

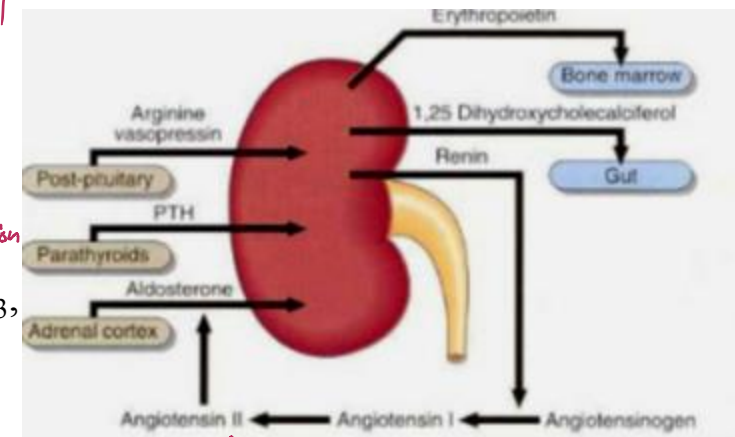
# Renal failure

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Dr. Iman Mansi

# Kidney Functions

- ① Urine formation. → diluted or concentrated depending on amount of water and electrolyte.
- ② Fluid and electrolyte balance.
- ③ Regulation of acid-base balance.
- ④ Excretion of the waste products of protein metabolism.
- ⑤ Excretion of drugs and toxins. → ال liver بولها ر خارج عشان ريس لها excretion عن طريق ال urine.
- ⑥ Secretion of hormones:

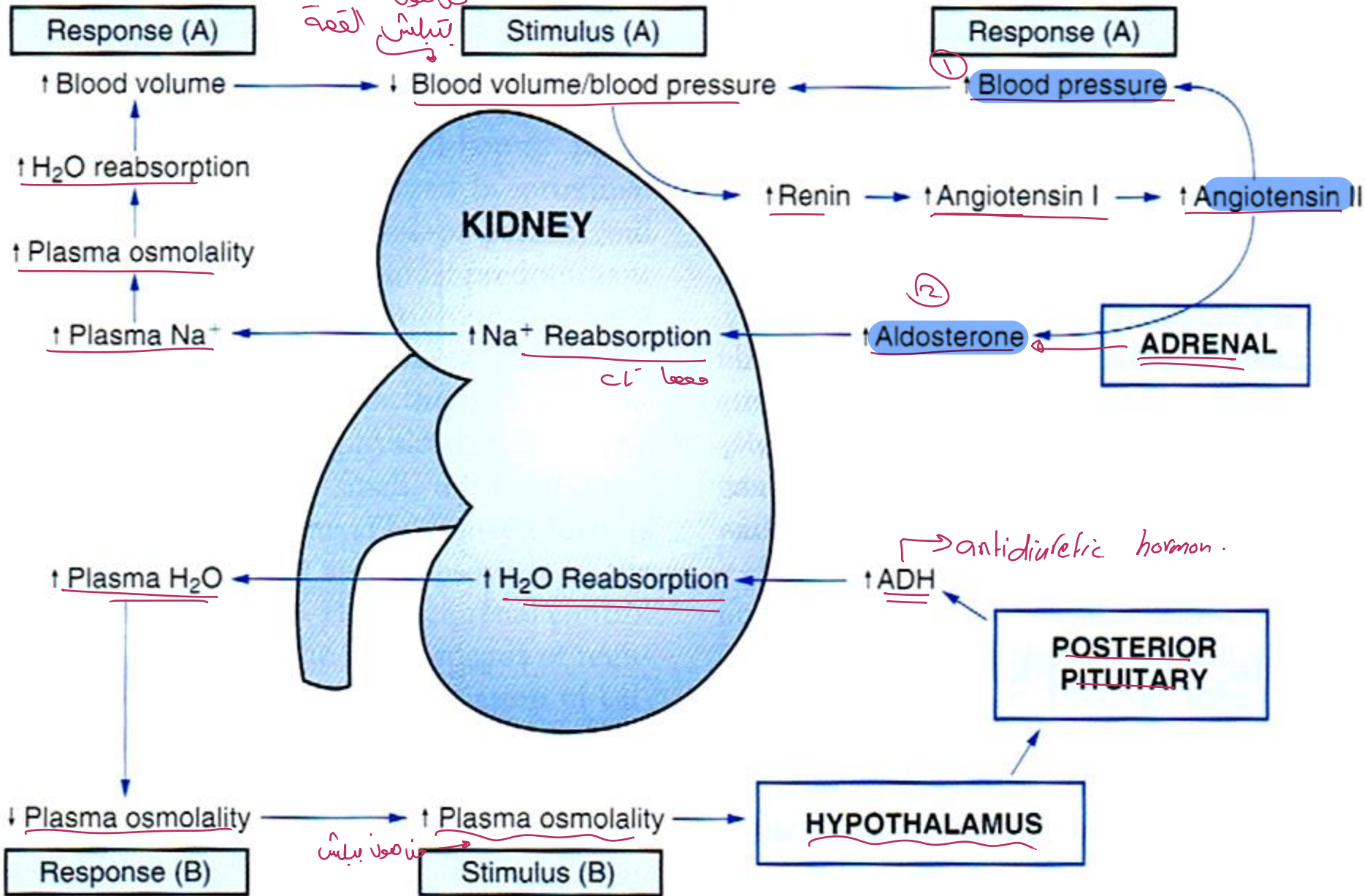


Renin, Erythropoietin, 1,25-Dihydroxy vitamin D<sub>3</sub>, Prostaglandins

Active Form of Vitamin D

1. بيفيه ال active form  
2. بيفيه ال enzyme ال بيفيه ال active form

في حالات ال hypovolemia → Pressure في ال kidney عشان تكون فاذرة انها بفعلة filtration  
في حالات ال hypoxia ال sensor of hypoxia found in the kidney.  
to the bone marrow → induced formulation of RBCs



# Kidney

**Nephron**, functional unit of kidney, consists of <sup>①</sup>glomerulus, <sup>②</sup>Bowman's capsule, <sup>③</sup>proximal tubule, <sup>④</sup>loop of Henle, <sup>⑤</sup>distal tubule, <sup>⑥</sup>collecting duct (shared by many nephron).

- ❑ **Glomerulus**: ball of fenestrated capillaries. → size زي المنخل إليها حصين → 67 K dalton بجمركه
- ❑ **Bowman's capsule**: Cup/Capsule that surrounds the glomerulus.
- ❑ **Proximal tubule**: convoluted tubule on the side of the Bowman's capsule. It is the <sup>①</sup>major site for reabsorption (nutrient, salts and water) and secretion (except for  $K^+$ , the secretion of which is the job of distal convoluted tubule in response to aldosterone). → amino acid, sugar, electrolyte.
- ❑ **Loop of Henle**: U shaped loop that dips into the renal medulla. countercurrent multiplier mechanism occurs here.
  - **Descending limb**: water reabsorption by osmosis (permeable to water, but not to solute). → الانه اد descending بي هو النازل بس فيه amount of water ← reabsorption
  - **Bottom of U**: most concentrated. → بقل ← water ← بزيد تركيزه ← electrolyte
  - **Ascending limb**: salt reabsorption (permeable to salt, but not water).

excretion  
في  
ال  
distal  
tubule  
وال  
Na<sup>+</sup>



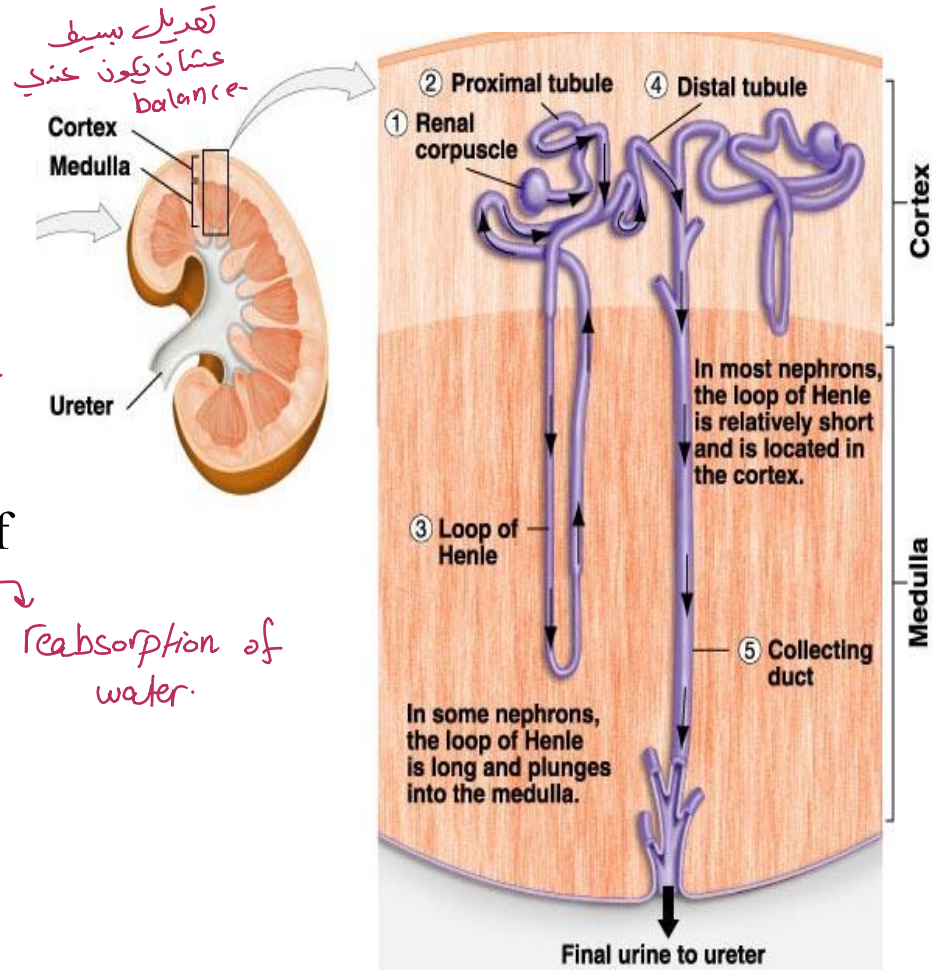
# Kidney

- **Distal tubule**: convoluted tubule on the side of the collecting duct. hormone-controlled (fine tunes the work done by the proximal tubule) reabsorption of salts and water.

Aldosterone-controlled secretion of  $K^+$

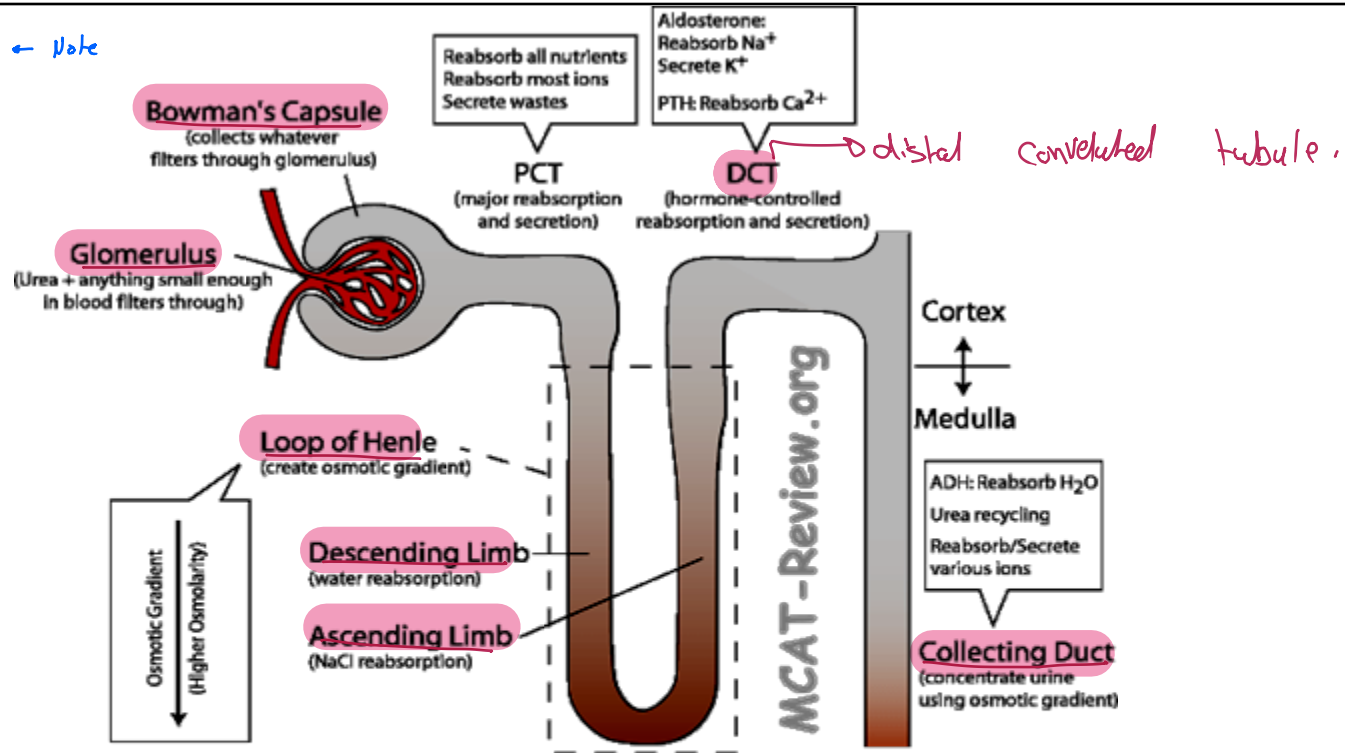
→ Reabsorption of water and  $Na^+$   
→ excretion of  $K^+$

- **Collecting duct**: the distal tubules of many nephrons drain here. ADH-controlled reabsorption of water, hormone-controlled reabsorption/secretion of salts.



# Kidney and nephrons

Note ← الشفلات المكتوبة  
بالرسمه وعلوية الدكتور  
شرحهم فوق  
اعتبرها مراجعة لعلوفاكم



## Quick facts:

PCT	proximal convoluted tubule
DCT	distal convoluted tubule
pH homeostasis	tubules secrete $\text{H}^+$ if blood too acidic don't reabsorb (same effect as secrete) $\text{HCO}_3^-$ if too basic
urea recycling	urea diffuse out of collecting duct back into loop of Henle help maintain osmotic gradient
Wastes secreted by PCT	$\text{NH}_4^+$ , Creatinine, Organic Acids
Loop of Henle	The longer the loop of Henle, the more concentrated the urine can be produced
Countercurrent Mechanism	Powered by $\text{NaCl}$ pumps in upper ascending limb. Results in osmotic gradient down loop of Henle

# Formation of urine

## □ Glomerular filtration

- Filtration is a passive process which is powered by hydrostatic pressure.  
 ← لڏڻ ۾ ڪو به ڪم نه ٿو اچي ۽ هائڊرو اسٽيٽڪ پريشر (hydrostatic pressure) جي ڪري ٿو.
- All substances and ions are filtered out, as long as its small enough.
- The amount of filtrate that flows out of all the renal corpuscles of both kidneys every minute is called the **glomerular filtration rate (GFR)**. In the normal adult, this rate is **about 125 ml/min**
- Proteins with molecular weights lower than that of albumin (68,000 daltons) are filterable → بعد ۾ ڦيرائي سگهجن ٿا.
  - ← Catabolism.
- Negatively charged molecules are less easily filtered than those bearing a positive charge

هڪو ٻيو ڪم نه ٿو اچي  
 علو الٽريشن  
 ↓  
 اڌا ضايع ٿين ٿا  
 فرق پيدا ٿو  
 pressure  
 ↓  
 kidney ۾  
 ٽيڪسٽرڪل  
 وڌيڪ ٿين ٿا

positively charged molecules  
 ڦيرائي سگهجن ٿا  
 filtration.

جڏهن ته albumin وڏا ٿاڻا ٿين ٿا → molecular weight

فيلٽريشن ۾ ڪم ڪندڙ  
 ← membrane ڪو ٻيو ڪم نه ٿو اچي  
 phospholipid  
 → negatively charged  
 ← ڦيرائي سگهجن ٿا يا نه ٿا  
 charged molecules.

# Formation of urine

## □ Secretion and reabsorption of solutes

- Proximal convoluted tubules reabsorb all the nutrients and most of the ions.
- Materials that are reabsorbed include water, glucose, amino acids, urea (partially), and ions such as  $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{Ca}^{2+}$ ,  $\text{Cl}^-$ ,  $\text{HCO}_3^-$ , and  $\text{HPO}_3^-$ .
- Waste products are left in the filtrate (as urea), And also actively excreted ( $\text{NH}_4^+$ , creatinine, organic acids).
- Glucose and amino acids are reabsorbed by an active process co-transported with ( $\text{Na}^+$ ) ions. need ATP.
- Loop of Henle reabsorbs water and salt using the countercurrent mechanism.
- Distal convoluted tubules selectively reabsorb or secrete substances based on hormonal control. (aldosterone).
- Collecting duct reabsorb water to concentrate urine if ADH present. (Also can secrete and reabsorb substances based on hormonal control)
- Regulation of blood pH: secrete  $\text{H}^+$  when blood too acidic, not to reabsorb  $\text{HCO}_3^-$  when blood too basic.

reabsorbed  
↓  
back to  
blood

← مَبْعُودٌ بِالْ  
tubules  
عَنْ  
تَلَوُّهَا  
فِي الْحَبْسِ

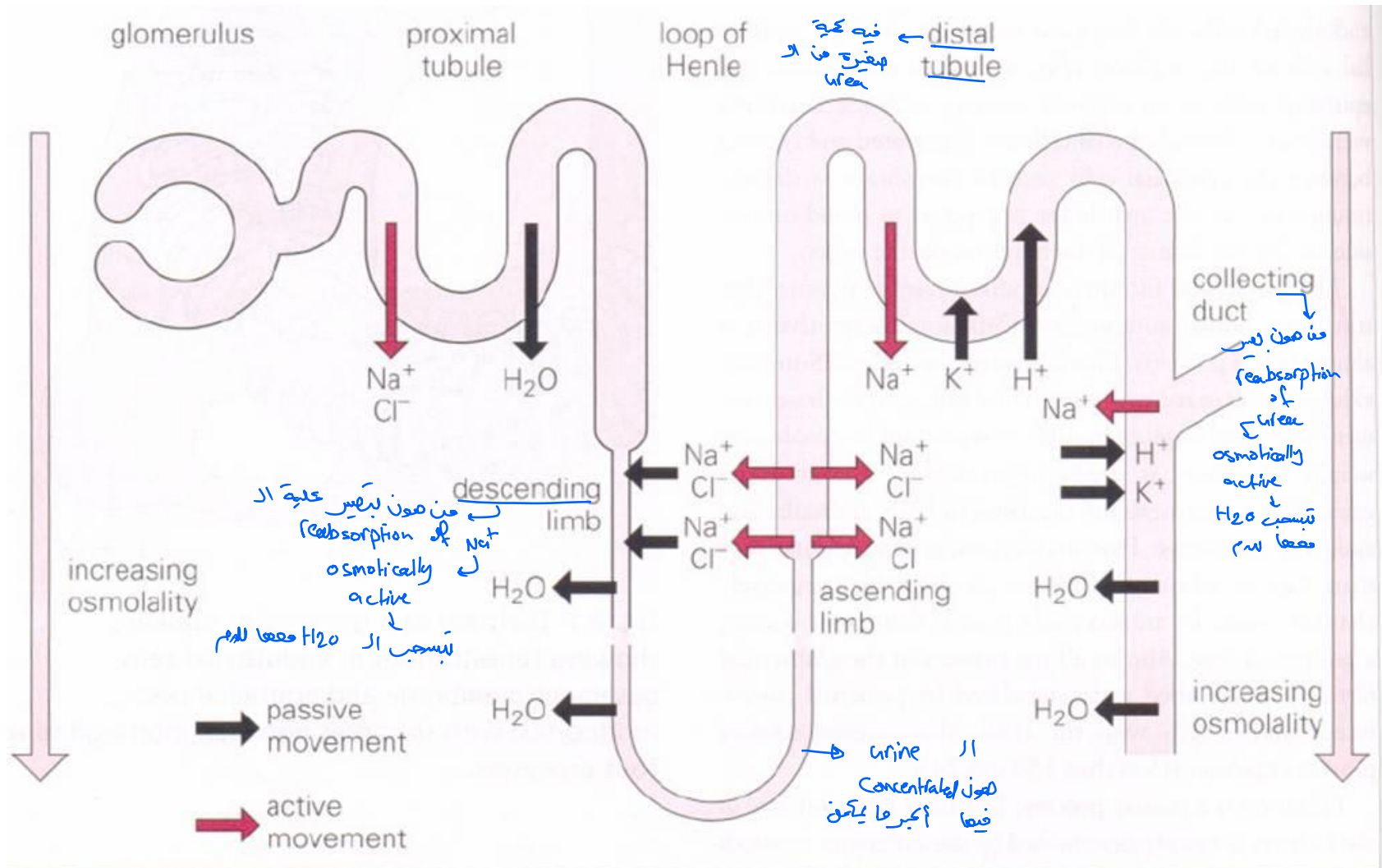
← يَرْجِعُ صَافٍ  
Nat

# Formation of urine

- Concentration of urine *reabsorption. لانه في جزء منها ما رلها*
  - The distal convoluted tubule contains dilute solution of urea.
  - The collecting duct concentrates it by water reabsorption (facilitated diffusion) when ADH is present.
  - Water reabsorption in the collecting duct is possible because the loop of Henle has very high osmolarity (very concentrated) at the bottom.
- Countercurrent multiplier mechanism (basic function)
  - NaCl pump on ascending limb creates an osmotic gradient down the loop of Henle, which is used by the collecting duct to concentrate urine.
  - Descending limb: water flow out of filtrate, impermeable to salt.  
Ascending limb: salt flow out of filtrate, impermeable to water.
  - The gradient-producing power of each individual NaCl pump multiplies down the length of the loop of Henle. Longer the loop of Henle, greater the osmotic gradient, more concentrated urine can be produced.
  - What is urea recycling? Urea at the bottom of collecting duct leaks out into the interstitial fluid and back into the filtrate. Contributes to the high osmolarity at the bottom of the loop of Henle.

# Urine formation

عالية  $\text{Na}^+$  + urea  $\rightarrow$  reabsorption  
 ← osmotically active substances  
 ←  $\text{H}_2\text{O}$  في ال tubules  $\rightarrow$  concentrated urine.





# Endocrine function of kidney

## ➤ Secretion of hormones:

- ① Renin: produced by juxtaglomerular cells of the renal medulla as a result of reduced kidney perfusion. (hypovolemia)
- ② Erythropoietin: secreted by cells near to proximal tubule as a response to blood oxygen levels. It affects bone marrow to produce erythrocytes  
↳ hypoxia induced it → to bone marrow → produced RBCs
- ③ 1,25-Dihydroxy vitamin D<sub>3</sub>: act in the formation of the active form of vitamin D<sub>3</sub>
- ④ Prostaglandins: increases renal blood flow, sodium and water excretion, and renin release

تجاذب  
homeostasis II  
in kidney.

# Elimination of Nonprotein Nitrogen Compounds

- Nonprotein nitrogen compounds (NPN) are waste products formed in the body as a result of the degradative metabolism of nucleic acids, amino acids, and proteins. The three principal compounds are urea, creatinine, and uric acid. (1) (2) (3)

➤ ① **Urea** (Neutral)

➤ Urea makes up the majority (>75%) of the NPN waste. Urea synthesis occurs in the liver from ammonia.

➤ The kidney is the only significant route of excretion for urea.

➤ It is readily filtered by the glomerulus. In the collecting ducts, 40-60% of urea is reabsorbed. The reabsorbed urea contributes to the high osmolality in the medulla, which is one of the processes of urinary concentration

Concentrated urine

reabsorption 2/ تسحب بعض الماء  
osmotically active ← ليس هي تساهم تكون  
لأنها

عبارة  
عن نواتج  
عمليات ال  
metabolism  
في الجسم

go from  
liver to  
kidney  
to excreted

ammonia  
↓  
buffer  
إذا صار عندي مشكلة بال kidney  
أعبر من ال urea (لا تزد  
عن ال intestine وتحويل ل ammonia  
↓  
hyperammonia  
to brain  
يحدث

← لا نستخرج حاليًا kidney function test

← وفي كمية صغيرة يتطلع هذا gut عن طريق ال intestine

← لا يسر لنا reabsorption 2/ تسحب بعض الماء

← ليس هي تساهم تكون osmotically active

⇒ قدرة الكلى على التخلص من *concentrated urine* راجع تفقدتها في حالة الفشل الكلوي *renal failure*.

# Elimination of Nonprotein Nitrogen Compounds

## ② Creatinine (Natural from Muscles. Nonprotein nitrogen compound)

➤ Muscle contains creatine phosphate, a high-energy compound for the rapid formation of ATP catalyzed by creatine kinase (CK).

have its own glycogen + oxygen + ATP → على شكل creatine phosphate.

Every day up to 20% of total muscle creatine (and its phosphate) spontaneously dehydrates and cycles to form the waste product creatinine.

➤ Creatinine is readily filtered by the glomerulus but not reabsorbed by the tubules.

\* Female or male  
لأنه أقل عند الذكور  
لأنه أقل عند الإناث

## ③ Uric acid

➤ uric acid is the primary waste product of purine metabolism (adenine and guanine)

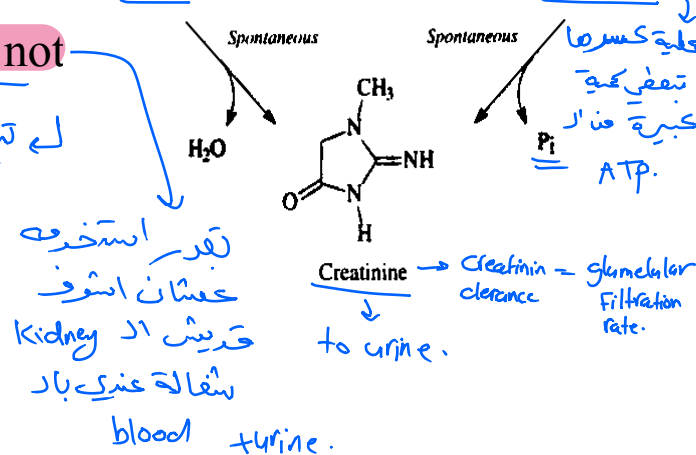
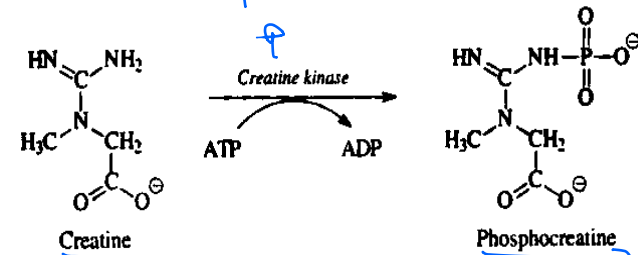
الذوبانية  
بأقل معدومة

like creatinine, uric acid is readily filtered by the glomerulus, but undergoes a complex cycle of reabsorption and secretion as it crosses through the nephron.

← إعادة امتصاص  
في الكلى

يعطي لأي زيادة  
في الكلى. دليل على الفشل الكلوي

phosphorylation.



تقدر استخراجه  
عن طريق أسفوف  
كبدش الكلى  
شغالة عنده بار

→ ↑ uric acid → cause Gout + kidney stones.

# Renal assessment

- Renal function tests focus largely on glomerular clearances, as assessed by creatinine and urea measurements

(1)

(2)

- Tubular functions are assessed by protein measurements (eg, urine electrophoresis)

(1)

- The analysis of urine for analytes, such as pH, glucose, ketones, and bilirubin, continue to be important screening tests for many non-renal diseases, such as diabetes mellitus, ketoacidosis, hemolysis, and liver disease

(4)

(1)

(2)

(3)

(4)

gallbladder disease.

kidney function, diabetes

diabetic ketoacidosis

تجسس تحليل عن طريق اد urine  
بين عشان اشوف الشغل ل organ  
ثاني اوحسان اشوف مرض صين.

(Non-renal disease).

creatinine clearance  
الاعراض كافية لا نزم اخذ بعين

1. age
2. sex
3. weight.
4. height.
5. serum creatinine.

total creatinin + uric acid  
أعلى من 3% من ال nephrons  
طول ما عدد ال kidney لها شغلة + ال urea  
ولا واحد منهم ال يرتفع.

# Renal assessment

- Measurement of GFR
  - 1. Clearance tests
  - 2. Plasma creatinine
  - 3. Urea, uric acid and  $\beta$ 2-microglobulin
- Renal tubular function tests
  - 1. Osmolality measurements
  - 2. Specific proteinuria
  - 3. Glycouria → المفروض ما يكون في عندي سكر بال urine.
  - 4. Aminoaciduria → problem in tubules.
- Urinalysis
  - 1. Appearance
  - 2. Specific gravity and osmolality
  - 3. pH → urinary tract disease → kidney disease
  - 4. Glucose → problem in tubules → diabetes.
  - 5. Protein
  - 6. Urinary sediments

ال proteins الزقل من 68 kdalton  
 ليس لها عملية filtration وبعدين  
 catabolism + reabsorption في ال tubules.  
 ↓  
 في عندي مشكلة بال ال tubules هاي ال proteins  
 راح يسير لها filtration وما راح يسير لها reabsorption  
 بتطلع بال urine.  
 ↓  
 اخذت sample فوال urine ولقيت  
 ال proteins زي  
 حصصا زقل من 68  
 ↓  
 معناتو في عندي  
 مشكلة بال tubules  
 ال proteins بس أكبر من 68  
 زي ال albumin  
 ↓  
 معناتو في عندي  
 مشكلة بال kidney  
 بال glomerulus.

# Analytic procedures

- To assess the various aspects of nephron function, including glomerular filtration and proximal and distal tubular secretion and reabsorption, many tests are performed

## Clearance Measurements

- All laboratory methods rely on the measurement of waste products in blood, usually urea and creatinine. which accumulate when the kidneys begin to fail.
- Renal failure must be advanced, with only about 20-30% of the nephrons still functioning, before the concentration of either substance begins to increase in the blood. The rate at which creatinine and urea are removed or cleared from the blood into the urine is termed clearance

Volume of plasma  
من البلازما  
أي أننا نقيس  
من الـ creatinine  
خلال دقيقة  
واحدة.

Clearance is defined as that volume of plasma from which a measured amount of substance can be completely eliminated into the urine per unit of time expressed in ml/minute

- Measurement of clearance is used to estimate the rate of glomerular filtration

↳ 125 mL/min  
↓  
Normal.



# Creatinine

➤ Creatinine is a nearly ideal substance for the measurement of clearance

يعني جاني عندي شغلتي ممكن  
تختلف عن شخص لشخص في الـ

It is an endogenous metabolic product synthesized at a constant rate for a given individual and cleared essentially only by glomerular filtration (it is not reabsorbed and is only slightly secreted by the proximal tubule).

distribution

or

metabolism

الشيءات

بوتها بعين الاختبار

إذا المانة ياب بي

أحياسا مادة

exogenous

من خارج الجسم

not false

Analysis of creatinine is simple and inexpensive using colorimetric assays.

غير مكلفة وسهل قياسها

والأجهزة متوفرة في جميع

المختبرات -

# Creatinine Clearance and GFR

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- Calculation of creatinine clearance has become the standard laboratory method to determine glomerular filtration Rate (GFR).
- This value is derived by mathematically relating the serum creatinine concentration to the urine creatinine concentration excreted during a period of time, usually 24 hours
- Specimen collection must include both a 24-hour urine specimen and a serum creatinine value, ideally collected at the midpoint of the 24-hour urine collection.
- The urine container (<sup>①</sup>clean, <sup>②</sup>dry and <sup>③</sup>free of contaminants or preservatives) must be kept refrigerated throughout the duration of both the collection procedure and the subsequent storage period until laboratory analysis can be performed.
- The concentration of creatinine in both serum <sup>①</sup> and urine <sup>②</sup> is measured by the applicable methods

# Creatinine Clearance and GFR

- The total volume of urine is carefully measured, and the creatinine clearance is calculated using the following formula (Cockcroft-Gault formula)

$$C_{Cr} \text{ (mL/minute)} = \frac{U_{Cr} \text{ (mg/dL)} \times V_{Ur} \text{ (mL/24 hours)}}{P_{Cr} \text{ (mg/dL)} \times 1440 \text{ minutes/24 hours}} \times \frac{1.73}{A}$$

Creatinine clearance.  $\rightarrow$  Volume of urine  
 Creatinine amount in urine  $\downarrow$  Creatinine amount in plasma  
 24 hours.  $24 \times 60 \text{ minutes} = 1440 \text{ minutes}$   
 collection of urine sample.

where  $\text{Cr}_{\text{Cl}}$  = creatinine clearance

$U_{Cr}$  = urine creatinine concentration

$V_{Cr}$  = urine volume excreted in 24 hours

$P_{Cr}$  = serum creatinine concentration

- 1.73/A normalization factor for body surface area

$$1.85 \times 10^3$$

Volume of urine = 1.85 L = 1850 mL      plasma creatinine = 0.8 mg/dL

ml  
urine creatinine = 25 mg/dL

time of urine collection = 21 hours

surface area = 1.65

= 21 × 60 = 1260 minutes.

$$\text{creatinine clearance} = \frac{25 \times 1850}{0.8 \times 1260} \times \frac{1.73}{1.65} = 48.1 \text{ mL/minute.}$$

← (stage 3 renal failure).  
← "نسبة الوحدة بالكروين" لا زالت عالية.

CKD stages

① more than 90 → beginning of proliferation, swelling (something abnormal in kidney)  
→ stage one

② 60 - 90 → stage 2

③ 30 - 60 → stage 3

④ 15 - 30 → stage 4

⑤ less than 15 → stage 5 (end stage renal failure).  
↓  
dialysis.

# Reference ranges for creatinine clearance

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- Male: 97- 137 mL/minute per 1.73 m<sup>2</sup>
- Female: 88-128 mL/minute per 1.73 m<sup>2</sup>
- Creatinine clearance normally decreases with age, with a decrease of about 6.5 ml/minute per 1.73m<sup>2</sup> for each decade of life  
10 years. ↪

# تقریری Estimated Glomerular Filtration Rate

- The estimated GFR (eGFR) is calculated each time a serum creatinine is reported.  
↳ only in serum.
- The equation is used to predict GFR and is based on serum creatinine, age, body size, gender, and race, without the need of a urine creatinine
- Because the calculation does not require a timed urine collection, it should be used more often than the traditional creatinine clearance and result in earlier detection of chronic kidney disease

estimated GFR

$$\Rightarrow \text{GFR (mL/minute)} = \frac{(140 - \text{Age}) \times \text{Weight (kg)}}{72 \times S_{\text{Cr}} (\text{mg/dL})} \times (0.85 \text{ if female})^*$$

Serum creatinine.  
(Eq. 24-6)

- If serum creatinine is measured in mg/dl, serum creatinine is multiplied by factor 72
- If serum creatinine is measured in μmol/L, the constant is 1.23 for men and 1.04 for women



EX: female age = 75 year. Scr = 0.8 mg/dL

weight = 60 kg

$$\textcircled{1} \text{ GFR} = \frac{(140 - 75) \times 60 \times 0.85}{72 \times 0.8} = 57.6 \text{ mL/minute.}$$

↓  
Stage 3

② Scr = 0.6

$$\text{GFR} = \frac{65 \times 60 \times 0.85}{72 \times 0.6} = 76.7 \text{ mL/minute.}$$

③ Scr = 70 μmol/L → أنبىء للوحدة female

$$\text{GFR} = \frac{65 \times 60 \times 1.04}{70} = 57.9 \text{ mL/minute.}$$

EX: age = 55 year male Scr = 75 μmol/L

weight = 70 kg

$$\text{GFR} = \frac{(140 - 55) \times 70 \times 1.23}{75} = 97.6 \text{ mL/minute.}$$

↓  
Normal.

# Urea

لأنه في جزءٍ راجحٍ يُسَرَّه reabsorption فليسَ دقيقاً  
وما يُعَدُّ عليها عشان أعرِّف بأي Stage المَرِين

Urea clearance was one of the first clearance tests performed.

Urea is freely filtered at the glomerulus and approximately 40% reabsorbed by the tubules. For this reason, it does not provide a full clearance assessment and is no longer widely used

- Older clearance tests used administration of <sup>①</sup>inulin, <sup>②</sup>sodium [<sup>125</sup>I] <sup>③</sup>iothalamate, or <sup>④</sup>p-aminohippurate to assess glomerular filtration or tubular secretion
- These tests are <sup>①</sup>time-consuming, <sup>②</sup>expensive, and <sup>③</sup>difficult to administer and, for the most part, have been discontinued.

لما ما يُستَخدَم حَالِيّاً .

يكون  
مرتفعة  
كثير  
أو  
end  
stages of  
renal  
failure.

# Urine Electrophoresis

→ assessment kidney function or tubules function

- Owing to the efficiency of renal glomerular filtration and tubular reabsorption, normal urinary protein excretion is only about 50-150 mg/24 hours.  
immune system. ← يمكن استخدامه عشوائياً لتشخيص إذا المريض عند مشاكل بال.

- Proteinuria may develop when there are defects in renal reabsorption or glomerular capillary permeability or when there is a significant increase in serum immunoglobulins.  
مشكلة بال ← tubules

- As a result, urine electrophoresis is used primarily to distinguish between acute glomerular nephropathy and tubular proteinuria.  
① ②

- It is also used to screen for abnormal monoclonal or polyclonal globulins.

نوع الـ antibodies الموجودة عنياً بال urine

- Positive identification and subtyping of the urinary paraproteins can be performed by immunofixation electrophoresis.

نوع الـ proteins الموجود بال urine هو بالي ← يوجد عندي إذا المشكلة بال glomerulus tubules  
← الـ proteins جميعاً أقل ← tubules problem  
← الـ protein جميعاً أكبر وأقل عن ← glomerulus problem

# Urine Electrophoresis

- Newer protein assays, such as urine microalbumin, serum  $\beta 2$ -M, cystatin C, and serum and urine myoglobin, can provide important prognostic information useful for patient management.

**Microalbuminuria** is useful for early detection of **diabetic nephropathy**

Small amount of albumine excreted in urine

في عمليات زراعة الكلية ← يعرف انه المناعة تلبست تقاوم ال kidney

- **$\beta 2$ -M** is useful for early **renal transplant rejection**.

protein filtrated and reabsorbed. Reversible.

- **Myoglobin** clearance rates are helpful in predicting **rhabdomyolysis induced acute renal failure**.

لأنه تكسر بالعضلات ← ال myoglobin يمس بطلع من

التوكسين عالي بالدم مبرار urine قليل  
له مضائق عندي مشكلة بال kidney  
لازمه فاعم بطلع urine بار

الحلايا للدم ← اذا تم يرتفع بالدم بين برفو يرتفع  
بار urine مضائقه أحمره حنيمة لونه قاعد بطلع من الجسم

- **Cystatin C** is used in detecting **early changes in kidney function**

غالي

7g /dL ← albumine في الدم  
↓  
70g /L → 70000 mg/L in blood  
in urine → 25-75 mg/L

albumin in urine ← 50 - 150 mg/day  
بالواقع الطبي ما عندي غير  
 $\frac{50}{2L} - \frac{150}{2L} \rightarrow 25-75 \text{ mg/L}$   
→ urine in 24 hours

ال Kit ياك يستخدما عشان أقيس  
 ال albumin في الدم لا يمكن استخراجه  
 أقيس ال albumin بار urine  
 بار blood قليلة جدا

The kit Not sensitive  
 for albumine in urine.

# Microalbumin

not  
micro  
size  
its  
micro  
quantity.

- Urine microalbumin measurement is important in the management of patients with diabetes mellitus, who are at serious risk of developing nephropathy over their lifetimes
- Type 1 has a 30-45% risk, and Type 2 has a 30% risk
- In the early stages of nephropathy <sup>①</sup>there is renal hypertrophy <sup>②</sup>hyperfunction, and <sup>③</sup>increased thickness of the glomerular and tubular basement membranes

كمية قليلة  
 فقط في ال  
 albumine  
 ال تقيس  
 تطلع بار  
 urine.  
 (early stages).

immuno assay → we give a human protein for animal  
 to detect albumine in urine serum ↓

ال animal ال تعرف على ال foreign body  
 ↓  
 تبتدأ antibodies ← بوند عينة جنسا و تضيف عليها عينة ال urine  
 ال antibodies ترتب ال albumine مع ال antibodies  
 ال تترسب

# $\beta$ 2-Microglobulin $\rightarrow$ filtered then reabsorbed.

- $\beta$ 2-Microglobulin ( $\beta$ 2-M) is a small, nonglycosylated peptide (MW, 11.8 KDa) found on the surface of most nucleated cells  
لحم يوجد على السطح لآلي خلية نوية  
nucleus.
- The plasma membrane sheds  $\beta$ 2-M as a relatively intact molecule into the surrounding extracellular fluid so stable levels in normal patients
- Its serum elevated levels indicate increased cellular turnover as seen in myeloproliferative and lymphoproliferative disorders, inflammation, and renal failure  
 $\rightarrow$  damaged of cells.  
 $\uparrow \downarrow \beta$ -microglobulin.
- $\beta$ 2-M is easily filtered by the glomerulus. About 99.9% is then reabsorbed by the proximal tubules and catabolized  
إذا كان في ارتفاع فماتوا ال immune system  
ع بعدا ج ال kidney وحشان أضع ألي-كلى  
damage بطني
- Measurement of serum  $\beta$ 2-M is used clinically to assess renal tubular function in renal transplant patients (high when organ rejection)  
immune suppressed.
- $\beta$ 2-M is more efficient marker of renal transplant rejection than serum creatinine values (independent on lean muscle mass)



# Myoglobin → skeletal and cardiac muscle. →

لا يعرف injury فيهم ال  
myoglobin بيس طلع لبرا

- Myoglobin is associated with acute skeletal and cardiac muscle injury
- In rhabdomyolysis, myoglobin release from skeletal muscle is sufficient to overload the proximal tubules and cause acute renal failure  
reversible. ← بيس تيرب بار Kidney و بعل  
acute renal failure.
- Early diagnosis and aggressive treatment of elevated myoglobin may prevent or lessen the severity of renal failure. Recently, myoglobin clearance has been proposed as an effective early indicator of myoglobin-induced acute renal failure. A high clearance or a low clearance and low serum concentration indicates low risk and a low clearance and high serum concentration indicates high risk.  
① ← كيناما فوق.
- Serum and urine myoglobin can be measured easily and rapidly by immunoassays. Urine myoglobin can also be measured by dipstick methods after removing hemoglobin, but this method has a lack of sensitivity and specificity.

# Cystatin C

- Cystatin C is a low-molecular-weight protein produced by nucleated cells. It is freely filtered by the glomerulus and reabsorbed and catabolized by the proximal tubule.
- Produced at a constant rate, levels remain stable if kidney function is normal
- Measurement of cystatin C to be at least as useful as serum creatinine and creatinine clearance in detecting **early changes in kidney function**. Cystatin C can be measured by immunoassay methods

# Urinalysis

## Physical Characteristics

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- Initial morning specimens are preferred, particularly for protein analyses, because they are more concentrated from overnight retention in the bladder
- The urine should be freshly collected into a clean, dry container with a tight-fitting cover
- It must be analyzed within 1 hour of collection if held at room temperature or else refrigerated at 2°-8°C for not more than 8 hours before analysis
- Bacterial multiplication will cause false-positive nitrite tests, and urease-producing organisms will degrade urea to  $\text{NH}_3$  and alkalinize pH
- Loss of  $\text{CO}_2$  by diffusion into the air adds to this pH elevation, which causes cast degeneration and red-cell lysis
- The urine container must be sterile if the urine is to be cultured

# Urinalysis

## Physical Characteristics

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- **Visual Appearance.** Color intensity of urine correlates with concentration: the darker the color, the more concentrated the specimen
  - Yellow and amber are generally due to urochromes (derivatives of urobilin), whereas a yellowish-brown to green color is a result of bile pigment oxidation.
  - Red and brown after standing are due to porphyrins, whereas reddish-brown in fresh specimens comes from hemoglobin or red cells.
  - Brownish- black after standing is seen in alkaptonuria (a result of excreted homogentisic acid) and in malignant melanoma (in which the precursor melanogen oxidizes in the air to melanin). Drugs and some foods, such as beets, also may alter urine color.
- **Odor:** The characteristic pungent odor of fresh urine is due to volatile aromatic acids
  - Urinary tract infections impart a noxious, fecal smell to urine, whereas the urine of diabetics often smells fruity as a result of ketones.

# Urinalysis

## Physical Characteristics

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- **Turbidity** The cloudiness of a urine specimen depends on pH and dissolved solids composition.
  - Thread-like cloudiness is observed when the specimen is full of mucus. In alkaline urine, suspended precipitates of amorphous phosphates and carbonates may be responsible for turbidity whereas in acidic urine, amorphous urates may be the cause
- **Volume.** The volume of urine excreted indicates the balance between fluid ingestion and water lost from the lungs, sweat, and intestine.
  - Polyuria is observed in diabetes mellitus and insipidus (in insipidus, as a result of lack of ADH), as well as in chronic renal disease, acromegaly (overproduction of the growth hormone)

# Renal diseases

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- Common renal diseases include infectious and inflammatory processes to the glomerulus, tubules, and urinary tract, obstructions of normal kidney function, and acute and chronic renal failure.
- rapid deterioration of renal function → accumulation in blood of nitrogenous wastes that would normally be excreted in urine.
- Patient presents with rapidly ↑ blood urea nitrogen (BUN) & serum creatinine (SrCr).

# Etiology

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## Prerenal Causes

- Patients who are dependent on prostaglandin-mediated vasodilation to maintain renal perfusion can develop RF simply from ingestion of NSAIDs.
- Patients with renal hypoperfusion (e.g., from renal artery stenosis, congestive heart failure, or intrarenal small vessel disease) who are dependent on angiotensin II-mediated vasoconstriction of efferent renal arterioles to maintain renal perfusion pressure may develop ARF on ingesting **ACE inhibitors**.

# Etiology

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## Intrarenal Causes

- can be divided into
  - specific **inflammatory diseases** (e.g., vasculitis, glomerulonephritis, drug-induced injury)
  - **acute tubular necrosis** resulting from many causes (including ischemia, poisons, & hemolysis).
- **Tubular damage can commonly be due to aminoglycoside antibiotics & rhabdomyolysis**, in which myoglobin, released into bloodstream after crush injury to muscle, precipitates in renal tubules.
- **Sepsis** is one of the most common causes of acute renal failure - combination of prerenal & intrarenal factors.

## Postrenal Causes

- result in **urinary tract obstruction**, such as renal stones.



# Pathogenesis

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- All forms of ARF, if untreated, result in **acute tubular necrosis (ATN)**, with sloughing of cells that make up renal tubule.
- ARF **may be reversible** depending on timing of intervention between onset of initial injury & eventual ATN

# Clinical Manifestations

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- Initial symptoms: fatigue & malaise, probably early consequences of loss of ability to excrete water, salt, & wastes via kidneys.
- Later, more profound S&S of loss of renal water & salt excretory capacity: dyspnea, orthopnea, rales, prominent S3, & peripheral edema.
- Altered mental status reflects toxic effect of uremia on brain, with ↑ blood levels of nitrogenous wastes & fixed acids.
- Clinical manifestations depend on cause & stage of disease at which patient comes to medical attention.
  - Patients with renal hypoperfusion first develop **prerenal azotemia** (↑BUN without tubular necrosis), a direct physiologic consequence of ↓ GFR.
  - Without treatment, prerenal azotemia may progress to **ATN** - often requiring supportive dialysis before adequate renal function is regained.

# Clinical Manifestations

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- The earliest manifestation of prerenal azotemia is  $\uparrow$  ratio of BUN to SrCr. Normally 10–15:1, this ratio may  $\uparrow$  to 20–30:1 in prerenal azotemia, with a normal or **near-normal serum creatinine**.
- Urinalysis:
  - Urine is maximally concentrated (up to 1500 mOsm/L) in prerenal azotemia.
  - However, with progression to acute tubular necrosis, the ability to generate a concentrated urine is largely lost ( $<$  than 350 mOsm/L)
  - granular casts, tubular epithelial cells, & epithelial cell casts are found in ATN.

# Chronic Renal Failure (CRF)

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## Clinical Presentation

- in addition to those observed in ARF:
- Osteodystrophy,
- Neuropathy,
- Bilateral small kidneys by abdominal x-ray film or ultrasonography,
- Anemia

## Etiology

- The most common cause of CRF is **diabetes mellitus**, followed closely by hypertension & glomerulonephritis.
- Polycystic kidney disease, obstruction, & infection are among the less common causes

# Pathogenesis

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## Development of Chronic Renal Failure

- Irreversible loss of nephrons → > functional burden is borne by fewer nephrons → ↑ glomerular filtration pressure & hyperfiltration ("hypertension" at level of nephron) → fibrosis & scarring (**glomerular sclerosis**) → the rate of nephron destruction & loss ↑ → **uremia**
- In CRF there is combination of toxic effects of:
  - (1) retained products normally excreted by kidneys (e.g., nitrogen-containing products of protein metabolism)
  - (2) normal products such as hormones now present in ↑ amounts
  - (3) loss of normal products of kidney (e.g., erythropoietin)
- Excretory failure results also in fluid shifts, with ↑ intracellular Na<sup>+</sup> & water & ↓ intracellular K<sup>+</sup>.
- **Effects on metabolism:**
  - (1) ↓ in basal body temperature (perhaps because of ↓ Na<sup>+</sup>-K<sup>+</sup> ATPase activity)
  - (2) ↓ lipoprotein lipase activity with accelerated atherosclerosis.

# Clinical Manifestations

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## **Na<sup>+</sup> Balance & Volume Status**

- Some degree of Na<sup>+</sup> & water excess, reflecting loss of renal route of salt & water excretion.
- Continued excessive Na<sup>+</sup> ingestion contributes to CHF, HTN, ascites, peripheral edema, & weight gain.
- Excessive water ingestion contributes to hyponatremia.

# Clinical Manifestations

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## K<sup>+</sup> Balance

- Hyperkalemia is a serious problem especially when GFR ↓ below 5 mL/min → aldosterone-mediated K<sup>+</sup> transport in distal tubule ↑ in compensatory fashion.
  - Treatment with K<sup>+</sup>-sparing diuretics, ACE inhibitors, or β-blockers—drugs that may impair aldosterone-mediated K<sup>+</sup> transport—can, therefore, precipitate dangerous **hyperkalemia** in a patient with CRF.
- CRF patients are at > risk of hyperkalemia in the face of sudden loads of K<sup>+</sup> from either endogenous sources (e.g., hemolysis, infection, trauma) or exogenous sources (e.g., stored blood, K<sup>+</sup>-rich foods, or K<sup>+</sup>-containing medications).

## Metabolic Acidosis

- ↓ capacity to excrete acid & generate buffers
- Can usually be corrected with 20–30 mmol (2–3 g) of sodium bicarbonate by mouth daily.

# Clinical Manifestations

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## Mineral & Bone

- ❑ Several disorders of phosphate,  $\text{Ca}^{2+}$ , & bone metabolism
- ❑ Key factors:
  - (1) ↓ absorption of  $\text{Ca}^{2+}$  from gut,
  - (2) overproduction of PTH,
  - (3) disordered vitamin D metabolism,
  - (4) chronic metabolic acidosis → **enhanced bone resorption**.
- ❑ Hyperphosphatemia contributes to development of hypocalcemia → serves as additional trigger for secondary hyperparathyroidism → ↑ blood PTH levels.
- ❑ → further depletion of bone  $\text{Ca}^{2+}$  → **osteomalacia & osteoporosis** of CRF



# Clinical Manifestations

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## Cardiovascular & Pulmonary Abnormalities

- ❑ CHF & pulmonary edema are most commonly due to volume & salt overload.
- ❑ HTN is a common finding, usually on the basis of fluid & Na<sup>+</sup> overload.
  - **Hyperreninemia** (↓ renal perfusion triggers failing kidney to overproduce renin → ↑ elevate systemic BP.
- ❑ ↑ cardiovascular risk remains the leading cause of mortality in this population (MI, stroke, & peripheral vascular disease).
- ❑ Cardiovascular risk factors: HTN, hyperlipidemia, glucose intolerance, chronic ↑ cardiac output, & valvular & myocardial calcification due to ↑ Ca<sup>2+</sup> x PO<sub>4</sub><sup>3-</sup> product

# Clinical Manifestations

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## Hematologic Abnormalities

- ❑ Normochromic, normocytic anemia, with hematocrits typically in the range of 20–25%, is a consistent feature.
  - Lack of production of erythropoietin (mainly)
  - Bone marrow suppressive effects of uremic poisons
  - Bone marrow fibrosis due to ↑ blood PTH
- ❑ Abnormal hemostasis (↑ bruising, ↑ blood loss at surgery, ↑ incidence of spontaneous GI & cerebrovascular hemorrhage).
- ❑ ↑ susceptibility to infections, due to leukocyte suppression by uremic toxins.
- ❑ Acidosis, hyperglycemia, malnutrition, & hyperosmolality also contribute to immunosuppression.
- ❑ Invasiveness of dialysis & use of immunosuppressive drugs in renal transplant patients also contribute.

# Clinical Manifestations

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## **Endocrine and Metabolic Abnormalities**

- ❑ Women have low estrogen levels → amenorrhea & inability to carry pregnancy to term.
- ❑ Low testosterone levels, impotence, oligospermia are common findings in men
- ❑ ↑ half-life of insulin → stabilizing effect on diabetic patients whose blood glucose was previously difficult to control.

## **Dermatologic Abnormalities**

- ❑ Pallor because of anemia,
- ❑ Hematomas as a result of clotting abnormalities,
- ❑ Pruritus & excoriations as a result of  $\text{Ca}^{2+}$  deposits from secondary hyperparathyroidism.



# Treatment of chronic renal failure

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- In situations of chronic renal failure, aggressive therapeutic approaches based on **dialysis** and **transplantation** have enabled prolonged survival of what was once a terminal condition
- Variations in dialysis techniques have made this process more available and convenient and, with the implementation of powerful immunosuppressive drugs, widespread renal transplantation is now limited only by the availability of appropriate donor organs.



A 52-year-old man with a history of AIDS, hypertension, diabetes mellitus, and alcohol abuse was found unconscious in his home by his roommate. In the emergency department, he was hypotensive (103/60), febrile ( $T = 101^{\circ}$ ), and unresponsive. CT scan of the abdomen showed cholecystitis and gallstones. Laboratory data is listed below. (Case developed by Cynthia Batangan Santos, MD, Pathology Resident, Hartford Hospital Department of Pathology and Laboratory Medicine, Hartford, CT. Modified and printed with permission.)

The patient was diagnosed with acute renal failure. He was given IV fluids; BUN fell to 68 mg/dL and creatinine to 2.2 mg/dL. The patient's blood culture report was positive for *E. coli*. He was treated with tobramycin and cefepime. The patient contin-

ued to deteriorate and died 5 days after admission. Cause of death was multiorgan failure secondary to AIDS, sepsis, and alcoholic cirrhosis.

## Questions

1. What is the significance of the patient's elevated CK? Explain why the doctor ordered a CKMB and troponin level. What can you conclude about the patient's cardiac status?
2. What is the cause of his acute renal failure?
3. What is the significance of the patient's large urine hemoglobin?
4. How would you interpret this patient's liver function tests considering his clinical history?

Drugs of Abuse: Serum Ethanol	Negative: 84 mg/dL	Urinalysis: Hemoglobin WBC RBC	Large: 4 hpf (0-4) 2 hpf (0-4)
CK	3308 U/L (24-204)	BUN	71 mg/dL (8-21)
CKMB	15 ng/mL (0-7.5)	Creatinine	4.1 mg/dL (0.9-1.5)
CKMB rel. index	0.5 (0-4)	ALP	443 U/L (45-122 )
Troponin T	<0.01 ng/mL (0-0.4)	AST	305 U/L (9-45)
pH	7.50	ALT	78 U/L (8-63)
PCO <sub>2</sub>	27 mm Hg	GGT	724 U/L (11-50)
Total CO <sub>2</sub>	15 mmol/L	Total bilirubin	2.7 mg/dL (0.2-1.0)
		Direct bilirubin	2.4 mg/dL (0-0.2)



## CASE STUDY 24-2

A 45-year-old man presented to the hospital with alcohol withdrawal. After drinking a pint of brandy daily for the past 5–6 years, he decided to stop drinking 4 days ago. He experienced tremors and then visual and auditory hallucinations. On arrival at the hospital, he was diaphoretic and tachycardic, with a pulse rate of 102. His chemistry results are shown below.

Na <sup>+</sup>	130 mmol/L	Total protein	7.1 g/dL
K <sup>+</sup>	3.7 mmol/L	Albumin	3.7 g/dL
Cl <sup>-</sup>	90 mmol/L	ALP	63 U/L
CO <sub>2</sub>	20 mmol/L	AST	42 U/L
BUN	81 mg/dL	ALT	16 U/L
Creatinine	4.0 mg/dL	GGT	131 U/L
Magnesium	1.4 mg/dL	CK	591 U/L
Alcohol	Negative	Total bilirubin	0.5 mg/dL

Medical history included arthritis, hypertension, depression, and alcoholism. He had been taking an anti-inflammatory medication for arthritis and an antidepressant. Overnight, he became agitated and re-

quired increasing doses of a benzodiazepine, together with physical restraints for behavior control. The next morning, he was transferred to the ICU where he was evaluated for acute renal failure. The patient was rehydrated and his arthritis and antidepressant medications were withheld. Lab test results are listed below:

Na <sup>+</sup>	139 mmol/L	Creatinine	1.4 mg/dL
K <sup>+</sup>	3.5 mmol/L	CK	1626 U/L
Cl <sup>-</sup>	107 mmol/L	CKMB	3.4 ng/mL
CO <sub>2</sub>	23 mmol/L	Relative index	0.2
BUN	16 mg/dL		

### Questions

1. Is the patient still in acute renal failure?
2. What was the cause of his acute renal failure?
3. Why has the patient's electrolyte status improved?
4. Why is his CK highly elevated?



## CASE STUDY 24-3

A 78-year-old woman with a history of hypertension, aortic thoracic graft, and esophageal reflux disease complained of fever (100°) and weakness. She had been treated 3 weeks before at the hospital for a urinary tract infection. She was admitted to the hospital for a diagnostic workup and transfusion. Her laboratory results are listed below:

Na <sup>+</sup>	129 mmol/L	Hct	25.6%
K <sup>+</sup>	3.7 mmol/L	Hgb	8.5 g/dL
Cl <sup>-</sup>	97 mmol/L	WBC	9,700
CO <sub>2</sub>	19 mmol/L		
BUN	52 mg/dL		
Creatinine	3.2 mg/dL		

Urine culture was positive for *Citrobacter*. Urinalysis results are listed below:

Color	Hazy/yellow
Specific gravity	1.015
pH	5
Blood	Large
Protein	2+
Glucose	Negative

Ketones	Negative
Nitrates	Negative
RBC	>25
WBC	1-4
Casts	Granular, 1-4

The patient's renal function continued to decline, and she was put on hemodialysis. A renal biopsy was performed that showed end-stage crescent glomerulonephritis. Two days later, the patient suffered a perforated duodenal ulcer that required surgery and blood transfusion. Subsequently, she developed coagulopathy and liver failure. Her condition continued to deteriorate in the next few days, and she died following removal of life support.

### Questions

1. Looking at the urinalysis, what is the significance of the 2+ protein and >25 RBCs?
2. What is the most likely cause of glomerulonephritis?
3. Why was the patient put on hemodialysis?

### Case History 10

A male aged 35 presenting with loin pain has a serum creatinine of  $150 \mu\text{mol/l}$ . A 24-hour urine of 2160 ml is collected and found to have a creatinine concentration of  $7.5 \text{ mmol/l}$ .

- Calculate the creatinine clearance and comment on the results.

An error in the timed collection was subsequently reported by the nursing staff, and the collection time was reported to be 17 hours.

- How does this affect the result and its interpretation?