Psoriasis

PHYSICALLY DISABLING AND
EMOTIONALLY DEVASTATING

Mircea Betiu

Background

- Psoriasis is an inflammatory, noncontagious, genetically determined skin disorder that most commonly appears as inflamed, edematous – erythematic-papular-plaque skin lesions covered with a silvery white scale.
- Up to 2% of the population develop Ps during their lifetime; Ps can be present at any time from the first few weeks of life until 80 or more years of age; most patients experience onset in the third decade of life.
- Stress, trauma and infections may induce Ps in susceptible individuals.

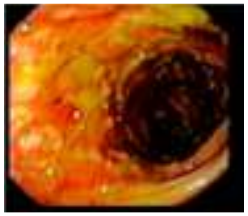
Psoriasis, an inherited disease

If you have psoriasis, what is the risk to:

- Your unrelated neighbor? About 2%
- Your sibling? 15-20%
- Your identical twin? 65-70%
- Your child? 25%

Psoriazis "Dincolo de piele" – comorbiditati multiple

Inflamaţie oculară
Uveită / episclerită



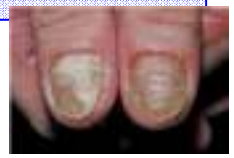
Boala Crohn 9.6–11%
Colita ulcerativă 5.7%

Efect psihologic:
- Depresie reactivă
- Ideaţie suicidală
- Alcoolism
- Stigmatizare

Sindrom metabolic:
- Hipertonie
- Dislipidemie
- Diabet insulino-rezistent 11,7%
- Adipozitate

⇒ **Mortalitate cardio vasculară crescută 21,9%**

Psoriazis artropatic
7–30%
- Artrite periferice
- Spondilită / sacroileită
- Dactilită / tenosinovită
- Entezită
- Osteită / periostită



Afectare unghială
50-78%

Dezechilibru lipometabolic 5,2 %
- Colesterol
- Trigliceride
- Apolipoproteine

Psoriasis: Associated Factors

- Genetic Factors:

  - 30% of people with psoriasis have had psoriasis in family

  - Autosomal dominant inheritance: definite genetic linkage between Ps and the **HLA-Cw6 phenotype**

- Nongenetic Factors:

  - Mechanical, ultraviolet, chemical injury

  - Infections: Strep, viral, HIV

  - Prescription Drugs, stress, endocrine, hormonal, obesity, alcohol, smoking

Genetics

PSORS			
Locusul genic PSORS (psoriasis susceptibility genes)	**Poziţie cromozomială**	**Locusul genic**	**Poziție cromozomială**
PSORS1(50%)	**6p21.3** (zona critică este de un interval de 300kb lângă zona caudală a centromerului din classa I MHC)	***PSORS6***	**19p13–q13**
PSORS2	**17q25**	***PSORS7***	**1p35–34**
PSORS3	**4q32–35**	***PSORS8***	**16q12–13**
PSORS4	**1cen–q21**	***PSORS9***	**4q31–34**
PSORS5	**3q21**	***PSORASI0***	**16q12**

Genetics and Pathogenesis

- Psoriasis and the Immune System
  - The major histocompatibility complex (MHC)
    - Short arm of chromosome 6
  - Histocompatibility Antigens (HLA)
    - HLA-Cw6
    - HLA-B13, -B17, -B37, -Bw16, - B27 (for arthritis)
  - T-lymphocyte-mediated mechanism

Physiolopatology

- The pathological process is a combination of epidermal hyperproliferation and activation of inflammatory pathways with accumulation of inflammatory cells.

- The hyperplasia of the epidermis results from both a shortened epidermal cell cycle (from an average normal turnover of 28 days to 3-5 days) and an increase in the proliferative cell population

Psoriasis physiopatology

- T-cell mediated inflammatory dz
  - Epidermal hyperproliferation secondary to activation of immune system
  - Altered maturation of skin
  - Inflammation
  - Vascular changes

Physiopathology

- Autoimmune function
  - Significant evidence is accumulating that psoriasis is an autoimmune disease.
  - Lesions of psoriasis are associated with increased activity of T cells in underlying skin.
  - Guttate psoriasis has been recognized to appear following certain immunologically active events, such as streptococcal pharyngitis, cessation of steroid therapy, and use of antimalaria drugs.
- Superantigens and T cells
  - Psoriasis is related to excess T-cell activity. Experimental models can be induced by stimulation with streptococcal superantigen, which cross-reacts with dermal collagen.
- Also of significance is that 2,5-6% of those with HIV develop psoriasis during the course of the disease

STAT-3 and psoriasis

- The exact pathogenesis of psoriasis remains unclear. Signal transducer and activator of transcription-3 (STAT3) is a possible important link between keratinocytes and immunocytes during psoriasis evolution

- Signal transducer and activator of transcription 3 (STAT3), a protein involved in transmitting extracellular signals to the nucleus, is crucial to the development of the skin disease psoriasis

STAT activation

Cytokines and growth factors that activate STAT proteins

Cytokines and growth factors	Activated STAT proteins
IFNα, IFNβ, IFNγ, IL-10, EGF, NGF, PDGF	STAT1
IFNα, IFNβ	STAT2
IL-2, IL-6, IL-7, IL-9, IL-15, oncostatin M GH, EGF, NGF, insulin	STAT3
IL-12	STAT4
IL-2, IL-3, IL-5, IL-7, IL-9, IL-15, GM-CSF, GH, prolactin, erythropoietin, thrombopoietin,	STAT5a, STAT5b
IL-4	STAT6

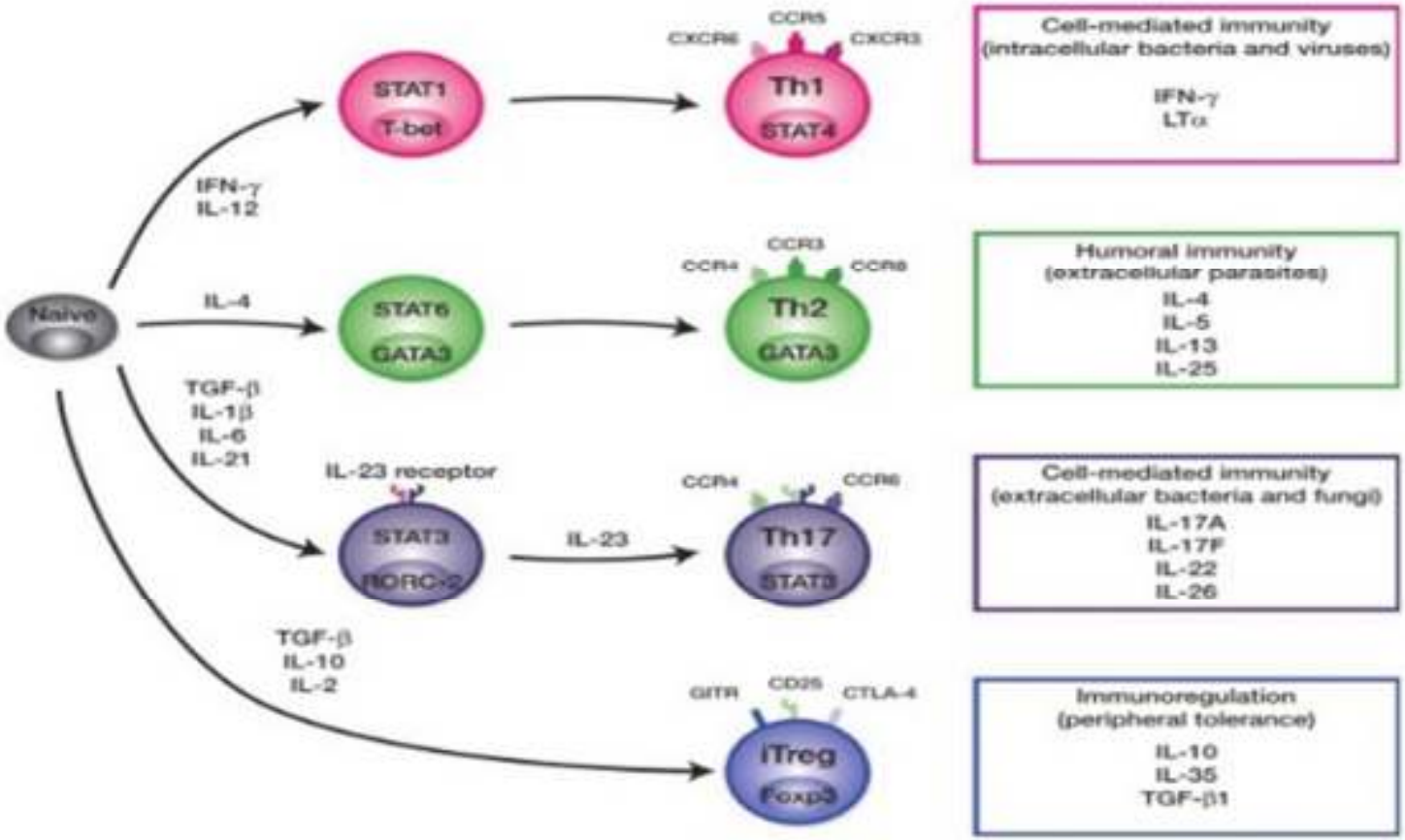
Note: EGF—epidermal growth factor; NGF—nerve growth factor; PDGF—platelet-derived growth factor; GM-CSF—colony-stimulating factor of granulocytes and macrophages; GH—growth hormone; IGF-I—insulin-like growth factor I.

Message Home

- STAT3 protein has emerged as an important determinant of whether the naïve T cell differentiates into regulatory (Treg) or an inflammatory (Th17) T cell lineage.
- STAT3 also has potent anti-inflammatory effects and regulates critical cellular processes such as, cell growth, apoptosis and transcription of inflammatory genes.
- Dysregulation of STAT3 pathway has therefore been implicated in the development of chronic inflammatory diseases, as well as, a number of malignant and neurodegenerative diseases.
- New insights from animal models of psoriasis as an exemplar of critical roles that STAT3 pathways play in inflammatory diseases including psoriasis and on how inhibiting STAT3 can be exploited to mitigate pathogenic autoimmunity(Egwuagu Cytokine 47 (2009) 149–156)

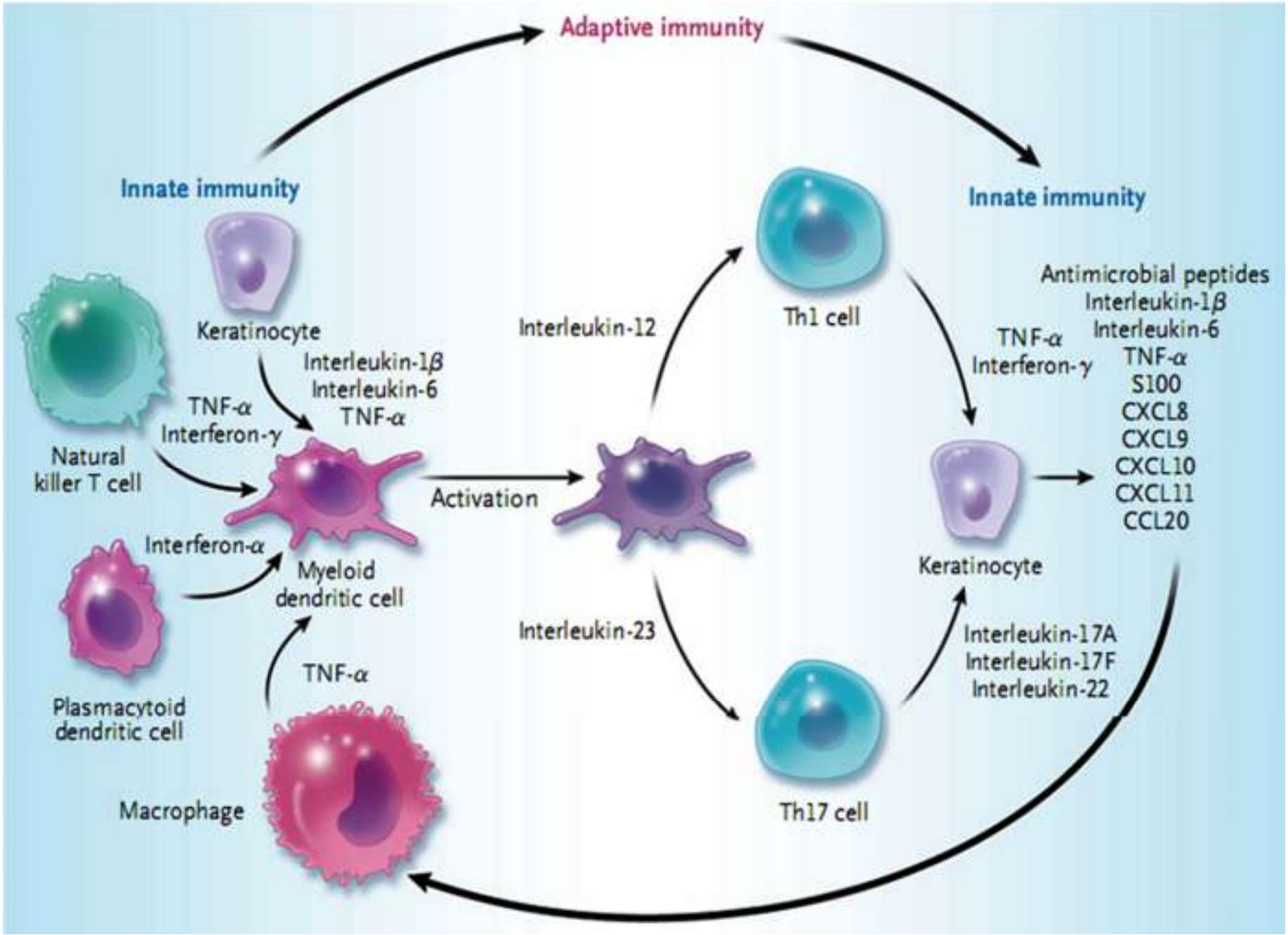
Message Home

- Stat3 is Key intracellular signaling molecule important in Th17 development and mediates IL-22–induced keratinocyte hyperproliferation.
- Blocking of stat3 pathway is good-to-excellent (similar to TNF-a inhibitors): major signaling pathway inhibition may have expected good clinical results in psoriasis .

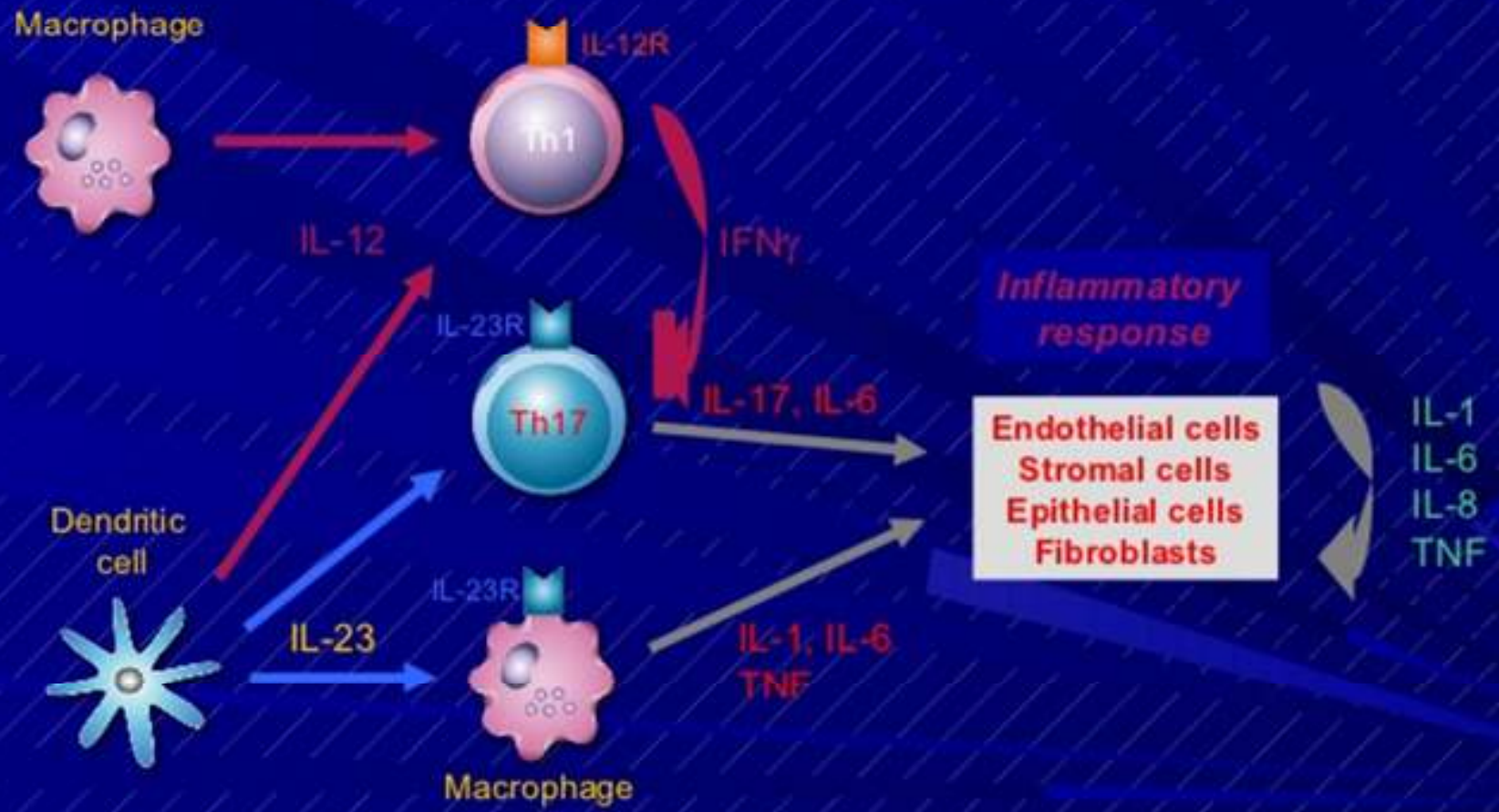


- Interleukin-23 (IL-23) helps to maintain the lesion by leading to the development of Th17 cells.
- These in turn produce necrosis factor-alpha (TNF-a), IL-17 and IL-22.
- IL-22 is believed to drive many of the epidermal changes in psoriasis.
- Many autoimmune diseases, including psoriasis, are characterized by high levels of Th17.

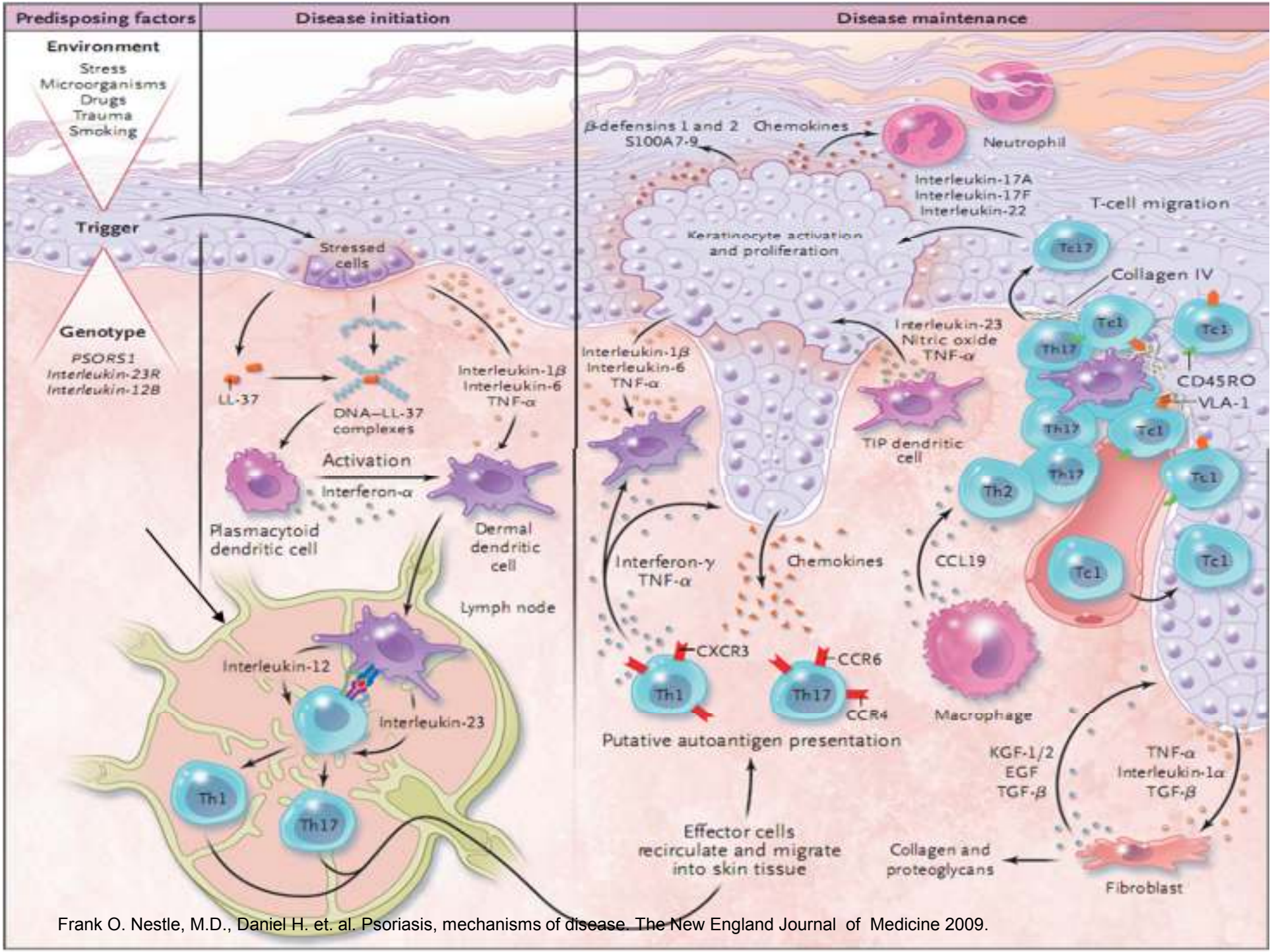
Journal of Investigative Dermatology 2009;129:1339–1350.


Adaptive immunity
Innate immunity
Innate immunity
Keratinocyte
Interleukin-1β
Interleukin-6
TNF-α
TNF-α
Interferon-γ
Natural killer T cell
Interleukin-12
Th1 cell
Antimicrobial peptides
Interleukin-1β
Interleukin-6
TNF-α
S100
CXCL8
CXCL9
CXCL10
CXCL11
CCL20
TNF-α
Interferon-γ
Activation
Keratinocyte
Interferon-α
Myeloid dendritic cell
Interleukin-23
Interleukin-17A
Interleukin-17F
Interleukin-22
TNF-α
Plasmacytoid dendritic cell
Macrophage
Th17 cell

Roles of IL-23 on T Helper 17 cells in Chronic Inflammation in Psoriasis



Adapted from Iwakura & Ishigame, J Clin Invest 116:1218-1222 (2006)

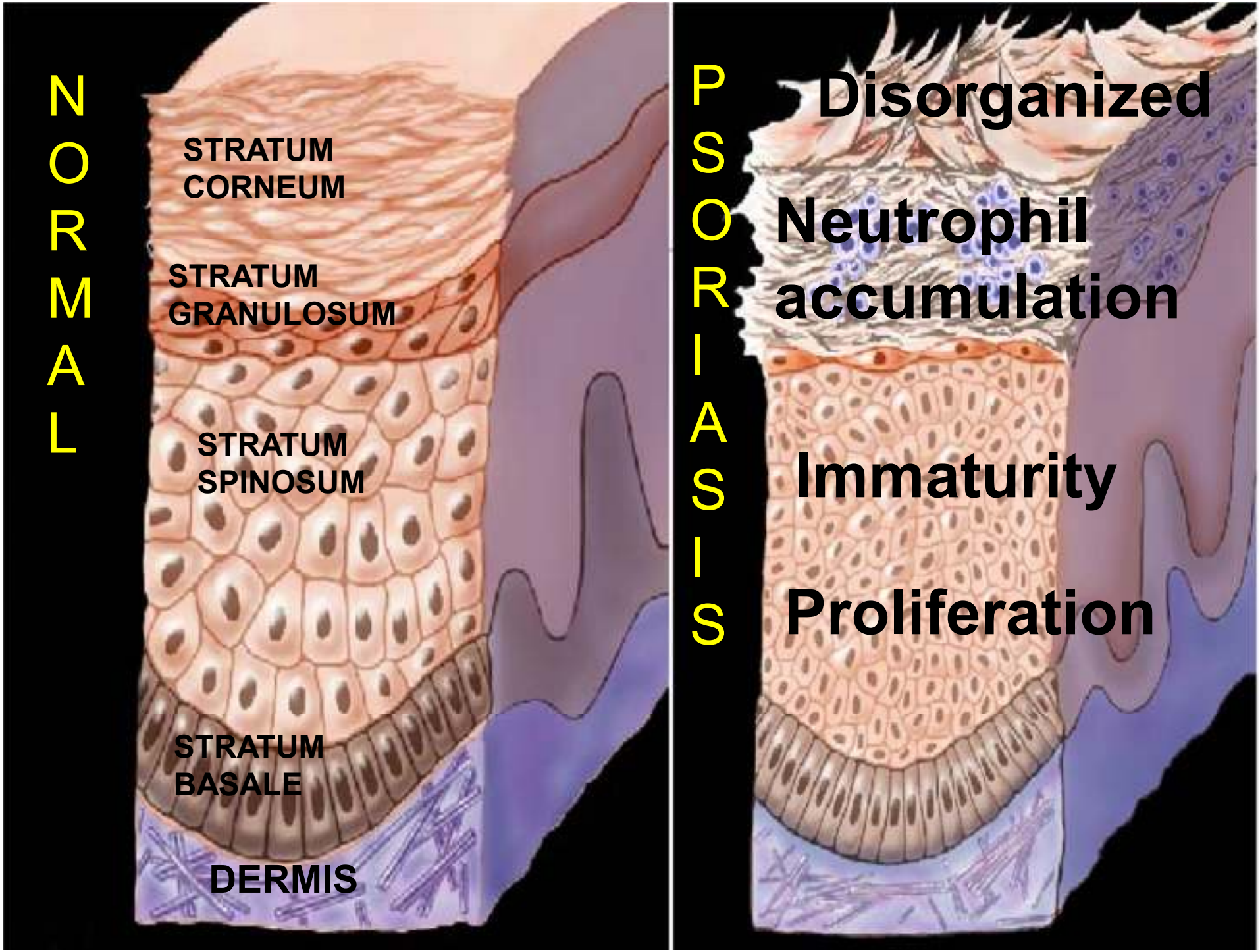


Frank O. Nestle, M.D., Daniel H. et. al. Psoriasis, mechanisms of disease. The New England Journal of Medicine 2009.

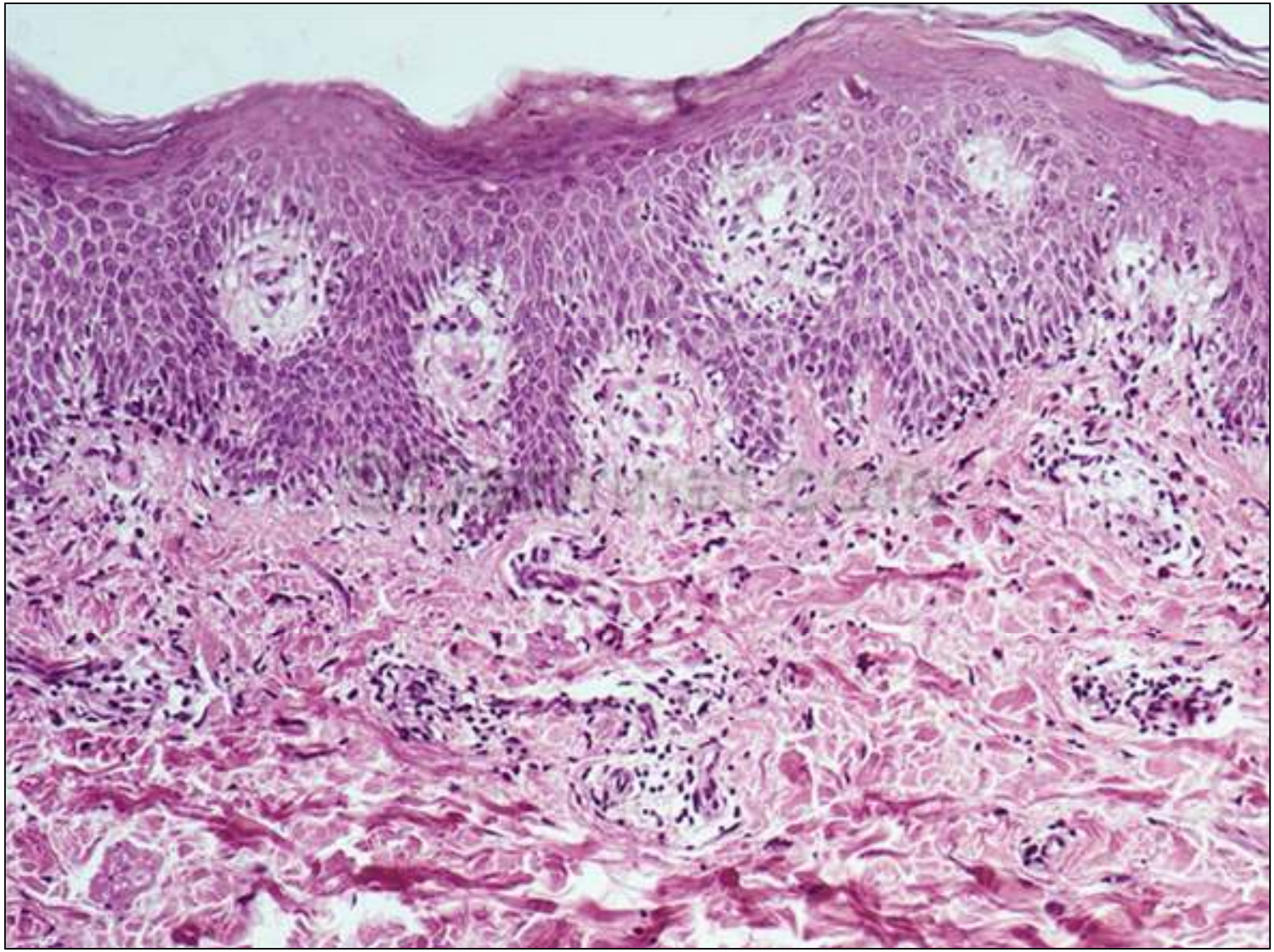
Histopathology – Cardinal Features

- Marked thickening of the epidermis (acanthosis)
- Absence of the granular layer
- Retention of the nuclei in the horny layer (parakeratosis)
- Accumulations of polymorphs in the horny layer (Munro's microabscesses)
- Dilated capillary loops in the upper dermis.

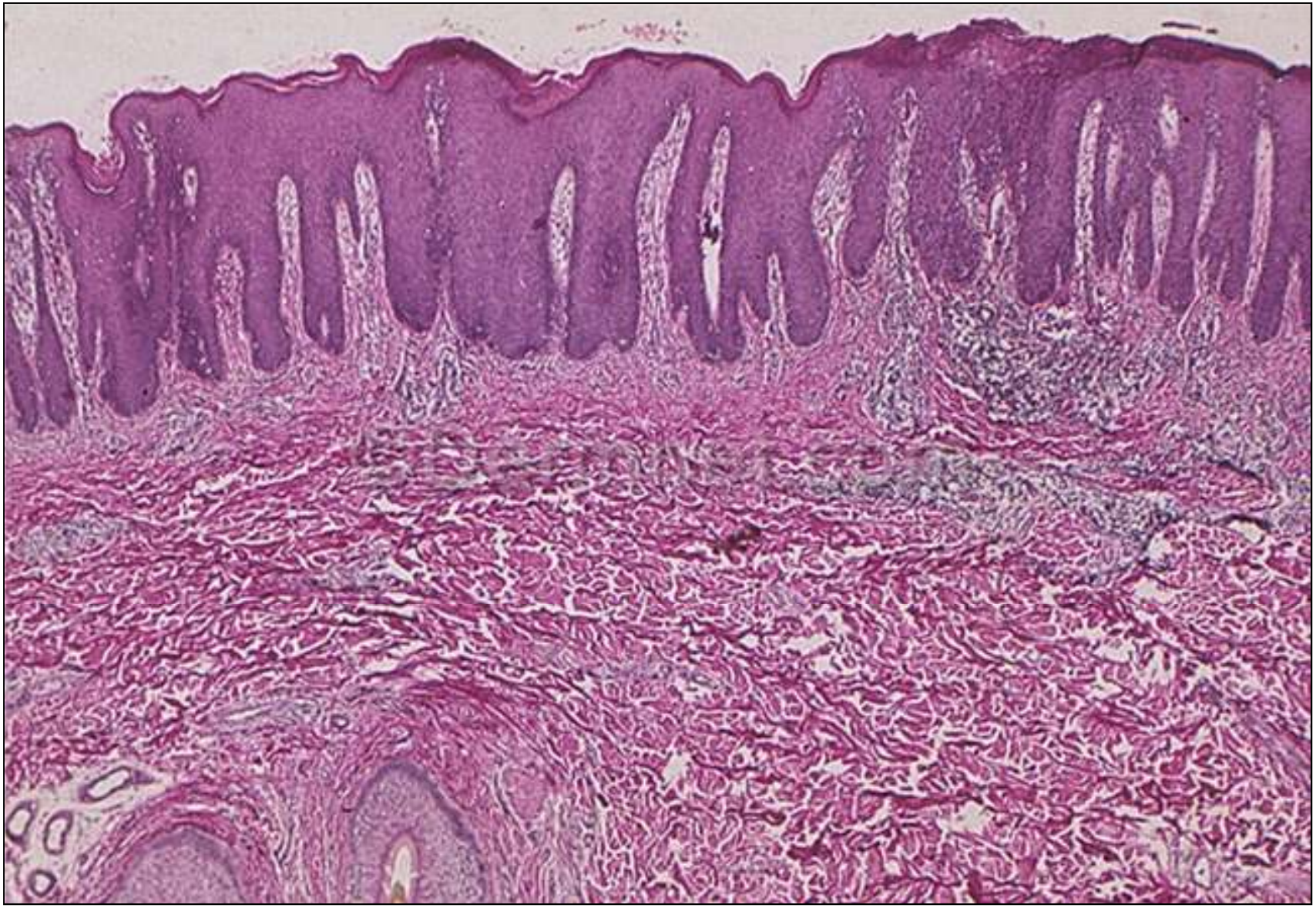
PS vs N histopathology


NORMAL
STRATUM CORNEUM
STRATUM GRANULOSUM
STRATUM SPINOSUM
STRATUM BASALE
DERMIS
PSORIASIS
Disorganized
Neutrophil accumulation
Immaturity
Proliferation

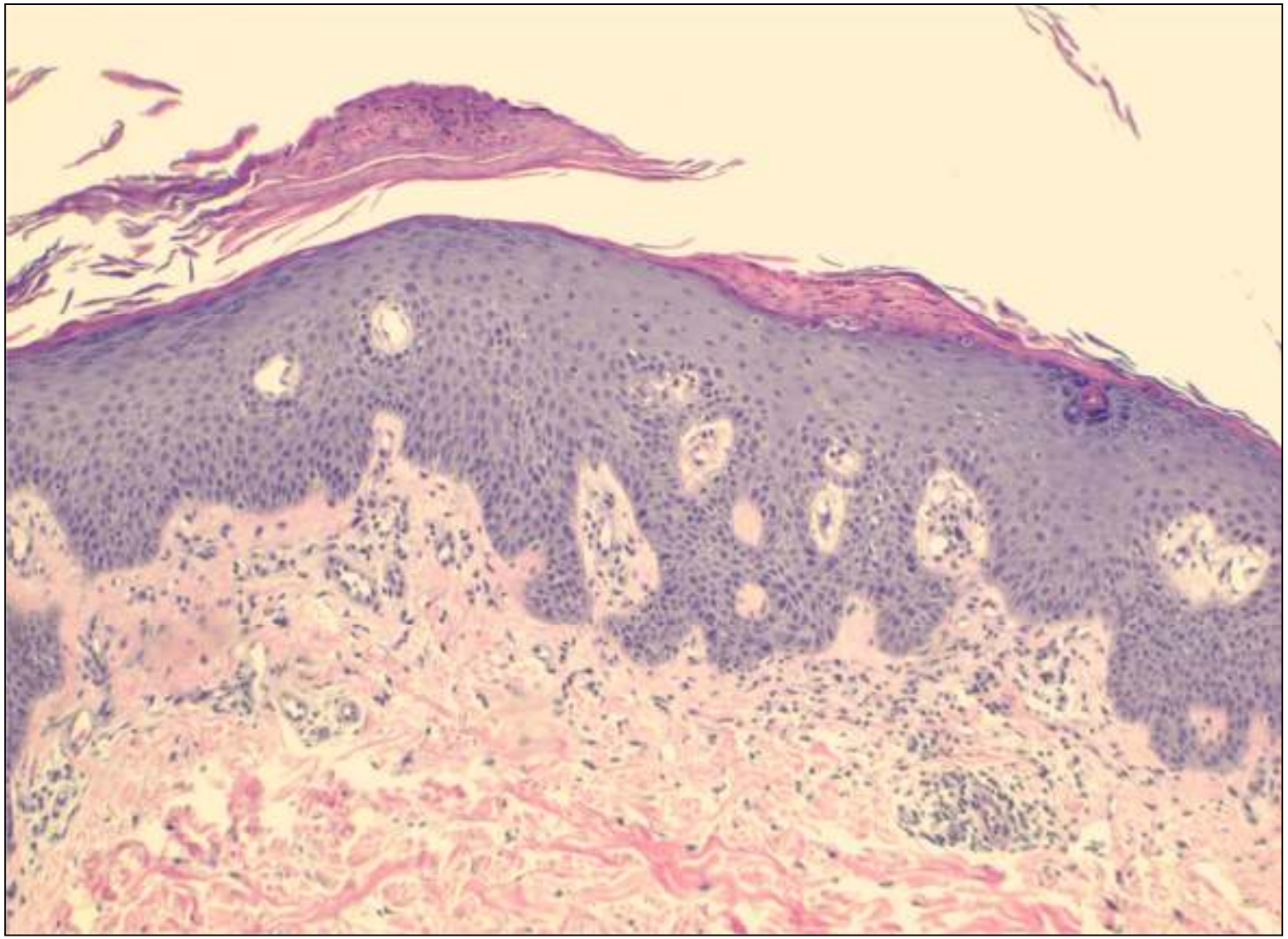
Ps histopathology



PS histopathology



Ps histopathology

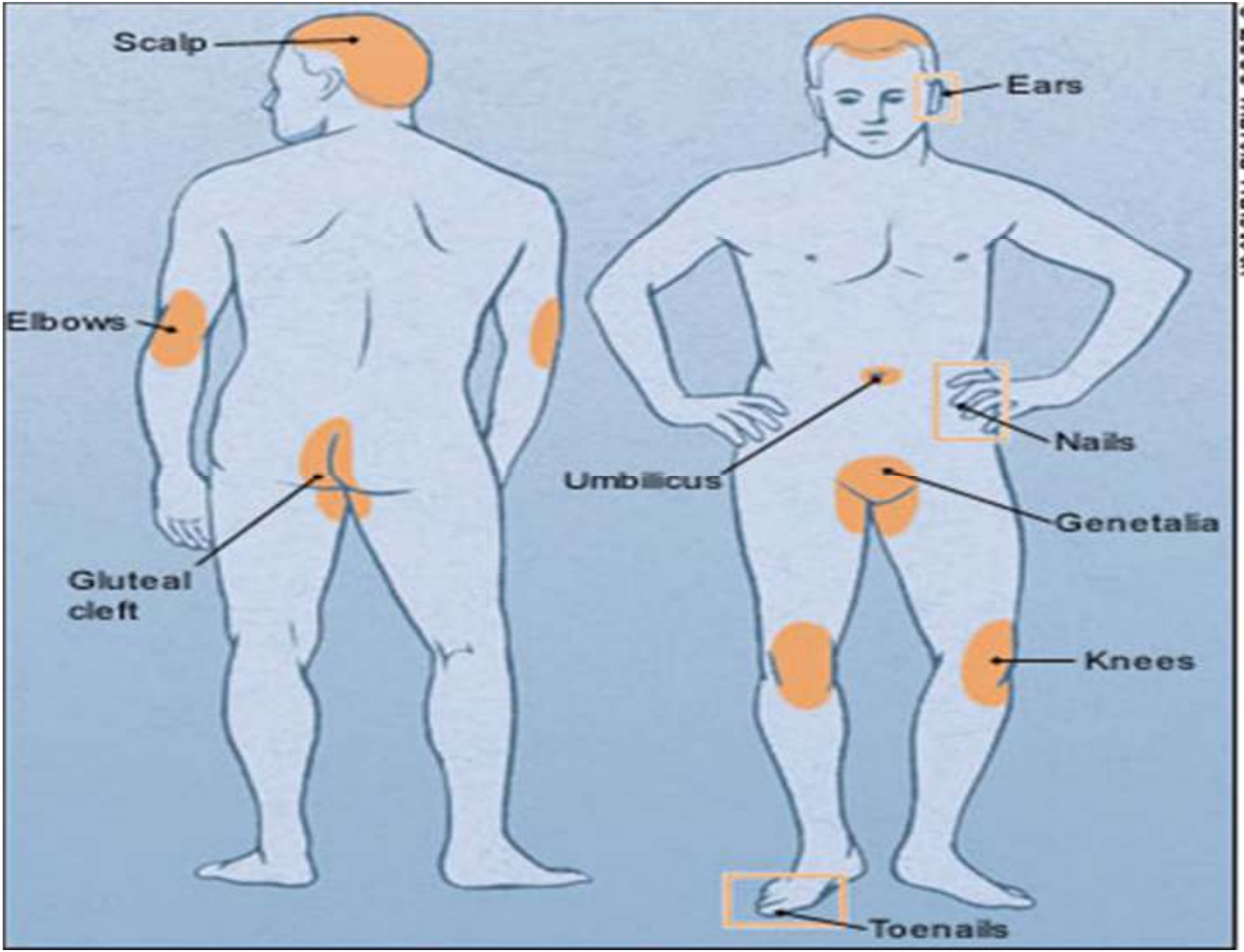


Clinical Patterns of Psoriasis

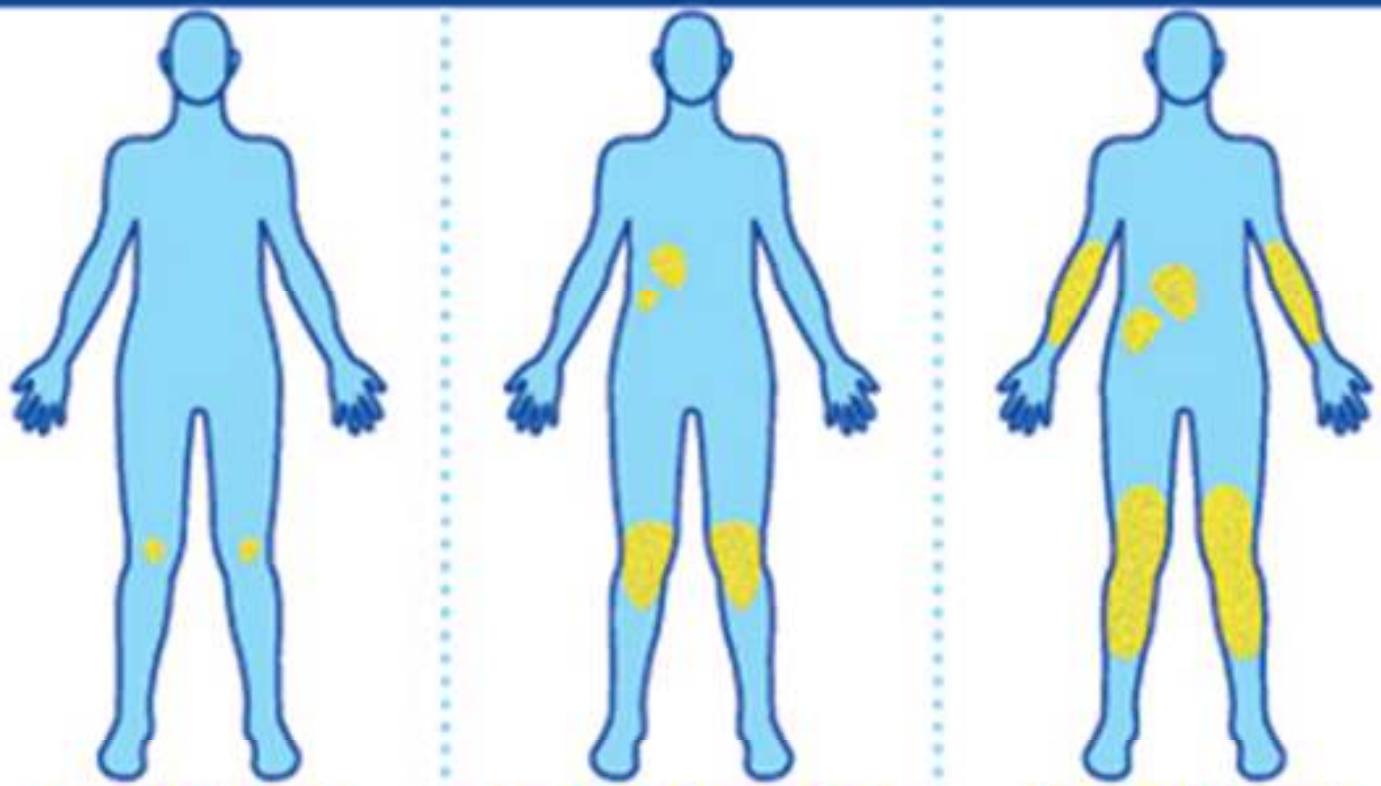
- Classical plaque (psoriasis vulgaris)
- Scalp Ps
- Nail Ps
- Guttate
- Flexural
- “Brittle”
- Erythrodermic
- Acute pustular (of von Zumbusch)
- Chronic palmoplantar pustular (of Barber)
- Arthropathic Ps

Psoriasis: Clinical Presentation

Type	Characteristics
Plaque psoriasis	Dry scaling patches (AKA common psoriasis) 75%
Guttate psoriasis	Drop-like dots, occurs after strep or viral infection 12%
Erythrodermic psoriasis	Exfoliation of fine scales (total body “dandruff”), widespread, often accompanied by severe itching and pain 7%
Pustular psoriasis	Pus-like blisters, noninfectious, fluid contains white blood cells 2%
Nail psoriasis	Seen on toenails and fingernails, starts as numerous pits, at times progresses to yellowing, crumbly, and thickened nail; nails may slough
Palmar/Plantar psoriasis	Erythema, thickening and peeling of the skin, blistering is often present. Can lead to disability.
Psoriatic arthritis	Inflammation, swelling, and joint destruction
Scalp psoriasis	Plaque-type lesion


Scalp
Ears
Elbows
Nails
Umbilicus
Genetalia
Gluteal cleft
Knees
Toenails
© 2000 Marcia Harstock

PSORIASIS COVERAGE & SEVERITY



MILD

Less than 3% of the body has psoriasis

MODERATE

3%-10% of the body has psoriasis

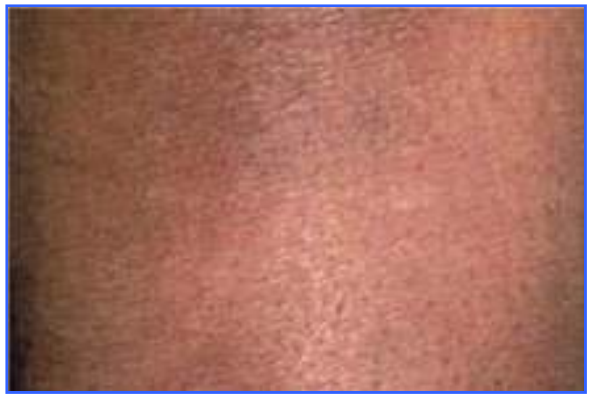
SEVERE

More than 10% of the body has psoriasis

1% = Surface area of the hand

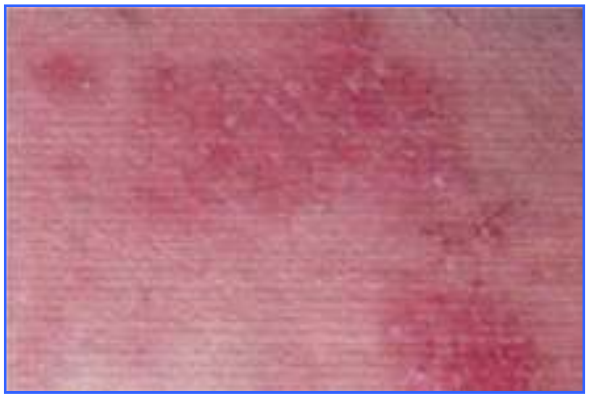
OLA Photonumeric Guidelines

(overall lesion assessment)

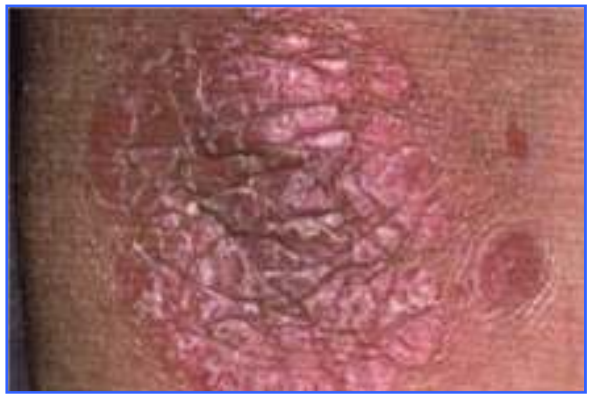


0 = none

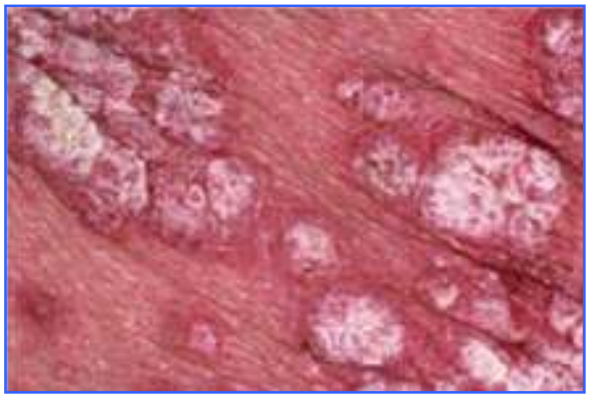
1 = minimal



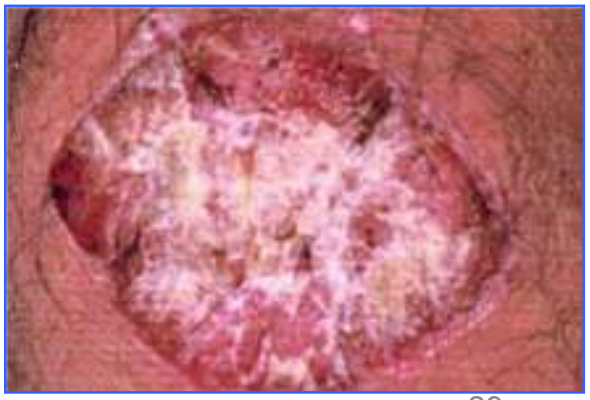
2 = mild



3 = moderate



4 = severe

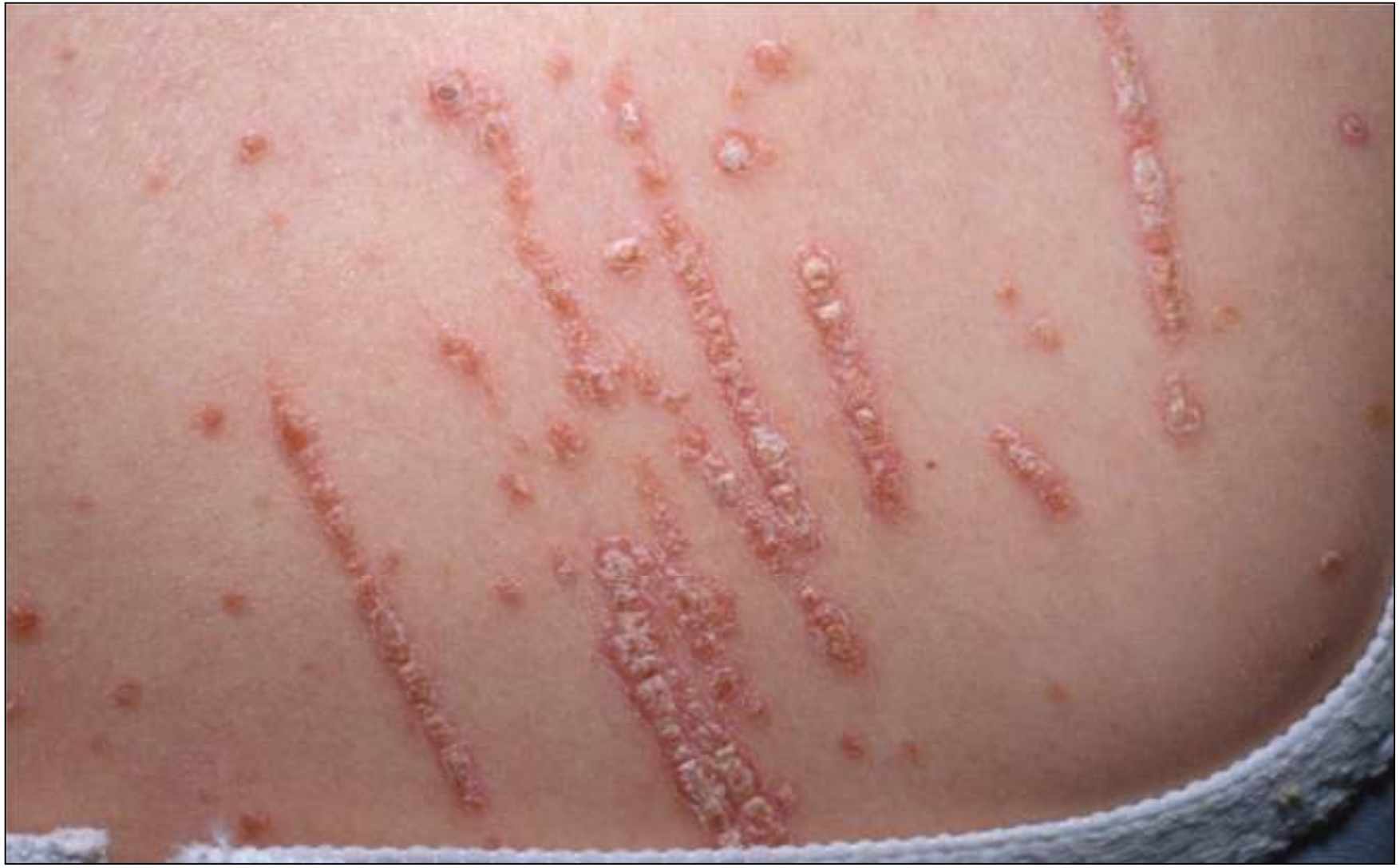


5 = very severe

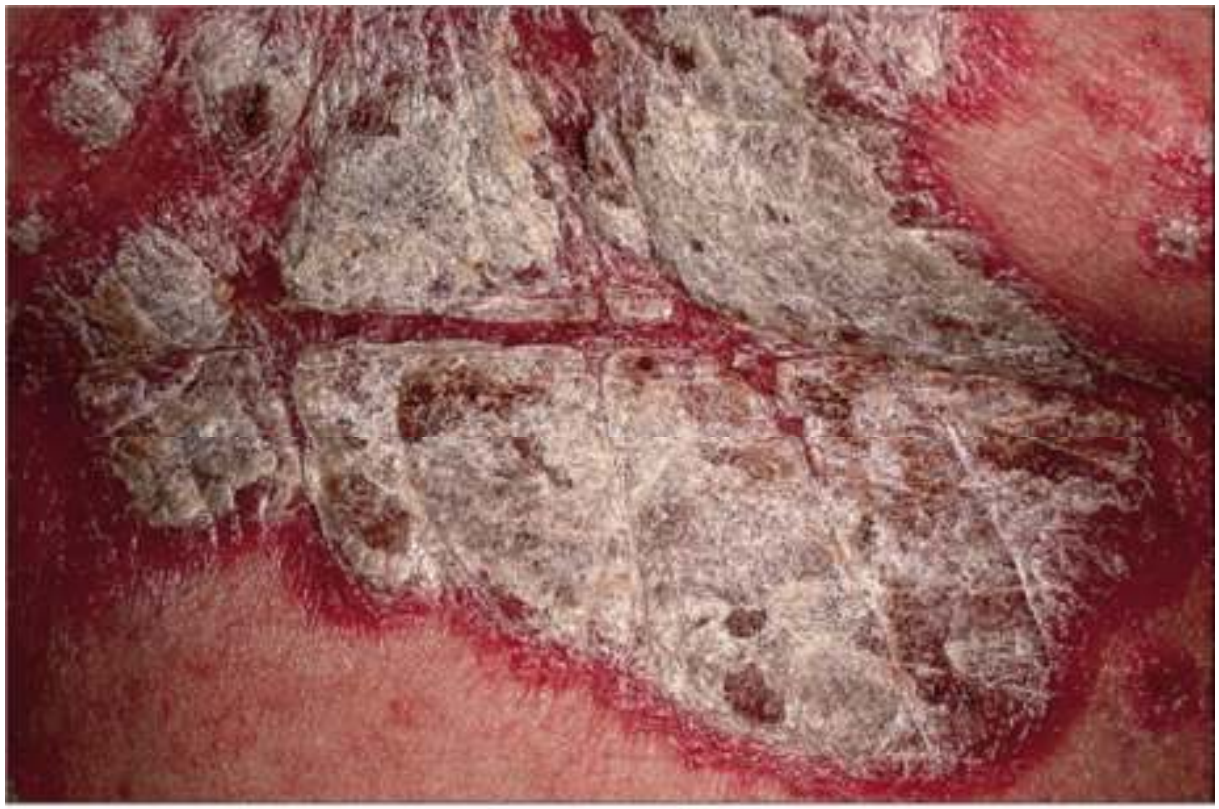
Chronic Plaque Psoriasis (psoriasis vulgaris)

- The commonest pattern
- Single or multiple red plaques (papules) varying from a few millimeters to several centimeters in diameter with a scaly surface
- Psoriatic step-by-step triad obtained by scraping:
- silvery (stearin) staining
- terminal (wet) plate
- cappilary-point haemorrhage (Auspitz sign)
- Predilection for extensor surfaces: the knees, the elbows and the base of the spine
- Lesions are often symmetrical
- The scalp and nails are often affected and the arthropathy may also occur
- Psoriatic plaques may appear at the site of trauma or scarring – Koebner or isomorphic phenomenon

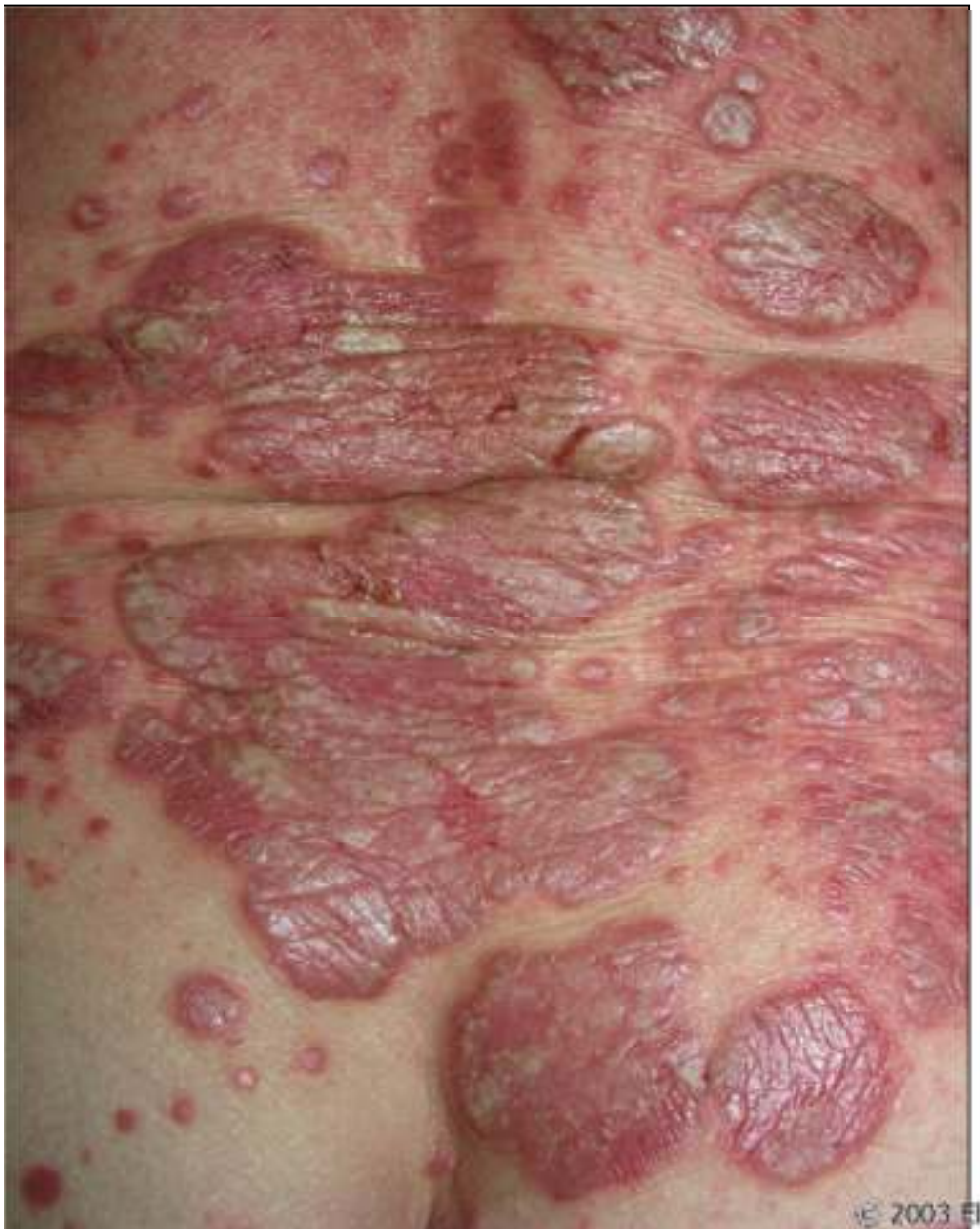
Köbner phenomenon

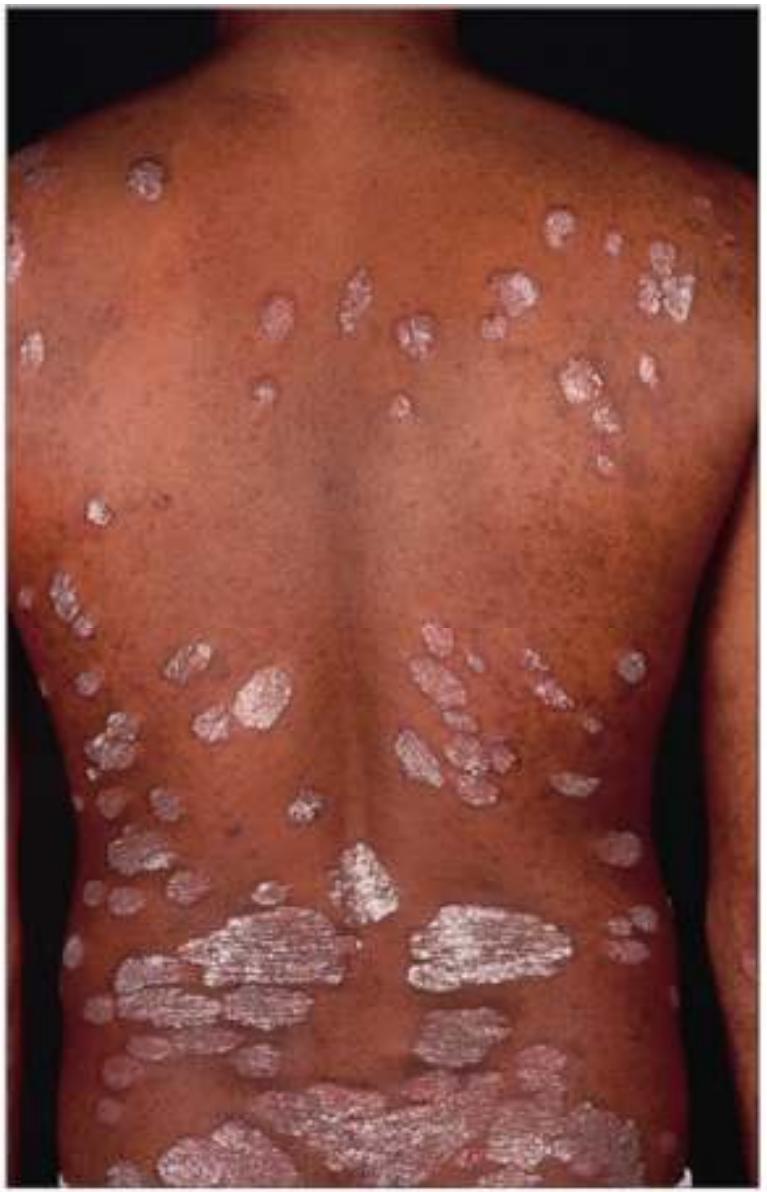


Psoriatic Plaque

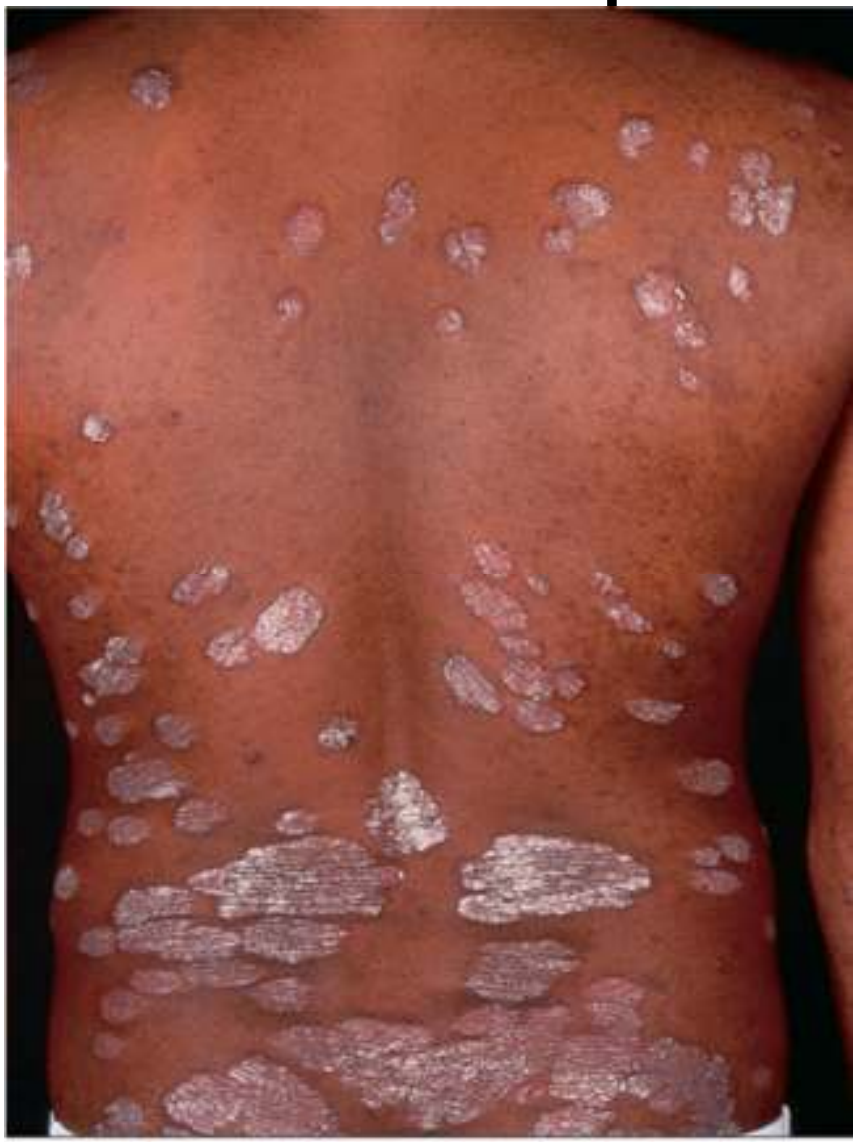


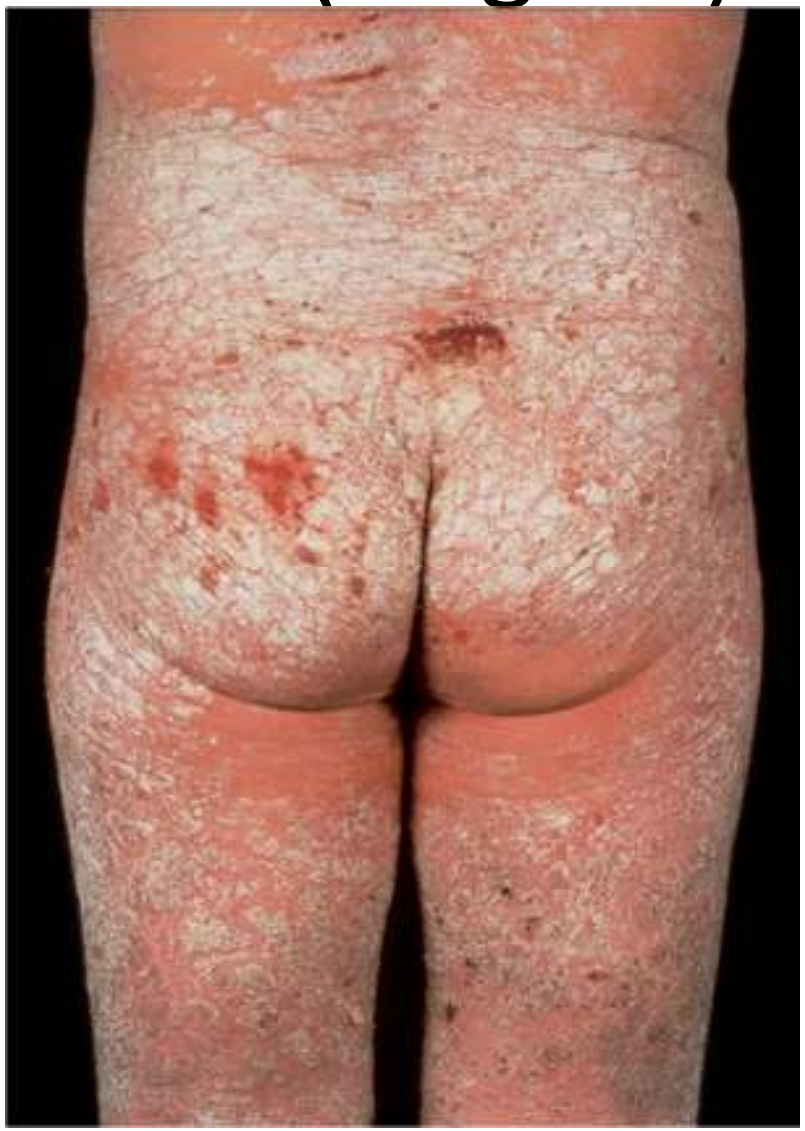
Chronic Plaque PS



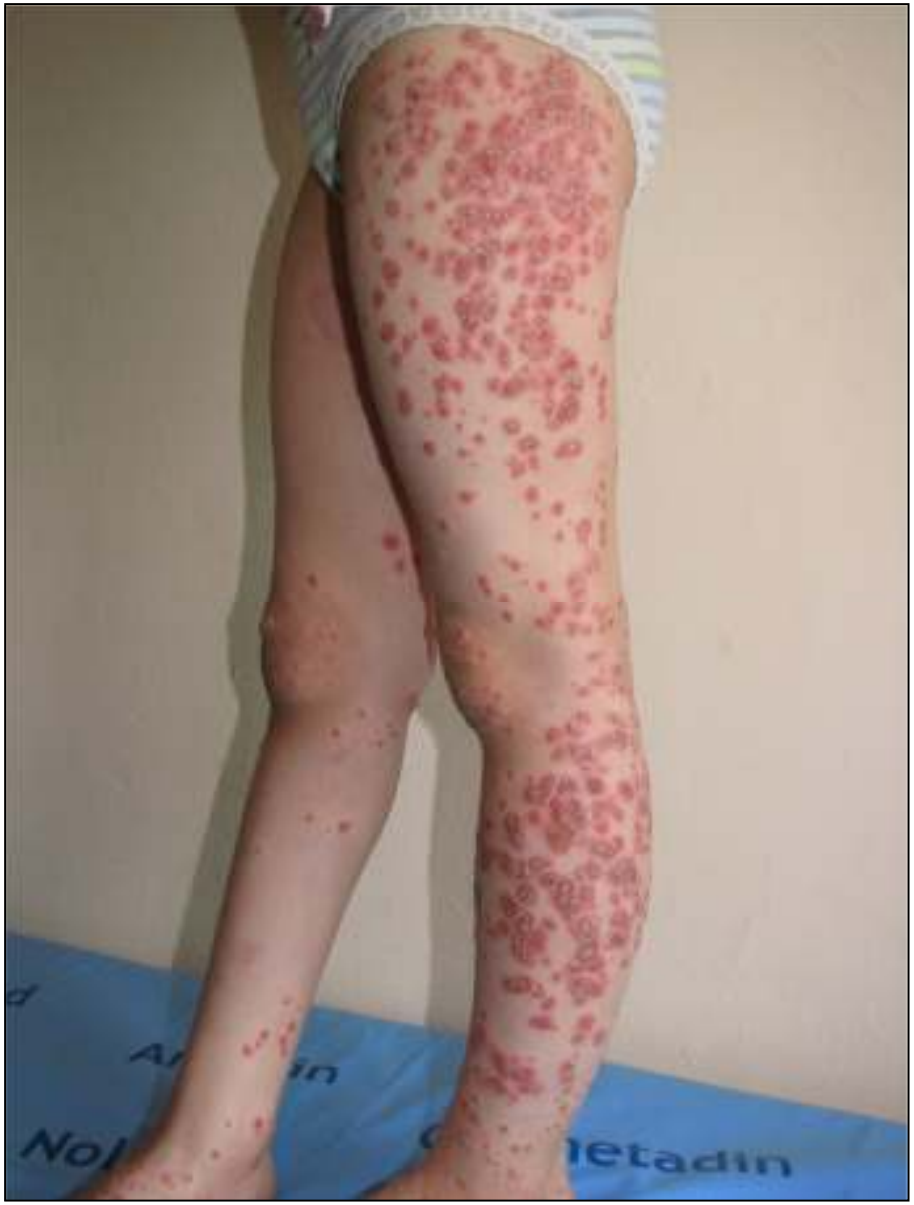


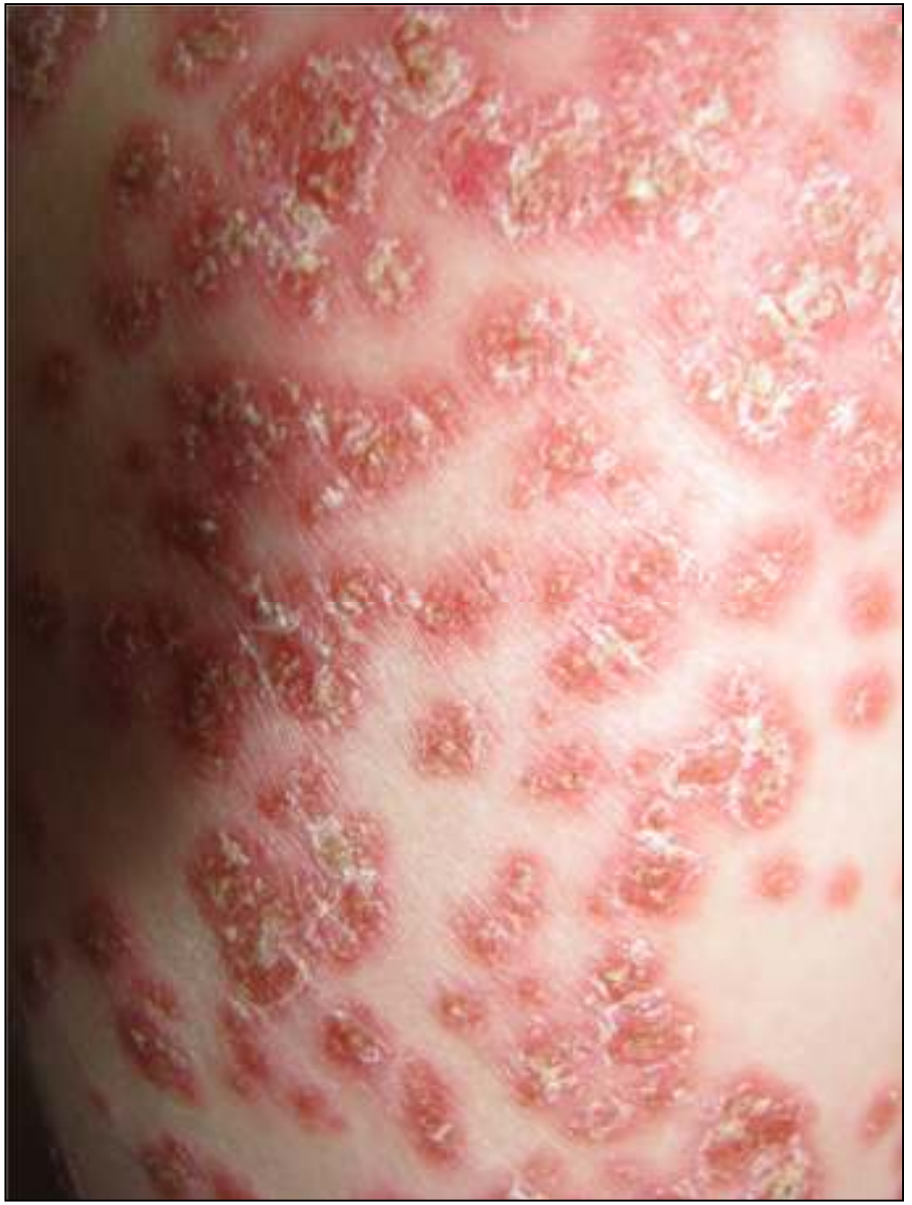
Chronic Plaque Psoriasis (vulgaris)



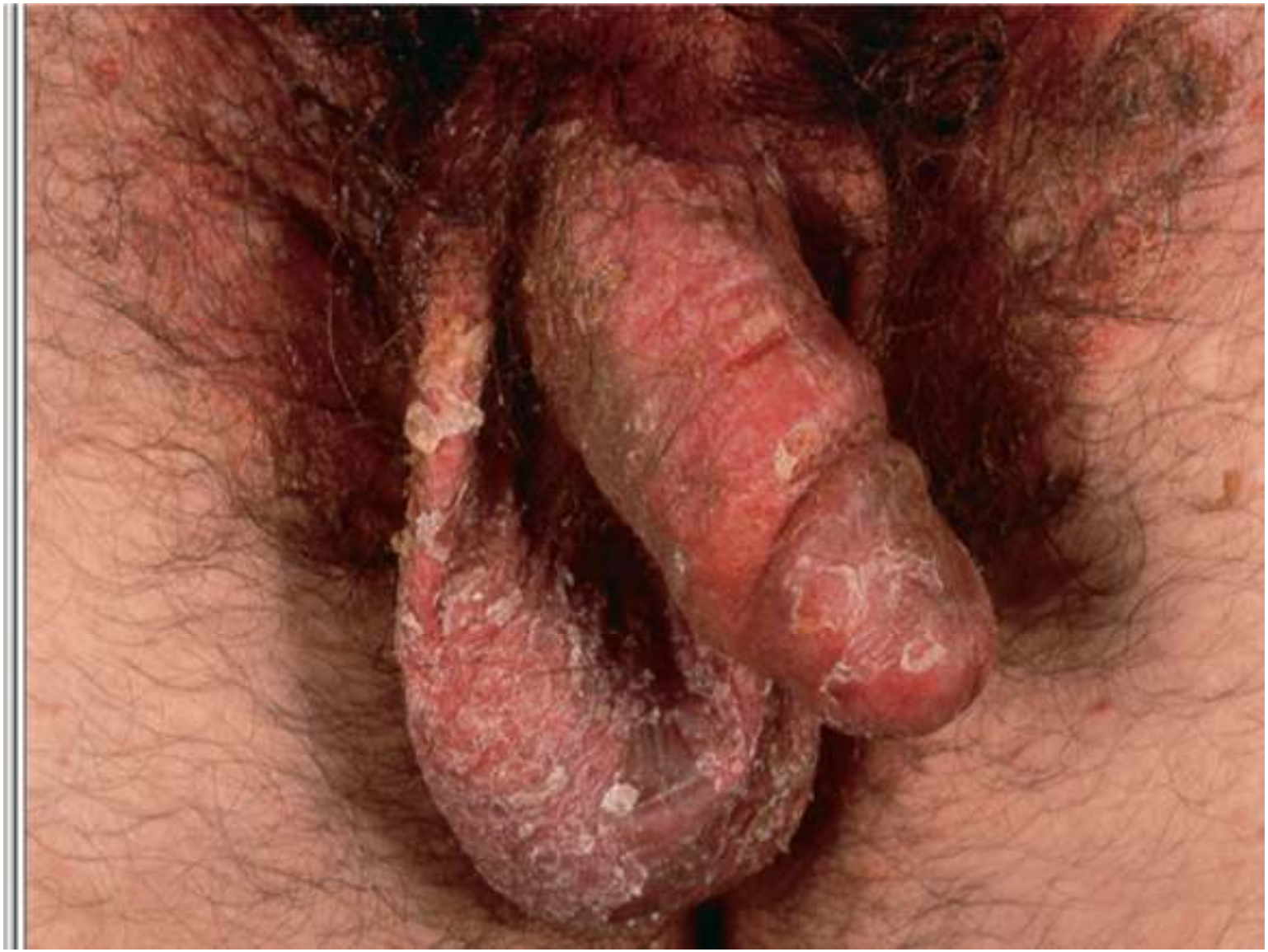


Psoriazis vulgar

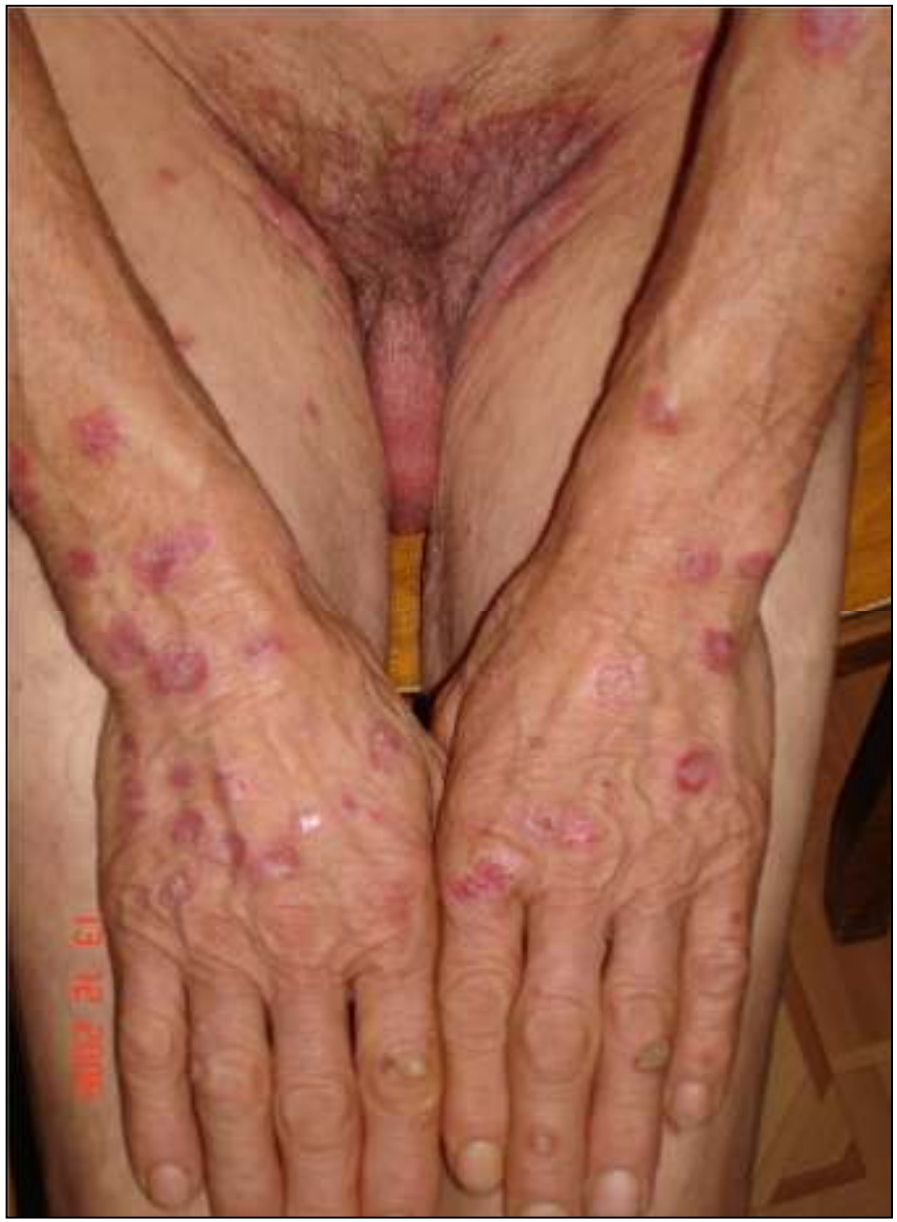


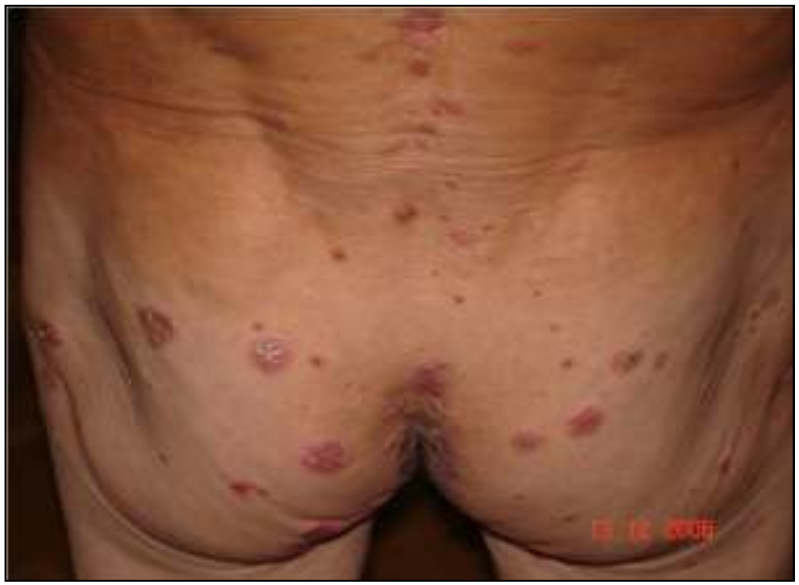


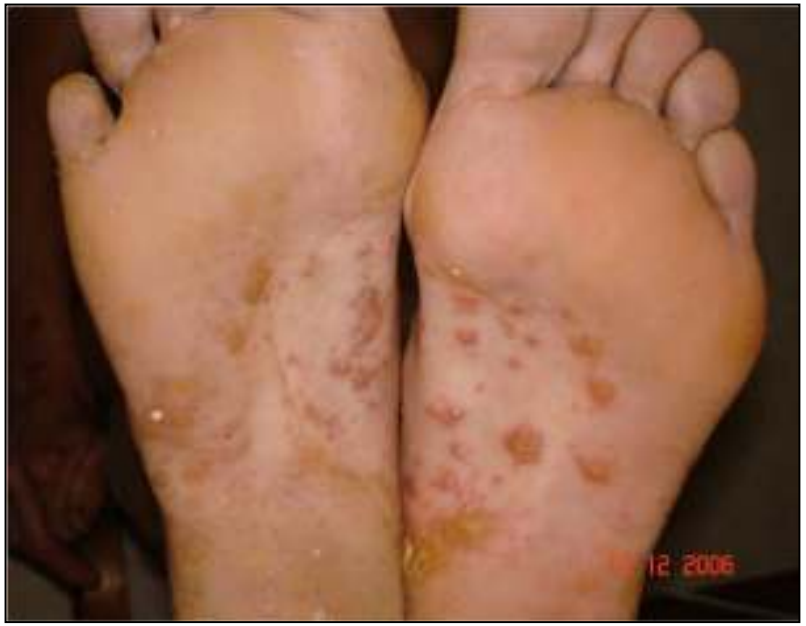
Psoriazis genital



Nummular PS

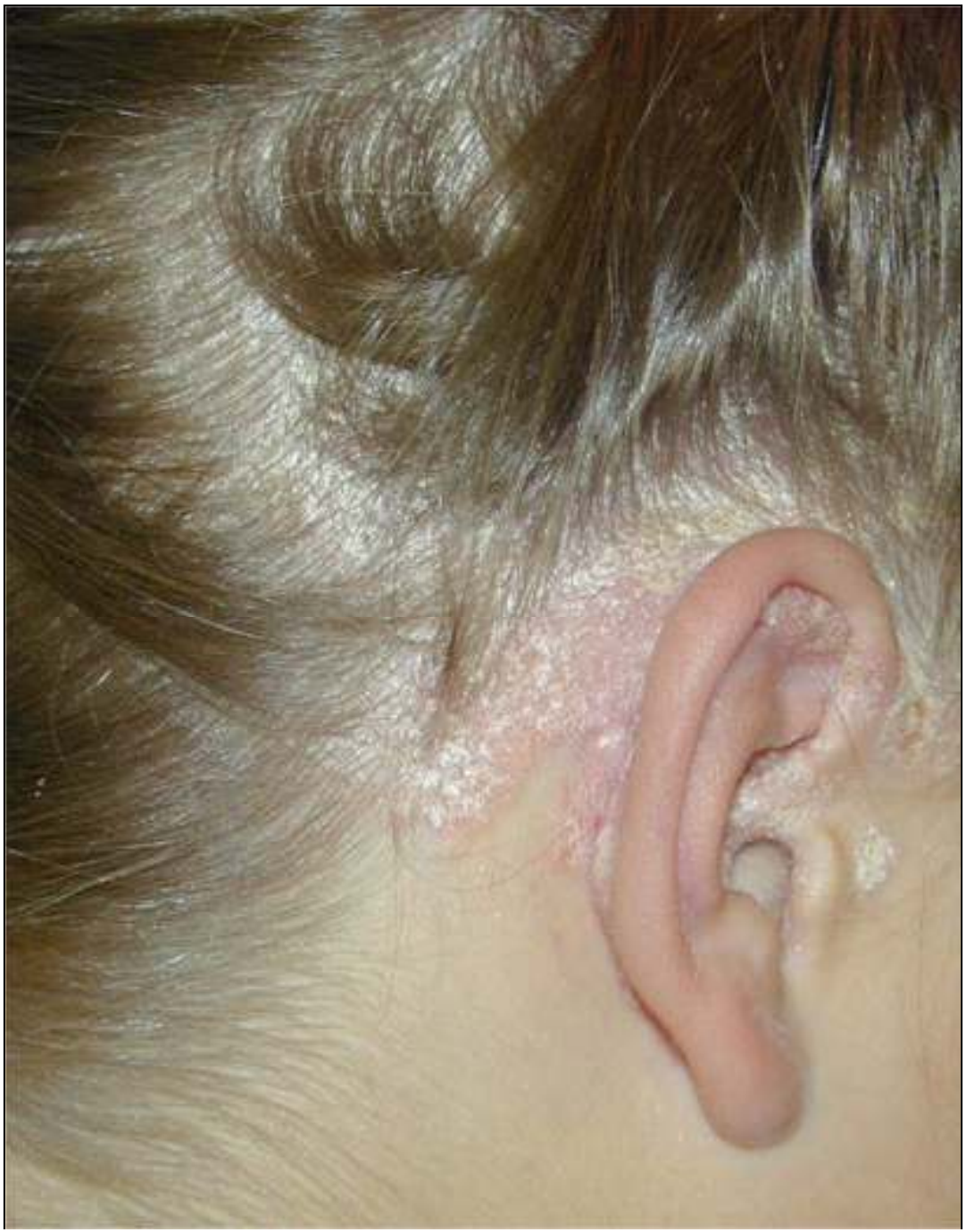




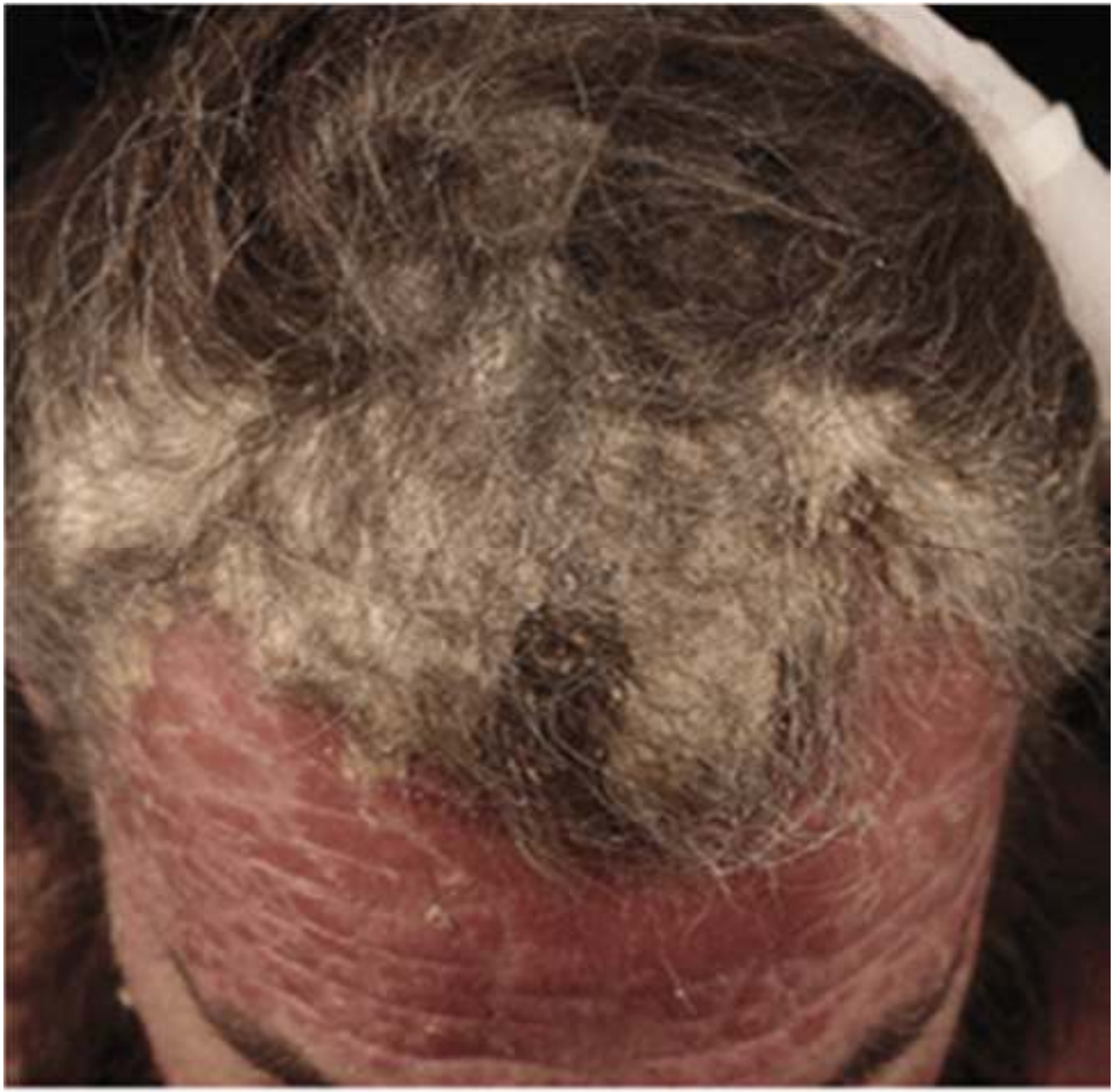


Scalp Psoriasis

- Scalp may be affected alone
- Can be difficult to distinguish from severe seborrhoeic dermatitis
- Lesions vary from one or two plaques to a sheet of thick scale covering the whole scalp surface
- Often, very thick plaques develop, especially at the occiput (nape)
- Even decades of persistent scalp Ps have remarkable little effect on the hair, but hair loss is not as uncommon as previously stated.



Scalp PS



Scalp PS

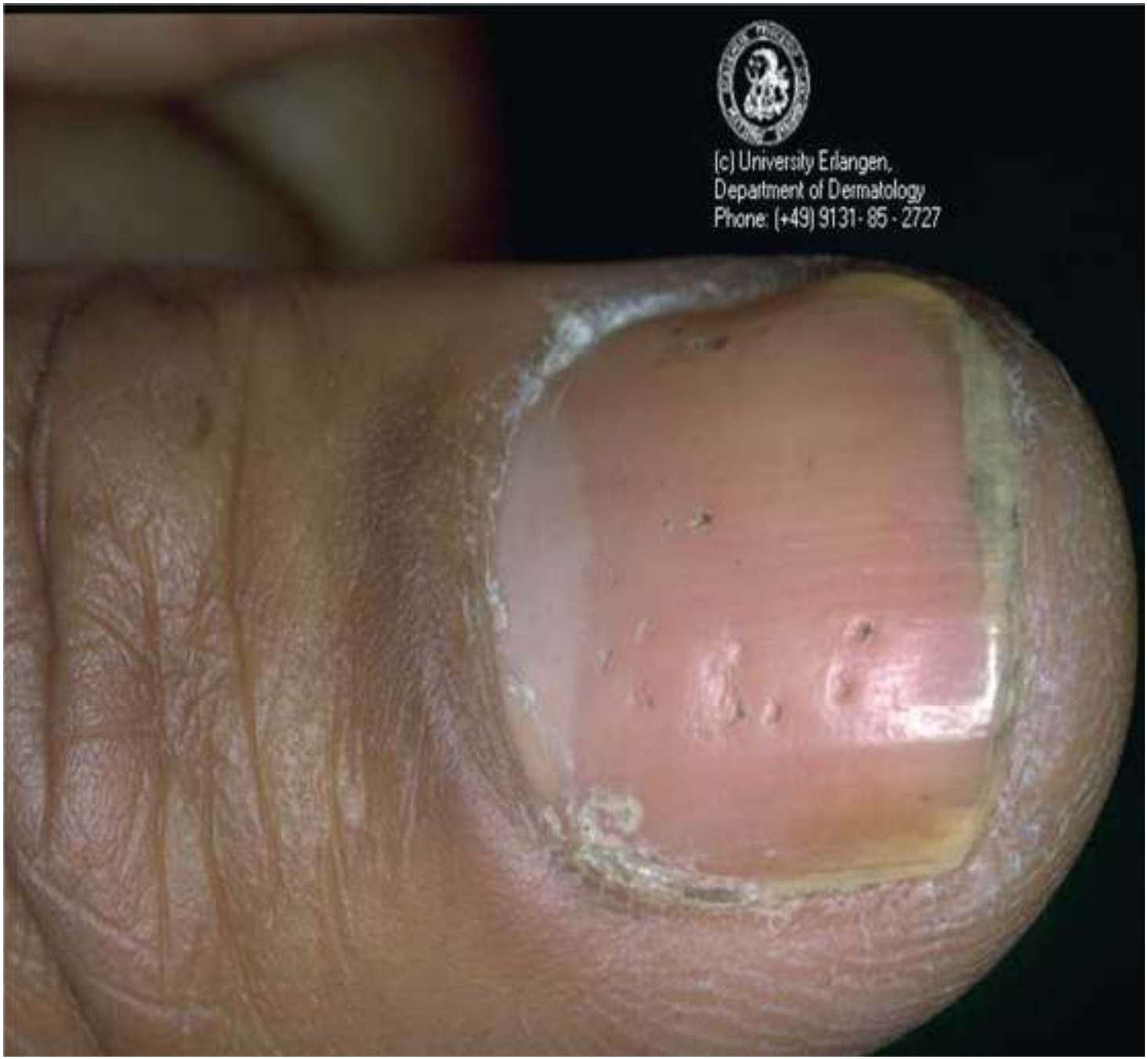
Nail PS

- In 80% of psoriatic patients, more in PS arthritis
- Fingernails>Toenails
- Four changes
  1. Onycholysis (= separation from nail bed)
  2. Pitting*
  3. Subungual debris accumulation
  4. Color alterations

*Pitting rules out a fungal infection


Debris
accumulation
Pitting

Nail PS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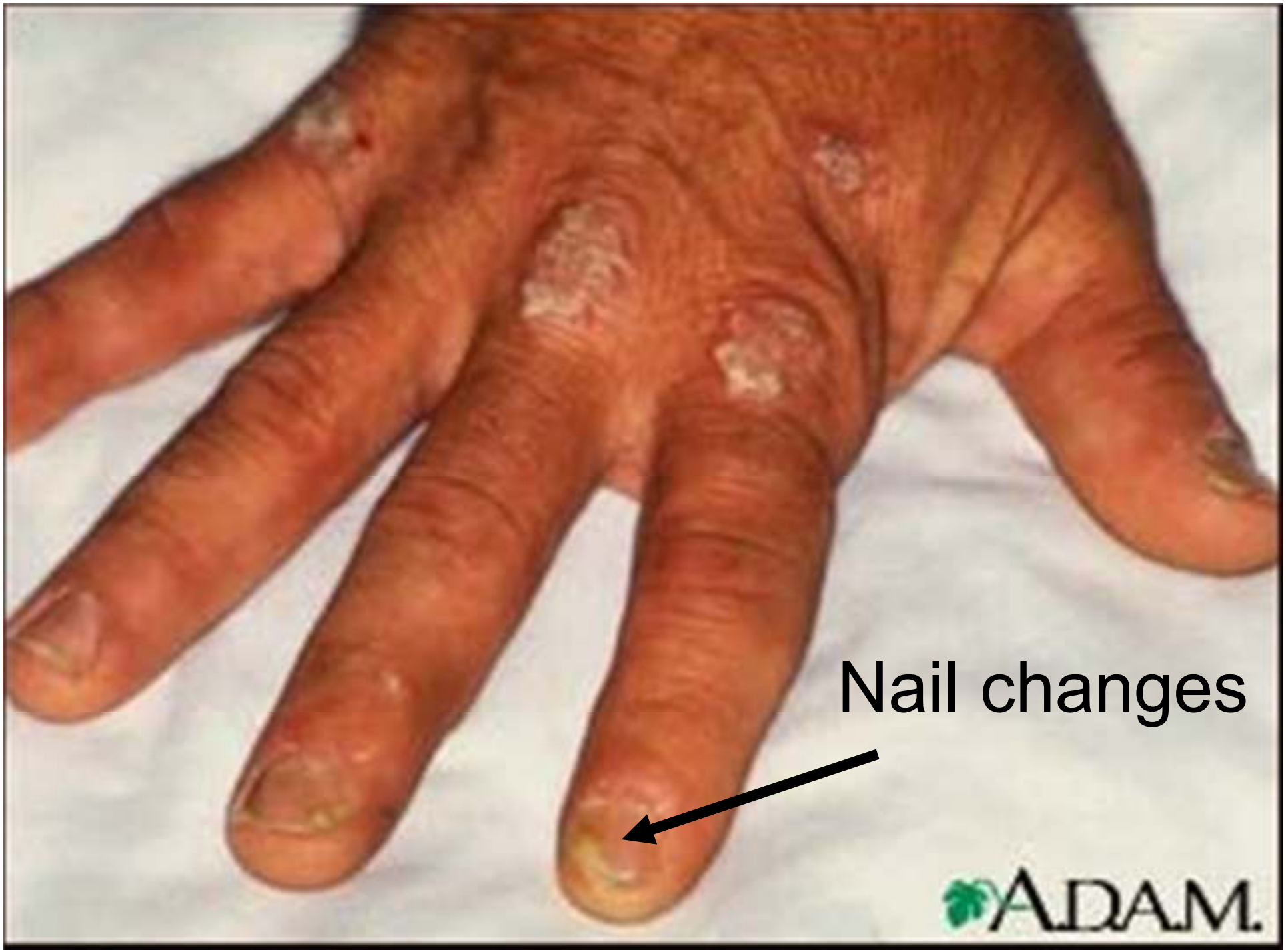
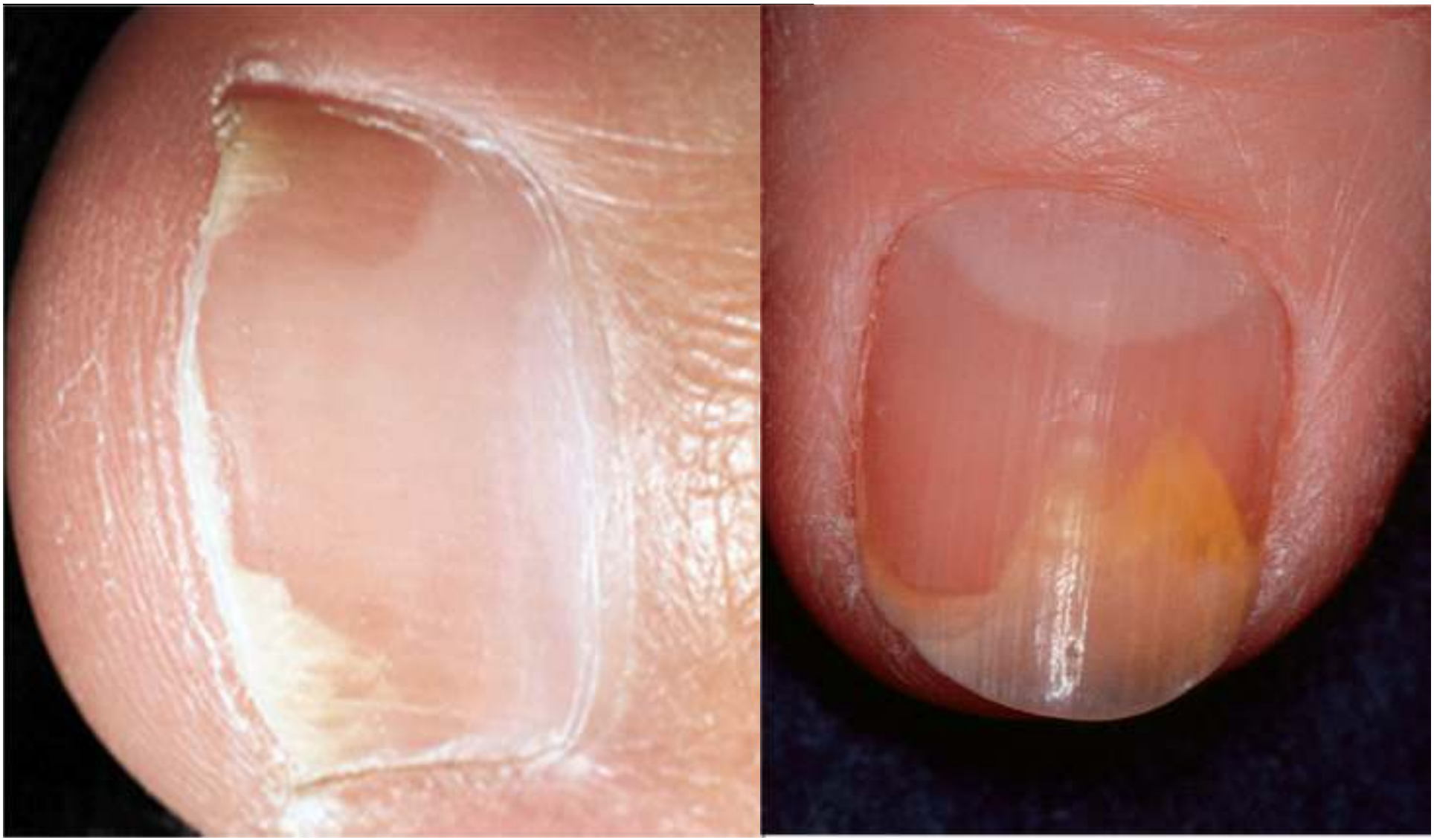

Nail changes
A.D.A.M.

Nail PS

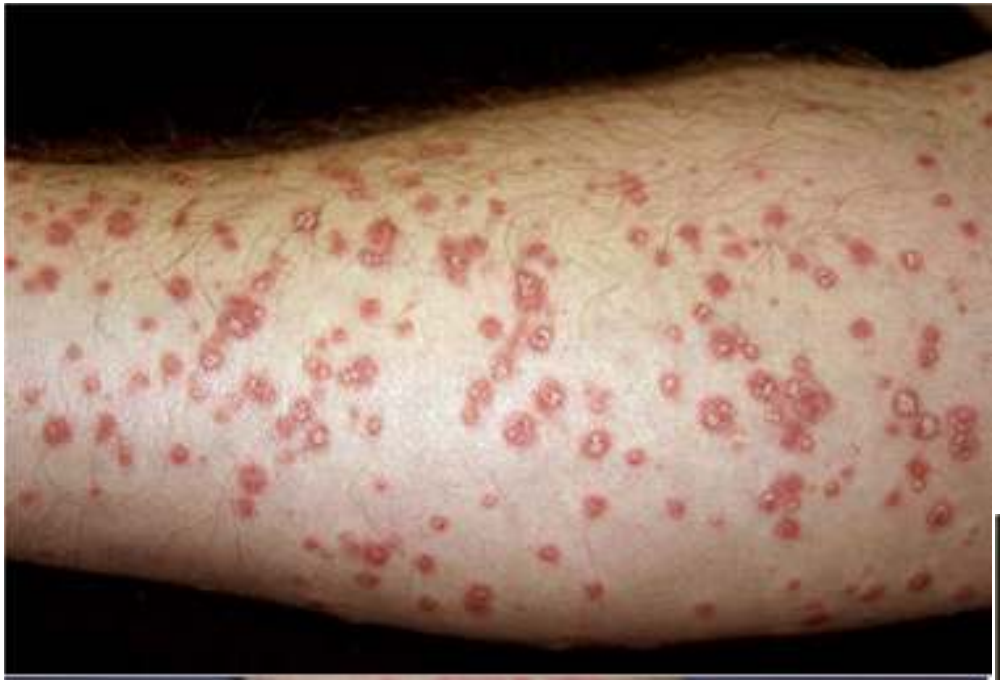


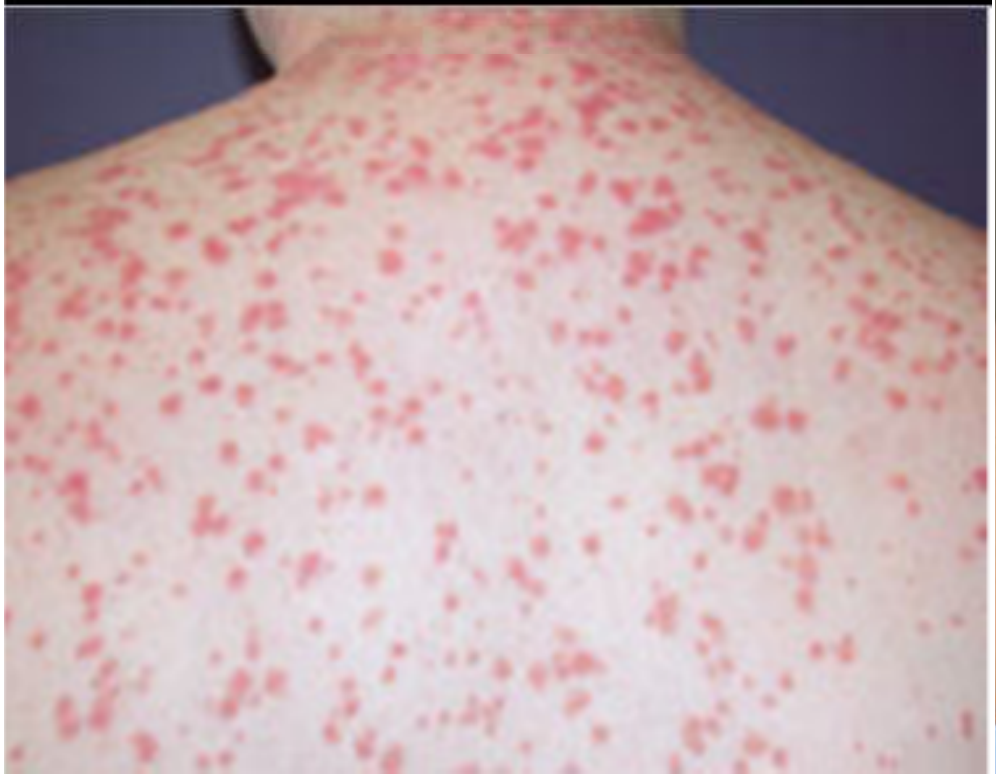
Guttate Psoriasis

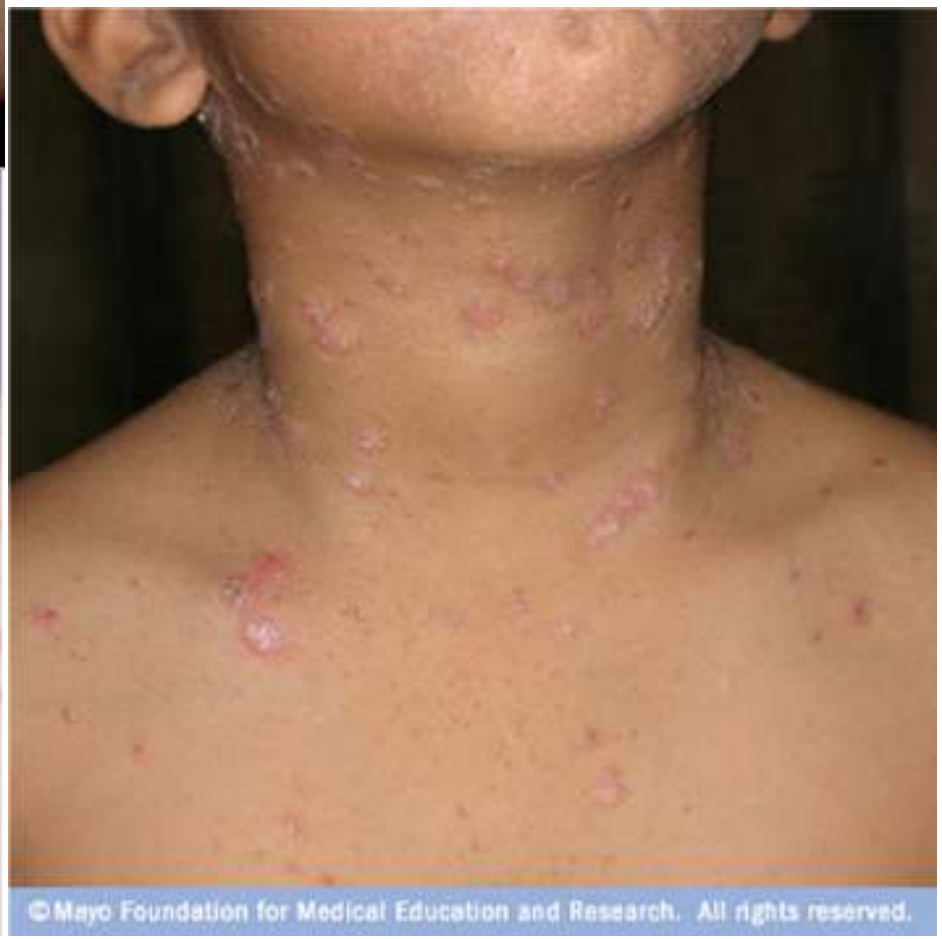
- Often develops suddenly and may follow an infection, especially a streptococcal sore throat
- It is common in adolescents and young adults
- Lesions are about one centimeter in diameter and are usually round in shape
- Itch is common
- Lesions can enlarge and become plaque Ps


Guttate Psoriasis
A.D.A.M.

Guttate PS



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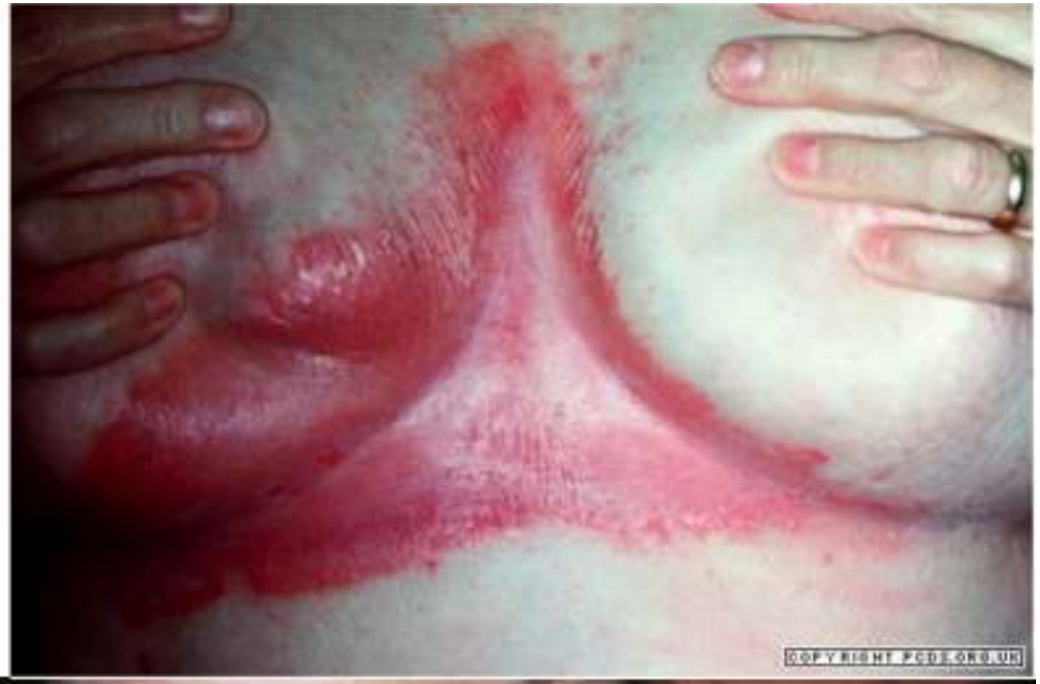
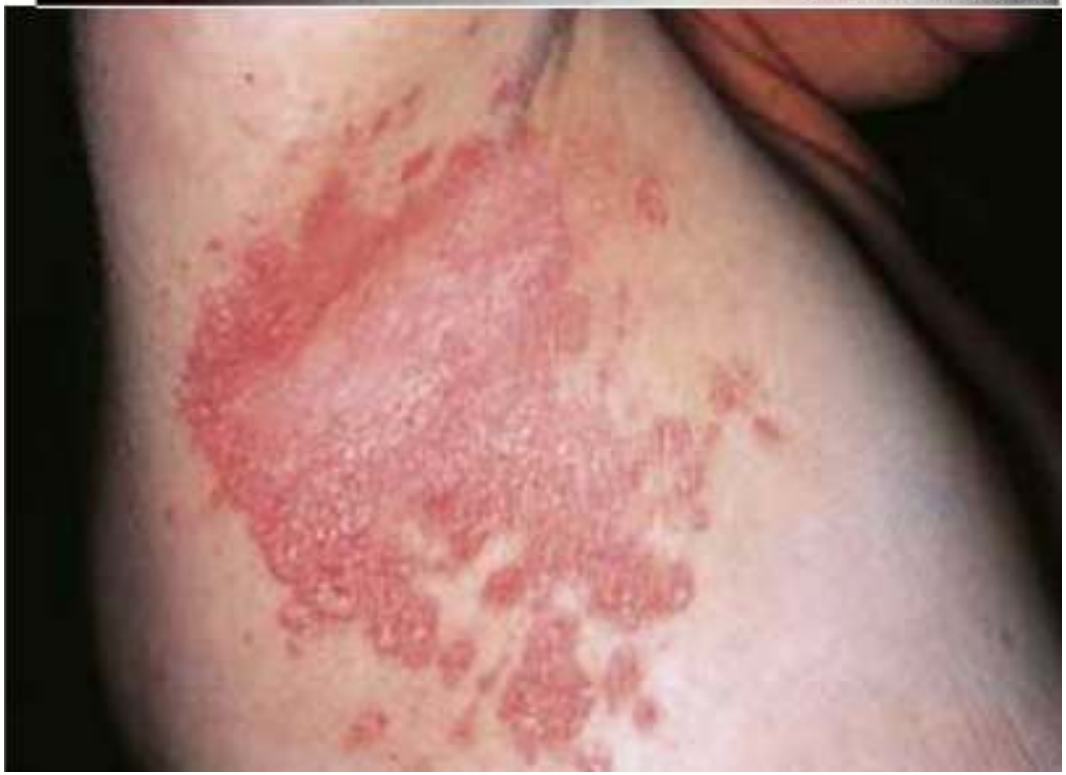
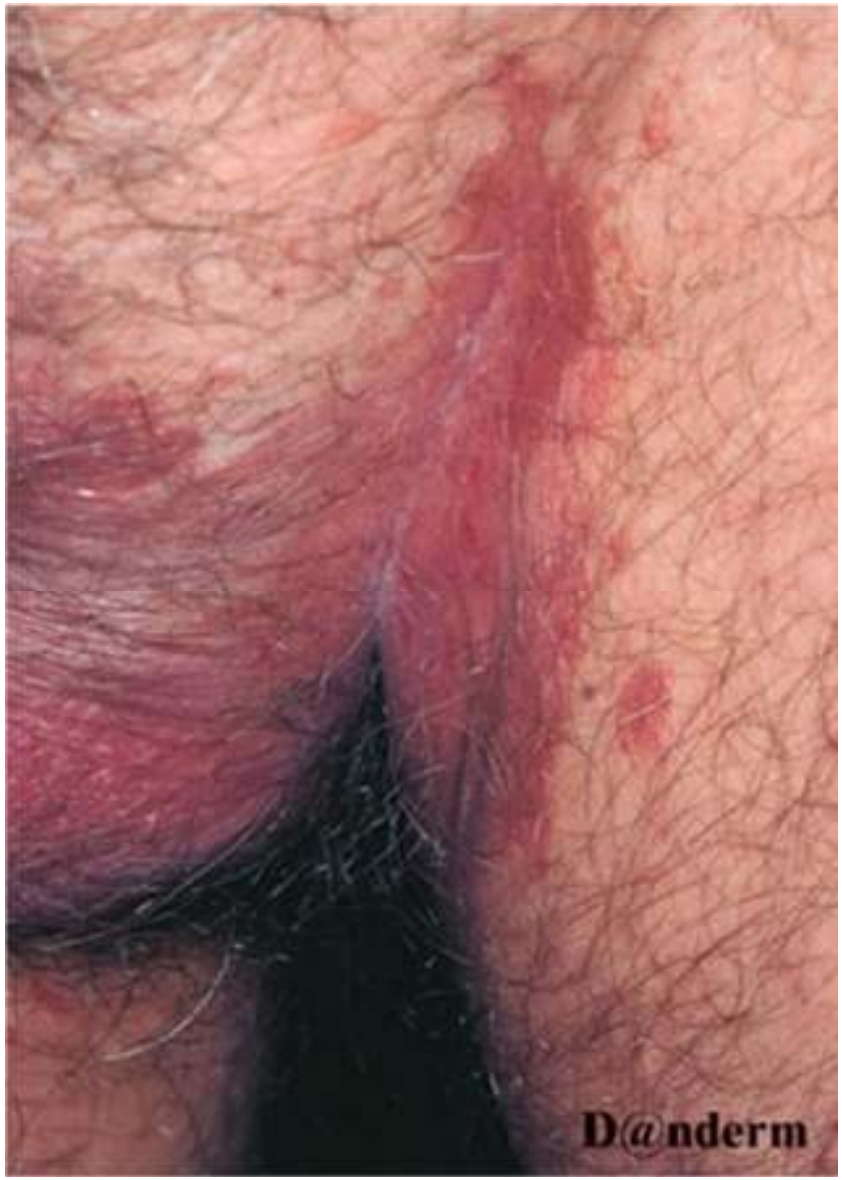
Flexural Psoriasis (inverse psoriasis)

- Lesions may occur in the groin, natal cleft, axillae, umbilicus, submammary and gluteal folds
- Psoriatic balanitis is a form of inverse Ps, that is represented by erythematous plaques on the glans penis
- Maceration inevitably occurs, and the scale surface is often lost, leaving a beefy erythematous appearance
- It is often itchy

Flexural PS

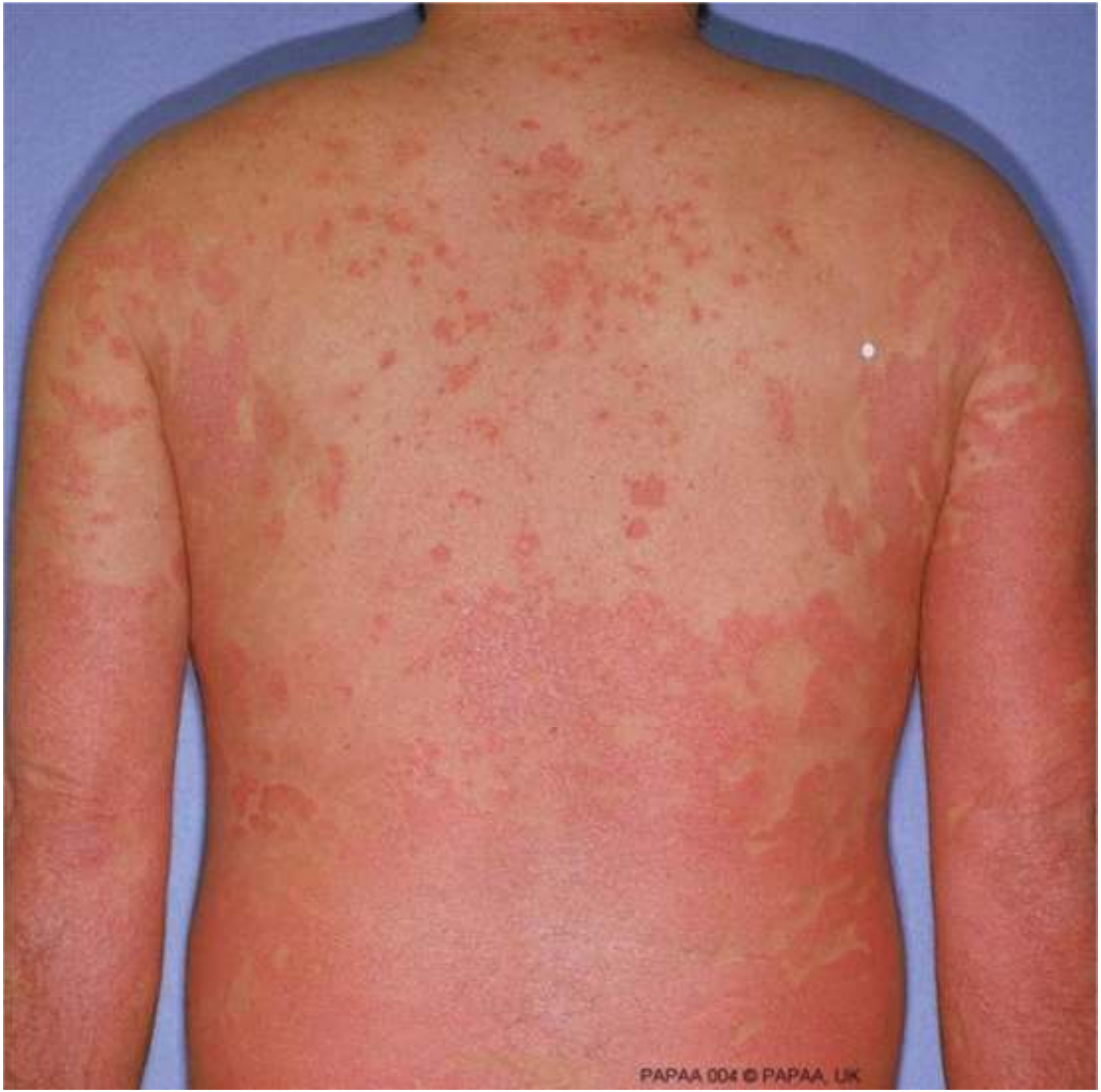






Brittle Psoriasis (instable Ps)

- Lesions consist of thin, irritable scaly areas
- Lesions may arise de novo or develop suddenly in a patient whose Ps has been stable for years
- Systemic steroid therapy and potent topical steroids can induce stable Ps to become “brittle”\
- Lesions may rapidly generalize, leading to erythroderma or acute pustular Ps

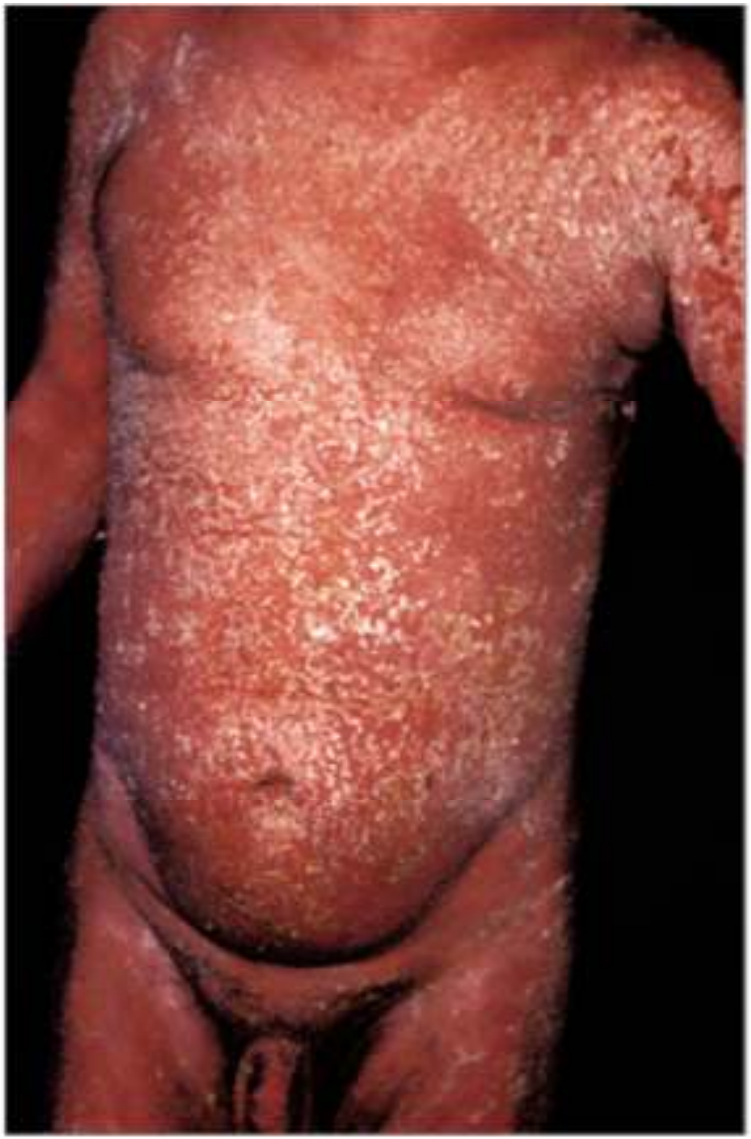


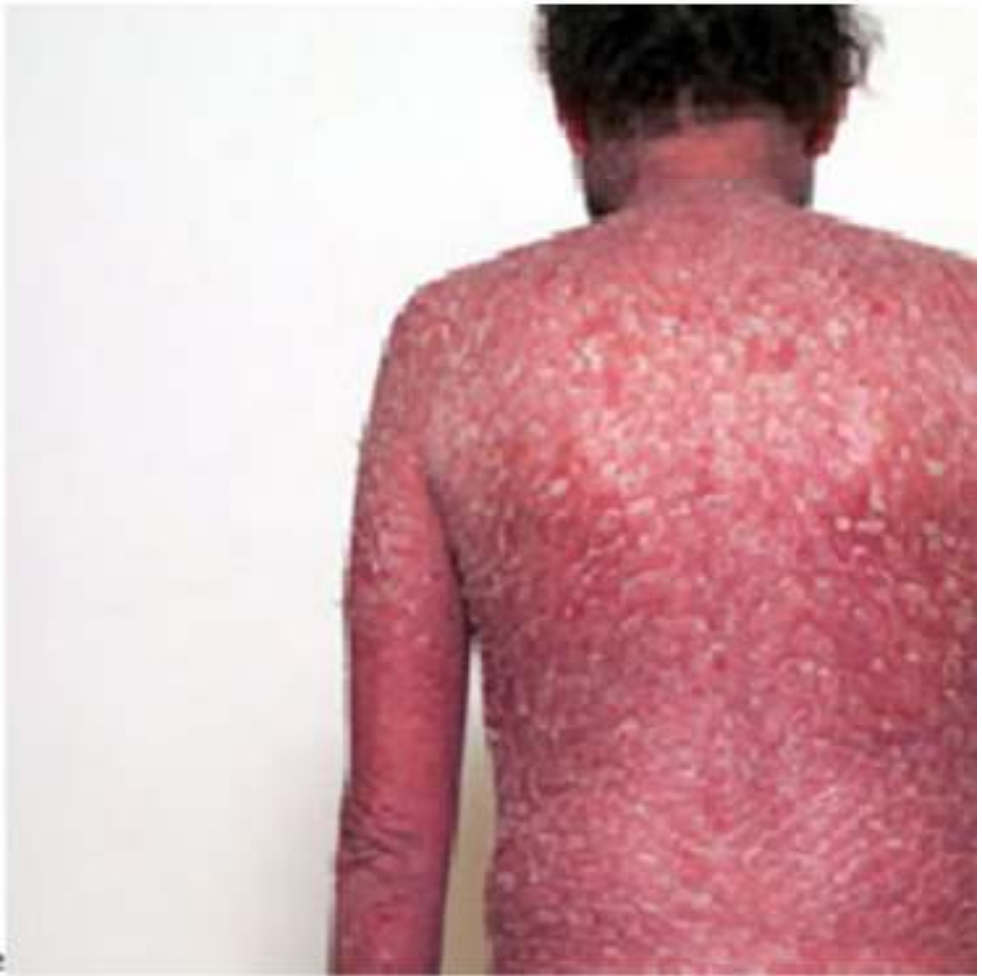
Brittle Ps

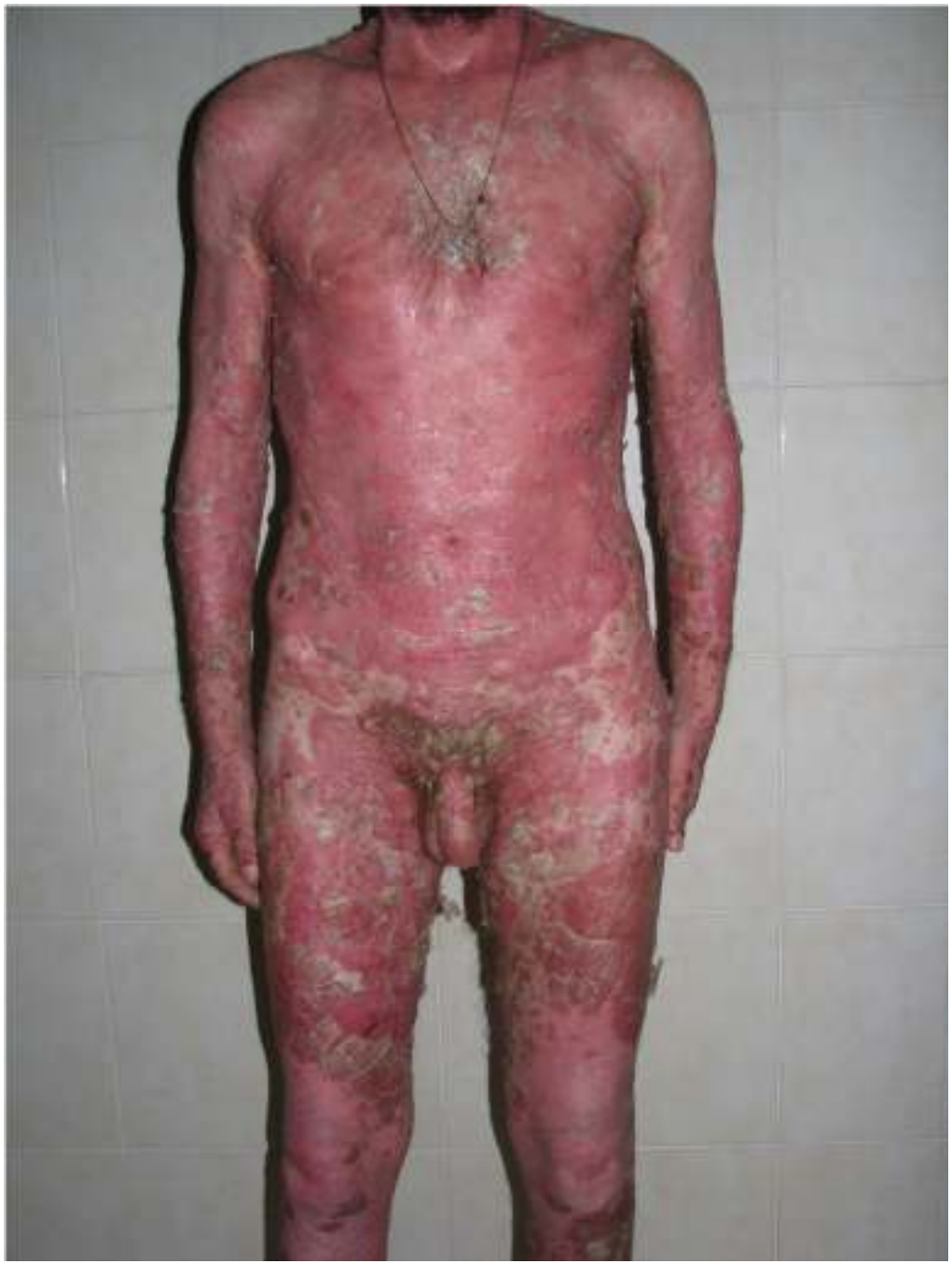
Erythrodermic Psoriasis

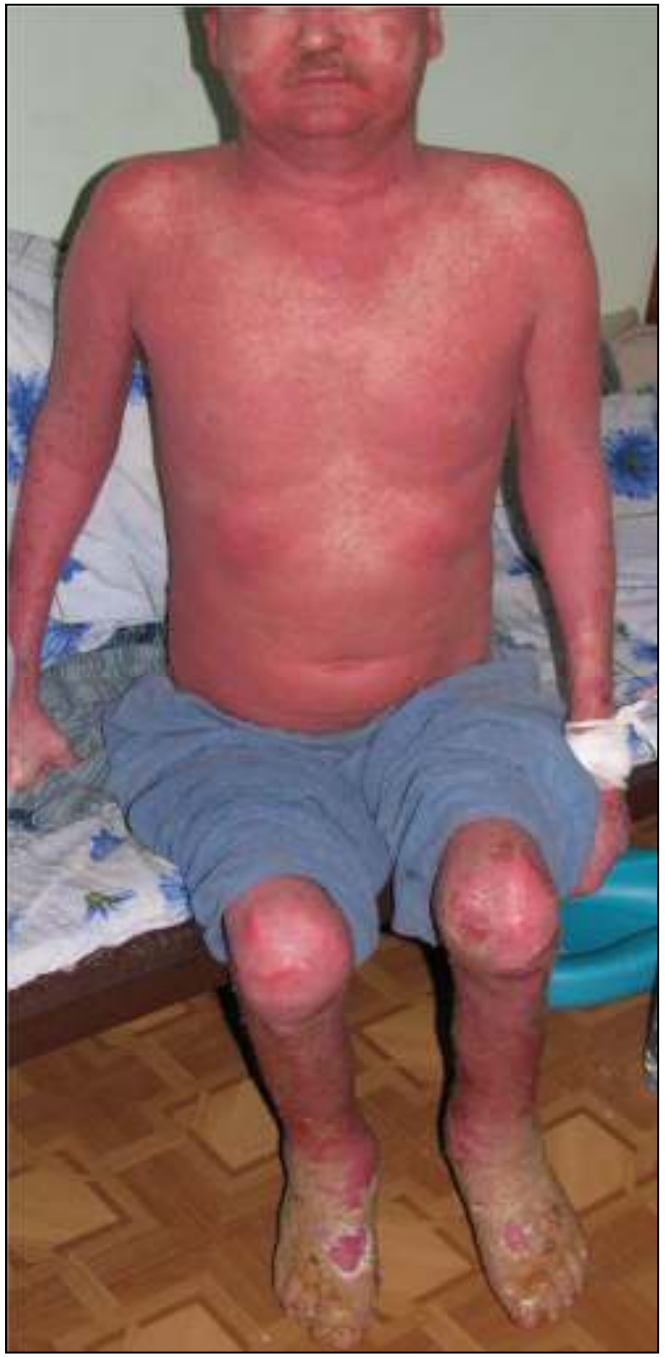
- When psoriatic plaques merge to involve most, or all, of the skin a state of erythroderma or exfoliative dermatitis results; it may appear de novo
- The skin is red, hot and scaly; hair and nail loss can develop; itching is severe
- There may be a generalized lymphadenopathy
- There is a loss of control of temperature regulation accompanied by bouts of shivering
- Complications: cardiac failure, renal failure, sudden death due to central hypothermia.

Erythrodermic Psoriasis





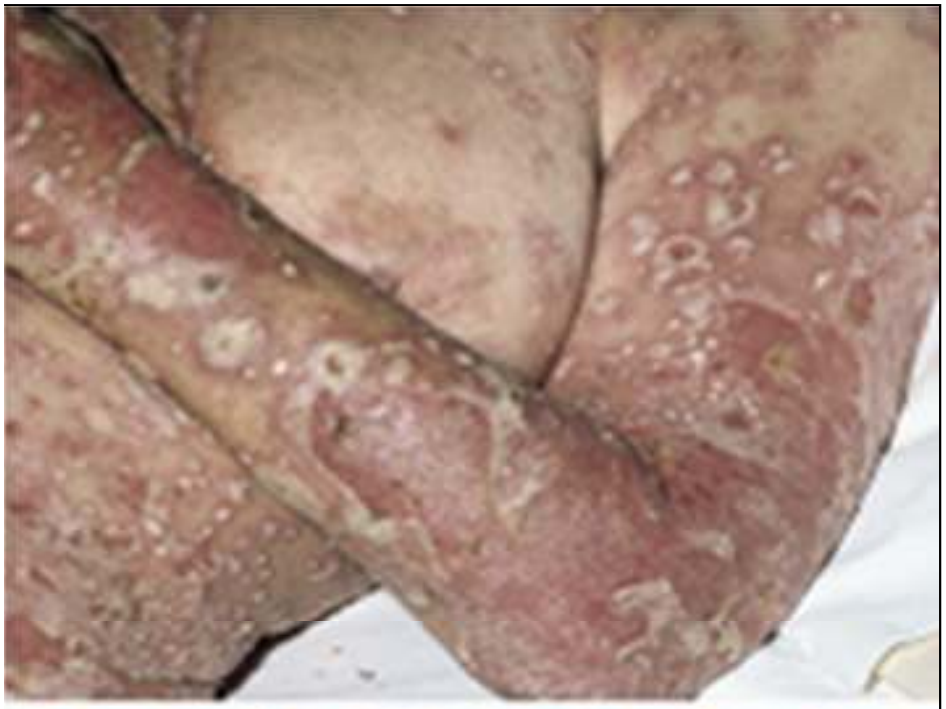


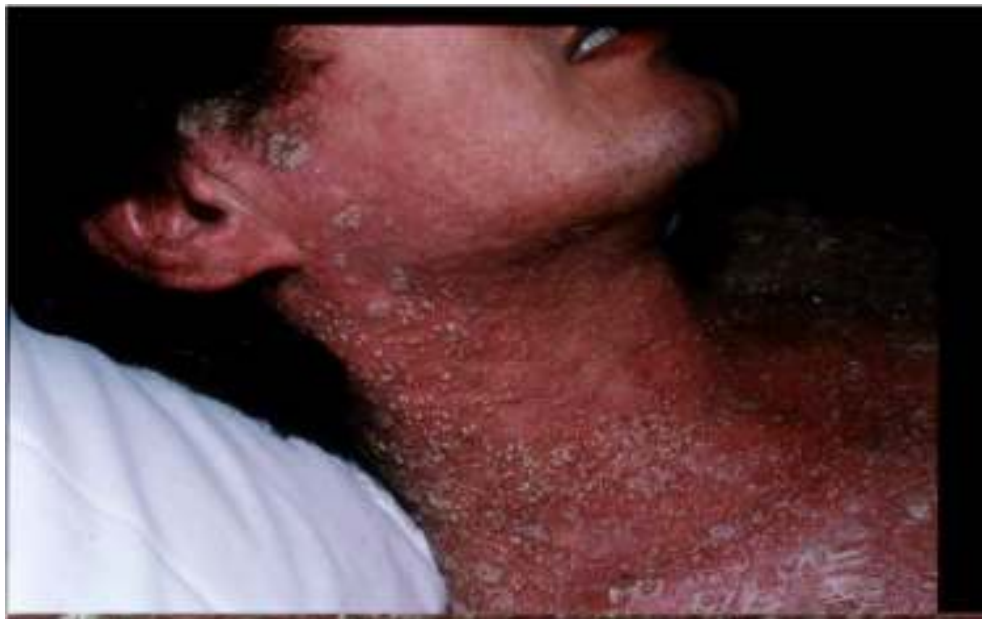


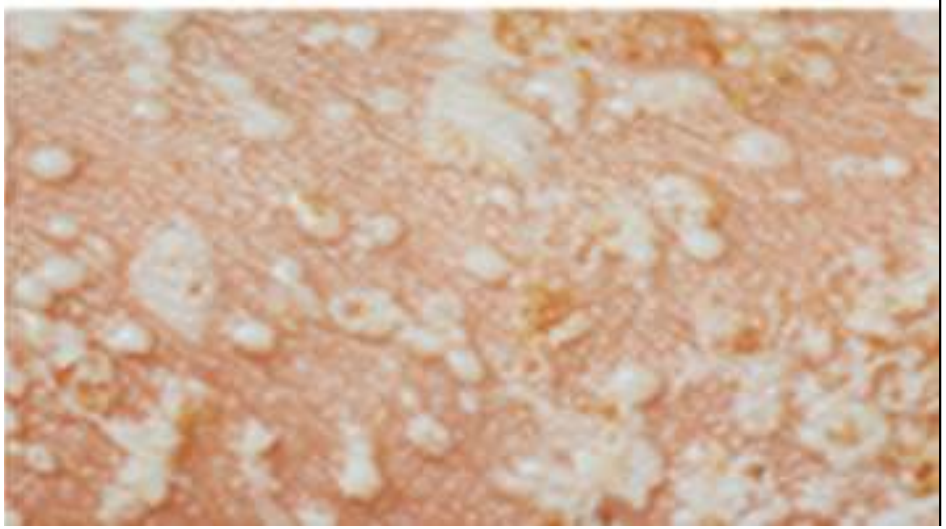
Acute Pustular Psoriasis (of von Zumbusch)

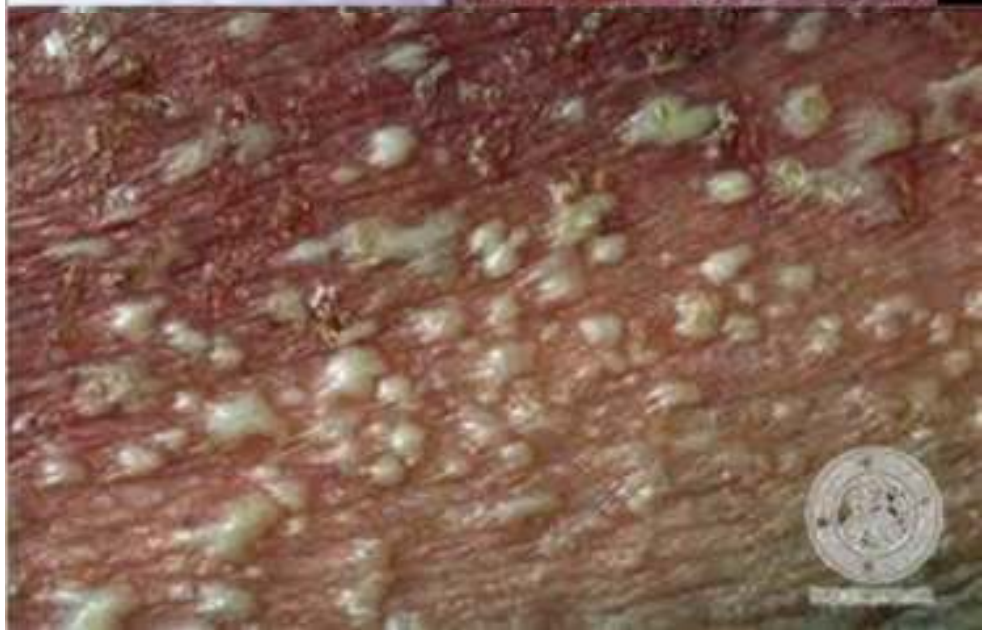
- This is a life-threatening condition
- Patients with or without pre-existing Ps suddenly develop widespread erythema, superimposed on which are pustules
- Pustules can coalesce into lakes of pus (Kogoj-Lapierre pustules)
- The pustules are sterile
- The patient has a high, swinging fever and is toxic and unwell, with a leucocytosis
- If untreated, may die, often of secondary infections.

Zumbusch acute pustular Ps





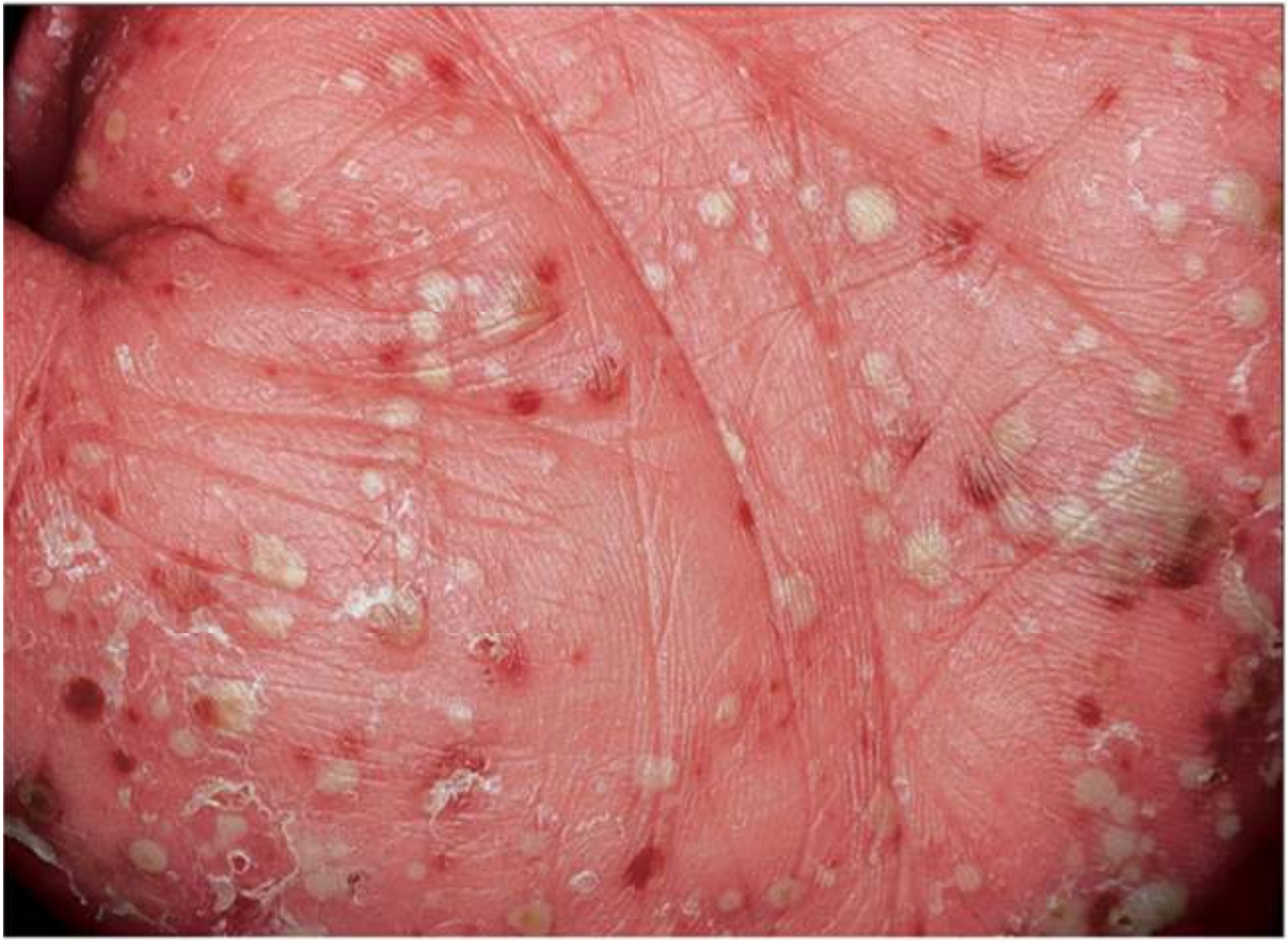




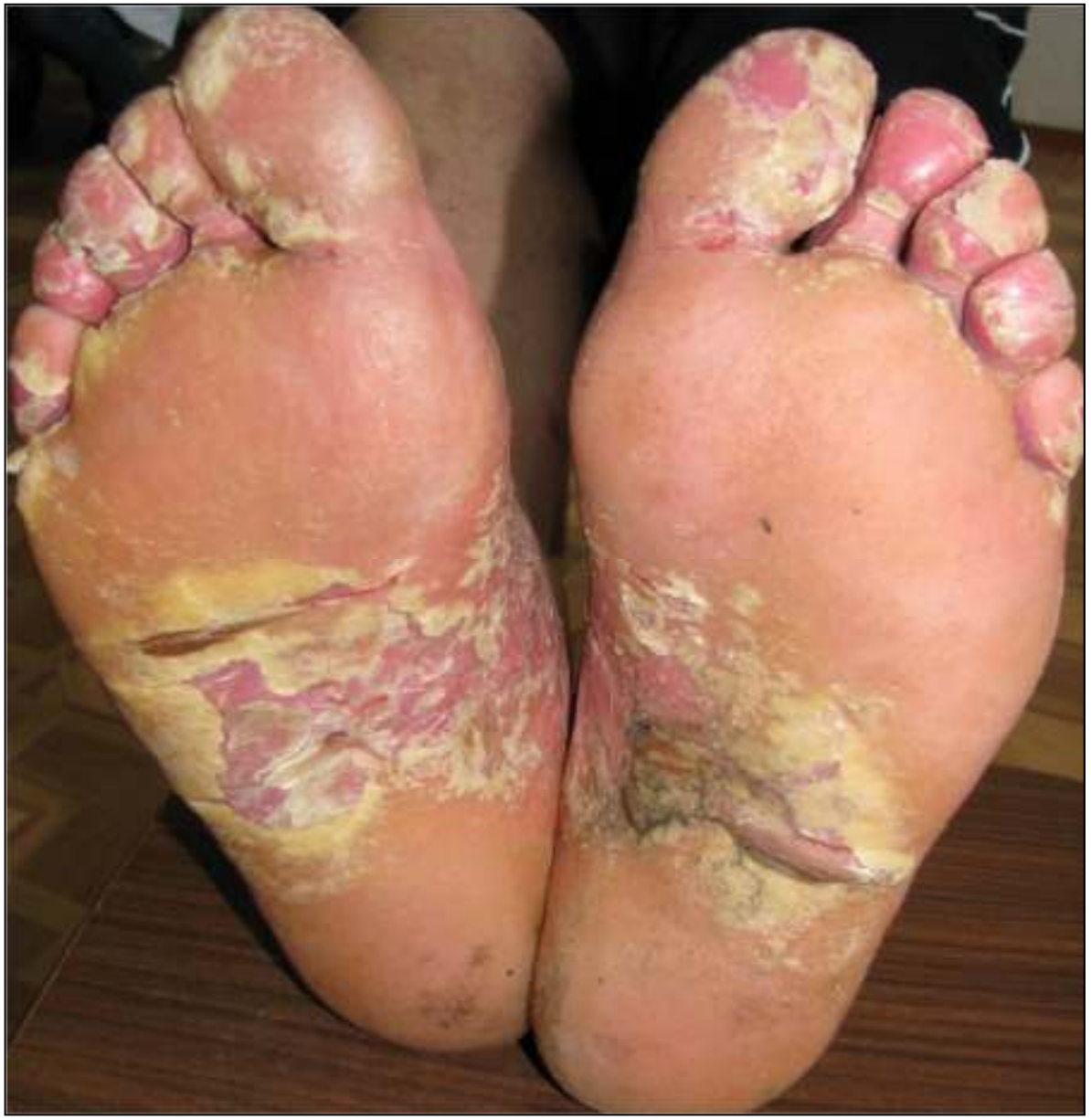
Chronic Palmo-Plantar Psoriasis (of Barber)

- It is unusual for patients to have chronic palmo-plantar pustulosis in association with other forms of Ps
- The typical changes consist of erythematous patches with numerous pustules
- These gradually change into brown, scaly spots and peel off
- Lesions may involve a small area of one hand or foot, or cover the entire surface of both palms and soles
- This may lead to considerable disability

Chronic palmo-plantar PS of Barber



Palmo-plantar Ps



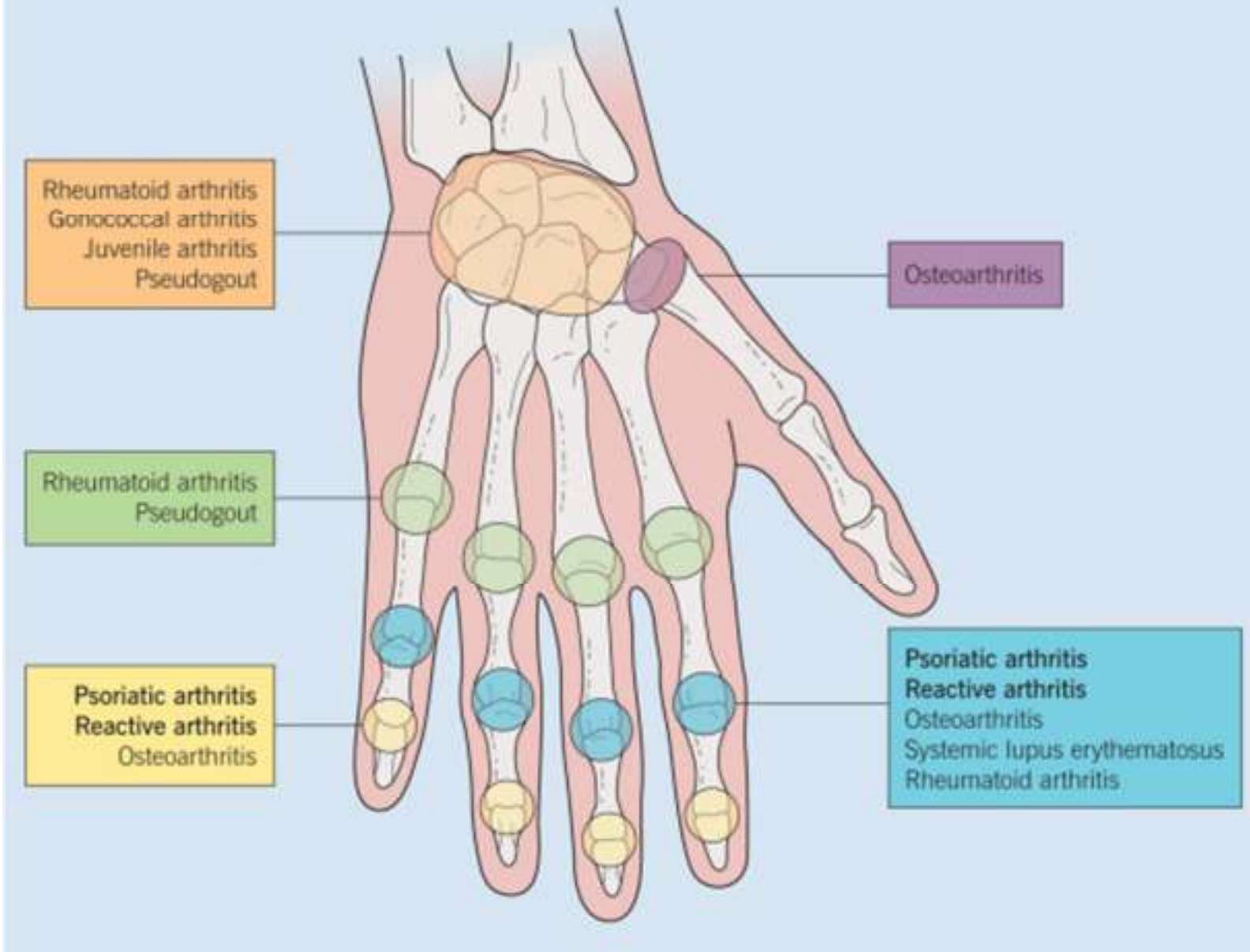
Arthropathic Psoriasis

- One of the most unpleasant complication of Ps is arthropathy, affecting up to 10% of psoriatics
- There are four basic clinical patterns:
- distal interphalangeal joint involvement (DIP form)
- seronegative rheumatoid-like joint changes
- large joint mono- or polyathropathy
- spondylitis
- Psoriatic arthropathy is erosive and may result in joint destruction
- Psoriatics who develop the spondylitic for are usually HLA B27 positive, as in Reiter's syndrome.

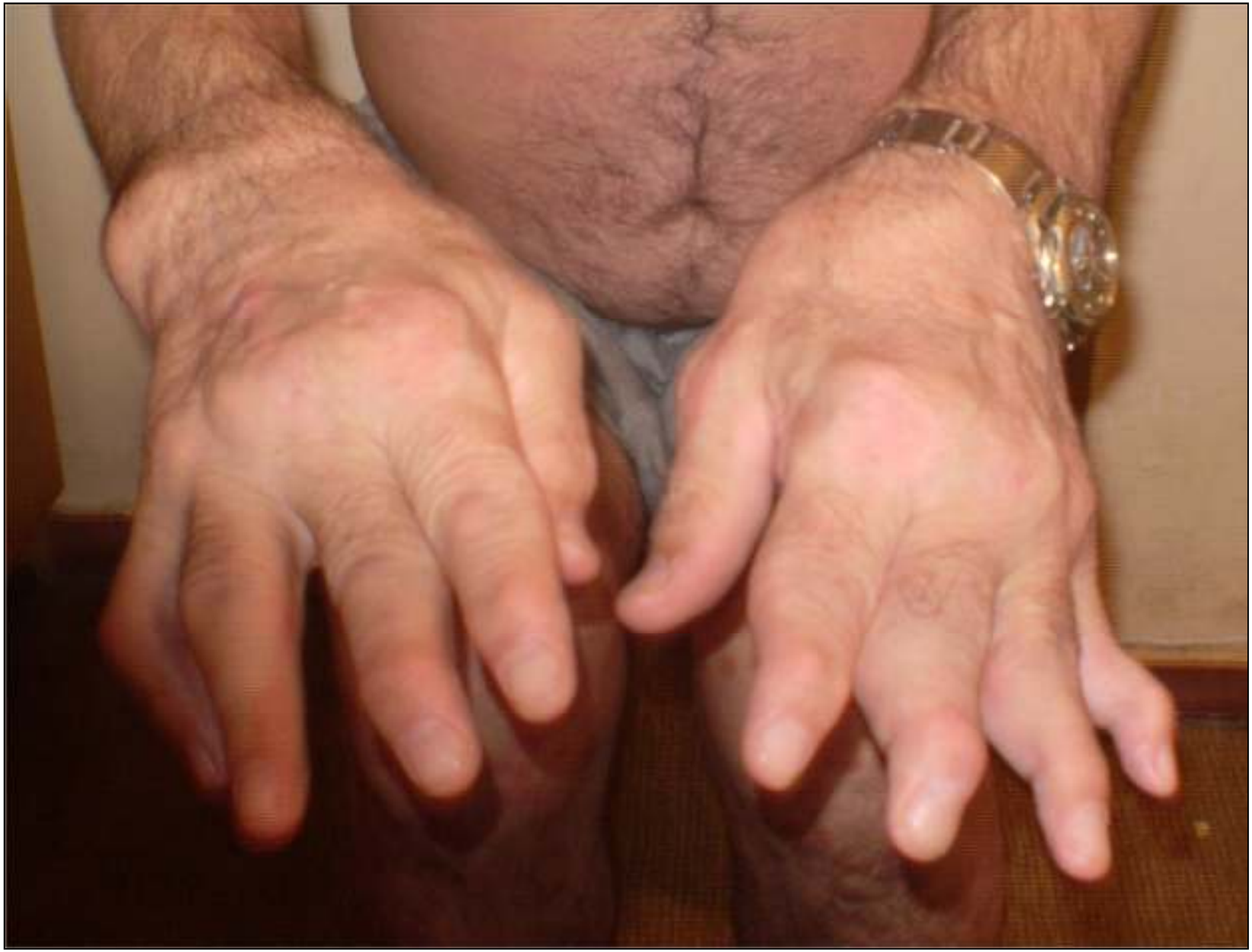
Psoriatic Arthritis

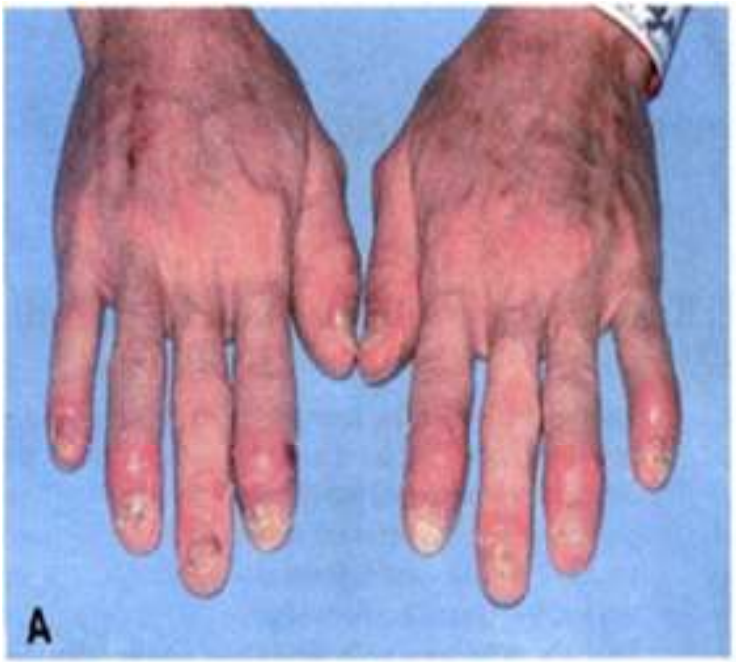
- In 10-20% of psoriasis patients
- Peripheral interphalangeal joints
- No elevated serum levels of rheumatoid factors (as seen in rheumatoid arthritis, yet has all other features)
- Often seen in patients with nail and scalp psoriasis

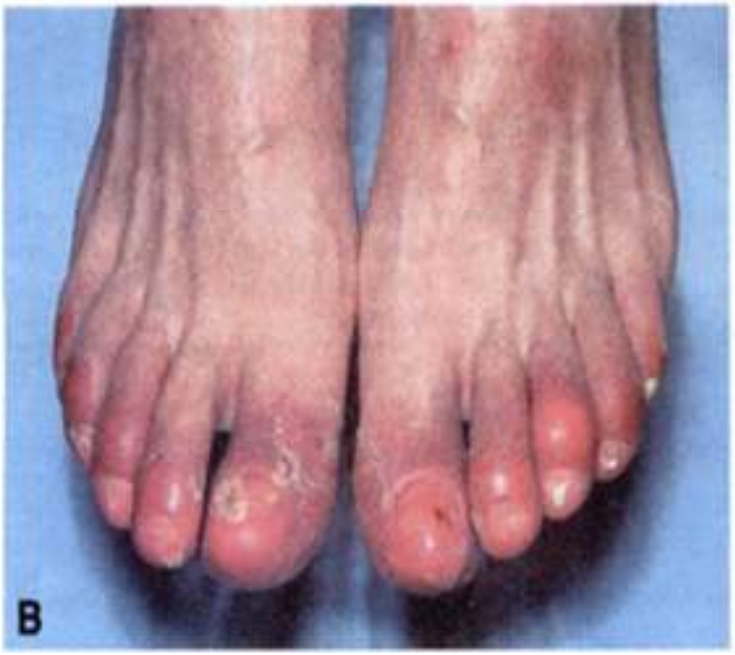
SITES OF INVOLVEMENT IN PSORIATIC ARTHRITIS AND REACTIVE ARTHRITIS

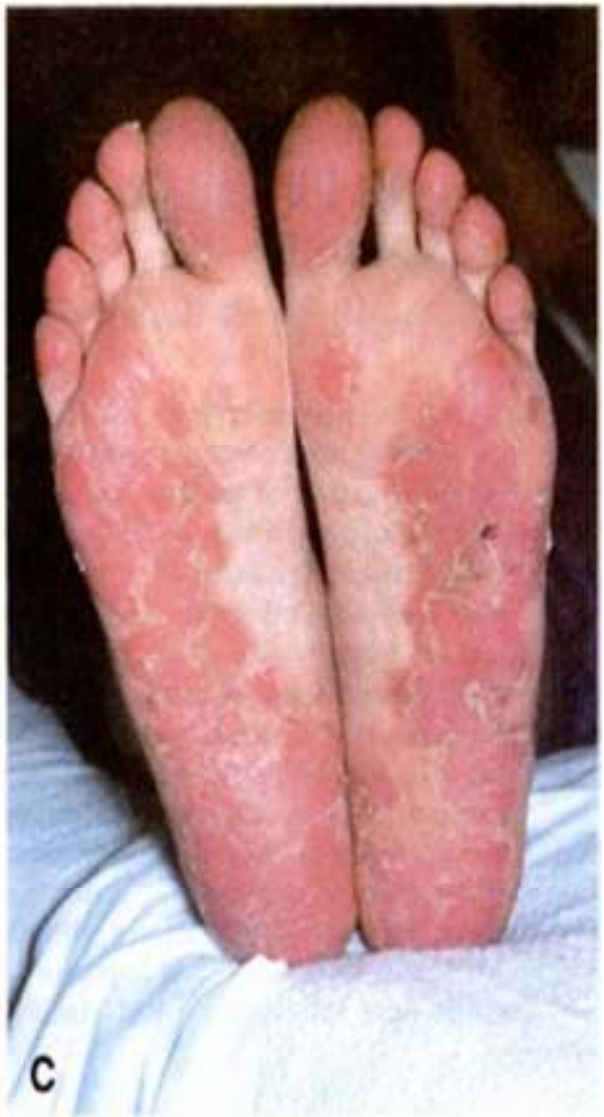


PS arthritis









PS arthritis

Treatment of Psoriasis

- It is an old adage that if there are many treatments for a disease, none works perfectly – this is certainly true of psoriasis
- Although each modality is useful in some patients, all represent a compromise in terms of safety, effectiveness and convenience
- Many patients require a regimen of different agents for different sites at different times.

Lubrication

Removal of scales

Slow down lesion proliferation

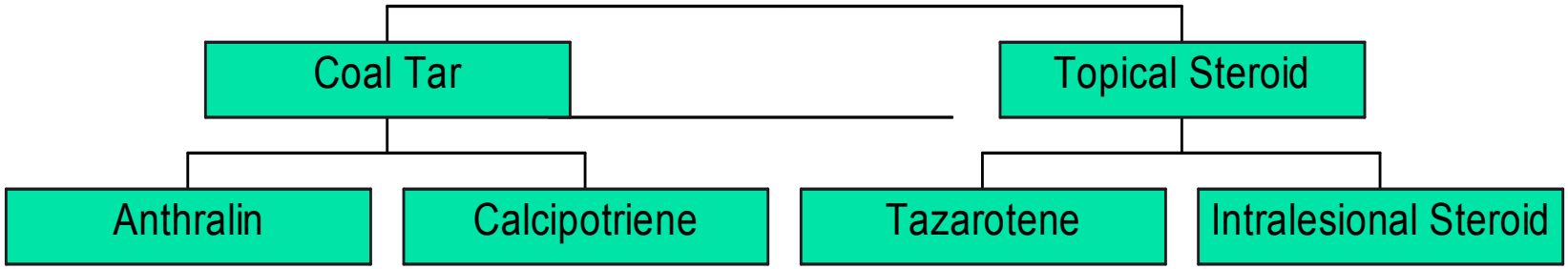
Treatment

Pruritus management

Season and climate

Lessen patient stress

Step 1



Supplementary Tx

Climatotherapy

Moisturizers

Keratolytics

Step 2

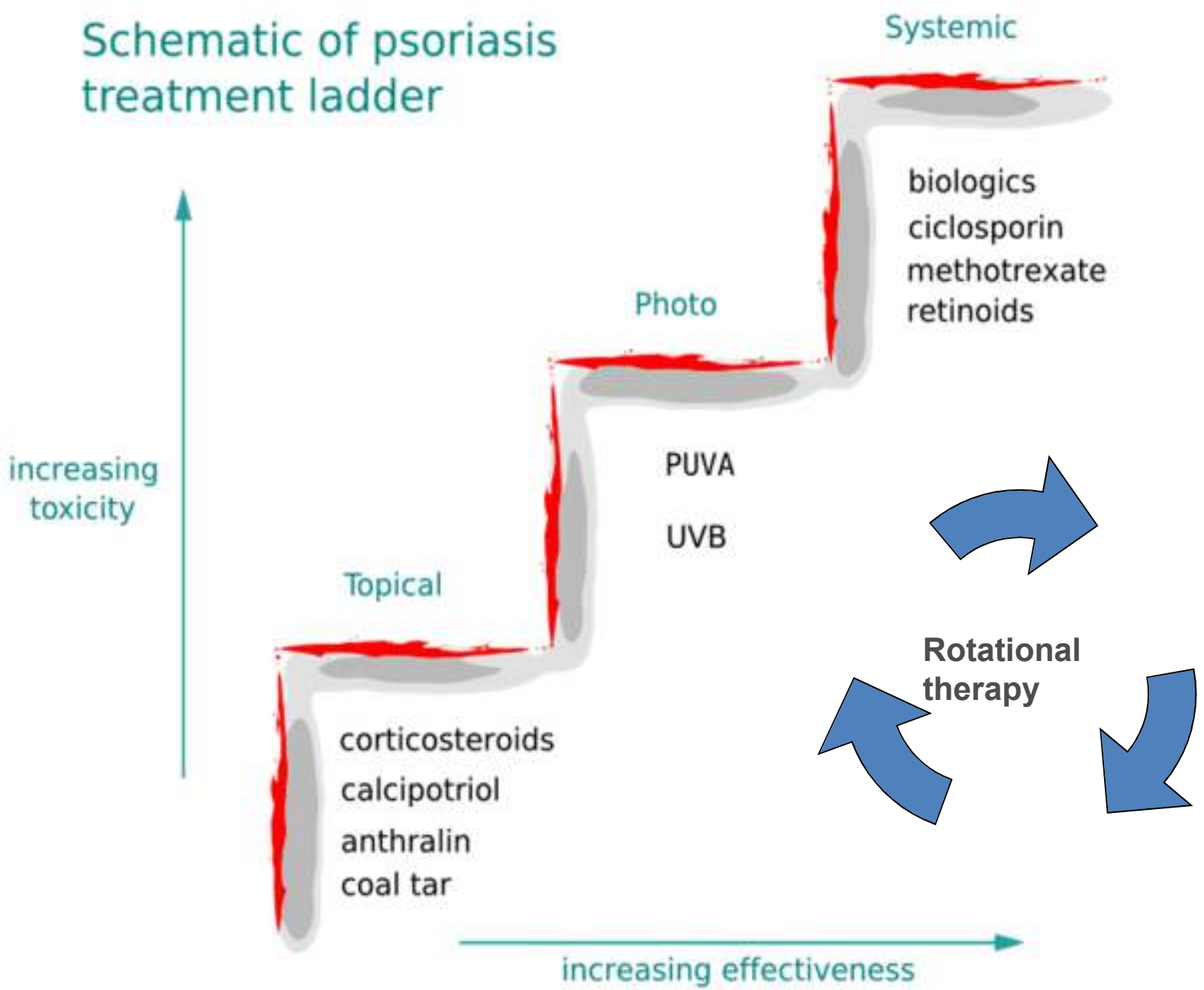
PUVA → PUVA + Step 1 agent

Step 3

Acitretin → Methotrexate → Cyclosporine → Rotational: 12-24 months of each step 3 agent

Step 4

Enbrel/Remicade/Amevive/Raptiva


Schematic of psoriasis treatment ladder
Systemic
biologics
ciclosporin
methotrexate
retinoids
Photo
PUVA
UVB
Topical
corticosteroids
calcipotriol
anthralin
coal tar
increasing toxicity
increasing effectiveness
Rotational therapy

Treating Psoriasis
Topical Agents

- Emollients
- Tar
- Salicylic acid
- Topical steroids
- Dithranol (anthralin)
- Vitamin D analogues (calcipotriol, tacalcitol, etc)
- Vitamin A analogues (tretinoin, tazaroten, etc.)
- Ultraviolet radiation (UVA, UVB)

Treating Psoriasis
Systemic Agents

- PUVA (psoralen + ultraviolet A)
- Retinoids (acitretin, etretinate, isotretinoin)
- Cytotoxics (methotrexate, azathioprine, hydroxiurea)
- Systemic steroids
- Ciclosporin
- TNFα inhibitors (infliximab, etanarcept, etc.)

Biologics

Produsul	Indicaţii/ mecanism de acțiune
Infliximab (Remicade) – 149 kDa, Ac monoclonal chimeric umanizat, iv	AR, SA, AP, Pso, BC, RCUH, BBh Cupleaza TNF-α
Adalimumab (Humira) – 148 kDa, Ac monoclonal uman, sc	AR, SA, AP, Pso, BC Cupleaza TNF-α
Certolizumab pegol (Cimzia) 40 kDa, fragment Fab recombinat umanizat, sc	AR, BC Cupleaza TNF-α
Golimumab (Simponi) 147 kDa, Ac monoclonal uman, sc	AR, SA, AP Cupleaza TNF-α
Etanercept (Enbrel) 150 kDa, proteină de fuziune rec TNF p75, sc	AR, SA, AP, Pso Cuplează TNF-α si limfotoxina-α(TNF-β)
Efalizumab – (Raptiva) interzis de EMEA	Blochează CD11a subunitatea al LFA-1 (lymphocyte function-associated antigen 1)
Alefacept – nu în Europa	Blochează molec. costimulatoare LFA-3/CD2 Pso
Ustekinumab (Stelara) – anti IL 12 şi IL 23	Ac monoclonal p/u p- 40 din IL-12 și IL-23

AR – artrită reumatoidă; SA – spondilartropatie ankilozantă; AP – artrită psoriazică; Pso – psoriazis; BC – boală Crohn; RCUH – colită ulcerativă; BBh – boală Behcet

Biologics in PS

Infliximab	•Psoriasis •Rheumatoid arthritis •Ankylosing spondylitis •Psoriatic arthritis •Crohn disease •Ulcerative colitis
Etanercept	•Psoriasis •Rheumatoid arthritis •Psoriatic arthritis •Juvenile idiopathic arthritis
Adalimumab	•Psoriasis •Rheumatoid arthritis •Juvenile idiopathic arthritis •Psoriatic arthritis •Ankylosing spondylitis •Crohn disease
Ustekinumab	•Psoriasis

Treatment	Annual Cost
Steroids	500-2,000
Dovonex	2,000-8,000
UVB	1,850
PUVA	3,300
Soriatane	6,150
Methotrexate	1,500-2,150
Cyclosporine	4,800
Biologics	10,000-15,000

Emollients and Moisturizers

- Moisturizes, lubricates and soothes dry and flaky skin.
- Produces occlusive film to limit water evaporation from skin. Increased hydration allows stratum corneum to swell- scaling decreases, skin is more pliable.
- Adverse Effect: contact dermatitis, folliculitis (rare)

Keratolytics = “SKIN LIFTERS”

- Helps remove scales and reduce hyperkeratosis
- Salicylic Acid 2-6%
- Enhance absorption of other drugs
- AE: N/V, tinnitus, hyperventilation (rare =salicylism)

Tars

- Coal Tar – made from crude coal
- Decreases epidermal cell mitosis and scale development
- Reduces sebum production
- Anti-inflammatory effects
- 5% coal tar concentration most effective (1%-6%)

Coal Tar

- Problems with coal tar:
  - Smell
  - Sting
  - Stain
  - Sensitize

Coal Tar

- Very useful in guttate psoriasis and for scalp psoriasis as a shampoo
- Not recommended as 1st line tx:
  - Erythrodermic & Pustular
  - Irritation may lead to Koebner's phenomenon
- Use only on lesions that are well separated, not too big
- Phototoxic response→ sunburn may become erythematous

Corticosteroids

- Reduce inflammation, itching and scaling
- Anti-inflammatory effect
  - Decrease in vascular permeability, decreasing dermal edema and leukocyte penetration into skin
- Antiproliferative effect
- Immunosuppressive effect

Corticosteroids

Level of Potency	Corticosteroid	Commercial Products
Ultra-high	Halobetasol propionate Clobetasol propionate Betamethasone dipropionate Diflorasone diacetate	Ultravate crm/oint Temovate crm/oint Diprolene oint Psorcon oint
High	Halcinonide Amcinonide Betamethasone dipropionate Mometasone furoate Diflorasone diacetate Fluocinonide Desoximetasone	Halog crm Cylocort oint Diprolene AF crm Elocon oint Florone oint Lidex crm,gel,oint Topicort crm,oint,gel
Mild to high	Halcinonide Triamcinolone acetonide Betamethasone dipropionate Fluocinonide	Halog oint,crm,soln Aristocort A oint Diprosone crm Lidex-E crm

Corticosteroids

Level of Potency	Corticosteroid	Commercial Products
Mild	Hydrocortisone valerate Triamcinolone acetonide Flurandrenolide Mometasone furoate Fluocinolone acetonide	Westcort Kenalog crm and oint Cordran oint Elocon crm Synalar oint
Low to mild	Hydrocortisone valerate Triamcinolone acetonide Flurandrenolide Betamethasone dipropionate Hydrocortisone butyrate Flucolone acetonide	Westcort crm Kenalog crm and oint Cordran crm Diprosone lotion Locoid crm Synalar crm
Low	Alclometasone dipropionate Betamethasone valerate Fluocinolone acetonide Hydrocortisone, dexamethasone, prednisolone, methylprednisolone	Aclovate crm and oint Valisone lotion Synalar soln and crm

Corticosteroids

- Ointments: helps hydrate; good for dry, hyperkeratotic, scaly lesions
- Cream: for use on all areas, useful for infected lesions
- Solutions: for scalp psoriasis, often contain alcohols which can be painful with open lesions

Corticosteroids

- Adverse Effects: (esp. with occlusion)
  - Systemic absorption
  - Dermal atrophy
  - Telangiectasis
  - Ecchymoses
  - Peri-orbital acne
  - Poor wound healing
  - Pyogenic infections

Vitamin D3

- Isolated from cod liver oil in 1936
- Made in human skin through reaction:
  7-dehydrocholesterol & UV light
- Calcitriol's properties in psoriasis:
  1. Increase cellular differentiation
  2. Inhibits cellular proliferation

Vitamin D3

- Adverse Effects:
  - Hypercalcemia
  - Hypercalciuria
  - Mild calcitriol intoxication: renal stones
  - Not for long term use, therefore analogues were developed

Vitamin D3 Analogue

- Calcipotriene (Dovonex®)
  - Indication = Moderate plaque psoriasis
  - Reduces scaling and thickness of plaque, but not the erythema; what would you use in combo?
  - Max weekly cumulative dose: 5mg
    = 100gm of 50 mcg/gm or 2 tubes
  - Applied BID x 8 weeks

Vitamin D3 Analogues

- Calcipotriene (Dovonex®)
  - Not for pustular or erythrodermic psoriasis due to increased systemic absorption
  - AE: irritation, hypercalcemia (when applied in large amounts)
  - CI in pregnancy, lactation, children

Retinoids

- Vitamin A derivatives

- MOA:
    1. Normalization of abnormal keratinocyte differentiation
    2. Reduction in keratinocyte proliferation
    3. Reduction in inflammation

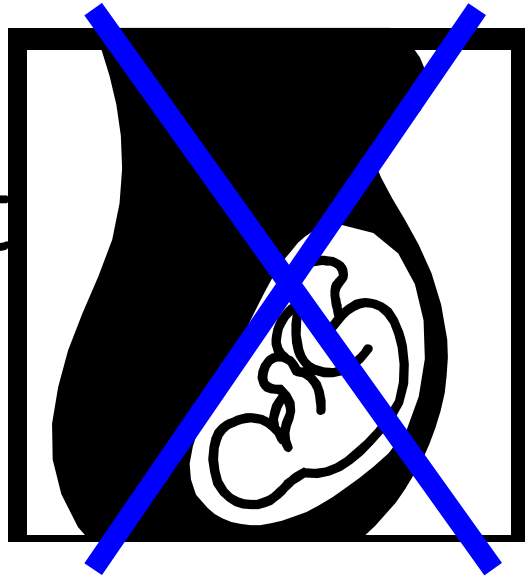
Oral Retinoids

- Etretinate & Acitretin (Soriatane®)
- Second generation retinoids
- For pustular and erythrodermic psoriasis
- Etretinate withdrawn from US market- 1998
- Acitretin= active metabolite of etretinate
- Reserved for treatment of severe forms of psoriasis due to side effects.

Soriatane : Dosage

- Usual dose: 25-50mg/day as single dose
- Dosage form: 10mg, 25mg capsules

Soriatane : Precaut



- Avoid in severe liver and kidney dz
- Avoid in patients with h/o alcohol dz
  - ETOH = reverse metab to etretinate
- Teratogenic- CI in pregnancy
  - Contraception one month before treatment and at least 3 years after
- Monitor: serum lipids, LFTs, serum creatinine (problematic as alternatives have similar limitations)

Soriatane : Adverse Effects

- Peeling, drying skin
- Diffuse alopecia
- Nail changes
- Sticky, clammy skin
- Muscle pain
- Calcification of ligaments

Soriatane

Hepatotoxicity	33% of patients had an elevation of AST (SGOT), ALT (SGPT) or LDH Black Box Warning
Alopecia	50-75% of patients
Mucocutaneous	50-75% skin peeling 25-50% dry skin 25-50% pruritus 23% dry eyes
Lipid Metabolism	66% increase in triglycerides 33% increase in cholesterol 40% reduction in HDL

Topical Retinoids

- Tazarotene (Tazorac®)
  - Third generation retinoid
  - Stable plaque psoriasis (up to 20% of body surface area involvement)
  - Severe facial psoriasis
  - Water based emollient gel or cream

Tazarotene (Tazorac®)

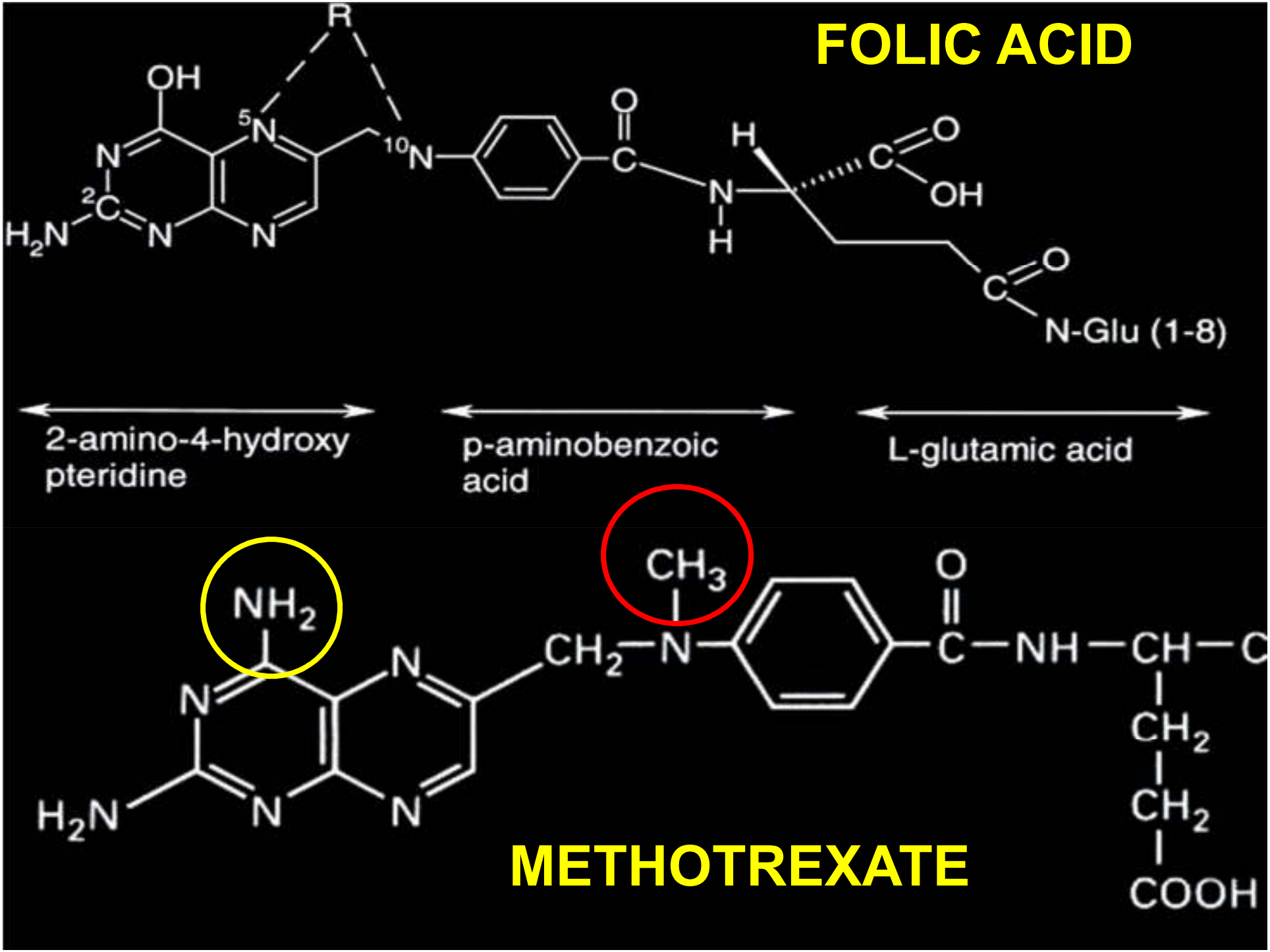
- Apply once daily x12 weeks
- AE: pruritus, burning, erythema
- ? More selective retinoid than Soriatane resulting in fewer ADRs
- Oral formulation pending at FDA

Counseling points

- Apply a moisturizer to the skin before using the Tazorac; it can dry out the skin.
- Apply it once per day about 30 minutes before bedtime.
- Rub about a pea-sized amount only into each lesion; it can irritate normal skin.
- If it spreads to the unaffected skin, wash it off with water. Zinc oxide can protect the skin
- Apply sunscreen

Methotrexate

- For moderate-severe psoriasis non-responsive to topical treatment
- MOA:
  - binds to DHFR which leads to reduction of tetrahydrofolate, which inhibits pyrimidine synthesis. Pyrimidine is needed for formation of DNA base pairs, therefore decrease in DNA replication esp rapidly dividing cells as in skin
  - Induces apoptosis of activated T cells


FOLIC ACID
R
OH
5N
10N
N
2C
H2N
N
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C
N
H
H
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O
OH
C
O
N-Glu (1-8)
2-amino-4-hydroxy pteridine
p-aminobenzoic acid
L-glutamic acid
NH2
CH3
CH2
N
O
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CH2
CH2
COOH
METHOTREXATE

Response to Methotrexate

- Suppression of B cells and macrophages
- Induces T-cell apoptosis
- Suppresses IL-1 and IL-8 production by peripheral blood mononuclear cells
- Reduces T cell production of interferon-gamma and TNF

Methotrexate: Precautions

- Contraindicated:
  - Pregnancy, lactating mothers
  - Renal & liver problems
  - Preexisting severe anemia, leukopenia, thrombocytopenia
  - Alcoholics
  - Active infectious disease

Methotrexate: Dosage

- Initial: 2.5-5mg q12h x3 doses qweek
- Titrate up weekly by 2.5mg increments [if blood counts (weekly then monthly) and LFTs (q4 month)allow] until symptoms respond
- Injections: IM or SQ
  - Max: 50mg/week, but some 75mg/week

Methotrexate: Adverse Effects

- Headache, chills, fever, fatigue, abdominal pain, nausea, vomiting, dizziness
- Pruritus, alopecia, urticaria, ecchymosis, sunburn (phototoxicity)
- Osteopathy- rare & at low doses
- Pulmonary fibrosis- CXR yearly
- Obtain liver biopsy after each 1.5gm
- Folate rx on days NOT taking MTX

Cyclosporine

- For psoriatic lesions resistant to other therapies
- MOA: prevention of IL-2 transcription, prevention of primary T-cell activation and reduction of T cell cytokines.

Cyclosporine: Dosage

- Oral Cyclosporine Microemulsion: Neoral
- Capsules, solution
- Initial: 2.5 mg/kg/day split BID x4 wks
- May increase dose at 2 week intervals of ~0.5 mg/kg/day increments
- Max: 5 mg/kg/day
- Relapse:
  - 6 weeks (50%)-16 weeks (75%)

Cyclosporine:Adverse Effects

- Headaches, paresthesias, flu-like symptoms, abdominal pain, nausea.
- Hypertension
- Nephrotoxicity:acute ↓ blood flow; chronic form α dose and duration
- Neurotoxicity
- Hepatoxicity
- Hyperglycemia
- Should be used as short term therapy (<1 year) to avoid further adverse effects (gingival hyperplasia, hyperlipidemia, hirsutism, etc).

Phototherapy

- Used over 100 years for moderate-severe psoriasis
- UVA (315-400 nm), UVB (290-315 nm)

- 313 nm = most effective wavelength for psoriasis

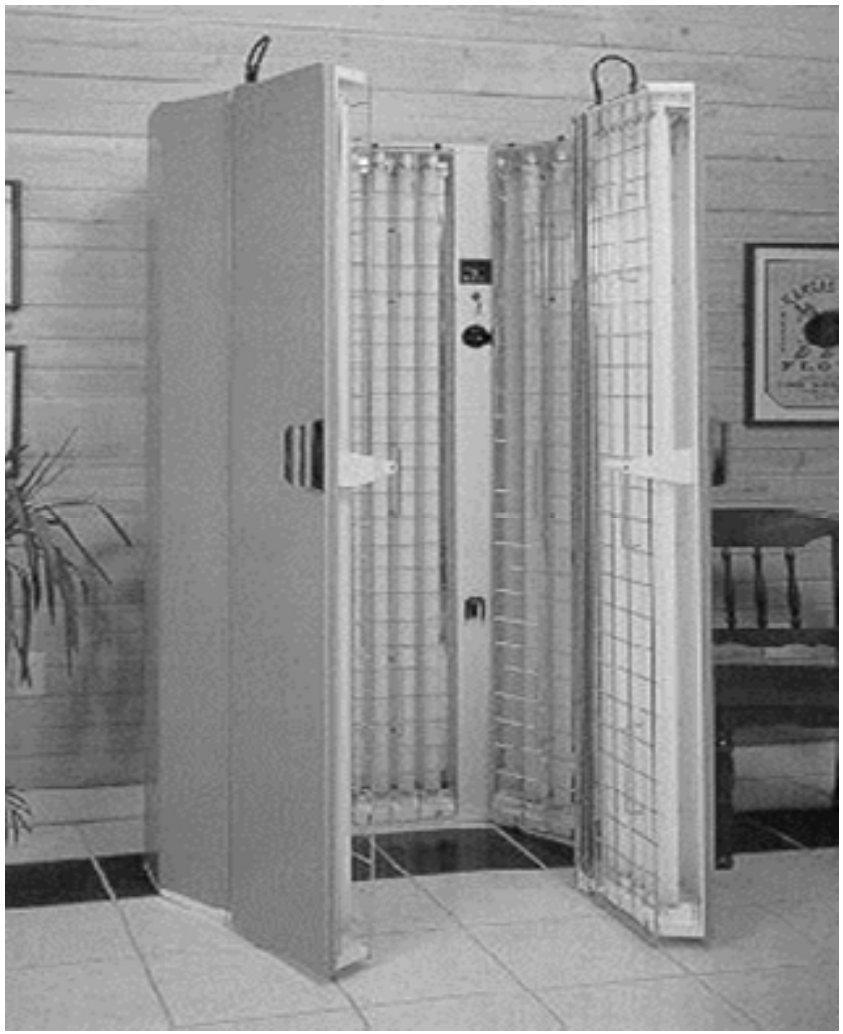
Phototherapy

- Ultraviolet B
  - Relatively non-toxic
  - Can be used as a single-agent
  - Usually combined with lubricants
  - Ingram's regimen (Anthralin)
  - Goeckerman's regimen (Tar)

Phototherapy

Phototherapy

Phototherapy



Phototherapy

PUVA

- PUVA= Psoralen + Ultraviolet A
- Theories of MOA:
  1. Psoralen intercalates into DNA, inhibiting DNA replication and thus, inhibiting epidermal cell hyperproliferation
  2. Free radical formation damages cell membrane, cytoplasmic contents and nucleus of epidermal cells…inhibiting growth of cells.
  3. Increased apoptosis of activated T-cells

Oral PUVA

- Psoralen = “P” in PUVA = a photosensitizer
- Methoxsalen (Oxsoralen-Ultra, 8-MOP)
- 10 mg capsules
- Given 2 hours before UVA irradiation
- Symptomatic control of severe, recalcitrant disabling psoriasis, not responsive to other therapy after biopsy confirmed diagnosis

PUVA

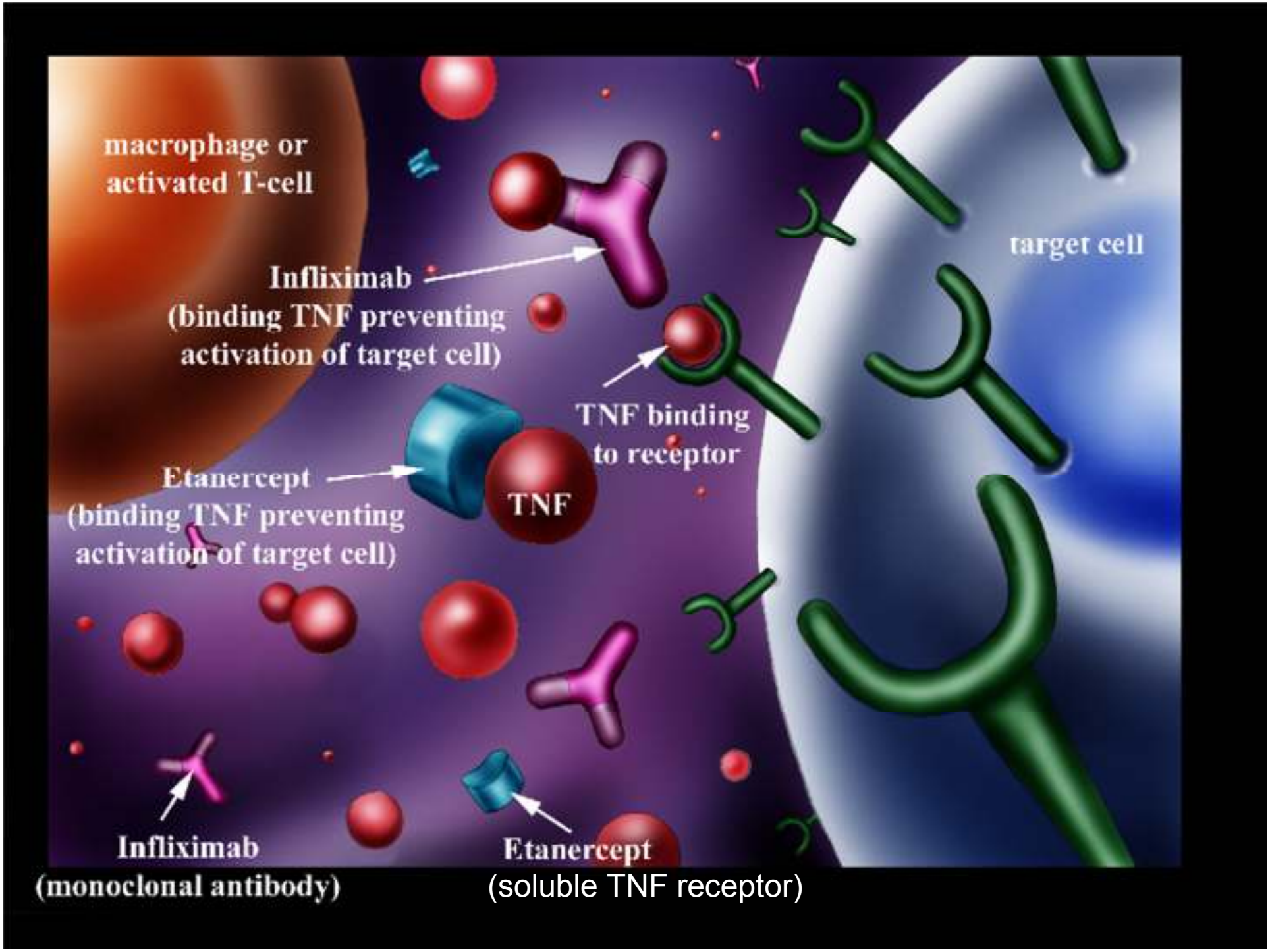
- Phototoxicity
  - Related to quantity of psoralen and amount of UVA applied
  - Reaction peaks 48-72hrs after treatment
  - Erythema, blistering, edema
- Administer 2-4x/ week
- Tanning occurs, so gradually increase dose of UVA
- ~20 sessions over 4-8 weeks clears lesions

Oral PUVA: Adverse Effects

- Constipation, diarrhea, nausea, vomiting, pruritus, delayed-onset erythema
- Oral psoralens distribute to entire body and eyes: protect eyes and skin from sunlight 6 hours after treatment
- Long-term: premature aging, cataracts, skin cancer (rare)

First Generation Biologicals

- Infliximab & Etanercept: immunomodulators
- used initially for rheumatoid arthritis; work against TNF-alpha


macrophage or
activated T-cell
target cell
Infliximab
(binding TNF preventing
activation of target cell)
TNF binding
to receptor
Etanercept
(binding TNF preventing
activation of target cell)
TNF
Infliximab
(monoclonal antibody)
Etanercept
(soluble TNF receptor)

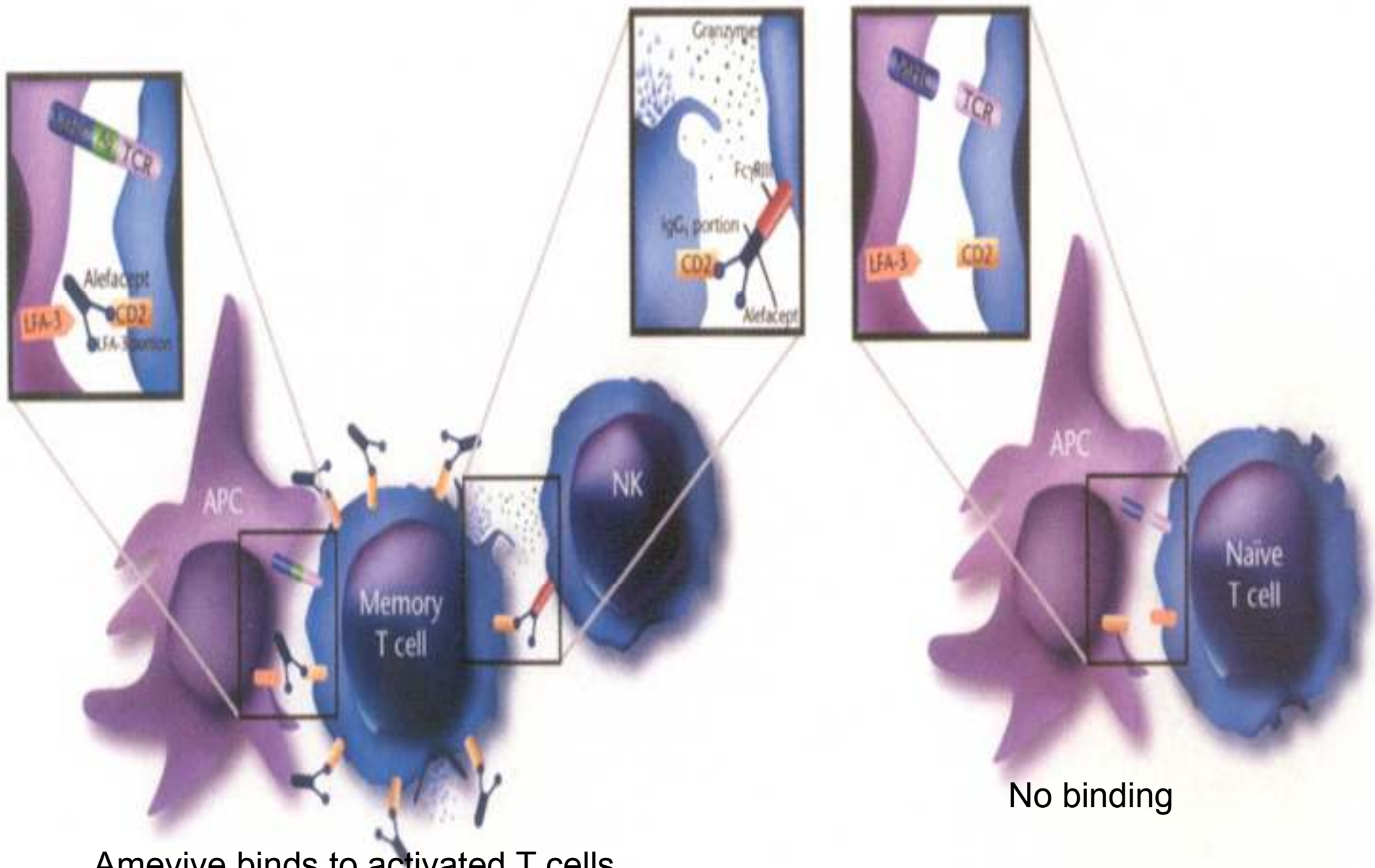
TNF Inhibitors

- Both Remicade and Enbrel are quite effective (>75% of psoriatics respond) even if only skin is affected
- Enbrel SQ once* or twice weekly; Remicade IV

  0, 2 and 6 weeks
- Concerns: exacerbate MS and TB, induce SLE and CHF, palliative not curative

New Therapies

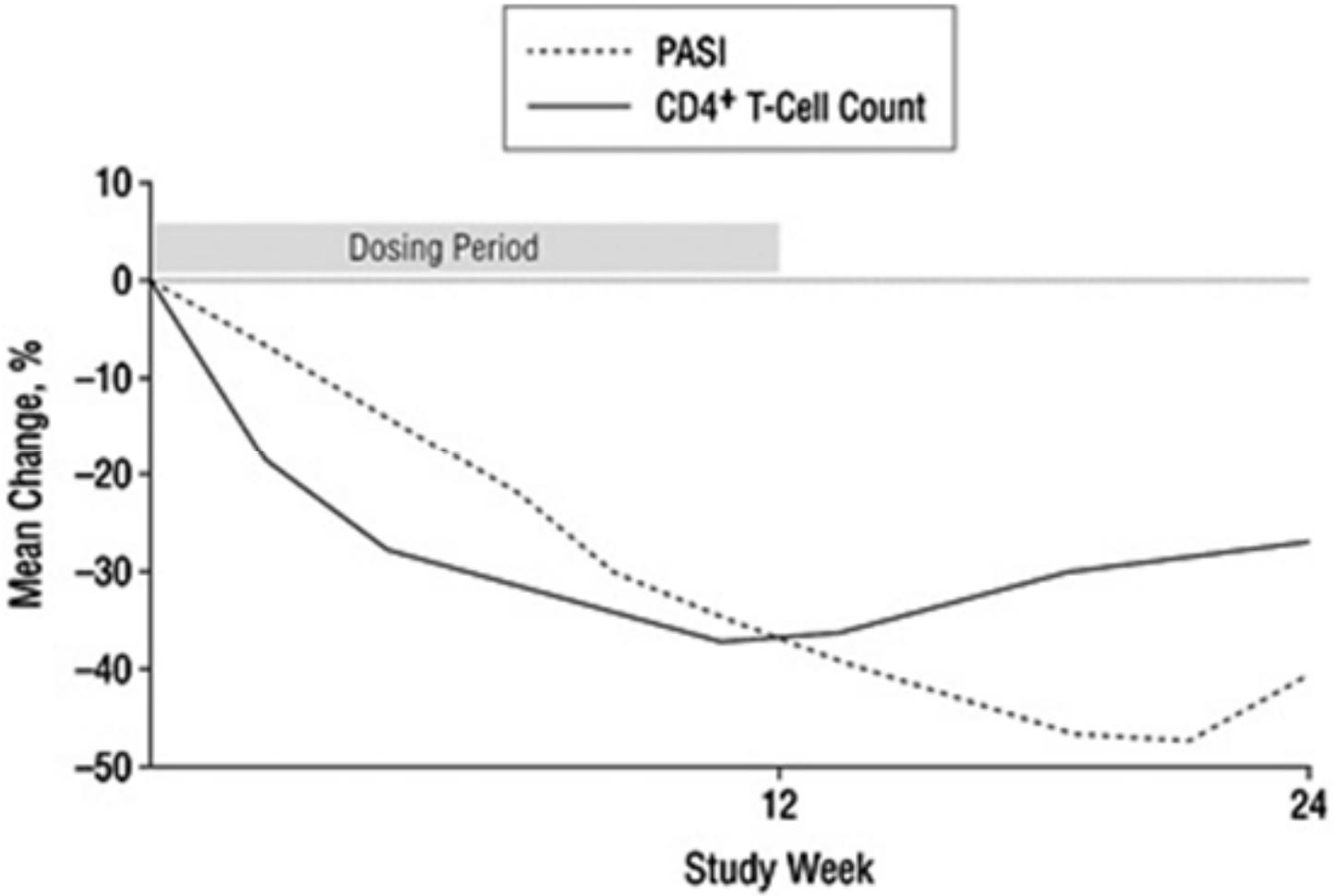
- Alefacept (Amevive)
  - Inhibits CD45RO+ memory effector T lymphocytes, by binding to their CD2 receptor also leads to apoptosis
  - Administered IV or IM qweek x12 wks
  - AE: dizziness, chill, nausea, cough



Amevive binds to activated T cells

No binding

Psoriasis Area Severity Index (PASI) and CD4+ T-cell count



Amevive response

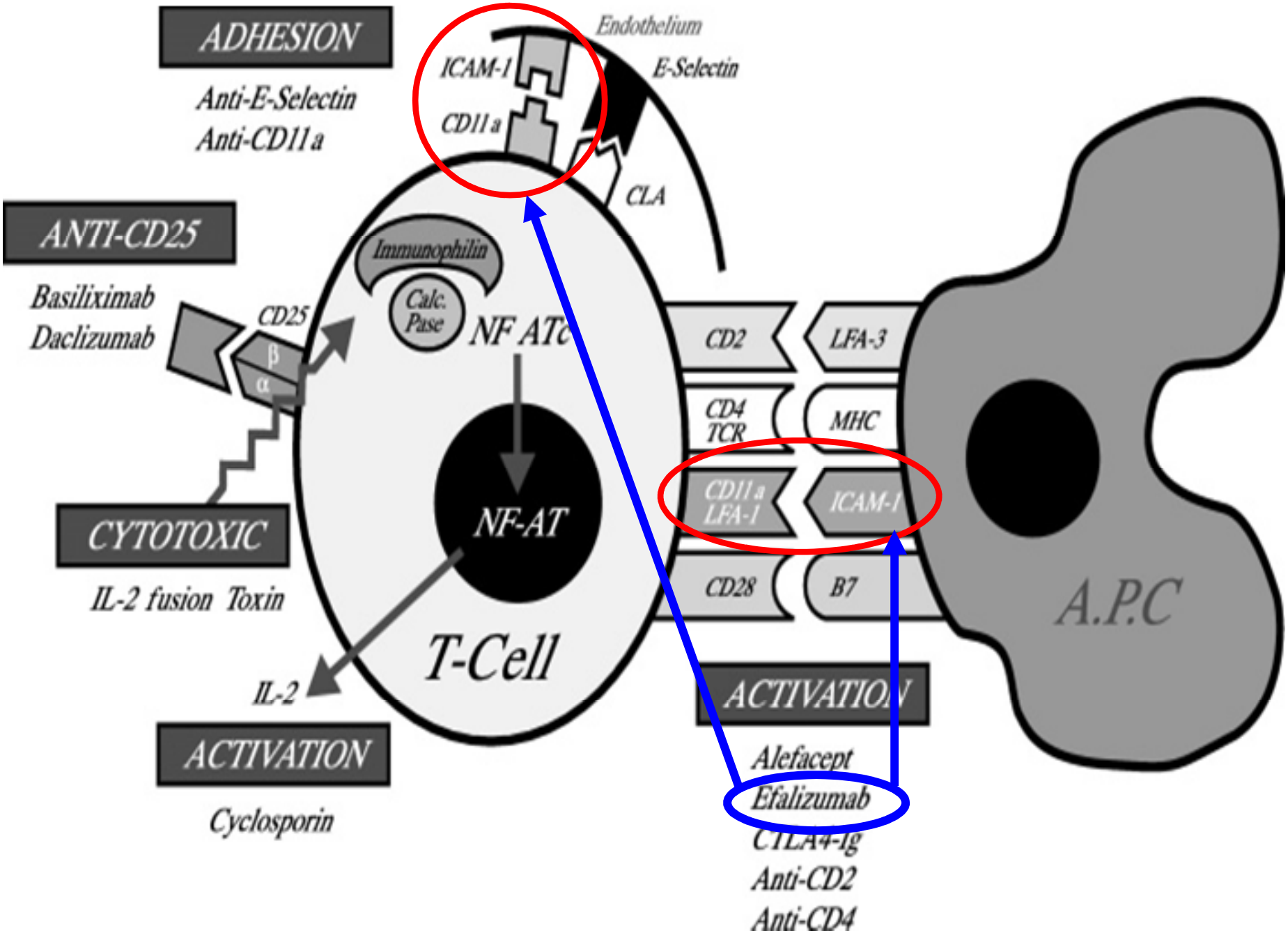
- The recommended dose of AMEVIVE® is 7.5 mg given once weekly as an IV bolus or 15 mg given once weekly IM injection (F=63%).
- The recommended regimen is a course of 12 weekly injections (t1/2 = 270 hrs)
- Retreatment with an additional 12-week course may be initiated provided that CD4+ T lymphocyte counts are within the normal range, and a minimum of a 12-week interval has passed since the previous course of treatment. Data on retreatment beyond two cycles are limited
- No flares reported

Amevive Cautions

- May induce malignancies; avoid in patients with systemic malignancy
- May lead to infections
- Has been associated with liver damage esp in ETOH abuse

Raptiva

- Efalizumab (*Raptiva*) is a humanized monoclonal antibody of CD11a that works by blocking T-cell binding and trafficking into the dermis and epidermis.
- FDA approved October 29, 2003


ADHESION
Anti-E-Selectin
Anti-CD11a
ICAM-1
CD11a
Endothelium
E-Selectin
CLA
ANTI-CD25
Basiliximab
Daclizumab
CD25
β
α
Immunophilin
Calc. Pase
NF ATc
NF-AT
CYTOTOXIC
IL-2 fusion Toxin
T-Cell
IL-2
ACTIVATION
Cyclosporin
CD2
LFA-3
CD4
TCR
MHC
CD11a
LFA-1
ICAM-1
CD28
B7
A.P.C
ACTIVATION
Alefacept
Efalizumab
CTLA4-Ig
Anti-CD2
Anti-CD4

Raptiva

- Indicated for adults with mod/severe chronic psoriasis
- SQ admin, priming dose 0.7 mg/kg (to lessen 1st dose reax of HA, fever, N&V) then 1 mg/kg q wk.
- ADR: infxns, malignancy, ↓ platelets, worsen psoriasis, avoid immunizations
- Use beyond one year unknown, re-start of Tx often poor response=suppressive not remittive like Amevive