Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

CONGENITAL ADRENAL HYPERPLASIA & TESTICULAR FEMINIZATION SYNDROME.

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

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Color index: Important | Doctors notes | Further explanation.

OBJECTIVES:

- ✓ Adrenal steroidogenesis.
- ✓ **C**ongenital adrenal hyperplasia syndrome.
    1. Types.
    2. Biochemical characteristics.
    3. Clinical manifestations.
- ✓ Testicular feminization syndrome.

ADRENAL GLANDS

The zona glomerulosa:	The zona fasciculata & reticularis:	The adrenal medulla:
secretes aldosterone	secrete cortisol & the adrenal androgens	secretes catecholamines (mainly epinephrine)

❖ Glucocorticoids & Mineralocorticoids

Glucocorticoids:	Mineralocorticoids:
○ Steroids with **cortisol-like** activity. ○ Potent **metabolic regulators** & **immunosuppressants**. ○ Acts as an insulin antagonist	○ Steroids with **aldosterone-like** activity. ○ Promote **renal sodium reabsorption**. ○ Potassium excretion

HERMAPHRODITISM OR INTERSEX

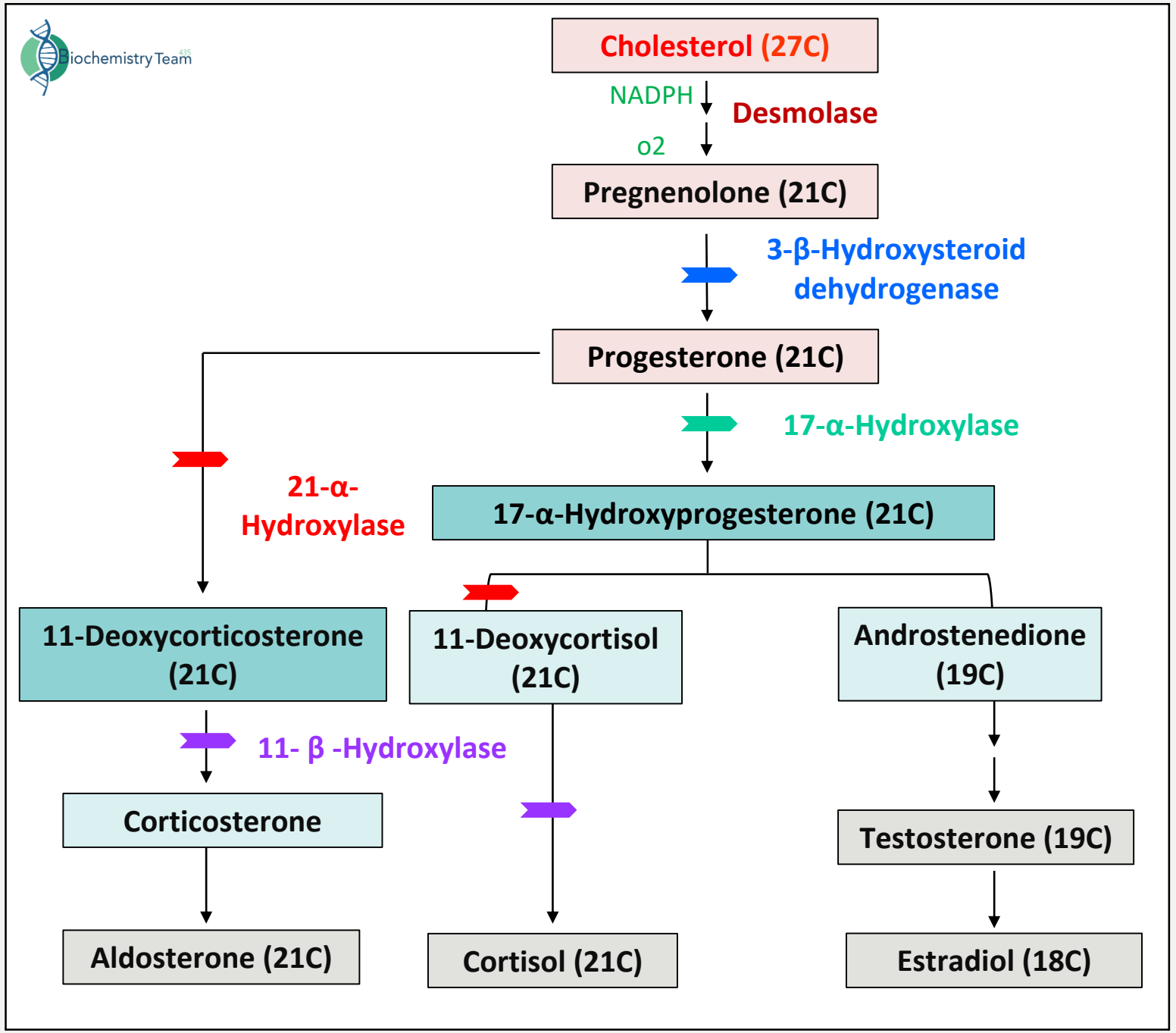
- **Intersex**: A person has neither standard male or standard female anatomy.
- Discrepancy between type of gonads and external genitalia

True hermaphrodite	Female pseudohermaphrodite (FPH)	Male pseudohermaphrodite (MPH)
ovary plus testis. The individual has both ovarian and testicular tissue.	only ovary this is the most important in this lecture!) Genetic and gonadal female with partial masculinization such as an enlarged clitoris resembling a penis and labia majora resembling a scrotum.	only testis A genetic and gonadal male with feminization or incomplete masculinization.

1-STEROIDOGENESIS AND CONGENITAL ADRENAL HYPERPLASIA SYNDROME

- Cholesterol is the parent compound for all steroid hormones. It is oxidized and then isomerized to progesterone which is further modified to the other steroid hormones by desmolase.
- A defect in the activity or amount of an enzyme in this pathway can lead to:
  - A **deficiency** in the synthesis of hormones After the affected step.
  - An **excess** in the hormones or metabolites before that step.
- Because all members of the pathway have potent biologic activity, serious metabolic imbalance occur with enzyme deficiencies.
- Collectively these disorders are known as the **congenital adrenal hyperplasia**.

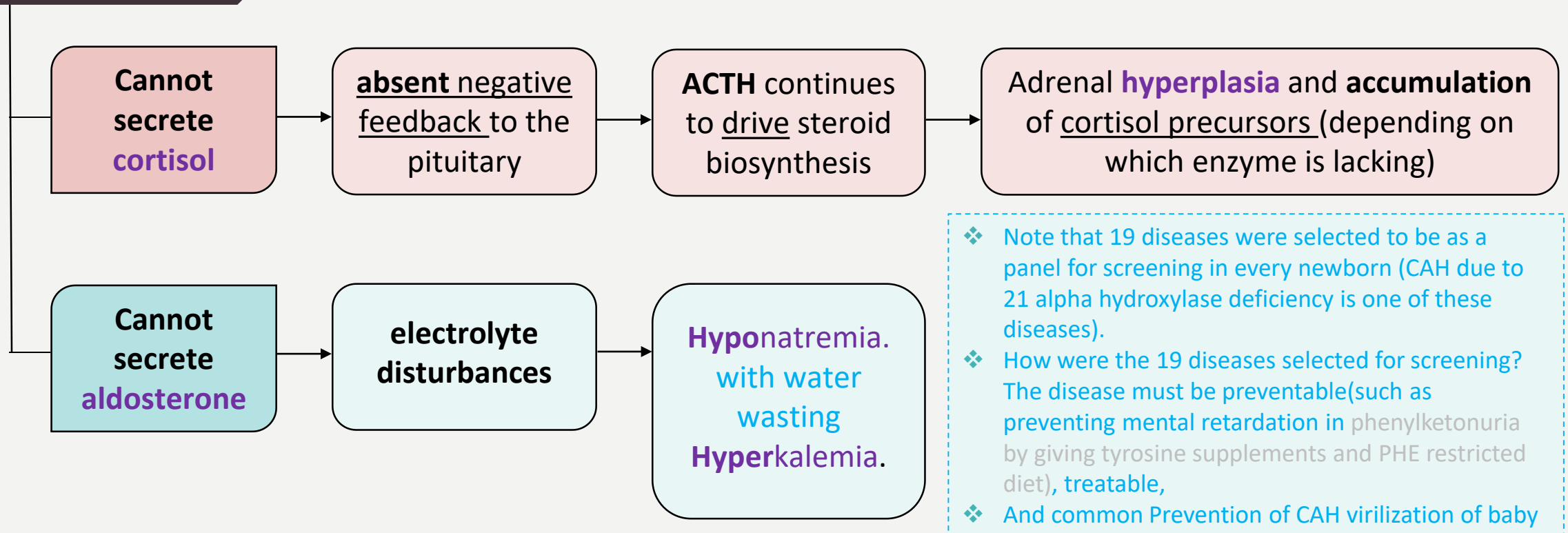
الجزئية الاولى من المحاضرة كلها بتشتغل على هالخطوات فاحفظوهم واكتبوهم بورقة على جنب وتبعوا معنا القصة..



CONGENITAL ADRENAL HYPERPLASIA (CAH) SYNDROMES

- It is the result of an **inherited** enzyme defect in **steroid biosynthesis.** Due to mutations in the genes coding for the genes coding for said enzymes.
- The condition might be **fatal** unless diagnosed **early.**

The adrenals:



- Note that 19 diseases were selected to be as a panel for screening in every newborn (CAH due to 21 alpha hydroxylase deficiency is one of these diseases).
- How were the 19 diseases selected for screening? The disease must be preventable(such as preventing mental retardation in phenylketonuria by giving tyrosine supplements and PHE restricted diet), treatable,
- And common Prevention of CAH virilization of baby is done by giving glucocorticoids (cortisone) to allow the negative feedback to occur thus decreasing ACTH → decreased testosterone which will inhibit virilization of the baby girl

Congenital Adrenal Hyperplasia (CAH) Syndromes

- **21-α-Hydroxylase**
- **11- β -Hydroxylase**
- **17-α-Hydroxylase**
- **3-β-Hydroxysteroid dehydrogenase**

❖ **21 *α*-hydroxylase** acts on: both **progesterone** & **17 *α*-hydroxyprogesterone** .

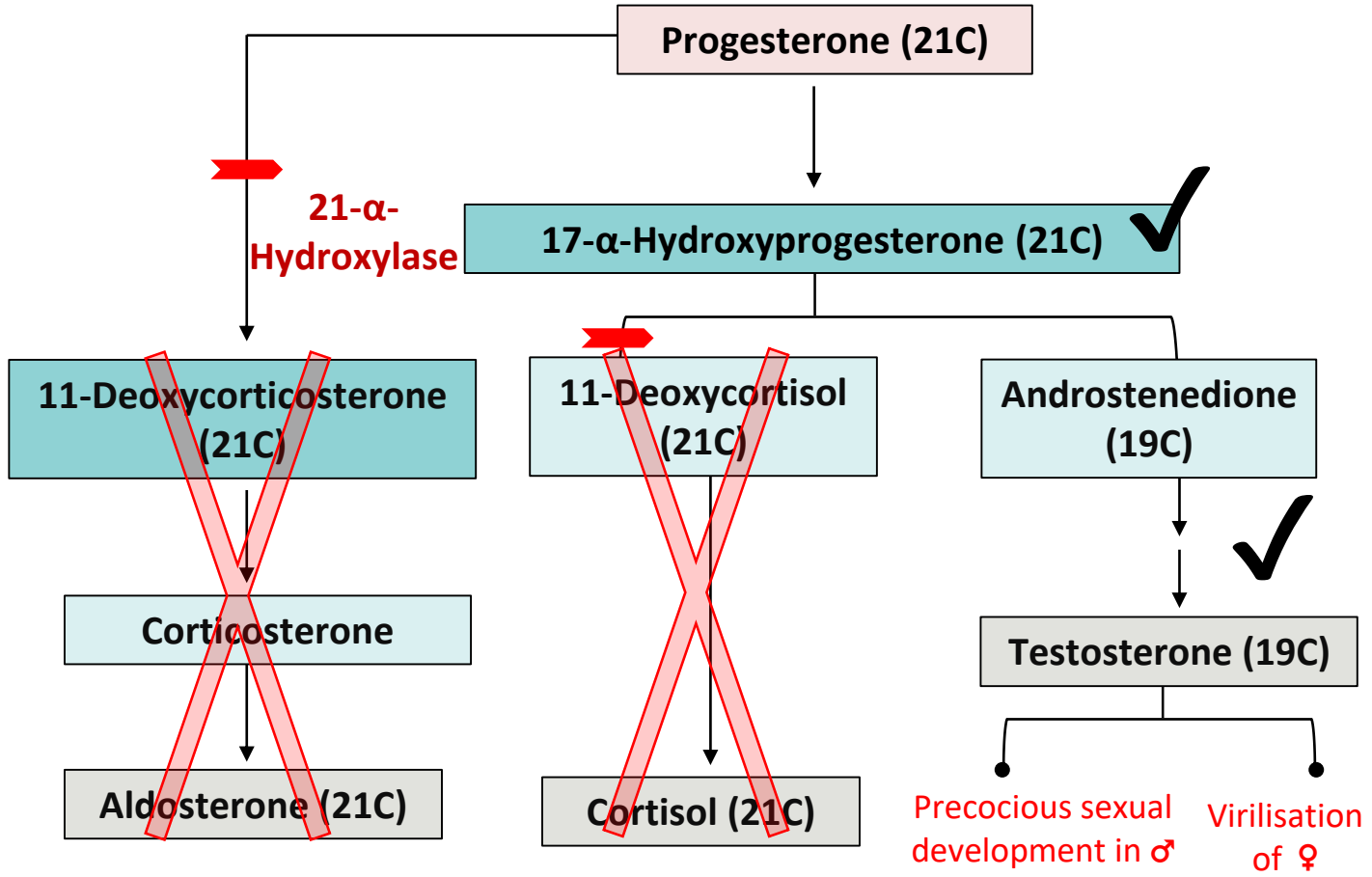
❖ So if the enzyme is deficient:

- ➢ **11-Deoxycorticosterone** won't be synthesized from **progestearone**
- ➢ **11-deoxycortisol** won't be synthesized from **17 *α*- hydroxyprogesterone.**

→ This will lead to lack of both **aldosterone** & **cortisol**

- ➢ On the other hand, excessive **Androstenedione** will be formed → converted to **testosterone** in peripheral tissues → **Virilization of females** and **precocious sexual development in males.**

كأن عندي كوب من ورق وفيه ثلاثة ثقوب وجيت سديت ثقبين وخليت بس ثقب واحد.. المويه بالبداية بتتسرب من الثلاثة ثقوب لكن بعدين بتتسرب من ثقب واحد.. كذلك الباثواي اللي عندنا طريقين بينسدون وواحد بيظل مفتوح فلمن يزيد الاي سي تي اتش ويأمر الكورتكس.. الكورتكس ماراح يكون عنده الا طريق واحد متاح!



Congenital Adrenal Hyperplasia (CAH) Syndromes

- 21-α-Hydroxylase
- 11- β -Hydroxylase
- 17-α-Hydroxylase
- 3-β-Hydroxysteroid dehydrogenase

21-α-Hydroxylase

❖ **The most common type of CAH (90%).**

❖ **Autosomal** recessive condition.

common in Caucasians (one in every one thousand babies)

Clinical presentation:

Based on severity:	
Severe cases:	**less severe cases:**
Mineralocorticoid deficiency → salt & H_2O loss → **hypovolemia** & **shock** → **neonatal adrenal crisis**	**Late** presentation (adult life) is possible. (Partial enzyme defect)
Based on degree of enzyme deficiency:	
Complete enzyme defect (classic form):	**Partial enzyme defect** (non-classic form):
↑ stimulation of adrenal androgen production → **virilization in baby girls** & **precocious puberty in boys**.	late onset form → **menstrual irregularity** & **hirsutism** in young females.

Pathogenesis:

❖ Impaired synthesis of **both** cortisol & aldosterone.

- ↓ **[cortisol]**→↑ **ACTH secretion** → **Adrenal gland hyperplasia**.
- Accumulated **17α-hydroxyprogesterone** are diverted to the biosynthesis of sex hormones →signs of **androgen excess**:
  - **Ambiguous** genitalia in newborn girls (**FPH**)
  - Rapid postnatal growth in both sexes.

Complete defect: if the takes place in the active site of the enzyme.
Partial defect: if it occurs in the co-factor binding site of the enzyme (not in the active site).

Congenital Adrenal Hyperplasia (CAH) Syndromes

- **21-α-Hydroxylase**
- **11- β -Hydroxylase**
- **17-α-Hydroxylase**
- **3-β-Hydroxysteroid dehydrogenase**

Laboratory diagnosis:

- ↑ **plasma [17-hydroxyprogesterone]** as early as **4** days after birth.
- Serum sample taken at least **2 days after** birth (Why? earlier samples may contain maternally derived 17-hydroxyprogesterone).

Classic (complete) deficiency	Late-onset (partial) deficiency if 17 alpha hydroxy progesterone was BORDERLINE
• characterized by markedly elevated serum levels of 17-hydroxyprogesterone	• May require corticotropin **(ACTH) stimulation test**: • Measure base-line and stimulated levels of 17-hydroxyprogesterone. ✓ **High level** of 17-hydroxyprogesterone after stimulation is diagnostic. ✓ **if normal:** aldosterone and cortisol should be elevated.

❖ Genetics:

Mutations in the CYP21 gene:	***Deletion – ****Nonsense** most common here- *****Missense**
DNA testing:	For **pre**natal diagnosis and **confirmation** of diagnosis.

A sample from the amniotic fluid or a blood sample from both parents (because it's recessive, so both parents most have the mutation).

*Deletion/ insertion: either adding or deleting a nucleotide results in frame shift and gives different translation outcome.

طبعا احنا نعرف ان الترانسليشن يتم عن طريق الكودونز بحيث كل 3 نيوكلوتيدز يعطوني كودون معين وبالتالي الناتج يعطيني انزايم معين، فلو انضاف او انحذف أي نيوكلوتيد في السيكوينس حق الترانسليشن راح يتغير الناتج من العملية بالكامل، لأن الكودونز راح تتغير بسبب الإضافة او الحذف.

**A nonsense mutation is the substitution of a single base pair that leads to the appearance of a stop codon where previously there was a codon specifying an amino acid. (replacement of one of the nucleotides results in premature stop codon.)

***A missense mutation is when the change of a single base pair causes the substitution of a different amino acid in the resulting protein.

Congenital Adrenal Hyperplasia (CAH) Syndromes

- 21-α-Hydroxylase
- 11- β -Hydroxylase
- 17-α-Hydroxylase
- 3-β-Hydroxysteroid dehydrogenase

11- β –Hydroxylase deficiency

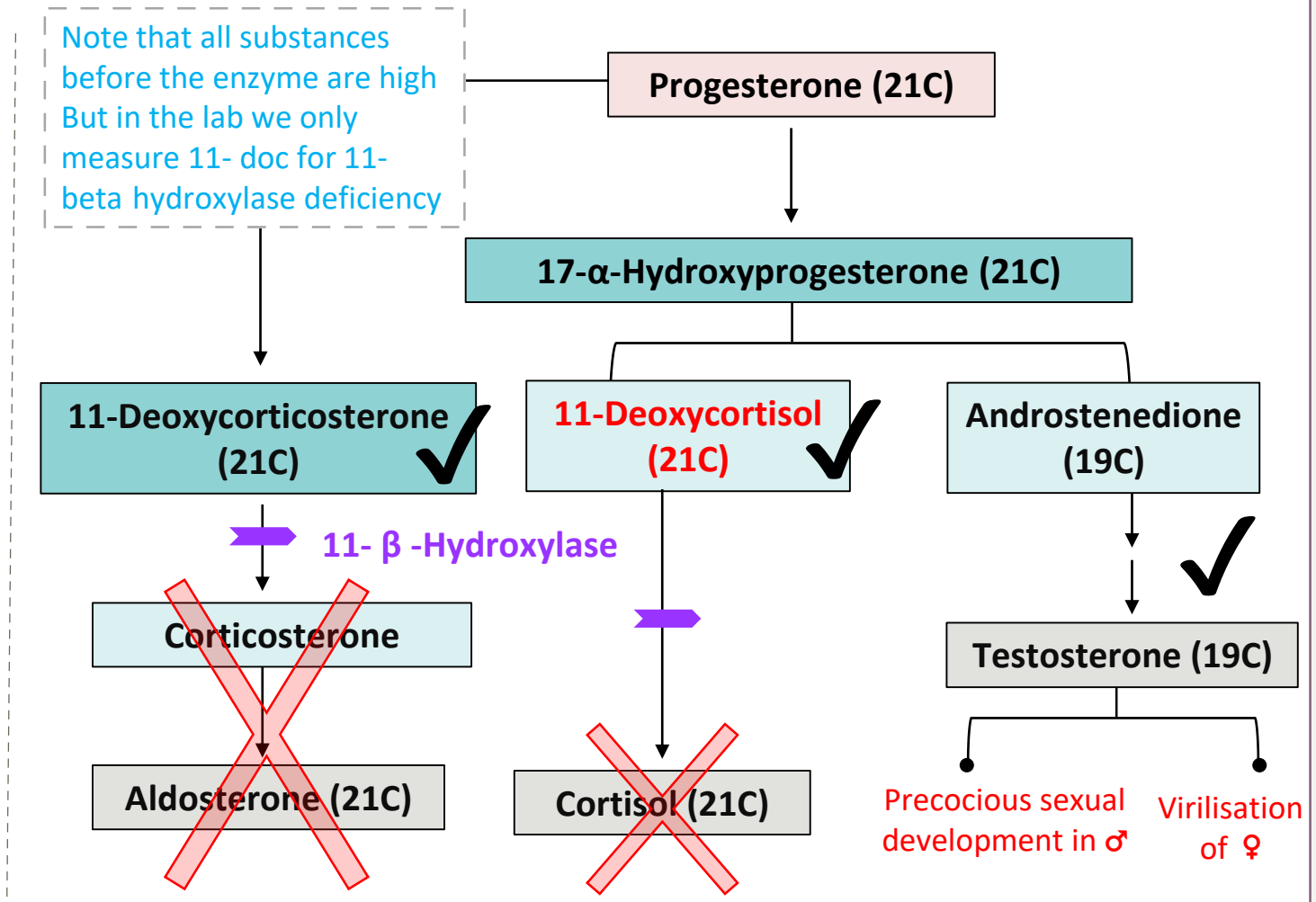
❖ **leads to:**

- ➢ High concentrations of **11-deoxycortisol**.
- ➢ high levels of **11-deoxy-corticosterone** with mineralocorticoid effect.
  - salt and water retention.
  - **Suppresses renin/angiotensin system → low renin hypertension.**

  (a type of hypertension which NOT caused by high levels of renin)
- ➢ **Decrease** in serum **cortisol**, **aldosterone**, and **corticosterone**.

❖ **Clinical presentation:**

- **Musculanization** in females (FPH).
- Early **virilization** in males.



Congenital Adrenal Hyperplasia (CAH) Syndromes

21-α-Hydroxylase | 11- β -Hydroxylase | 17-α-Hydroxylase | 3-β-Hydroxysteroid dehydrogenase

17-α-Hydroxylase

❖ **Characterized by:**

- ↑ **Progesterone**
- Virtually **no** **sex hormones** or **cortisol** are produced.

❖ **Clinical features:**

- Increased production of mineralocorticoid causes **sodium** and **fluid** retention and, therefore, **hypertension**.
- All patients have female genitalia.

3-β-Hydroxysteroid dehydrogenase

❖ **Characterized by:**

- ↑ **Pregnenolone**
- - Virtually **no** **glucocorticoids**, **minerlaocortocoids**, or active **androgens**, or **estrogens**.

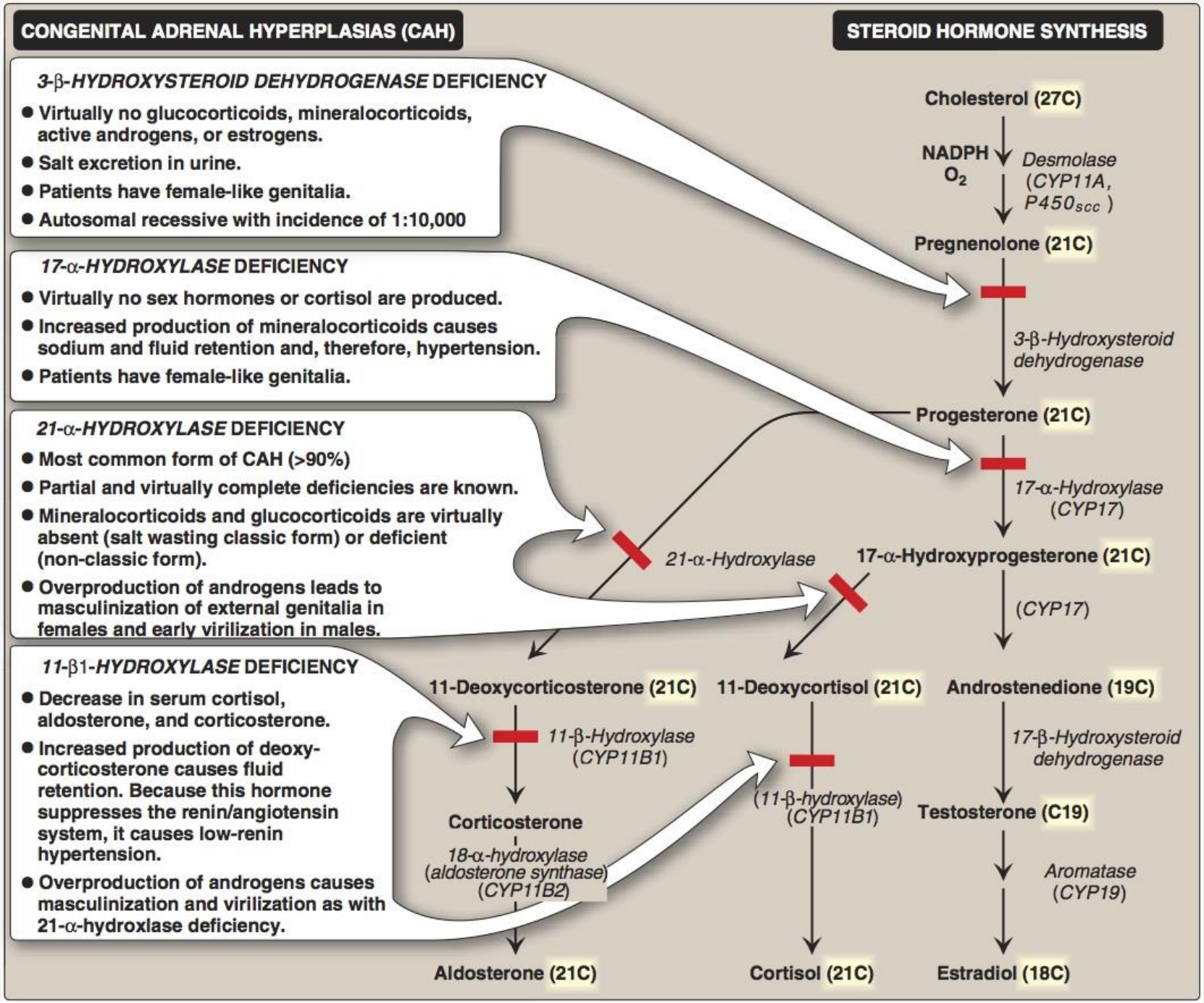
❖ **Clinical features:**

- Marked **salt excretion** in urine.
- All patients have **female genitalia**.

*ملاحظة: هالنوعين موب مذكورين بالسلايدز مباشرة ولا انشرحوا لكن موجودين بالصورة الموجودة بالشريحة القادمة "والصورة كانت بالسلايدز"

Biochemistry Team 435

Summary:



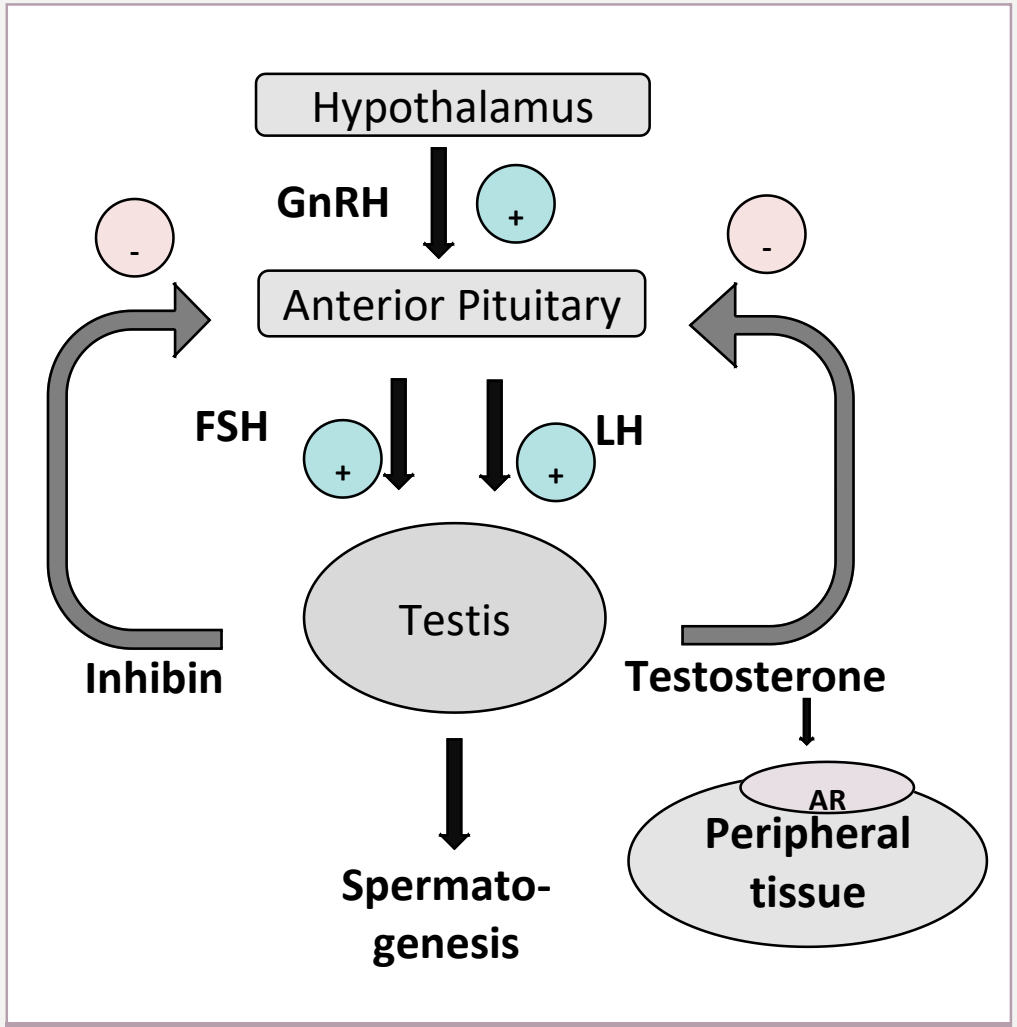
2-TESTICULAR FEMINIZATION SYNDROME (ANDROGEN INSENSITIVITY SYNDROME)

❖ Disorders of Male Sexual Differentiation

- They are **rare** group of disorders
- **The defect may be in:**

Testosterone production	Androgen receptors
Impaired testosterone production. Due to several etiologies such as radiation.	**Inactive** androgen receptors → target tissues **CANNOT** respond to stimulation by circulating testosterone; e.g., **Testicular feminization syndrome.** Genes coding for receptors have mutations.

- hypothalamus will secrete GnRH which will stimulate anterior pituitary (increases LH and FSH).
- **LH** will act on **leydig** cells which will secrete testosterone
- **FSH** will act on **Sertoli** cells for spermatogenesis and the production of FSH.
- testosterone inhibits LH while inhibin mainly inhibits FSH.



Control of testicular function by the gonadotrophins

2-TESTICULAR FEMINIZATION SYNDROME (ANDROGEN INSENSITIVITY SYNDROME)

- **46,XY karyotype**
- **X**-linked **recessive** disorder
- Patients have normal testes & produce normal amounts of **müllerian-inhibiting factor (MIF),** therefore, affected individuals **DO NOT have** fallopian tubes, a uterus, or a proximal (upper) vagina.

جاهم سؤال العام الماضي والي قبله عن هالنقطة.

Androgen receptor resistance → **high** testosterone blood level → In peripheral tissue, **testosterone** will be converted into **estradiol** (by **aromatase**) → **feminization**

Means -although he is a male- the external genitalia will be like females.

❖ Clinical picture:

Complete androgen insensitivity syndrome (CAIS):	**Partial androgen insensitivity syndrome (PAIS):**
• CLEAR Female external genitalia with **normal** labia, clitoris, and vaginal introitus (MPH)	• Mildly **virilized female external genitalia** (**clitorimegaly** without other external anomalies) • Mildly **undervirilized male external genitalia** (***hypospadias** and/or **diminished penile size**).

*A congenital condition in males in which the opening of the urethra is on the underside of the penis.

2-TESTICULAR FEMINIZATION SYNDROME (ANDROGEN INSENSITIVITY SYNDROME)

❖ Diagnosis:

1. Karyotype:	• Differentiate an **under** masculinized male from a masculinized female. • Look for Y Chromosome.
2. **Fluorescent in situ hybridization** (FISH):	• Presence of a **Y chromosome** can be confirmed by probes for the ***SRY* region** of the Y chromosome. • These offer a much quicker turnaround time than conventional karyotypes. نفس الكاريوتايبنق "تعلمنا اذا فيه واي أو لا" الفرق ان الفش اسرع وتوفر وقتنا الثمين..
3. **Imaging Studies "**Pelvic ultrasound**":**	• **Absence** of fallopian tubes and uterus. الالترا ساوند يأكد تراه ذكر ماعنده فاولابيان تيوب ولا يوترس
4. **DNA tests and mutation analysis for androgen receptor gene:**	• Complete or partial gene deletions, point mutations, or small insertions/deletions
5. **Increased (or normal) testosterone and dihydrotestosterone blood levels**	

Check your understanding!

Q1:Which of the following is the most common enzyme deficiency in CAH:

A. 21 alpha hydroxylase.
B. 11 beta hydroxylase .
C. 17 alpha hydroxylase.
D. 3 beta hydroxysteroid dehydrogenase.

Q2: Which of the following will be high in case of 21 alpha hydroxylase:

A. Testosterone.
B. 17-α-Hydroxyprogesterone.
C. Androstenedione.
D. All of the above.

Q3: Which of the following will be low in case of 21 alpha hydroxylase:

A. Androstenedione.
B. Progesterone.
C. Aldosterone.
D. Cortisol

Q4: In Testicular Feminization Syndrome The defect may be in:

A. Testosterone production.
B. 17-α-Hydroxyprogesterone.
C. Androgen receptors .
D. Both A&C.

Q5:Which of the following have mineralocorticoid effect:

A. 11-Deoxycorticosterone.
B. 11 beta hydroxylase.
C. 11-Deoxycortisol.
D. 17-α-Hydroxyprogesterone.

Q6: Which of the following will be high in case of 11 beta hydroxylase:

A. Progesterone.
B. 17-α-Hydroxyprogesterone.
C. 11-Deoxycorticosterone.
D. All of the above.

Q7: Which of the following will be low in case of 11 beta hydroxylase:

A. 17-α-Hydroxyprogesterone.
B. Cortisol.
C. Aldosterone.
D. Both B & C.

Q8:Which of the following enzymes will convert testosterone to estrogen:

A. 21 alpha hydroxylase.
B. 11 beta hydroxylase.
C. aromatase.
D. 3 beta hydroxysteroid dehydrogenase.

1.A 2.D 3.C&D 4.D 5.A 6.D 7.D 8.C

Check your understanding!

Mini cases by Dr. Rana:

❖ Patient has the following results On biochemical investigation:
- Testosterone and 17 hydroxy progesterone are **high**
- Aldosterone and cortisol are **low**

✓**what is the enzyme deficient?** 21-alpha hydroxylase
✓**An important Q that may be asked: what is the diagnostic metabolite in CAH due to 21 alpha hydroxylase?**
17-alpha hydroxyprogestrone

❖ Patient has the following biochemical investigation results:
- **High** testosterone and **high** 11-DOC and **low** cortisol and aldosterone

✓ **What is the deficient enzyme?** 11-beta hydroxylase
✓ **What is the difference in 21-alpha hydroxylase and 11-beta hydroxylase deficiency?**
21-alpha hydroxylase deficiency will have hypotension as a symptom due to lack of aldosterone while 11-beta hydroxylase will have hypertension due to high levels of 11-DOC which has a mineralocorticoid activity

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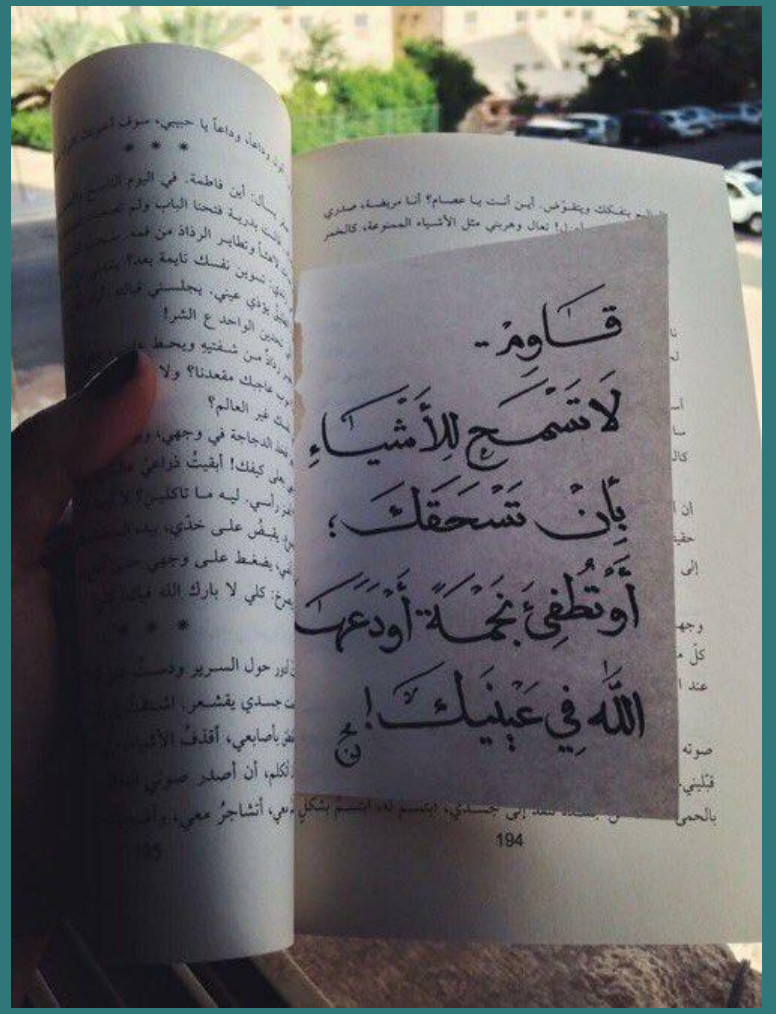

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Resources:

- 435's slides.
- Lippincott's illustrated reviews: Biochemistry – sixth edition.
- Hypospadias – Mayo clinic