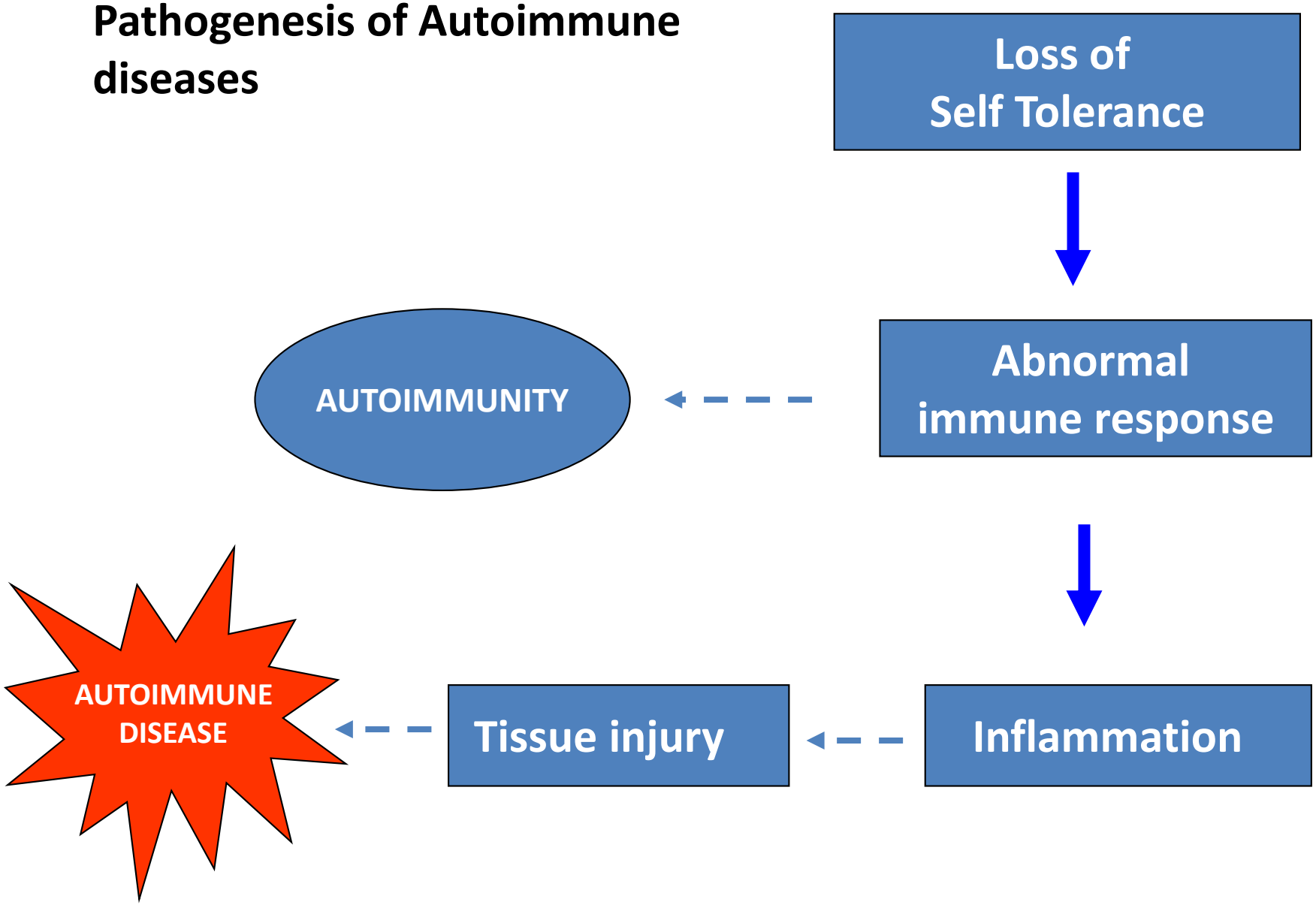
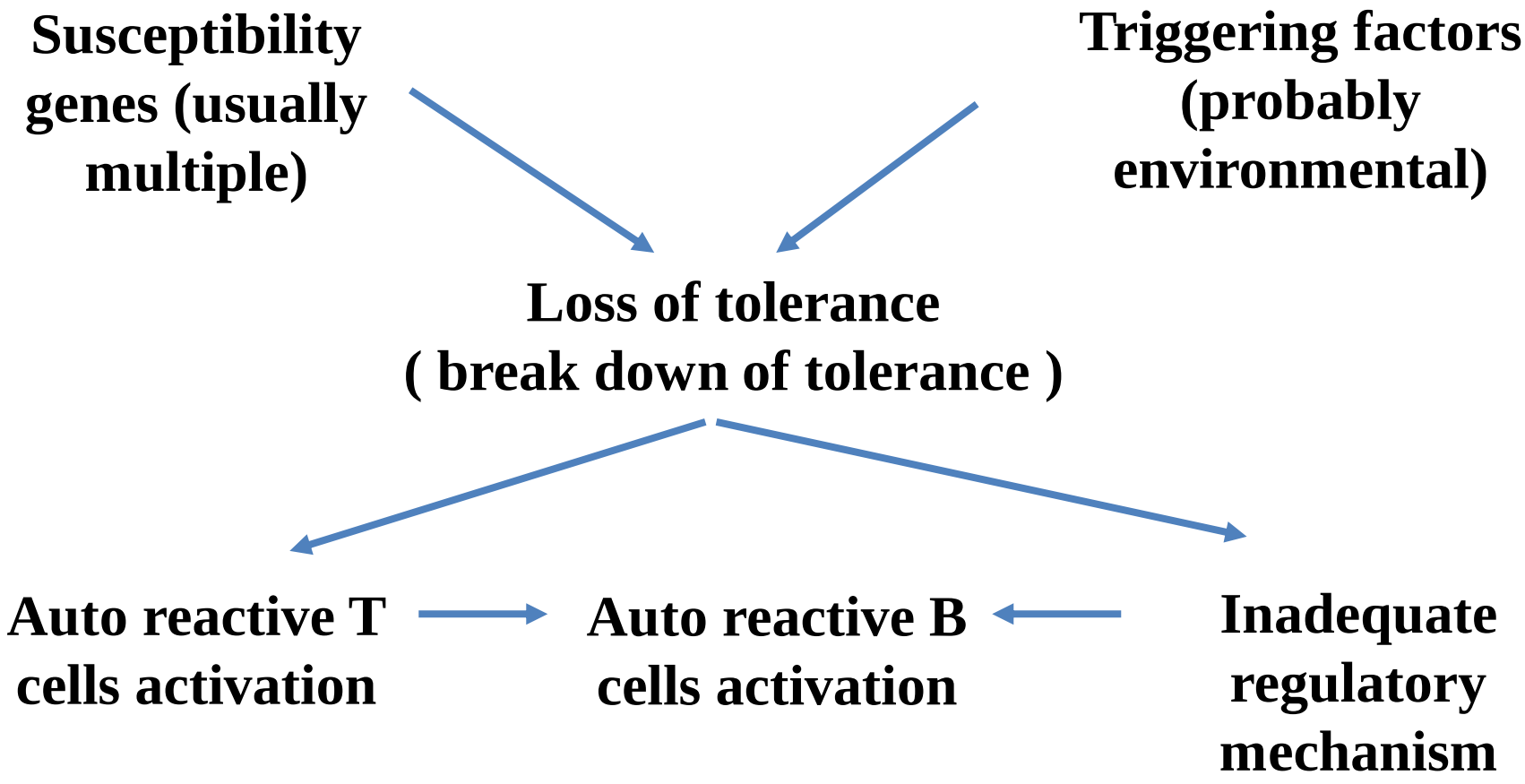
# Autoimmune & Immunodeficiency

Isbandiyah dr, SpPD

# Pathogenesis of Autoimmune diseases

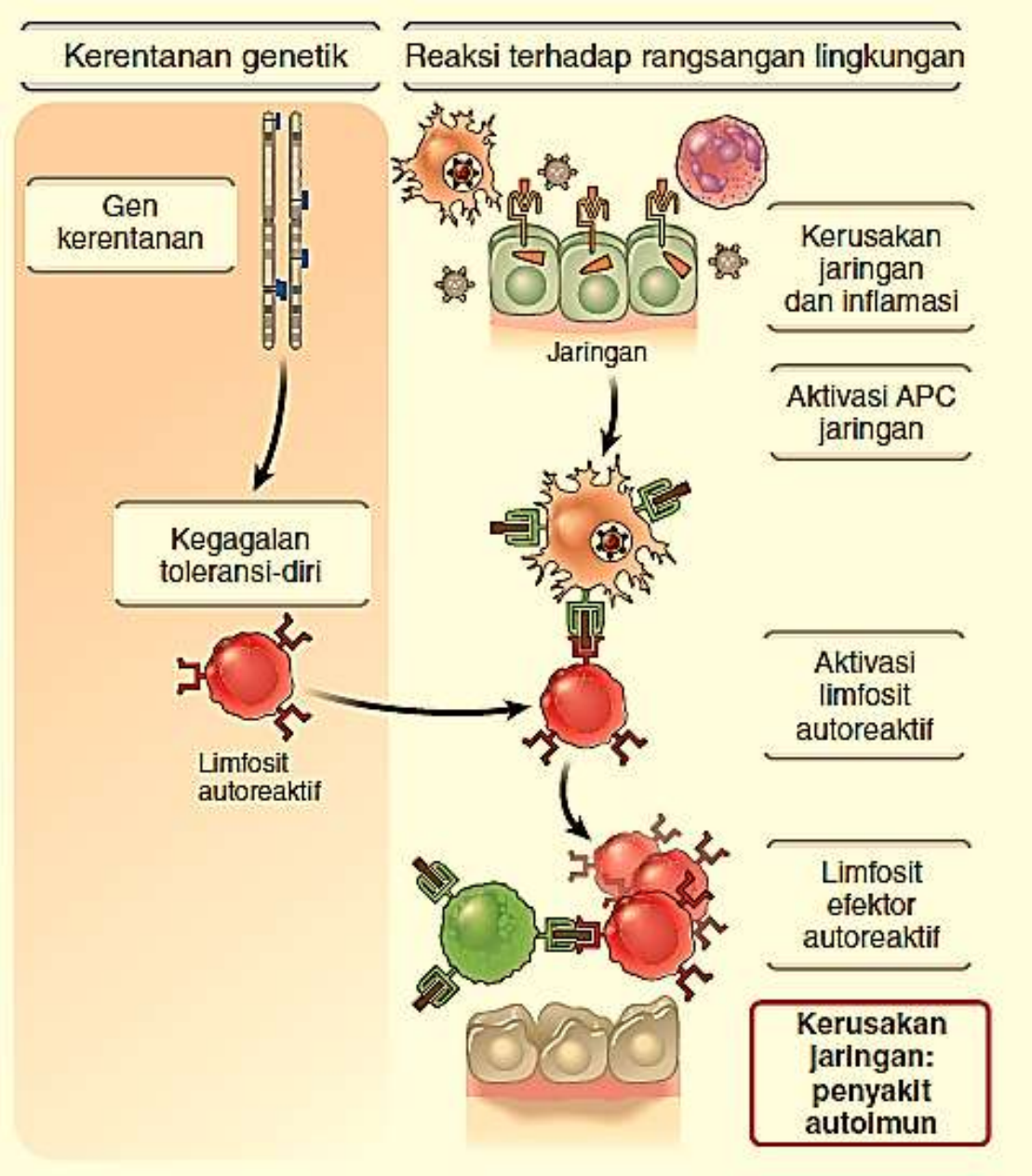


# Causes of Autoimmunity

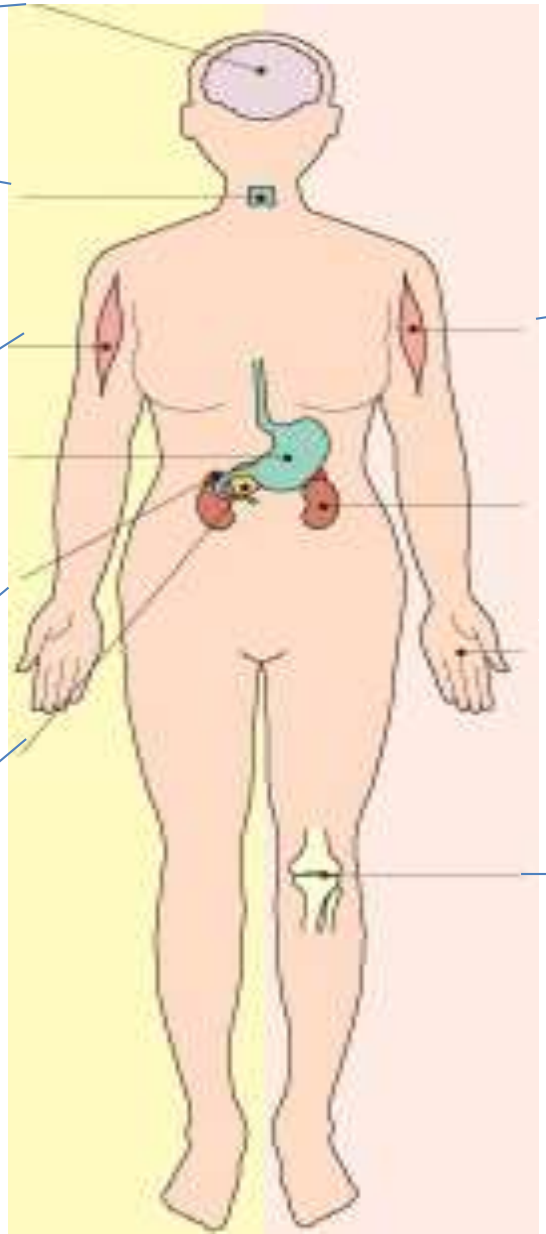



**Tolerance can break down in the thymus ( genetic reason ) or in the periphery ( environmental )**

# Mekanisme autoimunitas



# Two types of autoimmune disease



**Brain**

**Thyroid**

**Hashimoto's**
**primary myxedema**
**thyrotoxicosis**

**Muscle**
**myasthenia gravis**

**Stomach**
**Pernicious anemia**

**Adrenal**

**Addison's disease**

**Pancreas**

**Insulin – dependent**
**diabetes mellitus**

**Muscle**
**dermatomyositis**

**Kidney**
**SLE**

**Skin**
**Scleroderma**
**SLE**

**Joints**
**Rheumatoid arthritis**

# Autoimmune diseases are hypersensitivity reactions triggered by self-antigen

## Immune-pathogenesis of autoimmune diseases

- **Antibody-mediated ( type II hypersensitive reactions) : auto immune hemolytic anemia**
- **Immune-complex-mediated ( type III ) : SLE, glomerulonephritis, vasculitis**
- **Cell-mediated ( type IV) : rheumatoid arthritis , type I diabetes mellitus**

| Syndrome | Autoantigen | Consequence |
|---|---|---|
| **Type II antibody against cell-surface or matrix antigens** | | |
| Autoimmune hemolytic anemia | Rh blood group antigens, I antigen | Destruction of red blood cells by complement and $FcR^+$ phagocytes, anemia |
| Autoimmune thrombocytopenic purpura | Platelet integrin GpIIb:IIIa | Abnormal bleeding |
| Goodpasture's syndrome | Noncollagenous domain of basement membrane collagen type IV | Glomerulonephritis, pulmonary hemorrhage |
| Pemphigus vulgaris | Epidermal cadherin | Blistering of skin |
| Acute rheumatic fever | Streptococcal cell-wall antigens. Antibodies cross-react with cardiac muscle | Arthritis, myocarditis, late scarring of heart valves |

| Syndrome | Autoantigen | Consequence |
|---|---|---|
| **Type III immune-complex disease** | | |
| Mixed essential cryoglobulinemia | Rheumatoid factor IgG complexes (with or without hepatitis C antigens) | Systemic vasculitis |
| Systemic lupus erythematosus | DNA, histones, ribosomes, snRNP, scRNP | Glomerulonephritis, vasculitis, rash |
| Rheumatoid arthritis | Rheumatoid factor IgG complexes | Arthritis |

| Syndrome | Autoantigen | Consequence |
|---|---|---|
| **Type IV T cell-mediated disease** | | |
| Insulin-dependent diabetes mellitus | Pancreatic β-cell antigen | β-cell destruction |
| Rheumatoid arthritis | Unknown synovial joint antigen | Joint inflammation and destruction |
| Experimental autoimmune encephalomyelitis (EAE), multiple sclerosis | Myelin basic protein, proteolipid protein, myelin oligodendrocyte glycoprotein | Brain invasion by CD4 T cells, weakness |

# Autoantibodies against cell-surface receptors

| Diseases mediated by autoantibodies against cell-surface receptors | | |
|---|---|---|
| **Syndrome** | **Antigen** | **Consequence** |
| Graves' disease | Thyroid-stimulating hormone receptor | Hyperthyroidism |
| Myasthenia gravis | Acetylcholine receptor | Progressive weakness |
| Insulin-resistant diabetes | Insulin receptor (antagonist) | Hyperglycemia, ketoacidosis |
| Hypoglycemia | Insulin receptor (agonist) | Hypoglycemia |

**THYROIDITIS HASHIMOTO**

- **ANTIBODI ANTI-TIROGLOBULIN (PD 60-75% PASIEN)**
- **MENYERANG WANITA USIA PERTENGAHAN 10X PRIA**
- **THIROIDITIS KRONIK, INFILTRASI LIMFOSIT T CD4 DAN CD8**
- **GEJALA HIPOTIROIDISM**
- **JUGA TDP ANTIBODI ANTI-SEL PARIETAL**

**THYROTOXICOSIS / GRAVES**

- **ANTIBODI : ANTI-RESEPTOR TSH**
- **= DIFFUSE TOXIC GOITER = EXOPHTHALMIC GOITER**
- **60-70 % PENDERITA DG KLN MATA: PROPTOSIS, CONJUNGTIVITIS, PERIORBITAL ODEM**

**ANEMIA PERNISIOSA**

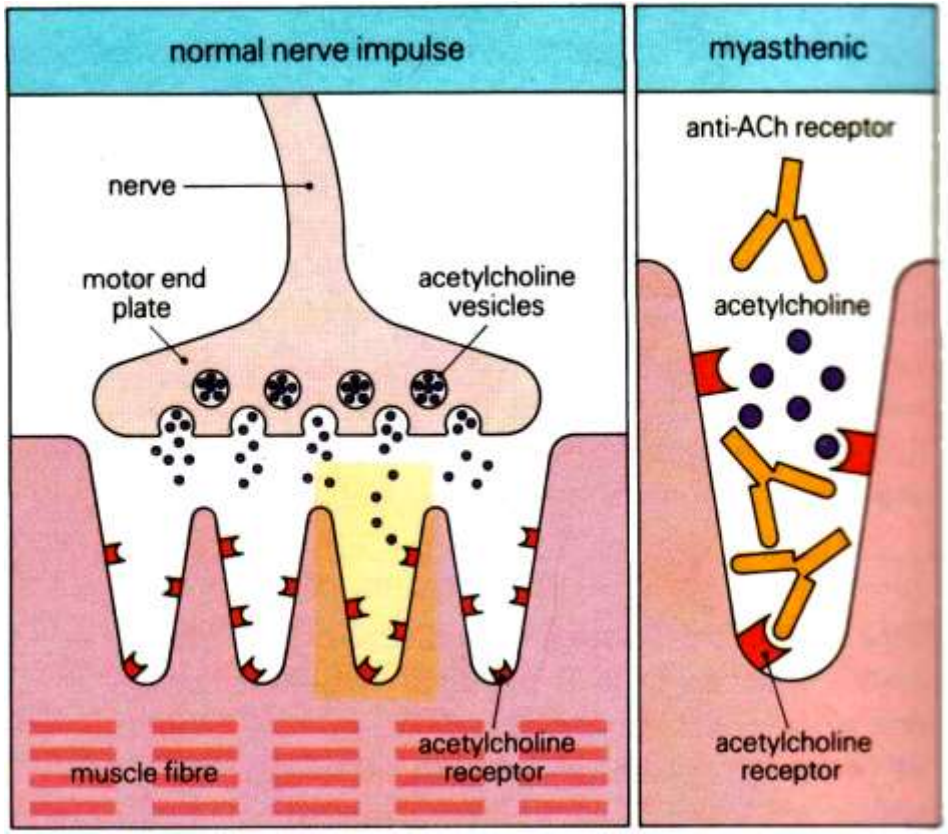
- **ATROFI MUKOSA GASTER**
- **PRODUKSI FAKTOR INTRINSIK TERGANGGU**
- **ANTIBODI : ANTI-SEL PARIETAL (PD 95% PENDERITA) → ABS VIT B12 TERGANGGU**
- **GEJALA : ANEMIA MEGALOBLASTIK**
- **TDP ANTIBODI-ANTI TIROID (PD 50% PENDERITA)**

**I D D M / JUVENILE DM**

- **DM TIPE I**
- **ANTIBODI : THD PULAU2 LANGERHANS → KERUSAKAN SEL β → PRODUKSI INSULIN TERGANGGU**
- **TDP *ISLET CELLS ANTIBODY* (ICA)**
- **INSULINITIS → INFILTRASI CD4 DAN CD8 PD PL2 LANGERHANS**

**MYASTENIA GRAVIS**

- **KELEMAHAN OTOT LURIK**
- **ANTIBODI : ANTI-RESEPTOR ASETILCHOLIN (PD 90% PENDERITA) → MENGHAMBAT TRANSMISI NEUROMUSKULER**
- **GEJALA DINI : PD OTOT ORBITA (DIPLOPIA & PTOSIS), OTOT MUKA, LIDAH DAN EKSTR. SUP**



**A I H A**

- **ANTIBODI ANTI-ERITROSIT**
- **ETIOLOGI; ? , DIDUGA FAKTOR LUAR (OBAT, VIRUS)**
- **Dx: COOMS' TEST**
- **T.D : 1. TIPE HANGAT**
  - **AGLUTINASI ERI TERJADI PADA SUHU 37°C**
  - **IDIOPATK/ PRIMER (50%) DAN SEKUNDER (LIMPOPROLIPERATIF, TUMOR, VIRUS, OBAT, SLE)**
  - **KELAS IgG**

  **2. TIPE DINGIN**
  - **AGLUTINASI PD 4°C, MENGIKAT KOMPLEMEN**
  - **KHUSUS PD GOL DARAH I (ANTIBODI-ANTI I →PD PENDERITA PNEUMONIA e.c MIKOPLASMA PNEUMONIA)**

  **3. DONATH LANDSTEINER**
  - **HEMOLISIN**
  - **AGLUTINASI PD 4°C**
  - **KELAS IgG**

**I T P**

- **ANTIBODI ANTI-PLATELET**
- **MANIFESTASI : PTECHIAE, ECCHIMOSIS, EPISTAKSIS, PERDARAHAN GIT DAN UTI, SPLENOMEGALI**
- **AKUT (TR: < 20.000/ML) & KRONIK (TR: 30.000-100.000/ML)**

**SIROSIS BILIER PRIMER**

- **PENYAKIT RADANG HATI GRANULOMATOUS KRONIK**
- **ANTIBODI ANTI-MITOKHONDRIA PD 99% PENDERITA**
- **TERUTAMA MENYERANG WANITA PADA USIA PERTENGAHAN**
- **MANIFESTASI: PRURITUS / CHOLESTASIS, JAUNDUCE**

**SJOGREN‘S SYNDR**

- **KEKERINGAN PD MATA (KERATOCONJUNCTIVITIS SICCA) DAN MULUT (XEROSTOMIA)**
- **ANTIBODI: THD RNA PD SAL. KEL LUDAH DAN AIR MATA MITOCHONDRIA, OTOT POLOS DAN TIROID**
- **BERHUBUNGAN DG RA DAN SLE**

**ARTRITIS REUMATOID**

- **PENYAKIT KRONIK SISTEMIK,**
- **MANIFESTASI UTAMA SENDI: POLIARTRITIS (T.U SENDI KECIL)**
- **ANTIBODI : ANTI-IgG (FAKTOR REUMATOID)**
- **PREDISPOSISI GENETIK : HLA-DR4**
- **PEREMPUAN USIA PERTENGAHAN 3 X LAKI**

# Kriteria Diagnosis RA

1. Kaku pagi (morning stiffness) : min 2 jam
2. Artritis pada 3 daerah.
3. Artritis pada persedian tangan
4. Simetris
5. Nodul reumatoid
6. Factor reumatoid serum.
7. Radiologis yang khas.

Harus memenuhi 4 dari 7 kriteria.

Kriteria 1 sampai 4 minimal selama 6 minggu.

# SYSTEMIC LUPUS ERYTHEMATOSUS

- Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with a wide spectrum of clinical and serological manifestations
- caused by autoantibody production, complement activation, and immune complex deposition.
- **affects many systems, including the skin, musculoskeletal, renal, neuropsychiatric, hematologic, cardiovascular, pulmonary, and reproductive systems**

Ali A et al, 2019. DOI: 10.7759/cureus.3288

Lam Ng V et al. *Am Fam Physician.* 2016;94(4):284-294.

# ETIOPATHOGENESIS OF SLE

- not entirely clear,
- it is believed that it results from the complex interaction between genetic and hormonal factors, and environmental exposures
- SLE has an unpredictable course that represents a challenge in the understanding of this disease

Ali A et al. 2019 DOI: 10.7759/cureus.3288

# laboratory tests

## Routine laboratory tests

Urinalysis for blood (suggests active glomerular disease) and protein,
microscopy for red cell casts, uPCR or uACR.

- CBC, SCr, LFTs, serum albumin ,Choleterol, urinary 24h protein
- CRP (typically not raised unless serositis; can be a useful discriminator).

## Immunological tests

ANA (>95%; sensitive but not specific)

Anti-dsDNA (increased specificity ,less sensitive)

C3 and C4 (reduced)

Anticardiolipin antibodies and lupus anticoagulant

Anti-C1q antibodies (associated with activity)

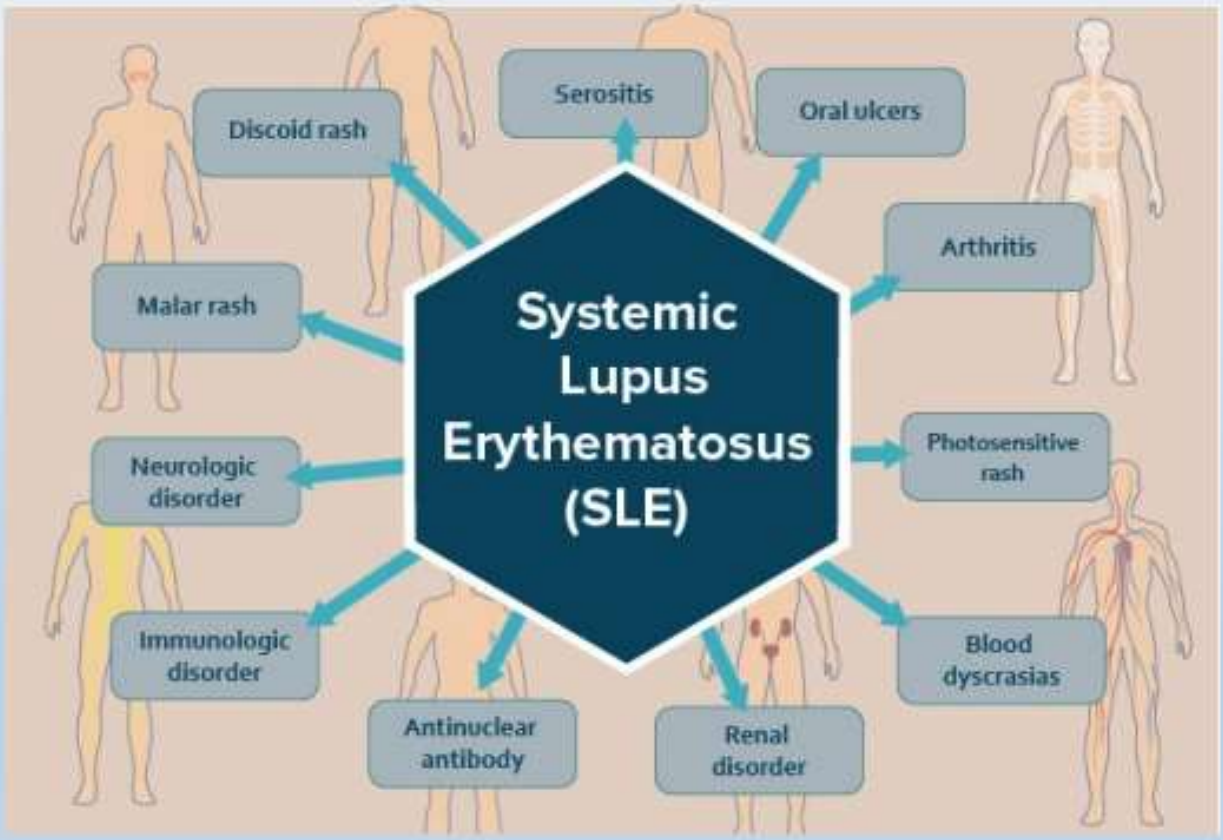
Sm antibodies ( strongly associated with the diagnosis of lupus and the presence of nephritis but are present in only about 25% to 30% of patients)

| Criteria | Definition |
|---|---|
| Malar rash | Fixed erythema, flat or raised, over the malar eminences, tending to spare the nasolabial folds |
| Discoid rash | Erythematous raised patches with adherent keratotic scaling and follicular plugging; atrophic scarring occurs in older lesions |
| Photosensitivity | Skin rash as a result of unusual reaction to sunlight, by patient history or physician observation |
| Oral ulcers | Oral or nasopharyngeal ulceration, usually painless, observed by a physician |
| Arthritis | Non-erosive arthritis involving two or more peripheral joints, characterised by tenderness, swelling or effusion |
| Serositis | a. Pleuritis: convincing history of pleuritic pain or rub heard by a physician or evidence of pleural effusion or<br>b. Pericarditis: documented by ECG or rub or evidence of pericardial effusion |
| Renal disorder | a. Persistent proteinuria >0.5 g per day or >3+ if quantitation is not performed or<br>b. Cellular casts: may be red cell, haemoglobin, granular tubular, or mixed |
| Neurological disorder | a. Seizures: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance) or<br>b. Psychosis: in the absence of offending drugs or known metabolic derangements (eg, uraemia, acidosis, or electrolyte imbalance) |
| Haematologic disorder | a. Haemolytic anaemia with reticulocytosis, or<br>b. Leucopenia: <4000/mm³, or<br>c. Lymphopenia: <1500/mm³, or<br>d. Thrombocytopenia: <100 000/mm³ in the absence of offending drugs |
| Immunologic disorder | a. Anti-DNA: antibody to native DNA in abnormal titre, or<br>b. Anti-Sm: presence of antibody to Sm nuclear antigen, or<br>c. Positive finding of antiphospholipid antibodies based on: (1) an abnormal serum concentration of IgG or IgM anticardiolipin antibodies, (2) a positive test result for lupus anticoagulant using a standard method, or (3) a false positive serologic test for syphilis known to be positive for at least 6 months and confirmed by *Treponema pallidum* immobilisation or fluorescent treponemal antibody absorption test |
| Antinuclear antibody | An abnormal titre of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with 'drug-induced lupus' syndrome |

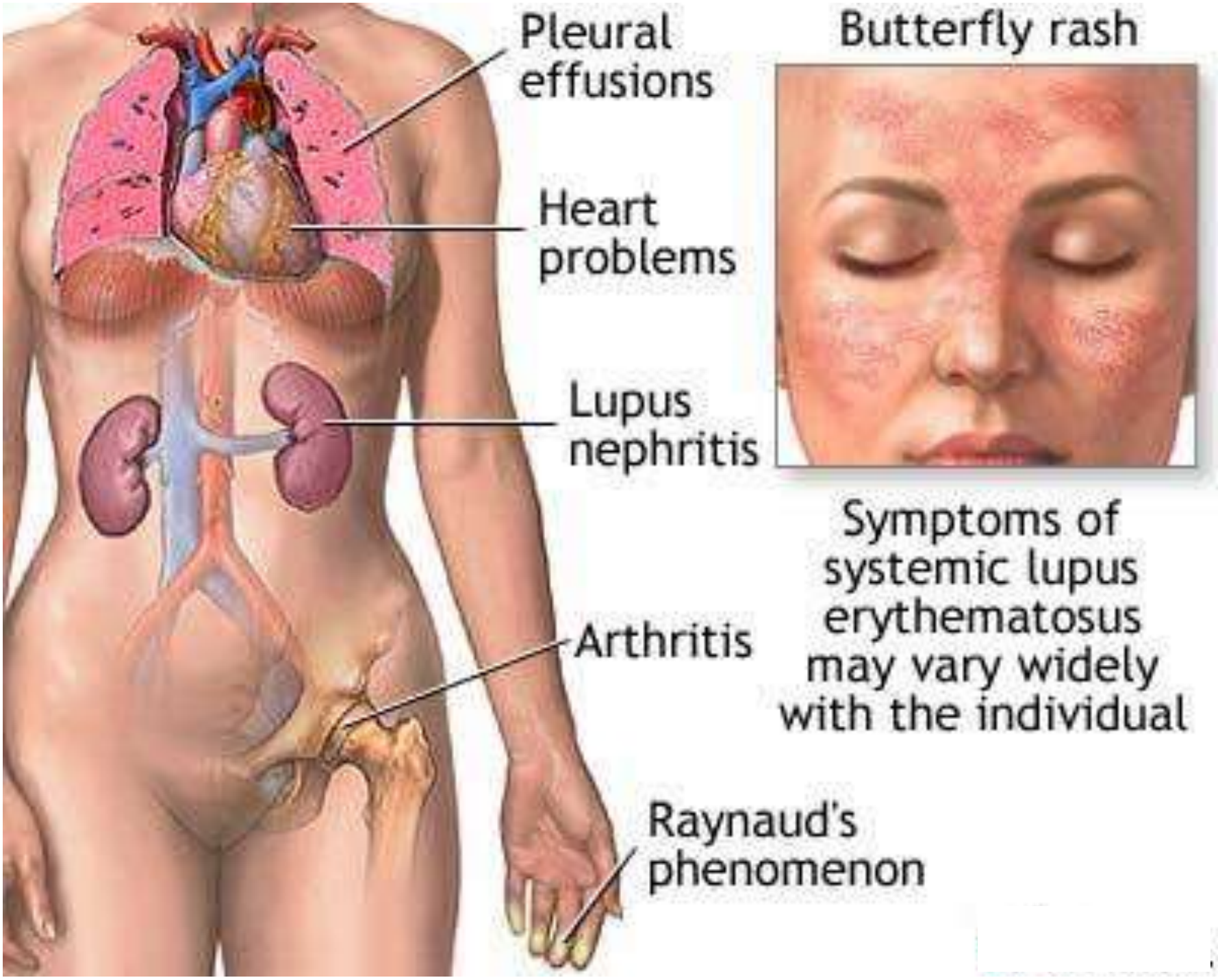
Adapted from Hochberg 1997.

Table 2 The American College of Rheumatology revised classification criteria for systemic lupus erythematosus

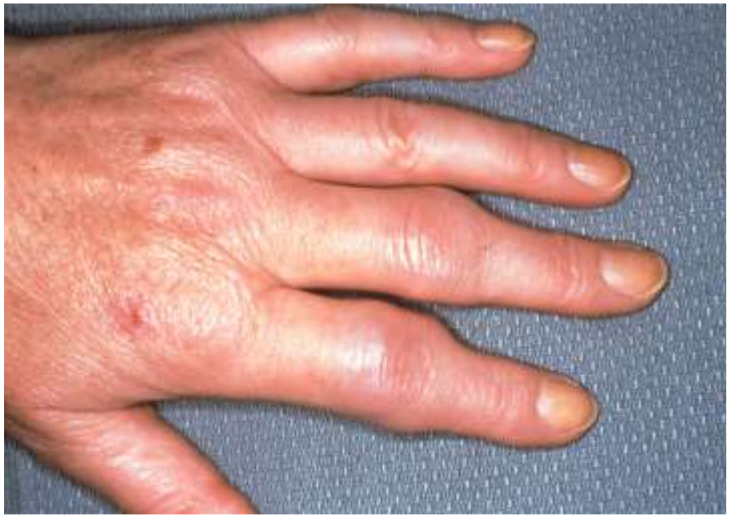
# Diagnose

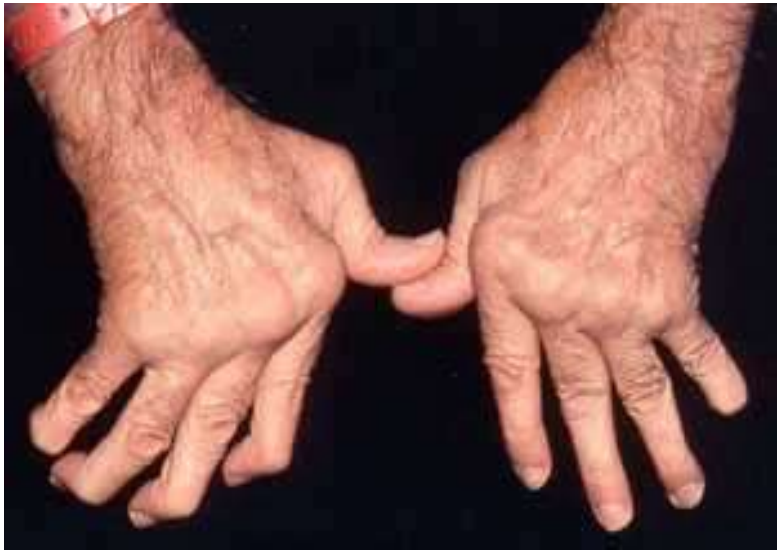


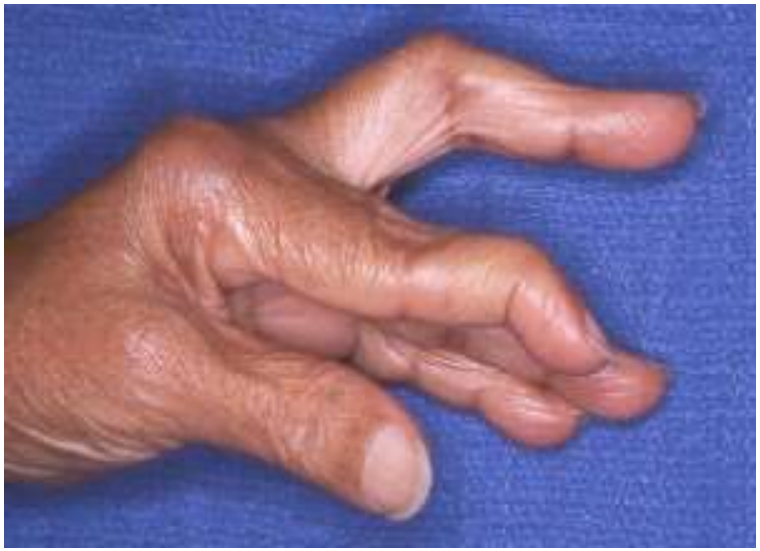

Dhawan R & Guice A. Medscape January5, 2016

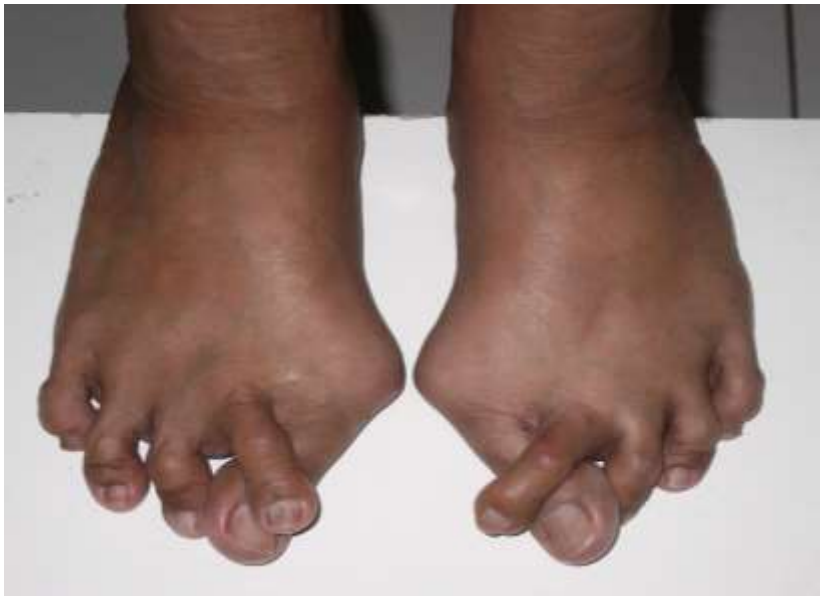

Pleural effusions
Heart problems
Lupus nephritis
Arthritis
Raynaud's phenomenon
Butterfly rash
Symptoms of systemic lupus erythematosus may vary widely with the individual

# Rheumatoid joints

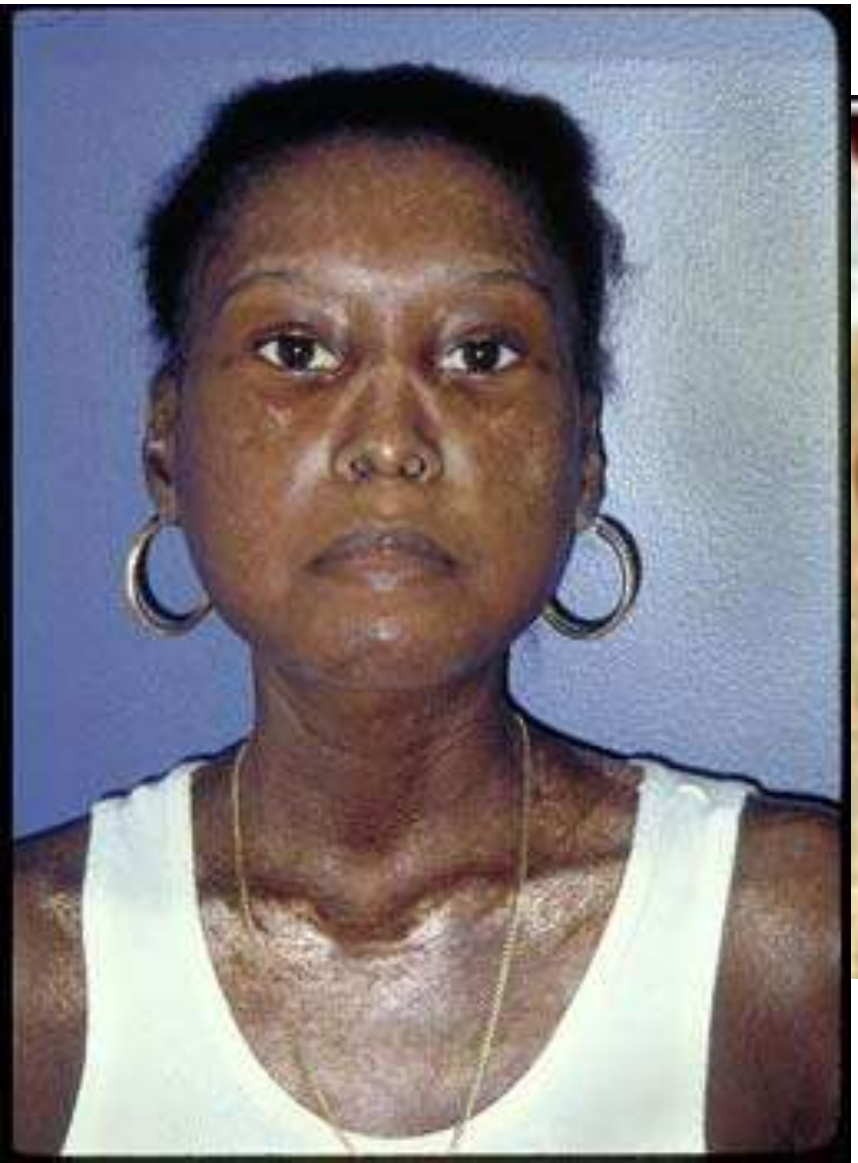


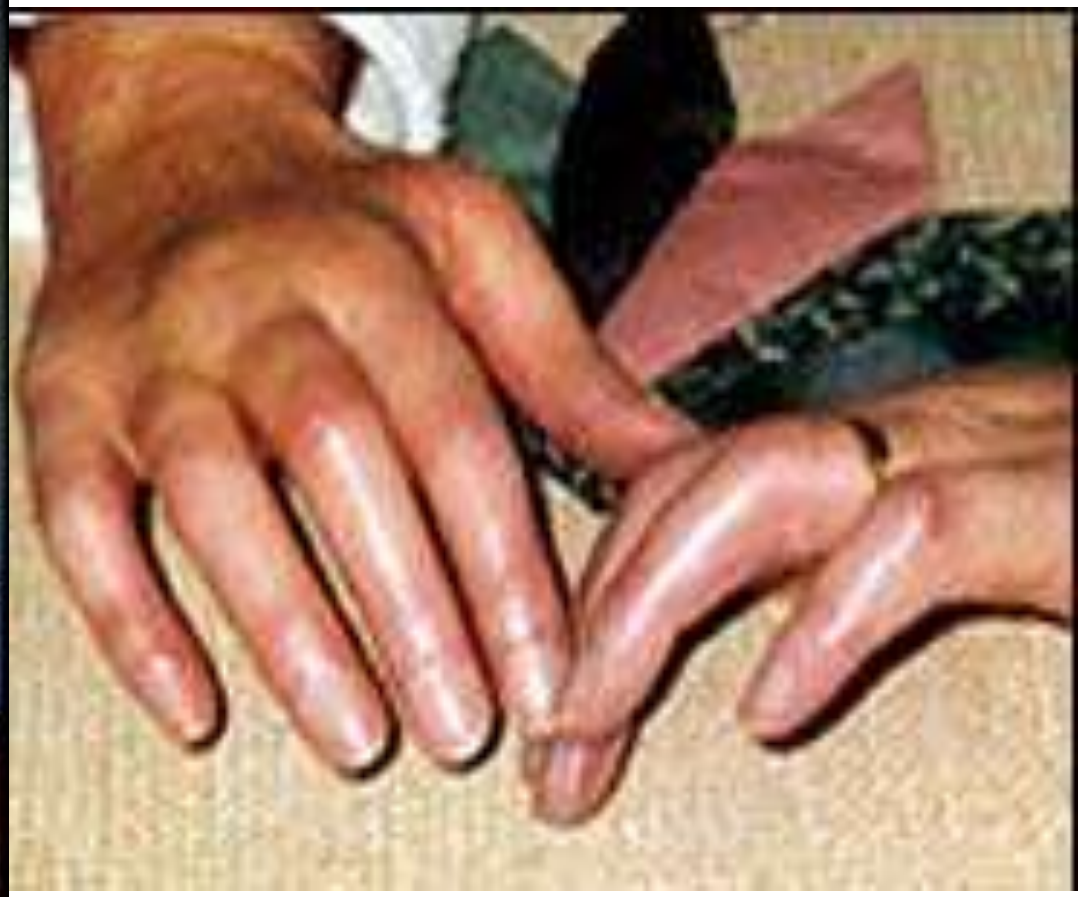




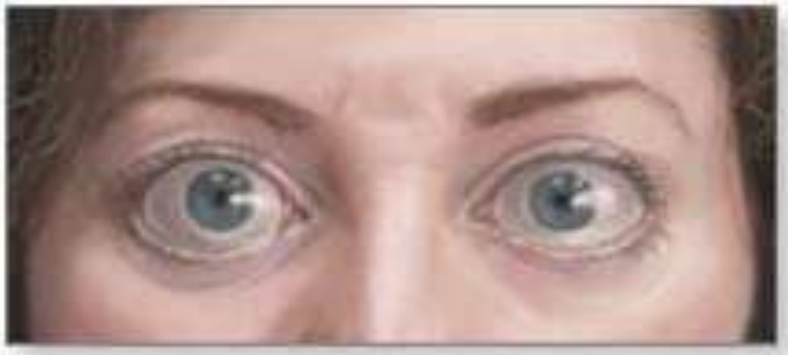


# Scleroderma (Systemic Sclerosis)

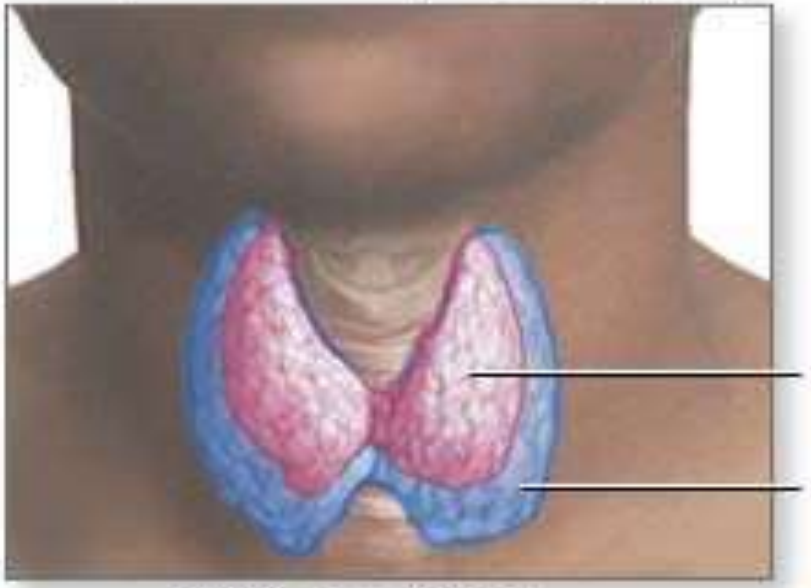




# Grave's Disease



Exophthalmos (bulging eyes)



Diffuse goiter

# Myasthenia Gravis


A.D.A.M.

# IMMUNODEFICIENCY

*Slide resources : 1.American Academy of Asthma, Allergy and Immunology (AAAAI) downloaded on March 13,2012 ; 2.Abbas Cellular and Molecular Immunology*

# Introduction

- Immunodeficiency disorders occur when the body's immune response is reduced or absent
- T or B cell lymphocytes (or both) do not work as well as they should, or when your body doesn't produce enough antibodies.

# CLASIFICATION

- Def. immune non specific
- Def. immune specific

Def. Immune specific

1. Congenital (primary) immunodeficiencies
2. Acquired (secondary) immunodeficiency
3. Fisiologic immunodeficiency

# CLINICAL SIGNIFICANCY

- Increased susceptibility to infection (bacteria, viruses, other microorganisms)
- Increased susceptibility to certain types of cancer
- Associated with an increased incidence of autoimmunity

# CONGENITAL ID

**CID** are genetic defects that result in an increased susceptibility to infection in infancy and childhood.

- Defects in innate immunity
- Severe combined immunodeficiencies
- Defects in B cell development and activation
- Defects in T lymphocyte activation and function
- Multisystem disorders with immunodeficiencies

# ACQUIRED ID

Acquired ID are not genetic abnormalities, but acquired during life.

- Complications from malnutrition, neoplasms and infections.
- Complications from drug therapies (eg: immunosuppressive or cytotoxic drugs)
- Surgical removal of spleen
- **HIV infection**

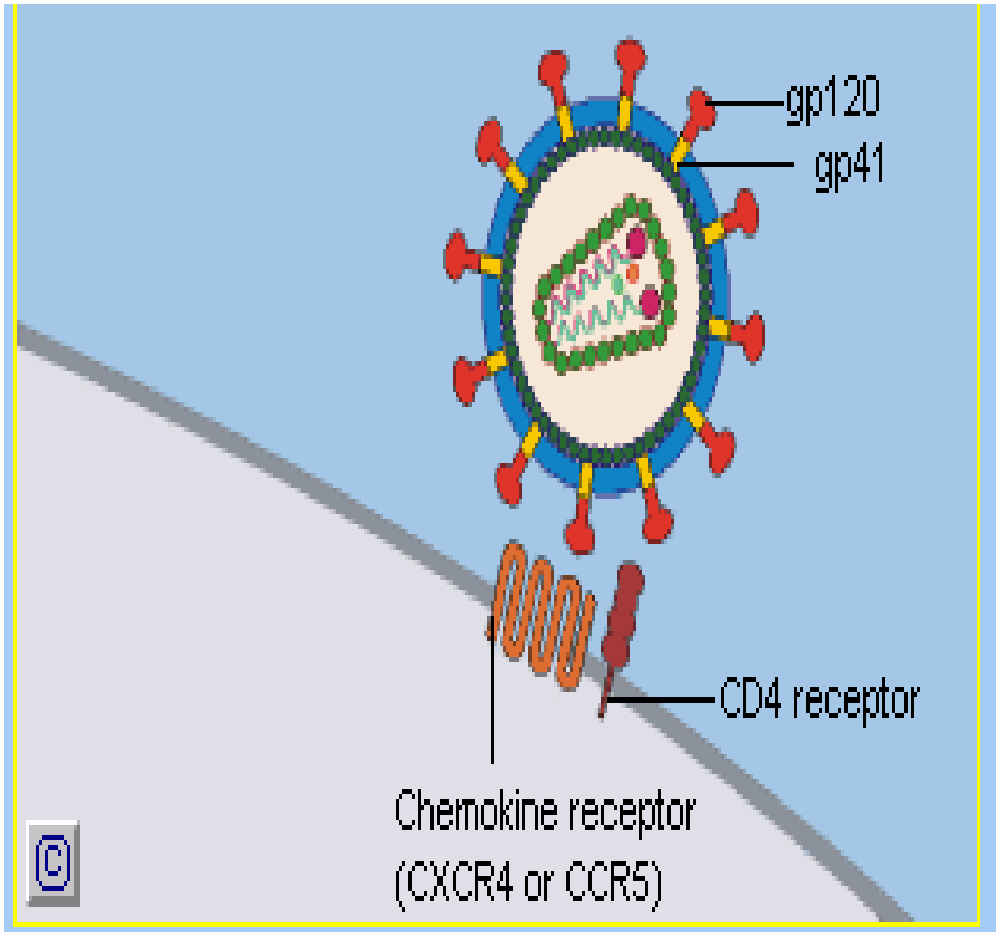
# Causes of Secondary (Acquired) Immunodeficiency

- Cancer (immunoproliferative diseases)
- Cytotoxic drugs or radiation
- Malnutrition
- Splenectomy
- Immunosuppressive therapies
- Stress/emotions
- Aging (thymic atrophy)
- Infection

| Cause | Mechanism |
| --- | --- |
| Human immunodeficiency virus infection | Depletion of CD4+ helper T cells |
| Protein-calorie malnutrition | Metabolic derangements inhibit lymphocyte maturation and function |
| Irradiation and chemotherapy treatments for cancer | Decreased bone marrow precursors for all leukocytes |
| Cancer metastases to bone marrow | Reduced site of leukocyte development |
| Removal of spleen | Decreased phagocytosis of microbes |

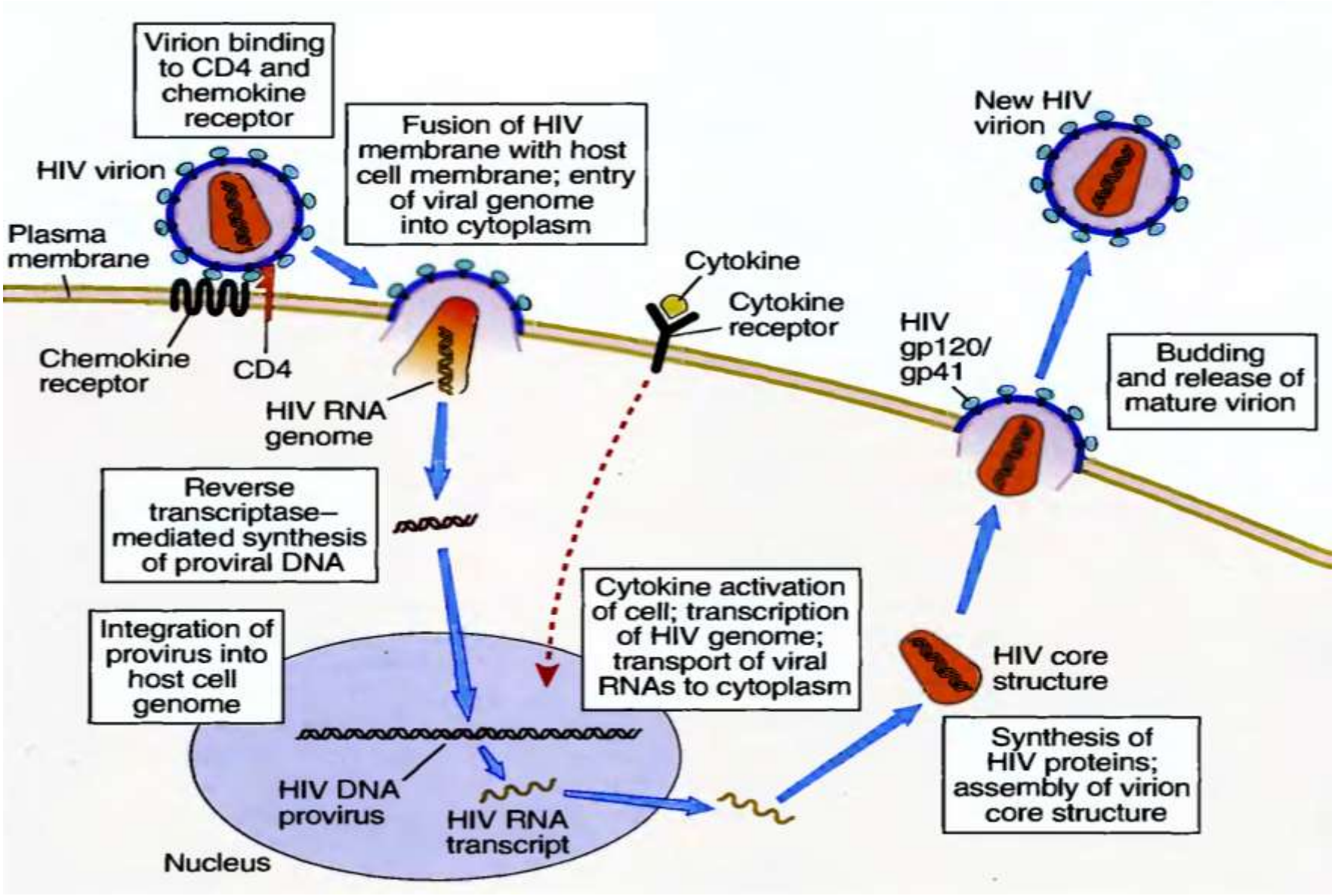
# Immunodeficiency in HIV infection

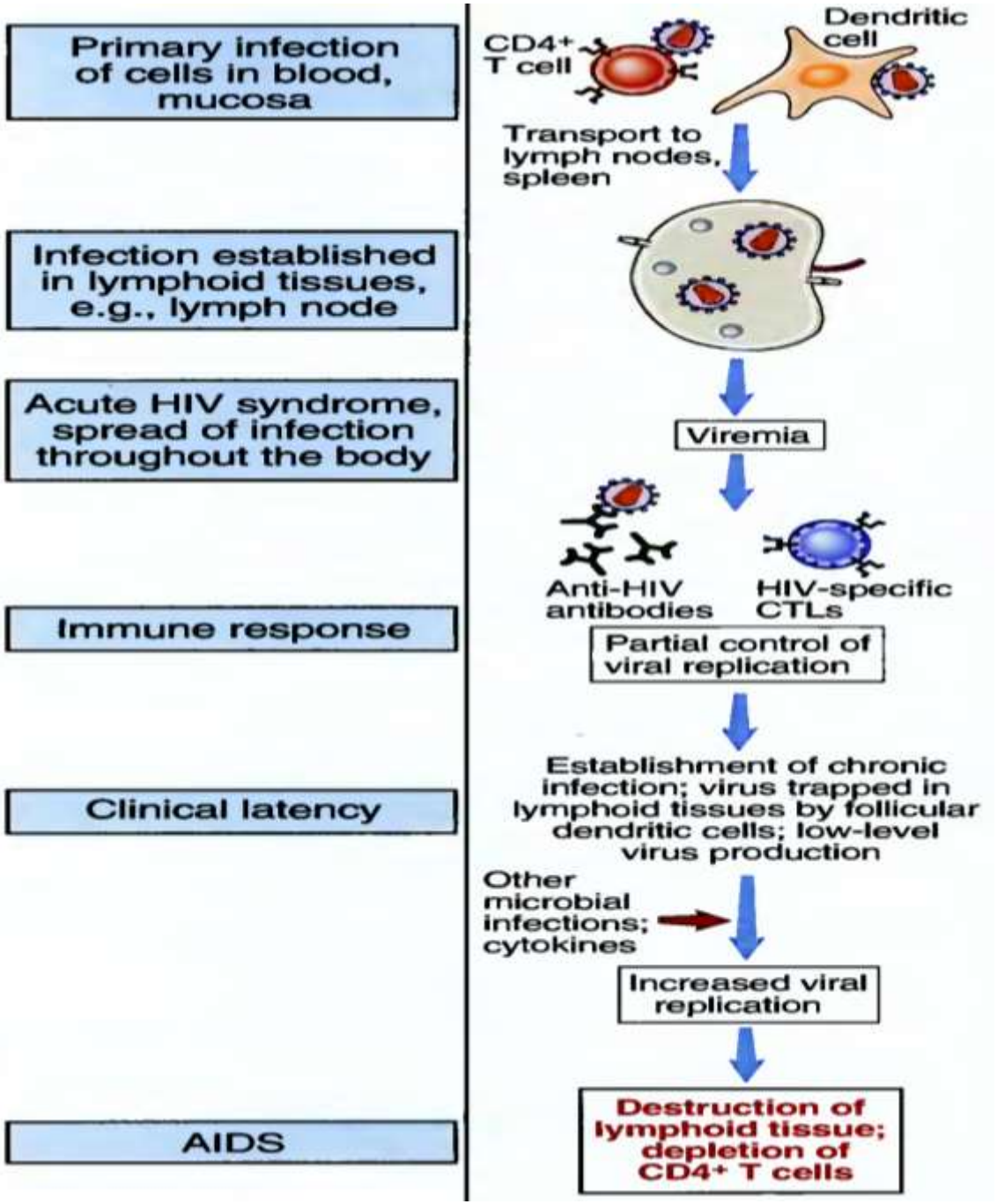
# Cell receptors for HIV




- CD4 are receptors for HIV
- Recognized by HIV through gp120
- Chemokine reseptor CXCR4 atau CCRs are needed for viral entry

# HIV life cycle



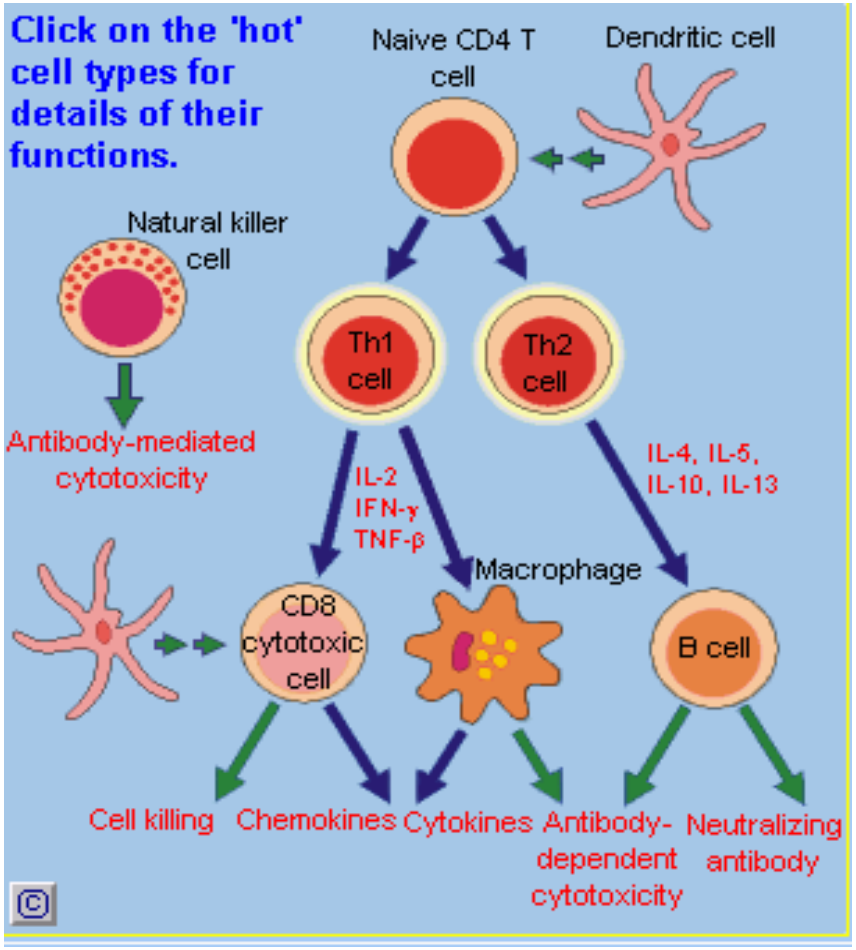



# Progression of HIV infection

HIV disease begins with acute infection, partly controlled by the adaptive immune response.

Advances to chronic progressive infection of peripheral lymphoid tissues.

# Cell targets




Major targets：

CD4+ lymphocytes

Monocytes/macrophages

Minor targets:

Langerhan cells, monocyte precursor CD34+, triple negative tymocyte (CD3/CD4/CD8), dendrite cells

# Opportunistic Infections in AIDS Patients

| Infections | |
|---|---|
| Parasites | *Toxoplasma* spp.<br>*Cryptosporidium* spp.<br>*Leishmania* spp.<br>*Microsporidium* spp. |
| Intracellular bacteria | *Mycobacterium tuberculosis*<br>*Mycobacterium avium intracellulare*<br>*Salmonella* spp. |
| Fungi | *Pneumocystis carinii*<br>*Cryptococcus neoformans*<br>*Candida* spp.<br>*Histoplasma capsulatum*<br>*Coccidioides immitis* |
| Viruses | Herpes simplex<br>Cytomegalovirus<br>Varicella zoster |

| Malignancies |
|---|
| Kaposi's sarcoma - HHV8<br>Non-Hodgkin's lymphoma, including EBV-positive Burkitt's lymphoma<br>Primary lymphoma of the brain |

Figure 11-30 Immunobiology, 6/e. (© Garland Science 2005)