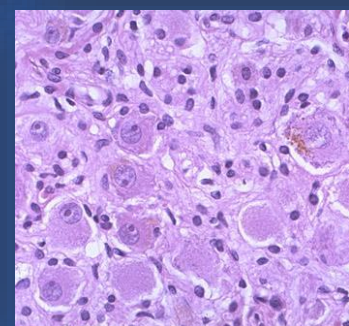
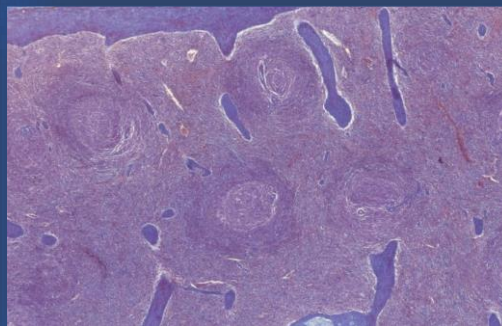
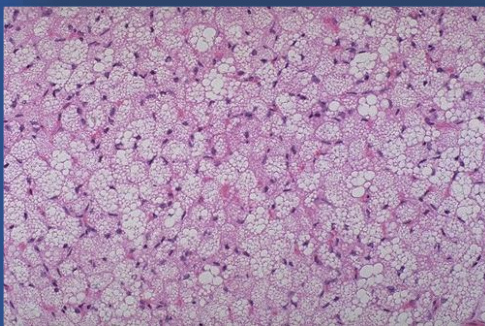
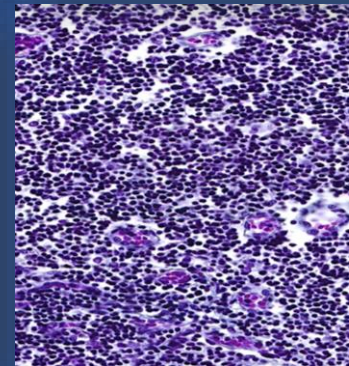
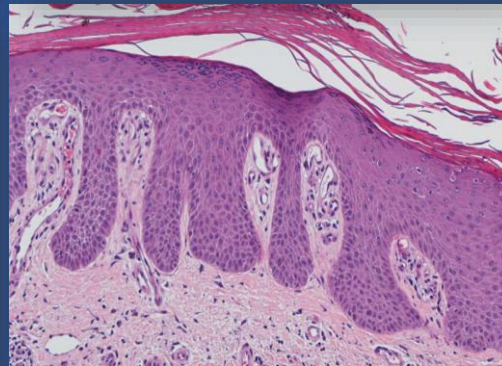
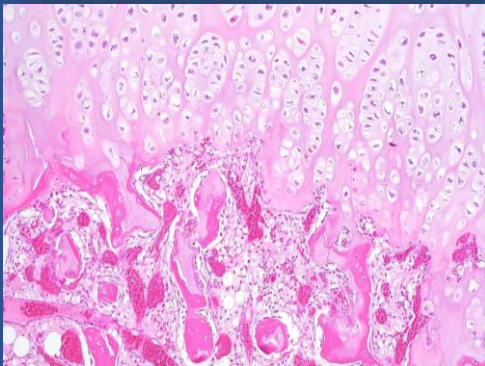
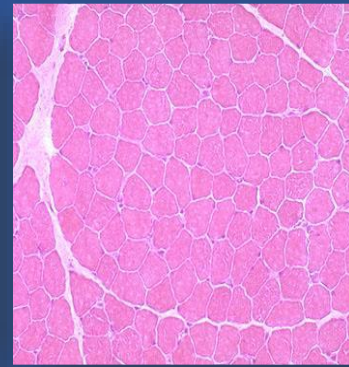
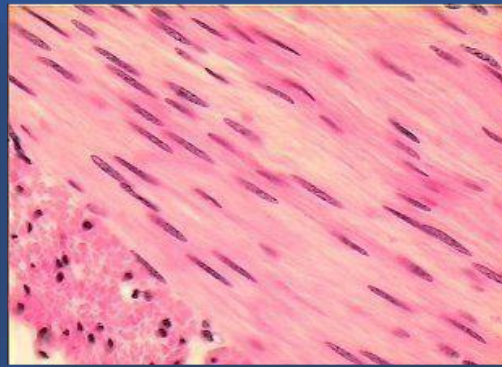
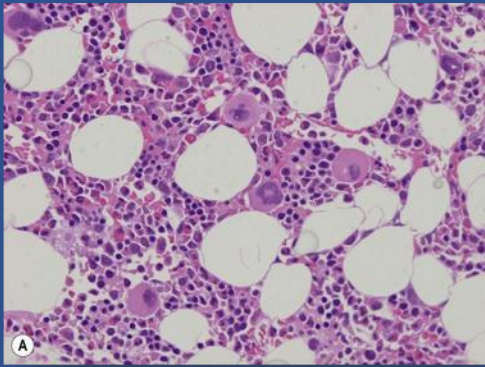


Briefly Texts Color Atlas of **Histology**

Organ-Systems with Self-Assessment Sections
and Color Photomicrographs



Vinida Bundit, M.D., Ph.D

Department of Anatomy,
Faculty of Medicine
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Briefly Texts Color Atlas of Histology Organ-Systems with Self-Assessment Sections and Color Photomicrographs

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Preface

Upon my retirement, I would like to share my knowledge and experience on Histology which I have lectured my second year medical students in the department of Anatomy, Faculty of medicine, Chulalongkorn University for more than 30 years. This is my second English edition that I have edited for my medical students without getting any profit.

This E-book on Histology in organ-systems has 11 chapters. Its' contents consist of briefly reviewing on texts, more than 500 full-colored oversized photomicrographs for use in the histology laboratory including self-assessment section for each chapter (10 items) for identification of tissues and organs with answers afterwards.

I always welcome comments, suggestions and constructive criticism of this E-book. These may be addressed at Department of Anatomy, Faculty of medicine, Chulalongkorn University .

Finally, I would like to thank Department of Anatomy, Faculty of medicine, Chulalongkorn University for extending my retirement more than 10 years. Therefore, it has given me the excellent chance to create this second book for my second year medical students. For format in setting word and index, I would like to thank my teaching assistance of department of Anatomy, Faculty of medicine in the year of 2561-2562.

They are: Prem Wangchareon, MD.

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CHAPTER I : INTEGUMENTARY SYSTEM

The skin, or integumentary, is the largest organ of the body and consists of two main layers: (1) the **epidermis**, composed of stratified squamous epithelium that is keratinized, and (2) the **dermis**, composed of connective tissue. Under the dermis is a layer of loose connective tissue called the **hypodermis**, which is also referred to as the subcutaneous tissue or, by gross anatomists, as the superficial fascia. The hypodermis contains large amounts of adipose tissue, which are contributed to thermal insulation and storage of metabolic energy and act as a shock absorber.

The epidermis gives rise to nails, hair follicles (producing hairs), sebaceous glands, and sweat glands, also known as **skin appendages**. On the palms of the hands, and soles of the feet, the epidermis has an outer keratinized layer that is thicker than that over the other parts of the body. Therefore, skin is classified into two types, i.e., (1) **thick skin**, i.e., palm and sole, and (2) **thin skin**, i.e., scalp, eyelids, abdominal skin, etc.

There are neither hairs nor sebaceous glands in thick skin. The interface between the epidermis and the dermis is more complex in thick skin than thin skin. The fingerlike projections of the dermis into the base of the epidermis, **the dermal papillae**, are much longer and more closely spaced in thick skin. This provides greater resistance to frictional force acting on skin. The dermal papillae are complemented what appear to be similar epidermal protrusions, called **epidermal ridges** or **rete ridges**.

The skin has several functions:

1. Protection from injury: mechanical function.
2. As a water barrier to prevent dehydration.
3. Regulation of body temperature: conservation and dissipation of heat.
4. Nonspecific defense: barrier to microorganisms and housing of immunocompetent dendritic cells.
5. Excretion of salts
6. Synthesis of vitamin D.
7. As a sensory organ.
8. Sexual signaling.

The **epidermis** consists of four different cell types:

- (1) **Keratinocytes** (ectodermal-derived cells), are the predominant cell type, so called because its major product is keratin, an intermediate filament protein.
- (2) **Melanocytes** (neural crest-derived cells), are responsible for the production of melanin. The cell body is located in the stratum basale. Melanocytes and keratinocytes are not associated to each other by desmosomes.
- (3) **Langerhans cells** (bone marrow-derived dendritic cells): are found in the stratum Malpighi. Their cytoplasmic processes are associated with keratinocytes through E-cadherin. Langerhans cell is a peripheral dendritic cell of the immune system. It migrates to a local lymph node to present antigens to T cells to initiate responses against foreign antigens. The nucleus of a Langerhans cell is indented, and the cytoplasm contains characteristic tennis racket-shape inclusions (Birbeck granules) associated with the protein langerin.

- (4) **Merkel cells** (neural crest-derived cells), are tactile mechanoreceptors but may also have a neuroendocrine function. They are associated with the basal lamina. The cytoplasm contains granules. A small nerve plate is connected to myelinated axon.

Keratinocytes are distributed in five strata or layers:

- (1) Stratum basale (basal cell layer): presence of mitotically active cells, the stem cells of the epidermis, hemidesmosomes, and desmosomes.
- (2) Stratum spinosum (spinous or pickle cell layer): desmosomes, first appearing lamella bodies, keratin, etc.
- (3) Stratum granulosum (granular cell layer): keratohyalin granules and discharging lamellar bodies, contributing to formation of the water barrier of the epidermis and tight junctions.
- (4) Stratum lucidum (clear cell layer), predominantly in thick skin
- (5) Stratum corneum (cornified cell layer).

Stratum Malpighi is the combination of stratum basale and stratum spinosum. Keratinocytes are associated with each other by **desmosome**, but basal cells are attached the basal lamina with **hemidesmosomes**. The molecular and structural components of the hemidesmosome are of considerable importance for understanding the cause of *blistering diseases* of the skin.

Skin blistering diseases: **Bullous pemphigoid** is an autoimmune blistering disease similar to pemphigus vulgaris (called 'pemphigoid', similar to pemphigus). Blisters or bullae develop at the *epidermis-dermis junction* when circulating IgG cross-reacts with bullous pemphigoid antigen 1 or 2. IgG-antigen complexes lead to the formation of complement complexes (C3, C5b, and C9), which damage the attachment of *hemidesmosomes* and perturb the synthesis of anchoring proteins by basal cells. The product of local toxins causes the degranulation of mast cells and release of chemotactic factors attracting eosinophils. Enzymes released by eosinophils cause *blister or bullae*.

The differentiation of keratinocytes is characterized by:

- (1) The expression of specific keratin pairs in each layer:
keratins 5 & 14 in the stratum basale; keratins 1 & 10 in the stratum spinosum, and keratins 2e & 9 in the stratum granulosum.
- (2) The presence in the stratum graulosum of lamellar bodies, containing the glycolipid acetylglucosylceramide extruded into the extracellular space to form a multi-lamellar lipid layer, and keratohyalin granules.
- (3) The presence in the stratum corneum of cornified cell envelope, an involucrin-small proline-rich-loricrin protein complex associated with keratin-filaggrin aggregates inside the cell. The extracellular multi-lamellar lipid layer is anchored to involucrin.
- (4) The presence of desmosomes and tight junctions (containing claudin-1 and claudin-4, are found in the stratum graulosum).

Components of the epidermal permeability barrier

1. Multi-lamellar lipid layer linked to involucrin
2. Cornified cell envelop is a specialized structure that reinforces the plasma membrane of keratinocytes at the desmosome plaque sites.
3. Keratin-filaggrin complex
4. Tight junctions in the stratum granulosum

Wound healing. Skin is repaired rapidly to maintain an efficient protect barrier. Wound healing consists of four stages:

- (1) Formation of a fibrin-platelet clot at the site of injury.
- (2) Recruitment of leukocytes to protect the site from infection. Keratinocytes and endothelial cells express *cytokine CXC* (cysteine-x-cysteine) and its receptor to recruit leukocytes. Monocytes recruited to the injury site become macrophages.
- (3) Neovascularization and cellular proliferation. *Granulation tissue*, rich in blood capillaries, is seen.
- (4) Tissue remodeling. Keratinocytes express plasminogen activator to convert plasminogen within the fibrin clot into *plasmin*. Plasmin and matrix metalloproteinases (produced by fibroblasts in the dermis) free basal keratinocytes from their basal lamina anchorage site and re-epithelization starts.

Epidermal growth factor and keratinocyte growth factor stimulate re-epithelization. Fibroblasts in the dermis, stimulated by platelet-derived growth factor (PDGF) and transforming growth factor- β , start to proliferate. A number of fibroblasts change into *myofibroblasts*, and contraction of the dermis occurs (healing with scar).

- The **dermis** consists of two layers:
 - (1) The **papillary layer** is the loose connective tissue with collagen bundles and thin elastic fibers.
 - (2) The **reticular layer** is dense irregular connective tissue with collagen bundles and thick elastic fibers.

There are three interconnected blood vessel plexuses in the dermis.

- (1) The subpapillary plexus is located along the papillary layer.
- (2) The cutaneous plexus is located at the papillary-reticular layer interface.
- (3) The hypodermis or subcutaneous plexus is located in the hypodermis.

The primary function of the vascular network is *thermoregulation*; the secondary function is nutrition of the skin and appendages.

Arteriovenous anastomoses (shunts) between arterial and venous circulation bypass the capillary network. They are common in the reticular and hypodermic region of the extremities (hands, feet, ears, lips, nose) and play a role in *thermoregulation* of the body

- Sensory receptors of skin are specialized neurons and epithelial-like cells that receive and convert a physical stimulus into an electrical signal transmitted to the central nervous system.

There are seven mechanoreceptors in skin.

Sensory receptor	functions	Location
1.Meissner (tactile) corpuscle	Encapsulated tactile in the dermal papilla	In fingers of hand and foot, lips, and tongue.
2.Merkel disk	Neural crest-derived cell located in the basal layer of the epidermis, Non-encapsulated high-resolution tactile receptor.	In fingertips and lips.
3.Ruffini end organ or bulbous corpuscle	Responds to stretching and also to warmth, in the deep dermis.	Detects skin stretch and deformations within joints.
4.Pacinian corpuscle	Sensitive to pressure , in hypodermis and deep fascia.	In the bone periosteum, joint capsules, pancreas, breast, and genitals.
5.Free nerve endings	Lack myelin or Schwann cells, respond to pain and temperature .	In epidermis and corneal epithelium.
6. Peritrichial nerve ending	The myelinated portions of nerve ending form a palisade of naked terminals along external sooth sheath of the hair follicle, surrounded by circumferential terminals. stimulated when the hairs movement .	Nerve fibers wrapped around the base of hair follicle just under the sebaceous glands.
7.Krause end bulb	Encapsulated thermo-receptor; it detects cold .	In the eyes, the mucous of the lips and tongue, and the epineurium.

There are only **four** primary mechanoreceptors in human skin: (1) Merkel disk, (2) Meissner corpuscle, (3) Ruffini ending, (4) Pacinian corpuscle. The first two receptors are located at the epidermal-dermal junction; the other two are located in deep dermis and hypodermis.

- **Skin appendages**

1. **Hairs**

Hair follicles are tubular invaginations of the epidermis responsible for the growth of the hair. They are constantly cycle between:

- (1) Growth (anagen) phase
- (2) Regression (catagen) phase
- (3) Resting (telogen) phase

Each hair follicle consists of two parts:

- (1) The hair shaft, which includes the medulla, cortex, and cuticle, the latter associated with the internal root sheath.

The hair shaft is surrounded by:

- i. The external root sheath, a downgrowth of the epidermis.
- ii. The internal root sheath, generated by the hair bulb (the hair matrix cells) is made up of three layers of soft keratin.

- (2) The hair bulb, the expanded end portion of the invaginated hair follicle. A vascularized connective tissue core (dermal papilla) project into the hair bulb, in close proximity to matrix cells.

The hair follicle is surrounded by connective tissue (associated with the external root sheath, a down-growth of the epidermis). The dermal extends into the hair bulb.

Hair is generated from the base of the hair bulb which has two layers: the matrix zone, where all mitotic activity occurs, and the keratogenous zone, where hair cells undergo keratinization.

Zone of dividing cells of the hair matrix is comparable to the stratum basale of the epidermis. It contains melanocytes that give color to the hair by passing melanin to matrix cells.

Two structures are associated with the hair follicle:

- (1) The arrector pili muscle, originating from the external root sheath of the hair follicle to the epidermis. The autonomic nervous system controls the arrector pili muscle, which contracts during fear, strong emotions, and cold temperature. The hair stands up and the attachment site of the smooth muscle bundle at the epidermis forms a small groove, also called goose flesh.
- (2) The sebaceous glands, with their excretory ducts connected to the lumen of the hair follicle.

Migratory pathways of bulge stem cells of the skin

Bulge stem cells is located at the external root sheath of the hair follicle can follow independent cell migration pathways:

- (1) In the *bulge stem cell-epidermis* pathway, bulge stem cells migrate upward into the inter-follicular dermis along the basal lamina. Bulge stem cells proliferate within the stratum basale and differentiated vertically into the keratin-rich cells of the stratum corneum.
- (2) In the *bulge stem cell-sebaceous gland* pathway, bulge stem cells respond to morphogenetic signals to generate sebaceous glands.

(3) In the bulge *stem cell-hair* pathway, bulge stem cells migrate downward and give rise to a population of matrix cells located at the apex of the dermal papilla. These cells are responsible for producing new hair.

2. Glands of the skin:

(1) **Sebaceous gland:** It is a holocrine and simple saccular gland extending over the entire skin except for palms and soles. Their short ducts, lined by a stratified squamous epithelium continuous with the external root sheath of the hair, open into the hair canal. The sebaceous gland consists of two cell types.

- i. Basal cells divide by mitosis and accumulate lipids as they move into the central part of the acinus, i.e., they generate sebum-producing cells lost during the holocrine secretory process.
- ii. Sebum-secreting cells on top of the basal cells begin to store the oily secretion within cytoplasmic droplets.

Sebum is oily secretion of sebaceous cells. In addition, sebaceous glands produce **cathelicidin**, and human **β -defensins**, endogenous AMPs that enhance the aqueous-lipid protective barrier of the epidermal surface.

(2) **Sweat glands:** There are two types, i.e., Eccrine sweat glands, and Apocrine sweat glands. These two types release their secretion by a merocrine process, except the mammary gland.

i. **Eccrine sweat glands** are simple coiled tubular glands. The primary function is control of body temperature. They are distributed over the entire body surface except for the lips and part of the external genitalia, and are innervated by cholinergic nerves. The secretory portions of the eccrine sweat gland consist of three cell types:

1. Basal clear cells, separated from each other by *intercellular canaliculi*. Mitochondria and basal infoldings in clear cells are typically found in cells in fluid and electrolyte transport.
2. Apical dark cells, secrete glycoproteins, including AMPs human β -defensins, cathelicidin, and dermicidin.
3. Myoepithelial cells, whose contractile activity assists in the release of secretion into the glandular lumen. They are located between the basal lamina and the basal domain of clear cells

The excretory portion is lined by stratified cuboidal epithelium and opens into the epidermis.

ii. **Apocrine sweat glands** are coiled and occur in the axilla, areola, and nipple of the mammary gland, mons pubis, and circumanal area. They contain secretory acini larger than those in the eccrine sweat glands. The secretory cells are higher cuboid cells, and associated with myoepithelial cells at their basal surface, as cuboidal cells in the eccrine sweat glands. The excretory duct opens into the canal of the hair follicle. Apocrine sweat glands are functional after puberty and are supplied by adrenergic nerves.

Two special examples of apocrine sweat glands are the ceruminous glands in the external auditory meatus and the glands of Moll of the margins of the eyelids.

(3)**Mammary glands** (see in the chapter female reproductive system). The mammary gland is a branched (compound) organ with lactiferous ducts and tubule-alveolar secretory units forming a lobule in lactating gland. It secretes milk lipids by *apocrine secretion* and milk protein casein by *merocrine secretion*.

3. Fingernail:

The nails are hard **keratin plates** covering the **nail bed**, the surface of the skin consisting of the stratum malpighii.

- (1) Nail plates are formed by scales of cornified epithelial cells. The proximal edge of the plate is the **root or matrix** of the nail, where the whitish crescent-shaped **lunula** is located.
- (2) The **hyponychium** is the union between the nail bed and the nail plate at the fingertip. It is the stratum corneum of the epidermis and functions to render the nail bed impermeable for protection purposes. If this structure is disrupted, fungal invasion produces *onychomycosis*.
- (3) The proximal edge of the plate is covered by the **eponychium**, a projection of the stratum corneum of the skin.

KEYWORDS: Epidermis, Dermis, Hypodermis, Stratified squamous epithelium of epidermis, Stratum basale, Stratum corneum, Stratum germinativum, stratum granulosum, Stratum lucidum, Stratum Malpighi, Keratinocytes, Melanocytes, Langerhan's cells, Merkel's cells, Skin appendages, Hair follicles, Bulge stem cells of skin, Apocrine sweat glands, Eccrine sweat glands, Sebaceous glands, Nail, Dermal papilla, Epidermal ridges, Arrector pili muscle, Nail plate, Nail bed, Hyponychium, Eponychium, Desmosomes, Hemidesmosomes, Sensory receptors of skin.

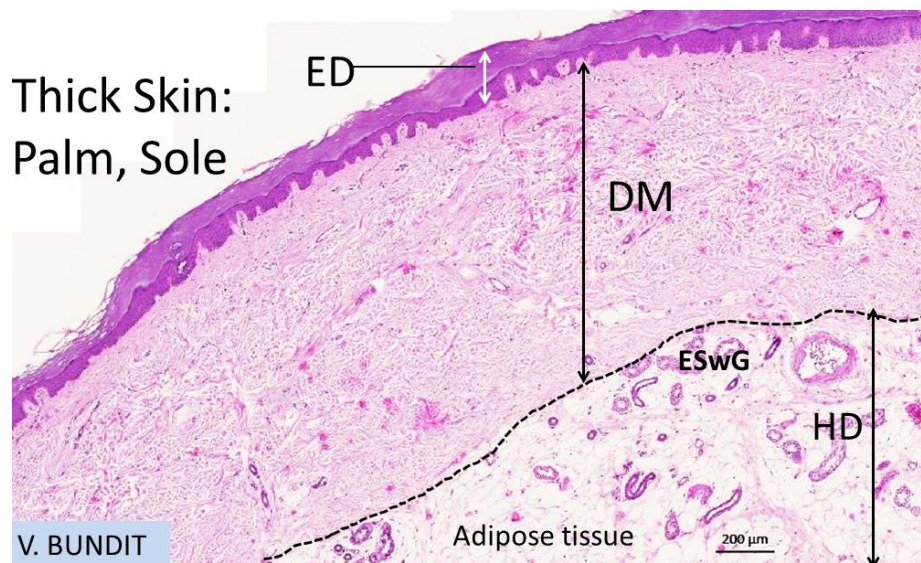


Figure 1-1: Photomicrograph of the thick skin (palm and sole). The epidermis (ED) is at the top, the remainder of the field consists of dermis (DM) and hypodermis (HD). ESeG = Eccrine sweat glands are found in both DM and HD. There is no hair follicle nor a sebaceous gland in the thick skin. Thick skin has much thicker epidermal layer, subjected to the most abrasion than skin in any other location.

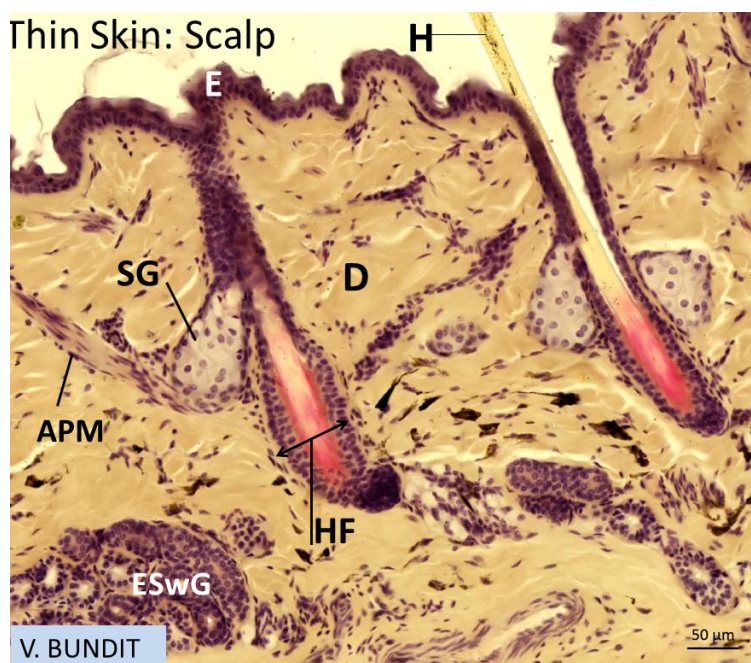


Figure 1-2: Photomicrograph of the thin skin (scalp). APM = Arrector Pili Muscle, D = Dermis, E = Epidermis, ESwg = Eccrine Sweat Gland, H = Hair shaft, HF = Hair Follicle, SG = Sebaceous Gland. The thin skin contains hair follicles, sebaceous glands, and eccrine sweat glands, etc. There is a thin keratin in the epidermis.

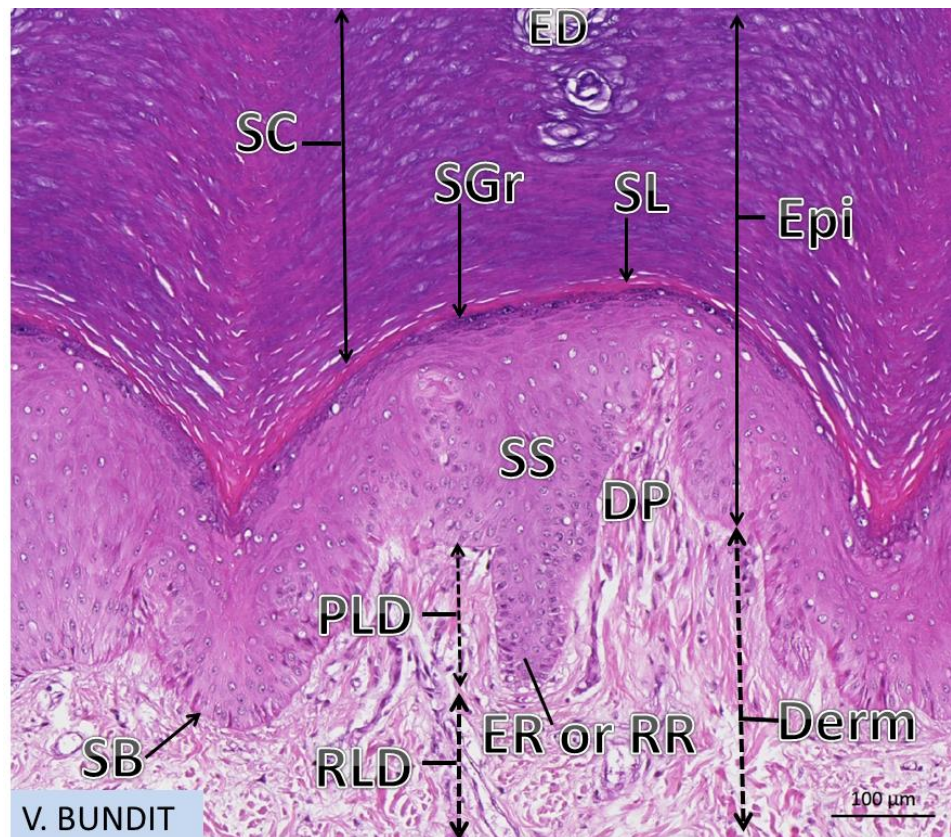


Figure1-3: Photomicrograph of the layers of thick skin. The skin of sole shows epidermis (Epi) containing the extremely thick stratum corneum (SC). Remaining layers are the stratum lucidum (SL, not seen in the thin skin), the stratum Granulosum (SGr), the stratum Spinosum (SS), and the stratum Basale (SB), respectively. The epidermal duct (ED) of the sweat gland is seen on the top. Dermis (Derm) contains the dermal papillae (DP), protrusions of connective tissue that lie between the interpapillary pegs. The dermis consists of the papillary layer (PLD, loose connective tissue) and the reticular layer (RLD, dense irregularly connective tissue).

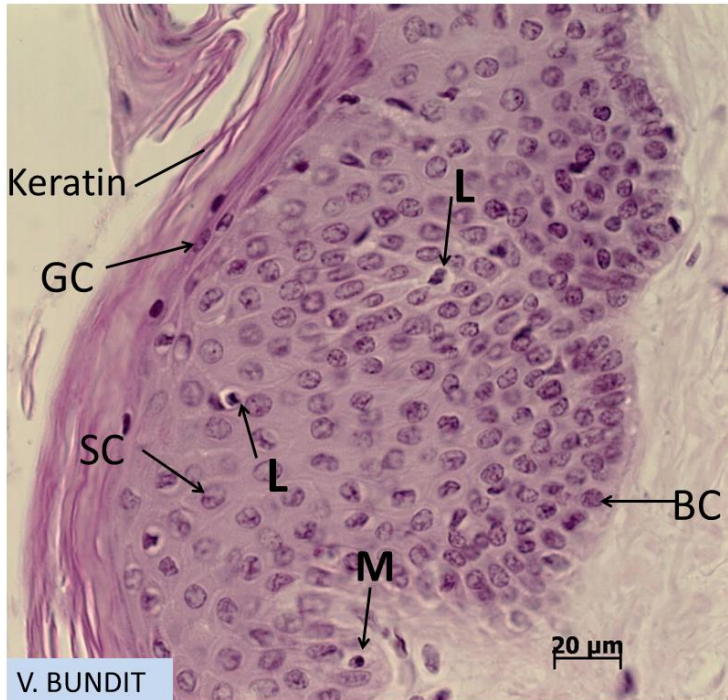


Figure 1-4: Photomicrograph of the stratified squamous epithelial layer of the epidermis consists of four distinct cell types: (1) **Keratinocytes** are the predominant cell type, also called because its major product is keratin, an intermediate filament, i.e., GC (Granular cell), SC (Spinous or prickle cell), BC (Basal cell), (2) **Melanocytes** (M) produce melanin, (3) **Langerhans** cells (L) act as antigen-trapping cells interacting with CD8+T cells, and (4) **Merkel cells** (not shown) are involved in tactile sensation.

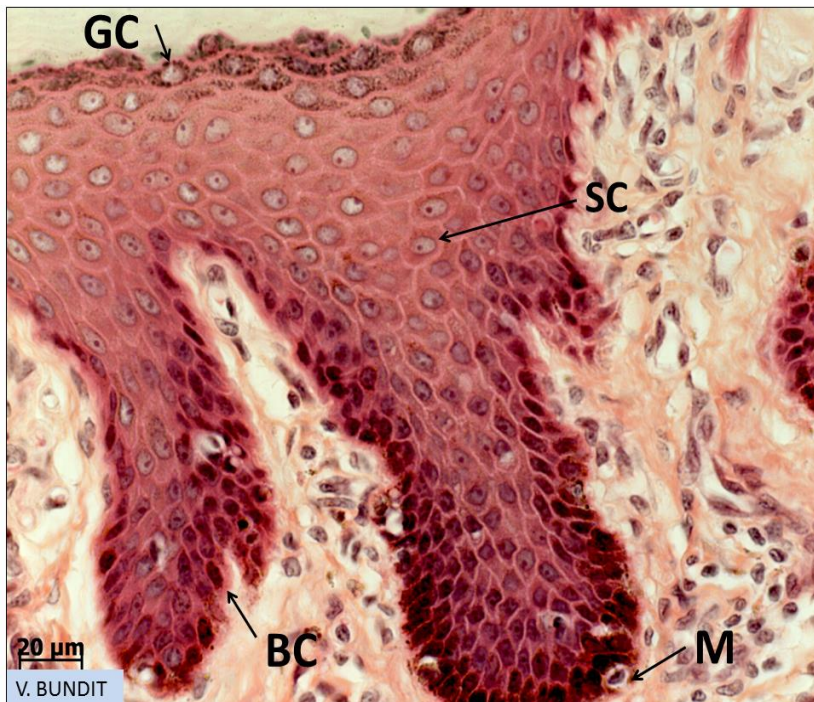


Figure 1-5: Photomicrograph of the high magnification of the epidermis shows Basal Cell (BC) as the cuboidal cell, Granular Cell (GC, containing keratohyalin granules), Spinous Cell (SC, first appearing cytoplasmic lamellar bodies), and Melanocyte (M, observing in the basal cell layer).

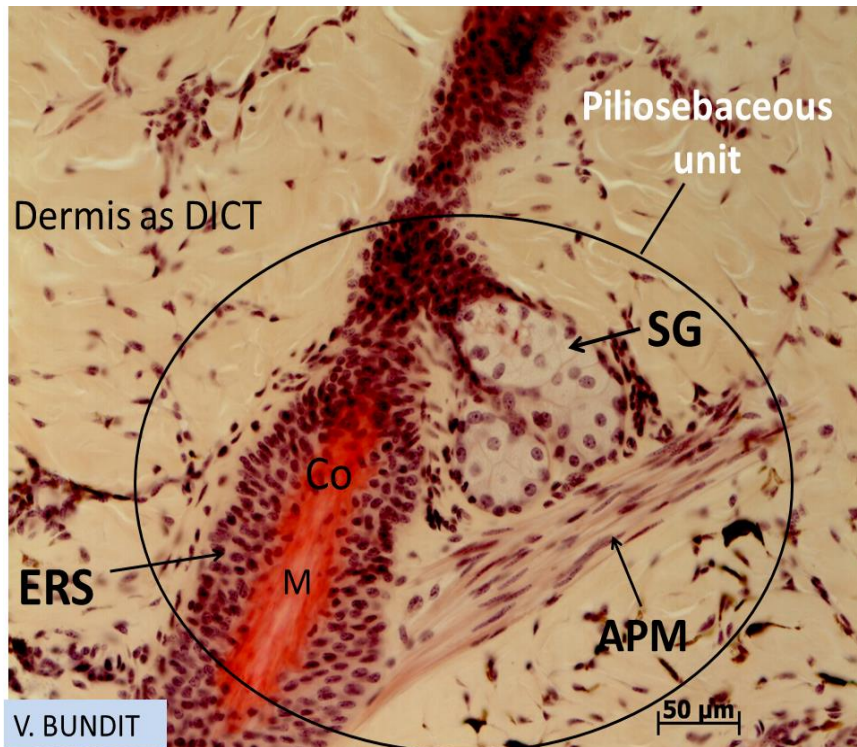


Figure 1-6: Photomicrograph of skin appendages. Bulge stem cells are located in the external root sheath (ERS) of the hair follicle, called the follicular bulge which contains stem cells, clonogenic keratinocytes, can migrate and generate the hair shaft, the epidermis, and sebaceous gland, forming pilosebaceous units. APM=Arrector Pili Muscle, DICT=Dense irregularly connective tissue, SG=Sebaceous Gland.



Figure 1-7: Photomicrograph of Sebaceous gland. It develops from the epithelial cells of the hair follicle and discharge the sebum into the follicle, from where it reaches the skin surface. The hair follicle consists of the external root sheath (eRS) surrounding the hair shaft. Cluster of sebaceous cells, most of which display a wash-out or finely reticulated cytoplasm. A series of cells filled with an increasingly greater amount of lipid and closer to the opening of the sebaceous gland through the junction (**arrowhead**) between the gland and the external root sheath. Cell at the periphery of the gland is basal cell.

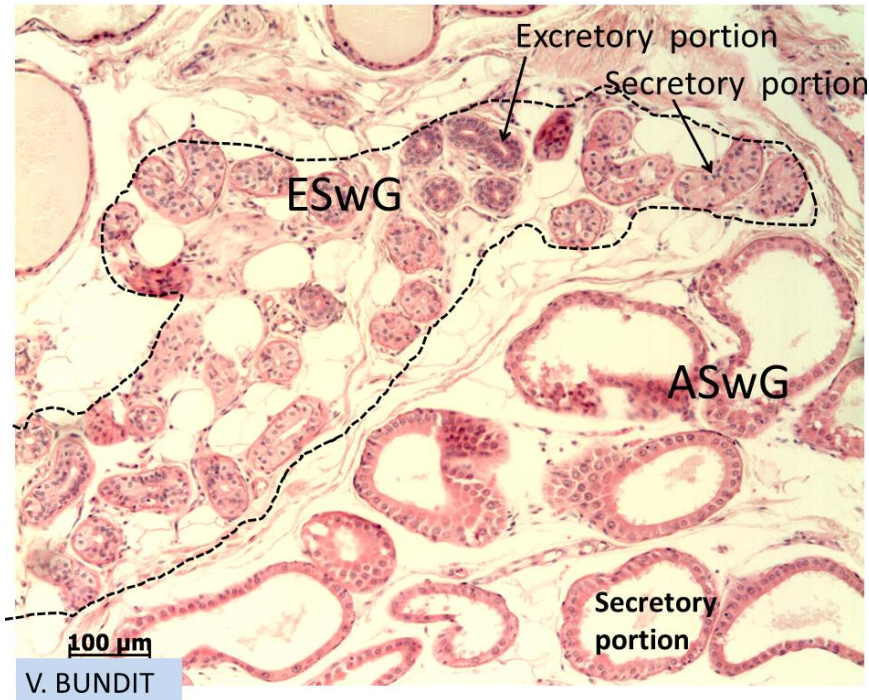


Figure 1-8: Photomicrograph of the eccrine sweat gland (ESwG) and the apocrine sweat gland (ASwG). ESwG shows both secretory and excretory portion whereas the secretory acini possess narrow lumens. ASwG shows the secretory acini with large lumen.

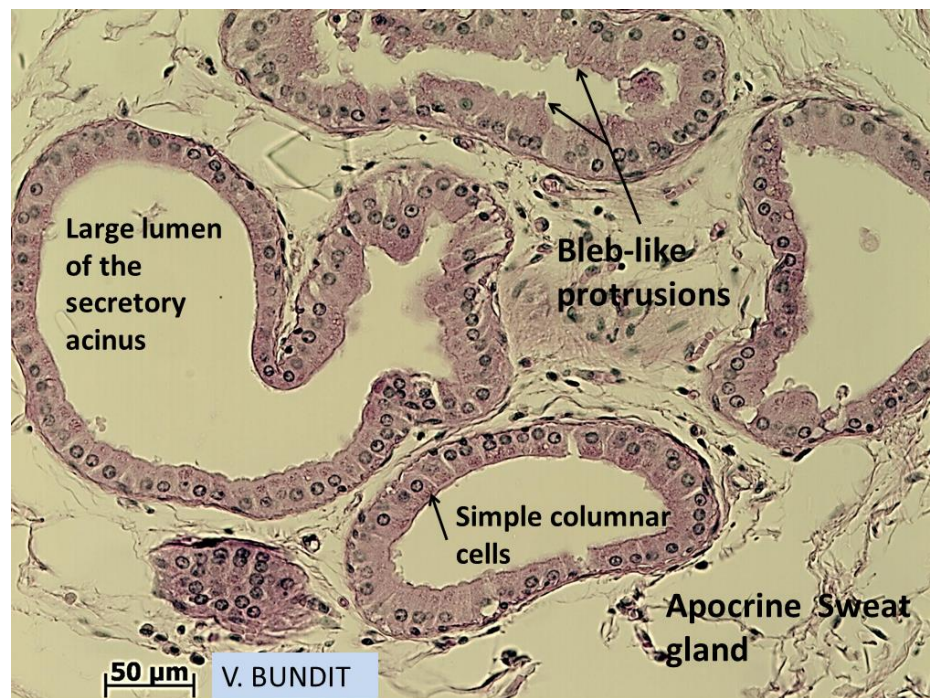


Figure 1-9: Photomicrograph of high magnification of the apocrine sweat gland. The secretory acini are lined with simple columnar epithelium and large lumens. The individual cells vary in height, and some show the bleb-like protrusions.

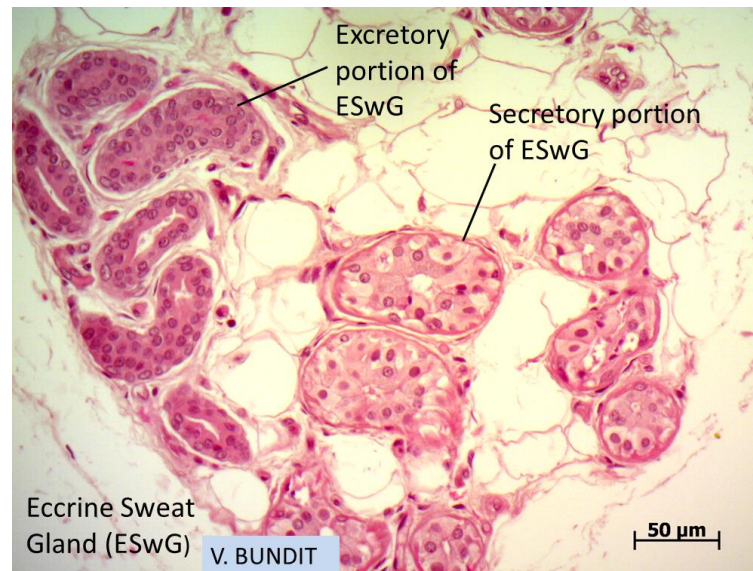


Figure 1-10: Photomicrograph of high magnification of the eccrine sweat gland (ESwG). The secretory portion has a wider diameter and larger lumen than the excretory portion. The epithelium of secretory portion is simple columnar; the excretory portion is two cell layers thick, namely stratified cuboidal. Also, the secretory portion possesses a myoepithelial component.

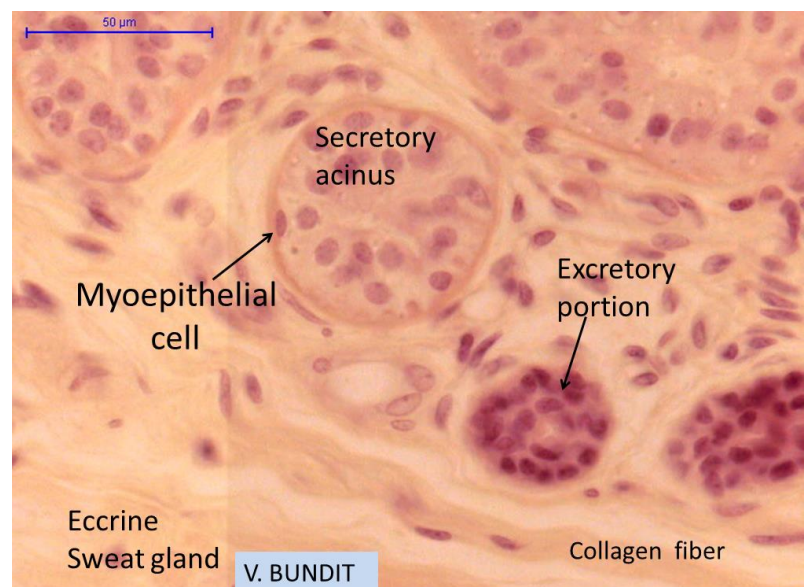


Figure 1-11: Photomicrograph of the eccrine sweat gland shows the myoepithelial cell surrounding the secretory acinus.

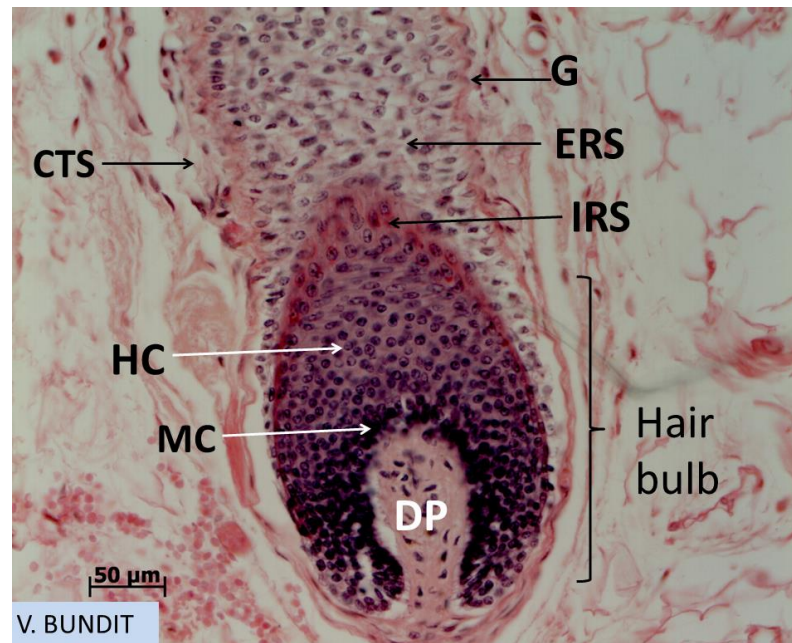


Figure 1-12: Photomicrograph of the hair follicle. The growing end of a hair follicle consists of an expanded bulb of epithelial cells that is invaginated by a dermal papilla (DP) of connective tissue. The epithelial cells surrounding the DP at the very tip of the follicle constitute the matrix, the region of hair follicle where matrix cell (MC) division occurs. As the cells leave the matrix, they form cell layers that will become the shaft of the hair and the inner root sheath (IRS) and external root sheath (ERS) of the hair follicle. Outside the ERS is the glassy membrane (G) that is continuous with the basement membrane of the epidermis. CTS= Connective Tissue Sheath. HC=Hair Cortex.

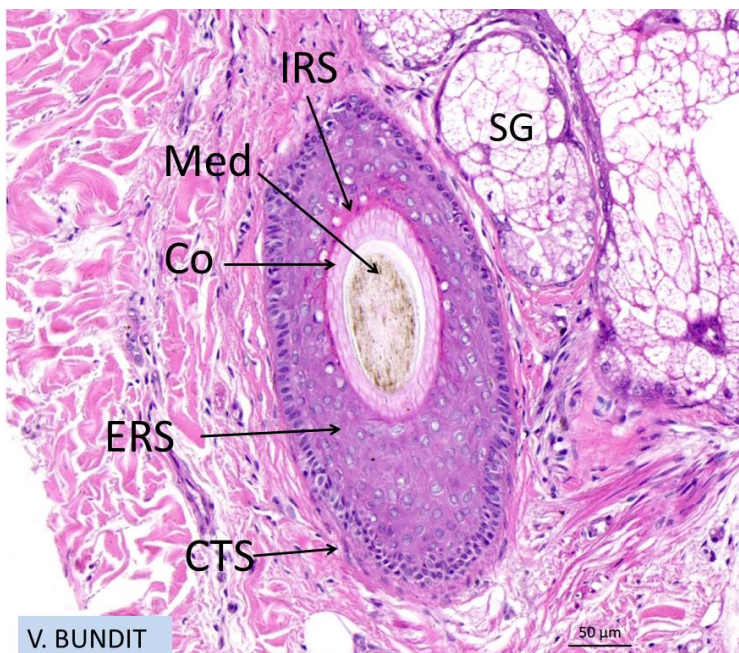


Figure 1-13: Photomicrograph of x-section of a hair follicle shows the surrounding connective sheath (CTS), External root sheath (ERS), Inner root sheath (IRS), Cortex of the hair (Co), and Medulla of the hair (Med). SG=Sebaceous gland.

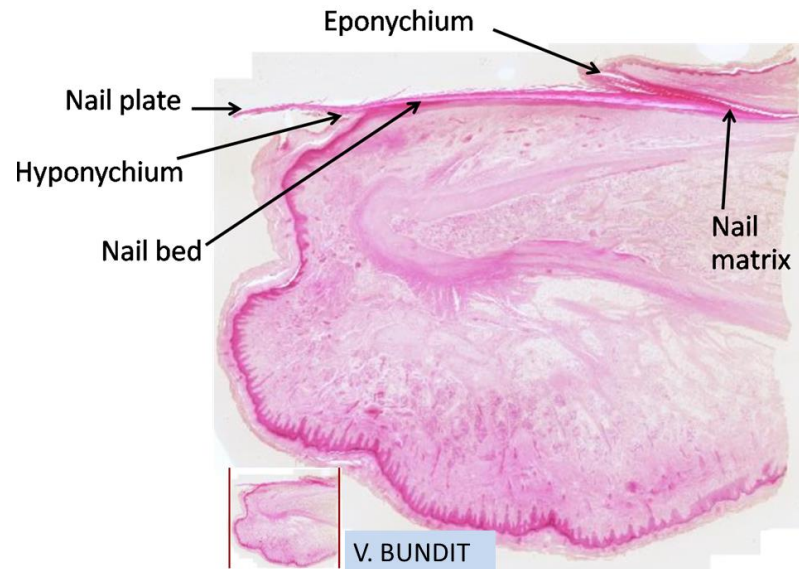


Figure 1-14: Photomicrograph of the sagittal section from a finger nail shows the proximal nail fold and its epidermal extension, the eponychium or cuticle. The nail root, the most proximal region of the nail plate, is formed like the hair root by a matrix of proliferating, differentiating keratinocytes. The mature nail plate remains attached to the nail bed, which consists of basal and spinous epidermal layers (Stratum malpighii) over dermis, but is pushed forward on this bed by continuous growth in the nail matrix.

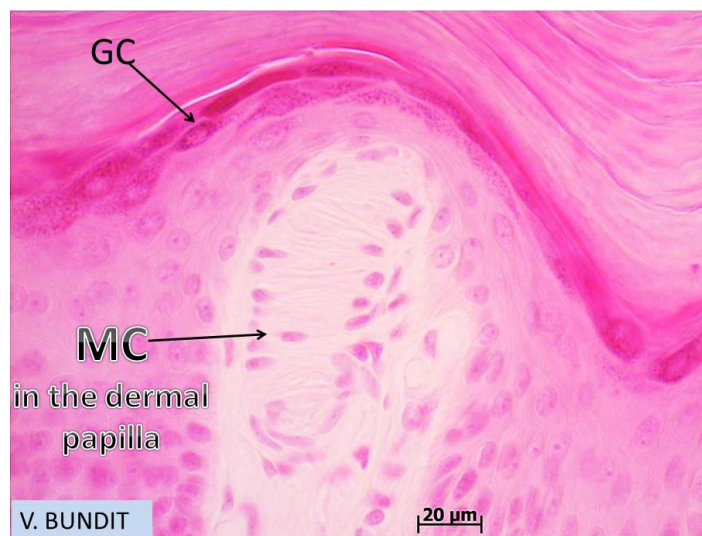


Figure 1-15: Photomicrograph of high magnification of a Meissner 's corpuscle (MC). It is located in the dermal papilla. The flat spiral path of the neuron (not seen) and its supporting cells. MCs possess the fibrous capsules and are particularly numerous near the tips of the fingers and toes. GC=Granular cell.

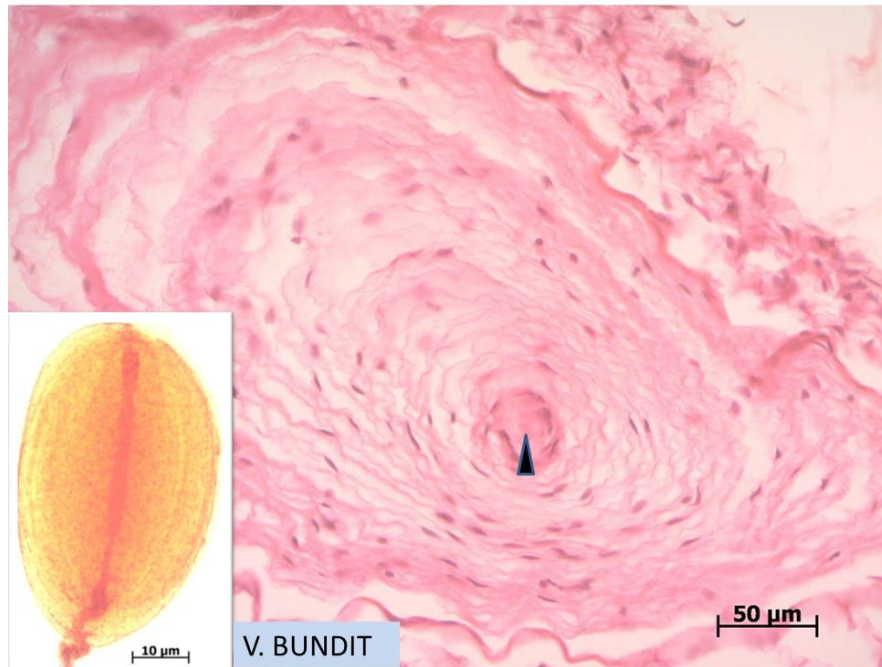


Figure 1-16: Photomicrograph of high magnification of the concentric layers or lamellae of the Pacinian corpuscle. The neural portion of the Pacinian corpuscle travels longitudinally through the center of the corpuscle which an **arrowhead** points to centrally located nerve fiber

CHAPTER II: LYMPHATIC TISSUES AND IMMUNO-LYMPHATIC ORGANS

The **lymphatic system** consists of groups of cells, tissues, and organs that monitor body surfaces and internal fluid compartments and react to presence of potentially harmful substances. **Lymphocytes** are the definitive cell type of lymphatic system and effector cells in the response of the immune system to harmful substances. In this system, there are the **diffuse lymphatic tissues, lymphatic nodules, lymph nodes, spleen, bone marrow, and thymus**. The various lymphatic organs and lymphatic tissues are often collectively referred to as the **immune system**. Lymphatic vessels connect parts of system to the blood vascular system.

Lymphatic tissues serve as sites where lymphocytes proliferate, differentiate, and mature. In **thymus, bone marrow, and gut-associated lymphatic tissue (GALT)**, lymphocytes are “educated” to recognize and destroy specific antigens. These are now **immunocompetent cells** that can distinguish between “self” (molecules normally present within an organism) and “nonself” (foreign molecules-i.e., those not normally present).

Organization of the immune-lymphatic system: The lymphatic system consists of **primary** and **secondary lymphoid organs**. The primary lymphoid organs produce the cell components of the immune system. They are the bone marrow, and the thymus. The secondary lymphoid organs are the sites where immune responses occur. They are the lymph nodes, the spleen, tonsils, and aggregates of lymphocytes and antigen-presenting cells in the lung (bronchial-associated lymphoid tissue, BALT), and the mucosa of the digestive tract (gut-associated lymphoid tissue, GALT), including Peyer's patches.

The main function of the immune-lymphatic system is to protect the body against pathogens or antigens (any substances that can induce a specific immune response). The basis for this defense mechanism, or immune response, is the ability to distinguish between self-antigens and non-self (foreign) antigens.

The two key cell components of the immune system are lymphocytes and accessory cells.

- **Lymphocytes** possess three (some text said only two) groups: (1) **B cells**, originated and differentiated in the bone marrow and responding to cell-bound or cell-free antigens. (2) **T cells**, originated in the bone marrow, differentiated in the thymus, and responding to cell-bound antigens. (3) **NK (Natural killer) cells** destroy virus-infected cells and tumor cells, but this activity does not depend on antigen activation.

- **Accessory or supporting cells** interact with lymphocytes and play important roles in the presentation of antigen to lymphocytes and the regulation of immune responses. These cells include the **monocyte-derived cells** (macrophages and dendritic cells), **neutrophils**, **basophils**, **eosinophils**, **reticular cells**, **follicular dendritic cells**, and **epithelia-reticular cells** (in thymus). The follicular dendritic cells, present in lymphatic nodules in lymph nodes, do not derive from the bone marrow.

There are two types of immunity:

- (1) **Innate or natural immunity** does not require previous exposure to a pathogen or antigen, involves the epithelial barriers, phagocytic cells (macrophages and neutrophils), natural killer cells, and proteins of the complement system (synthesized by hepatocytes).
- (2) **Adaptive or acquired immunity** does require previous exposure to pathogen or antigen, can be mediated by antibodies produced by plasma cells (**humoral immunity**), or requires the uptake of a pathogen by an antigen-presenting cell interacting with T cells and B cells (**cell-mediated or cellular immunity**)

Antigen-presenting cells to T cells are the basic of cell-mediated immunity, and the mechanism of clonal selection of immune-competent T cells in the thymus. In the mouse, the presentation of antigens is carried out by a cell surface protein complex called **major histocompatibility complex (MHC)**. The MHC-equivalent in humans is called **human leukocyte antigen (HLA)**.

There are two types of MHC molecules: (1) **Class I MHC**, and (2) **Class II MHC**.

Different types of cells in lymphatic tissue are identified by **specific cluster of differentiation (CD or co-receptor CD) markers** on their surface. The **co-receptor CD8**, present on the surface of **cytolytic T cells**, binds to **class I MHC**, the **co-receptor CD4**, present on the surface of **helper T cells**, binds to **class II MHC**.

In addition to co-receptors, members of the immunoglobulin superfamily, T cells have a **TCR (T cell receptor) complex** on the surface. Antigen recognition requires the participation of three components: (1) Class I or II MHC, (2) TCR, and (3) Co-receptor CD4 or CD8.

component of lymphoid organ

- I. **Lymphatic Vessels** are the route by which cells and large molecules pass from the tissue spaces back to the blood. They begin as networks of blind capillaries in loose connective tissue. Lymphatic vessels are most numerous beneath the epithelium of skin and mucous membrane. These vessels remove substances and fluid from extracellular spaces of the connective tissue, thus producing **lymph**. As lymph circulates through the lymphatic vessels, it passes through lymph nodes. Within the lymph nodes, foreign substances (antigens) conveyed in the lymph are trapped by the follicular dendritic cells. The antigen exposed on the surface of follicular dendritic cells can be processed by **APCs (Antigen-presenting cells)** present within the lymph node.

Lymphocytes enter lymph nodes by two routes: afferent lymphatic vessels and through the wall of high endothelial venules (HEVs) in the deep cortex. They leave the lymph node via an efferent lymphatic vessel. Ultimately, the lymphocytes enter a major lymphatic vessel via the right lymphatic trunk that opens into the junction of the right internal jugular and right subclavian vein.

II. Diffused lymphatic tissue and lymphatic nodules guard the body against pathogenic substances and are the sites of initial immune response.

Ila. Diffuse lymphatic tissue or mucosa-associated lymphatic tissue (MALT) is the form of lymphatic tissue which is associated with mucous membrane. MALT is located in the gastrointestinal, respiratory, and genitourinary tract. These lymphatic tissues are not enclosed by capsules. Lymphocytes and other free cells of this tissue are found in the **lamina propria** (sub-epithelial tissue) of these tracts.

Ilb. Lymphatic nodules are discrete concentrations of lymphocytes contained in a meshwork of reticular cells. Lymphatic follicles or nodules, are sharply defined but not encapsulated. A lymphatic nodule consisting chiefly of small lymphocytes is called **primary nodules**. Most nodules are **secondary nodules** and have distinctive features as followings:

- A **germinal center** (B cell zone) is located in the central region of the nodule and appears lightly stained. It is a morphologic indication of lymphatic tissue response to antigen and contains the large immature lymphocytes (lymphoblasts and plasmoblasts), follicular dendritic cells (not derived from the bone marrow), macrophages, and plasma cells.
- A **mantle zone** or **corona** is the area at the outer ring of small lymphocytes that encircles the germinal center.

III. Mucosa-associated lymphatic tissue (MALT) consists of diffuse lymphatic tissue and nodules and is named according to the region or organ in which it appears. They are found in special locations, i.e., tonsils, Peyer's patches (GALT), Bronchial ALT, Gall bladder ALT and etc. All of the mucosa with diffused lymphatic tissues exposed to the external environment in which developed lymphatic nodules, as a consequence of encounters with antigen.

IIIa. Tonsils form a ring of lymphatic tissue at the entrance of the oropharynx.

- **Palatine tonsils** consist of dense accumulations of lymphatic tissue located in the mucous membrane. The **squamous epithelium** that forms the surface of tonsil dips into underlying connective tissue in numerous places, forming **tonsillar crypts**. Tonsils usually contain numerous lymphatic nodules and do not possess afferent lymphatic vessels. Lymph drain from the lymphatic tissue of the tonsil via efferent lymphatic vessels.
- **Pharyngeal tonsils** (adenoids) possess the same histological features as the palatine tonsils except the location and the stratified columnar epithelium covered the surface.
- **Lingual tonsils** at the base of the tongue contain aggregates of lymphatic nodules.

IIIb. Peyer's patches are located in the ileum (distal portion of the small intestine) and consist of numerous aggregations of lymphatic nodules containing T and B lymphocytes. In addition, numerous isolated single (solitary) lymph nodules are located along both large and small intestine.

IIIc. The **vermiform appendix** arises from the cecum. The lamina propria is heavily infiltrated with lymphocytes and contained numerous lymphatic nodules.

IV. Lymph nodes are small encapsulated organs located along the pathway of lymphatic vessels. The function of lymph nodes is to filter the lymph, maintain and differentiate B cells, and hose T cells. Lymph nodes detect and react to lymph-borne antigens.

A lymph node is surrounded by a dense irregularly connective tissue known as **capsule** that sends partition as **trabeculae** inside the lymph node. The stroma of the lymph node consists of a three-dimensional network of **reticular fibers** (type III collagen). The convex surface of the lymph node is the entry side of several afferent lymphatic vessels with valves. Lymph percolates through the sub-capsular sinus and para-trabecular sinus. The concave side of the lymph node is hilum, the site where an artery enters the lymph node and vein and efferent lymphatic vessel drain the structure.

The lymph node consists of:

- (1) The outer, **cortex**: is subdivided into an outer (**superficial, nodular**) **cortex**, where **B-cell-containing lymphatic nodules** are present, and a **deep or para-follicular cortex**, where **T cells (CD4⁺)** predominate or the thymus-dependent cortex.

A lymphatic nodule or follicle consists of a mantle (dark cap area) and a germinal center, containing proliferating B cells interacting with follicular dendritic cells (FDCs). Macrophages are present and function to take particulate matter from lymph node as well as opsonized antigens and also phagocytose apoptotic cells. FDCs have an antigen-presenting function. B and T cells reach the lymph node through the **post-capillary (high endothelial) venules (HEV)** present in the inner or **deep cortex**

- (2) The inner, **Medulla**: contains **medullary cords**, housing B cells, plasma cells, and macrophages, separated by **medullary sinuses**, endothelial cell-lined spaces containing lymph arriving from the cortex region of the node. Large blood vessels are present in the medulla close to the hilum.

Note: Word pathway of lymphocyte circulation within a lymph of a lymph node.

- (i) Lymphocytes enter the lymph node with the flow of lymph via afferent lymphatic vessels which carry lymph from the surrounding tissues and neighboring lymph nodes into elaborate network of lymphatic sinuses. The wall of sinuses allows lymph to percolate freely into the superficial and deep cortex allowing lymphocytes to engage in immunosurveillance. The lymphocytes that enter the tissue next migrate back to the sinuses and leave the lymph node via efferent lymphatic vessels.
- (ii) Lymphocytes that migrate to lymph node from the blood enter the deep cortex via high endothelial venules (HEVs) and also migrate to the superficial cortex. Here lymphocytes perform the same functions as lymphocytes that enter via lymphatic vessels. They also leave the lymph node via the efferent lymphatic vessels.

V. Thymus is the production of T cells from thymocytes derived from bone marrow and the site of T-cell education.

The thymus derives from **endodermic third pharyngeal pouch** (also the site of origin of the inferior parathyroid glands). It is fully formed and functional at birth. Thymus persists as large organ until about the time of puberty when T-cell differentiation and proliferation are reduced and most of the lymphatic tissue is replaced by adipose tissue (involution).

The thymus is surrounded by a connective tissue as **capsule**, which subdivides it into thymic lobules as **trabeculae**. Blood vessels are present in the trabeculae and capsule. The thymus consists of several incomplete lobules. Each lobule has a complete cortex and a medulla shared with adjacent lobules.

Two important features are: (1) **the lack of lymphatic nodules in the cortex** and, (2) **the presence of Hassall's corpuscles in the medulla**.

Two relevant functional features are: (1) the **blood-thymus barrier**, present in the cortex of the thymus, and (2) **post capillary venules** at the cortico-medullary junction.

The thymic parenchyma contains developing T cells in an extensive meshwork (stroma) formed by **thymic epithelial cells** (TECs or epithelia-reticular cells) interconnected by **desmosomes**. TECs derive from a common precursor, which gives rise to thymic cortical and medullary epithelial cells when the transcription factor *Foxn1* is active. Inactivation of the *Foxn1* gene prevents the development of the thymus, resulting in failure of T cell development leading to a **congenital immunodeficiency**.

Cortical TECs express on the surface MHC molecules required for clonal selection. Medullary TECs are activated by the *aire* gene, express self-proteins necessary for clonal deletion of auto-reactive T cells. Mutations in the *aire* gene cause a number of auto-immune diseases.

The blood-thymus barrier consists of 3 layers:

- (1) thymic cortical epithelial cells joined by desmosomes, basal lamina produced by thymic cortical epithelial cells,
- (2) capillary endothelial cells and its basal lamina, and capillary endothelial cells linked by tight junctions,
- (3) perivascular connective tissue space occupied by macrophages. These three layers provide the necessary protection to developing immunocompetent lymphocytes circulating in the bloodstream.

Hassall's corpuscles are thymic epithelial cells forming onion-like layers. They produce cytokine thymic stromal lymphopoietin, which stimulates thymic dendritic cells to complete the maturation of single-positive T cells to optimize negative selection and ensure tolerance.

Mature T cells, completing their differentiation under the guidance of thymic medullary epithelial cells, migrate across the endothelium into the lumen of a cortico-medullary post-capillary venule.

V. Spleen is the largest secondary lymphoid organ has a dual function, i.e., (1) **filtering** the blood and, (2) reacting **immunologically to blood-borne antigens**.

The spleen is covered by a **capsule** consisting of dense, irregular connective tissue with elastic and smooth muscle fibers. The capsule gives rise to **trabeculae** that carry blood vessels (trabecular arteries and veins) and nerves.

The spleen lacks a cortex and a medulla and has **two major components** with distinct functions.

- (1) The **white pulp** is the immune component of the spleen, i.e., these components detect and react to blood-borne antigens.
- (2) The **red pulp** is a filter that removes aged and damaged red blood cells and microorganisms from circulating blood.

The splenic artery enters the hilum, giving rise to trabecular arteries. As an artery leaves the trabecula, it becomes invested by sheath of T cells forming a **periarteriolar lymphoid sheath (PALS)** and penetrates a lymphatic nodule (the white pulp). The blood vessel is known central artery or follicular arteriole.

The **marginal zone** is located between the red and white pulp and receives radial arterioles from the central artery or arteriole.

The central arteries and its branches leave the white pulps to become the penicillar arteries which end as **macrophage-sheathed capillaries**. Terminal capillaries either directly into splenic sinusoids (**closed circulation**) or terminate as open-ended vessels within the red pulp, splenic cord (**open circulation**). Splenic sinusoids are drained by pulp veins, to trabecular veins, to splenic veins.

The distinctive structural features are:

- (1) It lacks of a cortex and a medulla.
- (2) Similar to lymph node, the white pulp is a lymphatic nodule-like equivalent, i.e., it has a germinal center, a mantle populated by **B cells**, and **antigen-presenting cells**. Contrary to lymphatic nodule that involves in lymph, but the white pulp has an artery/arteriole surrounded by **T cells, the PALS**. Therefore, the white pulp is populated by the immune cells required to trap and process **blood-borne antigens**.
- (3) The **red pulp** has two components involved in blood filtration and clearance of aged red blood cells, i.e., **splenic sinusoids** and **splenic cords**.

The **splenic sinuses** are surrounded by an incomplete basal lamina and loose reticular cells. Therefore, blood cell inside-out trafficking is facilitated by the inter-endothelial cell slits and the loose stroma.

The **splenic cords** separate splenic sinuses and contain macrophages, plasma cells, and blood cells. In fact, macrophages in spleen start the recycling of **hemoglobin** of scavenged red blood cells resulting in the production of **bilirubin**.