Embryology and Desmosomes

Embryology Refresher

- Gametes (oocytes and spermatozoa)
  - Descendents of primordial germ cells (46, 2N)
  - Meiosis (oogenesis or spermatogenesis)
    - 2 divisions (I and II)
    - Results in 23, 1N
    - Allows genetic variability
    - Maintain # of chromosomes

Embryology Refresher

- Oogenesis
  - Primordial germ cells originate in wall of yolk sac
    - Arrive at ovary wk 4
    - Diff to oogonia (46, 2N)
  - Oogonia enter meiosis I→primary oocytes (46, 4N)
    - All primary oocytes formed by 5th month
    - Arrested in prophase (dictyotene) of meiosis I until puberty

Embryology Refresher

- Oogenesis
  - During ovarian cycle, completion of meiosis I→secondary oocyte (23, 2N) and 1st polar body (degenerates)
  - 2nd oocyte→meiosis II→ovulation occurs at metaphase
    - Arrested in metaphase of meiosis II until fertilization
  - At fertilization completes meiosis II→mature oocyte (23, 1N) and second polar body

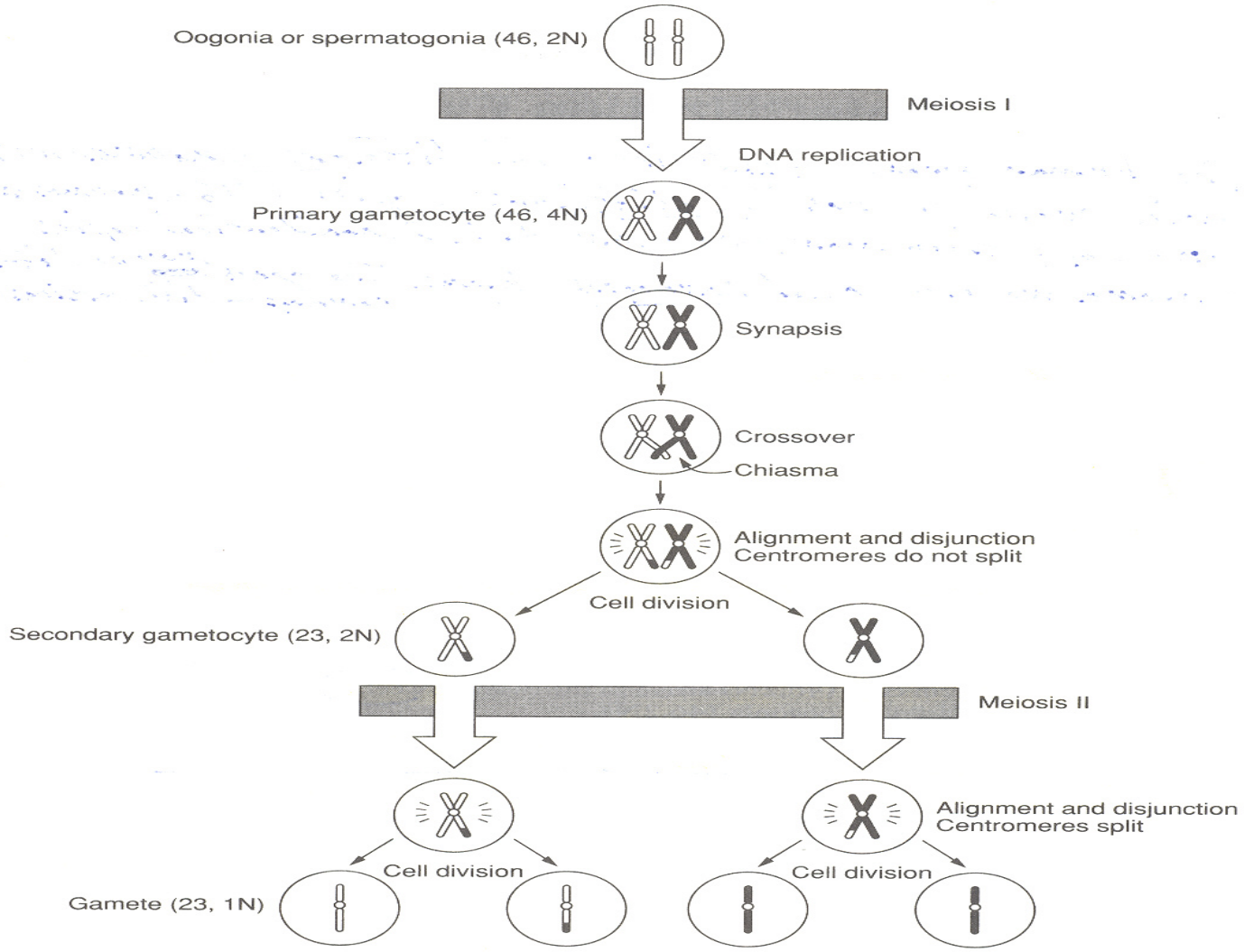


Figure 1-1. Meiosis. Note that only one pair of homologous chromosomes is shown (*white* = maternal origin; *black* = paternal origin). Synapsis is the process of pairing of homologous chromosomes. The point at which the DNA molecule crosses over, the chiasma, is where the exchange of small amounts of maternal and paternal DNA takes place. (Modified with permission from Fix JD and Dudek RW: *BRS Embryology*, Baltimore, Williams & Wilkins, 1995, p 4.)

Embryology Refresher

- Spermatogenesis
  - Primordial germ cells (46, 2N) arrive at testes wk 4
  - Dormant until puberty
  - At puberty diff. to type A spermatogonia (46, 2N)

Embryology Refresher

- Type A spermatogonia undergo mitosis→more type A or type B
- Type B→meiosis I→primary spermatocytes (46, 4N)
- Primary spermatocytes complete meiosis I→2 secondary spermatocytes (23, 2N)
- Secondary spermatocytes complete meiosis II→4 spermatids (23, 1N)

Embryology Refresher

- Human genome has 23 ***different*** chromosomes of which each cell has 2 copies (=46 total)
- 1 copy from mom
- 1 copy from dad
- 2 nonidentical copies of a chromosome are called?
- Different versions of genes are?

Embryology Refresher

- Fertilization occurs where?
- Male and female pronuclei fuse to form?
- Zygote is successively cleaved to form?
- At 32 cell stage blastomeres form?
- What forms when fluid is secreted within morula?
- Inner cell mass becomes?
- Outer cell mass becomes?

IV. CLINICAL CORRELATIONS

A. Hydatidiform mole. A blighted blastocyst leads to death of the embryo, which is followed by hyperplastic proliferation of the trophoblast within the uterine wall.

B. Choriocarcinoma is a malignant tumor of the trophoblast that may occur following a normal pregnancy, abortion, or a hydatidiform mole.

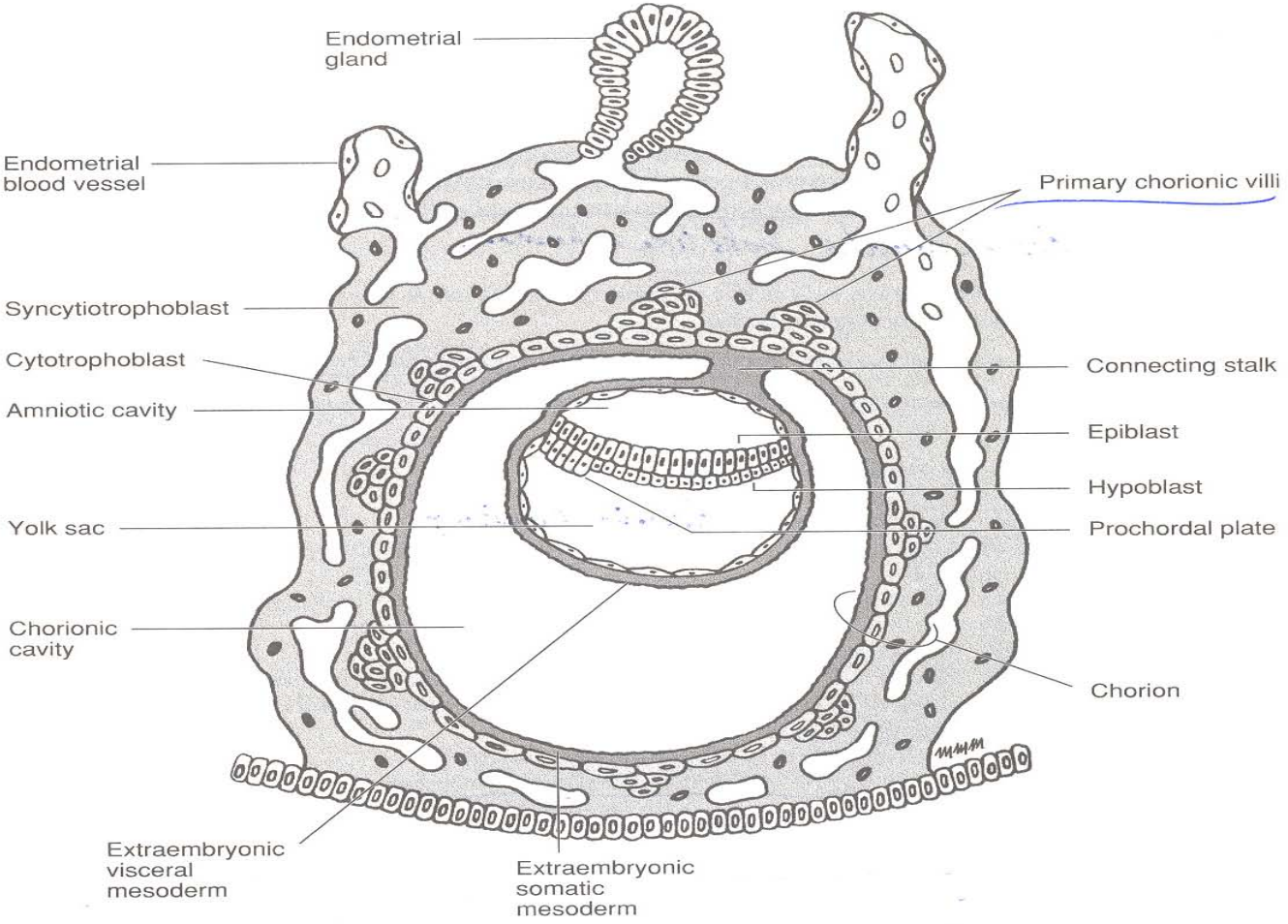


Figure 3-1. A day 14 blastocyst. At this stage, formation of the bilaminar embryonic disk occurs, and implantation within the endometrium is completed.

Embryology Refresher

- Embryonic period occurs?
- What is the process that establishes the 3 primary germ layers (ectoderm, mesoderm, and endoderm)?
- The formation of what marks the initiation of gastrulation?

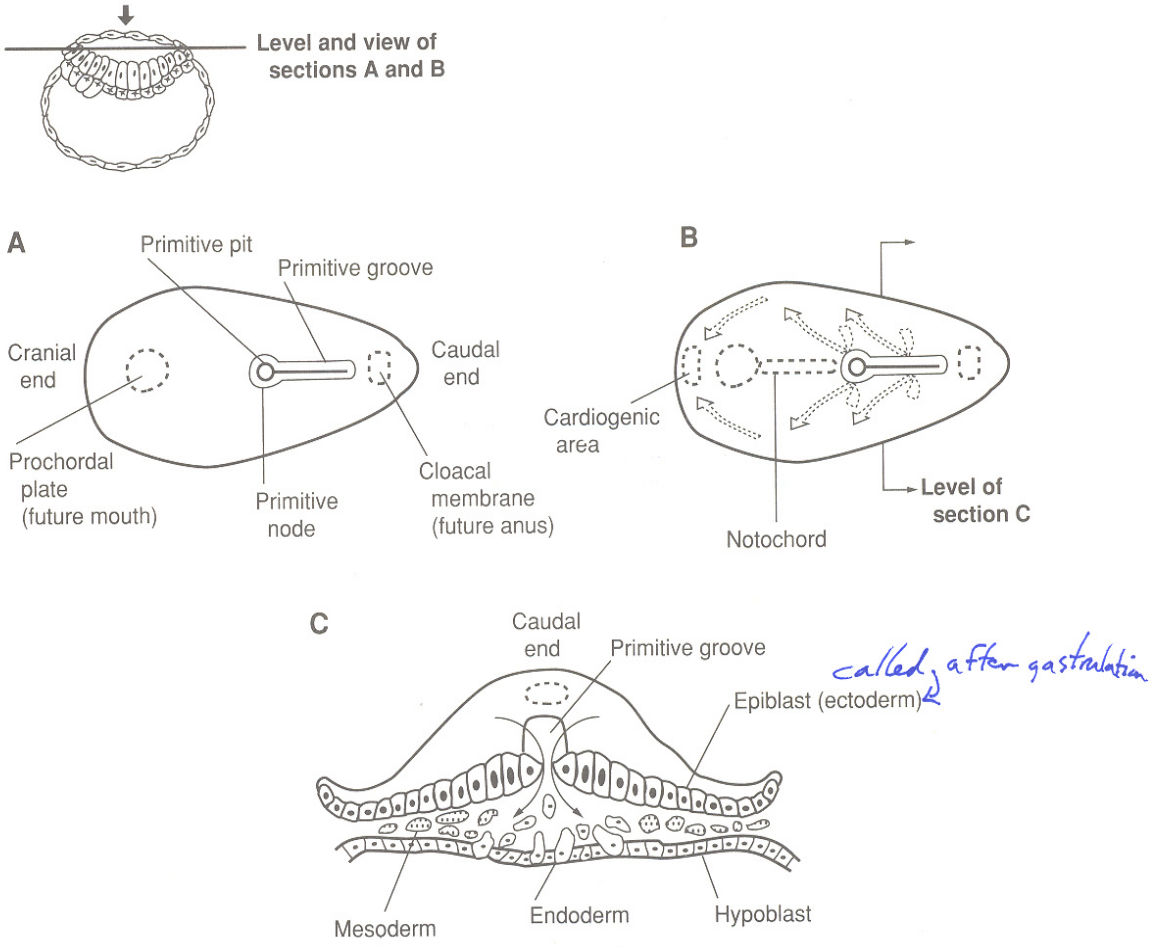


Figure 4-1. Gastrulation. The embryoblast in the upper left-hand corner is provided for orientation. (A) Dorsal view of the epiblast. The primitive streak consists of the primitive groove, node, and pit. (B) *Arrows* show the migration of cells through the primitive streak. The notochord (i.e., mesoderm located between the primitive node and the prochordal plate) induces the formation of the neural tube. The cardiogenic area is the future heart. (C) Epiblast cells migrate to the primitive streak and insert themselves between the epiblast and the hypoblast. Some epiblast cells displace the hypoblast to form endoderm; the remainder migrate cranially, laterally, and along the midline to form mesoderm. After gastrulation, the epiblast is called ectoderm. (Modified with permission from Fix JD and Dudek RW: *BRS Embryology*, Baltimore, Williams & Wilkins, 1995, p 30.)

Embryology Refresher

- Ectoderm
  - Surface ectoderm
    - Epithelial lining of ant 2/3 of tongue, hard palate, sides of mouth, ameloblasts (teeth), and parotid glands and ducts
    - Mammary glands
    - Epithelial lining of lower anal canal
    - Epithelial lining of distal penile urethra
    - Epidermis, hair, nails, sweat and sebaceous glands

Embryology Refresher

- Ectoderm
  - Neuroectoderm
    - CNS stuff
  - Neural Crest
    - Melanocytes

Embryology Refresher

- Mesoderm
  - Lateral
    - Lymphatic system
    - CVS
  - Intermediate
  - Paraxial
    - Dermis
    - Extraocular muscles
    - Skeletal muscles of trunk and head and neck
    - Intrinsic muscles of the tongue

Embryology Refresher

- Endoderm
  - Epithelial lining of:
    - Post 1/3 of tongue
    - Floor of mouth
    - Palatoglossal and palatopharyngeal folds
    - Soft palate
    - Vagina
    - Female urethra and most of male urethra
    - Auditory tube

Embryology Refresher

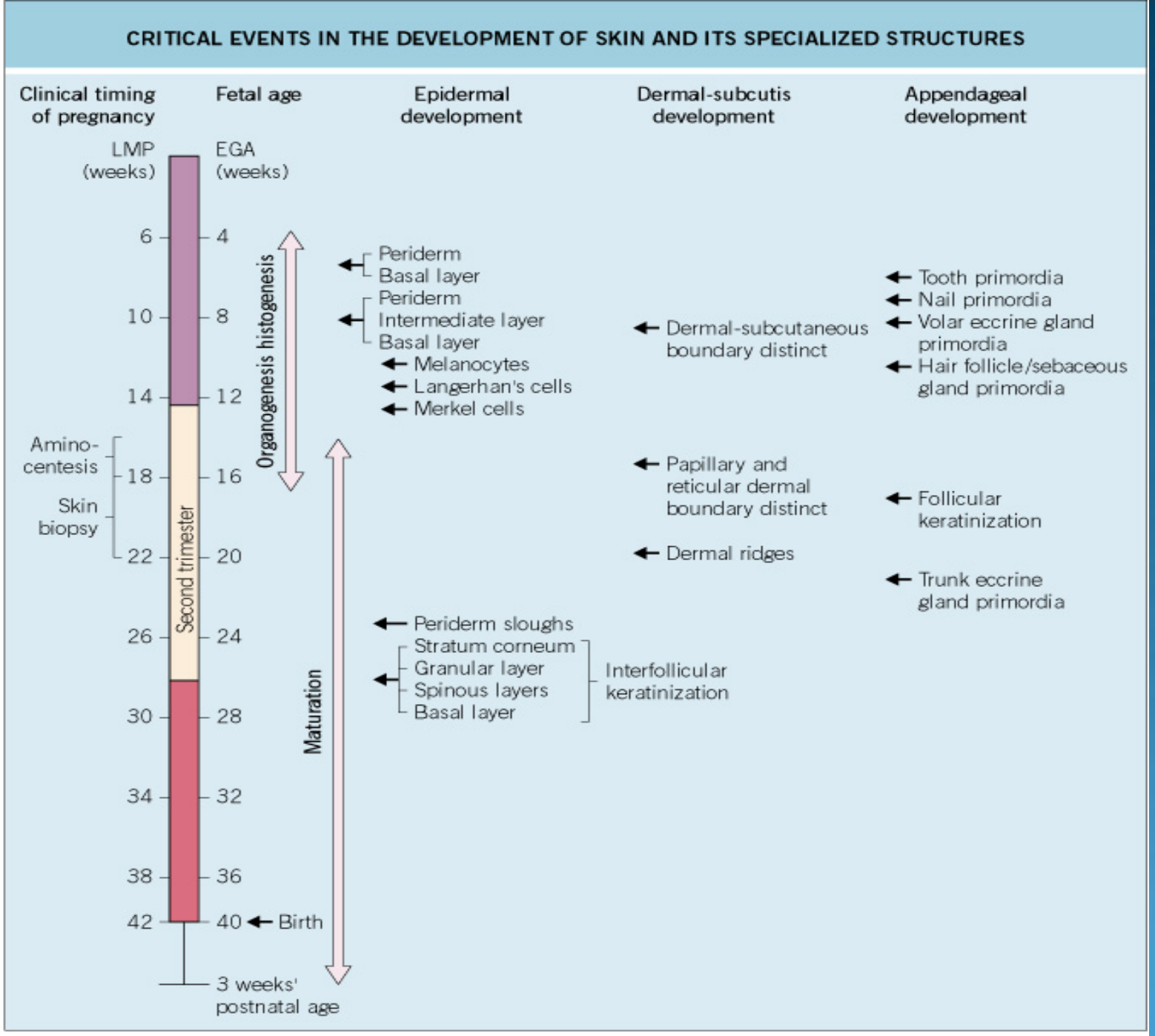
- Fetal erythropoiesis occurs in (order)?
- What does a persistent cervical sinus lead to?
- What does aberrant development of the 3rd and 4th pharyngeal pouches lead to?
- 3rd pouch dorsal—inf parathyroids
- 3rd pouch ventral—thymus
- 4th pouch sup parathyroids

Embryology Refresher

- Most common site of ectopic thyroid tissue?
- Tongue innervation:
- Taste?
- CN 7, 9, 10
- Pain?
- CN V3, 9, 10
- Motor?
- CN 12

Embryology of the Skin

- High Points
  - Morphogenesis of all skin components (except non-volar swear glands) is underway by end of 1st trimester
  - Differentiation of epidermis and appendages occurs primarily in 2nd trimester
  - EGA—Fertilization occurs day 1, lags by 2 weeks (used in Fitz and Bolognia)
  - LMP—1st day of last menstrual period
    - OB/GYNs, fertilization day 14



Epidermis

- 1st month primitive single layer epidermis creates periderm
- Periderm
  - Specialized embryonic structure
  - Covers epidermis until keratinization occurs
  - Then degenerates
  - Cells attached by tight junctions
  - Studded with microvilli
    - Large single blebs→multiple blebs

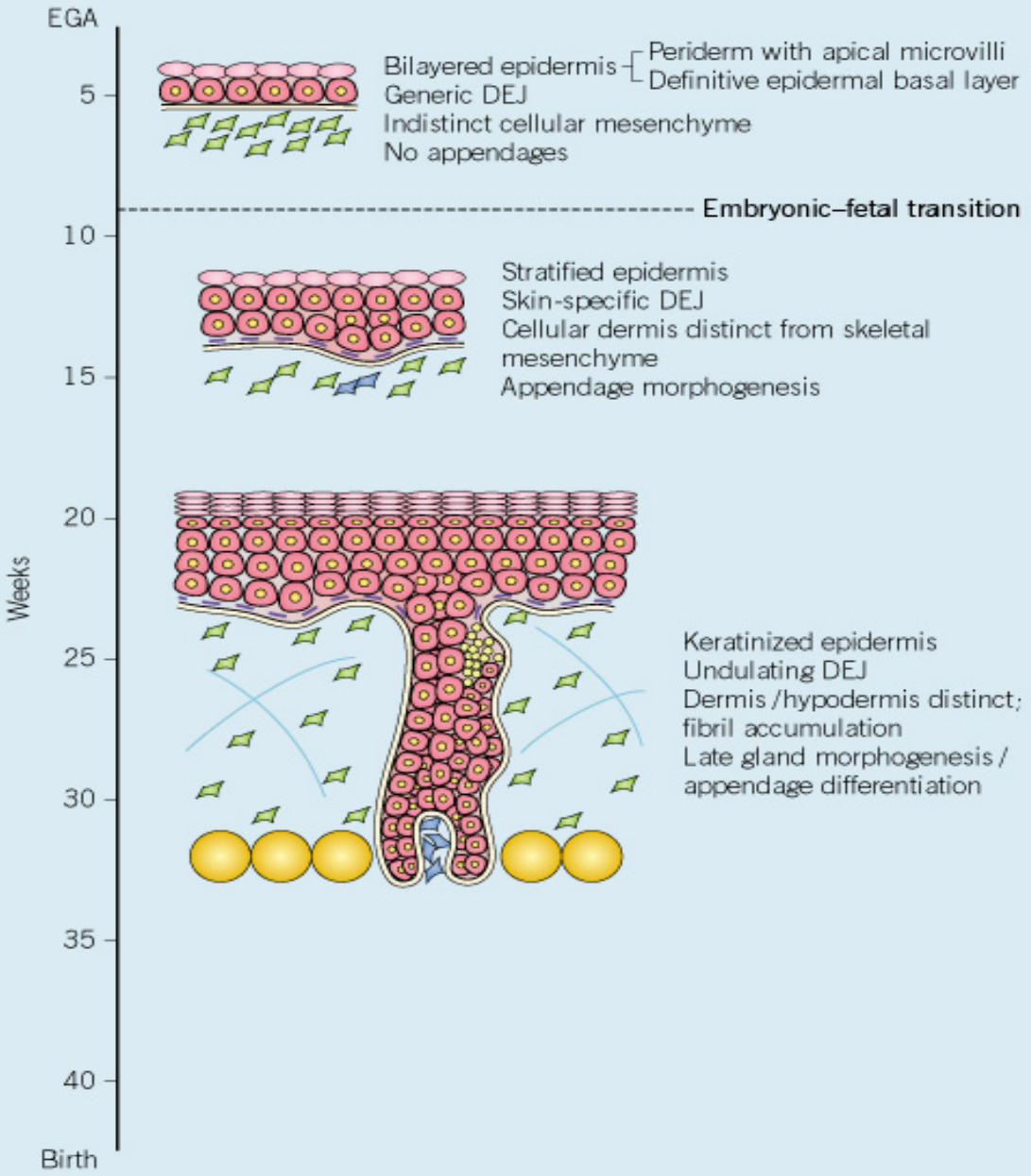
Epidermis

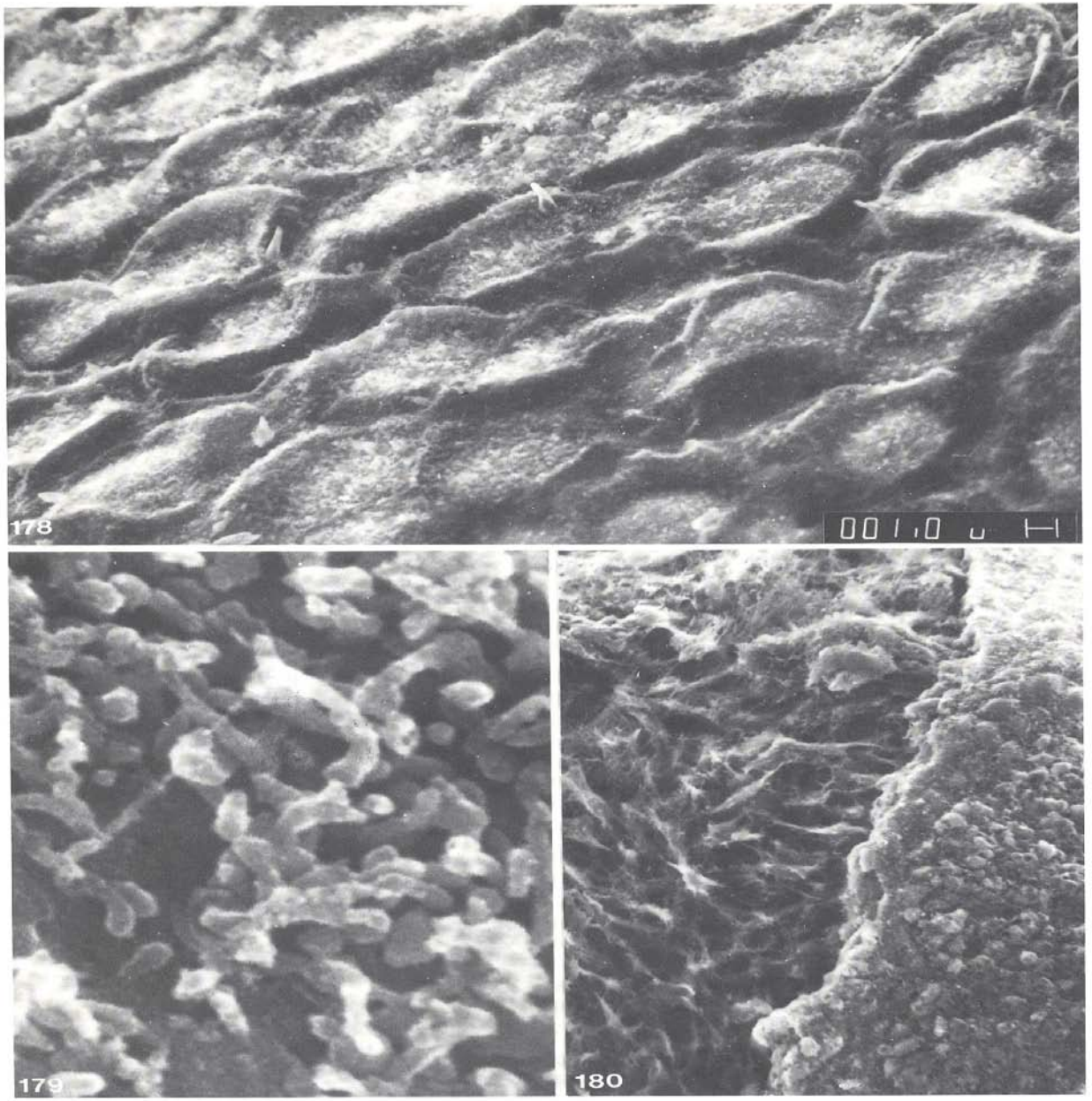
- Periderm
  - Cells attached by tight junctions
  - Studded with microvilli
    - Large single blebs→multiple blebs
  - Possible role in diffusion or exchange of substances across fetal skin

Epidermis

- Periderm
  - Cells detach from underlying epidermis→sloughed into amniotic fluid
  - Becomes part of vernix caseosa
    - Prevents maceration from amniotic fluid
  - Sloughing via apoptosis
    - DNA fragmentation
    - TGase 1 and 3 detected

DEVELOPMENT OF THE EPIDERMIS





Figures 178–180. The skin. **(178)** Peridermal cells on the surface of primitive epidermis. **(179)** Microvilli on the surface of peridermal cells. **(180)** Primitive skin composed of surface ectoderm (on the right) and underlying mesenchyme (on the left).

Epidermis

- Organogenesis wks 3-8
- Bone marrow hematopoiesis begins at 8 wks EGA (transition from embryo to fetus)
- Epidermal Stratification begins 8 wks EGA
- Completed by 2nd trimester

Epidermis

- Epidermal stratification begins with formation of intermediate layer
  - Int. layer between basal and periderm layer
  - Highly proliferative
  - ***p63 required for epidermal stratification***
  - Several new layers added over next few wks
    - By 22-24 wks, 4-5 layers plus periderm

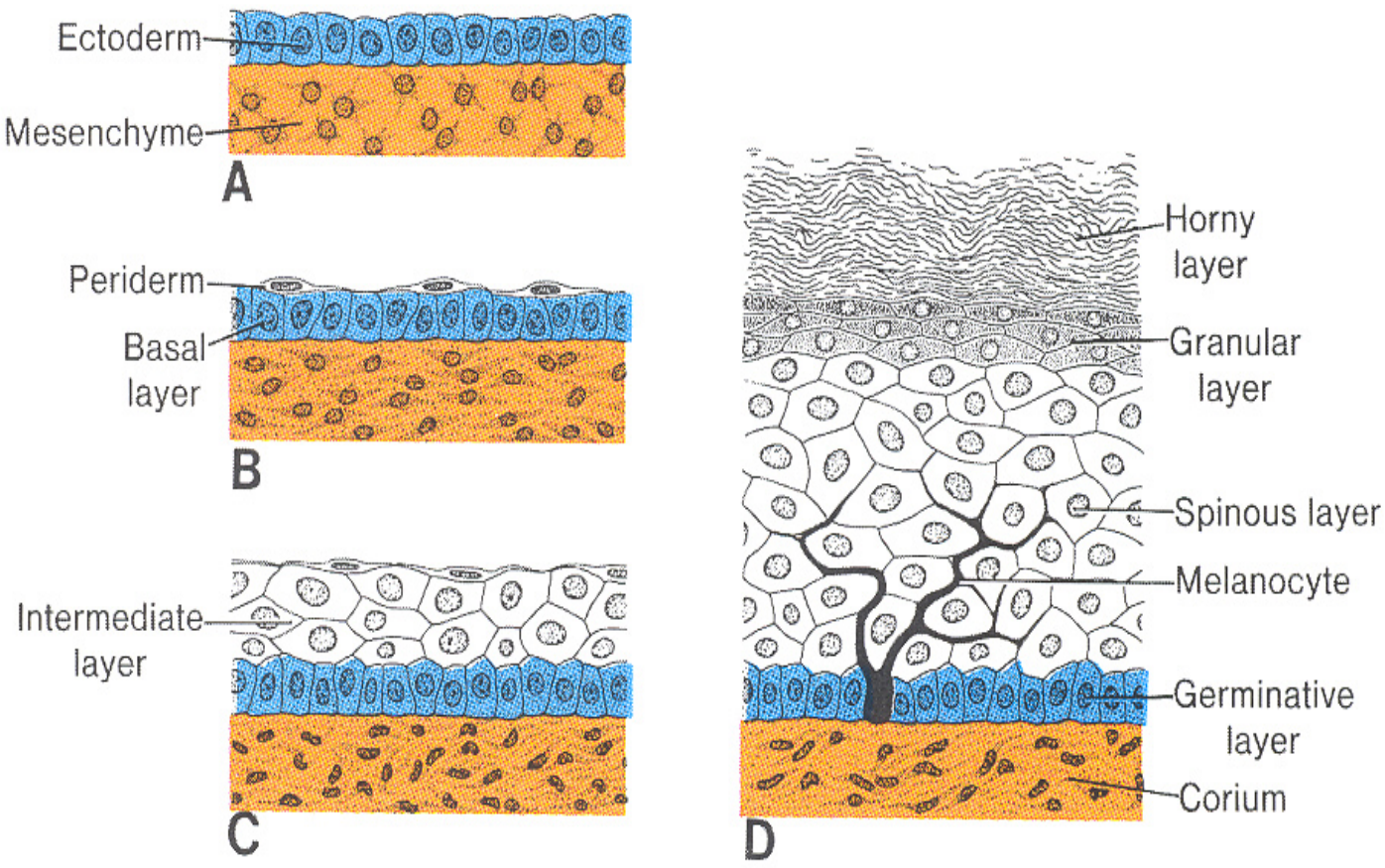


Figure 18.1. Formation of the skin at various stages of development. **A.** 5 weeks. **B.** 7 weeks. **C.** 4 months. **D.** Birth.

Epidermis

- Keratinization
  - Begins 2nd trimester
  - Matures by mid 3rd trimester
  - Keratinization of appendages begins 11-15
  - Keratinization of epidermis begins 22-24 wks
    - Begins on head, face, palms, soles
    - 24 wks s. corneum few layers

Epidermis

- Progression of keratinization
  - # of keratohyalin and lamellar body granules increases
  - Increase in # of organelle-depleted cornified cells
  - Neonate's skin barrier not completely mature until a few weeks after birth
    - Full barrier function 3 wks of age

Defects of Epidermal Maturation

- X-linked ichthyosis
- Steroid sulfatase
- Lamellar ichthyosis
- TGase 1
- Responsible for cross-linking precursor proteins to form insoluble cornified envelope
- Born with collodion membrane→shed→large polygonal platelike hyperpigmented scales

Specialized Cells in Epidermis

- Melanocytes
  - Neural crest along dorsal neural tube
  - Migrate to epidermis and hair follicles via mesenchyme
    - Also migrate to uveal tract, leptomeninges, and cochlea
  - Present in epidermis by mid 1st tri (50 days)
  - Fully functional 2nd tri
  - Melanin production 3-4 months
  - Melanosome transfer 5 months
  - Newborn skin not fully pigmented at birth

Specialized Cells of the Epidermis

- Melanocytes (Receptor-Ligands)
  - **Steel factor** binds to **KIT** receptor on melanocytes and melanoblasts
  - Mutations in KIT gene?
  - **Endothelin B receptor, endothelin 3**
  - **Pax3** critical in migration from neural crest and activation of melanocyte proliferation
  - Piebaldism and 4 types of Waardenburg's syndrome caused by failure of adequate number of melanoblasts to reach distal sites

MIGRATION OF MELANOCYTES FROM THE NEURAL CREST

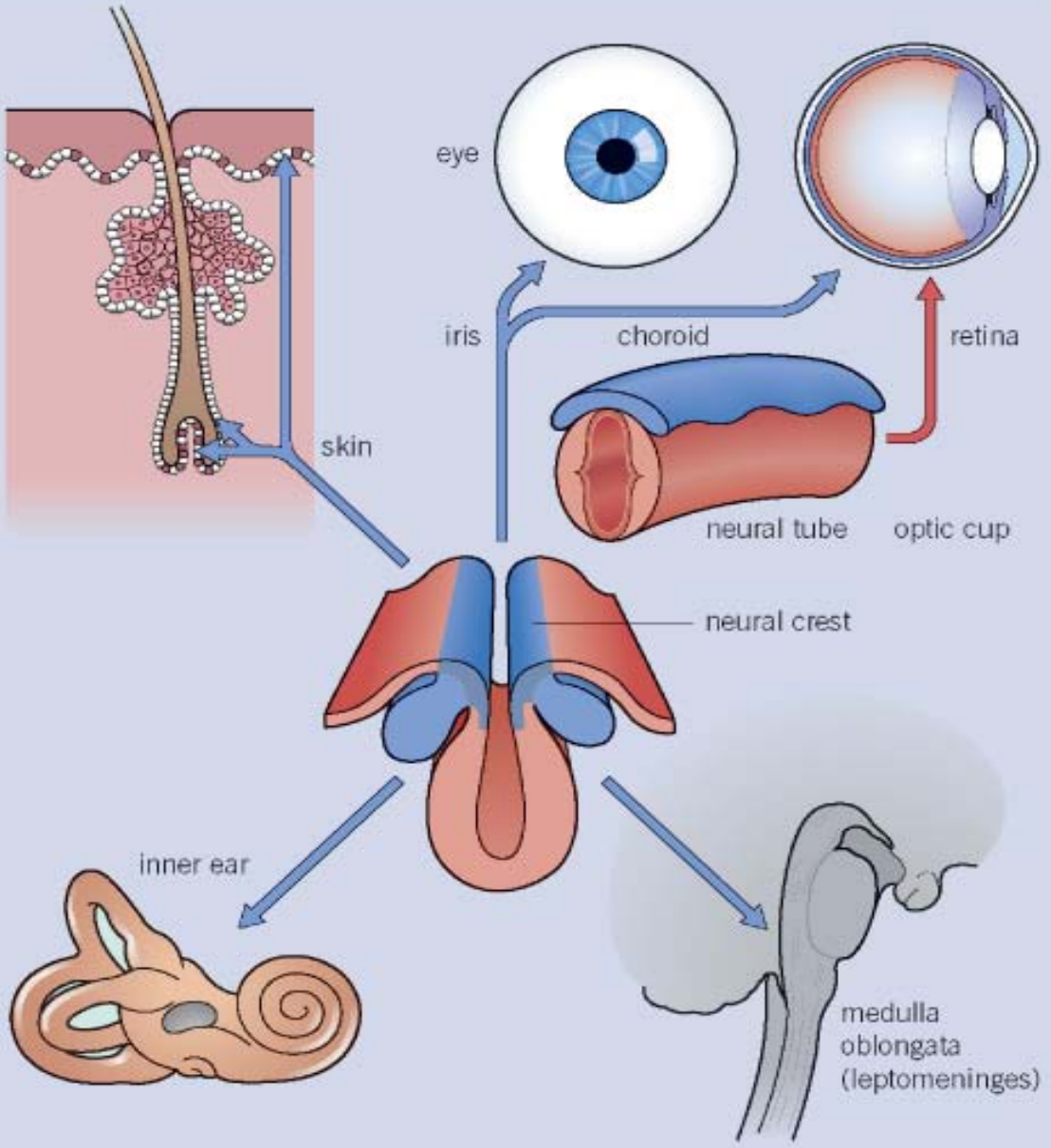


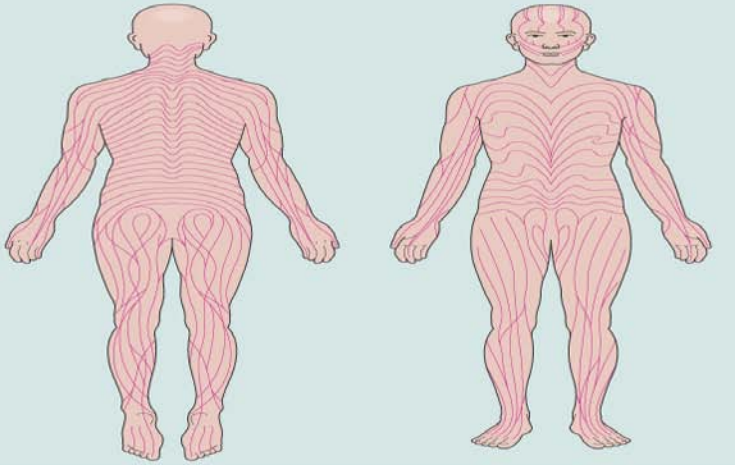
Table 66.3 **Disorders of melanocyte development.** AD, autosomal dominant; AR, autosomal recessive.

DISORDERS OF MELANOCYTE DEVELOPMENT					
Human disease	Mouse model	Mode of inheritance*	Gene mutated (chromosome)	Protein	Function
Piebaldism	Dominant spotting	AD	*KIT* (4q11–12)	Kit tyrosine kinase	Melanocyte migration/development
Waardenburg syndrome					
WS1	Sploch	AD	*PAX3* (2q35)	Pax3 transcription factor	Transcription factor/melanocyte survival
WS2	Microphthalmia	AD	*MITF* (3p12–14)	MITF transcription factor	Transcription factor/melanocyte survival
WS3	Sploch	AD	*PAX3* (2q35)	Pax3 transcription factor	Transcription factor/melanocyte development
WS4	Dominant megacolon	AD and AR	*SOX10* (22q13)	SRY-box containing gene 10	Transcription factor/melanocyte development
	Lethal spotting		*EDN3* (20q13.2–13.9)	Endothelin 3	Melanocyte development
	Piebald spotting		*EDNRB* (13q22)	Endothelin B receptor	Melanocyte development

*AD, autosomal dominant; AR, autosomal recessive.

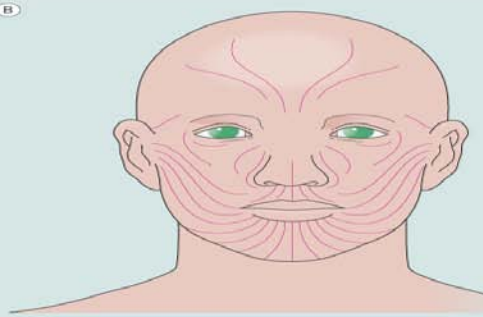
BLASCHKO'S LINES

A



BLASCHKO'S LINES ON THE FACE

B



BLASCHKO'S LINES ON THE SCALP

D

BLASCHKO'S LINES ON THE CHIN AND NECK

C

BLASCHKO'S LINES ON THE MALE GENITALIA

E

Specialized Cells of Epidermis

- Langerhans cells
  - Appear 40 days
  - Express HLA DR
  - High levels of ATPase
  - Expression of CD1a and production of Birbeck granules (mature) begins at 8 wks

Specialized Cells of Epidermis

- Merkel Cells
  - Highly innervated neuroendocrine cells; mechanoreceptors
  - Detected at 8-12 wks in palmoplantar epidermis→later in interfollicular skin
  - Identified by cytoplasmic dense core granules, cytokeratin 20, and neuropeptide expression
  - Dense on volar skin
  - ***Probably* derived from pluripotent keratinocytes, not neural crest**

Dermis

- Dermis origin varies by body site
  - Face and anterior scalp→Neural crest (facial dysmorphia in Waardenburg's)
  - Back→Dermomyotome of embryonic somite
  - Extremities and ventral trunk→lateral plate mesoderm

Dermis

- Embryonic fibroblasts are pluripotent cells→adipocytes, fibroblasts, and cartilage-producing cells
- Dermal cells situated under epidermis by 6-8 wks
- At this stage:
  - Able to synthesize collagen, but ratio of collagen III to I is 3:1 (reverse in adults)
  - No demarcation b/w cells→dermis and cells→musculoskeletal components

Dermis

- At 60 days (embryonic-fetal transition), superficial mesenchyme becomes distinct from skeletal components
- 12-15 wks: distinguish fine weave pattern of papillary dermis from reticular dermis
- Large collagen fibers accumulate in 2nd and 3rd tri
- 22-24 wks: elastic fibers detected

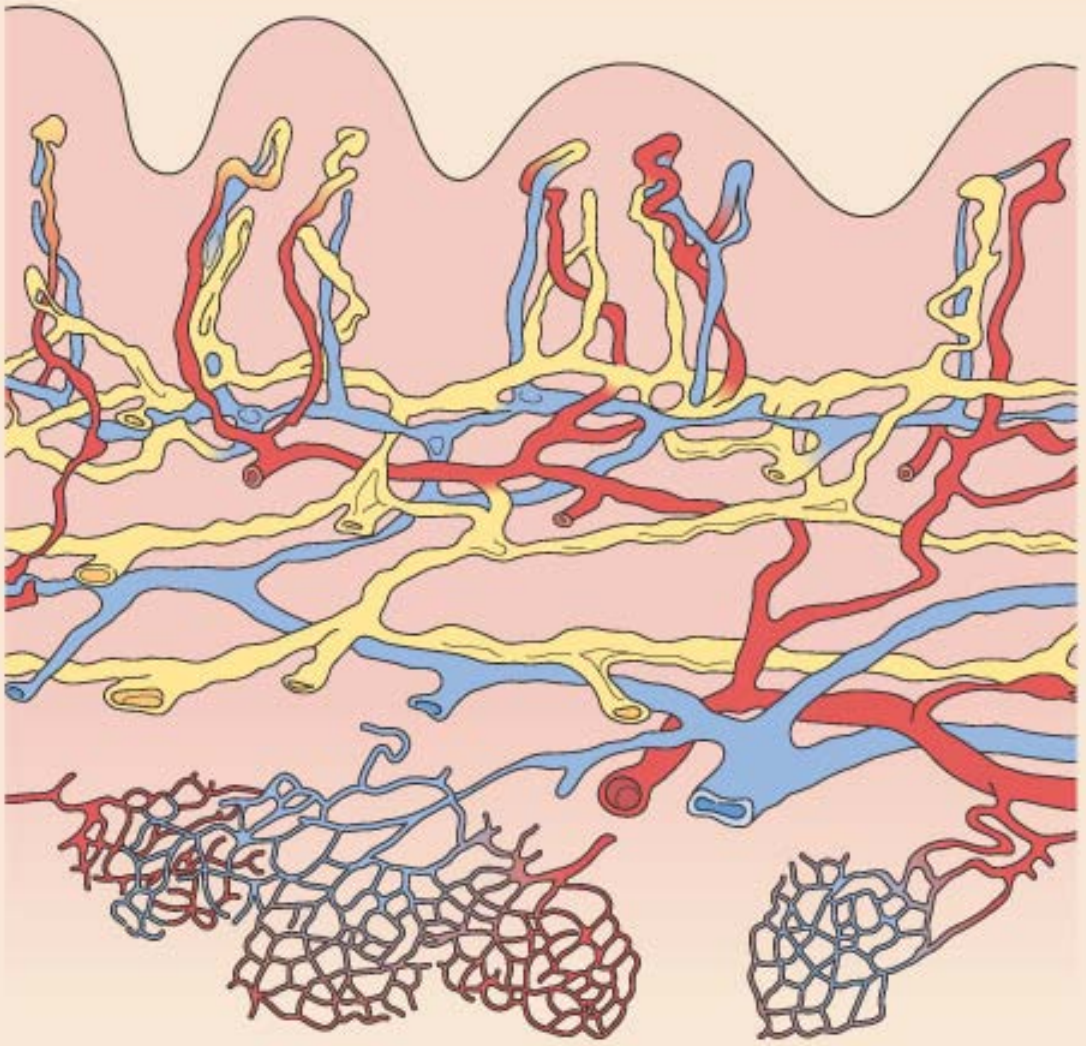
Dermis

- Differences b/w embryonic and adult dermis
  - Embryo: watery, cellular→Adult: more fibrous and acellular
  - Embryo: extracellular gel-like matrix of large well-hydrated proteoglycans→Adult: rigid fibrous
  - End of 2nd trimester shift from non-scarring to scarring
  - At birth thick and well organized but still thinner and more cellular than adults

Why important?

- Goltz syndrome—focal dermal hypoplasia
  - X-linked dominant
  - Boys die in utero
  - Girls, functional mosaicism
  - Islands of dermal hypoplasia follow Blaschko's lines; bordered by normal dermis

OUTLINE OF THE CUTANEOUS VASCULAR SYSTEM



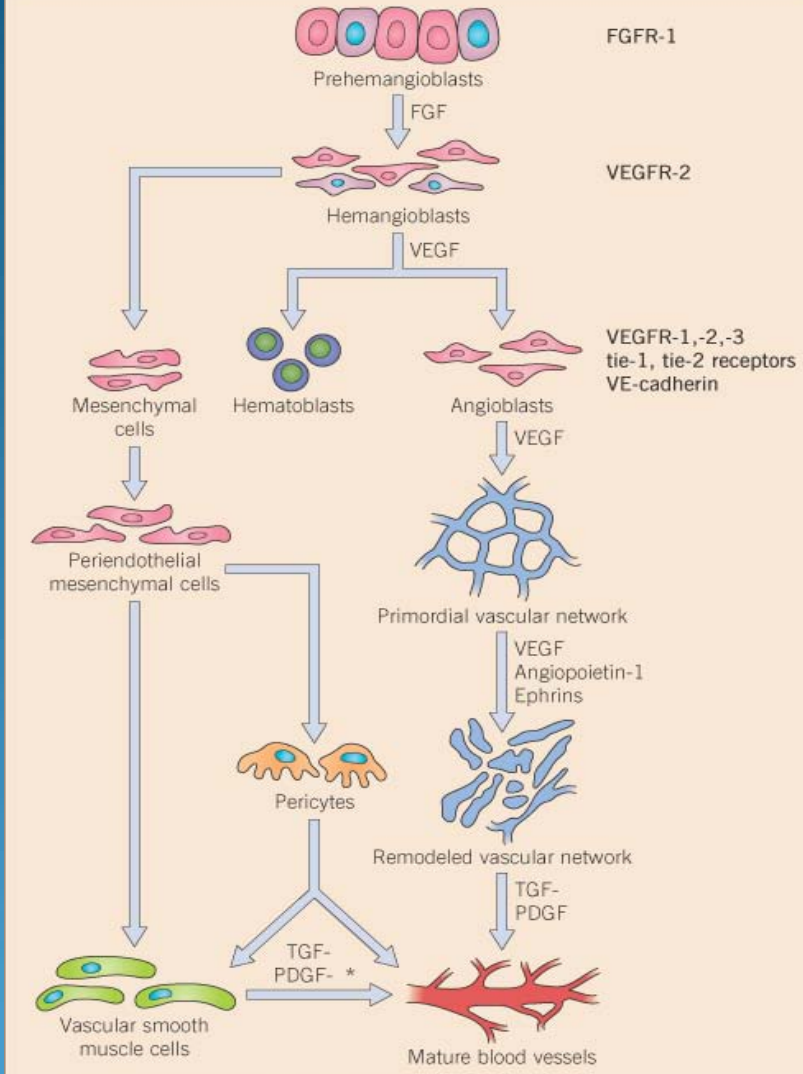
Vasculature

- Vasculogenesis
  - Differentiation of angioblasts into endothelial cells that form a primitive vascular network
  - Angioblasts originate in extraembryonic mesoderm of yolk sac
  - Hemangioblasts differentiate into hematopoietic cells and angioblasts

Vasculature

- Angioblasts express receptors: VEGFR-1,-2,-3, tie-1, tie-2, VE-cadherin
- **VEGF** stimulation
- Angioblasts coalesce to form dorsal aorta and large vessel primordia
- Angioblasts form a lumen→endothelial cells

CONSECUTIVE STEPS OF VASCULOGENESIS AND EARLY ANGIOGENESIS DURING EMBRYOGENESIS



FGFR	Fibroblast growth factor receptor
FGF	Fibroblast growth factor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
TGF	Transforming growth factor
PDGF	Platelet derived growth factor
*	Secreted by endothelial cells

Vasculature

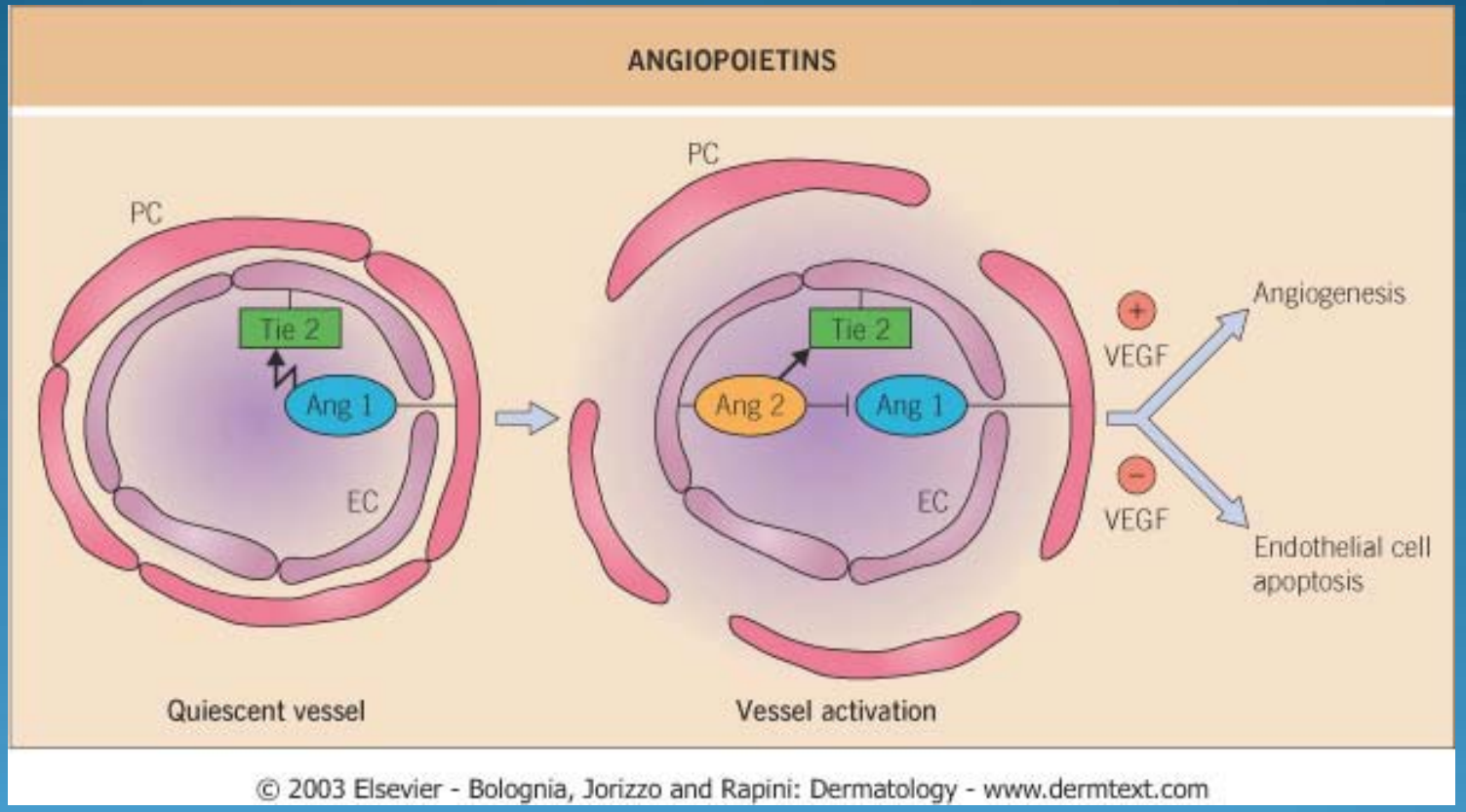
- Angioblasts form a lumen→endothelial cells
- Formation of primordial vascular plexus
  - Sinusoidal capillaries
  - Polygonal honeycomb pattern
- Establishment of interendothelial adherence jcts requires **VE-cadherin**

Vasculature

- Primordial vascular plexus surrounded by mesenchymal cells→pericytes and vascular smooth muscle cells
- Then remodeling under influence of VEGF, angiopoietins, and ephrins
- Major mechanism for new blood vessel formation—angiogenesis (sprouting)
- Other mechanism—intussusception: division of vascular lumen→new vascular space

Vasculature

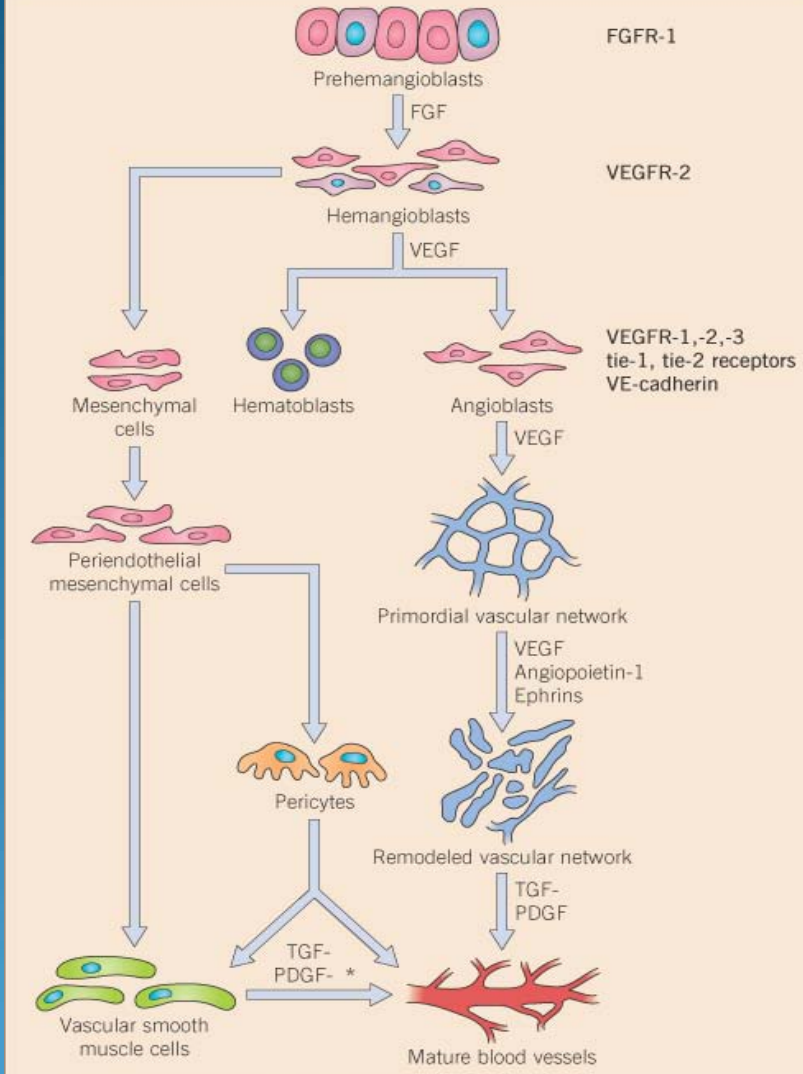
- Tie-2 tyrosine kinase R is expressed on endothelial cells
- Angiopoietin-1—vessel maturation
  - Activates tie-2→vascular sprouting and remodeling
- Angiopoietin-2
  - Can inhibit Ang-1
  - Promotes angiogenesis in presence of VEGF
  - Vessel regression in absence of VEGF



Vasculature

- Ephrin-ephrin interactions determine vascular identity
- Ephrin B2 is on arterial endothelium
- Ephrin B4 (B2s receptor) is on venous endothelium
- Both define boundaries b/w arterial and venous endothelial cells

CONSECUTIVE STEPS OF VASCULOGENESIS AND EARLY ANGIOGENESIS DURING EMBRYOGENESIS



FGFR	Fibroblast growth factor receptor
FGF	Fibroblast growth factor
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor
TGF	Transforming growth factor
PDGF	Platelet derived growth factor
*	Secreted by endothelial cells

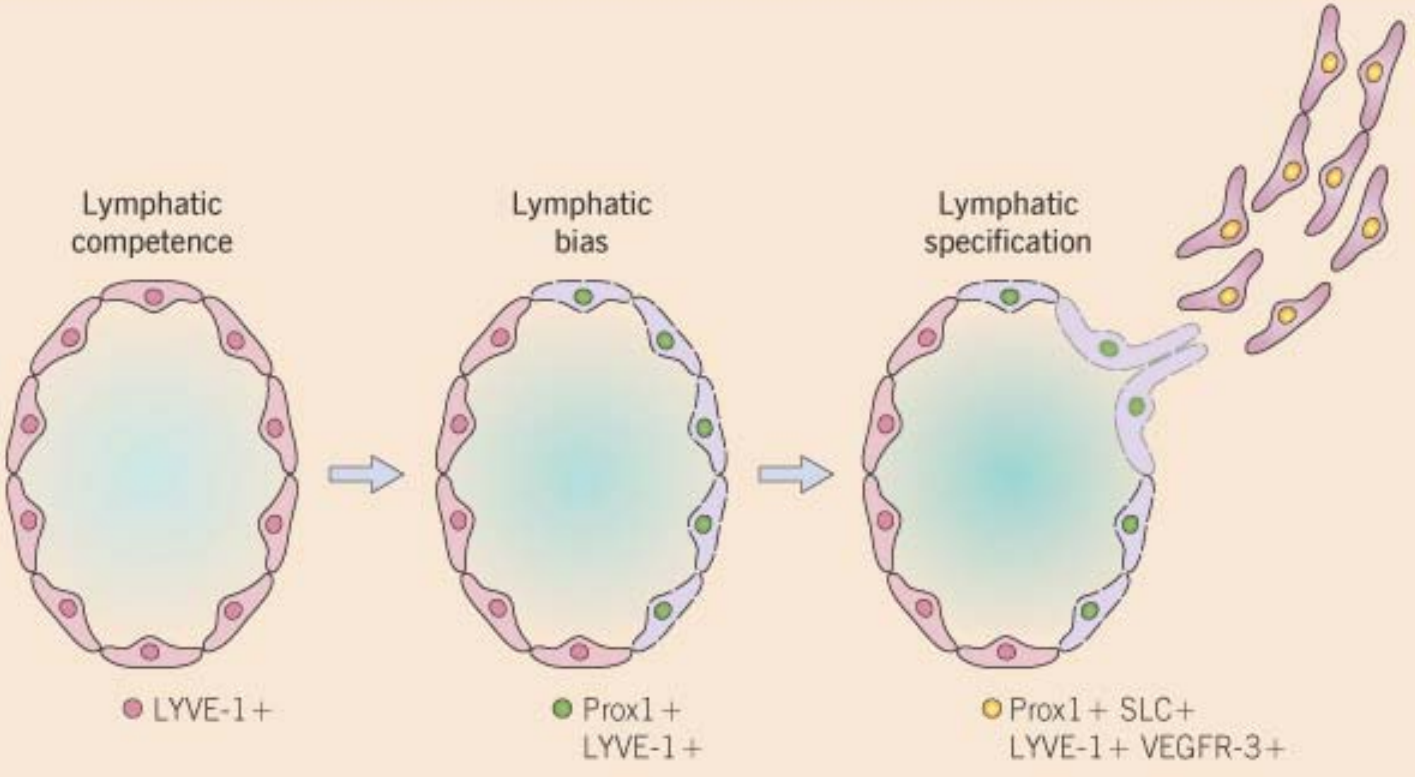
Lymphatics

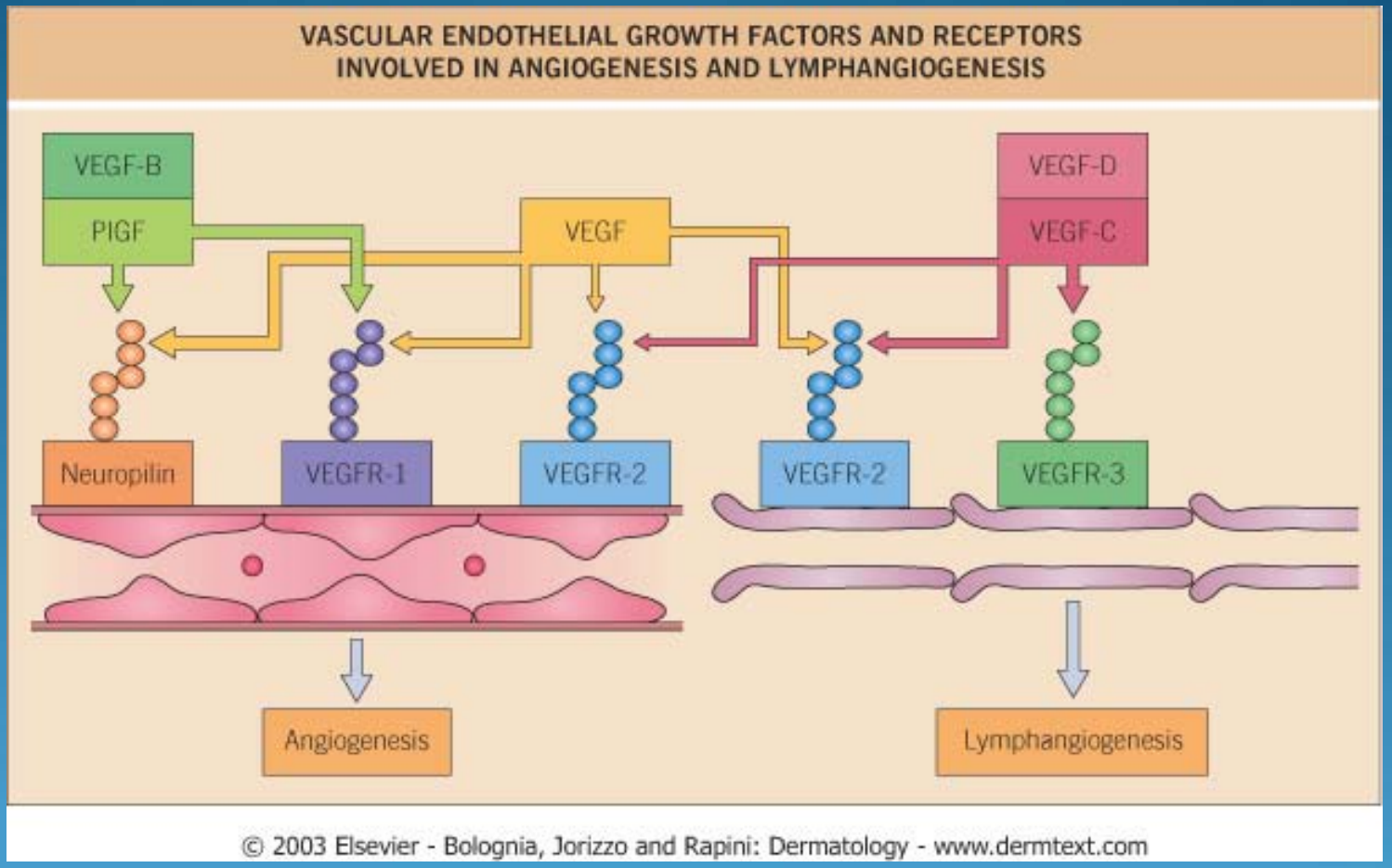
- Primitive lymph sacs through to originate from venous endothelial cell buds
- Peripheral lymphatics originate from lymph sacs and sproud into tissues with capillaries
- Homeobox gene Prox1 specific marker for lymphatic endothelial cells
  - Prox1 deficiency→absence of lymphatic system in mice

Lymphatics

- Markers of lymphatic system
  - VEGFR-3—receptor for VEGF-C and VEGF-D
  - Podoplanin
  - LYVE-1

EMBRYONIC DEVELOPMENT OF THE LYMPHATIC VASCULAR SYSTEM




VASCULAR ENDOTHELIAL GROWTH FACTORS AND RECEPTORS
INVOLVED IN ANGIOGENESIS AND LYMPHANGIOGENESIS
VEGF-B
PIGF
VEGF
VEGF-D
VEGF-C
Neuropilin
VEGFR-1
VEGFR-2
VEGFR-2
VEGFR-3
Angiogenesis
Lymphangiogenesis
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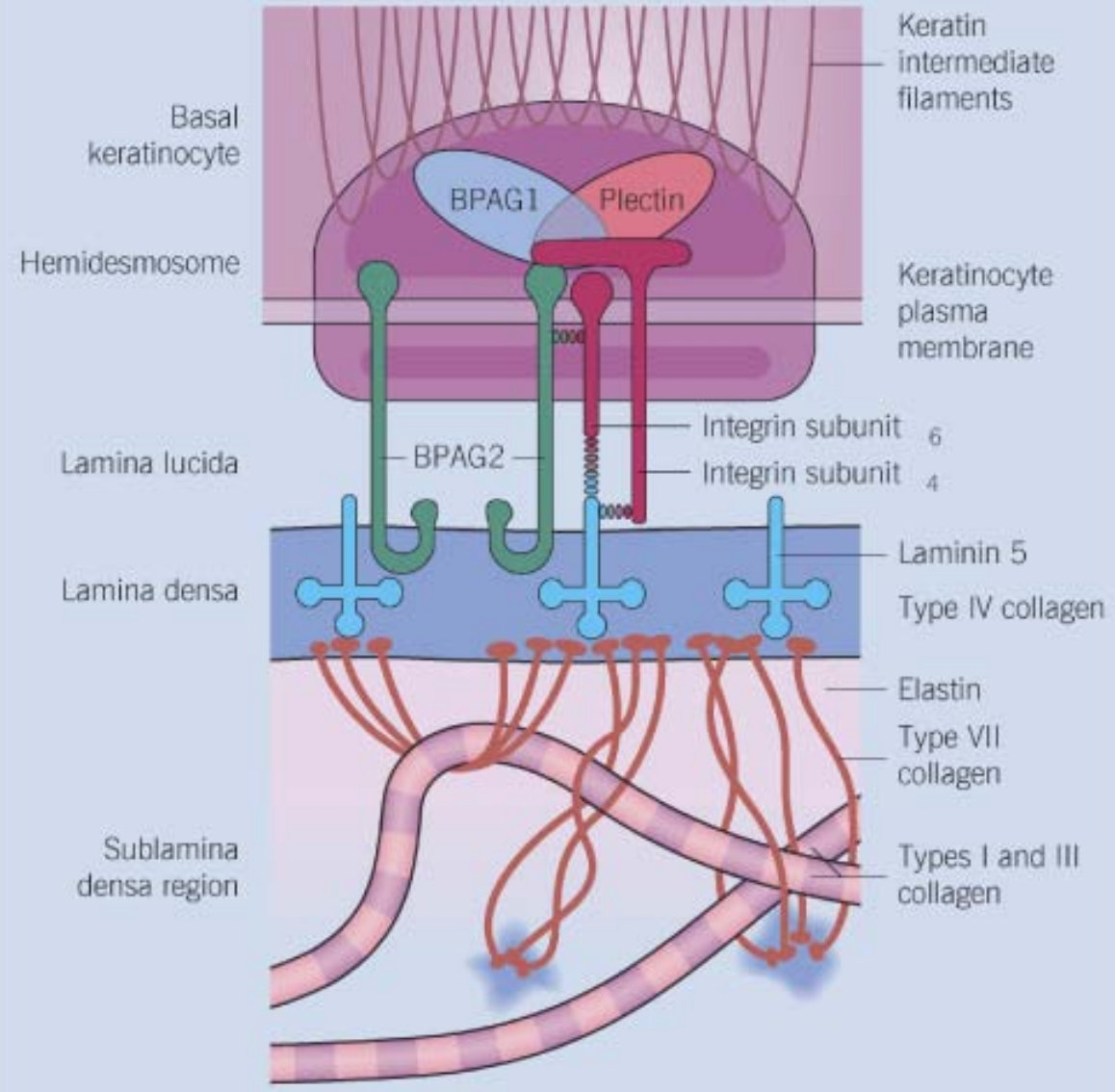
DEJ

- Components first appear 8 wks (with epidermal stratification)
- Almost all structures in place by 12 wks
- BM proteins derived from basal keratinocytes (ectoderm)
  - HD proteins (BPAG1, plectin), BPAG2, integrin subunits α6β4, types IV and VII collagen, laminins 5 and 6 and HSPGs

DEJ

- Dermal fibroblasts (mesoderm) produce
  - Nidogen (entactin), types IV and VII collagen and other proteins translocated to the plasma membrane of basal keratinocytes
- Plasma membrane of basal keratinocytes—localizational and organizational cues for fibroblast-derived proteins
  - Cues provided by **integrins**

EPIDERMAL BASEMENT MEMBRANE

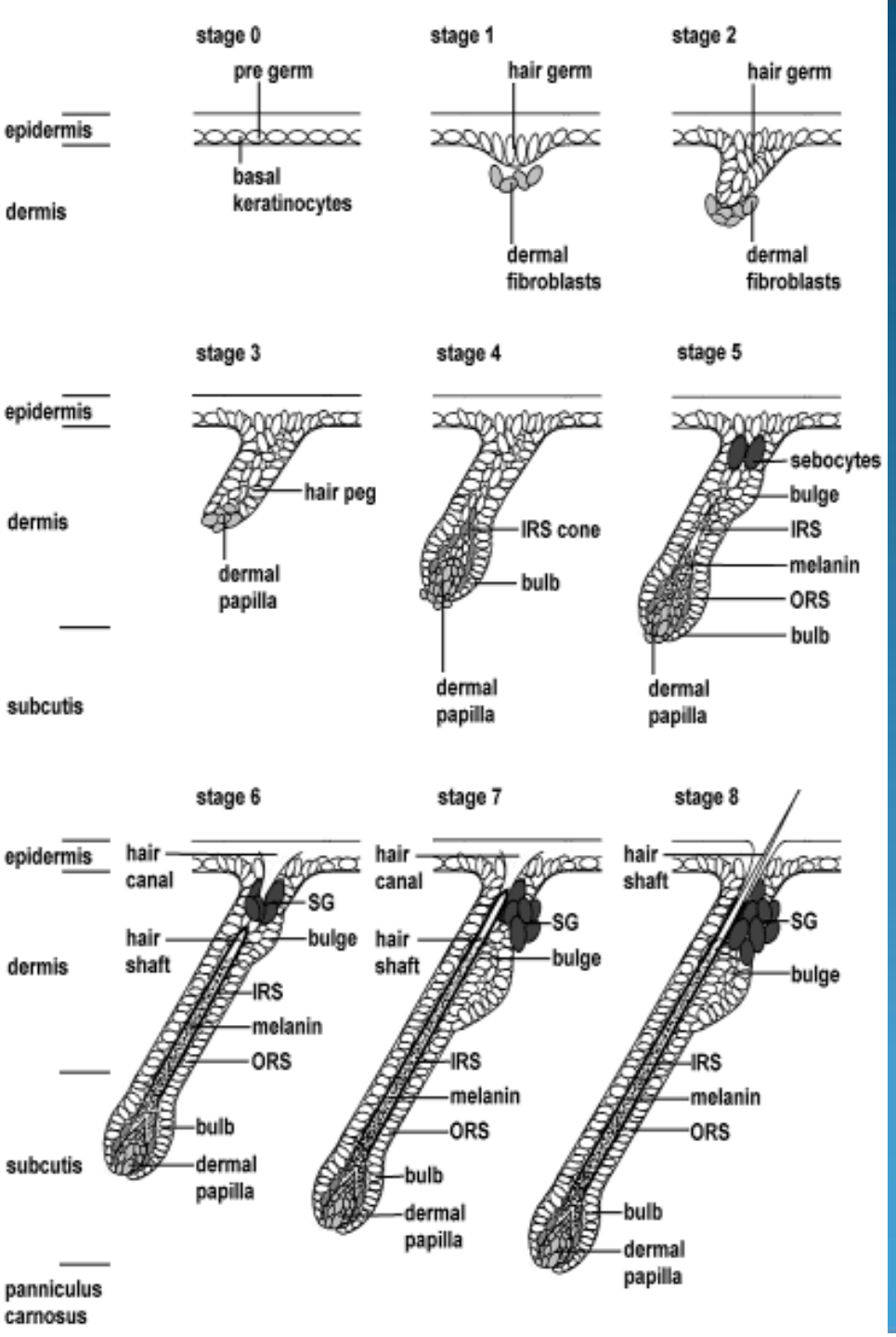


Hair

- No new hair follicles form after birth
- 10 wks follicle formation begins on head (esp. eyebrows and upper and lower lips
- 12-14 wks base of presumptive hair follicle invaginates, enveloping presumptive dermal papilla cells forming bulbous hair peg
- 16 wks follicles develop cephalocaudally and ventrally
- 19-21 wks hair canal fully formed and scalp hairs visible above skin surface

Hair

- Follicle formation initiated by signals from dermis→formation of follicular placode or anlage
- Placodes seen wk 10 on scalp and face
- Placodes instruct dermis to condense→dermal papilla
- Dermal papilla instruct placode cells to proliferate and extend deeper into dermis→peg stage hair
- Invagination of base of hair follicle (wks 12-14) envelopes dermal papilla cells→bulbous hair peg


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
epidermis
dermis
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
epidermis
dermis
subcutis
panniculus carnosus

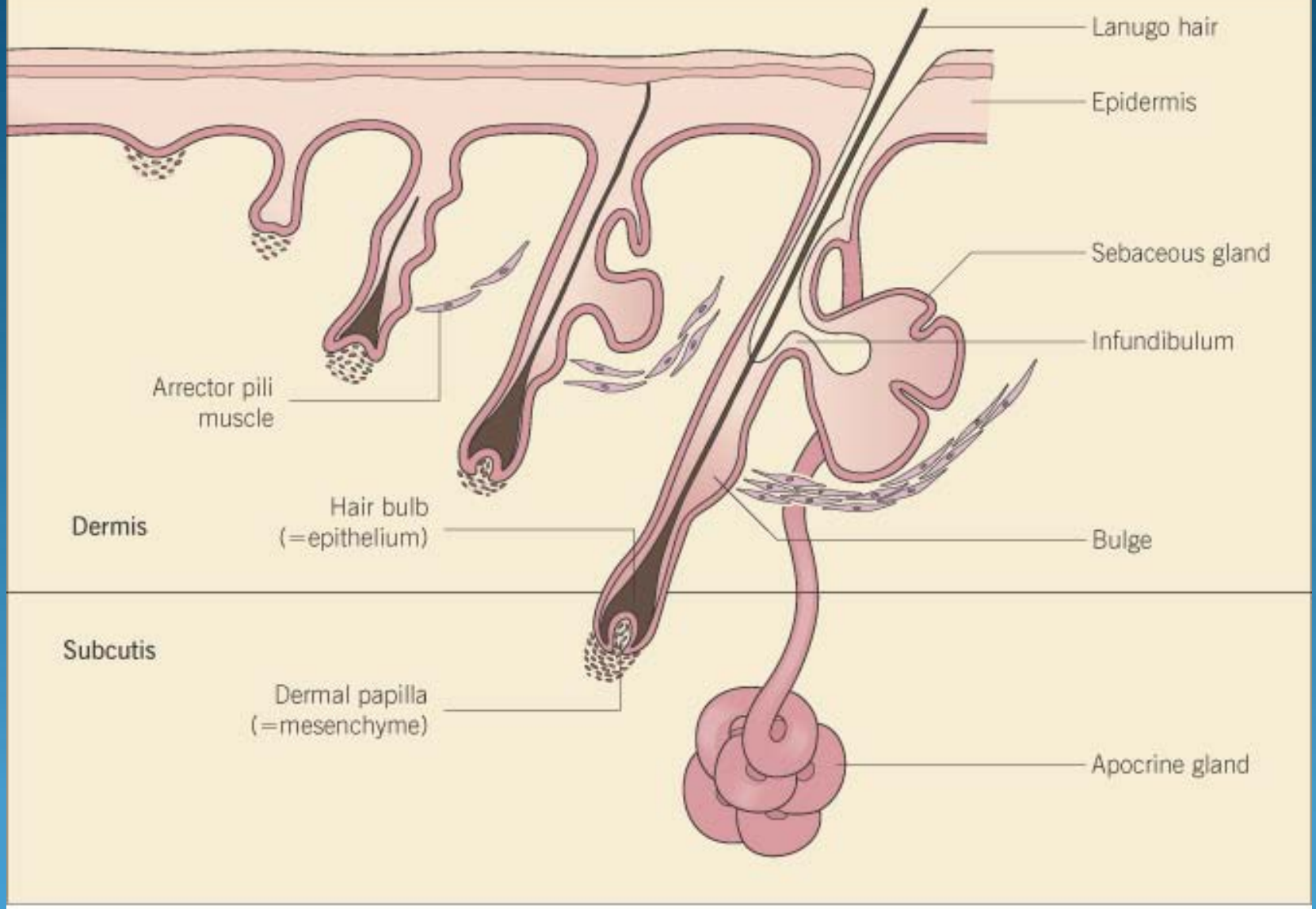
Hair

- 19-21 wks hair canal fully formed
- 24-28 wks go from anagen→catagen→telogen
- Telogen hairs shed in amniotic fluid
- Enter 2nd cycle
- Most hairs become thicker and coarser with subsequent growth cycles (vellus→terminal)

Hair

- Bulbous Peg Phase
  - Hair follicles differentiate in 2nd tri→7 concentric layers
    - ORS, IRS (Henley's, Huxley's, cuticle), hair shaft cuticle, cortex, and medulla
  - Melanocytes interspersed among keratinocytes
  - 3 distinct bulges
    - Upper bulge→apocrine gland
    - Middle bulge→sebaceous gland
    - Deeper bulge→insertion point of arrector pili muscle (hair bulge)

FETAL DEVELOPMENT OF THE HAIR FOLLICLE



Hair Fodder

- Undifferentiated epithelium?
- B-catenin
- Germ phase?
- Sonic Hedgehog
- Bulbous Peg Phase?
- NOTCH1

Sebaceous Glands

- Parallel follicular development
- First 13-16 wks
- Middle bulge (aka superficial)
- Maternal hormones cause hypertrophy
- Unless stimulated by maternal hormones or endogenous (tumor) become quiescent

Eccrine Glands

- Palmoplantar eccrine development begins with formation of large mesenchymal bulges or pads (paw pads)
  - Pads regress by 3rd trimester
- Parallel ectodermal ridges overly pads
  - Curves form fingerprints
- Like hair and nails
  - Begin to develop 1st trimester
  - Fully developed by 2nd trimester

Eccrine Glands

- Eccrine gland primordia bud along ectodermal ridges at wks 14-16
- Buds elongate
- Dermal component canalized by wk 16
- Epidermal component canalized by wk 22
- Apocrine and interfollicular eccrine glands do not begin to form until 5th month
- Apocrine glands function transiently in 3rd trimester, quiescent in neonate
- Eccrine glands do not function in utero, only function after birth

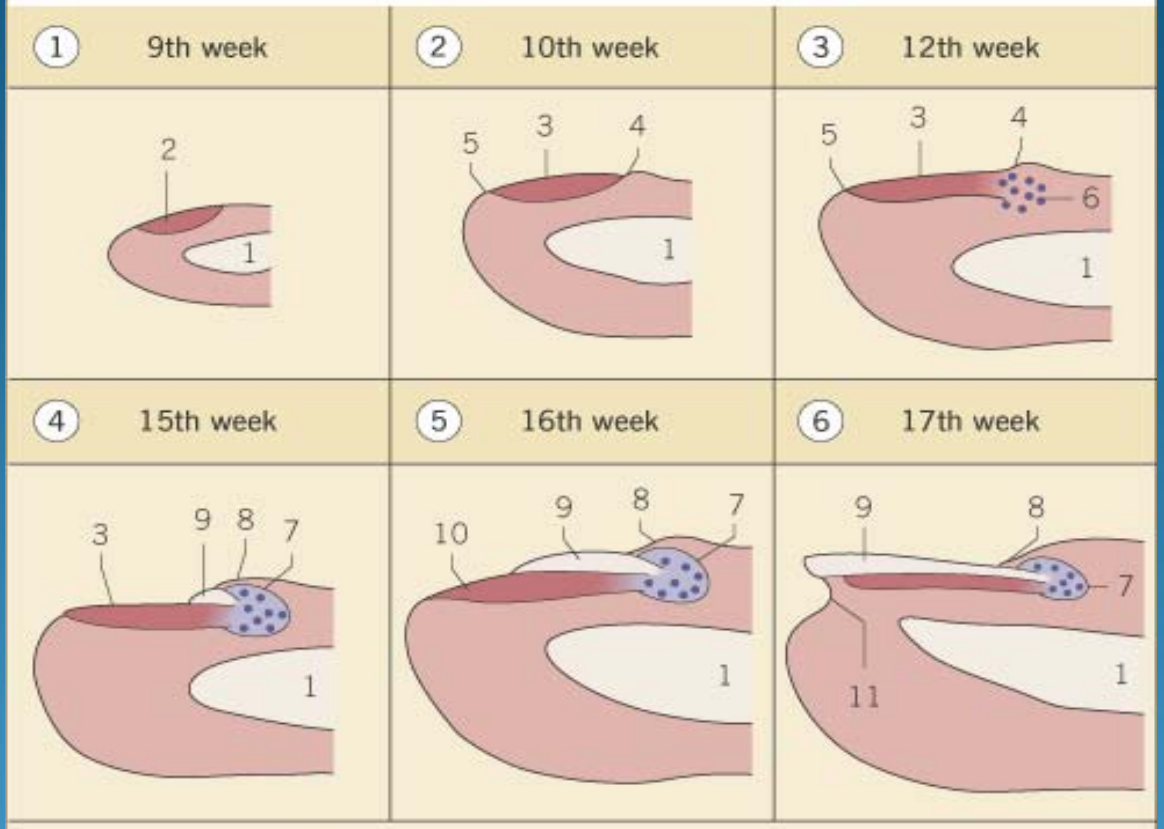
Nails

- Begins 8-10 wks from same primitive epidermis that gives rise to hair, sweat glands, and s. corneum
- Complete 5th month
- Future nail bed demarcated by folds visible by 8-10 wks
- Ectoderm invaginates along proximal end→proximal nail fold
- Nail bed on dorsal digit—first skin structure to keratinize at 11 wks
- Keratinization begins distally→continues to proximal nail fold

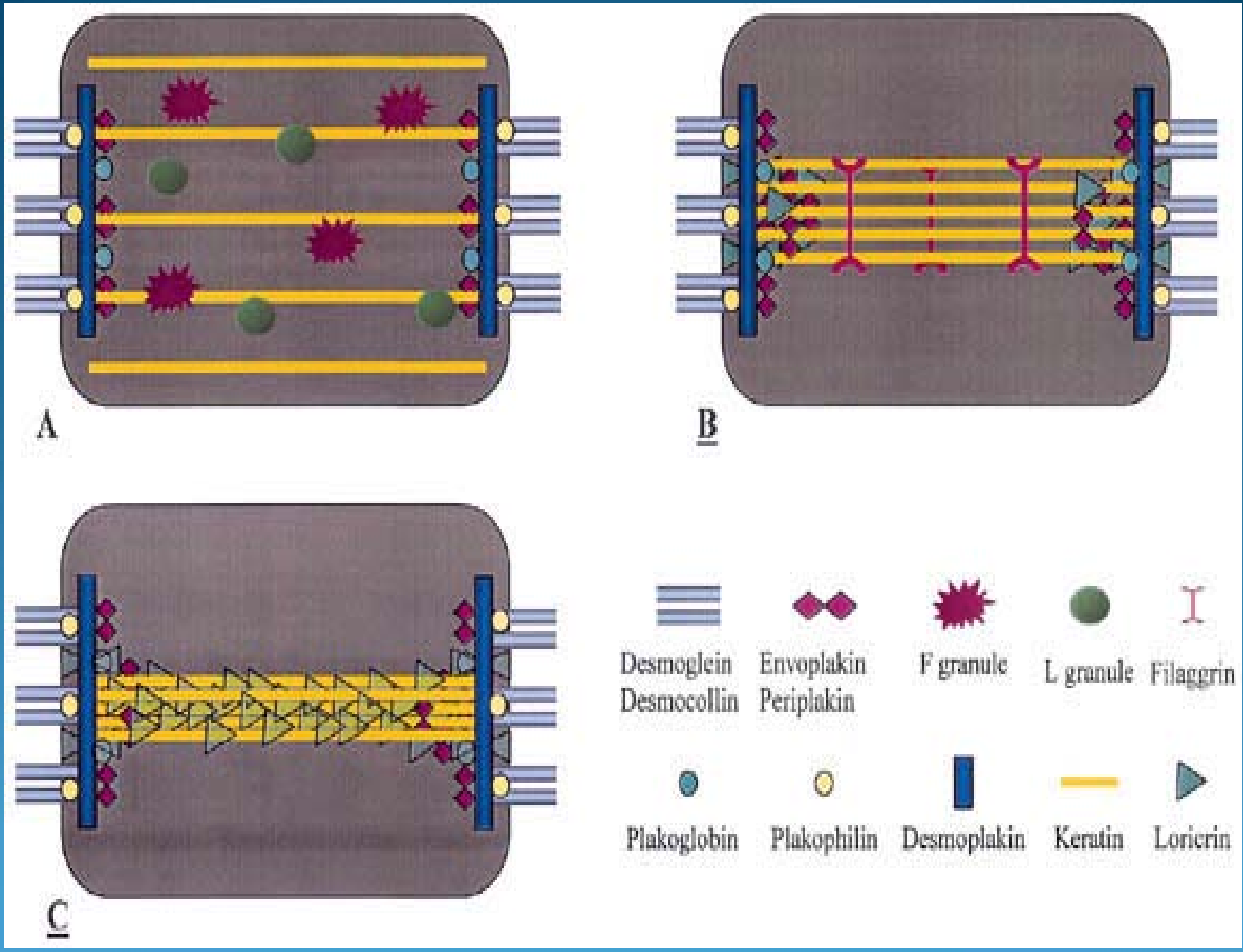
Nails

- First preliminary nail is shed
- Replaced by hard differentiated nail plate
  - Emerges 4th month from under proximal nail fold
  - Completely covers nail bed by 5th month
- Predictable and constant time course of nail development→used to estimate gestational age at term

EMBRYOLOGICAL DEVELOPMENT OF THE NAIL APPARATUS



1 Developing cartilage/bone
2 Nail anlage
3 Nail field with its proximal (4) and distal (5) fold
6 Primordial matrix
7 (Fully developed) nail matrix
8 Proximal nail fold
9 Nail plate
10 Nail bed
11 Hyponychium


A
B
C
Desmoglein
Desmocollin
Envoplakin
Periplakin
F granule
L granule
Filaggrin
Plakoglobin
Plakophilin
Desmoplakin
Keratin
Loricrin