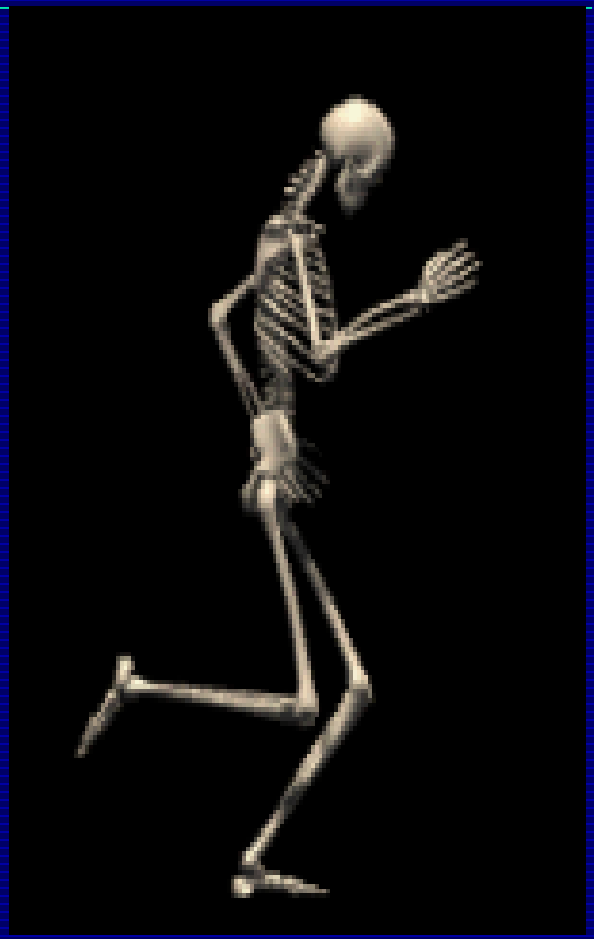
Bone and joint diseases

April 25, 2017

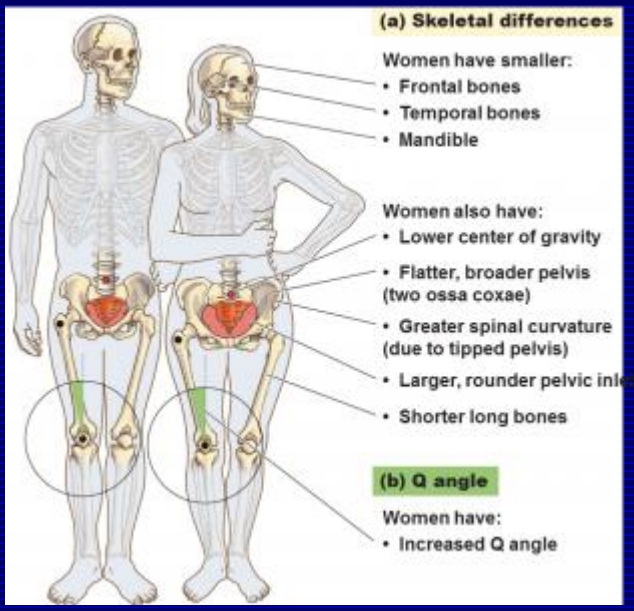
Bone properties

- Bones
  - stiff
  - do not bend when loaded.
  - flexible - absorb the energy imposed by loading as potential energy by elastic then plastic deformation.
  - Structural failure may occur if bones deform too little or too much.
- High remodeling reduces the mineral content of bone, resulting in loss of stiffness.



Bone properties

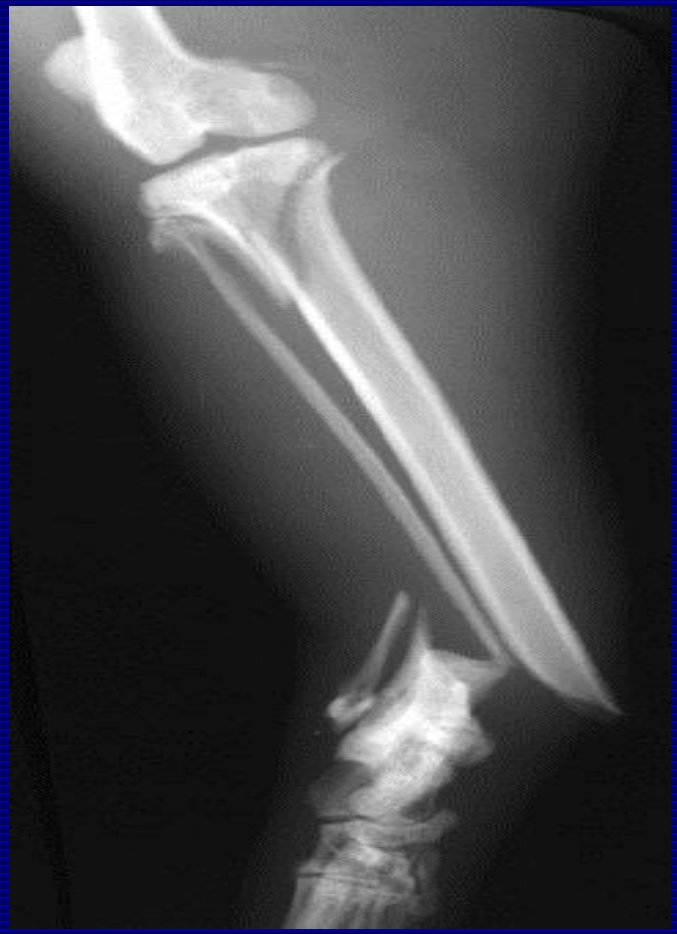
- Age- and menopause-related abnormalities in bone remodeling produce loss of material and structural properties.
- Sex hormone deficiency
  - increases the volume of bone resorbed
  - reduces the volume of bone formed.
    - The contributions made by differences in material composition, tissue mineral content, collagen type and cross-linking) structure (bone size, cortical thickness and porosity, trabecular number, thickness, connectivity), and other factors (microdamage burden, osteocyte density) to sex and racial differences in bone fragility remain poorly defined.



Skeletal fragility

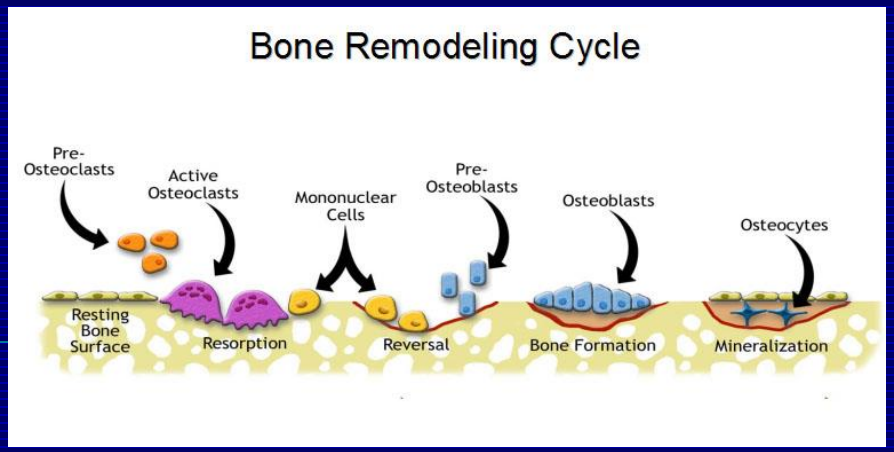
Skeletal fragility can result from:

- failure to produce a skeleton of optimal mass and strength during growth;
- excessive bone resorption resulting in decreased bone mass and microarchitectural deterioration of the skeleton;
- and an inadequate formation response to increased resorption during bone remodeling.

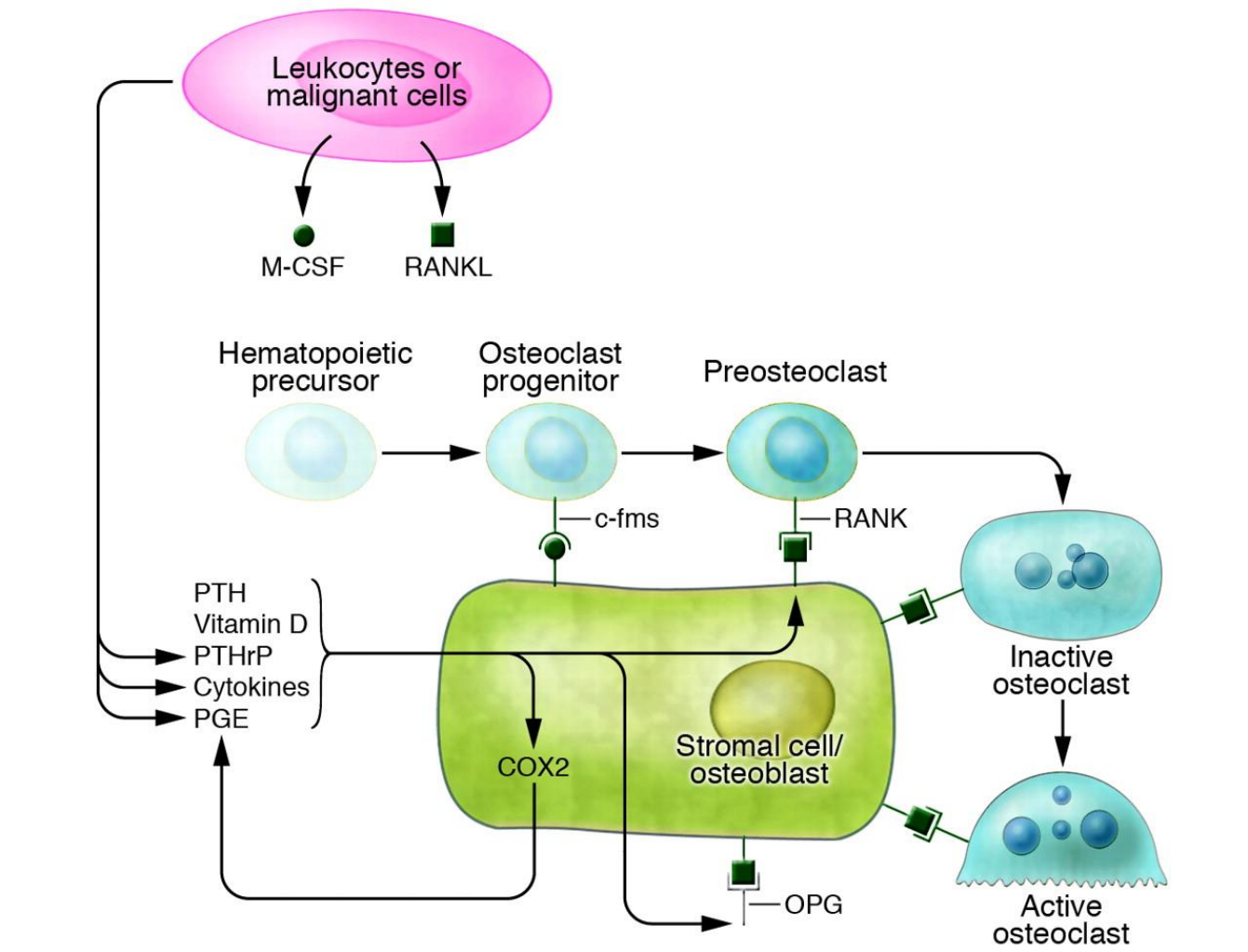


Bone remodeling

- ***Osteoclast activation***
- ***Resorbtion phase-*** due to osteoclast activation- short period
- ***Reverse phase-*** bone surface is covered by mononuclear cell
- ***Formation phase-*** osteoblast production in bone matrix - long.



Regulation of osteoclast formation and activity



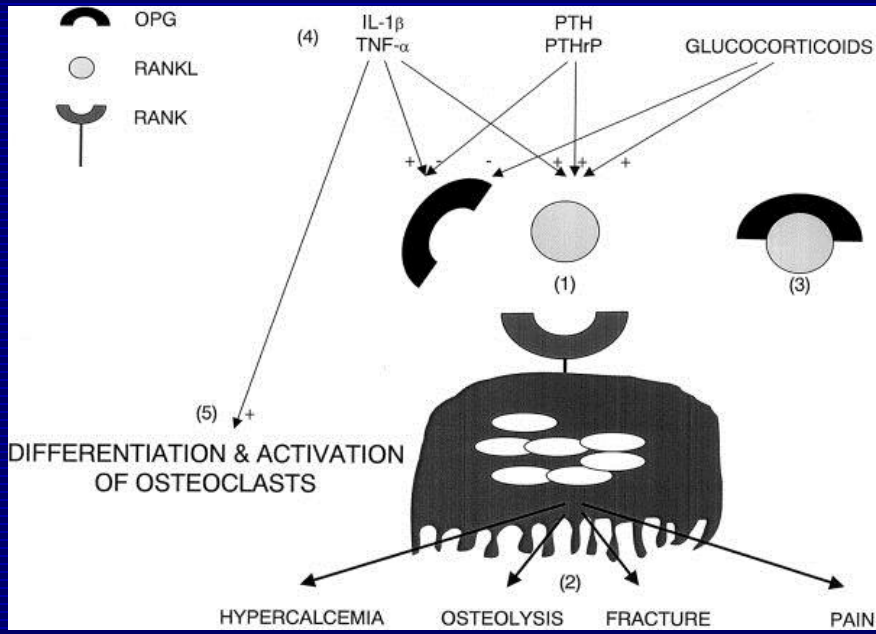
Raisz, L. G. J. Clin. Invest. 2005;115:3318-3325

Osteoclasts activation

- Regulation of osteoclast formation and activity.
  - contact between cells of the osteoblast and osteoclast lineages.
  - to stimulate differentiation and proliferation of hematopoietic progenitors, which then express RANK as preosteoclasts.
  - Osteoclast differentiation and activity are stimulated by RANK/RANKL interaction, and
  - this interaction can be blocked by soluble OPG.

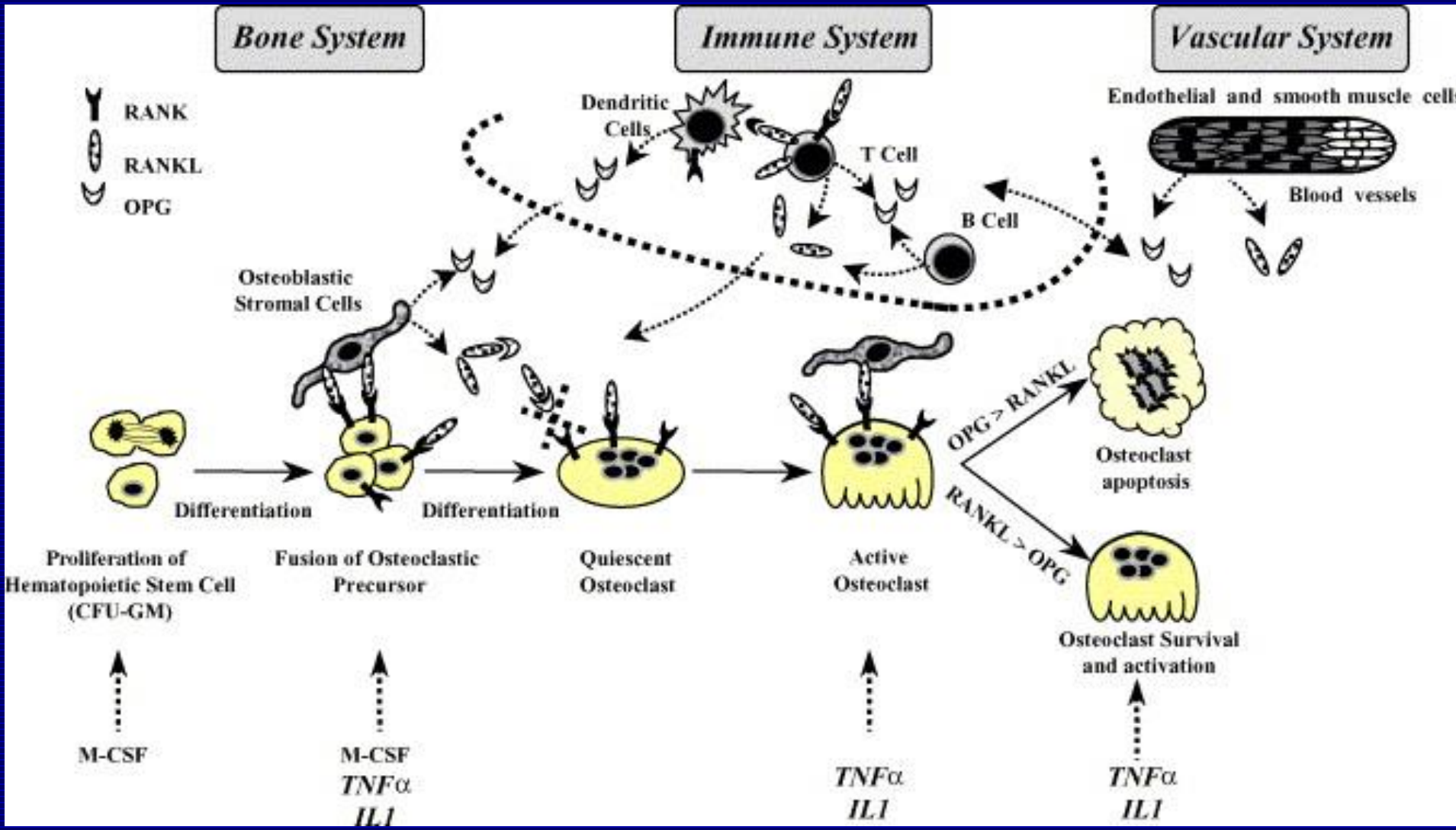
Ligand for receptor activator nuclear factor- kappa B ligand (RANKL) a osteoprotegrin (OPG) as final effector cytokines in malignant sceletal diseases (to the previous picture).

- 1) Interaction RANKL with RANK supports differentiation and activation ofi osteoclasts
- 2) Activated osteoclasts cause humoral hyperkalcemia in malignant tumors, osteolytic metastases, pathological fractures ind in pain-related malignancies.
- 3) OPG functions as receptor neutralizing RANKL which obstuct its ligation with RANK.
- 4) many growth factors, cytokines, hormons converge at the level of RANKL and OPG and regulate differenciation and activation of osteoclasts. Il-1 and TNF support production of RANKL and OPG, while PTH, PTHrP and glucocorticoids increase production of RANKL, but dicrease OPG production
- 5) to some extent, IL-1 and TNF are able to modulate differentiation and activation of osteoclasts independently on RANKL and RANK.



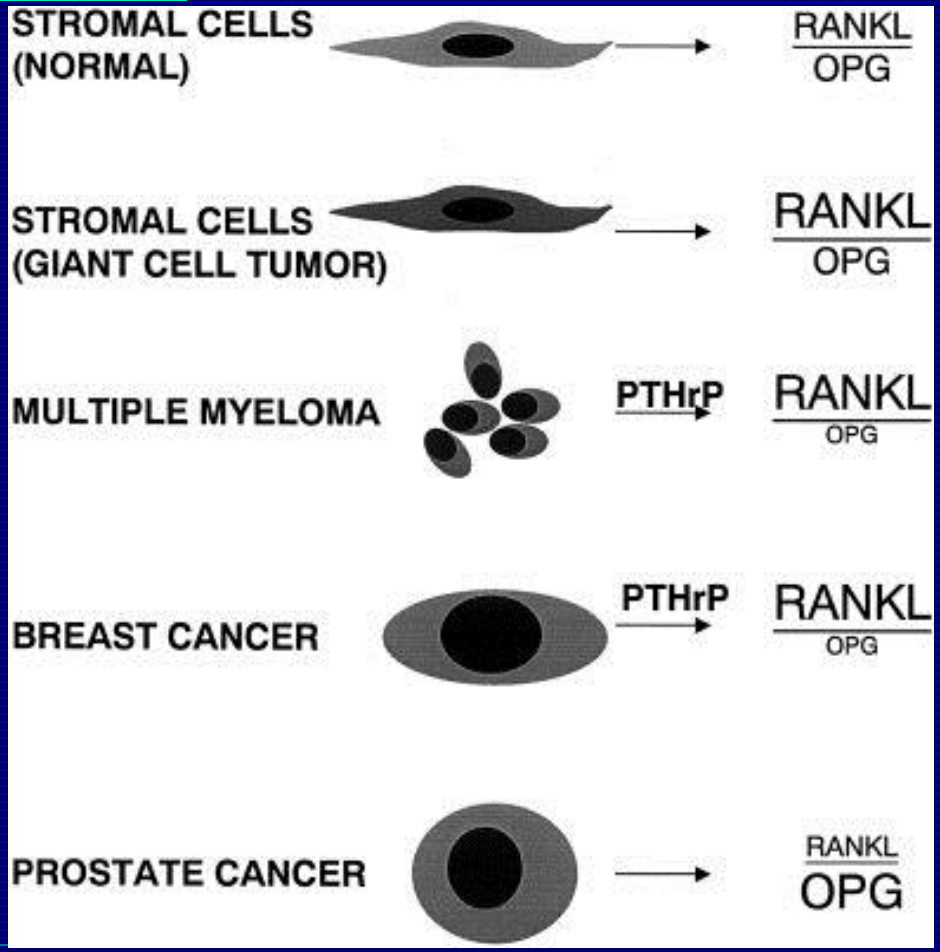
OPG/RANK/RANKL as a common effector in bone immune system and a vascular system (to the previous figure)

- OPG, RANK and RANKL are selectively produced by many cell types in diferent tissue: lymphocytes, osteoblasts and endothelial cells.
- RANKL is functioning as a survival factor for dendritic cells and as a osteoclastogenic factor after RANK ligation.
- OPG inhibits osteolysis and blocks RANKL/RANK interaction.
- OPG/RANKL/RANK triad is considered a osteoimmunomodulating complex.


Bone System
Immune System
Vascular System
RANK
RANKL
OPG
Dendritic Cells
T Cell
B Cell
Endothelial and smooth muscle cells
Blood vessels
Osteoblastic Stromal Cells
Differentiation
Differentiation
OPG > RANKL
RANKL > OPG
Osteoclast apoptosis
Proliferation of Hematopoietic Stem Cell (CFU-GM)
Fusion of Osteoclastic Precursor
Quiescent Osteoclast
Active Osteoclast
Osteoclast Survival and activation
M-CSF
M-CSF
TNFα
IL1
TNFα
IL1
TNFα
IL1

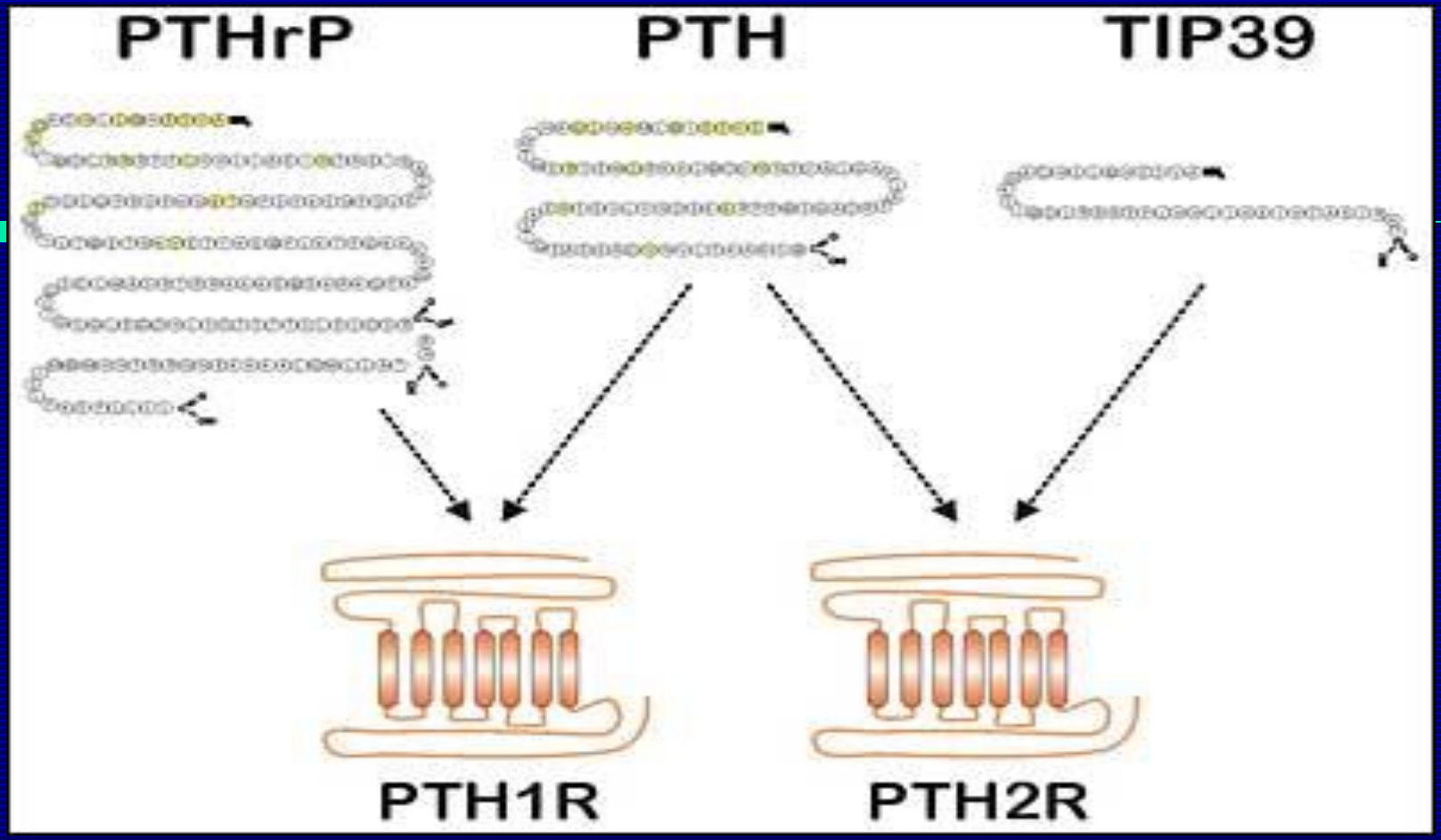
Osteoclasts activation

- Under pathologic conditions, inflammatory and malignant cells can increase osteo-clastogenesis by producing soluble or membrane-bound M-CSF and RANKL as well as PTH-related protein (PTHrP), cytokines, and prostaglandins.

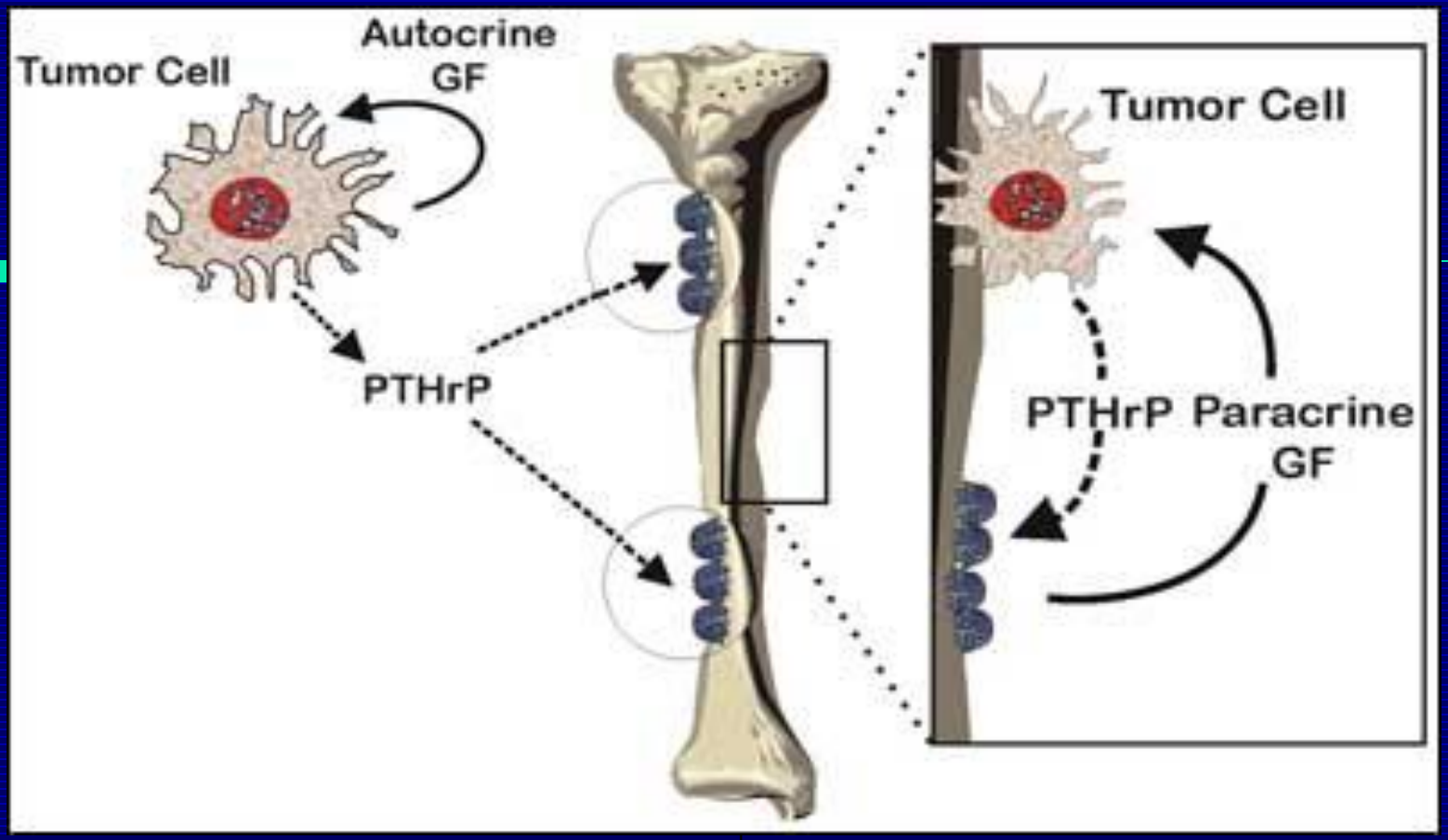


Parathyroid Hormone Relation Peptide (PTHrP)

- PTHrP was discoverde as mediator of syndrome ***"humoral hypercalcemia of malignancy" (HHM***).
- During the syndrome inn different type of cancer (in absebce of metastases) similar compounds to PTH are produceds which is related to:
- ***Hypercalcemia***
- ***Hypophosphatemia***
- ***Increased cAMP exctretion by urine***
- The effects are similar to those caused by PTH; no PTH levels are detected.



Genetic families of PTH and PTHrP: PTHrP, PTH and TIP39 are probably members of the same fgenetic family. Their receptors PTH1R and PTH2R are 7 transmembrane G protein-coupled receptors.

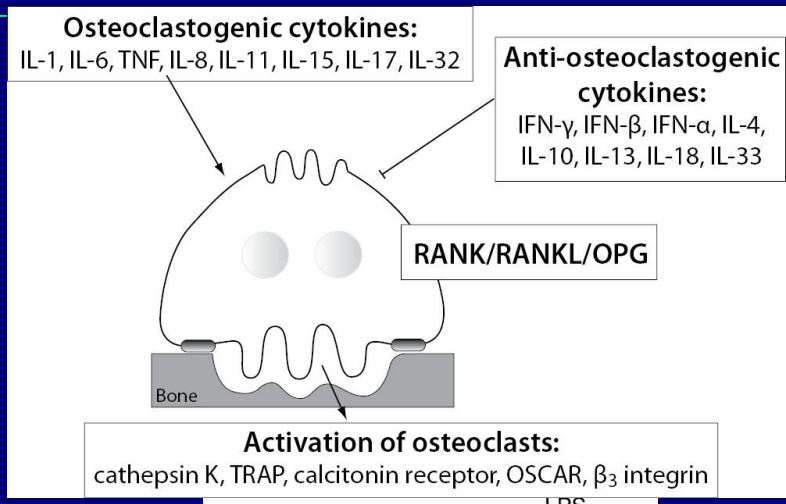


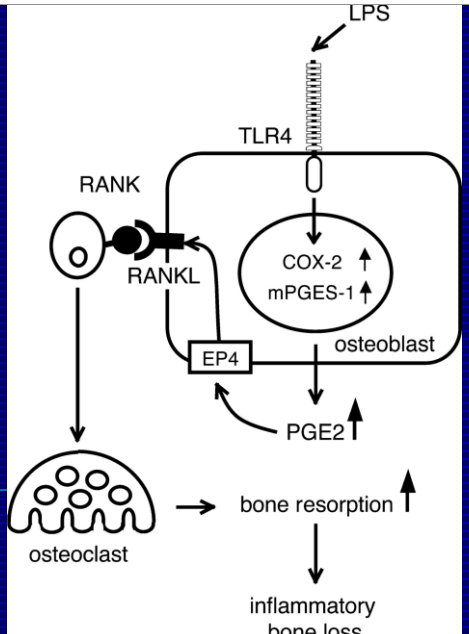
Production of PTHrP regulated by growth factor (GF) in tumor states. Tumor cells are able to be stimulated at a distance (outside the bone) by autocrine growth factors to an increased production of PTHrP. It reaches via circulation the bone tissue and supports bone resorption. Metastatic tumor cells in the bone are able to secrete PTHrP supporting bone resorption and paracrine growth factors which further support PTHrP production.

Gene	Mutation	Disease
RANK	18 bp duplication	Familial expansile osteolysis
	27 bp duplication	Early onset Paget's disease
	15 bp duplication	Expansile skeletal hyperphosphatasia
RANKL	Deletion of amino acids 145-177	Autosomal recessive osteopetrosis
	A single nucleotide change (596T-A) in exon 8 of both alleles	Autosomal recessive osteopetrosis
	Deletion of two nucleotides (828_829delCG)	Autosomal recessive osteopetrosis
OPG	Deletion making OPG inactive	Juvenile Paget's disease
	20 bp deletion resulting in premature termination of OPG translation	Juvenile Paget's disease

Cytokines, prostaglandins

- There is evidence that polymorphisms of IL-1, IL-6, TNF- α, and their receptors can influence bone mass in humans.
- Prostaglandins have both stimulatory and inhibitory actions; the predominant effect of PGE2, which is the major prostaglandin produced by bone cells, is to stimulate both resorption and formation.
  - Prostaglandins, particularly PGE2, are produced by bone cells largely through the action of inducible cyclooxygenase 2 (COX2).
  - COX2 is induced by most of the factors that stimulate bone resorption and thus may enhance the response to these agents. Treatment with COX inhibitors blunts the response to impact loading and fluid shear stress, indicating that prostaglandins play an important role in the response on mechanical forces, and this may be enhanced by estrogen. In epidemiologic studies, small increases in BMD and decreases in fracture risk have been reported in individuals using NSAIDS.



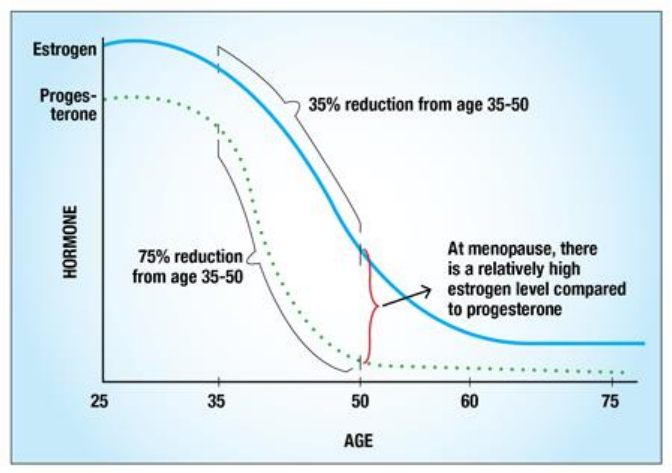


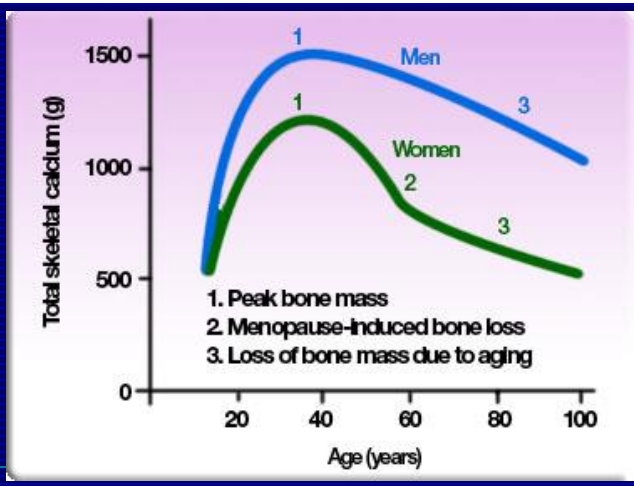
Cytokines, prostaglandins, NO, and leukotrienes

- NO is produced by bone cells and is a cofactor for the anabolic response to mechanical loading. However, unlike prostaglandins, NO may inhibit bone resorption, perhaps by increasing OPG production.
- Leukotrienes, the products of lipoxygenase, can affect bone by stimulating resorption and inhibiting formation.

Estrogen influence on bone state

- Estrogen is critical for
  - epiphyseal closure in puberty in both sexes and
  - regulates bone turnover in men as well as women.
- Estrogen has a greater effect than androgen in inhibiting bone resorption in men, although androgen may still play a role.
- Estrogen may also be important in the acquisition of peak bone mass in men.
- Osteoporosis in older men is more closely associated with low estrogen than with low androgen levels.

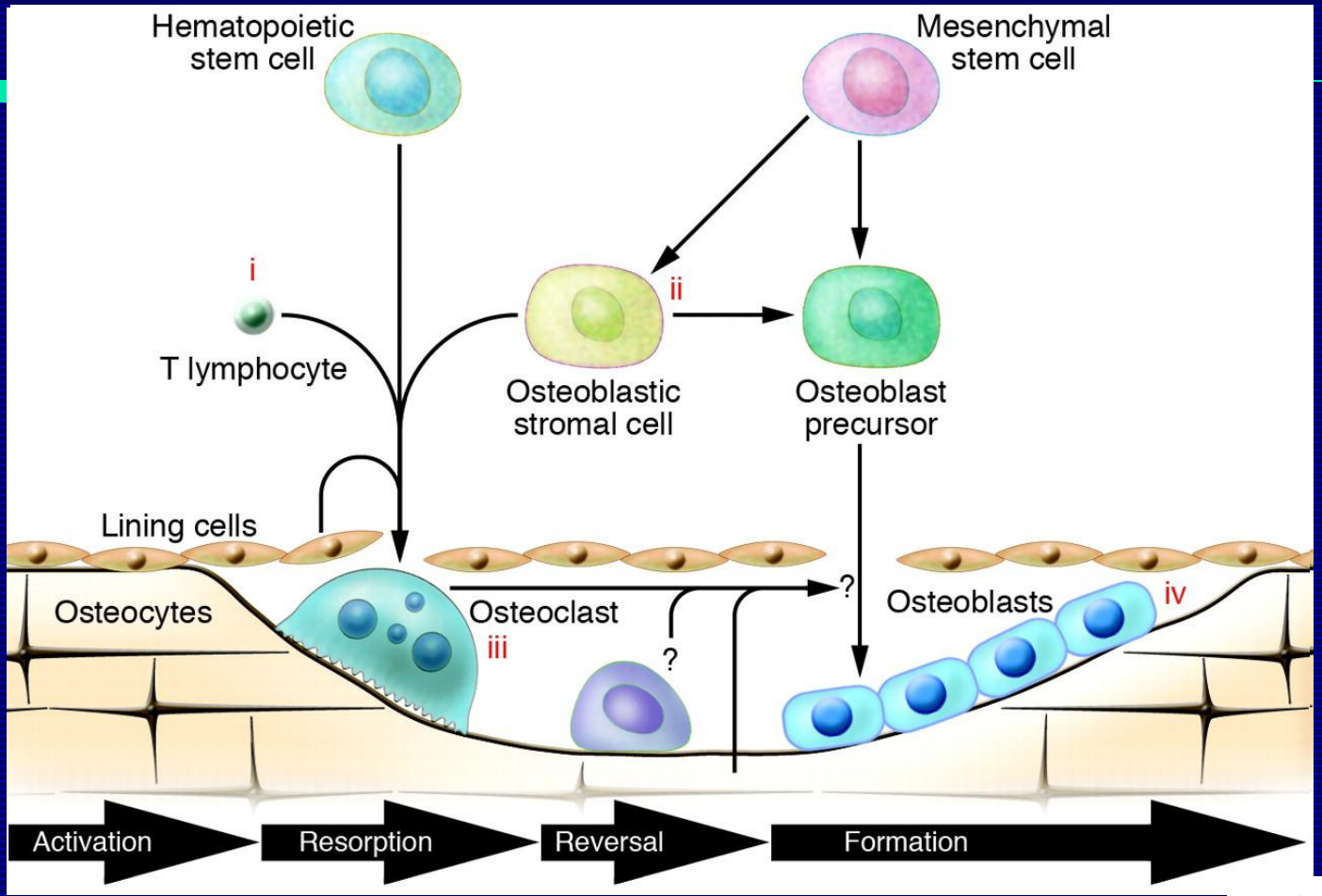




Central role of estrogen deficiency - today

- An increase in bone resorption, and not impaired bone formation, appears to be the driving force for bone loss in the setting of estrogen deficiency.
- The rapid and continuous bone loss that occurs for several years after the menopause indicate an impaired bone formation response, since in younger individuals going through the pubertal growth spurt, even faster rates of bone resorption can be associated with an increase in bone mass.
- However, the increased bone formation that normally occurs in response to mechanical loading is diminished in estrogen deficiency, suggesting estrogen is both anti-catabolic and anabolic.

Remodelling of bones. Estrogen action places (i)



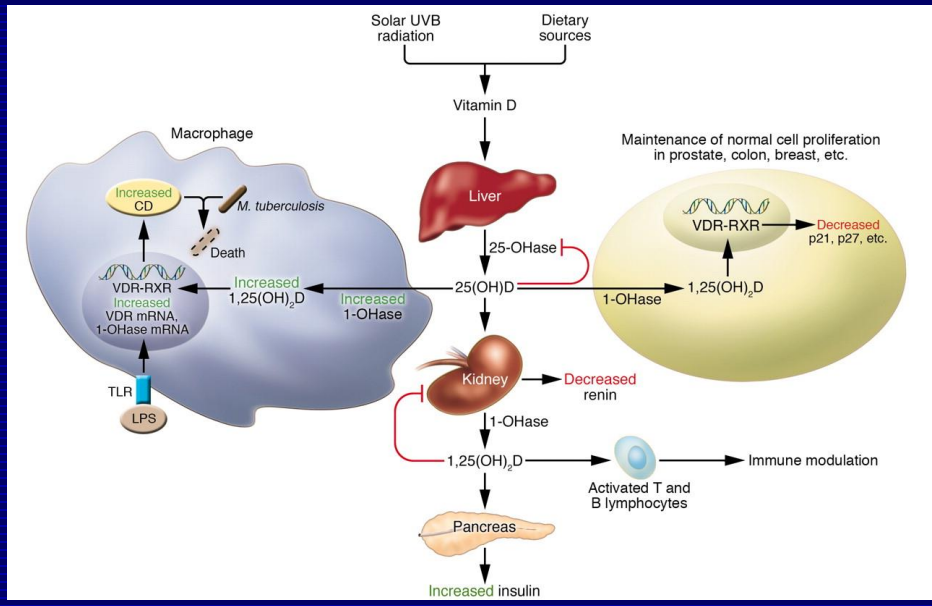
Raisz, L. G. J. Clin. Invest. 2005;115:3318-3325

Collagen abnormalities

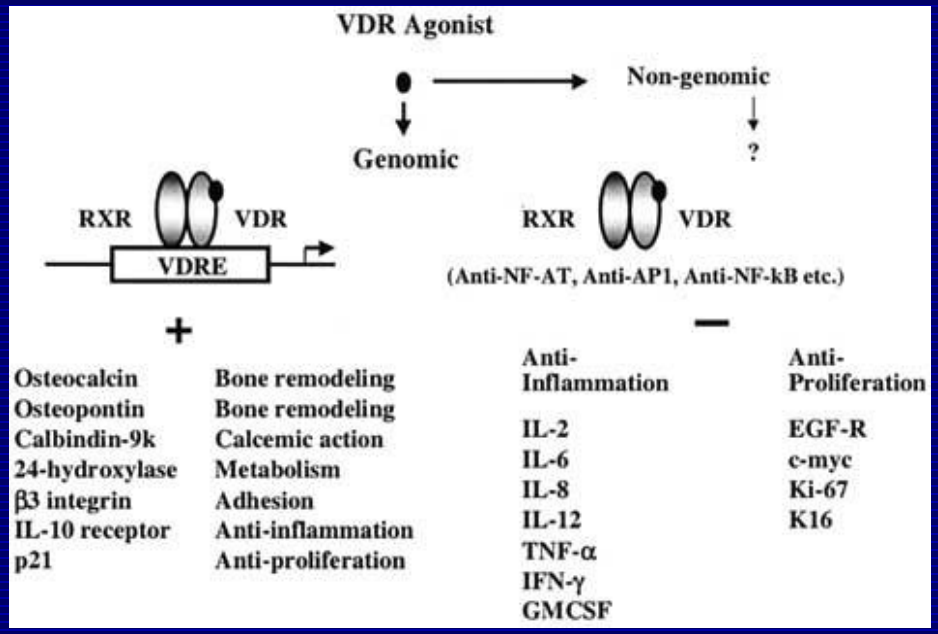
- A polymorphism of the first intron of the gene coding for the type I collagen 1 chain and increased levels of homocysteine can influence fracture risk independent of BMD (bone mass density).
  - This may be due to differences in helix formation or cross-linking of collagen, challenging the concept that mineral and matrix composition are normal in osteoporosis and that only structural abnormalities account for skeletal fragility.

Calcium, vitamin D, and parathyroid hormone

- The active 1,25 dihydroxy vitamin D (calcitriol),
  - optimal intestinal absorption of calcium and phosphorus,
  - exerts a tonic inhibitory effect on parathyroid hormone (PTH) synthesis,
  - dual pathways that can lead to secondary hyper-parathyroidism.
- Vitamin D deficiency and secondary hyperparathyroidism can contribute to
  - accelerated bone loss and
  - increasing fragility, but also to
  - neuromuscular impairment that can increase the risk of falls.



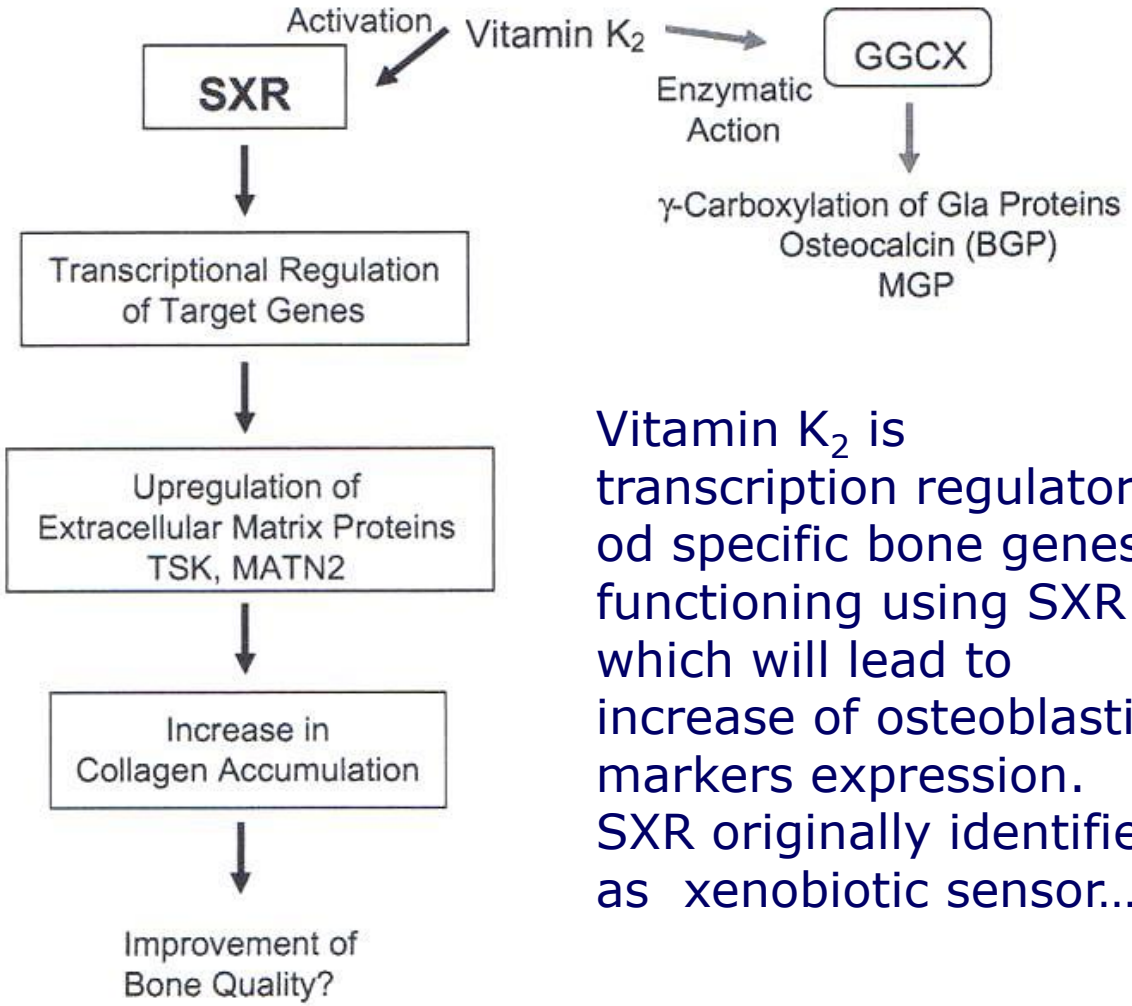
Regulation of gene expresssion by VDR



Vitamin K and bones

- cofactor for γ-carboxylase, enzyme which catalyses conversion of specific residuals of glutamic acid to Gla residuals
- γ-carboxylation of proteins of bone matrix which contain Gla as MGP (= matrix Gla protein) a osteokalcin.
  - Uncompleted γ-carboxylation of osteocalcin and MGP during vitamin K decrease lead to osteoporosis and high risk of fractures.
- stimulates synthesis of osteoblastic markers and bone deposition.
- decreases bone reabsorbtion by inhibition of osteclasts formation and by decrease of their resorbtion activity.

- Vitamin K_2 treatment induces osteoclast apoptosis, but inhibits osteoblasts apoptosis which is leading to increased bone formation.
- Vitamin K_2 supports osteocalcin expression (increases its mRNA) which can be further modulated by 1, 25-$(OH)_2$ vitamin D_3.



Vitamin K_2 is transcription regulator od specific bone genes, functioning using SXR which will lead to increase of osteoblastic markers expression. SXR originally identifies as xenobiotic sensor…

Fig. 3. SXR- and vitamin K_2-dependent regulatory mechanisms of bone metabolism in osteoblastic cells. SXR promotes collagen accumulation in osteoblastic cells by regulating the transcription of its target genes including those encode extracellular matrix proteins. Vitamin K_2 plays a role in the posttranslational modification of Gla proteins by functioning as a coenzyme of γ-glutamyl carboxylase (GGCX) and also acts as a potent SXR ligand in bone metabolism

Local and systemic growth factors

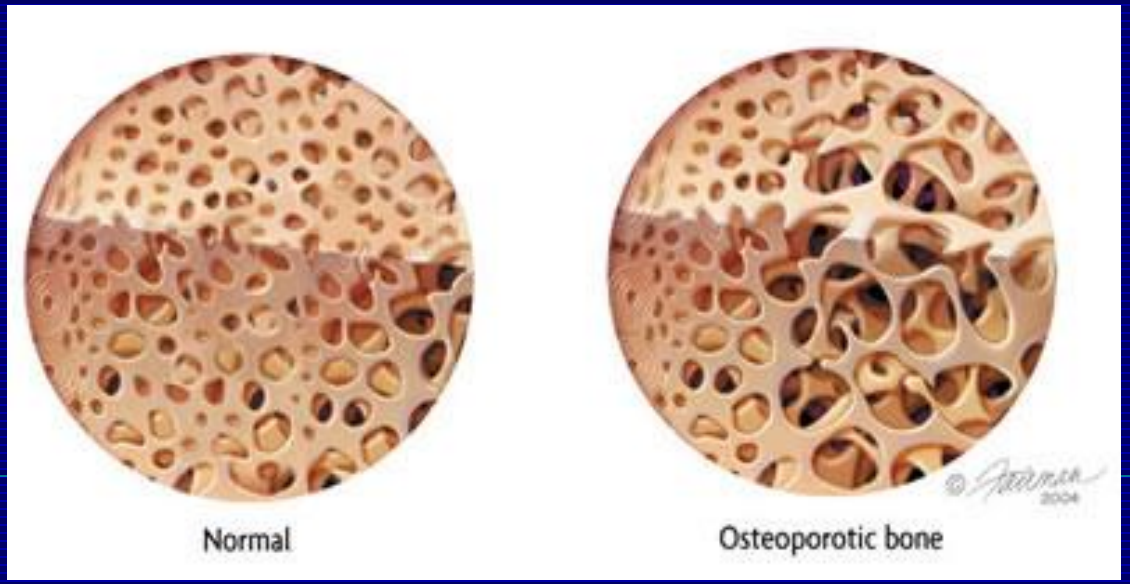
- Remodeling imbalance, characterized by an impaired bone formation response to increased activation of bone remodeling, is an essential component of the pathogenesis of osteoporosis. This may be due, in part, to an age-related decrease in the capacity of osteoblasts to replicate and differentiate. However, it seems likely that specific defects in the production or activity of local and systemic growth factors will also contribute to impaired bone formation.

Metabolic bone diseases

- Osteoporosis
  - (estrogen deficiency, glucocorticoids increase, vitamin K2 deficiency?)
- Osteodystrophy
  - (primary and secondary hyperparathyreoidism)
- Ostemalacia/ rickets
  - vitamin D defficiency)

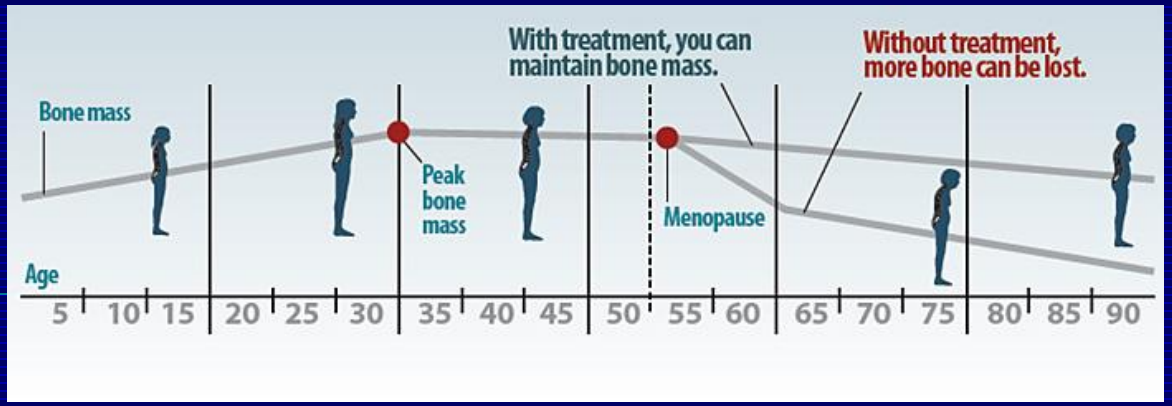
Metabolic bone diseases

- Osteoporosis remains the most common metabolic abnormality of bone. It has been described as “a silent epidemic” affecting one in two women and one in five men, older than 50 years of age, during their lifetime.
- It is now defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone resulting in fractures with little or no trauma.



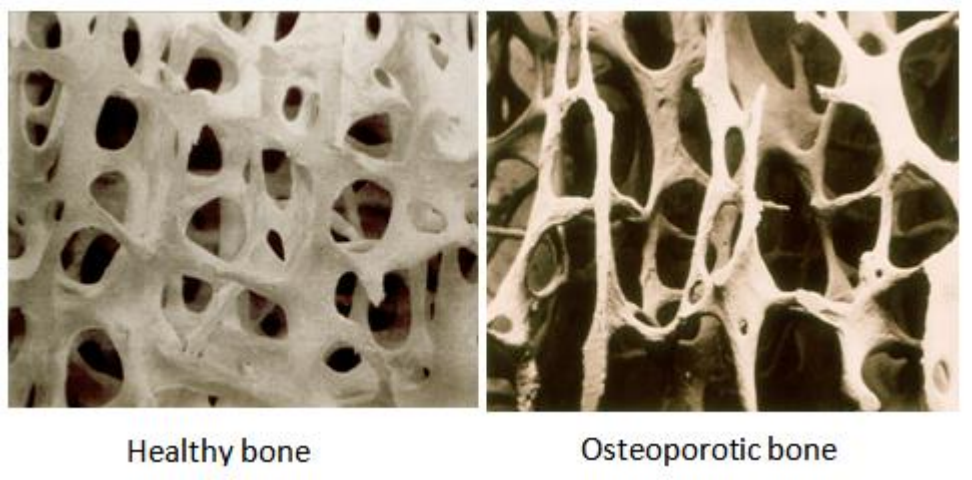
Osteoporosis

- The bone mass of an individual in later life is a result of the peak bone mass accrued during intrauterine life, childhood, and puberty, as well as the subsequent rate of bone loss.
- Although genetic factors strongly contribute to peak bone mass, environmental factors in intrauterine life, childhood, and adolescence modulate the genetically determined pattern of skeletal growth.



Osteoporosis

- is a skeletal disease characterised by low bone mass and microarchitectural deterioration with a resulting increase in bone fragility and hence susceptibility to fracture.
- Caucasin population: about 50% of women and 20% of men older than 50 years will have a fragility fracture in their remaining lifetime.



Etiopathogenesis of osteoporosis

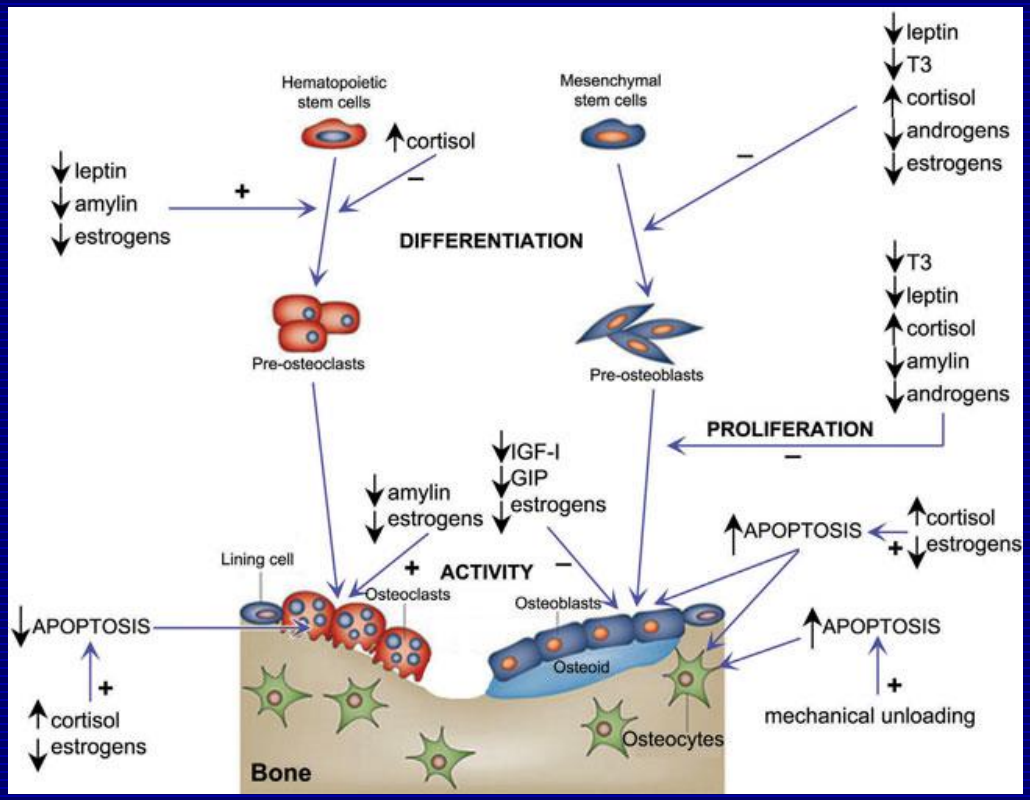
- complex interactions among local and systemic regulators of bone cell function.
- The heterogeneity of osteoporosis may be due to
  - differences in the production of systemic and local regulators,
  - changes in receptors,
  - signal transduction mechanisms,
  - nuclear transcription factors, and
  - enzymes that produce or inactivate local regulators.
- Since the first human osteoporosis study indicated an association among bone mass, fragility, and polymorphisms in the *vitamin D receptor* (*VDR*) gene, more than 30 candidate genes have been reported that might influence skeletal mass and fragility.
- Since osteoporosis is a complex, polygenic disorder, the contributions of specific gene polymorphisms are likely to be relatively small, but may still be clinically important.

Osteoporosis - causes

- Glucocorticoids excess
- Estrogene deficiency
- Vitamin K2 deficiency?

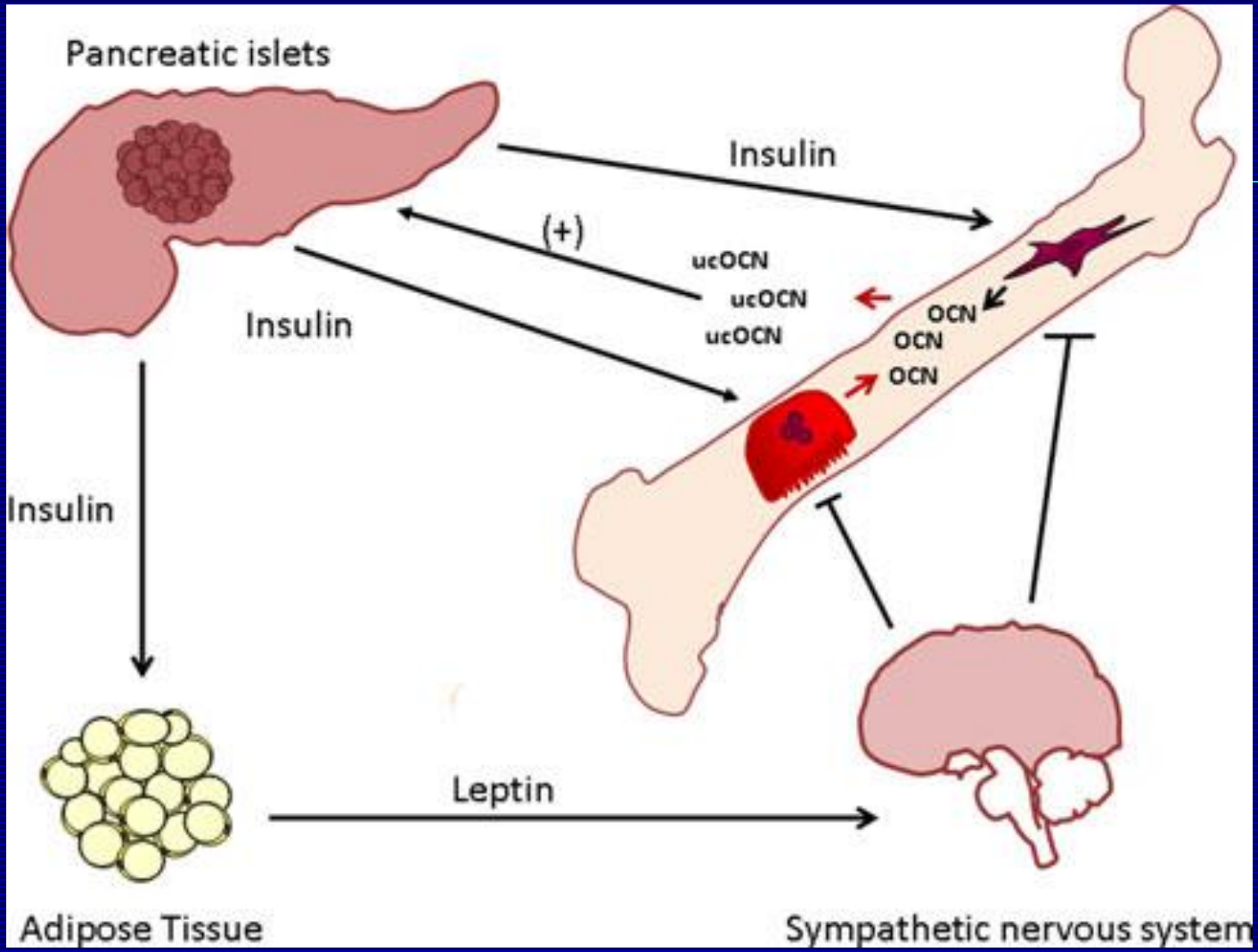
Osteoporosis induced by cortisol

- Cortisol modifies proliferative and mewtabolic activities of bone cells
- Cortisol inhibits osteoblastogenesis
- Reduces half-life time of osteoblasts which is leading to decreased bone formation



Common adverse effects of glucocorticoid therapy-**glucocorticoid-induced osteoporosis**

- Glucocorticoid-induced osteoporosis is the most common type of iatrogenic osteoporosis and a frequent cause of secondary osteoporosis.
- An estimated 50% of patients taking glucocorticoids for longer than 6 months will develop secondary osteoporosis.
- The absolute risk for glucocorticoid-induced osteoporosis is higher in patients aged 65 years or older given their baseline age-related fracture risk, although the relative risk of fracture related to glucocorticoid use may be even higher in patients under 65.



Cortisol generally antagonizes insulin …

Osteomalacia and rickets

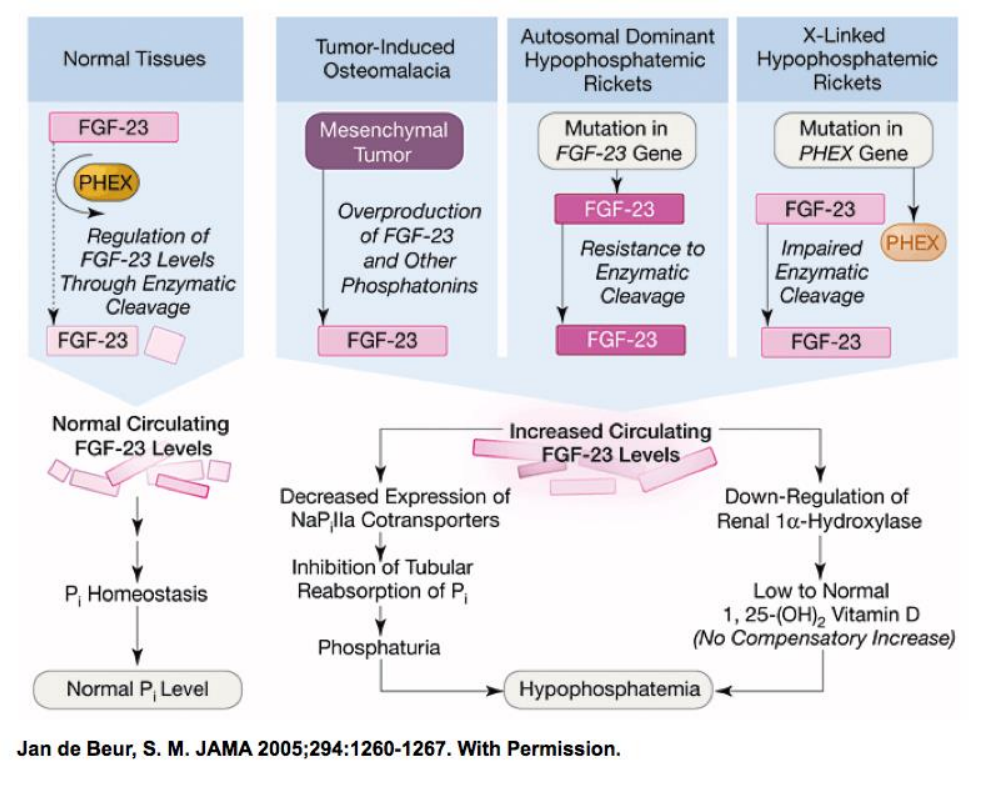
- Classically, the deficiency of vitamin D, essential for the absorption of calcium, has been the major cause of rickets in the child and osteomalacia in the adult
- resulting in absence or delay in the mineralization of growth cartilage or newly formed bone collagen.

Osteomalacia and rickets

- A consequence of a low serum phosphate and normal serum calcium.
- Two such conditions are *x-linked hypophosphatemic rickets/osteomalacia* and *oncogenic osteomalacia*.
- When present, the signs of rickets and osteomalacia in the low serum phosphate states are indistinguishable from the classic hypocalcemic states.

X-linked hypophosphatemic osteomalacia

- The condition is characterized by low tubular reabsorption of phosphate in the absence of secondary hyperparathyroidism.
- X-linked hypophosphatemia occurs in about 1 in 25,000 and is considered the most common form of genetically induced rickets.



Jan de Beur, S. M. JAMA 2005;294:1260-1267. With Permission.

Oncogenic osteomalacia

- Oncogenic osteomalacia is a paraneoplastic syndrome in which a bone or soft tissue tumor or tumor-like lesion induces hypophosphatemia and low vitamin D levels that reverse when the inciting lesion is resected.

Oncogenic osteomalacia

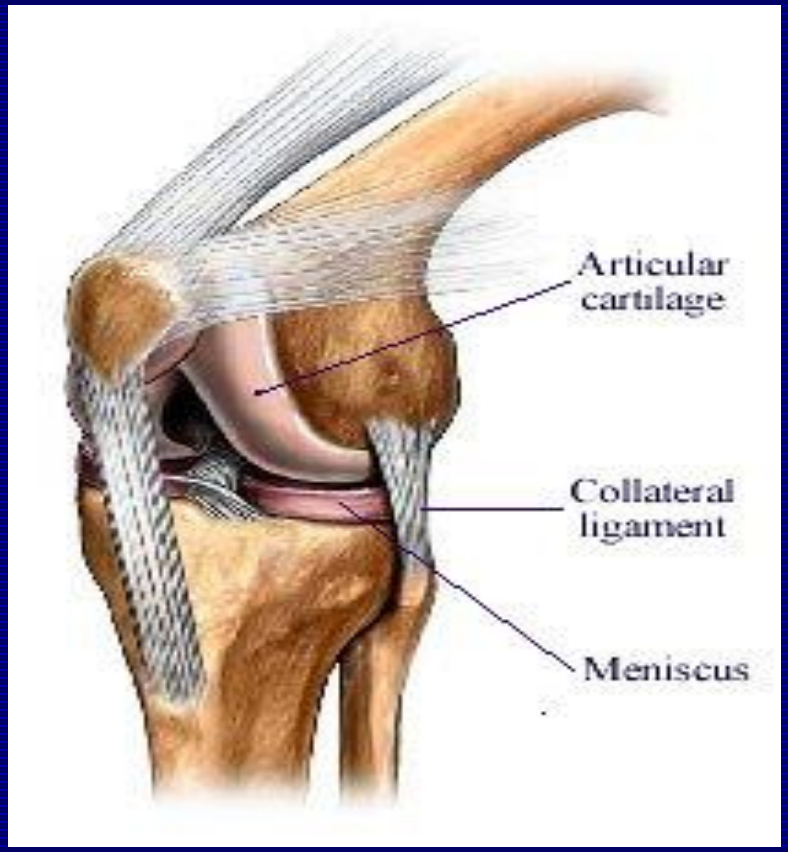
- ***Phosphotonin***
  - a humoral factor,
  - has been identified in clinical and experimental studies as being responsible for the serum biochemical changes.
  - causes hyperphosphaturia by inhibiting the reabsorption of phosphate by the proximal renal tubules.

- Fibroblast growth factor 23, phosphate-regulating gene with homologies to endopeptides located on the ‘x’ chromosome (PHEX) and matrix extracellular phosphoglycoprotein (MEPE) are candidates proposed for the production of phosphatonin and the altered pathophysiology in oncogenic osteomalacia.

Articular diseases

- irreversible destruction of the cartilage, tendon, and bone that comprise synovial joints
  - rheumatoid arthritis (RA) and
  - osteoarthritis (OA).

- While cartilage is made up of proteoglycans and type II collagen, tendon and bone are composed primarily of type I collagen.



Rheumatoid Arthritis

- The prevalence of rheumatoid arthritis in most Caucasian populations approaches 1% among adults 18 and over and increases with age, approaching 2% and 5% in men and women, respectively, by age 65
- The incidence also increases with age, peaking between the 4th and 6th decades
- Both prevalence and incidence are 2-3 times greater in women than in men
- Monozygotic twins 13.5% vs dizygotic twins 3.5%

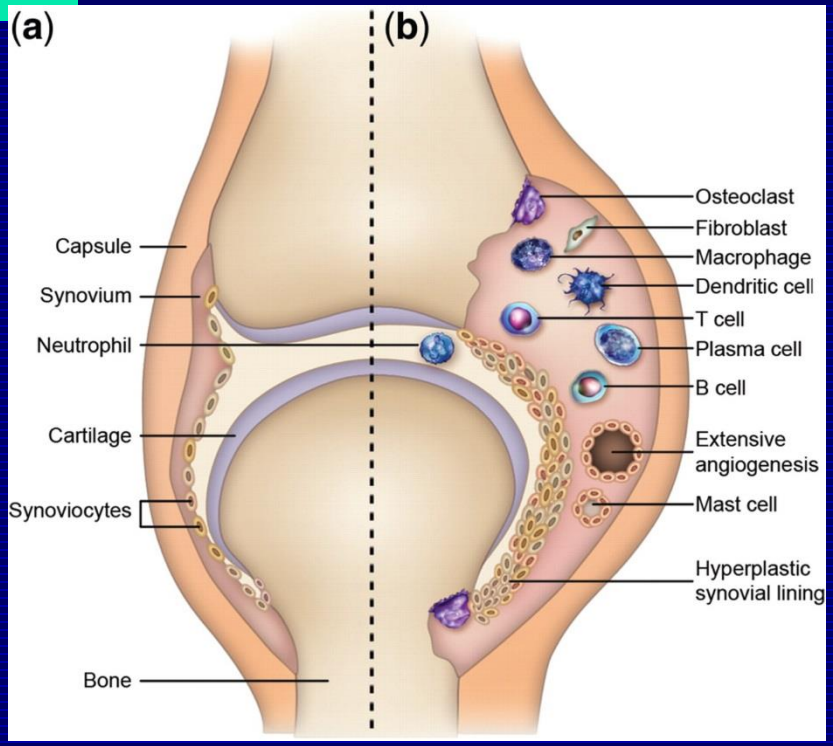
“One must from time to time attempt things that are beyond one’s capacity.”

—Pierre-Auguste Renoir

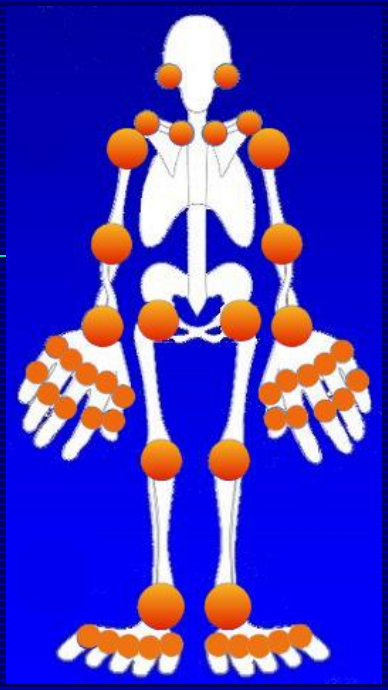
Rheumatoid Arthritis

- Rheumatoid arthritis is an autoimmune disease affecting the joints, tendons, and bones, resulting in inflammation and destruction of these tissues.

- The term ‘arthritis’ is used to denote clinically apparent soft tissue swelling or fluid (not bony overgrowth alone).



Rheumatoid Arthritis



- Description
  - Morning stiffness
  - Arthritis of 3 or more joints
  - Arthritis of hand joints
  - Symmetric arthritis
  - Rheumatoid nodules
  - Serum rheumatoid factor
  - Radiographic changes

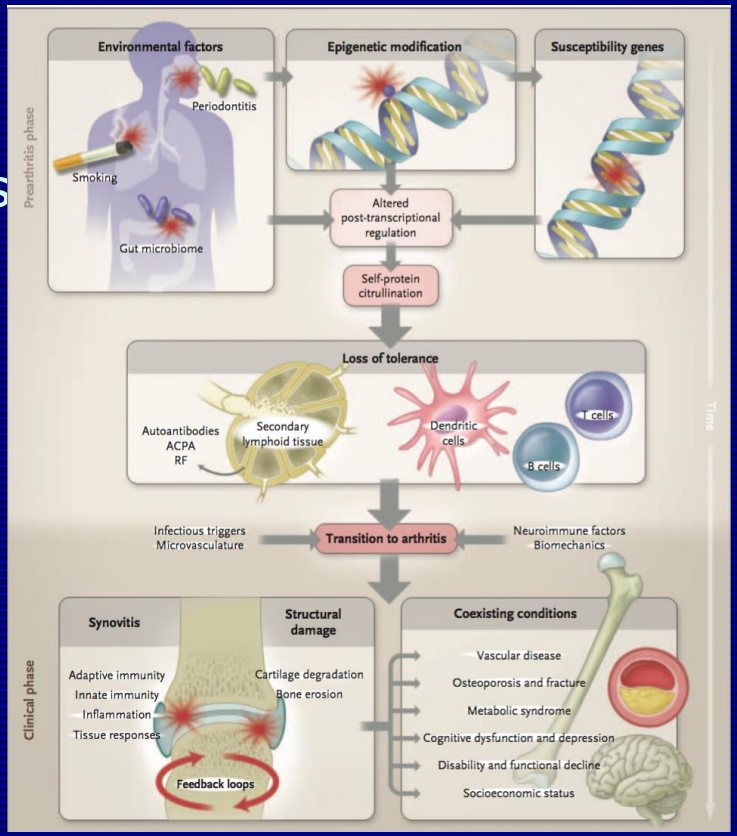
- having rheumatoid arthritis – positive 4 of 7 criteria, with criteria 1-4 present for at least 6 weeks

Functional Presentation and Disability of RA

- In the initial stages of each joint involvement, there is warmth, pain, and redness, with corresponding decrease of range of motion of the affected joint
- Progression of the disease results in reducible and later fixed deformities
- Muscle weakness and atrophy develop early in the course of the disease in many people

Rheumatoid Arthritis

- Pathogenesis of RA
  - complex interaction between genetic and environmental factors and
  - the repeated activation of innate and adaptative immunite system
  - evolves into the breakdown of immune tolerance, aberrant autoantigen presentation and antigen-specific T and B cells activation.



- Genetic factors have an important role in the susceptibility to rheumatoid arthritis
  - HLA-DRB

First step – joint disease?

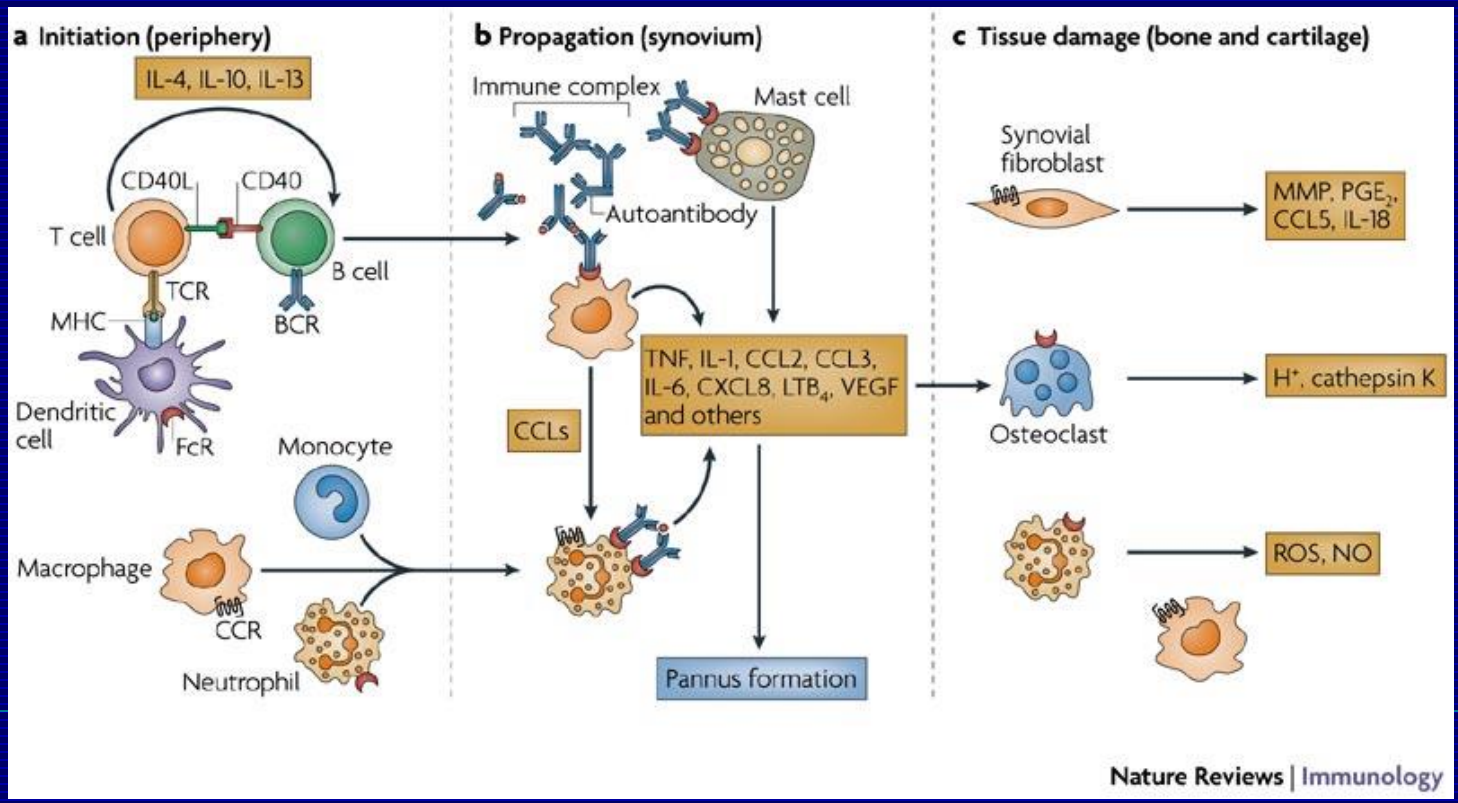
- Although the synovium is the principal site of pathology in the established phase of disease, it may not be the site where the disease is initiated.

- Systemic immune abnormalities in individuals without joint symptoms, and a lack of immune infiltrates in the synovium during the earliest phase before clinical signs and symptoms of arthritis, point to other tissues being important in the initiation of adaptive immune reactions.

- Important tissues for research include bone marrow, lymph nodes, the gut, periodontal tissue, the lung and the neuroendocrine system.

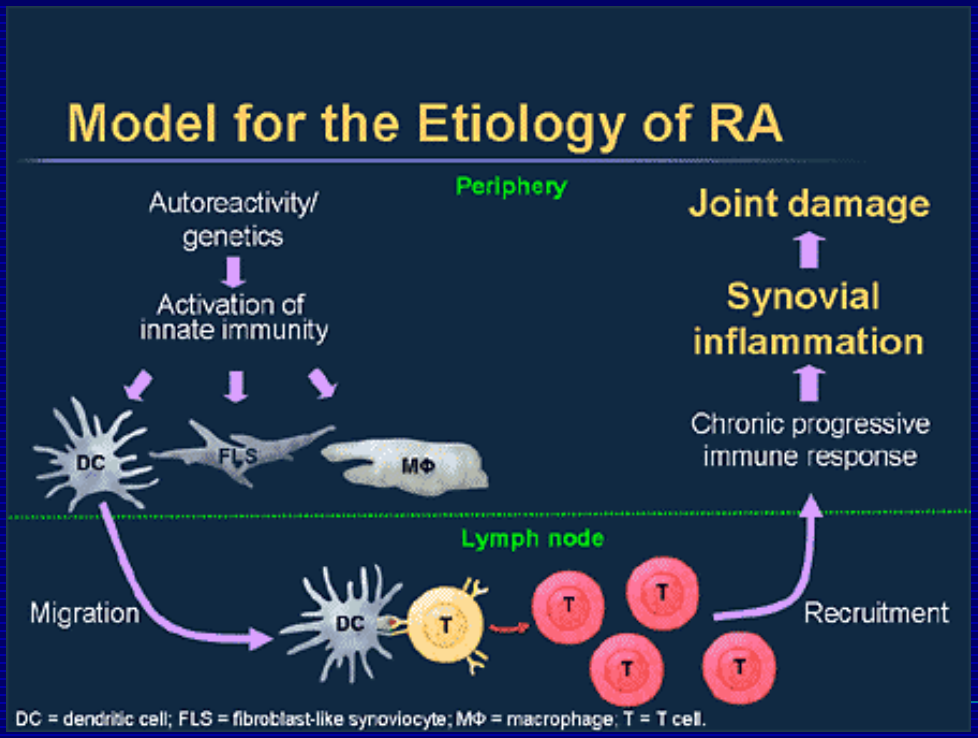
RA without clinical arthritis

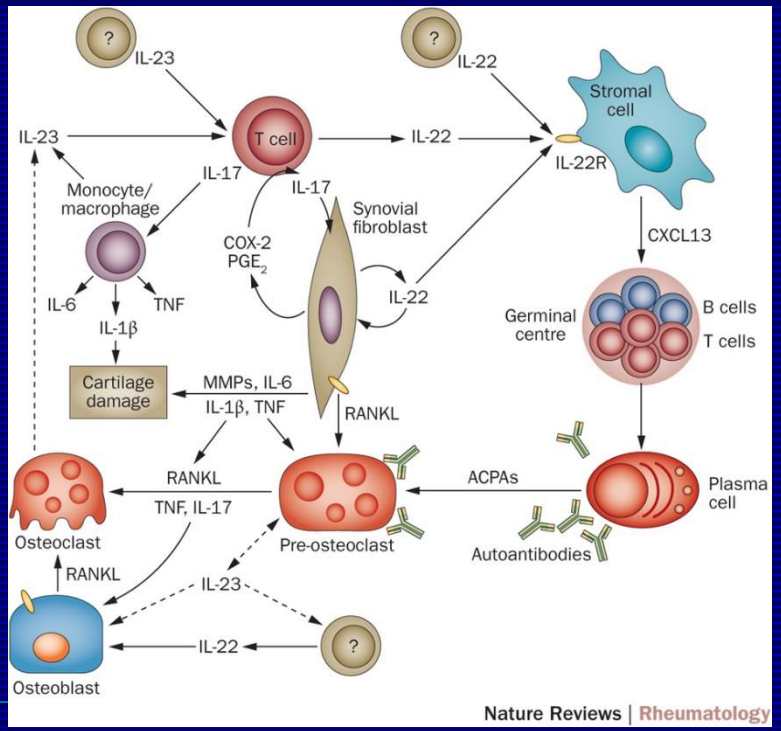
- An initial phase, characterised by systemic autoimmunity without synovial inflammation, may be followed by a shorter phase during which asymptomatic synovitis is present.



RA progression

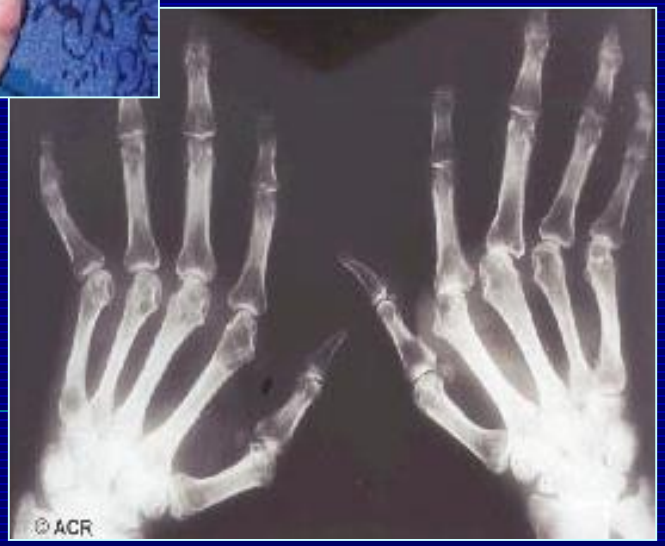
- events culminate in synovial inflammation, hyperplasia and bone destruction leading to joint swelling and deformity and to systemic inflammation.





Clinical Presentation of RA

Severe RA



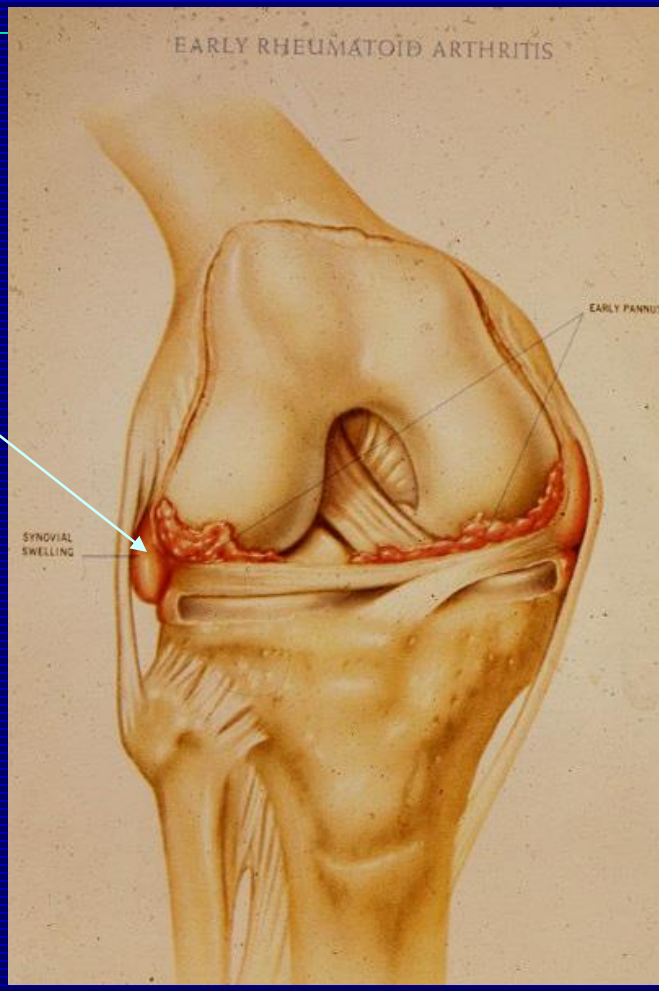
Early RA

Intermediate RA

Latinis KM, et al. *The Washington Manual™ Rheumatology Subspecialty Consult.* Philadelphia, Pa: Lippincott Williams & Wilkins; 2004.

RA progression

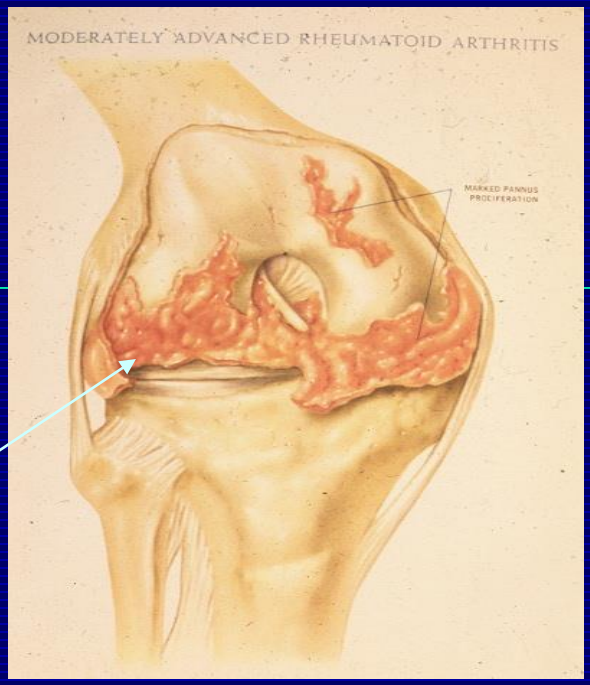
- **Early Pannus**
  - **Granulation, inflammation at synovial membrane, invades joint, softens and destroys cartilage**



RA progression

Mod advanced Pannus

joint cartilage disappears, underlying bone destroyed, joint surfaces collapse

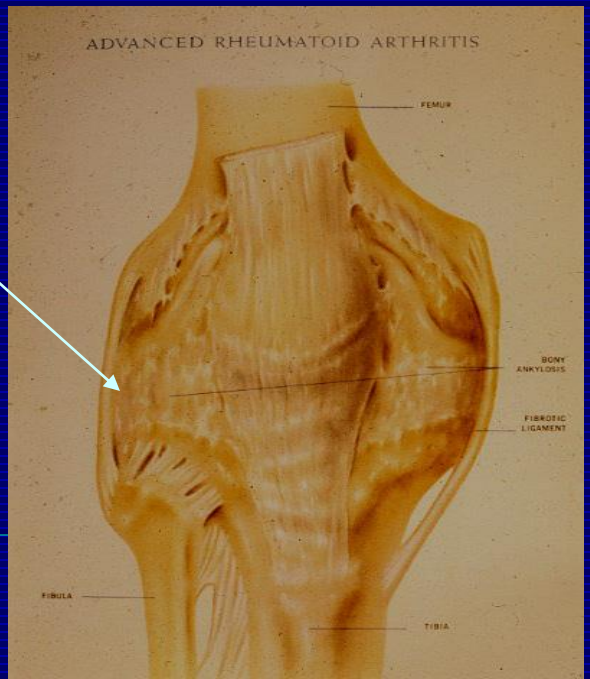


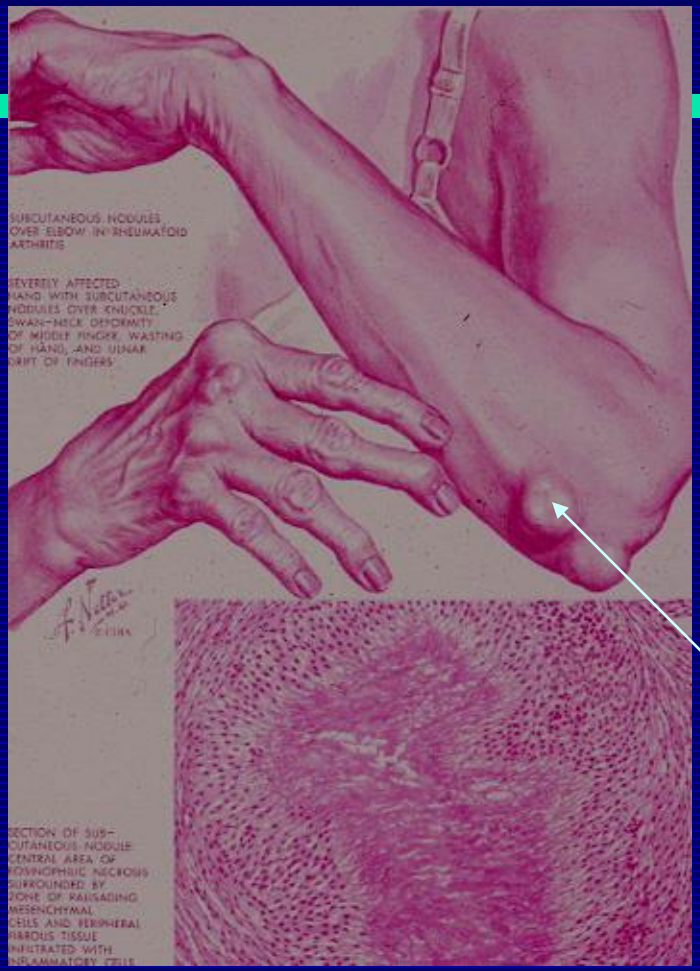
Fibrous Ankylosis

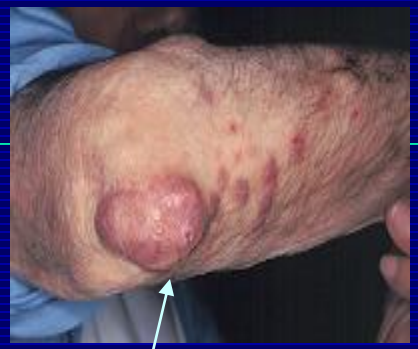
Fibrous connective tissue replaces pannus; loss of joint otion

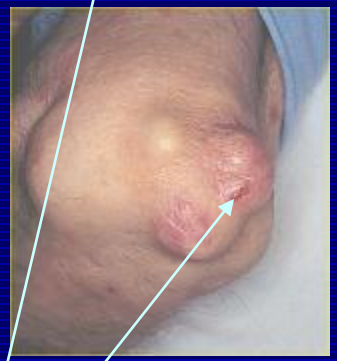
Bony Ankylosis

Eventual tissue and joint calcification









Subcutaneous nodules

(disappear and appear without warning)

Diagnostic Tools in Rheumatoid Arthritis

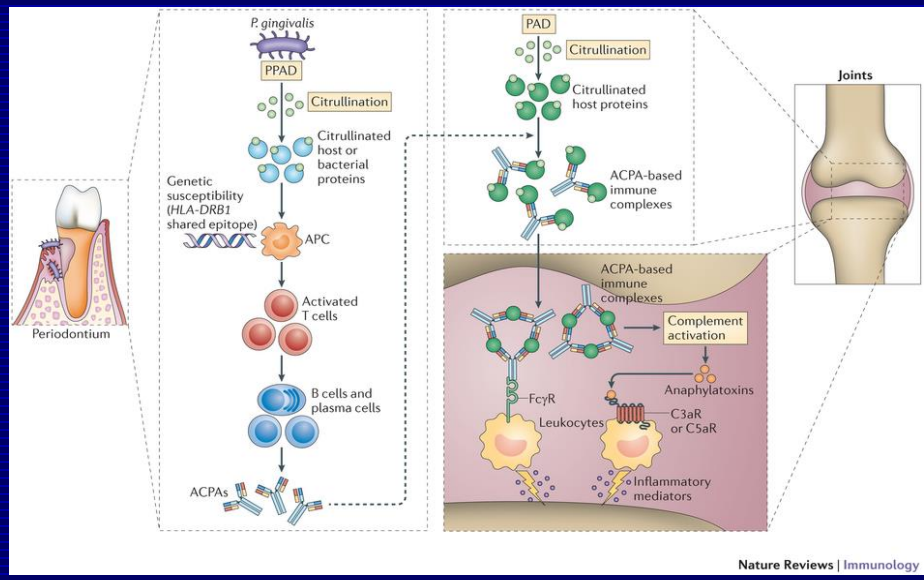
- Rheumatoid factor
- Anti-CCP antibodies
- Plain X-ray
- MRI
- Ultrasound

Rheumatoid Factor

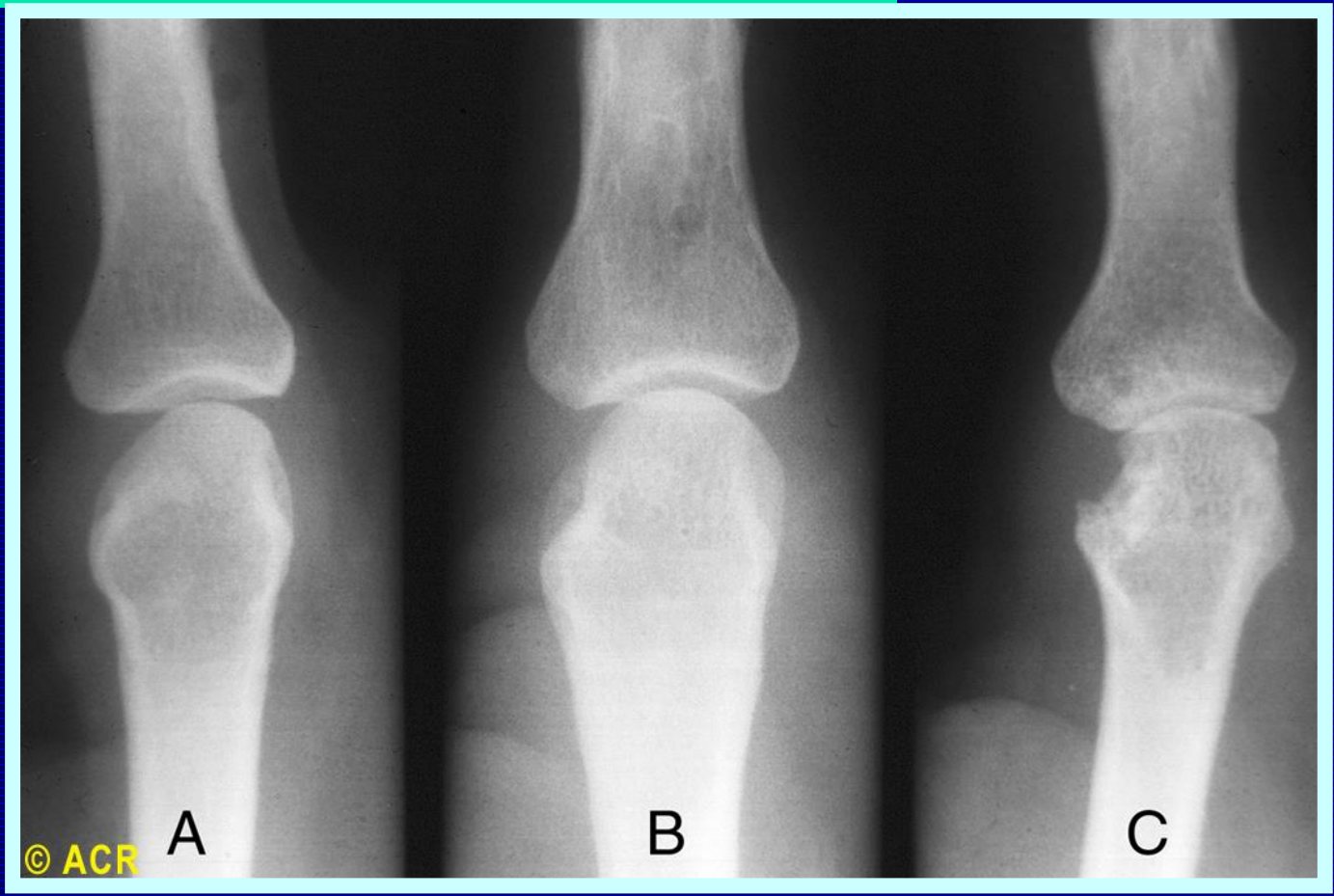
- Antibody directed against the Fc portion of IgG
- Present in approximately 80% of RA patients
  - Sensitivity for RA is ~80%
  - Specificity is 85-95%
- May be involved in disease pathogenesis
- Higher levels tend to be associated with poorer prognosis
- Found in other conditions, especially Hepatitis C

Anti-Cyclic Citrullinated Peptide (CCP) Antibodies in RA

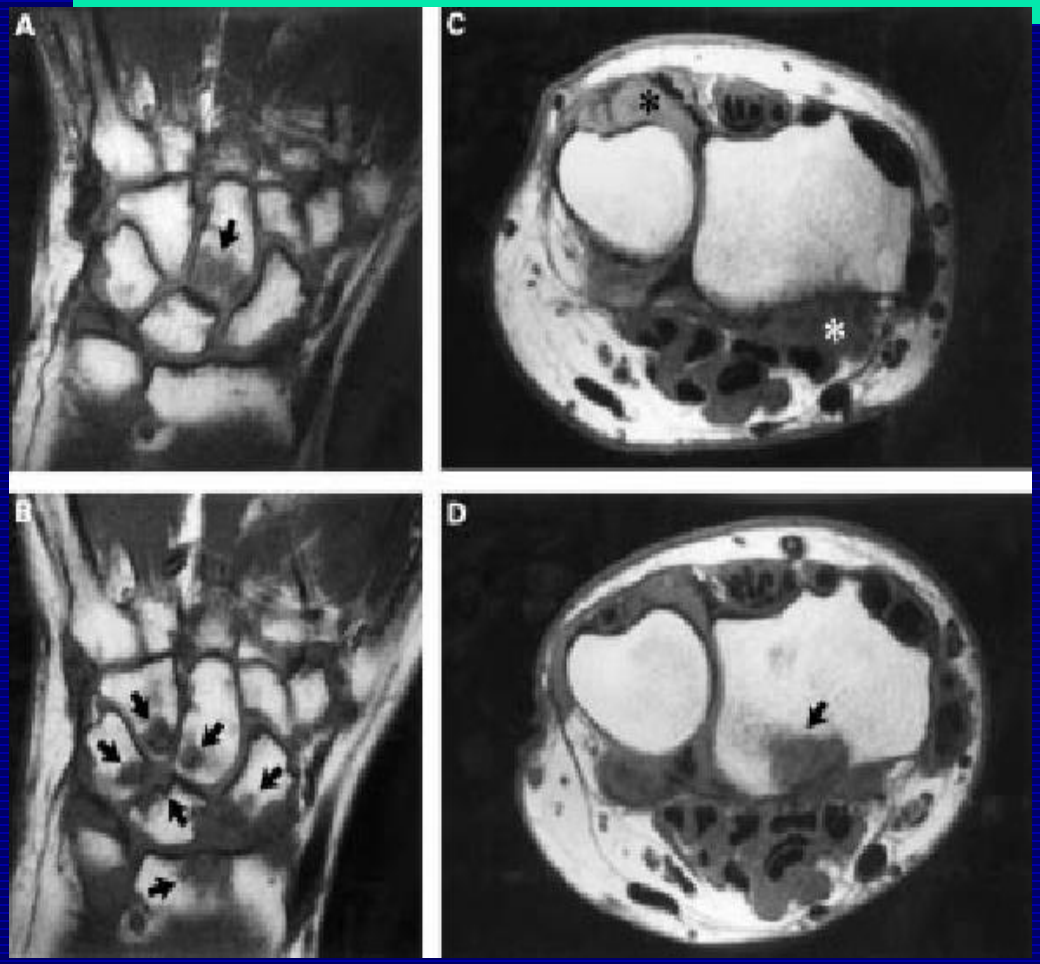
- Anti-citrulline Abs produced in RA synovium
- Early RA Diagnosis
  - sensitivity 48%; specificity 96%
  - seen in 2% of pts with other autoimmune diseases and infections (vs. 14% for RF)
  - less than 1% of healthy controls
- Predicts erosive disease PPV - 63% and NPV - 90%
- Present years before the onset of symptoms. 34% of blood samples obtained 2.5 yr before onset of symptoms (vs. 1.8% of controls)



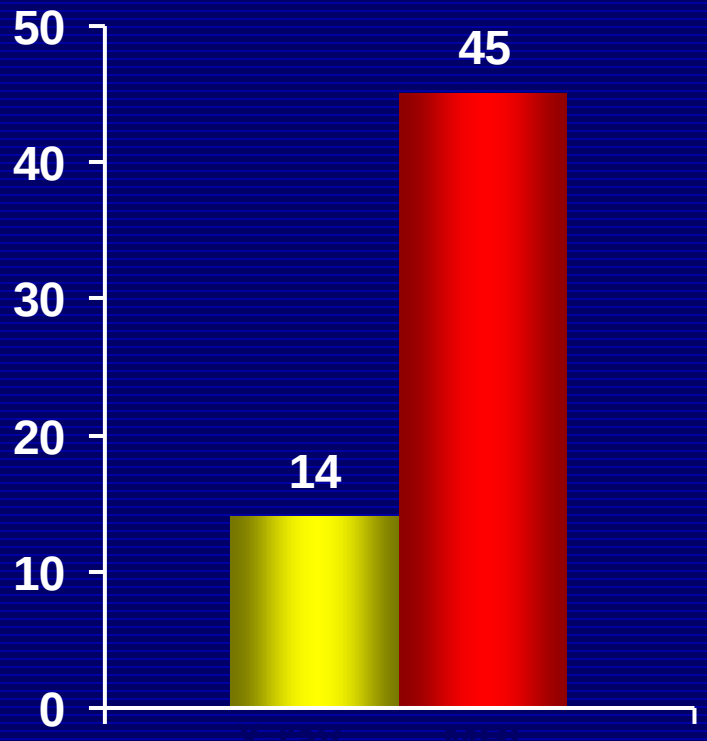
Plain X-ray



Magnetic Resonance Imaging as a Diagnostic Tool

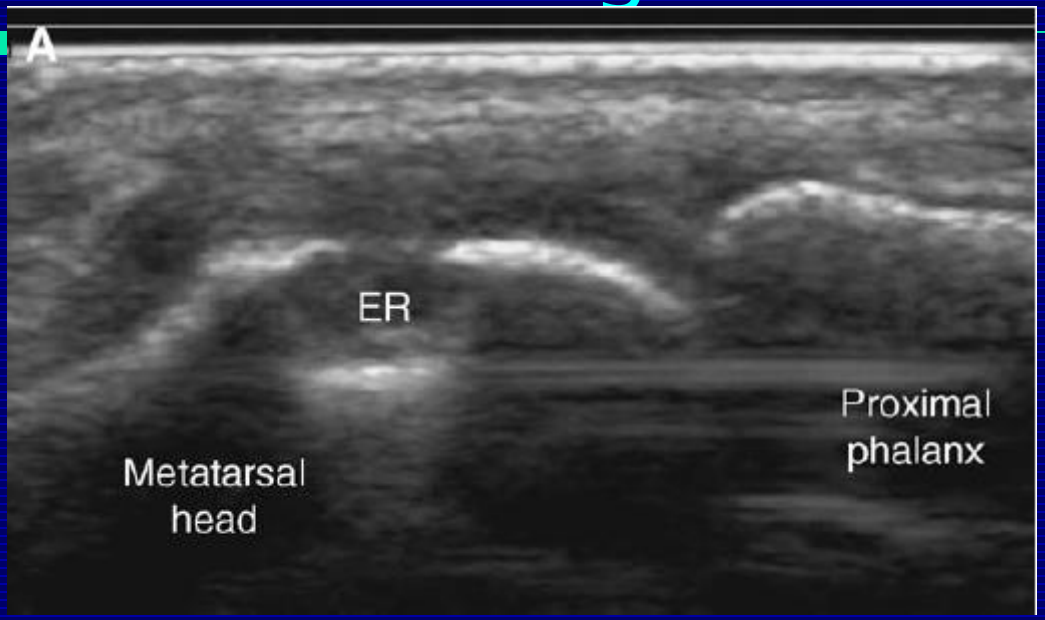


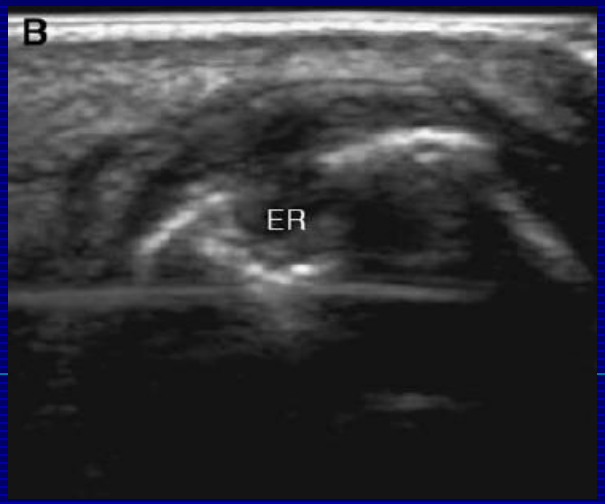
Erosions Detected: X-rays vs MRI (%)



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

Ultrasound as a Diagnostic Tool





Keen et al. *Rheum Dis Clinic N Am 31* (2005) 699-714

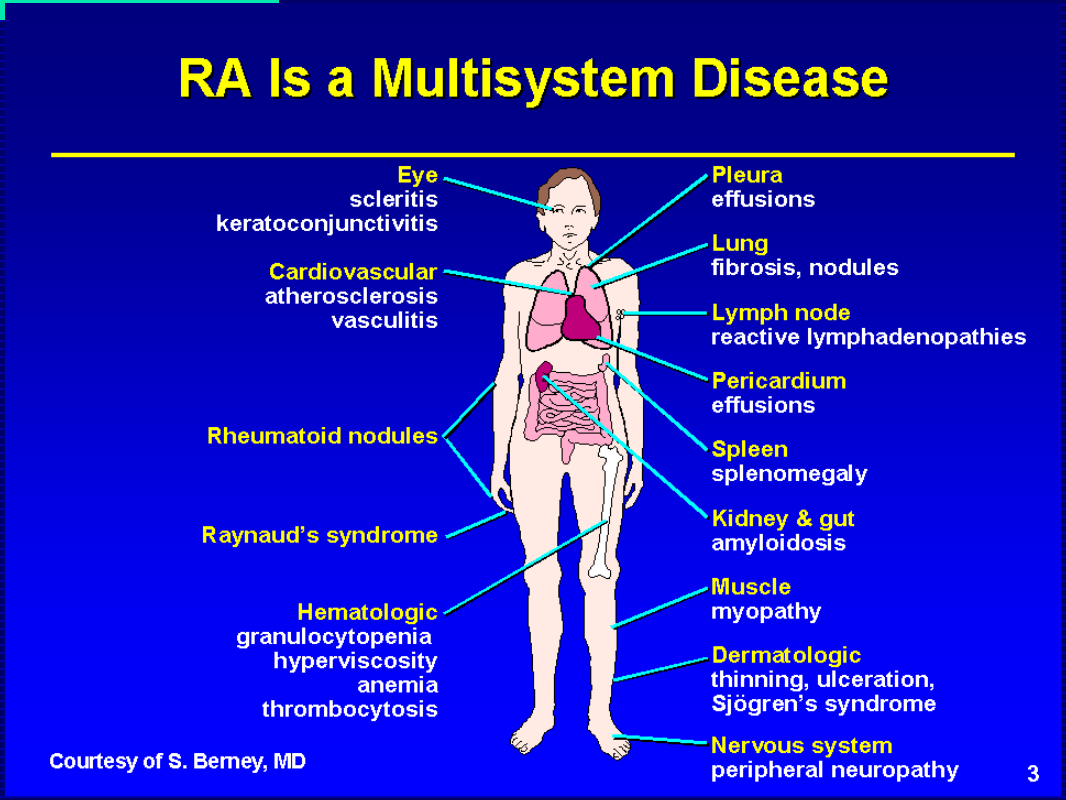
Features Related to Poor Outcomes

- Extra-articular disease
- High rheumatoid factor titer, positive anti-CCP antibody
- Poor functional status
- Involvement of multiple joints
- Radiographic erosions
- Sustained elevation of acute-phase reactants (eg, ESR)
- Low socioeconomic status/educational level
- Increased genetic risk of developing RA plus smoking

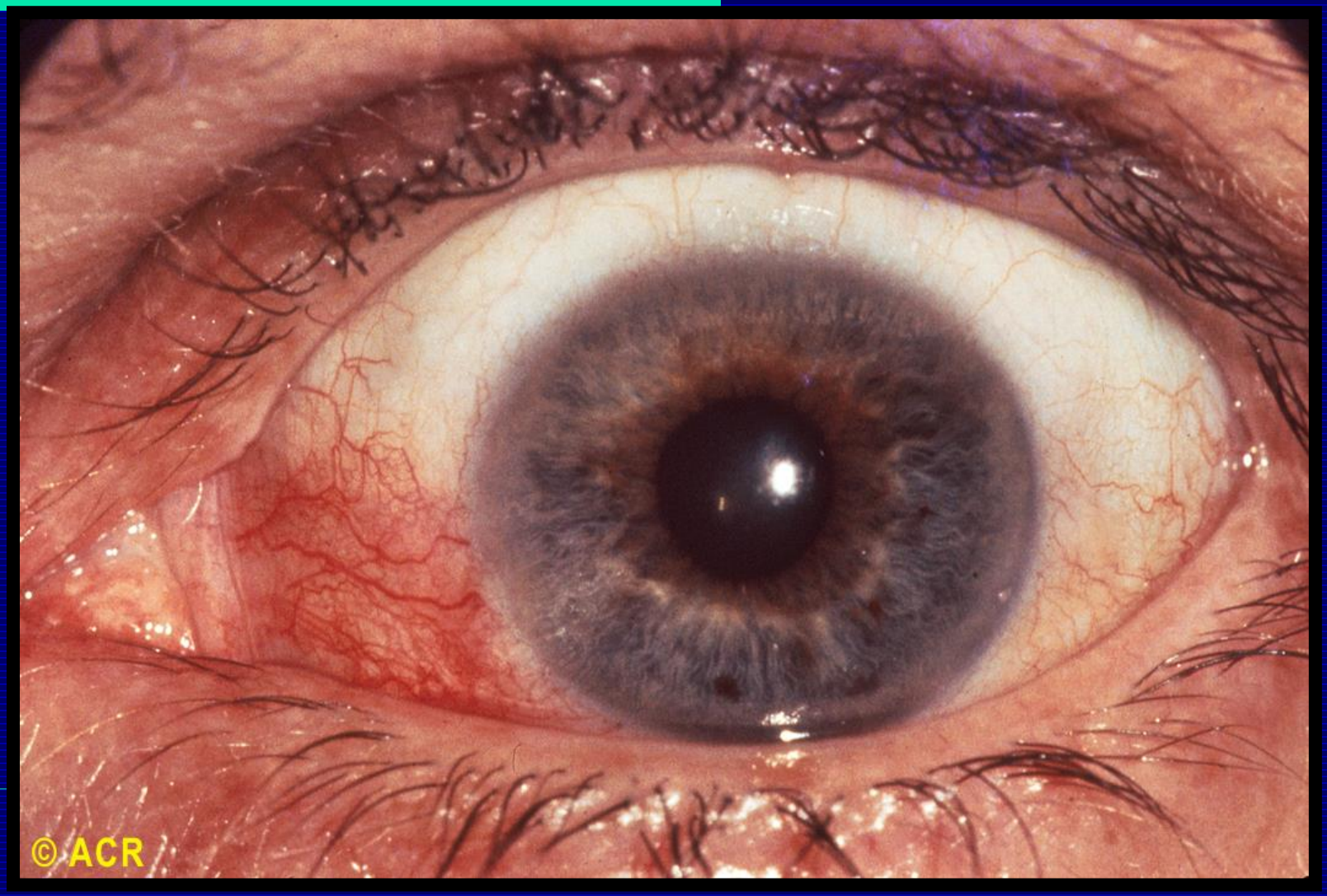
Anaya JM, et al. *Ann Rheum Dis*. 1994;53:782-783. Pincus T, et al. *Balliere's Clin Rheumatol*. 1992;6:161-191. Furst DE. *Rheum Dis Clin North Am*. 1994;20:309-319. Padyukov L, et al. *Arthritis Rheum*. 2004;50:3085-3092.

Complications of Rheumatoid Arthritis

- Complications:
  - Carpal tunnel syndrome, Baker's cyst, vasculitis, subcutaneous nodules, Sjögren's syndrome, peripheral neuropathy, cardiac and pulmonary involvement, Felty's syndrome, and anemia



Rheumatoid arthritis: episcleritis

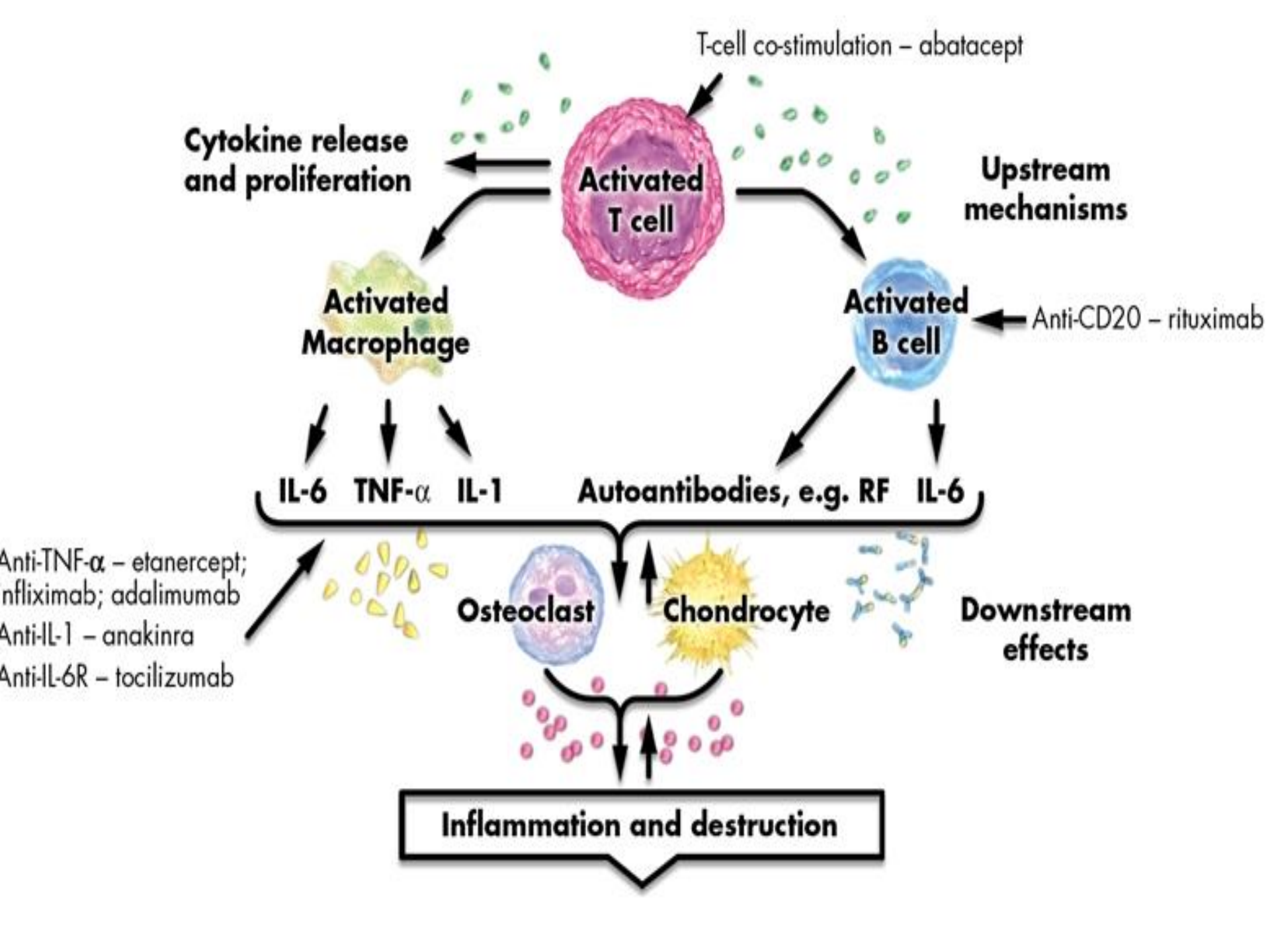


Treatment before the BIOLOGICS

- NSAIDs for stiffness
- Corticosteroids for inflammation and to suppress the autoimmunity
- Disease Modifying Anti rheumatic Drugs (DMARDs)
  - Drug of choice -Methotrexate 7.5-25mg weekly
  - But also Cyclosporine, Azathioprine, cyclophosphamide

Monoclonal antibodies and RA

- Tumor Necrosis (alpha) Inhibitors 5 FDA approved
  - Infliximab (Remicaid) an infusion
  - Etanercept (Enbrel) against soluble TNF receptors
  - Adalimunab (Humira) against soluble and membrane bound TNF receptors
  - Certolizumab (Cimza) pegylated
  - Golimumab (Simponi)
- Rituximab (rituxan) anti CD20 B cells
- Abatacept anti Costimulation blocking CD80/86 CD28
- Anakinra (Kineret) anti IL 1 receptor LOW EFFECT
- Tocilizumab (Actemra) anti IL 6

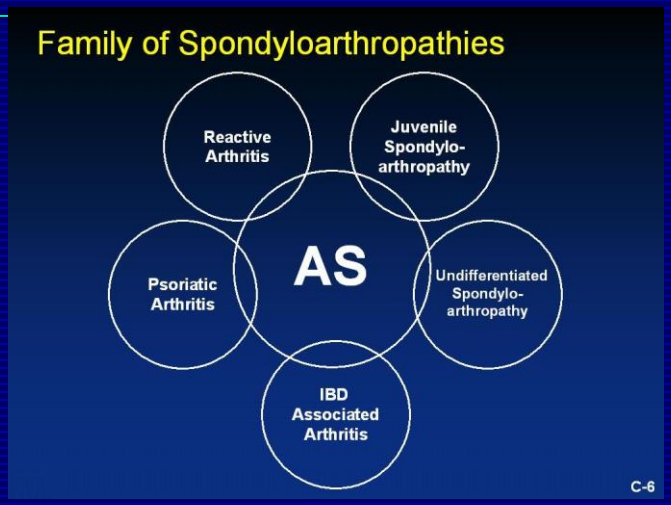

T-cell co-stimulation – abatacept
Cytokine release and proliferation
Activated T cell
Upstream mechanisms
Activated Macrophage
Activated B cell
Anti-CD20 – rituximab
IL-6
TNF-α
IL-1
Autoantibodies, e.g. RF
IL-6
Anti-TNF-α – etanercept; infliximab; adalimumab
Anti-IL-1 – anakinra
Anti-IL-6R – tocilizumab
Osteoclast
Chondrocyte
Downstream effects
Inflammation and destruction

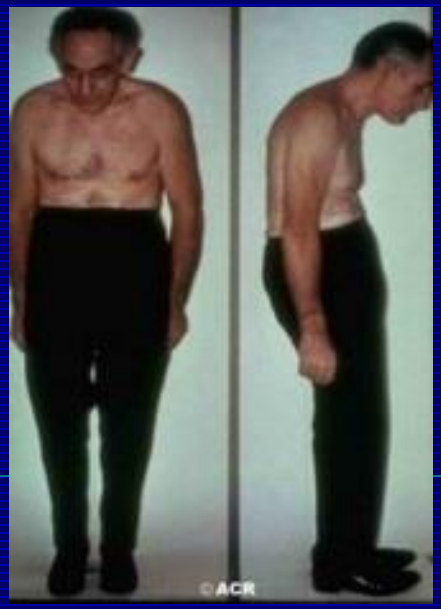
RA Therapies: The Next Generation

- Biosimilars
- Anti-IL-6 receptor
  - Sarilumab
- Anti-IL-17A
  - Secukinumab
- Anti-IL-20
- Anti-CD22
  - Epratuzamab
- Chemokine inhibitor: CCX354-L2
- PDE4 inhibitor: aprimilast

Seronegative Spondyloarthropathy

- Consist of a group of related disorders that include Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis, and arthritis in association with inflammatory bowel disease
- Occurs commonly among young men, with a mean incidence between ages 25 and 34
- The prevalence is about 1%
- The male-to-female ratio approaches 4 to 1 among adult Caucasians
- Genetic factors play an important role in the susceptibility to each disease





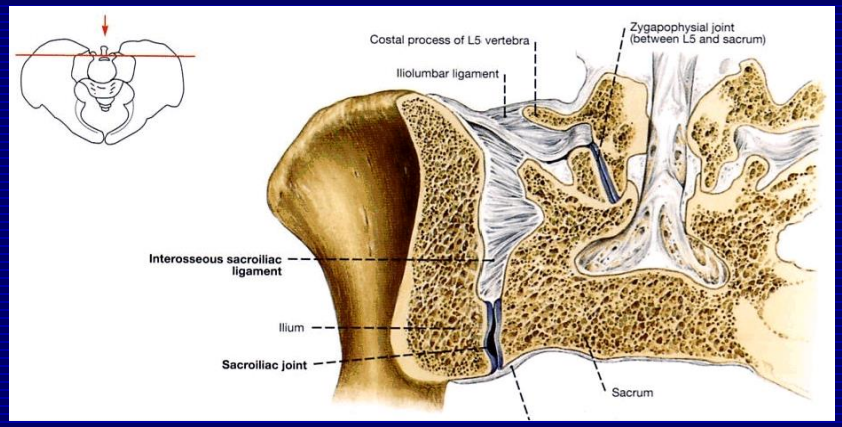
Seronegative Spondyloarthropathy

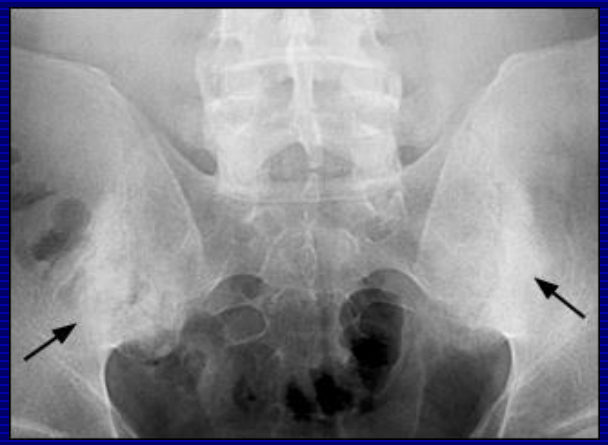
- The spondyloarthropathies share certain common features, including the absence of serum rheumatoid factor, an oligoarthritis commonly involving large joints in the lower extremities, frequent involvement of the axial skeleton, familial clustering, and linkage to HLA-B27

- These disorders are characterized by inflammation at sites of attachment of ligament, tendon, fascia, or joint capsule to bone (enthesopathy)

Sacroiliitis

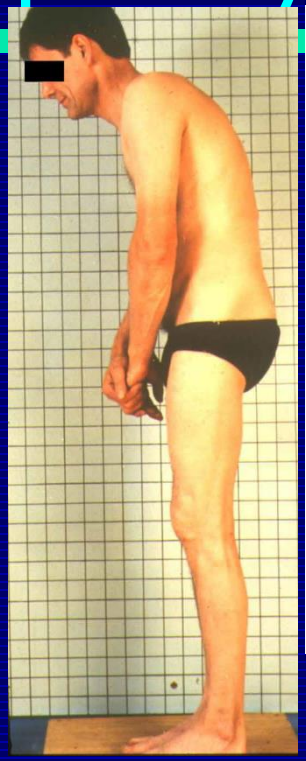
- Sacroiliitis is an inflammation of the sacroiliac joint.
  - Symptoms usually include a fever and reduced range of motion.
- Picture of individual with – sacroiliitis and Ankylosing Spondylitis. The arrows point to the inflamed and narrowed SI joints. They are white due to bony sclerosis around the joints

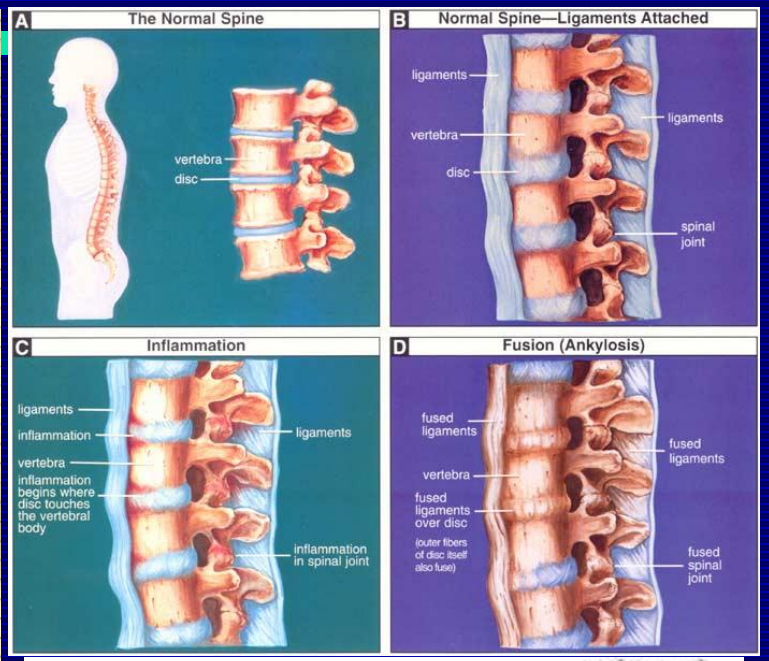




Ankylosing Spondylitis

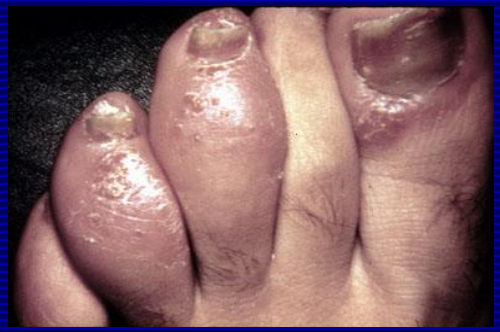
- Chronic disease that primarily affects the spine and may lead to stiffness of the back.
- The joints and ligaments become inflamed. The joints and bones may fuse.
- The effects are inflammation and chronic pain and stiffness in the lower back that usually starts where the lower spine is joined to the pelvis or hip.
- Diagnosis: X-rays, and blood tests for HLA-B27 gene





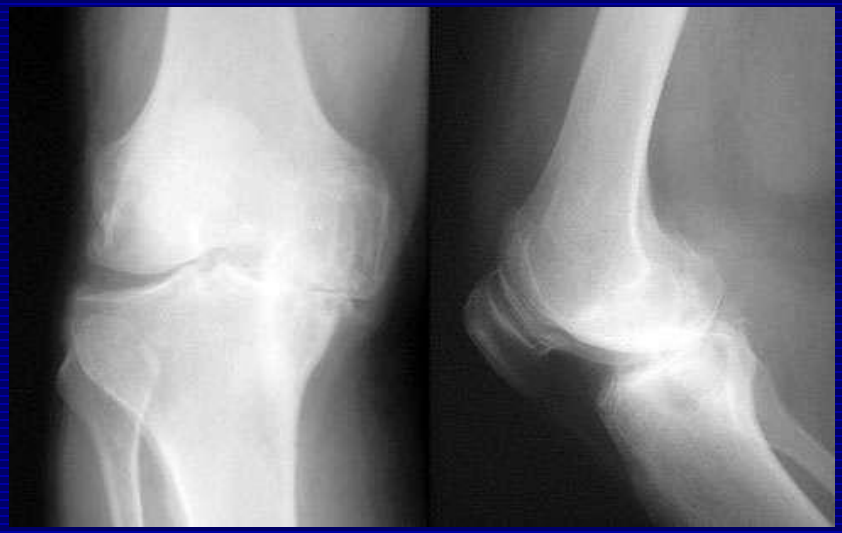
Psoriatic Arthritis

- Causes pain and swelling in some joints and scaly skin patches on some areas of the body.
- The symptoms are:
  - About 95% of those with psoriatic arthritis have swelling in joints outside the spine
  - Silver or grey scaly spots on the scalp, elbows, knees and/or lower end of the spine.
  - Pain and swelling in one or more joints
  - Swelling of fingers/toes that gives them a "sausage" appearance.



Degenerative Joint Disease (Osteoarthritis)

- is characterized by progressive loss of cartilage and reactive changes at the margins of the joint and in the subchondral bone
- The disease usually begins in one's 40s
- Prevalence increases with age and the disease becomes almost universal in individuals aged 65 and older
- Primarily affects weight-bearing joints such as the knees, hips, and lumbrosacral spine



Degenerative Joint Disease

- In early disease, pain occurs only after joint use and is relieved by rest
- As the disease progresses, pain occurs with minimal motion or even at rest
- Nocturnal pain is commonly associated with severe disease

Image of the knee joint with arthritis clearly present

Thank you for your attention