# Immunology in Rheumatic Diseases

- Knowledge of immunology forms the basis of understanding many of the Rheumatologic diseases and has become the focus of many exciting new treatment strategies …….

## AIMS OF THIS LECTURE

- Introduce the important components of the immune system
- Show how they interact & protect the body **(IMMUNITY)**
- Without attacking itself (TOLERANCE)
- Demonstrate what happens when things go wrong & the body turns against itself (AUTOIMMUNITY)
- Provide examples of immunology in clinical Rheumatology

## Topics covered

1. Immune mechanisms
2. Tolerance
3. Autoimmunity

4. Rheumatologic diseases
   - Rheumatoid arthritis
   - Systemic Lupus Erythematosis
   - Spondarthropathies
   - Inflammatory myopathies
   - Systemic sclerosis
   - Osteoarthritis

## 1. IMMUNE MECHANISMS

2. Tolerance
3. Autoimmunity

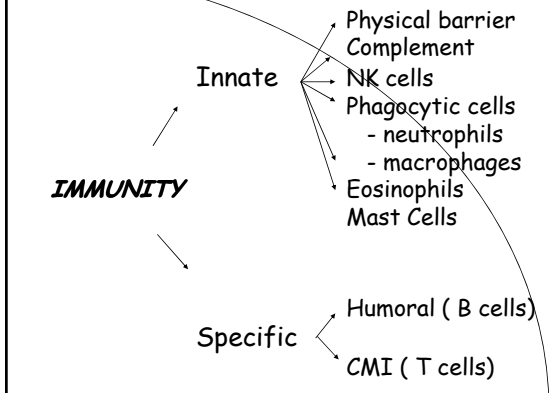
4. Rheumatologic diseases
   - Rheumatoid arthritis
   - Systemic Lupus Erythematosis
   - Spondarthropathies
   - Inflammatory myopathies
   - Systemic sclerosis
   - Osteoarthritis

## Immune Mechanisms

- Overview
- Specific components
  - Physical barrier
  - Complement
  - Cells
  - MHC
  - Cytokines
- Activation of adaptive immune system by the innate system

## Immunity Can Be Divided Into 2 Main Components:

1. Innate immunity
   - Rapid acting, nonspecific
2. Specific or adaptive immunity
   - Slower onset of action
   - Targets pathogens that escape the innate immune system
   - Activated by the innate immune system

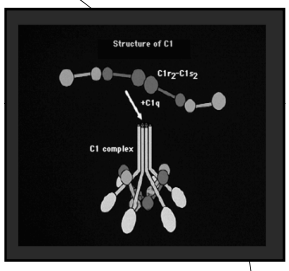



## Barriers against infection

- Microorganisms are kept out of the body by:
  - Skin
  - Bactericidal fluids eg tears
  - Secretion of mucous
  - Gastric acid
  - Microbial antagonism

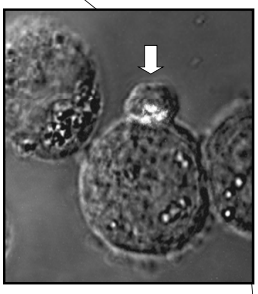
## Complement

- A group of serum proteins
- which act in an enzymatic cascade
- Produce molecules involved in
  - Cell lysis
  - phagocytosis
  - inflammation



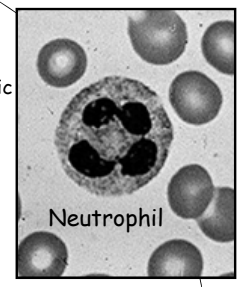

## Cells in the Innate System (1)

- NK ( Natural killer) cells
  - Large granular lymphocyte
  - Lyses viral infected cells & tumor cells
  - *Note the smaller NK cell destroying its target cell by pore forming perforins*



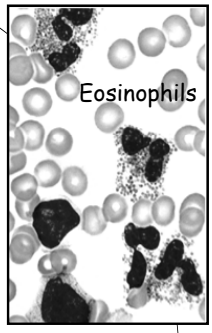
## Cells in the Innate System (2)

- Phagocytic cells
  1. Neutrophils
     - 70% of circulating WCC
     - Major circulating phagocytic cell
  2. Macrophages
     - Large phagocytic cell derived from blood monocyte
     - Also acts as an antigen presenting cell ( APC)



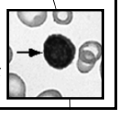
## Cells in the Innate System (3)

- Eosinophils
  - Granulocytes important in the killing of parasites
- Mast cells
  - Contain abundant granules
  - complement components trigger degranulation
  - results in release of inflamatory mediators including histamine & leukotrienes



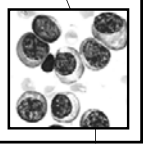

## Cells in the adaptive system(1)

- **B & T lymphocytes**
  - are the major cells of the adaptive system
- **CD4 T cells**
  - help to stimulate B cell antibody production
  - activate macrophages
- **CD8 T cells** ( cytotoxic cells)
  - kill target cells expressing foreign antigen

LYMPHOCYTE 

## Cells in the adaptive system (2)

- **B cells**
  - May mature to become plasma cells producing antibodies. The function of antibodies are to :
    - directly stimulate or neutralise its target
    - Activate complement
    - form a bridge between the target & cytotoxic cell eg macrophages & NK cells) → Antibody dependant cellular cytotoxicity ( ADCC)
  - Act as antigen presenting cells
    - (More about these cells later…….)

PLASMA CELLS 

## Antigen Presenting Cells

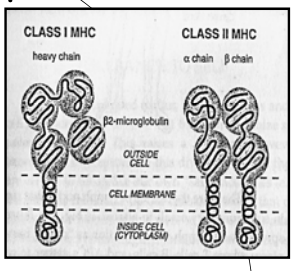
- Unlike the other cells, $T_H$ cells only recognise antigen that is properly presented with MCH by other cells
- These specialised cells are called antigen presenting cells
- They include macrophages, B cells, fibroblasts & dendritic cells

## Major Histocompatibility Complex (MHC)

- Antigen is ingested by the antigen presenting cell then presented on its surface in molecules called major Histocompatibility complex
- MHC are also the molecules responsible for rejection in transplant organs

## Major Histocompatibility Complex

- MHC proteins = HLA (Human Leucocyte Antigen) in humans
- Molecules on cell surfaces which can display antigen
- Products of a region of highly polymorphogenic genes on chromosome 6
- 2 types :
- Class I &
- Class II



## Comparison of MHC Class I & II Molecules

| | Class I | Class II |
|---|---|---|
| Genes | HLA A/B/C | HLA D |
| Expressed on | All nucleated cells | APCs – B cells, macrophages & dendritic cells |
| Size | 9 to 10 amino acids (smaller) | 12 to 28 amino acids (larger) |
| Source of antigen displayed | Intracellular eg viral infections | Extracellular eg bacterial infections |
| Antigen presented to | CD8+ T cells | CD4+ cells |

( APC = Antigen presenting cell)

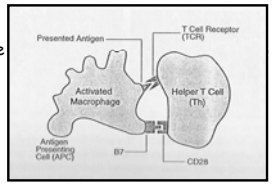
## Activation of the Adaptive Immune System

- Antigens that escape the innate immune system encounter the adaptive system
- Adaptive immune system – powerful ∴must be activated

## Activation of the Adaptive Immune System

In this diagram, the macrophage represents the innate system & the $T_H$ cell, the adaptive system

2. Ag presented on cell surface with MHC

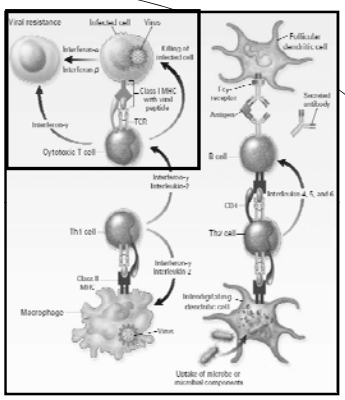



3. T cell recognises its cognate Ag

1. APC eg Macrophage ingests Ag

4. 2nd signal required = protein on APC + a $T_H$ cell receptor

5. ACTIVATION
&
6. Cytokine production

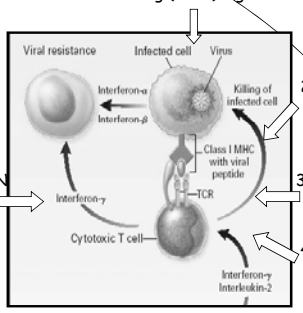


This diagram shows the immune system in action.

Take a closer look.....

## Do these steps look familiar?

1. Ag (virus) ingested




2. Ag presented on cell surface with MHC

5. ACTIVATION
&
6. Cytokine production

3. T cell recognises its cognate Ag

4. 2nd signal required = protein on APC + a T cell receptor

## Cytokines

- Cells of the immune system communicate with each other using cytokines

## Cytokines

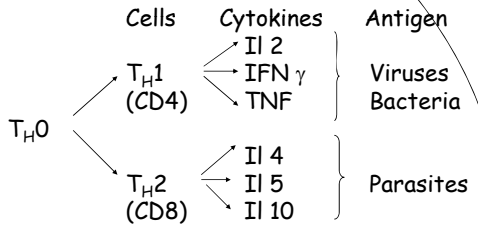
- Protein hormones
- Mediate the effect of the innate & specific immunity
- Autocrine/ paracrine/endocrine
- Effects include cell activation, division, apoptosis, movement

## Cytokine types

- *Interleukins* –
  - produced by leucocytes & have effects mainly on WBC
- *Chemokines* –
  - chemoattractants
- *Colony stimulating factors* –
  - differentiation & proliferation of stem cells
- *Interferons* –
  - interfere with viral replication
- Eg.
  Il-2 = a growth factor that stimulates CTLs & NK cells to proliferate
  TNF activates primed macrophages & NK cells

## Cells & cytokine production

Cells produce different subgroups of cytokines which will instruct the innate & adaptive systems to produce cells & antibodies against specific antigens.
Here is an example




1. **Immune Mechanisms**

## 2. TOLERANCE

3. Autoimmunity

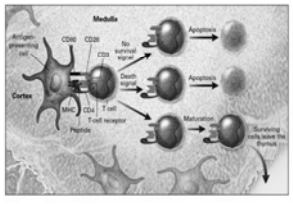
4. Rheumatologic diseases
   - Rheumatoid arthritis
   - Systemic Lupus Erythematosis
   - Spondarthropathies
   - Inflammatory myopathies
   - Systemic sclerosis
   - Osteoarthritis

## Tolerance Is…….

the immunologic unresponsiveness to self antigens

- It allows the immune system to protect the body without turning against itself
- The focus is on the adaptive immune system
- T & B cells must be able to discriminate self from non self
- This occurs centrally & peripherally

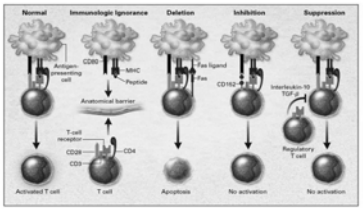
## Central T Cell Tolerance




NEJM 2001;344(9): 655 – 664.

- T cells are produced in the bone marrow & migrate to the thymus.
- Here they go through a rigorous selections process.
- Only T cells that react to antigen but not self exit.
- The rest die by apoptosis.

## Peripheral T Cell Tolerance




If autoreactive T cells enter the circulation, there are several mechanisms that can prevent an autoimmune reaction.

NEJM 2001;344(9): 655 – 664.

## B Cell Tolerance

- CENTRAL
  - Clonal deletion of autoreactive B cells in the bone marrow, spleen & lymph nodes.
- PERIPHERAL
  - Lack of help from T cells is the predominant factor.

1. **Immune Mechanisms**
2. **Tolerance**

## 3. AUTOIMMUNITY

4. Rheumatologic diseases
   - Rheumatoid arthritis
   - Systemic Lupus Erythematosis
   - Spondarthropathies
   - Inflammatory myopathies
   - Systemic sclerosis
   - Osteoarthritis

## Autoimmunity

- Breakdown in mechanisms preserving tolerance to self
- Severe enough to cause a pathological condition

## Autoimmune diseases

- Organ specific e.g.
  - Insulin dependant diabetes
  - Myasthenia gravis
- Multisystem e.g.
  - Rheumatoid arthritis
  - SLE

## Mechanisms

GENETIC FACTORS
- Aberant MHC/HLA - present self peptide
- Autoreactive T & B cells

ENVIRONMENTAL FACTORS
- Infectious/ noninfectious triggers
- Hypothesis : Molecular mimicry

AUTOIMMUNE DISEASE

Molecular mimicry :
The antigen looks similar to a self-peptide. As a result, the body produces an immune response to the trigger factor as well as to self.

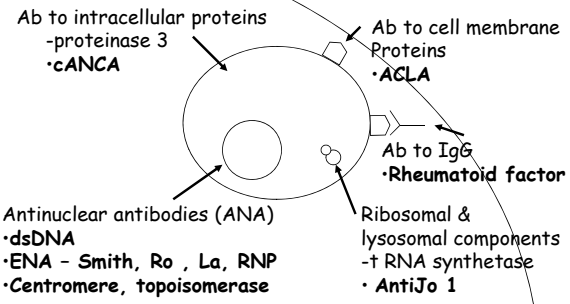
## Autoantibodies in Connective Tissue Diseases

- Produced by B cells
- May pathogenic eg.
  - Form immune complexes in lupus nephritis
- Markers of certain diseases
- Not diagnostic
  - Apart from rheumatic disorders, they may be found in normal population & with other conditions
  - *Therefore only test when clinically indicated.*

## Autoantibodies associated with disease

| DISEASE | AUTOANTIBODY |
|---|---|
| Rheumatoid Arthritis | Rheumatoid factor |
| SLE | ANA,dsDNA, Smith |
| Scleroderma | ANA,centromere, topoisomerase |
| Antiphospholipid Syndrome | Anticardiolipin (ACLA) |
| Sjogren's syndrome | Ro, La |
| Polymyositis | Jo-1 |
| Dermatomyositis | Mi-2 |
| Wegener's granulomatosis | C-ANCA |

## Cellular Targets for autoantibodies




This diagram depicts the autoantibodies & their respective target antigens

1. Immune Mechanisms
2. Tolerance
3. Autoimmunity

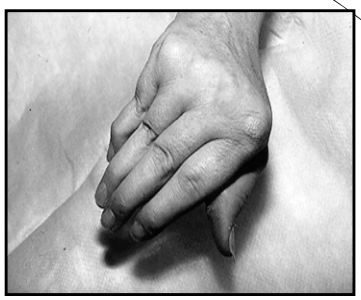
## 4. Rheumatologic conditions

- Rheumatoid arthritis
- Systemic Lupus Erythematosis
- Spondarthropathies
- Inflammatory myopathies
- Systemic sclerosis
- Osteoarthritis

The above disease will be used to highlight some of the concepts of Immunology in Rheumatology.

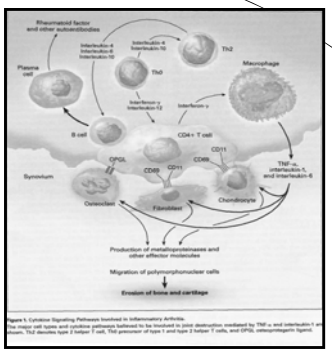
Note that the details of each pathway does NOT have to be memorised.

## Rheumatoid Arthritis



A symmetrical peripheral polyarthritis of unknown aetiology that leads to joint deformity & destruction due to erosion of cartilage & bone

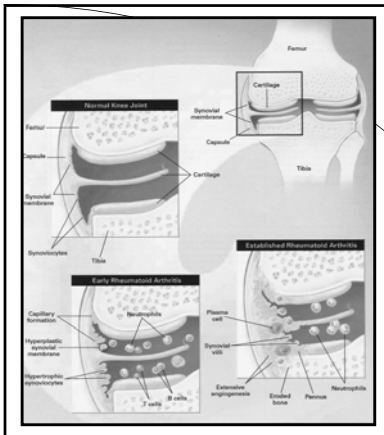
## The immune mechanisms in RA



- Note:

1. The interaction between the cells of the innate & adaptive immune systems
2. The cytokines produced are targets for newer therapy in RA

NEJM 2001; 344 (12): 907 – 916




## RA

- The inflammatory process results in damage to cartilage & bone

NEJM 2001; 344 (12): 907 – 916.

## Rheumatoid Factor

TABLE 74.3 SENSITIVITY AND SPECIFICITY OF RHEUMATOID FACTOR

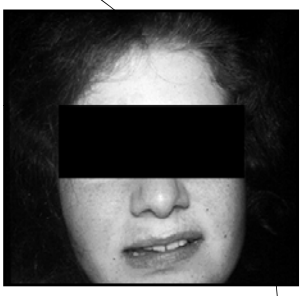
| Diagnosis | ≥15U/ml | ≥50U/ml | ≥100U/ml |
|---|---|---|---|
| Rheumatoid arthritis | 66* | 46 | 26 |
| Sjögren's syndrome | 62 | 52 | 33 |
| Systemic lupus erythematosus | 27 | 10 | 3 |
| Mixed connective tissue disease | 23 | 13 | 6 |
| Scleroderma | 44 | 18 | 2 |
| Polymyositis | 18 | 0 | 0 |
| Reactive arthritis | 0 | 0 | 0 |
| Osteoarthritis | 25 | 4 | 4 |
| Healthy controls | 13 | 0 | 0 |
| Sensitivity (%) | 66 | 46 | 26 |
| Specificity (%) | 74 | 88 (92†) | 95 (98†) |

* Percentage of positive patients. †Specificity when a diagnosis of Sjögren's syndrome can be excluded.

- Rheumatoid Factor is an autoantibody produced in RA
- It is however produced in several other conditions ∴ the clinical features are important in making the diagnosis

## Systemic Lupus Erythematosis

A generalised connective tissue disorder affecting many organs and characterised by the production of many autoantibodies



## ARA Criteria for the diagnosis of SLE

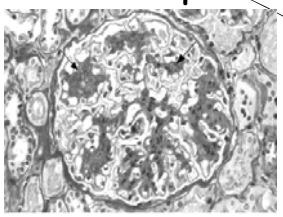
- Note:

1. Many organs can be affected
2. Several auto-antibodies are associated with SLE

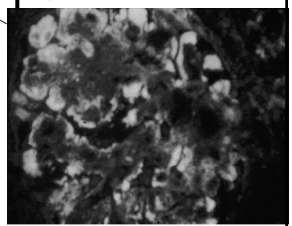
ARA Criteria for Diagnosis of Systemic Lupus Erythematosus

| Criterion | Definition |
|---|---|
| Malar rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds |
| Discoid rash | Erythematosus raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring may occur in older lesions |
| Photosensitivity | Skin rash as a result of unusual reaction to sun-light, by patient history or physician observation |
| Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician |
| Arthritis | Nonerosive arthritis involving 2 or more peripheral joints, characterized by tenderness, swelling, or effusion |
| Serositis | Pleuritis — convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion OR<br>Pericarditis — documented by EKG, rub or evidence of pericardial effusion |
| Renal disorder | Persistent proteinuria greater than 0.5 grams per day or greater than 3+ if quantitation not performed OR<br>Cellular casts — may be red cell, hemoglobin, granular, tubular, or mixed |
| Neurologic disorder | Seizures OR psychosis — in the absence of offending drugs or known metabolic derangements (uremia, ketoacidosis, or electrolyte imbalance) |
| Hematologic disorder | Hemolytic anemia — with reticulocytosis OR<br>Leukopenia — less than 4,000/mm3 total on two or more occasions OR<br>Lymphopenia — less than 1,500/mm3 on two or more occasions OR<br>Thrombocytopenia — less than 100,000/mm3 in the absence of offending drugs |
| Immunologic disorders | Positive antiphospholipid antibody OR<br>Anti-DNA — antibody to native DNA in abnormal titer OR<br>Anti-Sm — presence of antibody to Sm nuclear antigen OR<br>False positive serologic test for syphilis known to be positive for at least six months and confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test |
| Antinuclear antibody | An abnormal titer of antinuclear antibody by immuno fluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome |

## Lupus Nephritis



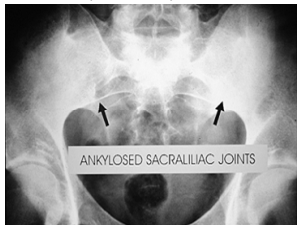
**Mesangial proliferative glomerulonephritis** Light micrograph of a mesangial glomerulonephritis showing segmental areas of increased mesangial matrix and cellularity (arrows). This finding alone can be seen in many diseases, including lupus nephritis and IgA nephropathy. Courtesy of Helmut Rennke, MD.

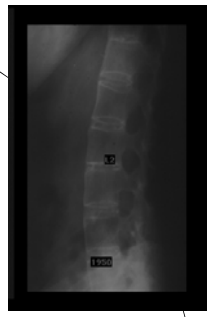


**Diffuse proliferative lupus nephritis** Kidney biopsy from a patient with diffuse proliferative lupus nephritis showing, on immunofluorescence microscopy, massive lumpy bumpy deposits of IgG. Courtesy of Peter H. Schur, MD.

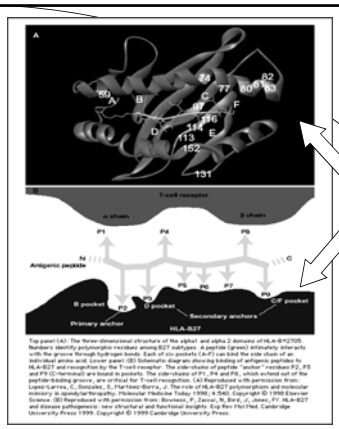
- The kidney biopsy on the right is from a patient with diffuse proliferative lupus nephritis shows massive deposits of IgG on immunofluorescence

## Ankylosing Spondylitis



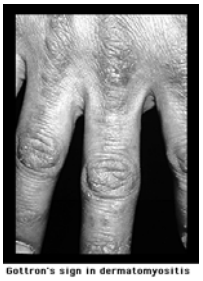
AS is a chronic inflammatory disease of the axial skeleton manifested by back pain & progressive stiffness of the spine



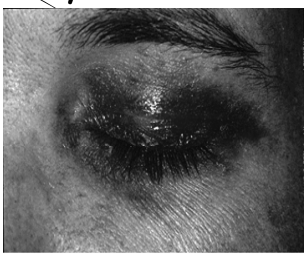
## Ankylosing Spondylitis

- The prevalence of the MHC, HLA B27 is high in Caucasians but rare in Black populations with Ankylosing Spondylitis

## Dermatomyositis



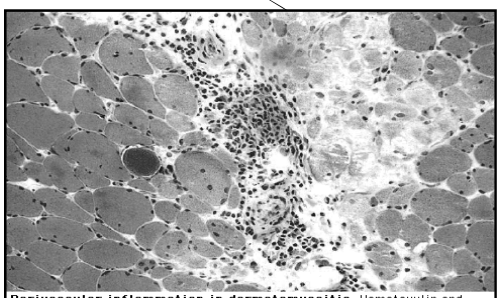
Gottron's sign in dermatomyositis



Heliotrope rash in dermatomyositis A

An idiopathic inflammatory myopathy associated with certain characteristic cutaneous manifestations

Note: the inflammatory infiltrate in the muscle biopsy of this patient with Dermatomyositis



**Perivascular inflammation in dermatomyositis** Hematoxylin and eosin stain (20x) of a muscle biopsy from a patient with dermatomyositis showing perivascular and perimysial inflammation, as well as perifascicular necrosis. Courtesy of William W Pendlebury, MD.

## Scleroderma

The term encompasses a heterogeneous group of conditions linked by the presence of thickened sclerotic skin lesions

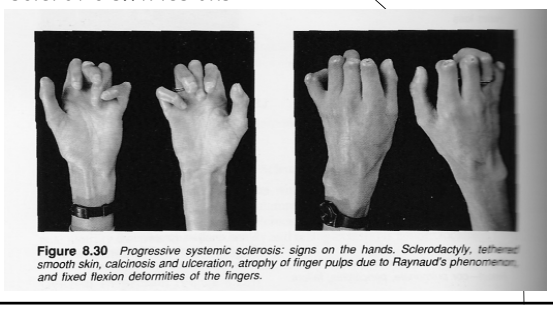
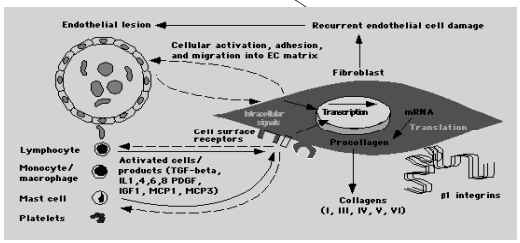


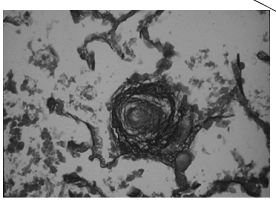
**Figure 8.30** *Progressive systemic sclerosis: signs on the hands. Sclerodactyly, tethered smooth skin, calcinosis and ulceration, atrophy of finger pulps due to Raynaud's phenomenon, and fixed flexion deformities of the fingers.*

The inflammatory process in Scleroderma results a marked fibrotic precess responsible for many of the clinical features

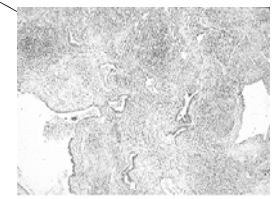



**Paracrine interactions between cells involved in scleroderma** – Activated cells of the immune system, endothelial cells, and fibroblasts are all capable of releasing cytokines and growth factors which might exert a paracrine or autocrine influence on other cells. This could in turn modulate cellular properties and induce production of the same or other factors. Thus, there is the potential for local cytokine loops to initiate and perpetuate the immunologic, vascular, and fibrotic components of scleroderma.

## Scleroderma Lung Disease



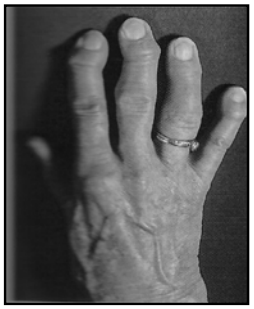
**Pulmonary arterial disease in scleroderma** Primary pulmonary vascular disease in a patient with scleroderma characterized by marked lamellar intimal thickening. Similar "onion-skin" changes can be seen in the small arteries in scleroderma renal disease. Courtesy of Professor B Corrin, Royal Brompton and National Heart Hospital, London, UK.



**Cellular infiltrate in fibrosing alveolitis** Lung biopsy from a patient with scleroderma, fibrosing alveolitis, and ground glass opacification on high resolution CT scan. Note the marked interstitial cellular infiltration. Courtesy of Professor B Corrin, Royal Brompton and National Heart Hospital, London, UK.

2 important lung diseases which occur due to the inflammatory process in Scleroderma

## Osteoarthritis



Immune mechanisms have even been shown to play a role in OA…….

## Immune pathways in Osteoarthritis

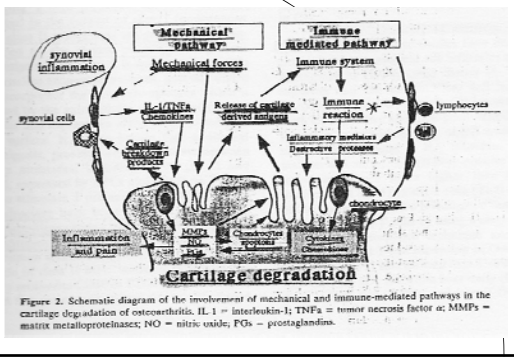



Figure 2. Schematic diagram of the involvement of mechanical and immune-mediated pathways in the cartilage degradation of osteoarthritis. IL 1 = interleukin-1; TNFa = tumor necrosis factor α; MMPs = matrix metalloproteinases; NO = nitric oxide; PGs = prostaglandins.

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## The End…….