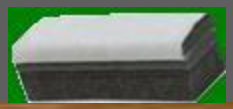
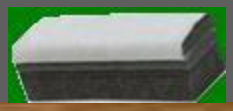
CELL INFLAMMATION AND REPAIR

Dr K P Arun



INTRODUCTION

- **Latin – *inflammare* (to set on fire)**
- **Inflammation** is an important part of body's Defense Mechanism
- Inflammation is "dynamic response of vascularized tissues to injury"
- It is a complex multistep process of tissue response to injury & consists of
  - Vascular responses
  - Migration and activation of leucocytes
  - Systemic reactions
- The purpose of Inflammation is to defend against injurious agent and start healing & repair of injured tissue

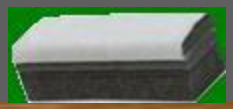


INTRODUCTION…

- Inflammation brings together defense forces such as WBC, antibodies and other chemicals and also bringing more nutrients and healing factors to the site of injury
- However, inflammation may also be potentially harmful (RA, Hay Fever, Atherosclerosis & etc)
- Anti – inflammatory drugs ideally control the harmful effect of inflammation without affecting its beneficial effects

Clinical signs of inflammation:

- Classic five signs:
  - Rubor (redness)
  - Tumor (swelling)
  - Calor (Heat)
  - Dolor (pain) and
  - Functio laesa (Loss of function)

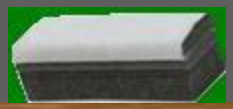


INTRODUCTION…

- Rubor (redness)
- Calor (Heat)

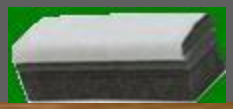
} due to increased blood flow at inflamed site

- Tumor (swelling) – due to accumulation of fluids
- Dolor (pain) - due to release of chemicals that stimulate nerve endings



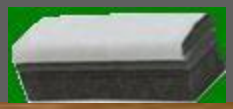
DIFFERENT TYPES OF INFLAMMATION

- ***Acute inflammation:*** Most common form which is for short duration followed by healing
- ***Chronic inflammation:*** Inflammation remains for long time
- ***Pyogenic / Suppurative:*** When excess fluid and WBC leak out they form „Pus“



DIFFERENT TYPES OF INFLAMMATION…

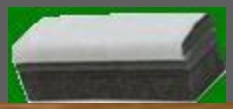
- Collection of this fluid in tissue space is an „Abscess“. The fluid may be an
  - „Exudate“ (due to difference in permeability of blood vessel which contains proteins, cell debris etc.) or
  - „Transudate“ (due to osmotic or hydrostatic imbalance which is a micro filtrate of plasma)
- When an abscess enlarges it may open onto surface causing „Sinus“ or
- When it opens into another organ it is known as „Fistula“



MECHANISM OF INFLAMMATION

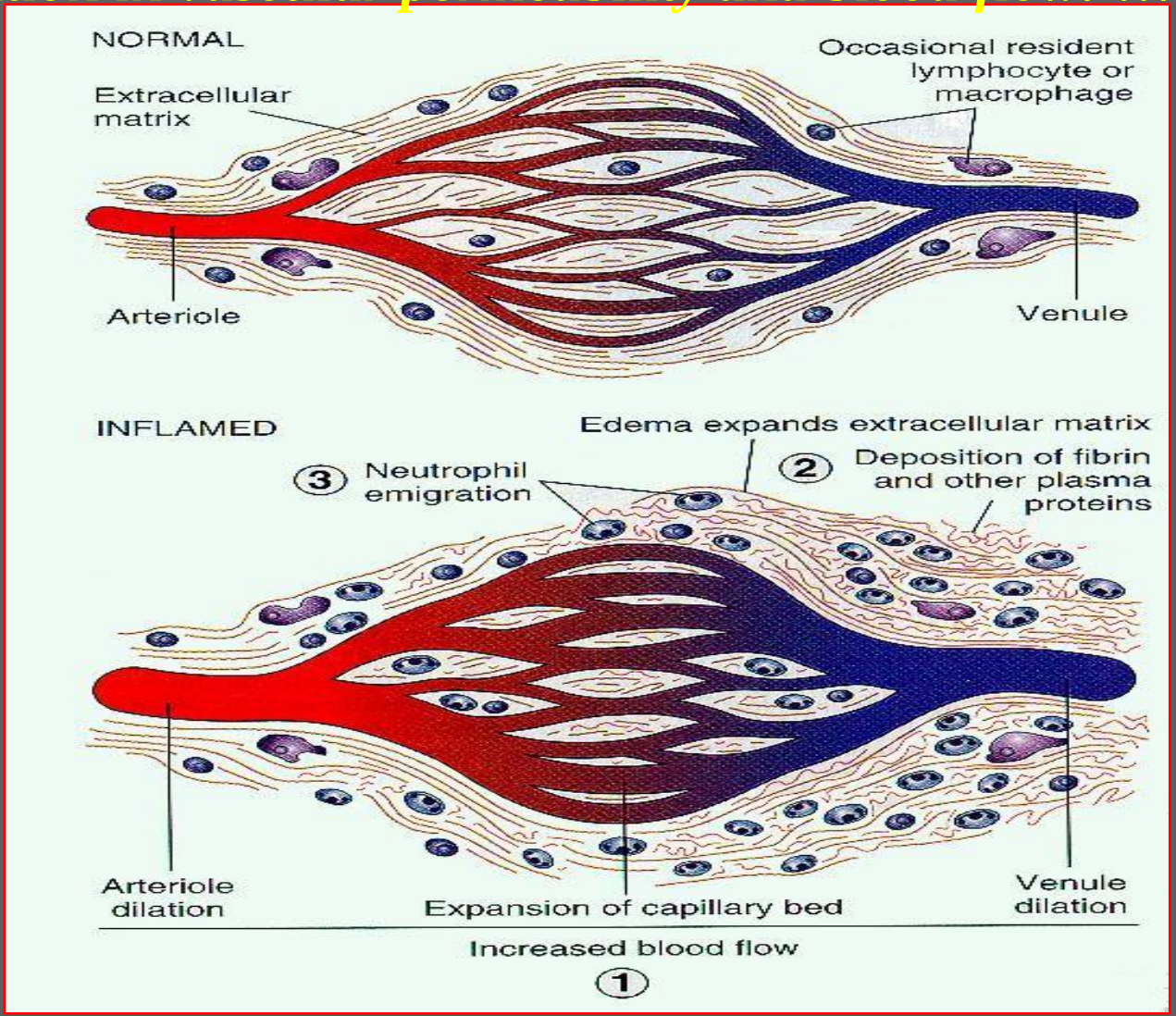
1. Alteration in vascular permeability and blood flow:

- In response to injury, there may be a ***transient vasoconstriction*** *(which lasts only for few seconds)* which is sometimes not at all observed
- This is immediately followed with ***vasodilatation*** due to stimulation of mast cells (physical, chemical, immunologic) which releases histamine (causes dilation of capillaries and contraction of endothelial cells of vascular wall)
- Increased blood flow ***(Hyperemia)*** results in increased hydrostatic pressure in the capillaries
- Blood vessels become leaky allowing escape of fluids ***(transudation),*** proteins & cells ***(exudation)*** into tissue space causing edema



MECHANISM OF INFLAMMATION…

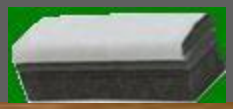
1. Alteration in vascular permeability and blood flow: …



MECHANISM OF INFLAMMATION…

❖ ***Five mechanisms for increased vascular permeability:***

- Gaps due to endothelial contraction (Histamines, Bradykinin, Leukotrienes)
- Direct injury causing necrosis and detachment
- Leucocyte dependent injury (release of toxic oxygen species, proteolytic enzymes)
- Increased transcytosis
- New blood vessel formation (immature endothelial cells with poor intercellular junction)



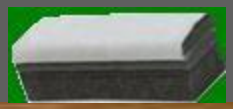
MECHANISM OF INFLAMMATION…

- This results in increased pressure in the interstitium which stimulates pain fibers through pressure receptors (also may be stimulated by the direct effects of bradykinin) to produce pain

MECHANISM OF INFLAMMATION…

2. Migration of WBCs (Inflammatory Cells):

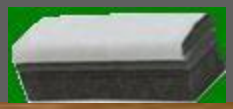
- Vascular dilatation increases the volume of blood to the tissue site but also changes the flow characteristics within the vessel
- Dilatation increases cross sectional area of the vessel and decreases the net flow rate per unit area
- Increased vascular permeability with fluid loss increases the cell concentration ***(Stasis)***
- This causes cells to fall out of the central region of the vessel ***(Margination)*** and begin to tumble along the epithelial surface ***(Rolling)***



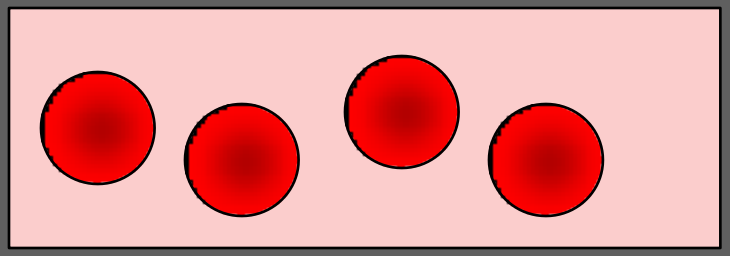
MECHANISM OF INFLAMMATION…

2. Migration of WBCs (Inflammatory Cells):…

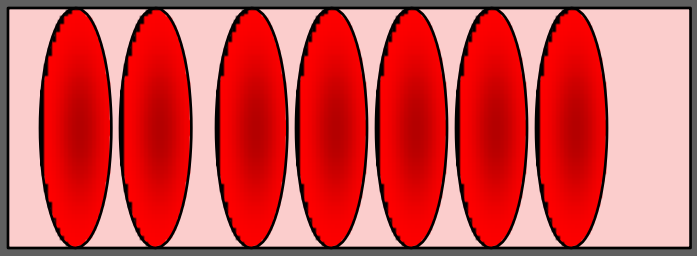
- Specialized receptors known as ***cellular adhesion molecules*** (selectins, integrins and immunoglobulins) facilitate binding between endothelial cells and leukocytes ***(Stable Adhesion)***
- Chemo-attractants ***(chemotactic factors)*** can now do their job of getting cells out of vessels ***(extravasation, transmigration)*** and to the site of injury
- If the infiltrate is composed predominantly of neutrophils and some macrophages, we call it ***„Acute Inflammation'***
- If the infiltrate is composed of macrophages, lymphocytes and /or plasma cells, we call it ***'Chronic Inflammation'***



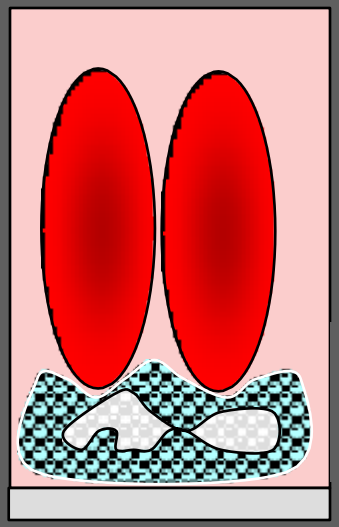
MECHANISM OF INFLAMMATION…



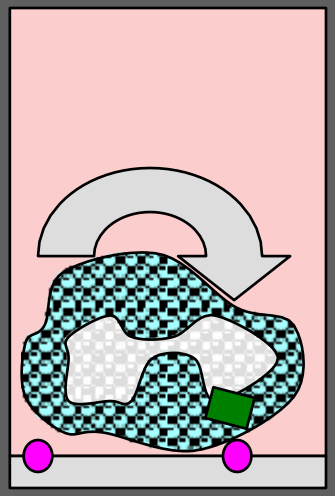
Slowing



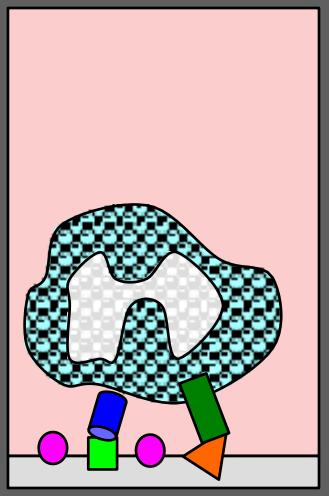
Concentration



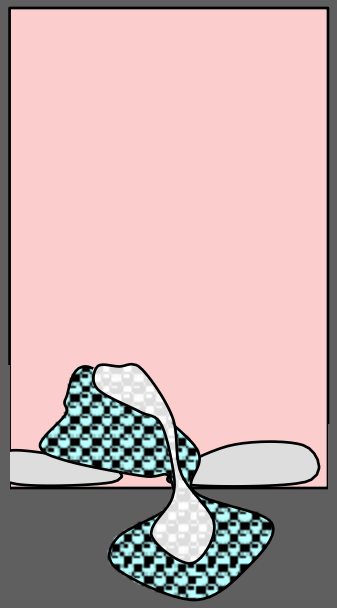
Margination



Rolling



Adhesion



Transmigration

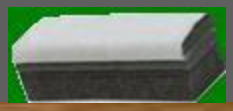
MECHANISM OF INFLAMMATION…

2. Migration of WBCs (Inflammatory Cells):…

❖ Antibodies and other chemical mediators of inflammation serve to neutralize the injurious agents such as microbes

The Cells of Inflammation:

- **Neutrophils** – first cell on the scene after injury
- **Eosinophils** – arrive on the scene a little later and last longer
- **Lymphocyte** – marker of chronic inflammation
- **Macrophage** – involves in phagocytosis
- **Plasma cells** – B-lymphocytes which produce antibody
- **Endothelial cells** – involves angiogenesis
- **Fibroblasts** – manufacture collagen



MECHANISM OF INFLAMMATION…

- Both
  - ***Alteration in Vascular Permeability & Blood Flow***
  - ***Migration of WBCs***

  are caused or regulated by ***chemical mediators of inflammation*** such as histamine, serotonin, bradykinin & prostaglandins

Neu tro p h i l s mo vi n g to th e si te…

INFLAMMATORY MEDIATORS

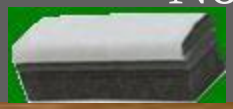
Vasoactive amines:

HISTAMINE:

- ✓ Stored in connective tissue, mast cells, blood basophils and platelet granules
- ✓ Promotes contraction of smooth muscles (as in asthma)
- ✓ Dilatation of arterioles, and vascular permeability (contraction of endothelial cells in venules)

SEROTONIN:

- ✓ Action is similar to histamine
- ✓ Not present in human mast cells



INFLAMMATORY MEDIATORS

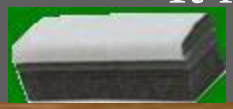
Plasma Proteases:

COMPLEMENT SYSTEM:

- ✓ C3a, C5a (vascular permeability), C5a (chemotaxis), C3b (opsonization) and C5b-9 (cell lysis)
- ✓ These mediate biologic reactions against microbial invasion

KININ SYSTEM:

- ✓ Bradykinin
- ✓ This increases vascular permeability, causes contraction of smooth muscles and dilatation of vessels
- ✓ It may also directly stimulate pain fibers



INFLAMMATORY MEDIATORS

CLOTTING SYSTEM:

✓ Activated by Factor XII

Arachidonic Acid Metabolites:

LEUCOTERINS:

✓ They act primarily as effectors of vascular permeability, vascular wall constriction or leukocyte chemotaxis

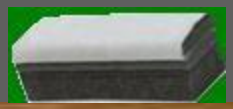
INFLAMMATORY MEDIATORS

CYTOKINES:

- IL-1 (interleukin-1)
- TNF (tumor necrosis factor)
  - ✓ These stimulate both collagen and collagenase production by fibroblasts

NITRIC OXIDE:

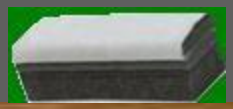
- ✓ It causes vasodilation and reduces platelet activation and aggregation
- ✓ In macrophages, the free radical nature of NO is toxic to microbes



INFLAMMATORY MEDIATORS

GROWTH FACTORS:

- ✓ *EGF (epidermal growth factor)*
- ✓ *PDGF (platelet derived growth factor)*
- ✓ *FGF (fibroblast growth factor)*
- ✓ *VEGF (vascular endothelial growth factor)*
  - These mediators are involved in the proliferation and production of vessels and collagen during the repair phase of inflammation.

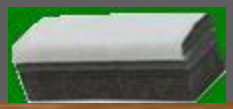


BASIC PRINCIPLES OF WOUND HEALING

- Wound healing is a complex and dynamic process with the wound environment changing with the changing health status of the individual

- In any natural disaster the damaging forces must be identified and stopped before repair work can begin

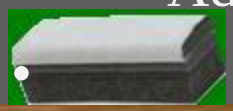
- So too in wound care the basic underlying causes and factors that affect healing must be identified and controlled



BASIC PRINCIPLES OF WOUND HEALING…

❖ Following are some of the common underlying causes or factors, which may interfere with wound healing:

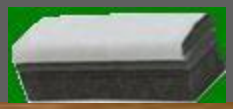
- Trauma
- Physical and chemical burns
- Animal bites or insect stings
- Pressure
- Vascular compromise
- Immunodeficiency
- Malignancy
- Connective tissue disorders
- Metabolic disease (DM)
- Nutritional deficiencies
- Psychosocial disorders
- Adverse effects of medications



BASIC PRINCIPLES OF WOUND HEALING…

*Wounds Heal in **Four** Phases:*

- Hemostasis
- Inflammation
- Proliferation or Granulation
- Remodeling or Maturation

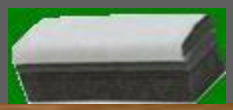


BASIC PRINCIPLES OF WOUND HEALING…

Kane's analogy** to the repair of a **damaged house** provides a wonderful framework to explore the **basic physiology of wound repair

Summary of phases of wound healing:

Phase of Healing	Days post injury	Cells involved in phase	Analogy to house building
Hemostasis	Immediate	Platelets	Capping of damaged pipe lines
Inflammation	Day 1 – 4	Neutrophils	Unskilled laborers to clean up the site



BASIC PRINCIPLES OF WOUND HEALING…

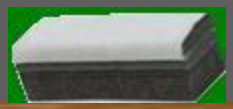
Summary of phases of wound healing:

Phase of Healing	Days post injury	Cells involved in phase	Analogy to house building
Proliferation	Day 4 – 21	Macrophages	Supervisor
Granulation		Lymphocytes	Specific laborers at the site
		Angiocytes (Pericytes)	Plumbers
		Neurocytes	Electricians
Contracture		Fibroblasts	Framers
		Keratinocytes	Roofers and siders

BASIC PRINCIPLES OF WOUND HEALING…

HEMOSTASIS:

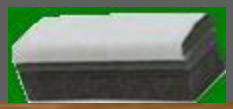
- In wound healing damaged blood vessels must be sealed
- The *platelet* is the cell which is sealing off the damaged blood vessels
- The blood vessels themselves constrict in response to injury but this spasm ultimately relaxes
- The platelets secrete vasoconstrictive substances to aid in this process to form a stable clot sealing the damaged vessel
- Under the influence of ADP (adenosine diphosphate) leaking from damaged tissues the platelets aggregate and adhere to the exposed collagen



BASIC PRINCIPLES OF WOUND HEALING…

HEMOSTASIS…

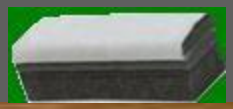
- They also secrete factors which interact with and the intrinsic clotting cascade through the production of *thrombin*, which in turn initiates the formation of *fibrin* from *fibrinogen*
- The fibrin mesh strengthens the platelet aggregate into a stable hemostatic plug
- Finally platelets also secrete cytokines such as *platelet-derived growth factor* (PDGF), which is recognized as one of the first factors secreted in initiating subsequent steps
- Hemostasis occurs within minutes of the initial injury unless there are underlying clotting disorders



BASIC PRINCIPLES OF WOUND HEALING…

INFLAMMATION PHASE:

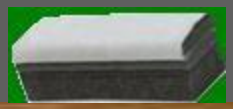
- The second stage of wound healing
- Presents as erythema, swelling and warmth often associated with pain
- This stage usually lasts up to 4 days post injury
- *Neutrophils or PMN's (polymorphonucleocytes)* clean up the debris
- The inflammatory response causes the blood vessels to become leaky releasing plasma and PMN‟s into the surrounding tissue
- The neutrophils phagocytes debris and microorganisms and provide the first line of defense against infection
- They are aided by local *mast cells*



BASIC PRINCIPLES OF WOUND HEALING…

INFLAMMATION PHASE…

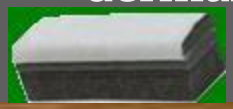
- As fibrin is broken down as part of this clean-up the degradation products attract the next cell involved
- Macrophages are able to phagocyte bacteria and provide a second line of defense
- They also secrete a variety of chemotactic and growth factors such as
- *fibroblast growth factor (FGF)*
- *epidermal growth factor (EGF)*
- *transforming growth factor (TGF)*



BASIC PRINCIPLES OF WOUND HEALING…

PROLIFERATIVE PHASE (PROLIFERATION, GRANULATION AND CONTRACTION):

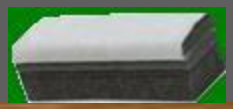
- The granulation stage starts approximately four days after wounding and usually lasts until day 21 in acute wounds depending on the size of the wound
- It is characterized clinically by the presence of pebbled red tissue in the wound base and involves replacement of dermal tissues and sometimes subdermal tissues in deeper wounds as well as contraction of the wound
- The *fibroblasts* which secrete the collagen framework on which further dermal regeneration occurs



BASIC PRINCIPLES OF WOUND HEALING…

PROLIFERATIVE PHASE (PROLIFERATION, GRANULATION AND CONTRACTION)…

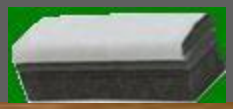
- Specialized fibroblasts are responsible for wound contraction
- The *pericytes* which regenerate the outer layers of capillaries
- The *endothelial cells* which produce the lining *(angiogenesis)*
- *Keratinocytes* which are responsible for *epithelialization*
- In the final stage of epithelialization, contracture occurs as the Keratinocytes differentiate to form the protective outer layer or stratum corneum



BASIC PRINCIPLES OF WOUND HEALING…

REMODELING OR MATURATION PHASE:

- Wound repair the healing process involves remodeling the dermal tissues to produce greater tensile strength
- The principle cell involved in this process is the *fibroblast*
- Remodeling can take up to 2 years after wounding and so, healed wounds can break down so dramatically and quickly if attention is not paid to the initial causative factors



Wound Healing

When Does a Wound Become Chronic?

- In healthy individuals an acute wound should heal within three weeks

- If a wound does not follow the normal route it may become stuck in one of the stages and the wound becomes chronic

- Chronic wounds are thus defined as wounds, which have "failed to proceed through an orderly and timely process to produce anatomic and functional integrity, or proceeded through the repair process without establishing a sustained anatomic and functional result"