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***Sronegative  
Spondyloarthropathies***

Dr. M Jokar

# Definition

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- The spondyloarthropathies are a group of disorders that share certain clinical features and an association with the HLA-B27 allele

# Spondyloarthropathies

## ESSG Criteria

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### Primary

- **Inflammatory Back Pain**
- OR**
- **Synovitis**
  - Asymmetric
  - Predominantly in lower extremities

### Secondary

- **Plus one of following:**
  - Psoriasis
  - IBD
  - Positive family history
  - Urethritis, cervicitis, or acute diarrhea within 1 month of arthritis
  - Alternating buttock pain
  - Enthesopathy
  - Sacroiliitis



# Sronegative Spondyloarthropathies

- Ankylosing spondylitis(AS)
- Reiter's syndrome, reactive arthritis
- Psoriatic arthritis
- Enteropathic arthritis and spondylitis
- Juvenile-onset spondyloarthropathy
- Undifferentiated spondyloarthropathy

# HLA-B27: Disease Associations

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Disease	Association
Ankylosing Spondylitis	> 90%
Reiter's Syndrome	80%
Reactive Arthritis	85%
Inflammatory Bowel Disease	50%
Psoriatic Arthritis	
With Spondylitis	50%
With Peripheral Arthritis	15%
Whipple's Disease	30%

# Ankylosing spondylitis (AS)





# What is Ankylosing Spondylitis?

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***‘ankylos’***  
***‘spondylosis’***  
***‘itis’***

Inflammatory disease of the spine that can lead to stiffening of the back

# ○○ Ankylosing Spondylitis

- **Ankylosing spondylitis (AS) is an inflammatory disorder of unknown cause that primarily affects the axial skeleton; peripheral joints and extraarticular structures may also be involved**



# Ankylosing Spondylitis

- **Primary AS**
- **Secondary:**
  - IBD**
  - Reactive Arthritis**
  - Psoriatic Arthritis**

# EPIDEMIOLOGY

- Prevalence: less than 0.01%
- Usually begins in the second or third decade
- The prevalence in men is approximately three times that in women
- ♂♂ Striking correlation with the histocompatibility antigen HLA-B27
- The general prevalence of B27 is 7%
- over 90% of patients with AS have inherited this antigen
- The association with B27 is independent of disease severity.

# EPIDEMIOLOGY

- 1 to 6% of adults inheriting B27 have been found to have AS
- In families of patients with AS, the prevalence is 10 to 30% among adult first-degree relatives inheriting B27
- Concordance rate in identical twins is estimated to exceed 65%



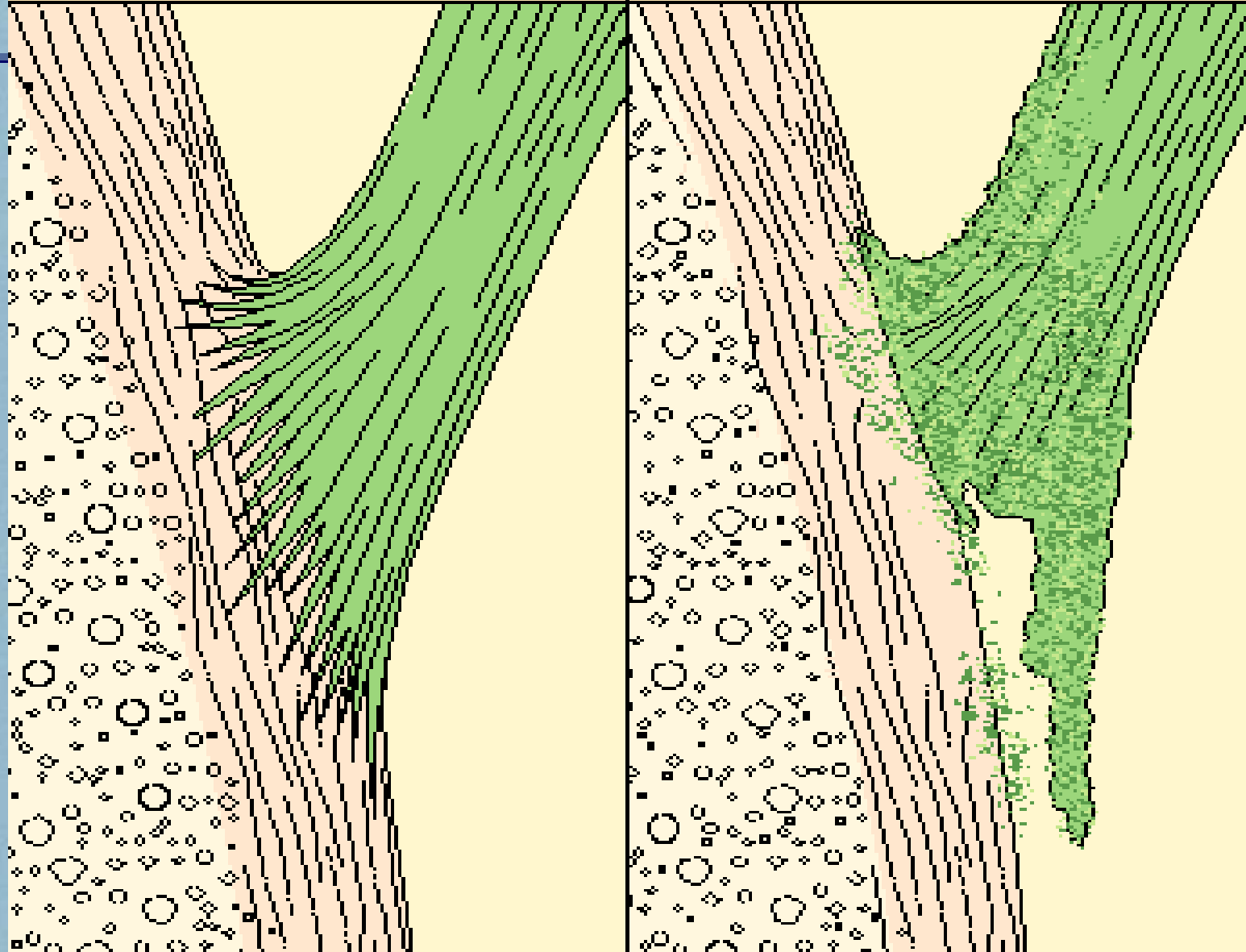
# PATHOLOGY

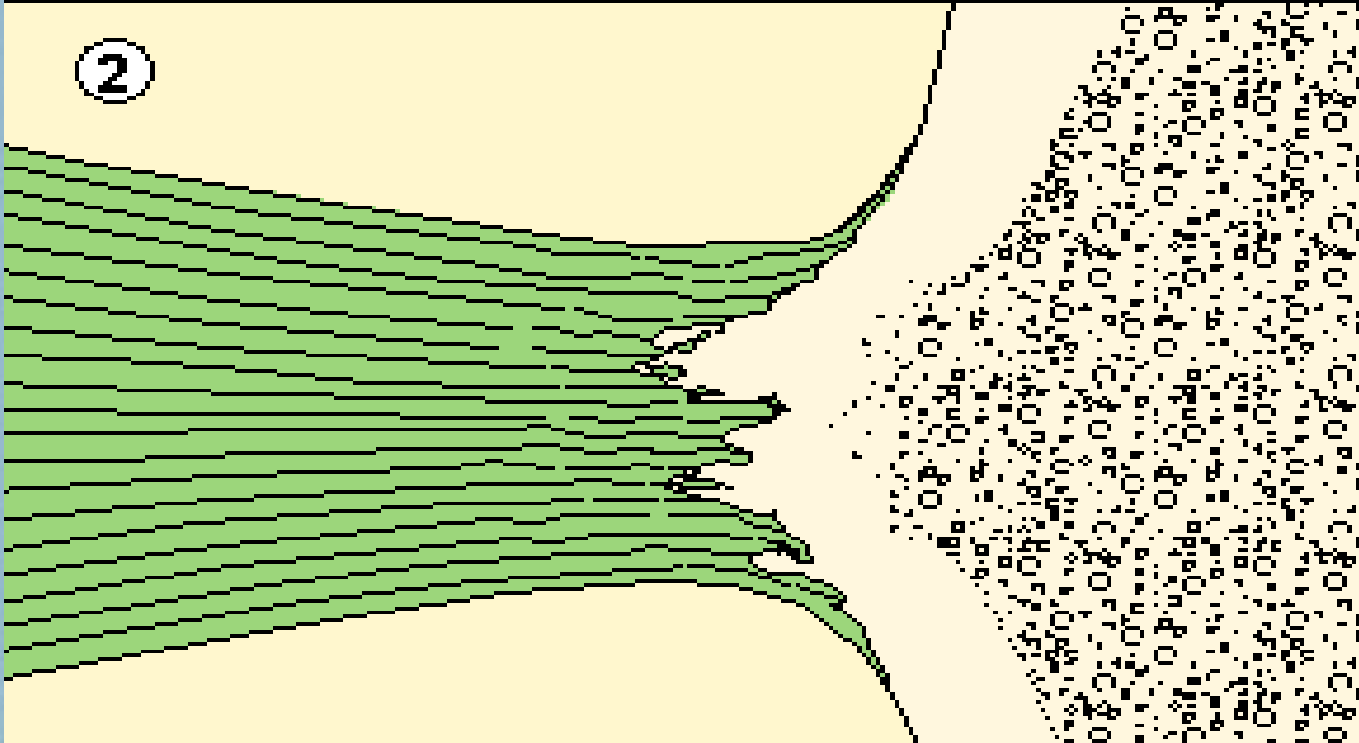
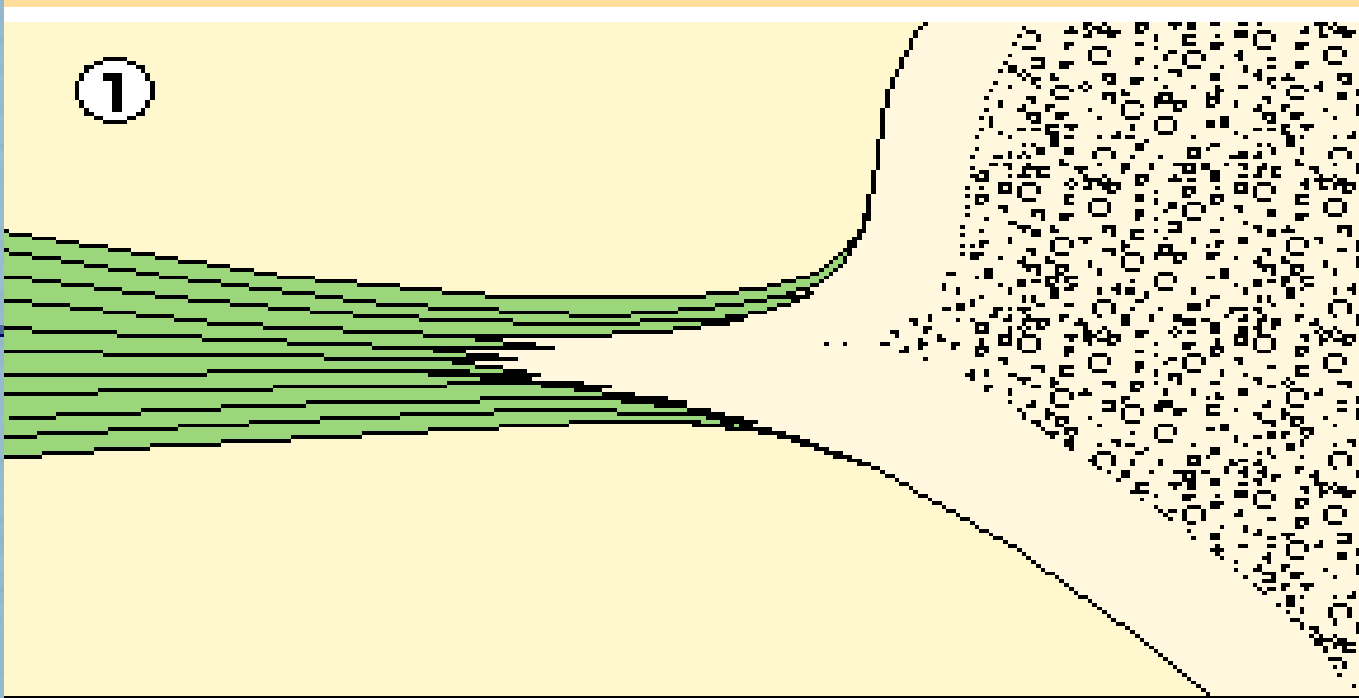
- The *enthesis*, the site of ligamentous attachment to bone, is thought to be the primary site of pathology in AS, particularly in the lesions around the pelvis and spine.
- Enthesitis is associated with prominent edema of the adjacent bone marrow and is often characterized by erosive lesions that eventually undergo ossification.

# INFLAMMATORY ENTHESOPATHY OF A TENDON ATTACHMENT

Normal attachment of tendon fiber to bone

Inflammation and erosion in inflammatory enthesopathy



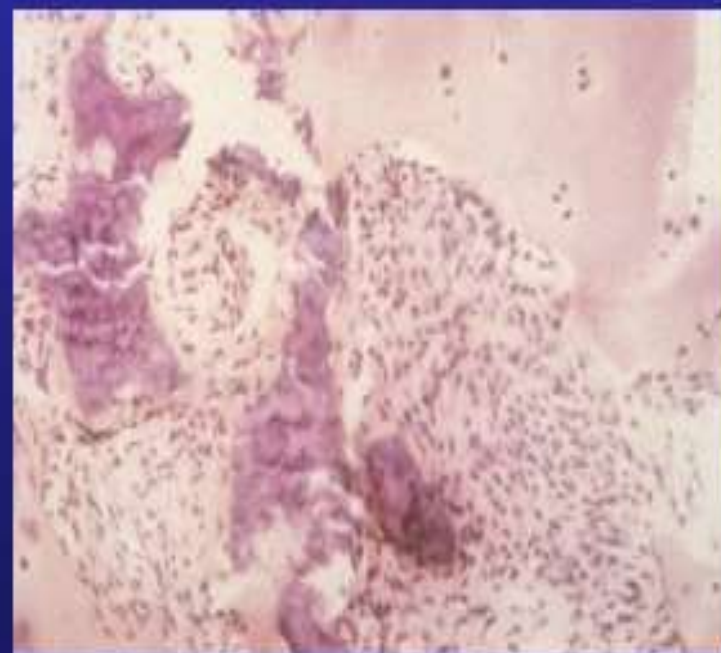
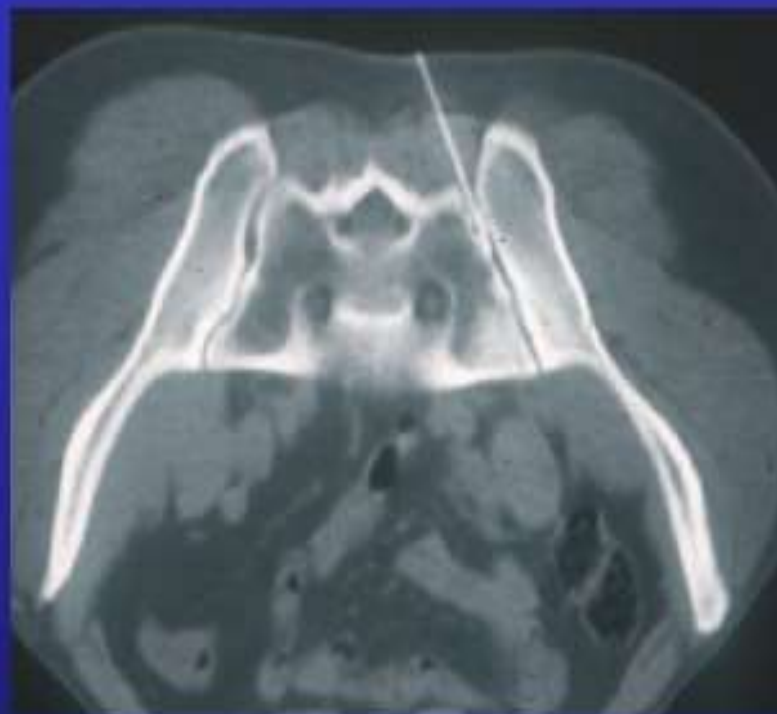




# PATHOLOGY

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- Sacroiliitis is usually one of the earliest manifestations of AS
- The early lesions consist of subchondral granulation tissue containing lymphocytes, plasma cells, mast cells, macrophages, and chondrocytes; infiltrates of lymphocytes and macrophages in ligamentous and periosteal zones; and subchondral bone marrow edema.



# Pseudo-Widening of Right SI Joint





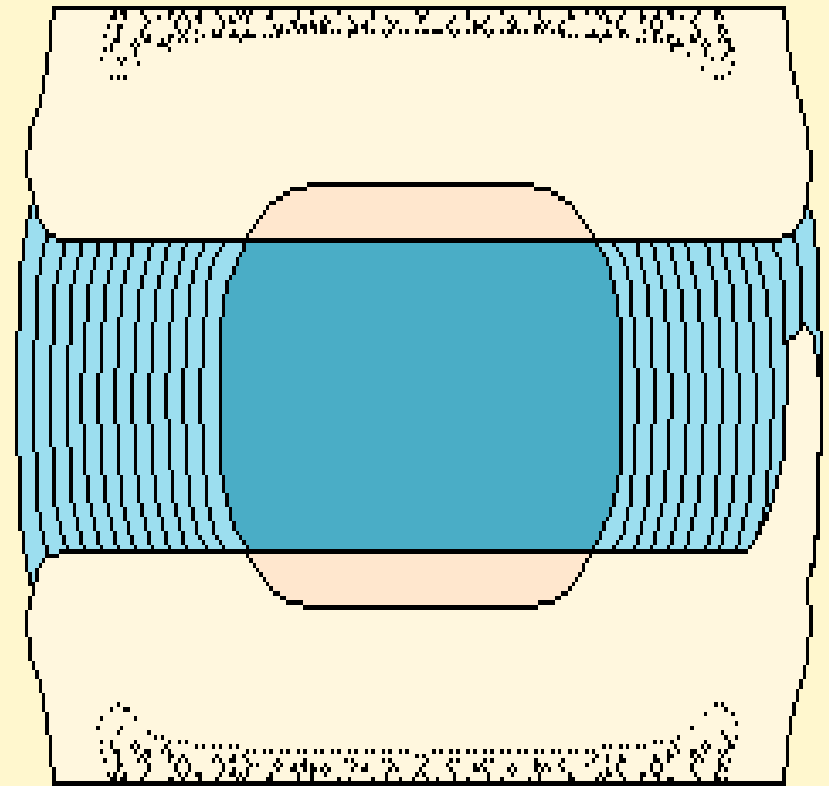
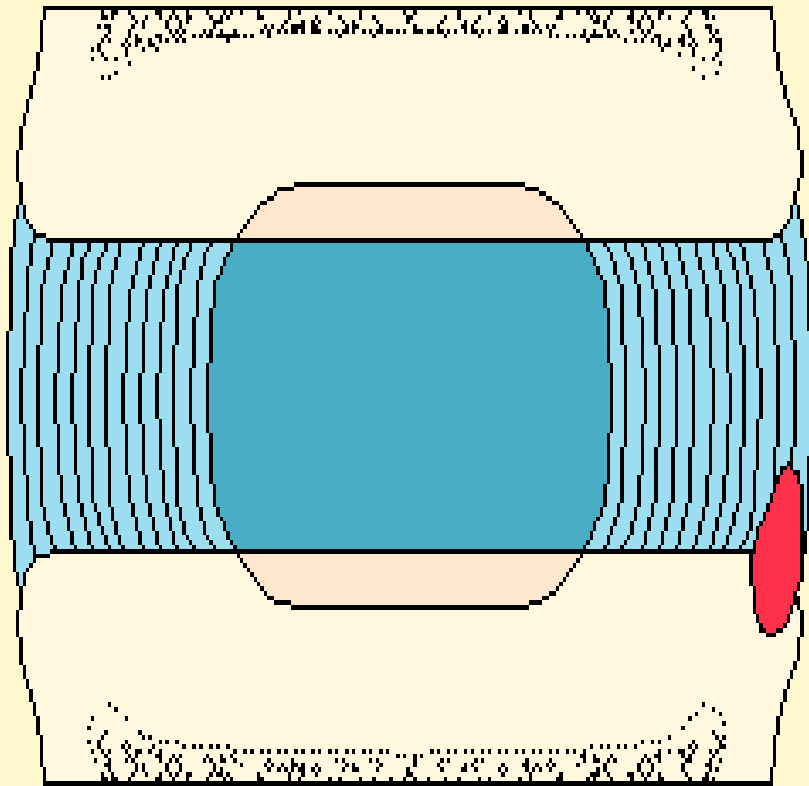
# PATHOLOGY

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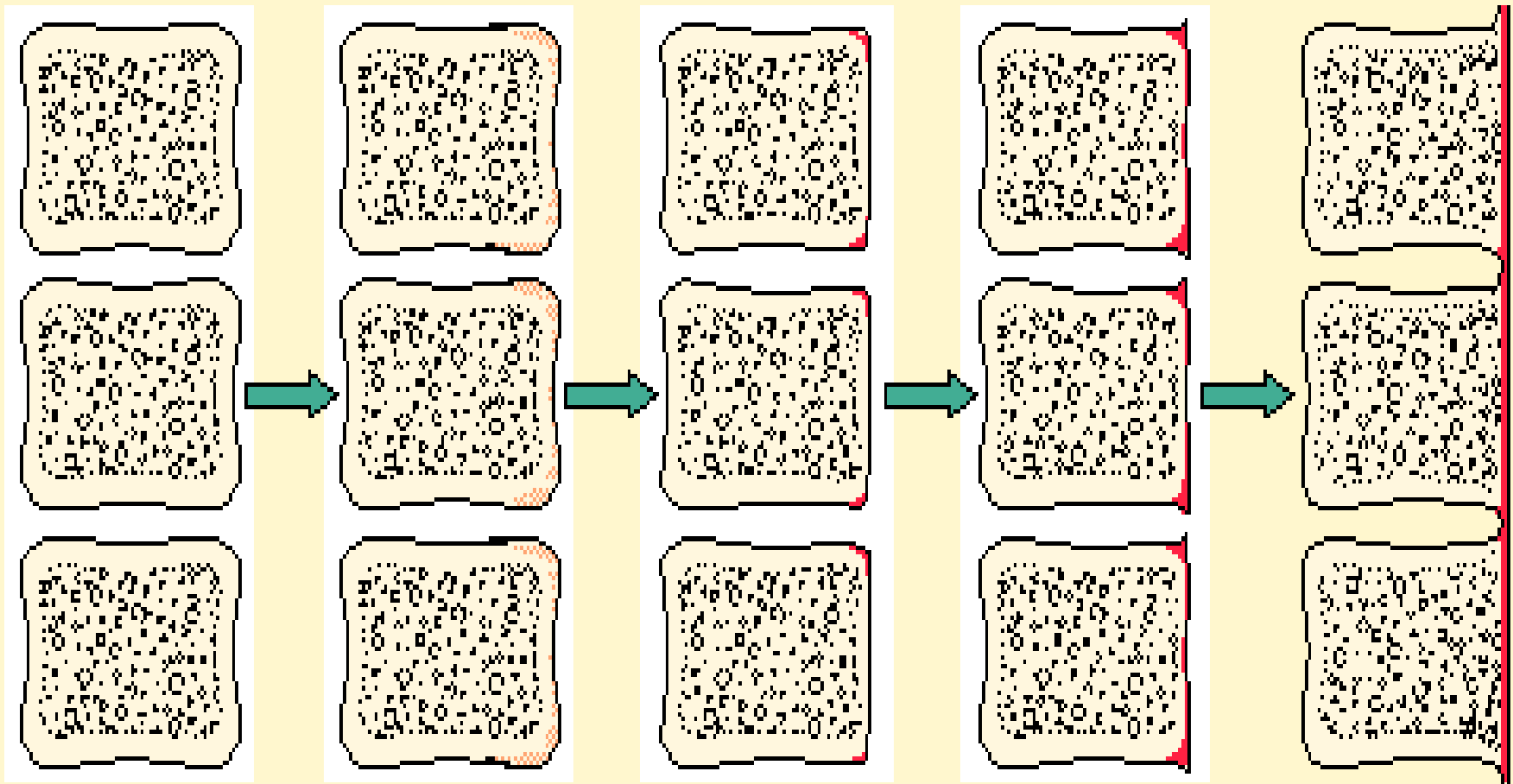
- The irregularly eroded, sclerotic margins of the joint are gradually replaced by fibrocartilage regeneration and then by ossification. Ultimately, the joint may be totally obliterated

Next

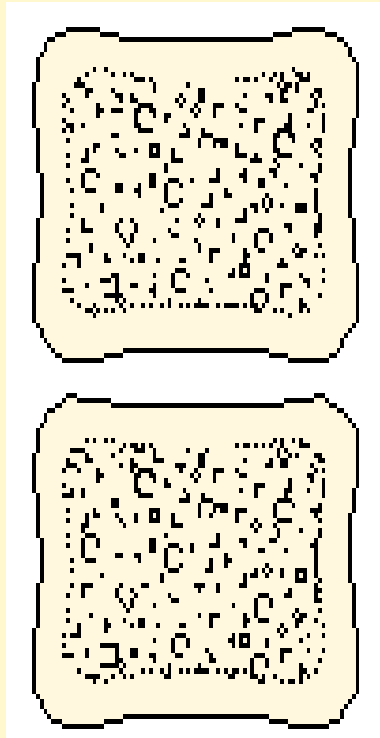
## CHANGES AT THE VERTEBRAL RIM IN ANKYLOSING



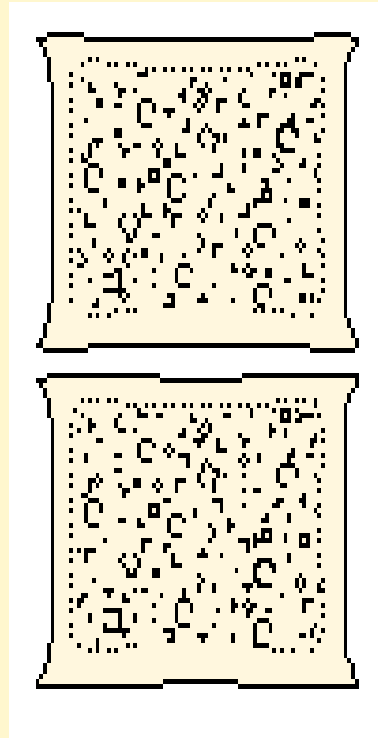
# EVOLUTION OF SYNDESMOPHYTES



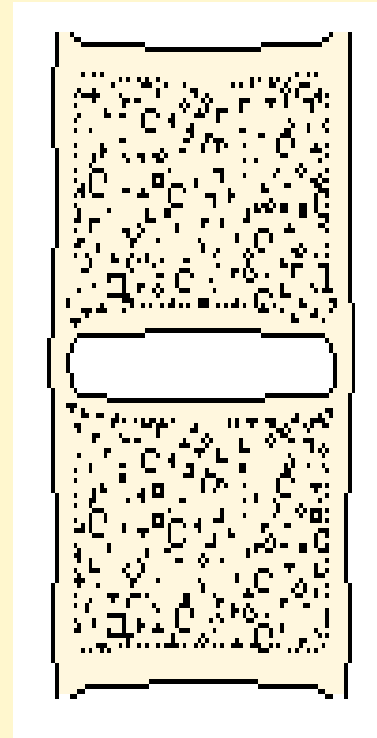
## BONY CHANGES IN VERTEBRAL COLUMN



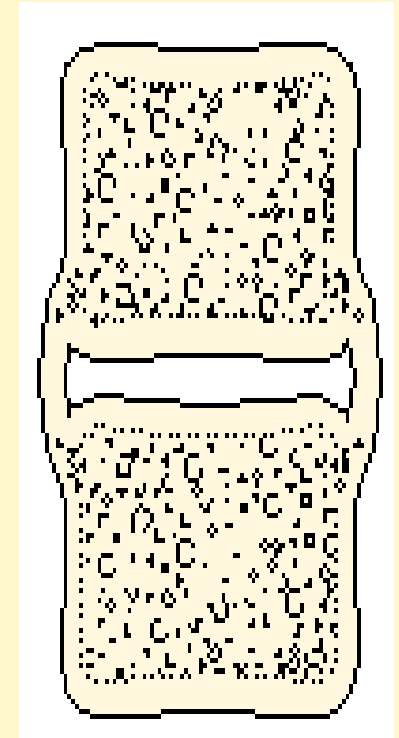
Normal



Osteophytes

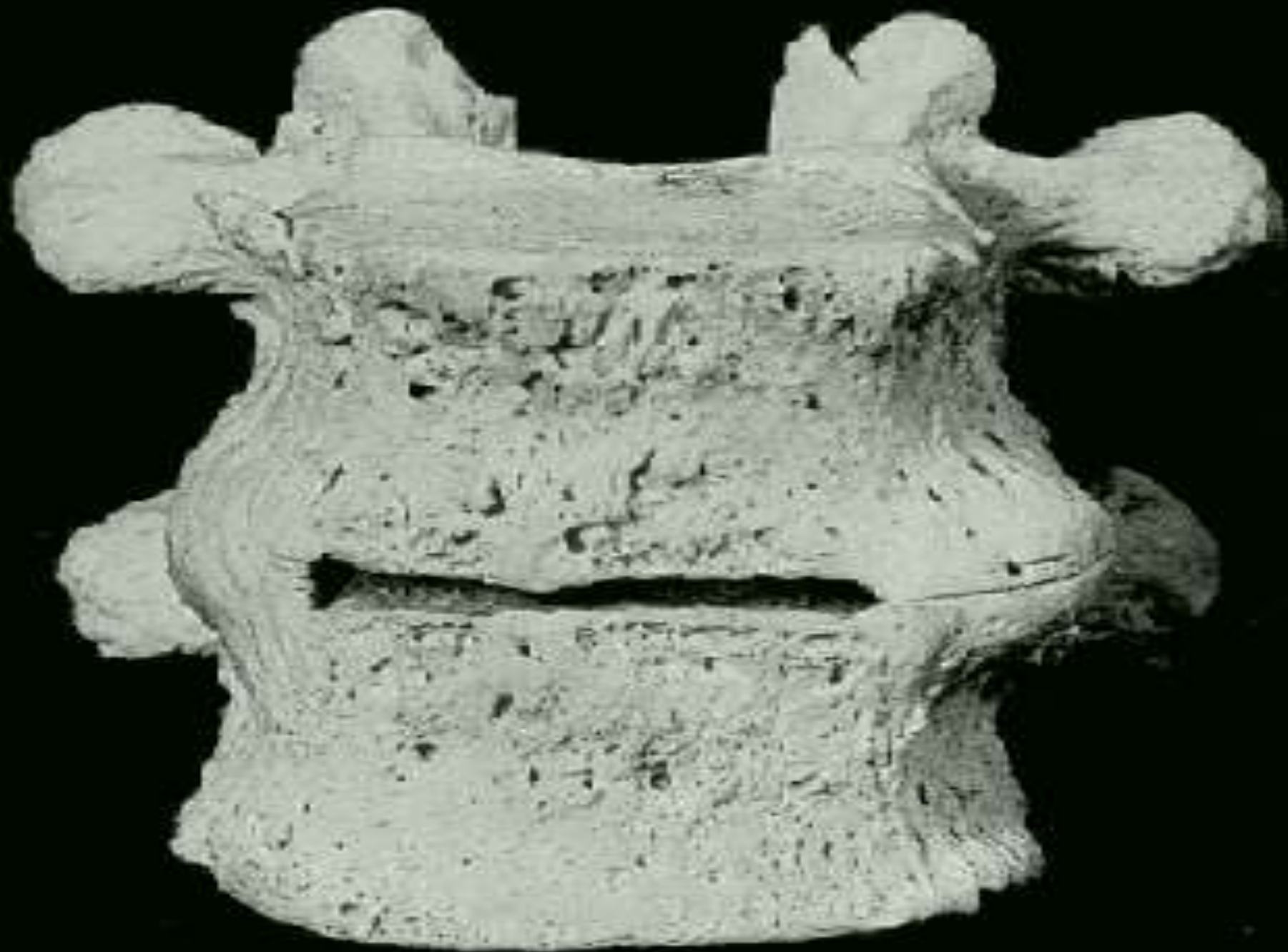


Syndesmophytes



Non-marginal  
Syndesmophytes





# PATHOLOGY

- **spine**
- inflammatory granulation tissue at the junction of the annulus fibrosus the margin of vertebral bone.
- The outer annular fibers are eroded and eventually replaced by bone, called a *syndesmophyte*,
- then grows by continued enchondral ossification, ultimately bridging the adjacent vertebral bodies
- . Ascending progression of this process leads to the "bamboo spine" observed radiographically

# PATHOLOGY

- Spine
- Other lesions in the spine include diffuse osteoporosis, erosion of vertebral bodies at the disk margin, "squaring" of vertebrae, and inflammation and destruction of the disk-bone border. Inflammatory arthritis of the apophyseal joints is common, with erosion of cartilage by pannus, often followed by bony ankylosis.



# PATHOLOGY

- **Peripheral Joints**

**synovial hyperplasia, lymphoid infiltration, and pannus formation, but the process lacks the exuberant synovial villi, fibrin deposits, ulcers, and accumulations of plasma cells seen in rheumatoid arthritis**



# PATHOGENESIS

- **Incompletely understood**
- **HLA-B27**
- **Immune-mediated**
- **Enteric bacteria may play a role.**
- **Elevated serum titers of antibodies to certain enteric bacteria, particularly *Klebsiella pneumoniae*, are common**

# Genetics and ankylosing spondylitis

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- **Strong association with HLA-B27**
- **Prevalence of AS – associated with wild world distribution of HLA-B27**
- **90-98% of patients with AS are HLA-B27 positive**
- **Only 1-2% of HLA-B27 positive adults may develop AS**

# HLA B 27

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- **HLA-B27 encompasses 27 different alleles encoding 23 different proteins**
- **23 subtypes of HLA-B27 – HLA-B2701-2723**
- **HLA-B2705 –most widespread**
- **HLA-B27 contributes only part of the genetic risks**



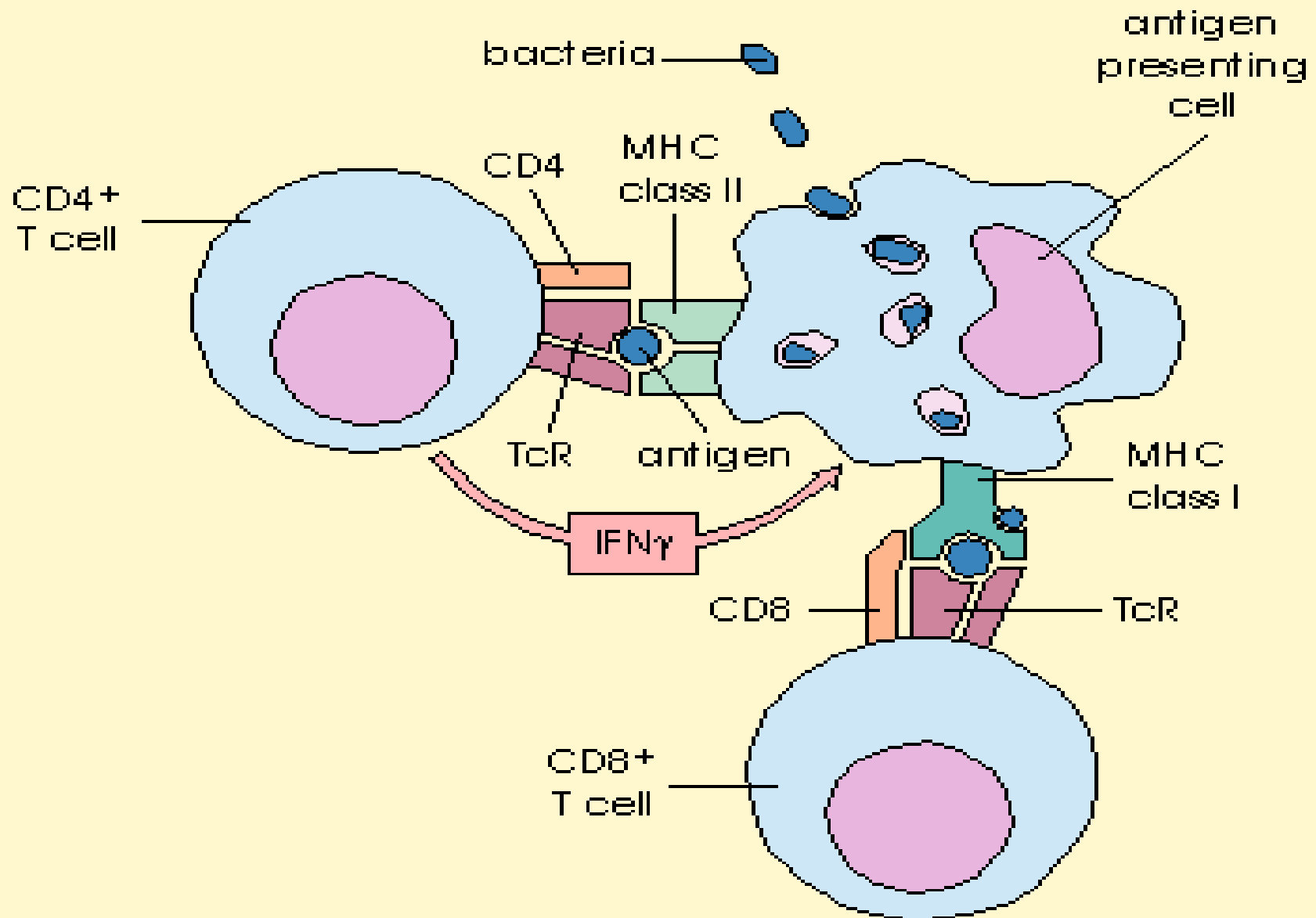
# Genetic factors involved in AS

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- HLA-class II
- Low molecular proteasome
- Polymorphisms of  $TNF\alpha$
- Major histocompatibility complex class II – MICA
- Genes encoding IL-1RA,IL-6,IL-10,CYP2D6



# MODEL OF CELLULAR INTERACTIONS INVOLVED IN THE RECOGNITION OF BACTERIAL PEPTIDES BY CD8<sup>+</sup> T CELLS



# Clinical Features of AS

## **Skeletal**

**Axial arthritis (eg, sacroiliitis and spondylitis)**

**Arthritis of 'girdle joints' (hips and shoulders)**

**Peripheral arthritis uncommon**

**Others: enthesitis, osteoporosis, vertebral, fractures, spondylodiscitis, pseudoarthrosis**

## **Extraskeleta**

**|**

**Acute anterior uveitis**

**Cardiovascular involvement**

**Pulmonary involvement**

**Cauda equina syndrome**

**Enteric mucosal lesions**

**Acute anterior uveitis**

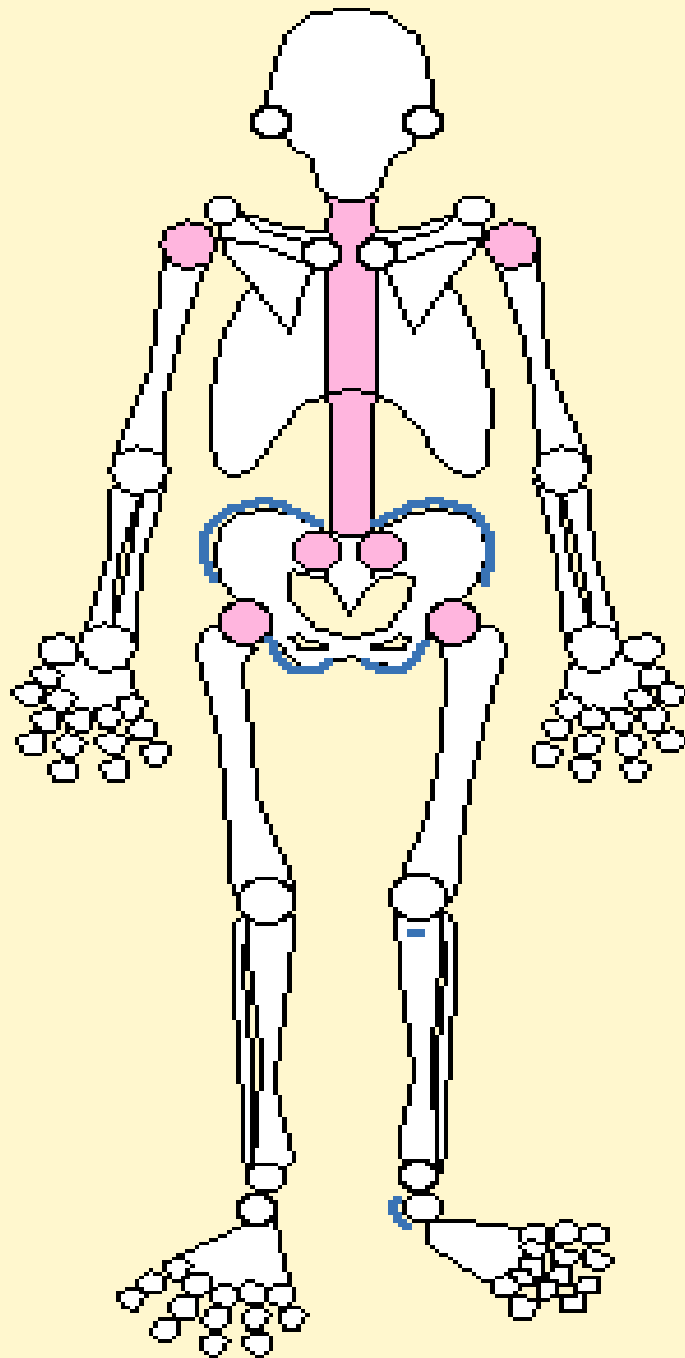
# CLINICAL MANIFESTATIONS

- **Late adolescence or early adulthood**
- **The median age in western countries is 23**
- **In 5% of patients, symptoms begin after age 40**
- **The initial symptom is usually dull pain, insidious in onset, felt deep in the lower lumbar or gluteal region, accompanied by low-back morning stiffness of up to a few hours' duration that improves with activity and returns following periods of inactivity**

# CLINICAL MANIFESTATIONS

- Within a few months of onset, the pain has usually become persistent and bilateral. Nocturnal exacerbation of pain that forces the patient to rise and move around may be frequent.





— sites of enthesopathy

# CLINICAL MANIFESTATIONS

- Enthesopathy

iliac crests, greater trochanters, ischial tuberosities, tibial tubercles, and heels

# CLINICAL MANIFESTATIONS

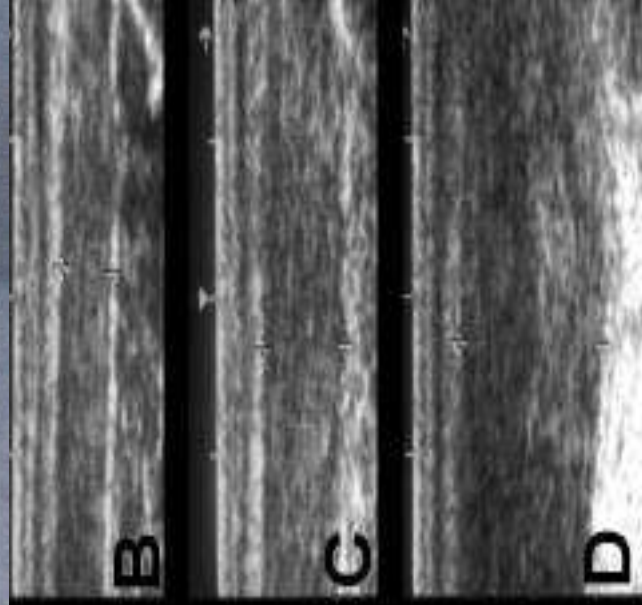
- Peripheral joints
- **Hips and shoulders ("root" joints) occurs in 25 to 35% of patients**
- Arthritis of peripheral joints other than the hips and shoulders, usually asymmetric, occurs in up to 30% of patients and can occur at any stage of the disease.

# Extraskkeletal manifestations

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- **Constitutional symptoms**
- **Acute anterior uveitis**
- **Cardiovascular disease**
- **Pulmonary disease**
- **Neurologic involvement**
- **Renal involvement**





# extraarticular manifestation

- Eye





# Uveitis



- Anterior
- Acute and unilateral
- Red and painful eye
- Photophobia, lacrimation
- Attacks usually subside in 4-8 weeks
- Without sequelae
- More common in HLA-B27 positive

# Cardiovascular

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- **May be clinically silent although clinically important**
- **Ascending aortitis**
- **Aortic valve incompetence**
- **Conduction abnormalities**
- **Cardiomegaly**
- **Pericarditis**

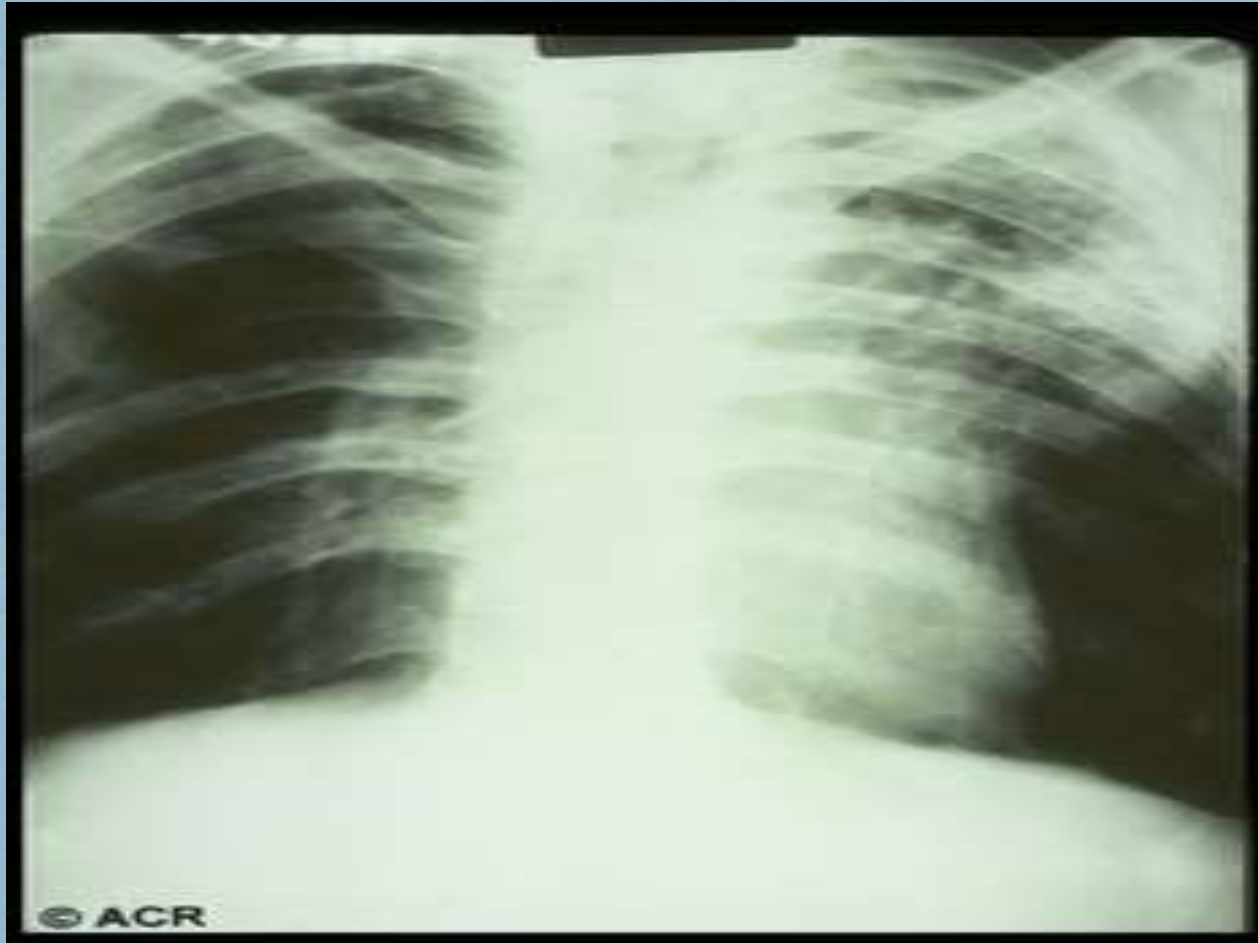


# Pulmonary disease

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- **Progressive fibrosis of the upper lobes**
- **Eventual secondary colonization with aspergillus**
- **Impaired pulmonary ventilation due to involvement of thoracic joints**
- **Restrictive lung disease**

# Apical Fibrosis



# Neurologic involvement

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- **Fracture, instability or compression of vertebrae**
- **Atlanto-axial subluxation**
- **Ossification of the posterior longitudinal ligament resulting in compressive myelopathy**
- **Cauda equina synd :lumbosacral roots, pain , sensory loss, urinary&bowel symptoms**

# Renal involvement

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- **Immunoglobulin A (IgA) nephropathy**
- **Secondary amyloidosis**
- **High incidence of prostatitis**



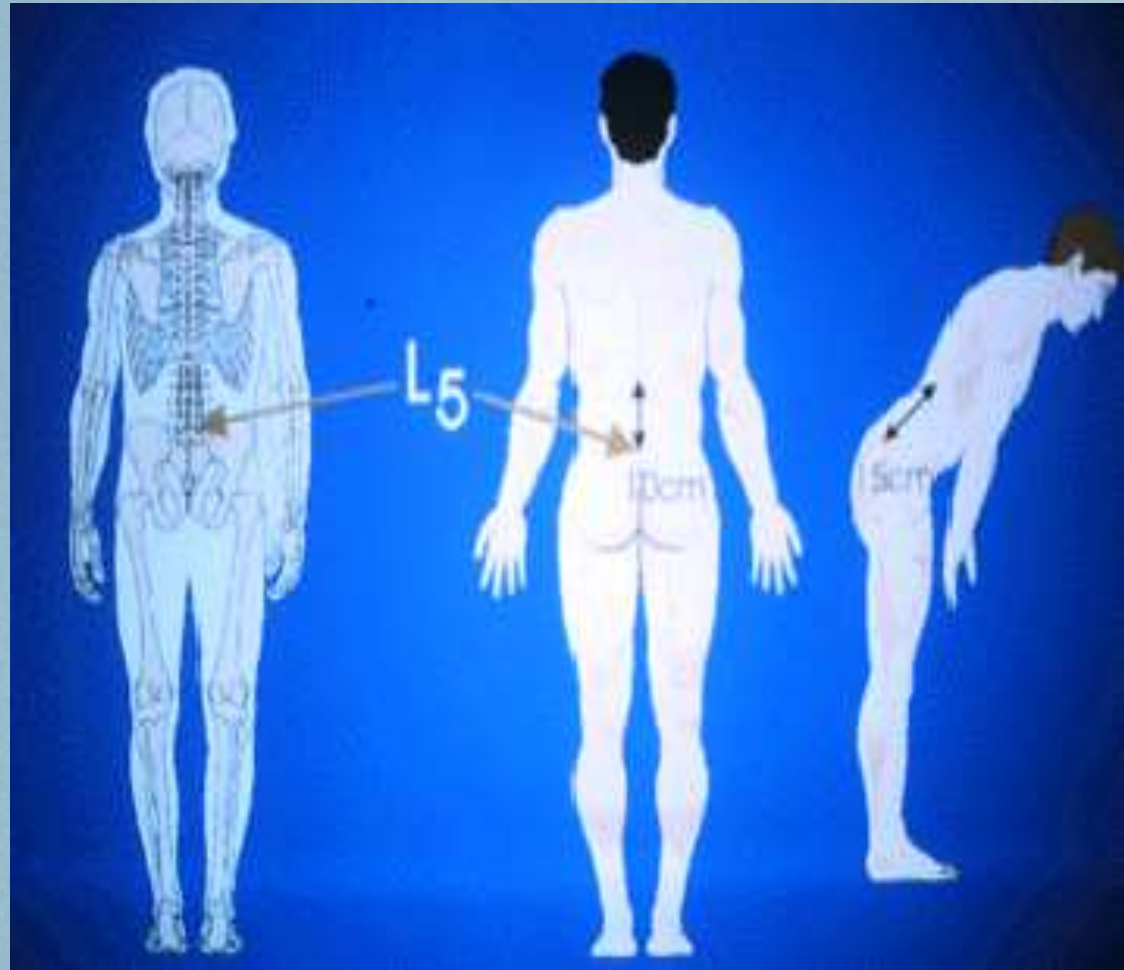
# Physical examination

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- Evidence of sacroiliitis
- Expansion of the lumbar spine –Schober test
- Chest expansion < below 5 cm
- Enthesitis
- Posture –forward sloop of the neck, stiffness of the spine , loss of lumbar lordosis, thoracic kyphosis

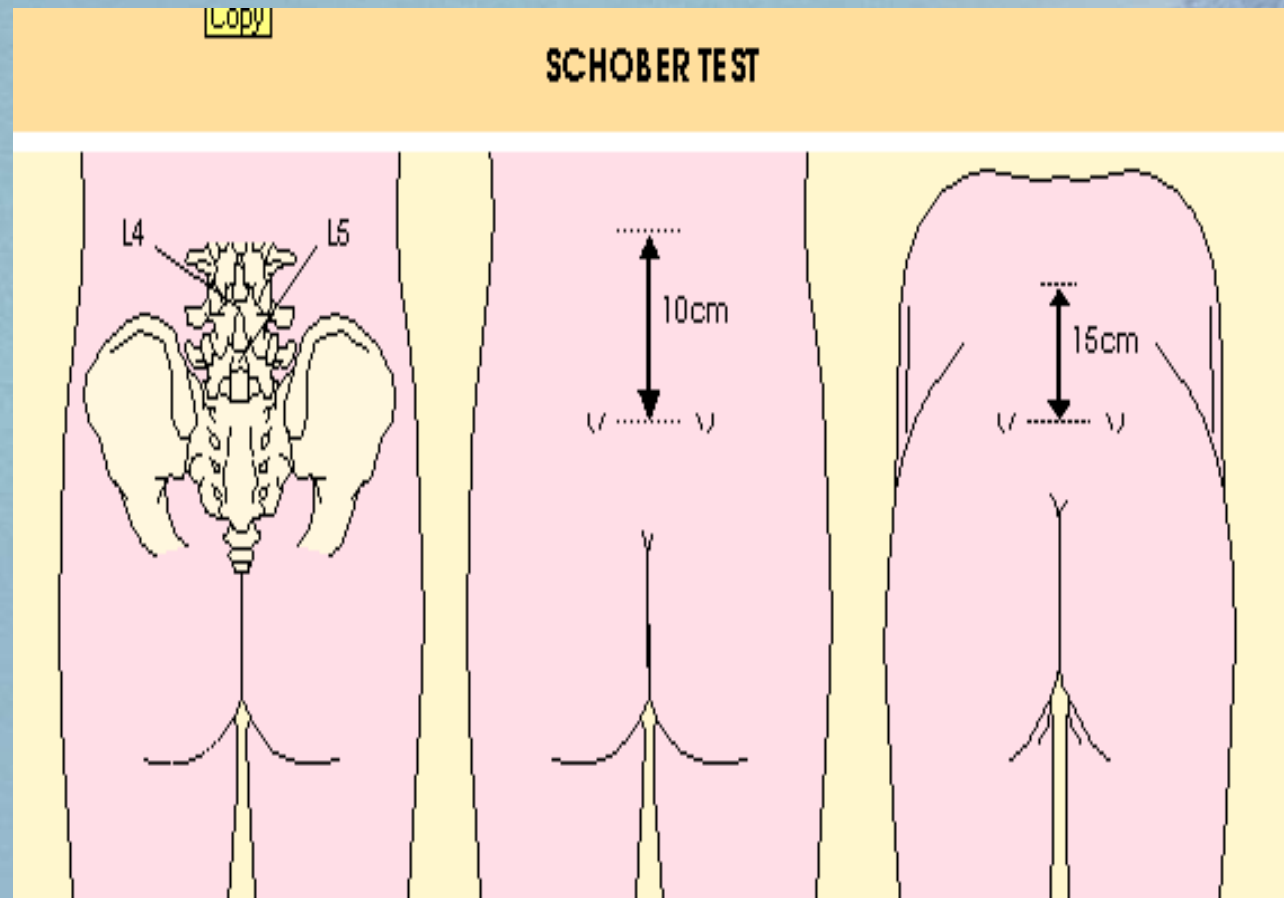
# physical findings

- loss of spinal mobility

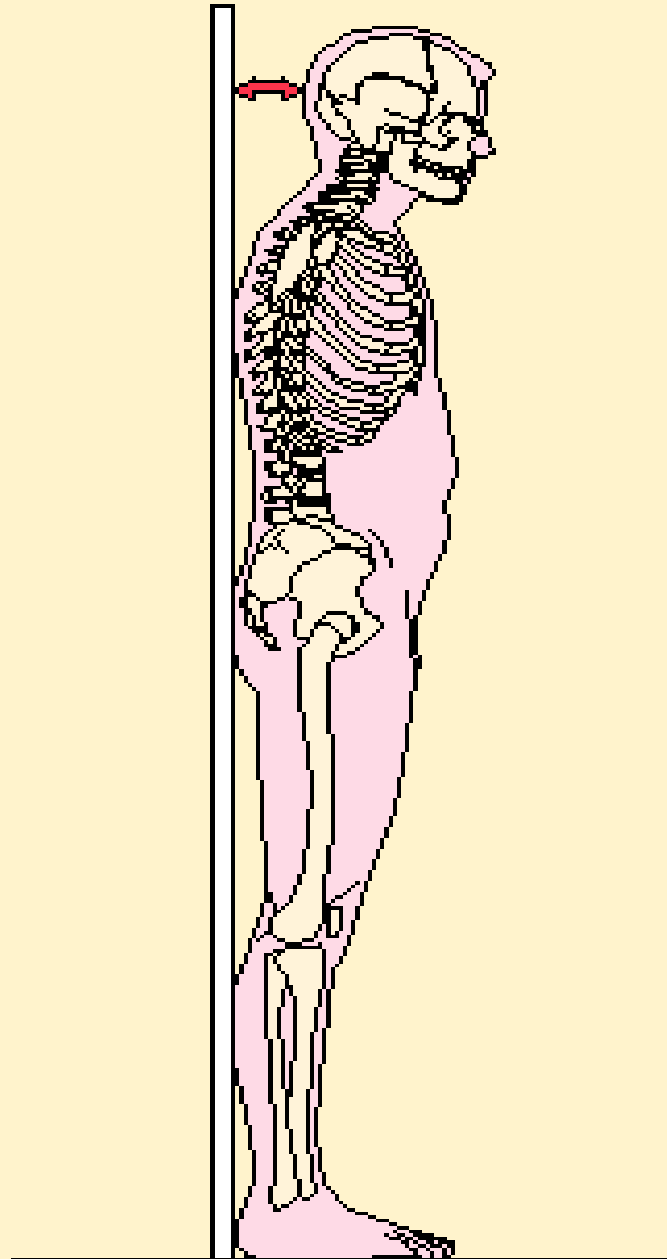


# physical findings

- The Schober tes



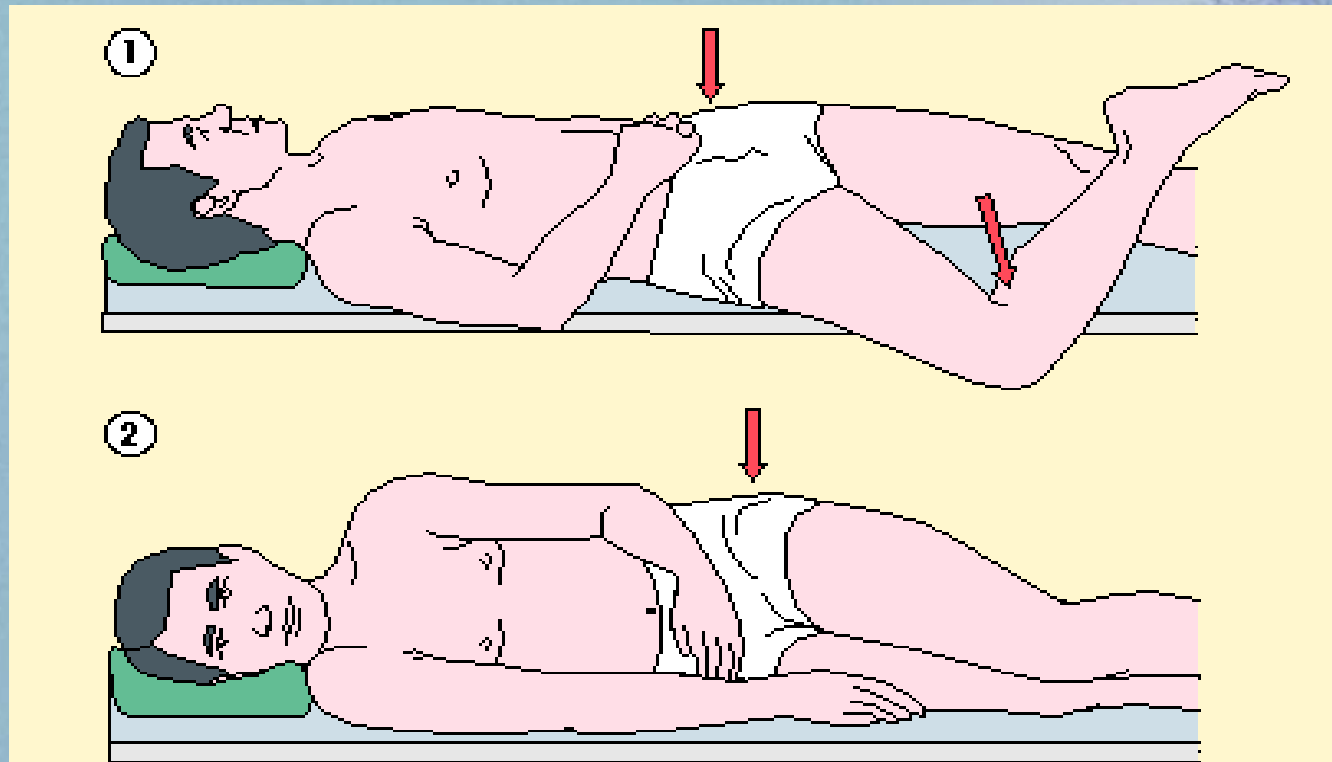
Next  
OCCIPUT-TO-WALL TEST





# physical findings

- sacroiliac joints tenderness

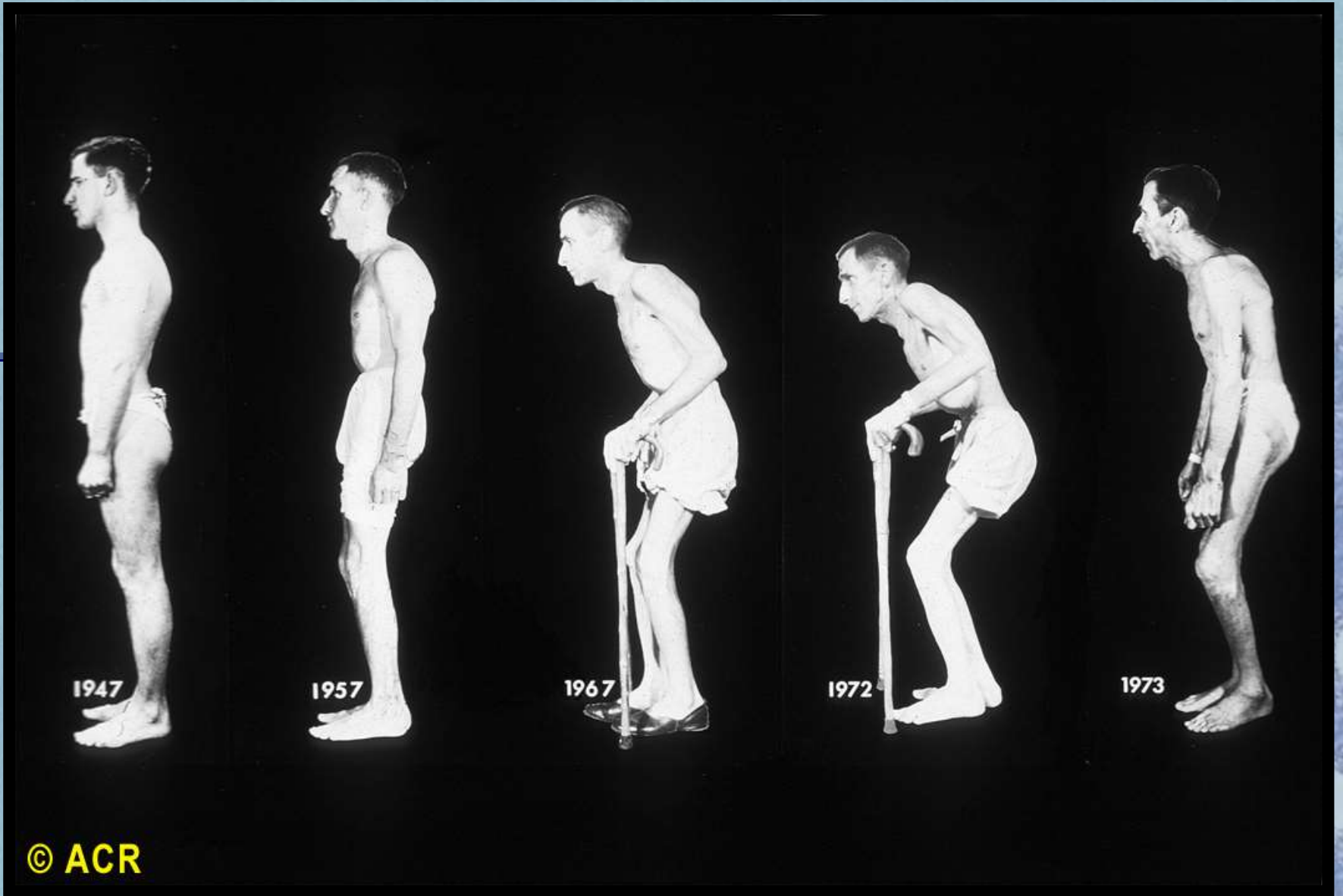


# physical findings

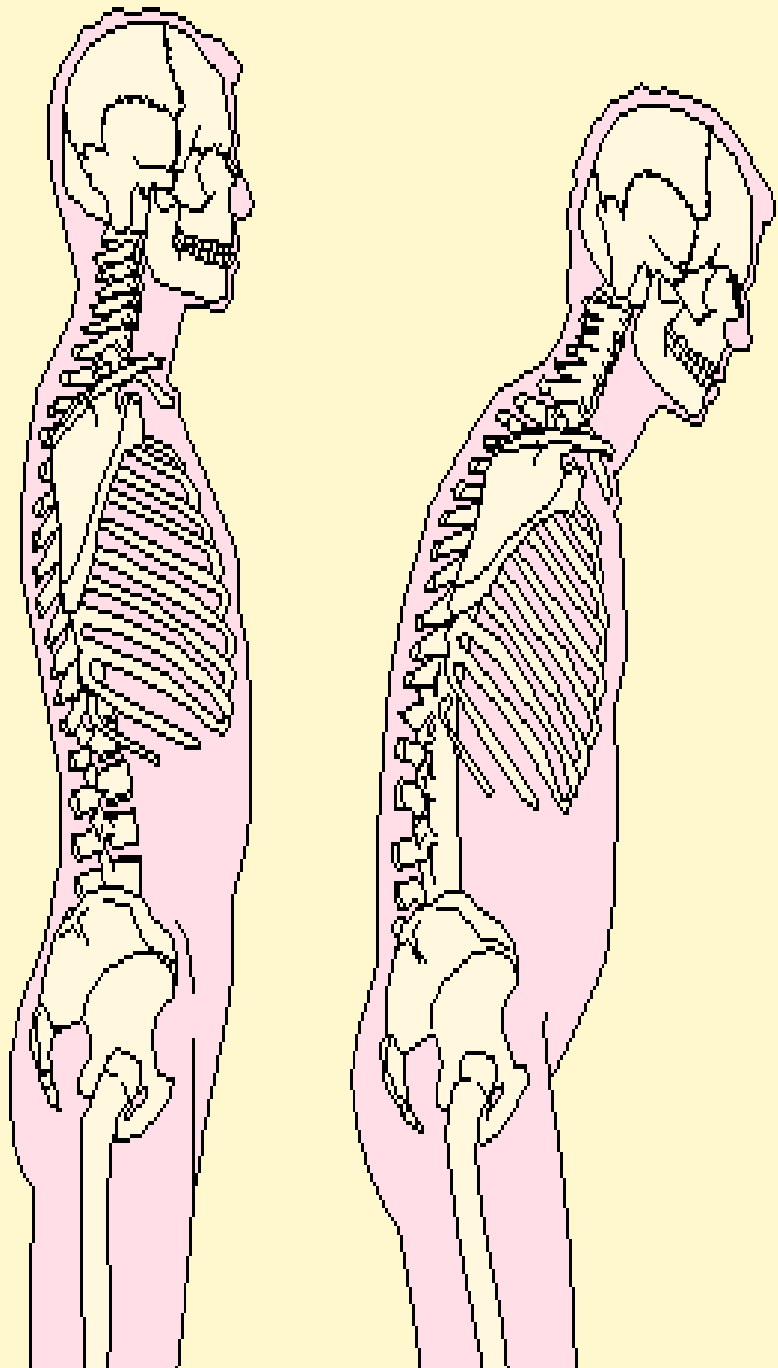
- Chest expansion

# course

- Extremely variable
- **Typical severe untreated case**
- The patient's posture undergoes characteristic changes
- **The disease in women tends to progress less frequently to total spinal ankylosis,**
- Increased prevalence of isolated cervical ankylosis and peripheral arthritis in women
- **The most serious complication of the spinal disease is spinal fracture**









# LABORATORY FINDINGS

- HLA-B27
- ESR
- CRP
- Anemia

# Radiographic and imaging

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- **Sacroiliitis**
- **Whiskering at enthesis (calcaneous, ischial tuberosities, femoral trochanters)**
- **Squaring of vertebrae**
- **Syndesmophytes**
- **Spinal osteoporosis**
- **Hip, shoulder**



# RADIOGRAPHIC FINDINGS

- sacroiliitis

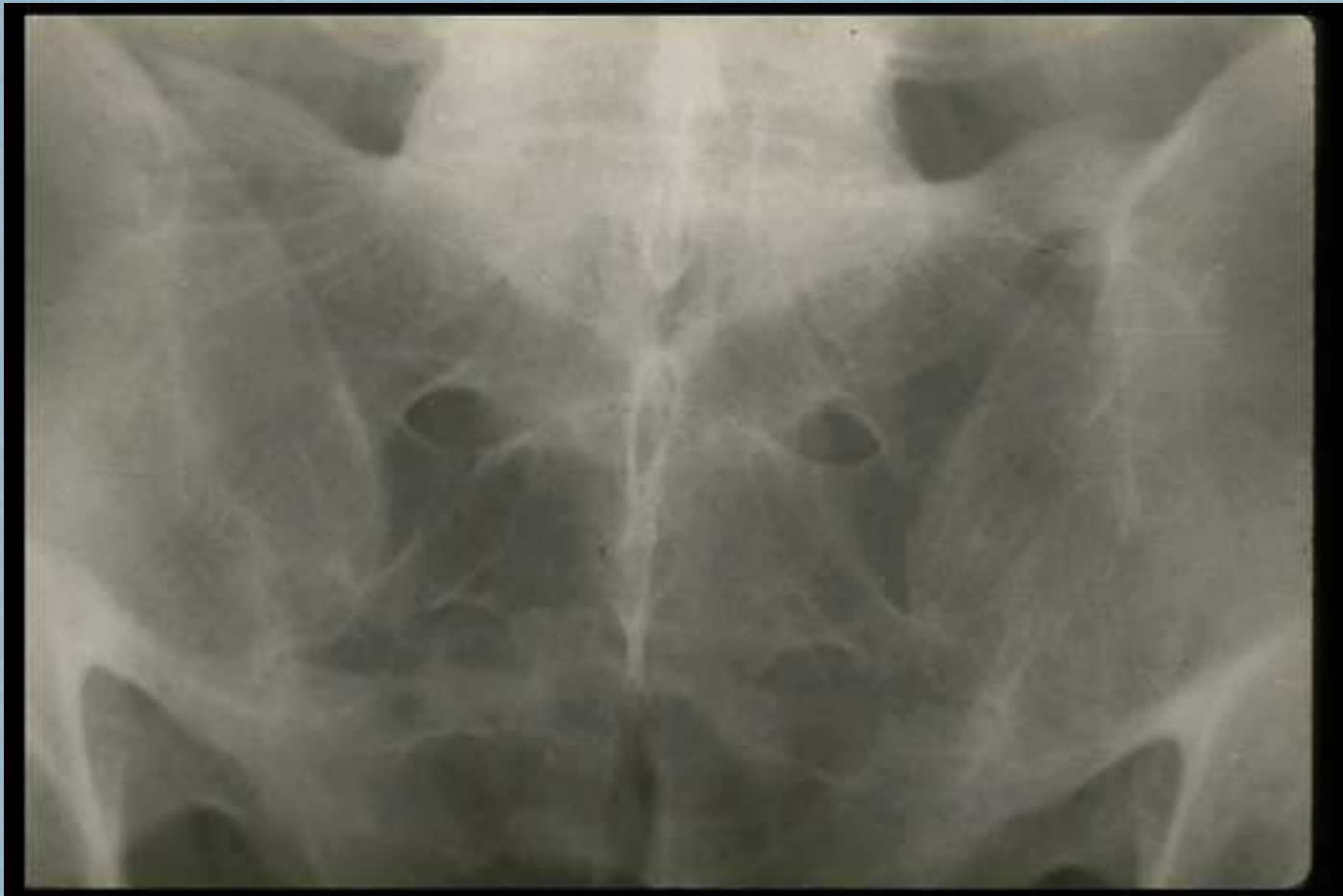




# Pseudo-Widening of Right SI Joint



# Fusion of Bilateral Sacroiliac Joints







# Elbow enthesopathy



© www.rheumtext.com - Hochberg et al (eds)

# Enthesopathy of heels









# Modified New York Criteria for the Diagnosis of AS

- Clinical Criteria

- Low back pain, > 3 months, improved by exercise, not relieved by rest
- Limitation of lumbar spine motion, sagittal and frontal planes
- Limitation of chest expansion relative to normal values for age and sex

- Radiologic Criteria

- Sacroiliitis grade  $\geq 2$  bilaterally or grade 3 – 4 unilaterally

# Definite ankylosing spondylitis

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Unilateral grade 3 or 4 or

Bilateral grade 2-4 sacroiliitis  
and any clinical criterion

## Probable ankylosing spondylitis

- a. The three clinical criteria are present
- b. The radiologic criteria is present without clinical criteria

# Conventional Medical treatment for AS

- Physiotherapy
- NSAIDs
- Sulfasalazine—peripheral arthritis, acute phase response
- Methotrexate
- Corticosteroids (p.o, IA, IV)
- Pamidronate
- Anti-TNF  $\alpha$  therapies



# Treatment

- Exercise
- NSAIDs(Indomethacin 150mg)
- Sulfasalazine
- MTX
- Corticosteroids
- Biologic agents



