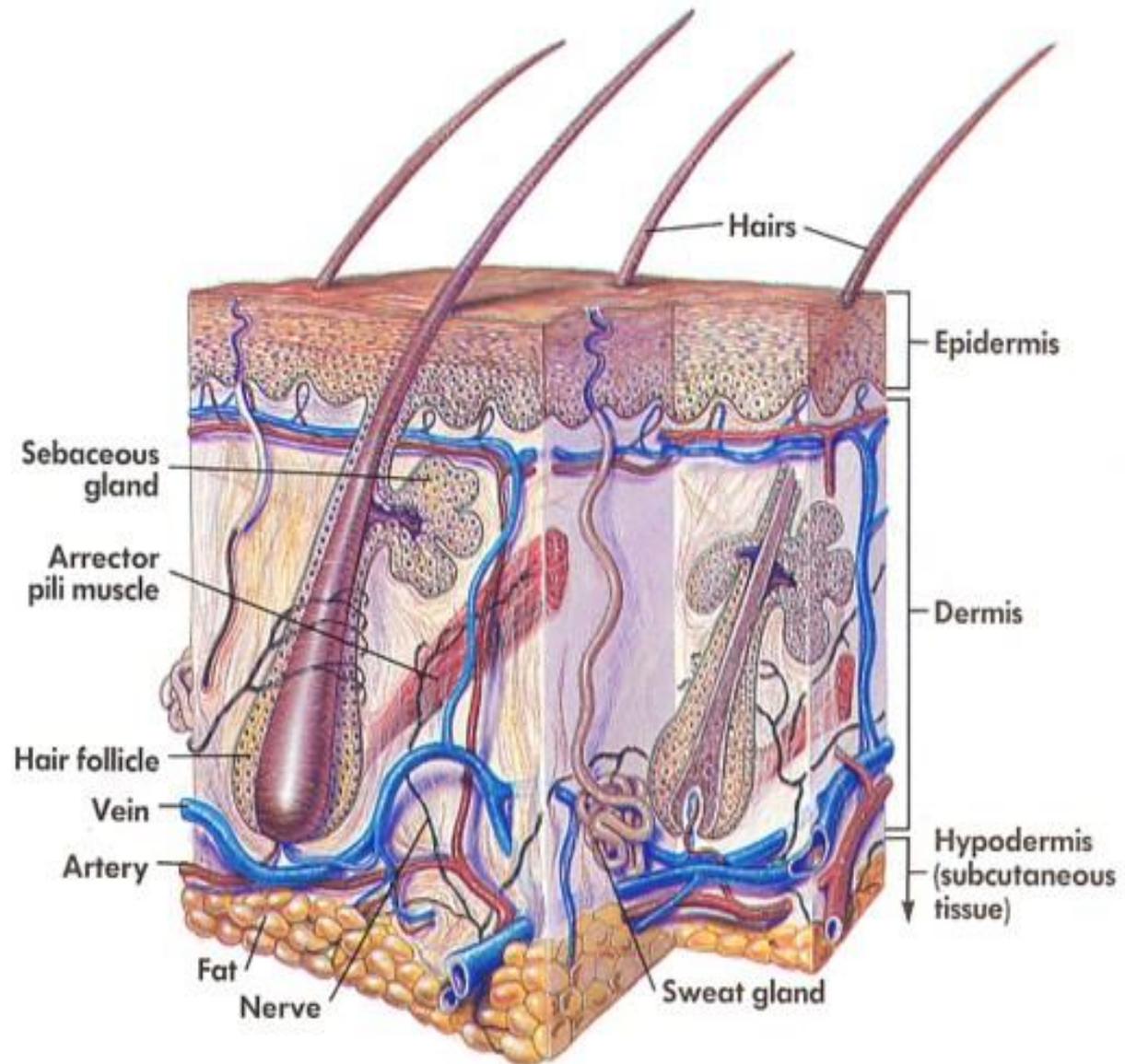


Basic Science of the Skin

- The skin is the largest organ of the human body (16% of total body wt.)
- The skin is composed of:
 - Epidermis
 - Dermis
 - Subcutaneous tissue

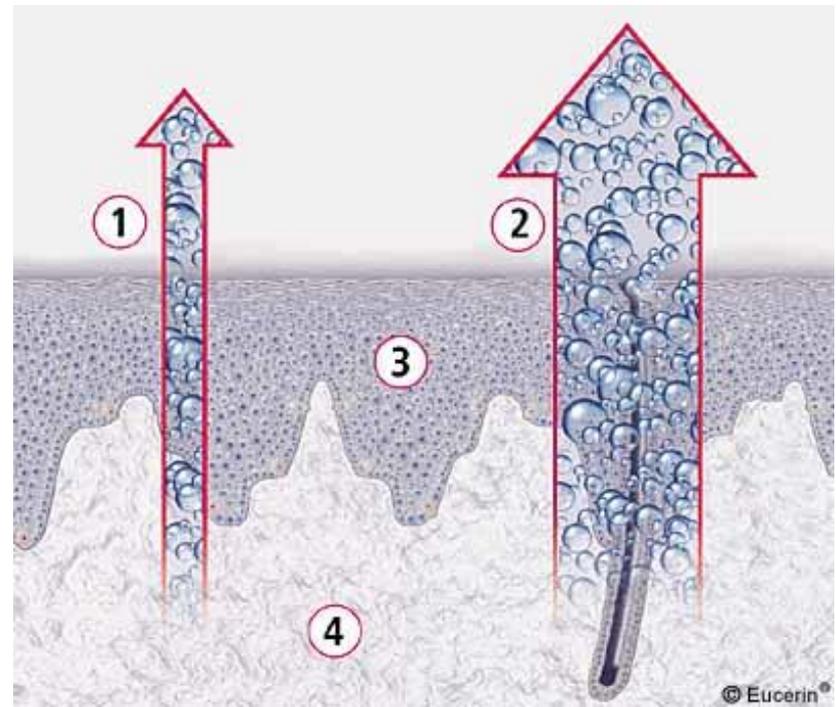


The Epidermis

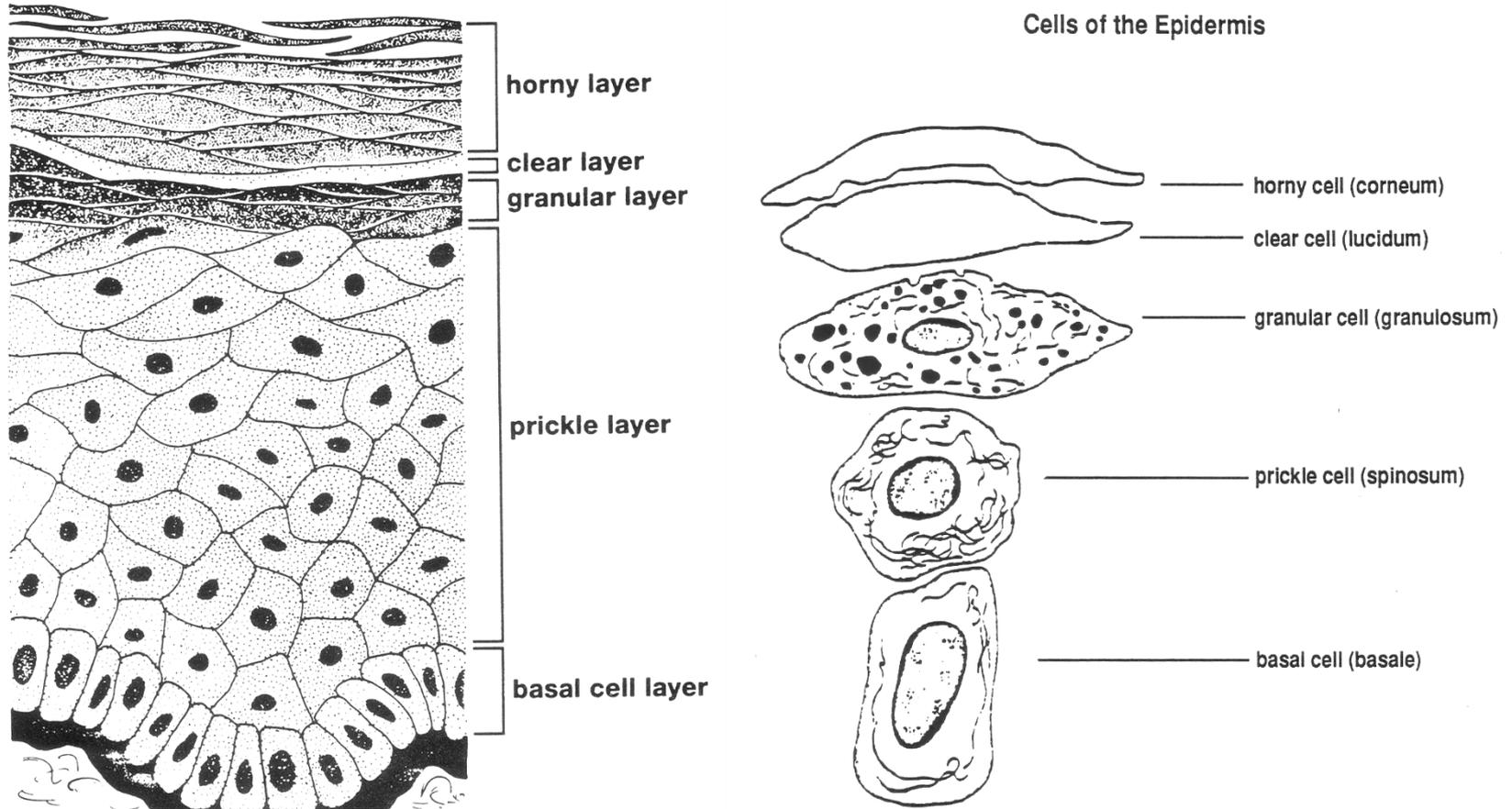
- The epidermal barrier:
 - Limit passive water loss from the body
 - Reduce the absorption of chemicals from the environment
 - Prevent microbial infection

Transepidermal Water Loss

- The water produced during respiration is normally lost through the skin.
- It moves through the epidermis as water vapor, hence called transepidermal water loss (TEWL).
- TEWL varies with body site, with normal values of ~ 6 grams/m²/hour.



Epidermal layers and cells

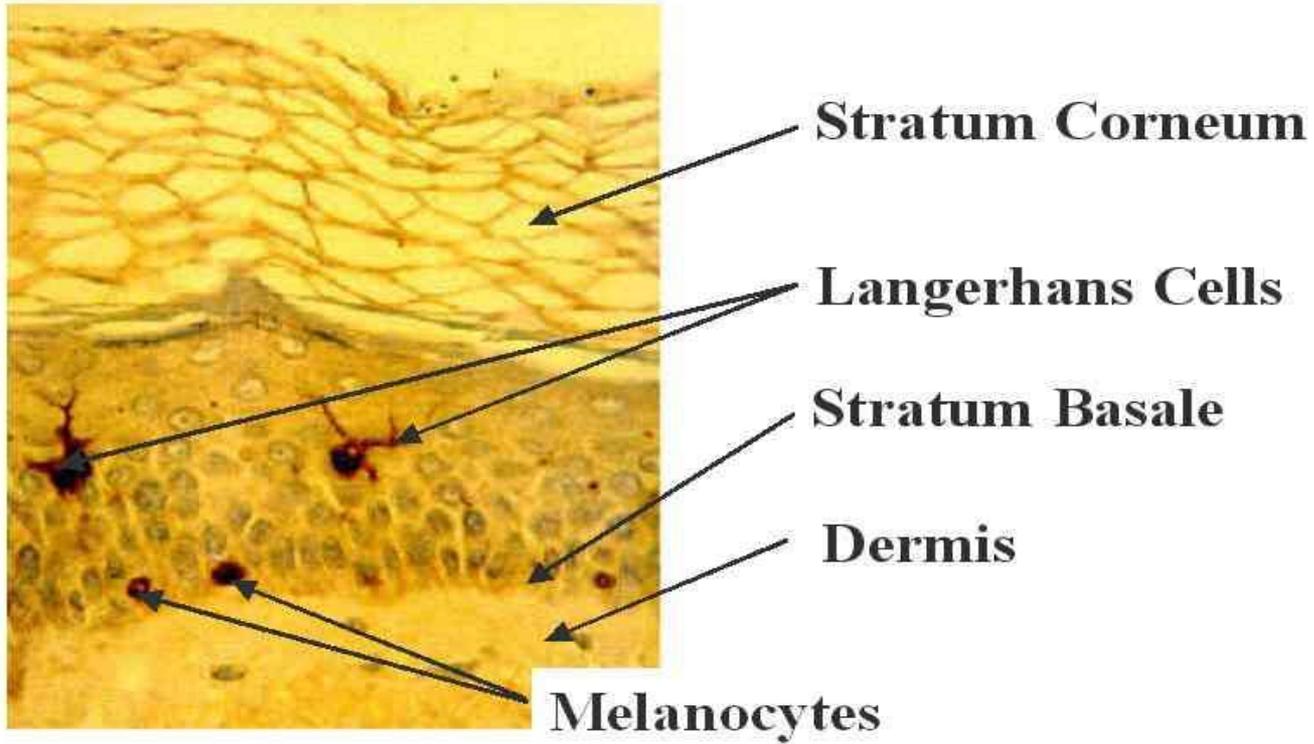


Layers of the Epidermis

English	Latin	Alternate
Basal cell layer	<i>Stratum basale</i>	<i>S Germinativium</i> Malpighian layer
Prickle layer	<i>S. Spinosum</i>	Malpighian layer
Granular Layer	<i>S. Granulosum</i>	Malpighian layer
Clear Layer	<i>Stratum Lucidum</i>	
Horny Layer	<i>Stratum Corneum</i>	

Epidermis:

- The top layer of the skin is itself divided into layers.
- The main barrier to water loss and entry of compounds in the skin is the SC.
- Understanding the SC is key to understanding the behavior of topical products
- The predominant cell type of the epidermis is keratinocytes
- They make keratins; the major structural proteins of the SC
- There are 2 other cell types in the epidermis:
 1. Melanocytes
 2. Langerhans cells



Courtesy of SB Hoath, MD

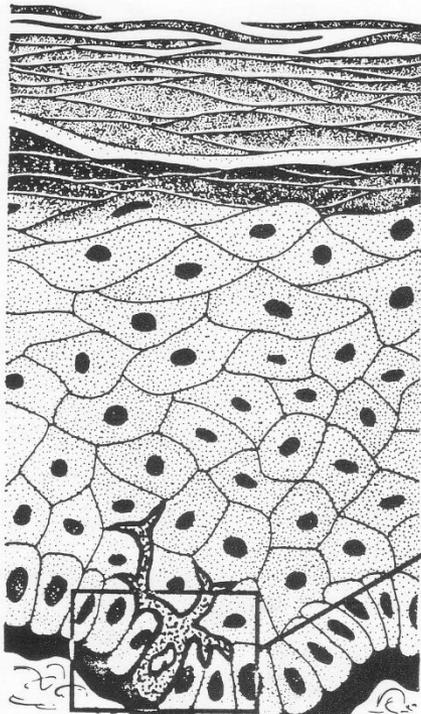
Epidermis

Melanocytes:

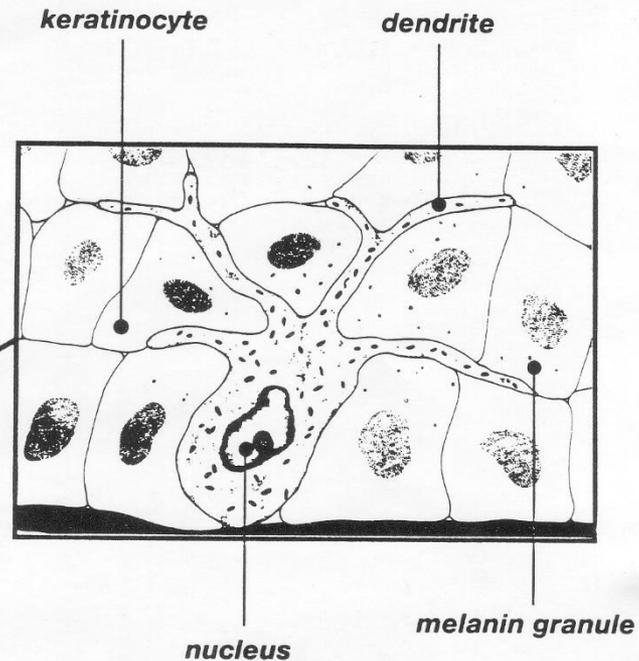
- the pigment producing cells of the skin and hair
- Found in the basal layer and make pigment granules called melanosomes containing melanin
- Melanosomes are transferred to the epidermal keratinocytes
- They impart some protection to the cell nucleus from UV light and give the skin its color

Melanocytes: The melanocyte is a dendritic cell that sits in the basal layer of the epidermis and transfers pigment to keratinocytes in the form of pigment granules called melanosomes.

Layers of the Epidermis



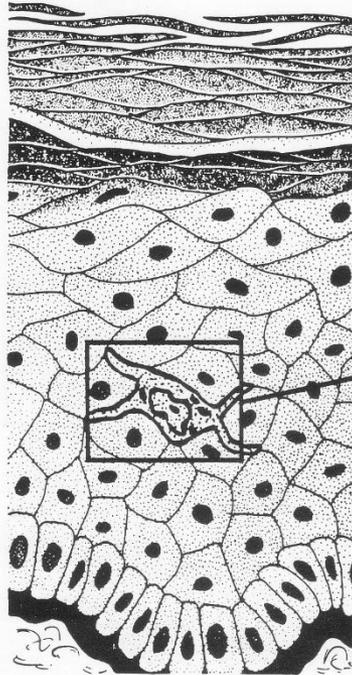
Melanocyte



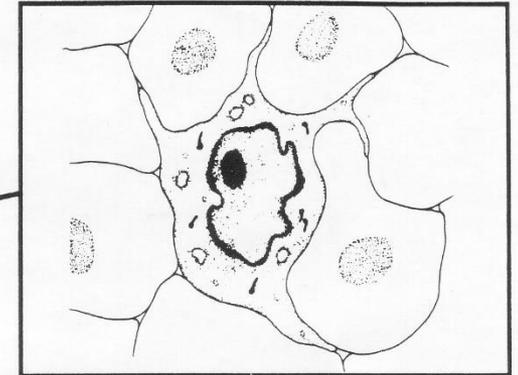
The Langerhans' Cell

- Dendritic immune cells
- Antigen-presenting cell of the skin
- Important to the immune function of the epidermis
- Participate in contact allergy

Layers of the Epidermis



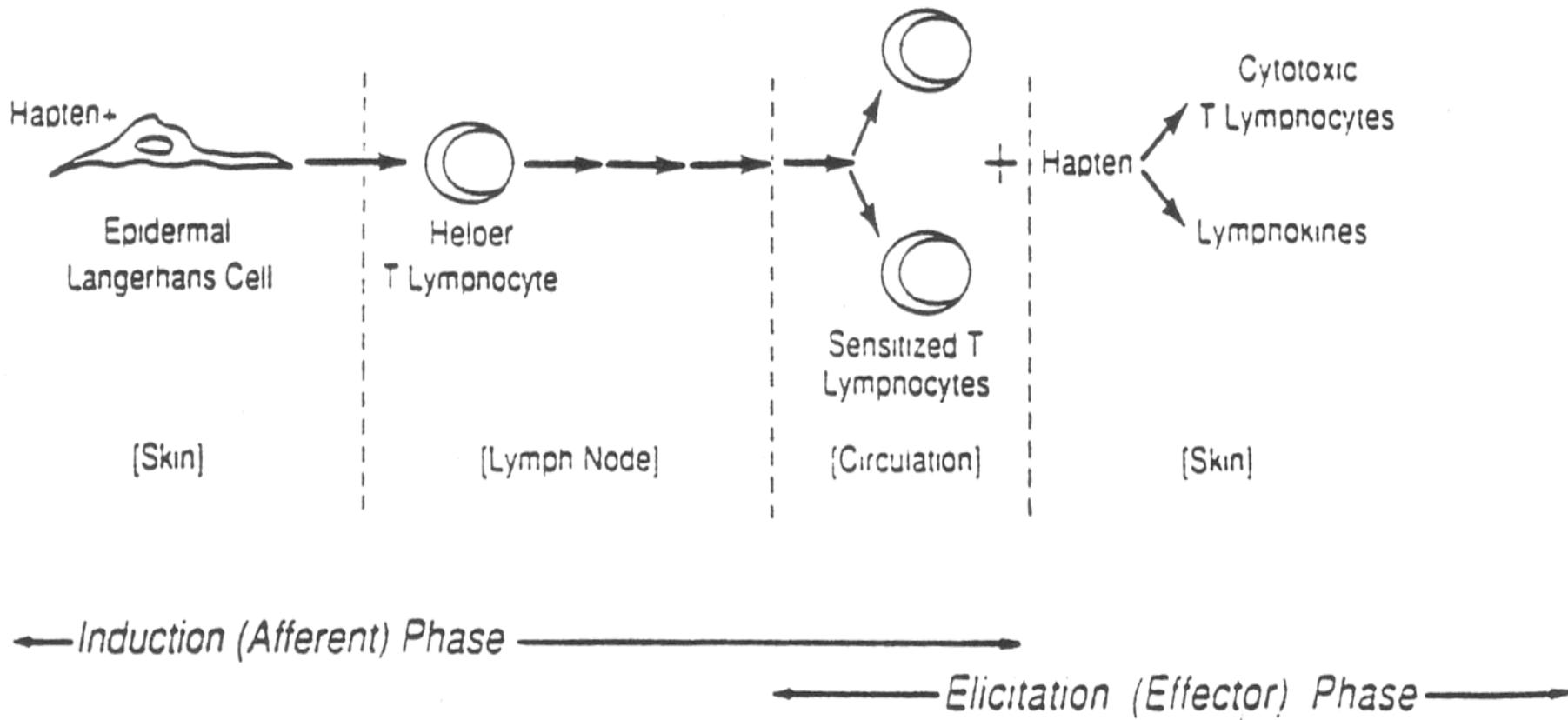
Langerhans' Cell



Contact sensitization

- Small molecules (Haptens) penetrate and bind to proteins.
- Hapten-protein complex recognized by Langerhans cells
- Move to lymph nodes and stimulate clonal proliferation of sensitized t-cells
- T-cells return to epidermis to mount reaction

Contact sensitization



The Finn chamber



Photo from *Color text of Contact Dermatitis*, Larsen, Adams and Maibach, W. B. Saunders Co. Philadelphia 1992

10/22/2022

Saja Hamed, Ph.D

Patch testing for contact allergy

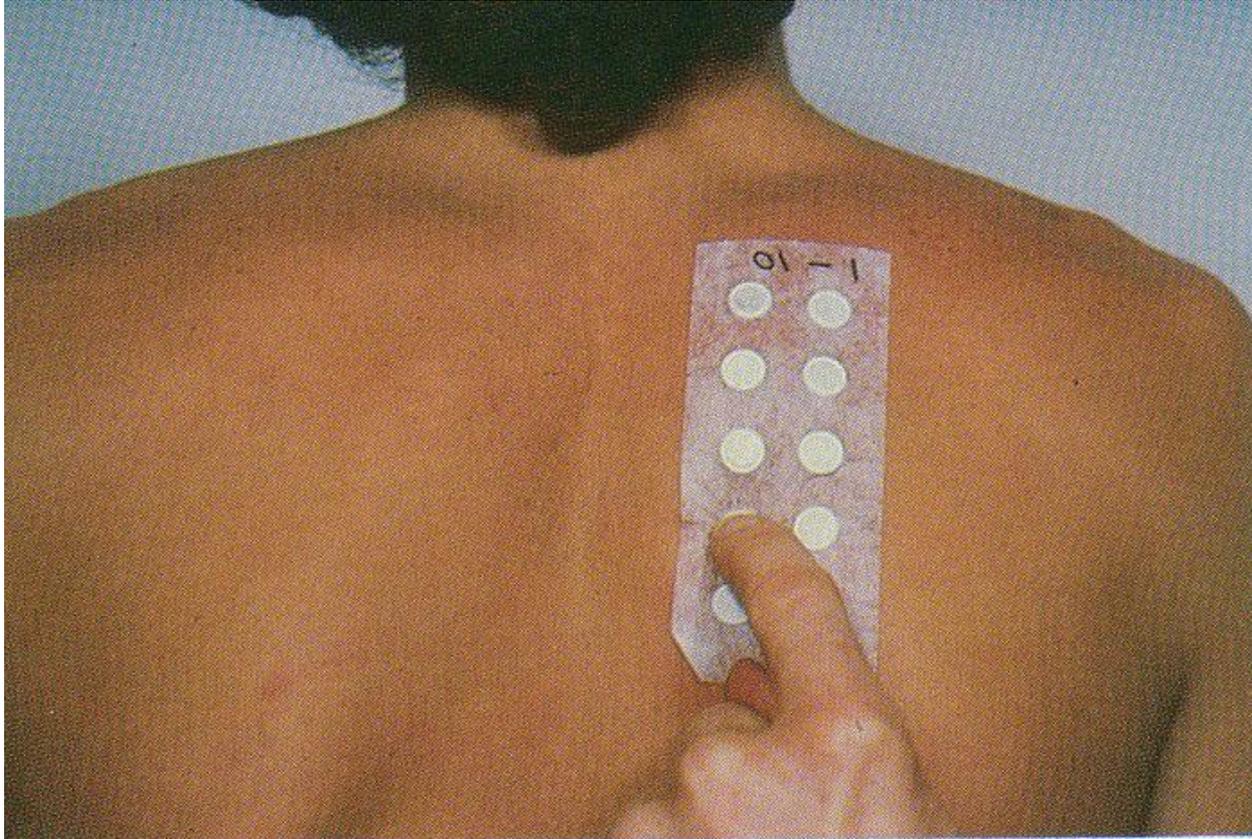


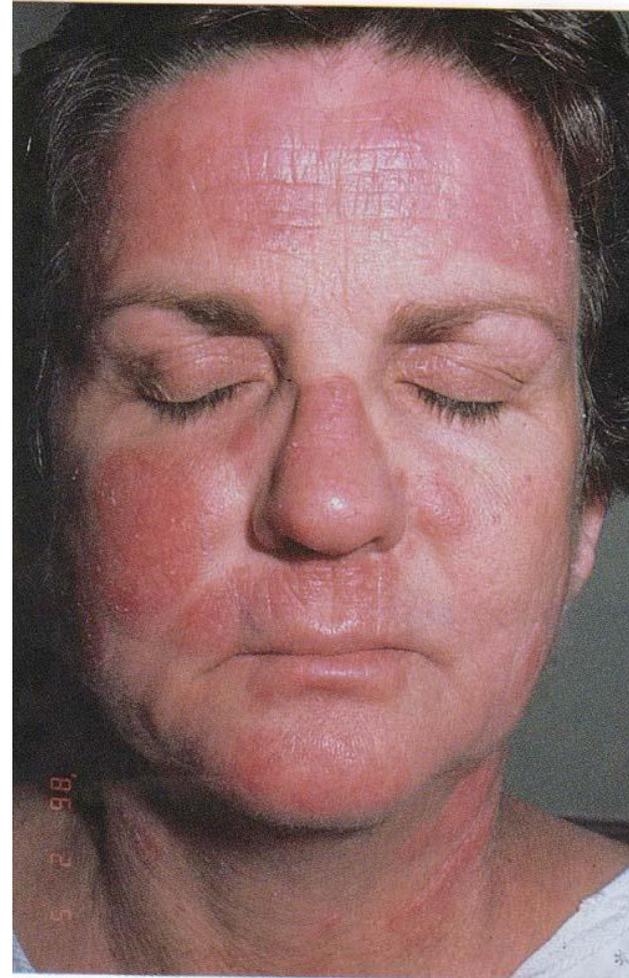
Photo from *Color text of Contact Dermatitis*, Larsen, Adams and Maibach, W. B. Saunders Co. Philadelphia 1992

A positive reaction



Photo from *Color text of Contact Dermatitis*, Larsen, Adams and Maibach, W. B. Saunders Co. Philadelphia 1992

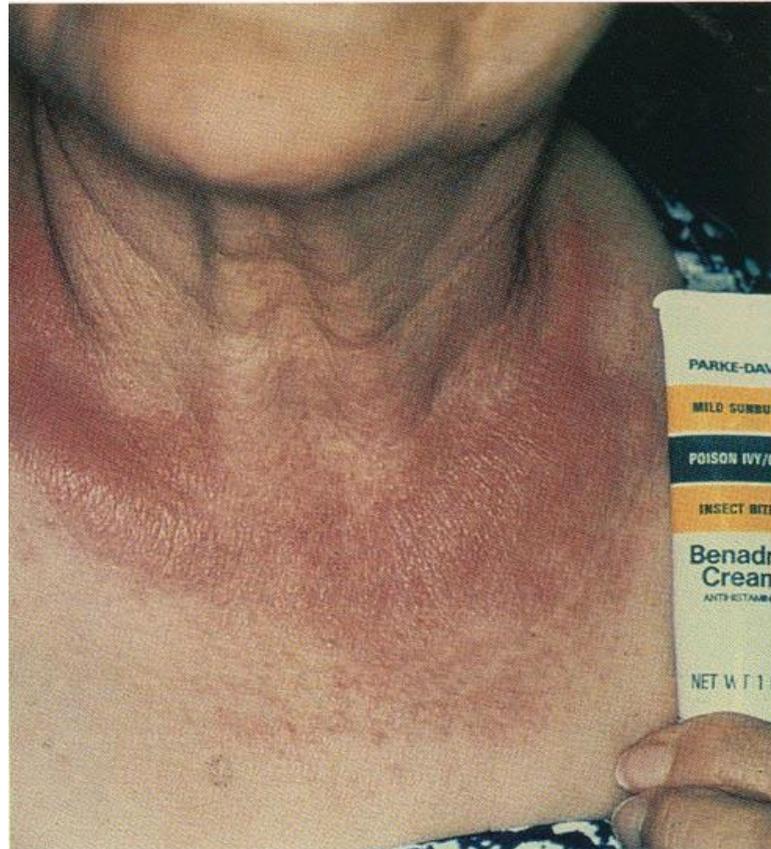
Most reactions
to cosmetic
products are to
preservatives
or fragrances



Courtesy of Frances J. Storrs, M.D.
IMIDAZOLIDINYL UREA

Photo from *Color text of Contact Dermatitis*, Larsen, Adams
and Maibach, W. B. Saunders Co. Philadelphia 1992

Benadryl



Courtesy of Alexander A. Fisher, M.D.

DIPHENHYDRAMINE

Photo from *Color text of Contact Dermatitis*, Larsen, Adams and Maibach, W. B. Saunders Co. Philadelphia 1992

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Cinnamal



CINNAMIC ALDEHYDE (CINNAMAL)

Photo from *Color text of Contact Dermatitis*, Larsen, Adams and Maibach, W. B. Saunders Co. Philadelphia 1992

Nickel

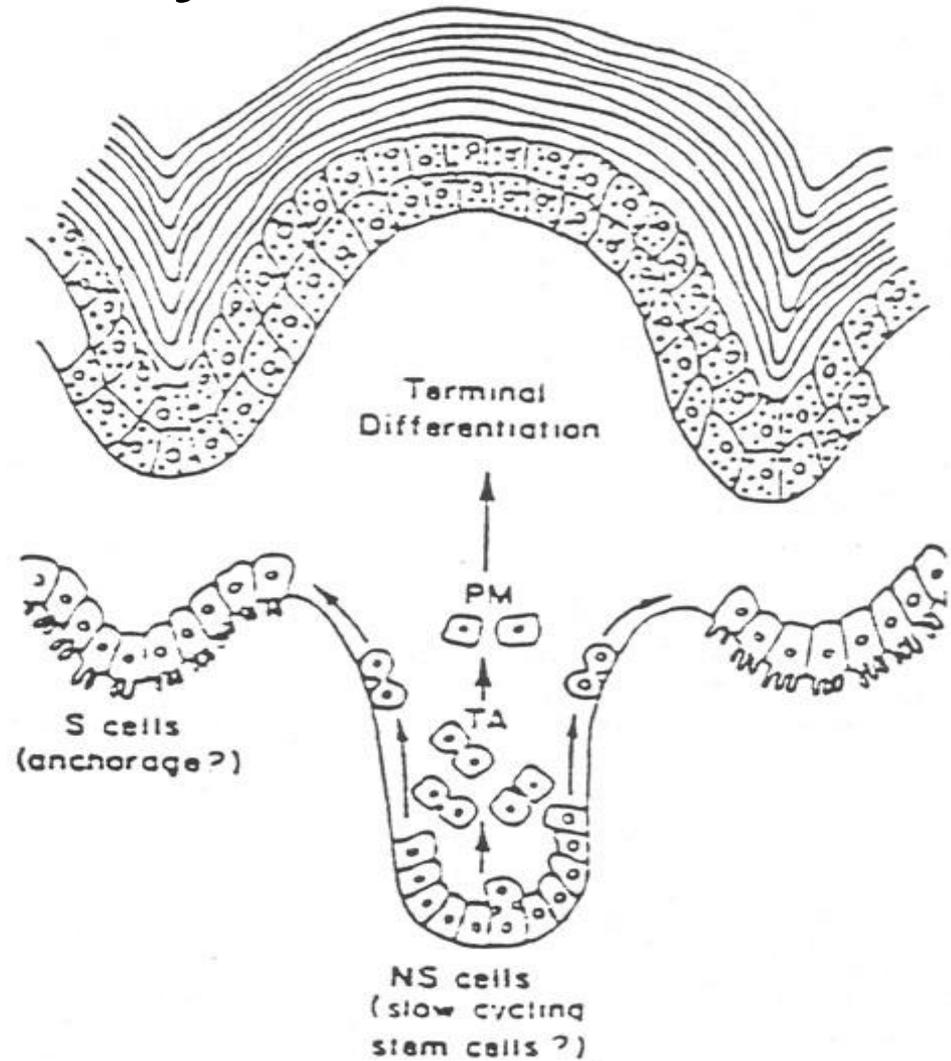


Courtesy of Alexander A. Fisher, M.D.

NICKEL

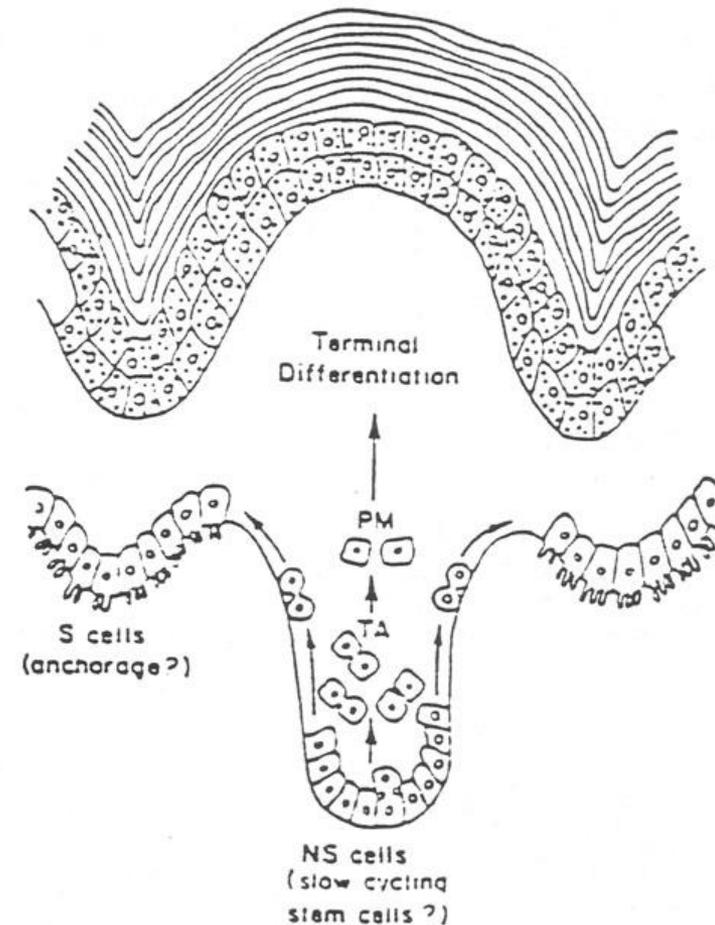
Keratinocytes

- Keratinocytes are the cells that make up the majority of the epidermis
- produced by stem cells which reside at the base of the epidermis.
- When the stem cells divide they create “daughter cells” which slowly move to the top of the epidermis
- The process of daughter cells maturation and moving to the top is called keratinization



Timing is everything in SC formation

- Keratinization process is also referred to as the “cell cycle”
- Normal cell cycle of the epidermis is 26 -42 days
- Desquamation process normally occurs invisibly with shedding of individual cells
- Disturbances of this process may result in accumulation of partially detached keratinocytes



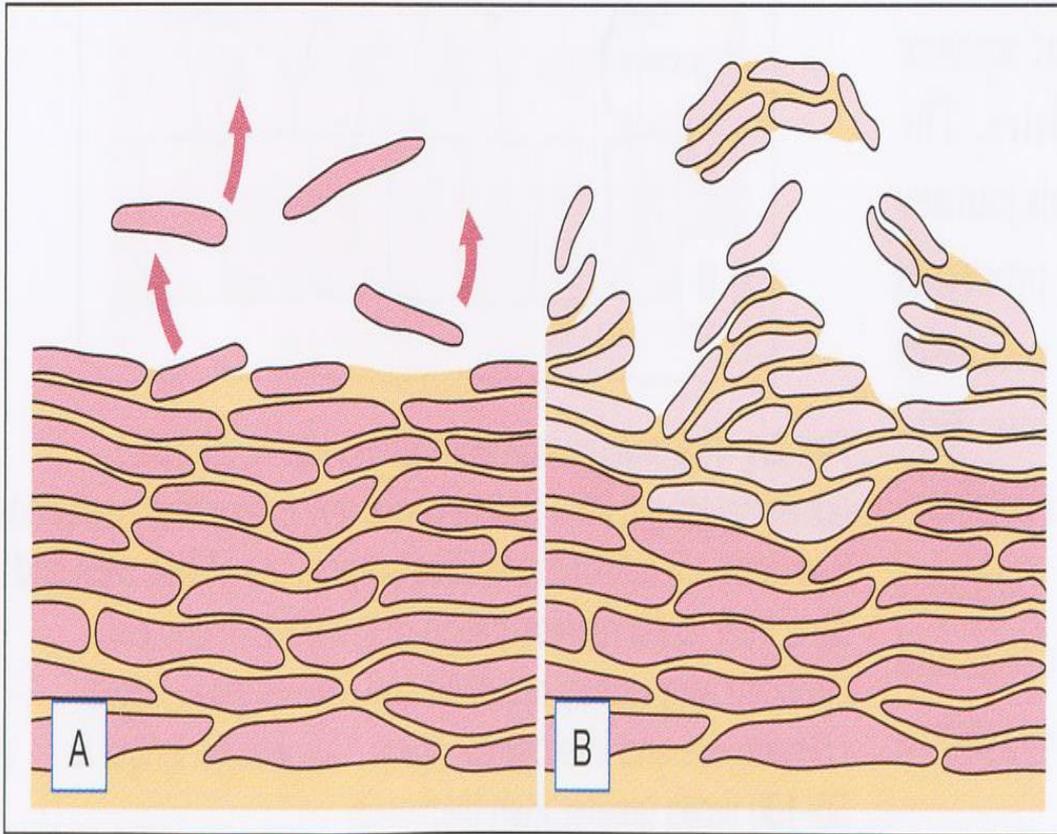


Fig. 2.3 (A) Stratum corneum fully hydrated at the skin surface with normal desquamation and release of effete corneocytes. (B) Stratum corneum with reduced hydration in the superficial layers leading to incomplete desquamation and a build up of attached cells at the skin surface (skin dryness)

Psoriasis



e. Psoriasis

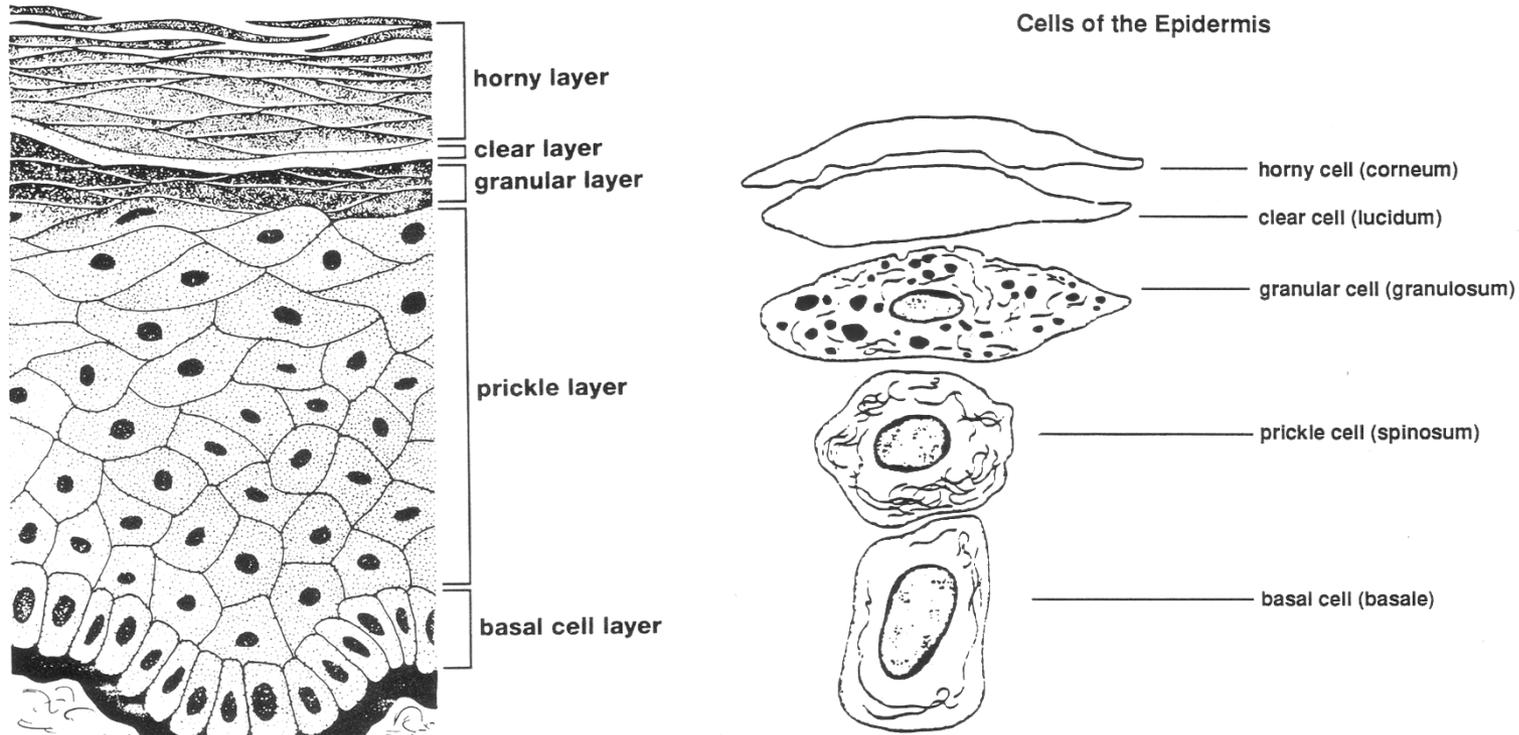
Psoriasis

A hyperproliferative hyperkeratosis

In psoriasis the skin turns over much too fast. Nucleated cells can be found in psoriatic plaques. These cells are called parakeratotic and should not exist in the SC

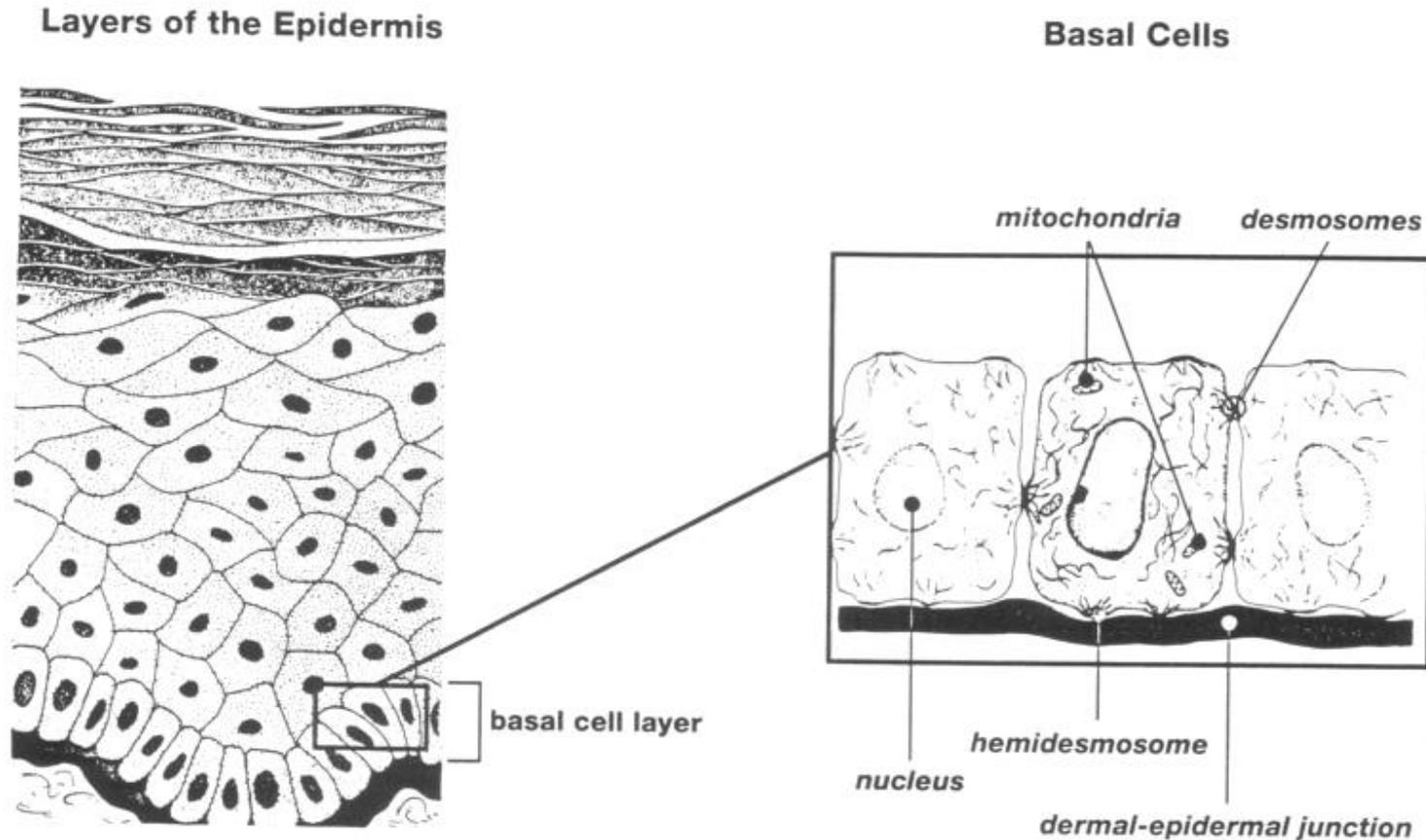


Epidermal layers and cells

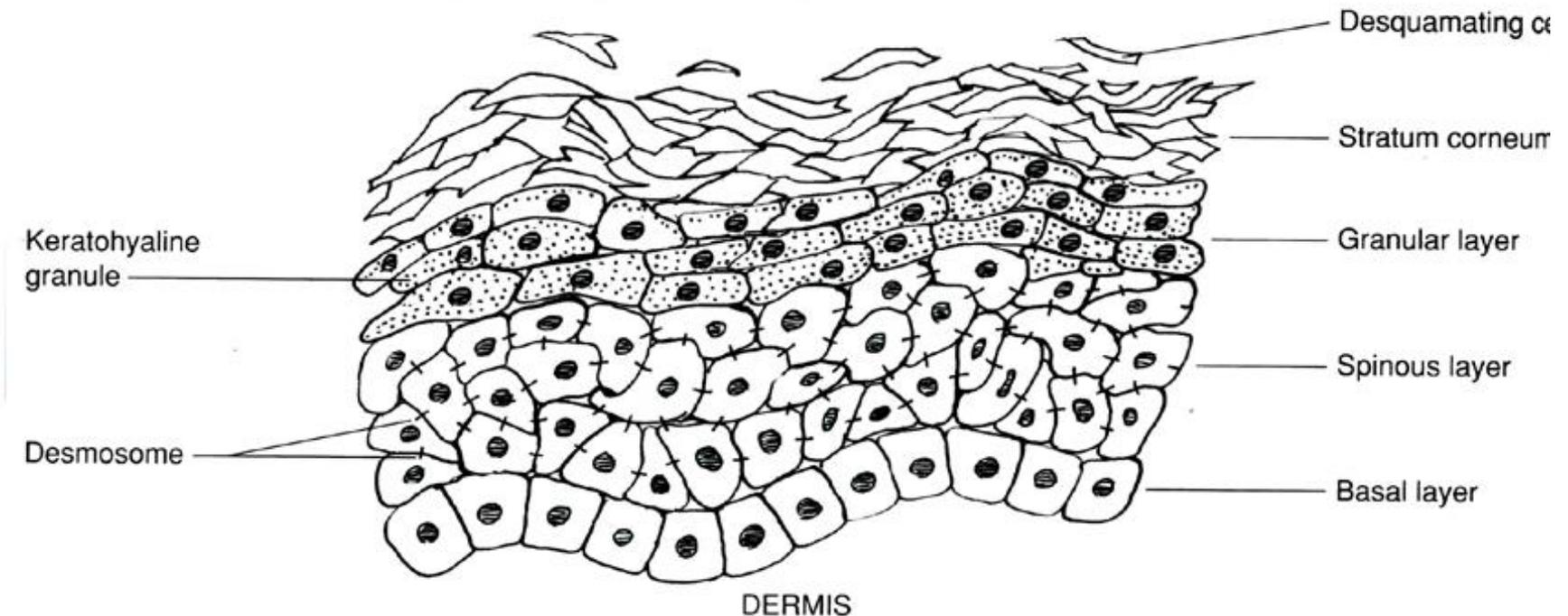


- As daughter cells move through the epidermis and mature, they develop different characteristics
- The layers of the epidermis are named for these characteristics

Basal layer: located at the base of the epidermis, cells are cuboidal in shape, responsible for maintaining the epidermis by continually renewing the cell population



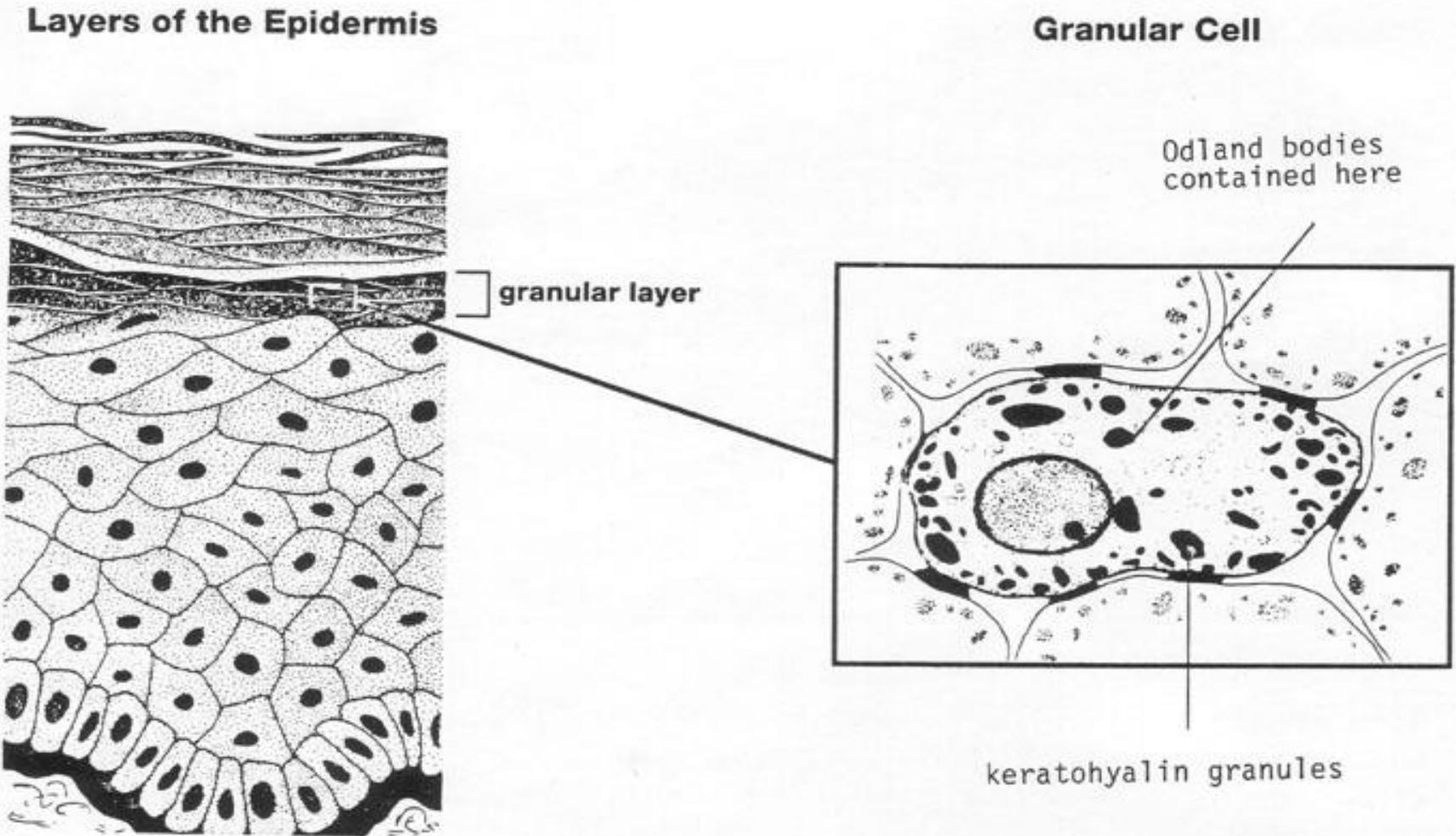
Spinous layer: the cells have spiny attachments called desmosomes



Granular layer:

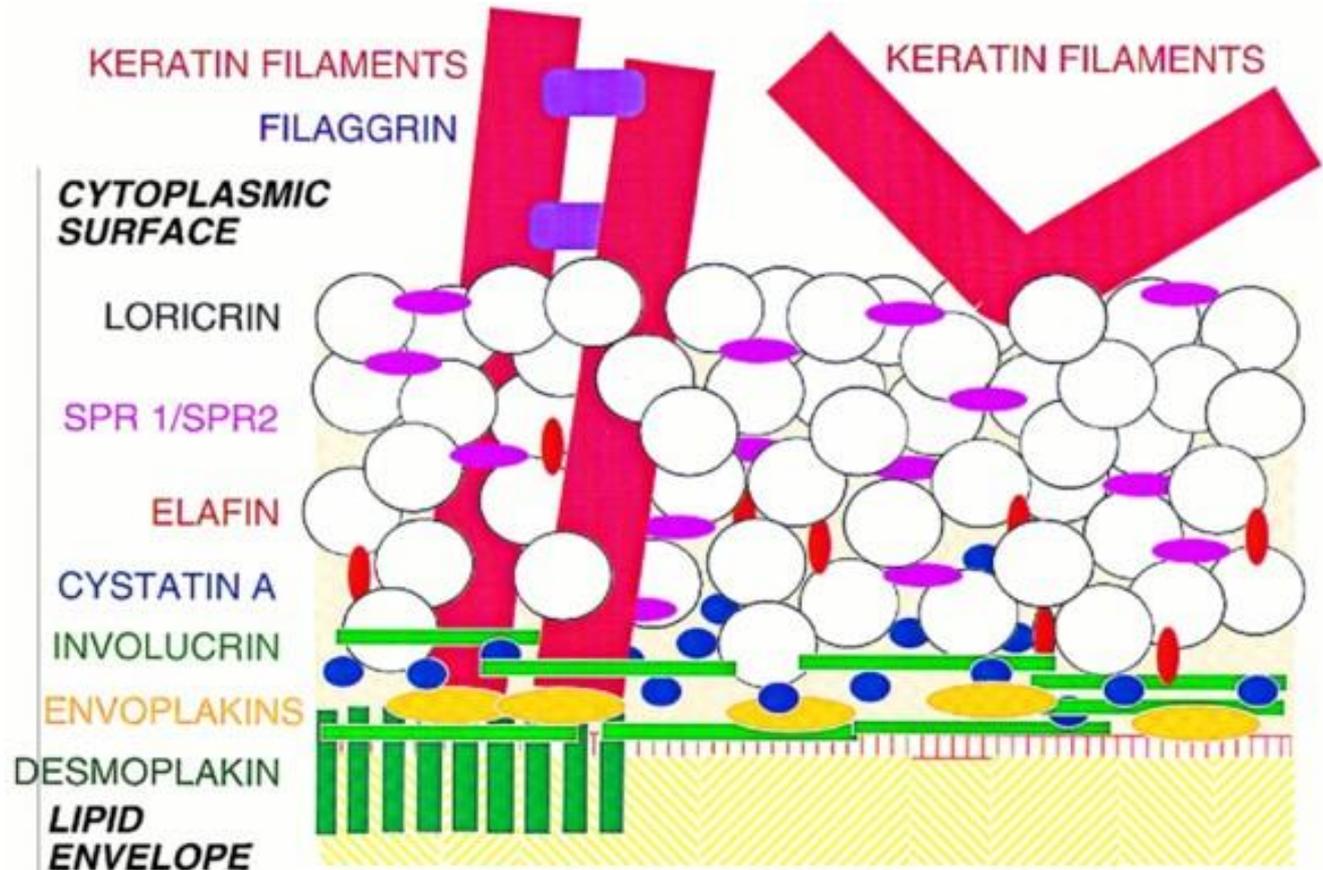
- Is named for the granules that appears in the cells:
 1. Keratohyalin granules: full of protein (filaggrin, Loricrin)
 2. Lamellar bodies: contain lipids, proteolytic enzymes involved in desmosomes hydrolysis, defensins
- At the granular layer keratinocytes are transformed to corneocytes also called squames to form the SC:
 1. The nucleus is digested
 2. The cytoplasm disappears
 3. The lipids are released into the intercellular space
 4. The cell membrane is replaced by a cell envelope (made of cross-linked protein with lipids covalently attached to its surface)

Granular layer:



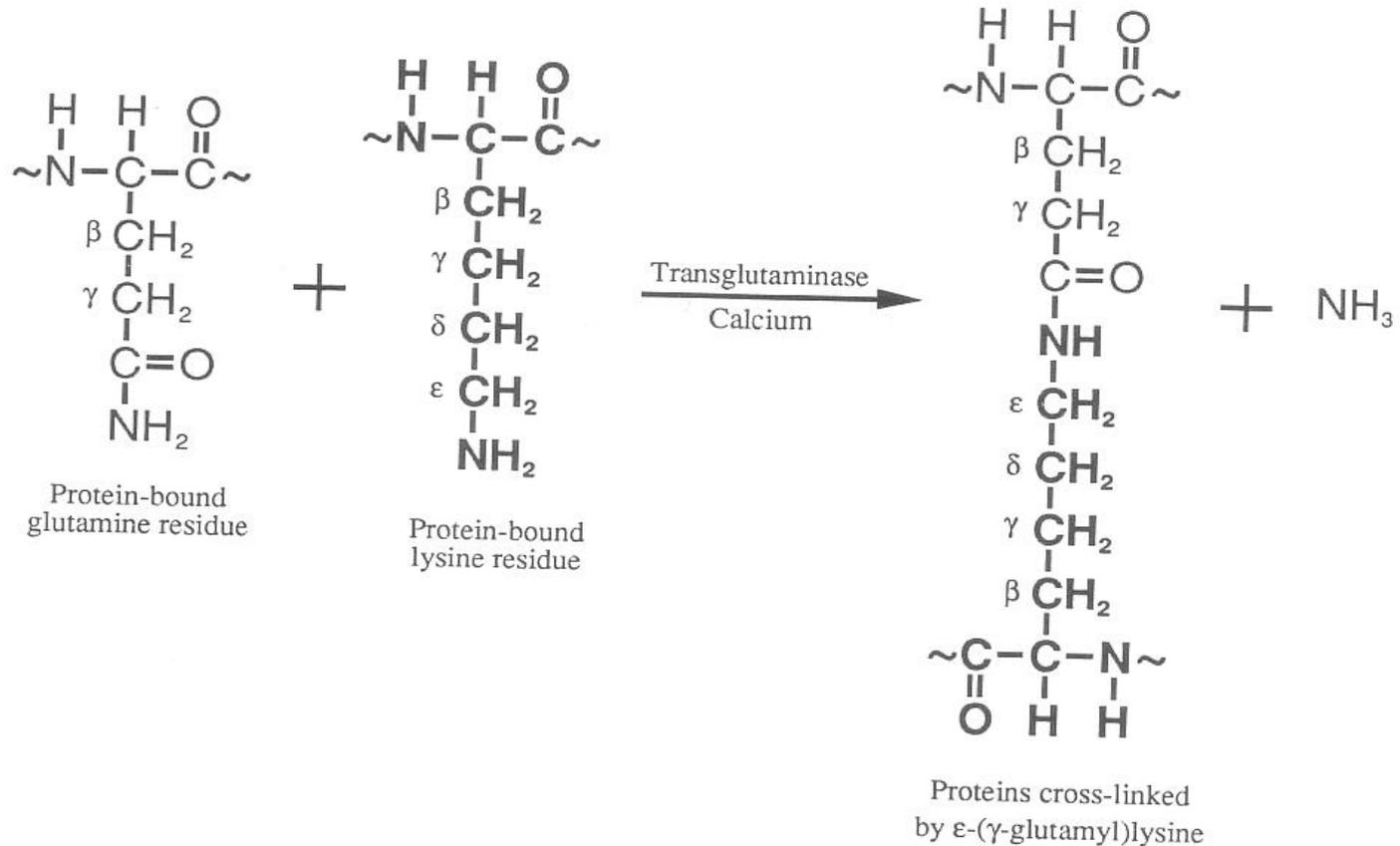
The cornified cell envelope (after Steinert)

- 15 nm thick
- 66% Loricrin
- Involucrin is on the outer surface
- Keratin fibers attach to inner surface
- Lipids are attached to the outer surface

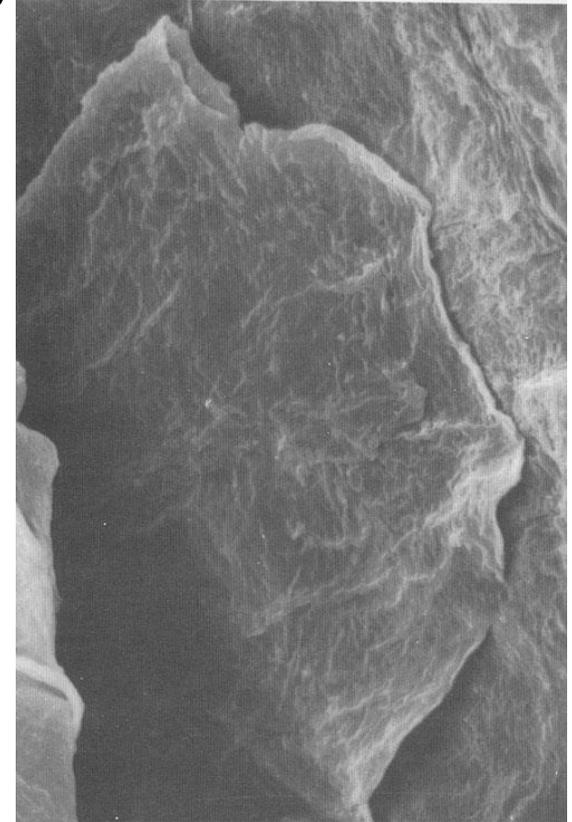
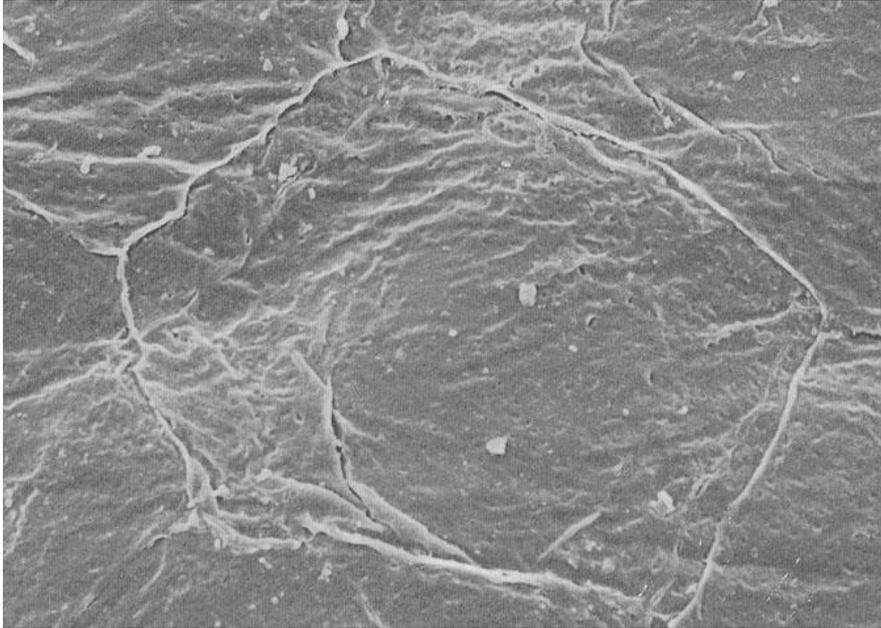


Transglutaminase:

A membrane bound enzyme that forms the cornified cell envelope by cross-linking proteins with isopeptide bonds.



SEM of Corneocytes



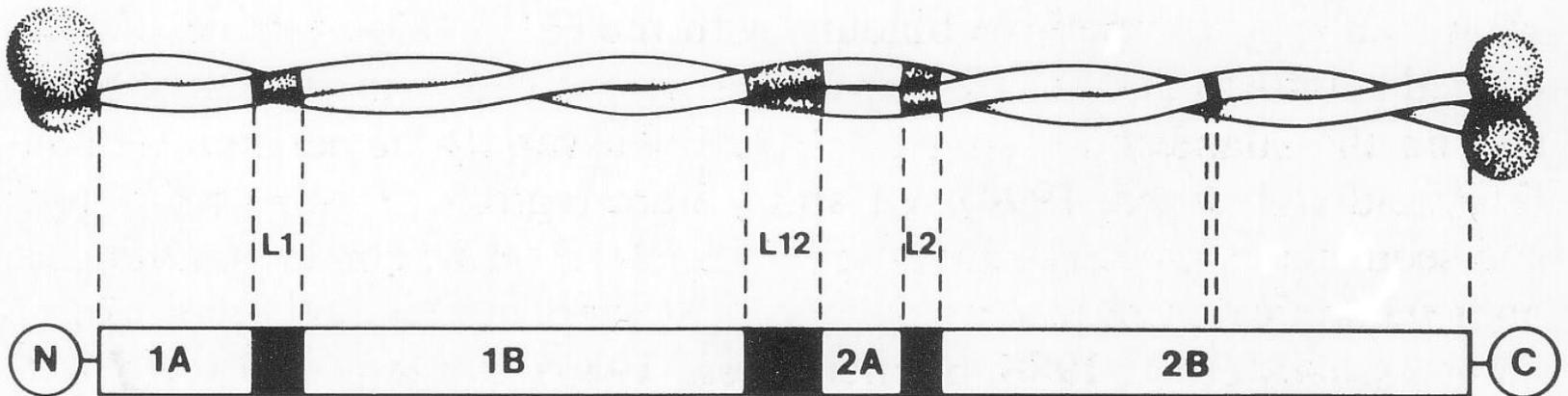
- The corneocytes that results from this transformation is a flat cell (a hexagon or pentagon) with a surface area of $1000\mu\text{m}^2$ and a thickness of 0.5 to $1\mu\text{m}$

Keratohyalin Proteins

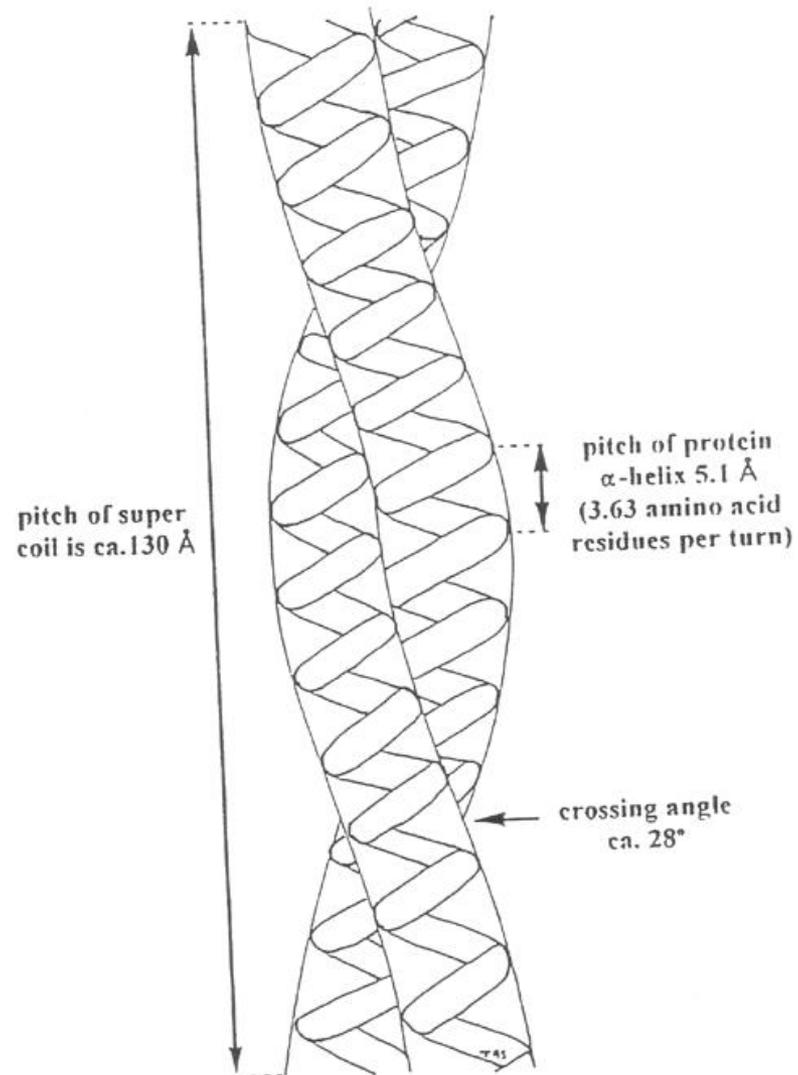
- Filaggrin:
 - Contains a high level of positively charged amino acids
 - Filament-aggregating proteins
 - The role of filaggrin is to help form the keratin microfibrils
 - After filaggrin forms the microfibrils it is modified to come off the microfibrils
 - It is then digested by enzymes to produce important components of the natural moisturizing factor (NMF) of the SC

Formation of the coiled-coil

Two keratin chains interact to form a coiled-coil.

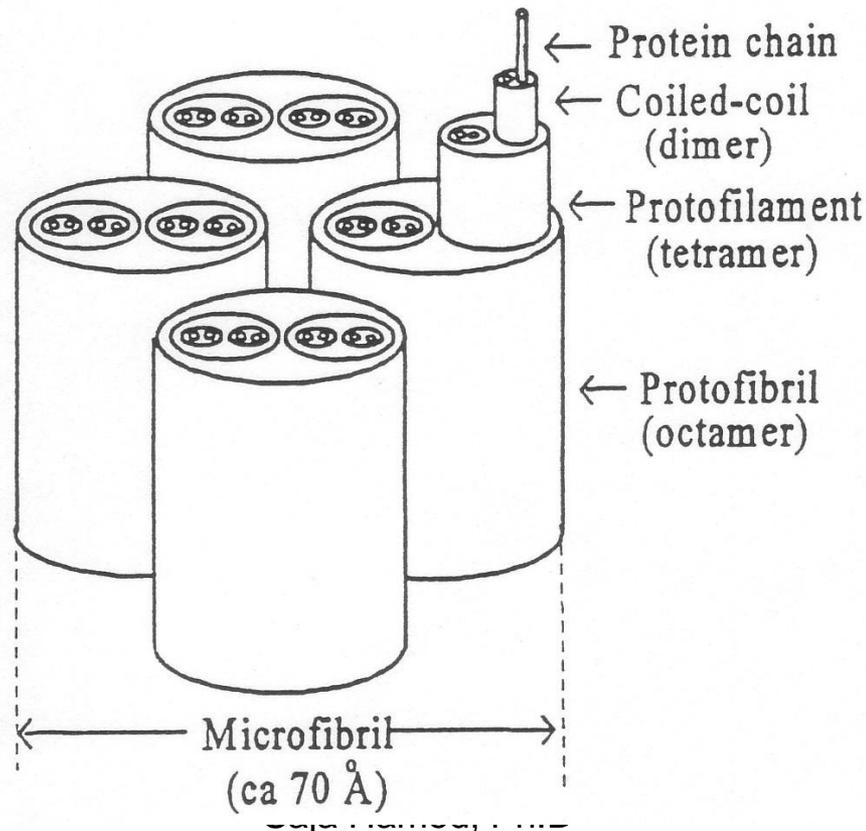


The Coiled Coil



The microfibril

In the stratum granulosum filaggrin interacts with keratin coiled-coils causing condensation to a 32 chain structure called the microfibril



- At the SG/SC interface keratinocytes are transformed to corneocytes
- Keratinocytes are normal cells with the normal constituents of cells i.e cell membrane, nucleus, cytoplasm
- Corneocytes or squames are flat cells with no cytoplasm, full of condensed keratin fibers and covered by a very tough structure called the cell envelope

Stratum Corneum

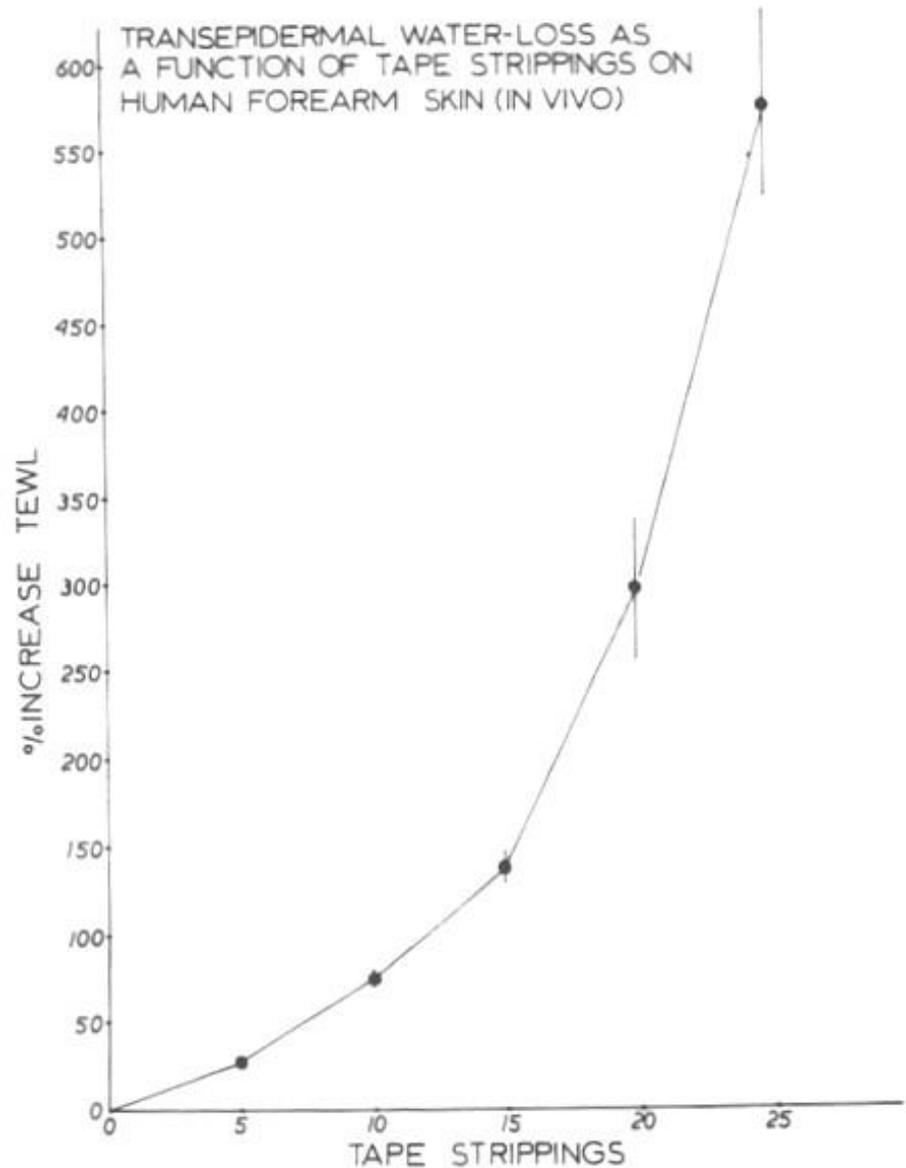
- On most body sites it is 12 to 16 cell layers thick
 - Flattened cells called corneocytes or squames with resistant cell envelope and covalently attached lipids
 - Content is keratin filaments
 - Squames joined by desmosomes (protein glue spots)
- Intercellular lipids (lipids outside the squames)
 - Multiple layers of polar but relatively hydrophobic lipids between cells
 - Ceramides, cholesterol and long chain fatty acids

SC thickness and TEWL with Body Site

BODY SITE	SC LAYERS	TEWL
Face n = 84	9 ± 2	No Data
Forehead n = 8	9 ± 1	No data
Eyelid n = 16	8 ± 2	15
Cheek n = 43	10 ± 2	11
Upper Arm n = 2	14	4
Back n = 3	13 ± 3	5
Abdomen n = 44	14±4	4
Thigh	16±4	4
Forearm n = 4	16±4	4-6*

Data from Ya-Xian et al Arch Dermatol Res 291:555-559(1999)

The barrier to water loss through the skin (TEWL) is the stratum corneum and removing the SC by tape stripping leads to dramatically increased TEWL



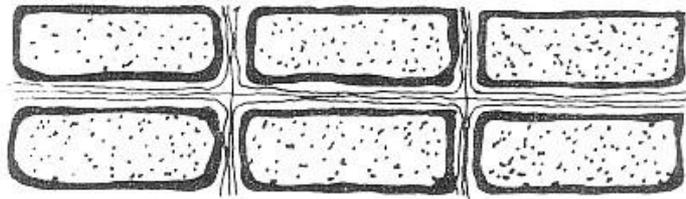
From MS thesis of Scott Coapman UC 1988

Stratum Corneum

- The SC is modeled as a brick wall
- Bricks = The corneocytes with their resistant cell envelopes and keratin microfibrils
- The bricks are linked by desmosomes
- Mortar = layers of lipids found between cells
- The lipid is the main barrier to water passing out through the SC

The SC is composed of protein-rich corneocytes embedded in a bilayer lipid matrix arranged in a “brick and mortar” fashion

STRATUM CORNEUM



COMPONENTS

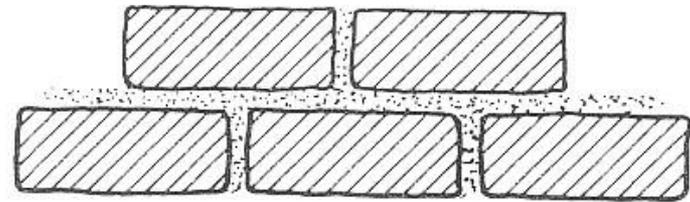
Corneocytes

IC Lamellar Lipid

IR

IR

BRICK WALL

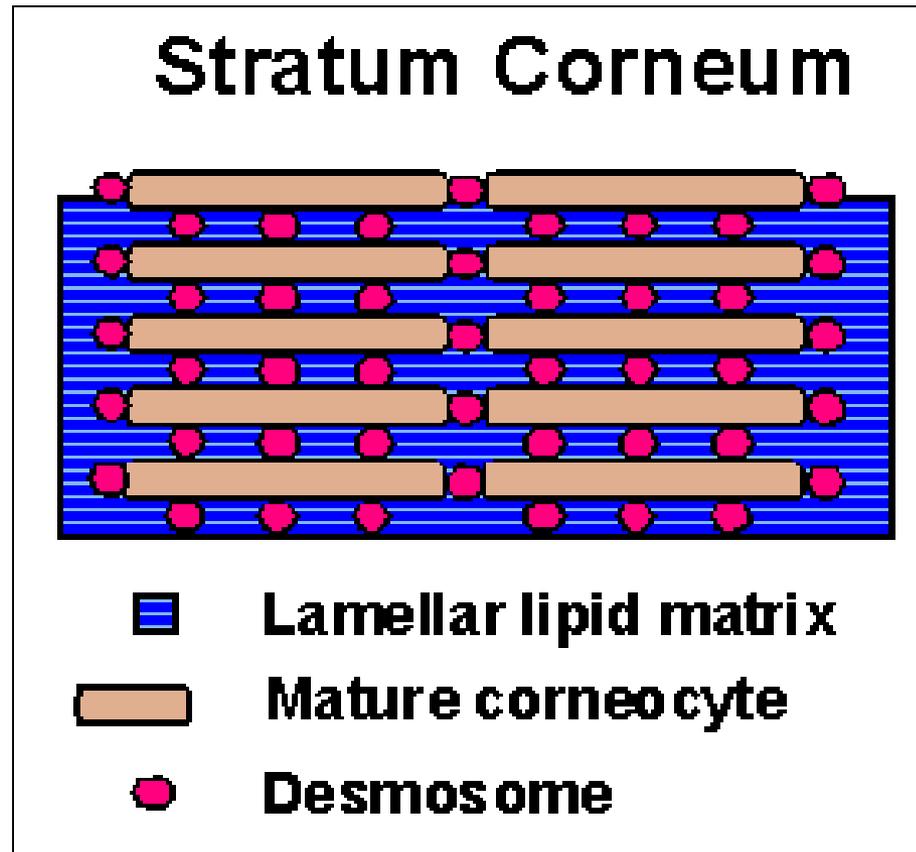


COMPONENTS

Bricks

Mortar

In the SC the bricks are joined together by protein glue spots called desmosomes

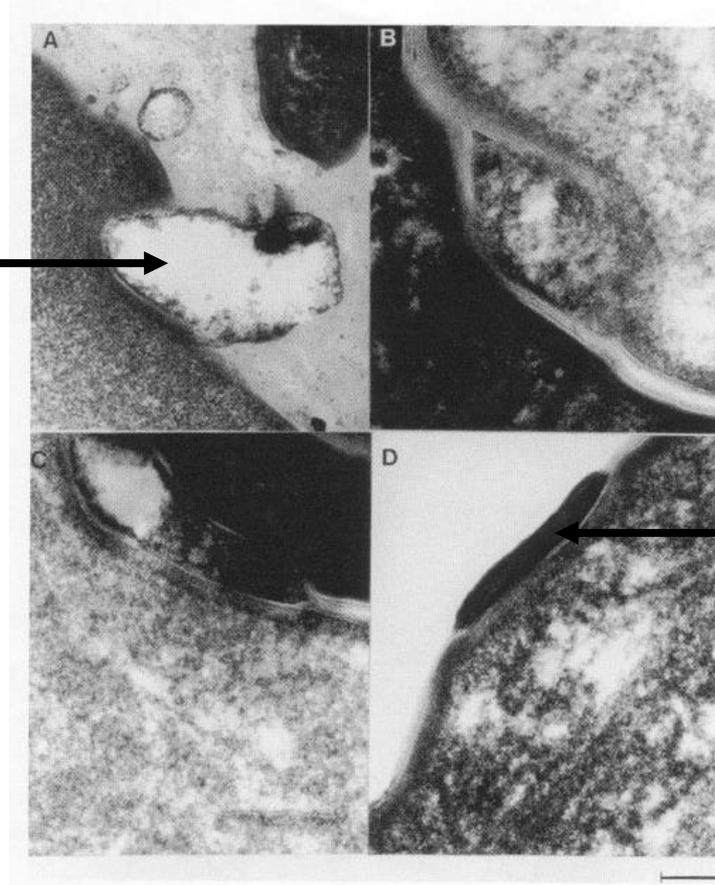


Desmosomes in the SC

Desmosomes are digested to allow desquamation

Upper SC

Digested desmosome



Lower SC

Intact desmosome

Rawlings et al (JSCC **45**, 203, 1994)

Stratum Corneum

- The lipids organize into multiple layers between the SC cells
- The SC contains no phospholipids
- Phospholipids are broken down by phospholipases in the lower SC
- This produces fatty acids which may play a role in producing the acid pH of the SC (SC surface pH 4-5.5)
- The SC acidic pH (acid mantle) may play a role in protecting against colonization of skin surface by harmful bacteria

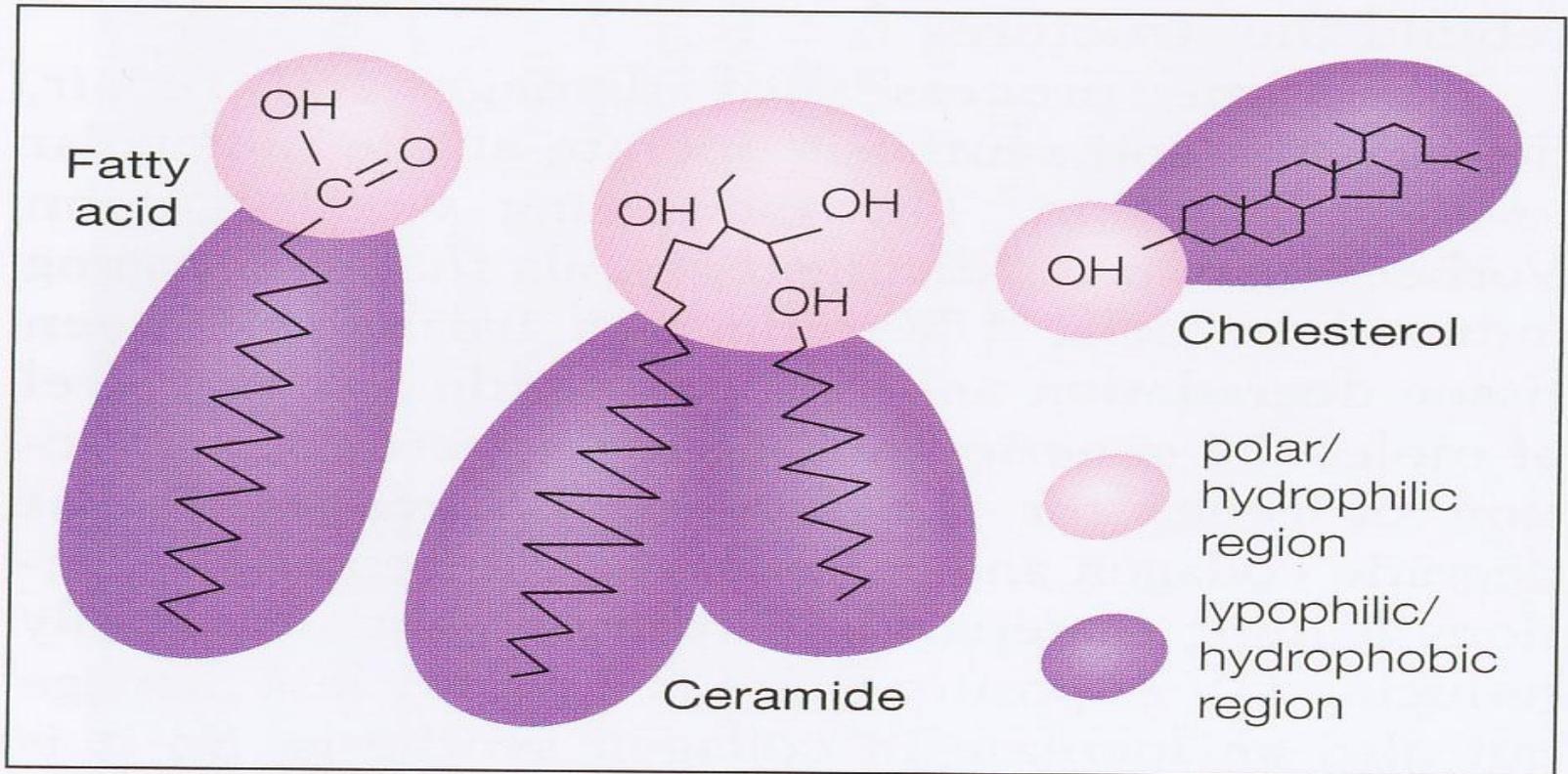
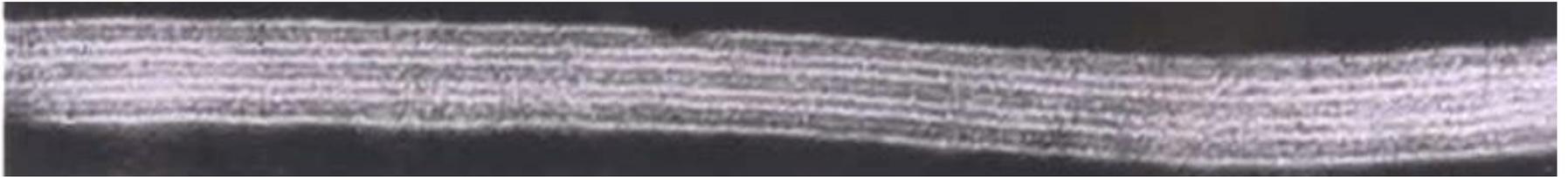


Fig. 2.4 Three classes of polar lipids, ceramides, fatty acids, and cholesterol, are the main constituents of the lipid matrix of the stratum corneum

The barrier lipids of the SC

There are multiple lipid layers
between the cells



Micrograph courtesy of Ronald Warner

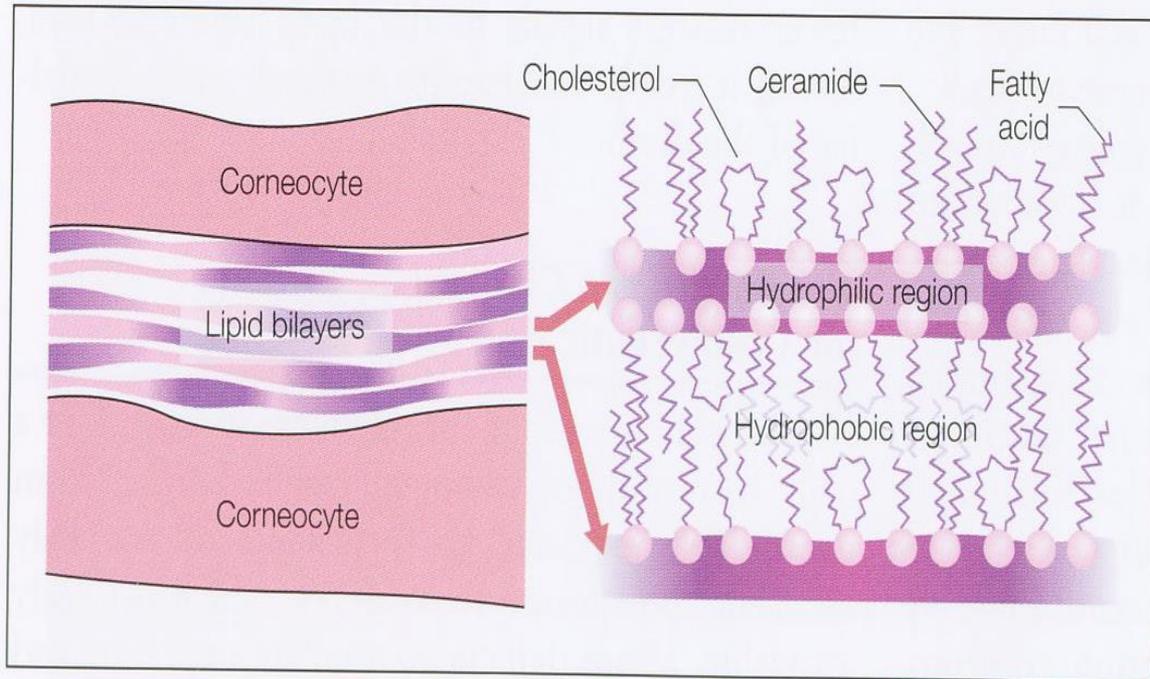
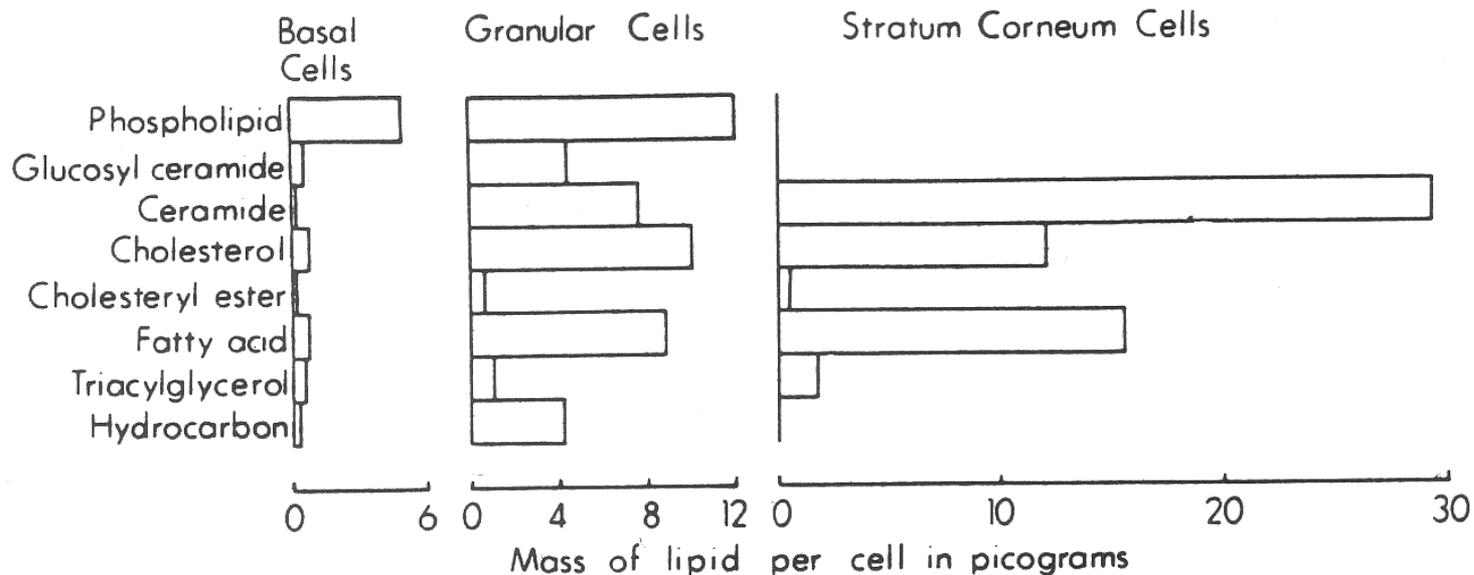


Fig. 2.5 The stratum corneum lipid matrix has a multiple bilayer organization formed by the spontaneous alignment of polar and non-polar regions of the ceramide, cholesterol, and fatty acid molecules

Lipid distributions in the epidermis

Note that there are no phospholipids in the SC



Stratum Corneum

- The Horny layer function as a protective layer It defends us against:
 - Dehydraton (i.e. prevent transepidermal water loss (TEWL))
 - External toxins
 - Bacterial infection
 - Protect the more fragile keratinocytes below from mechanical disruption
- Byproducts formed from the breakdown of filaggrin (i.e. amino acids and their metabolites) are called Natural Moisturizing Factor (NMF)
- Extracellular lipids and intracellular NMF play an important role in skin hydration

Natural Moisturizing Factor

- Inside the cells of the SC
- NMF consists of lactate, amino acids, pyrrolidone carboxylic acid (PCA)
- Gives the SC its humectant (water-binding) qualities
- It is made of very water soluble chemicals so that it can absorb large amounts of water even when humidity levels are low
- This enables the SC to retain a high water content even in a dry environment
- It also provides an important aqueous environment for enzymes

Natural Moisturizing Factor

- Ichthyosis vulgaris patients → severe dryness and scaling of the skin
- Normal skin washed with soap has lower levels of NMF compared to skin not washed with soap
- Levels of NMF decline with age → contribute to the increased incidence of dry skin in the elderly population

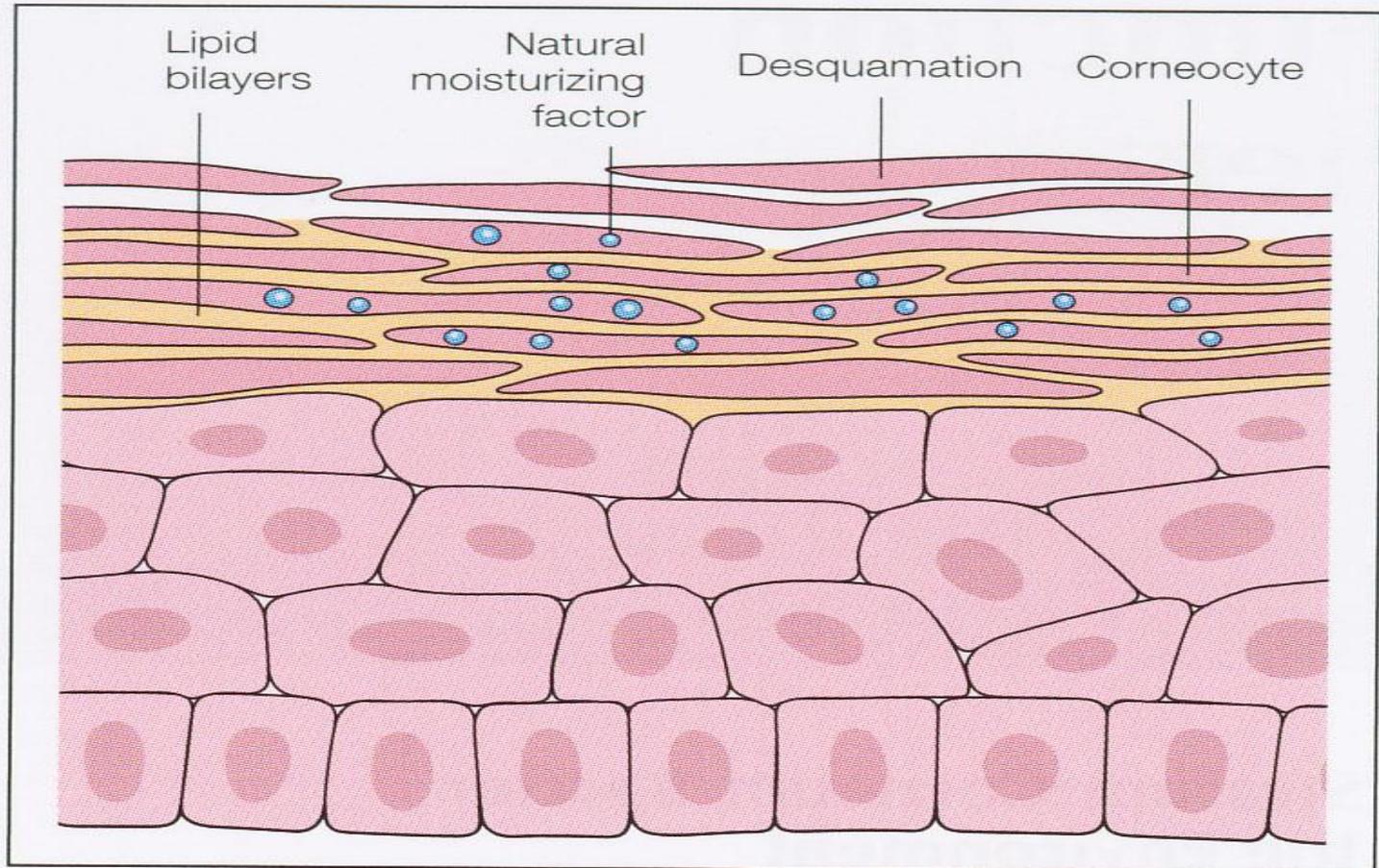


Fig. 2.2 The four key processes for the formation and functioning of the stratum corneum

Ichthyosis vulgaris results from a defect in profilaggrin synthesis.



Dermis

- It is responsible for the **thickness** of skin:
 - Varies over different parts of the body
 - Double between the ages of 3 and 7 years and at puberty
 - Decrease with aging
- Consists mostly of collagen
- Primary cell type is fibroblasts
- They produce collagen, elastin, other matrix proteins, and enzymes (e.g. collagenase)
- Nerves, blood vessels, sweat glands, and immune cells (e.g. mast cells, lymphocytes, and macrophages)

Dermis:

- The dermis is composed of an amorphous intercellular substance. Within this amorphous substance are:
 - **Cells of the dermis**
 - **Collagen and elastin fibers**
 - **Blood vessels**
 - **Nerves and sensory organ**
 - **sebaceous glands**
 - **Hairs**
 - **Sweat glands**
- Its upper level has projections that extend into depressions in the epidermis

- *Papillary dermis:*
 - uppermost portion
 - Contain fine , delicate type III collagen fibers
- *Reticular dermis:*
 - lower portion
 - It is a net of thick, dense connective tissue composed primarily of thick type I collagen fibers
 - Type I collagen provides support and bulk to the skin

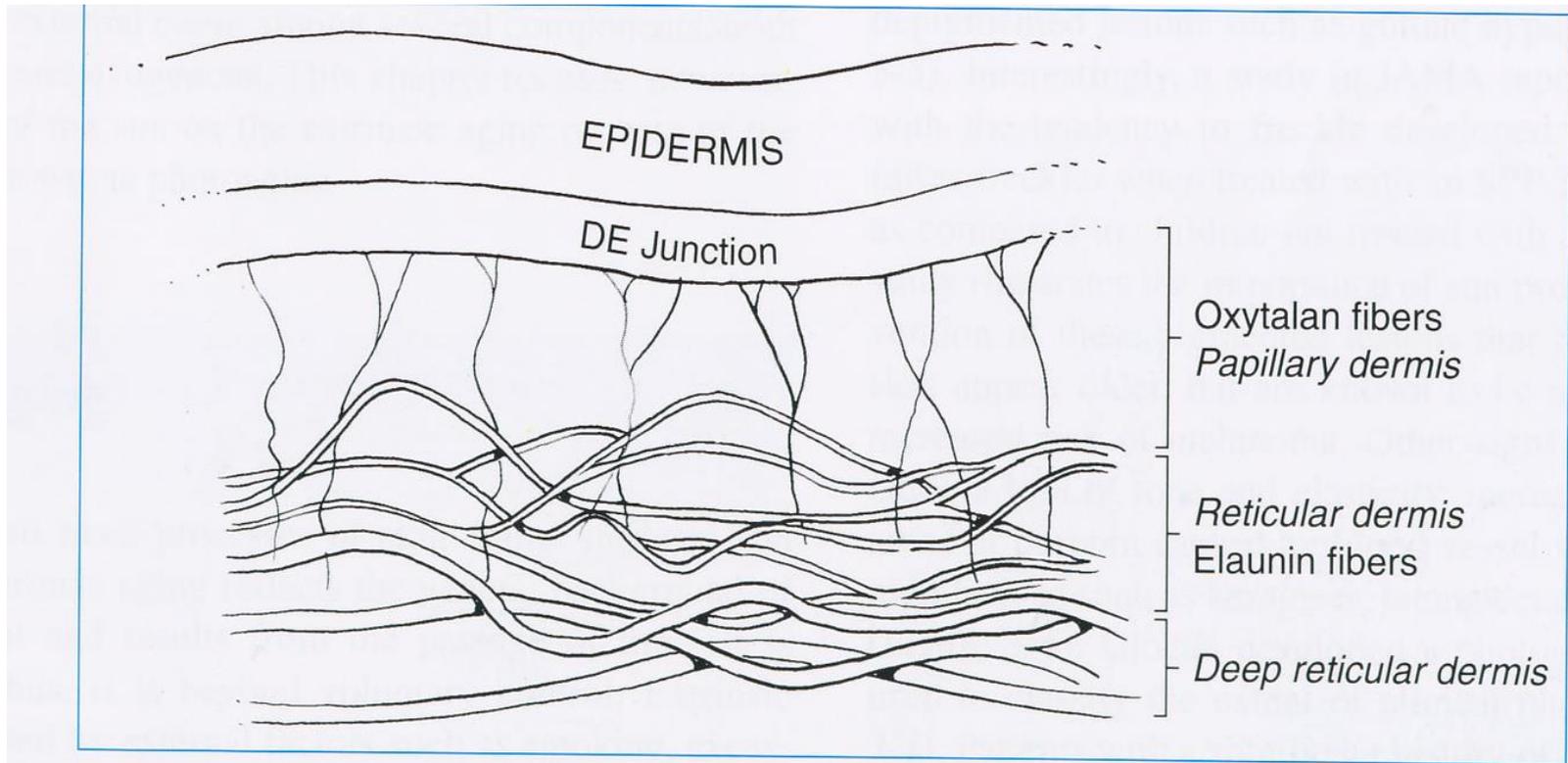
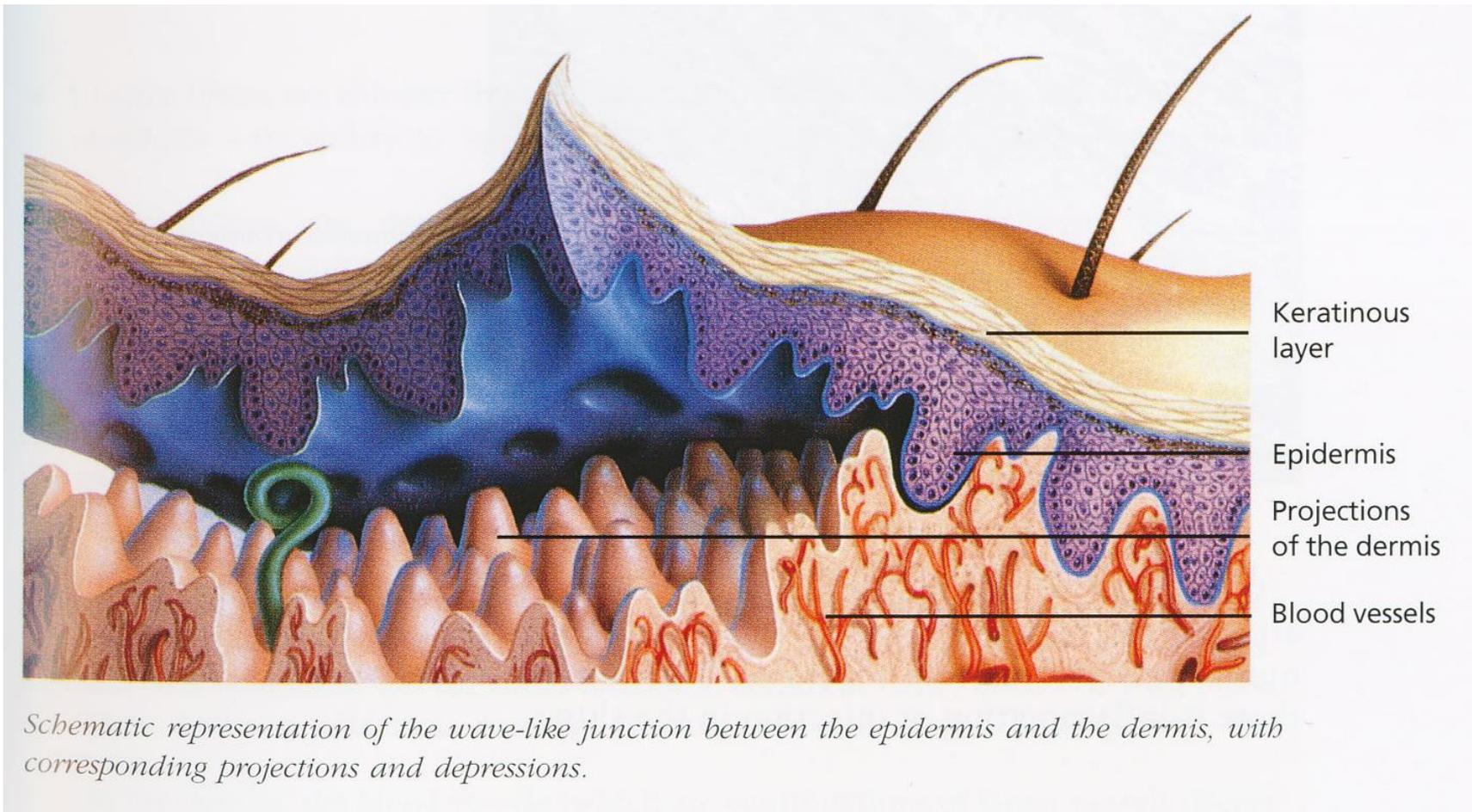


Figure 2-2.

The elastic fiber network in the dermis consists of immature oxytalan fibers in the superficial dermis and the more mature elaunin fibers in the middle dermis. The most mature elastic fibers are unnamed and are found in the deep reticular dermis.

The junction between the epidermis and dermis is known as the dermal-epidermal junction (DEJ)



Collagen

- Give the skin its strength
- Comprises 70-80% of dermis dry weight
- A complex family of 18 proteins (11 are present in the dermis)
- Is synthesized in the fibroblasts as procollagen:
 - Proline (Prolyl hydroxylase) → hydroxyproline
 - Lysine (lysyl hydroxylase) → hydroxylysine
 - Both reactions require the presence of Fe⁺⁺, ascorbic acid, and α -ketoglutarate

Major Collagen Types Found in the Dermis

Type	Other Name	Location	Function	% of Dermis	Associated Diseases
I		Bone, tendon, skin	Gives tensile strength	80%	Aging
III	“Fetal collagen”	Dermis, gastrointestinal vessels	Gives compliance	15%	Aging
IV		Basement membranes	Forms a lattice		
V		Diffuse, dermis	Unknown	4-5%	
VII		Anchoring fibrils	Stabilizes DEJ		EBA, dystrophic EB
XVII	BPAG2 (BP180)	Hemidesmosome	Stability		BP, HG

Collagen is found in many vital structures of the DEJ and in the dermis. Defects in these collagens, or antibodies directed toward these important collagens, can result in dermatologic diseases.

Elastin

- They are thinner than collagen fibers
- Responsible for the skin's elasticity
- Forms a delicate, freely branching fibers which can be stretched by 100% or more but return to their original length when the stress is removed
- Elastin degrades with significant levels of sun exposure = Elastosis
- Collagen and elastic fibers are embedded in a water-binding, gelatinous like ground substance that contains glycosaminoglycans

Ground substance

- Proteoglycans
- Role:
 - Support for other dermal components
 - Mediate attachment of fibroblasts and growth factors involved in dermal repair

Glycosaminoglycans (GAGs)

- Polysaccharide chains composed of repeating disaccharide units that are linked to a core protein
- They bind water → may contribute to the maintenance of salt and water balance
- GAGs content decrease with aging
- The most abundant GAGs in the dermis is Hyaluronic acid (HA) and dermatan sulfate
- HA is a popular ingredients in cosmetic products because it acts as a humectant

What is the Net Charge of the proteins found in the skin's upper layer?

- Isoelectric Point= 3.5-4.5
- PH=4.5-5.5
- Conditioning
- Hand sanitizers