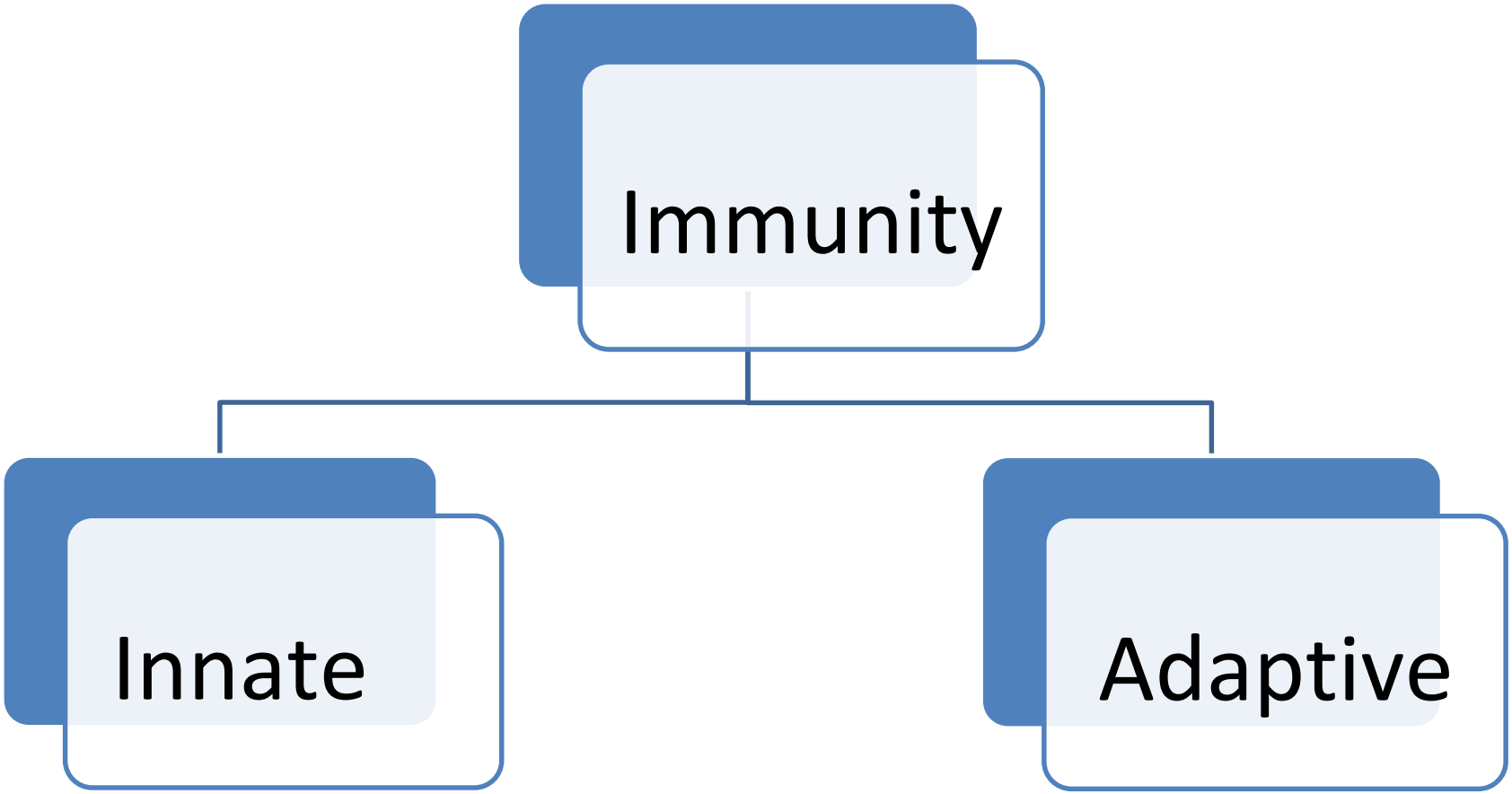
IMMUNITY

Dr.K.SUBASHREE

Definition

- Protection from infectious pathogens

Normal immune response



Innate immunity

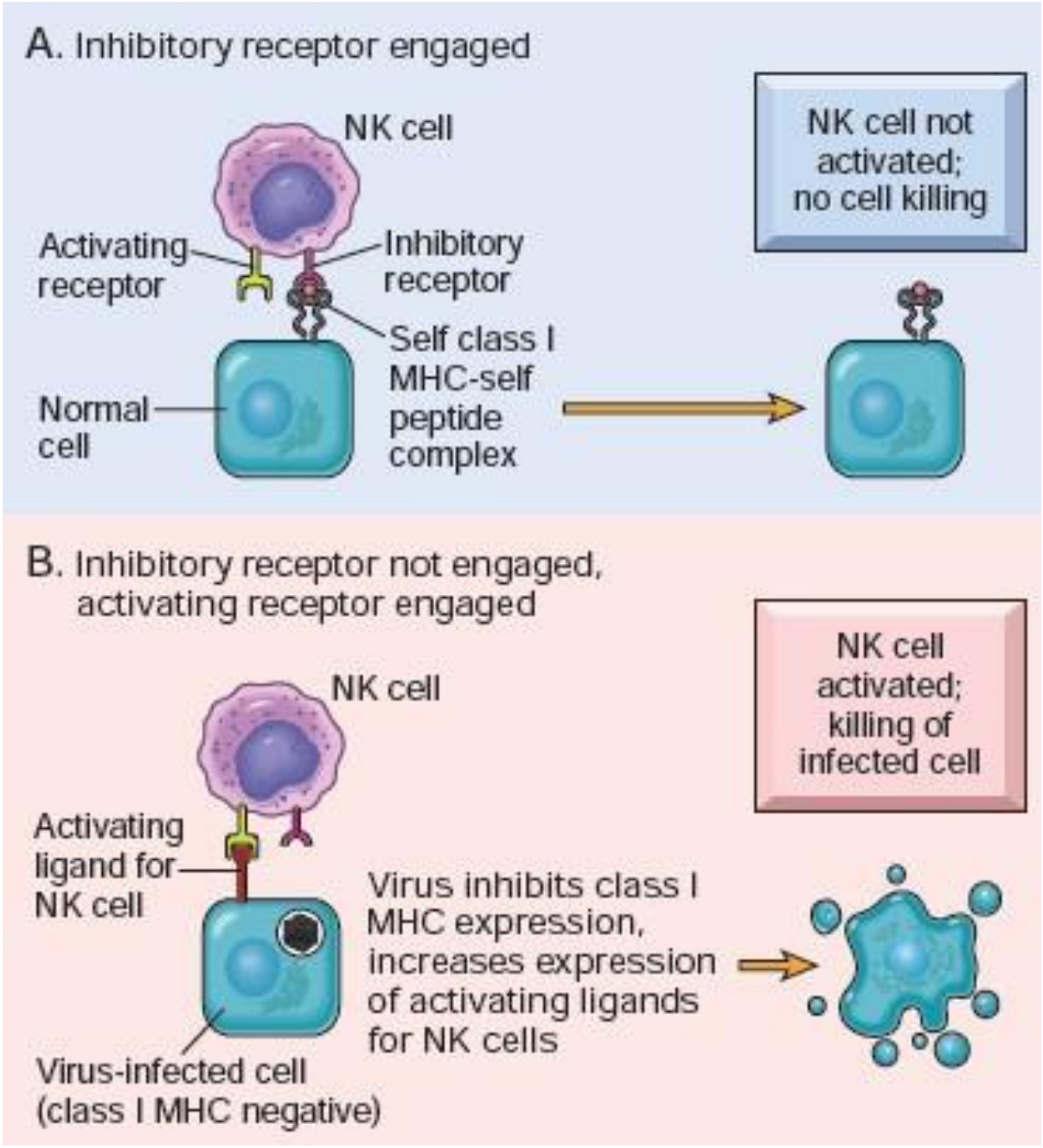
- Natural or native immunity
- Before infection

Components

- Epithelial barriers:
  HOW?
  - Mechanical barrier – Antimicrobial molecules:
- Defensins
- Phagocytic cells:
  - Neutrophils
  - Macrophages
- Dendritic cells:
  - Antigen presenting cells
  - Receptors which sense microbes and cells of tissue damage.
  - IFN 1 and viral cytokines • Plasma protiens
- N K cells:
  - Viruses
  - Intracellular bacteria

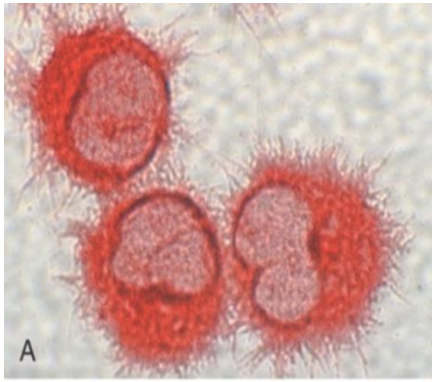
Natural Killer cells

- 10 – 15 % of peripheral lymphocytes
- No TCR or Ig
- Large granular lymphocytes:
  - Larger than small lymphocyte
  - Abundant azurophilic granules
- Early line of defense against viral infetions and tumors


A. Inhibitory receptor engaged
NK cell
Activating receptor
Inhibitory receptor
Self class I MHC-self peptide complex
Normal cell
NK cell not activated; no cell killing
B. Inhibitory receptor not engaged, activating receptor engaged
NK cell
Activating ligand for NK cell
Virus inhibits class I MHC expression, increases expression of activating ligands for NK cells
Virus-infected cell (class I MHC negative)
NK cell activated; killing of infected cell

Dendritic cells

- Antigen presenting cells for primary T cell receptor
- Interdigitating dendritic cells
- Follicular dendritic cells
- Fine cytoplasmic processes – dendrites



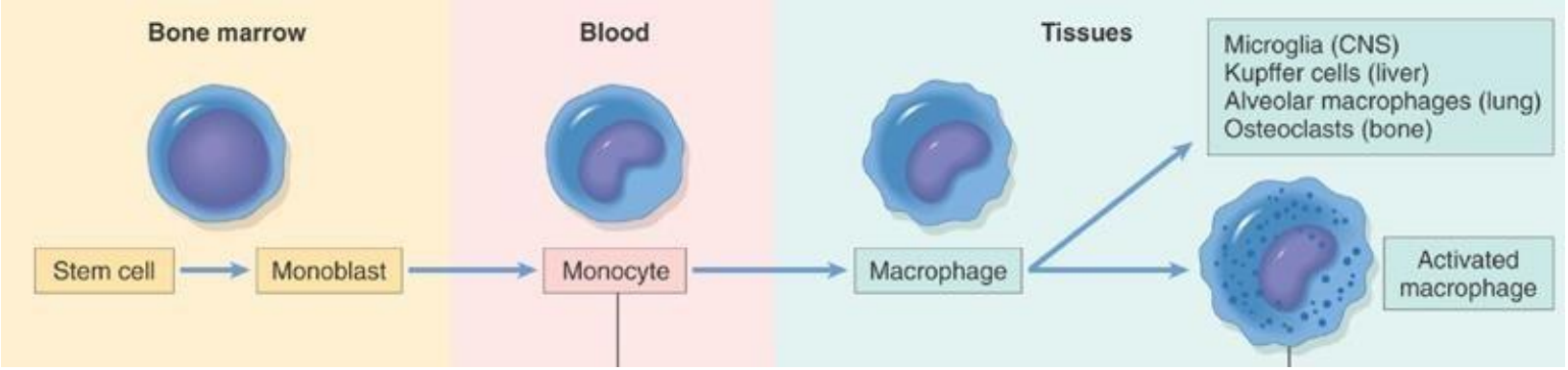
Y Antigen presenting cell?

- Right place to capture antigen:
  - Under epithelia
  - Interstium of tissues
- Many receptors for microbes(TLR , Mannose)
- Microbes → DC move to T cell zones of lymphoid organs
- Molecules for activation of T lymphocytes

Follicular dendritic cells

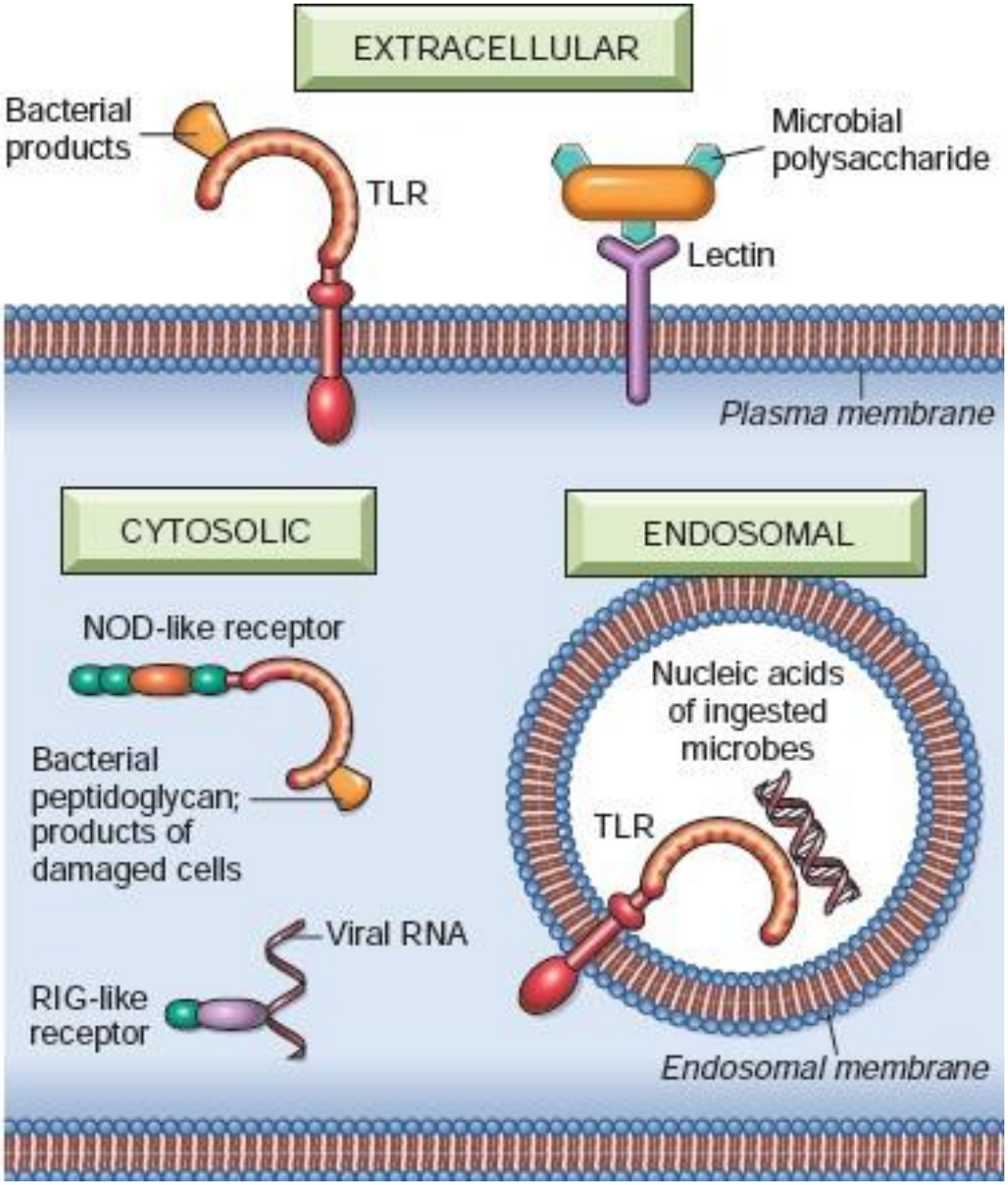
- Germinal center of lymphoid follicles
- Humoral immune response
- Fc receptors for IgG and receptors for C3b
- Traps antigen bound to antibodis or complements

Macrophages



Innate immunity

- **Pathogen associated molecular patterns:**
  - Cells of innate immunity – components of microbes – kill
- **Danger associated molecular patterns:**
  - Leucocytes – injured and necrotic cells
- **Pattern recognition receptors:**
  - Cellular receptors – recognize - molecules

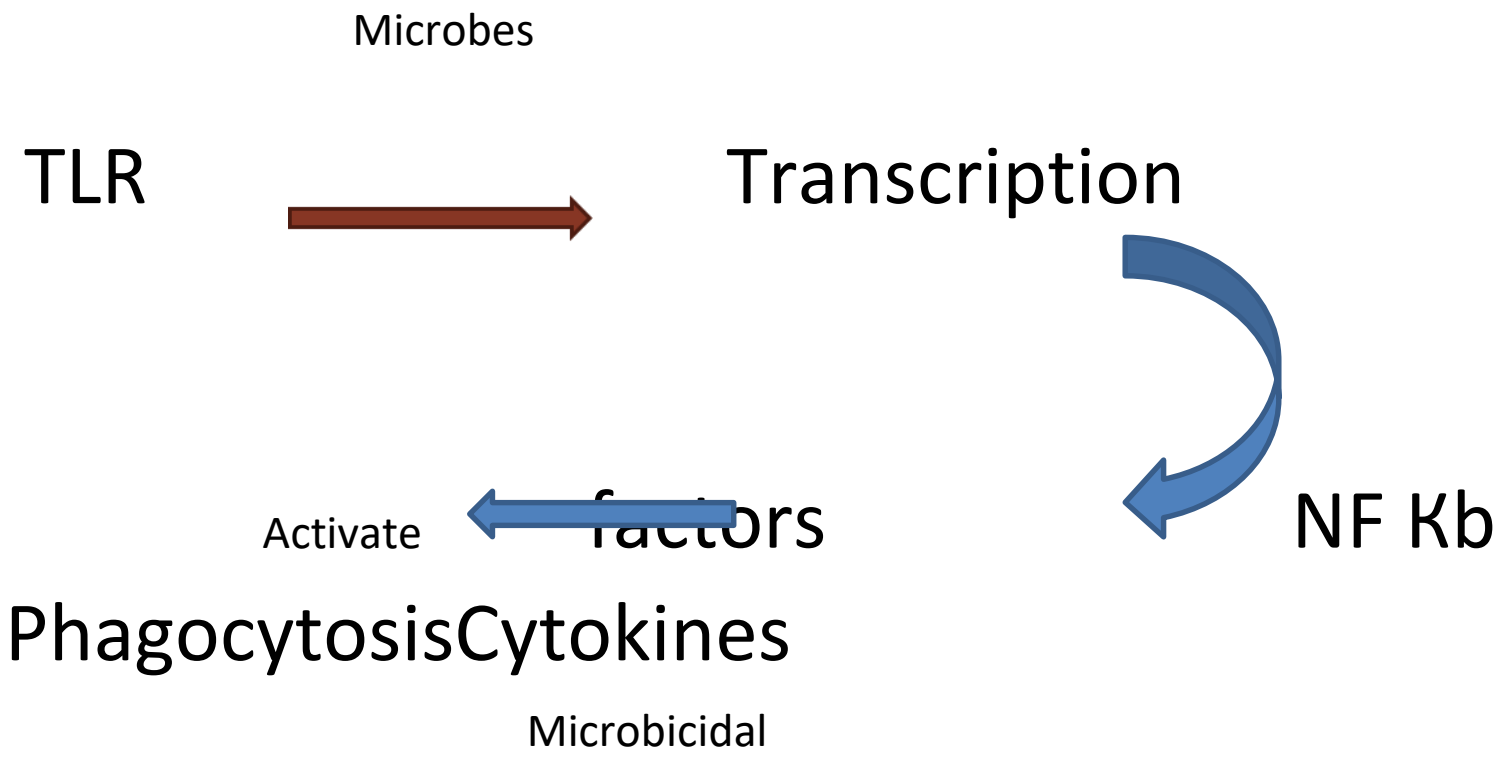

EXTRACELLULAR
Bacterial products
TLR
Microbial polysaccharide
Lectin
Plasma membrane
CYTOSOLIC
ENDOSOMAL
NOD-like receptor
Bacterial peptidoglycan; products of damaged cells
Nucleic acids of ingested microbes
TLR
Viral RNA
RIG-like receptor
Endosomal membrane

Toll like receptors

- Drosophilia

- Toll - “**Weird**”

Mechanism of action

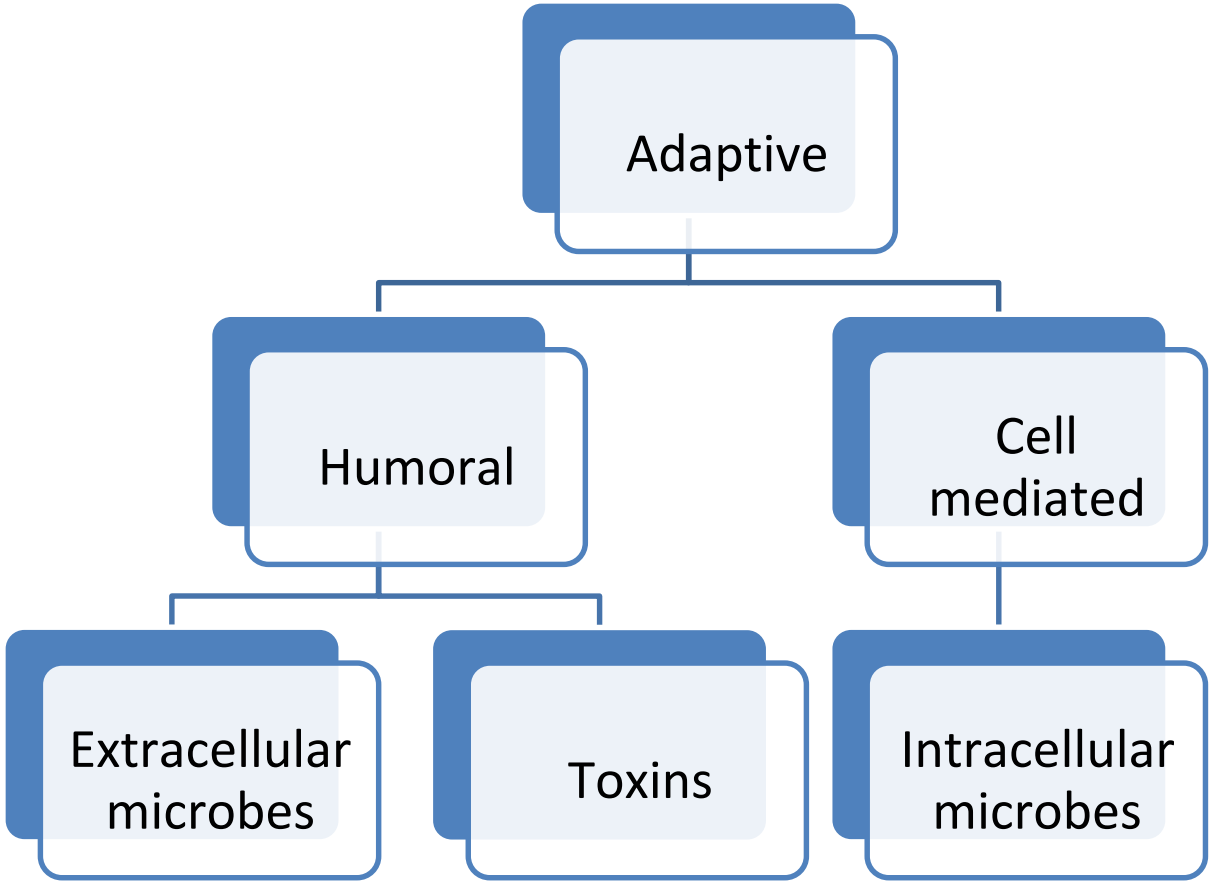


Cellular reactions of innate immunity

- Inflammation:
  - Leucocytes

- Antiviral defense:
  - Dendritic cells
  - NK cells

Adaptive immunity



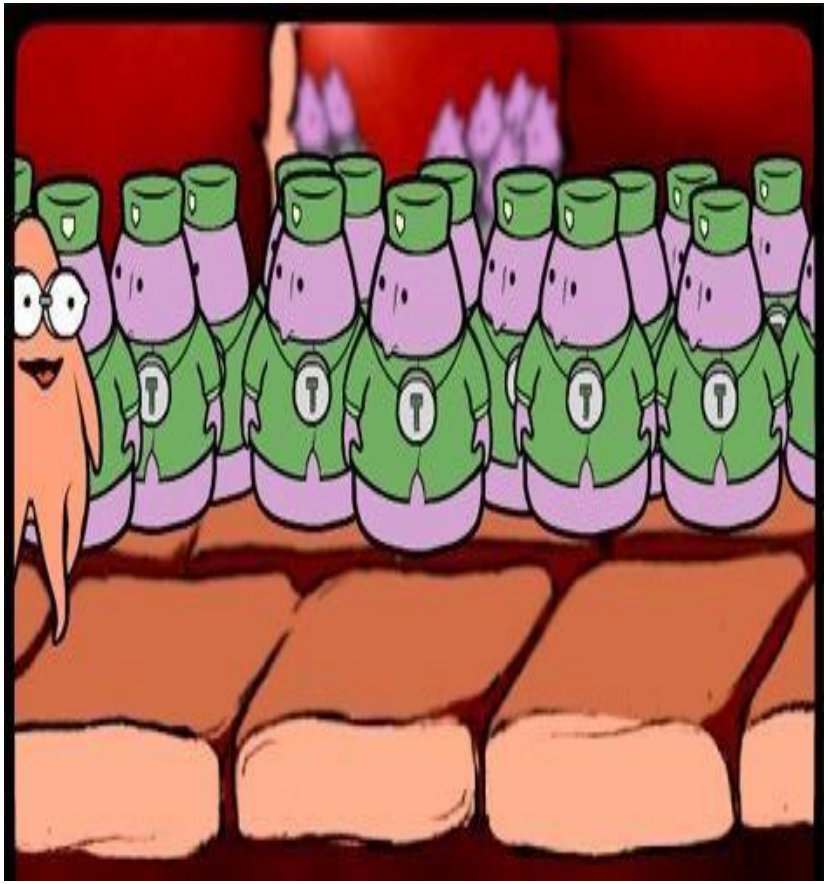
Cells of adaptive immunity

- B CELLS:
  - Bone marrow derived – Humoral immunity

- T CELLS:
  - Thymus derived
  - Cell mediated

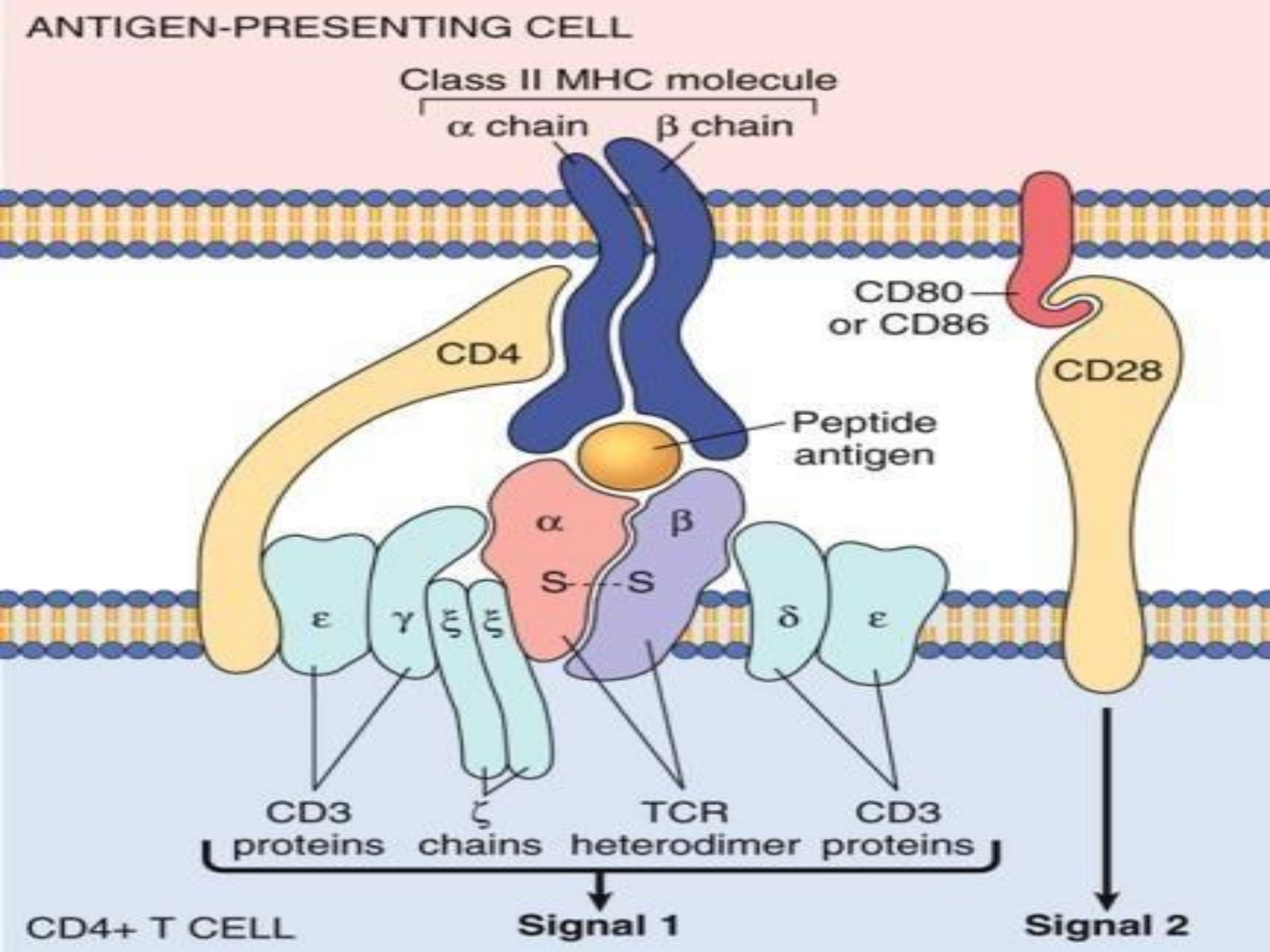
T lymphoctes

- Precursors of Thymus
- Location:
  - Blood : 60 – 70 %
  - Peripheral lymphoid organs
- T cell receptor:
  - Recognition of specific cell bound Ag



TCR

- T cells :
- Disulphide linked heterodimer
- □ and β polypeptide chain
- Antigen binding region and constant region


ANTIGEN-PRESENTING CELL
Class II MHC molecule
α chain
β chain
CD80
or CD86
CD28
CD4
Peptide
antigen
α
β
S
S
ε
γ
ξ
ξ
δ
ε
CD3
proteins
ζ
chains
TCR
heterodimer
CD3
proteins
CD4+ T CELL
Signal 1
Signal 2

- CD 4 :
  - 60 % of mature CD 3 +
  - Binds to Class II MHC molecules
  - Cytokine secreting helper T cells → Macrophage

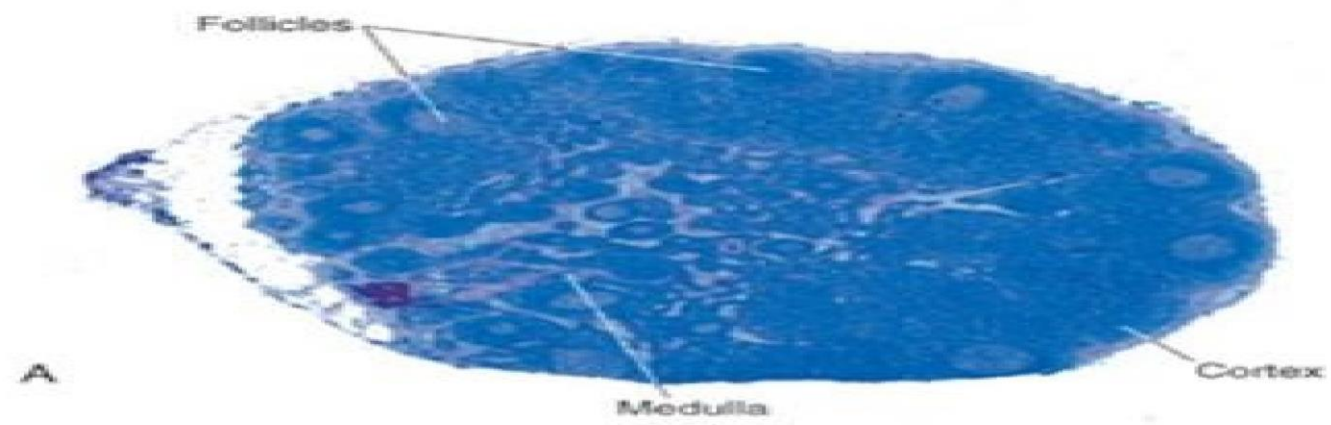
Inflammation

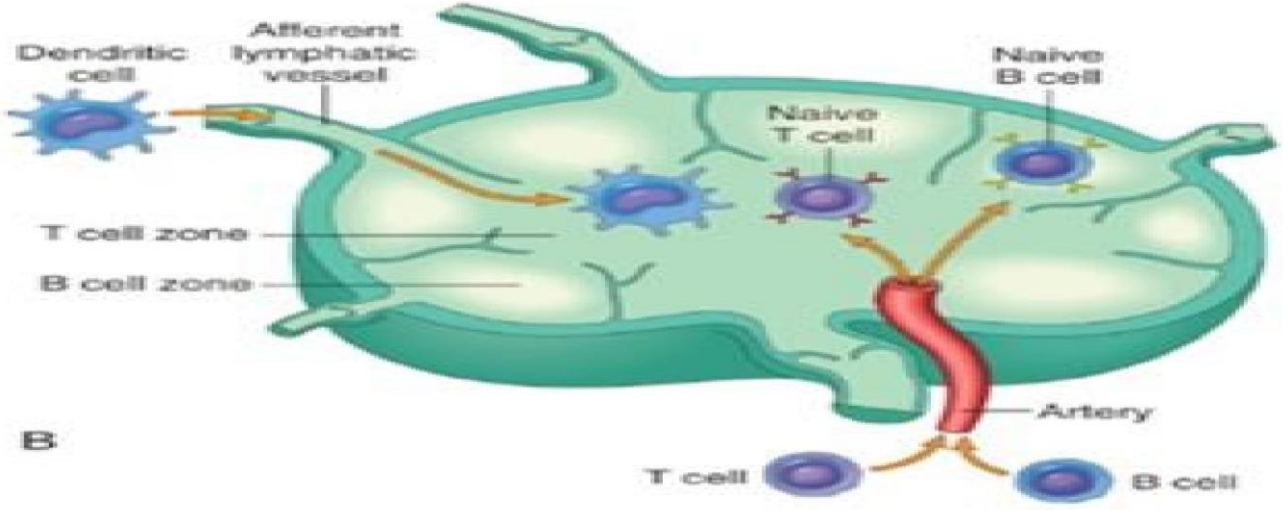
B Lymphocytes

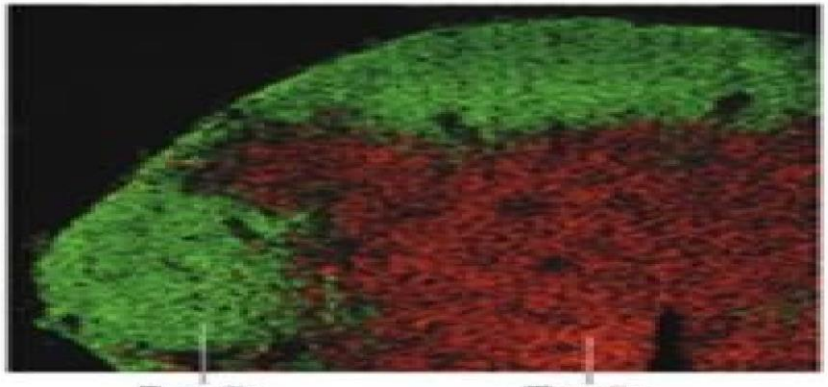
- CD 8:
  - 30% of T cells
  - Cytotoxic (KILLER) T cells
  - Bind to class 1 MHC molecules

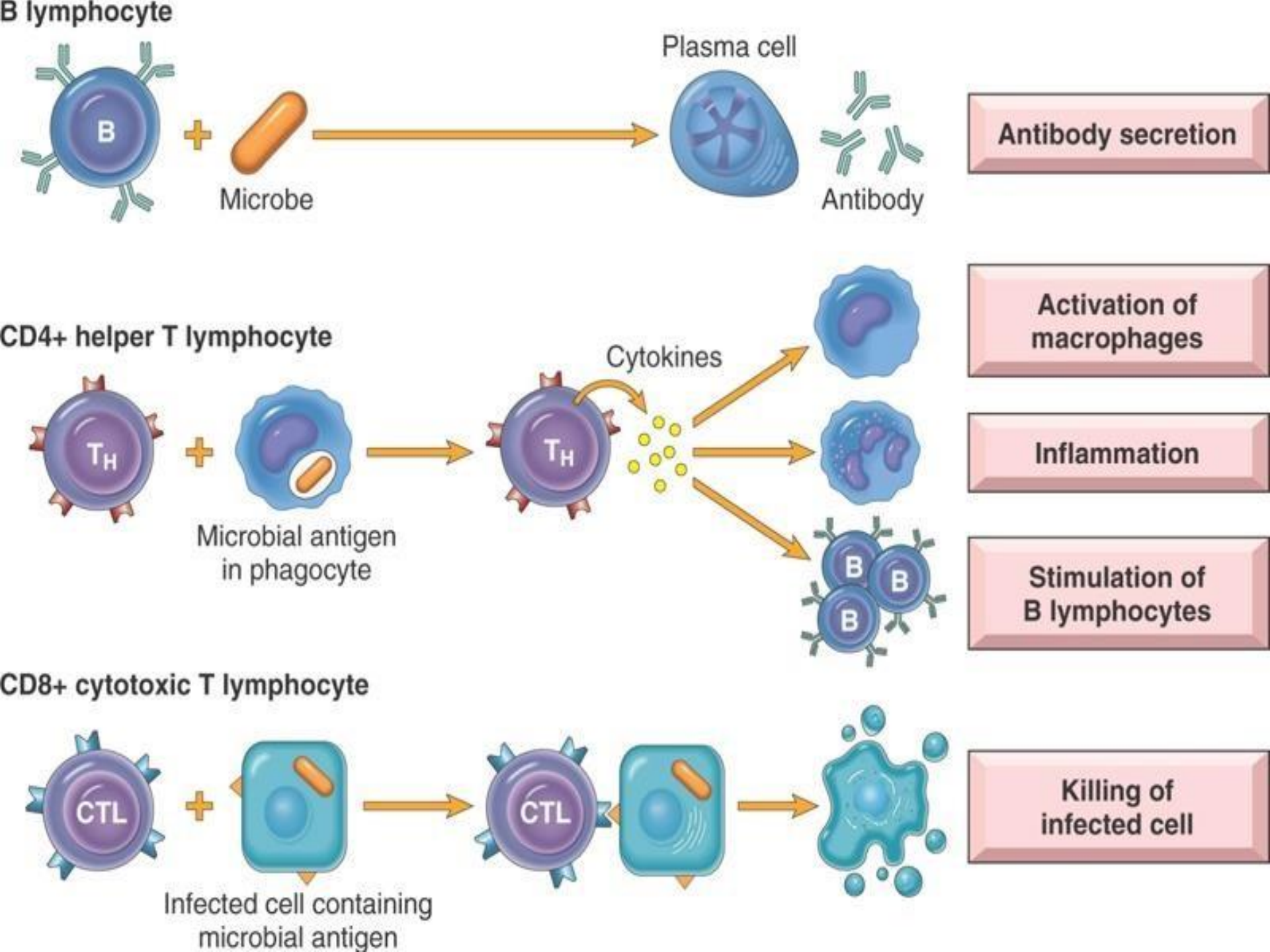
B lymphoctes

- Precursors in bone marrow
- 10 – 20 % of circulating peripheral lymphocytes
- Recognition : B cell antigen receptor complex
- Antigen binding component of B cell:
  - Membrane bound Ab IgM and IgD


Follicles
A
Cortex
Medulla


Dendritic cell
Afferent lymphatic vessel
Naive B cell
Naive T cell
T cell zone
B cell zone
B
Artery
T cell
B cell

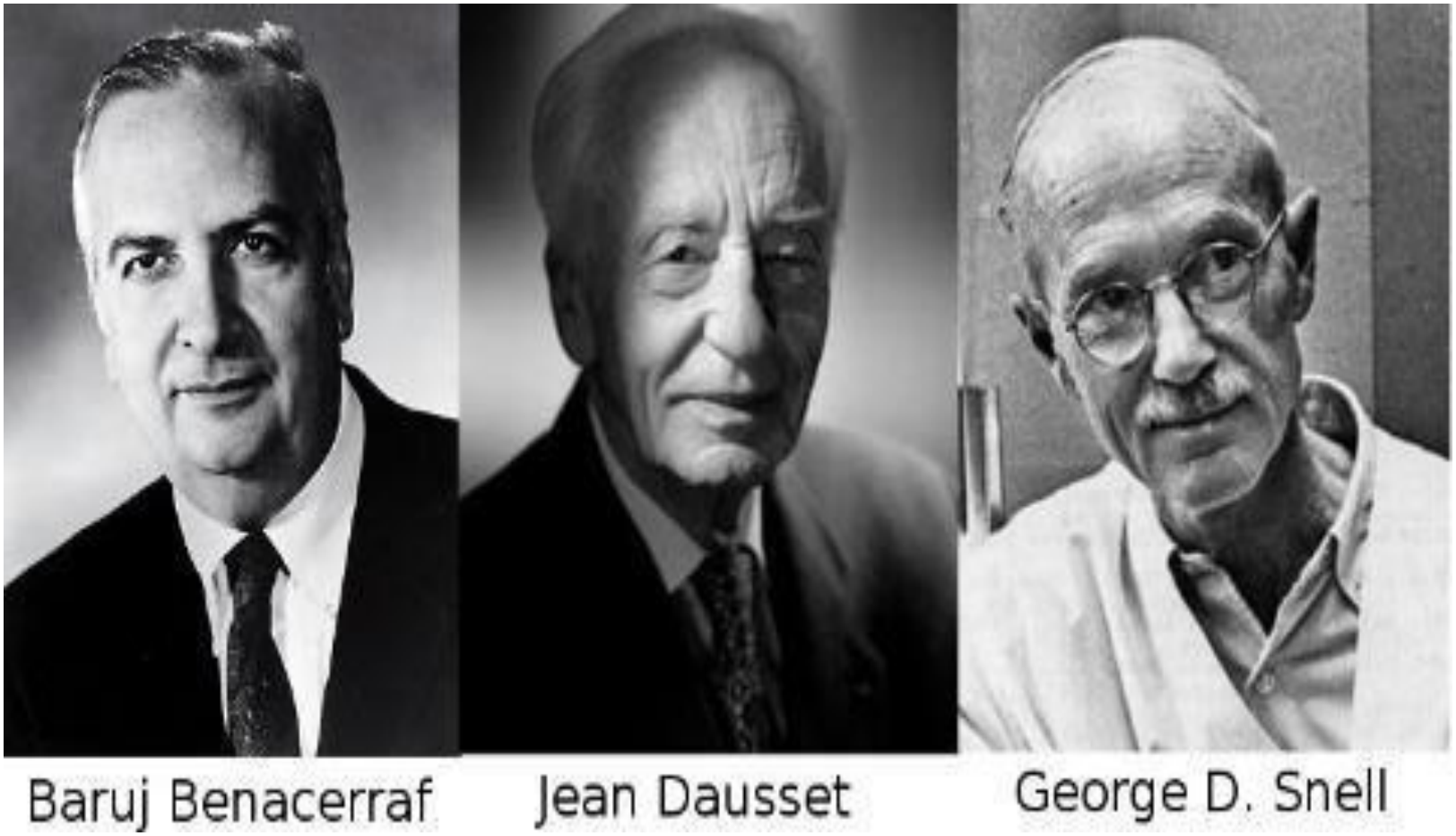

C
B cells
T cells


B lymphocyte
B
Microbe
Plasma cell
Antibody
Antibody secretion
CD4+ helper T lymphocyte
TH
Microbial antigen
in phagocyte
Cytokines
TH
Activation of
macrophages
Inflammation
B
B
B
Stimulation of
B lymphocytes
CD8+ cytotoxic T lymphocyte
CTL
Infected cell containing
microbial antigen
CTL
Killing of
infected cell

CELLS	MARKERS
T CELLS	CD 1 CD 3 CD 4 CD 5 CD 8
B CELLS	CD 10 CD 19 CD 20 CD 21 CD 23 CD 79a
NK CELLS	CD 16 CD 56
LEUCOCYTE COMMON ANTIGEN	CD 45

MAJOR HISTOCOMPATIBILITY COMPLEX

MAJOR HISTOCOMPATIBILITY COMPLEX

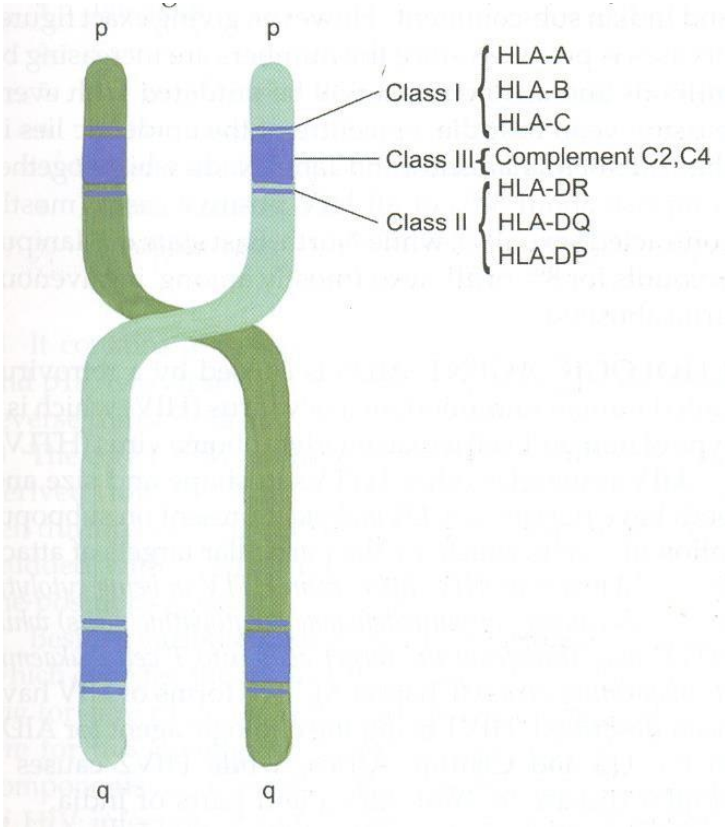


MAJOR HISTOCOMPATIBILITY COMPLEX

- Products of genes which evoked rejection of transplanted organs
- Chromosome 6 (short arm)
- 240 genes
- Human leucocyte antigen:
  - Proteins encoded on Leucocytes

CLASSES

- CLASS I
- CLASS 11
- CLASS 111



Human HLA complex

Complex	HLA								
MHC class	II			III		I			
Region	DP	DQ	DR	C4, C2, BF		B	C	A	
Gene products	DP αβ	DQ αβ	DR αβ	C′ proteins	TNF-α TNF-β	HLA-B	HLA-C	HLA-A	

MHC CLASS I

- Expression:
  - All nucleated cells
  - Platelets

- Encoded by closely linked loci:
  - HLA -A – HLA -B
  - HLA –C
- Heterodimer

Polymorphic α / heavy chain

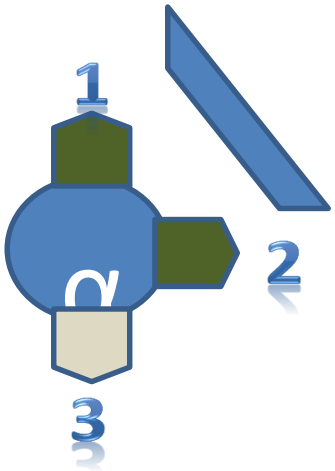
(44 kD)

NON COVALENT

Non polymorphic β2 microglobulin

(12 kD)

Not encoded in MHC



CLEFT / GROOVE PEPTIDE BINGING

- **DISPLAYS:**
  - Cytoplasmic microbes (Viral antigens)
- Tumor cells
- **RECOGNISED BY:**
  - Cd 8 + T lymphocyte

MHC CLASS II

- Expression:

– Antigen presenting cells

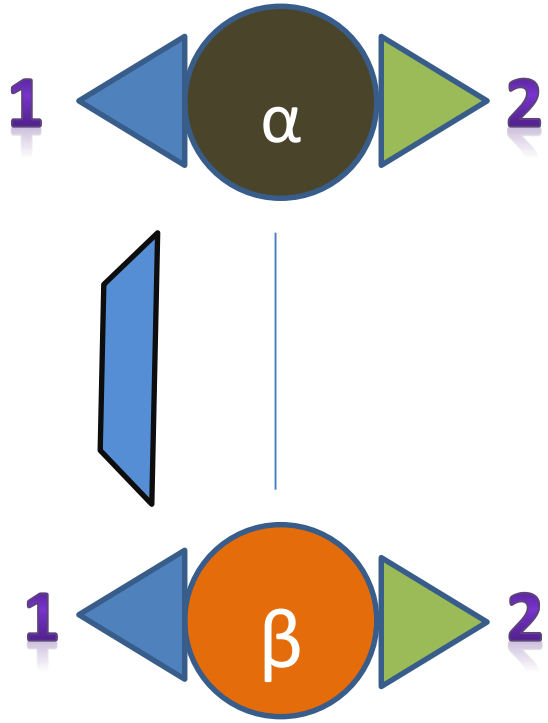
- Dendritic cells
- Macrophages
- B cells

- Encoded in :

– HLA D

- HLA DP
- HLA DQ
- HLA DR

- Heterodimer



NONCOVALENT

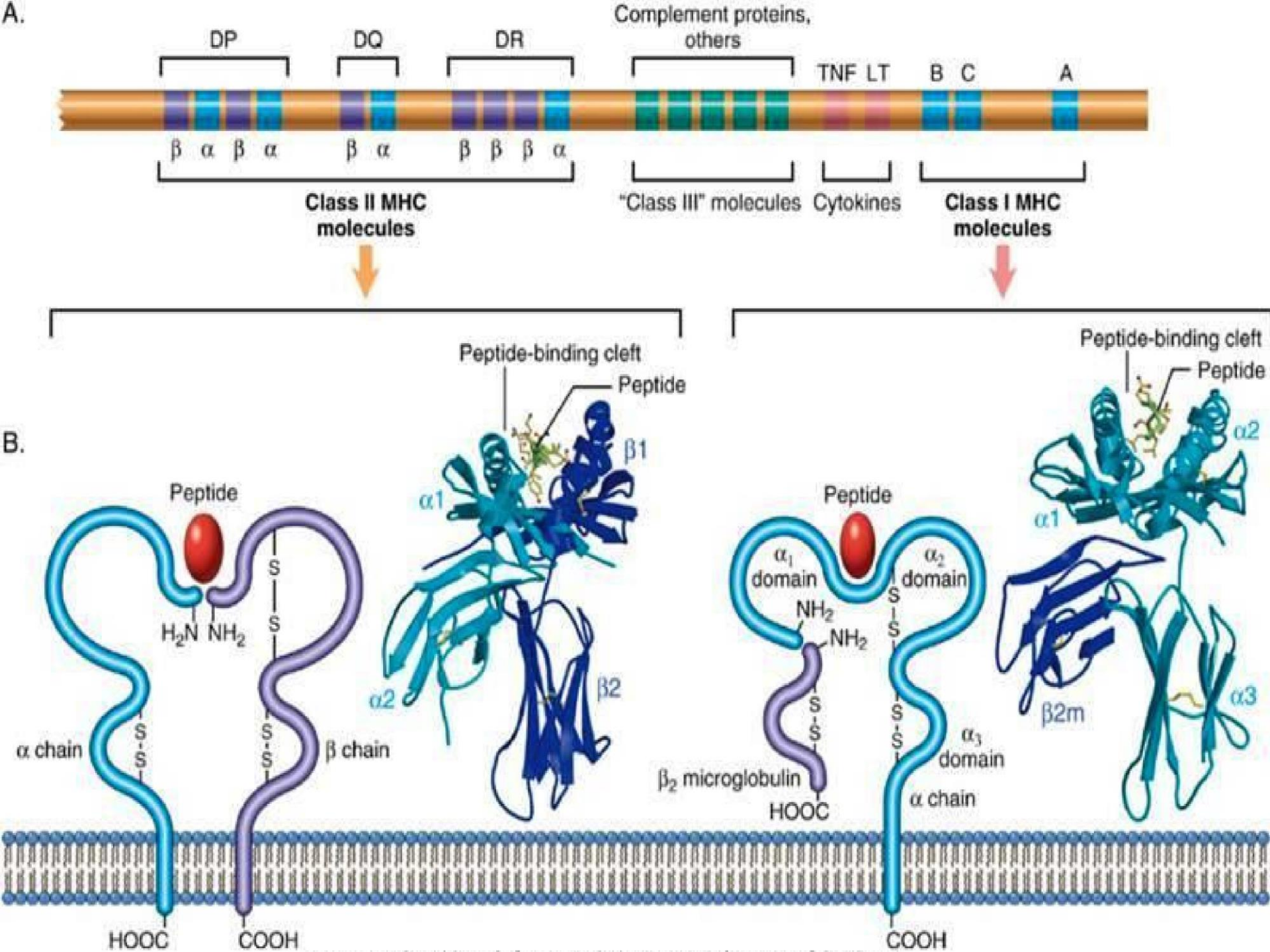
POLYMORPHIC

MHC CLASS III

- Includes complement components
  - C2
  - C3
  - BF

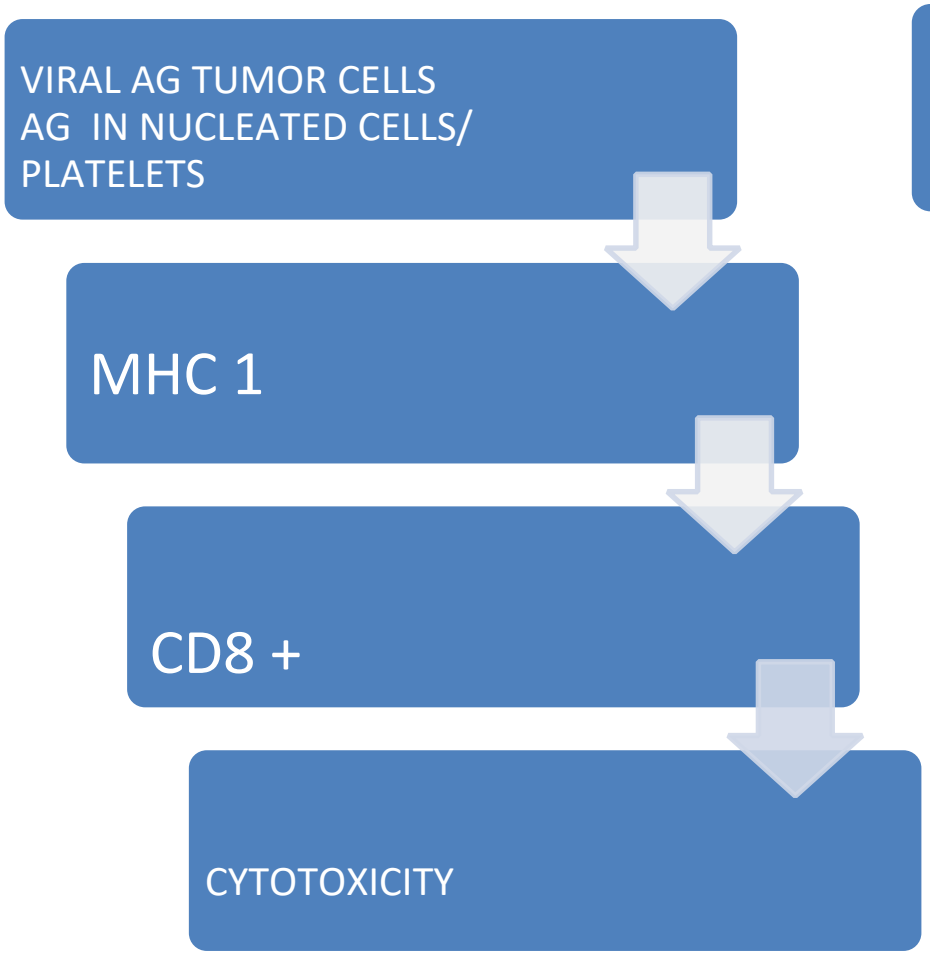
  } Genes encoding TNF & lymphotoxin

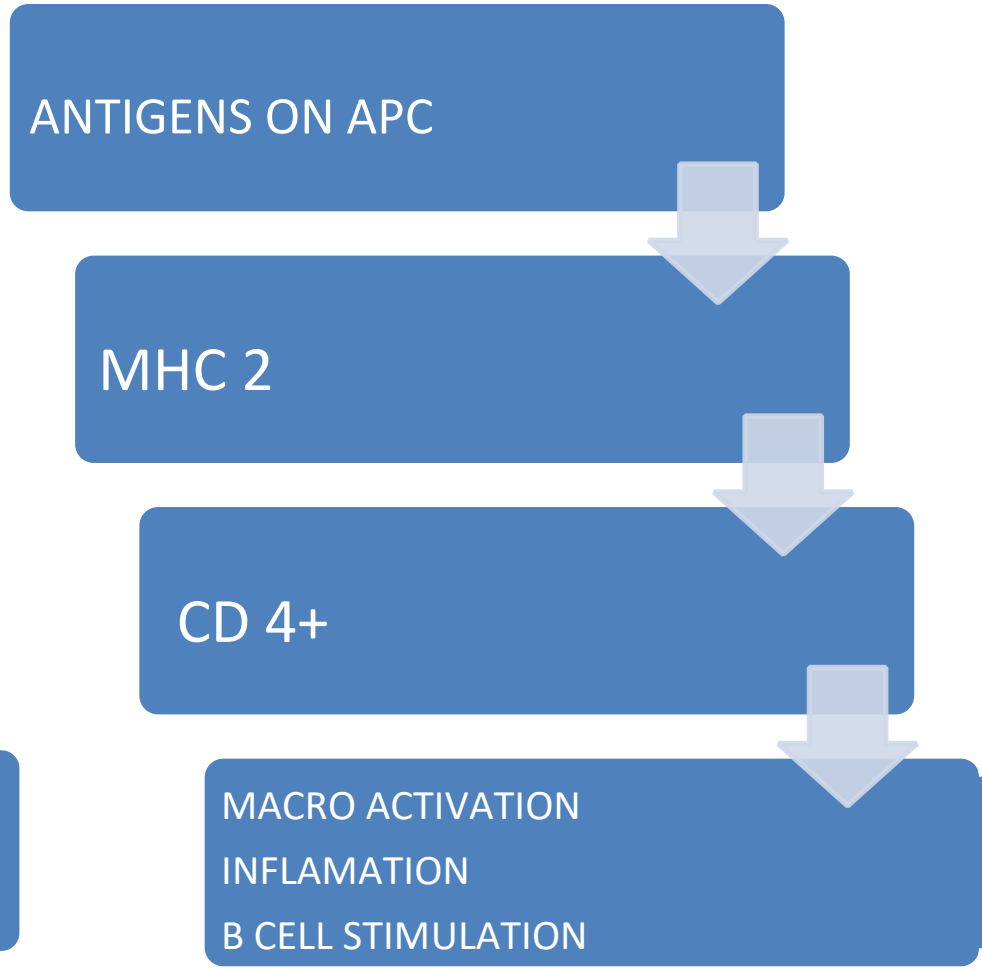
- Genetically linked to class I & II molecules
- Do not form part of peptide display system
- Not used in antigen identification


A.
DP
DQ
DR
Complement proteins, others
TNF LT
B C
A
β α β α
β α
β β β α
Class II MHC molecules
"Class III" molecules
Cytokines
Class I MHC molecules
B.
Peptide-binding cleft
Peptide
β1
α1
α2
β2
Peptide
H2N NH2
S S
α chain
β chain
HOOC
COOH
Peptide-binding cleft
Peptide
α2
α1
Peptide
α1 domain
α2 domain
NH2
NH2
β2m
α3
α3 domain
β2 microglobulin
HOOC
α chain
COOH

MHC	EXPRESSION	FXN	PEPTIDE BINDING DOMAIN	SIZE OF BINDIN PEPTIDES	LOCUS
I	NUCLEATED CELLS PLATELETS	CD 8 + T CELLS RECRUITMENT	α 1 α 2	8–10 AA	A B C
II	APC: DENDRITIC CELLS MACROϕ B CELLS	CD 4 + T CELLS RECRUITMENT	α1 β1	13–18 AA	DP DQ DR
III	C 2 & 3 HSP TNF	NO ROLE IN Ag DISPLAY			

Regulation of immune system





Role of cells of immunity

- Hypersensitivity reactions
- Autoimmune disorders
- Rejection of transplant tissues
- Immuno deficiency syndromes

Hypersensitivity reactions

- Excessive response to antigen
- Exogenous Ag
- Endogenous Ag

Gel and Coombs classification.

- Type 1- Immediate
- Type 2- Antibody mediated
- Type 3- Immune complex mediated

- Type 4- Cell mediated

Immediate (type 1) hypersensitivity

- Rapid immunologic reaction occurring in a previously sensitized individual that is triggered by the binding of an antigen to IgE antibody on the surface of mast cells.

Immediate (type 1) hypersensitivity

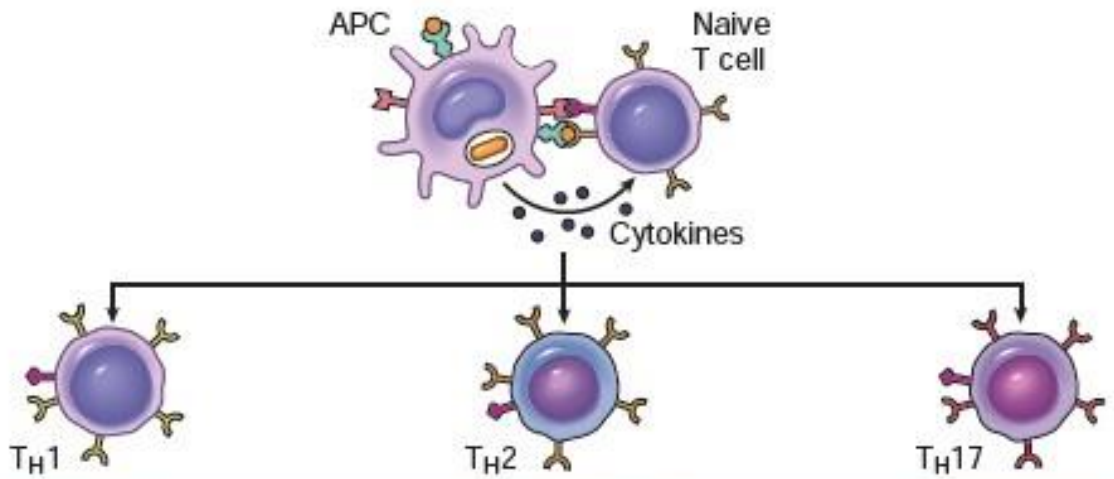
- Occur and resolve quickly
- Mediated by serum IgE
- Systemic and local tissue dysfunction
- Genetic predisposition

- Systemic reaction:
  - Most often follows injection of an antigen into a sensitized individual (e.g., by a bee sting), but can also follow antigen ingestion (e.g., peanut allergens).
  - Sometimes, within minutes the patient goes into a state of shock, which may be fatal.
- Local reactions:
  - Localized cutaneous rash or blisters (skin allergy, hives)
  - Nasal and conjunctival discharge
  - Hay fever, bronchial asthma
  - Allergic gastroenteritis (food allergy).

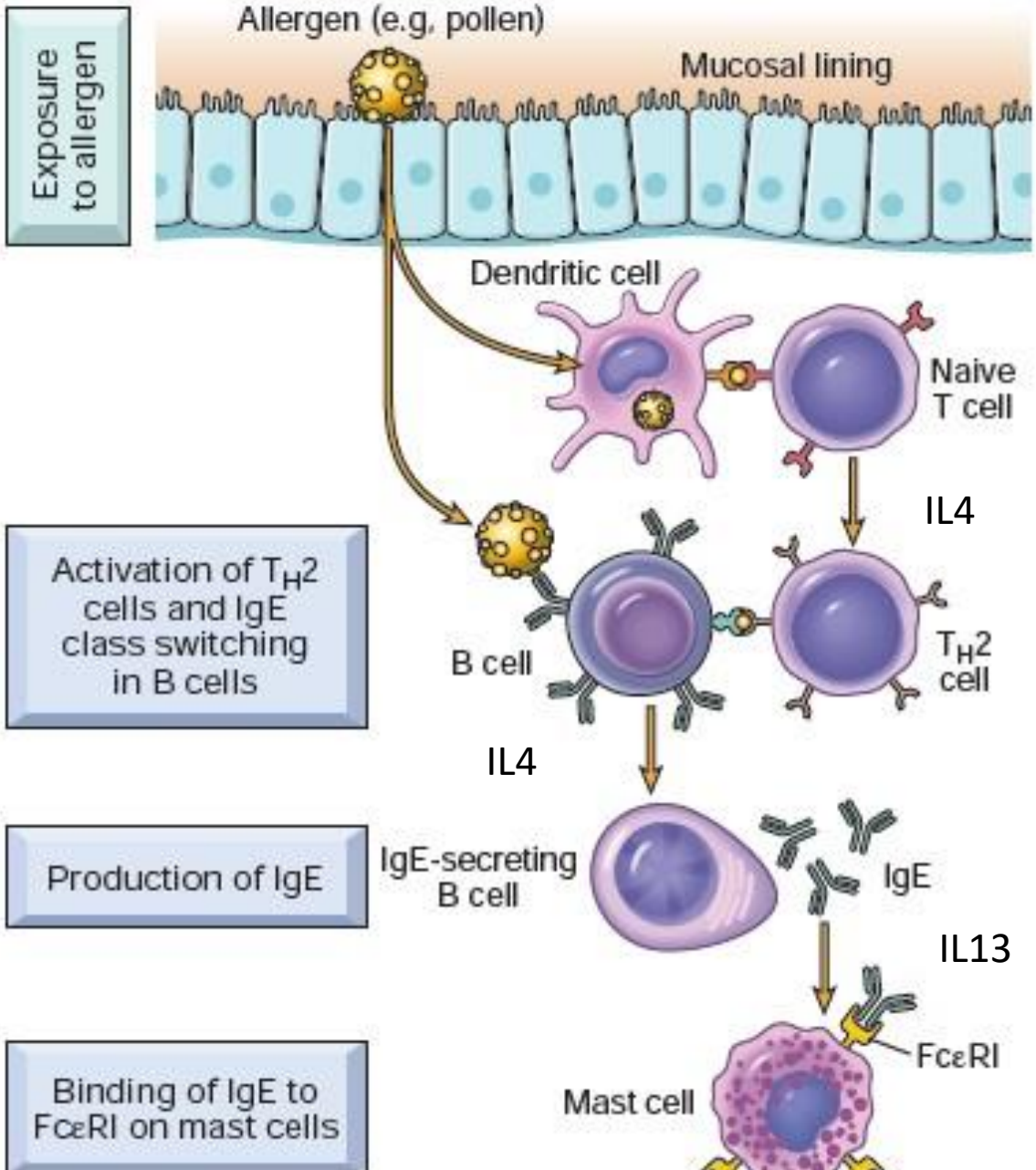
Localised Reaction

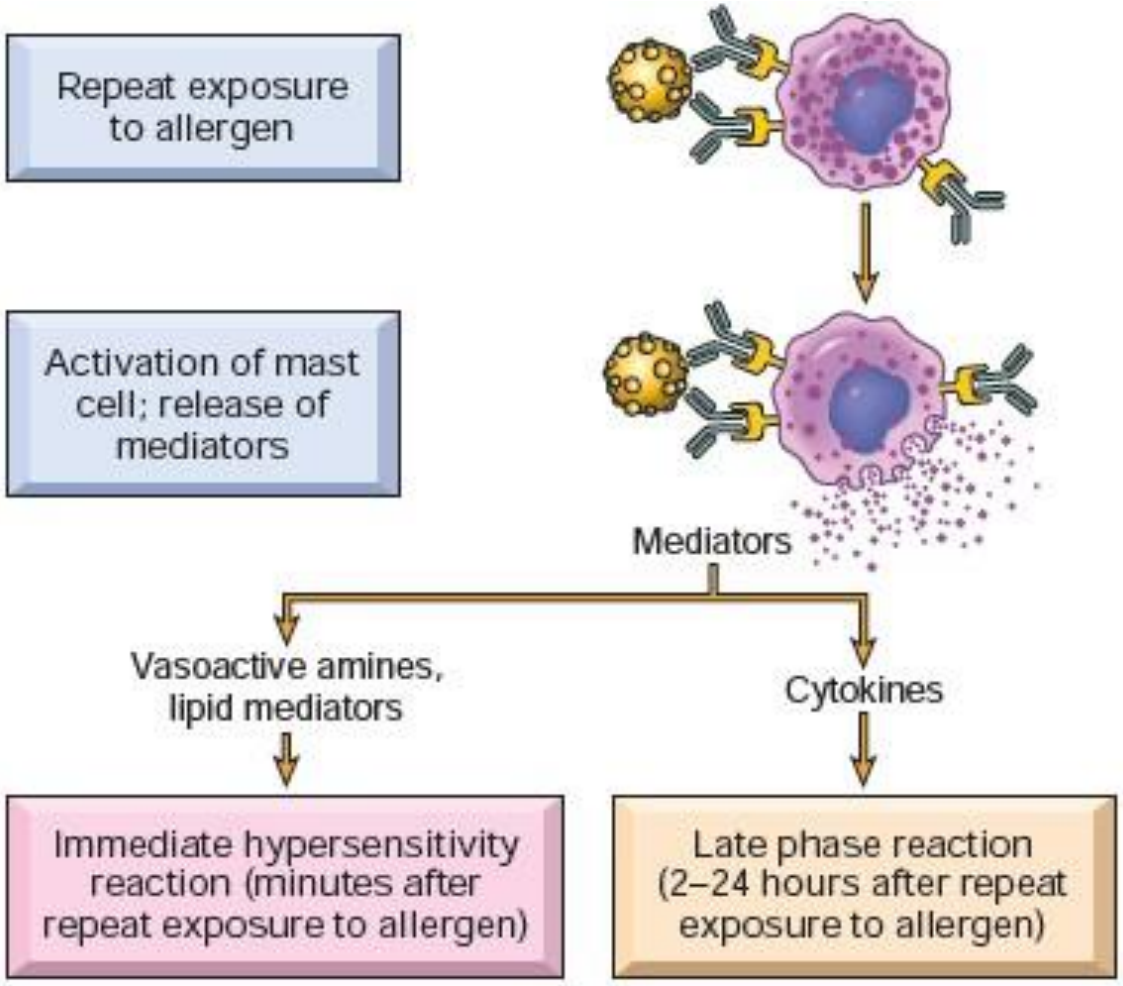
- Immediate phase reaction
  - vasodilation, vascular leakage, and depending on the location, smooth muscle spasm or glandular secretions.
  - within minutes after exposure to an allergen and tend to subside in a few hours.
- Late-phase reaction*:*
  - 2 to 24 hours later without additional exposure to antigen and may last for several days.
  - Infiltration of tissues with eosinophils, neutrophils, basophils, monocytes, and CD4+ T cells, as well as tissue

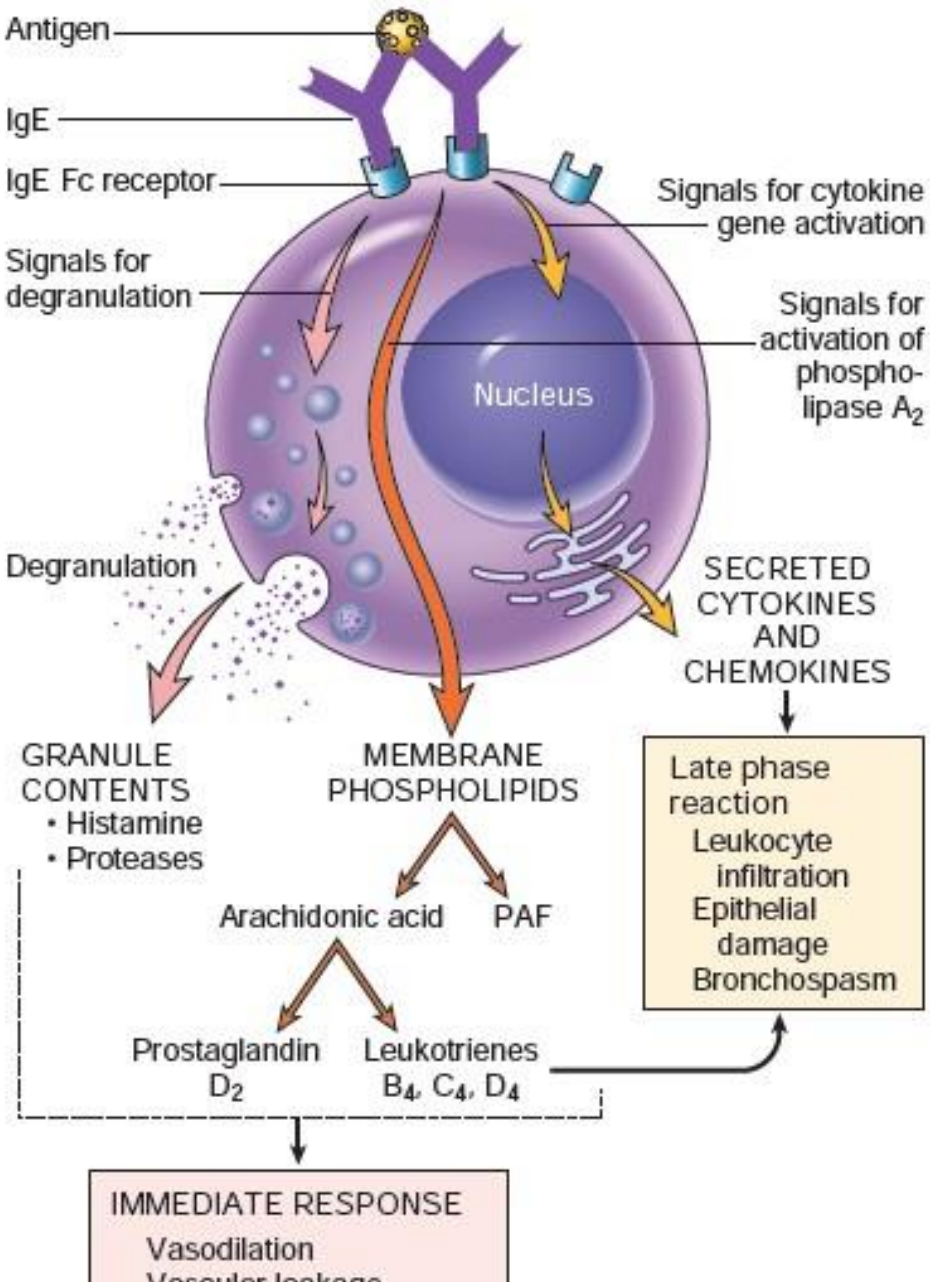
destruction, typically in the form of mucosal epithelial cell damage.



Major cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, granulomatous inflammation)	Allergies	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, MS)


Exposure to allergen
Allergen (e.g, pollen)
Mucosal lining
Dendritic cell
Naive T cell
IL4
Activation of T_H2 cells and IgE class switching in B cells
B cell
T_H2 cell
IL4
Production of IgE
IgE-secreting B cell
IgE
IL13
Binding of IgE to FcεRI on mast cells
FcεRI
Mast cell


Repeat exposure to allergen
Activation of mast cell; release of mediators
Mediators
Vasoactive amines, lipid mediators
Cytokines
Immediate hypersensitivity reaction (minutes after repeat exposure to allergen)
Late phase reaction (2–24 hours after repeat exposure to allergen)


Antigen
IgE
IgE Fc receptor
Signals for degranulation
Signals for cytokine gene activation
Signals for activation of phospho-lipase A_2
Nucleus
Degranulation
SECRETED CYTOKINES AND CHEMOKINES
GRANULE CONTENTS
• Histamine
• Proteases
MEMBRANE PHOSPHOLIPIDS
Arachidonic acid
PAF
Prostaglandin D_2
Leukotrienes B_4, C_4, D_4
Late phase reaction
Leukocyte infiltration
Epithelial damage
Bronchospasm
IMMEDIATE RESPONSE
Vasodilation

The biological mediator on effect stage

1. Histamine:

Dilate blood vessel Increase vascular permeability

2. Leukotrienes:

Bronchial smooth muscles contract ——— Asthmas

3. Prostaglandin:

High concentration of PGE ——— Inhibit the secretion of histamine low concentration of PGE ——— promote the release of histamine

4. Platelet activating factor (PAF) :

Agglutinate and activate platelets to release histamine

5. Eosinophil chemotactic factor（ECF-A）:

6. Bradykinin : Vasodilator function

Table 6-2 Examples of Disorders Caused by Immediate Hypersensitivity

Clinical Syndrome	Clinical and Pathologic Manifestations
Anaphylaxis (may be caused by drugs, bee sting, food)	Fall in blood pressure (shock) cause by vascular dilation; airway obstruction due to laryngeal edema
Bronchial asthma	Airway obstruction caused by bronchial smooth muscle hyperactivity; inflammation and tissue injury caused by late-phase reaction
Allergic rhinitis, sinusitis (hay fever)	Increased mucus secretion; inflammation of upper airways, sinuses
Food allergies	Increased peristalsis due to contraction of intestinal muscles

ATOPY :

- Predisposition to develop localised immediate hypersensitivity reactions to variety of inhaled and ingested allergens

- Inc levels of IgE

- Inc IL-4 producing TH2 cells

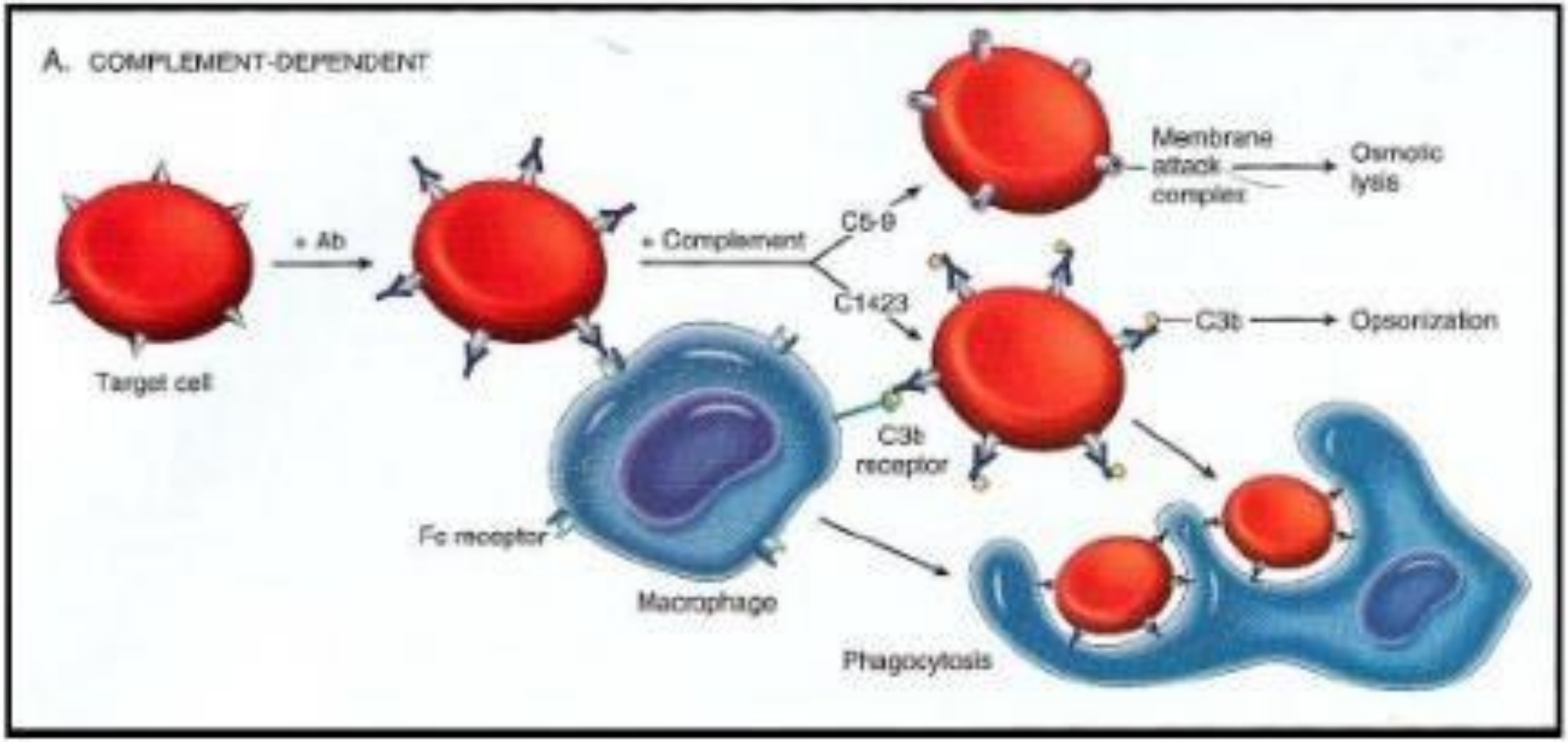
Type II (antibody mediated) hypersensitivity reaction

- Antibodies that react with antigens present on cell surfaces or in the extracellular matrix cause disease by destroying these cells, triggering inflammation, or interfering with normal functions.

Type II hypersensitivity reaction

- *Opsonization and Phagocytosis*
- *Antibody mediated cellular cytotoxicity*
- *Inflammation*
- *Antibody mediated cellular Dysfunction*

Opsonization and Phagocytosis

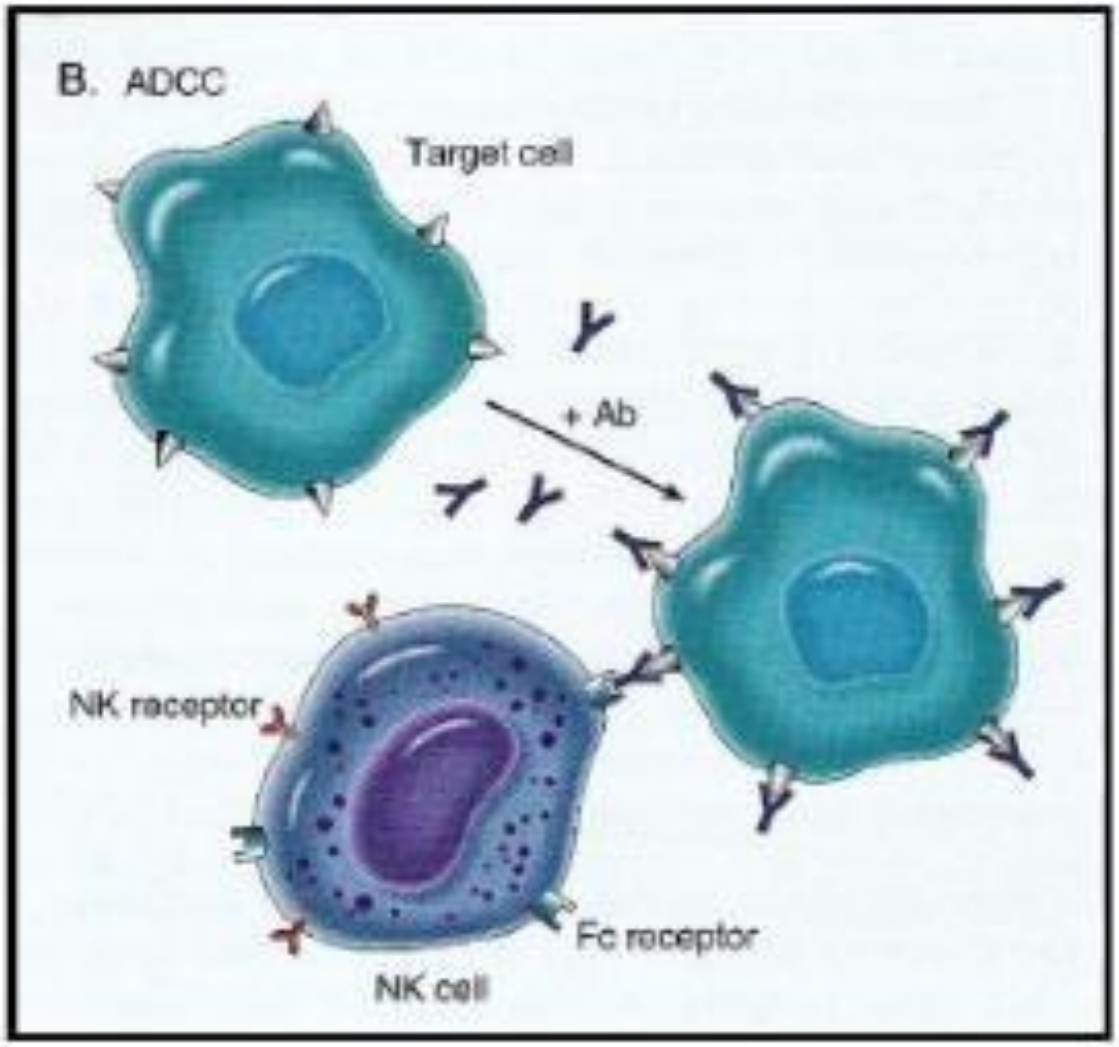


Examples

- Autoimmune hemolytic aneamia
- ITP

Antibody mediated cellular cytotoxicity

- Cells coated with IgG antibody bind to the target (NK cells and macrophages) by their receptors for the Fc fragment of IgG, and cell lysis proceeds without phagocytosis.


B. ADCC
Target cell
+ Ab
NK receptor
Fc receptor
NK cell

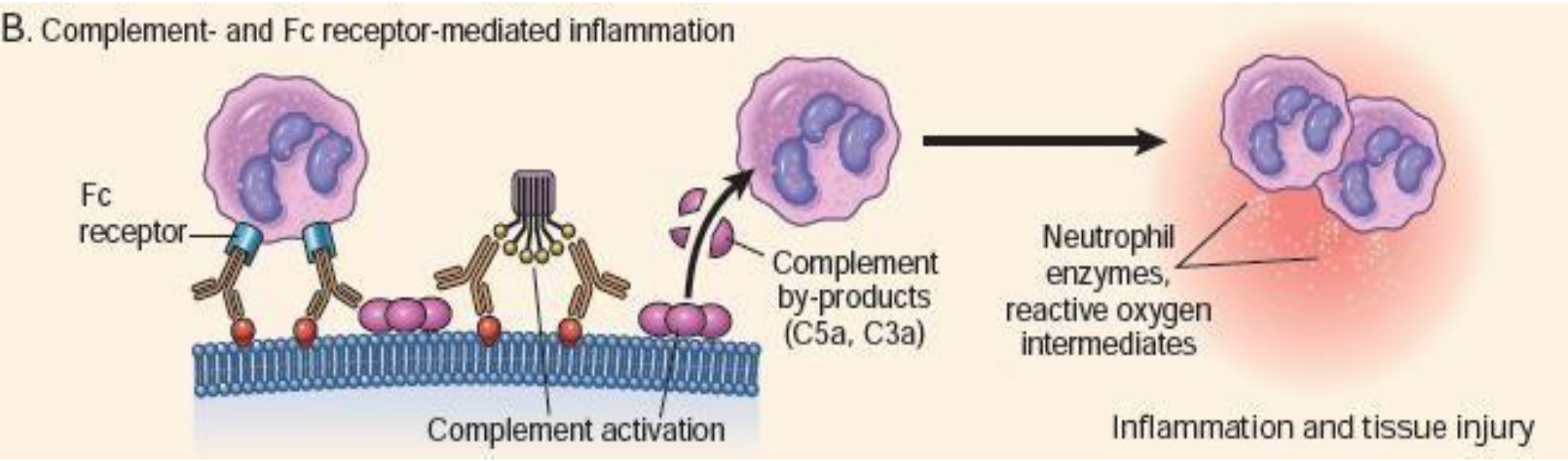
Common disease of type II hypersensitivity

1)Transfusion reaction hemolysis : mismatch of ABO blood group, severely destroy RBC nonhemolysis : repeat transfusion of allogenic HLA drug anaphylactic shock： penicilline

2) Hemolytic disease of newborn

Mother Rh^- : first baby Rh^+(Ab), second baby Rh^+,

fetal RBC destroyed



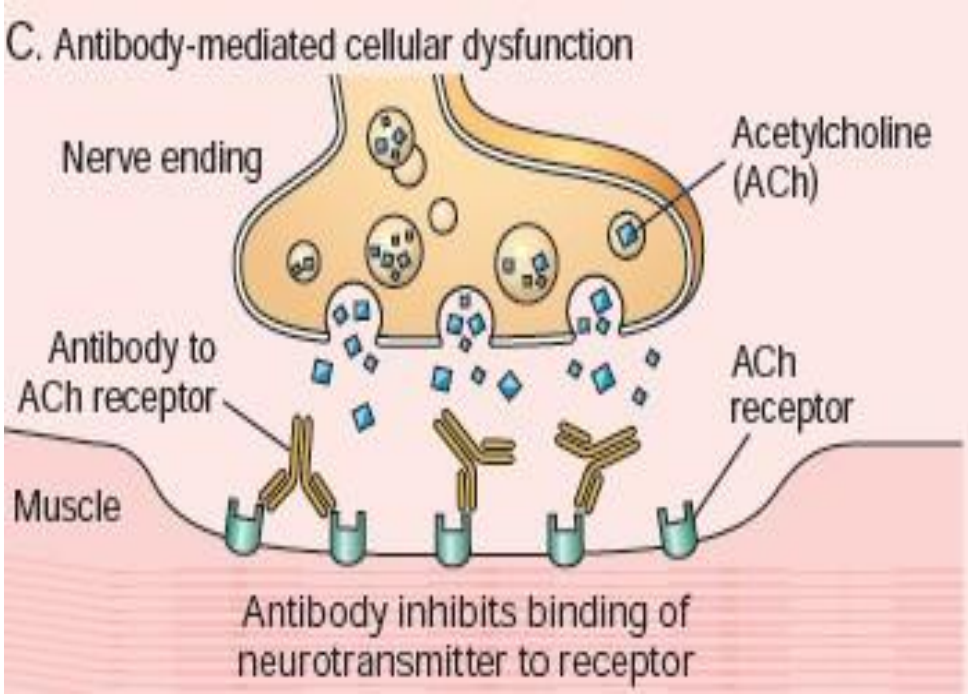
Inflammation

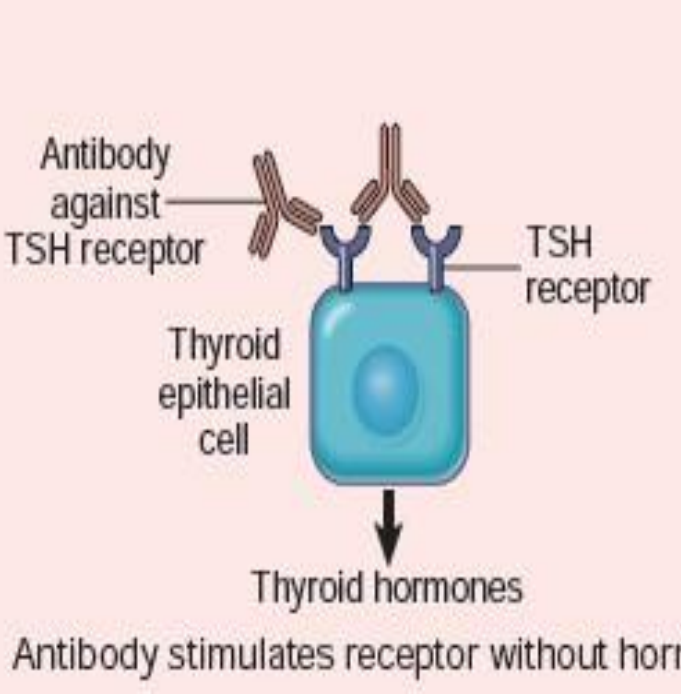
- Antibodies deposit in fixed tissues, such as basement membranes and ECM

Examples

- Good pastuer syndrome
- Vasculitis ANCA associated

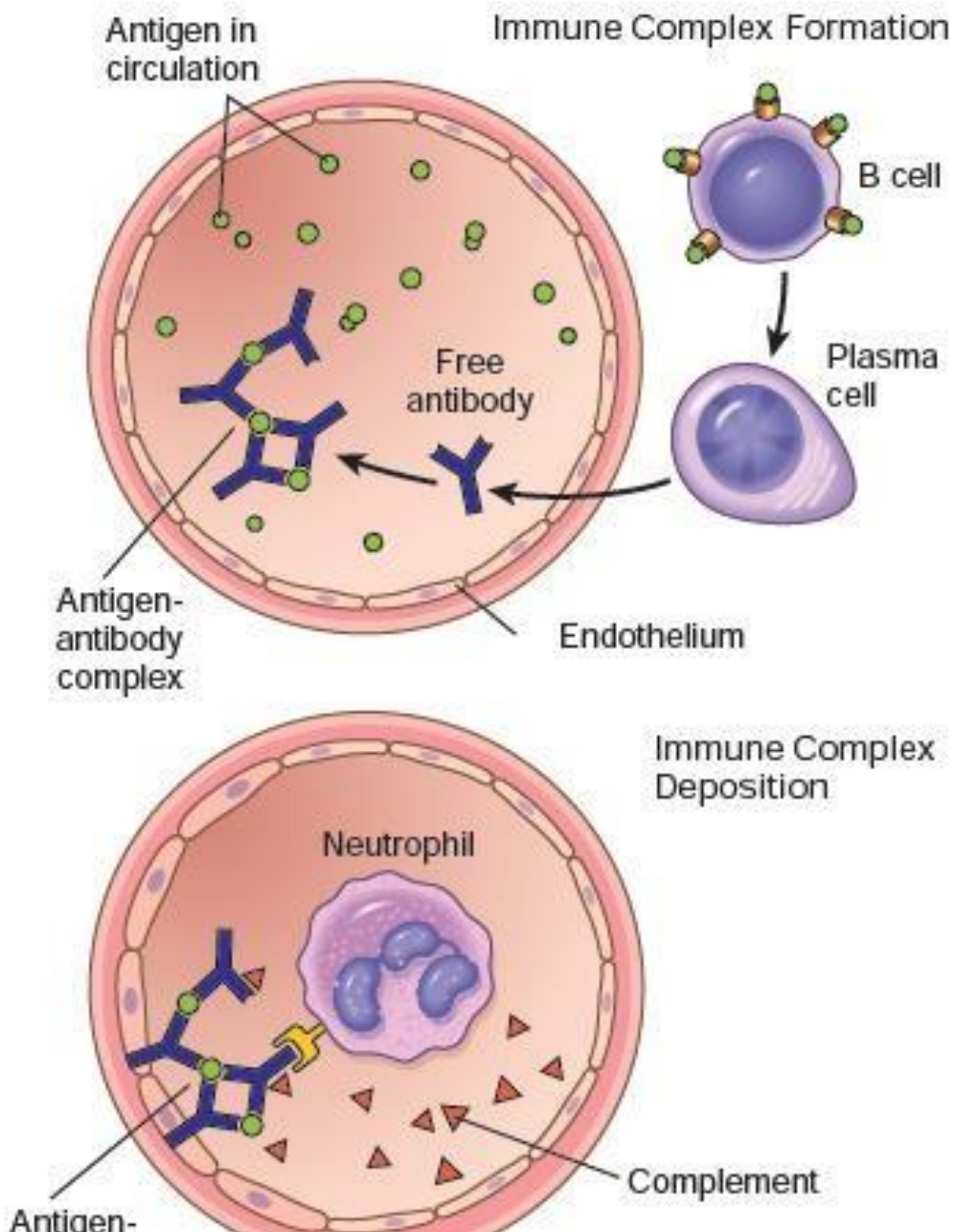
Antibody mediated cellular Dysfunction

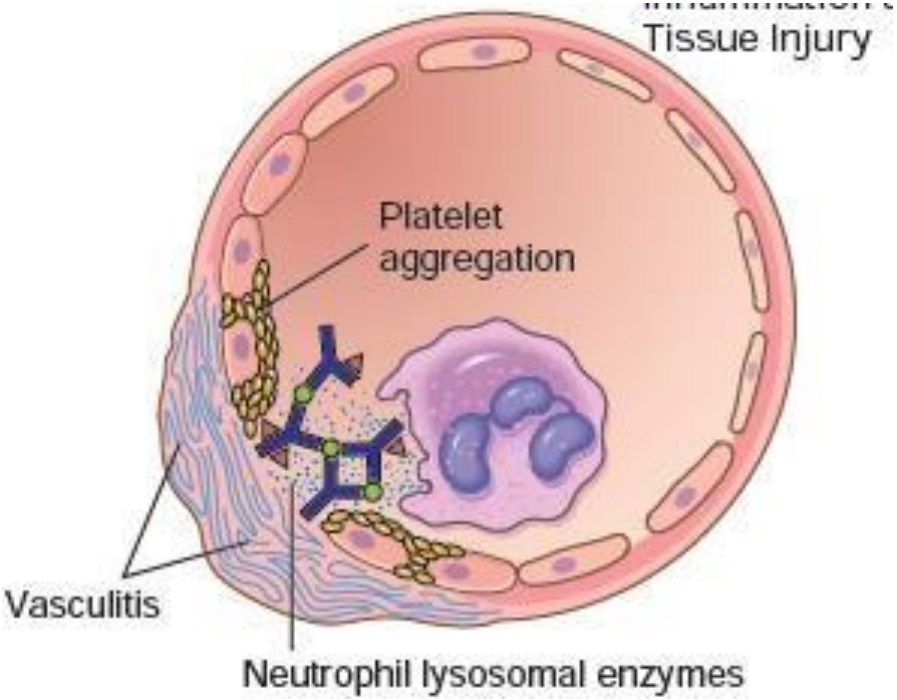




Type III hypersensitivity

Antigen-antibody complexes produce tissue damage mainly by eliciting inflammation at the sites of deposition.


Antigen in circulation
Immune Complex Formation
B cell
Plasma cell
Free antibody
Antigen-antibody complex
Endothelium
Immune Complex Deposition
Neutrophil
Complement


Tissue Injury
Platelet aggregation
Vasculitis
Neutrophil lysosomal enzymes

Sites of deposition : glomeruli , serosal surfaces , joints , skin , heart , small blood vessels

- ***Morphology :***
- Acute necrotising vasculitis with necrosis of vessel wall and neutrophil infiltration ;
- Fibrinoid necrosis

- Hypercellular glomeruli

Disease	Antigen Involved	Clinicopathologic Manifestations
Systemic lupus erythematosus	Nuclear antigens (circulating or "planted" in kidney)	Nephritis, skin lesions, arthritis, others
Poststreptococcal glomerulonephritis	Streptococcal cell wall antigen(s); may be "planted" in glomerular basement membrane	Nephritis
Polyarteritis nodosa	Hepatitis B virus antigens in some cases	Systemic vasculitis
Reactive arthritis	Bacterial antigens (e.g., *Yersinia*)	Acute arthritis
Serum sickness	Various proteins, e.g., foreign serum protein (horse antithymocyte globulin)	Arthritis, vasculitis, nephritis
Arthus reaction (experimental)	Various foreign proteins	Cutaneous vasculitis

Systemic Immune Complex Disease

ACUTE SERUM SICKNESS

- prototype of systemic immune complex disease

- one time a sequela to the administration of foreign serum (e.g., immune serum from horses used for passive immunization.)

- Described in early 1900s by Clemens von Pirquet.

  diphtheria infection were being treated with horse serum , he noted that some of these patients developed arthritis, skin rash, and fever, and the symptoms appeared more rapidly with repeated injection of the serum.

- the treated patients produced antibodies to horse serum proteins, these antibodies formed complexes with the injected proteins, and the disease was due to the antibodies or immune complexes.

- He called this disease "serum disease".

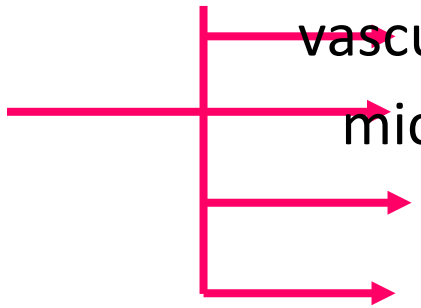
- In modern times the disease is infrequent **Arthus Reaction**

* This is a local immune complex deposition phenomenon (4-10 hrs after injection)
  e.g. diabetic patients receiving insulin subcutaneously

* Local reactions in the form of → edema, erythema, necrosis

* Immune complexes ——— in small blood vessels

leading to → vasculitis, microthrombi formation



vascular occlusion

necrosis

Type	Disodrer	Mechanism
IMMEDIATE	Anaphylaxis Allergies Bronchial asthma	IgE Ab → Vasoactive amines from mast cells → Inflammatory cells
Ab MEDIATED	Autoimmune hemolytic anemia Good pasture syndrome	IgG,IgM binds Ag ↓ Phagocytosis ↓ Leucocytosis
IMMUNE COMPLEX MEDIATED	SLE GN Serum sickness Arthus reaction	Ag-Ab complex → Comp activation ↓ Leucocyte → Enzymes
CELL MEDIATED	Tuberculosis Type 1 DM RA IBD	Activated T lymphocytes

Autoimmune diseases

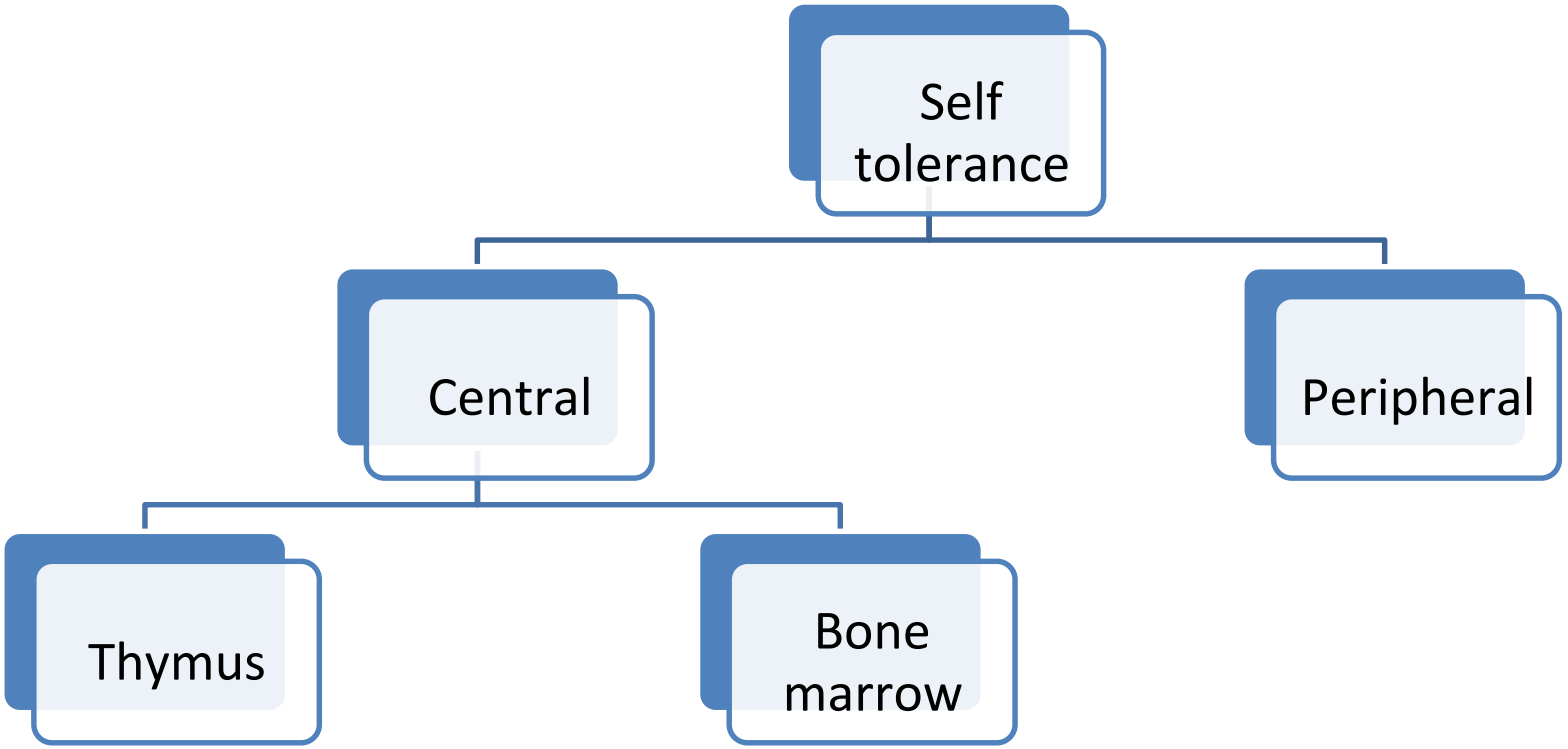
- Immune reaction against self antigen
- Serum autoantibodies:
  - Old age
  - Tissue damage

Pathologic autoimmunity

- Immune reaction specific for self Ag or self tissue
- Not secondary to tissue damage
- Absence of well defined cause of disease

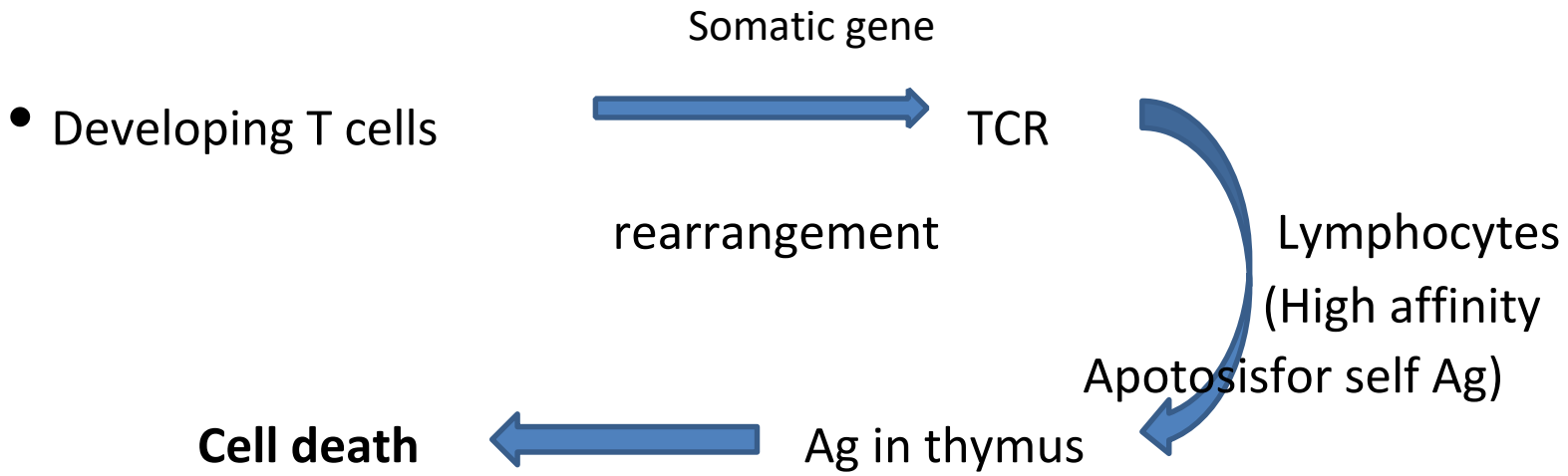
Self tolerence

- Lack of responsiveness to self antigens



Central tolerance

- **Thymus** :



Negative selection

Regulatory T cells

- Bone marrow:

Receptor editing

B cells

Bone marrow self antigens

Gene rearrangement of Ag receptor

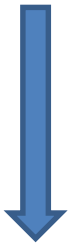
New Ag receptor on B cell with no axn against self Ag

Peripheral tolerance

- Anergy
- Suppression by regulatory T cells
- Deletion by activation induced cell death

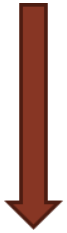
Anergy:

Antigens with out co stimulators



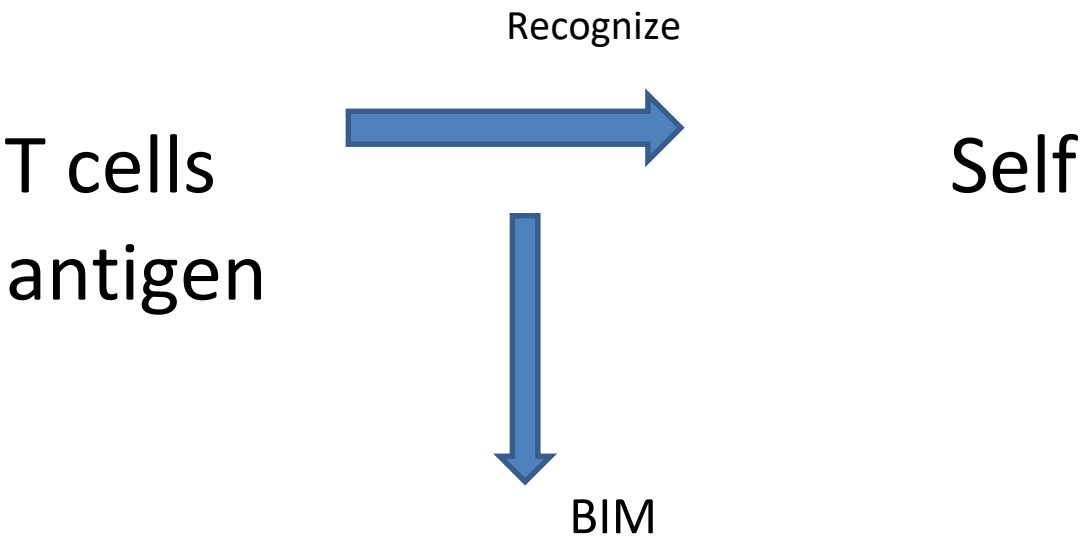
T cell exposure

Negative signals



Fxnal Inactivation of T cells

Deletion by activation induced cell death



CELL DEATH

Autoimmune diseases

- SLE
- DLE
- Rheumatoid athritis
- Sjogrens syndrome
- Systemic sclerosis
- Inflammatory myopathies

Ab	SLE	DLE	Systemic sclerosis (Diffuse)	Limited sclerderma	Sjogrens syndrome
Generic ANA	>95 %	>95 %	70 – 90 %	70 – 90 %	50 – 80 %
Anti ds DNA	40 – 60%				
Anti histone	50 – 70 %	>90 %			
Anti Sm	20 – 30 %				
SS A (Ro)	30 – 50 %				70 – 95 %
SS b (La)	10 – 15 %				60 – 90 %
Scl 70			28 – 70 %	10 – 18 %	
Anti centromer			22 – 36 %	90 %	

Systemic Lupus erythematosus

- **Autoimmune** disease involving **multiple organs**, characterized by a vast array of **autoantibodies**, particularly antinuclear antibodies (ANAs), in which injury is caused mainly by **deposition of immune complexes** and binding of antibodies to various cells and tissues.
- **A**cute or insidious in its onset

- Chronic, remitting and relapsing, often febrile, illness.
- 1 in 2500 in certain populations.
- Women (9 : 1) during the reproductive age group of 17 through 55 years.
- 20s and 30s, it may manifest at any age, even in early childhood.

ETIOLOGY

- Genetic Factors
- Immunological Factors
- Environmental Factors

GENETIC

- Complex disease :- MHC & NON MHC Genes
- Increased Risk in family members
- Increased Risk in Monozygotic twins

2. Environmental factors

1. UV light UVB flares SLE.

   UV induces keratinocytes to produce IL1 ;
   apoptosis in cells and renders DNA immunogenic

2. Drug-induced lupus.

   Hydralazine, Procainamide , Beta-blockers ,
   Isoniazid , Penicillamine

3. Allergy.

   Does it induce lupus flare? No direct evidence.

4. Infection.

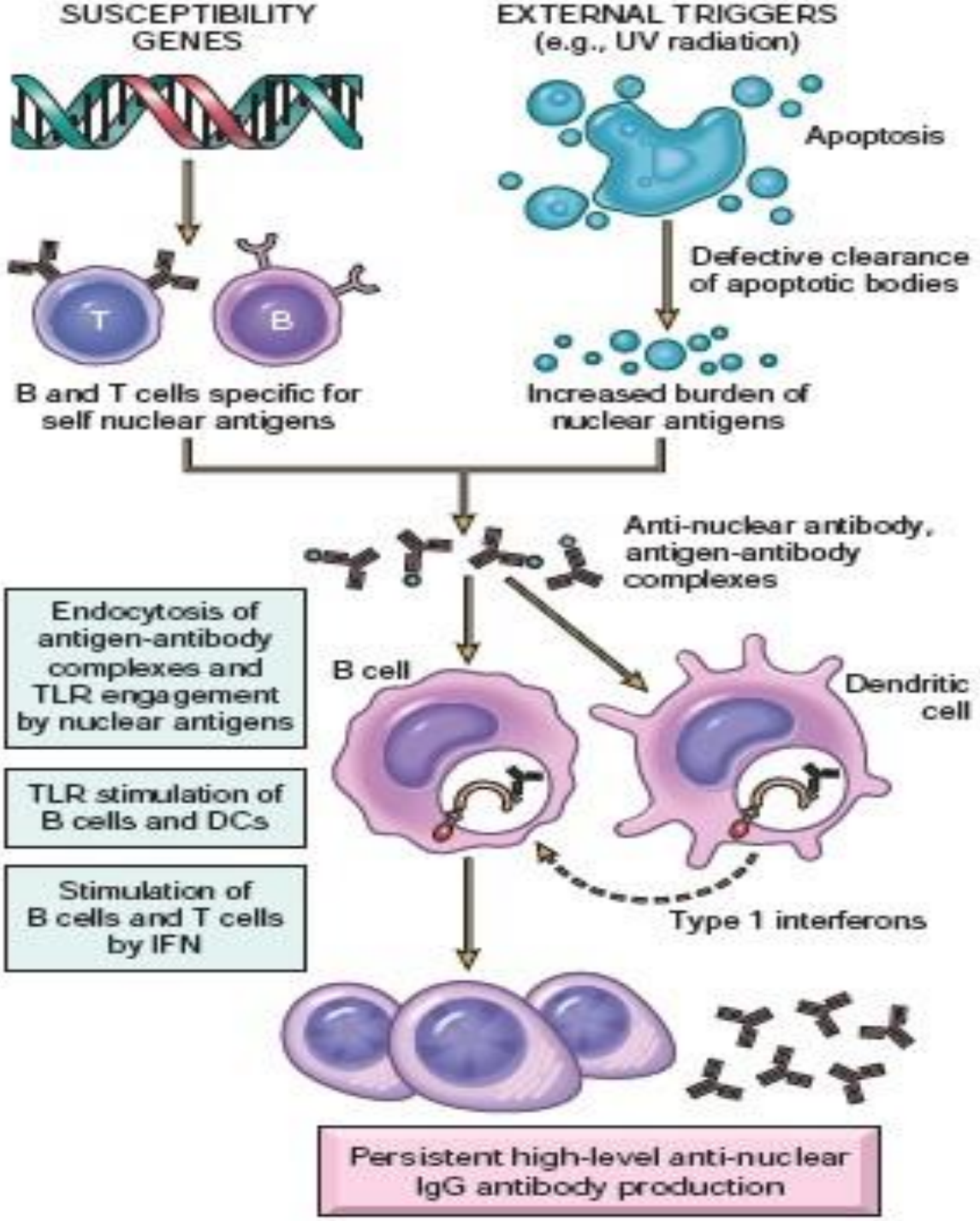
Mechanism might include molecular mimicry between external Ag and a self-Ag, non specific activation of T or B cells.

There has been recent interest in EBV, CMV and other virus.

3. Abnormal immune system

- **Sustained presence of autoantigens: • impaired clearance of apoptotic cells**

- **Hyperactivity in B and T lymphocyte.**
- **Overproduction of IL-6 and IL-10**
- **Defective regulatory mechanism.**


SUSCEPTIBILITY GENES
EXTERNAL TRIGGERS (e.g., UV radiation)
Apoptosis
Defective clearance of apoptotic bodies
T
B
B and T cells specific for self nuclear antigens
Increased burden of nuclear antigens
Anti-nuclear antibody, antigen-antibody complexes
Endocytosis of antigen-antibody complexes and TLR engagement by nuclear antigens
B cell
Dendritic cell
TLR stimulation of B cells and DCs
Stimulation of B cells and T cells by IFN
Type 1 interferons
Persistent high-level anti-nuclear IgG antibody production

LAB DIAGNOSIS

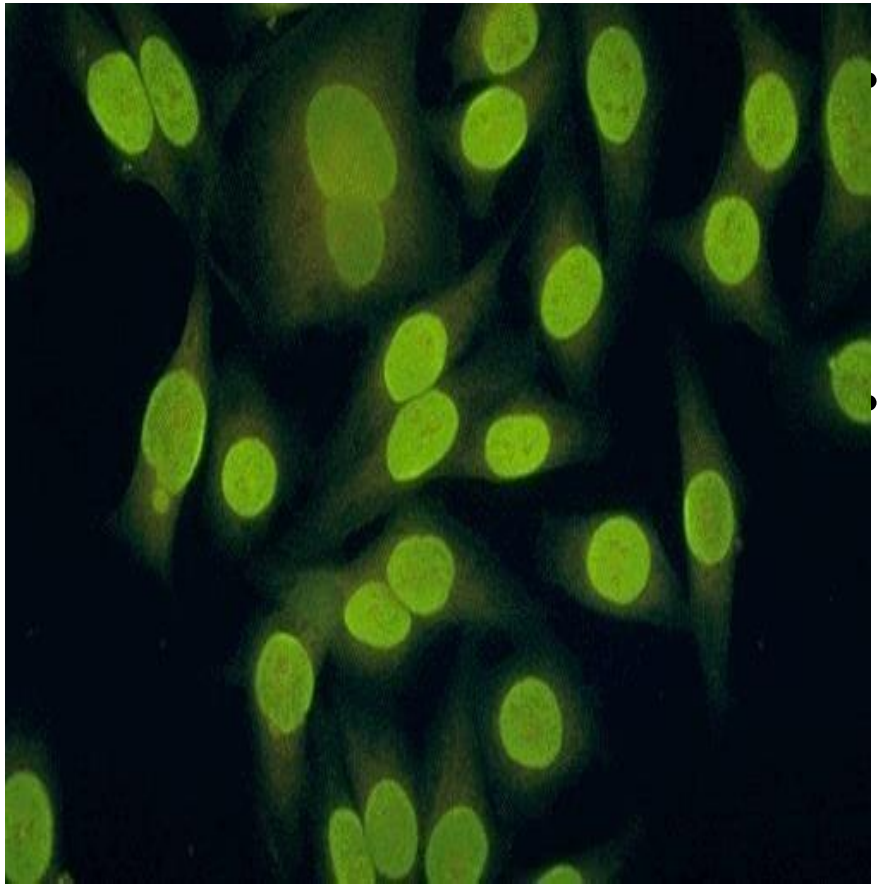
- **Technique used to detect ANAs – Indirect IFpattern suggests the type of Ab.**

i) **Diffuse nuclear staining** = Ab to chromatin histones rarely double stranded DNA **ii) Rim or peripheral staining** – ds DNA.

iii) **Speckled pattern** (least specific) – non DNA nuclear constituents. Eg; SM, RNA,SS-A, SS-B reactive ag.

iv) **Nucleolar pattern** – Few spots in the nucleus – ab to RNA in SS.

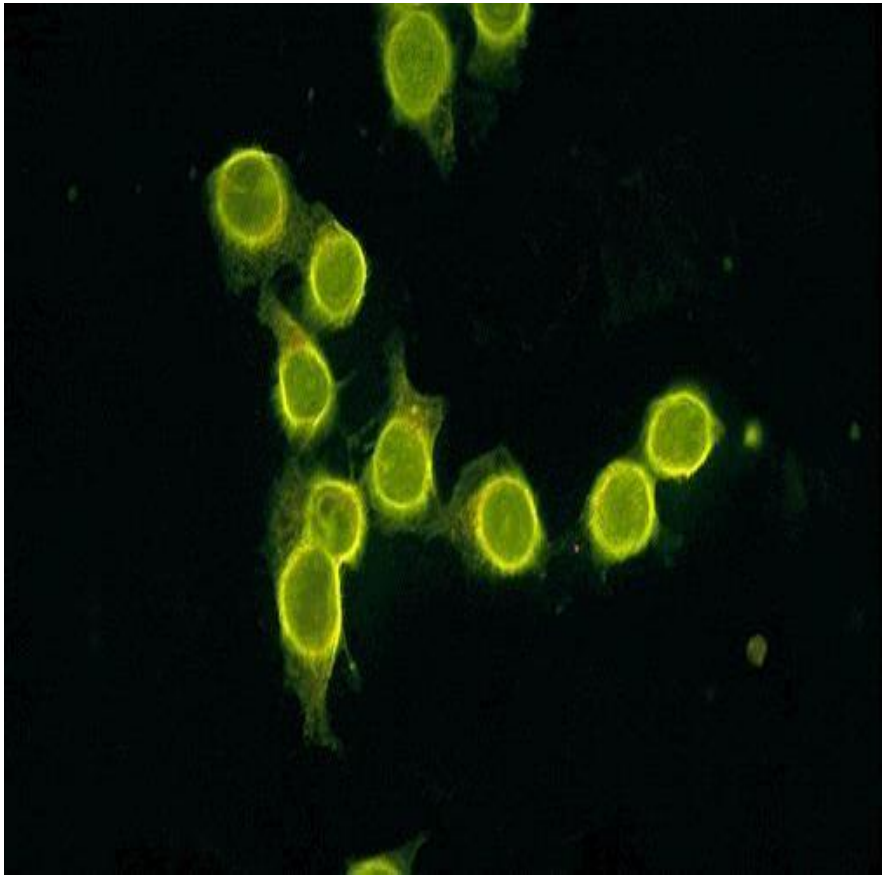
Immunoflourescence



chromatin histones

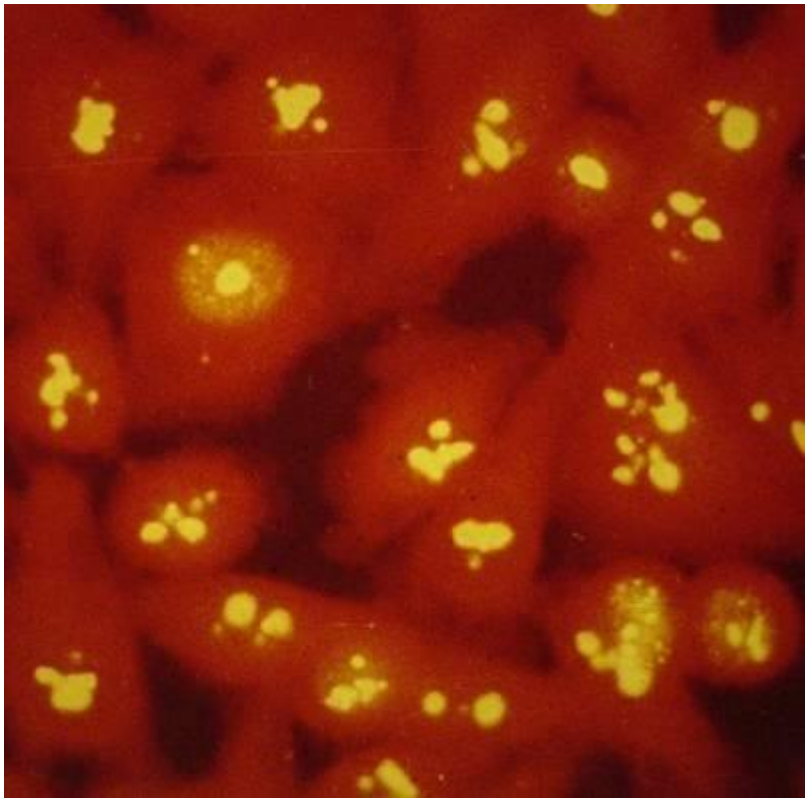
- This rim (peripheral) pattern of linear bright

- Homogenous pattern is the most common pattern with autoimmune diseases overall.

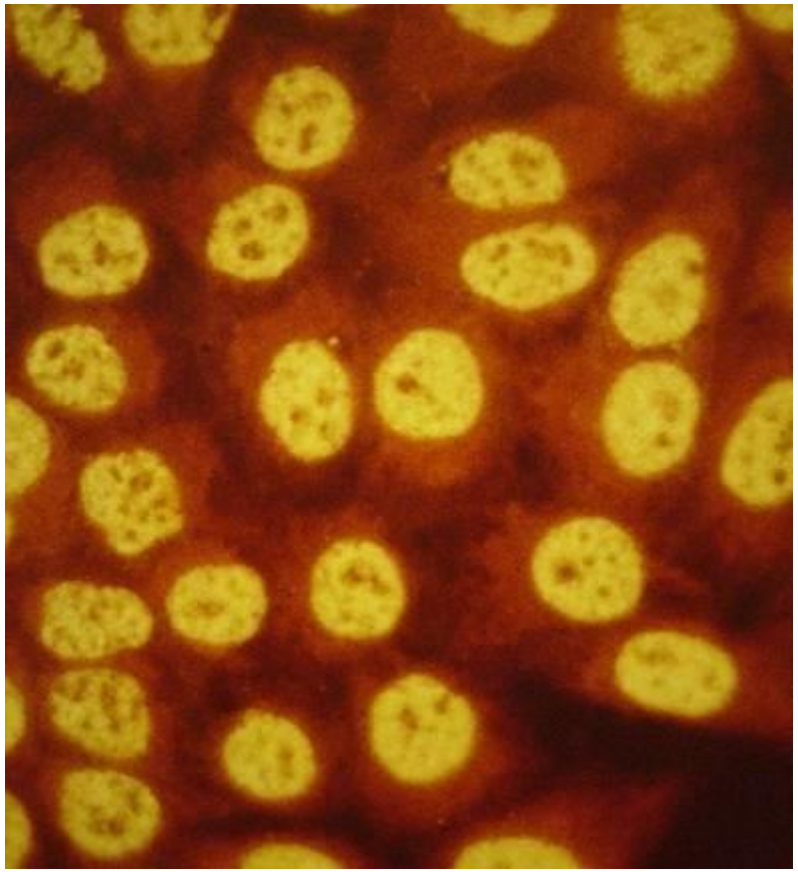


green staining around the periphery of nuclei

- dsDNA



- **Nucleolar pattern**
- **AB to RNA**



- **Speckled pattern**
  Scl70, SSA, SSB, Sm

ANTIBODIES

Homogenous , diffuse nuclear staining	Abs to chromatin,histones
Rim/Peripheral staining	Abs to double stranded DNA
Speckled Pattern	Abs – Sm Ag, SS-A, SS-B, Ribonucleoproteins
Nuclear Pattern	Ab - RNA

ANA Detection Methods

Screening methods

Immunofluorescence (Late 1950's)

ELISA

Confirmatory methods

Counter-immuno electrophoresis

Specific ELISA

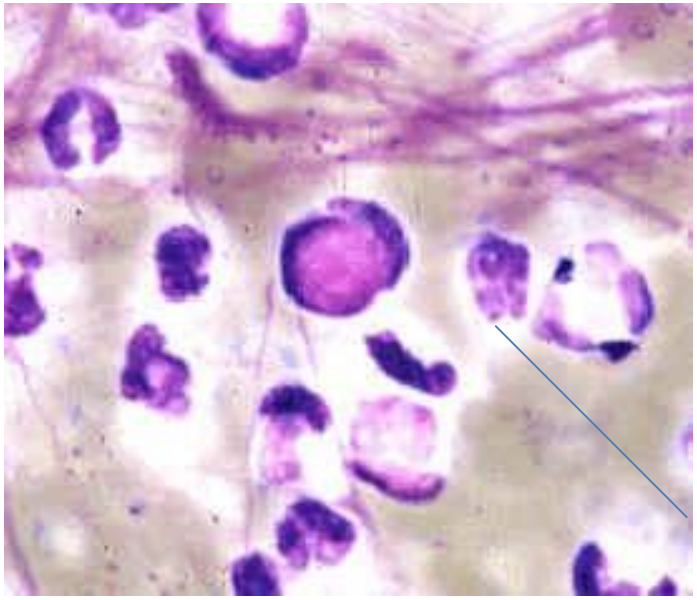
Line immunoassay

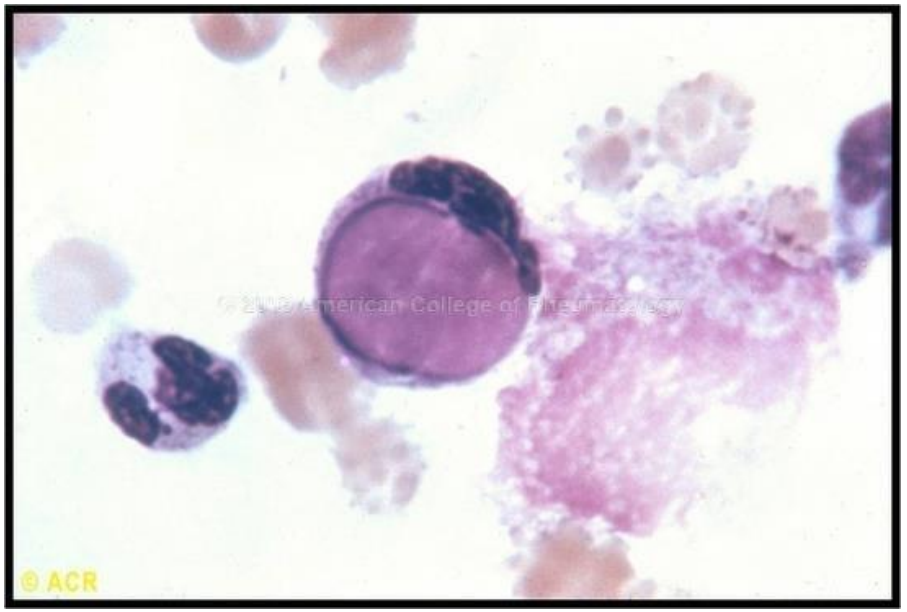
Blot immunoassay

Radioimmunoassay

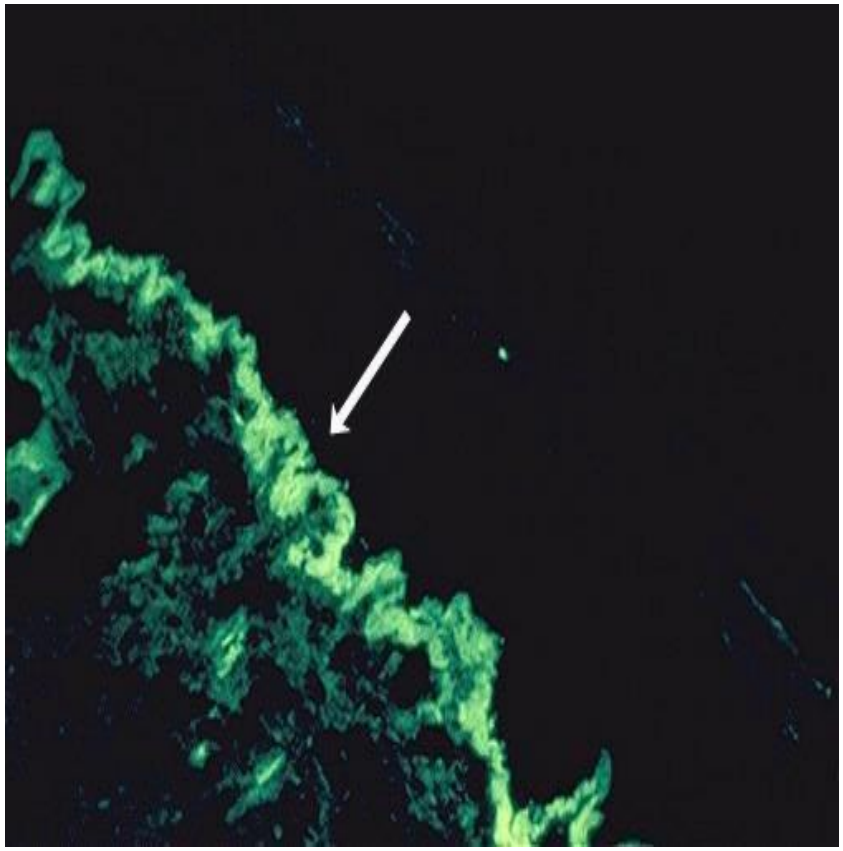
LE Cell

- The LE cell is a phagocyte (neutrophil or macrophage) that has engulfed the antibody-coated nucleus of an injured cell





Lupus band test



- Immunofluorescence of skin with antibody to IgG demonstrates a band-like deposition of immune complexes that is bright green at the dermal epidermal junction in this skin biopsy taken from an area with a visible rash.

Clinical manifestations of SLE

CLINICAL FEATURES

1. Malar rash: Fixed erythema over malar areas, sparing nasolabial folds
2. Arthritis:Tenderness, swelling, effusion in 2 or more peripheral joints
3. Discoid rash: Erythematous raised patches with keratotic scaling and follicular plugging
4. Renal disorder A) proteinuria>0.5g/24hour or 3+ or B) cellular casts
5. Antinuclear antibody
6. Serositis: A) pleuritis or B) pericarditis
7. Photosensitivity: Skin rash after exposure to sunlight, history or physical exam
8. Oral ulcers: Oral or nasopharyngeal, painless, by physical exam
9. Neurological disorder: A) seizures or B) psychiatric disorder

10. Haematological disorder: A) haemolytic anaemia or B) leucopenia or C) thrombocytopenia

11. Immunologic disorder: A) positive LE cells or B) raised anti-native DNA antibdy binding or C) anti-Sm antibody or D) false positive serological test for syphilis.

General symptoms

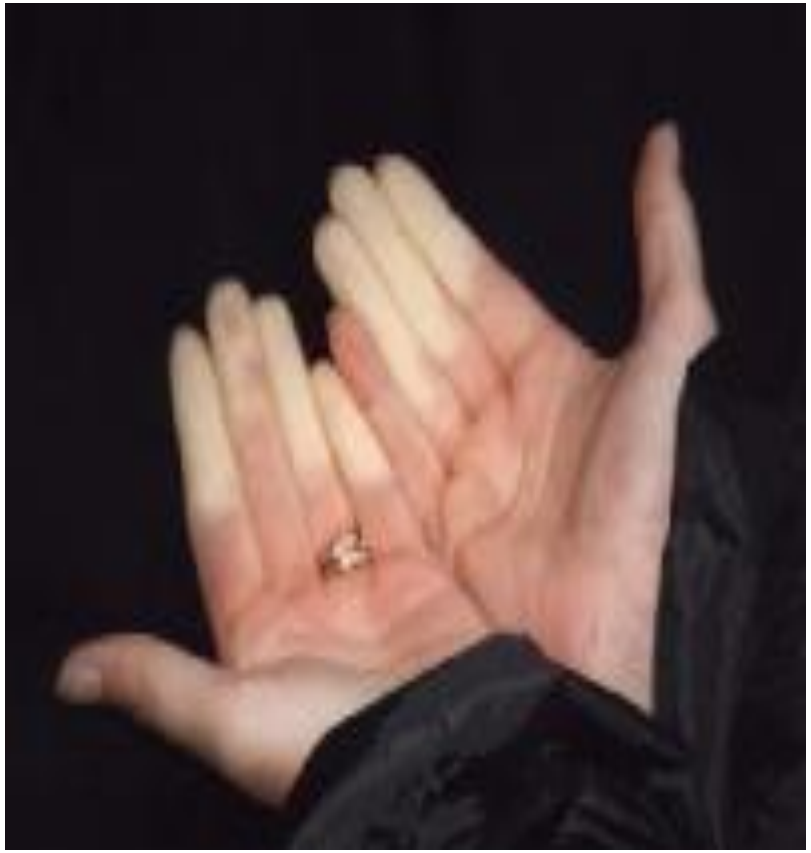
The most common symptoms listed as initial complaints are fatigue, fever, and weight loss.

- ***Fever*:** fever secondary to active disease was recorded from 50% to 86%. No fever curve or pattern is characteristic.
- ***Fatigue*** is common in patients with SLE, especially during periods of disease activity

Low grade fever, anemia, or any source of inflammation can result in fatigue.

- ***Raynaud's phenomenon*** is commonly found in lupus. It lack specificity.

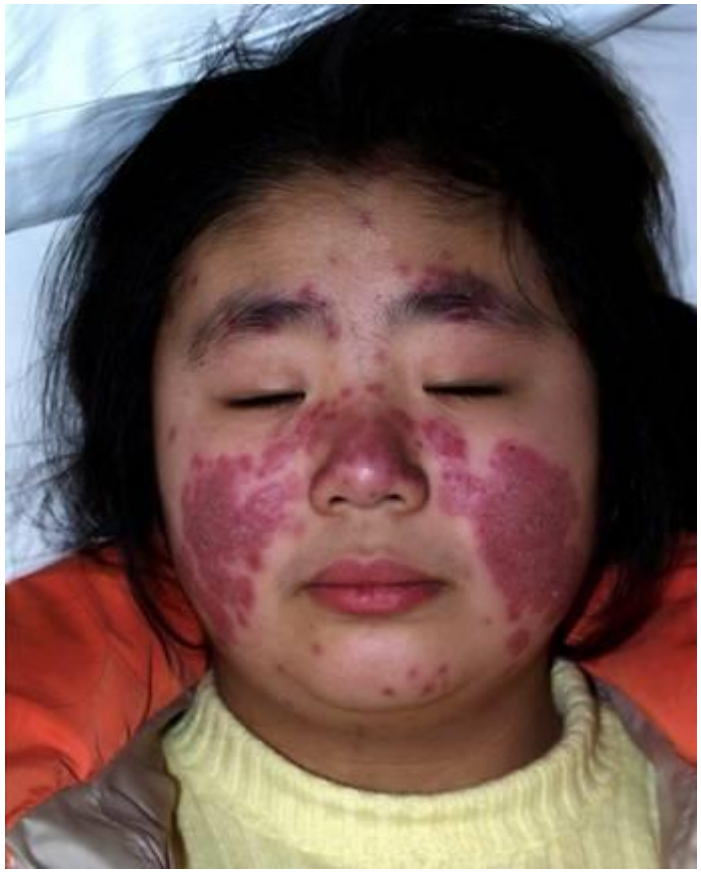
(a triphasic reaction of distal digits to cold or emotion, in which the skin colour changes from white to blue to red)



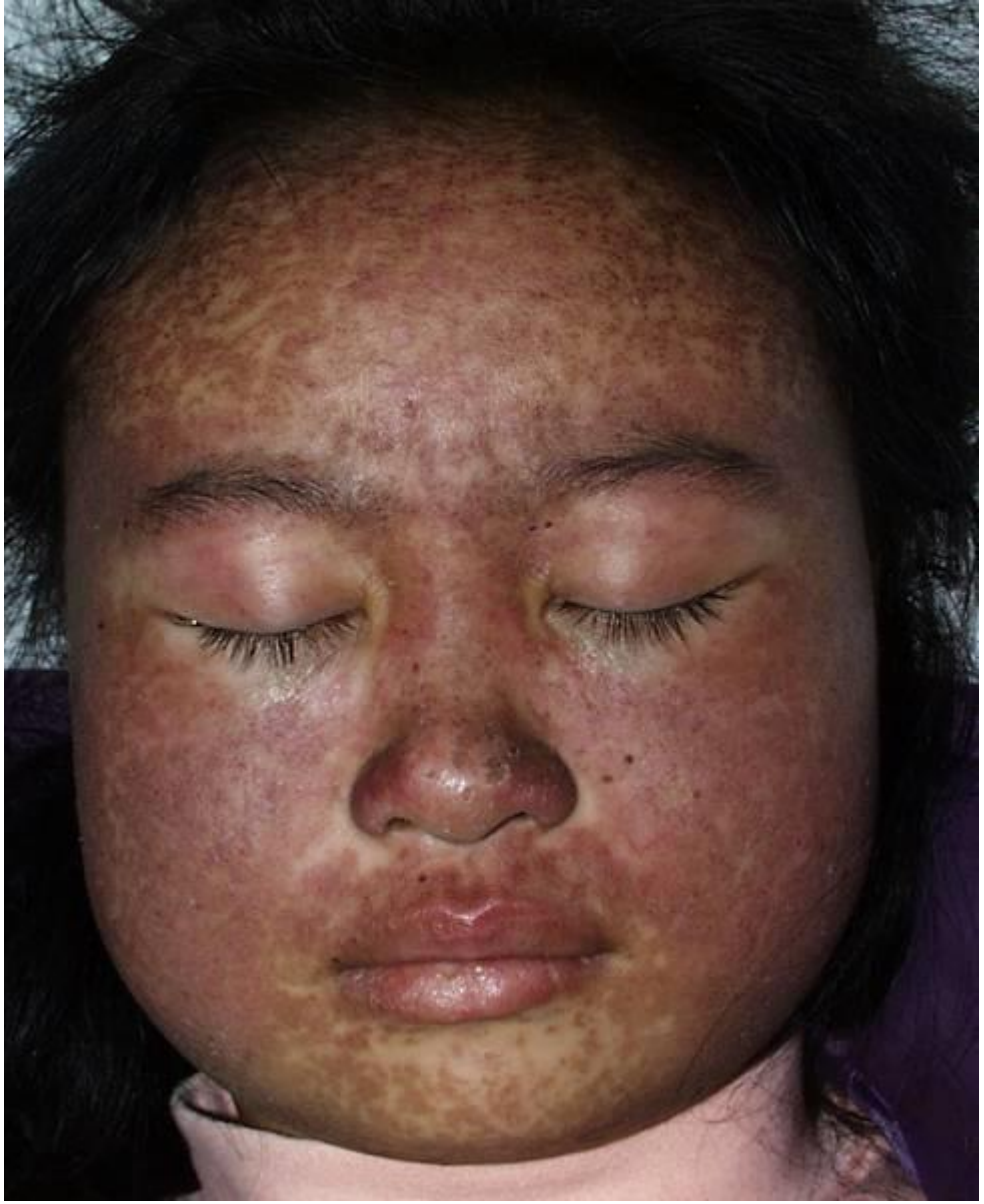
Dermatological involvement

- Up to 85% of SLE
- Butterfly rash
- Maculopapular eruption
- Discoid lupus
- Relapsing nodular non-suppurative panniculitis
- Vasculitic skin lesin
- Livedo reticularis

- **Purpuric lesions**
- **Alopecia**
- **Oral ulcer**
- ***Malar rash***:
- **This is a "butterflyshaped" red rash over the cheeks below the eyes and across the bridge of the nose. It may be a flat or a raised rash. The rashes are made worse by sun exposure.**

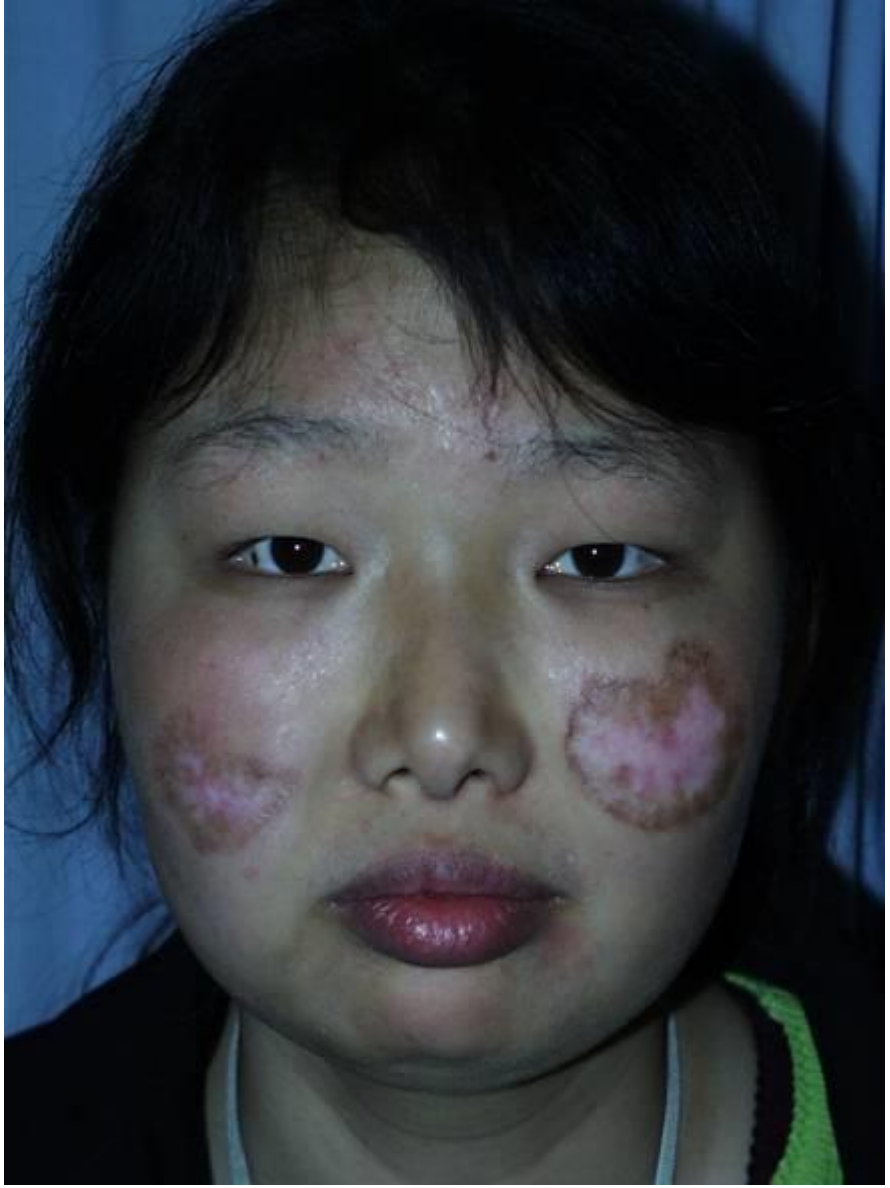


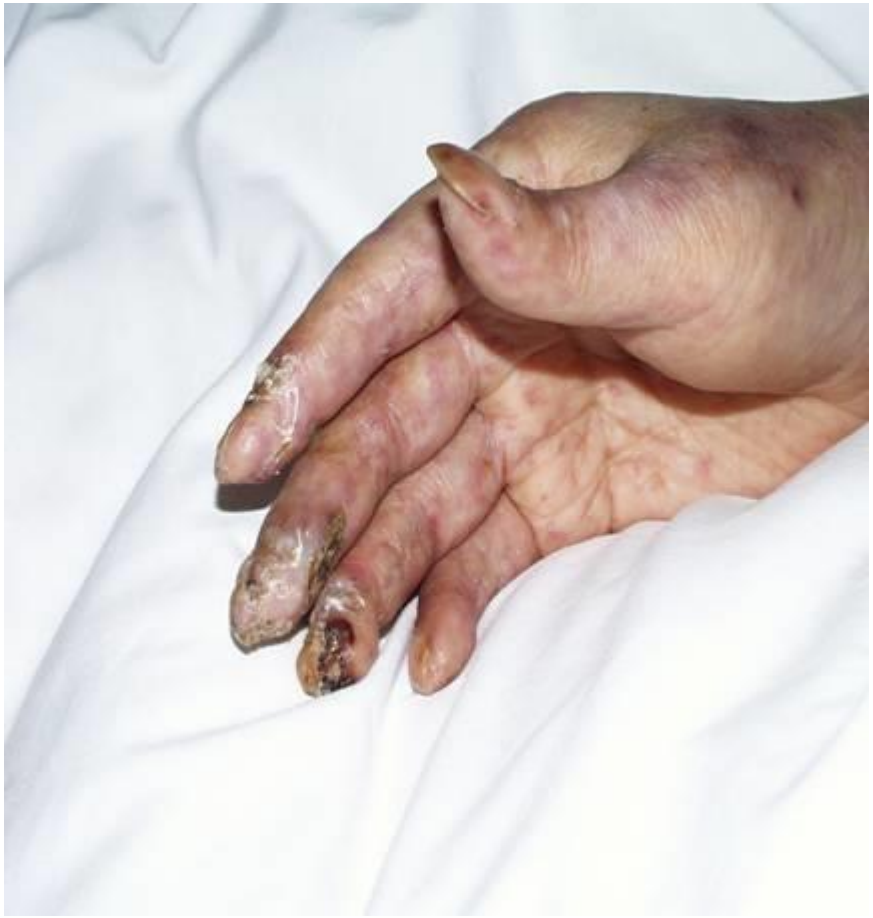
- ***Maculopapular eruption***



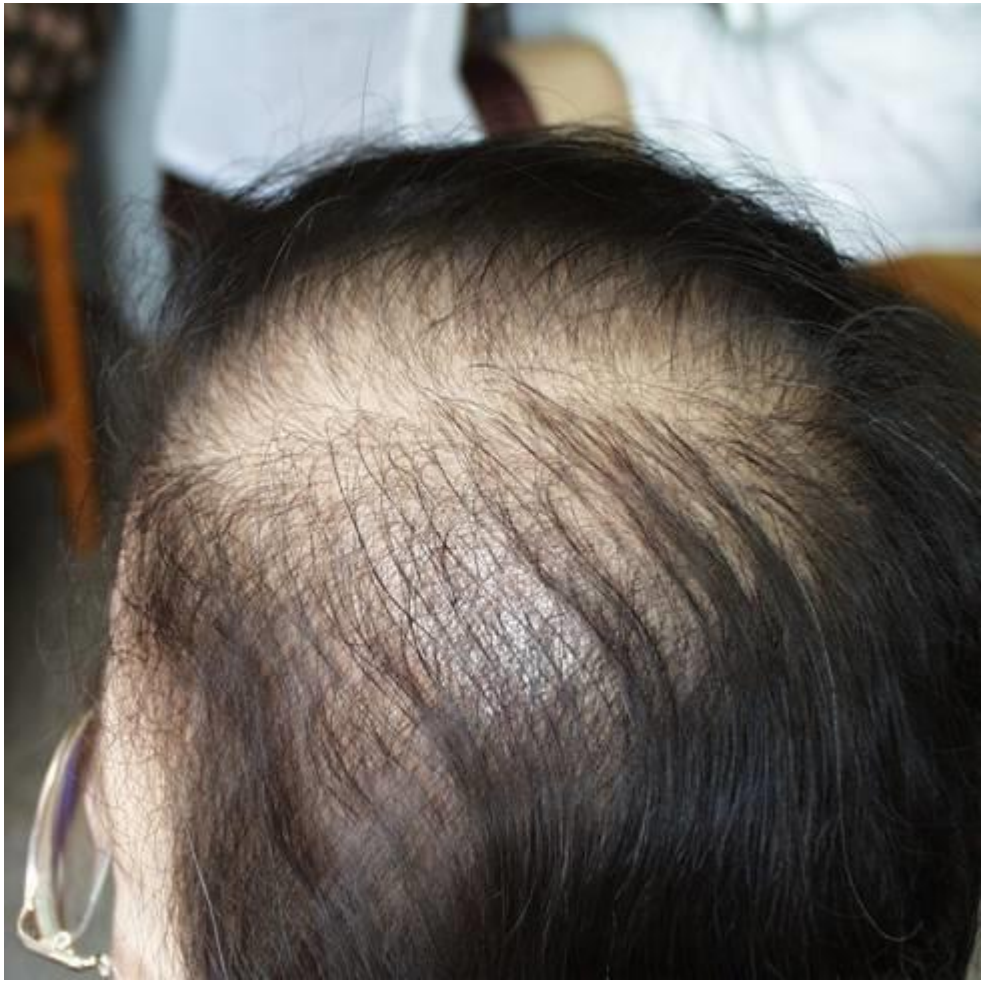
- ***Discoid lupus***

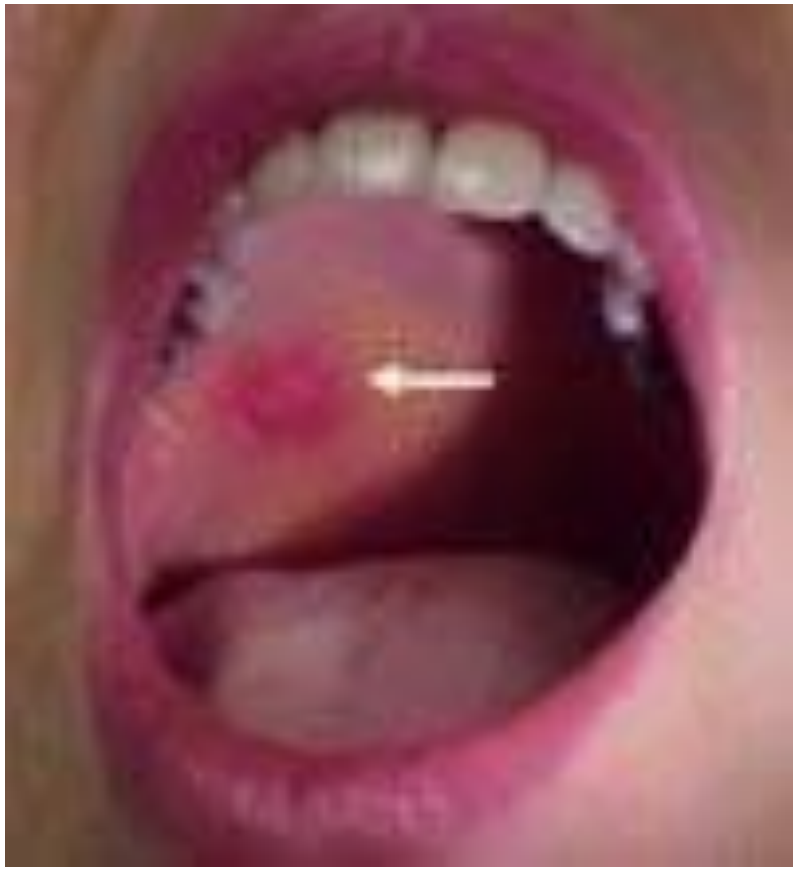
  These are red, raised patches with scaling of the overlying skin.
- ***Vasculitic skin lesin***





- ***Alopecia***





- ***Oral ulcer*:**

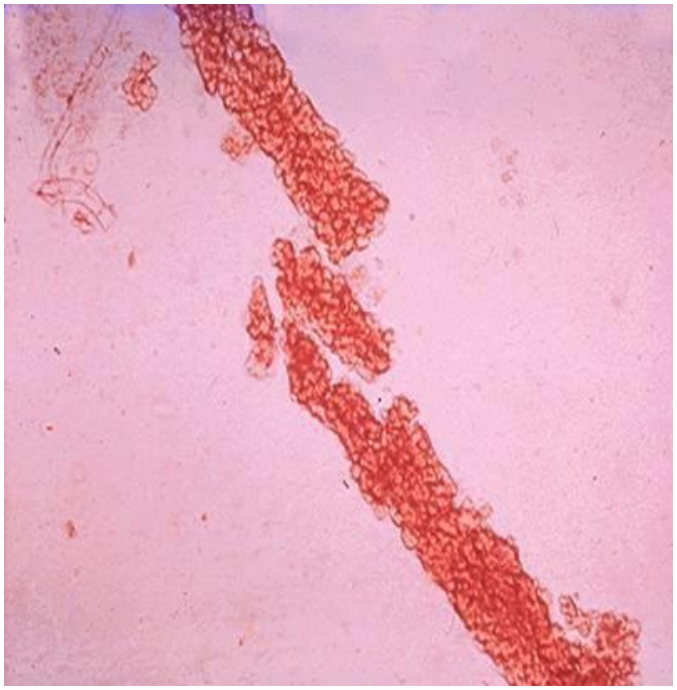
- **Painless sores in the nose or mouth**

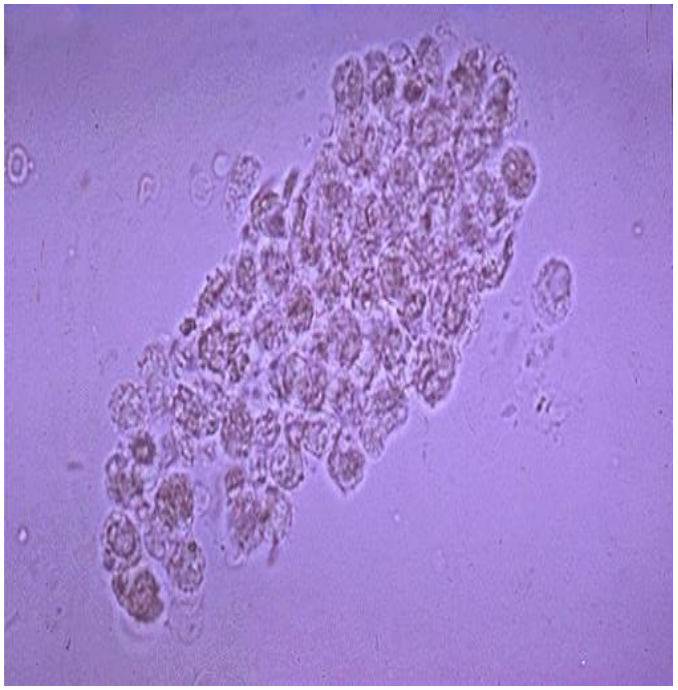
Musculoskeletal system

- **The arthritis of lupus is usually found on both sides of the body and *does not cause deformity* of the joints.**
- **Swelling and tenderness must be present.**
- **The most frequently involved joints are those of the hand, knees, and wrists.**

Kidney system

- **Haematuria**
- **Proteinuria (>0.5g protein/d or 3+)**
- **Cast**

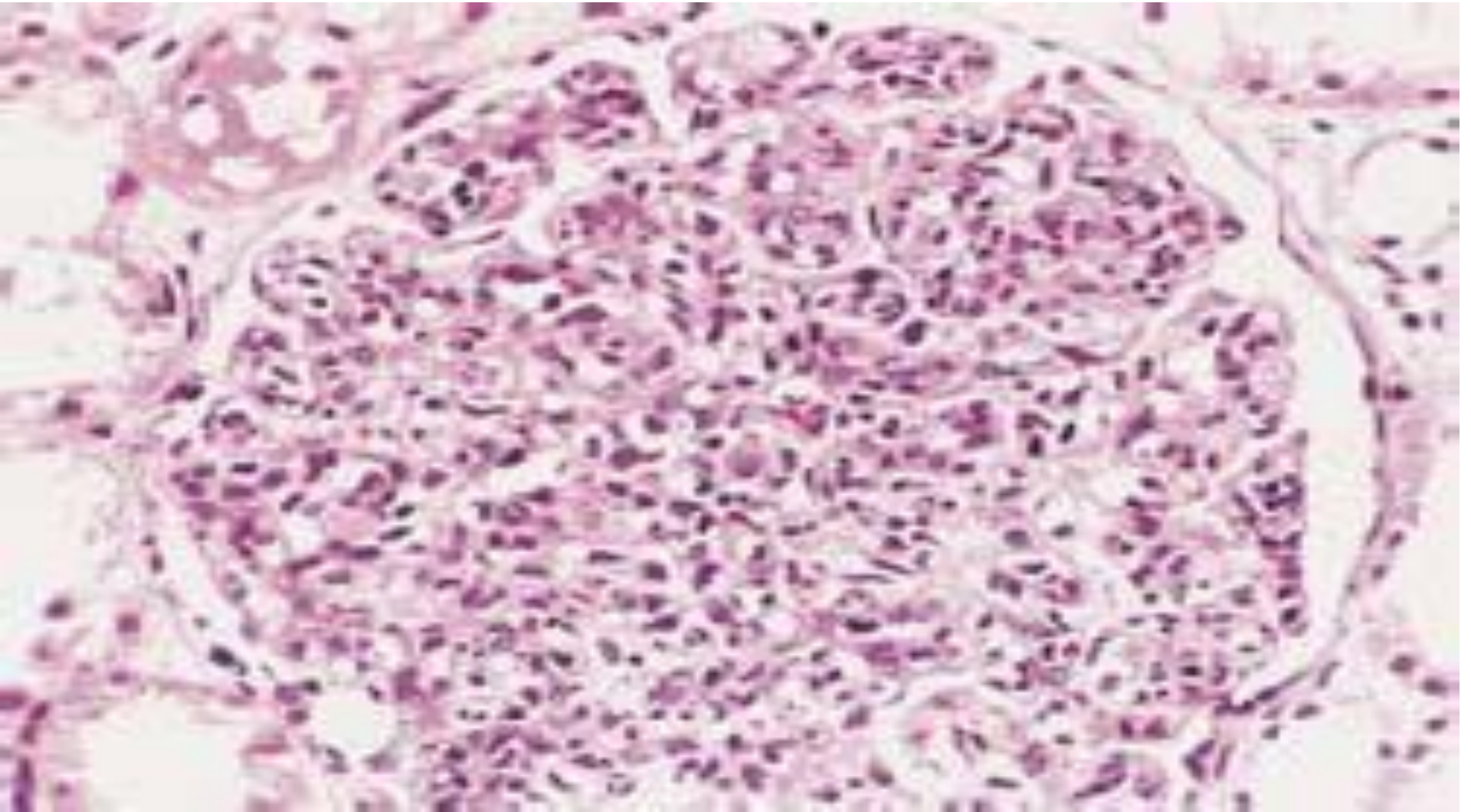




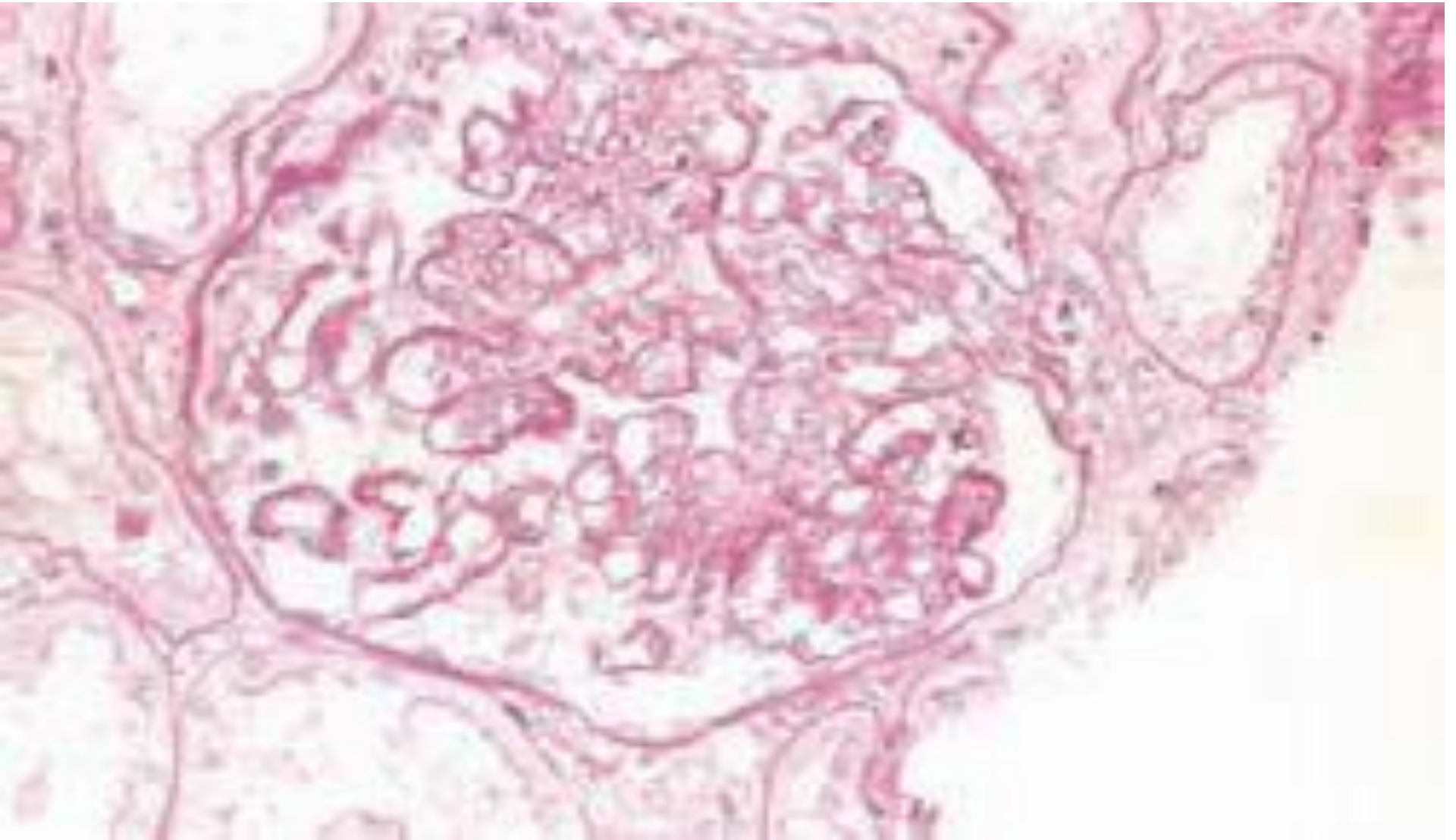
ISN / RPS CLASSIFICATION OF LN

CLASS 1	Minimal Mesangial LN
CLASS 2	Mesangial Proliferative LN
CLASS 3	Focal LN
CLASS 4	Diffuse LN
CLASS 5	Membranous LN
CLASS 6	Advanced Sclerosing LN

Lupus nephritis, diffuse proliferative type. Note the marked increase in cellularity throughout the glomerulus.



Lupus nephritis showing a glomerulus with several "wire loop" lesions representing extensive subendothelial deposits of immune complexes.



EM: Electron dense immune complexes – in
– mesangial, subepithelial,
intramembranous or subendothelial.

LM: **Wire loop lesion** – reflect active disease.

Changes in interstitium, tubules.

Nervous system

- **The brain , nerve problems and psychiatric syndromes are common in lupus affecting up to two-thirds of people.**

- **Potential disorders include seizures, nerve paralysis, severe depression, and even psychosis.**

Hematological abnormalities

- **Red blood cells**

- *Normochromic, Normocytic anemia* is frequently found in SLE. They appears to be related to chronic inflammation, drug-related haemorrhage.

- *Hemolytic anemia* as detected by the Coombs' test is the feature of SLE.

- Platelets.

  Thrombocytopenia (<100*10^9/L) appears to be mediated by anti-platelet antibodies or/and antiphospholipid antibodies.

- **White blood cell**

Leucopenia (<4.0*10^9/L), its cause is probably a combination of

- destruction of white cells by autoantibodies,
- decreased marrow production, - increased or marginal splenic pooling, - and complement activation.
- immunosuppressive drugs used in the treatment of SLE

Pulmonary manifestations

- **Pleurisy** it is the most common manifestation of pulmonary involvement of SLE. The volume is small to moderate , unilateral or bilateral. exudative in character**.**
- Lung

  1) ***acute lupus pneumonitis***: fever, dyspnoea, cough with scanty sputum, hemoptysis, tachypnea and pleuritic chest pain.

2) **pulmonary hemorrhage**

3) **chronic diffuse interstitial lung disease.**

the diagnosis should not be made until infectious processes such as viral pneumonia, tuberculosis, and other bacterial, fungal and pneumocystis carinii infection have been completely excluded.

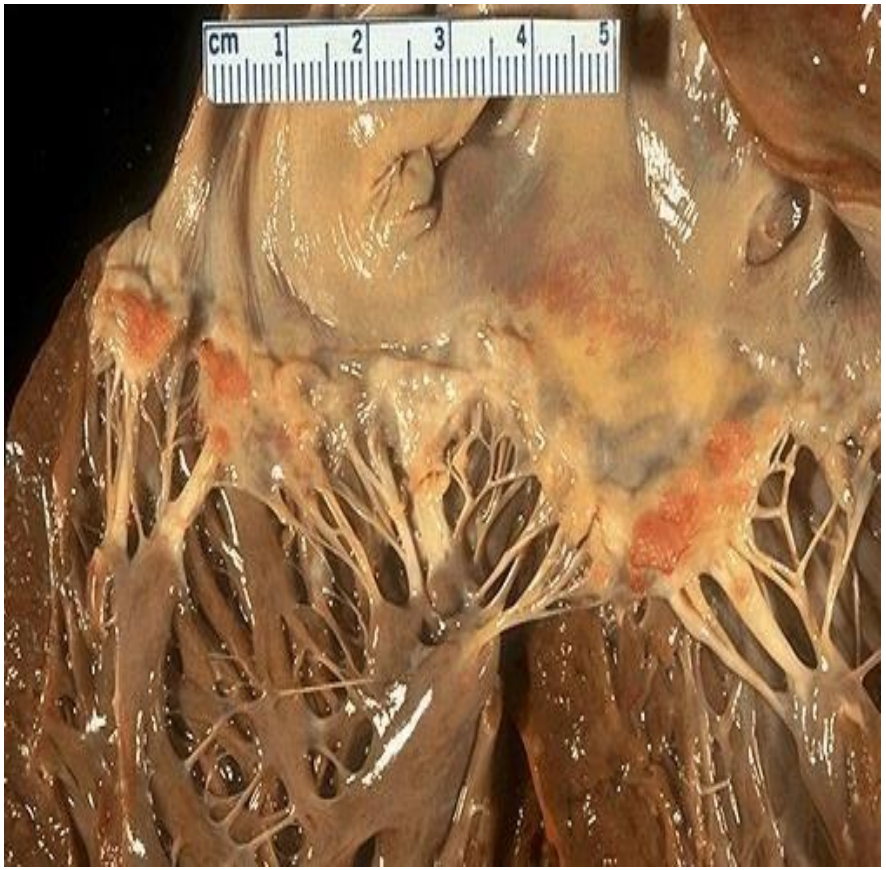
Cardiovascular manifestations

- ***Pericarditis*** **is the most common cardiac manifestation of SLE.**

- ***Myocarditis*** **(the clinical features of lupus myocarditis resembles that of viral myocarditis)**

- **Libman-Sacks *endocarditis* and valvular disease**

- ***Hypertension*****, cardiac failure**



SLE can be associated with endocarditis.

Shown here is LibmanSacks endocarditis in which there are many flat, reddish-tan vegetations spreading over the mitral valve and chordae.

Gastrointestinal and hepatic manifestation

- **Esophagitis, dysphagia, nausea, vomiting: (drug related in most cases)**

- **Chronic intestinal pseudo-obstruction, mesenteric vasculitis, protein-losing enteropathy**

- **Pancreatitis**

- **Lupus hepatitis**

Antiphospholipid syndrome

- **Primary and Secondary**

- Antiphospholipid syndrome (APS) is characterized by recurrent arterial and /or venous thrombosis, fetal loss , cerebral or ocular ischemia and thrombocytopenia , cardiac valvular vegetations

AMYLOIDOSIS

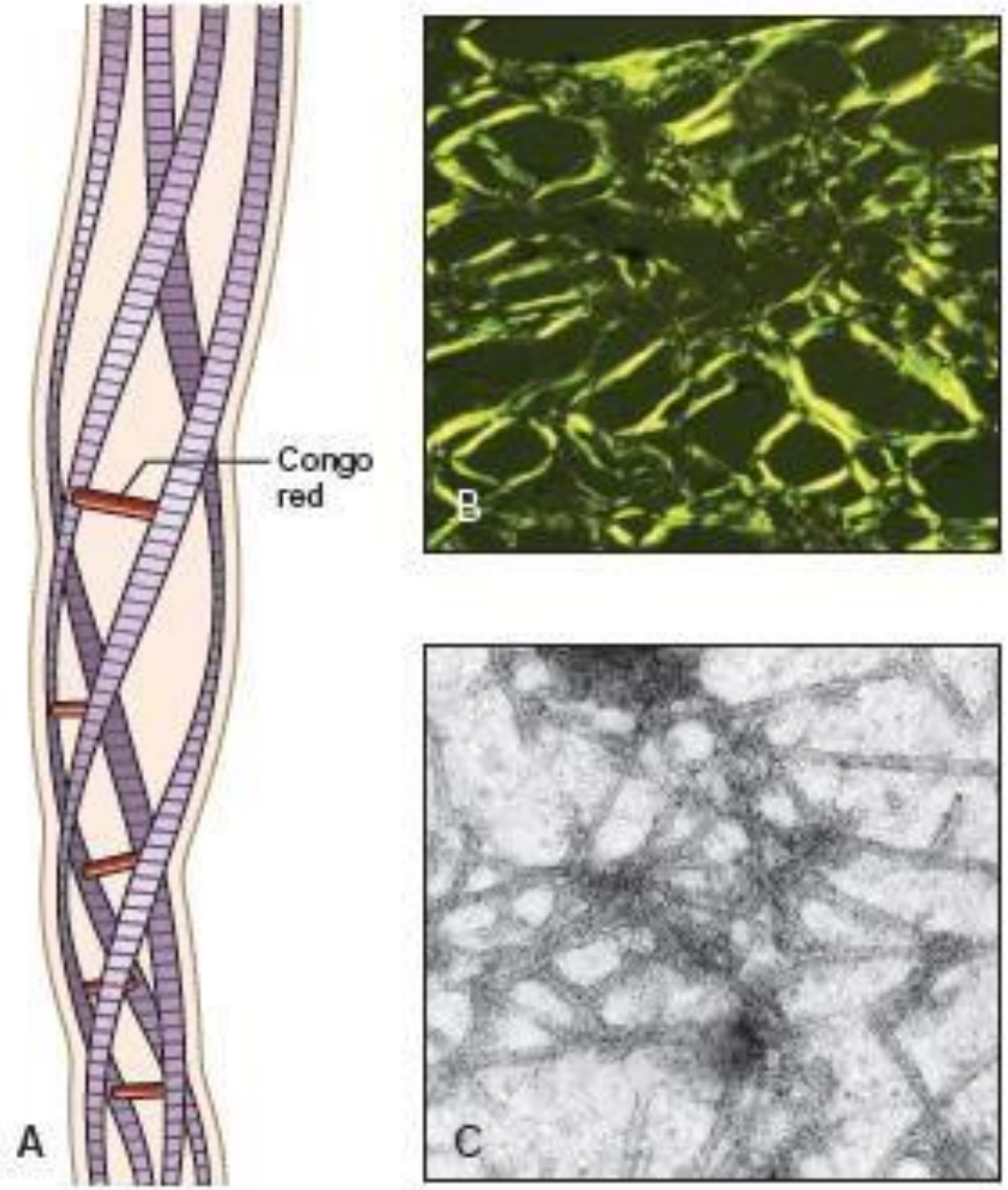
WHAT IS AMYLOID?

- Amylose-starch like staining
- Extracellular
- Amorphous
- Eosinophilic

PHYSICAL NATURE OF AMYLOID

- Non branching fibrils of indefinite length
- Diameter of 7.5 to 10 nm
- Identical in all types of amyloidosis

- X ray crystallography and infrared spectroscopy:
  - Apple green birefringence
- EM:
  - Cross beta pleated structure


Congo red
A
B
C

CHEMICAL NATURE OF AMYLOID

- 95% - fibril proteins
- 5% - P component, glycoproteins
- 20 forms
- 3 most common- AL-amyloid light chain
  AA-amyloid associated

Abeta amyloid

PATHOGENESIS

- Amyloidosis results from abnormal folding of proteins
- Deposited as fibrils and disrupt normal function
- Misfolded proteins are unstable
- Self associate forming oligomers and fibrils

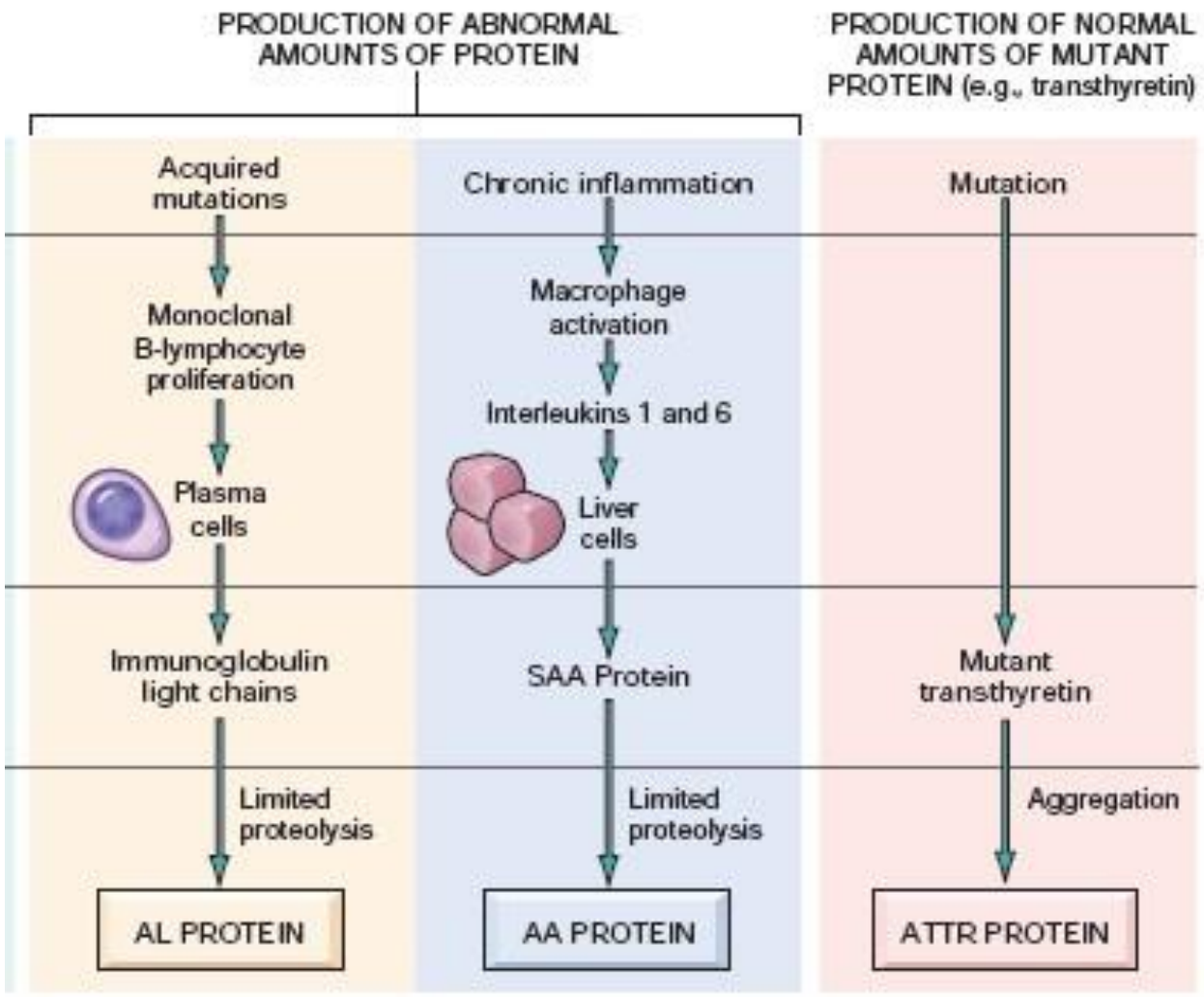
CLASSIFICATION OF AMYLOIDOSIS

- SYSTEMIC AMYLOIDOSIS
  - Primary –immunocyte dyscrasias-AL
  - Secondary-reactive-chronic inflammation-AA
  - Hemodialysis associated-Abeta2 m
- HEREDITARY AMYLOIDOSIS
  - Familial mediterranean fever-AA
  - Familial amyloidotic neuropathies-ATTR
- SYSTEMIC SENILE AMYLOIDOSIS-ATTR
- LOCALIZED AMYLOIDOSIS
  - Senile cerebral –Alzheimer disease-Abeta

- Endocrine

- Medullary carcinoma of thyroid-Acal
- Islets of langerhans-AIAPP

- Isolated atrial amyloidosis-AANF


PRODUCTION OF ABNORMAL AMOUNTS OF PROTEIN
PRODUCTION OF NORMAL AMOUNTS OF MUTANT PROTEIN (e.g., transthyretin)
Acquired mutations
Chronic inflammation
Mutation
Monoclonal B-lymphocyte proliferation
Macrophage activation
Interleukins 1 and 6
Plasma cells
Liver cells
Immunoglobulin light chains
SAA Protein
Mutant transthyretin
Limited proteolysis
Limited proteolysis
Aggregation
AL PROTEIN
AA PROTEIN
ATTR PROTEIN

- Primary –immunocyte dyscrasias-AL

- Secondary-reactive-chronic inflammation-AA

SYSTEMIC AMYLOIDOSIS

PRIMARY AMYLOIDOSIS

- Immunocyte dyscrasias
- AL amyloid
- Lamda chains

– Hemodialysis associated-Abeta2 m

- Bence Jones protein
- Amyloidotic potential
- Suceptibility to degradation
- Mesodermal tissues-muscle, heart, skin, tongue

– Primary –immunocyte dyscrasias-AL

– Secondary-reactive-chronic inflammation-AA

SYSTEMIC AMYLOIDOSIS

REACTIVE SYSTEMIC AMYLOIDOSIS

- Inflammatory conditions
- Tuberculosis,Bronchiectasis,Chronic osteomyelitis

– Hemodialysis associated-Abeta2 m

- Rheumatoid arthritis
- Heroin abusers
- Renal cell carcinoma,Hodgkins lymphoma
- Liver, spleen, kidney, adrenal glands

– Primary –immunocyte dyscrasias-AL

SYSTEMIC AMYLOIDOSIS

– Secondary-reactive-chronic inflammation-AA

– Hemodialysis associated-Abeta2 m

SYSTEMIC AMYLOIDOSIS

- HEMODIALYSIS ASSOCIATED
  - Beta 2 microglobulin
  - Carpel tunnel syndrome

CLASSIFICATION OF AMYLOIDOSIS

- SYSTEMIC AMYLOIDOSIS
  - Primary –immunocyte dyscrasias-AL
  - Secondary-reactive-chronic inflammation-AA
  - Hemodialysis associated-Abeta2 m
- HEREDITARY AMYLOIDOSIS
  - Familial mediterranean fever-AA
  - Familial amyloidotic neuropathies-ATTR

- SYSTEMIC SENILE AMYLOIDOSIS-ATTR
- HEREDOFAMILIAL AMYLOIDOSIS
  - FAMILIAL MEDITERRANEAN FEVER
    - Autosomal recessive
    - Autoinflammatory syndrome
    - Pyrin gene
    - AA

CLASSIFICATION OF AMYLOIDOSIS

- SYSTEMIC AMYLOIDOSIS
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  - Familial mediterranean fever-AA
  - Familial amyloidotic neuropathies-ATTR

- SYSTEMIC SENILE AMYLOIDOSIS-ATTR

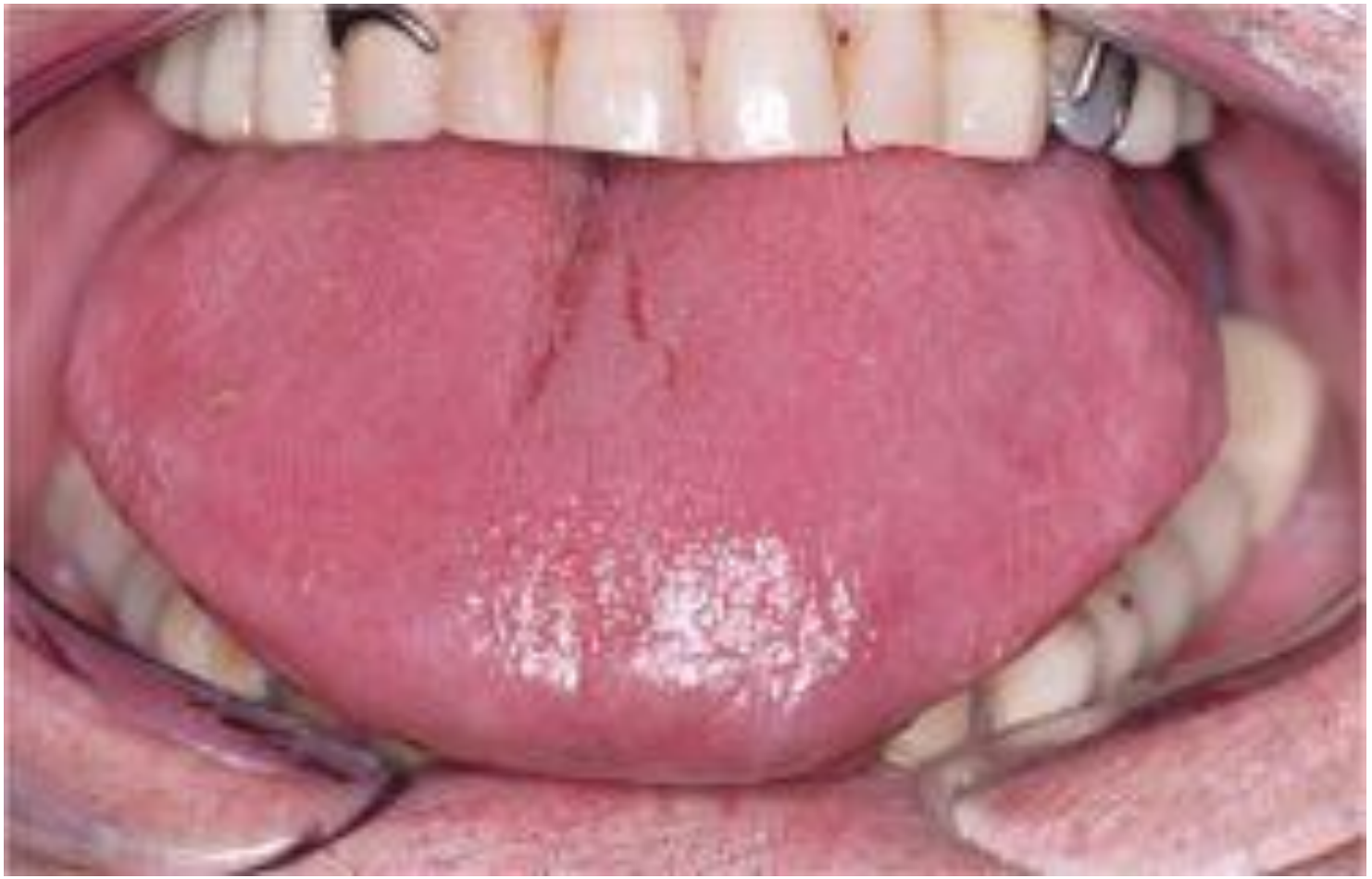
AMYLOID OF AGING

- Senile systemic amyloidosis
  - Cardiac amyloidosis
  - Restrictive cardiomyopathy
  - Arrhythmias
  - Normal TTR

AMYLOIDOSIS

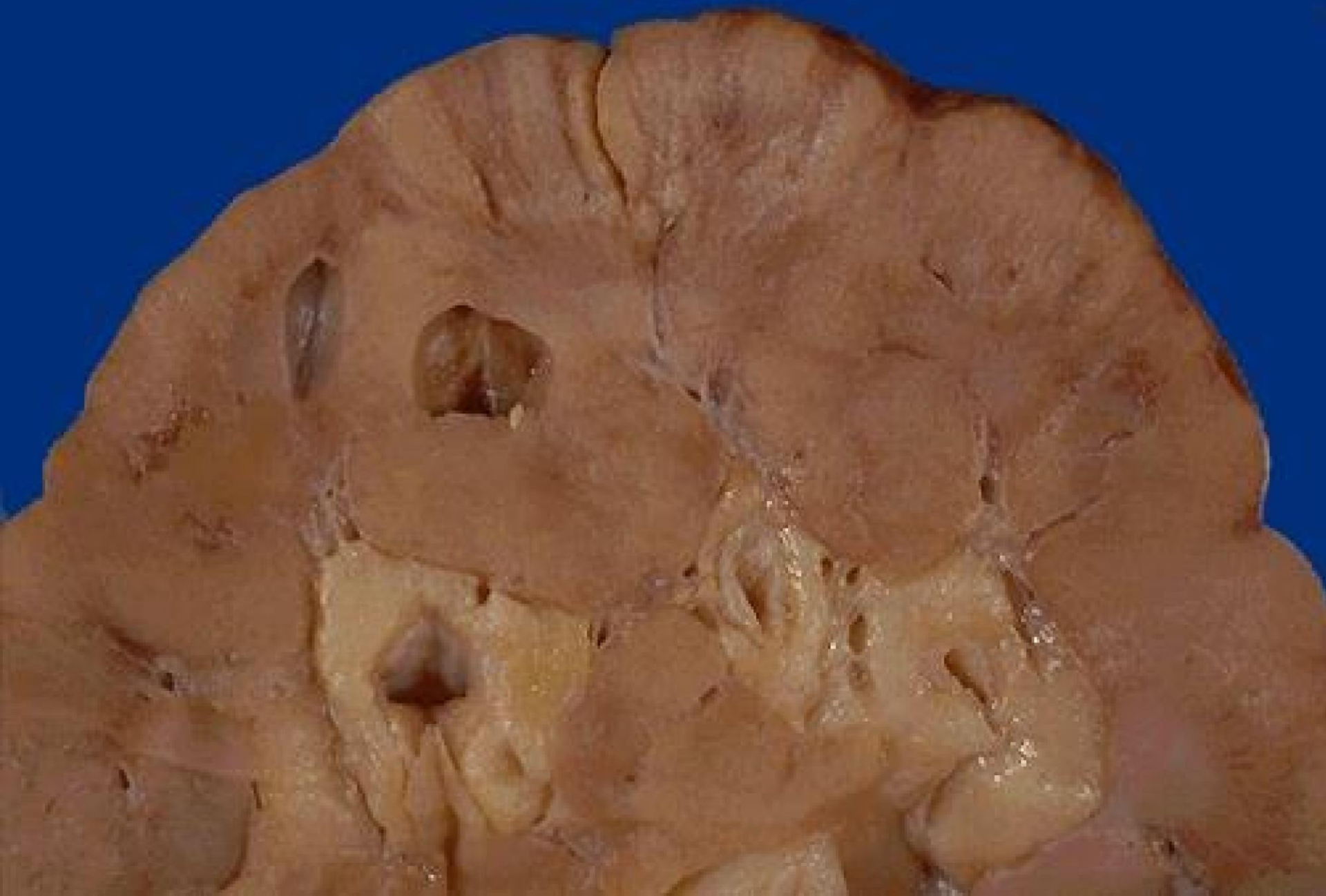
- LOCALIZED AMYLOIDOSIS
  - Single organ or tissue

- Lung, larynx, skin, bladder, tongue, eye
- Lymphocytes ,plasma cells



GROSS FEATURES

- Enlarged
- Pale ,firm and waxy
- Waxy degeneration or lardaceous disease
- Amyloid stains purple with iodine solution
- Changing to blue colour on addition of sulfuric acid



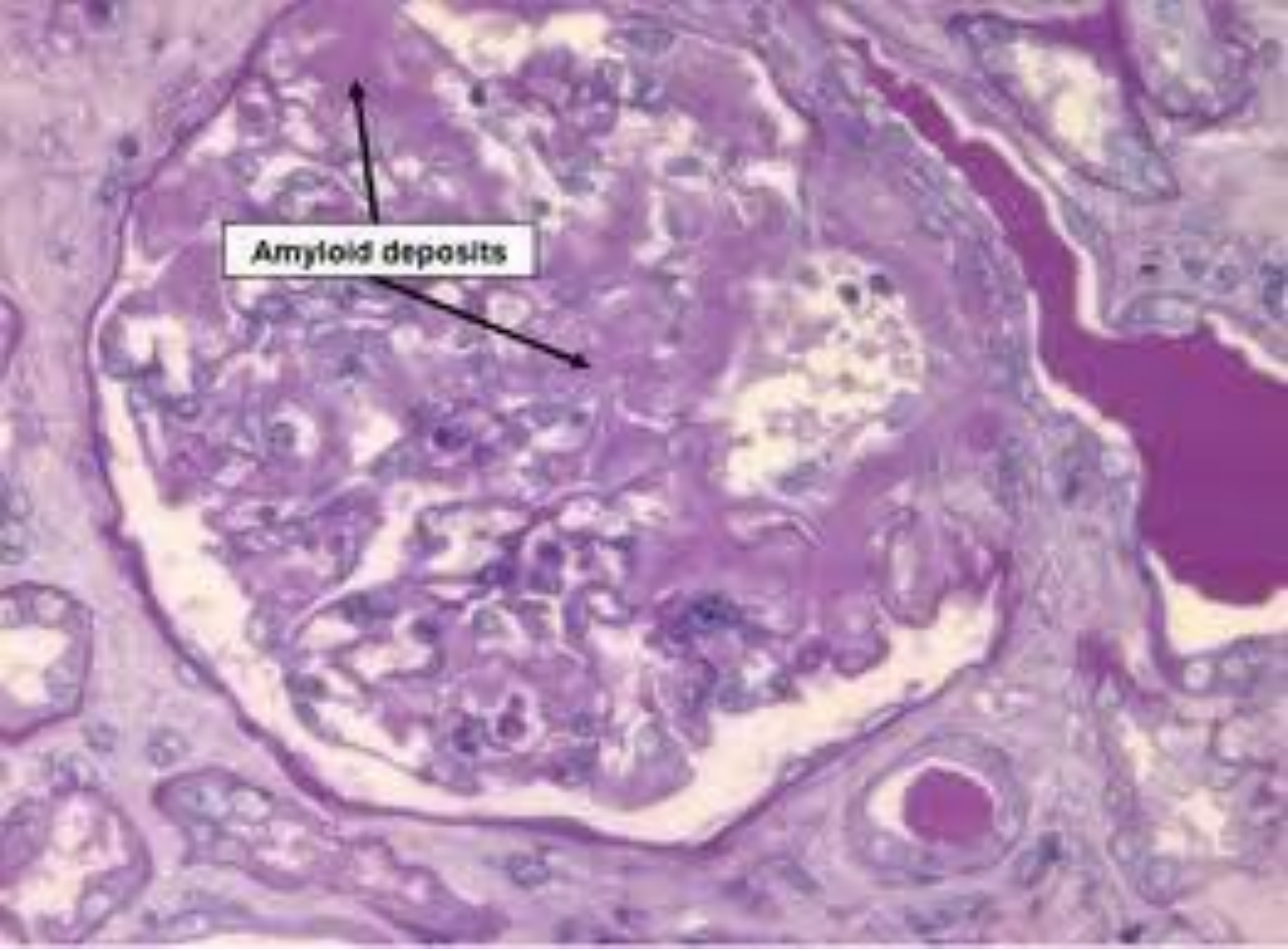
GROSS FEATURES

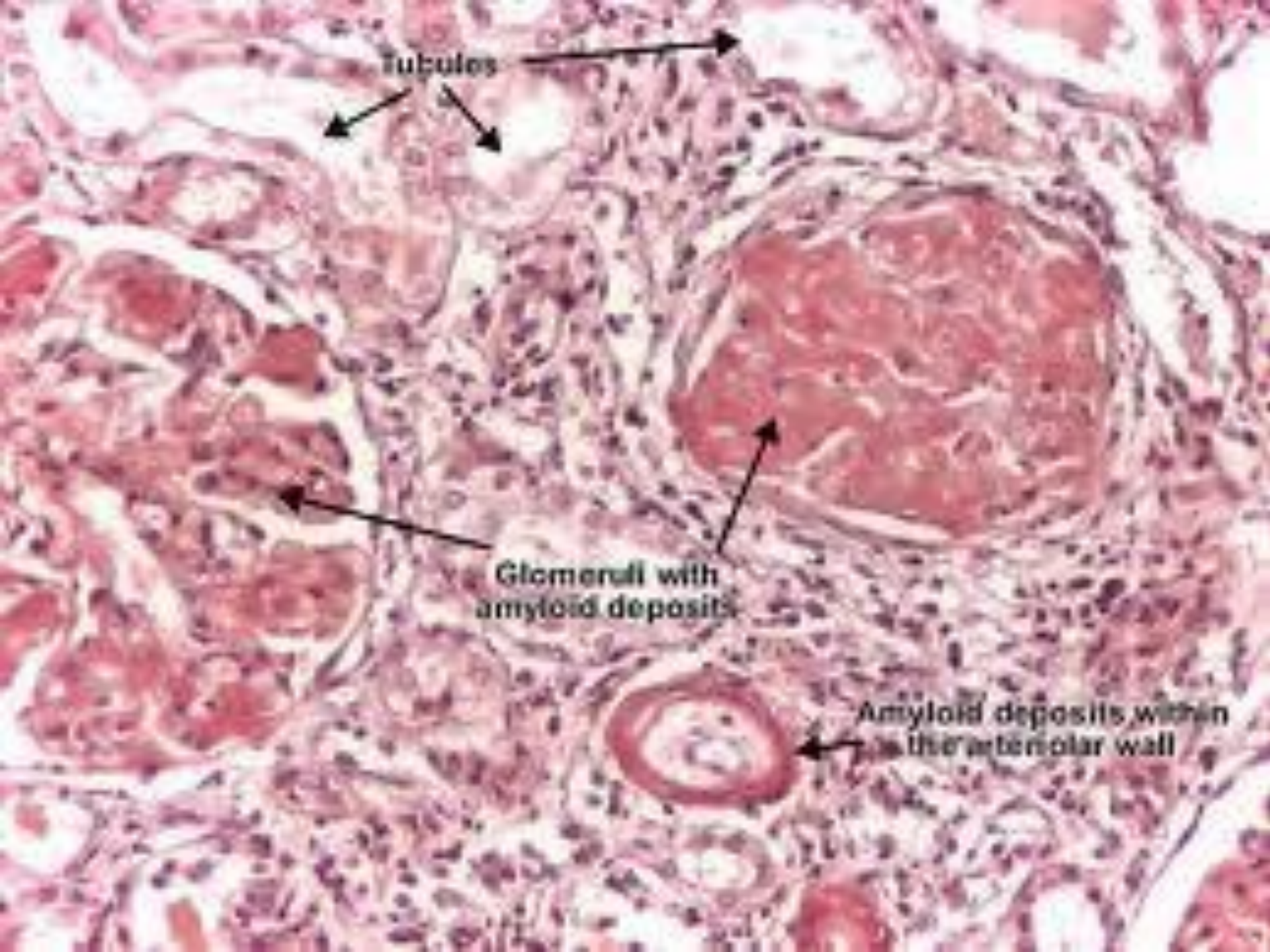
- Immersion in lugol`s iodine containing 0.1 M of hydrochloric acid
- Rinsing in water
- Mounting iodine glycerol
- 9 parts glycerol;1 part iodine
- Presence of linear carbohydrate residue

KIDNEY

- Gross
  - Normal size ,color
  - Shrunken
- Histology
  - Glomeruli-mesangial deposits
  - Distortion of the vascular tuft

– Obsolescent glomerulus


Amyloid deposits


Tubules
Glomeruli with amyloid deposits
Amyloid deposits within the arteriolar wall

SPLEEN

- Moderate to marked splenomegaly
- SAGO SPLEEN
  - Splenic follicles
  - Tapioca like granules
- LARDACEOUS SPLEEN
  - Walls of splenic sinuses
  - Map like areas

LIVER

- Moderate to marked hepatomegaly
- Space of Disse
- Pressure atrophy
- Disappearance of hepatocytes
- Vascular involvement
- Deposits in the kupffer cells

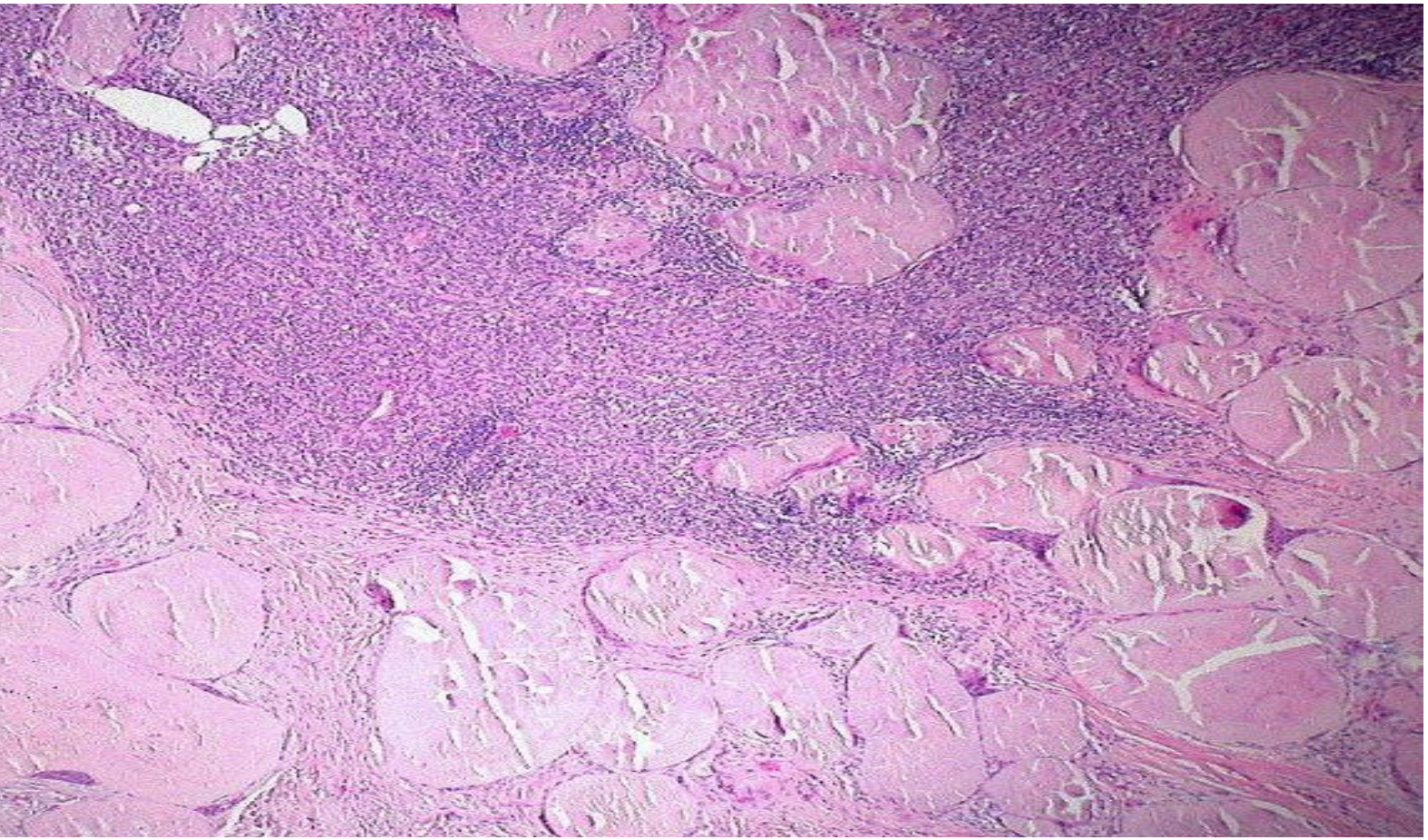
HEART

- Systemic amyloidosis
- Senile systemic amyloidosis
- Enlarged ,firm
- Focal subendocardial
- Myocardial
- Pressure atrophy

DIAGNOSIS

- Congored stain fat and bone marrow-87%.
- Rectal biopsy and subcutaneous fat-75%.
- Biopsy of liver, kidney, heart-100%.
- Lymphnode involvement-17% to 36%.

MICROSCOPY



STAINS FOR AMYLOID

H&E	Pink hyaline amorphous
Congored	Apple green birefringence
Methyl or crystal violet	Metachromasia
Sulfated alcian blue	Blue green
Thioflavine T	Secondary fluorescence
IHC	Positive immunoreactivity

STAINING CHARACTERISTICS

- Best demonstrated with frozen sections
- Practically most specimens are paraffin embedded
- Satisfactory staining obtained after routine formalin fixation
- Fixation not to be prolonged

STAINING CHARACTERISTICS

- Positive control sections to be used
- Freshly cut positive sections
- Tissue containing massive deposits of long duration-Less intense stain
- Small newly formed deposits-intense stain

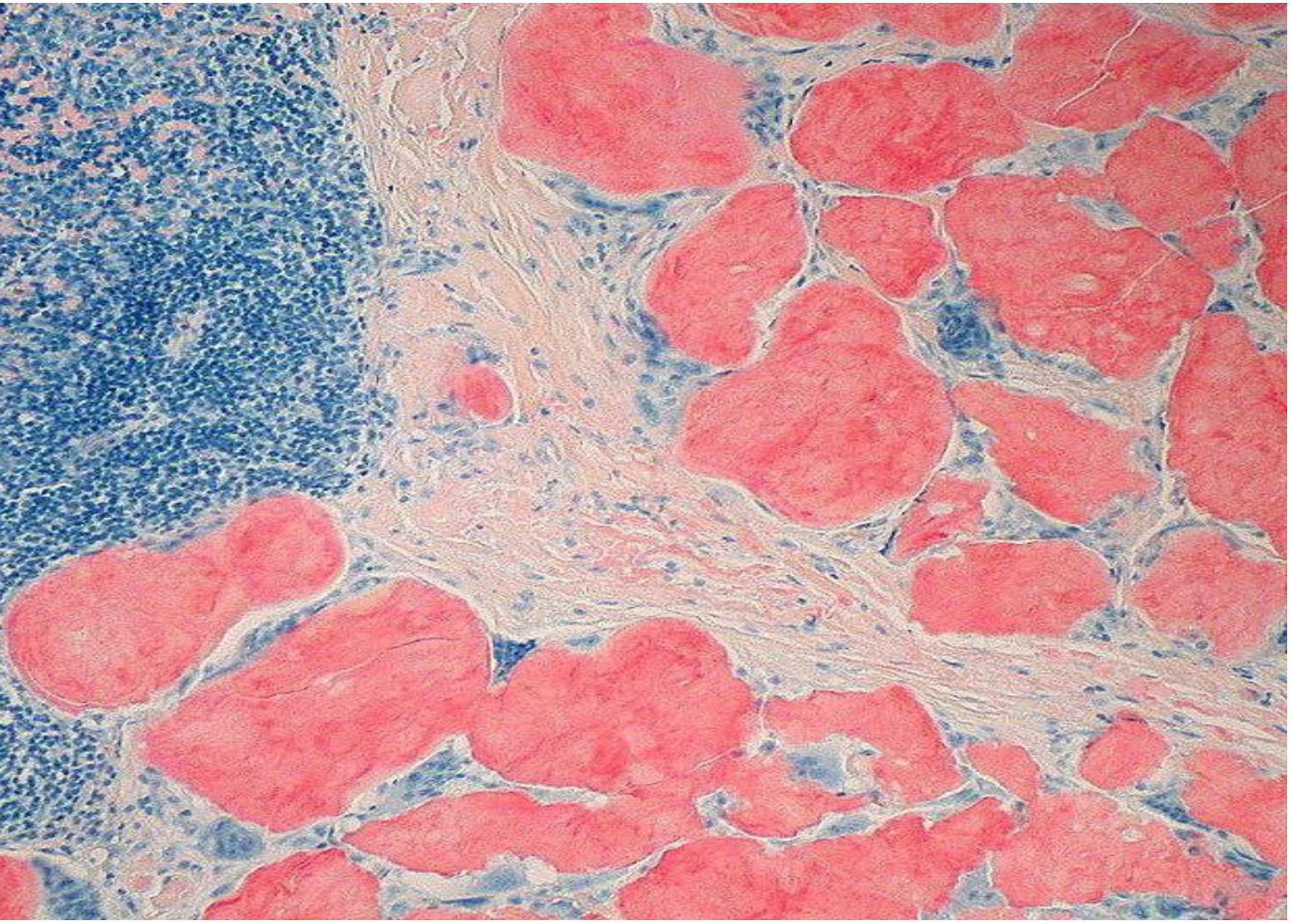
CONGO RED STAIN

- Acidic diazo dye
- First introduced as colorant for cotton industry
- Bennhold demonstrated selective affinity of this dye for amyloid
- It contains two identical halves
- Each composed of phenyl ring bound to naphthalene moiety by diazo group

CONGO RED STAIN

- Linear molecule
- Largely hydrophobic
- Staining of amyloid is with hydrogen bond
- Electro chemical bonds with other tissue

CONGO RED STAIN



HIGHMAN`S CONGO RED TECHNIQUE

- Formalin fixation
- Solutions-0.5% congo red in 50% alcohol

  0.2% KOH in 80% alcohol
- Stain in congo red-5 minutes
- Differentiate with alcoholic potassium hydroxide solution for 3 to 10 seconds
- Counterstain in alum hematoxylin
- Dehydrate, clear and mount

ALKALINE CONGO RED STAIN

- Method of choice
- No differentiation step, high concentration of sodium chloride
- Solutions to be freshly made
- Stock solutions

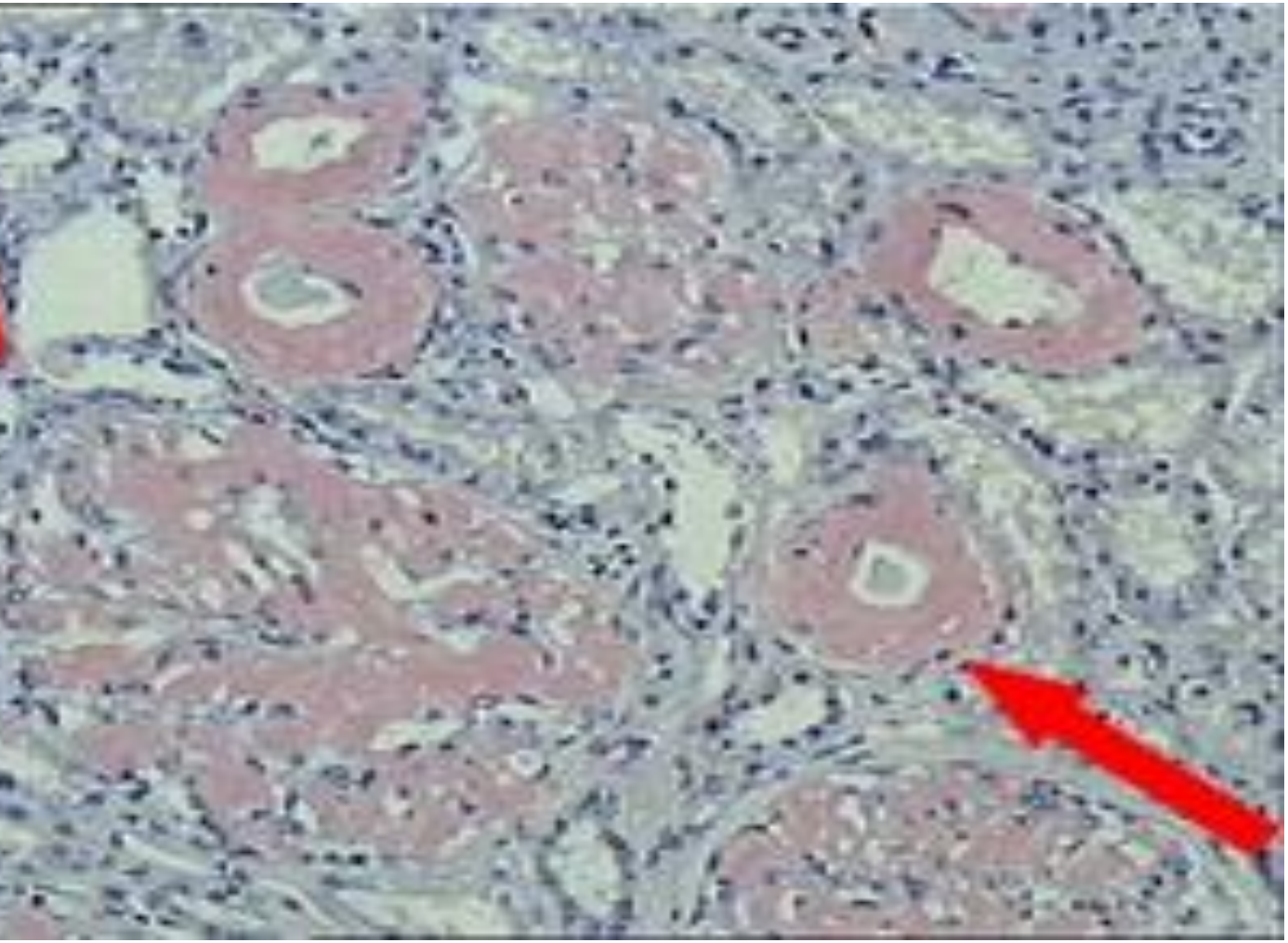
  A-Saturated sodium chloride in 80% ethanol

  B- saturated congo red in 80% ethanol saturated with sodium chloride

ALKALINE CONGO RED STAIN

- Stain nuclei in alum hematoxylin
- Immerse in alkaline sodium chloride solution for 20 minutes
- Transfer directly to alkaline congo red solution for 20 minutes
- Rinse briefly in alcohol ,clear and mount
- ADV- Decreased background staining

CONGO RED STAIN



HIGH pH CONGO RED TECHNIQUE

- Congo red stain buffered to Ph 10
- Glycine buffer pH 10-

  0.1 M glycine 30ml

  0.1 M sodium chloride 30 ml

  0.1 M sodium hydroxide 40ml

SIRIUS RED TECHNIQUE

- Cotton dye sirius red F3B
- Mechanism of staining similar to congo red
- Disadvantage of precipitation of staining solution
- Fixation-not critical

SIRIUS RED TECHNIQUE

- Dissolve 0.5 g sirius red F3B in 45 ml distilled water
- Add 50 ml absolute alcohol and 1ml 1% sodium hydroxide
- Stirring the solution vigorously add 20% sodium chloride(4 ml), just to produce fine precipitate
- Leave stand over night and filter

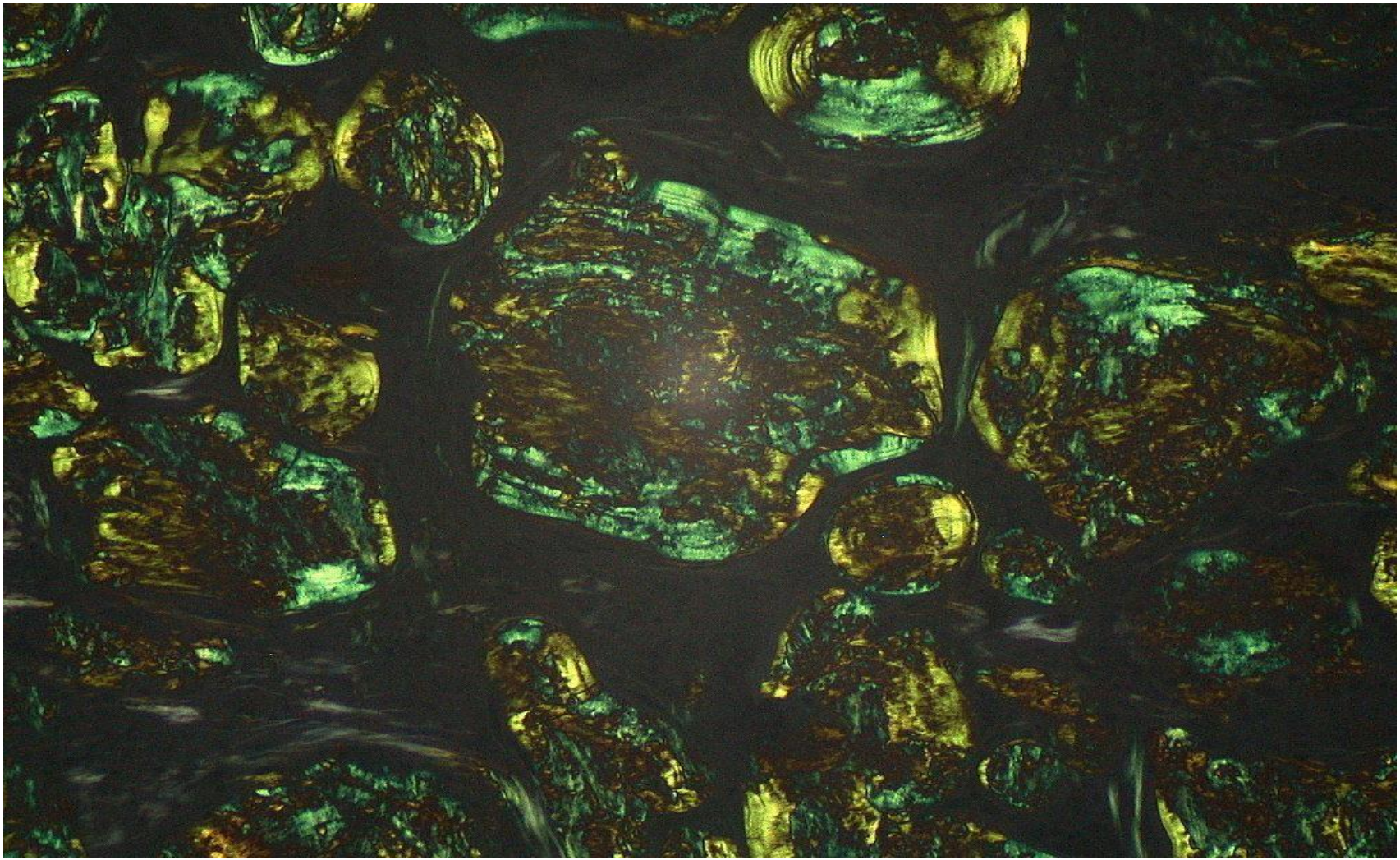
SIRIUS RED TECHNIQUE

- Stain nuclei in alum`s hematoxylin
- Rinse in water and 70% ethanol
- Treat with sirius red solution for 1 hour
- Wash in tap water for 10 minutes
- Dehydrate, clear and mount

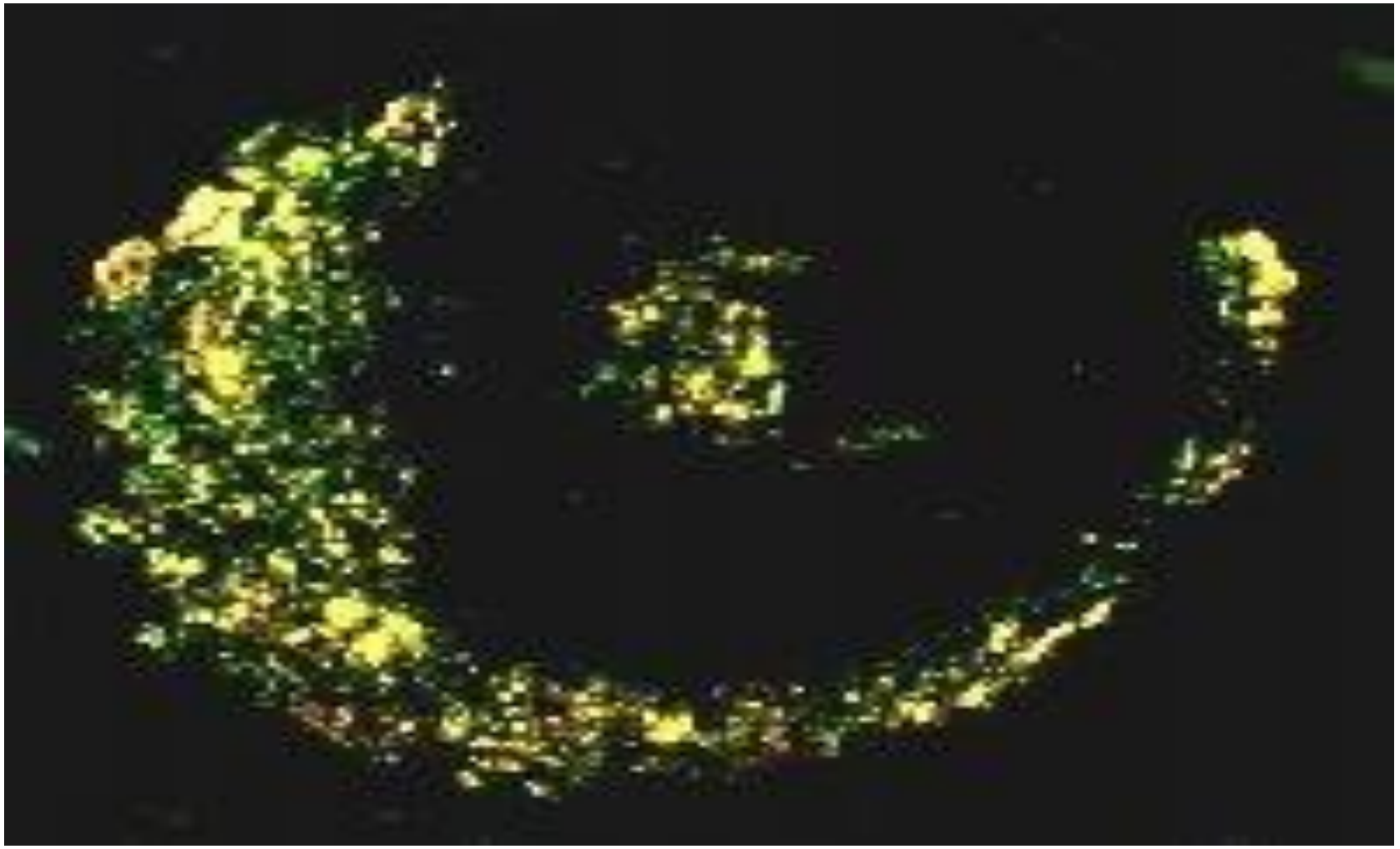
POLARIZING MICROSCOPY

- Two differing refractive index
- Two rays of light vibrating in perpendicular plane travel at different velocity
- Different RI
- Positive birefringence-slow ray parallel to length of fiber or crystal
- Negative birefringence
- Interference colours produced when two rays are united under analyser

POLARIZING MICROSCOPY



POLARIZING MICROSCOPY



POLARIZING MICROSCOPY

- Apple green birefringence given by other filamentous structures
- Cellulose and chitin
- Dense collagen
- Thickness of section critical,8 to 10 micrometer
- Too thin –faint red, thick-yellow

TOLUIDINE BLUE

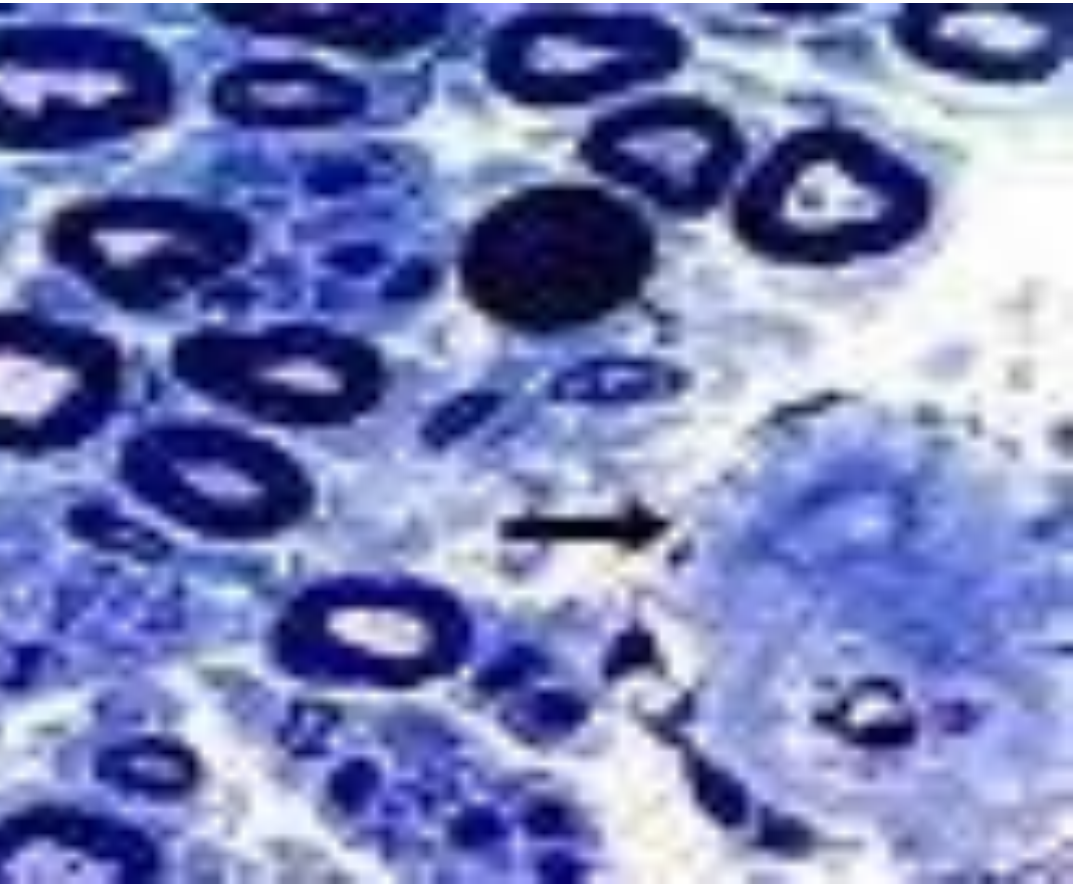
- Stains many tissue orthochromatic blue colour
- Dark red birefringence with amyloid
- Stain solution-1% toluidine blue in 50% isopropanol
- Stain in toluidine solution for 30 minutes-37 deg

TOLUIDINE BLUE

- Blot section then place in absolute isopropanol for 1 minute
- Clear in xylene and mount
- Some amyloid deposits,especially those of endocrine origin are negative
- Minimal deposits difficult to visualise

- Cartilage matrix,mast cell granules,mucopolysachcarides stain.

TOLUIDINE BLUE



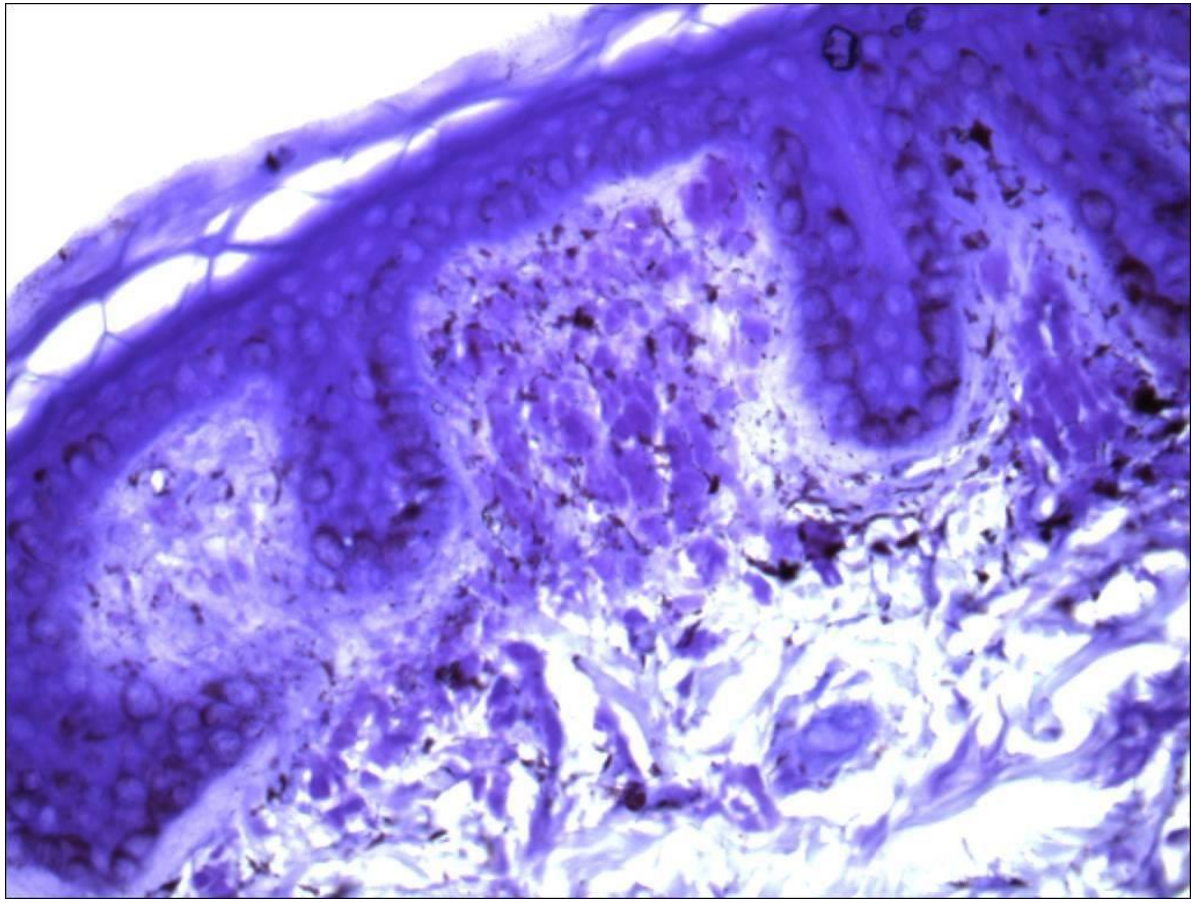
METHYL OR CRYSTAL VIOLET

- Oldest staining method
- Low sensitivity and specificity
- Staining solution-dissolve 2g of crystal violet in 20 ml of 95% alcohol
- Add 80 ml of 1% aqueous ammonium oxalate
- Dissolve using the minimum of heat
- Cool and filter

METHYL OR CRYSTAL VIOLET

- Stain in crystal violet solution,5 min
- Wash and differentiate in weak acetic acid
- Wash and mount in modified apathy`s medium
- Amyloid , mucin, renal hyaline-red-purple
- Background blue

METHYL OR CRYSTAL VIOLET



ACQUIRED FLOURESCENCE METHODS

- Fluorescence of amyloid following treatment with flourochromic dye
- Thiazole dyes like diphenyl brilliant yellow, thiazole yellow, clayton yellow or thioflavin T
- Dye interacts with quaternary structure of beta pleated sheet

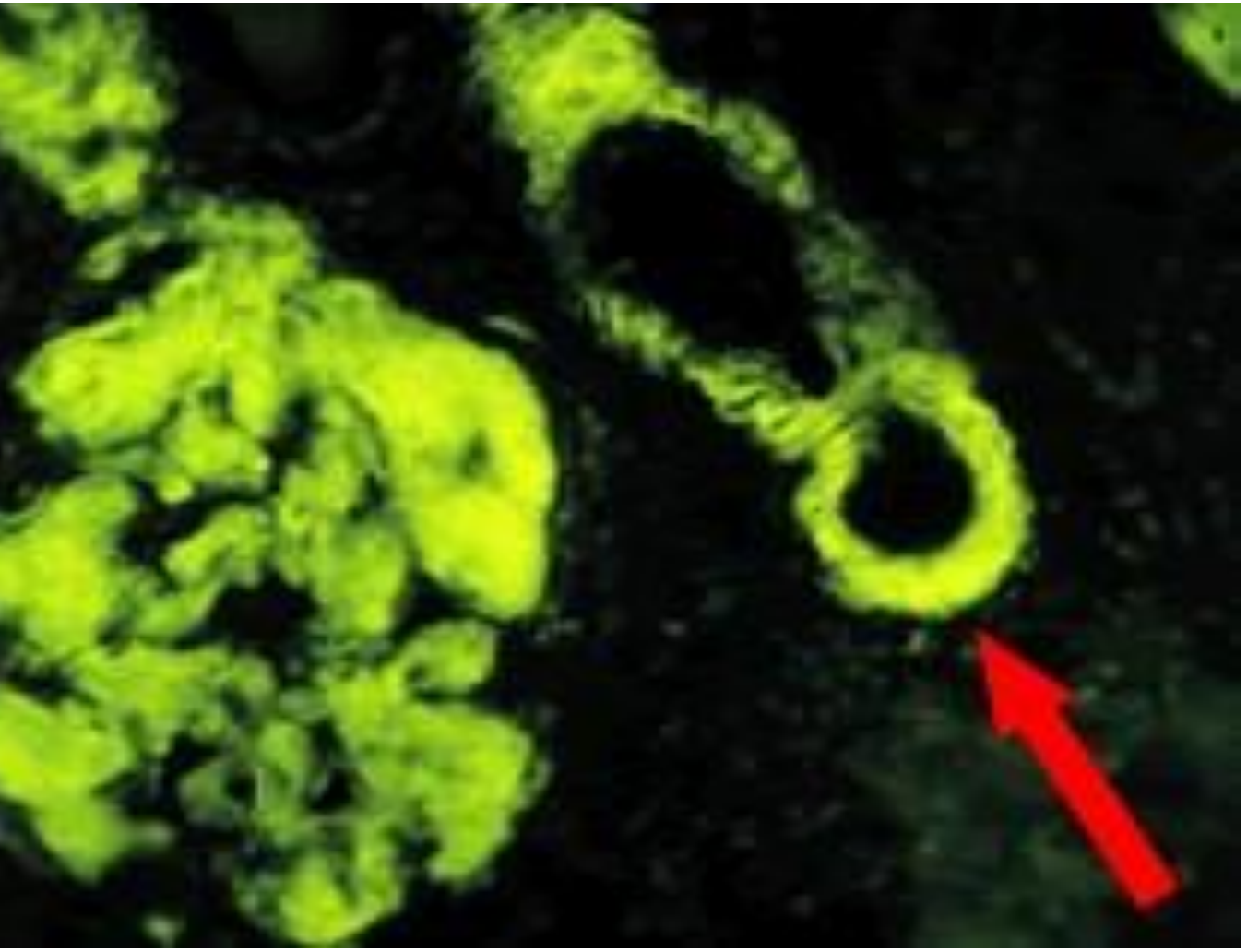
THIOFLAVIN T METHOD

- Fixation not critical
- Solution-1% aqueous thioflavin T
- Alum hematoxylin for 2 minutes
- Wash in water, stain in thio flavin T for 3 min
- Rinse and differentiate in 1% acetic acid 20 min
- Wash, clear,mount in non flourescent mount

THIOFLAVIN T METHOD

- Using UV light source-amyloid,elastic tissue show silver blue fluorecence
- Using blue light fluorescence quartz-yellow flourescence
- High sensitivity
- Stains fibrinoid,arteriolar hyaline,keratin,paneth cells,zymogen
- Acid Ph increases selectivity

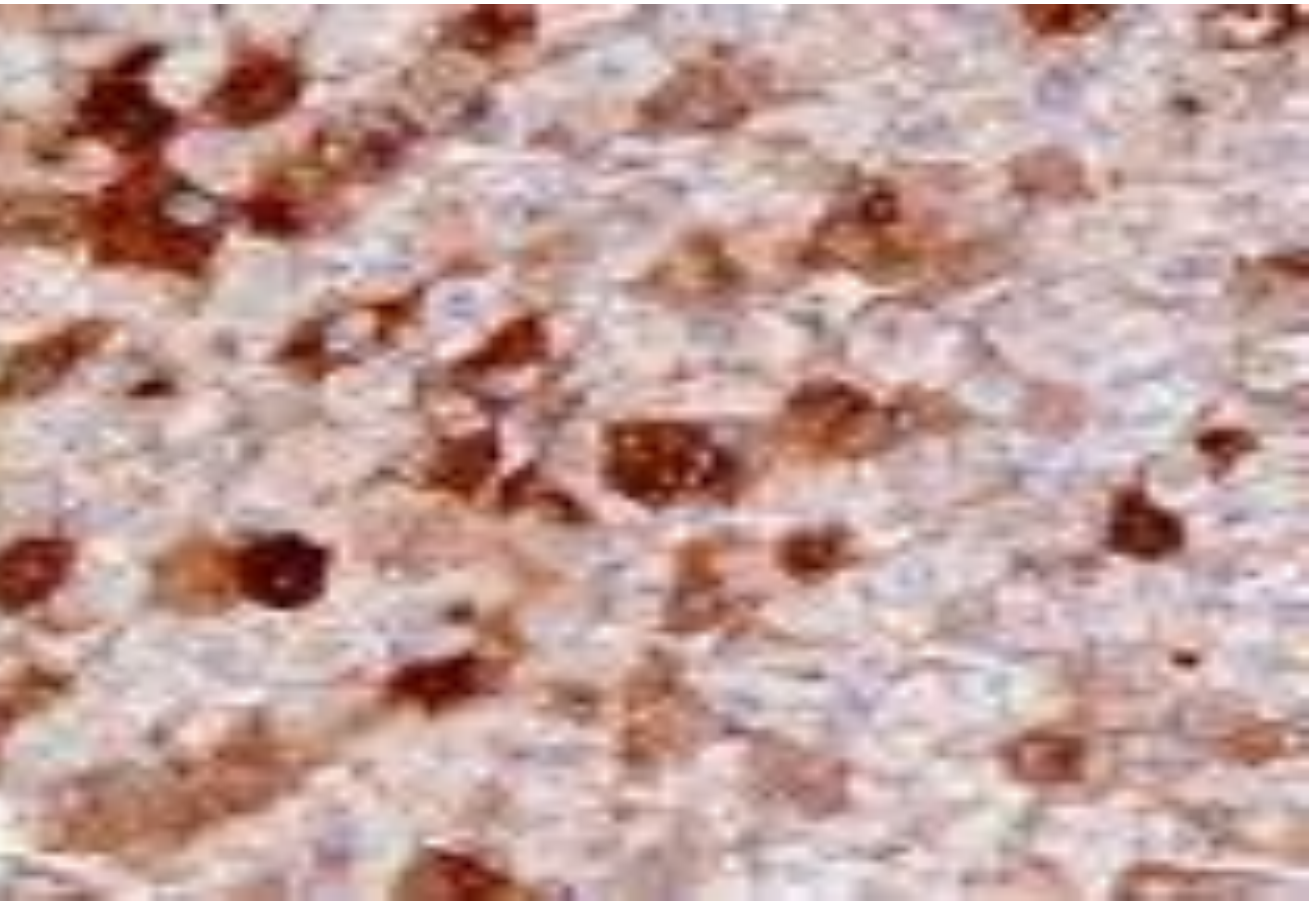
THIOFLAVIN T METHOD



MISCELLANEOUS METHODS

- Variable PAS stain due to glycoprotein AP component
- Alcian blue-uptake can be increased with pepsin treatment
- Alcian blue-borax with celestine blue-hemalum and von gieson conter stain
- Non specific

IMMUNOHISTOCHEMISTRY



SOLID TISSUE TRANSPLANT

First Transplant in the world

TYPES OF TRANSPLANT

- Autograft:
  - Transplant to self
- Allograft:
  - Transplant between two genetically non identical members of same species
- Isograft:
  - Transplant between two genetically identical members of same species
- Xenograft :
  - Between species transplant

Rejection of TissueTransplants

- Cell mediated rejection

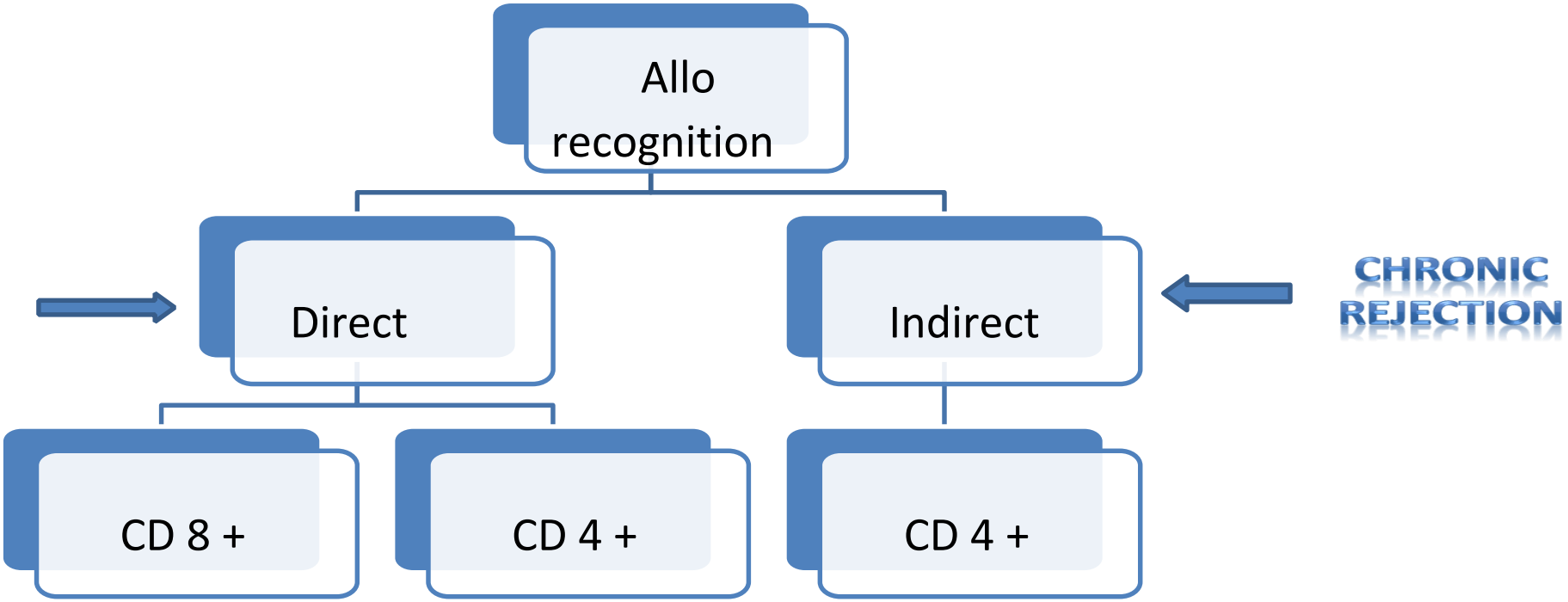
- Antibody mediated rejection

T cell mediated rejection

- Cellular rejection

- Difference in highly polymorphic HLA alleles

Allorecognition



Direct pathway

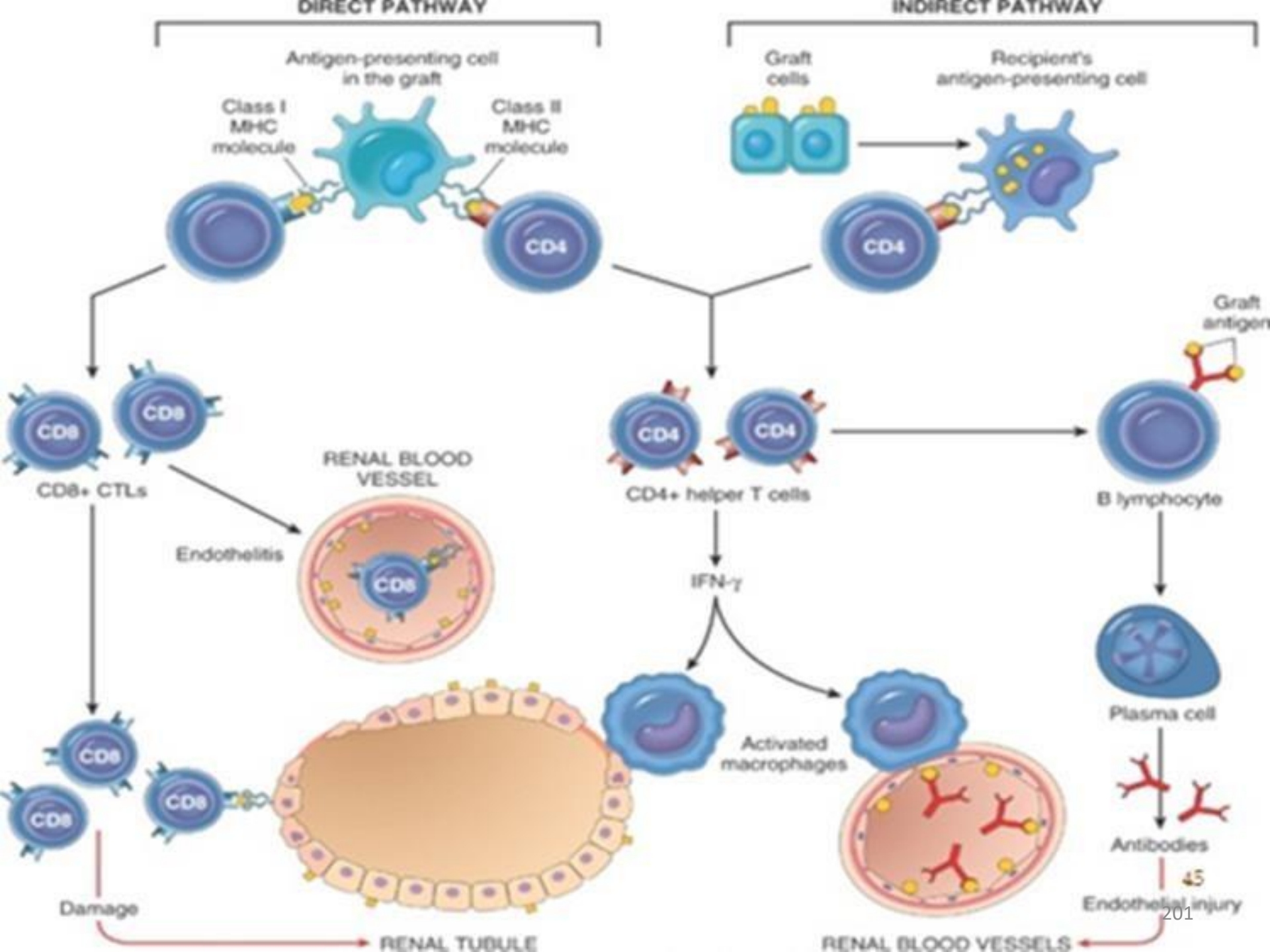
- **Antigen presenting cells** : Graft dendritic cells
- CD 8 + T cells – Recognise MHC Class 1 molecules

  Kills Graft organ ← CTL
- CD 4 + T Cells – Recognise MHC Class 2 molecules → Delayed

  Hypersensitivity ← T Helper cells

Indirect pathway

- **Antigen presenting cells** : Recipient dendritic cell
- Similar to physiological processing and presentation of the other antigens
- CD 4 + T cells
- Hypersensitivity reation

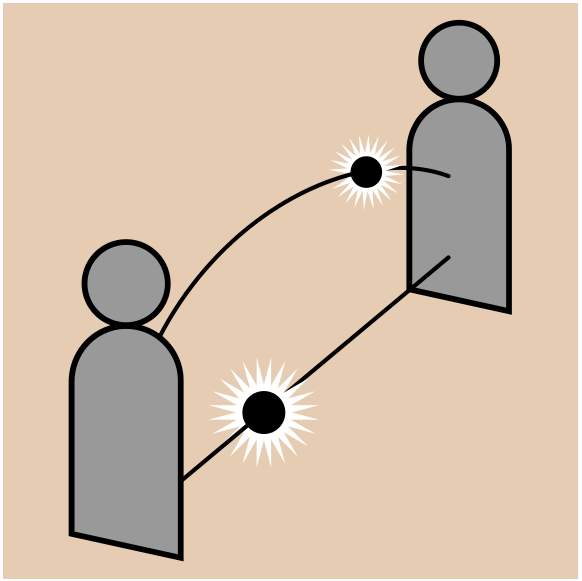

DIRECT PATHWAY
INDIRECT PATHWAY
Antigen-presenting cell in the graft
Class I MHC molecule
Class II MHC molecule
CD4
Graft cells
Recipient's antigen-presenting cell
CD4
Graft antigen
CD8
CD8
CD8+ CTLs
RENAL BLOOD VESSEL
Endothelitis
CD8
CD4
CD4
CD4+ helper T cells
IFN-γ
B lymphocyte
Plasma cell
Antibodies
CD8
CD8
CD8
Activated macrophages
Damage
RENAL TUBULE
RENAL BLOOD VESSELS
Endothelial injury

Introduction

- .
- An cell mediated reaction of donor origin against recipient tissues
- It requires:
  - a donor graft with immunologically competent cells
  - a recipient unable to mount immune response
  - recipient expresses tissue antigens that are not present in the donor.

Criteria for Development of GvHD

- Graft contains immunologically competent cells



- Host appears foreign to the graft; it has alloantigens that are capable of antigenically stimulating the graft
- Host is unable to mount an effective immunological reaction against the graft

Patients at High Risk for GvHD

- Allogeneic & autologous hematopoietic cell transplantation (most common cause)

- Solid organ transplantation (liver, small bowel)

Types of GvHD

- Acute (<100 days posttransplant)
  - triad of dermatologic , hepatic and GI manifestations.
  - usually occurs between10-30 days posttransplant
  - 40-80% incidence

- Chronic (>100 days posttransplant)
  - diverse range of affected organ systems
  - 70-90% evolve from acute GVHD
  - 20% occur de novo
  - 10% occur after acute GVHD resolves

Genetic basis

- HLA dependant factors:

  1. Major Histocompatibility Complex (MHC) 2. Minor Histocompatibility Antigens (mHA)

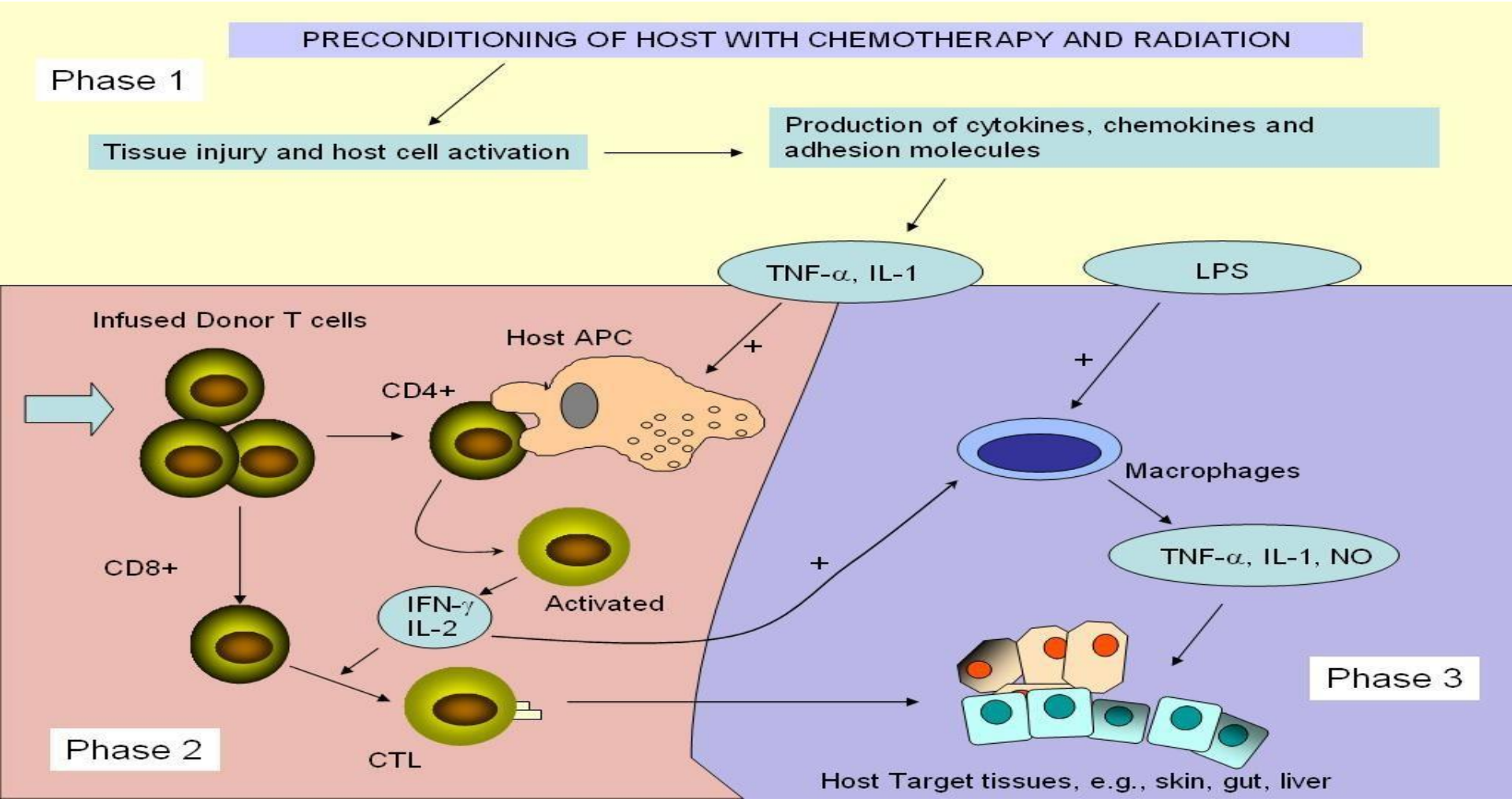
- Non HLA dependant factors:

  1. Cytokine gene polymorphisms
  2. NOD2/CARD 15 polymorphisms

Pathogenesis of acute GvHD

Consists of 3 sequential steps:

- Phase I – Afferent phase or Host tissue damage from chemoradiation
- Phase II – Donor T cell response to host antigens
- Phase III – Effector phase or Inflammatory and cytolytic effects



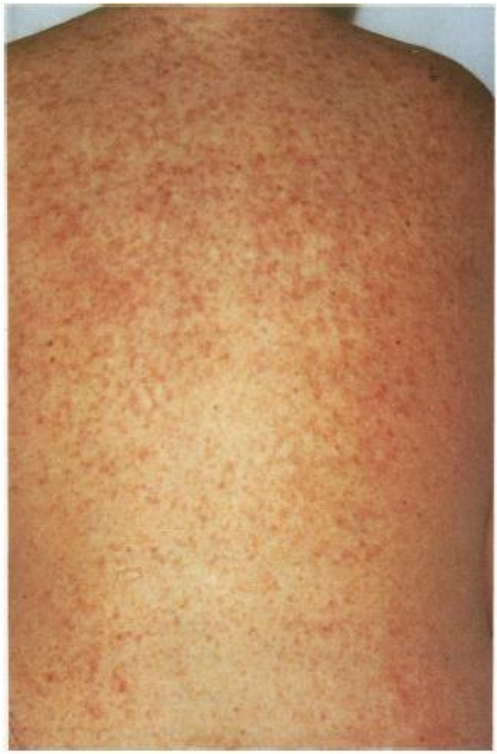
Pathogenesis of Acute GvHD

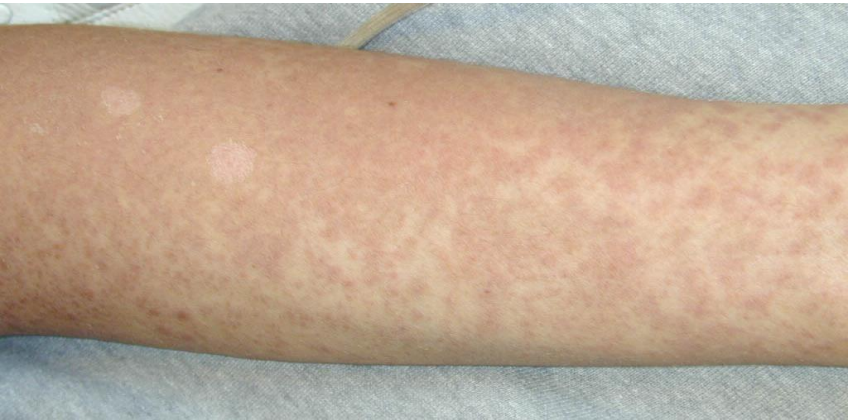
Risk factors

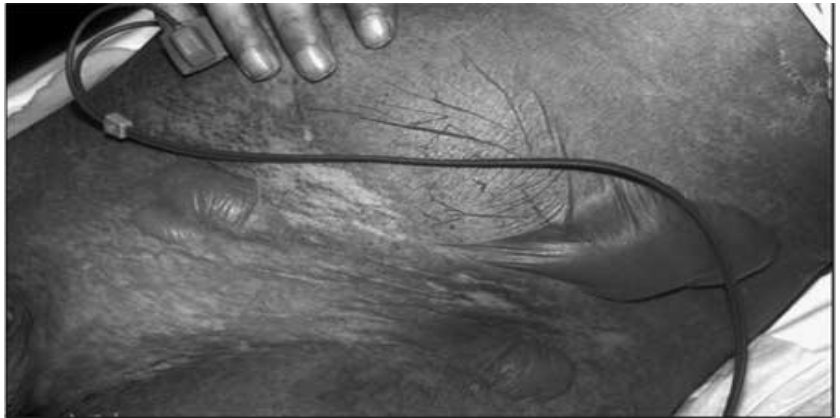
- alloreactivity
- sex mismatch
- donor parity • age
  - recipient age
- 20%, 30%, and 80%
- at <20, 45-50, and >50
  - donor age

Acute GvHD – Dermatological

- Painful or pruritic erythematous macules of palms, soles, trunk, limbs
- Confluent erythema,







erythroderma and/or papule formation

- Subepidermal bullae and vesicle formation

Acute GVHD – GI

- Anorexia
- Dyspepsia
- Crampy abdominal pain

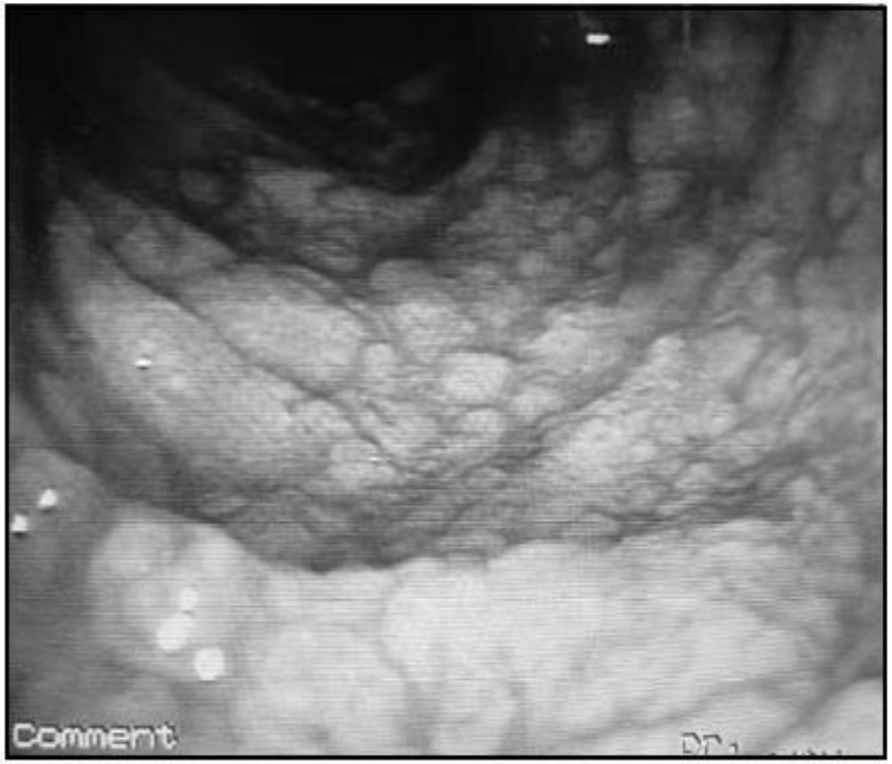
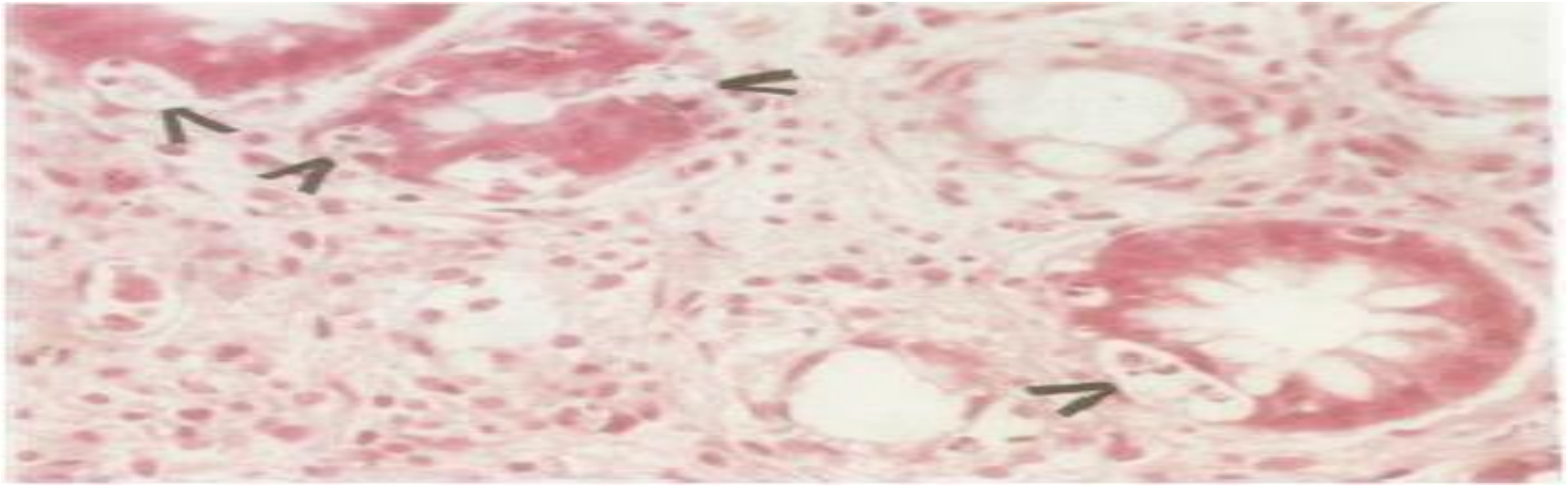


Figure 3 Enteroscopic view of small bowel in stage IV acute GvHD (same patient as Figure 2). There is a striking atrophy of the villae, ulceration and bleeding. Biopsy of affected gut may lead to GI tract perforation and/or sepsis. These appearances were associated with severe diarrhea, malabsorption, intestinal ileus and severe pain.

- Diarrhea (secretory diarrhea may persist despite NPO)
- Intestinal bleeding
- Ileus

Histological features of acute rectal GvHD



Single cell necrosis of individual glandular crypt cells

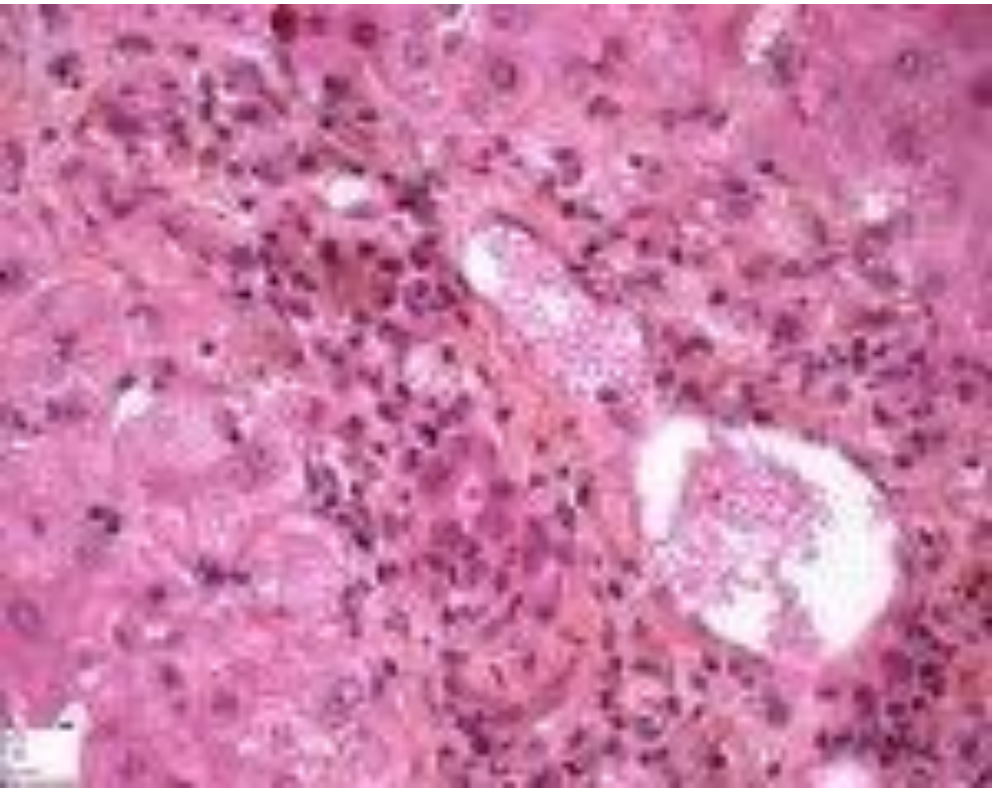
- Stromal inflammatory infiltrate
- Similar features in jejunum and duodenum in upper GI GvHD

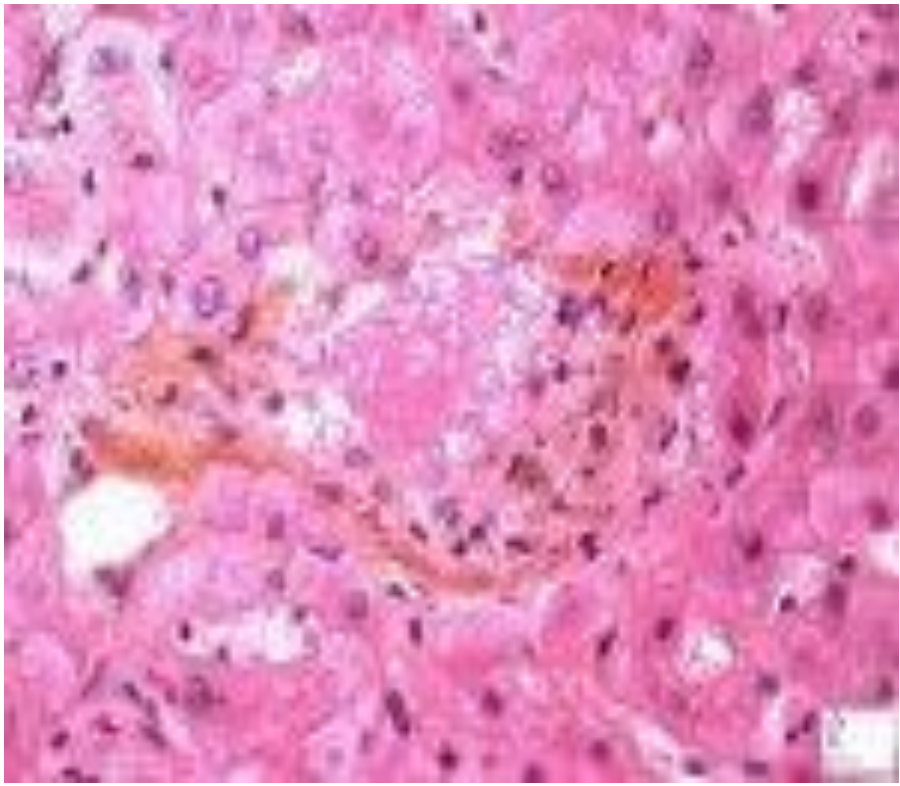
Acute GvHD – Hepatic

- Asymptomatic elevations in bilirubin, ALT, AST, alkaline phosphatase similar to cholestatic jaundice

- Histological examination of the liver shows:

- bile duct atypia
- necrosis of individual epithelial cells producing cytoplasmic vacuolation
- sparse peribiliary inflammatory infiltrate
- cholestasis





I	<25%
II	25 – 49%
III	50 – 74%
IV	75 – 100%

Why liver, GIT & skin are commonly involved?

- organs with a high cell turnover - continual expression of differentiation antigens triggers increased immune surveillance

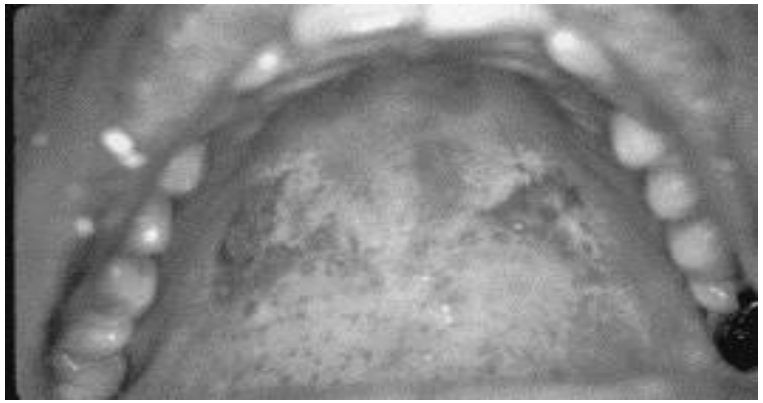
- may harbour latent viruses which may act as a target for donor immune surveillance.

Grading of GvHD

- Grade 1 – skin only with 50% of body surface
- Grade 2 – skin, including total body erythema plus mild liver & gut involvement
- Grade 3 – skin & mild to moderately severe liver or gut or both
- Grade 4 – as for grade 3 but includes desquamation, decrease in performance status

Clinical features of Chronic GvHD

- It can affect various organs including dermatological, ocular, respiratory, neuromuscular, GI and liver
- Has many similarities with autoimmune conditions like SLE, Sjogren's syndrome and RA
- Skin manifestations are similar to scleroderma

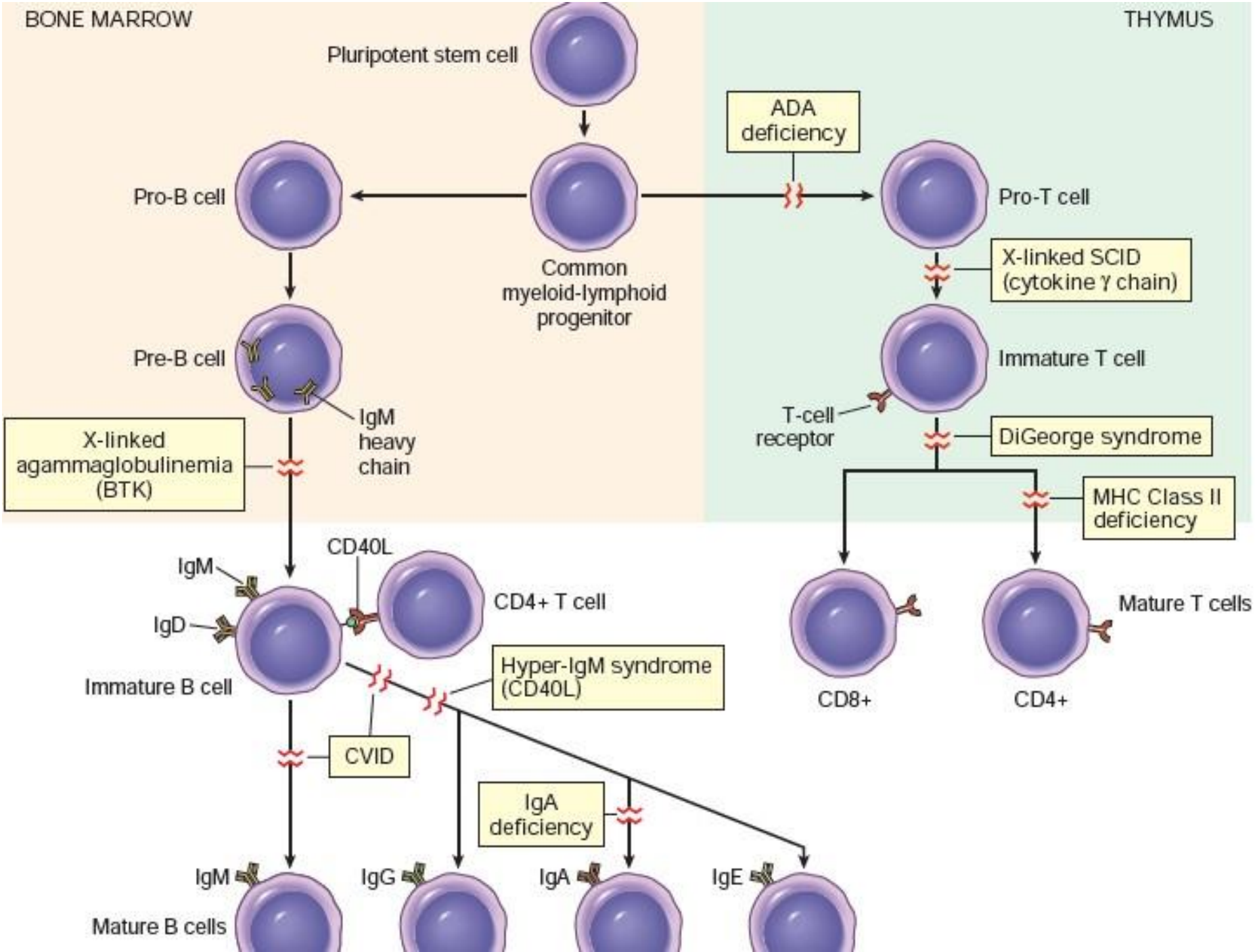


IMMUNODEFICIENCY

Defect in 1 or more components of immune system Types:

- **PRIMARY OR CONGENITAL**:
  - Genetically determined
  - **Cellular/humoral-adaptive immunity**
  - **Defense mechanism-innate immunity**
  - Susceptible to recurrent, severe infection;

- **SECONDARY OR ACQUIRED**: As a consequence of other diseases or environmental factors.e.g – Human Immunodeficiency Virus

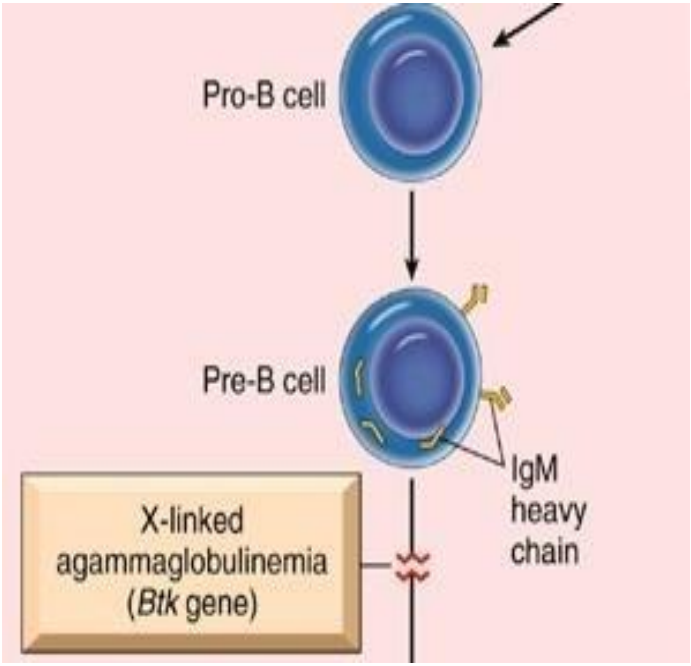

BONE MARROW
THYMUS
Pluripotent stem cell
ADA deficiency
Pro-B cell
Common myeloid-lymphoid progenitor
Pro-T cell
X-linked SCID (cytokine γ chain)
Pre-B cell
IgM heavy chain
Immature T cell
T-cell receptor
X-linked agammaglobulinemia (BTK)
DiGeorge syndrome
MHC Class II deficiency
IgM
CD40L
IgD
CD4+ T cell
Mature T cells
Immature B cell
Hyper-IgM syndrome (CD40L)
CD8+
CD4+
CVID
IgA deficiency
IgM
IgG
IgA
IgE
Mature B cells

HUMORAL

- BRUTON'S AGAMMAGLOBULINEMIA
- COMMON VARIABLE IMMUNODEFICIENCY
- ISOLATED IgA DEFICIENCY
- HYPER IgM SYNDROME

BRUTON AGAMAGLOBULINAEMIA (XLA)

- X-linked agammaglobulinemia
- Failure of B cell precursors → Mature B cells
- Bruton tyrosine kinase mutation-**Xq21.22**



CLINICAL PICTURE

- Males
- 6months of age

- Recurrant bacterial infections(Hemophilus influenzae, streptococcus pneumoniae,staphylococcus aureus)
- Virusesenterovirus(echovirus,poliovirus,coxsackievirus)
- Protozoan-giardia lamblia

CLASSIC CHARACHTERISTICS OF THE DISEASE:•

Absent B cells

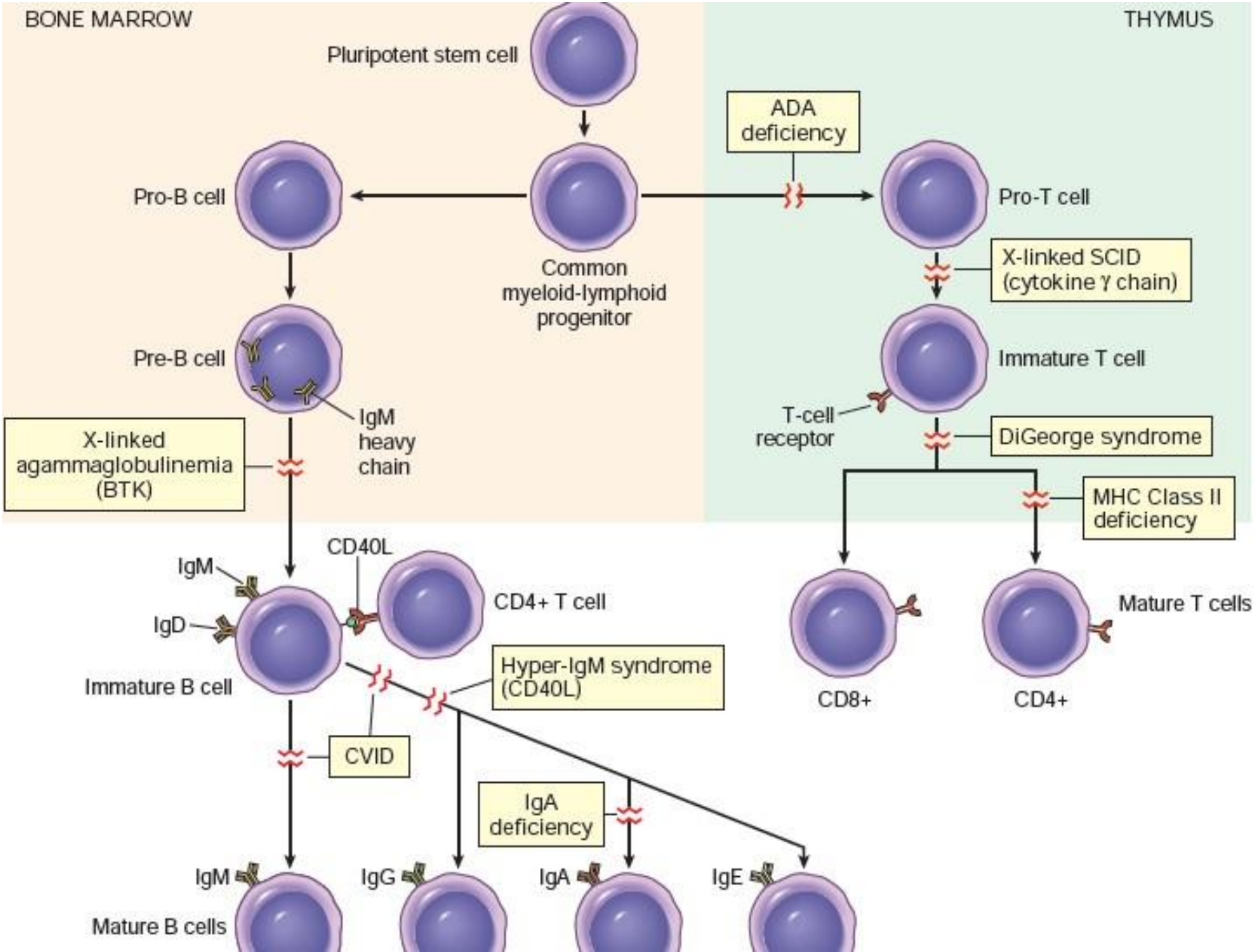
- Underdeveloped germinal centres

- Absent plasma cells
- Normal T-cell mediated reaction

HUMORAL

- **BRUTON'S AGAMMAGLOBULINEMIA**

- **COMMON VARIABLE IMMUNODEFICIENCY**


BONE MARROW
THYMUS
Pluripotent stem cell
ADA deficiency
Pro-B cell
Common myeloid-lymphoid progenitor
Pro-T cell
X-linked SCID (cytokine γ chain)
Pre-B cell
IgM heavy chain
Immature T cell
T-cell receptor
X-linked agammaglobulinemia (BTK)
DiGeorge syndrome
MHC Class II deficiency
IgM
CD40L
IgD
CD4+ T cell
Mature T cells
Immature B cell
Hyper-IgM syndrome (CD40L)
CD8+
CD4+
CVID
IgA deficiency
IgM
IgG
IgA
IgE
Mature B cells

COMMON VARIABLE IMMUNODEFICIENCY

- B cells are normal
- Defect in maturation to plasma cells
- Decreased IgM, IgG and IgA or only IgG and IgA
- ABNORMALITY-**BAFF,ICOS**
- Both sex-affected
- Hyperplastic lymphoid follicles
- High frequency –autoimmune disorders
- Increased risk of lymphoid malignancy

HUMORAL

- **BRUTON'S AGAMMAGLOBULINEMIA**
- **COMMON VARIABLE IMMUNODEFICIENCY**
- **ISOLATED IgA DEFICIENCY**

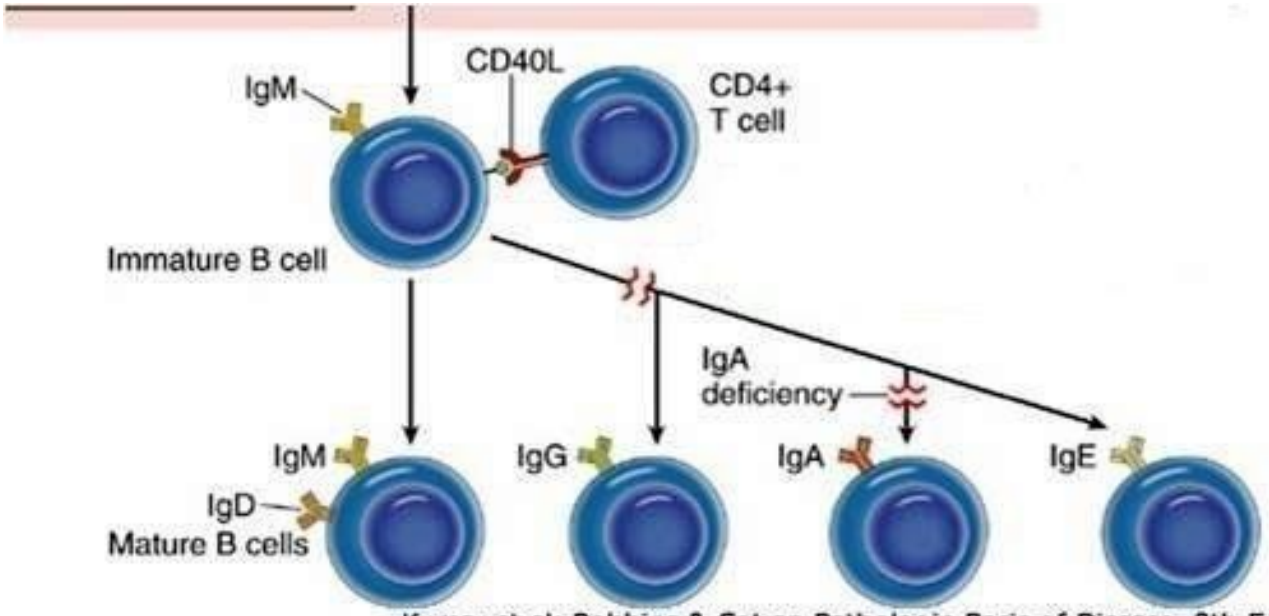
SELECTIVE IG CLASS DEFICIENCY

- e.g. **IgA deficiency**
- Due to defect in isotype switching
- Low levels of serum & secretory IgA

- Familial
- Acquired-ass with toxoplasmosis, measles,viral infection
- Recurrent respiratory, gastrointestinal , genitourinary infection
  - Transfusion with IgA containing blood

- ANAPHYLAXIS

HUMORAL



Kumar et al: Robbins & Cotran Pathologic Basis of Disease, 8th Edition.
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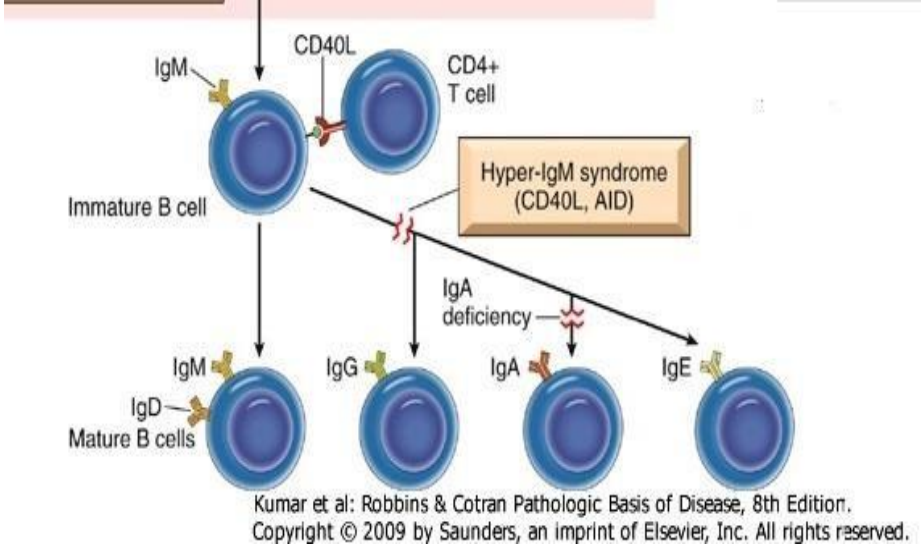
- **BRUTON'S AGAMMAGLOBULINEMIA**
- **COMMON VARIABLE IMMUNODEFICIENCY**
- **ISOLATED IgA DEFICIENCY**
- **HYPER IgM SYNDROME**

HYPER IGM SYNDROME

+ atypical infection (PCP, cryptosporidia)



- Deficiency in IgG, IgA and IgE
- Increased IgM in serum
- B cells express IgD and IgM on membrane
- **X-linked**
- Mutations in gene encoding **CD40L** → **Xq26**
- Autoimmune hemolytic anemia, thrombocytopenia, neutropenia
- Recurrent infections

CELL-MEDIATED

- **DI GEORGE SYNDROME**

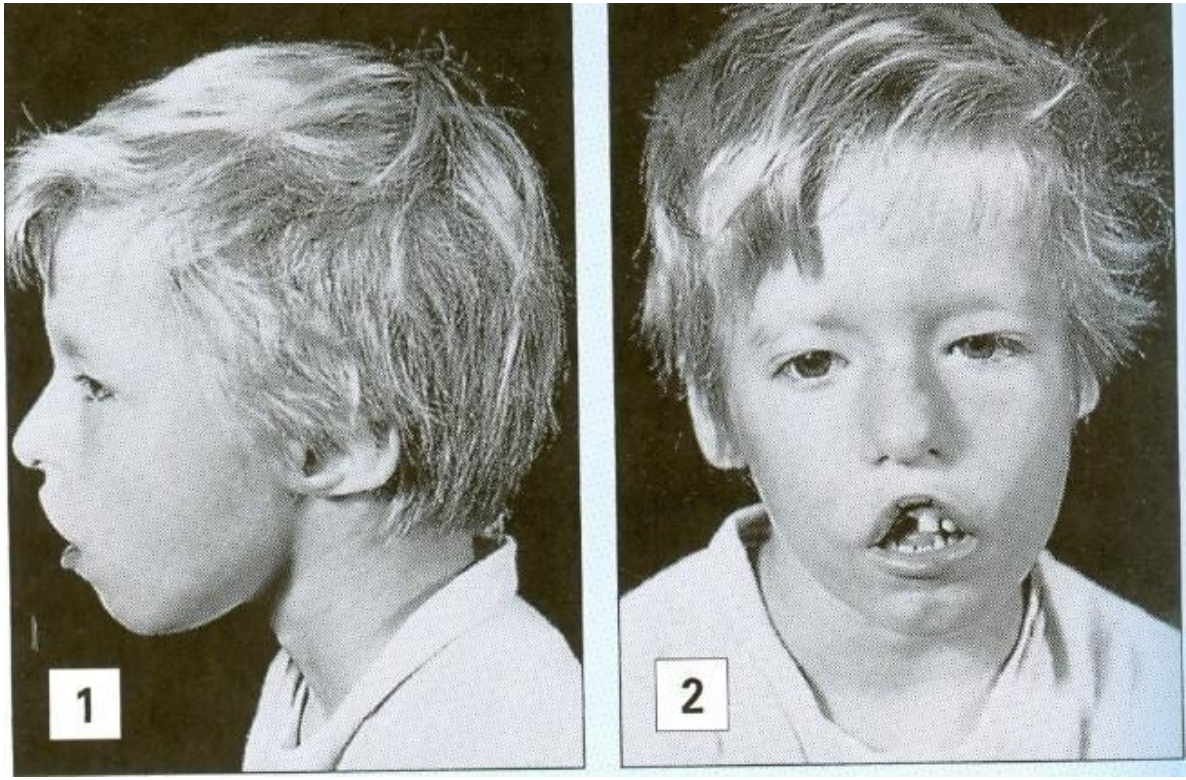
- **SEVERE COMBINED IMMUNODEFICIENCY**
  - **DIGEORGE SYNDROME**

- **Thymic hypoplasia**

- **Lack of T helper (Th) cells , Cytotoxic T cells (CTL) and T regulatory (Treg) cells**
- **B cells** are **present** but T-dependent B cell responses are defective
- Anti-viral and anti-fungal immunity impaired
- Developmental defect in the 3rd and 4th pharyngeal pouch
- Results in facial defect and congenital heart disease
- Treated with thymic transplant
- Autosomal dominant trait

DIGEORGE SYNDROM - CATCH 22

***c**ardiac defects*
***a**bnormal facies*
***t**hymic hypo/aplasia*
***c**left palate*
***h**ypocalcemia*
*deletion **22**q11*



CELL-MEDIATED

- **DI GEORGE SYNDROME**

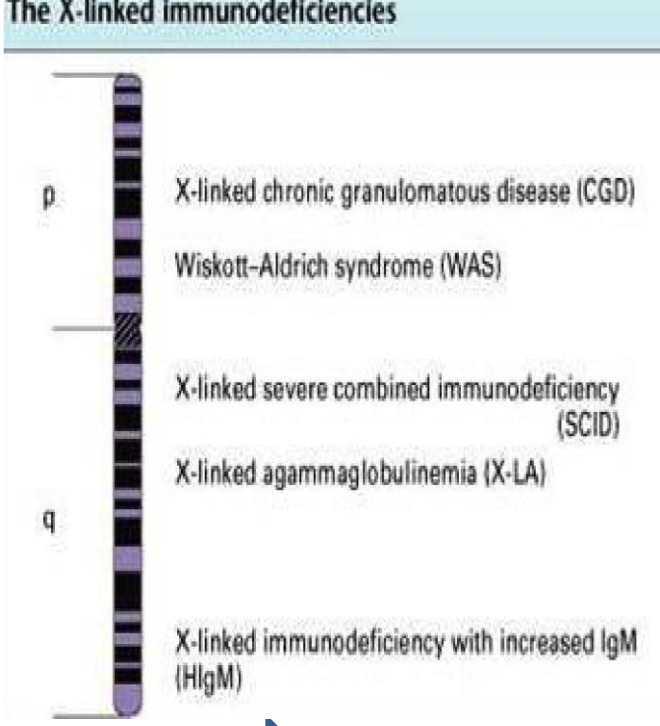
- **SEVERE COMBINED IMMUNODEFICIENCY**

SEVERE COMBINED IMMUNODEFICIENCY

(SCID)

- Defects-humoral & cell mediated immune responses
- Myeloid and erythroid cells are normal.
- Generally lethal
- Susceptible to bacterial, viral and fungal infections.
- Affected infants-oral candidiasis,extensive diaper rash,failure to thrive.

IMMUNODEFICIENCY WITH THROMBOCYTOPENIA



- **WISKOTT-ALDRICH** syndrome • X-linked recessive disorder
- Thrombocytopenia,eczema,recurrent infection death
- Normal thymus
- Secondary depletion of T lymphocytes in peripheral blood
- Low IgM levels

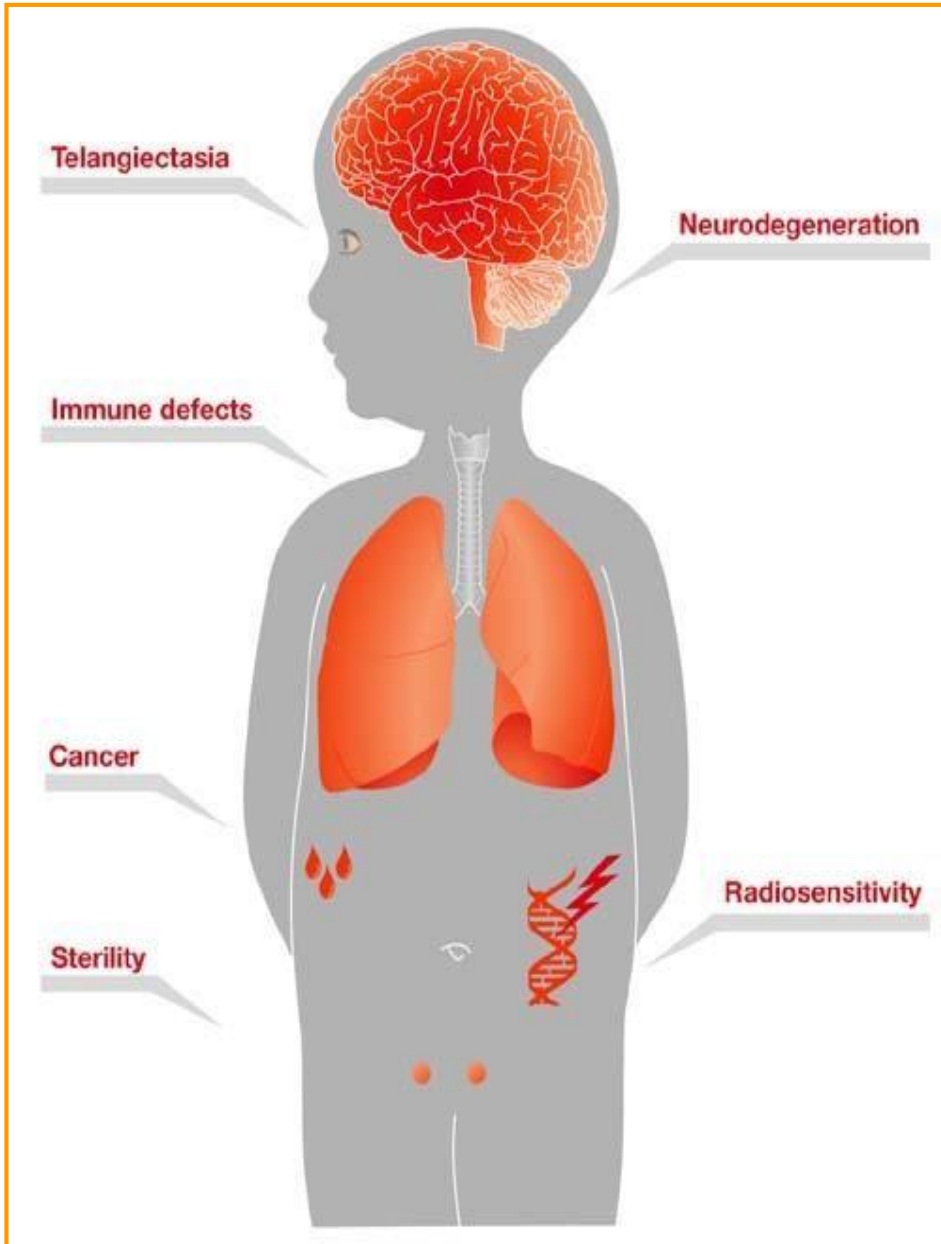
- IgG level-normal
- Mutation in gene encoding

  WASP Xp11.23

  ATAXIA

  TELANGIECTASIA

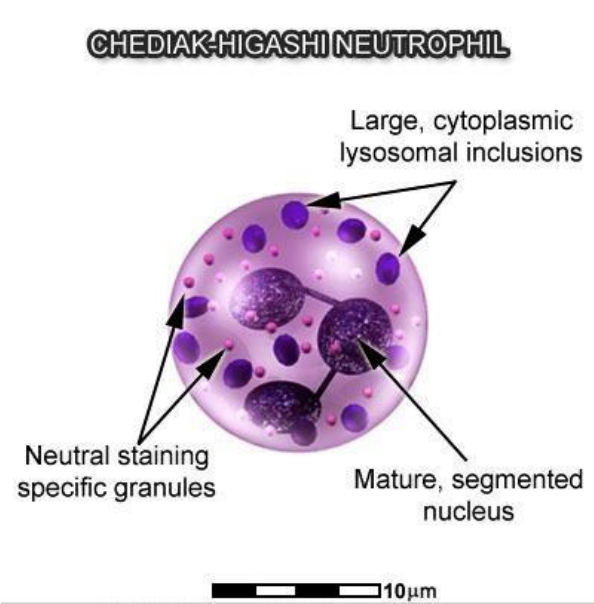
- DNA repair defect
- Mutation-**11q23**
- 80%-low IgG2
- 60%-low IgA
- άfetoprotein levels
- FEATURES:-



- **Cerebellar deterioration**
- **Oculocutaneous telangiectasia**
- **Immunodeficiency**
- **Genomic Instability**
- **Acute sensitivity to ionizing radiation**
- **Predisposition to malignancy**

CHEDIAK-HIGASHI SYNDROME

- Rare **autosomal recessive** condition.
- Have inefficient and prolonged bacterial killing.
- Microtubule defect-fusion of lysosomal granules • Features :○ recurrent bacterial infections, ○ partial albinism, ○ giant lysosomal granules ○ neurologic complications

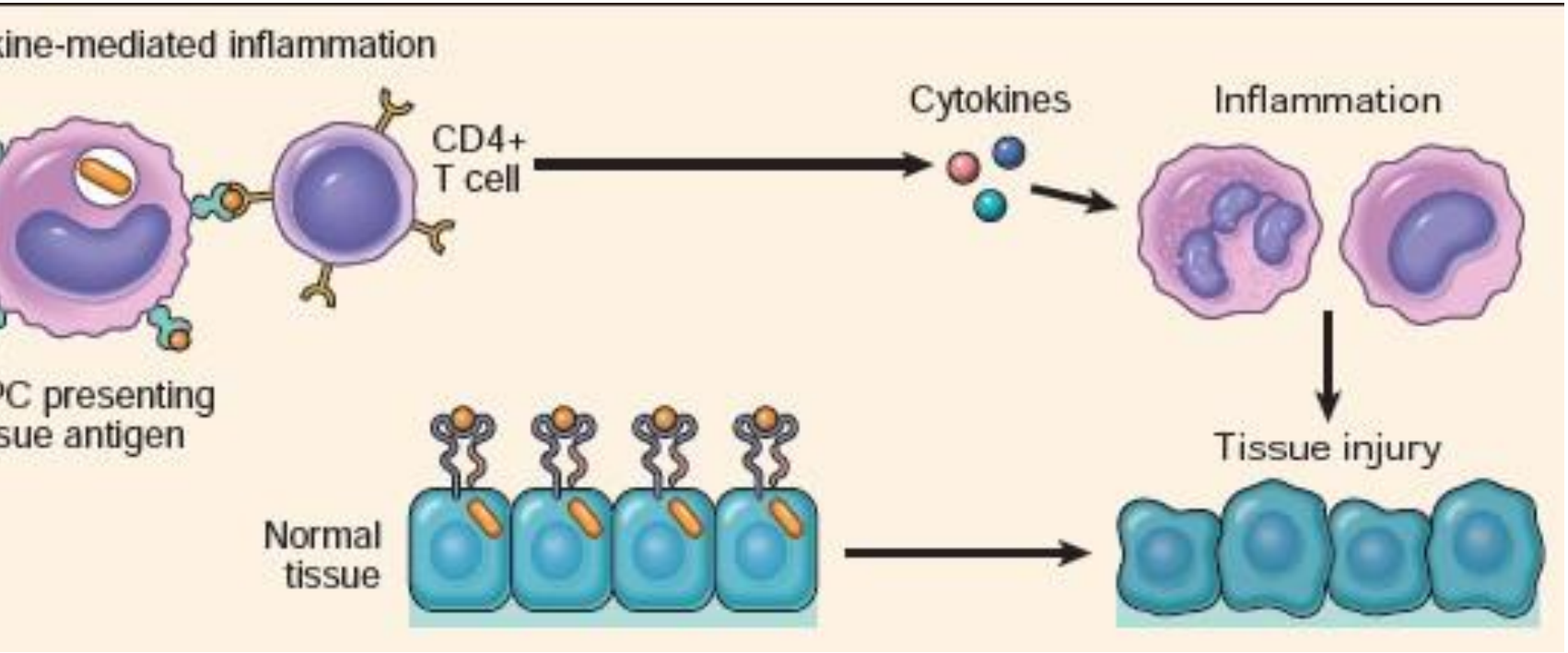


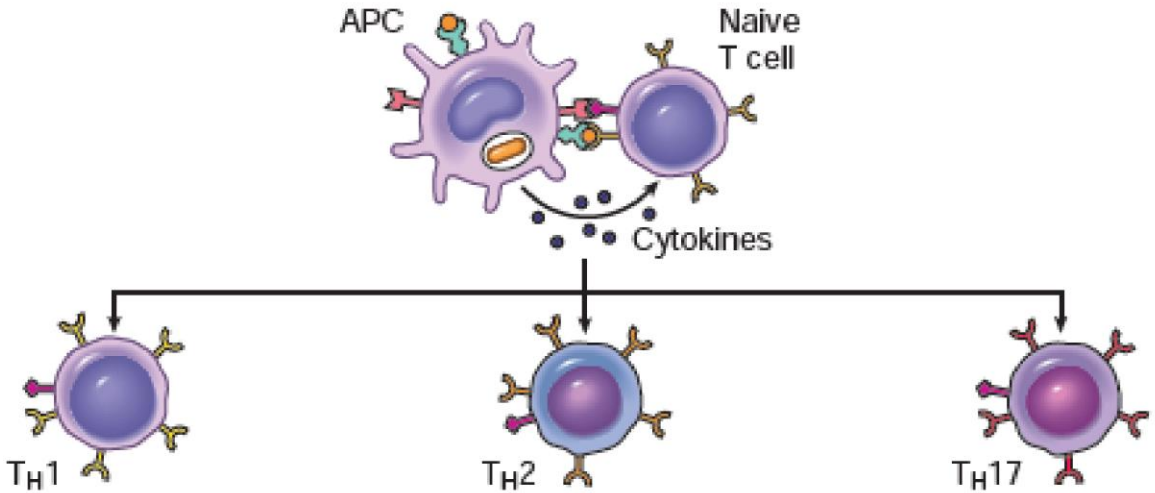
Type 4 (CELL MEDIATED) hypersensitivity

- Cell-mediated type of hypersensitivity is caused by inflammation resulting from cytokines produced by CD4+ T cells and cell killing by CD8+ T cells
- CD4+ T cell–mediated hypersensitivity:
  - Induced by environmental and self antigens including autoimmune diseases
- CD8+ T cell–mediated hypersensitivity:

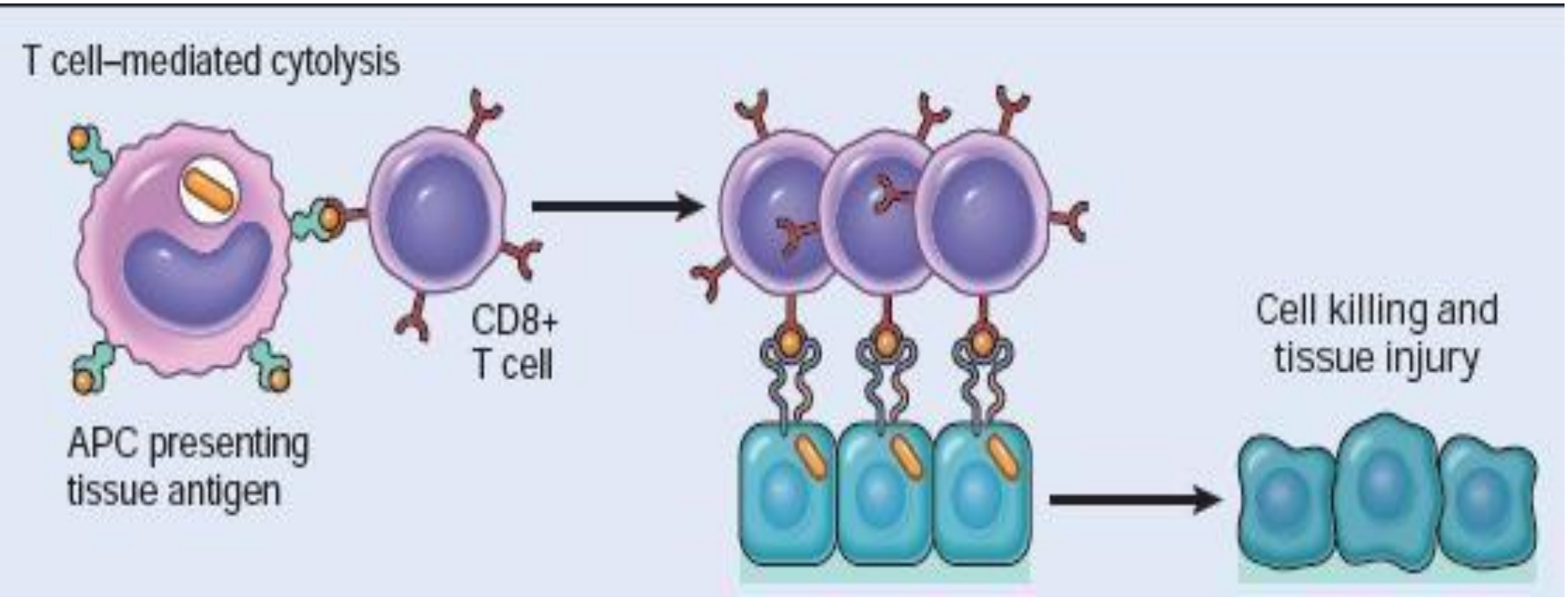
- Involved in some of these autoimmune diseases and in viral infections.

CD4+ T Cell–Mediated Inflammation





	T_H1	T_H2	T_H17
Major cytokines produced	IFN-γ	IL-4, IL-5, IL-13	IL-17, IL-22
Cytokines that induce this subset	IFN-γ, IL-12	IL-4	TGF-β, IL-6, IL-1, IL-23
Immunological reactions triggered	Macrophage activation, stimulation of IgG antibody production	Stimulation of IgE production, activation of mast cells and eosinophils	Recruitment of neutrophils, monocytes
Host defense against	Intracellular microbes	Helminthic parasites	Extracellular bacteria, fungi
Role in disease	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, granulomatous inflammation)	Allergies	Autoimmune and other chronic inflammatory diseases (such as IBD, psoriasis, MS)



Mechanisms of killing :

A) Perforin granzyme dependent killing :

-preformed mediators in lysosomal granules of CD8 cells -Granzymes - - - activates caspases - - - - apoptosis of target cells

B) fas – fas ligand dependent killing

Activation of CD8 cells expressing Fas ligand - - - - Apoptosis

Types of Delayed Hypersensitivity

ved Reaction	maximal time	reaction
-Mote	24 hours	
act	48-72 hours	
rculin	48-72 hours	
ulomatous	at least 14 days	

Jones-Mote Hypersensitivity

- Now referred to as “cutaneous basophil hypersensitivity”
- Basophils are prominent as secondary infiltrating cells.
- Basophilic infiltration of area under epidermis
- Induced by soluble (weak) antigens
- Transient dermal response

- Prominent in reactions to viral antigens, in contact reactions, skin allograft rejections, reactions to tumor cells and cases of hypersensitivity pneumonitis (allergic alveolitis)

Contact Hypersensitivity

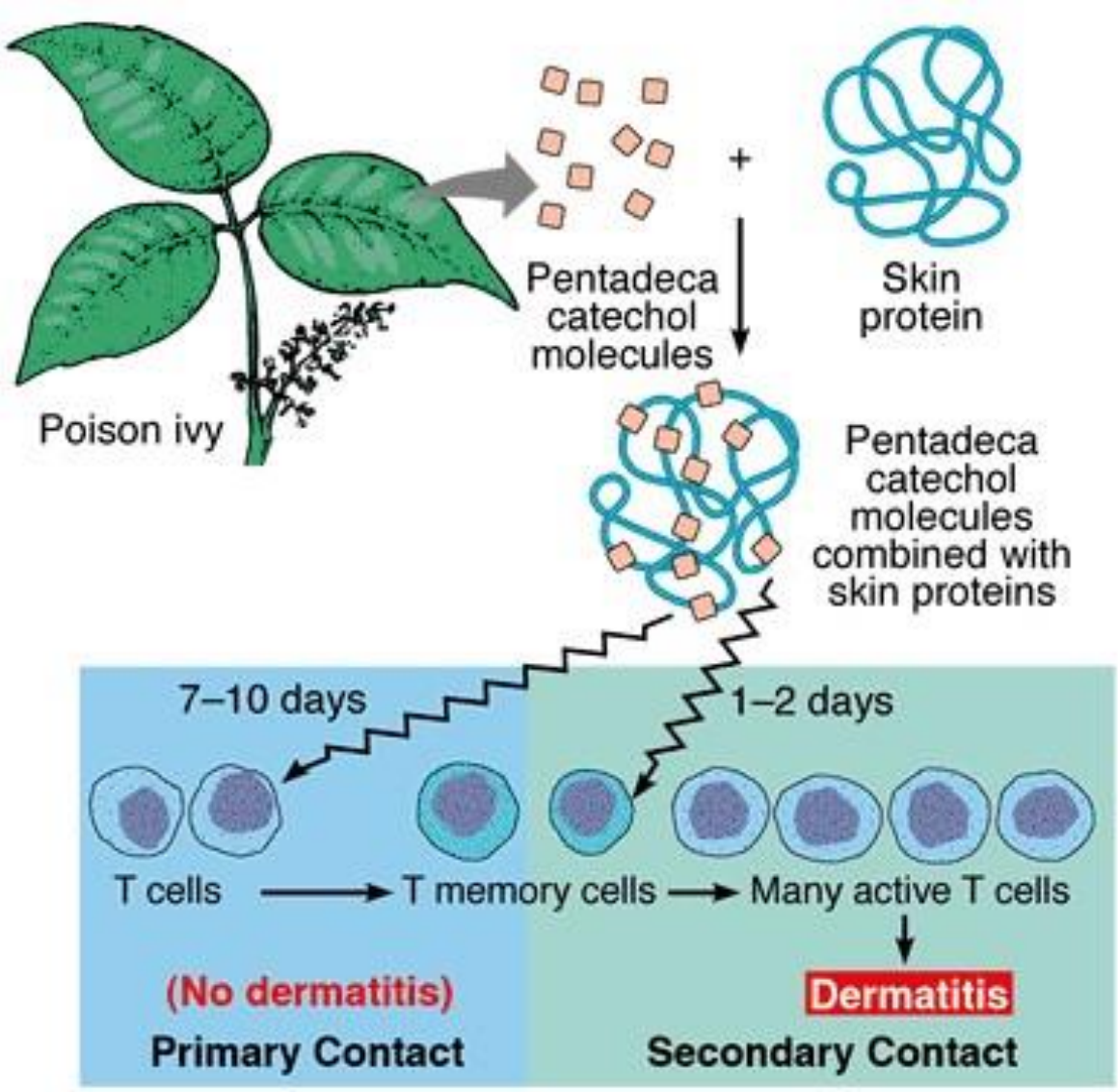
- Usually maximal at 48 hours

- Predominantly an epidermal reaction

- Langerhans cells are the antigen presenting cells – a dendritic antigen presenting cell
  - carry antigen to lymph nodes draining skin
- Associated with hapten-induced eczema
  - nickel salts in jewellry , picryl chloride , acrylates , p-Phenylene diamine in hair dyes , chromates , chemicals in rubber , poison ivy (urushiol)

Allergic Contact Dermatitis Response to Poison Ivy

Hapten


Poison ivy
Pentadeca catechol molecules
+
Skin protein
Pentadeca catechol molecules combined with skin proteins
7–10 days
1–2 days
T cells
T memory cells
Many active T cells
(No dermatitis)
Primary Contact
Dermatitis
Secondary Contact

Tuberculin Hypersensitivity

- Maximum at 48-72 hours
- Redness and induration 8 -12hrs
- Inflitration of lesion with mononuclear cells ; perivascular cuffing ; inc vascular permeability
- Plasma proteins escape – dermal edema , fibrin deposition

- First described as a reaction to the lipoprotein antigen of tubercle bacillus
- Responsible for lesions associated with bacterial allergy
  – cavitation, caseation, general toxemia seen in TB

- May progress to granulomatous reaction in unresolved infection

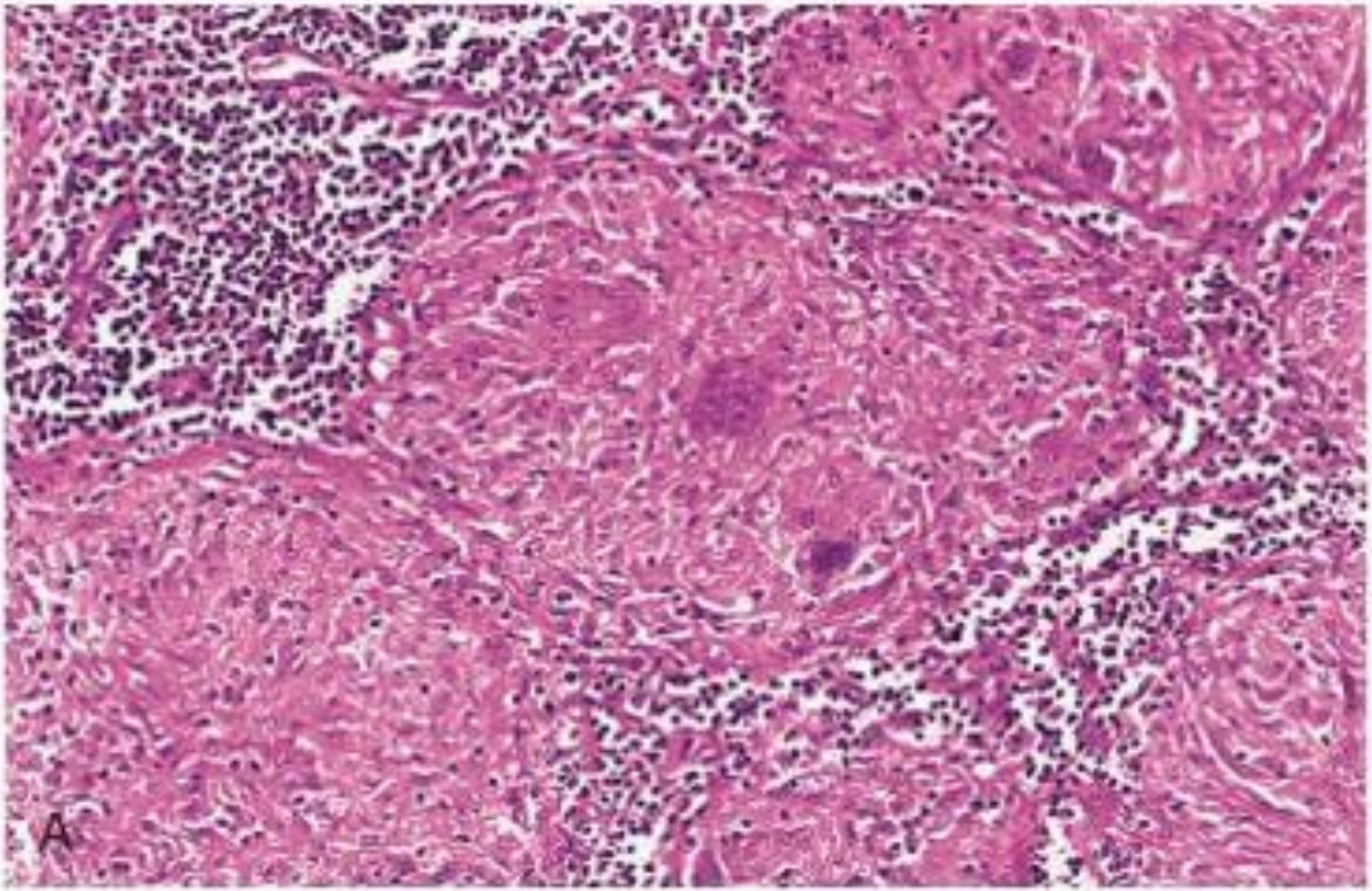
Granulomatous Hypersensitivity

- Clinically, the most important form of DTH, since it causes many of the pathological effects in diseases which involve T cell-mediated immunity

- Maximal at 14 days

- Continual release of cytokines

- Leads to accumulation of large numbers of macrophages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