

بِسْمِ اللّٰهِ الرَّحْمٰنِ الرَّحِیْمِ
(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)



جناح

Pharmacology | FINAL 2

Skin Pharmacology pt.2



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Quiz on the last lecture!

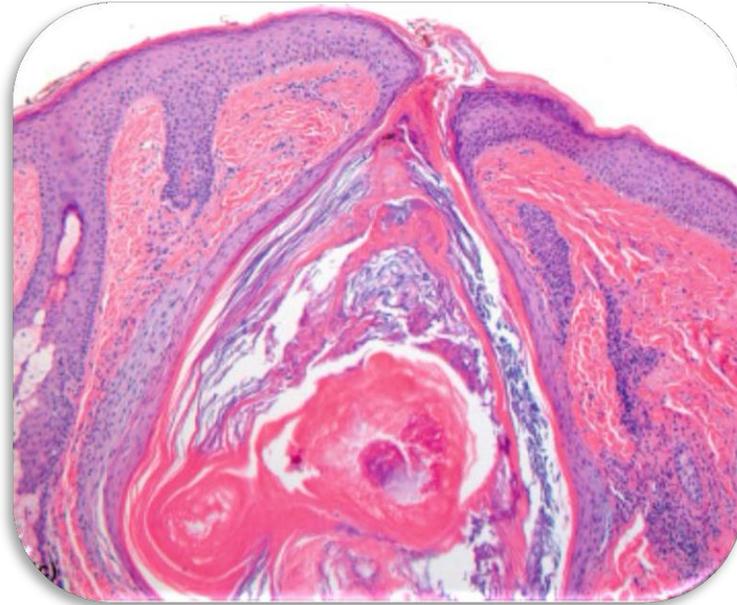


Figure (1): Acne vulgaris

REMEMBER FROM GENERAL PHARMACOLOGY

- Bacteriostatic refers to an agent that **inhibits** bacterial **growth**, while bactericidal describes an agent that **kills** bacteria.
- A special side effect associated with Clindamycin is pseudomembranous colitis.
- Clindamycin and erythromycin are antibiotics that inhibit bacterial protein synthesis.

Does that ring a bell?

- Acne develops when **excess oil** (sebum) is produced, leading to **clogged hair follicles**. As a result, **bacteria** (*Cutibacterium acnes*) thrive in these clogged pores, causing infection. The body then initiates an **immune response** against the clogged pores and bacteria, which explains the pathophysiology of acne.
- Acne progresses as follows,
 - **Comedonal lesions**, if inflamed **Inflammatory lesions** **Nodulocystic lesion**, if not treated early **Scarring**.
- Depending on the stage/kind of acne, proper treatment is indicated.
 - ✓ As acne progresses, more extensive treatment is given.

Lotion VS. Cream VS. Gel VS. Solution

Feature	Lotion	Cream	Gel	Solution
Consistency	More liquid than cream	Thicker than lotion	Semi-solid, light	Very liquid / watery
Water Content	High	Moderate	High (water or alcohol base)	Very high
Oil Content	Low to moderate	High	Very low or none	Very low
Best for Skin Type	Most skin types	Dry or sensitive skin	Oily skin	Oily skin
Application on Hairy Areas	Acceptable	Not ideal	Usually acceptable	Best for hairy areas
Alcohol Content	Usually none	None	Sometimes present	Often contains alcohol
Effect of Alcohol	—	—	May dry skin slightly	Dries skin and removes excess oil

There are further comparisons, but this is what was mentioned in the lecture.

Topical Therapy (Indications)

Usually given for:

- comedonal acne
- mild to moderate inflammatory acne

Topical Therapy

Depending on the type of the skin (oily/dry) and the condition, we choose the preparation's type:

- Cream for sensitive or dry skin.
- Lotion for any skin type.
- Gel for oily skin as it has high oil content.
- Solution for oily skin

Topical Therapy (Anti Comedonal Agents)

[] = Concentration

- Topical Retinoids, [] = 0.025% - 0.5%
 - Retinoids are vitamin A derivatives.
- Azelaic acid
- Salicylic acid

* لا يصلح العلم لطالب متلاعب؛ تارة يقرأ ويتعب، وتارة

يلهو ويلعب، فإن العلم محبٌ غَيُورٌ.

- احْرِضْ عَلَى وَقْتِكَ كُلَّ الْحَرْصِ، وَعَظِّصْ عَلَيْهِ بِنَاجِدِيكَ،

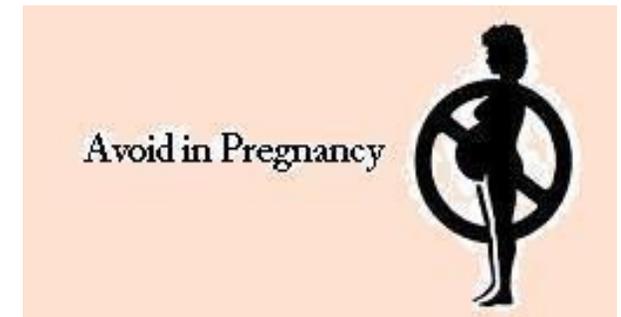
وَلَا تَضَيِّعْ شَيْئًا مِنْ عَمْرِكَ، إِلَّا فِي الْإِفَادَةِ أَوِ الْإِسْتِفَادَةِ.

Topical Retinoids (Adapalene, Differin)

Topical Retinoids 0.025% - 0.5%

- Because of their photosensitivity, it's better to **apply them at night.**
- **Always apply test dose.**
- **Start at low concentrations.**
- Although their systemic manifestations are minimal (not easily absorbed), they should be **Avoided in pregnancy , category X; affect fetus.(TERATOGENIC)**

➤ Remember, **category X** means that it has confirmed risk, thus contraindicated in pregnancy, even if applied topically it will be absorbed and go to the systemic circulation .



Topical Retinoids (Adapalene, Differin)

➤ Side Effects:

- When the drug is first applied, it causes a temporary exaggeration of acne, known as **pustular flare**.

➤ Why the exaggeration?

- Acne lesions, including deep-seated pustules and comedones, may already be present beneath the skin's surface. The medication promotes skin cell turnover and exfoliation, which helps unclog pores and bring these lesions to the surface more quickly.
- **Photosensitivity.**
- **Skin irritation and erythema.** (common topical side effect)
- **Dryness, forcing people to use moisturizers, and peeling.**

Mnemonic: Retinoids Side effects: Puppies Frequently Irritate Eager Dogs

Pu = Pustular flare, **Frequently**= Photosensitivity, **Irritate** = irritation, **eager** = erythema, **Dogs** = Dryness

Azelaic Acid 15-20%

➤ Mechanisms:

- 1. Competitive inhibitor of mitochondrial oxidoreductases and of 5 alpha-reductase, inhibiting the conversion of testosterone to 5-dihydrotestosterone, giving it the potential to treat baldness when used in combination with other agents. (Remember Finasteride, a trichogenic drug).**
 - Acne can be due to hormonal changes during puberty (14-25yr stage of intense hormonal changes) , where dihydrotestosterone levels increase, enhancing acne.
 - Azelaic Acid affects acne by lowering secondary sex hormones levels.
- 2. It also possesses bacteriostatic activity to both aerobic and anaerobic bacteria including Propionibacterium acnes (cutibacterium acnes).**
- 3. It possesses an anti-inflammatory and antioxidant properties, clearing free radicals that can be damaging to the skin.**

Azelaic Acid 15-20% – Continued.

- Can be produced chemically, but also naturally from **Malassezia furfur** (pathogen of tinea versicolor)
- If given topically it reduce the local effect of DHT so the acne production decrease (As mentioned before using this drug orally for treating hair loss or baldness, it can have a side effect related to sex function but when used topically they don't occur), **Applied twice daily.**

!Any acidic drug can cause erythema and irritation.

➤ **Side Effects**

- **Acid, so erythema and irritation.**
- **Decrease in pigmentation, therefore, it can be used clinically to treat hyperpigmentation.** (see next slide)

Mnemonic: Azelaic Acid Soothes New Eruptions, Improving Dermal Clarity.
Soothes =BacterioStatic, New =Number 2 (twice) , Eruptions= erythema, improving =irritation, improving dermal clarity =decrease in pigmentation (by meaning or just the D in dermal)).

Salicylic Acid: [] = 0.5 - 2%

Similar to aspirin which is used as antipyretic drug (acetyl salicylic acid)

- It acts as **Keratolytic** agent, helping to cleanse and clear the pores. As previously discussed, one of the main causes of acne is the **clogging of pores** on the patient's face. This obstruction leads to the accumulation of **sebum produced by the sebaceous glands**, along with **dead skin cells and cellular debris**. Consequently, the use of **salicylic acid**, which is commonly included in **daily facial cleansers**, helps to remove these obstructions and promote pore clearance. For this reason, physicians often advise individuals who use facial washes to pay attention to the **presence and formulation of salicylic acid**, as it enhances **exfoliation** and improves skin cleansing. Additionally, salicylic acid exhibits **mild antibacterial activity**, similar to that observed with **azelaic acid**.
- **It belongs to the same class of drugs as aspirin (salicylates).**
- **Anti-inflammatory capability.**

- As discussed in the previous lecture, acne develops through several stages. However, not all patients progress through every stage of the disease. Some individuals remain at the initial stage, which is characterized by the formation of comedones (blackheads), while others progress to the inflammatory stage where inflammatory lesions develop.
- In such cases, the use of salicylic acid can be beneficial. In addition to its keratolytic effect that helps clear clogged pores, salicylic acid also possesses mild anti-inflammatory properties. Therefore, its use during the inflammatory phase of acne may help reduce inflammation and improve the overall condition of the skin.

- **Can reduce swelling and redness and unplugging blocked skin pores to allow pimples to shrink.**
- Used for comedonal lesions, mild to moderate lesions.
- **applied twice daily**
- The concentration of salicylic acid we use in these patches is 10%. This concentration is applied directly to the affected areas, leading to substantial thickening of the keratin layer. As a result, it is particularly effective in removing warts and corns. However, it is vital to apply it only to the targeted area, as this concentration can cause dryness, irritation, and further thickening, potentially expanding the affected regions. Even if someone does not have these patches, they can use an aspirin tablet—similar to those taken by anti-bleeding patients (e.g., by grandparents)—by crushing it, mixing it with petrolatum (or Vaseline), and creating a 10% solution to apply to the warts and corns.
- Side effects: **skin dryness; keratolytic, and irritation; acid.**

Salicylic Acid 0.5 - 2%

- For high doses, the risk of systemic absorption, thus toxicity, should be considered.
- As it's related to aspirin, it **shouldn't** be given to patient with aspirin sensitivity or a patient with a condition that aspirin is contraindicated.

NOTE: About the concentrations you only need to distinguish between 10%(For warts and corns) Vs 0.5-2% (For acne)

• Topical Therapy (Anti Inflammatory Agents) Found in facial washes

Benzoyl Peroxide 2.5 - 10% **bleaching agent** (cause *discoloration of fabrics and clothing*)

- It releases H_2O_2 , so it has free radicals and oxygen.
- Anaerobic bacteria are sensitive for oxygen, so it **Exhibits bactericidal effects against Cutibacterium acnes.**
- As it can form an acid (Benzoic acid), it has **Keratolytic effects to prevent and clear clogged pores, and anti-inflammatory properties to reduce redness and swelling.**
- **Avoid leaving for long periods of time on the skin to minimize irritation.**
 - Benzoyl peroxide is a potent irritant, and the skin requires time to accommodate to its effects. Consequently, treatment typically begins with a once-daily application, gradually increasing to twice daily as the **skin develops tolerance**. Additionally, it can bleach fabrics; therefore patients should allow it to dry completely before contact with clothing or bedding not advisable to apply benzoyl peroxide before sleep, as **prolonged** contact with the skin during the night can lead to **increased irritation**.
- **dryness of skin**

Similarly, hydrogen peroxide also releases peroxide and is frequently used to treat oral inflammations. It kills the bacteria that cause gingivitis and periodontitis in patients.

Mnemonic: Benny kills Acne, irritating Dry skin. Benny = Benzoyl, kills = keratolytic + bactericidal, Acne = Anti-inflammatory, irritating = irritation, Dry skin = dryness of skin

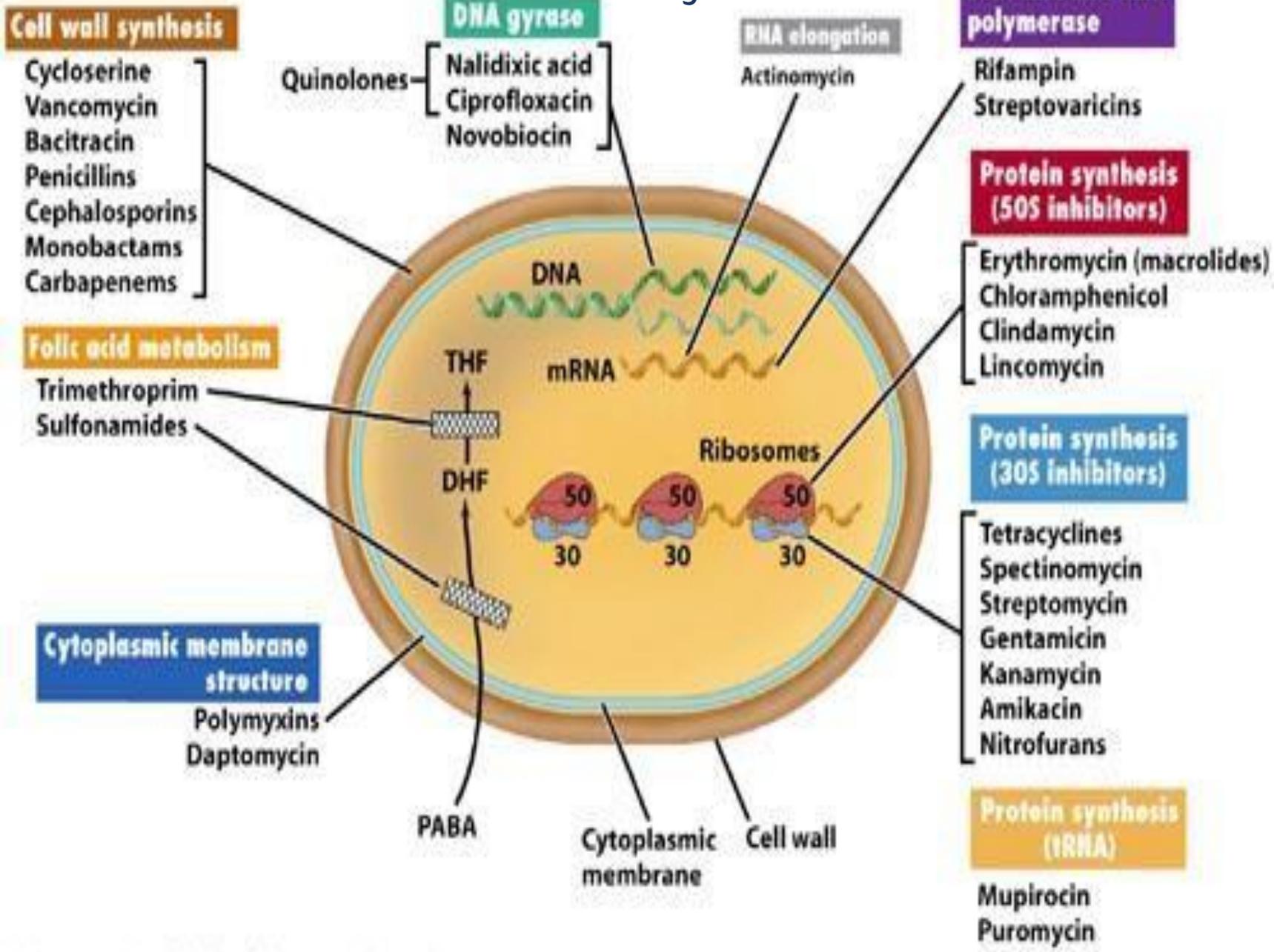
Topical Therapy (Anti Inflammatory Agents)

Some Antibacterial agents can be used topically in a combination with other agents (anti inflammatory agents) and/or systemically for the treatment of Acne, agents used topically include:

- **Clindamycin.**
- **Erythromycin** (can also be used systemically).
- **Apply twice** daily for the treatment of acne.
- **A common adverse effect is skin dryness.**
- **Clindamycin and erythromycin** (Antibacterial) **may also be employed in Combination therapy, examples include:**
 - **5% Benzoyl Peroxide and 3% Erythromycin**
 - **5% Benzoyl Peroxide and 1% Clindamycin**
 - **Topical antibiotics and Azelaic acid or Tretinoin**

Don't memorize the percentage only what can we combine with what

Only to remember!!



These agents are protein synthesis inhibitors; for example, clindamycin and erythromycin, which belongs to a class of drugs known as macrolides, Both inhibit 50S ribosomal subunit, but they are different classes.

- Typically, these are administered orally, so we do not always have to worry about side effects. However, it is important to note that if they are given systemically, we must be more vigilant about their side effect profile.

Clindamycin

- When clindamycin is applied topically it is **10% absorbed systemically**, so, there still exists a **possibility of *Pseudomembranous colitis* in susceptible individuals**.
 - Recall that pseudomembranous colitis is a serious side effect associated with clindamycin, the treatment vancomycin or metronidazole.
- Formulations of clindamycin include:
 1. **The hydroalcoholic vehicle and foam formulation (commercial name: Evoclin), may cause drying and irritation of the skin, with complaints of burning and stinging.**
 - Individuals with certain skin types may experience irritation from the hydroalcoholic vehicle formulation. In such cases, transitioning to the water-based gel is recommended, as it is generally better tolerated and less likely to cause irritation especially for the sensitive skin also for oily skin type it's better. The cream have water and lipid so we use it for normal skin type,
 2. **The water-based gel and lotion formulations; well tolerated and less likely to cause irritation. Allergic contact dermatitis is uncommon.**

Clindamycin is also available in fixed-combination topical gels with benzoyl peroxide (commercial names: Acanya, BenzaClin, Duac), and with tretinoin (commercial name: Ziana).

Don't worry about the different preparations

You can skip this slide except for the topic of antimicrobial resistance

Erythromycin

- In topical preparations, erythromycin base rather than a salt is used to facilitate penetration.

- 
- One of the possible complications of long-term topical therapy is the development of **antibiotic-resistant** strains of organisms, including staphylococci.

- Adverse local reactions to erythromycin solution may include a burning sensation at the time of application and drying and irritation of the skin.

Metronidazole

Also used for the treatment of Amebiasis (*Entamoeba histolytica*).

- Metronidazole is often mistakenly classified as an antifungal due to its similarity in name to the azole class of antifungal agents. However, Metronidazole is not an antifungal; it is primarily an **antiparasitic** and antibacterial agent, effective against anaerobic bacteria.
- **Effective in the treatment of rosacea (الوردية).**
- **Rosacea: common skin condition that causes blushing or flushing and visible blood vessels in your face. It may also produce small, pus-filled bumps (becoming pustular rosacea, a subtype of rosacea). These signs and symptoms may flare up for weeks to months and then go away for a while.**



Metronidazole

- The mechanism of action is unknown.
 - but it may relate to the inhibitory effects of metronidazole on **Demodex brevis** (a parasite believed to be a contributing factor to the development of pustular rosacea); This drug may act as an anti-inflammatory agent (since it decreases swelling and erythema) by direct effect on neutrophil cellular function.
 - Adverse local effects include dryness, burning, stinging and **excessive tearing**.
 - Caution should be exercised when applying metronidazole near the eyes to avoid excessive tearing.

Systemic therapy

A drug that its function depends on it being absorbed to the systemic circulation.

Indications - reasons for therapy:

- **Moderate inflammatory acne non-responsive to topical therapy**, the drugs that have been mentioned previously).
- **Nodulocystic acne.**

Types of *systemic therapy* :

- **Oral Antibiotics**
- **Isotretinoin**
- **Hormonal Therapy** (used only if topical therapy and oral antibiotics failed to make significant progress. Also, multiple tests should be done first to know the exact cause of acne development).

Oral Antibiotics (used for 3-6 months)

Don't work just right away.

Tetracycline : protein synthesis inhibitor, **they are contraindicated to be used by children or adolescents (<15 y.o.) since it deposit in the bone and teeth causing yellowing of teeth.**

- **Tetracycline 500mg X BD**
- **Doxycycline 100mg X BD**
- **Minocycline 100mg X OD**
- **Erythromycin 500mg X BD**
- **combined with topical therapy**

- OD ="Once Daily".
- BD =Bis in Die, which is Latin for "Twice a Day".

- Tetracycline, doxycycline, and minocycline are commonly employed in the systemic treatment of acne due to their combined **antibacterial (bacteriostatic) and anti-inflammatory** effects on *Propionibacterium acnes*.
- A theory that suggests an additional MOA beside being antibacterial and anti-inflammatory that doxycycline has been shown to inhibit matrix metalloproteinases (MMPs, especially **MPP-9**), enzymes responsible for the degradation of the extracellular matrix (ECM). By suppressing MMP activity, doxycycline promotes the **preservation of ECM and collagen**, ultimately contributing to **improved skin structure and appearance**.

Isotretinoin (Accutane) indicated in

- Under the umbrella of tretinoin family (Retinoids).
- Used for long periods (6 months minimum, average 9 months, some patients up to 12 month).
- **severe nodulocystic acne.**
- **Non-responsive acne.**
- **severe psychological distress.**

Isotretinoin (RoAccutane) side effects

- Isotretinoin is not immediately prescribed due to the **numerous potential side effects** associated with its use:
 - 1. Teratogenic**, never prescribed for pregnant women because it will cause fetus malformation.
 1. Remember isotretinoin is a Vit A derivative.
 - 2. mucosal dryness**, so it's prescribed with moisturizers and eyedrops.
 - 3. Lipid abnormalities** (triglycerides, HDL, LDL) are frequent, and elevated triglycerides may lead to acute pancreatitis with fatal hemorrhagic pancreatic (rare) reported.
 - 4. photosensitivity**, so use of sunscreen is essential.
 - 5. Arthralgias.**
 - 6. Alteration of liver enzymes** (increased, we should measure liver enzymes levels before treatment; if enzymes are already high, we are scared of the liver enzymes to increase to a level that cause damage to the liver; for that purpose we measure liver enzymes every month for patient undergoing treatment and have shown increased liver enzymes before treatment).

Isotretinoin (RoAccutane) side effects

7. hypertriglyceridemia and hypercholesterolemia, so regular monitoring of triglycerol and cholesterol is essential.

• **Tumerogenic in animals**

Teratogenicity is a significant risk in patients taking isotretinoin; therefore, the FDA mandates that women of childbearing potential must use an effective form of contraception for at least 1 month before, throughout isotretinoin therapy, and for one or more menstrual cycles following discontinuance of treatment.

A negative serum pregnancy test must be obtained within 2 weeks before starting therapy in these patients, and therapy should be initiated only on the second or third day of the next normal menstrual period.

Isotretinoin May Pose A Little Catastrophe Increasing Lipid Targets.
May = Mucosal dryness, Pose= Photo sensitivity, A = Arthralgias, Little = Alteration of liver enzymes., Catastrophe = increase in cholesterol, Targets= Teratogenic.
The catastrophe means it has a lot of side effects and not immediately prescribed, Lipid targets = hypertriglyceridemia

Isotretinoin (RoAccutane)

- **Retinoic Acid (Tretinoin):** is the acid form of Vitamin A.
- **Stabilizes lysosomes, increases RNA polymerase activity, increases PGE₂, cAMP, and cGMP levels** (both cAMP and cGMP are vasodilators, more blood supply and nourishment), and increases the incorporation of thymidine into DNA, so more cell regeneration.
- **Decreases cohesion between epidermal cells and increases epidermal cell turnover.** This will result in expulsion of open comedones and the transformation of closed comedones into open ones. (الحبات المغلقة بتفتح والمفتوحة يقطع منها العمل).
- **Also, promotes dermal collagen synthesis, new blood vessel formation, and thickening of the epidermis, which helps diminish fine lines and wrinkles.**
- **Women should avoid becoming pregnant for at least one month after discontinuing isotretinoin treatment, as the drug can remain in the body for up to one month. Additionally, women should refrain from donating blood while undergoing treatment with isotretinoin, as the donated blood could potentially be transfused to a pregnant woman, thereby posing a risk to the developing fetus.**

Additional Resources:

رسالة من الفريق العلمي:

يقول ﷺ: إن القلوب بين إصبعين من أصابعه يقلبها كيف يشاء، فالمعنى أن الله جل وعلا هو الذي بيده تثبيت الأمور، فالمؤمن يسأل ربه الثبات على الإيمان والثبات على الحق، فالقلوب تتقلب وهي بين إصبعين من أصابع الله، وهذا يُجرى على ظاهره، فيثبت الله الأصابع على الوجه اللائق به سبحانه، وأن الله جل وعلا بيده تصريف الأمور وتقليب القلوب كيف يشاء؛ فهذا يقلب فيرتد عن دينه، وهذا يقلب فيسلم، وهذا يقلب قلبه فيقع في المعاصي.

قال الله ﷻ: ﴿وَنَقَلْبُ أَفْئِدَتِهِمْ﴾

لا شيء أسرع تقلباً وتقلتاً من القلب!

وكان رسولنا ﷺ يكثر من قول:

"يا مقلب القلوب ثبت قلبي على دينك"

فلما سئل عن ذلك قال: إن القلوب بين إصبعين من أصابع

الرحمن يقلبها كيف شاء.. فكيف بحالنا!

فالقلوب بيد الله جل وعلا، هو الذي يصرفها كيف يشاء [؟]، ولذلك كان من دعاء النبي ﷺ: «يا مقلب القلوب ثبت قلبي على دينك»، وكان يأمر أصحابه بالإكثار من هذا الدعاء؛ لأن العبد مهما بلغ من العلم والإيمان فإنه محتاج إلى تثبيت الله له، فالهداية والثبات بيد الله وحده، يهدي من يشاء ويثبت من يشاء، ولهذا ينبغي للمؤمن أن يكثر من سؤال الله الثبات، وأن يلجأ إليه دائماً أن يصرف قلبه على طاعته ويثبته على الحق حتى

For any feedback, scan the code or click on it.



Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			