THE BULLOUS DISEASES IN NEWBORNS

3rd ITALIAN-TURKISH-IRANIAN PEDIATRIC MEETING
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GNNNP

What is a bubble ?

It ‘s a pathological manifestation due to the formation, in the junction between epidermis and dermis or in the lower part of the epidermis, of a slit which rapidly fills exudate, making a real cavity full of liquid.

Causes and pathogenic mechanisms

The pathogenic mechanisms are multiple , but they always have in common the weakening factor of cohesion between the epidermis and dermis, or between individual cells of the epidermis: may be genetic factors, thermal, biotic, autoimmune.

SCHEMATIZATION OF MULTIPLE CAUSES OF BULLOUS DISEASES IN NEWBORN

GENETIC DERMATOSIS

Eritrodermia ittiosiforme bollosa congenita (ipercheratosi epidermolitica)
Ittiosi bollosa di Siemens
Acrodermatite enteropatica
Aplasia cutis congenita
Incontinentia pigmenti
Peeling skin syndrome
Pachionichia congenita
Porfiria eritropoietica congenita
Dermatosi erosiva e vescicolosa congenita a cicatrizzazione reticolata
Sindrome di Hay-Wells (anchiloblefaron-displsia ectodermica-labio-palatoschisi)

OUTHER INJURIES

Bolle da suzione
Bolle iatrogene (elettrodi, fototerapia, farmaci topici)
Ustione

INFECTIOUS PATHOLOGIES

Impetigine bollosa
Sindrome delle 4 S (Stafilococcal Scaled Skin Syndrome, SSSS)
Herpes simplex neonatale
Varicella congenita e neonatale
Sifilide congenita

AUTOIMMUNE DISEASES

Pemfigo neonatale
Pemfigoide gestationis neonatale (Herpes gestationis)
Pemfigoide bolloso
Dermatosi bollosa a IgA lineari

INFLAMMATORY, PROLIFERATIVE PHARMACOLOGICAL DISEASES

Mastocitosi bollosa
Sindrome di Stevens-Johnson e di Lyell

The Bullous Epidermolysis in newborns: definition

Illness characterized by the onset of

blisters following minimal trauma than in

normal subjects do not cause any injury

Epidemiology

- The overall prevalence of simple BE, junctional BE, dystrophic BE in the population is estimated at 1/130.000 in the United States, 1/100.000 in Italy, 1/20.000 in Scotland.
- Kindler Syndrome is very rare, it is probably underdiagnosed, and currently about 200 cases are described.

Hereditary Bullous Epidermolysis

It is the generic term for a group of genetically determined bullous diseases of the skin that share skin fragility as a common failure. This fragility is caused by mutations in various structural proteins of the epidermis and the dermoepidermal junction. The clinical symptoms and prognosis depend on which adhesive structure is missing, and thus, on the location of the skin disruption.

Epidermolysis bullosa

Various forms:

Simple BE : Epidermolytic, AD

Junctional BE : lethal, AR

Dystrophic BE: dermolytic, AD,AR

Kindler's Syndrome

Fine JD et al. The classification of inherited epidermolysis bullosa. J.Am. Acad. Dermatology 2008;58:931-50.

Simple Bullous Epidermolysis

Intraepidermal bullous are the most common lesions, representing the **50%** of cases. The EBS are divided into two subtypes:

- Basal E. due to cytolysis of basal keratinocytes, with the presence of predominantly cutaneous bullous lesions that resolve without scarring more.
- Suprabasal E. where the lesions are formed in the suprabasal layers of the epidermis and include three different types. They are transmitted in AD and AR form and are due to mutations in the genes KRT5, KRT14 (keratin 5 and 14), PLEC1 (plectin), PKP1 (Placofilin1), DSP (Desmoplachin)

Basal epidermolysis includes 9 variants, 5 of which are rare:

- **Frequent variants**: localized (Weber-Cockayne), generalized (Köbner), BES Dowling-Mear, BES with Muscular Dystrophy (PLEC1)
- **Rare variants**: BES with mottled pigmentation or form with circinate erythema migrans, recessive form, BES with pyloric atresia, BES of Ogna.

Suprabasal Epidermolysis: includes 3 forms, all extremely rare

- Lethal Acantholytic (gene DSP), BE for deficiency of placofilin 1or syndrome of Mc Grath, superficialis BE.

Junctional bullous epidermolysis

Characterized by blisters between the epidermis and dermis at the level of the lamina lucida of the basement membrane. There are several variants due to mutation of genes LAMA3, LAMB3, LAMBC2 (laminin 3-3-2), COL17A1 (collagen type XVII), ITGB4 (integrine 4). This form is about **10-15%** of cases.

Current classification:

Generalized junctional of Lear Herlitz
Generalized junctional not-Herlitz
Localized junctional not-Herlitz
Junctional EB with pyloric atresia
Rare variants of junctional forms
Laryngo-onycho-cutaneous syndrome
Reverse Junctional BE
Junctional late-onset

Dystrophic Bullous epidermolysis

Bullous lesions are localized under the dense lamina of the skin basement membrane in the papillary dermis. They are characterized by slow healing with scarring and formation of milia. This form is about **25-35%** of cases. There are two major subtypes based on the mode of transmission AD or AR, with different clinical variants.

All variants of Dystrophic Be are due to mutations in the COL7A1 gene coding for type VII collagen, the main component of the anchoring fibrils that ensure the adhesion of the basement membrane of stratified epithelia to the underlying mesenchyme.

Kindler Syndrome

Characterized by fragility of skin and mucosa, photosensitivity, progressive poikiloderma with extensive atrophy

Diagnosis

Clinical manifestations combined with immunofluorescence antigen mapping and/or electronic microscopy examination of a skin biopsy allow to define the BE type and subtype. The molecular diagnosis is nowadays feasible in all BE subtypes and required for prenatal diagnosis.

The extent of skin and mucosal lesions depende on BE subtype and patient age. In the more severe BE subtypes lifelong generalized blistering, chronic ulcerations and scarring sequelae lead to multiorgan involvement, major morbidity and life-threatening complications.

Therapy

In the absence of a cure, patient management remains based on preventive measures, together with symptomatic treatment of cutaneous and extracutaneous manifestations and complications.

Owing to its nature and severity, RDBE presents unique challenges for developing successful therapies that simultaneously alleviate the plethora of complications while having a significant impact on survival and quality of life.

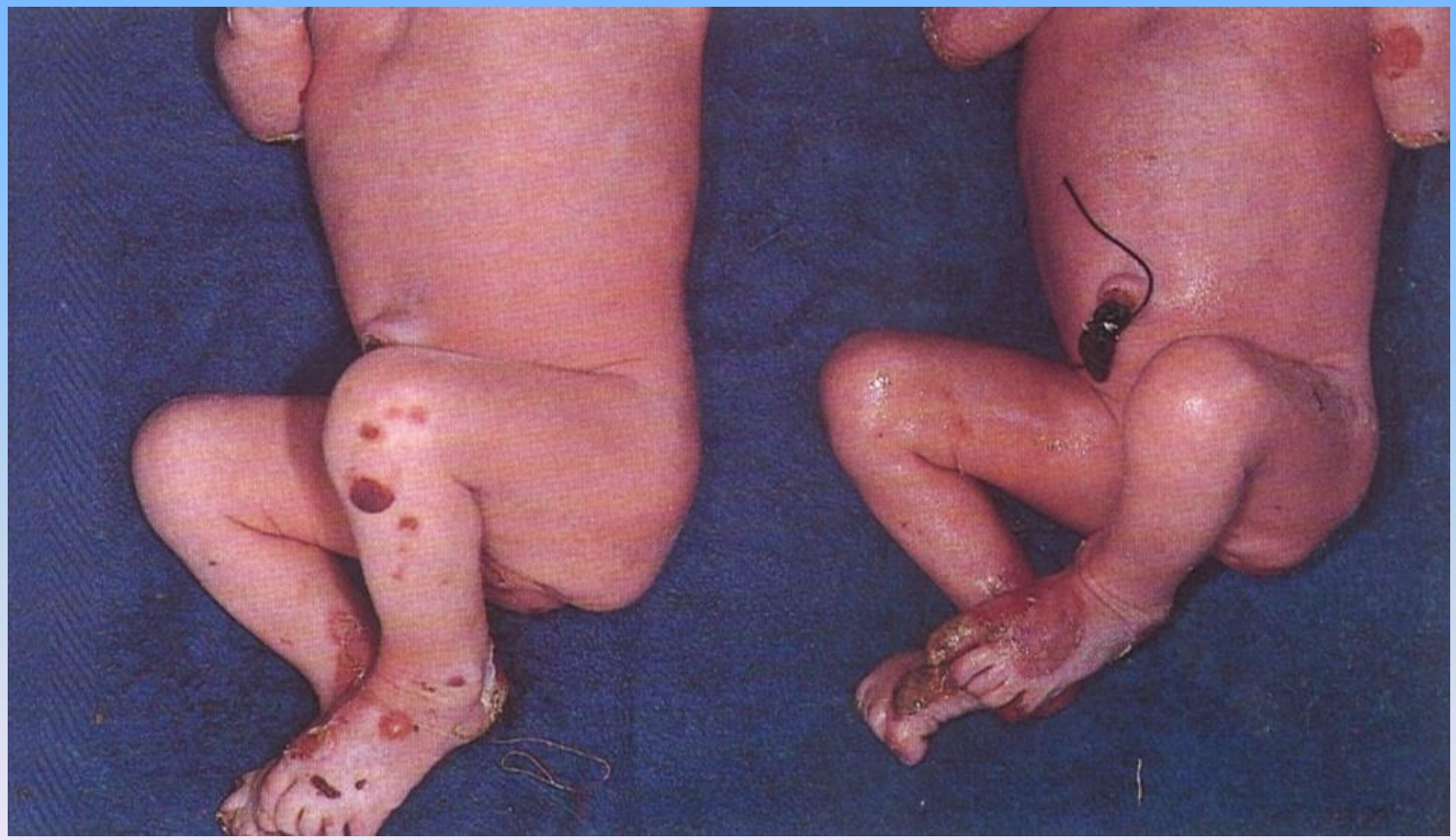
Recent approaches such as allogeneic cellular therapy, gene therapy, and protein therapy show promise.

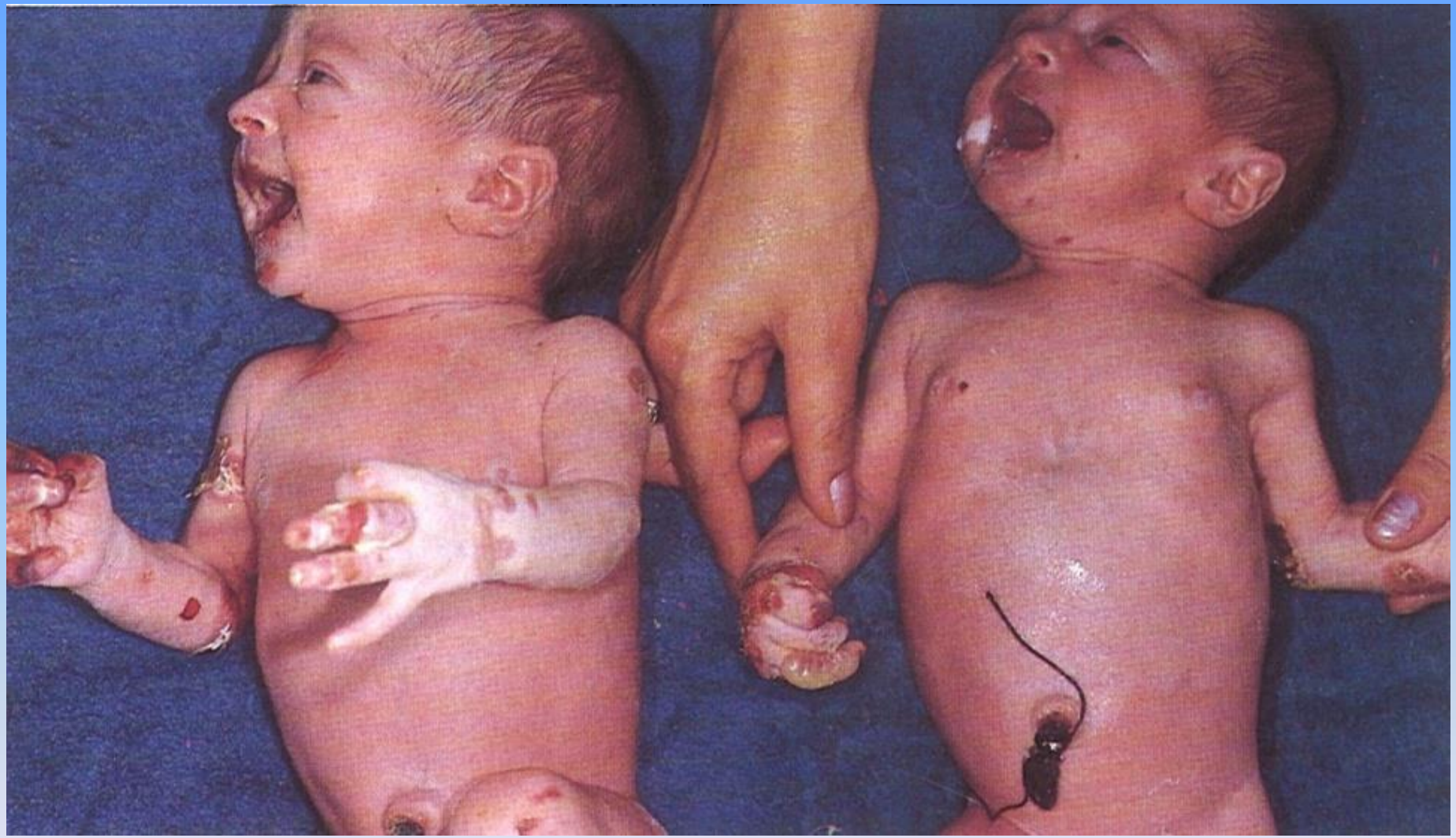
Clinical manifestations of BE

Large bubbles
Very often eroded
Symmetric distribution in the trauma
Easy rupture of bubbles forming crusts and erosions with low-cut flanges
Cute interposed between bubbles apparently normal

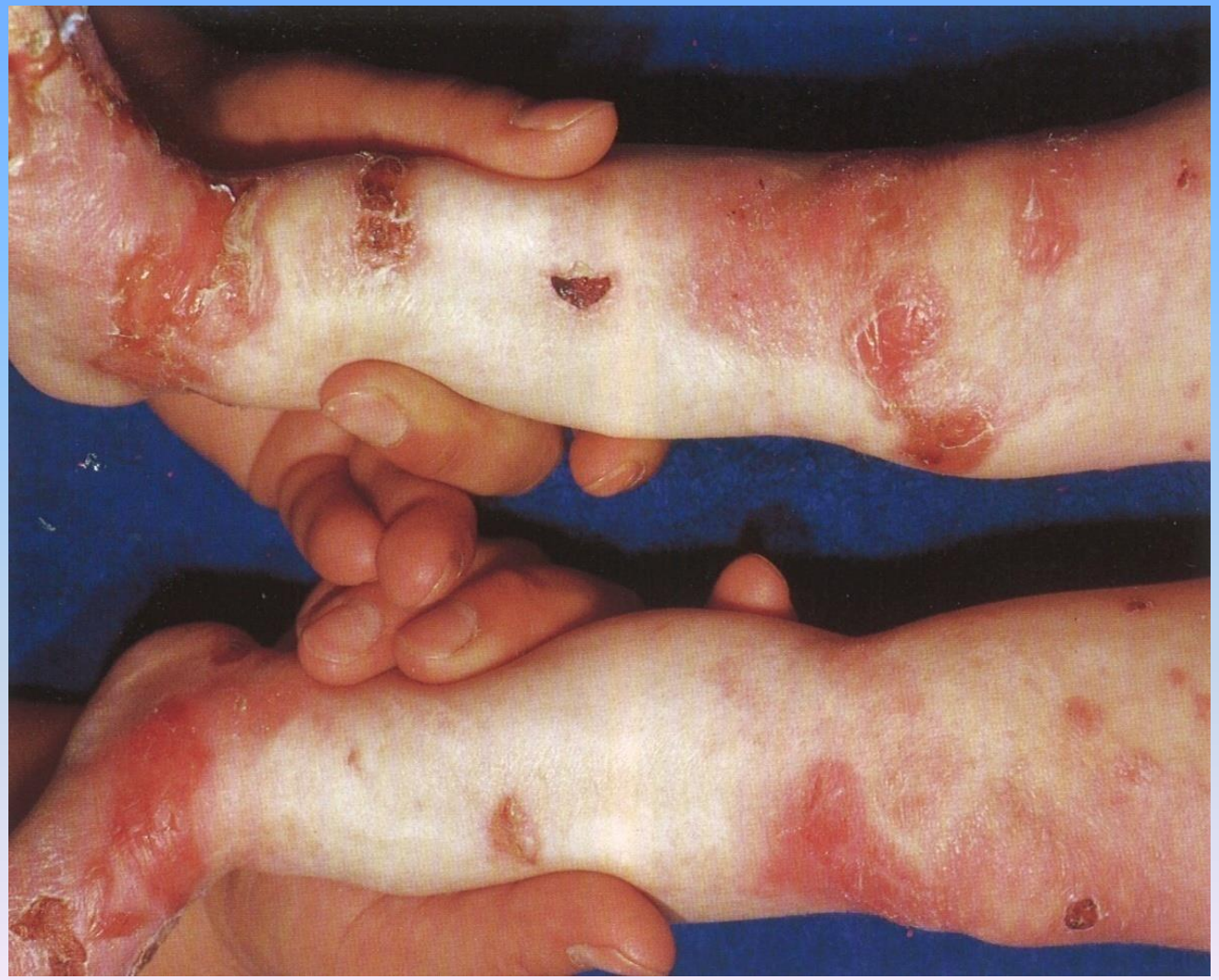
Simple bullous Epidermolysis in tweens

lesions prevalently to legs and arms in areas under manipulation and macrotrauma

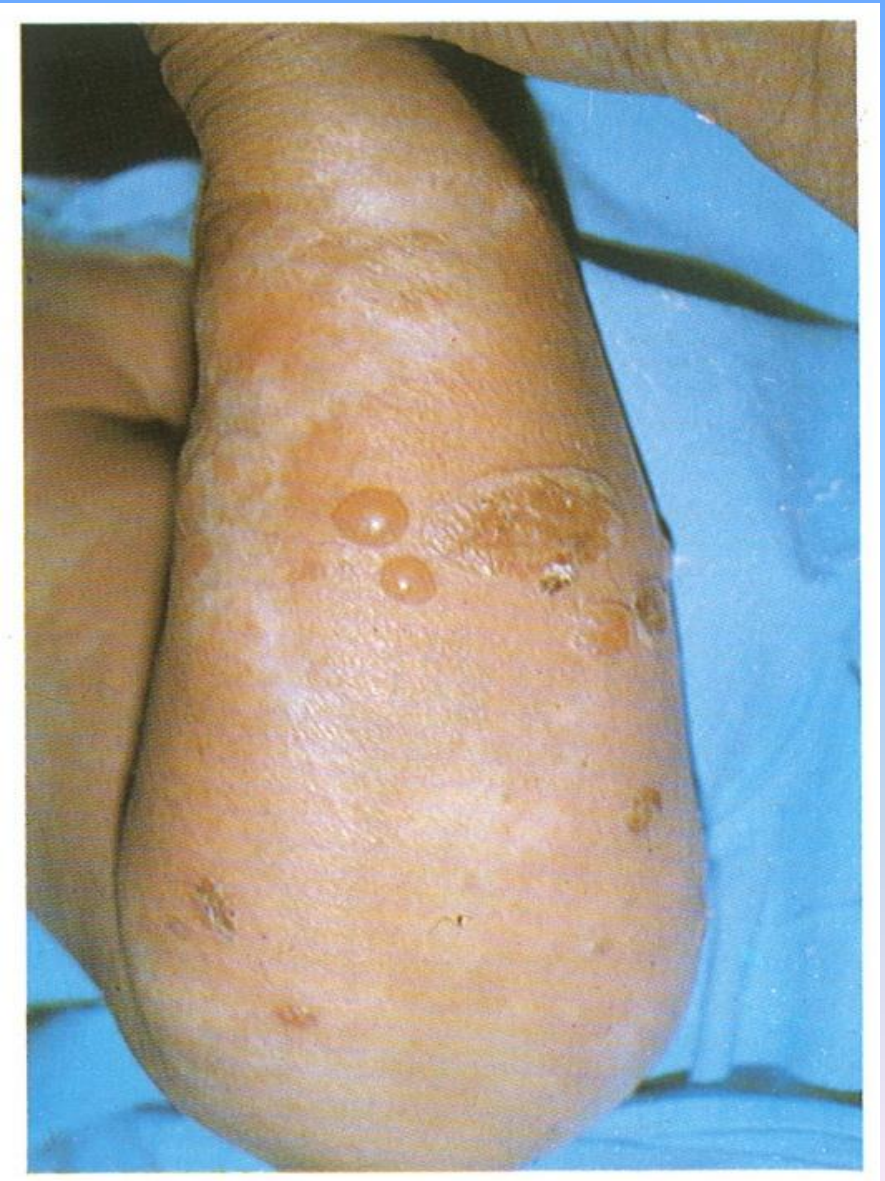




Junctional Bullous Epidermolysis

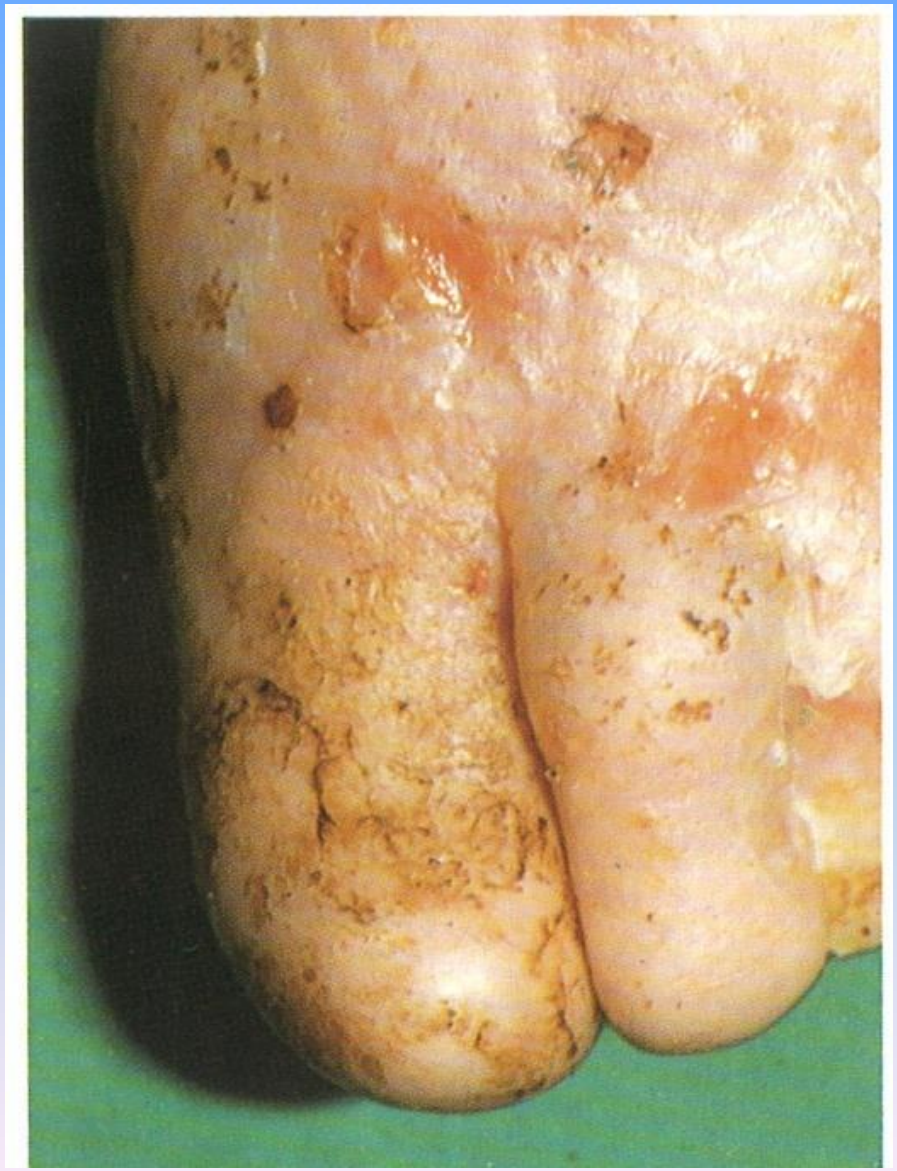


Basal Epidermolysis



Dystrophic bullous Epidermolysis

pseudosyndactyly with nearly complete fusion of fingers and toes



Junctional bullous Epidermolysis: laringo-onico-cutaneous form

Differential diagnosis

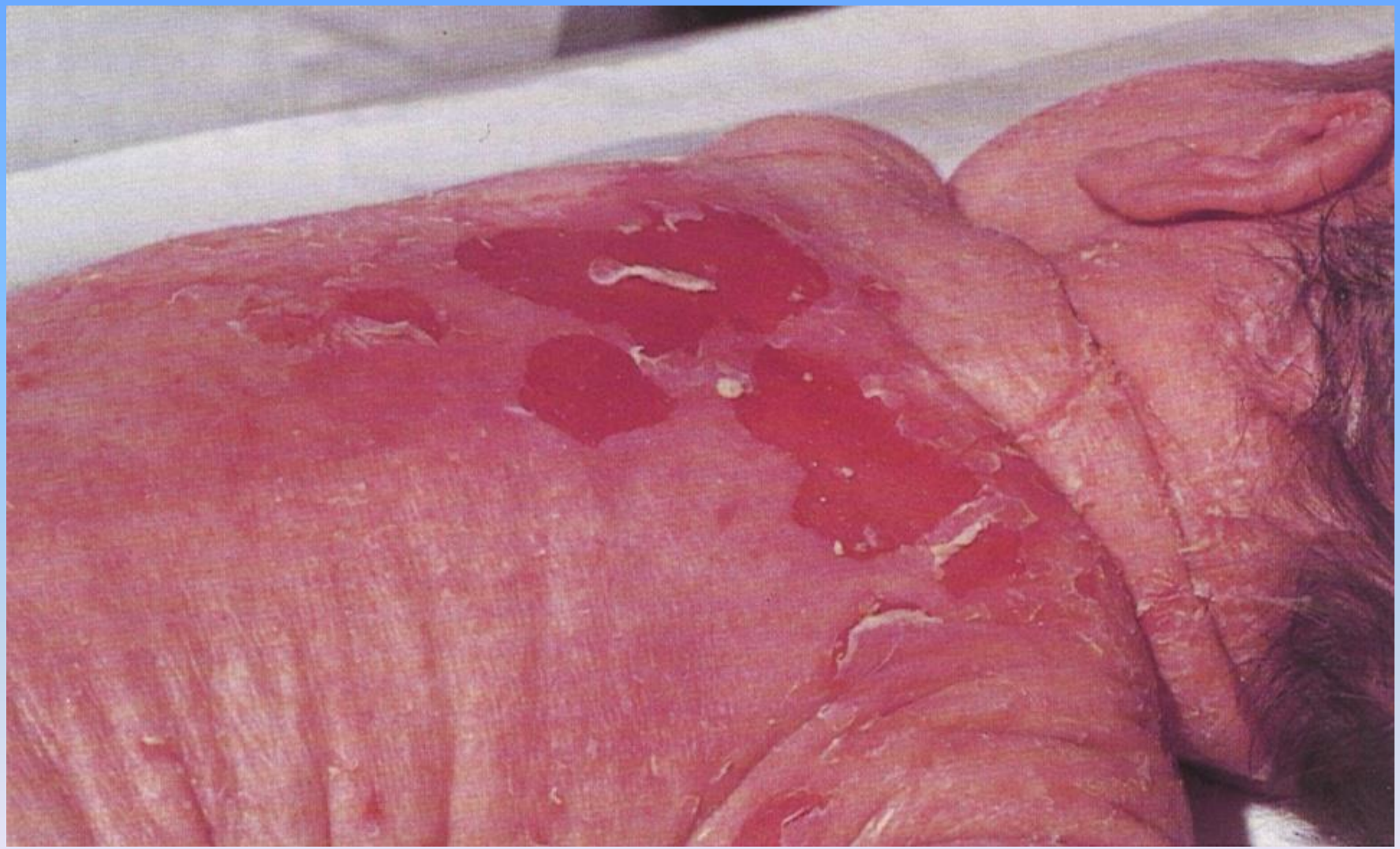
With which disease can be confused with similar expression?

- Congenital bullous ichthyosis
- Incontinentia pigmenti
- Staphylococcal bullous pyoderma
- Luetic Pemphigus
- Autoimmune bullous diseases (pemphigus, herpes gestationis)
- Bullous mastocytosis
- Transient dermatolisis of newborn
- Collodion Baby Syndrome

Congenital bullous ichthyosis

Serious hereditary disease transmitted in an autosomal dominant fashion.
At birth reddened skin covered by bullous manifestations. In the following days we can see less bubbles and a lot of desquamation

Congenital bullous ichthyosis



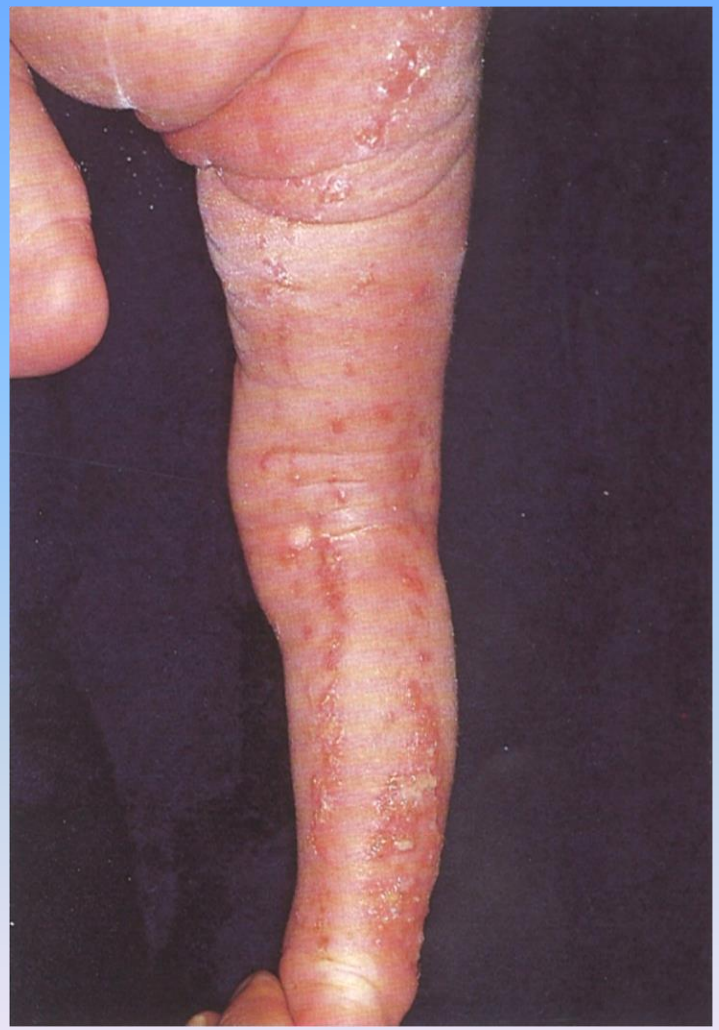
Incontinentia pigmenti

Hereditary disease transmitted in an X-linked modality.

Injuries: exudative at birth, vesiculobullous (with a diameter of a few millimeters), later verrucose, characteristically pigmented, and finally atrophic, mosaic spread, along the lines of Blasko.

Lines of Blasko

strips of healthy skin alternating with strips of diseased skin parallel to each other



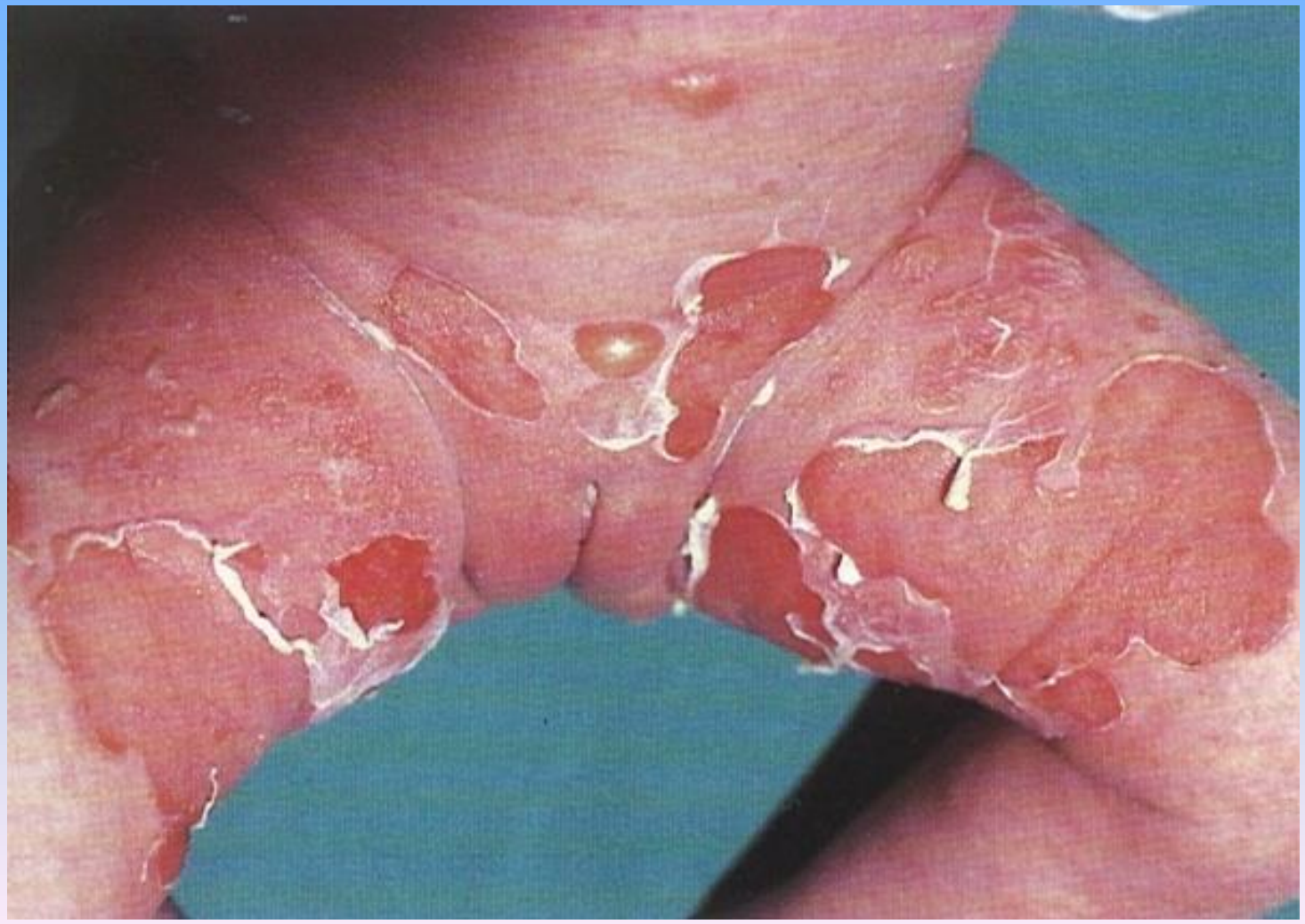
Bullous Staphylococcal pyoderma

It is the most frequent disease to cause bullous manifestations in newborns.

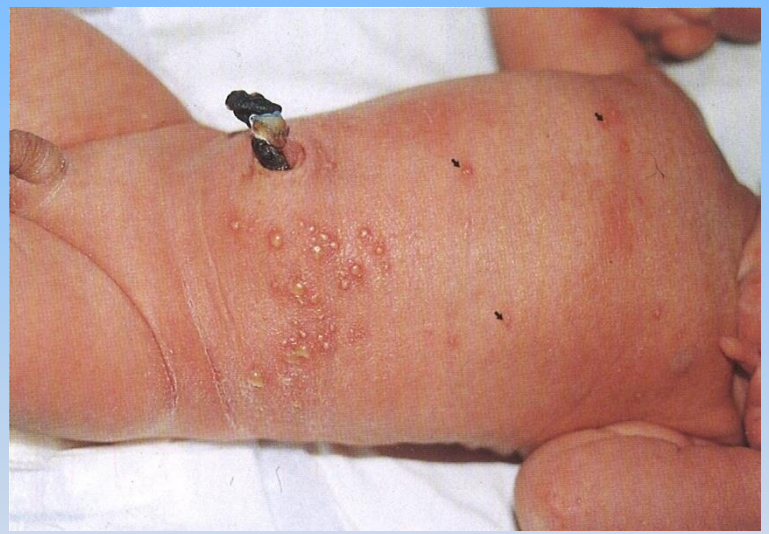
The bubbles are situated in the periorificial sites, that quickly spread to the suburbs, and finally they break.

Different types of Aureus Staphylococcal infection

(middle gravity)

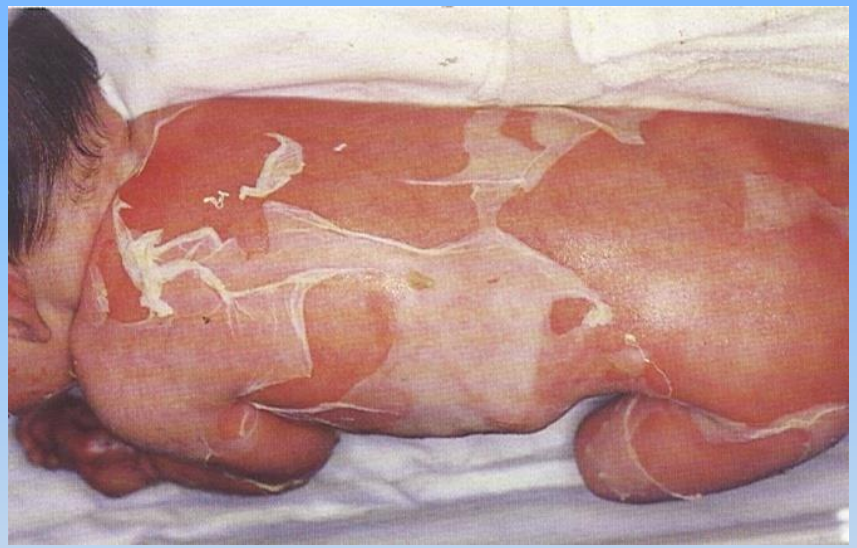


Neonatal toxic erythema and staphylococcal pyoderma



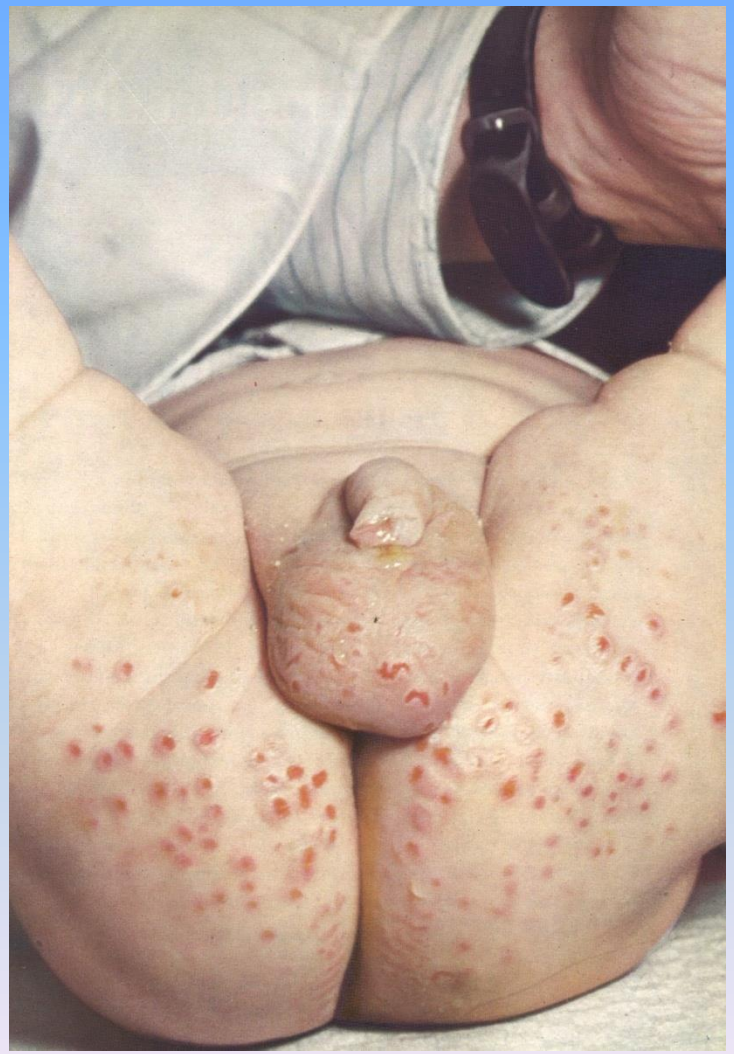
With black arrows are indicated the NTE lesions (Sterile pustules). Near the umbilical line we can see a typical staphilococcal lesion, like cluster or brunch of grapes.

Heated skin syndrome
Staplilococcal Scalded Skin Syndrome (SSSS)



It is the most dangerouse form of Staphylococcal infection: the epidermis can be completely unglued and often the illnes is lethal

Papular rash



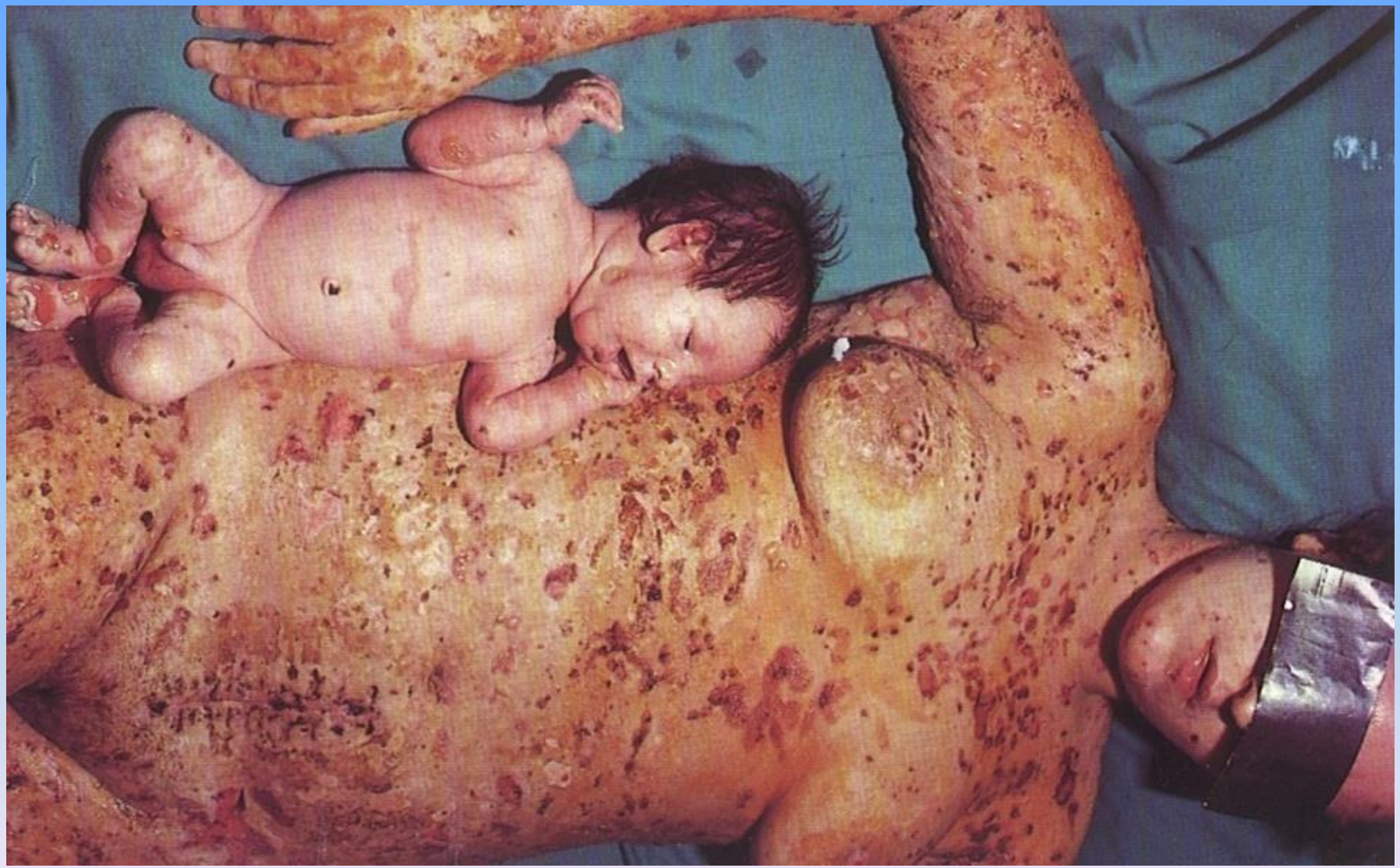
It is variety of intertrigo especially affecting little infants

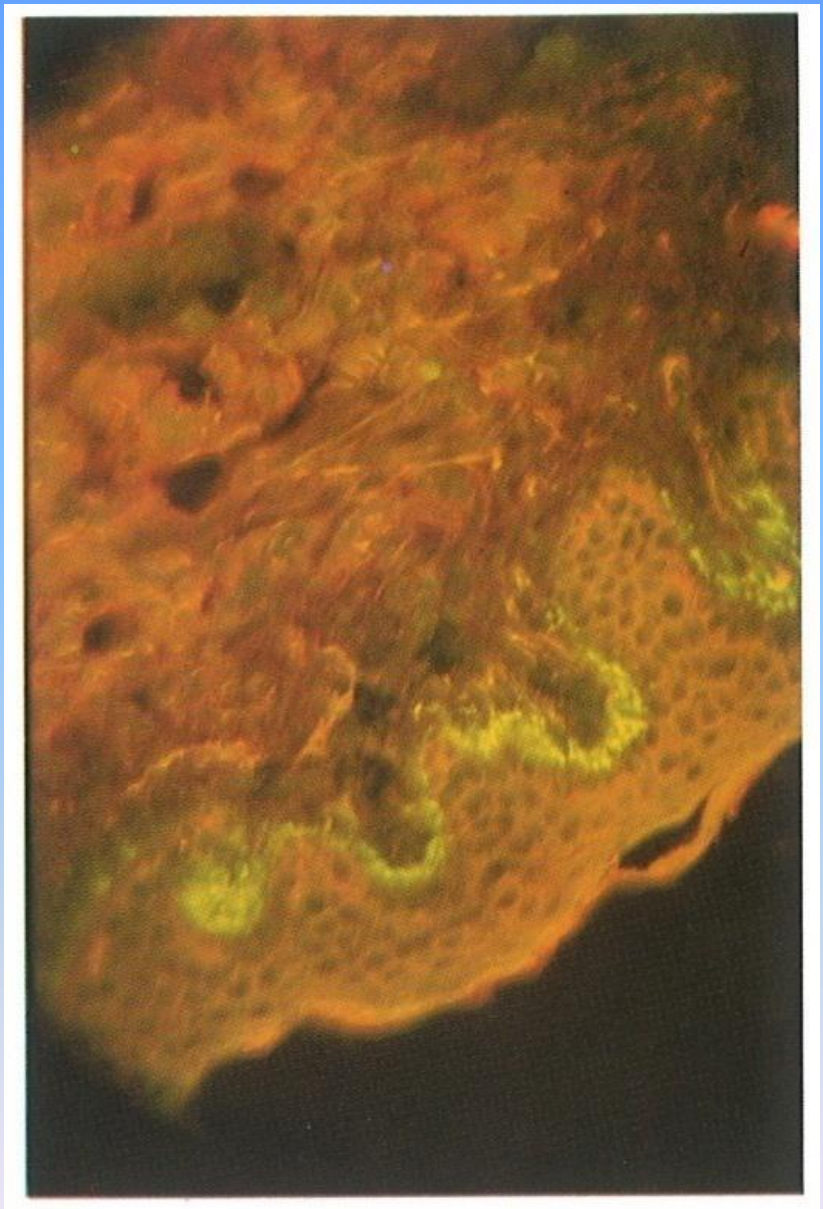
Prolonged contact with urine-soaked diapers gives rise to a papular rash in the groin, scrotum, buttocks and anal region.

Pemfigo –herpes gestationis

Bullous autoimmune manifestations in the mother's and newborn.
Pathogenesis: IgG autoantibodies against the intercellular structures anchor the epidermis (pemphigus) or against the dermo-epidermal junction (herpes gestationis)

Herpes gestationis

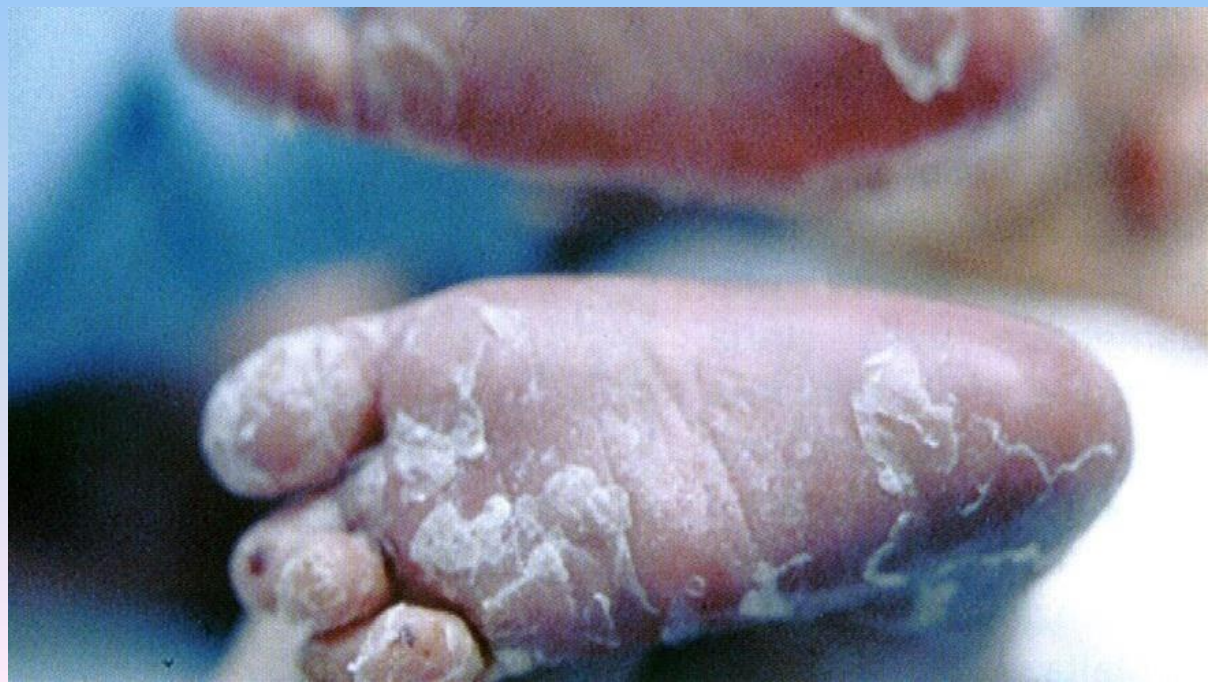




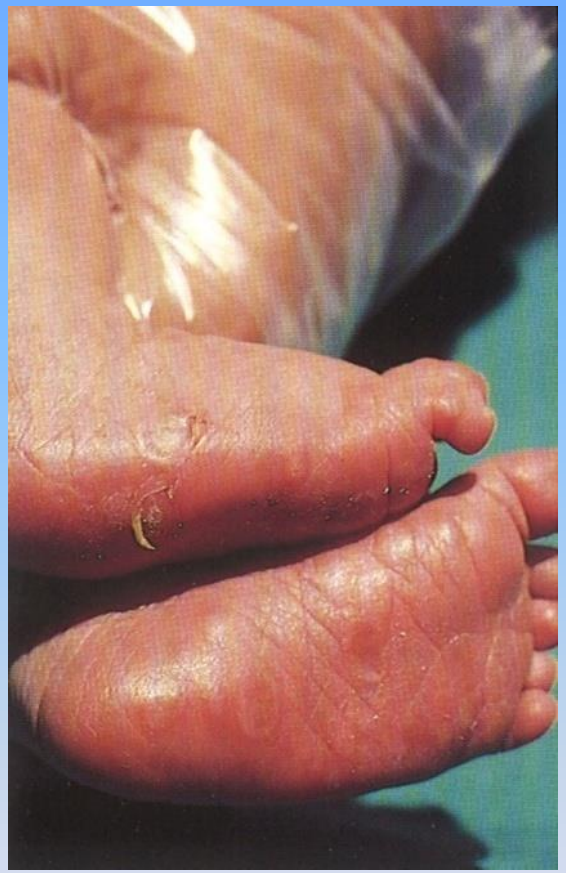
H. Gestationis IgA deposits, bright green fluorescence at the level of the dermal papillae of the skin.

Luetic pemphigus

Form of congenital syphilis transmitted to the fetus from the mother sick
Triad: rhinitis, cheilitis, pemphigus palmo-plantar



Bullous palmoplantar sifiloderma



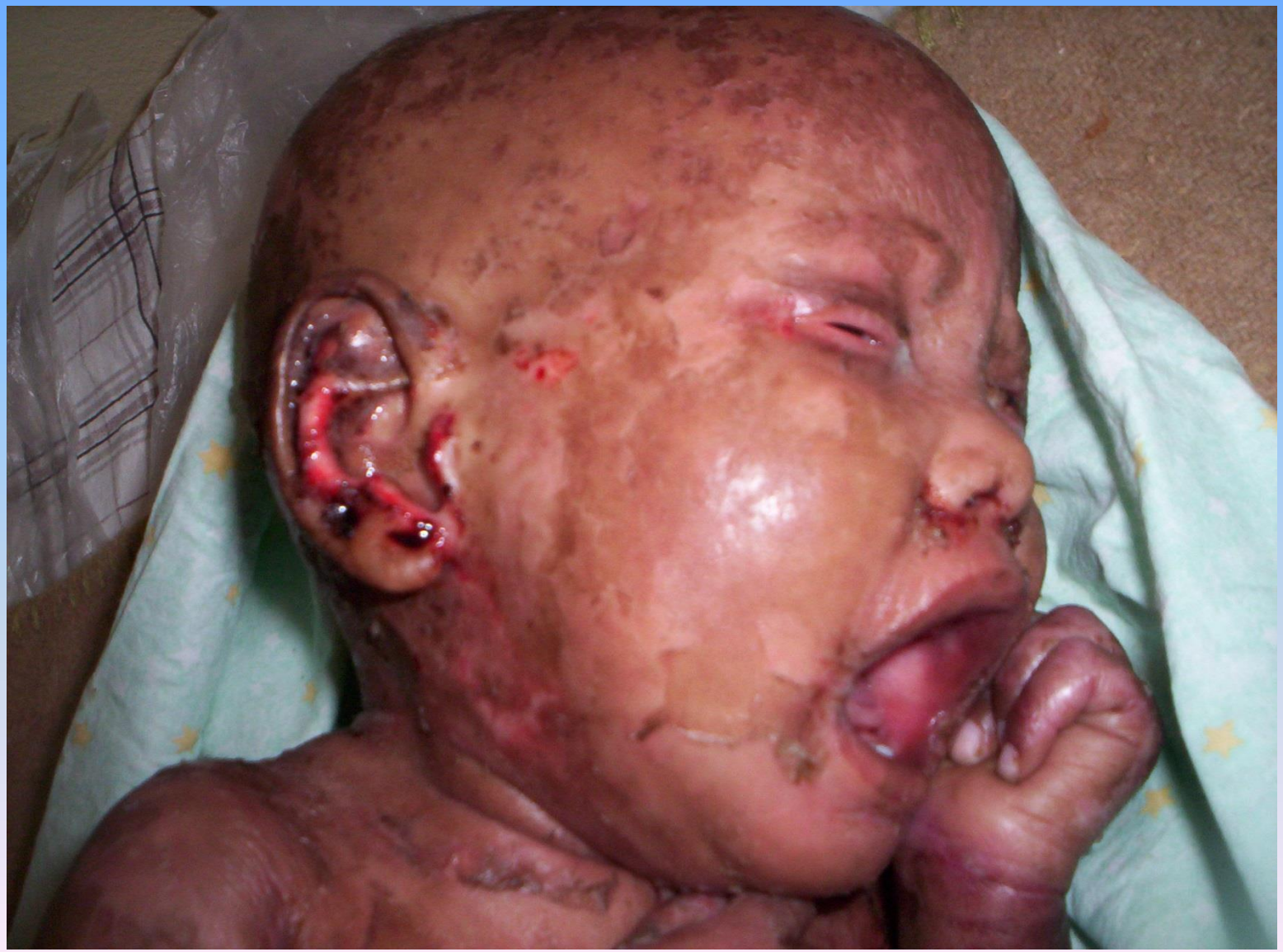
When the blisters break their base is infiltrated by typical annular papular lesions

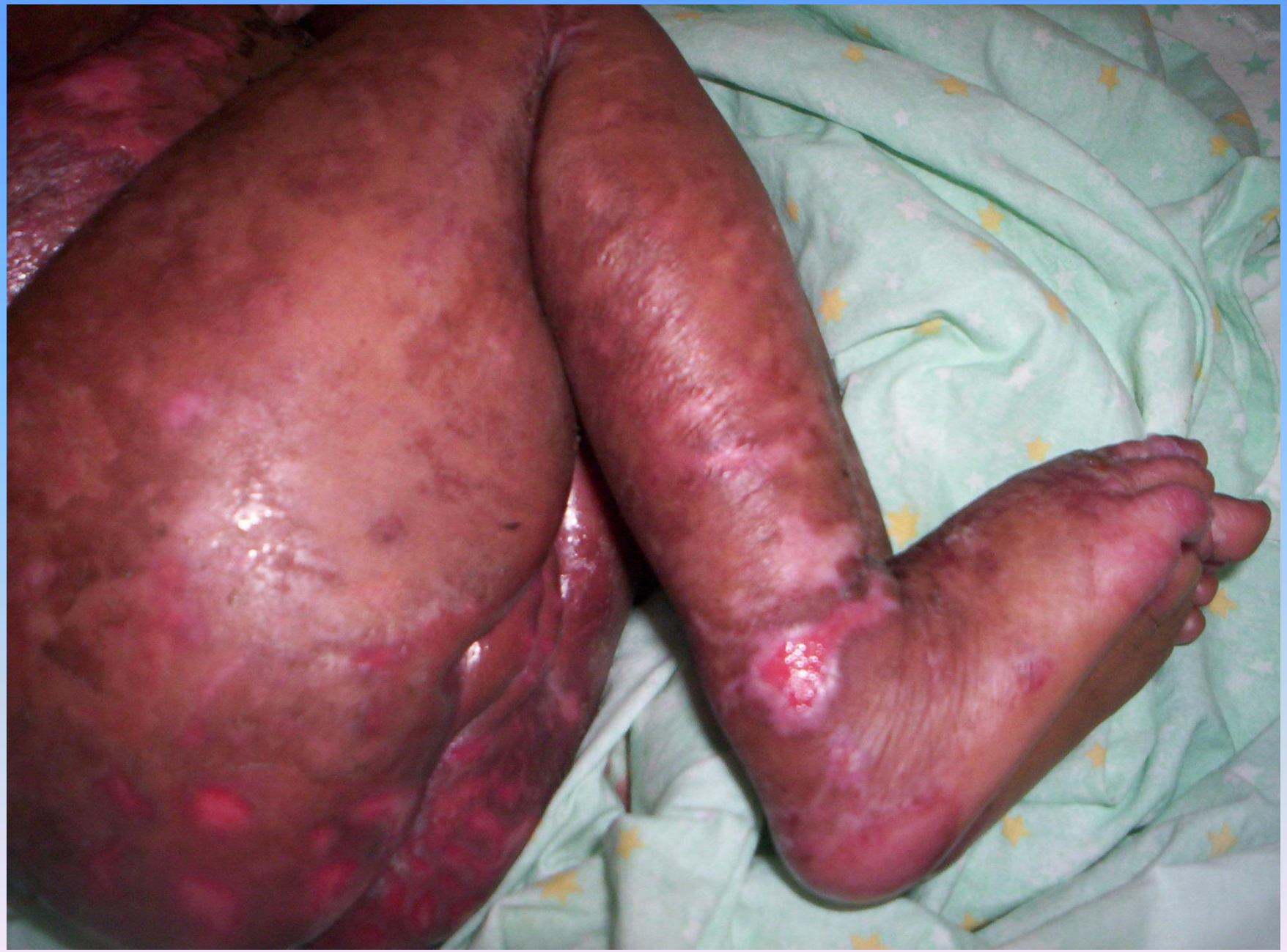
Congenital syphilis

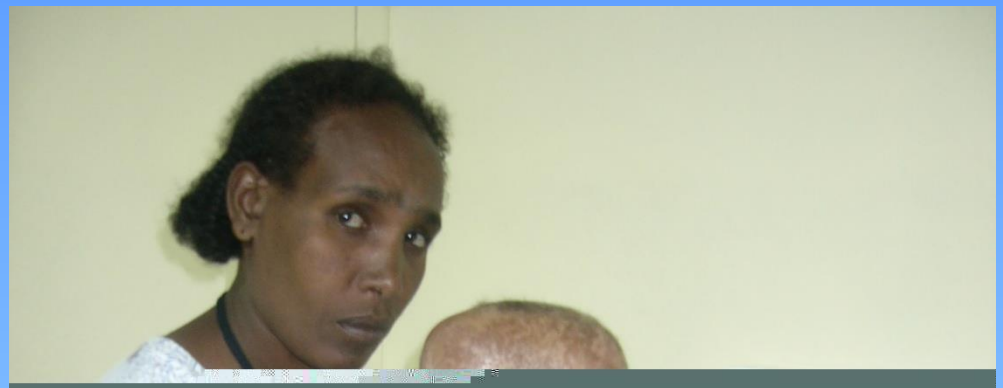
Fetus can be interested from the 4th month of pregnancy.
It is possible expulsion, abortion or, more frequently, it will be born a child that in the first days or weeks of extrauterine life manifest bullous lesions of the skin and mucous membranes (syphilitic pemphigus) that balk at scars

Associated visceral lesions: hepatosplenomegaly, nephritis, meningitis (convulsions), epiphyseal long bones (pseudoparalysis Parrot), osteochondritis, periostitis.
The late-onset form appears around age 7 and includes dental and dystrophic bone lesions, interstitial keratitis and deafness. Triad of Hutchinson

Neonatal Syphilis







Therapy

Crystalline penicillin G 50,000 U / kg IV every 12 hours for 7 days

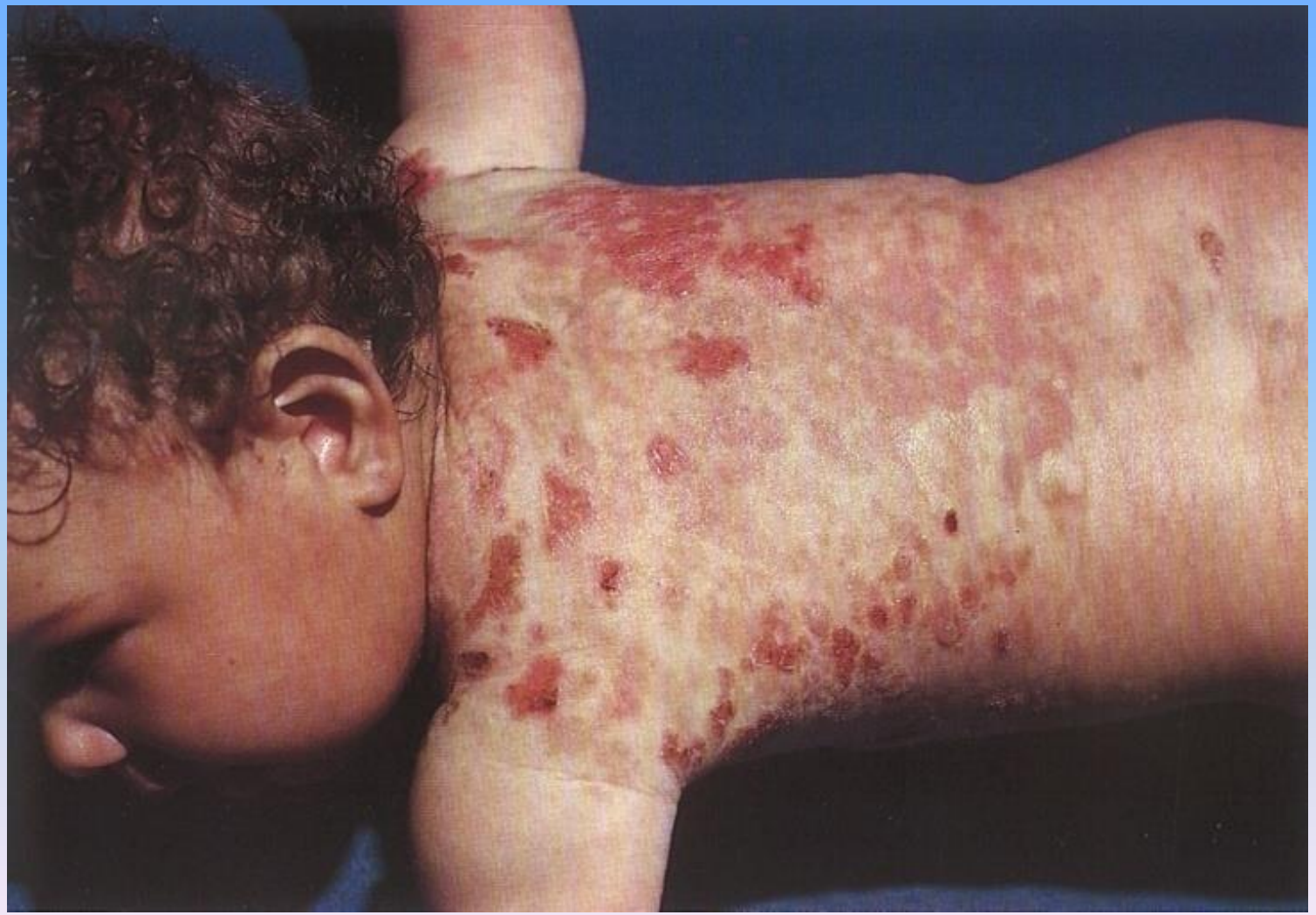
+

Rehydration therapy + cortison + vitamin + Topical antibiotics

Bullous mastocytosis

Most severe form of neonatal mastocytosis
Bubbles present on the first days of life (massive infiltration of mast cells in the skin)
Redness of the face during crisis
Thick skin like leather
The healing is natural in many years

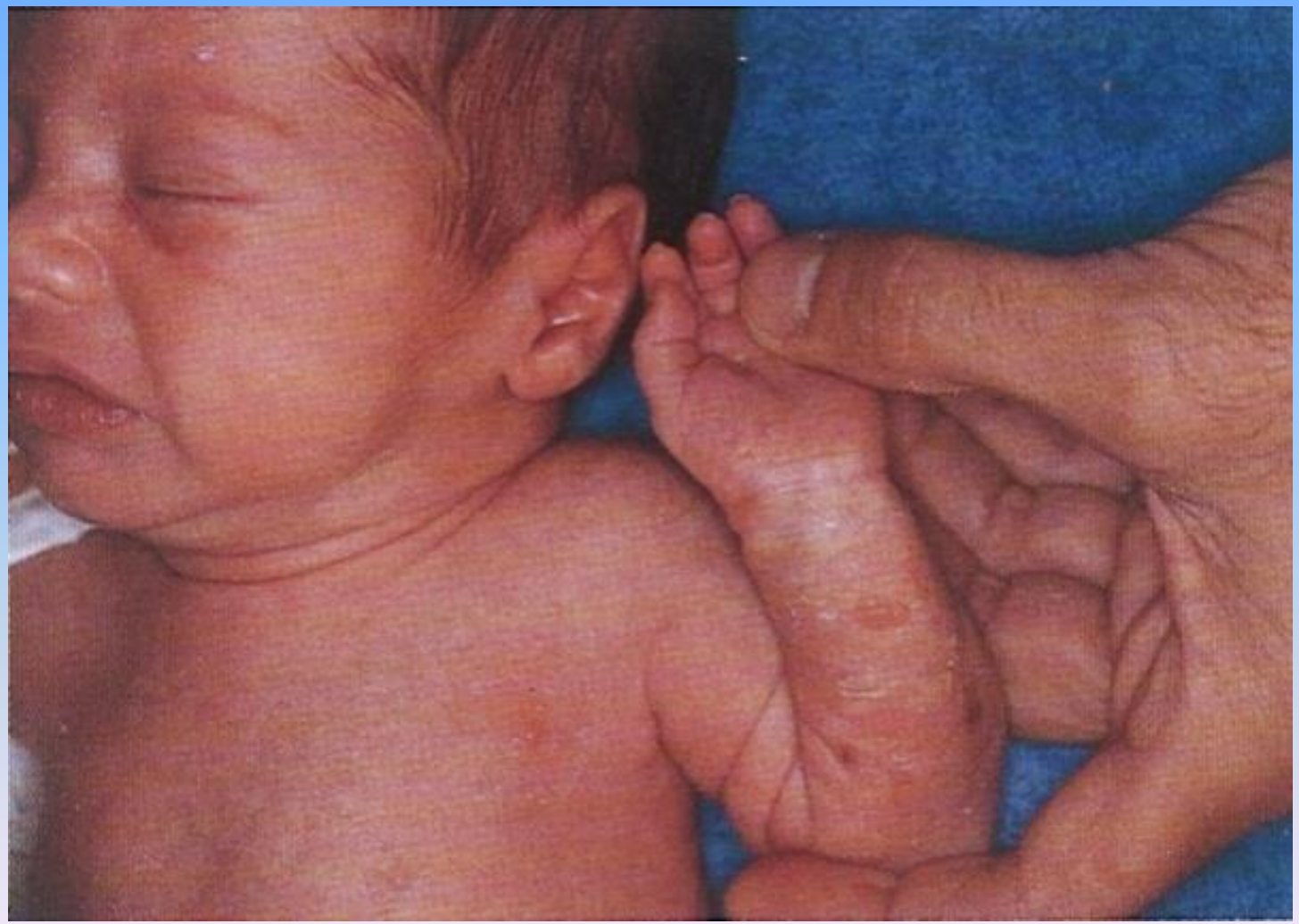
Bullous mastocytosis

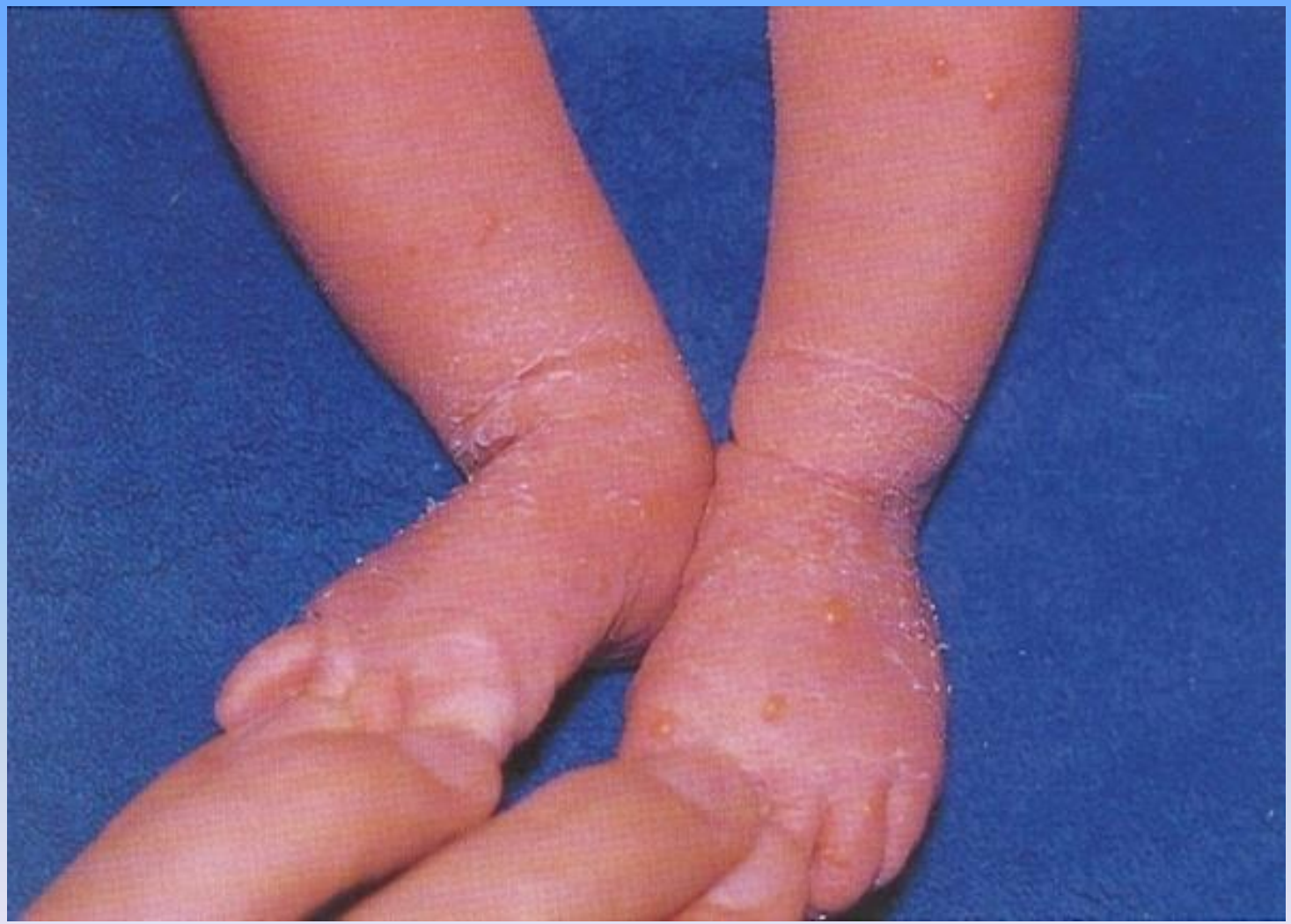


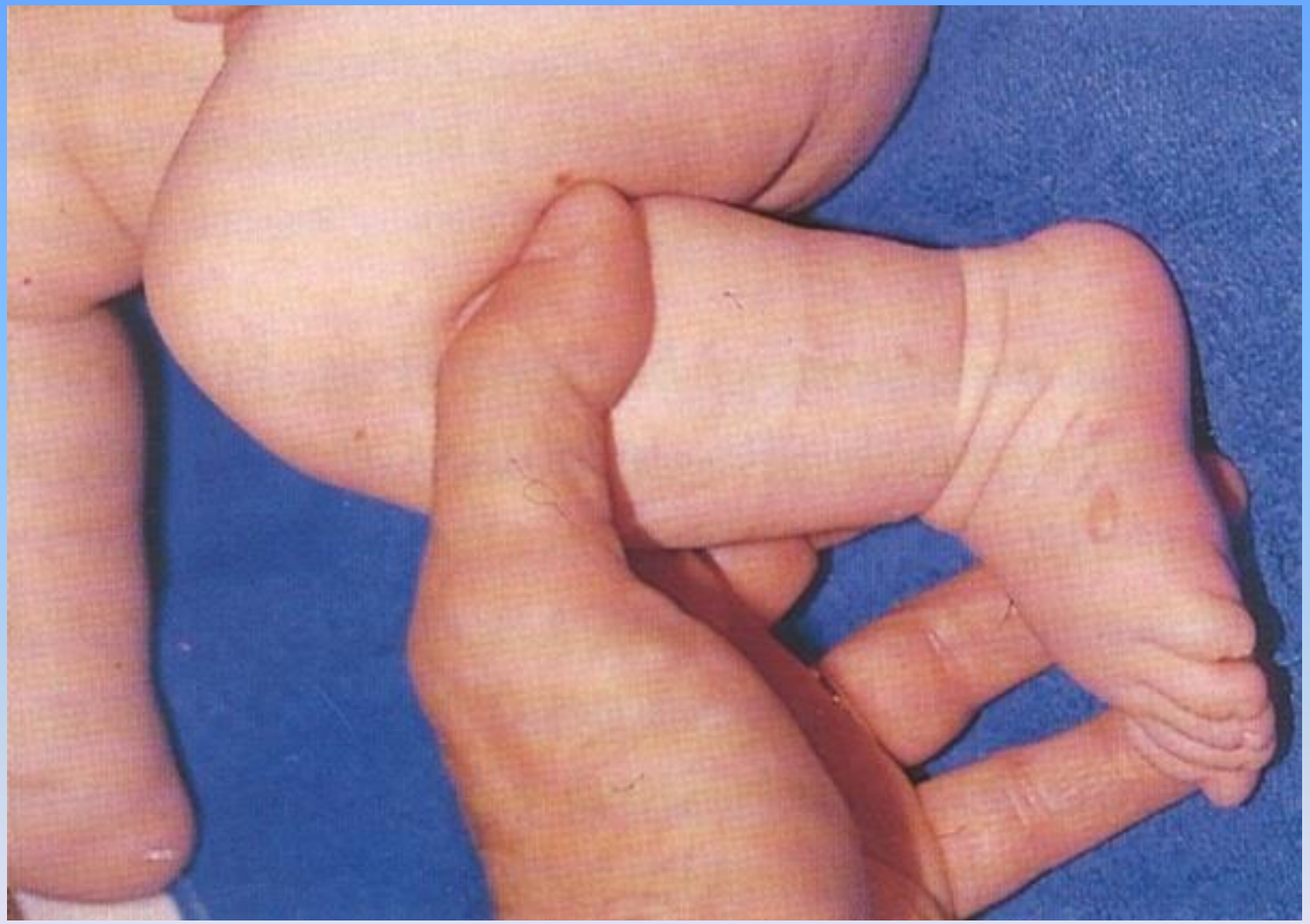
Transient Dermolisis of newborn

AD, Dystrophic Bullous epidermolysis or Dermolytic BE
Bullous eruption, acroposta, present at birth
At the level of the dermo-epidermal junction
The skin can be inflamed or not in the first 2 weeks or more of life of newborn
Spontaneous regression

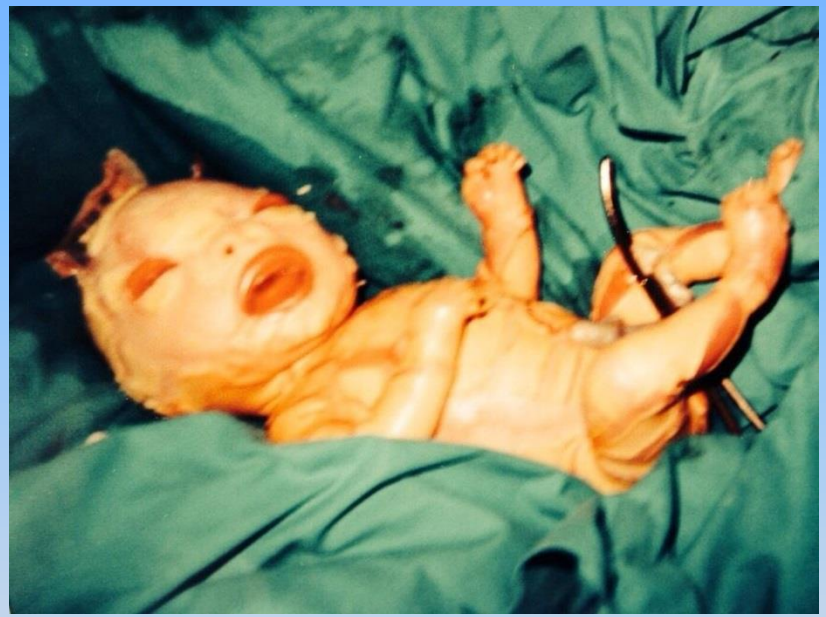
Transient Dermolisis of newborn







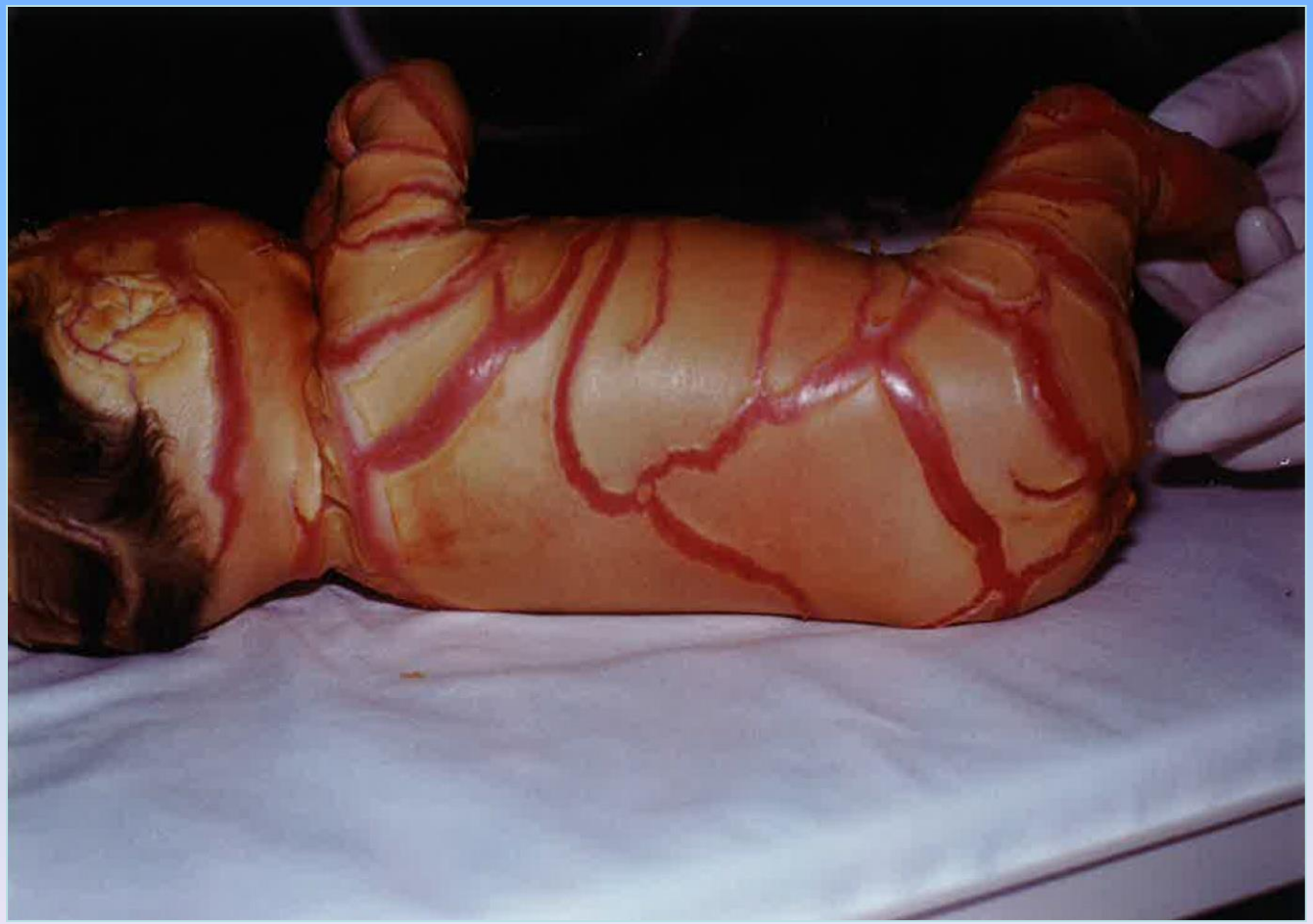
Collodion baby



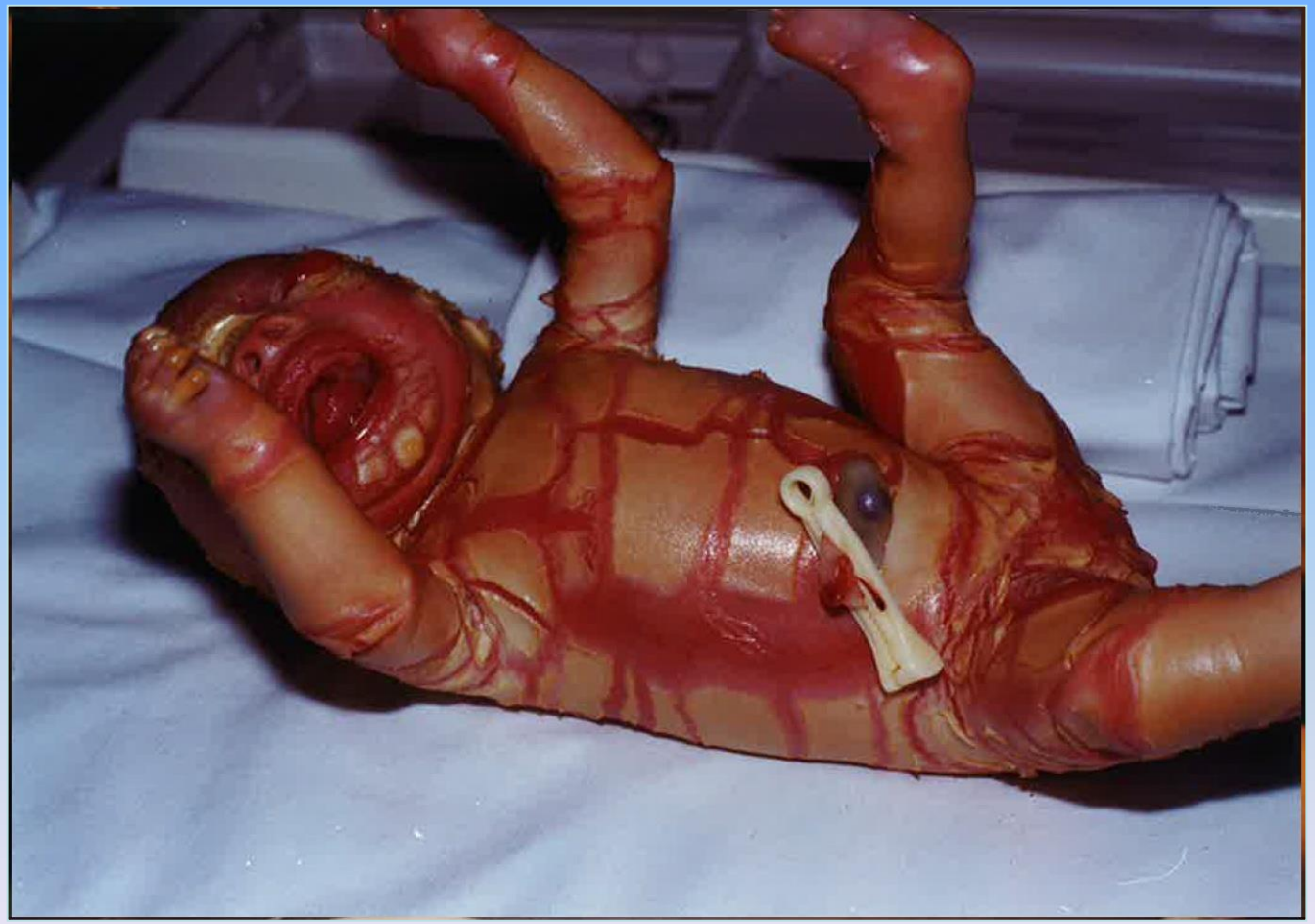
The skin of newborn is redness, the baby seems dressed with a translucent membrane like a collodion.

In few days that translucent membrane parchs and removes in large flanges.

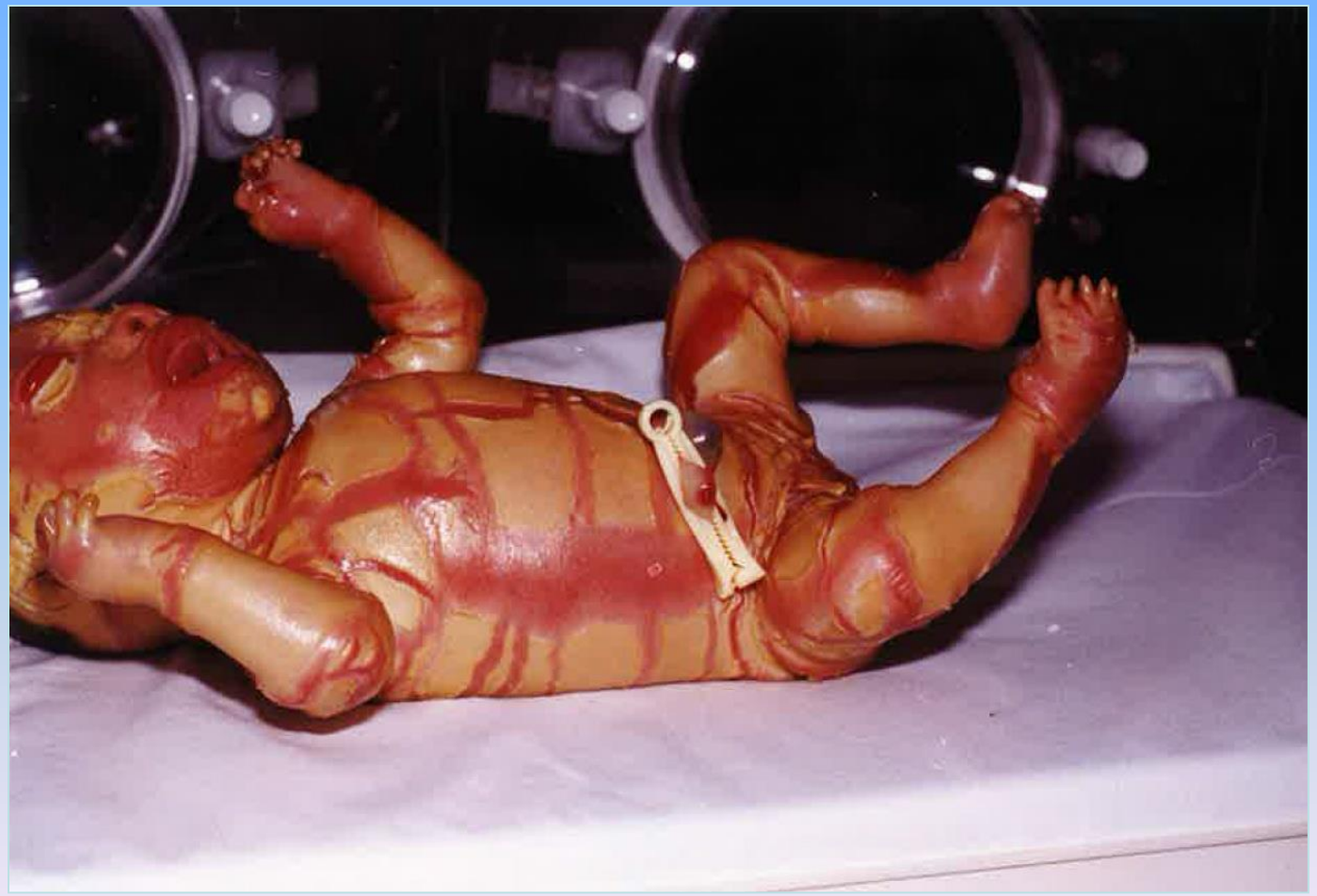
A new Collodion strain: tiger variety



Collodion baby



Collodion baby

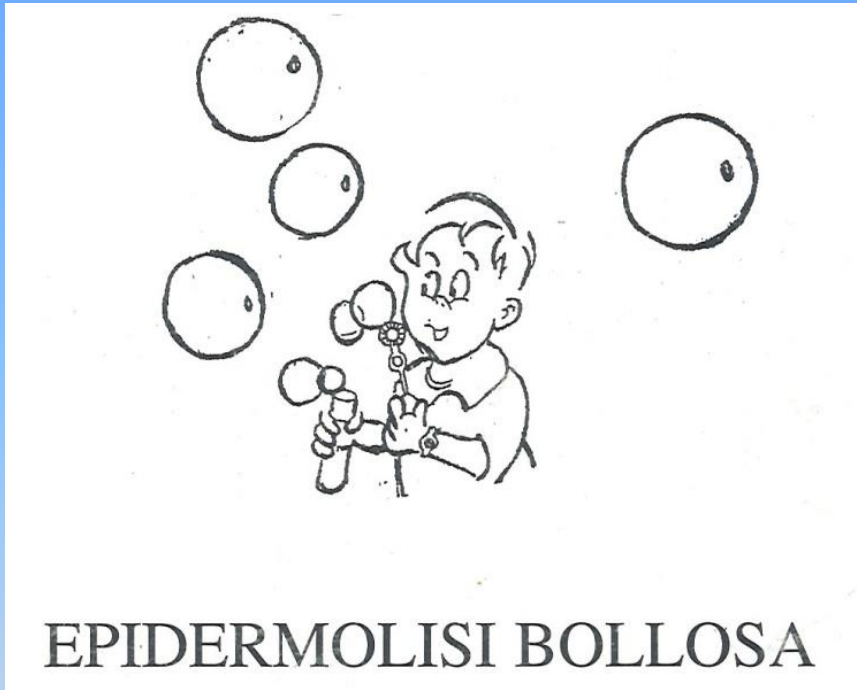


Conclusions

These ancient images teaches us that observation, professionalism and an expert eye can help us to formulate a clinical diagnosis .....

…..a correct diagnosis useful for the safety of our patients and their families

We must give to our children…



….born to have a bright future…….

…playing and dreaming

in a world without bubbles….

happy to live .... without problems

Gloria virtutem post fortia facta coronat

ITALIAN ARABIC PEDIATRIC SOCIETY
SOCIETA' ITALO ARABA DI PEDIATRIA