### Maturation of the Skin

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## Conflicts

Ad hoc Task Force on Sunscreen Use American Academy of Dermatology

### Determinants of Topical Bioavailability



It is the complex interaction of drug substance, formulationdosage 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.





JAMA | Preliminary Communication

#### Effect of Sunscreen Application Under Maximal Use Conditions on Plasma Concentration of Sunscreen Active Ingredients A Randomized Clinical Trial

Murali K. Matta, PhD; Robbert Zusterzeel, MD, PhD, MPH; Nageswara R. Pilli, PhD; Vikram Patel, PhD; Donna A. Volpe, PhD; Jeffry Florian, PhD; Luke Oh, PhD; Edward Bashaw, PharmD; Issam Zineh, PharmD, MPH; Carlos Sanabria, MD; Sarah Kemp, RN; Anthony Godfrey, PharmD; Steven Adah, PhD; Sergio Coelho, PhD; Jian Wang, PhD; Lesley-Anne Furlong, MD; Charles Ganley, MD; Theresa Michele, MD; David G. Strauss, MD, PhD

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ClinicalTrials.gov Identifier: NCT03582215

# Dr. Bashaw Mandate/Request

"Maturation of the skin, and how it changes as we age"
 – Sun exposure not withstanding

"Any other element I wish to discuss"



- Function of the skin
- Maturation of the skin
  - Embryology
  - Aging
- Skin dysfunction at-risk populations
  - Preemies, infants
  - -AD
  - Elderly, photoaged
- "Other points of importance"
  - Risks of UVR
  - Sunscreens what we do & don't know

## References

#### Henry Lim



#### Neonatal and Infant Dermatology



## 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





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Ectoderm basal cell 🙅 Peridermal cell Intermediate cell



Granular cell Cornified cell









#### 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





# 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 what lies beneath...



# And deeper yet..The Dermis

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







FIGURE 1.6 🕑 Architecture of normal human skin at birth. (A) Schematic representati...

# Skin maturation – when it goes 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

# But what if the "most special delivery" arrives early?



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

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

# **Embryogenesis of the Skin**



The epidermis appears EGA day 18-20!

STRUCTURE	ADULT	TERM	PRETERM
Epidermal thickness	50 mm	50 mm	27.4 mm
Stratum corneum thickness	15 cell	15 cell	Few cells
	9.3 mm	9.3 mm	4.1 mm
Density of keratin filaments	Normal	Normal	Smaller bundles
Frequency of desmosomes	Normal	Normal	Fewer
Melanosomes	Normal	Fewer	One-third of term infant
Dermal–epidermal junction	Ridged	Flat but complete	Flat but complete
Anchoring filaments	Normal	Normal	Fewer and smaller
Anchoring fibrils	Normal	Normal	Fewer and smaller
Hemidesmosomes	Normal	Normal	Fewer and smaller
Papillary dermal collagen	Normal	Normal	Edematous, loosely organized

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



#### **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

Compound	Product	Toxicity
Alcohols <sup>124,125</sup>	Skin antiseptic	Cutaneous hemorrhagic necrosis, elevated blood alcohol levels
Aniline <sup>16</sup>	Dye used as a laundry marker	Methemoglobinemia, death
Adhesive remover solvents <sup>129</sup>	Skin preparations to aid in adhesive removal	Epidermal injury, hemorrhage and necrosis
Benzocaine <sup>142</sup>	Mucosal anesthetic (teething products)	Methemoglobinemia
Boric acid <sup>24</sup>	Baby powder, diaper paste	Vomiting, diarrhea, erythroderma, seizures, death
Calcipotriol <sup>143</sup>	Topical vitamin D <sub>3</sub> analogue	Hypercalcemia, hypercalcemic crisis
Chlorhexidine <sup>120</sup>	Topical antiseptic	Systemic absorption but no systemic toxic effects; skin burns in preterm infants

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

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

- 21 Cetta F, Lambert GH, Ros SP: Newborn chemical exposure from overthe-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



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?



## And what about aging skin?



- Dermal & SC atrophy
- heterogeneous keratinocytes
- DEJ flattening, alteration of immune cells
- Elastic fiber abnormalities





## Effects of UVR on the skin





Changes in elastic fibre organization with skin photoageing. (A) Skin from a region that has not been exposed to solar radiation. (B) Skin from a region exposed to solar radiation. The skin fragments were obtained from participants in the same age group (45–50 years). Disorganization of the elastic fibres (arrows) with fragmented material and accumulation characteristic of solar elastosis are observed in the skin exposed to solar radiation. Haematoxylin–eosin staining. Magnification 20×.

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#### A concerning theoretical risk

#### A theoretical risk to our reefs...and planet



# A known, REAL risk of sun exposure with often devastating consequences

## Let's get down to it

Safety of Oxybenzone (Schneider, S, Lim, HW. JAAD 2019 Jan;80(1):266. Detroit)

- Photoallergen
- Endocrinologic effects and adverse effects on coral reefs: only in animal model and in laboratory settings, respectively

### Oxybenzone

(Schneider, S, Lim, HW. JAAD 2019 Jan;80(1):266. Epub 2018 Nov 14)

- Endocrinologic effects in rat model
- No known safety issues in humans (has been in us in the US since 1978)
- Oxybenzone kills adult coral reefs, and deforms DNA in the larval stage (in laboratory settings)
- Detected in fish (low concentration)

### UV Filters in Water and Coral in Hawaii

(Mitchelmore, CL, et al. Sci Total Environ 2019 June; 670:398. Maryland, USA)



Range of Mean Surface Seawat Concentrations at 19 sites, Oah HI (parts per trillion): BP-3 = 0.1 to 136.2 ng L<sup>-1</sup> EHMC (octinoxate) = not detecte OC = < LOD to 26.9 ng L<sup>-1</sup> OS = 33.1 to 96.0 ng L<sup>-1</sup> HMS = 53.0 to 444.9 ng L<sup>-1</sup>

Lethal concentration-50 for coral cells in vitro: 8-340 parts per billion (Downs, CA, et al. Arch Environ Contam Toxicol 2016; 70:265)



**TiO<sub>2</sub> and ZnO Nanoparticles** 

(Schneider, S, Lim, HW. Photodermatol Photoimmunol Photomed 2018 Nov 18. Epub Mohammed, YH, et al. JID 2019 (Feb); 139:308. Australia)

- No evidence of clinically relevant percutaneous penetration; no side effects in human
- Not sufficient data on inflamed skin where epidermal barrier function has been compromised.
- Environmental adverse effects: very low

#### Efficacy of Filters (5% in the Same Vehicle)



**Courtesy of La Roche-Posay** 

#### **Sunscreens: Photoaging and Skin Cancer**

(Hughes, MCB.... Green, AC. Ann Intern Med 6/13; 158:781 Brisbane, Australia; Green, A., Lancet 1999; 354:723. van der Pols, JC,.... Green, A. Cancer Epidemiol Biomarkers Prev 12/2006; 15:2546. Brisbane, Australia)

- A 4.5 yr + 8 yr f/u study of 1621 residents of Nambour, Queensland, randomly assigned to daily SPF16 broad spectrum sunscreen group, vs. control
- Sunscreen group had decreased
  - SCC
  - BCC
  - Photoaging



#### Sunscreens and NMSC

(Green, A., Lancet 1999; 354:723. van der Pols, JC,.... Green, A. Cancer Epidemiol Biomarkers Prev 12/2006; 15:2546. Brisbane, Australia)

- A 4.5 yr + 8 yr f/u study of 1621 residents of Nambour, Queensland, randomly assigned to daily SPF16 broad spectrum sunscreen group, vs. control.
- SCC incidence rates: significantly decreased by 38%
- BCC incidence rates: decreased by 25%, but not significantly



### Sunscreen Use & the Development of New Nevi in White Children

#### Randomized trial on the use of sunscreen as a preventive agent for reducing moles in children

- 458 1<sup>st</sup>- 4<sup>th</sup> graders in Canada followed over 3 years; half given counseling & sunscreen
- Sunscreen group developed significantly fewer moles (24 vs. 28)
- Effect most marked in freckled children (~35% fewer moles with sunscreen use)
   Subsequent study showed fewer nevi on trunk in rx'd group

Gallagher RP et al JAMA 2000;283:2955-2960; Lee TK et al JAAD 2005;52:786



### Sunscreen Does Protect Against Skin Cancers Including M.M.



- Original trial conducted in Australia
- 1621 white pts 25-75 years
- Initial study-5 years of sunscreen application
- F/U study MM incidence 1992-2006
  - 22 comparison control
    11 sunscreen group
  - Thickness 1.2 mm 0.53 mm

Green AC et al J. Clin Oncology 2010.28.7078

#### Sunscreen Usage and Melanoma Risk All Melanomas



Discretionary Daily

#### Sunscreen Usage and Melanoma Risk Invasive MMs



■ Discretionary ■ Daily

# Any problems with the study?



- P values borderline significance
- But...hazard ratios
  - 50% reduction for all melanomas
  - 73% reduction in hazard related to invasive melanoma alone
  - Melanoma may be prevented by sunscreen use

Editorial J Clin Oncol 2010 2010.31.7529

# Variability in patient population studied....



# Do patients know how much to use?

- 2mg/cm<sup>2</sup>
- Is that supposed to help?
- Adults easy 1 ounce –
- Kids harder



## **Desperation move**





**Rowan Jacobsen** 

Jan 10, 2019

## Is Sunscreen the New Margarine?

**Outside online** 

# Standard common sense approach

- Sun protection is the rule
- Avoidance & Physical protection
  - Hats
  - Glasses
  - Clothing
  - Umbrellas
- Sunscreen second line



# Skin maturation Summary

- The proper, sequential & complete maturation of the epidermis is crucial for appropriate barrier protection
- Preemies, & those with impaired barriers are at risk for increased absorption of H20 & noxious agents
- Melanoma is a horrible cancer related to UVR exposure
- Sunscreen is an important component of sun protection