SKIN
INTRODUCTION

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REVIEW OF SKIN HISTOLOGY

Epidermis

- The most superficial layer of the skin
- 90% of cells are keratinocytes undergoing terminal maturation.
- This involves increased keratin production and migration toward the external surface, (cornification).

Epidermis

- Keratinocytes
- Squamous epithelial cells are normally bound tightly together by cell junctions (desmosomes)
- Produce abundant amounts of keratin protein
- Both serve to create a tough, durable physical barrier.
- In addition, keratinocytes secrete soluble molecules such as cytokines and defensins that augment and regulate cutaneous immune responses

Epidermis

- Non-keratinocyte cells that inhabit the epidermis:
- Melanocytes within the epidermis are responsible for the production of melanin and pigment formation.
- Melanin (brown pigment) absorbs and protects against potentially injurious ultraviolet (UV) radiation in sunlight.
- Darker skin result from increased melanin production, not an increased number of melanocytes.
- Merkel cells are sensory mechanoreceptors.

Skin

- Langerhans cells are antigen-presenting dendritic cells that lie with the epidermis.
- MHC-II expression
- Secrete MIF-1α, IL-12, !L-15
- Migrate from the skin to regional lymph nodes where they present their antigenic cargoes to T lymphocytes

Skin

- T-cells stimulated by dendritic cells in regional lymph nodes express CTLA (cutaneous lymphocyte associated antigen) an adhesion molecule
- Express chemokine receptors such as CCR4 and CCR10
- Home back to the dermis
- Directed in part by chemokines secreted by activated keratinocytes
- CD4+, CD8+, T_{reg} cells present
- Small numbers of B-cells also present
- Skin microbiome also conditions immune response

Table 3-1

Structural and Staining Characteristics of Representative Skin Cells

Cell Type	Location	Characteristic Structure(s)	Immunostain(s)	Histochemical Stain(s)
Keratinocyte	Entire epidermis, adnexae	Tonofilaments, desmosomes	Cytokeratins (CKs) (see sections below)	
Melanocyte	Basal cell layer	Melanosomes	S100, MART-1/ Melan-A, HMB45, MITF, SOX10	Fontana-Masson, DOPA, tyrosinase, sliver nitrate
Langerhans cell	Mid epidermis	Birbeck granules	S100, CD1a, langerin	ATPase
Merkel cell	Basal layer, bulge of hair follicle	Neurosecretory granules	CK20, chromogranin, synaptophysin	Neuron-specific enolase
Fibroblast	Entire dermis	Spindle-shaped with prominent rough endoplasmic reticulum	Vimentin, procollagen, CD34 (no specific markers)	Masson trichrome for collagen
Dermal dendrocyte	Superficial dermis	Elongated dendrites	Factor XIIIa	
Endothelial cell	Vascular plexuses	Weibel–Palade bodies, factor VIII	CD31, CD34	
Mast cell	Perivascular space	Scroll-containing secretory granules	C-kit, tryptase	Giemsa, toluidine blue
Macrophage	Perivascular space	Lysosomes	CD68, CD163	
Eccrine/apocrine gland	Epidermis and dermis	Ducts and secretory coils containing granules	Epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA)	PAS for apocrine gland
Sebaceous gland	Dermis	Lipidized epithelial cells	EMA	
Nerve fiber	Around vessels and adnexae	Neurofilaments	S100, anti-neurofilament antibodies	Bodian, osmium tetroxide

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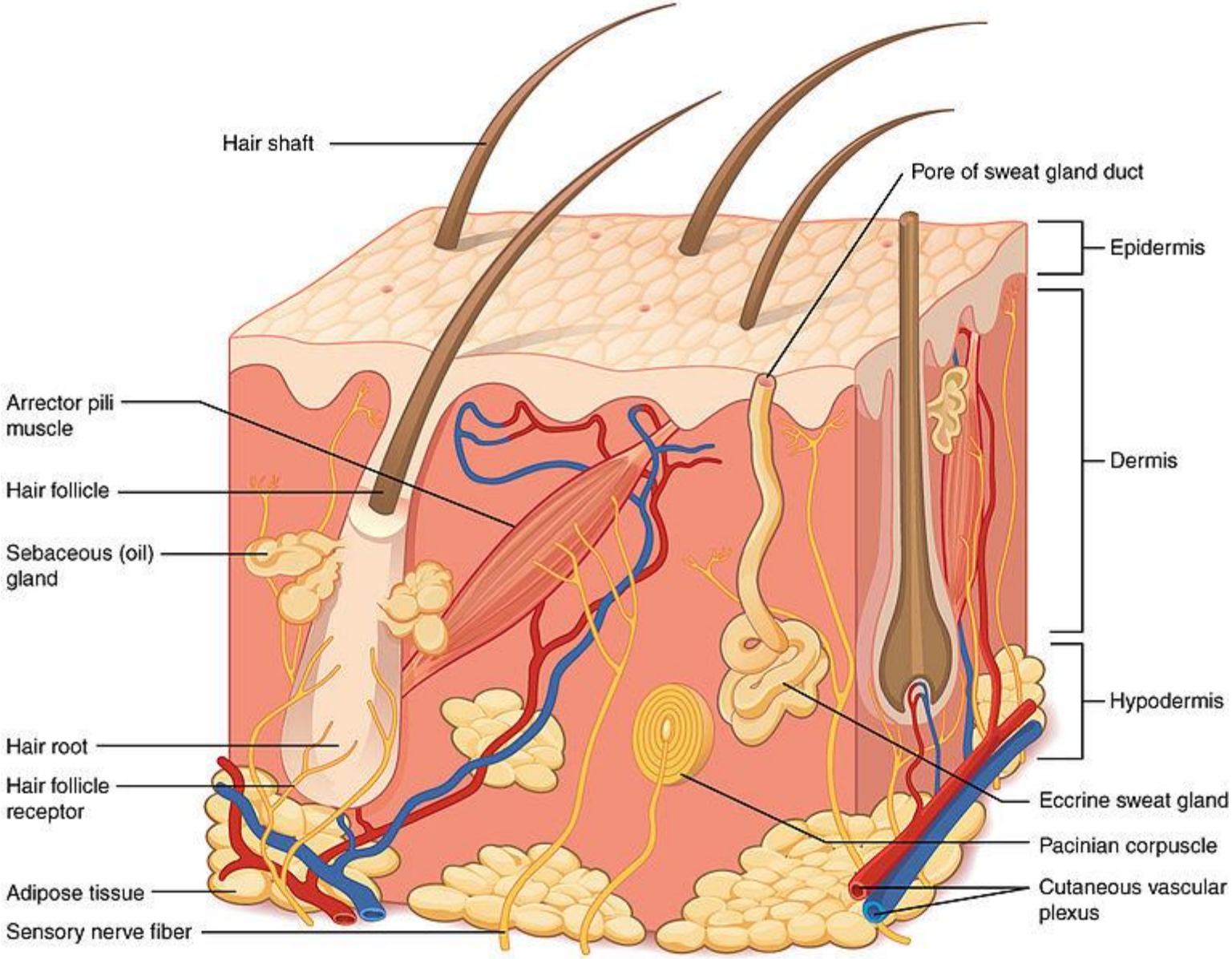

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Levels of epidermis

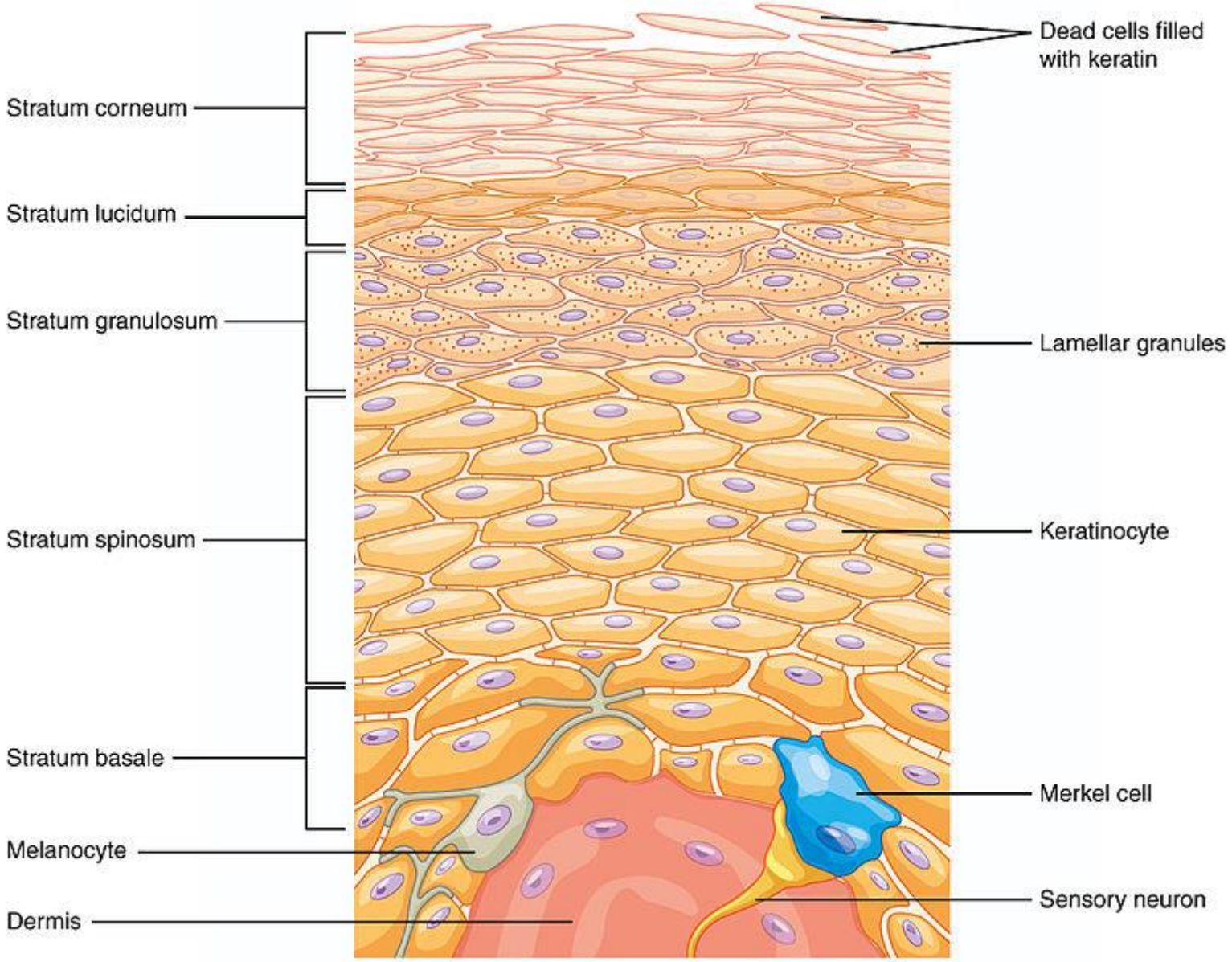
- Stratum basale:
- Actively dividing stem cells along basement membrane
- Mitosis of keratinocytes occurs in this layer.
- Dendritic processes extend between keratinocytes
- Melanocytes found in this layer
- Merkel cells are located in epithelial basal cell layer and may have neuroendocrine or mechanoreceptor functions.
- Stratum spinosum:
- Keratinocytes are joined by tight intercellular junctions (desmosomes).

Levels of epidermis

- Stratum granulosum:
- Cells secrete lamellar bodies and containing lipids and proteins (“waterproofing”)
- Keratohyaline granules present in keratinocytes.
- Histidine and cysteine rich proteinss that bind intermediate keratin filaments
- Stratum lucidum:
- Cells lose nuclei and increase keratin production.

Levels of epidermis

- Stratum corneum:
- Anucleate cells continue to produce keratin.
- A keratinocyte typically takes between 30 – 40 days to travel from the stratum basale to the stratum corneum.



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Epidermis

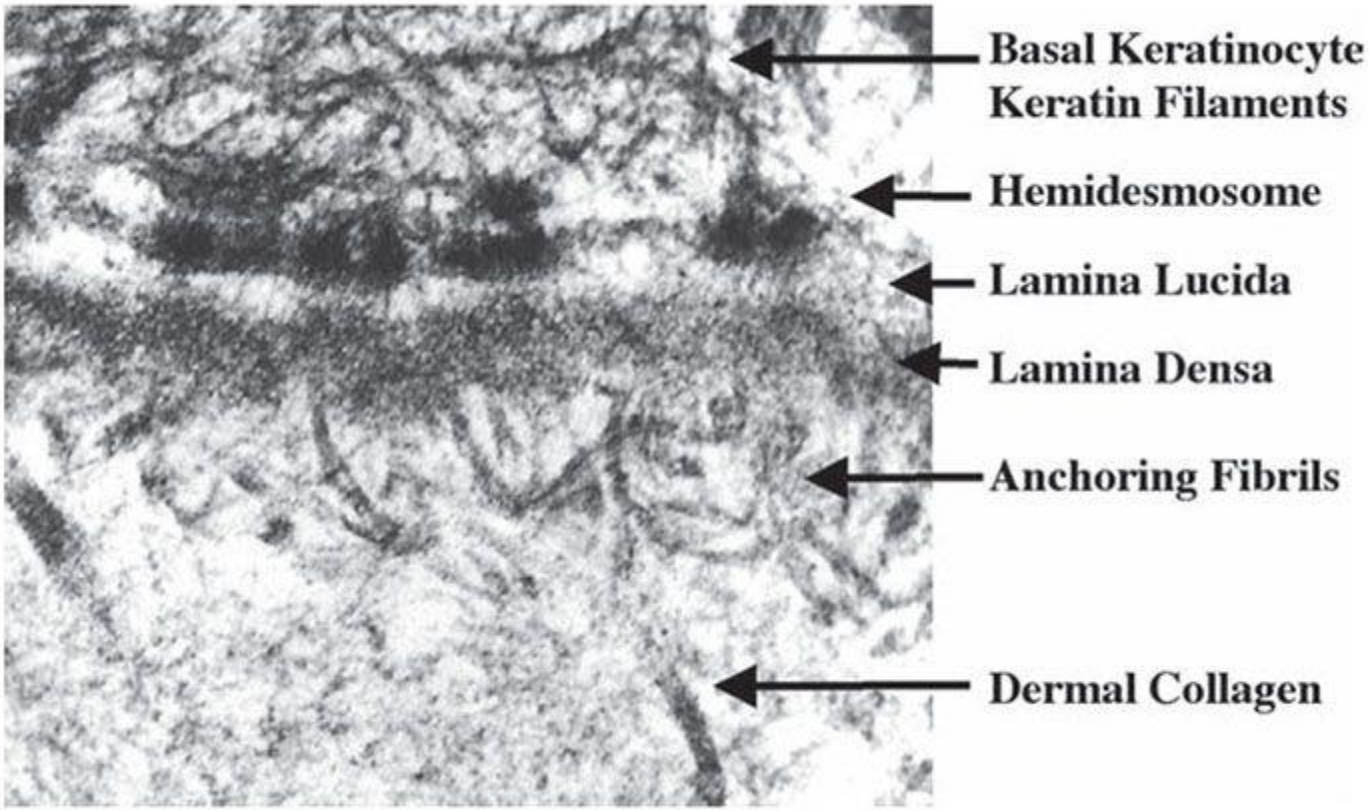
- Architecturally, the epidermal layer has an undulant undersurface in two-dimensional sections
- Downward invaginations (retes)
- The epidermal rete form a honeycomb of interconnected ridges
- Interdigitating mesenchymal cones (dermal papillae).
- Dermal papillae represent rounded conical invaginations not dissimilar to the undersurface of an egg carton.

Basement membrane

- Trilaminar
- The plasma membrane at the undersurface of basal cells shows hemidesmosomes
- Possess only one intracytoplasmic attachment plaque to which tonofilaments from the interior of the basal cell are attached
- Beneath the plasma membrane of the basal cells is a lucent zone (lamina lucida) that separates the plasma membrane from the lamina densa
- The lamina densa itself is anchored to the underlying dermis in part by anchoring fibrils.
- Contains Type VII collagen

Basement membrane

- The anchoring fibrils connect with islet-like anchoring plaques (resembling basement membrane) in the subjacent dermis.
- These anchoring structures are interwoven with the dermal interstitial type I and type III collagen fibers
- Result in the adhesion of the basement membrane to the dermis.
- Elastic fibers consisting of microfibril bundles and individual microfibrils are attached to the undersurface of the lamina densa



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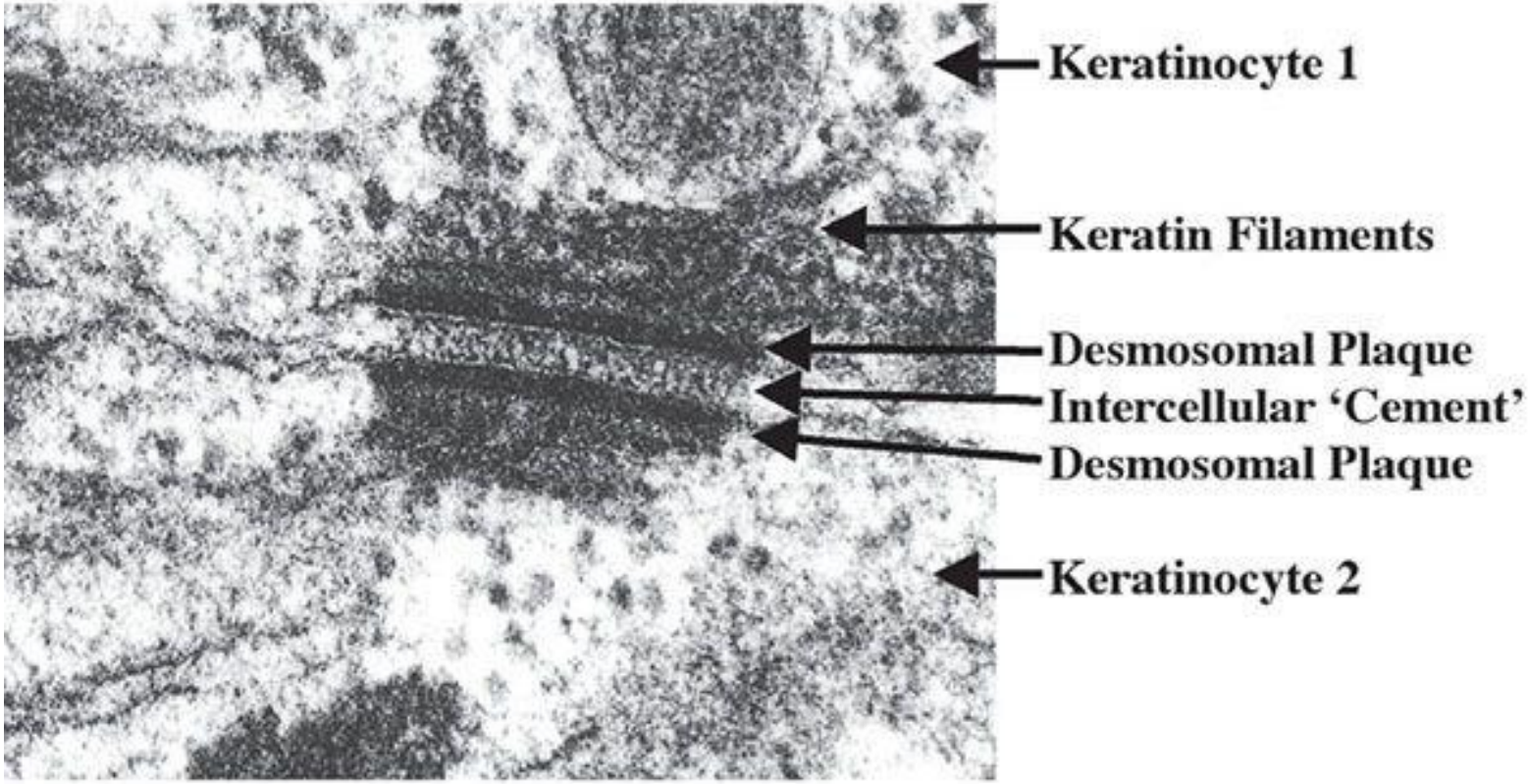

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Dermis

- The dermis is immediately deep to the epidermis and is tightly connected to it through a highly-corrugated dermo-epidermal junction.
- The dermis has only two layers, which are less clearly defined than the layers of the epidermis.
- Papillary dermis is characterized by loose connective tissue beneath epidermis
- Reticular dermis is characterized by dense connective tissue in deeper dermis

Dermis

- Fibroblasts synthesize the extracellular matrix, which is predominantly composed of collagen and elastin.
- Mast cells are histamine granule-containing cells of the innate immune system.
- Langhan's cells
- Blood vessels
- Cutaneous sensory nerves and neural end organs are responsible for physical sensations that run that gamut from pleasurable to painful, including touch, vibration, itchiness, cold, and heat.

Skin appendages

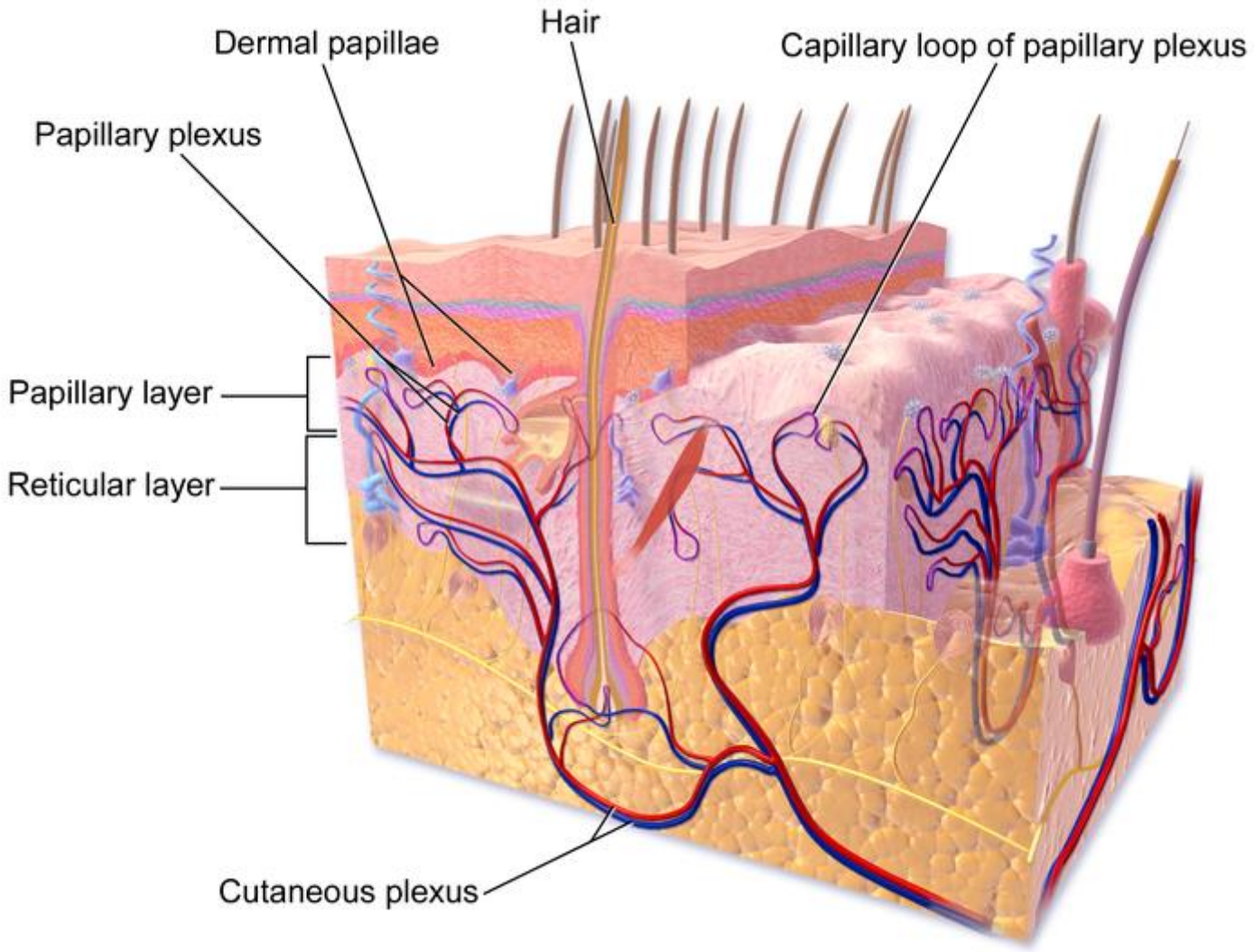
- Hair follicles, nails, sebaceous and sweat glands are derived from the epidermis and descend into the dermis during development.
- There are two main types of sweat glands:
- Eccrine glands are the major sweat glands of the human body.
- They release a clear fluid, comprised chiefly of sodium chloride and water.
- Involved in thermoregulation.
- Cholinergic innervation

Skin appendages

- Apocrine glands are larger sweat glands
- Located in the axillary and genital regions.
- Secrete an oily substance containing pheromones.
- Can be broken down by cutaneous microbes (especially, Corynebacterium) producing body odor.
- Sympathetic innervation

Skin appendages

- Hair follicles and sebaceous glands combine to form a pilosebaceous unit
- Only found on hirsute skin.
- Sebaceous glands secrete via a holocrine mechanism into the hair follicle shaft.
- The hair follicle itself is associated with an arrector pili muscle, which contracts to cause the follicle to stand upright.
- Hair follicles contain niches harboring epithelial stem cells capable of regenerating superficial epithelial skin structures.



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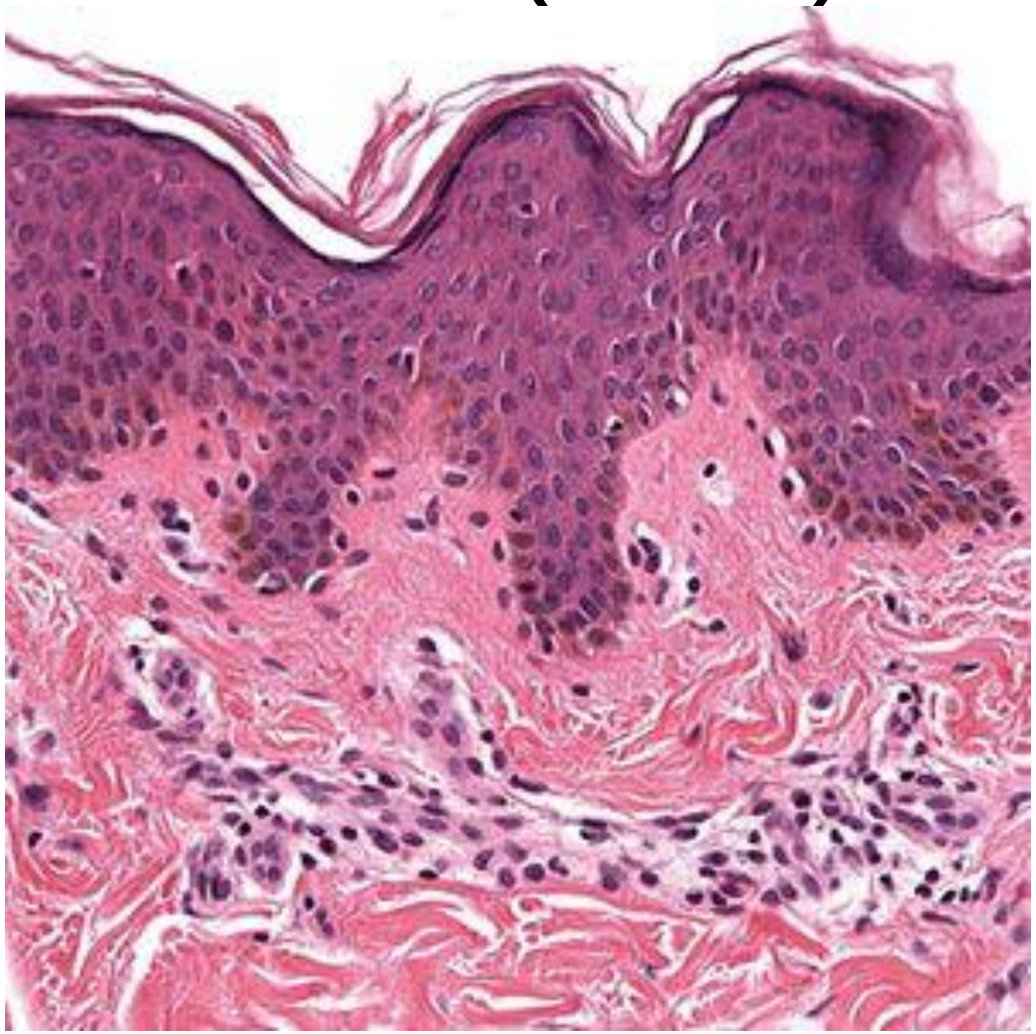
Skin (adult)



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NOMENCLATURE

Table 25-1 Nomenclature of Skin Lesions

Macroscopic Lesions	Definition
Excoriation	Traumatic lesion breaking the epidermis and causing a raw linear area (i.e., deep scratch); often self-induced
Lichenification	Thickened, rough skin (similar to a lichen on a rock); usually the result of repeated rubbing
Macule, Patch	Circumscribed, flat lesion distinguished from surrounding skin by color. Macules are 5 mm in diameter or less, patches are greater than 5 mm.
Onycholysis	Separation of nail plate from nail bed
Papule, Nodule	Elevated dome-shaped or flat-topped lesion. Papules are 5 mm or less across, while nodules are greater than 5 mm in size.
Plaque	Elevated flat-topped lesion, usually greater than 5 mm across (may be caused by coalescent papules)
Pustule	Discrete, pus-filled, raised lesion
Scale	Dry, horny, platelike excrescence; usually the result of imperfect cornification
Vesicle, Bulla, Blister	Fluid-filled raised lesion 5 mm or less across (vesicle) or greater than 5 mm across (bulla). Blister is the common term for either.
Wheal	Itchy, transient, elevated lesion with variable blanching and erythema formed as the result of dermal edema
Microscopic Lesions	**Definition**
Acanthosis	Diffuse epidermal hyperplasia
Dyskeratosis	Abnormal, premature keratinization within cells below the stratum granulosum
Erosion	Discontinuity of the skin showing incomplete loss of the epidermis
Exocytosis	Infiltration of the epidermis by inflammatory cells
Hydropic swelling (ballooning)	Intracellular edema of keratinocytes, often seen in viral infections
Hypergranulosis	Hyperplasia of the stratum granulosum, often due to intense rubbing
Hyperkeratosis	Thickening of the stratum corneum, often associated with a qualitative abnormality of the keratin
Lentiginous	A linear pattern of melanocyte proliferation within the epidermal basal cell layer
Papillomatosis	Surface elevation caused by hyperplasia and enlargement of contiguous dermal papillae
Parakeratosis	Keratinization with retained nuclei in the stratum corneum. On mucous membranes, parakeratosis is normal.
Spongiosis	Intercellular edema of the epidermis
Ulceration	Discontinuity of the skin showing complete loss of the epidermis revealing dermis or subcutis
Vacuolization	Formation of vacuoles within or adjacent to cells; often refers to basal cell-basement membrane zone area

DIAGNOSTIC CLUES

Diagnostic clues

- Pruritis is common in:
- Obstructive biliary disease
- Uremia
- Polycythemia vera (after a warm shower or bath).
- Scabies (mite)
- Atopic dermatitis
- Contact dermatitis (red, weepy skin)
- Lichen planus.
- Psoriasis

Lesion distribution

- Dermatomal/zosteriform:
- Unilateral and lying in the distribution of a single spinal afferent nerve root
- Herpes zoster.
- Blaschkoid:
- Following lines of skin cell migration during embryogenesis
- Generally longitudinally oriented on the limbs and circumferential on the trunk, but not perfectly linear; implies a mosaic disorder
- Incontinentia pigmenti or inflammatory linear verrucous epidermal nevus as examples

Lesion distribution

- Lymphangitic:
- Lying along the distribution of a lymph vessel; implies an infectious agent that is spreading centrally from an acral site, usually a red streak along a limb
- Staphylococcal or streptococcal cellulitis

Lesion distribution

- Sun exposed:
- Occurring in areas usually not covered by clothing, namely the face, dorsal hands, and a triangular area corresponding to the opening of a V-neck shirt on the upper chest
- Examples:
- Photodermatitis
- Subacute cutaneous lupus erythematosus
- Polymorphous light eruption
- Squamous cell carcinoma.

Lesion distribution

- Sun protected:
- Occurring in areas usually covered by one or more layers of clothing
- Usually a dermatosis that is improved by sun exposure
- Parapsoriasis or mycosis fungoides as examples
- Acral:
- Occurring in distal locations, such as on the hands, feet, wrists, and ankles
- Palmo-plantar pustulosis as an example

Lesion distribution

- Truncal:
- Occurring on the trunk or central body.
- Extensor
- Occurring over the dorsal extremities, overlying the extensor muscles, knees, or elbows
- Psoriasis as an example
- Flexor:
- Overlying the flexor muscles of the extremities, the antecubital and popliteal fossae
- Atopic dermatitis as an example

Lesion distribution

- Intertriginous:
- Occurring in the skin folds, where two skin surfaces are in contact, namely the axillae, inguinal folds, inner thighs, infra-mammary skin, and under an abdominal pannus;
- Often related to moisture and heat generated in these areas
- Candidiasis as an example
- Localized:
- Confined to a single body location
- Such as cellulitis

Lesion distribution

- A generalized eruption consisting of inflammatory (red) lesions is called an exanthema (rash).
- A macular exanthema consists of small circumscribed skin lesions (macules)
- Drug or other allergic reaction as examples
- A papular exanthema consists of small circumscribed raised white skin lesions (papules)
- Contact dermatitis or fungal infection as examples
- A vesicular exanthema consists of vesicles
- Viral exanthem
- Drug eruption

Lesion distribution

- Bilateral symmetric distribution occurs with mirror-image symmetry on both sides of the body
- Vitiligo
- Plaque-type psoriasis
- Universal: involving the entire cutaneous surface
- Erythroderma
- Alopecia totalis (total hair loss)