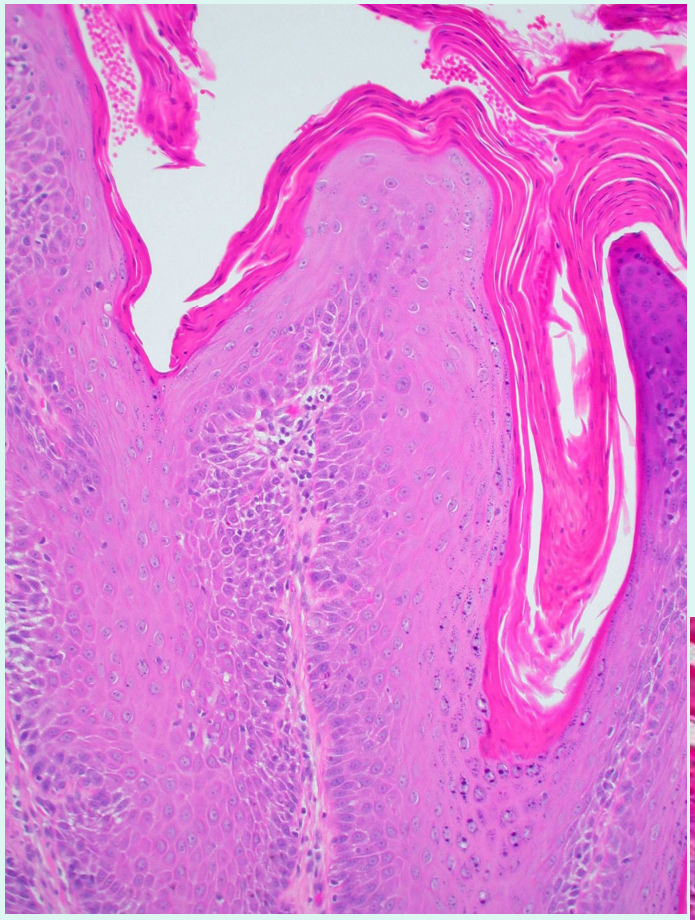
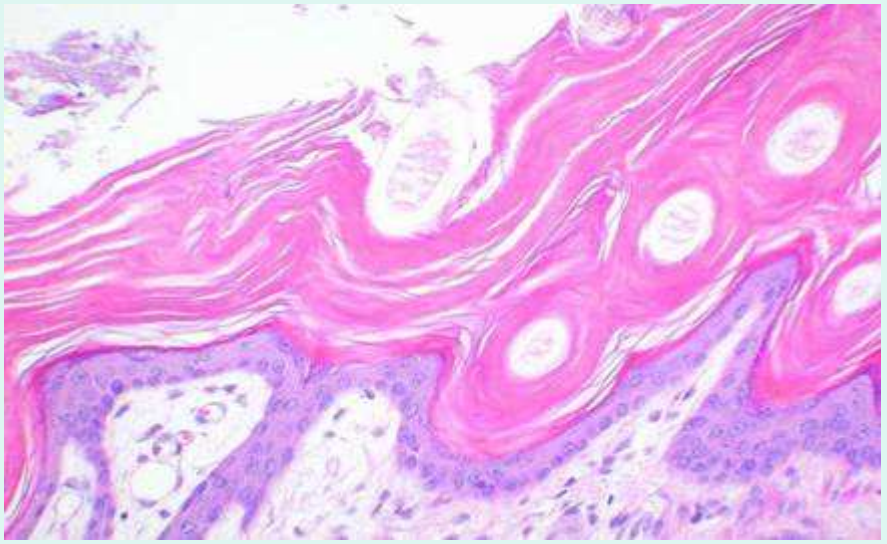
Pathologic changes associated with the stratum corneum

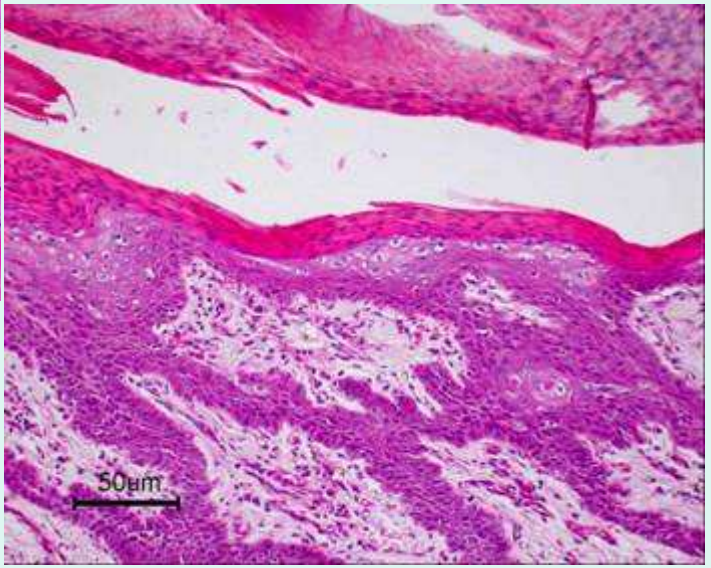
EA Mauldin
Laboratory of Pathology and Toxicology
School of Veterinary Medicine
University of Pennsylvania



Zinc-responsive



GR Ichthyosis



NME


Normal Stratum Corneum

Evolving Stratum Corneum Concepts

1. Unimportant, desquamation (up to 1960)
2. Tough, impermeable “plastic wrap” (up to 1975)
3. Structural/biochemical “mortar and bricks” (current)
4. Persistent metabolic activity “living” (current)
5. Interactive with underlying tissue (current)
    - Metabolic responses
    - Signaling cascades
    - Biosensor

Interface with the ambient environment

Protective Functions

- Integrity and resilience
- Inhibit contact with noxious substances, xenobiotics and allergens
- Antimicrobial defense
- Prevent water loss
- UV protection

Evolving Concepts…….

Stratum Corneal abnormalities →

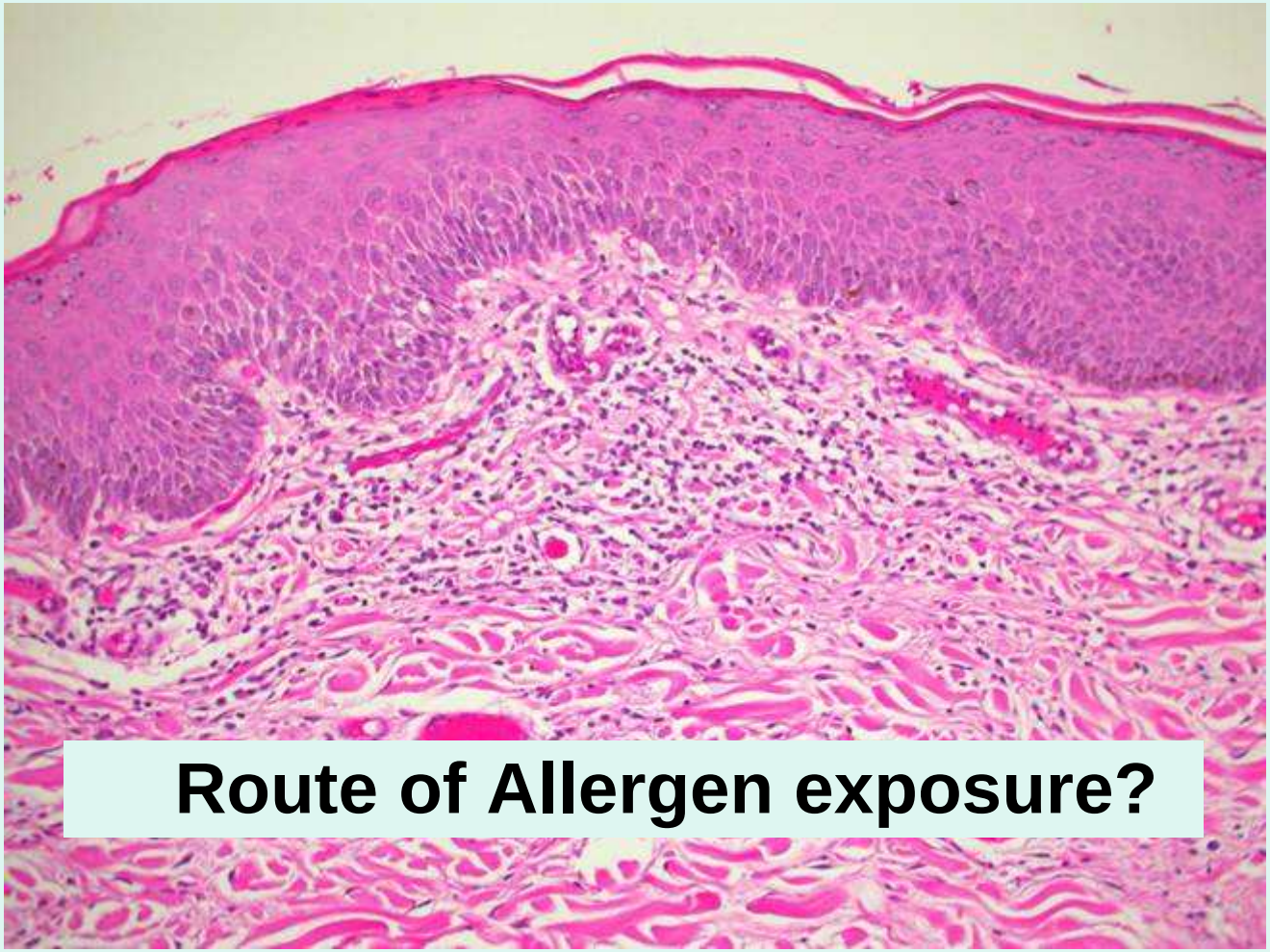
altered barrier function

→Loss of integrity/elasticity

→Water loss

→Inflammation

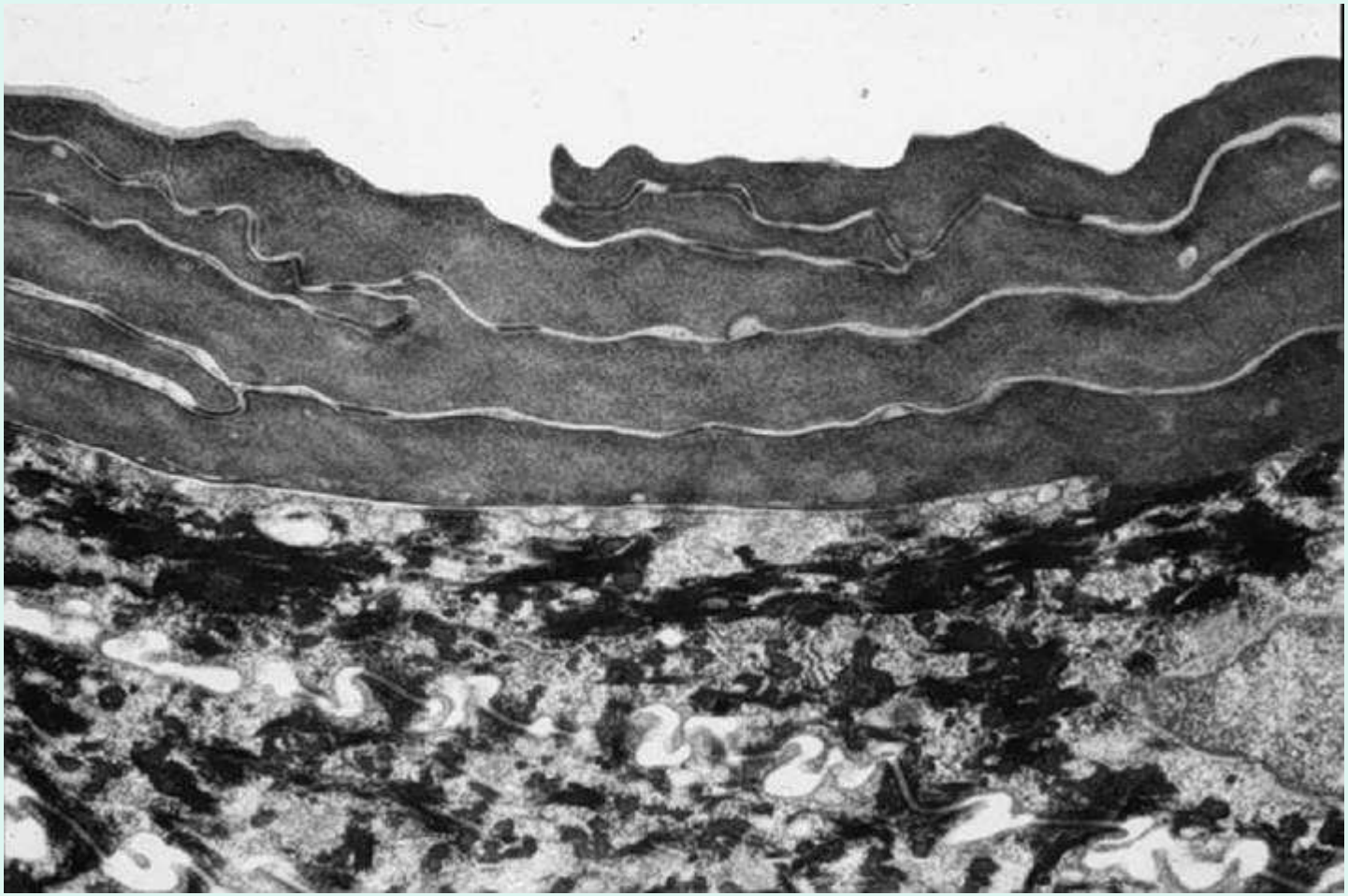
→Pathogen entry


Route of Allergen exposure?

Evolving Concepts…….

- Could a genetically impaired skin barrier lead to systemic sensitization to allergens through the skin?

- Could skin barrier dysfunction contribute to the rapid increase in atopy and allergic asthma in the past three decades?



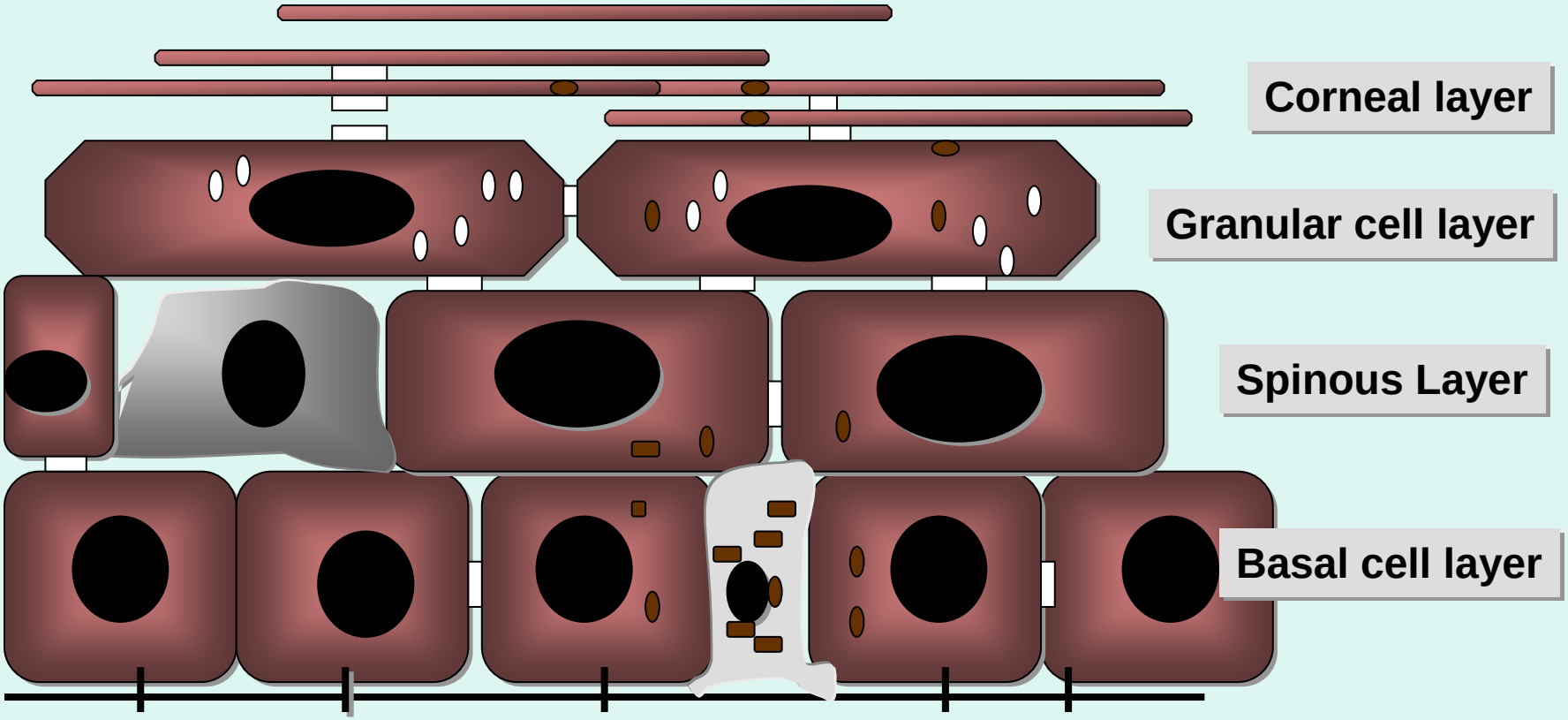
Corneal Function: Restrict water movement

- Lipid content
- Injury → “leaky” → water loss→ xerosis
- Xerosis typical of AD in humans
  - Conflicting studies in dogs

Corneal Function: Antimicrobial

- Continuous desquamation
- Antimicrobial peptides
- pH
  - Hydrolases
  - Urocanic acid
  - Phospholipids→ free fatty acids
- pH in dogs

Cornification



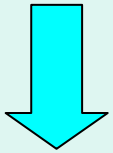
Steps in Cornification

Lipid formation

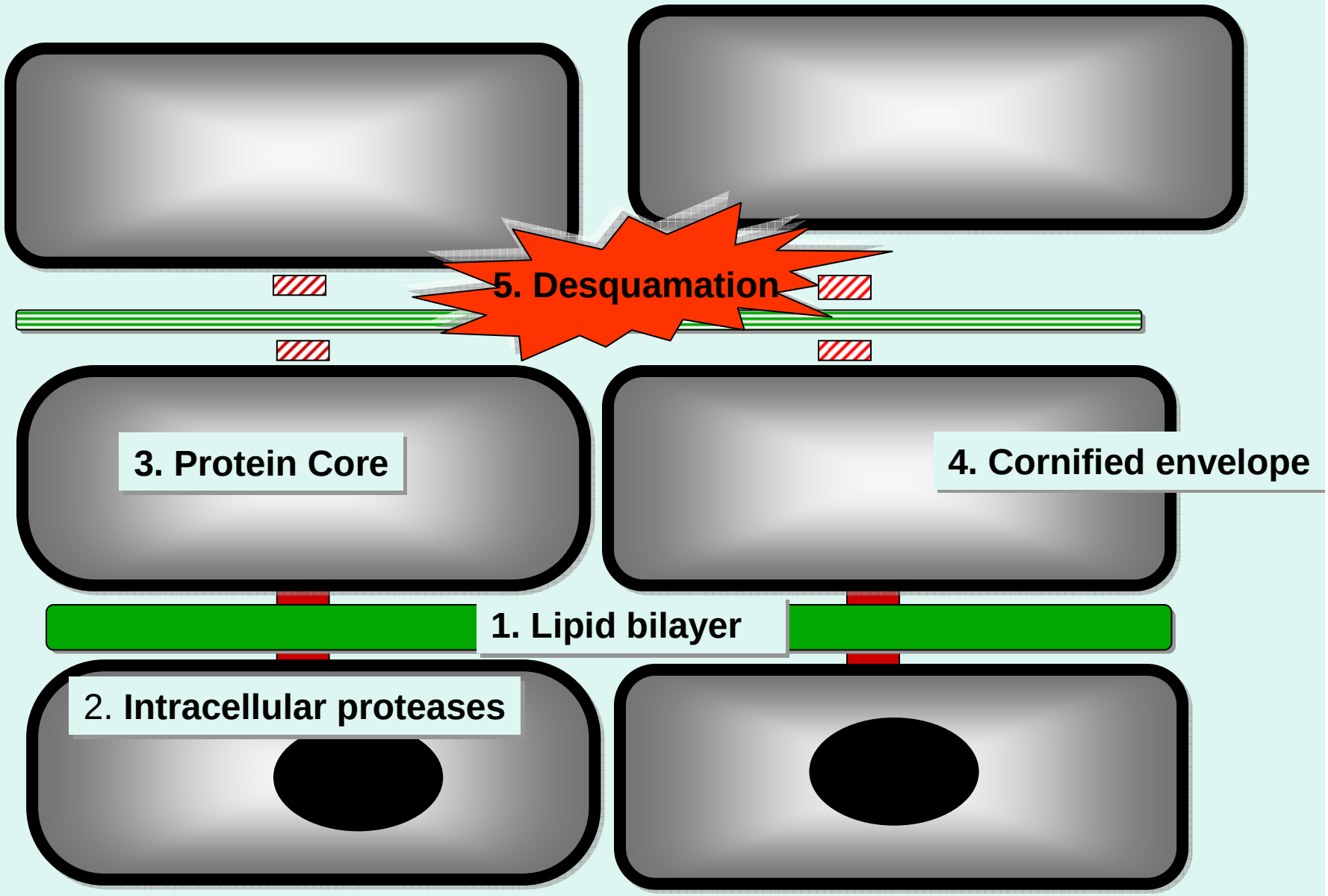
Dissolution of nucleus and organelles

Aggregation of intermediate filaments

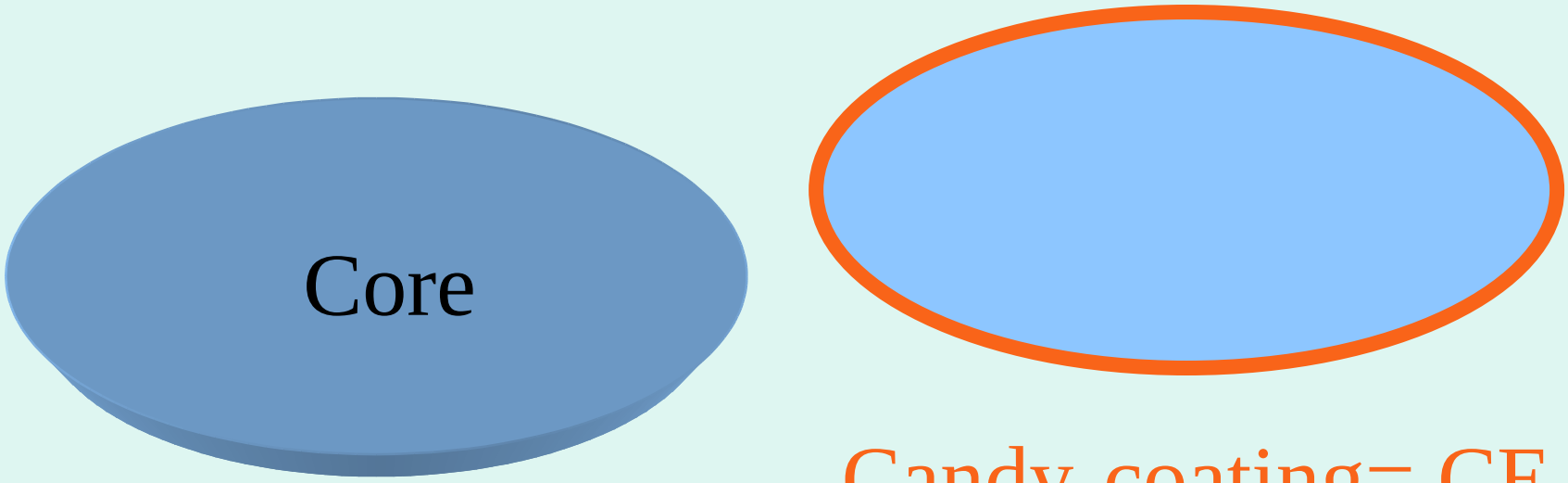
Formation of the cornified envelope



Desquamation


5. Desquamation
3. Protein Core
4. Cornified envelope
1. Lipid bilayer
2. Intracellular proteases

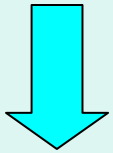
Mentos Model of Cornification



Candy-coating= CE

Steps in Cornification

1. Lipid formation
2. Dissolution of nucleus and organelles
3. Aggregation of intermediate filaments
4. Formation of the cornified envelope



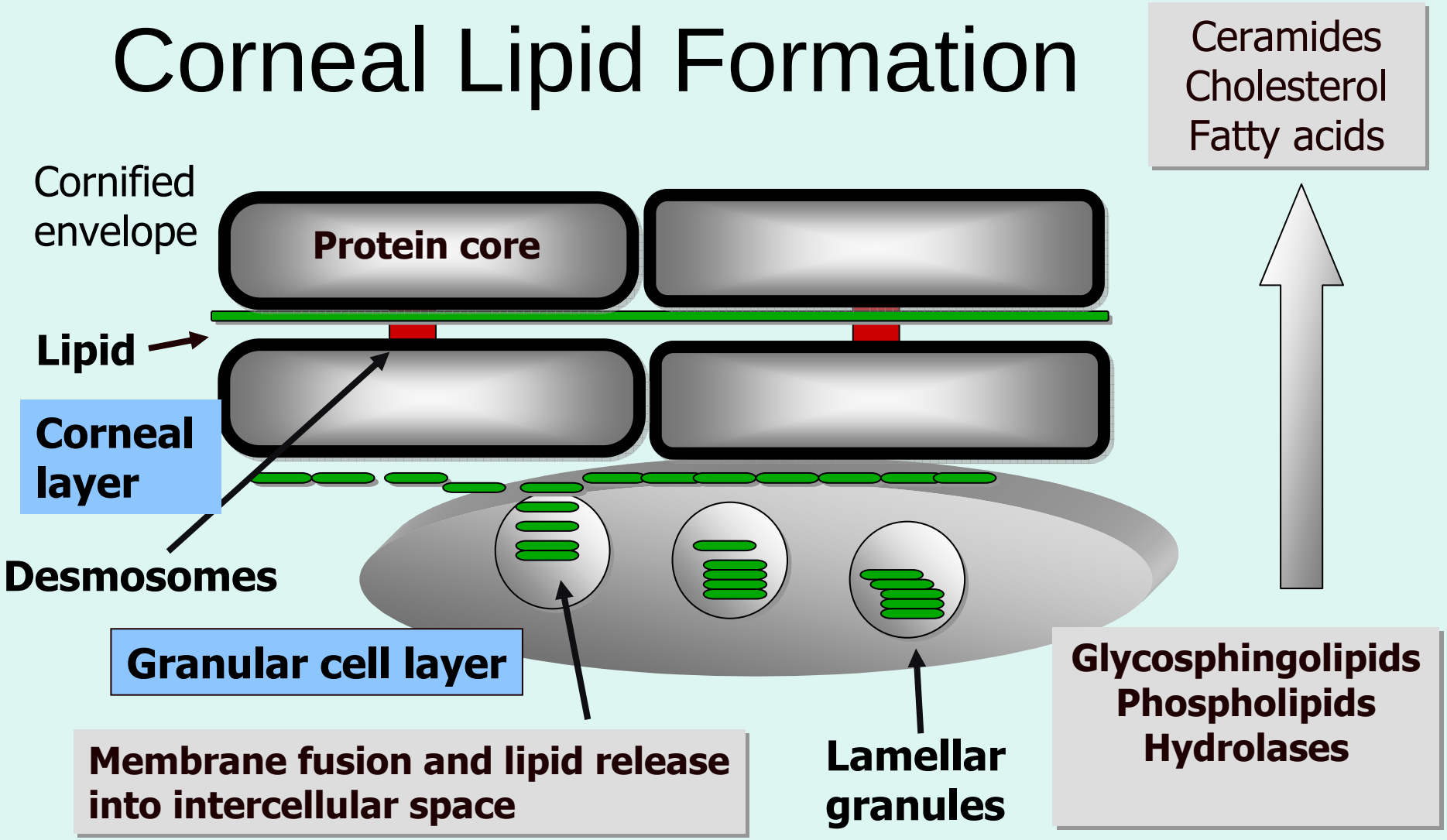
5. Desquamation

1. Lipid Formation

Lamellar bodies

- Ellipsoidal organelles- similar to lysozymes
- Form in basal cell layer
- Most concentrated in SG
- Fuse with cell membrane at SG/SC junction
- Supply lipids and enzymes to SC

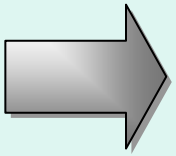
Corneal Lipid Formation



Fitzpatrick TB, Eisen AZ, Wolf K. et. al. Dermatology in General Medicine, 4th ed. 1993, Vol 1.

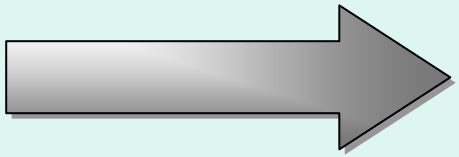
Lamellar Granule Content

Glycosylceramides→ Ceramides
Sphingomyelin→ Ceramides
Phospholipids→ FFA
Cholesterol→



- **Cohesion**
- **Hydration**
- **Antimicrobial action**
- **Chemical defense**

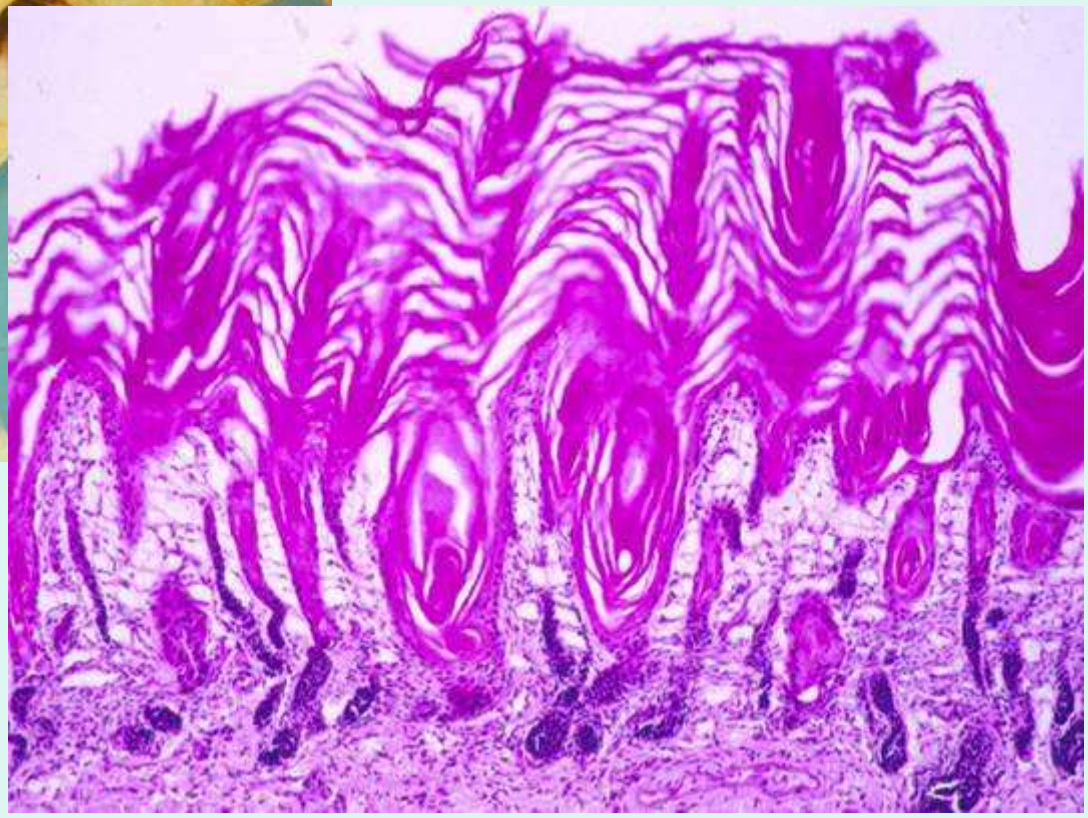
Proteases, lipases, acid phosphatase, glycosidases



Decreased in AD

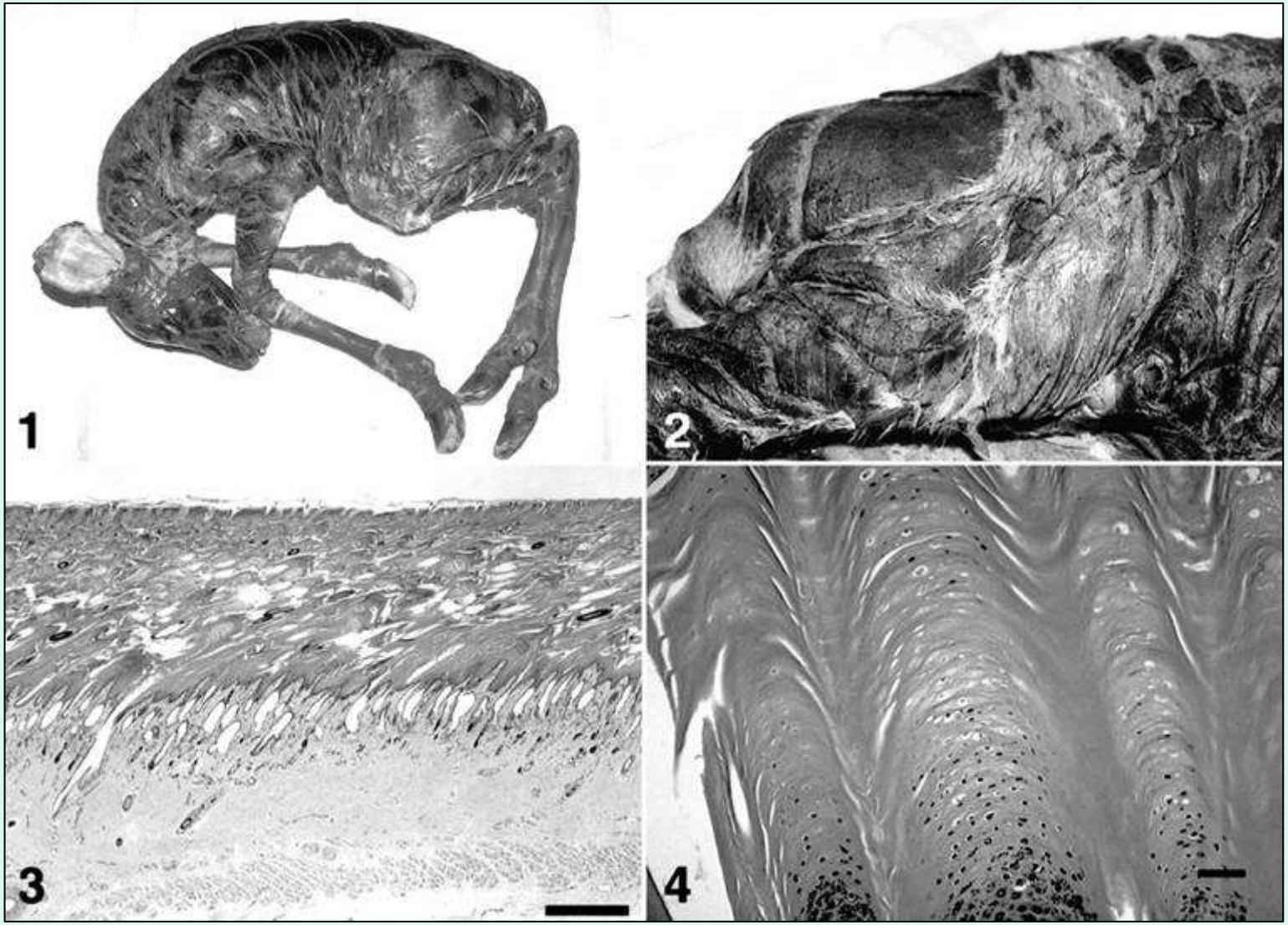
Defects in Lipid Formation

- Harlequin ichthyosis
- Atopic dermatitis?
  - Decreased ceramide
  - Defective lamellar body extrusion
  - Defects in enzymes that modify lipids
  - Abnormal lipid in dogs?



Harlequin ichthyosis

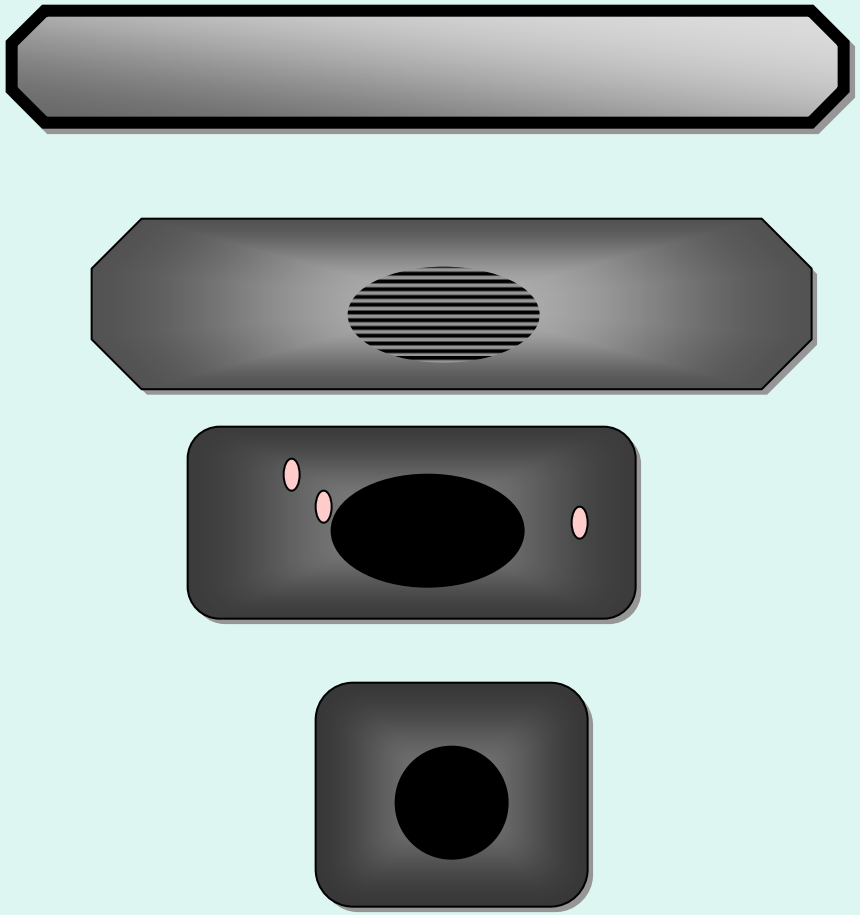
Courtesy of R. Dunstan

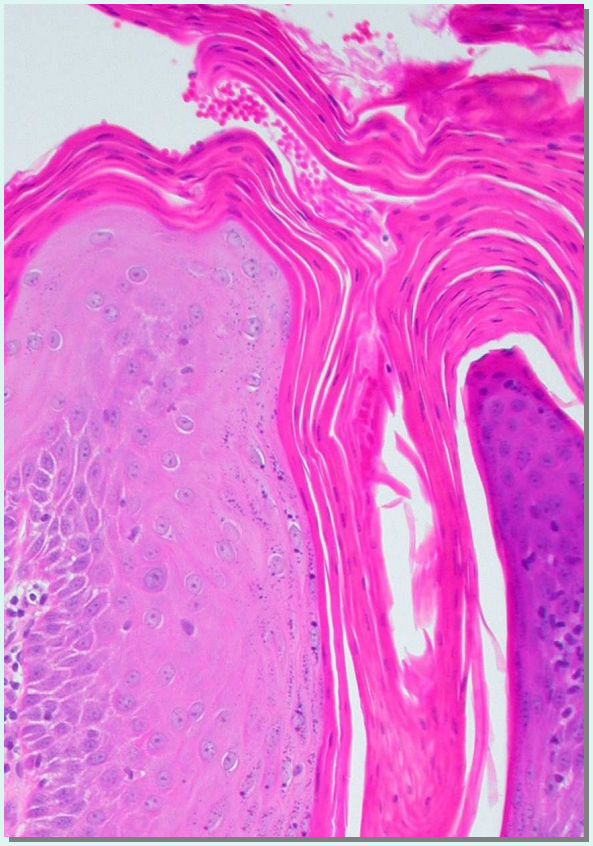


HI in Greater Kudu calves

Chittick, *Vet Pathol*. 2002

2. Release of Proteases





Retained nuclei- parakeratosis

3. Aggregation of keratin filaments

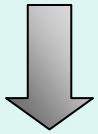
Keratohyalin granules

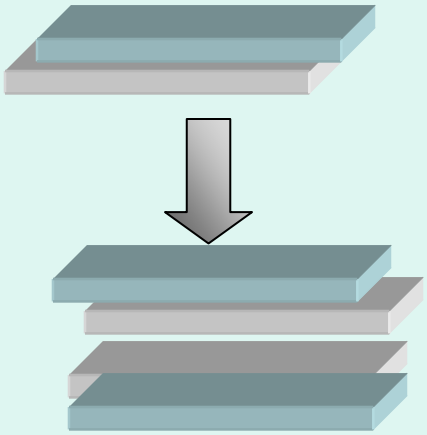
- Profilaggrin → Filaggrin
  - Aggregates keratin intermediate filaments
  - Forms the protein core
- Filaggrin→ histadine→ Urocanic acid
    - Contribute to pH
    - UV function

Keratins

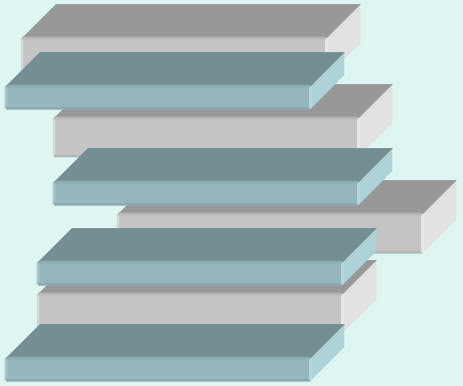
Type 1 acidic K10-K20

Type 2 basic K1-K9





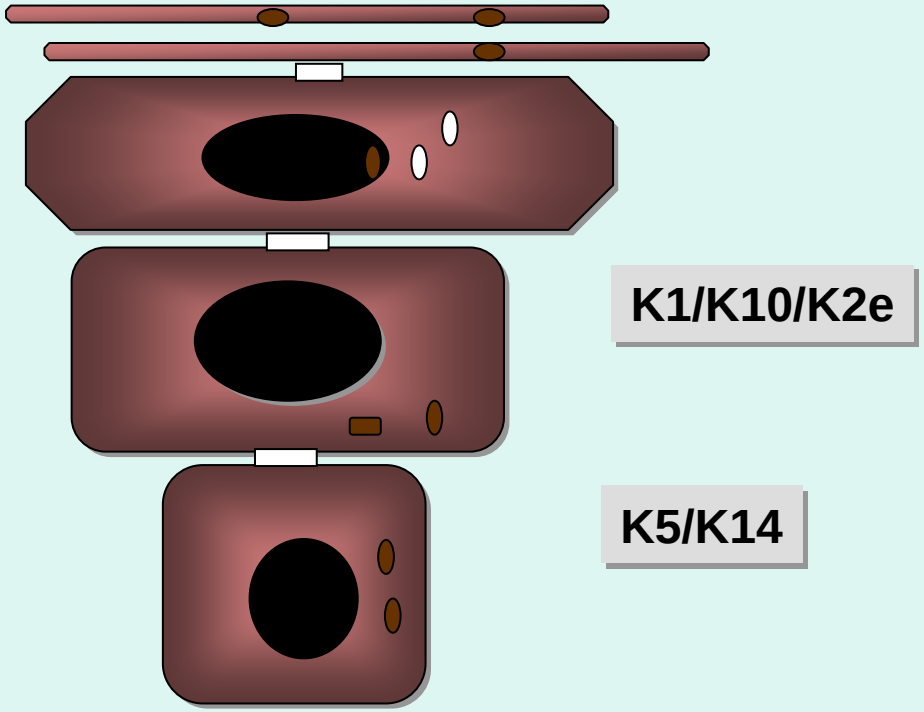
Protofilament



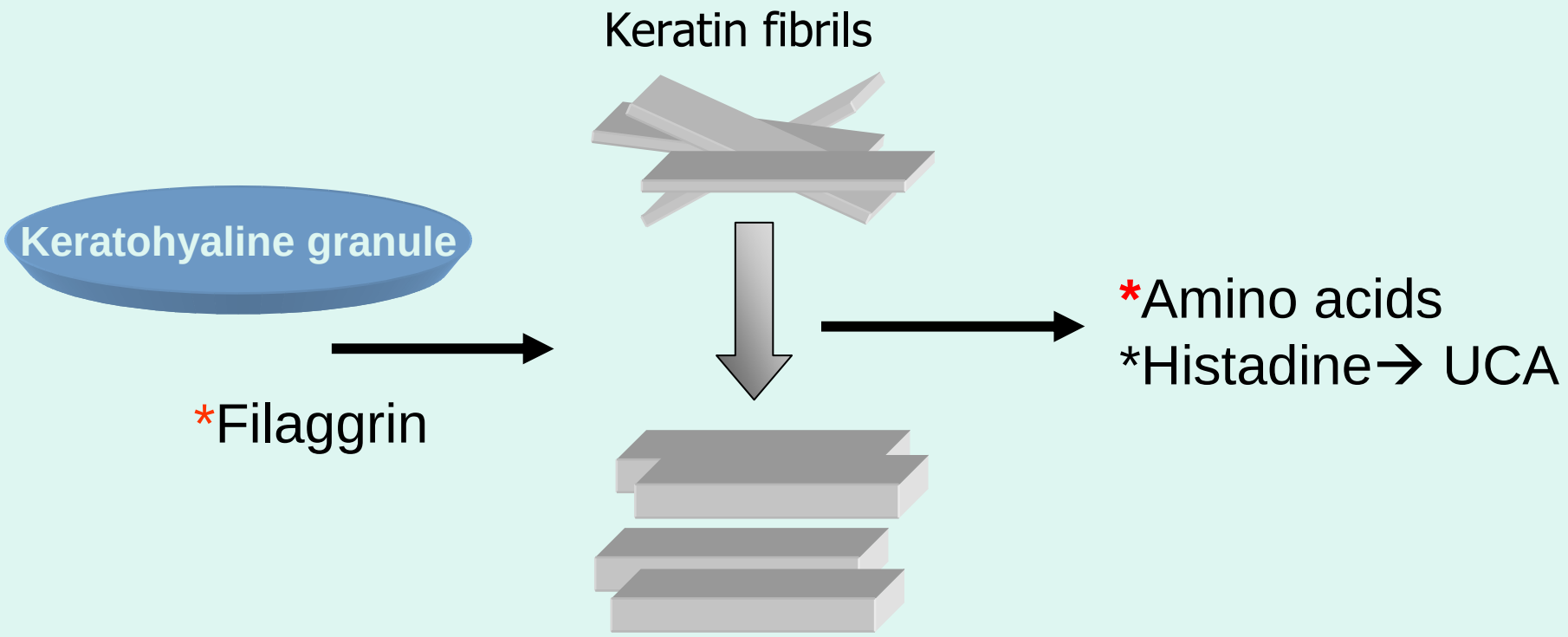
Profibrils

Intermediate Filaments

- Type1
  - Acidic
  - Smaller kd
  - 9-23
- Type 2
  - Basic
  - Larger kd
  - 1-8



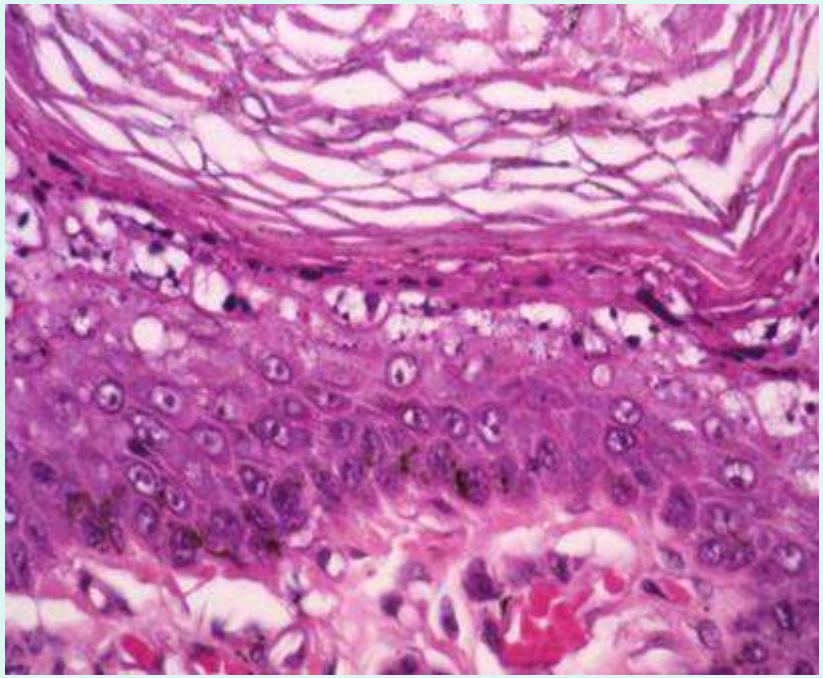
Aggregation of Intermediate filaments



***Decreased in AD**

Mild recessive epidermolytic hyperkeratosis of the Norfolk terrier
Courtesy of K. Credille

Epidermolytic hyperkeratosis



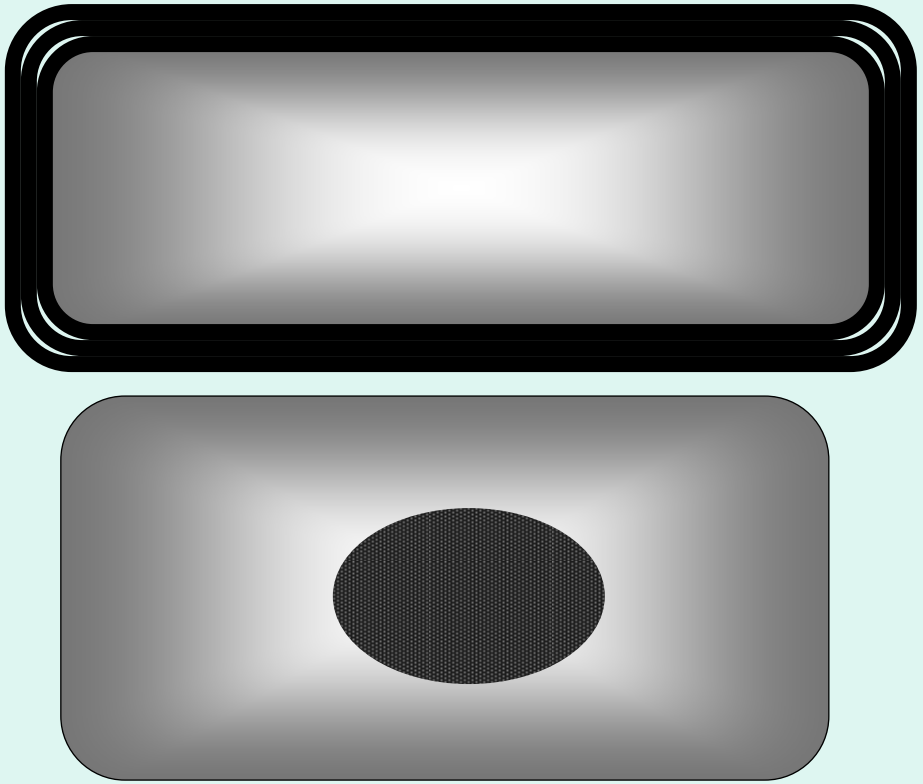
Courtesy of K. Credille

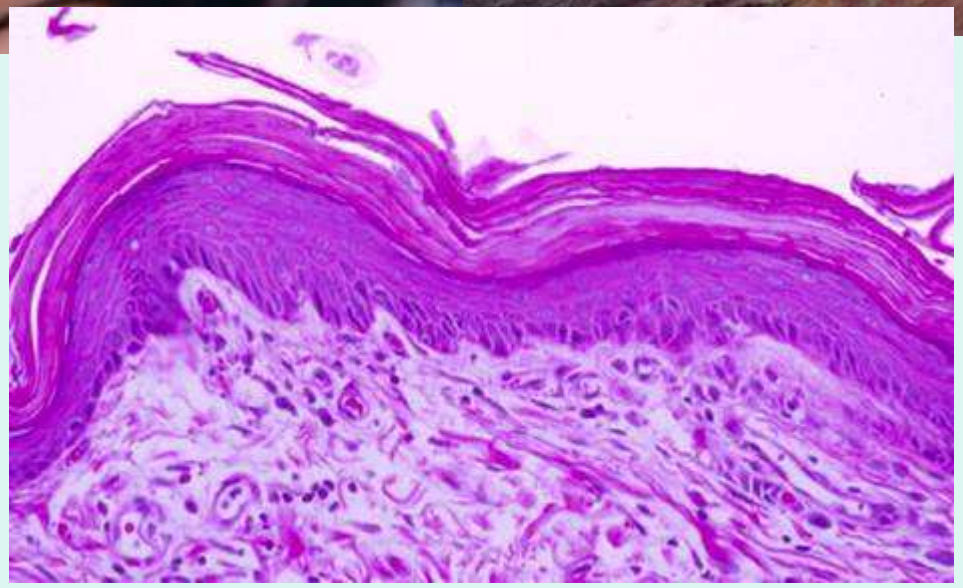
4. Formation of cornified envelope

- Replace plasma membrane

- Cross-link small protein molecules
  - Loricrin, involucrin

- **Transglutaminases** (TGM1)



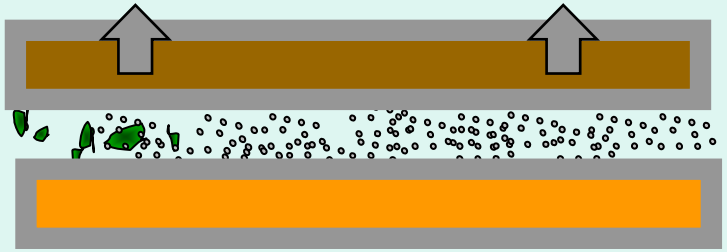


K. Credille.

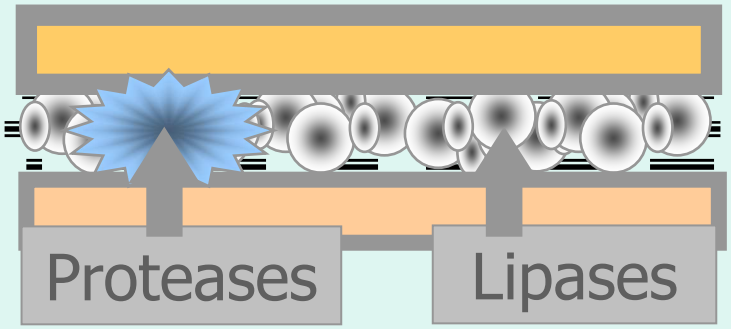
Lamellar ichthyosis

5. **Desquamation**

Surface stratum corneum

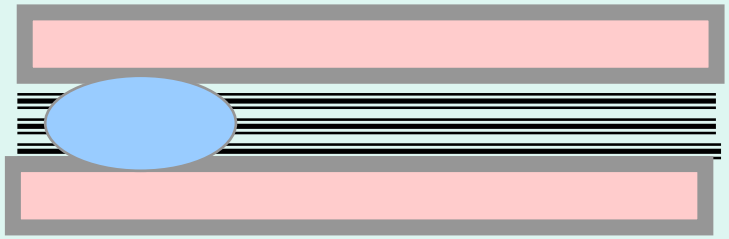


Total degradation of corneodesmo-somes and lipids



Degradation of corneodesmo-somes and lipids

Lower stratum corneum

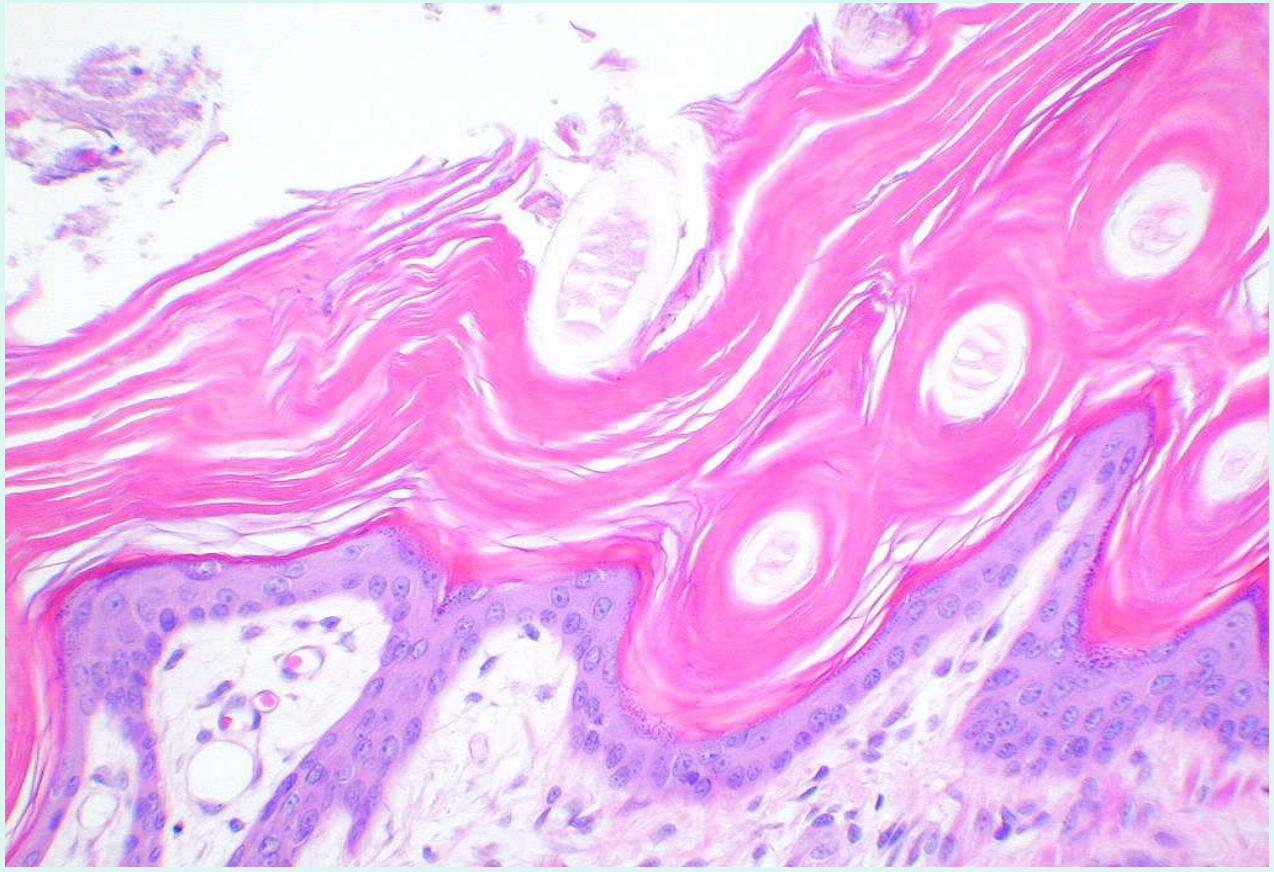


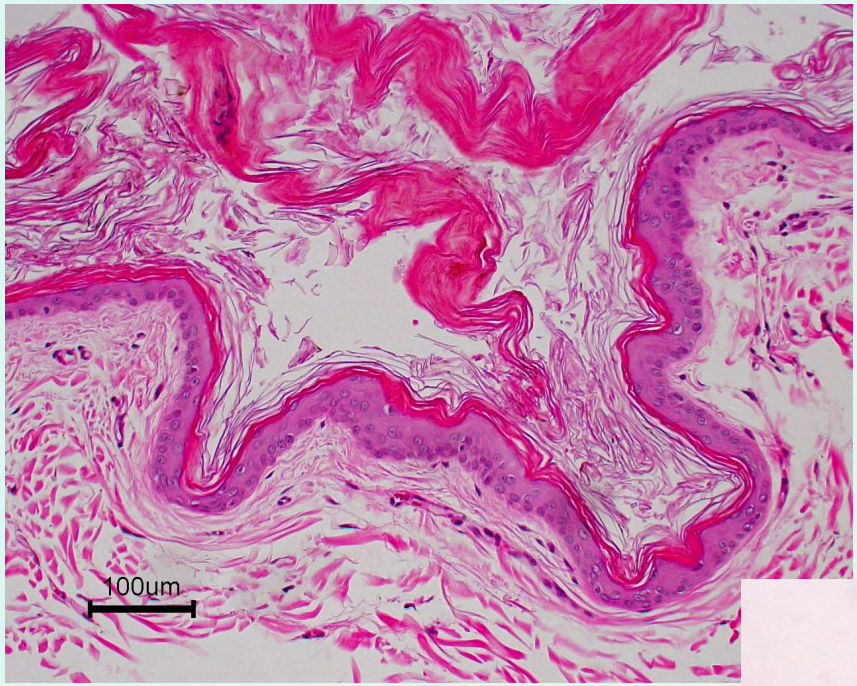
Intact corneodesmo-somes and lipid configuration

K. Credille AAVD 1998

Golden Retriever Ichthyosis

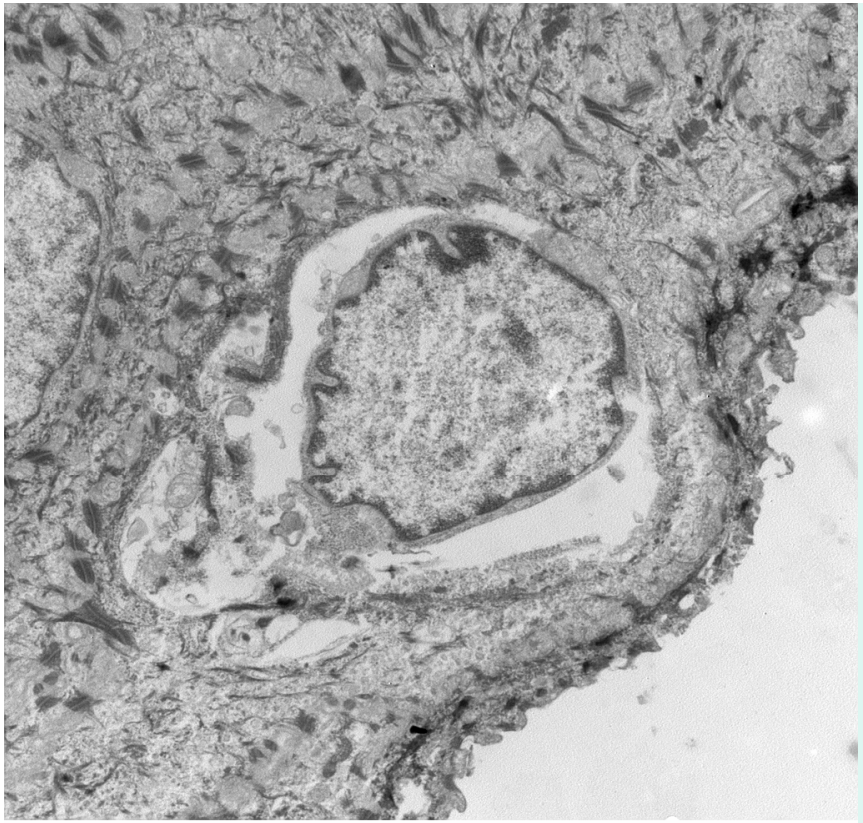
Golden Retriever Ichthyosis





Golden retriever ichthyosis


50um



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Direct Mag: 10000x
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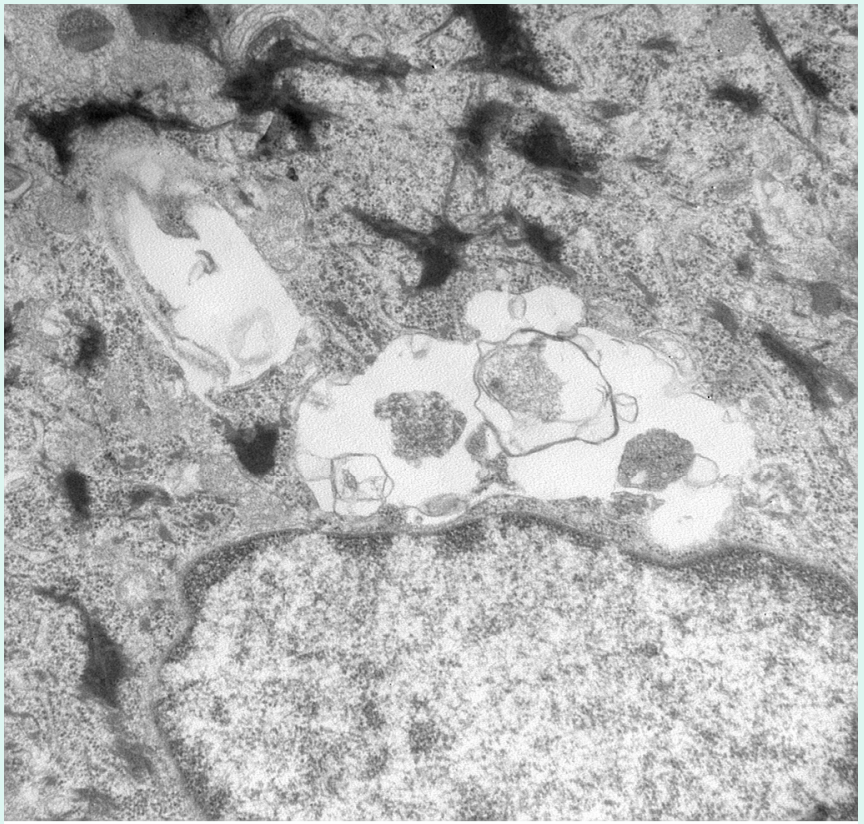

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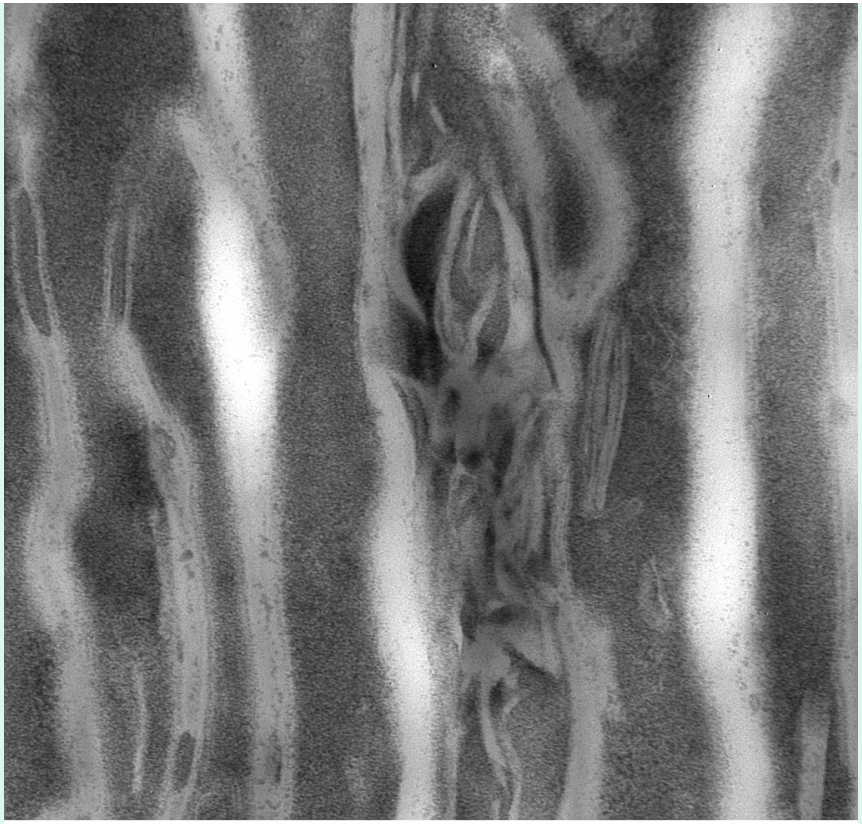

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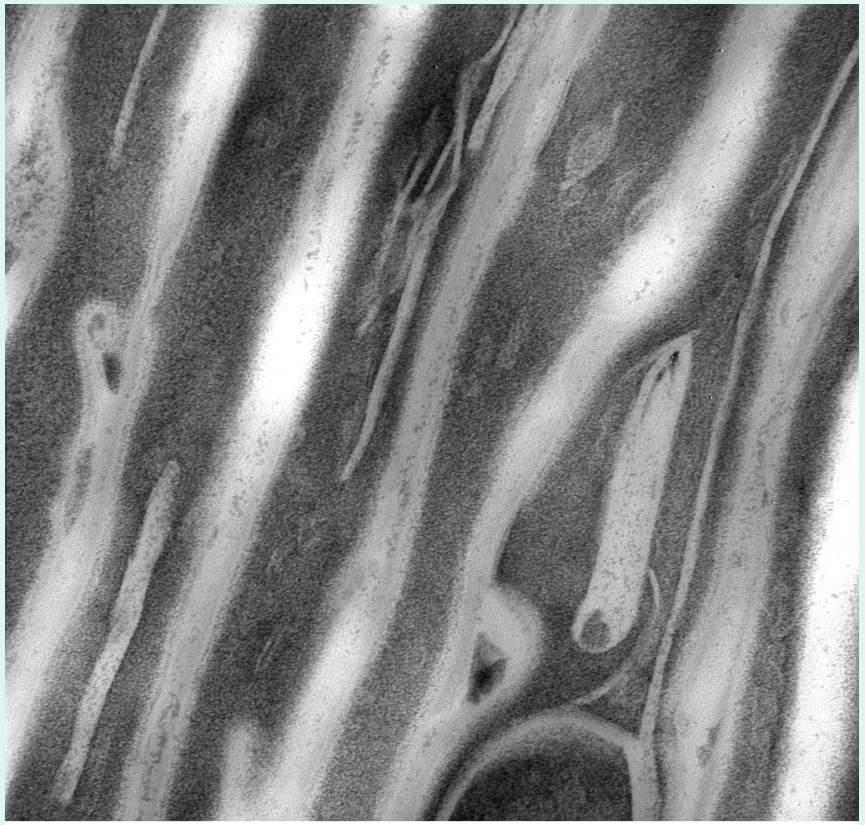

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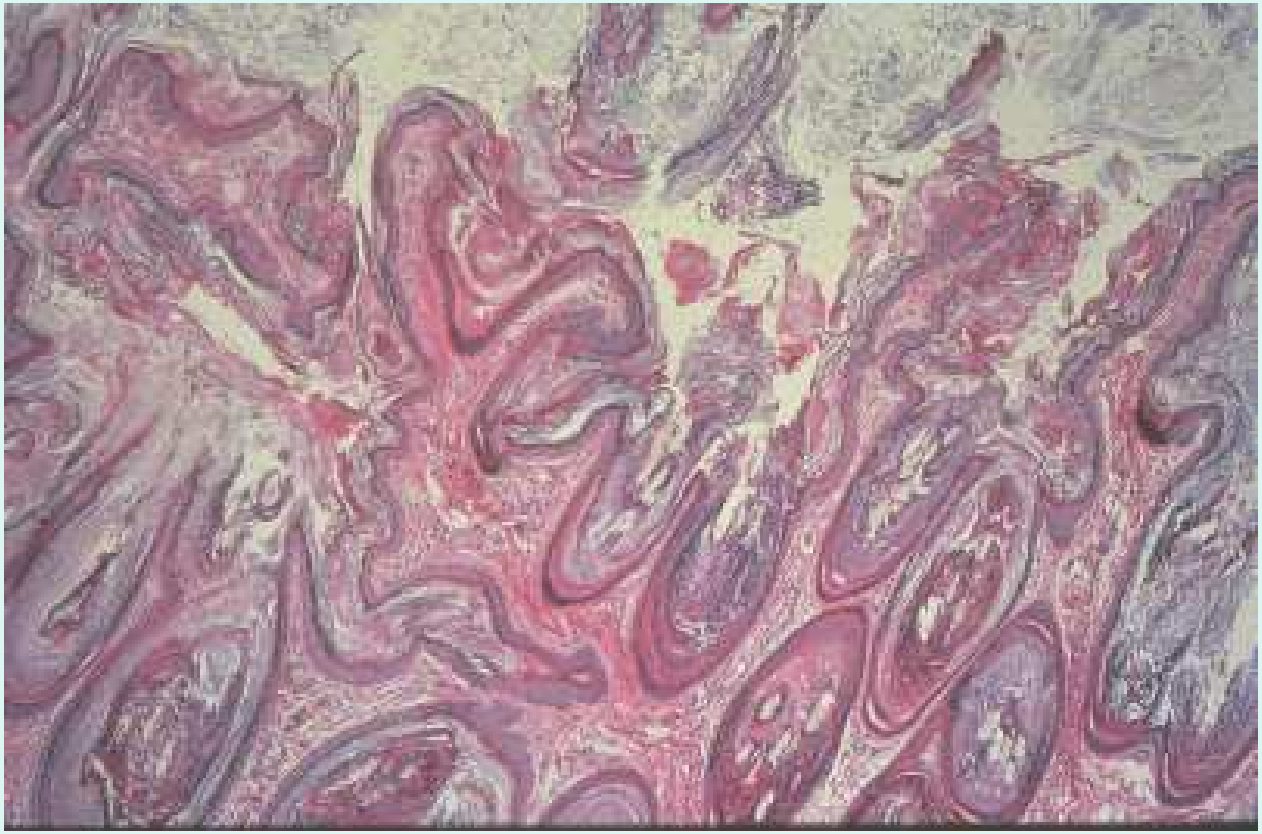
GR Ichthyosis
Retained membranous material

Vitamin A Responsive Dermatosis

Vitamin A responsive Dermatosis



1. Lipid formation → HI

2. Dissolution of nucleus/organelles→ metabolic disease

3. Keratin filaments → epidermolytic hyperkeratosis

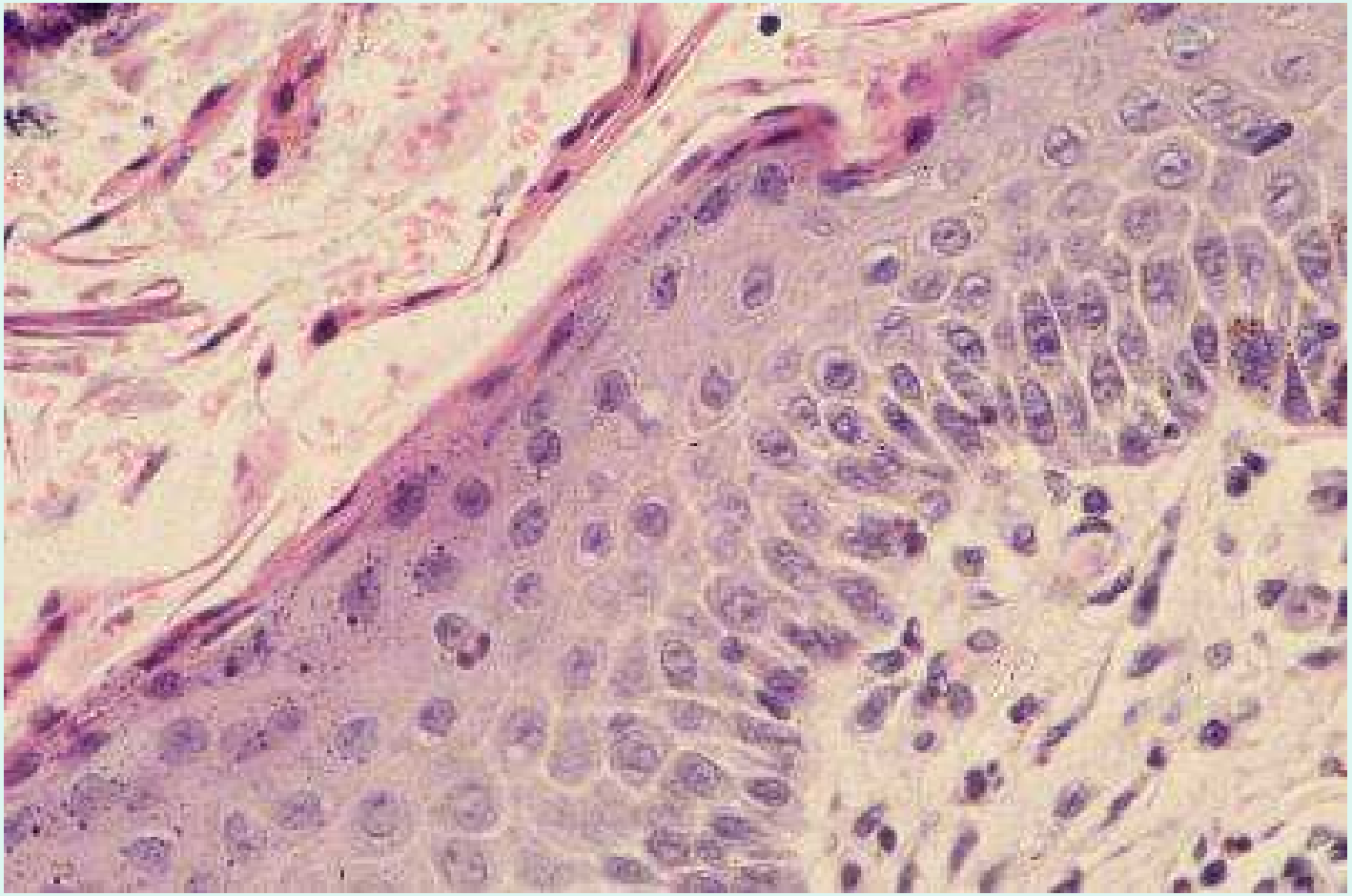
4. Formation of the CE → Lamellar ichthyosis

5. Desquamation

Abnormalities of Cornification **Hyperkeratosis**

- Primary
  - Structural proteins or lipids involved in cornification
  - Lamellar bodies → harlequin ichthyosis
  - Transglutaminase → lamellar ichthyosis
  - Lipid transporter proteins→ lamellar ichthyosis (canine?)
  - Filaggrin→ ichthyosis vulgaris
  - Keratin filaments→ epidermolytic hyperkeratosis
- Secondary
  - To almost any insult- allergic disease, endocrine disorders, parasitic and bacterial infections, etc.

Allergic Dermatitis



Corneal layer dysfunction and AD

- Disrupted barrier function
  - Decreased ceramides
  - Inc. permeability to irritant/allergens (Lab invest 2002)
  - Inc. TEWL→ xerosis
  - Inc.pH
- Inflammation→ Th2 cytokines
  - Secondary infection

LETTERS

nature
genetics

Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis

Colin N A Palmer [1,15], Alan D Irvine[2,15], Ana Terron-Kwiatkowski[3], Yiwei Zhao[3], Haihui Liao[3], Simon P Lee[1], David R Goudie[4], Aileen Sandilands[3], Linda E Campbell[3], Frances J D Smith[3], Gráinne M O'Regan[2], Rosemarie M Watson[2], Jo E Cecil[5], Sherri J Bale[6], John G Compton[6], John J DiGiovanna[7,8], Philip Fleckman[9], Sue Lewis-Jones[10], Gehan Arseculeratne[10], Ann Seargeant[11], Colin S. Monro[11], Brahim El Houate[12], Ken McElreavey[12], Liselotte B Halkjaer[13], Hans Bisgaard[13], Sonmath Mukhopadhyay[14] & W H Irwin McLean[3]

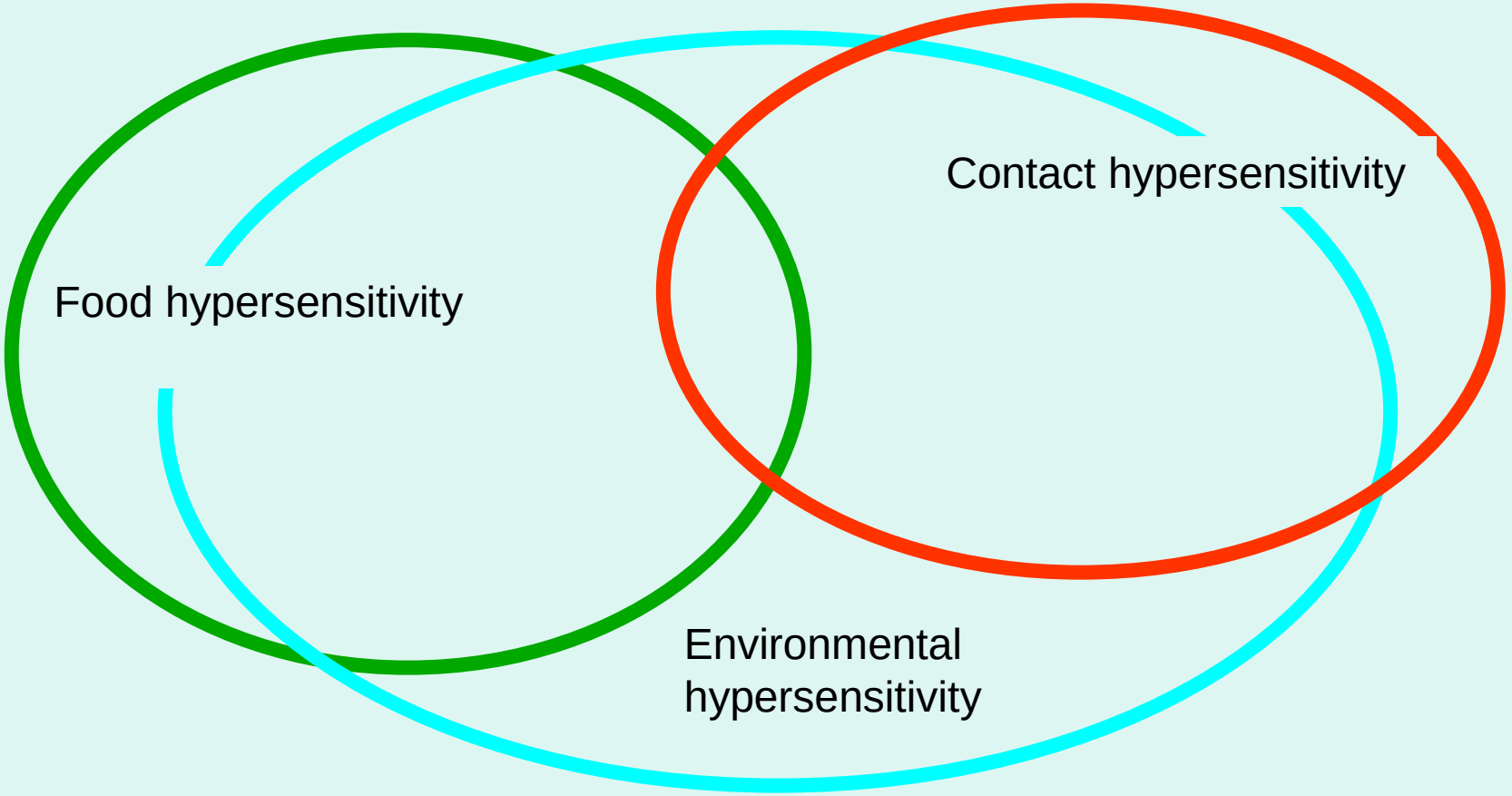
Nature Genetics 38:4 April 2006

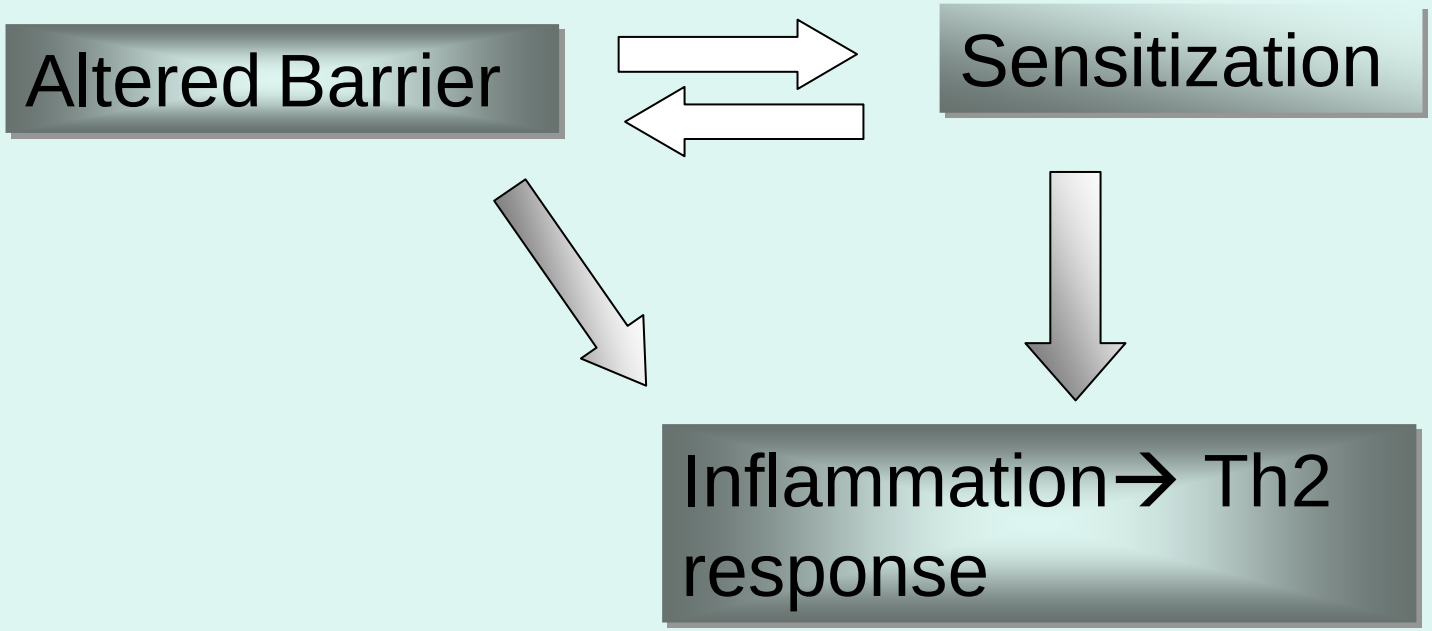
Controversy over route of allergen exposure in dogs

- Location of lesions
- Lack of asthma in atopic dogs
- Inability to cause skin lesions in dogs sensitized via inhalation
- Histologic changes- similarity b/w contact models and natural AD

- **1999 ACVD task force recommendation→ "allergic inhalant dermatitis" should no longer be used**

Altered Barrier Function?




Altered Barrier
Sensitization
Inflammation→ Th2 response

Implications for Treatment

- Decrease cutaneous contact with allergens
- Restore barrier function- topically
  - Application of lipids dramatically improves barrier function in humans
- Restore barrier function – dietary manipulation