

# **Skin, mamma (structure and development)**

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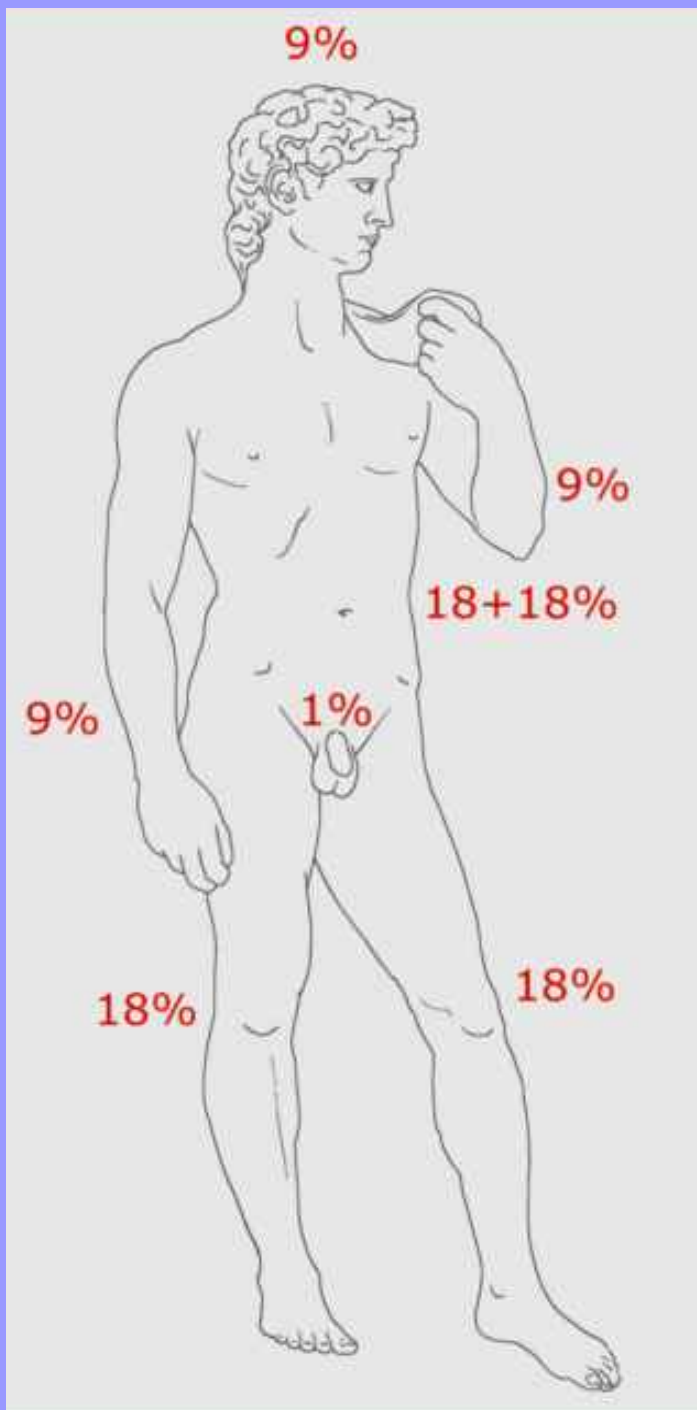
**May 31, 2012**



**Body surface – 1.6 m<sup>2</sup>, 16% of the body's weight**

**Many different functions:**

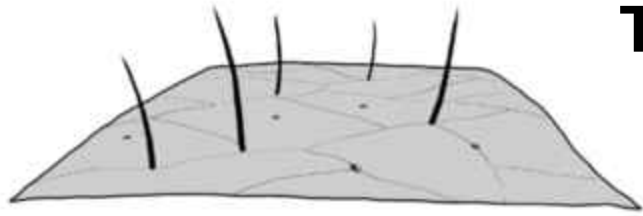
- **Protection** against mechanical, chemical and thermal injuries, against invasion of many pathogenic microorganisms
- **Defense mechanisms** of the body (content of cells of immune system)
- **Maintaining of body temperature** (variable blood circulation, discharge of fluids (sweat))
- **Regulation of water balance** (protection against desiccation, route for loss of fluid and mineral salts via the secretion of its glands,
- Sense organ (perception of pressure, temperature and pain)
- **Communicating organ** (autonomic system, blushing, pallor, piloerection)
- Skin shows electrical resistance



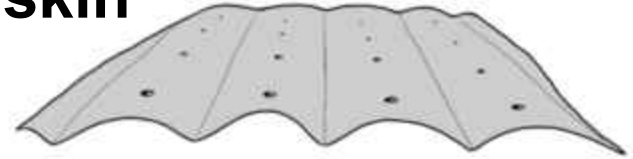
To determine the extent of the burn, the body surface area burned must be known. The area can be estimated using a formula, **the rule of nine.**



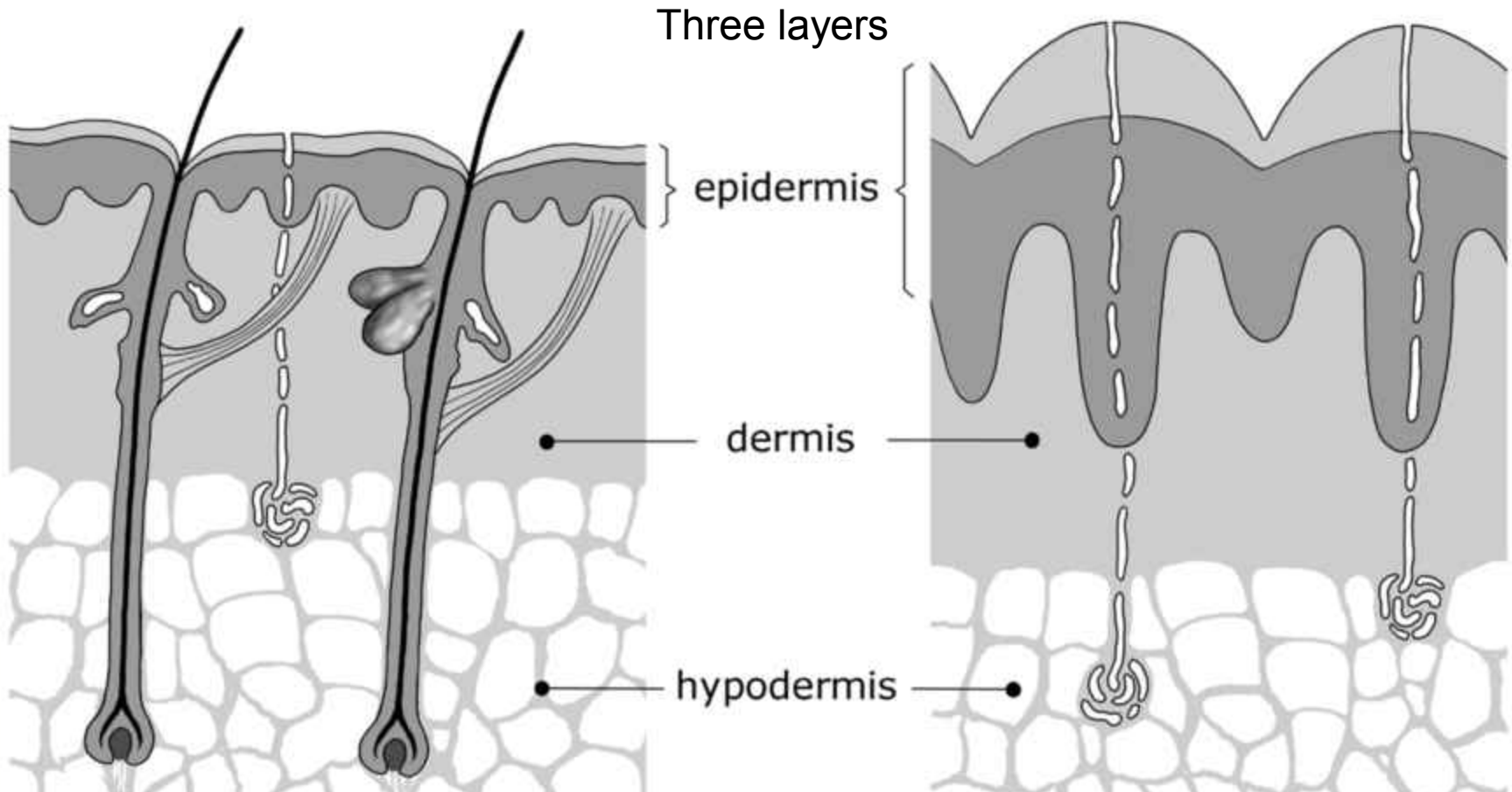
## Two types of skin



Polygonal areas

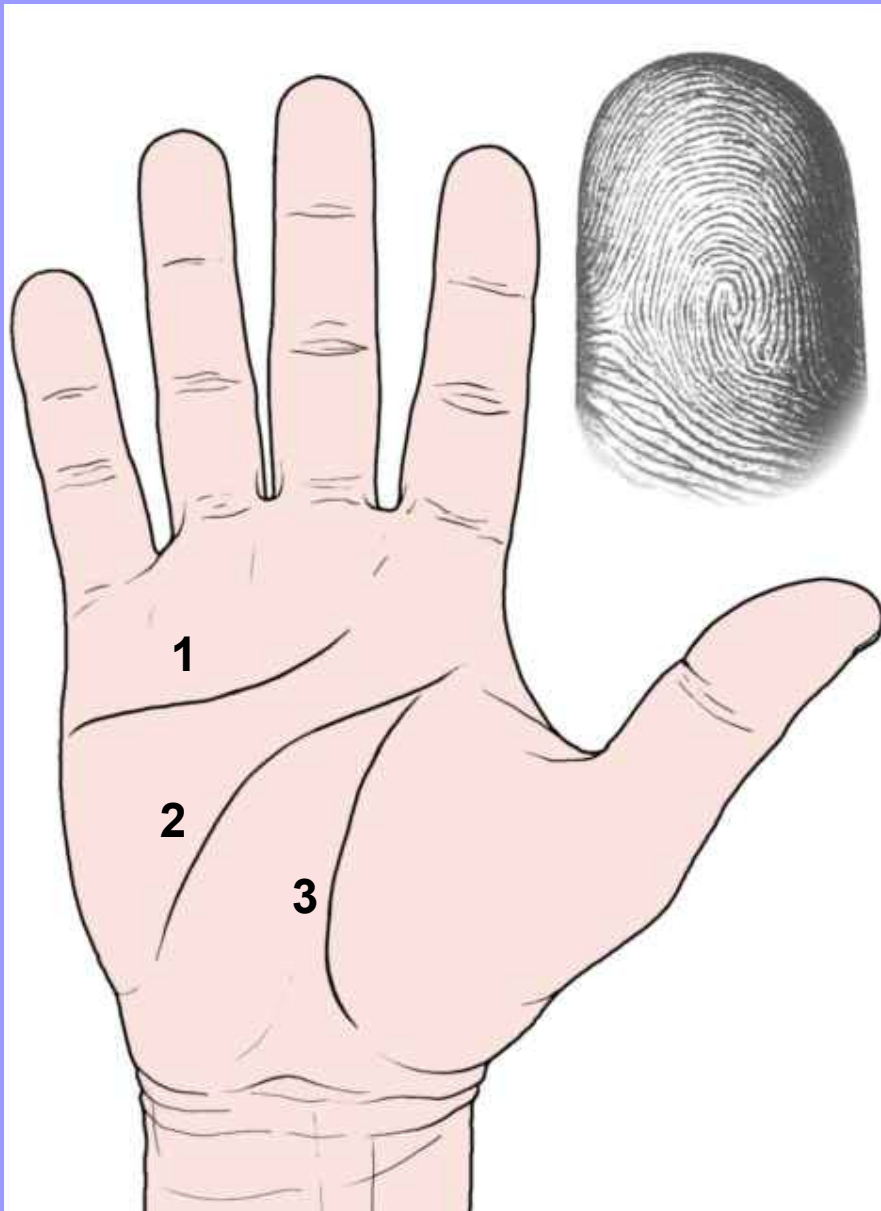


Parallel ridges

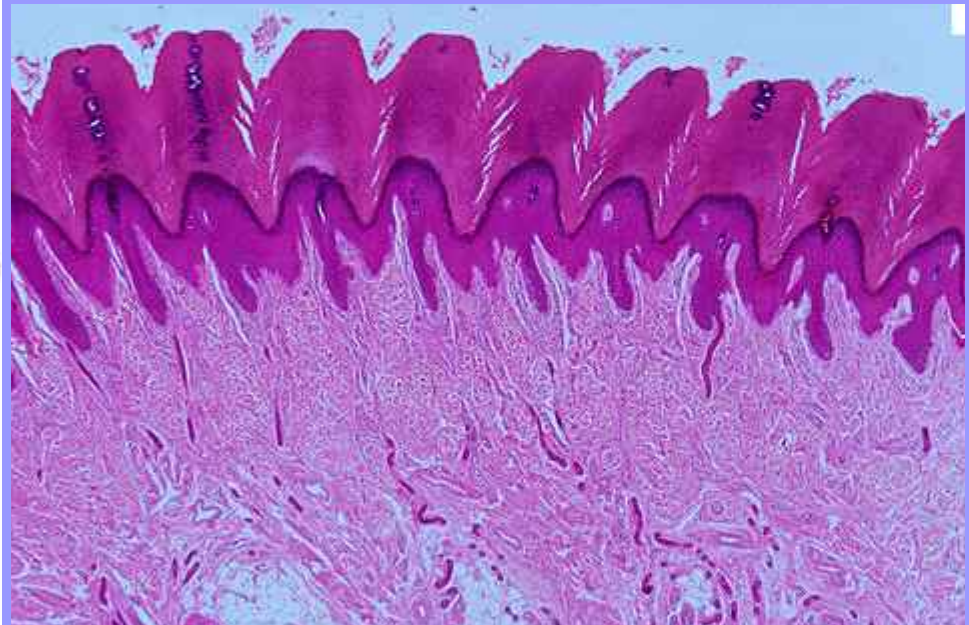


Hairy skin

Glabrous (hairless) skin



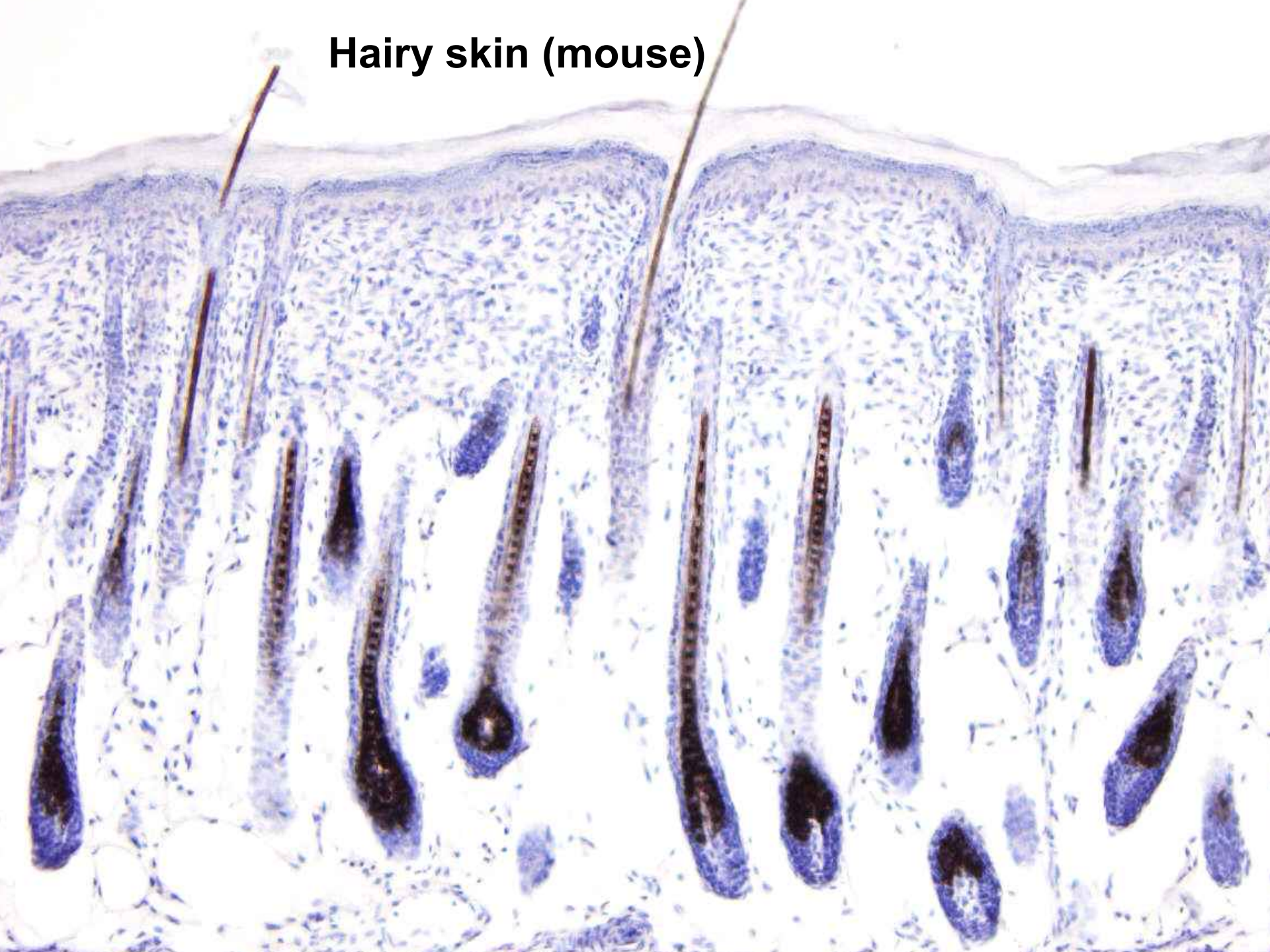
Palm of the hand: papillary ridges and larger flexure lines, fingerprint ridges: - whorl, loops

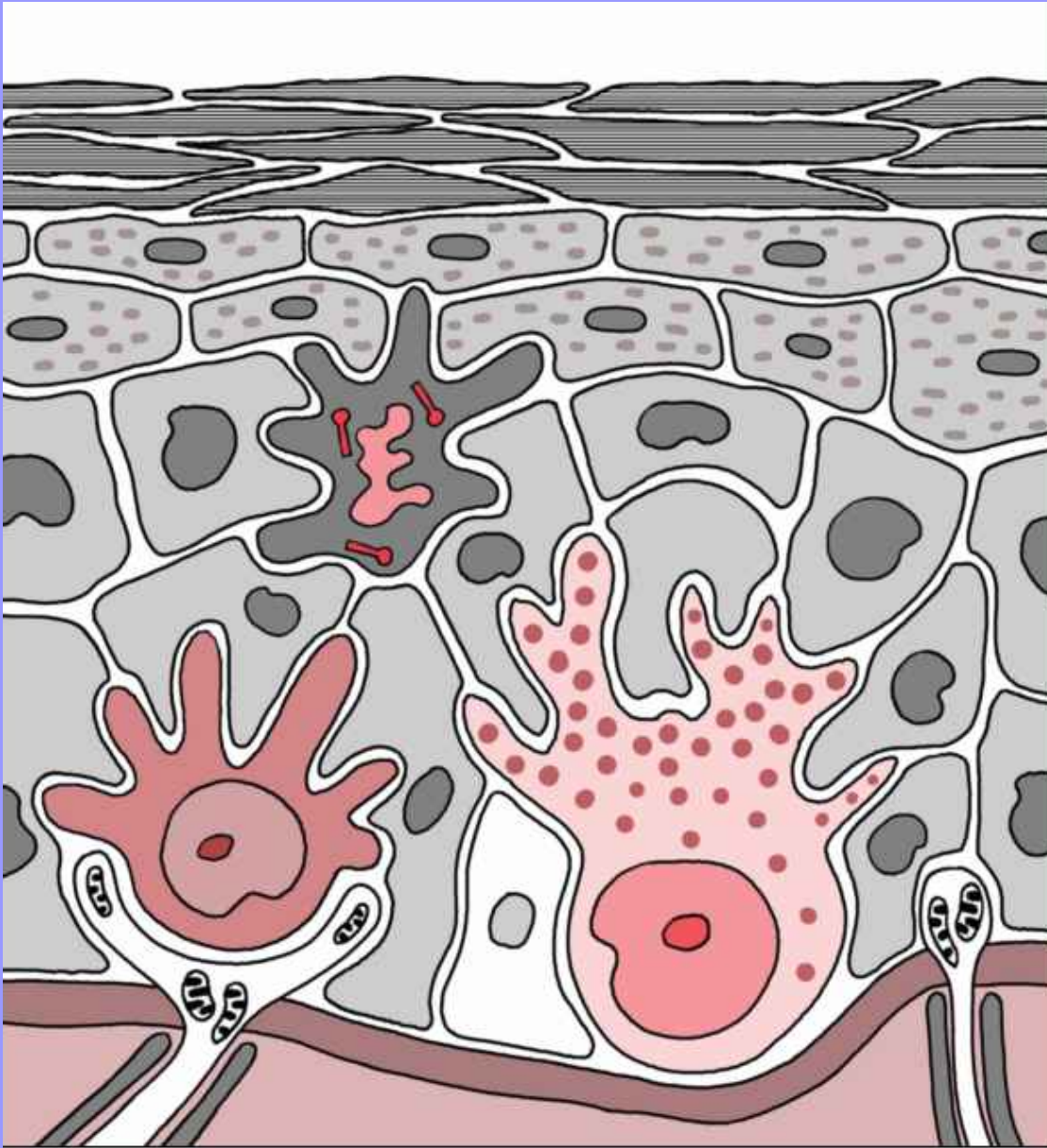


1 – linea occlusionis digitorum trium ulnarium  
2 – linea manus clausae  
3 – linea oppositionis pollicis



**Hairy skin (mouse)**





Keratinocytes

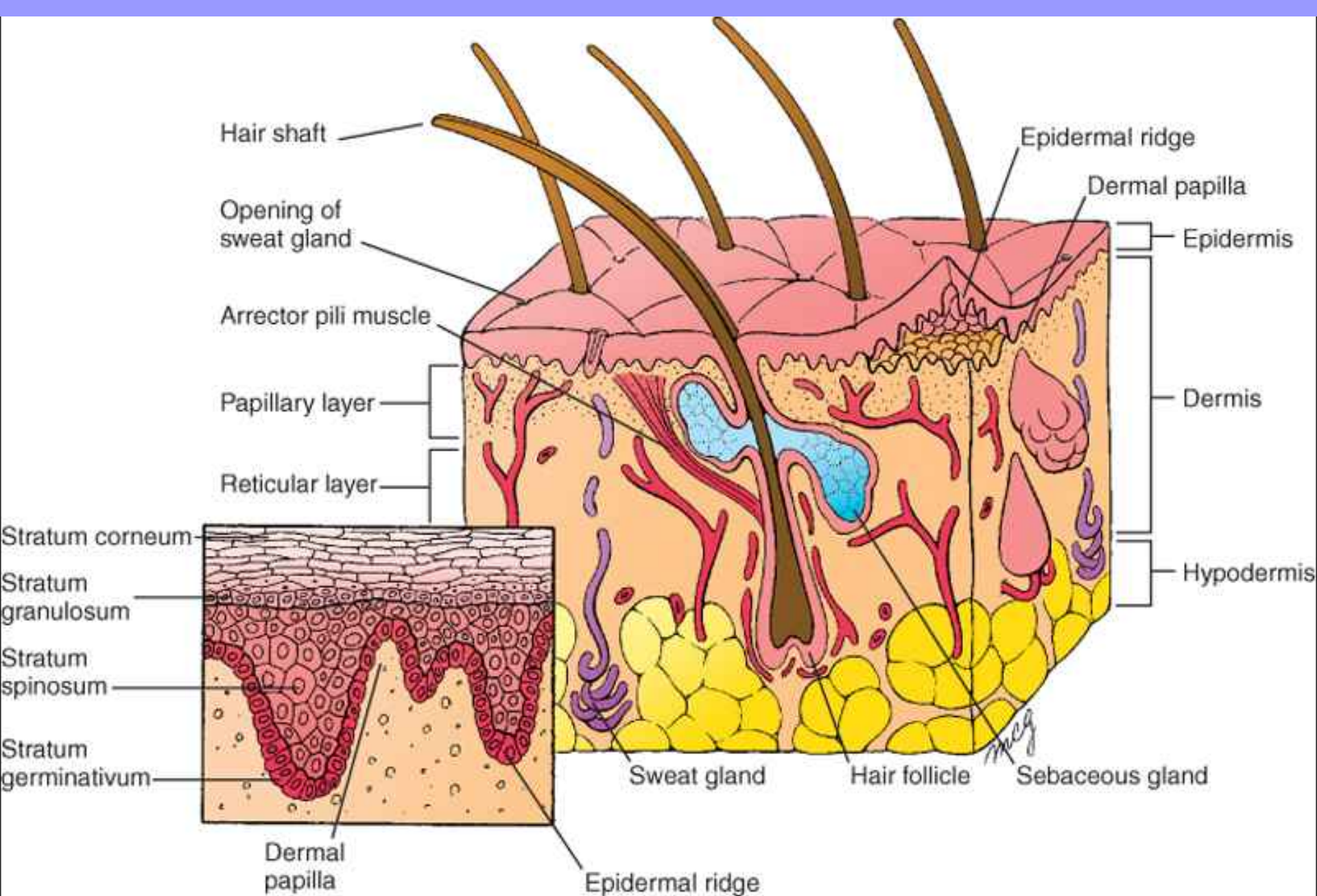
Langehans cells

Melanocytes

Merkel cells

Stratified keratinized squamous epithelium of the skin is formed by keratinocytes and epidermal immigrans

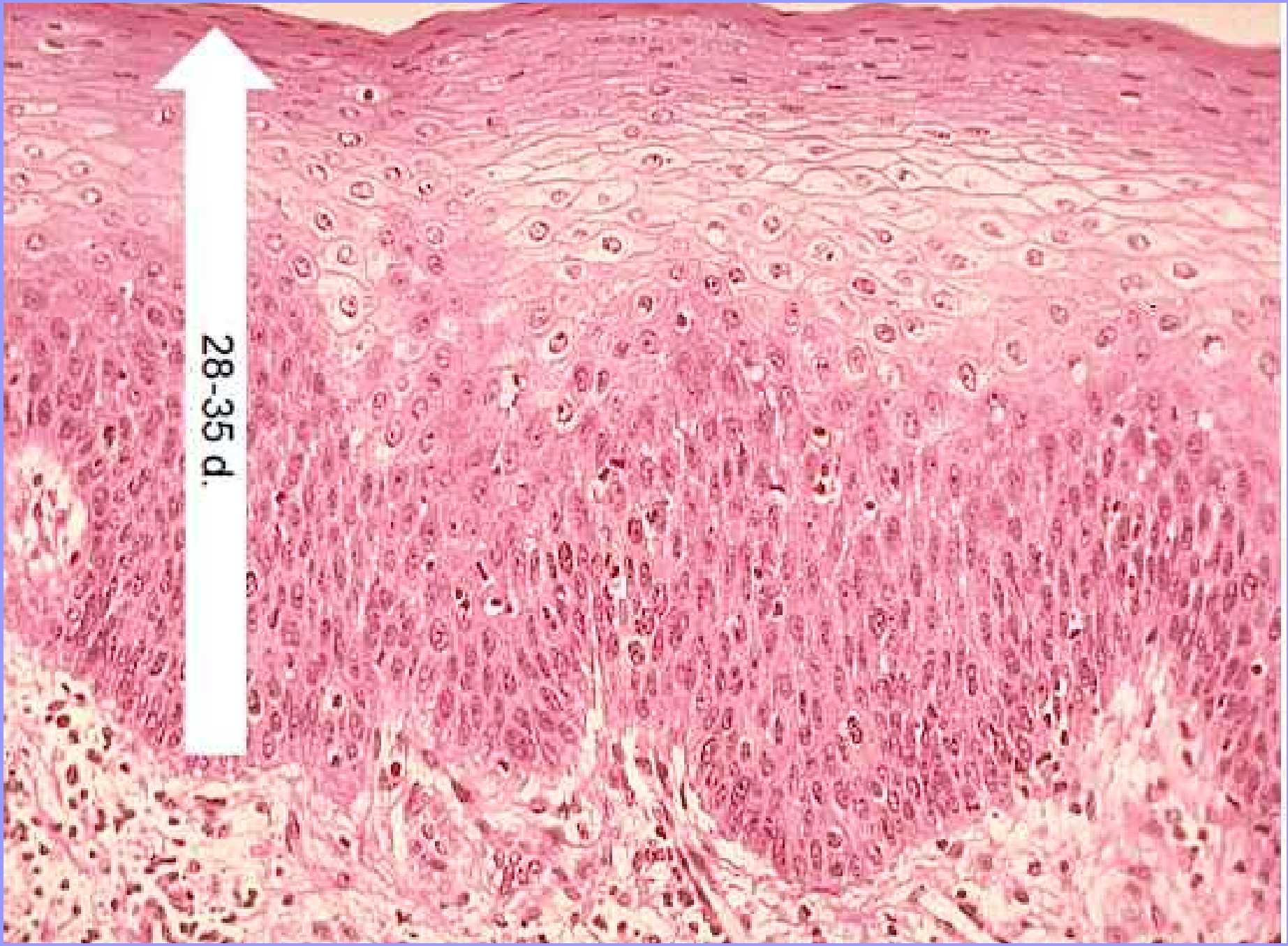




Schoenwolf et al: Larsen's Human Embryology, 4th Edition.

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28-35 d.

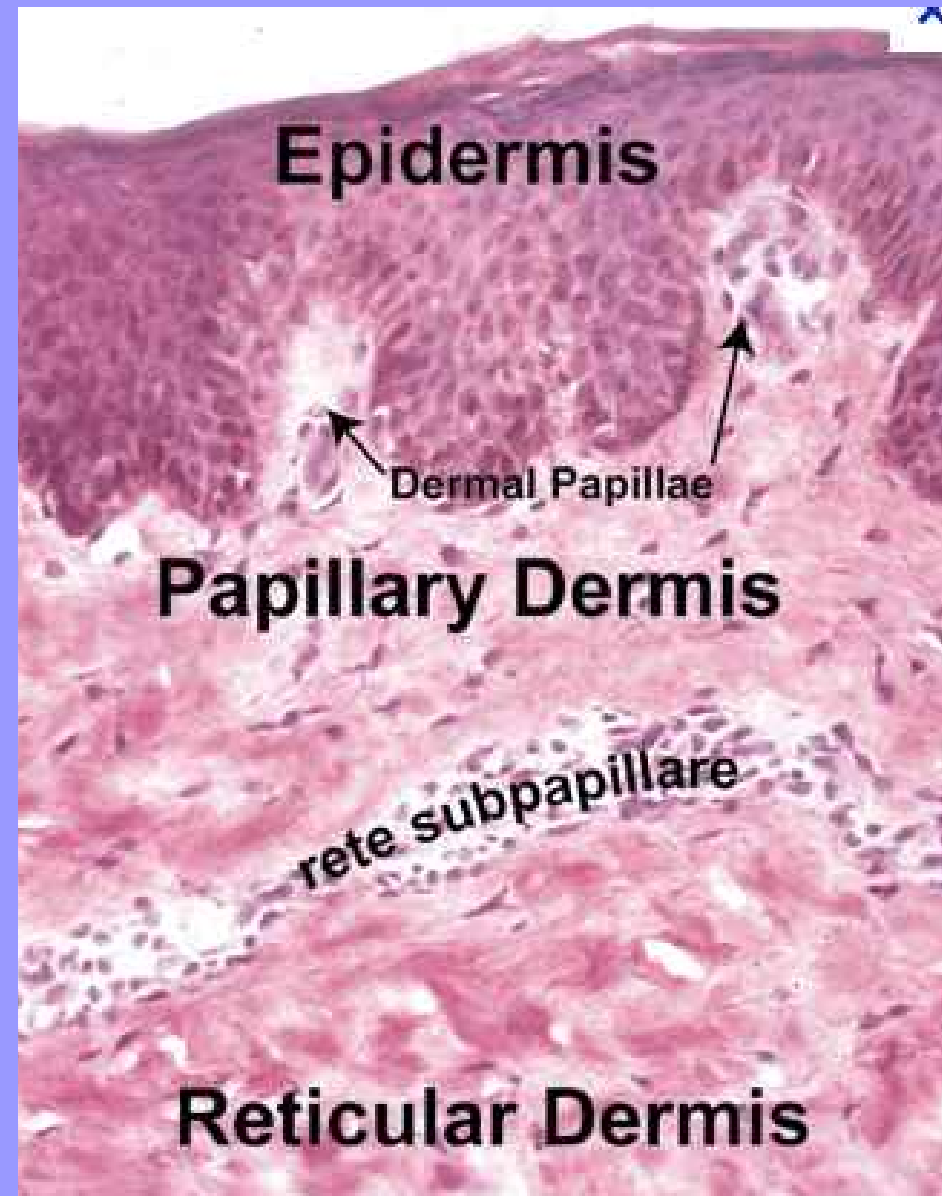
## **Dermis**

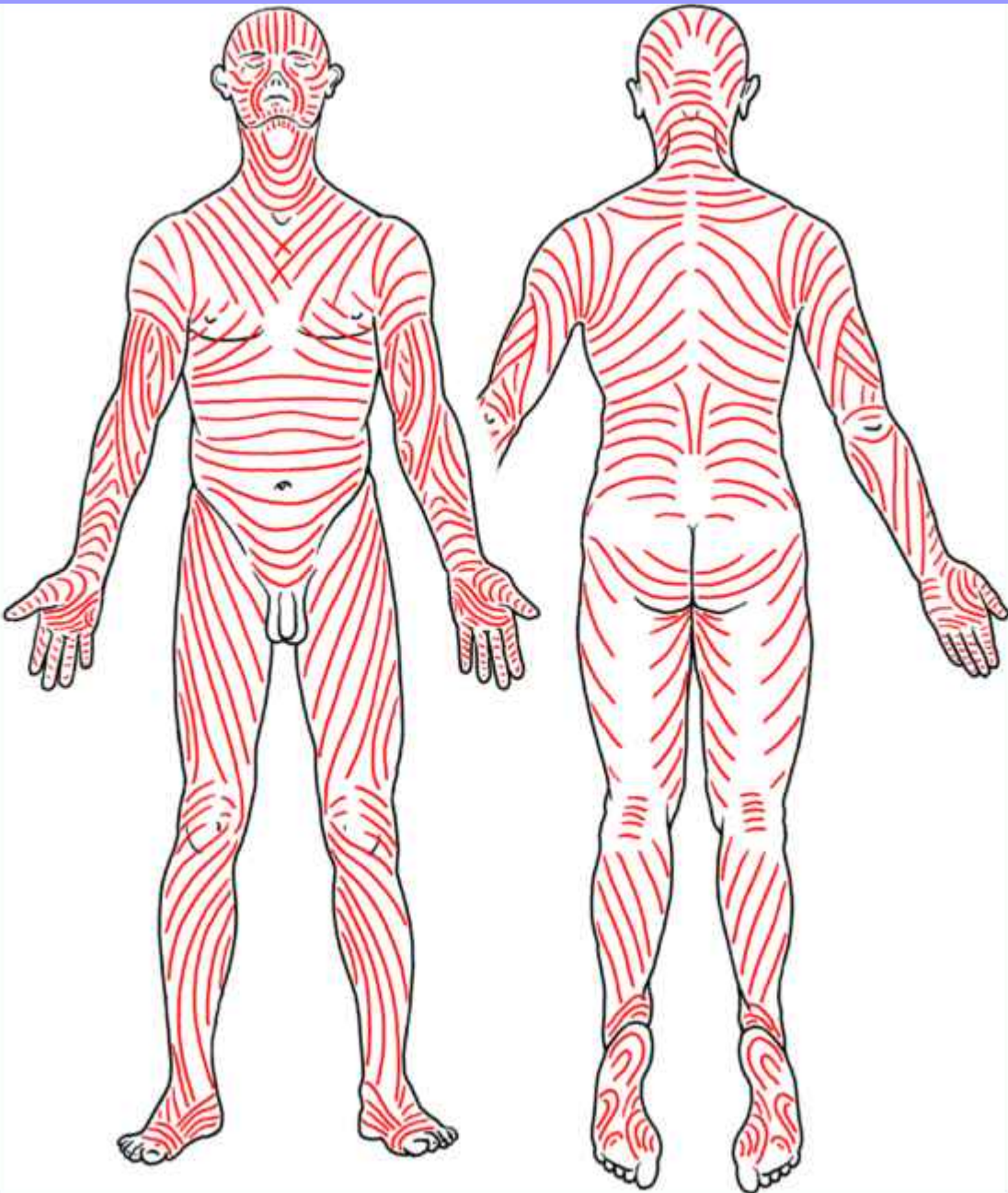
### **Stratum papillare**

is composed of loose connective tissue forming fingerlike projections called *papillae*. They extend toward the epidermis and contain terminal networks of capillaries and tactile corpuscles (Meissner's corpuscles)

### **Stratum reticulare**

lies under the papillary region and is much thicker. It is composed of dense irregular connective tissue and receives its name from the containing collagenous, elastic and reticular fibres.





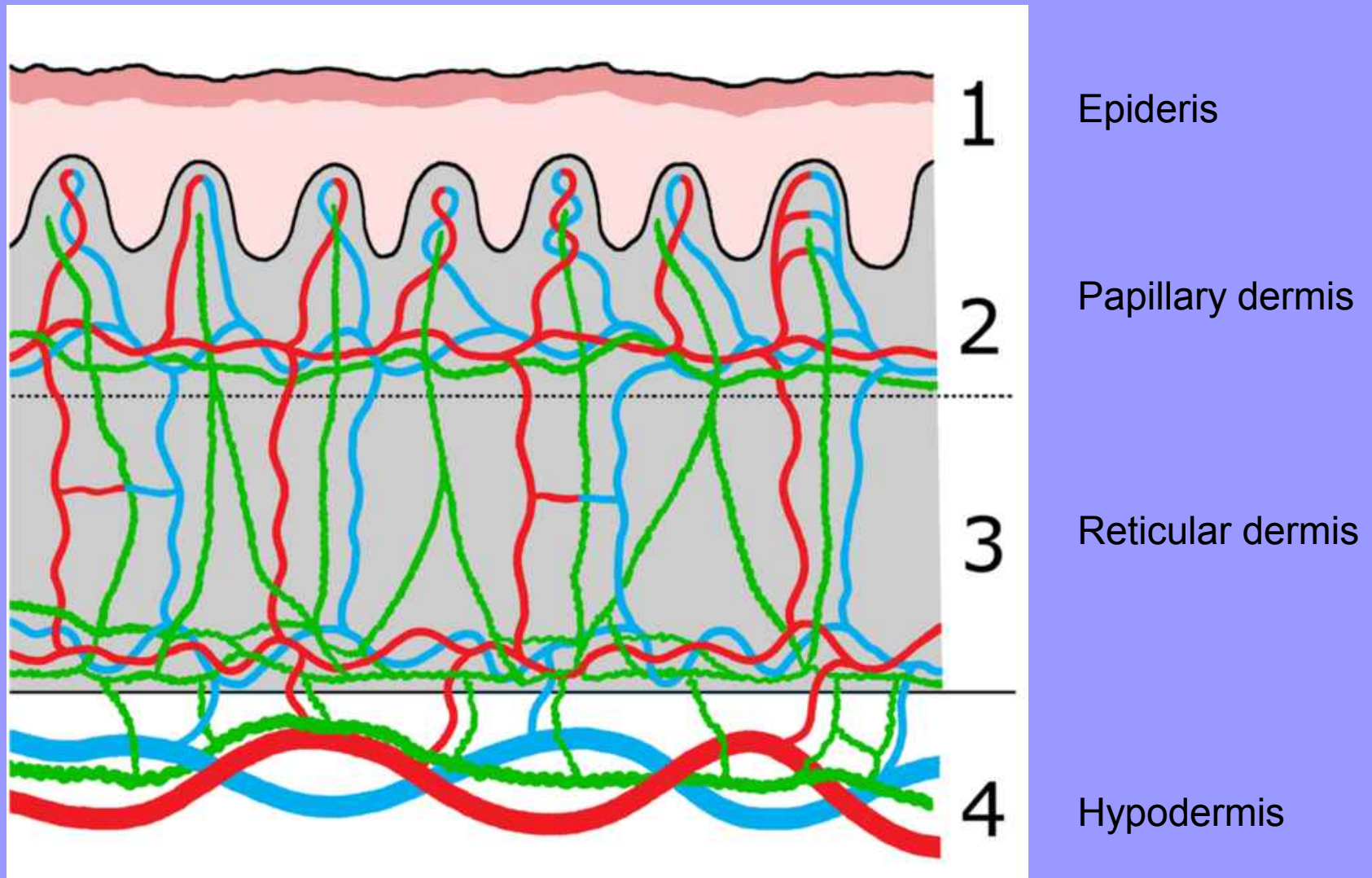
The direction of collagen fiber network of dermis differs in different parts of the body

An incision in the course of lines produces slit, an incision at right angle to the course of lines produces gape

Systematic investigation have revealed a **system of preferred lines for incisions in skin**



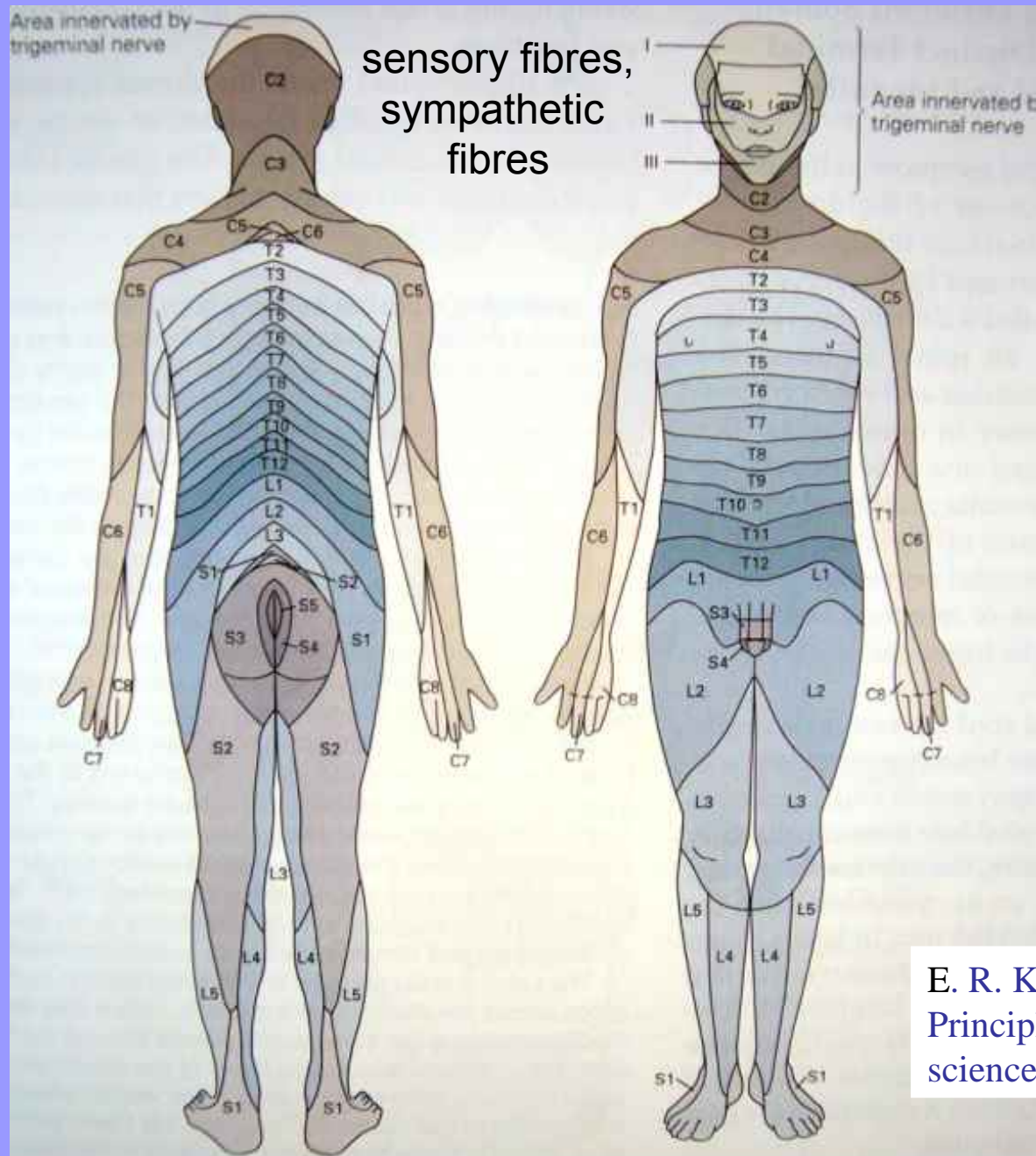
# The distribution of microvascular plexuses and lymphatic collectors (green) in the skin





Infrared thermography, thermovision

# Segmental innervation (dermatomes) of the skin

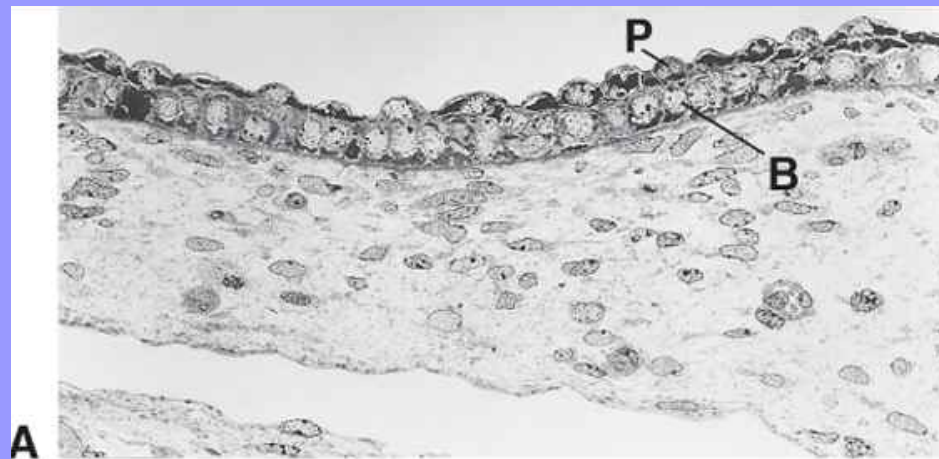


E. R. Kandel et al.:  
Principles of neural  
sciences. 2000



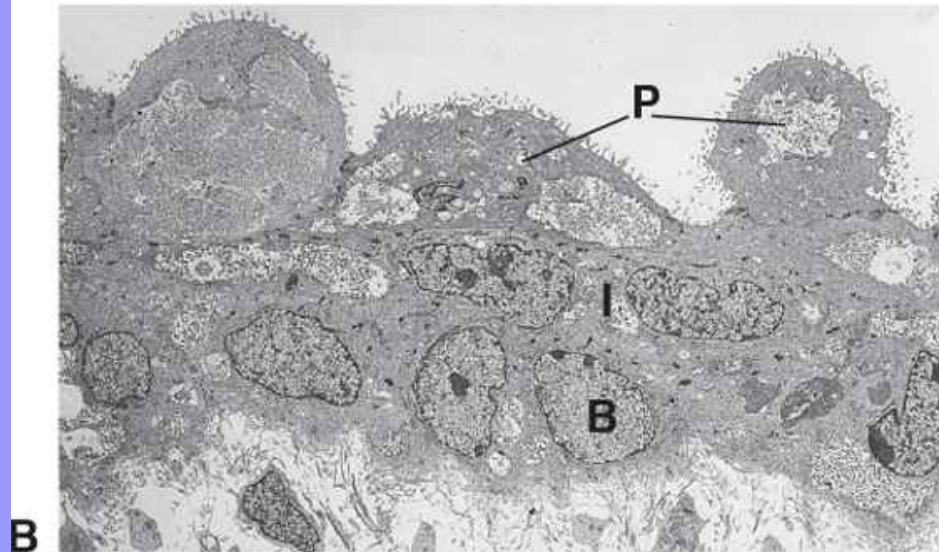
# Development of the skin

Differentiation of ectoderm into the primitive epidermis (week 8 -24)



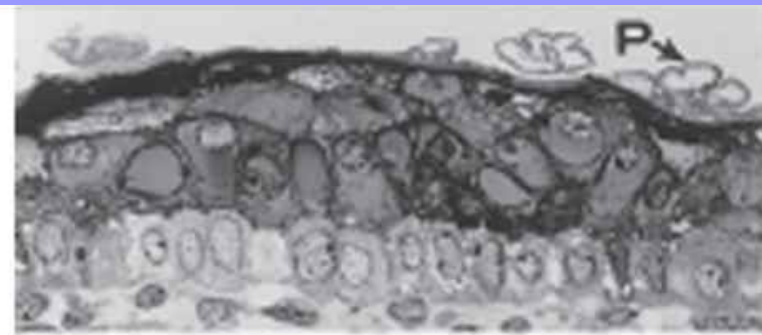
8 weeks

P - periderm

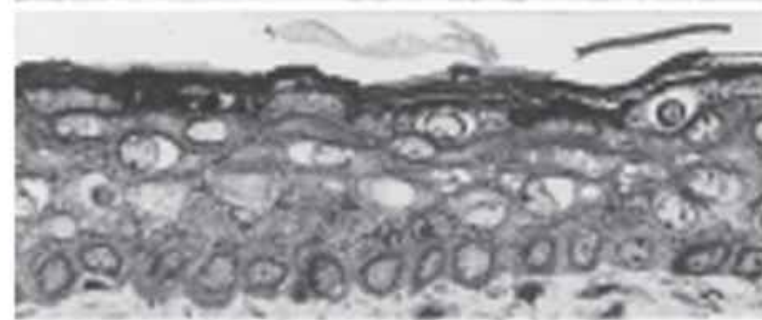


11 weeks

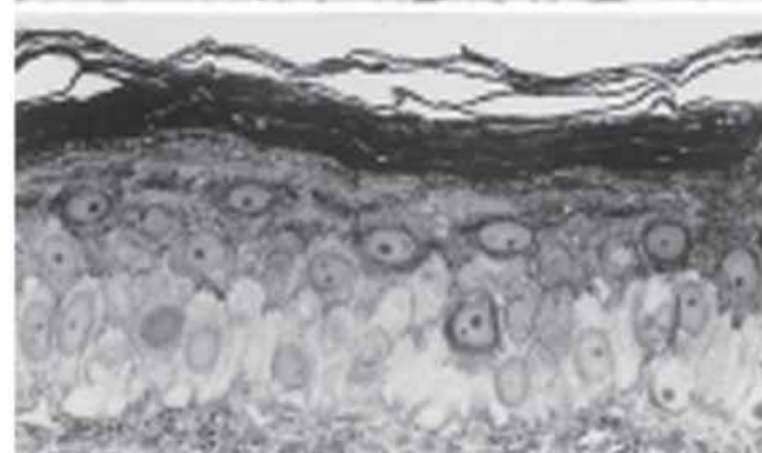
17 weeks



24 weeks

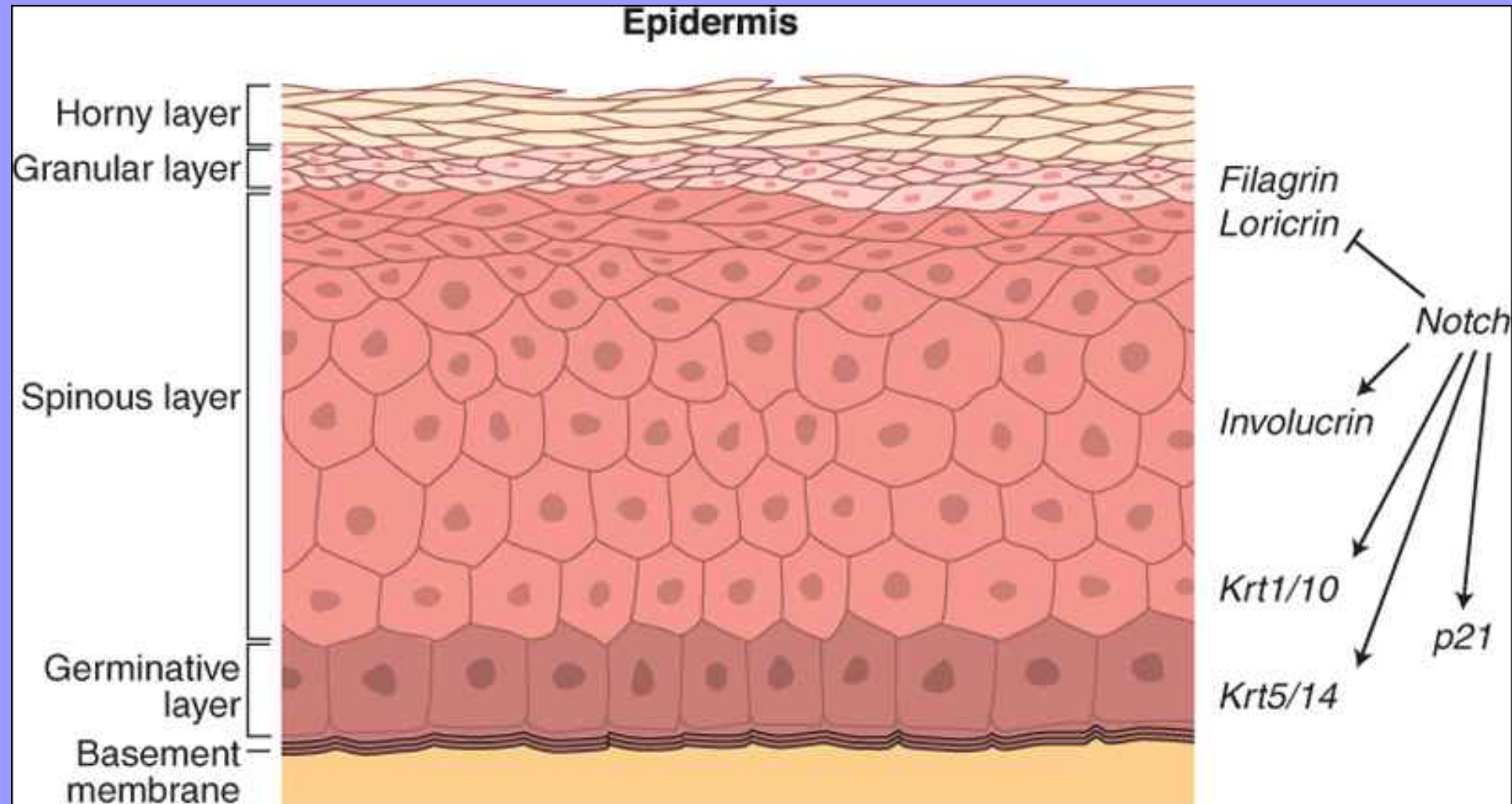


Adult



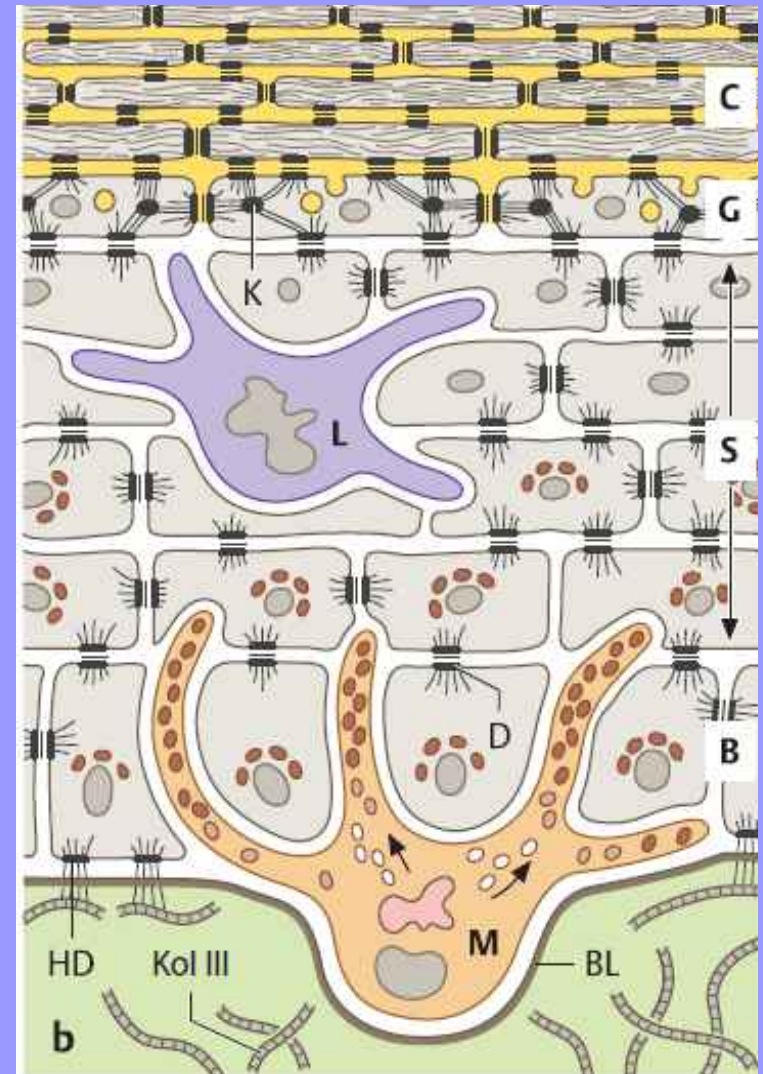
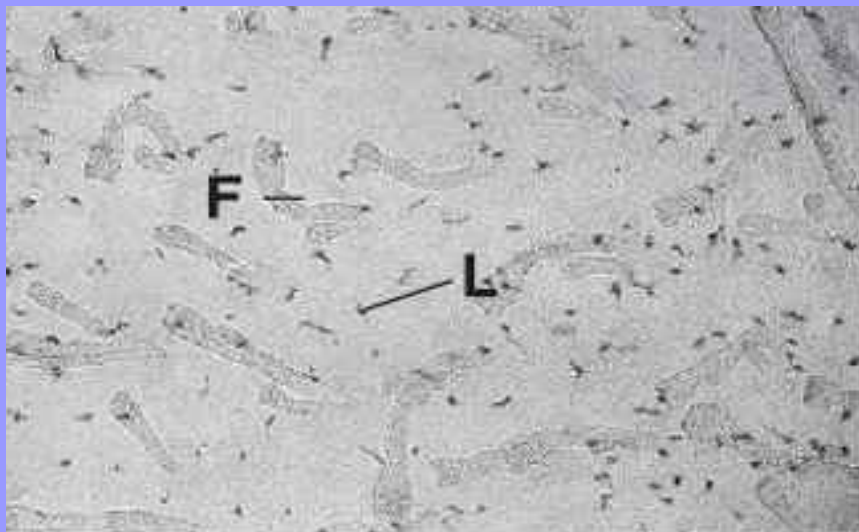
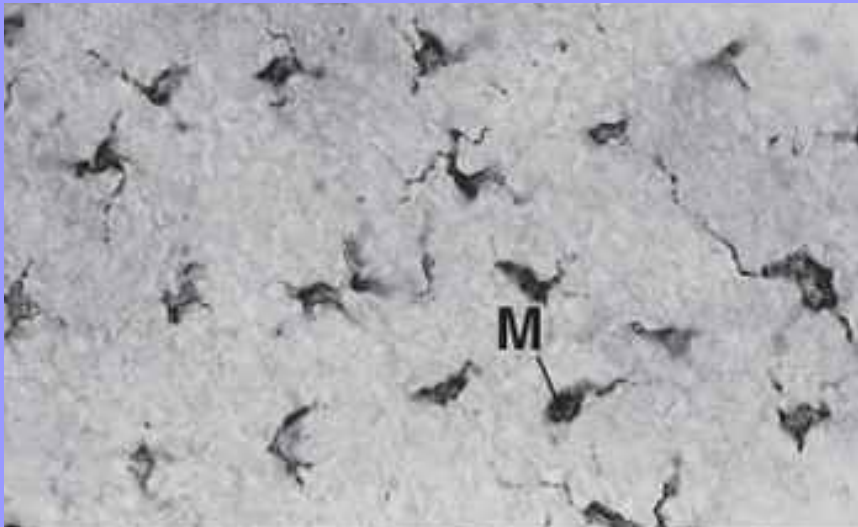
# Differentiation of epidermis

Different expression of Keratins and envelope proteins  
Is induced by Notch signaling





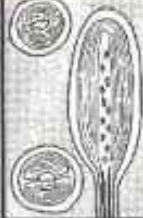





# Colonization of epidermis by melanocytes (M) and Langerhans cells (L)





Endings	Structure	Localization	Synonyms
Free nerve endings		Epidermis: stratum granulosum	
Type I			
Merkel nerve endings		Epidermis: stratum basale	Brown bodies: Iggó corpuscles Merkel cell-neurit. complex
Simple bulboid nerve endings		Dermis: stratum papillare	Papillary nerve endings Free nerve endings of the dermis
Type II			
Dendritic bulboid nerve endings		Hair sinus hair: mesenchymal sheath, ridged skin: stratum papillare	Hair palisade NE SH: lanciform NE RS: Meissner's corpuscles Ruffini end-bulbs Dogiel end-bulbs Genital corpuscles
Simple encapsulated corpuscle with inner core		Dermis: below the epidermal cone	Krause end-bulbs Golgi-Mazzoni corpuscles Mucocutaneous end-organs Paciform corpuscles Innominate corpuscles
Type III			
Pacinian corpuscles		Deep layers of the dermis	Vater-Pacini corpuscles Rauber's end-organs

## Classification of sensory receptors according to structure and localization

Abbildung 6: Klassifikation sensibler Nervenendigungen aus HALATA (1975).

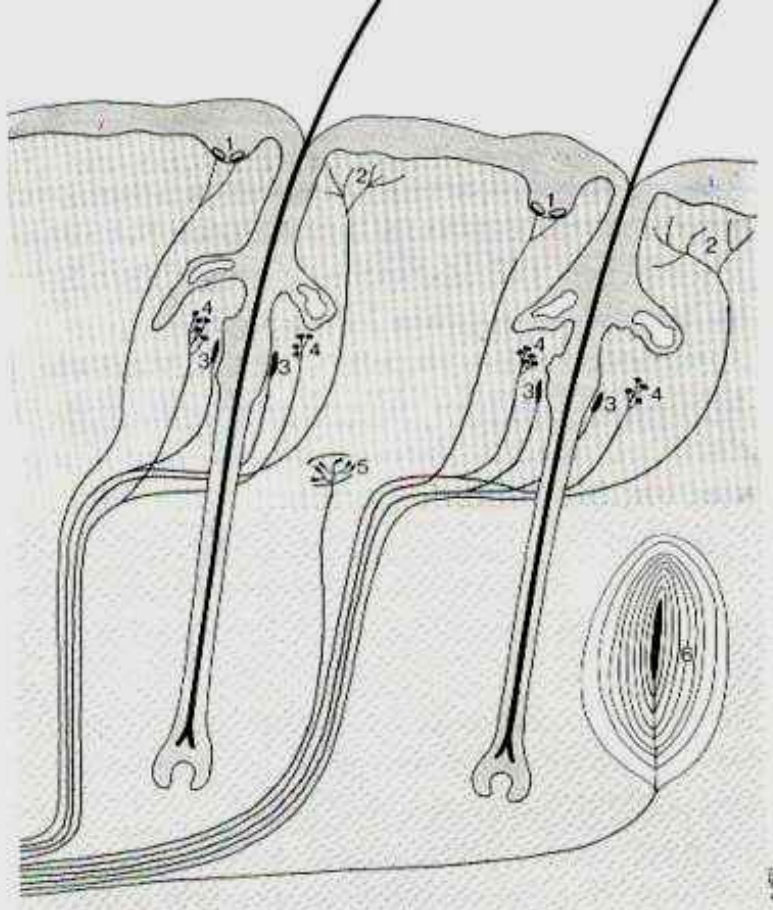


Abbildung 61: Schematische Darstellung der Innervation der behaarten Haut. Die Epidermis zwischen den Haarfollikeln enthält die sogenannten Tastscheiben oder auch Pinus-Scheiben (1). In der Papillarschicht liegen freie Nervenendigungen (2). Die Lanugohaare sind meistens durch lanzettförmige Nervenendigungen (3) und Pilo-Ruffini Komplexe (4) innerviert. In der Tiefe der Dermis liegen zwischen den Haarfollikeln Ruffinische Körperchen (5) und im Fettpolster die Vater-Pacinischen Lamellenkörperchen (6) (aus HALATA, 1990a).

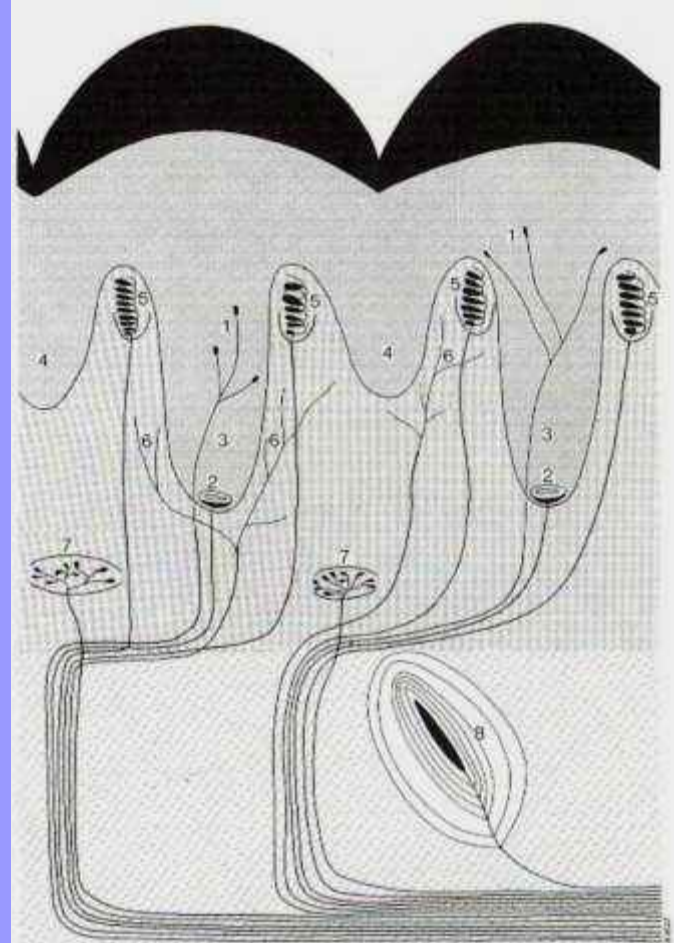


Abbildung 56: Schematische Darstellung der Innervation der Leistenhaut. Die freien Nervenendigungen in der Epidermis (1) liegen überwiegend in den Drüsenleisten. Die Merkselschen Nervenendigungen (2) findet man in der Basalschicht der Drüsenleiste. In den Bindegewbspapillen zwischen den Drüsen- (3) und Haftleisten (4) befinden sich Meissnersche Körperchen (5). Die freien Nervenendigungen (6) liegen in der Papillarschicht der Dermis, die Ruffinischen Körperchen (7) in der Retikularschicht. Große Vater-Pacinische Körperchen (8) findet man im Panniculus adiposus (aus HALATA, 1990a).

**Sensory receptors in hairy skin**

**and in glabrous skin**



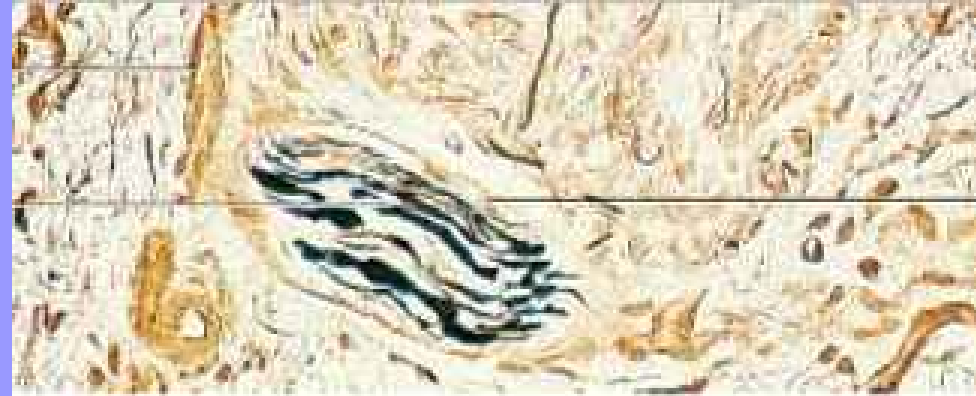
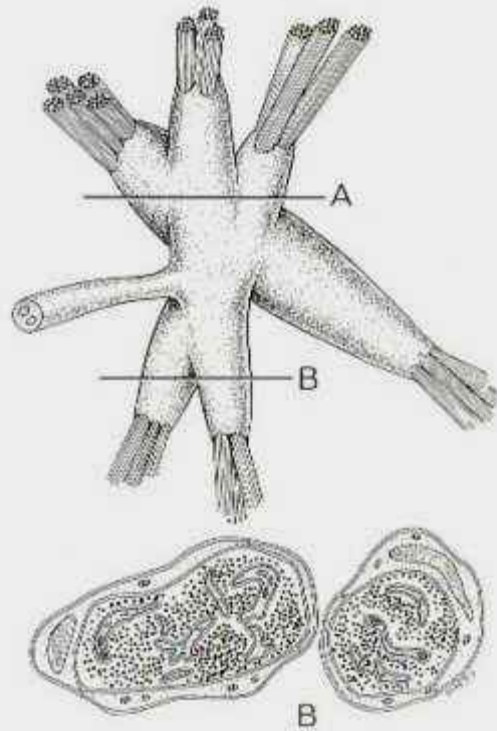
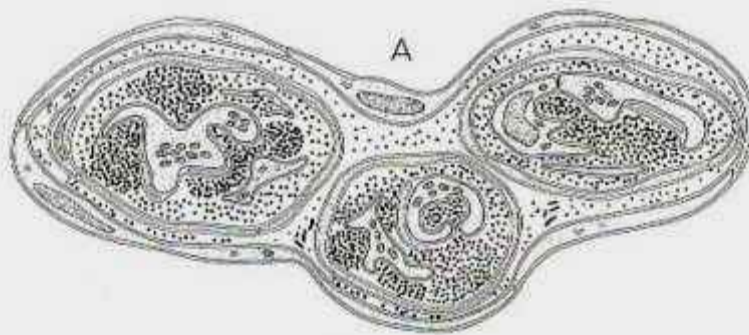


Abbildung 39: Halbschematische Darstellung eines Ruffinischen Körperchens aus der Gelenkkapsel. Das Körperchen besteht aus drei Zylindern, deren Längsachse parallel zur Richtung der kollagenen Fasern des Stratum fibrosum verläuft. Zwei afferente markhaltige Axone innervieren das Körperchen. A und B – Querschnitte durch die Zylinder. 1 – perineurale Kapsel, 2 – Nerventerminalen. Aus HALATA und MUNGER (1980 b).

**Ruffini's corpuscle**



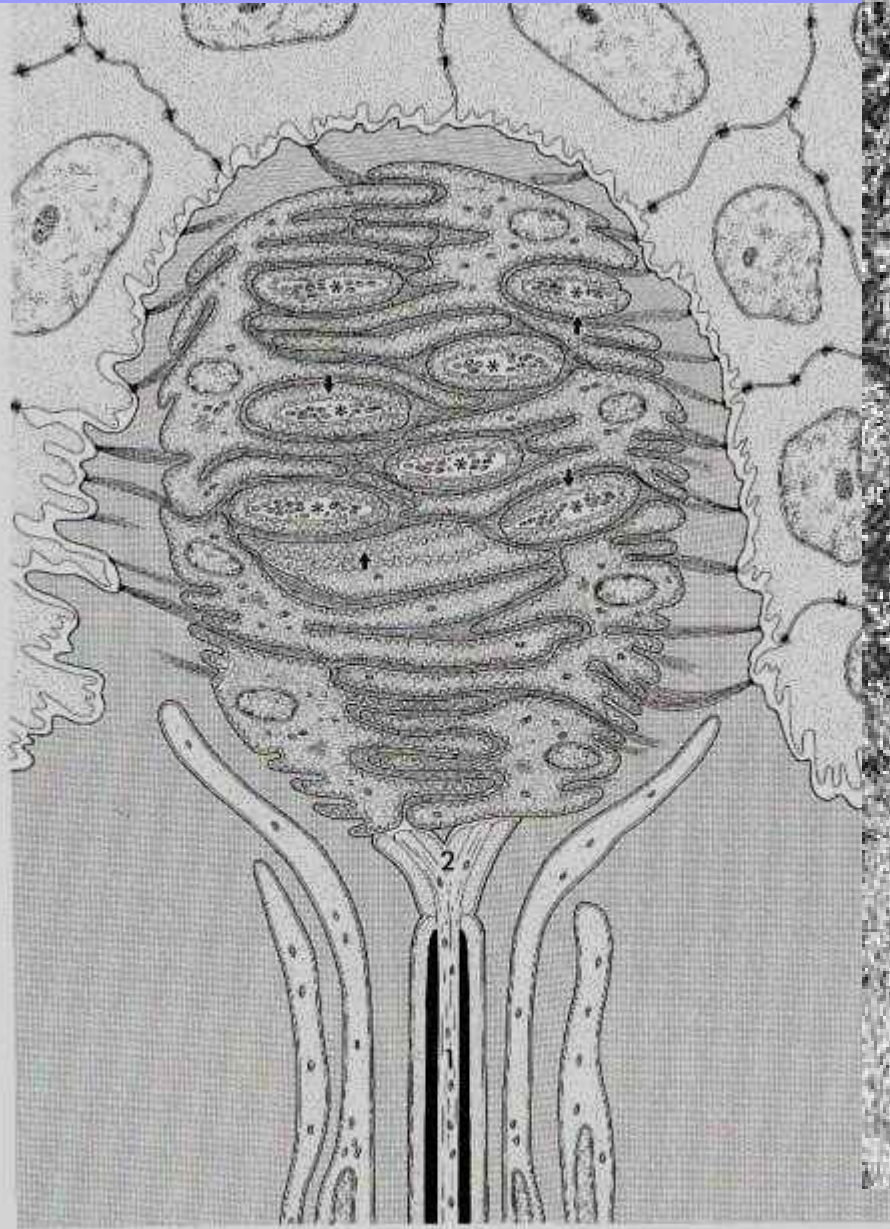


Abbildung 24: Halbschematische Darstellung eines Meissnerschen Körperchens in der Papillarschicht der Leistenhaut. Das afferente Axon (1) ist markhaltig und verzweigt sich (2). Die marklosen Äste weisen terminale Verdickungen auf (\*), die von dünnen Ausläufern der terminalen Schwannschen Zellen (Pfeile) umgeben sind. Die Zellkerne der Schwannschen Zellen liegen in der Peripherie des Körperchens. Bündel kollagener Fibrillen der Papillarschicht ziehen durch die Spalten zwischen den terminalen Schwannschen Zellen hindurch und fixieren das Körperchen in seiner Lage. In Anlehnung an ANDRES und VON DÜRING, 1973 und HALATA, 1975.

**Meissner's corpuscle**

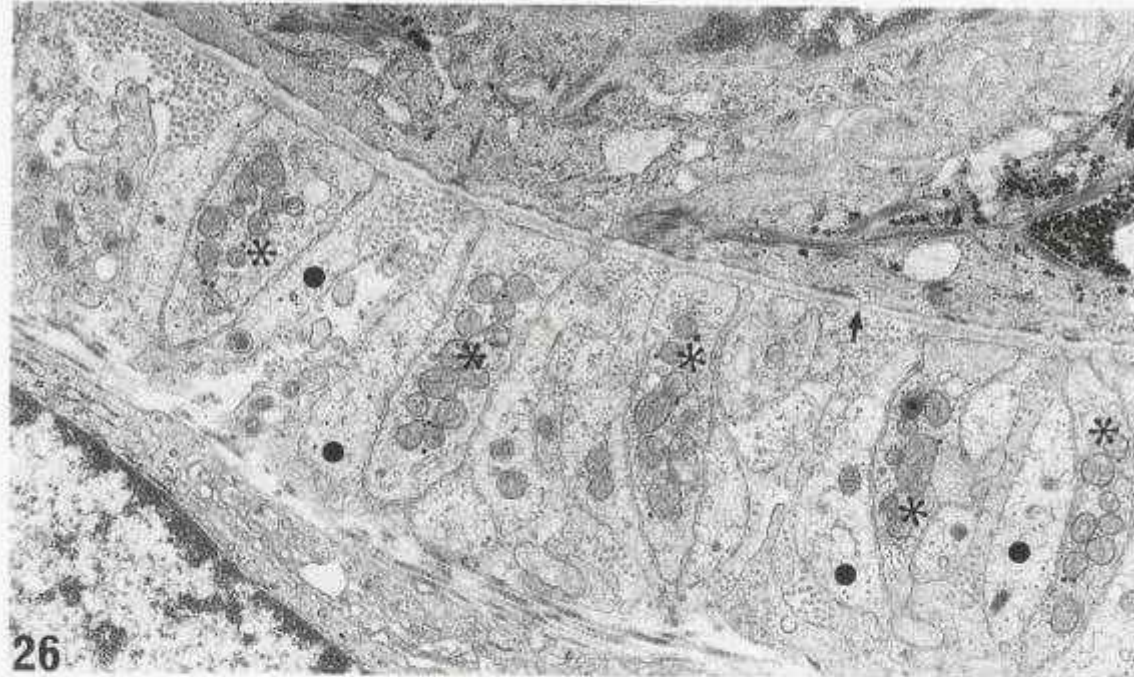


Abbildung 26: Lanugohaar aus dem oberen Abschnitt des Planum nasale der Hauskatze im Querschnitt. Die lanzettförmigen Nerventerminalen (\*) enthalten Ansammlungen von Mitochondrien und haben Kontakt mit der Basallamina des Haarfollikels (Pfeile). Die zytoplasmatischen Lamellen der Schwannschen Zellen (Punkte) weisen Mikrovesikulationen auf. Hauskatze (*Felis silvestris f. catus*): EM Bild. 11400 X.

## Lancet-like sensory endings on hair follicle



Abbildung 27: Halbschematische Darstellung der Palisaden von lanzettförmigen Nervenendigungen eines Lanugohaares im Querschnitt. 1 – Haarschaft, 2 – basale Schicht des Haarfollikelepithels, 3 – Nerventerminalen, 4 – Schwannsche Zellen mit ihren zytoplasmatischen Lamellen, 5 – Fibroblasten der Bindegewebskapsel des Haarfollikels, (Pfeile) – Basallamina.



# Pacinian corpuscle

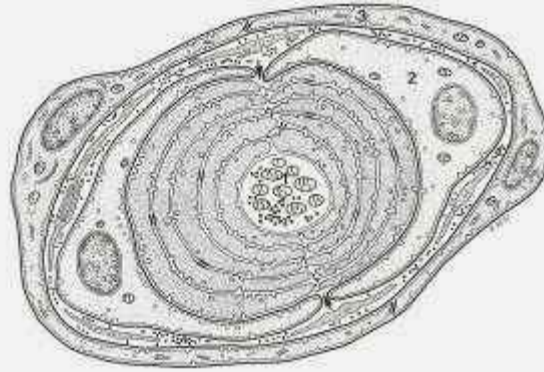


Abbildung 32: Halbschematische Darstellung eines kleinen Pacinischen Körperchens im Querschnitt. 1 – terminales Axon, 2 – Schwannsche Zellen, 3 – perineurale Kapsel, (Pfeile) Längsspalten des Innenkolbens.

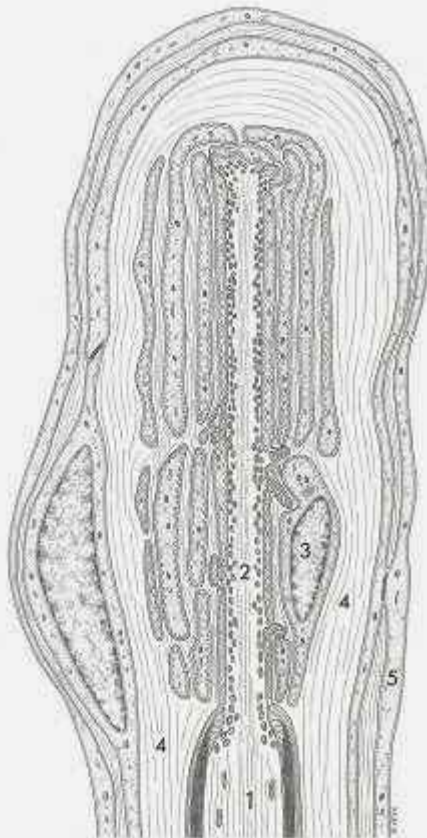
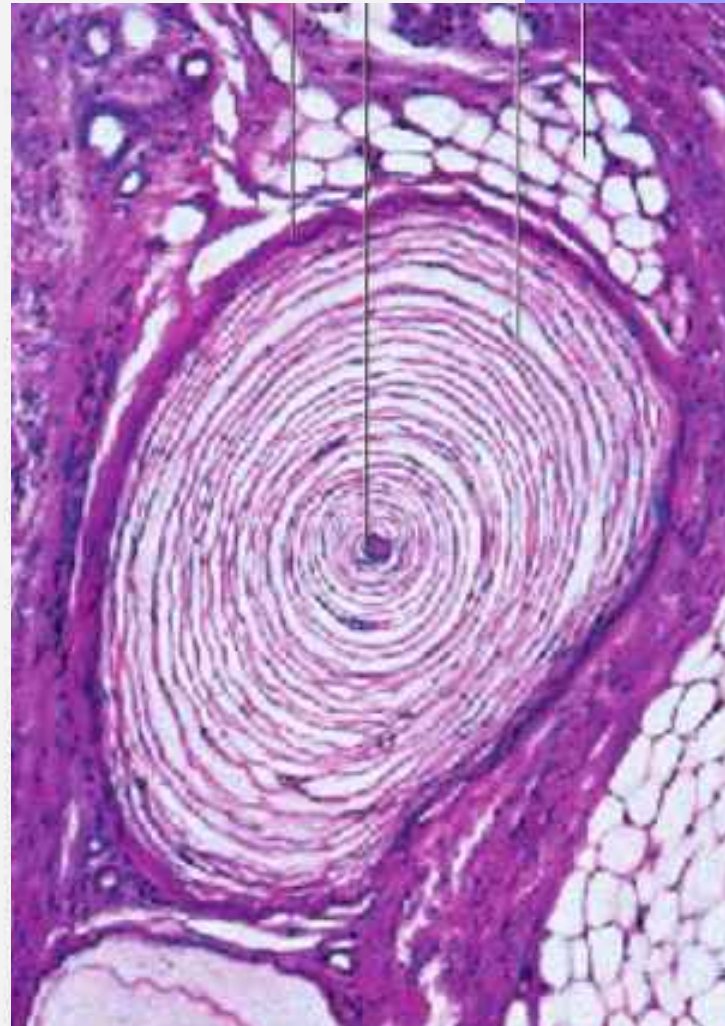
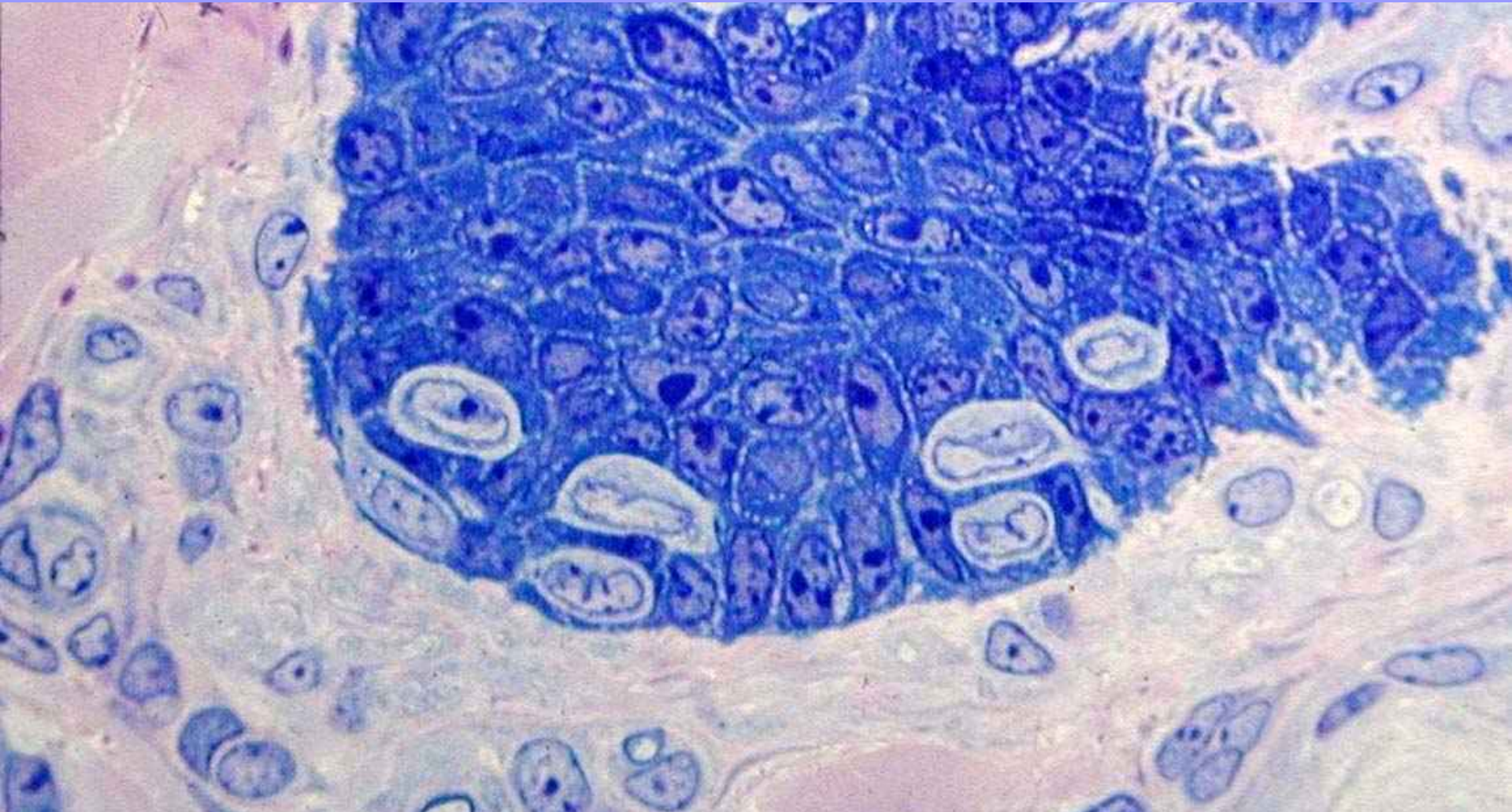


Abbildung 33: Halbschematische Darstellung eines kleinen Pacinischen Körperchens im Längsschnitt. 1 – markhaltiges Axon, 2 – terminales Axon, 3 – terminale Schwannsche Zelle mit ihren zytoplasmatischen Lamellen, 4 – Subkapsularraum mit kollagenen Fibrillen, 5 – perineurale Kapsel.



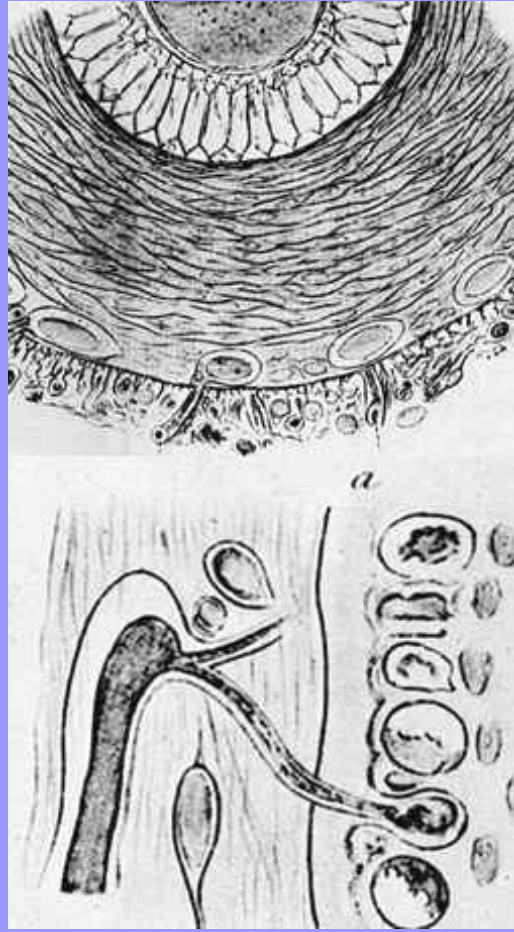
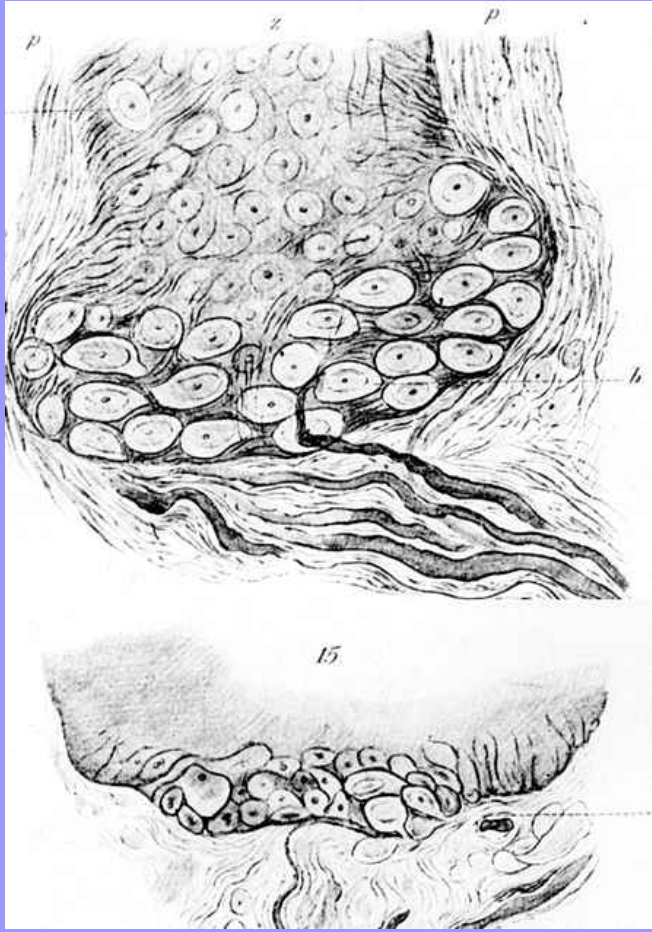


Merkel cells are large light cells in the basal layer of epidermis and in mucous membranes of ectodermal origin in vertebrates

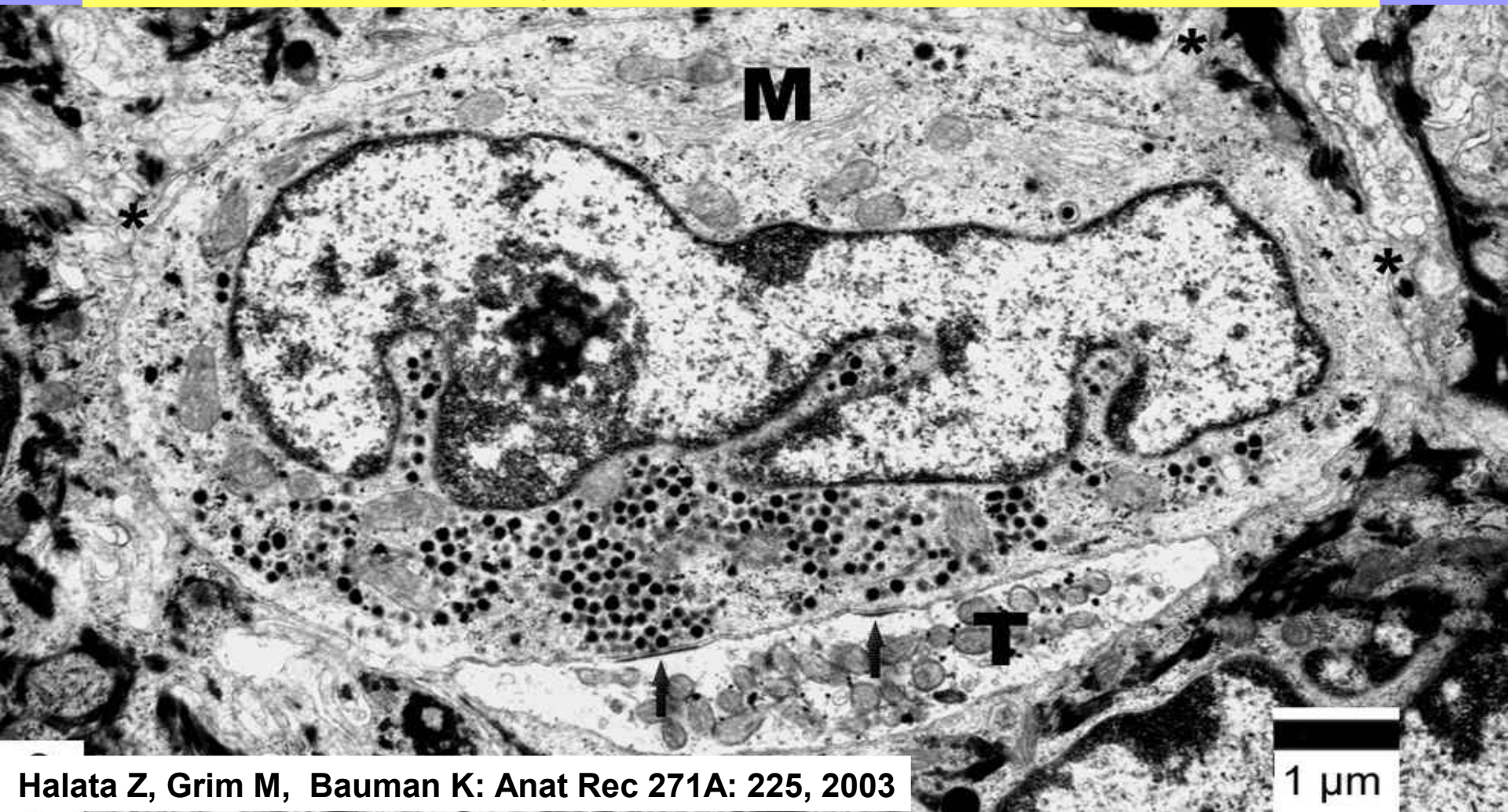




F. S. Merkel (1875) :  
„Tastzellen“ of the skin of birds and mammals



Merkel cells are transducers of tactile stimuli  
in slowly adapting mechanoreceptors of the skin



Halata Z, Grim M, Bauman K: Anat Rec 271A: 225, 2003

Human MCs represent 3.6 - 5.7% of basal epidermal cells  
from glabrous and hairy skin (Fradette et al., 2003)



# Skin appendages

are derived from the skin and serve a particular function including sensation, contractility, lubrication and heat loss.

**Hairs:** lanugo, pili, capilli, cilia, supercilia, tragi, vibrissae, hirci, pubes, barba

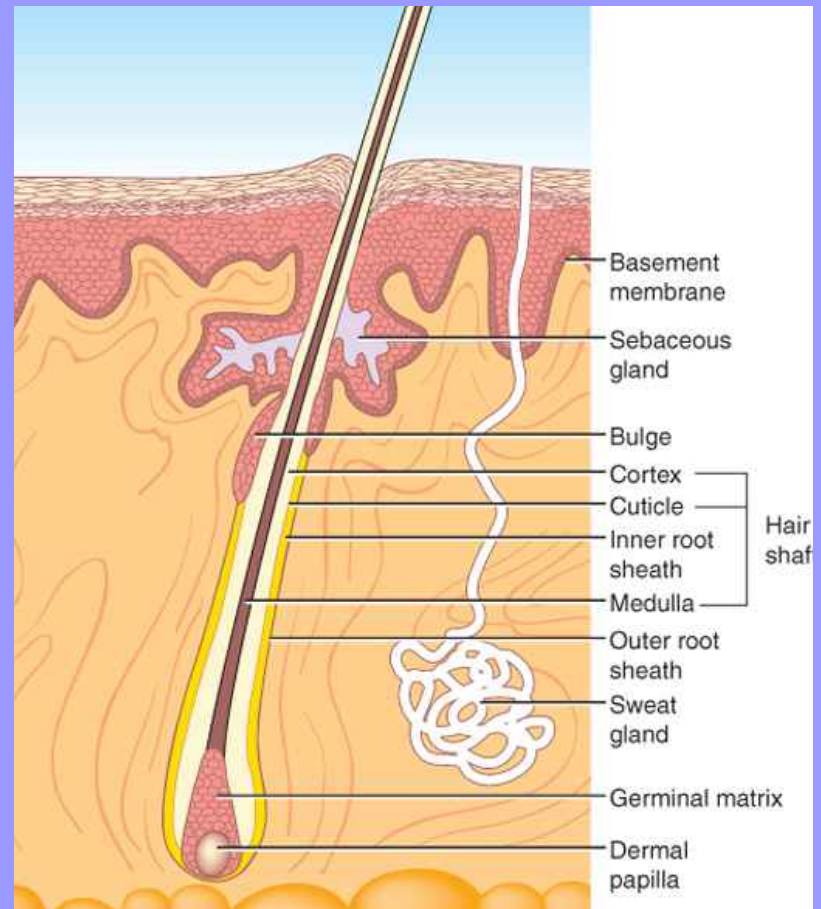
## Nails

## Glands

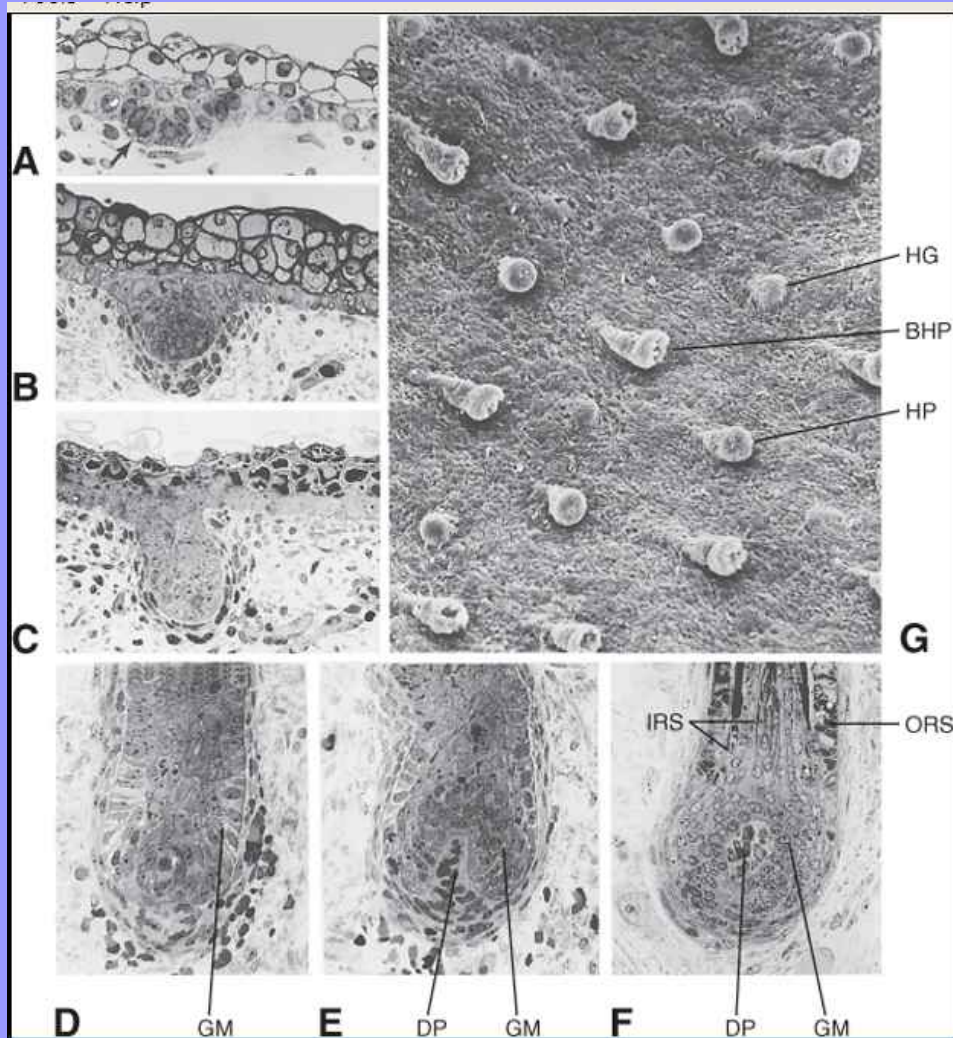
Sweat glands

Apocrine glands

Sebaceous glands



# Development of hair follicle (month 3-10)

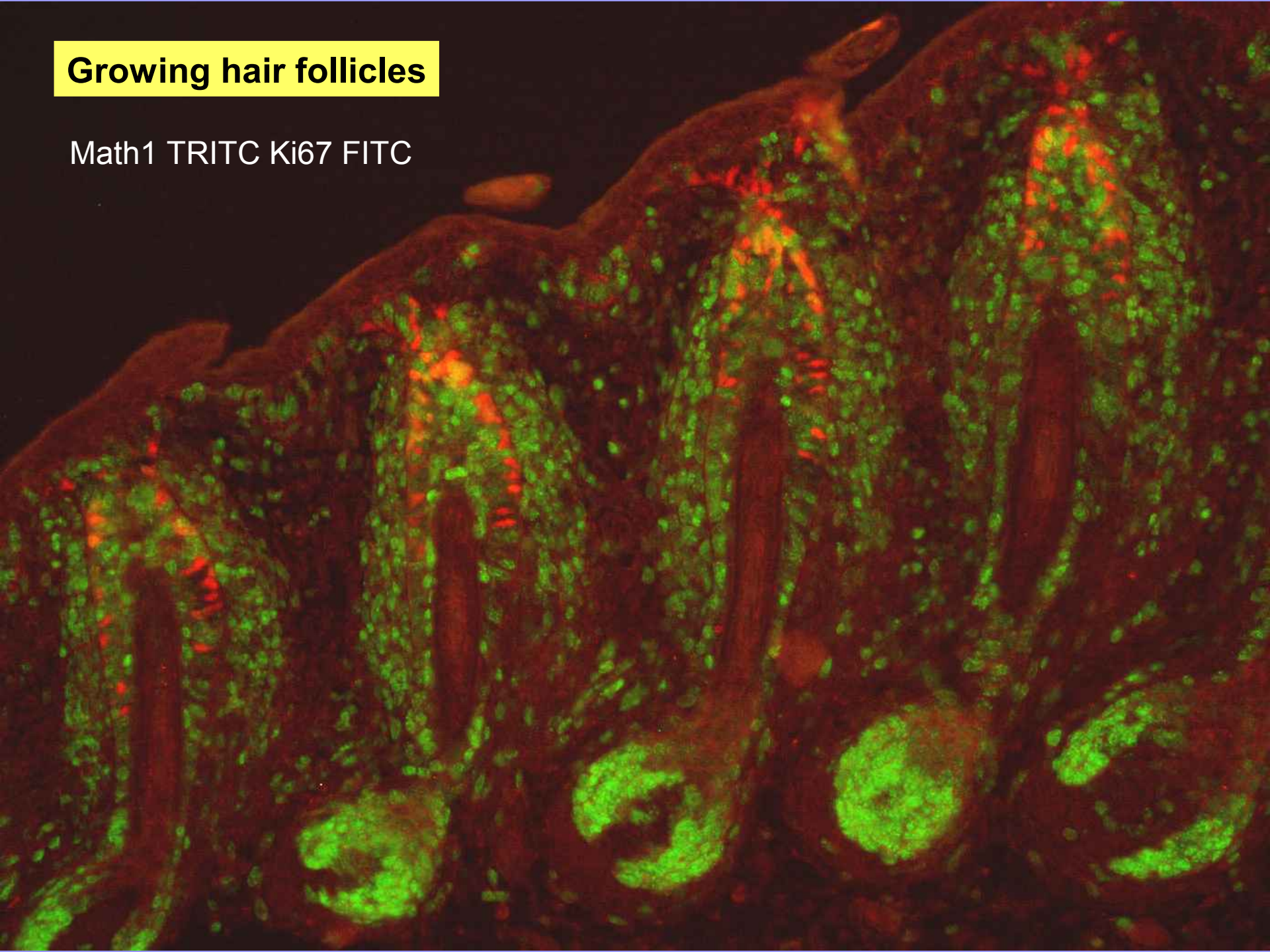


Shh signaling



## Growing hair follicles

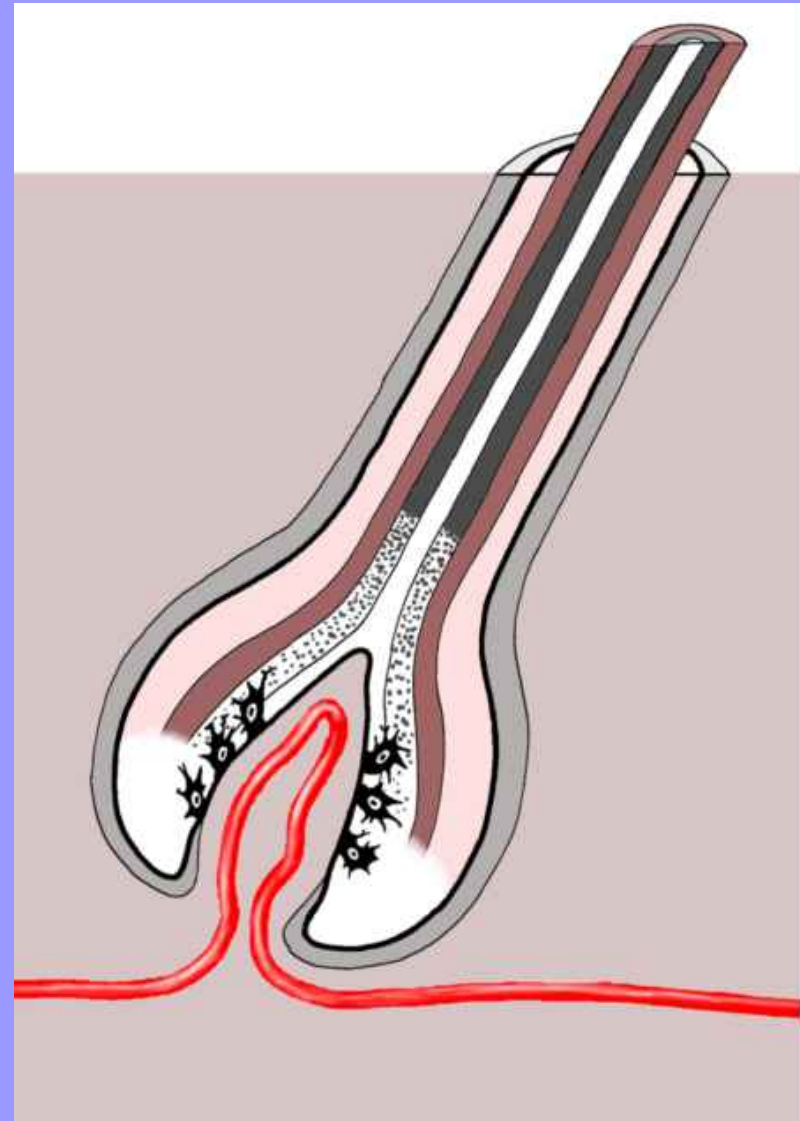
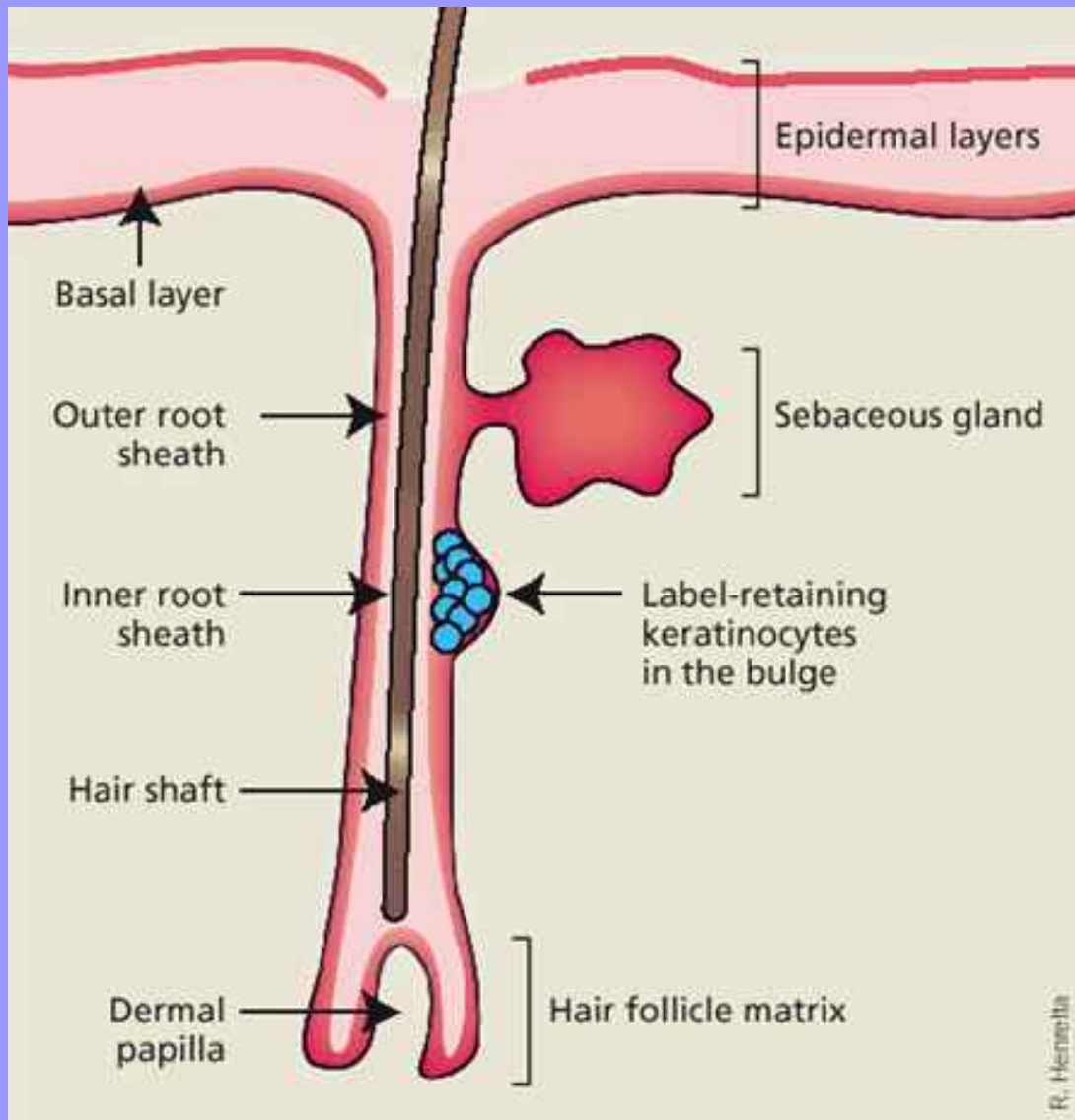
Math1 TRITC Ki67 FITC

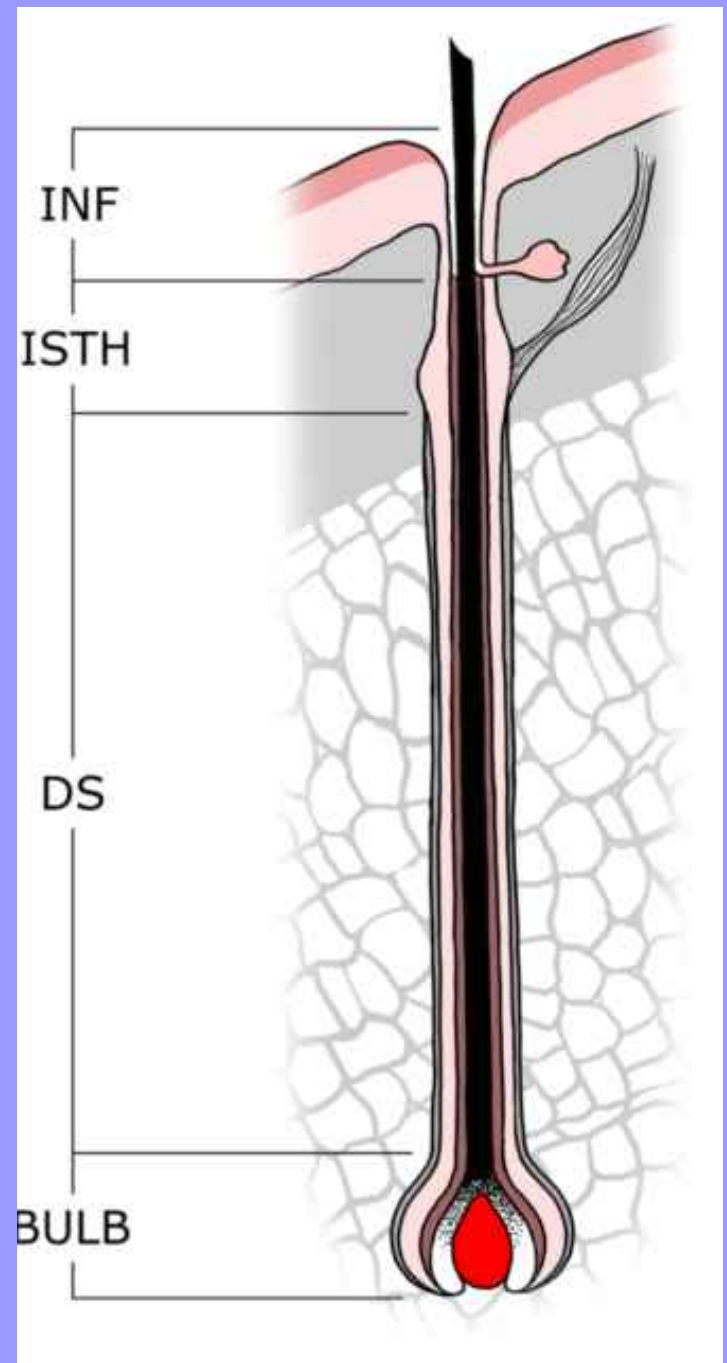
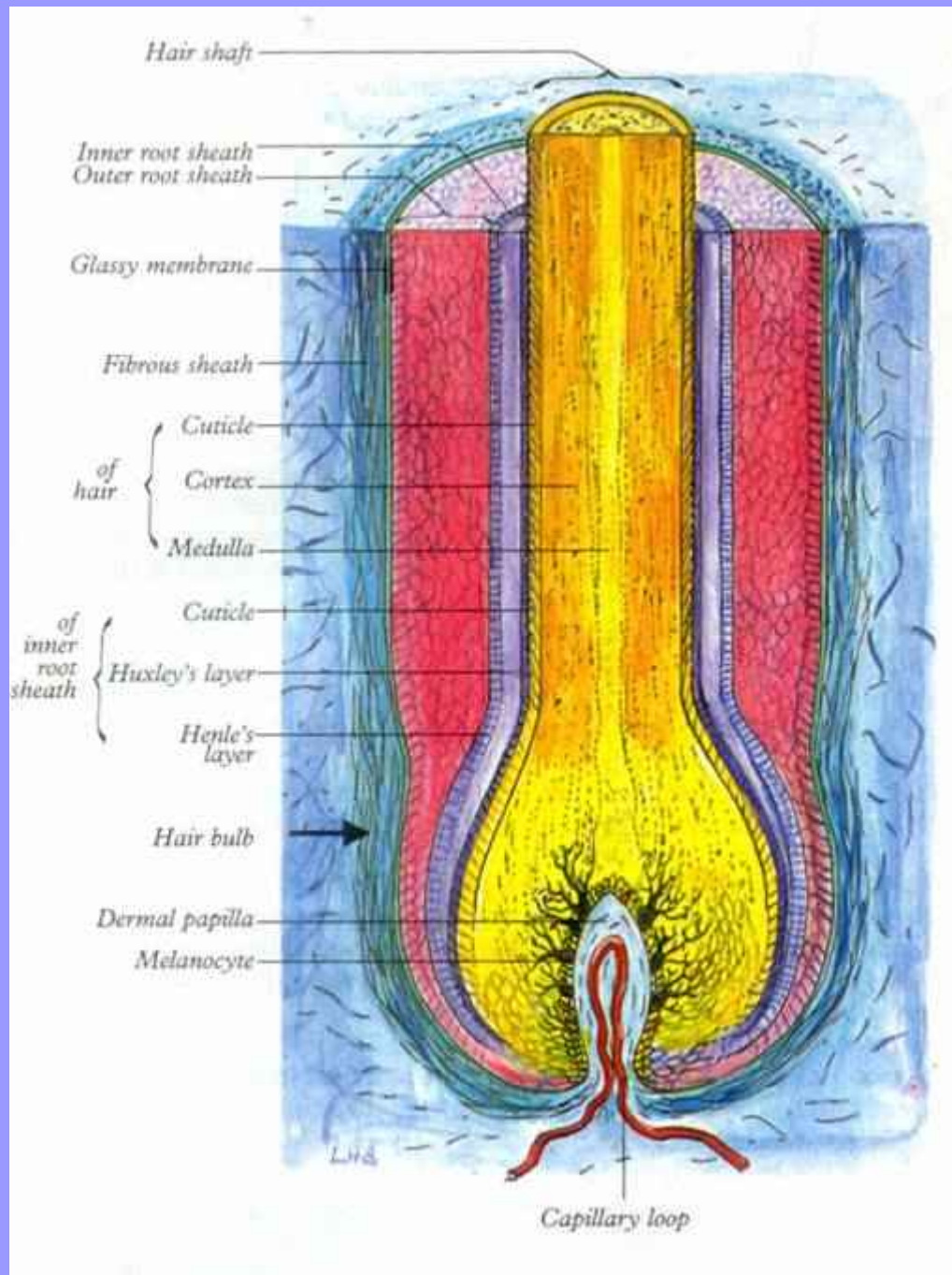






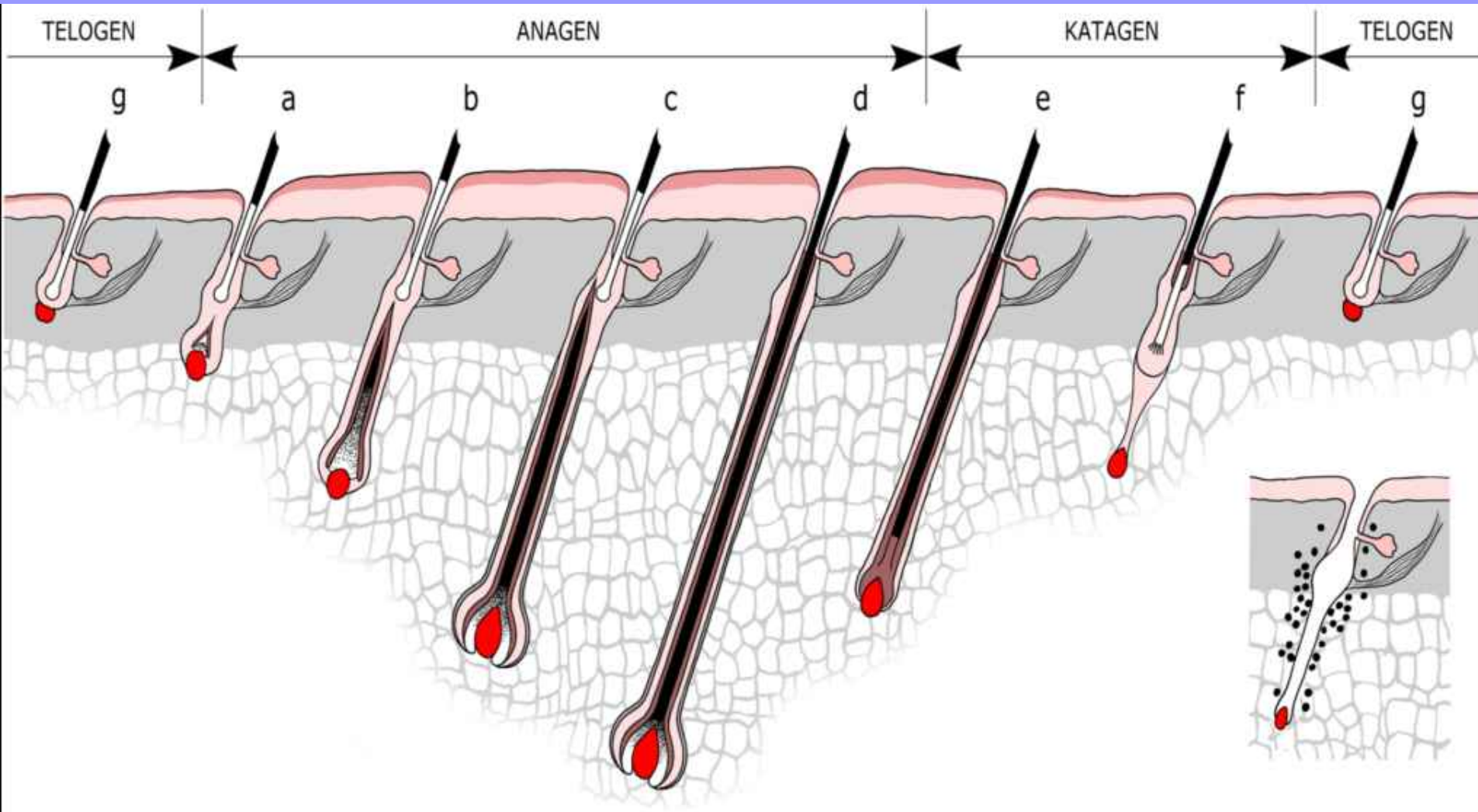
# Hair follicle







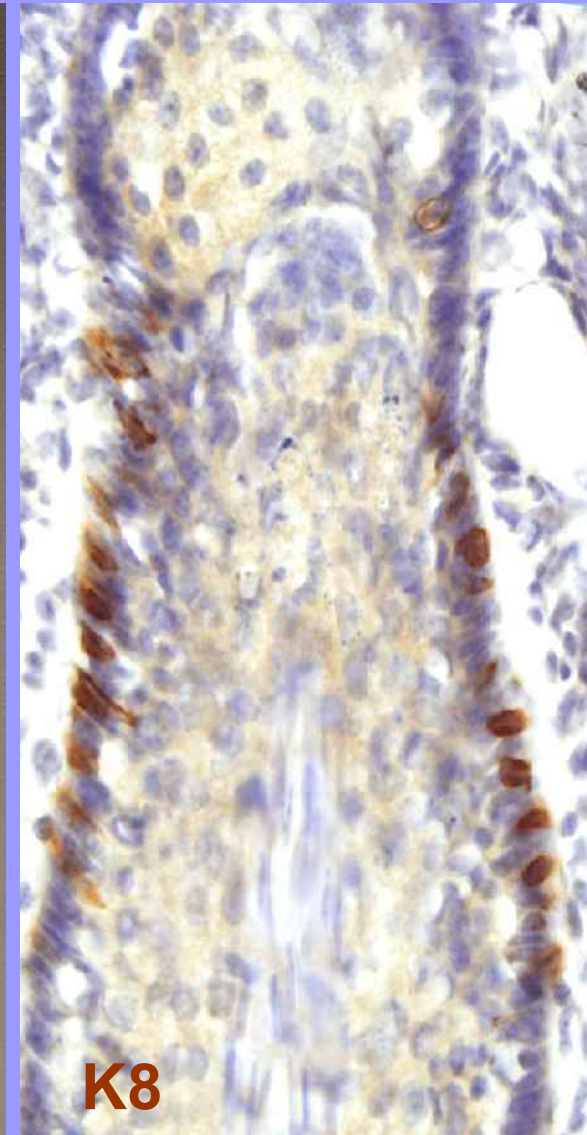
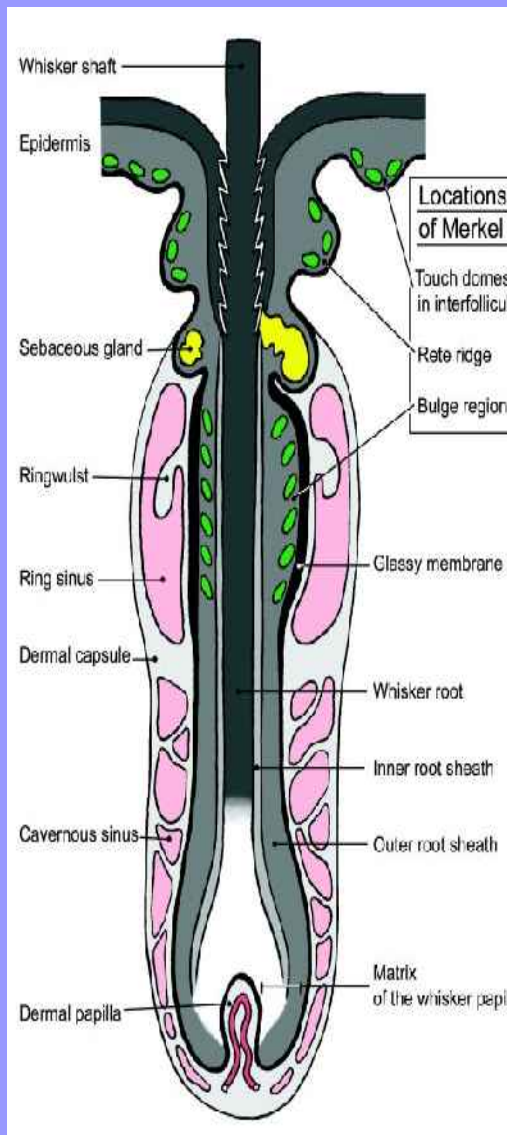
# Hair cycle stages





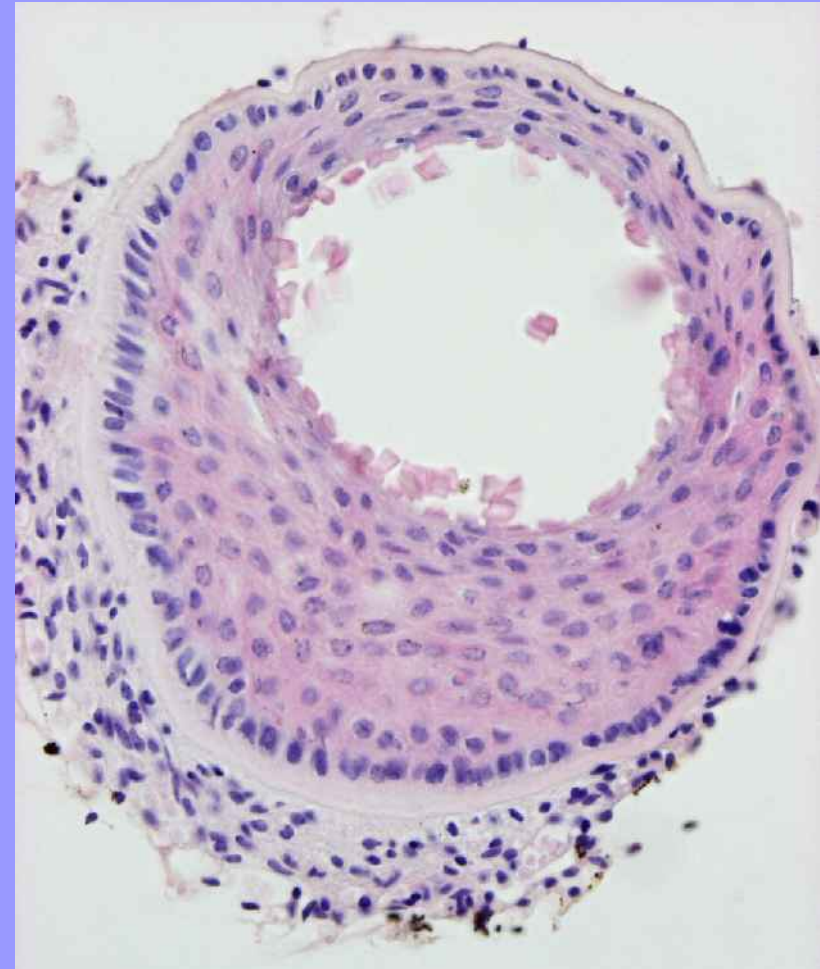
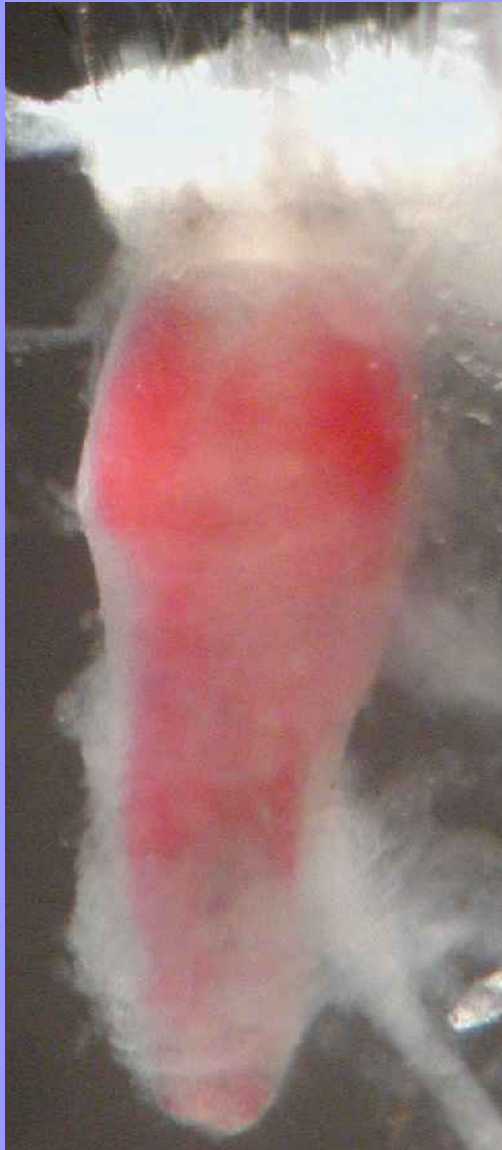


# Merkel cells in whisker hair follicle

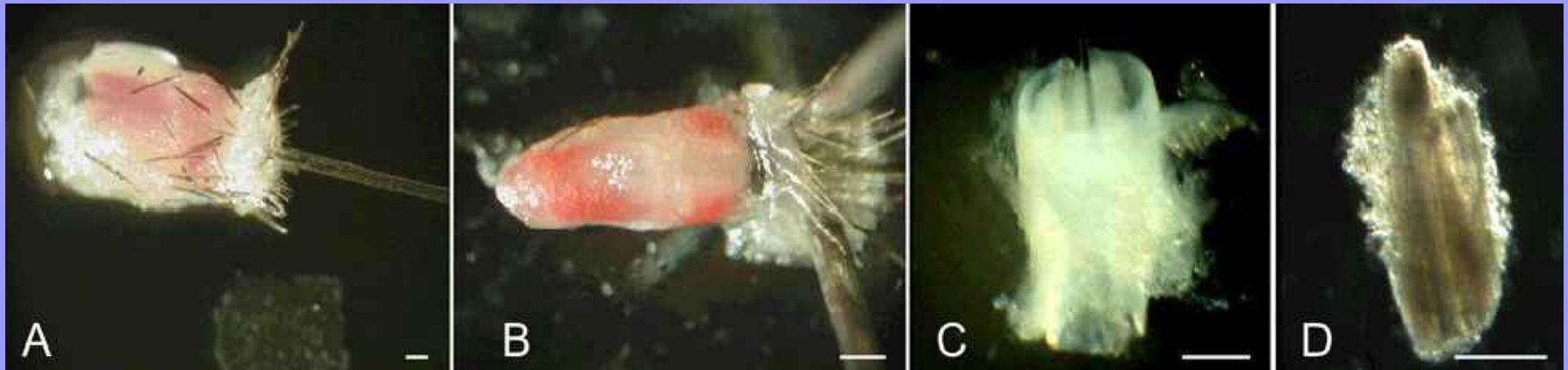




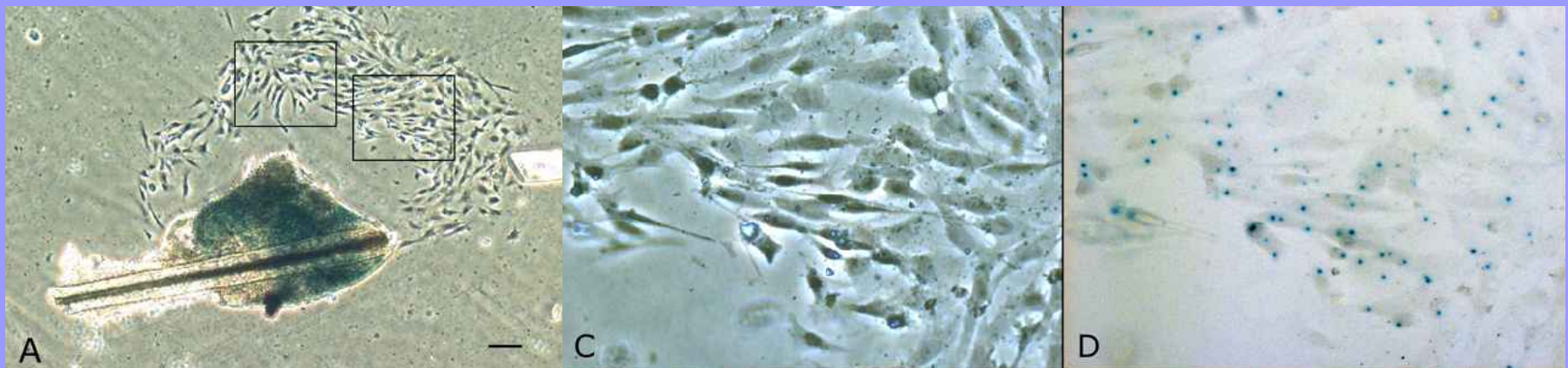
# The follicle of sinus hair (whisker) blood sinus, innervation, bulge



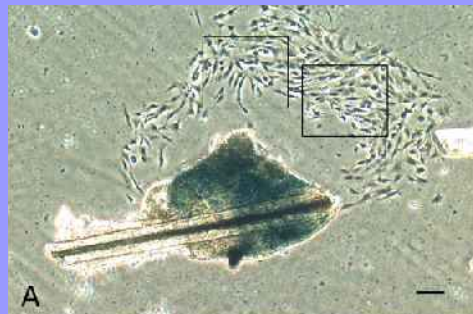
# Dissection of the bulge from adult whisker follicle



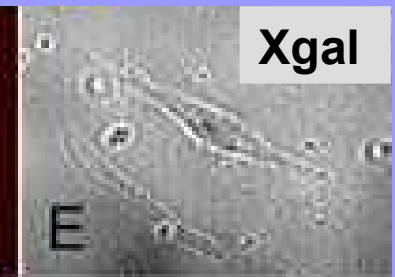
Xgal + NCCs emigrated 4 days after explantation



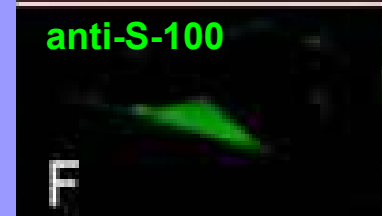
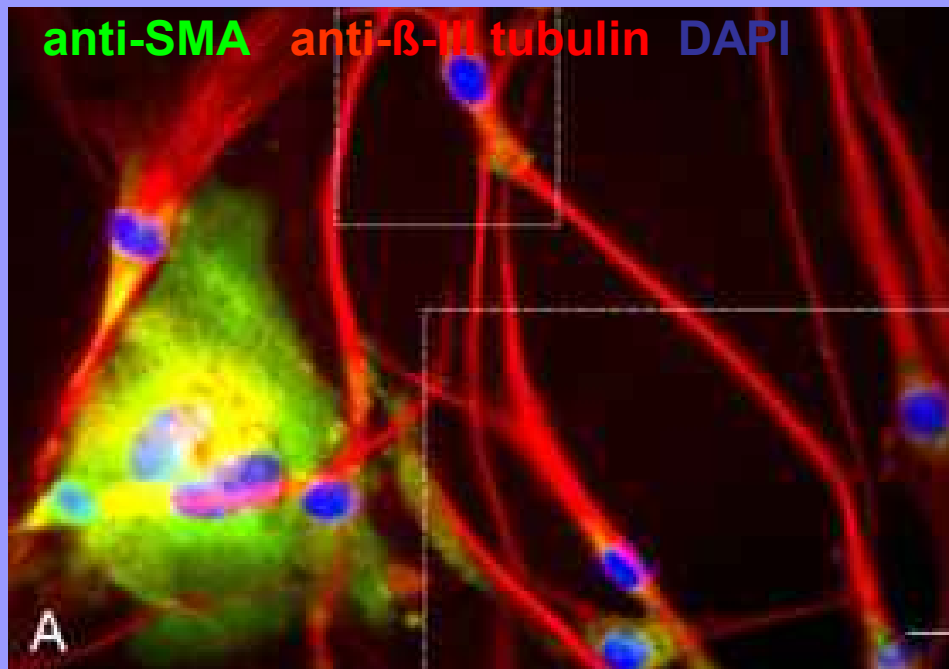
# Bulge explant-derived NCCs are pluripotent



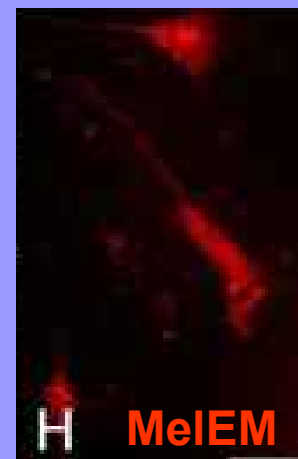
Schwann cells



Smooth muscle cells    Neurons

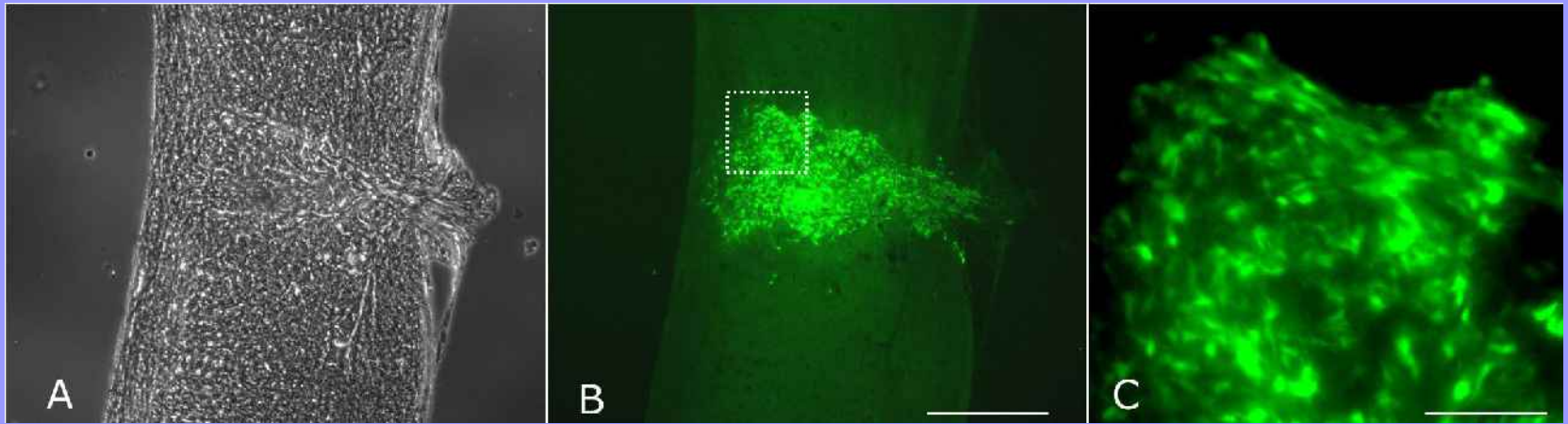


Melanocytes    Chondrocytes

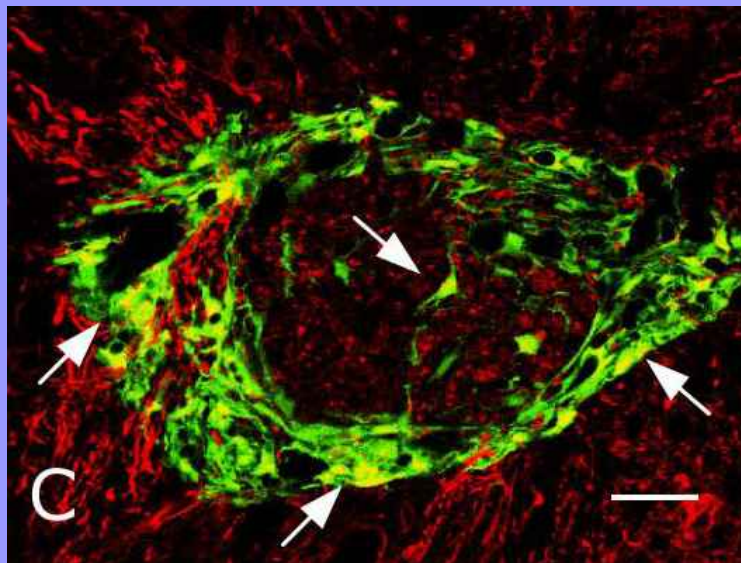


Dev Dyn 231:258-269, 2004; Embryo Today 72:162-172, 2004  
Supp. by LN 00A065 and VZ 111100003-3

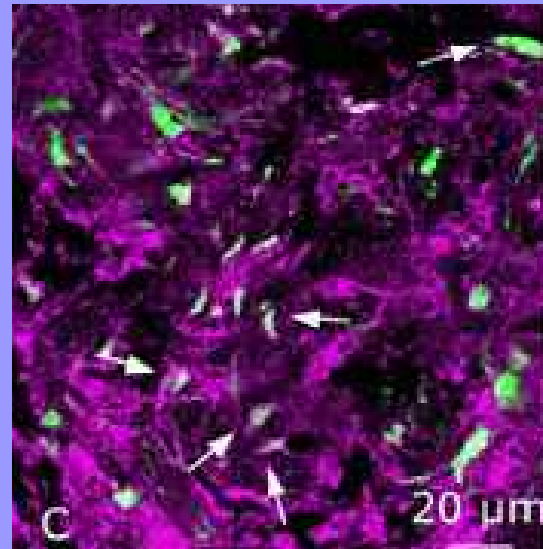




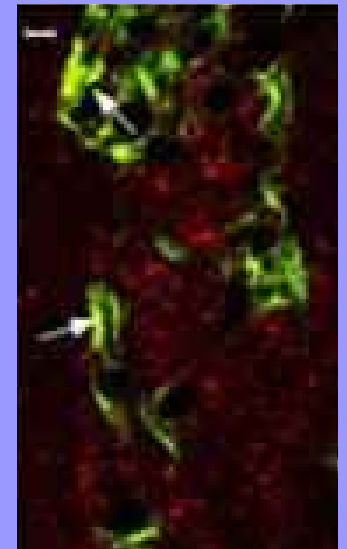
## Morphology of EPI-NCSC implants in the lesioned spinal cord



**Nestin**



**GAD67**



**RIP**



US008030072B2

(12) **United States Patent**  
**Sieber-Blum et al.**

(10) **Patent No.:** **US 8,030,072 B2**  
 (45) **Date of Patent:** **Oct. 4, 2011**

(54) **METHOD OF ISOLATING EPIDERMAL  
 NEURAL CREST STEM CELLS**

(75) Inventors: **Maya Sieber-Blum**, Brookfield, WI  
 (US); **Milos Grim**, Prague (CZ)

(73) Assignees: **Newcastle University**, New Castle Upon  
 Tyne (GB); **Univerzita Karlova V**  
**Praze**, Prague (CZ)

Claudinot, S., et al., "Long-term renewal of hair follicles from clonogenic multipotent stem cells," PNAS 102:14677-14682 (2005).  
 Fernandes, K.J., et al., "A dermal niche for multipotent adult skin-derived precursor cells," Nature Cell Biology 6:11:1082-1093 (2004).

Ito, M., et al., "Stem cells in the hair follicle bulge contribute to wound repair but not to homeostasis of the epidermis," Nature Medicine 11:12:1351-1354 (2005).

Kruger, G.M., et al., "Neural Crest Stem Cells Persist in the Adult Gut but Undergo Changes in Self-Renewal, Neuronal Subtype

*Primary Examiner* — **Thaïan N. Ton**

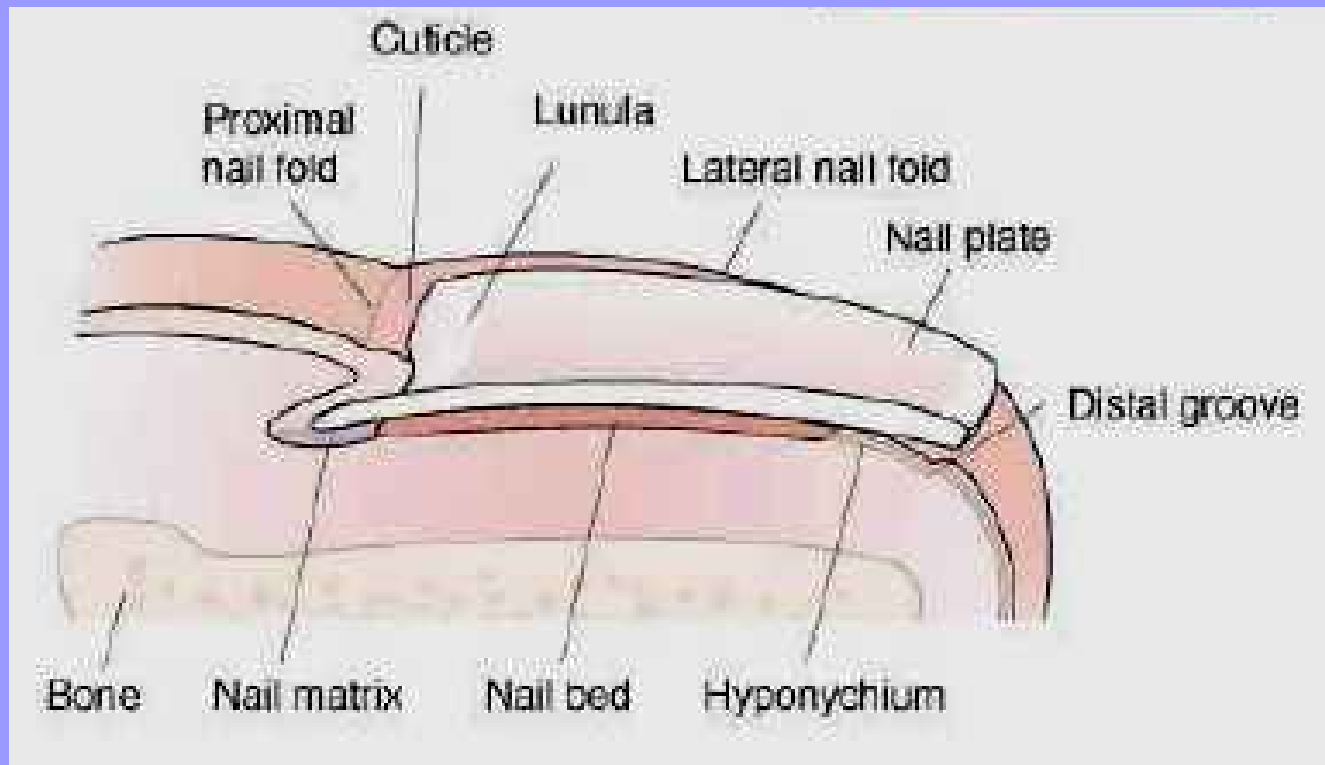
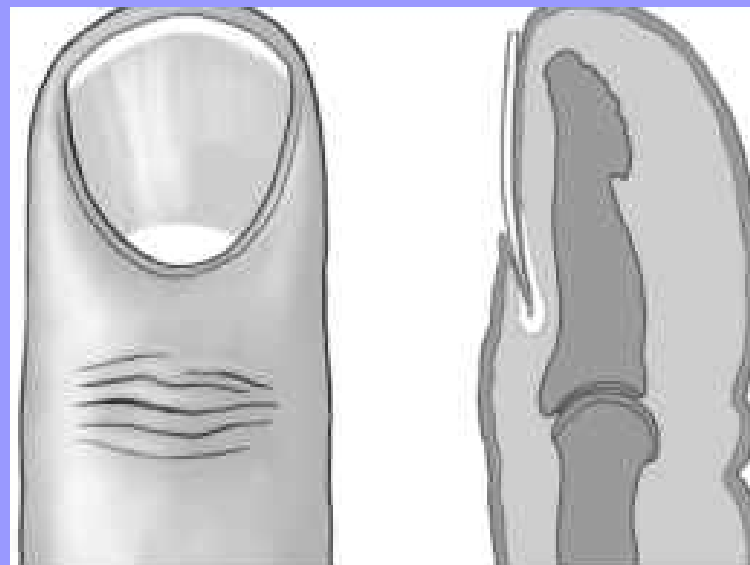
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## (57) **ABSTRACT**

The present invention describes novel methods for isolating a substantially pure cell population of non-embryonic epidermal neural crest stem cells from the bulge-region of mammalian hair follicles. Also disclosed is the substantially pure cell population of follicular bulge-derived neural crest stem cells for medical research and therapeutic use.

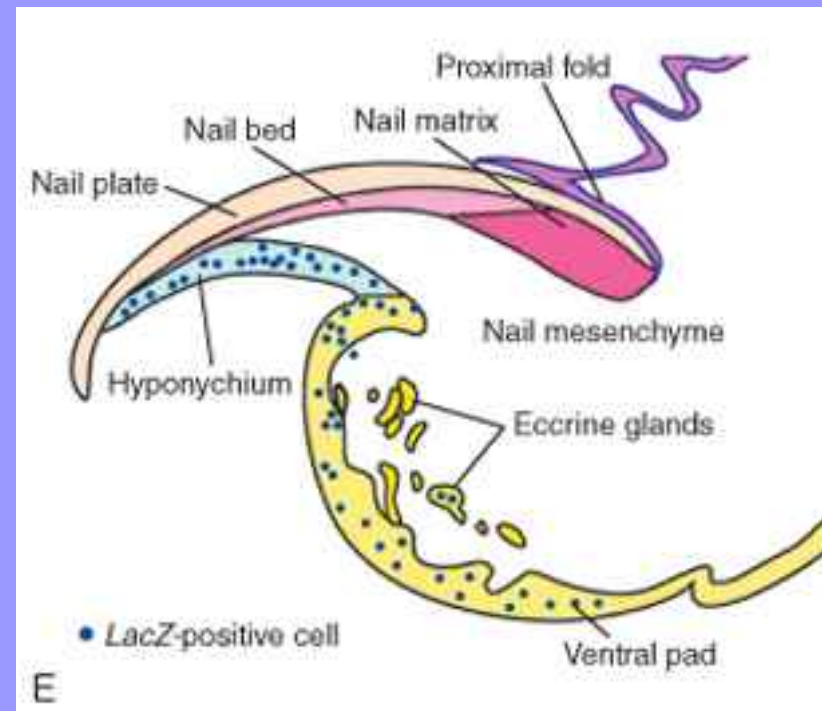
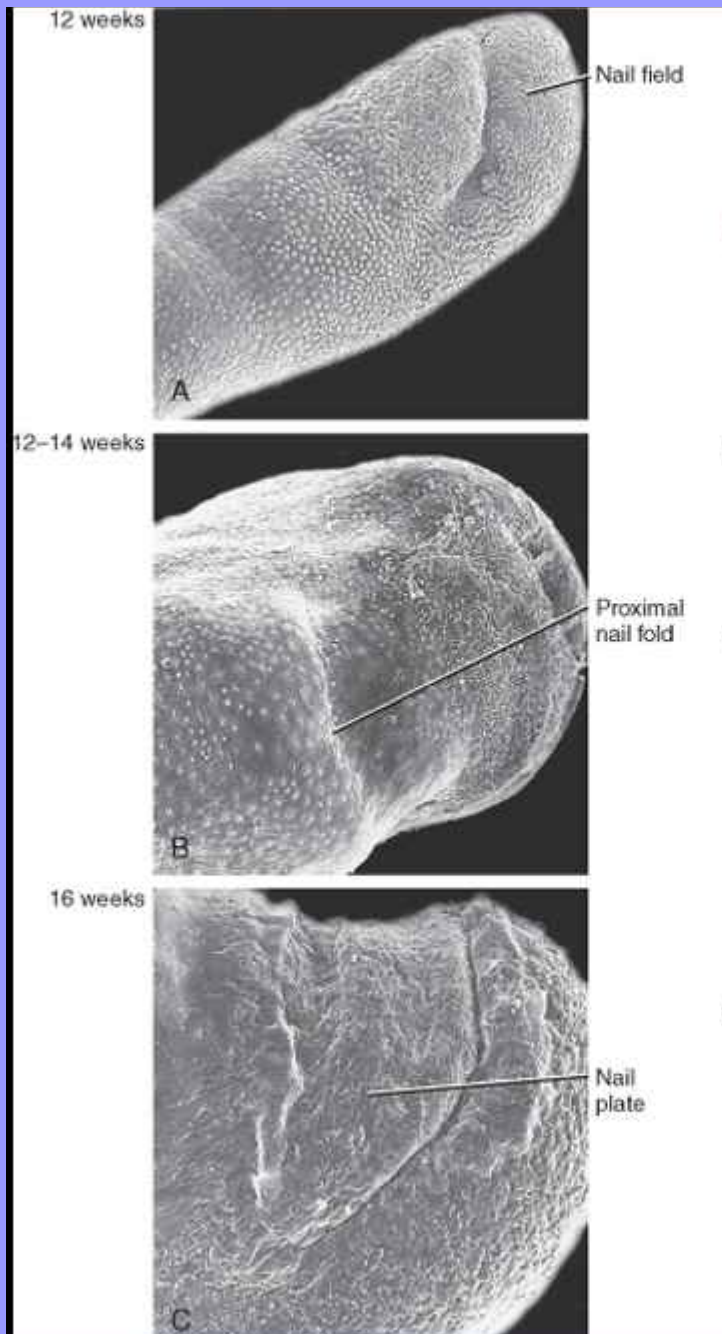
# Nail

is a horn-like envelope covering the dorsal aspect of the terminal phalanges of fingers and toes





## Development of the nails (between 12 and 14 weeks)



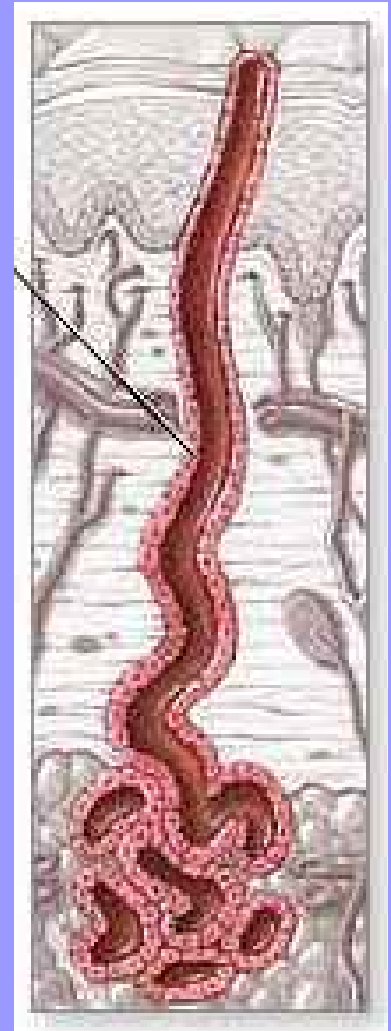
## **Eccrine sweat glands**

unbranched long tubular structures with coiled secretory portion innervated with sympathetic cholinergic fibres.

**Sweat** – hypotonic fluid with sodium and chloride ions. Daily production depends on thermal and emotional stimuli (400 ml – 10 l per day). Their frequency ranged from 80 to over 600/cm<sup>2</sup>. The total number: between 1.6 and 4.5 million.

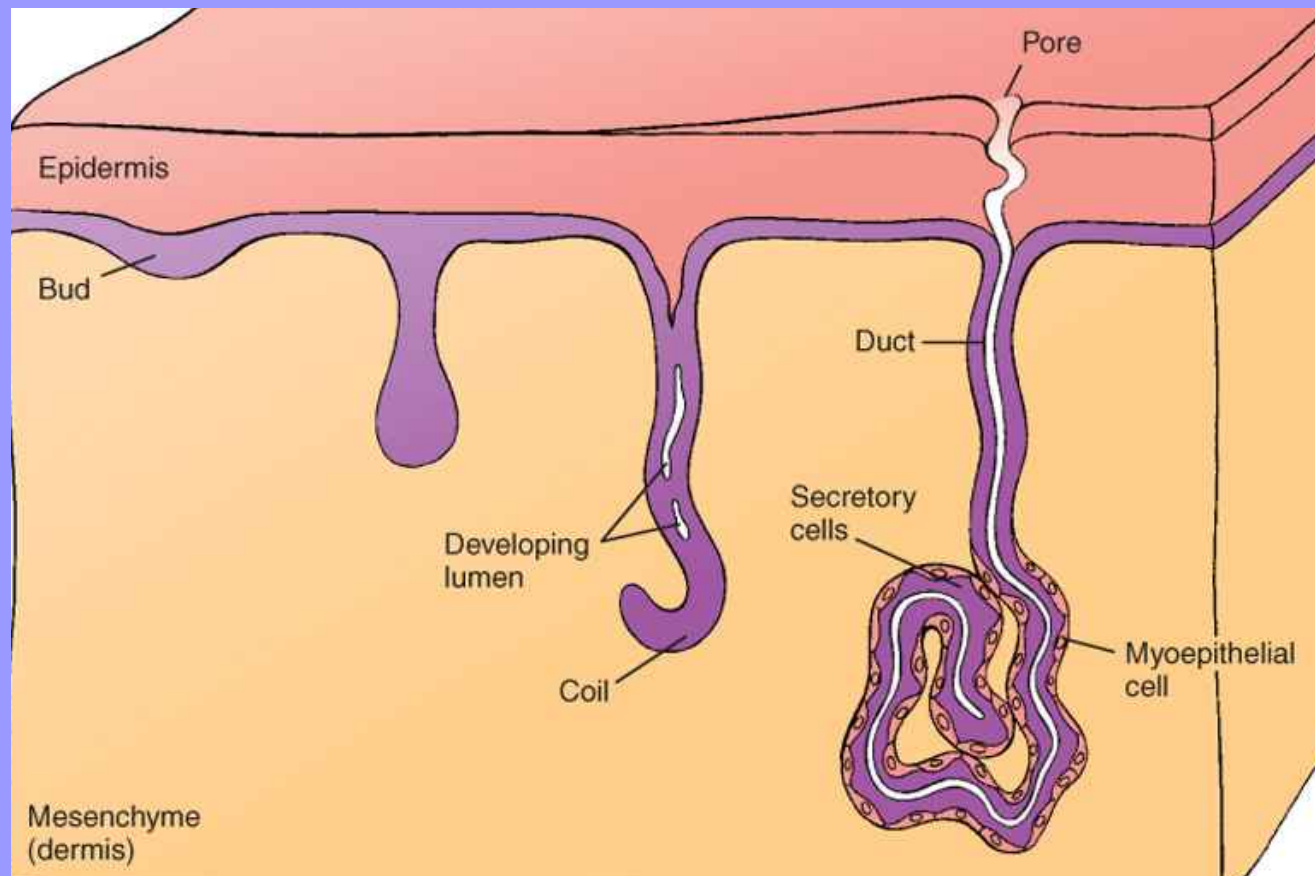
**Function: thermoregulation, excretion**

**Apocrine sweat glands (glandulae circumanales, ceruminosae, nasales, axillares, ciliares)** are larger and are limited to axilla and perianal areas. Apocrine gland secretions also contain pheromones that communicate information to other individuals by altering their hormonal balance..



## Development of sweat glands

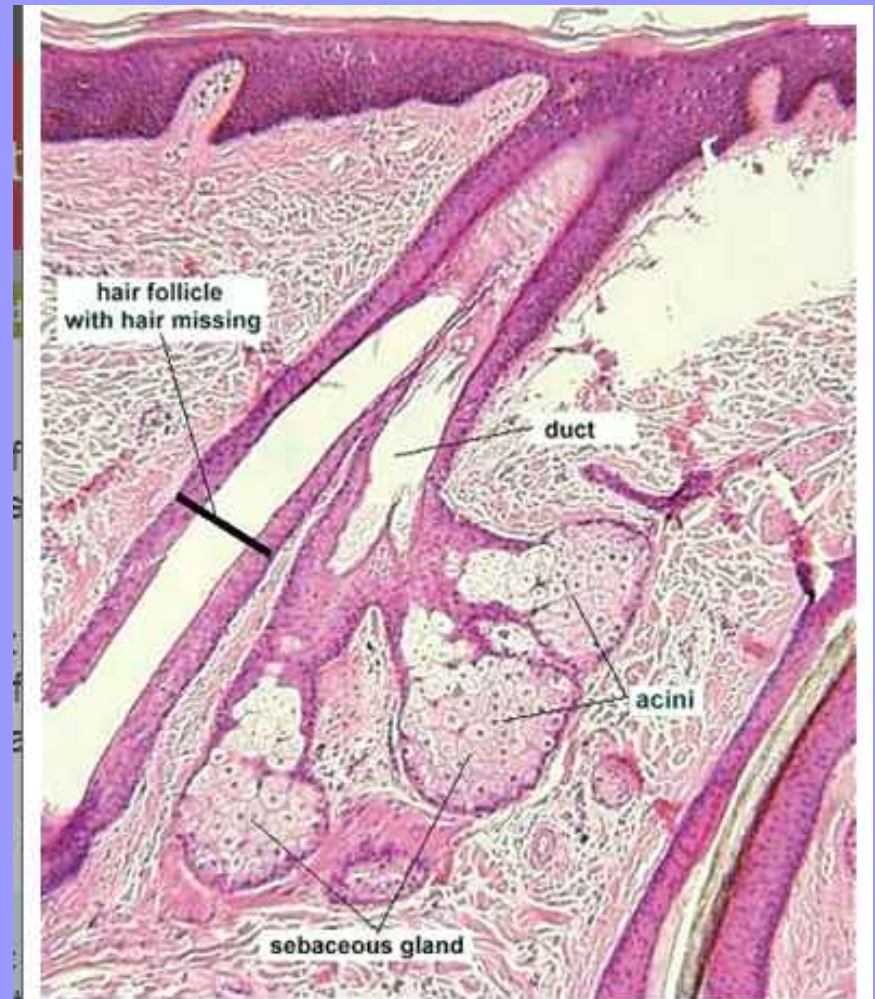
elongated down growths appear at about 20 weeks, the outer cells differentiate into a layer of smooth muscle, the inner cells become the secretory cells of the gland.



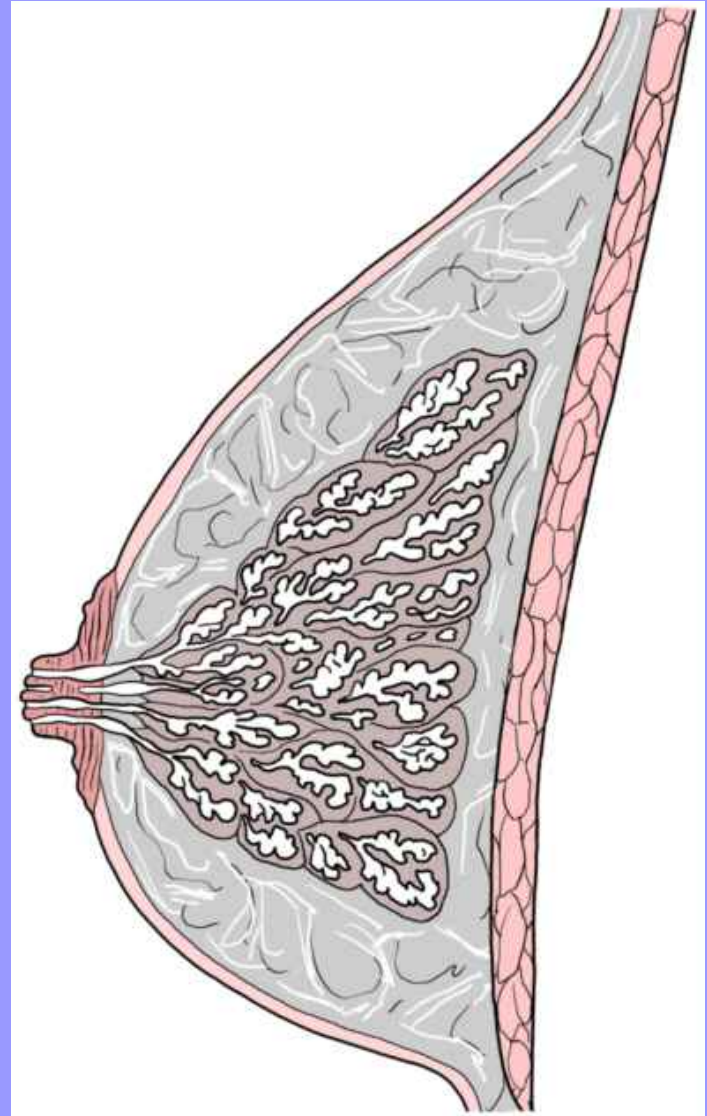
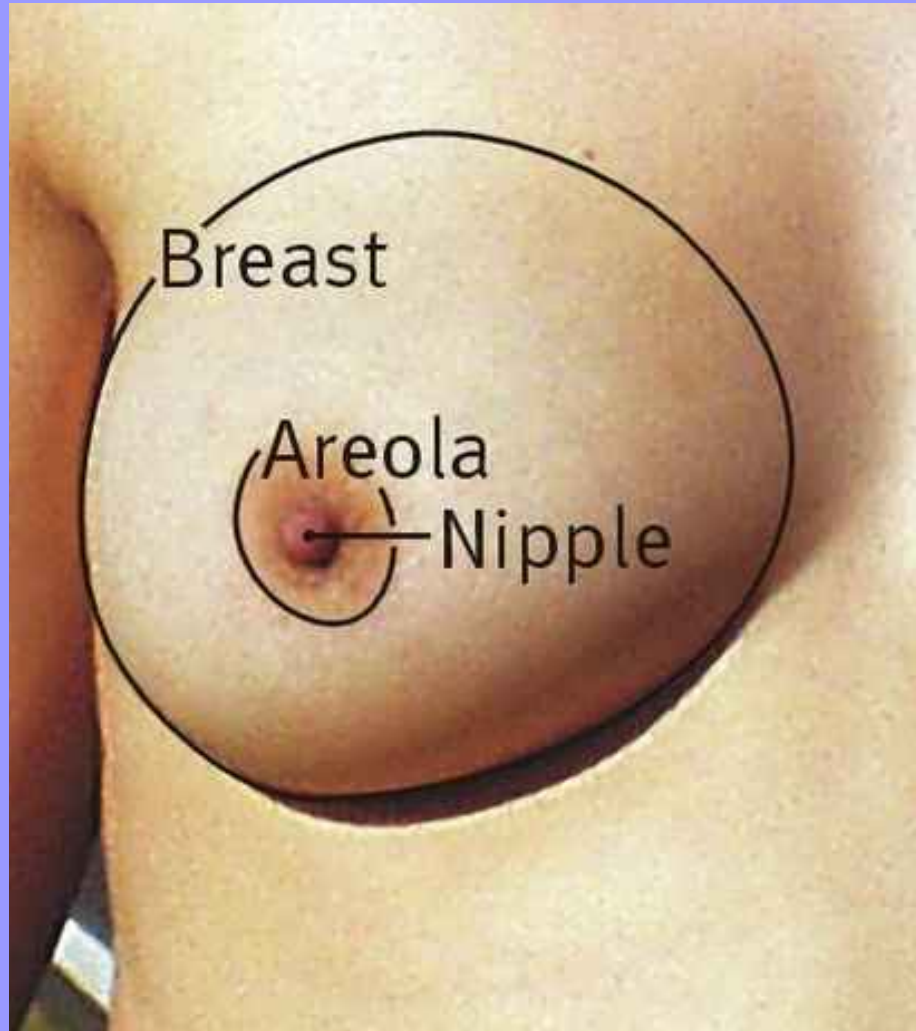


## Sebaceous glands

small glands producing a mixture of fats and cellular debris, **sebum**, usually are attached to hair follicles. They are distributed over the entire body in hairy skin.

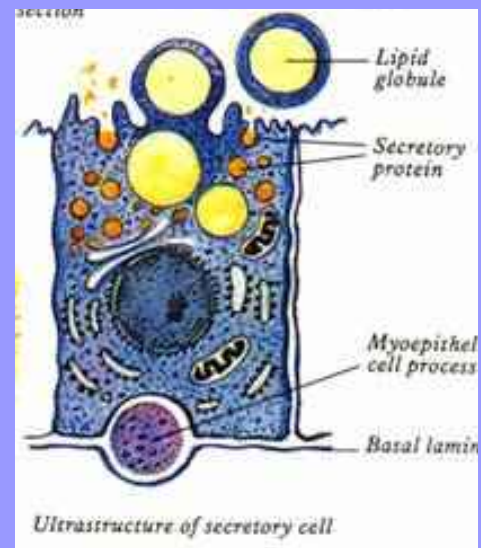
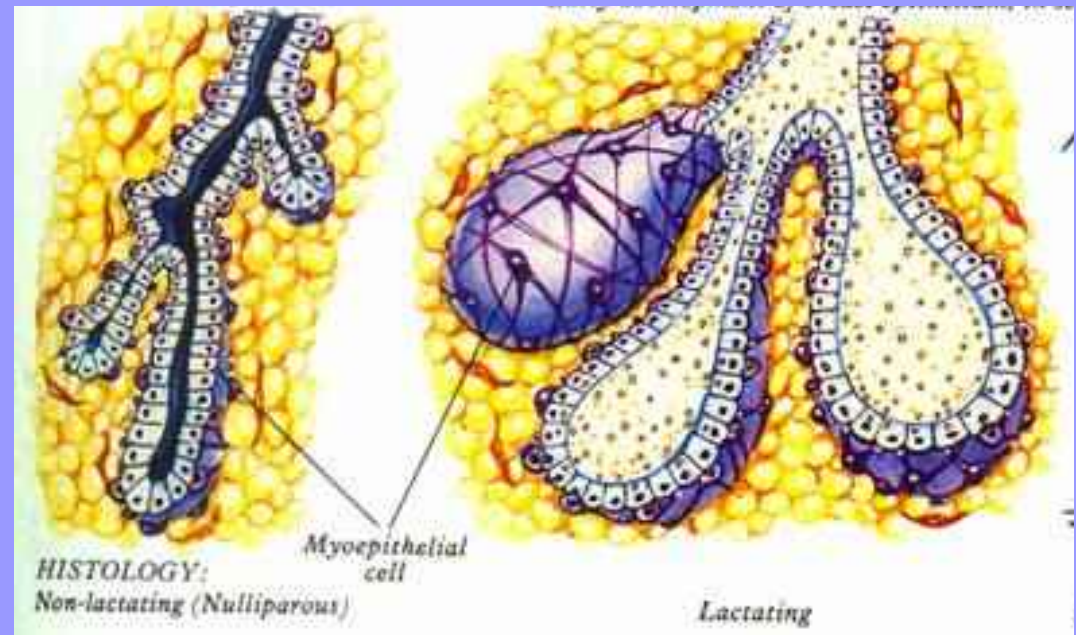
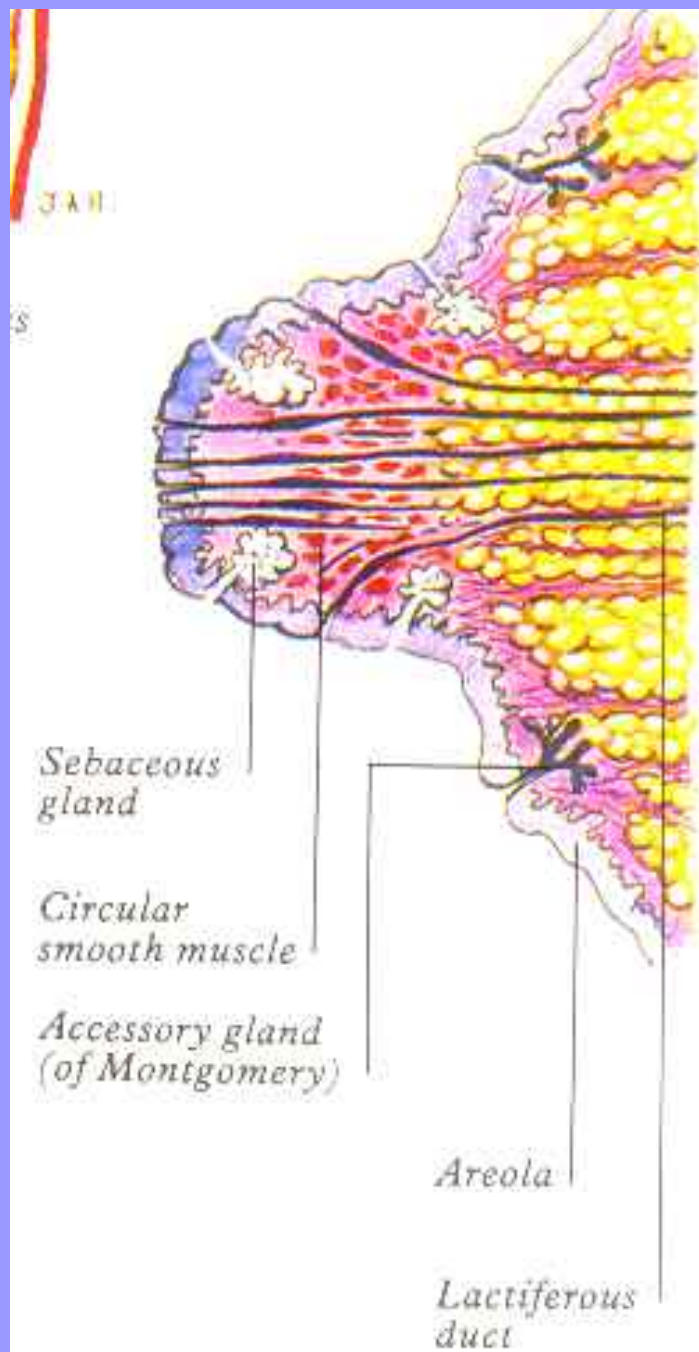


# Female breast (mamma) and mammary gland





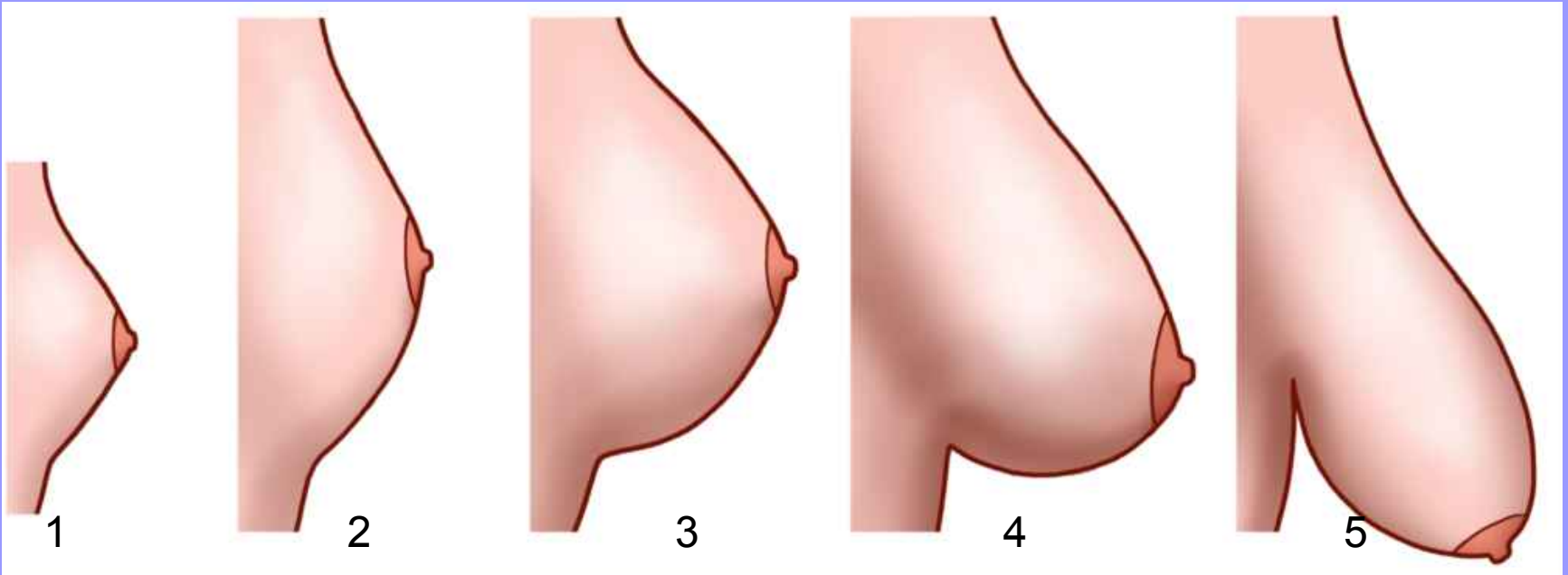
# Mammary gland - structure





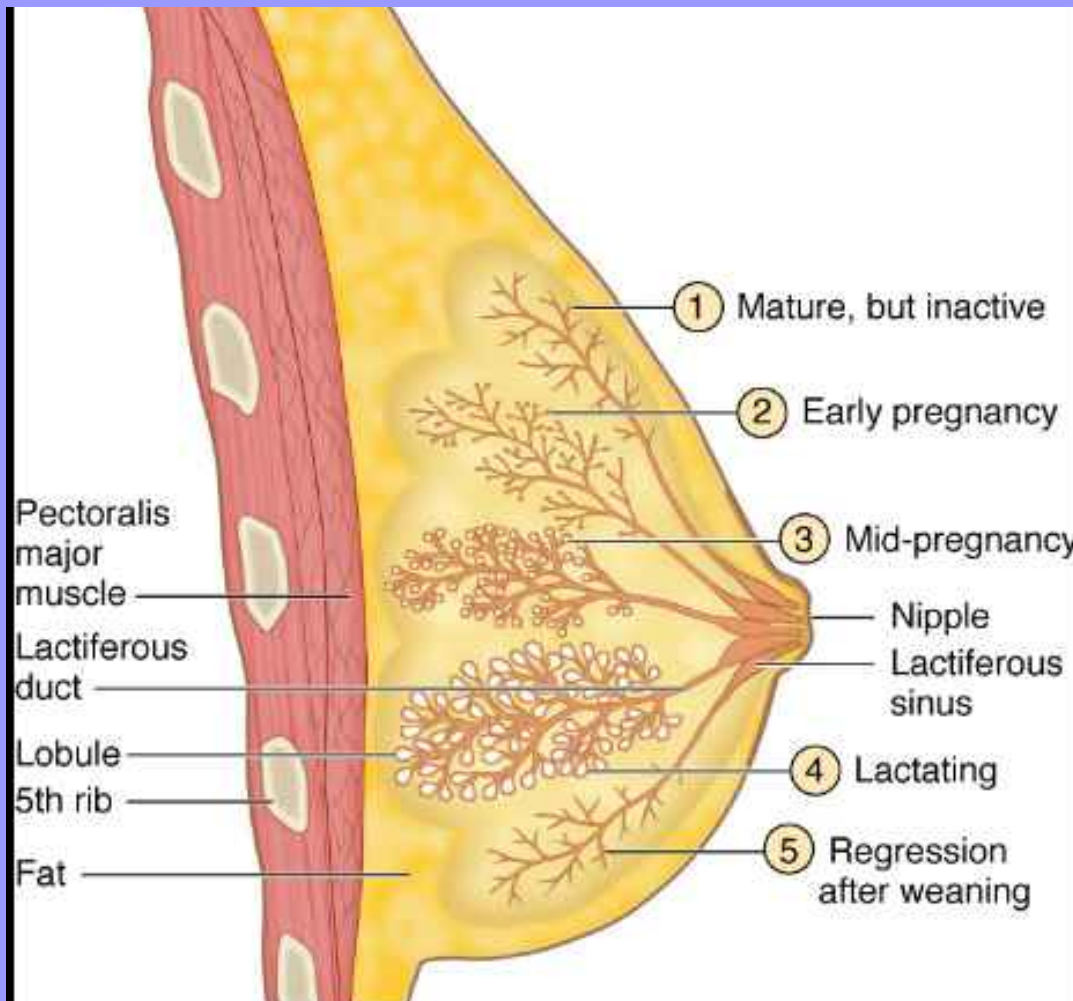
# The breast and its different forms

1 - mamma papilata, 2 - mamma disciformis, 3 - mamma spheroida, 4 - mamma piriformis, 5 - mamma pendula



## Effects of hormones

**Estrogens** affect the growth of the tubular system, **Progesterone** induces development of the alveoli. **Prolactin** stimulates milk production, **Oxytocin** controls release of milk. **Tactile stimulation** of the nipples maintains the release of prolactin and oxytocin (**neurohormonal reflex**)



## Mammary gland

The sequence of changes that occur in the duct system and secretory units before, during, and after pregnancy and lactation.

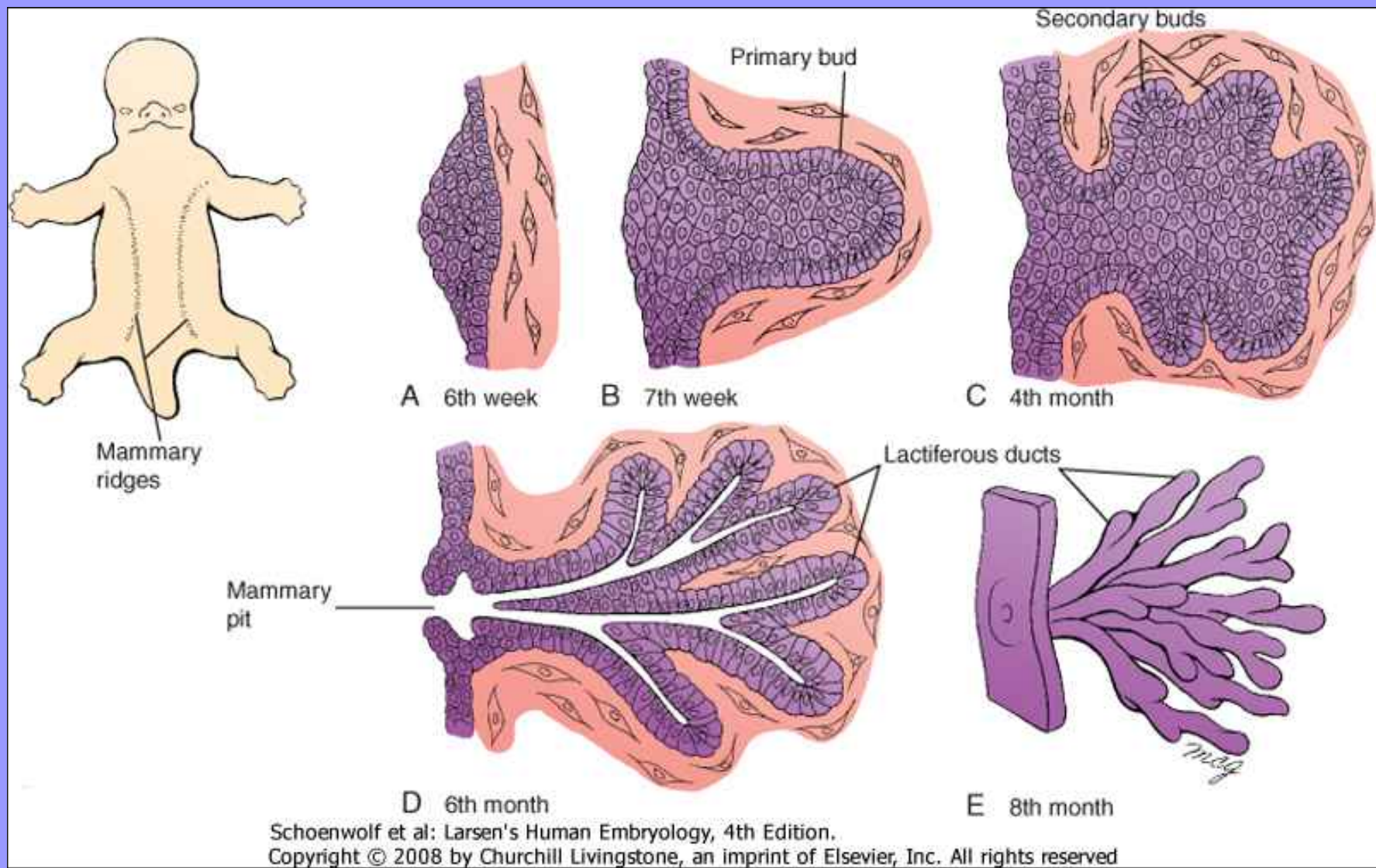
(1) Before pregnancy, the gland is inactive, with small ducts and only a few small secretory alveoli.

(2) Alveoli develop and begin to grow early in a pregnancy.

(3) By mid—pregnancy, the alveoli and ducts have become large and have dilated lumens. (

(4) At parturition and during the time of lactation, the alveoli are greatly dilated and maximally active in production of milk components.

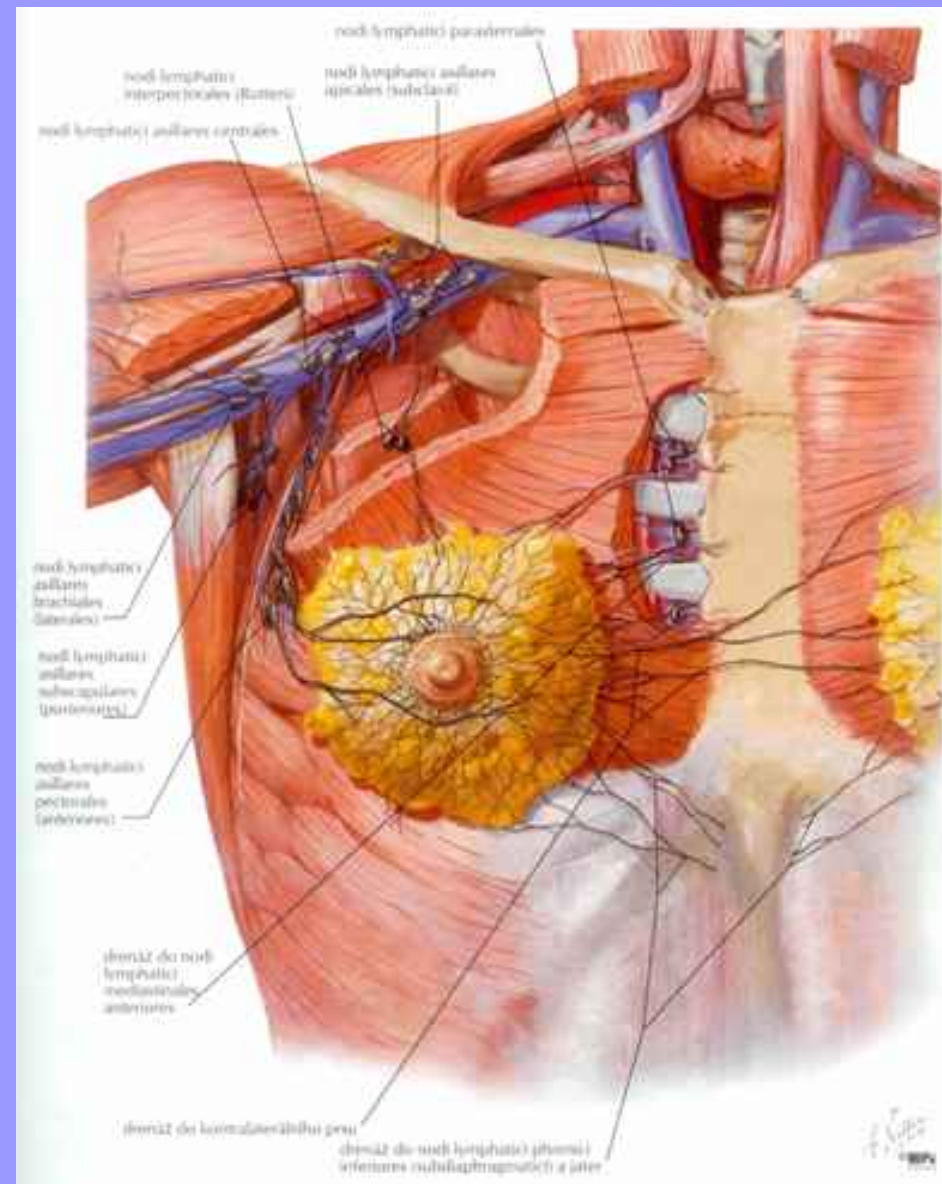
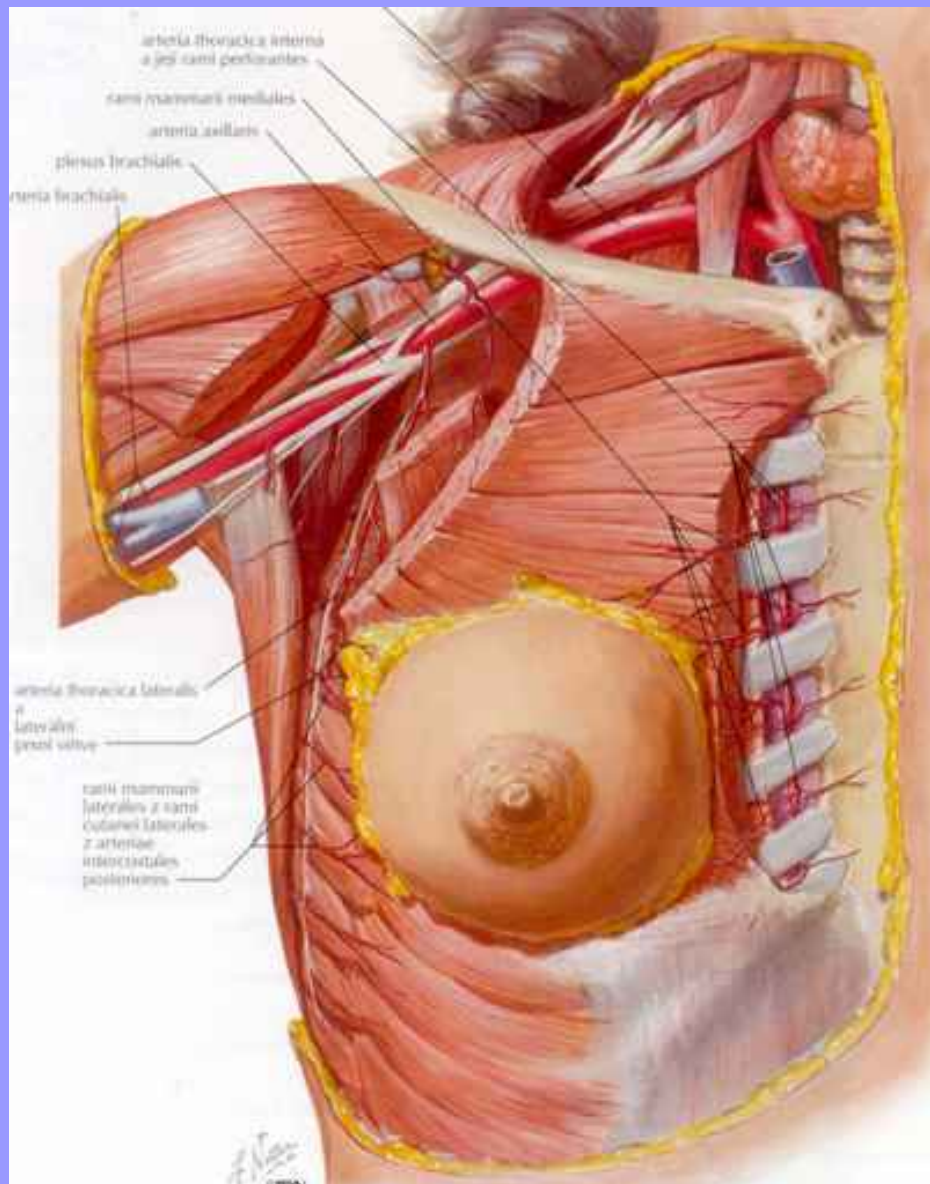
(5) After weaning, the alveoli and ducts regress with apoptotic cell death.



**Development of the mammary glands.** Mammary ridges at the 4th week  
A, B – ridge ectoderm forms primary buds, C,D - secondary buds become  
canalized to form lactiferous ducts

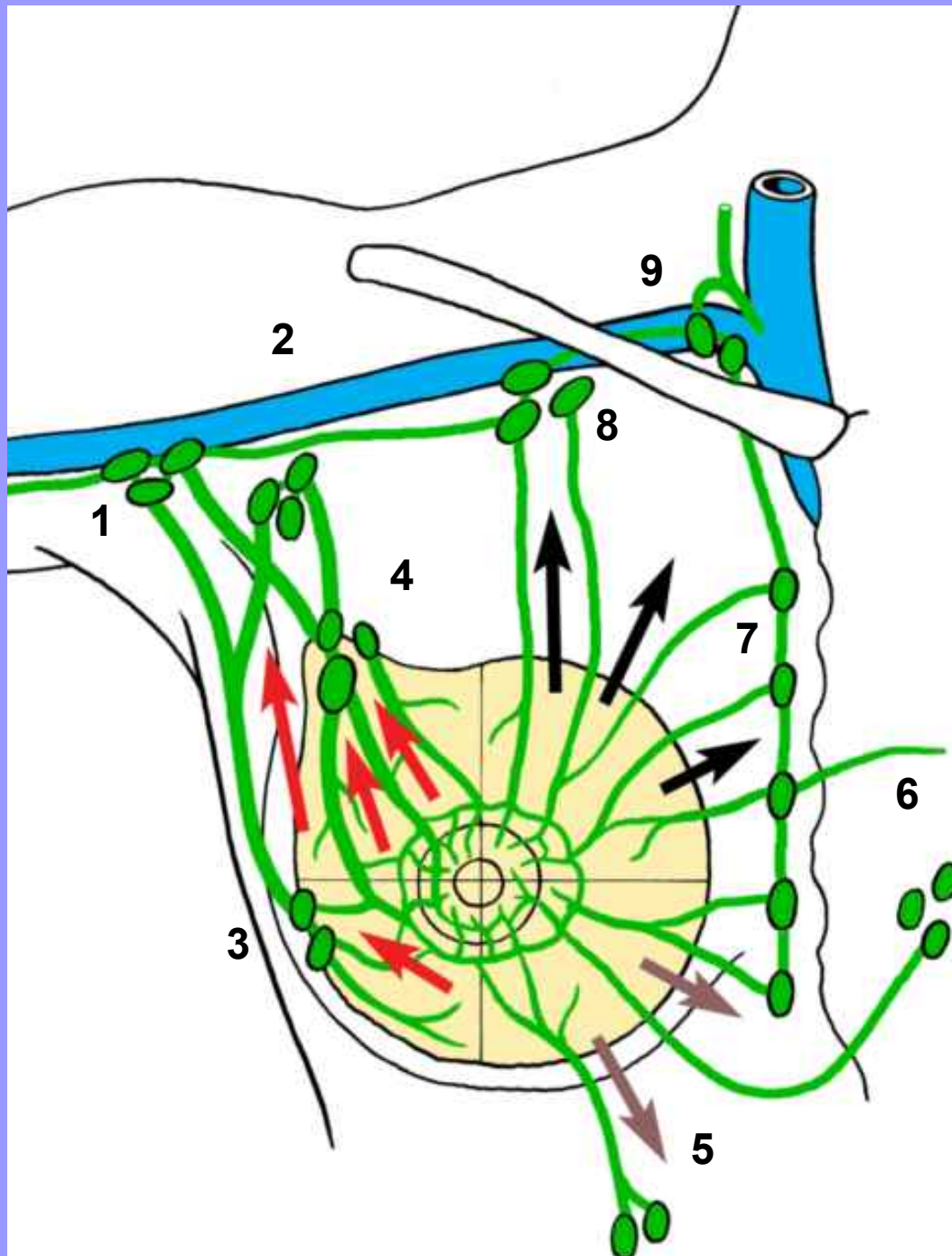


# Mammary gland - blood supply and lymphatic drainage

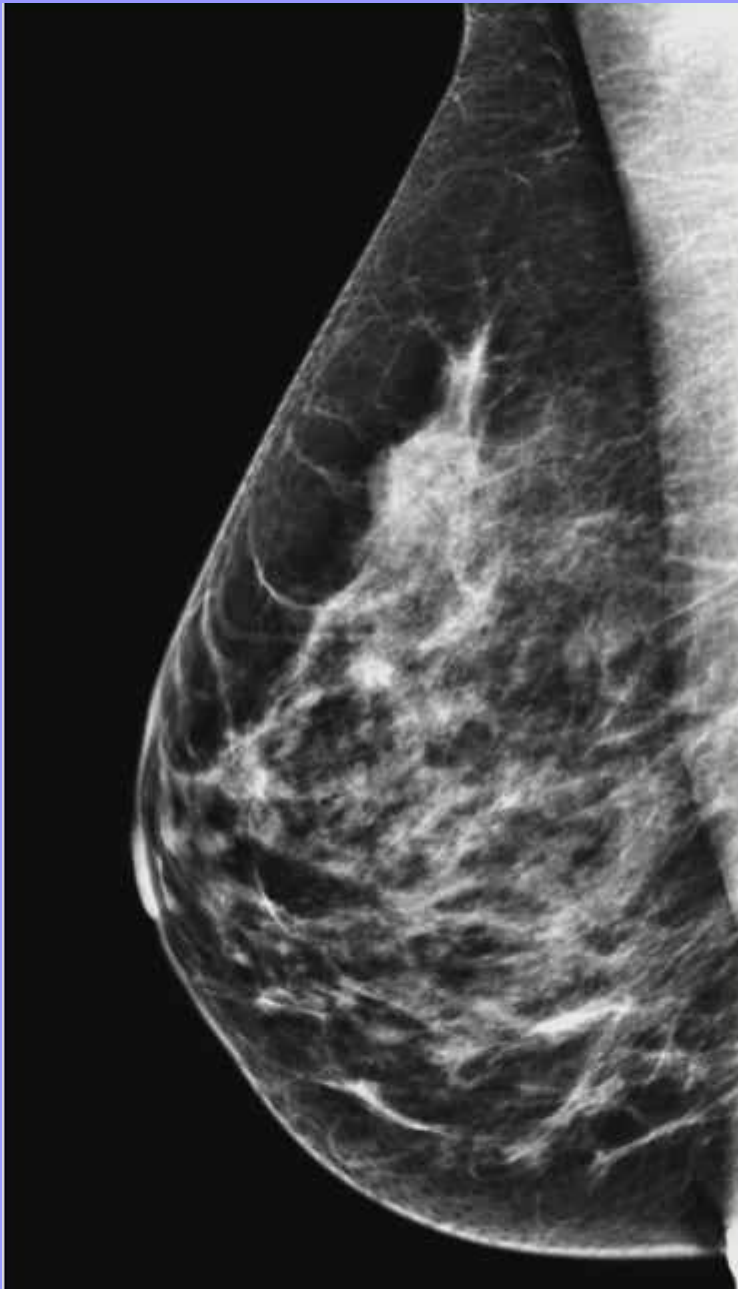


# Lymphatic drainage of the breast.

Subareolar lymphatic plexus.



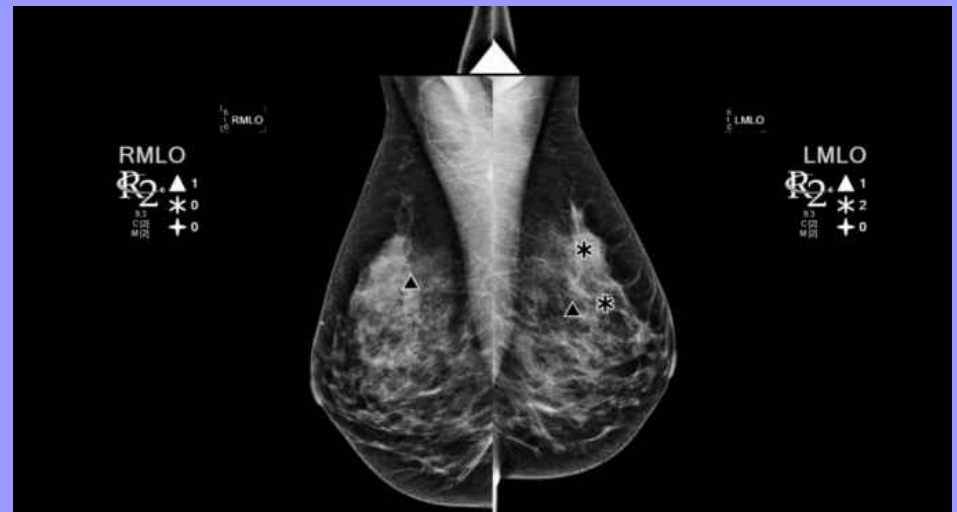
- 1- nodi axillares laterales,
- 2 - nodi axillares centrales,
- 3 - nodi axillares pectorales,
- 4 - nodi interpectores,
- 5 - nodi phrenici inferiores,
- 6 - nodi mediastinales ant.,
- 7 - nodi parasternales,
- 8 - nodi infraclaviculares,
- 9 – nodi supraclaviculares,



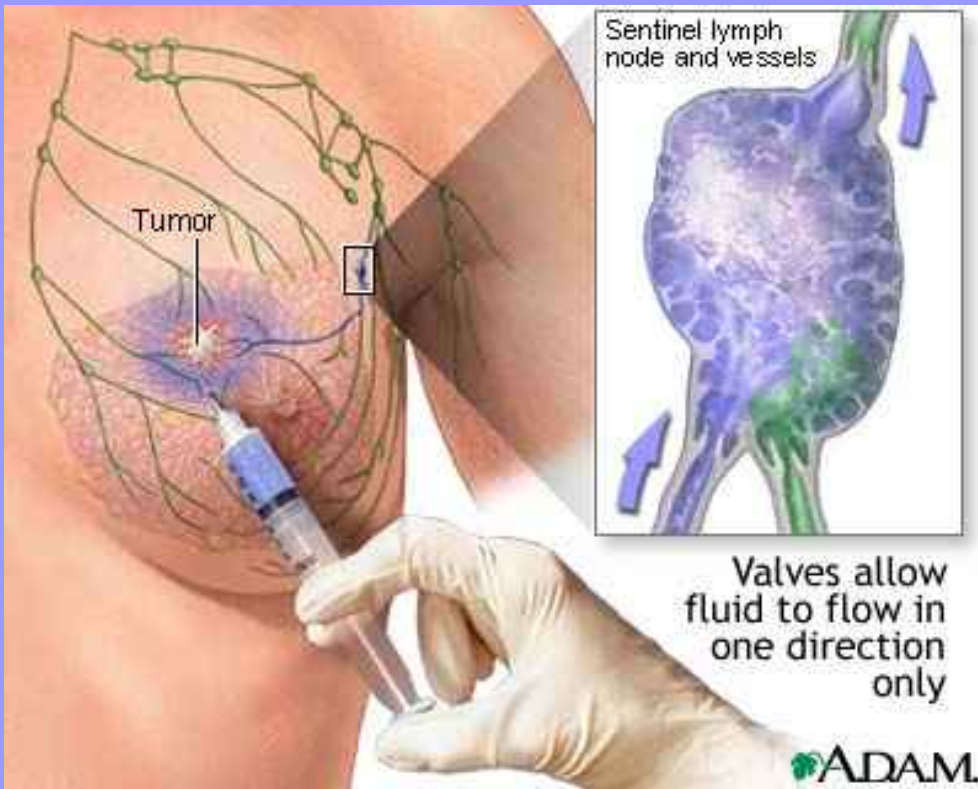
# Mammography

Radiographic technique used to detect breast masses and is used as a diagnostic and a screening tool.

The goal of mammography is the early detection of breast cancer, typically through detection of characteristic masses and/or microcalcifications.

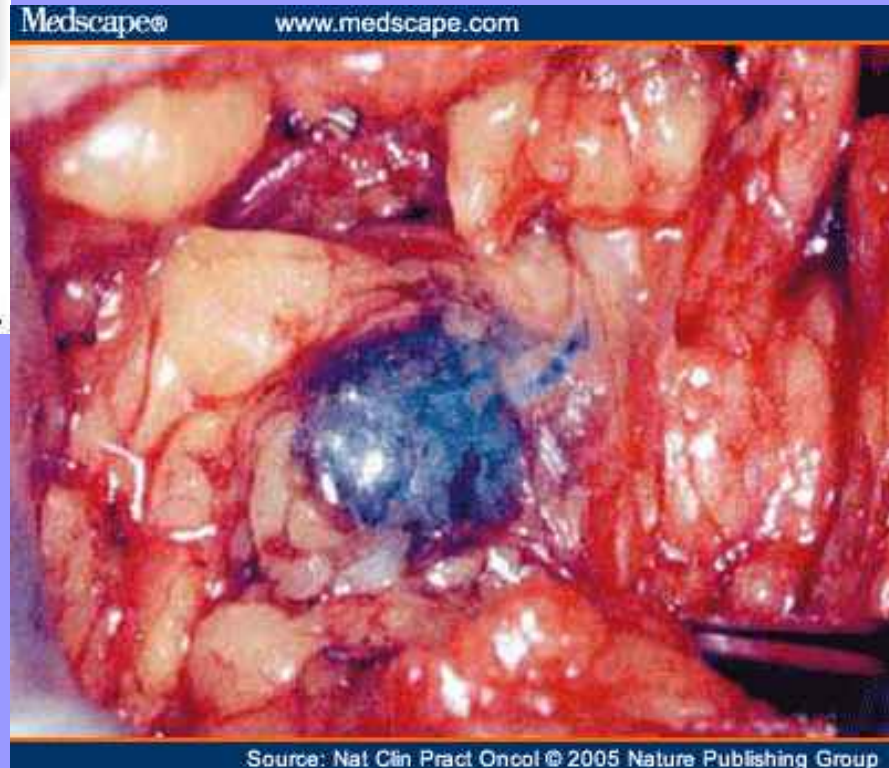






Lymphatic mapping and sentinel lymphadenectomy is becoming an important surgical technique for assessing axillary status in breast cancer. Excision of the sentinel node provides a specimen for focused histopathologic analysis.

**Sentinel lymphatic node detection.** Intraoperative mapping of the lymphatic tract draining to the sentinel node may use vital blue dye and/or radioactive tracer.



Relationship Between the  
Lymphatic Drainage of the Breast  
and the Upper Extremity: A  
Postmortem Study. David  
Pavlista, and Oldrich Eliska  
Ann Surg Oncol  
Published online : 24 April 2012

Conclusions. Lymphatic drainage  
of the upper extremity and breast  
are closely related in the caudal  
part of the axilla,  
which could explain lymphedema  
after surgery if damaged.

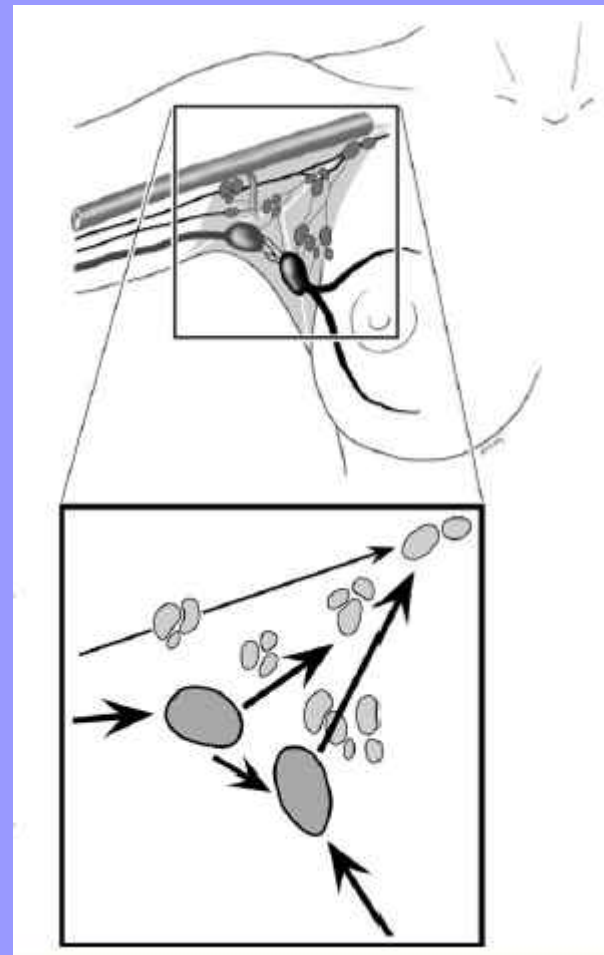


FIG. 5 Final scheme of lymphatic  
drainage of the breast and the  
upper extremity in axilla. Black  
arrows indicate direction of patent  
blue flow

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Good luck in the final exam !

