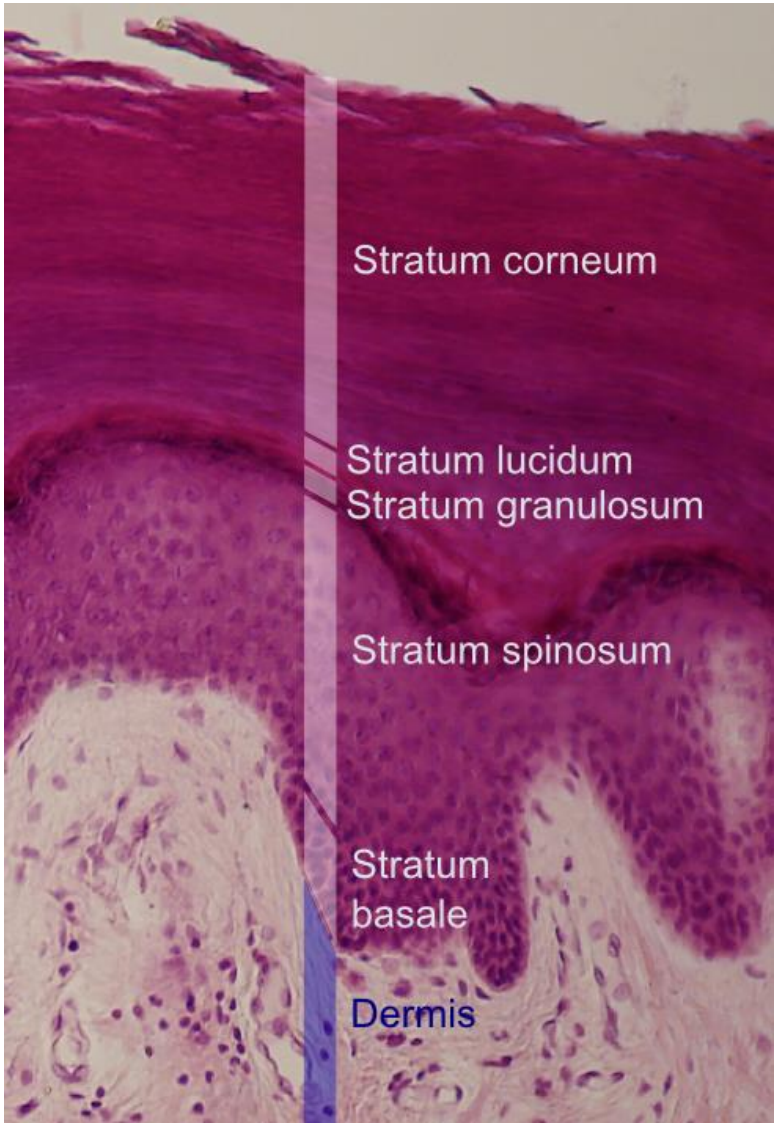
Skin

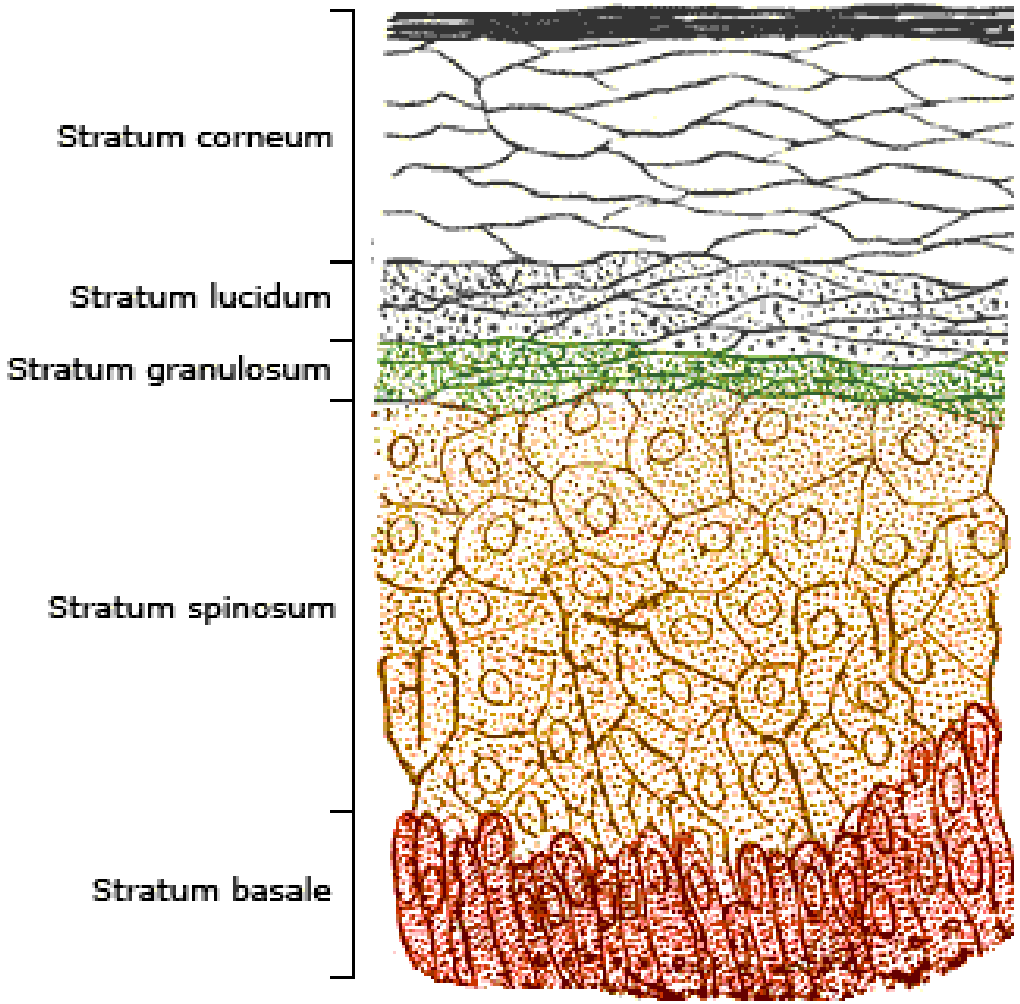
Jason Ryan, MD, MPH

Skin

- Largest organ in the body
- Barrier against infection
- Prevents water loss
- Three layers
  - Epidermis: keratinocytes (squamous epithelial cells)
  - Dermis: connective tissue, vessels
  - Subcutaneous fat (also called hypodermis or subcutis)



Mikael Häggström/Wikipedia



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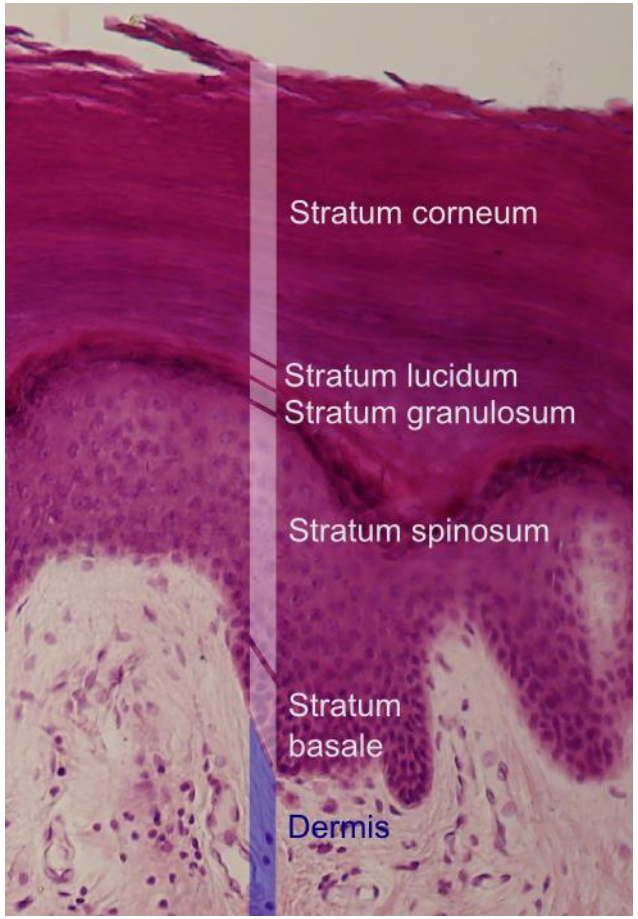
Epidermal Layers

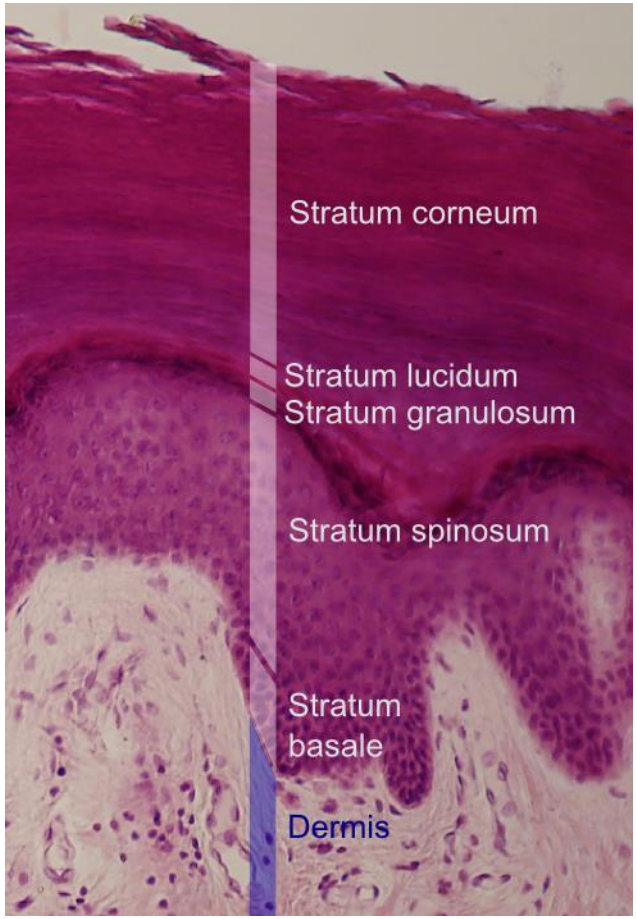
- Stratum Basalis
  - **Stem cells**
- Stratum Spinosum
  - **Desmosomes** form spines
- Stratum Granulosum
  - Keratohyalin granules
  - Form keratin filaments



Mikael Häggström/Wikipedia

Epidermal Layers

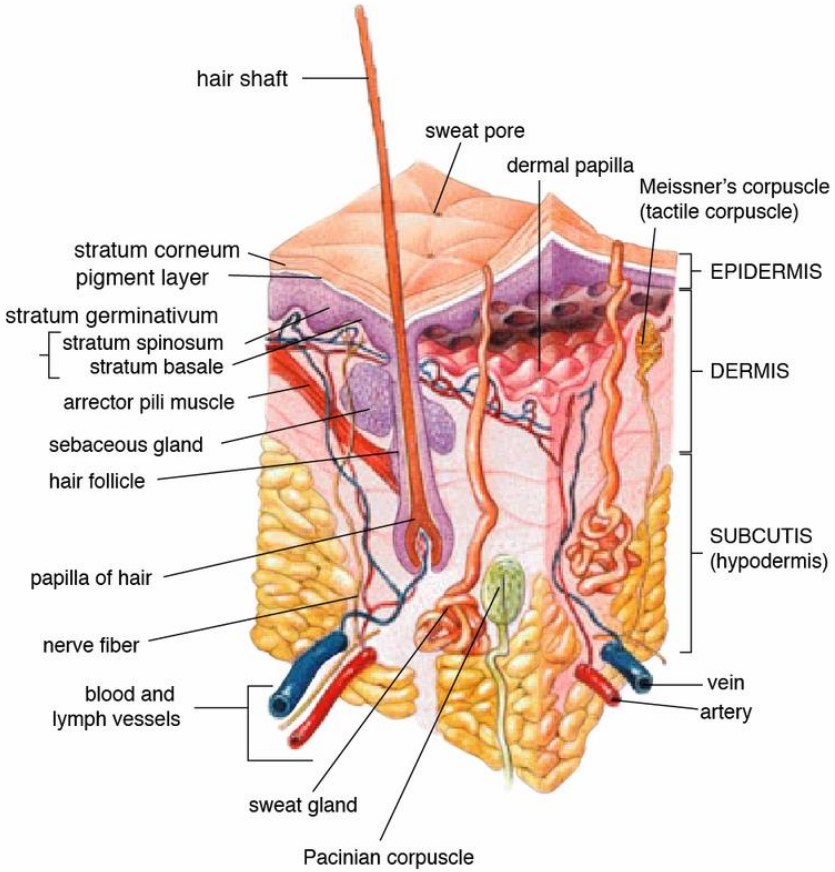
- Stratum Lucidum
  - Clear layer of dead skin cells
- Stratum Corneum
  - **Anucleated** cells
  - Filled with keratin filaments



Mikael Häggström/Wikipedia

Dermis

- Connective tissue
- Blood vessels



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Dermatopathology

- Terms used to describe **microscopic** findings
- Used in analysis of **skin biopsies**
- Hyperkeratosis
- Parakeratosis
- Hypergranulosis
- Spongiosis
- Acantholysis
- Acanthosis

Hyperkeratosis

- Thickening of **stratum corneum**
- Excess quantity of keratin

Nephron/Wikipedia

Hyperkeratosis

Psoriasis

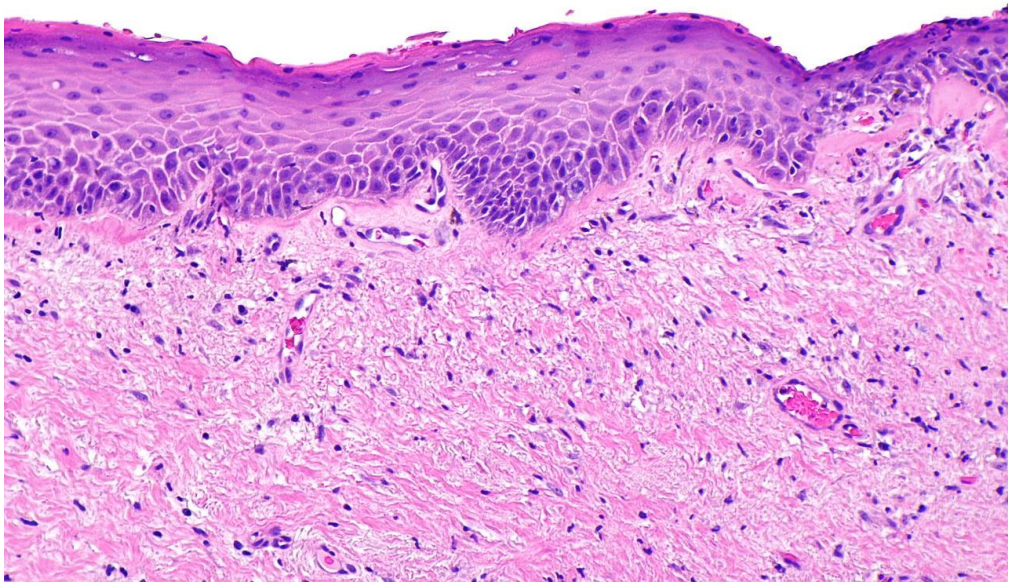
Eisfelder/Wikipedia

Callus

Public Domain

Parakeratosis

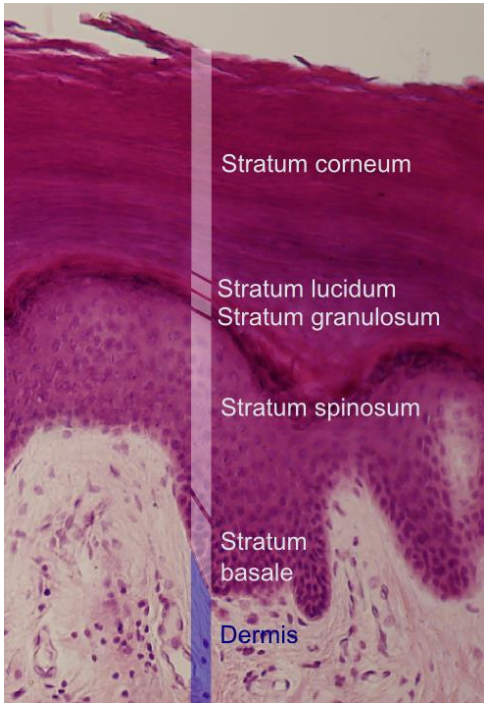
- Hyperkeratosis + **retained nuclei** in stratum corneum
- Indicates hyperproliferation
- Seen in skin diseases (psoriasis) and malignancies



Nephron/Wikipedia

Hypergranulosis

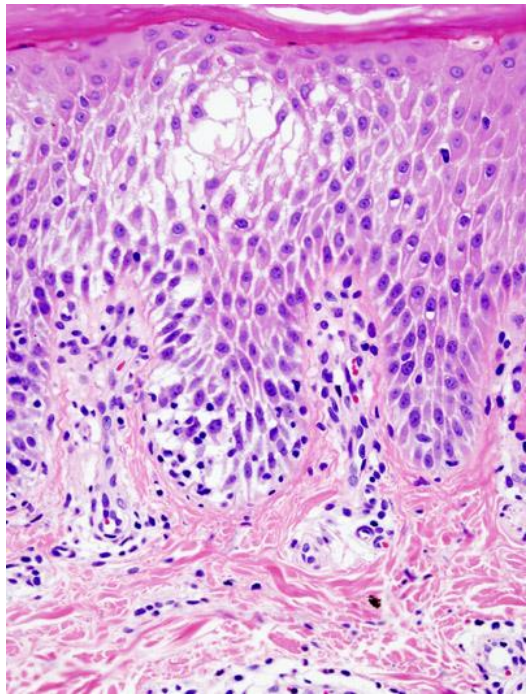
- Increased thickness of **stratum granulosum**
- Classic finding in **lichen planus**



Mikael Häggström/Wikipedia

Spongiosis

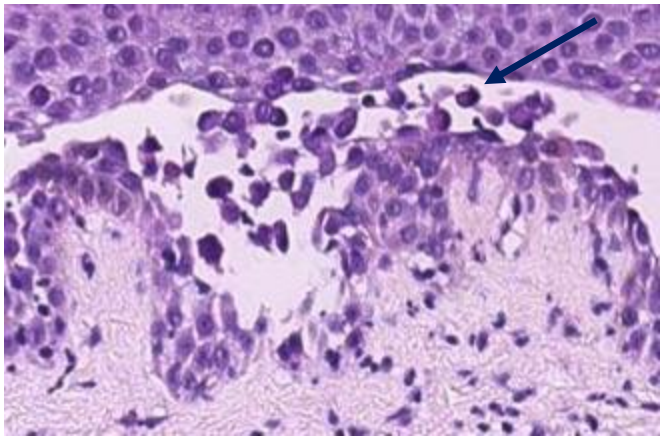
- Fluid accumulation (edema) of epidermis
- Seen in eczema, many other skin disorders



KGH/Wikipedia

Acantholysis

- **Loss of connections** between keratinocyte
- Often loss of desmosomes
- “Rounded” keratinocytes
- Detached, floating freely in epidermis
- Key feature of **pemphigus vulgaris**



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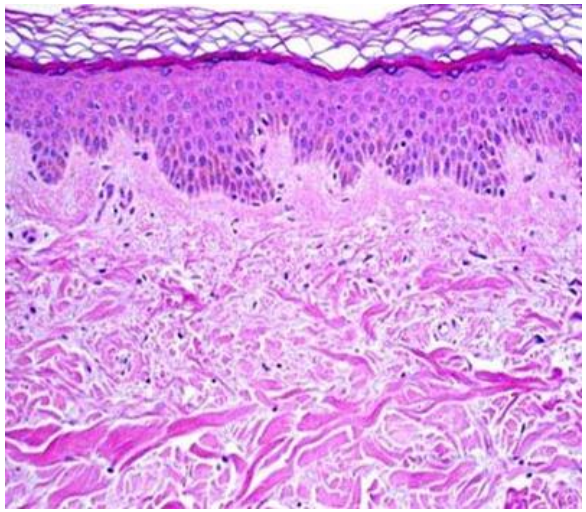
Acanthosis

- Diffuse epidermal hyperplasia
- Elongated rete ridges
- **Spinous layer** thickening

Normal



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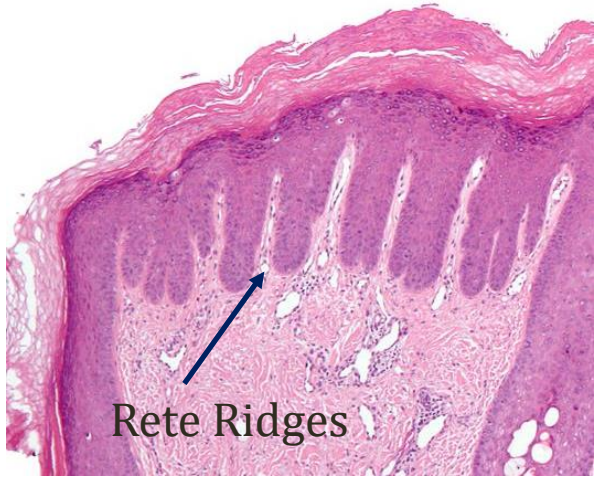
Acanthosis



Nephron/Wikipedia

Acanthosis Nigricans

- Nigricans = darkened
- Hyperpigmented (dark) plaques on skin
- Intertriginous sites (folds)
- Classically neck and axillae
- Associated with insulin resistance
  - Often seen obesity, diabetes
- Rarely associated with malignancy
  - Gastric adenocarcinoma most common

Madhero88/Dermnet.com

Skin Lesions

- **Primary lesions**
  - Directly caused by disease process
  - Described using standard terminology
  - Macules, papules, vesicles, bulla
- **Secondary lesions**
  - Modification of primary lesion
  - Or caused by trauma, external factors
  - Scale, crust, erosion, fissure, ulcer

Macules and Patches

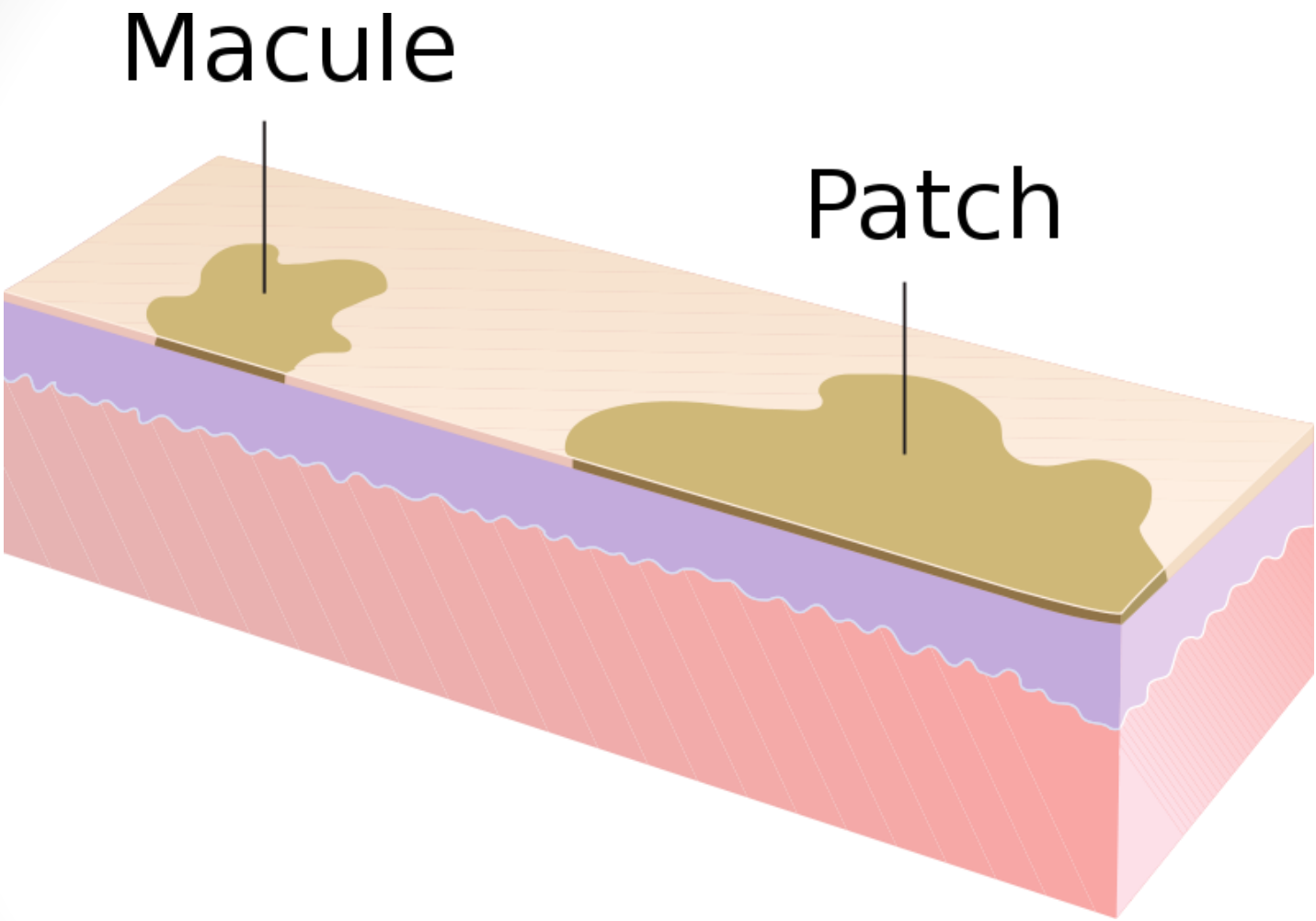
- Flat lesions (not raised)
- Macule: <1cm
- Patch: >1cm

Freckle
(macule)

Loyna/Wikipedia

Stork Bite Birthmark
(Patch)

Abigail Batchelder/Flikr

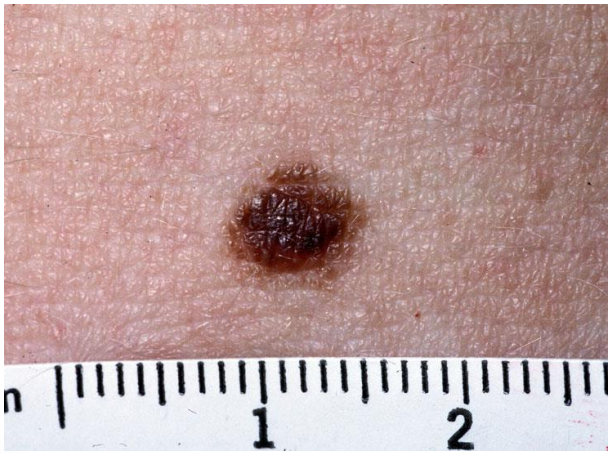


Madhero88/Wikipedia

Papules and Plaques

- Raised lesions
- Papule: <1cm
- Plaque: >1cm

Mole/nevus
(papule)



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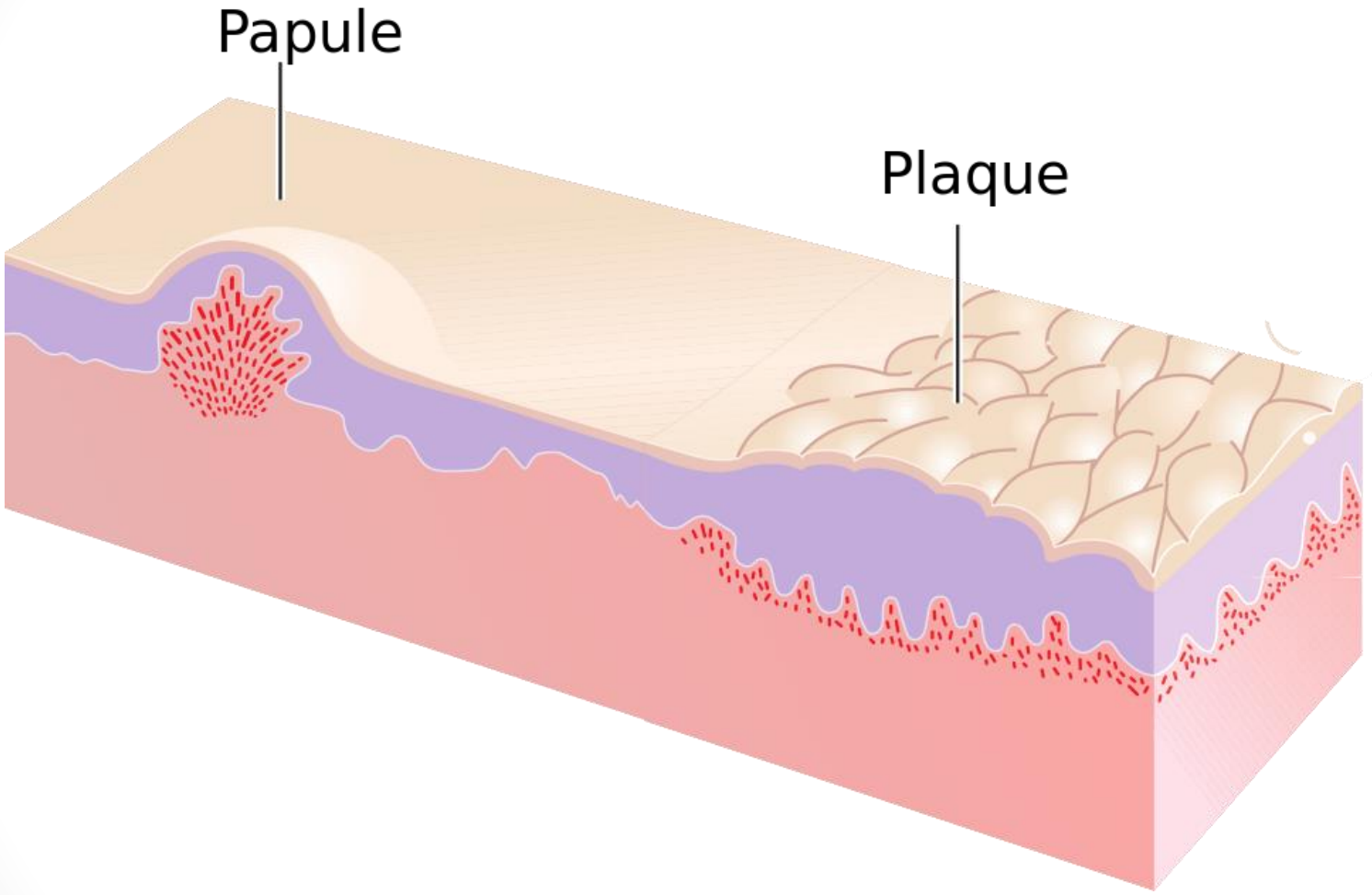
Psoriasis
(plaque)

James Heilman, MD/Wikipedia



Madhero88/Wikipedia

Maculopapular Rash

- Collection of small skin lesions
- Some flat (macules)
- Some raised (papules)
- “Morbilliform” – looks like measles
- Common in many disorders
  - Drug rash
  - Scarlet fever
  - Syphilis
  - Rubella

Public Domain

Vesicles and Bulla

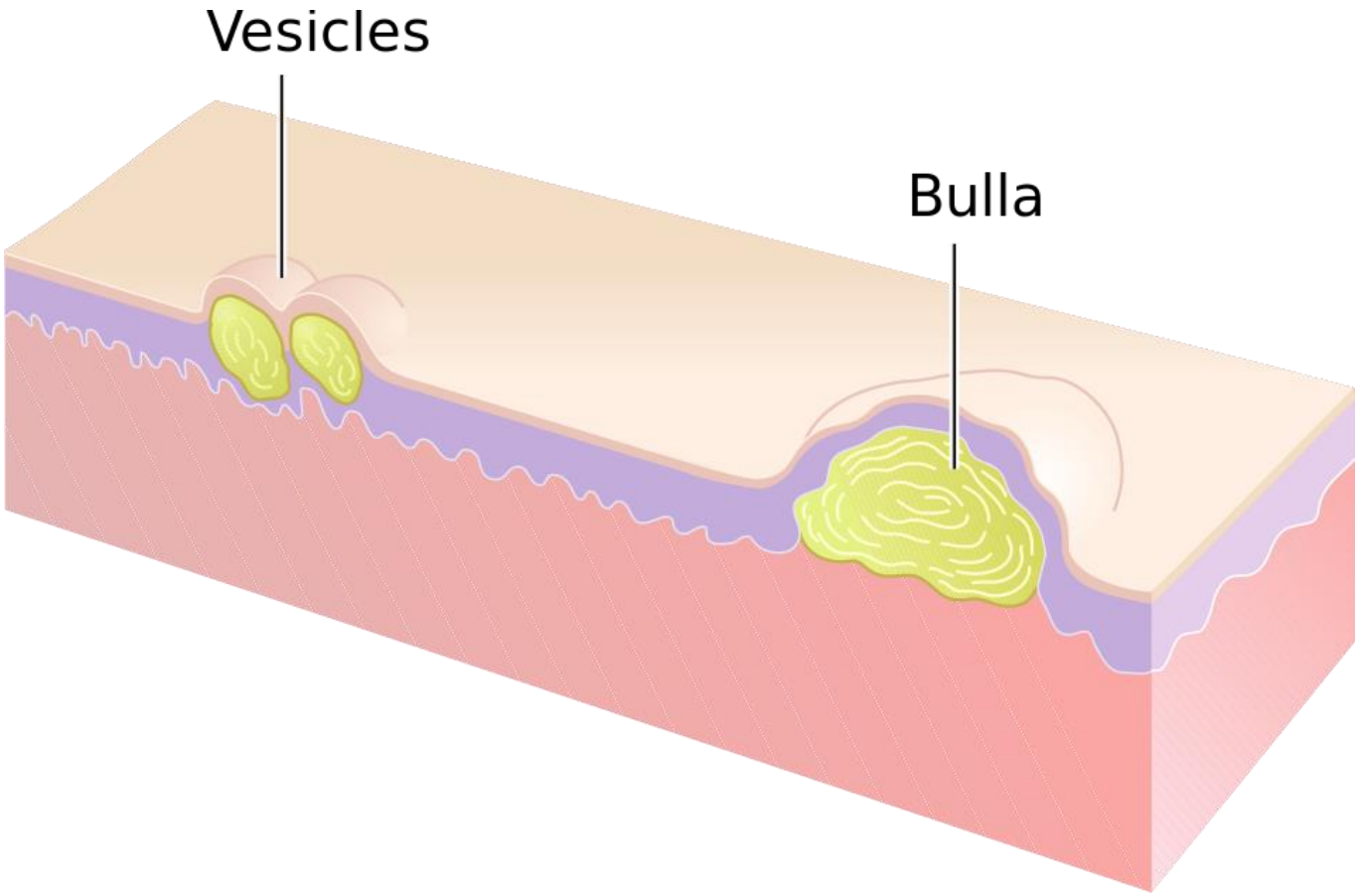
- Fluid-filled lesions (blisters)
- Vesicle: <1cm
- Bulla (plural = bullae): >1cm

Chickenpox
(vesicles)

Mariegriffiths/Wikipedia

Bullous pemphigoid
(bulla)

S. Murthy/Slideshare



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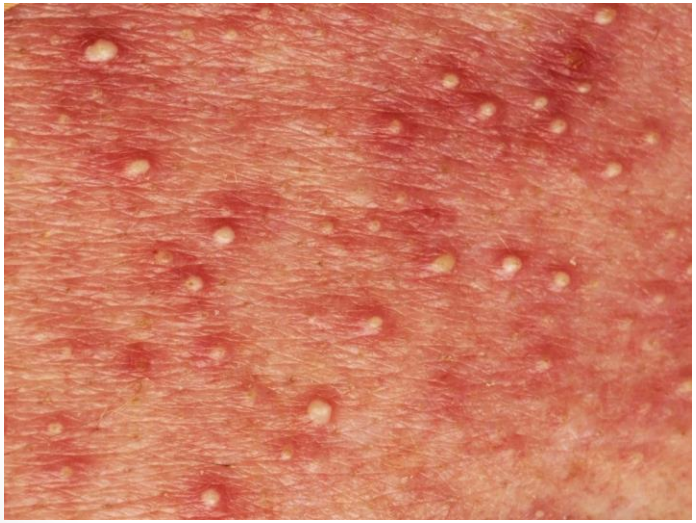
Pustule

- Pus-filled vesicle
- White center

Pustular psoriasis



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Acne

Wikipedia/Public Domain

Wheal

- Smooth, elevated papule or plaque
- Surrounded by erythema (redness)
- ***Itchy***
- Caused by **dermal** edema
- Component of urticaria (allergic reaction)

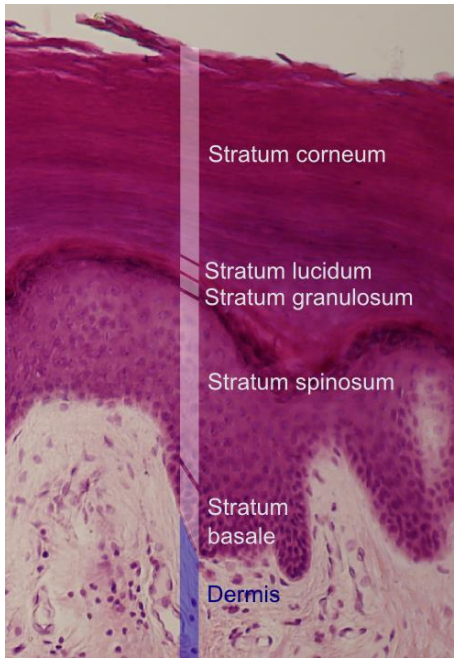
Public Domain

Scale

- Secondary lesion
- Peeling/flaking of **stratum corneum**

Psoriasis

Eisfelder/Wikipedia



Mikael Häggström/Wikipedia

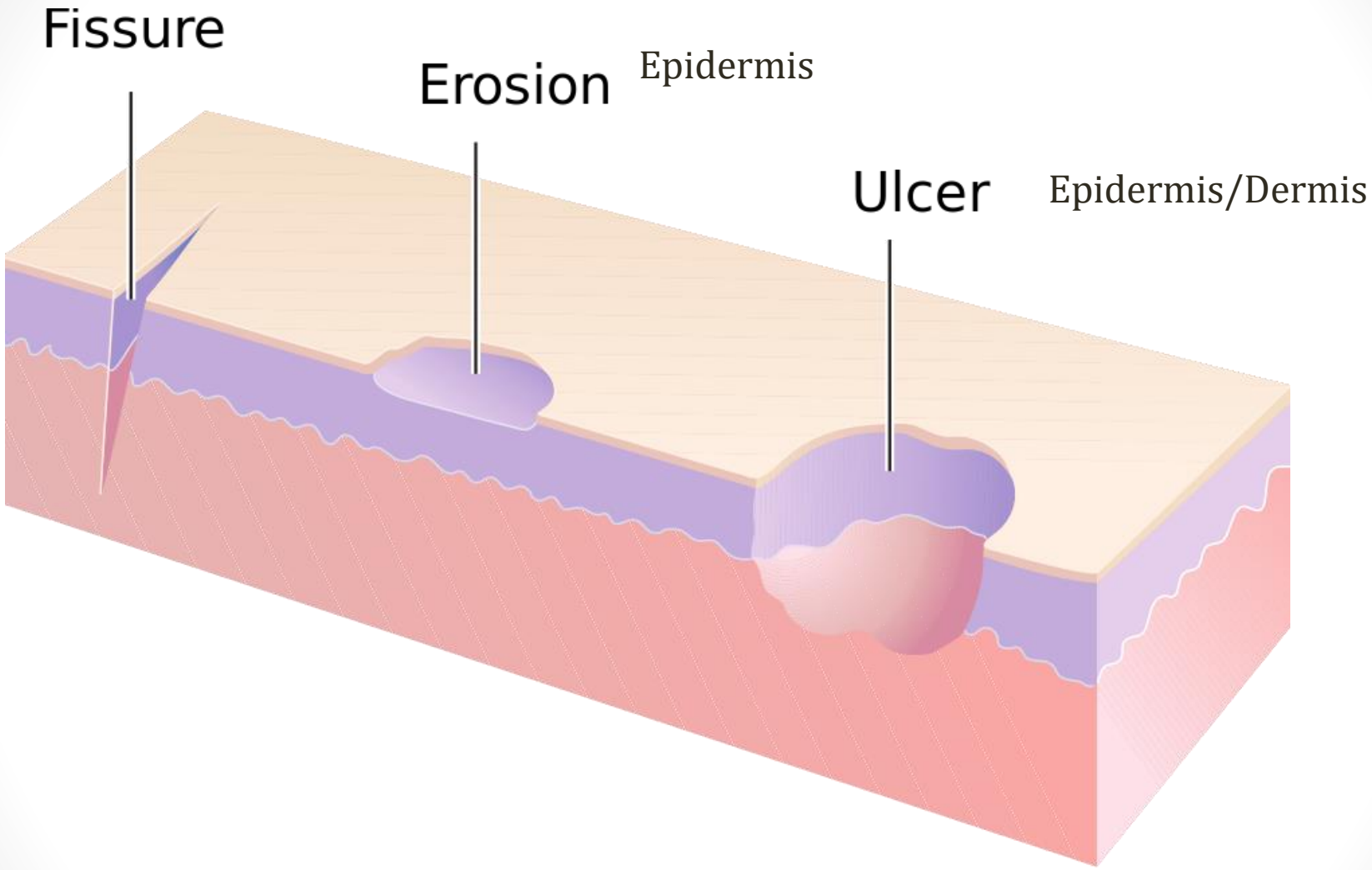
Crust

- Secondary lesion
- **Dried exudate** of skin lesion

Impetigo

CNX OpenStax/Wikipedia

Narrow tear with walls
Epidermis or dermis



Madhero88/Wikipedia

Epithelial Cells

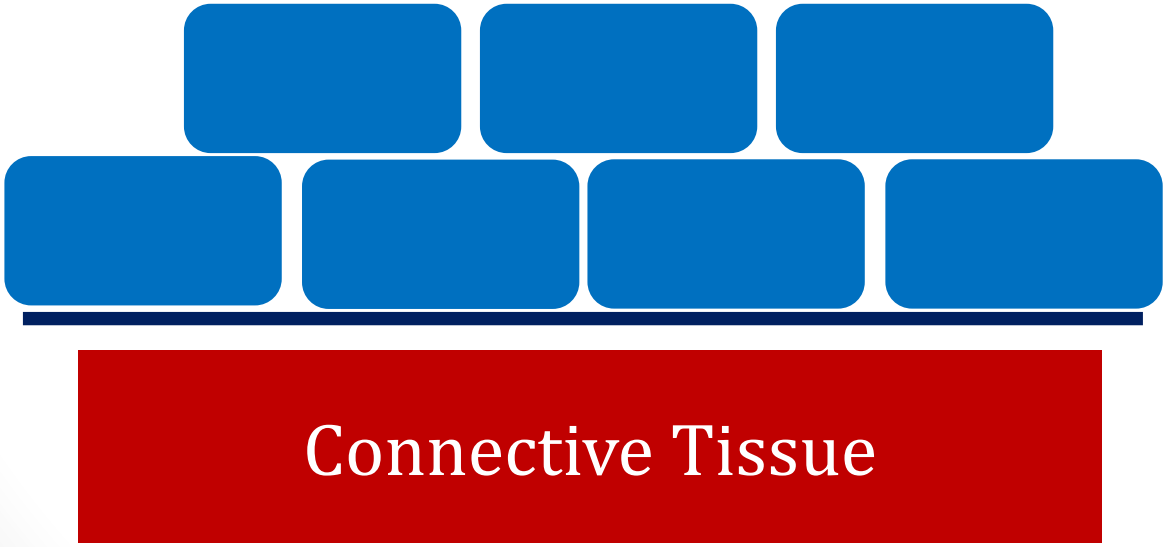
Jason Ryan, MD, MPH

Epithelial Cells

- Form the epithelium
- Line cavities/surfaces of body
- Skin, lung, GI tract
- Secrete substances (endocrine/exocrine glands)
- One of four types of animal tissue:
  - Muscle
  - Nerve
  - Connective

Basement Membrane

- Fibrous, extracellular matrix of proteins
- Anchors epithelial cells to connective tissue

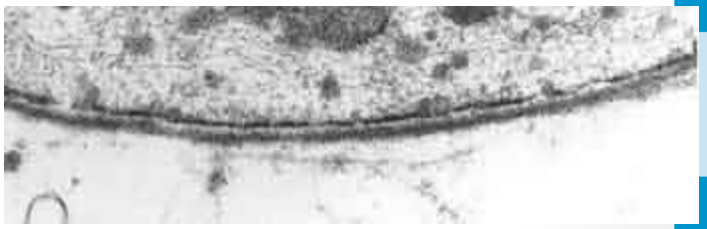


Basement Membrane

Basement Membrane

- Two layers
- Basal lamina
  - Extracellular matrix secreted by epithelial cells
  - Contains **laminin** proteins
  - **Type IV collagen** (Goodpasture's/Alport syndrome)
- Reticular lamina (reticular connective tissue)
  - Reticular = like a net
  - Anchors basal lamina to connective tissue

Basal Lamina



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Cell Polarity

- Sheets of epithelial cells bind together
- Different functions for each side of cell (“polarized”)

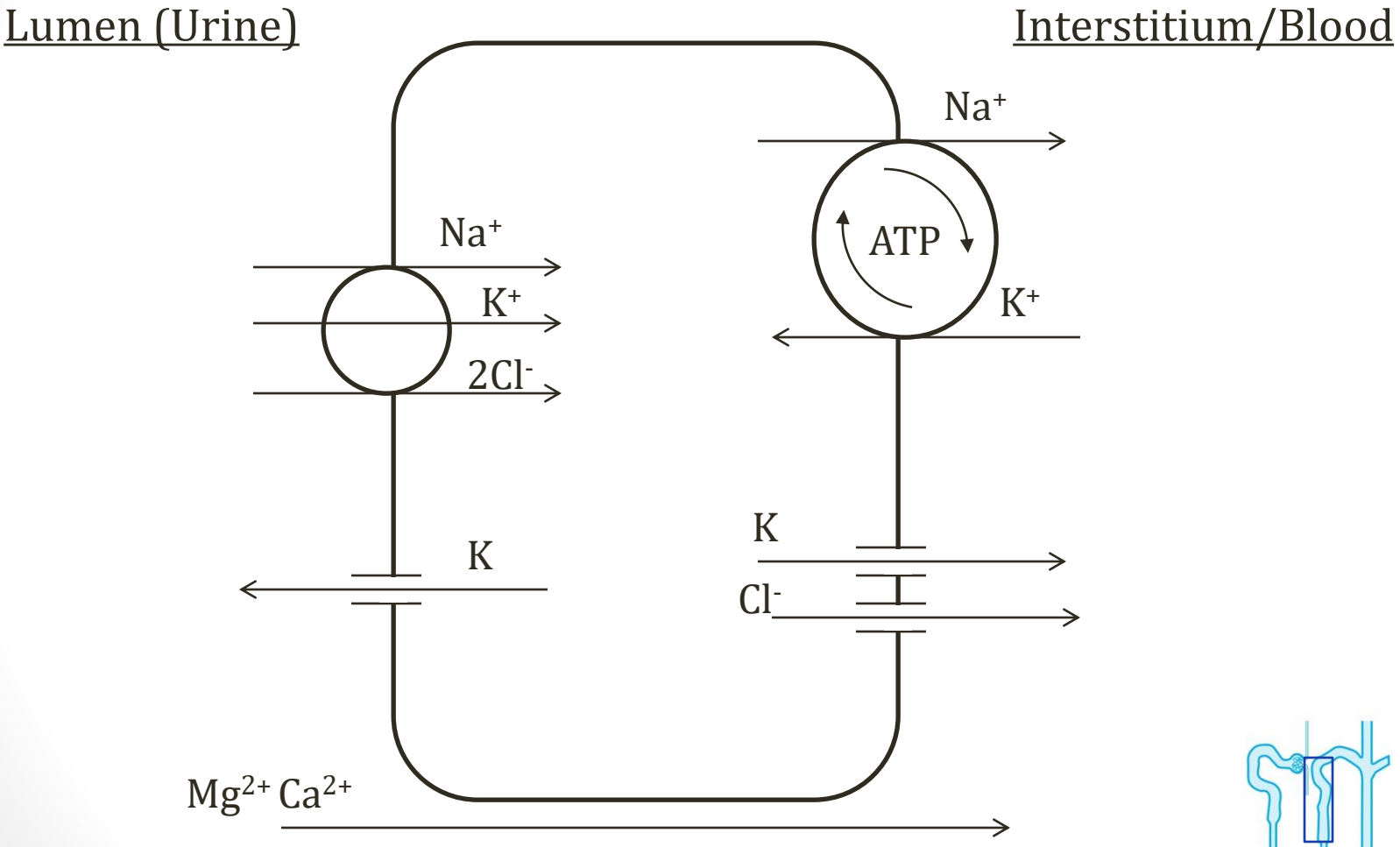
Basement Membrane

Cell Polarity

- Side facing cavity/lumen: **apical** membrane
  - Lumen of blood vessel
  - Lumen of GI tract
  - Lumen of nephron
  - Outside of body
- Side away from cavity/lumen: **basolateral** membrane

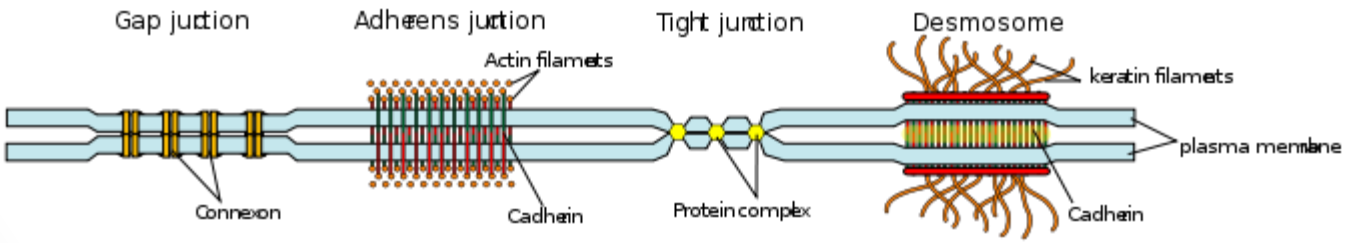
Basement Membrane

Tubular Epithelial Cells



Epithelial Cell Junctions

- Join plasma membranes of adjacent cells
- Four types:
  - Tight junctions
  - Adherens junctions
  - Gap junctions
  - Desmosomes



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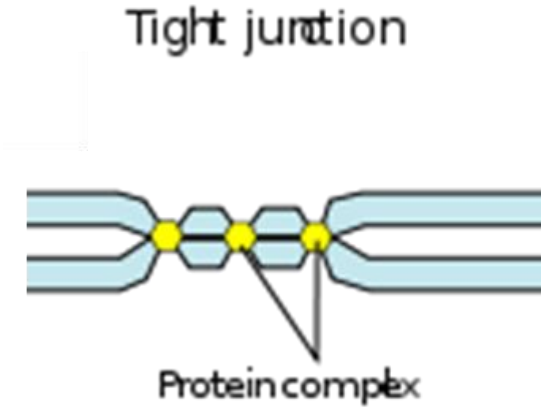
Tight Junctions

Occluding Junctions or Zonula Occludens

- ***Seals*** two cell membranes together
- **Barrier** to paracellular movement between cells
- Found near apical membrane
  - Most apical adhesion between cells
- Built from key proteins:
  - Occludin
  - Claudin



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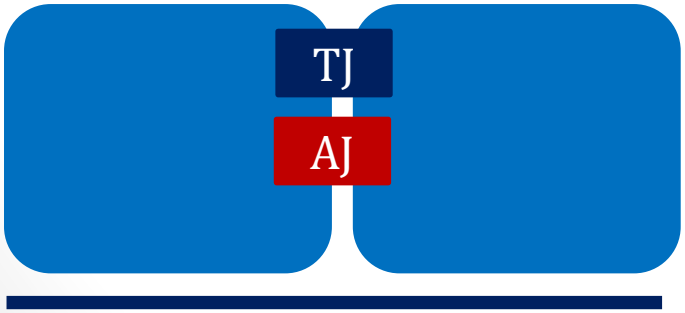
Basement Membrane

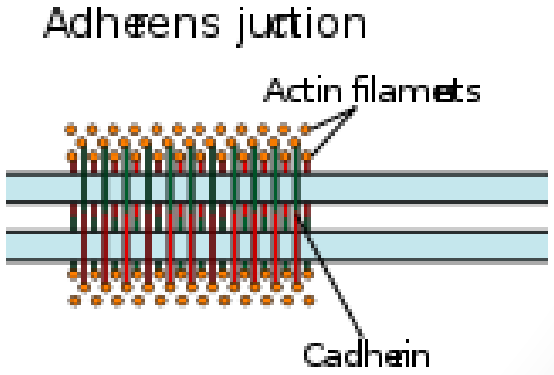
Adherens Junctions

Belt Desmosomes or Zonula Adherens

- Found below tight junctions
- Anchors cells to one another
- Forms belt around cells
- **Cadherin**
  - Cell membrane glycoprotein
  - Attach to *actin* filaments in cells



Basement Membrane



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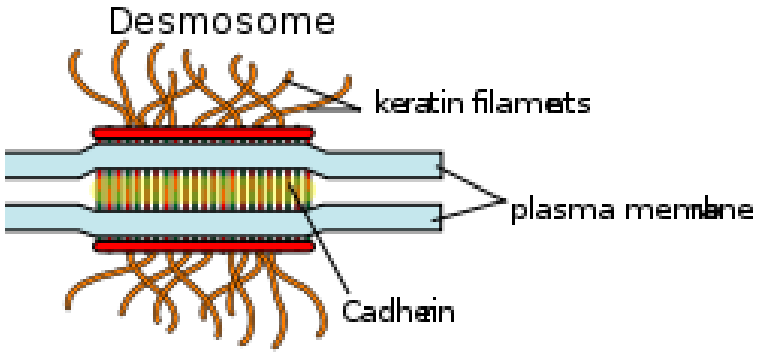
Cadherin

- Calcium-dependent adhesion (CAD) proteins
- Glycoproteins
- Many subtypes
- **E-cadherin:** lost in some forms of breast cancer

Desmosomes

Spot Desmosome or Macula Adherens

- Macula = Latin for spot
- "Spots" of cell-cell attachment (not belts)
- Common in the **skin**
- Attached to **intermediate filaments**
  - Made of **keratin**
  - Found in cell cytoplasm
- Linked by cadherins



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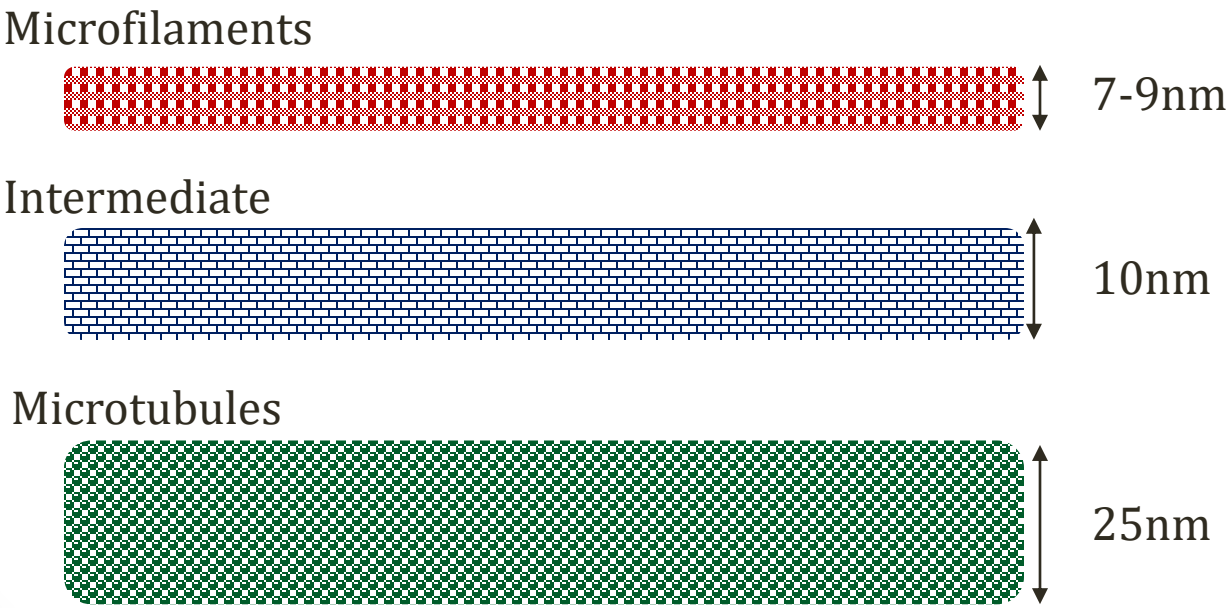
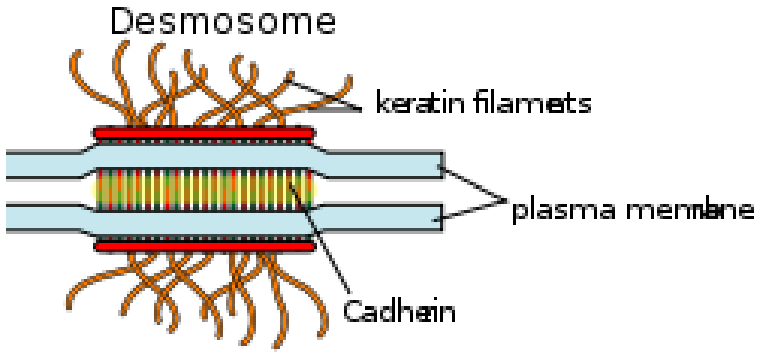
Keratins

- Tough, fibrous structural proteins
- Found in hair, skin
- Also horns, claws, hooves
- Keratin monomers assemble intermediate filaments



Hemidesmosomes

- Similar to desmosomes
- Contain intermediate filaments of keratin
- Linked by **integrins**
- Attach epithelial cells to basement membrane
  - Laminin (basal lamina), collagen



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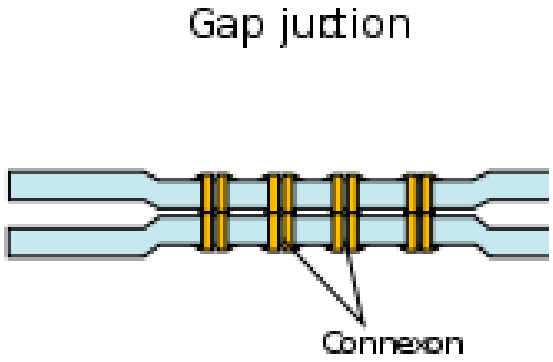
Gap Junctions

- Channel connections
- **Connexins**: protein molecules
- Form structure called connexon
- Allow small molecules to pass
- Too small for proteins, nucleic acids



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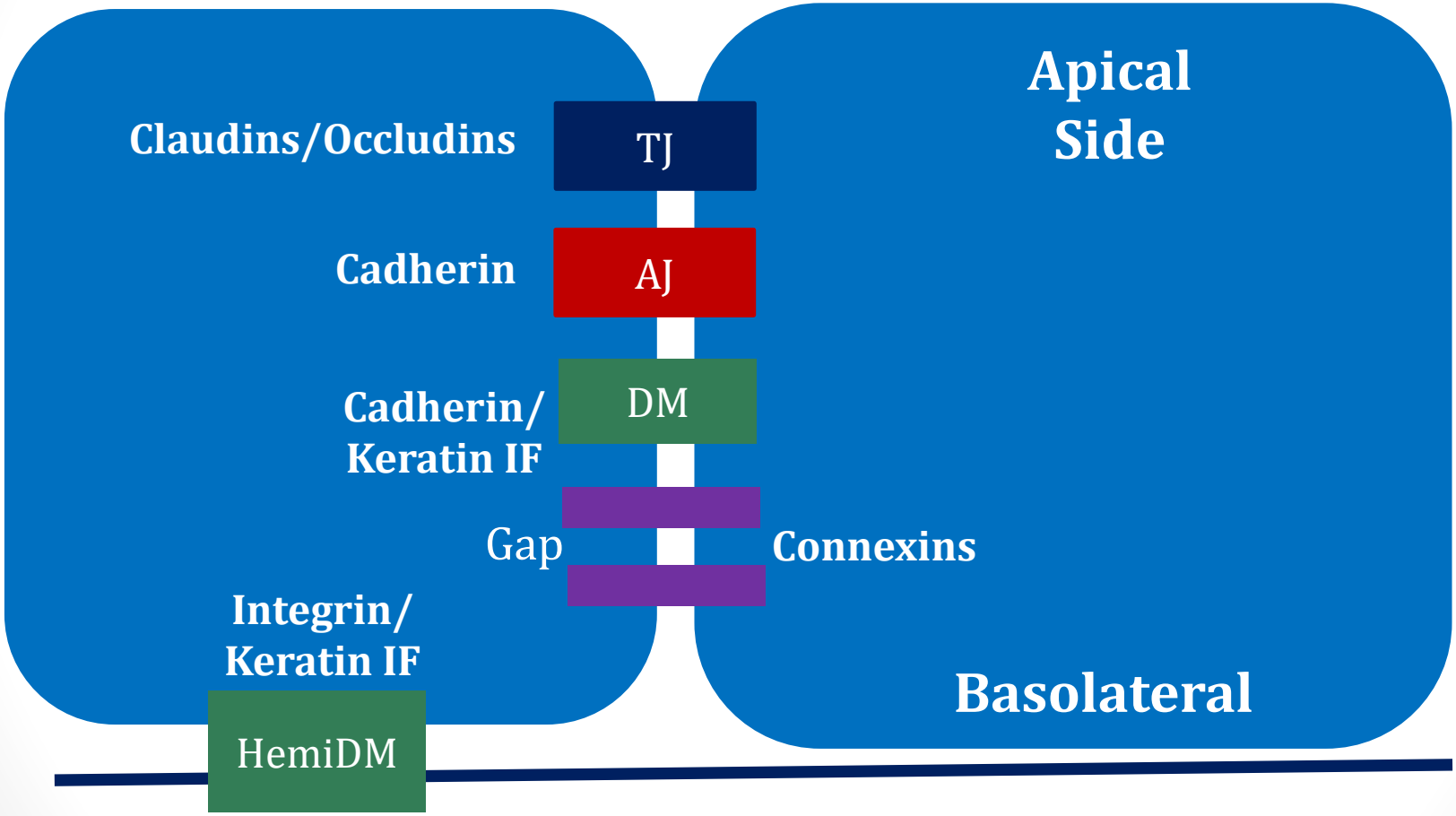
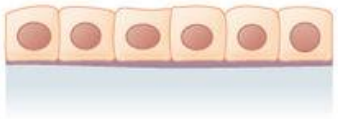
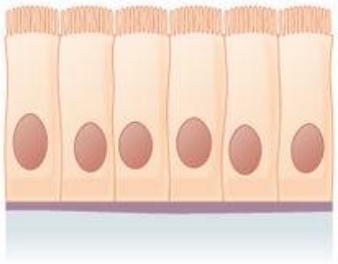
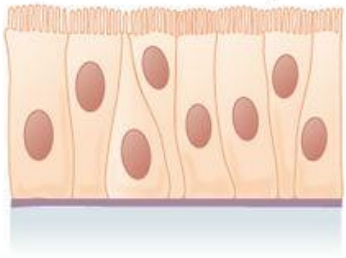
Epithelial Junctions

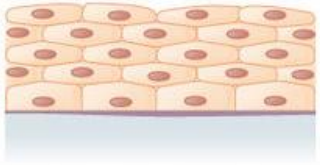
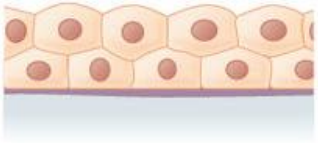
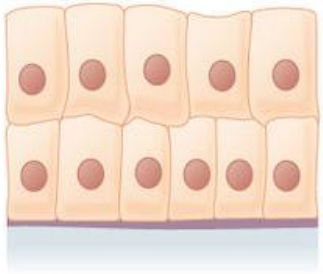
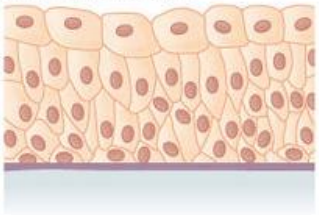


Epithelial Cell Types

Cells	Location	Function
Simple squamous epithelium 	Air sacs of lungs and the lining of the heart, blood vessels, and lymphatic vessels	Allows materials to pass through by diffusion and filtration, and secretes lubricating substance
Simple cuboidal epithelium 	In ducts and secretory portions of small glands and in kidney tubules	Secretes and absorbs
Simple columnar epithelium 	Ciliated tissues are in bronchi, uterine tubes, and uterus; smooth (nonciliated tissues) are in the digestive tract, bladder	Absorbs; it also secretes mucous and enzymes
Pseudostratified columnar epithelium 	Ciliated tissue lines the trachea and much of the upper respiratory tract	Secretes mucus; ciliated tissue moves mucus

OpenStax College/Wikipedia

Epithelial Cell Types

Cells	Location	Function
Stratified squamous epithelium 	Lines the esophagus, mouth, and vagina	Protects against abrasion
Stratified cuboidal epithelium 	Sweat glands, salivary glands, and the mammary glands	Protective tissue
Stratified columnar epithelium 	The male urethra and the ducts of some glands	Secretes and protects
Transitional epithelium 	Lines the bladder, uretha, and the ureters	Allows the urinary organs to expand and stretch

Skin Disorders

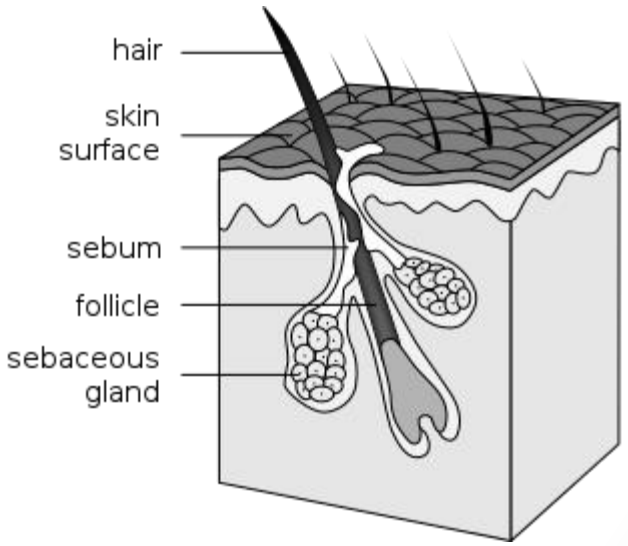
- Pemphigus vulgaris
  - Autoantibodies to desmosomes
- Bullous pemphigoid
  - Autoantibodies to hemidesmosomes

Skin Disorders I

Jason Ryan, MD, MPH

Acne

- Inflammation of **hair follicles and sebaceous glands**
  - Exocrine glands in skin in dermis
  - Secrete oily substance called sebum
  - Often contain hair follicles ("Pilosebaceous unit")
- Complex, multifactorial etiology



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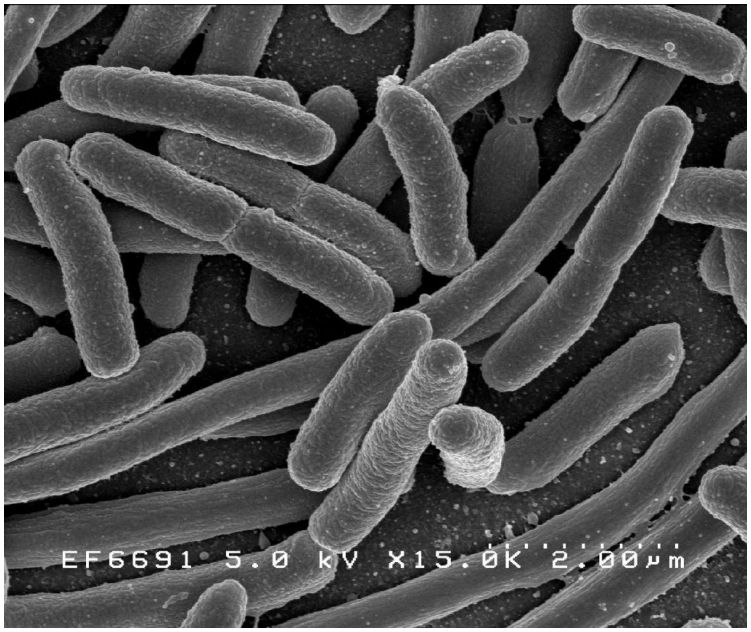
Acne

- Sebaceous glands enlarge at **puberty**
  - **↑ androgens** → ↑ sebum
  - Adolescent acne: men > women
  - Men with androgen insensitivity: no acne
  - Women with excess androgens (PCOS): acne
- Increased **sebum and keratin**
  - Keratinocytes line hair shafts → keratin
  - Blocks ducts
  - Bacterial growth behind blockage

Acne

- Sebum: growth medium for bacteria
- ***Propionibacterium acnes***
  - *Cutibacterium acnes*
- Anaerobic bacterium
- Normal skin flora



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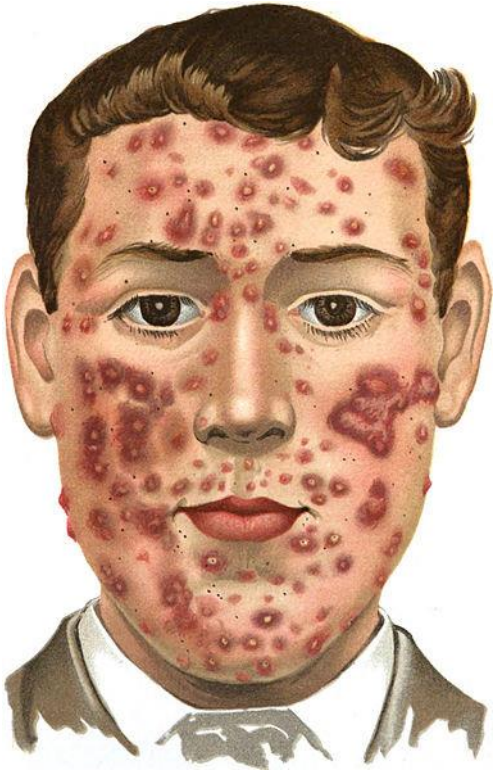
Acne

- **Comedones** allow bacterial growth
  - Comedo: debris blocking sebaceous duct (bumps on face)
  - Comedone: plural of comedo
  - Microcomedo: microscopic comedo (not visible)
  - Lipid-rich environment for bacterial growth
  - Bacteria use triglycerides in sebum as fuel
- Inflammation from bacterial proliferation

Acne

- Affects most hormone-responsive glands
  - **Face**, neck, chest, upper back



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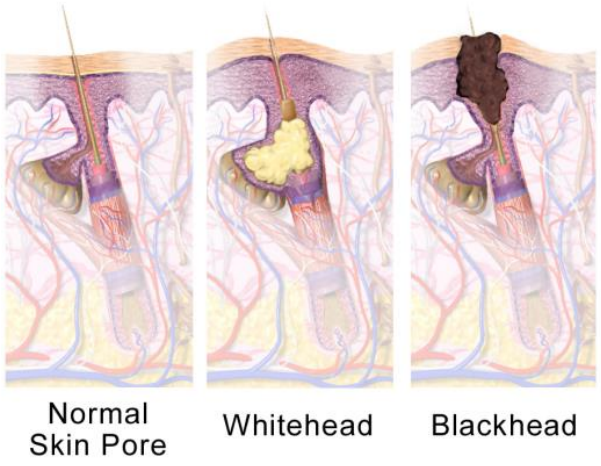
Acne

- Multiple lesion types
  - Open comedos: blackheads
  - Closed comedos (by skin): whiteheads
  - Inflammatory lesions (papules/pustules)
- Scarring and hyperpigmentation may occur

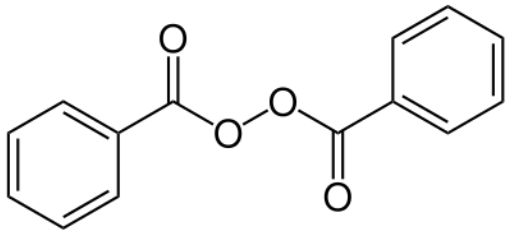


BruceBlaus/Wikipedia

Acne

Treatment

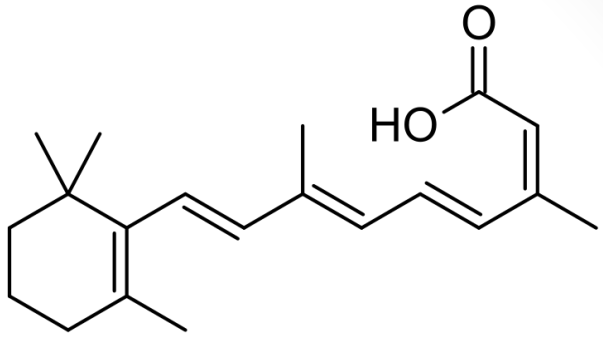
- Benzoyl peroxide (topical)
  - Breakdown keratin, unblocks pores (comedolytic)
  - Bactericidal to *P. acnes*
- Antibiotics
  - Decrease *P. acnes* colonization of skin
  - Clindamycin and erythromycin
- Retinoids (vitamin A derivatives)



Benzoyl Peroxide

Isotretinoin

Accutane

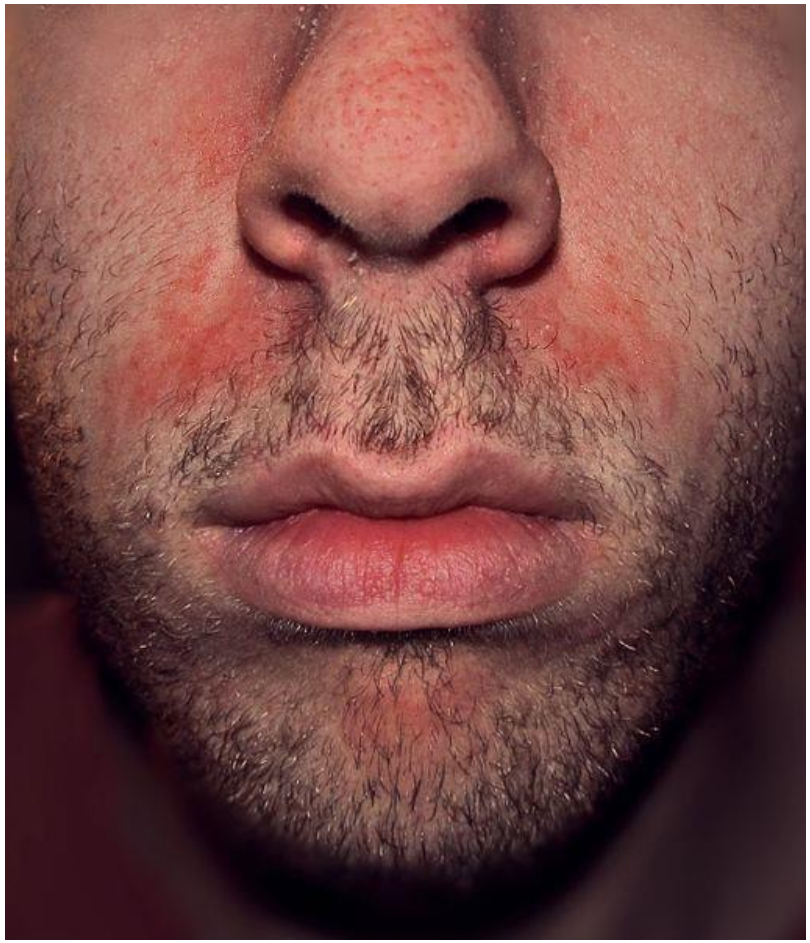


- 13-*cis*-retinoic acid
- Metabolites bind to nuclear receptors
  - Retinoic acid receptors (RAR)
  - Retinoid X receptors (RXR)
- **Decreases keratin production** in follicles
- Less follicular occlusion
- Highly ***teratogenic***
- OCP and/or pregnancy test prior to Rx

Seborrheic dermatitis

- Red plaques with scale (flaky skin)
- Occurs on **face and scalp**
  - Areas with lots of sebaceous glands
- Poorly understood pathogenesis
  - No inflammation of sebaceous glands
  - Associated with fungal infection by Malassezia
- Treatment: topical antifungals and corticosteroids

Seborrheic dermatitis

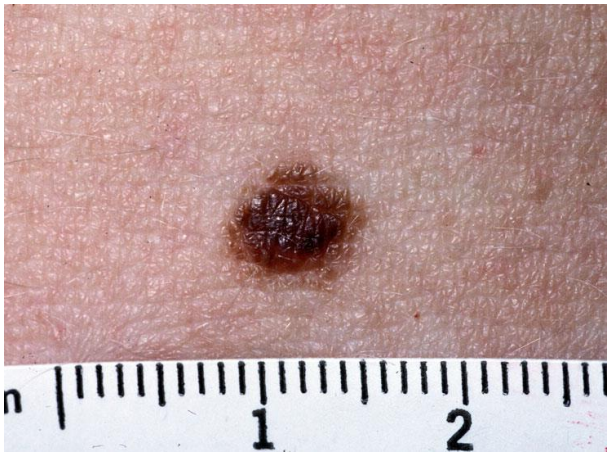


Roymishali/Wikipedia

Melanocytic Nevus

Moles

- Benign neoplasm of melanocytes
- Tan/brown pigmented lesions
- **Uniform color**
- Often round or oval shape
- Usually <6mm



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Melanocytic Nevus

Moles

- Congenital
  - Present at birth
  - Often have hairs growing from lesion
- Acquired
  - Appear in childhood
  - Increase in number during adolescence
  - Peak count in 30s
  - Regress with age

Melanocytic Nevus

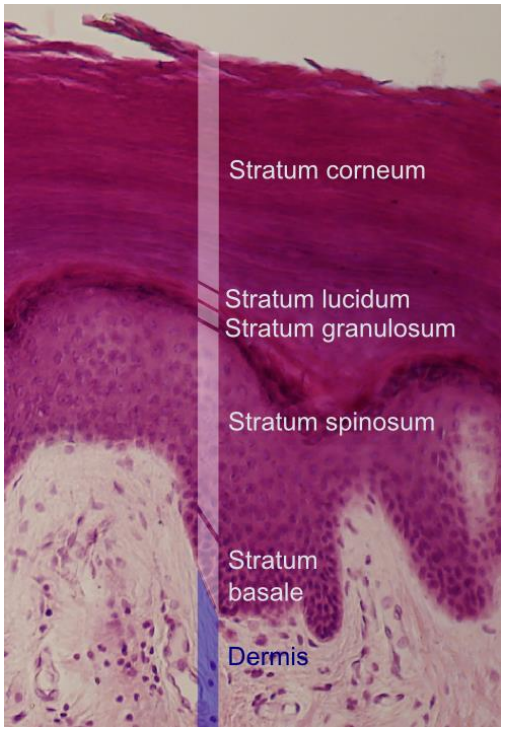
Moles

- Rarely develop dysplasia → melanoma
  - Atypical features may warrant biopsy/removal
  - Not removed prophylactically for prevention

Wikipedia/Public Domain

Acquired Nevi

- Junctional nevi
  - Growth along dermal-epidermal junction
  - Often found in children
- Compound nevi
  - Growth extends into dermis
- Intradermal nevi
  - Loss of junctional lesion
  - Found only in dermis
  - Common in adults



Mikael Häggström/Wikipedia

Pseudofolliculitis barbae

Razor bumps, shave bumps

- Inflammation from trapped hairs
- Associated with shaving
- Entrapment of recently cut, very short hairs
- Firm papules/pustules in area of beard growth
- Common in black men (up to 80%)
- 3% white men

Wikipedia/Public Domain

Psoriasis

- Chronic inflammatory skin disorder
- Well-demarcated **plaques**
- Pink or salmon colored
- Silver-white scale
- Most commonly on **extensor surfaces**
  - Knees
  - Elbows

Psoriasis

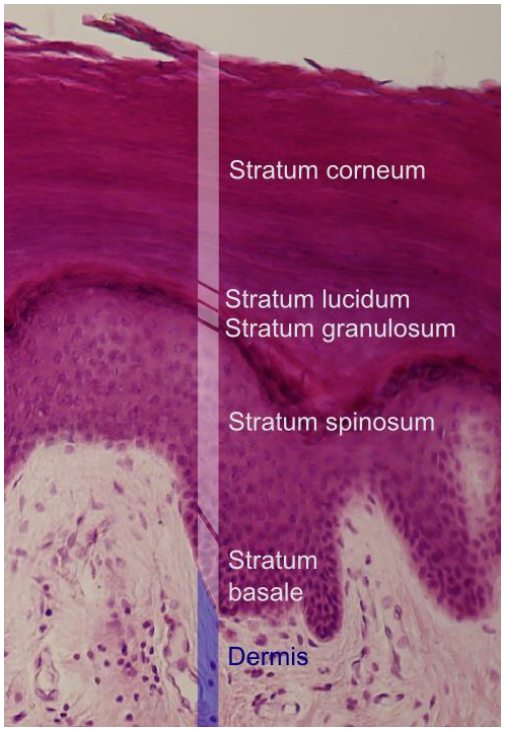
Jacopo188/Wikipedia

Psoriasis

- Pathogenesis poorly understood
- Combination of genetic and environmental factors
- Believed to be **autoimmune**
- Strong association with **HLA-C**

Psoriasis

- Acanthosis (thickening of epidermis)
- Parakeratotic scaling
  - **Retained nuclei** in stratum corneum
  - Indicates hyperproliferation
- Stratum spinosum
  - Increased in size
- Stratum granulosum
  - Thinned or absent
- Munro microabscesses
  - Neutrophils in stratum corneum



Mikael Häggström/Wikipedia

Psoriasis

Dermis blood vessels close to surface
Scale breaks → bleeding (**Auspitz sign**)

Public Domain

Psoriasis

- Most common type: **plaque psoriasis**
- Multiple other less common subtypes
  - Guttate psoriasis
  - Pustular psoriasis
  - Erythrodermic psoriasis
  - Inverse psoriasis

Psoriasis

- Commonly involves **nails**
  - **Nail pitting**
  - Onycholysis (separation of nail from nailbed)
- About 1/3 of patients develop **psoriatic arthritis**
  - Seronegative spondyloarthritis
  - More common in patients with nail findings

Public Domain

Rosacea

- Common skin disorder (3% population)
- Affects adults > 30
- Celtics and Northern Europeans: greatest risk
- Affects light-skinned individuals

Rosacea

- **Inflammatory** skin condition
- Complex, poorly understood pathology
- Chronic redness of **nose and cheeks**
- Papules and pustules
  - May look similar to acne but no comedones

M. Sand et al./Wikipedia

RicHard-59/Wikipedia

Rosacea

Other features

- **Facial flushing**
  - Often triggered by environmental stimuli
  - Cold, heat, sun, hot drinks, spicy foods, **alcohol**
- **Phymatous rosacea**
  - Skin hypertrophy
  - Thickened skin
  - Most commonly on nose (rhinophyma)

Public Domain

Seborrheic keratosis

- Common benign tumors
- Proliferation of immature keratinocytes
- Occurs in older patients (>50)
- Arise spontaneously
- Commonly on trunk

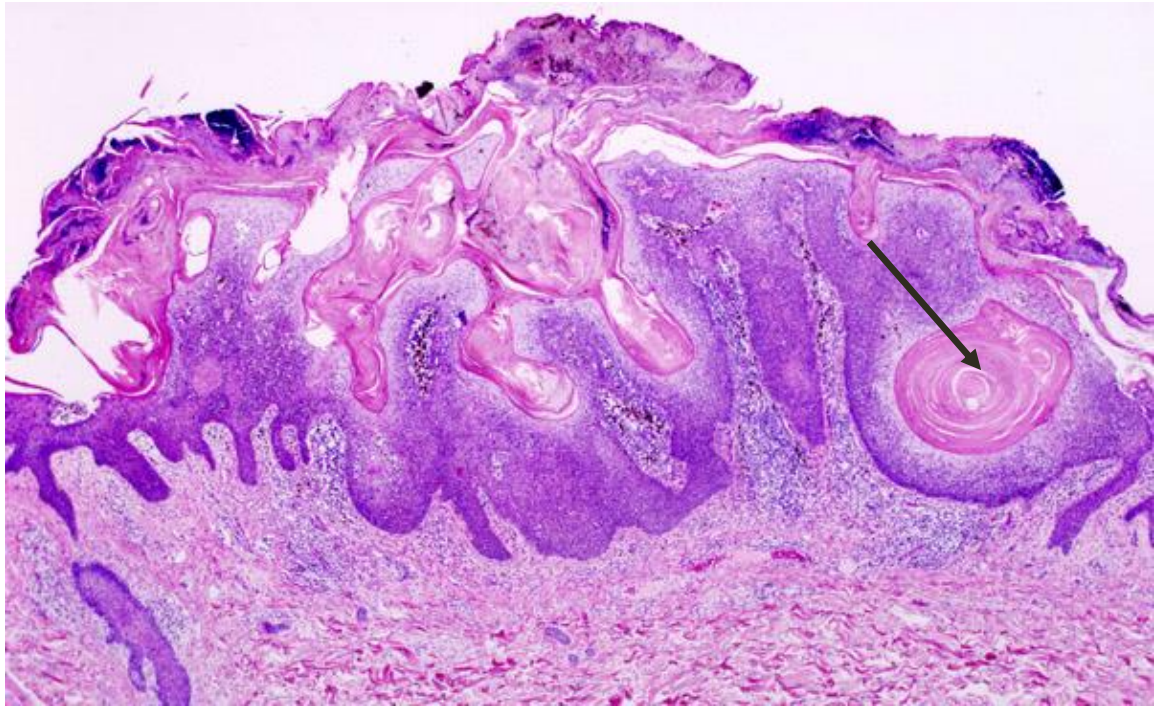
Seborrheic keratosis

- Flat
- Well-demarcated
- Round or oval
- Dark, velvety surface
- “Stuck on”

James Heilman, MD

Seborrheic keratosis

- Dark cells similar to basal skin cells
- Keratin-filled cysts ("horn cysts")



KGH/Wikipedia

Leser-Trelat Sign

- "Explosive onset" of multiple itchy SK lesions
- Probably caused by cytokines
- Associated with malignancies
  - Gastric adenocarcinoma most common

James Heilman, MD

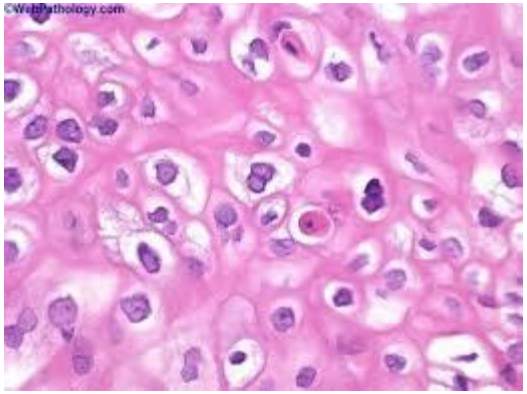
Verrucae

- Warts
- Cellular proliferation caused by HPV
- Many types
  - Verruca vulgaris (skin - most common)
  - Verruca plana (skin - flat wart)
  - Condyloma acuminatum (venereal warts)

Verruca Vulgaris

Cutaneous Warts

- Most common manifestation of HPV infection
- Transmitted by contact with virus
- Common on hands
- Epidermal hyperplasia
- Koilocytosis
  - Cytoplasmic clearing ("halos") around nucleus



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Skin Disorders II

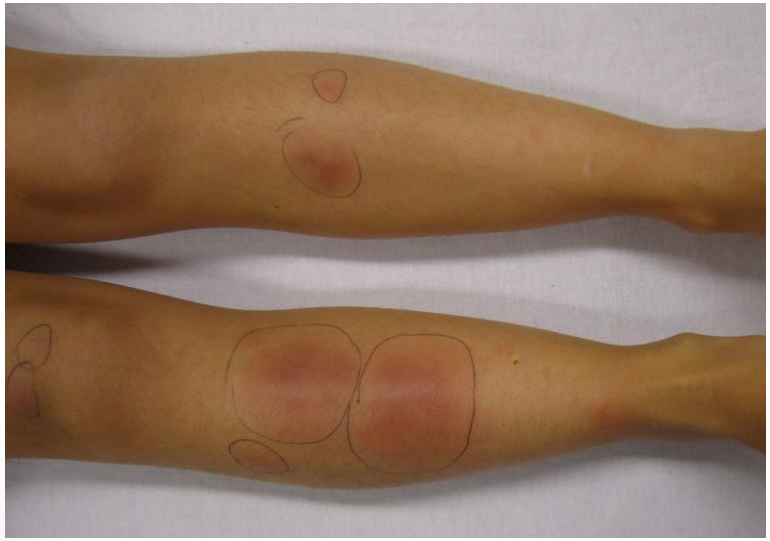
Jason Ryan, MD, MPH

Erythema Nodosum

- Type IV hypersensitivity reaction
- **Panniculitis**
  - Inflammation of subcutaneous fat
- Often idiopathic
- Many triggers:
  - Infection (most commonly Strep)
  - Crohn's disease (may precede flare)
  - Sarcoidosis
  - Coccidioidomycosis

Erythema Nodosum

- **Painful**, red nodules
- Most commonly on shins

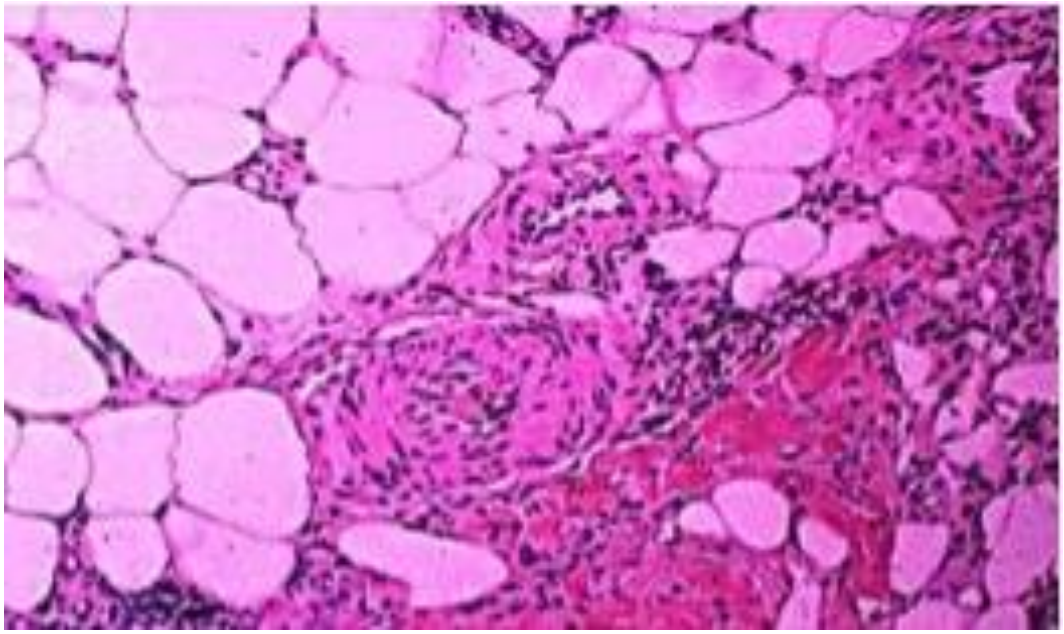


James Heilman, MD

Erythema Nodosum

Pathology Findings

- **"Septal panniculitis"**
  - Inflammation septa of fat between dermis and fascia
  - Contrast with "lobular": inflammation of fat lobules

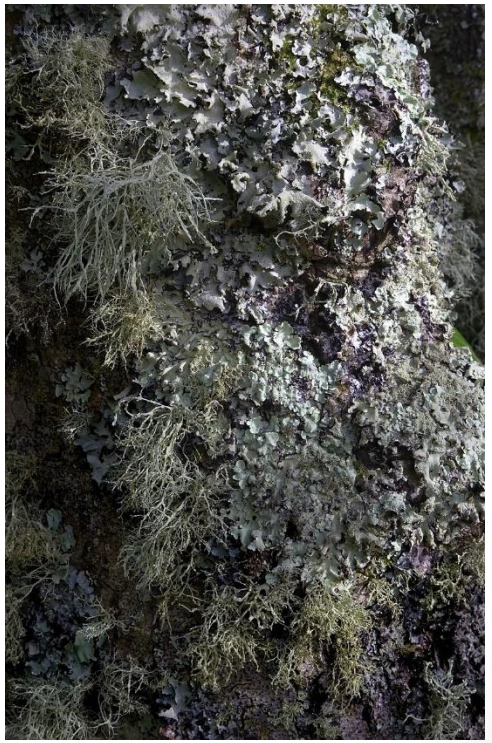


Specialclass/Sideshare

Lichen Planus

- Rare, chronic inflammatory skin disorder
- “Lichen” = tree moss
- “Planus” = flat
- Occurs in adults
- Unknown pathogenesis
- Resolves spontaneously over years
- Associated with **hepatitis C**

Lichen on tree



Lichen Planus

- **6Ps**
  - "**P**ruritic, **P**urple, **P**olygonal, **P**lanar, **P**apules and **P**laques"
- **Itchy (often intense)**
- Purple flat lesions
- Multiple, symmetric usually on arms/legs/wrists
- Wrists, ankles are common sites

James Heilman, MD

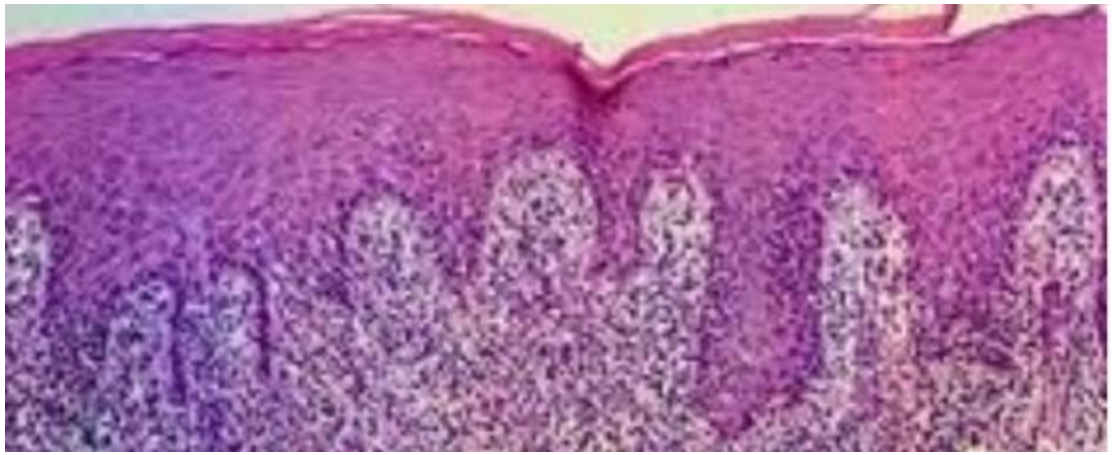
Lichen Planus

- **Mucosal** involvement
  - Mouth, tongue
  - Glans penis
- **Wickham striae**: white dots/lines
  - Caused by hypergranulosis (classic feature of LP)
  - Best seen on oral lesions

James, Candice, Mai/Wikipedia

Lichen Planus

- Lymphocytes at dermal-epidermal junction
- Hyperkeratosis
- Hypergranulosis
- **"Sawtooth" pattern** of rete ridges



G Salunkhe/Slideshare

Pityriasis Rosea

- Acute, self-limited skin rash
- Eruption of skin lesions
- Self-limited
- Resolves 2-3 months
- Usually no treatment required
- Cause unknown (possibly viral)

Pityriasis Rosea

- Begins with **"herald patch"**
  - Single red/salmon-colored lesion
  - Round or oval
  - Well demarcated
  - Chest, neck, or back
- Days later: Multiple lesions on trunk
  - Multiple similar, smaller lesions
  - Groups of lesions
  - Follow skin lines on back
  - **"Christmas tree distribution"**

James Heilman,MD /Wikipedia

Pityriasis Rosea

James Heilman,MD /Wikipedia

Burns

- 1st degree/superficial: epidermis only
  - Painful, red, blanch with pressure
  - No blisters
  - Heal within 7 days
- 2nd degree/partial thickness: epidermis, some dermis
  - Blisters
  - Painful, blanch with pressure
  - Heal within 7 to 21 days

Bejinhan/Wikipedia

Snickerdo/Wikipedia

Burns

- 2nd degree/full thickness: epidermis, most dermis
  - Yellow or white
  - Painful to pressure only
  - Do not blanch
  - Heal with scarring

Wikipedia/Public Domain

Burns

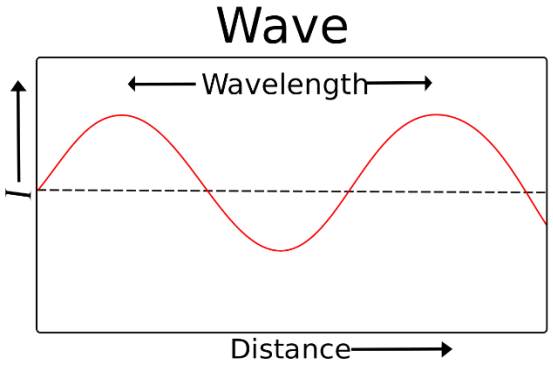
- 3rd degree: entire epidermis and dermis
- 4th degree: skin and superficial fat

Wikipedia/Public Domain

Wikipedia/Public Domain

Sunburn

- Delayed inflammatory response of skin
- Caused by ultraviolet radiation (UVR)
- Two forms UV radiation
  - UVB radiation: wavelength 280 to 320 nm
  - UVA radiation: wavelength 320 to 400 nm
- Both may cause sunburn
- **UVB range** most effective at causing sunburn



Sunburn

- Damage to epidermis and dermis
- UV radiation → DNA damage → apoptosis
- "Sunburn cells": keratinocytes undergoing apoptosis
- Vasodilation
- Release inflammatory mediators
- Self-limited

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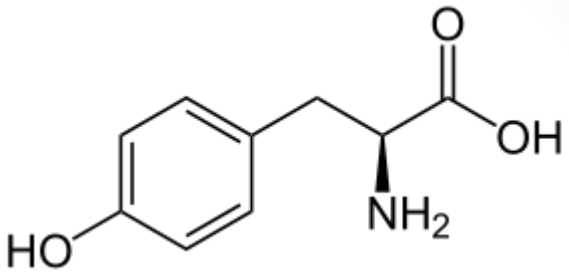
Pigment Disorders

Jason Ryan, MD, MPH

Melanin



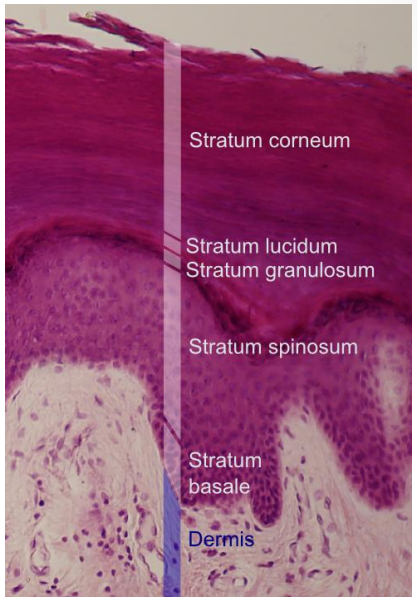
Tyrosine

- Black/brown pigment
- Gives color to skin and hair
- Protects from ultraviolet radiation
- Formed from amino acid **tyrosine**

Public Domain

Melanin

- Synthesized in **melanocytes**
  - Specialized secretory cells
  - Derived from *neural crest*
- Found in **basal layer of epidermis**
- Synthesize melanin in **melanosomes**
- Melanosomes transferred to keratinocytes



Mikael Häggström/Wikipedia

Freckles

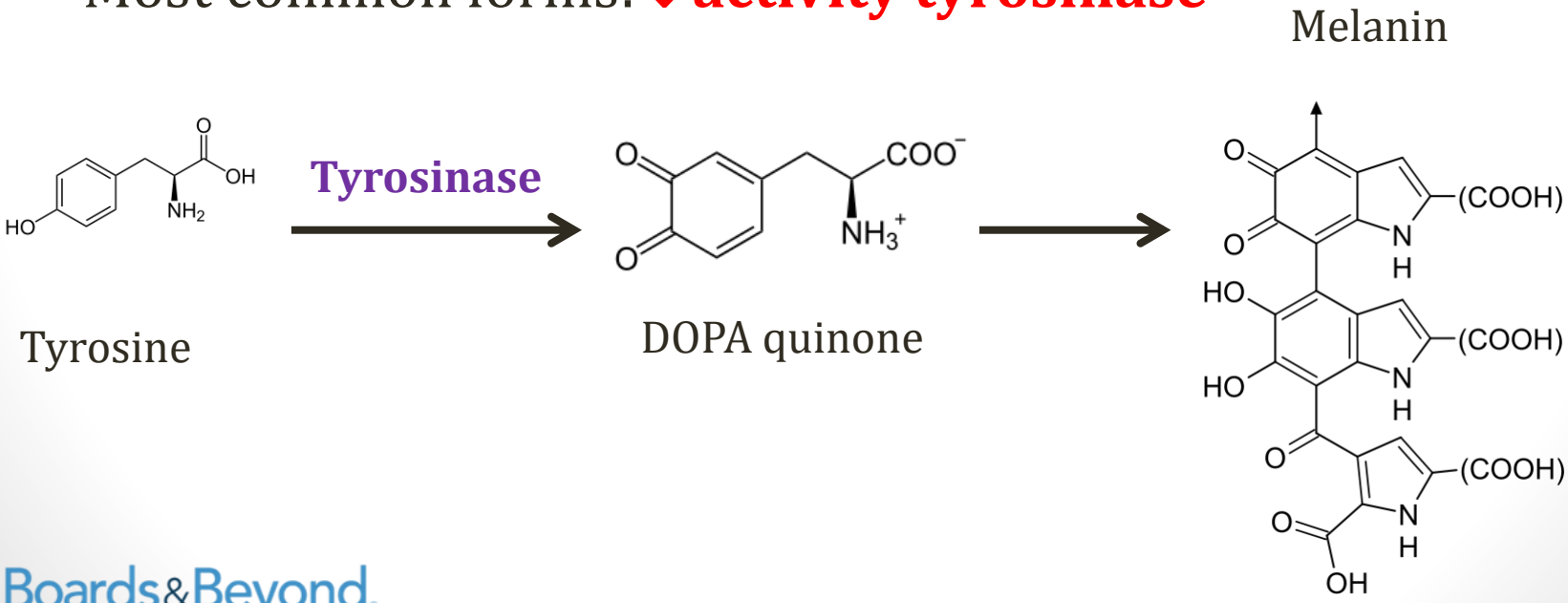
- Small brown/dark macules (flat)
- Can darken on exposure to sun
- **Increased amounts of melanin**
- Normal melanocyte number/density

Loyna/Wikipedia

Albinism

Oculocutaneous Albinism (OCA)

- Family of genetic disorders
- Autosomal recessive
- Absent/reduced melanin synthesis in melanocytes
  - Normal *number* of melanocytes
- Most common forms: **↓ activity tyrosinase**



Albinism

Oculocutaneous Albinism (OCA)

- Hypopigmentation of hair, skin, eyes
- White hair, pink skin color, blue eyes
- ↑ risk of **sunburns**
- ↑ risk of **skin cancer**
  - **No UV light protection**
  - Basal cell carcinoma
  - Squamous cell carcinoma
  - Melanoma

Muntuwandi/Wikipedia

Melasma

- Acquired ***hyper*pigmentation**
- Irregular areas of tan/dark macules on face
- Often symmetrical
- Sun-exposed areas of face
- Most common in women with dark complexions

Kylie Aquino/Flikr

Melasma

- Triggered by UV light in susceptible woman
- ↑ melanin synthesis
- Onset often with **pregnancy** or **OCP**
  - ↑ estrogen
  - "Mask of pregnancy"
  - May resolve after pregnancy
- Cosmetic problem
- Treatment:
  - Sun protection
  - Skin lighteners: Hydroquinone (inhibits tyrosinase)

Vitiligo

- Acquired, localized pigment disorder
- **Autoimmune destruction of melanocytes**
- Asymptomatic depigmented (white) macules/patches
- No clinical signs of inflammation (warmth)
- Treatment: steroids, immunosuppressants

James Heilman, MD/Wikipedia

Vitiligo

- Dark skinned individuals
  - Obvious areas of depigmentation
- Light skinned individuals
  - Failure to tan in localized region
- Cosmetic problem

James Heilman, MD/Wikipedia

Vascular Lesions

Jason Ryan, MD, MPH

Blood Blister

- Traumatic bleeding in dermis
- Intact epidermis
- Many vascular tumors look similar
  - Diagnosis by patient characteristics
  - Single vs. multiple

Esinam/Wikipedia

Angiosarcoma

- Rare tumor of blood or lymph vessels
  - Sarcoma = tumor of mesenchyme origin
  - Angio = blood vessel (endothelial origin)
  - Lymphangiosarcoma = derived from lymph endothelium
  - Hemangiosarcoma = derived from vascular endothelium
  - Hemangioma = benign version
- Purple nodules or plaques
- Poor prognosis

Hai Trieu/Slideshare

Angiosarcoma

- Occur in liver
  - Associated with vinyl chloride exposure
- Occur in breast
  - Often following radiation therapy
  - Often in setting of lymphedema after mastectomy

Angiosarcoma

- Occur beneath skin
  - Usually **head and neck** (sun exposed areas)
  - Often scalp or face
  - Arise from **dermis**
  - Older, white males
  - Median age: 65 to 70
  - Male to female ratio: 2:1

Bacillary Angiomatosis

- Zoonotic infection by **Bartonella**
  - Bartonella quintana and Bartonella henselae
- End-stage HIV and AIDS patients
- Systemic infection → blood vessels in skin
- Presents as **numerous red/purple nodules**
- Similar appearance to Kaposi sarcoma

Wikipedia/Public Domain

Kaposi Sarcoma

- Common in **HIV/AIDS**
- Angioproliferation
- **HHV-8** (Human Herpesvirus-8)
- Key differences from bacillary angiomatosis
  - Kaposi Sarcoma: Lymphocytes
  - BA: Neutrophils/lymphocytes

Wikipedia/Public Domain

Pyogenic Granuloma

Lobular capillary hemangioma

- Benign vascular tumor
- Blood vessel hyperplasia due to **growth** stimuli
- Most often on skin
  - Trunk, arms, legs, head, neck
  - Can be mucosal: lips, gums
- Classic stimuli: **pregnancy** and **trauma**
- Often bleed profusely
- Surgically removed

Makotosan/Wikipedia

Cherry Hemangioma

- Benign capillary proliferations
- Common in **middle-aged or elderly**
- Develop with aging
- Usually multiple
- Classically on the trunk
- May bleed from trauma

Public Domain

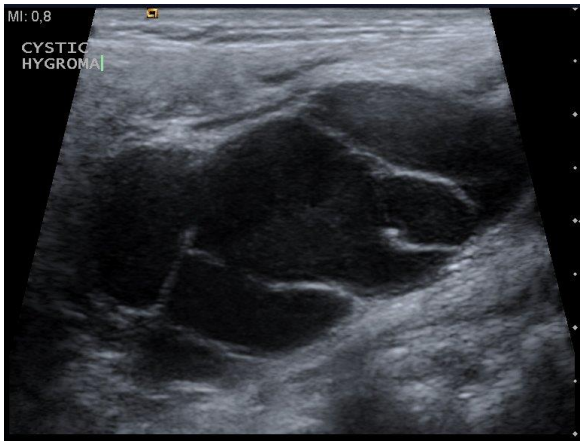
Cystic Hygroma

- Congenital malformation (newborns)
- Large cyst containing lymph (benign)
  - Caused by obstruction of lymph drainage
- Classically develops on neck

Timothyjosephwood/Wikipedia

Cystic Hygroma

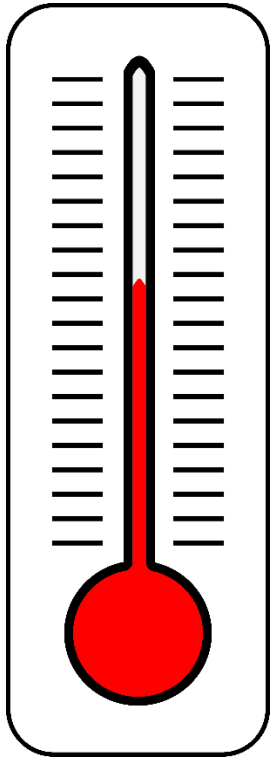
- Often identified on **prenatal ultrasound**
- Increased risk of fetal aneuploidy and malformations
  - Trisomy 21 (Down) and Turner syndrome (XO)
  - Cardiac and skeletal malformations
- Increased risk of miscarriage or fetal death
- Often found together with nuchal translucency



Nevit Dilmen/Wikipedia

Glomus Tumor

- **Glomus body**
  - Structure in dermis of skin
  - Most numerous in fingers and toes
  - Contains modified smooth muscle cells
  - Regulates skin temperature
  - Shunts blood away from surface in cold
  - Preserves heat



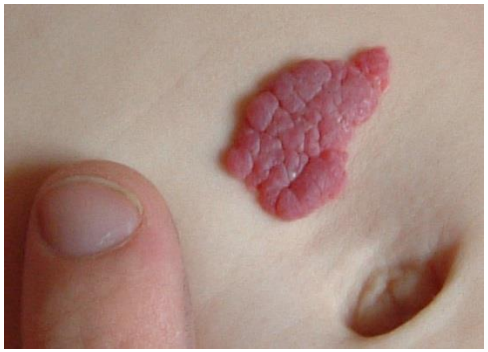
Wikipedia/Public Domain

Glomus Tumor

- Benign growth of **modified smooth muscle** cells
- Occurs in fingers and toes
- Usually at tips/ends
  - "Subungual" = under nailbed
- Pink/purple papule or nodule
- **Painful** especially when exposed to **cold**
  - "Paroxysms of pain"
  - "Cold sensitivity"

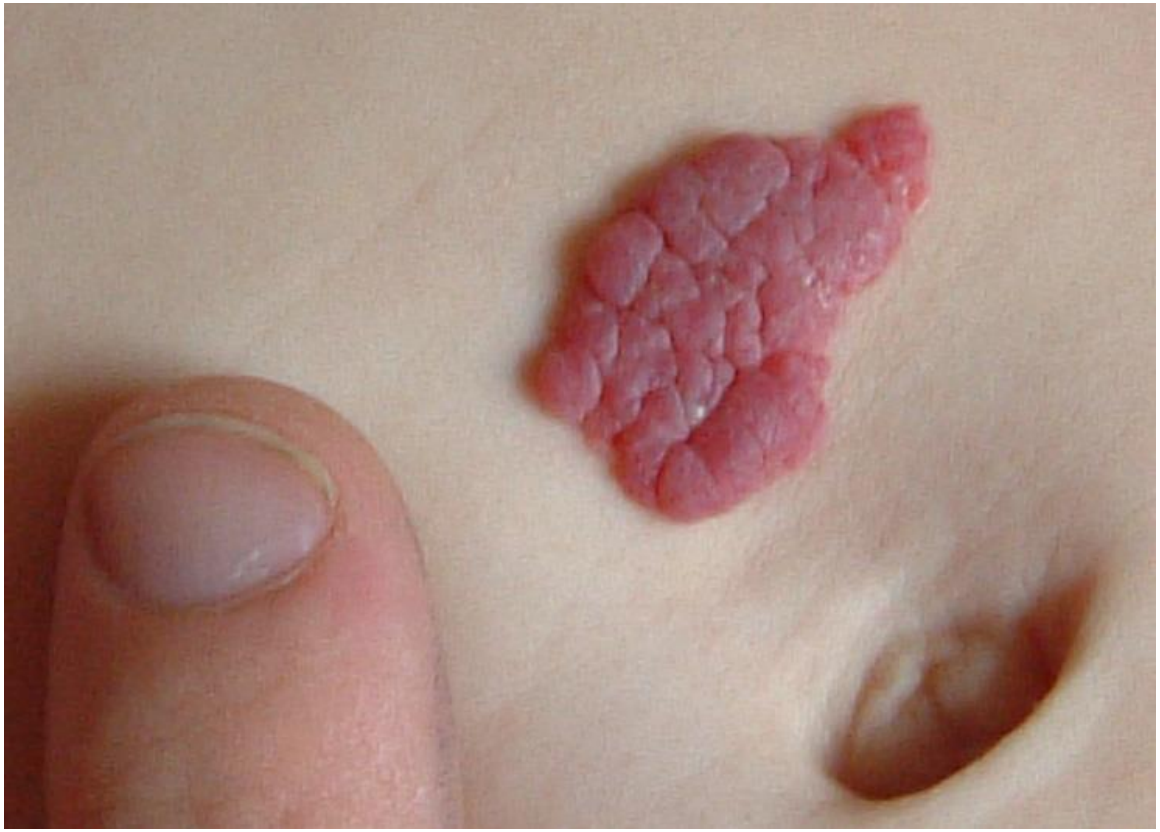
Strawberry Hemangioma

- Benign hemangioma
  - Excess proliferation of blood vessels
- Appear in newborns
  - Common: Up to 10% Caucasian babies in some studies
  - Usually a single lesion
  - Usually not present at birth
  - Usually identified first few days/months after birth
- Involute within few years



Zeimusu /Wikipedia

Strawberry Hemangioma



Zeimusu /Wikipedia

Nevus Simplex

Stork bite/Salmon Patch

- Capillary malformation (not a tumor)
- Common on eyelids or back (nape) of neck
- “Birthmark”
- Pink-red macule
- Up to 60 percent of infants
- Fade first few years of life

Wierzman/Wikipedia

Nevus Flammeus

Port Wine Stain

- Malformation of dermal capillaries and venules
- Slow/low blood flow
- Pink/red patches
- Often unilateral
- Blanch when pressed
- Do not regress
- Grow as child grows
- **Sturge-Weber syndrome**

Lee Health/Vimeo

Skin Infections

Jason Ryan, MD, MPH

Impetigo

- **Superficial** skin infection
- Neutrophils collect beneath stratum corneum
- Macules → papules → rupture → erosions
- Dried sebum → "Honey-colored" crust
- Highly contagious

CNX OpenStax/Wikipedia

Impetigo

- Impetigo contagiosa (non-bullous)
  - Traditional, most common form
  - Face and extremities
  - Caused by S. aureus
  - Also “Beta-hemolytic step” – mostly S. Pyogenes (group A)
  - Honey crusted lesions

CNX OpenStax/Wikipedia

Impetigo

- Bullous impetigo
  - Seen in children
  - Trunk commonly involved
  - S. aureus

Public Domain

S. Aureus Exfoliative Toxin

Exfolatin

- Destroys keratinocyte attachments
- Cleaves **desmoglein 1** complex
  - Desmosome protein
  - Links keratinocytes together
- Affects **stratum granulosum**
- Leads to bullous impetigo

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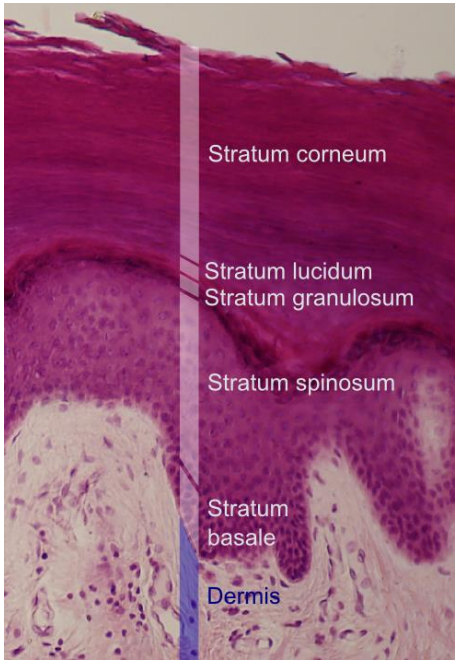


Mikael Häggström/Wikipedia

Scalded Skin Syndrome

Public Domain

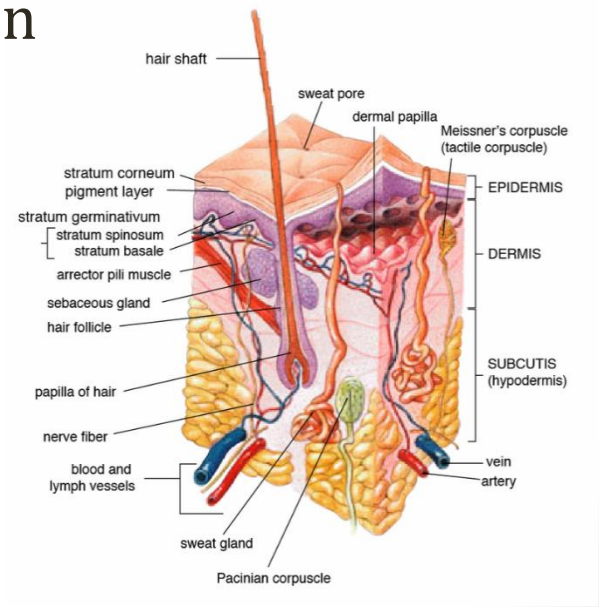
- Newborn disease
- Colonization of skin with S. Aureus
- *Diffuse* exfoliative toxin
- Classically occurs 3 to 7 days of age
- Fever, diffuse erythema
- Sloughing of skin
- Damage intraepidermal
- **Heals completely with no scar**
- Nikolsky's sign: skin slips off with gentle tug
- Treatment: antibiotics

Erysipelas and Cellulitis

- Bacterial skin infections that often overlap
- Differ mainly by layer of skin involvement
- Skin break/trauma → bacterial entry
- Redness, warmth
- Sometimes fever
- Usually unilateral
- Most common on legs (lower extremities)
- Erysipelas also on face

Erysipelas

- **Superficial dermis**
- Young children and older adults
- Usually Group A strep (S. Pyogenes)
- Acute onset: fevers, chills, rash
- Clear demarcation rash/normal skin



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Erysipelas

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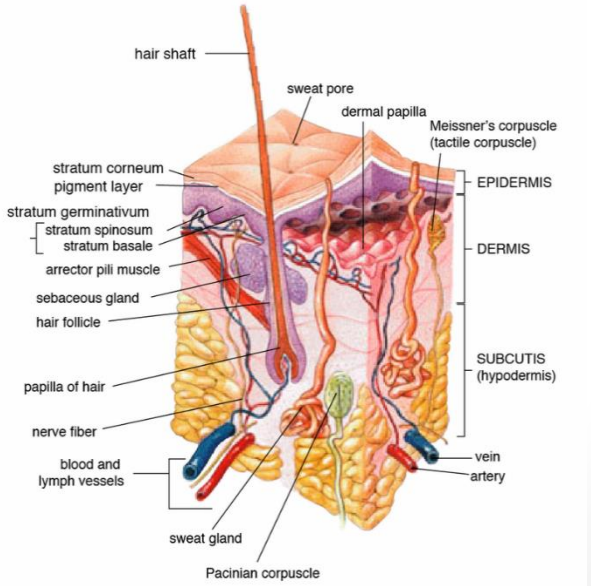
Cellulitis

- **Deep dermis**
- Subcutaneous fat
- Middle-aged and **elderly** (rarely children)
- Group A strep (S. Pyogenes) or S. Aureus
- Slower onset
- Rash, focal pain, warmth over days
- Ill-defined, spreading border



Wikipedia/Public Domain

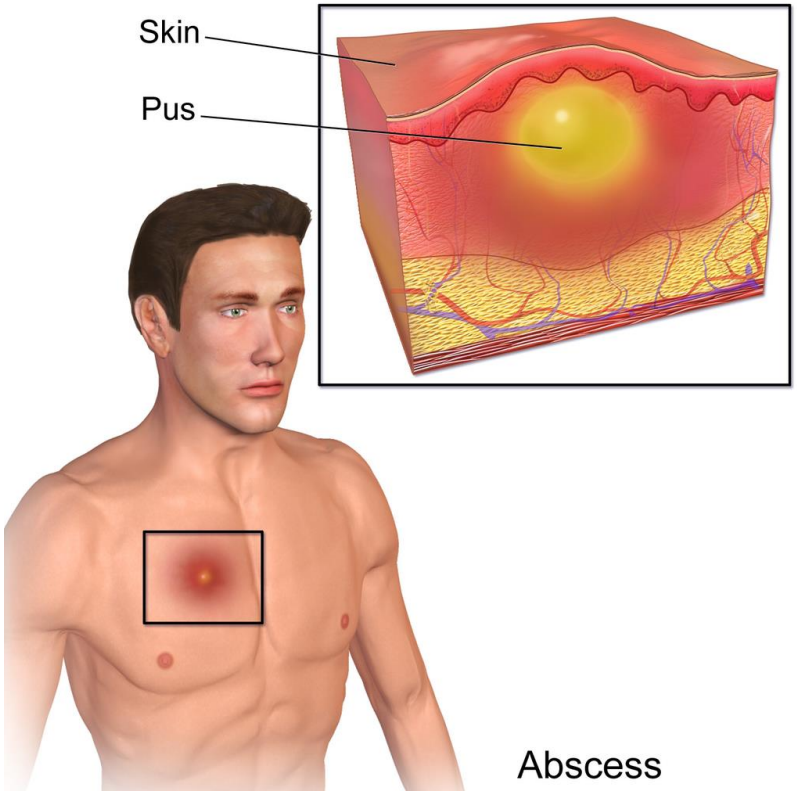
Cellulitis

Pshawnoah/Wikipedia

Skin Abscess

- Collection of **pus** (neutrophils, bacteria)
- Walled-off in **dermis or subcutaneous space**
- Usually S. aureus
- Red, painful nodule
- Tense, raised skin
- May complicate cellulitis/erysipelas
- Usually requires incision and drainage

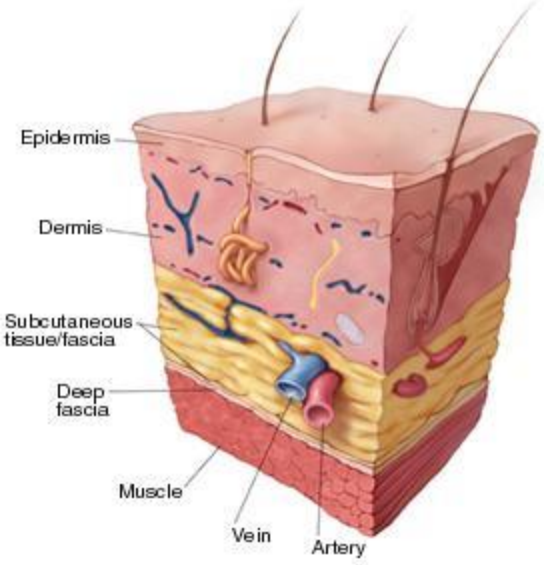
Skin Abscess

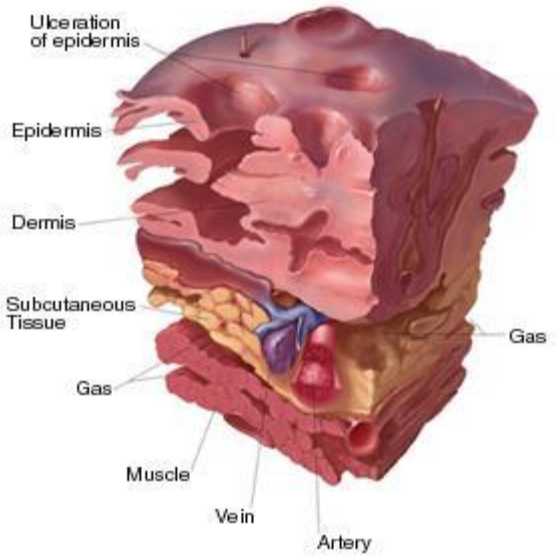


BruceBlaus/Wikipedia

Necrotizing Fasciitis

- Infection of **fascia**
- Involves muscle fascia and subcutaneous fat
- Destruction (necrosis) of tissue above fascia





Pousettet/Wikipedia

Necrotizing Fasciitis

- Skin color changes: red-purple-blue-gray-black
- Bullae
- Pain and tenderness
  - May be “out of proportion to exam”
  - Apparently minor rash with exquisite tenderness
  - Patient may mistake infection for muscle injury
  - Eventually pain stops (anesthesia) from nerve destruction

Necrotizing Fasciitis

- Crepitus
  - Crackling sound when skin is pressed
  - From gas under skin
  - Methane and CO2 from bacteria

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Necrotizing Fasciitis

Piotr Smuszkiewicz/Wikipedia

Necrotizing Fasciitis

- Often fulminant and deadly
- Infection spreads along muscle fascia
  - Poor blood supply → uncontrolled spread
- Requires urgent **surgical debridement**

Public Domain

Necrotizing Fasciitis

- Type 1:
  - Polymicrobial
  - Often anaerobes (Bacteroides, Clostridium, etc.)
  - Strep, staph, others
  - Occurs in diabetics, immunocompromised, vascular disease
  - Usually occurs **following surgery**
- Type 2:
  - Group A strep (sometimes Staph)
  - Occurs in otherwise healthy people after **skin injury**

Necrotizing Fasciitis

- Classic case:
  - Minor skin trauma
  - Or diabetic/immunocompromised after surgery
  - Redness/warmth (can be confused with cellulitis)
  - Pain out of proportion to exam
  - Fever, hypotension

Blistering Disorders

Jason Ryan, MD, MPH

Blisters

- Fluid-filled skin lesions
  - Separation of skin layers
  - Space filled with fluid
- May rupture
- Vesicle: <1cm
- Bulla (plural = bullae): >1cm
- Many causes
- Burns
- Friction

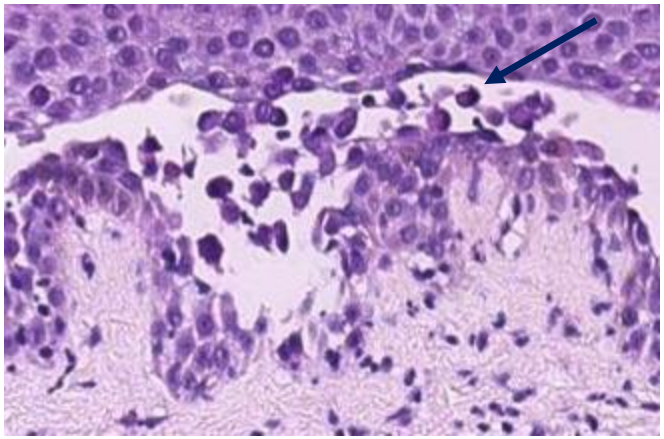
Frazzmatazz/Wikipedia

Pemphigus

- *Pemphig*: from Greek word for blister
- Hallmark: **acantholysis**
  - Loss of connections between keratinocytes
- Involve mucous membranes (mouth) and skin
- Subtypes:
  - **Pemphigus vulgaris (most common)**
  - Pemphigus foliaceus
  - IgA pemphigus
  - Paraneoplastic pemphigus

Acantholysis

- **Loss of connections** between keratinocytes
- Often loss of desmosomes
- “Rounded” keratinocytes
- Detached, floating freely in epidermis
- Key feature of **pemphigus vulgaris**



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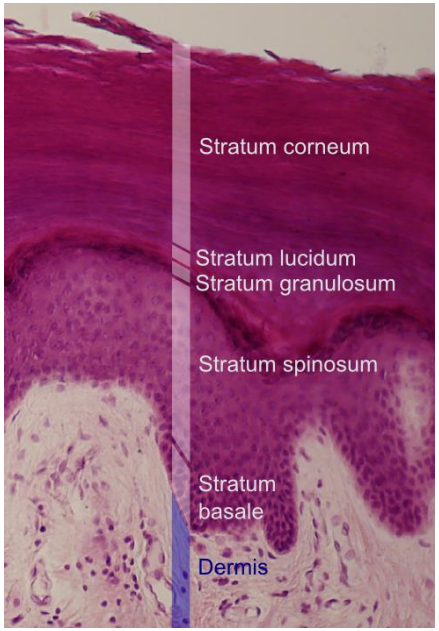
Pemphigus vulgaris

- Autoantibodies against **desmoglein**
  - Component of **desmosomes**
  - Type II hypersensitivity reaction
- Disrupts connections in **stratum spinosum**
  - Fluid collects above basal layer
- Occurs mostly in adults (30 to 60)
- Nikolsky's sign
  - Skin slips off with gentle tug
  - Also seen in Staph Scalded Skin (child)
  - Also seen in Stevens-Johnson syndrome



Mikael Häggström/Wikipedia

Pemphigus vulgaris

- Large, flaccid bullae that easily burst (not tense)
- Often few intact bullae, most rupture and scabbed
- Often presents first with **oral bullae** and **ulcerations**
  - Painful chewing/swelling

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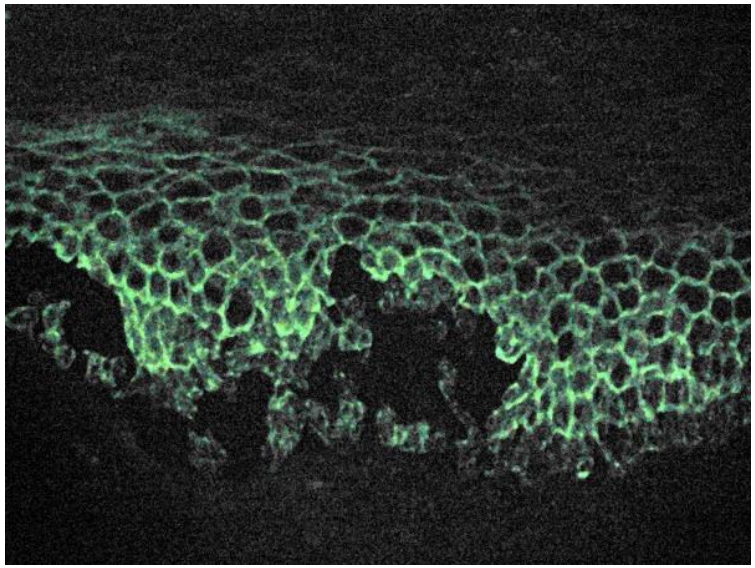
Pemphigus vulgaris

- Classic finding: (+) immunofluorescence for IgG
  - **"Reticular" pattern**: like a net
- Treatment: immunosuppressants
- Increased mortality: infection, side effects of Rx



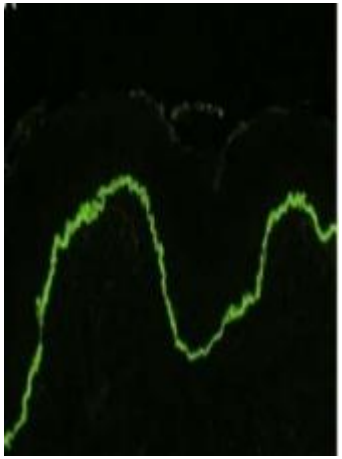
Emmanuelm/Wikipedia

Bullous pemphigoid

- "Pemphigoid": looks like pemphigus
- Autoantibodies against **hemidesmosomes**
  - Bullous pemphigoid antigens (proteins)
  - BP180, BP230
  - Attach epithelial cells to the basement membrane

Bullous pemphigoid

- Bullae are **subepidermal, nonacantholytic**
  - Less fragile (flaccid) than pemphigus vulgaris
  - Numerous intact, tense bullae
  - Less ruptured bullae with scabs
- Biopsy: **Eosinophils** and lymphocytes
- Immunofluorescence: **line at base of epidermis**



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Bullous pemphigoid

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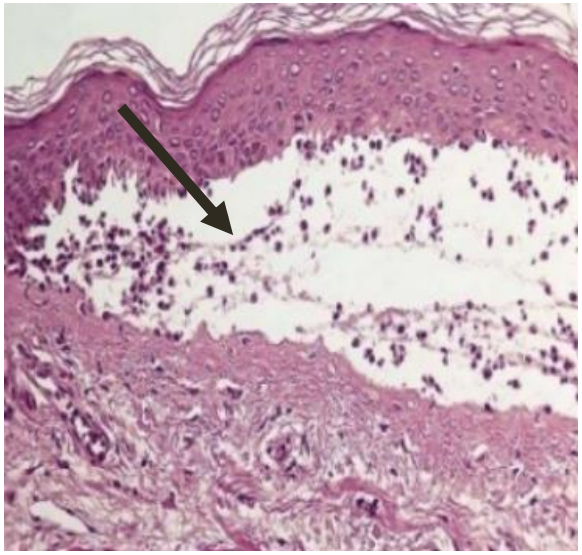
Eosinophils in blister



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Bullous pemphigoid

- Occurs in the **elderly** (median age 80 in one study)
- Rarely involves mouth
- Absent Nikolsky's sign
- Treatment: immunosuppressants
- Also increased mortality
  - Less than pemphigus
  - Less bullae rupture → less chance of infection

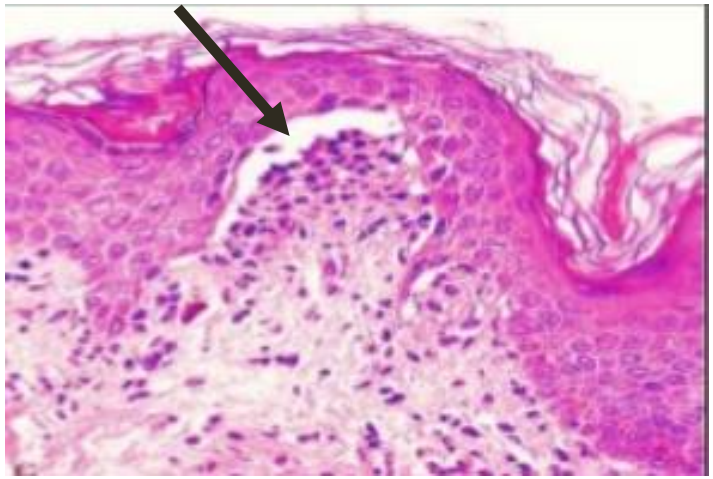
Dermatitis Herpetiformis

- Skin condition associated with **celiac disease**
- Herpes-like lesions on skin
  - Papules/vesicles in bilateral groups ("herpetiform")
- **Pruritic (itchy)**
- Classically on extensors: elbows, knees

Madhero88/Dermet.com

Dermatitis Herpetiformis

- **IgA deposition** in **dermal papillae**
  - Numerous, small lesions at tips of dermal papillae
- Occurs in individuals with genetic gluten sensitivity
- Antibodies triggered by gluten cross-react at skin
- Biopsy: microabscesses (spaces) at tips of papillae
- Neutrophils



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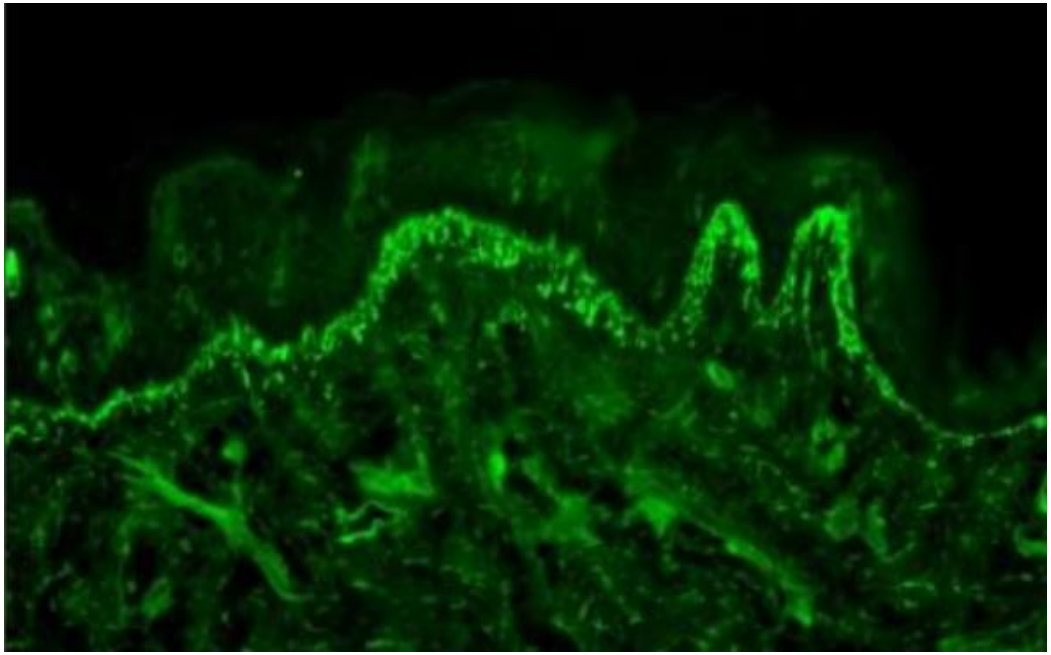
Dermatitis Herpetiformis

IgA Deposition at tips of dermal papillae on IF



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Antibody Blistering Disorders

	Antibodies	Target	Location
Pemphigus	IgG	Desmosomes	Stratum Spinosum
Bullous Pemphigoid	IgG	Hemidesmosomes	Basement Membrane
Dermatitis Herpetiformis	IgA	-- (Gluten-related)	Dermal papillae

Hypersensitivity Disorders

Jason Ryan, MD, MPH

Allergic Skin Reactions

- Urticaria = hives
- Urticaria = pruritic, raised wheals and angioedema
- Angioedema = deep mucocutaneous swelling

Urticaria

- Allergic skin reaction
- Usually caused by **mast cell degranulation**
  - Type I hypersensitivity reaction
  - Antigen binding to IgE antibodies on mast cells
  - **Histamine** release
- No changes to epidermis
- ***Dermal*** edema
- Dilation of lymph vessels
  - For fluid drainage

James Heilman, MD/Wikipedia

Urticaria

- Usually acute and self-limited
- Resolves within days/weeks
- May be treated with antihistamines and steroids
- May be a component of **anaphylaxis**
  - Wheezing
  - Mucosal swelling (lips/tongue)
  - Hypotension
  - Syncope

Atopic Dermatitis

Eczema

- Chronic disorder with flares/remission
- Also a **hypersensitivity** disorder
  - Complex, incompletely understood pathogenesis
  - T-cells, cytokines
- Usually "extrinsic": reaction to environmental antigens
  - Less common form: intrinsic
- Usually occurs in children
- Red, pruritic (itchy) rash

Eisfelder/Wikipedia

Atopic Dermatitis

Eczema

- Over 80% patients: **↑ serum IgE levels**
- 70% of patients: **family history** of atopic diseases
  - Commonly co-occurs with allergic rhinitis/asthma
  - "Atopic march"
- **Filaggrin**
  - Protein of stratum corneum
  - Filaggrin deficiency impairs skin barrier
  - Filaggrin gene mutations → increased risk of eczema
  - Skin dry and scaly
  - Easy entry of allergens

Atopic Dermatitis

Eczema

- Babies: face (cheeks) and scalp
- Children/adults:
  - Thickened ("lichenified") plaques
  - Skin flexures
  - Antecubital and popliteal fossae

Gzzz/Wikipedia

Care_SMS/Flikr

Contact Dermatitis

- Similar clinical features to eczema
- ***Localized*** to area of skin contact with allergen
- **Type IV hypersensitivity** disorder

Wikipedia/Public Domain

Dr.khatmando/Wikipedia

Contact Dermatitis

- Classic causes (irritants)
  - Poison ivy
  - Nickel (jewelry)
  - Laundry detergents
- Treatment:
  - Remove irritant
  - Steroids

Drug Rash

- "Non-immediate" reaction to drug
- Often seen with some penicillin antibiotics
- Maculopapular
- Itchy or may be non-pruritic
- Absence of fever, wheezing, joint pain
- **Days or weeks** after starting drug
- **Type-IV (T-cell-mediated) mechanism**

Romano A et al. **Diagnosis of nonimmediate reactions to B-lactam antibiotics**. Allergy 2004

Stevens-Johnson Syndrome

- Severe skin reaction
- Type IV hypersensitivity disorder
- May also involve mucous membranes
- Usually triggered by **drugs**
- Hallmark: **necrosis of the epidermis**
- Nikolsky sign
  - Skin slips off with gentle tug
  - Also seen in Staph Scalded Skin (child)
  - Also seen in Pemphigus vulgaris

Stevens-Johnson Syndrome

- Prodrome
  - 1-3 days before skin findings
  - **Fever**
  - Flu-like malaise
- Lesions start on **face/chest**
- Spread symmetrically
- Red, tender skin
- Progresses to vesicles/bullae
- **Sloughing of skin**
- Mucosal lesions: 90% cases

Dr. Thomas Habif/Wikipedia

Stevens-Johnson Syndrome

- Toxic epidermal necrolysis
  - Severe form SJS (>30% skin)
- High mortality
  - SJS 1-5%; TEN 25-35%

Pixabay/Public Domain

Erythema multiforme

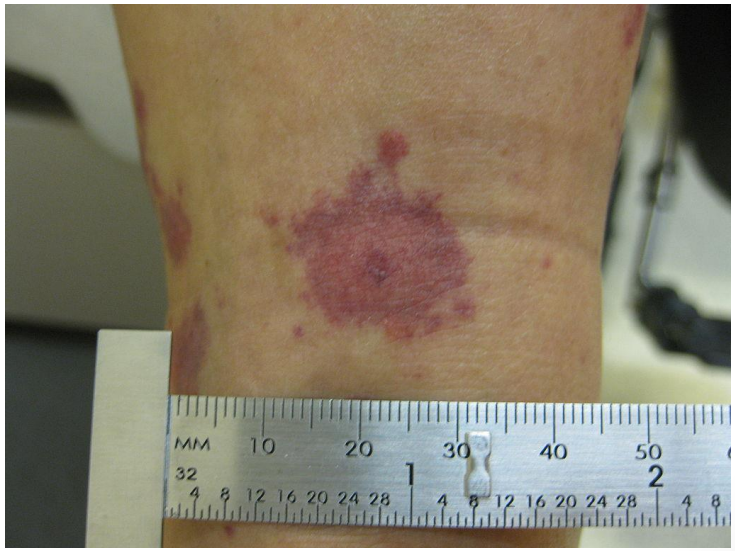
- Skin disorder associated with infections (90% cases)
  - **Herpes simplex virus (most common)**
  - Mycoplasma pneumoniae (often in children)
- Also associated with some drugs
  - Sulfa drugs
  - NSAIDs
  - Phenytoin
- Also some cancers and autoimmune diseases

Erythema multiforme

- Pathogenesis unclear
- Most data from HSV-related cases
- **Cell-mediated (type IV) autoimmune**
- Triggered by viral antigens in keratinocytes

Erythema multiforme

- Multiple lesion types (multiforme)
  - Macules, papules, vesicles
  - Lesions similar for one patient
  - May differ between patients
- Hallmark: **"Target lesion"**
  - Dark/dusky central area
  - Surrounding red rings



Kilbad/Wikipedia

Erythema multiforme

- Symmetrical distribution
- Starts on “extensor surfaces of acral extremities”
  - Backs of hands, feet
  - Contrast with SJS: face
- Spreads to center (“centripetal spread”)
- May involve mucous membranes
  - Mouth, eye, genitals
  - Erythema
  - Erosions (painful)
  - Bullae

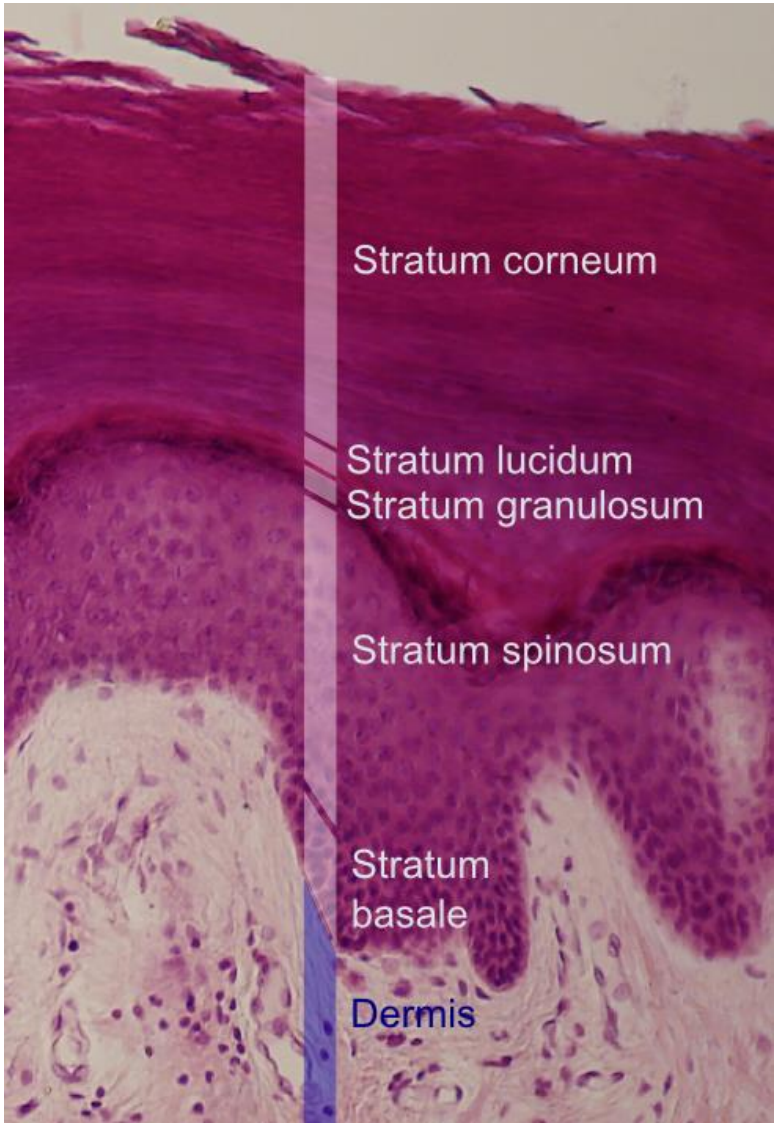
James Heilman, MD /Wikipedia

Erythema multiforme

- Typical case
  - Oral or genital HSV eruption (or other trigger)
  - EM skin eruption occurs few days to 2 weeks later
  - Lesions evolve over 3-5 days
  - Resolve within 2 weeks (no treatment)
  - Rarely severe cases require steroids or other Rx

Skin Cancer

Jason Ryan, MD, MPH

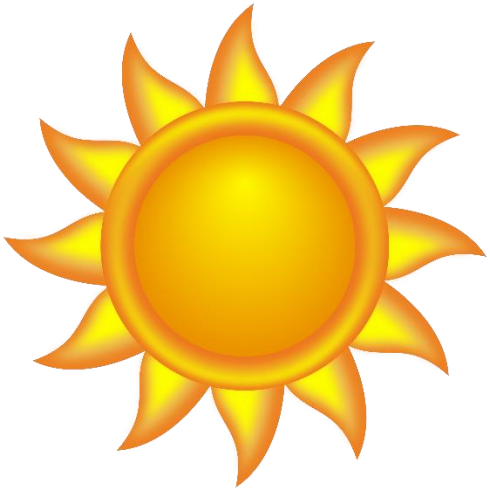


Mikael Häggström/Wikipedia

Actinic Keratosis

Solar keratosis

- Premalignant skin lesions
- Caused by **sun exposure**
- Growth of atypical epidermal keratinocytes
- Can lead to **squamous cell carcinoma**
  - Increasing degrees of dysplasia → malignancy



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Actinic Keratosis

Solar keratosis

- Round, red/brown papules or plaques
- Sun exposed areas
- Biopsy: Hyperkeratosis, epidermal cell dysplasia
- **Parakeratosis**: retained nuclei in stratum corneum

Future FamDoc

Future FamDoc

Squamous Cell Carcinoma

- 2nd most common skin cancer
- Arises from squamous cells in epidermis
- Occurs in sun-exposed areas
  - Face, lip, ears, hands
  - DNA damage by UV light
- Occurs in older patients
  - Rare <45 years old
  - Common > 75 years old
- Less than 5% metastasize to regional nodes
- Rarely metastasize beyond nodes

Squamous Cell Carcinoma

- Red, scaling plaques with sharp borders
- More advanced lesions: ulcerate, keratin production
- May crust or bleed

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Squamous Cell Carcinoma

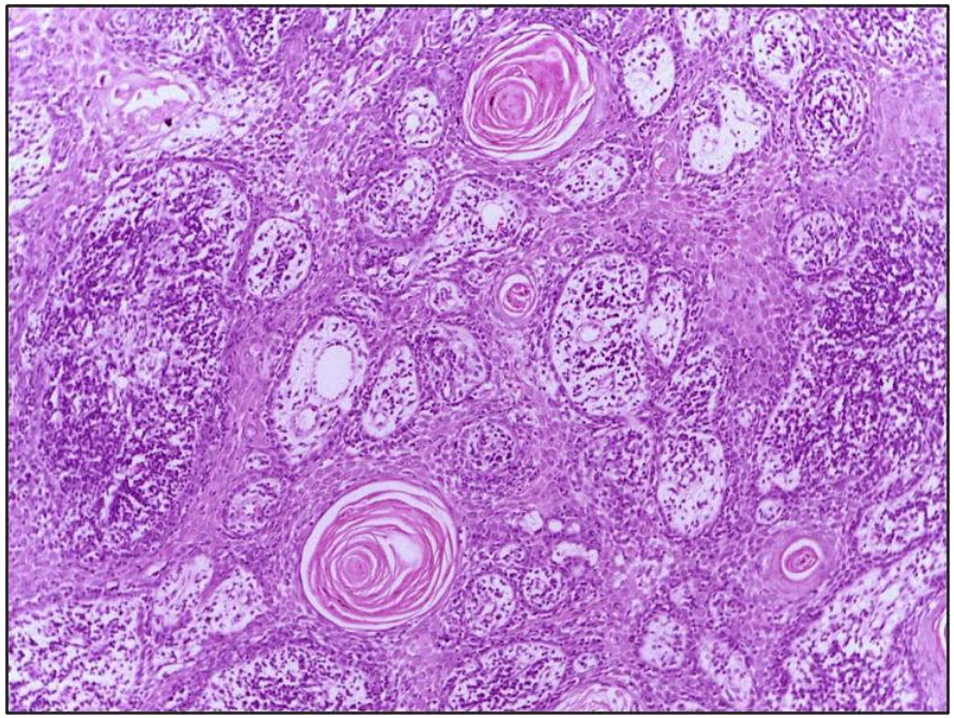
Risk Factors

- Sun exposure
- **Chronic immunosuppression**
  - Organ transplant, HIV, long term glucocorticoids
- **Chronic skin inflammation**
  - Burns, chronic ulcers, draining sinus tracts
- **Arsenic exposure**
  - Found in contaminated drinking water

Squamous Cell Carcinoma

Pathology

- Classic finding: **keratin pearls**



Department of Pathology, Calicut Medical College

Keratoacanthoma

- Variant of SCC ("squamoproliferative tumor")
- Usually benign, self-resolving
- "Dome-shaped" nodule with central hyperkeratosis
- Classic feature: rapid growth (weeks) → regression
- Removed surgically or followed for regression

Jmarchn /Wikipedia

Bowen's Disease

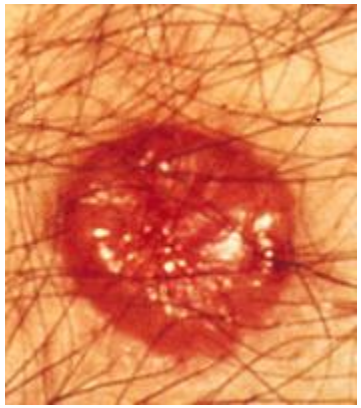
- Squamous cell carcinoma in situ
- Well-demarcated, scaly patch or plaque

Klaus D. Peter, Gummersbach, Germany

Basal Cell Carcinoma

- Most common skin cancer
- Slow growing
- Rarely metastasize
- Most found early and excised
- Occur in sun-exposed areas
- Lowest potential for recurrence or metastases
  - Basal < squamous < melanoma

Basal Cell Carcinoma



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- **"Pearly"** papules or nodules
  - May have telangiectasias on surface
  - Dilated blood vessels
- May ulcerate with crust in center
- Borders may be "rolled" (rounded, thickened)

M. Sand et al./Wikipedia

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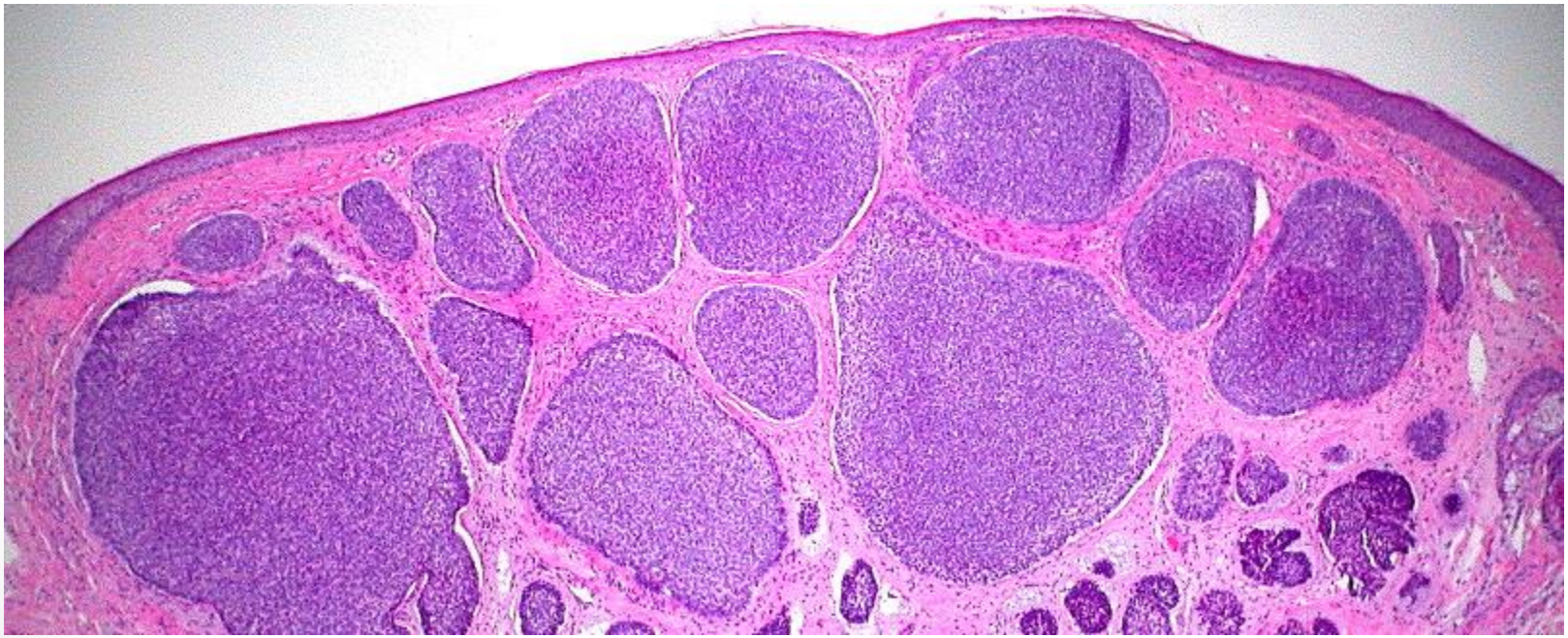
Basal Cell Carcinoma

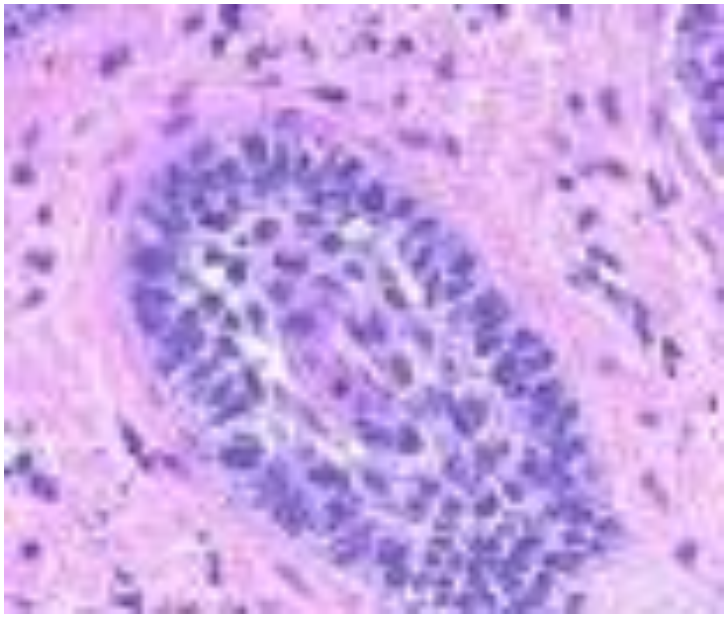
- Nests of “basaloid” dark cells in dermis



Ed Uthman, MD

Basal Cell Carcinoma

- “Palisading nuclei”
- Cells at periphery of nests line up in parallel



Ed Uthman, MD

Superficial BCC

- Special variant of BCC (~30% of BCCs)
- Light red to pink plaque
- Slight scale
- Most commonly occur on the trunk

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Treatment SCC and BCC

- Surgical excision
- Cryotherapy
- Electrosurgery
- Radiation therapy
- Topical chemotherapy
- High risk lesions excised
  - Larger lesions
  - Recurrent lesions
  - Lesions in specific locations
  - Immunosuppressed patients (SCC)

Melanoma

- Highly malignant form of skin cancer
- **ABCDE**
  - Asymmetrical
  - Irregular border
  - Color variation
  - Diameter > 6mm
  - Evolving over time

Wikipedia/Public Domain

Melanoma

Types

- Superficial spreading
  - Most common subtype
  - 75% of melanomas
- Nodular
  - 15 to 30% of melanomas
  - Aggressive subtype
  - Grow vertically
  - 50% melanoma deaths

Nodular

0x6adb015/Wikipedia

Melanoma

Types

- Lentigo maligna
  - Lentigo = small, flat, dark spot (large freckle)
  - Confined to epidermis
  - Lentigo maligna = growing dark spot **confined to epidermis**
  - Sometimes called "melanoma in situ"
  - Lentigo maligna melanoma = invasion of dermis
  - ***Slow growing*** → years to develops
  - Spreads, darkens, becomes lumpy
  - Occurs in elderly

Lentigo maligna

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Melanoma

Types

- Acral lentiginous
  - Least common type (<5%)
  - Palms, bottom of foot, under nails
- Most common type **dark-skinned patients**
  - Asians
  - African-Americans

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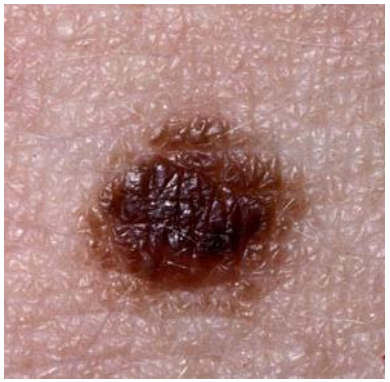
Melanoma

Risk Factors



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- Sun exposure
  - Especially severe sunburns in childhood
- Nevi
  - 1/3 melanomas arise from dysplastic nevi
  - High number of nevi associate with melanoma risk
- Light-sensitivity of skin type
  - Light skin pigmentation
  - Freckles
  - Poor tanning ability

Melanoma

Diagnosis

- Biopsy
- No single diagnostic feature
  - Nests of melanocytes
  - Atypical cells, irregular nuclear shape
- Tumor markers: **S100**
  - Calcium binding protein in nucleus
  - Highly sensitive (low specificity)

GoodFreePhotos

Melanoma

Treatment and Prognosis

- Tumor cells initially grow **radially**
  - Spread along epidermis and upper dermis
- Eventually tumor shifts to **vertical growth phase**
  - Tumor cells invade downward in dermis
- ↑ depth of tumor = ↑ risk of metastasis
  - **Breslow thickness**
  - Distance from granular epidermis to deepest tumor cells

Melanoma

Treatment and Prognosis

- Treatment: excision with wide margins
- Metastasis
  - Hematogenous and lymphatic
  - Lungs, liver, brain (most common causes of death)

Pixabay

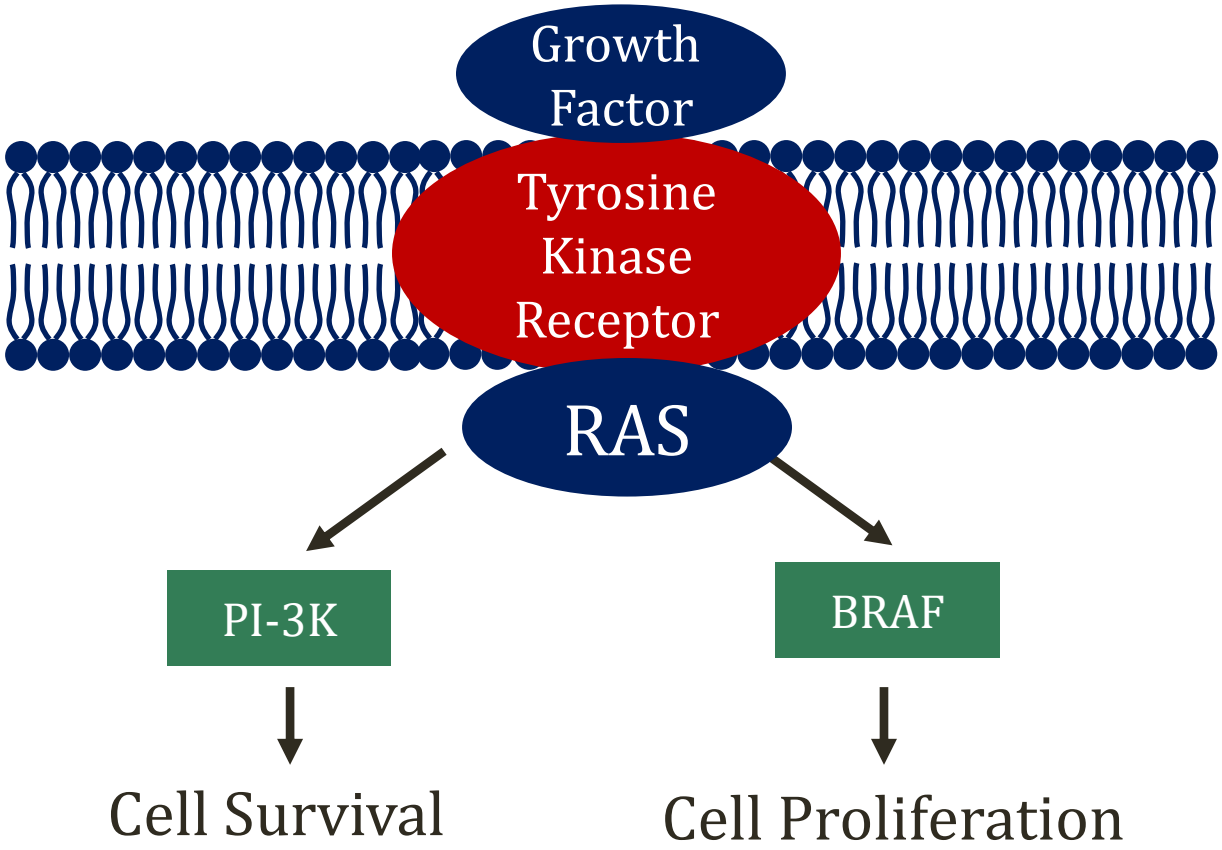
Melanoma

Genetics

- **BRAF gene mutations**
  - Common (40 – 50%) in sporadic melanomas
  - BRAF = proto-oncogene
  - Triggers cell proliferation on RAS activation
- **V600E mutation** of BRAF gene
  - 90% BRAF mutations = V600E mutation
  - Treatable with BRAF inhibitors
  - Vemurafenib and dabrafenib
  - Increase survival in melanoma with V600E mutation

Melanoma

Genetics



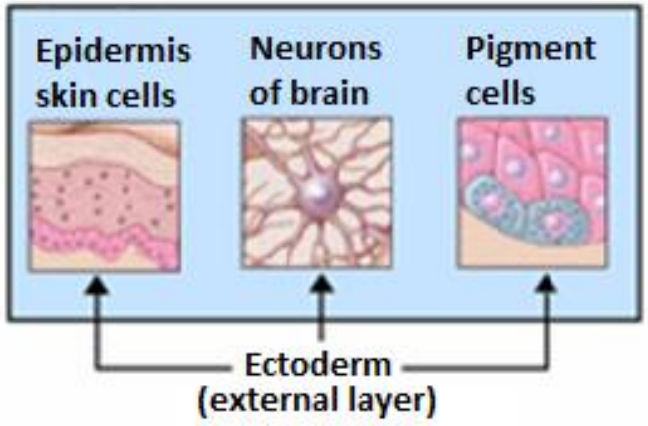
Neurocutaneous Disorders

Jason Ryan, MD, MPH

Neurocutaneous Disorders

Phakomatoses

- Genetic disorders of **skin**, **nerves** and **eye**
  - Other structures sometimes involved (bones, kidneys)
- Structures derived from ***ectoderm***
- Neurofibromatosis
- Tuberous Sclerosis
- Sturge-Weber syndrome
- von Hippel-Lindau disease



Nyq/Wikpiedia

Neurofibromatosis

- Familial cancer syndrome
- Genetic disorder
- Autosomal dominant
- Mutations in NF1 or NF2 genes
  - NF1: Most common type
- **Nerve tumors** with **skin and eye findings**

Neurofibromatosis 1

NF1/von Recklinghausen disease

- Mutation of NF1
  - **Tumor suppressor gene** on chromosome 17
  - Encodes for neurofibromin (tumor suppressor protein)
  - Restricts RAS function
  - Mutation → RAS overactivity → uncontrolled growth
- Autosomal dominant with 100% penetrance
  - All gene carriers have disease
  - Children of affected individuals → 50% chance of disease
- **Variable expressivity**
  - Some patients: mild features
  - Other patients: severe features

Neurofibromatosis 1

NF1/von Recklinghausen disease

- Neurofibromas
  - Benign tumors
  - Develop on nerves
  - Often cutaneous nerves

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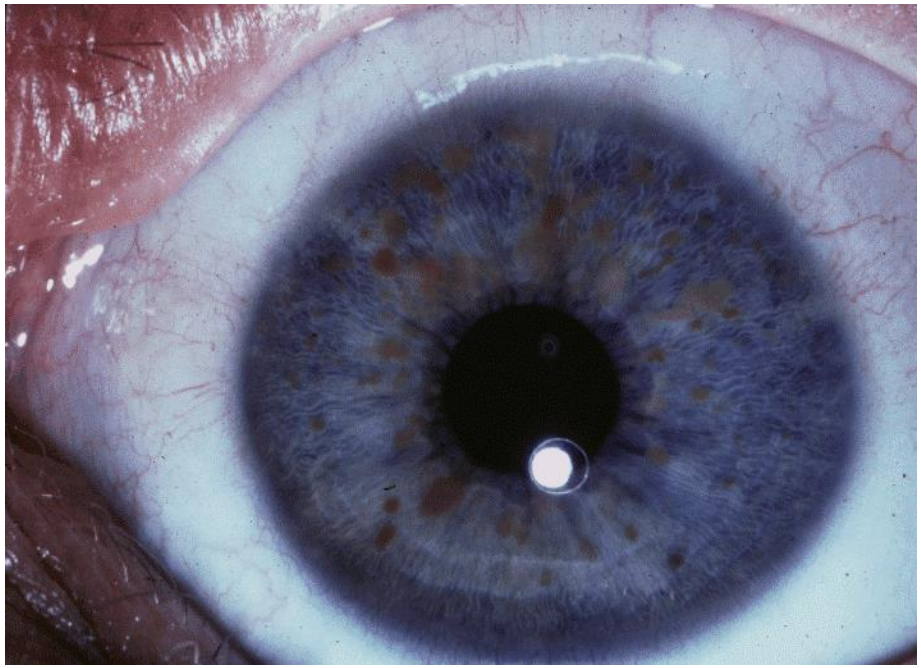
Neurofibromatosis 1

NF1/von Recklinghausen disease

- Lisch nodules
  - Brown spots on iris



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Neurofibromatosis 1

NF1/von Recklinghausen disease

- Café-au-lait spots
  - "Coffee with milk"
  - Light brown macules
- Freckles
  - Not random
  - Clusters in skin folds
  - Axilla and groin

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Neurofibromatosis 1

NF1/von Recklinghausen disease

- **Optic gliomas**
  - Usually develop by 3 years of age
- **Bone abnormalities**
  - Curvature of long bones
  - Facial deformity of eye socket
  - Scoliosis
- **Intellectual impairment**

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Neurofibromatosis 1

NF1/von Recklinghausen disease

- **Hypertension**
  - Renal artery stenosis
  - Rarely pheochromocytoma
- **Malignant tumors**
  - Some neurofibroma become malignant
  - Usually not skin lesions
  - Peripheral nerve sheath tumors
  - Occurs in adolescence or adulthood
  - Presents as pain or sudden growth of neurofibroma

Neurofibromatosis 1

NF1/von Recklinghausen disease

- Diagnostic criteria
  - Six or more café-au-lait spots
  - Two or more neurofibromas
  - Freckles in axilla or groin
  - Optic glioma
  - Two or more Lisch nodules
  - Bone lesions
  - 1st degree relative with NF1

Neurofibromatosis 1

NF1/von Recklinghausen disease

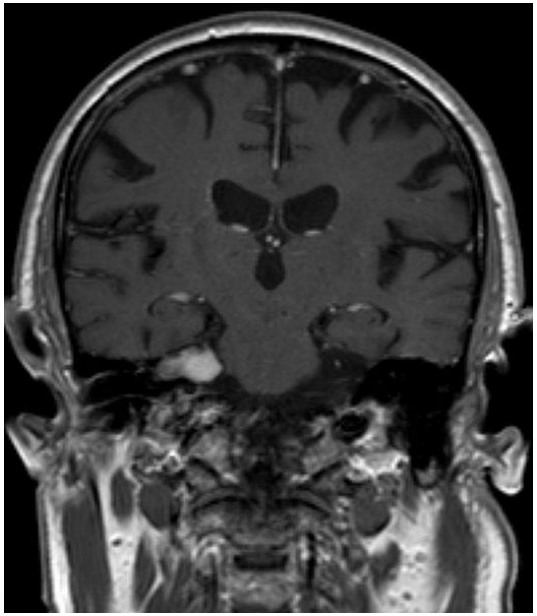
- Birth to 2 years
  - Café-au-lait spots
  - Bone abnormalities
  - Optic gliomas
- Age 2 to 6
  - Lisch nodules
  - Developmental delay
- Adolescence (puberty)
  - Cutaneous neurofibromas

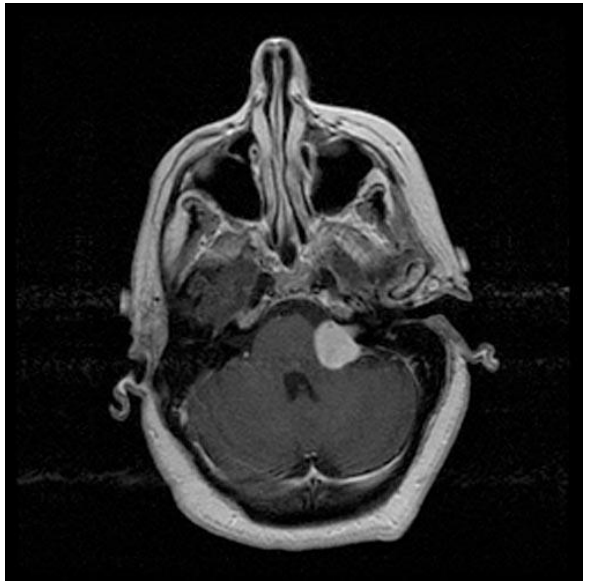
Neurofibromatosis 2

- Less common than NF1
- Also autosomal dominant
- Mutation of NF2 gene
- Major features: CNS tumors
- **Bilateral schwannomas**
  - "Acoustic neuromas"
  - Occur in almost all patients
- Meningiomas

Schwannoma

- Schwann cells: Glial (non neurons) of PNS
- Classically located to CN VIII
- Hearing loss, tinnitus, ataxia





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Tuberous Sclerosis

- Familial cancer syndrome
- Hallmark: **hamartomas**
  - Benign malformation of cells/tissue
  - Resembles tissue of origin (skin, lung, spleen)
- Main clinical feature: **seizures**
  - CNS hamartomas

Tuberous Sclerosis

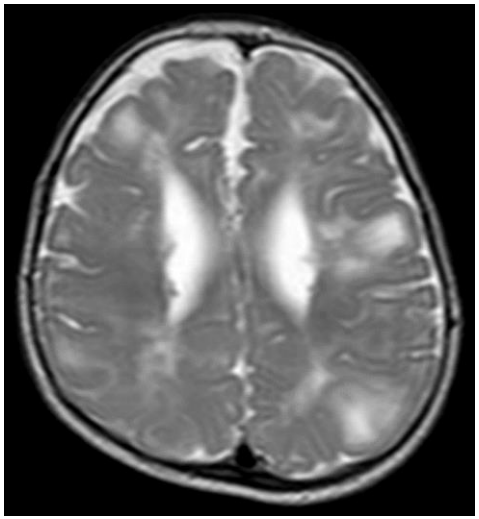
- Autosomal dominant with variable expressivity
  - De novo mutations: 80% cases (no family history)
- Mutation in TSC1 or TSC2 gene
  - TSC1: Hamartin
  - TSC2: Tuberin
- Proteins inhibit mTOR
  - Mechanistic target of rapamycin
  - Kinase
- Mutation → mTOR overactivity → cell growth
  - Especially cell size

Tuberous Sclerosis

- Widespread tumor formation
- Involves MULTIPLE organ systems
- Numerous hamartomas and other neoplasms
- Classic features
  - **Seizures** – most common presenting feature
  - "Ash leaf spots": Pale, hypopigmented skin lesions
  - Facial skin spots (angiofibromas)
  - Intellectual impairment (mental retardation)

CNS Tumors

- **Cortical tubers**
  - Distorted cortex
  - Seizures
- **Subependymal nodules**
  - Ependyma = lining of ventricles



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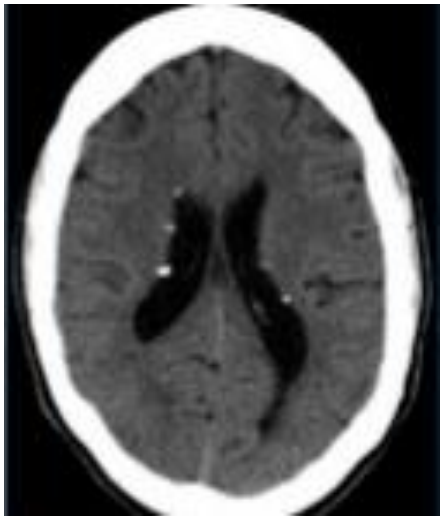
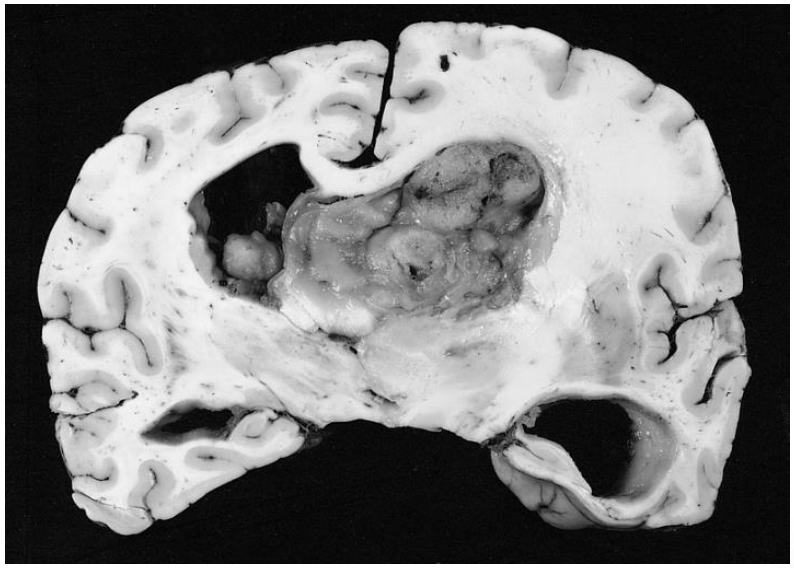


Hytham Nafady

Tuberous Sclerosis

Subependymal giant cell astrocytomas

- Low grade **astrocytoma**
- Usually occur at interventricular foramen
- May obstruct ventricles → **hydrocephalus**



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Tuberous Sclerosis

Angiofibromas

- Fibrous papules usually on face

Herbert L. Fred, MD and Hendrik A. van Dijk

Tuberous Sclerosis

Ash Leaf Spots

- Hypopigmented macules
- Usually oval or elliptical

Mohd Hanafi

Tuberous Sclerosis

Shagreen patches

- Connective tissue hamartoma
- Usually found on lower back
- “Orange peel” or “leathery” texture

K. Chinnasamy

Tuberous Sclerosis

Ungual fibromas

- Fibromas beneath nailbeds

R. Verma/Public Domain

Tuberous Sclerosis

Rhabdomyomas

- Tumors of muscle cells
- Benign (do not metastasize)
- Classic cardiac feature of TS (90% cases)
- Sometimes detected prenatal
- Tumor **embedded in ventricular wall**
- Rare symptoms from obstruction, arrhythmia

Tuberous Sclerosis

Renal Angiomyolipomas

- Most frequent renal manifestation
- Multiple/bilateral
- Proliferation of epithelioid cells around vessels
- Growth and **hemorrhage** → pain
- May cause renin-dependent **hypertension**
- Risk of **chronic kidney disease**
  - Compression of normal renal tissue

Tuberous Sclerosis

Renal Angiomyolipomas

Hellerhoff/Wikipedia

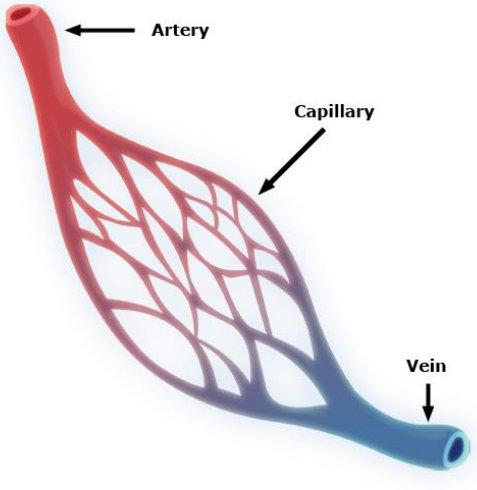
Tuberous Sclerosis

Classic Case

- Child/infant
- Seizures
- Ash-leaf spots
- Angiofibromas

Sturge-Weber Syndrome

- Congenital vascular disorder of **capillaries**
  - Spontaneous gene mutation in early development
  - ***Not inherited***
- Three classic features
  - Port-wine stain on face (birthmark)
  - Leptomeningeal angioma (brain tumor)
  - Increased ocular pressure (glaucoma)



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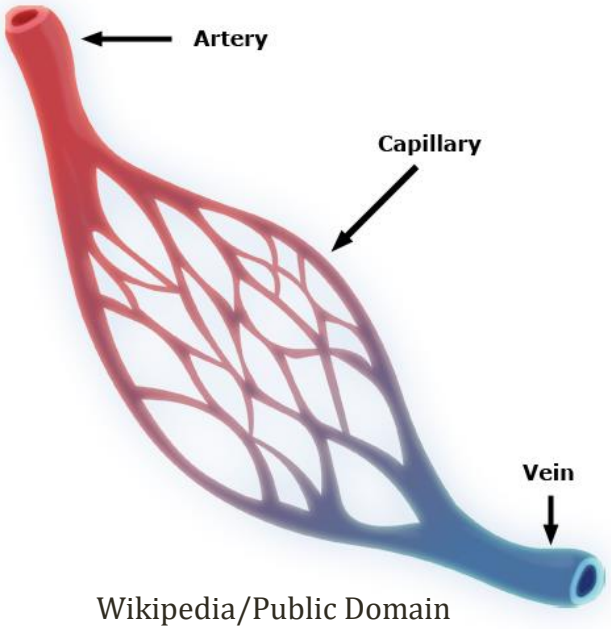
Sturge-Weber Syndrome

Genetics

- Spontaneous mutation in **GNAQ gene**
- Occurs after fertilization (**somatic mutation**)
- **Mosaicism** (some cells normal, some mutated)
- Abnormal **capillary** formation/growth



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Sturge-Weber Syndrome

Port-Wine Stain/Nevus Flammeus

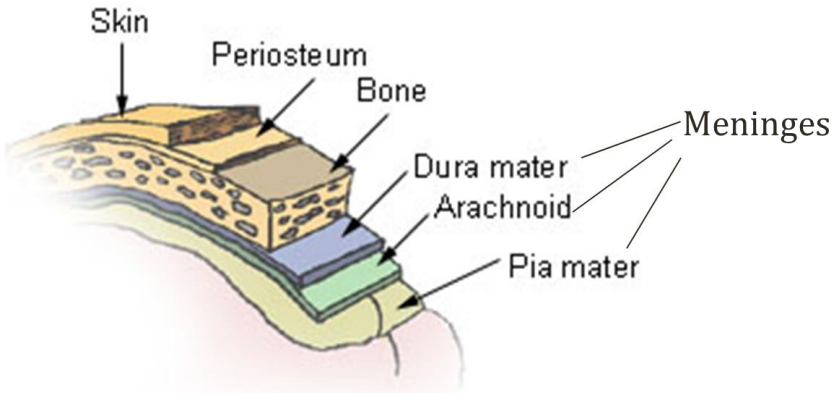
- Malformation of dermal capillaries and venules
- Occurs on face in SWS
- Unilateral
- $1^{st}/2^{nd}$ trigeminal area
- Slow/low blood flow
- Pink/red patches
- Apparent at birth
- Does not regress
- Grows as child grows

Lee Health/Vimeo

Sturge-Weber Syndrome

Leptomeningeal angioma

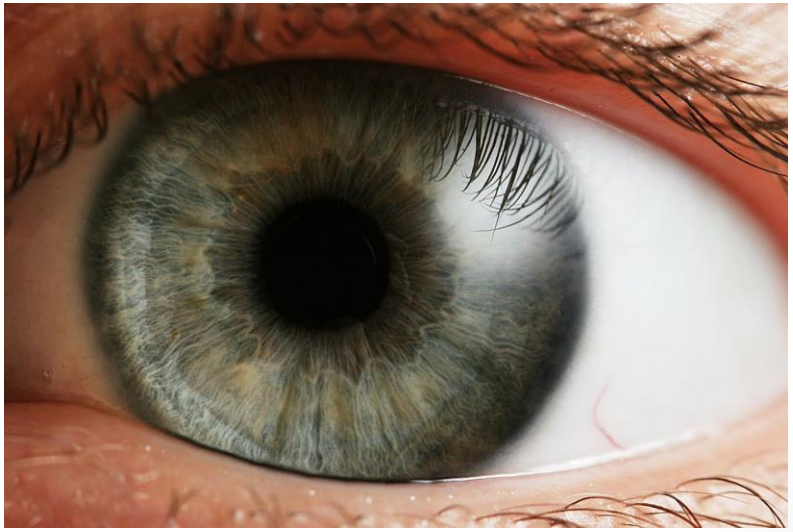
- Leptomeninges: pia mater and arachnoid
- Angioma: capillary-venous malformation
- Occurs on **same side as port-wine stain**
- May cause seizures (80% patients)
  - Often begin first 2 years of life
- May cause hemiparesis, headaches



Sturge-Weber Syndrome

Glaucoma

- In infancy or early adulthood
- Exact mechanism unclear
  - Abnormalities anterior chamber angle
  - Elevated venous pressure in episclera
  - Choroidal hemangiomas
- Causes vision impairment



Petr Novák, Wikipedia

Sturge-Weber Syndrome

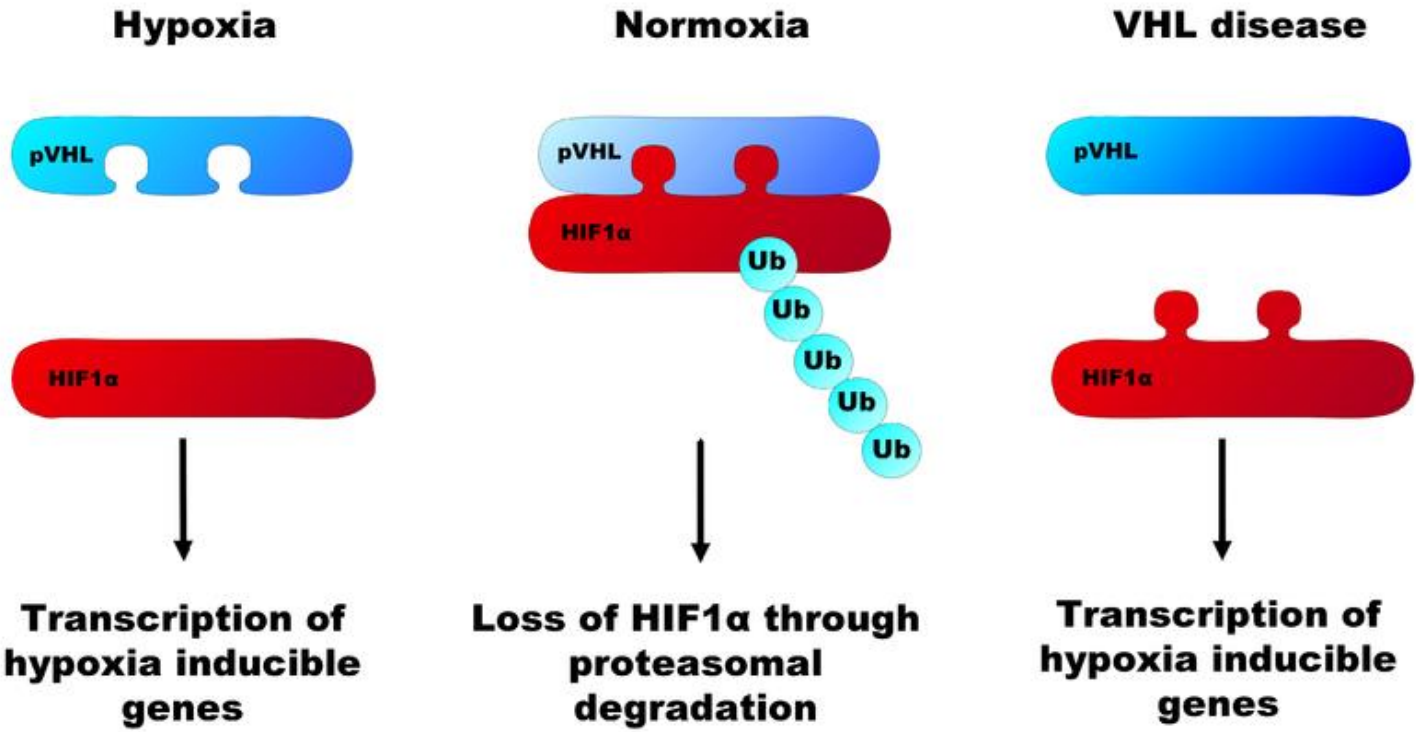
Classic Case

- Newborn with port wine stain
- Seizures
- Glaucoma

von Hippel-Lindau Disease

- Genetic cancer syndrome
- Multiple benign/malignant tumors
- von Hippel-Lindau (*VHL*) gene
  - Chromosome 3
  - Codes for VHL tumor suppressor protein
- **Ubiquitination** of **hypoxia-inducible factor**
  - Post-translational modification
  - Addition of ubiquitin to proteins (small protein)
  - Tags proteins for destruction in proteasome
- Cells behave as if hypoxic → blood vessel growth

von Hippel-Lindau Disease



Simon Caulton/Wikipedia

von Hippel-Lindau Disease

- Multiple **hemangioblastomas**
  - Clumps of capillaries ("angiomatosis")
  - Bright red on gross examination
  - Well-circumscribed, benign
  - No invasion or metastasis
  - Symptoms: compression of other structures, hemorrhage
- Occur in CNS
- Rarely occur sporadically outside VHL
- Classic locations: cerebellum, spinal cord, retina

von Hippel-Lindau Disease

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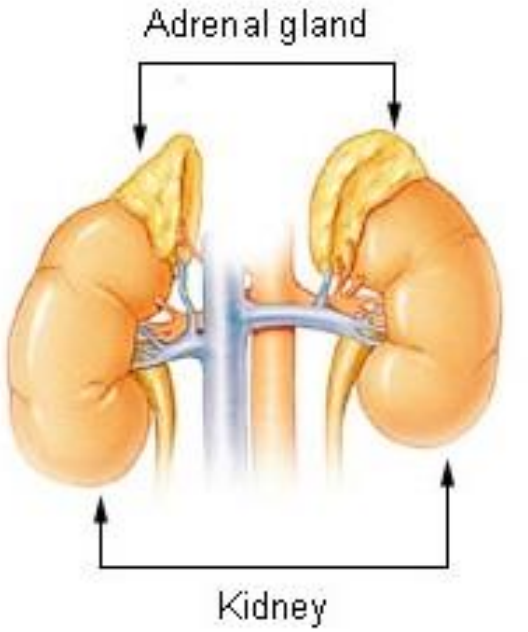
von Hippel-Lindau Disease

- Renal cysts
- Renal cell carcinomas (bilateral)
- Pheochromocytomas



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von Hippel-Lindau Disease

- Requires "two hits"
  - One abnormal gene inherited (germline mutation)
  - Second spontaneous mutation → disease
  - Similar to retinoblastoma, Li-Fraumeni, FAP
  - "Autosomal dominant"
- Onset usually late childhood to young adulthood
  - Takes years for second hit to occur