

Spontaneous Congenital Dystrophic Epidermolysis Bullosa in Sprague Dawley Rats

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Introduction

The term “epidermolysis bullosa” encompasses a group of inherited mechanobullous skin disorders characterized by blistering and sloughing of the epidermis at or around the level of the basement membrane due to defects in the cytoskeleton of the basal keratinocytes or the basement membrane zone. Epidermolysis bullosa variants have been described in many species as well as humans. A naturally-occurring, reproducible model of dystrophic epidermolysis bullosa, the most severe variant, has not been described in laboratory rats.

Signalment and Gross Findings

Four pups in a litter of Sprague-Dawley rats at Texas A&M developed hemorrhagic and blistering skin lesions approximately three days after birth and were euthanized. Age-matched controls from the same litter were normal. Four months later, two more litters from the same sire presented with approximately one third of the pups displaying identical lesions. At this time, several unaffected siblings of the third litter were allowed to mature, and bred in an attempt to reproduce the disease. Four more litters were produced from various parental matches, again with approximately one quarter to one third of the pups displaying similar lesions.



Figure 1: The skin appears thin and wrinkled, and peels away easily from the underlying subcutis.

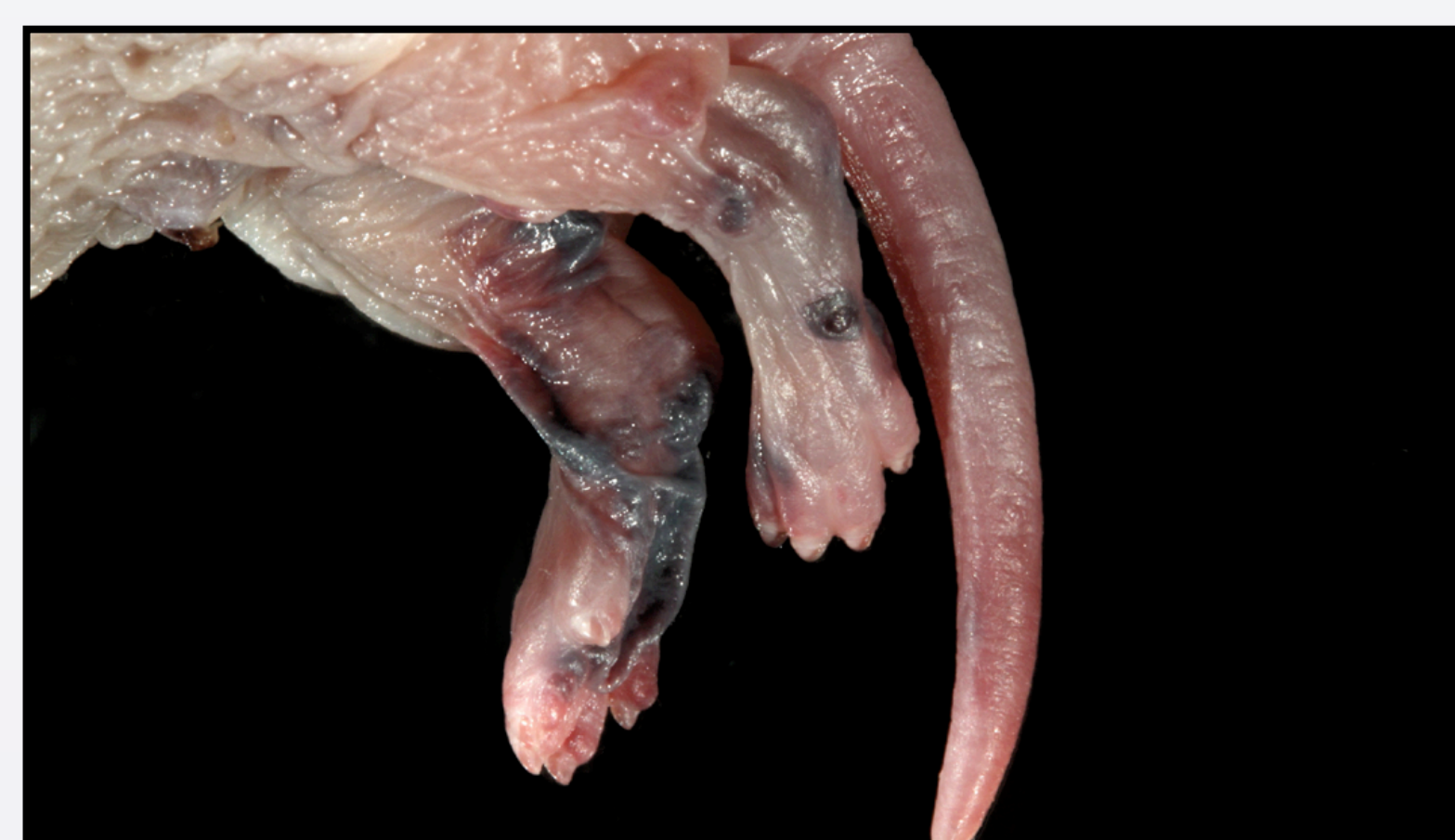


Figure 2: Variable areas of vascular congestion, hemorrhage, and necrosis are also apparent, particularly at the extremities. Also note the pseudosyndactyly (fusion of digits).



Figure 3: Lesions around the extremities and oral cavity are presumed to be initiated by low-grade trauma such as suckling and walking.

Histopathology Findings

Microscopic findings were consistent among all grossly affected pups. Particular around the extremities, there are multiple dermo-epidermal clefts containing variable amounts of hemorrhage, edema, and fibrin. Clefts are bordered on both sides by intact epithelium. Other affected areas include the oral cavity, tongue, and tail, although skin on the dorsum and flank is less affected than the forelimbs and trunk.

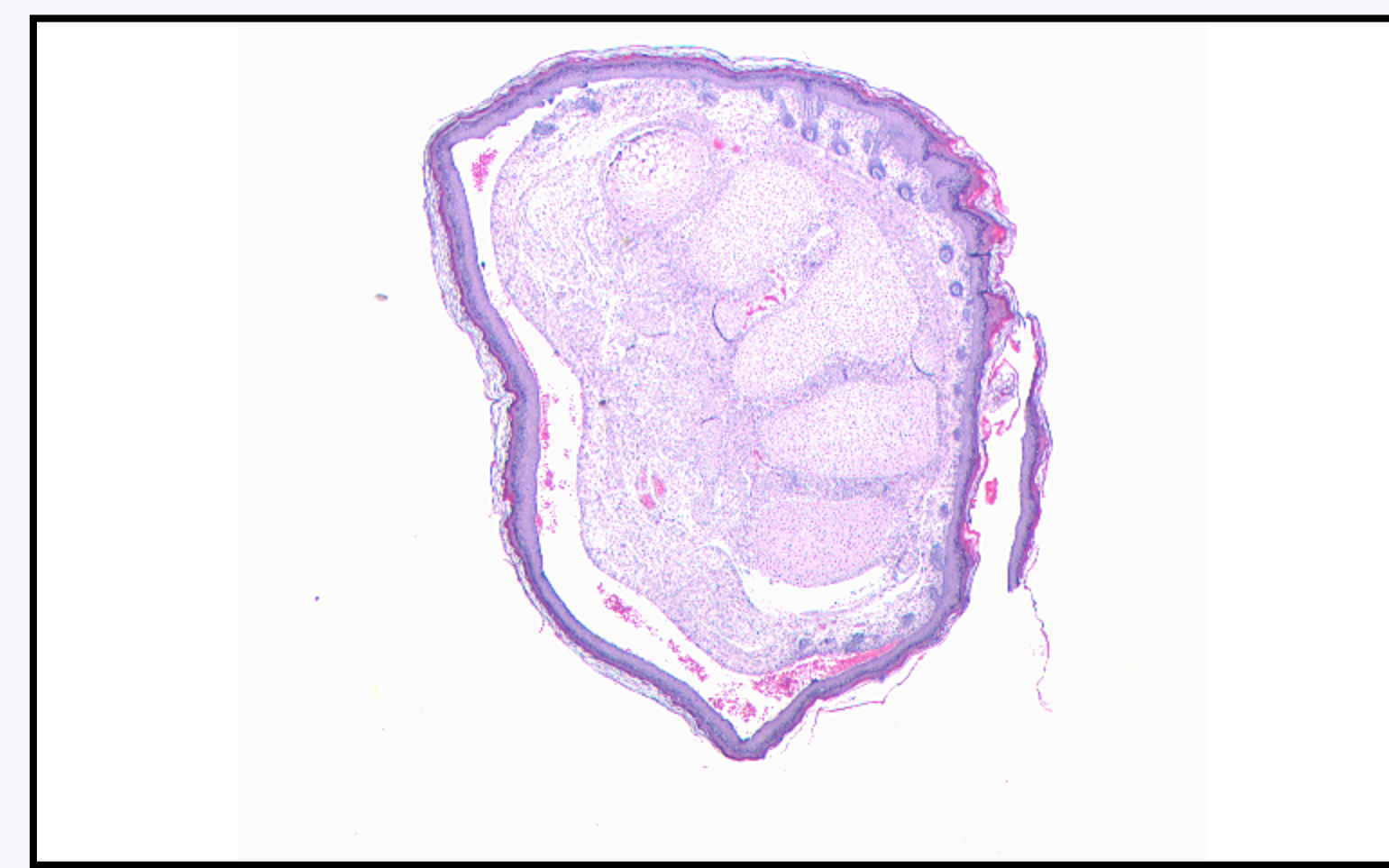


Figure 4: Cross section through the distal limb, revealing cleft formation between the dermis and epidermis.

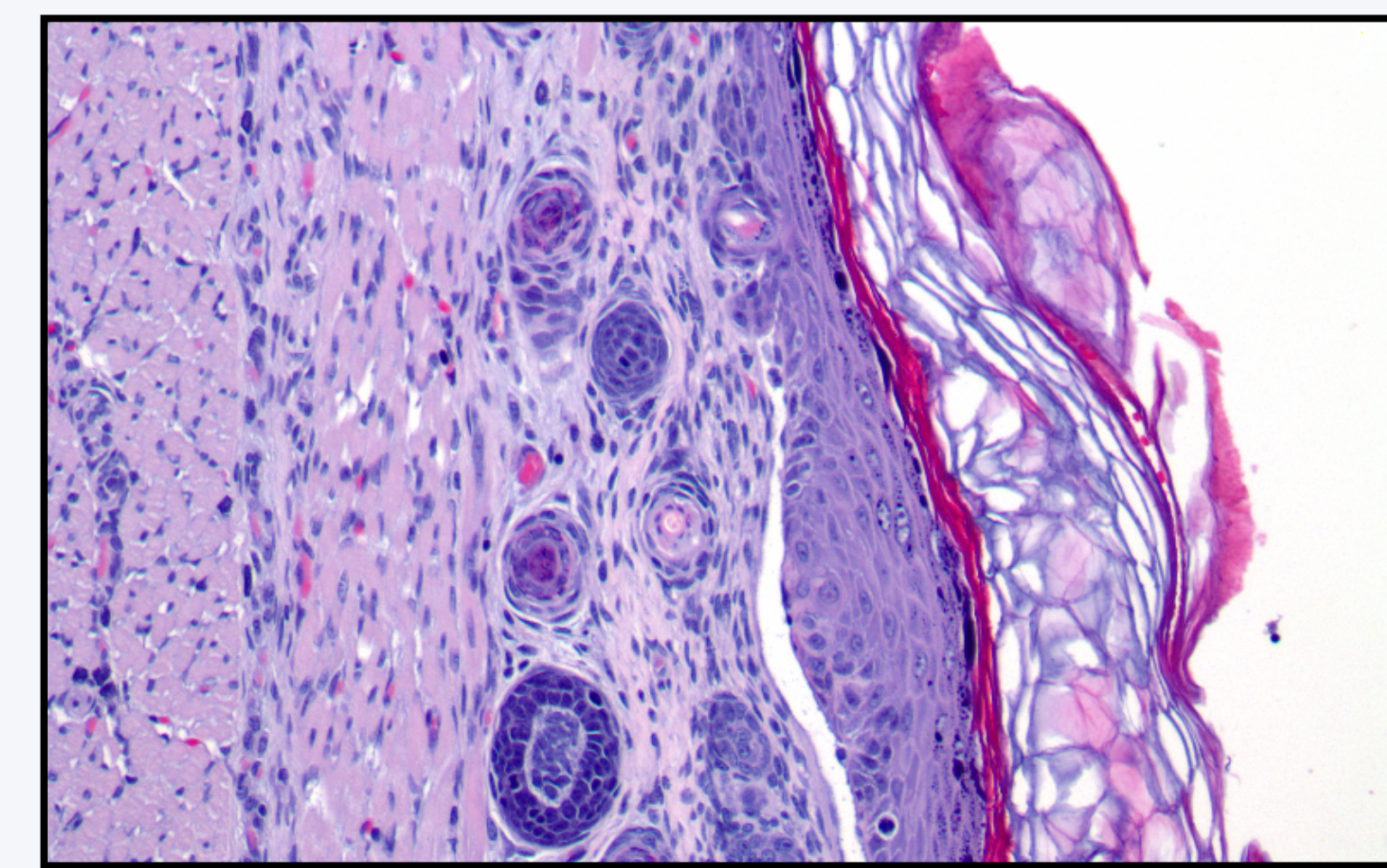


Figure 5: Intact border of a cleft. Note the epidermal hyperplasia and hyperkeratosis.

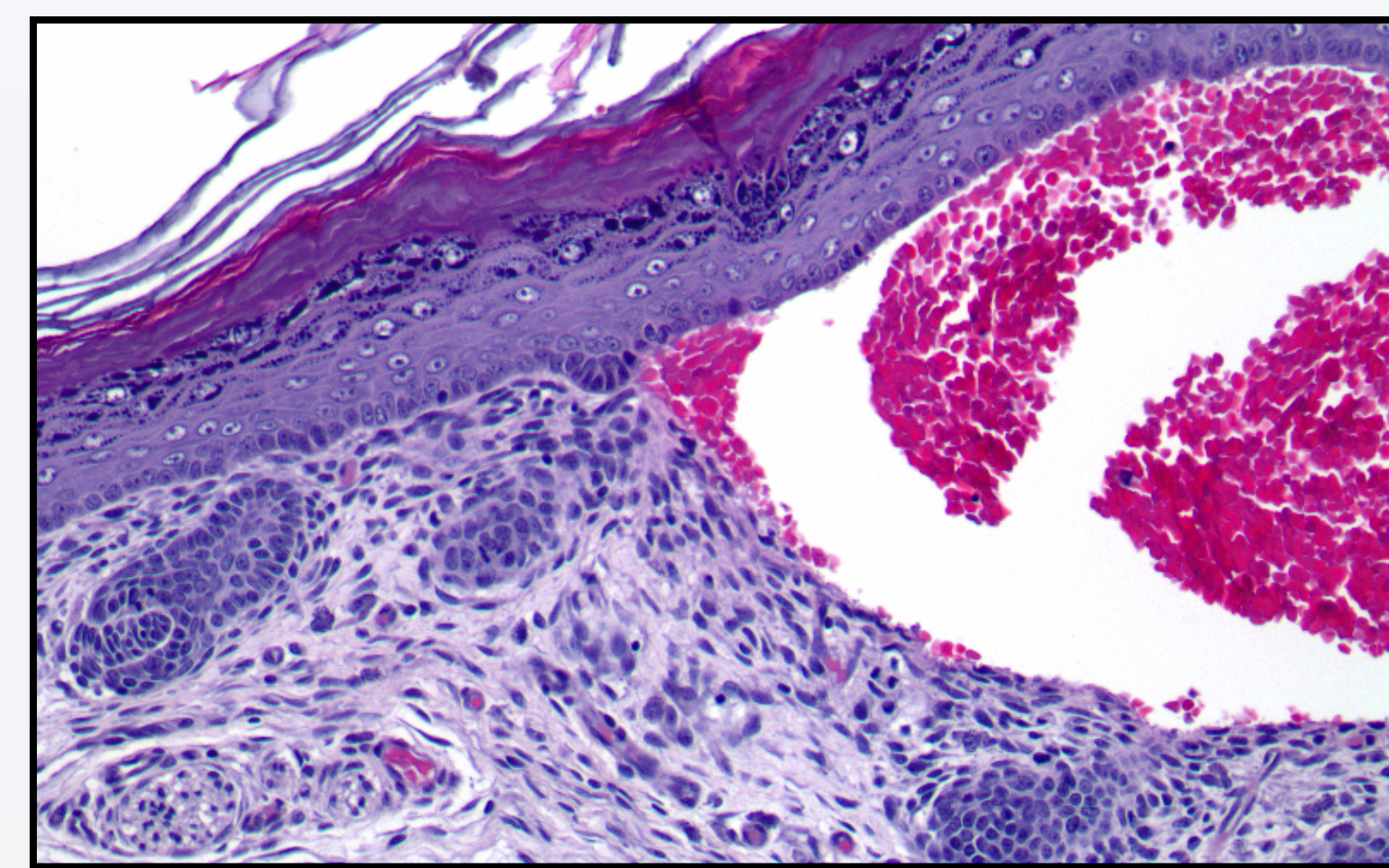


Figure 6: Clefts variably contain hemorrhage, fibrin, and cellular debris.

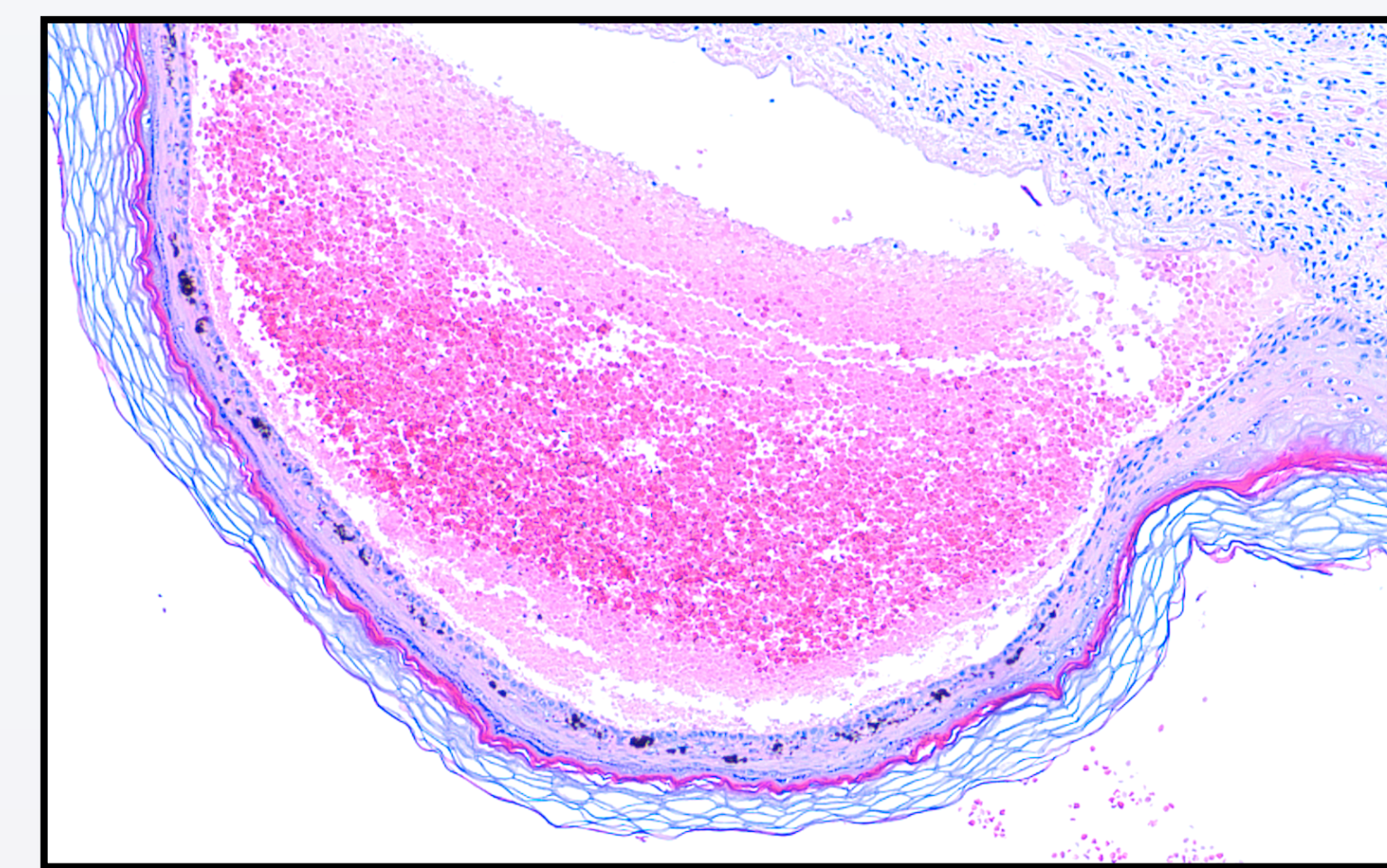


Figure 8: Clefts sometimes are large enough to form hemorrhagic bullae.

Additional Diagnostics

Transmission electron microscopy confirms separation of the epidermis from the dermis below the level of the lamina densa, which still remained adhered to the roof the cleft. Anchoring fibrils are also markedly reduced. All other structures are within normal limits.

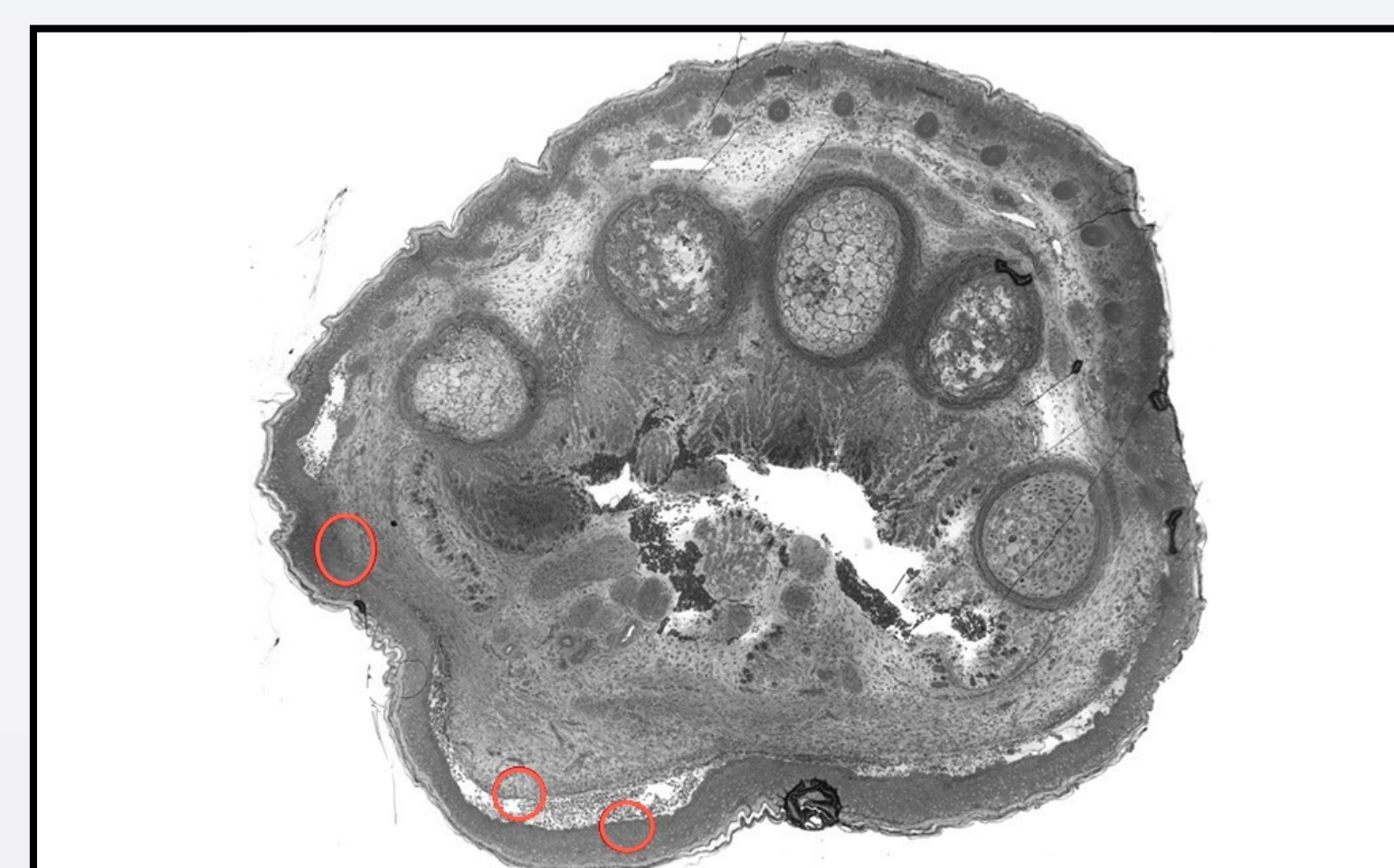


Figure 8: TEM images of the roof and floor of the clefts as well as intact areas were taken.

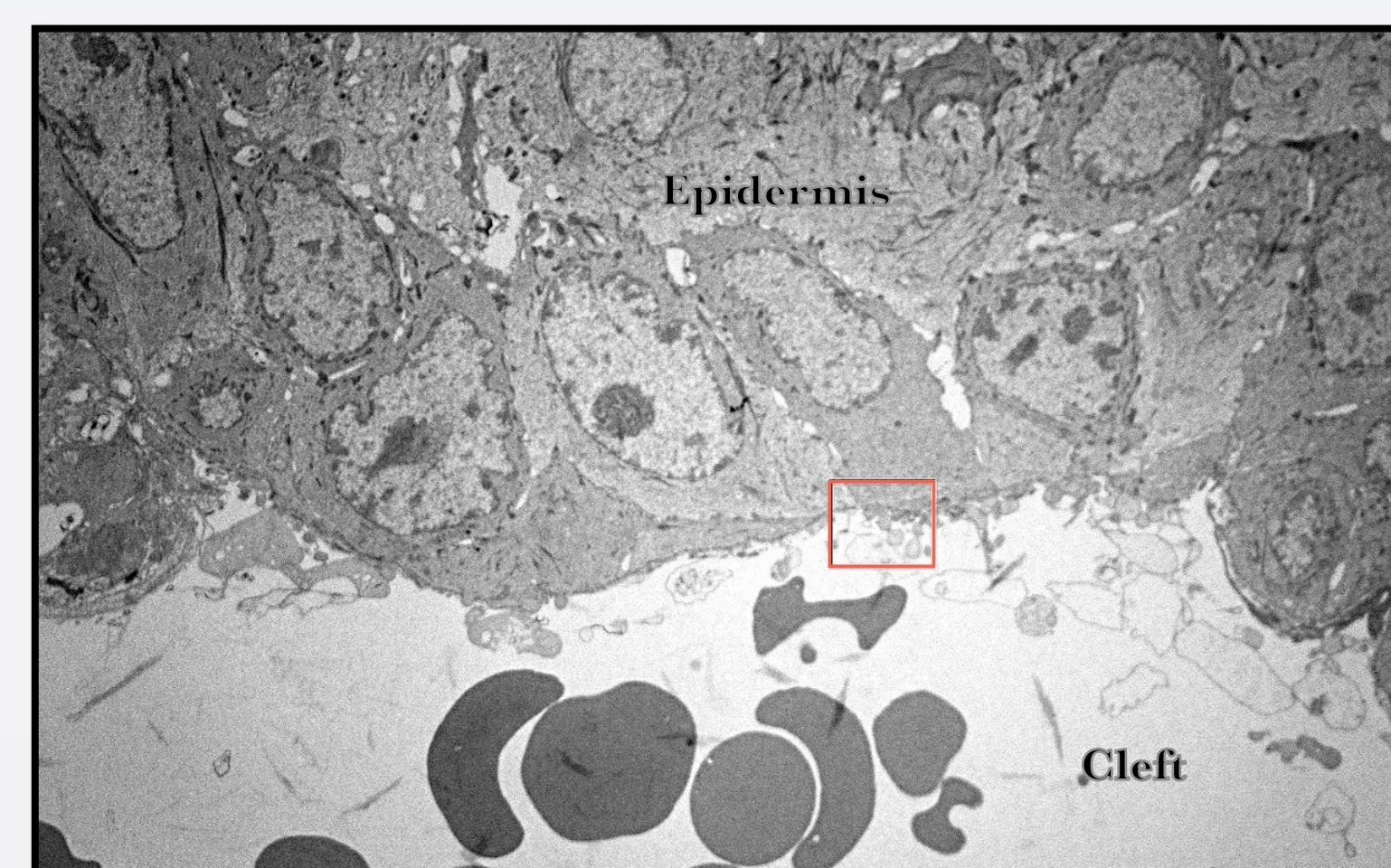


Figure 9: The epidermis (top) has separated completely from the dermis, with extravasated erythrocytes within the space.

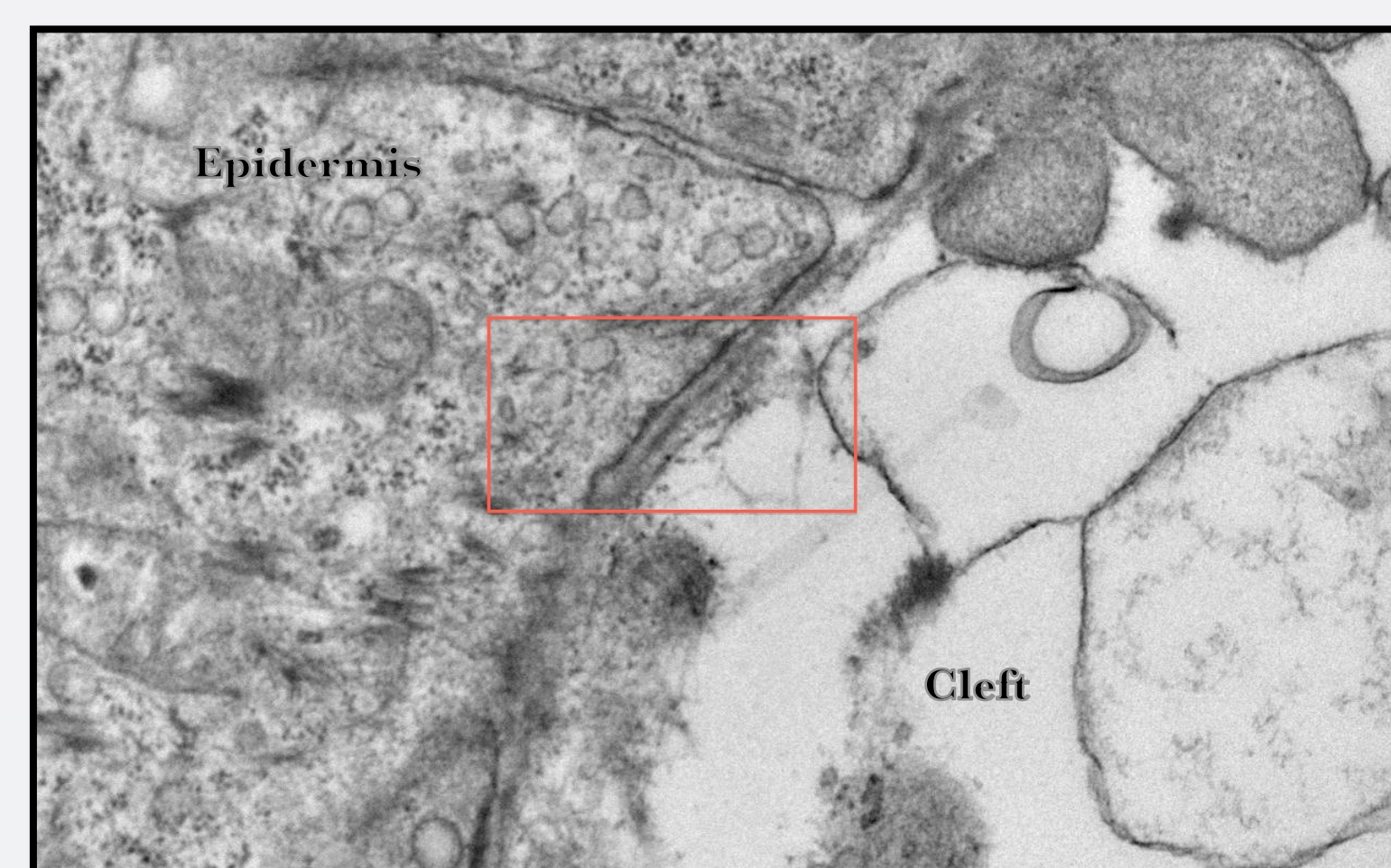


Figure 10: A magnification of the rectangle in Figure 9 reveals the basement membrane (rectangle). The epidermis is to the left.

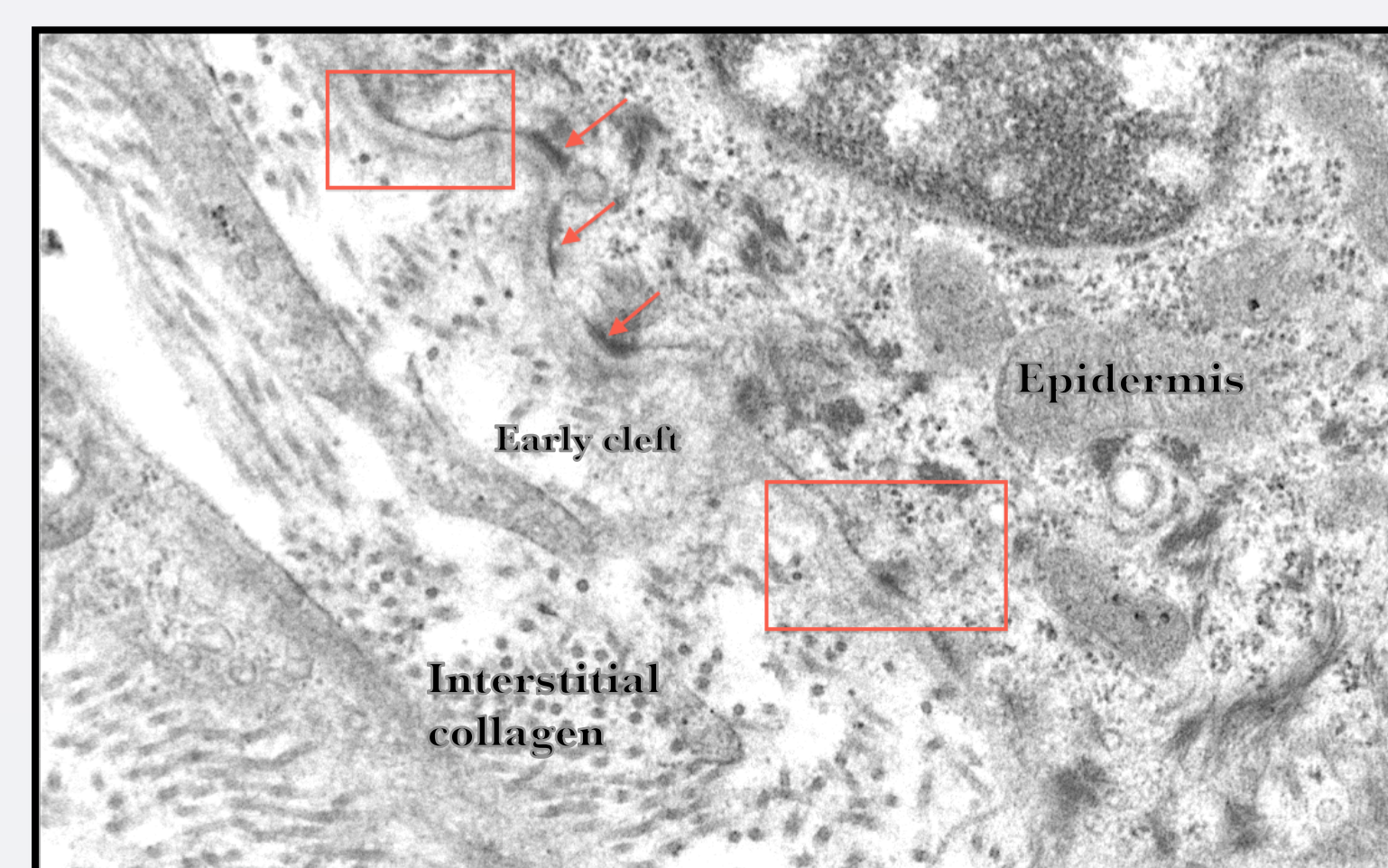


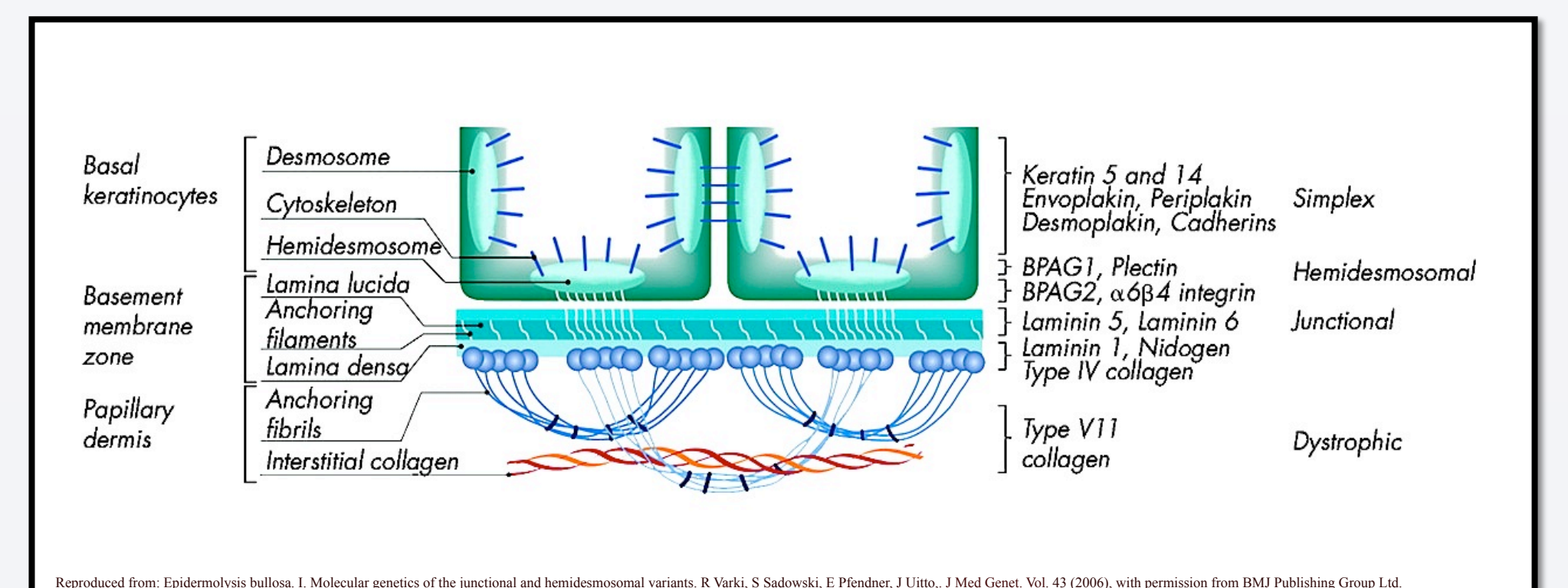
Figure 11: Basement membrane with intact lamina densa (rectangles), hemidesmosomes (arrows), and lack of normal anchoring fibrils.

Discussion

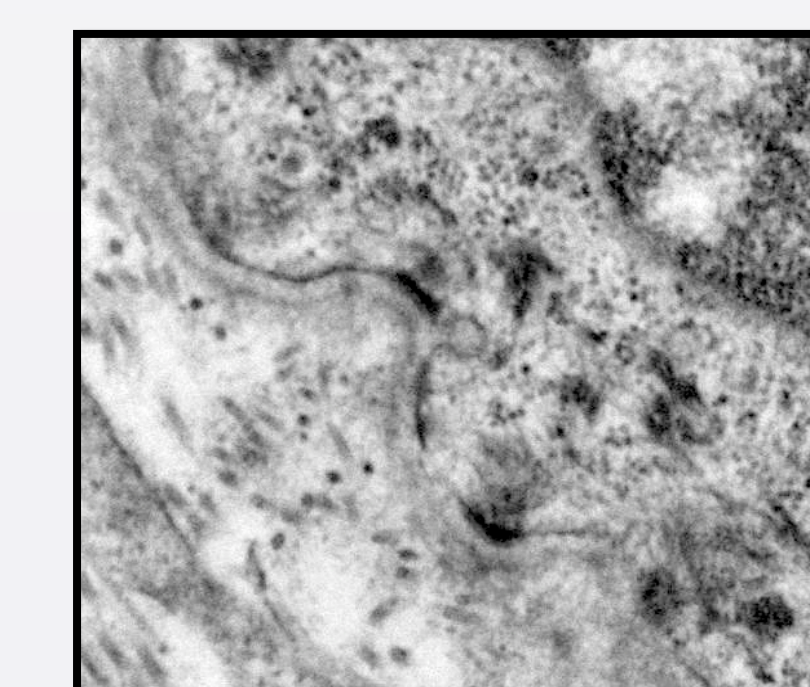
EB in Humans and Animals: Children with epidermolysis bullosa have been referred to as “crystal skin children” and “cotton wool babies” due to the fragility of their skin. Variants of EB have been reported in horses, ruminants, cats, and dogs, with most cases being singular or in small inbred groups. One of the most well-characterized variants seen in animals is the recessive junctional epidermolysis bullosa of Belgian draft horses.



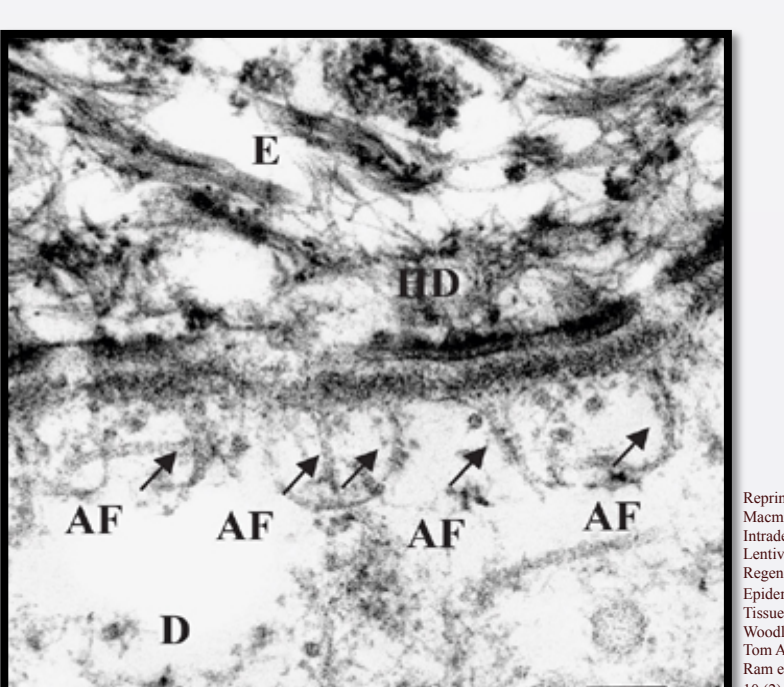
EB Subtypes: The subtype of epidermolysis bullosa depends on the specific genetic defect; each affects a different component of the dermo-epidermal junction. Epidermolysis bullosa simplex (SEB) is most common and results in mild blistering of areas where contact irritation occurs, such as the palms of the hand and soles of the feet. The more severe variants are junctional epidermolysis bullosa (JEB) and dystrophic epidermolysis bullosa (DEB). A single litter of Sprague Dawley rats presented with gross findings similar to our series, but the defect was at the level of the hemidesmosomes. Our case series is extremely similar to the transgenic mouse model of DEB, which uses a $-/-$ COL7A1 knockout.



Dystrophic Epidermolysis Bullosa: DEB, the most severe subtype, is caused by a defect in Collagen VII due to mutation of the COL7A1 gene. Type VII collagen is normally synthesized by keratinocytes and forms the anchoring fibrils that extend from the lamina densa to the dermis. A lack of proper anchoring fibrils results in separation of the epidermis from the underlying papillary dermis.



Lack of well-defined, normal anchoring fibrils in current rats.



Normal anchoring fibrils (AF)

Conclusions

- Based on the gross lesions, microscopic cleaving, and TEM determination of separation below the lamina densa and lack of normal anchoring fibrils, our cases are most 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 DEB occurring naturally and reproducibly in the rat.