Acne & Melasma

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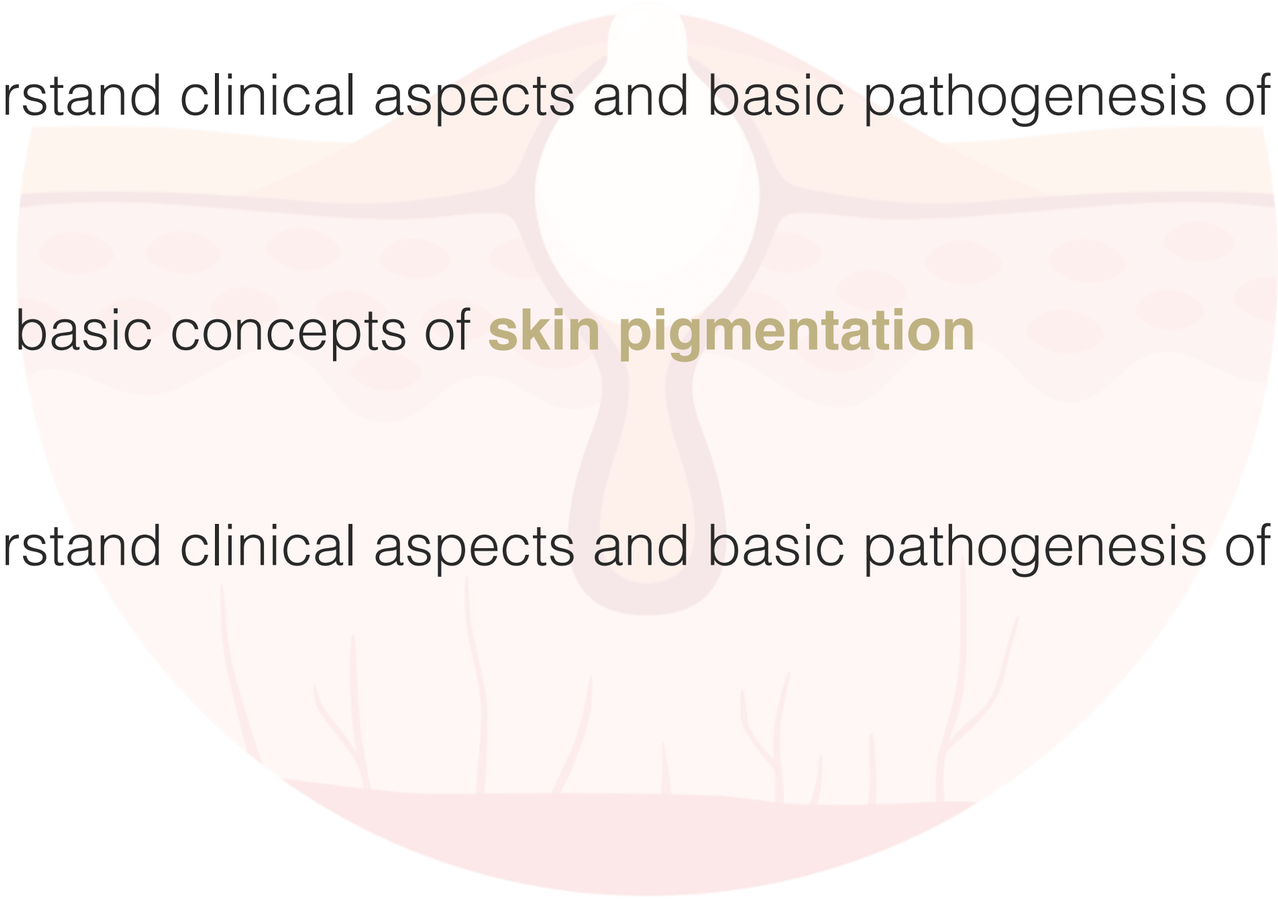
** This presentation is used for academic purposes only.*

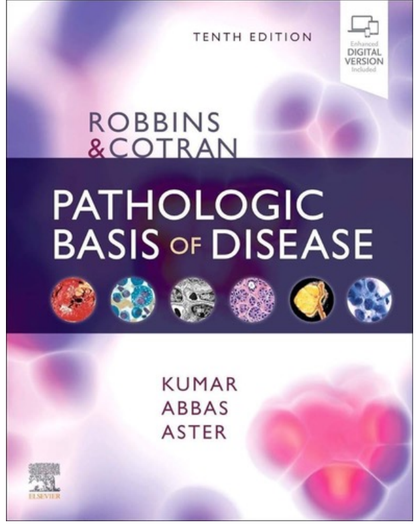
Learning objectives

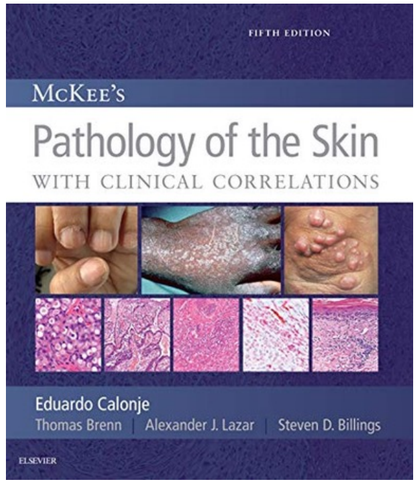
1 To understand clinical aspects and basic pathogenesis of **acne vulgaris**

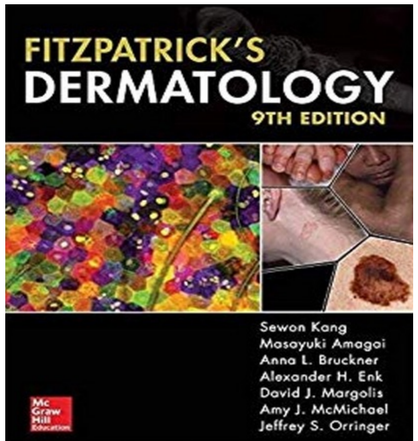
2 To learn basic concepts of **skin pigmentation**

3 To understand clinical aspects and basic pathogenesis of **melasma**









References & suggested readings

Robbins and Cotran pathologic basis of disease,10th edition, 2021, Kumar et al, Saunder Elsevier.

McKee's Pathology of skin with clinical correlation, 4th edition, 2012, McKee et al, Elsevier Health Sciences.

Fitzpatrick's Dermatology 9th edition. McGraw-Hill, 2018.


Acne

Acne vulgaris

- A chronic inflammatory skin disease of **pilosebaceous units**
- Commonly affecting approximately 10% of the population worldwide
- Approximately 85% occurs in **teenagers** (but can persist into adulthood)
- No racial and sexual predilection (often more severe in males, reflecting androgen levels)
- Has important impacts on emotional functioning, social functioning, relationships, leisure activities, daily activities, sleep, school, and work
- Associated with increased risks of stigmatization, bullying, depression, anxiety, poor self-esteem, and suicidal ideation
- Mainly presents with **open or closed comedones**, **papules**, **pustules**, or **nodules** on the **face or trunk**, and may result in pain, erythema, hyperpigmentation, or scars

Acne vulgaris

- **Etiologies and factors**: genetics, environmental variables (temperature, pollution, humidity, sun exposure, mineral oils / halogenated hydrocarbons), nutrition, hormonal state, stress, smoking, comedogenic medicines (such as androgens, halogens, corticosteroids), bacteria, and cosmetics
- **Influencing factors:** increased androgenic state (PCOS, tumors of adrenal gland or ovary), skin irritation (detergent, soap, skin picking), family history, stress, diets

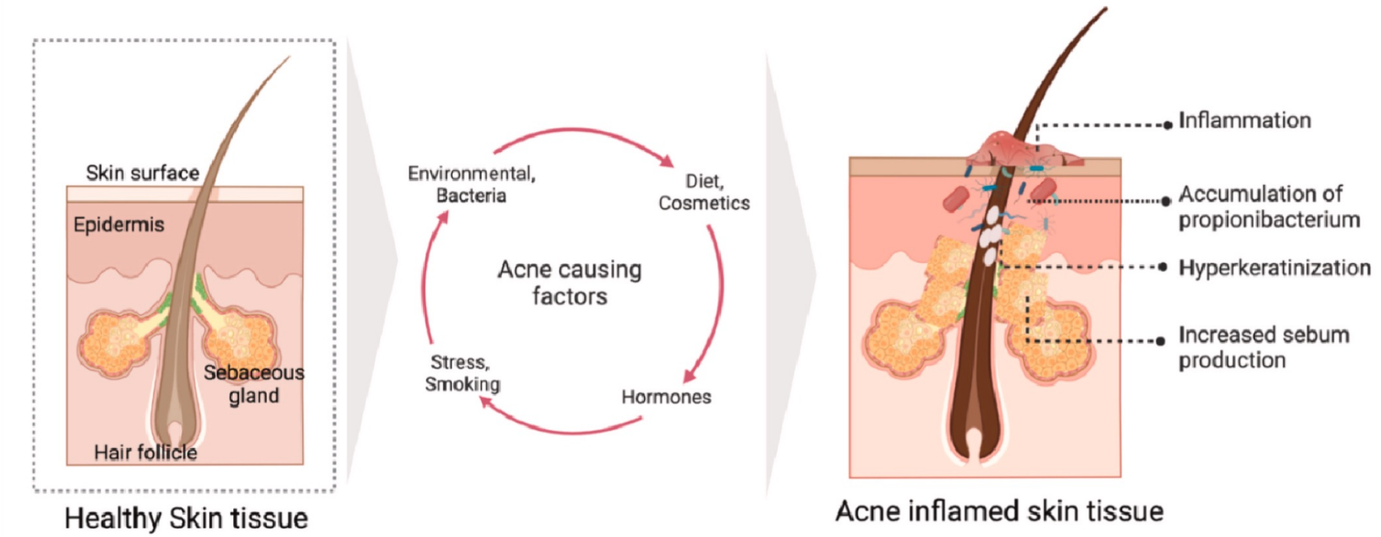
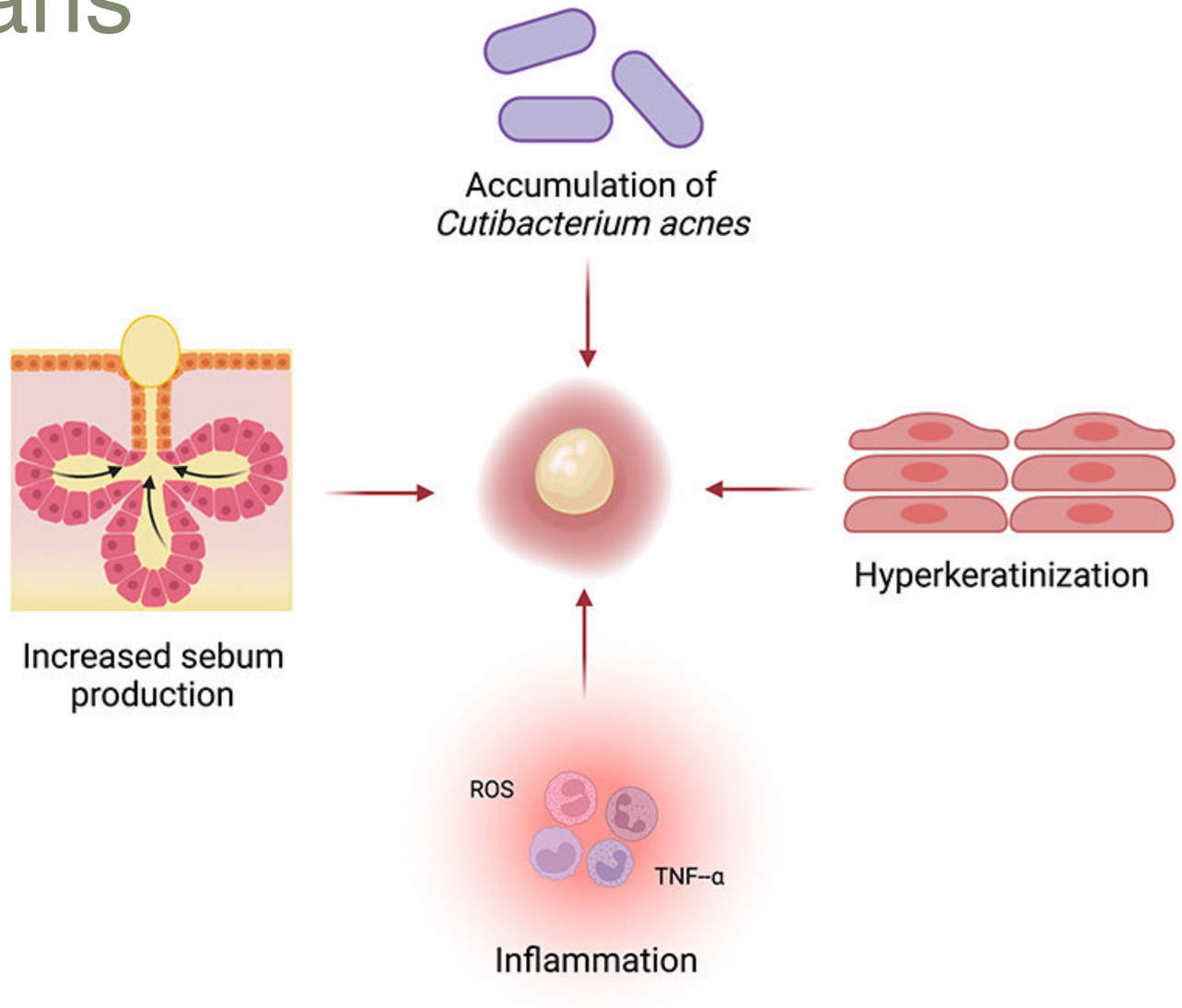


Fig. 1. Schematic illustration of healthy/normal skin tissue vs acne inflamed skin tissue, various factors (environmental, bacterial, diet, stress, smoking and relevant hormonal imbalance among others) contributing to the formation and development of acne.

Acne vulgaris



<u>Four</u> major mechanisms contributing to acne pathogenesis

Acne vulgaris

1. **Increase in sebum production**
   - Androgen hormones (specifically testosterone) and Insulin growth hormone (IGH-1), increase sebum synthesis and secretion.
   - Clearly correlated with severity and frequency of acne lesions

2. **Abnormal follicular hyperkeratinization of the pilosebaceous units**
   - Keratinocytes proliferate and are not shed into the lumen, leading to the accumulation of irregular desquamated corneocytes in the pilosebaceous follicles coupled with lipids (plugging follicular infundibulum).
   - Formation of microcomedone (acne precursor)

Acne vulgaris

3. **Microbial colonization with *Cutibacterium acnes***
   - *Cutibacterium acnes* (*C.acnes*), formerly known as *Propionibacterium acnes*, an anaerobic, lipophilic, gram-positive pathogen that prefers to colonize in sebaceous follicles because they produce large amounts of sebum and provide excellent anaerobic habitat for bacterial growth
   - Plays a substantial part in pathophysiology of **inflammatory acnes**
   - Secretes lipase enzyme that metabolizes triglycerides of sebum into glycerol and **pro-inflammatory fatty acids**, which can lead to the formation of comedones and inflammation on the skin

Acne vulgaris

4. **Complex inflammatory mechanisms**
   - When immune system (both innate and acquired) detects *C.acnes*, the inflammatory process begins.
   - *C.acnes* has a strong inflammatory effect which may produce chemotactic factors for neutrophils recruitment (also lymphocytes and macrophages).
   - Cause follicular damage, rupture, and release of germs, fatty acids, and lipids into the dermis - producing inflammatory lesions such as papules, nodules, pustules, and cysts)
   - Neutrophils produce reactive oxygen species (ROS), which damage follicular epithelium and contribute to acne inflammation.

Acne vulgaris

Two types of skin lesions:

1. **Non-inflammatory lesions**
    - Microcomedones : acne precursors)
    - Open (black-headed) comedones : small follicular papules containing central black keratin plug (oxidized lipids and melanin)
    - Closed (white-headed) comedones : follicular papules without visible central plug (keratin plug trapped beneath epidermal surface, potential lesions of follicle rupture and inflammation)
2. **Inflammatory lesions**
    - Papules : tender to touch
    - Pustules : containing pus, with white/yellow tip
    - Nodules : deep collections
    - Cysts : largest lesions

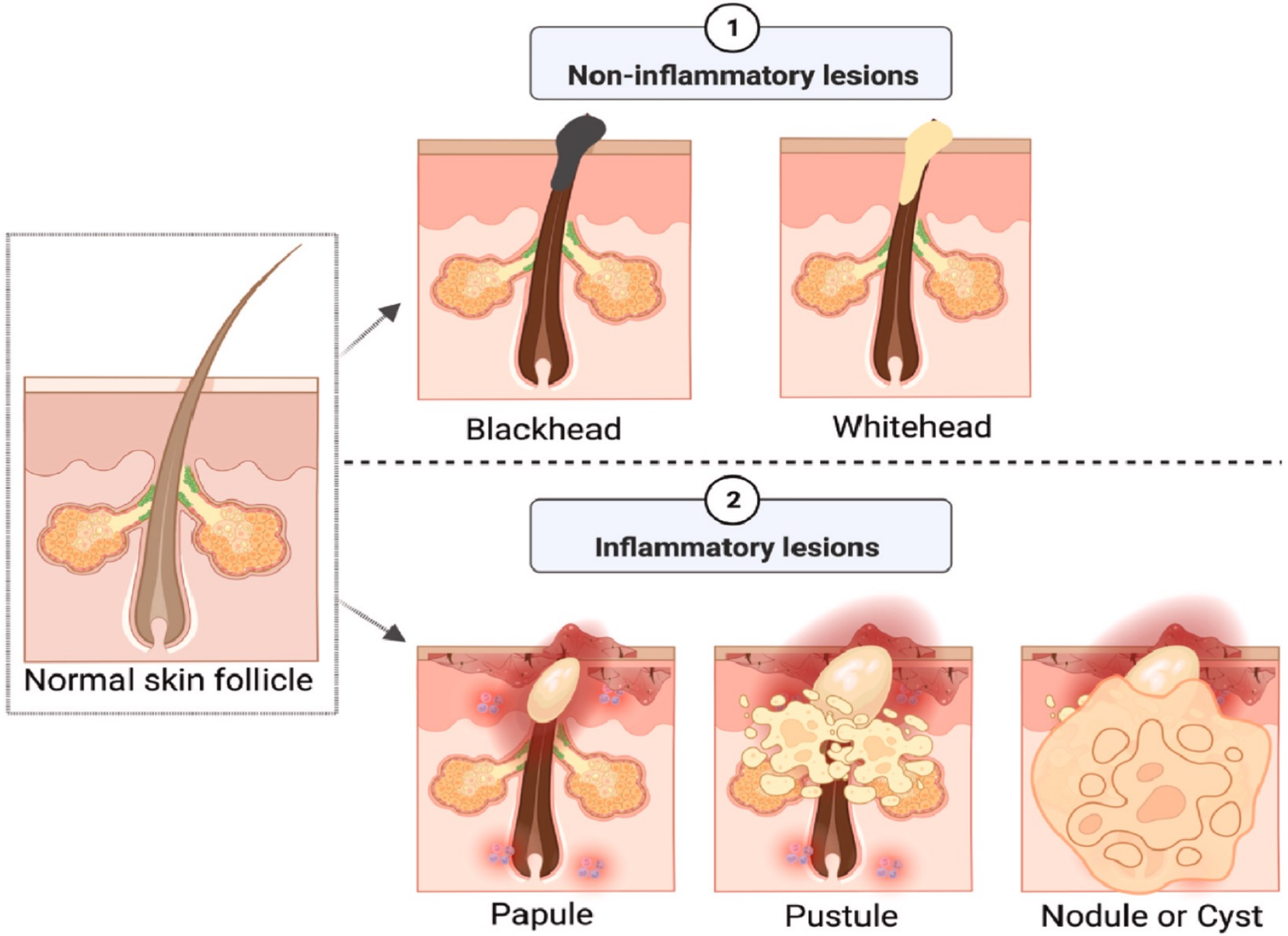
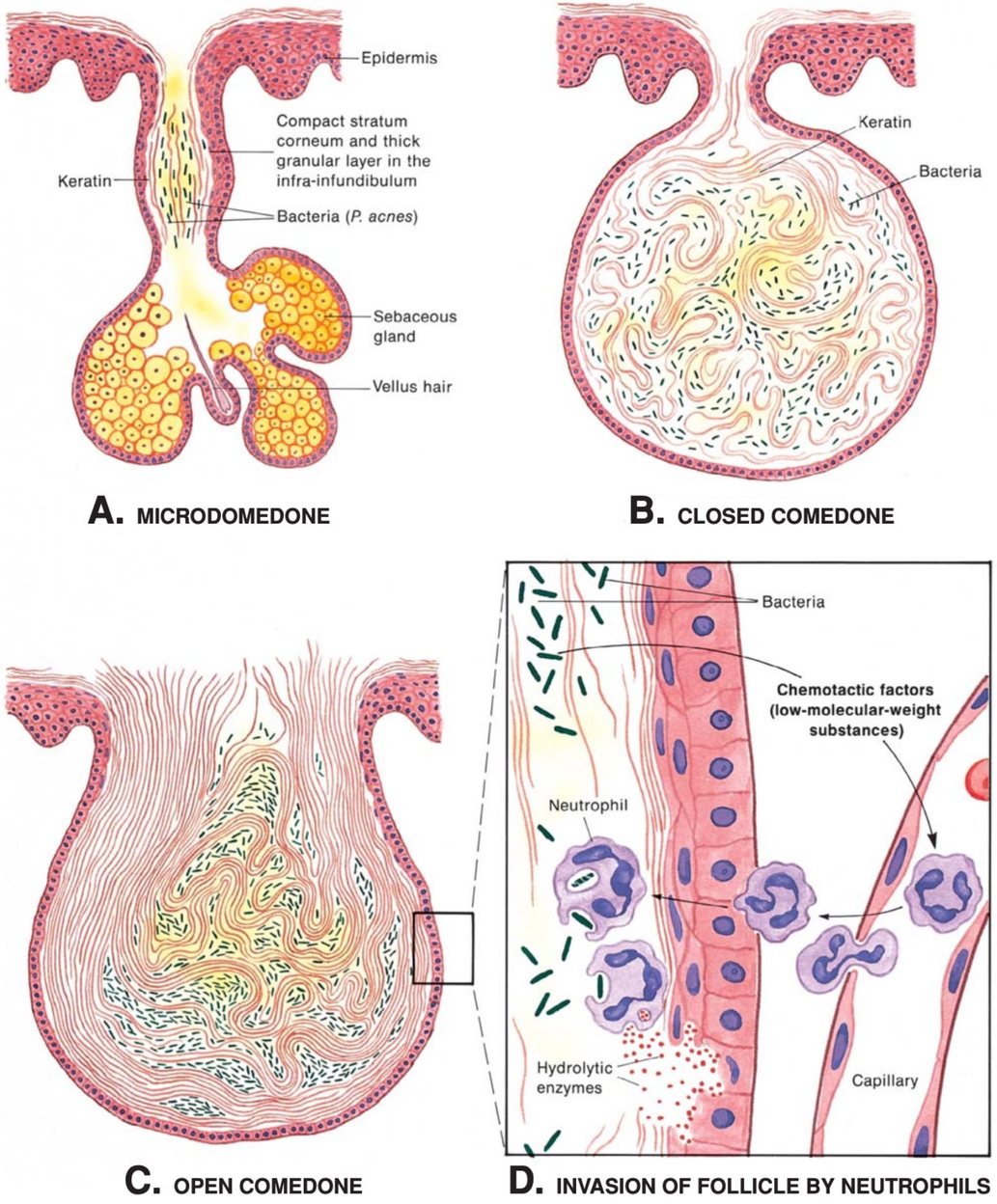


Fig. 2. Schematic illustration of major distinguishing of the two types of lesions (non-inflammatory, inflammatory) and their pathogenies.



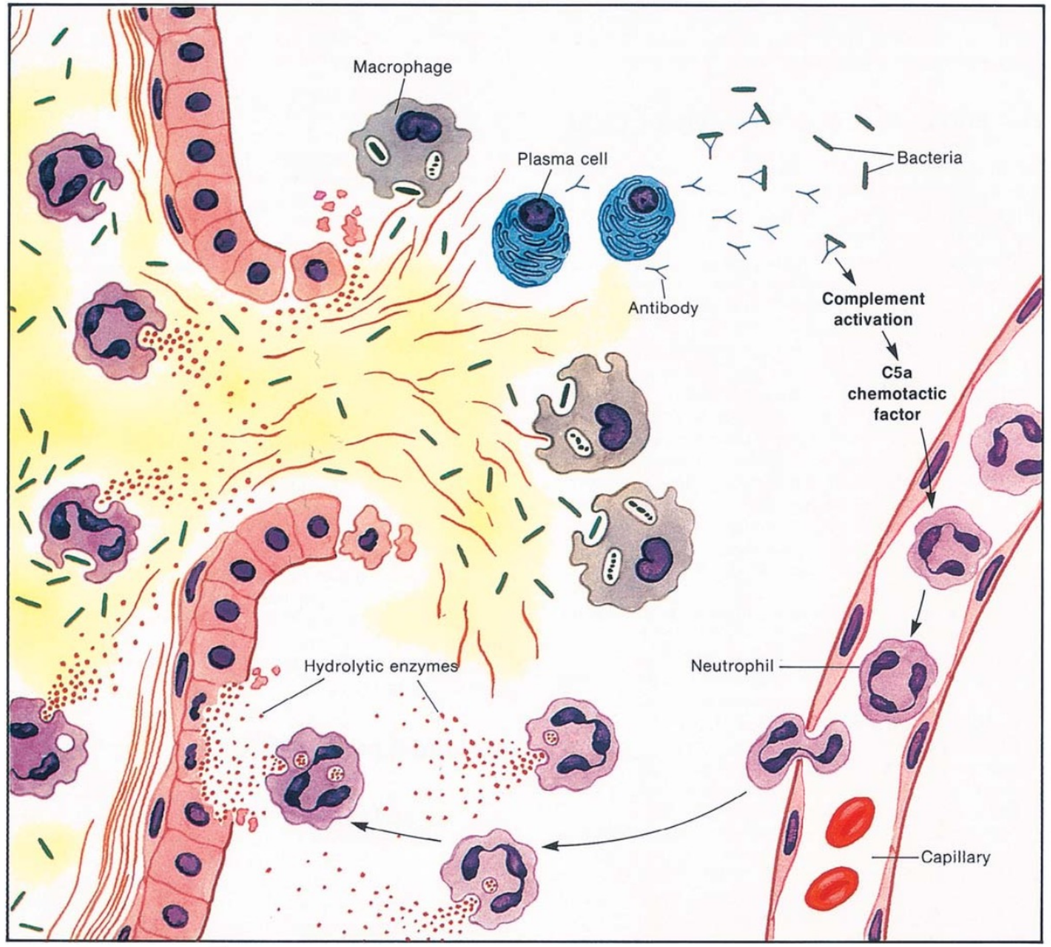
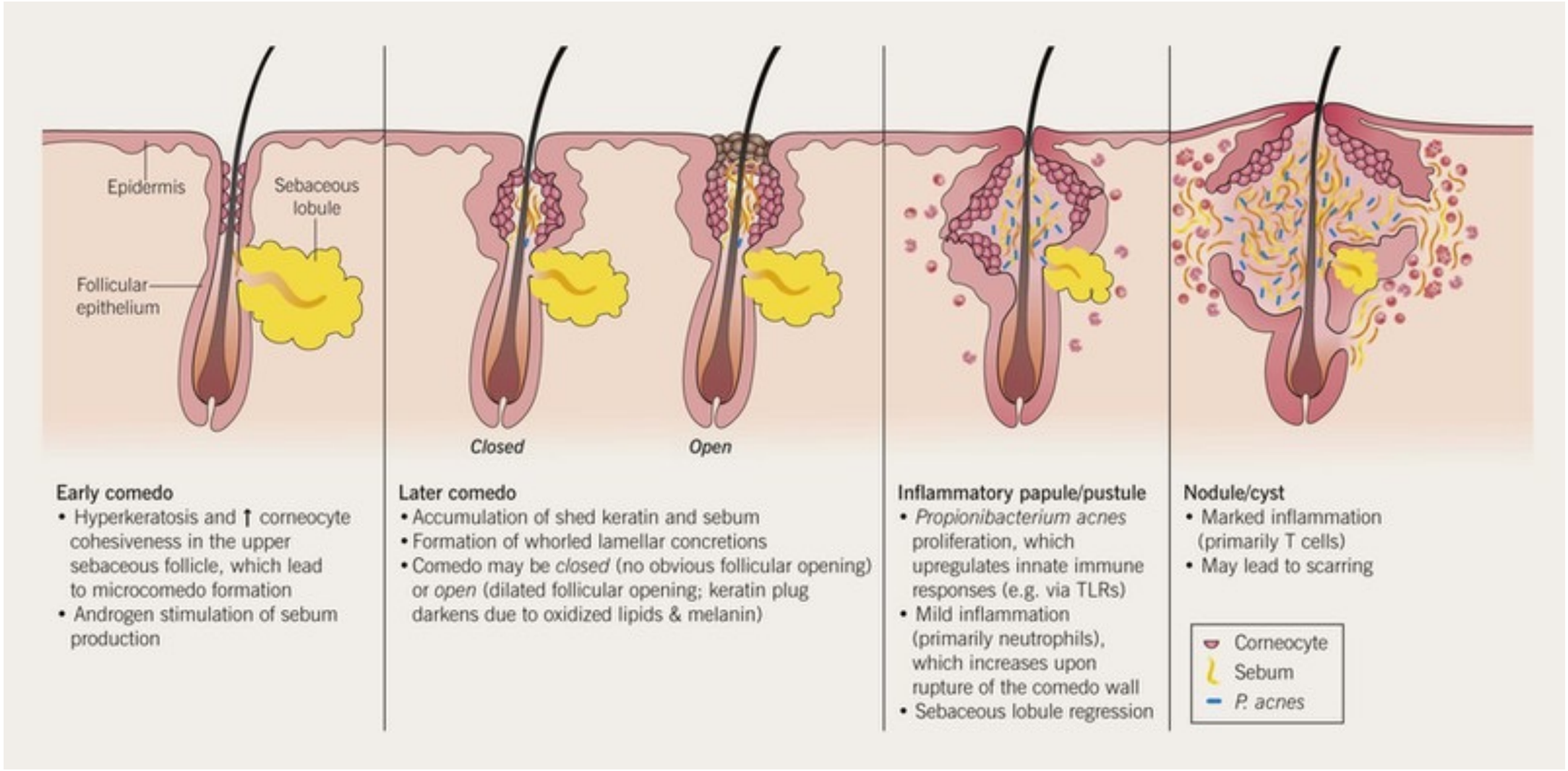
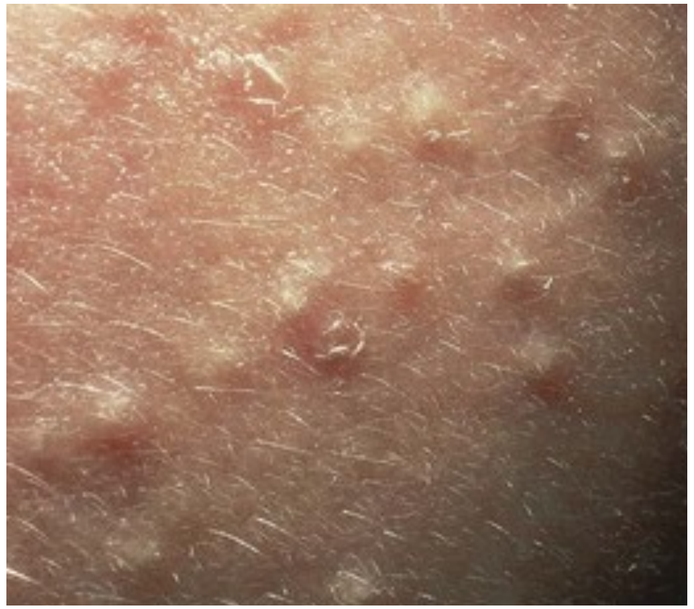


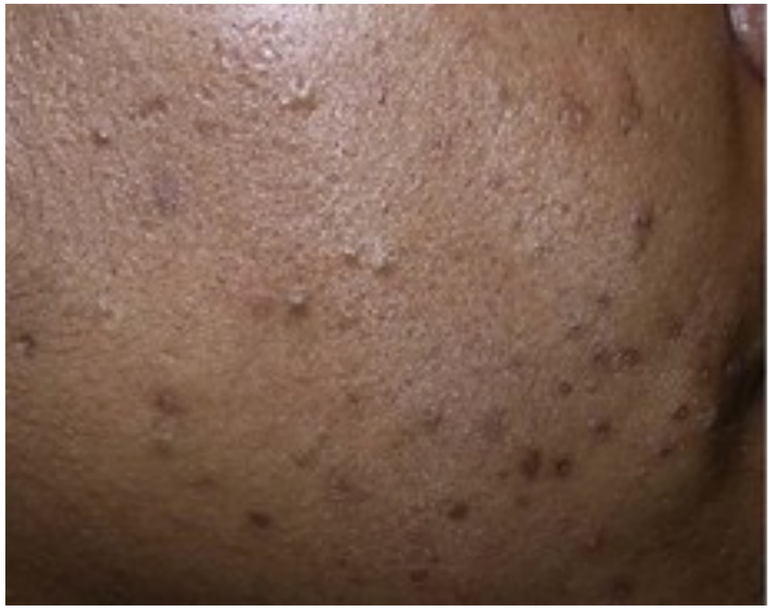
FIGURE 28-41. Acne vulgaris. The pathogenesis of follicular distention, rupture and inflammation is depicted. Acne is a disease of the follicular canal of a sebaceous follicle. A compact stratum corneum and a thickened granular layer in the infrainfundibulum are the beginning of the formation of a comedone. Microcomedones **(A)** and closed **(B)** and open **(C)** comedones form. Excessive sebum secretion occurs, and the bacterium *Propionibacterium acnes* proliferates. The organism produces chemotactic factors, leading to neutrophil migration into the intact comedone. Neutrophilic enzymes are released, and the comedone ruptures, inducing a cycle of chemotaxis and intense neutrophilic inflammation **(D, E)**. (*continued*)



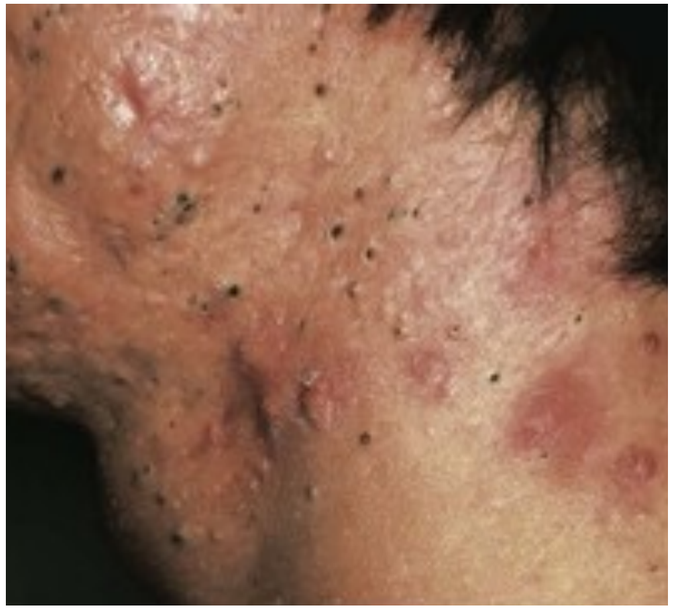
Stages and different types of acne lesion



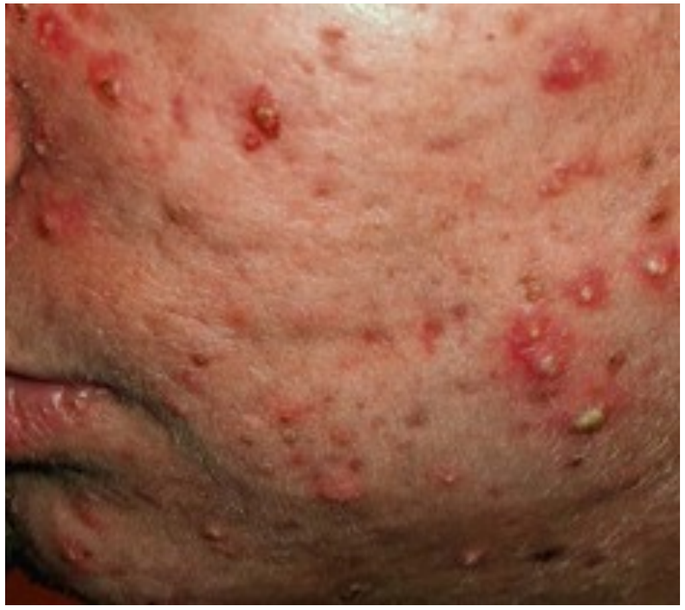
Closed comedones



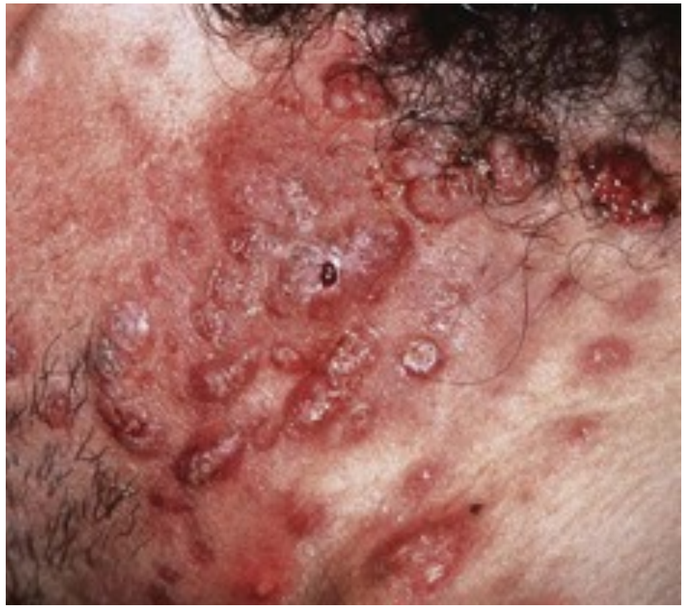
Closed and open comedones



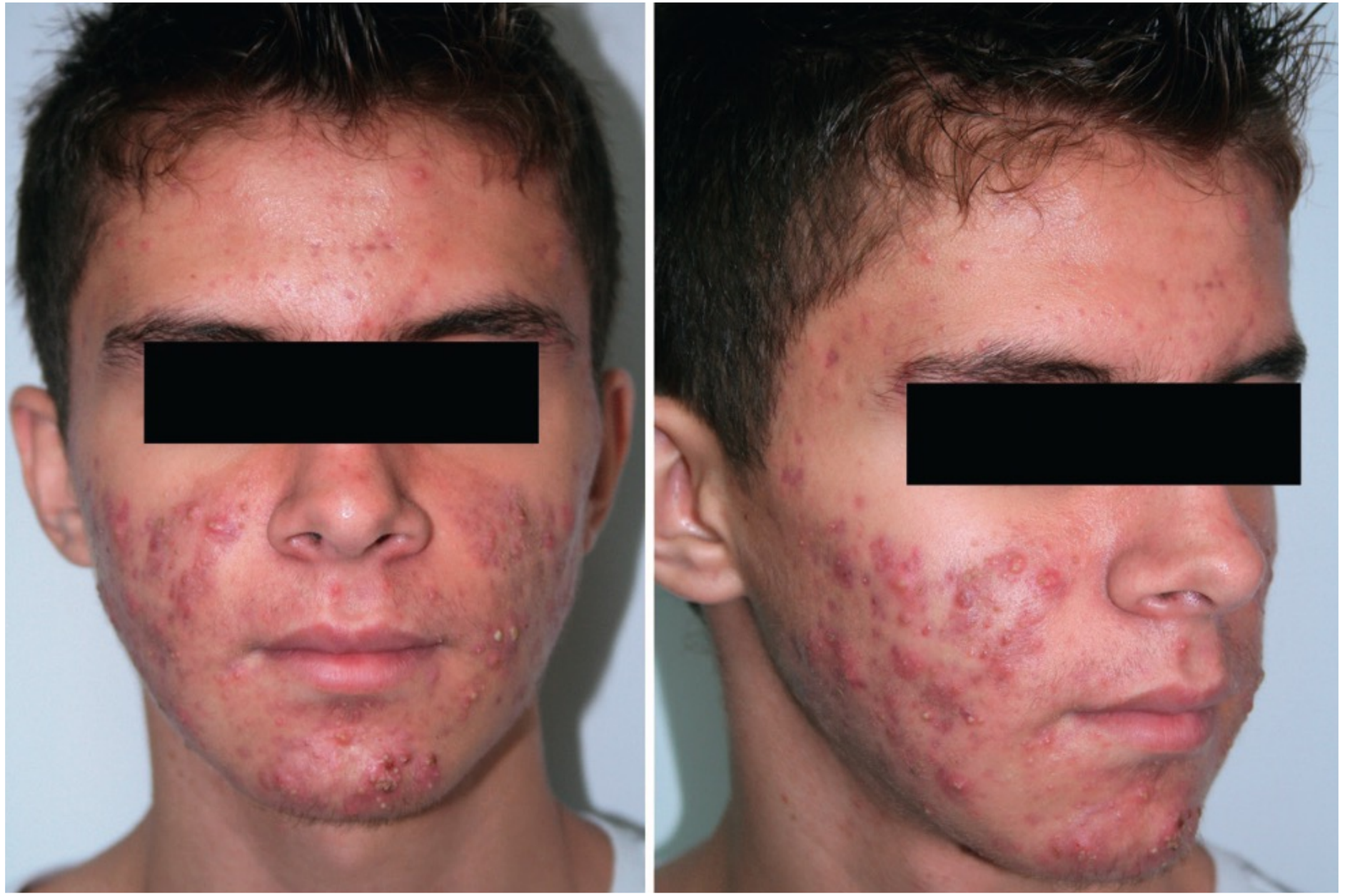
Closed comedones



Papules and pustules



Nodulocystic acnes

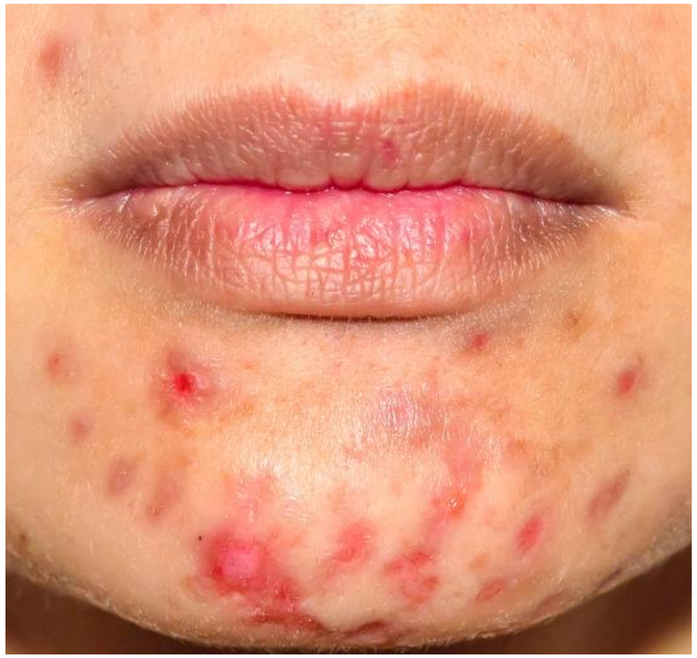


Acne vulgaris

Other presentations of acne

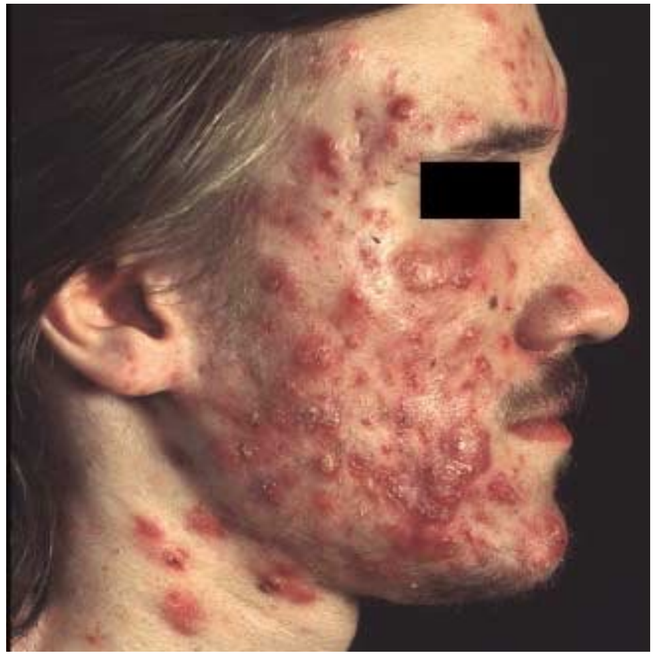
- **Acne vulgaris** is the most prevalent form of acne (99% of all acne cases)
- Acne is also classified into **several forms** (resembling acne vulgaris histologically, but different in clinical situation, severity, and accompanying symptoms):
    - Acne conglobate
    - Acne rosacea
    - Acne fulminans
    - Acne cosmetica
    - Acne excoriée (picker's acne)
    - Acne medicamentosa (e.g. anabolic steroids, corticosteroids, isoniazid, lithium, and phenytoin)

Other presentations of acne



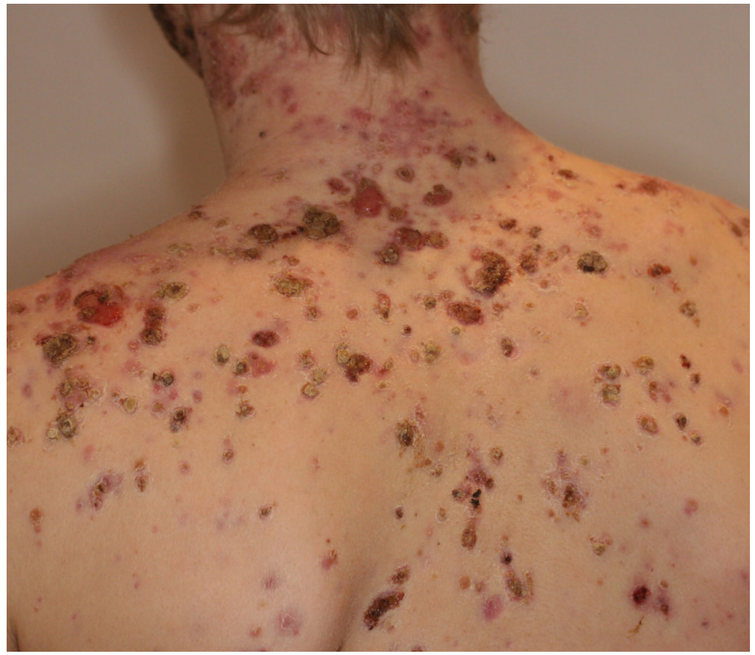
Acne excoriée

- Mild comedones that compulsively are chronically picked, scratched, and squeezed
- Leading to scarring



Acne conglobata

- Severe form of nodulocystic inflammatory acnes,
- Tender, disfiguring, interconnecting sinuses, draining tracts, deep burrowing, and scarring
- Back, chest, face
- Young male predominance

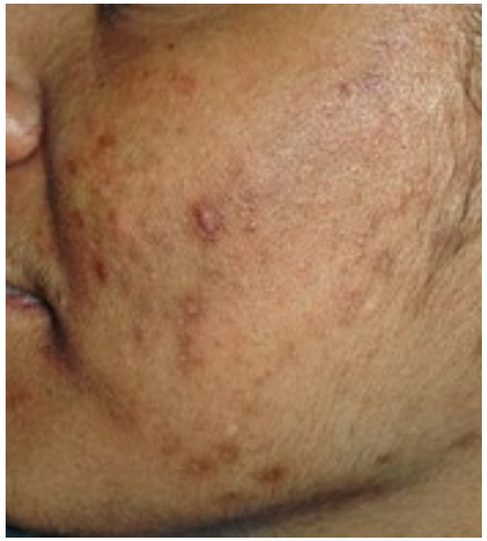


Acne fulminans

- Acnes eruption of large and multiple inflammatory nodules with ulceration, oozing, and crusting
- Pre-existing acnes triggered by isotretinoin
- Cause systemic symptoms
- Male predominance

Complications of acne

- Leading to **scarring** (atrophic, hypertrophic, keloidal) and **dyspigmentation** of the affected skin (post-inflammatory hyperpigmentation or erythema), and necessitating prolonged and persistent therapy
- Acne vulgaris typically causes discomfort, emotional suffering, deformity, and possibly permanent scars. In addition to this, patients may have feelings of anxiety and embarrassment, both of which contribute to **mentally depressed state.**



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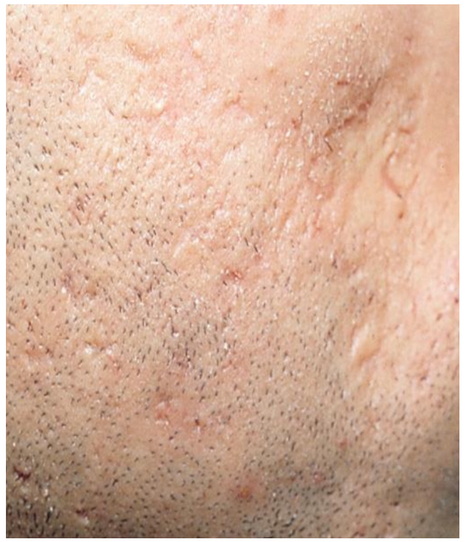
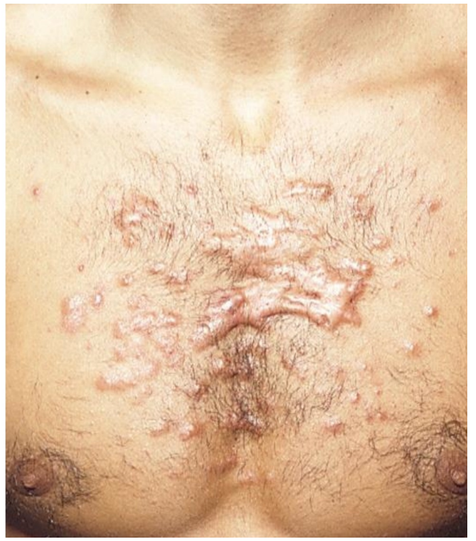


Atrophic acne scar



Keloidal scar

Acne vulgaris

Author:
Yan Yu
Reviewers:
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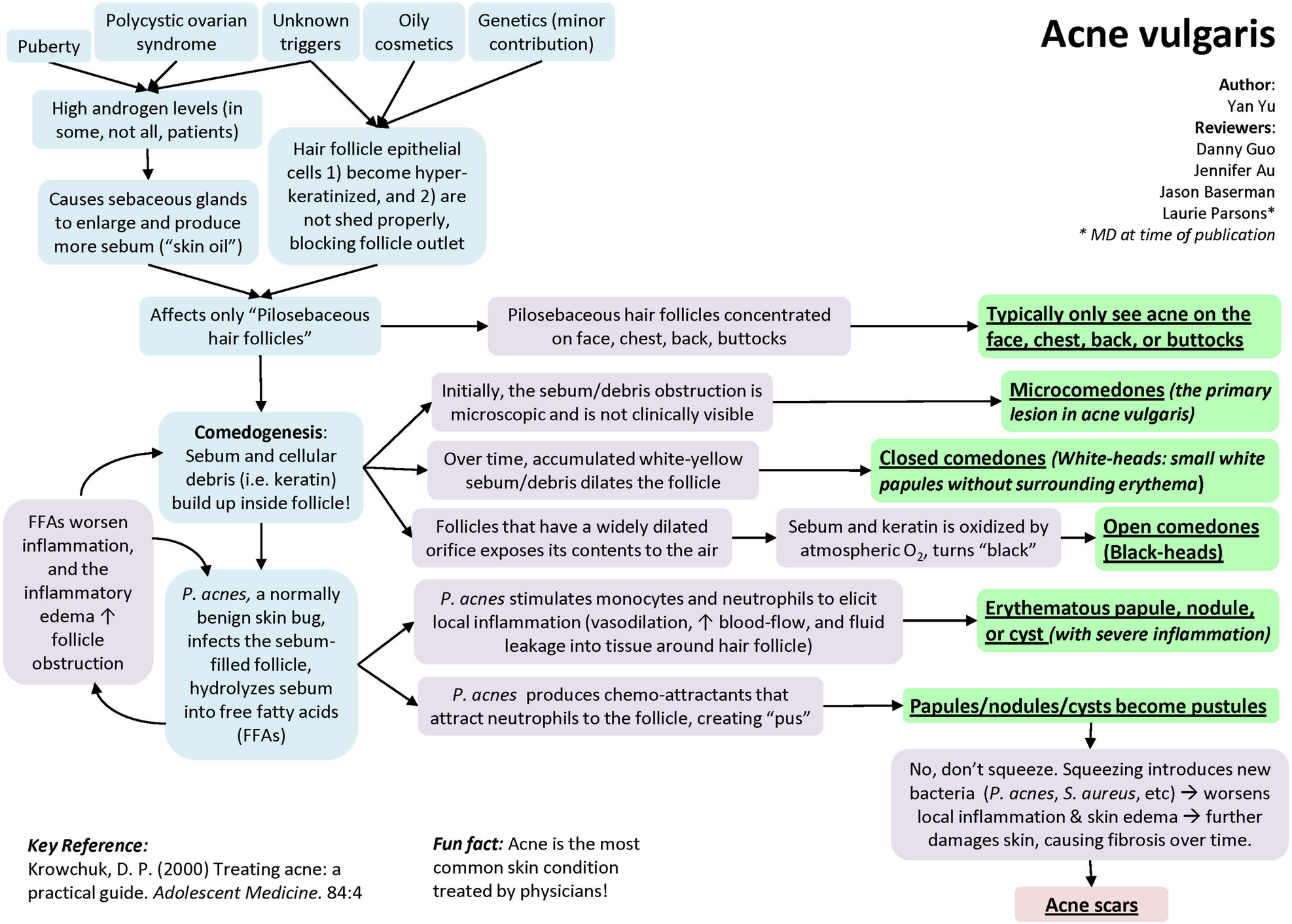
Jennifer Au
Jason Baserman
Laurie Parsons*
** MD at time of publication*

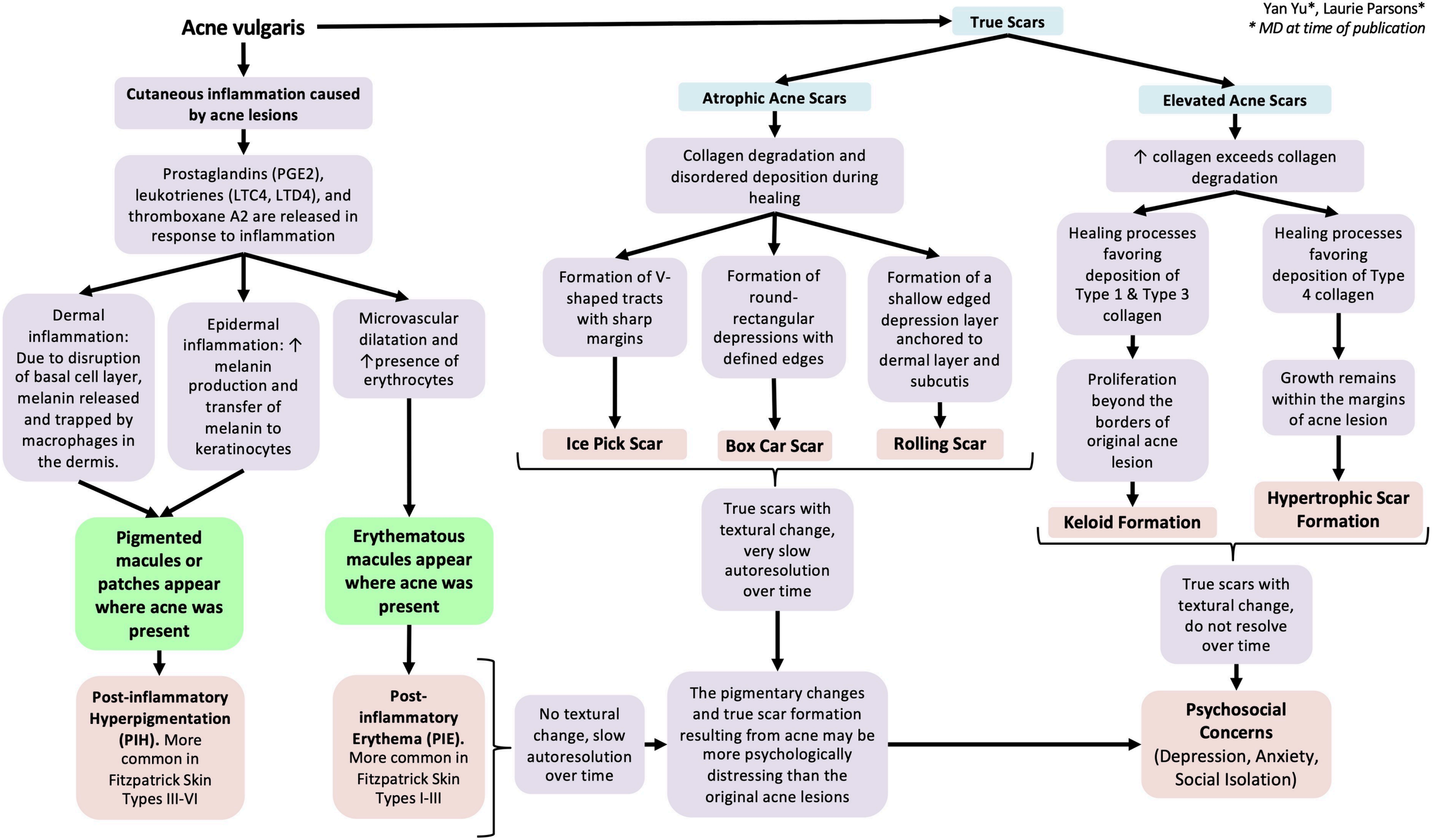


Key Reference:
Krowchuk, D. P. (2000) Treating acne: a practical guide. *Adolescent Medicine.* 84:4

Fun fact: Acne is the most common skin condition treated by physicians!

Acne vulgaris: *Complications*

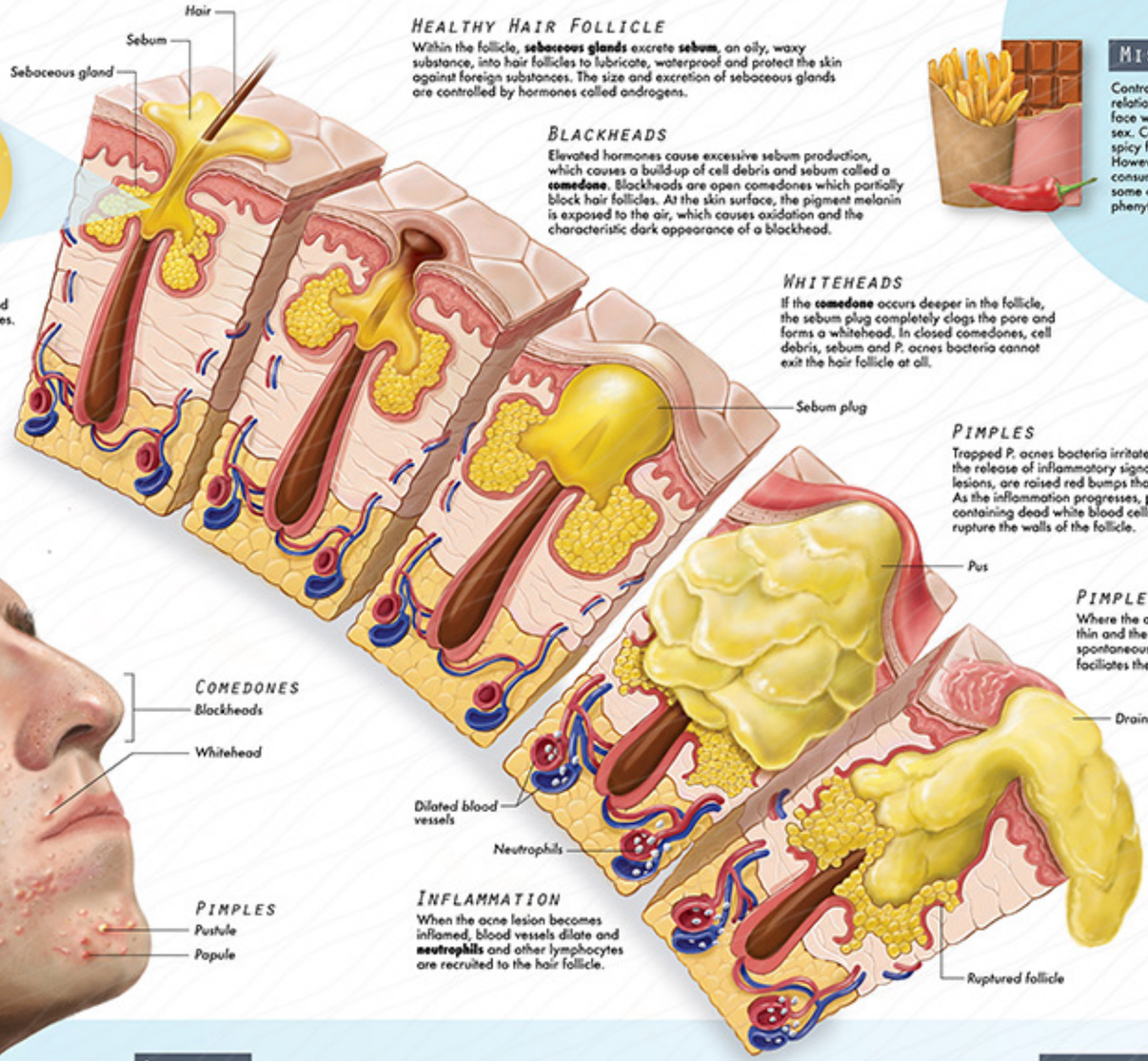
Authors: Stephen Williams
Reviewers: Mehul Gupta, Lauren Lee, Yan Yu*, Laurie Parsons*
** MD at time of publication*



ACNE VULGARIS

Acne vulgaris is a chronic skin disease affecting most teenagers undergoing puberty and often persists into adulthood. Other conditions affecting hormonal levels can also trigger acne, including pregnancy, menstruation, and stress. Occlusion of the skin surface with greasy products (e.g.cosmetics and lotions), tight clothing and sweating can also produce acne. Acne occurs when hair follicles become clogged with dead skin cells and sebum, oil from the skin. **Comedones**, **blackheads** or **whiteheads**, form when sebum partially or completely clogs the hair follicle. Trapped within the pore, ***Propionibacterium acnes***, bacteria that normally occur in hair follicles, can irritate the epithelium and cause an inflammatory immune response. Inflamed comedones form **pimples**, including **papules** and **pustules**.

Propionibacterium acnes bacteria feed on sebum and cell debris within hair follicles.



Healthy Hair Follicle

Within the follicle, **sebaceous glands** excrete **sebum**, an oily, waxy substance, into hair follicles to lubricate, waterproof and protect the skin against foreign substances. The size and excretion of sebaceous glands are controlled by hormones called androgens.

Blackheads

Elevated hormones cause excessive sebum production, which causes a build-up of cell debris and sebum called a **comedone**. Blackheads are open comedones which partially block hair follicles. At the skin surface, the pigment melanin is exposed to the air, which causes oxidation and the characteristic dark appearance of a blackhead.

Whiteheads

If the **comedone** occurs deeper in the follicle, the sebum plug completely clogs the pore and forms a whitehead. In closed comedones, cell debris, sebum and *P. acnes* bacteria cannot exit the hair follicle at all.

Misconceptions

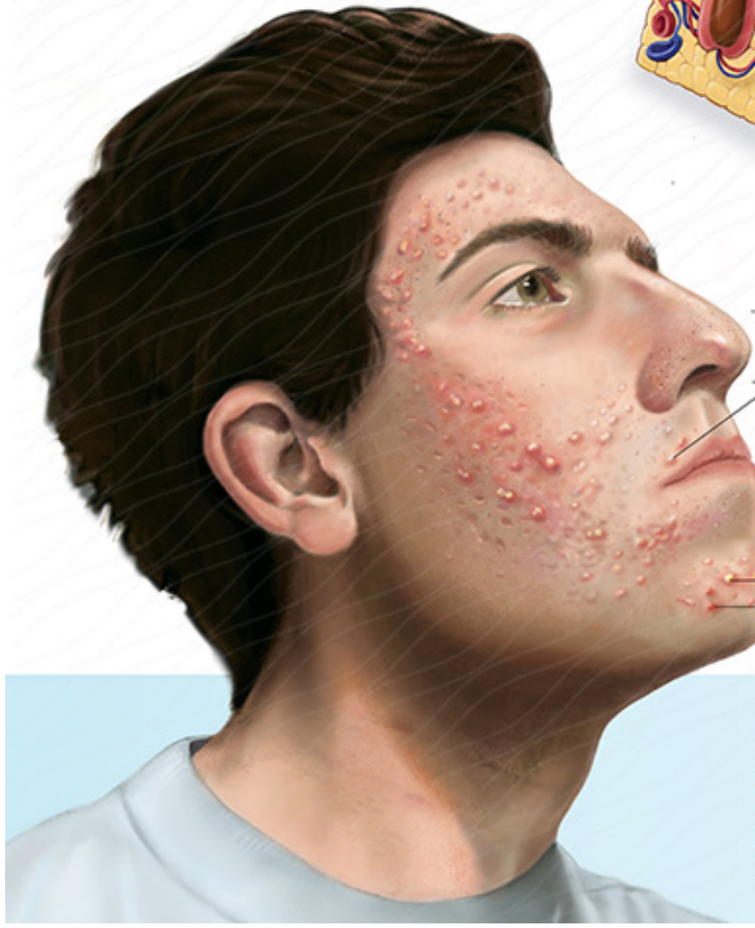
Contrary to popular belief, there is no relationship between acne formation and face washing frequency, masturbation or sex. Consumption of chocolate, greasy or spicy foods also do not cause acne. However, there are studies that link dairy consumption, high-glycemic diets and some drugs (corticosteriods, lithium, phenytoin etc.) to acne formation.

Pimples

Trapped *P. acnes* bacteria irritate the epithelium, stimulating the release of inflammatory signals. **Papules**, inflamed acne lesions, are raised red bumps that feel warm and painful. As the inflammation progresses, **pustules** may form if pus containing dead white blood cells and bacteria fill and rupture the walls of the follicle.

Pimple Drainage

Where the abscess is close to the skin, the skin is thin and the pus may break through to drain spontaneously. Drainage of the pustule facilitates the healing of the lesion.



Inflammation

When the acne lesion becomes inflamed, blood vessels dilate and **neutrophils** and other lymphocytes are recruited to the hair follicle.

Scarring

Abnormal healing of moderate to severe acne lesions can cause scarring due to either excessive or inadequate collagen deposition. There are four main types of acne scars. Laser, radiofrequency, or ultrasound treatments can minimize the appearance of scars.

Treatment

Common treatments include benzoyl peroxide, which target bacteria, and retinoids, which prevent dead cells from clogging pores. In women, oral contraceptives can be used to lower androgen levels, which decreases sebum production.

Grading of acne severity

SEVERITY	EDF CLASSIFICATION DESCRIPTION	IGA CLASSIFICATION DESCRIPTION *
Grade 0	NA	Clear; residual hyperpigmentation and erythema may be present
Grade 1	Comedonal acne	Almost clear; a few scattered comedones and a few scattered papules
Grade 2	Mild to moderate papulopustular acne	Mild; easily recognizable; less than half the face is involved; some comedones and some papules and pustules may be visible
Grade 3	Severe papulopustular acne, moderate nodular acne	Moderate; more than half the face is involved; many comedones, papules and pustules are visible and one nodule may be present
Grade 4	Severe nodular acne, conglobate acne	Severe; the entire face is involved, covered with comedones, papules, and pustules; a few nodules and cysts are observed

EDF: European Dermatology Forum; IGA: Investigator Global Assessment

Management of acne

Topical therapies (mainstay of treatment)

- Topical retinoids : comedolytic and anti-inflammatory, improve dyspigmentation
- Benzoyl peroxide : anti-microbial and mildly comedolytic
- Topical antibiotics : anti-microbial and anti-inflammatory
- Fixed-dose topical combinations: BP + retinoids +/- antibiotics
- Clascoterone* : a topical antiandrogen directly binding androgen receptor and inhibits androgen-mediated lipid and inflammatory cytokine synthesis from sebocyte
- Salicylic acid : comedolytic
- Azelaic acid : comedolytic, anti-bacterial, anti-inflammatory

Systemic antibiotics

- Doxycycline
- Minocycline
- Sarecycline

Management of acne

Hormonal agents:

- Combined oral contraceptives
- Spironolactone
- Intralesional corticosteroid

Oral isotretinoin: reduces size and secretion of sebaceous glands, decreases surface and ductal level of sebum-dependent C.acnes indirectly, inhibits comedogenesis by normalizing keratinocyte keratinization, and anti-inflammation

Physical modalities:

- Acne lesion extraction
- Chemical peels (glycolic acid, trichloroacetic acid, mandelic acid, etc.)
- Laser and light-based devices
- Microneedle radiofrequency devices
- Photodynamic therapy

NICE Acne Guideline – What's the latest for Dermatologists?

First line treatment options	Form	Acne severity	Advantages	Disadvantages	Breastfeeding	Pregnancy
Fixed combination of topical adapalene with topical benzoyl peroxide	once daily in the evening	Any severity	• Topical • Does not contain antibiotics	• Can cause skin irritation, photosensitivity, and bleaching of hair and fabrics	✗	✓ with caution
Fixed combination of topical tretinoin with topical clindamycin	once daily in the evening	Any severity	• Topical	• Can cause skin irritation and photosensitivity	✗	✗
Fixed combination of topical benzoyl peroxide with topical clindamycin	once daily in the evening	Mild to Moderate	• Topical	• Can cause skin irritation, photosensitivity, and bleaching of hair and fabrics	✓ with caution	✓
Fixed combination of topical adapalene with topical benzoyl peroxide, plus either oral lymecycline or oral doxycycline#	once daily in the evening once daily	Moderate to Severe	• Oral component may be effective in treating affected areas that are difficult to reach with topical treatment (such as the back) • Treatment with adequate courses of standard therapy with systemic antibiotics and topical therapy is a MHRA requirement for subsequent oral isotretinoin	• Topical adapalene and topical benzoyl peroxide can cause skin irritation, photosensitivity, and bleaching (topical benzoyl peroxide) of hair and fabrics • Oral antibiotics may cause systemic side effects and antimicrobial resistance • Oral tetracyclines can cause photosensitivity • Not for use under the age of 12	✗	✗
Topical azelaic acid plus either oral lymecycline or oral doxycycline# #if contraindicated or not tolerated consider trimethoprim or an oral macrolide	twice daily once daily	Moderate to Severe			✗	✗
Topical benzoyl peroxide* *consider if above treatment options are contraindicated or person wishes to avoid topical retinoid or an antibiotic	once daily in the evening	Any severity	• Topical • Does not contain topical retinoid or antibiotic	• Can cause skin irritation, photosensitivity, and bleaching of hair and fabrics	✓ with caution	✓

Referral to specialist care

Urgently refer people with acne fulminans on the same day to the on-call hospital dermatology team, to be assessed within 24 hours.

Refer people to a consultant dermatologist-led team if any of the following apply:

- diagnostic uncertainty
- acne conglobata
- nodulo-cystic acne

Consider referring people to a consultant dermatologist-led team if they have:

- mild to moderate acne that has not responded to 2 completed courses of treatment
- moderate to severe acne which has not responded to previous treatment which contains an oral antibiotic
- acne with scarring
- acne with persistent pigmentary changes
- acne of any severity, or acne-related scarring, causing or contributing to persistent psychological distress or a mental health disorder

Consider referral to mental health services if a person with acne experiences significant psychological distress or a mental health disorder, including those with a current or past history of:

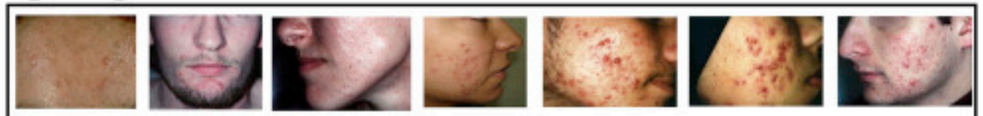
- suicidal ideation or self-harm
- a severe depressive or anxiety disorder
- body dysmorphic disorder

Consider condition-specific management or referral to a specialist (for example a reproductive endocrinologist), if a medical disorder or medication (including self-administered anabolic steroids) is likely to be contributing to a person's acne.

Take into account that the risk of scarring increases with the severity and duration of acne.

NICE Acne Guideline 2021

Managing Acne



MILD MODERATE SEVERE

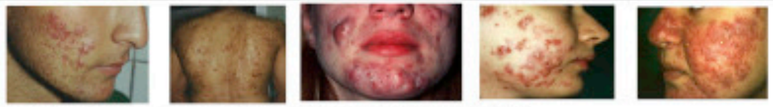
Comedonal	Papular/pustular	Papular/pustular	Moderately Severe - Severe
Topical Retinoid or Fixed combination with retinoid > BPO or Azelaic Acid > Salicylic Acid	Fixed Combination or BPO or Topical Retinoid or Azelaic Acid	Fixed Combination Preferred ± Hormonal therapy and/or Oral Antibiotic*	Fixed Combination + Oral Antibiotic Preferred Or + Oral Isotretinoin Or + Oral Hormonal Therapy

If patient responds, treat until clear or almost clear

Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

* Particularly if the trunk is involved

Managing Very Severe Acne



NODULAR and/or CONGLOBATE ACNE

Males	Females
Oral Isotretinoin or Fixed Combination + Oral Antibiotics	Oral Isotretinoin + anti-androgenic hormonal therapy or Fixed Combination + Oral Antibiotics (consider high dose) and/or oral anti-androgenic hormonal therapy

If patient responds, treat until clear or almost clear

Maintenance Therapy: Topical Retinoid or Retinoid/BPO Combination

If Response is Poor

- ✓ Check non-drug related reasons (seborrhea, stress and diet, Malassezia furfur, G- bacteria, comedogenic skin care products, endocrine profile) and exclude hidradenitis suppurativa/acne inversa
- ✓ Check drug-related reasons (type/dose antibiotic, microbial resistance, spot treatment, consider adding prednisone, for females check use of anti-androgenic agents)
- ✓ Consider intralesional injections of steroids or mechanical removal of macrocomedones
- ✓ Probe patient's adherence (application technique, missed doses, tolerability)
- ✓ Ask about adverse events

JAAD 2018

Management of Acne Vulgaris

Adults, adolescents, and preadolescents (≥ 9 years) with acne vulgaris

Baseline Evaluation

SEVERITY ASSESSMENT:
- Acne objective severity should be assessed consistently, using the Physician Global Assessment (PGA) or other scales
- Assess satisfaction with appearance, extent of scar / dark marks, treatment satisfaction, long-term acne control, and impact on quality of life.

Routine microbiological and endocrine testing are not indicated

Mild

Moderate to severe

TOPICAL TREATMENTS

Multimodal therapy combining multiple mechanisms of action is recommended

Multimodal Topical Therapy

- Topical retinoids
- BP
- Topical antibiotics
  - *Monotherapy is not recommended*

Fixed-dose combinations

- Topical antibiotic & BP
- Topical retinoid & BP
- Topical retinoid & antibiotic
  - *Concomitant use of BP can prevent the development of antibiotic resistance.*

- Clascoterone
- Salicylic acid
- Azelaic acid

PHYSICAL MODALITIES

- Pneumatic broadband light added to adapalene

SYSTEMIC ANTIBIOTICS

Limit systemic antibiotic use when possible to reduce the development of antibiotic resistance and other antibiotic-associated complications.

Use concomitant BP and other topical treatment

- Doxycycline
- Minocycline
- Sarecycline
- Doxycycline over azithromycin

HORMONAL AGENTS

- Combined oral contraceptives
- Spironolactone
  - *Potassium monitoring is of low usefulness in patients without risk factors for hyperkalemia (e.g., older age, medical comorbidities, medications).*
- Intralesional corticosteroids
  - *Adjuvant treatment for larger acne papules or nodules at risk of acne scarring or for rapid improvement in inflammation and pain.*

ISOTRETINOIN

- Isotretinoin
  - *Patients with psychosocial burden or scarring should be considered candidates for isotretinoin.*
  - *We recommend monitoring only LFT and lipids*
  - *Population-based studies have not identified increased risk of neuropsychiatric conditions or inflammatory bowel disease with isotretinoin.*
  - *For persons of pregnancy potential, pregnancy prevention is mandatory.*
- Daily dosing over intermittent dosing
- Either lidose-isotretinoin or standard isotretinoin

Key:
- Strong recommendation in favor of the intervention
- Conditional recommendation in favor of the intervention
- Strong recommendation against the intervention
- Conditional recommendation against the intervention

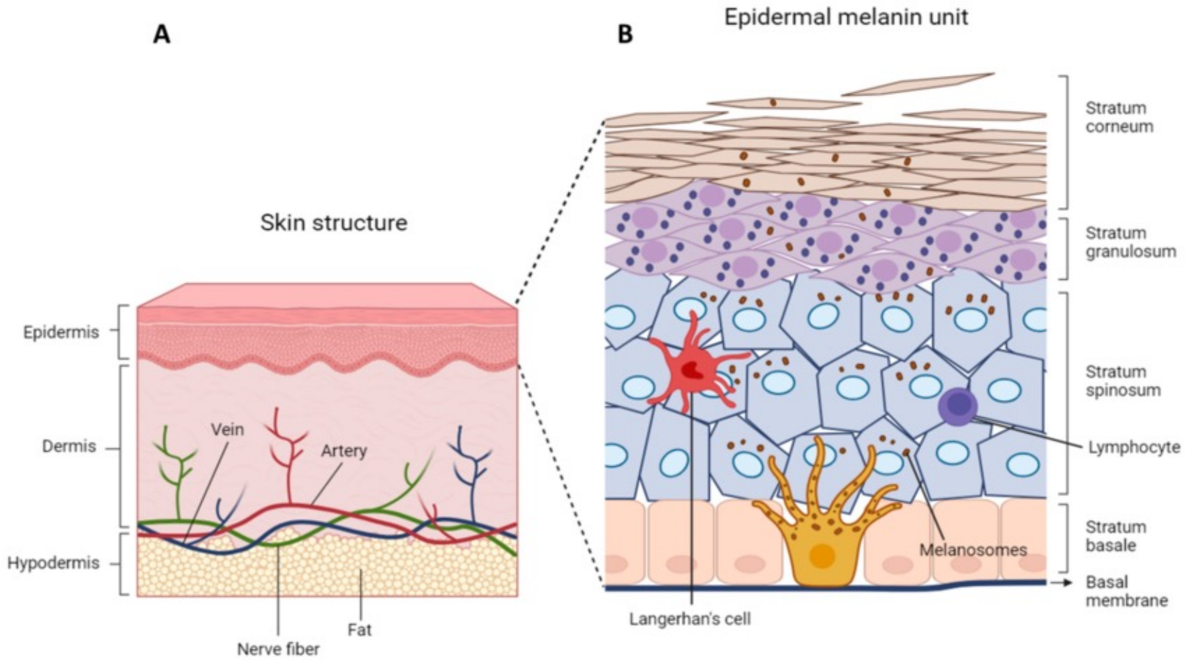
Abbreviations: BP: Benzoyl peroxide; LFT: Liver function test

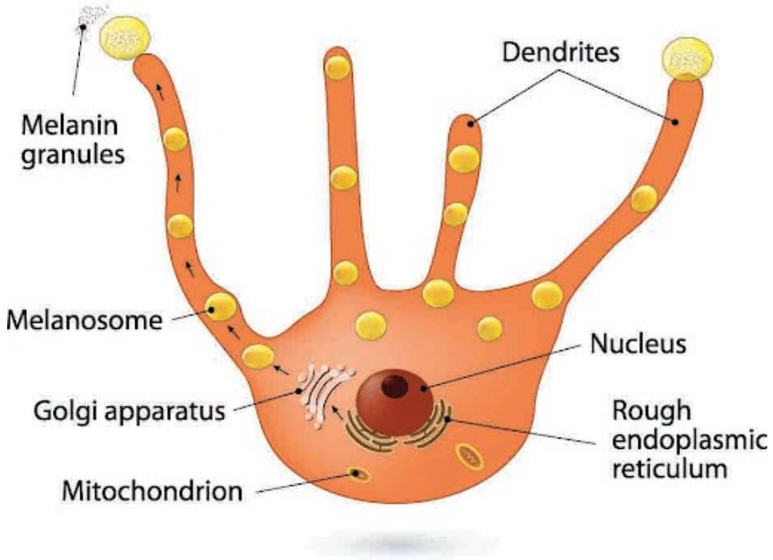
JAAD 2024


Melasma

Melanocytes

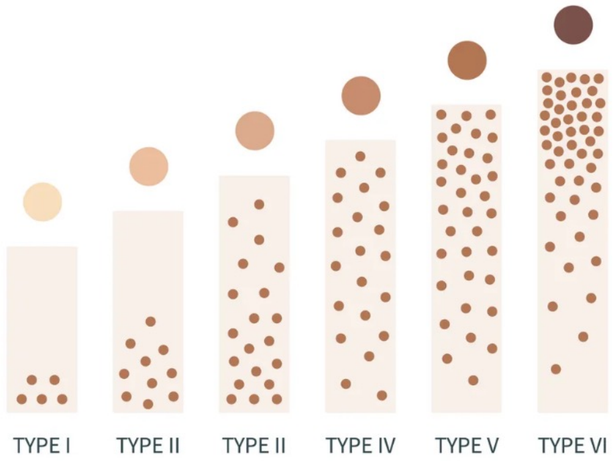
- Melanocytes locates in stratum basale (at dermo-epidermal junction)
- Each melanocyte is highly branched and functionally connected to underlying fibroblasts in dermis and to approximately 36 keratinocytes through dendritic processes.
- This grouping (1 melanocyte per 36 keratinocytes) is called **epidermal melanin unit.**

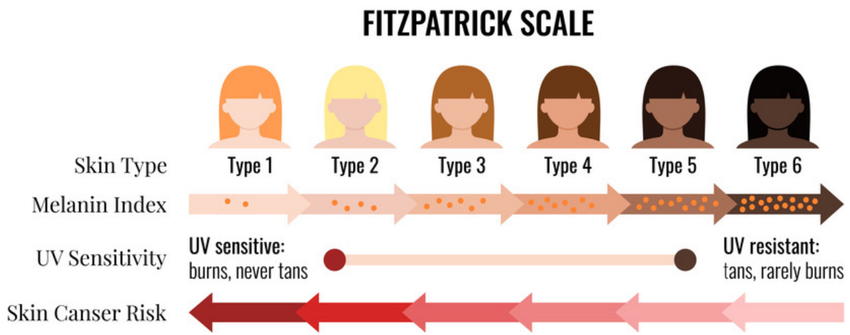


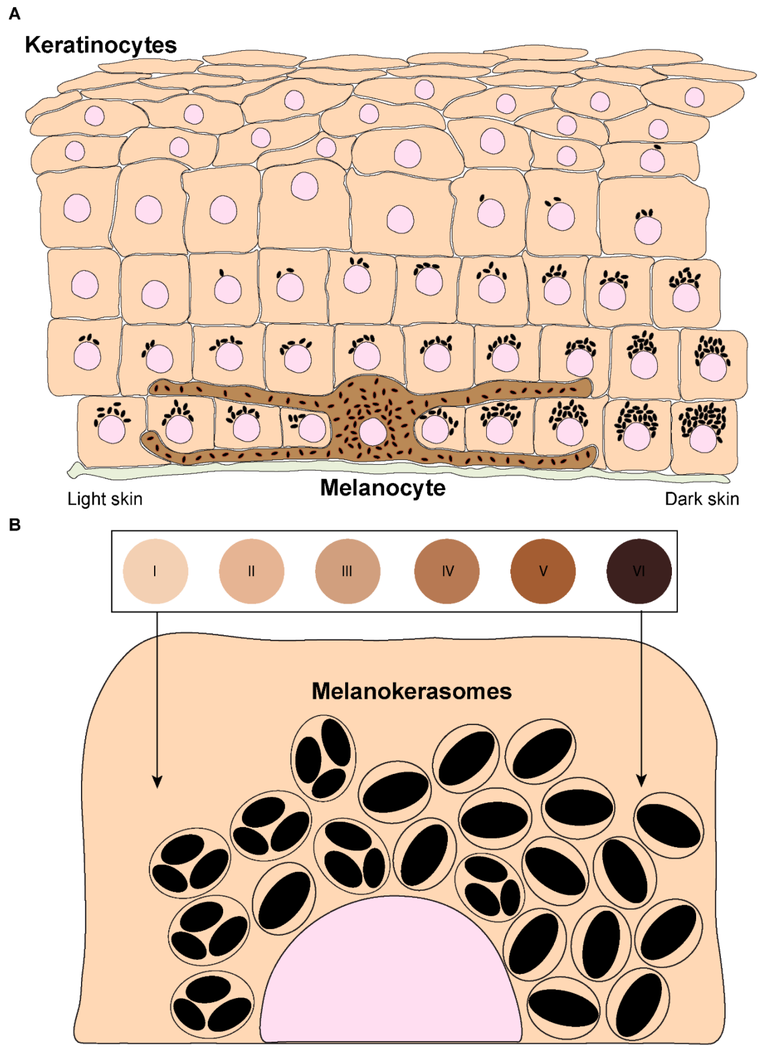


Skin pigmentation (complexion)

- Skin color is <u>not</u> affected by the differences in melanocyte densities, which remain constant in every skin phototype.

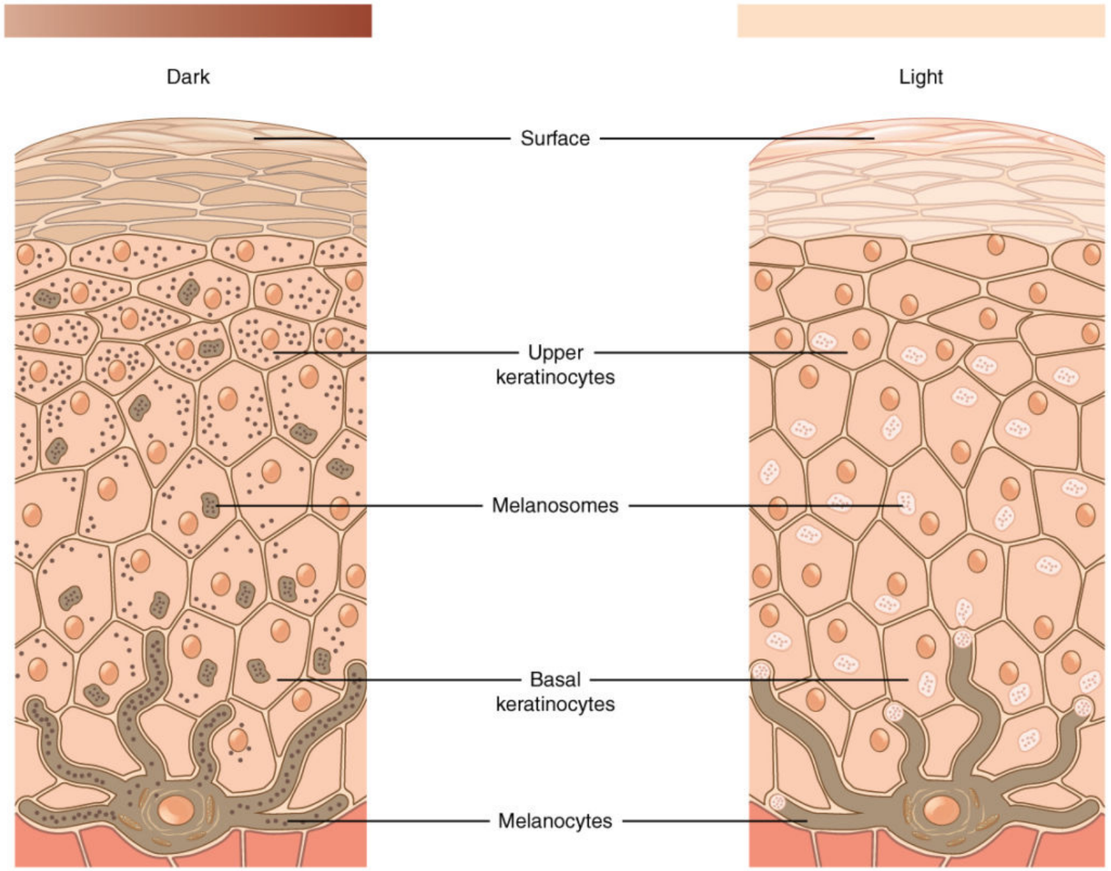






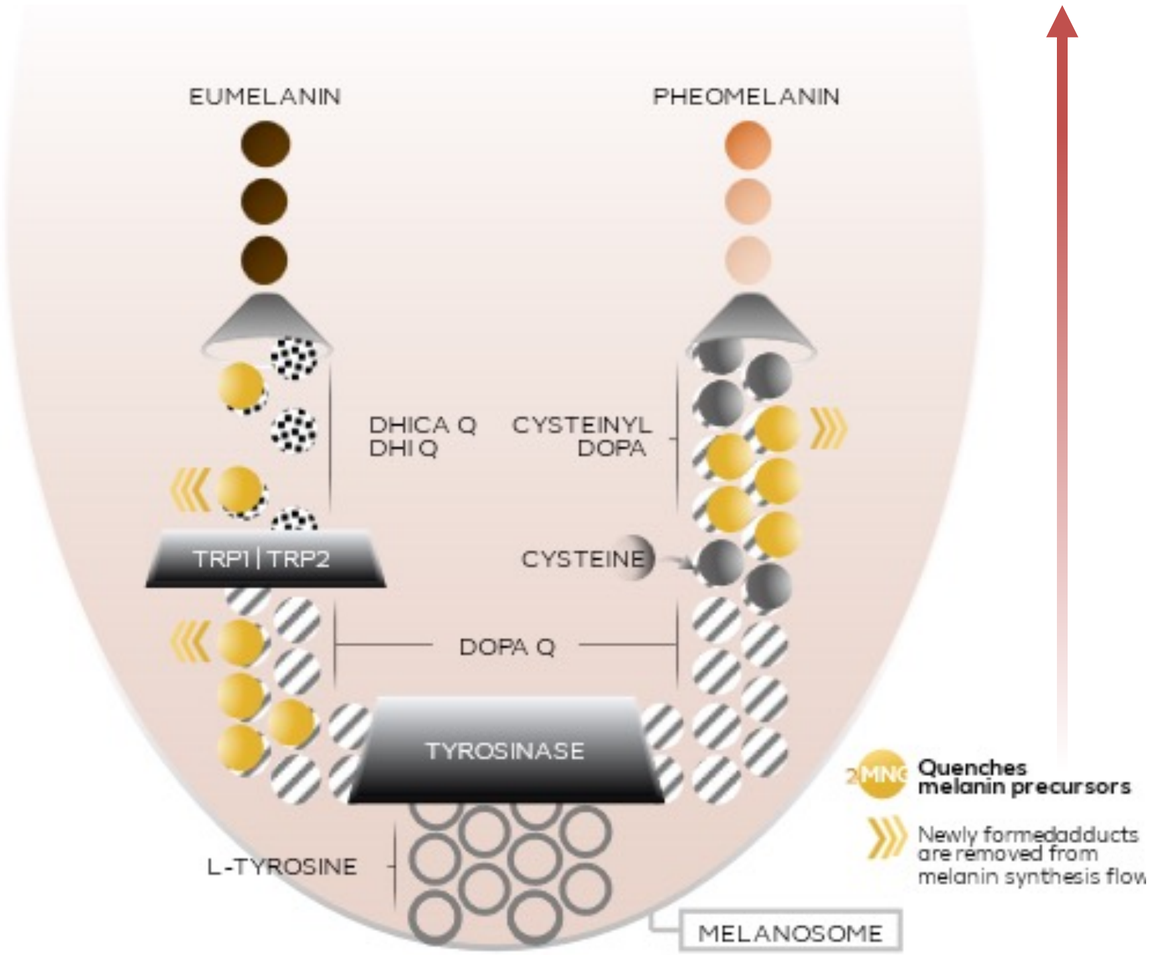
Melanogenesis

- Melanin synthesis occuring within melanosomes and their transfer from melanocytes to neighboring keratinocytes determines **skin pigmentation.**
- With time, the keratinocytes and melanosomes migrate to the surface of the skin and are shed with the desquamation process.
- Melanosomes are larger in high phototypes than low phototypes and are packaged as a single unit rather than in groups.
- Since clustered melanosomes are degraded more efficiently, in high phototype skin, a delay in melanosomes degradation inside the keratinocytes can contribute to the higher level of skin pigmentation.



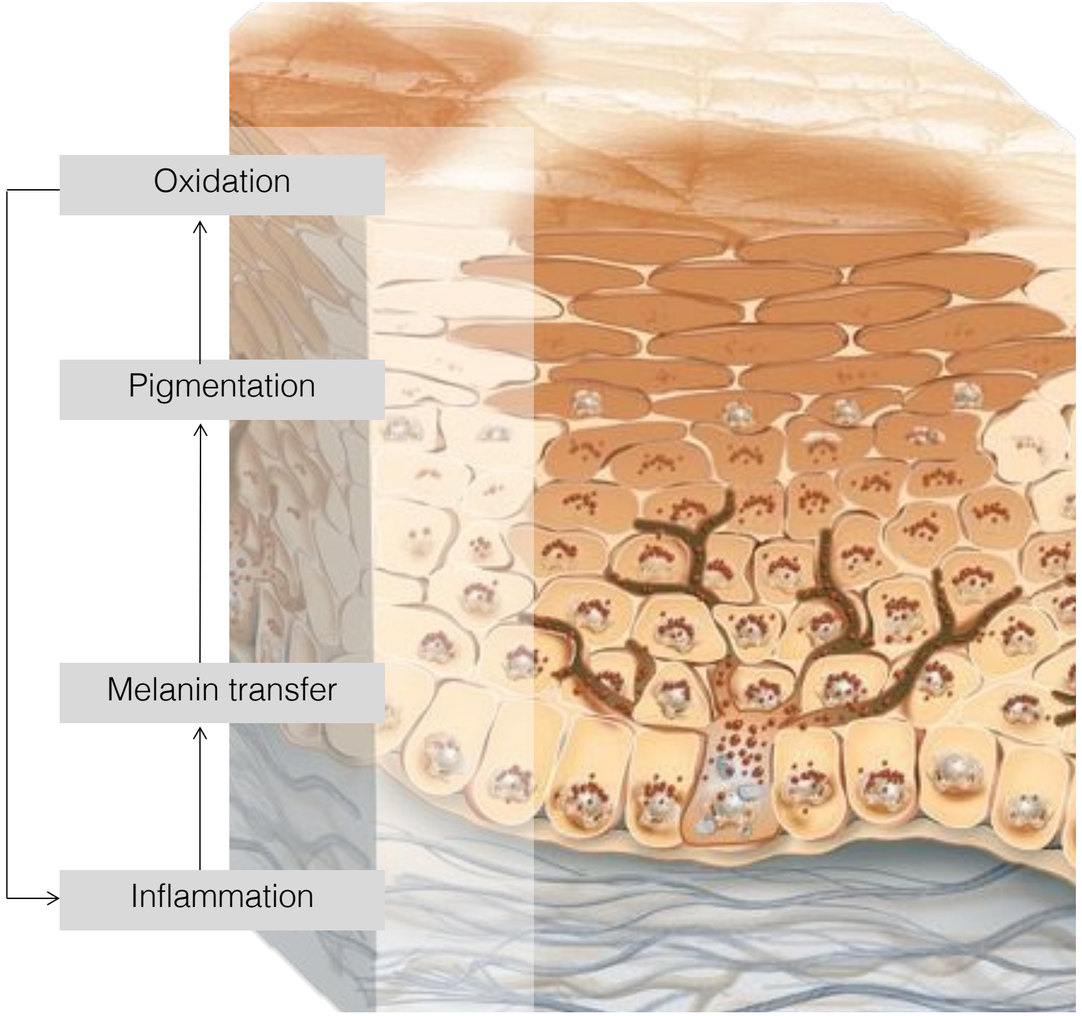
Melanogenesis

- When exposed to UV radiation, melanin is redistributed near the nuclei of keratinocytes, resulting in the creation of **supranuclear cap**, functioning as a natural sunscreen, **safeguarding DNA by absorbing and dispersing UV radiation**.
- Melanin is synthesized as dark-colored (brown–black) insoluble **eumelanin**, and light-colored (red–yellow) **pheomelanin**
- The rate-limiting step of melanogenesis is the oxidation of tyrosine by **tyrosinase.**

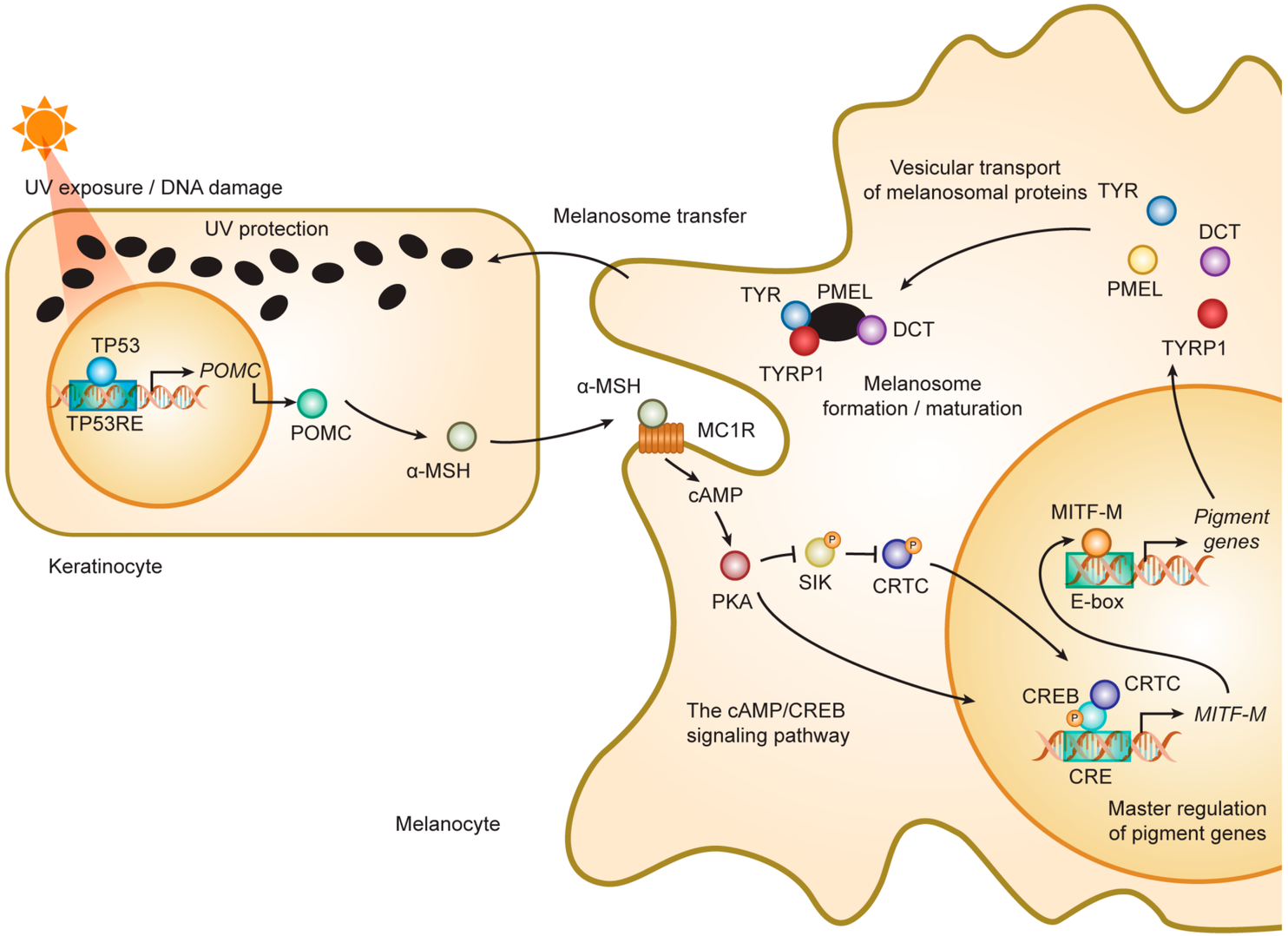


Melanocyte response to UV radiation

- Acute effect of UV on the skin is **induction of inflammation.**
- Skin exposed to UV is associated with an **increased number of active melanocytes.**
- Therefore, resulting in **increased melanocyte tyrosinase activity**, **elongation and branching of melanocyte dendrites,** and **increased number and size of melanosomes**



Melanocyte response to UV radiation



Disorders of **hypo**pigmentation

Congenital:

1. Circumscribed:
   - Piebaldism
   - Nevus depigmentosus
2. Generalized:
   - Albinism
   - Phenylketonuria
   - Homocystinuria

Nutrition:

- Kwashiokor
- Selenium deficiency

Endocrine:

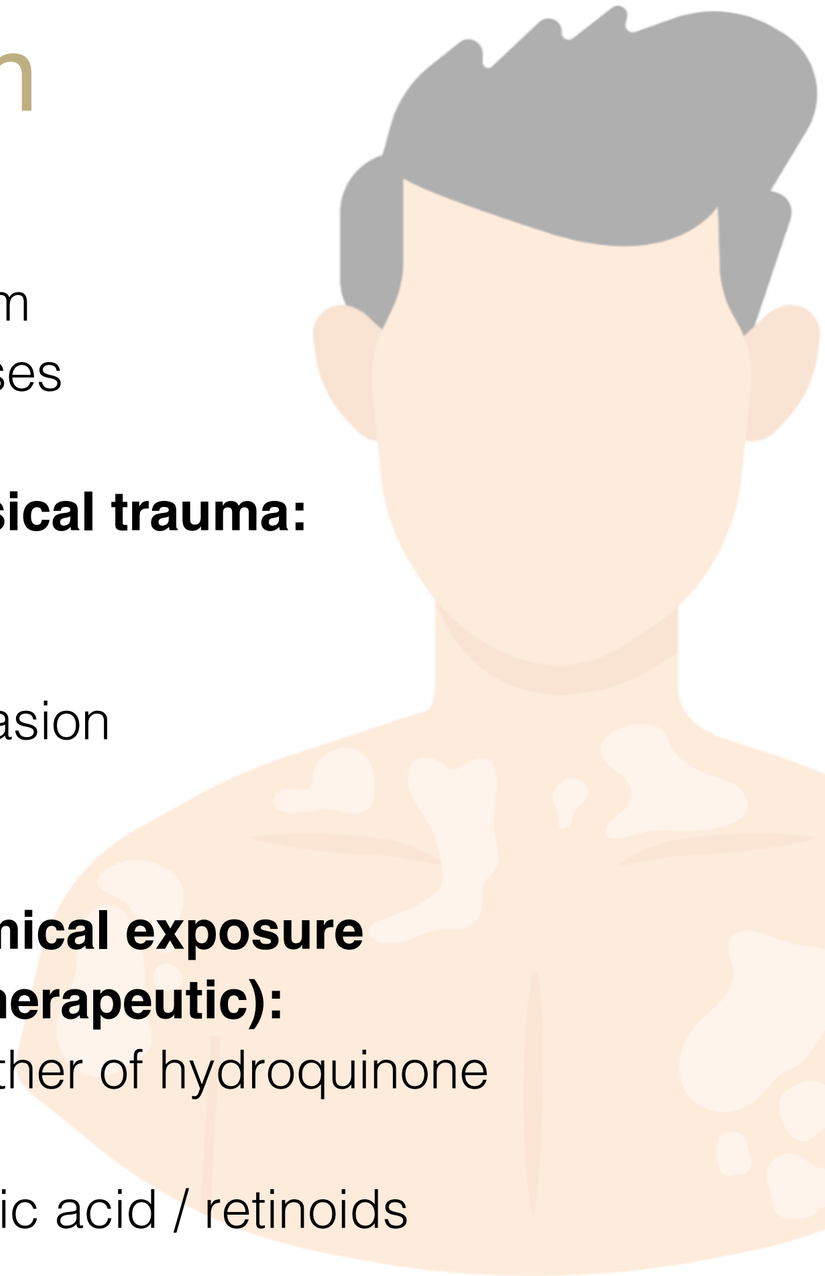
- Hypothyroidism
- Thyroid diseases

Secondary to physical trauma:

- Burn
- Trauma
- Post-dermabrasion
- Post-laser

Secondary to chemical exposure (occupational or therapeutic):

- Monobenzyl ether of hydroquinone
- Phenol
- Steroid / azelaic acid / retinoids



Disorders of **hyper**pigmentation

Genetic:

- Freckles
- Lentigo
- Peutz-Jeghers syndrome
- Café-au-lait spots
- Xeroderma pigmentosa

Endocrine:

- Addison's disease
- Cushing syndrome
- Pregnancy
- Renal failure

Metabolic:

- Biliary cirrhosis
- Hemochromatosis
- Porphyria

Nutrition:

- Malabsorption
- Pellagra

Drugs:

- Minocycline
- Arsenic
- Psoralens
- Busulfan
- Contraceptives

Post-inflammatory:

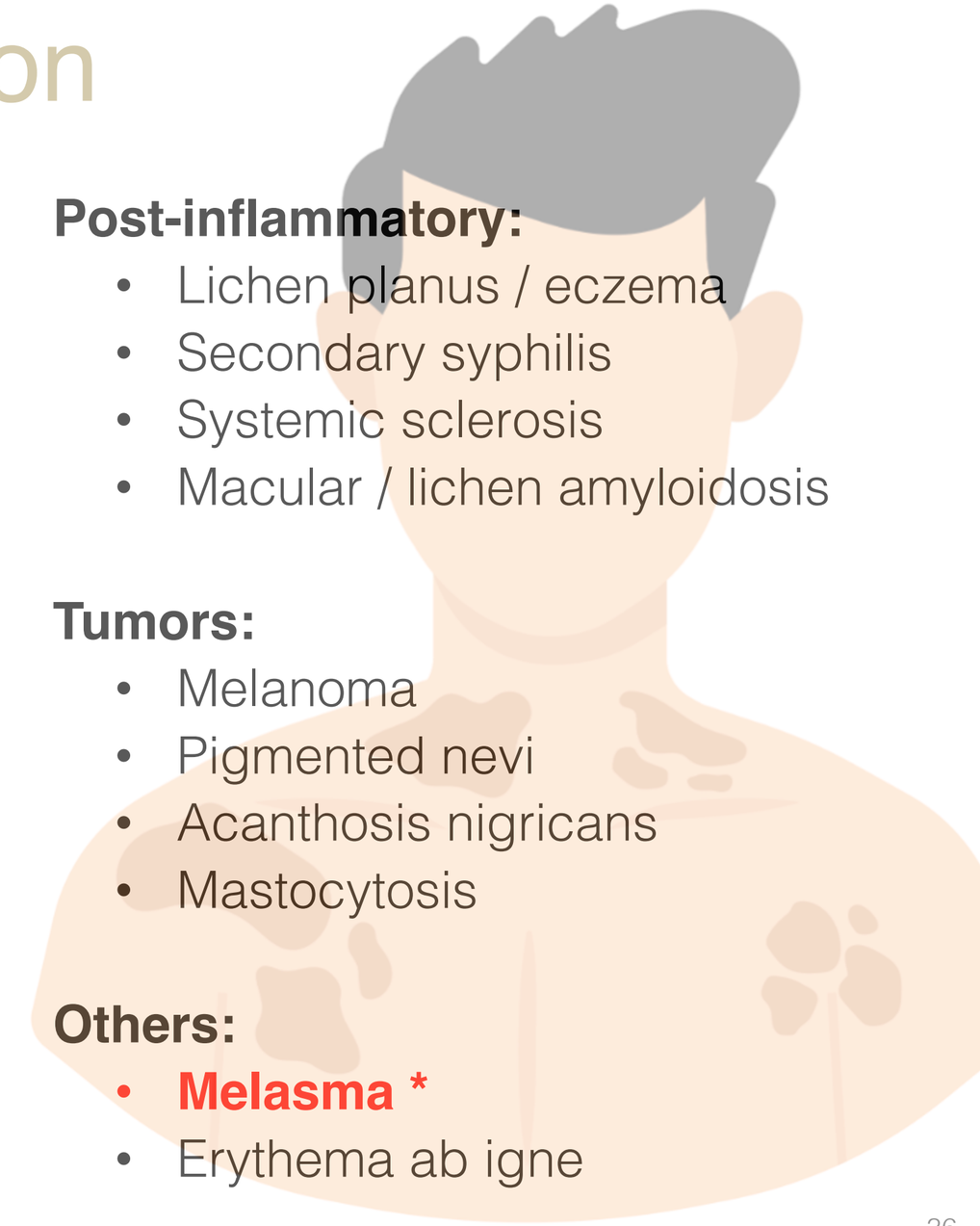
- Lichen planus / eczema
- Secondary syphilis
- Systemic sclerosis
- Macular / lichen amyloidosis

Tumors:

- Melanoma
- Pigmented nevi
- Acanthosis nigricans
- Mastocytosis

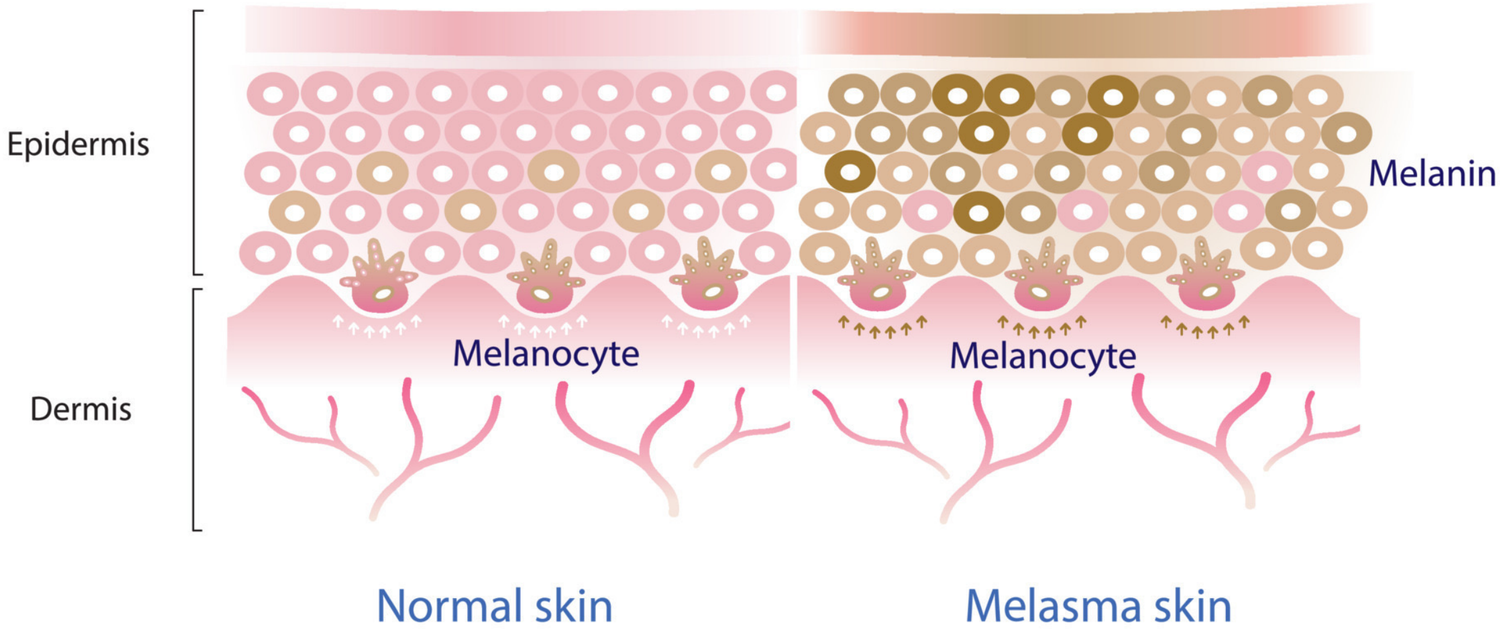
Others:

- **Melasma ***
- Erythema ab igne



Melasma

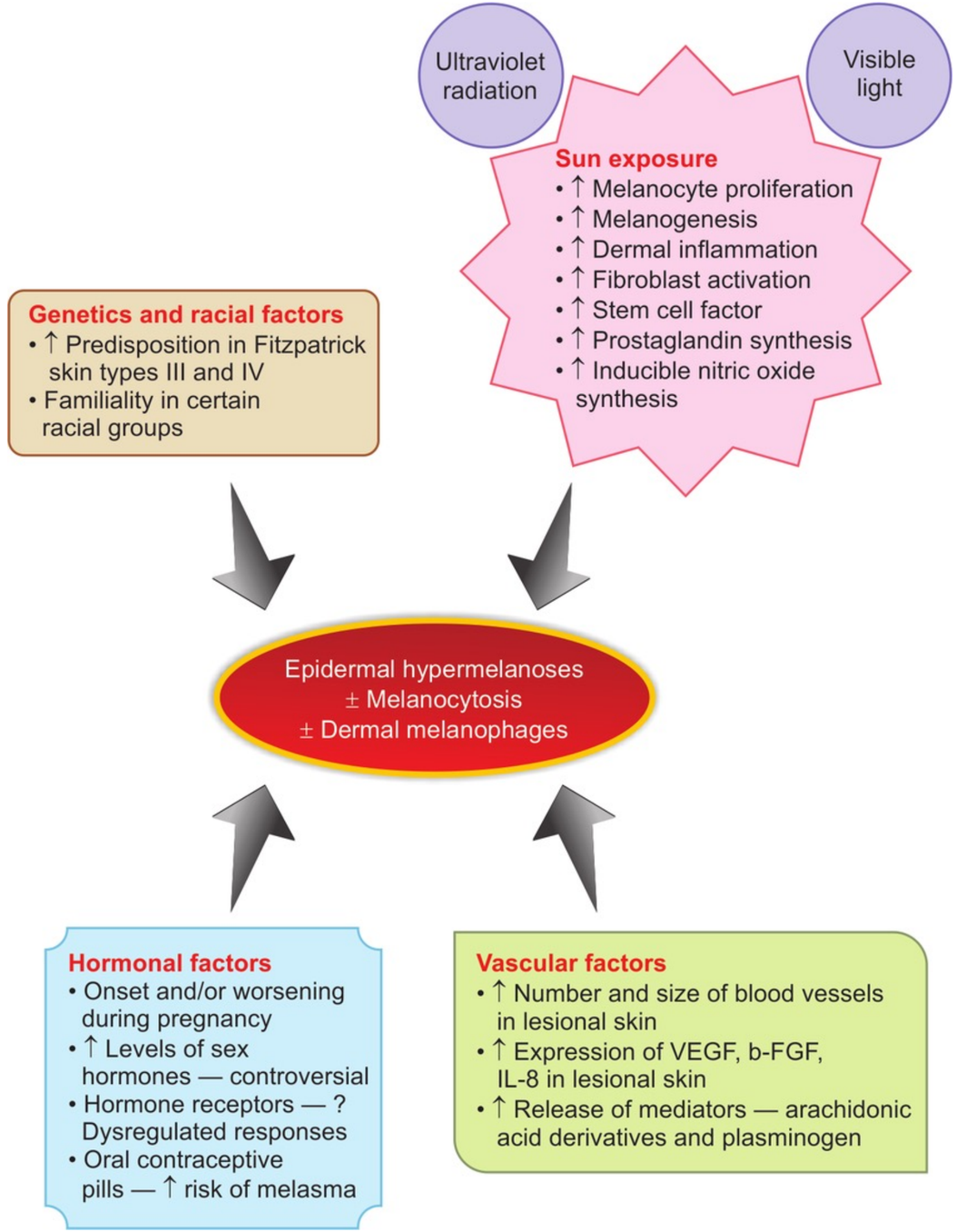
- A common **acquired hyperpigmentary disorder** with multiple etiologies that has a significant impact on quality of life
- Mostly starts between ages of 20 and 40 years with **female** predominance
- Occurs in all population groups (higher prevalence among high phototypes)



Etiologies and risk factors

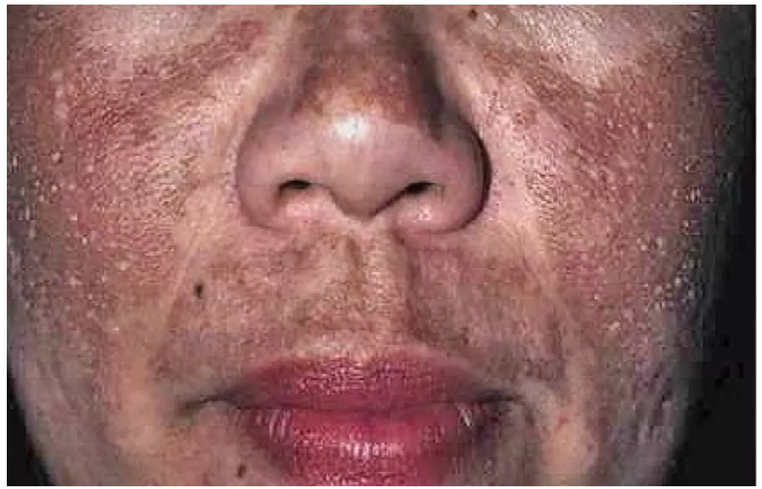
Although the pathogenesis remains unclear, **several etiologic factors** have been identified including:

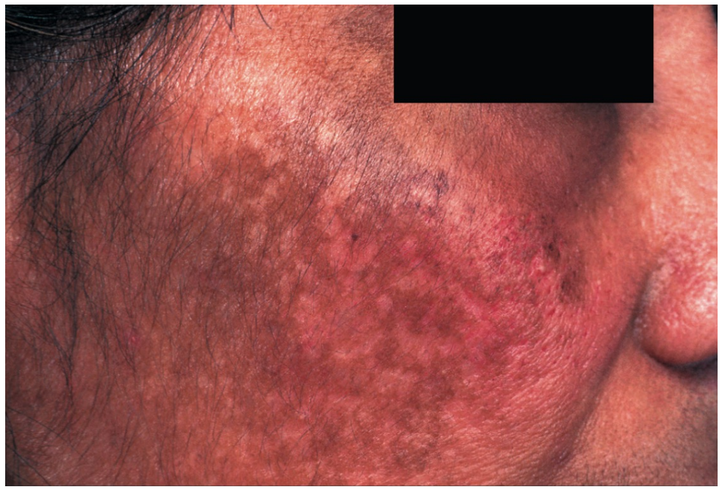
- **Exposure to ultraviolet (UV) radiation and visible light**
- **Hormonal factors**
- Familial predisposition
- Pregnancy
- Exogenous hormone use (OCs)
- Cosmetics and photosensitizing drugs
- Procedures and inflammatory processes of the skin

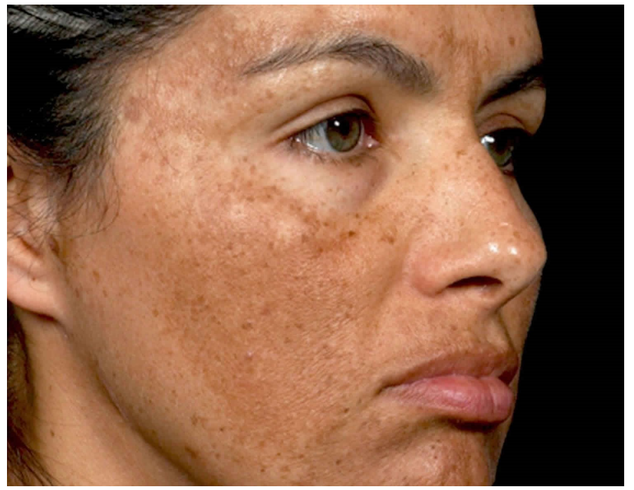


Clinical features of melasma

- Characterized by **irregular light-to-dark brown confluent or speckled hyperpigmented macules** involving **sun-exposed skin** (marked predilection for **face**) with bilateral and symmetrical disposition, and irregular borders
- The areas usually involved in are malar, forehead, upper lips, and chin.
- Most common clinical patterns are centrofacial and malar, but mandibular involvement may also be seen.





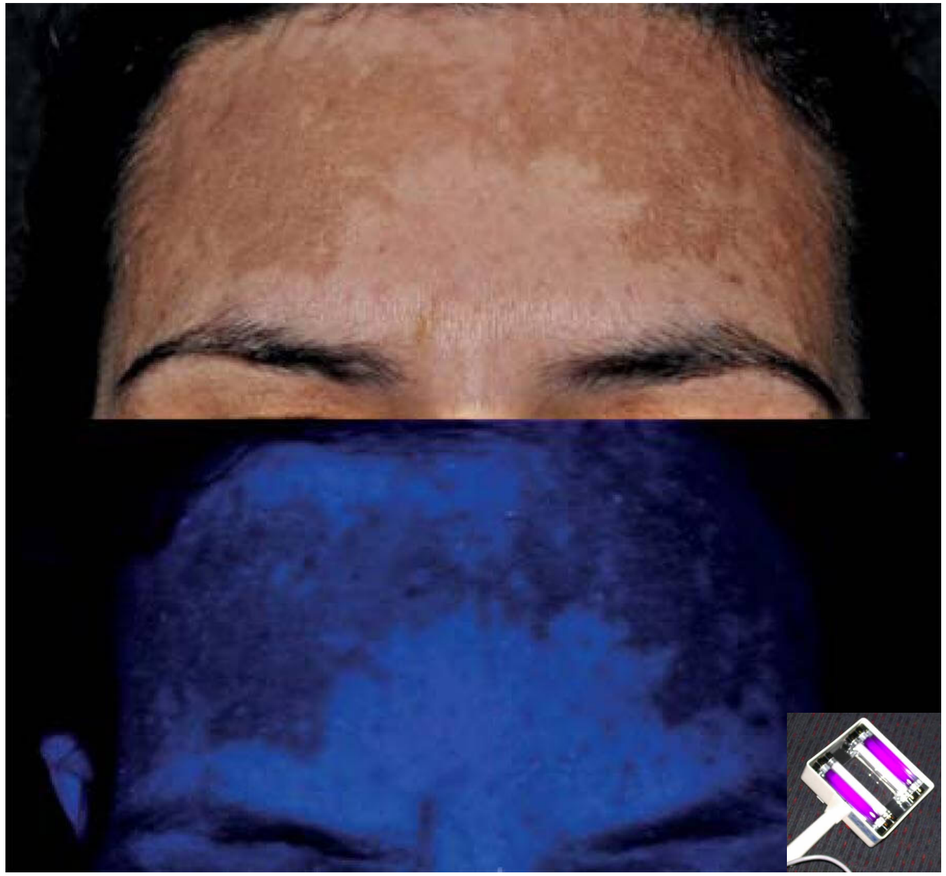


Clinical features

- Melasma may be defined as either **epidermal, dermal,** or **mixed** depending on **Wood's lamp examination.**
- Although Wood's lamp examination remains useful to determine whether most of the pigmentation is in the **epidermis** (and thus should better respond to topical depigmenting agents) or in the **dermis**.

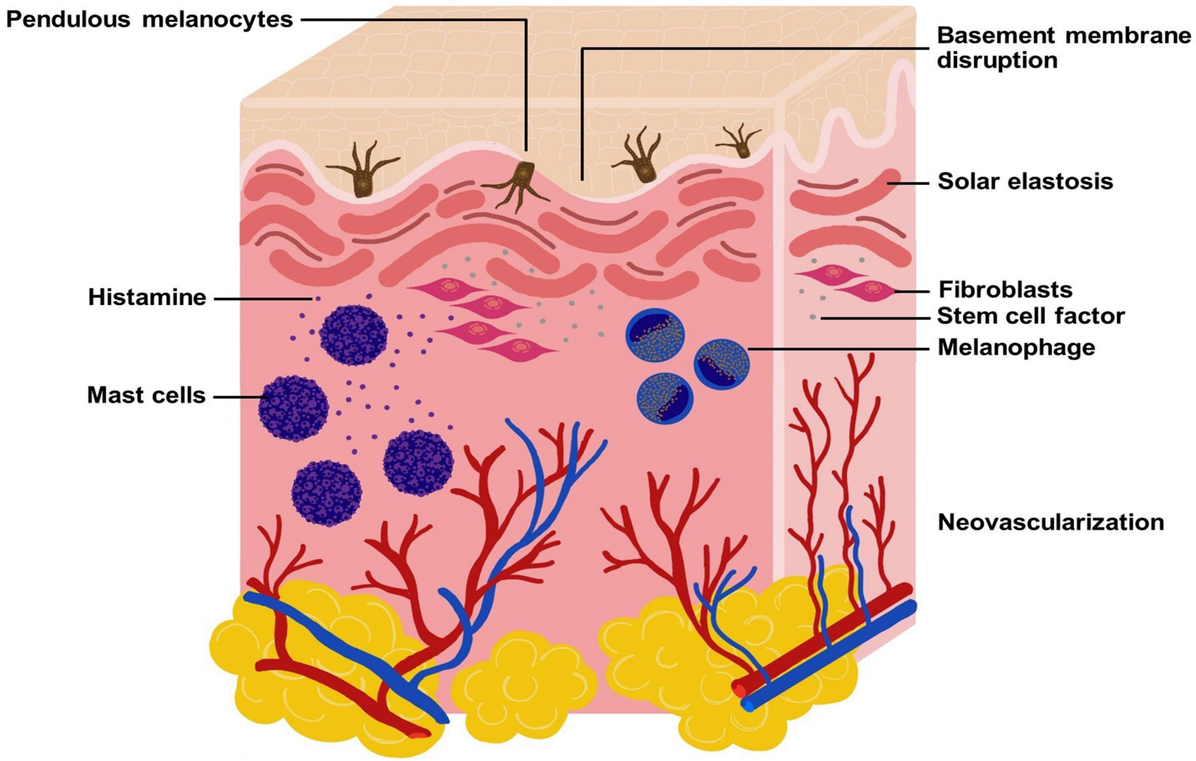
Prognosis:

- Pigmentation usually fades after parturition, but may persist for months or years.
- After discontinuing oral contraceptives, it takes long time to fade.
- After pregnancy, it may never fade completely.



Pathogenesis of melasma

- Despite the fact that melasma is characterized by **epidermal hyperpigmentation**, the histopathological changes involve both the epidermis and dermis.
- **Increased melanin pigments in all epidermal layers**, and some degree of epidermal thinning
- Other **dermal pathologic changes*** in lesional melasma:
  - Basement membrane disruption
  - Pendulous melanocytes
  - Melanophages
  - Mast cells
  - Stem cell factor
  - Solar elastosis
  - Neovascularization



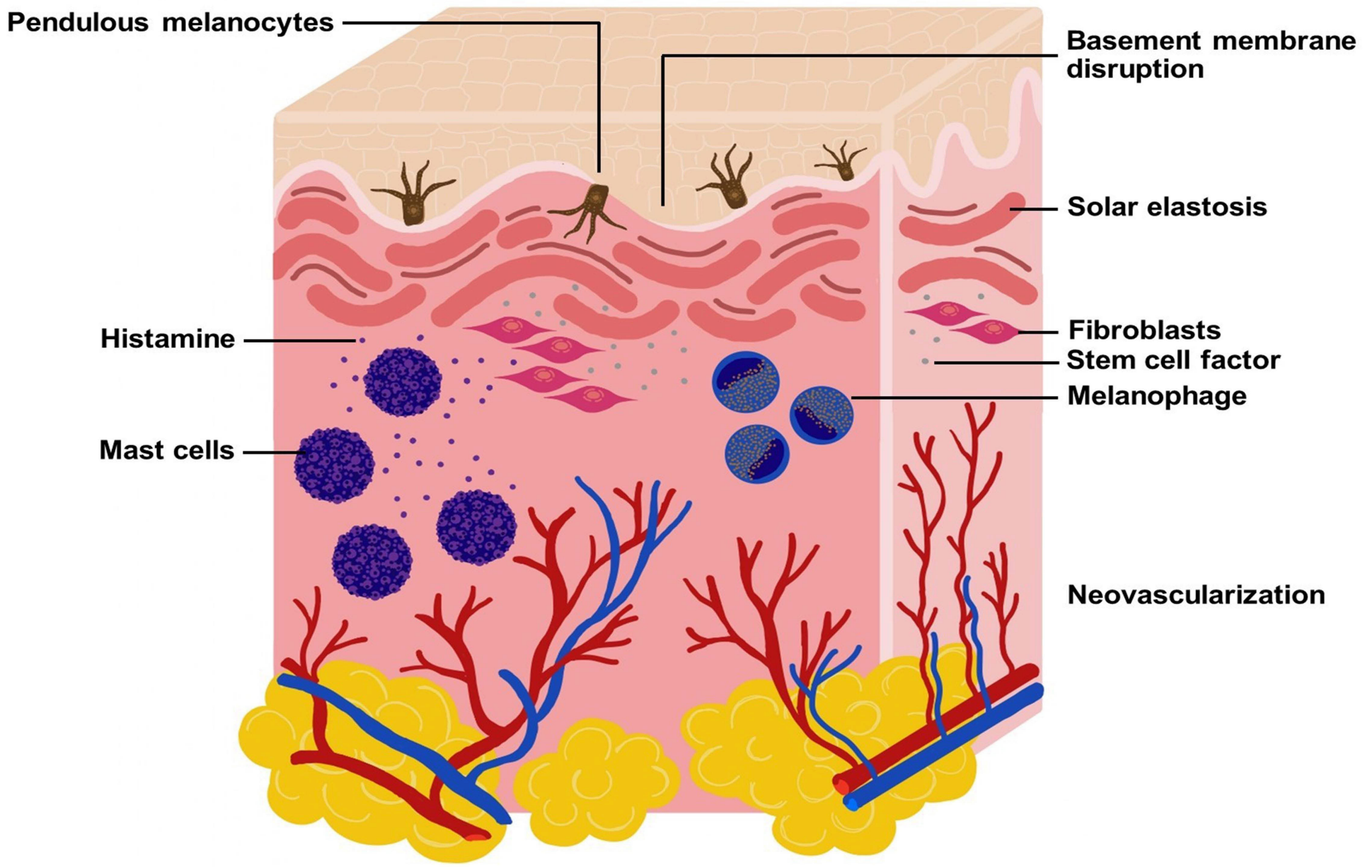
Cells involving in melasma pathogenesis

Cells	Definition	Role of Each Cell Involved in Dermal Pathologic Process
Pendulous melanocytes	- Melanocytes that protrude into the dermal layer and related to the hyperactivity of melanocytes	- Loss of basement membrane and cadherin expression by chronic UV exposure lead melanocytes to migrate deeper into the dermis
Melanophages	- Melanin-containing macrophages	- The phagocytized melanin in cytoplasmic granules within dermis layer leading to persistent of pigmentation
Fibroblasts	- Dermal resident cells, which can produce collagen and other fibers	- Upregulate the tropoelastin mRNA gene expression and elastin production by chronic UV radiation - Overexpress the cadherin 11 resulting in an increase of MMP-1 and MMP-2 expression and basement membrane disruption - Increased expression of stem cell factor
Mast cells	- Inflammatory cells that mediate inflammatory responses - The granules contain of several cytokines such as tryptase and histamine, which can be stimulated by the UV exposure	- Tryptase can activate the pro-collagenase enzymes leading to collagen degradation and elastotic materials - Produce VEGF leading to neovascularization - Produce inflammatory mediators such as TNF-α, TGF-β, IL-8

Abbreviations: IL-8, interleukin-8; MMP, matrix metalloproteinase; mRNA, messenger ribonucleic acid; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α; UV, ultraviolet; VEGF, vascular endothelial growth factor.

Phansuk K, Vachiramon V, Jurairattanaporn N, Chanprapaph K, Rattananukrom T. Dermal Pathology in Melasma: An Update Review. Clin Cosmet Investig Dermatol. 2022;15:11-19.

Dermal pathologic changes in melasma



- Basement membrane disruption
- Pendulous melanocytes
- Melanophages
- Mast cells
- Stem cell factor
- Solar elastosis
- Neovascularization

Basement membrane disruption

- Found in 95.8% of melasma lesions
- Chronic UV exposure results in the increase in **MMP-2** and **MMP-9** (also called gelatinase) activities (especially in UV-induced photoaging) which could degrade type IV collagens (components of epidermal basement membrane) and disrupt the basement membrane.
- In the same way, **MMP-1** also destroys type I collagen in the dermal layer.

Pendulous melanocytes

- Refers to melanocytes that protrude into the dermal layer is a sequence from basement membrane disruption
- **Cadherin** mediates the process of adhesion between keratinocytes and melanocytes for intercellular signaling. Once melanocytes lose their cadherin expression (due to chronic UV exposure), keratinocytes cannot control them.
- Melanocytes can then **migrate deeper into the dermis** below, leading to **constant hyperpigmentation** in melasma.

Melanophages

- Melanin-containing macrophages found in the dermis of pigmented skin lesions
- Melasma lesions contain **increased free melanin and melanophages in dermis**
- Melanophages were more commonly associated with dermal or mixed types of melasma than epidermal types.

Stem cell factor and c-KIT receptor

- **Stem cell factor** is a mitogenic growth factor for human melanocytes proliferation (stimulating DNA synthesis of human melanocytes through tyrosine kinase ligand–receptor-mediated signal transduction pathways), secreted by keratinocytes and fibroblasts.
- **c-KIT receptor** (tyrosine kinase receptor) is located on the melanocyte cell membrane and essential in melanogenesis.
- UV-B light exposure can upregulate transcription and expression of stem cell factor and c-KIT receptor.

Stem cell factor and c-KIT receptor (cont.)

- Stem cell factors secreted by fibroblasts could be a paracrine factor that functions in melanogenesis.
- In melasma lesions, higher expression of stem cell factor and c-KIT receptor was more often observed within the lesional sites than in the perilesional site.

Solar elastosis

- Photodermal aging typically has been shown to involve **dermal thinning** due to a decrease in fibroblast number, reduced collagen synthesis, and **increased UV-induced collagen degradation.**
- In response to these effects, the dermal elastin network is also destroyed. Consequently, elastin synthesis decreases, and the elastic fibers will become increasingly degraded and leaded to the **deposition of elastotic materials** in the dermis layer.

Mast cells

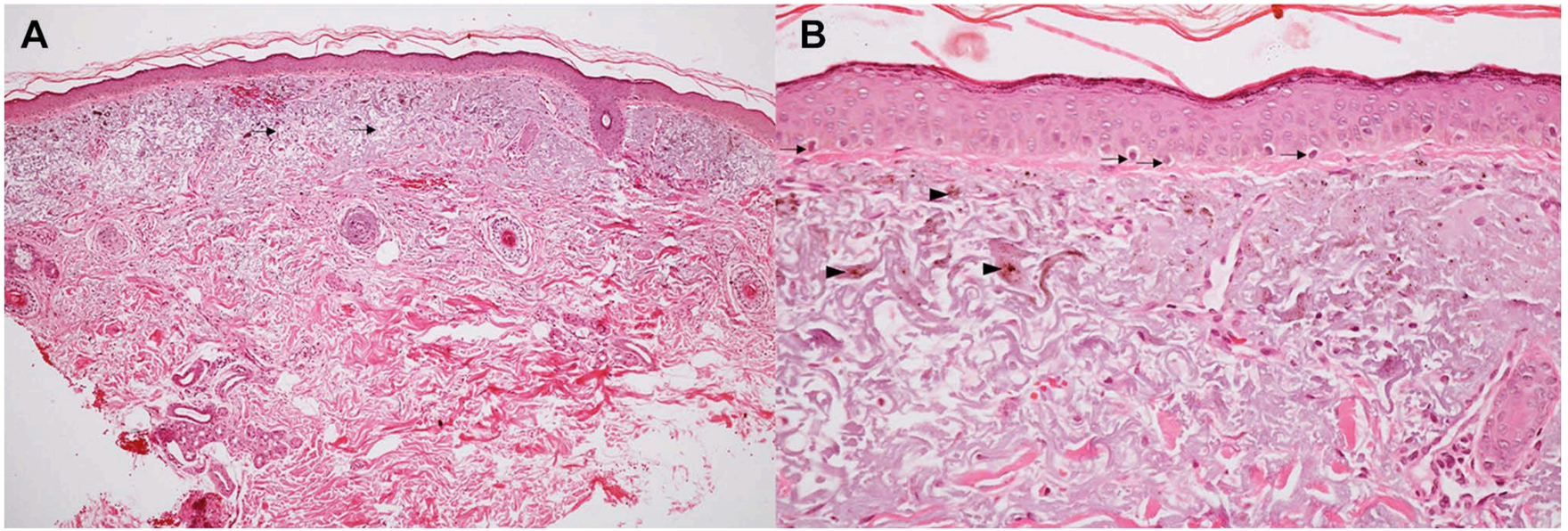
- Mast cells in the dermis play a role in both UV-induced photoaging and melanogenesis through the mechanism of **histamine** and **tryptase** release.
- Histamines are released after UV radiation exposure and bind with H2-receptors on melanocytes, leading to stimulation of cAMP and subsequent protein kinase A activation, inducing melanogenesis.
- Tryptase changes pro-collagenase enzyme (proMMP-3, proMMP-1) to the active form, resulting in collagen fibers degradation and the skin will suffering a loss of elasticity,
- In addition, mast cells can produce angiogenesis factors or cytokines (**VEGF**, FGF-2), leading to **neovascularization** within melasma lesion.

Neovascularization

- Melasma lesions show **increase in vascular density and size**.
- After UV radiation, keratinocytes are stimulated to upregulate VEGF through multiple mechanisms, resulting in **significantly promoted tyrosinase activity**, **melanocyte size**, and ultimately **hyperpigmentation effects**.

Histopathology of melasma

- The number of melanocytes in **not increased**, but they become **enlarged** and **more dendritic** (hypermetabolic state).
- **Increased melanin deposition** in both epidermis and dermis
- **Dermal pathologic changes:** increased solar elastosis, mast cells, melanophages, dermal vascular channels
- Loosening of the basement membrane



Melanin deposition in the epidermis and **solar elastosis** in the dermis (arrow) (x100)

Pendulous melanocytes in the basal layer of epidermis (arrow) and **increased dermal melanophages** (arrowhead) (x400)

Management of melasma

The use of sunscreen SPF > 30 with protection against visible light is mandatory in the management of melasma.

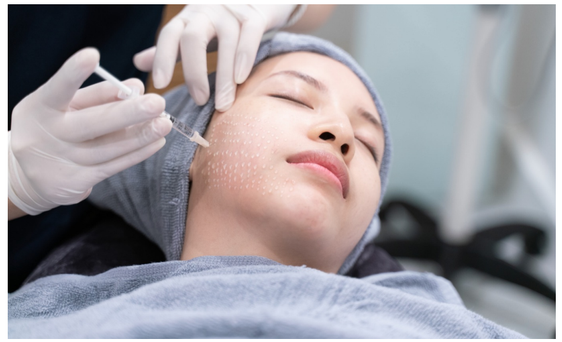
Management of melasma

First-line treatment: Topical treatment (depigmenting agents)

- Hydroquinone (HQ)
- Kligman's formula (combined HQ, tretinoin, and fluorinated corticosteroid)
- Others: Kojic acid, azelaic acid, ascorbic acid, arbutin, thiamidol, cysteamine, tranexamic acid (or in combination)

Second-line treatment: Chemical peeling

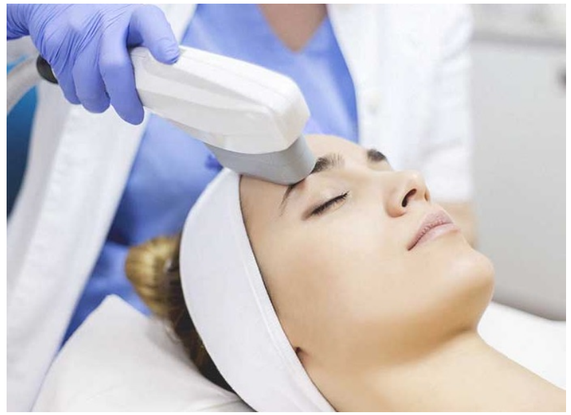
- Glycolic acid, trichloroacetic acid, Jessner's solution
- Mesotherapy



Management of melasma

Third-line treatment: Lasers and light therapies

- 1064-nm Q-switched neodymium-doped yttrium aluminium garnet laser (QS Nd:YAG) (in toning mode)
- Picosecond lasers
- Pulsed dye laser (PDL)
- Intense pulsed light (IPL)
- Fractional 1550-nm non-ablative laser
- Copper-bromide laser



Q&A

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