Atopic dermatitis

- strongly pruritic chronic or chronically relapsing non-infectious dermatitis with variable morphology and clinical course, usually starting during early childhood

- often associated with positive personal or family history of allergic rhinitis, conjunctivitis and bronchial asthma.
- genetic predisposition
- In about 80% associated with ↑ IgE levels

Atopic dermatitis - epidemiology

Incidence in population: 0,5 - 5%

(higher incidence – scandinavian countries)

infants	**20%**
children under 2 y	**15%**
children under 14 y	**12%**
adults	**2-5%**

Atopic dermatitis

two forms, same clinical picture

extrinsic 80% — **elevated IgE**

sensitization to airborne and/or food allergens (sIgE)

- association with allergic rhinoconjunctivitis and/or allergic asthma

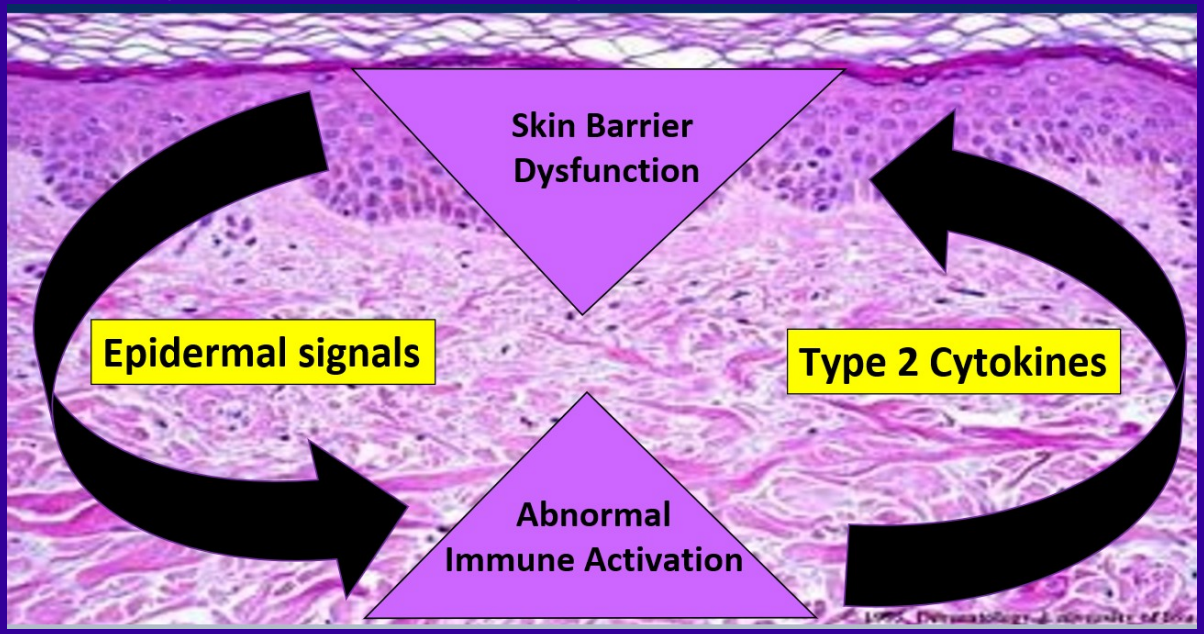
intrinsic 20% — **normal levels of IgE**

skin barrier disturbace

Etiopathogenesis of AD: unknown

genetic predisposition

1) skin barrier disturbance
2) hyperreactivity of the skin



environmental triggers:

1) irritant substances, allergens
2) stress
3) many others ….

I. skin barrier disturbance

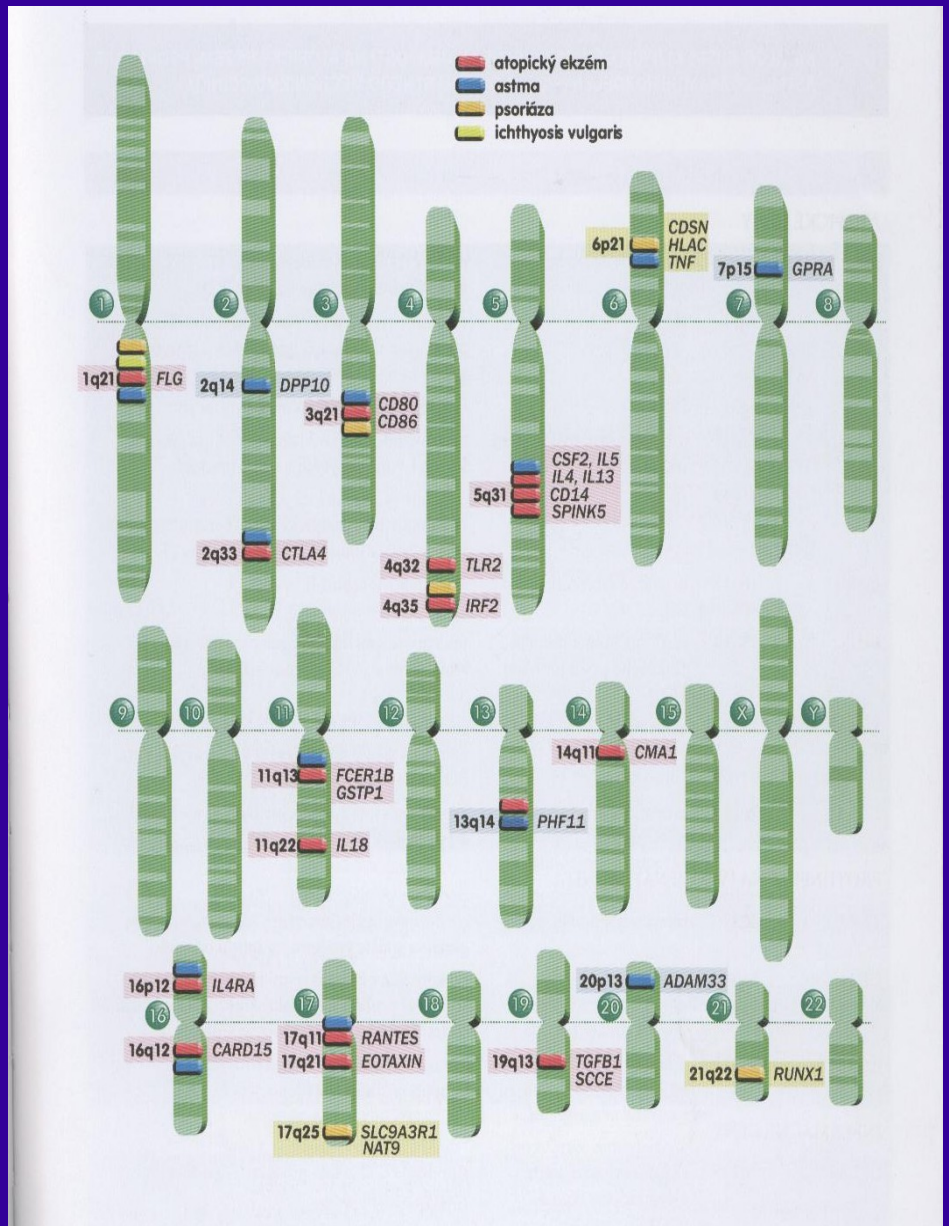
Genetically conditioned:

Filaggrin: null mutation of FLG R501X and 2282del4 alleles lead to increased permeability of skin barrier and they are associated with AD (in about 50% cases), as well as with ichtyosis vulgaris

Claudin- 1, corneodesmosin

Increased activity of serin proteases

Genes involved in AD



skin barrier disturbance

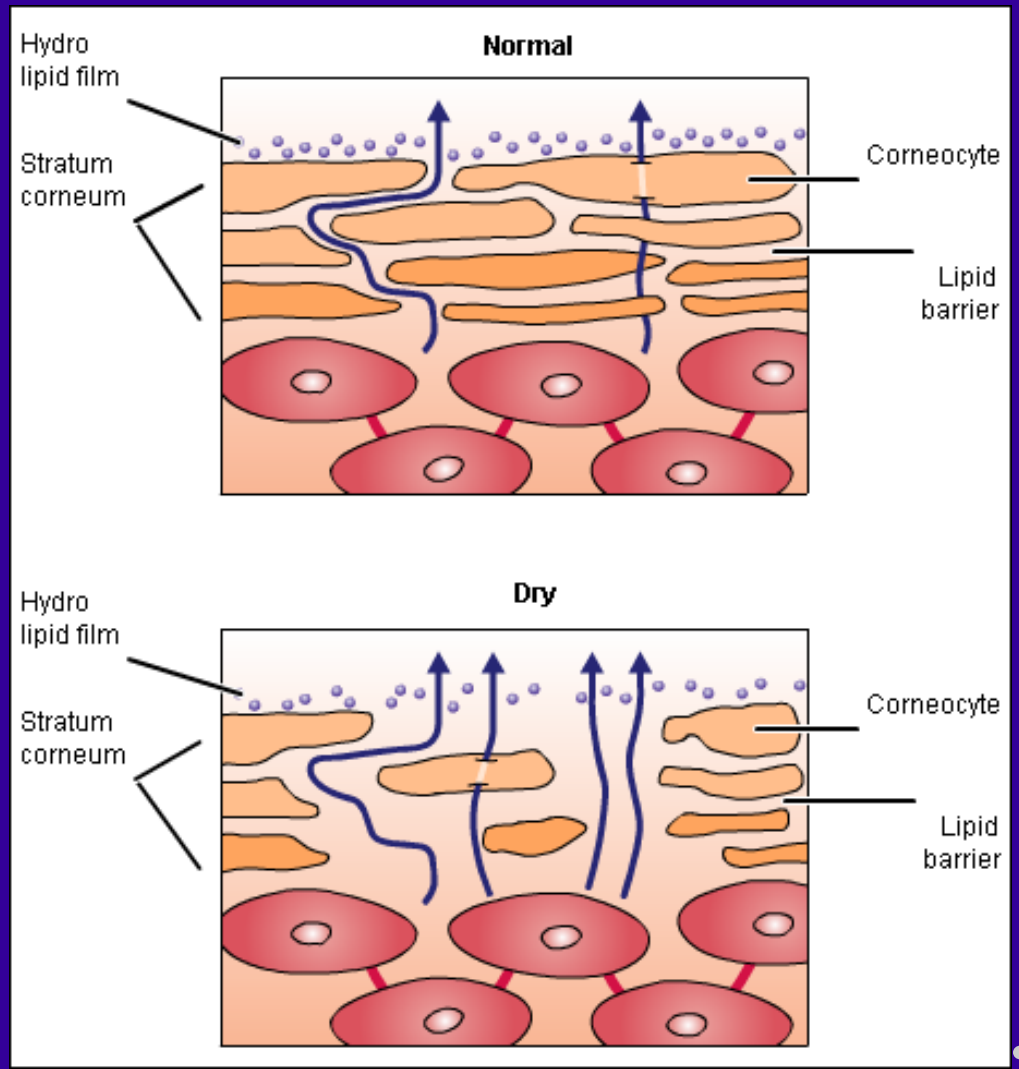
- Defective synthesis of ceramides

  (takes place in lamellar bodies in granular layer of epidermis)

  ↓

  decreased ability to bind water in the skin

skin barrier disturbance



AD and skin barrier

Defective structure and function of skin barrier

↓

insufficient hydration (TEWL ↑)

↓

dryness - xerosis

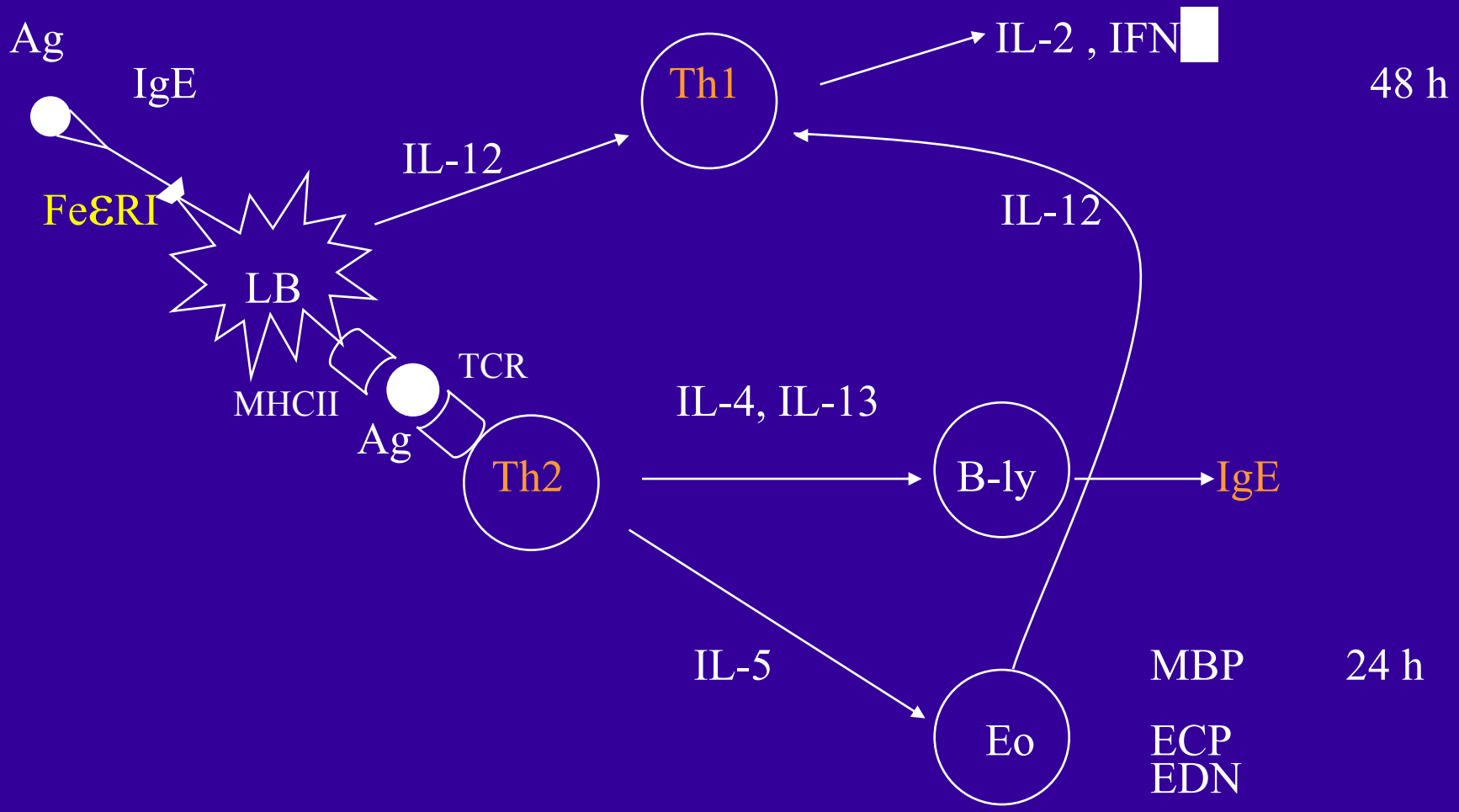
↓

increased irritability of the skin

possibility of contact sensitization

II: Immunological abnormalities in AD

biphasic model of AD (Th2 → Th1 shift)



III. Staphyloccus aureus and AD

- colonization of AD lesions in 74 - 96% atopic patients, 30 - 56% even on „healthy“ skin

Mechanisms:

- Defective skin barrier with „naked“ laminin and fibronectin enables SA binding the skin

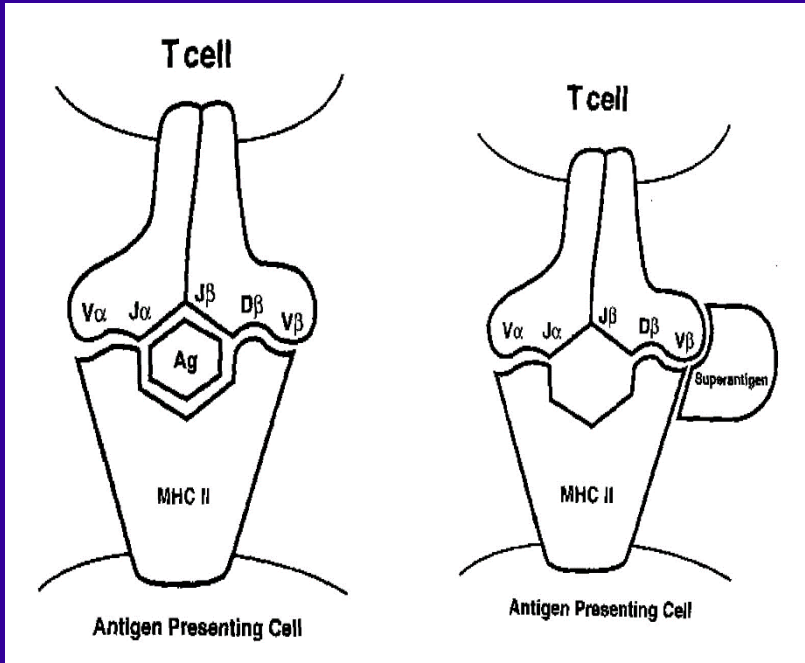
- Decreased defensive mechanisms: defective signallization via TLR 2

[redacted] defensine a kathelicidine

[redacted]roduction of IFN [redacted]

Staphyloccus aureus and AD

1) Toxic effect: staphylococcal exfoliatine
2) Stimulation of sIgE production (sIgE → stimulation of basophils → histamine)
3) superantigens: SEA- SEE a TSST-1



- without previous processing by LC
- able to bridge V chain of TC Receptor,
- not necessary exact conformity of all 5 subunits of the receptor

  1000x stimulation
- non-specific but huge stimulation of Tly

  (1 SA even 20% of circulating lymph.)

Triggering and mainaining factors of AD

Allergy (house dust mites, pollen, pets, molds, foods – milk, eggs, wheat, soya, nutts, fish)

Microbes – Staphylococcus aureus

Irritant substances (water,detergents etc.)

- climatic (temperature, wind, low humidity ..)

Psychological stress

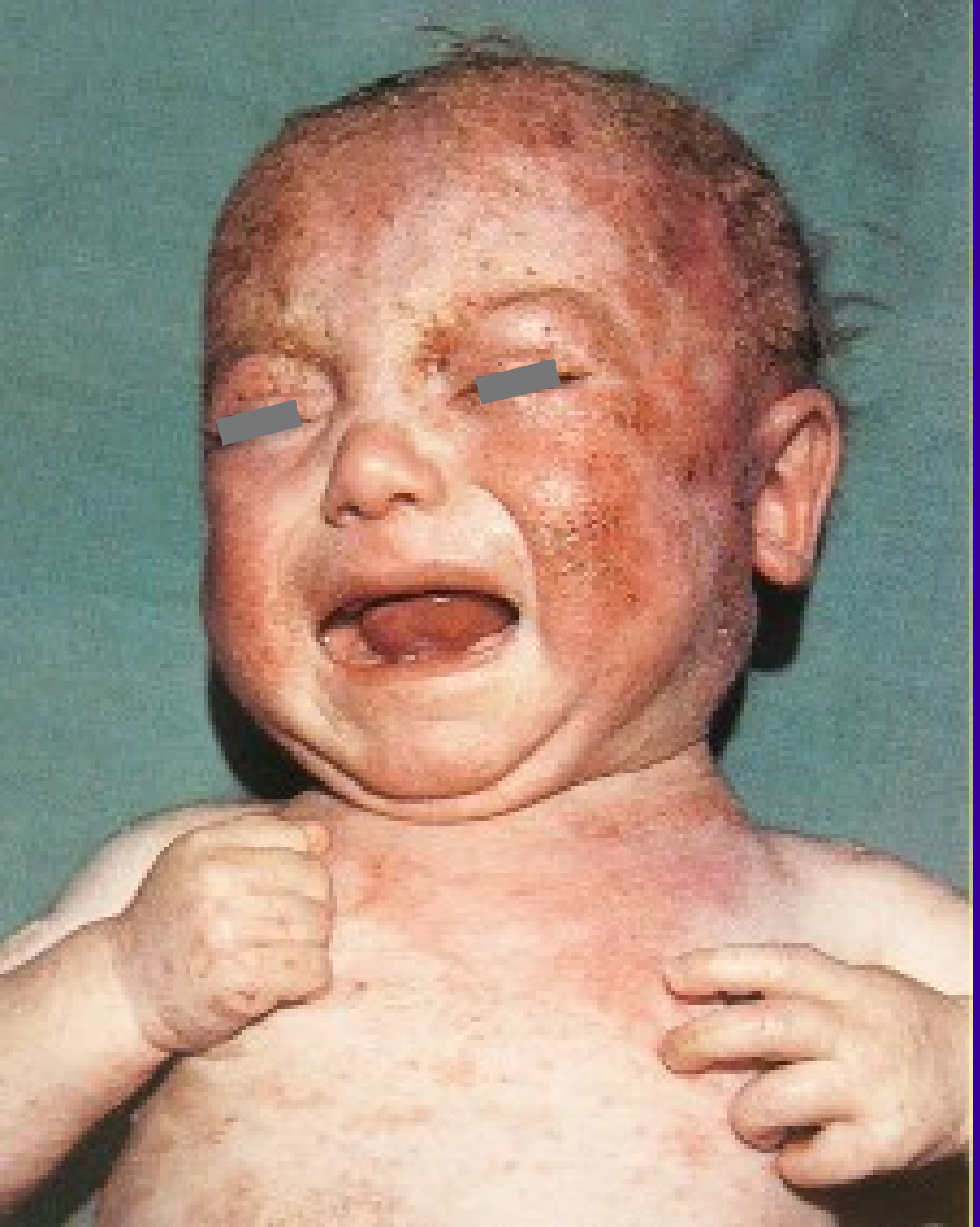
Clinical picture of AD

AD in infants

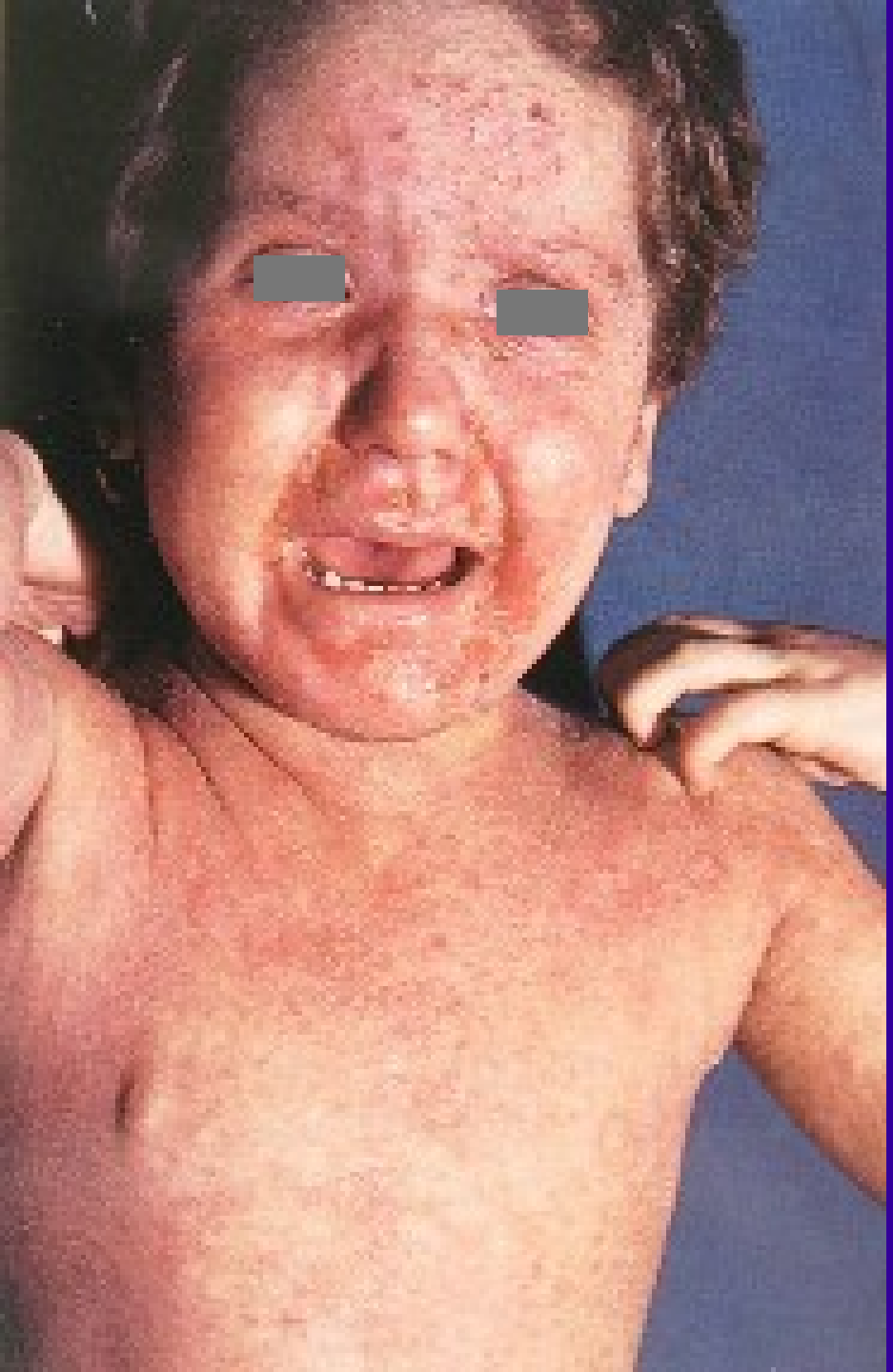
Exudative form – acute eczema (oozing, crusting)

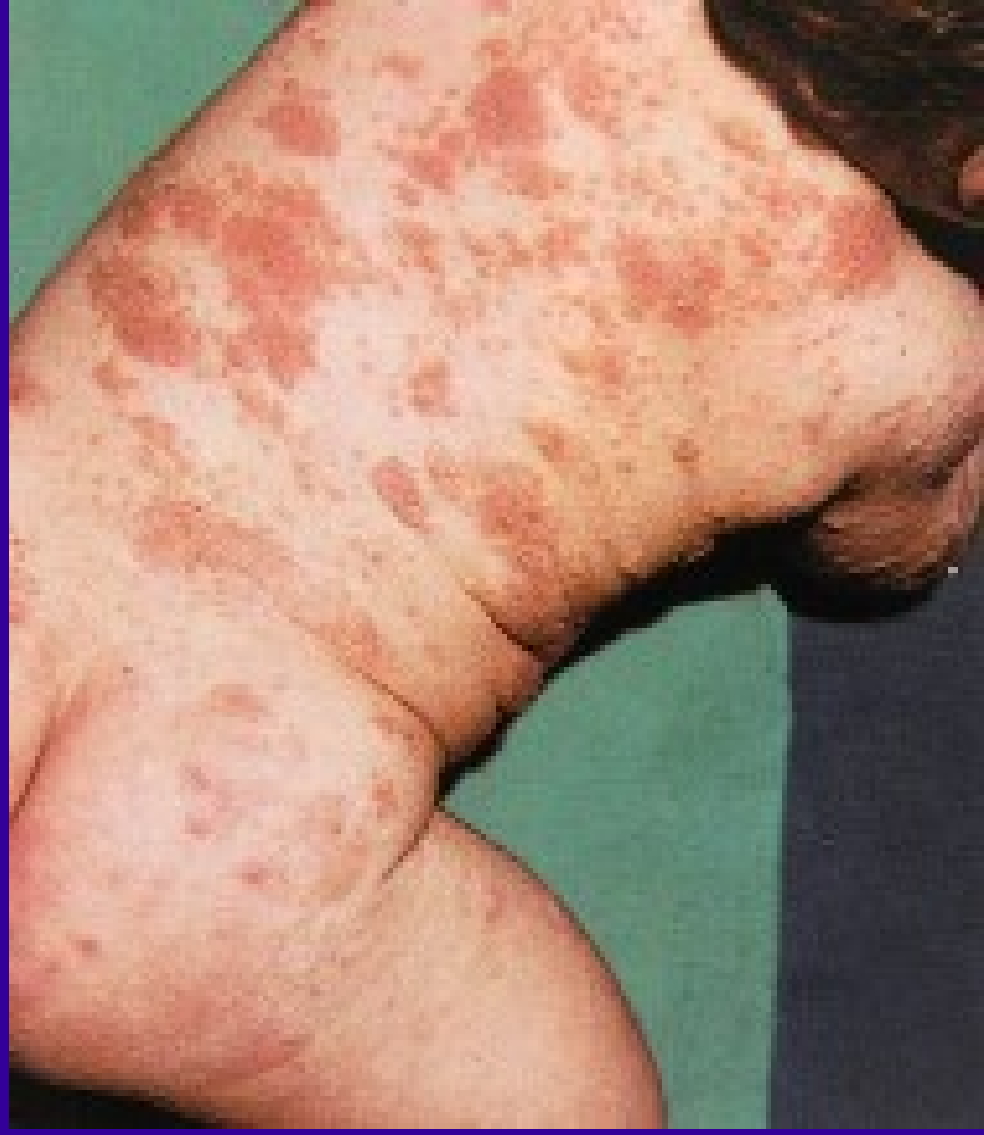
- **Localization** - periorally
  - periorbitally

- **Possibility of spreading - erythroderma**



Atopic dermatitis – Infant AD





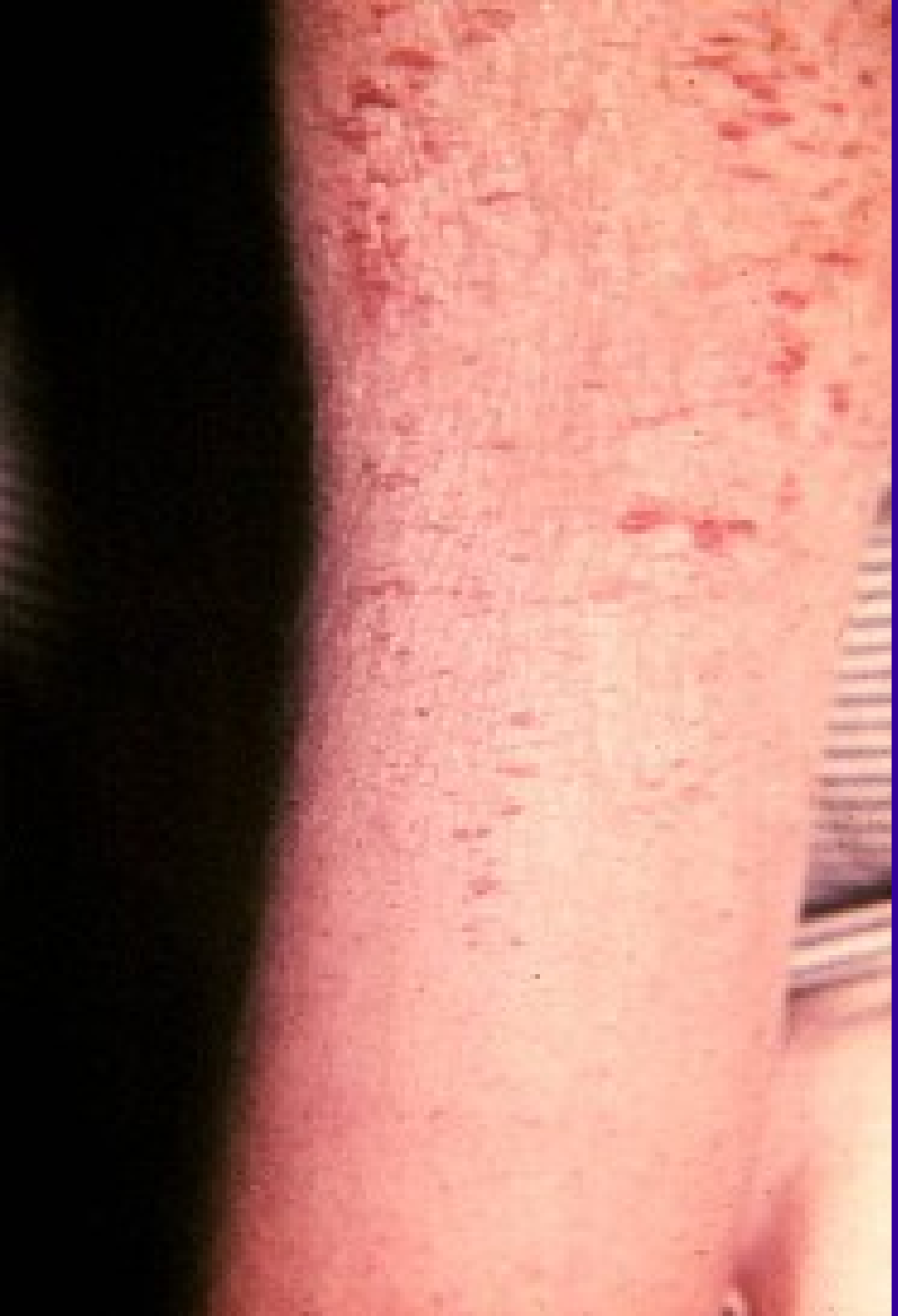
Infant AD

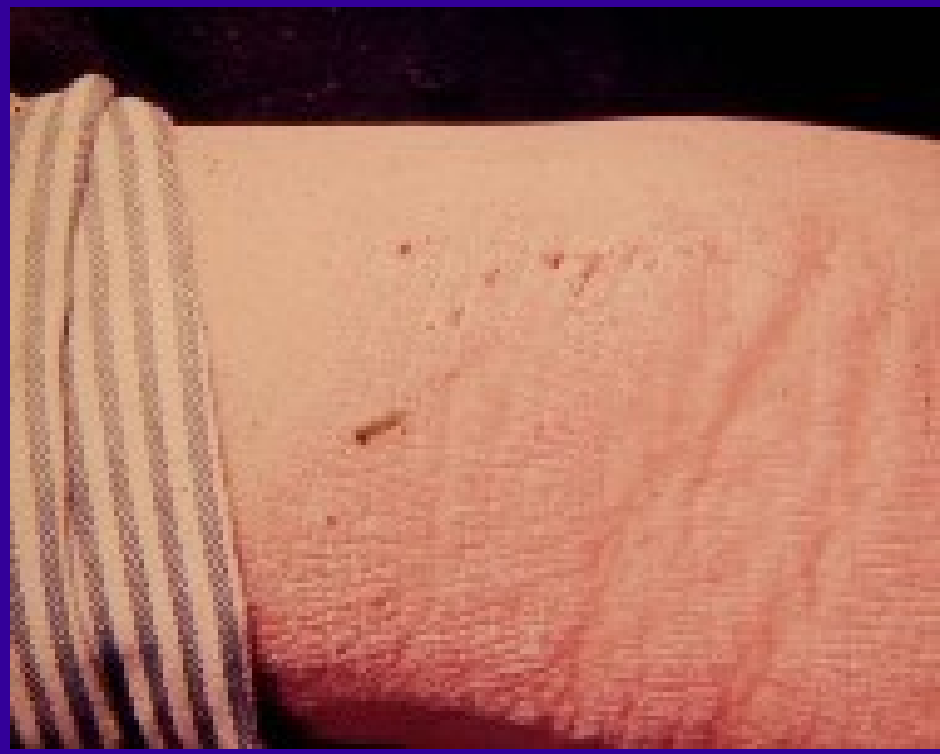
Clinical picture of AD

AD in children and adolescents

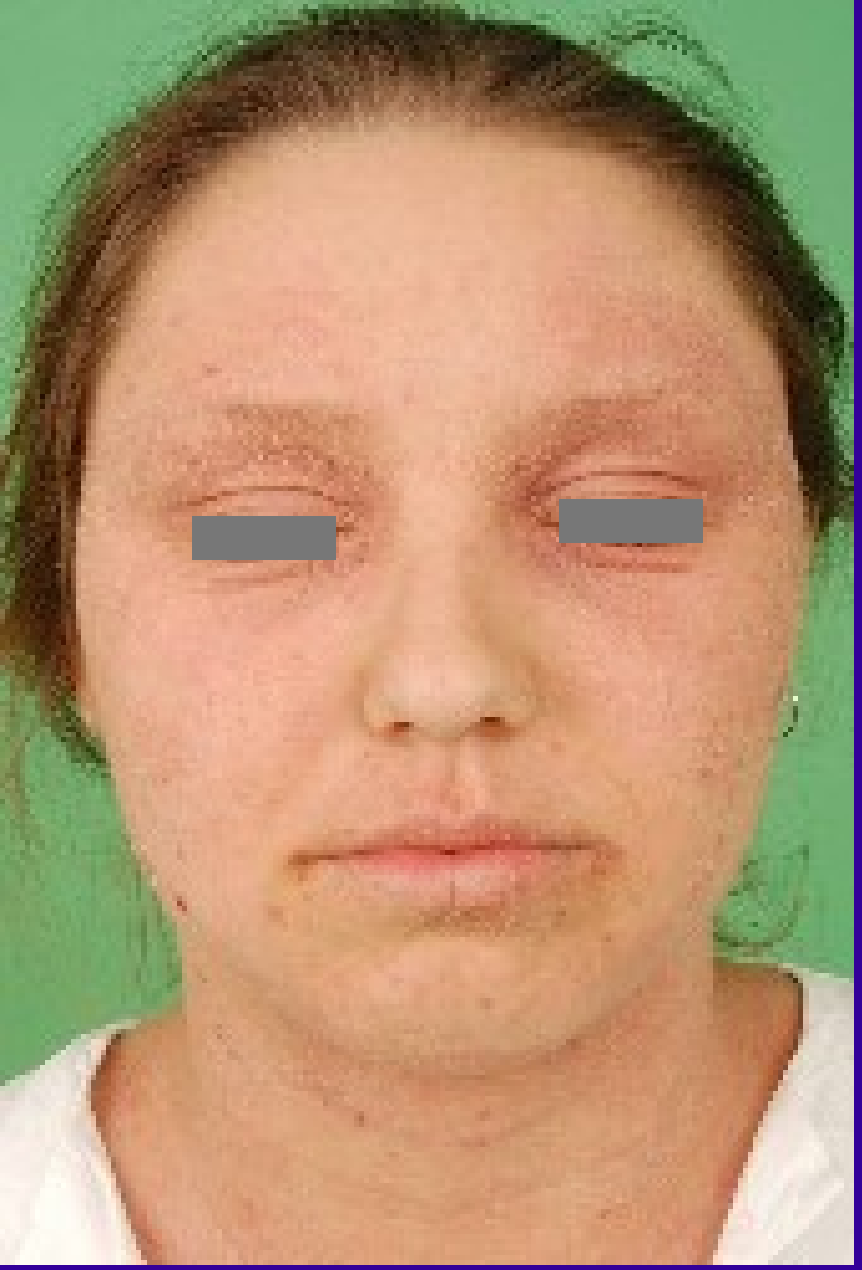
Decrease of exudation - lichenification

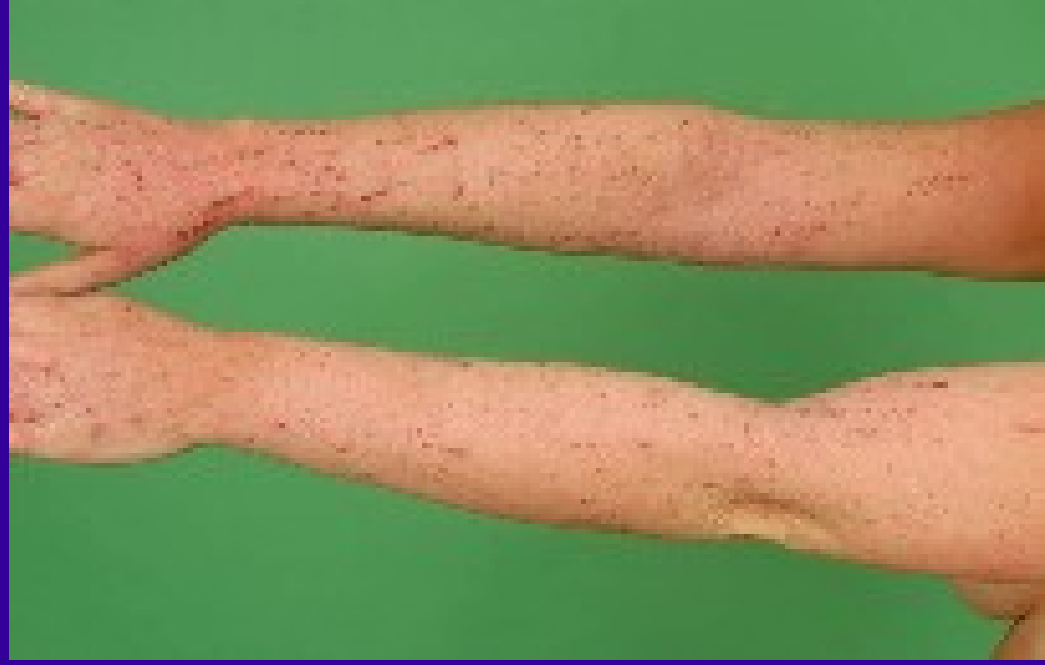
- most often – flexural eczema
  - facial eczema
- less often - erythroderma

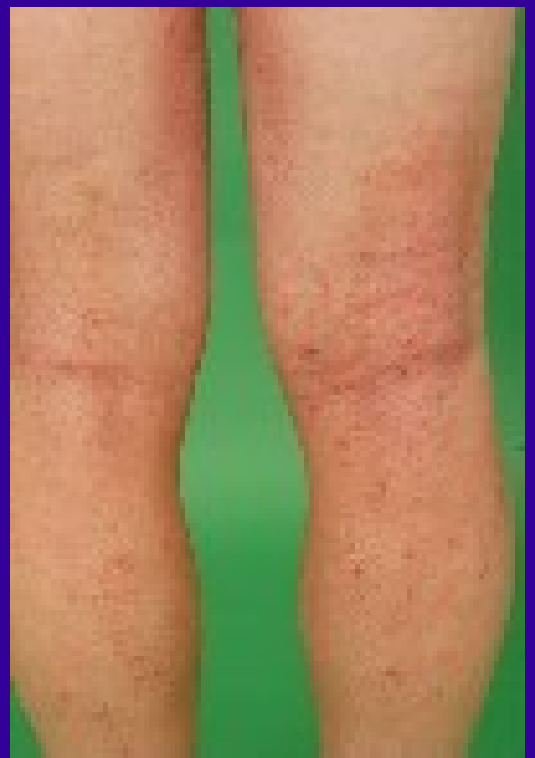


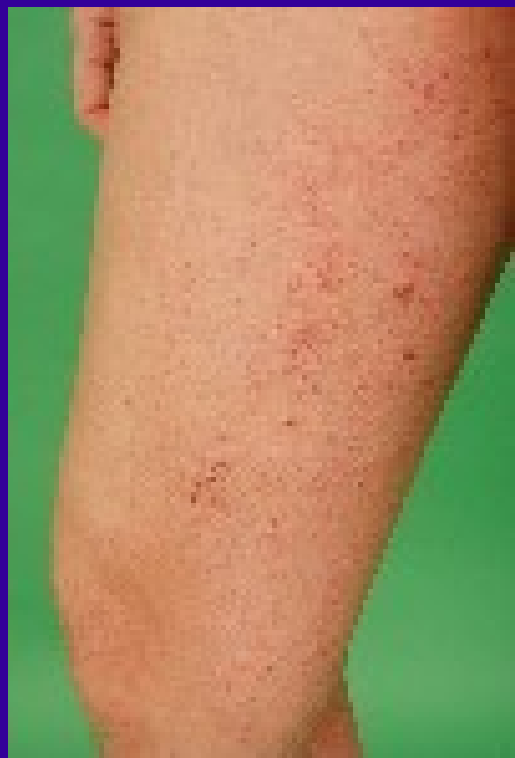


Atopic dermatitis – flexural eczema









Atopic dermatitis – erytrodermic form

Clinical picture of AD

AD in adults

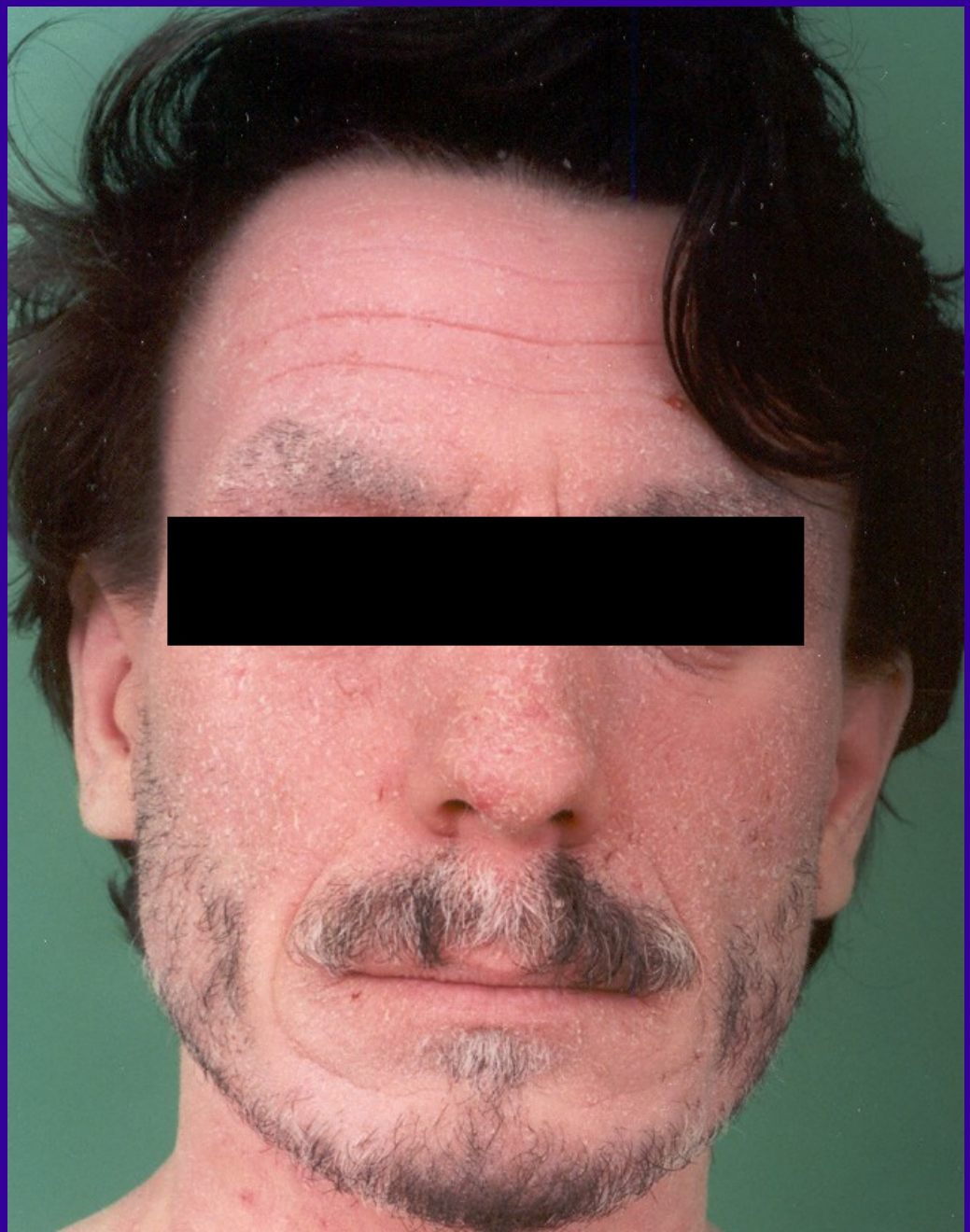
(about 15% of cases appear after puberty)

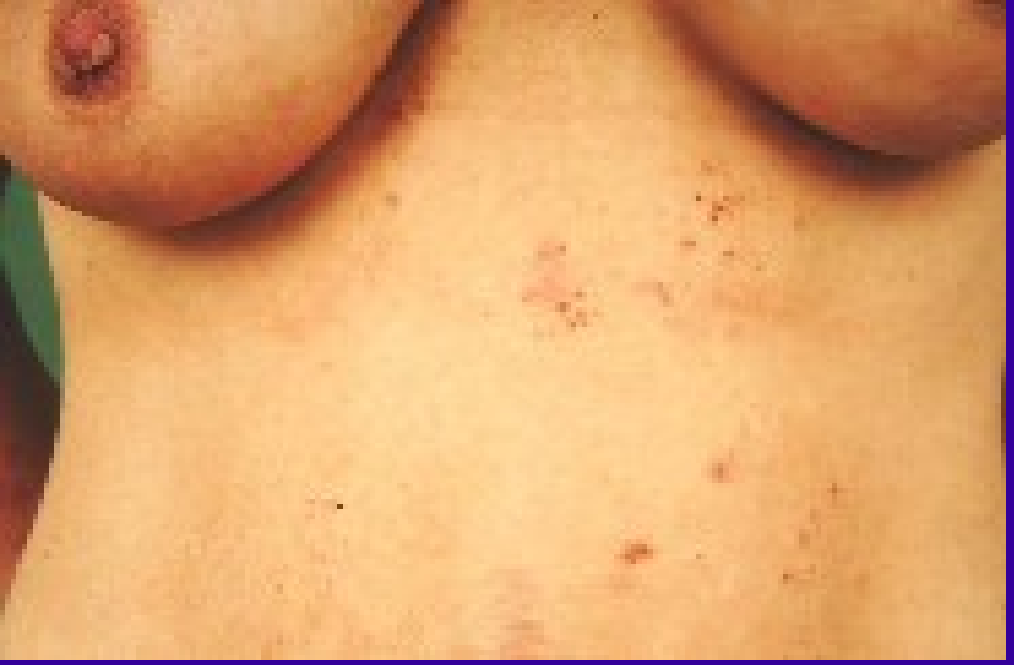
- **head& neck**
- **flexural**
- **prurigininous**
- **neurodermitic**
- **erythrodermic**

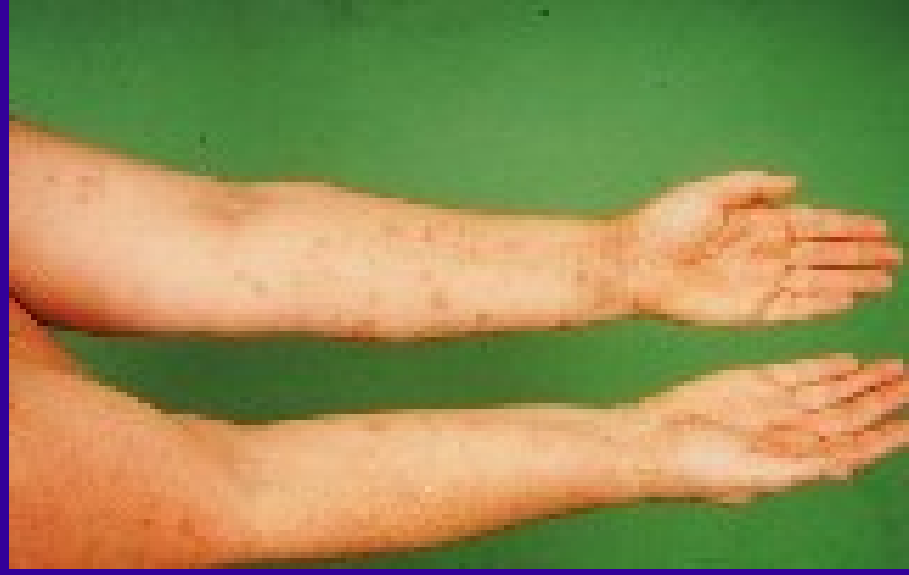
chronic course

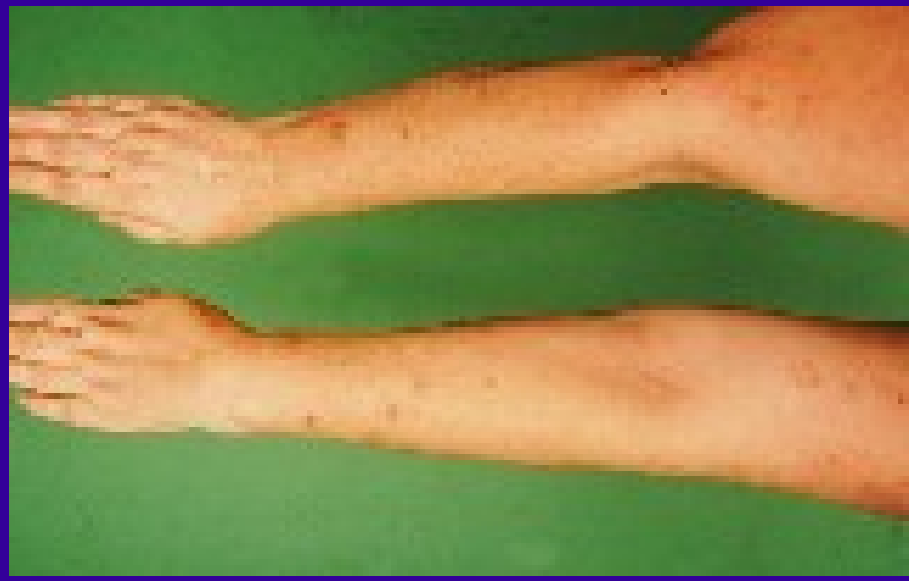
acute flares

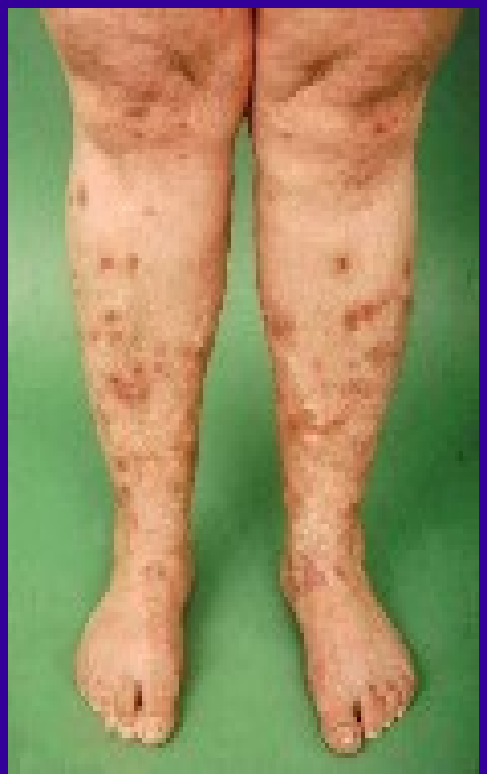
possible



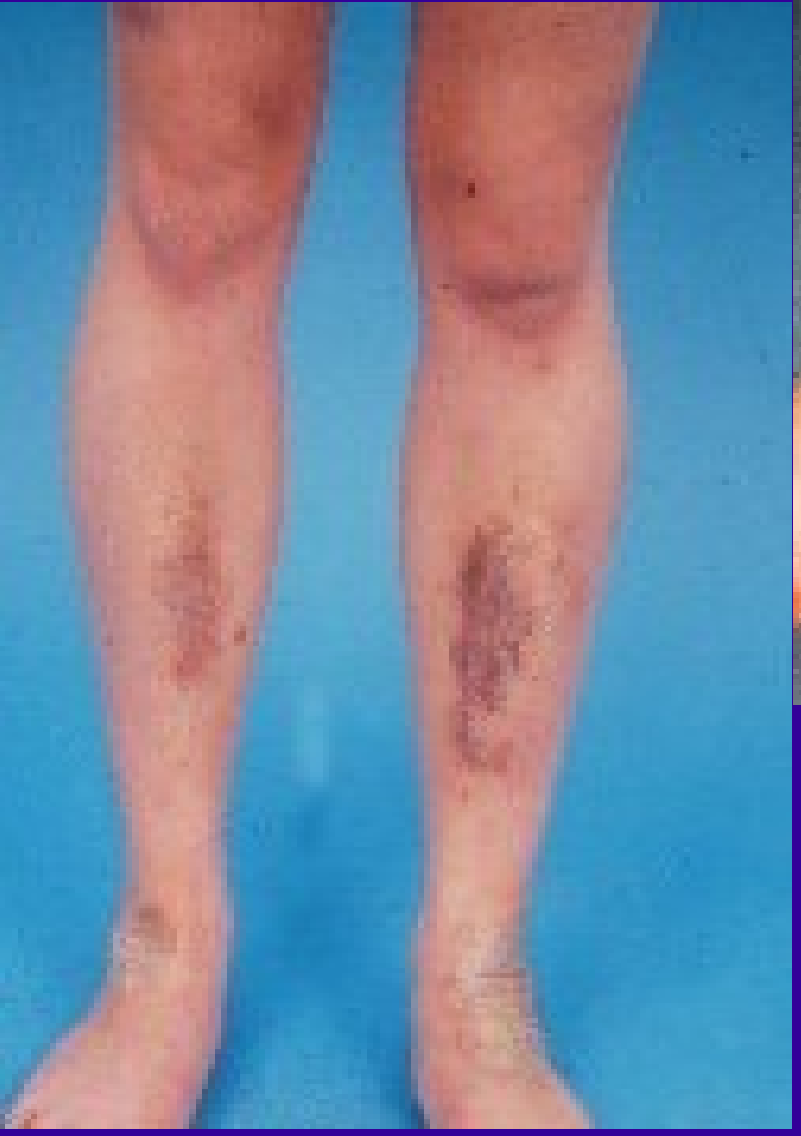


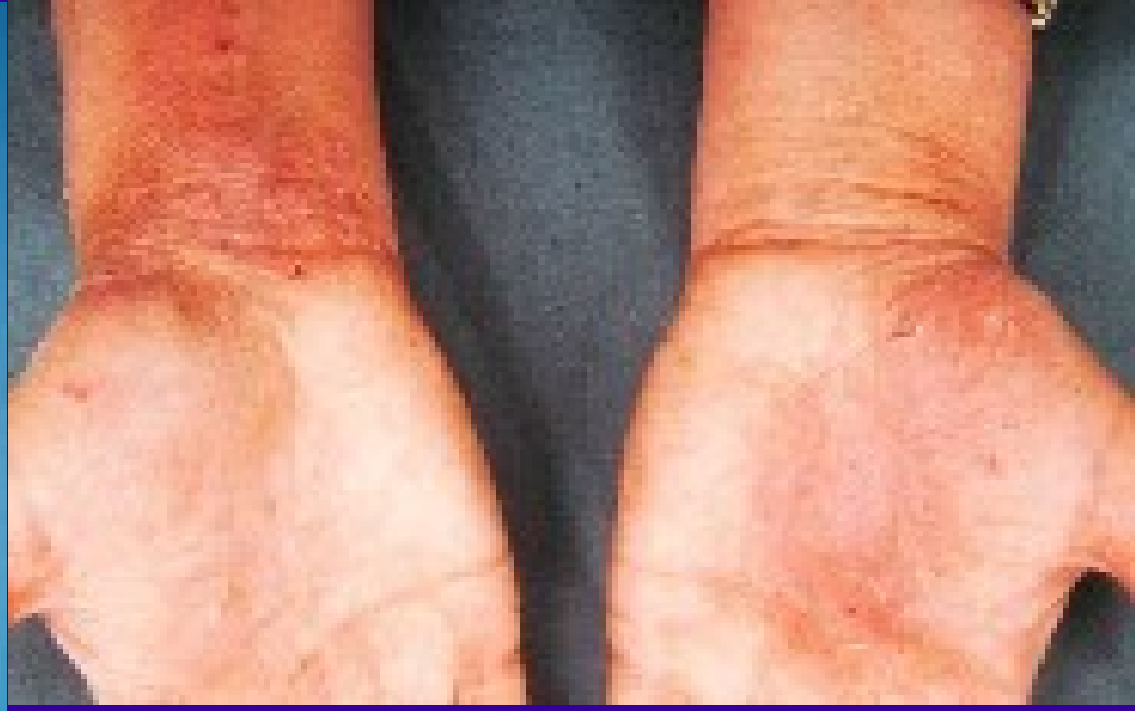


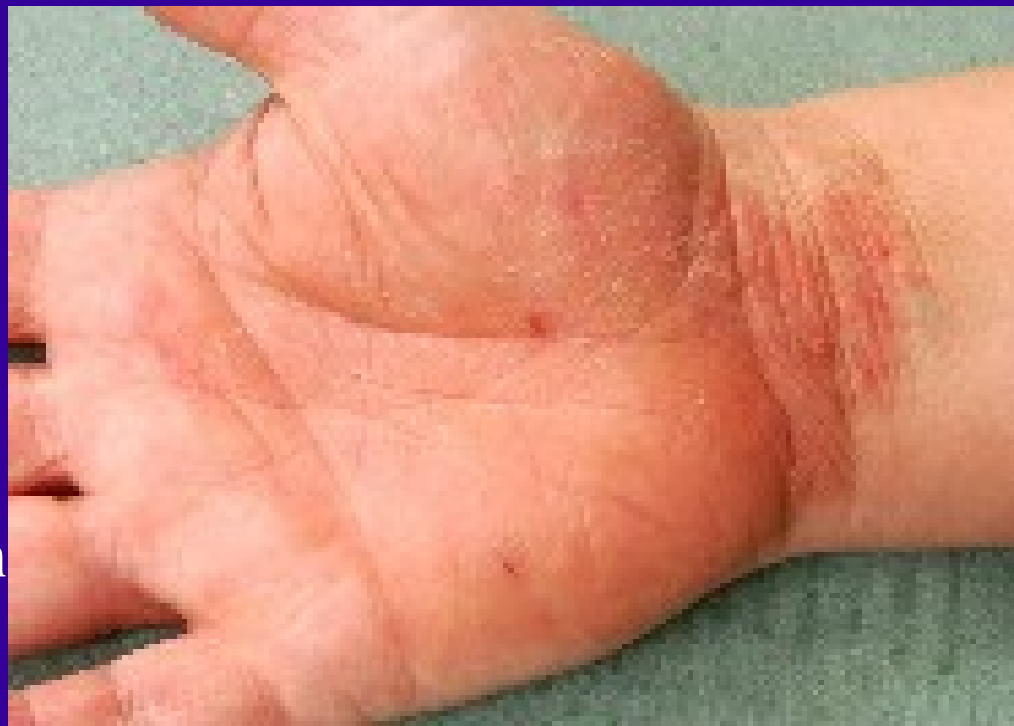




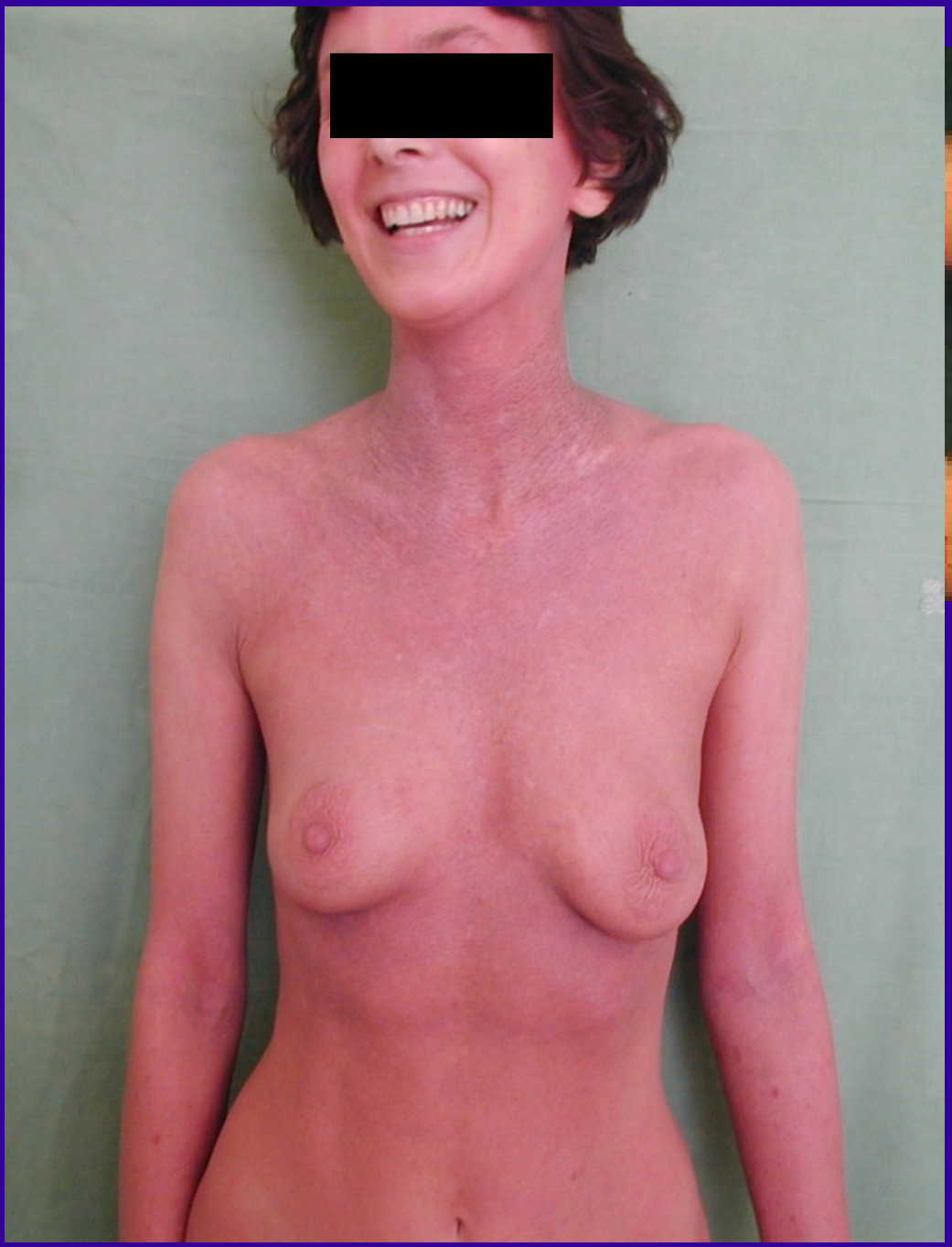
Adult AD – pruriginous form

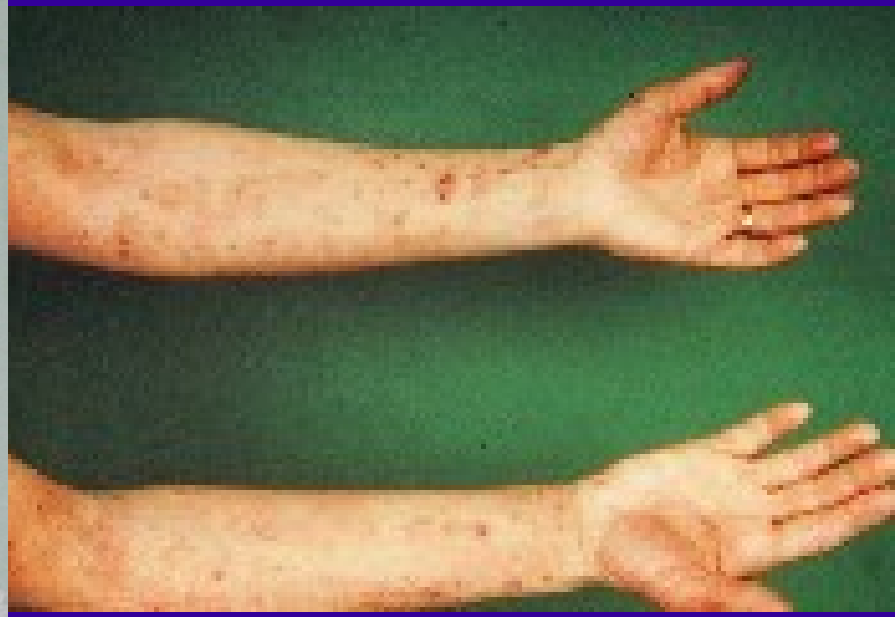






Adult AD – neurodermitic form



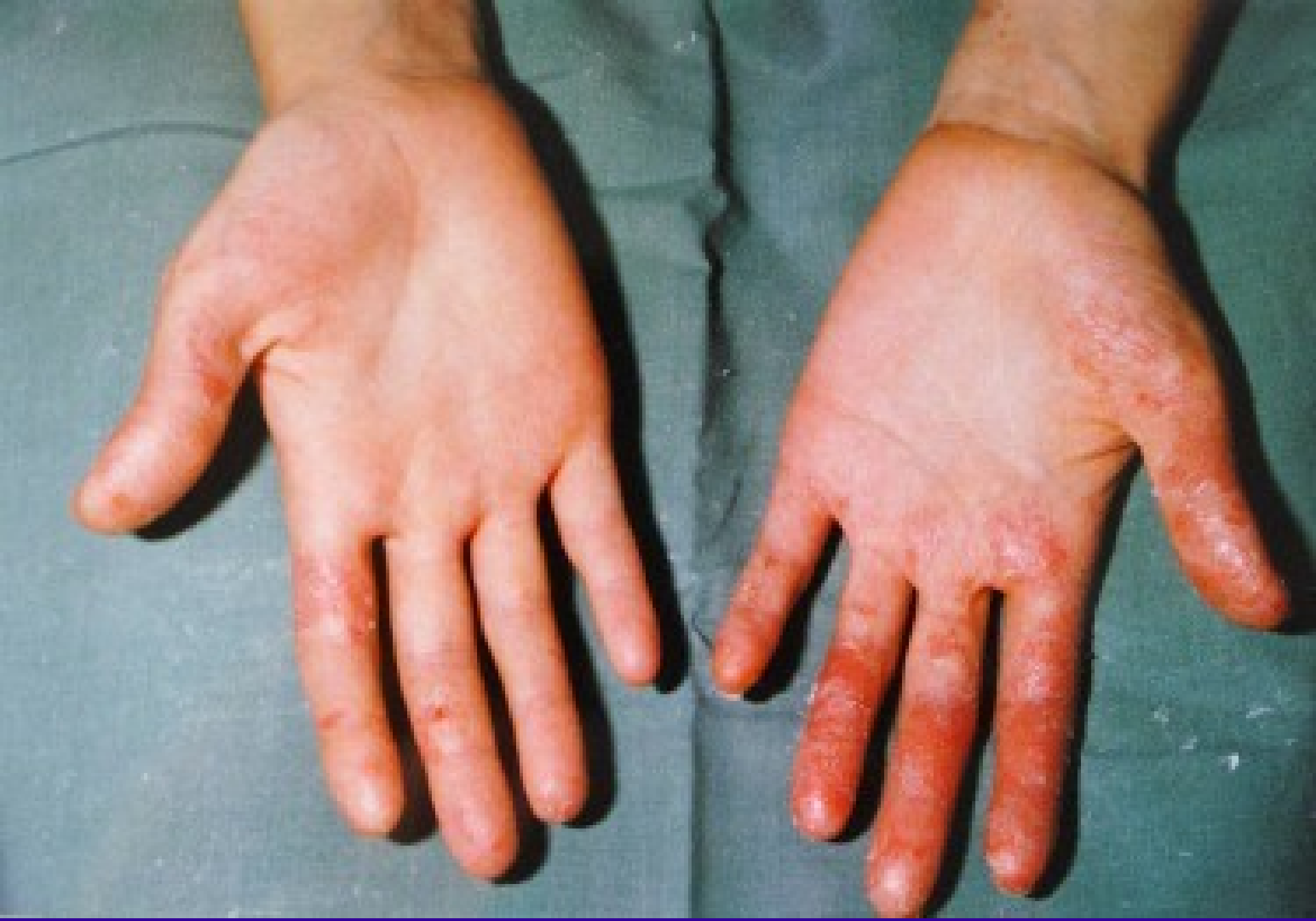


Adult AD – erythrodermic form

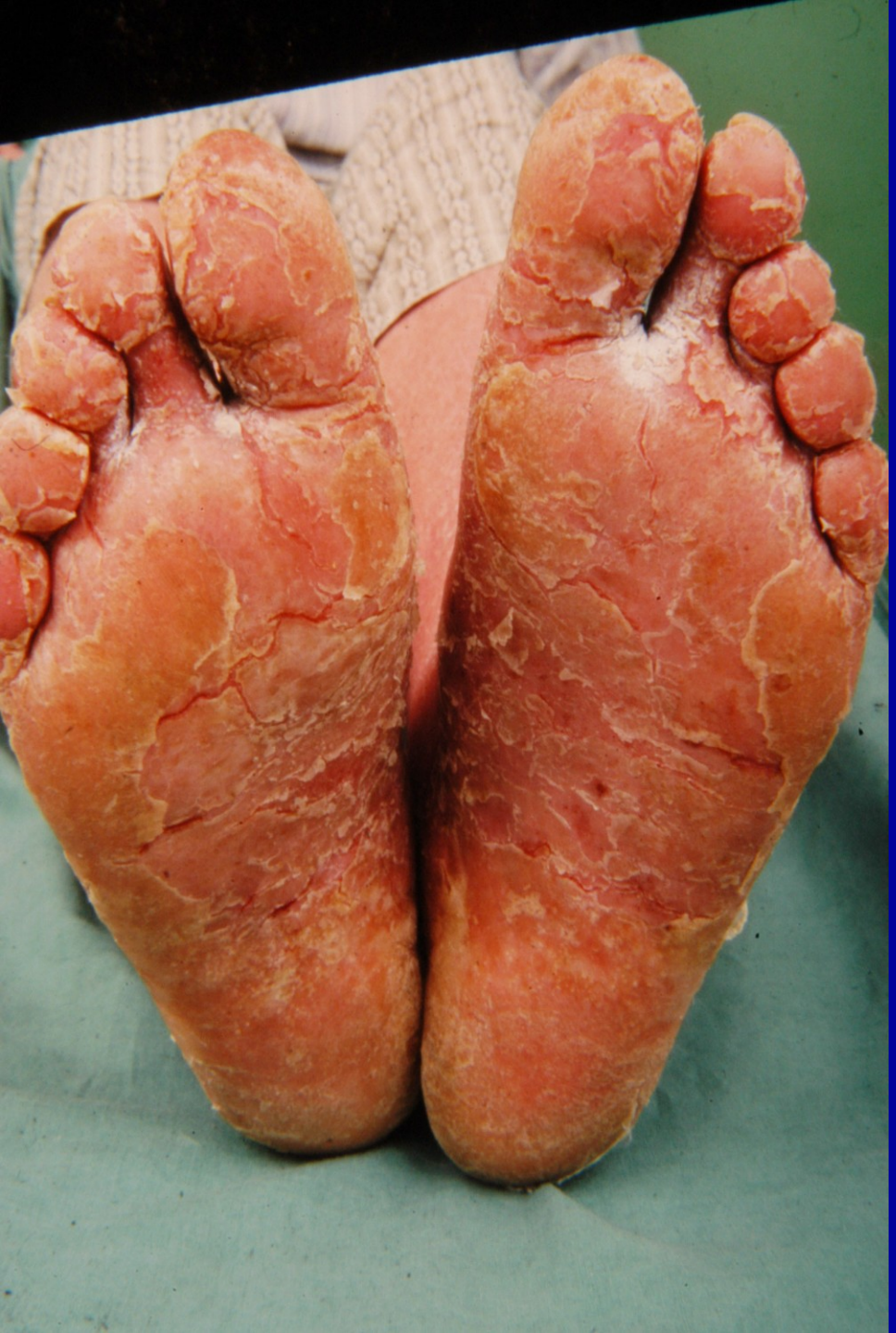
AD in adults

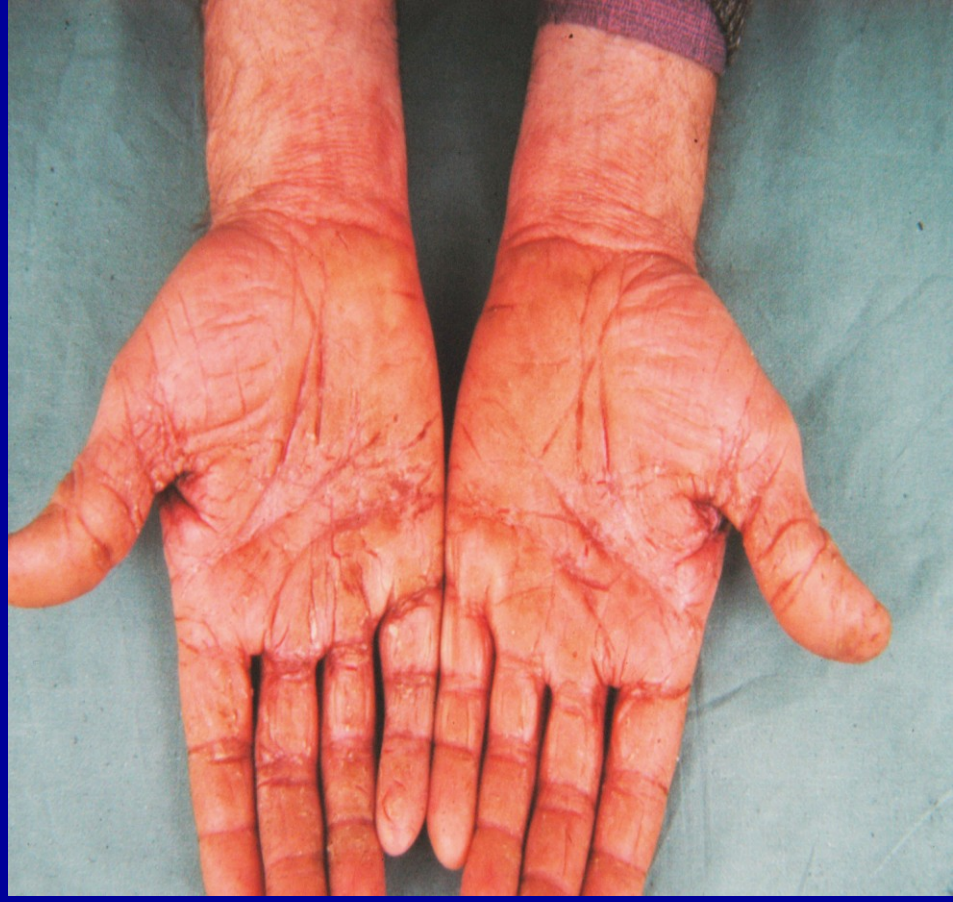
- **atypical forms** - nummular, dyshidrotic, hyperkeratotic forms

- **minimal forms** - cheilitis sicca, stomatitis angularis, pulpitis sicca, intertrigo retroauricularis, aj.

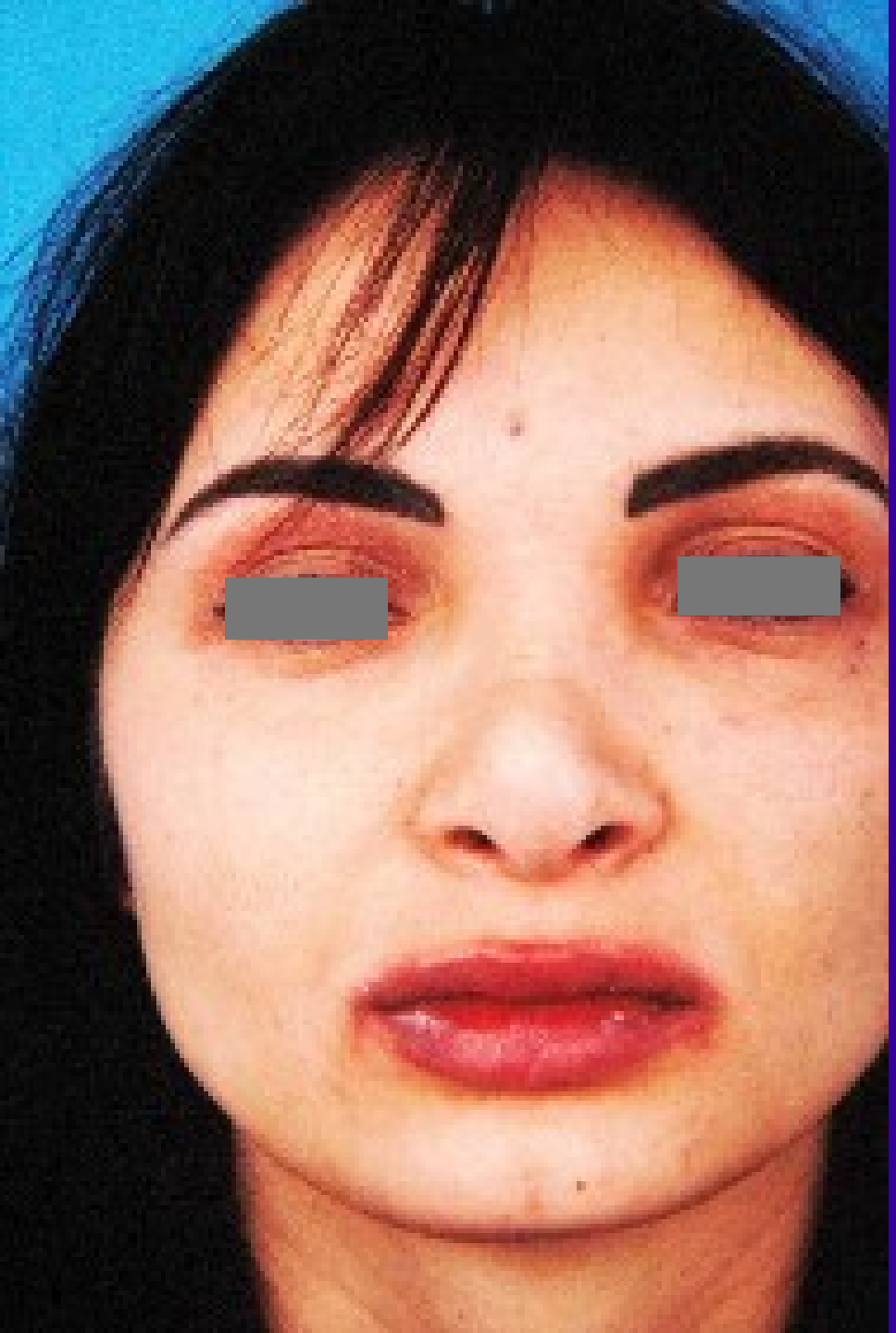


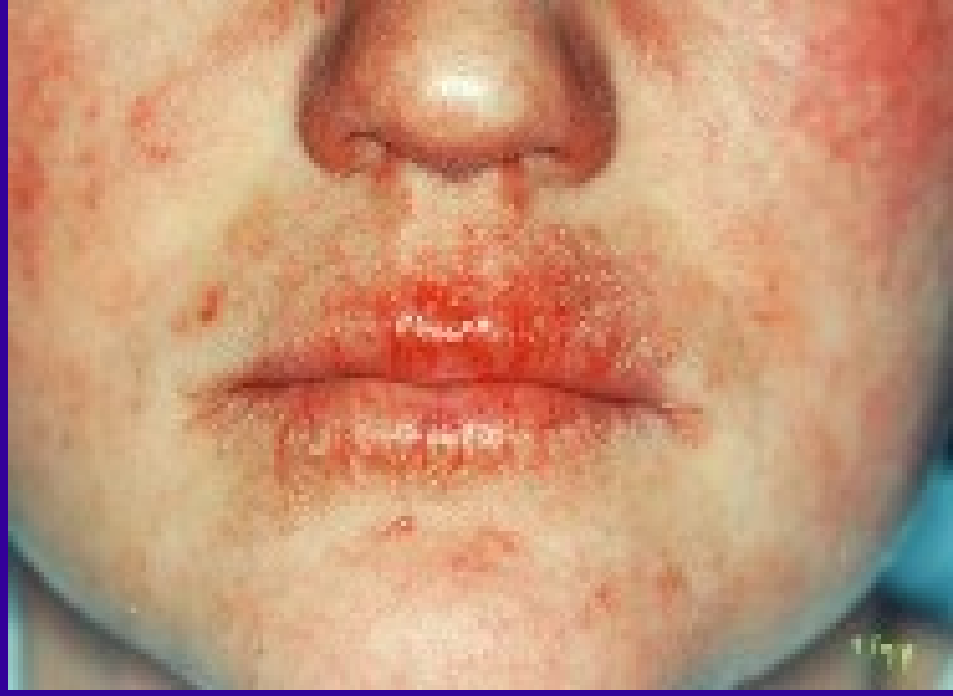
Adult AD - dyshidrotic form



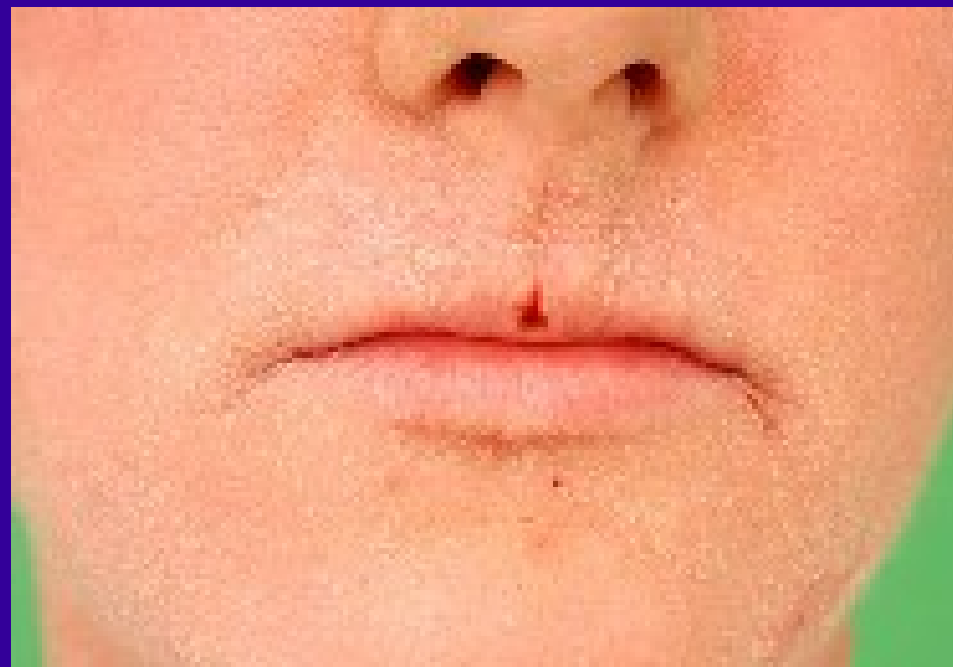


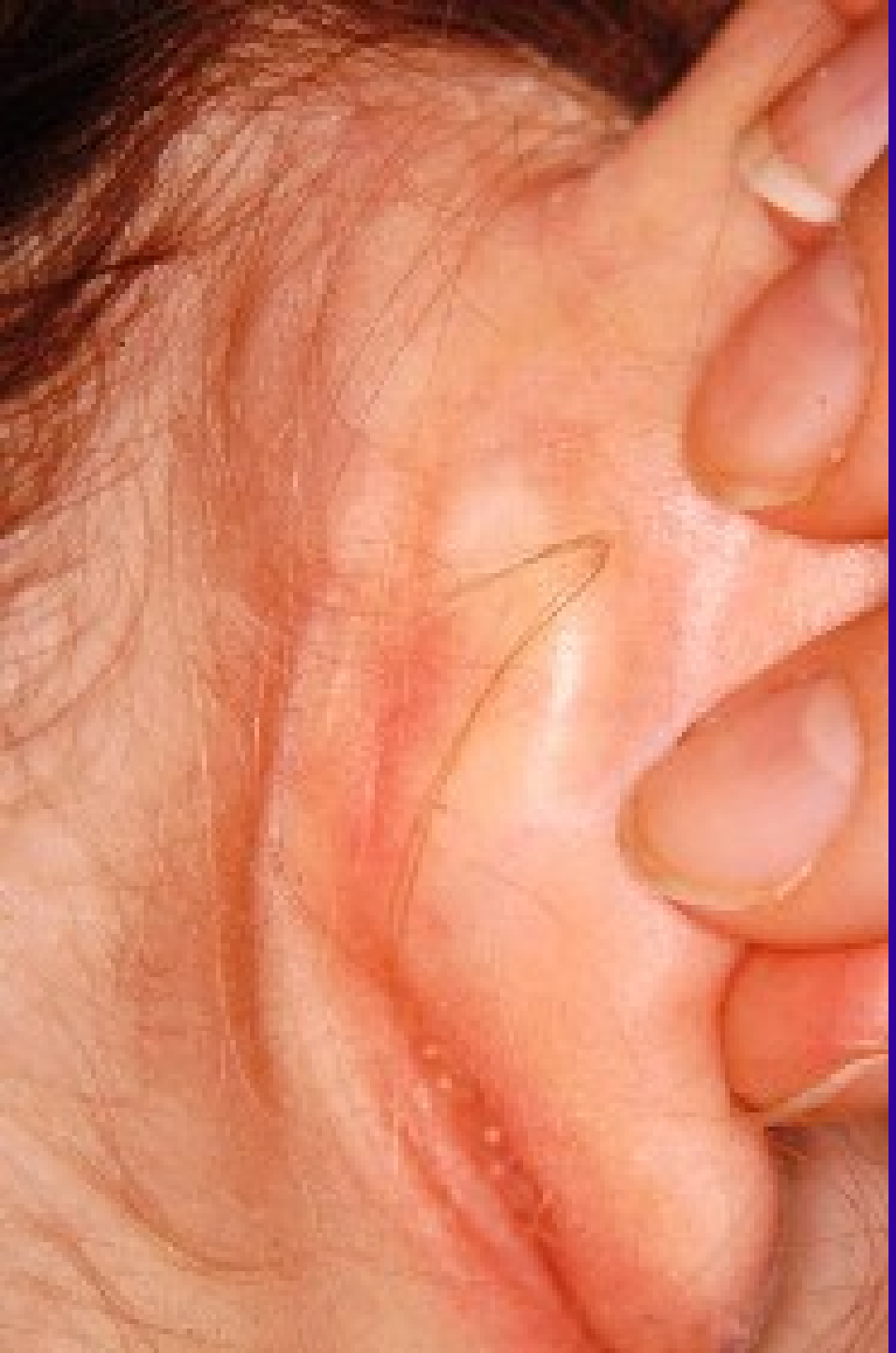
Eczema atopicum hyperkeratoticum

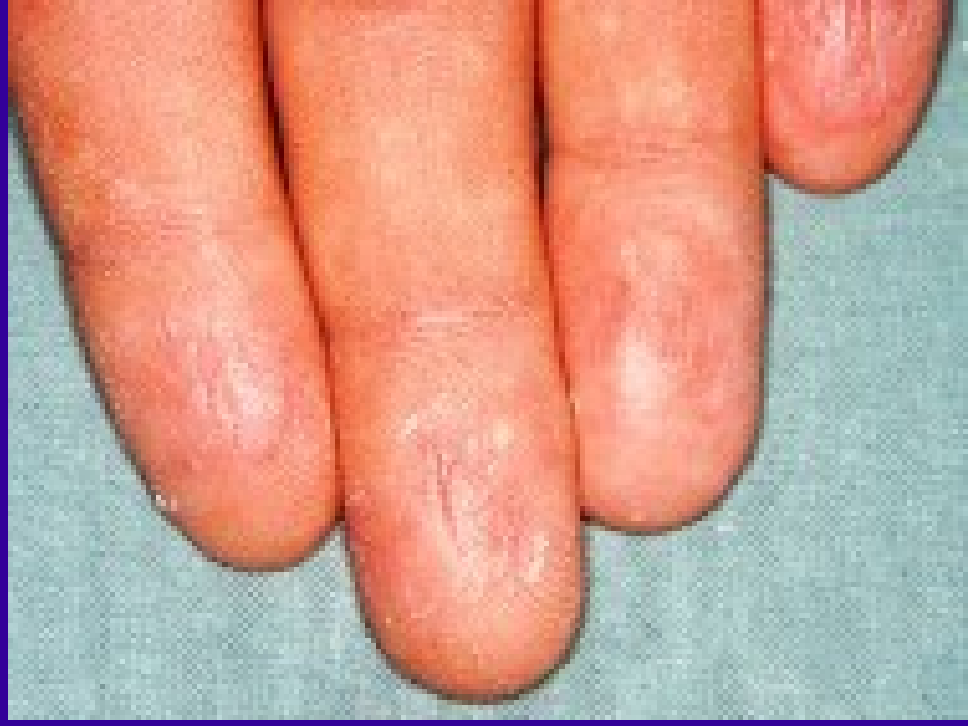




AD eyelid dermatitis, lip dermatitis







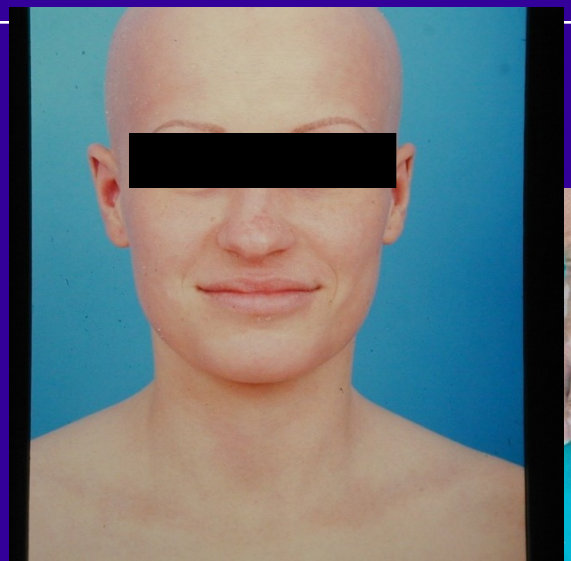
AD retroauricular dermatitis

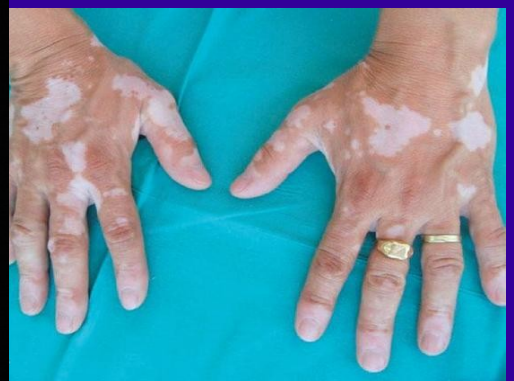
Complications of AD

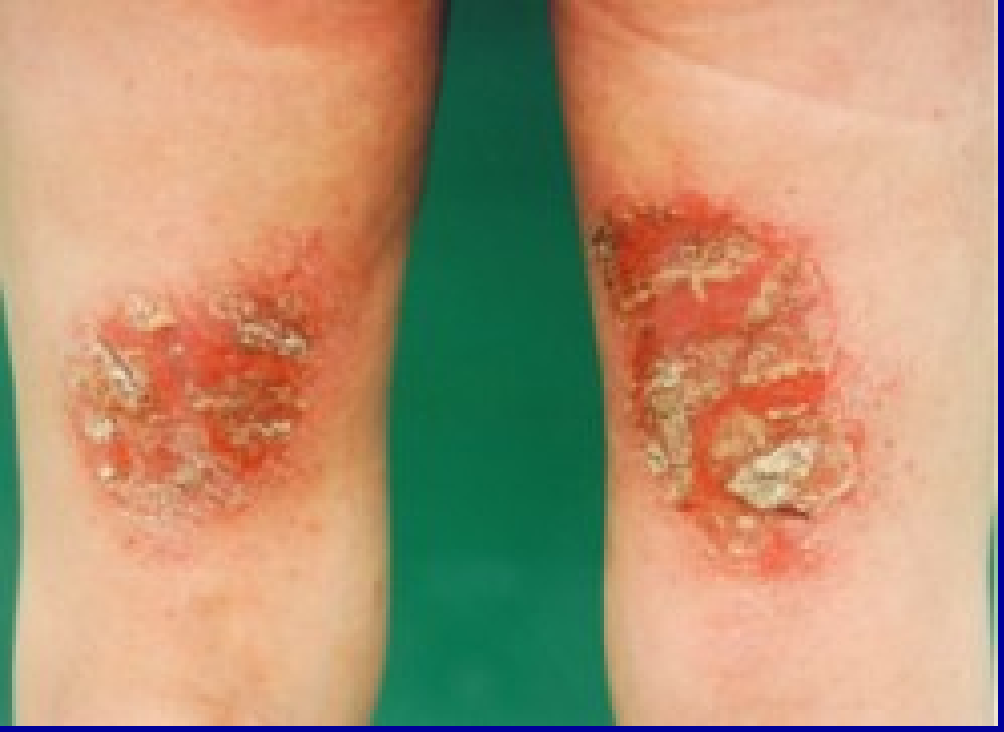
bacterial - impetiginization (St. aureus)
viral – herpetication-HSV, warts, mollusca
fungal (Tr. rubrum, Pityrosporum ovale)
contact sensitization (nickel, fragrances, KS…)

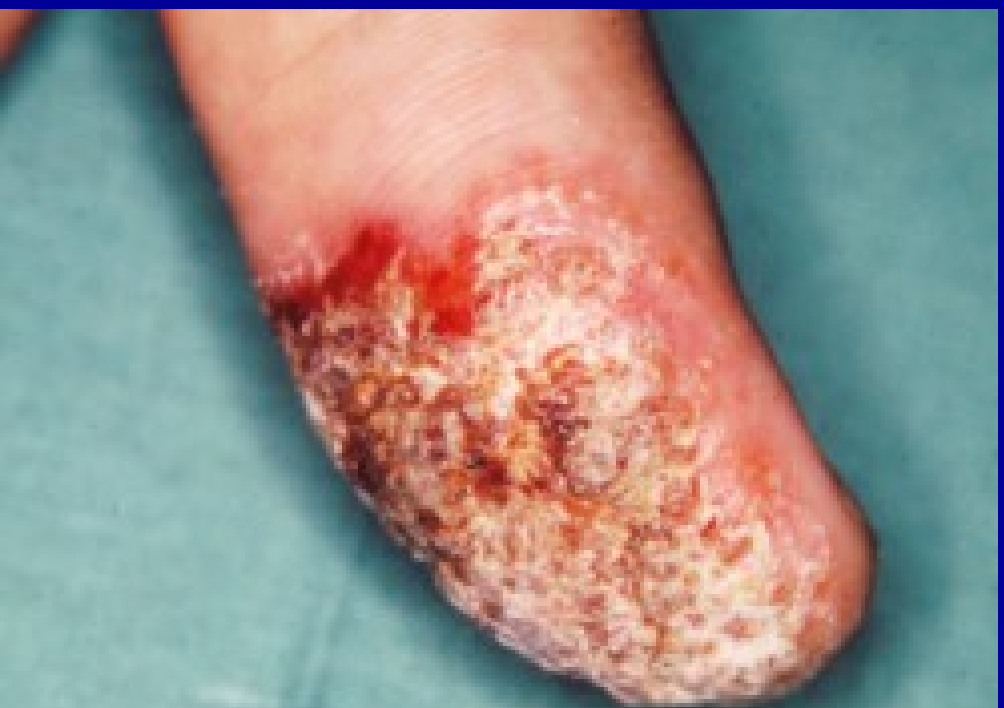
association:

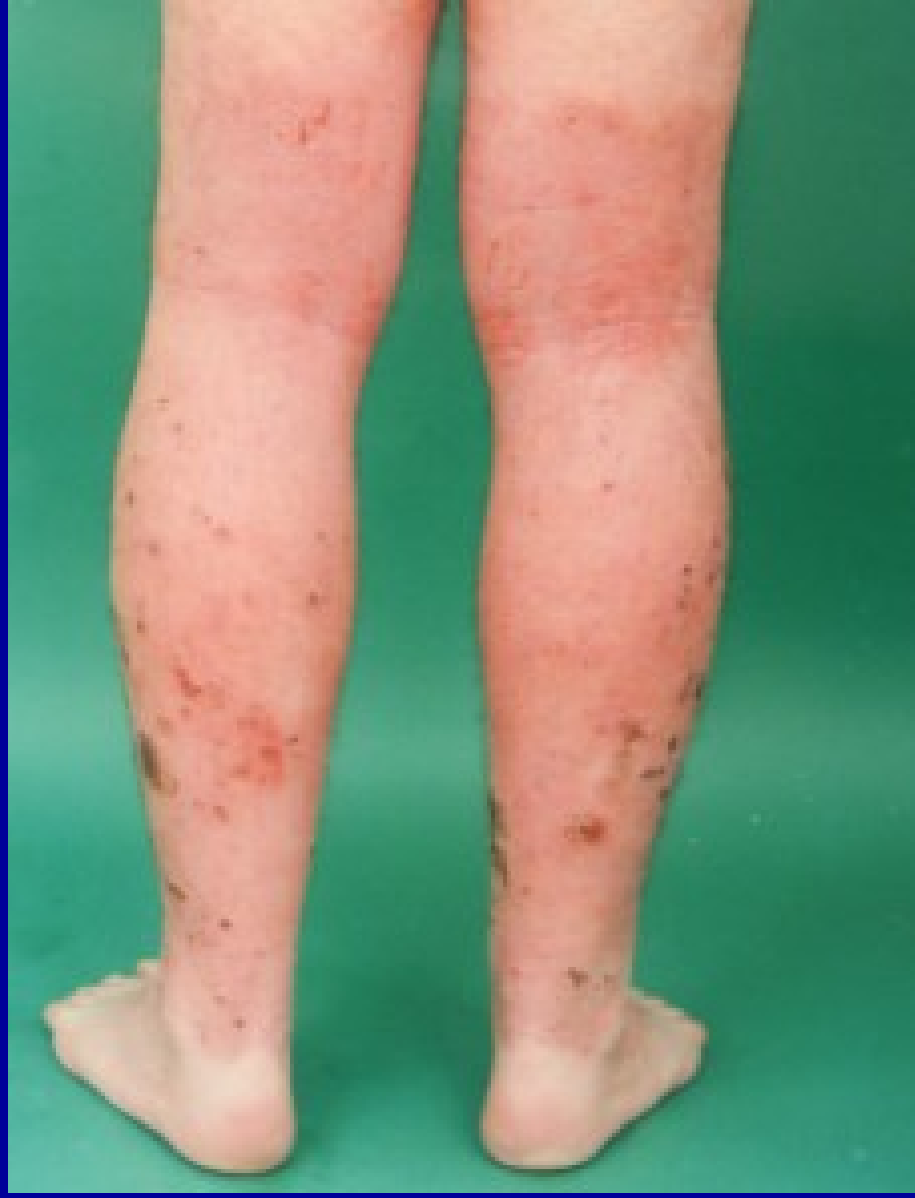
- **alopecia areata**
- **ichtyosis vulgaris**
- **vitiligo**



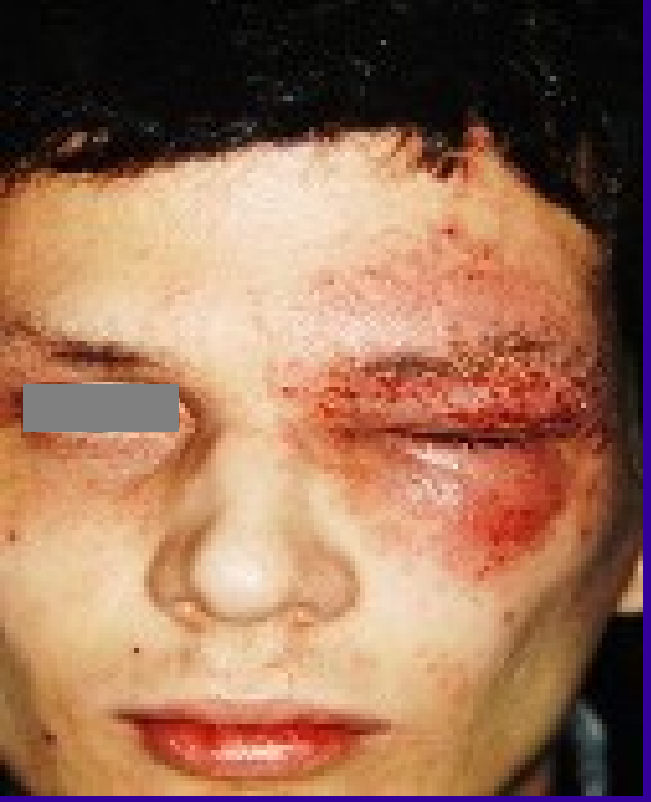
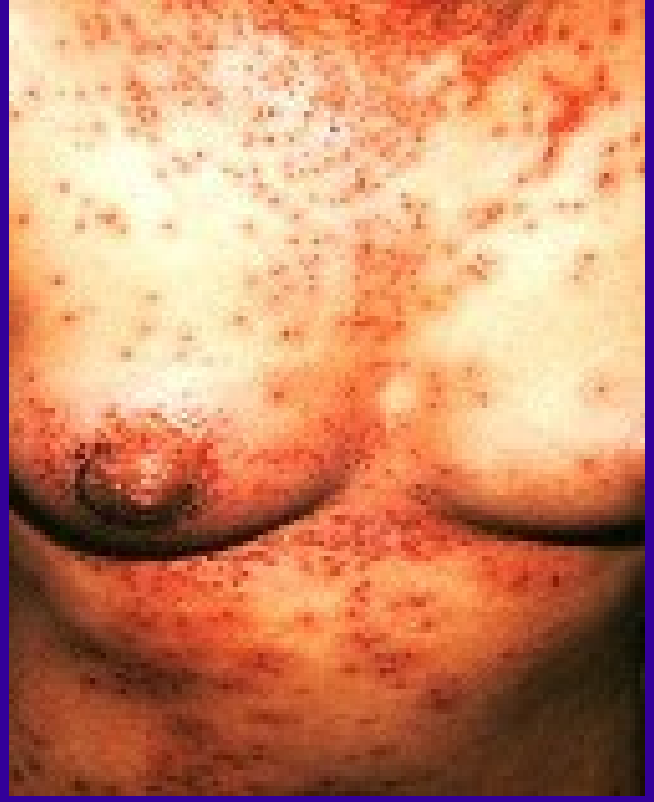
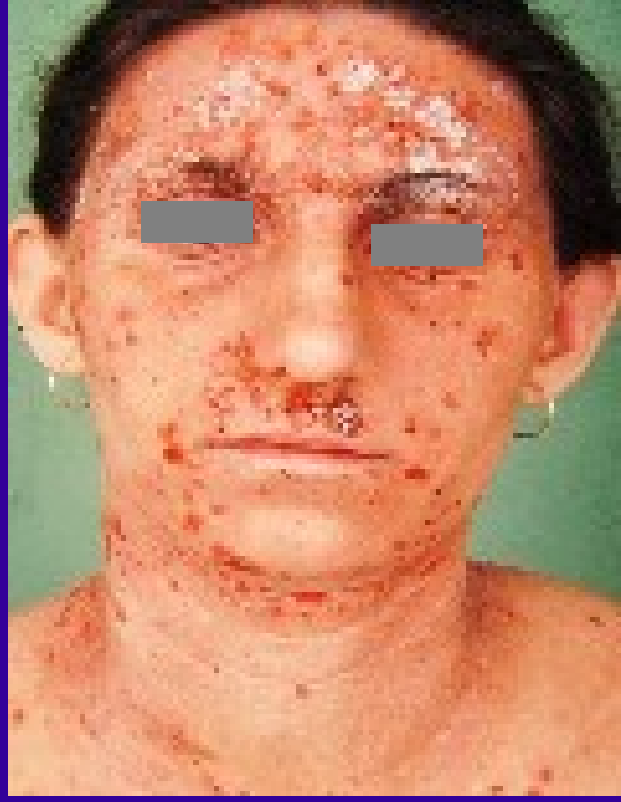
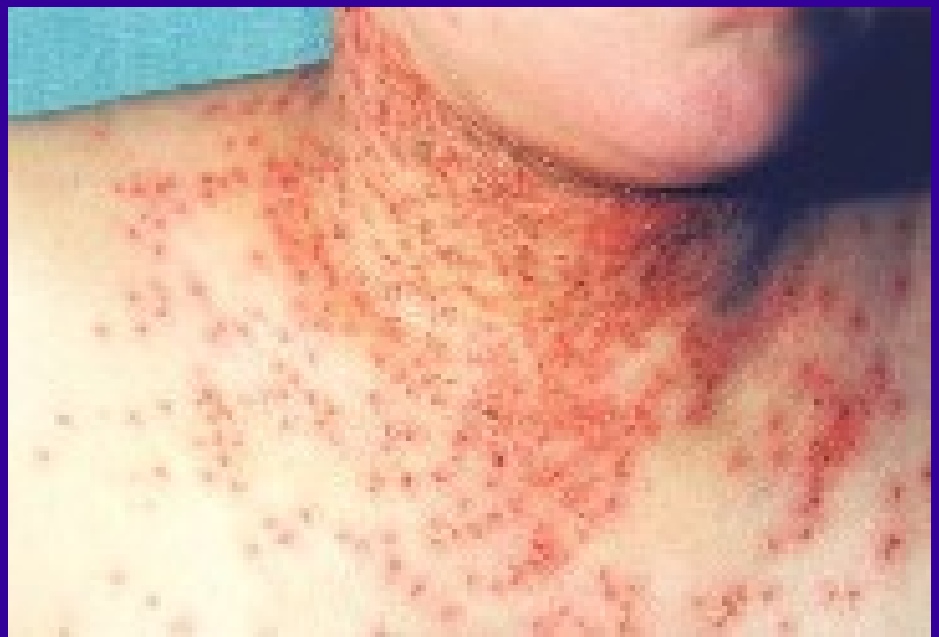




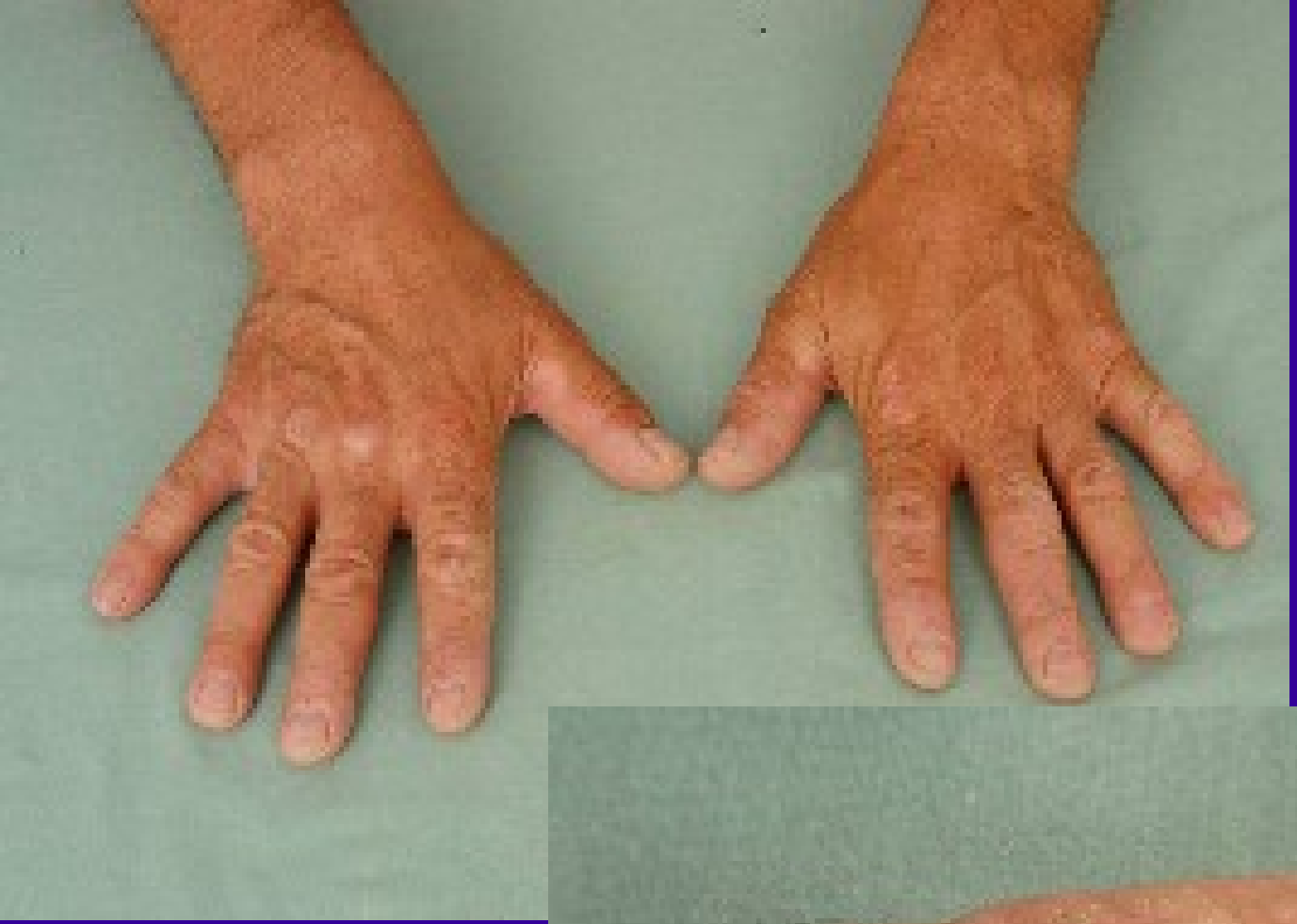


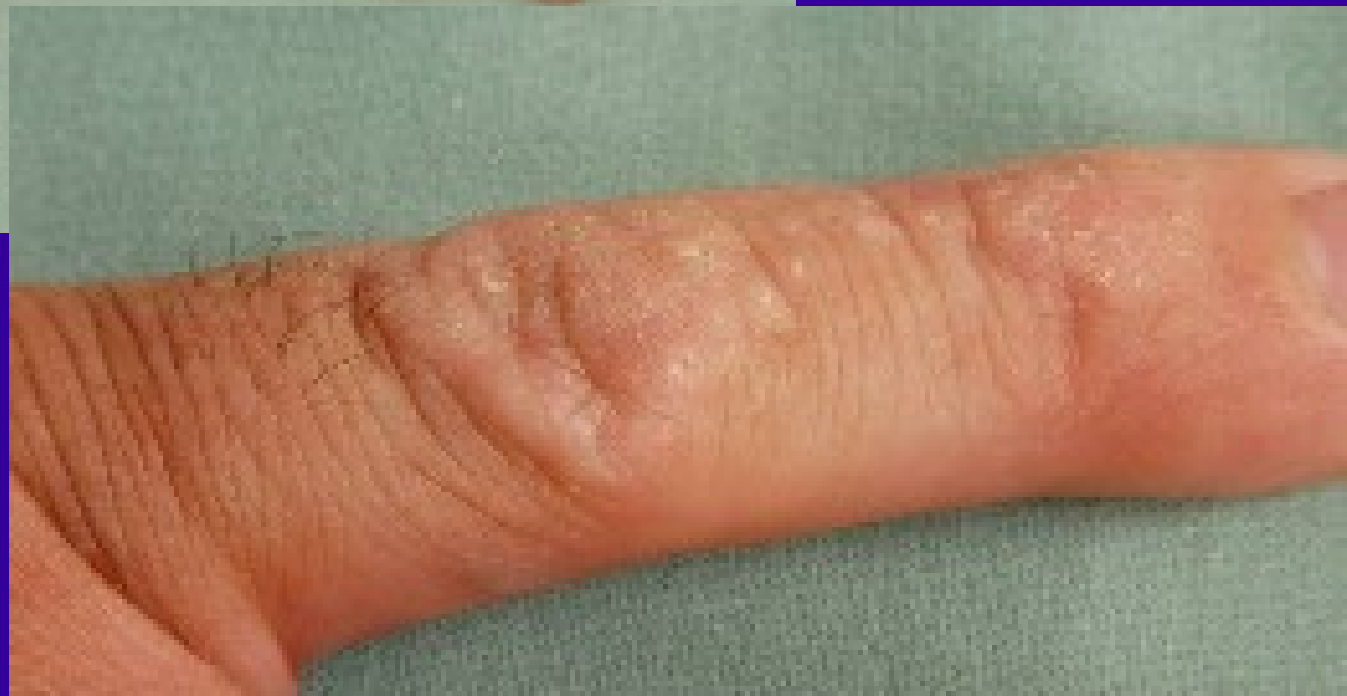


Eczema atopicum impetiginisatum

Eczema atopicum herpeticatum





Eczema atopicum – verrucae vulgares – warts

Treatment of AD

mild form of AD (30-40% of patients):

education of pacient (or parents)

identification of triggering factor
and their elimination

emmolients and baths

topical corticosteroids

pimecrolimus

antihistamines during flares

Treatment of AD

- mid-severe form of AD (40-50% of patients):

  treatment similar as in mild form

  \+ tacrolimus

  or

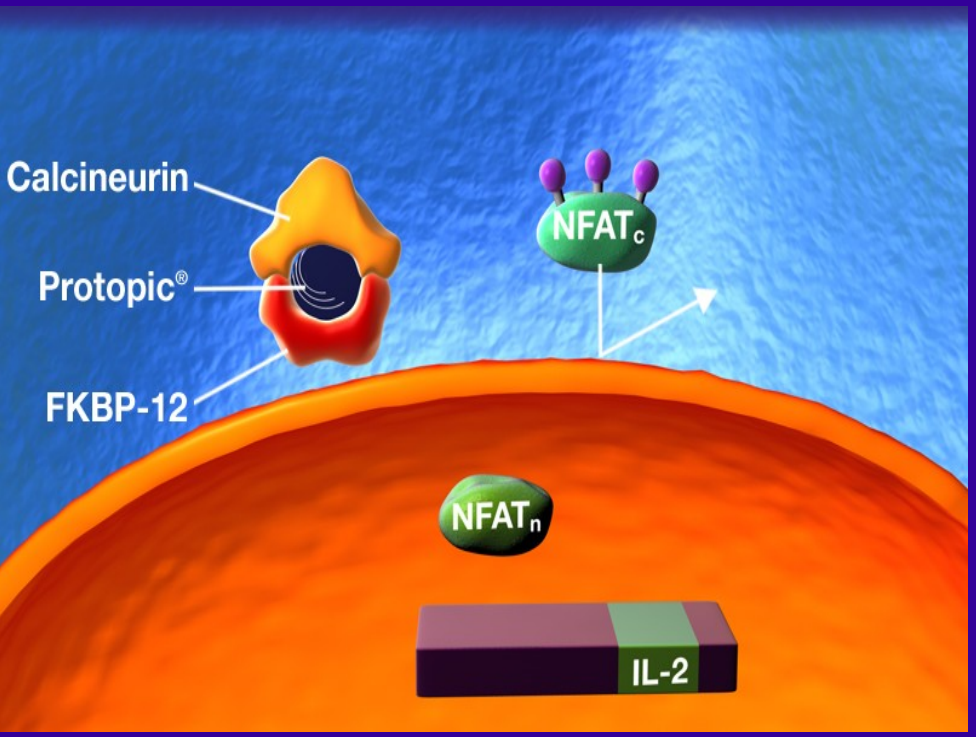
  hospitalization – lab. and clinical tests (triggers)

  traditional topical treatment /tar/

  or

  phototherapy (UVB 311nm, UVA-1)

Tacrolimus (PROTOPIC oinment)



- Topical Immunomodulator
- Blocks calcineurin
- antiinflammatory
- antipruritic
- Long - term treatment
- No skin atrophy

Treatment of AD

- severe form of AD (5-10% patients)

  phototherapy (PUVA, UVA-1)

  systemic corticosteroids (short courses)

  imunosupressives: cyclosporine A, MMF, AZT,MTX

  new therapies: i.v. Ig

  JAK, PDE ihibitors

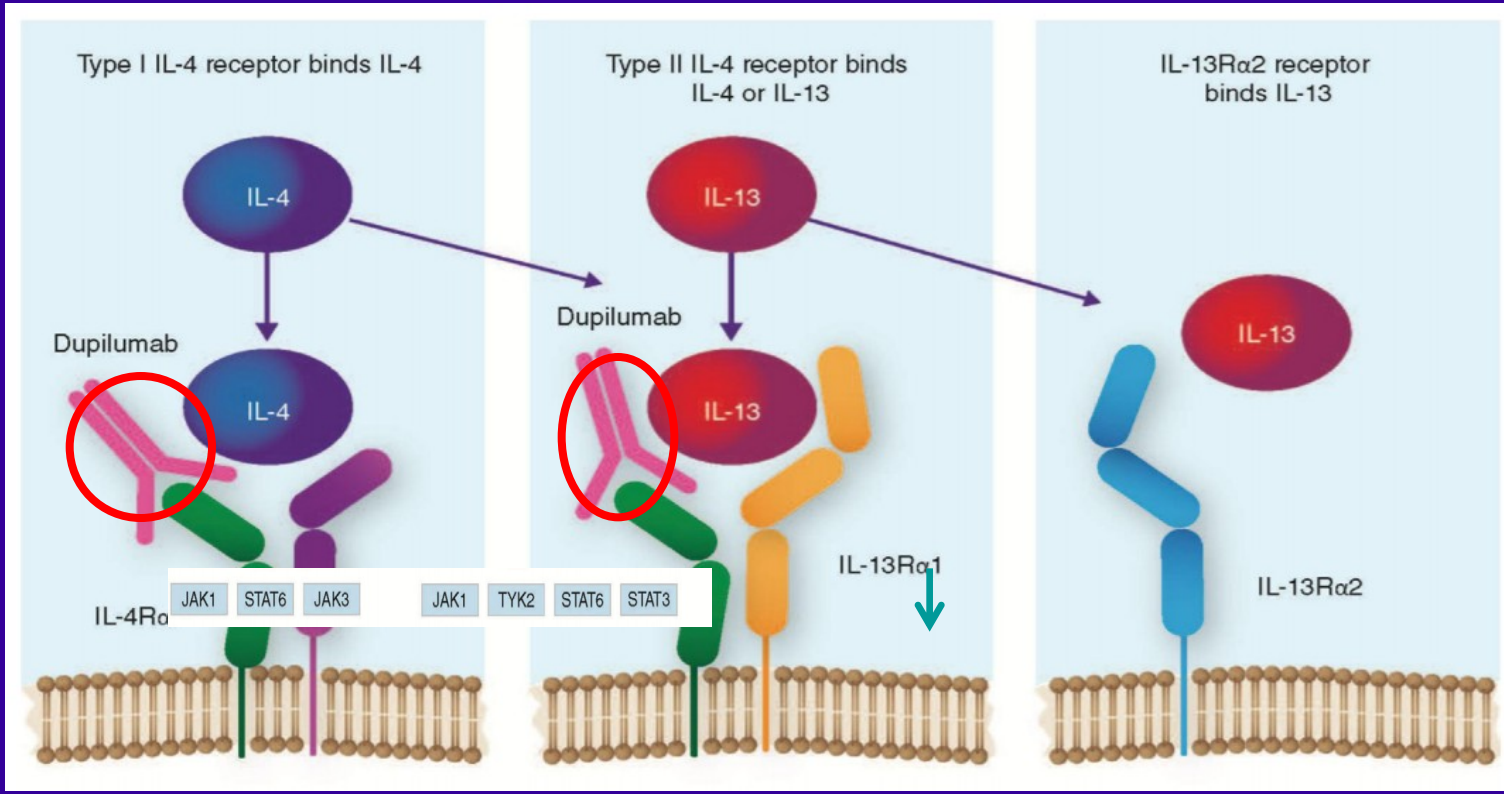
  biologicals (dupilumab....)

New treatments of AD

	PHASE 1	PHASE 2			PHASE 3	Approved
Interleukin Inhibitors	**ARGX-112**1-3 IL-22R1	**Bermekimab**6,7 IL-1α	**Secukinumab**8 IL-17A	**Risankizumab**9,10 IL-23	**Tralokinumab**11 IL-13	**Dupilumab**12 IL-4Rα
	PF-068170244,5 IL-33-related	**Benralizumab**13,1 IL-5Rα	**MOR10615** IL-17C	**REGN350016**,17 IL-33	**Nemolizumab**18 IL-31RA	Dupilumab 300 mg q2v is licensed for treating moderate-to severe AD in adult patients12
		Lebrikizumab19 IL-13	**Fezakinumab**20 IL-22	**Etokimab**21,22 IL-33		
			Spesolimab23,24 IL-36	**LY337588**25,26 IL-33		
JAK/SYK Inhibitors					**Upadacitinib**28 JAK1	
			ASN00227 SYK/JAK		**Abrocitinib**29 JAK1	
					Baricitinib30 JAK1/JAK2	
Other Inhibitors	**EDP106631** Undisclosed					
	EDP181531 Undisclosed	**DS10732**,33 CD40	**Tezepelumab**34,35 TSLP	**KY 100536** OX40L	**Serlopitant**37,38 NK-1R	
	LOU 06439-41 BTK	**Adriforant**41 H4R	**GBR 83042** OX40	**KHK408343**,44 OX40	**Tradipitant45** NK-1R	

Dupilumab - mechanism of action

human IgG4 class monoclonal antibody that specifically binds to the α subunit of the IL-4 and 13 receptors, thereby blocking the activation of protein kinases JAK 1 or 3 or TYK2



Effect of dupilumab treatment