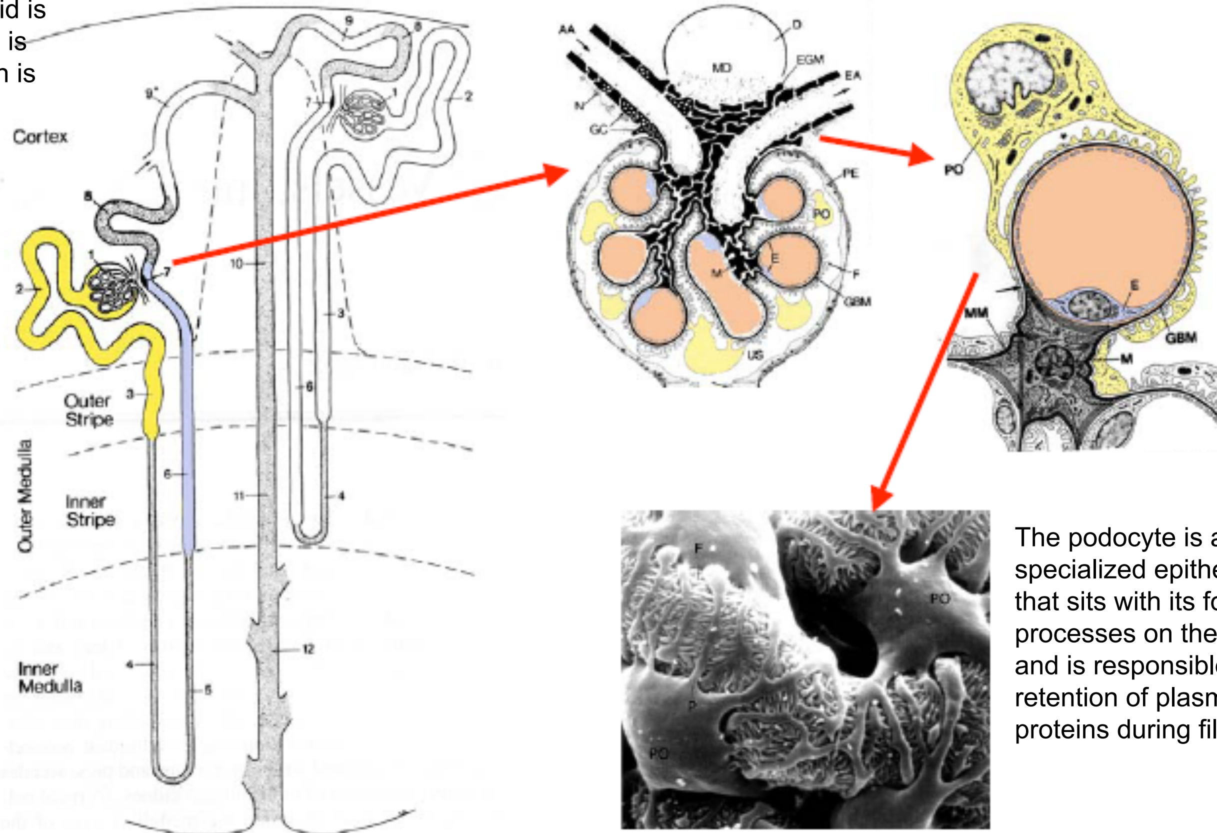
Endocrine Functions

	Chronic Kidney Disease
• Erythropoietin	EPO↓ → Anemia
• Renin	Renin↑ → Hypertension
• 1,25 $(OH)_2$Vit D_3	Vit D_3↓ → sHPT

Glomerular Filtration

Each glomerulus connects to its distal tubule via the macula densa, where composition of tubular fluid is measured. If composition is not correct, glom. filtration is shut off.

The macula densa consists of specialized tubular epithelial cells, which secrete renin and thereby control the tone of the afferent and efferent arteriole.



The podocyte is a specialized epithelial cell that sits with its foot processes on the GBM and is responsible for retention of plasma proteins during filtration.

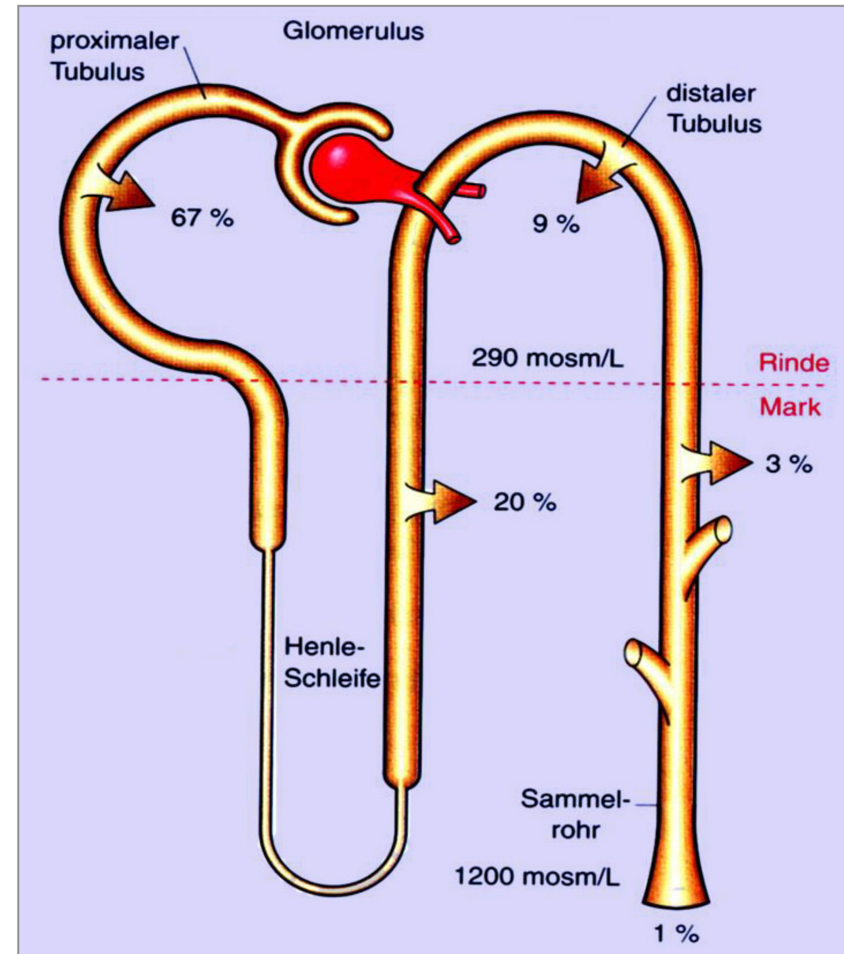
modified Neilson&Couser - 1995

Tubular Sodium Reabsorption

97-99% of filtered sodium is reabsorbed, 1-3% is excreted

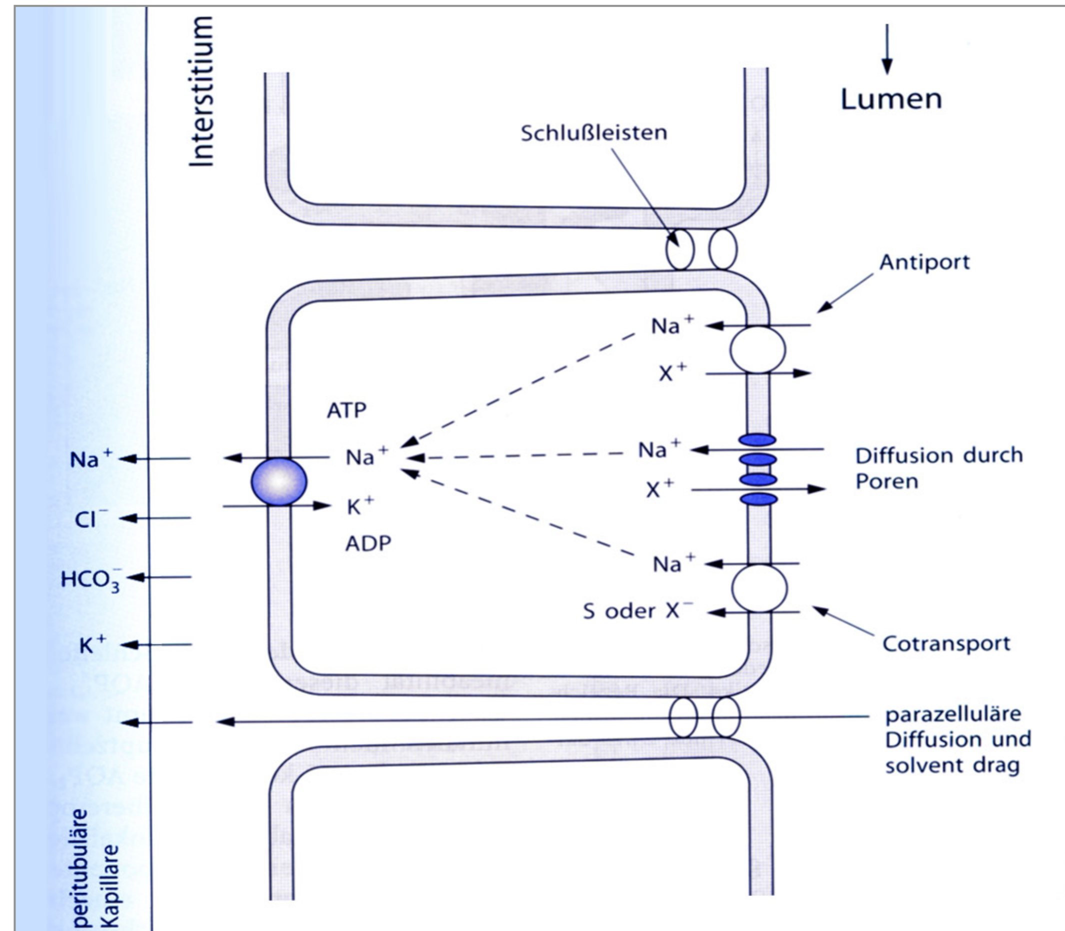
10^6 Nephrons / kidney:
GFR: 180 L/24h (=120 ml/min)
= 15x extracellular volume

Filtered Na^+: 25.000 mmol/24h
= 1.5 kg/24h



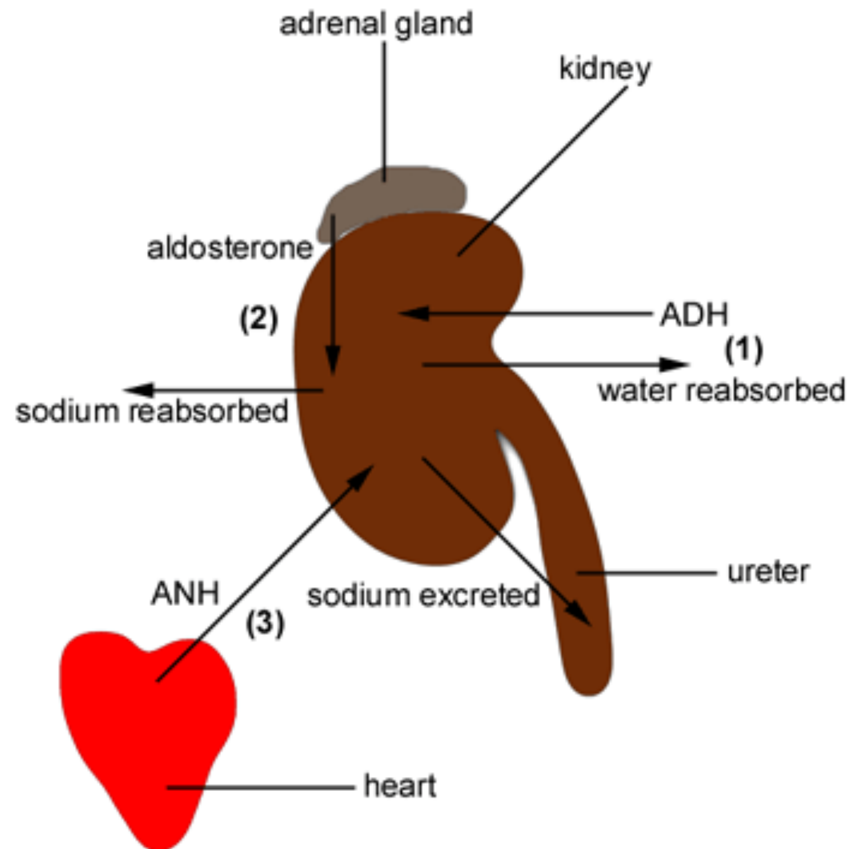
Tubular Sodium Reabsorption

Basolateral side:
Pumps are transporting sodium into the extracellular space against a concentr. gradient, using ATP as energy source, thereby lowering intracelllular sodium.



Luminal side:
Channels for diffusion, antiport or cotransport. No energy necessary; the antiports and cotransporters are using the sodium gradient as driving force.

Regulation of Sodium and Water Balance



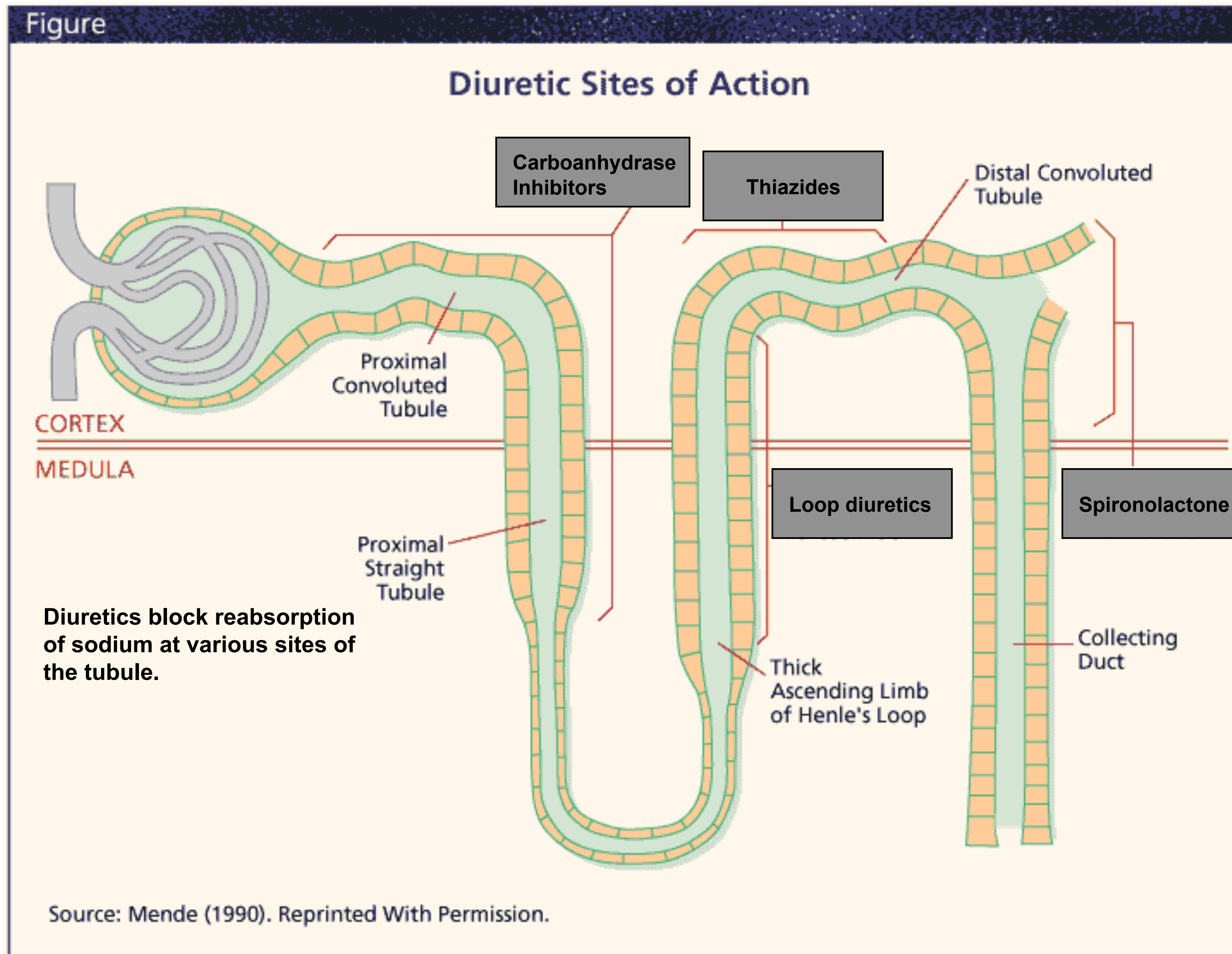
Three major hormones are involved in regulating sodium and water balance in the body at the level of the kidney:

(1) ADH (antidiuretic hormone) from the posterior pituitary acts on the kidney to promote water reabsorption.

(2) Aldosterone from the adrenal gland acts on the kidney to stimulate sodium reabsorption, thus preventing its loss in the urine.

(3) ANP (atrial natriuretic peptide) from the atrium of the heart acts on the kidney to promote sodium excretion.

Diuretics: Sites of Action



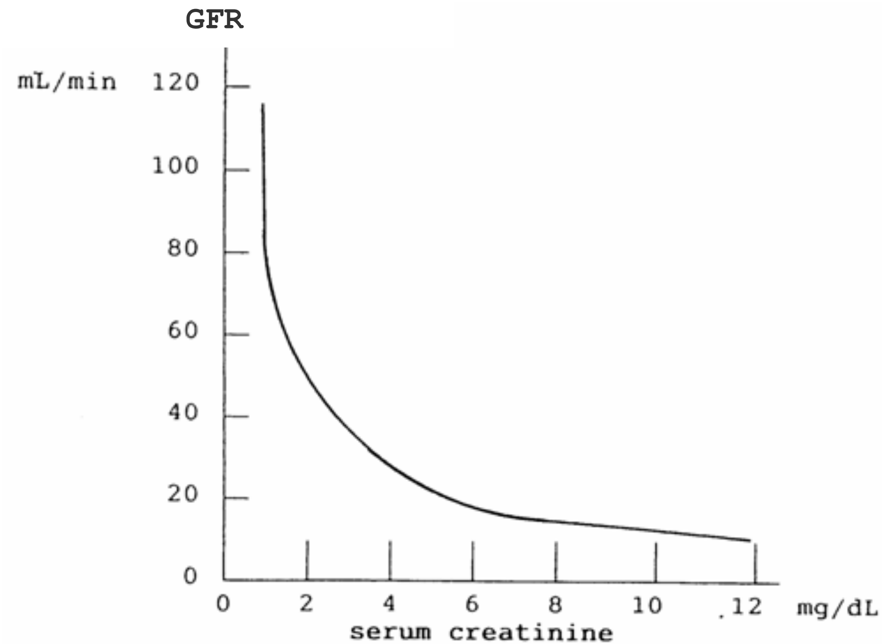
Source: Mende (1990). Reprinted With Permission.

Determination of renal function
Serum Creatinine vs. GFR

Creatinine is formed in muscle from creatine phosphate by nonenzymatic dehydration.

The amount of creatinine produced is related to muscle mass and remains remarkably constant from day to day.

Creatinine is excreted by the kidneys in a 70 kg person at a rate of 1 g/24h.



Creatinine Clearance

$$C_{Cr} = \frac{U_{Cr} \times V}{P_{Cr}}$$

Table 3. Formulas to estimate creatinine clearance and glomerular filtration rate

Cockroft-Gault equation

Creatinine clearance (mL/min) =

$$\frac{(140 - \text{age, yr}) \times \text{lean body weight (kg)}}{P_{cr}(\text{mg/dL}) \times 72} [\times 0.85 \text{ in women}]$$

MDRD equation

GFR (mL/min/1.73m²) = $170 \times [P_{cr}]^{-0.999} \times [\text{age, yr}]^{-0.176} [\times 0.762 \text{ in women}]$ or $[\times 1.180 \text{ in black patients}] \times [\text{SUN (mg/dL)}]^{-0.170} \times [\text{albumin}]^{+0.318}$

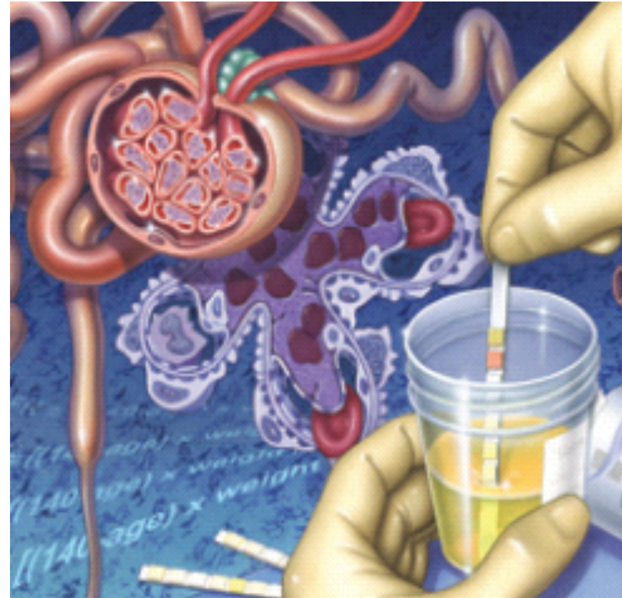
GFR calculator

http://www.kidney.org/professionals/kdoqi/index.cfm

GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; P_{cr}, plasma creatinine; SUN, serum urea nitrogen.

Urine Dipstick

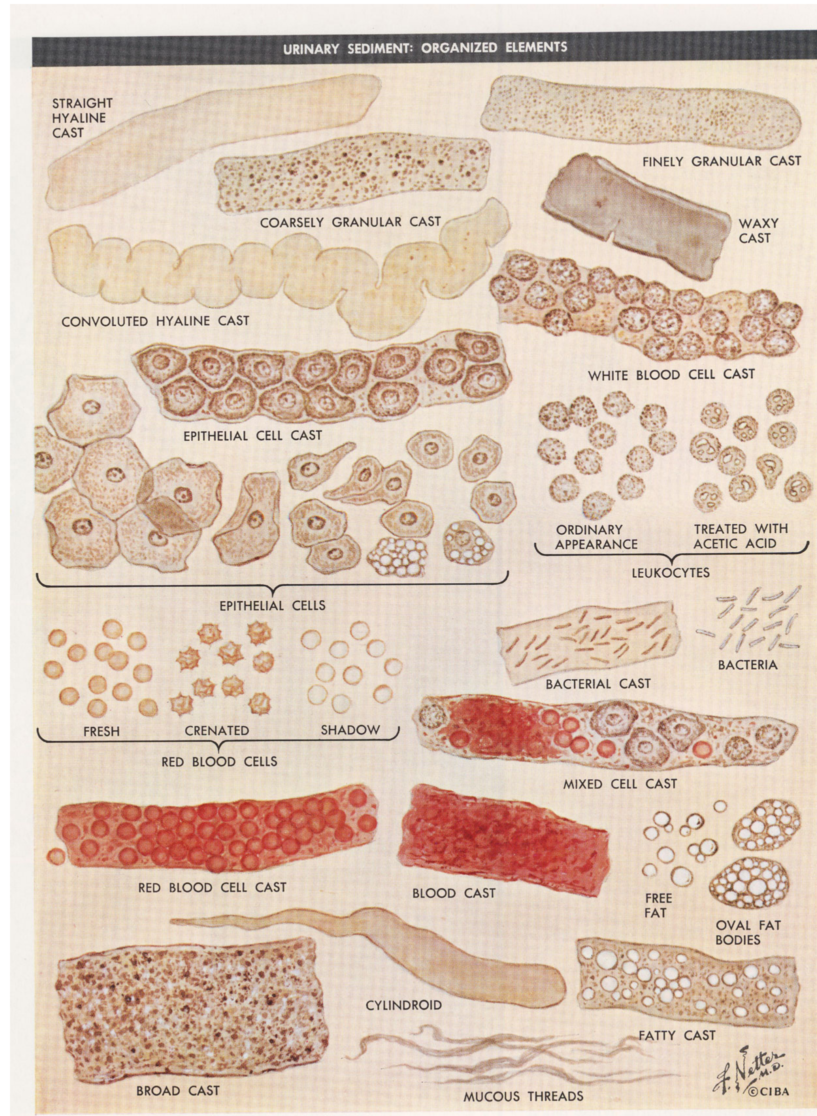
pH: 5 – 6;   pH >7 (urinary tract Infection)
Glucose: positive (Diabetes mellitus)
Leuko: positive (urinary tract infection)
Nitrit: positive (urinary tract infection)
Proteinuria: <150 mg/24h
Ery: positive (Stone disease, Glomerulo-
nephritis, Tumor)



Renal disease in its early stages is diagnosed in the urine.

Only when renal function is compromised (GFR <50 ml/min), renal disease can be diagnosed by measuring serum creatinine.

Urinary Sediment



Kidney disease

Glomerulonephritis

Clinical Manifestations

Asymptomatic
Proteinuria <3g /24h and/or microhematuria

Rapid progressive Glomerulonephritis
Nephritic sediment: Hematuria, Leucocyturia, Proteinuria (< 3g/24h), rapid loss of GFR

Nephrotic Syndrome
Proteinuria >3 g/24h, Hypalbuminemia <3 g/dl, Hypercholesterinemie, GFR initially normal, edema

Chronic Glomerulonephritis
Reduced GFR, Proteinuria, Hypertension and reduced kidney size

Minimal Change Glomerulopathy

S.M. ♂ (24J), 2007

S-Crea: 1.0 mg/dl

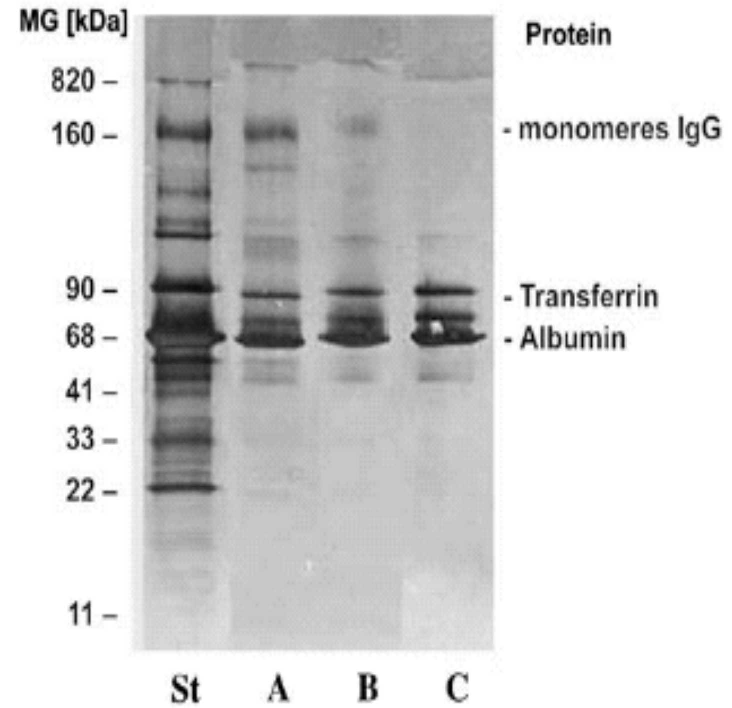
GFR: 115 ml/min

Protein: 10.900 mg/g (<100 mg/g)

Albumin/Crea: 9.300 mg/g (<30 mg/g)

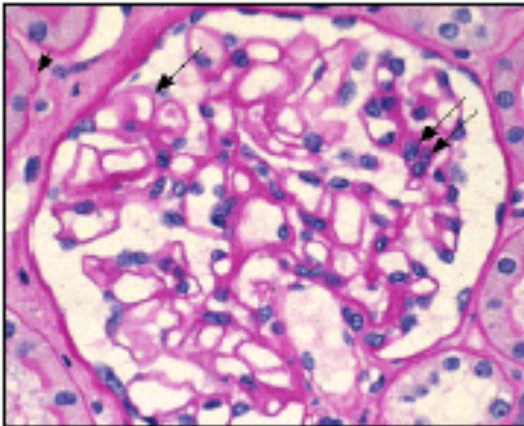
IgG/Crea: 110 mg/g (<10 mg/g)

α_1-M/Crea: 20 mg/g (<10 mg/g)

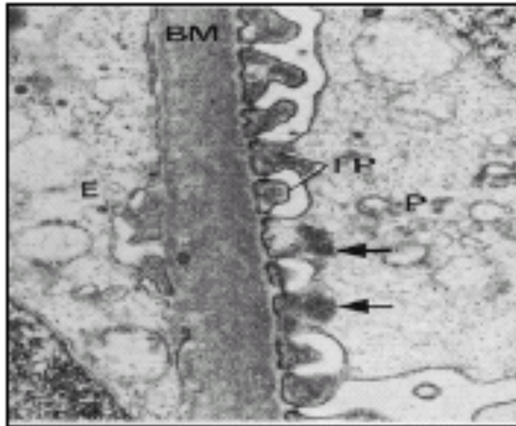


Steroids

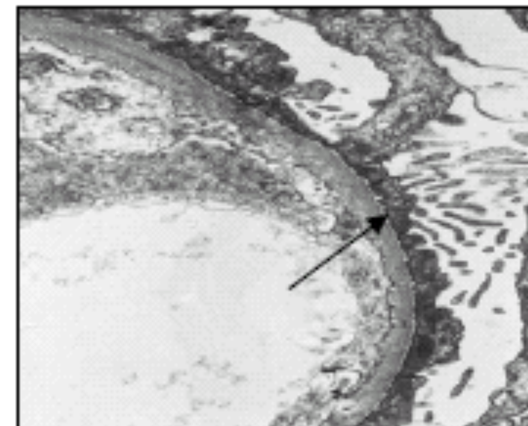
Minimal Change Glomerulopathy



Minimal change
Light microscopy



Normal Kidney
Electron microscopy

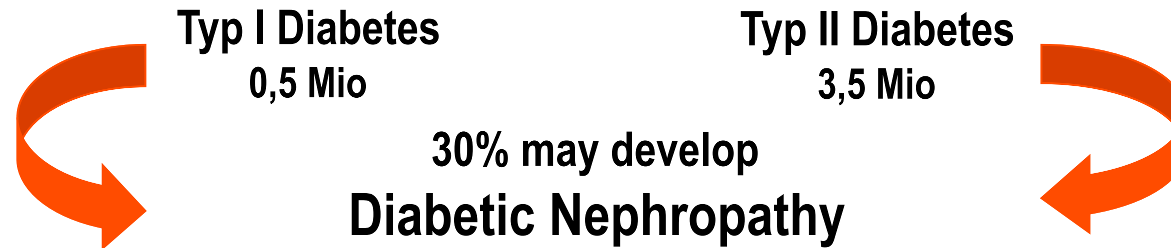


Minimal Change
EM: Fusion of foot processes

Clinical manifestation: Nephrotic Syndrome & edema
GFR normal / RR normal

Therapy: Glucocorticoids

Epidemiology of Diabetic Nephropathy (Ger)



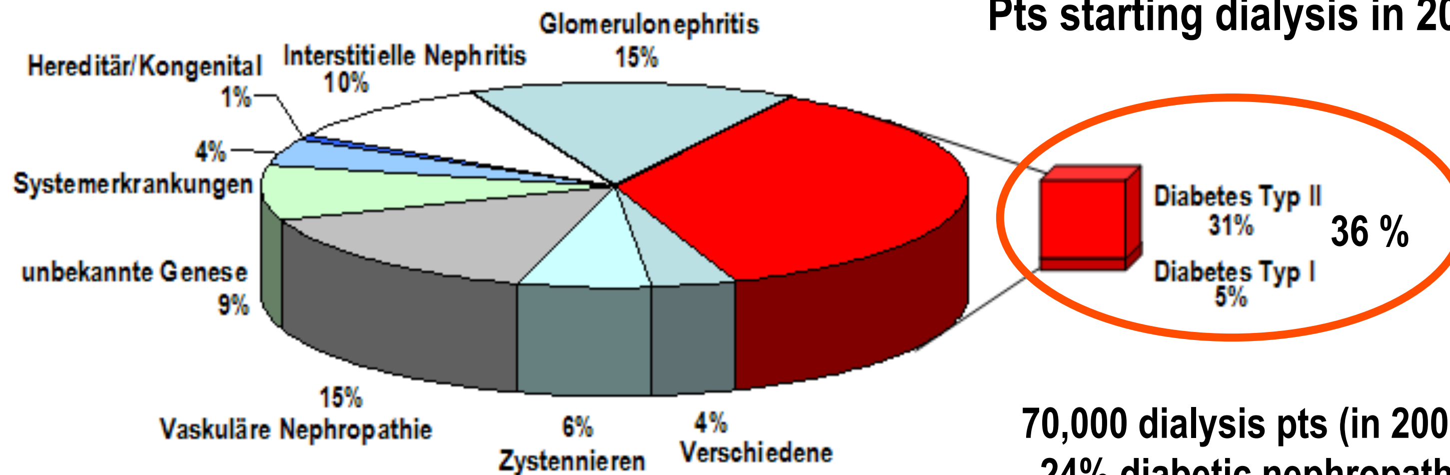
Typ I Diabetes
0,5 Mio

Typ II Diabetes
3,5 Mio

30% may develop
Diabetic Nephropathy

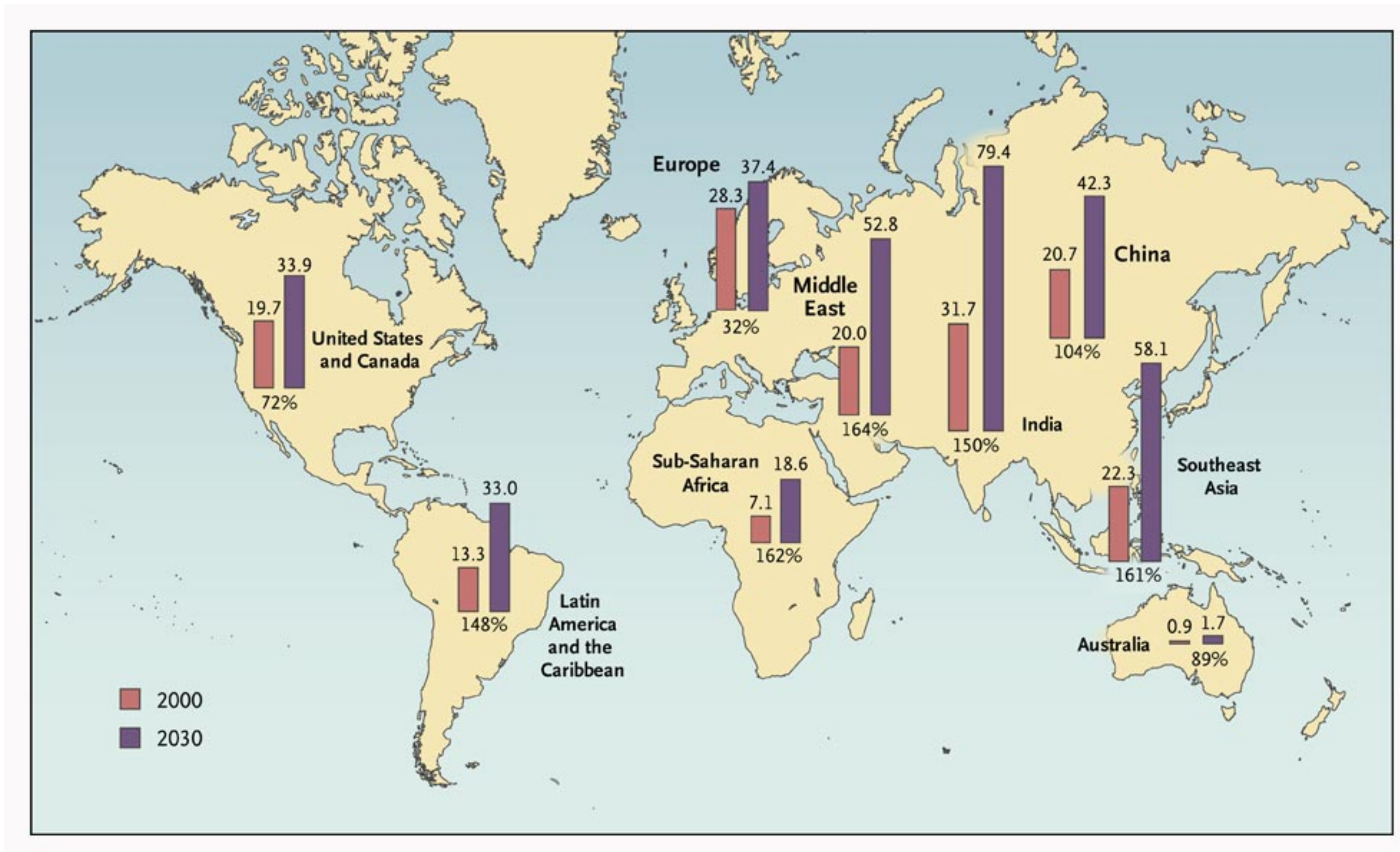
Most frequent cause of end-stage renal failure

Pts starting dialysis in 2008:



70,000 dialysis pts (in 2008):
24% diabetic nephropathy

Millions of Cases of Diabetes in 2000 and Projections for 2030



Hossain P et al. N Engl J Med 2007;356:213-215

Diabetes is not a disease of the industrialized countries any longer. There are already more cases in India than in Europe or in the US, with explosive growth rates over the next three decades.

The NEW ENGLAND JOURNAL of MEDICINE

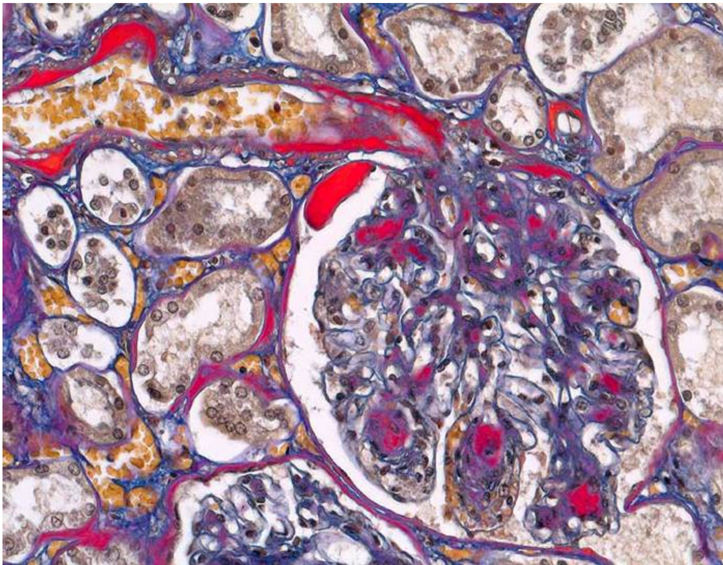
Diabetic Nephropathy

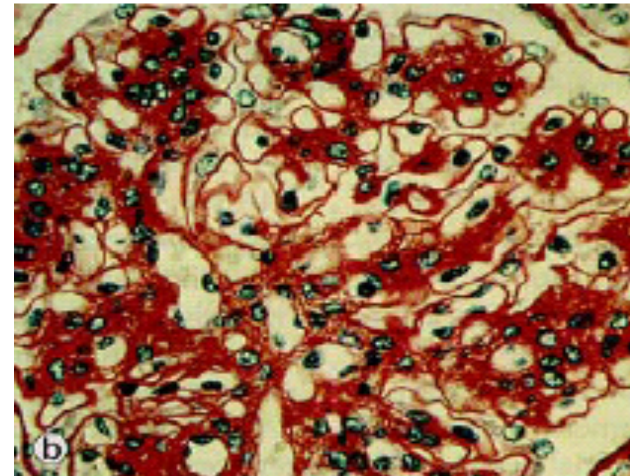
Microalbuminuria

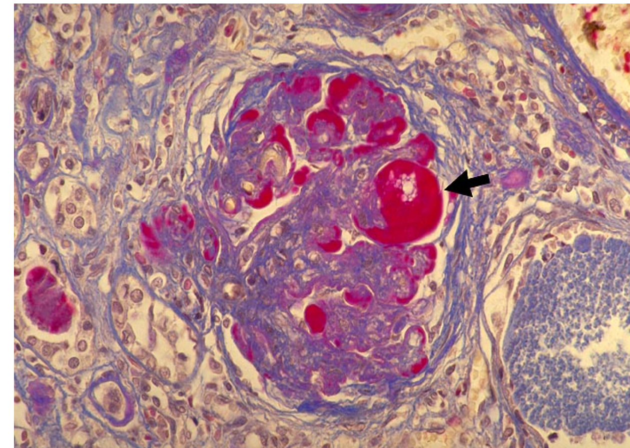
Normal albumin excretion:	**<30 mg/24h**
Microalbuminuria:	**30-300 mg/24h**
Macroalbuminuria:	**>300 mg/24h**

Microalbuminuria:
First clinical sign of diabetic nephropathy. Can also be found in pts with fever, chronic heart failure or hypertension.

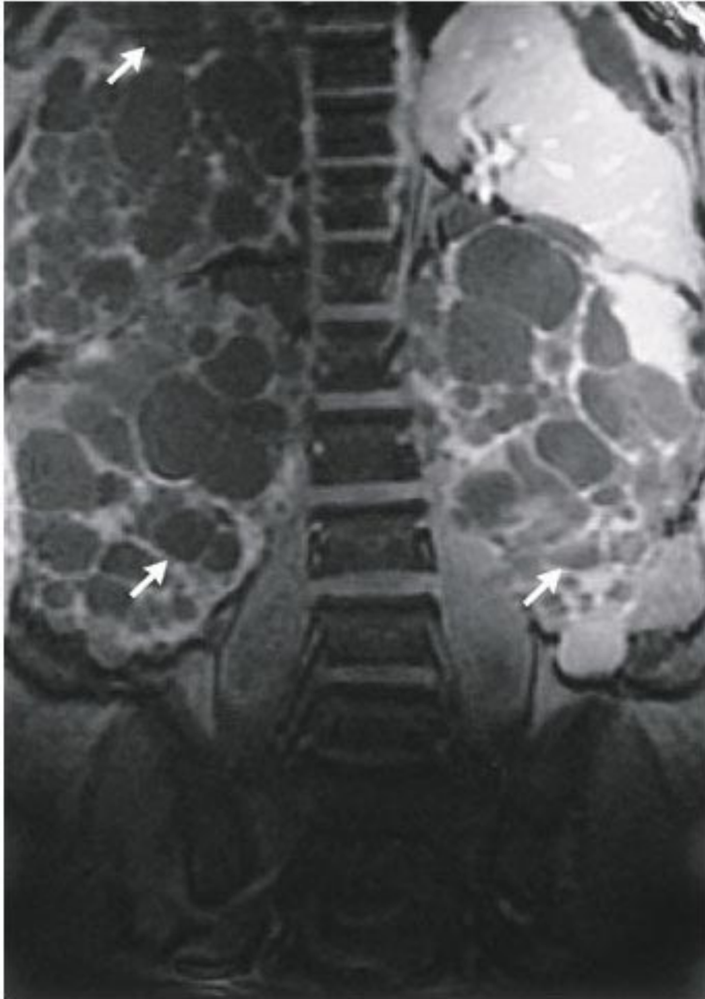
Diabetic Nephropathy
Nodular Glomerulosclerosis
Kimmelstiel-Wilson







A 45-year-old man with autosomal dominant polycystic kidney disease presented to the urology clinic for consideration of bilateral nephrectomy as treatment for severe abdominal pain and distention



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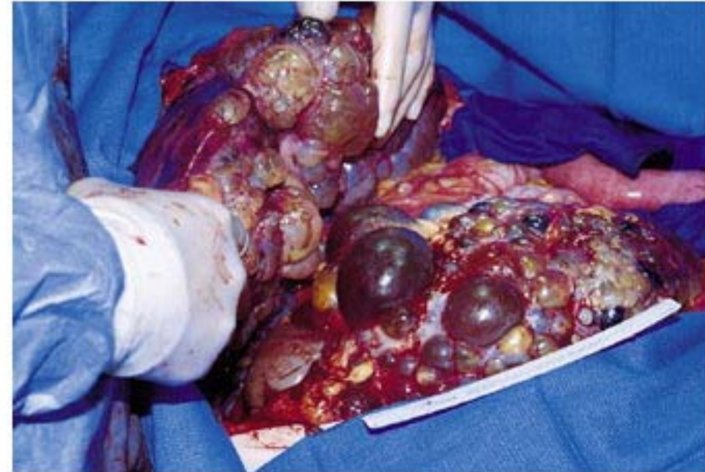
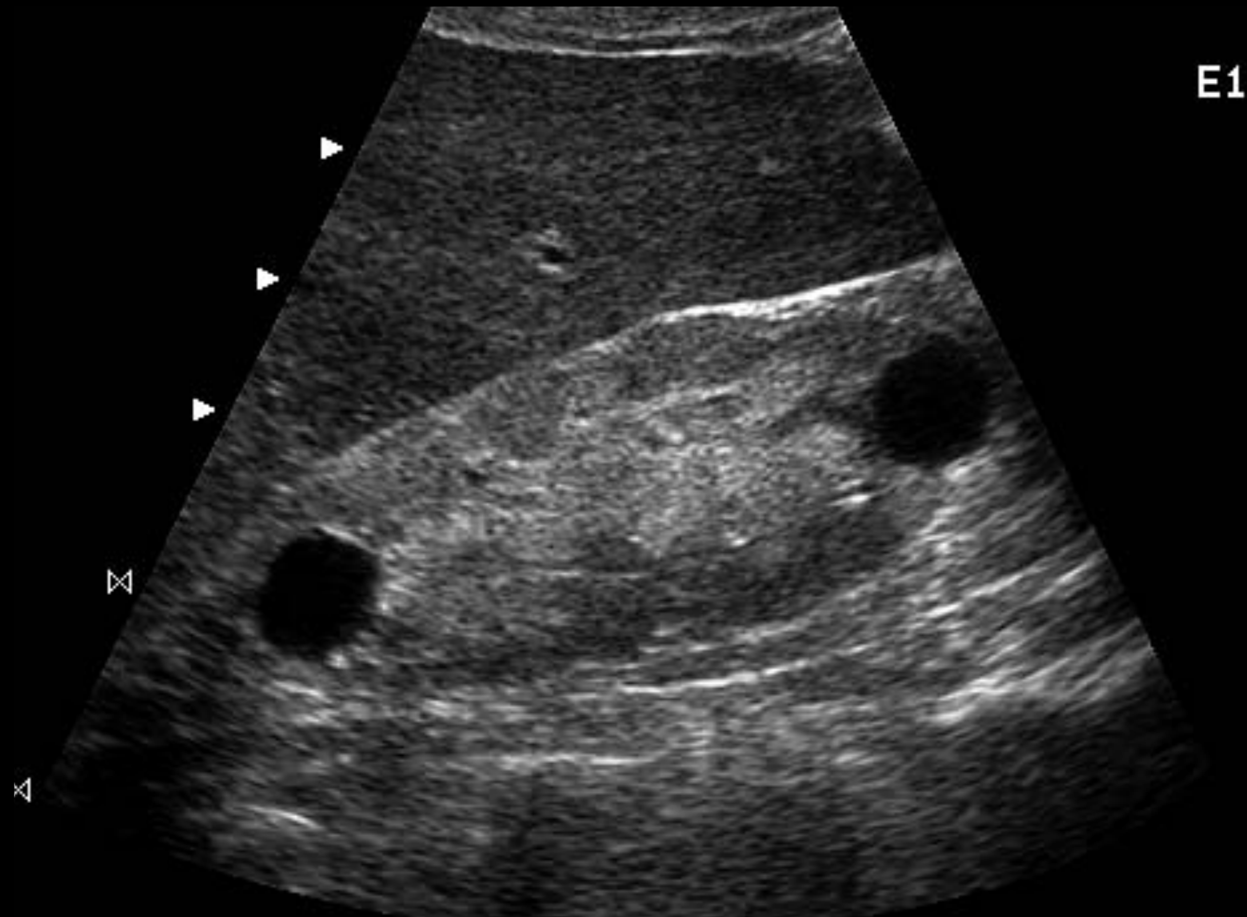


B

Brown J. N Engl J Med 347:1504, 2002

Ultrasound image of 2 simple renal cysts

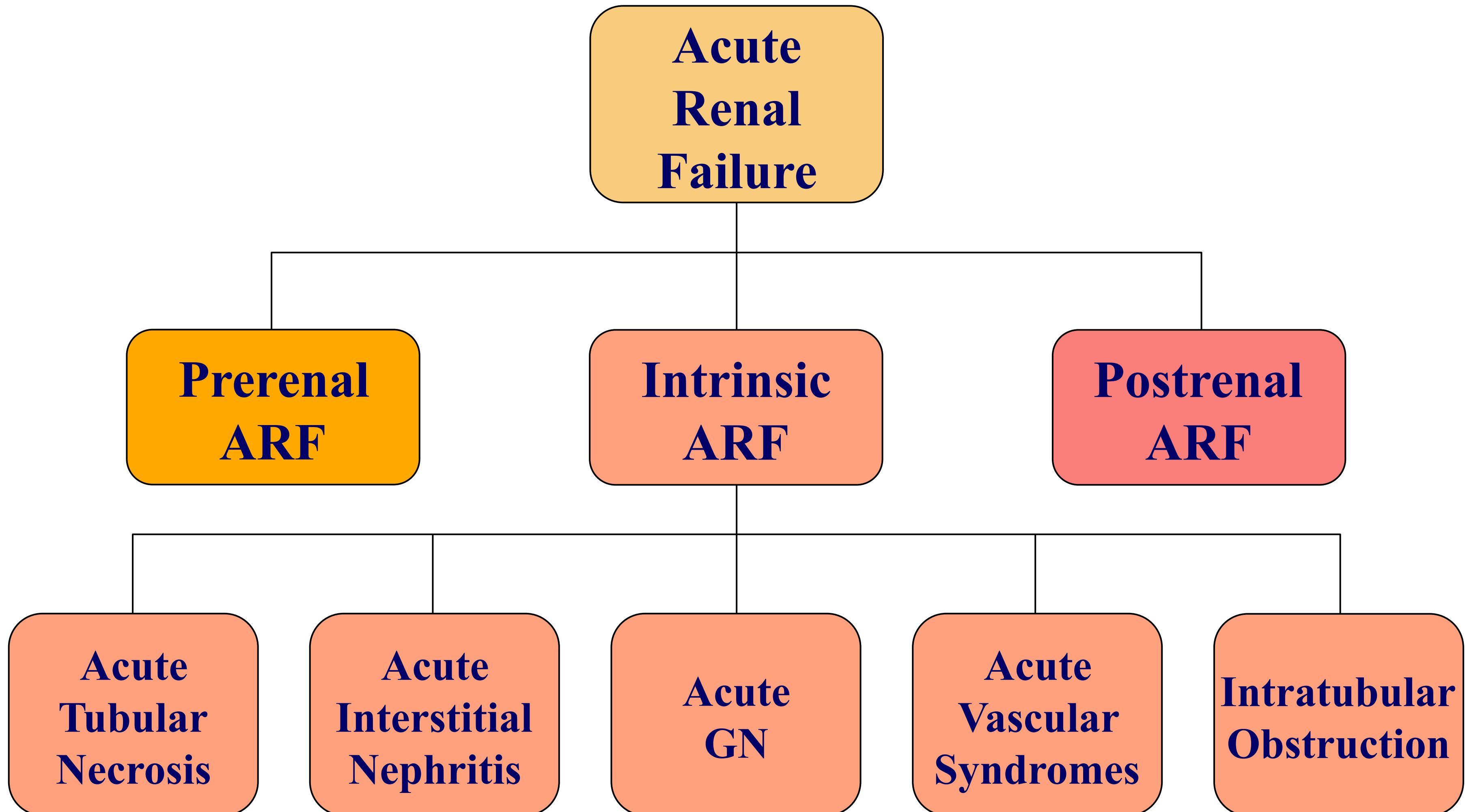


Acute Kidney Injury

Definition

- The loss of renal function (measured as GFR) over hours to days
- Expressed clinically as the retention of nitrogenous waste products in the blood

Etiologies of Acute Renal Failure



52-year old male with chills & fever on the A43 motorway

Emergency room, Sat. afternoon:

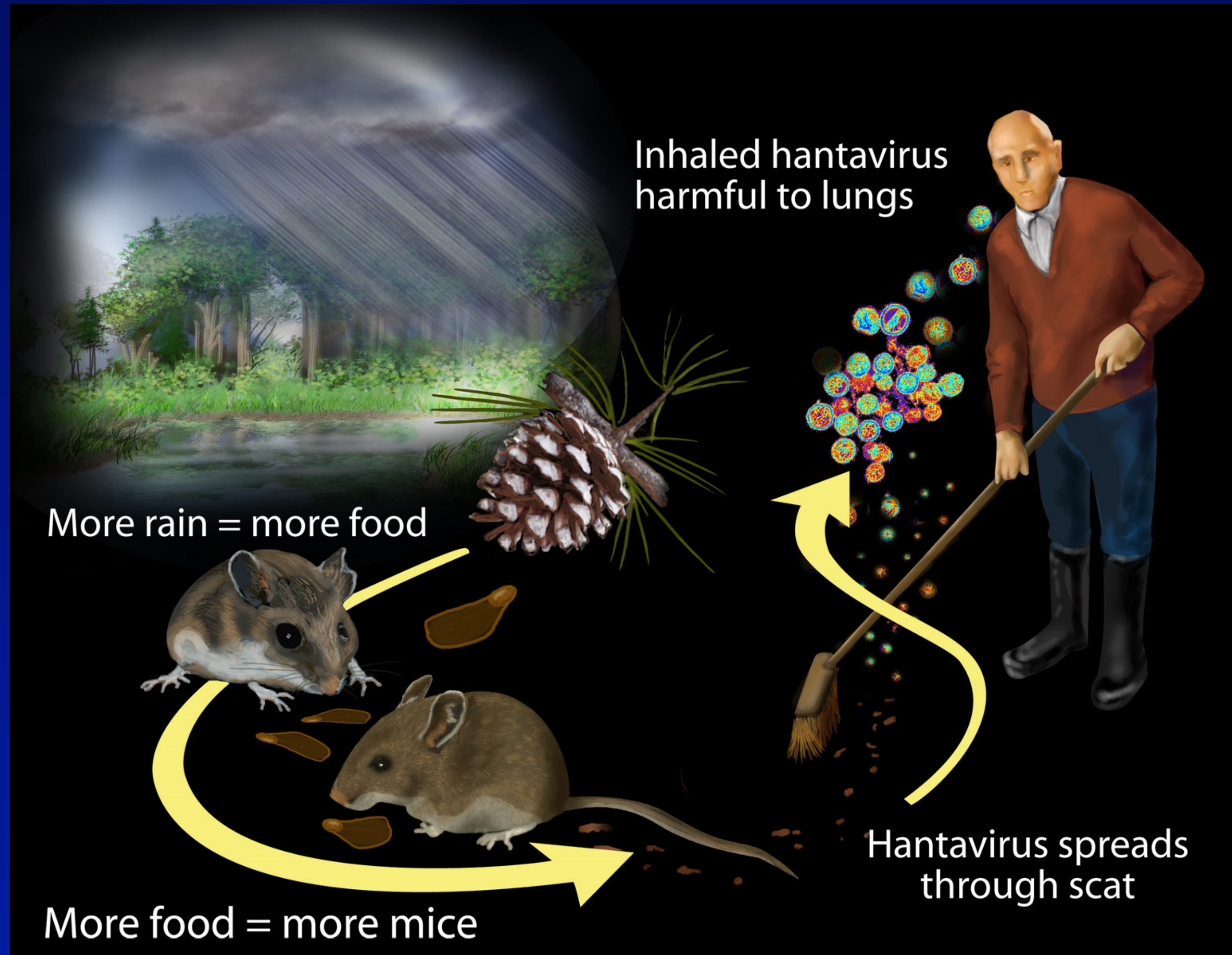
Male, 52 years, married

Last weekend: Golf Tournamant

Friday: Backpain & fever

- Crea: 3.6 mg/dl
- Urine: Leuco ++, Ery +, Protein +
- Platelets: 55.000/µl

Hanta: Transmission of Virus



Courtesy: National Science Foundation

Prerenal Acute Renal Failure

- **Volume Depletion:** Diarrhea

- **Decreased effective blood volume:**
  - Congestive heart failure
  - Cirrhosis
  - Nephrotic syndrome

ARF on the isle of Tenerife

52-year-old female:

- Diarrhea, fever & abdominal pains since 1 week
- RR: 90/60, heart rate: 95/min, dry mucous membranes
- Hb: 14.9 g/dl, CRP: 21 mg/dl, Crea: 4.5, BUN 135 mg/dl
- Potassium: 5.6 mmol/l
- Urine: normal / Na: 7 mmol/l

Obstructive acute renal failure

- **Upper tract obstruction**
  - Intrinsic
    - nephrolithiasis
    - papillary necrosis
    - blood clot
    - transitional cell cancer

- **Lower tract obstruction**
    - benign prostatic hypertrophy
    - prostate cancer
    - transitional cell cancer
    - urethral stricture
    - bladder stones
    - blood clot
    - neurogenic bladder

Each patient with acute renal failure has to undergo ultrasound imaging to exclude postrenal obstruction

Acute Renal Failure: Management

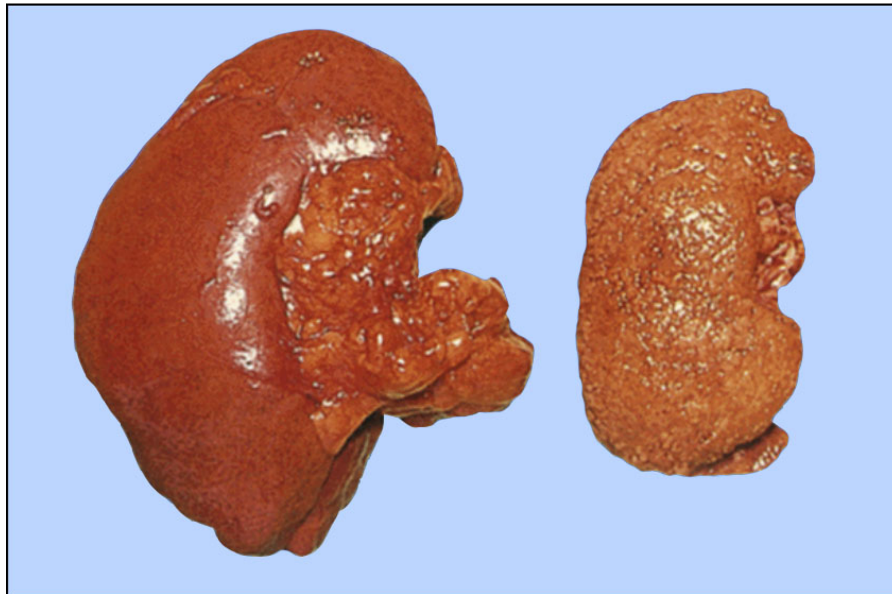
- **Prerenal ARF**
  - **Volume repletion**
  - **Inotropic support** (only if RR is not reponding to volume repletion)
  - **No diuretics**
- **Postrenal ARF**
  - **bladder catheterization**
  - **percutaneous nephrostomy or ureteral stents**
  - **fluid management during post-obstructive polyuria**

Acute Renal Failure: Management

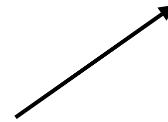
- Intrinsic ARF
  - General supportive care
    - fluid management
    - diuretics
    - bicarbonate supplementation
    - phosphate
    - drug dosing
    - Nutrition
    - Dialysis

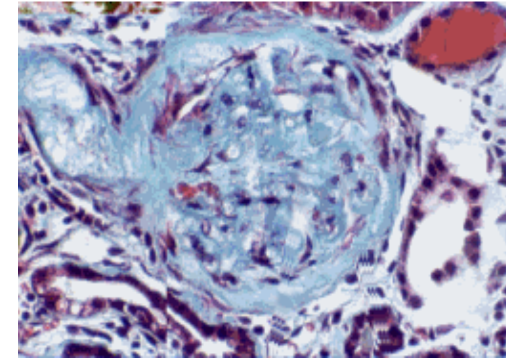
Chronic Kidney Disease

Fibrotic kidney

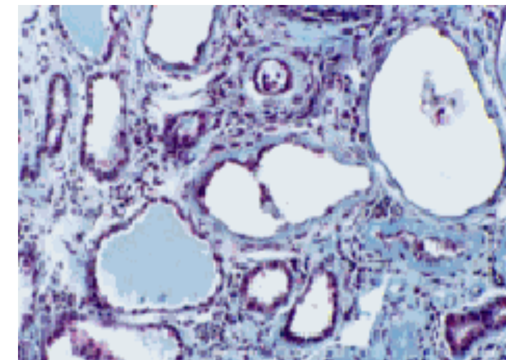


Normal kidney Atrophic kidney

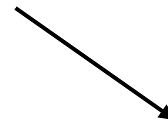


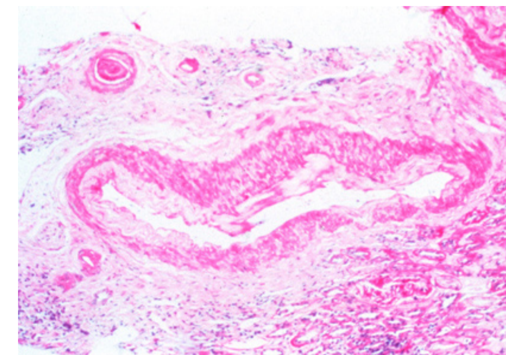


Glomerulosclerosis



Tubulointerstitial fibrosis

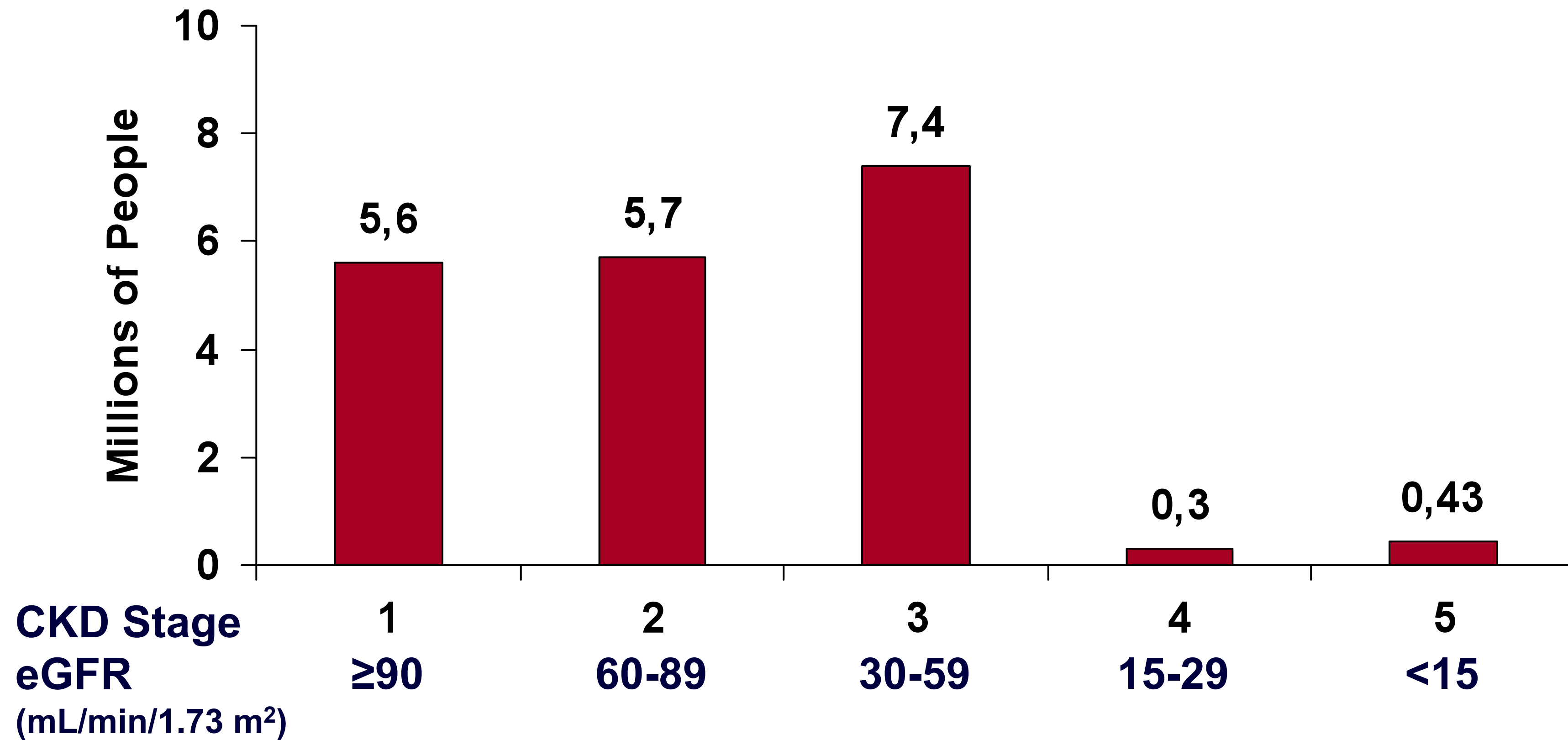




Atherosclerotic changes

Chronic Kidney Disease

12% of the adult US Population



Coresh et al. J Am Soc Nephrol. 2005;16:180-188;

WHAT ARE THE TREATMENT OPTIONS FOR THE PATIENT WITH ESRD?

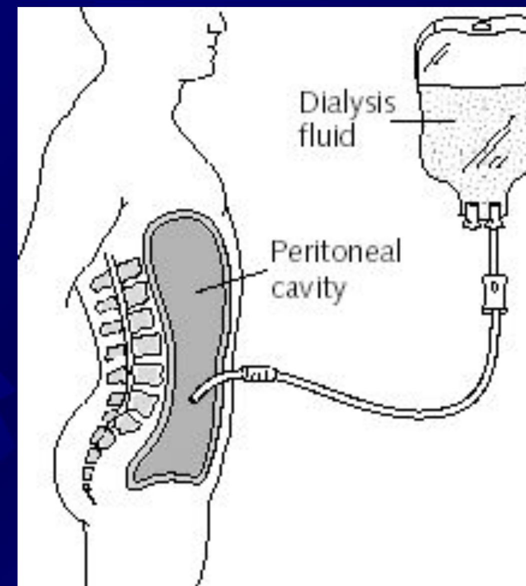
- Dialysis
  - Hemodialysis
  - Peritoneal dialysis
- Kidney transplantation

HOW DOES IT WORK?

- It is usually performed in a dialysis center 2-3x a week
- Each treatment lasts from 3-5 or more hours.
- During treatment, the patients can read, write, sleep, talk, or watch TV

HOW DOES IT WORK?

- A fluid called *dialysis solution* is put into the abdomen and captures the waste products from the blood
- After several hours, the used solution is drained from the abdomen thru the tube, taking the wastes from the blood with it. Then the patient fills his abdomen with fresh dialysis solution and the cycle is repeated.



Kidney Transplantation