What's New In Rheumatology: RA, SLE, PsA

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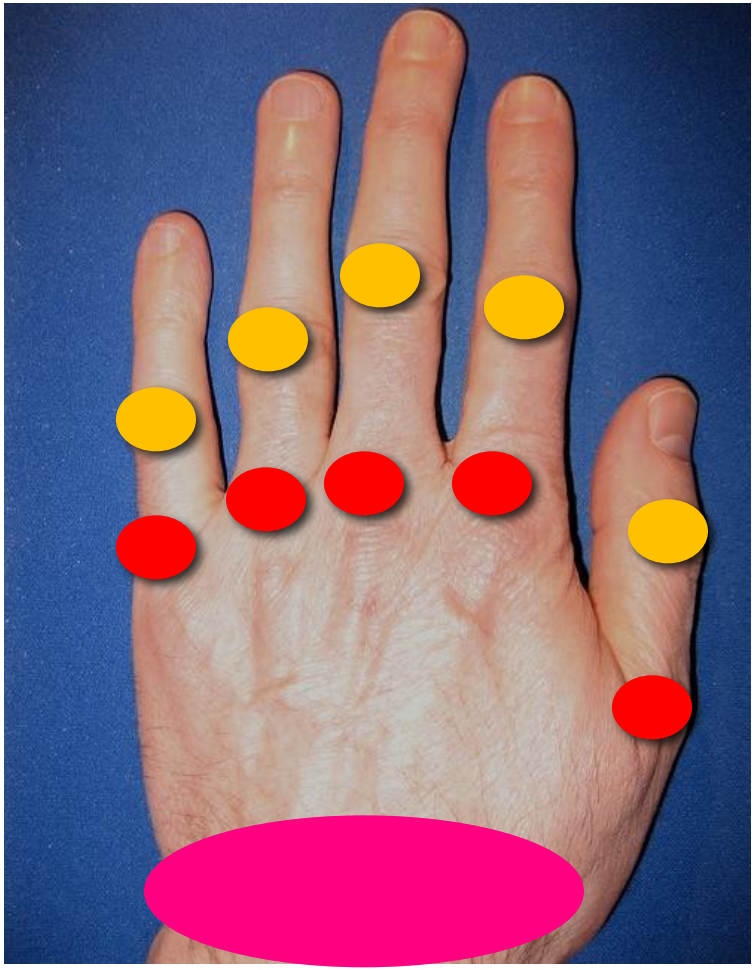
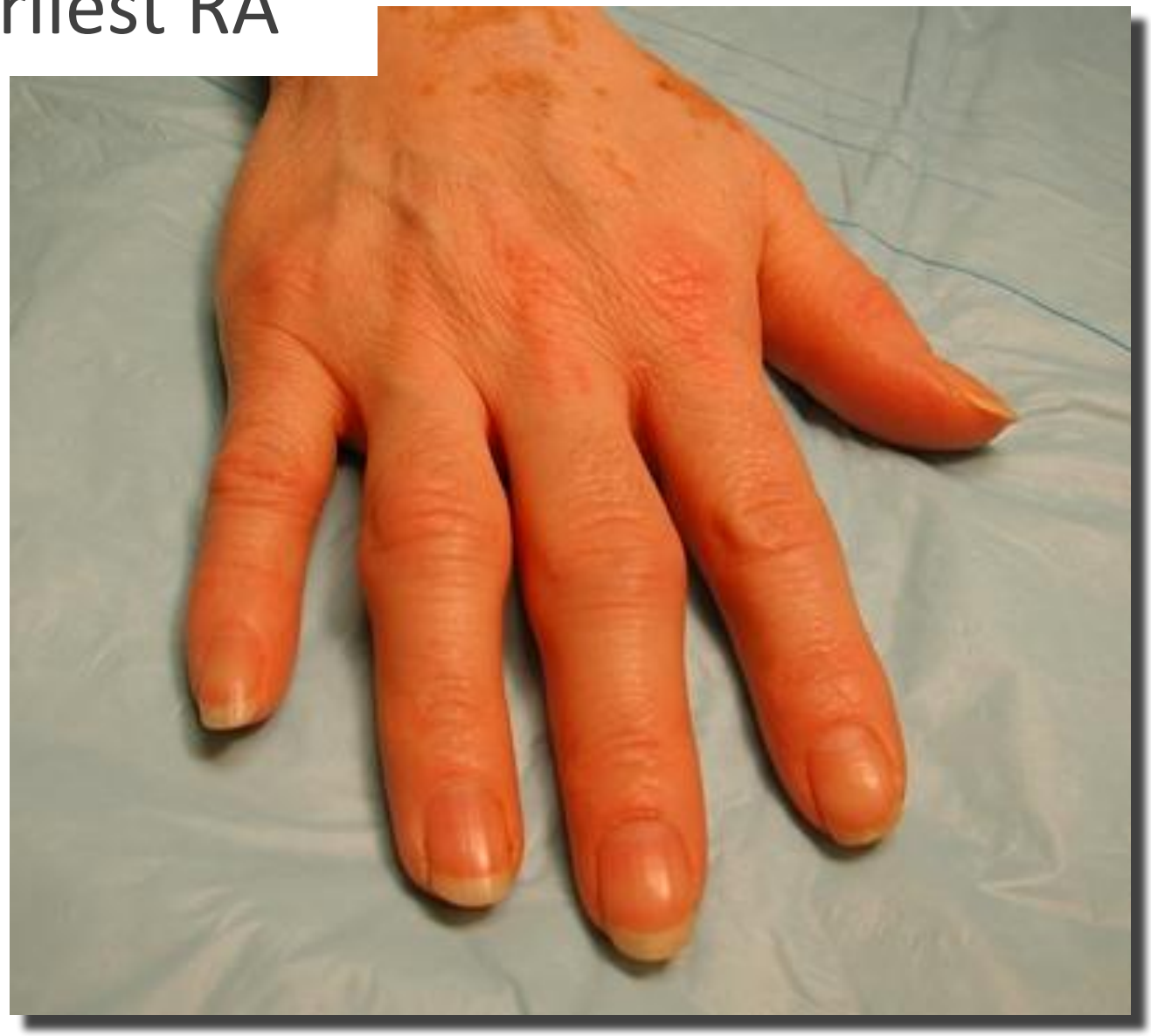
Rheumatoid Arthritis

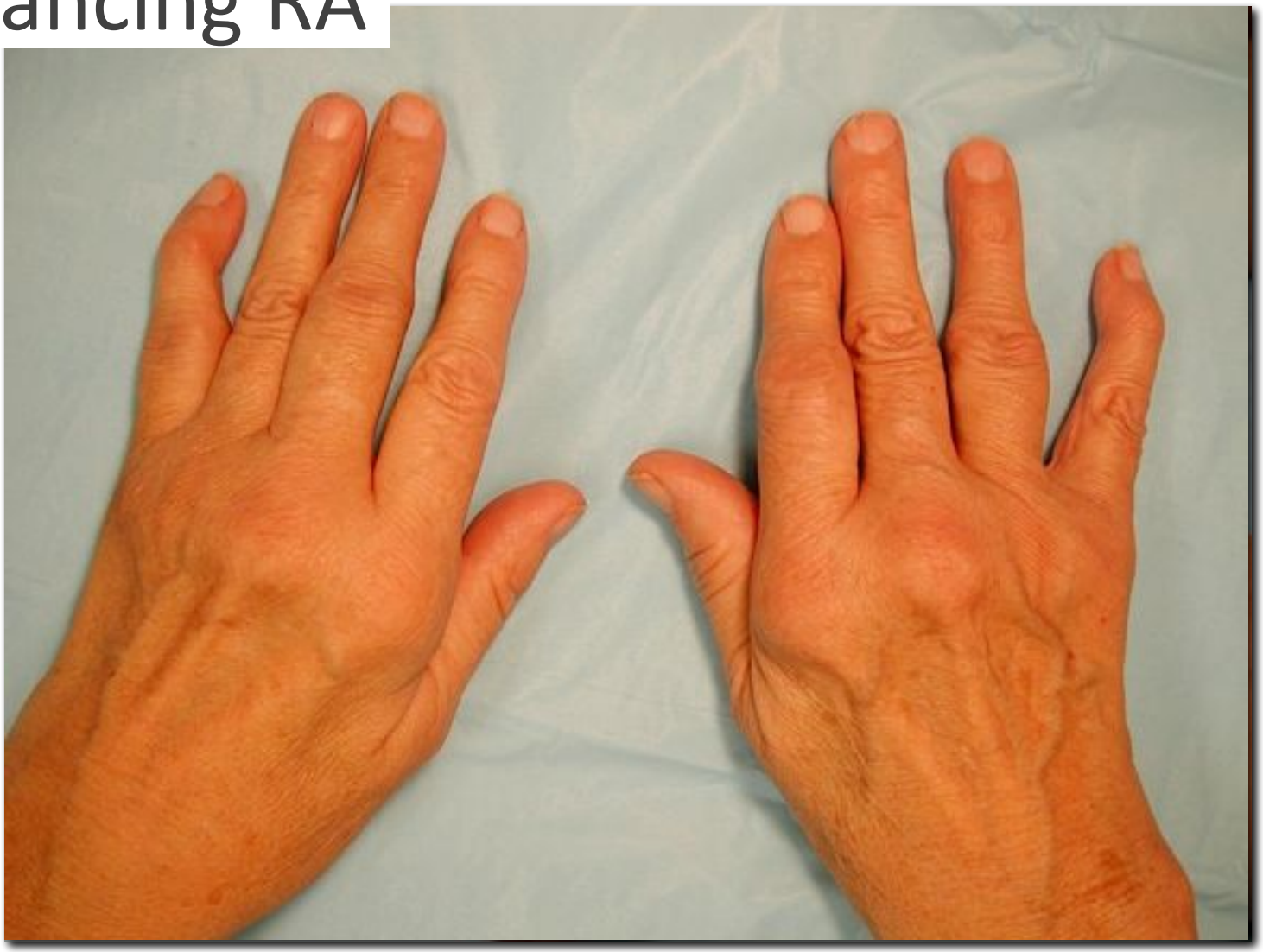
- Inflammatory polyarthritis
- Women > men
- AM stiffness > 30 minutes
- Laboratory tests
  - ESR/CRP
  - Rheumatoid factor
  - CCP
- Radiographic changes
  - Marginal erosions
  - Subluxation
  - Deviation
  - Osteopenia
- Joint distribution…..



Earliest RA

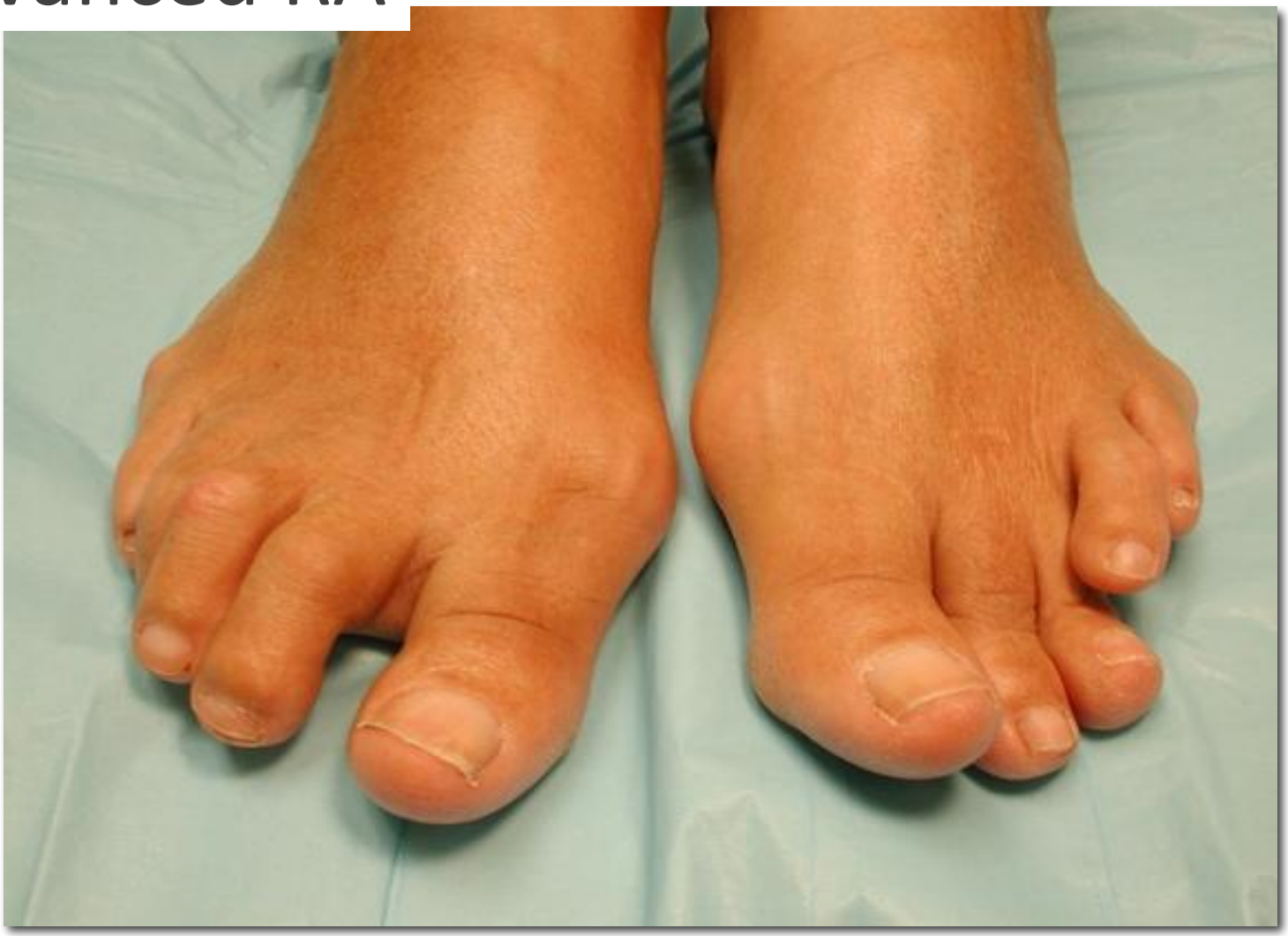


Advancing RA



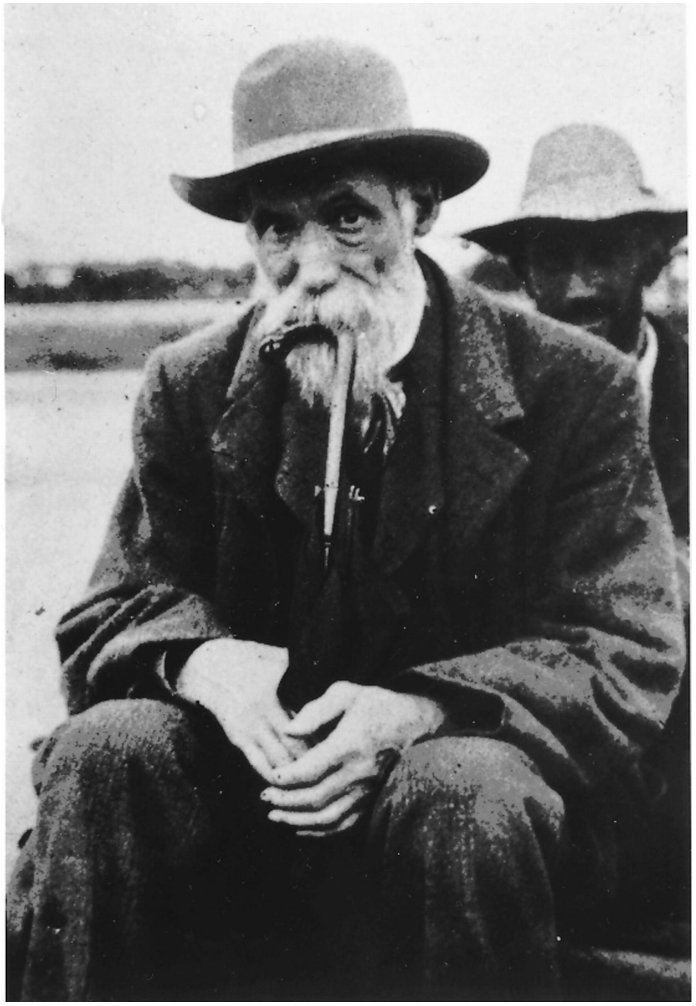
Note MCP prominence

Advanced RA

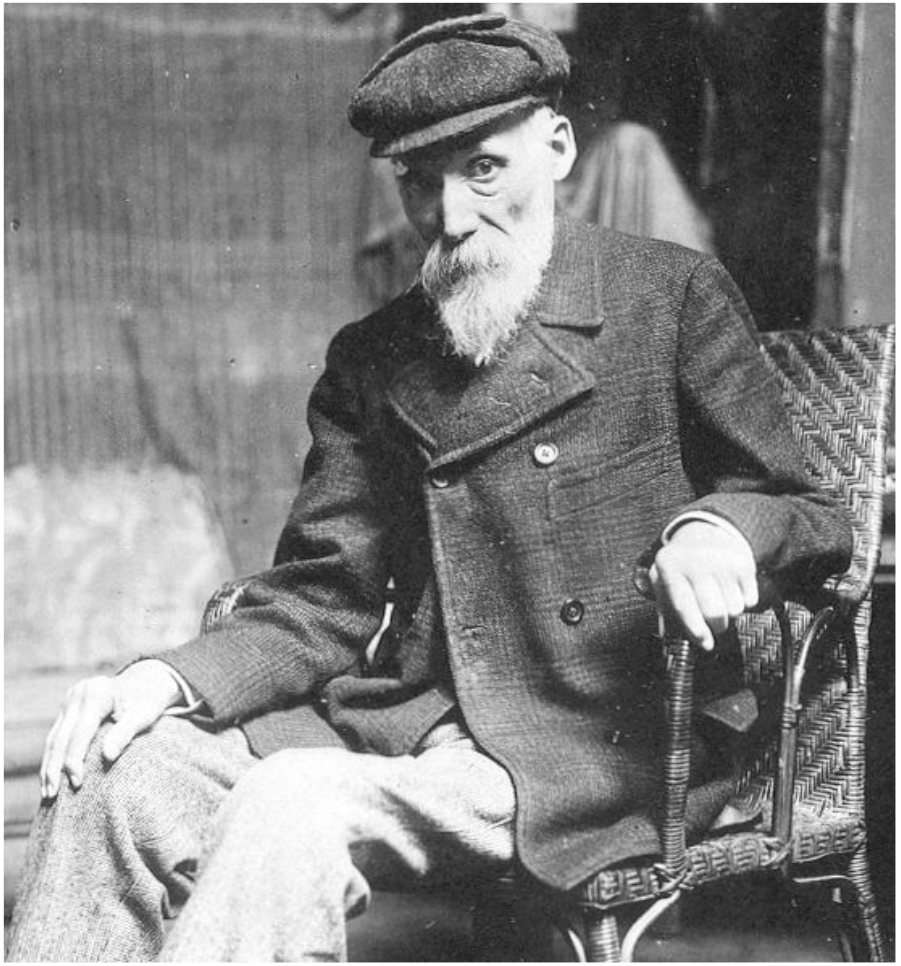


Note ulnar deviation and MCP subluxation
As well as cock up deformities of toes

The arthritis begins



1896



1901

BMJ

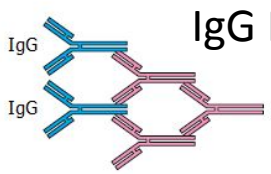
The arthritis progresses

1903

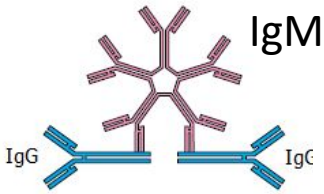
1911

Autoantibodies in Rheumatoid Arthritis: *Rheumatoid Factor*

- Rheumatoid factor is an antibody directed against the patients own IgG



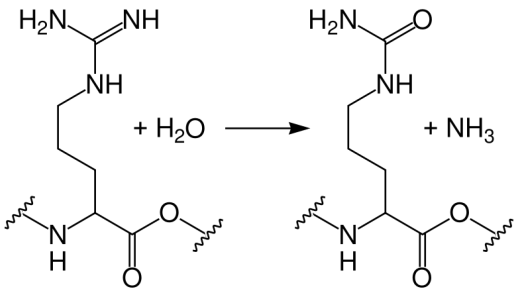
- Sensitivity of 75% and specificity of 50%; can be seen in other diseases
  - *Hepatitis B&C, TB, fungal infections, Sjogren's syndrome, mixed connective tissue disease, Waldenstrom's macroglobulinemia, etc*



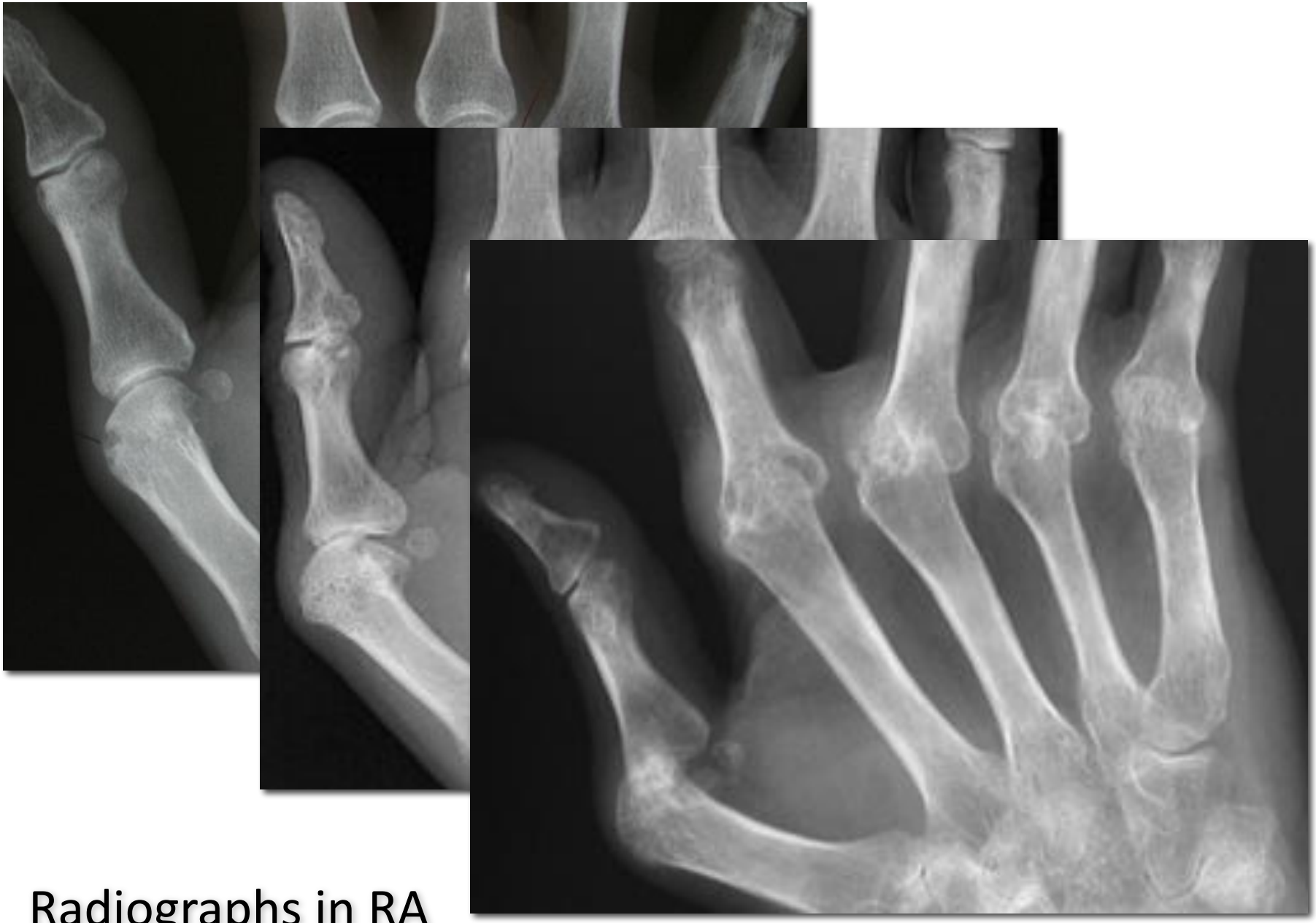
- Higher level generally means worse prognosis
- May not appear until after arthritis begins

Autoantibodies in Rheumatoid Arthritis: Cyclic Citrullinated Antibody

- Citrulline is an amino acid not found in human proteins
- Citrulline is formed by the action of PADs (peptidylarginine deiminases) induced during inflammation deiminates arginine to form citrulline

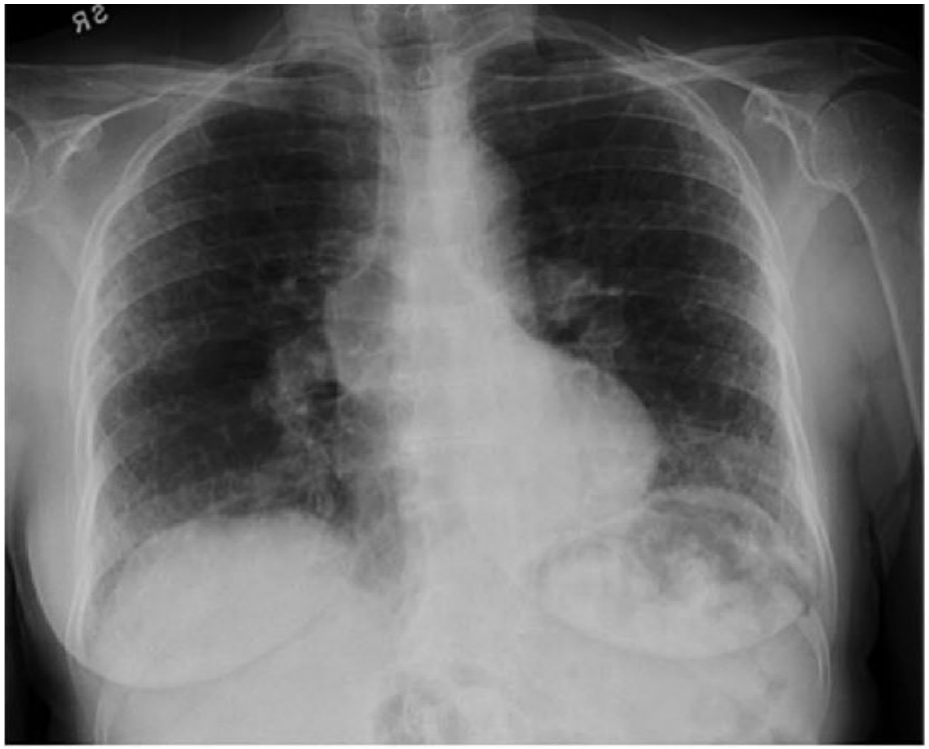


- In RA, sensitivity of CCP 70-80% and **specificity of 95%**
- Level predicts severity of disease
- *May be present years before clinical disease; benign autoimmune state present before clinical disease*



Radiographs in RA

Rheumatoid Arthritis: Extra-Articular Disease



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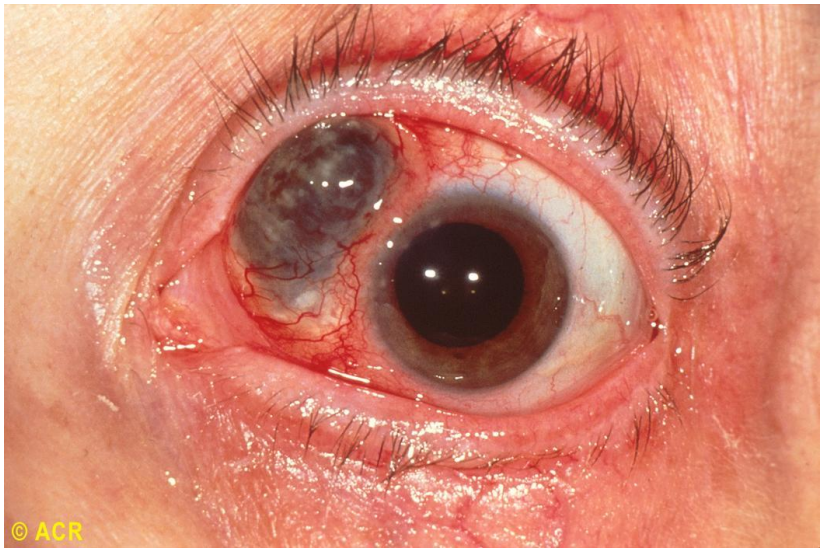
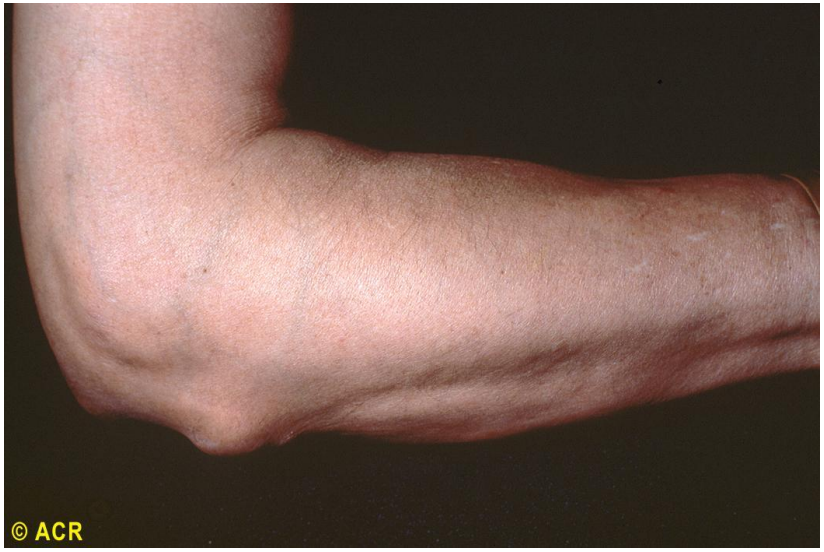


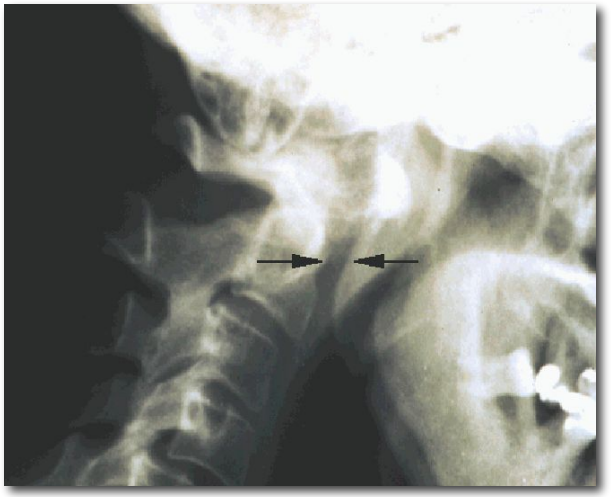
Scleritis/Scleromalacia

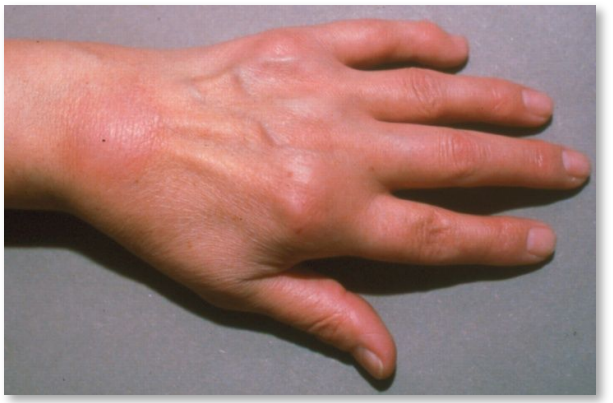


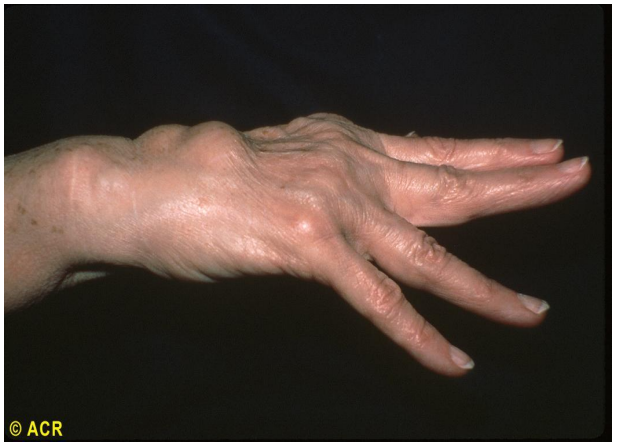
Nodules

Complication of RA

- C1-C2 subluxation
  - Neck pain, myelopathy, C spine flexion/extension views, MRI
- Septic arthritis
  - Large joints, Staph > Strep > gram negatives
- Tendon ruptures
  - Especially ring/little finger extensor tendons
- Rheumatoid Vasculitis (PAN like)
  - Male, foot drop, wrist drop, skin ulcers, GI



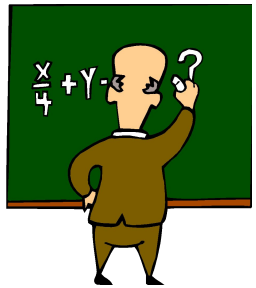




Irving Kushner, M.D.

J Rheumatol 1989;16:1-4

"What we need in RA is a drug for which one does not need a statistician to see the beneficial effects"



Changes in Treatment Approaches to RA

Very early intervention

Biologics

Combination therapy

Early intervention

Methotrexate

Treatment pyramid

Single-drug therapy

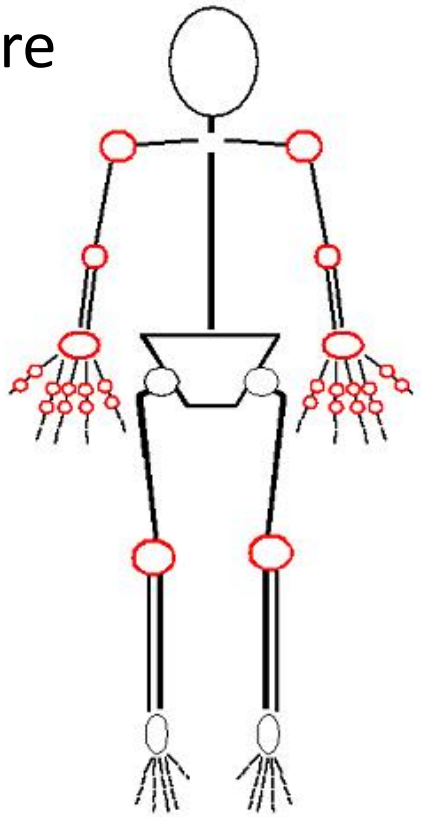
1910 1920 1930 1940 1950 1960 1970 1980 1990 2000 2010

Therapy of RA 2019

- Early recognition, early therapy
- Aggressive Rx for patients with concerning features
  - Erosions at presentation
  - Extra-articular features ie nodules
  - Large number of joints involved
- Methotrexate is anchor medication
- *Routine measure of disease activity with modification of therapy every 3 months to achieve low disease activity or remission*

Clinical Disease Activity Index: CDAI

- # Tender joints + # swollen joints + how patient feels about disease activity (0-10) + how provider feels about disease activity (0-10) = CDAI score
  - 0-3 remission
  - 4-10 low disease activity
  - 11-20 moderate disease activity
  - >20 high disease activity



Therapies For RA 2019

- **Conventional DMARDs**
  - Methotrexate
  - Hydroxychloroquine
  - Leflunomide
  - Sulfasalazine
- **Anti-TNF Agents**
  - Etanercept
  - Adalimumab
  - Infliximab
  - Certozilumab
  - Golimumab
- **Anti-B Cell Therapy**
  - Rituximab
- **Anti-T Cell Therapy**
  - Abatacept
- **Anti-IL-6 Receptor Antagonist**
  - Tocilizumab/Sarilumamab
- **JAK Inhibitor**
  - Tofacitinib/barcitinib
- **IL-Receptor Antagonist**
  - Anakinra

Patient Presentation

- 36 yr old woman with 2 months of pain and stiffness in hands, wrists, knees, and feet. Reports 60 minutes of stiffness in the morning and feels better with activity. Ibuprofen helps
- On examination, she has tenderness/swelling in the MCPs, PIPs, small effusions in both knees, and tenderness/swelling in the MTPs.
- CDAI score is 13 + 12 + 8 + 8 = 41 high disease activity
- Labs: CCP > 300, Rheumatoid factor 376 IU
- Next steps?

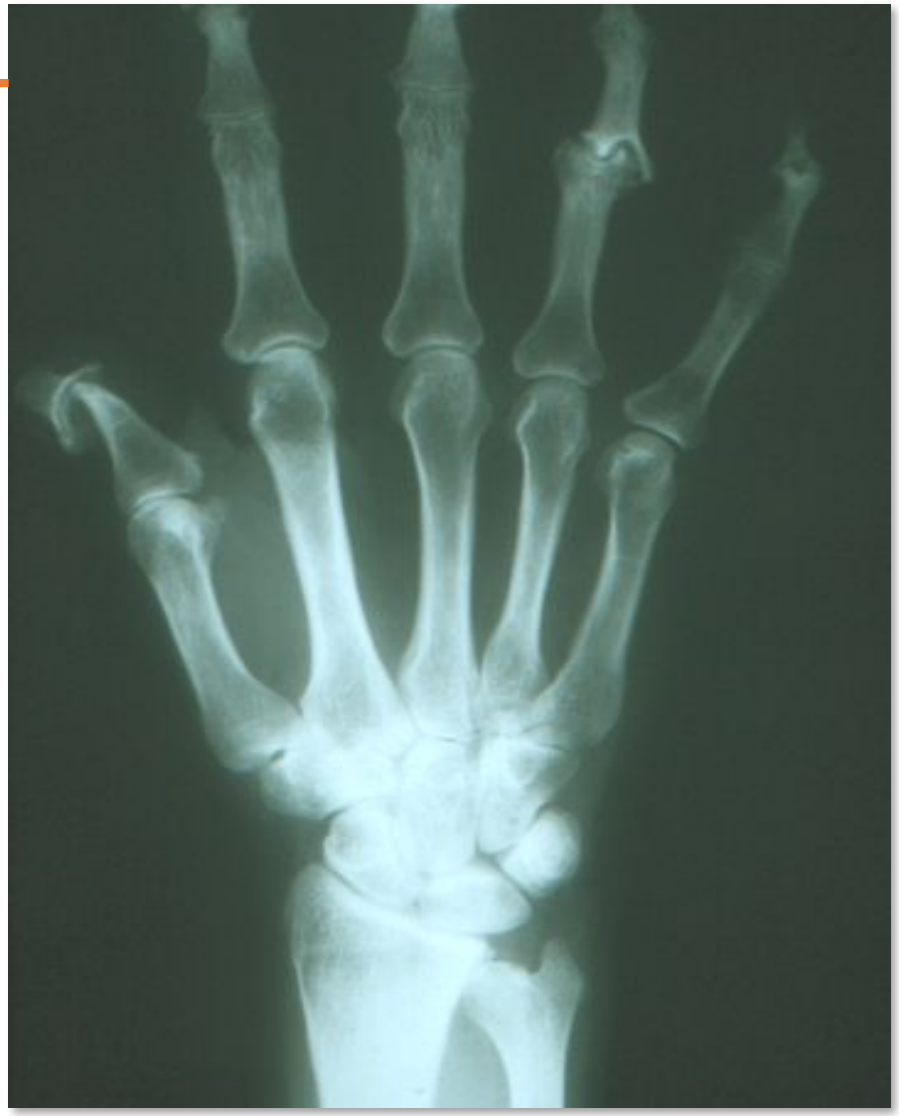
Next Steps

- Initiate methotrexate 7.5 mg/week and folic acid 1 mg/day
- Month 1: minimal improvement but no SE; CBC, AST/ALT normal; increase methotrexate weekly to 15 mg/week
- Month 2: CDAI down to 20, no SE, Nl labs
- Month 3: CDAI down to 15, no SE, Nl labs; methotrexate increased weekly to 20 mg per week
- Month 4: CDAI down to 12, no SE, Nl labs
- Month 5: CDAI 14, no SE, Nl labs
- Month 6: CDAI 14, no SE, Nl labs, Etanercept 50 mg sc weekly added
- Month 7: CDAI 4, no SE, Nl labs

Patient Presentation:

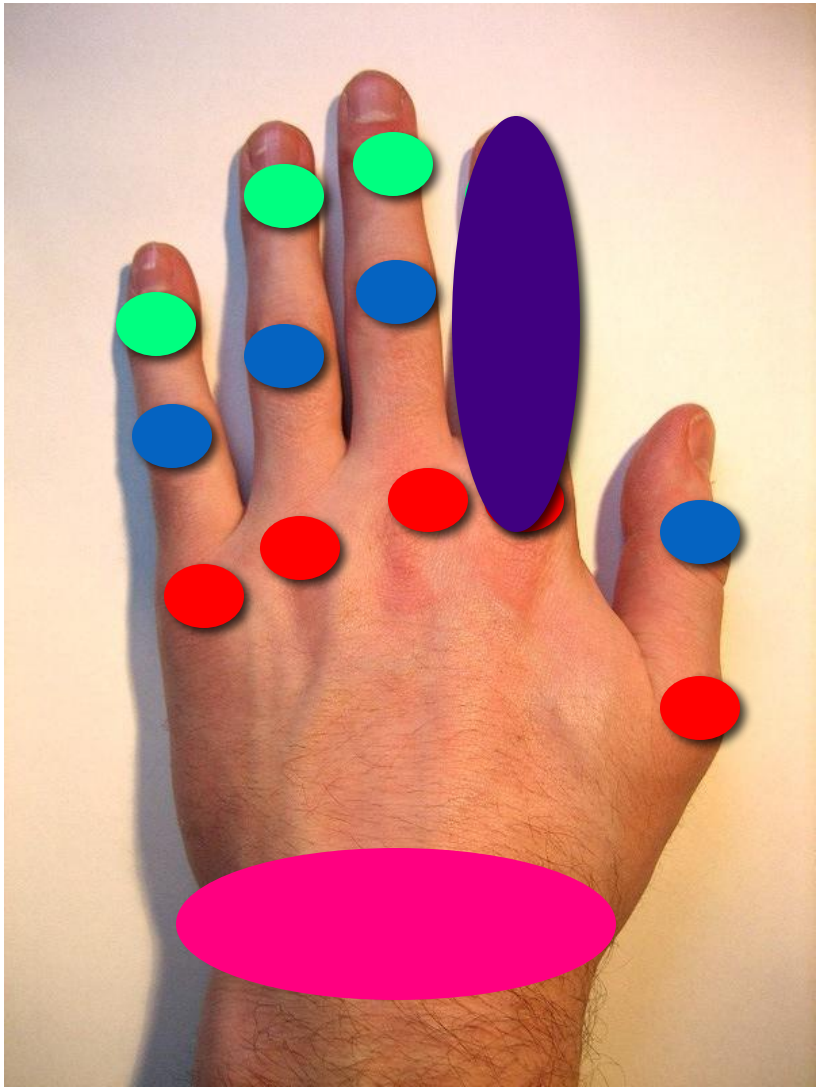
A 55 y/o male with arthritis has this x-ray. The term used to describe this finding is :

1. Opera glass deformity
2. Pencil point deformity
3. Pencil in a cup deformity
4. Saber tooth deformity

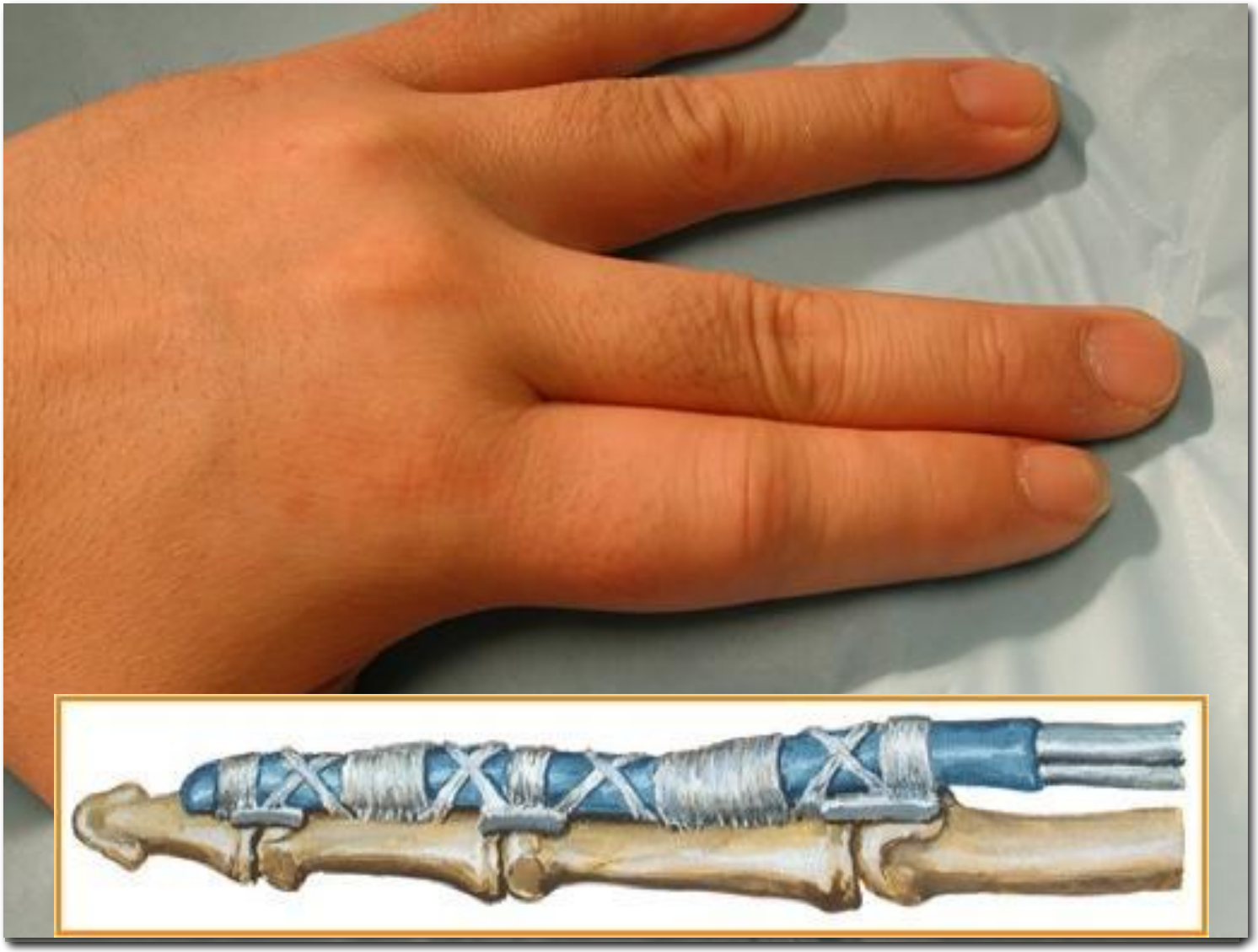


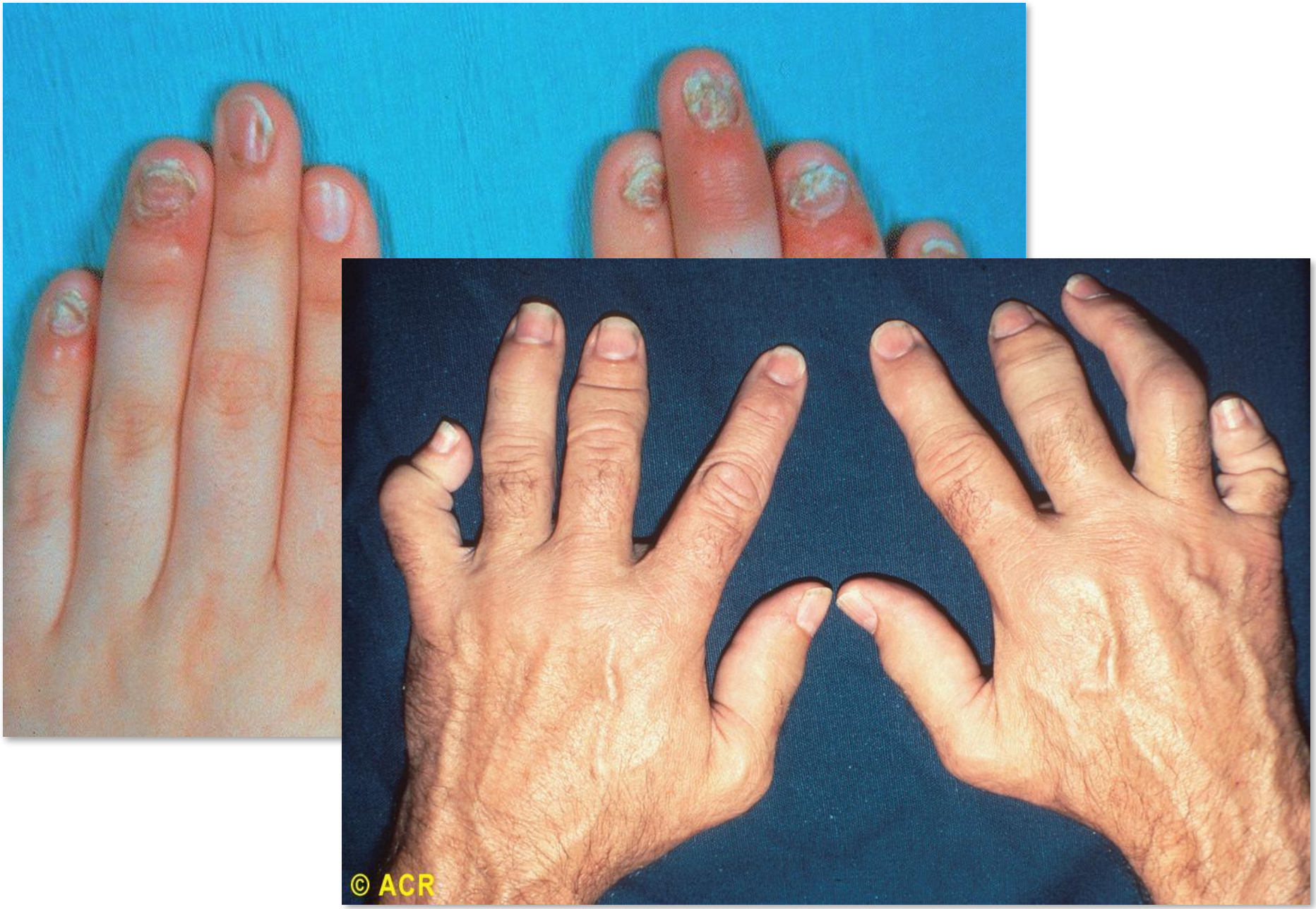
Psoriatic Arthritis

- Men = women
- 7-20% of psoriasis pts develop PsA
- Types of disease
  - Pauciarthritis
  - Polyarthritis
  - DIP invovement
  - Arthritis mutilans
  - Spondylitis
- Enthesopathy
- Joint distribution…



Dactylitis aka “Sausage Digit”

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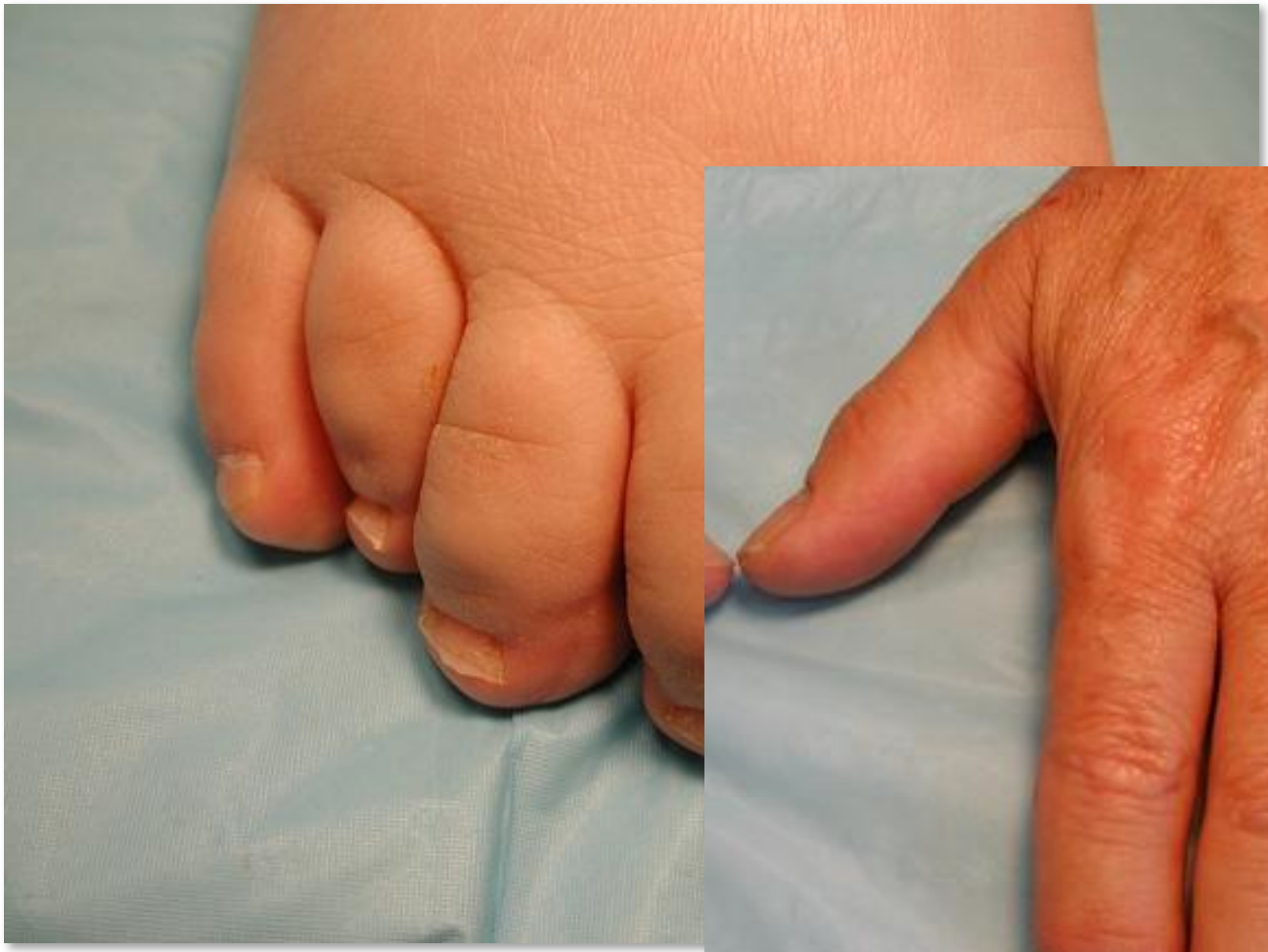
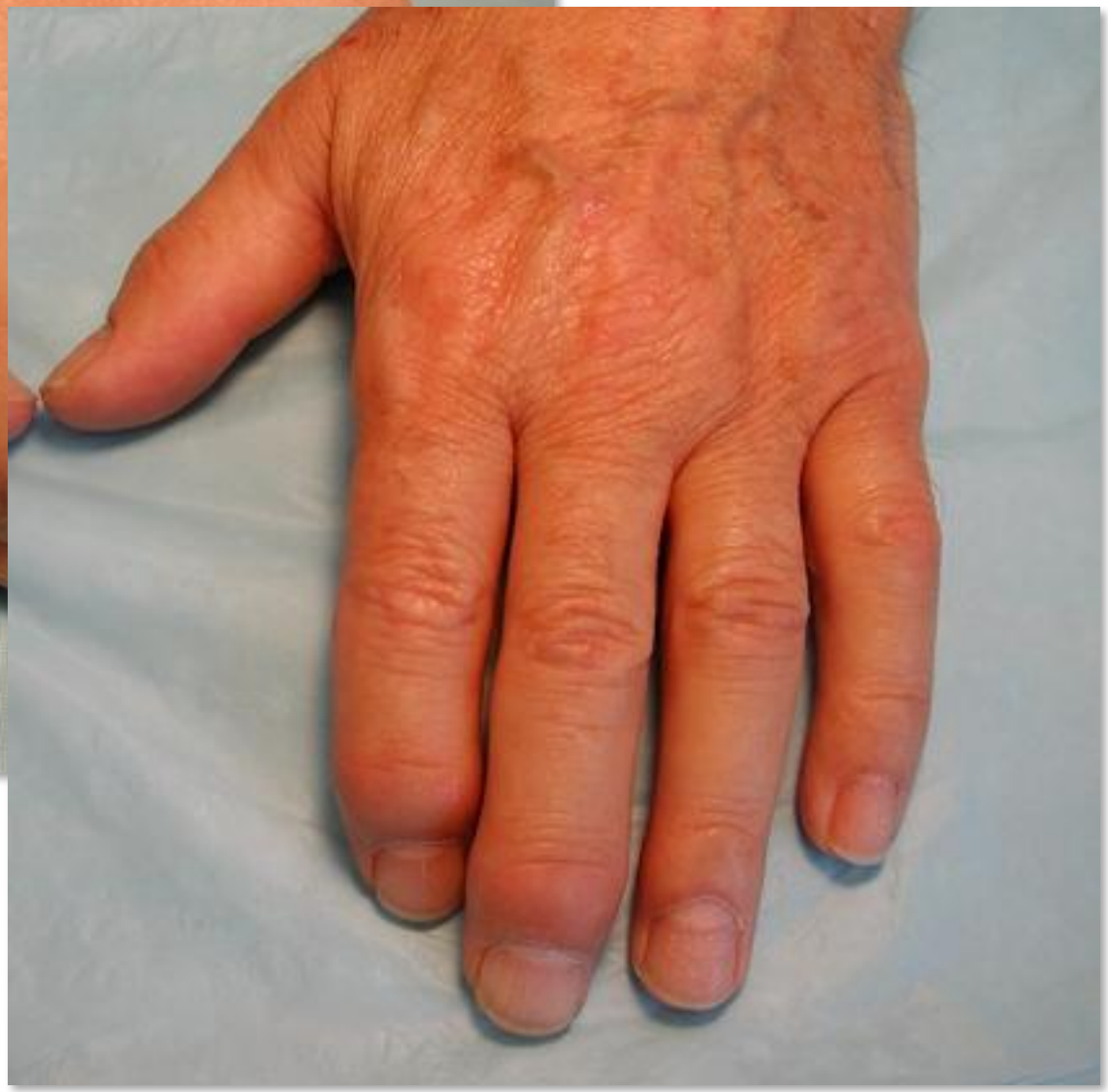
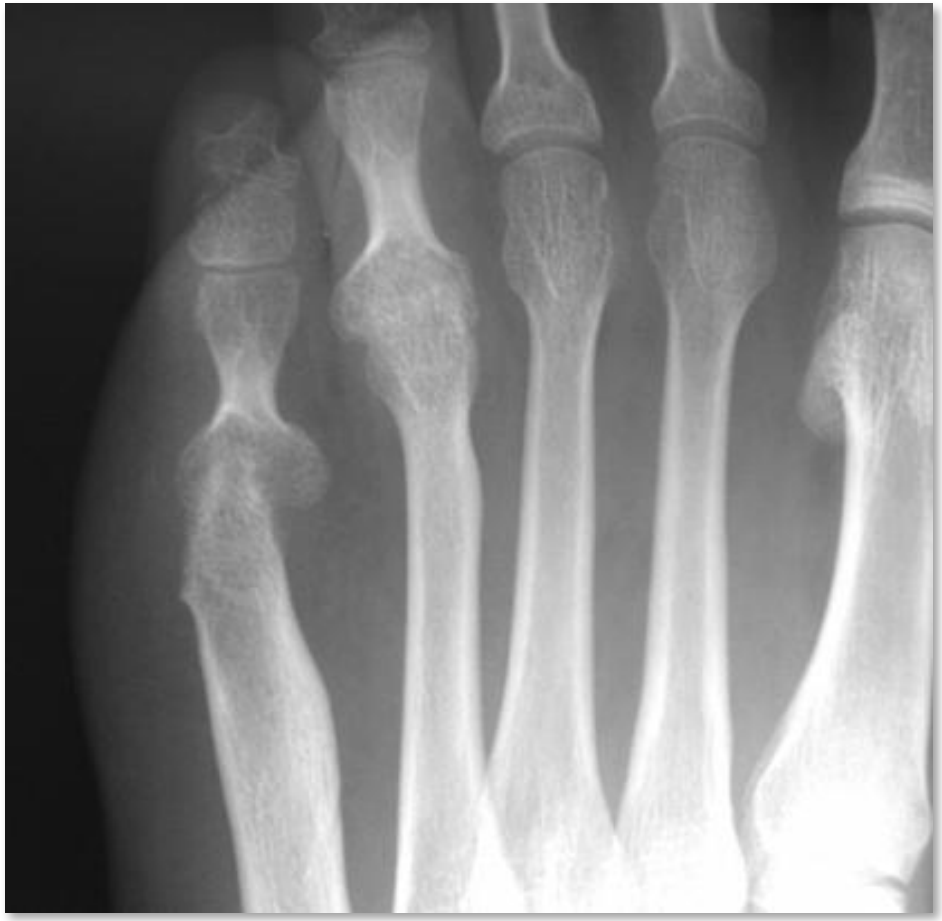
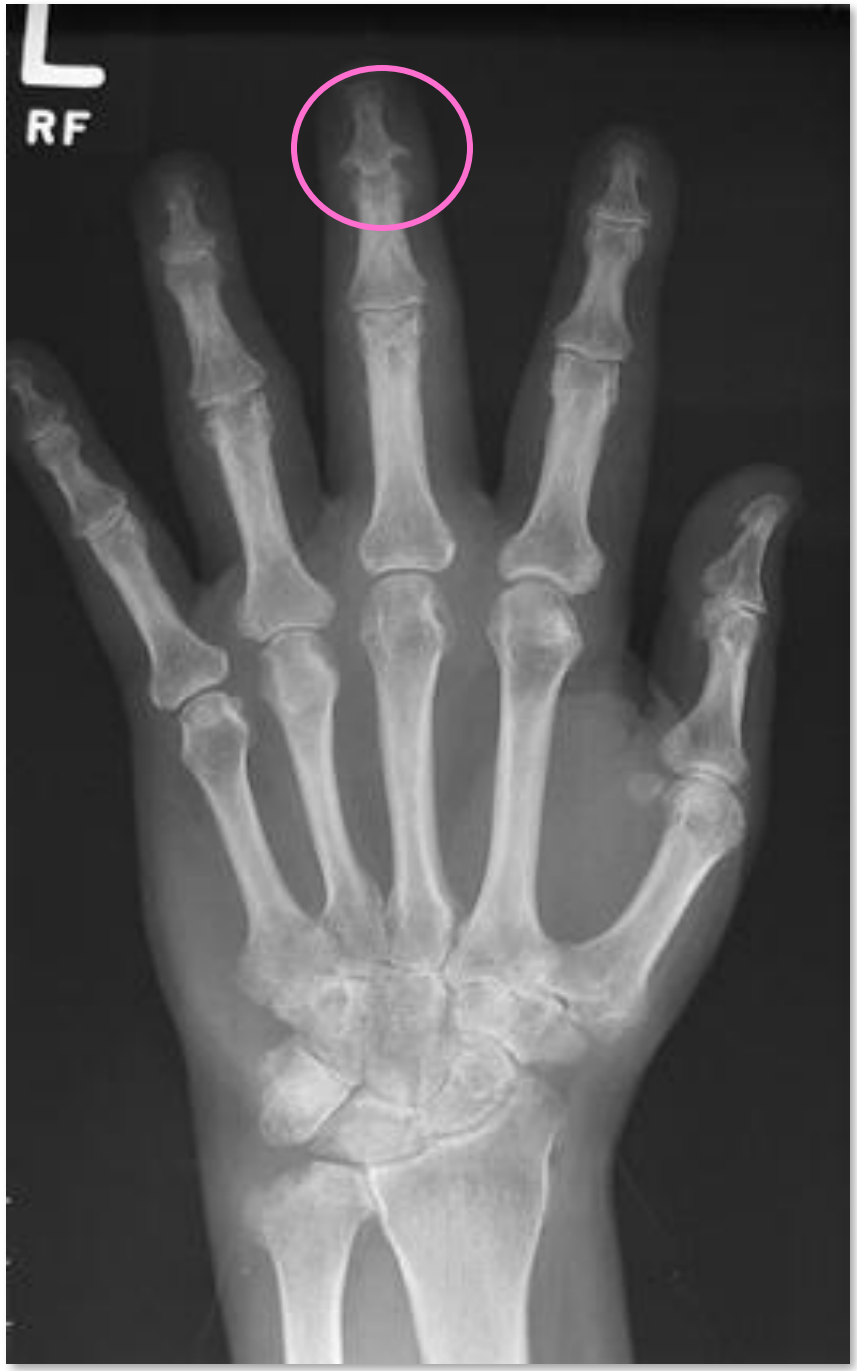


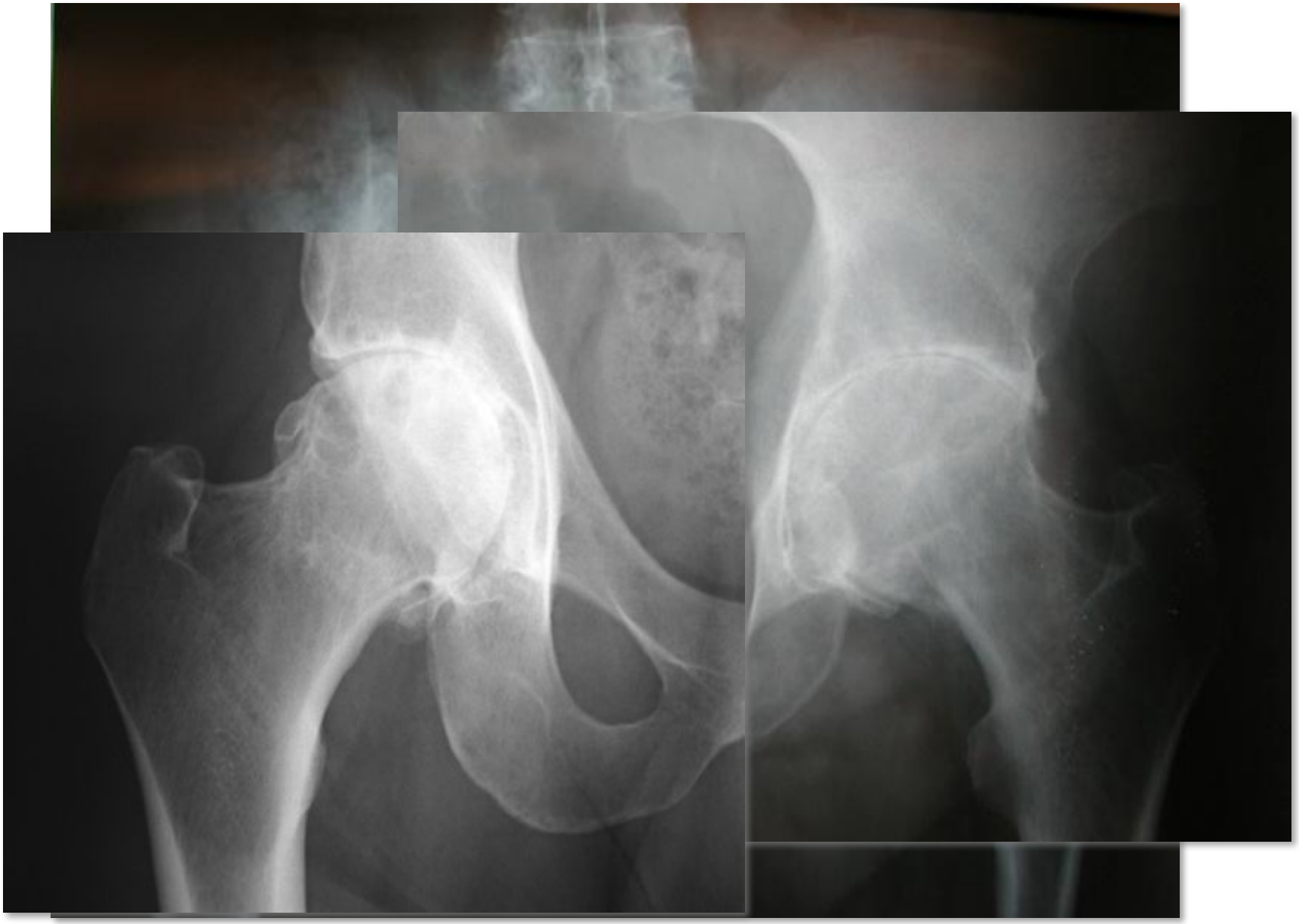


Psoriatic Arthritis: Radiographic features



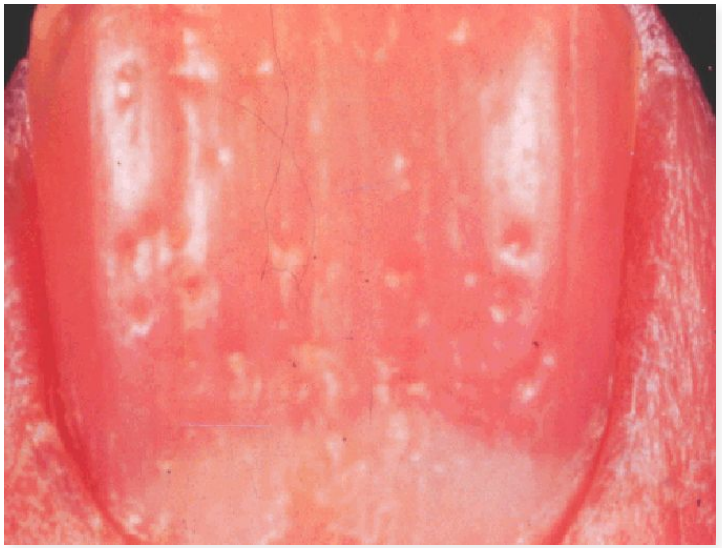


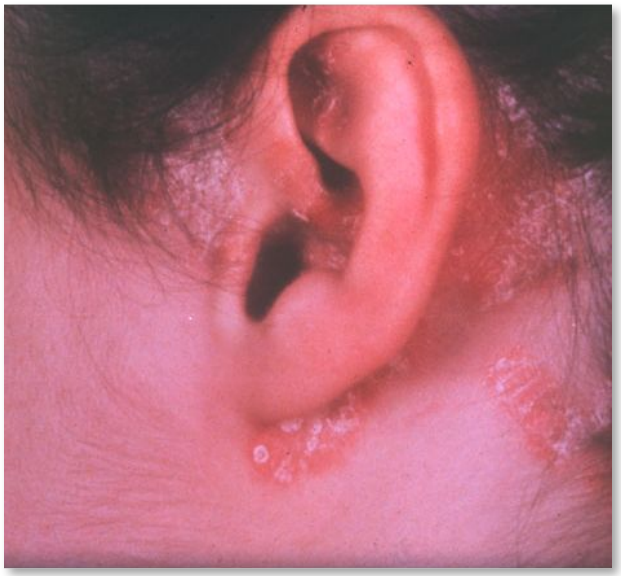
Psoriatic Arthritis: Sacroilitis and large joint involvement



PsA Treatment Issues

- NSAIDs/Low dose prednisone
- Methotrexate
- TNF inhibitors
- Aprimelast (PD4 inhibitor)
- Sekukinumab & ixekizumab (IL-17 inhibitor)
- Ustekinumab (IL-12/23 inhibitor)
- Tofacitinib (JAK inhibitor)



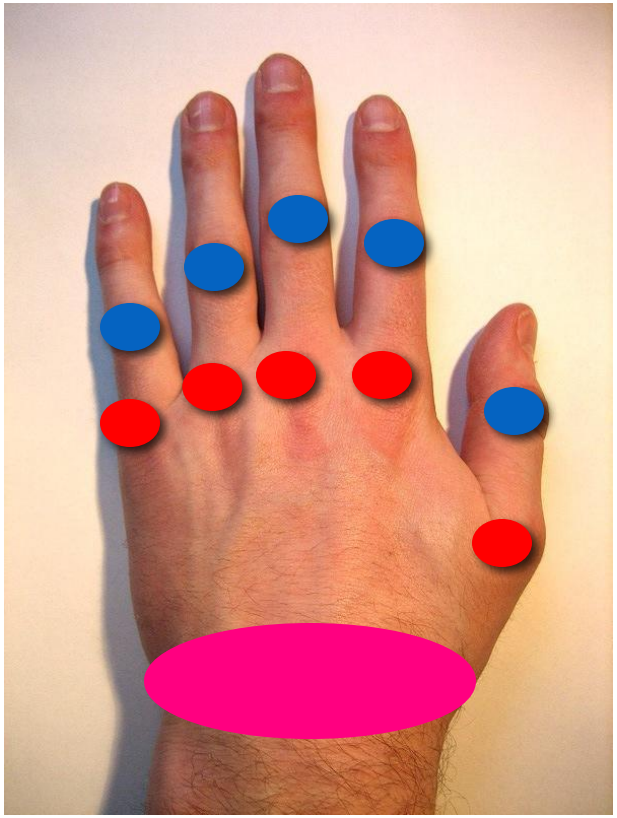


Treatment pointers

- Single joint, minimal skin: NSAIDs for joints, topicals for skin, joint injection in large joint
- Moderate to severe joint and skin: methotrexate, TNF, IL-17 inhibitor, tofacitinib
- Needlephobia: methotrexate, apremilast, toficitinib
- Sacroilitis: TNF inhibitors, IL-17 inhibitors
- Uveitis/iritis: methotrexate, TNF inhibitors
- Remember 3 patterns of joint disease
  - Inflammatory, Mechanical, Fibromyalgia
- ***Not all joint pain in psoriasis is psoriatic arthritis***

Systemic Lupus

- Women > men
- Hispanic, Chinese, African
- Inflammatory pattern
- Polyarthritis
- Laboratory tests helpful
  - ANA/SSA/Panel
- Often tenderness with mild swelling
- Joint distribution…..

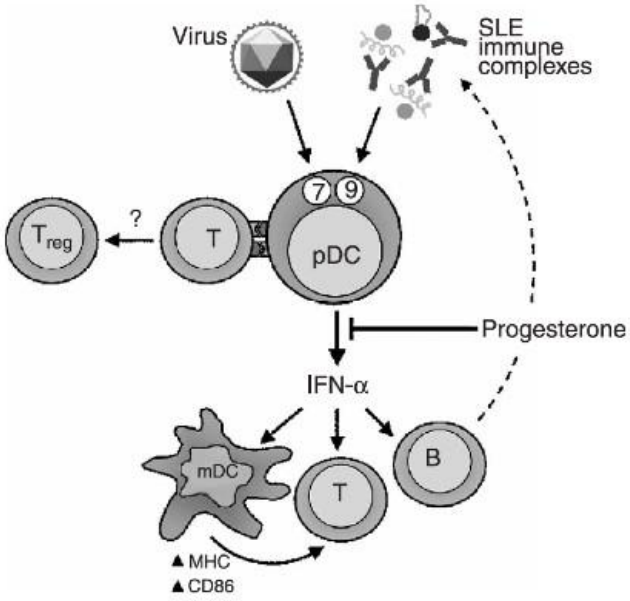


Etiology of SLE

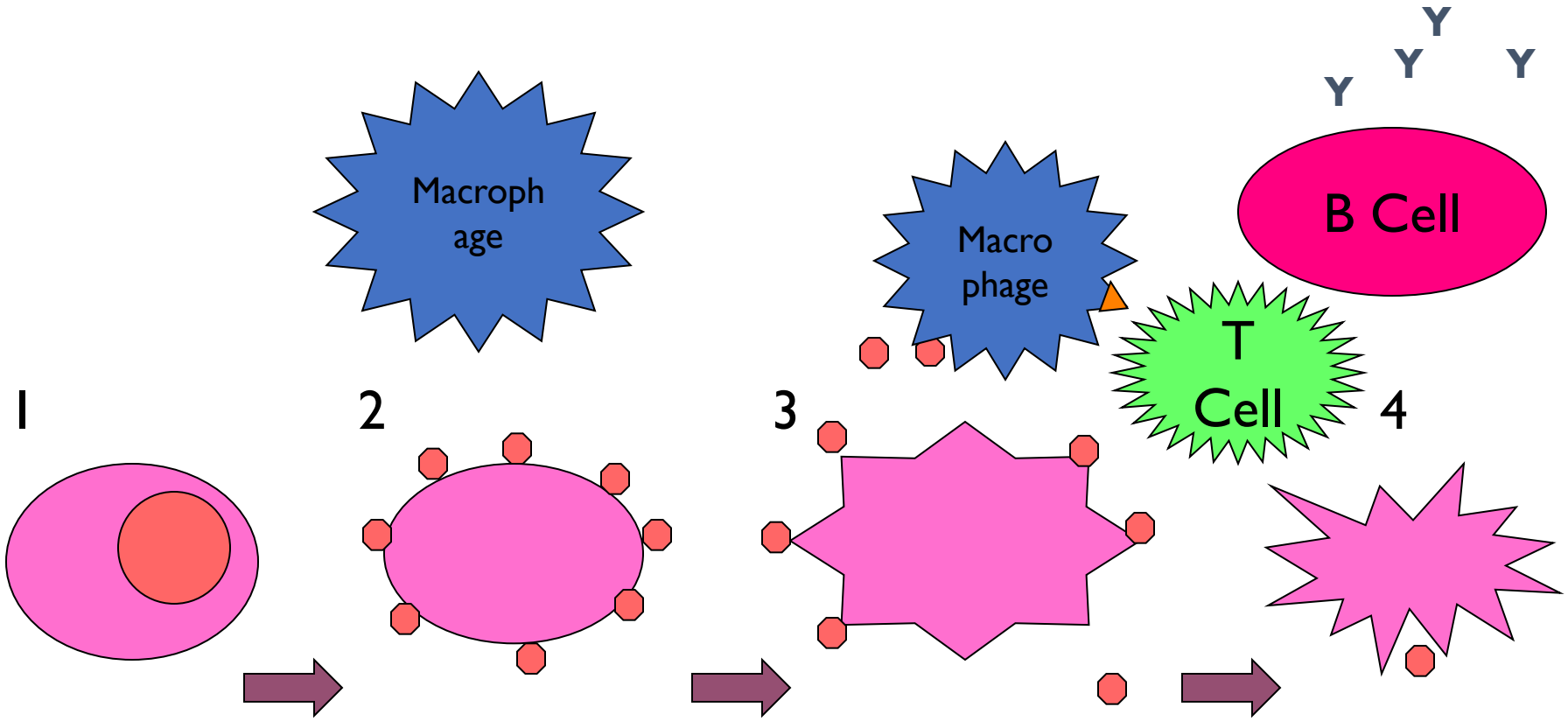
- **Genetics**
  - High concordance with monozygotic twins
  - Up to 12% of relatives may have SLE
  - Deficiencies in C2, C1q, C4, low levels of CR1 may influence development or expression of SLE
- **Hormonal**
  - Estrogens immunostimulatory; androgens tend to be immunosuppressive;
  - High dose estrogen containing BCP increase risk of developing SLE
  - Progestins may be protective.

Etiology of SLE

- **Environmental**
  - SLE Pts have higher titers to EBV and make Abs to retroviral protein sequences homologous to HLA antigens; Molecular mimicry?
  - Some infectious agents able to stimulate ANAs i.e. parvovirus B19
- **Immune**
  - Increase in a-interferon may lead to development of SLE
  - Defects in apoptosis may allow system to see self-antigens that are normally cleared



Apoptosis and Nucleosomes



Dying cell chromatin from nucleus organized into nucleosomes on cell surface for clearance

Macrophage normally clear cell debris quickly but defect in apoptosis and clearance allows antigens to "linger"

Nucleosome DNA becomes immunogenetic Specific T cells then stimulate B cells to produce Abs to nuclear antigens

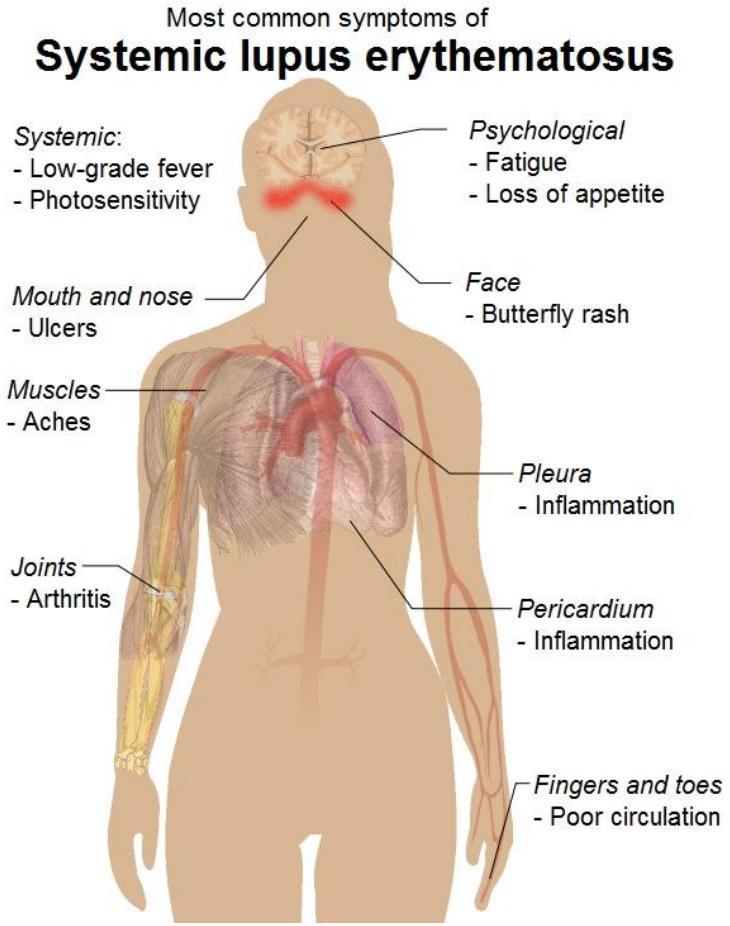
Princess Bride

Miracle Max Explains the Dangers of Partially Cleared Nuclear Debris

Miracle Max: Whoo-hoo-hoo, look who knows so much. It just so happens that your friend here is only MOSTLY dead. There's a big difference between mostly dead and all dead. Mostly dead is slightly alive.

When to think SLE?

- Young woman
- Multisystem involvement
- Objective abnormalities
  - Hair loss
  - History of ITP
  - AM joint stiffness/joint swelling
  - Rash/photosensitivity
  - Low WBC especially lymphopenia; thrombocytopenia
  - Active renal sediment
- *Aches and pains and fatigue are not objective manifestations of SLE*



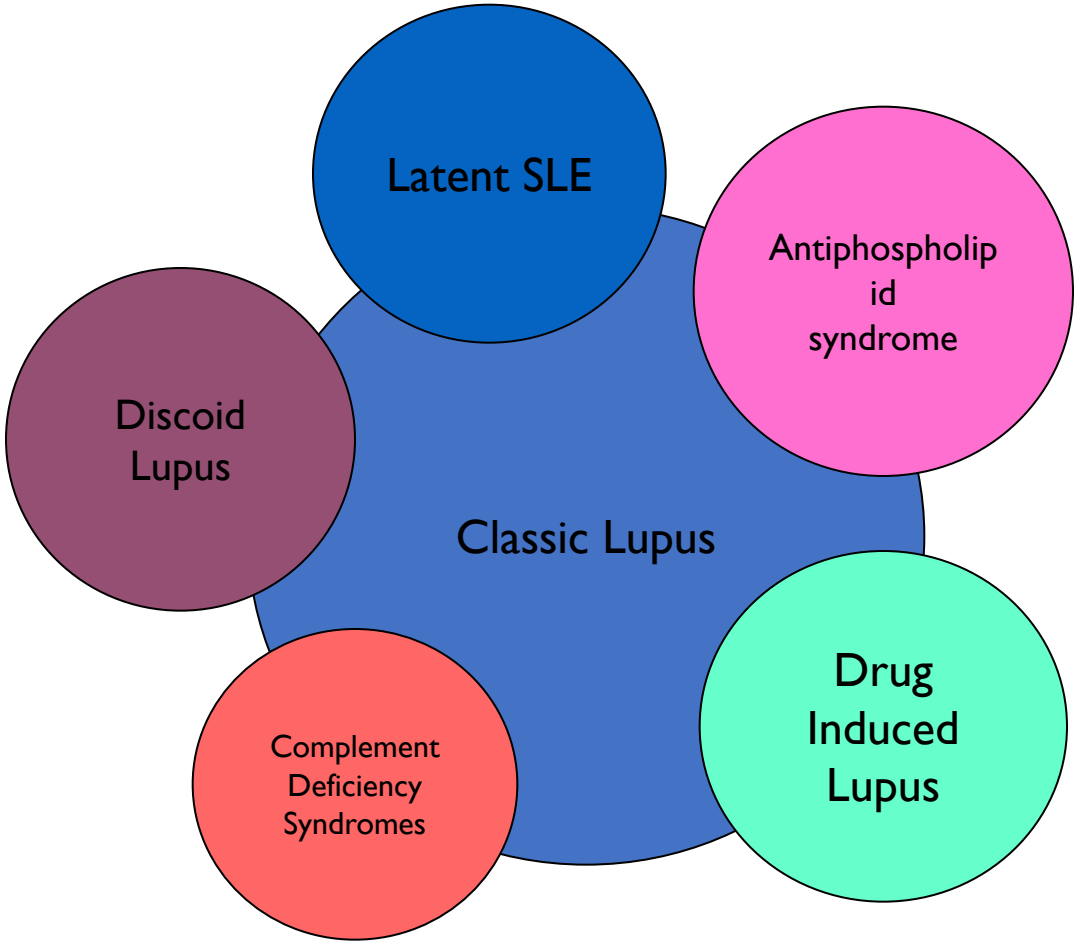
Wikepedia

SLE Criteria: SOAP BRAIN MD

Criteria	Description
Serositis	Pleuritis, pericarditis
Oral ulcers	Typically non-painful
Arthritis	Non-erosive, Jaccoud arthropathy
Photosensitivity	Rash in sun exposed area
Blood dyscrasia	Leukopenia, lymphopenia, anemia, etc
Renal disorder	Proteinuria, hematuria, casts
ANA	Elevated titer by IFA
Immune abn	DsDNA, Sm, APLA, etc
Neurologic disease	Seizures, psychosis etc
Malar Rash	Fixed rash on face over nasal bridge
Discoid rash	Scaring rash typically on face, scalp

ANA + 3 other criteria for SLE Dx

Clinical Subsets in SLE



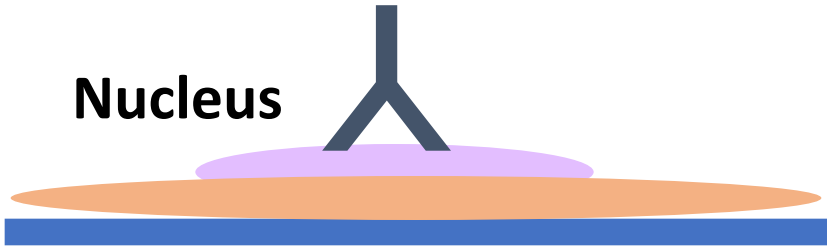
Step 1: FANA Technique

Step 1:

Patient Ab

Patient serum containing ANAs placed on slide containing HEp-2 cells. ANAs attach to cell nucleus

Nucleus

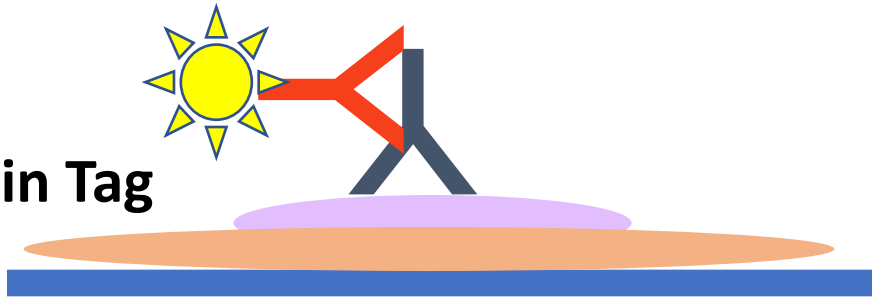


Slide

Antihuman IgG

Step 2:

Fluorescein Tag

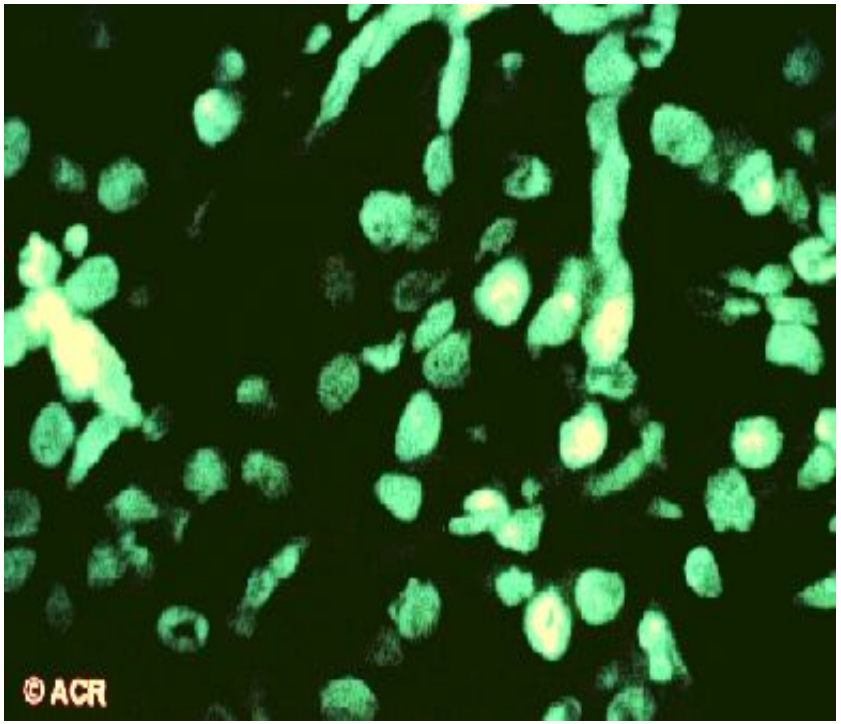


The preparation is washed and fluorescent labelled anti-immunoglobulin is added. Preparation glows when viewed under fluorescence microscope

Fluorescent Antinuclear Antibody (FANA)

Four basic FANA patterns representing antibodies to specific groups of nuclear antigens:

- Homogeneous
- Speckled
- Nucleolar
- Centromere



Step 2: Extractable Nuclear Antigens

Autoantibody name	Abbrev	Association
Anti-Sjogren's syndrome A	SSA	Found in SLE and Sjogrens syndrome. Associated with rashes and arthritis. Also rash, arthritis, and abnormalities in heart conduction in newborns if mother has this autoantibody
Anti-Sjogrens' syndrome B	SSB	Less common in SLE; more often in Sjogren's syndrome
Double stranded DNA	DsDNA	This autoantibody goes up and down with disease activity. Found in SLE patients with more severe disease such as CNS, kidney, or heart involvement.
Anti-ribonuclear protein	RNP	People with this antibody can have Raynaud's (hands turn white with cold exposure), arthritis, and lung fibrosis or pulmonary hypertension
Anti-Smith	SM	Similar to RNP but also associated with kidney disease
Anti-ribosomal P	none	As discussed can be seen in people with CNS disease
Anti-phospholipid	APLA	Associated with blot clots; only about 40-50% of people with these antibodies will develop a clot
Lupus anticoagulant	LAC	Similar to APLA

Why ANAs Keep Rheumatologists Busy

Sensitivity of FANA - 95%

Positive rate in population - 3%

Prevalence of SLE in population - 0.05%

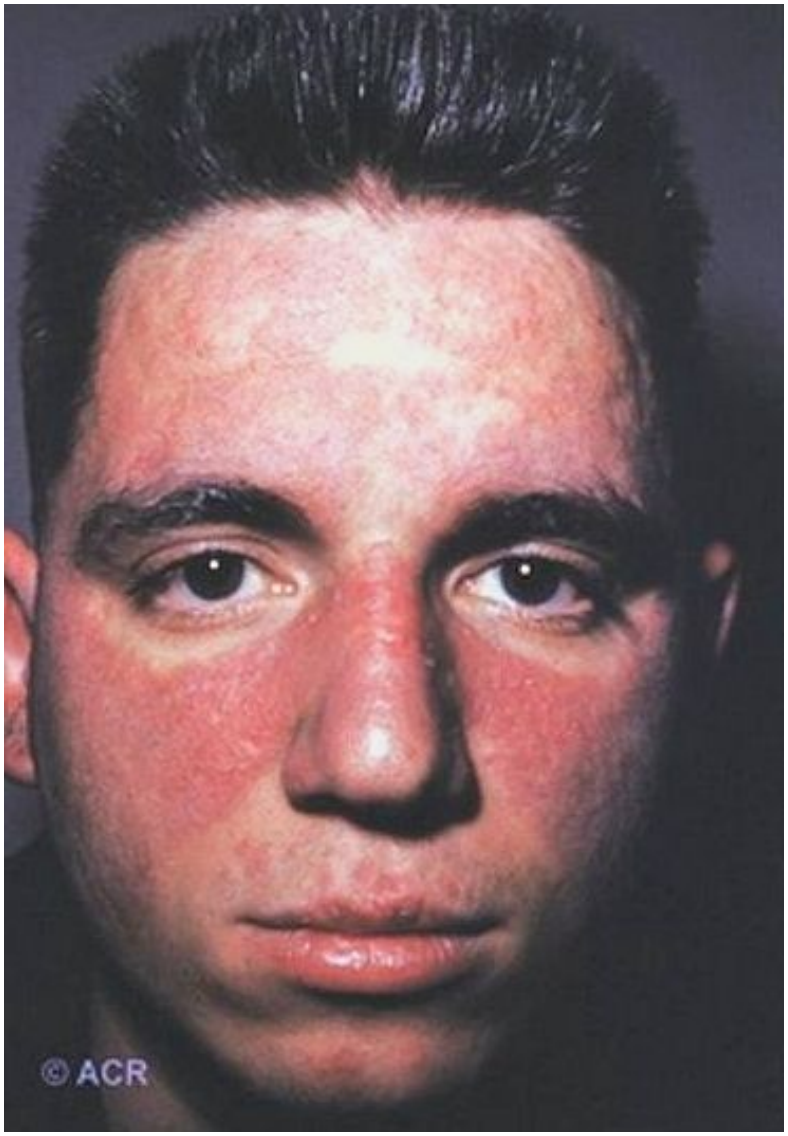
If 100,00 people had ANA checked:
50 with SLE will have a true + FANA
and 2,450 will have a false + FANA!

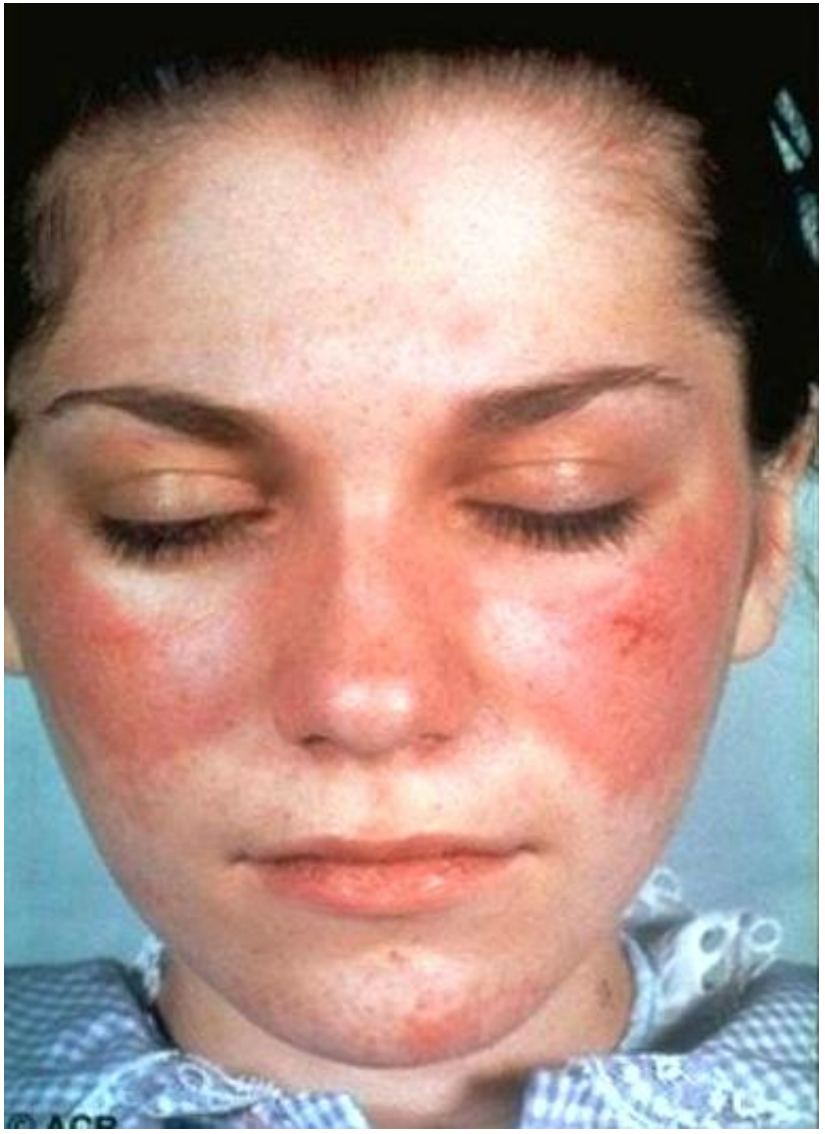
Helpful ANA Hints

- A positive FANA in isolation is not useful especially in low titer i.e. 1:40, 1:80
- Higher level FANA in isolation; watch and consider checking anti-thyroid antibodies
- Isolated low level ENA antibodies are likely also not clinically significant i.e. low level RNP
- Dx of SLE requires + FANA & 3 other criteria; many Pts are labeled with the diagnosis of SLE who actually have fibromyalgia
- Check antiphospholipid antibodies after Dx; if positive get some help! (miscarriage, DVT, PE, thrombocytopenia)

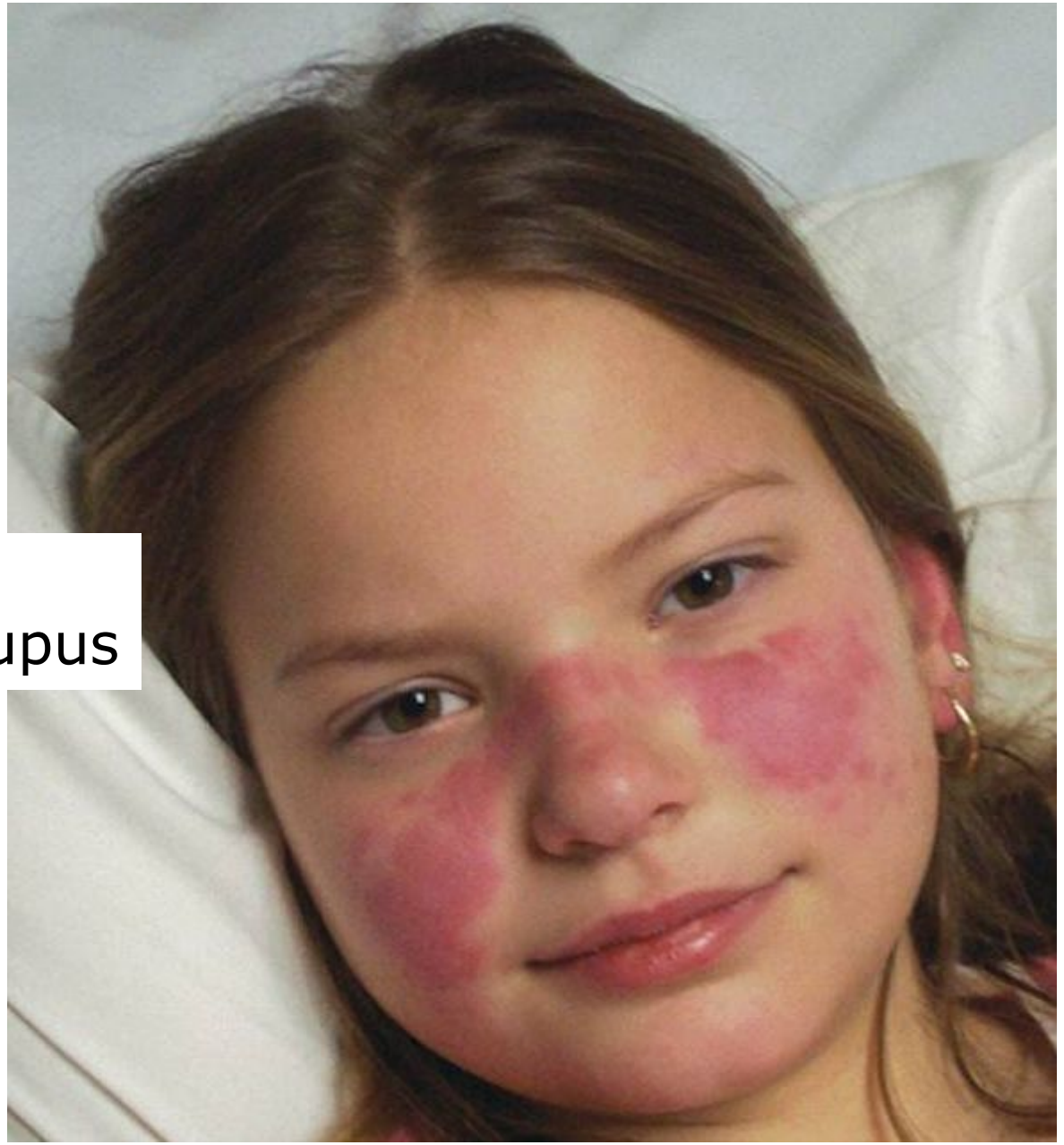
Acute Cutaneous Lupus

DDX: rosacea, seborrhea, fungus, pemphigus, flushing

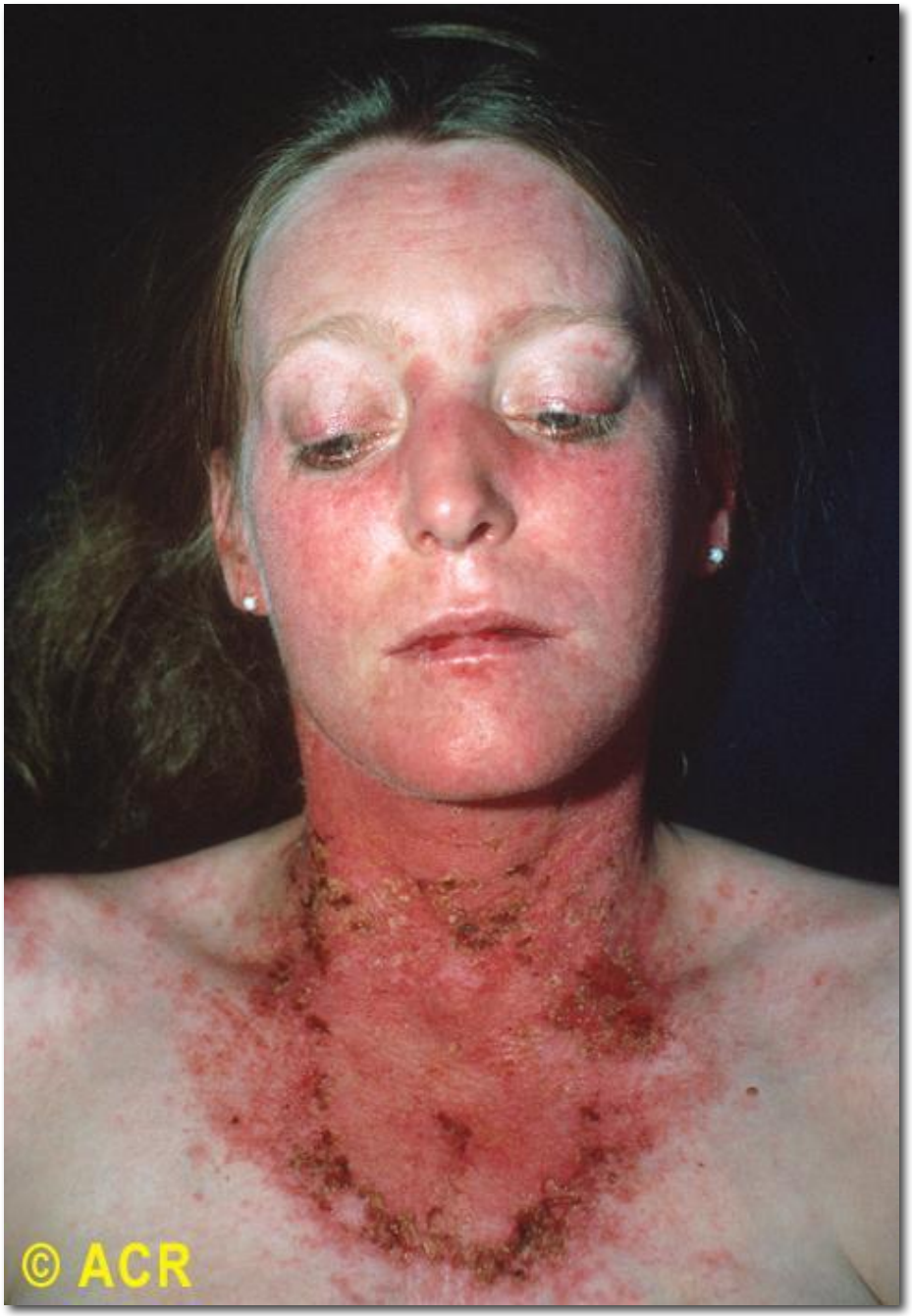




Butterfly rash
Acute cutaneous lupus

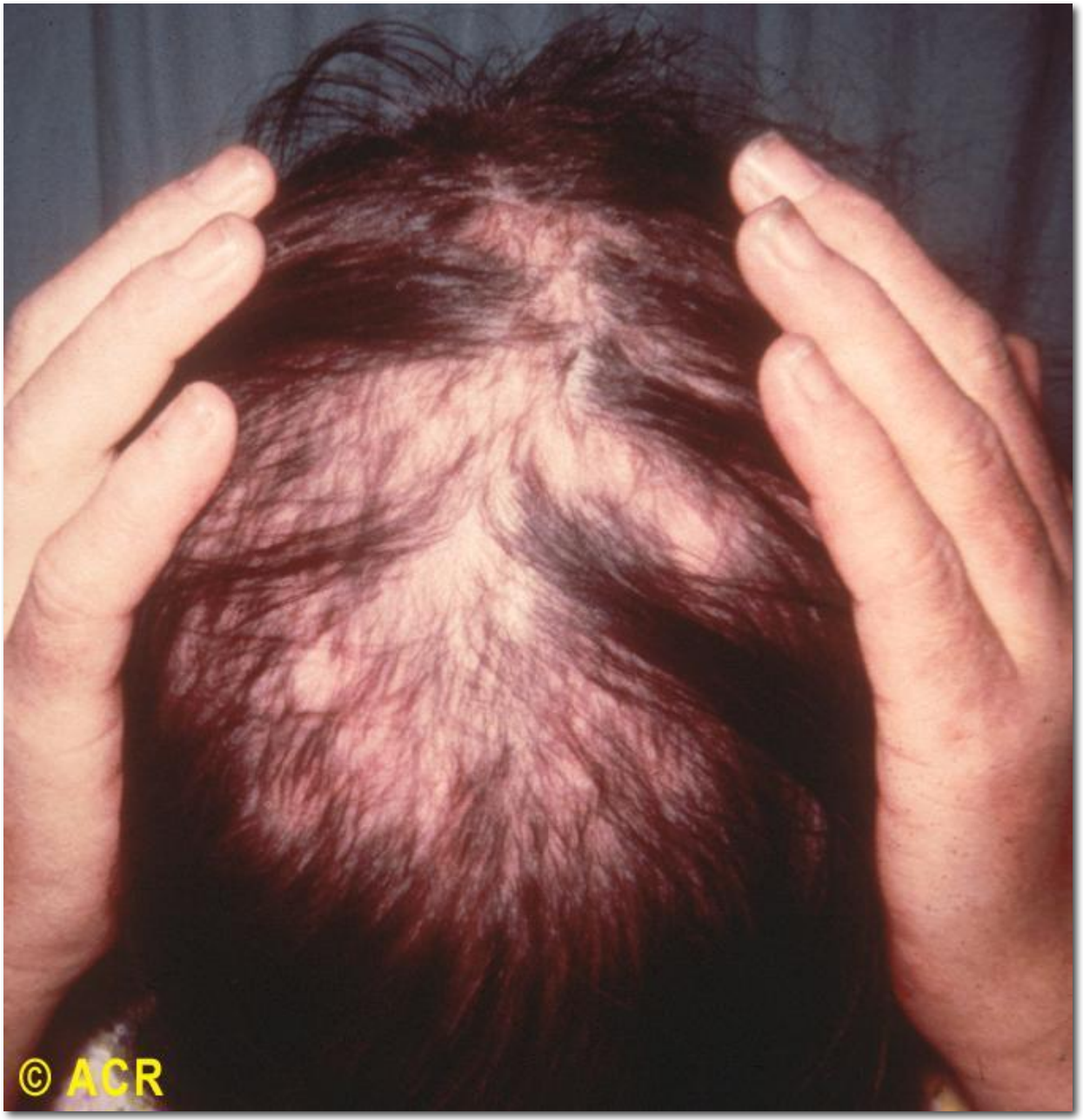


Photosensitivity
Occurs in 25%

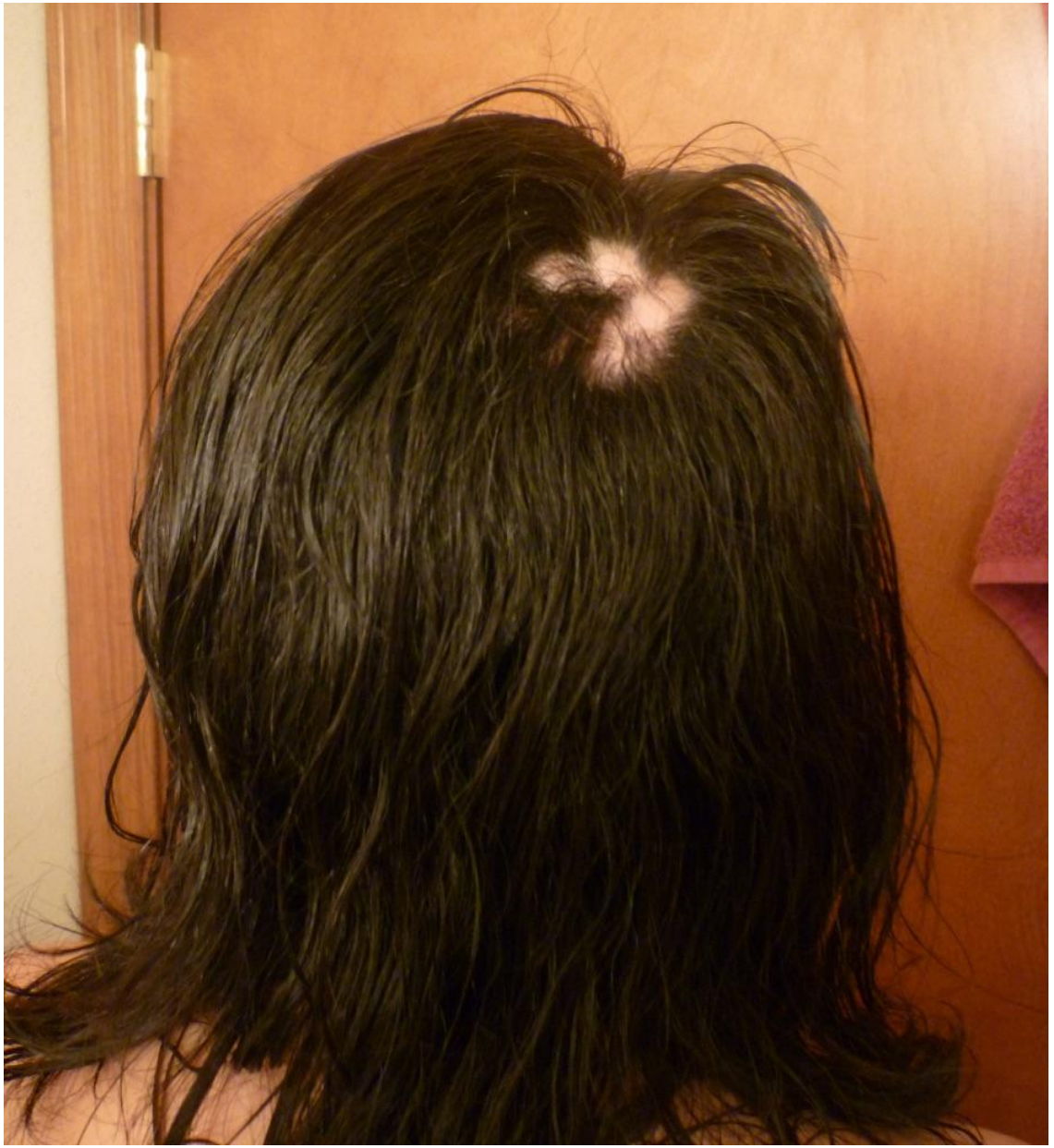


Diffuse alopecia

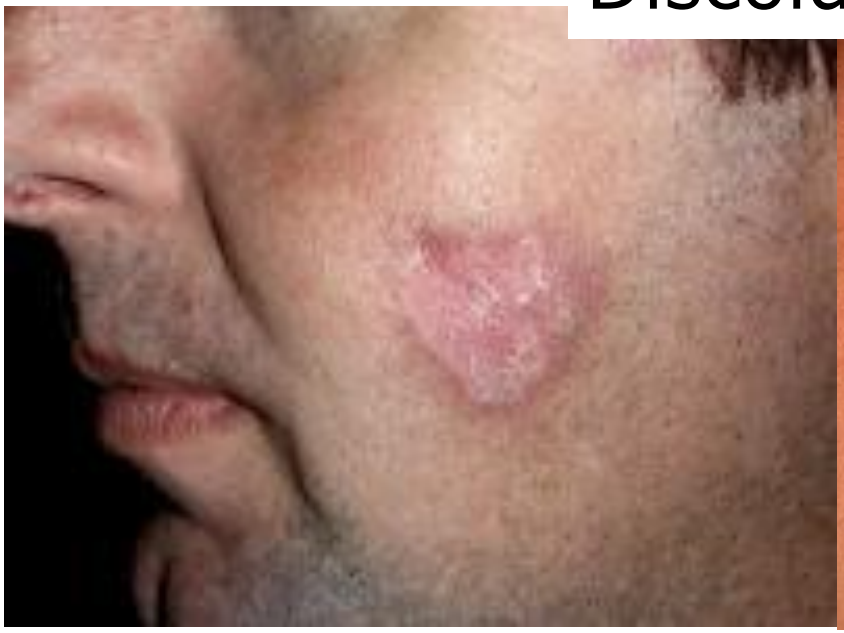
Non-scarring

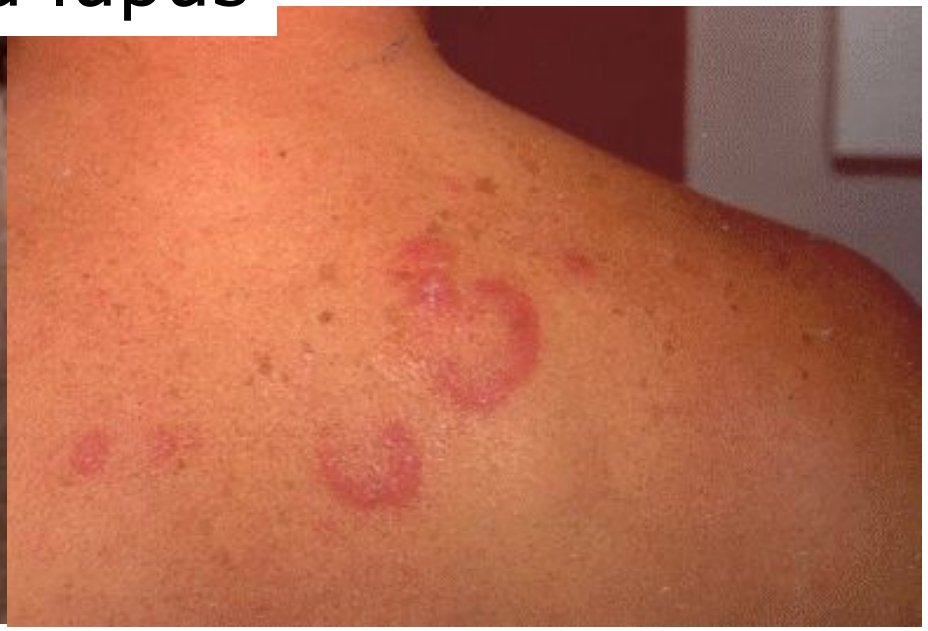


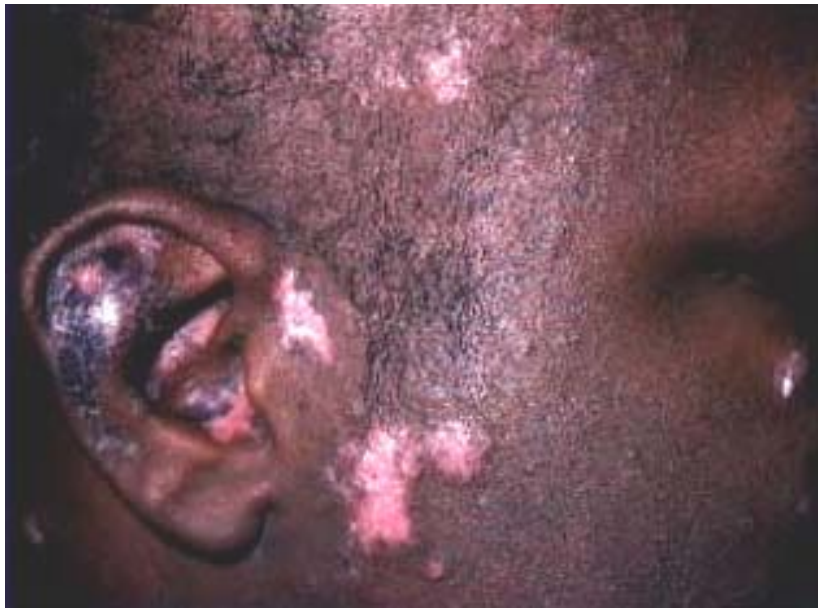
Alopecia areata

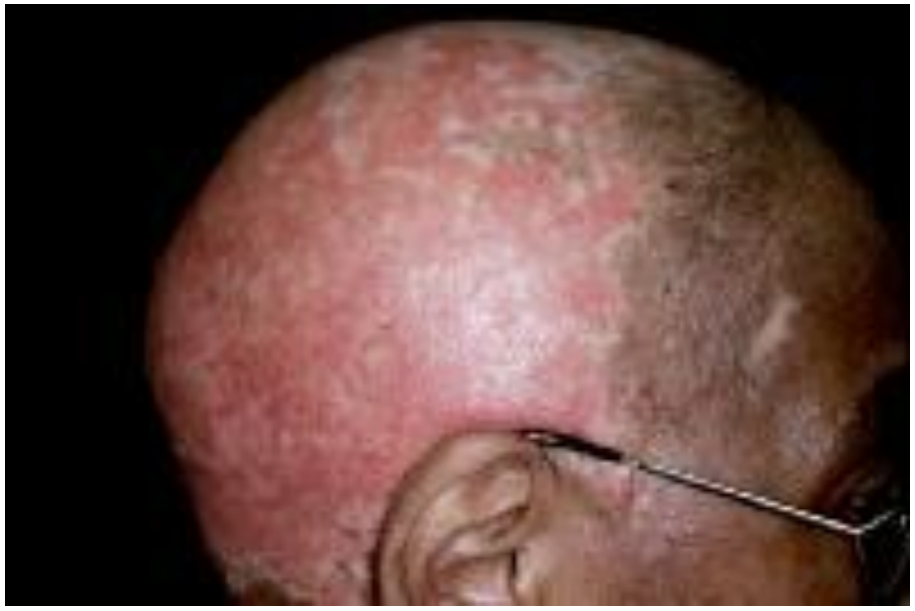


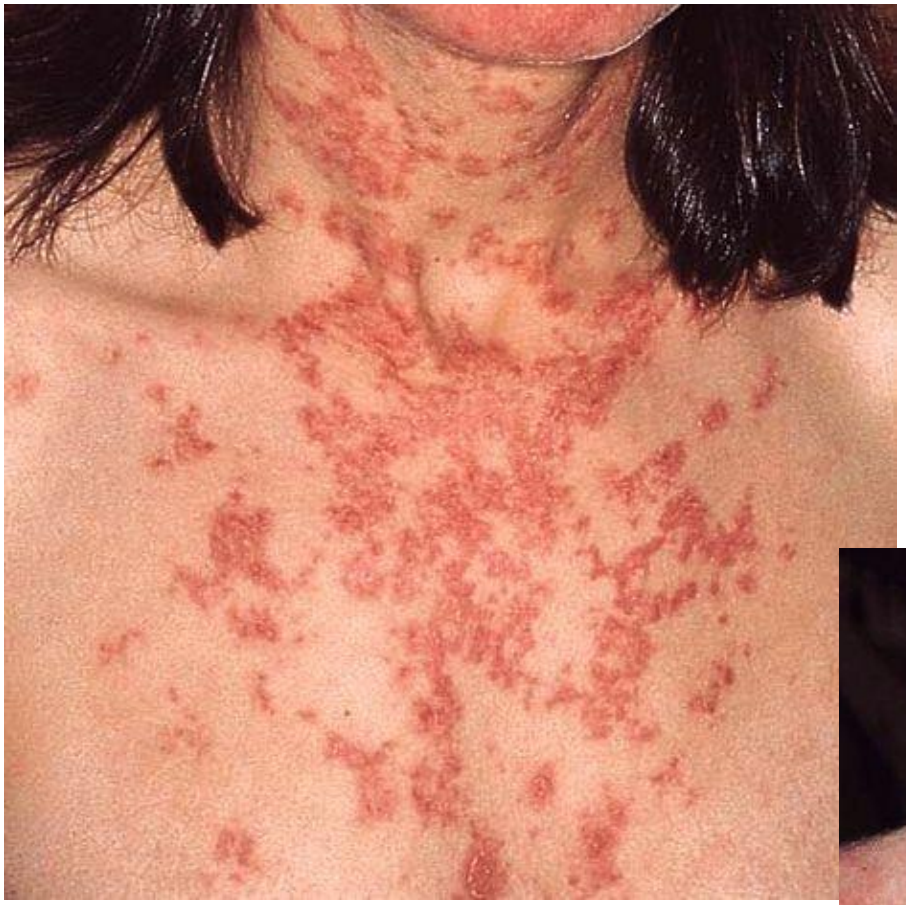
Discoid lupus



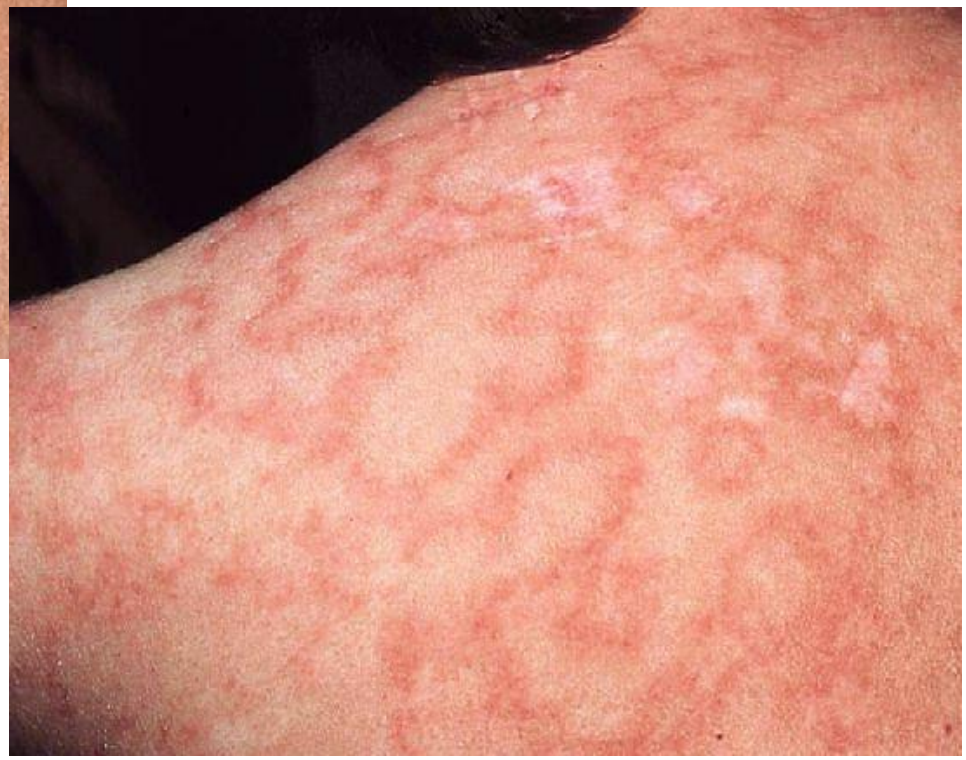






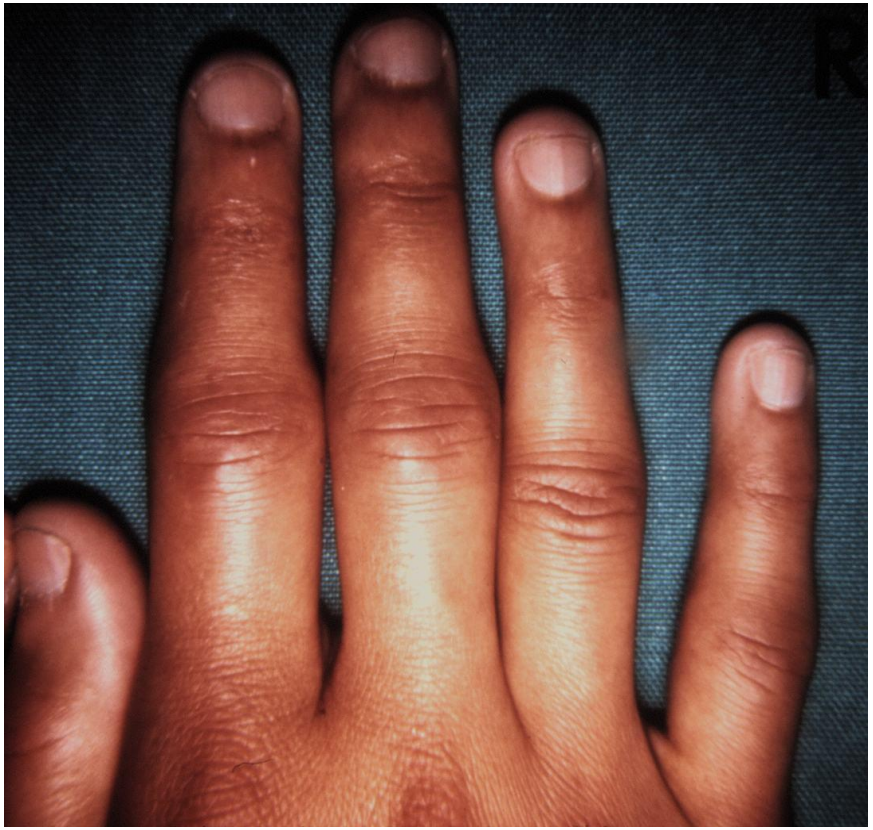


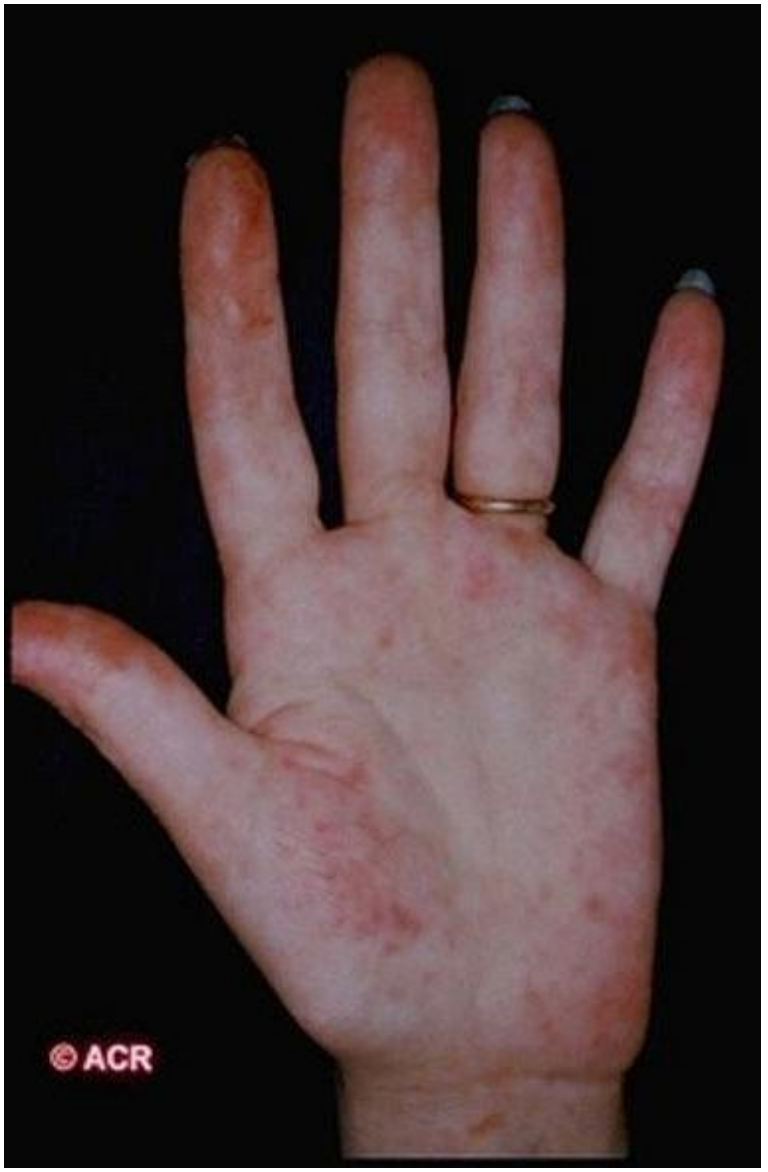
Subacute Cutaneous Lupus
Very photosensitive



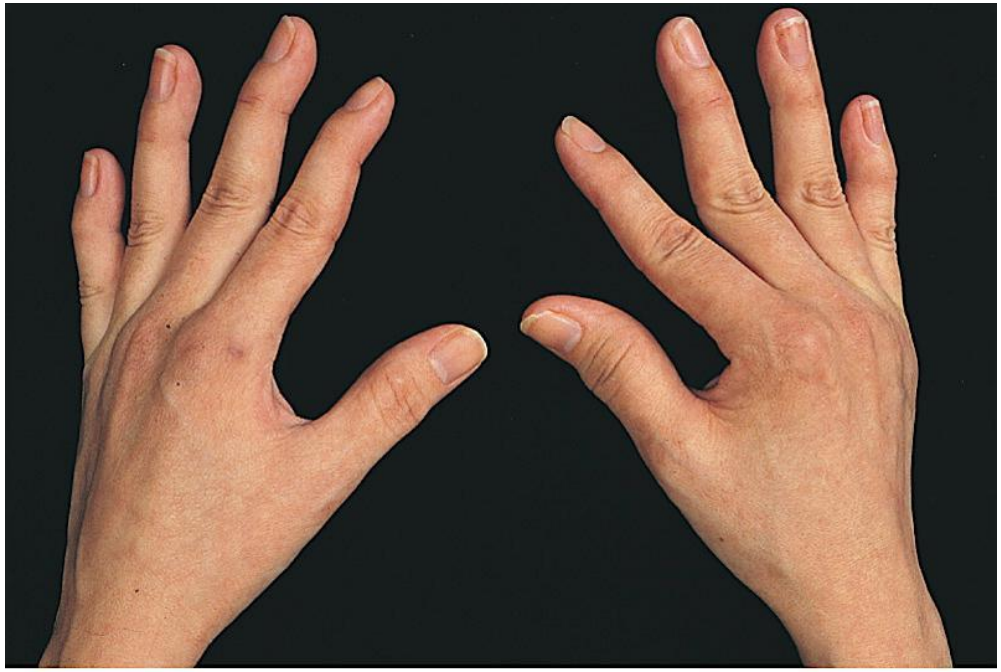
www.archrheumatol.net/atlas

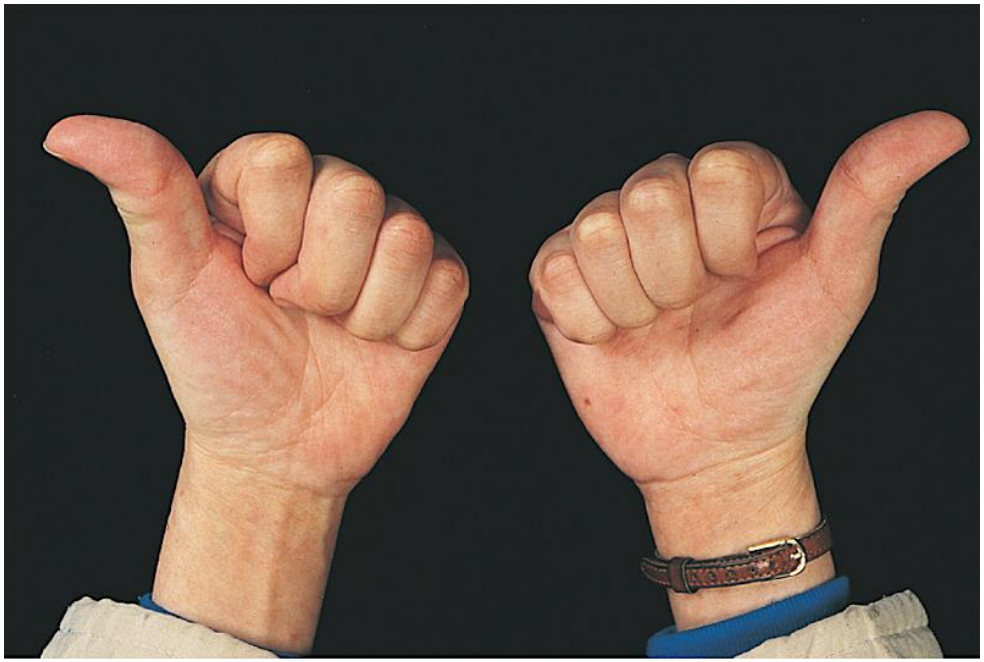
SLE Arthritis and Hand Vasculitis

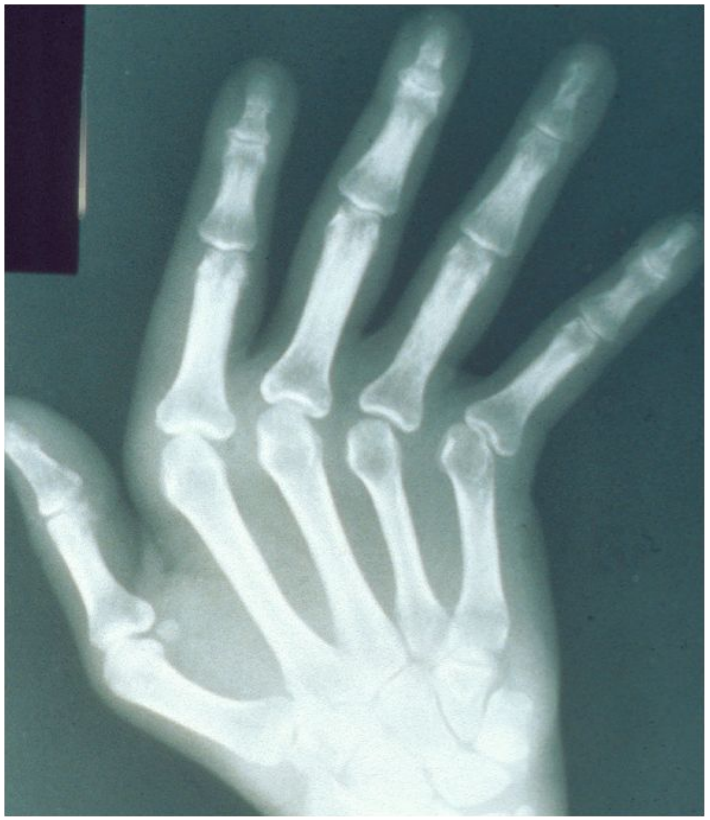




Jaccoud Arthritis







Lupus Nephritis

Classification of GN

I Normal

II Mesangial

IIIA Focal segmental

IIIB Focal proliferative

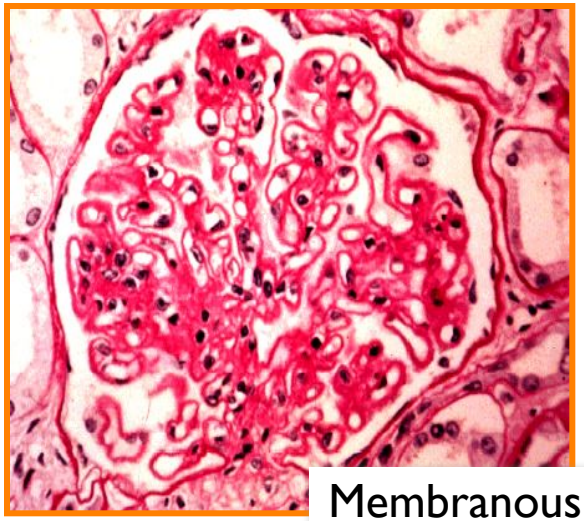
IV Diffuse proliferative

V Membranous

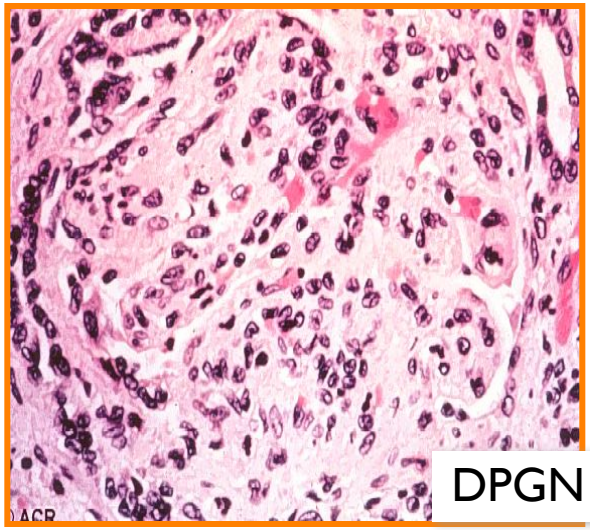
VI Advanced sclerosing

Activity vs chronicity index

Biopsy useful in choosing therapy



Membranous



DPGN

Treatment Issues in SLE

- Prednisone for all types of SLE
  - Dose should be based on severity of manifestations
  - Pulse steroids for most severe manifestations
- NSAIDs for joint pain or serositis
- Hydroxychloroquine for all forms of SLE alone or combined with other agents
- Mycophenolate for serious organ involvement
- Cyclophosphamide for most serious disease
- Belimumab (anti-Blys) for pts not fully controlled

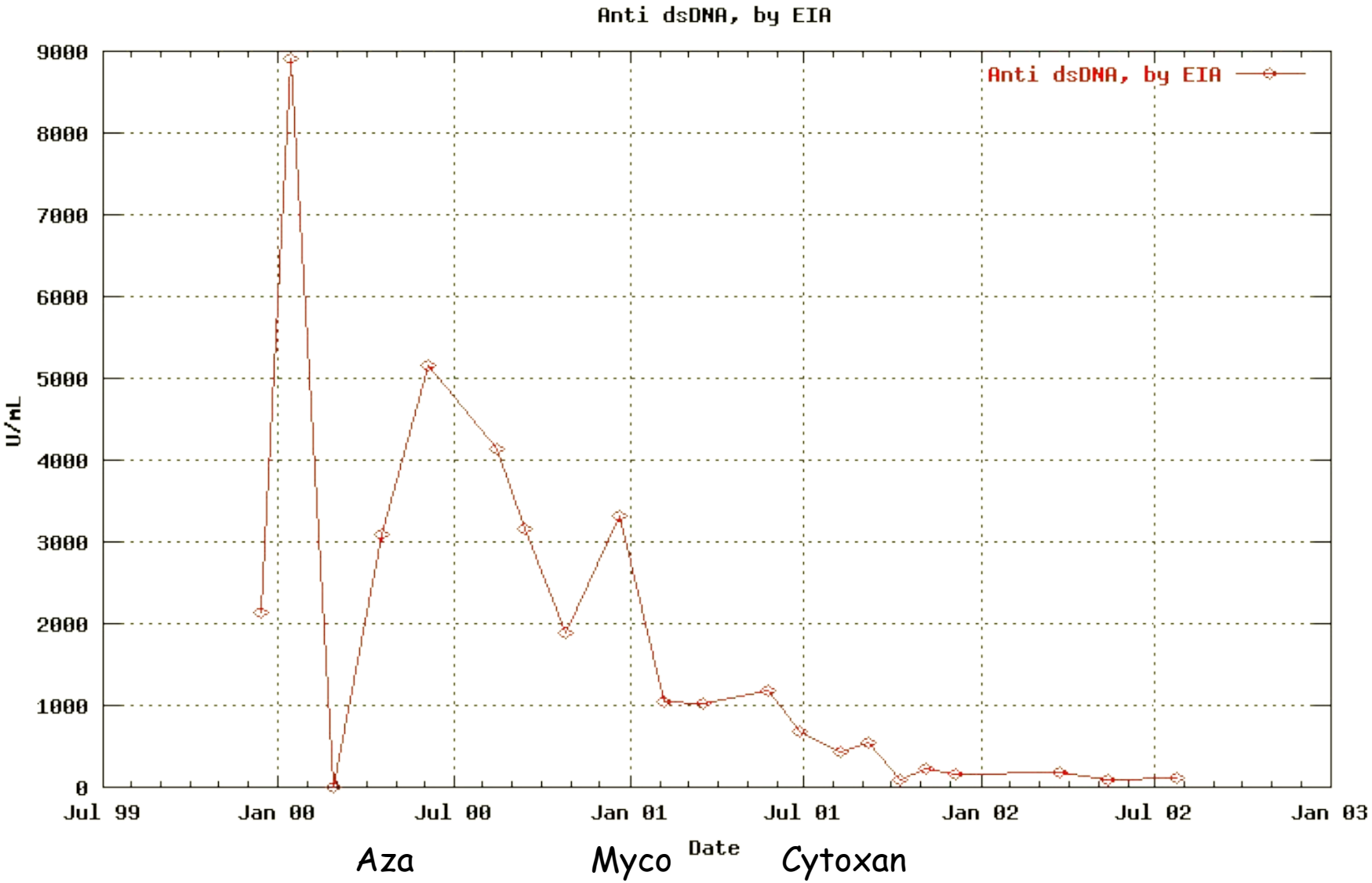
Patient with SLE

- Oct 1999: 24 y/o Asian woman Dxed with SLE age 22. Features Raynaud's, arthritis, and malar rash. Rxed with methotrexate 10 mg/week, plaquenil 200 mg BID, and intermittant doses of prednisone
- Developed Sx and Sx of nephritis with biopsy showing DPGN
- Jan 2000: Started on azathioprine (max dose 200 mg/d), prednisone 30 mg/day, plaquenil 400 mg/day, MTX stopped.

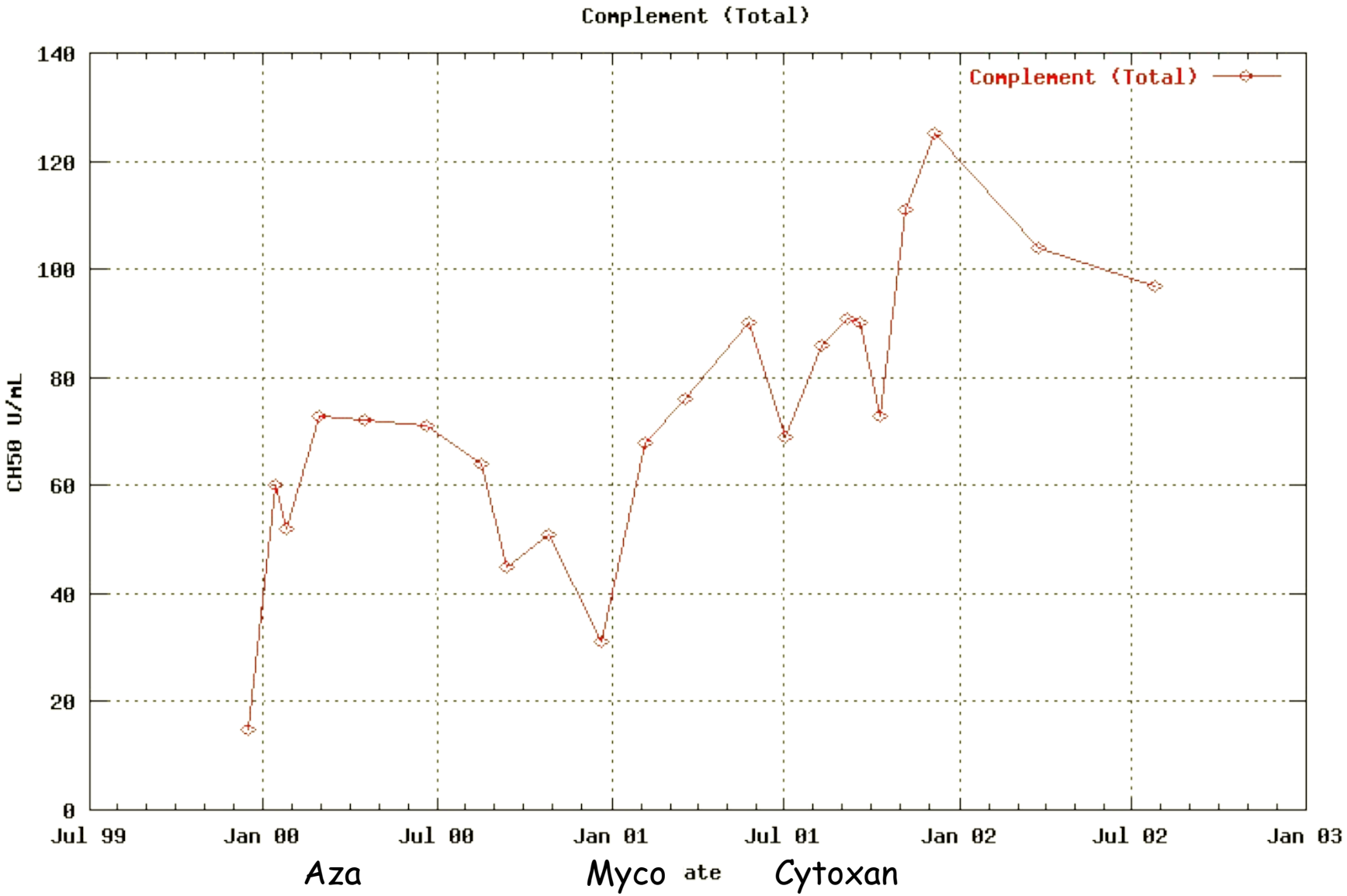
Patient with SLE

- Jan 2001: Started mycophenelate 2 g/d and bolus solumedrol (1 gram each). Oral prednisone to 40 mg/day
- June 2001: Cyclophosphamide (up to 1.2 g/mo) and bolus solumedrol. (8 cycles with one consolidation dose) Proteinuria from 6 grams/day to 200 mg/day
- Azathioprine restarted; prednisone 10 mg/d

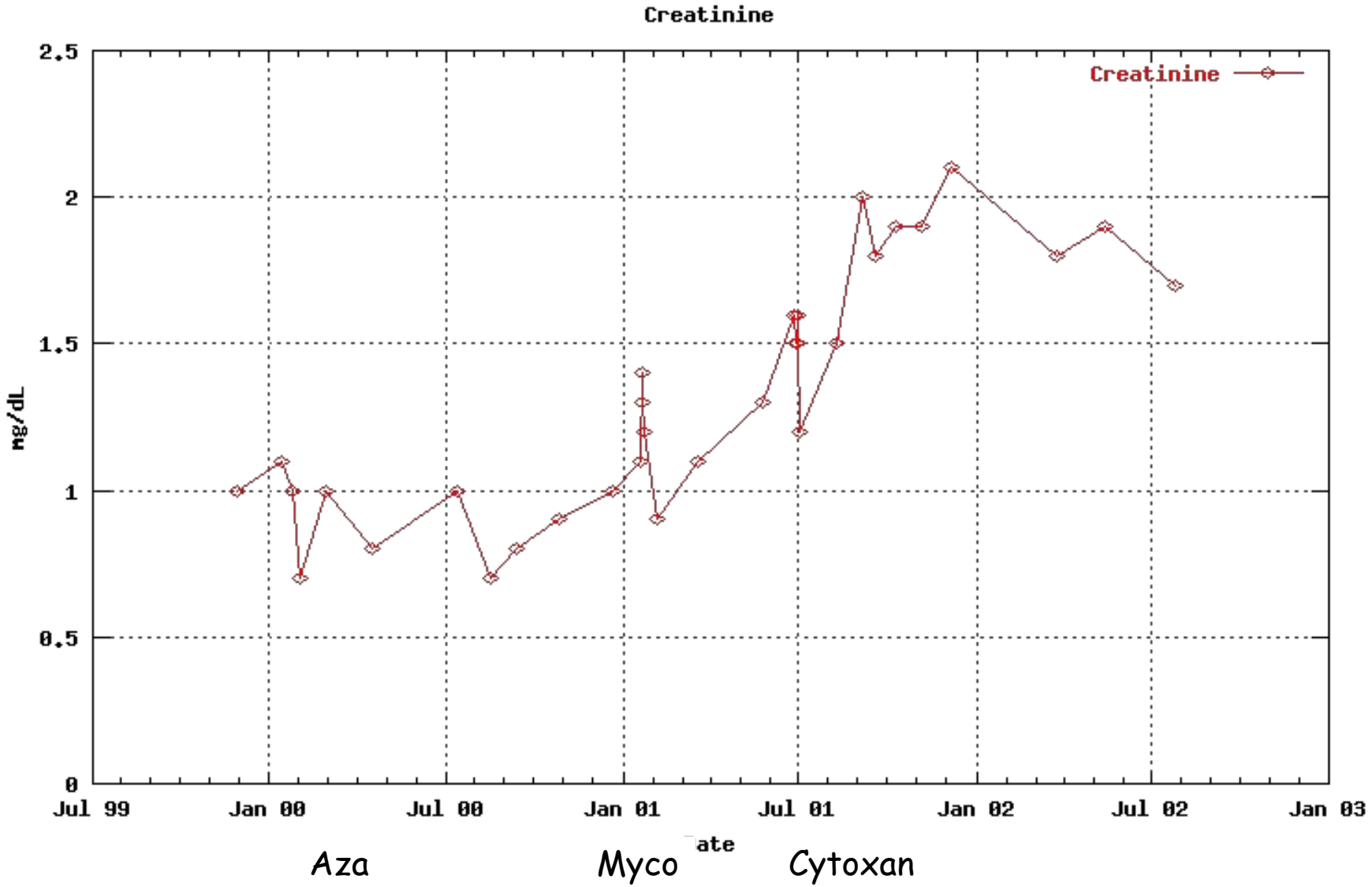
DsDNA


Anti dsDNA, by EIA
Anti dsDNA, by EIA
U/mL
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
Jul 99
Jan 00
Jul 00
Jan 01
Jul 01
Jan 02
Jul 02
Jan 03
Date
Aza
Myco
Cytoxan

CH50


Complement (Total)
Complement (Total)
CH50 U/mL
140
120
100
80
60
40
20
0
Jul 99
Jan 00
Jul 00
Jan 01
Jul 01
Jan 02
Jul 02
Jan 03
Aza
Myco ate
Cytoxan

Creatinine


Creatinine
Creatinine
mg/dL
2.5
2
1.5
1
0.5
0
Jul 99
Jan 00
Jul 00
Jan 01
Jul 01
Jan 02
Jul 02
Jan 03
Aza
Myco
ate
Cytoxan

Important Primary Care Issues

- Treat HTN!
- Exercise - non-impact loading activity important for osteoporosis, pain control, fatigue
- Immunizations - recombinant or attenuated vaccines ok; titers lower? Avoid live virus vaccines if on significant meds
- Address lipids!
- Drugs that cause DSLE do not exacerbate SLE
- Combined LD estrogen BCPs do not appear to flare illness but avoid in Pt with aPL or history of thrombosis; progesterone only regimens useful and may affect disease course positively? physical barriers

Summary

- Rheumatoid arthritis
  - Early Dx early therapy
  - CCP testing is very helpful
  - Feel comfortable with methotrexate
- Psoriatic arthritis
  - Not all joint pain in psoriasis is PsA
  - Methotrexate covers a variety of forms of PsA
- SLE
  - ANA testing very useful; be careful who you test
  - Plenty of primary care work in SLE


STOP