Epidermolysis Bullosa

Introduction

- EB encompasses many clinically distinctive disorders with 3 features in common
  - Genetic transmission
  - Blister formation
  - Mechanical fragility of the skin
- 3 major forms of inherited EB
  - Simplex
  - Junctional
  - Dystrophic

History

- First described by von Hebra in 1870
- Simplex and dystrophic separated by Hallopeau in 1898
- Junctional EB described by Herlitz in 1935
- National EB Registry established in 1986

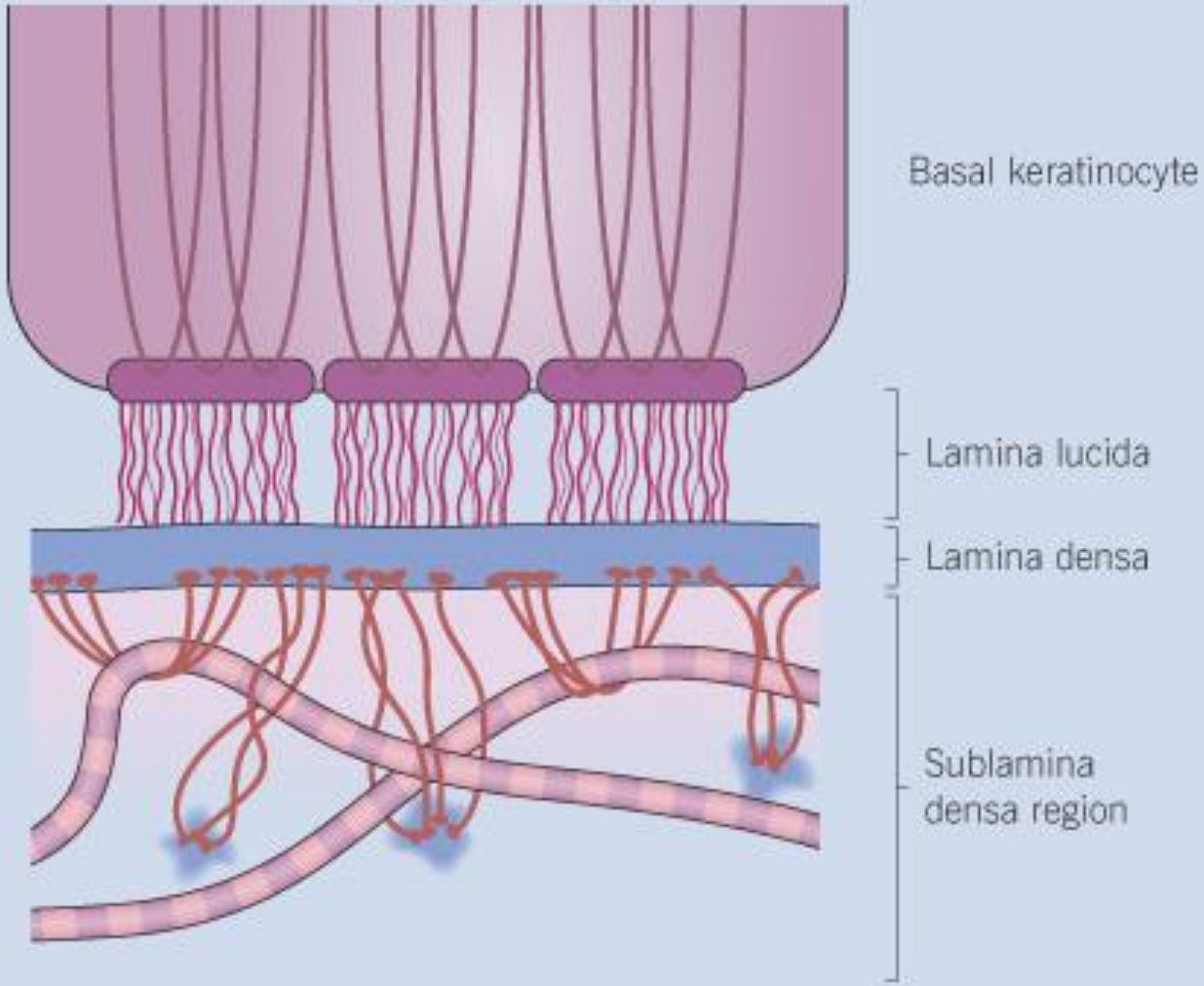
Epidemiology

- Prevalence estimate in 1990 was 8.22 per million
- 5 year incidence estimates: 19.6 per one million live births
- EB simplex is most common
- Recessive dystrophic EB is least common

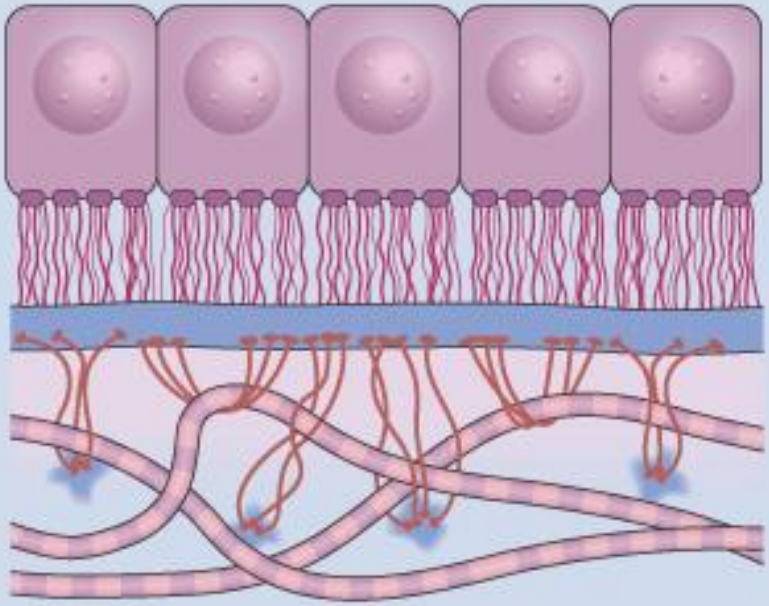
Pathogenesis

- Mutations of structural proteins of the epidermis
  - EBS
    - Intraepidermal tonofilaments- K5, 14
  - Junctional EB
    - Intralamina lucida- anchoring filaments and hemidesmosome, laminin 5, BP Ag 2, α6 β4 integrin
  - Dystrophic EB
    - Sublamina densa- anchoring fibrils, collagen VII

FOUR MAJOR ULTRASTRUCTURAL SUBREGIONS OF THE EPIDERMAL BASEMENT MEMBRANE



CLEAVAGE PLANES IN EPIDERMOLYSIS BULLOSA



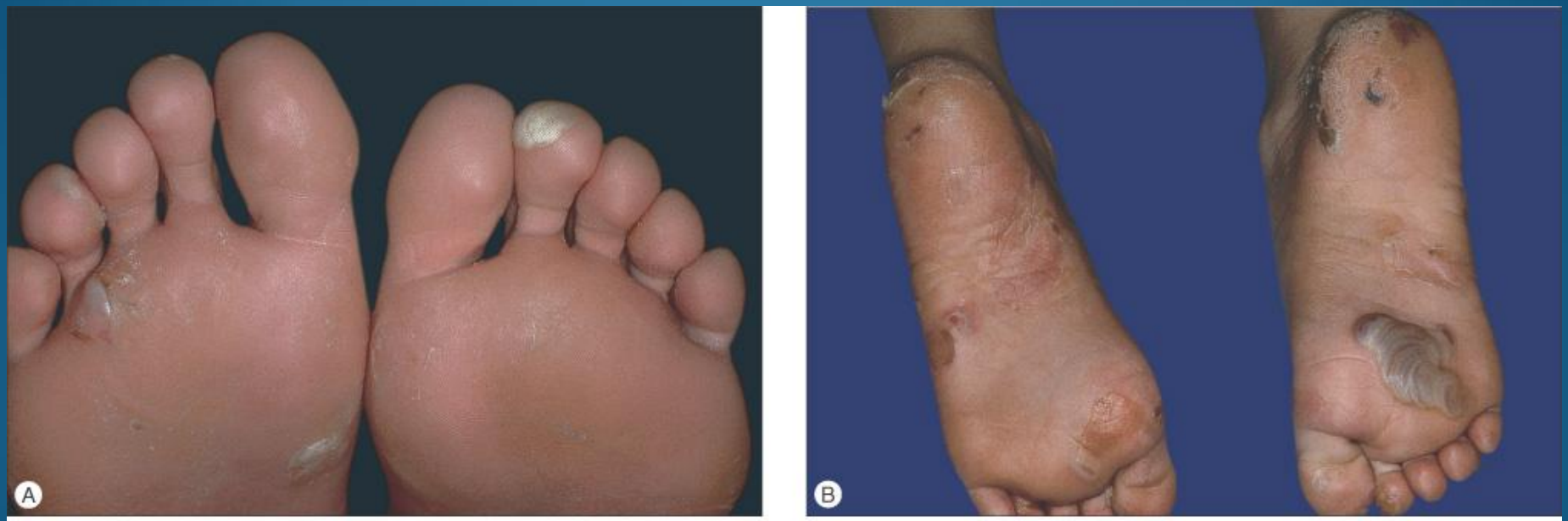
EB Simplex

- Intraepidermal split
- Keratins 5 and 14 (basal layer)
- 11 subtypes known, but 4 main AD inherited
- 4 subtypes
  - Weber- Cockayne
  - Koebner
  - Dowling- Meara
  - EBS with mottled pigmentation
- Rare subtype of EBS with muscular dystrophy- defect in plectin

EBS- Weber- Cockayne

- Localized recurrent bullous eruption on hands and feet
- Can appear as chronic form in infancy or later in life
- Exacerbated in hot weather or with prolonged walking- i.e. military
- May have hyperhidrosis
- Intraepidermal and suprabasal- no scarring
- Tx: Drysol bid can reduce blistering; treat infection

EBS- Weber- Cockayne

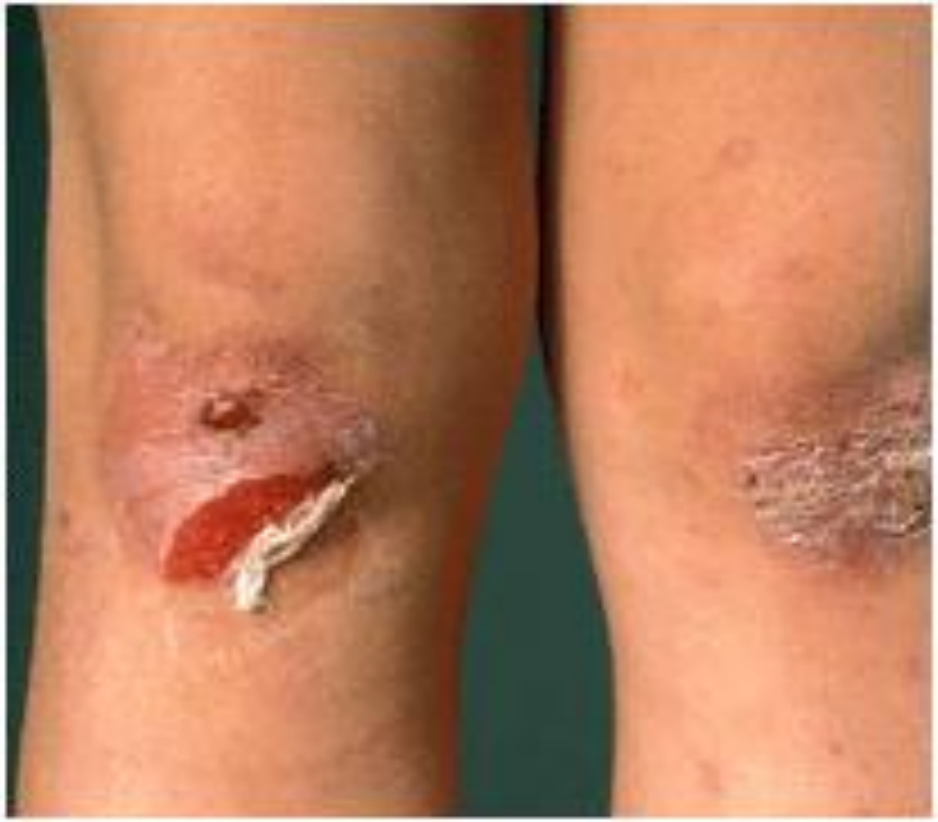


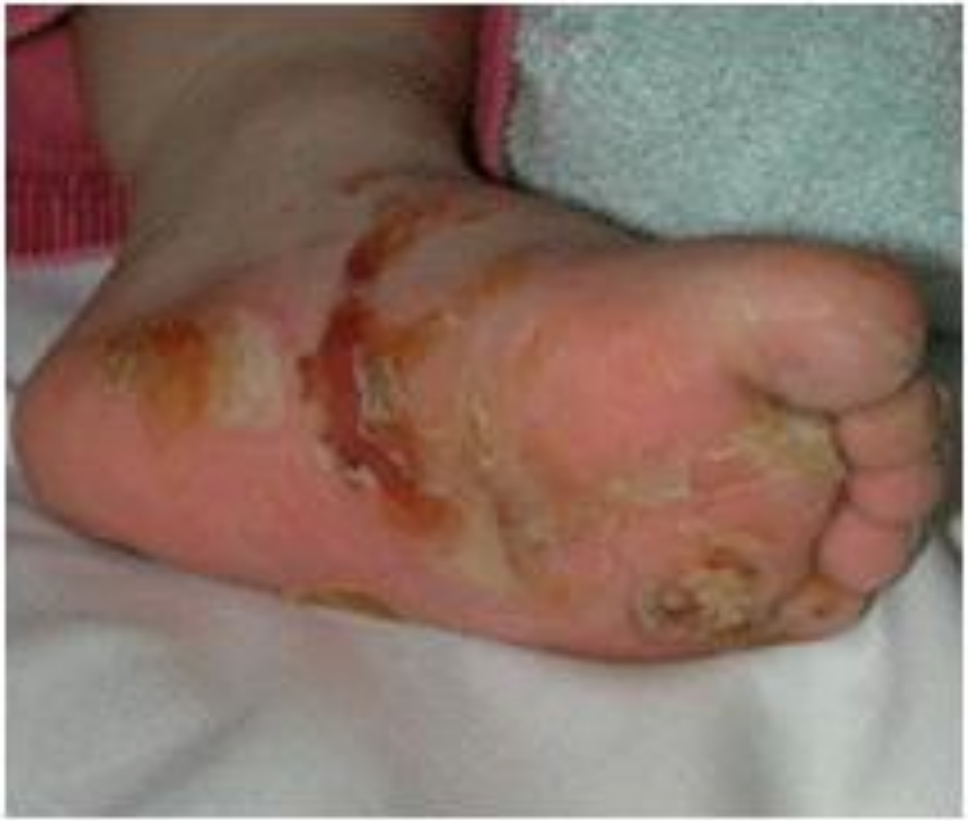
EBS- Weber- Cockayne

EBS- Koebner

- Generalized form
- 1/ 500,000 births
- Vesicles, bullae, and milia over hands, elbows, knees, feet
- Birth or soon after
- Recurs when child begins to crawl or walk
- Worse in the summer
- Lesions are sparse with no severe atrophy
- Usually no mucous membrane or nail involvement
- Tx: treat local infection, avoid trauma

EBS- Koebner

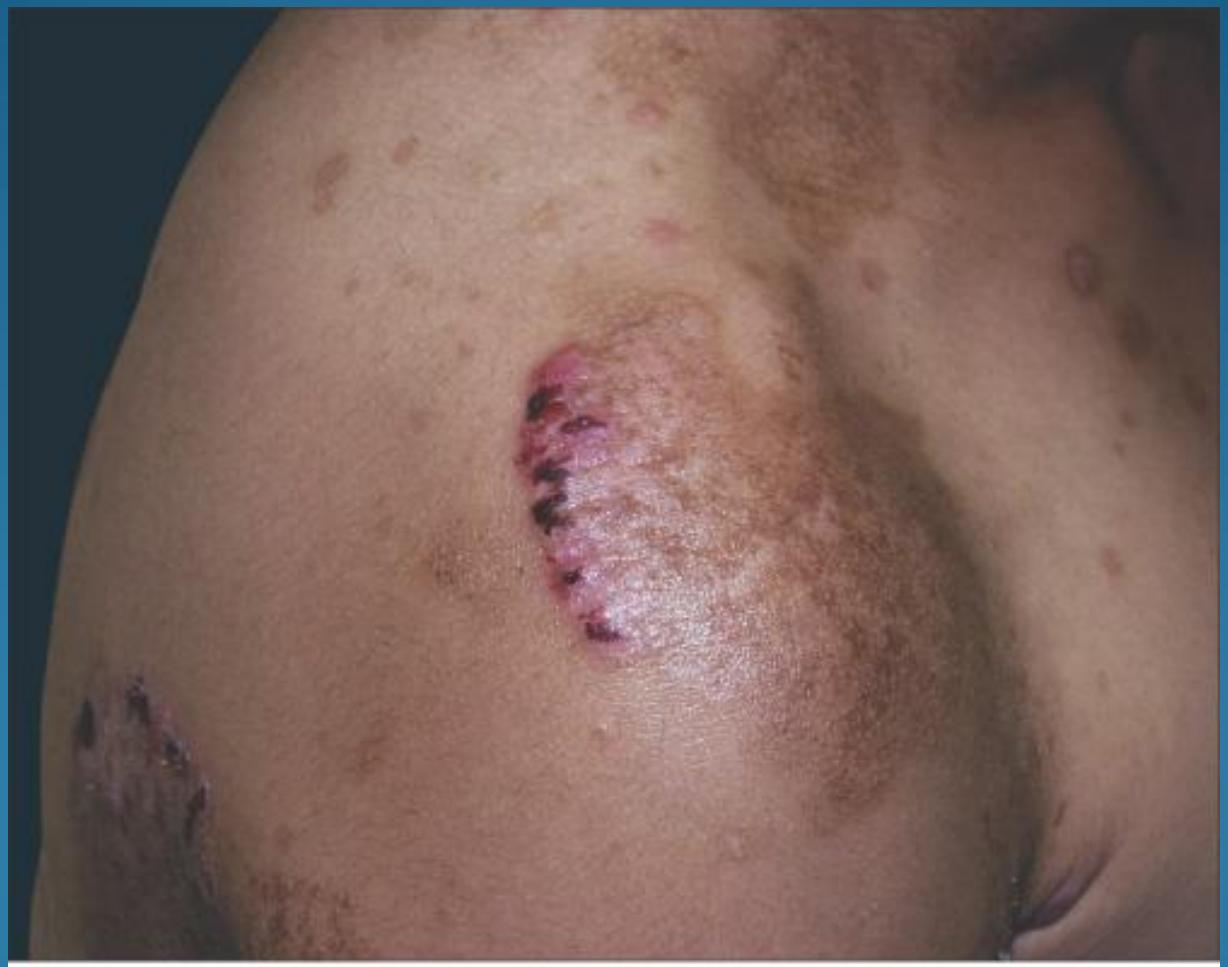




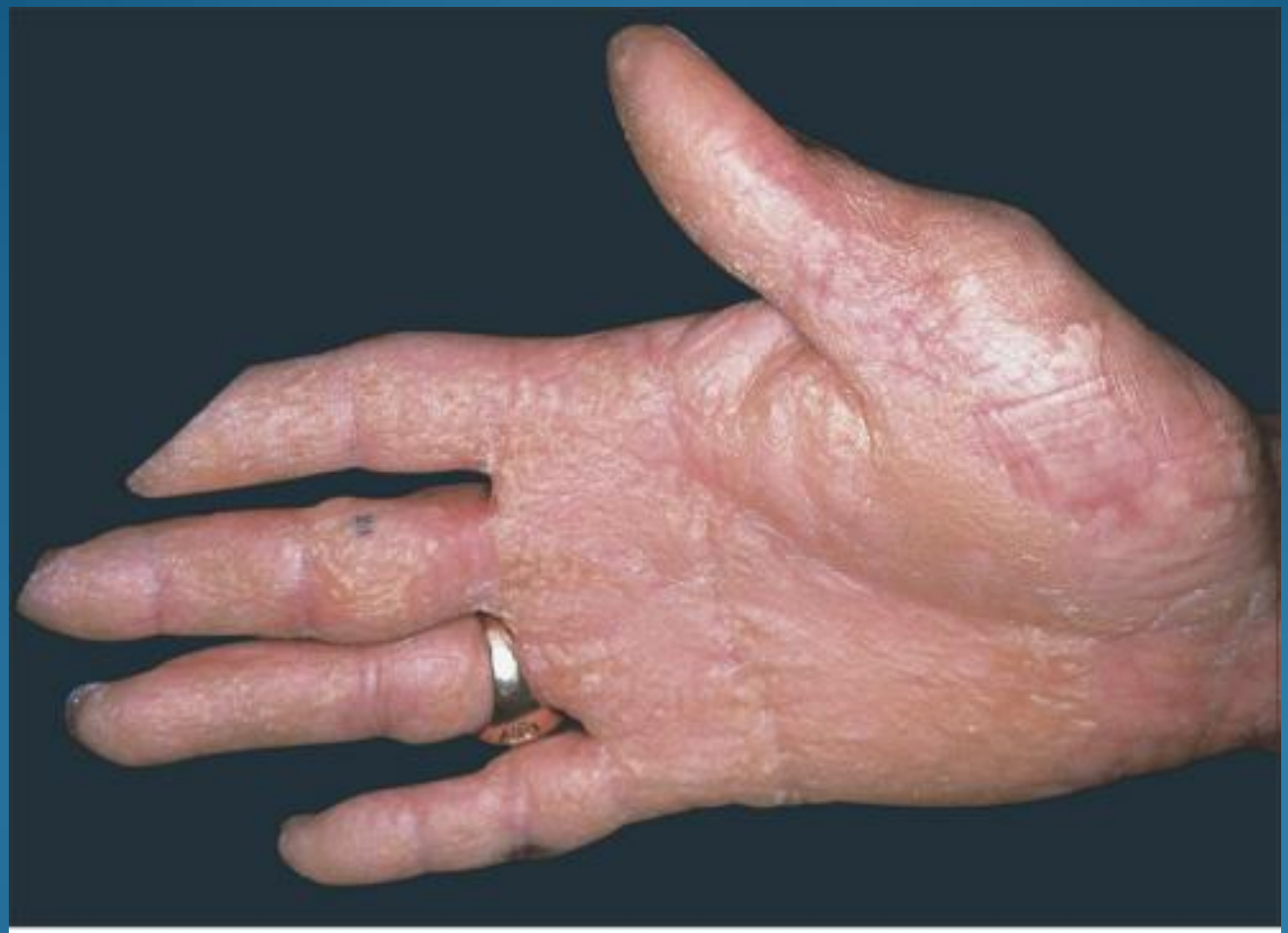
EB Herpetiformis- Dowling- Meara

- Circinate configuration in infancy
- May have milia, but no scarring
- Oral mucosa is involved
- Nails shed and can regrow
- Blistering improves with age
- May have hyperkeratosis of palms and soles after 6- 7 y.o.
- **Clumped tonofilaments** on EM

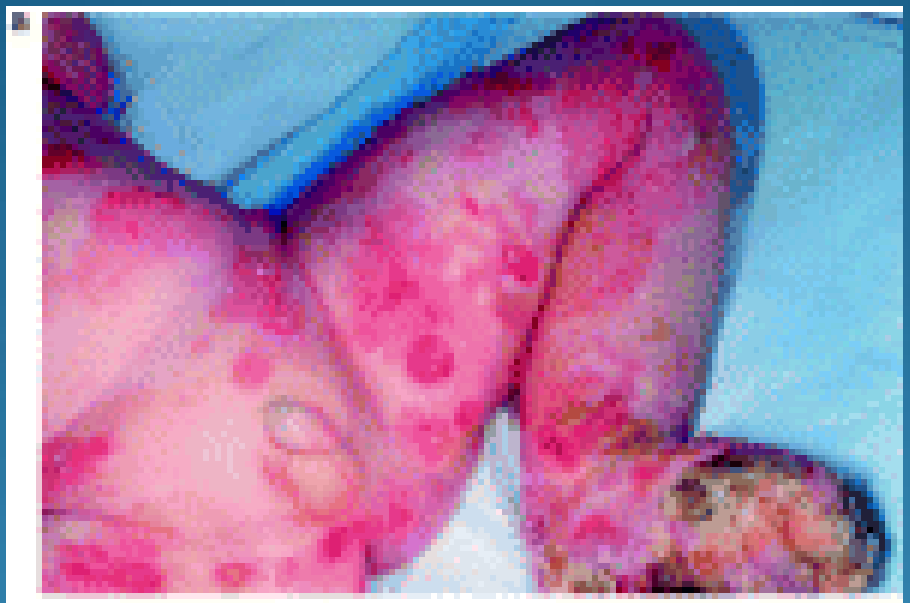
Dowling- Meara

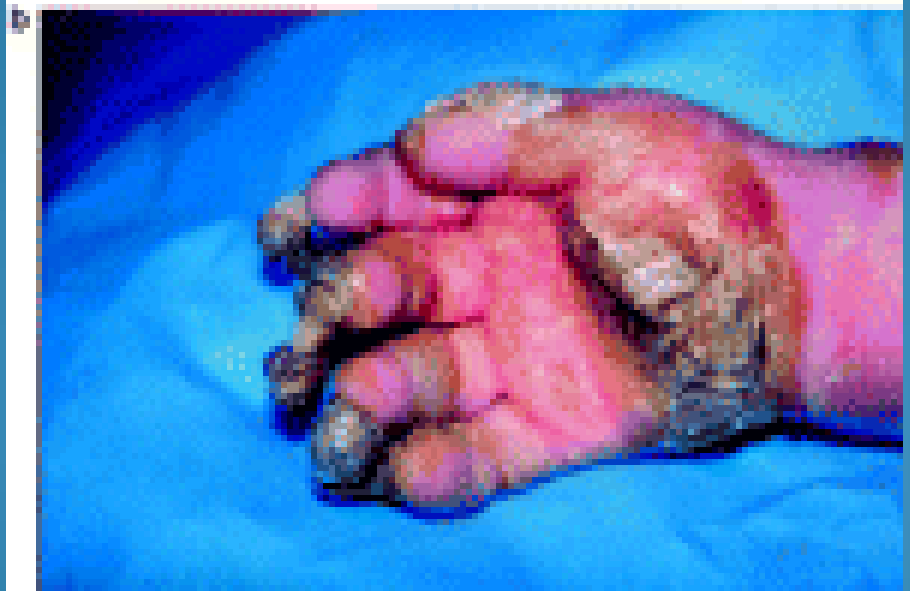


Dowling- Meara



Dowling- Meara





EBS with mottled pigmentation

- One Swedish family
- Scattered hyper- and hypopigmented macules
- Mottled pigmentation fades after birth
- Seasonal blisters in acral areas
- Vacuolization of the basal layer

EBS with muscular dystrophy

- Autosomal recessive
- Widespread blisters at birth
- Absent plectin in skin and muscles
- Scarring, milia, atrophy, nail dystrophy, dental anomalies, laryngeal webs, urethral strictures
- Muscular dystrophy begins in childhood or later

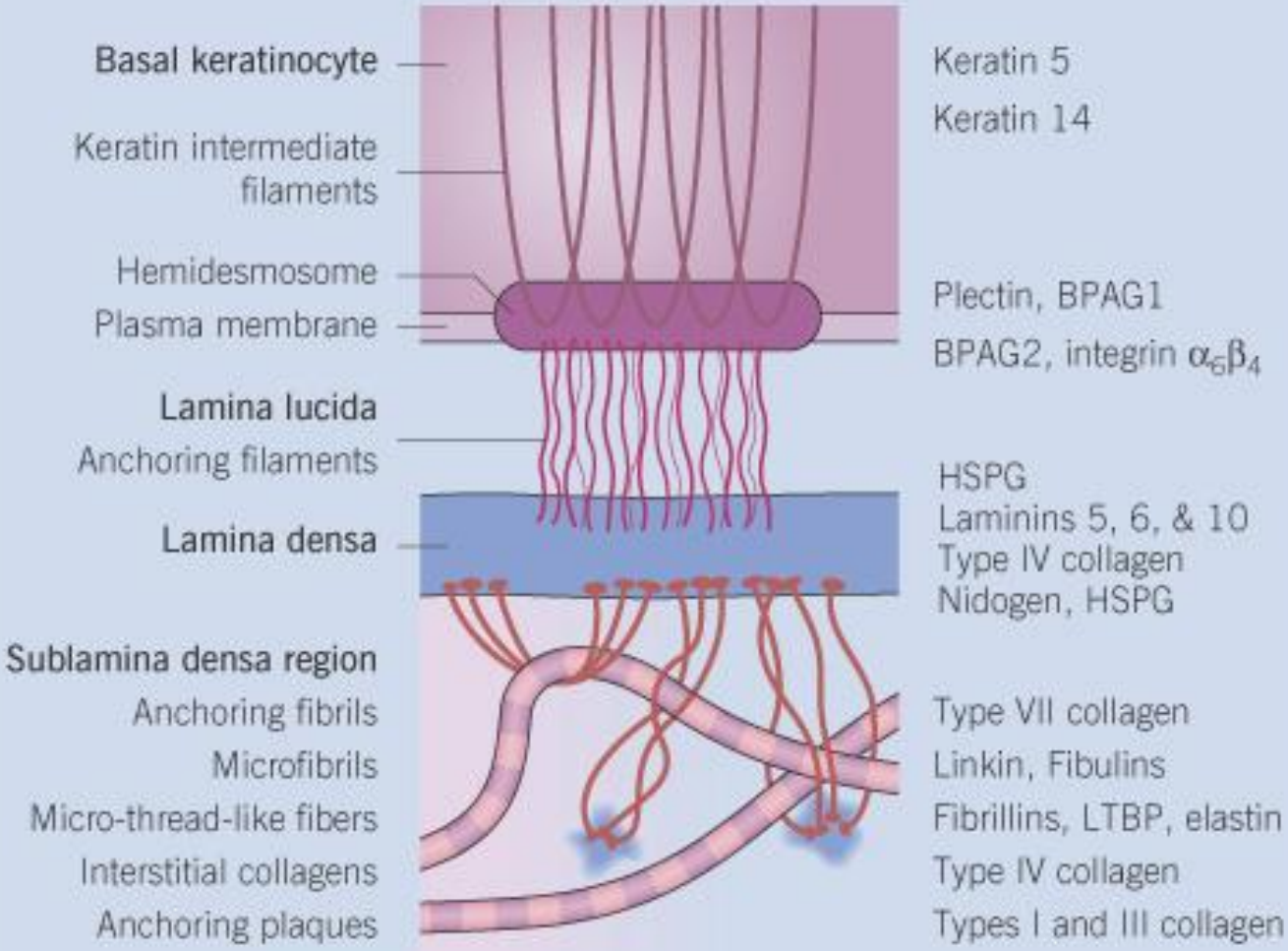
EBS Ogna

- Generalized bruising and hemorrhagic blisters
- Autosomal dominant
- Small, acral, sanguinous blisters at birth

Junctional EB

- Autosomal recessive
- Intralamina lucida split
- 3 subtypes
  - Herlitz (JEB gravis)- laminin 5
  - Non-Herlitz (generalized atrophic benign)- laminin 5 or BP Ag 2
  - JEB with pyloric atresia- α6 β4 integrin

COMPONENTS OF EPIDERMAL BASEMENT MEMBRANE



Junctional EB- Herlitz

- Severe generalized blistering
- May be present at birth
- May be fatal within a few months due to extensive denudation
- Relative sparing of hands
- Perioral and perinasal hypertrophic granulation tissue
- No scarring or milia

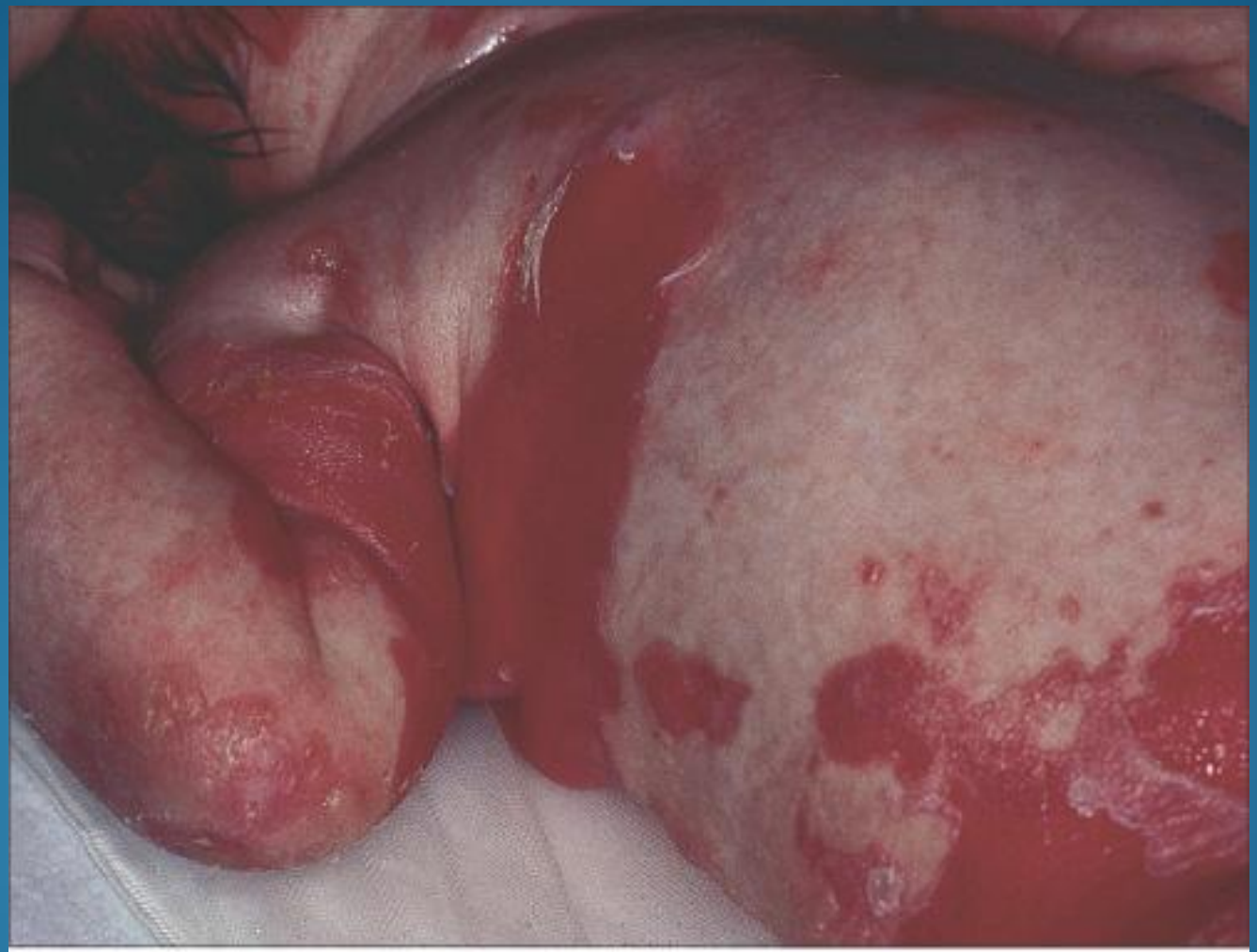
Junctional EB- Herlitz

- Enamel hypoplasia and pitting of teeth
- Laryngeal and bronchial lesions can cause respiratory distress and potentially be fatal
- Can affect GI tract, gallbladder, cornea, vagina
- After infancy- growth retardation, refractory anemia
- Mutations in polypeptide subunits of laminin 5
  - LAMA3
  - LAMB3
  - LAMC2

Junctional EB- Herlitz

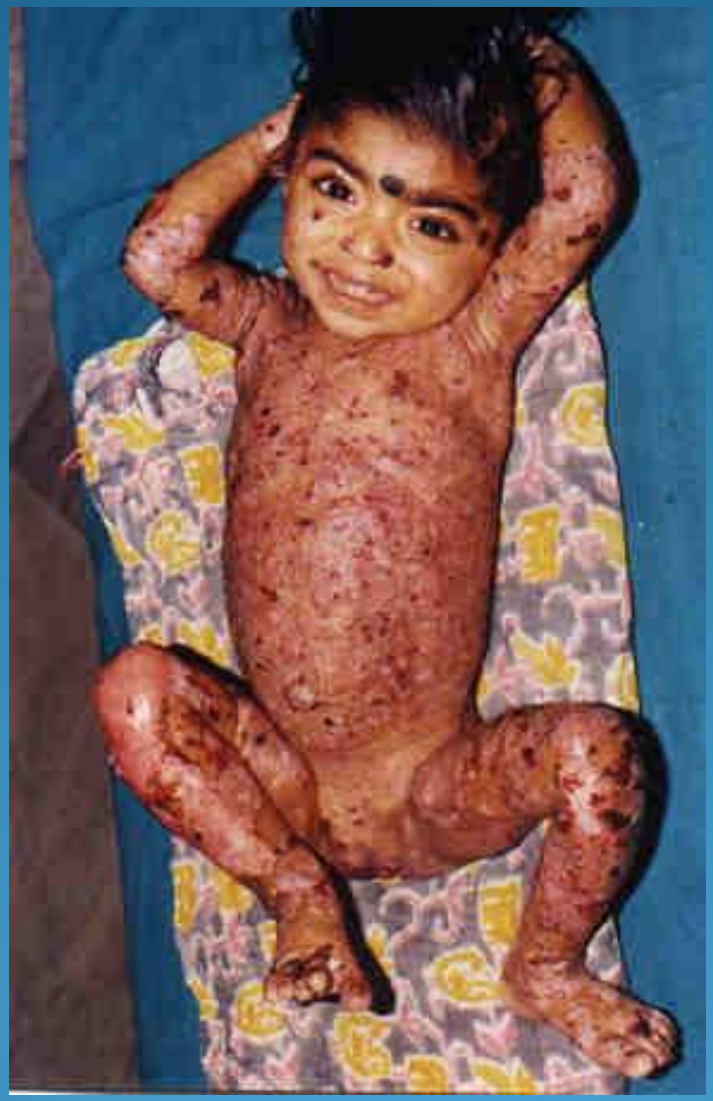
- Wound care and infection control
- May use epidermal autografts of cultured keratinocytes of uninvolved skin grown on collagen sponges

Junctional EB- Herlitz



Junctional EB- Herlitz

Junctional EB- Herlitz



Junctional EB- non-Herlitz (generalized atrophic benign)

- Onset at birth
- Generalized blisters and atrophy
- Mucosal involvement
- Dystrophic or absent nails
- Atrophic alopecia
- Enamel defects
- Reports of multiple SCCs
- Patients often survive to adulthood

Junctional EB- non-Herlitz (generalized atrophic benign)

- Hemidesmosomes reduced or absent
- Mutations in COL17A1- encoding for BP Ag 2

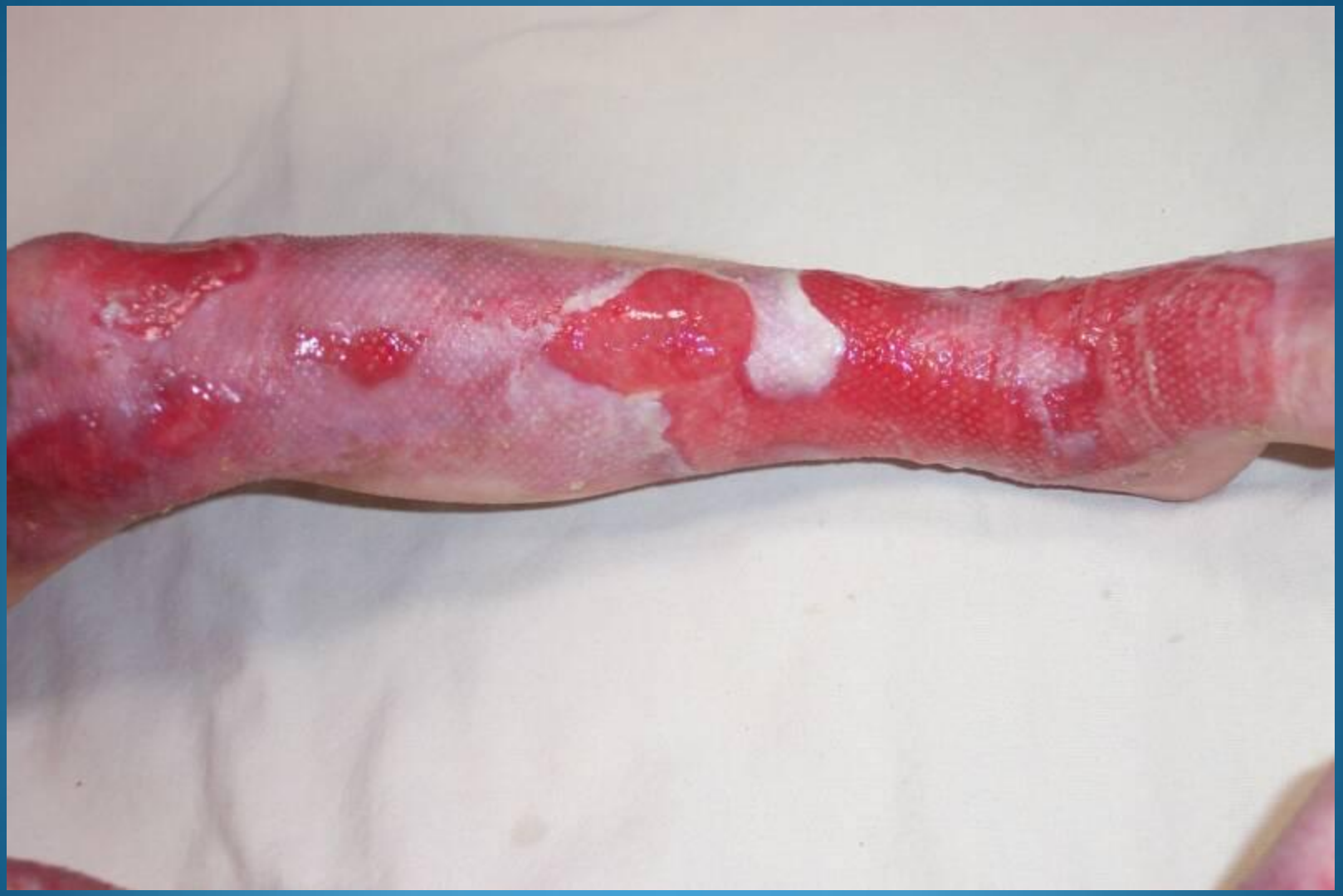
Junctional EB with Pyloric Atresia

- Presents at birth
- Severe mucocutaneous fragility
- Gastric outlet obstruction
- If they survive neonatal period, blistering will improve
- Scarring of urinary tract can occur
- Mutation in $\alpha 6$ or $\beta 4$ integrin

Cicatricial Junctional EB

- Described in 1985 by Haber et al
- Blisters heal with scarring, which leads to syndactyly and contractures
- Stenosis of anterior nares
- Rudimentary hemidesmosomes

Junctional EB



Dystrophic EB

- Autosomal dominant or recessive
- Mutations in COL7A1 encoding for collagen VII
- Subepidermal blistering that heals with scarring
- Anchoring fibrils deficient or defective

Dominant Dystrophic EB

- Vesicles and bullae on extensor surfaces of extremities
- Most pronounced over toes, fingers, knuckles, ankles, elbows
- Flesh-colored scarlike areas (albopapuloid) occur on trunk, often in adolescence
- Nikolsky sign is present
- Healing with scarring and atrophy

Dominant Dystrophic EB

- Milia on rims of ears, dorsal hands, extensor arms and legs
- Mucous membranes involved
- Laryngeal involvement can manifest as persistent hoarseness
- Dysphagia from pharyngeal scarring
- Scarring of the tip of the tongue
- Normal teeth

Dominant Dystrophic EB

- Nail dystrophy
- Partial alopecia of scalp
- No body hair
- Dwarfism
- Contractures and claw-like hands
- Atrophy of phalangeal bones and pseudosyndactyly

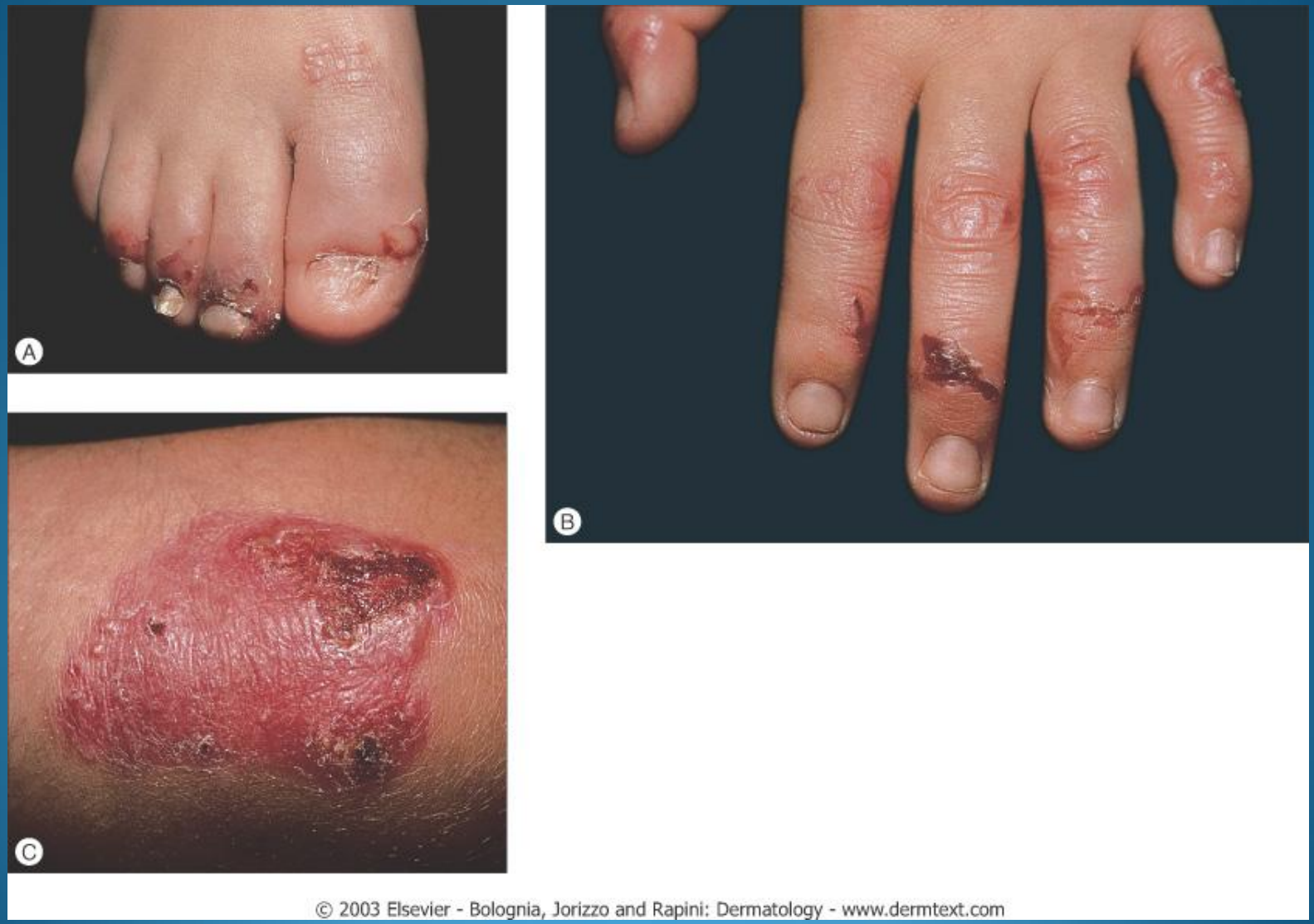
Dominant Dystrophic EB

- Albopapuloid (Pasini) is more severe form
- Cockayne- Touraine is more limited and no albopapuloid lesions are seen
- Non-inflammatory supepidermal bulla on path
- EM- cleavage beneath the basal lamina, reduced and rudimentary anchoring fibrils

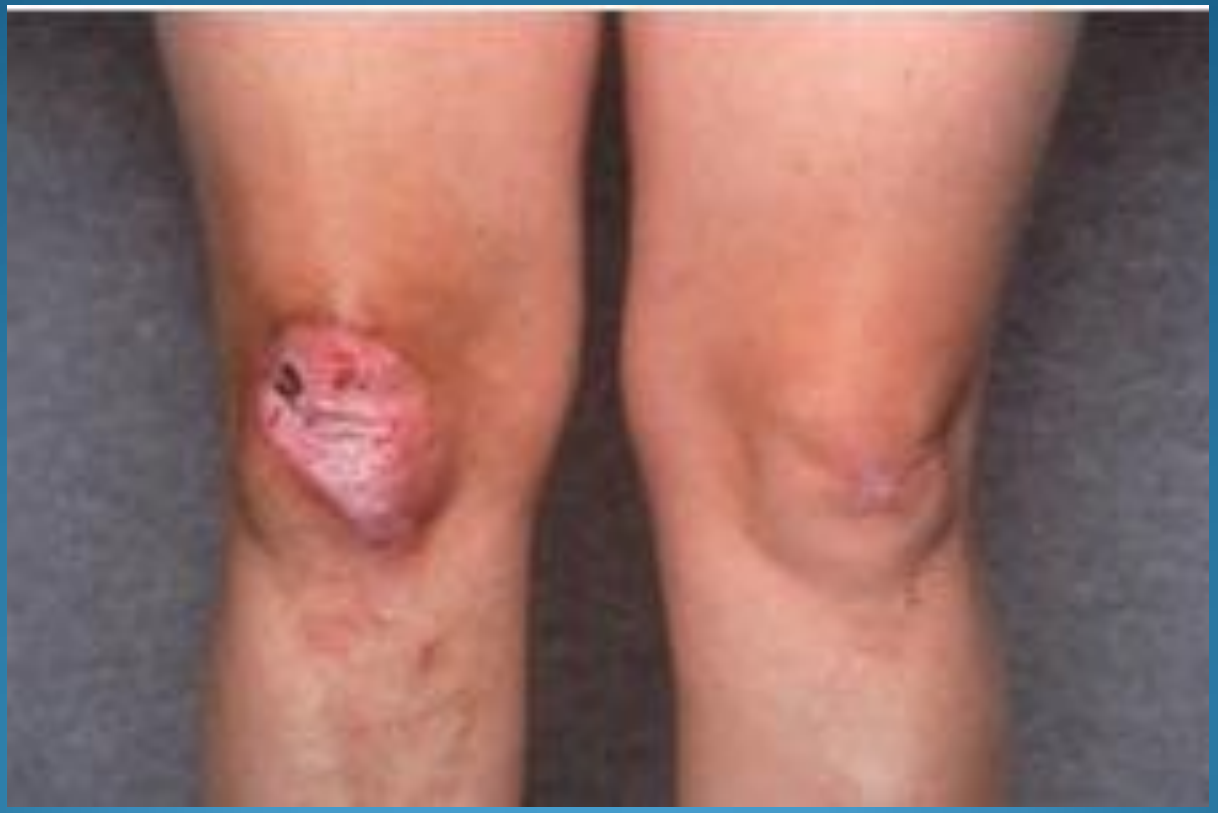
Dominant Dystrophic EB

- Skin grafts and allogenic cultured keratinocytes can be used in treating non-healing skin defects
- Blistering will decrease with time

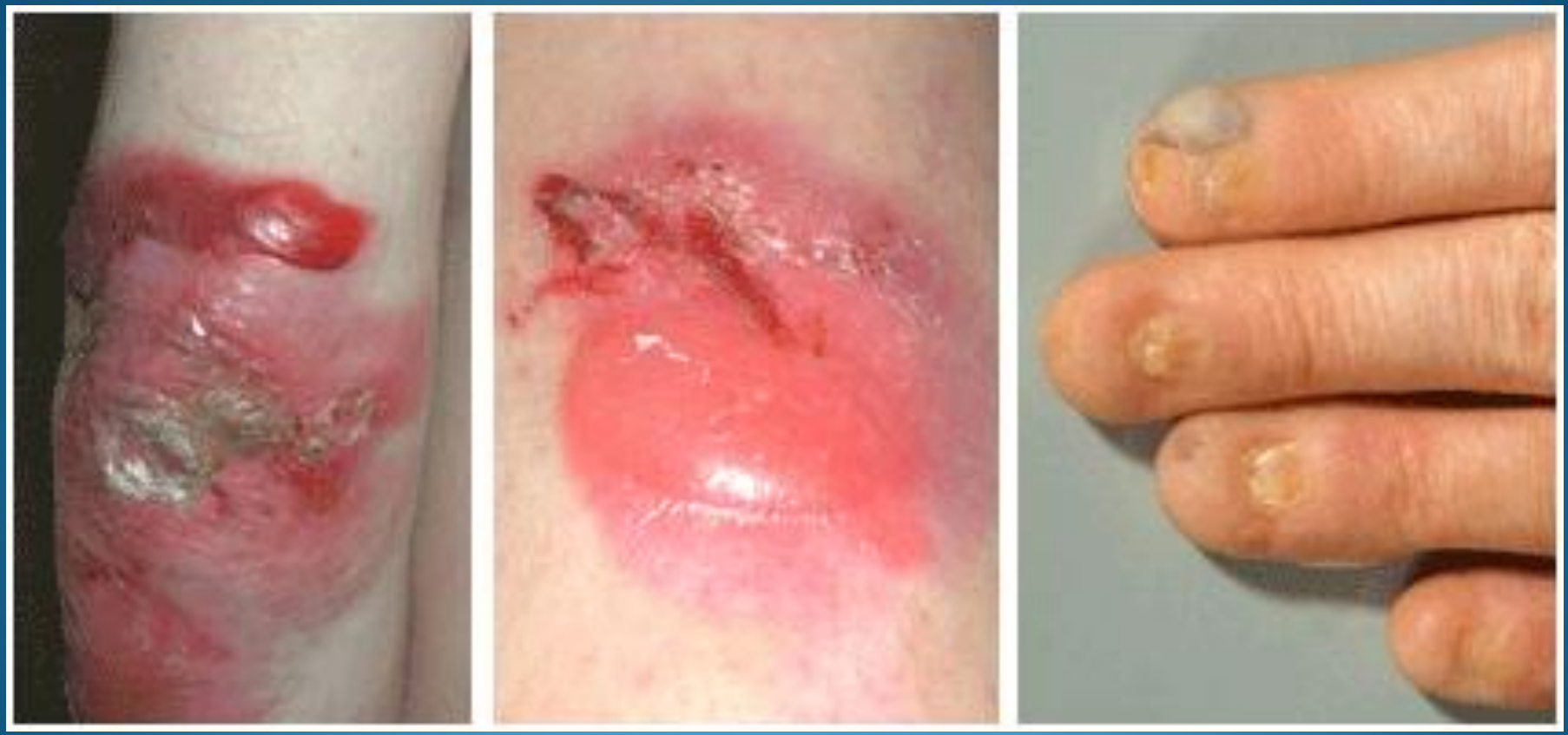
Dominant Dystrophic EB



Dominant Dystrophic EB



Dominant Dystrophic EB



Bart's Syndrome

- Autosomal Dominant
- Mechanoblisters
- Congenital localized absence of skin on lower extremities
- Renal aplasia
- Mandibulofacial dysostosis

Recessive Dystrophic EB

- Mutations in gene encoding type VII collagen (COL7A1)
- 3 variants
  - Generalized
    - Mild or mitis
    - Severe (Hallopeau- Siemens)
  - Localized
  - Inverse

Recessive Dystrophic EB- mild/ mitis

- Blisters primarily on hands, feet, elbows, knees
- Limited complications

Recessive Dystrophic EB- Hallopeau-Siemens

- Generalized cutaneous and mucosal blistering at birth
- Encasement of fingers and toes in scar tissue- mitten deformity
  - 90% by age 25
- Microstomia and many dental caries
- May have esophageal stricture
- Anemia and growth retardation are possible
- Nutritional deficiency can lead to a fatal cardiomyopathy (selenium deficiency)

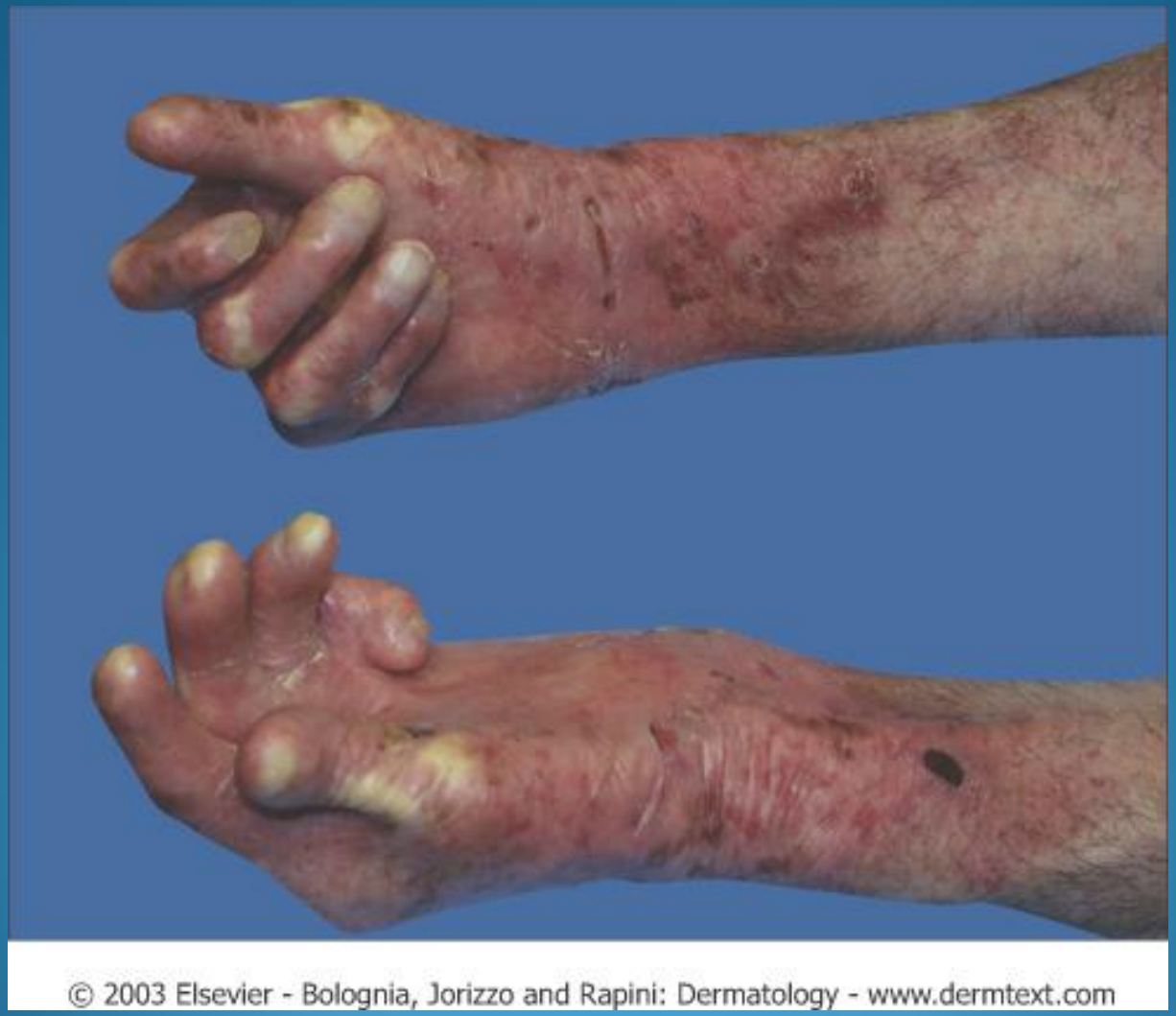
Recessive Dystrophic EB- Hallopeau-Siemens

- Fatal systemic amyloidosis (AA) has been reported
- Risk of melanoma
  - 1.5% by age 12
- High risk of SCCs
  - 22% by age 25, 50% by age 35, 77% by age 60
  - Often metastasize
  - Unresponsive to chemotherapy and radiation
  - Leading cause of death at or after mid- adolescence
  - Most patients die within in 5 years after dx of SCC

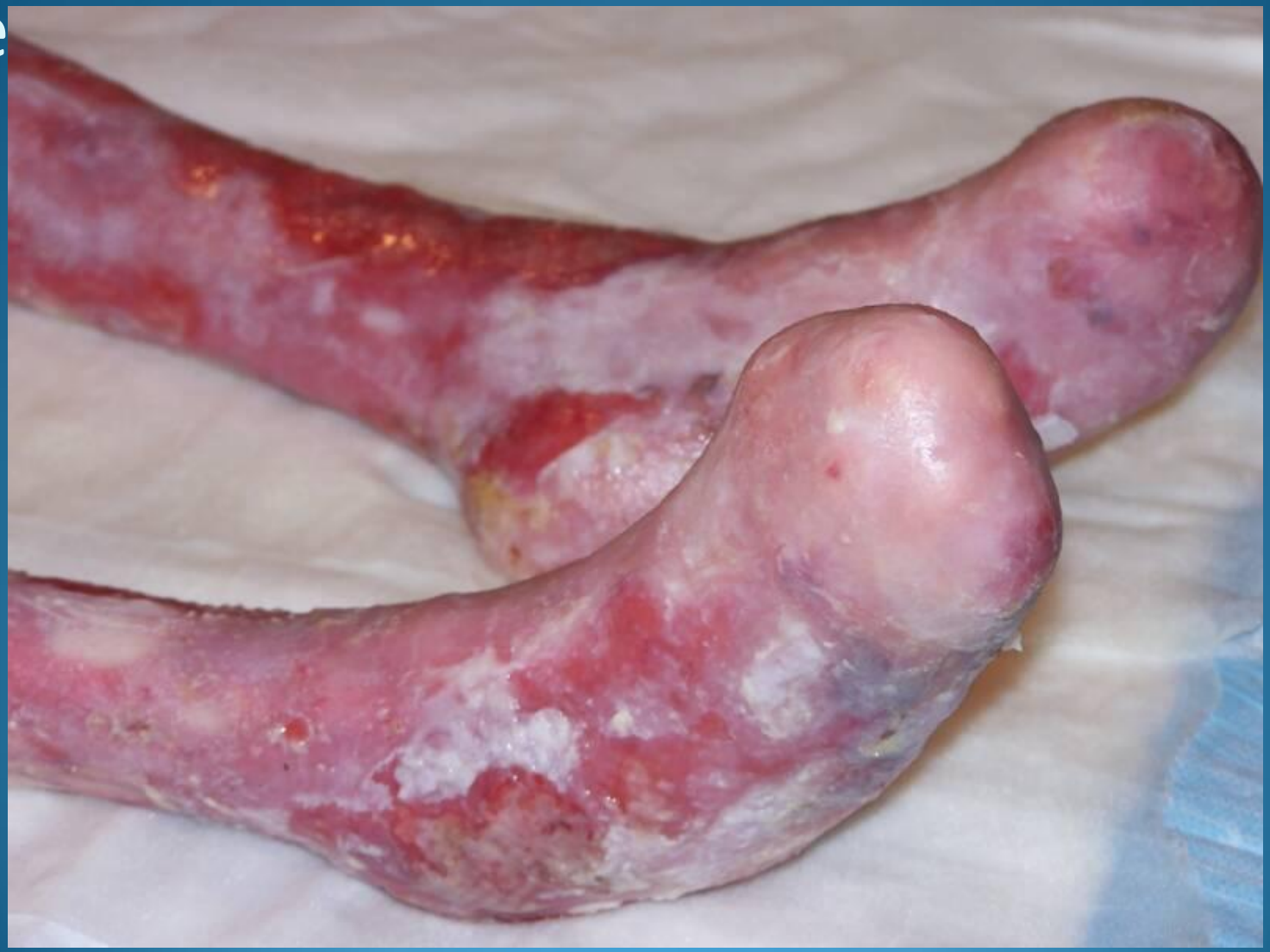
Recessive Dystrophic EB- Hallopeau-Siemens

- Educate family and refer to DEBRA (Dystrophic Epidermolysis Bullosa Research Association of America)
- Treatment is mainly palliative
  - Aggressive dental intervention
  - Nutritional support
  - Skin grafts
  - Cultured keratinocytes

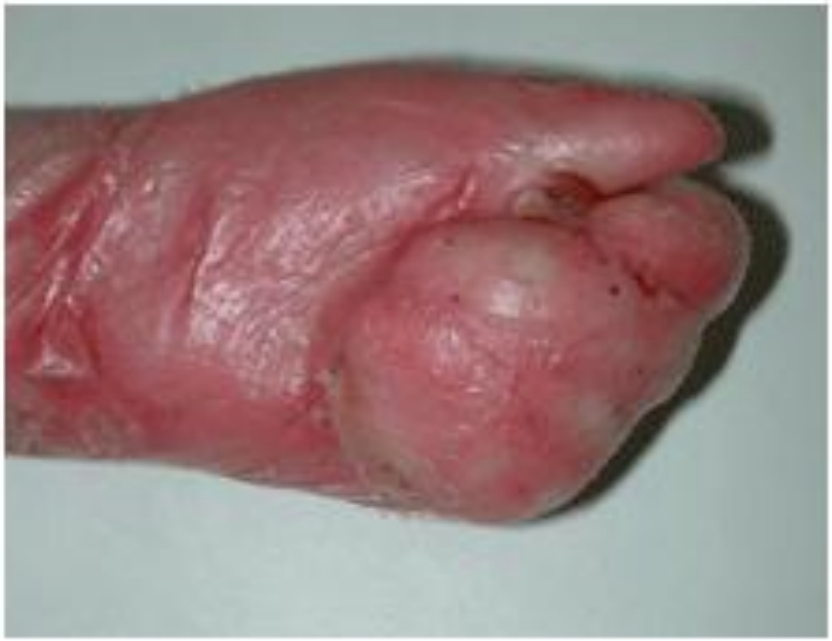
Recessive Dystrophic EB- Hallopeau-Siemens

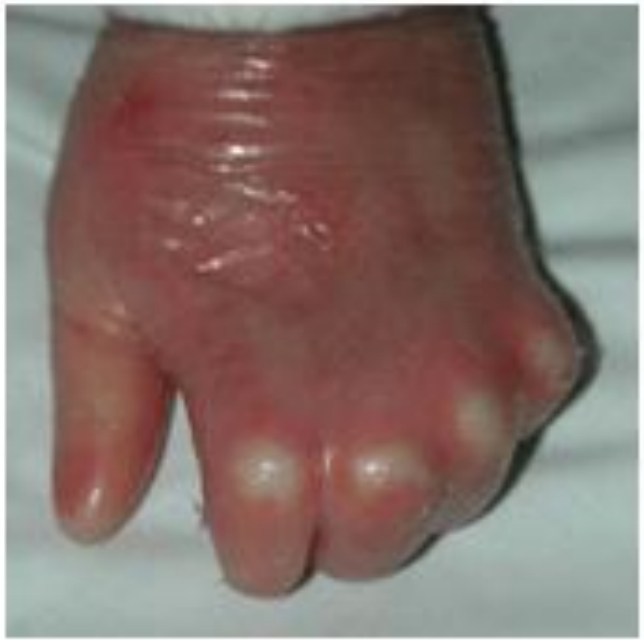


Recessive Dystrophic EB- Hallopeau-Sie



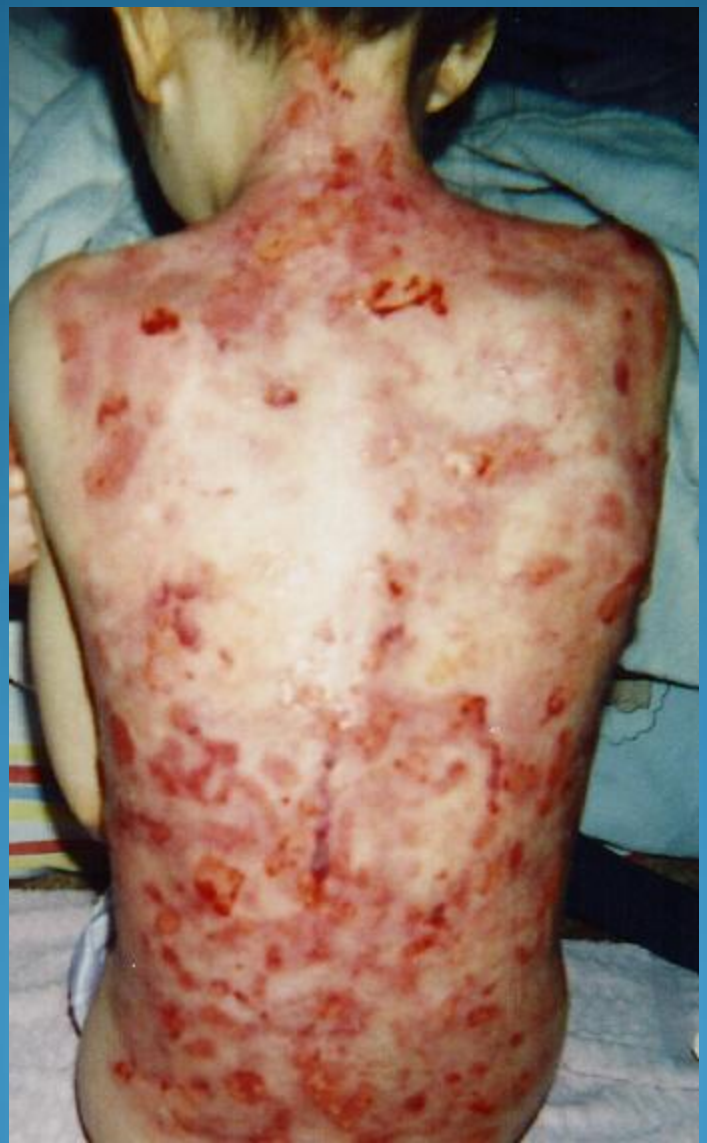
Recessive Dystrophic EB- Hallopeau-Siemens





Mutilation bei EBD (Hände)

Recessive Dystrophic EB- Hallopeau-Siemens



Approach to the Patient

- History and physical exam
- Skin biopsies for IF, EM
  - Rubbing skin with an eraser can lead to a subclinical lesion that demonstrates the split histologically
- Immunofluorescent mapping
  - EBS- BP Ag, laminin, type IV collagen all at base
  - Dystrophic EB- BP Ag, laminin, type IV collagen all at roof
  - Junctional EB- BP Ag on roof, type IV collagen at base
- Gene mutation analysis if needed
- Genetic counseling
  - Amniocentesis and chorionic villus sampling available

Treatment

- Supportive skin care
  - Maintain cool environment
  - Avoid trauma
  - Avoid and treat infection
  - Biologic dressings
  - Autologous and allogenic skin grafts
  - Surgical intervention for contractures and SCCs

Treatment

- Tissue engineered skin equivalents
  - Missing or defective protein produced by recombinant methods and applied directly to blistered skin
- Gene therapy?

Treatment

- Extracutaneous involvement
  - Pediatric dentist
  - Nutritional supplementation
  - Treat anemia
  - GI, GU, ophtho specialists as indicated

Epidermolysis Bullosa Acquisita

- Criteria proposed in 1971
  - Clinical lesions of dystrophic EB- skin fragility, trauma-induced blistering, atrophic scarring, milia, nail dystrophy
  - Adult onset
  - Lack of family h/o EB
  - Exclusion of other bullous disease
  - IgG at basement membrane by DIF
  - IgG beneath basal lamina

Epidermolysis Bullosa Acquisita

- Criteria have since been expanded

Epidermolysis Bullosa Acquisita

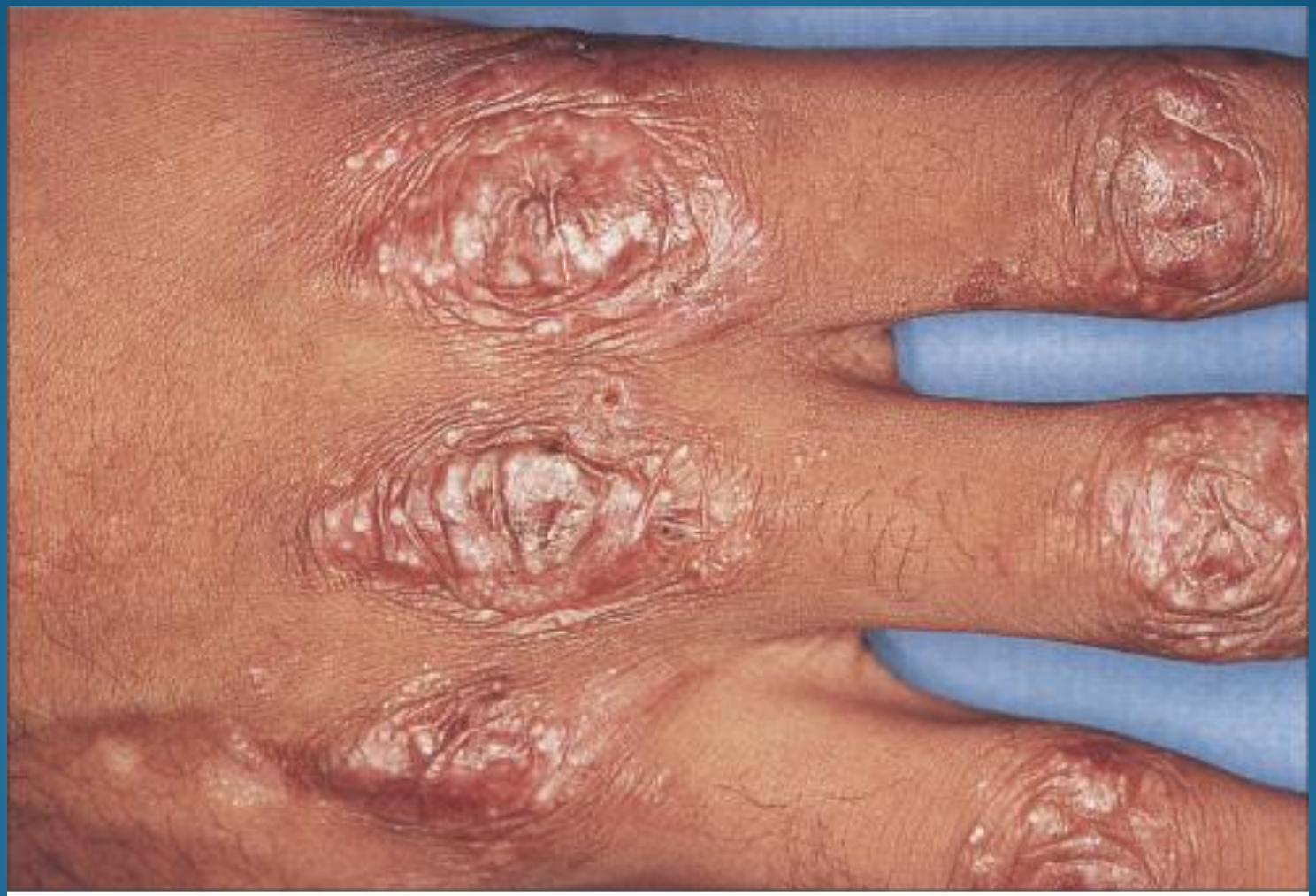
- Acquired EB with autoimmunity to collagen VII (component of anchoring fibrils)
- Can be similar to DEB, BP, or CP
- Can be in children or adults
- Very rare- 0.25 per million
- In some patients, autoantibodies to NC1 domain of collagen VII in the lamina densa

Epidermolysis Bullosa Acquisita

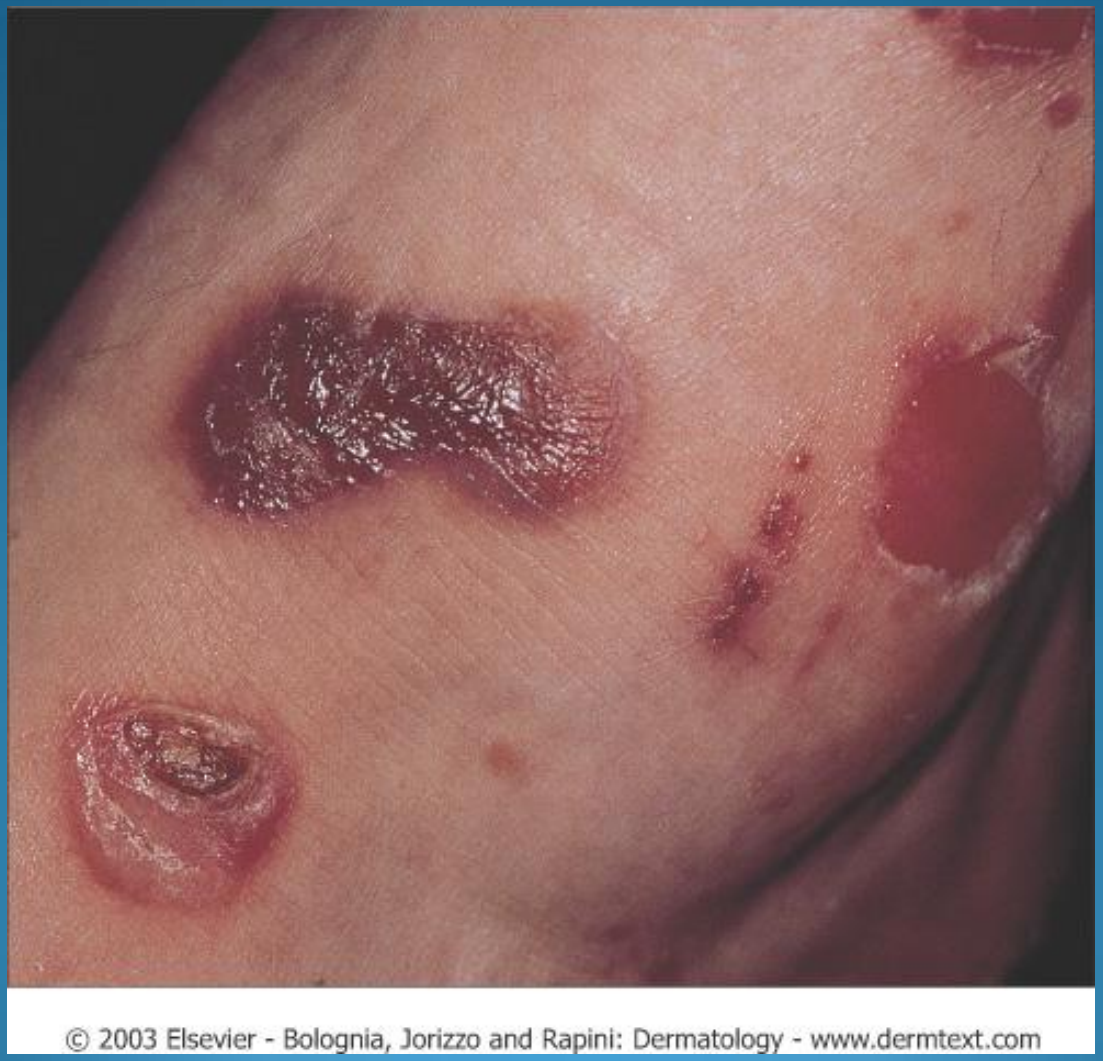
- Blisters in areas prone to trauma
- Heal with atrophic scarring and milia
- Can have mitten deformity
- MM involvement variable
- Associated with: IBD, SLE, RA, thyroiditis, DM, myeloma, lymphoma, leukemia, amyloidosis
- DIF: IgG on dermal side of salt split skin
- Treat with immunosuppressants such as cyclosporine; extracorporeal photochemotherapy has shown benefit

Epidermolysis Bullosa Acquisita

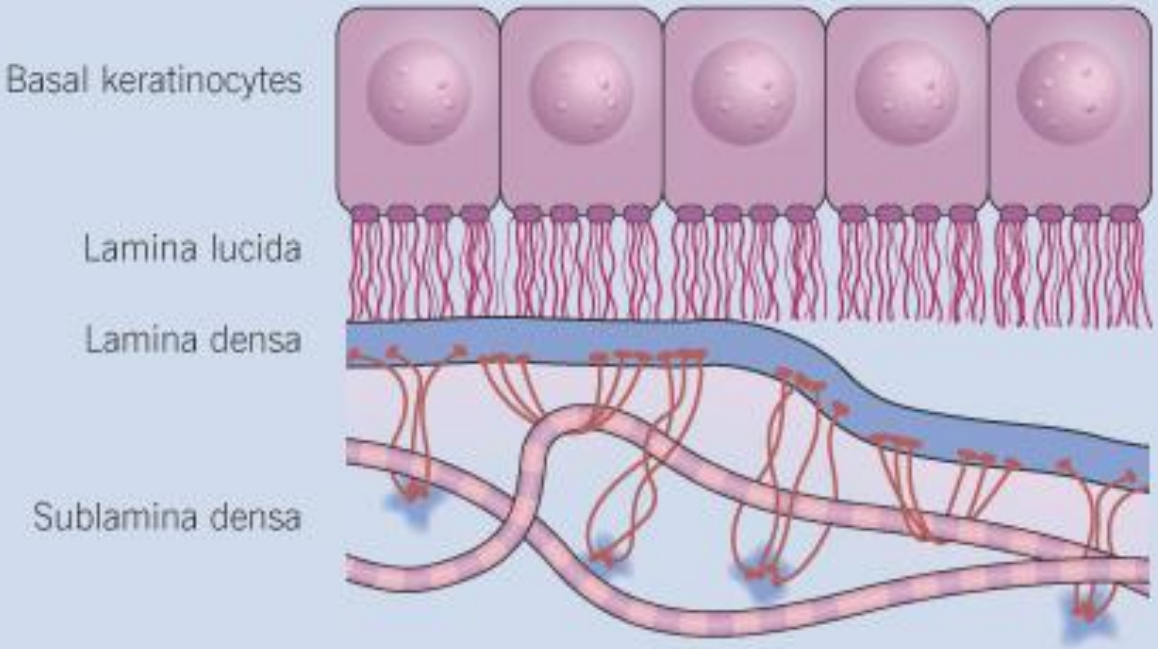
Epidermolysis Bullosa Acquisita



Epidermolysis Bullosa Acquisita



COMMON LOCALIZATION OF AUTOANTIBODIES IN INDIRECT IMMUNOFLOURESCENCE MICROSCOPY STUDIES OF SALT-SPLIT SKIN



Bullous pemphigoid
Pemphigoid gestationis
Linear IgA bullous dermatosis
Cicatricial pemphigoid

Anti-epiligrin cicatricial pemphigoid
Epidermolysis bullosa acquisita
The bullous eruption of systemic lupus erythematosus

EBA Salt-split Skin- IgG stains the floor