BIOM9420

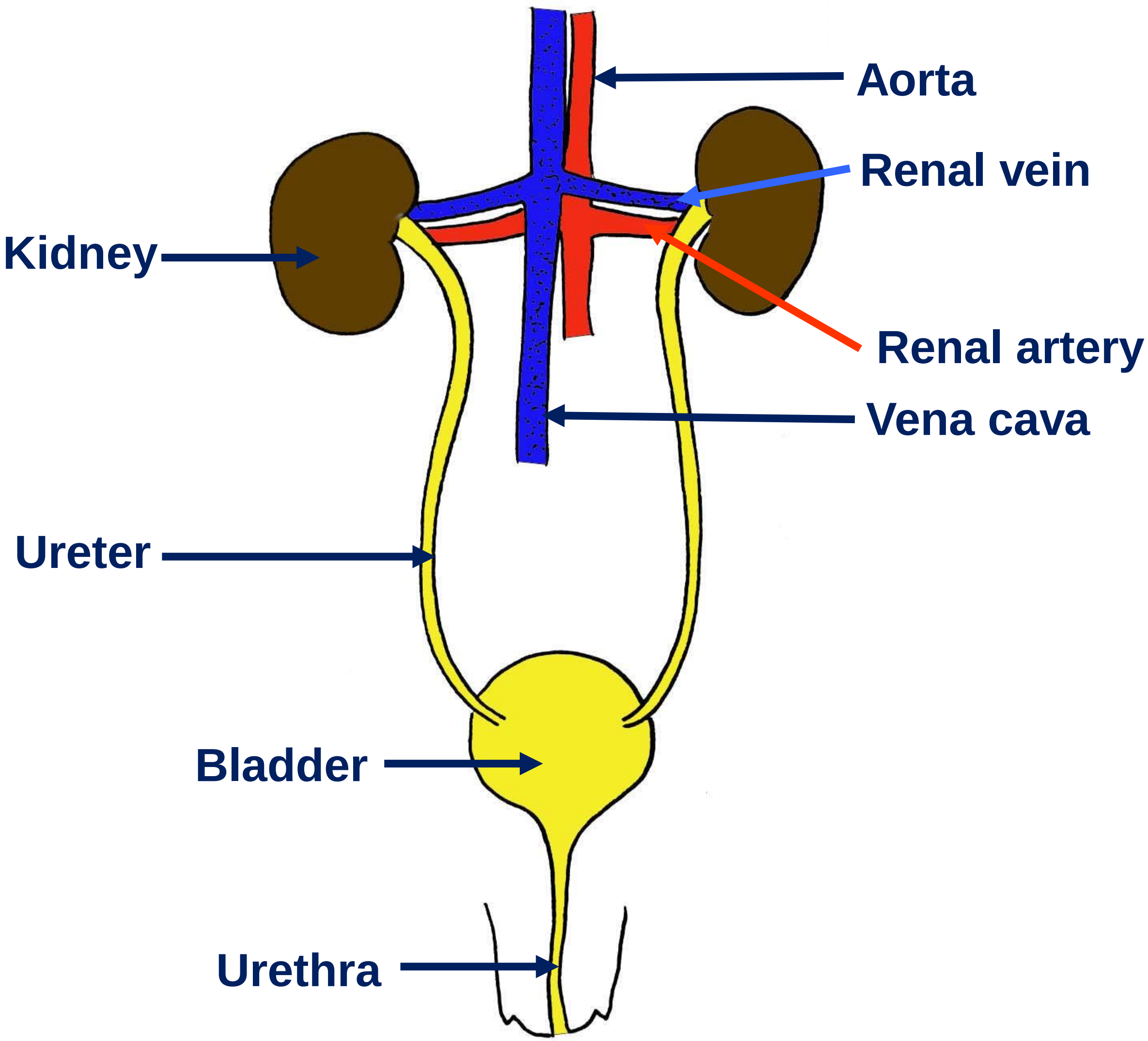
Clinical Laboratory Science

KIDNEY FUNCTION DIAGNOSTICS

DR KANG LIANG

kang.liang@unsw.edu.au

The urinary system

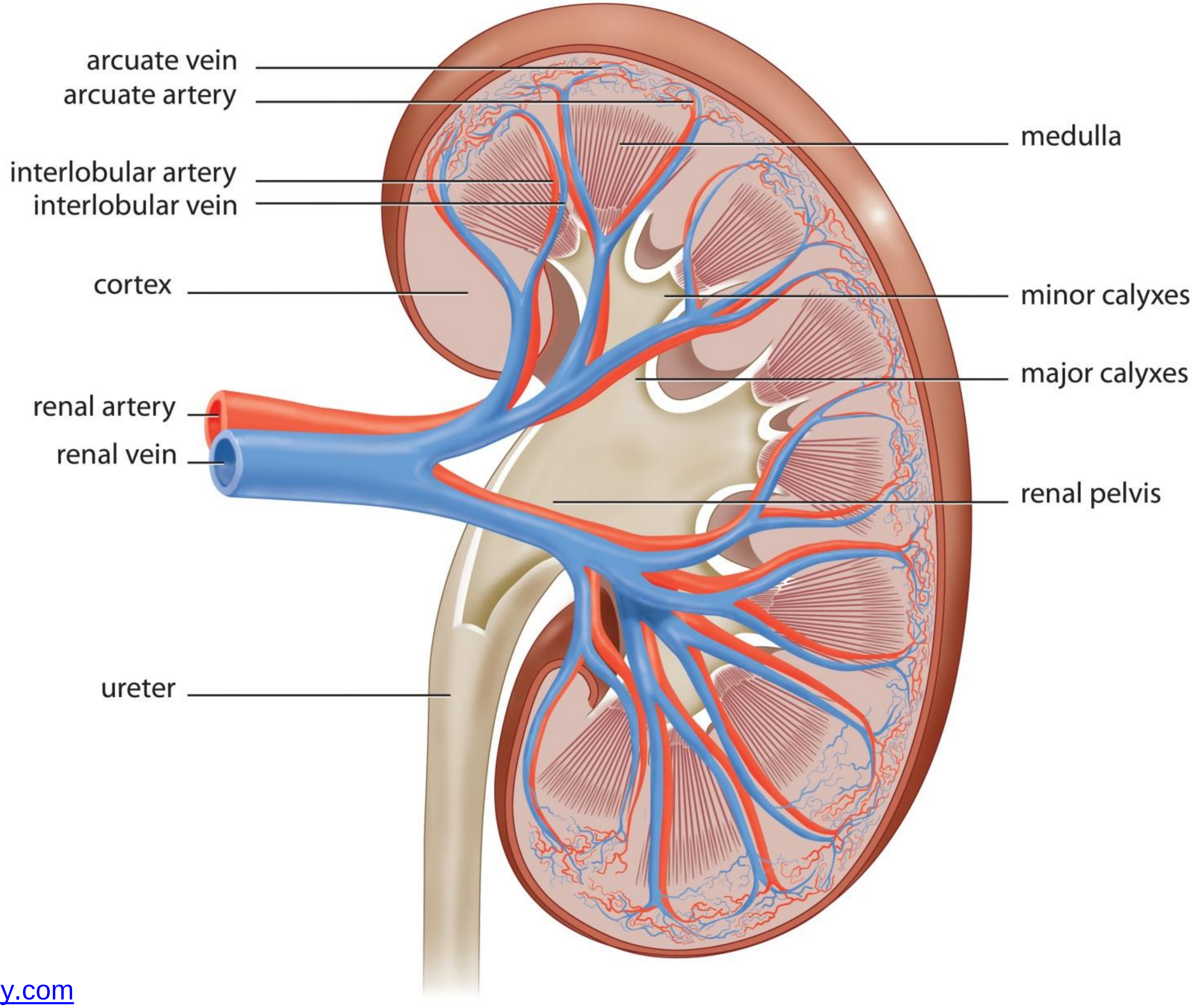


Copyright © 2016 Paul Billiet [ODWS]

Functions of the kidney

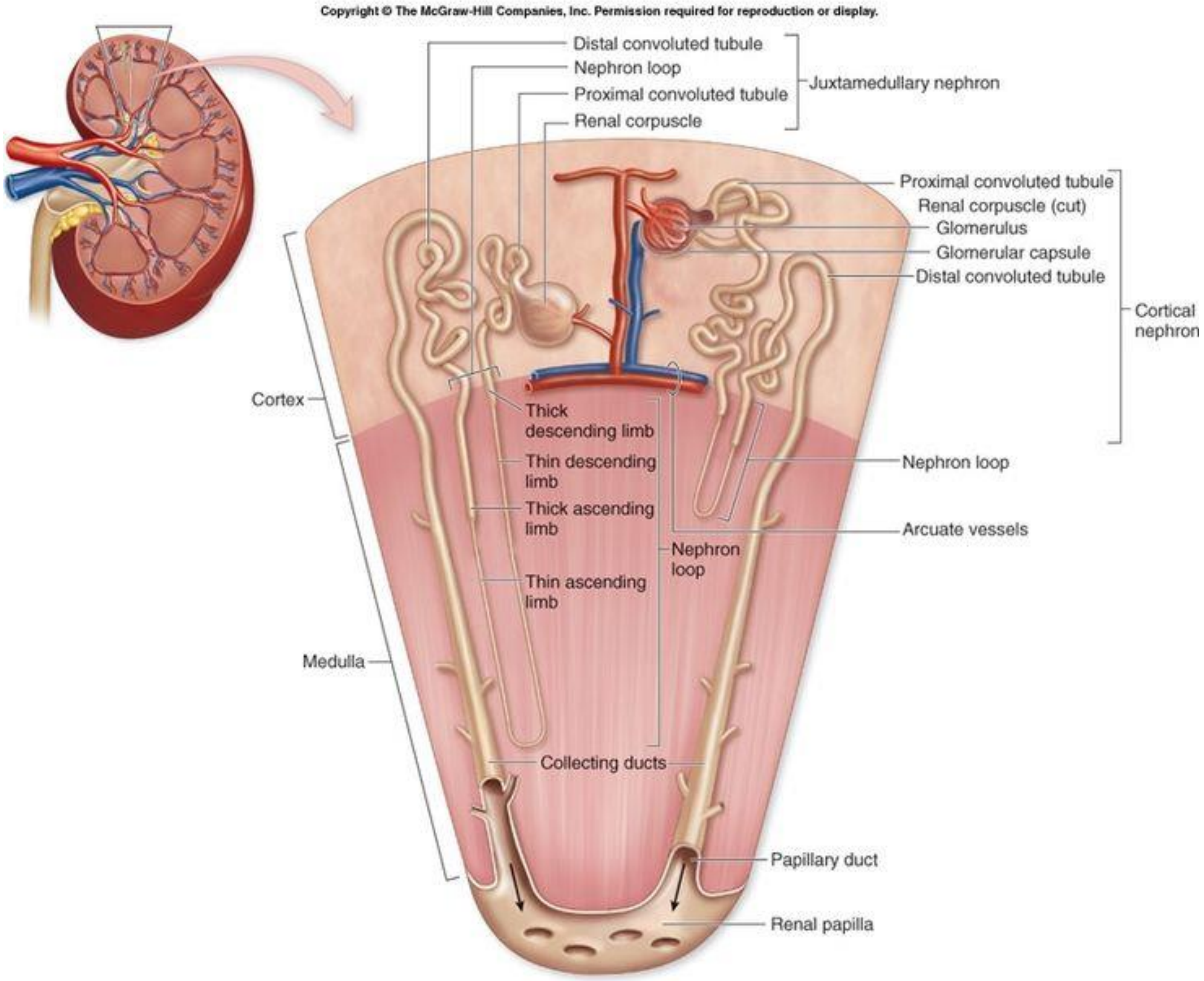
- Filtration of waste products from the blood
  - Filter a huge volume of blood – 1300 mL/min.
  - Urine output ~ 1ml/min
  - Filter out nitrogenous waste products - Urea produced by breakdown of amino acids ~10-20 mg/ dL
  - Drug and hormone elimination - Insulin and drug clearance
- Fluid and electrolyte balance
  - Acid base
  - Salts - Na^+, K^+, Ca^{2+}, Mg^{2+}
  - Regulation of extracellular fluid - blood pressure
- Endocrine functions
  - erythropoietin, calcitriol and renin
  - also contribute to the degradation of certain hormones– such as insulin (forms insulinase – cleaves insulin) or parathyroid hormone

Kidney structure



www.interactive-biology.com

Nephron

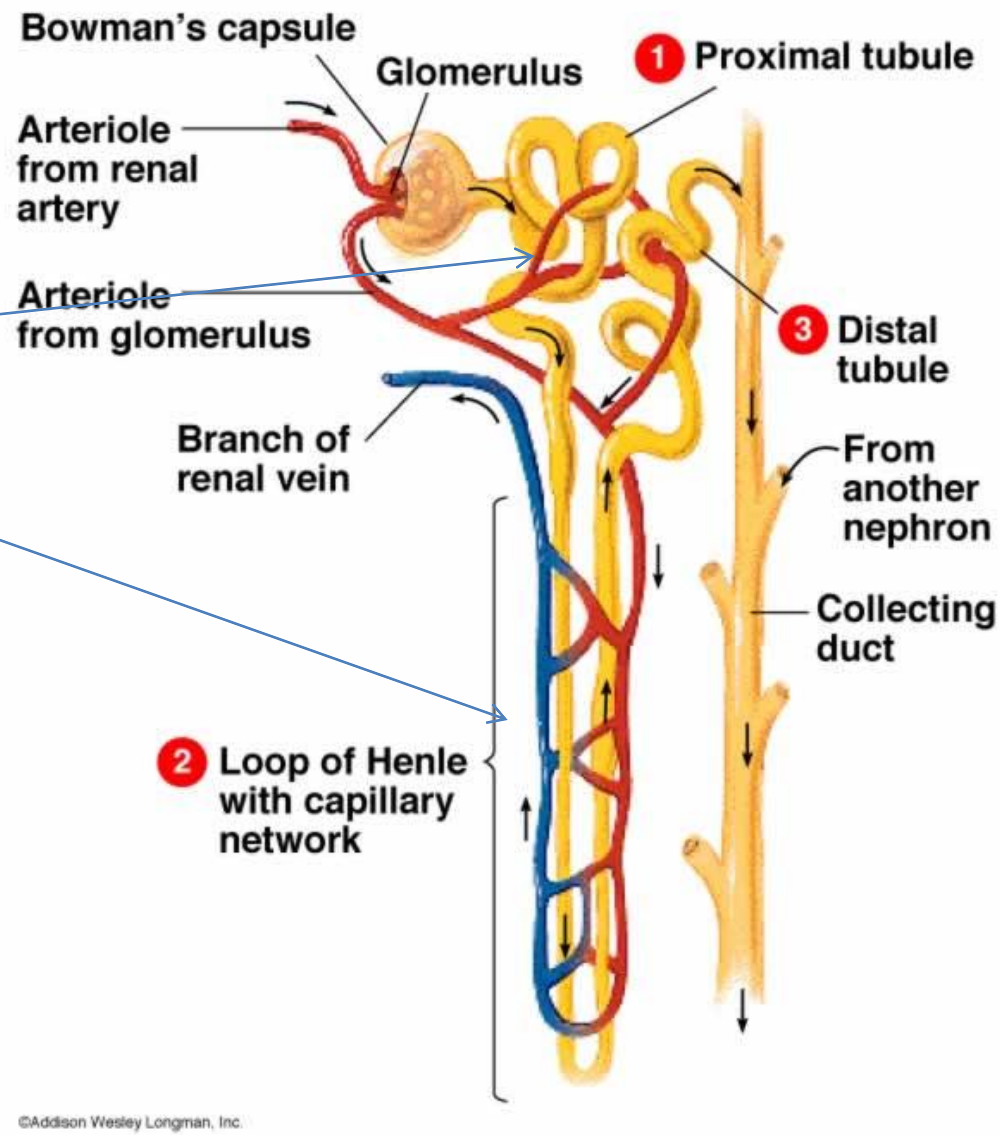


Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.
Distal convoluted tubule
Nephron loop
Proximal convoluted tubule
Renal corpuscle
Juxtamedullary nephron
Proximal convoluted tubule
Renal corpuscle (cut)
Glomerulus
Glomerular capsule
Distal convoluted tubule
Cortical nephron
Cortex
Thick descending limb
Thin descending limb
Thick ascending limb
Thin ascending limb
Nephron loop
Nephron loop
Arcuate vessels
Medulla
Collecting ducts
Papillary duct
Renal papilla

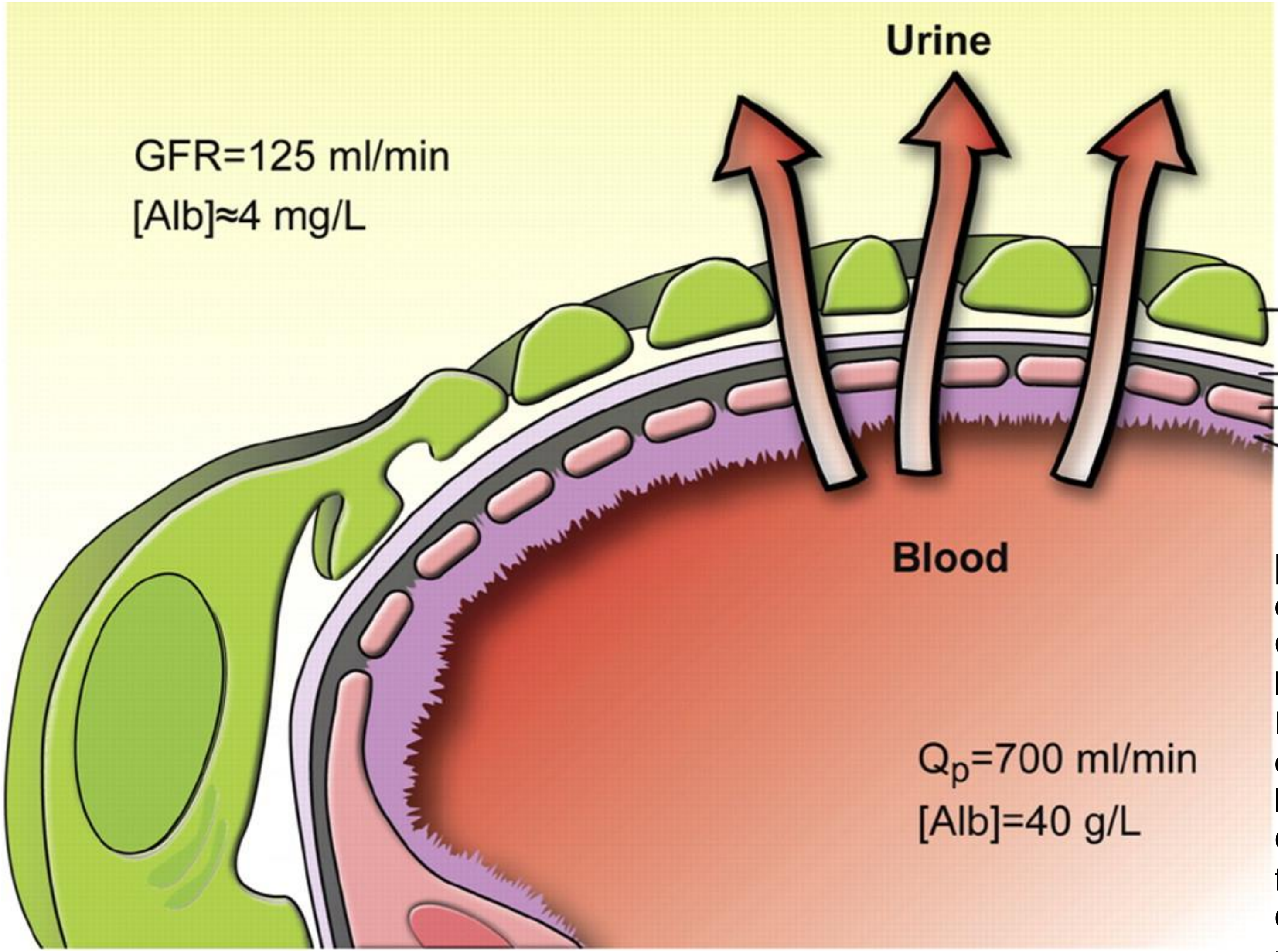
Nephron

Blood
Afferent arteriole
Glomerulus
Efferent arteriole
Peritubular capillaries
Vasa recta

Filtrate
Bowman's capsule
Proximal tubule
Loop of Henle
Distal tubule
Collecting duct



Glomerular Filtration

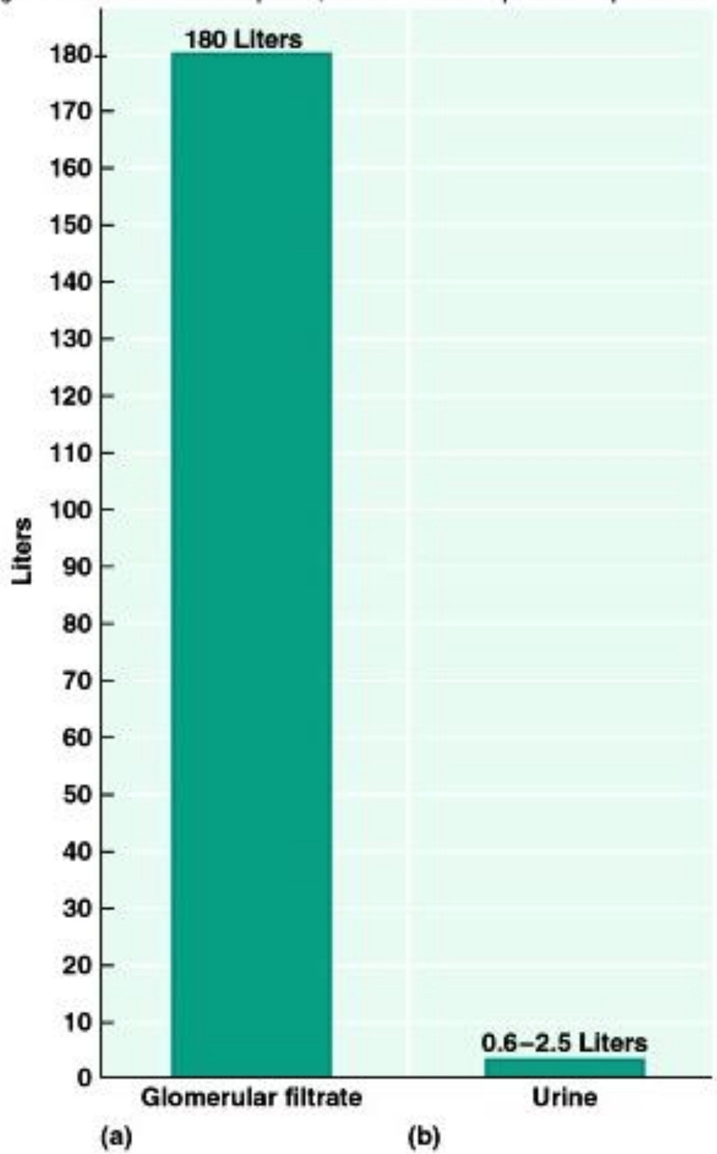


[Alb] = Albumin concentration
GBM = glomerular basement membrane
ESL = Glomerular endothelial surface layer
GFR = the glomerular filtration rate;
Q_p = the plasma flow rate

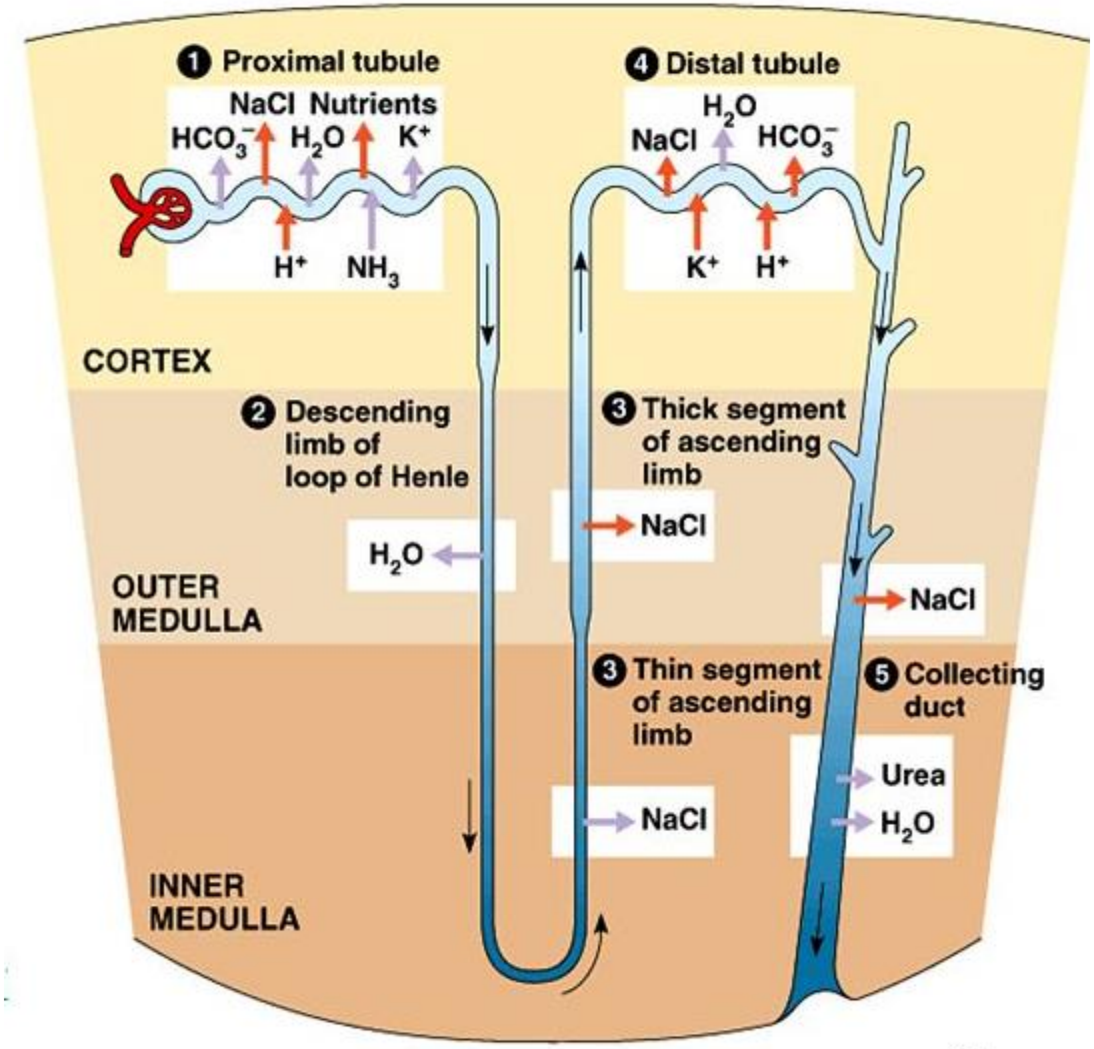
Glomerular Filtration Rate

- Volume of plasma filtered / unit time
- Approx. 180 L /day
- Urine output is about 1- 2 L /day
- About 99% of filtrate is reabsorbed

Copyright © The McGraw-Hill Companies, Inc. Permission required for reproduction or display.



Filtration and Reabsorption



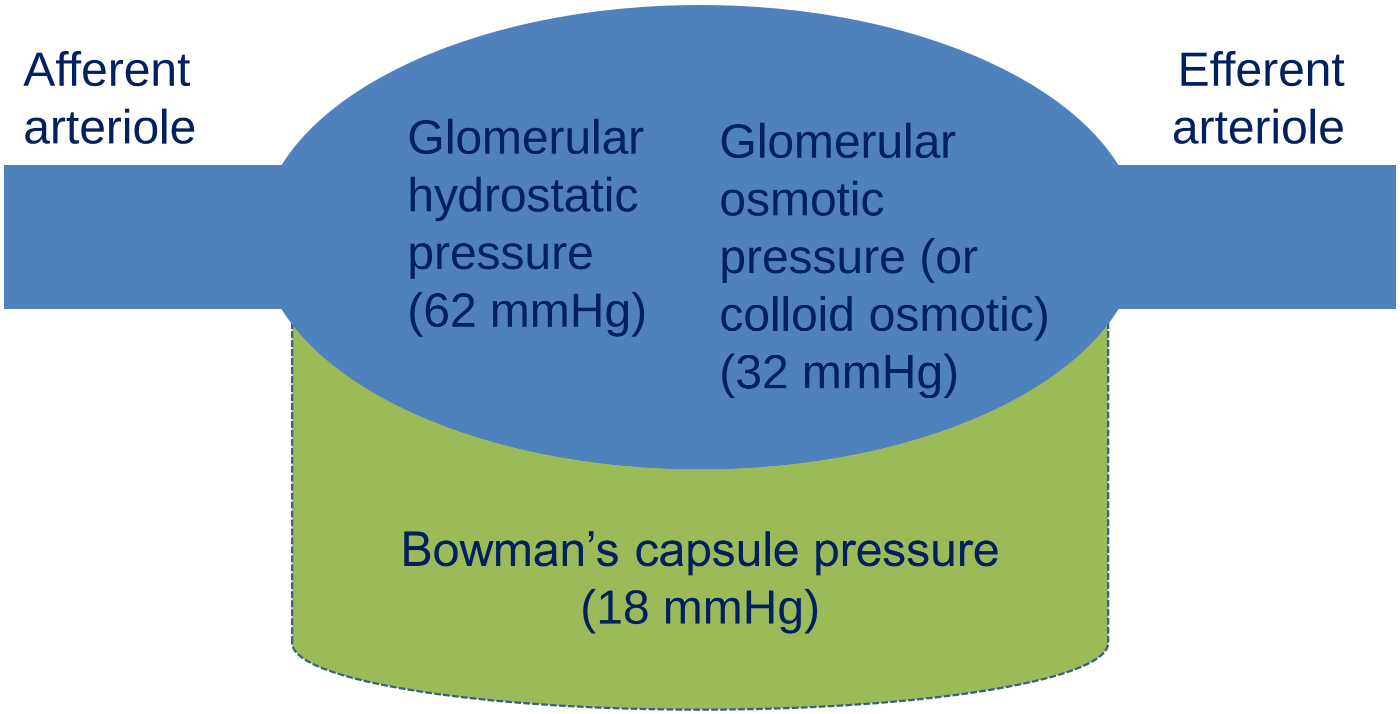
Filtration and Reabsorption

Substances Secreted or Reabsorbed in the Nephron and Their Locations (Table 5)				
Substance	**PCT**	**Loop of Henle**	**DCT**	**Collecting ducts**
Glucose	Almost 100 percent reabsorbed; secondary active transport with Na^+			
Oligopeptides, proteins, amino acids	Almost 100 percent reabsorbed; symport with Na^+			
Vitamins	Reabsorbed			
Lactate	Reabsorbed			
Creatinine	Secreted			
Urea	50 percent reabsorbed by diffusion; also secreted	Secretion, diffusion in descending limb		Reabsorption in medullary collecting ducts; diffusion
Sodium	65 percent actively reabsorbed	25 percent reabsorbed in thick ascending limb; active transport	5 percent reabsorbed; active	5 percent reabsorbed, stimulated by aldosterone; active
Chloride	Reabsorbed, symport with Na^+, diffusion	Reabsorbed in thin and thick ascending limb; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; symport
Water	67 percent reabsorbed osmotically with solutes	15 percent reabsorbed in descending limb; osmosis	8 percent reabsorbed if ADH; osmosis	Variable amounts reabsorbed, controlled by ADH, osmosis

Filtration and Reabsorption

Bicarbonate	80–90 percent symport reabsorption with Na^+	Reabsorbed, symport with Na^+ and antiport with Cl^-; in ascending limb		Reabsorbed antiport with Cl^-
H^+	Secreted; diffusion		Secreted; active	Secreted; active
NH_4^+	Secreted; diffusion		Secreted; diffusion	Secreted; diffusion
HCO_3^-	Reabsorbed; diffusion	Reabsorbed; diffusion in ascending limb	Reabsorbed; diffusion	Reabsorbed; antiport with Na^+
Some drugs	Secreted		Secreted; active	Secreted; active
Potassium	65 percent reabsorbed; diffusion	20 percent reabsorbed in thick ascending limb; symport	Secreted; active	Secretion controlled by aldosterone; active
Calcium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion		Reabsorbed if parathyroid hormone present; active
Magnesium	Reabsorbed; diffusion	Reabsorbed in thick ascending limb; diffusion	Reabsorbed	
Phosphate	85 percent reabsorbed, inhibited by parathyroid hormone, diffusion		Reabsorbed; diffusion	

Filtration and Reabsorption



Net filtration pressure (10 mmHg) = Glomerular hydrostatic pressure (62 mmHg) - Bowman's capsule pressure (18 mmHg) - Glomerular oncotic pressure (32 mmHg)

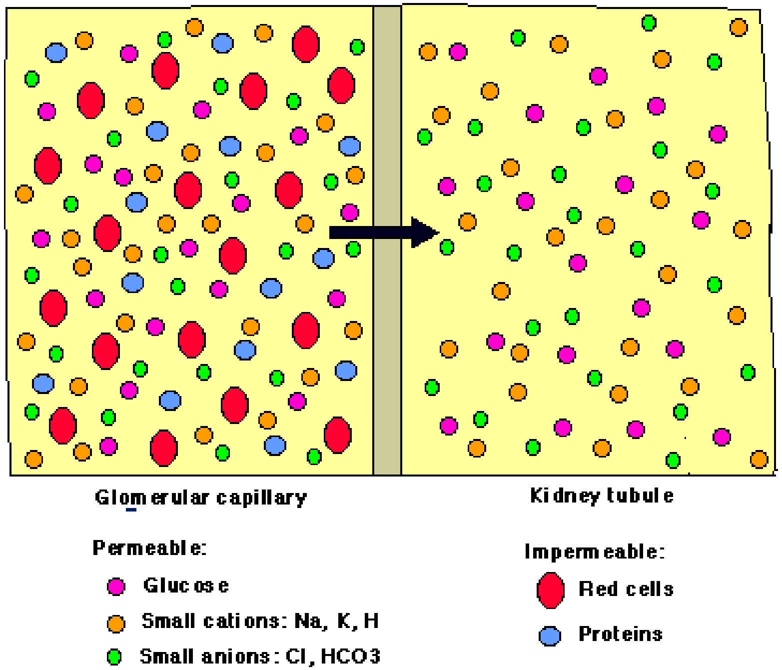
Filtration and Reabsorption

Ultrafiltration

Blood
Glucose
Amino acids
Urea
Salts
Water

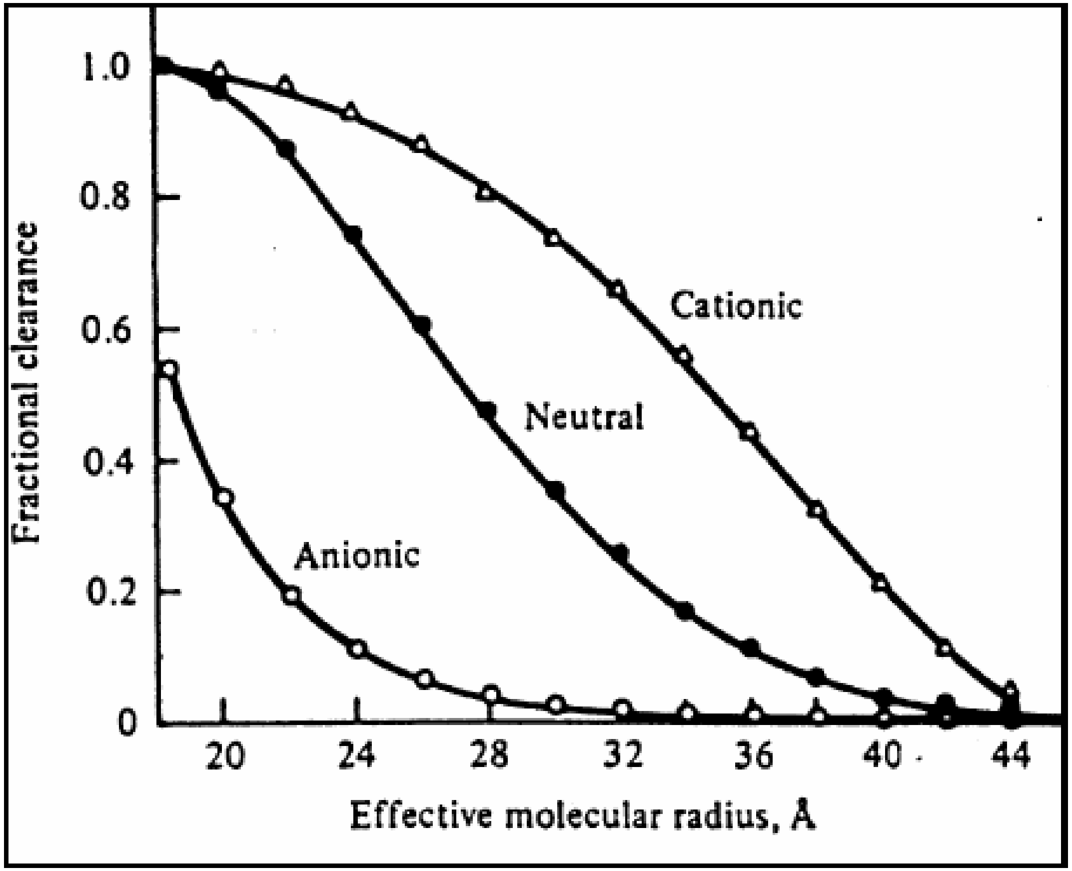
Plasma proteins
Red blood cells
Platelets

Solutes	Plasma	Filtrate
Na+ (mol/L)	151	144
Cl- (mol/L)	110	114
Glucose (mol/L)	5	5
Urea (mol/L)	5	5
Proteins (mg/L)	740	3.5



What is filtered in the glomerulus?

- Depends on size and charge.



Tubule – reabsorption and secretion

- Reabsorption
  - Na^+ : Cl^- and H_2O will follow
  - K^+, HCO_3^-
  - Amino acids
  - Glucose (although not completely if glucose transport is overloaded – diabetes)

- Mechanisms
  - Passive diffusion
  - Facilitated diffusion
  - Active transport (Na^+)
  - Co-transport
  - Counter-transport
  - Osmotic flow

Osmolarity

- Osmolar concentration of plasma and is proportional to the number of particles per litre of solution
- The body is a collection of compartments separated by semipermeable membranes.
- Water will flow among them until the osmotic pressure is the same in all.
- The normal osmolarity of body fluids is 0.3 osmoles/L

 (this is equivalent to a pressure of about 7 atm)

Isotonic saline = 9 g/L Na Cl

Hypertonic are more concentrated.

Hypotonic are less concentrated.

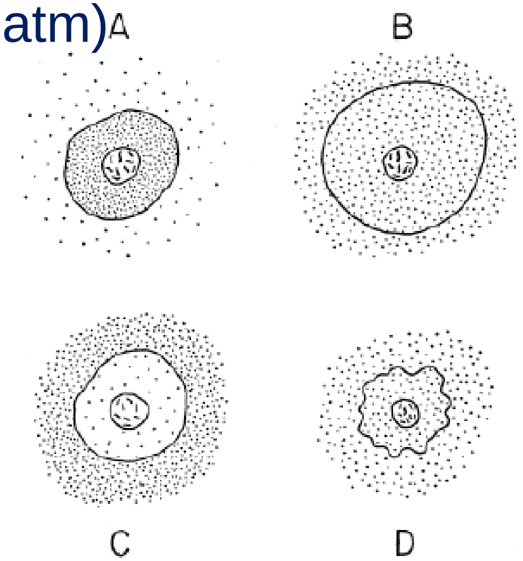


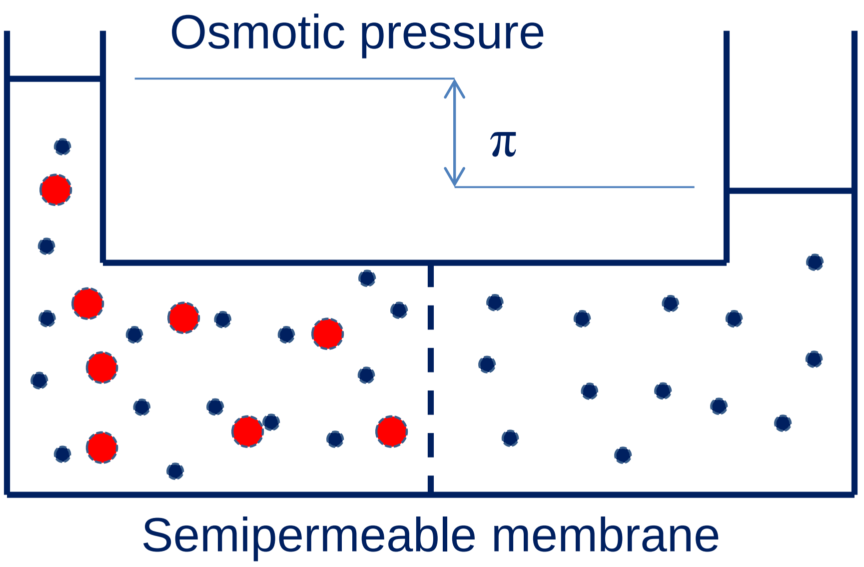
Figure 33–7. Establishment of osmotic equilibrium when cells are placed in a hypo- or hypertonic solution.

Oncotic pressure

If the pores are large compared to solutes such as NaCl, but comparable to or smaller than plasma proteins, only the proteins can induce an osmotic flow.

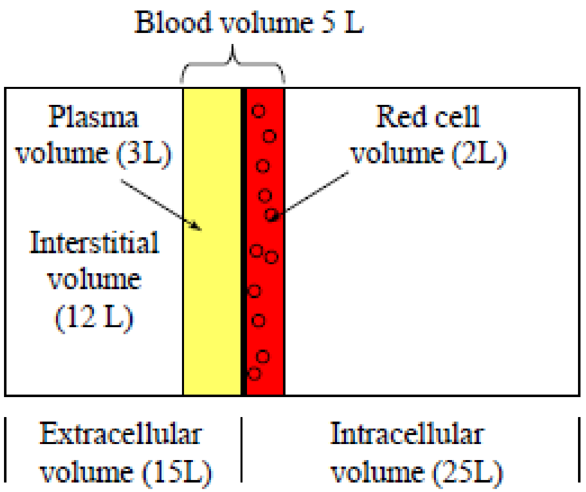
The osmotic pressure due to plasma proteins is called the oncotic pressure and is normally ~ 25 mmHg.

The protein concentration in interstitial fluid is lower. This difference is important in maintaining proper hydration of tissues



Body fluids/compartments

- Body fluids can be divided into
  - Intracellular/extracellular
  - Intravascular/extravascular
  - Interstitial (extravascular and extracellular)

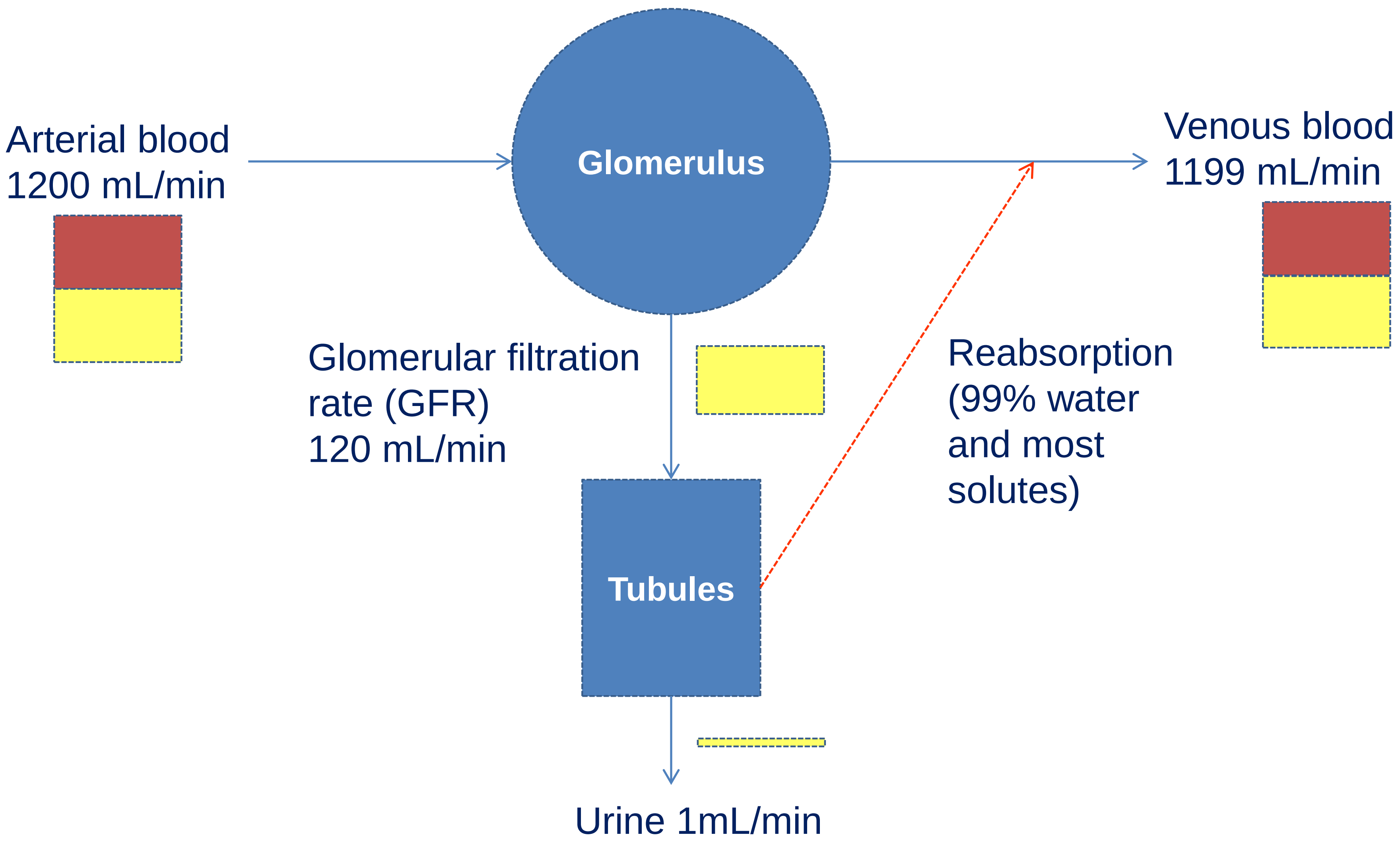


- The membrane separating intra/extracellular is ~ perfectly semipermeable.

- All solutes are osmotically active.

- The barrier separating intra/extravascular is more porous. Small solutes pass through gaps easily but passage of proteins is restricted. Therefore only large solutes (proteins) are osmotically active.

Overview of kidney function



Kidney diseases

- **Nephritis** – inflammation of the kidney
- **Nephrotic syndrome** – proteinuria (more protein in the urine). Caused by large pores in the epithelium of the glomeruli (podocytes).
- **Nephritic syndrome** – proteinuria and haematuria (blood and protein in the urine). Caused by large pores in the epithelium of the glomeruli (podocytes)
- **Glomerulonephritis** – inflammation of the glomeruli. Indicated by haematuria and/or proteinuria, nephrotic syndrome, nephritic syndrome.

Kidney diseases

- **Diabetic nephropathy** – disease of the capillaries of the glomeruli. Nephrotic syndrome. A major cause of renal failure and the need for dialysis.

- **Interstitial nephritis** – infection or reaction to drugs (e.g. antibiotics). Affects the interstitium surrounding the tubules. Signs are systemic – fever.

- **Pyelonephritis** –Urinary tract infection that usually starts in the lower urinary tract, caused by bacteria enter the body through the urethra and begin to multiply and spread up to the bladder. From there, the bacteria travel through the ureters to the kidneys. Indicated by white blood cells in urine.

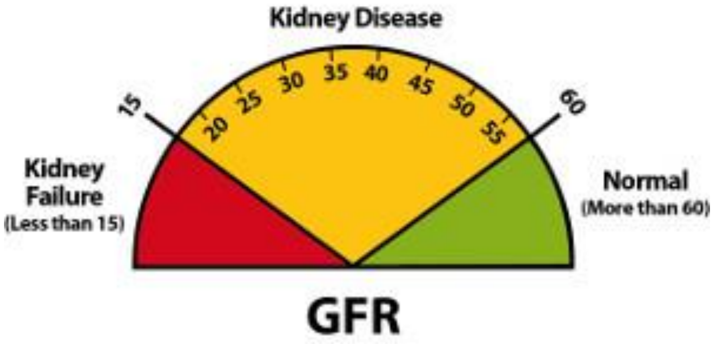
Acute renal failure

- Rapid loss of renal function. May be reversible.
- Signs
  - Oliguria or anuria (little or no urine)
  - Levels of waste N products in the blood are elevated.
  - Change in acid/base balance
  - K retention
  - Fluid retention

- Diagnosis – elevated serum creatinine and urea
- Causes:
  - Pre-renal – related to blood supply – hypotension due to shock, dehydration
  - Intrinsic: damage to the kidney
  - Post-renal: obstruction of the urinary tract

Chronic renal failure

- Progressive loss of renal function as indicated by the glomerular filtration rate (GFR).
- Causes:
  - Diabetic nephropathy
  - Hypertension
  - Glomerulonephritis
- Detection
  - Increase in serum creatinine and urea
  - Increase in serum K levels
  - Fluid volume overload
- Classify severity according to GFR:
  - Stage 4: GFR : 15-30ml/min (get ready for dialysis)
  - Stage 5: GFR: <15 ml/min (requires dialysis)



Diagnostics

- What is in blood or serum?
  - Urea
  - Sodium
  - Bicarbonate
  - Creatinine
  - Potassium
  - Glucose

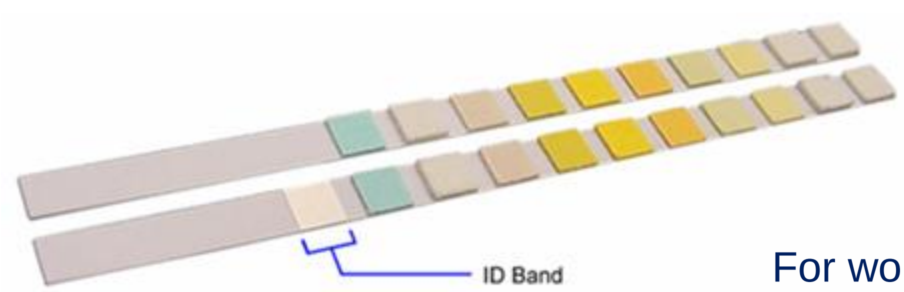
- Anything in urine that shouldn’t be there?
  - Protein
  - Red blood cells
  - White blood cells
  - Glucose

- Renal function tests
  - GFR

Multistix - Urinalysis

SIEMENS Multistix 10 SG strips for urinalysis provide a fast, convenient way of testing 10 separate reagents in urine. These include testing for:

Glucose
Bilirubin
Ketone
Specific Gravity
Blood
pH
Protein
Urobilinogen
Nitrite
Leukocyte Esterase



For working principles visit:
https://en.wikipedia.org/wiki/Urine_test_strip

Renal clearance (K_i) of a species

- Clearance is the rate at which a species, i, is excreted by the kidneys (E_i) divided by its concentration in plasma (C_i).
- Candidate markers for GFR:
  - Urea
    - Endogenous product of protein intake
    - Filtered and absorbed
    - Synthesis varies with diet.
  - Creatinine
    - An endogenous product of muscle metabolism
    - Near constant production
    - Filtered, but some secreted
  - Inulin (an inert carbohydrate)
    - Filtered only
    - Not made by body; must be injected

Urea

- Used historically as a marker of GFR
- Freely filtered but both re-absorbed and excreted into urine
- Reabsorption into blood increased with volume depletion, can therefore underestimate GFR
- Diet, drug, disease affect urea production
- Product of protein catabolism
- Reabsorbed in proximal tubule

Serum creatinine concentration

- Measures the level of creatinine in the blood
- A breakdown product of creatine phosphate released from skeletal muscle at a steady rate.
- Filtered by the glomerulus
- Normal value 0.6 to 1.2 mg/dL
- Inversely proportional to GFR
- Good way to follow changes in GFR
- Increased values indicate:
  - Impaired renal function
  - High protein diet
  - Large muscle mass (body builders)
  - Drugs

Creatinine Clearance

- Measure serum and urine creatinine levels and urine volume and calculate serum volume cleared of creatinine.
- Same issues with serum creatinine, except muscle mass.
- 24 h urine collection to determine creatinine (Cr) clearance:

$$Cr\ clearance = \frac{Cr\,\dfrac{excreted}{unit\_time}}{[Cr]_{serum}} = \frac{[Cr]_{urine} \times V}{[Cr]_{serum}}$$

- This represents the volume of serum completely cleared of creatinine per unit time
- This closely approximates GFR as almost all creatinine is cleared via glomerular filtration although it is not an exact measure of GFR as some is not filtered and some is secreted into the proximal tubule.
  - When GFR is below 30 mL/min, the tubular secretion exceeds the amount filtered and can give a false elevation.

Creatinine clearance example

- $[Cre]_{urine}$ = 72 mg/dL
- $[Cre]_{serum}$ = 2 mg/dL
- V = 2 L
- Time = 24 h

$$Cr\ clearance = \frac{72\,\frac{mg}{dL} \times 2L/day}{\frac{2mg}{dL}} = 72\,\frac{L}{day} = 50\ mL/min$$

Creatinine clearance

- Can estimate creatinine clearance from the plasma creatinine concentration
- Many empirical formulae available:
- Eg Cockcroft-Gault formula adjusts for body weight, age and sex:

$$Creatinine\ clearance = \frac{(140 - age) \times mass\ (kg)}{72\ \times serum\ creatinine\ (\frac{mg}{dL})} \times 0.85\ (if\ female)$$

- Useful for initial diagnosis, accuracy not great.

Renal clearance (K_i) of a species

- This is a measure of GFR when using an ideal tracer:
  - An ideal tracer for GFR is:
    - Easily passed by the glomerulus
    - Not secreted or reabsorbed in the tubules
    - Only eliminated by the kidneys
    - Not metabolised
    - Not retained (100% eliminated)

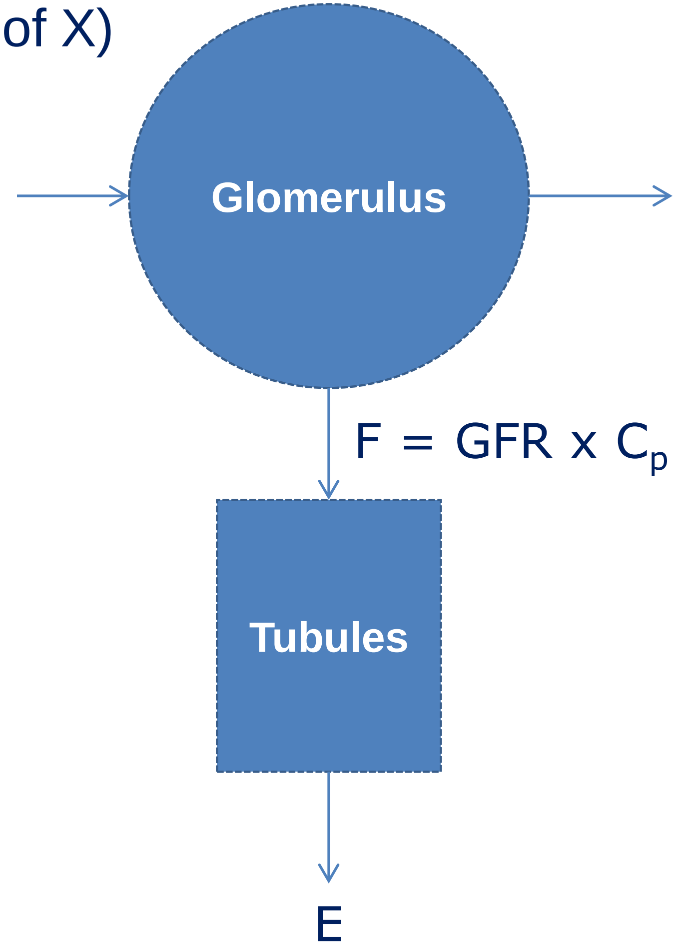
- Ideal tracers include:
  - Inulin (sugar with molecular mass 5500)
  - ^{51}Cr-EDTA

GFR using an ideal tracer

Filtered load, F = GFR x plasma concentration of X

Excretion, E = F (no reabsorption of X)

Therefore, K = GFR



GFR using an ideal tracer

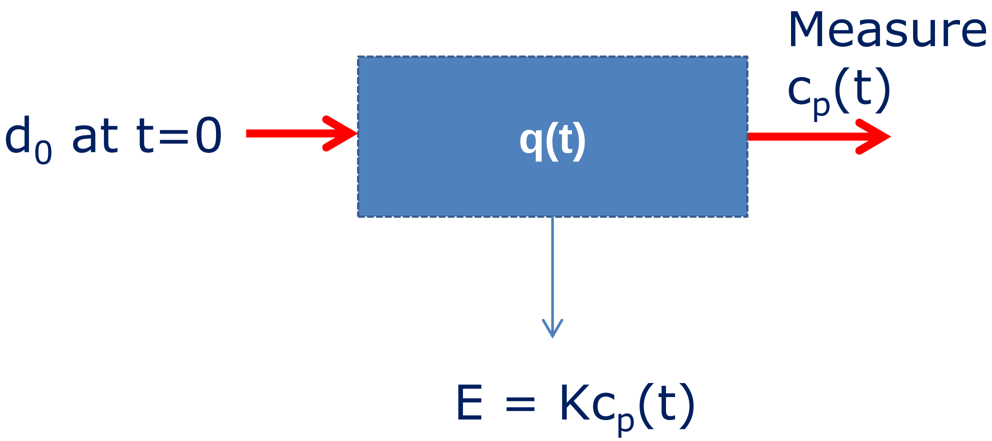
Inject an amount, d_0, of the tracer intravenously.

Starting 5-10 min after injection, take blood samples and measure the concentration of the tracer in the plasma, $c_p(t)$.

Let q(t) be the amount of tracer remaining in the system at time *t*.

Material balance:

Rate of accumulation = Rate of input - Rate of output + Rate of production - Rate of consumption



GFR using an ideal tracer

Rate of input = 0?

Rate of output = $Kc_p(t)$ (no other excretion route)

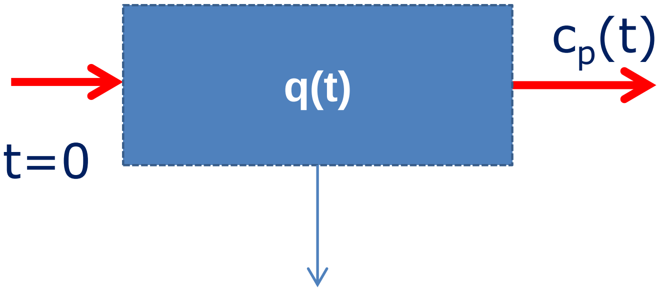
Rate of production = 0 (tracer is exogenous)

Rate of accumulation = $\frac{dq}{dt}$

Rate of accumulation = Rate of input - Rate of output + Rate of production - Rate of consumption

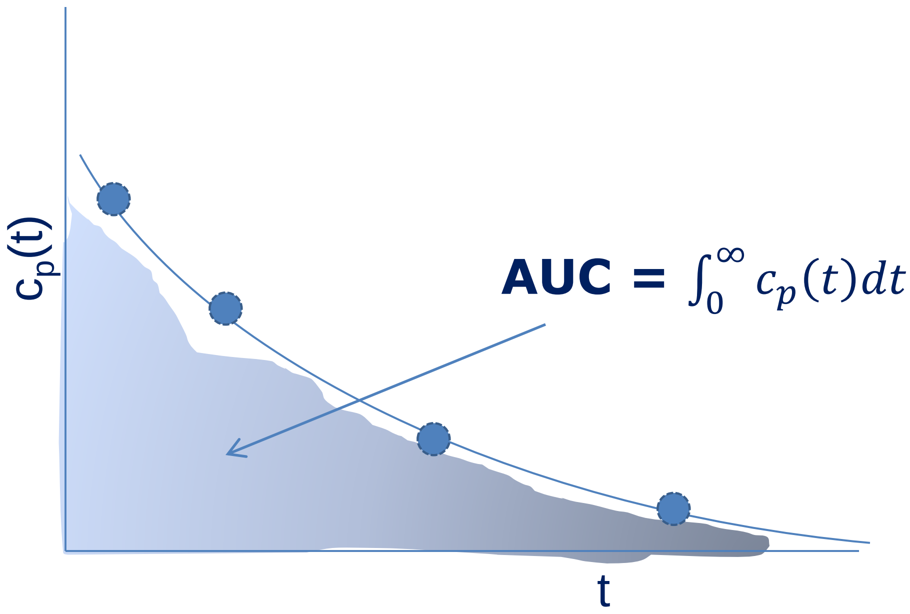
$$\frac{dq}{dt} = -Kc_p(t) \qquad q(0)=d_0$$

$$\int_{d_0}^{0} dq = -\int_{0}^{\infty} Kc_p(t)dt = -d_0$$



GFR using ideal tracer

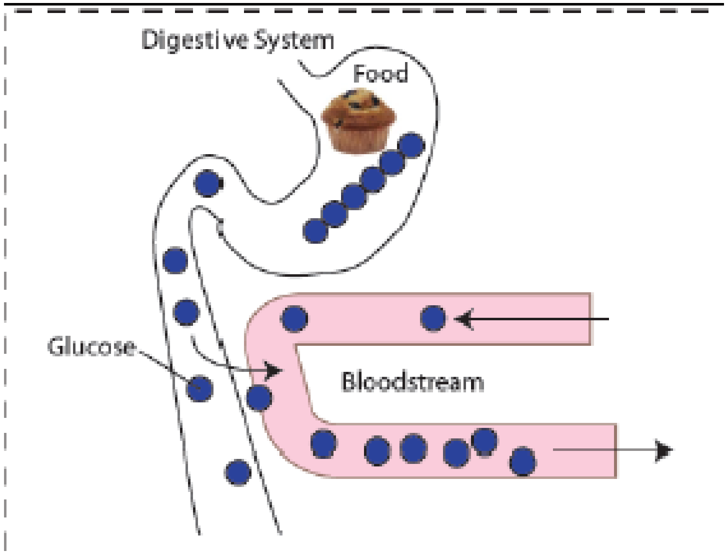
$$K = \frac{d_0}{\int_0^\infty c_p(t)dt}$$

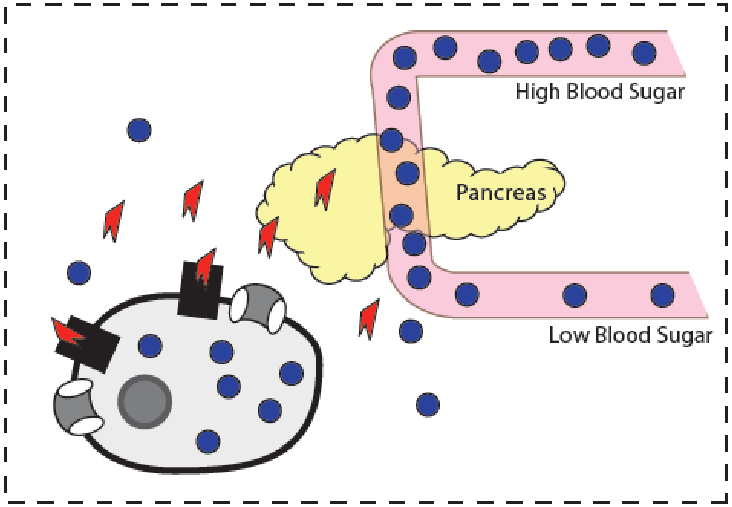


As long as there are enough measurements of the tracer concentration in plasma to calculate the area under the curve (AUC), we can estimate K.

Insulin, glucose and diabetes

- Most of the food we eat is turned into glucose for our body to use as energy. Blood carries the glucose to each of the cells in our body. The body always has some glucose for energy to keep it going, but too much glucose in the blood isn't good for our health. Thus we need to regulate the amount of glucose in our blood.
- The regulation of blood glucose is via a feedback control mechanism. A high blood glucose level acts as a stimulus for the pancreas to secrete insulin, a hormone that helps the glucose diffuse out of the blood and into the cells. This lowers blood glucose levels.





Insulin, glucose and diabetes

- Most cells carry insulin receptors on their cell membrane. Binding of insulin to the receptor signals glucose transport proteins in the cell membrane to open and allow glucose to diffuse out of the blood and into the cells.
- Diabetes means that your blood glucose level is too high because glucose cannot get into the cells.
- Type I diabetes is caused by the immune system attacking the pancreatic islet cells that produce insulin. This results in no insulin production.
- Type II diabetes is when insulin is produced, but the insulin receptors do not respond to the insulin.