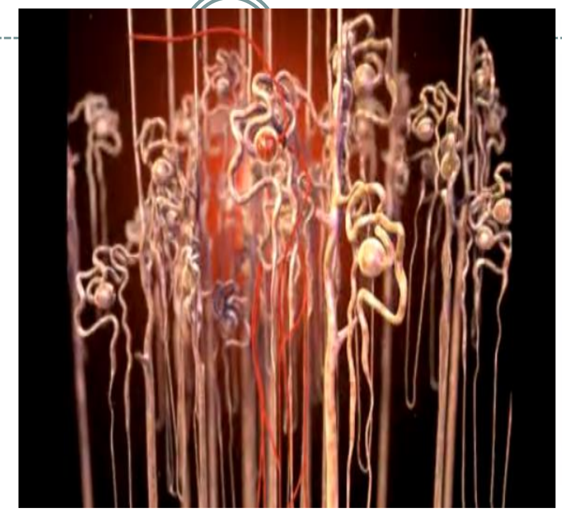
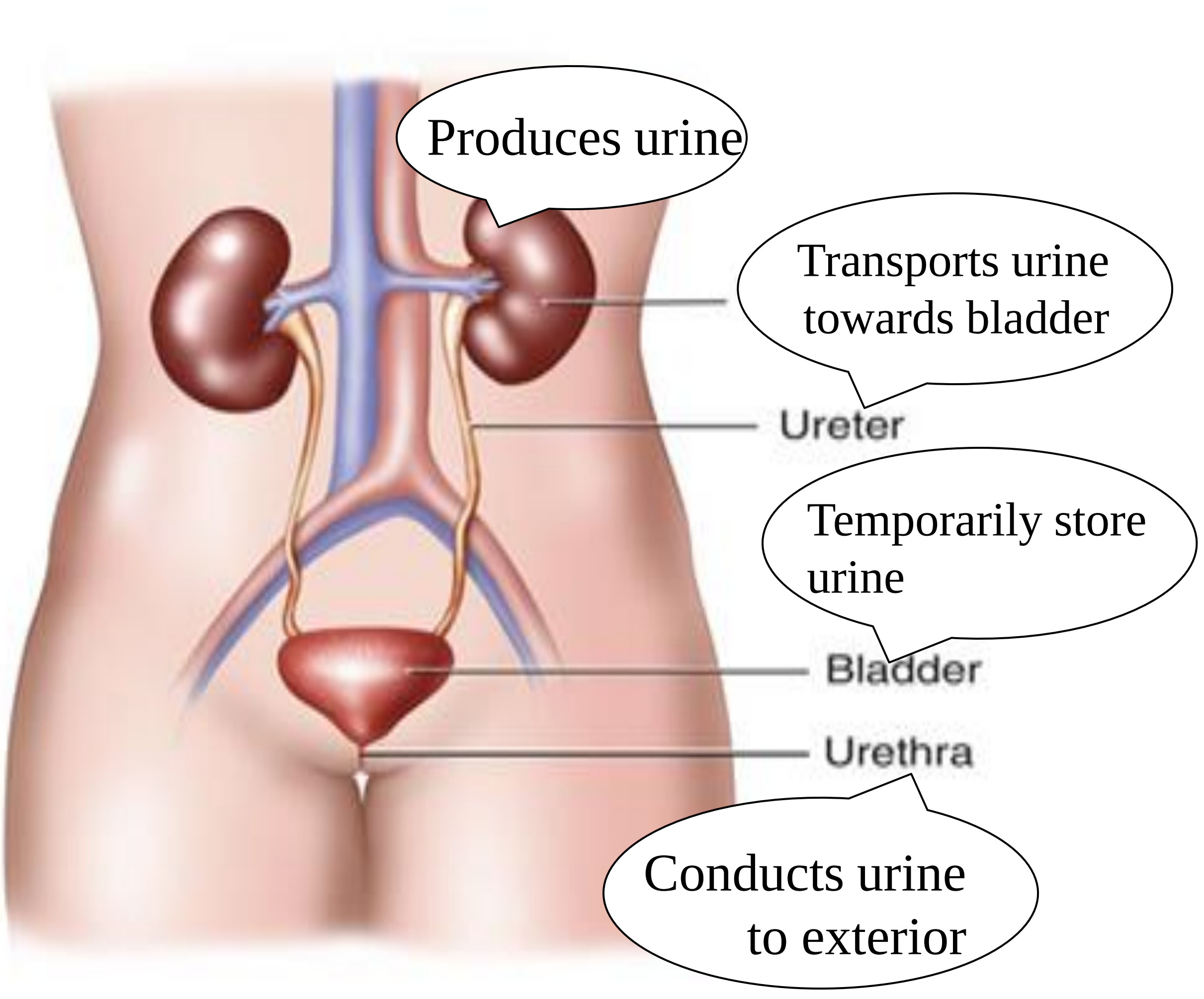
Renal Function Tests

AND GENERAL URINE TESTS

Renal Function test (RFT)



An Introduction to the Urinary System

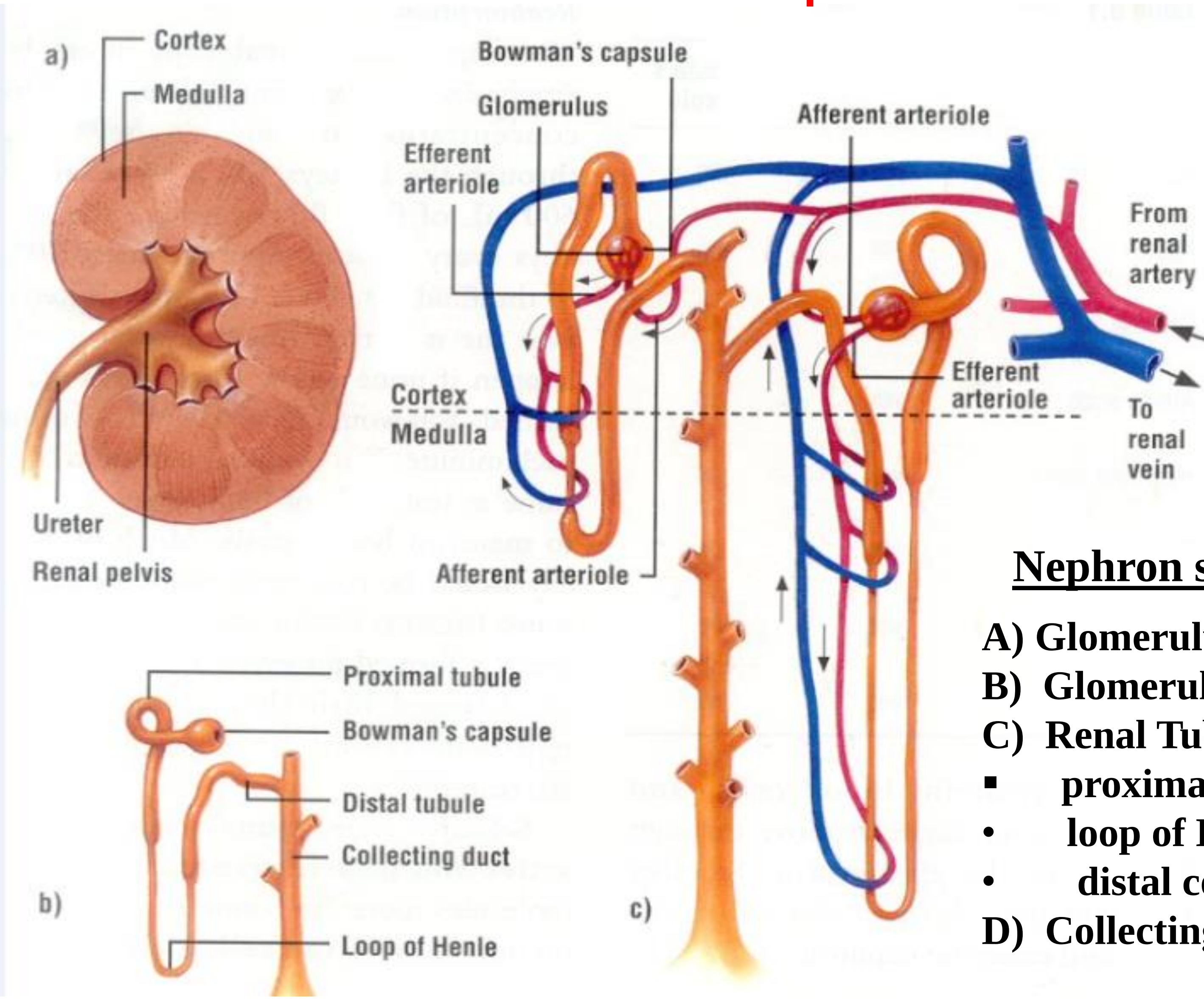


Kidneys Structure

Functional units :

- The nephron is the functional unit of the kidney
- Each kidney contains about 1,000,000 to 1,300,000 nephrons.
- The nephron is composed of glomerulus and renal tubules.
- The nephron performs its homeostatic function by ultra filtration at glomerulus and secretion and reabsorption at renal tubules.

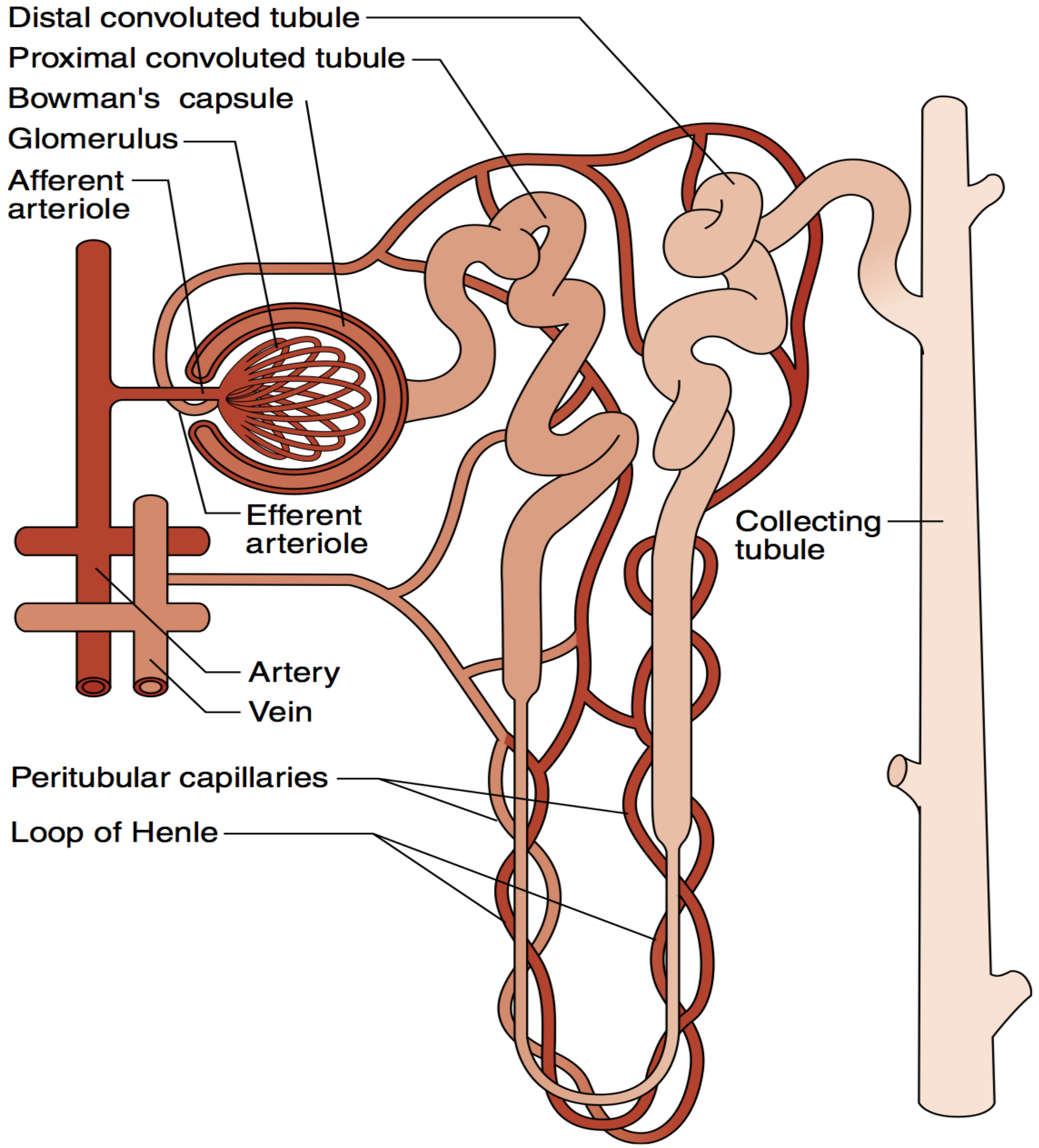
Each kidney consists of one million functional units: Nephrone



Nephron structure

A) Glomerulus
B) Glomerular Capsule
C) Renal Tubule
- proximal convoluted tubule
- loop of Henle
- distal convoluted tubule

D) Collecting Duct



Representation of a nephron and its blood supply

Each nephron is a complex apparatus comprised of five basic parts:

1. **Glomerulus: functions to filter incoming blood.**

- **Factors facilitate filtration:**
  - **high pressure in the glomerular capillaries, which is a result of their position between two arterioles.**
  - **the semipermeable glomerular basement membrane, which has a molecular size cutoff value of approximately 66,000 Da.**

The volume of blood filtered per minute is the glomerular filtration rate (GFR), and its determination is essential in evaluating renal function.

Each nephron is a complex apparatus comprised of five :basic parts

2-Proximal convoluted tubule:

Returns the bulk of each valuable substance back to the blood circulation.
75% of the water, sodium, and chloride.
100% of the glucose (up to the renal threshold)
proteins
almost all of the amino acids, vitamins, and varying amounts of urea, uric acid, and ions, such as magnesium, calcium and potassium.

With the exception of water and chloride ions, the process is active; that is, the tubular epithelial cells use energy to bind and transport the substances across the plasma membrane to the blood.

Secretes products of kidney tubular cell metabolism, such as hydrogen ions, and drugs, such as penicillin.

Each nephron is a complex apparatus comprised of :five basic parts

3-Loop of Henle:

Facilitates the reabsorption of water, sodium, and chloride.

The osmolality in the medulla in this portion of the nephron increases steadily from the corticomedullary junction inward

Each nephron is a complex apparatus comprised of :five basic parts

4-Distal convoluted tubule:

-The filtrate entering this section of the nephron is close to its final composition.

-Effects small adjustments to achieve electrolyte and acid-base homeostasis (under the hormonal control of both antidiuretic hormone (ADH) and aldosterone).

The distal convoluted tubule is much shorter than the proximal tubule, with two or three coils that connect to a collecting duct.

Each nephron is a complex apparatus comprised of :five basic parts

5-Collecting duct:

The collecting ducts are the final site for either concentrating or diluting urine.

The hormones ADH and aldosterone act on this segment of the nephron to control reabsorption of water and sodium.

Chloride and urea are also reabsorbed here.

Kidney functions :

- **Regulation of :**

- water and electrolyte balance.
- acid base balance.
- arterial blood pressure.

- **Excretion & Elimination:**
  removal of organic wastes products from body fluids (urea, creatinine, uric acid).

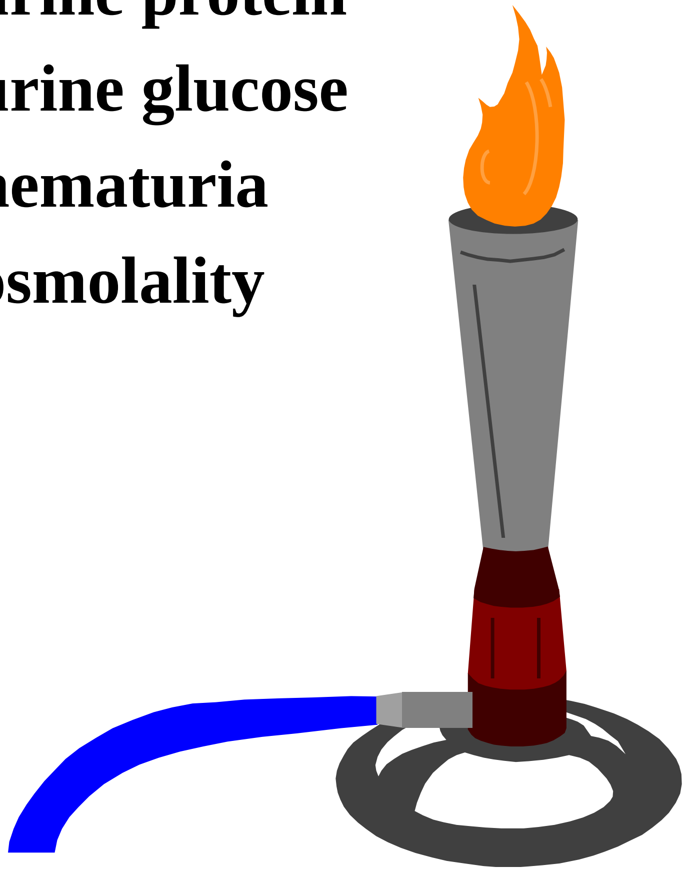
- **Hormonal Function: Secretion of erythropoietin & activation of vitamin D and activation of angiotensinogen by renin**

- **Metabolic Function: site for gluconeogenesis**
- **Homeostatic regulation:**
  -Water -Salt Balance -Acid - base Balance

Laboratory tests of renal function

- glomerular filtration rate (GFR)
- plasma creatinine
- plasma urea
- urine volume
- urine urea
- minerals in urine

- urine protein
- urine glucose
- hematuria
- osmolality



What gets filtered in the glomerulus ?

Freely filtered (filtered = passed)	**Not filtered (not passed)**
• H_2O • Elements : (Na^+, K^+, Cl^-, Mg^{2+} , PO^4) • Urea • Creatinine • Insulin	• Protein • Blood cells • glucose

- **2- System of tubules**

Re-absorption of water and important particles occurs on these tubules

Reabsorption from glomerular filtrate

	% Reabsorbed
Water	99.2
Sodium	99.6
Potassium	92.9
Chloride	99.5
Bicarbonate	99.9
Glucose	100
Albumin	95-99
Urea	50-60
Creatinine	0 (or negative)

Reabsorption can be active or passive,
and occurs in virtually all segments of the nephron

Urine Formation

- **Urine formation requires :**

➢ **Glomerular Filtrationn**

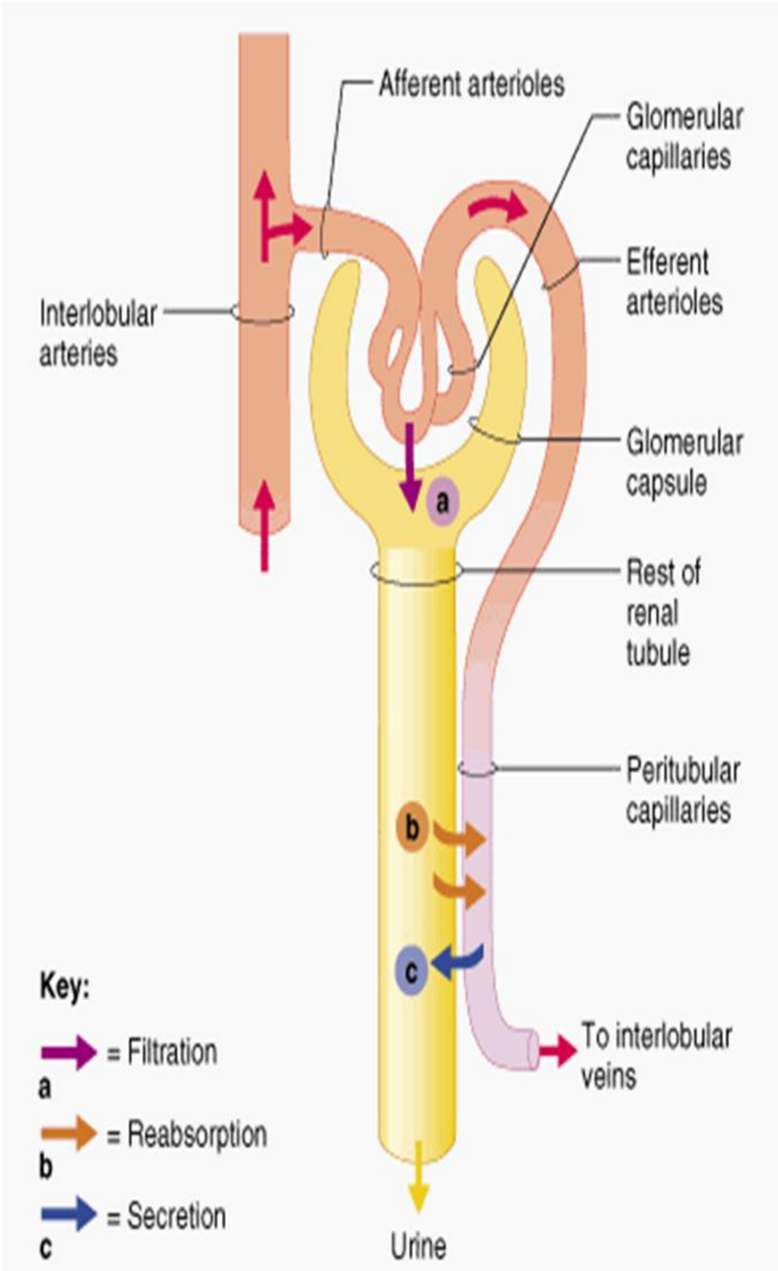
Due to differences in pressure, water&small molecules move from the glomerulus capillaries into the glomerular capsule

➢ **Tubular reabsorption**

from the many molecules are reabsorbed (diffusion, facilitated nephron into the capillary diffusion, osmosis, and active transport)
i.e. Glucose is actively reabsorbed with transport carriers. If the carriers are inactive glucose appears in the urine indicating diabetes

➢ **Tubular secretion**

Substances are actively removed from blood and added to tubular fluid (active transport) ie. H+, creatinin, and some drugs are moved by active transport from the blood into the distal convoluted tubule



Why to test the renal functions?

- Many diseases affect renal function.
- In some, several functions are affected.
- In others, there is selective impairment of glomerular function or one or more of tubular functions.
- Most types of renal diseases cause destruction of complete nephron.

Kidney – basic data

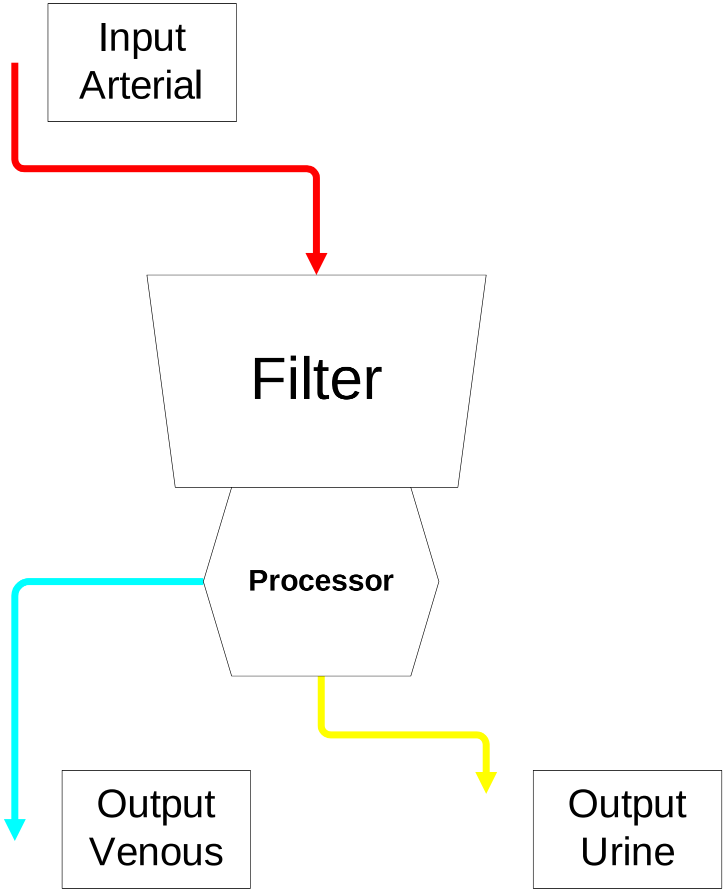
- **Urine excreted daily in adults: 1.5L**
- **Kidney only calculated 1% of total body weight, despite it**
- **The renal blood flow= 20% of cardiac output**
- **Plasma renal flow= PRF 600 mL/Min./1.73 M^2**
- **Reflects two processes**
  - **Ultrafiltration (GFR): 180 L/day**
  - **Reabsorption: >99% of the amount filtered**

Renal threshold

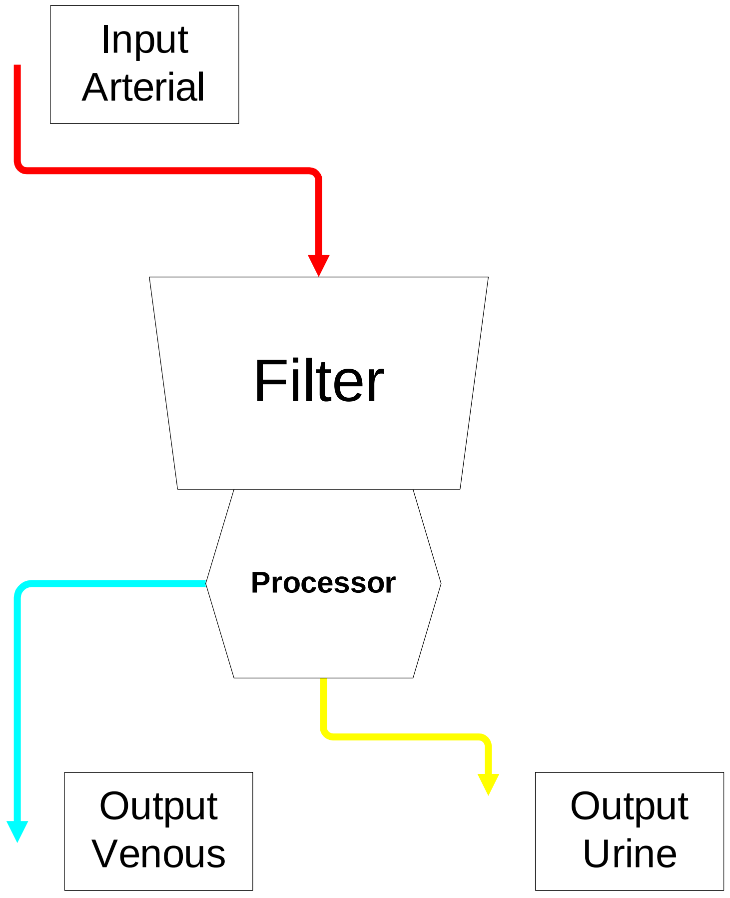
- **Renal threshold of a substance is the concentration in blood beyond which it is excreted in urine**
- **Renal threshold for glucose is 180mg/dL**
- **Tubular maximum (Tm): maximum capacity of the kidneys to absorb a particular substance**
- **Tm for glucose is 350 mg/min**

Kidney Function

- A plumbers view

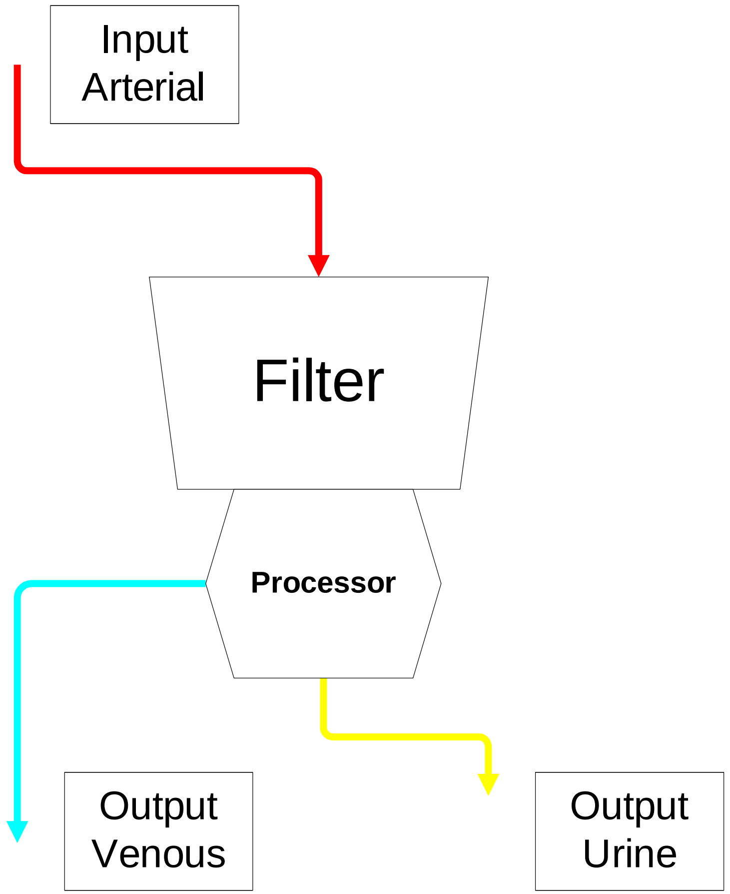


How do you know it's broken?



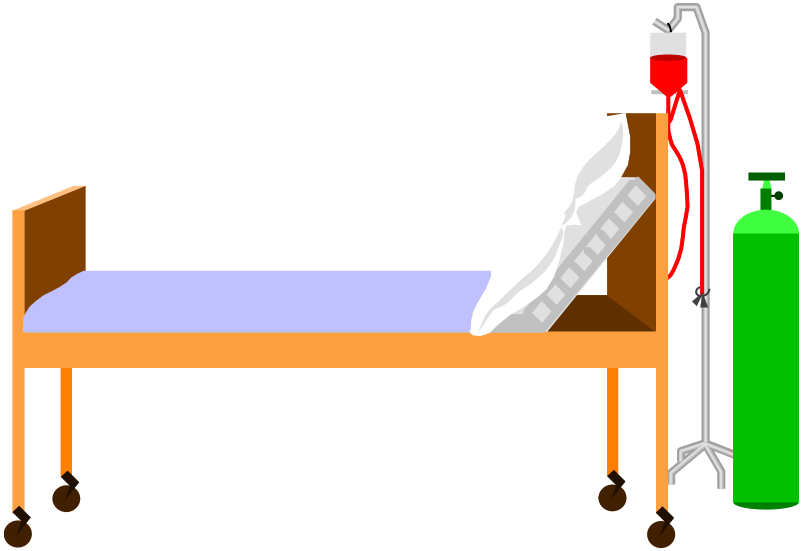
- **Decreased urine production**
- **Clinical symptoms**
- **Tests**

Where can it break?



- **Pre-renal**
- **Renal (intrarenal)**
- **Post-renal (obstruction)**

Causes of kidney functional disorders



- **Pre-renal** ***e.g.*** **decreased intravascular volum**
- **Renal** ***e.g.*** **acute tubular necrosis**
- **Postrenal** ***e.g.*** **ureteral obstruction**

Signs and Symptoms of Renal Failure

- **Symptoms of Uraemia** ***(nausea, vomiting, lethargy)***
- **Disorders of Micturation** ***(frequency, nocturia(excessive urination at nigh), dysuria))***
- **Disorders of Urine volume** ***(polyuria, oliguria, anuria)***
- **Alterations in urine composition** ***(haematuria, proteinuria, bacteriuria, leukocytouria, calculi)***
- **Pain**
- **Oedema** ***(hypoalbuminaemia, salt and water retention)***

Why Test Renal Function?

- To identify renal dysfunction.
- To diagnose renal disease.
- To monitor disease progress.
- To monitor response to treatment.
- To assess changes in function that may impact on therapy (e.g. Digoxin, chemotherapy).

When should you assess renal function?

- Older age
- Family history of Chronic Kidney disease (CKD)
- Decreased renal mass
- Low birth weight
- Diabetes Mellitus (DM)
- Hypertension (HTN)
- Autoimmune disease
- Systemic infections
- Urinary tract infections (UTI)
- Nephrolithiasis
- Obstruction to the lower urinary tract
- Drug toxicity

Biochemical Tests of Renal Function

- **Measurement of GFR**
  - **Clearance tests**
  - **Plasma creatinine**
  - **Urea, uric acid and β2-microglobulin**

- **Renal tubular function tests**
  - **Osmolality measurements**
  - **Specific proteinurea**
  - **Glycouria**
  - **Aminoaciduria**

- **Urinalysis**
  - **Appearance**
  - **Specific gravity and osmolality**
  - **pH**
  - **osmolality**
  - **Glucose**
  - **Protein**
  - **Urinary sediments**

Biochemical Tests of Renal Function

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Routine KFTs include the measurement of :

- Serum creatinine (Cr).
- Creatinine clearance.
- Serum urea.

Both serum Cr and creatinine clearance are used as kidney function tests to :

- Confirm the diagnosis of renal disease.
- Give an idea about the severity of the disease.
- Follow up the treatment.

Renal Function TESTS

Blood Tests

- Urea or BUN.
- Creatinine.
- uric acid.
- levels of several elements : Na^+, K^+, Cl^-, Ca^{2+}, Mg^{2+}, H_2CO_3 and phosphorus

Urine Tests

- glomerular filtration rate (GFR)
- urine volume
- urine urea
- minerals in urine
- urine protein
- urine glucose
- hematuria
- Osmolality

- **Many factors can affect on kidney function leads to kidney damage;**

- **Anatomical structure (congenital disease)**
- **Infections**
- **Diabetes**
- **Renal stones**
- **Smoking**
- **Diet and water**

- Most common causes :Diabetes and high blood pressure

- .

Kidney damage occurs in stages that can early detected.

Abnormal results of kidney function tests may be obtained due to a temporary renal dysfunction.

Therefore, the test should be performed repeatedly and interpreted on the basis of a series of results

Biochemical Tests of renal function

In acute and chronic renal failure, there is effectively a loss of function of whole nephrons

- **Filtration is essential to the formation of urine ➔ tests of glomerular function are almost always required in the investigation and management of any patient with renal disease.**
- **The most frequently used tests are those that assess either the GFR or the integrity of the glomerular filtration barrier.**

Measurement of glomerular filtration rate

GFR can be estimated by measuring the urinary excretion of a substance that is completely filtered from the blood by the glomeruli and it is not secreted, reabsorbed or metabolized by the renal tubules.

- **Clearance is defined as the (hypothetical) quantity of blood or plasma completely cleared of a substance per unit of time (e.g. inulin).**
- **Clearance of substances that are filtered exclusively or predominantly by the glomeruli but neither reabsorbed nor secreted by other regions of the nephron can be used to measure GFR.**

Accurate measurement of GRF by clearance tests requires determination of the concentration in plasma and urine of a substance that is:

- **Freely filtered at glomeruli.**
- **Neither reabsorbed nor secreted by tubules.**
- **Its concentration in plasma needs to remains constant throughout the period of urine collection.**
- **Better if the substance is present endogenously.**
- **Easily measured.**

Creatinine meets most of these criteria.

Clearance is the volume of plasma cleared from the substance excreted in urine per minute.

It could be calculated from the following equation:

$$\text{Clearance (ml/min)} = \frac{U \times V}{P}$$

U = Concentration of creatinine in urine μmol/l

V = flow rate of urine per min

P = Concentration of creatinine in serum or plasma μmol/l

- **Creatinine clearance is usually about 110 ml/min in the 20-40 year old adults.**

- **It falls slowly but progressively to about 70 ml/min in individuals over 80 years of age.**

- **In children, the GFR should be related to surface area, when this is done, results are similar to those found in young adults.**

Biochemical Tests of Renal Function

- **Measurement of GFR**
  - **Clearance tests**
  - **Plasma creatinine**
  - **Urea, uric acid and β2-microglobulin**

Creatinine

- **1 to 2% of muscle creatine spontaneously converts to creatinine daily and released into body fluids at a constant rate.**
- **Endogenous creatinine produced is proportional to muscle mass, it is a function of total muscle mass ➔the production varies with age and sex**
- **Dietary fluctuations of creatinine intake cause only minor variation in daily creatinine excretion of the same person.**
- **Creatinine released into body fluids at a constant rate and its plasma levels maintained within narrow limits ➔ Creatinine clearance may be measured as an indicator of GFR.**

Creatinine clearance and clinical utility

- **The most frequently used clearance test is based on the measurement of creatinine.**
- **Small quantity of creatinine is reabsorbed by the tubules and other quantities are actively secreted by the renal tubules ➔ So creatinine clearance is approximately 7% greater than inulin clearance.**
- **The difference is not significant when GFR is normal but when the GFR is low (less 10 ml/min), tubular secretion makes the major contribution to creatinine excretion and the creatinine clearance significantly overestimates the GFR.**

Creatinine clearance clinical utility

- An estimate of the GFR can be calculated from the creatinine content of a 24-hour urine collection, and the plasma concentration within this period.
- The volume of urine is measured, urine flow rate is calculated (ml/min) and the assay for creatinine is performed on plasma and urine to obtain the concentration in mg per dl or per ml.

$$(4.1)\quad \text{Clearance} = \frac{U \times \dot{V}}{P}\ \text{mL/min}$$

U = urinary creatinine concentration (μmol/L)
$\dot{V}$ = urine flow rate [mL/min or (L/24 h)/1.44]
P = plasma creatinine concentration (μmol/L)

Creatinine clearance in adults is normally about of 120 ml/min,

The accurate measurement of creatinine clearance is difficult, especially in outpatients, since it is necessary to obtain a complete and accurately timed sample of urine

Creatine clearance and clinical utility

- **The 'clearance' of creatinine from plasma is directly related to the GFR if:**
  - **The urine volume is collected accurately**
  - **There are no ketones or heavy proteinuria present to interfere with the creatinine determination.**
- **It should be noted that the GFR decline with age (to a greater extent in males than in females) and this must be taken into account when interpreting results.**

Use of Formulae to Predict Clearance

- **Formulae have been derived to predict Creatinine Clearance (CC) from Plasma creatinine.**
- **Plasma creatinine derived from muscle mass which is related to body mass, age, sex.**
- **Cockcroft & Gault Formula**

CC = k[(140-Age) x weight(Kg))] / serum Creatinine (µmol/L)

k = 1.224 for males & 1.04 for females

- ***Modifications required for children & obese subjects***
- ***Can be modified to use Surface area***

Cockcroft-Gault Formula for Estimation of GFR

- **As indicated above, the creatinine clearance is measured by using a 24-hour urine collection, but this does introduce the potential for errors in terms of completion of the collection.**

- **An alternative and convenient method is to employ various formulae devised to calculate creatinine clearance using parameters such as serum creatinine level, sex, age, and weight of the subject.**

- An example is **the Cockcroft-Gault Formula**:

$$\text{GFR} = \frac{K \times (140 - \text{age}) \times \text{Body weight}}{\text{Serum creatinine } (\mu\text{mol/L})}$$

- **where K is a constant that varies with sex:**
  1.23 for male & 1.04 for females.
- **The constant K is used as females have a relatively lower muscle mass.**

Cockcroft-Gault Formula for Estimation of GFR: Limitations

- It should not be used if
  - Serum creatinine is changing rapidly
  - the diet is unusual, e.g., strict vegetarian
  - Low muscle mass, e.g., muscle wasting
  - Obesity

Serum Cr is a better KFT than creatinine clearance because:

- Serum creatinine is more accurate.
- Serum creatinine level is constant throughout adult life

Creatinine clearance is only recommended in the following conditions:

- Patients with early (minor) renal disease.
- Assessment of possible kidney donors.
- Detection of renal toxicity of some nephrotoxic drugs.

Normal adult reference values:

Urinary excretion of creatinine is 0.5 - 2.0 g per 24 hours in a normal adult, varying according to muscular weight.

- Serum creatinine : 55 – 120 μmol/L

(Males) - Creatinine clearance: 90 – 140 ml/min

(Females) 80 – 125 ml/min

A raised serum creatinine is
a good indicator of impaired renal function

But normal serum creatinine
does not necessarily indicate normal renal function as serum creatinine may not be elevated until GFR has fallen by as much as 50%

Biochemical Tests of Renal Function

- Measurement of GFR
  - Clearance tests
  - Plasma creatinine
  - Urea, uric acid and β2-microglobulin

Measurement of nonprotein nitrogen-containing compounds

Catabolism of proteins and nucleic acids results in formation of so called nonprotein nitrogenous compounds.

Protein

↓ Proteolysis, principally enzymatic

Amino acids

↓ Transamination and oxidative deamination

Ammonia

↓ Enzymatic synthesis in the "urea cycle"

Urea

Plasma Urea

Urea is the major nitrogen-containing metabolic product of protein catabolism in humans,

- ✓ **Its elimination in the urine represents the major route for nitrogen excretion.**
- ✓ **More than 90% of urea is excreted through the kidneys, with losses through the GIT and skin**
- ✓ **Urea is filtered freely by the glomeruli**
- ✓ **Plasma urea concentration is often used as an index of renal glomerular function**
- ✓ **Urea production is increased by a high protein intake and it is decreased in patients with a low protein intake or in patients with liver disease.**

Plasma Urea

Many renal diseases with various glomerular, tubular, interstitial or vascular damage can cause an increase in plasma urea concentration.

- **The reference interval for serum urea of healthy adults is 5-39 mg/dl. Plasma concentrations also tend to be slightly higher in males than females. High protein diet causes significant increases in plasma urea concentrations and urinary excretion.**
- **Measurement of plasma creatinine provides a more accurate assessment than urea because there are many factors that affect urea level.**

- **Nonrenal factors can affect the urea level (normal adults is level 5-39 mg/dl) like:**
  - ✓ **Mild dehydration,**
  - ✓ **high protein diet,**
  - ✓ **increased protein catabolism,**
  - ✓ **muscle wasting as in starvation,**
  - ✓ **reabsorption of blood proteins after a GIT haemorrhage**
  - ✓ **treatment with cortisol or its synthetic analogous**

Clinical Significance

- **States associated with elevated levels of urea in blood are referred to as uremia or azotemia.**
- **Causes of urea plasma elevations:**
  - **Prerenal: renal hypoperfusion**
  - **Renal: acute tubular necrosis**
  - **Postrenal: obstruction of urinary flow**

Uric acid

- **In human, uric acid is the major product of the catabolism of the purine nucleosides, adenosine and guanosine.**
- **Purines are derived from catabolism of dietary nucleic acid (nucleated cells, like meat) and from degradation of endogenous nucleic acids.**
- **Overproduction of uric acid may result from increased synthesis of purine precursors.**
- **In humans, approximately 75% of uric acid excreted is lost in the urine; most of the reminder is secreted into the GIT**

Uric acid

- **Renal handling of uric acid is complex and involves four sequential steps:**
  - **Glomerular filtration of virtually all the uric acid in capillary plasma entering the glomerulus.**
  - **Reabsorption in the proximal convoluted tubule of about 98 to 100% of filtered uric acid.**

- **Subsequent secretion of uric acid into the lumen of the distal portion of the proximal tubule.**
- **Further reabsorption in the distal tubule.**

- **Hyperuricemia is defined by serum or plasma uric acid concentrations higher than 7.0 mg/dl (0.42mmol/L) in men or greater than 6.0 mg/dl (0.36mmol/L) in women**

Plasma β2-microglobulin

- **β2-microglobulin is a small peptide (molecular weight 11.8 kDa),**
- **It is present on the surface of most cells and in low concentrations in the plasma.**
- **It is completely filtered by the glomeruli and is reabsorbed and catabolized by proximal tubular cells.**
- **The plasma concentration of β2-microglobulin is a good index of GFR in normal people, being unaffected by diet or muscle mass.**
- **It is increased in certain malignancies and inflammatory diseases.**
- **Since it is normally reabsorbed and catabolized in the tubules, measurement of β2-microglobulin excretion provides a sensitive method of assessing tubular integrity.**

Role of Biochemical Testing

- **Presentation of patients: -**
  - ***Routine urinalysis***
  - ***Symptom or physical sign***
  - ***Systemic disease with known renal component.***
- **Effective management of renal disease depends upon establishing a definitive diagnosis: -**
  - ***Detailed clinical history***
  - ***Diagnostic imaging and biopsy***
- **Role of biochemistry: -**
  - ***Rarely establishes the cause***
  - ***Screening for damage***
  - ***Monitoring progression.***

Creatinine Clearance

- **Timed urine collection for creatinine measurement (usually 24h)**
- **Blood sample taken within the period of collection.**
- **Normal range = 120-145ml/min**

Problems: -

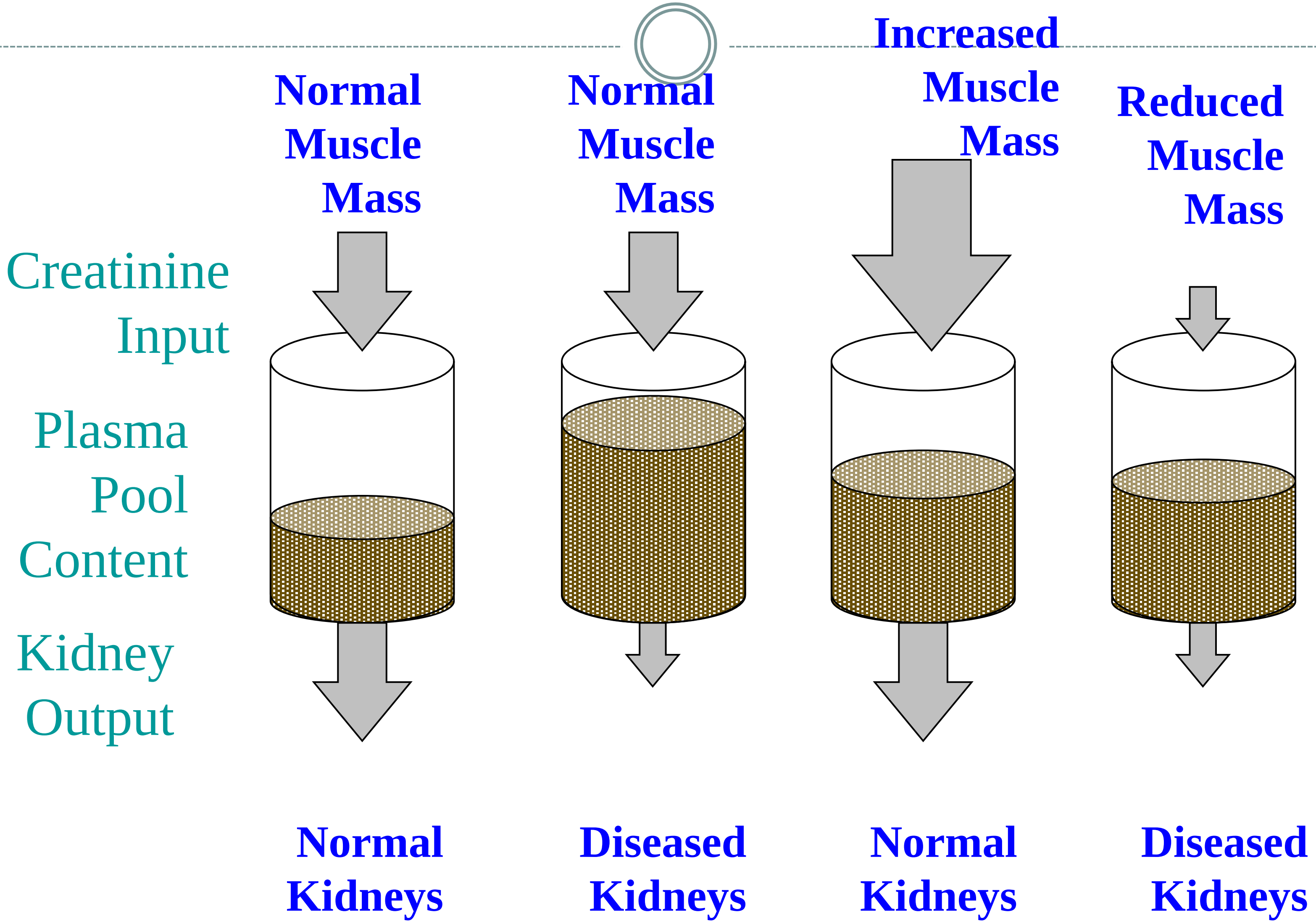
- **Practical problems of accurate urine collection and volume measurement.**
- **Within subject variability = 11%**

Plasma Creatinine Concentration

Difficulties: -

- **Concentration depends on balance between input and output.**
- **Production determined by muscle mass which is related to age, sex and weight.**
- **High between subject variability but low within subject.**
- **Concentration inversely related to GFR.**
    - **Small changes in creatinine within and around the reference limits = large changes in GFR.**

Effect of Muscle Mass on Serum Creatinine



Acute Renal Failure (ARF)

Metabolic features:

- **Retention of:**
  - Urea & creatinine
  - Na & water
  - potassium with hyper-kalaemia
  - Acid with metabolic acidosis

Classification of Causes:

- **Pre-renal**
  - reduced perfusion
- **Renal**
  - inflammation
  - infiltration
  - toxicity
- **Post-renal**
  - obstruction

Pre-renal versus intrinsic ARF

Test	Result	
	Pre-renal	**Renal**
Urea & Creatinine	**Disproportionate rise in Urea**	**Tend to rise together**
Protein in urine	**Uncommon**	**Present on dipstick testing**