Maturation of the Skin

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UCSD & Rady Children’s Hospital
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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, 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.
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

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”
Overview

• 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
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.....

Diagram showing the development of the neural plate, neural fold, and neural tube.
Periderm – protects the basal epidermal layer
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
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 representation...
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?
<table>
<thead>
<tr>
<th></th>
<th>EMBRYONIC</th>
<th>EARLY FETAL</th>
<th>LATE FETAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Periderm</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shedding of periderm</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Epidermis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal layer</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Intermediate layer</td>
<td>X</td>
<td></td>
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<tr>
<td>Granular layer</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cornified layer</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Cell junctions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Desmosomes</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tight junctions</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Hemidesmosomes</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Appearance of specialized non-keratinocyte cells</td>
<td></td>
<td></td>
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<tr>
<td>Langerhans cells</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Melanocytes</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Merkel cells</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Epidermal appendages</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Embryogenesis of the Skin

The epidermis appears EGA day 18-20!
<table>
<thead>
<tr>
<th>STRUCTURE</th>
<th>ADULT</th>
<th>TERM</th>
<th>PRETERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal thickness</td>
<td>50 mm</td>
<td>50 mm</td>
<td>27.4 mm</td>
</tr>
<tr>
<td>Stratum corneum thickness</td>
<td>15 cell</td>
<td>15 cell</td>
<td>Few cells</td>
</tr>
<tr>
<td>Density of keratin filaments</td>
<td>9.3 mm</td>
<td>9.3 mm</td>
<td>4.1 mm</td>
</tr>
<tr>
<td>Frequency of desmosomes</td>
<td>Normal</td>
<td>Normal</td>
<td>Fewer</td>
</tr>
<tr>
<td>Melanosomes</td>
<td>Normal</td>
<td>Fewer</td>
<td>One-third of term infant</td>
</tr>
<tr>
<td>Dermal–epidermal junction</td>
<td>Ridged</td>
<td>Flat but complete</td>
<td>Flat but complete</td>
</tr>
<tr>
<td>Anchoring filaments</td>
<td>Normal</td>
<td>Normal</td>
<td>Fewer and smaller</td>
</tr>
<tr>
<td>Anchoring fibrils</td>
<td>Normal</td>
<td>Normal</td>
<td>Fewer and smaller</td>
</tr>
<tr>
<td>Hemidesmosomes</td>
<td>Normal</td>
<td>Normal</td>
<td>Fewer and smaller</td>
</tr>
<tr>
<td>Papillary dermal collagen</td>
<td>Normal</td>
<td>Normal</td>
<td>Edematous, loosely organized</td>
</tr>
</tbody>
</table>
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
<table>
<thead>
<tr>
<th>Compound</th>
<th>Product</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohols $^{124,125}$</td>
<td>Skin antiseptic</td>
<td>Cutaneous hemorrhagic necrosis, elevated blood alcohol levels</td>
</tr>
<tr>
<td>Aniline $^{16}$</td>
<td>Dye used as a laundry marker</td>
<td>Methemoglobinemia, death</td>
</tr>
<tr>
<td>Adhesive remover solvents $^{129}$</td>
<td>Skin preparations to aid in adhesive removal</td>
<td>Epidermal injury, hemorrhage and necrosis</td>
</tr>
<tr>
<td>Benzocaine $^{142}$</td>
<td>Mucosal anesthetic (teething products)</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>Boric acid $^{24}$</td>
<td>Baby powder, diaper paste</td>
<td>Vomiting, diarrhea, erythoderma, seizures, death</td>
</tr>
<tr>
<td>Calcipotriol $^{143}$</td>
<td>Topical vitamin D$_3$ analogue</td>
<td>Hypercalcemia, hypercalcemic crisis</td>
</tr>
<tr>
<td>Chlorhexidine $^{120}$</td>
<td>Topical antiseptic</td>
<td>Systemic absorption but no systemic toxic effects; skin burns in preterm infants</td>
</tr>
<tr>
<td>Substance</td>
<td>Use</td>
<td>Adverse Effects</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Methylene blue</td>
<td>Amniotic fluid leak</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>$N,N$-dimethyl-$m$-toluamide (DEET)</td>
<td>Insect repellant</td>
<td>Neurotoxicity</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Topical antibiotic</td>
<td>Neural deafness</td>
</tr>
<tr>
<td>Phenolic compounds (pentachlorophenol, hexachlorophene, resorcinol)</td>
<td>Laundry disinfectant, topical antiseptic</td>
<td>Neurotoxicity, tachycardia, metabolic acidosis, methemoglobinemia, death</td>
</tr>
<tr>
<td>Phenylephrine</td>
<td>Ophthalmic drops</td>
<td>Vasoconstriction, periorbital pallor</td>
</tr>
<tr>
<td>Povidone–iodine</td>
<td>Topical antiseptic</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Topical anesthetic</td>
<td>Methemoglobinemia</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Keratolytic emollient</td>
<td>Metabolic acidosis, salicylism</td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>Topical antibiotic</td>
<td>Kernicterus (sulfur component), agranulocytosis, argyria (silver component)</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Topical immunomodulator</td>
<td>Elevated blood levels of immunosuppressive medication</td>
</tr>
<tr>
<td>Triple dye (brilliant green, gentian violet, proflavine hemisulfate)</td>
<td>Topical antiseptic for umbilical cord</td>
<td>Ulceration of mucous membranes, skin necrosis, vomiting, diarrhea</td>
</tr>
<tr>
<td>Compound</td>
<td>Product</td>
<td>Concern</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Ammonium lactate</td>
<td>Keratolytic emollient</td>
<td>Possible lactic acidosis</td>
</tr>
<tr>
<td>Benzethonium chloride</td>
<td>Skin cleansers</td>
<td>Poisoning by ingestion, carcinogenesis</td>
</tr>
<tr>
<td>Coal tar</td>
<td>Shampoos, anti-inflammatory ointments</td>
<td>Excessive use of polycyclic aromatic hydrocarbons are associated with an increased risk of cancer</td>
</tr>
<tr>
<td>Glycerin</td>
<td>Emollients, cleansing agents</td>
<td>Hyperosmolality, seizures</td>
</tr>
<tr>
<td>Propylene glycol</td>
<td>Emollients, cleansing agents</td>
<td>Excessive enteral and parenteral administration has caused hyperosmolality and seizures</td>
</tr>
<tr>
<td>Triclosan</td>
<td>Deodorant and antibacterial soaps</td>
<td>Toxicities seen with other phenolic products</td>
</tr>
</tbody>
</table>


And what about those with impaired skin barriers?
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

UV radiation

Absorption by photoreceptors in skin

Release of immune mediators in skin

Changes in antigen presenting cells

Generation of T-regulatory cells

Immunosuppression

UV radiation

DNA damage trans to cisurocanic acid
membrane changes

Release of platelet activating factor, prostaglandins, cytokines (e.g. TNF-α, IL-10), neuropeptides and neuroendocrine hormone

LOCAL

DNA damage and changes in Langerhans cell numbers and function

Loss of IL-12 and Th1 cytokines induction of T regulatory cells, secreting IL-10 epidermal influx of macrophages

SYSTEMIC

Changes in dendritic cells

Loss of IL-12 stimulation of IL-10 induction of NK-cell secreting IL-10
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×.
“Any other element I wish to discuss”

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

Courtesy Henry Lim
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


Range of Mean Surface Seawater Concentrations at 19 sites, Oahu, HI (parts per trillion):

- BP-3 = 0.1 to 136.2 ng L⁻¹
- EHMC (octinoxate) = not detected
- OC = < LOD to 26.9 ng L⁻¹
- OS = 33.1 to 96.0 ng L⁻¹
- HMS = 53.0 to 444.9 ng L⁻¹

Coral collections from shallow waters or deeper waters

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$_2$ 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

Courtesy Henry Lim MD
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.

- 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

Courtesy Henry Lim MD
Sunscreens and NMSC


- 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 1st-4th 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

Relative Risk

- Red: Discretionary
- Blue: Daily

1

0.5
Sunscreen Usage and Melanoma Risk

Invasive MMs

Relative Risk

- Discretionary
- Daily

Risk: 1
Risk: 0.27
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/cm²
- Is that supposed to help?
- Adults – easy 1 ounce –
- Kids - harder
Desperation move
Is Sunscreen the New Margarine?
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 H2O & noxious agents.
• Melanoma is a horrible cancer related to UVR exposure.
• Sunscreen is an important component of sun protection.