The Approach to a Patient with Multiple Aches and Pains

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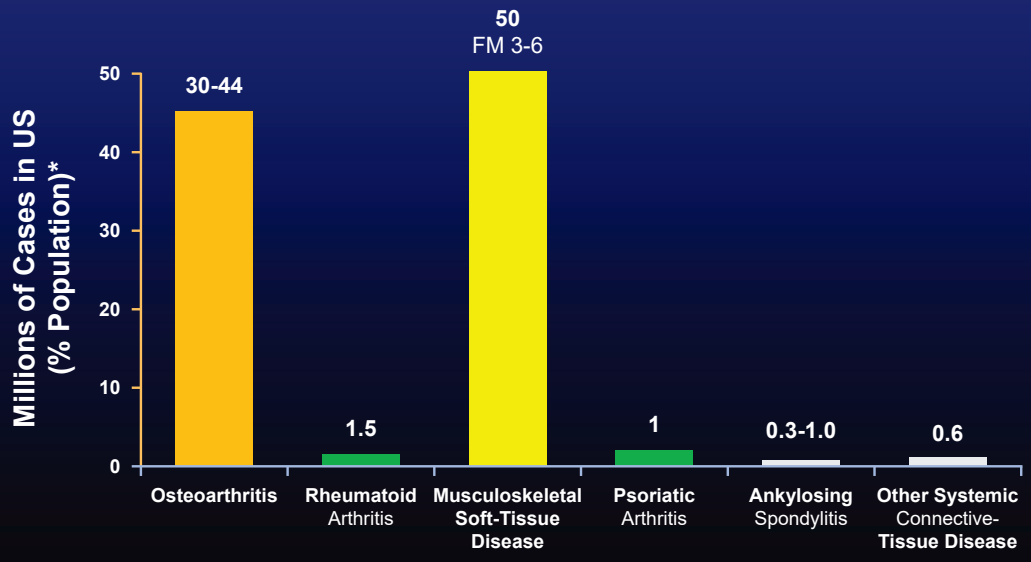
I will not discuss any off-label use and/or investigational use in my presentation

Learning Objectives

- Recognize the importance of pathophysiology in understanding rheumatic disease –target tissue and characteristic joint distribution
- Distinguish inflammatory from non-inflammatory (degenerative) arthritis and non-articular (soft-tissue) rheumatic conditions.
- Effective use of laboratory and imaging studies in rheumatologic diagnosis
- Identify the features that distinguish fibromyalgia from other rheumatic diseases
- The potential relationships between long COVID-19 and rheumatic diseases

Arthritis Care: An Increasing Burden on Healthcare Resources

Prevalence of Diagnosed Musculoskeletal Disorders



*Data updated 2008 (2016 data 51.8 million with "arthritis")
†National Osteoporosis Foundation. www.nof.org. Dec 6, 2000.
The Arthritis Foundation Fact Book for the Media. Atlanta, Georgia. Arthritis Foundation; 1994:1-4.

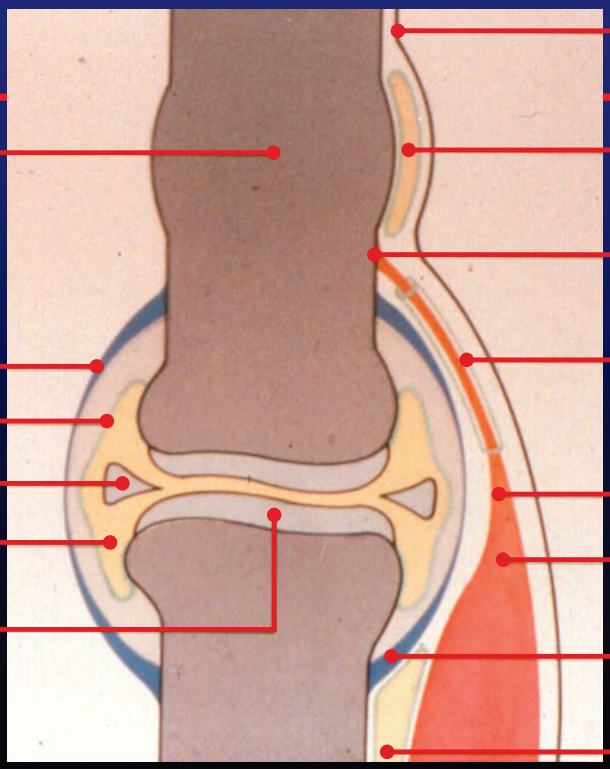
The Most Common Musculoskeletal Problems Encountered in a Primary Care Office

- Degenerative: Osteoarthritis
- Inflammatory: Rheumatoid arthritis
  Spondyloarthritis
  -Psoriatic arthritis
  -Ankylosing spondylitis
- Non-articular: Fibromyalgia

Two Pragmatic Principles for Recognizing Arthritis

- **I.** Every arthritis has a specific target tissue:
  - Osteoarthritis: articular cartilage
  - Rheumatoid arthritis: synovium
  - Spondyloarthritis: enthesis
- Fibromyalgia does **NOT** have a target tissue

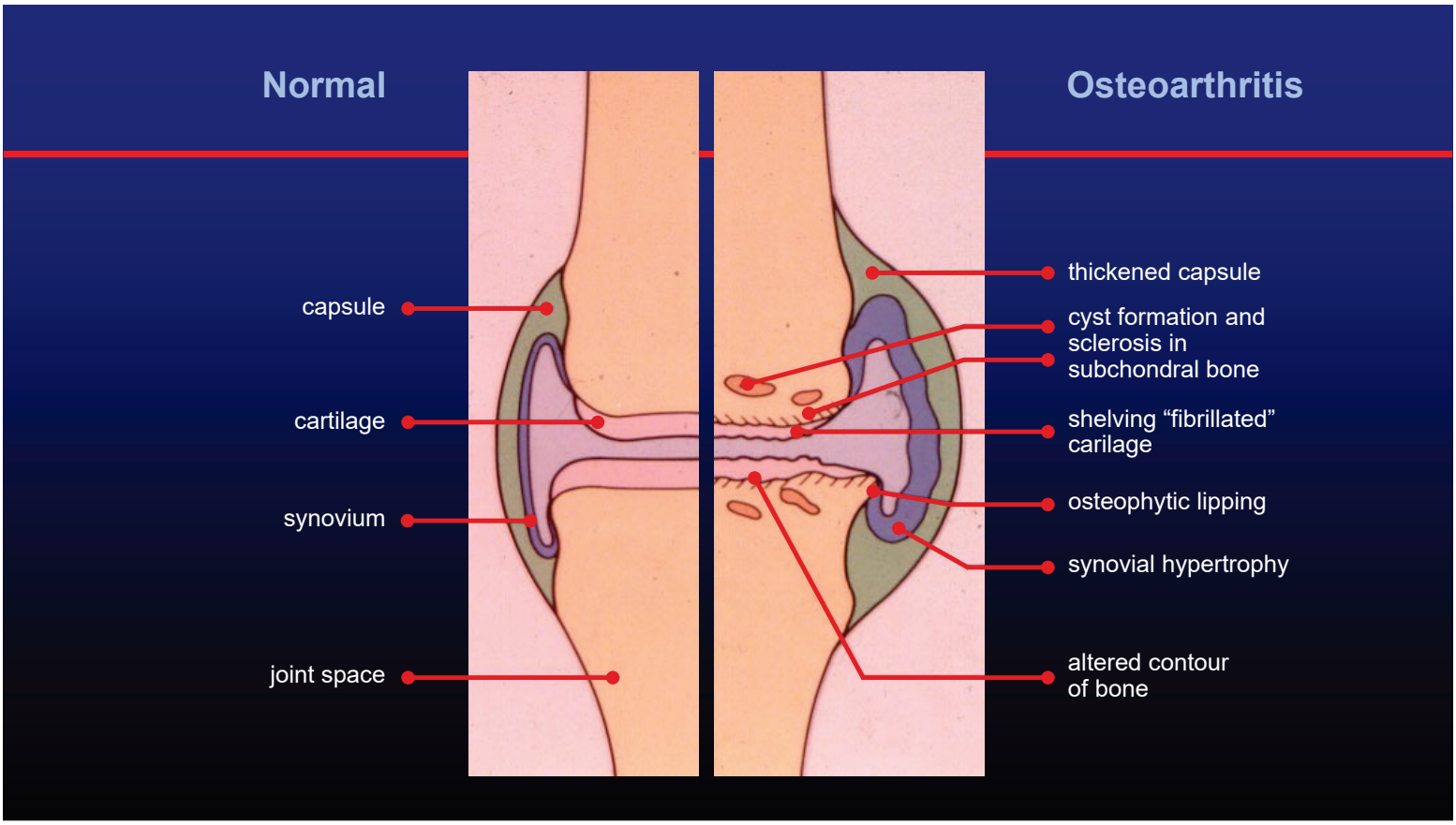
Schematic of a Finger Joint



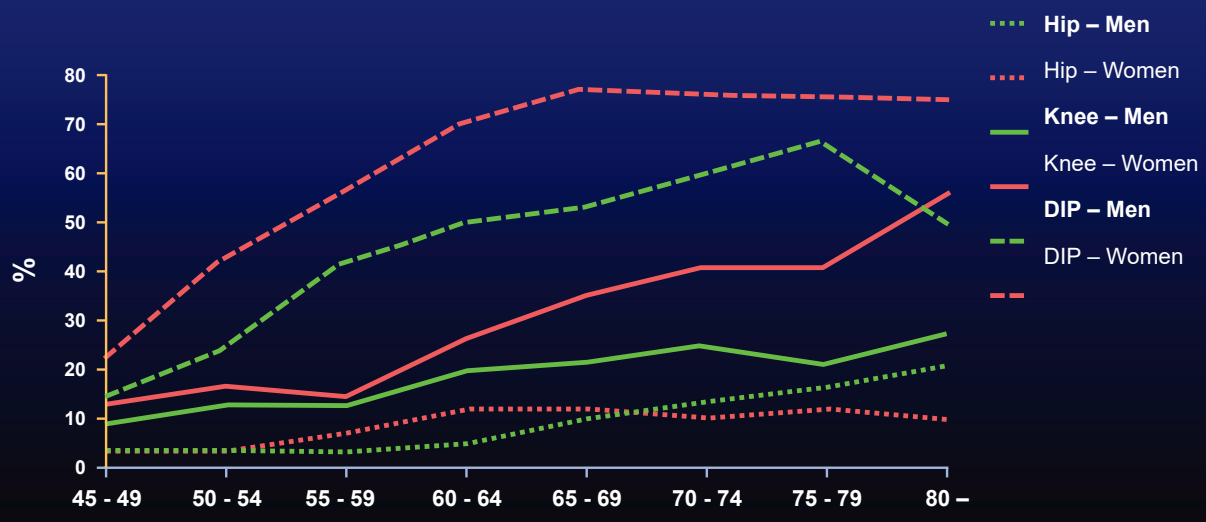
Two Pragmatic Principles for Recognizing Arthritis

- **II.** Every arthritis has a specific pattern of joint distribution:
  - **Osteoarthritis (OA):** symmetrical pattern involving mechanical degradation of hyaline cartilage
  - **Rheumatoid arthritis (RA):** symmetrical synovitis
  - **Spondyloarthritis (SpA):** asymmetric inflammation of enthesis and synovium

Osteoarthritis

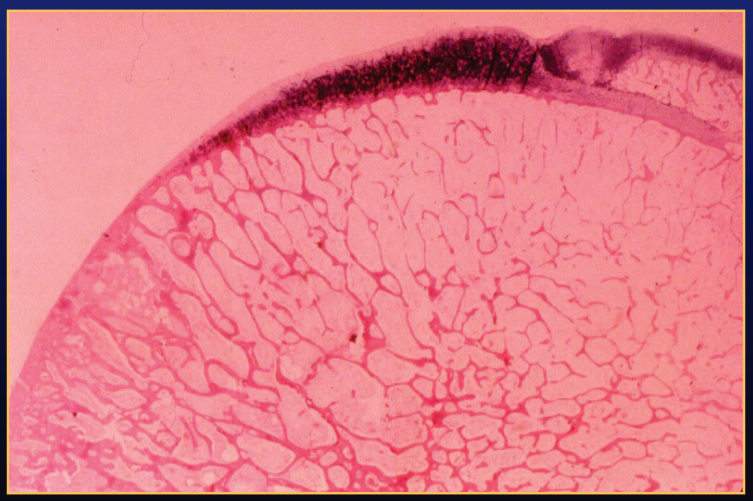


Prevalence of Radiological OA in a Dutch Population



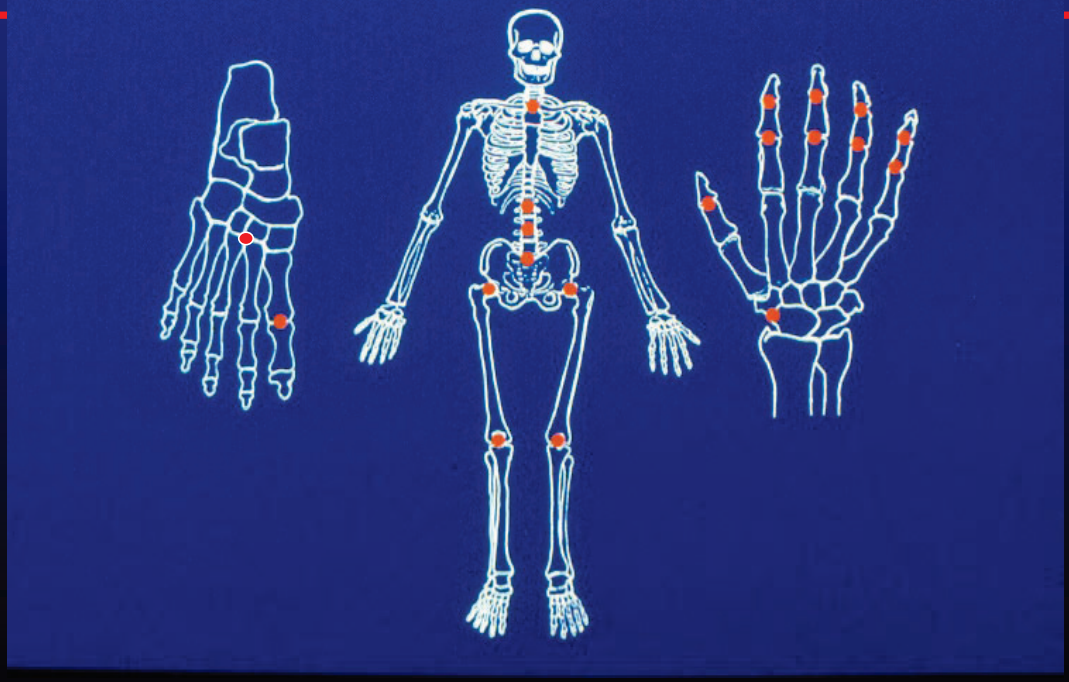
Oxford Textbook of Rheumatology 2004.

Osteoarthritis Late
Complete Loss of Cartilage



Note asymmetric cartilage loss

Joints Commonly Involved in Osteoarthritis



Osteoarthritis: Cervical Spondylosis

Disc space narrowing at C5-6 and C6-7

Neuroforaminal narrowing by encroaching osteophytes

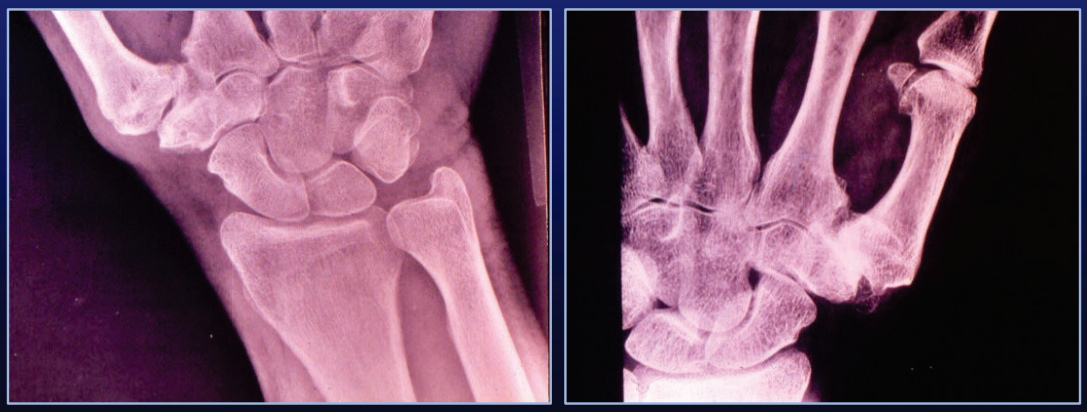
Osteoarthritis: Heberden's Nodes

Two bony prominences at the DIP joint; note irregular joint space narrowing and marginal osteophytes; number and symmetry correlated with OA knee

Osteoarthritis: Bouchard's Nodes

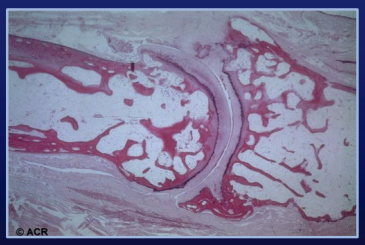
Note bony enlargement of the PIP joints;
she also has Heberden's nodes

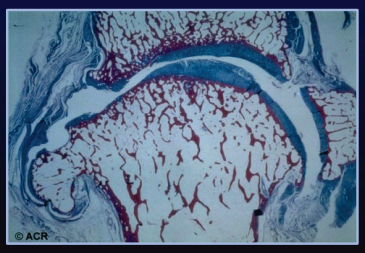
Osteoarthritis
First Carpometacarpal Joint



Osteoarthritis: Hands

Genetics of Osteoarthritis





Heberden's and Bouchard's nodes

Sisters of women with Heberden's nodes were 3x as likely to have generalized osteoarthritis as those in the general population: Stecher, 1941

Chopstick Arthropathy

OA of the IP joint of the thumb and the second and third PIP and MCP joints.

Hunter, et al. Arth Rheum 2004; 50: 1495.

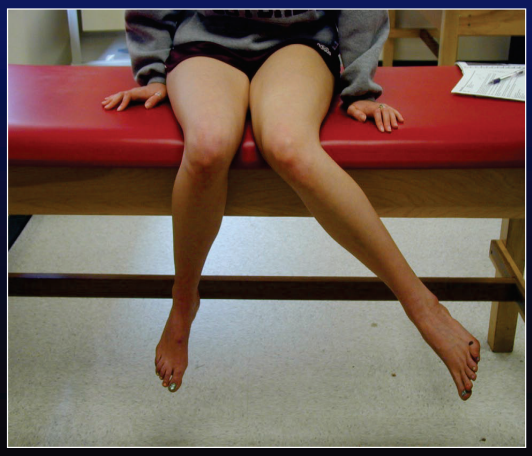
Osteoarthritis: Lumbar Spine

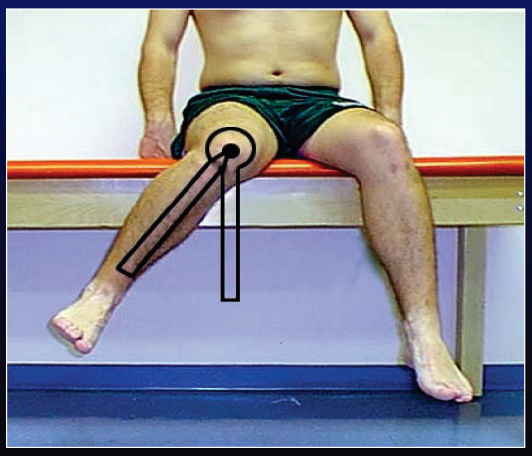
Acute back pain
with stooping

Disc space narrowing and vacuum disc
at L4-5 with Grade I spondylolisthesis

Osteoarthritis: Hip

Suspect hip osteoarthritis if internal rotation <24 degrees and groin symptoms





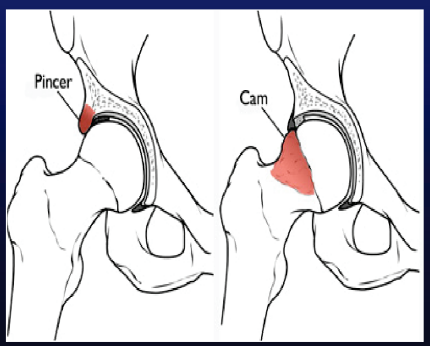
Holla JFM. Arth Care Res 2012;64:59-65

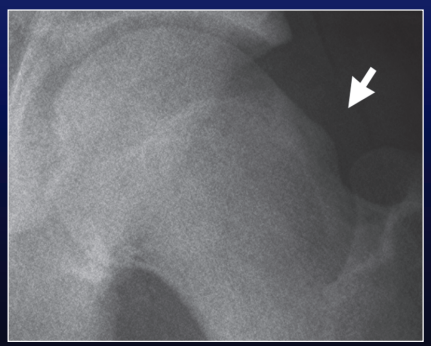
Osteoarthritis: Hip

Progressive loss of superior cartilage and femoral head deformity

Osteoarthritis: Cam-type deformity in young men

Groin pain in typically young men: femoroacetabular impingement syndrome



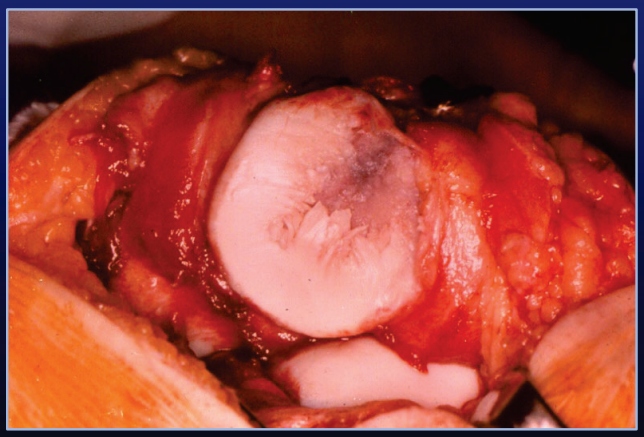


A “pincer” effect can be caused by either an osteophyte on the acetabulum or a bump on the femoral neck

Both present give highest risk. Prevalence men: 15-17%; women 4-6%

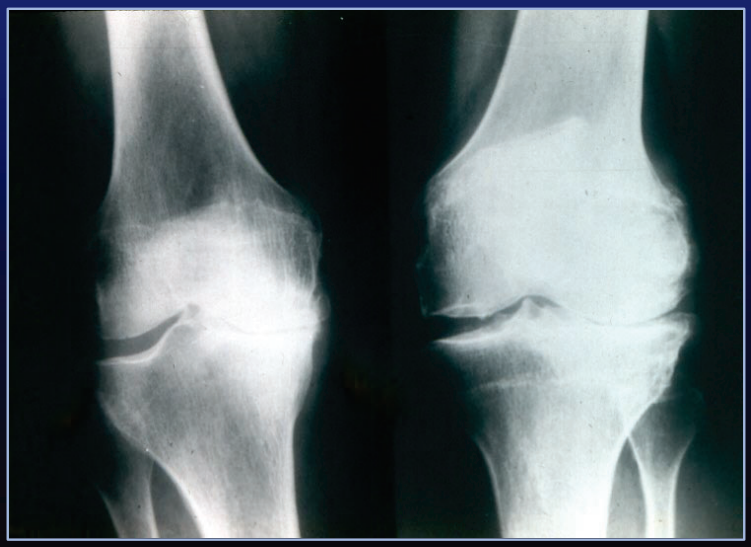
Jung KA, et al. Bone Joint Surg (Br) 2011;93-B:1303–7.

Osteoarthritis: Knee



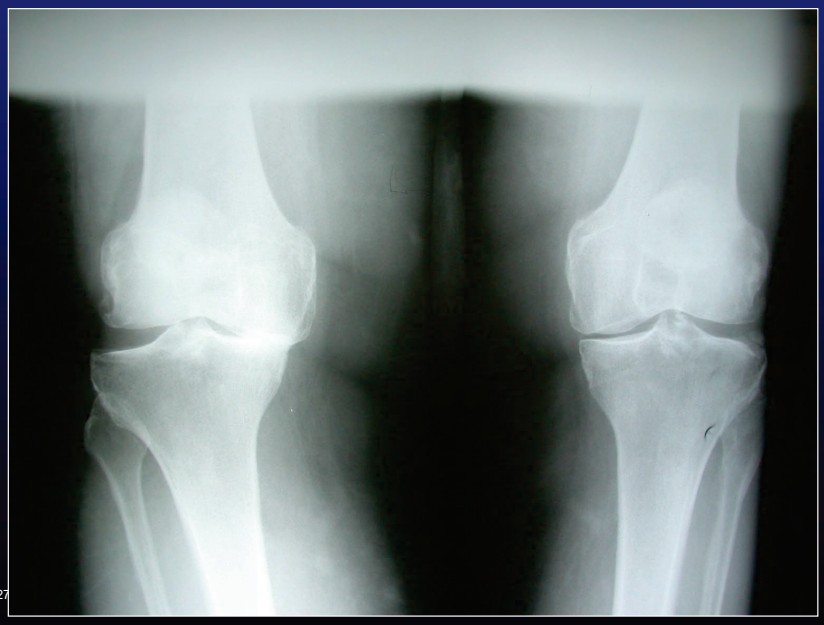
Tri-compartmental cartilage degeneration:
Note irregular bare areas with exposed bone

Asymmetric Cartilage Loss in OA of the Knee



Asymmetric joint space narrowing causing varus or valgus deformity

Osteoarthritis of the Knees



Both valgus and varus alignment abnormalities are the principal factor in progression; nullifies effect of weight reduction. Even minor alignment changes are important.

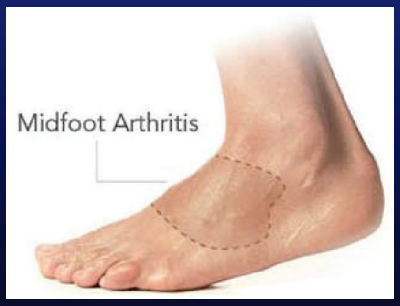
- Felson D. Arth Rheum 2/13

Hallux Rigidus and Hallux Valgus Deformity in OA

Degenerative changes are confined to the first MTP joint

Bunion and Overlapping Toes in OA

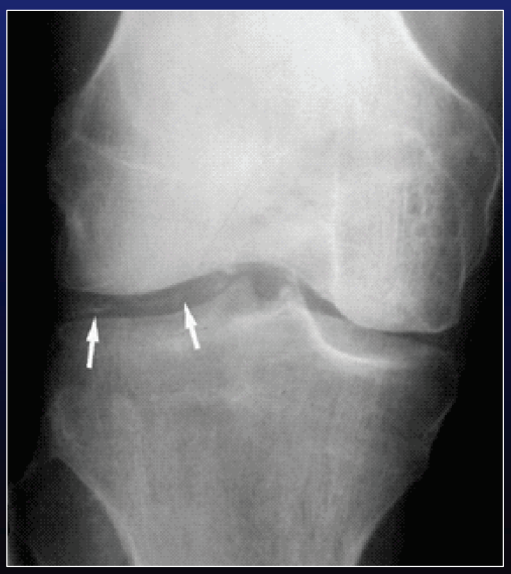
Midfoot OA: as common as the first MTP joint

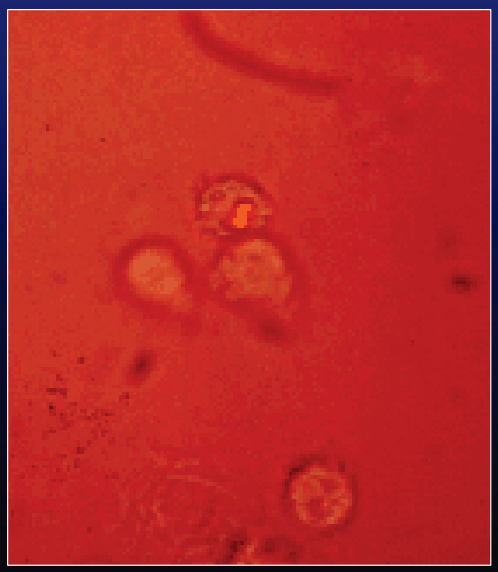


Erosive Osteoarthritis

Note “gull-wing” appearance of the PIP joint

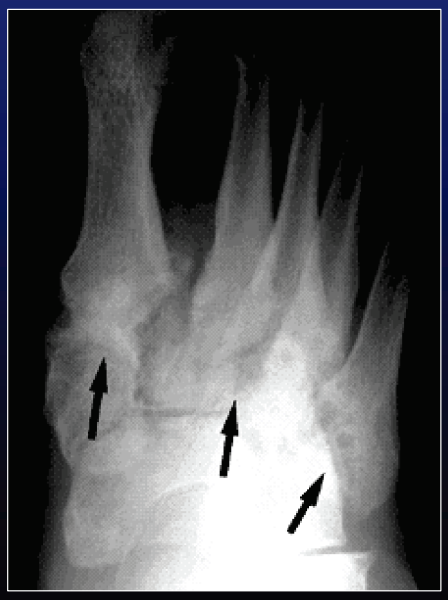
Inflammatory OA : Calcium Pyrophosphate Deposition Disease: CPPD





A common cause of inflammatory reaction in an osteoarthritic joint

Charcot Arthropathy: proprioceptive defect in Diabetic Neuropathy



A 50-year-old Man with Painful Knuckles

Note joint space narrowing and osteophytes at the MCP joints

A 50-year-old Man with Painful Knuckles

A 50-year-old Man with painful knuckles

- Serum iron = 150 µg/dL (50-160)
- Transferrin saturation = 62.5% (15-50)
- TIBC = 240 µg/dL (300-360)
- Ferritin = 1081ng/mL (27-360)
- ESR = 11 mm/hour, C-Reactive Protein negative
- Liver function tests elevated 1.5 normal
- Genotype: C282Y/C282Y (other gene H63D)

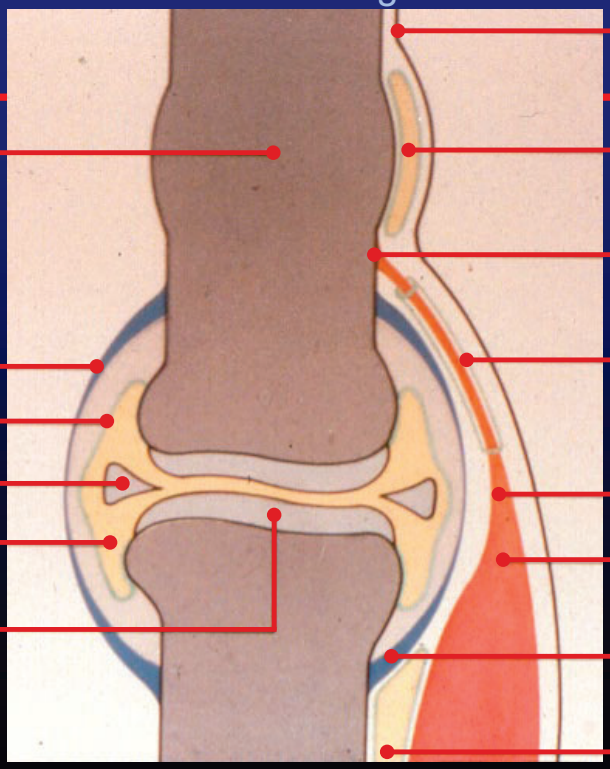
- Diagnosis: Hemochromatosis

Osteoarthritis

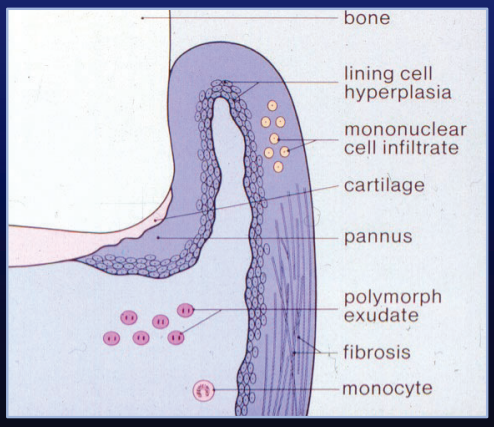
- No systemic symptoms
- Morning stiffness under 30 minutes
- ESR and C-reactive protein are normal
- Very uncommon in patients under 40 except for trauma or certain inherited patterns
- No pathognomonic serologic test for OA

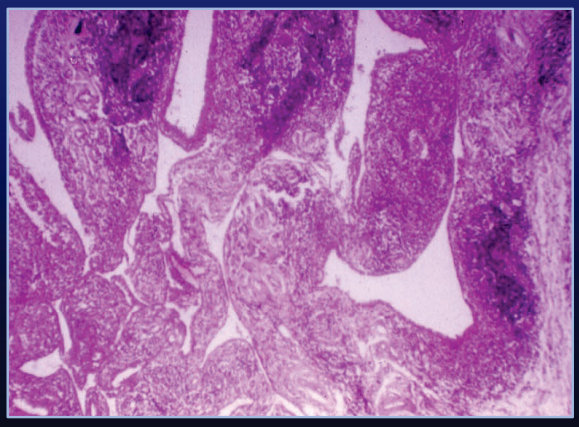
Rheumatoid arthritis

Schematic of a Finger Joint



RA: Proliferative Synovium with Invasion of Cartilage and Bone

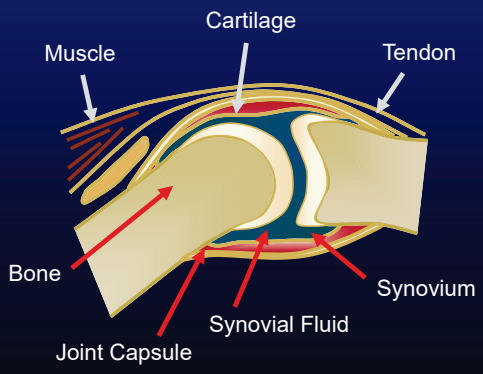




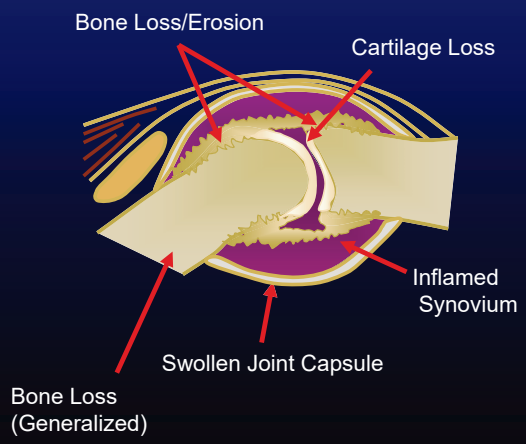
Note synovial proliferation and reduplication with intense lymphoid activity

Difference between Normal Joint and Joint Affected by Rheumatoid Arthritis

Normal Joint



Joint Affected by RA



Adapted from US Department of Health and Human Services Handout on Health. Publication 04-4179.

Synovitis

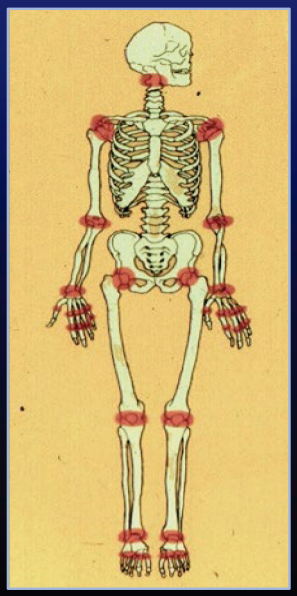
- Swelling is confined to the area of the joint capsule
- Synovial thickening feels like a firm sponge
- Definitive diagnosis of RA requires 6 weeks of inflammatory arthritis

Principle

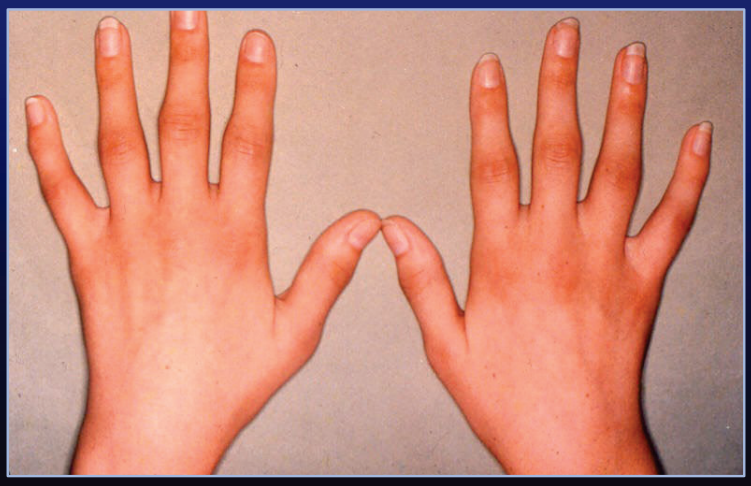
- Every arthritis has a specific pattern of joint distribution:
  - Osteoarthritis: symmetrical pattern involving mechanical degradation of hyaline cartilage
  - **Rheumatoid arthritis: symmetrical synovitis**

Rheumatoid Arthritis: Joint Distribution

- Symmetric polyarthritis
- Corresponds to the distribution of synovial lined joints
- Note absence of axial involvement except at C1-2



Early RA: Symmetrical Synovitis



Note fusiform swelling of the PIP joints and less obvious swelling of the MCP joints and wrists
The DIP joints are not affected

Radionuclide Scan in Early RA

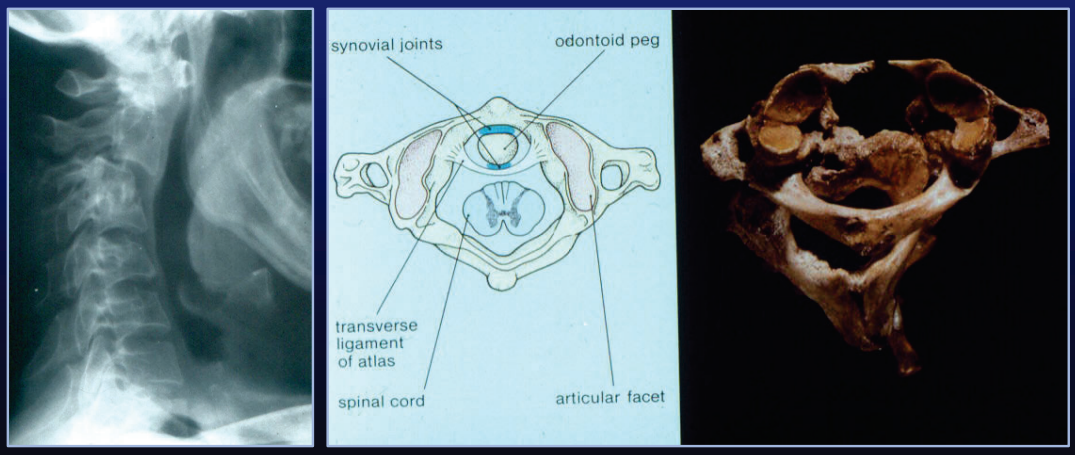
Note intense symmetric uptake at the PIP, MCP joints and wrists
Note sparing of the DIP joints

Viral Arthritis and COVID-19 infection

- Most viral arthritis are caused by enteroviruses: Coxsackie A and B, and Echoviruses
- Joint symptoms are migratory and short-lived (2-4 days)
- Hepatitis A,B, and C – mostly myalgia and arthralgia
- Most viral arthritis do not persist beyond 4 weeks (HIV only 24 hours)
- Parvovirus B19 and Chikungunya may cause prolonged arthritis
- Rubella and post-rubella vaccination may persist to a year
- COVID-19 infection provoke muscle and body aches within 2-14 days, not a true arthritis
- Several case reports of reactive arthritis within a few weeks of COVID-19 infection, seronegative and HLA-B27 negative* and post-vaccine**

*Hønge BL, et al. BMJ Case Rep 2021;14:e241375. doi:10.1136/bcr-2020-241375
**Qi-June An, et al. Reactive arthritis after COVID-19 vaccination. Hum Vaccin Immunother. 2021 Sep 2;17(9):2954-2956.

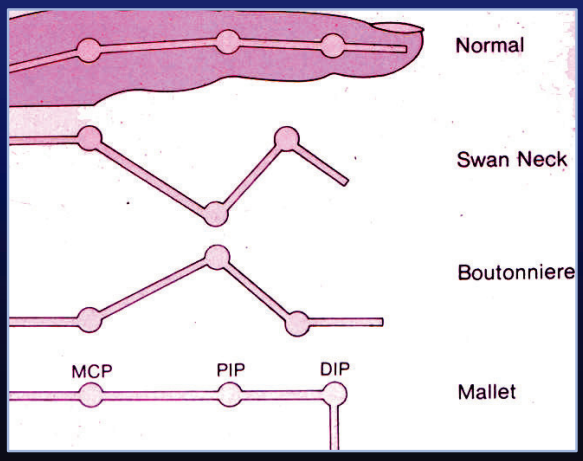
RA: Atlantoaxial Subluxation



Separation of the posterior surface of the atlas and the anterior surface of the odontoid process exceeds 3 mm

Overlapping bony rings compromise the spinal cord

RA: Finger Deformities

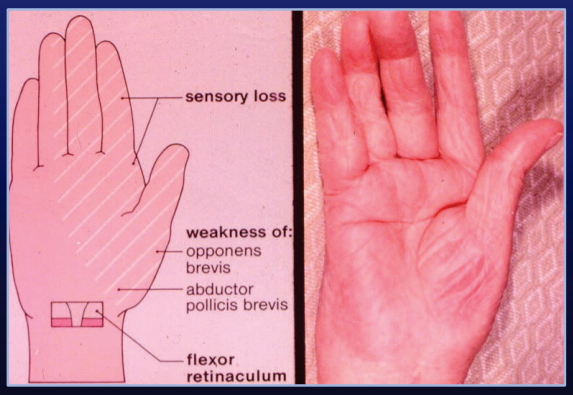


Deformity of the fingers
caused by weakness of the intrinsic muscles
and slippage of ligaments

RA: Hand Deformities

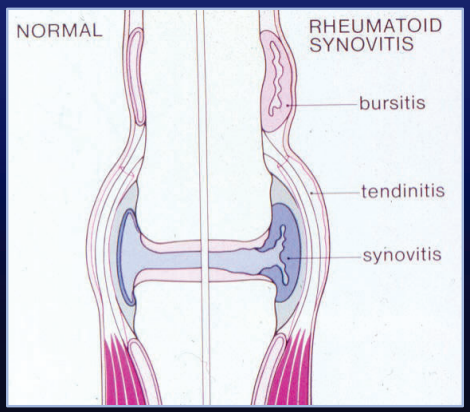
Collapse of the thumb, ulnar deviation and muscle atrophy

RA: Wrist



Wrist synovitis restricts extension with weakening of grip and trapping of the median nerve causing carpal tunnel syndrome

RA: Extensor Tendon Rupture



Painless rupture of extensor tendon typically in the morning

RA: Knee Swelling and Popliteal Cyst

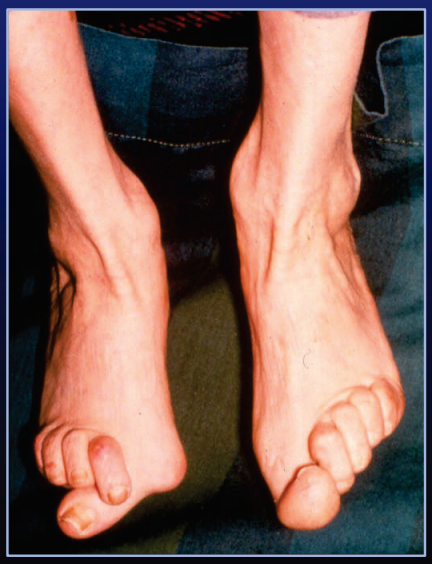
Dissection of Popliteal Cyst; Rupture causes Pseudo-thrombophlebitis

RA: Feet

Metatarsalgia, Callus Formation and Subluxation

RA: Foot Deformities

Collapse of arches and
overlapping toes



Rheumatoid Nodules

Prominent and Subtle painless rheumatoid nodules

The Value of X-rays in Rheumatoid Arthritis

- For a Symmetric polyarthritis that satisfies ARA Criteria for rheumatoid arthritis:
  - Perform X-rays of the hands and feet
  - Repeat them at 1 year or sooner if the disease is not controlled

Early x-rays are normal

Rheumatoid Arthritis

How fast is joint damage progressing?

Successive x-rays taken 9 months apart

A. Soft-tissue swelling, no erosions

B. Thinning of the cortex on the radial side and minimal joint space narrowing

C. Marginal erosion at the radial side of the metacarpal head with joint space narrowing

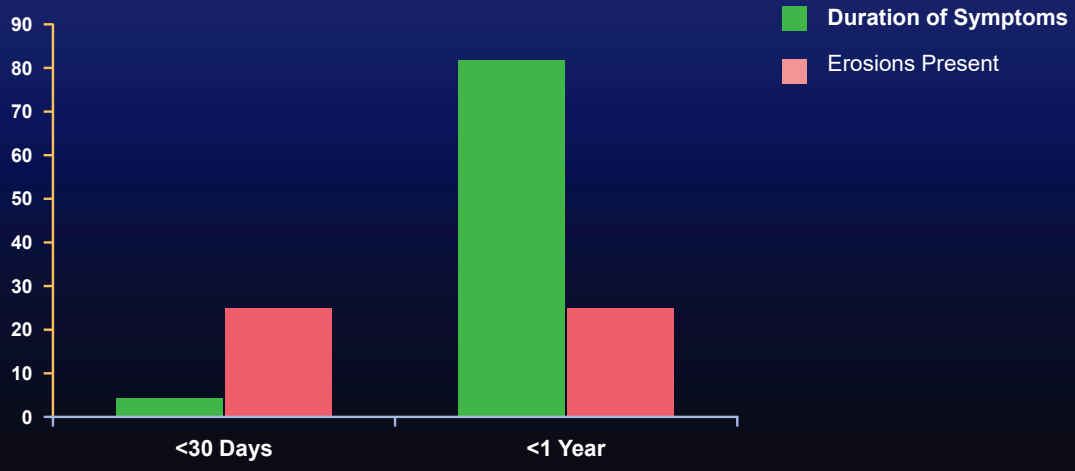
ACR Clinical Slide Collection, 1997.

Rheumatoid Arthritis

- Frequency distribution of erosions in the foot

Arthritis Care Res 2008;59:1729

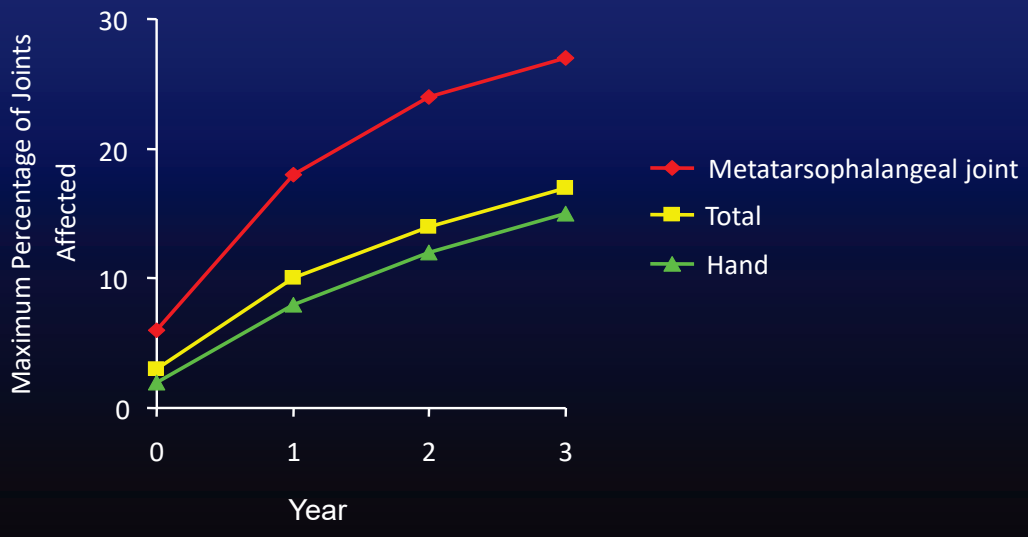
25% of Patients in an Early Arthritis Clinic Already Had Erosions at the First Visit



474 patients seen in an early RA clinic; 141 had definite or probable RA

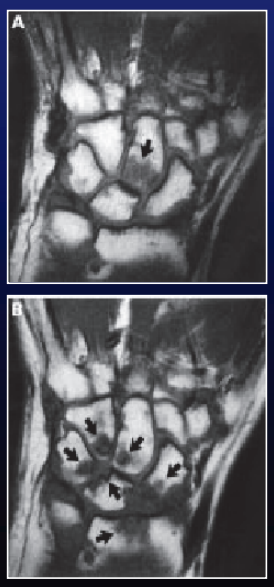
Van der Horst-Bruinsma, et al. *Br J Rheumatol.* 1998;37:1084.

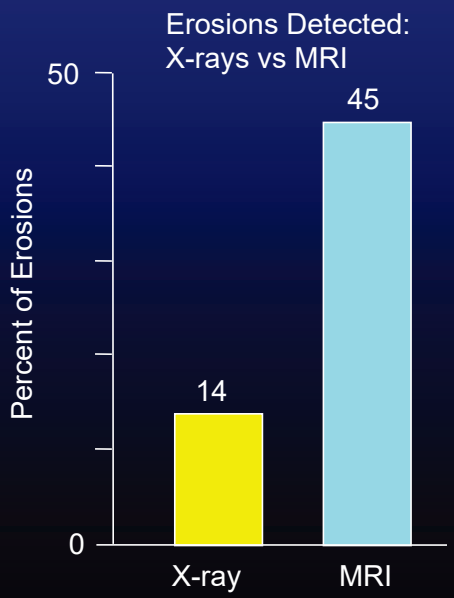
Joint Erosions Occur Early in Rheumatoid Arthritis



van der Heijde DM, et al. *J Rheumatol*. 1995;22:1792-1796. Fuchs HA, et al. *J Rheumatol*. 1989;16:585-591. McQueen FM, et al. *Ann Rheum Dis*. 1998;57:350-356.

Magnetic Resonance Imaging as a Diagnostic Tool





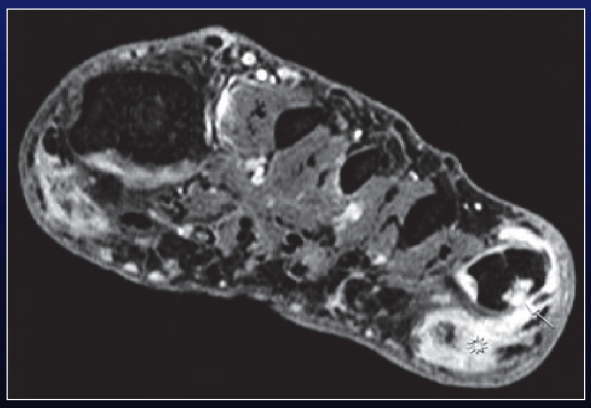
McQueen FM, et al. Ann Rheum Dis. 1999; 58:156-163; McQueen FM, et al. Ann Rheum Dis. 1998; 57: 350-356

MRI Scan of the MCP Joints as an Index of Disease Progression in RA

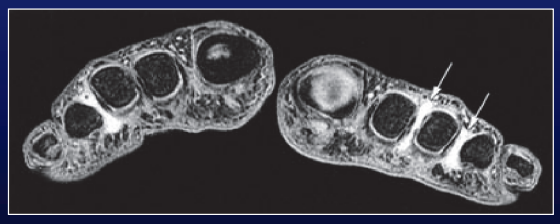
An MRI of metacarpophalangeal joints 2-5 shows synovial hypertrophy and flexor tenosynovitis

MRI scan of the feet in Early RA

High sensitivity: 97% synovitis, 80% erosions



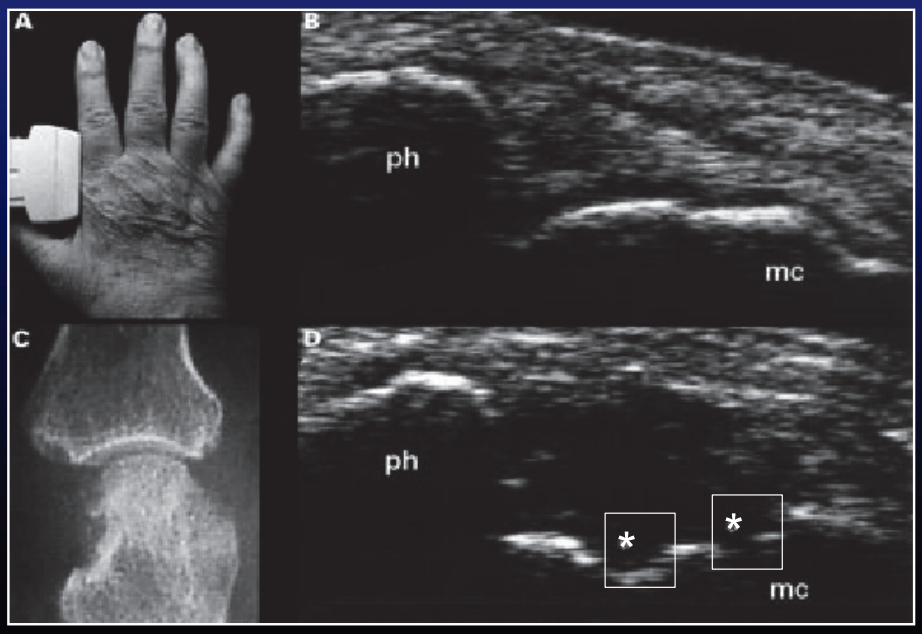
Erosions at 5th MTP



Tenosynovitis between toes

MRI scans of the wrist, taken when patients first present with RA, can predict radiographic erosions at two years. McQueen F, et al. *Ann Rheum Dis* 2001;**60**:859–868

Diagnosis of RA: Utility of Ultrasonography



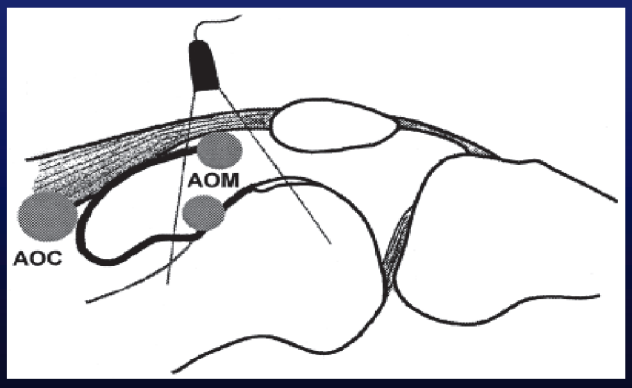
Healthy Subject

RA Patient

*Erosion; mc = metacarpal head; ph = phalanx

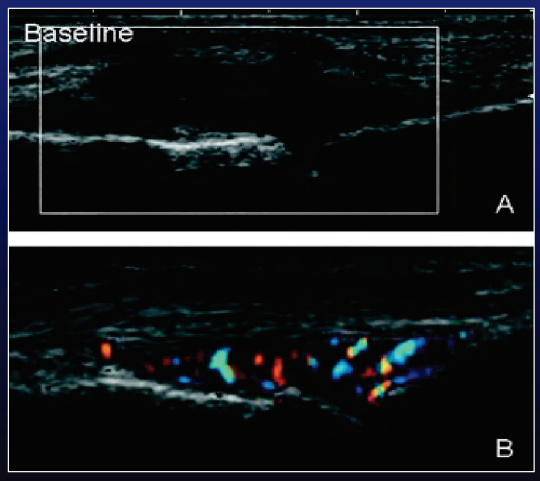
Grassi W, et al. Ann Rheum Dis. 2001; 60:98-103

Diagnosis of RA: Utility of Ultrasonography – Power Doppler Measures Vascularity

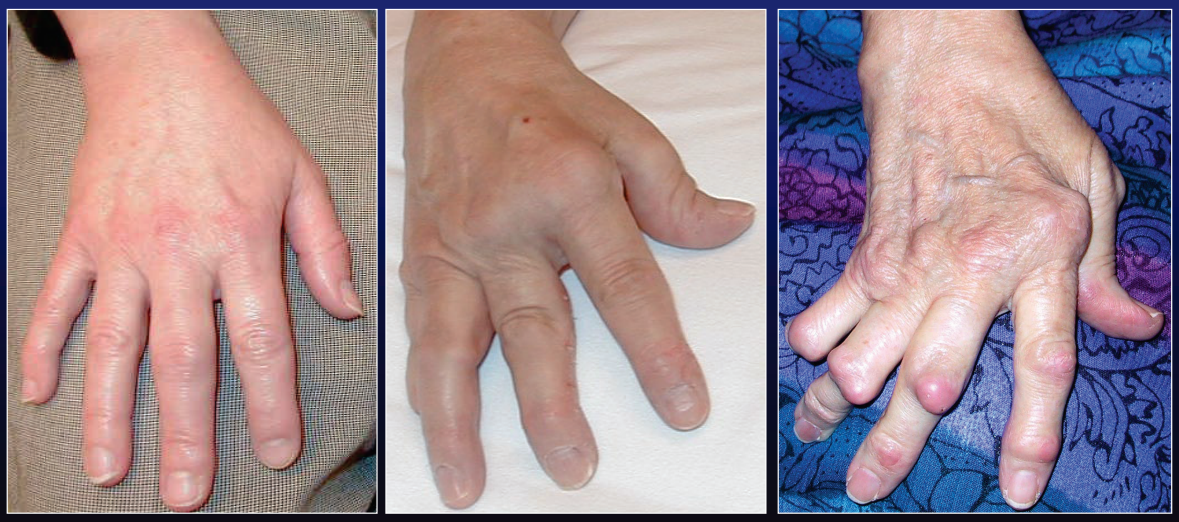


* AOM: Area of Measurement

* AOC: Area of Calibration



Progression of Rheumatoid Arthritis



Early Intermediate Late

Photographs courtesy of Cush J. 2002.

RA: Severe Hand Deformity

Radiographic progression correlates well with deformities and disability

Useful Tests in Inflammatory Arthritis

- ESR and CRP reflects general systemic inflammation
- Rheumatoid factor is positive in 80% of RA patients
- Anti-CCP antibody is positive in 70+% of RA patients
- ANA needs to be interpreted with great caution in patients with musculoskeletal pain.
  - It does NOT imply a diagnosis of SLE

RF: van Zeben D, et al. Ann Rheum Dis 1992; 51:1029
Anti-CCP : Zendman AJ, et al. Rheumatology (Oxford) 2006; 45:20.
ANA: Abeles AM, et al. Am J Med. 2013 Apr;126(4):342-8.

Rheumatoid factor, anti-CCP and RA

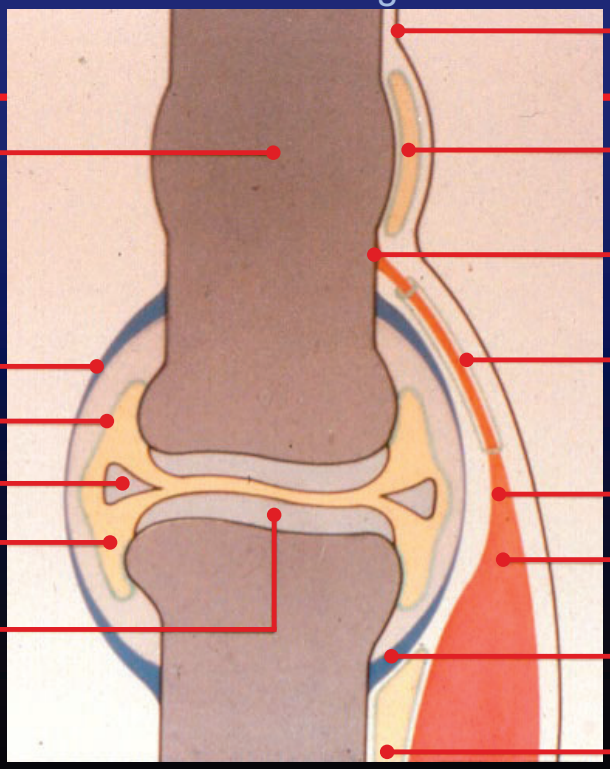
- 15% are persistently RF-negative and tend to have milder disease
- Anti-citrulline antibody may be positive in RF-negative patients
- Combination of + RF and anti-CCP in early RA predicts high risk for persistent RA (Smolen J, Aletaha D. Nature Rev Rheum 2015)
- A new marker 14-3-3 η (eta) improves diagnostic sensitivity from 60-91% for either RF or anti-CCP to 72-100 with either one of 3 markers. (Maksymowych W, et al. Arth Res Ther 2014;16:R99)

Seronegative spondyloarthropathy: ankylosing spondylitis, psoriatic arthritis

Principle

- Every arthritis has a specific target tissue:
  - Osteoarthritis: articular cartilage
  - Rheumatoid arthritis: synovium
  - **Spondyloarthritis: enthesis**

Schematic of a Finger Joint

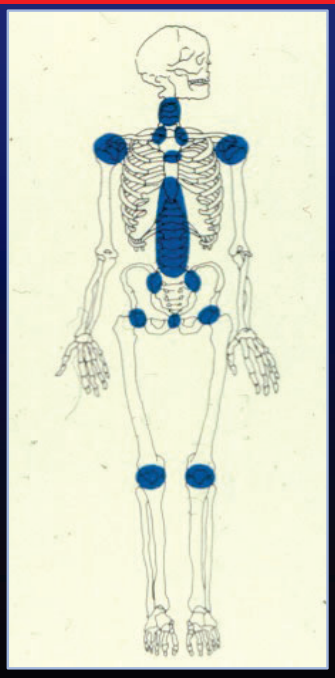


Spondyloarthritis

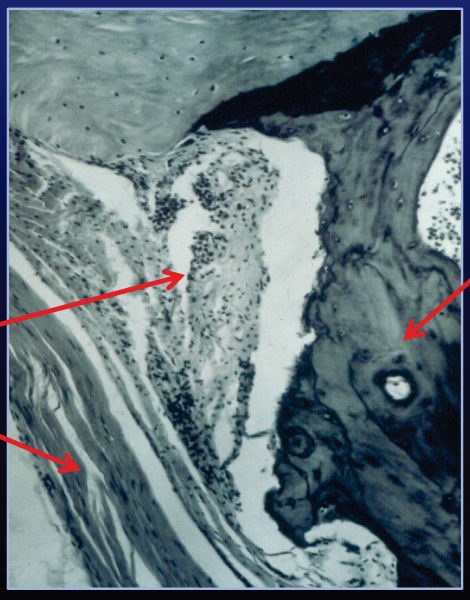
- Ankylosing spondylitis
- Psoriatic arthritis
- Reactive arthritis
- Arthritis of inflammatory bowel disease
- **Characteristics:**
  - Negative rheumatoid factor
  - spinal involvement and sacroiliitis
  - Asymmetric oligoarthritis
  - Sausage digits

Spondyloarthritis

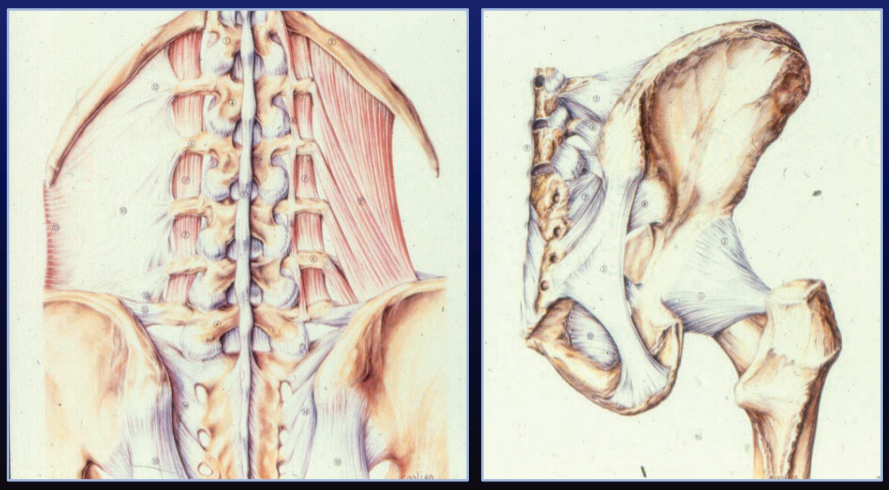
- Axial Involvement: shoulders and hips are included
- Common targets highlighted
- Pattern is symmetrical in ankylosing spondylitis and asymmetric in psoriatic arthritis



Enthesopathy



Spinal Ligaments

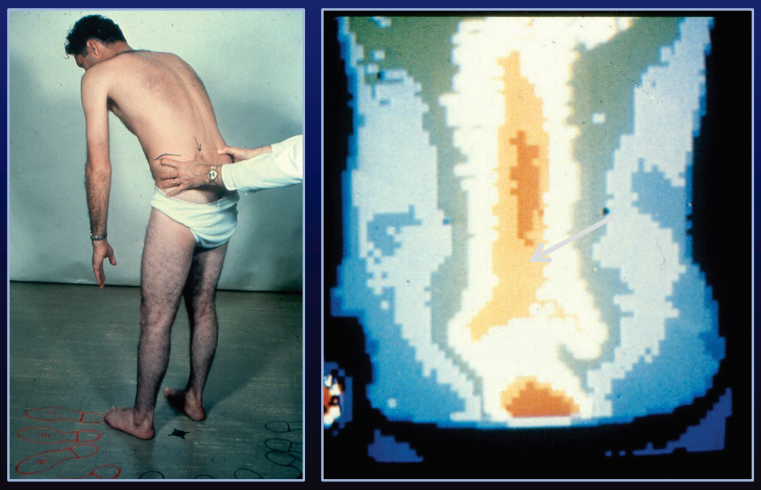


Entheseal inflammation at the ligaments is the principal cause of spinal symptoms

Principle

- Every arthritis has a specific pattern of joint distribution:
  - Osteoarthritis: symmetrical pattern involving mechanical degradation of hyaline cartilage
  - Rheumatoid arthritis: symmetrical synovitis
  - **Seronegative spondyloarthropathy: asymmetric inflammation of enthesis and synovium**

Spinal Inflammation



Limited flexion. Thermogram shows increased spinal temperature

Spinal Inflammation

Restricted lateral flexion and pectoral muscle wasting

Spinal Immobility

Complete fusion of axial skeleton with poor posture

When Should You Suspect Inflammatory Back Pain?

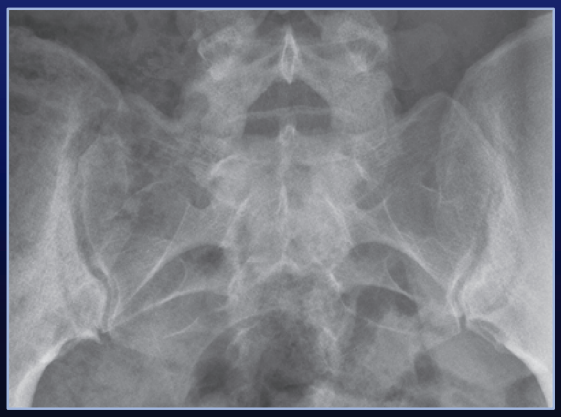
- Young male
- Morning stiffness greater than 30 minutes
- Back pain is worse with rest and better with movement
- Unable to sleep through the night: usually awakens in the early hours of the morning
- Alternating buttock pain but no true radicular symptoms

Hamilton L, et al. Rheumatology (Oxford). 2014 Jan;53(1):161-4.

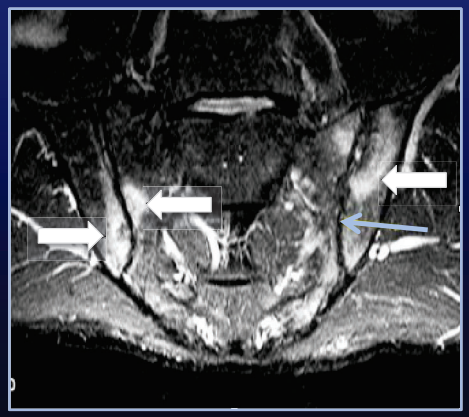
Sacroiliitis

Sclerosis, irregular joints and pseudowidening

MR Imaging of Sacroiliac Joints: Most Sensitive Way to Detect Sacroiliitis: nr-axSpA



X-rays show normal sacroiliac joints



White areas on STIR indicate bone marrow edema

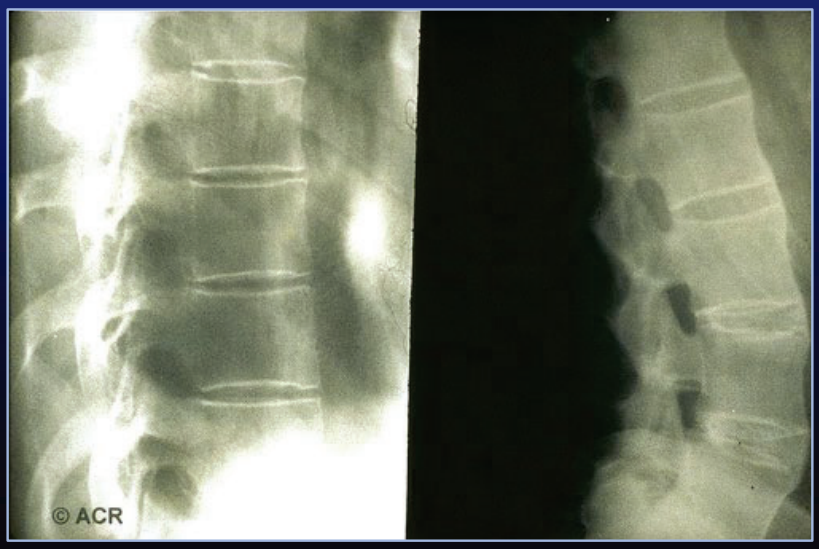
Progression of nonradiographic axial SpA: 6.4% in 5 years, 17.3% at 10 years, 26.4% at 15-years. Wang 2015 SPARTAN

Sacroiliac Joint Fusion

Fusion of sacroiliac joints in late sacroiliitis

Spinal Fusion: Syndesmophytes

Spinal Fusion: Syndesmophytes



Squaring of the vertebral bodies Syndesmophytes

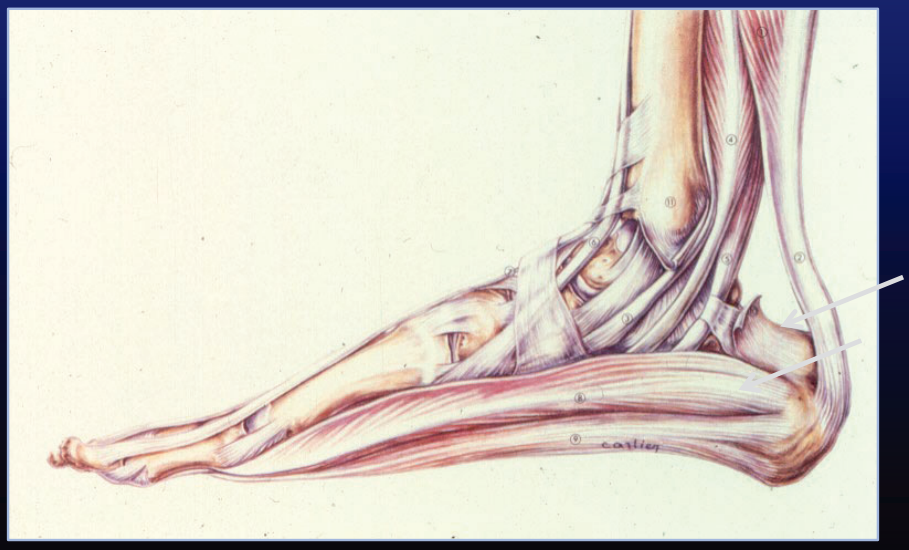
The Bamboo Spine

Complete fusion of the spine

Enthesitis in Peripheral Joints (Typically PsA and ReA)

Inflamed Achilles tendon on the left

Enthesitis: Achilles Tendinitis and Plantar Fasciitis

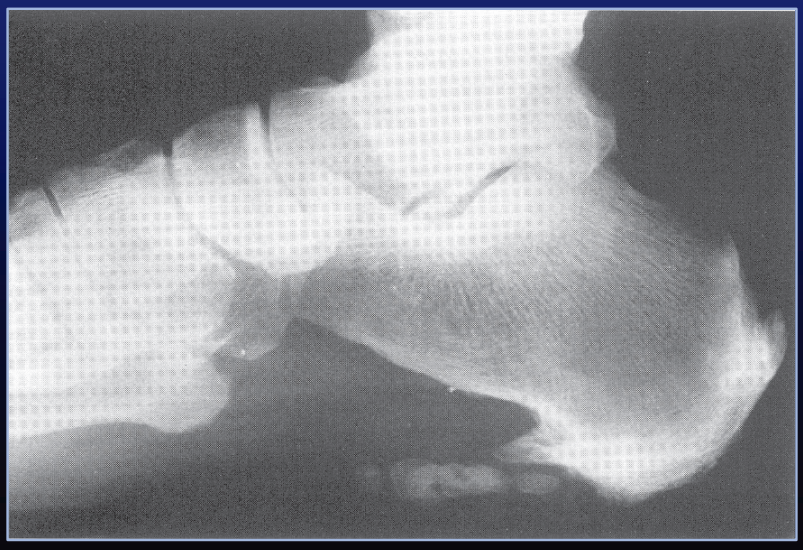


Sites of entheseal inflammation

Psoriatic arthritis: Enthesopathy

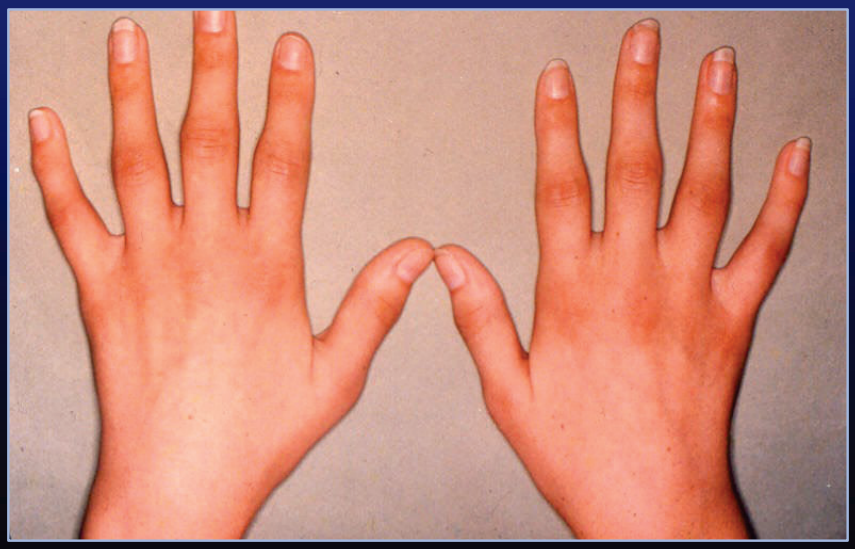
Regions of tenderness

SpA : Enthesopathy



Note sclerosis, fluffy periostitis and new bone formation

RA Symmetrical Synovitis



Psoriatic Arthritis (PsA): Asymmetry

Rheumatoid Arthritis: Synovitis

PsA: The Sausage Digit

Dactylitis caused by ligamentous inflammation

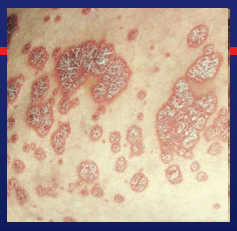
PsA: The Sausage Digit

PsA: Arthritis Mutilans

Note dystrophic nails and telescoping of digits

Variants of Psoriasis

- Plaque Psoriasis- >80%
- Guttate Psoriasis
- Scalp Psoriasis
- Palmoplantar Psoriasis
- Erythrodermic Psoriasis
- Inverse Psoriasis “pinking”



Plaque

Guttate

Palmar-Plantar

Pustular

Erythrodermic

Inverse

Slide courtesy of Paul S Yamauchi, MD, PhD.

Psoriasis: Nail Pitting, Onycholysis

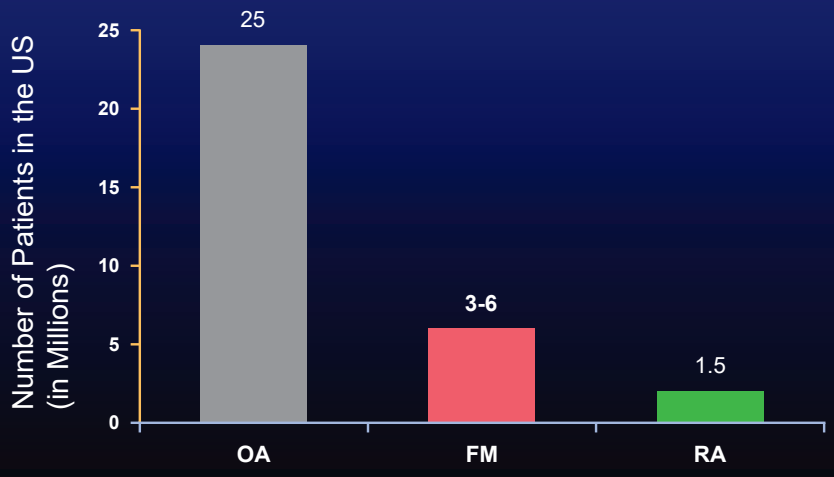
Nail involvement 40-50% in psoriasis without arthritis
80% in patients with psoriatic arthritis

What Distinguishes Psoriatic Arthritis from Rheumatoid Arthritis?

- Asymmetry
- Spine involvement
- Sausage digits
- Absence of nodules
- Psoriasis may be subtle and easy to miss

Fibromyalgia

Fibromyalgia More Prevalent than Rheumatoid Arthritis



Fibromyalgia

- A clinical syndrome characterized by chronic widespread pain and tenderness to palpation at specific body sites
- Fibromyalgia has no target tissue but an easily recognizable clinical presentation

The Paradox of Fibromyalgia: No Target Tissue

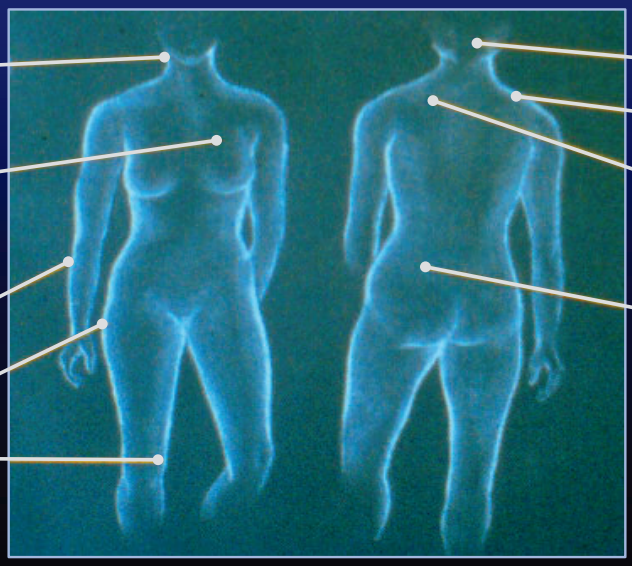
- Normal passive range of joint motion
- Minimal mechanical disability
- Absence of muscle weakness or atrophy
- Normal ESR
- Normal radiographs, electromyogram, etc

ACR Fibromyalgia Criteria

- From History: widespread pain of 3 months duration
- From Examination: tender points defined by digital palpation with a force of 4 kg pain experienced in at least 11 of 18 tender point sites

Wolfe F, et al. *Arthritis Rheum.* 1990;33:160-72.

Map of 18 Possible Tender-Points in Fibromyalgia



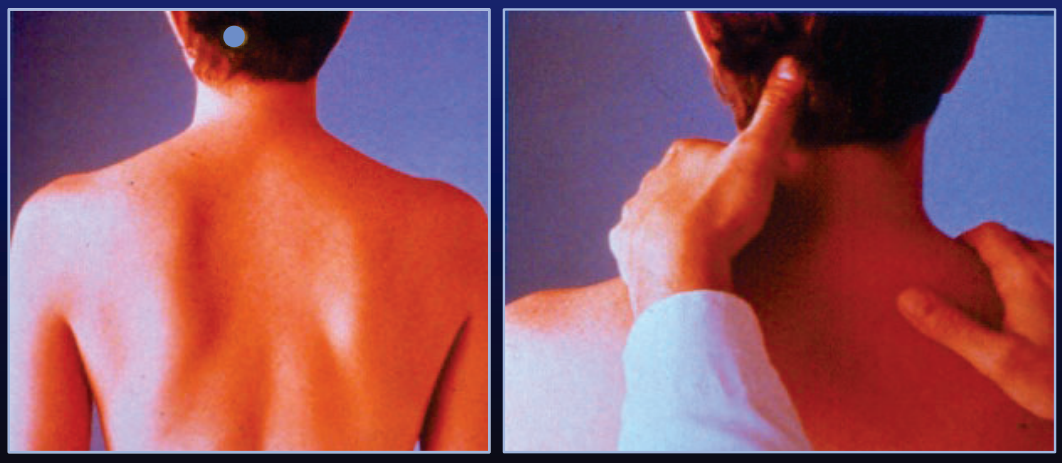
Panel Consensus; Wolfe, et al. 1990.

The Tender Point: Key to Fibromyalgia Diagnosis

- Excessively tender, discrete area of soft tissue
- Palpated with thumb or first two fingers
- Palpation pressure: ~4 kg/cm, enough to whiten nail

Wolfe, et al. 1990.

Tender-Point Palpation: I. Head



● Insertion of suboccipital muscle

Tender-Point Palpation: IV. Neck and Chest

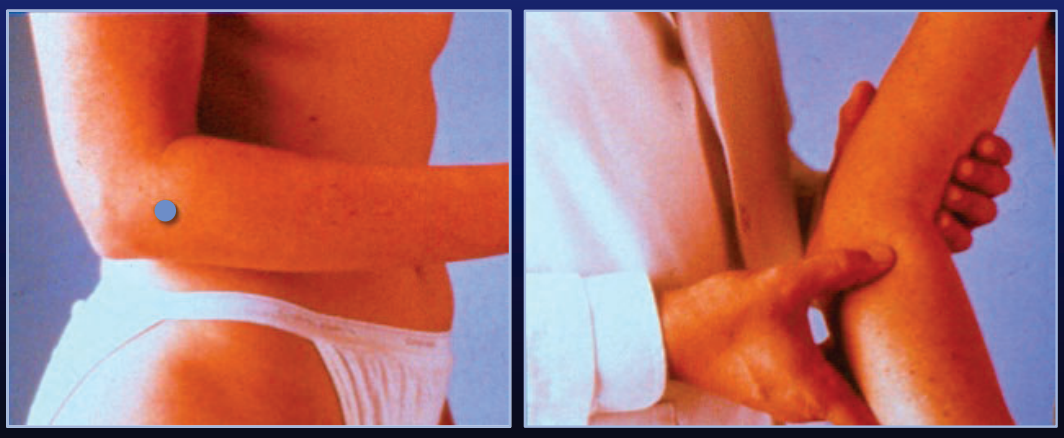
● Lower sternomastoid

▲ Second costochondral junction

Tender-Point Palpation: II. Upper Back

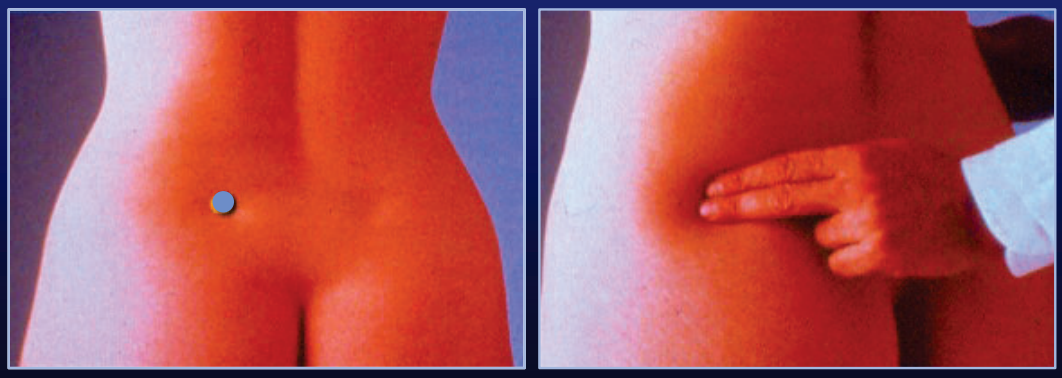
- Mid upper trapezius
- Origin of supraspinatus

Tender-Point Palpation: V. Arms



- Lateral epicondyle

Tender-Point Palpation: III. Lower Back



● Upper outer buttock quadrant

Tender-Point Palpation: VI. Legs

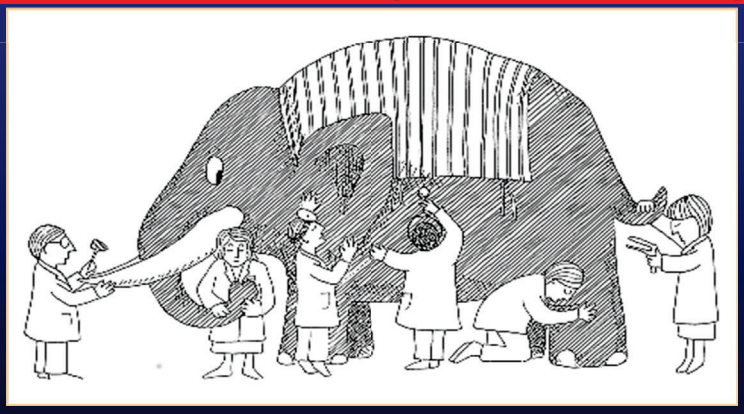
● Prominence of greater trochanter

▲ Medial fat pad of the knee

Fibromyalgia Patients Have Widespread Somatic Symptoms

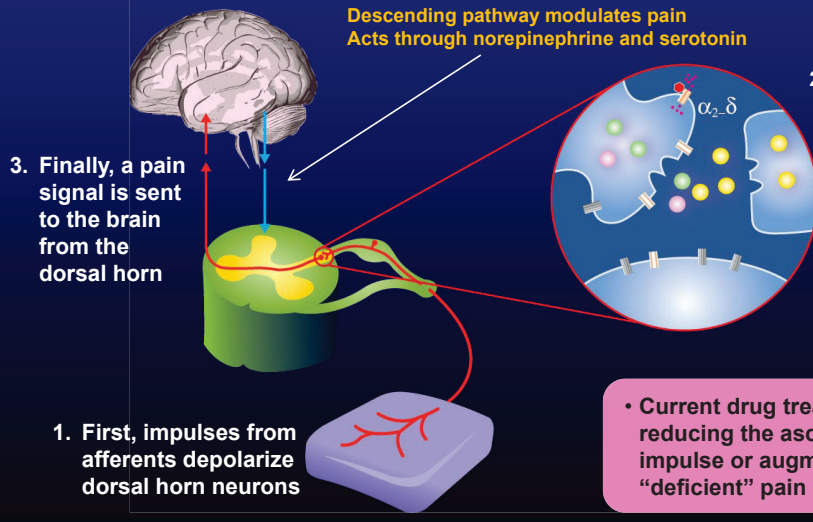
Criterion	% Positive
Widespread Pain	**97.6**
Tenderness 11 of 18 tender points	90.1
Fatigue	**81.4**
Morning stiffness > 15 minutes	77.0
Sleep disturbance	74.6
Parasthesias	62.8
Headache	52.8
Anxiety	47.8
Dysmenorrhea	40.6
Sicca symptoms	35.8
Prior depression	31.5
Irritable bowel syndrome	29.6
Urinary urgency	26.3
Raynaud's phenomenon	16.7

Syndromes That Overlap with Fibromyalgia



The neurologist sees chronic headache,
the gastroenterologist sees IBS,
the otolaryngologist sees TMJ syndrome,
the cardiologist sees costochondritis,
the rheumatologist sees fibromyalgia,
and the gynecologist sees PMS.

Pathophysiology of Fibromyalgia: The Role of Central Sensitization



3. Finally, a pain signal is sent to the brain from the dorsal horn

2. Then, extracellular Ca^{2+} and nitric oxide diffuse into neurons and cause exaggerated release of substance P and glutamate; this results in neuronal hyperexcitability

1. First, impulses from afferents depolarize dorsal horn neurons

- Current drug treatment is aimed at reducing the ascending "exaggerated" impulse or augmenting the descending "deficient" pain modulating pathway

Despite extensive research, the pathogenesis of pain in FM is not clearly understood. However, central sensitization has emerged as a leading theory of disease mechanism.

Staud. *Arthritis Res Ther* [serial online]. 2006;8:208; Henriksson. *J Rehabil Med*. 2003;41(suppl 41):89-94.

PASC (Post-Acute Sequelae of SARS-CoV-2 infection)

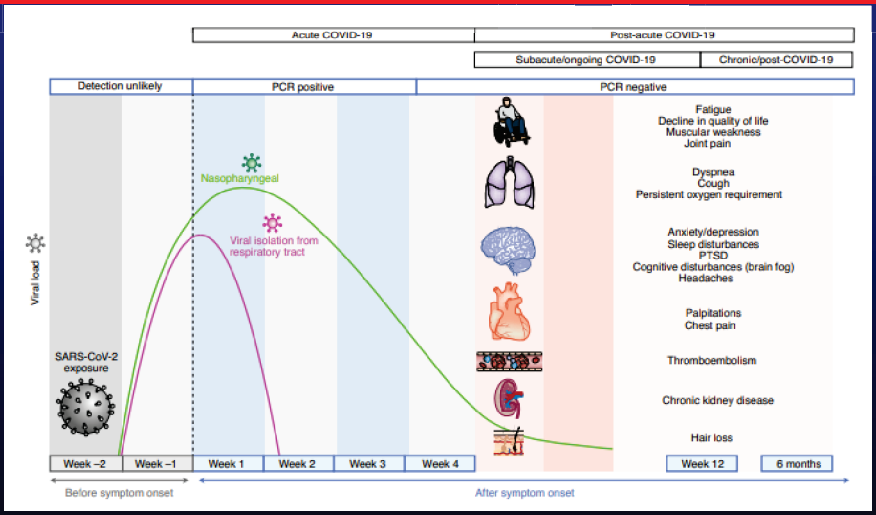
- 4182 incident cases (no prior issues)
  - Symptoms > 4 weeks: 13.3%
  - Symptoms > 8 weeks: 4.5%
  - Symptoms > 12 weeks: 2.3%

- Increasing age (up to 70)
- Increasing BMI
- Female sex
- >5 symptoms during first week of illness
- Pre-existing, activity-limiting conditions
- Lower socioeconomic status

Nalbandian A, et. al. Nature Medicine 2021;27:601-15

Post-Acute Sequelae of SARS-CoV-2 infection

A Nalbandian, ER al.
Nature Medicine
2021;27:601-15



Italian web study: 30.7% of "long COVID-19" meet 2010 ACR Criteria for Fibromyalgia*
Ursini F, et al RMD Open 2021;7:e001735. doi: 10.1136/rmdopen-2021-001735

Data from the first 305 patients in the Cleveland Clinic Fibromyalgia Clinic cohort

Fatigue	98.7%
Widespread pain for three months or more	97.1%
Current depression (PHQ-9 score > 10)	88.6%
Unrefreshing sleep	85.8%
Headaches	82.5%
Difficulty concentrating	79.5%
Memory difficulty	75.5%
Urinary frequency	67.5%
Constipation alternating with diarrhea	61.8%
Current severe or moderate-to-severe depression (PHQ-9 score ≥ 15)	45.8%
Anxiety	41.8%

PHQ-9 = Patient Health Questionnaire-9

Kaouk S, Wilke W, Gota C. Int. J. Clin. Rheumatol. (2018) 13(2), 82-93

Proposed infectious agents in CFS

- Epstein-Barr Virus
- Human herpesvirus-6 (HHV-6)
- Cytomegalovirus (CMV)
- Coxsackie B
- Toxoplasmosis
- Chronic Lyme disease
- Retrovirus HTLV-II
- Chronic candidiasis
- Enterovirus
- Ross River virus
- Borna disease virus
- XMRV *
- MLV (both due to contamination of specimens)

* Silverman, et al retracted their original publication in Science. See references.

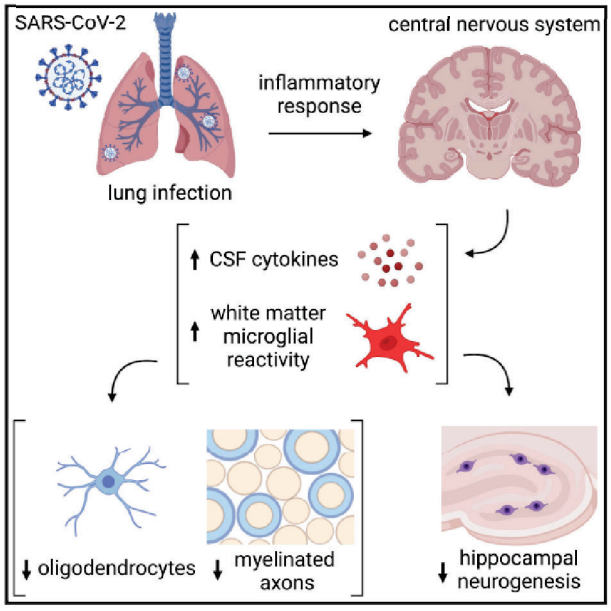
Pathological findings in PASC

- Persistence of SARS-CoV-2 nucleic acids in multiple organs (Fauci), 7/14 in small bowel
  - Han C, et al. Am J Gastro Han C, et al. Am J Gastroenterol. 2020;115(6):916-923. doi:10.14309/ajg.0000000000000664
- Persistent cutaneous basophil hypersensitivity – delayed type reaction caused by T cell seen with mRNA vaccines (treat with antihistamines?)
  - Askenase P. N Engl J Med 2021; 385:1720-1721
- High CCL11 (chemokine) in 48/63 with long COVID (Chemo Brain)
  - Fernandez-Castaneda A, et al. BioRxiv doi: https://doi.org/10.1101/2022.01.07.475453
- Elevated CSF protein in 2/13 PACS 69% had oligoclonal bands
  - Apple A, et al. Ann Clin Translational Neur 2022; doi: 10.1002/acn3.51498

Pathological findings in PASC

- (i) greater reduction in grey matter thickness and tissue-contrast in the orbitofrontal cortex and parahippocampal gyrus,
- (ii) greater changes in markers of tissue damage in regions functionally-connected to the primary olfactory cortex, and
- (iii) greater reduction in global brain size. (Brain scans 141 days apart)
  - Douaud G, et al. Nature 2022; preprint March 7, 2022
- elevated levels of CSF immune activation and immunovascular markers in individuals with cognitive post-acute sequelae of SARS-CoV-2 infection (PASC). Patients whose cognitive symptoms developed during the acute phase of COVID-19 had the highest levels of brain inflammation
  - Joanna Hellmuth, MD. AAN 2022 Annual Meeting (April 2022)
- Dramatic improvement in brain fog and other PACS symptoms within 3 days of treatment with nirmatrelvir/ritonavir (Paxlovid) - 3 cases UCSF 5-5-2022

Pathological findings in PASC



Highlights

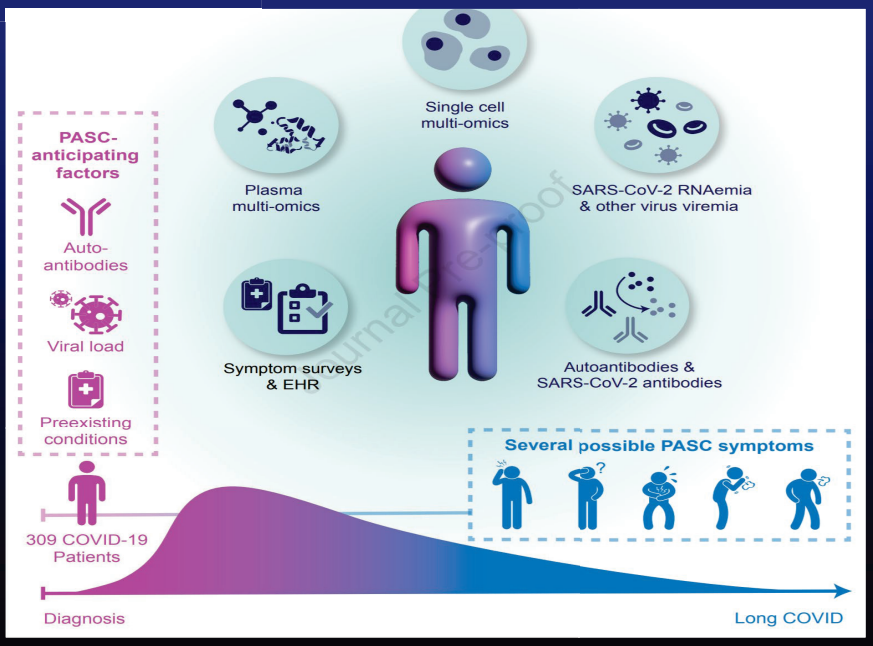
- Respiratory COVID induces CSF cytokine elevation and microglial reactivity
- CCL11 activates hippocampal microglia and impairs neurogenesis
- Respiratory COVID causes persistent loss of oligodendrocytes and myelinated axons
- Respiratory influenza causes similar but less persistent cellular dysregulation

Fernández-Castañeda et al., 2022, Cell *185*, 2452–2468
July 7, 2022 © 2022 The Author(s). Published by Elsevier Inc.
https://doi.org/10.1016/j.cell.2022.06.008

Factors that predict PASC

Presence of autoantibodies had the highest predictive value

Su Y, et al. January 24, 2022
DOI:https://doi.org/10.1016/j.cell.2022.01.014



Conclusions

- Examine the whole patient
- Identify the target tissue and joint distribution
- Recognize synovitis
- Interpret laboratory studies in the context on the clinical picture