Use + Share + Adapt

{ Content the copyright holder, author, or law permits you to use, share and adapt. }

- **Public Domain – Government**: Works that are produced by the U.S. Government. (17 USC § 105)
- **Public Domain – Expired**: Works that are no longer protected due to an expired copyright term.
- **Public Domain – Self Dedicated**: Works that a copyright holder has dedicated to the public domain.
- **Creative Commons – Zero Waiver**
- **Creative Commons – Attribution License**
- **Creative Commons – Attribution Share Alike License**
- **Creative Commons – Attribution Noncommercial License**
- **Creative Commons – Attribution Noncommercial Share Alike License**
- **GNU – Free Documentation License**

Make Your Own Assessment

{ Content Open.Michigan believes can be used, shared, and adapted because it is ineligible for copyright. }

- **Public Domain – Ineligible**: Works that are ineligible for copyright protection in the U.S. (17 USC § 102(b)) *laws in your jurisdiction may differ*

{ Content Open.Michigan has used under a Fair Use determination. }

- **Fair Use**: Use of works that is determined to be Fair consistent with the U.S. Copyright Act. (17 USC § 107) *laws in your jurisdiction may differ*

Our determination **DOES NOT** mean that all uses of this 3rd-party content are Fair Uses and we DO NOT guarantee that your use of the content is Fair.

To use this content you should **do your own independent analysis** to determine whether or not your use will be Fair.
Rheumatoid Arthritis/Pathogenesis and Clinical Presentation of Joint Inflammation and Destruction

M2 Musculoskeletal Sequence

Fall 2008
David A. Fox, M.D.
Reading Assignment
Primer on the Rheumatic Diseases, 13th edition
Chapter 6A, pp 114-121
Chapter 6B, pp. 122-132

Optional in-depth reading
Arthritis and Allied Conditions – A textbook of Rheumatology, WJ Koopman, Ed.
Chapter 52, pp. 1089-1115, 15th Edition

Learning Objectives
1. Understand how to distinguish rheumatoid arthritis (RA) from other forms of arthritis, such as osteoarthritis.
2. Understand the main clinical features of RA in the joints.
3. Understand the major theories concerning the cause of RA.
4. Understand mechanisms of tissue destruction in the RA joint.
5. Understand the role of TNF (tumor necrosis factor) and other key cytokines in RA.

NOTE: The lecture will include interaction with a patient who has had RA for 29 years, and demonstration of some changes that RA can cause in the joints – material that is not included in this handout. The first half hour will focus on an interview with the patient, including opportunities for the students to ask questions.
NB is a 71-year old woman who was diagnosed with rheumatoid arthritis in 1977, involving the hands, wrists, elbows, shoulders, feet and eventually cervical spine. Family history is notable for autoimmune disease affecting both of the patient’s daughters, one with rheumatoid arthritis and the other with systemic lupus. During the first ten years of her illness medical treatment included salicylates, non-steroidals, intramuscular gold, oral gold and prednisone. Methotrexate was first administered in 1989 and her initial visit at the University of Michigan was in 1993. Due to the rheumatoid arthritis the patient had to retire from her position as a high school English teacher.
Rheumatoid Arthritis: 1987 Revised Diagnostic Criteria

Patients must have 4 of 7 criteria:

- *Morning stiffness lasting at least 1 hour
- *Simultaneous arthritis of 3 or more joints
- *Arthritis of hand joints
- *Symmetrical arthritis
- Rheumatoid nodules
- Abnormal serum rheumatoid factor
- Typical changes on PA x-ray film of hand and wrist

* Must persist for at least 6 weeks
Patients may also have another rheumatic disease so long as RA criteria are met.
RA no longer to be designated classical, definite, or probable.

| **Factors Useful for Differentiating Early RA from Osteoarthrosis (Osteoarthritis)** |
|-------------------------------------------------|-----------------|----------------------------|
| **Age of onset**                                | RA: Usually age 20-65 peak incidence in 50’s | Osteoarthrosis: Increases with age |
| **Predisposing factors**                        | HLA-DR4         | Trauma, obesity (OA of the knee), congenital abnormalities (e.g., shallow acetabulum) |
| **Symptoms, early**                             | Morning stiffness | Pain increases through the day and with use |
| **Joints involved**                             | Hands (metacarpophalangeal, proximal interphalangeal joints) wrists, elbows, shoulders, hips, knees, ankles, feet cervical spine. The thoracic spine, lumbar spine and distal interphalangeal joints of the hand are almost never affected. | Distal interphalangeal joints (Heberden’s nodes), proximal interphalangeal joints (Bouchard’s nodes), weight-bearing joints (hips, knees), spine (any region). |
| **Physical findings**                           | Soft tissue swelling, warmth, deformities | Bony osteophytes, minimal soft tissue swelling early |
| **Radiographic findings**                       | Periarticular osteopenia, marginal erosions | Subchondral sclerosis, osteophytes, cartilage loss |
| **Laboratory findings**                         | Increased erythrocyte sedimentation rate: rheumatoid factor, anemia, thrombocytosis, hypoalbuminemia | Normal |
Causes of Chronic Inflammatory Polyarthritis
(a partial list)

- Rheumatoid arthritis
  - Systemic rheumatic disease
    - Systemic lupus
    - Scleroderma
    - Polymyositis
    - Vasculitis
  - Spondylarthropathies
    - Ankylosing spondylitis
    - Reiter’s syndrome
- Psoriatic arthritis
- Gout
- Pseudogout
- Rheumatic fever
- Juvenile rheumatoid arthritis
<table>
<thead>
<tr>
<th>Joints Involved</th>
<th>Common With</th>
<th>Rare In</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temporomandibular</td>
<td>Rheumatoid arthritis, juvenile rheumatoid arthritis</td>
<td>Gout</td>
</tr>
<tr>
<td>Larynx (crico-arytenoid)</td>
<td>Rheumatoid arthritis</td>
<td>All other</td>
</tr>
<tr>
<td>Elbows, wrists, metacarpophalangeals</td>
<td>Any synovitis</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>Distal interphalangeal joints (hand)</td>
<td>Osteoarthritis, psoriatic arthritis</td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Hips</td>
<td>Osteoarthritis, rheumatoid arthritis</td>
<td>Gout</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>Rheumatoid arthritis, juvenile rheumatoid arthritis, psoriasis, osteoarthritis, spondyloarthropathies</td>
<td>Gout</td>
</tr>
<tr>
<td>Thoracolumbar spine</td>
<td>Spondyloarthropathies:</td>
<td>Gout, Rheumatoid Arthritis</td>
</tr>
<tr>
<td></td>
<td>Ankylosing spondylitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psoriatic arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reiter’s syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inflammatory bowel disease-associated arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osteoarthritis</td>
<td></td>
</tr>
</tbody>
</table>
## Synovial Fluid Leukocyte Count ($x10^3$)

<table>
<thead>
<tr>
<th>Condition</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>64</th>
<th>128</th>
<th>PUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>xxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>xxxxxxxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvenile rheumatoid arthritis</td>
<td>xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td>xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Clinical Spectrum of RA

J. Cush, 2002. (All images)
PIP swelling
PIP nodules, MCP swelling/subluxation
Boutoniere deformity of the fingers
Ulnar deviation, MCPs of right hand
Extensor tendon synovitis leading to rupture of extensor tendons
Thenar atrophy from wrist synovitis and median nerve compression
MTP deformities
MTP subluxation with plantar ulceration
Development of bone erosion
Radiographic Evaluation of Arthritis

1. Soft tissue swelling
2. Periarticular demineralization
3. Articular erosions
4. Reactive bone formation
5. Joint narrowing
6. Joint deformity
7. Distribution of involvement
## Radiographic Features of Rheumatoid Arthritis and Osteoarthritis in the Hand

<table>
<thead>
<tr>
<th>Rheumatoid Arthritis</th>
<th>Radiographic Findings</th>
<th>Osteoarthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>prominent, fusiform</td>
<td>soft tissue swelling</td>
<td>mild, focal</td>
</tr>
<tr>
<td>prominent, early</td>
<td>periarticular demineralization</td>
<td>not present</td>
</tr>
<tr>
<td>surface, pocketed or cystic</td>
<td>articular erosions</td>
<td>occasionally, cystic</td>
</tr>
<tr>
<td>minimal</td>
<td>reactive bone formation</td>
<td>prominent osteophytosis and subchondral sclerosis</td>
</tr>
<tr>
<td>mid to late, uniform</td>
<td>joint narrowing</td>
<td>early, irregular</td>
</tr>
<tr>
<td>late, subluxations and dislocations</td>
<td>joint deformity</td>
<td>early, mild subluxation</td>
</tr>
<tr>
<td>wrists, metacarpophalangeal and proximal interphalangeal joints</td>
<td>distribution of involvement</td>
<td>distal interphalangeal, proximal interphalangeal and 1st carpometacarpal joints</td>
</tr>
<tr>
<td>early, asymmetric and non-uniform</td>
<td></td>
<td>asymmetric and non-uniform</td>
</tr>
<tr>
<td>late, symmetric and uniform</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MTP erosions
End-stage RA
Pannus eroding cartilage and bone
Hypothesis for the Cause of RA

Synoviocyte transformation, synoviocyte interaction with macrophages, cartilage and bone

Cellular immune mechanisms
(T cells, cytokines, monocytes)

Humoral immune mechanisms
(RF, immune complexes, complement)

Infection
## Microbial Organisms Proposed as Possible Triggers for RA

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>gram positive cocci</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mycobacteria</td>
</tr>
<tr>
<td></td>
<td>proteus</td>
</tr>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td></td>
<td>mycoplasma</td>
</tr>
<tr>
<td>Viral</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td></td>
<td>parvovirus</td>
</tr>
<tr>
<td></td>
<td>retroviruses</td>
</tr>
<tr>
<td></td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td></td>
<td>rubella</td>
</tr>
<tr>
<td></td>
<td>human herpes virus 6</td>
</tr>
</tbody>
</table>
Twin Studies in RA

Concordance (%)

- Lawrence (N = 93 twin pairs)
- Aho et al (N = 261 twin pairs)
- Silman et al (N = 203 twin pairs)

Genetic Susceptibility

- Familial aggregation and twin studies suggest that genetics may play a role in the development of RA
- Multiple genes involved
- In many populations (excluding most southern Europeans), approximately 80% of patients with RA share a common amino acid sequence in HLA-DR4 molecules (QKRAA) (shared epitope hypothesis)
- The presence of multiple copies of QKRAA may also predict disease severity
- Several non-MHC loci identified, all related to cellular immune responses
Hypothesis for the Cause of RA

Synoviocyte transformation, synoviocyte interaction with macrophages, cartilage and bone

Cellular immune mechanisms (T cells, cytokines, monocytes)

Humoral immune mechanisms (RF, immune complexes, complement)

Infection

1920  1940  1960  1980  2000
Autoantibodies in Rheumatoid Arthritis

- rheumatoid factor (RF)
- anti-nuclear antibodies
- anti-type II collagen
- anti-type IX collagen
- anti-cardiolipin
- anti-neutrophil cytoplasmic antibodies
- anti-keratin antibodies
- anti-perinuclear factor
- anti-calpastatin
- anti-citrullinated peptides (anti-CCP)
RHEUMATOID FACTOR

IgG

IgM
Rheumatoid Factor-
Evidence for a Role in the Pathogenesis of RA

- Most patients with RA have elevated levels of rheumatoid factor.
- High titers of rheumatoid factor correlate with severe articular disease and with development of extra-articular manifestations.
- Pre-existing elevations of rheumatoid factor predict subsequent development of RA.
- Rheumatoid factor production is prominent in RA synovial tissue, and such rheumatoid factors show evidence of antigen-driven affinity maturation.
- Rheumatoid factor can enhance formation of pathogenic immune complexes.
- B cells bearing surface rheumatoid factor can trap antigens contained in immune complexes and present them to primed T cells.
### Occurrence of Rheumatoid Factor in Various Diseases

<table>
<thead>
<tr>
<th>IgM Rheumatoid Factor</th>
<th>Rheumatoid Factor</th>
<th>Noninfectious diseases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequently Present</td>
<td>Usually Absent</td>
<td></td>
</tr>
</tbody>
</table>

#### Rheumatic diseases
- Rheumatoid arthritis
- Sjogren’s syndrome (with or without arthritis)
- Systemic lupus erythematosus
- Progressive systemic sclerosis
- Polymyositis/dermatomyositis
- Cryoglobulinemia

#### Infectious diseases
- Bacterial endocarditis
- Tuberculosis
- Syphilis
- Infectious hepatitis
- Leprosy
- Schistosomiasis

#### Noninfectious diseases
- Normal aged individuals
- Diffuse interstitial pulmonary fibrosis
- Cirrhosis of liver, chronic active hepatitis
- Sarcoidosis
- Waldenstrom’s macroglobulinemia
Anti-CCP and RA

- CCP = cyclic citrullinated peptides
- Arginine $\xrightarrow{\text{PADI}}$ citrulline
- PADI = peptidyl arginine deiminase
- Citrullinated proteins abundant in inflamed synovium
- Smoking $\xrightarrow{\text{citrullination}}$ citrullination of proteins in the lung
Risk Factors for RA

- Genetic
  - MHC Class II alleles
  - Multiple other genes

- Environmental
  - ? infection
  - smoking
Relative Risk of seropositive RA in Individuals with Different SE Genotype

Source: Padyukov, Silva, Stolt, Alfredsson, Klareskog; A&R 2004;50:3085-92
Predicting RA Before its Clinical Onset

- Genes
- Smoking
- Anti-CCP
Hypothesis for the Cause of RA

Synoviocyte transformation, synoviocyte interaction with macrophages, cartilage and bone

Cellular immune mechanisms (T cells, cytokines, monocytes)

Humoral immune mechanisms (RF, immune complexes, complement)

Infection

1920  1940  1960  1980  2000
Evidence for a Central Role for T cells in RA

1. Large numbers of T cells and antigen-presenting cells are present in synovial tissue and fluid.
2. Synovial T cells express activation and memory markers.
3. T cell subsets and possibly clonal T cell populations, accumulate in RA joints in a non-random manner.
4. RA is associated with specific MHC class II alleles (DR and/or DQ).
5. RA is associated with a polymorphism at PTPN22, a tyrosine phosphatase that regulates signaling through the T cell receptor.
6. T cell-directed therapeutic interventions may be effective in RA, and are clearly effective in animal models.
7. T cell cytokines, such as IL-17, that are present in RA joints, mediate biologic effects highly relevant to the pathogenesis of joint inflammation and damage.
Proposed Antigenic Targets for T cells in RA

**Microbial antigens**
- Superantigens, such as staphylococcal toxins
- Epstein-Barr virus antigens
- Heat shock proteins
- Mycobacterial antigens
- Parvovirus antigens
- Peptidoglycan from gram+ bacteria

**Autoantigens**
- Collagen (Type II and other types)
- gp39
- Cartilage link protein
- Cartilage proteoglycan
- 205kDa synovial fluid antigens
- Immunoglobulin binding protein (BiP)
- Heat shock proteins
- Class II MHC (shared epitope)
- IgG (Fc portion)
- RA33 (heterogeneous nuclear ribonucleoprotein A2)
- Filaggrin
- Glycosaminoglycans
RA a Th-17 disease?

- IL-17 is found in abundance in arthritic joints and serum
- Administration of IL-17 worsens CIA (collagen-induced arthritis, an animal model of RA)
- IL-17 R and IL-17 knockout mice develop less severe arthritis
- Neutralizing antibody to IL-17 reduces severity of CIA
- IL-23 deficient mice develop less severe arthritis
- Recent human study shows IL-17 and TNF mRNA in RA synovium predict aggressive disease
IL-17

- 17 kD cytokine
- Secreted by activated and memory T cells, recently defined as a distinct Th subset
- Six isoforms, termed IL-17 A-F
- “IL-17” = IL-17A
- Induced by IL-6 and TGF β
IL-23 and IL-17

- IL-23 is a cytokine made by APC’s
- IL-23 and IL-12 are both heterodimers
- IL-23 and IL-12 share an identical p40 subunit
- IL-23 also contains a p19 subunit, IL-12 a p35 subunit
- IL-12 induces gamma-interferon
- IL-23 induces IL-17
- Co-stimulatory signals can also induce IL-17 when TCR is triggered
T-Helper Cell Differentiation

Christina M Tato and John J. O'Shea, Nature 441, 11 May 2006
Hypothesis for the Cause of RA

Synoviocyte transformation, synoviocyte interaction with macrophages, cartilage and bone

Cellular immune mechanisms (T cells, cytokines, monocytes)

Humoral immune mechanisms (RF, immune complexes, complement)

Infection
Image of cell-cell interactions in rheumatoid arthritis removed
Cell-cell Interactions in RA Synovium

- Leukocyte–endothelial
- T cell–dendritic cell
- T cell–macrophage
- Macrophage–fibroblast
- T cell–fibroblast
- B cell–fibroblast
Cytokines

- Intercellular messenger molecules
- Synthesis
  - Heterogeneity of cell types
  - Inducible
- Effects
  - Primarily local (systemic when produced in abundance)
  - Mediated through
    - Cell-associated receptors on target cells
    - Intracellular signaling and gene transcription
- Regulation controlled at many steps
  - Message induction
  - Soluble receptors
  - Soluble receptor antagonists
Role of Cytokines and Cytokine Inhibitors in Chronic Inflammation

- TNFα (Pro-inflammatory)
- IL-1 (Pro-inflammatory)
- Soluble TNF Receptor
- IL-10 (Anti-inflammatory)
- IL-1 Receptor Antagonist (Anti-inflammatory)

Synthesis and Actions of TNF
Key Actions Attributed to TNF

- **Macrophages**: ↑ Pro-inflammatory cytokines, ↑ chemokines → Increased inflammation
- **Endothelium**: ↑ Adhesion molecules → Increased cell infiltration, ↑ Vascular endothelial growth factor (VEGF) → Increased angiogenesis
- **Hepatocytes**: ↑ Acute phase response → Increased CRP in serum
- **Synoviocytes**: ↑ Metalloproteinase synthesis → Articular cartilage degradation
- **Osteoclast Progenitors**: ↑ RANKL expression → Bone erosions
Activates IL-1

Attacks cartilage

Matrix metalloproteases prostaglandin E\textsubscript{2} IL-6

Helps stimulate migration through endothelium into synovial tissue

Adherence of T-cells and monocytes from circulation

Endothelial Cell

Synovial Fibroblast

Monocyte

Monocyte

Osteoclast

IL-1

Monocyte

ODF

IL-8

Source Undetermined
Actions of IL–1 and Endogenous IL–1Ra

Source of original image:
Role of Interleukin−1 in RA

- Pro-inflammatory cytokine
- Triggers production of other proinflammatory cytokines, including TNF
- Causes T cell/neutrophil accumulation in synovium by inducing expression of endothelial adhesion molecules
- Stimulates production of collagenase and stromelysin
- Stimulates osteoclast differentiation through intermediary TNF family cytokine, RANKL

TNF and IL-1 Play a Critical Role in Osteoclast Differentiation

- **Proliferation**
  - CFU-M
  - M-CSF
  - Cells of monocytes/macrophage lineages
  - CTR (-)
  - TRAP (-)

- **Differentiation**
  - M-CSF + RANKL
  - Prefusion osteoclasts (pOCs)
  - CTR (+)
  - TRAP (+)

- **Survival & Fusion**
  - TNF
  - M-CSF
  - RANKL
  - IL-1
  - Multinucleated osteoclasts
  - CTR (+)
  - TRAP (+)
  - Ruffled border (-)

- **Activation**
  - IL-1
  - TNF
  - Activated osteoclasts
  - CTR (+)
  - TRAP (+)
  - Ruffled border (+)

RANKL:OPG and the Rate of Progression of Joint Destruction in RA

- RANKL promotes joint destruction
- OPG ameliorates RANKL-induced destruction of joints
- The RANKL:OPG ratio correlates well with the rate of joint destruction
- In RA osteoclasts destroy bone while synovial fibroblasts destroy cartilage

## Role of Cytokines in Rheumatoid Arthritis Synovium

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Producing Cells</th>
<th>Target Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Synovial Macrophages and/or Fibroblasts</td>
<td>T cells</td>
</tr>
<tr>
<td>IL-1 ( \beta )</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>TNF( \alpha )</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>endothelium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IL-6</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>IL-8</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>IL-15</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>IL-17</td>
<td>+</td>
<td>-</td>
</tr>
</tbody>
</table>
Additional Source Information
for more information see: http://open.umich.edu/wiki/CitationPolicy

Slide 5: Source Undetermined
Slide 13: Source Undetermined
Slide 14: Source Undetermined
Slide 15: Source Undetermined
Slide 16: Source Undetermined
Slide 17: Source Undetermined
Slide 18: Source Undetermined
Slide 19: Source Undetermined
Slide 20: Source Undetermined
Slide 21: Source Undetermined
Slide 24: Source Undetermined
Slide 25: Source Undetermined
Slide 26: Source Undetermined
Slide 27: Source Undetermined
Slide 28: Source Undetermined
Slide 29: Source Undetermined
Slide 32: David Fox
Slide 36: Source Undetermined
Slide 41: David Fox
Slide 53: Source Undetermined
Slide 54: Source Undetermined
Slide 57: Source Undetermined
Slide 58: David Fox
Slide 59: Source Undetermined
Slide 62: David Fox
Slide 65: Sources Undetermined