HANDWRITTEN NOTES

DAMS

PATHOLOGY

CRISP, CONCISE, CONCEPTUAL

Integrated Edition

Student first @DAMS

DAMS Publications

Published by Delhi Academy of Medical Sciences (P) Ltd.

HEAD OFFICE
Delhi Academy of Medical Sciences (P.) Ltd.
House No.: 3, Green Park,
New Delhi-110 016
Phone : 011-4009 4009, 9899664533
http://www.damsdelhi.com
Email: info@damsdelhi.com

ISBN : 978-93-89309-74-4

First Published 1999, Delhi Academy of Medical Sciences

Typeset by Delhi Academy of Medical Sciences Pvt. Ltd., New Delhi (India).

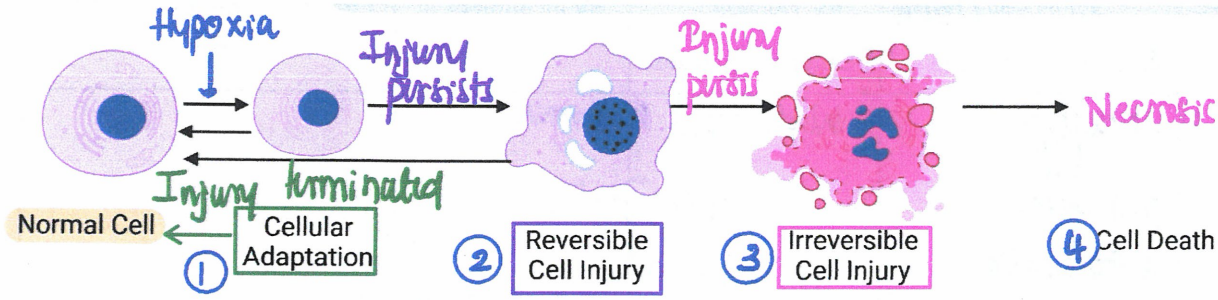
HOW TO MAKE BEST USE OF NOTES?

A Message by Mentor Duo Specially for you,

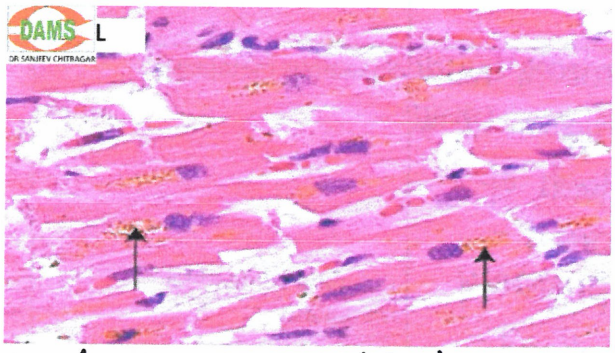
- *Read the notes thoroughly, they are absolutely concise, crisp & conceptual and hence it is best advised not to add a lot of extra information to them as that will dilute the quality.*
- *Images have been provided alongside to aid in better understanding and also help you solve image-based questions, these images have been specially picked by the faculty so have a high probability of being asked in exams.*
- *Notes are handwritten in a way to help make them easier to retain, a lot of tables, graphs and algorithms have been used to simplify the learning.*
- *While reading notes try and use the CFAQ technique —*
    A. *Use the C to denote concept part in the notes and ensure you are clear with this part in the first go if not then it's advisable to listen to this part of the video from your course.*
    B. *Use the F To denotes facts in your notes, it is okay if you can't remember them in first go but will need repeat reading. But these facts are important for exams as they could be integrated to clinical questions.*
    C. *Use A to denote applied parts, this is how concepts and facts are asked indirectly in exams. This will also help you develop MCQ solving skill.*
    D. *Use Q to denote areas where faculty has said it's a direct question or a PYQ or a potential question.*
- *This technique will help you summarize your notes In way that your second reading will become easy and faster.*
- *Active space has been provided with these notes to make your own annotations alongside and this will help you maintain one single notebook for one subject.*
- *Try and solve MCQs with every topic from DQB. Your goal should be to start with at least 30 MCQs every day and then increase to at least 50 MCQs every day. Also, when you do a topic wrong write it alongside the notes that this topic needs to be read again but mark only the specific area that you have done wrong not the whole topic.*
- *After the topic is covered then in the active space try and summarize the topic in the form of mind map. This will help in active recall and make your revision easier.*

Best Wishes & Happy Learning!!!!!

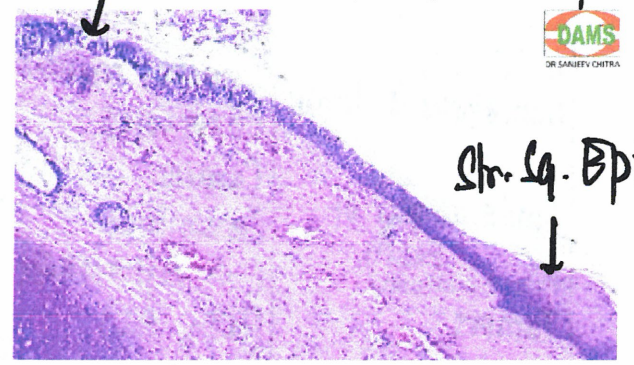
1. CELLULAR RESPONSES TO INJURY



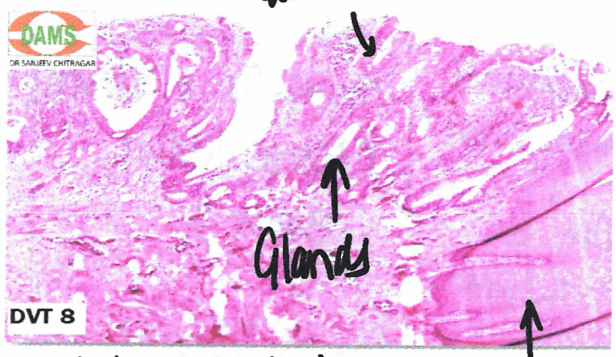
Irreversible Injury times:
Neurons: _____minutes
Myocardium: _____ minutes



Lipofuchsin (Brown color)
Spl. Stain- Sudan black

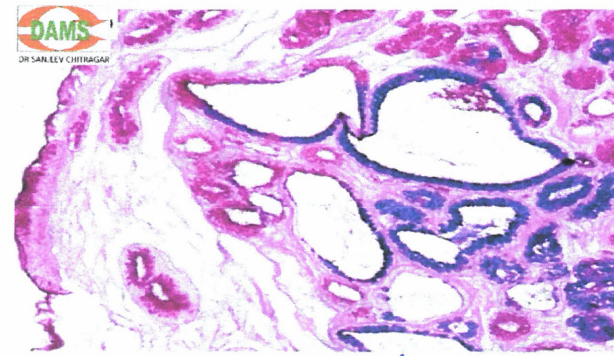


Δ= Sq. metaplasia



Intestinal metaplasia
Str. Sq. Epi

Alcian Blue – PAS

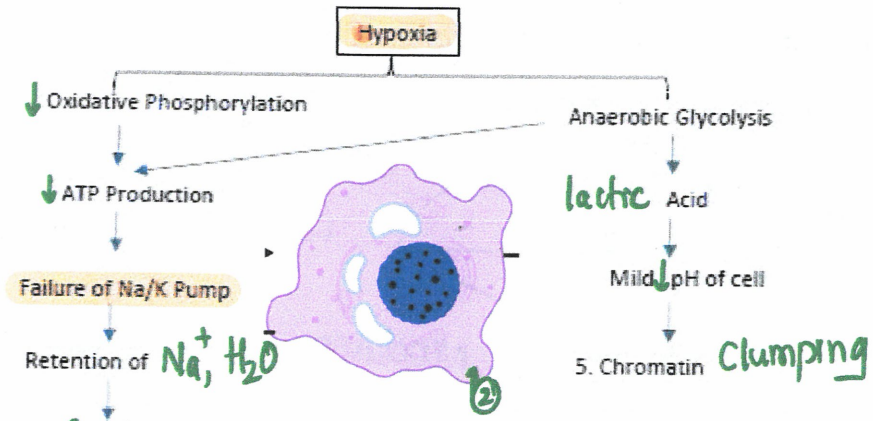


Alcian Blue- intestinal mucin
PAS- Gastric mucin

Cellular Adaptations

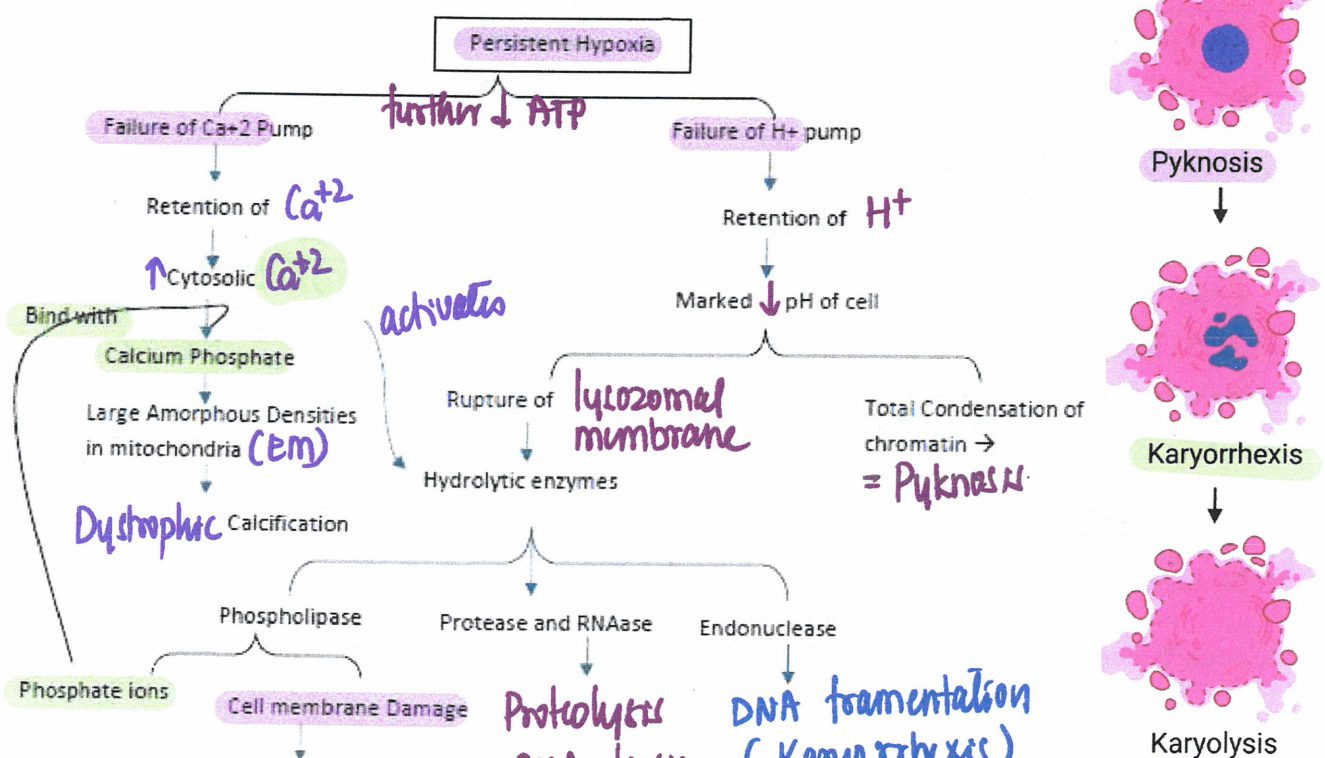
	Atrophy	Hypertrophy	Hyperplasia	Metaplasia
Gross	↓Organ Size	↑Organ Size	↑Organ Size	
Micro-scopy	↓ cell Size / Count ↓ Cellular Organelle	↑ cell Size ↑Cellular Organelle	↑Cell number	Change of one cell to another cell
Mechanism	1) Ubiquitin → ⊕ proteolysis → ↓ organelle 2) Autophagic Vacuole fuses → lysozome → hydrolysis of organelle fails to fuse → persist in cell Eg: Lipofuschin	↑ Work load / ↑ Stimulus → ↑ Growth factor → ↑ organelle → ↑ cell size	↳ DNA Replication → ↑ cell count	Recurrent injury → Reprogramming of stem cell → New cell production (Resistant to injury) Named after new cell
Examples	Disuse atrophy: immobilised limbs Ischemic atrophy: Senile atrophy of Brain Pressure atrophy: Tumors Denervation atrophy: Hemiplegia, Nutritional atrophy: PEM Brown atrophy (Lipo-fuschin) myocardium in old age Endocrine atrophy: Post menopausal atrophy of uterus, Breast, ovaries	Skeletal muscle (Exercise) Cardiac Concentric (↑ Afterload) (HTn, AS) Eccentric ↑ preload (AR) Smooth muscle Uterus - puberty, pregnancy Glands of Breast - Lactation, pregnancy	Smooth muscle Pregnant uterus Glands of breast - pregnancy Erythroid hyperplasia in high altitude BPH Endometrial hyperplasia → Can be premalignant	Squamous metaplasia: Resp tract - Smoking, Vitamin A def; Endocervix - Chr. Cervicitis Columnar/ intestinal metaplasia: Esophagus - Chr. acid Reflux Oncocytic metaplasia (Thyroid) (Hurthle cell) - Hashimoto Mesenchymal metaplasia: myositis ossificans (Horse Riders, Boxer) → Pre malignant

Reversible Cell Injury



1. Cell Swelling (Earliest morphological feature of cell injury)
2. Membrane Blebs
3. Organelle Swelling → Dilation of Endoplasmic reticulum → pinnacles Vacuoles - Hydropic Change
4. Detachment of Ribosomes (Seen on EM)

Irreversible Cell Injury



Free Radical Injury

Most potent ROS = $OH^{\cdot}$ (Hydroxyl anion)

Highly Oxidizing agent with single unpaired electron in outer most orbit.

These are derived from **Oxygen** thus known as Reactive O_2 Species (ROS)

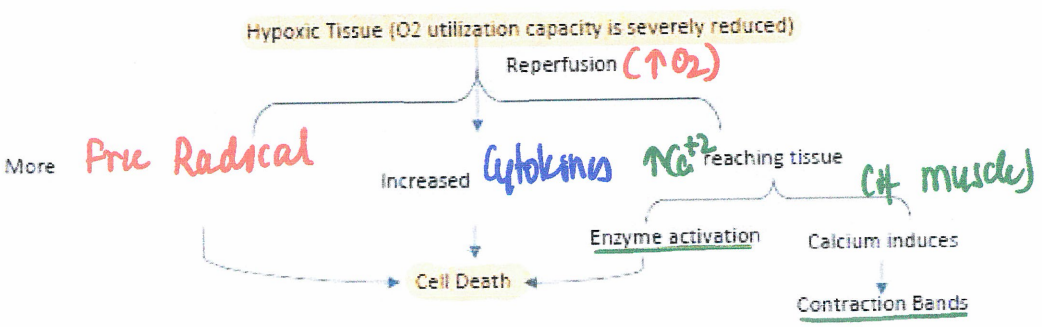
They can Oxidize

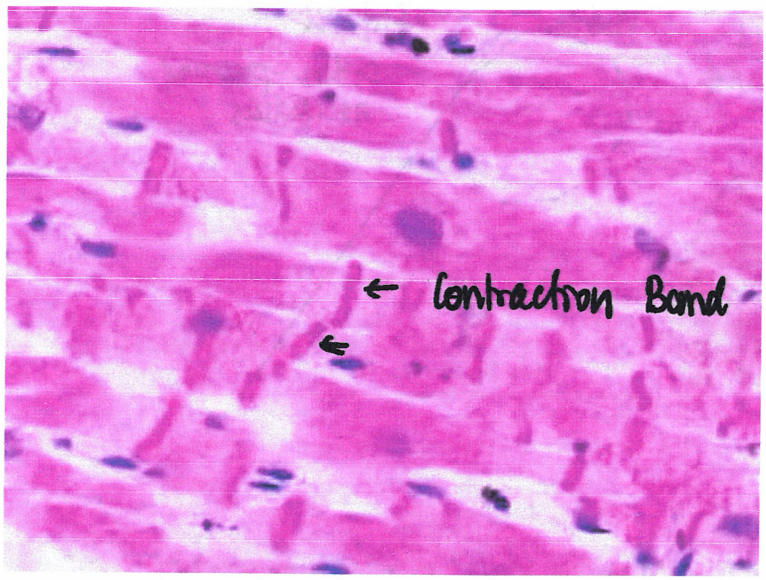
1. Lipids → most sensitive → cm Damage → Cell Death
2. Proteins → mis folded protein → Cell Death
3. DNA → mutation in DNA → Neoplasm

Sources of ROS	Scavengers of ROS
1. Radiation (Ionising, UV Rays) $H_2O \rightarrow H_2O_2$	1 Antioxidants Vitamin A, C, E Minerals Se, Zn, Mo
2 Fenton Reaction $Fe^{+2} \rightarrow Fe^{+3} OH^{-} \rightarrow Fe^{+2} OH^{\cdot}$	2. Ferritin, Transferrin Ceruloplasmin
3. Chemical Eg: CCl_4, Drugs	3 Enzymes $O_2^{\cdot} \rightarrow H_2O_2$ Superoxide dismutase (SOD)
4. Incomplete Reduction of O_2 $O_2 \rightarrow O_2^{\cdot}$ (Superoxide anion)	Glutathione peroxidase $OH^{\cdot} \rightarrow H_2O_2$
5. Bactericidal enzymes NADPH Oxidase, Myeloperoxidase	Catalase (Peroxisomal $H_2O_2 \rightarrow H_2O$ Scavenger)

Role of ROS in Health and Disease

1. **Premature Ageing** - Skin of face ages faster
2. Diseases - Hemochromatosis, Wilson Disease
3. Reperfusion Injury: Injury occurring after Reperfusion of hypoxic tissue





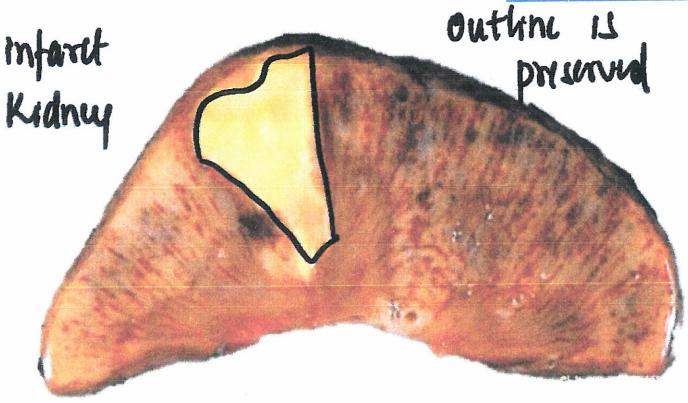
Contraction Band Necrosis

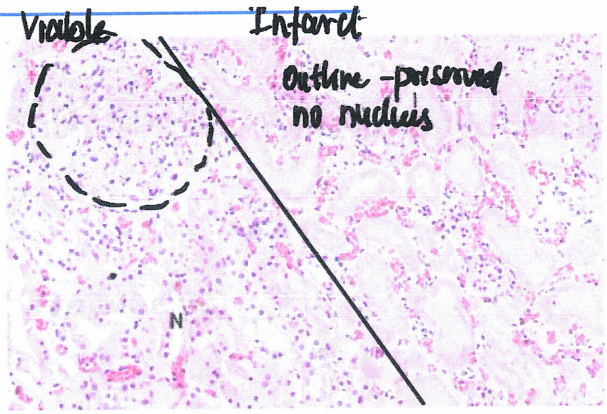
Cell Death

Necrosis: Sequalae of irreversible cell injury, MC type of cell death

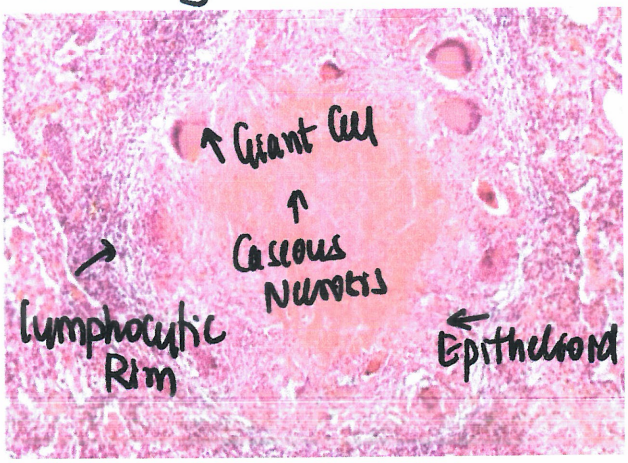
Always Pathological, Associated with inflammation, Passive (ATP not Reqd)

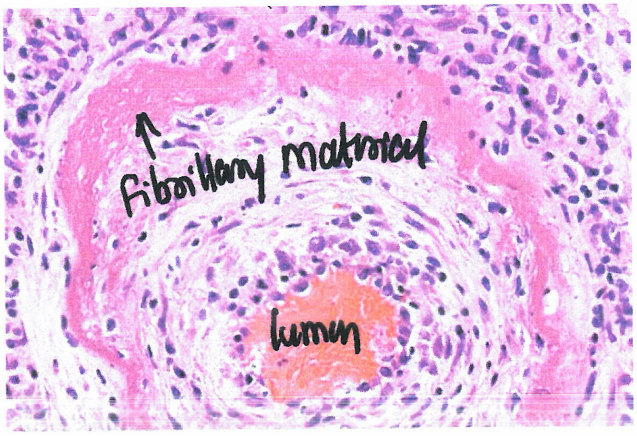
Type of Necrosis	Mechanism	Morphology	Other features/ Examples
Coagulative Necrosis	Hypoxia→death	Cellular & Organ outlines are preserved Kanyolysis	All Solid organ infarct Except Brain, Dry Gangrene, Zenkers Degeneration, Burns
Liquefactive Necrosis	Liquifaction of Nectotic tissue usually due to enzymatic digestion	Outlines are lost	Pus/Abscess, fungal infection, Wet gangrene Brain Infarct
Caseous Necrosis	Cytotoxic cell Death (Type IV HSR)	Cheese like (Fatty) material deposited	TB, histoplasma Nocardia
Fat Necrosis	Trauma Enzymatic (Pancreatitis) →	pseudocyst ↑ FN of omental fat	Subcutaneous, Breast Omental fat
Fibrinoid Necrosis	Fibrin/fibrin like material is deposited in necrotic tissue		Rheumatic Carditis malignant hypertension Vasculitis - lupus, PAN, M-PA, Kawasaki





Necrotising Granuloma



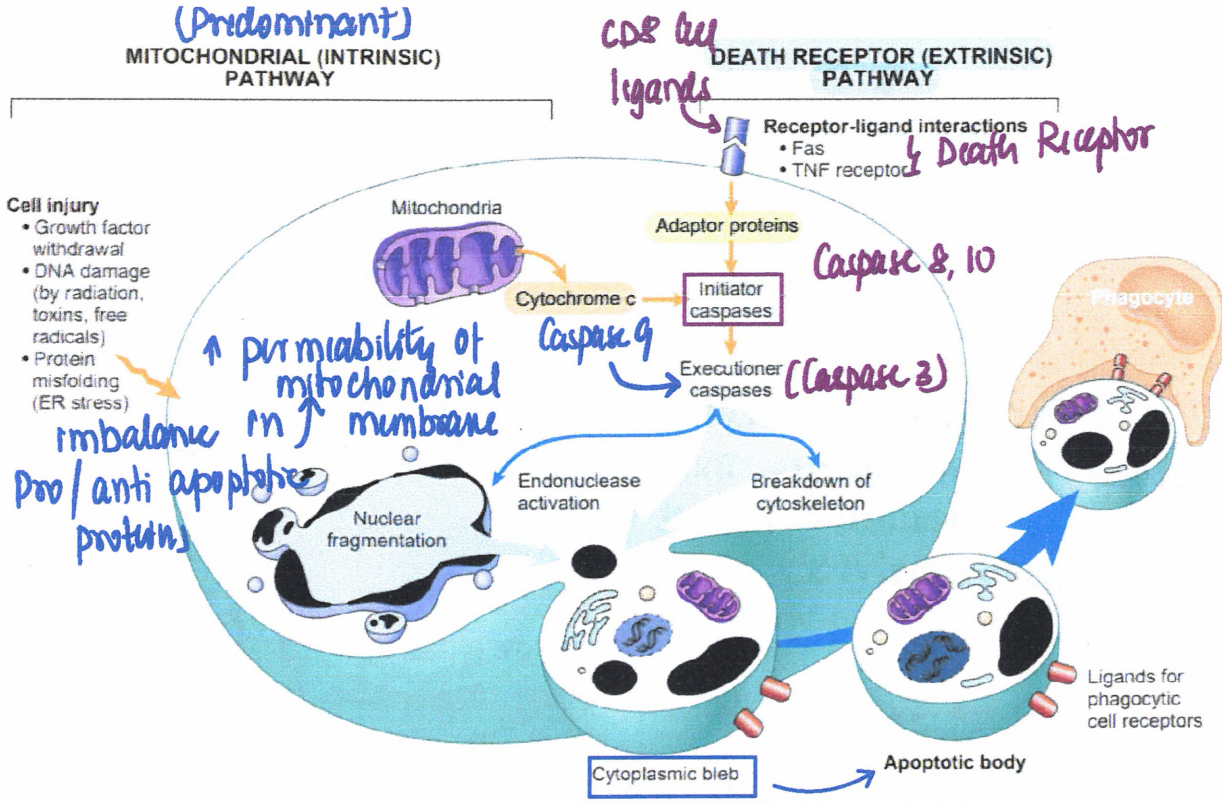


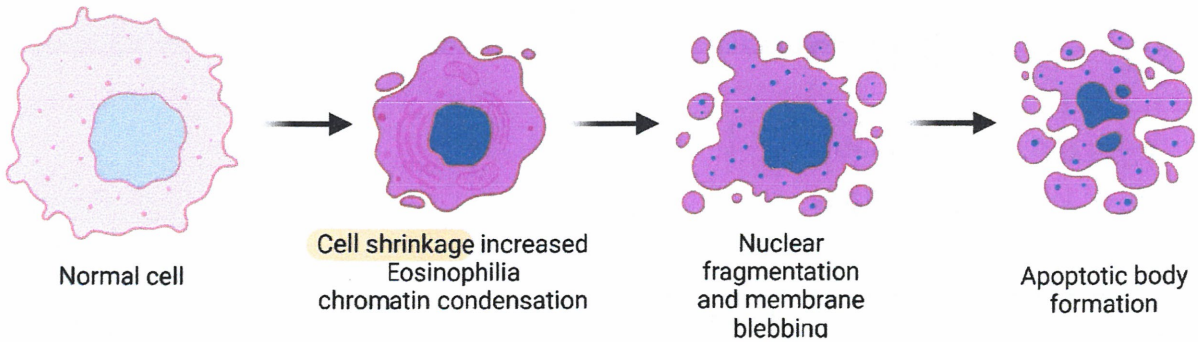
Active (ATP Req'd), no Infl, **Apoptosis** - Aka Programmed Cell Death

Physiological	Pathological
1) Embryogenesis 2) Thymic involution 3) Death of Self Reactive lymphocytes 4) " " Cells after fn is served 5) " " DNA Damaged Cell	1) Chemo & Radio therapy induced Death 2) Death of viral infected cell 3) Steroid induced death of B cell

Mechanism of apoptosis

Antiapoptotic (BH1-4) Proteins	Bcl-2, Mcl-1, Bcl-XL
Proapoptotic (BH1-3) proteins	BAK, BAX
Regulated Apoptosis initiators (BH3 only)	BAD, BID, BIM, NOXA, PUMA





Necroptosis

Exhibits characteristics of both necrosis and apoptosis → Trigger is Genetically programmed

↓
morphology, mechanism

Mechanism → TNFα ⊕ → TNFα Receptor (Death Receptor) → Necrosome (RIP-I & III)

↓ ATP ↑ ROS

↓

Necrosis

Aka 1) programmed necrosis
2) Caspase independent apoptosis

Eg: Steatohepatitis, pancreatitis, Reperfusion injury, CMV infection

Pyroptosis

Bacterial infection → Inflammasome → Caspase I → Caspase II
↓
activates IL-1 → Cell Death
↓
Inflammation

Ferroptosis

↑ Fe or ↓ Glutathione peroxidase → ↑ ROS → Cell Death
morphology: CM Damage, mitochondria shrinkage, loss of Cisterns
Nucleus - normal
Eg: Hemochromatosis

Autophagy - Cell eating its own organelle

Starvation → Cell eats up its own organelle (Senile, toxic)
↓
Sirtuins (NAD dependent histone deacetylase)
↓
after DNA Expression
↓
↑ Insulin Sensitivity ↓ Cancer
↓ Cardiac hypertrophy

Detoxification → ↑ longevity of Cell

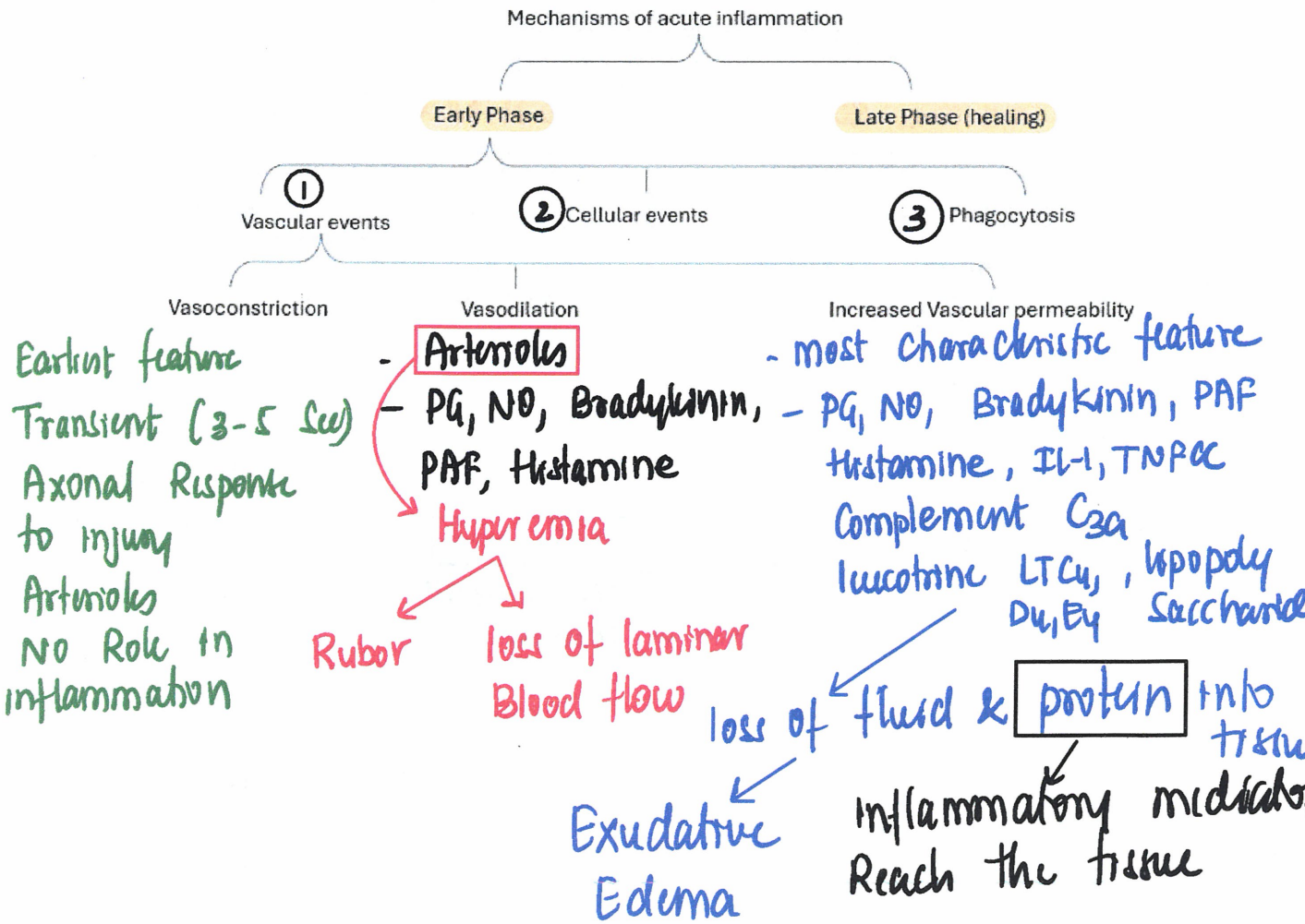
Calcification

	Dystrophic calcification	Metastatic calcification
Mechanism →	Ca + phosphate (CM Damage)	↑ Serum Ca → deposited in healthy tissue
Sites	Any where (but Dead tissues)	lungs, Kidney, stomach
Serum Calcium	Normal	↑↑
Examples	TB, Atherosclerosis Psammoma bodies	Renal stones lytic bone lesions hypervitaminosis D Sarcoidosis

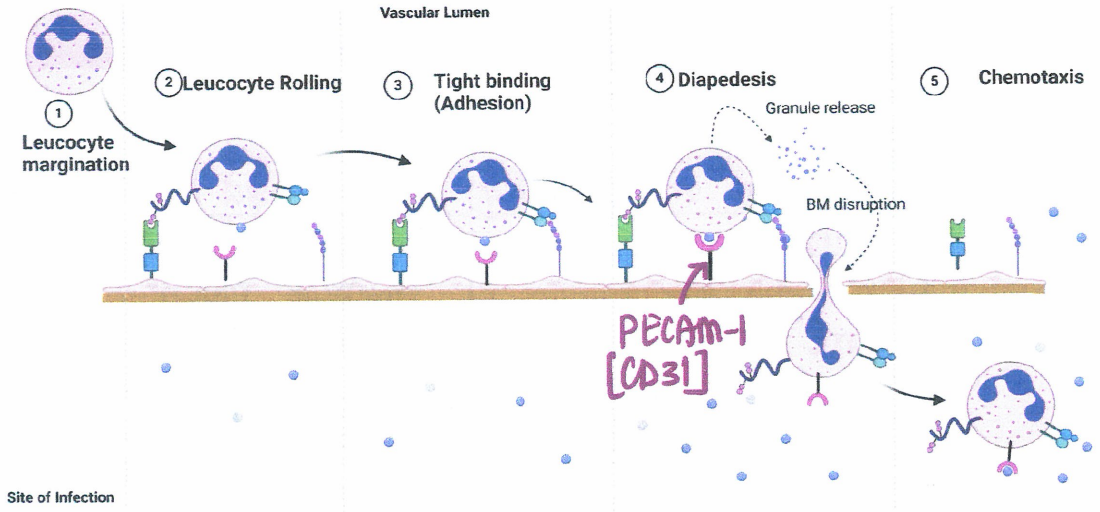
2. INFLAMMATION REPAIR

Feature	Acute inflammation	Chronic Inflammation
Onset & Duration	Early, Short lived (Two days)	late, prolonged (months-years)
Principal cells	Neutrophils	macrophage, lymphocyte
Signs	Rubor (Redness) Calor (↑ temp) Dolor (pain) Tumor (Swelling) Functio lesa (loss of fn) (Transient loss of fn)	Shrunken organ Induration permanant tissue destruction (loss of fn) Weight loss
Repair/Healing	Regeneration	Fibrosis

Mechanisms of acute inflammation



2. Cellular Events



Cellular Event	features	Mediators
Margination	movement of leucocyte from Centre → periphery	An Vasodilator
Rolling	Weak binding to endothelium	P-Selectin (plt), L-Selectin (leucocyte) E-Selectin (endo)
Adhesion	Tight binding to endothelium	Integrins
Transmigration (Diapedesis)	movement across the blood vessel [venules]	CD 31 binding → neutrophil activation → Degranulation → Endo injury
Chemotaxis (Tissue migration)	movement in tissue → Chemo - Chemical, Taxi - movement	Chemotaxin Eg! IL-1, TNFα, LT B4, C5a, LPS; Chemokine (Cell Specific) IL-8 → Neutrophils, Eotaxin - Eo, mcp, mip → macrophage, monocyte

Phagocytosis

Done by Various Receptors on Neutrophils / macro

1. Pathogen Recognition -

TLR, NLR, RLR, CLR

↑ Can Recognise molecular patterns

Pathogens

PAMP - Pathogen associated molecular pattern

Necrotic cell

DAMP - Damage associated molecular pattern

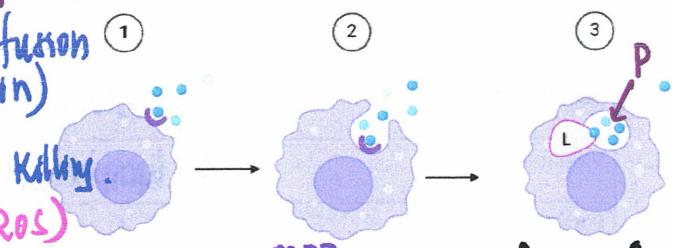
2. Engulfment → formation of phagosome

3. Intracellular killing phago-lysosome fusion (Lyst protein)

1) O_2 indipendent: Cathepsin, Defensins, Cathecidins

Enzymatic Killing

O_2 Dipendent (ROS)



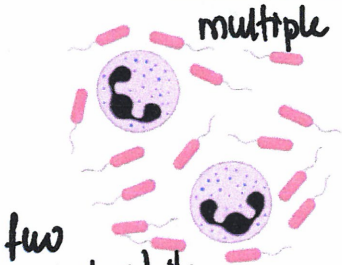
$O_2 \xrightarrow{\text{NADPH Oxidase}} O_2^{\cdot} \xrightarrow{SOD} H_2O_2 + Cl \xrightarrow{MPO} OHCl^{\cdot} \rightarrow OH^{\cdot} \; OCl^{-}$

MPO-halide System = most potent bactericidal

Local Effects of Inflammation

1. Dolor (pain) PGE_2, Bradykinin ⊕→ free nerve endings → pain

2. Neutrophil Extracellular traps (NET)



two Neutrophils

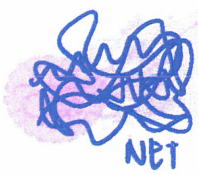
multiple Bacteria → inflammatory mediator ⊕↓

Arginine Deaminase (in neutrophils)

Arginine → Citrulline

= Chromatin Decondinsation → Kills the neutrophils

Chromatin forms a mesh = NET



NET

In Severe inflammation → Excessive NET

Excessive tissue damage (including Vessel Damage)

↑ predisposition to Sepsis, ↑ DIC

Function of NET 1) To trap Organism → limits infections (↓ Sepsis)

Composition of NET

1) DNA → Can trigger Auto Ab → ANA, ANCA
2) Cytokines
3) Enzymes → tissue destruction

Systemic effects of inflammation

1. Fever: IL-1, TNFα ⊕ | BBB → Hypothalamus → PGE_2 → Vasodilation (Affects thermoregulator)

Endogenic Pyrogens	IL-1, TNFα, PGE_2 (central)
Exogenic Pyrogens	Lipopolysaccharides

2. Leukocytosis: During inflammation → ↑ WBC production → ↑ TLC

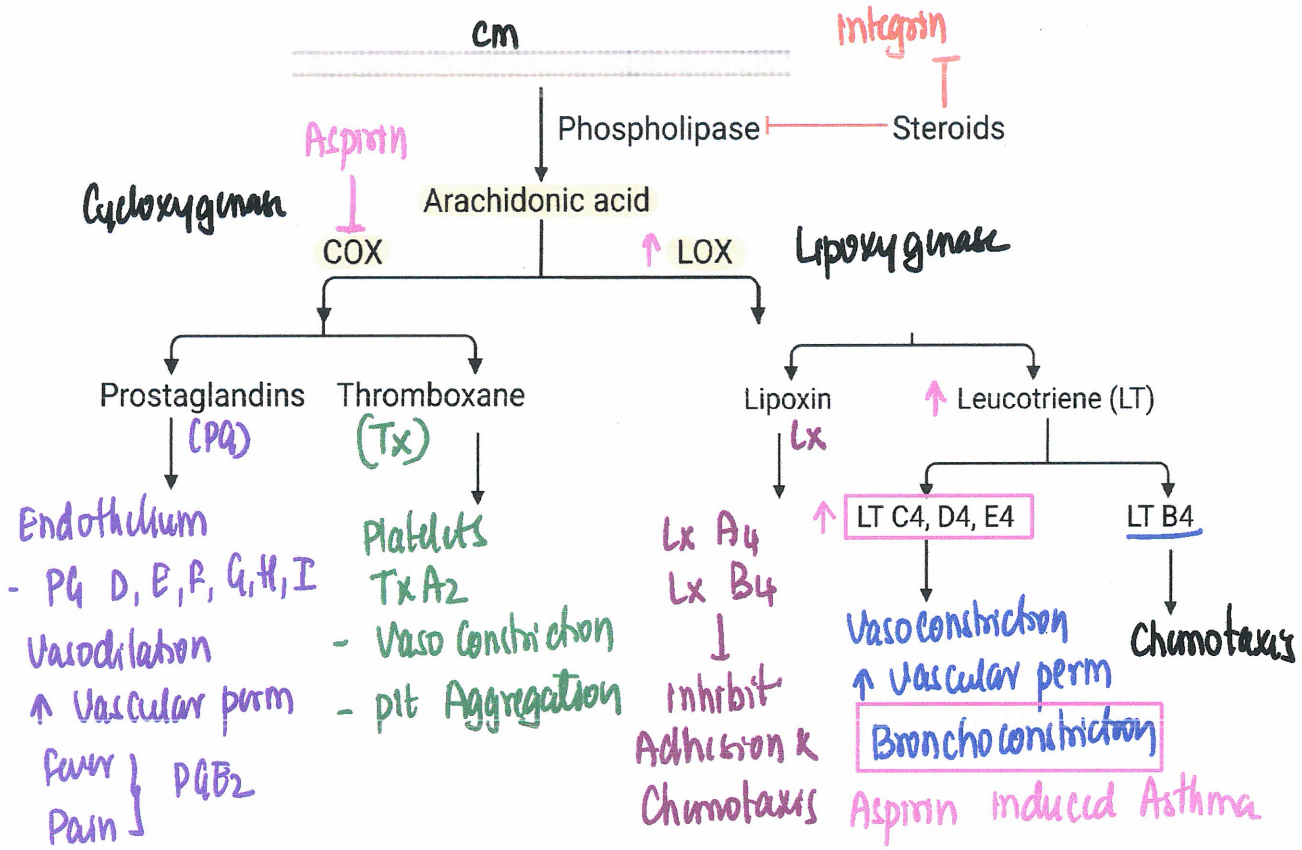
Bacterial infection	↑ Neutrophils
Viral infection	↑ lymphocytes
Parasitic infection	↑ Eosinophils

3. Acute phase reaction: During inflammation certain protein increase or decrease in blood

Positive Acute phase reactants (↑↑)	Negative Acute phase reactants (↓↓)
Globulin, α_1AT, Ferritin, Hepcidin, Haptoglobin, VWF, F-8, F-B, Fibrinogen D-Dimer CRP,	Albumin, transthyretin, transferrin transcortin Retinol binding protein

Functions of Acute Phase reactants: 1) To enhance organism clearance
2) To minimise tissue damage

Arachidonic acid metabolites

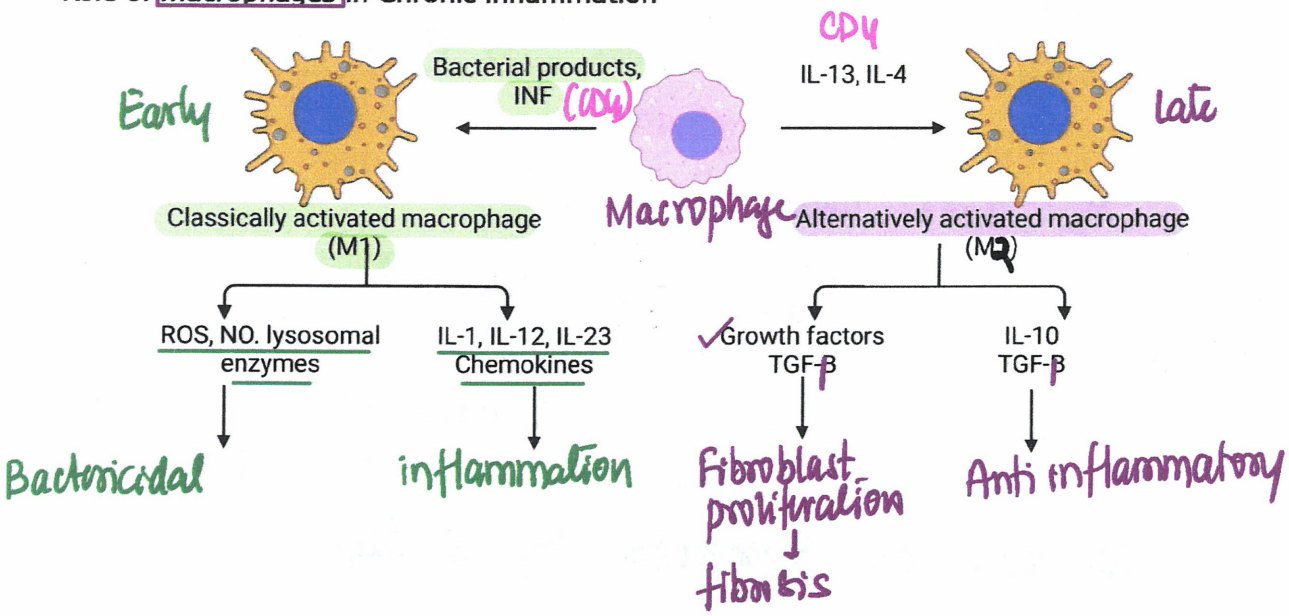


Chronic inflammation

Causes:

1. Persistent infections
2. Hypersensitivity/ Autoimmune Disease
3. Prolonged exposure to toxins

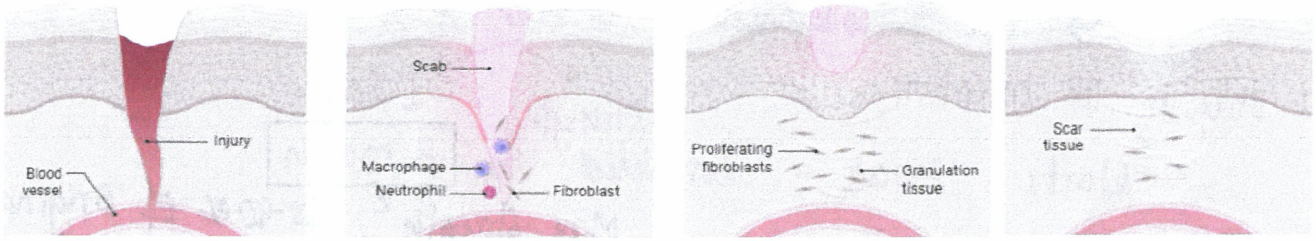
Role of macrophages in Chronic inflammation



Cutaneous Wound Healing

Primary Intention	Secondary intention (Spontaneous)	Tertiary intention
Edges are Closed Eg: Small wounds, Superficial, Sutured more Strength less Scar	Edges far away Eg: untreated deep wounds more Scar less Strength	Aka: Delayed primary Eg: Delayed Suturing Quaternary intention - use of extranious tissue to ↓ wound size Eg: Skin Graft, flaps

Mechanisms of Healing by primary intention



1) Hemostatic Changes — Fibrin Clot · Starts two min → completed < 24 hrr.
Fibrin + Platelets (first cell arrive)
function - 1) stop bleeding 2) Growth factors

2) Inflammatory Changes
Neutrophils — start two hrs → max by 1 day
macrophage - start 1 d max 1-3 days.
fn = to clear debris, organism
M_2 - TGFβ (Growth factors)

3) Proliferative Changes
A. Epithelial proliferation → Basal Epithelial proliferation starts 1 day
↳ completes by 2-3 days
Barrier is Re-established
first post-op is done after 3 days
↓
All layer are Regenerated by 5 days

B. Blood Vessel proliferation (granulation tissue) = Angiogenesis
VEGF, PDGF, FGF, TGF, Angiopoietins
Starts - 3 days. max by 3-5 days

C. Fibroblast proliferation (= Collagen Deposition)
Collagen starts 5-7 days
Type III >> I (Cross links (↑ strength))
Type III → inhibits Crosslinking
max Collagen by 3 weeks (max Scar) strength is low
Type III : I = 4:1

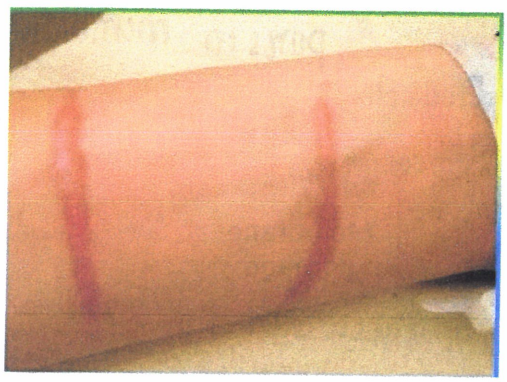
4) Remodeling Phase
↳ Type III Collagenase → ↓ Collagen (Type III)
↑ strength, ↓ Scar
Only in 1° intention
Starts - 3 week - Completed by 3 month
Max strength, 80-90% of original

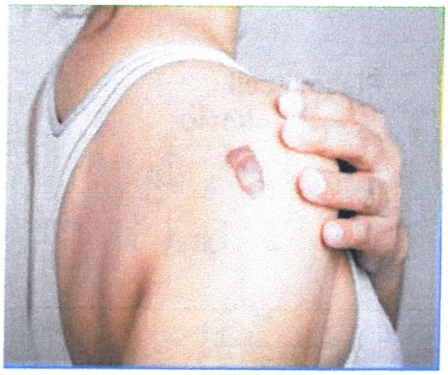
Factors delaying wound healing

General factors	Local factors
1. Old age 2. Poor nutrition 3. NSAIDS, Steroids 4. Uncontrolled DM 5. Bleeding disorder 6. Cold temperature 7. Extremities 8. Systemin infection	1. Local Infection: organism → Staph Aureus → Surgeons hands Prevention - proper hand wash 2. Poor blood supply 3. Foreign body (Sutures) 4. Movement

Excessive scaring

Hypertrophic Scar (HS)	Keloid
Delayed / Defective Remodelling ↓ no ↓ in Scar more Scar, less strength Collagen = Type III > I C/F Scar is limited to wound margin No Recurrence HPE - parallel Collagen bundles	Genetic polymorphism lead to haphazard arrangement of Collagen ↓ ↓ No Crosslinking = ↓ strength ⊕ fibroblast Type I > III C/F Scar keeps Expanding (Beyond wound margin) - Site - Head neck, shoulder, Chest more common in blacks - Recurrence is Rule HPE - Haphazard Collagen





3. DISORDERS OF IMMUNITY

Feature	Innate immunity	Adaptive Immunity
Appears from	By birth	Acquired
Ag Sensitization	No need	Must
Ag Specificity	⊖, non Specific	⊕
Ag Memory	–	+
Onset	immediate	Delayed
Examples	All Epithelia (Barrier) Body fluids, Gastric pH Compliments, Neutrophils, macrophage, NK cells Cough, Sneeze,	Humoral Cell mediated

Adaptive immunity