Congenital Dystrophic Epidermolysis Bullosa in Sprague Dawley Rats

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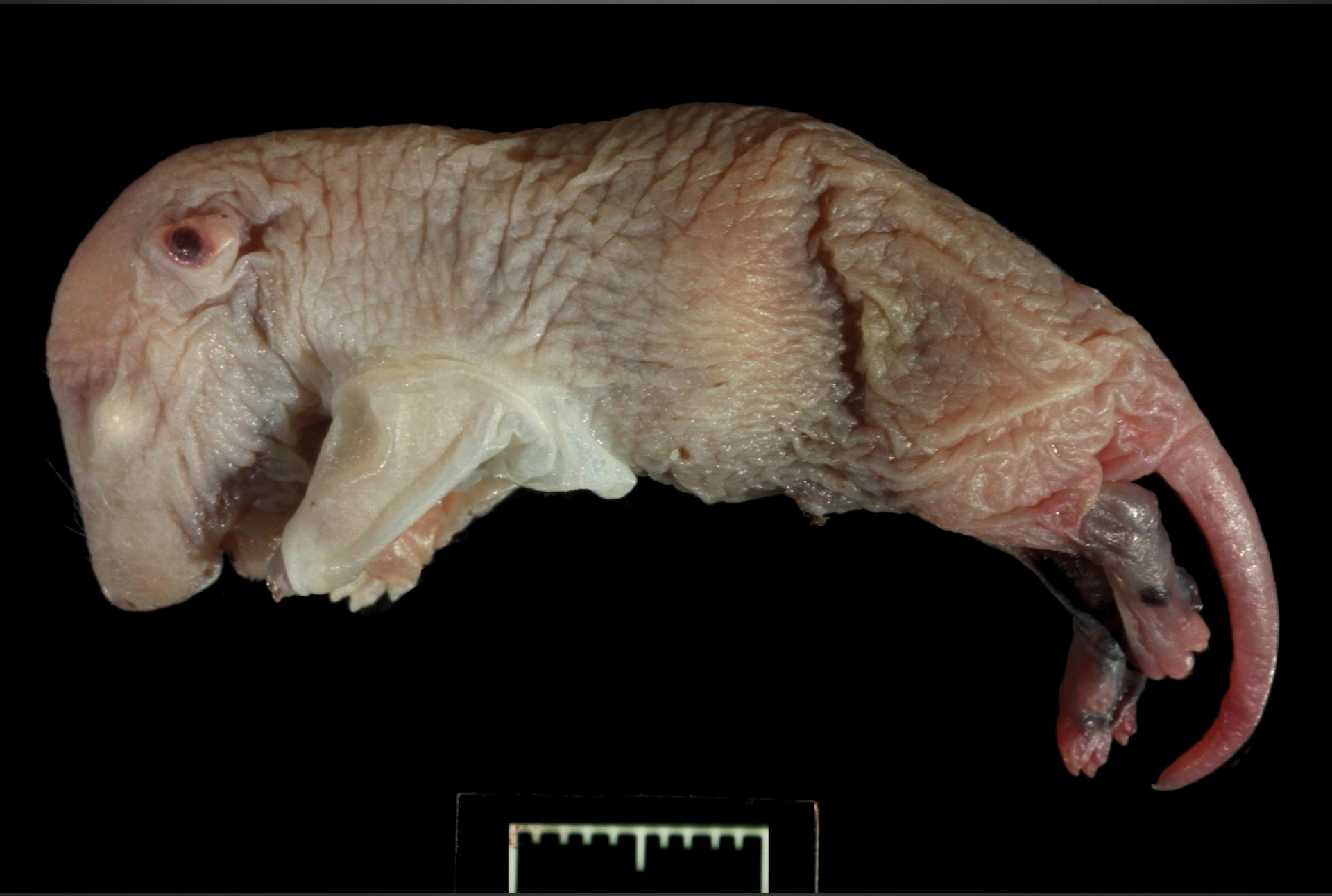
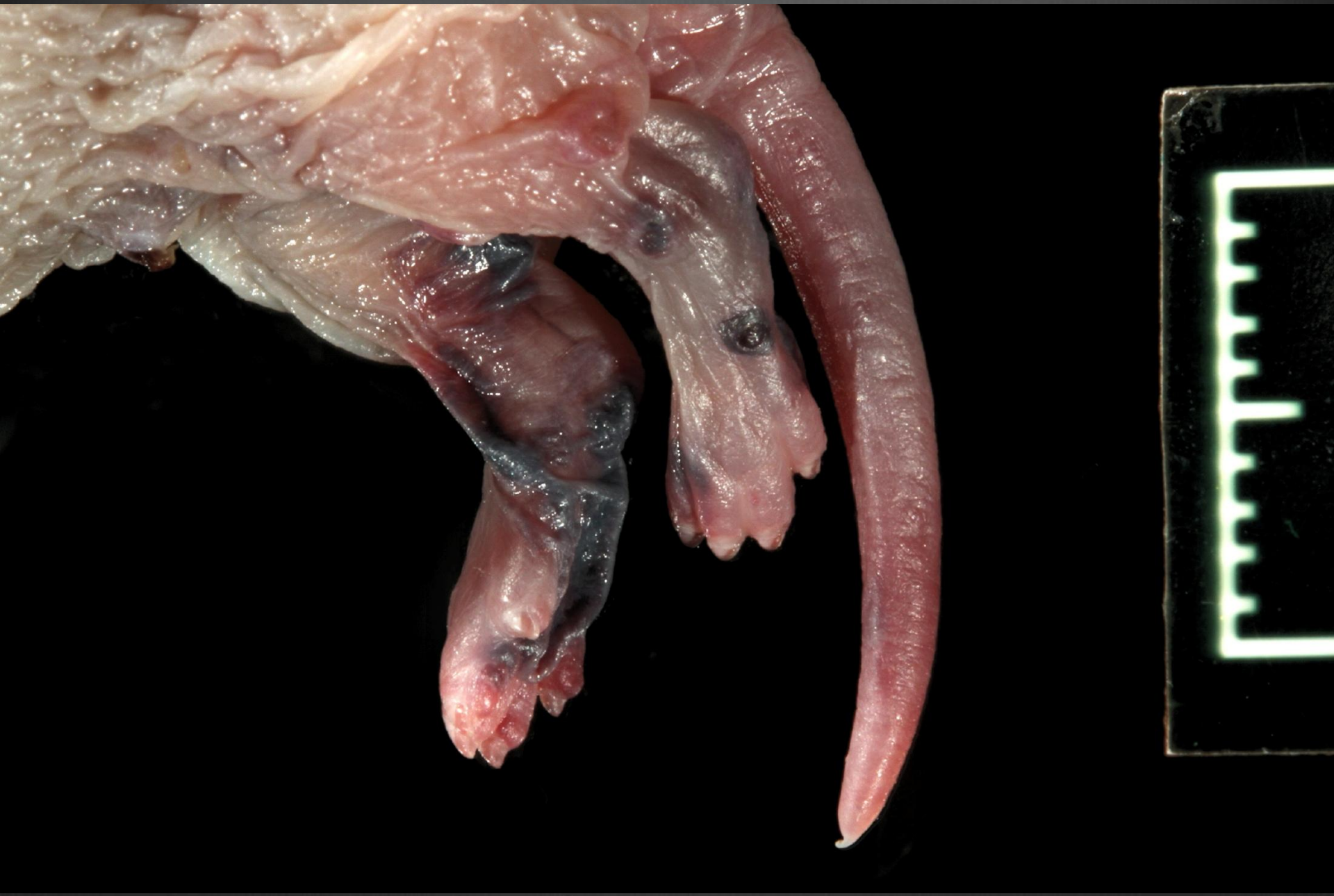
History

- **Four pups in a litter of Sprague-Dawley rats were euthanized due to failure to nurse and the presence of tan to black, crusty discolorations on the distal limbs and feet.**
- **Additional lesions around the oral cavity, tongue, tails, and ears.**
- **Rats were breeders only and not experimental.**

Gross Findings

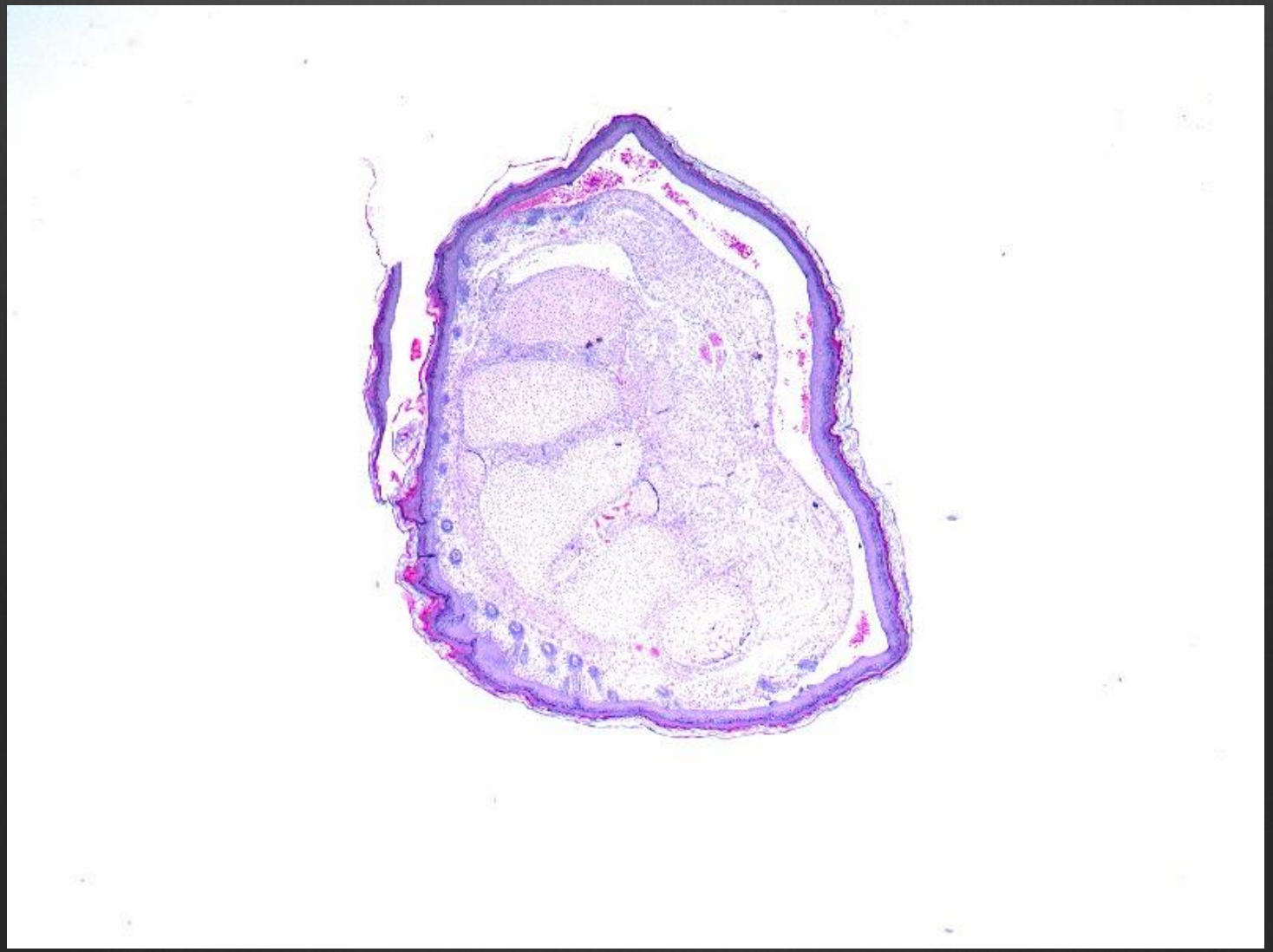


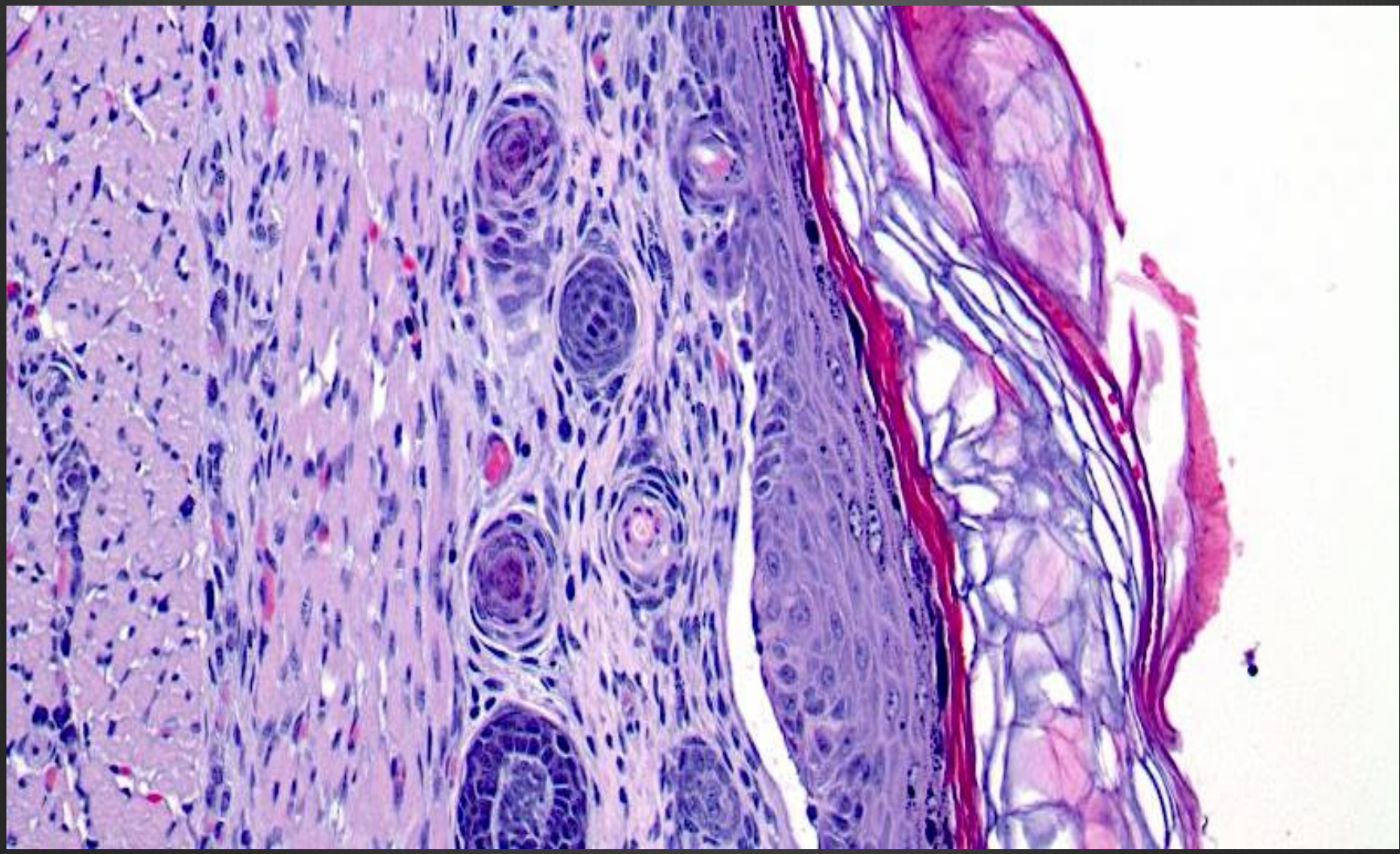


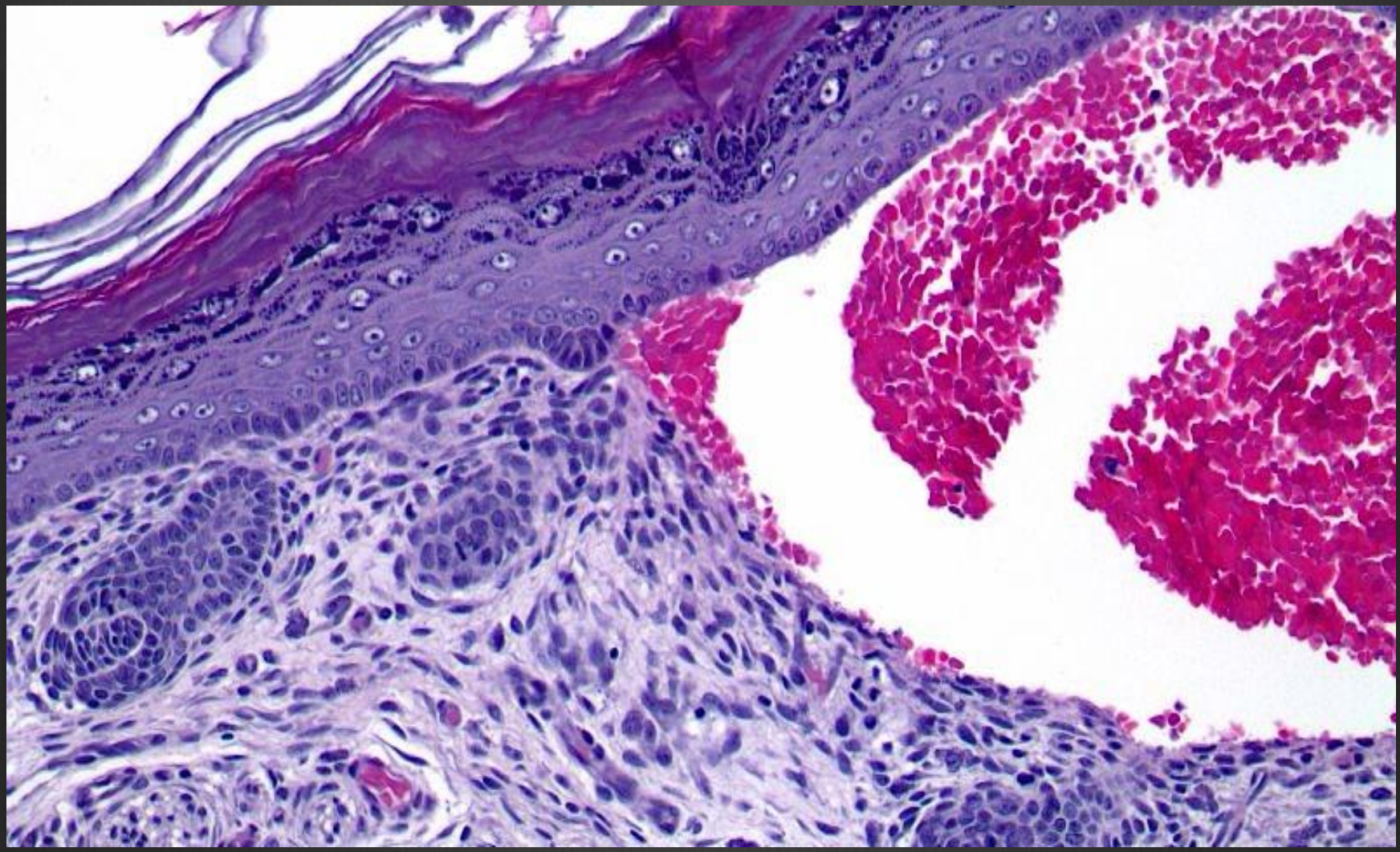
Timeline

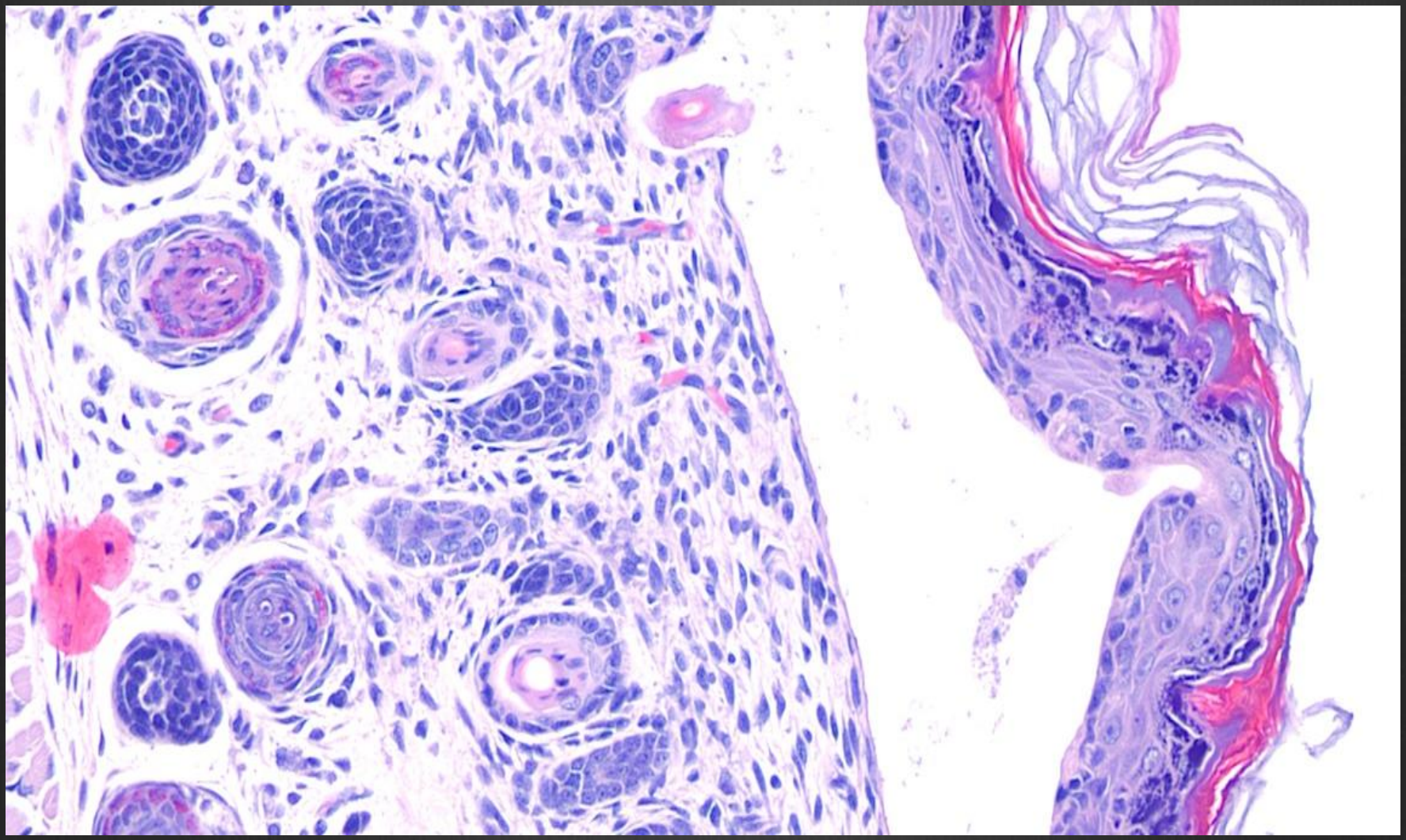
- **T11-N027:** 4 pups affected out of unknown litter size.
- **T11-N043:** 6 pups out of 16 affected.
- **T11-N069:** 3 pups out of 9 affected. It was determined that the third litter had the same sire as the second. Unaffected siblings bred.
- **T11-N090:** Two litters, with 6 out of 21 total pups affected.
- **T12-N006:** Two litters, with 3 out of 16 total affected.

Histologic Findings





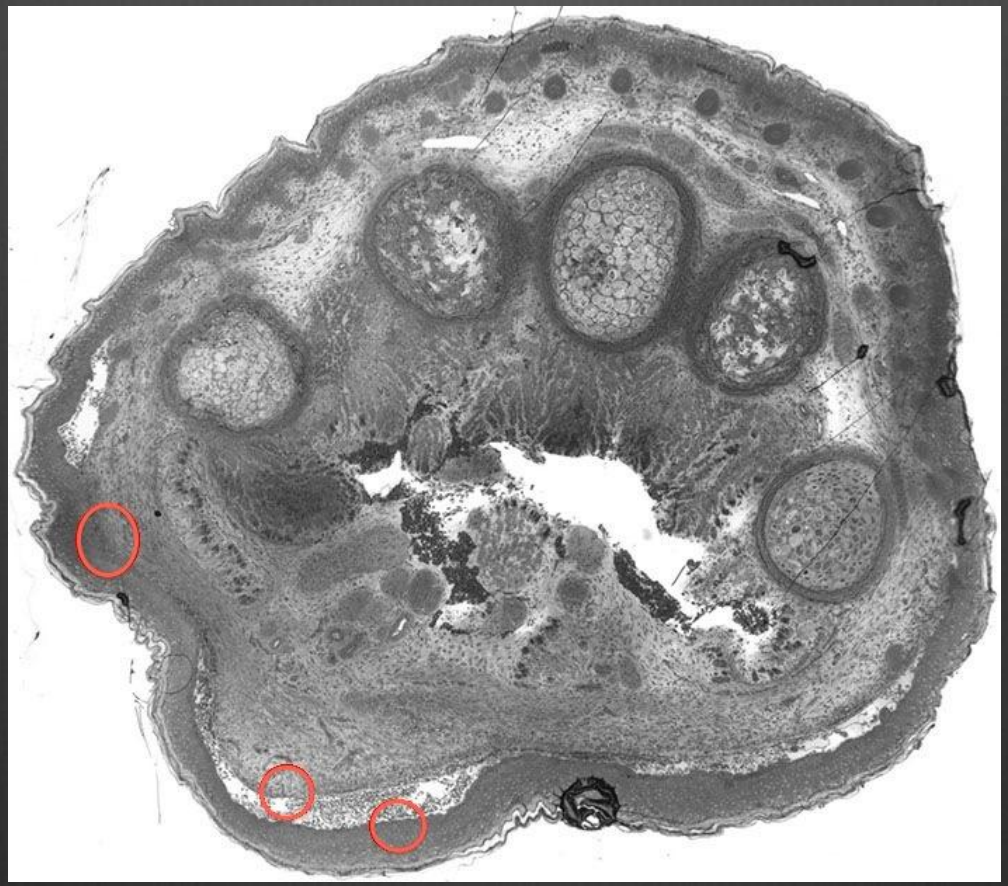


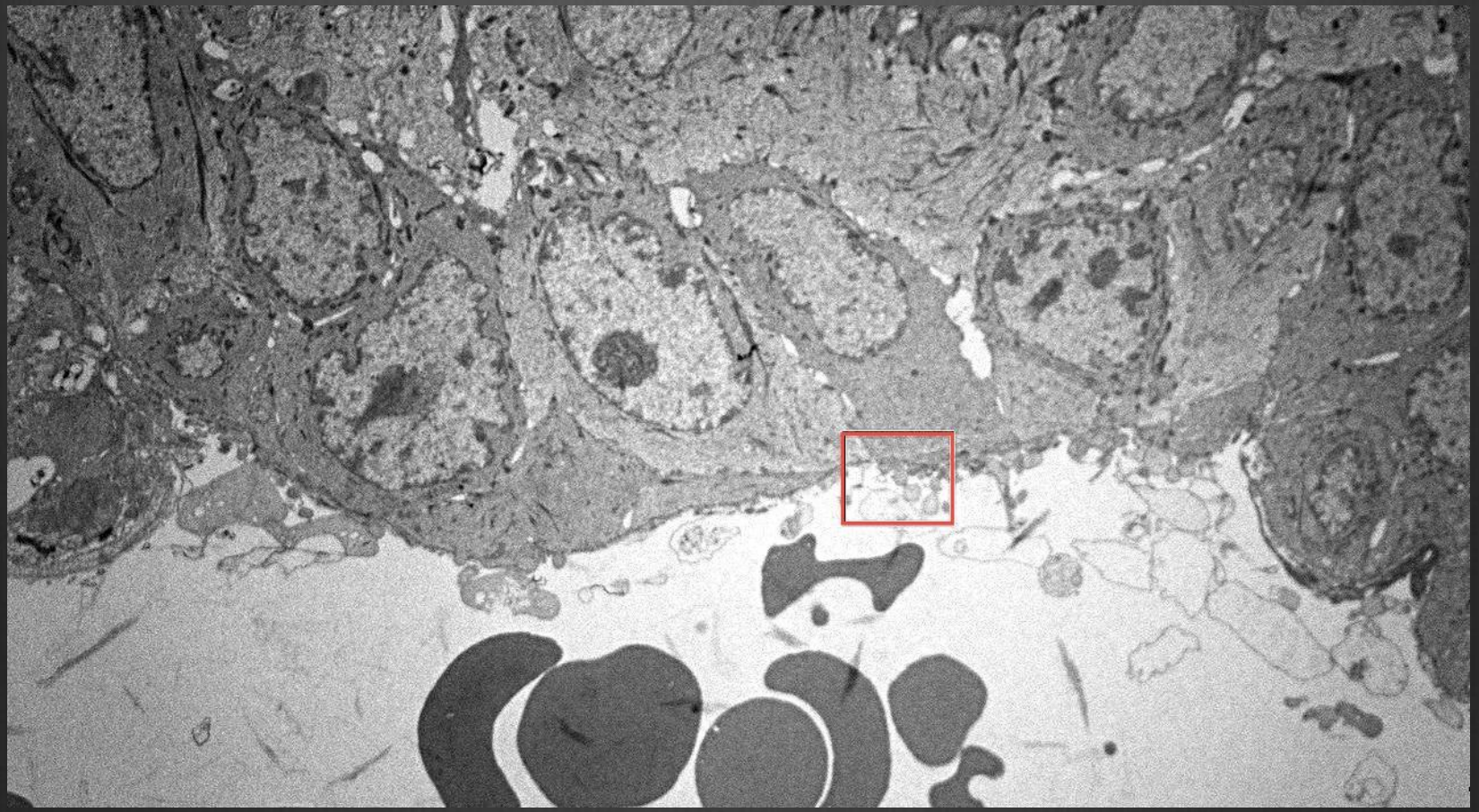


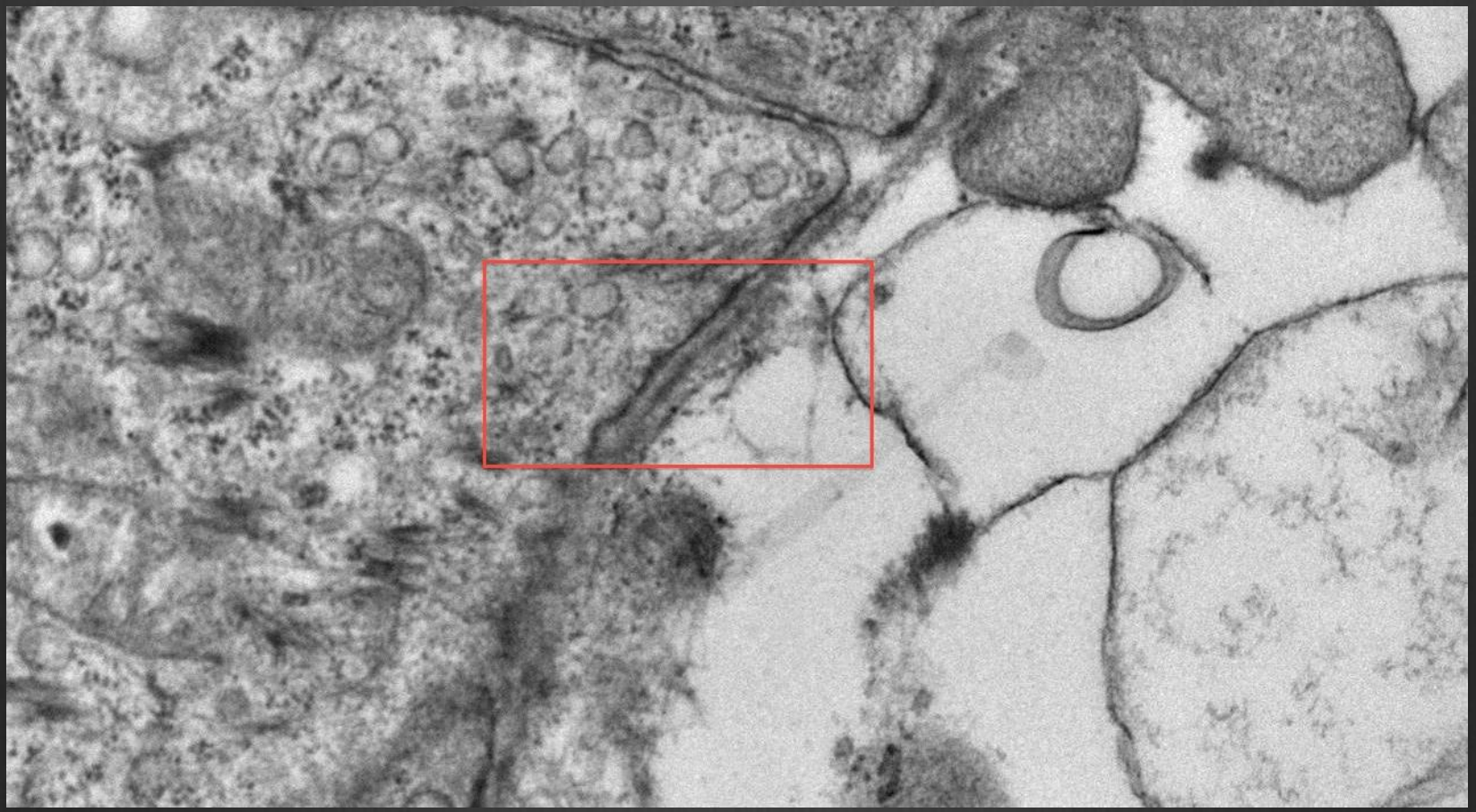
TEM

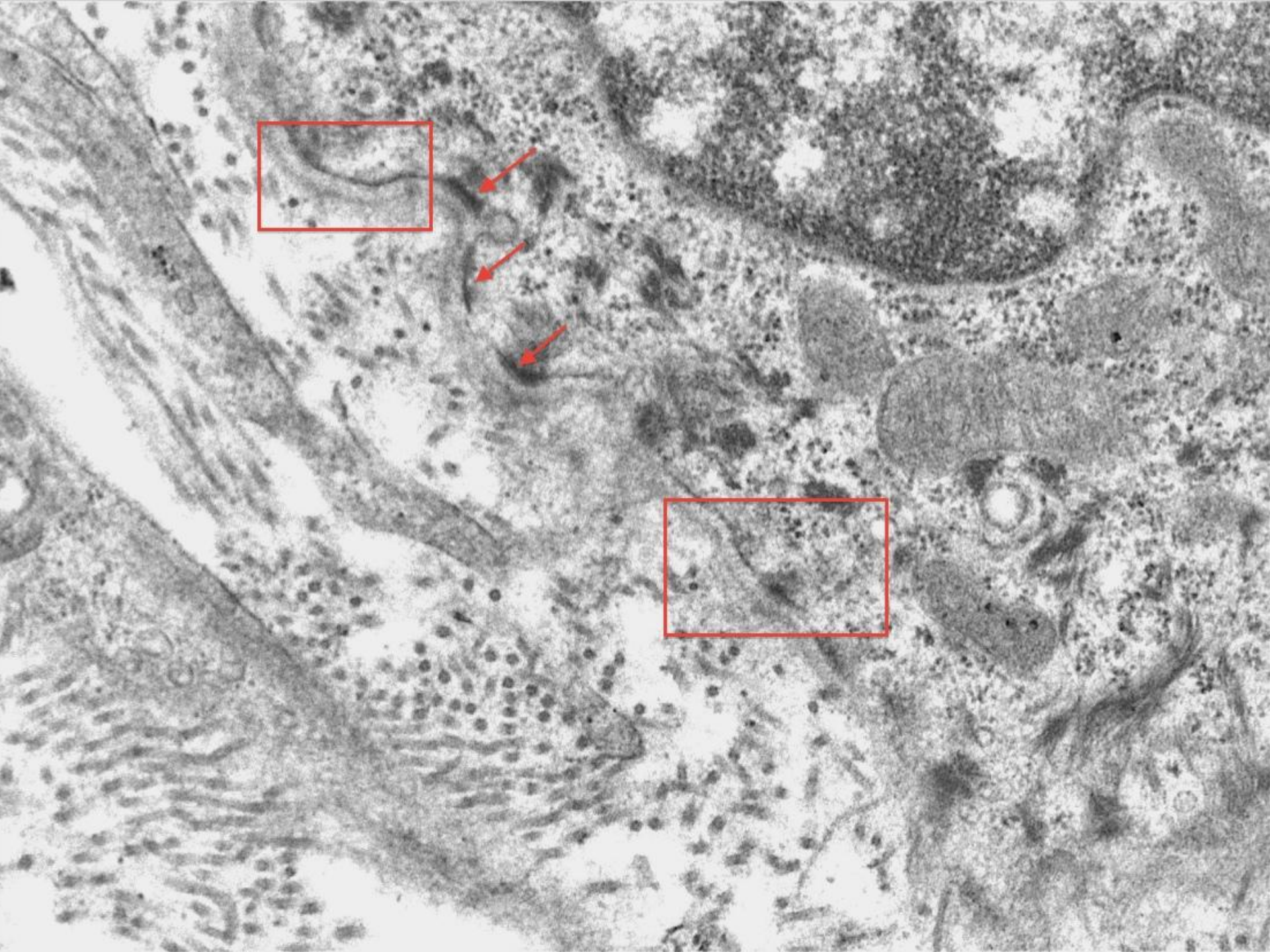
- Samples from Litter 4a and 4b (parents were unaffected siblings of Litter 3)
- Exact determination of level of cleft formation
- Evaluation of basement membrane components
- Evaluation of keratinocytes, hemidesmosomes, etc.

TEM Findings









Epidermolysis Bullosa

- **Rare mechanobullous disease**

- **Epidermolysis Bullosa Simplex (SEB): Intra-epidermal clefting above BMZ.**

- **Junctional Epidermolysis Bullosa (JEB): Herlitz (lethal, congenital) or non-Herlitz. Clefting within BMZ.**

- **Dystrophic Epidermolysis Bullosa (DEB): Hallopeau-Siemens type (more severe) and non-Hallopeau Siemens-type. Clefting below BMZ.**

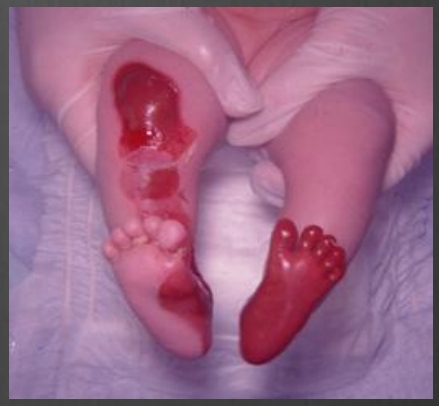


Photo credit:
http://drugline.org/

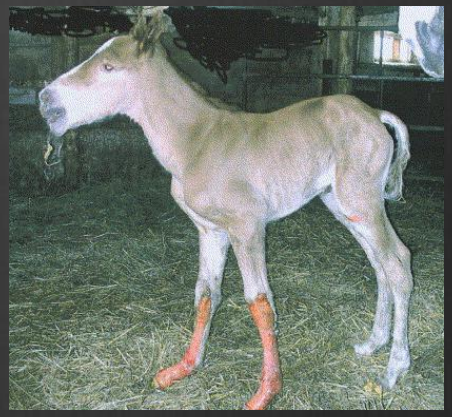


Photo credit:
Dr. John Baird,
Guelph

Epidermolysis Bullosa

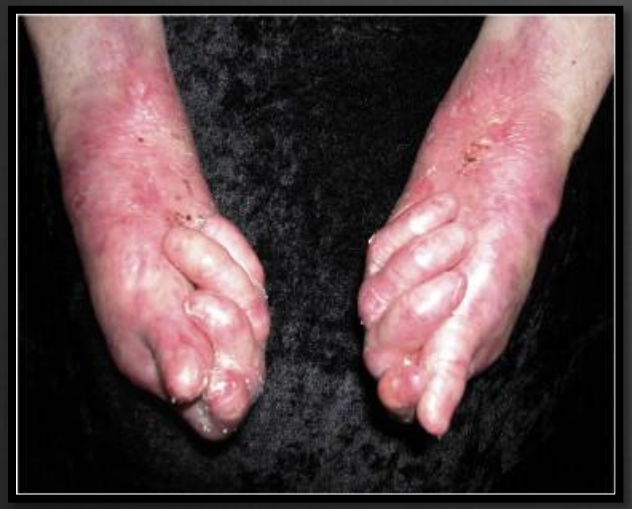


Photo credit:: Lizbeth RA et al, Clinics in Dermatology, (2012).

- **Reported in several animal species (dog, horse, cat, cow, small ruminant) as well as humans**
- **Can be inherited or acquired**
- **Other abnormalities: absence of skin (aplasia cutis congenita), nail dystrophy, hypotrichosis, pseudosyndactyly, and pyloric atresia.**

Epidermolysis Bullosa

- **Management: lancing and draining of blisters, special nonadherent dressings, antibiotic treatment, special clothing and shoes.**

- **More severe cases: skin grafts, tracheostomy, esophageal dilatation, gastrostomy tubes**

- **Research with retrovirus/WT collagen, skin grafts, bone marrow transplants, intradermal injection of WT fibroblasts.**

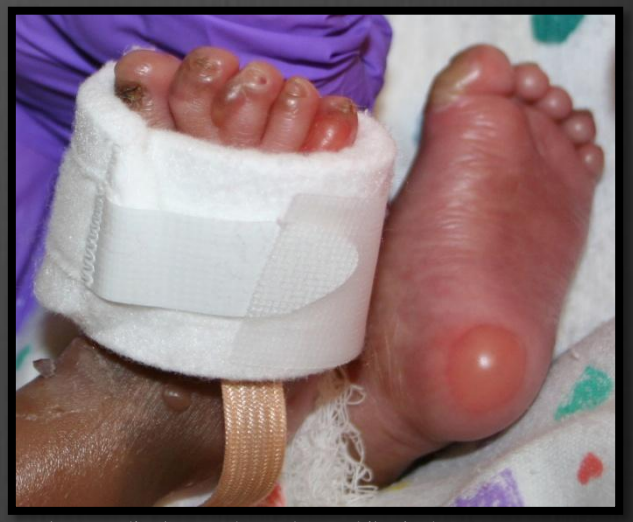
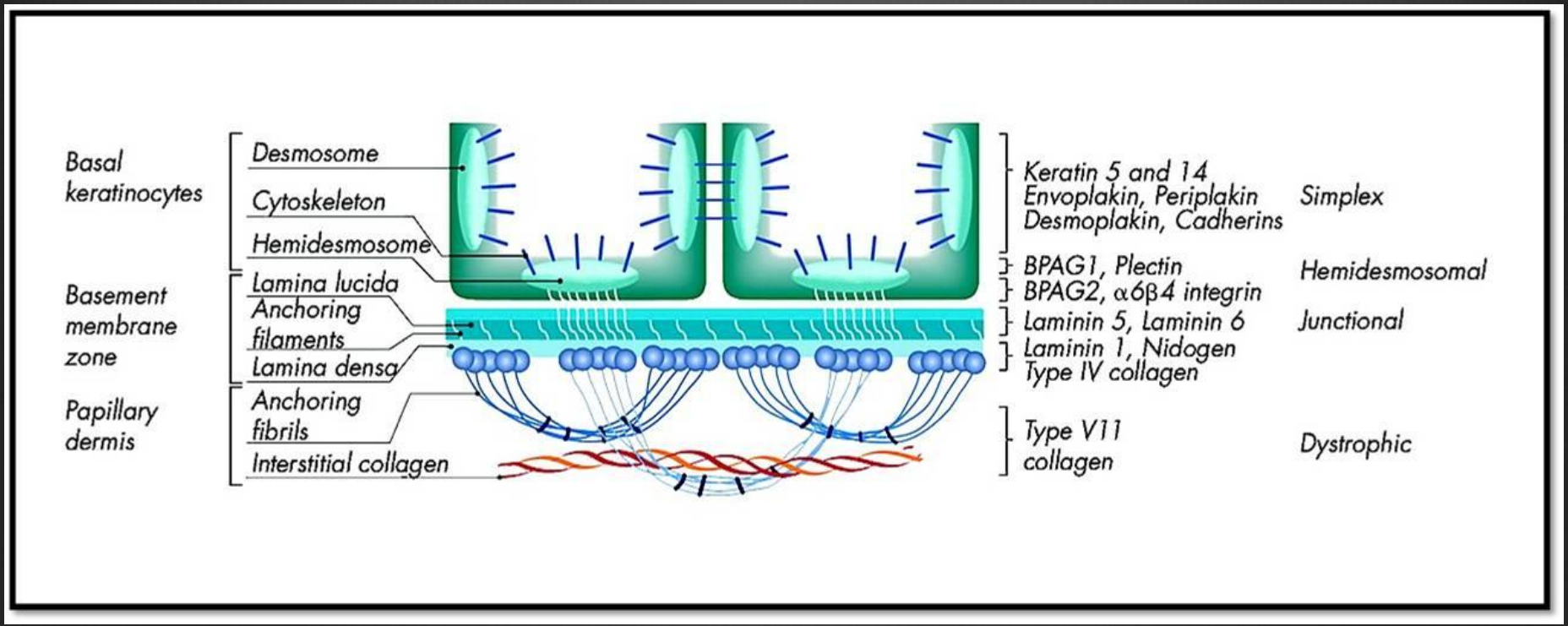


Photo credit: http://dermatlas.med.jhmi.edu

Basement Membrane



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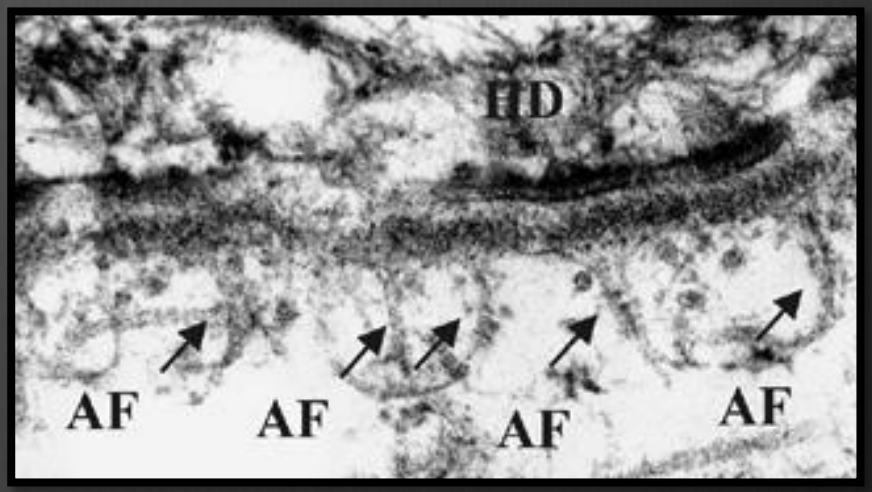
Collagen VII

- **Collagen VII is the main component of the anchoring fibrils that attach the lamina densa to the papillary dermis**
- **Secreted by keratinocytes → dimerizes → disulfide bonds and reorganization → formation of fibrils**



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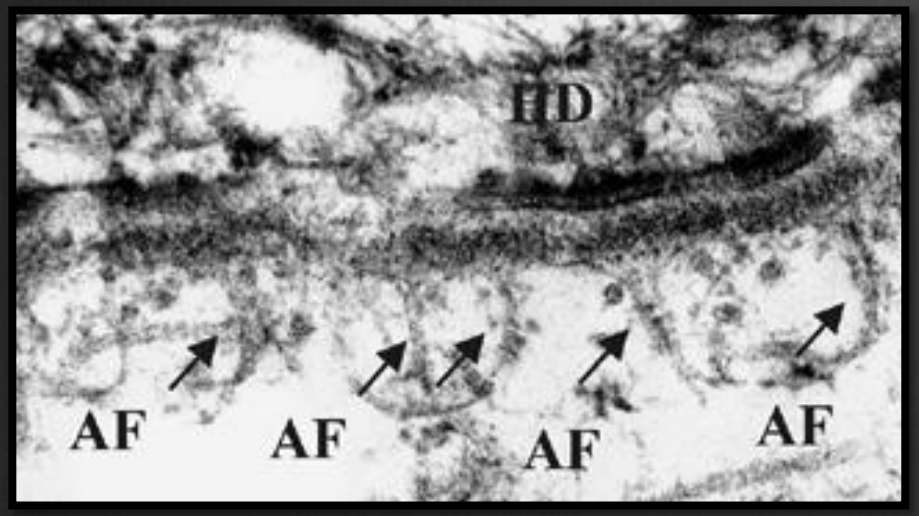
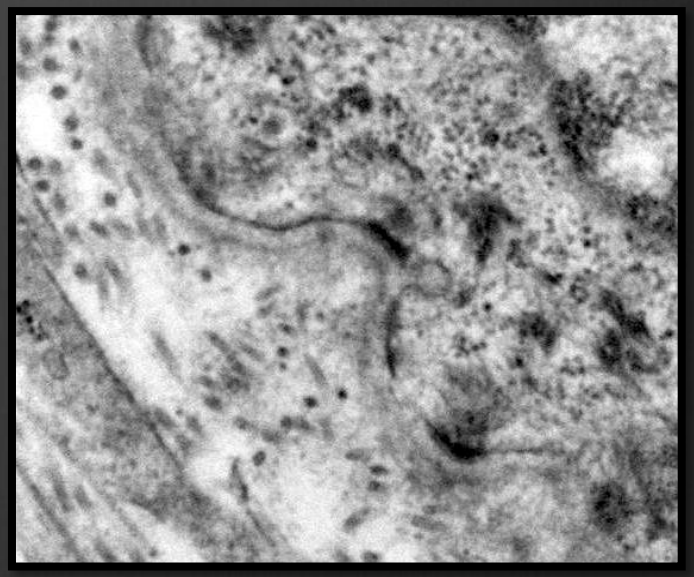
Collagen VII and DEB

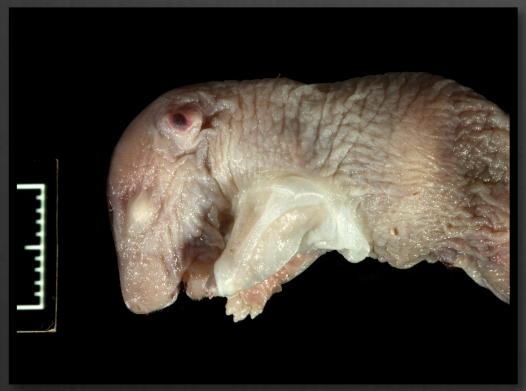
- **A mutation in the COL7A1 gene causes Dystrophic Epidermolysis Bullosa (almost 400 mutations identified).**
- **Current transgenic mouse model (-/- COL7A1) shows changes identical to these cases.**
- **One single EB case in SD rats – hemidesmosomes abnormal, no follow-up.**

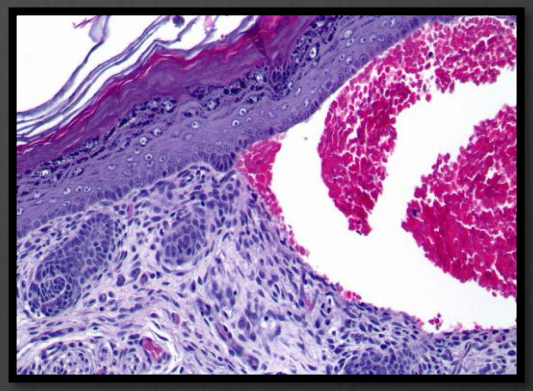


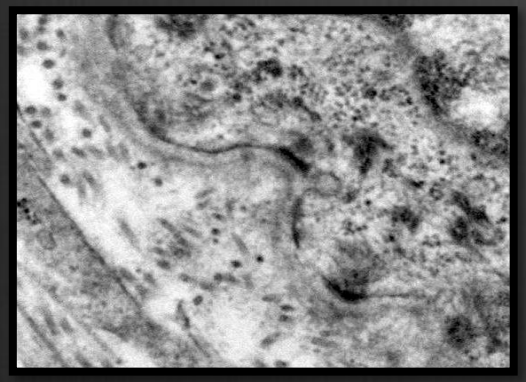


Recap

- ☑ Blistering skin disease visible 24-48hrs after birth
- ☑ Histologic clefting with variable hemorrhage, edema, etc.
- ☑ TEM confirmation of clefting below lamina densa and lack of normal anchoring fibrils
- ☑ Successfully reproduced several times using clinically normal heterozygotes from affected litters, showing a recessive pattern







Conclusions

- **Based on the gross lesions, microscopic clefting, and TEM determination of separation below the lamina densa and lack of normal anchoring fibrils, our cases are consistent with dystrophic epidermolysis bullosa (DEB).**
- **We were also able to reproduce this disease repeatedly and reliably through natural means, with affected proportions indicating a recessive mode of inheritance.**
- **This is the first report of spontaneous and heritable DEB in the rat; DEB in laboratory animals is currently within the realm of transgenics.**

Acknowledgments

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Questions?