Psoriasis and other skin conditions

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Psoriasis

Diagnosis, treatment and mapping the patient journey

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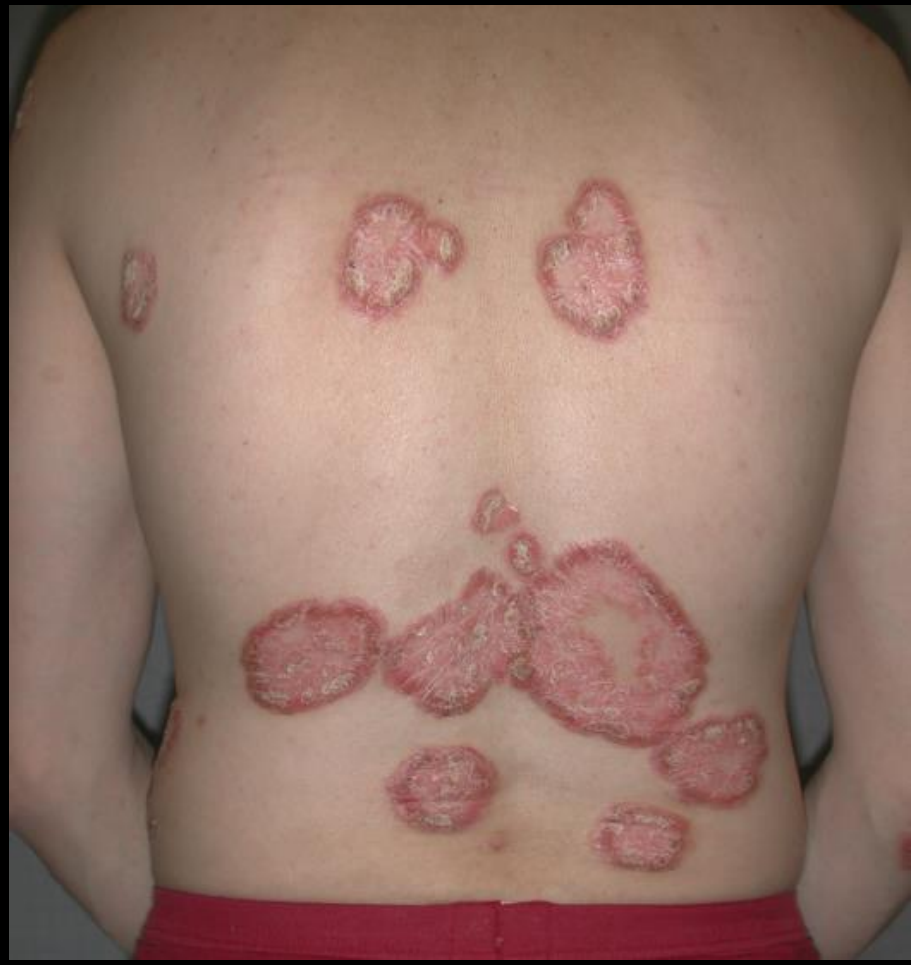
Declaration of Interest

Clinical trials conducted at Sinclair Dermatology, June 2015

Sponsor	Clinical trial title	Start date	Forecast end date	Completed by June 30 2016?
Novartis Pharmaceuticals	A multicenter, double-blinded, randomized withdrawal extension study of subcutaneous secukinumab in pre-filled syringes to demostrate long-term efficacy, safety and tolerability up to 4 years in subjects with moderate to severe chronic plaque-type psoriasis completing preceding psoriasis phase III studies with secukinumab	Dec 2011	2017	No
Novartis Pharmaceuticals	A randomised, double-blinded, placebo-controlled, multicenter study to demonstrate the efficacy at 16 weeks of secukinumab 150 and 300 mg s.c. and to assess safety, tolerability and long term efficacy up to 132 weeks in subjects with moderate to severe palmoplantar psoriasis	22 Oct 2013	2016	No
Novartis Pharmaceuticals	A randomised, double-blinded, placebo-controlled, multicenter study to demonstrate the efficacy at 16 weeks of secukinumab 150 and 300 mg s.c. and to assess safety, tolerability and long term efficacy up to 132 weeks in subjects with moderate to severe nail psoriasis	24 Sep 2014	2016	No
Novartis Pharmaceuticals	A 52-week, multicenter, randomized, double-blinded study of subcutaneous secukinumab to demonstrate effocacy as assessed by Psoriasis Area and Severity Index at 16 weeks of treatment compared to ustekinumab and to assess long-term safety, tolerability and efficacy in subjects with moderate to severe plaque psoriasis	22 May 2014	2016	No
Merck	A 64-Week, Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Design Study to Evaluate the efficacy and Safety/Tolerability of Subcutaneous SCH 900222/MK-3222, Followed by an Optional Long Term Safety Extension Study, in subjects With Moderate-to-Severe Chronic Plaque Psoriasis (Protocol No. MK-3222-010)	26 Apr 2013	2019	No
Celgene	A Phase 3B, multicenter, randomised, placebo-controlled, double-blind, double-dummy, study of the efficacy and safety of apremilast (CC-10004), Etanercept, and placebo in subject with moderate to severe plaque psoriasis	13 Feb 2014	2016	Yes
Coherus Biosciences	A Double-blinded, randomised, parallel-group, active-control study to compare the efficacy and safety of CHS-0214 versus Enbrel in subjects with chronic Plaque Psoriasis (CHS-0214-04) (RaPsOdy)	23 Oct 2014	2016	No
Janssen Research & Development	A Phase 3, multicenter, randomized, double-blind, placebo and active comparator-controlled study evaluating the efficacy and safety of Guselkumab for the treatment of subjects with Moderate to severe plaque-type psoriasis	19 Feb 2015	2018	No
Regeneron	A randomised, double-blind, placebo-controlled study to demonstrate the efficacy and long-term safety of dupilumab in adult patients with moderate-to-severe atopic dermatitis	20 Mar 2015	2018	No
Medimmune	A Phase 2b, randomized, double-blinded, placebo-controlled, dose-ranging study to	14 Apr 2015	2018	Yes

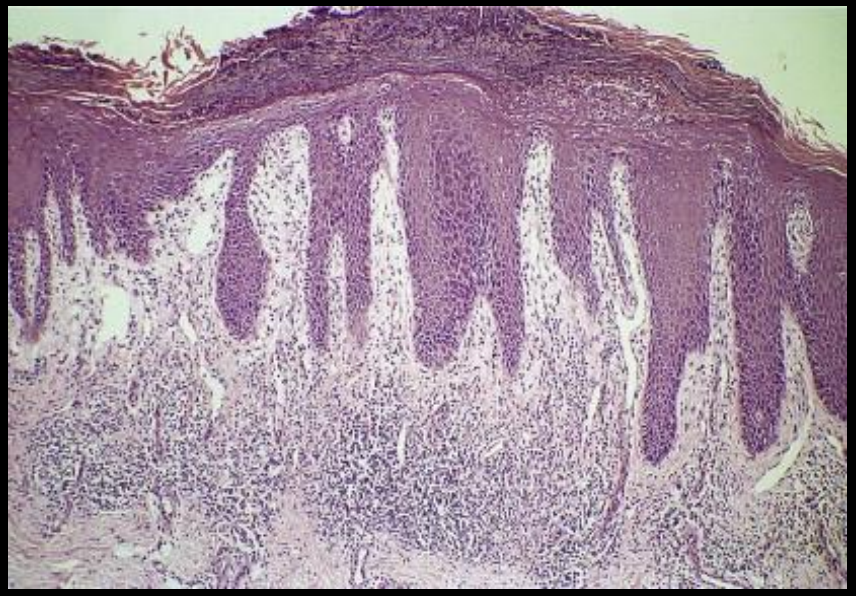
Overview

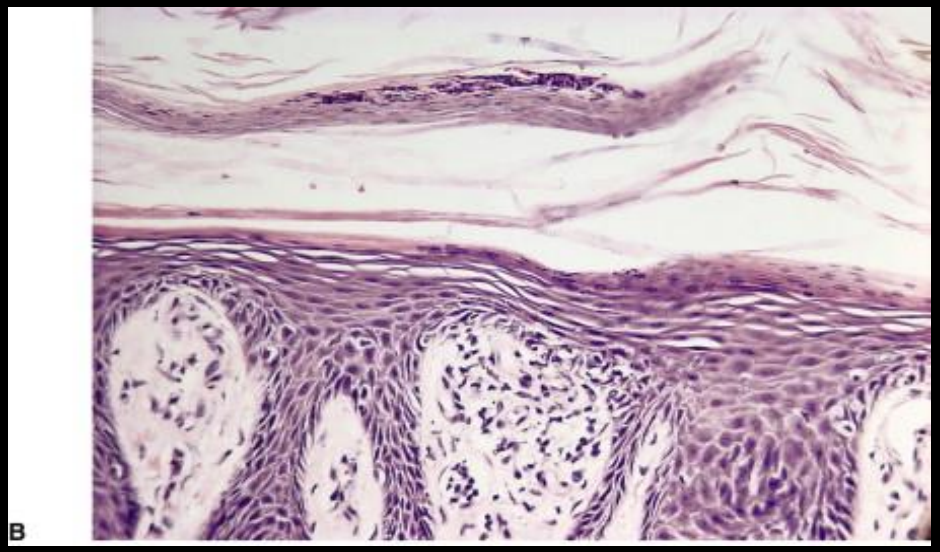
- Prevalence 2%
- Two age peaks:
  - 20–30 YO
  - 50–60 YO
- 2/3 mildly affected
- Chronic, relapsing
- 30% itchy
- Significant quality of life Δ
- Psoriatic arthritis 5–30%



Overview

- Inheritance important
- T cell immunity a key
- Cytokines induce neutrophils
- Rapid epidermal turnover
- Altered epidermal function
- Systemic effects (joints, metabolic)



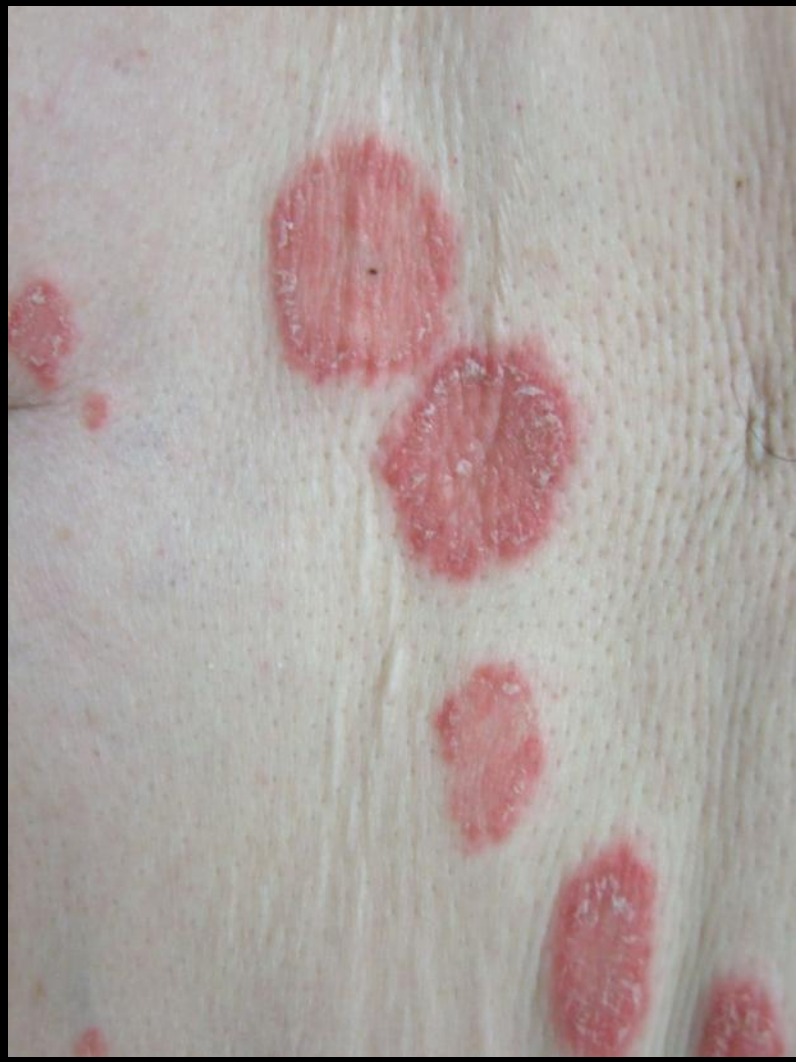


Genetics:

- Polygenic
- Twins: monozygotic vs dizygotic

Susceptibility genes:

- PSORS-1 locus = HLA Cw6 & corneodesmosin genes
- HLA Cw6:
  - 90% c early-onset psoriasis
  - 50% c late onset psoriasis
  - 7% normal population



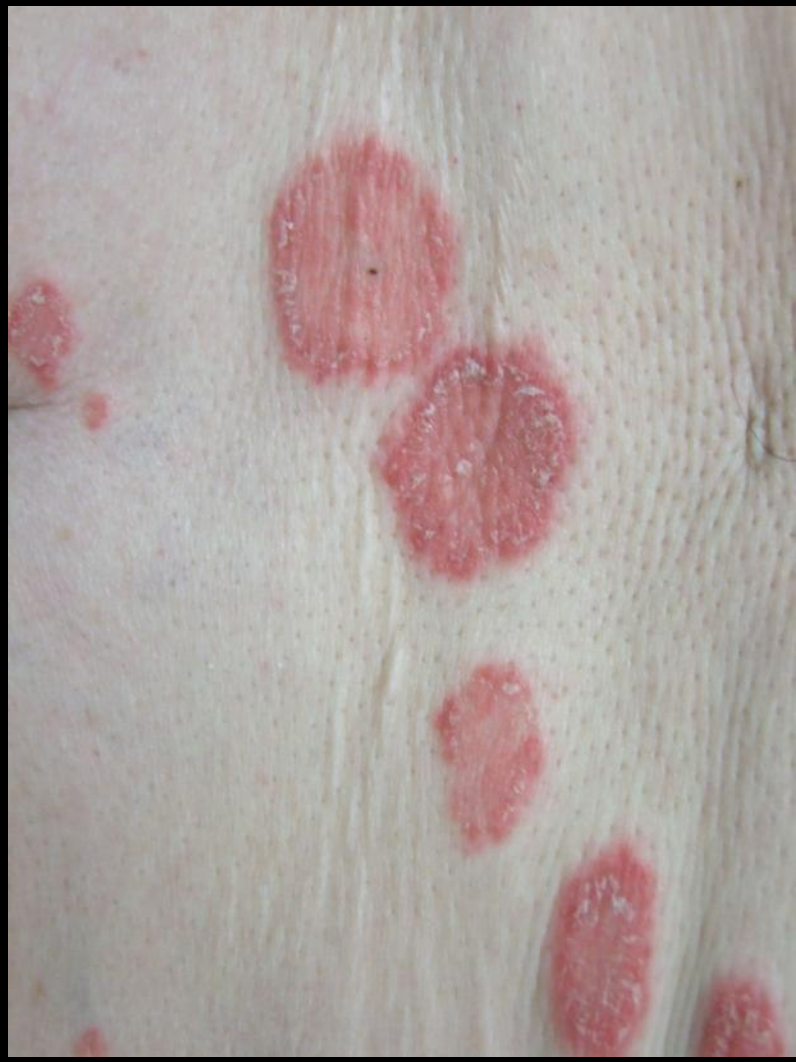
Genetics:

- PSORS-2: - recently identified:

  - Caspase recruitment domain family-14 (CARD14)
  - Mutant gene higher activation of NF-κB activating transcription factor

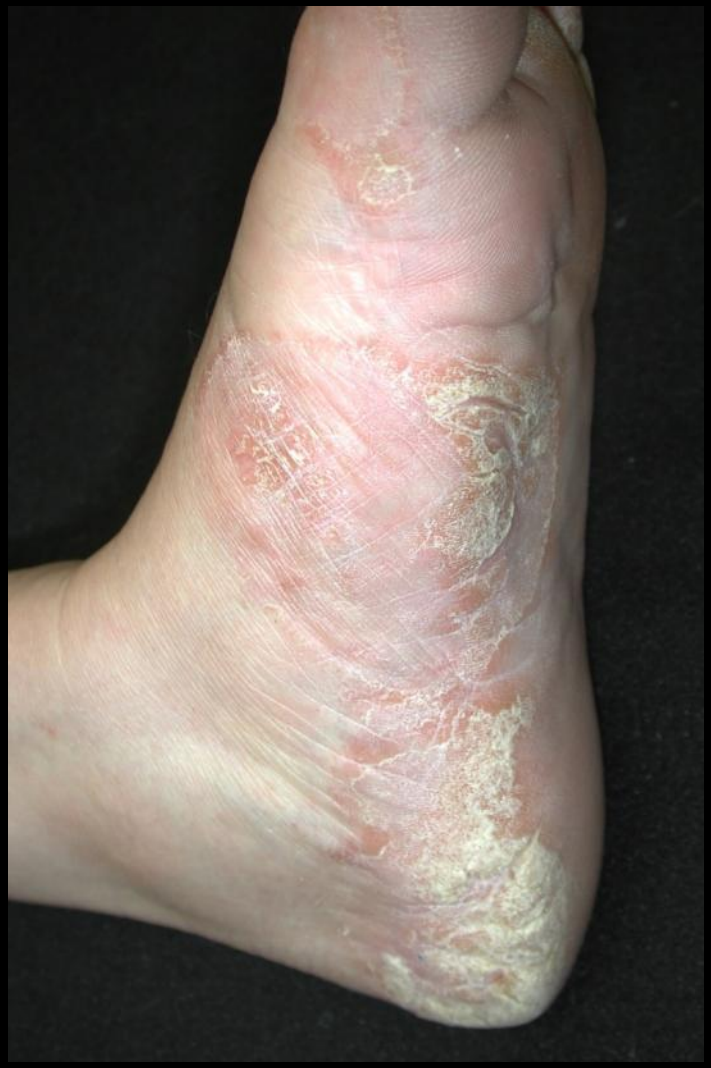
- Roles of genes for:

  - IL-12B & IL-12 receptor
  - IL-23A & IL-23 receptor
  - IL-4 to IL-13 gene cluster
  - ERAP1 (role in MHC class I processing)
  - And more



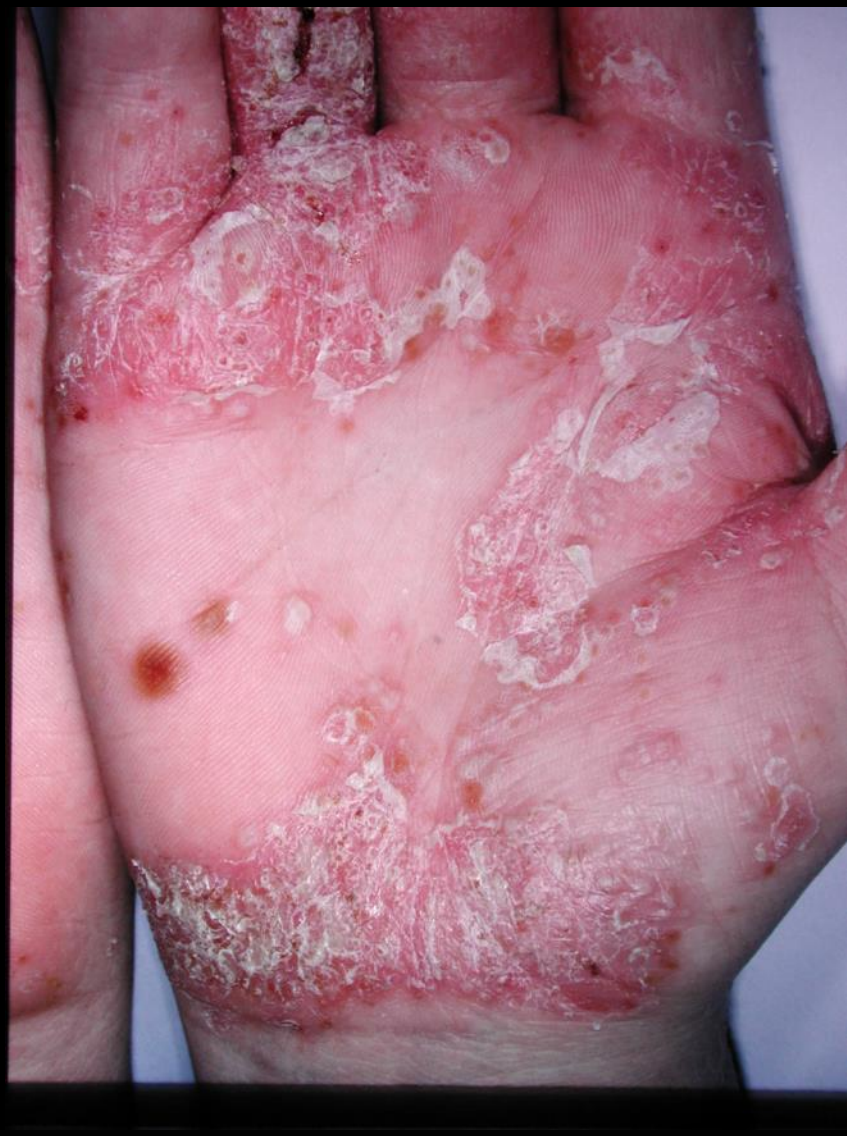
Genetics:

- *PSORS1* = most prevalent (@ 50% of heritability)
- *PSORS2*, *PSORS3* & *PSORS4* associated c gene loci of susceptibility for:
  - Metabolic syndrome
  - Type 2 diabetes
  - Familial hyperlipidemia
  - Cardiovascular disease



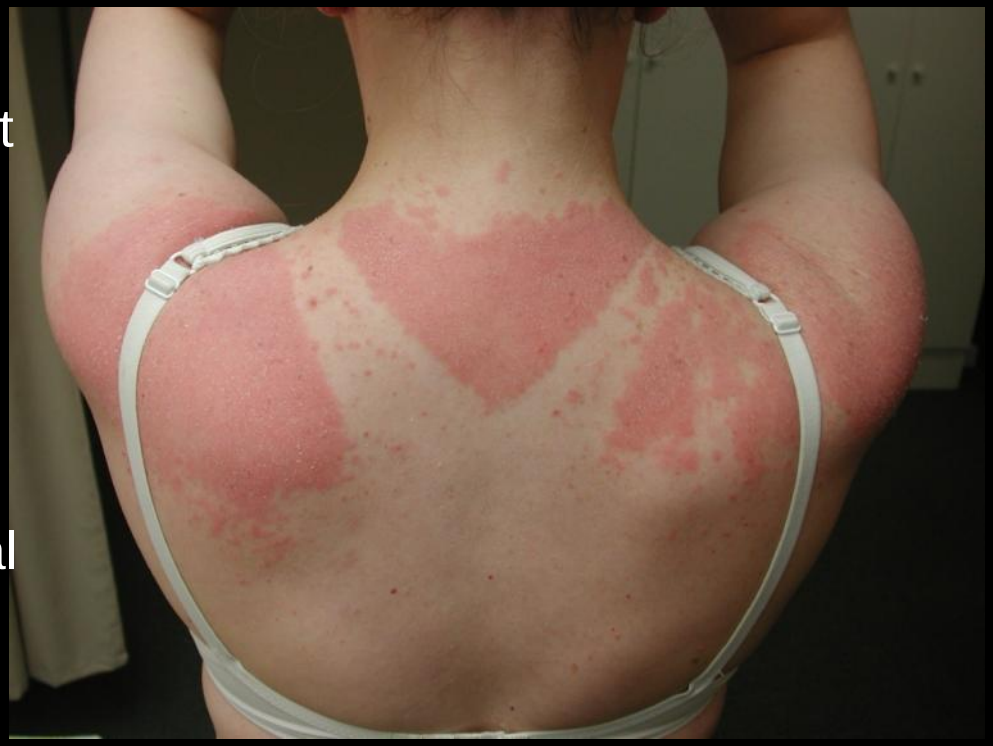
Immunology:

- T cell driven
  - T_H1 response (macrophage driven intracellular immunity)
  - T_H17 response (extracellular immunity & auto-immunity)
- Key cytokines
  - IFNγ
  - TNFα
  - IL-17
  - IL-23
  - More



Precipitating / aggravating factors

- Infection
  - Streptococcal sore throat
  - HIV
- Drugs
  - Lithium
  - B-blockers
  - Antimalarials
  - Corticosteroid withdrawal
- Physical injury
  - Scratching
  - Sunburn
- Stress
- Excessive alcohol



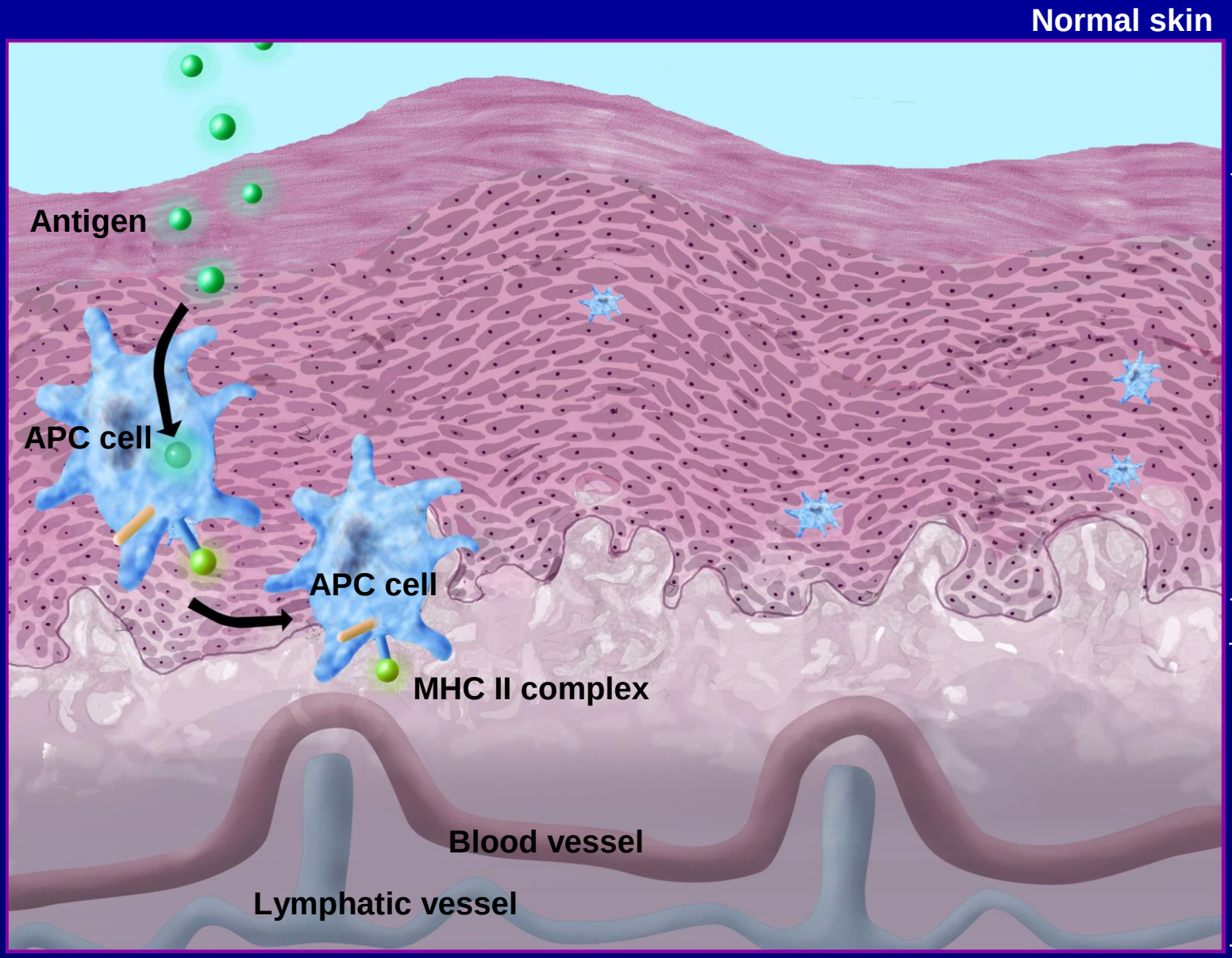
A Changing View of Psoriasis Pathogenesis

- Previous view (pre-1990s)
- Abnormal keratinocyte growth and development
- Pathologic changes within cells causing hyperplasia

- New view (post-1990s)
- Immune system disorder
- Abnormal T-cell activation and migration and irregular cytokine cascade result in pathological changes in keratinocytes and angiogenesis

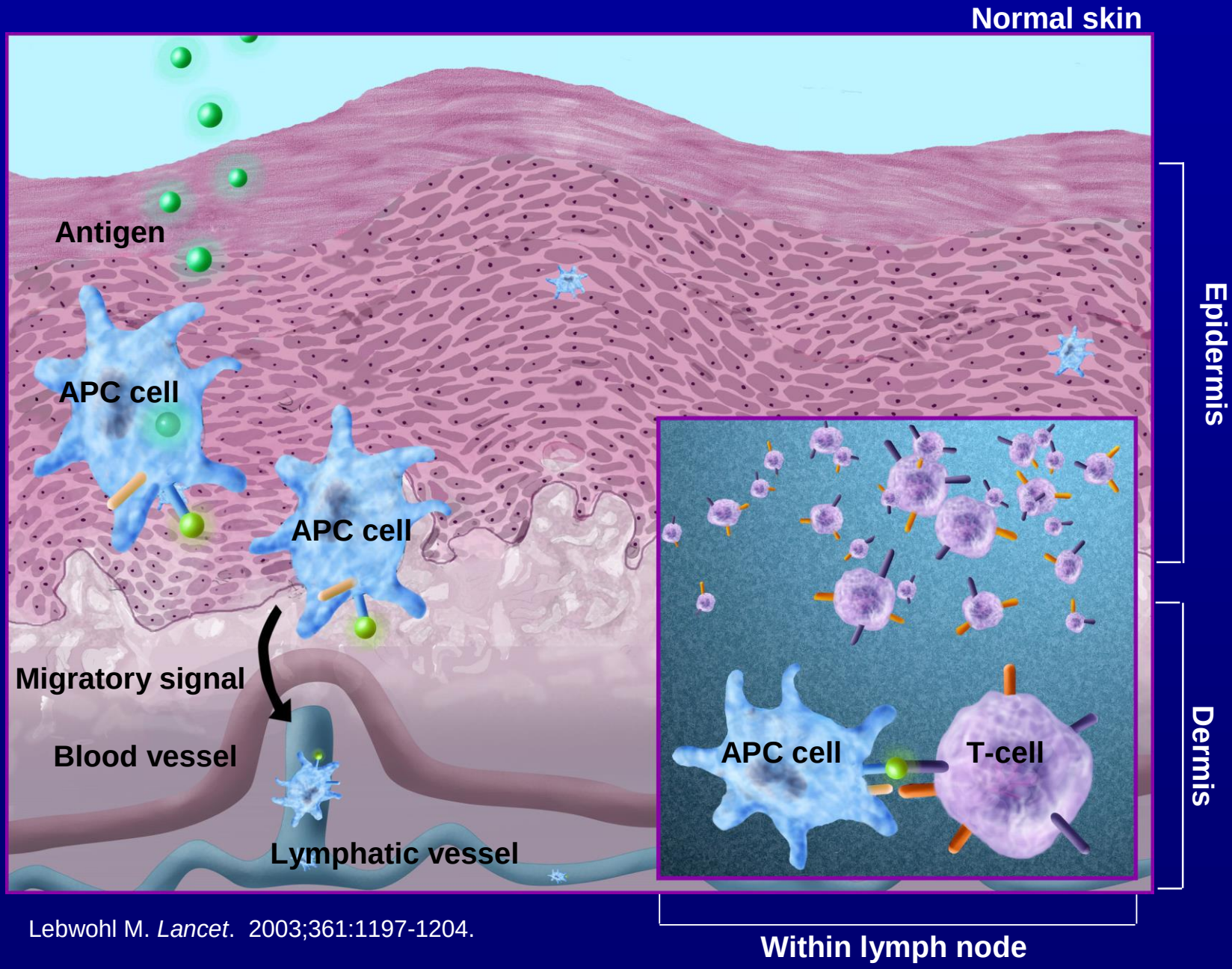
Krueger J. *J Am Acad Dermatol.* 2002;46:1-23.
Mehlis SL. *J Am Acad Dermatol.* 2003;49:S44-50.

Activation of Antigen-presenting Cells



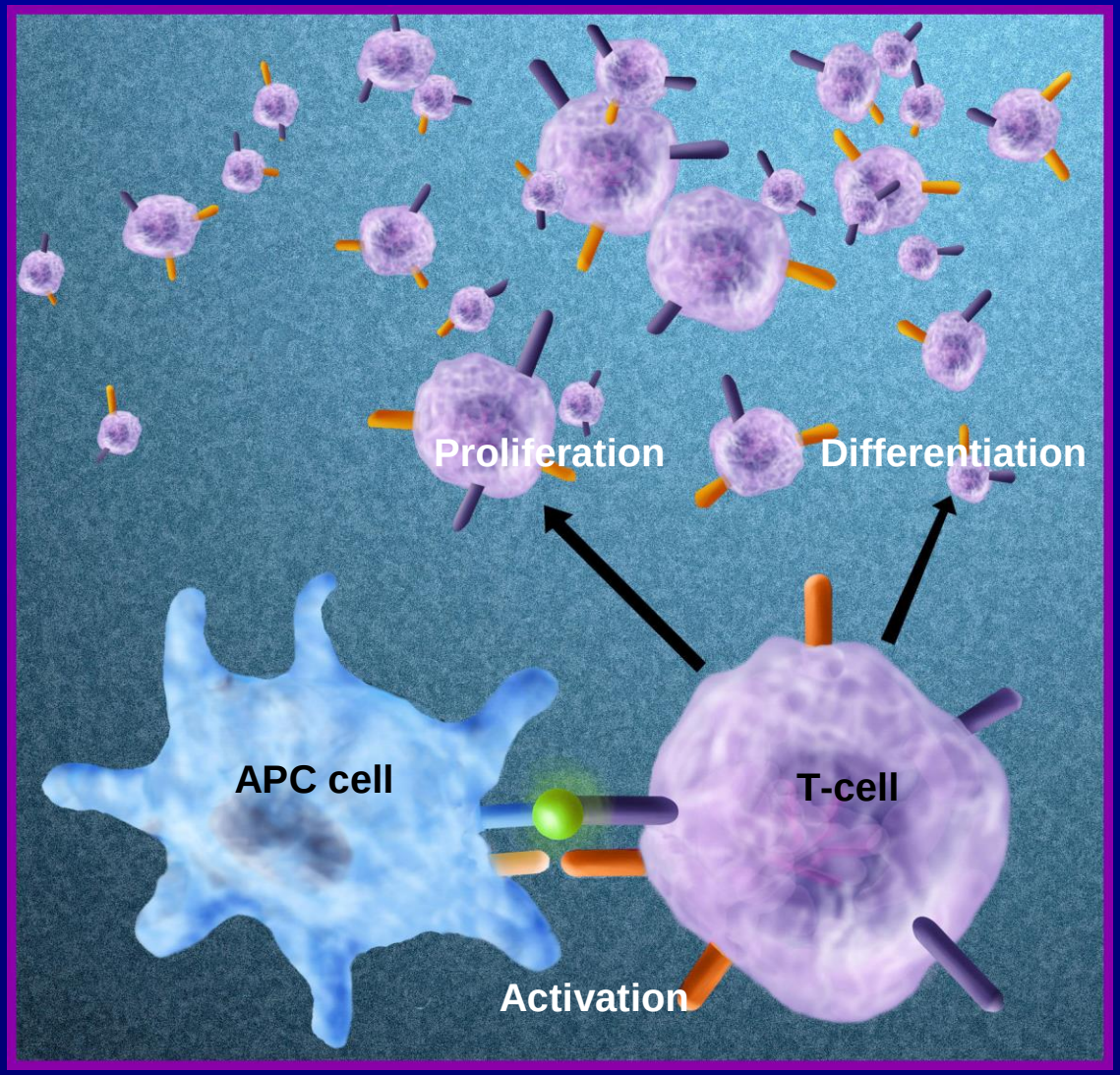
Lebwohl M. *Lancet*. 2003;361:1197-1204.

APC Migrates to Lymph Nodes



Lebwohl M. *Lancet*. 2003;361:1197-1204.

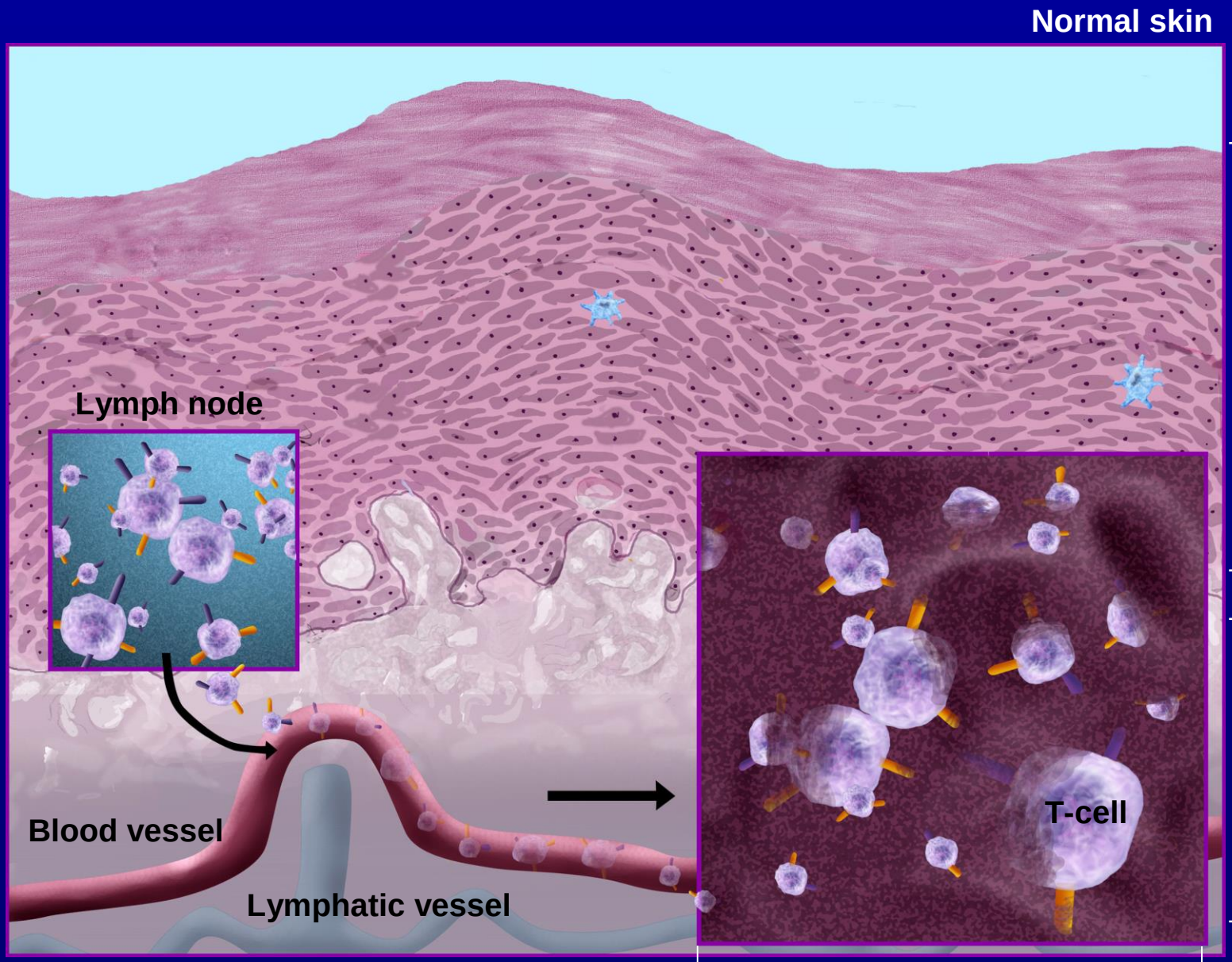
T-Cell Activation Within Lymph Node



Lebwohl M. *Lancet*. 2003;361:1197-1204.

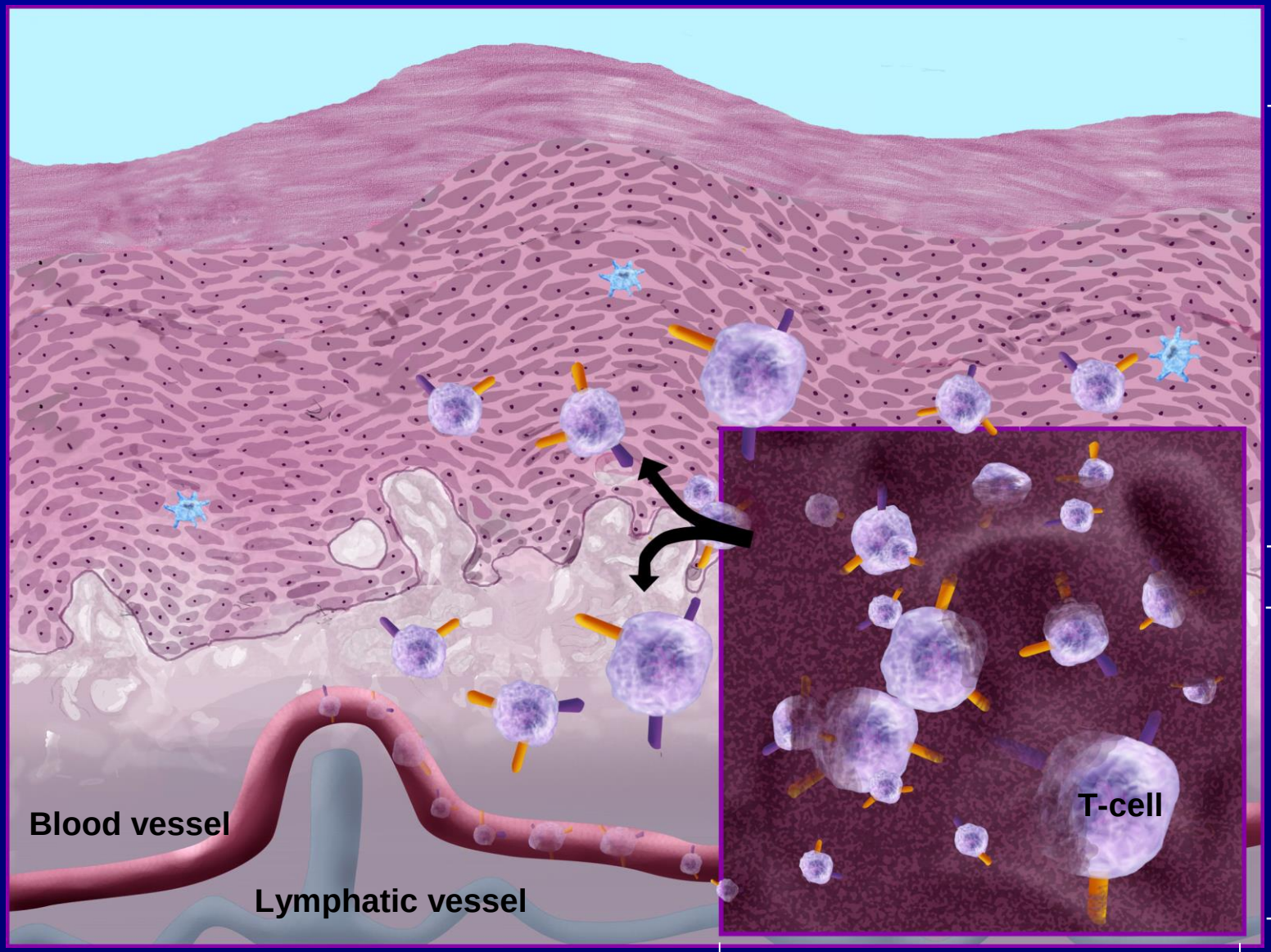
Krueger J. *J Am Acad Dermatol.* 2002;46:1-23.

T-Cell Circulates Through Blood Vessels



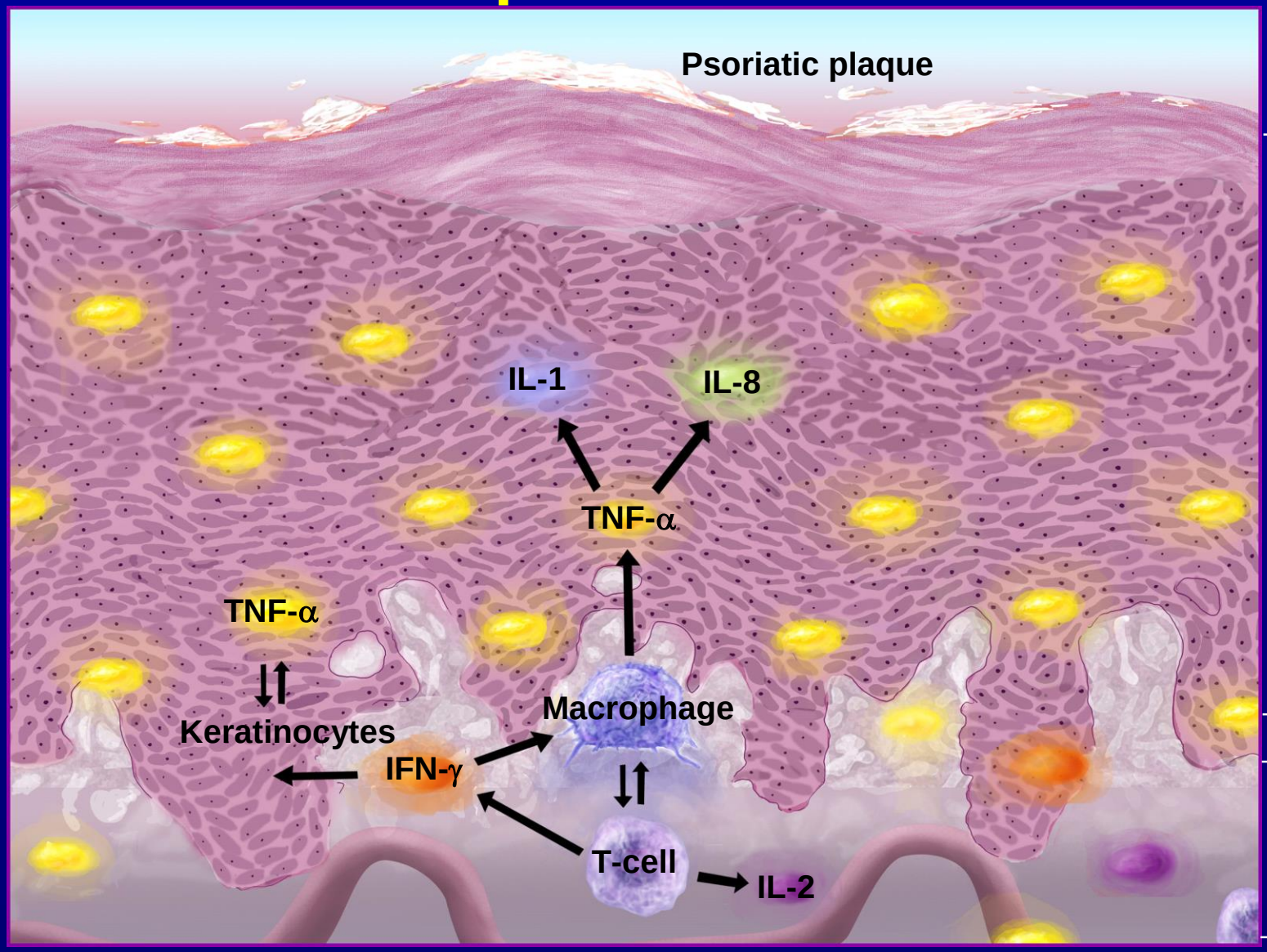
Lebwohl M. *Lancet*. 2003;361:1197-1204.

T-Cell Migrates into Dermis and Epidermis



Krueger J. *J Am Acad Dermatol.* 2002;46:1-23.

Overexpression of TNF-α and Psoriatic Plaque Formation



Lebwohl M. *Lancet*. 2003;361:1197-1204.

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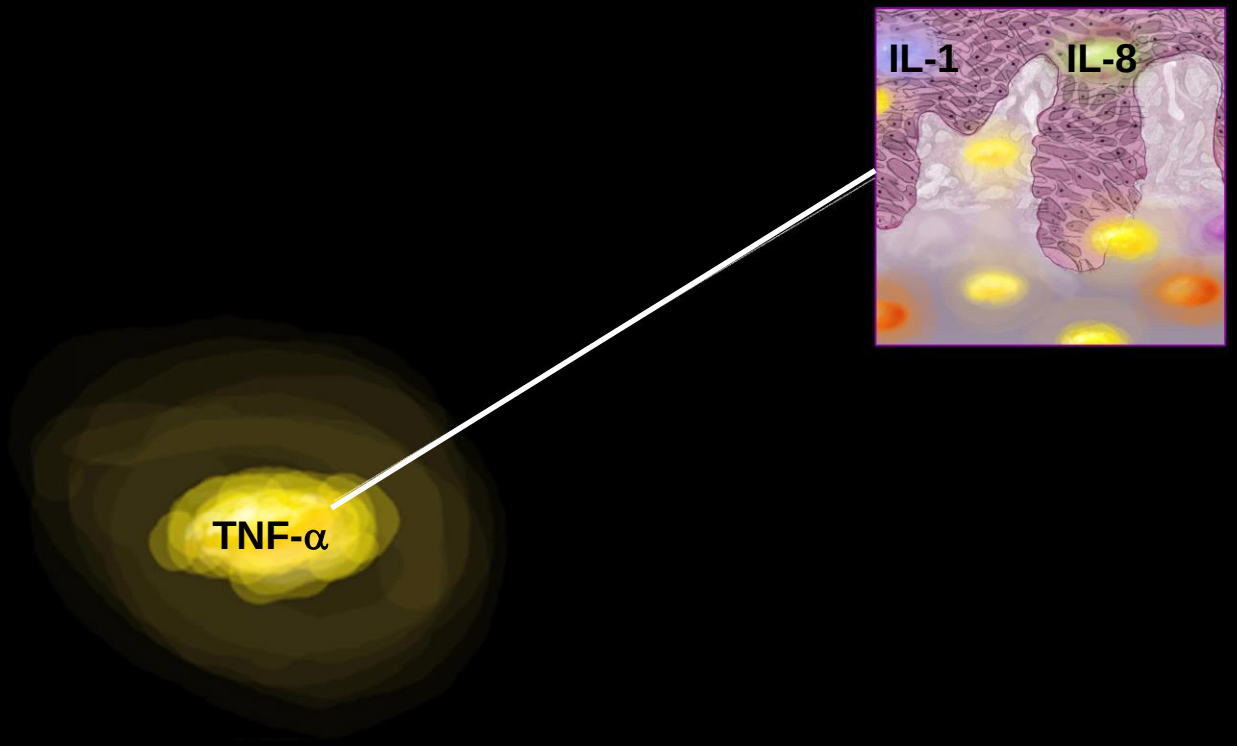
Victor FC. *Clin Dermatol*. 2003;21:392-397.

Roles of TNF-α in Psoriatic Plaque Formation



Stimulates proinflammatory cytokines including IL-1 and IL-8[1]

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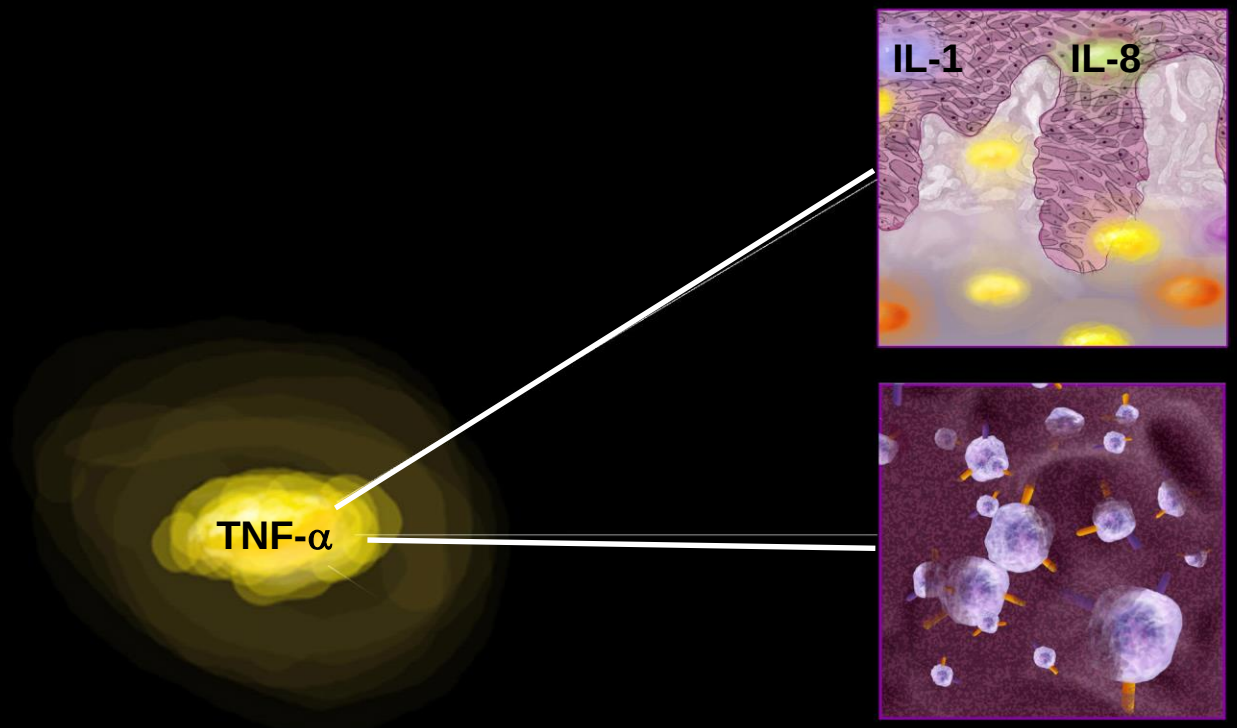
Roles of TNF-α in Psoriatic Plaque Formation



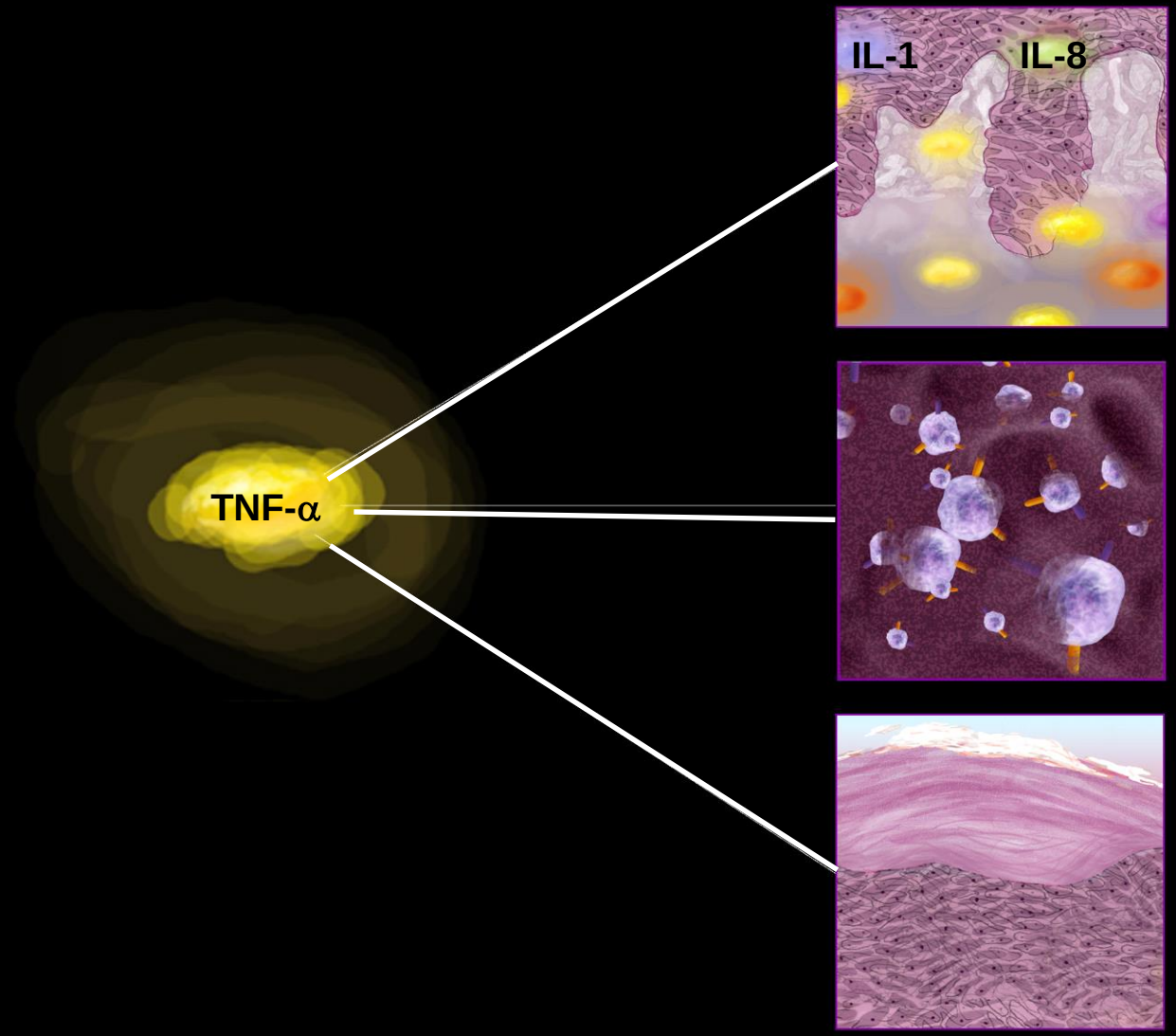
Stimulates proinflammatory cytokines including IL-1 and IL-8[1]

Induces vascular adhesion molecules necessary for the adhesion and migration of proinflammatory cells[2]

[1]Victor FC. *Clin Dermatol*. 2003;21:392-397.

[2]Terajima S. *Arch Dermatol Res*. 1998;290:246-252.

Roles of TNF-α in Psoriatic Plaque Formation



Stimulates proinflammatory cytokines including IL-1 and IL-8[1]

Induces vascular adhesion molecules necessary for the adhesion and migration of proinflammatory cells[2]

Promotes hyperproliferation of keratinocytes[3]

[1]Victor FC. *Clin Dermatol*. 2003;21:392-397.

[2]Terajima S. *Arch Dermatol Res*. 1998;290:246-252.

[3]Mehlis SL. *J Am Acad Dermatol*. 2003; 49 :S44-50

Psoriasis is a T-Cell–Mediated, Autoimmune Disorder

- **Major pathogenic findings in psoriasis are:**
  - Abnormal differentiation and hyperproliferation of keratinocytes
  - Infiltration of inflammatory components
- **Previous hypotheses**
  - Direct activation of epidermal keratinocytes by physical, chemical or ultraviolet injury
  - Subsequent release of cytokines and antigen-independent activation of T cells
- **Current understanding**
  - Persistent T-cell stimulation which drives abnormal keratinocyte proliferation and differentiation
  - A result of autoimmune, antigen-dependent mechanisms

Psoriasis Diagnosis

Types of psoriasis

- Plaque
- Guttate
- Erythrodermic
- Flexural
- Pustular
  - Localised
  - Generalised
- Local forms
  - Scalp
  - Nail
  - Flexural
  - Palmo-plantar

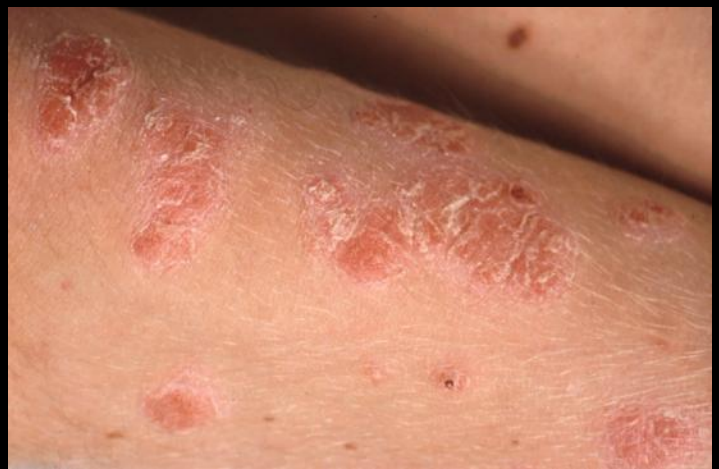
Nails
- Pitting
- Onycholysis
- Subungual hyperkeratosis
- Salmon spots

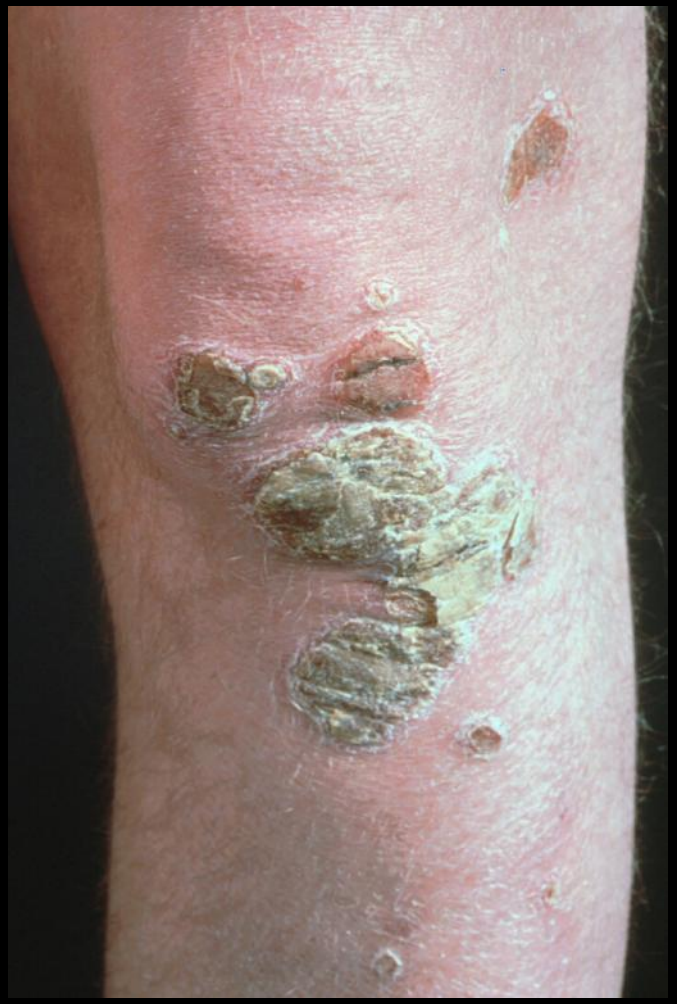
Arthritis
- Oligoarthritis
- Distal symmetrical polyarthritis
- Ankylosing Spondylitis
- Rheumatoid-like
- Arthritis mutilans

Psoriasis

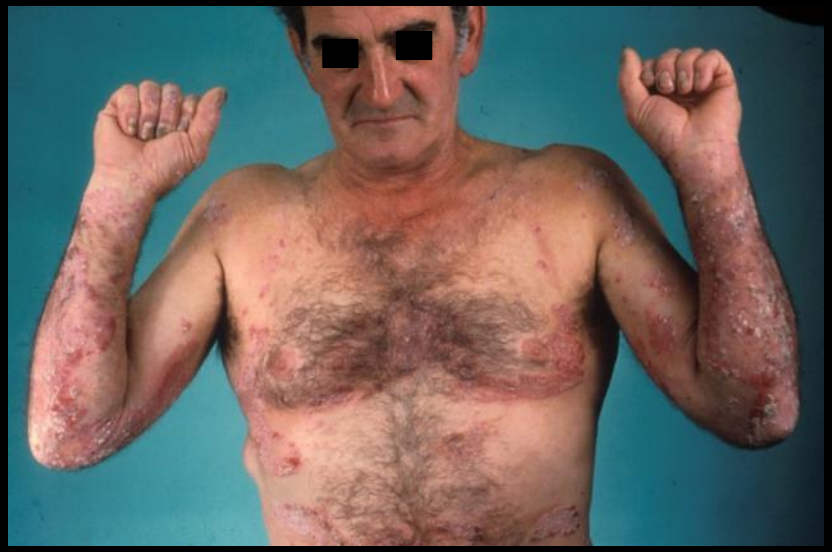
Plaques

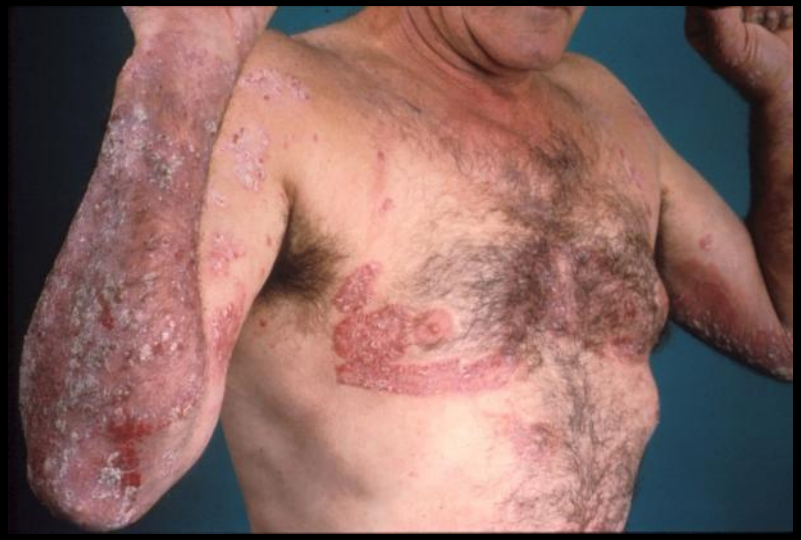
- Red
- Scaly
- Well demarcated
- Slightly itchy
- Often symmetrical





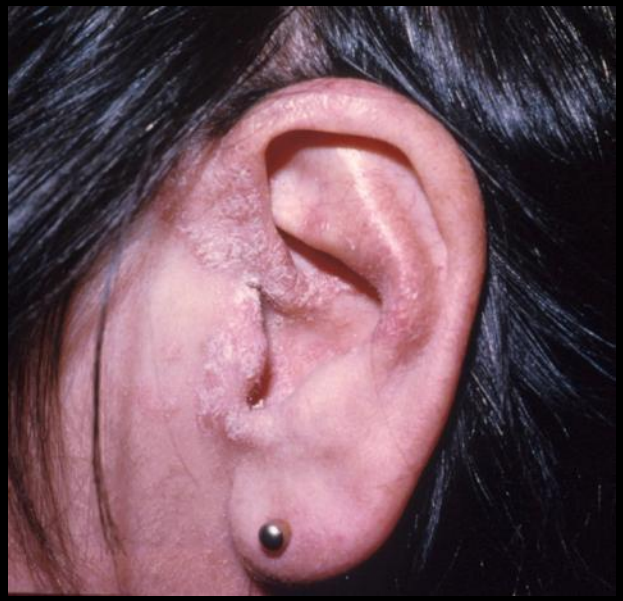
Psoriasis



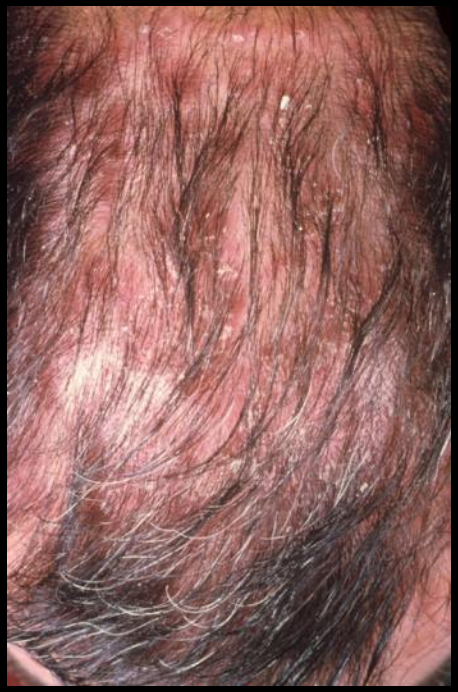


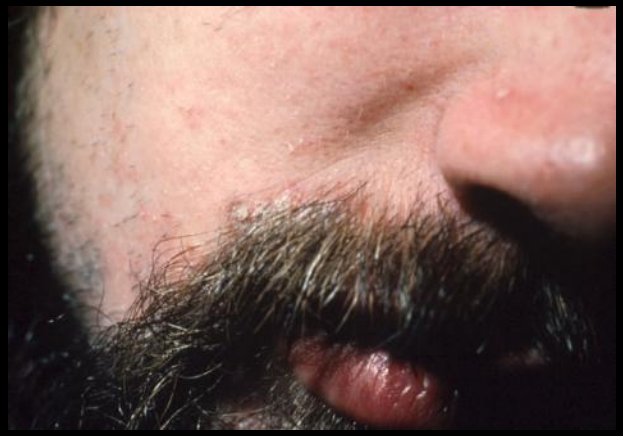
Plaque psoriasis

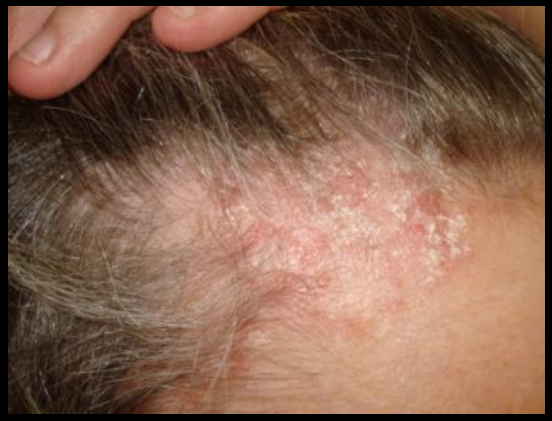
Psoriasis

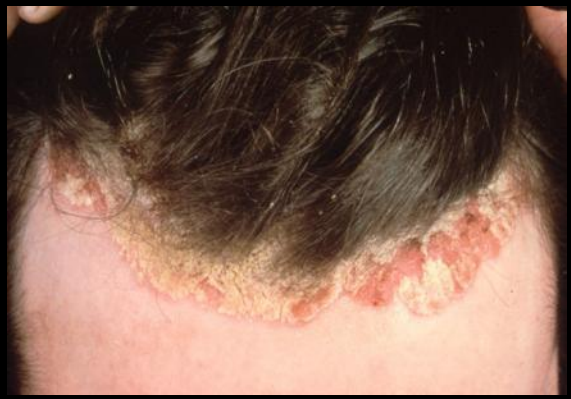


Different sites requiring special consideration

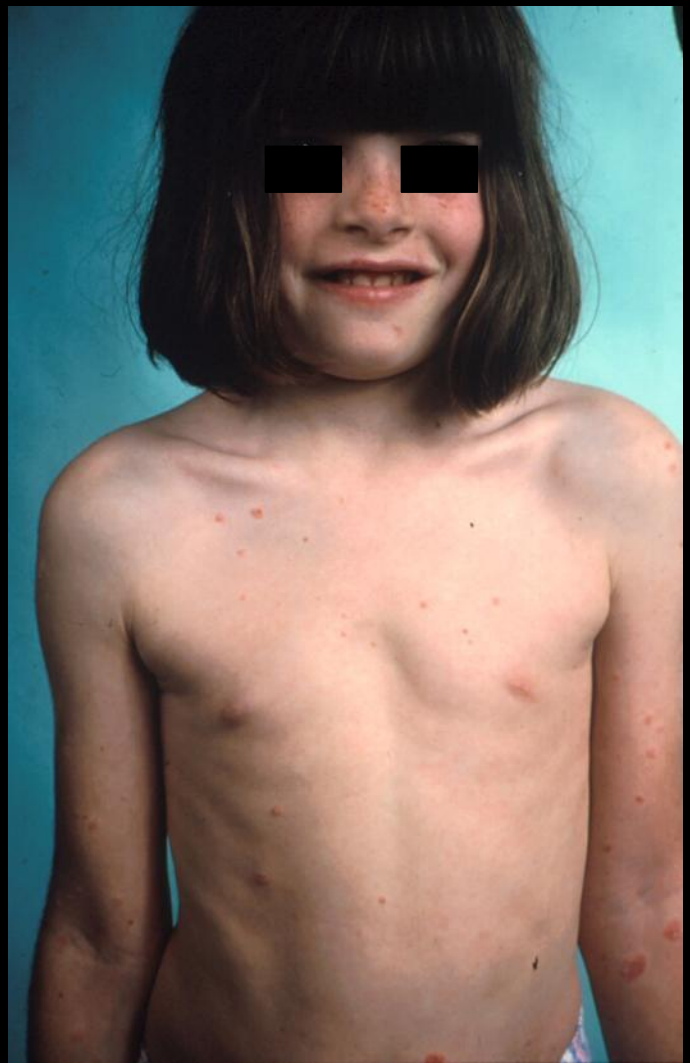




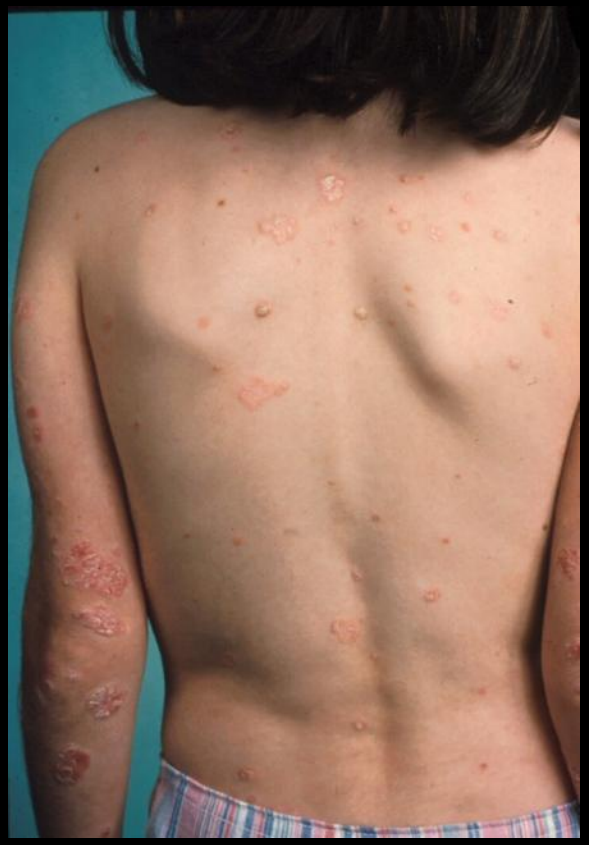




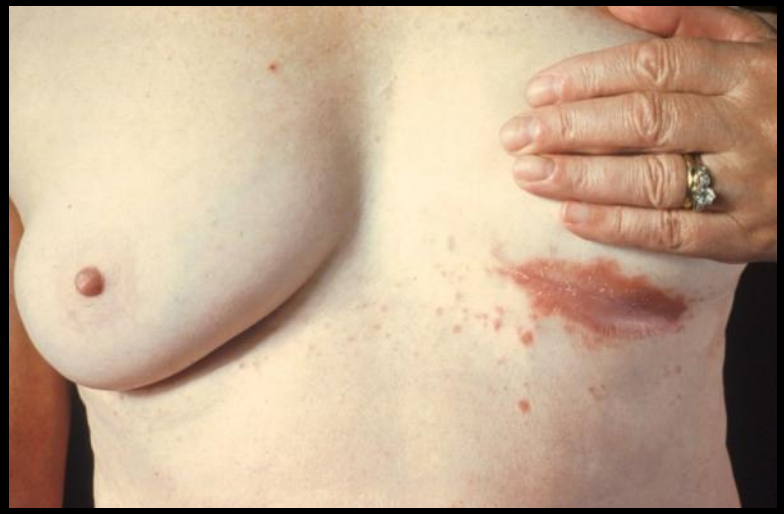
Psoriasis



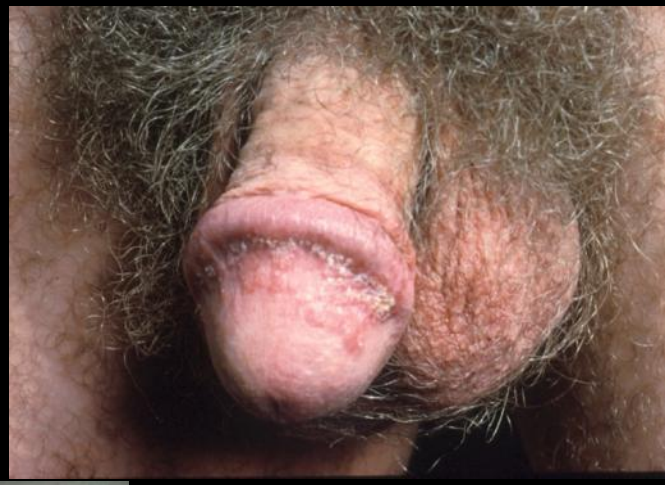
Acute guttate psoriasis

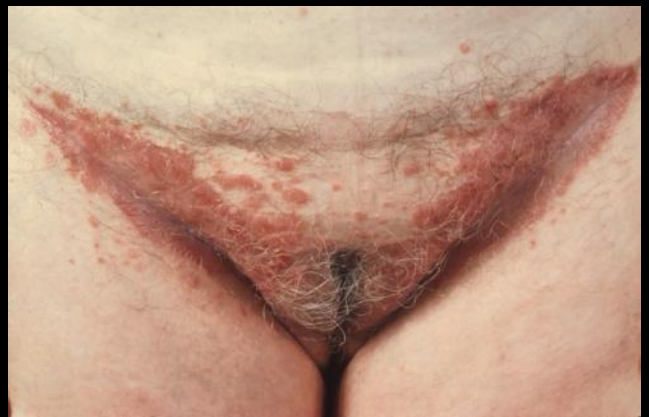


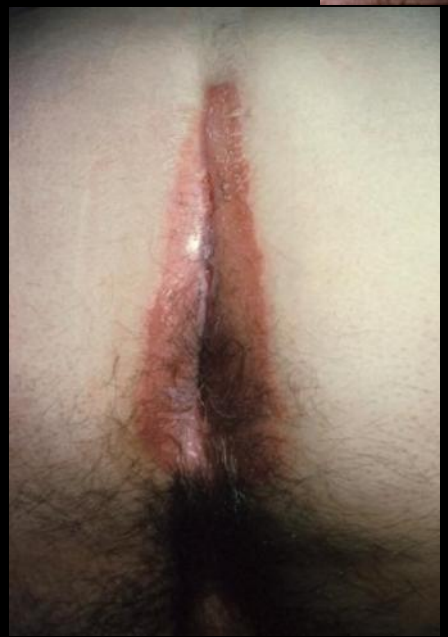
Psoriasis



Flexural psoriasis

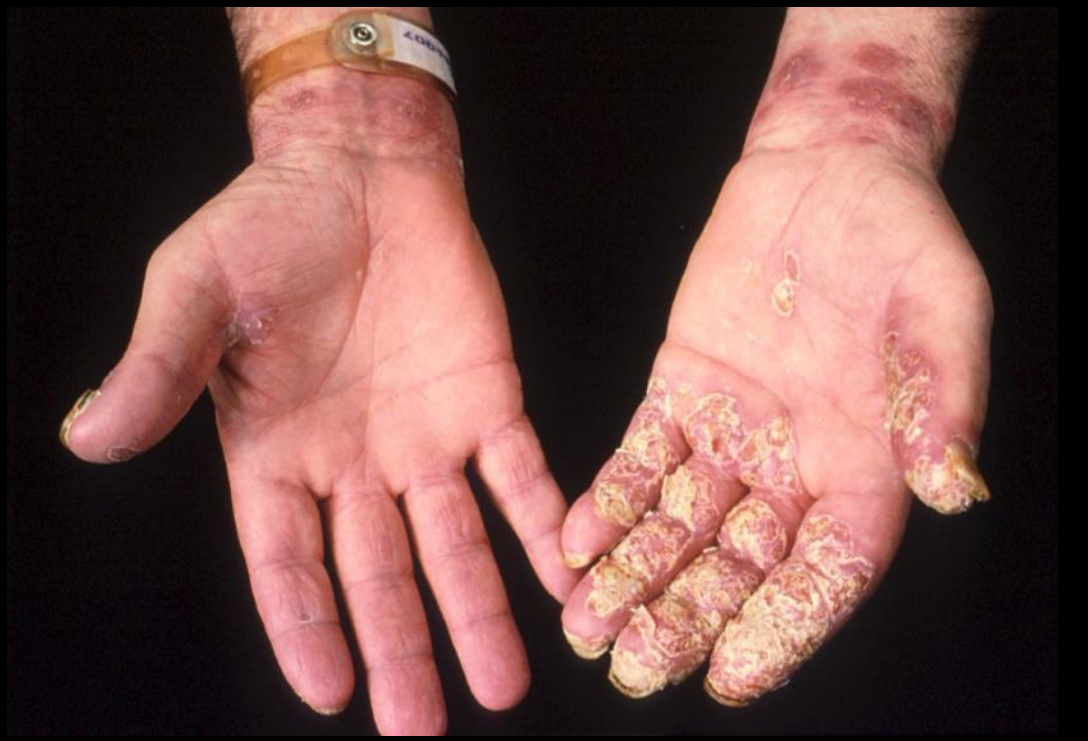


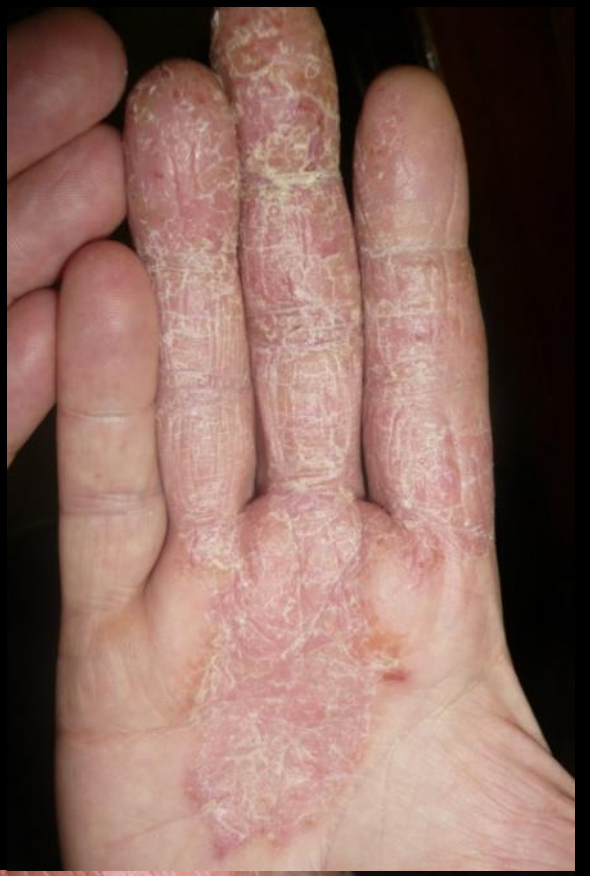


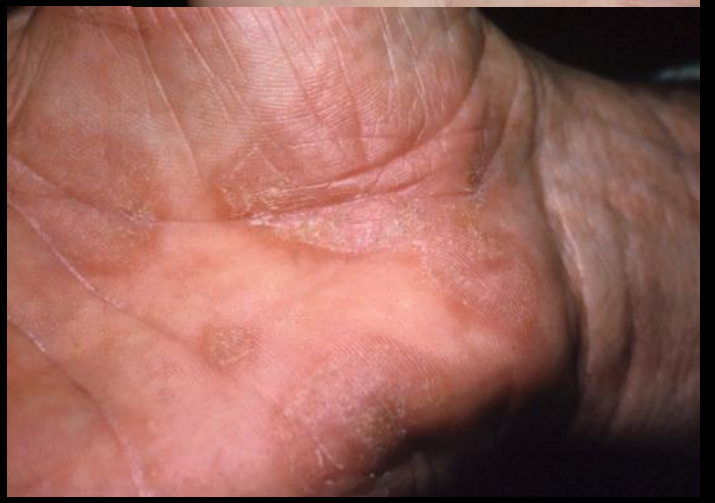


Psoriasis

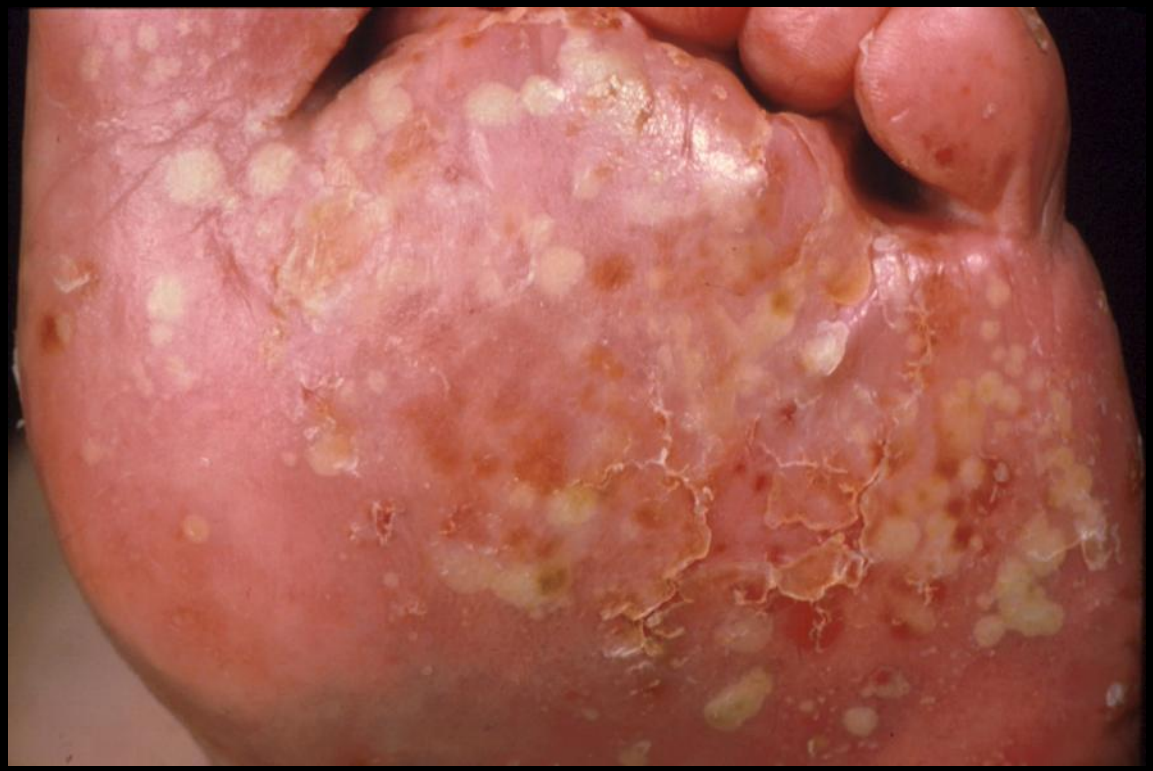
Hand psoriasis





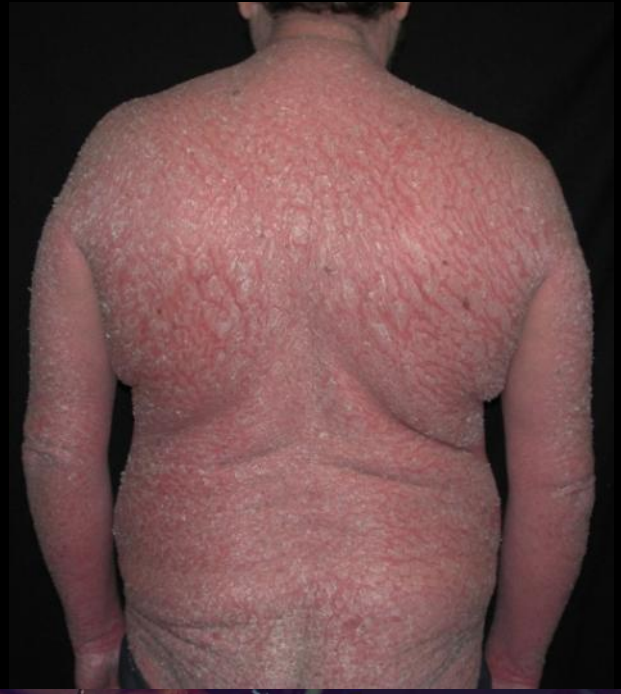


Psoriasis



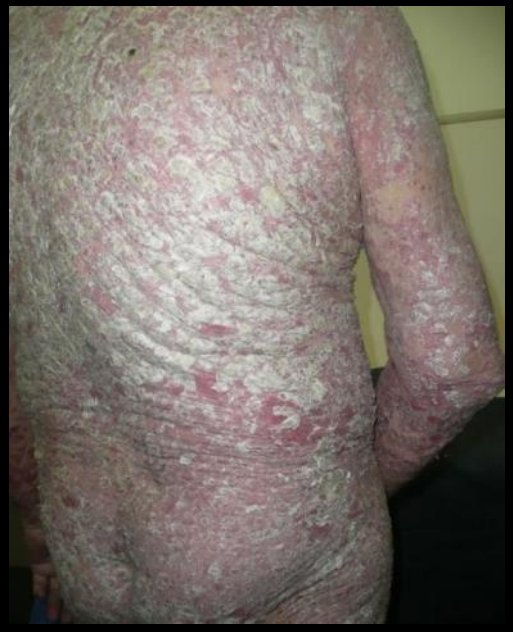
Plantar pustular psoriasis

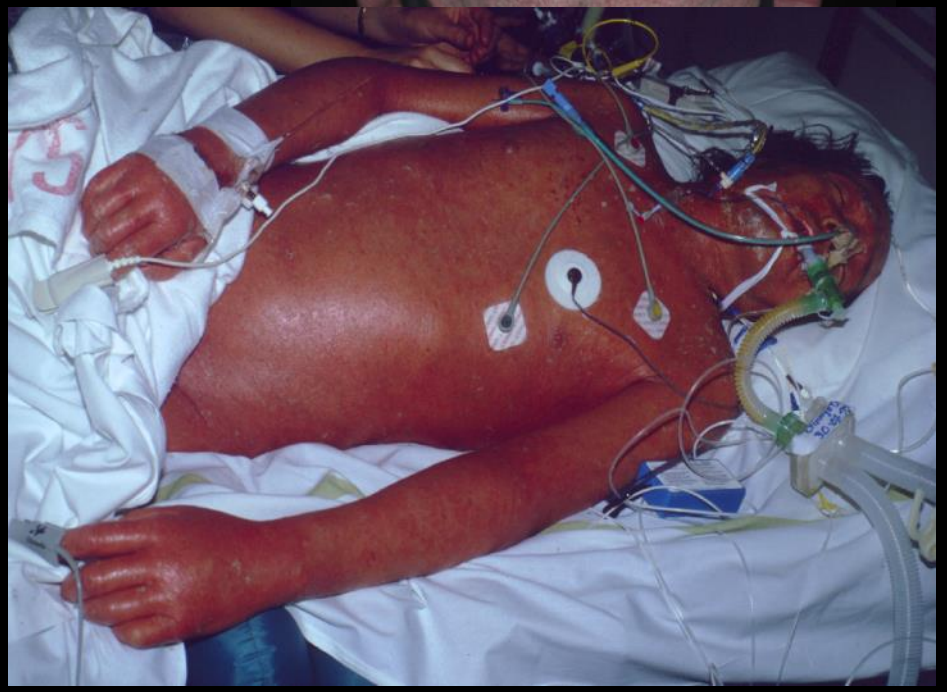
Clinical types



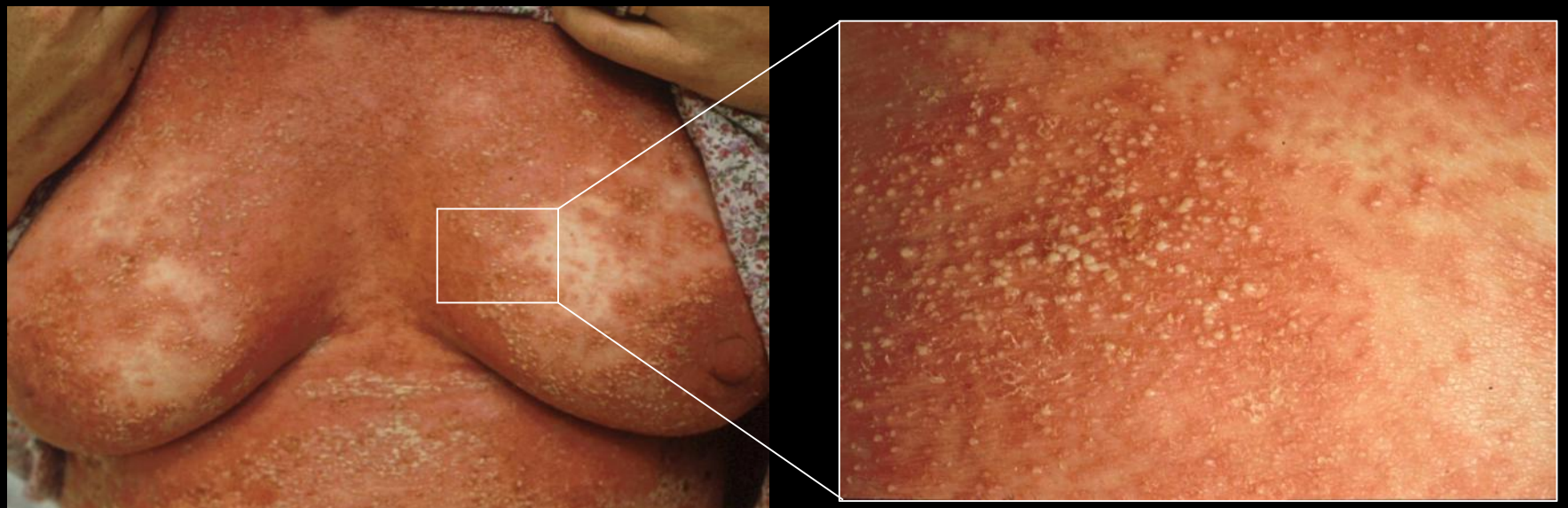
Erythrodermic psoriasis:

- most severe form
- > 90% BSA
- may be febrile, sore, unwell
- poor temperature regulation
- high output heart failure



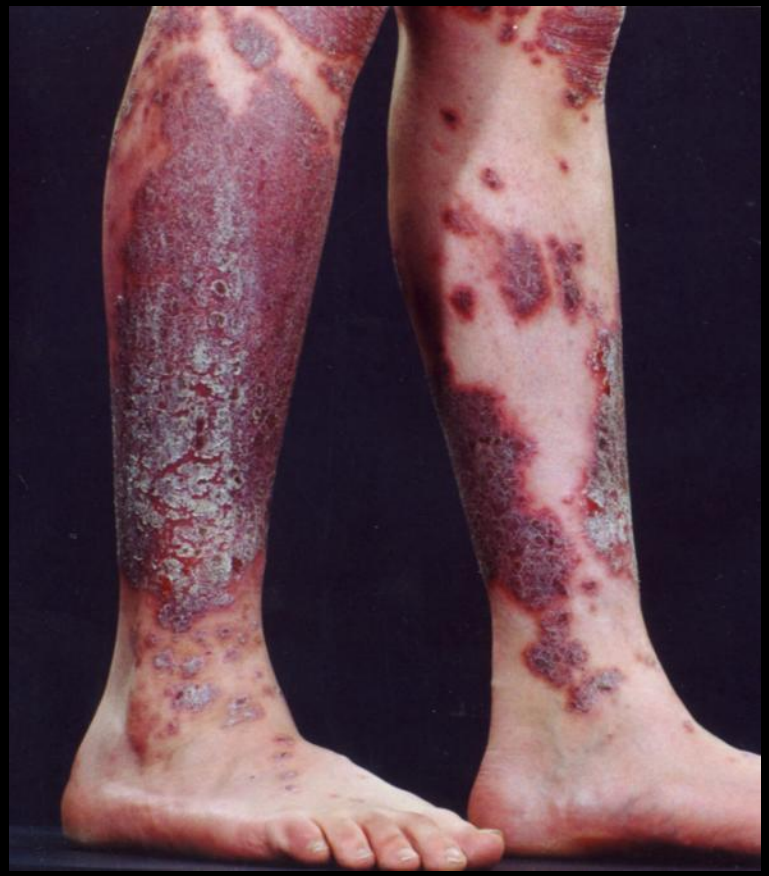


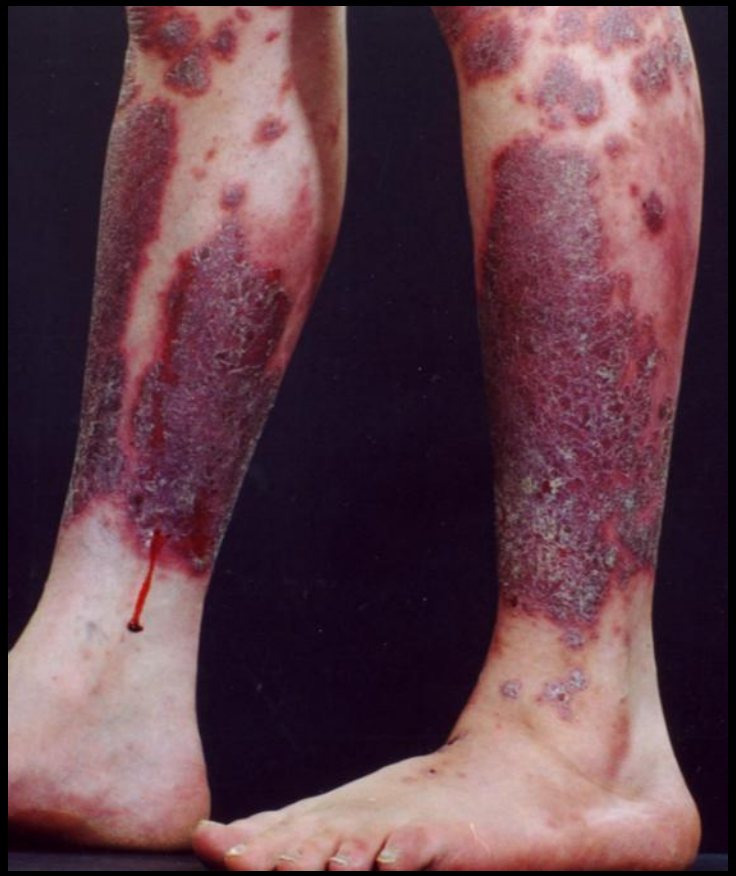
Psoriasis



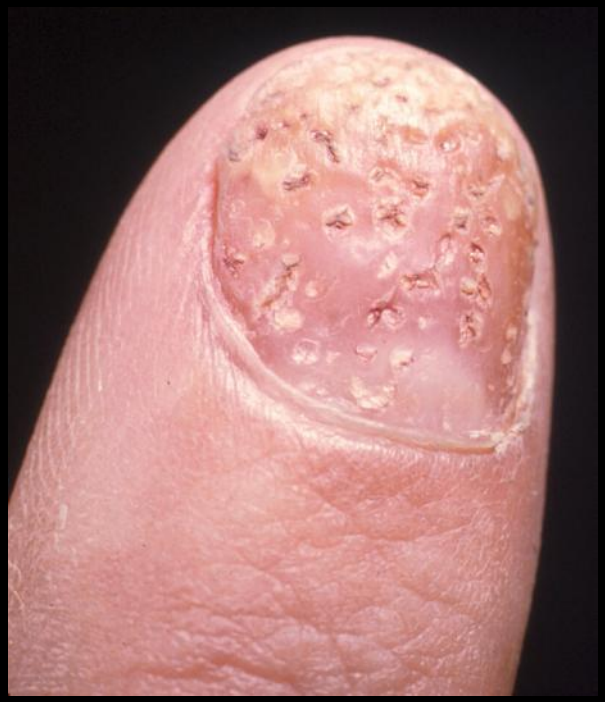
Generalized pustular psoriasis

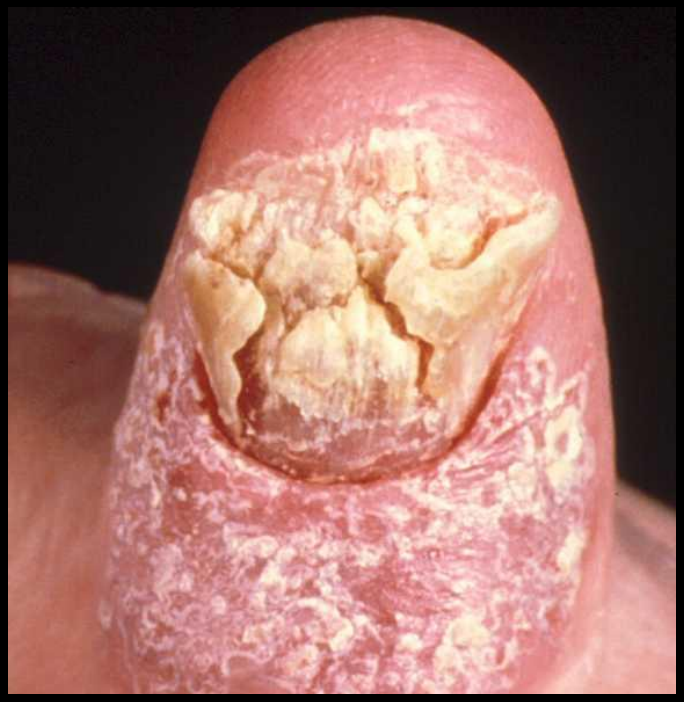
Rupoid Psoriasis



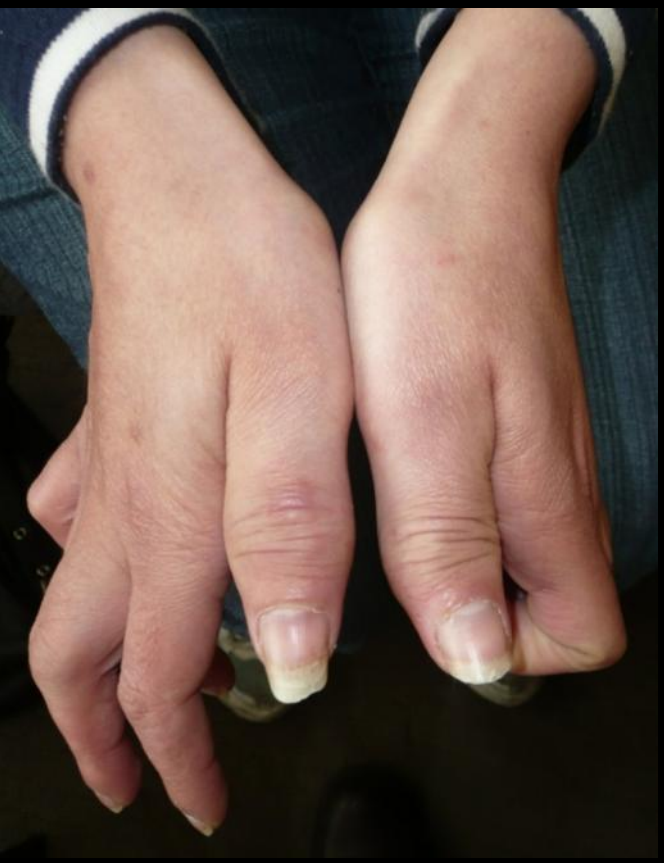


Psoriasis

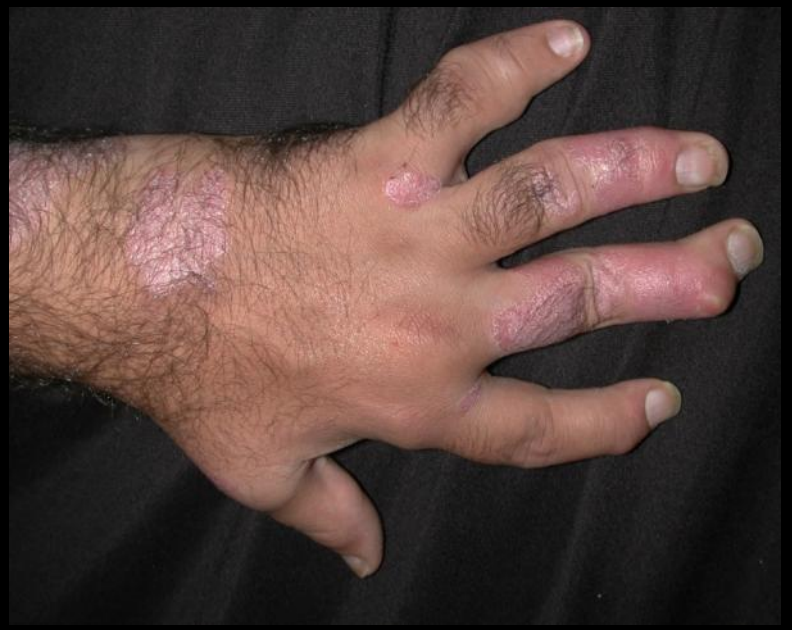


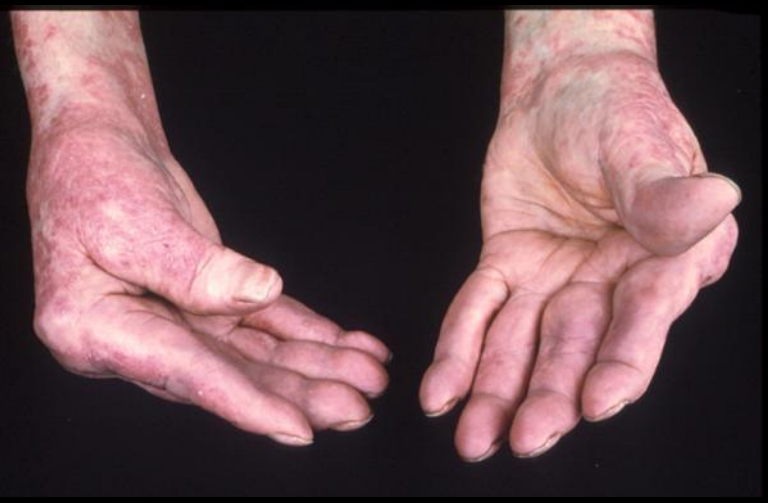


Nail pitting and subungual hyperkeratosis

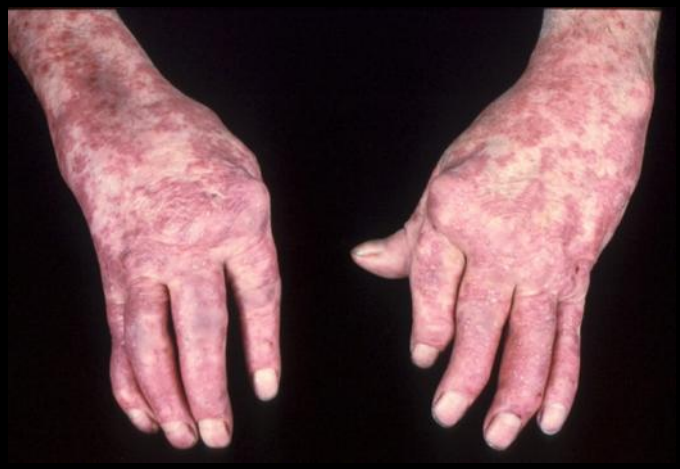


Psoriasis





Psoriatic arthritis



Comparison of Psoriasis With Other Chronic Conditions

Psoriasis has a negative impact on physical and mental aspects of life that is similar to other major chronic conditions

Condition	*Physical Component Rank*	*Mental Component Rank*
Psoriasis	**10**	**9**
Healthy Adults	**1**	**1**
Dermatitis	**2**	**8**
Arthritis	**6**	**7**
Cancer	**3**	**6**
Chronic Lung Disease	**8**	**10**
Hypertension	**5**	**2**
MI	**7**	**4**
CHF	**11**	**5**
Type 2 Diabetes	**9**	**3**
Depression	**4**	**11**

1 = Little Impact; 11 = Great Impact

Psoriasis is not life-threatening but has a significant impact on patient quality-of-life – it causes as much disability as other major medical diseases

First Line Treatment

- TOPICAL CREAM, OINTMENT, LOTION & GEL
  - Glucocorticosteroids
  - Calcipotriol
  - Tar
  - Dithranol
  - Keratolytics
  - Retinoids (Tazarotene)
  - Pimecrolimus, tacrolimus

How to use the topical formulations

1

Shake the bottle before removing the cap, so that the gel mixes well. Comb your hair to remove any loose scales, and part your hair before applying the gel.

2

Apply some Daivobet® gel to your index finger, from the tip of the finger to the first crease in the finger. This is called a fingertip unit (FTU). Usually, an amount between 2 and 8 FTUs a day is enough to treat your scalp.

3

Gently rub the gel only on the areas of the scalp affected by psoriasis. Wash your hands thoroughly after applying the gel. Avoid getting the gel on other parts of the body (especially the face, mouth and eyes).

If you get the gel in your eyes, rinse your eyes with clean water, and tell your doctor. Wipe off any gel that has accidentally come into contact with skin that is not affected by psoriasis.

4

To get the best results, do not wash your hair immediately after applying the gel. Let the gel remain on your scalp for a few hours; for example, overnight, or during the day, or between returning home from work and going to bed. Do not bandage, cover or wrap the treated area. Avoid contact with fabric that is easily stained by grease (e.g. silk).

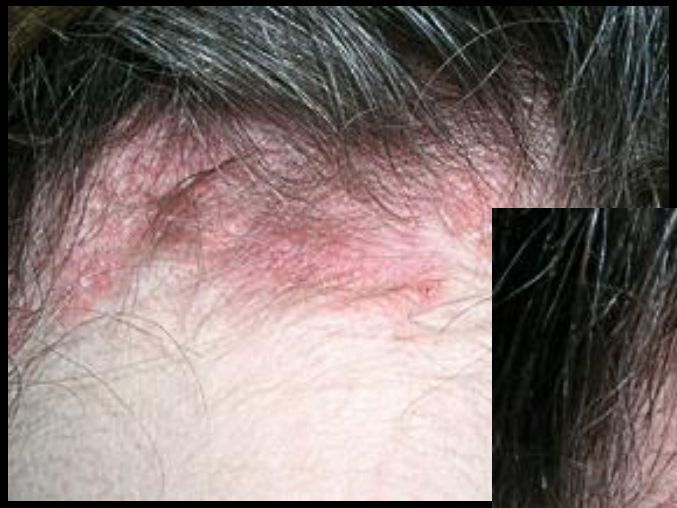
5

While your hair is still dry (prior to wetting your hair), rub a mild shampoo into the areas where the gel was applied. This will allow the gel to wash out easily. Leave the shampoo on the scalp for a couple of minutes.

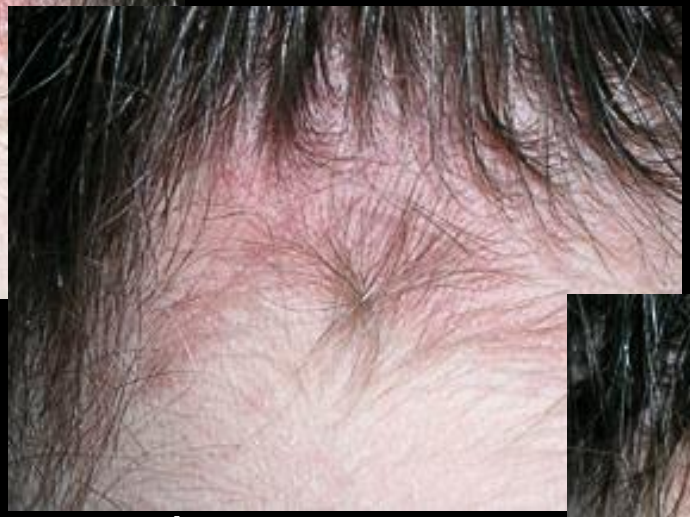
6

After you have applied the shampoo to dry hair and left it for a few minutes, e.g. while cleaning your teeth, rinse the gel from your hair, then wash and style it as usual.

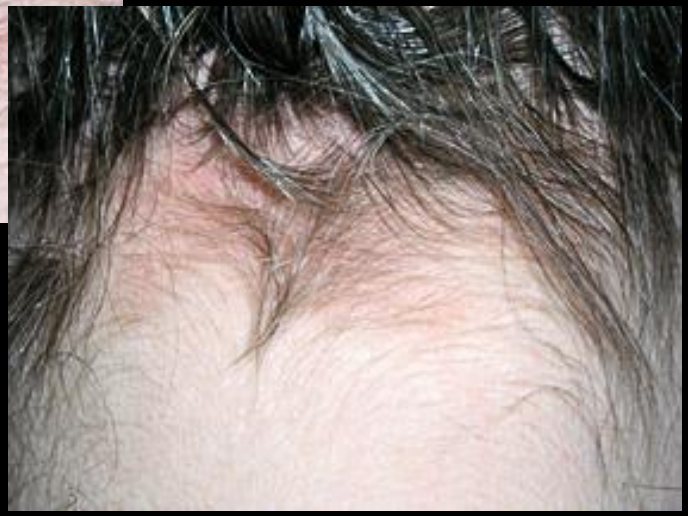
Daivobet gel: Rapid onset of action



Week 0

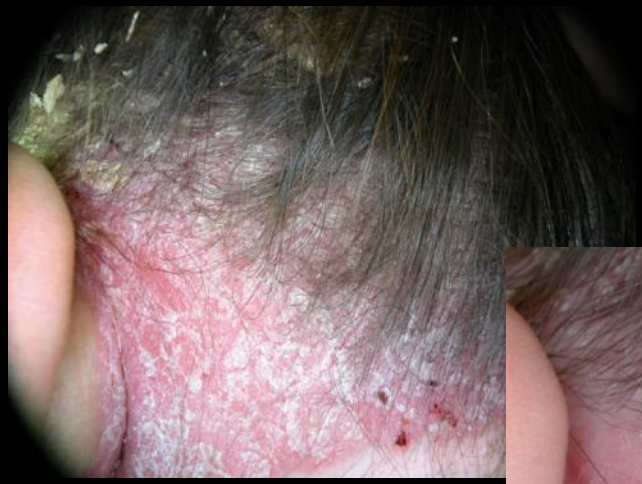


Week 1

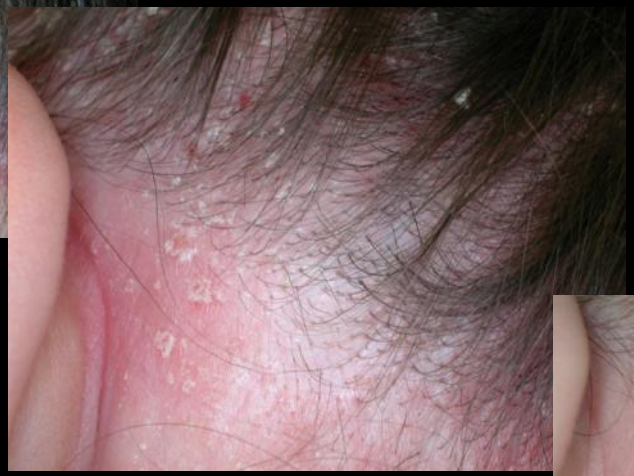


Week 2

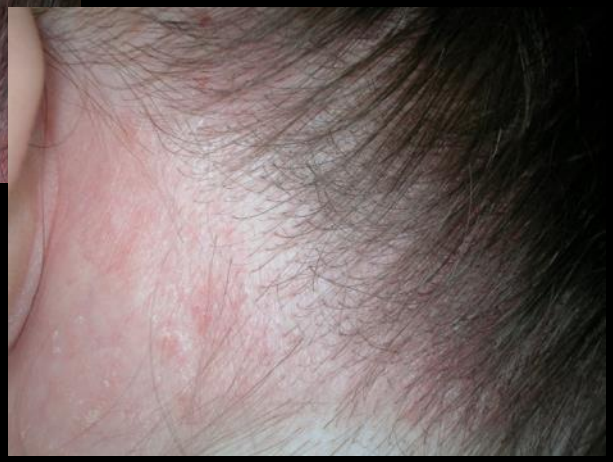
Daivobet gel: Rapid onset of action



Week 0



Week 1



Week 4

Patient Opinion on Psoriasis Treatment

A National Psoriasis Foundation survey of 40,350 members (>17,000 respondents) found:

- Patients underestimate disease severity
- Average of 26 minutes/day to treat with topicals
- Severe psoriasis patients dissatisfied with treatment
  - 87% reported treatment with topical agents
  - 78% frustrated with lack of efficacy

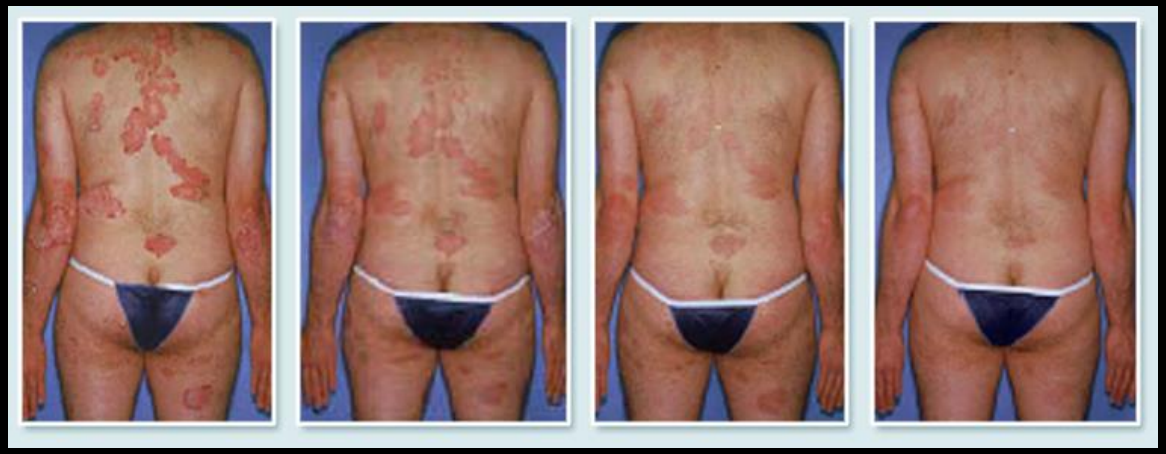
Second Line Treatment

- PHOTOTHERAPY
  - UVB
    - Narrowband
    - **Broadband**
      - Whole body
      - Localised
  - PUVA
    - Oral
    - Bath
    - Topical
  - Excimer laser

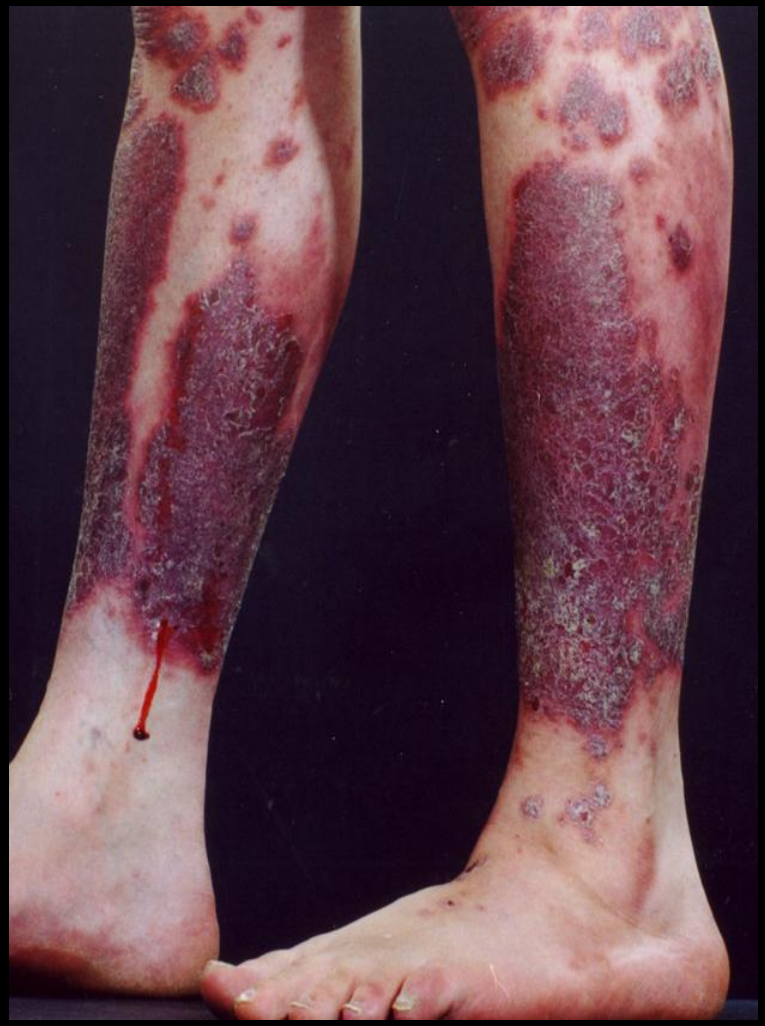
Third Line Treatment

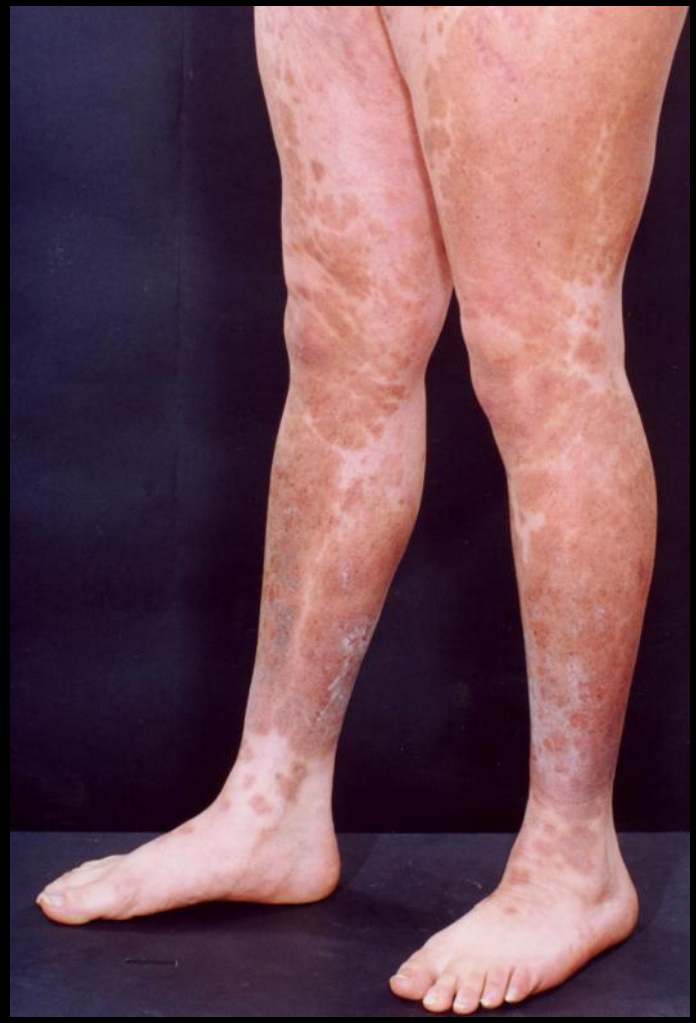
- SYSTEMIC AGENTS
  - Methotrexate
  - Acitretin
  - Cyclosporin
  - Apremilast
- Biologic therapies
  - ~~Amevive~~
  - ~~Raptiva~~
  - Enbrel
  - Ramicade
  - Humira
  - Stellara
  - Cosentyx

Response to Biologic Therapy

	Baseline	1 month	3 months	6 months
				
PASI score	31.6	5.7	1.3	0.6
PASI % improvement		82	96	98

At 10 weeks





PASI Score

- Requirement for biologic therapy
- Patient must have tried and failed to achieve adequate response from or had unacceptable toxicity with 3 out of 4 of Cyclosporin, UVB, Neotigason, Methotrexate
- Failure to respond documented with PASI score before and after treatments

Duration of Remission of Psoriasis Therapies

Therapeutic intervention	Length of remission/relapse
Anthralin	3.9 to 6 months
Topical corticosteroids	Fluocinonide cream: 55% relapsed in 12 weeks Betamethasone dipropionate ointment: 66% relapsed in 84 days; 80% relapsed over 6 months
Calcipotriene	Mean relapse-free period 43.3 days
Tazarotene	18% to 37% relapsed within 12 weeks
UVB	41% relapsed within 1 month; 83% relapsed by 6 months
PUVA	42% still clear 1 year after treatment
Etretinate	Average of 8 weeks before any sign of increasing psoriasis or appearance of new lesions
Cyclosporine	Average of 6 weeks before PASI returns to 50% of the baseline pretreatment value
Methotrexate	Median time to relapse 10 weeks to 6 months

Limitations/Toxicities of Available Antipsoriatic Therapies

Systemics	
Cyclosporine	♦ Renal toxicity and hypertension ♦ Potential for ↑ cancer risk ♦ Hyperlipidemia
Methotrexate	♦ Hepatotoxicity ♦ Bone marrow suppression
Retinoids	♦ Teratogenicity ♦ Hyperlipidemia ♦ Skeletal abnormalities
UV Light	♦ Skin cancer
Topicals	♦ QOL; patient time requirements ♦ Adrenal suppression ♦ Thinning of skin; striae; telangectasia

What is the patient journey?

- *Rash noticed by friend or family*
- *Go to pharmacist for advice*
- *If limited disease and diagnosis clear:*
  - *Tar shampoo*
  - *Hydrocortisone cream*
  - *Salicylic acid or Derm-Eze for scale*
  - *Menthol cream for itch*
  - *Tar cream for elbows and knees*
- *If extensive disease or diagnosis unclear refer to GP*
  - *Prescribe first line treatments*
  - *+/- referral to dermatologist for second and 3rd line treatments*

What is the patient journey?

- *Back to pharmacy with prescription*
  - *Advice regarding which cream goes where*
  - *Dose - How much to use*
  - *How long before patient sees a response*
  - *When and how to stop cream*
  - *When to take tablets and potential interactions*
  - *Additional shampoos, soaps, cosmetics and moisturisers*
  - *Advice regarding sun protection*
  - *PBS safety net*
  - *Importance of going back to GP for review appointment – usually within 6 weeks*
  - *Drugs to avoid – e.g. plaquenil, lithium (Doctor may not have obtained a full drug history)*

Case study: “Rebekah Hall”

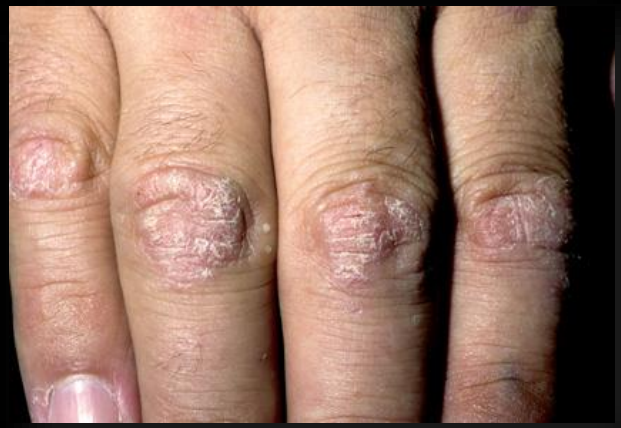
- 28-year-old woman
- Presents with bilateral dry, red, scaly patches on her knees, feet, knuckles and elbows, with occasional itchiness
- 3 months since onset
- Feels that condition is worsening
- No history of atopy

“Rebekah Hall" is not a real patient. Image is used for illustration purposes only.

Physical examination

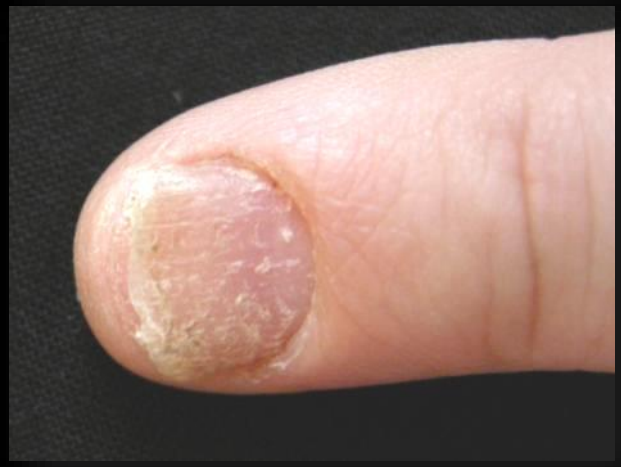
Knuckles

- Lesions on knuckles
- Right hand is worse



Nails

- Pitting
- Discoloration



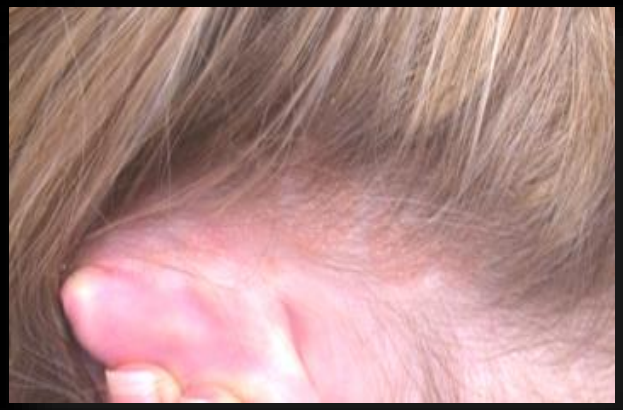
Physical examination

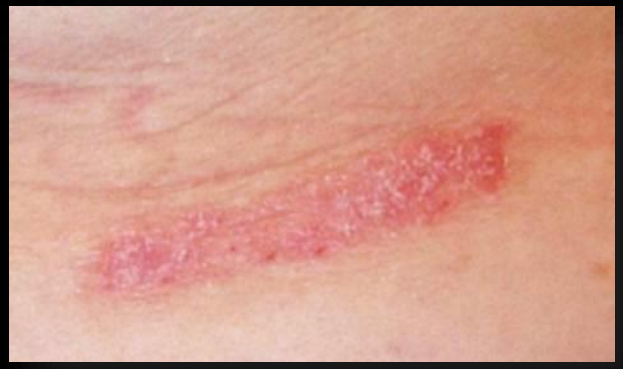
Scalp

- Patchy scaling
- Persistent “dandruff”
- Scaling around external acoustic meati

Trunk

- Mild lesions on lower back

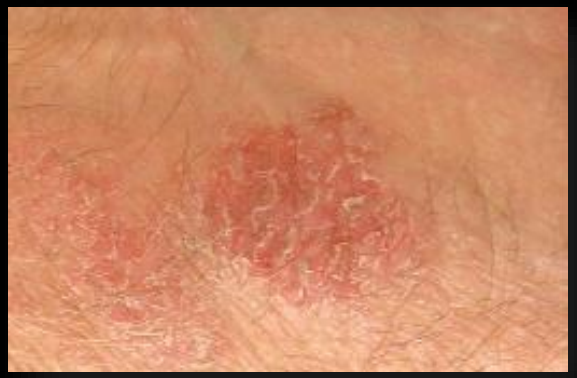




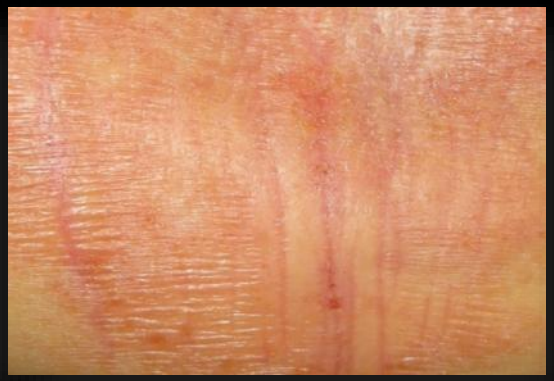
Discussion

What is your
provisional diagnosis?

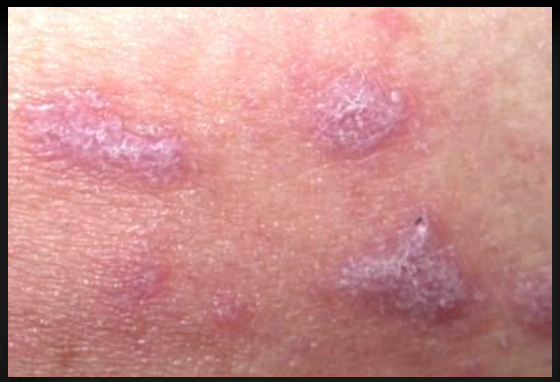
Differential diagnoses



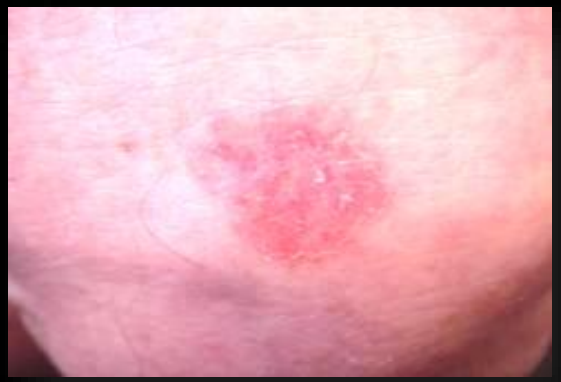
Contact dermatitis



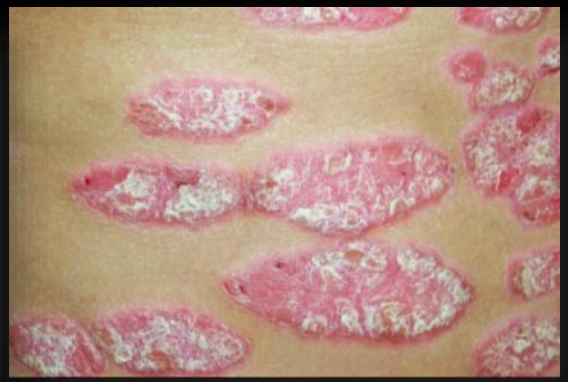
Eczema



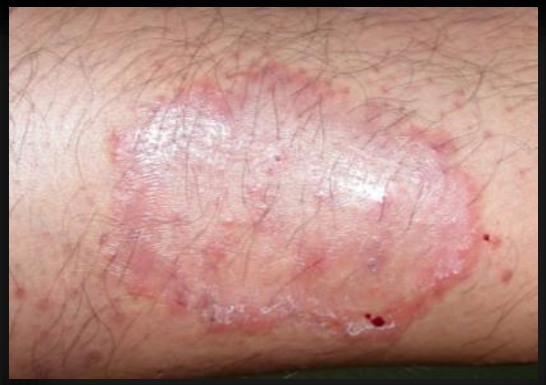
Lichen planus



Neoplasms



Psoriasis



Tinea

Rebekah Hall: diagnosis

- Rebekah is diagnosed with psoriasis vulgaris
- Psoriasis vulgaris, or chronic plaque psoriasis, is the most common form of psoriasis, affecting 85–90% of people with psoriasis[1]

Likely triggers[2]

- Genetic propensity
- Stress
- Skin trauma

1. Psoriasis Australia. Key statistics. 2010. http://psoriasisaustralia.org.au. 2. Menter A, et al. *Fast Facts: Psoriasis.* 3rd ed. Oxford: Health Press; 2008.

Discussion

What treatment options could you offer?

Rebekah Hall: treatment

Body

- Dithranol 1%
- Soap substitute to wash it off

Scalp

- Tar shampoo

Rebekah Hall: 2 weeks later

- Rebekah returns with very mild initial improvement of her body and scalp psoriasis
- She admits to skipping the daily treatment required because:
  - Dithranol irritates her skin and leaves brown patches
  - She dislikes the smell of coal tar
- She asks if there is anything different she can try

Discussion

What other treatments options might be more suitable for Rebekah?

Rebekah Hall: treatment

Body

- Calcipotriol/betamethasone dipropionate ointment
- Emollients as required

Scalp

- Calcipotriol/betamethasone dipropionate gel

Prognosis

- Incurable but manageable with the right treatment regime
- Nail involvement increases likelihood of arthritis[1]
- Scalp psoriasis may also be an indicator of joint symptoms later in life[2]

1. Menter A, et al. *Fast Facts: Psoriasis.* 3rd ed. Oxford: Health Press; 2008. 2. Wozel G, et al. *J Dtsch Dermatol Ges.* 2011;9:70-4.

Summary

- Careful examination of the skin, nails and scalp is important in diagnosing chronic skin lesions, particularly psoriasis
- Psychological assessment and monitoring of patients are important
- Treatment adherence should be monitored for best clinical outcomes
- When prescribing drugs, be mindful of patient's overall health
- Appropriate treatment, psychological support and a good healthcare professional–patient relationship are key factors in maximising treatment adherence