Hair Anatomy and Physiology

Basics

- Hair has little remaining physiologic importance, but great psychological importance.
- Five million total hair follicles in the adult human, without significant racial or sexual differences
  - Scalp has highest density, but declines with age from 1135/cm^2 at birth to
  - 300-500/cm^2 in adults for a total of 100,000 follicles.

Basics

- Ethnic differences in hair shape are the result of differences in follicle shape.
  - The follicle keratinizes (hardens) 1st & molds the hair to its shape
    - Caucasian=round to oval
    - Black=elliptical/flattened
    - Asian=round, also largest diameter

Embryology and Development

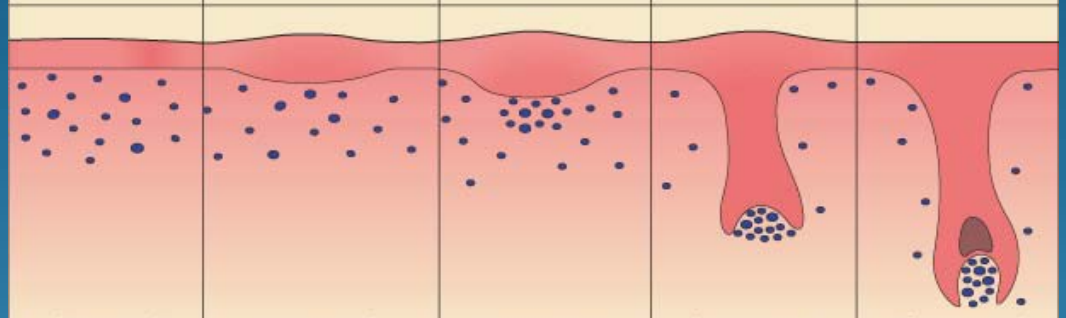
- Early formation of hair follicles depends on a very complicated series of mesenchymal epithelial interactions that are being actively investigated.
- Why study these complex interactions?
  - One day it may be possible to induce new follicle development as a treatment for the scarring alopecias
- Timeline:
  - 10 Weeks: Follicle formation begins on the head (particularly eyebrows, lower and upper lip)
  - 16 weeks: Follicles develop cephalocaudally over rest of the body
  - 22 weeks: New follicle formation complete

Embryology

- No hair follicles form after birth (under normal circumstances)
- The nonrandom symmetric distribution is probably determined by patterning genes such as *hox, msx, en* that were originally discovered in *Drosophila*
- The establishment of a dermal papilla (DP) is vital to the development of all hair follicles.
- DP is a group of specialized dermal fibroblast cells.
- They are derived from the embryonic mesoderm
- They aggregate in the dermis just below the epidermis.

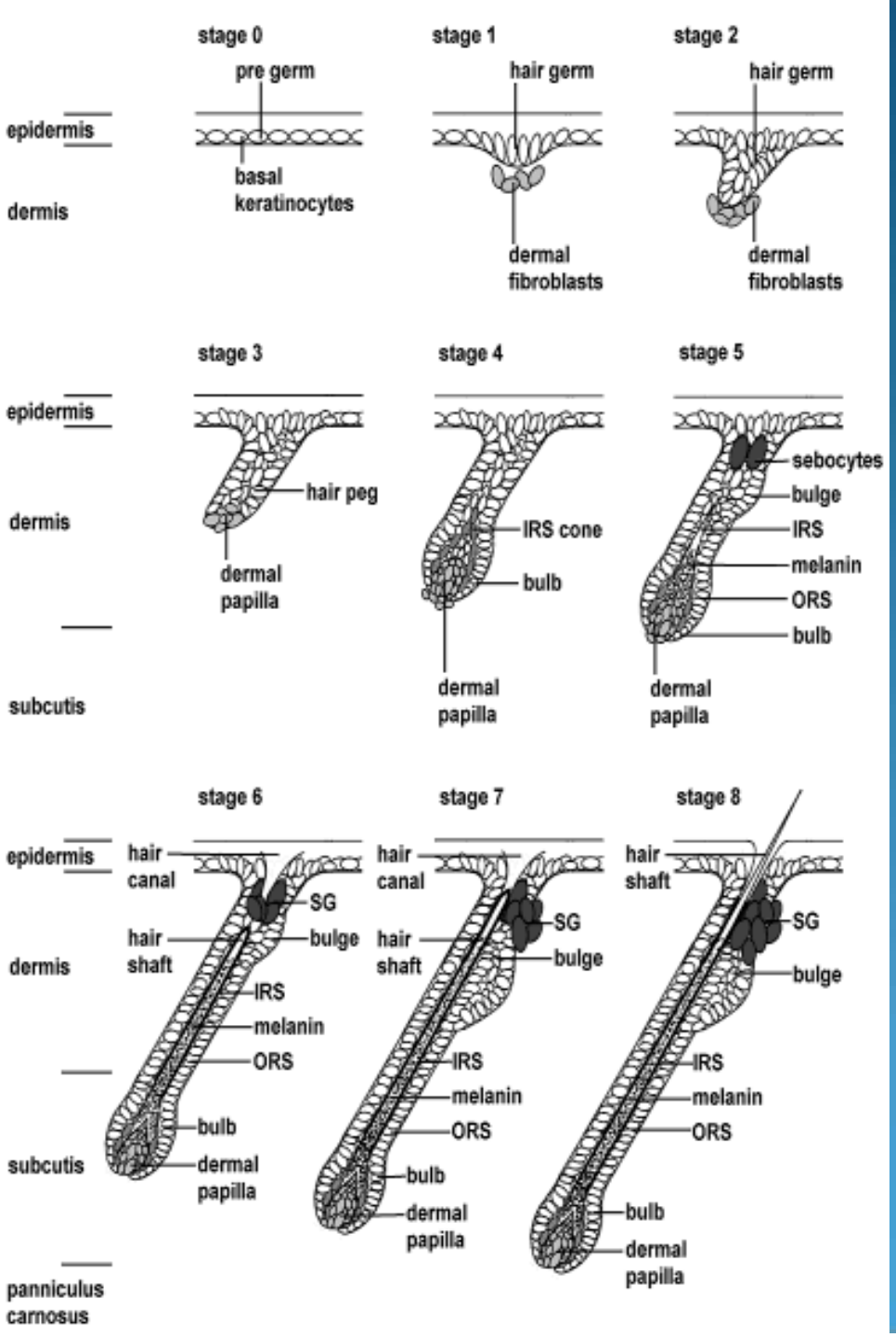
KEY SIGNALING EVENTS IN MURINE HAIR FOLLICLE DEVELOPMENT

Induction		Organogenesis		Cytodifferentiation
Undifferentiated epithelium (0)	Placode (1)	Germ (2)	Peg (3–4)	Bulbous peg (5–8)



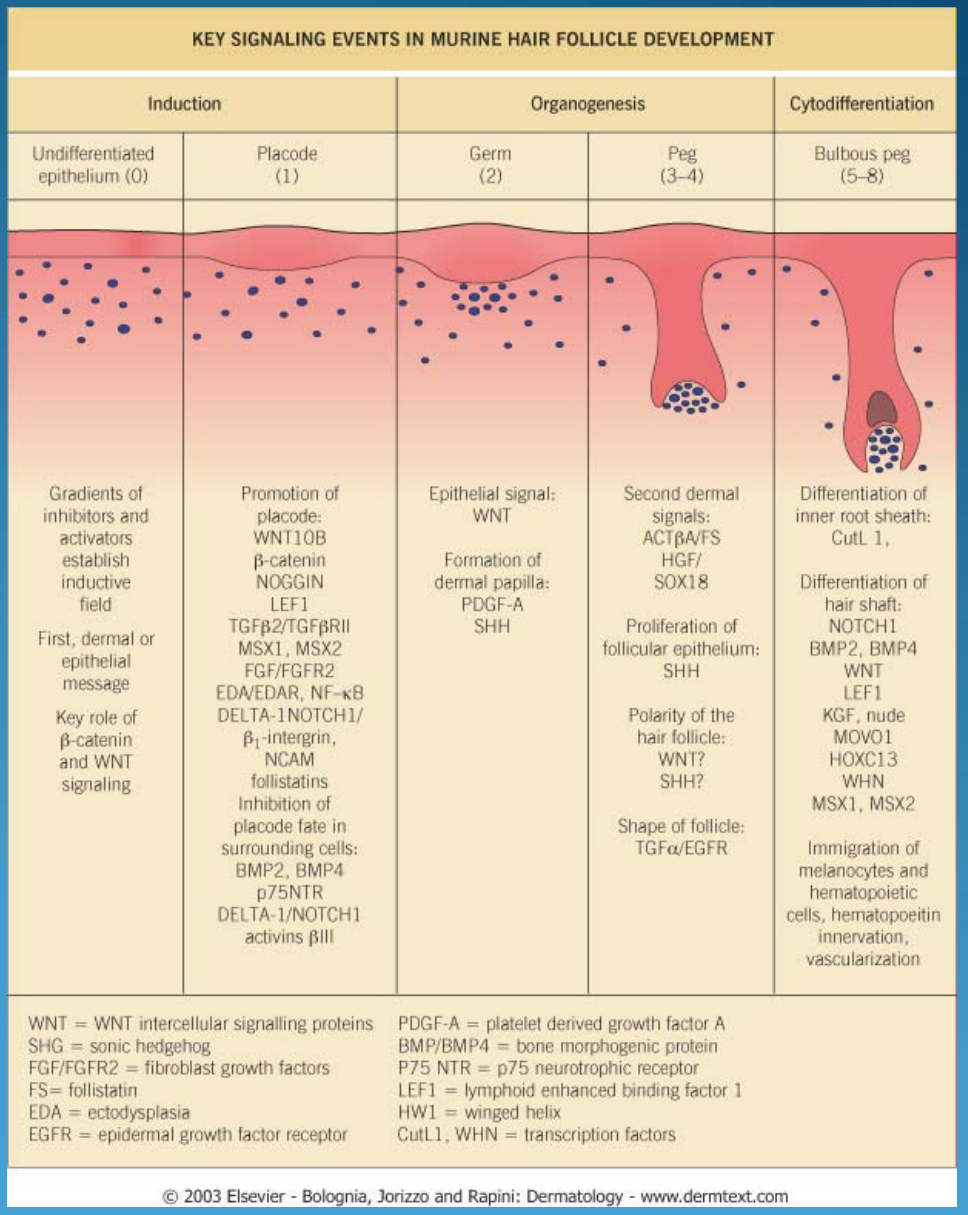
Gradients of inhibitors and activators establish inductive field First, dermal or epithelial message Key role of β-catenin and WNT signaling	Promotion of placode: WNT10B β-catenin NOGGIN LEF1 TGFβ2/TGFβRII MSX1, MSX2 FGF/FGFR2 EDA/EDAR, NF-κB DELTA-1NOTCH1/ β_1-intergrin, NCAM follistatins Inhibition of placode fate in surrounding cells: BMP2, BMP4 p75NTR DELTA-1/NOTCH1 activins βIII	Epithelial signal: WNT Formation of dermal papilla: PDGF-A SHH	Second dermal signals: ACTβA/FS HGF/ SOX18 Proliferation of follicular epithelium: SHH Polarity of the hair follicle: WNT? SHH? Shape of follicle: TGFα/EGFR	Differentiation of inner root sheath: CutL 1, Differentiation of hair shaft: NOTCH1 BMP2, BMP4 WNT LEF1 KGF, nude MOVO1 HOXC13 WHN MSX1, MSX2 Immigration of melanocytes and hematopoietic cells, hematopoeitin innervation, vascularization

WNT = WNT intercellular signalling proteins
SHG = sonic hedgehog
FGF/FGFR2 = fibroblast growth factors
FS= follistatin
EDA = ectodysplasia
EGFR = epidermal growth factor receptor
PDGF-A = platelet derived growth factor A
BMP/BMP4 = bone morphogenic protein
P75 NTR = p75 neurotrophic receptor
LEF1 = lymphoid enhanced binding factor 1
HW1 = winged helix
CutL1, WHN = transcription factors


stage 0
pre germ
basal keratinocytes
stage 1
hair germ
dermal fibroblasts
stage 2
hair germ
dermal fibroblasts
epidermis
dermis
stage 3
hair peg
dermal papilla
stage 4
IRS cone
bulb
dermal papilla
stage 5
sebocytes
bulge
IRS
melanin
ORS
bulb
dermal papilla
subcutis
stage 6
hair canal
SG
hair shaft
bulge
IRS
melanin
ORS
bulb
dermal papilla
stage 7
hair canal
SG
hair shaft
bulge
IRS
melanin
ORS
bulb
dermal papilla
stage 8
hair shaft
SG
bulge
IRS
melanin
ORS
bulb
dermal papilla
panniculus carnosus

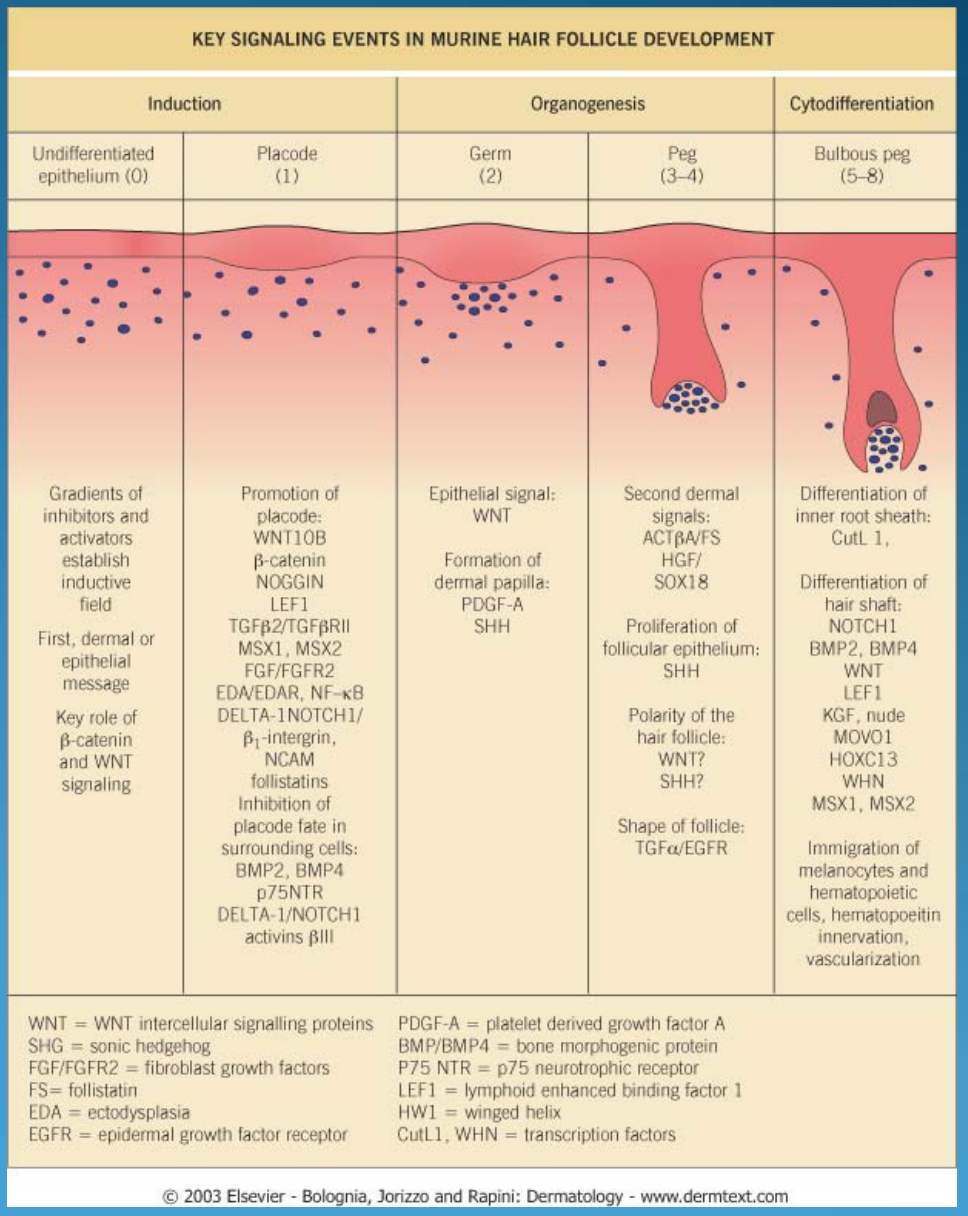
Embryology

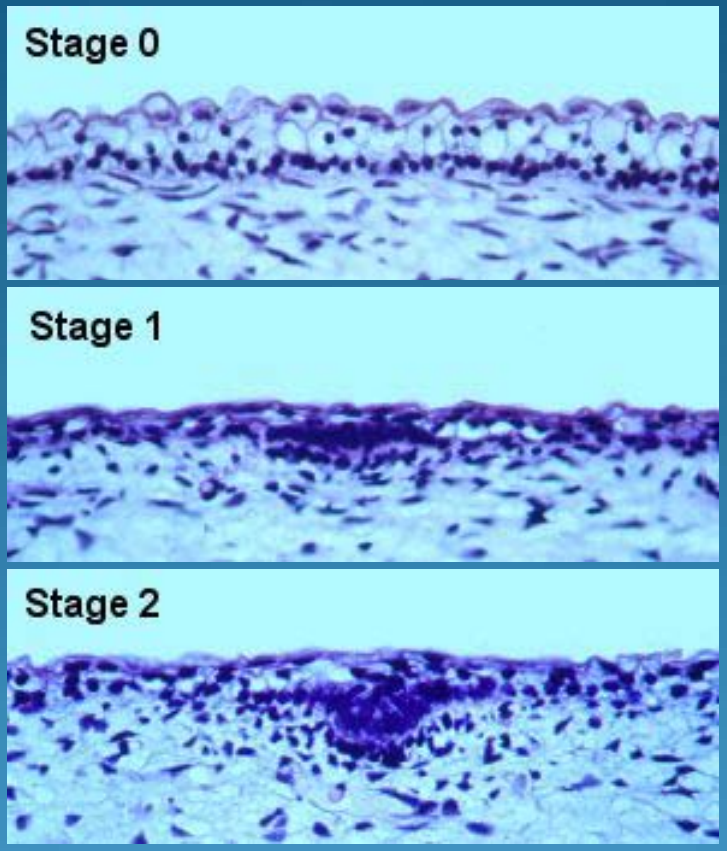
- **Undifferentiated Epithelium:**
  - β-catenin is thought to be the first signal from the *mesenchyme (dermis)* to start the process
  - β-catenin degradation is prevented by WNT signaling molecules allowing it to bind to intranuclear LEF factors (LEF=Lymphoid enhancer-binding factor)



Embryology

- **Placode Stage:**
  - Epithelial Placode: Small collection of cells that 1st appear in otherwise homogenous epithelium around 10 weeks in response to dermal signal
  - Some of these signals are promoters, some inhibitors
- **Germ Phase:** (Formation of Dermal Condensate)
  - Sonic Hedgehog protein (SHH) is thought to be a major player.

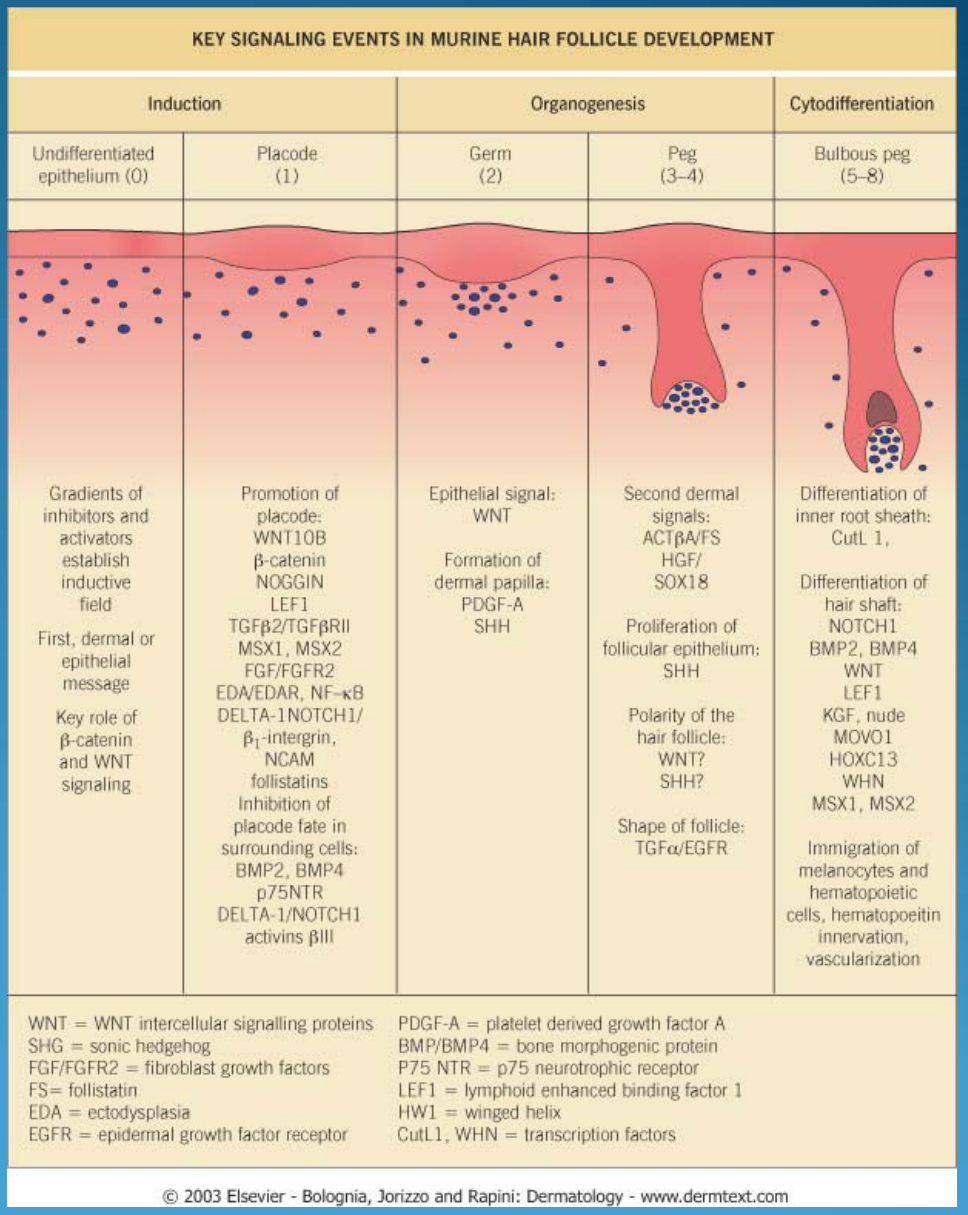




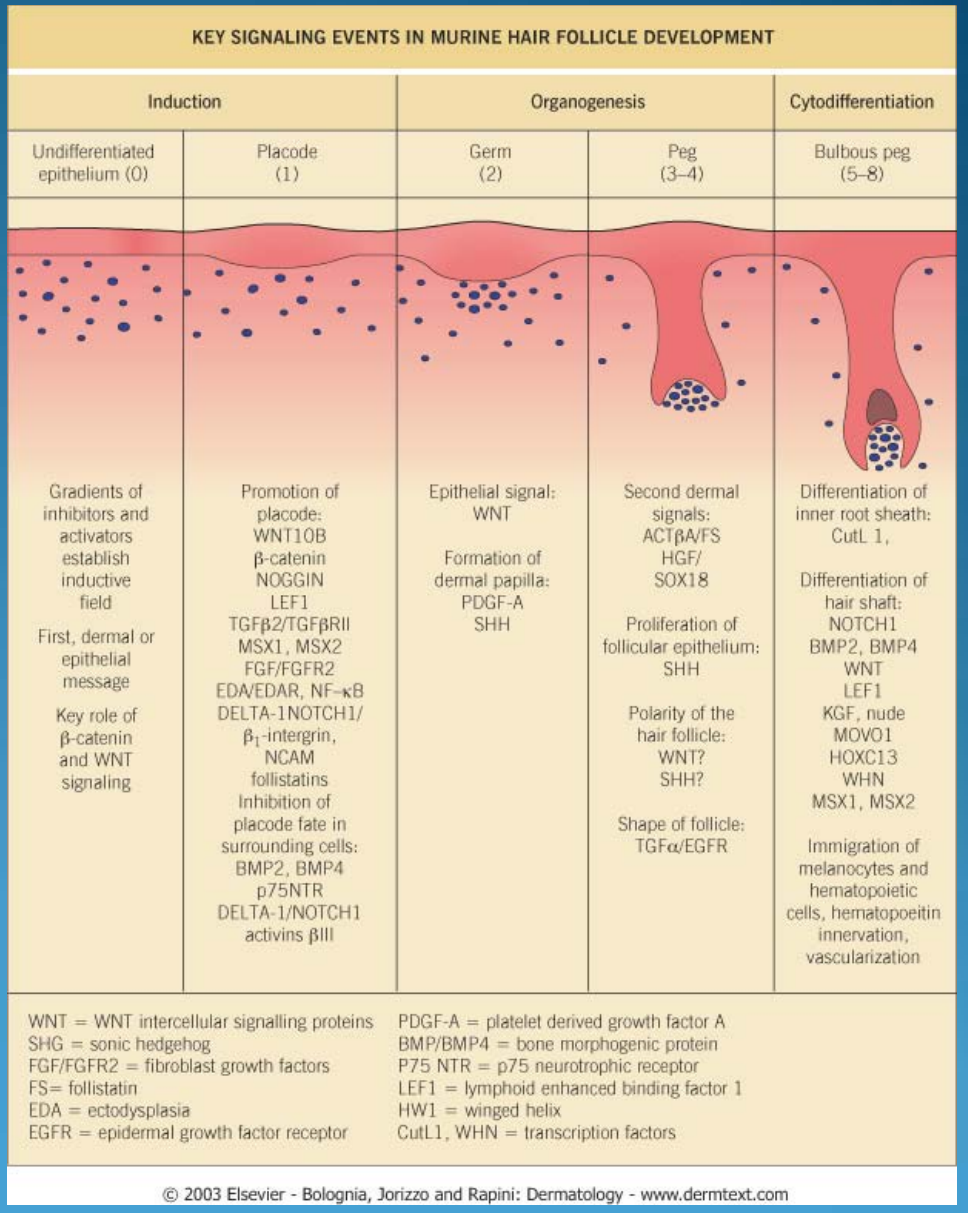
The very first stages of hair follicle embryogenesis are shown in the pictures above. At stage 0, before hair follicle development, the epidermis and dermis are uniform. At stage 1, a few dermal fibroblast-like cells aggregate below the epidermis and the epidermal cells above the aggregation become larger. At stage 2 the epidermal cells start proliferating and push down into the dermis following the dermal papilla cells.

Embryology

- **Peg Phase:**
  - The dermal condensate signals the follicular epithelium (peg) to proliferate and grow down into the dermis, again SHH is implicated
  - The dermal condensate becomes enveloped by the follicular epithelial cells and the Dermal Papilla is formed

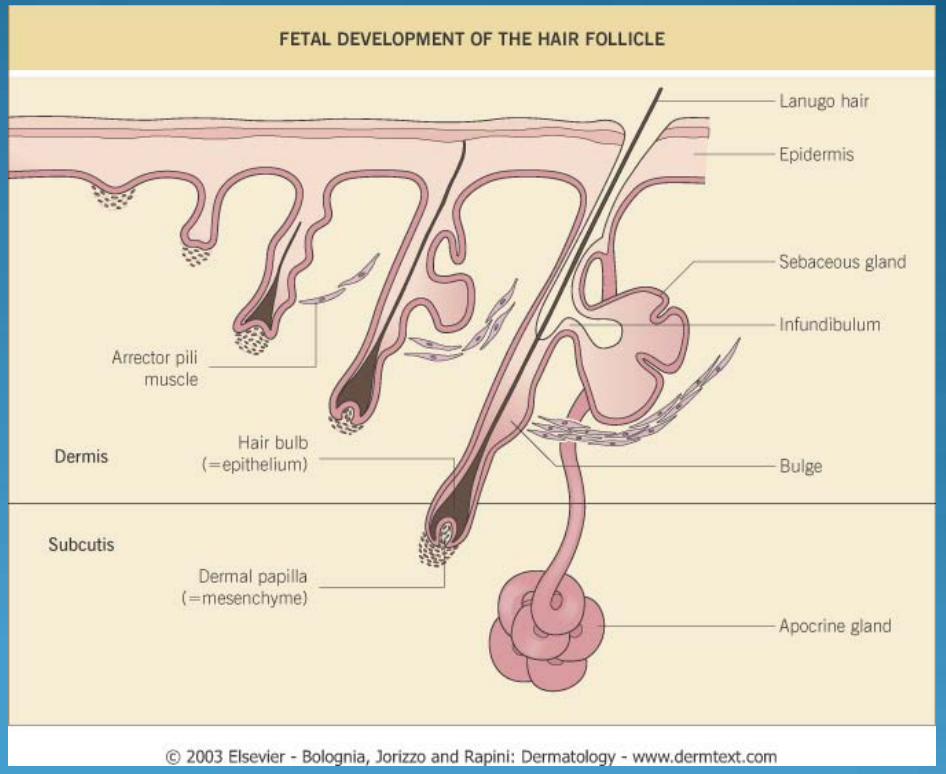


- **Bulbous Peg Phase:**
  - At least 7 different epithelial layers constituting the components of the mature hair follicle are formed; NOTCH1 is thought to be a key factor in this differentiation.



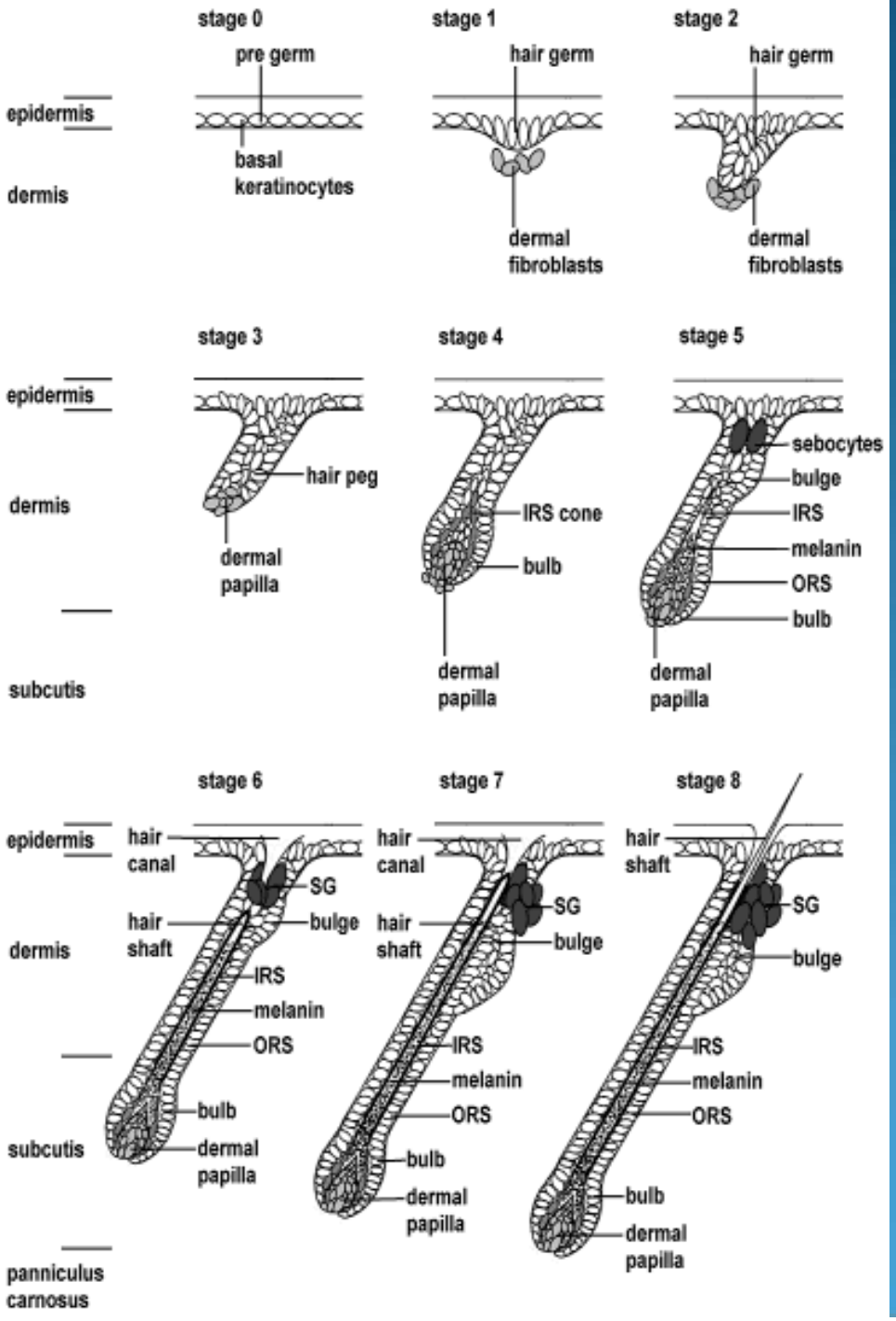
Embryology

- **Bulbous Peg Phase:**
  - At this time, 3 bulges appear on the follicle wall
    - Upper forms APOCRINE glands in appropriate locations
    - Middle forms SEBACEOUS glands
    - Lower forms the important HAIR BULGE and is the site of arrector pili muscle attachment
  - Melanocytes become interspersed among the keratinocytes



Embryology

- As the epidermal plug penetrates down into the dermis mesodermal cells congregate around it.
- The mesodermal cells develop into a fibrous follicular sheath or collagen capsule to encase the epidermal cells.


stage 0
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stage 8
hair shaft
SG
bulge
IRS
melanin
ORS
bulb
dermal papilla
epidermis
dermis
subcutis
panniculus carnosus

Embryology

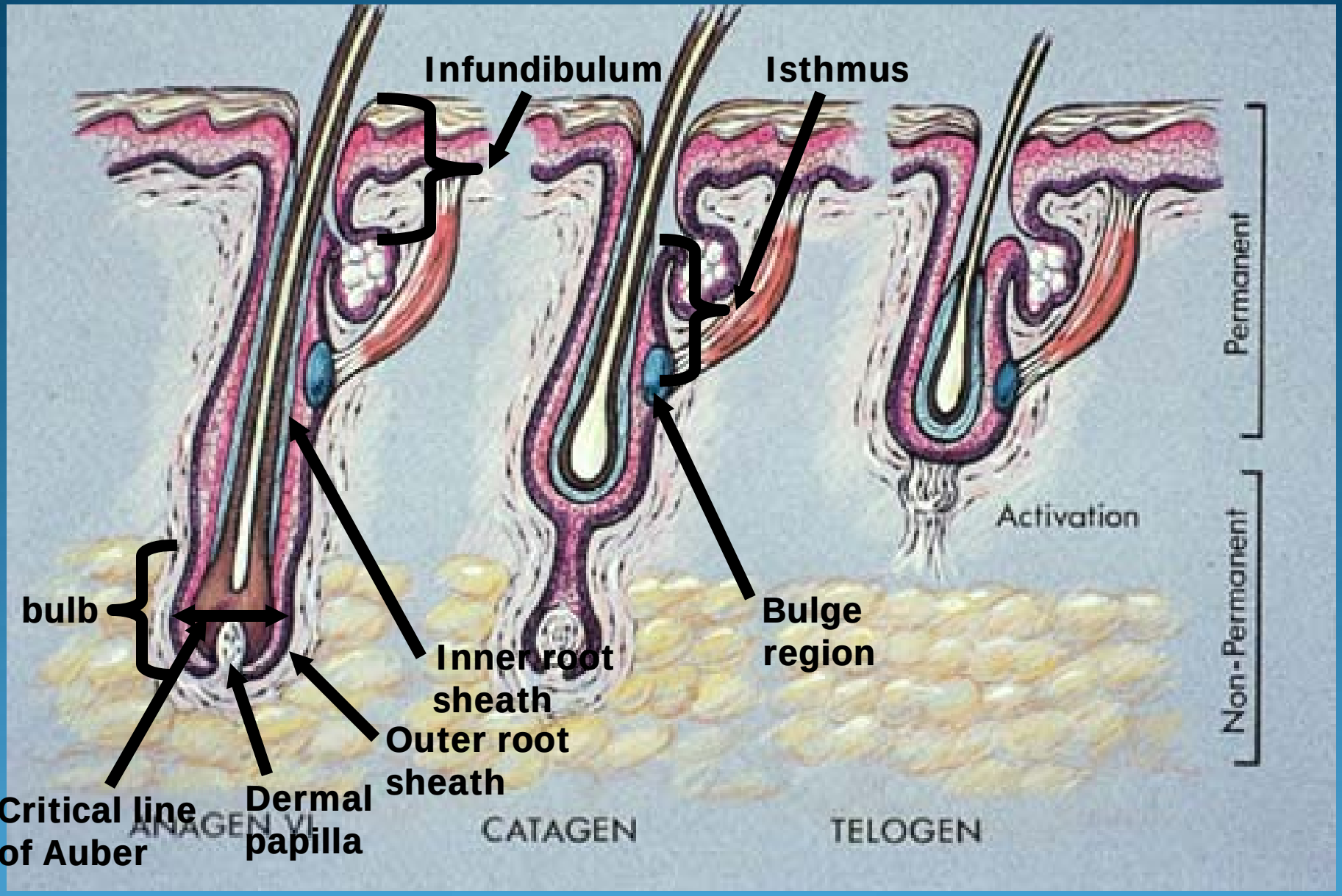
- **Final Follicle Formation Stage:**
  - Center of the hair peg disintegrates and keratinizes, forming a canal
  - Lanugo hair begins to develop
    - Shed from scalp & eyebrows at 32-36 weeks to allow terminal hair growth in these areas.
    - Persists on the rest of the body until 4-6 months of age

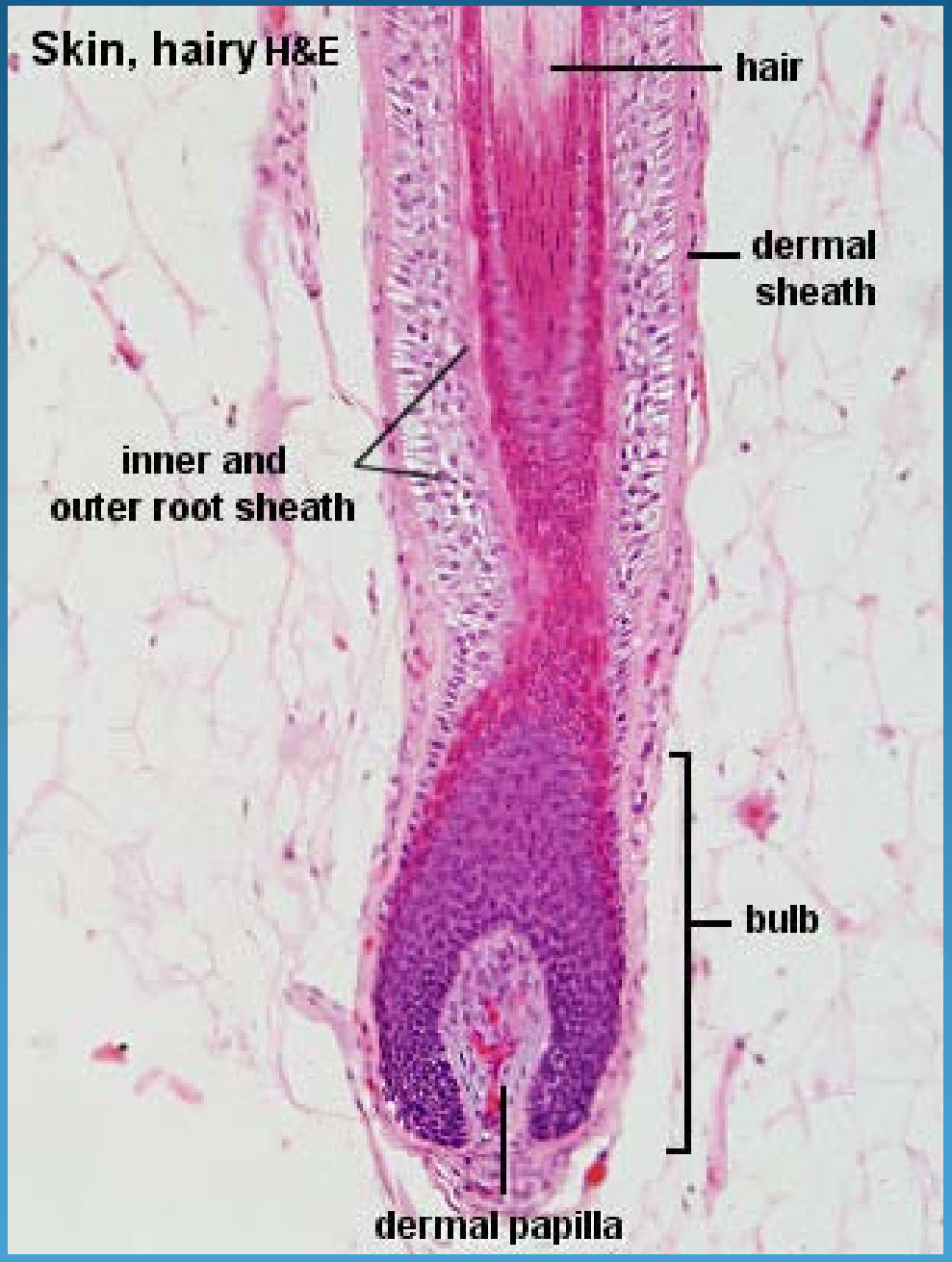
Where embryologically does the matrix cells originate from? What about the dermal papillary cells?

1. Ectoderm
2. Mesoderm

Anatomy

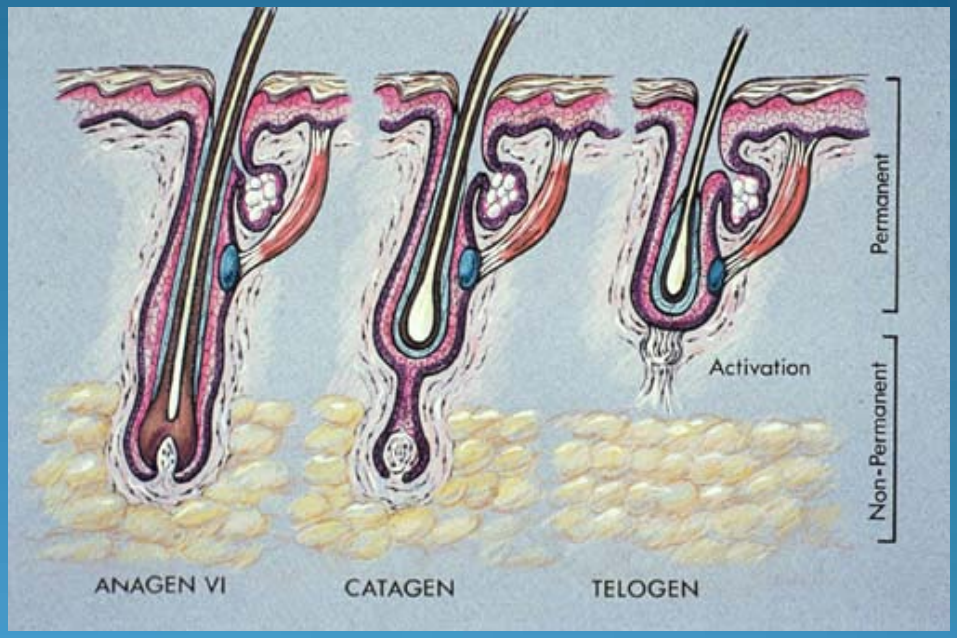
- Hair Types:
  - Terminal
    - Large
    - Pigmented
    - Medullated
    - 1-100cm long
    - 60um diameter
  - Lanugo
    - Fetal
    - nonmedullated
  - Vellus
    - Small
    - little to no pigment
    - Nonmedullated
    - <2cm long
    - <30um diameter


Infundibulum
Isthmus
bulb
Inner root sheath
Outer root sheath
Bulge region
Critical line of Auber
Dermal papilla
ANAGEN VI
CATAGEN
TELOGEN
Activation
Permanent
Non-Permanent


Skin, hairy H&E
hair
dermal sheath
inner and outer root sheath
bulb
dermal papilla

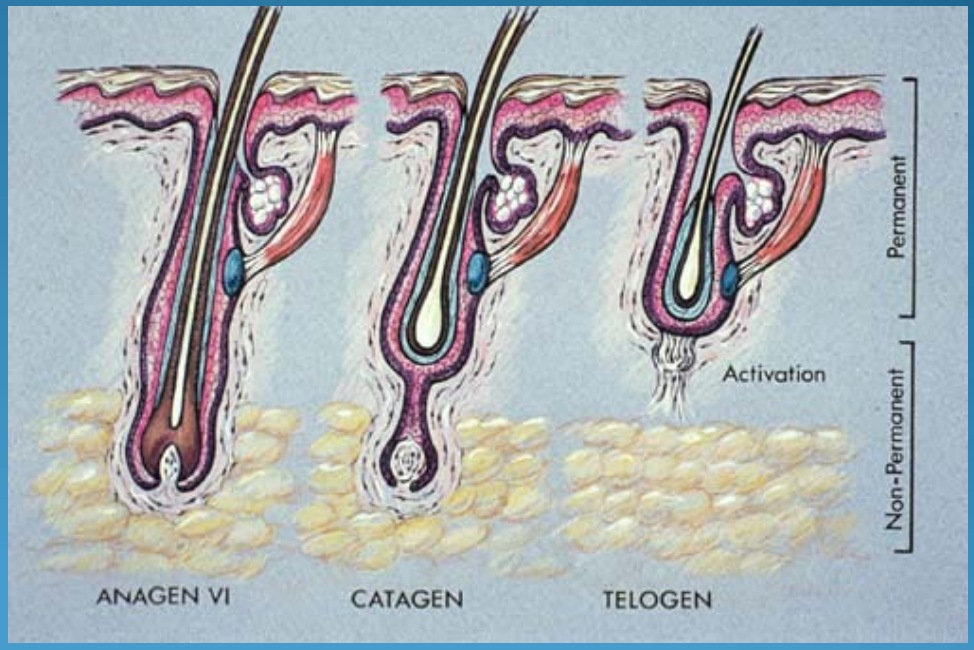
Longitudinal Anatomy (surface to deep)

- Dynamic, has both permanent and transient features
- PERMANENT:
  - Infundibulum
    - Epidermal surface to opening of the sebaceous gland.
    - Forms a stable conduit for the hair shaft
    - May see Demodex, yeast, etc. here



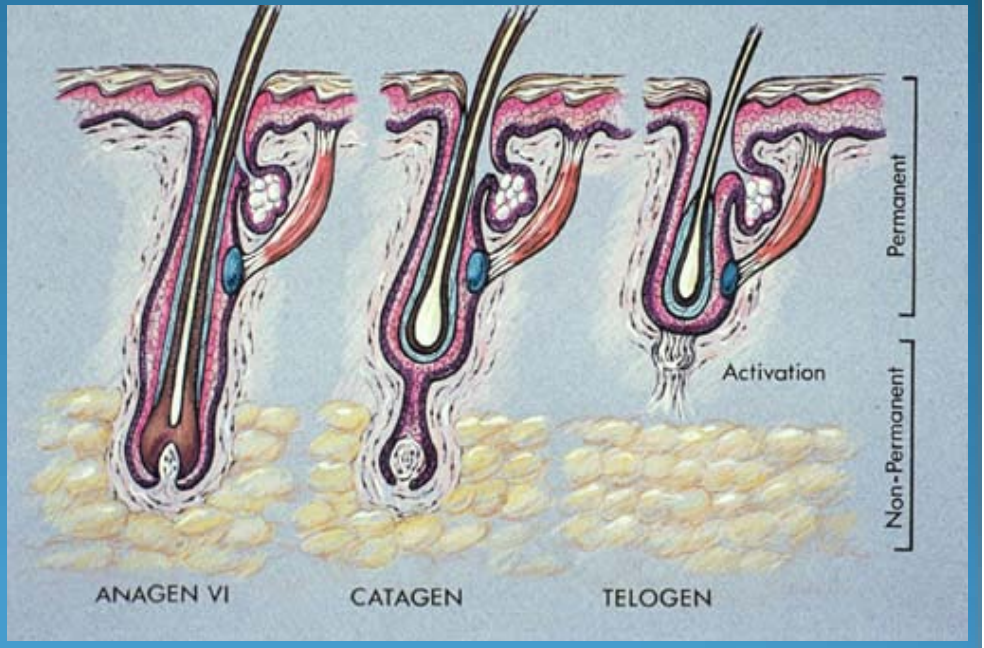
Longitudinal Anatomy (surface to deep)

- Isthmus
  - Located between the sebaceous gland and the Hair Bulge.
  - Anchors the hair shaft to the ORS during catagen



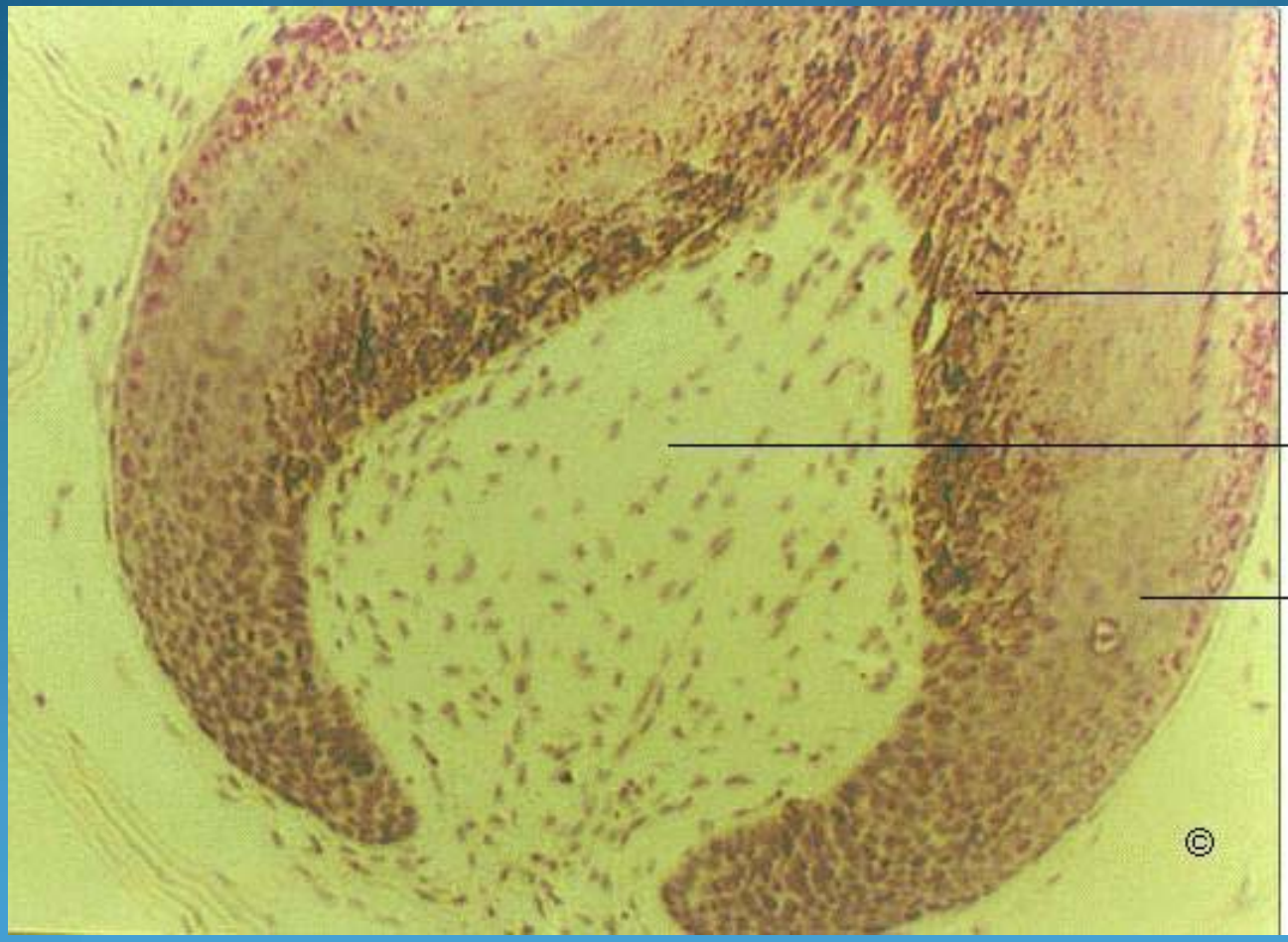
Longitudinal Anatomy (surface to deep)

- TRANSIENT:
  - Suprabulbar Area or Lower Follicle
    - Located from Bulge to Hair bulb
  - Hair Bulb
    - Contains the matrix cells which envelope the dermal papilla
    - Matrix cells divide very rapidly, 2nd only to hematopoetic cells
      - They are the source of epidermal cells
      - Differentiate and become keratinized to form
        - Hair cortex
        - Surrounding hair cuticle of hair shaft
        - Inner root sheath (IRS)
        - Outer root sheath (ORS)



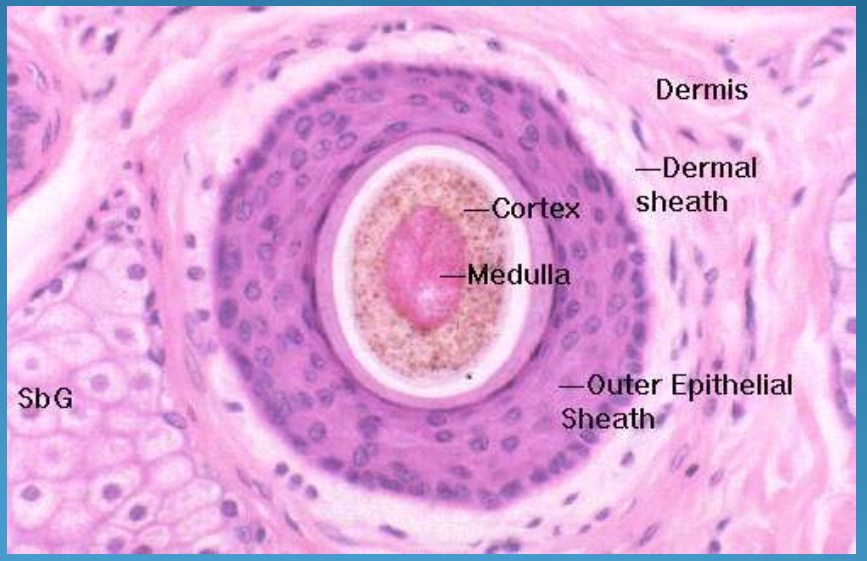
Longitudinal Anatomy (surface to deep)

- Transient
  - Hair Bulb
    - Critical Line of Auber
      - widest diameter of bulb
      - highest mitotic activity
    - Dermal Papilla
      - Dictates the embryonic generation of a hair follicle
      - Modifies the extent of proliferation and differentiation of the epithelial hair germ, and thus controls the size of the hair follicle
      - Derived from the dermis mesenchyme
      - Consists of small group of fibroblast cells derived from the mesoderm
      - Basement membrane or glassy membrane separates the DP cells from the hair fiber/sheath cells.
      - The bigger the DP the thicker the hair fiber


Melanocytes
Dermal papilla
Hair cortical cells

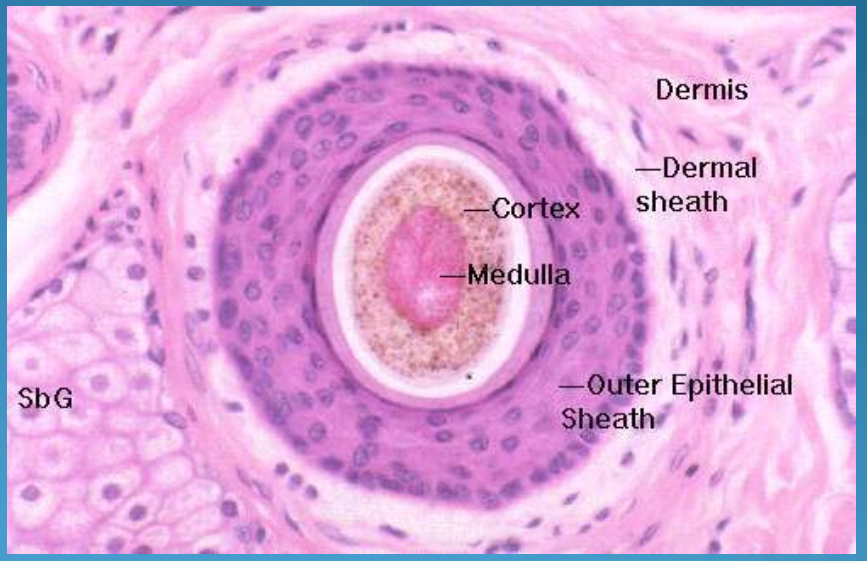
Cross Sectional Anatomy (center to periphery)

- Medulla
  - Found only in large terminal hairs
  - Generated from matrix cells at tip of dermal papilla
  - Appears amorphous since it only partially keratinizes
  - Contains CITRULLINE (like IRS)



Cross Sectional Anatomy (center to periphery)

- Cortex
  - Thick layer of elongated keratinocytes formed from matrix cells
  - Makes up the bulk of the hair shaft
  - Contains melanin granules
- Hair Cuticle
  - Single outer layer of imbricated keratinocytes (like roof tiles) that interlock with the IRS Cuticle



Cross Sectional Anatomy (center to periphery)

- Inner Root Sheath (IRS)
  - Made up of 3 layers
  - Does NOT contain melanin
  - Formed from matrix cells (at periphery of follicle) in pace with the hair shaft
  - It dictates the shape of the hair since it hardens (keratinizes) first
  - IRS cells are shed into the infundibulum as the hair shaft grows
  - Products of the sebaceous gland help break down the IRS
  - Contains CITRULLINE (Like Medulla)

Which layer of the inner root sheath keratinizes first?

Henle's

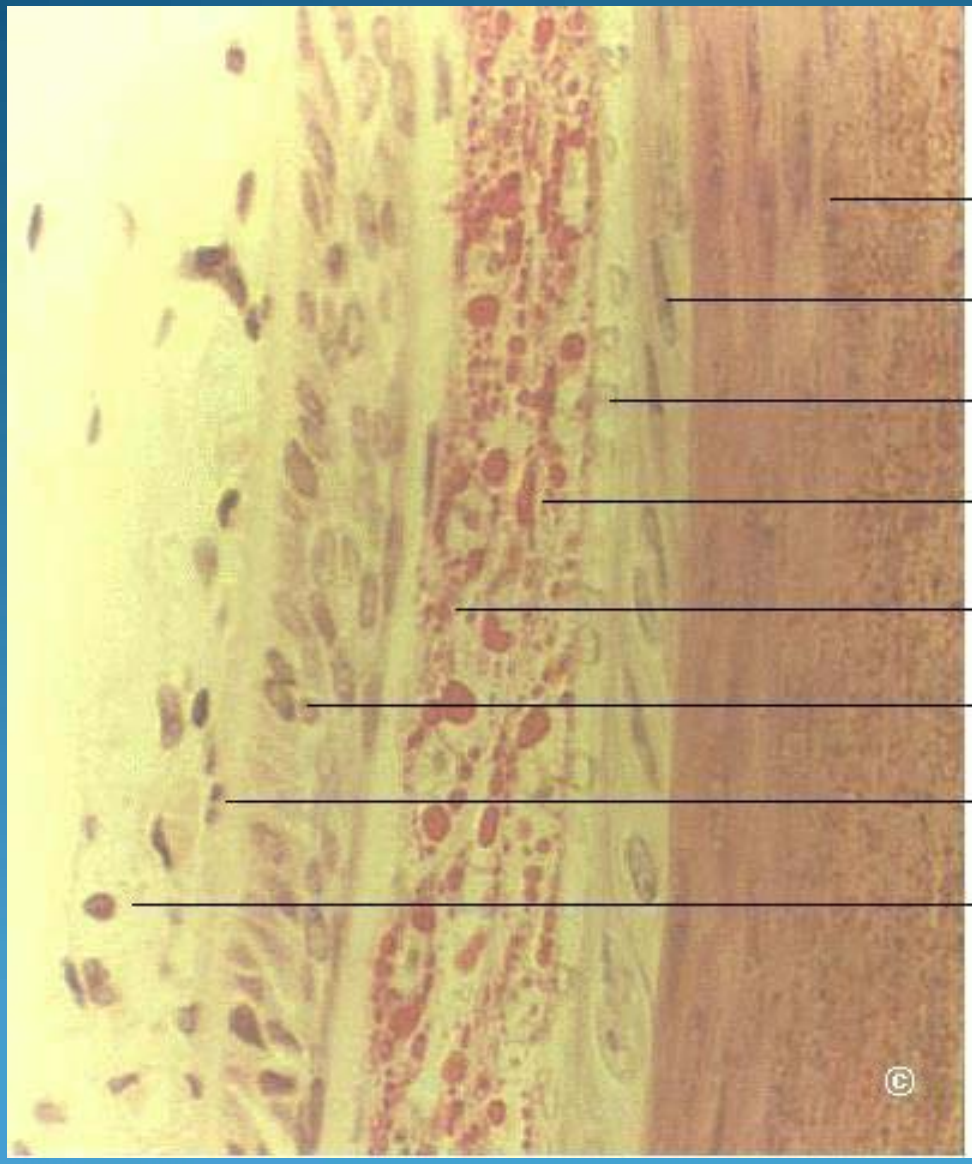
Bonus

What are the other two layers of the inner root sheath?

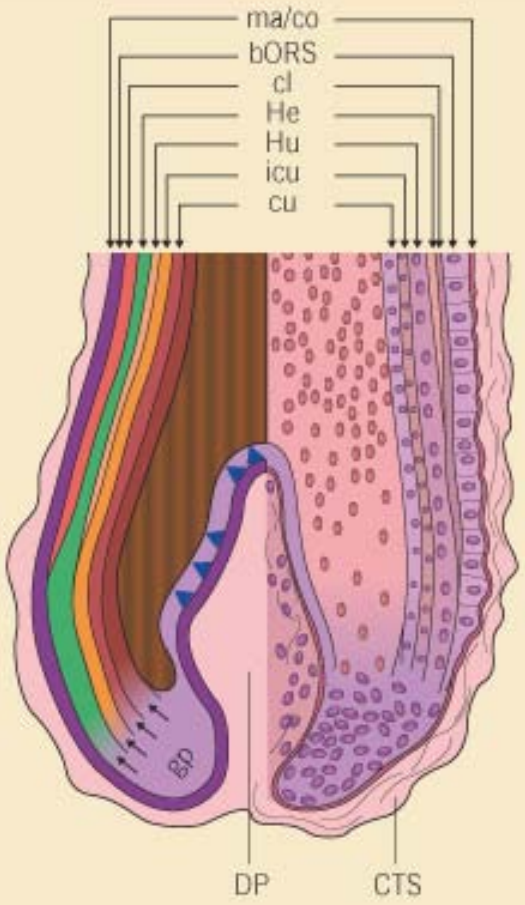
Huxley's and cuticle

Cross Sectional Anatomy (center to periphery)

- Layers of IRS
  - IRS Cuticle (Inner)
  - Huxley's Layer (Middle) 3-4 cells thick
  - Henle's Layer (Outer) One cell layer thick. FIRST TO BE KERATINIZED!
  - Contain Keratins 1/10 (like upper layers of epidermis)
- Keratinization order
  - (1) Henle's
  - (2) Cuticle of IRS/Hair
  - (3)Huxley's


Hair cortex
Hair cuticle
Inner root sheath cuticle
Inner root sheath Huxley layer
Inner root sheah Henle layer
Outer root sheath
Basment membrane
Dermal sheath

THE ONSET OF EXPRESSION OF SPECIAL KERATINS IN THE HAIR BULB



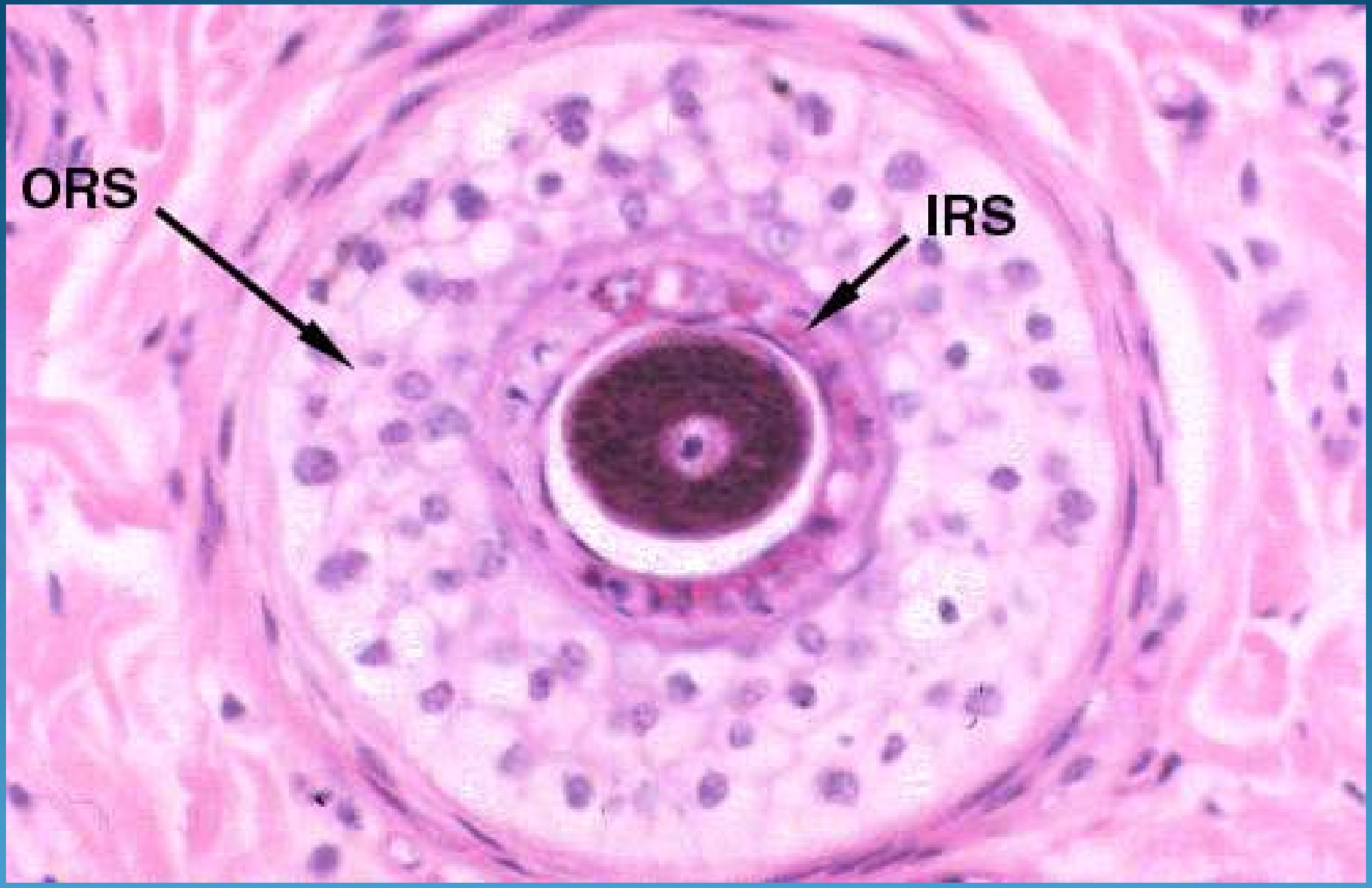
DP=dermal papilla
CTS=connective tissue sheath
bORS=basal layer of the ORS (k14)
cl=companion layer (k6hf)
He=Henle layer (k6irs)
Hu=Huxley layer (k6irs)
icu=cuticle of the IRS (k6irs)
cu=hair shaft cuticle (hHa2)
ma/co=hair shaft medulla and cortex (hHa5)
gp=germinative pool

Cross Sectional Anatomy (center to periphery)

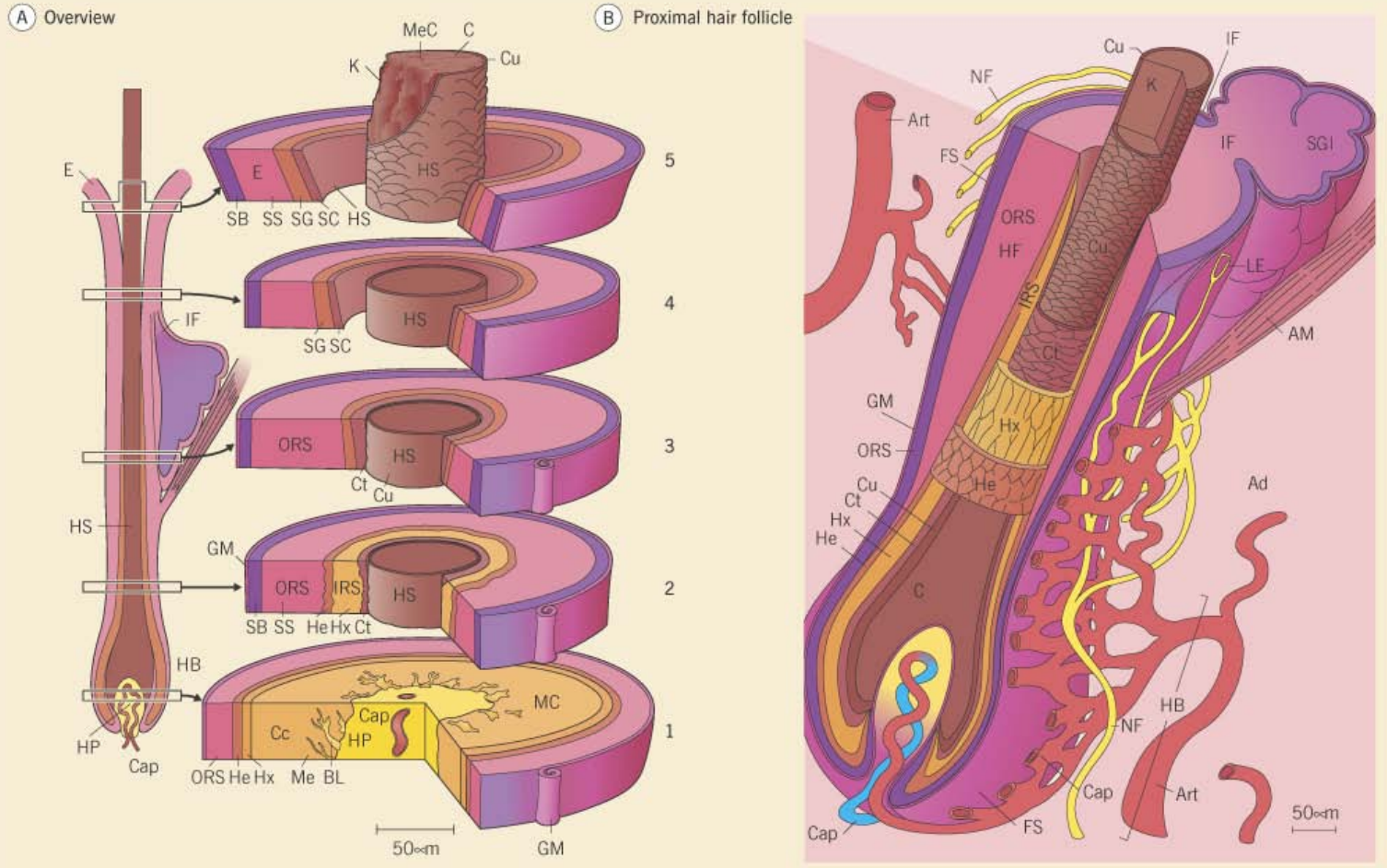
- Outer Root Sheath (ORS)
  - Unclear if this is derived from the Matrix or not
  - AREA WHERE MOST BCC's ARISE
  - Hair casts form from this layer
  - Contains the Hair Bulge
    - This area consists of a cluster of biochemically distinct cells that are the slowest cycling and longest-lived of the follicular unit.
    - Express K19 which is a stem cell marker
    - Believed to be source of cells to form the matrix with each new follicular cycle.
  - Reservoir for melanocytes, Langerhans cells, Merkel cells, epidermal cells that repopulate the epidermis after injury
  - K5/14 (like basal layer) & K6/16 (proliferating keratins) present

Cross Sectional Anatomy (center to periphery)

- Glassy or Vitreous Membrane:
  - A-cellular basement membrane bounding the entire follicle
  - Becomes corrugated in catagen, therefore, can be used as marker of this phase
- Fibrous Root Sheath
  - Outermost layer
  - continuous with the dermis


ORS
IRS

TERMINAL HAIR FOLLICLE IN ANAGEN VI



IF=infundibulum
Is=isthmus
HS=hairshaft
HP=hair papilla
Cap=capillary
ORS=outer root sheath
IRS=inner root sheath
HC=Henle layer

HX=Huxley layer
MC=hair matrix cells
E=epidermis
SG=sebaceous gland
C=hair shaft cortex
Cu=cuticle
NF=nerve fibres
AM=arrector pili muscle

GM=glassy membrane
Ad=adipocytes
BL=basal lamina
HF=hair follicle
SB=stratum basale
SS=stratum spinosum
SG=stratum granulosum
SC=stratum corneum

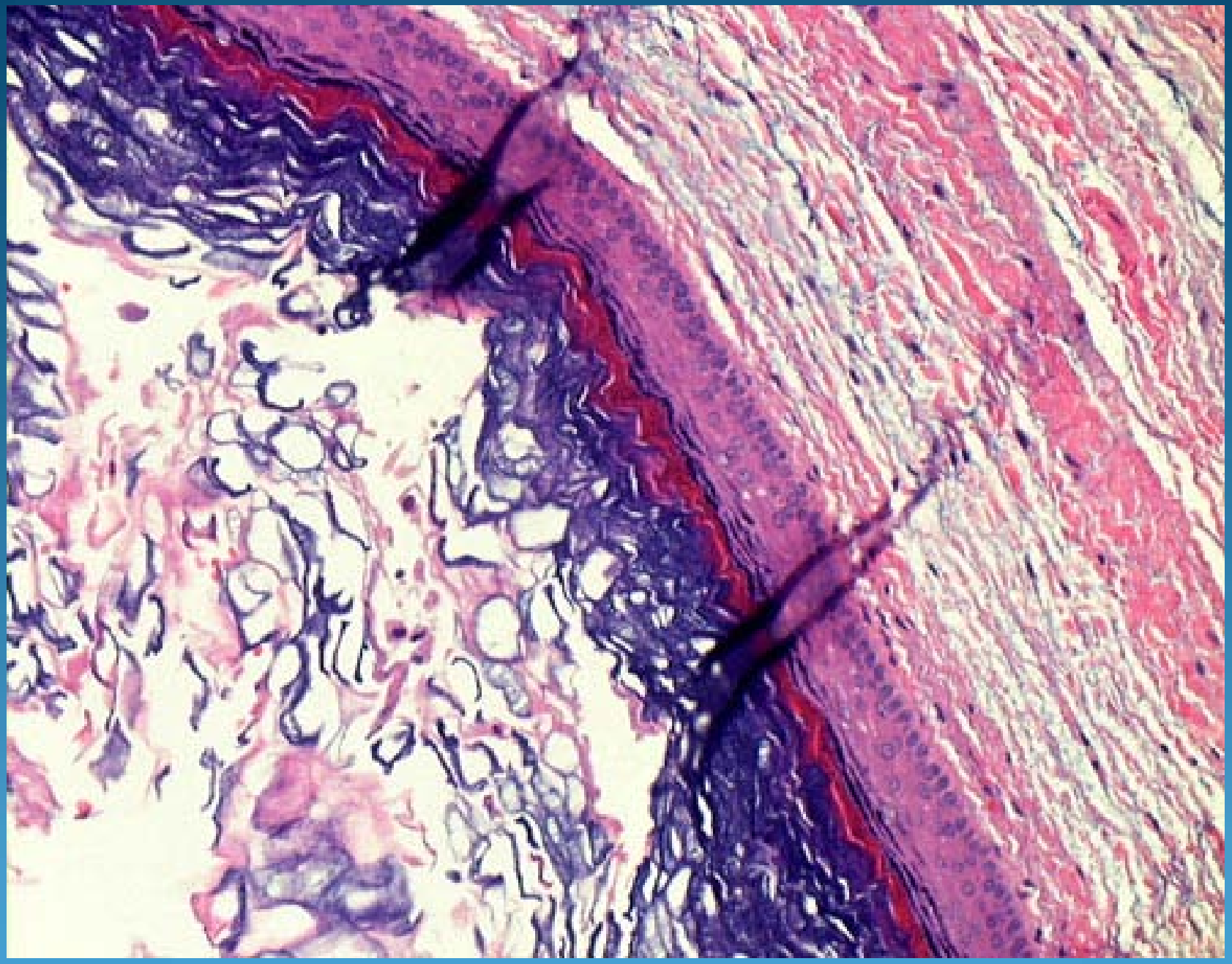
K=hard keratins
Ct=cuticle
MeC=medullary cells
HB=hairbulb
FS=follicular sheath
Me=melanocyte
Art=arterioles

Hair Keratinization

- Cortical keratins
  - classified as “hard” keratins as opposed to epidermal “soft” keratins
  - Have a higher Cysteine content which allows for more disulfide bonds and greater durability
  - These bonds are broken and reestablished by perms and straighteners (alkali substances)
- Cortical Keratins are divided into 2 types:
  - Ha = Acidic 1-8 (Chromosome 17)
  - Hb = Basic 1-6 (Chromosome 12): Monilethrix #6
  - Occur in pairs with a highly conserved alpha helical domain like epidermal keratins

Hair Keratinization

- ORS and Hair Shaft undergo Tricholemmal keratinization without the appearance of a granular layer
- IRS keratinizes in a manner similar to the epidermis via the formation of Trichohyalin granules which are categorized as soft keratins



Cysts

- Epidermal inclusion cyst
  - Derived from the infundibulum
  - Will see trichohyalin granules
  - Soft keratin like epidermis
- Tricholemmal cyst
  - Derived from the isthmus
  - Will not see trichohyalin granules
  - Hard keratin like hair and ORS

Hair Growth Cycle

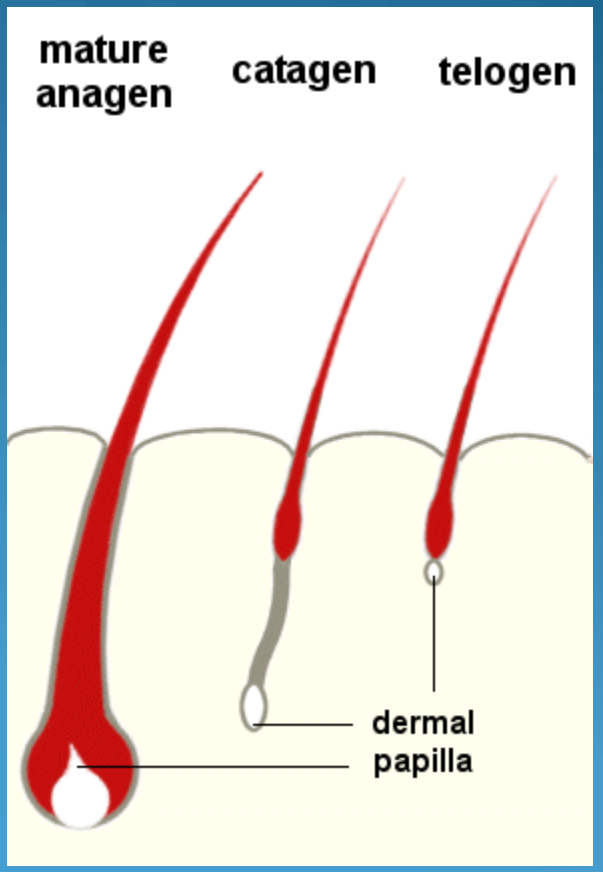
- All animals (except Merino sheep & poodles) have hair that cycles between active (Anagen) & resting (Telogen) states
- Human hair exhibits mosaic growth except for lanugo hair in early life
- Hair length is dependent on length of Anagen
  - Scalp hair has the longest anagen phase (3-7 years)
  - eyebrows have the shortest Anagen phase

What are the three phases of hair growth?

1. Anagen
2. Catagen
3. Telogen

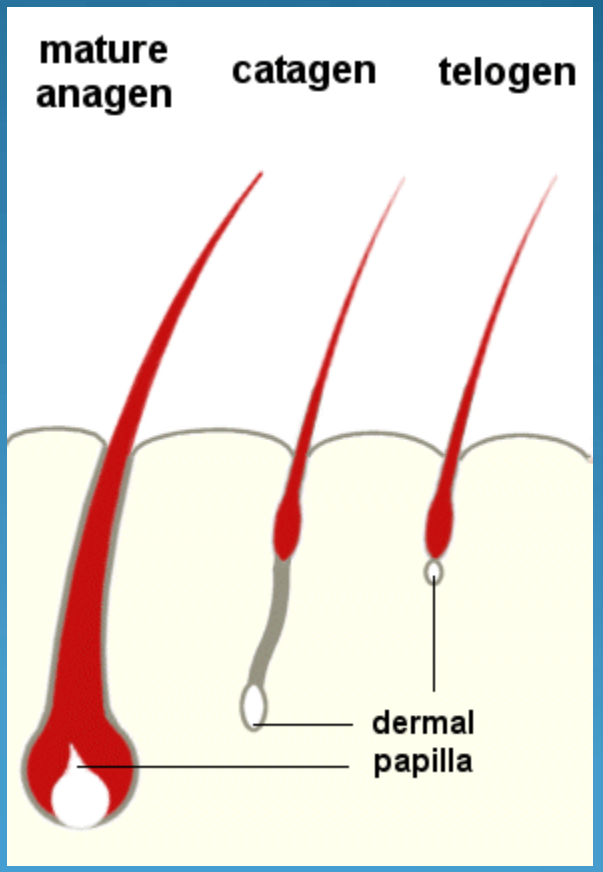
Hair Growth Cycle

- Anagen
  - Growth phase
  - The root of the hair is embedded deep in the dermis/subcutis
  - Large and has pigment
  - Lasts for 3-6 years



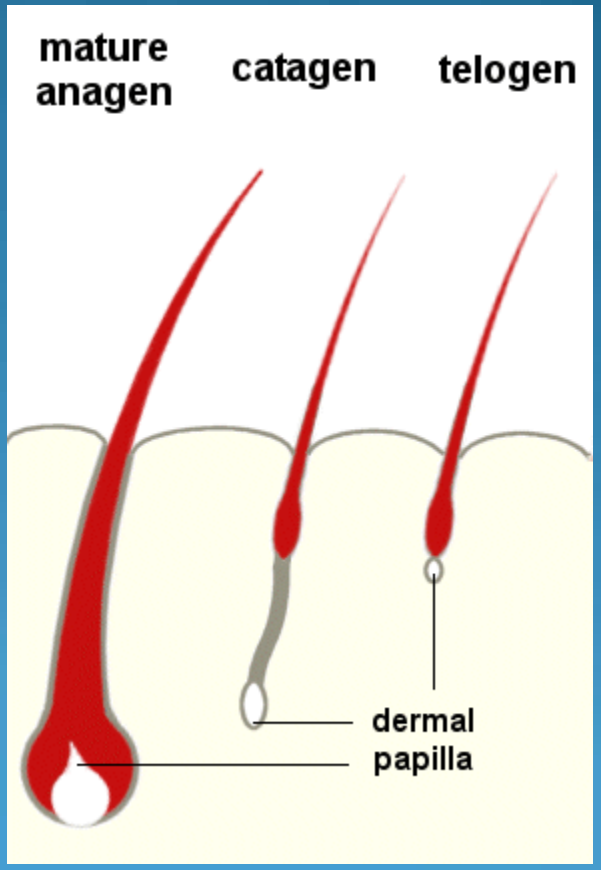
Hair Growth Cycle

- Catagen
  - Regression phase
  - Hair does not grow
  - Moves closer towards the epidermis
  - Takes the form of a club hair
  - Lasts about 2-3 weeks



Hair Growth Cycle

- Telogen
  - Resting phase
  - Hair can now be considered dead
  - It will fall out
  - Gets smaller and lighter
  - Moves towards the epidermis
  - Pushed out by new hair growing in
  - Lasts 3 months



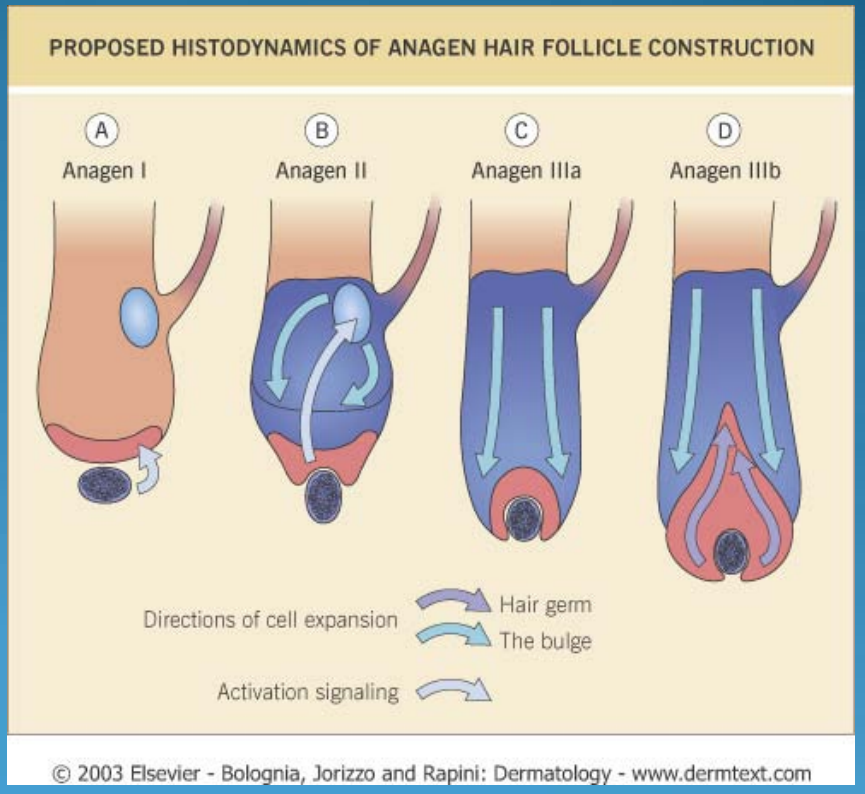
Hair Growth Cycle

- **ANAGEN:**
  - 80-90% of scalp hair in growing phase
  - Unclear what physiologic events stimulate growth
  - assumed that factors from the dermal papilla regulate anagen onset
  - Keratinocyte Growth Factor (KGF or FGF-7) is implicated
    - complicated process involving redundant signals
  - Cyclosporin, Minoxidil, PTH-related peptide & estrogen receptor antagonists induce anagen in mice

Substance	Site of action	Effect on hair growth
Basic fibroblast growth factor (bFGF)	Dermal papilla	Increase
Platelet-derived growth factor (PDGF)	Dermal papilla	Increase
Transforming growth factor beta (TGF- beta)	Dermal papilla	Decrease
Hepatocyte Growth Factor (HGF)	Dermal papilla / Hair matrix	Increase
Macrophage Stimulating Protein (MSP)	Dermal papilla / Hair matrix	Increase
Interleukin 1-alpha (IL-1- alpha)	Hair matrix	Decrease
Fibroblast growth factor type 5 (FGF5)	Hair matrix	Decrease
Epidermal growth factor (EGF)	Hair matrix	Decrease
Keratinocyte growth factor (KGF)	Hair matrix	Increase
Insulin-like growth factor I (IGF-I)	Hair matrix	Increase
Substance P	Unknown	Increase
Parathyroid hormone (PTH)	Unknown	Decrease
Estrogens	Unknown	Decrease

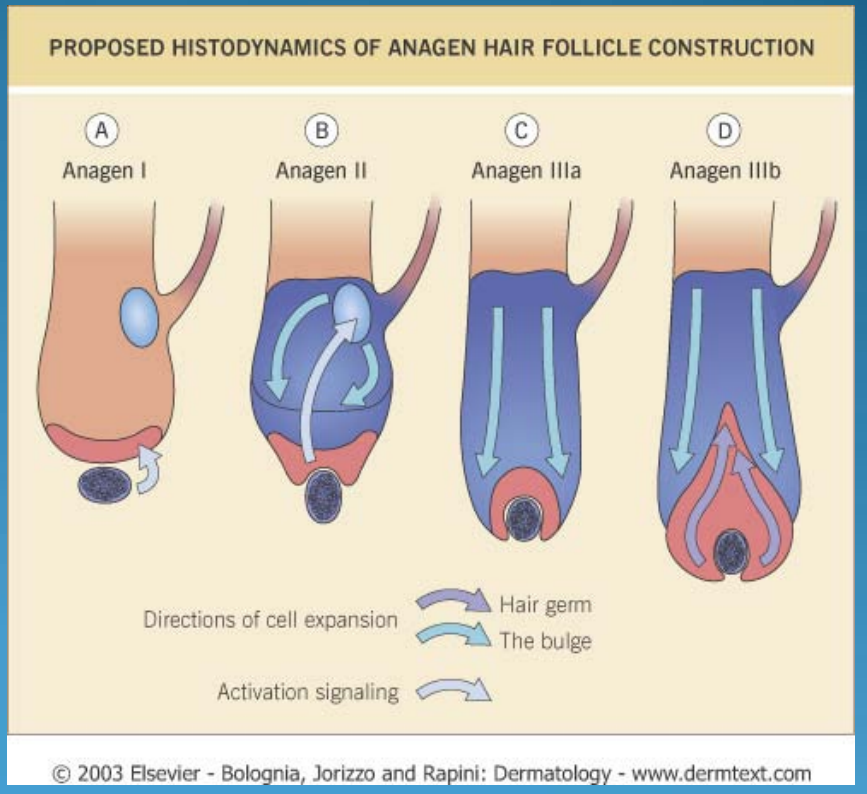
Hair Growth Cycle

- Six Stages of Anagen
  - 1. Stem cells in Bulge of ORS divide to produce secondary hair germ which becomes the matrix
  - 2. Germ cells proliferate downward enclosing the dermal papilla
  - 3. Matrix cells differentiate forming the Cortex and IRS.
    - These push upward as the hair bulb descends into the subcutaneous fat

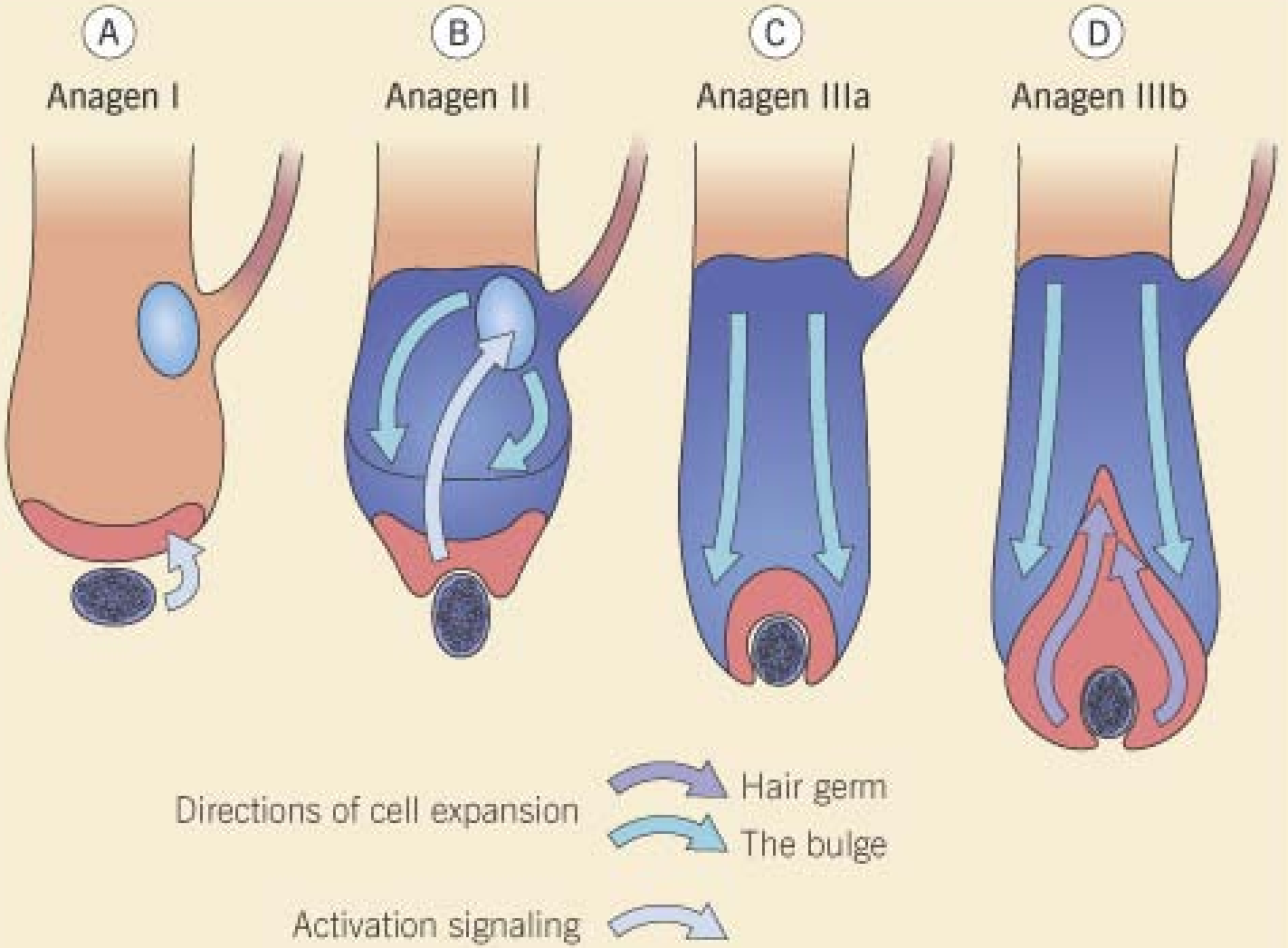


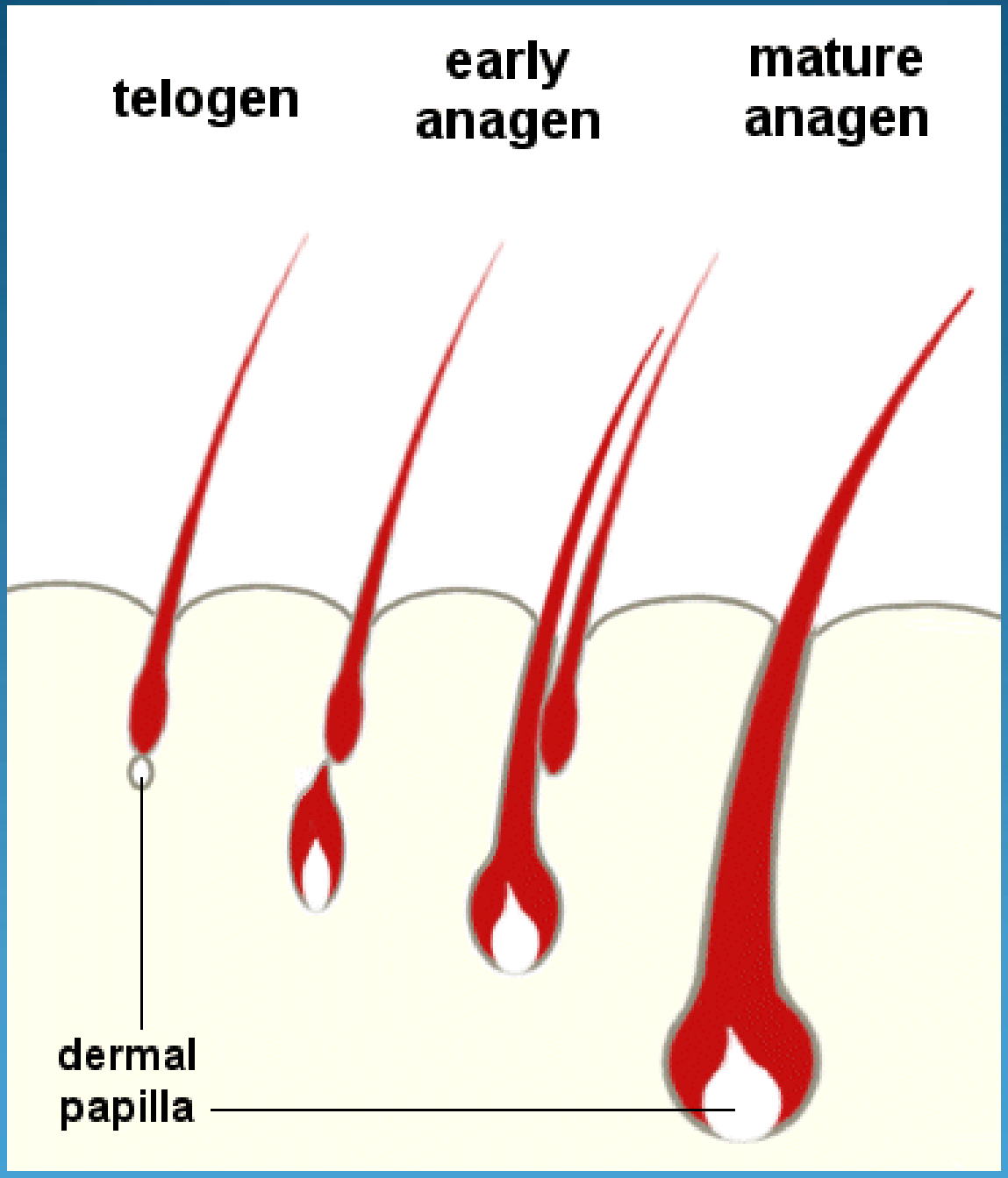
Hair Growth Cycle

- Six stages of Anagen
  - 4. Melanocytes send dendrites into the hair bulb and begin secreting melanin into keratinocytes
  - 5. Tip of hair emerges from the IRS
  - 6. Hair emerges from skin. Continues growing until Catagen
  - FGF-5 may be signal to end Anagen
    - if absent, catagen will still occur, but much later

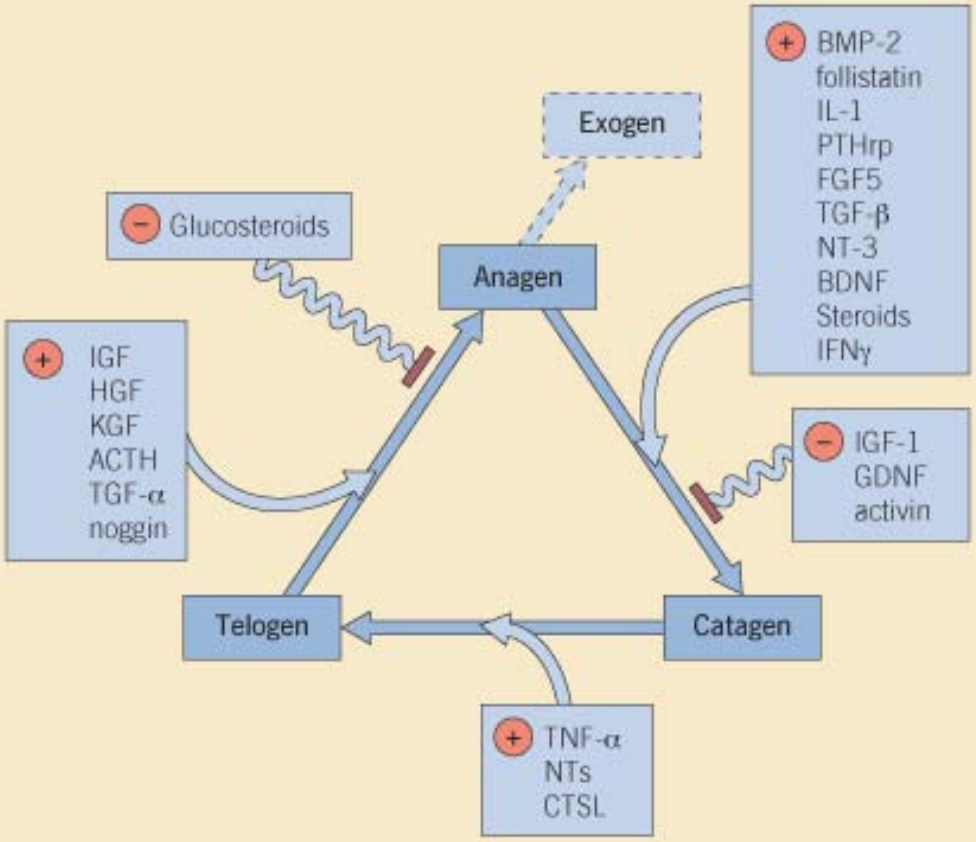


PROPOSED HISTODYNAMICS OF ANAGEN HAIR FOLLICLE CONSTRUCTION




telogen
early anagen
mature anagen
dermal papilla

SWITCHES IN THE LOCAL SIGNALING MILIEU DRIVE HAIR FOLLICLE CYCLING



BMP-2=bone morphogenic protein-2
IL-1=interleukin-1
PTHrp=parathyroid hormone related peptide
FGF5=fibroblast growth factor 5
NTs, NT-3=neurotrophins, neurotrophin-3
IGF-1=insulin-like growth factor-1
BDNF=brain-derived neurotrophin factor
TGF-α= transforming growth factor-α
HGF=hepatocyte growth factor
KGF=keratinocyte growth factor
ACTH=adrenocorticotropin
TGF-β=tumor necrosis factor-β
IFNγ=interferon gamma
CTSL=cathepsin L

Hair Growth Cycle

- **CATAGEN**
  - Lasts only 2-3 weeks
  - Only 1% of follicles in this stage
  - Mitosis ceases in the matrix and the cells keratinize forming a club hair
  - Apoptosis occurs
  - Melanocytes stop producing pigment
  - Melanocytes withdraw their dendrites so the club end of the hair is NOT pigmented
  - The Suprabulbar area collapses like an accordion and involutes while the vitreous membrane becomes thick and corrugated

Hair Growth Cycle

- **CATGEN**
  - IRS disintegrates & the ORS forms a sac from which the next generation hair germ will form
  - The dermal papilla follows the collapsing bulb and comes to rest just below the Bulge.
  - If this fails to happen no more hairs will be formed. This is seen in the mouse hairless gene and in a Pakistani family (Atrichia with Papular Lesions)

Hair Growth Cycle

- **TELOGEN**
  - Period of complete inactivity lasting about 100 days (3 months) in the scalp
  - 5-10% of follicles
  - Scalp loses 100-150 telogen hairs a day, which is only a small percentage of the total # of hairs in this phase.
  - Club Hair either falls out during telogen or is pushed out by new hair growth during the next anagen phase.

Hair Growth Cycle

- **EXOGEN**
  - There is speculation that hair shedding might be an active process
  - For example, if 10% of scalp hairs (~10,000) are in telogen, then why does one only lose 100 hairs a day
  - Hair shedding might involve release by Desmoglein 3 which is believed to anchor the club hair during Telogen

What is your diagnosis?

Loose anagen hair syndrome

Findings: ruffled cuticles and deformed hair bulbs

Control of Hair Growth

- Scalp hair grows at 1cm/month or 0.34mm/day
- Plucking telogen hairs seems to advance the onset of anagen
- Shaving has no effect on hair growth or diameter
- Differences in maximal achievable scalp hair length are the result of different anagen lengths
- Follicles are inherently programmed to cycle
- There are other control mechanisms, especially via the endocrine system

Control of Hair Growth Hormones

- Androgens
  - THE MOST IMPORTANT hormonal regulators
  - Act through receptors in the dermal papilla
  - Increases the length of anagen, diameter, and growth rate in susceptible follicles
  - Paradoxically cause shorter anagen time, miniaturization, and slower growth in areas such as the scalp.
  - Axillary & Pubic hair respond to testosterone, rest of body hair only responds to DHT made by 5-alpha reductase.

Control of Hair Growth Hormones

- Androgens
  - 5-alpha reductase deficiency have axillary & pubic, but no body hair, balding or prostatic hypertrophy)
  - 5αR Type I: Sebaceous glands
  - Type II: Prostate and dermal papilla
  - Puberty
    - Pubic hair responds 1st
    - Axillary & beard hair growth ~2 years later.
    - Adult pattern not fully complete until 4th decade

Control of Hair Growth Hormones

- Estrogens
  - Prolongs anagen but decreases the growth rate.
  - Responsible for the post-partum telogen effluvium
- Thyroxine
  - Advances onset of anagen
  - increases growth rate.
  - Excesses can be stressful and lead to telogen effluvium.
  - Deficiency can do the same in addition to slowing growth rate.