Disease Modifying Anti-Rheumatic Drugs (DMARDs)

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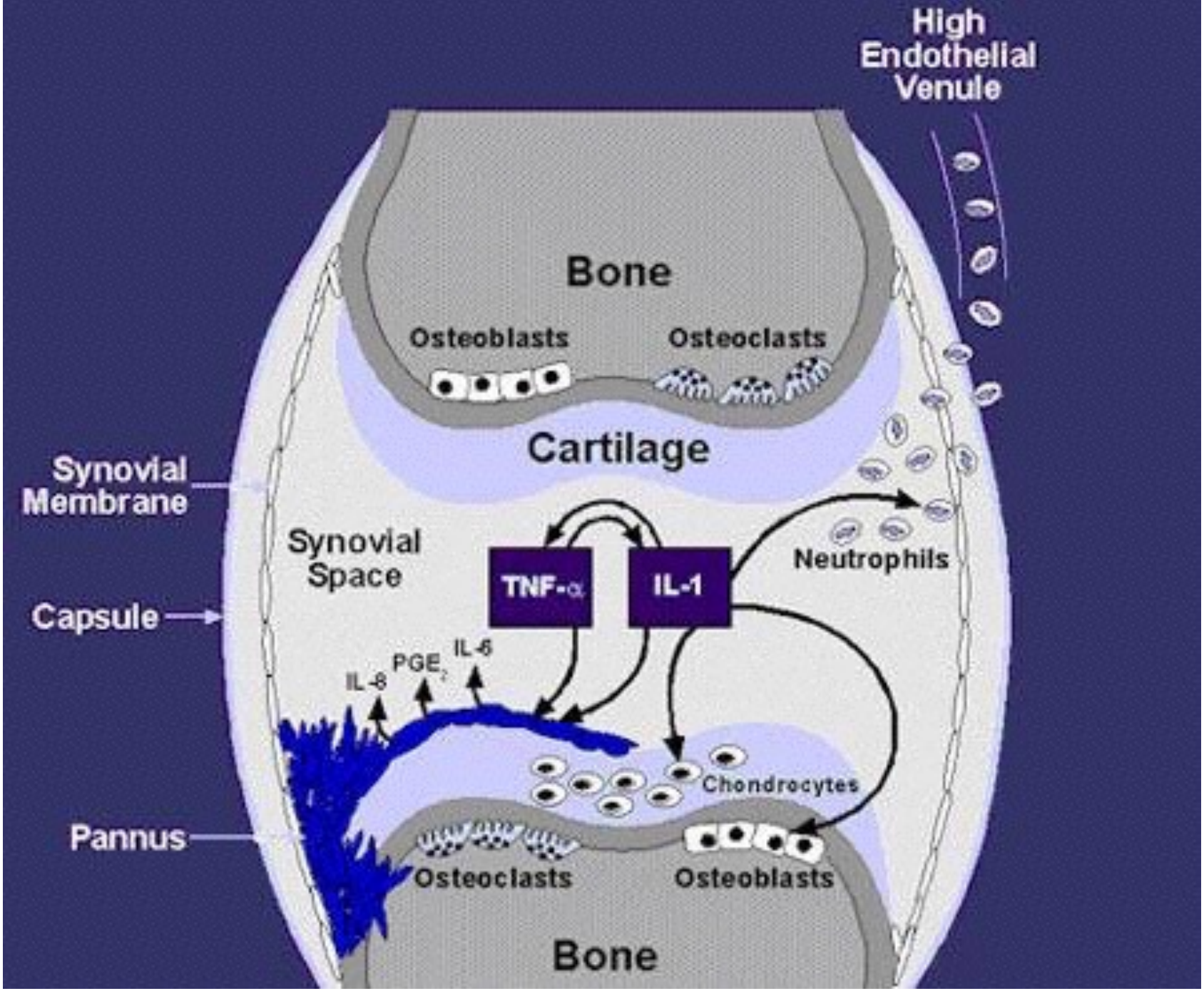
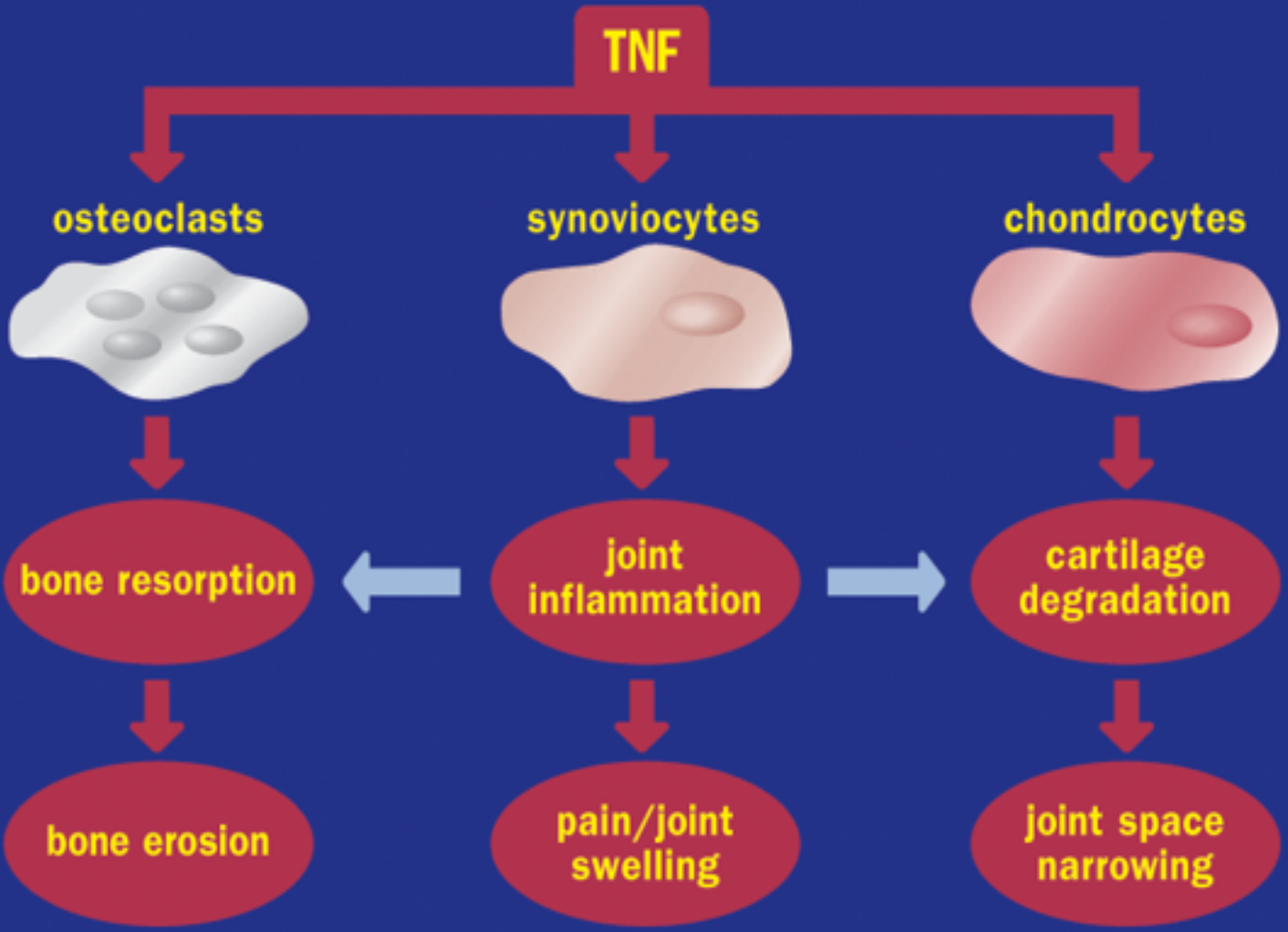
Rheumatoid arthritis

- Chronic synovial inflammation
- Autoimmune
- Cytokine networks are responsible for inflammation & joint destruction
- Tumor Necrosis Factor-α (TNF-α)
- Interleukins - 1,6,17

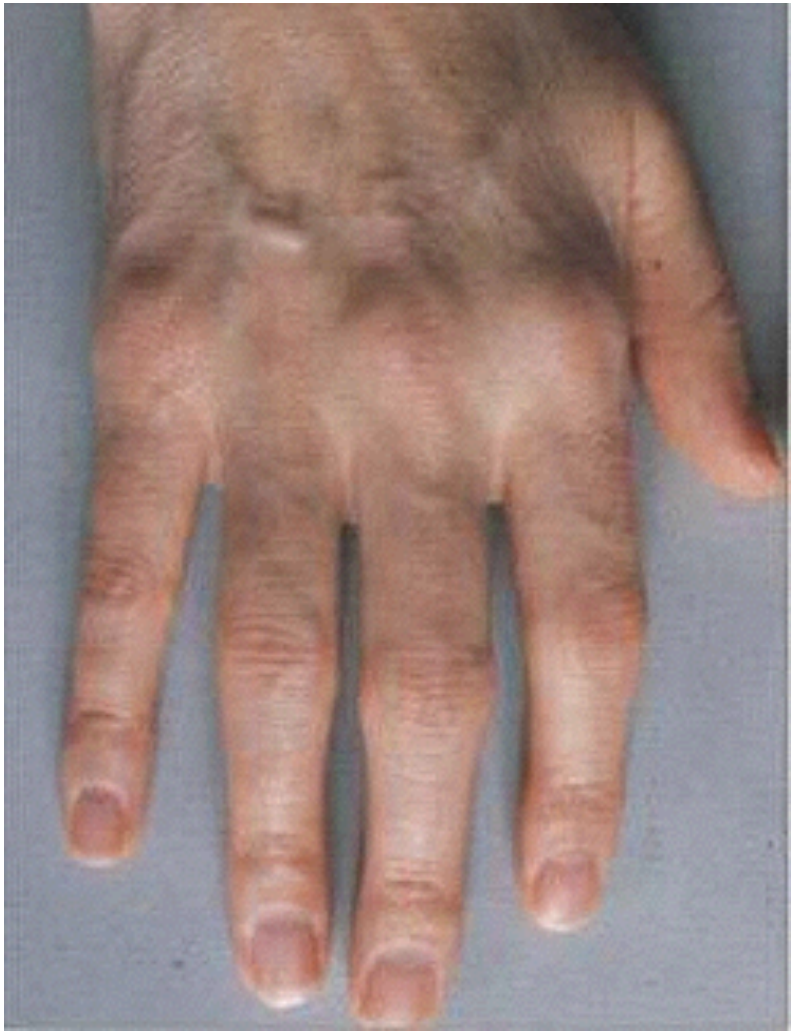

High Endothelial Venule
Bone
Osteoblasts
Osteoclasts
Cartilage
Synovial Membrane
Synovial Space
TNF-α
IL-1
Neutrophils
Capsule
IL-8
PGE2
IL-6
Chondrocytes
Pannus
Osteoclasts
Osteoblasts
Bone

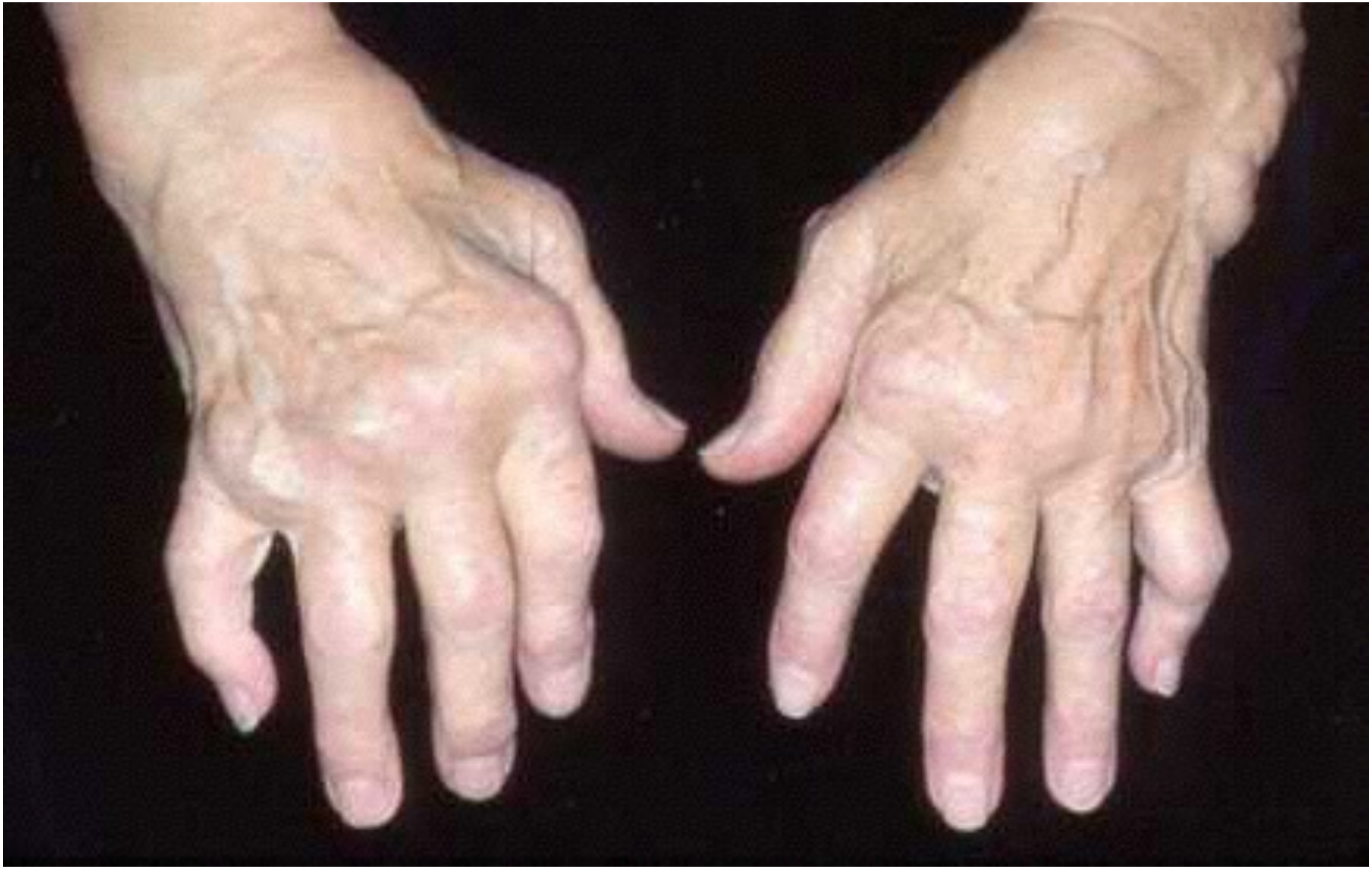
Destructive effects of TNF

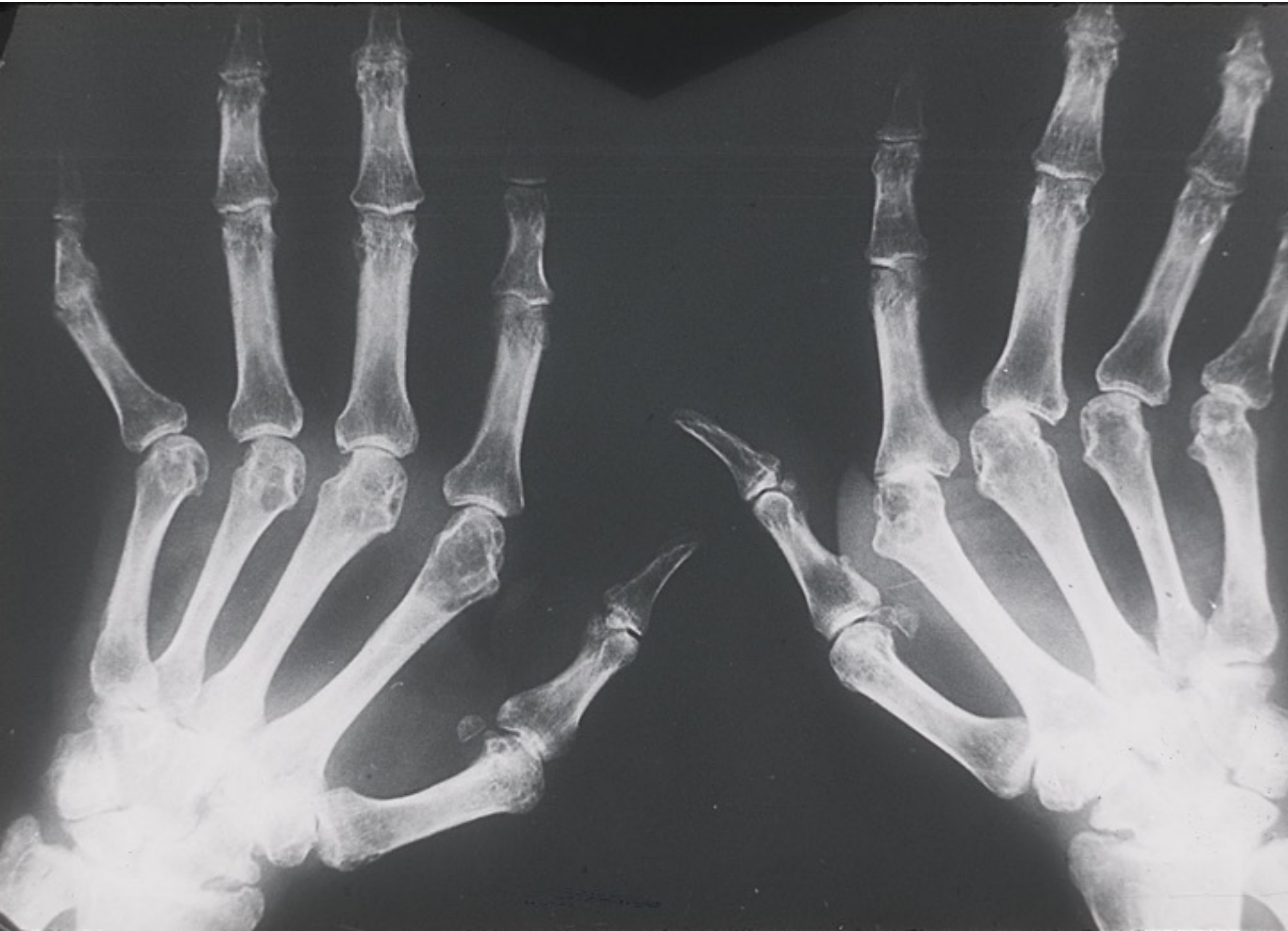


Disability in Early RA

- Inflammation
  - Swollen
  - Stiff
  - Sore
  - Warm
- Fatigue
- Potentially Reversible







Drugs for RA

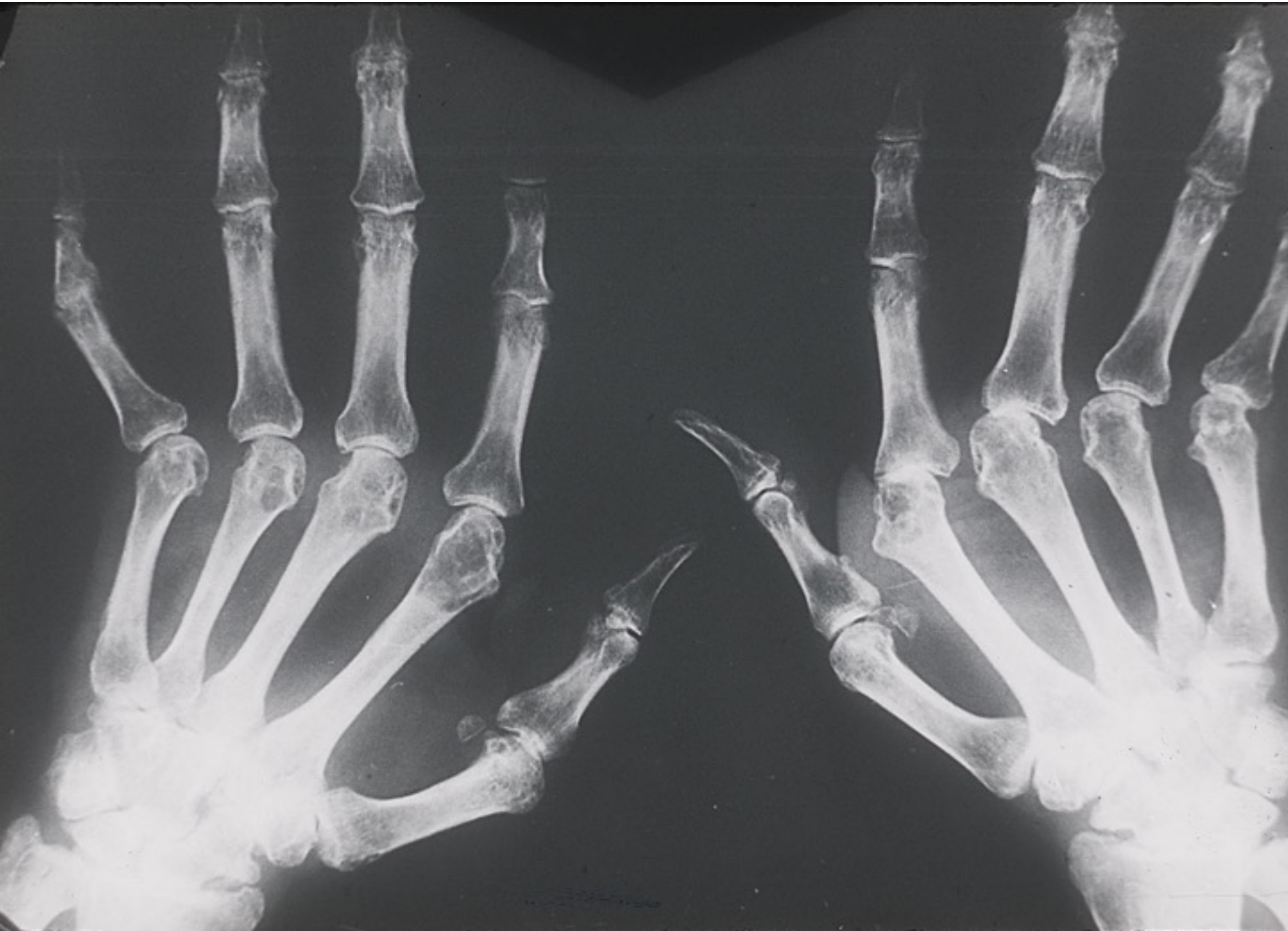
- Nonsteroidal anti-inflammatory drugs (NSAIDs)
- Disease-modifying anti-rheumatic drugs (DMARDs)
  - Synthetic
  - Biologic
- Glucocorticoids

DMARDs

Disease Modifying Anti-Rheumatic Drugs

- Reduce swelling & inflammation
- Improve pain
- Improve function

•Have been shown to reduce radiographic progression (erosions)



Synthetic DMARDs

- Methotrexate
- Sulphasalazine
- Chloroquine
- Hydroxychloroquine
- Cyclophosphamide
- Cyclosporin
- Leflunomide
- Mycophenolate Mofetil

Methotrexate (MTX)

- “Gold standard” for DMARD therapy (first line DMARD treatment of RA)

- Absorption variable
- Elimination mainly renal
- General Mechanism of action: Dihydrofolate reductase inhibitor
- ↓ thymidine & purine nucleotide synthesis

MTX adverse effects

Mechanism of action at the low doses in RA inhibition of aminoimidazolecarboxamide ribonucleotide (AICAR) transformylase and thymidylate synthetase.

AICAR, accumulates intracellularly, competitively inhibits AMP deaminase, leading to an accumulation of AMP.
The AMP is released and converted extracellularly to adenosine, which is a potent inhibitor of inflammation.

MTX adverse effects

- Hepatotoxicity
- Bone marrow suppression
- Dyspepsia, oral ulcers
- Pneumonitis
- Teratogenicity

- Folic acid reduces GI & BM effects
- Monitoring
- FBC, ALT, Creatinine

Sulphasalazine

- Sulphapyridine + 5-aminosalicylic acid

- Remove toxic free radicals
- Remission in 3-6 month

- Elimination hepatic

- Dyspepsia, rashes, BM suppression

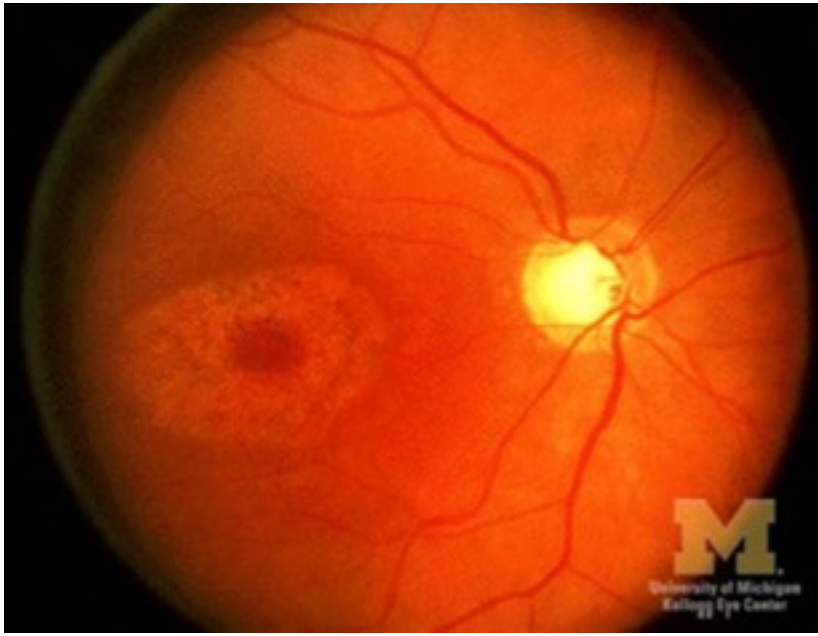
Chloroquine, Hydroxychloroquine

- Mechanism unknown
- Interference with antigen processing ?
- Anti- inflammatory and immunomodulatory

- For mild disease
- Take a month to see the effect

Side effects

- Irreversible Retinal toxicity, corneal deposits
- Ophthalmologic evaluation every 6 months



Leflunomide

- Competitive inhibitor of dihydroorotate dehydrogenase (rate-limiting enzyme in de novo synthesis of pyrimidines)

- Reduce lymphocyte proliferation

Leflunomide

- Oral
- T ½ - 4 – 28 days Elimination hepatic

- Action in one month
- Avoid pregnancy for 2 years

Side effects

- Hepatotoxicity
- BM suppression
- Diarrhoea
- rashes

CYCLOPHOSPHAMIDE

Mechanism of Action

Cyclophosphamide is a synthetic DMARD. Its major active metabolite is phosphoramide mustard, which cross-links DNA to prevent cell replication. It suppresses T-cell and B-cell function by 30–40%; T-cell suppression correlates with clinical response in the rheumatic diseases.

CYCLOPHOSPHAMIDE

Indications

Cyclophosphamide is active against rheumatoid arthritis when given orally at dosages of 2 mg/kg/d but not intravenously.

It is used regularly to treat systemic lupus erythematosus, vasculitis, Wegener's granulomatosis, and other severe rheumatic diseases.

Toxicities:

dose-related …… primarily in rapidly growing tissues: bone marrow, gastrointestinal tract, and reproductive system.

Nausea and vomiting

loss of appetite or weight

abdominal pain

diarrhea

hair loss

sores on the mouth tongue

changes in skin color

changes in color or growth of finger nails or toe nails

Cyclosporine

- Given, orally, IV, by inhalation, or as ophthalmic solution.
- Metabolized by P450 3A enzyme system with resultant multiple drug interactions and variability in bioavailability, and consequently, there is a need for routine drug monitoring.

Cyclosporine

- Nephrotoxicity.
- Hypertension.
- Hyperglycemia.
- Liver dysfunction.
- Hyperkalemia.
- Altered mental status, seizures.
- Hairsutism.
- Lymphoma and other cancers (Kaposi's sarcoma, skin cancer) due to induction of TGF-ß.

Cyclosporin Monitoring Parameters

- Cyclosporine trough levels.
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- Serum cholesterol.

Clinical Uses of Cyclosporine

1. Human organ transplantation,

2. Graft-versus-host disease after hematopoietic stem cell transplantation,

3. Selected autoimmune disorders, including uveitis, rheumatoid arthritis, psoriasis, and asthma.

Mycophenolate Mofetil

- Derived from a mold *Penicillium glaucus*.
- Hydrolyzed to mycophenolic acid, the active immunosuppressive moiety.
- Given orally or IV.
- Plasma levels are monitored.
- Can cause N,V, D, abdominal pain, headache, hypertension, and reversible myelosuppression, primarily neutropenia.

MYCOPHENOLATE

- MPA is a reversible inhibitor of the enzyme inosine monophosphate dehydrogenese (IMPDH).

- This leads to depletion of guanosine nucleotides

- Depletion of guanosine nucleotides has antiproliferative effects on lymphocytes (Both T and B-cells).

MYCOPHENOLATE

- MMF is effective for the treatment of renal disease due to systemic lupus erythematosus and may be useful in vasculitis and Wegener's granulomatosis.

- Although MMF is occasionally used at a dosage of 2 g/d to treat rheumatoid arthritis, there are no well-controlled data regarding its efficacy in this disease.

Combination therapy (using 2 to 3) DMARDs at a time works better than using a single DMARD

Common DMARD Combinations

- Triple Therapy
- Methotrexate, Sulfasalazine, Hydroxychloroquine

- Double Therapy
- Methotrexate & Leflunomide
- Methotrexate & Sulfasalazine
- Methotrexate & Hydroxychloroquine

BIOLOGIC THERAPY

- Complex protein molecules
- Created using molecular biology methods
- Produced in prokaryotic or eukaryotic cell cultures

BIOLOGIC THERAPY

Monoclonal Antibodies to TNF

- Infliximab
- Adalimumab

Soluble Receptor Decoy for TNF

- Etanercept

Receptor Antagonist to IL-1

- Anakinra

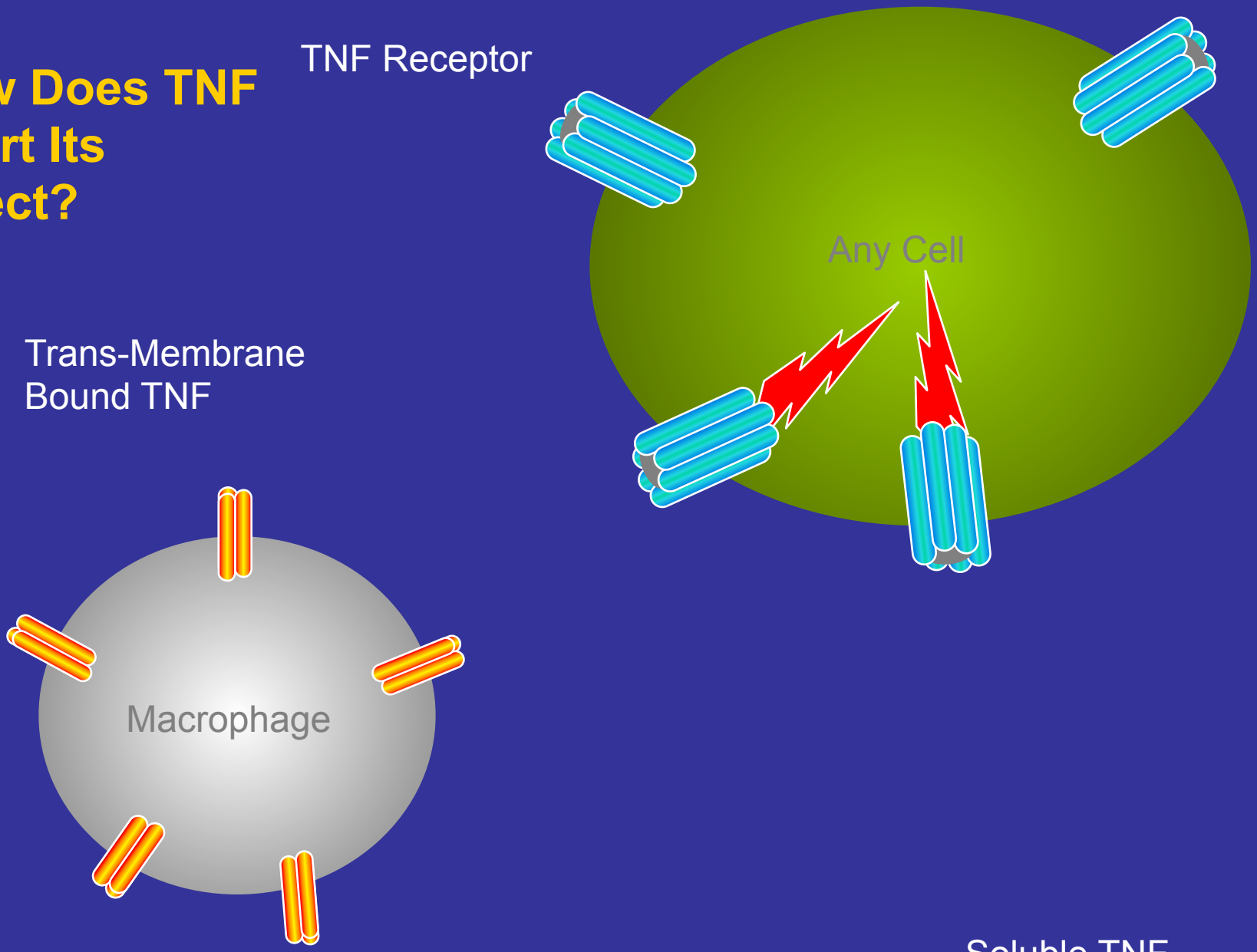
Monoclonal Antibody to CD-20

- Rituximab

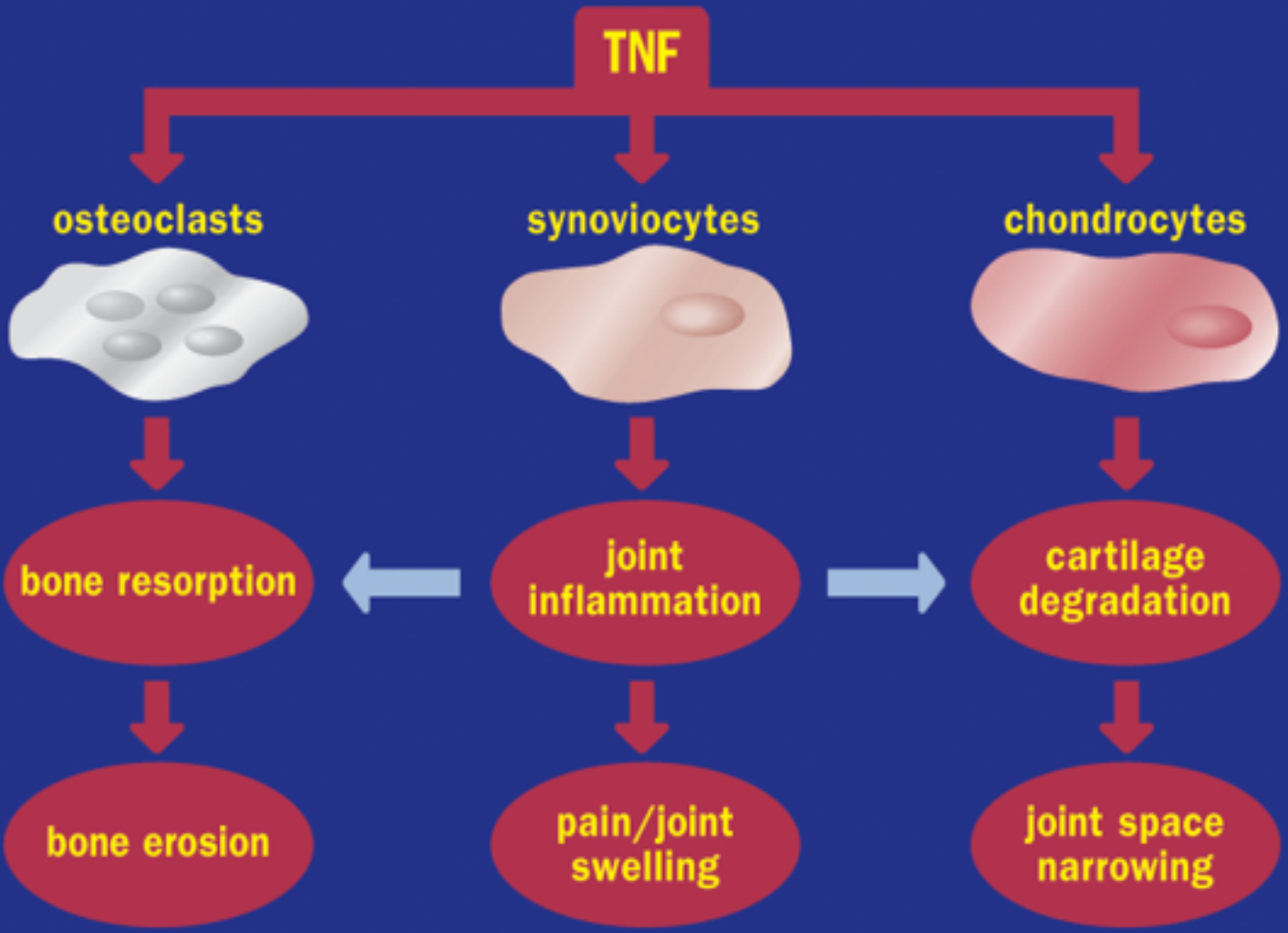
Tumour Necrosis Factor (TNF)

- TNF is a potent inflammatory cytokine
- TNF is produced mainly by macrophages and monocytes
- TNF is a major contributor to the inflammatory and destructive changes that occur in RA
- Blockade of TNF results in a reduction in a number of other pro-inflammatory cytokines (IL-1, IL-6, & IL-8)

How Does TNF Exert Its Effect?

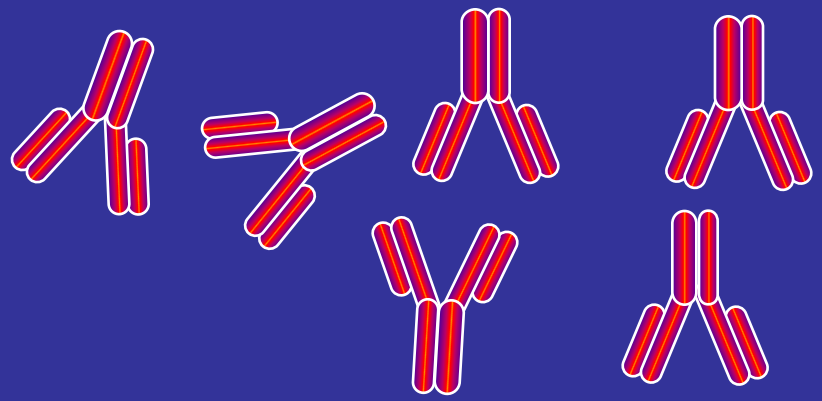


Destructive effects of TNF

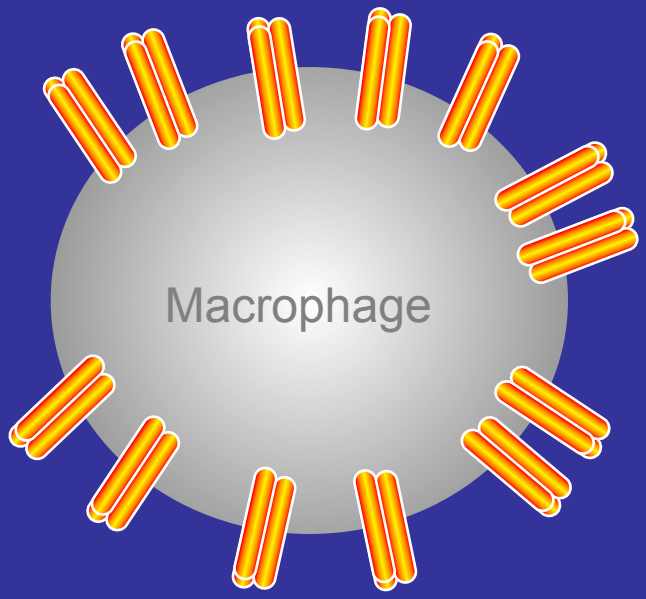


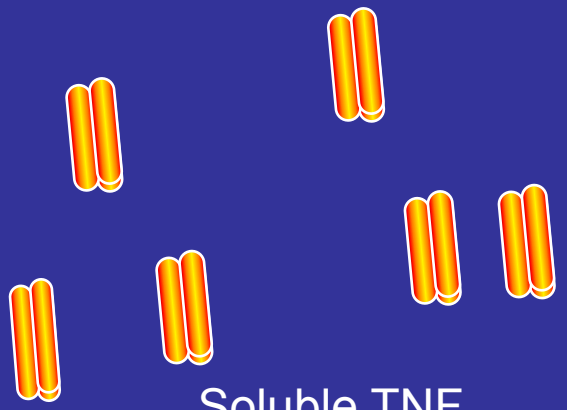
Strategies for Reducing Effects of TNF

Monoclonal Antibody (Infliximab & Adalimumab)



Trans-Membrane Bound TNF





Soluble TNF

Side Effects

- Infection
  - Common (Bacterial)
  - Opportunistic (Tb)
- Demyelinating Disorders
- Malignancy
- Worsening CHF

ABATACEPT

A modified antibody , fusion protein .

MOA: it contains the endogenous ligand CTLA-4 that binds to CD80 and 86, thereby inhibiting the binding to CD28 and preventing the activation of T cells.

Indications

Abatacept can be used as monotherapy or in combination with other DMARDs in patients with moderate to severe rheumatoid arthritis who have had an inadequate response to other DMARDs.

Adverse effects

There is a slightly increased risk of infection (predominantly of the upper respiratory tract.

Concomitant use with TNF-α antagonists is not recommended due to the increased incidence of serious infection.
Infusion-related reactions and hypersensitivity reactions, including anaphylaxis.

There is a possible increase in lymphomas.