Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

# ADDISON'S DISEASE

* Please check out this link to know if there are any changes or additions.

Dr Rana specifically said that any numbers and procedures in this lectures should NOT be memorized!

**Study hard!**

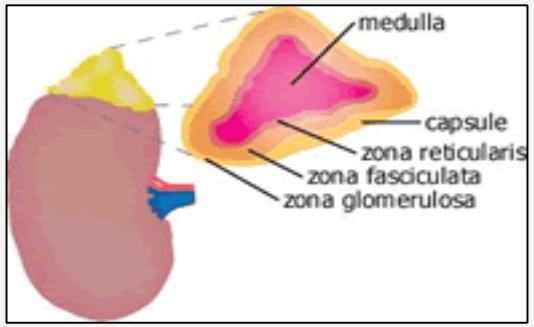
**Color index:** **Important** | Doctors notes | Further explanation.

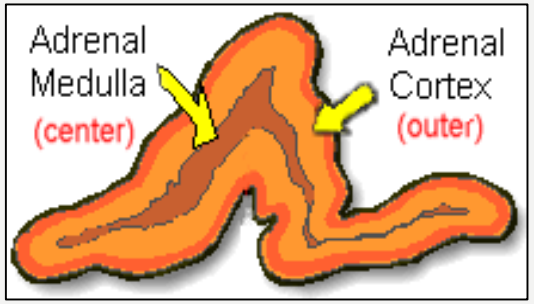
# OBJECTIVES:

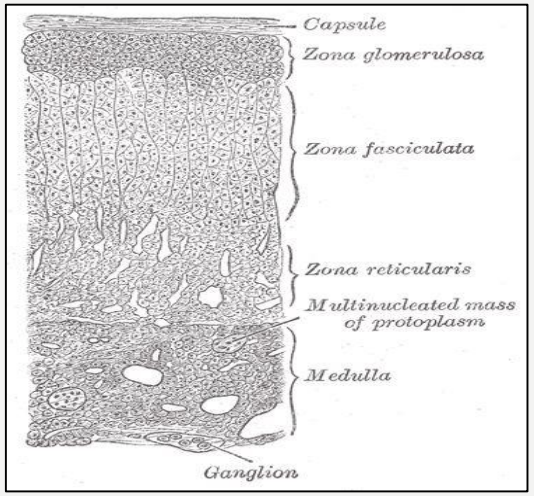
- ✓ To identify different causes of primary adreno-cortical hypofunction (Addison's disease).
- ✓ To identify secondary causes of adreno-cortical hypofunction.
- ✓ To understand the diagnostic algorithm for adreno-cortical hypofunction.
- ✓ To understand the interpretation of laboratory tests of adreno-cortical hypofunction.

# Introduction to the adrenal gland:

| ANATOMICALLY: | | |
|---|---|---|
| ➢ **The adrenal gland is situated on:** the **anteriosuperior** aspect of the kidney.<br>➢ **It receives its blood supply from:** the **adrenal arteries**. | | |
| **Histologically:** | | |
| The adrenal gland consists of <u>two distinct</u> tissues of different embryological origin, the **outer cortex** and **inner medulla**. | | |
| **The adrenal cortex comprises three zones based on cell type and function:** | | |
| The **outermost** zone | The **deeper** layers of the cortex | |
| **Zona glomerulosa** | **Zona fasciculata** | **Zona reticularis** |
| **Aldosterone** (the principal mineralocorticoid). | **Glucocorticoids** – mainly cortisol (95%) | **Sex hormones** |



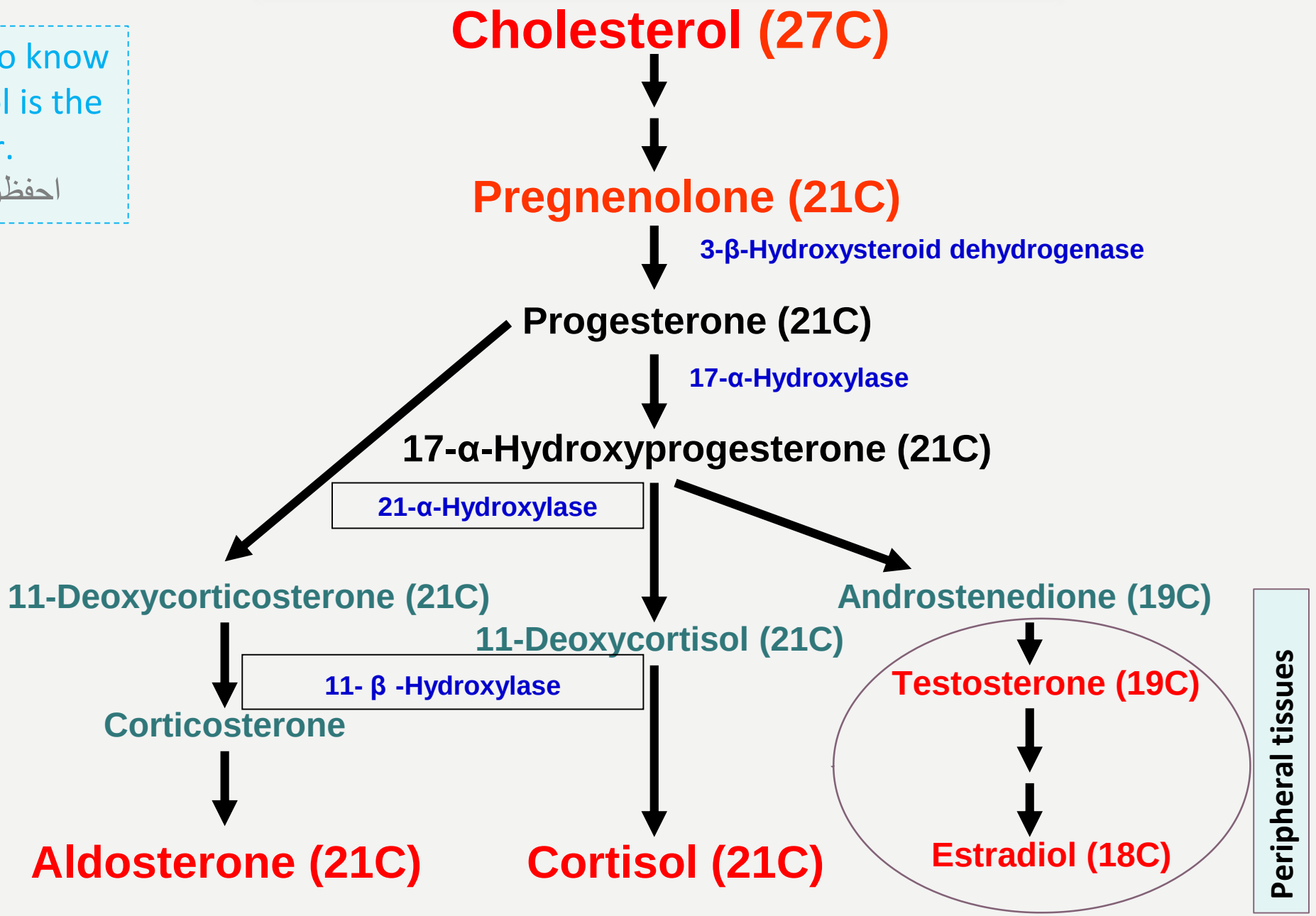




اقروهم على السريع..تخيلوا سؤال بايو ويسأل عن الزونا فسكيولاتا؟ وش بيخلون للهستو؟

# Steroid Hormone Synthesis

You only have to know that cholesterol is the precursor.
احفظوهم من الفزيو..



# ALDOSTERONE HORMONE

اعادة لكلام الفزيولوجي علشان كذا حشرناهم بسلايده.. لاتطولون على السلايدة هذا مو موضوعنا ولا تخصصنا!

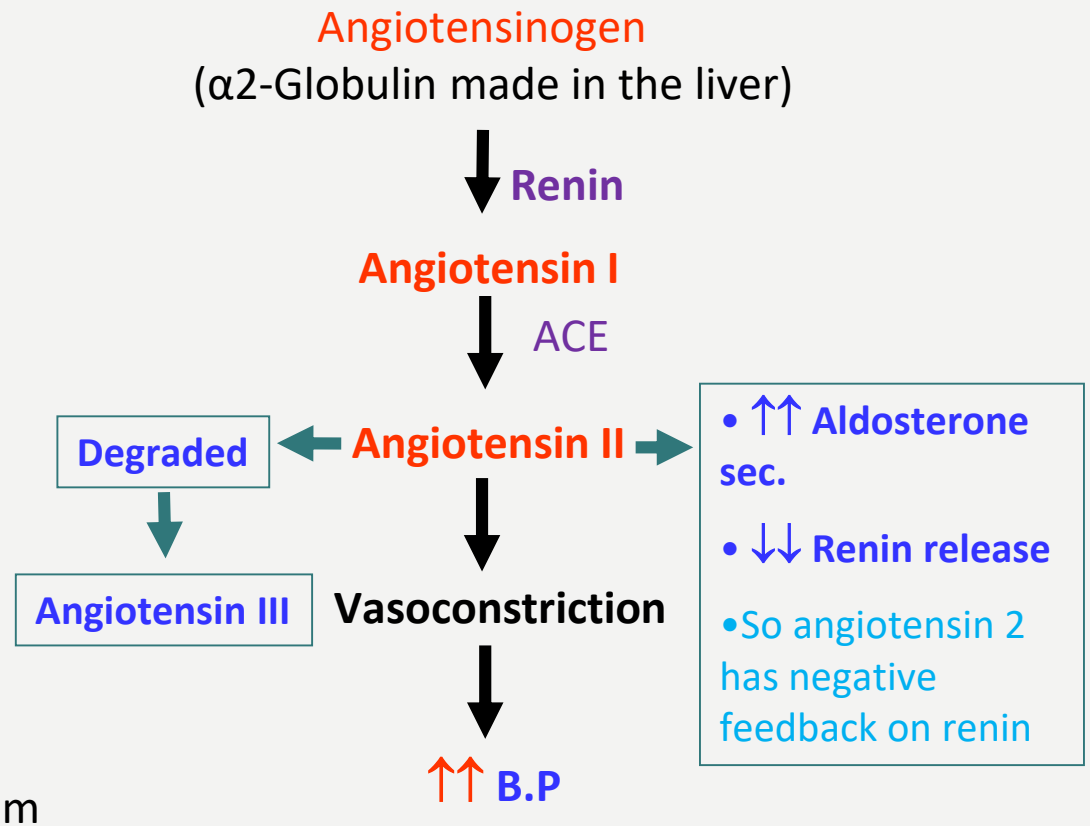
- Aldosterone is a major regulator of water and electrolyte balance, as well as blood pressure.
- **The principal physiological function of aldosterone is:** to conserve $Na^+$
  - **How?**
    - by acting on the distal convoluted tubule of kidney, leads to:
      - ↑↑ potassium excretion
      - ↑↑ sodium and water reabsorption

## ❖ RENIN-ANGIOTENSIN SYSTEM :

- It is the most important system controlling aldosterone secretion.
- It is involved in B.P. regulation.

**Renin:**

- A **proteolytic** enzyme produced by the **juxtaglomerular cells** of the afferent renal arteriole.
- Sensitive to B.P. changes through **baroreceptors**
- Released into the circulation in response to :
  - a fall in circulating blood volume.
  - a fall in renal perfusion pressure.
  - loss of $Na^+$.



# Adrenocortical hypofunction (AC)

**Primary AC hypofunction (destruction of adrenal gland, Addison's disease):**

**Secondary AC hypofunction**

In this case , even in high levels of ACTH there will still be adrenal hypofunction because the problem is in the adrenal itself

## Causes:

**1- Autoimmune.**
**2- Infection**, e.g., tuberculosis.
**3- Infiltrative lesions**, e.g., amyloidosis

## Symptoms:

precipitated by trauma, infection or surgery

| |
|---|
| 1- **Lethargy**, **weakness**, **nausea** & **weight** loss. |
| 2- **Hypotension** especially on standing (postural) |
| **3-Hypoglycemia**, ↓ $Na^+$, ↑ $K^+$ and **raised urea**<br>Note that in addison's : symptomatic treatment Sodium dextrose (Iv ) to treat hypotension |
| 4- Life threatening and need urgent care. |
| 5-Deficiency of both glucocorticoids and mineralocorticoids |
| 5- **Hyperpigmentation** (buccal mucosa, skin creases, scars). غالبا بيكون مكتوب بالكابس |

## HYPERPIGMENTATION IN ADDISON'S DISEASE

- Hyperpigmentation occurs because **melanocyte-stimulating hormone** (MSH) and (ACTH) share the same precursor molecule, **Pro-opiomelanocortin** (POMC).
- The anterior pituitary POMC is cleaved into:

ACTH, γ-MSH, and β-lipotropin.

- The subunit ACTH undergoes further cleavage to produce α-MSH, the most important MSH for skin pigmentation.
- In **secondary adrenocortical** insufficiency, skin darkening DOESN'T OCCUR.

Because in this case the ACTH will be low

Why the urea is raised? Due to dehydration (which is caused by vomiting mainly), while in "Cushing" the ↑ urea is due to proteolysis.

**EXTRA PICTURE**

POMC cleavage products

# Adrenocortical hypofunction (AC)

**Primary AC hypofunction (destruction of adrenal gland, Addison's disease):**

**Secondary AC hypofunction**

## Investigation of Addison's disease (AD)

- Normal serum cortisol and UFC (urine free cortisol) **does not** exclude AD.
- **Simultaneous measurement** of cortisol and ACTH improves the accuracy of diagnosis of primary adrenal failure:
  - ✓ **Low serum cortisol** ( <200nmol/L) **and High plasma ACTH**(Why? To compensate , to try to increase the level of cortisol ) (>200 ng/L)
- The patient should be **hospitalized**.
- **Basal measurement of:** Serum urea, $Na^+$, $K^+$ & glucose Serum cortisol and plasma ACTH. These measurement are essential here, but they aren't in cushing syndrome tests.
- **Definitive diagnosis** and **confirmatory tests** should be done later after crisis. Next slide →

# Adrenocortical hypofunction (AC)

**Primary AC hypofunction (destruction of adrenal gland, Addison's disease):**

**Secondary AC hypofunction**

## Investigation of Addison's disease (AD)

### 2. Adrenal antibodies

- Detection of adrenal antibodies in serum of patients with autoimmune Addison's disease.
- Or if we have a disease like SLE

### 1. Short tetracosactrin (Synacthen) test (Short ACTH stimulation test)

- Measure basal S. cortisol
- Stimulate with I.M. synthetic ACTH (0.25 mg)
- Measure S. cortisol 30 min after I/M injection (one injection)
  - **Normal: ↑ of S. cortisol** to >500 nmol/L because we have intact adrenal cells
  - **Confirm AD: Failure of S. cortisol to respond to stimulation**.
- **Abnormal results:**
  - Emotional stress
  - Glucocorticoid therapy
  - Estrogen contraceptives.

We must do Cortisol and ACTH Measurement first Then short syncathen test !

### 3. Imaging (Ultrasound/CT)

- **Ultrasound** or **CT** for adrenal glands for identifying the cause of primary adrenal failure.

الدكتورة تعدت المعلومة!

# Adrenocortical hypofunction (AC)

**Primary** AC hypofunction (destruction of adrenal gland, **Addison's disease**):

Secondary AC hypofunction

**Causes:**

- **Pituitary tumors**
- **Vascular lesions**
  **Ex**:stroke affecting pituatary
- **Head trauma**
- **Hypothalamic diseases**
- **Iatrogenic** (steroid therapy, surgery or radiotherapy)

## Investigations:

- **MRI for pituitary gland**
- **Short synacthen test:**
  No response - Adrenocortical cells **fail** to respond to short ACTH stimulation.
- **Low serum cortisol with low plasma ACTH.**
- **Insulin-induced hypoglycemia:**
  Adrenal failure secondary to pituitary causes
- **confirmatory test**

Next slide

# Adrenocortical hypofunction (AC)

**Primary AC hypofunction (destruction of adrenal gland, Addison's disease):**

**Secondary AC hypofunction**

## Depot Synacthen test (confirmatory test)

***Measure basal S. cortisol**

1. Stimulate with I.M. synthetic ACTH (1.0 mg) on each of three consecutive days
2. Measure S. cortisol at 5 hours after I.M. injection on each of the three days(While in the short one , we give only one injection)

**Interpretation of results:**

- **Addison's disease: No** rise of S. cortisol >600 nmol/L at 5 h after 3rd injection.
- **Secondary AC: Stepwise increase** in the S. cortisol after successive injections

Because we still have working adrenal cells, In this case these cells will not respond to small amount of stimulation (so no stimulation in the short ACTH stimulation test!
But in the depot , there will be stimulation so there will be an increase because there will be an increased functioning of the lazy cells (these cells may be lazy due to atrophy)

**Limitations:** لا تضيعون وقتكم عليها ما ابيكم تعرفونها

- **Hypothyroidism:** Thyroid deficiency must be corrected before testing of adrenocortical functions
- **Prolonged steroid therapy**

*Note that u should only **understand** the procedure **not** memorize it.

# INVESTIGATIONS – IMPORTANT!! زبدة المحاضرة

| | Addison's disease (primary AC) | Secondary AC |
|---|---|---|
| Screening | **Basal plasma ACTH and basal serum cortisol, glucose, urea** and **electrolytes** | |
| | **Low cortisol** | **Low cortisol** |
| | **High ACTH** | **Low ACTH** |
| Confirmation | Short ACTH stimulation test: **No response**<br>Long ACTH stimulation test: No response | Long ACTH stimulation test: Stepwise **increase** in S. cortisol |
| Others<br>"نشتغل على السبب" | ➢ Adrenal autoantibodies<br>➢ Ultrasound/CT adrenal glands | ➢ Insulin-induced hypoglycemia<br>➢ MRI pituitary gland |

الاختبار بيجي على شكل كايس وغالبا معه جدول فيه نتيجة المختبر "نفس الميد" وبيطلبون التشخيص..
اذا سكندري ← بيكونون الاثنين متشابهين "الكورتيزول والاي سي تي اتش".
اذا برايمري ← بيكونون متعاكسين ← الكورتيزول يعكس وش قاعد يصير بالضبط "قليل يعني هايبو" والاي سي ت تي اتش يعكس الكومبنسشين "عالي يعني الكوتيزول قليل ويبي يزيده".. لا ننسى ان البرايمري هايبوفنكشن هو نفسه اديسون
بالنسبة للفرذر فبعد مانعرف اذا هو برايمري او سكندري نروح نشوف وش السبب؟ هل هو مرض مناعي؟ نشوف الأجسام المضادة.. هل هو ورم؟ نحولهم على قسم الأشعة..وبس الحياة سهلة ☺

# CASE BY DR.RANA

Patient came to the ER, he presented with lethargy, tremor, he cannot stand.

They measured his **sodium** levels and found them to be **low**, but with **high potassium** . They put him on iv saline for his hypotension . Then they measured his **cortisol** levels and found them to be **low**, but he had **high ACTH** levels. After that a short synacthen test was down ,but there was **no response** . Then they also performed a long ACTH stimulation test and found that the cortisol **did not** significantly increase.

- **SO WHAT IS YOUR DIAGNOSIS?**
  - ✓ PRIMARY ADRENOCORTICAL INSUFFICIENCY !

- The exam will come in the same way!
- Dr rana noted that one of the **clues** for diagnosing Addison's: **hyperpigmentation**

# Check your understanding!

**Q1: Which hormone is the major regulator of water and Sodium (Na+) balance?**

A. Aldosterone
B. ADH
C. Renin
D. Cortisol

**Q2: Renin is secreted from the Juxtaglomerular cells in response to:**

A. A fall in circulating blood volume
B. A fall in renal perfusion pressure
C. Loss of Na+
D. All of the Above

**Q3: In response to increased levels of Angiotensin II, renin production and secretion**

A. Increases
B. Decreases
C. Is not affected
D. Initially increases then decreases sharply

**Q4: Normally in a Short tetracosactrin (Synacthen) test, there will be an ……. response to I.M injection of ACTH**

A. Positive
B. Negative
C. Absent
D. Mixed

**Q5: A patient came to the clinic complaining of hypotension, weakness, lethargy, and hypoglycemia, and showed hyperpigmentation. What is your provisional diagnosis?**

A. AC Hyper-function
B. AC Hypofunction
C. Diabetes Mellitus
D. None of the Above

**Q6. In continuation of the previous question, the patient's tests showed low serum cortisol, high serum ACTH, and circulating adrenal antibodies. Which disease does this patient most likely suffer from?**

A. Cushing disease
B. Cushing syndrome
C. Addison's Disease
D. Secondary AC hypofunction

**Q7: A patient with Addison's Disease will NOT show a stepwise increase in Cortisol levels in in the Depot Synacthen Test.**

A. True
B. False

1.A 2.D 3.B 4.A 5.B 6.C 7.A

## Done by: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## Resources:

- 435's slides and notes.
- Clinincal Biochemistry – sixth edition


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