# THE ARTHITIDES: FOCUS ON RHEUMATOID AND OSTEOARTHRITIS

MICHAEL PINCUS, DO
RHEUMATOLOGY
LAHEY HOSPITAL AND MEDICAL CENTER

# Disclosures

- No Disclosures

# Approach to the Arthritic Patient

- History is key
- Duration and onset
  - acute (hours/days) or chronic (insidious)
- Inflammatory or Non Inflammatory
  - If Inflammatory
    - Soft tissue (bursitis/myalgia) vs Articular
- Monoarticular vs Multiple
- Symmetric or Asymmetric
- Monoarticular -> Aspirate!
  - Acute
    - Inflammatory
      - Crystal
      - Infection
      - "pseudoseptic" presentation of a typically polyarticular disease
    - Non Inflammatory
      - Trauma
      - Hemarthrosis
- Polyarticular

# Approach to the Arthritic Patient

- Rash
  - AOSD→ dermatographism, urticaria
  - SLE→ ACLE, Malar, Tumid
  - Infections:
    - Lyme-> Erythema Chronicum Migrans
    - Reactive-> Keratoderma Blenorrhagicum
    - Virus/AOSD→ Maculopapular
  - Vasculitis→ Palpaple Purpura
  - Psoriatic→ Plaques
  - RA→ Rare
  - Bechet's→ Pustular, Pathergy+
  - Sarcoid → EN, Lupus Pernio
- Family History
  - AS> SLE > RA
- Constitutional Sxs
  - Fever
    - GCA, Vasculitis, SLE, AOSD, Peroidic FeverSyndromes/FMF Crystal, Acute Sarcoidosis
  - Weight Loss
    - GCA, Paraneoplastic

# Approach to the Arthritic Patient

- Organ Involvmenet
  - Renal
    - SLE, Vasculitis, Gout
  - Lung
    - Scleroderma, RA, Sjogrens,  Dermatomyositis and Anti-Synthase  syndromes
  - Heart
    - SLE, RA, GCA
  - Neuro
    - SLE, Sjogrens, Vasculitis, Sarcoid, Bechets, MAS/HLH
  - Ocular
    - HLA B27 related, RA, Bechets, Vasculitis
  - Mucosal
    - Bechets, Sjogren, IBD
  - Raynauds
    - Sjogrens, RA, SLE, Cryoglobulin, Antiphopholipid Syndromes

# Objectives: Rheumatoid Arthritis

- Learn epidemiology and proposed pathogenesis
- Review common and uncommon presentations of Rheumatoid Arthritis
- Become familiar with some of the old and new therapies

# Rheumatoid Arthritis: Pathogenesis to Treatment

# Epidemiology

- Affects all ethnicities
- Female: Male 2.5:1
- Peak incidence 4-5$^{th}$ decades
- Estimated prevalence is 1%, rates are declining
- Prevalence increases to 5% in females > 70
- Differences in prevalence
  - 0.1% rural Africans
  - 5% in Pima and Chippewa Indians

# Why???

- Genetics
- Hormonal factors
- Environmental influences
- Infectious exposures


"I never heard of anyone pulling a muscle while thinking."

# Genetics

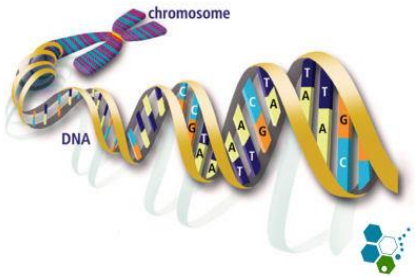
- Risk in first degree relative is 1.5x higher
- Concordance rate is higher with monozygotic twins (12%) as compared with dizygotic twins (3.5%)

Double Take: Twins with RA Fight It Together

# Genetics

- Major histocompatibility complex
  - Region of the genome shown to be associated with RA
  - Mapped to chromosome 6
  - Contains the genes for HLA DR used in antigen presentation

  - In different ethnicities, the predominant RA associated alleles vary:
    - HLA DRB1 0401, 0404 Caucasians
    - HLA DRB1 0405 Japanese
    - HLA DRB1 0101 Israeli
    - HLA DRB1 1402 Native Americans
  - Other diseases associated with the shared epitope:
    - HLA DRB1 0104 – MS, RA, DM1
    - HLA DRB1 0404 (CCP assoc) – RA,
      - autoimmune hepatitis



# Hormonal Influence

- Females 2-3 x more likely to develop RA
- Estrogen hypothesized to decrease apoptosis of B cells
- During pregnancy 75% of women are in remission and the disease flares after delivery
- Risk is reduced in women who have had children and may be further reduced with breast feeding
- Men have lower androgens and higher concentrations of estradiol

# Environmental Influences

- Tobacco
  - Exposure to smoke is well studied and the data is strong
    - 2 x increased risk in male smokers
    - 1.3 x increased risk in female smokers
  - Duration of tobacco also increases risk
  - Nicotine may not be the culprit ingredient in tobacco as smokeless tobacco is not associated with RA
  - Risk of developing disease decreases after smoking cessation

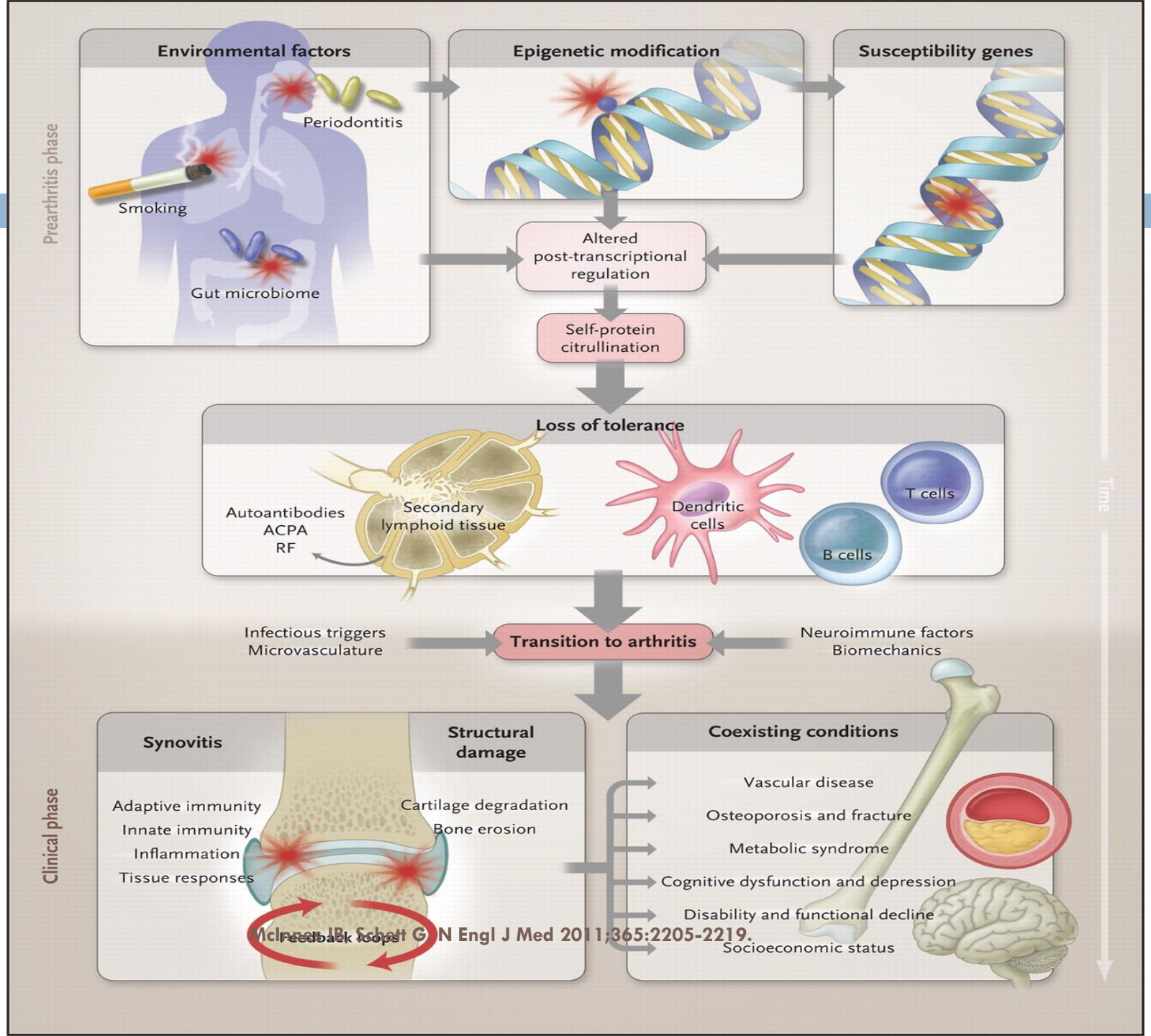
# Infectious Exposures

- Currently felt that it is not directly due to an active infection but from stimulation of the immune system from pathogen exposure

- Microbiome hypothesis
  - Theories on porphyromonas gingivalis a perodontopathic bacterium
  - High levels of Prevotella Copri and decreased Bacteroides species in the bowel

# Pathogenesis

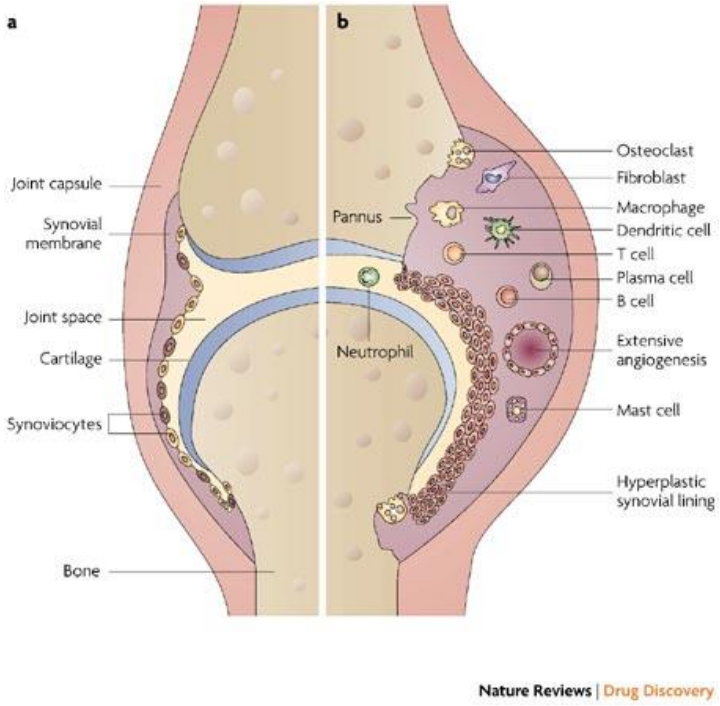
- Complex interaction between genes and environment-> loss of immune tolerance
- Given heterogeneous response to therapies in RA the current hypothesis is that it is not a single disease
- Many pathways lead to auto-reactivity with a similar clinical presentation




McInnes IB, Schett G. N Engl J Med 2011;365:2205-2219.

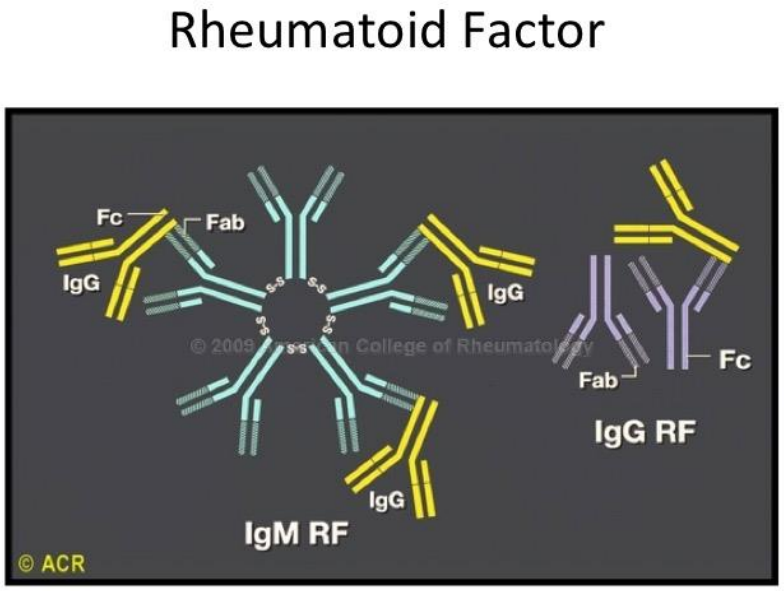
# Targets

- Synovium is the primary site of inflammation
  - Increased synoviocytes A and B
    - Lining is primary source of inflammation secreting cytokines
    - Villous projections invade cartilage and bone forming the pannus
    - Edema, blood vessel proliferation and increased cellularity lead to increased tissue volume
    - WBC counts >2000 are inflammatory, > 50,000 think infection first!



# Rheumatoid Factor

- Auto-antibodies directed at the FC portion of IgG
- RF Ab vs IgG and IgM are found in 90% of RA
  - IgM RF 70% sensitive, 80% specific
- RF is detected in 1-4% healthy individuals
- Produced with Hepatitis C, Sjogrens, Lymphoma



# Anti Cyclic Citrullinated Peptide Antibody (ACPA)

- Estimated sensitivity 80-90%, specificity 90%
  - When combined with RF, specificity >95%
  - Citrullination is the conversion of Aginine to Citrulline from PADI's (peptidyl aginine deiminase 2 and 4)
- Occasionally seen with psoriasis, psoriatic arthritis, autoimmune hepatitis, pulmonary TB
- Positivity of either or both RF and Anti-CCP Ab increases risk for a more aggressive disease
- Anti-CCP Ab can be positive up to 5-10 years prior to symptoms

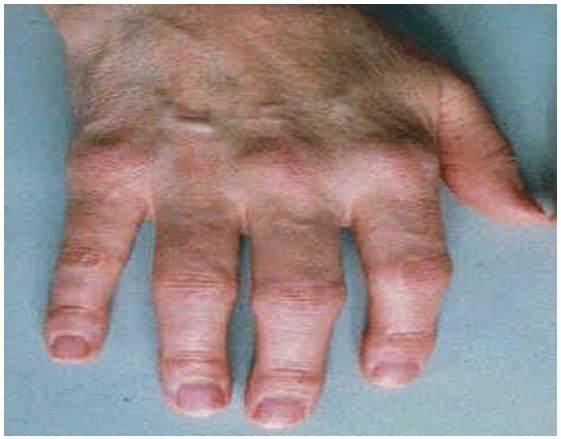
# RA: Presentation

"When a patient with arthritis walks in the front door, I try to go out the back door."

- *Sir William Osler*

# Most Common Presentation

- Often insidious, with a typical pattern of symmetric polyarthritis
  - Affects diarthrodial joints early
    - Wrists – Ulnar styloid
    - MCP metocarpalphalangeal
    - PIP proximal interphalangeal
    - MTP metatarsalphalangeal joints
  - Spares DIP distal interphalangeal and thoracolumbar spine
  - Ankles, knees, elbows, shoulders, cervical spine (often later)



# Most Common Presentation

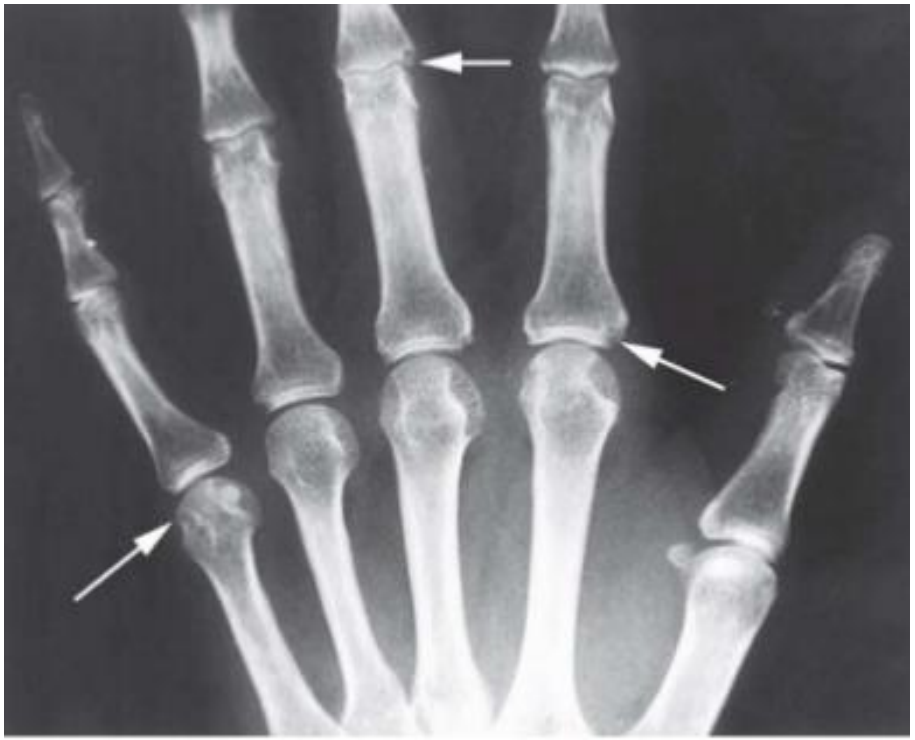
- Joint pain
- Morning stiffnesss- lasts greater than an hour
  - Improves with use
- Exam includes soft, boggy, tender joints with possible warmth and redness
- Proximal muscle pain similar to Polymyalgia Rheumatica
- Fatigue, malaise, and myalgia are due to systemic inflammation
- Decreased grip
- Carpal Tunnel Syndrome (estimated 20% on presentation)
  - Due to swelling

# Less Common Presentation

- Small percent have explosive onset of polyarthritis
- Monoarthritis
- Others with Palindromic Rheumatism
  - Transient self limited episodes lasting days to weeks
  - 50% go on to develop “typical” RA

# Imaging

- Peri-articular osteopenia
- Erosions
  - At the joint margin where the synovium inserts on bone
- Symmetric joint space narrowing



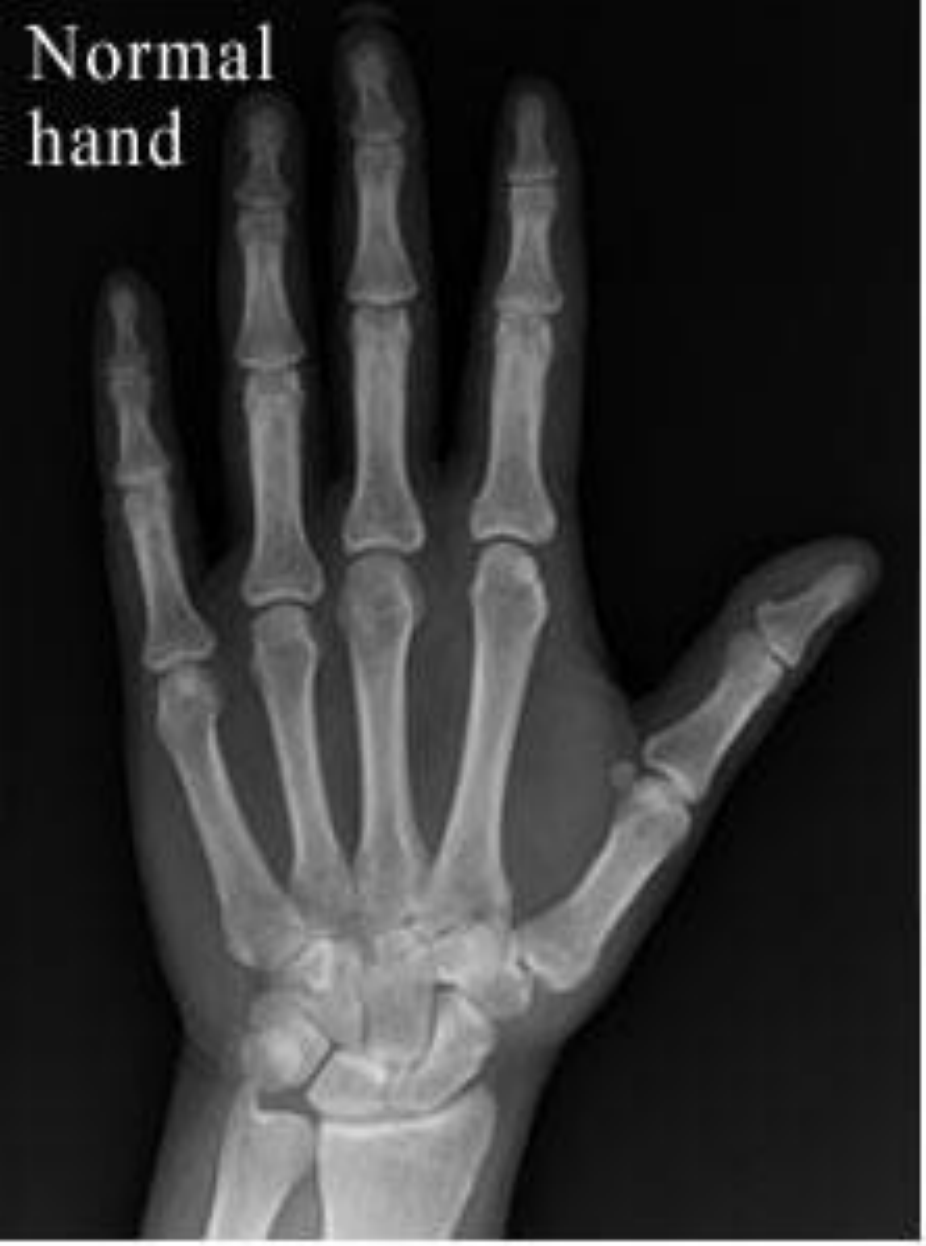



Figure 1

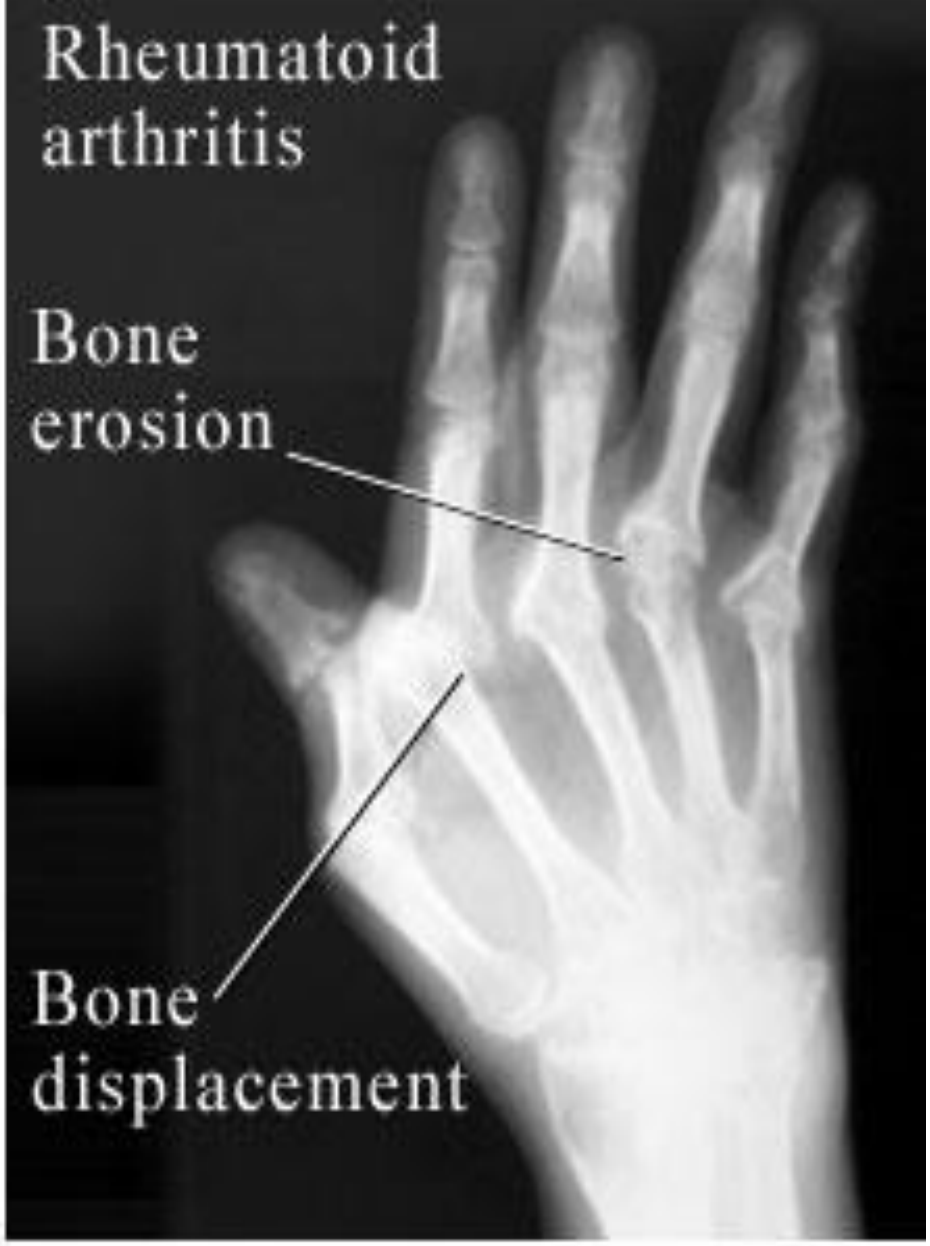
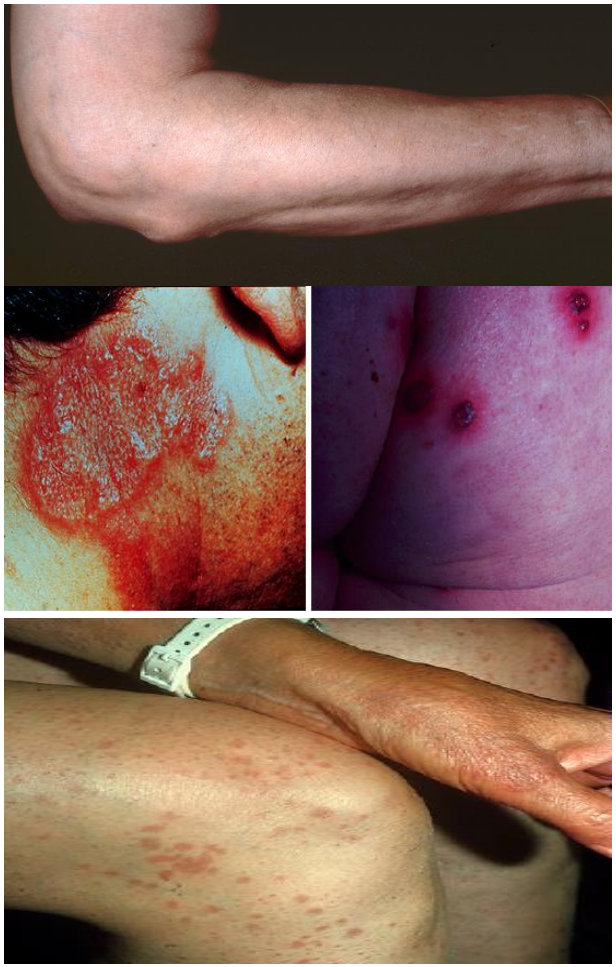



Figure 2

# Skin Findings

- Skin-Rheumatoid nodules
- Sweet's Syndrome
- Pyoderma Gangrenosum
- Neutrophilic dermatitis



Photos from uptodate

# Associated Issues

- Hematology
  - Anemia of chronic disease
    - Typically normocytic, normochromic with low serum iron, low transferrin or tibc, elevated Ferritin
  - Felty Syndrome
    - WBC < 4000, Neutropenia < 1,500
    - +/- splenomegaly, with thrombocytopenia, lymphadenopathy
    - LGH- Large granular lymphoctye syndrome
      - a spectrum of Felty's with a monoclonal expansion of large granular lymphocytes on bone marrow histology
  - Non Hodgkins Lymphoma 2-3x more frequent and RA activity increases risk

# Associated Issues

- Pulmonary
  - Pleuritis, pleural effusion
    - Low glucose < 60 mg/dL, WBC < 5000/mm3, pleural fluid to glucose ratio < 0.5, pH < 7.3
  - Interstitial lung disease
  - Methotrexate associated alveolitis
  - Caplan Syndrome-
    - pneumoconiosis related to mining dust (coal,asbestos, silica) and rapid development of multiple peripheral basilar nodules

# Associated Issues

- Ocular
  - Scleritis, episclertis → peripheral ulcerative keratitis
- Bone Health
  - Osteopenia/ Osteoporosis
- Cardiac
  - Common- Increased CAD risk
  - Uncommon – pericarditis, myocarditis

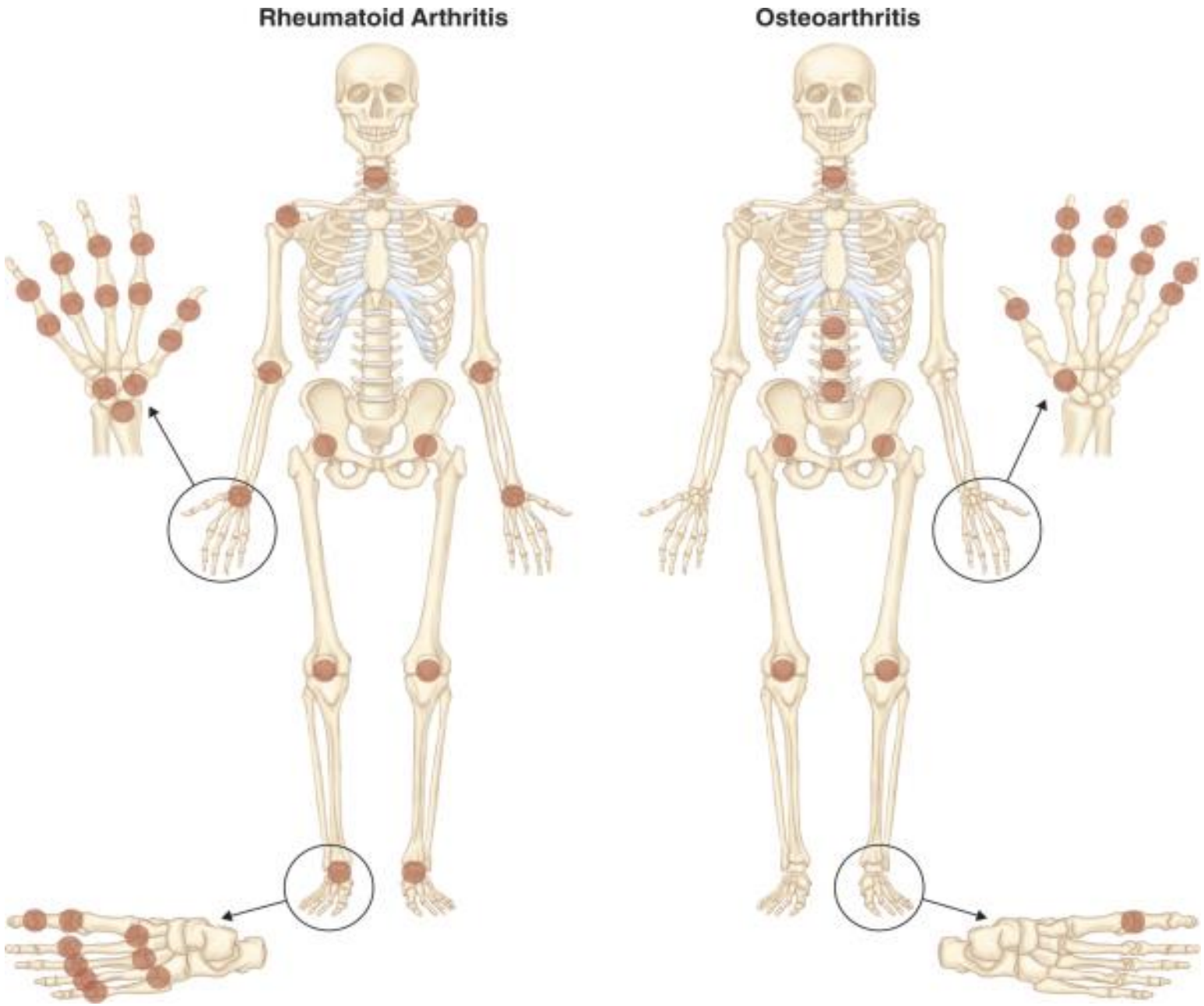
**Table 3.** The 2010 American College of Rheumatology/European League Against Rheumatism classification criteria for rheumatoid arthritis

| | Score |
|---|---|
| Target population (Who should be tested?): Patients who | |
| 1) have at least 1 joint with definite clinical synovitis (swelling)* | |
| 2) with the synovitis not better explained by another disease† | |
| Classification criteria for RA (score-based algorithm: add score of categories A–D; a score of ≥6/10 is needed for classification of a patient as having definite RA)‡ | |
| A. Joint involvement§ | |
| 1 large joint¶ | 0 |
| 2–10 large joints | 1 |
| 1–3 small joints (with or without involvement of large joints)# | 2 |
| 4–10 small joints (with or without involvement of large joints) | 3 |
| >10 joints (at least 1 small joint)** | 5 |
| B. Serology (at least 1 test result is needed for classification)†† | |
| Negative RF *and* negative ACPA | 0 |
| Low-positive RF *or* low-positive ACPA | 2 |
| High-positive RF *or* high-positive ACPA | 3 |
| C. Acute-phase reactants (at least 1 test result is needed for classification)‡‡ | |
| Normal CRP *and* normal ESR | 0 |
| Abnormal CRP *or* abnormal ESR | 1 |
| D. Duration of symptoms§§ | |
| <6 weeks | 0 |
| ≥6 weeks | 1 |

* The criteria are aimed at classification of newly presenting patients. In addition, patients with erosive disease typical of rheumatoid arthritis (RA) with a history compatible with prior fulfillment of the 2010 criteria should be classified as having RA. Patients with longstanding disease, including those whose disease is inactive (with or without treatment) who, based on retrospectively available data, have previously fulfilled the 2010 criteria should be classified as having RA.

# Differential Diagnosis

- Erosive Osteoarthritis
- Seronegative Arthritis/ Spondyloarthropathy
  - HLA B27 AS, Psoriatic, Reactive, Enteropathic
- Lyme Arthrtitis
- Viral Polyarthritis
  - Parvovirus
  - Leprosy
  - Chikangunya
- Hemochromatosis
- Gout/ Pseudogout
- Infection
- SLE


Rheumatoid Arthritis
Osteoarthritis

# Treatment

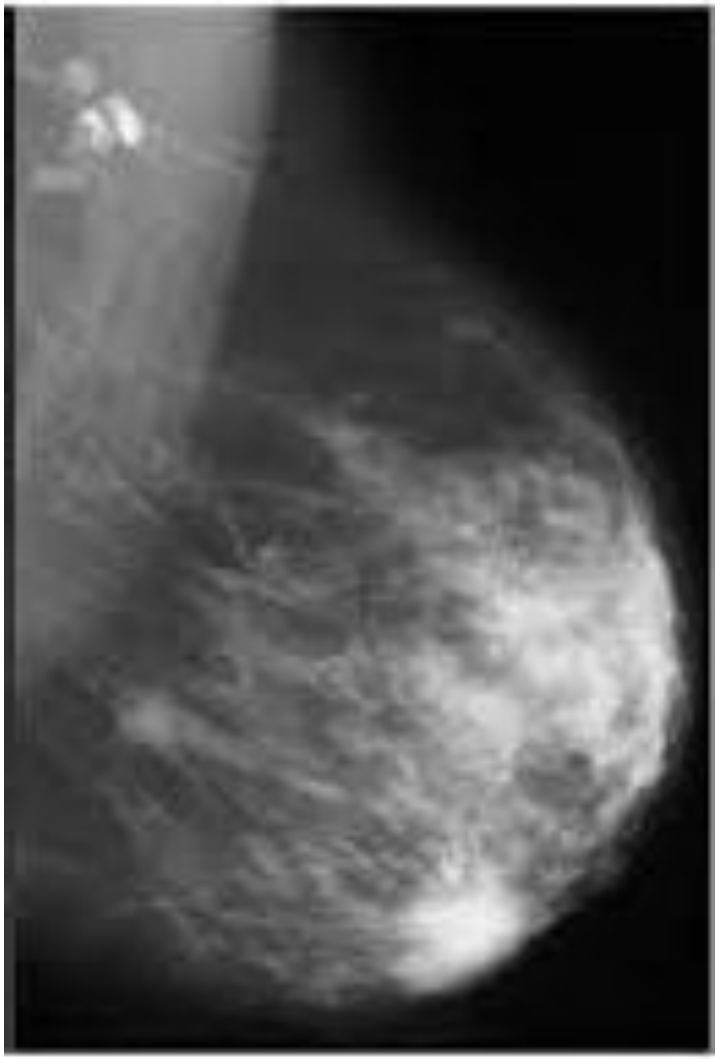

"YOUR SUNDAY FUNNY"
BY ASHLEY BOYNES-SHUCK
HERE'S A LIST OF POSSIBLE SIDE EFFECTS FROM YOUR RA MEDICINE.
Healthline

# Methotrexate


- Usually first line treatment
- Contraindicated with alcohol and pregnancy
- Rx once a week with folic acid (decreases stomatitis)
- Mechanism:
  - dihydrofolate reductase inhibitor, which increases adenosine which binds to TNF, IL-12 and IFN gamma
- Monitor LFTs, creatinine, CBC
- Variably absorbed
  - Split dosing or try intramuscular preparations
- Most biologics were studied with MTX

# Disease Modifying Anti-Rheumatic Drugs (DMARD)

- Hydroxychloroquine
  - Works in mild RA, used most with SLE
  - Least toxic and least amount of monitoring
  - Annual eye exams for retinal toxicity
- Sulfasalazine
  - Check G6PD
  - CBC, Liver monitoring while initiating therapy
- Leflunomide
  - Pyrimidine antagonist
  - Hepatotoxic and teratogenic
- Minocycline
  - Rarely used
  - Mild seropositive, early RA



# Treatment failures

- DMARD failure…the great debate
  - Add an anti-TNF agent?
  - Use a different biologic?
  - pursue “triple therapy” with 3 DMARDs?


TOP 20 DRUGS
IN THE WORLD 2017
1 HUMIRA adalimumab
2 HARVONI
3 Enbrel etanercept
4 Rituxan Rituximab
5 Remicade INFLIXIMAB
6 Revlimid
7 AVASTIN
8 Herceptin trastuzumab
9 Januvia
10 LANTUS
11 Prevnar 13
12 Xarelto rivaroxaban
13 EYLEA
14 LYRICA PREGABALIN
15 Neulasta
16 ADVAIR
17 COPAXONE
18 SOVALDI SOFOSBUVIR
19 Tecfidera
20 OPDIVO
Sources: Genetic Engineering & Biotechnology News, FiercePharma, Annual Reports, Company Websites, SEC Filings and Press Releases

# TNF Inhibitors

- Etanercept (Enbrel)
  - Fusion protein not an Ab
  - Lower infection rates?
- Certolizumab (Cimzia)
  - No complement activation
- Infliximab (Remicaide)
  - Monoclonal Ab (mouse)
- Golimumab (Simponi)
  - Human monoclonal Ab
- Adalimumab (Humira)
  - Human monoclonal Ab

# Abatacept (Orencia)


- IV (monthly) and SQ (weekly) preparations
- CTLA4 T cell co-stimulatory inhibitors bind CD80/86 on antigen presenting dendritic cells
  - Blocks the interaction between antigen presenting cells and T cells leading to down regulation of IL 2
  - Disrupts the activation of mature T cells which then activates B cells
- Contraindicated in COPD
- Can be used in CHF and renal insufficiency
- Takes months to work
- Mild increase risk of infections
- Comparable efficacy to TNF

# Tocilizumab (Actemra)
# Sarilumab (Kevzara)


- Monthly infusion or as a bimonthly injection
- IL 6 receptor Ab
  - IL 6 is secreted by macrophages and T cells
  - No renal adjustment
  - Contraindicated in liver disease
  - Side effects:
    - can cause LFT abnormalities (can continue up to 3x normal)
    - GI perforation
    - Black box warning for TB and infections

# Rituximab (Rituxan)

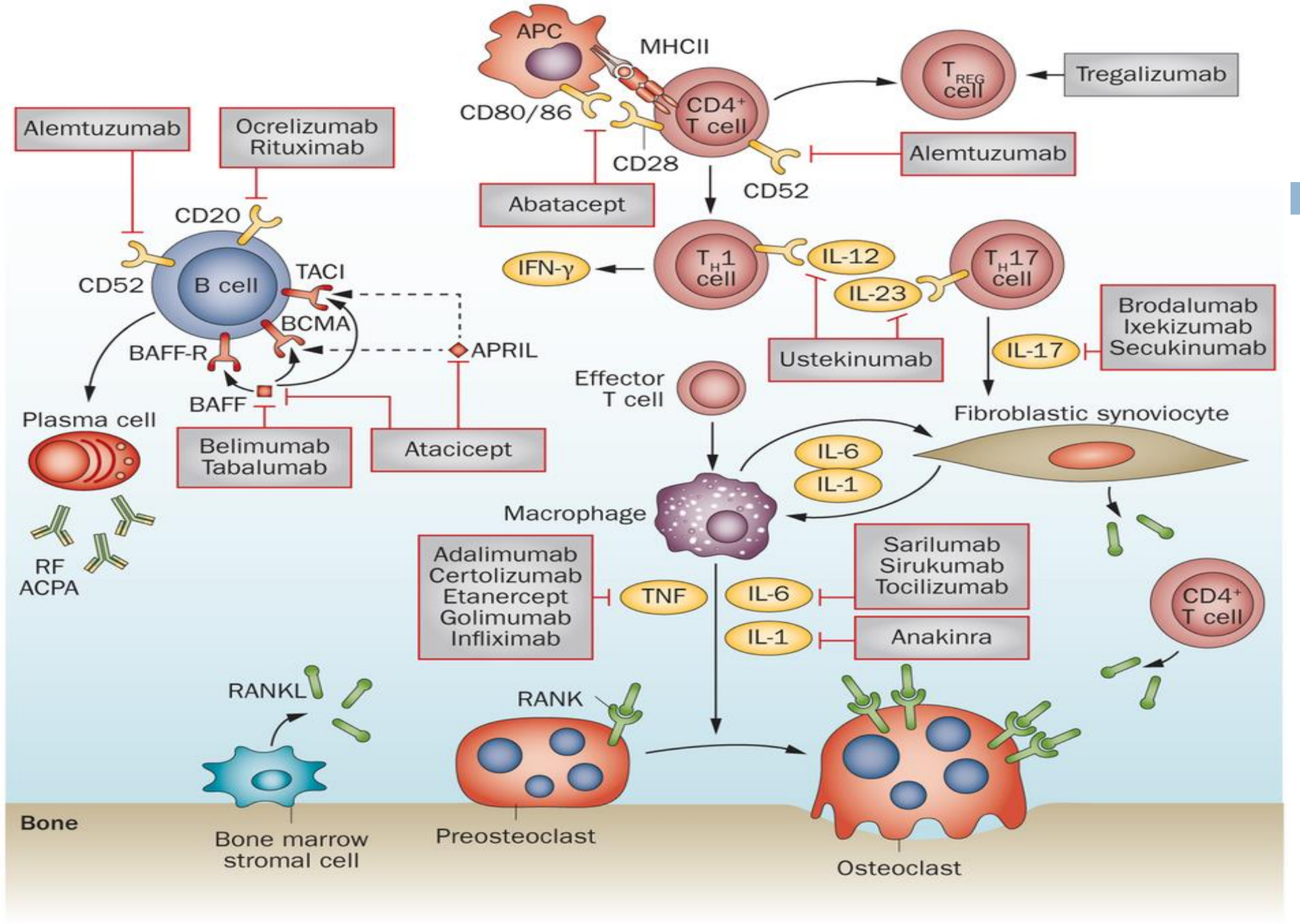

- Infusions 2 weeks apart every 6 months
- Depletes B cells by binding CD20, leading to growth arrest and apoptosis
- Can use with malignancy
- Side Effects:
  - Progressive multifocal leukoencephalopathy (Black Box) due to JC virus reactivation
  - Reactivation Hepatitis B, neutropenia, infusion reactions

# Tofacitinib (Xeljanz)


- Oral therapy
- Inhibits the JAK 1 and 3 enzyme which ultimately decreases gene expression leading to decreased cytokine and growth factor receptors
- Can be combined with methotrexate/DMARDS
- Re-activation TB is a concern and high risk for infections
- Indications for Ulcerative Colitis and Psoriatic Arthritis

# Anakinra (Kineret)


- Daily injection
- IL 1 receptor antagonist
- IL 1 stimulates T cells, IL 6 and others
- Objective is to stop the “inflammasome” aka sterile inflammatory response
- Cons: injection site reactions, headaches, nausea, nasopharyngitis


APC
MHCII
CD80/86
CD4+ T cell
CD28
CD52
Abatacept
Alemtuzumab
TREG cell
Tregalizumab
Alemtuzumab
Ocrelizumab
Rituximab
CD20
CD52
B cell
TACI
BCMA
BAFF-R
APRIL
BAFF
Belimumab
Tabalumab
Atacicept
Plasma cell
RF
ACPA
IFN-γ
TH1 cell
IL-12
IL-23
TH17 cell
Ustekinumab
IL-17
Brodalumab
Ixekizumab
Secukinumab
Effector T cell
Fibroblastic synoviocyte
IL-6
IL-1
Macrophage
Adalimumab
Certolizumab
Etanercept
Golimumab
Infliximab
TNF
IL-6
IL-1
Sarilumab
Sirukumab
Tocilizumab
Anakinra
CD4+ T cell
RANKL
RANK
Bone
Bone marrow stromal cell
Preosteoclast
Osteoclast

# Osteoarthritis

# Objectives: Osteoarthritis

- Understand the known cellular and inflammatory pathophysiology behind osteoarthritis
- Learn contributory factors in development
- Review current therapeutic options

# Epidemiology

- Osteoarthritis is the most common form of joint disease affecting 27 million in the US
- Strongly age related, although OA is NOT part of normal aging
- Uncommon prior to age 40

# Epidemiology

- Prevalence rises with age, with most over 70 having pathological changes
- OA is estimated to account for 30% of physician visits
- Frequently affected joints include:
  - Cervical spine, lumbar spine, IP joints of the hand, first carpo-metacarpal joint, first metatarsal-phalangeal joint, knees, and hips

# Basics

- Variable presentation and course
- Often insidious in onset
- Pain is the most common symptom
- Almost always bilateral
- Unilateral disease suggests trauma

# Why??

- One study evaluated hand skeletons of humans vs. macaques for OA as the presence of joint eburnation
- Much lower relative risk of thumb base OA in macaques 3.3% compared to humans 37%
- This may be due to the rudimentary design of the thumb
- Extrapolated that our MSK system was meant for four legged use without prehensile grip
- May explain the varied distribution of common sites

# Chronic pain is the illness of OA

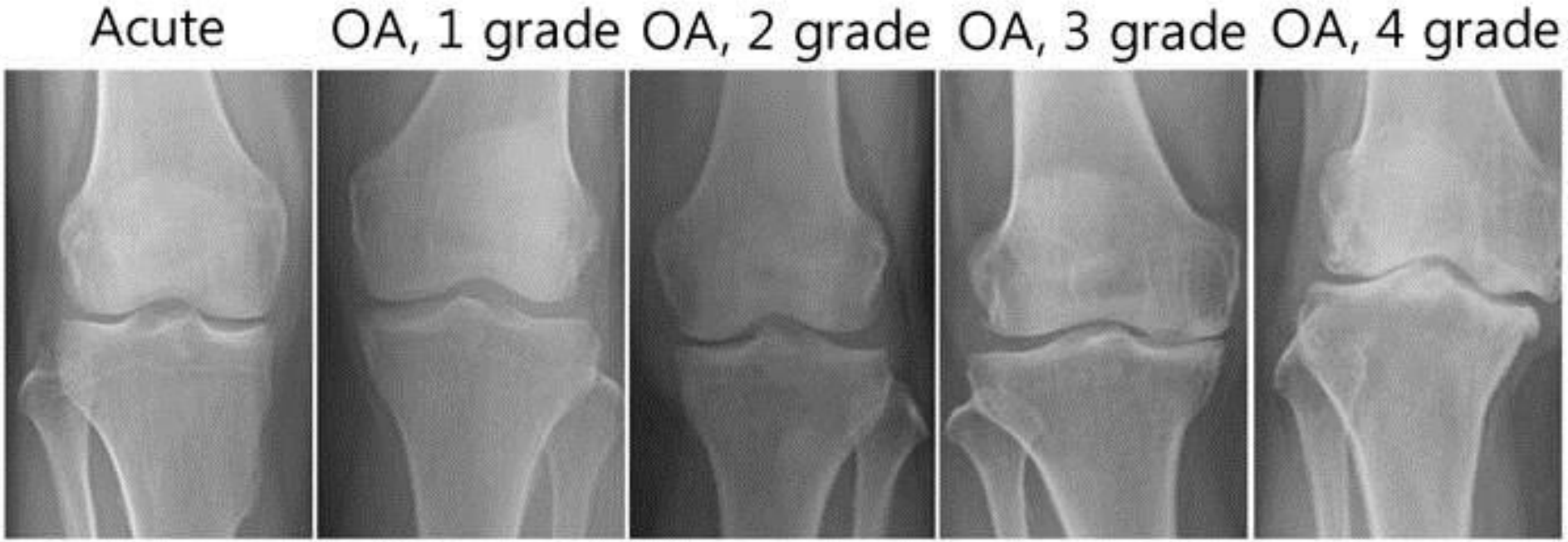
- Decreased social and recreational activities
- Decreased physical function
- Exacerbation of co-morbidities
- Decreased employment and workplace productivity
- Sleep disturbance
- Depression/anxiety
- Increased healthcare utilization

# Quality of Pain May Hint to Pathologic Origin

- Post exercise could be subchondral ischemia, aka bone angina “Deep seated aching”
- Pain at the joint margin may indicate stretching of the capsule/ligaments or overgrowing osteophytes
- Catching sensation may be associated with torn meniscus or loose body
- Pain with sitting in a low chair is often patello-femoral in origin

# Pain and radiographic changes

- It is estimated that ½ of patients with Kellegren and Lawrence grade ¾ report no pain
  - K/L: 0->4 measures osteophytes, joint space width, subchondral sclerosis and deformity of contour



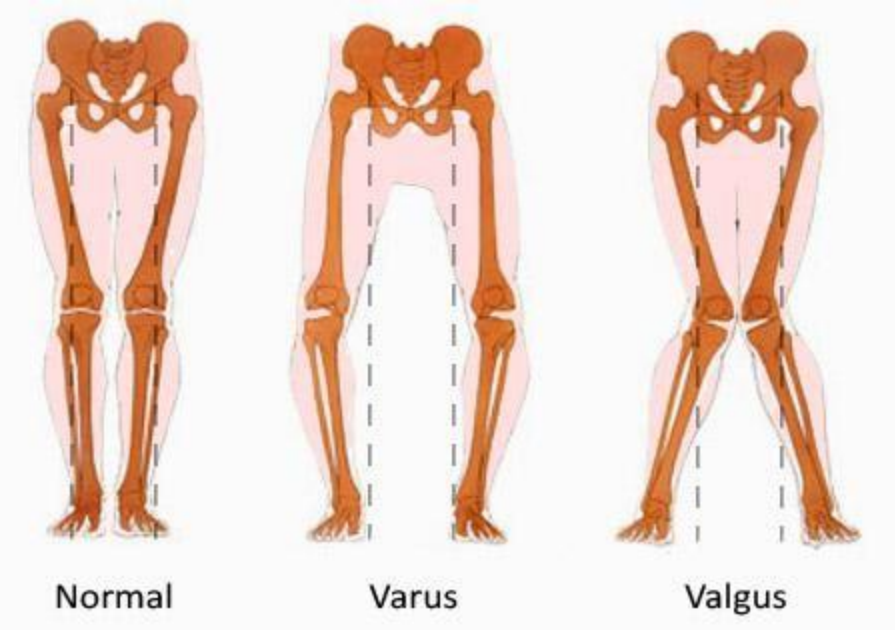

Ryu, JH, Lee A et. Al. Measurement of MMP Activity in Synovial Fluid in Cases of Osteoarthritis and Acute Inflammatory Conditions of the Knee Joints Using a Fluorogenic Peptide Probe-Immobilized Diagnostic Kit *Theranostics* 2012; 2(2):198-206.

# Risk Factors

- Age
  - Most strongly correlated with OA
  - Age related stress may arise from multiple factors: altered gait, muscle weakness, proprioception changes, increased body weight→ mechanical stress
  - Age related morphologic changes at the chondrocytes, ultimately affecting tissue repair

# Risk Factors: Malalignment

- It is debated whether mal-alignment causes to OA
- Evidence supports that both varus and valgus deformity are markers of severity and associated with risk for progression of knee OA



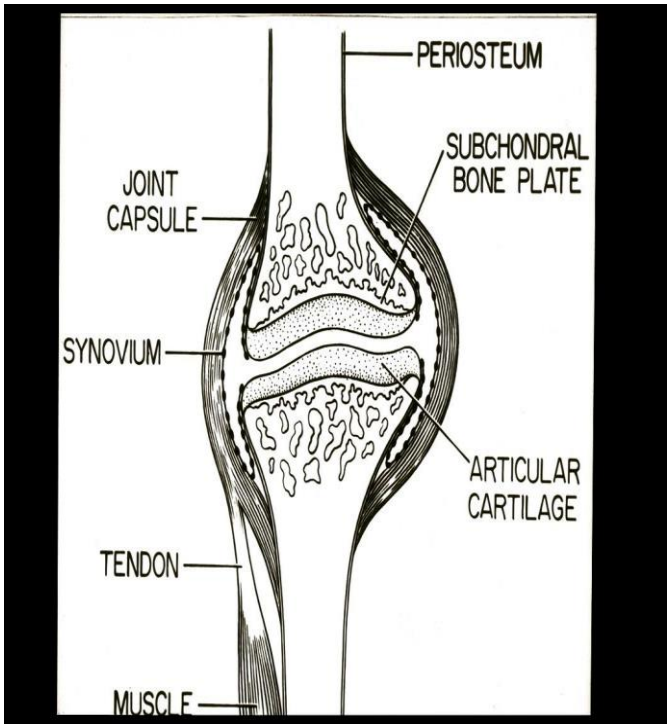
# OA…who gets worse?

- 13 year longitudinal study based on questionnaire data and radiograph scoring

| Risk factor | Odds Ratio |
|---|---|
| Age> 60 | 3.84 |
| Obesity | 11.1 |
| Knee injury | 2.62 |
| Valgus/Varus | 5.13 |
| Chondrocalcinosis | 2.01 |
| Heberden's Nodes | 5.87 |
| Generalized OA | 5.28 |

# Anatomy

- Articular Cartilage
  - Chondrocytes maintain extracellular matrix
    - Regulated by growth factors
    - Produces
      - Proteoglycans, Hyaluronin, Glycoproteins
- Synovium
  - Type A synoviocytes (macrophage like)
  - Type B synoviocytes (fibroblast like)
- Subchondral Bone
  - Osteophytosis
  - Subchondral cysts
  - Sclerosis

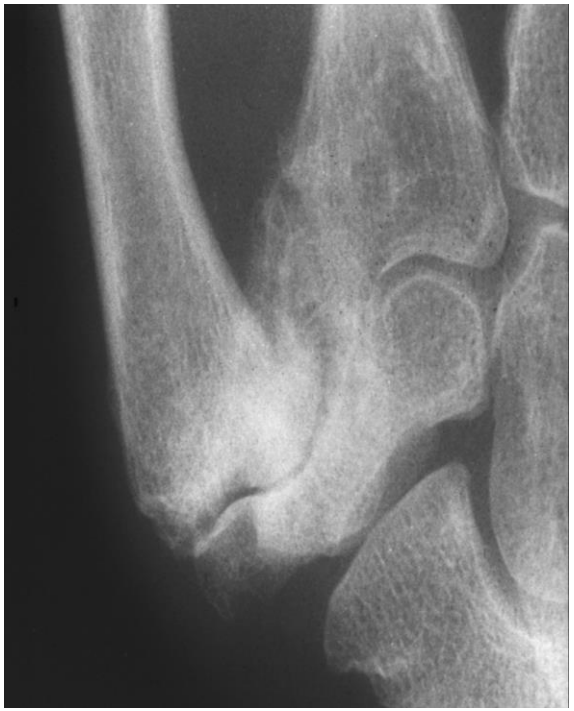


# Synovium

- Four types of OA synoviopathies:
  - Hyperplastic
    - Early OA- moderate synovial hyperplasia without capsular fibrosis, thickening, infiltrates or macromolecular debris
  - Inflammatory-
    - Moderately extensive lymphocytic infiltrates
    - Correlates with IL-1 beta/ MMP-1 expression by synoviocytes
    - Suggests a direct stimulatory role of inflammatory cells on synovial cells
  - Fibrotic- AKA capsular fibrosis
    - Late stage disease characterized by shortening and thickening of the joint capsule
  - Detritus rich
    - End stage due to bone and cartilage fragments incorporated into the synovium

# Subchondral Bone

- Directly related to pain in OA
  - Subchondral ischemia or increase venous pressure occurs
  - Osteonecrosis (bone death) has a pain free period, then pain is experienced with repair
  - Subchondral cysts and sclerosis = localized osteonecrosis

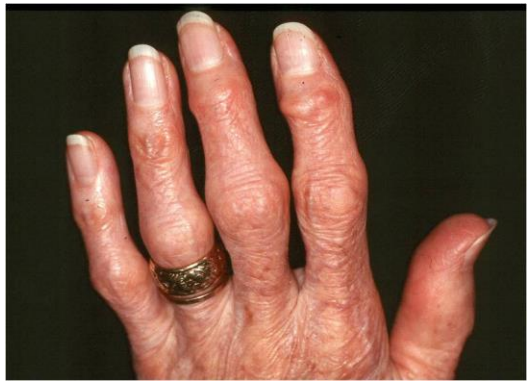


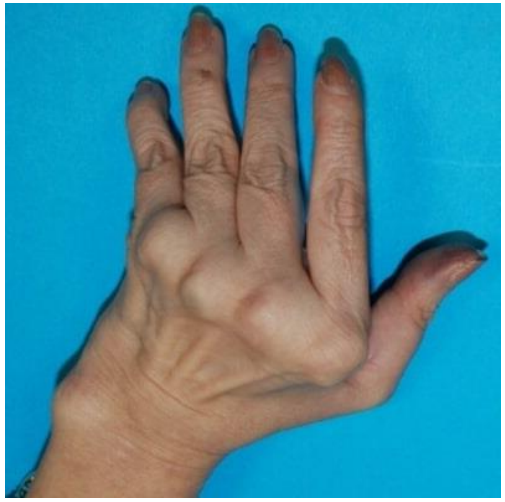
# Osteophytes

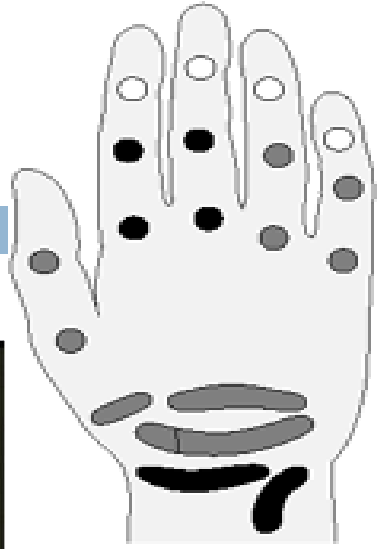
- Osteophytes - consistently found with pain
  - Mechanism unclear
  - May be due to distending periosteum

- Osteophyte formation
  - Osteocartilagenous outgrowths often at margins of joints
  - Considered a process of secondary chondroneogenesis

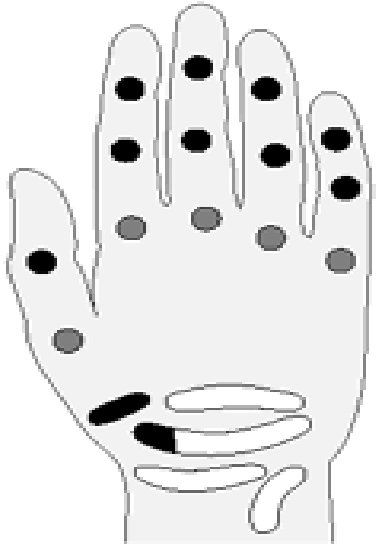
# Imaging



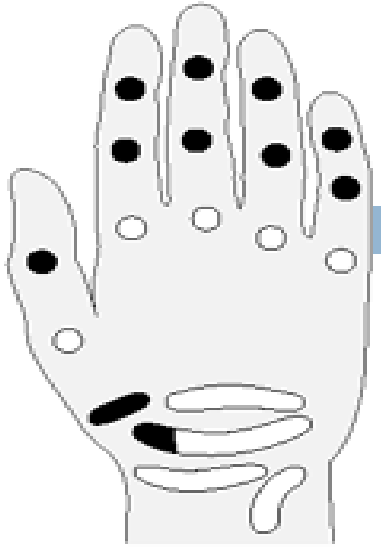




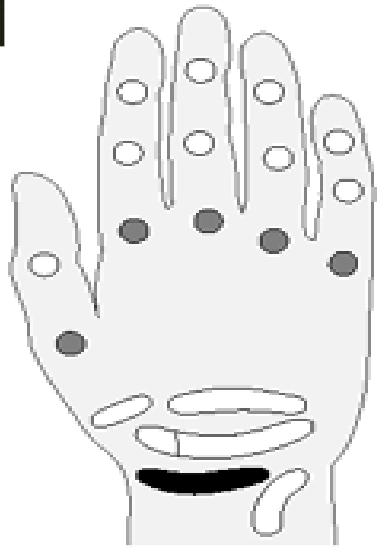
Rheumatoid Arthritis



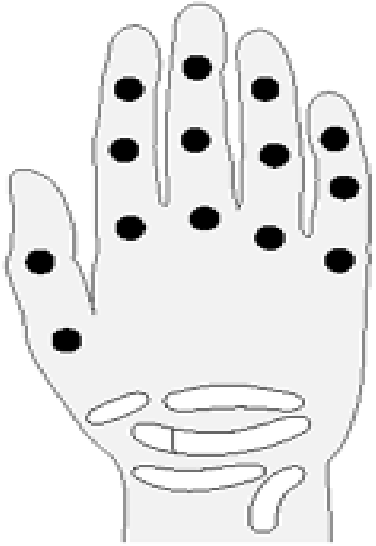
Degenerative Joint Disease



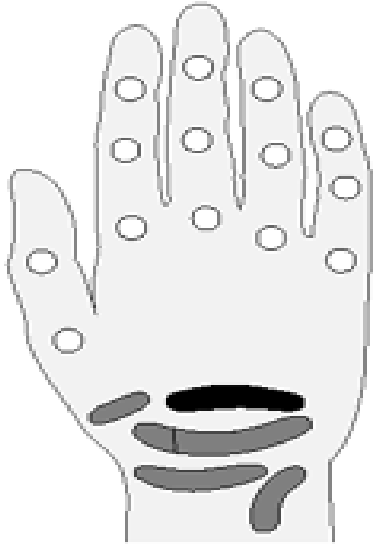
Inflammatory Osteoarthritis



CPPD Crystal Deposition Disease



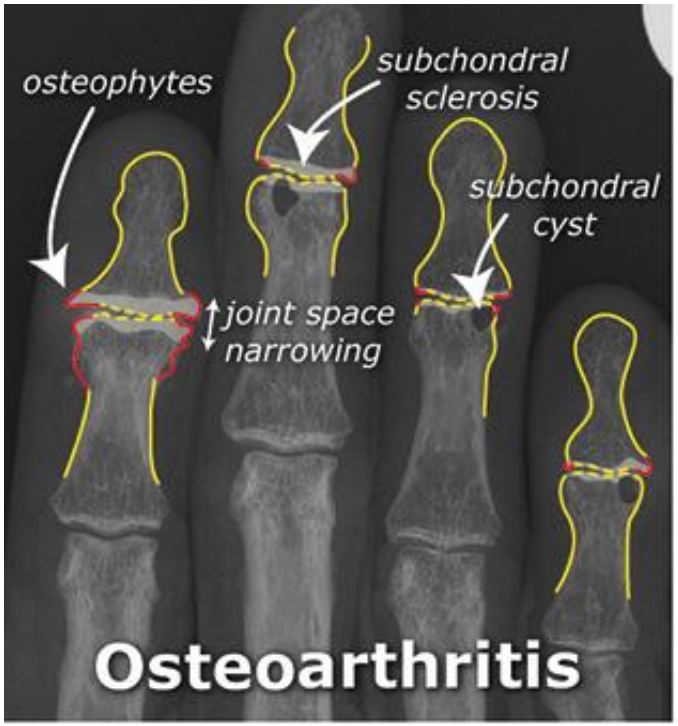
Psoriatic Arthritis

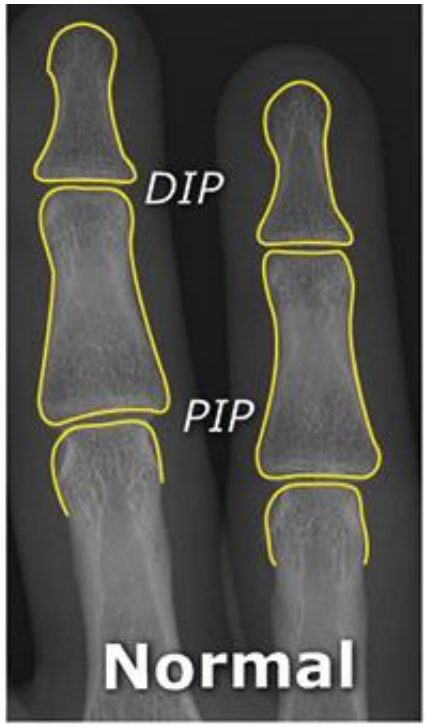


Gouty Arthritis

# Osteoarthritis Imaging

- Normal Mineralization
- Nonuniform loss of joint space
- Absence of erosions
- Osteophytes
- Cysts
- Subluxations



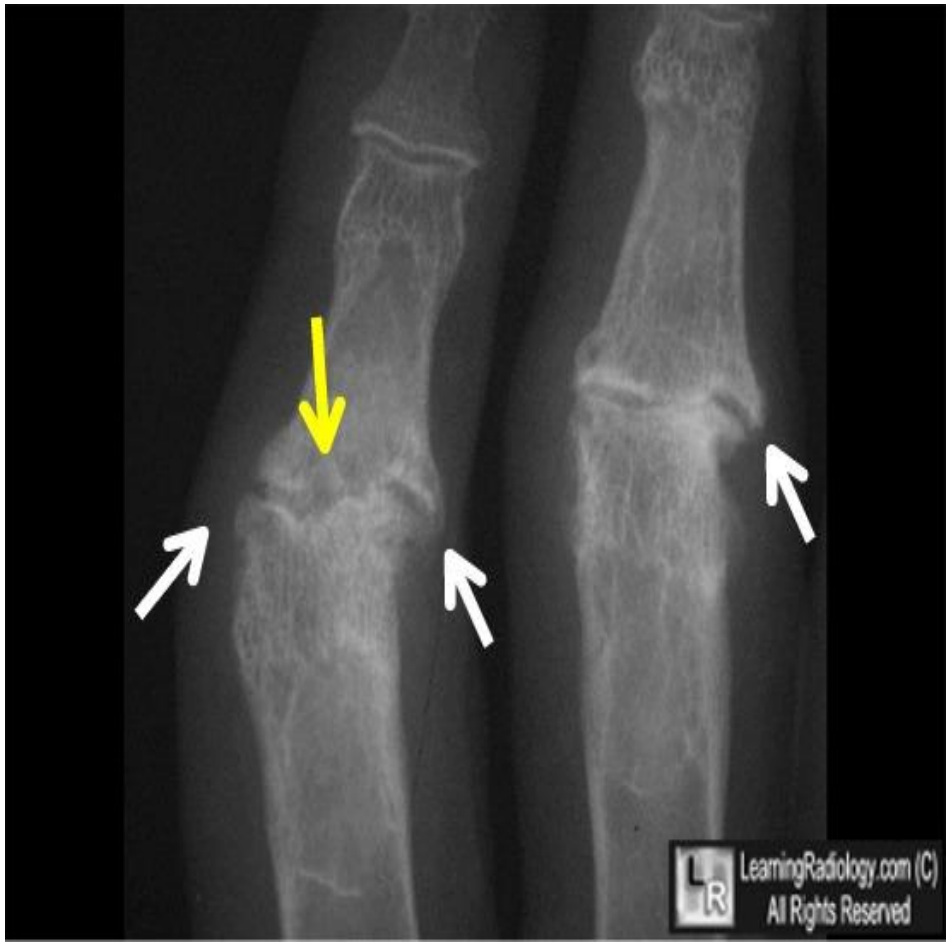



# Inflammatory/Erosive OA

- Difficult to differentiate from other inflammatory arthritides
  - Abrupt onset, marked pain and functional impairment
  - Involves hands only, distal and proximal interphalangeal joints
  - Inflammatory signs: swelling, warmth, erythema, stiffness
  - Imaging: central erosions, “seagull/sawtooth” pattern, osteophytes

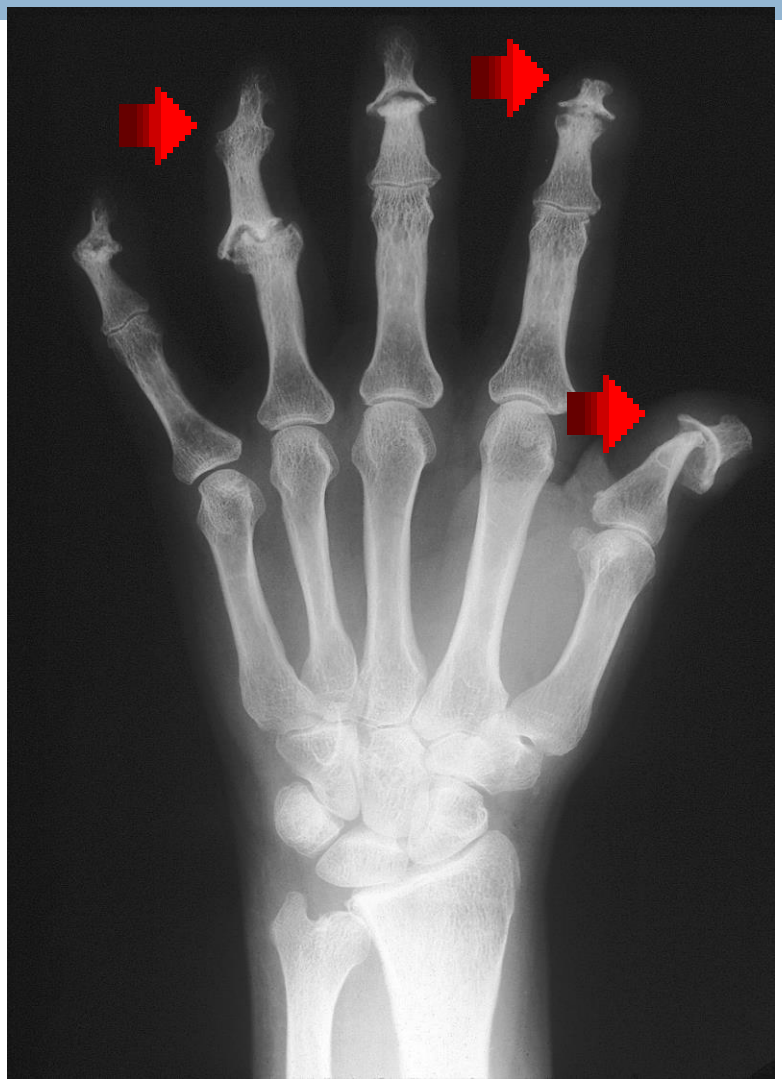
# Erosive OA – Close Up

- Central erosion of the proximal part of joint (yellow arrow)
- Bone overgrowth peripherally (white arrows) resembling a seagull's wings



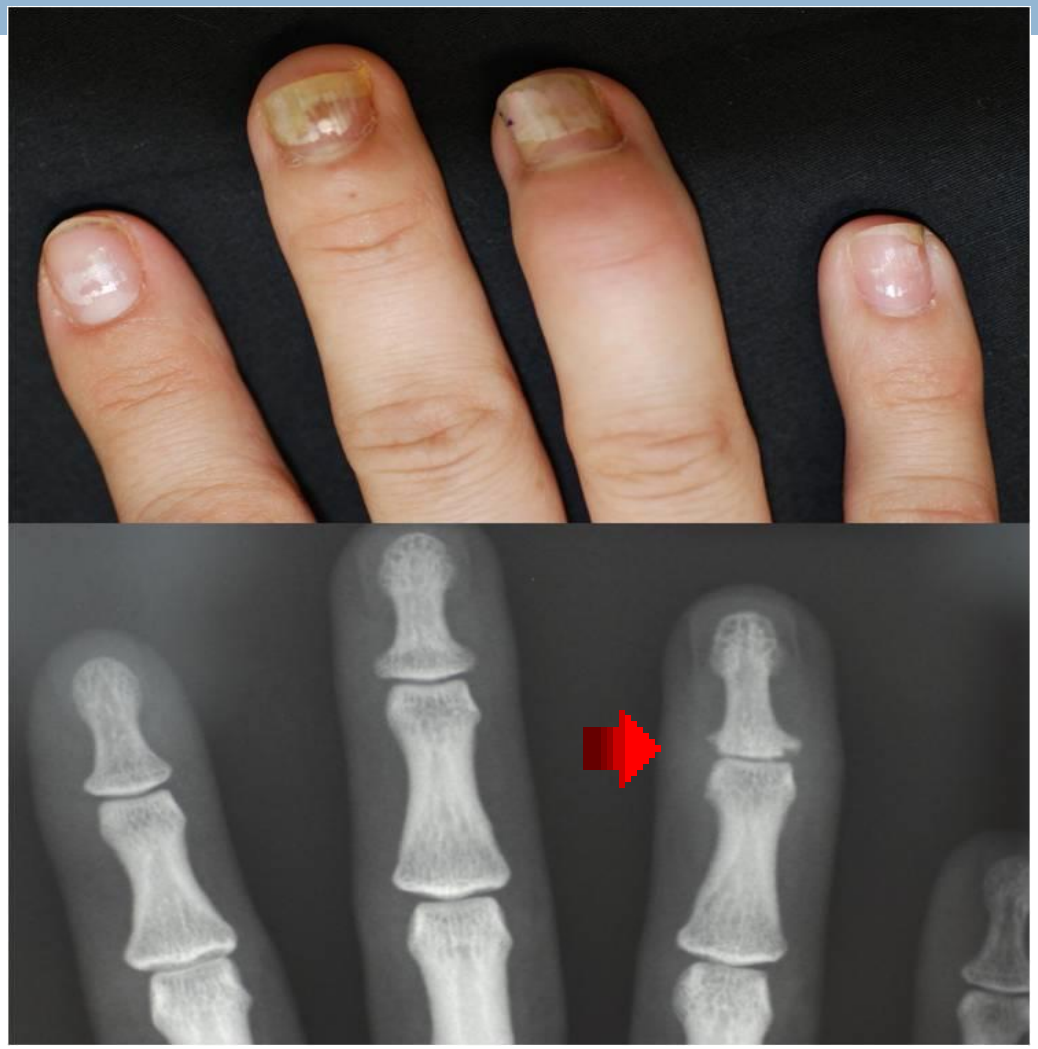
# Psoriatic Arthritis

- Resorption of the terminal tuft of the index finger and thumb is seen
- "Pencil in cup" deformity
  - Subchondral bone resorption of the distal interphalangeal joint of the thumb and middle fingers
- Distal interphalangeal joint of the ring finger has fused.



# OA vs PsA ?

- Marginal erosions
- Mild bony growth
  - whiskering



# OA Management

- No known cure
- Treatment goals
  - Reduce pain
  - Maintain/ improve mobility
  - Improve health related quality of life
- Multidisciplinary Approach
  - Exercise/ Tai Chi/ Yoga
  - Weight Loss
  - PT
  - Footwear Adjustments
  - Thermal modalities
  - Cane/ Walkers
    - Contralateral to affected joint
    - 20 degree elbow flexion
    - Improper height → shoulder dysfunction

# Targeting Obesity

- 44 patients were followed for 6 months following bariatric surgery, WOMAC showed approximately 50% improvement in pain

# Interventions

- Acetaminophen 3-4 g/day
- NSAIDS
  - Avoid in elderly or certain comorbidities
  - Topicals have similar efficacy as oral
  - COX 2 selective similar in efficacy as Non- Selective
- Intra-articular Injections
  - Steriods
  - Hylaluronic Acid (synvisc etc)
- Tramadol
- Replacement
- Conditional Recommendations
  - Knee Braces
  - Medial Patellar Taping
  - Wedged insoles
    - Lateral Wedges for medial OA
    - Medial Wedges for lateral OA

# NSAID RISK

- GI
  - Erosion/ulcer gastric mucosa
  - Nausea
- Renal
  - Reduced GFR
  - NA and water retention-> edema
- CV
  - Thrombotic events
  - Hypertension
  - Congestive Heart Failure
- CNS
  - Headache, insomnia, vertigo
- Other
  - Bleeding
  - Asthma exacerbations

# NSAID RISK

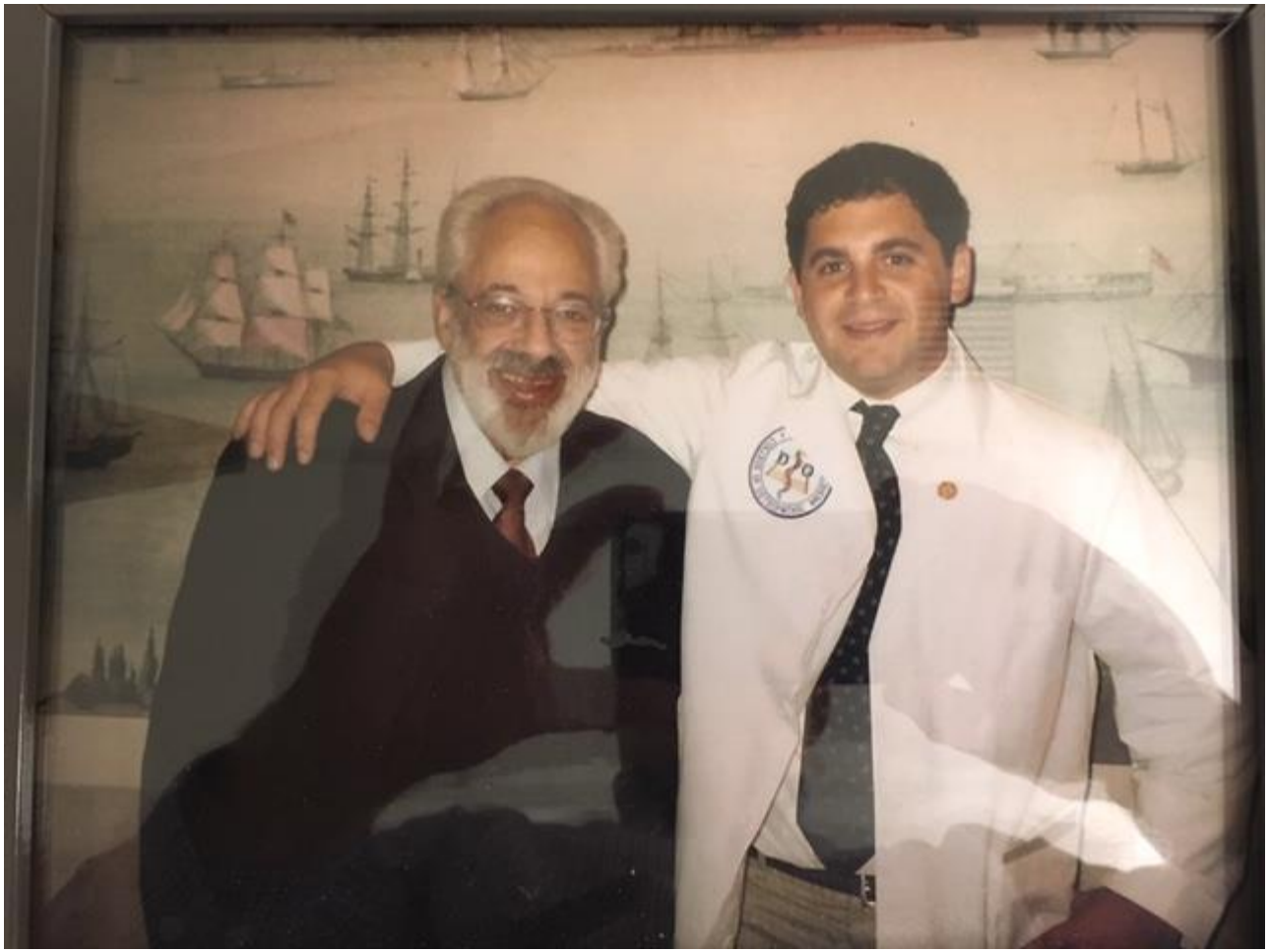
**Table 1. One-year risk of gastrointestinal bleeding due to NSAID[a]**

| Age range (years) | Chance of gastrointestinal bleed due to NSAID | Chance of dying from gastrointestinal bleed due to NSAID |
|---|---|---|
| | *Risk in any 1 year is 1 in:* | |
| 16-45 | 2100 | 12 353 |
| 45-64 | 646 | 3800 |
| 65-74 | 570 | 3353 |
| ≥ 75 | 110 | 647 |

# Glucosamine/Chondroitin

- GAIT trial 2006
  - Multicentered Placebo Controlled Trial enrolling 1583 subjects.
  - Arms included 1200 mg chondroitin, 1500 mg of glucosamine, both, 200 mg celecoxib or placebo
  - At 2 years, no treatment achieved a predefined threshold of clinically important differences compared with placebo (set at 20%)
  - One highlight: moderate to severe baseline pain, rate of resoponse was significantly improved compared to baseline 79.2 % vs 54.3 %
  - Follow up studies: Knees with K/L grade 2 radiographic OA appeared to have the greatest potential for modification by these treatments.

# Questions?



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