Special high-risk groups in which topical absorption concerns are higher

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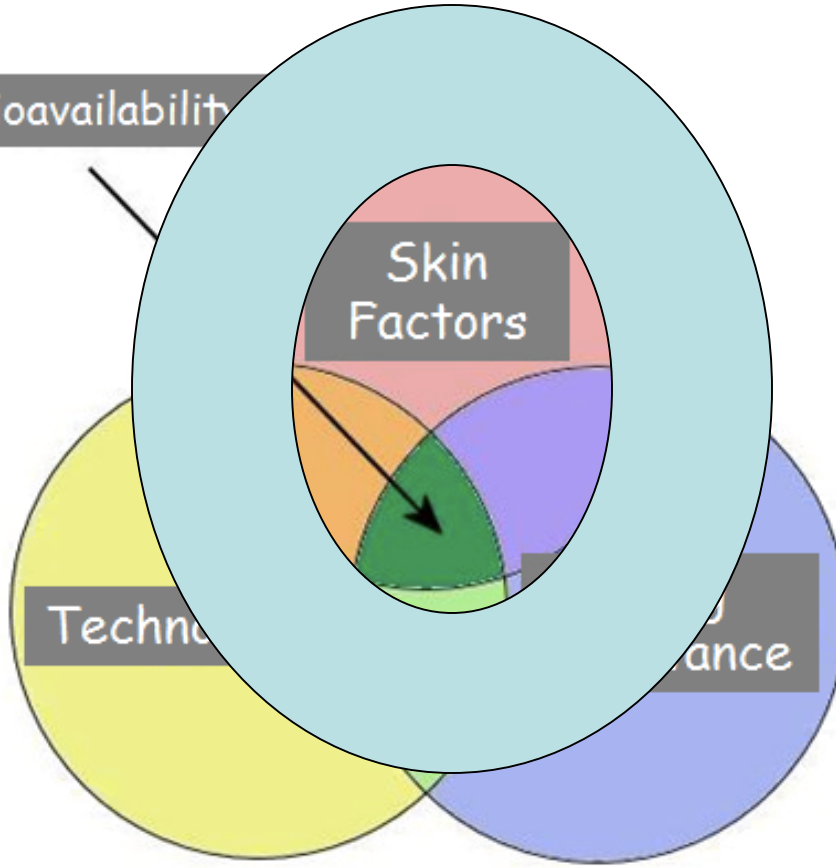
No Conflicts

Determinants of Topical Bioavailability

It is the complex interaction of drug substance, formulation-dosage form, and those skin factors that affect the barrier function of the skin that determines systemic drug availability, its profile over time, and product design selection.



Overview

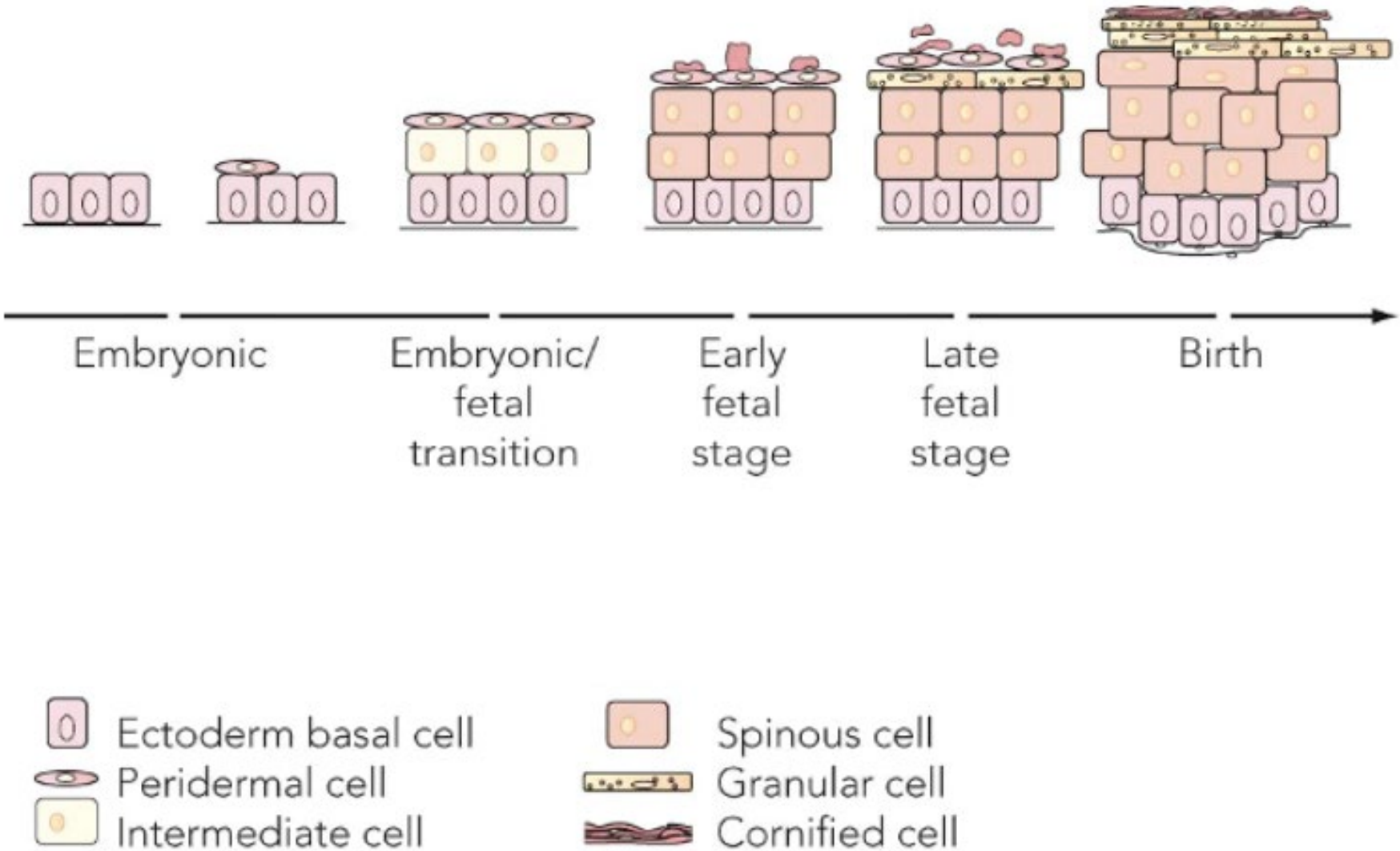
- Function of the skin
- Maturation of the skin
  - Embryology
  - Aging
- Skin dysfunction – at-risk populations
  - Preemies, infants
  - AD, Psoriasis
  - Elderly, photoaged

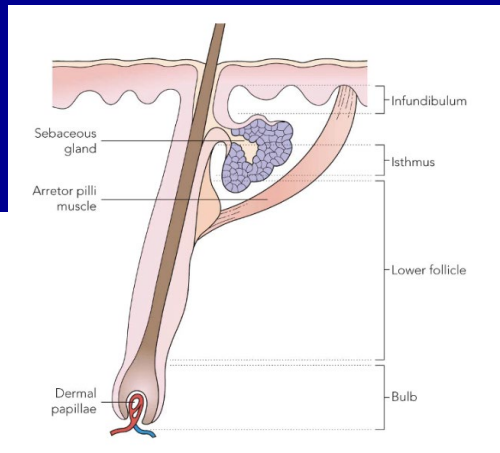
What does the skin do?

- Permeability barrier
- Protection
  - Infectious diseases
  - Noxious agents
  - UV radiation
  - Regulates body temp
- Wound repair
- Synthesizes essential nutrients
- Helps define outward appearance

In the beginning…..

Periderm – protects the basal epidermal layer





Epidermal stratification

Follicular keratinization

Interfollicular keratinization

Chorionic villous sampling

Amniocentesis

Fetal biopsy

0 1 2 3 4 5 6 7 8 9

Embyonic stage 0-8 weeks

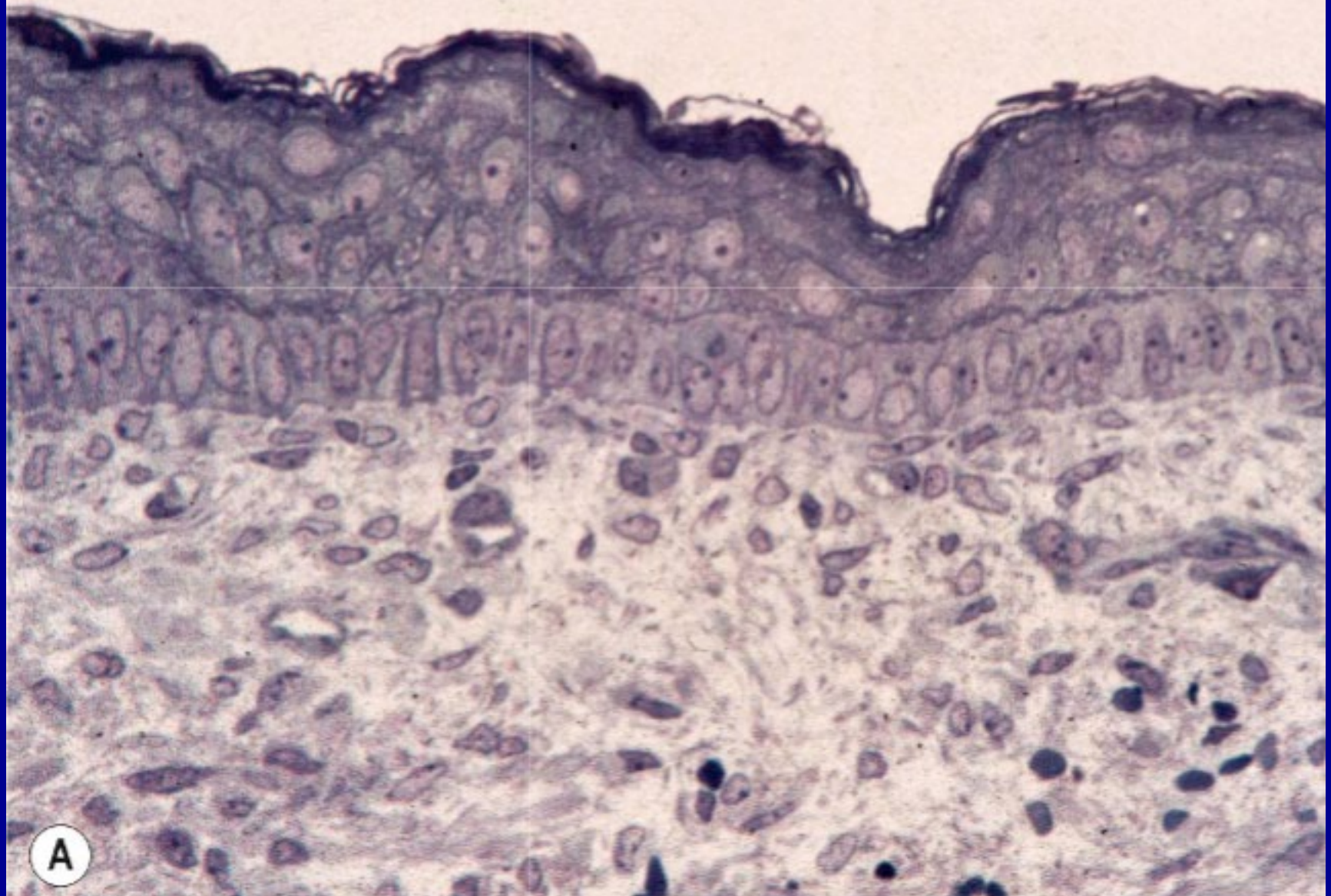
Embyonic/fetal transition 9-10 weeks

Early fetal stage 2-5 months

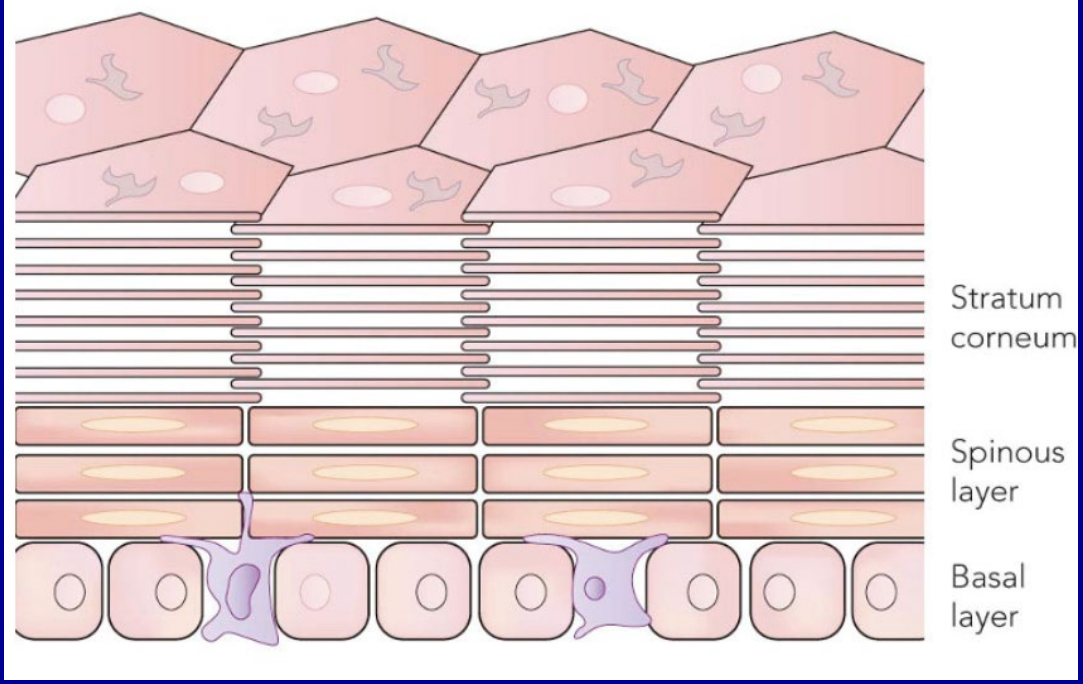
Late fetal stage 5-9 months

Birth

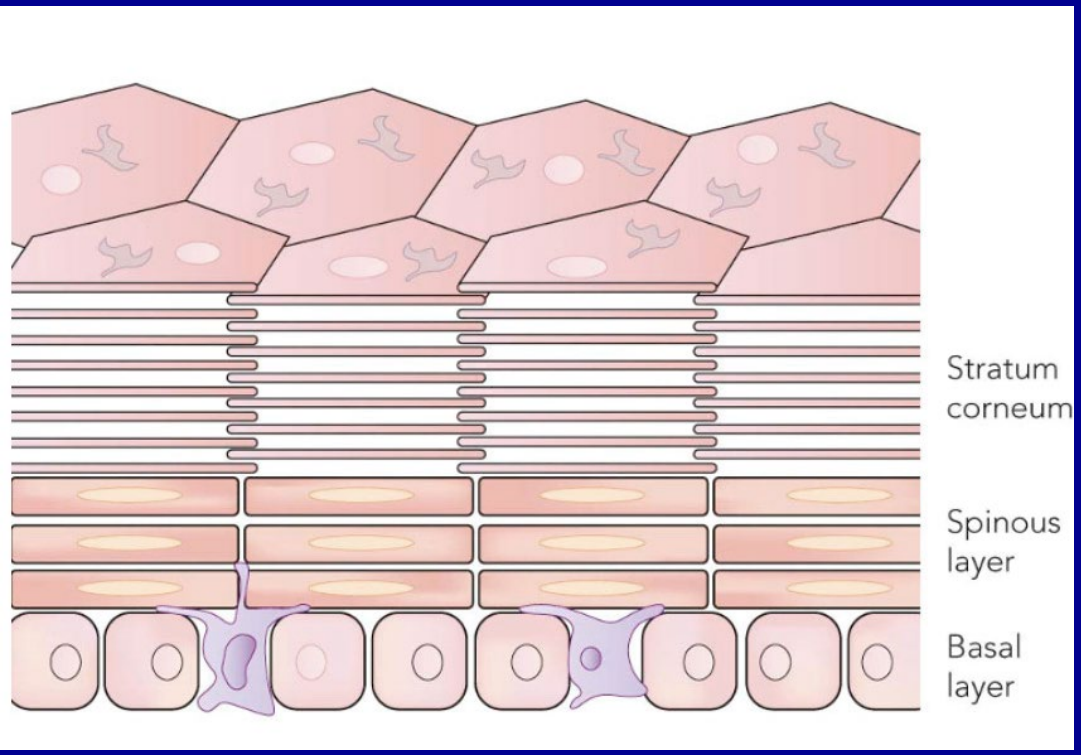
EGA 143

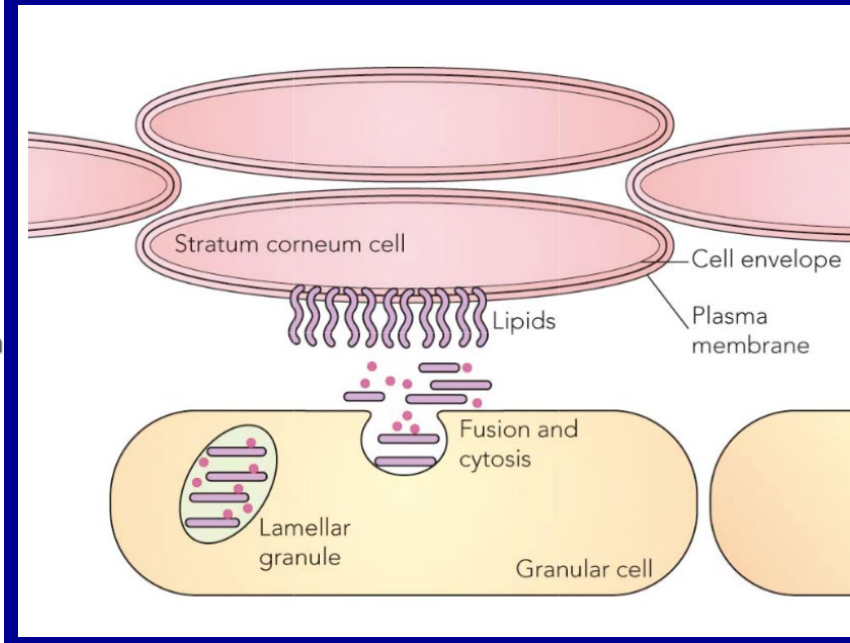


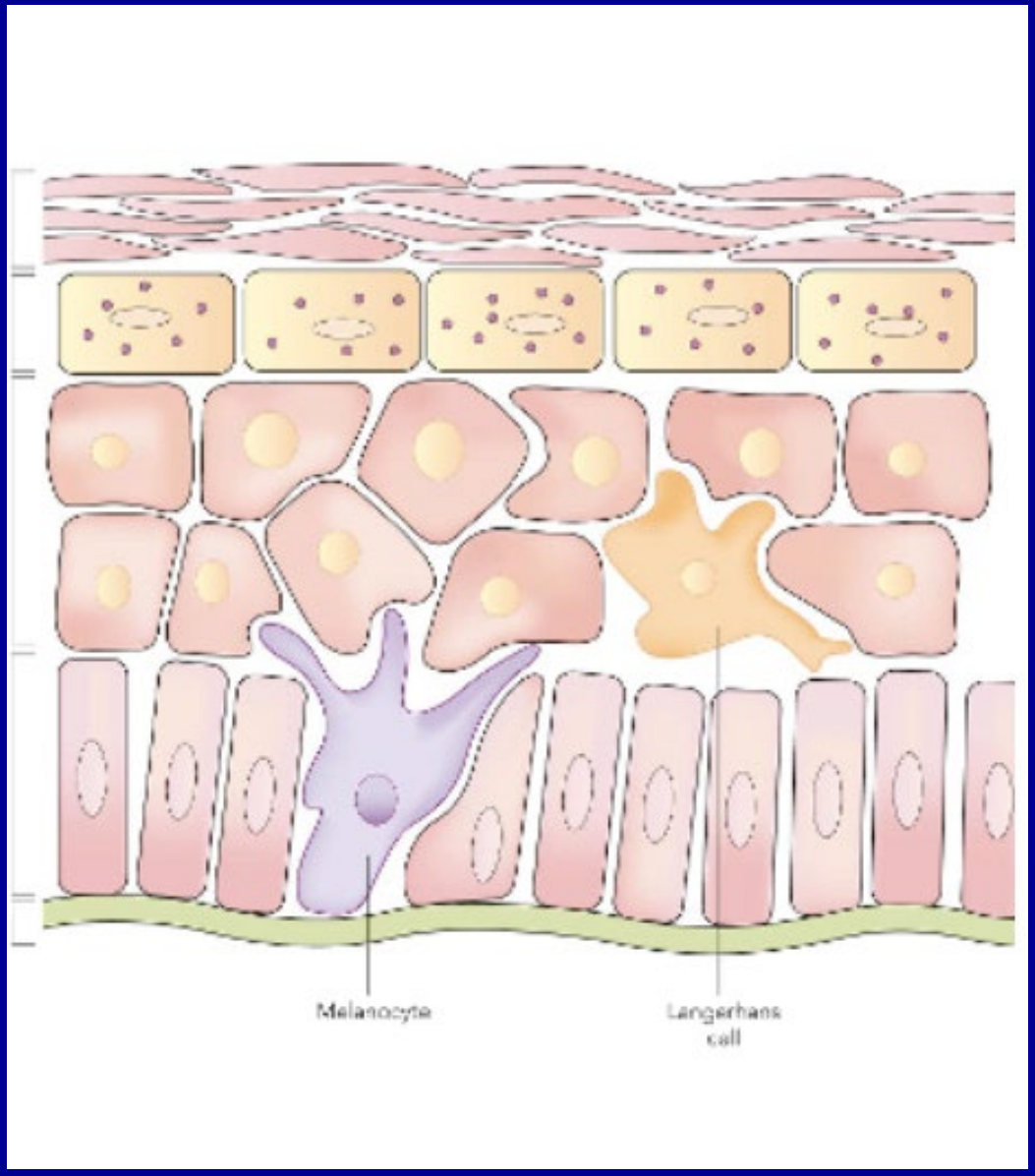
The Epidermis



- Multilayered keratinocytes
- Layers correlate with stage of differentiation
- Each stage – specific structural/enzymatic markers
- Final stage - anucleated nonviable cell
- Cornified layer – protection & water barrier function
- Fetus – 20-24 weeks to keratinize
- Adult -14-28 days

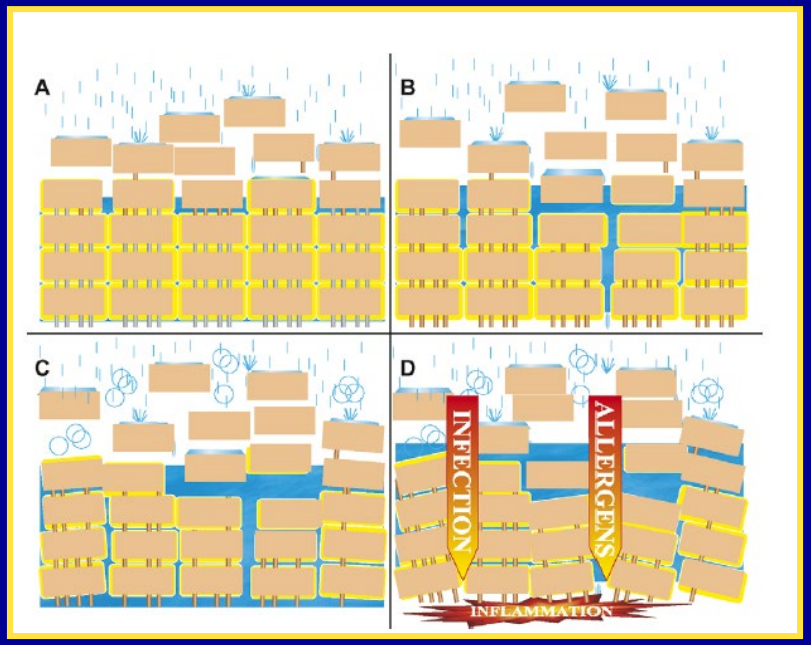

Stratum corneum
Spinous layer
Basal layer


Stratum corneum cell
Cell envelope
Lipids
Plasma membrane
Fusion and cytosis
Lamellar granule
Granular cell


Melanocyte
Langerhans cell

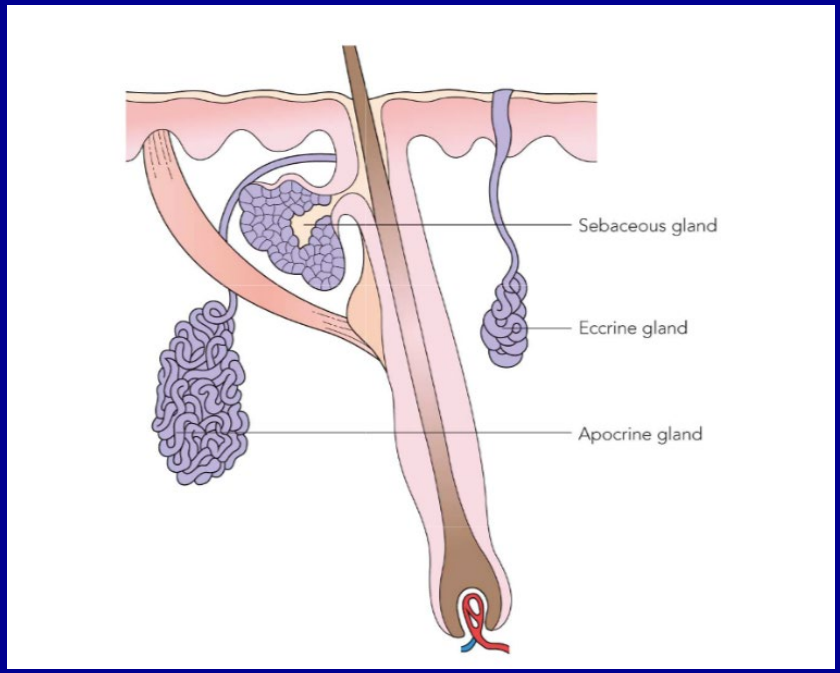
The “Bricks & Mortar” of the Epidermis

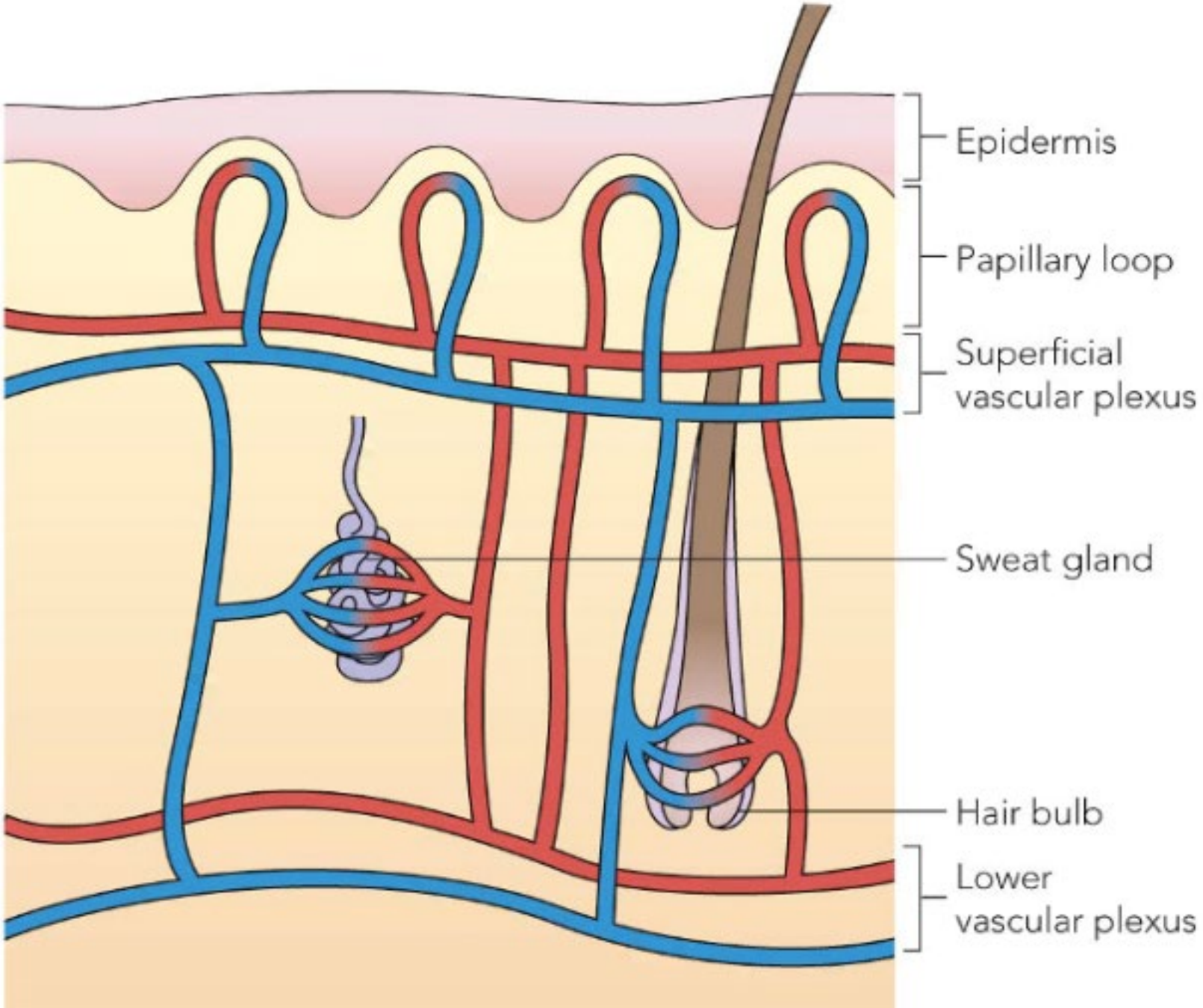
- **Extracellular lipid matrix**
  - Regulation of permeability, desquamation, antimicrobial peptide activity,
  - **Toxin exclusion**, **Selective Chemical Absorption**
- **Corneocytes**
  - Mechanical reinforcement
  - Hydration
  - Cytokine mediated inflammation
  - Protection from UVR



And deeper yet..The Dermis

- Majority of skin
- Pliability
- Elasticity
- Tensile strength
- Protection
- Thermal regulation
- Developmental collaboration
  - DEJ & appendages




Epidermis
Papillary loop
Superficial vascular plexus
Sweat gland
Hair bulb
Lower vascular plexus

Skin maturation – when it does go right it still isn't optimal at birth

- First 24 months

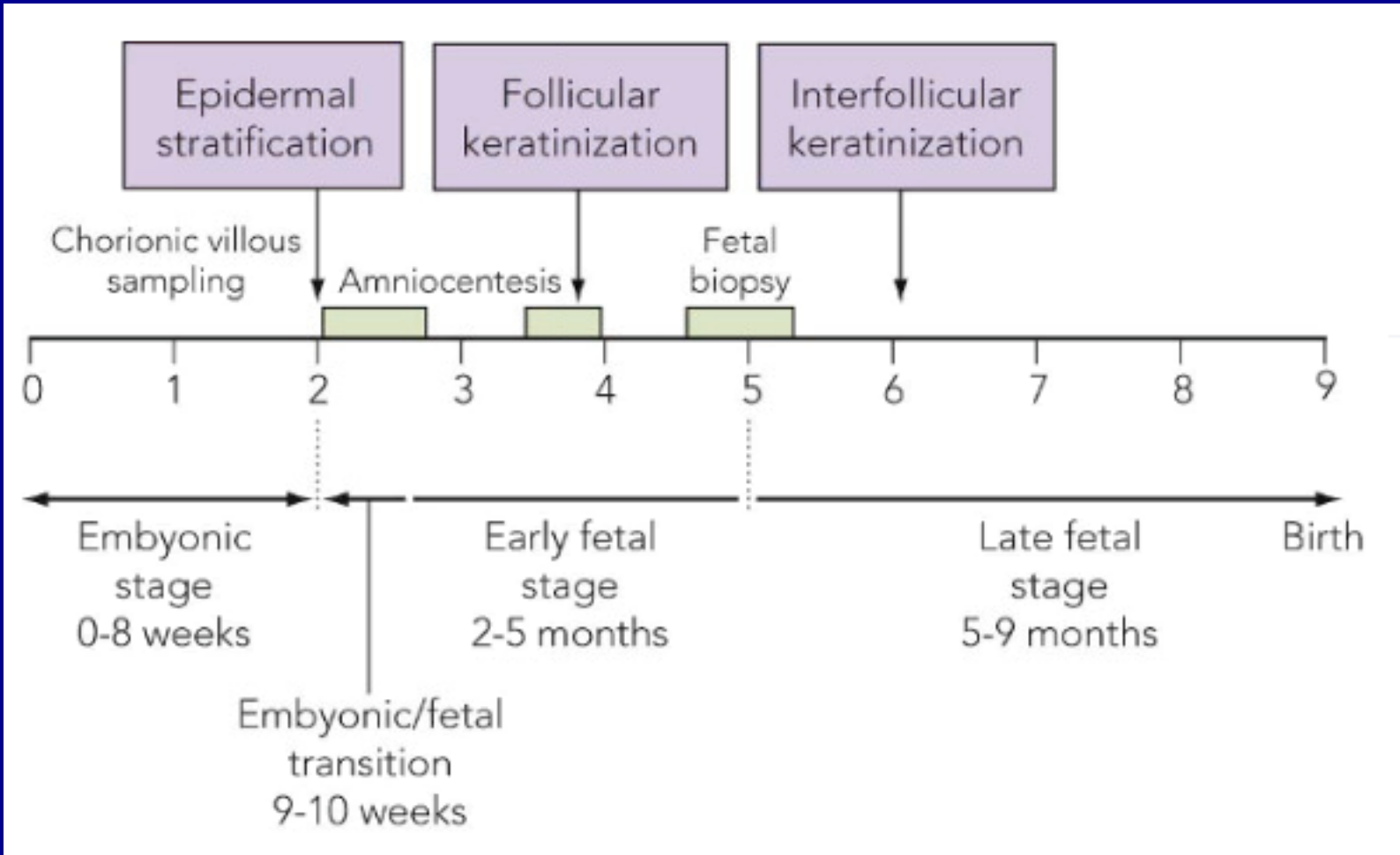
  SC 30% thinner than adults

  Suprapapillary epidermis 20% thinner
- SC hydration reduced in term infants, but increases by age 3 mos
- TEWL varies, but appears higher forearms

And what if the “most special delivery” arrives early?

E 4.1 Skin of an extremely premature infant (<24 weeks). Note

Embryogenesis of the Skin



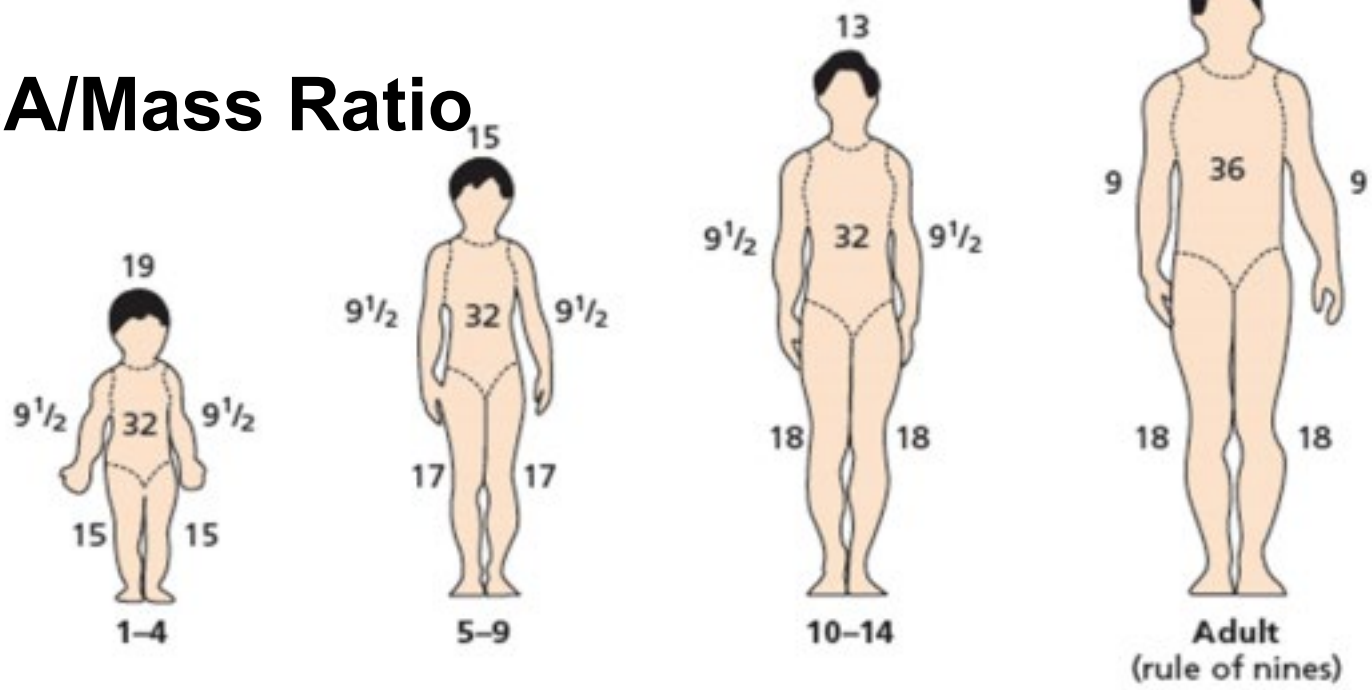
The epidermis appears EGA day 18-20!

	EMBRYONIC	EARLY FETAL	LATE FETAL
Periderm	X		
Shedding of periderm			X
Epidermis			
Basal layer	X		
Intermediate layer	X		
Granular layer			X
Cornified layer			X
Cell junctions			
Desmosomes	X		
Tight junctions	X		
Hemidesmosomes		X	
Appearance of specialized non-keratinocyte cells			
Langerhans cells		X	
Melanocytes		X	
Merkel cells		X	
Epidermal appendages			

Prematurity – When Permeability Goes Rogue

- Infants <28 weeks gestation – transient inadequate maturation of epidermis
  - Dehydration
  - Increased penetration of topical drugs/chemical
  - Infection
- Even FT infants not perfect – takes 3 weeks
- Premature – accelerated maturation

BSA/Mass Ratio



ANNALS of THE NEW YORK ACADEMY OF SCIENCES

Susceptibility of Children to Environmental Pollutants

Peter D. Sly, Felicity Flack

First published: 23 October 2008 | https://doi.org/10.1196/annals.1454.017 | Cited by: 51

Address for correspondence: Peter D. Sly, Telethon Institute for Child Health Research, PO Box 855, West Perth 6872, Australia. Voice: +61 8 9489 7810; fax: +61 8 9489 7706. peters@ichr.uwa.edu.au

Hazard of percutaneous absorption infants & children

Compound	Product	Toxicity
Alcohols[124,125]	Skin antiseptic	Cutaneous hemorrhagic necrosis, elevated blood alcohol levels
Aniline[16]	Dye used as a laundry marker	Methemoglobinemia, death
Adhesive remover solvents[129]	Skin preparations to aid in adhesive removal	Epidermal injury, hemorrhage and necrosis
Benzocaine[142]	Mucosal anesthetic (teething products)	Methemoglobinemia
Boric acid[24]	Baby powder, diaper paste	Vomiting, diarrhea, erythroderma, seizures, death
Calcipotriol[143]	Topical vitamin D_3 analogue	Hypercalcemia, hypercalcemic crisis
Chlorhexidine[120]	Topical antiseptic	Systemic absorption but no systemic toxic effects; skin burns in preterm infants

Mathes & Williams Skin of Premature Infant
Neonatal & infantile Derm 2015 p. 40

Methylene blue[148]	Amniotic fluid leak	Methemoglobinemia
N,N-dimethyl-*m*-toluamide (DEET)[113]	Insect repellant	Neurotoxicity
Neomycin[108]	Topical antibiotic	Neural deafness
Phenolic compounds (pentachlorophenol, hexachlorophene, resorcinol)[19]	Laundry disinfectant, topical antiseptic	Neurotoxicity, tachycardia, metabolic acidosis, methemoglobinemia, death
Phenylephrine[13]	Ophthalmic drops	Vasoconstriction, periorbital pallor
Povidone–iodine[122]	Topical antiseptic	Hypothyroidism
Prilocaine[86]	Topical anesthetic	Methemoglobinemia
Salicylic acid[149]	Keratolytic emollient	Metabolic acidosis, salicylism
Silver sulfadiazine[137,139]	Topical antibiotic	Kernicterus (sulfa component), agranulocytosis, argyria (silver component)
Tacrolimus[150]	Topical immunomodulator	Elevated blood levels of immunosuppressive medication
Triple dye (brilliant green, gentian violet, proflavine hemisulfate)[71]	Topical antiseptic for umbilical cord	Ulceration of mucous membranes, skin necrosis, vomiting, diarrhea

Mathes & Williams Skin of Premature Infant
Neonatal & infantile Derm 2015 p. 40

Topical agents that should be used with caution in the newborn

Compound	Product	Concern
Ammonium lactate	Keratolytic emollient	Possible lactic acidosis
Benzethonium chloride	Skin cleansers	Poisoning by ingestion, carcinogenesis
Coal tar	Shampoos, anti-inflammatory ointments	Excessive use of polycyclic aromatic hydrocarbons are associated with an increased risk of cancer
Glycerin	Emollients, cleansing agents	Hyperosmolality, seizures
Propylene glycol	Emollients, cleansing agents	Excessive enteral and parenteral administration has caused hyperosmolality and seizures
Triclosan	Deodorant and antibacterial soaps	Toxicities seen with other phenolic products

Neonatal Skin Care & Toxicology, Danby S et al Neonatal & Infantile Derm 2015 p. 53

21 **Cetta F, Lambert GH, Ros SP**: Newborn chemical exposure from over-the-counter skin care products. *Clin Pediatr.* 30:286-289 1991

22 **McCormack JJ, Boisits EK, Fisher LB**: An in vitro comparison of the permeability of adult versus neonatal skin. **Maibach HI Boisits EK** *Neonatal skin structure and function.* 1982 Marcel Dekker New York 149-164

23 **Amato M, Huppi P, Isenschmid M, et al.**: Developmental aspects of percutaneous caffeine absorption in premature infants. *Am J Perinatol.* 9:431-434 1992 PMID: 1418150

24 **Barrett DA, Rutter N, Davis SS**: An in vitro study of diamorphine permeation through premature human neonatal skin. *Pharm Res.* 10:583-587 1993 PMID: 8483842

And what about those with impaired skin barriers?

This Issue | Citations 142

Observation FREE

June 2001

Significant Absorption of Topical Tacrolimus in 3 Patients With Netherton Syndrome

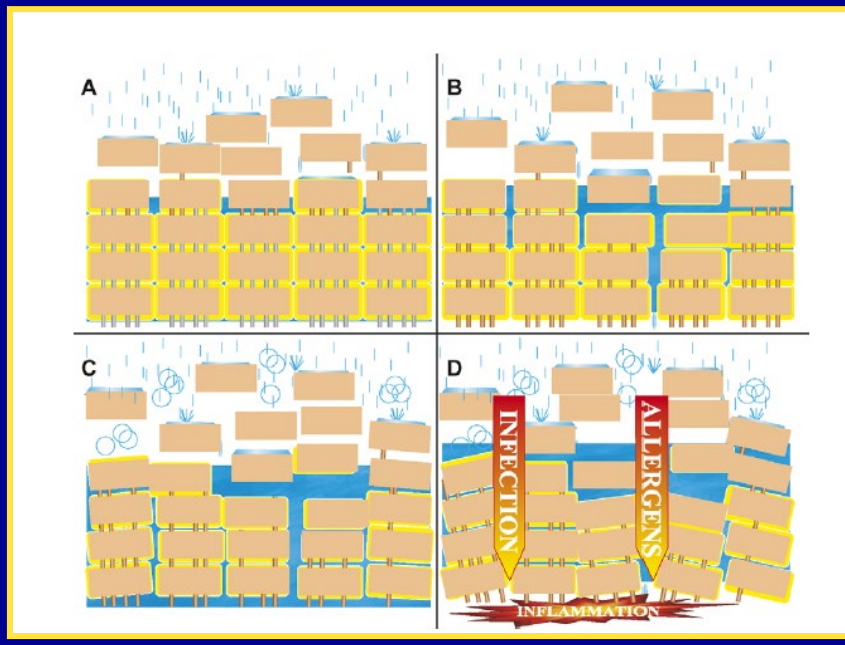
Angel Allen, MD; Elaine Siegfried, MD; Robert Silverman, MD; et al

» Author Affiliations | Article Information

Arch Dermatol. 2001;137(6):747-750. doi:10-1001/pubs.Arch Dermatol.-ISSN-0003-987x-137-6-dob10000

High risk groups to worry about re permeability

- Extreme preemies
- Preemies
- Impaired barrier
  - Nethertons, Ichthyosis, Atopic Dermatitis
- ? Anyone with inflamed skin?



Review

Skin Pharmacology and Physiology

Skin Pharmacol Physiol 2010;23:171–176
DOI: 10.1159/000288163

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Enhanced Absorption through Damaged Skin: An Overview of the in vitro Human Model

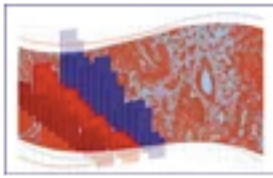
S. Gattu[a] H.I. Maibach[b]

[a]Irvine School of Medicine and [b]Department of Dermatology, University of California, San Francisco, Calif., USA

e 1. Penetration enhancement through tape-stripped/abraded skin

hod	Penetrant	MW	log K_{oct}	EF	Measured	Author
e stripped	caffeine	194	−0.07	19	flux	Akomeah et al. [16]
	methyl paraben	152	1.96	5.00	flux	
	angiotensin II	1,046	−1.7	25–69	flux	
	butyl paraben	194	3.6	3.00	flux	
	tritiated water	22	1.38	21.00	% dose absorbed	Bronaugh and Stewart [2
asion	caffeine	194	−0.07	64.00	flux	Akomeah et al. [16]
	methyl paraben	152	1.96	6.00	flux	
	angiotensin II	1,046	−1.7	57–93	flux	
	butyl paraben	194	3.57	3.00	flux	
	acyclovir	225	−1.56	36–220	flux	
	caffeine	194	0	1.60	% dose absorbed	Bronaugh and Stewart [2
	tritiated water	22	1.38	12.50	% dose absorbed	
	benzoic acid	122	1.9	2.10	% dose absorbed	
	cortisone	360	1.6	3.90	% dose absorbed	
	nicotinic acid	123	−0.2	11.50	% dose absorbed	
	phenol	92	1.482	1.70	% dose absorbed	
	propylene glycol	76	−1.7	5.30	% dose absorbed	
	urea	60	−2.6	7.10	% dose absorbed	

Enhancement in percutaneous penetration is more pronounced in hydrophilic compounds with low log K_{oct} values compared
philic compounds with high log K_{oct} values. MW = Molecular weight.



Journal of Applied Toxicology

Review Article | Full Access

Percutaneous absorption in diseased skin: an overview

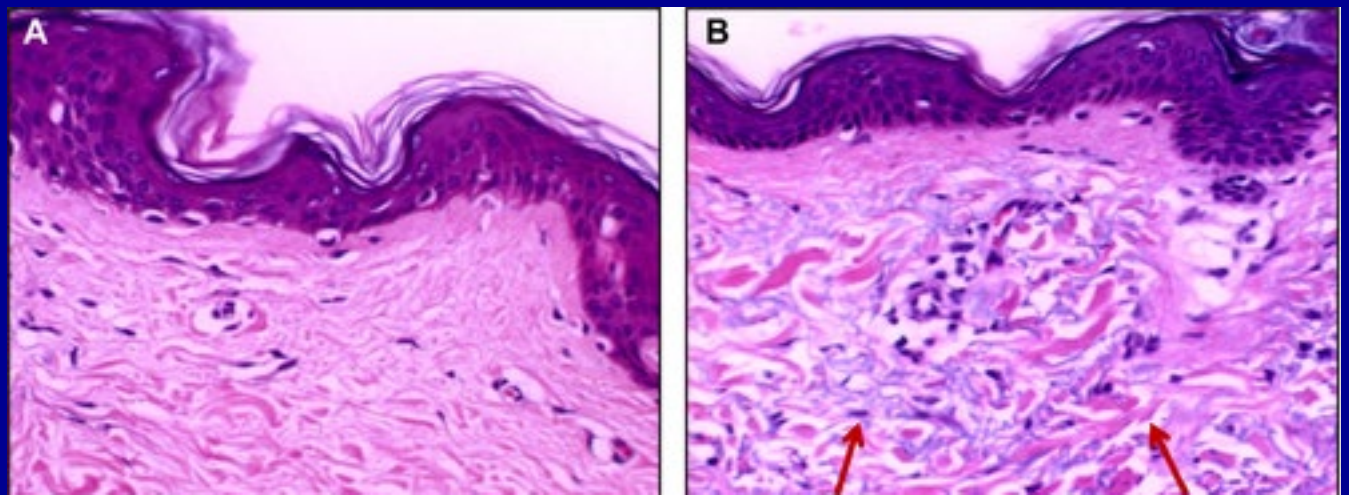
Audris Chiang ✉, Emilie Tudela, Howard I. Maibach

First published: 10 January 2012 | https://doi.org/10.1002/jat.1773 | Citations: 41

- Human studies show increased penetration in psoriatic and atopic dermatitis skin
- Hydrophilicity, hydrophobicity can impact absorption

And what about aging skin?

- Dermal & SC atrophy
- Heterogen keratinocytes
- DEJ flattening,
- Alteration of immune cells
- Elastic fiber abnormalities



Absorption concerns in high-risk groups Summary

- The proper, sequential & complete maturation of the epidermis is crucial for appropriate barrier protection
- Those at risk for enhanced penetration include
  - Preemies, term newborns, infants
  - Those with impaired barriers
    - Atopic derm
    - Psoriatics
    - Disorders of keratinization
    - Damaged & elderly skin?