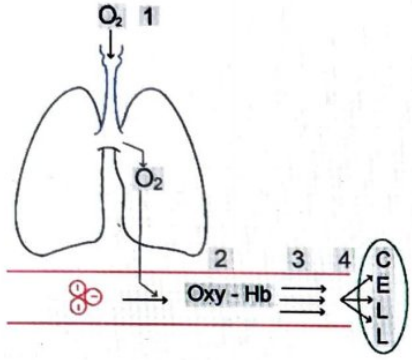
# 1 CONCEPT OF CELL INJURY

## HYPOXIA

- MC cause of cell injury: Hypoxia (↓ $O_2$)




**Types**

- Hypoxic hypoxia
  - High altitudes
  - COPD
- Anemic hypoxia
  - Anemia
  - CO poisoning
- Stagnant hypoxia
  - MC cause
  - Arterial obstruction → ischemia → ↓ oxygen
  - Venous obstruction
- Histo-toxic hypoxia
  - Cyanide poisoning

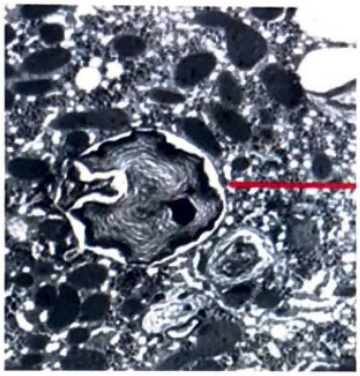
**Important Information**

- Sensitivity to Oxygen deprivation: Neurons (most sensitive) >> skeletal muscle cells >> fibroblast (least sensitive/resistant)

## REVERSIBLE CELL INJURY

00:07:03

- ↓ $O_2$ → Mitochondria affected → ↓ ATP
- 1st organelle affected in reversible cell injury: Mitochondria
- Cell membrane
  - ↓ ATP → ↓ $Na^+$-$K^+$ ATPase pump activity → ↑ $Na^+$ accumulation → ↑ water → cell swelling (1st microscopic change)
  - Cell swelling is also known as hydropic change
  - Myelin figures in cytoplasm (due to damage of phospholipid) is seen



Myelin figures

- Endoplasmic reticulum
  - RER is responsible for protein synthesis and requires energy. On ATP depletion it results in
    - → ↓ Protein concentration
    - → ↑ Misfolded proteins accumulation
- Metabolic changes
  - ↑ Lactic acid/pyruvic acid (due to absence of TCA cycle)
  - ↓ Glycogen
- Nucleus: clumping of chromatin
- ↓ ATP → ↑ $Ca^{2+}$ → enters mitochondria → amorphous/mitochondrial densities
  - Seen MC in prolonged cell injury
- Liver & Cardiac tissues show fatty change (accumulation of triglycerides in cytoplasm) in reversible cell injury.

**Previous Year's Questions**

Q. All are features of reversible cell injury EXCEPT? (AIIMS 2019)

A. Endoplasmic reticulum swelling
B. Dense deposition of mitochondria
C. Bleb formation
D. Detachment of ribosome

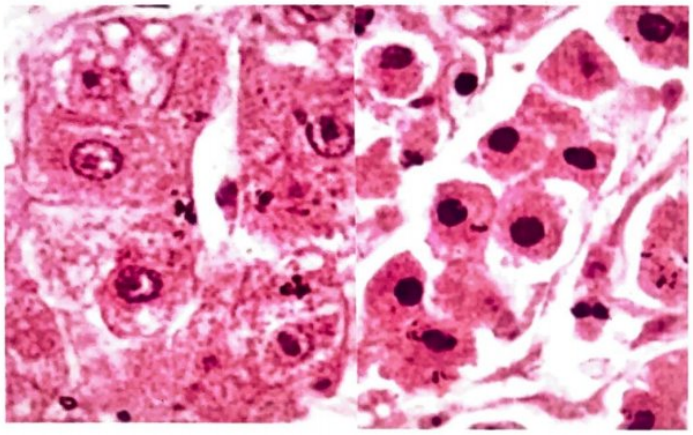
## IRREVERSIBLE CELL INJURY

00:15:41

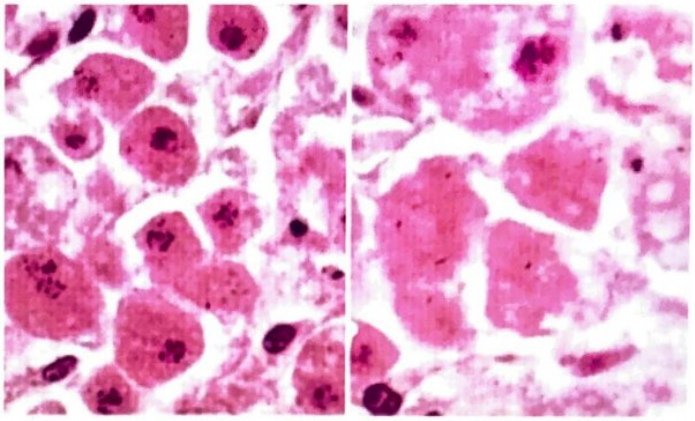
- Persistent hypoxia → ↓ mitochondrial function → ↓↓↓ ATP → ↑↑ Ca2+
- Increased calcium results in
  - Mitochondrial densities → cell death (higher in no compared to reversible cell injury)

- Activation of
  - Lysosomal enzymes (cell death)
  - Phospholipase (membrane damage)
  - Nucleases ("smear" pattern in gel electrophoresis)
    - → Nucleic acid condensation: Pyknosis
    - → Nucleic acid material fragmentation: Karyorhexis
    - → Complete breakdown of nuclear material: Karyolysis

- In heart
  - Reversible cell injury (angina) → cell swollen → membrane intact
  - Irreversible cell injury (MI) → membrane damage → troponin leak into blood



Normal Pyknosis



Karyorhexis Karyolysis

**Apoptosis**

- Longer duration of injury → ↑↑ mitochondrial permeability → leakage of cytochrome C → cell death

# 2 CELLULAR ADAPTATIONS

## ATROPHY

00:01:11

- Atrophy → absent growth
- Associated with ↓ Size & ↓ function of cells
- Reversible change

**Examples**

- Physiological Atrophy
  - Uterus after parturition
  - Organ Atrophy (fetal development) → notochord
- Pathological Atrophy
  - Denervation atrophy → polio virus infection (Anterior horn cell of spinal cord)
  - Inadequate Nutrition → protein energy malnutrition
  - Disuse atrophy → seen after fracture (nonuse of muscles)
  - Chronic ischemic atrophy → brain (Alzheimer's disease)

## HYPERTROPHY

00:06:37

- Hypertrophy: ↑ size of the cell → ↑ function of the cell
- Reversible in nature

**Examples**

- Physiological
  - Uterine hypertrophy → pregnancy
  - Skeletal muscles → weight lifting
- Pathological
  - Cardiac hypertrophy → HTN, Valvular disease

## HYPERPLASIA

00:09:13

- Hyperplasia → ↑ number of cells

### Important Information

- Simultaneous hypertrophy & hyperplasia can be seen in gravid uterus

**Examples**

- Physiological
  - Uterus & breast → Pregnancy
  - BM → Hemolytic anemia
- Pathological
  - Prostatic hyperplasia → ↑ DHT formation in elderly; benign condition
  - Endometrial hyperplasia → can progress to endometrial carcinoma

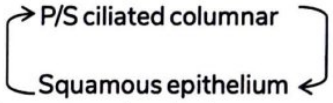
## METAPLASIA

00:17:54

- Change in nature of cells in presence of stress factor
- On stress → stem cells change in nature → metaplasia
- Benign & Reversible in nature

**Examples**

- Epithelial metaplasia
  - In lungs smoking can lead to squamous metaplasia



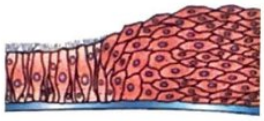

  - If the change persists for longer → cancer (squamous cell carcinoma of lung)
  - In stomach, GERD can cause intestinal columnar metaplasia of esophagus (Barrett's esophagus)

$$\text{Squamous epithelium} \xrightarrow{acid\ reflux} \text{Intestinal columnar epithelial cells}$$

- Connective tissue metaplasia
  - Myositis Ossificans → after trauma due to hemorrhage the muscle replaced by bone like tissue

### Previous Year's Questions

**Q. A 45 years old person who is chronic smoker came to the clinic with complaints of cough. The physician examines the patient and takes a biopsy. The picture in the biopsy was as the description below. Which of the following cellular changes has happened in this patient?** (NEET – Jan - 2020)



A. Hyperplasia
B. Dysplasia
C. Metaplasia
D. Anaplasia

# 3 IRREVERSIBLE CELL INJURY 1

## PATHOPHYSIOLOGY

Irreversible cell injury

Mitochondrial Dysfunction → CYT C LEAKAGE INTO CYTOPLASM → APOPTOSIS → CELL DEATH

Necrosis → ↓↓↓↓ ATP [d/t Hypoxia] → Energy dependent Ca2+ pumps → ↑↑ $Ca^{2+}$ inside the cell

- Mitochondrial Densities → Cell Death ←
- Enzyme Activation → Cell Death ←
  - Lysosomal enzymes
  - Phospholipase
  - Nucleases breaks nucleic acid

## NECROSIS

- Morphological changes in a tissue after cell death occurs

**SUBTYPES**

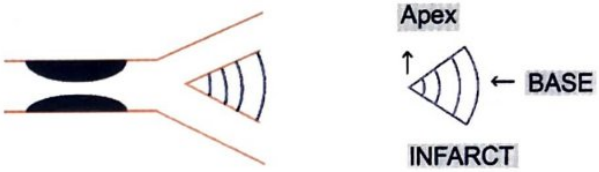
**COAGULATIVE NECROSIS**

- MC type of necrosis seen microscopically
- MC cause → ischemia
- Denaturation of proteins, inactivation of hydrolytic enzymes and intact structural outline

### Important Information

- Coagulative necrosis is associated with "Tombstone Appearance" → can be seen in all organs except CNS
- Seen in Zenker's degeneration → coagulative necrosis in skeletal muscle, associated with typhoid infection

- Neutrophilic infiltration is classically noted in COAGULATIVE necrosis (for clearing dead cells)




### Previous Year's Questions

Q. A wedge shaped are in the adrenal gland is affected. On HPE nucleus is not seen but cellular outlines are intact. Which type of necrosis is being described?
(JIPMER – Nov - 2018)

A. Coagulative
B. Liquefactive
C. Fibrinoid
D. Caseous

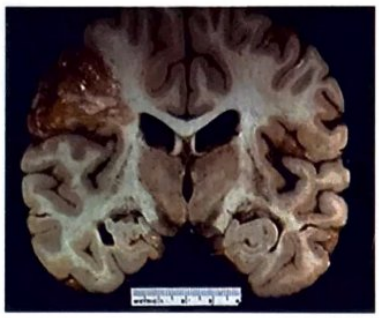
**Infarct**

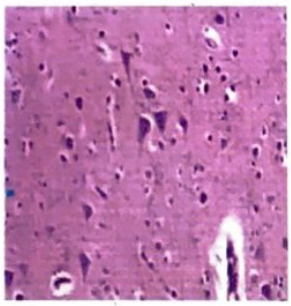
- Localized area formed due to ischemia, usually triangular in shape
- Apex of infarct points in the direction of site of obstruction
- Subtypes of Infarct-
  - White Infarct
    - → Seen in organs with end-arterial blood supply, particularly in solid organs
    - → Eg: Heart, Kidneys
  - Red Infarct
    - → Seen in Organs with loose Connective tissues

→ Seen in Organs with Dual blood supply like Lungs/ Liver

## LIQUEFACTIVE/COLLIQUATIVE NECROSIS 00:09:06

- Hydrolytic enzyme activation → Damage to tissues (liquefied)



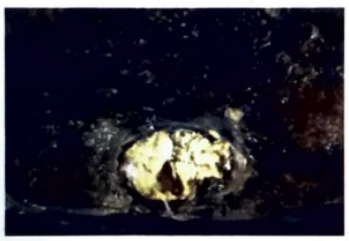


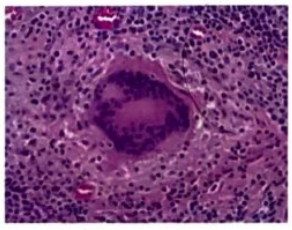
Normal Necrosis

- Structural outline not preserved microscopically
- Examples
  - CNS Ischemia → damage to glial cells leading to hydrolytic enzyme activation
  - Infections → associated with pus formation in Staphylococcus aureus infection

## CASEOUS NECROSIS

- 'Cheese - like' necrotic material
- Actually a combination of COAGULATIVE and liquefactive necrosis, with coagulative necrosis being the predominant contributor
- Seen in organisms with high lipid content like TB. It is also seen in other conditions like fungal infections (Histoplasmosis, coccidiodomycosis) and syphilis.
- Granulomatous reaction present.





Langhans cell

- Microscopic appearance: Langhans Giant cell/monocytic/lymphocytic infiltrations are seen
  - Associated with tubercular focus

## FAT NECROSIS

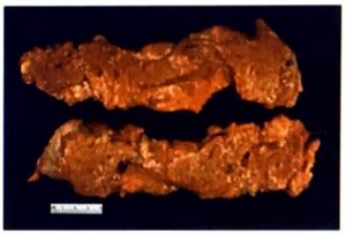
- Associated with organs with high fats or with high concentration of lipases
- Seen with injury to breast tissue, omentum tissue injury and pancreatitis

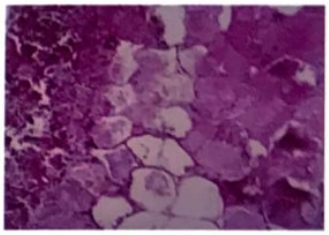
**Acute Pancreatitis**

Gall Stones / Alcohol
↓
Lipase activation
↓
Lipids → Fatty Acids + $Ca^{2+}$

Saponification ('Chalk-like' yellow white deposits)

- Sr. $Ca^{2+}$ level (↓↓) is an important prognostic factor to assess the severity of pancreatitis



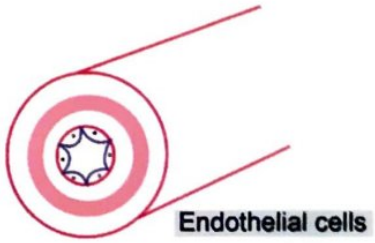


Fat necrosis

### Important Information

- In Pancreatitis, there is involvement of 2 types of necrosis
  - Pancreas → liquefactive necrosis
  - Peri-pancreatic fat → fat necrosis

## FIBRINOID NECROSIS 00:22:13



Endothelial Cell Injury

↓

Immune Complex formation

↓

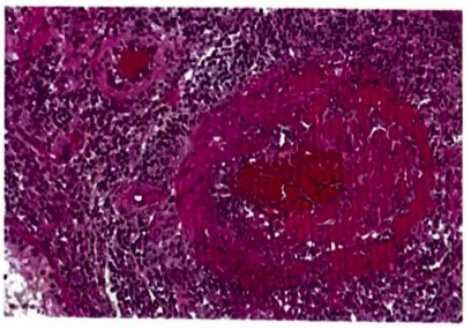
Entry or leakage of plasma protein to the vessel wall

↓

Inside the vessel wall (seen as pinkish appearance in the vessel), there is deposition of plasma protein

↓

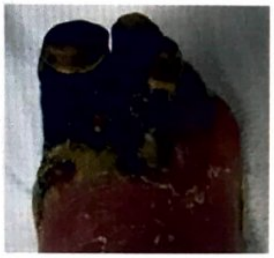
Fibrinoid Necrosis

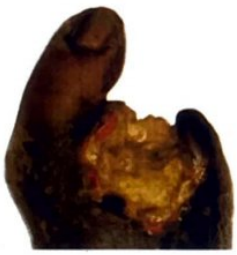


- Can be seen in
  - Malignant Hypertension
  - Aschoff Body in cardiac tissue
  - Immune Complex Disorder/Type 3 Hypersensitivity Reaction (PAN/HSP)

## GANGRENE

00:25:43





Dry gangrene  Wet gangrene

| Dry gangrene | Wet gangrene | Gas gangrene |
|---|---|---|
| • Ischemia (Decreased blood supply)<br>• Coagulative necrosis | • Ischemia + secondary infections<br>• Liquefactive necrosis | • Sub type of wet gangrene<br>• Associated with clostridium welchii/clostridium perfringens<br>• Clostridiuim welchii produces gas in the subcutaneous tissue |

# 4 IRREVERSIBLE CELL INJURY 2

## APOPTOSIS

- Apoptosis is a type of caspase-dependent programmed cell death.
- It is controlled by genes, and it affects a single cell or a small group of cells.

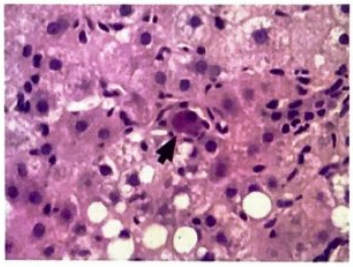
| Pro - apoptotic genes | Anti - apoptotic genes | Sensors |
|---|---|---|
| • BAK gene<br>• BAX gene<br>• P53 gene<br>• Glucocorticoids | • BCL-2 gene<br>• BCL - XL gene<br>• MCL-1 gene (responsible for resistance to chemotherapy)<br>• Sex Steroids | • BiM gene<br>• BAD gene<br>• PUMA gene<br>• NOXA gene |

**Physiological Apoptosis is seen in**

- Embryogenesis
  - Removal of tail cells present in developing fetus
  - Separation of fingers due to death of cells present between fingers. If apoptosis fails to occur, fingers will not separate resulting in a condition known as Syndactyly.
- Females of Reproductive Age group- During menstrual cycle, hormone (Estrogen) promotes formation of new layer of endometrium and shedding, as per its levels in various part of the cycle.
- ~~Self~~ Reactive B & T Cells

**Pathological apoptosis is seen in**

- DNA Damage → in response to a person's exposure to radiation or drugs.
- Viral infections of hepatitis → "Councilmann Body"



Apoptotic body

- Accumulation of misfolded proteins → Alzheimer's disease, Parkinsonism

**Pathways of apoptosis** 00:08:18

| Intrinsic / mitochondrial pathway | Extrinsic pathway |
|---|---|
| ↓ Growth factors<br>↓<br>BCL-2 inactivation<br>↓<br>BCL-2 replaced by BAK / BAX<br>↓<br>Mitochondrial permeability<br>↓<br>↑ Cytochrome-C in cytoplasm<br>↓<br>Activation of APAF-1 (Apoptosome)<br>↓<br>↑ Activation of Caspase 9<br>↓<br>Stimulate Caspase 3/ 6/ 7<br>↓<br>↑ Activation of Proteases & Endonucleases<br>↓<br>Cell Death | FAS –L / TNF α Release (in severe damage)<br>↓<br>FAS –L / TNF α + FAS –L / TNF-R<br>↓<br>Trimerization<br>↓<br>Activation of FADD<br>↓<br>Pro CASPASE 8/ 10 → Caspase 8/ 10<br>↓<br>↑ Activation of Caspase 3 /6 /7<br>↓<br>↑ Activation of Proteases & Endonucleases<br>↓<br>Cell Death |

- APAF-1 → Apoptosis Activating Factor 1, also called as apoptosome
- FADD → Fas Associate Death Domain
- IAP → Inhibitor of Apoptotic- protein, inhibits intrinsic pathway

## Previous Year's Questions

Q. BCL 2 protein is located in which of the following site? (JIPMER – May - 2018)

A. Cell membrane
B. Mitochondria
C. Nucleus
D. Cytosol

**Caspases**

- Cysteine containing special proteases acting on targets at the aspartic acid residues.

| Caspase type | Intrinsic pathway | Extrinsic pathway |
|---|---|---|
| Initiator | Caspase 9 | Caspase 8 (Worms), Caspase 10 (Humans) |
| Executioner | Caspase 3/6/7 | Caspase 3/6/7 |

## Previous Year's Questions

Q. APAF I is involved in the activation of which of the following caspases (AIIMS – June - 2020)

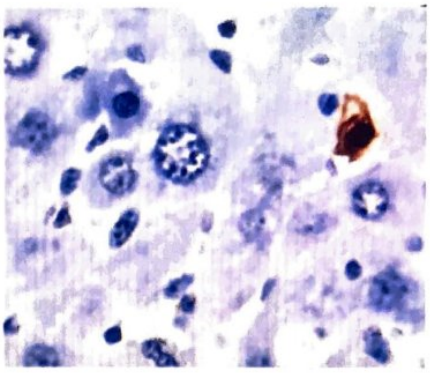
A. Caspase 8
B. Caspase 9
C. Caspase 3
D. Caspase 10

**Salient Features of Apoptosis**

- Cell shrinkage: Cell size decreases due to damage to structural proteins
- Chromatin Condensation
  - Caused due to endonuclease activation
  - Hallmark feature associated with apoptosis
- No cell membrane damage as there is no activation of phospholipase enzyme
- No Inflammation

**Tests to Detect Apoptosis**

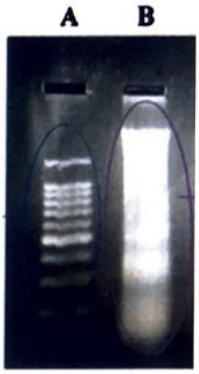
- Tunel Technique



Tunel staining

- Used for diagnosis of apoptosis
- dUTP dye is used and fragments of DNA are visualized by light microscope

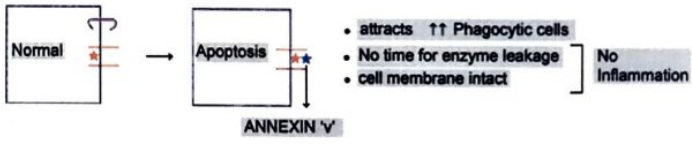
- Gel Electrophoresis: Apoptotic nucleic acid are found to be in Step-Ladder Pattern




## Important Information

- Normal nucleic acid → Single Band
- Necrotic nucleic acid → SMEAR Pattern

**Staining**




- Done by using ANNEXIN 'V' which attaches to flipped molecules or by using DAPI Stain.
- Molecules which can flip over, and hence are expressed more at the time of apoptosis, include:
  - Phosphatidyl Serine
  - C1q
  - Thrombospondin

**Clinical Significance of Apoptosis** 00:26:00

- Excessive apoptosis is seen in

- Neuro-degenerative disorders
- Viral infections

- Reduced apoptosis is seen in
  - Autoimmune disorders

**Important Information**

- Neurons are unique in the aspect that they do not have APAF-I. They instead secrete AIF (Apoptosis Initiating Factor) which directly activates proteases and endonucleases without Caspase activation.

## PYROPTOSIS

- It is a special type of apoptosis, with noted cellular swelling and inflammation.

Infections
↓
Intra-cellular Receptors (NOD-like Receptors)
↓
Inflammasome formed (multi molecular protein complex)

| Caspase I | Caspase II |
|---|---|
| ↓ | ↓ |
| IL-1 | Cell death |
| ↓ | |
| Fever | |

- Other Caspases which have an action similar to Caspase 1 would be Caspase 11, 4/5.
- Efferocytosis is the name of the process through which molecules like C1q and Thrombospondin attract phagocytes during apoptosis.

## NECROPTOSIS/ PROGRAMMED NECROSIS

00:34:32

- It is a Caspase-Independent programmed cell death.

TNF + TNF-®
↓
RIP 1 / 3 [Receptor Interacting Protein Kinase]

Phosphorylation of MLKL Protein — No Caspase activation
↓
CM damage & Inflammation ⊕

- Conditions where necroptosis is seen
  - Physiological → Mammalian Growth Plate
  - Pathological → Pancreatitis, Reperfusion injury, Parkinsonism, Steatohepatitis

# 5 FREE RADICAL INJURY

- Free radicals are chemical molecules with an unpaired electron ($e^-$) in its structure
- They have a high amount of energy in them and are highly reactive.
- They can cause damage to cell membrane, proteins and DNA.
- It is an auto-catalytic reaction while inflicting damage to DNA
- Proteins and most importantly Lipids, there is a release of more free radicals which further causes cellular damage and death.

**Important Information**

- Lipid Peroxidation, caused by free radicals, is implicated in aging and cancer Development (Due to damage to nucleic acids, resulting in mutations)

**Fenton Reaction** 00:03:52

$(Fe^{2+} \rightarrow Fe^{3+})$

Super oxide ion ($O_2^-$) → Hydrogen Peroxide ($H_2O_2$) → Hydroxyl - Radical ($OH^-$)

$O_2 \rightarrow$

↓

Free radical

↓

Damage to DNA / Proteins / Lipids

↓

Auto Catalytic Reaction

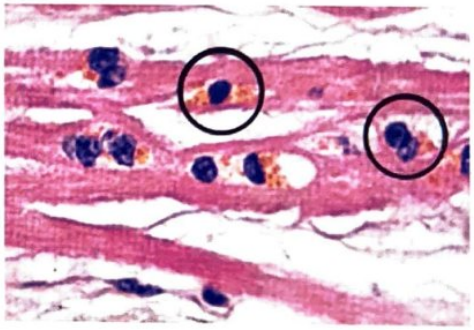
↓

Cell death

- Most Dangerous Free Radical Hydroxyl
- Fenton's reaction is associated with free radical formation in the presence of the metal Fe.
- Normal cells are able to protect themselves from free radical injury through Superoxidase dismutase
  - It converts superoxide ion to hydrogen peroxide
- Hydrogen peroxide conversion to water is by
  - Catalase enzyme
  - Reduction by Glutatione peroxidase, which adds H2 from reduced glutathione (GSH) to form Glutathione disulfide (GSSG)

**Causes of Free Radical Injury**

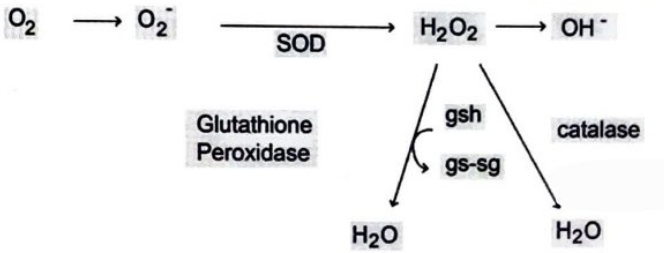
- Radiation injury: Ionizing radiation falls on water and releases hydroxyl radical
- Oxidative stress: Involved in aging, cancer and inflammation
- Reperfusion Injury
- Transitional metals in excess → Iron (Hemochromatosis), Copper (Wilson's disease)
- Chemicals: Carbon Tetrachloride used in dry cleaning factory ($CCl_4$), Paracetamol overdose



Lipofuscin

- Tell-Tale Sign → peri-nuclear deposition of brown colored lipid-derived pigment called Lipofuscin in Free Radical Injury (Aging).

## ANTI-OXIDANTS 00:17:31




**Superoxide Dismutase**

- SOD has two subtypes
  - Mitochondrial: Manganese is present as a co-factor

- Cytoplasmic: Copper and Zinc are present as co-factors
- Decreases free radical damage in brain.
- Mutation in SOD1 gene causes Amyotrophic Lateral Sclerosis

**Catalase**

- Converts hydrogen peroxide to water.
- It is also present in certain bacteria.

**Glutathione peroxidase**

- Requires reduced glutathione (GSH) to help the cell.
- During oxidative stress, GSSG: GSH Ratio increases.

**Vitamins A, E & C**

- Vitamin C is found to be the most important as it aids in neutralizing the hydroxyl free radical

**Plasma Proteins Binding With Metals**

- Transferrin/ Lactoferrin/ Ferritin binding with Iron
- Ceruloplasmin binding with Copper

# 6 PIGMENTATION

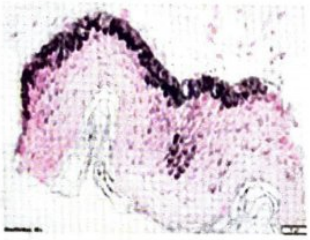
- Endogenous pigment
- Exogenous Pigment
  - Coal dust inhalation → Anthracosis (Asymptomatic)
  - Tattooing

## ENDOGENOUS PIGMENT

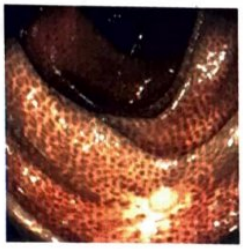
00:01:52

### Melanin

- Endogenous black pigment
- Provides Hair & Skin Color
- Tyrosine derived pigment
- Protects skin from UV rays
- Identified by Masson Fontana stain
- Pseudo-melanin is seen on large bowel of patients who are on chronic laxative therapy (senna) → PAS positive substance & present inside the macrophages



Masson Fontana stain



Melanosis Coli

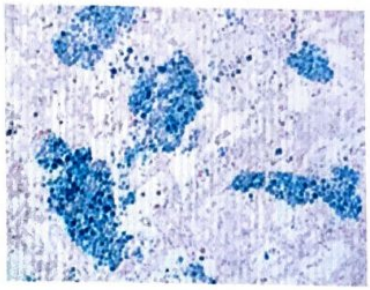
### Homogentisic Acid

- Deficiency of homogentisic acid oxidase → deposition of HA in cartilage/skin/bone/connective tissue (Ochronosis)
- Seen in Alkaptonuria urine turns black on exposure to air

### Hemosiderin

- Iron derived pigment (Fe → ferritin)
- Excess iron is stored in the form of ferritin
- Seen in
  - Hemochromatosis
  - Repeated blood transfusion (thalassemia)
  - Chronic Hemolytic anemia

- Pearls reaction: on application of Prussian blue, ferritin is unbound from protein and react with potassium ferrocyanide ferricyanide (blue violet color)

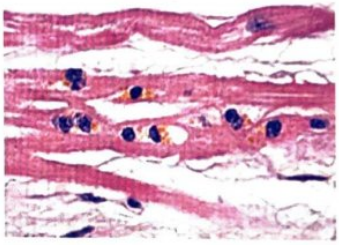


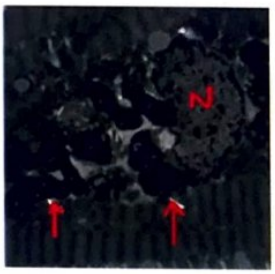
Hemosiderin

### Lipofuscin

00:09:21

- Aka lipochrome/wear & tear pigment/pigment of Ageing
- Lipid derived pigment
- Produced by lipid peroxidation/free radical injury
- Indicator of free radical injury: Lipofuscin
- Lipochrome: Golden brown color, peri-nuclear in location & deposited in lysosomes






Lipofuscin

- Seen in ageing/PEM/Cachexia
- Maximum lipofuscin deposition is seen in heart & liver

### Previous Year's Questions

Q. Staining of lipids is best seen in which of the following conditions? (INICET Nov 2020)

A. Frozen section
B. Liquid paraffin
C. Formalin fixed
D. Karnovsky stain

### Ageing

- DNA damage → DNA helicase defect (Werner syndrome)
  - Wermer syndrome → associated with MEN
- Protein misfolding
- Telomere Length
  - Normal cell undergoes 60-70 divisions → Hayflick's limit
  - Telomerase (responsible for maintaining telomere length) → over activity is seen
    - → Physiological → germ cells
    - → Pathological → cancer cells
- Associated with brown atrophy → lipofuscin

### Sirtuins

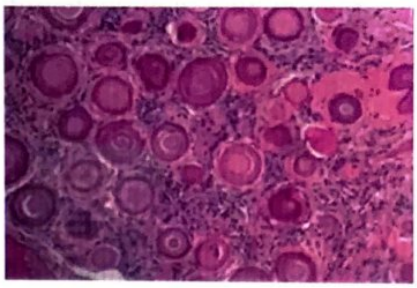
- Sirtuin 6 → ↑ life span
  - ↓ Free radical injury
  - ↑ Insulin sensitivity
  - ↓ Insulin like growth factor pathway
- Can be increased by calorie restriction/wine intake

## CALCIFICATION

00:22:51

| Dystrophic Calcification | Metastatic Calcification |
|---|---|
| • $S.Ca^{2+}$ → normal | • $S.Ca^{2+}$ ↑↑↑ |
| • Deposits in Dead/Degenerated tissues | • Deposits in living tissues |
| Conditions associated<br>• **R**heumatic heart disease<br>• **A**therosclerosis<br>• **T**B , Monckeberg Sclerosis<br>• **T**umors<br>o **M** – Meningioma/ Mesothelioma<br>o **O** – ovary<br>o **S** – Salivary gland<br>o **T** – Thyroid gland<br>o **P** – Prolactinoma<br>o **G** - Glucagonoma<br>(papillary Ca) | Conditions associated<br>• Hyperparathroidism<br>o 1° → parathyroid adenoma<br>o 2° → CKD<br>• ↑↑ Vitamin D<br>o Intoxication<br>o Sarcoidosis (↑ 1α-Hydroxylase)<br>o Williams syndrome<br>• Milk-Alkali syndrome<br>• Cancers → Breast Ca/MM |

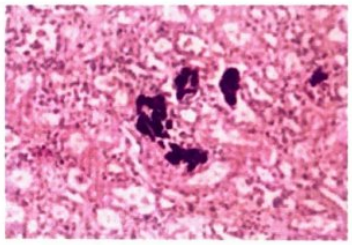
- $Ca^{2+}$ deposition is seen as Psammoma bodies



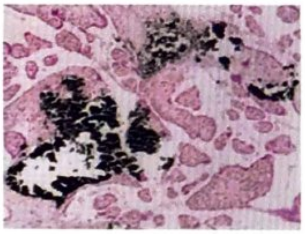
- $Ca^{2+}$ deposits in mitochondria in majority of cells → Lime Catcher Organelle
  - Exception: Renal cells → Deposits in Basement membrane
- Preferential calcium deposition organs: lungs > stomach > SA/PV
- Calcium has special affinity for tetracycline → used to assess bone turnover (Tetracycline Labelling)

### Microscopic appearance

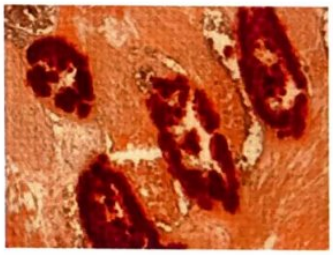
- H&E stain → Basophilic appearance of $Ca^{2+}$
- Von-kossa stain → stains $Ca^{2+}$ in black color & picks up large amount of $Ca^{2+}$
- Alizarian Red stain → helps in smaller deposition of $Ca^{2+}$



H&E Stain



Von-Kossa stain



Alizarian Red stain

### Previous Year's Questions

**Q. Dystrophic calcification seen in which of the following conditions?** (AIIMS – May - 2019)

A. Myositis ossificans
B. Paget's disease
C. Metastasis
D. Sarcoidosis

# 7 FERROPTOSIS

## INTRODUCTION

00:00:14

- Specific signals results in the iron accumulation and lipid peroxidation.
- Defence mechanism: reduced form of glutathione - dependent antioxidants

## MECHANISM

00:00:54

- Excess amount of iron or malfunctioning glutathione → results in more amount of reactive oxygen species(ROS)→ High chances of Lipid peroxidation → membrane damage → Cell death
- Fact 1 : started with specific signals
- Fact 2: It can be prevented by reducing concentration of intracellular iron; which distinguish from necrosis.
- Targeted organelle affected : Mitochondria

## Two specific findings

00:02:19

- Loss of mitochondrial cristae
- Outer mitochondrial membrane: complete rupture/damage

## MCQ Question

00:03:10

- Role played by iron dependent pattern of cell injury:
  - lipid peroxidation causing the injury in permeability in cell death
  - Free radicals exhaust the defensive mechanism of the cell.
- Two specific findings of mitochondria:
  - Loss of mitochondrial cristae and rupture of outer mitochondrial membrane

# CLINICAL QUESTIONS

1. A 49 Yr old male complaints of sudden onset of difficulty in breathing when he climbs up the stairs associated with diaphoresis and palpitations. Patient is a known case of Hypertension for 15 years on irregular compliance to antihypertensive drugs. ECG taken which revealed LVH. ECHO was done which revealed Ejection fraction of 40%. All of the following are transcription factors activated by signal transduction pathways of the given pathology, except:

A. GATA 4
B. NFAT
C. MEF 2
**D. MLL 1**

Solution

- In the given clinical scenario, Patient has Cardinal symptoms of Heart failure,
  - Palpitations
  - Diaphoresis
  - Dyspnea on exertion
- Patient is a known case of Hypertension with poor compliance to Antihypertensive drugs which lead to Left Ventricular Hypertrophy which concomitantly explains Heart failure, Echocardiography revealed an ejection fraction of 40%, which is usually seen in chronic pressure and volume overload conditions.
- Signalling pathways which trigger hypertrophy activate a set of transcription factors such as:
  - GATA 4
  - Nuclear factor of activated T-cells (NFAT)
  - Myocyte enhancer factor-2 (MEF2).
- These transcription factors work in coordination to increase the synthesis of muscle proteins that are responsible for hypertrophy.
- CARD→ MLL 1 (Mixed lineage leukemia protein-1) is a gene involved in acute leukemia.

Reference

- Robbins & Cotran Pathologic Basis of Disease 10th ed pgs-57,58

# LEARNING OBJECTIVES

## Unit 2 INFLAMMATION

- **Introduction to Inflammation & Vascular Changes**
  - Vascular Changes Seen in Inflammation
  - Mechanism of Vascular Leakage
  - Stasis
  - Virchow's Traid
- **Intravascular Cellular Changes**
  - Margination
  - Rolling
  - Adhesion
  - Leucocyte Adhesion Disorders
  - Trans-Migration
- **Extravascular Cellular Changes**
  - Chemotaxis
  - Phagocytosis
  - Recognition of Target Cell
  - Engulfment
  - Killing
  - Chediak-Higashi Syndrome
- **Oxygen Dependent & Independent Bacterial Killing**
  - Oxygen Independent Killing
  - Oxygen Dependent Killing
  - Chronic Granulomatous Disease
- **Neutrophil Extracellular Trap**
- **Preformed Chemical Mediators**
  - Histamine
  - Serotonin
  - Lysosomal Enzymes
- **Freshly Formed Chemical Mediators**
  - Nitric Oxide
  - Arachidonic Acid Metabolites
  - Anti-Inflammatory Drugs
  - Cytokines
  - Pyrogens
  - Chemokines
  - Interferons
- **Plasma Chemical Mediators**
  - Kinin System
  - Complement System
  - Regulatory Complement Protein
- **Chronic Inflammation & Wound Healing**
  - Different Macrophages
  - Role of lymphocytes
  - Granulomatous inflammation: Giant cells, types and Features
  - Wound healing: Abnormal Healing

# 8 INTRODUCTION TO INFLAMMATION & VASCULAR CHANGES

## BASIC CONCEPTS

- It is the response seen in vascularized connective tissues
- This response is usually protective, but sometimes harmful

Injury
↓
Response of body
↓
Changes in blood vessels & cells (connective tissue)

**Subtypes**

- Acute → Short duration, Neutrophils are involved
- Chronic → Long duration, Mono-nuclear WBCs (Lymphocytes/ Monocytes)

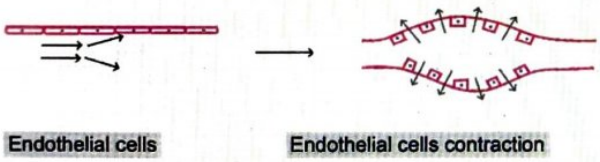
## VASCULAR CHANGES SEEN IN INFLAMMATION

00:01:11

- Vasoconstriction → 1st change in blood vessels
- Vasodilation → Primarily caused by Histamine

Normal | Rubor & Calor

- ↑ Vascular Permeability



Endothelial cells | Endothelial cells contraction

- With contraction of endothelial cells, space in between endothelial cells increases and contents get leaked out.
  - Fluids
  - Cells
  - Proteins

  } exudate → swelling/edema (Tumor)

### Important Information

- Most characteristic feature of Acute Inflammation: Vascular permeability
- MC mechanism involved: Endothelial cell contraction

**Mechanisms of Vascular Leakage** 00:03:33

| Mechanism | Type of response | Example |
|---|---|---|
| EC contraction | Immediate Transient Response | Thorn Prick |
| Direct EC injury | Immediate Sustained Response | Severe Burn, Septicemia |
| EC retraction | Delayed Transient Response (Cytokine-mediated) | Bacterial Infections |
| EC damage | Delayed Prolonged Leakage | Late Sun Burn |

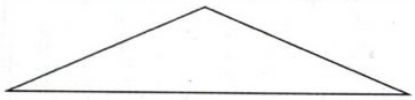
**Stasis**

↑ Vascular permeability
↓
↑ Hem concentration
↓
↓ Blood Flow
↓
Stasis
↓
↑ Chances of thrombosis/clot formation

- Inflammation is a 'pro-thrombotic' state

**Virchow's Triad**

Endothelial cell injury



Changes in blood flow | Hyper-coagulability

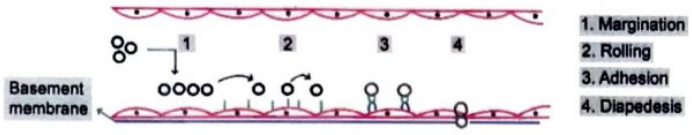
### Previous Year's Questions

Q. Virchow triad includes all except?

(FMGE - Jun - 2018)

A. Endothelial injury
B. Stasis of blood flow
C. Hypercoagulability
D. Platelet thrombus

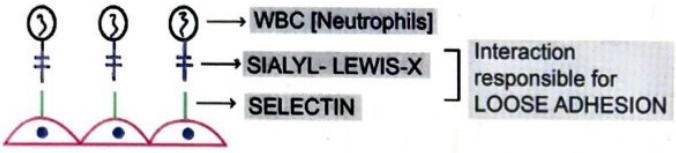
# 9 INTRAVASCULAR CELLULAR CHANGES




**Margination**

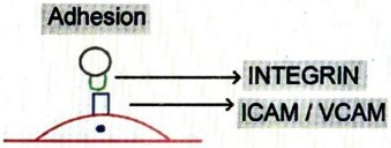
- WBC starts to move towards from margin

**Rolling**




- Aka Loose adhesion
- It is an interaction between selectins in endothelial cells and Sialyl-Lewis X molecule in WBC
- Selectins aka CD62
- Subtypes of Selectins
  - E → present on endothelial cells
  - P → present on Platelets, Endothelial cells
  - L → present on Lymphocytes
- Weibel Palade Body
  - E-selectin is present intracellularly in endothelial cells in low affinity state
  - It contains Von-Willebrand factor & Selectins

**Adhesion**

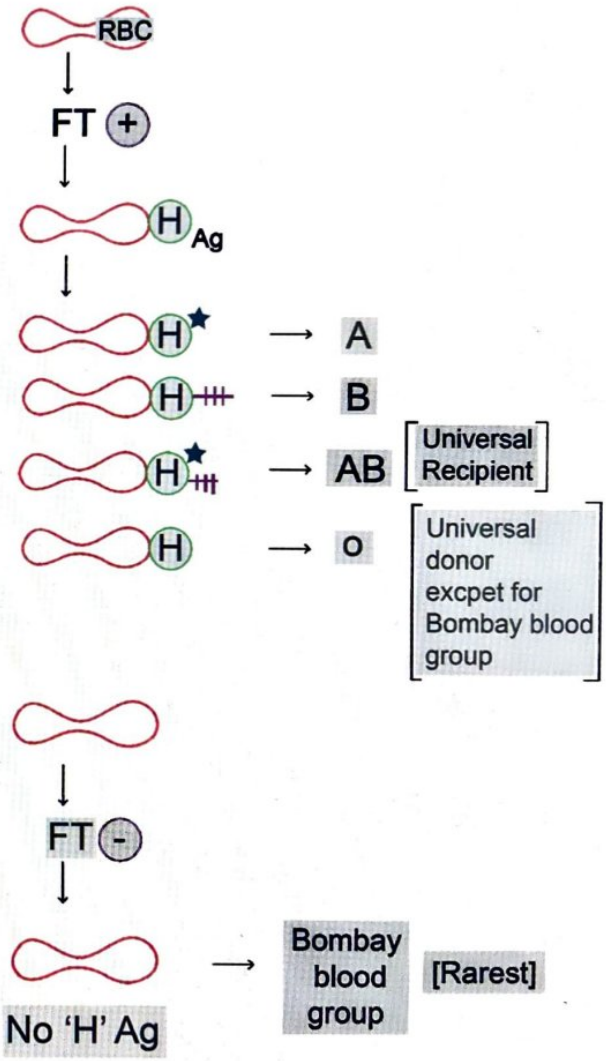



- Firm Adhesion
- Integrins in WBC, ICAM/VCAM in endothelial cells are responsible for adhesion
  - ICAM (Inter cellular adhesion molecules)
  - VCAM (vascular cellular adhesion molecules)
- Integrins also known as CD11a/LFA

**Leucocyte Adhesion Disorders (LAD)** 00:15:48

- Characterized by
  - ↑ Risk of infections
  - Neutrophilia
  - No pus formation

| LAD I | LAD II |
|---|---|
| • Integrin defect<br>• Delayed Separation of umbilical cord | • Selectin defect (Sialyl-Lewis X)<br>• Fucosyl transferase enzyme defect<br>○ Short stature<br>○ Bombay blood group |




Role of FT enzyme

**Trans-Migration** 00:25:08

- Aka Diapedesis → WBC
- CD31: Present on surface of platelet & endothelial cell → Homotypic interaction
  - Aka PECAM (Platelet Endothelial cell adhesion molecule)

- Trans-migration causes predominant involvement of venules
  - Exception: pulmonary circulation/lung (takes place in capillaries)
- Trans-migration
  - < 24hrs → neutrophils
  - > 24hrs → macrophage
  - Exception: trans-migration in parasitic infection → eosinophil, trans-migration in viral infection → lymphocytes

**Important Information**

- In pseudomonas infection, initial 2-4days is characterized by predominant neutrophil trans-migration

# 10 EXTRAVASCULAR CELLULAR CHANGES

## CHEMOTAXIS

- Chemical mediators are released to help aide movement of more WBCs towards the bacteria.
- This is an example of unidirectional/ targeted movement.
- Chemicals Responsible
  - Bacterial Products → Exogenous
  - C5a (Complement Protein)
  - LTB4 (Leukotriene-B4)
  - IL-8 (Interleukin-8)

  } Endogenous
- Major action of steroids → Chemotaxis Inhibition, Used in Autoimmune conditions

## PHAGOCYTOSIS

00:06:24

- Steps in Phagocytosis

A. Recognition
B. Engulfment
C. Killing

### A. RECOGNITION OF TARGET CELL

| WBC | | MICROBES |
|---|---|---|
| ↓ | | ↓ |
| Mannose binding receptor | ↔ | Mannose |
| Scavenger receptor | ↔ | some particles |

- Leukocyte activation occurs prior to phagocytosis.
- It maybe mediated by certain second-messengers like IP3/DAG.
- Phagocytosis is facilitated by Opsonisation.
- Opsonisation are chemicals which cover the bacteria and are preferentially killed.
  - Examples of Opsonins: Fc fragment of IgG, C3b, Fibrinogen/C-Reactive Protein

**Antibody formation**

Precursor B-cell
↓
B-Cell Tyrosine Kinase
Activated B-Cell
↓
Plasma Cell
↓
Immunoglobulin

- Bruton's disease refers to defect in BTK enzyme, affecting boys.
  - There is reduced antibody secretion → Hypo-gammaglobulinemia or Agammaglobulinemia
  - Opsonisation is defective in this condition.

**C-Reactive Peptide**

- Formed by the liver
- Is a plasma protein and is different from C-Peptide released by beta-cells of pancreas
- Is implicated in inflammatory conditions and Coronary Artery Disease

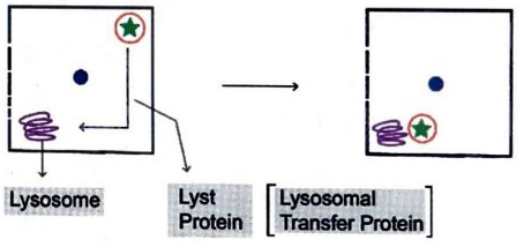
**Important Information**

- C-RP in Microbiology. is basically denoting the Carbohydrate Ag derived from the Pneumococcus (S. pneumonia)

### B. ENGULFMENT

- Through pseudopod formation
- Due to actin polymerization

### C. KILLING



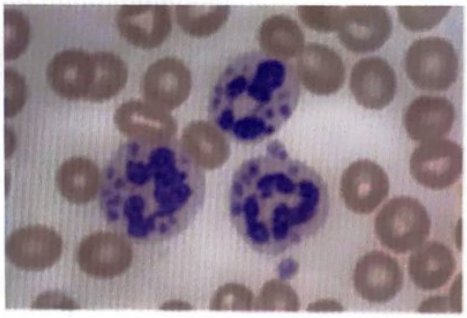

↓
Defect
↓
Chediak-Higashi Syndrome

**Chediak-Higashi Syndrome**

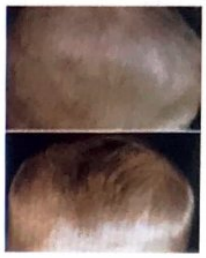
00:19:12

- LYST protein is required for normal function of
  - Neutrophils
  - Platelets
  - Melanocytes
  - Neural cells

- Clinical features
  - C → CNS Features
  - HE → Hemorrhage
  - DI → Decreased Immunity (Recurrent Infections)
  - AK → Albinism



Giant granules



Albinism

- Peripheral Blood Smear in C-H Syndrome shows giant granules in the cytoplasm

# 11 OXYGEN DEPENDENT & INDEPENDENT BACTERIAL KILLING

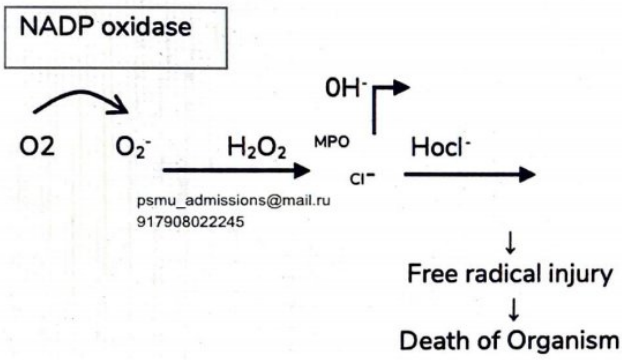
## OXYGEN INDEPENDENT KILLING

00:00:56

- Cathelicidin
- Lysozymes
- Lactoferrin
- Major basic protein
  - Present predominantly in eosinophils
  - Toxic for Parasite
- Defensins: cationic protein rich in arginine

## OXYGEN DEPENDENT KILLING

- Can take place by 2 mechanisms
  - $O_2$ derived free radicals
  - NO derived free radicals
- $O_2^- + NO \rightarrow ONOO^-$ (Peroxynitrite) → damage to bacteria
  - Important mechanism for macrophage, especially against mycobacterium




psmu_admissions@mail.ru
917908022245

- During infection, sudden increase in oxygen requirement occurs → Respiratory burst
- NADPH oxidase aka Respiratory burst oxidase/phagocytic oxidase

## CHRONIC GRANULOMATOUS DISEASE

00:09:51

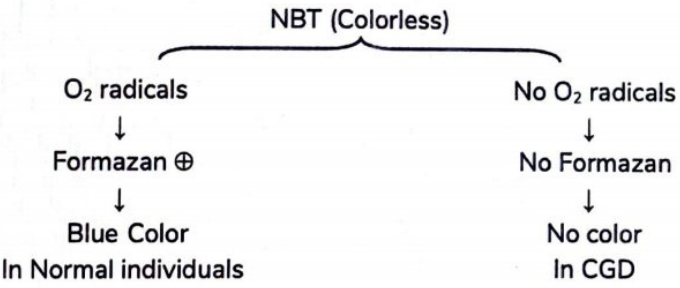
- Deficiency of NADPH Oxidase
- It is of 2 types
  - X-linked recessive (gp91PHOX) → defect of component in the membrane
  - Autosomal Recessive (gp47/67PHOX) → cytoplasmic protein defect

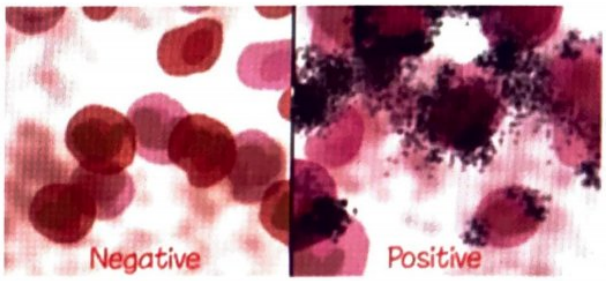
**Clinical features**

- ↑ Infections
- Formation of granuloma in different organs
- Infections by Catalase positive organism

**Diagnosis**

- Nitro-Blue Tetrazolium Test




  - Presence of granules is normal finding (positive)
- DHR test → flow cytometry
- Cytochrome 'C' reduction assay → tells amount of functional enzyme

**Treatment**

- Bone Marrow transplant
- IFN-γ

### Important Information

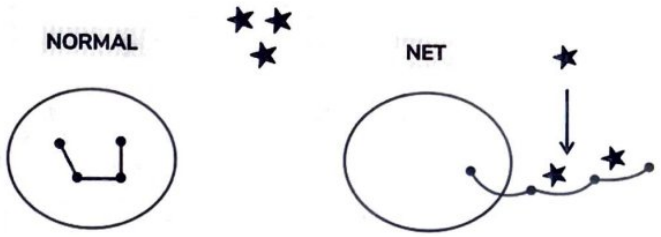
- MPO-Halide system is the most efficient bactericidal method used by neutrophils
- MPO deficiency → mild infections

# 12 NEUTROPHIL EXTRACELLULAR TRAP

- Extracellular fibrillary network
- Stimuli
  - Infectious pathogens
  - Inflammatory mediators

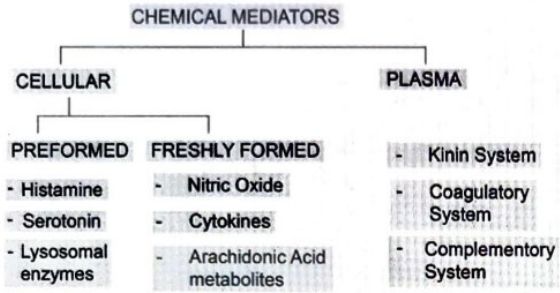
Arginine

ROS $\xrightarrow{\oplus}$ Arginine Deiminase → Citruline




- Citroline is responsible for Chromatin De-condensation in neutrophils
- Chromatin comes out of nucleus and it contains anti-bacterial property (elastse, MPO) → Kills the bacteria
- Chromatin cannot return inside the cell → Death of Neutrophil
- Exposure of chromatin material → ↑ risk of autoimmune diseases
  - ANA → SLE

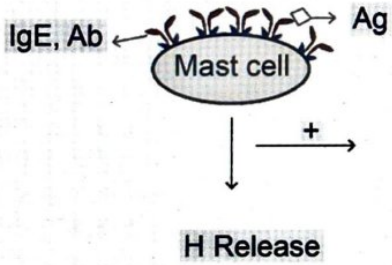
# 13 PREFORMED CHEMICAL MEDIATORS

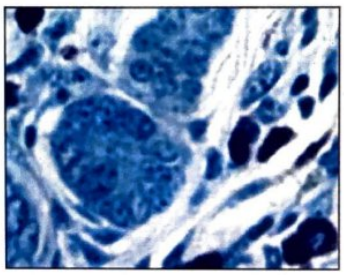



## CELLULAR PREFORMED MEDIATORS

### HISTAMINE

- Source
  - Mast cells (Richest Source)
  - Basophils
  - Platelets
- Functions
  - Vasodilation
  - Increase in Vascular Permeability
  - Bronchospasm
  - Itching
- Mast cells have receptors to bind to IgE antibody.
- IgE Cross linking leads to histamine release.



Toluidine blue

- Acidic Proteoglycans in Mast cells interact with the basic dye Toluidine Blue and the dark blue color here and help detect histamine release

**Stimuli for Histamine release**

- Physical factors - Temperature (Hot/Cold Urticaria)
- Viruses (Rhinoviruses)
- Anaphylotoxins
  - Bee venom (Mellitus) / Insect venom
  - Complement proteins (C2a/C3a/C4a/C5a)
- Drugs
  - Morphine
  - D-tubo curarine
- Allergens

**Important Information**

- Vancomycin: To be given slowly via IV. Rapid injection can cause Red Man Syndrome

### SEROTONIN (5- HYDROXYL TRYPTAMINE)

00:07:45

- Source
  - GIT (Richest source, present in Enterochromaffin cells)
  - Platelets
  - CNS
- Functions same as histamine

### LYSOSOMAL ENZYMES

- Responsible for oxygen dependent killing of bacteria
- Has two types of granules:
  - Primary: known as Azurophilic granules
  - Secondary: Alkaline phosphatase present in WBCs

**Important Information**

- Phospholipase A2 is present in both granules
- LAP score: In cases where Activated WBCs / Leukocytes are in elevated numbers, the score is increased.
- Example: Benign infections, Leukemoid reaction

# 14 FRESHLY FORMED CHEMICAL MEDIATORS

## NITRIC OXIDE (NO)

00:00:31

$$\text{L - Arginine} \xrightarrow{\text{eNOS}} \text{Nitric oxide}$$

- NO Vasodilation & inhibition of platelets
- Isoforms
  - eNOS → Endothelial Cells
  - iNOS → Inducible/Inflammation
  - nNOS → Neurons

NO

$$O_2^- \longrightarrow ONOO^-$$

- Peroxinitrite causes damage to microbes

### Previous Year's Questions

**Q. Which of the following amino acid is required for the formation of nitric oxide in blood vessels?**
(FMGE – Aug - 2020)

A. Citrulline
B. Arginine
C. Histidine
D. Tryptophan

## ARACHIDONIC ACID METABOLITES

00:03:37

Phospholipids
↓
Phospholipase A2 (rate limiting enzyme)
Arachidonic Acid (EFA)
↓
COX
$PgG_2 = PgH_2$

**$PgI_2$ (prostacyclin)**
- Vasodilation
- Inhibition of platelets

**$PgD_2/E_2/F_{2a}$**
- Vasodilation
- Permeability
- Pain ($PgE_2$)
- Pyrexia ($PgE_2$)
- Mucus ($PgD_2$)

**Thromboxane $A_2$**
- Platelet aggregation
- Vasoconstriction

- Other Essential FA
  - Linoleic Acid (most essential)
  - Linolenic Acid
  - DHA present in Breast milk essential for development of brain

### Previous Year's Questions

**Q. Which of the following causes vasodilation?**
(AIIMS – Nov - 2019)

A. Thromboxane A2
B. Prostaglandin E2
C. Histamine
D. Serotonin

**Anti-Inflammatory Drugs**
- Steroids act on Phospholipase $A_2$
- NSAIDs act on COX enzyme

| | |
|---|---|
| COX-1 (Constitutive function) | Stomach → Pg (protective function) |
| COX-2 (Inflammation) | Kidneys (physiological function) |

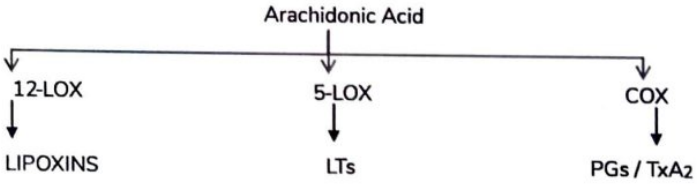
- Aspirin
  - Inhibit COX-1/COX-2 → Non-Selective
  - Anti-inflammatory action
  - Side effects → gastritis

AA
↓
5-LOX
Leukotrines
↓
$LTA_4$

**$LTB_4$**
- Chemotaxis
- Binding to EC

**$LTC_4/D_4/E_4$**
- ↑ Permeability
- Bronchospasm

- Leukotrienes aka SRS-A (Slow Reacting Substance of Anaphylaxis)
- 5-LOX inhibitor → Zileuton
- LT Receptor antagonist → Montelukast




- Lipoxins requires Neutrophils platelets & Inhibit inflammation

**Important Information**

- Fish oil is a good source of Lipoxins. it ↓ Inflammation → ↓ Incidence of CAD

## CYTOKINES

00:27:48

- Pleiotropy → more than one action by one cytokine
- Redundancy → more than one cytokines having common action
- It has Local & Systemic actions

### SYSTEMIC ACTIONS

- CNS → Sleepiness, ↓ appetite, ↑ COX activity (fever)
- BM
  - ↑ Neutrophil/lymphocyte/eosinophil in bacterial, viral and parasitic infections respectively
  - Shift to the left
  - Leukemoid reaction

### Liver

- Positive Acute Phase Reactants
  - Hepcidin → iron inhibitory protein (negative regulator of iron balance)
  - Ferritin
  - SAA Protein → ↑ in 2° Amyloidosis
  - Fibrinogen → ESR
    → ESR α Fibrinogen
    → ESR = 0 → Afibrinogenemia
  - CRP → increased in sepsis (New marker: Pro-calcitonin)
  - Thrombopoietin → ↑ platelets
- Negative Acute Phase Reactants
  - Albumin
  - Transferrin
  - Anti-Thrombin
  - TTR

### TNF-α

- Systemic effects (↓↓↓ appetite → cachexia)
- Macrophage activation → bacteria killing
- TNF-α antagonist therapy → ↑ risk of TB

### Pyrogens

00:46:13

- Exogenous → Bacterial toxins
- Endogenous → IL-1/IL-6/TNF-α/CNTF (Ciliary Neuro Trophic Factor)

### Anti-Inflammatory Cytokines

- IL-10
- TGF-β
- IL-6
- IL-4
- Adiponectin

} has dual action

### Cytokines: Individual Actions

- IL-1 → Systemic Effects of inflammation
- IL-2 → Autocrine action
- IL 3 → Hematopoiesis
- IL-4/5 → B-cell replication & Differentiation
- IL-6 → Systemic Effects of Inflammation
- IL-7 → B/T cell maturation (defect can cause SCID)
- IL-11 → ↑ Platelets
- IL-17 → secreted by T-cells, responsible for recruitment of neutrophils

## CHEMOKINES

00:52:51

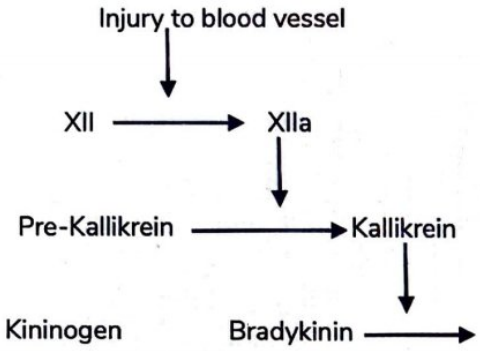
- α chemokine → CXC
  - Example: IL-8 (CXCL8) → attracts neutrophils
- ß chemokine: CC
  - MCP-1 → attracts monocytes
  - EOTAXIN → attracts Eosinophils
  - RANTES → regulates T-lymphocytes
- γ chemokines: C
  - Example: Lymphotactin → attracts Lymphocytes
- Fractalkine: $CX_3C$ → required for chemotaxis & in process of adhesion of monocytes & T-cell to endothelial cells
- Chemokines act through 2 receptors
  - CCR5 receptor → ß chemokine
  - CXCR4 receptor → α chemokine
  - These receptors help in entry of HIV into Host cells (Maraviroc blocks CCR5 receptor)

**INTERFERONS**

| | Source | Action | Clinical use |
|---|---|---|---|
| IFN-α | Leucocytes | Anti-viral | Viral infections |
| IFN-ß | Fibroblast | Immunomodulatory | Multiple sclerosis |
| IFN-γ | T cells | Macrophage activation | Chronic Granulomatous Disease |

# 15 PLASMA CHEMICAL MEDIATORS

## KININ SYSTEM

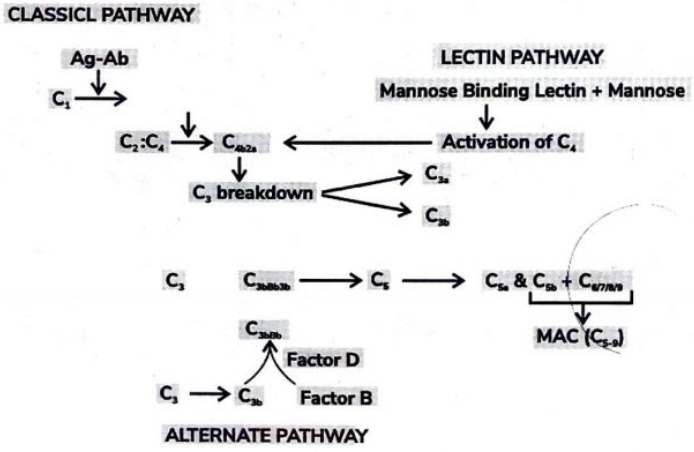



- Bradykinin causes
  - ↑ Permeability (most important)
  - Pain
  - Smooth muscle contraction (lungs)
- Bradykinin is destroyed by ACE (Angiotensin Converting Enzyme)
  - ACE inhibitor → ↑ Bradykinin concentration
  - Side effect: Dry cough
- Kallikrein is also associated with
  - Complement activation
  - Plasmin

## COMPLEMENT SYSTEM

00:05:45

- It consists of > 20 proteins ($C_1$ - $C_9$)
- Complement proteins are responsible for innate & adaptive immunity




- Alternate pathway
  - Activated by endotoxin (LpSA)/venom/(IgA >> IgD)
  - Properdin & factor H/I also at take part in alternate pathway

**Important Information**

- **Classical pathway: Levels of $C_1/C_2/C_3/C_4$ → reduced**
- **Alternate pathway: $C_1/C_2/C_4$ → normal: $C_3$ → reduced**

- Role of important proteins
  - C3a → Anaphylatoxin
  - C3b → opsonin
  - C5a → Anaphylatoxin/Chemotaxis
  - C5b → MAC → destruction of antigen

| Deficiency | Diseases |
|---|---|
| $C_1$ / $C_2$/ $C_4$ (Early complement proteins) | ↑ Autoimmune disorder (SLE) |
| $C_3$ | pyogenic infections |
| $C_5$ / $C_6$ / $C_7$ / $C_8$ (Late complement proteins) | Neisseria infection Toxoplasmosis |
| $C_9$ | No disease |

- $C_2$ is the MC complement protein deficiency

**Regulatory Complement Proteins** 00:23:49

- $C_1$ inhibitor deficiency → hereditary angioedema
  - F >>> M
  - Edema (Oral/larynx/GIT)
  - Non pitting edema
- $CD_{55}/CD_{59}$ defect → PNH (Paroxysmal Nocturnal Hemoglobinuria)
- $CD_{46}$/Factor H&I defect
  - Excessive activation of Alternate pathway → atypical HUS
- Factor H defect → ARMD (Age Related Macular Degeneration)

# 16 CHRONIC INFLAMMATION & WOUND HEALING

- 3 components
  - Ongoing inflammation
  - Tissue destruction (Hallmark feature)
  - Healing
- Cell for Chronic Inflammation is monocyte (circulation) → macrophage (tissue)

**Different Macrophages**

- Kidney - Mesangial cell
- Liver - Kupffer cell
- Bone - Osteoclast
- Placenta - Hoffbauer cell
- Brain - Microglia/gitter cells
- Spleen - Littoral cell

**Important Information**

Types of Macrophages

- $M_1$ type activated by INF γ secreted by T-cells and it ↑ inflammation
- $M_2$ type activated by IL-4 & IL-13 and it ↓ inflammation by promoting tissue fibrosis

**Role of lymphocytes** 00:06:01

- TH1 cells: Responsible for INF γ secretion → activation of M1 macrophage
- TH2 cells: Responsible for IL-4/IL-13 secretion → activation of M2 macrophage
- TH17 cells: Responsible for IL-17 secretion → recruitment of neutrophils

## GRANULOMATOUS INFLAMMATION

- Type of Chronic Inflammation
- Associated with formation of microscopic structure "granuloma" (macrophages surrounded by lymphocytes)
- No of lymphocytes in granuloma is minimal → naked granuloma

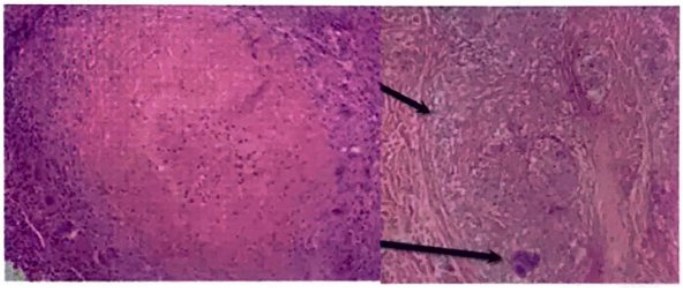
**Granuloma conditions**

- TB: Caseating Granuloma (soft granuloma)
- Sarcoidosis: Non-Caseating Granuloma/Hard granuloma/Naked granuloma
- Syphilis: Gumma
- Malaria: Durck Granuloma
- Q-Fever: Doughnut Granuloma
- IBD
  - Crohn's disease: Granuloma
  - Ulcerative colitis: No Granuloma
- Cat scratch disease: Stellate Granuloma
- Vasculitis: Temporal arteritis/Takayasu arteritis/Churg Strauss syndrome/Wegner's granulomatosis

**Giant cells**

- Upon INF γ macrophages are activated and modified into "Epitheloid Cell" – has secretory function.
- Multiple epitheloid cells fuse to form "giant cells"

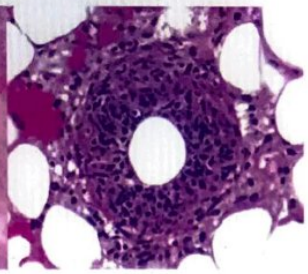
| Giant cell type | Features |
|---|---|
| Langhans Giant Cells | • Seen in TB<br>• Inverted U/ Horse shaped nuclei |
| Foreign Body Giant Cells | • Seen with sutures & talc |
| Warthin-Finkeldey Giant Cells | • Seen in measles<br>• Eosinophilic inclusions are seen |
| Reed-Sternberg Giant Cell | • Owl-eye appearance<br>• Seen in Hodgkin's Lymphoma |
| Touton Cell | • Peripheral cytoplasm has foamy appearance due to lipid deposition<br>• Seen in Xanthoma |



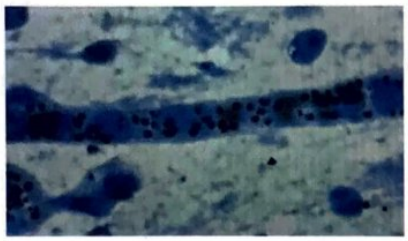
Caseating granuloma – TB

Sarcoidosis

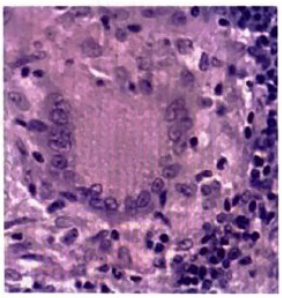
Cat-Scratch Disease



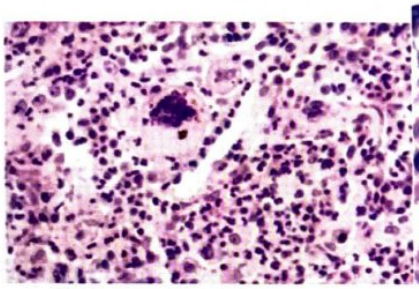
Q fever



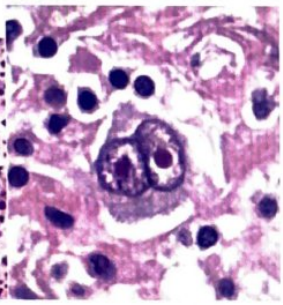
Cerebral malaria



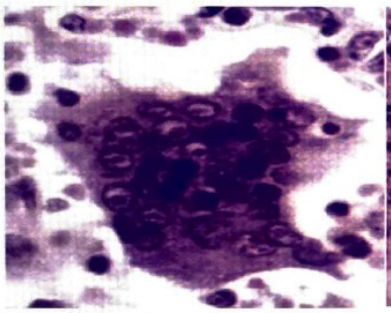
Langhan's GC



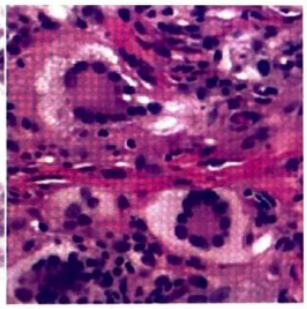
Foreign Body GC



Reed-Sternberg cell



Warthin-Finkeldey cell



Touton GC

## WOUND HEALING

- Wound healing takes place by 2 steps
  - Primary union
  - Secondary union
- Primary Union
  - Damage predominantly in the epithelial lining
  - Minimal loss of Connective tissue
  - Seen in clean, surgical, uninfected wound
- Secondary Union
  - Seen with blunt object injury
  - More loss of connective tissue resulting in scar formation

| Day | Feature |
|---|---|
| 0 | Blood Clot |
| 1 | Blood Clot + Neutrophilic infiltration |
| 2 | Thin Epithelial Layer |
| 3 | • Granulation tissue (collagen III)<br>• Composed of Macrophages + Fibroblasts + Blood vessels |
| 4/5 | GT + collagen deposition (max angiogenesis) |
| 14 | ↑↑ collagen + Fibrous tissue deposition |

- In secondary union, due to ↑ release of inflammatory chemicals resulting in the conversion of fibroblast → myofibroblast
- Myo-Fibroblast
  - Contains actin
  - It has the contraction ability: Scar Contraction / wound contraction

### Previous Year's Questions

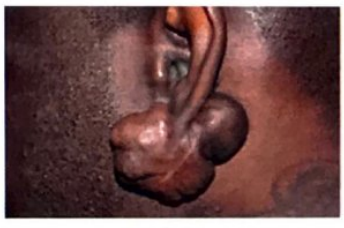
Q. Secondary healing mechanism is? (FMGE 2018)
A. Granuloma formation
B. Scab formation
C. Granulation Tissue
D. Neovascularization

**Collagen Remodeling** 00:37:42

- Collagen III → Collagen I (Zn)
- It depends on
  - Vit C
  - MMP (Matrix metallo-Proteinases)
- Strength of the wound after 1 week: 10%
- Strength of the wound never becomes 100%

**Abnormal Healing**

- Keloid: Extra deposition of granulation tissue vertically goes beyond margins
  - MC site for keloid formation: Sternum
- Hypertrophic Scar: Extra deposition of granulation tissue vertically but it is within the margin



Keloid

Hypertrophic Scar

# CLINICAL QUESTIONS

1. A 43-year-old man complains of a 1-week history of abdominal pain and yellow discoloration of his sclera. Physical examination shows right upper quadrant pain. Laboratory studies show increased serum levels of alkaline phosphatase (520 U/dL) and bilirubin (3.0 mg/dL). A liver biopsy revealed portal fibrosis, with scattered foreign bodies consistent with schistosome eggs. Which of the following inflammatory cells is most commonly to predominate in the portal tracts in the liver of this patient?

A. Basophils
**B. Eosinophils**
C. Macrophages
D. Monocytes

Solution

- Eosinophils are recruited in parasitic infestations and would be expected to predominate in the portal tracts of the liver in the patients with schistosomiasis.
- Eosinophils have leukotrienes and platelet-activating factor, as well as acid phosphatase and eosinophil major basic protein.
- Plasma cells are differentiated in to B lymphocytes that secrete large amounts of monospecific immunoglobulin.
- Diagnosis: Schistosomiasis

Reference

- Robbins 10th ed, Pg 397-398

# LEARNING OBJECTIVES

## Unit 3 IMMUNITY 1

- **Basics of Immune System Activation**
  - Innate Immunity
  - Adaptive Immunity
  - Activation Of Immune System
  - APC
  - MHC (Major Histocompatibility Complex)
  - T-Cell Activation
- **Hypersensitivity Reaction**
  - Type 1 Hypersensitivity Reaction
  - Type 2 Hypersensitivity Reaction
  - Opsonization & Phagocytosis
  - Inflammation
  - Cellular Dysfunction
  - Type 3 Hypersensitivity Reaction
  - Type 4 Hypersensitivity Reaction
  - Tuberculin Test
  - CD T-cell Activation

# 17 IMMUNITY

| Immunity | |
|---|---|
| **Innate Immunity** | **Adaptive Immunity** |
| • Non-specific<br>• No memory | • Specific<br>• Memory is present |

## INNATE IMMUNITY

00:05:22

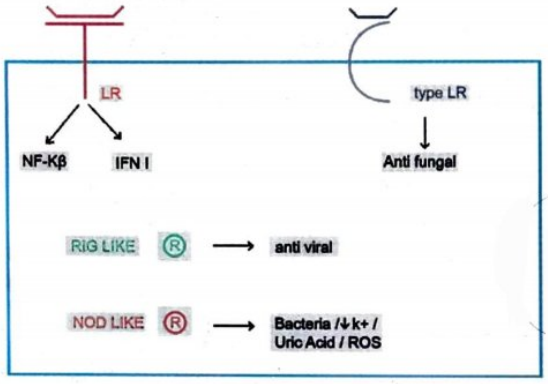
- Barriers
  - Anatomical barriers (Intact skin)
  - Physiological barriers (lysozyme is saliva, sweat)
- Protein molecules
  - C-reactive protein/Lectin/complement proteins
- Cells
  - Neutrophils
  - Macrophages
  - NK cells
    - → Recognizes and cause damage to virus infected/mutated cells

**Important Information**

- Bacteria: PAMP (required for infectivity of the bacteria)
- Inflammation (injured/necrotic cells): DAMP

## PATTERN RECOGNITION RECEPTORS

00:11:39




**Plasma membrane receptors**

- Toll Like Receptor activation leads to secretion of
  - Nuclear factor κβ activation associated with ↑ recruitment of WBC at the site of injury
  - Interferon I have anti-viral effect
- C-type Lectin Receptor
  - Effective against fungal infections

**Cytosolic receptors**

- Rig like receptors: Defense against virus
- NOD like receptors
  - Identifies bacteria, potassium efflux, uric acid & reactive oxygen species
  - Inflammasome associated with activation of caspase 1 and release of IL-1 (fever)

## ADAPTIVE IMMUNITY

00:19:21

**B-Cells**

- Upon activation coverts into activated B-cells/Plasma cells.
- Responsible for antibodies secretion.
- Contribute to Humoral immunity
- Effective against extracellular organism like bacteria

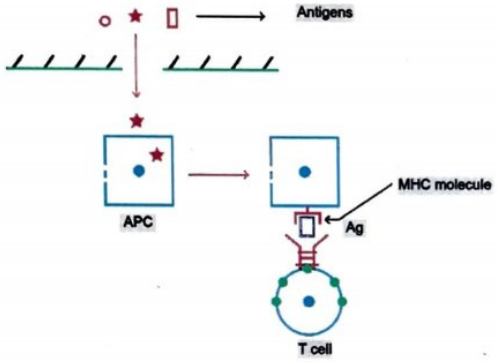
**T-Cells**

- Contribute to Cellular immunity
- Effective against intracellular microbes like virus & fungi

## ACTIVATION OF IMMUNE SYSTEM

00:22:37

- Antigen (Ag)
  - Proteinaceous: T-cell dependent
  - Carbohydrate/lipid: T-cell independent




- Clonal selection: only a particular type of T-cell is activated depending on the structure of the presenting antigen.
- T-cells
  - Effector T-cell (actively fights the infection)
  - Memory T-cell (Marker: CR45RO)

## APC

00:27:32

- Professional APC's (higher expression of MHC molecules)
  - B-cells (on direct stimulation by carb/lipid Ag it results in T-cell independent Ab secretion)
  - Macrophages ($CD_{13/14/15/33}$)
  - Dendritic cells
    - → Skin: Langerhans cell
    - → Lymph node/spleen: follicular dendritic cell (used by HIV as reservoir)
- Non-Professional APC's (lower expression of MHC molecules)
  - Thymic epithelial cells
  - Endothelial cells
  - Fibroblast
  - Glial cells
  - Pancreatic β-cells

## MHC (MAJOR HISTOCOMPATIBILITY COMPLEX)

### Previous Year's Questions

**Q. HLA is located on?**

(FMGE 2018)

A. Short arm chromosome 6
B. Long arm chromosome 6
C. Short arm chromosome 3
D. Long arm chromosome 3

- Present on chromosome 6p
- Present on surface of APC, responsible for presentation of processed antigenic peptide to immune cell in the body.

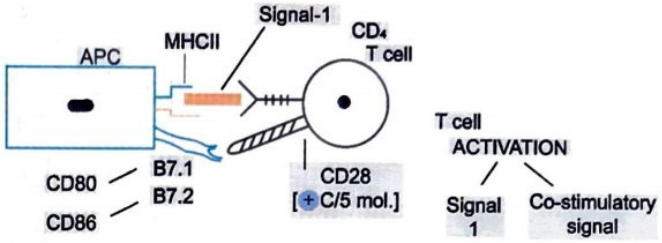

- Antigen binding cleft of MHC I made of α1, α2 (Distal α chains)
- Antigen binding cleft of MHC II made of α1, β1 (Distal α/β)
- Antigen + MHC I → $CD_8$ T-cells (MHC I dependent/MHC I restricted cells)
- Antigen + MHC II → $CD_4$ T-cells (MHC II dependent cells)
- MHC I is present on all nucleated cells and platelets are the only non-nucleated cells with MHC I.
- Alloantisera is used to detect MHC I
- Mixed Leukocyte Reaction (MLR) is used to detect MHC II
- $CD_4$: $CD_8$ T-cells → 2:1
- MHC is also known as HLA. And certain HLA associated with specific disorders

### Important Information

- HLA B-27 is associated with ankylosing spondylitis
- HLA DR3/DR4 is associated with type I DM
- HLA DQ2/DQ8 is associated with celiac sprue

## T-CELL ACTIVATION

00:40:56




- T-cell activation requires both signal 1 and costimulatory signal
- External antigen: generation of both signal 1 and costimulatory signal
- Self-antigen: generation of only signal 1 and not the costimulatory signal (T-cell Anergy)
  - Associated with self-tolerance
- Negative costimulatory signal: CTLA-4/PD-1 molecule of T-cell (↓ activation of T-cell upon self-antigen)

### Previous Year's Questions

**Q. Co-stimulatory factor of T-cell include all except.**

(JIPMER 2018)

A. B7.1
B. B7.2
C. B7.3
D. CD 40

### Cancer cells

00:51:54

- Cancer cells have ↑ expression of PD-L1/L2 molecule (program death ligand) and binds with PD-1 molecule results in inactivation of T-Cells
- Immune checkpoint blockade treatment is developed (monoclonal antibody blocks the interaction between PD-L1/L2 and CTLA-4/PD-1 molecule)
- Used in malignant melanoma, hodgkins and solid cancer
  - Side effect: ↑ risk of auto-immune disorders

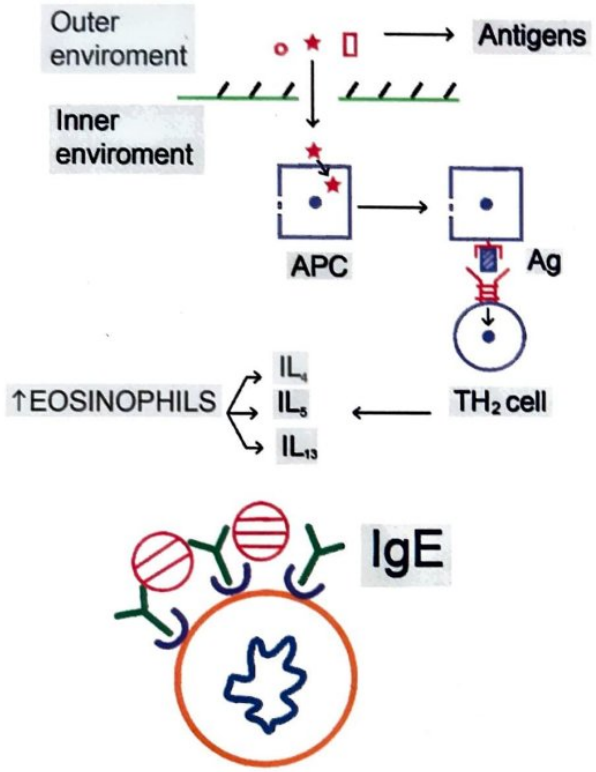
# 18 HYPERSENSITIVITY REACTIONS

- Hypersensitivity reaction → Tissue damage
- Gel combs classification → 4 subtypes of hypersensitivity reactions

## TYPE 1 HYPERSENSITIVITY REACTION

00:01:24

- Aka Immediate type HR




**First Exposure/Sensitization**

- IL-4 → IgE → attaches to mast cell → modified mast cells
- IL-5 → ↑ Eosinophils
- IL-13 → ↑ Mucus

**Re-exposure**

Mast cells + IgE
↓
Ag exposure
↓
Crosslinking of IgE antibody
↓
Mast cell activation
↓
Degranulation
↓
Early phase: Histamine/proteases/ECF; NCF
Late phase: Cytokines/AA metabolites

- AA metabolites
  - $PgD_2$
  - LTs
- Cytokines
  - IL-2
  - TNF α
  - IL-5 → recruitment of eosinophils → release of MBP/ECP → Tissue damage

**Examples**

- A: Allergies → atopy (difference in genetic makeup that makes immune system to react in exaggerated manner)
  - Asthma: exposure to house dust (in western countries – pollen grains)
  - Hay fever
  - Food: peanuts/seafood
- B: Bee Sting (Melittin)
- C: Casoni's Test, P-K reaction, Theobald-Smith phenomena
- D: Drugs → Penicillin → Anaphylaxis

### Previous Year's Questions

Q. A Boy presents in the emergency because of development of allergy due to pollen inhalation. Which of the following cells is important in the pathogenesis of this condition? (FMGE Aug 2020)

A. NK cell
B. Neutrophil
C. Helper T cell
D. Cytotoxic T cell

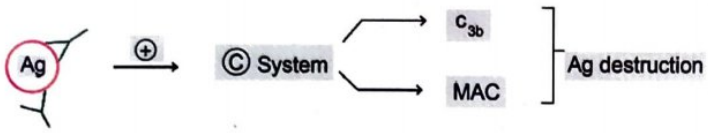
## TYPE II HYPERSENSITIVITY

00:19:27

- Aka Antibody Mediated HR/Cytolytic HR

## OPSONISATION & PHAGOCYTOSIS


- IgG (opsonin Ab) → Neutrophils, Macrophages → Phagocytose the Ab
- Ag + Ab → complement system activation → C3b attachment → attracts phagocytic cells
- MAC formation → damage to the antigen




**Examples**

- Blood transfusion reaction
- Erythroblastosis Fetalis/ Rh incompatibility of newborn
  - Mother → Rh –ve; Father → Rh +ve
- Autoimmune hemolytic anemia
- Autoimmune thrombocytopenia
- Autoimmune leucopenia

## INFLAMMATION

- Ag
- Ab

} Complement activation → C3a/C5a → WBCs → Tissue damage

**Examples**

- Acute rheumatic fever
  - Ab formation against bacteria
  - Structure of bacteria is similar to normal cardiac tissue/joints
  - Cross react → carditis/arthritis
- ANCA vasculitis
- Goodpasture syndrome
  - Ab → Non-collagenous part of α chain
  - α-chain is also present in BM of lungs & kidney
- Pemphigus Vulgaris

## CELLULAR DYSFUNCTION

- Aka type 5 HR
- Ab → ↑↑↑ Stimulation of receptor → Graves disease (hyperthyroidism)
- Ab → ↓↓↓ Stimulation of receptor → Myasthenia gravis
- Examples of cellular dysfunction
  - Pernicious anemia
  - Insulin resistant DM

**Examples of Type II HR**

- MY - Myasthenia gravis
- Blood - Blood transfusion Reactions, Rh incompatibility
- Group - Good pasture Syndrome; Graves disease
- IS - Immune Hemolytic Anemia; Immune Thrombocytopenia; Insulin resistant DM
- R - Rheumatic Fever
- H - Hyperacute graft rejection
- Positive - Pernicious anemia; Pemphigus vulgaris

### How to remember

- **Conditions associated with type II HR → My Blood Group Is RH Positive**

### Previous Year's Questions

**Q. A 55 – year old patient presented with difficulty in breathing and rashes after ingestion sea food: He has shown similar reaction in the past following consumption of the same food items. Which of the following hypersensitivity reaction do you relate with this?** (FMGE Dec 2020)

A. Type I
B. Type 2
C. Type 3
D. Type 4

## TYPE III HYPERSENSITIVITY REACTION

00:41:47

- Aka immune complex disease

Ag → Ab formation → Ag-Ab complex (Phase 1)
5-7 days ↓
Deposition of I/C (Phase 2)
(Glomerulus/serosa/LN/Skin/Synovium)
10-14 days ↓
Clinical features (Phase 3)

- Most dangerous immune complex are medium sized

### How to remember

- **Conditions associated with type III HR → SHARP**

**Examples**

- S - Serum Sickness, SLE
- H - Henoch-Schonlein Purpura
- A - Arthus Reaction (Localized type 3 HR & involves

BV)

- R - Reactive Arthritis, Type 2 Lepra reaction
- P - Post Streptococcal Glomerulonephritis/Polyarteritis nodosa
- SLE
  - Chronic phase
  - Acute phase
    → I/C → Complement Activation occurs → ↓↓↓ Serum $C_3$
- Damage to endothelial cells → Plasma protein deposition in BV wall → Fibrinoid necrosis
- Presence of neutrophilic infiltration is also seen

## TYPE IV HYPERSENSITIVITY REACTION

00:55:34

- Aka cell mediated HR
  - CD $4^+$ T-cell
  - CD $8^+$ T-cell

**Delayed Type HR**

- 1st Exposure: 2 mechanisms (Ag → APC → $T_H$/$TH_1$ cell)

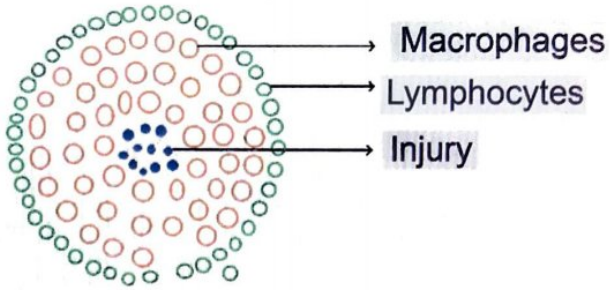
IL-12 → Helper T-cell → Differentiates into $TH_1$ → IFN γ → ↑ $TH_1$

(or)

Ag + APC → IL-1/6/23 → Naïve T-cell → Differentiates into $TH_{17}$ cell → Memory cells

- Re-exposure

Ag → Memory cell → IL-2/ IFN γ → ↑ $TH_1$ → ↑ Lymphocytes → Macrophage activation → Granuloma




### Important Information

- Granuloma associated with $TH_1$ cell → consists more number of activated macrophages
- Granuloma associated with $TH_{17}$ cell → consists more number of neutrophils

**Tuberculin test (Mantoux test)**

0.1ml of PPD → Inject intradermal into forearm → Check horizontal diameter of induration after 72hrs → If >10mm, Mantoux positive

- Helps in assessing
  - Exposure to Mycobacterium
  - Sufficient immune system activity
- Lepromin test/Mantoux test → delayed type IV HR

### How to remember

- Conditions associated with Type IV HR → RAM Chandra If DM/Psoriasis/Leprosy/TB

**Examples**

- RA - Rheumatoid Arthritis
- M - Multiple sclerosis
- Chandra - Contact Dermatitis
  - Female → chemicals
  - Poison ivy
- If → IBD
- DM (Type 1)/Psoriasis/Leprosy/TB

## $CD_8$T-cell activation

01:11:29

| $CD_8$T-cell activation | |
|---|---|
| Perforins (↑ permeability)<br>Granzyme<br>↓<br>Activation of caspase<br>↓<br>Destroys target cell | ↑↑FAS-L expression<br>↓<br>Fas receptor<br>↓<br>Extrinsic pathway of apoptosis activation<br>↓<br>Destroys target cell |

**Example**

- Graft rejection
- $CD_8$T-cells → virus infected cell / cancer cells
- Hepatitis
- Type 1 DM → CTLs → Insulitis
- $CD_8$T-cells → INF γ

### Important Information

- Killing of virus infected/cancer cells
  - MHC I dependent: $CD_8$T-cells
  - MHC independent: NK cells

# CLINICAL QUESTIONS

1. You are an Intern in OBG Department, you receive a case of Term Teenage Pregnancy in labor with Cephalo-Pelvic Disproportion. Your Resident doctor instructs you to get the blood investigations done ready as the patient is to be taken for an Emergency LSCS procedure, especially the resident asked u to get the Blood Grouping and Rh typing done first. Which of the following potentially represents the most dangerous situation?

A. Rh+ve mother with 2nd Rh-ve child
**B. Rh-ve mother with 2nd Rh+ve child**
C. Rh+ve mother with 1st Rh-ve child
D. Rh-ve mother with 1st Rh+ve child

Solution

- Rh-ve mother with 2nd Rh+ve child can result in the development of hemolytic disease of newborn or erythroblastosis fetalis. So, it is a dangerous condition.
- In hemolytic disease of the fetus and newborn (erythroblastosis fetalis), there is an antigenic difference between the mother and the fetus, and IgG anti-erythrocyte antibodies from the mother cross the placenta and cause destruction of fetal red cells.
- This condition is a type II hypersensitivity reaction.
- *This is Not to be confused with Hemorrhagic disease of the newborn* which is a coagulation disturbance in the newborns due to vitamin K deficiency. As a consequence of vitamin K deficiency there is an impaired production of coagulation factors II, VII, IX, X, C and S by the liver.

Reference

- Robbins 10th/pg 210 table 6.3

# LEARNING OBJECTIVES

## Unit 4 IMMUNITY II

- **Concepts of Tolerance & Basics of Autoimmune Disorder**
  - Central Tolerance
  - Peripheral Tolerance
  - Autoimmune Disorders
- **Autoimmune Disorder 1; SLE**
  - Risk Factors
  - Features Of Organ Involvement
  - Antibodies In Sle
  - Conditions Resembling Sle
- **Autoimmune Disorder 2**
  - Sjogren Syndrome
  - Systemic Sclerosis / Scleroderma
  - Limited Scleroderma
  - Diffuse Scleroderma
  - Autoantibodies
  - Mixed Connective Tissue Disease
  - $IgG_4$ Related Disease
  - Dermatomyositis
  - Polymyositis
- **Concepts of Organ Transplant**
  - Immune Activation
  - Hyper Acute Transplant Rejection
  - Acute Transplant Rejection
  - Chronic Graft Rejection
  - Reducing Risk of Rejection
  - Graft Versus Host Disease
- **Immunodeficiency Disorders**
  - Di-George Syndrome
  - Bruton's Disease
  - Common Variable Immunodeficiency Disease
  - IgA Deficiency
  - Hyper IgM Syndrome
  - Hyper IgE Syndrome
  - X-Linked Lymphoproliferative Syndrome
  - Ataxia Telangiectasia
  - Wiskott Aldrich Syndrome
  - Severe Combined Immunodeficiency Syndrome
- **Amyloidosis**
  - Primary Amyloidosis
  - Secondary Amyloidosis
  - Hemodialysis Associated Amyloidosis
  - Localized Amyloidosis
  - Hereditary Amyloidosis
  - Organs Affected in Amyloidosis

# 19 CONCEPT OF TOLERANCE & BASICS OF AUTOIMMUNE DISORDER

- ↓ Response of immune system to antigens [Self]
- Self-tolerance: proper response of immune system to self-antigen
- Activation of immune system against self-antigen → auto-immune diseases

**Types**
- Central tolerance
- Peripheral tolerance

## CENTRAL TOLERANCE
00:01:37

- Take place in LN/Bone marrow
- Deletion / Negative selection
  - Clonal deletion: deletion of Self-reactive B/T cells at the time of development by Apoptosis
  - T-cell → AIRE gene defect (autoimmune regulatory gene) → AI poly-endocrinopathy
- Receptor Editing
  - Seen in B cells

## PERIPHERAL TOLERANCE
00:05:39

**Anergy (Functional hypo-responsiveness)**
- B-Cell ↓: CD40 – CD40L (↓)
- T-Cell ↓: CD28 – B.7 (↓)
- Self-antigen → ↑↑ CTLA-4/PD-1
- Cancer cells also use this mechanism for survival
- New anti-cancer therapy: Immune surveillance

**T-Regulatory cell**
- Example: Fetus at pregnancy
- They secrete
  - IL 10 & TGF β
  - CTLA-4 & PD 1 → ↓ activation of B & T cell
- CD4 T-cells
  - IL-2 receptor/ CD25 polymorphism → ↑ Multiple sclerosis
  - FOXP3 defect: IPEX syndrome

### Important Information
- I - Immune dysregulation
- P - Poly-endocrinopathy
- E - Enteropathy
- X - X-linked Syndrome

**Antigen Sequestration**
- Immune Privileged Sites
  - B - Brain except chemoreceptor trigger zone/ Area postrema
  - E - Eye except optic nerve
  - T - Testis (Seminiferous Tubules) except epididymis

### How to remember
- BET

- In Trauma in B/E/T is exposed → Orchitis, Opthalmitis

### Previous Year's Questions
Q. Immune privilege site is. (JIPMER 2019)

A. Optic nerve
B. Seminiferous Tubule
C. Area postrema
D. Spinal cord

**Deletion of self-reactive B/T-cells**
- Done by process of programmed cell death
- ↑ Expression of FAS ligand/FAS receptor interaction → Apoptosis
- Self-reactive B/T cells have ↑ Bim (increases apoptosis)
- Defect in interaction → No Apoptosis → Auto Immune Lympho Proliferative Syndrome (ALPS)

## AUTOIMMUNE DISORDERS
00:19:37

**Genetic Factors**
- ↓ Tolerance
- HLA genes defects → HLA B-27 (ankylosing spondylitis)
- Non-HLA genes defects
  - PTPN–22 gene defect
    - → Responsible for controlled lymphocyte proliferation in normal individuals
    - → Defect → ↑ No of self-reactive lymphocyte → ↑ Auto-Immune Disease
  - NOD–2 (sensor for GI bacteria) → malfunction → IBD

→ IBD is not a classical example of auto-immune disorder rather a hyperactivity of immune system against GI commensals

- IL-2 Receptor is responsible for normal function of T regulatory cells
  → IL-2 Receptor defect → ↓ T Regulatory Cells → MS/T1DM

**Infections**

- ↑↑ APC activation (due to ↑ Co-stimulatory Signal)
- Molecular mimicry (Rheumatic fever)
- Spreading of cryptic epitope
  - Example: In RF, hidden Ag is exposed in neighboring areas of diseased part
- Polyclonal B-Cell Activation
  - Example: EBV & HIV
  - Viral infection → B-cell activation → some B-cells are spontaneously mutated → Auto Ab formation
- Hygiene Hypothesis
  - ↓ Infections → ↓IL-2 → ↓ maintenance of T Regulatory Cells → ↑ Autoimmune Disorders

**Miscellaneous Factors** 00:33:07

- Hormones (female >>> male)
- UV light (SLE0
- Release of sequestered Ag (B/E/T)
- Drugs

**Important Information**

- **Drugs increasing autoimmune disorders**
  - S - Sulfonamide
  - H - Hydralazine
  - I - Isoniazid
  - P - Procainamide

# 20 SYSTEMIC LUPUS ERYTHEMATOSUS

- Associated with failure of self-tolerance
- Multisystem disorder

**Important Information**

- Pathology: Damage to any blood cells (Type 2 HR) + damage to organ by I/C deposition and subsequent inflammation (Type 3 HR)

## RISK FACTORS

- Genetic factors
  - HLA DQ polymorphism
  - Deficiency of complement proteins ($C_1/C_2/C_4$)
- Environmental factors
  - UV rays
  - Female predominant (hormonal and genes specifically located in 'X' chromosome)
- Drugs
  - Immunologic factors
  - Hyper activation of B & T-Lymphocyte

### SLICC Clinical Immunologic Criteria

> 4 criteria [at least 1 clinical and 1 laboratory]

| Clincal | Labortory |
|---|---|
| 1. Acute cutaneous lupus | 1. ANA above lab ref range |
| 2. Chronic cutaneous lupus | 2. Anti-dsDNA above lab ref range [or 2x ref range if tested by ELISA] |
| 3. Oral or nasal ulcers | 3. Anti-SM |
| 4. Non scarring alopecia | 4. Antiphosphliopid antibody |
| 5. Arthritis | 5. Low complement [C3,C4,CH50] |
| 6. Serositis | 6. Direct coombs' test [do not count in the presence of hemolytic anemia] |
| 7. Renal | |
| 8. Neurologic | |
| 9. Hemolytic anemia | |
| 10. Leukopenia [<4000/mm$^3$] | |
| 11. Thrombocytopenia [<100,000/mm$^3$] | |

- Acute cutaneous lupus: photosensitive skin rash (malar rash on Nose Bridge)
- Chronic cutaneous lupus: discoid rash
- Oral or Nasal ulcers: painless
- Arthritis: ≥2 more peripheral joint involvement in which there's no damage to articular cartilage
- Serositis: pericarditis, pleuritis
- Renal: massive proteinuria or RBC cast in the urine
- Neurologic: decline in the brain function or seizures or epilepsy
- CH50 is indicator of activation of classical pathway
- Low complement levels indicate "active phase" of the disease
- Standalone criteria – presence of ANA/anti-ds DNA Ab + biopsy proven lupus nephritis

## FEATURES OF ORGAN INVOLVEMENT

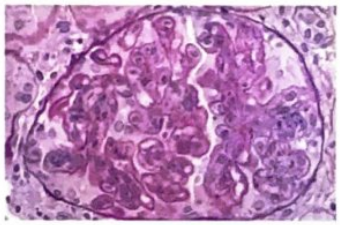
00:10:55

- Non-specific fever, weight loss, fatigue
- Oral cavity: painless aphthous ulcer
- Joint: non-erosive arthritis and no deformity
  - Musculoskeletal involvement in the commonest involvement in SLE
- Skin: malar/butterfly rash, photosensitive
  - Degeneration of basal layer of epidermis
  - Immunofluorescence: Ig at dermo-epidermal junction
- Lungs: pleuritic (MC) > interstitial fibrosis
  - Shrinking lung syndrome: weakness of diaphragm resulting in small lung
- Cardiac: pericarditis (MC) >> Libman Sacks Endocarditis (Mitral/Aortic valve involvement)
  - Accelerated atherosclerosis
- Spleen: "Onion skin appearance" due to fibrosis around penicilliary artery

**Important Information**

- Onion peel appearance in blood vessel of kidney – malignant HTN
- Onion peel appearance of bile ducts – primary sclerosing cholangitis

- Kidney: glomerulonephritis, tubule-interstitial nephritis
  - Type 4/diffuse proliferative glomerulonephritis is the most common and most severe
  - Sub-endothelial I/C deposition → circumferential thickening of the capillary (wire loop lesion)



- Full-house phenomenon: Immune-complex are associated with Ig/M/A, C3 protein and λ/κ light chains
- CNS: decline in cognitive function
- Blood: anemia in these patients is due to
  - Abnormal Ab (AIHA)
  - Anemia associated with chronic disease – most important cause

## ANTIBODIES IN SLE

00:25:25

### Previous Year's Questions

Which of the following cannot be diagnosed with +ve ANA?

(AIIMS 2018)

A. Drug induced lupus
B. SLE
C. Scleroderma
D. Sjorgen syndrome

- Anti-nuclear antibody: Most sensitive for diagnosis of SLE
- Anti-ds DNA/Anti smith antibody: most specific for the diagnosis of SLE
  - Predicts disease activity (Anti-ds DNA antibody)
  - Correlates with nephritis and vasculitis
- Anti-Ribosomal P antibody: associated with development of psychosis
- Predictor of SLE in pregnancy
  - Anti-Ro antibody: Neonatal lupus (congenital heart block)
    - → Can also be found in subacute cutaneous lupus, Sjorgen syndrome
    - → Associated with ↓ nephritis
  - Anti-β2 gp antibody: It is directed against phospholipid of endothelial cells, platelets and placental vessels resulting in recurrent abortions
    - → Increased risk of DVT/HVT/stroke
    - → Associated with APLA (Antiphospholipid Antibody Syndrome)

### Previous Year's Questions

Q. Which antibody is associated with reduced risk of lupus nephritis in SLE?

(JIPMER 2018)

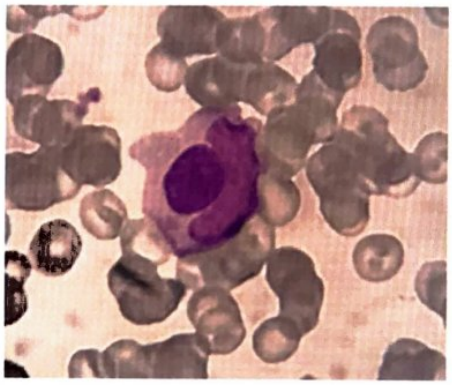
A. Anti-ribosomal P antibody
B. Anti-histone antibody
C. Anti-Ro antibody
D. Antinuclear antibody

- APLA
  - ↑aPTT is seen
  - Primary: unknown cause
  - Secondary: SLE (MC)

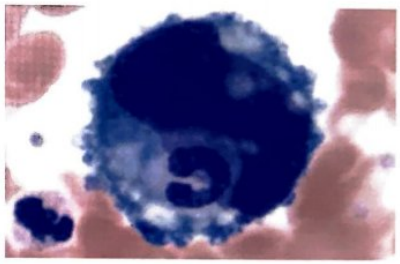
### Important Information

- Antibodies are directed against cardiolipin and Anti-β2 gp
- Cardiolipin antigen associated with false +ve VDRL (syphilis)
- DRVVT (Dilute Russell Viper Venom Test) helps in detection of auto-Ab

- LE Cell: Neutrophil and macrophages has denatured nuclear material (LE body) of another cell
  - Found in SLE >> RA, drug induced lupus

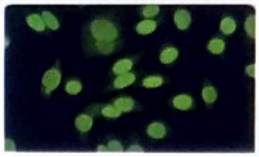
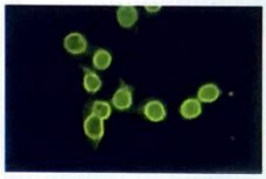
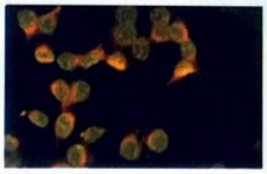
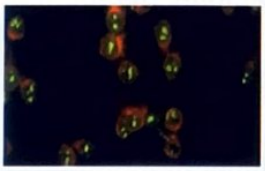
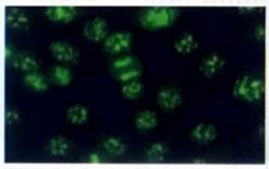


- TART cell: Macrophage that phagocytosed intact chromatin containing nuclei.
- Emperipolesis: Intact cell within cytoplasm of another cell
  - Found in Rosai Dorfman Disease, HL, CML/AML, MDS, MPD



Band cell within Megakaryocyte

- Organism used in IF detection of antibody: Crithidia

| Pattern | Antigen | Image |
|---|---|---|
| Homogenous or diffuse nuclear staining | Chromatin, histones |  |
| Rim or peripheral staining | Double stranded DNA |  |
| Speckled pattern (MC and least specific pattern) | Antibody against extractable (non-DNA) nuclear antigens like ribonucleoprotein, Sm antigen, SS-A and SS-B reactive antigen |  |
| Nucleolar pattern (seen in systemic sclerosis) | RNA (Bright fluorescence is seen within the nucleoli) |  |
| Centromeric pattern (seen in CREST syndrome) | Centromeres |  |

# 21 AUTOIMMUNE DISORDERS - 2

## SJOGREN SYNDROME

00:00:29

- Characterized by Lymphocytic infiltration of lacrimal glands & Salivary glands leading to fibrosis overtime

**Clinical features**

- Females
- Dry eyes/Dry mouth Syndrome → sicca syndrome
  - Gritty sensation of eyes and thickened secretion in conjunctiva
  - Saliva has antibacterial property, hence its absence can lead to bad breath, difficulty in swallowing and speech.
  - Parotid gland enlargement
- Sicca Syndrome can be 1°/2°
  - Associated with Rheumatoid Arthritis (cause of 2° Sicca Syndrome)

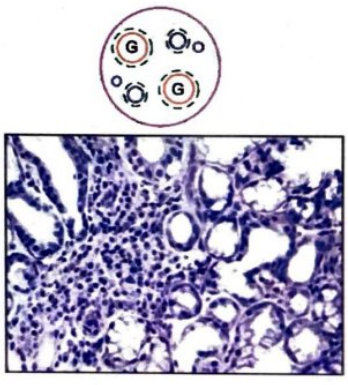
**DIAGNOSIS**

**Auto antibodies**

- They are non-confirmatory
- ANA +ve
- Anti RO Ab [SS-A] +ve
- Anti La Ab [SS-B] +ve
- Anti RO Ab: Associated with
  - Vasculitis
  - Nephritis
  - ↑ duration of disease

**Lip Biopsy**

- Confirmatory (IOC)
- Lymphocytic infiltration in and around glands & blood vessels
- ↑ Risk of marginal zone lymphoma (also seen in Hashimoto's thyroiditis)




### Previous Year's Questions

A 47yr old female presents with arthralgia, difficulty in swallowing the food and gritty feeling in the eye. He is also found to be having increased titers of ANA. Which of the following is the likely diagnosis? (FMGE 2020)

A. Rheumatoid arthritis
B. SLE
C. Serum sickness
D. Sjorgen syndrome

## SYSTEMIC SCLEROSIS (SCLERODERMA)

00:10:18

- Characterized by
  - ↑ Fibrous tissue deposition → skin & other organs
  - Damage to blood vessels

**Variants**

- Linear Scleroderma / Morphea
- Limited Scleroderma

**Limited Scleroderma**

- Initial involvement of Blood vessels [Raynaud's phenomenon]
- Affected blood vessels are narrowed → ↓ blood supply → pale white → blue → red
- Skin of Fingers/face/fore arm involved
- Late involvement of systemic visceral organs
- Anti-centromere Ab +ve
- CREST syndrome
  - **C** - Calcinosis
  - **R** - Raynaud's phenomenon
  - **E** - Esophageal dysmotility
  - **S** - Sclerodactyly
  - **T** - Telangiectasia

### Previous Year's Questions

Anti-centromere antibodies are seen in which of the following? (AIIMS 2018)

A. Drug induced lupus
B. SLE
C. Sjorgen syndrome
D. Scleroderma

**Diffuse Scleroderma**

- Skin + early visceral involvement
- Organ involvement
  - Esophagus: Dysphagia
  - GIT: malabsorption
  - Cardiac: pericarditis, pericardial **effusion, fibrosis**
  - Lungs: PAH (cause of death); Pulmonary **Fibrosis**
  - Kidney: ↑ **risk of renal failure**

**Autoantibodies**

- Anti-ANA Ab **+ve**
- Anti–DNA Topoisomerase **I Ab [Anti - SCL 70 Ab ⊕]**: specific antibody
  - Associated with ↑ **chances of**
    - → Peripheral Vascular Disease
    - → Lung involvement
- Anti-RNA Polymerase **III Ab**
  - **Associated with systemic sclerosis**
  - **3 important manifestations**
    - → **R - Renal**
    - → **N - Neoplasia**
    - → **A - Acute onset**

**Important Information**

- **Anti $U_3$ RNP Ab: Associated with systemic sclerosis**
- **Anti U 11/12 RNP Ab: Associated with ↑ risk ILD**

## MIXED CONNECTIVE TISSUE DISEASE

00:23:45

- Mixed Features of **SLE/Sclerosis/Polymyositis**
- Anti - $U_1$ RNA Ab
- Less severe renal involvement
- Better response to steroids

**Ig $G_4$ RELATED DISEASE**

- **Middle aged male → Plasma cells + T cells + Obliterative phlebitis**

↓

Ig G4

- Associations
  - Idiopathic retro peritoneal fibrosis/Ormond's disease
  - Riedel's thyroiditis
  - Mikulicz syndrome
  - Autoimmune **pancreatitis**
  - Kuttner's **Tumor (chronic sialadenitis)**
- Storiform pattern **of fibrosis is seen**
  - Also seen in Malignant Fibrous Histiocytoma
- **Treatment: Rituximab**

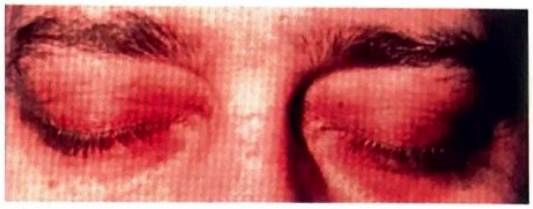
## DERAMATOMYOSITIS

00:31:06

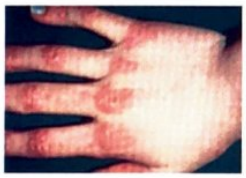
- Skin + Muscles + **Surrounding Blood vessels**
- 1° or associated **with cancers (stomach cancer)**

**Clinical features**

- Skin
  - Heliotrope rash
  - Gottron papules (seen on extensor surface)
- Muscle
  - **Proximal muscles involved early**
  - **Distal muscles involved later (↑ Creatinine Kinase value)**



Heliotrope rash

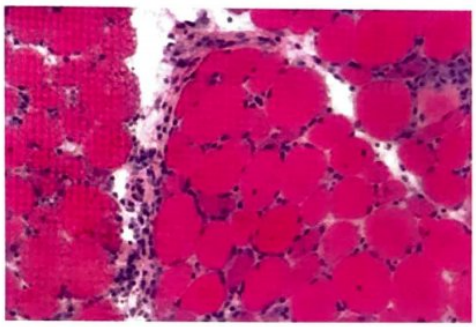


Gottron Papule

**Diagnosis**

- Auto Anti Bodies
  - ANA +ve
  - Anti Jo 1 Ab +ve: Mechanic hand
  - Anti Mi2 Ab +ve: skin features
  - Anti P 155 Ab +ve: Paraneoplastic syndromes
  - Anti P 140 Ab +ve: Juvenile Dermatomyositis

**Biopsy**



$CD_4$ T-cells

↓

Peri Mysial Inflammation

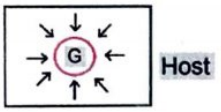
&

Peri Fascicular Atrophy

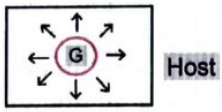

**POLYMYOSITIS** 00:38:52

- Skeletal muscle inflammation
- No skin involved
- Biopsy: Endomysial Inflammation ($CD_8$ T-Cells)

# 22 ORGAN TRANSPLANTATION



Transplant Rejection



Graft Vs Host Disease

**Types of graft** 00:02:01

- Auto-graft: self
  - Example: skin graft, Hair transplant, bone transplant
- Allograft: Different individual of same species
  - Example: Kidney transplant
- Iso-graft/Syngraft: Identical twin
- Xenograft: Different species
  - Example: Cardiac valves from pig & cow

### Important Information

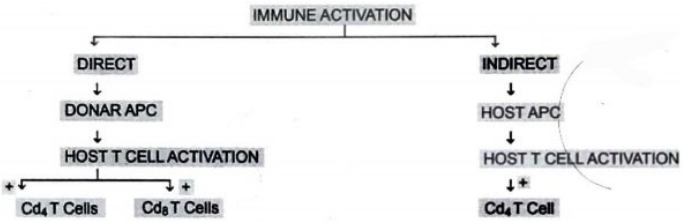
- Auto-graft: Least chance of rejection
- Xenograft: Maximum chance of rejection

### Previous Year's Questions

Q. An elderly diabetic male patient underwent kidney transplantation from his twin brother. The type of grafting is? (FMGE – Dec – 2020)

A. Allograft
B. Isograft
C. Xenograft
D. Autograft

## IMMUNE ACTIVATION 00:04:13




- Direct pathway is responsible for acute cellular rejection.
- Indirect pathway is responsible for chronic cellular rejection.

### HYPER ACUTE TRANSPLANT REJECTION 00:05:47

- Rejection occurs within minutes to hours
- H/O previous transplant, blood transfusion, multiparous
- Occurs due to preformed Ab – IgM (against ABO/HLA)
- Preformed Ab → Endothelial Cell damage → Thrombus

### Previous Year's Questions

Which graft rejection can be reversed once it is established? (JIPMER 2019)

A. Hyper-acute rejection
B. Acute rejection
C. Chronic rejection
D. Acute on chronic rejection

### ACUTE TRANSPLANT REJECTION

- Rejection occurs within Days to weeks (< 6 months)
- Reversible
- Acute cellular rejection: Activation of CD4/CD8 T-Cells results in
  - Tubular injury (Type 1 injury)
  - Endothelial injury – vasculitis, endothelitis (Type 2 injury)
- Acute humoral rejection: Ab → activation of complement system → $C_4D$ deposition in glomeruli (used as marker)

### CHRONIC GRAFT REJECTION

- Rejection occurs in months to years (> 6 months)
- MC type of transplant rejection
- Cellular: ↑ smooth muscle proliferation/fibrosis → narrowing of lumen → "Graft Arteriosclerosis"
  - Example: Glomerulo-sclerosis (deposition of fibrous tissue at glomerulus, duplication of BM)
- Humoral: Ab formation

## REDUCING RISK OF REJECTION 00:12:29

### HLA MATCHING

- HLA-A, HLA-B, HLA-C, HLA – DQB1, HLA - DRB1 (most important)
- Total score of matching = 10
- In practice HLA-A/B/C & DRB 1 considered predominantly (score = 8)

- In adults, Score 6 out of 8 is suitable for transplantation
- In cord blood, HLA-A/B/DRB 1 → 4 out of 6 should be matched

**DRUGS**

- Steroids
- Mycophenolate mofetil (MMF)
- Tacrolimus
- IV Ig
- Plasmapheresis
- Acute cellular rejection has the best response to drugs
- S/E of Drugs
  - ↑ Risk of opportunistic infections (CMV, EBV, Polyoma virus, HPV)
    - → CMV: nephritis, ocular complications
    - → EBV: Post transplant B-cell lymphoma
    - → HPV: ↑ squamous cell cancer
  - ↑ Cancers

**NATURE**

- HLA matching is important for kidney transplantation
- Transplantation of heart, lungs and liver: HLA matching is not required as certain other factors are more important such as
  - Time of organ harvestation from donor
  - Anatomical size of the organ

## GRAFT VERSUS HOST DISEASE

00:20:32

- Cause
  - Immuno-compromised host
  - Immuno-competent Graft
- GVHD is seen in
  - HSCT (Hematopoietic stem cells transplantation) is the MC reason for graft vs host disease
  - Liver transplantation
  - Un-irradiated Blood Transfusion

| | Skin | Liver | Intestine |
|---|---|---|---|
| **Acute GVHD (<100 days)** | Rash | Jaundice | Bloody diarrhea |
| **Chronic GVHD (>100 days)** | Fibrosis | Cholestatic jaundice | Esophageal stricture |
| | Thymic involution, ↓ lymphocytes in LN | | |

**T-Cells**

- T-cells are responsible for causing GVHD
- T-cells has also beneficial role
  - ↓ EBV infected B-cells
  - ↓ Leukemia cells
  - Engraftment of transplanted HSC

### Previous Year's Questions

**Cell responsible for "Graft Versus Host Disease" is.** (JIPMER 2017)

A. Donor T-cell
B. Host T-cell
C. Donor B-cell
D. Host B-cell

**HSCT Transplantation**

- MC cause of GVHD
- Immunodeficiency: MC complication of HSCT
  - Cause of death: CMV Pneumonitis
- GVHD Can be reduced by Autologous BMT/HSCT

# 23 IMMUNODEFICIENCY DISORDERS

- Primary → genetic defect, early presentation
  - Leukocyte disorders → LAD I/II, CHS, CGD, MPO deficiency
  - ↓↓ complement proteins → C2
  - Lymphocytes → B/T-Cells
- Secondary → acquired
  - PEM
  - Infections (HIV)
  - H/O of splenectomy
  - Immunosuppressive drugs

## DI-GEORGE SYNDROME

00:04:32

- T-Cell defect
- Associated with 22q11 deletion → TBX1 gene → ↓↓ 3/4th pharyngeal pouch → ↓ PTH
- 3/4th pharyngeal pouch are associated with development of thymus gland, ultimobranchial body, parathyroid gland.
- Manifestations
  - Congenital cardiac defect
  - Abnormal facies
  - T-Cells ↓
  - Cleft lip/palate
  - Hypocalcemia
  - 22q11 deletion
- Aka Velo-cardial facial syndrome

## BRUTON'S DISEASE

00:07:44

- B-Cell malfunction
- Associated with B-Cell Tyrosine Kinase defect
- Boys (male >> female)

Precursor B-Cell
↓ BTK
Immature B-cells
↓
B-Cells
↓
Plasma cells
↓
↓ Ab

- X-Linked hypogammaglobulinemia

### Clinical features

- Presents around 6 months (mother's antibodies are present in circulation for up to 6 months)
- ↓↓ Ig → Infection (strep pneumonia/H.Influenza)
- T-Cells → normal
- Underdevelopment of lymphoid areas (splenic follicles, LN, Tonsils)
- ↓ IgA → ↑ enterovirus/giardia
- Fulminant infections are caused by
  - Poliovirus: Paralytic poliomyelitis
  - Echovirus: Encephalitis

## COMMON VARIABLE IMMUNODEFICIENCY DISEASE

- Involvement of B-Cells >> T-Cells
- Precursor B-Cell → Immature B-Cell → B-Cell (BAFF receptor) → PC
- Underactivity of BAFF receptor/ICOS/TACI
- Problem at the level of plasma cell formation → ↓ Ig → sino-pulmonary infection/bacterial/viral/giardia infections
- Difference from Bruton's disease
  - B-Cells → normal in number
  - Hyperplasia of B-Cell location (LN/Spleen)
  - Male = Female
  - Late presentation
- ↑ Risk of autoimmune disorders → RA
- ↑ Risk of cancer → stomach cancer/lymphoid cancer

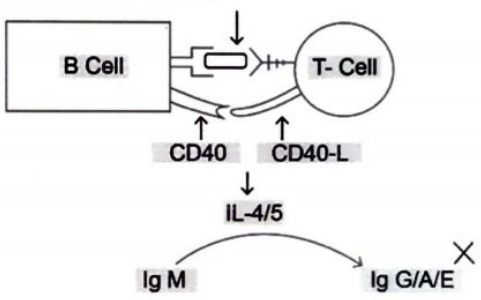
## IgA DEFICIENCY

00:21:43

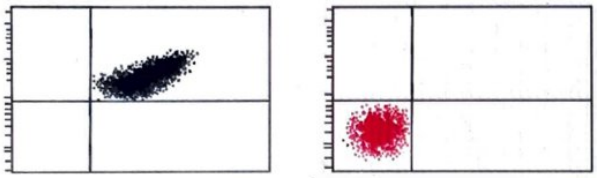
- MC immunodeficiency disorder
- IgA → ↑ Infections (lungs/GIT)
- Also associated with IgG2/IgG4 deficiency
- Presentation
  - ↑ Allergy
  - H/O blood transfusion → IgA → Anaphylaxis
  - ↑ Autoimmune disorders (SLE/RA)

## HYPER IgM SYNDROME

- Involvement of B-Cells & T-Cell → improper interaction
- Associated with X-Linked inheritance → CD40 Ligand
- AR → B-Cell(CD40/AID)



- ↑↑↑ IgM
  - Anemia
  - Thrombocytopenia
  - Leukopenia
- ↓ IgG → ↑ Infections/P.Jioverci infections
- B-Cells & T-Cell → Normal



Normal (CD 40)

## Previous Year's Questions

Q. Which of the following diseased in diagnosed with help of the flowcytometry pattern?
(AIIMS Nov 2019)

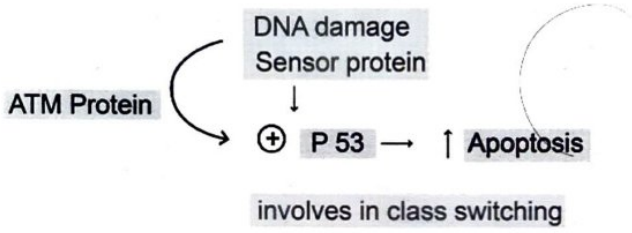
A. Bruton disease
B. Bare lymphocyte syndrome
C. Hyper IgM syndrome
D. Severe combined immunodeficiency disease

### HYPER IgE SYNDROME
- Aka Job Syndrome
- Characterized by ↑ IgE levels
- ↓↓ $TH_{17}$ → cold abscess (staph aureus)
- AD inheritance

### X-LINKED LYMPHOPROLIFERATIVE SYNDROME
- SLAM/SLAM associated protein → required for normal function of B/T/NK Cells
- Defect in SLAM/SLAM associated protein → ↑ risk of EBV → Fulminant Infectious mononucleosis
- Associated with ↑ risk of B-Cell cancers

### ATAXIA TELANGECTASIA

00:38:04




- Defect in ATM gene which is present at Chromosome 11 → functions as DNA Damage sensor

**Clinical features**
- Ataxia
- Dilated tortuous BV
- Neurological deficits
- ↓ Immunity (↓IgA/↓ $IgG_2$)
- ↑ Tumors

### WISKOTT ALDRICH SYNDROME
- X-Linked inheritance
- Defect in WASP protein → Xp11 defect
- Triad of
  - Recurrent infections
  - ↓ Platelets (Small sized platelets)
  - Eczema
- Ab changes
  - ↓↓ IgM
  - ↑↑ IgE
  - IgA → Normal / ↑

### SEVERE COMBINED IMMUNO DEFFICIENCY DISEASE (SCID)
- ↓↓ B/T-Cells

| X linked SCID | AR SCID |
|---|---|
| • Defect in Cytokine receptor → γ chain<br>• IL-7 → B/T cells<br>• IL-15 → NK cells<br>• IL-2/4/9/11<br>• ↓ CMI<br>• B-Cell → ↓ Ig | • ADA deficiency → ↑ deoxyadenosine → damage to B & T cells<br>• RAg<br>• JAK-3 → ↓↓ γ chain |

**Clinical features**
- ↑ Bacterial/protozoal Infections
- ↑ Viral/Fungal infections

**Treatment**
- Hematopoietic stem cell transplantation

# 24 AMYLOIDOSIS

- Group of conditions associated with Inflammation /Extra-cellular Fibrillary protein deposition
- Amyloid depositions → pressure atrophy in organs
- It is made if
  - Fibrillary protein (95%)
  - 'P' Protein (5%)

## GENERALISED / SYSTEMIC AMYLOIDOSIS

### PRIMARY AMYLOIDOSIS

- MC clinical association → plasma cell dyscrasia
- Also associated with multiple myeloma
- Abnormal plasma cell → Abnormal Ig (light chain > heavy chain)
- In plasma cell dyscrasia → overproduction of λ subtype of light chain
- Chemical nature of amyloid: AL (λ)

### SECONDARY AMYLOIDOSIS (REACTIVE)

- It is associated with
  - Chronic inflammation (RA/TB/IBD)
  - Cancers (RCC/Hodgkin's lymphoma)
- In both these conditions → ↑ IL-6/1 → Liver → SAA → migrates from serum into tissues
- Chemical nature of amyloid: AA

### HEMODIALYSIS ASSOCIATED AMYLOIDOSIS

- Associated with chronic renal failure
- Earlier used hemodialysis machines contain semi-permeable membrane → unable to filter $\beta_2$ microglobulin → amyloid
- Chemical nature of amyloid: $A\beta_2m$
- Has special affinity to joints (wrist, knee)

## LOCALIZED AMYLOIDOSIS

00:09:04

### Senile Cerebral Amyloidosis

Amyloid Precursor Protein $\xrightarrow{\beta/\gamma \text{ secretase}}$ Aβ-plaque

Aβ-plaque

↓

Damage to Meynert nucleus

↓

Interferes with neurotransmitter Ach

↓

Memory loss

- Clinically known as Alzheimer's disease
- Chemical nature of Amyloid: Aβ (APP)
- Gene for APP located on chromosome 21
- Down syndrome (Trisomy 21) → ↑ APP → ↑ Aβ → development of neuronal degeneration at early age

### Medullary Thyroid Cancer

- Arises from Para Follicular cells → secretes calcitonin → excess of calcitonin deposits as amyloid
- Chemical nature of amyloid: ACal
- Calcitonin levels can be used as a diagnostic marker

### Type 2 DM

- Involvement of pancreatic β-cells
- Deposition of Islet Associated Pancreatic Peptide (IAPP) → ↓ insulin
- Chemical nature of Amyloid: AIAPP

### Isolated Atrial Amyloidosis

- Stretching of atrial wall → ANF (Atrial Natriuretic Factor → amyloid
- Chemical nature of Amyloid: AANF

## HEREDITARY AMYLOIDOSIS

00:15:33

### Familial Mediterranean Fever

- AD condition
- Characterized by inflammation along with the release of IL-1 → Liver → Pyrin
- Pyrin is pyrexia causing protein & involvement of serosal surface (serositis/pleuritis)
- Inflammation → ↑SAA protein
- Chemical nature of amyloid: AA (Pyrin)
- Good response to NSAIDs & colchicine is seen

### Familial Amyloidotic Neuropathies

- TTR responsible for transport of thyroxine & vitamin A derivatives
- Altered TTR protein → interferes with nerve activity
- Chemical nature of Amyloid: ATTR

### Systemic Senile Amyloidosis

- In elderly, deposition of normal TTR in all organs of the body (especially heart) → Systemic Senile Amyloidosis
- Difference from familial amyloidotic polyneuropathy is that it has abnormal TTR deposition
- Chemical nature of Amyloid: ATTR

## ORGANS AFFECTED IN AMYLOIDOSIS

00:19:48

**Cardiac tissue**

- MC associated with 1° amyloidosis
- Amyloid is deposited on Sub-endocardial tissue and interferes with electrical conductivity of heart → arrhythmia (MC clinical manifestation)
- Amyloid deposition between cardiac fibers → cardiac fibers unable to relax → Restrictive Cardiomyopathy
- MC cause of restrictive Cardiomyopathy → Amyloidosis

**Kidney**

- MC & most severely affected organ from amyloidosis
- MC seen with 2° amyloidosis
- Initial Amyloid deposition is seen in Mesangial matrix, followed by progressive involvement of glomerulus
- Renal venules are not affected
- Nephrotic syndrome occurs leading to massive proteinuria

**Liver**

- Presence of hepatomegaly
- 1st part of the liver to be involved is 'Space of Disse' → Ito cell (responsible for vitamin A metabolism)

**Spleen**

- Involvement of Splenic Sinuses/Red Pulp → Lardaceous Spleen
- Involvement of Splenic Follicles/White Pulp → Sago Spleen

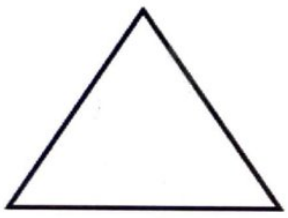
**Skin**

- Amyloid deposition around blood vessel → weak connective tissue → fragile BV → "Pinch purpura"
- Periorbital bleeding → Raccoon eyes
- Subcutaneous tissue is also involved → Abdominal fat aspiration (helps in diagnosis)

**Joints**

- Knee Joint Involved
- Wrist Joint involved → carpal tunnel Syndrome → median nerve affected
- Can be seen after dialysis

Carpal tunnel syndrome



Tenosynovitis Scapulo-Humeral Periarthrtis

**GIT**

- Tongue → Nodules → ↑ tongue size (macroglossia)
- Mucosa involvement → Tissues can be taken Oral/Rectal mucosa
  - Rectal mucosa biopsy is preferred
- Abdominal fat aspiration > rectal mucosa > oral mucosa

### Previous Year's Questions

Q. True/false amyloidosis? (AIIMS May 2019)

A. A beta 2 microglobulin is accumulated in senile amyloidosis.

B. Malignancy is the most common cause of amyloidosis in western counties.

C. Mostly it contains kappa light chains.

D. Apple green under UV light when stained with congo red.

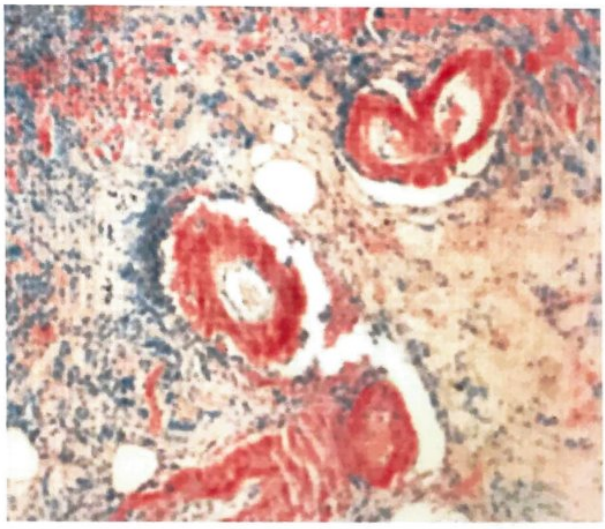
## DIAGNOSIS

00:32:51

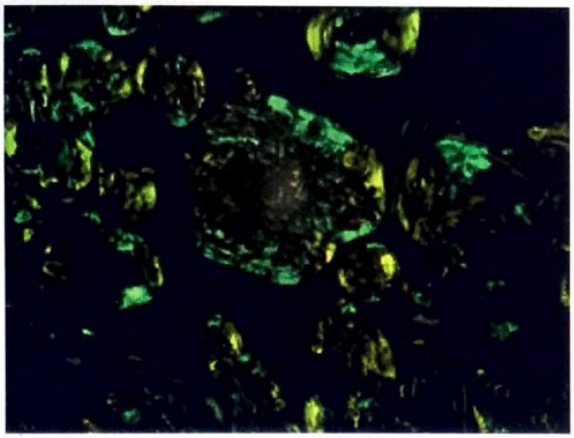
- Localized → biopsy from affected organ
- Abdominal Fat Aspiration → most sensitive test
- Biopsy → Rectal Mucosa

**Staining**

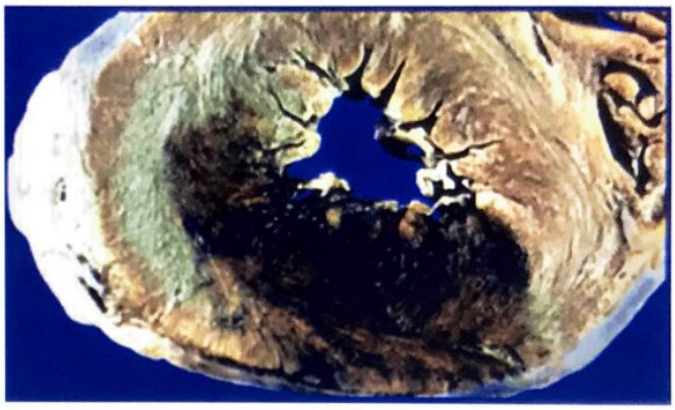
- Congo red
  - Under normal light: Pink red appearance
  - Under polarized light: Apple green birefringence (characteristic)
- PAS ⊕
- Thioflavin T/S → provides immunofluorescence to amyloid protein



Congo red stain



Apple green birefringence



Gross specimen

- Scintigraphy → done with the help of radiolabeled SAP

- Electron Microscopy → Non-branching Fibrils are observed
- Spectroscopy/Crystallography → β-plated structure
- Organ → Shows waxy appearance & ↑ size of organ
  - Iodine → Mahogany Brown appearance → washed with dilute $H_2SO_4$ → Blue color

# CLINICAL QUESTIONS

1. A 59-year-old female comes to her primary care physician with chief complaints of dyspnea on working and intractable coughing. She reported no fevers, chills, night sweats, or hemoptysis, however, did relate an approximate 20-pound weight loss over 6 weeks prior to presentation. The patient's general exam was within normal limits except for multiple, scattered erythematous to violaceous and tender skin nodules on her bilateral extremities. Her lungs were clear to auscultation and she had no palpable adenopathy. Punch biopsy of a right pretibial skin lesion showed a well-formed sarcoid type of granuloma with septal thickening and fibrosis True regarding granulomas seen here are all except-

**A. Large central area of necrosis is common**

B. Compact non cosseting granulomas

C. Giant cells are seen

D. Schaumann bodies and asteroid bodies may be seen

Solution

- Granulomas found in sarcoidosis are non-caveating, compact, with tightly clustered collection of epithelioid histiocytes
- They contain the following:
  - Asteroid Bodies
  - Schaumann bodies and
  - Birefringent crystals

Reference

Robbins, Pathologic Basis of Disease, 10e, p. 696-698

# LEARNING OBJECTIVES

## Unit 5 GENETICS

- **Introduction to Genetics**
  - Chromosomal Disorders
  - Karyotyping
  - Structural Defects
- **Single Gene Disorders**
  - Autosomal Dominant Disorders
  - Autosomal Recessive Disorders
  - Y-Linked Disorders
  - X-Linked Recessive Disorders
  - X-Linked Dominant Disorders
- **Non-Classical Inheritance Disorders**
  - Genomic Imprinting
  - Prader Willi Syndrome
  - Angelman Syndrome
  - Mitochondrial Inheritance
  - Triple Repeat Mutations
  - Fragile X Syndrome
  - Sherman's Paradox
- **Specific Cytogenic Disorders**
  - Down Syndrome
  - Screening
  - Turner Syndrome
  - Noonan Syndrome
  - Klinefelter Syndrome
  - Lyon's Hypothesis