PATHOLOGY

بسم الله الرحمن الرحيم

FINAL – Lecture 1

Tissue Repair (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

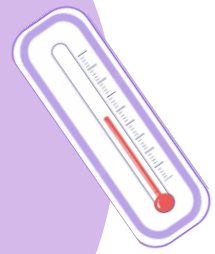
اللهم استعملنا ولا تستبدلنا

Written by:

- Laith Alhuniti
- Mahmood Al-Absi

Reviewed by:

- Laith Joudeh



Since this is the first final lecture and it is related to the six lectures on inflammation we discussed, here's a quick review of the mid-inflammation lectures:

So, if you recall it, skip the next 5 slides. Also, no quiz.

- **Inflammation** is the body's protective response by vascularized tissues to eliminate harmful agents, such as pathogens or injuries, and to initiate repair. Its critical functions include preventing infections from becoming fatal, promoting wound healing, and limiting tissue damage. Without inflammation, the body would face significant risks from even minor infections or injuries.

- **Key Phases of Inflammation (The Five R's):**
  1. Recognition of the harmful agent by immune cells.
  2. Recruitment of leukocytes (white blood cells) and plasma proteins to the site of injury.
  3. Removal of the harmful agent, often through phagocytosis.
  4. Regulation to control and eventually reduce the inflammatory response.
  5. Resolution or Repair of the damaged tissue.
  - These steps allow the immune system to respond efficiently, minimize tissue damage, and restore normal function.

- The **Cardinal Signs of Inflammation** are the main signs of inflammation, often observed in clinical settings, and they are:
  1. Heat (Calor): From increased blood flow.
  2. Redness (Rubor): Caused by vascular dilation.
  3. Swelling (Tumor): Due to fluid accumulation.
  4. Pain (Dolor): From pressure on nerves and inflammatory mediators.
  5. Loss of Function (Functio Laesa): Resulting from pain and tissue swelling.

- **Acute vs. Chronic Inflammation**:
  - Acute Inflammation: Rapid onset and short duration, with hallmark signs of swelling, heat, and redness. Neutrophils dominate the cellular response, and tissue typically returns to normal after the inflammatory response subsides.
  - Chronic Inflammation: Slower, prolonged response involving mononuclear cells (macrophages, lymphocytes). This can lead to ongoing tissue damage and fibrosis if inflammation persists.

Mechanisms of Acute Inflammation

1. **Vascular Phase**:
   - The initial response involves dilation and increased permeability of blood vessels, leading to plasma proteins and leukocytes leaving the bloodstream and entering the inflamed tissue. This phase contributes to redness and warmth at the inflammation site.
   - If the offending agent persists, sustained permeability changes occur, with fluids and proteins continuously leaking into the tissue, contributing to edema (swelling).

2. **Leukocyte Recruitment and Migration**:
   - Leukocytes migrate to the site of inflammation through chemotaxis, guided by chemoattractants such as cytokines, complement proteins, and bacterial products.
   - The two main types of fluid leakage observed clinically are:
   - Transudate: Fluid with low protein and cell content, often due to fluid imbalance.
   - Exudate: Fluid with high protein and cell content, indicating increased vascular permeability and a more severe inflammatory response.
   - Edema refers to fluid accumulation, while Pus (or purulent exudate) is rich in neutrophils, bacterial debris, and cell remnants, signaling intense acute inflammation.

3. **Phagocytosis and Pathogen Destruction**:
   - Phagocytosis: Neutrophils and macrophages engage in phagocytosis, engulfing pathogens. Key steps include:
   - Recognition and Attachment: Pathogens are identified by receptors on immune cells.
   - Engulfment: The pathogen is enveloped into a phagosome.
   - Intracellular Killing: Within the phagosome, reactive oxygen species (ROS) and enzymes destroy the pathogen.
   - Neutrophil Extracellular Traps (NETs): After neutrophils die, they release DNA and granule proteins, forming extracellular traps that immobilize pathogens and prevent their spread.
   - Nitric Oxide (NO): A powerful antimicrobial agent produced by macrophages; it reacts with other molecules to form radicals that can kill pathogens.
   - Granule Enzymes: Contained within neutrophils, these enzymes aid in microbial killing but can harm host tissue if not regulated. They are balanced by antiproteases to avoid excessive tissue damage.
   - Arachidonic Acid Metabolites (Eicosanoids): Derived from cell membrane phospholipids, eicosanoids include prostaglandins and leukotrienes, which amplify inflammation. Common drugs, such as NSAIDs and steroids, target these metabolites to reduce inflammation.

Leukocyte Types and Actions in Inflammation:

1. Neutrophils: The first responders in acute inflammation, they are short-lived but crucial for pathogen containment. They use ROS and enzymes to destroy pathogens within phagosomes.
2. Macrophages: Derived from monocytes, these cells have a longer lifespan and are involved in both acute and chronic inflammation phases. In chronic cases, they contribute to tissue repair but can also cause fibrosis.
3. Lymphocytes: T and B lymphocytes respond to specific antigens and participate in chronic inflammation. CD4+ T-cells, particularly Th1, Th2, and Th17 subsets, release cytokines that amplify the inflammatory response and recruit other immune cells.
4. Eosinophils: Typically associated with allergic responses and parasitic infections, they release granules that can damage tissue. They are also implicated in eosinophilic inflammation, a type of chronic inflammation affecting organs like the esophagus (eosinophilic esophagitis).

Advanced Inflammatory Mechanisms, Resolution, and Chronic Inflammation:

- **Termination** of Acute Inflammation:
  After the inflammatory response has eliminated or controlled the harmful agent, it must be downregulated to prevent excessive tissue damage. The body employs several mechanisms to terminate inflammation, ensuring it doesn't persist unnecessarily:
  - Rapid Mediator Degradation: Inflammatory mediators are released quickly but degrade fast due to their short half-lives, allowing for a swift reduction in inflammation once the threat subsides.
  - Apoptosis of Neutrophils: Neutrophils have short lifespans, undergoing programmed cell death shortly after completing their role.
  - Production of Stop Signals: Anti-inflammatory cytokines like TGF-β and IL-10 are produced in the later stages to suppress inflammation and promote repair.
  - Neural Inhibitors: The cholinergic system helps modulate inflammation by reducing the release of pro-inflammatory mediators like TNF.
- **Mediators of Acute Inflammation:**
  Inflammation relies on a complex network of mediators produced by cells at the injury site or circulating proteins. Key groups include:
  - Vasoactive Amines: Histamine and serotonin increase vascular dilation and permeability, contributing to local redness and swelling.
  - Lipid Mediators: Prostaglandins and leukotrienes are derived from arachidonic acid and promote various aspects of inflammation. NSAIDs inhibit prostaglandin synthesis to reduce inflammation, while specific asthma medications target leukotrienes.
  - Cytokines: IL-1, TNF, and IL-6 are major cytokines in acute inflammation. They increase vascular permeability, stimulate leukocyte recruitment, and cause systemic effects like fever.
  - Complement Proteins: Components like C5a serve as chemoattractants, directing immune cells to the infection site, while others form complexes that directly attack pathogens.
- Inflammation can produce **distinct structural changes visible under the microscope or with the naked eye**, helping clinicians identify the nature and intensity of the response:
  - Serous Inflammation: Characterized by cell-poor, protein-rich fluid (transudate), often seen in conditions like pleural effusions or skin blisters.
  - Fibrinous Inflammation: Marked by extensive vascular leakage with high fibrin content, commonly found in body cavities like the pericardium and pleura.
  - Purulent (Suppurative) Inflammation: Pus formation from intense neutrophil accumulation and tissue debris, typically due to bacterial infections (e.g., abscesses from Staphylococcus aureus).
  - Ulcerative Inflammation: Results in surface tissue defects, common in mucosal surfaces and skin, showing both acute and chronic inflammation features.

Outcomes of Acute Inflammation:

Acute inflammation has three primary outcomes, depending on the nature of the injury, the effectiveness of the immune response, and tissue characteristics:

1. Complete Resolution: Ideal outcome where tissue returns to its pre-inflammatory state after pathogen elimination and repair.
2. Healing by Fibrosis: Occurs when tissue destruction is extensive. Healing involves scar formation, which may impact the function of the affected tissue.
3. Progression to Chronic Inflammation: If acute inflammation fails to eliminate the harmful agent or if the agent is highly virulent, inflammation becomes prolonged, leading to chronic tissue damage.

Chronic Inflammation:

Chronic inflammation is prolonged and involves ongoing tissue injury, repair attempts, and fibrosis. Unlike acute inflammation, which is short-term and primarily involves neutrophils, chronic inflammation includes a broader array of immune cells:

1. Macrophages: Essential in both tissue destruction and repair. They are activated in chronic inflammation through either the M1 (pro-inflammatory) or M2 (anti-inflammatory) pathway.
2. Lymphocytes: T and B cells are key players in chronic inflammation. CD4+ T-helper cells release cytokines to perpetuate the response, while B cells produce antibodies.
3. Eosinophils and Mast Cells: Eosinophils contribute to tissue damage, particularly in allergic and parasitic infections. Mast cells release histamine and are active in both acute and chronic phases.

Common **causes of chronic inflammation** include:

1. Persistent Infections: Mycobacteria (e.g., tuberculosis) and certain fungi provoke granulomatous inflammation, a subtype of chronic inflammation with specific cellular organization.
2. Autoimmune Disorders: Diseases like rheumatoid arthritis and multiple sclerosis involve chronic inflammation as the immune system mistakenly attacks the body's own tissues.
3. Prolonged Exposure to Toxins: Substances like silica and cholesterol can cause chronic inflammatory responses leading to conditions such as silicosis and atherosclerosis.

TISSUE REPAIR:

- **Inflammation may cause injury and repair is critical after eliminating the enemy.**
- **Repair can be achieved by:**
    1. **Regeneration**
    2. **Scar & fibrosis**

Both require mediators and cellular proliferation, and interactions with the ECM.

Explanation of the previous slide:

- The tissue repair process is the last part of the inflammatory response (R5).
- Repair is a crucial step in the tissue repair process, which is the final phase of the inflammatory response (R5). After tissue injury, its repair is necessary, and the extent of repair depends on the amount and severity of damage.
- When regeneration is not possible, tissue replacement occurs through scarring and fibrosis. Both processes and the entire tissue repair process require chemical mediators, cellular growth, and cellular proliferation. Additionally, there is a complex interaction between the extravascular compartments, extracellular matrix (ECM), and ECM proteins.

TISSUE REGENERATION:

- **Regeneration requires growth factors and interactions between cells and matrix (ECM)**
- **Tissue types** Regeneration depends on tissue type:

Labile tissue	**Continuous regeneration: epithelia of mucosal surfaces,** and in bone marrow elements.
Stable tissue: More stable and more differentiated, they are normally with no inflammation but can be used and recruited upon stimulation by injury.	**Normally in G_0, but can be stimulated to regenerate when injured (liver, kidney, pancreas)**
Permanent tissue: They can't regenerate, usually replaced by scar tissue and this can be very serious.	**Terminally differentiated, non-proliferative (neurons and cardiac muscle, skeletal muscle)**

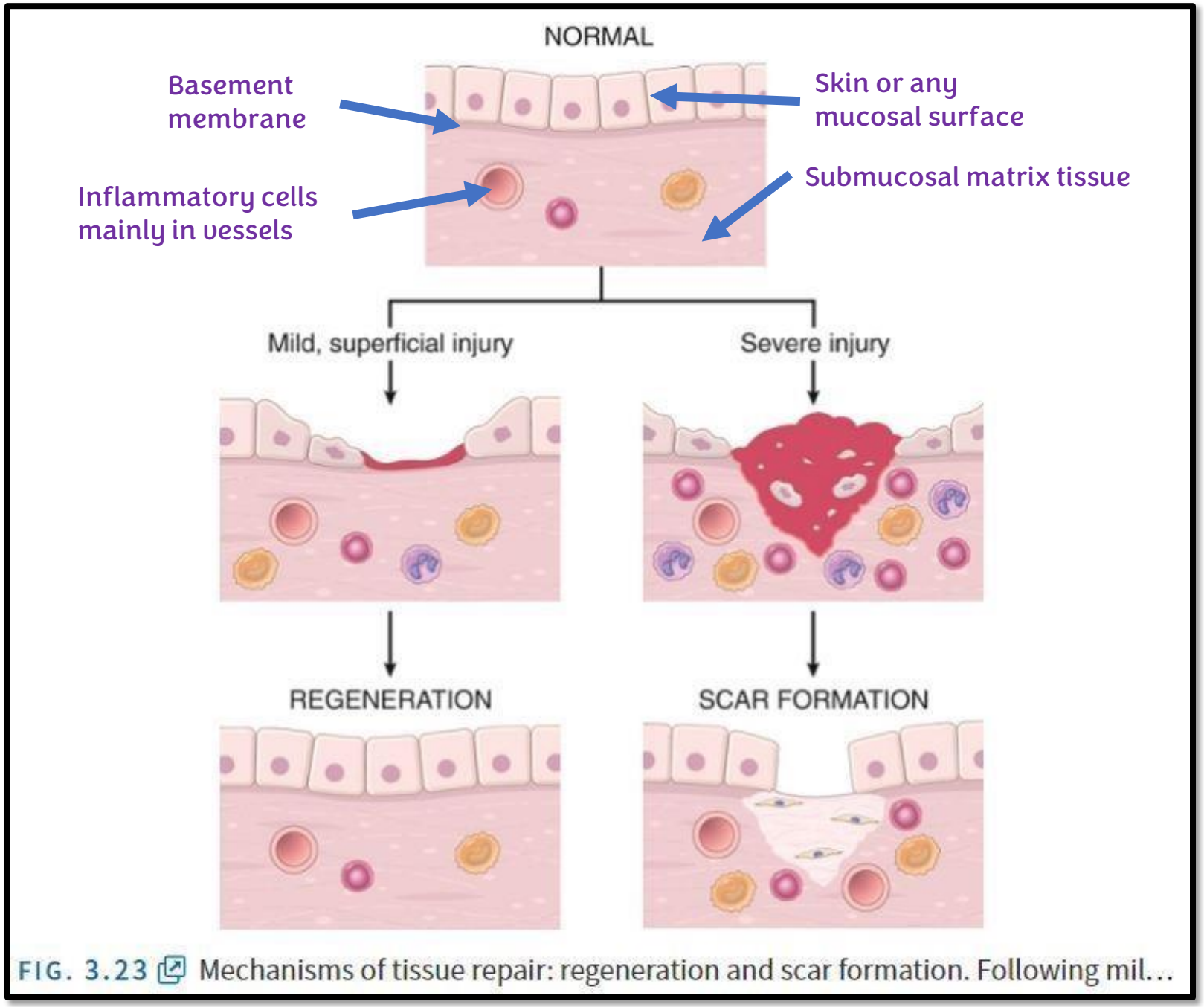


FIG. 3.23 Mechanisms of tissue repair: regeneration and scar formation. Following mil…

Explanation of the Picture

- On the left: Repair by First Intention. If we have a small, mild, superficial injury, such as a burn or scratch, regenerative mediators will be activated. The lost epithelium will be replaced by regenerating epithelial cells from the sides, filling the gap. If the plasma membrane remains intact, healing is usually quick, and the resulting tissue closely resembles the pre-injury state.
- On the right: Healing by Secondary Intention. If the injury is severe and significant tissue is lost – such as the basement membrane, superficial epithelium, and submucosal tissue – healing takes longer. In such cases, regeneration alone is insufficient, requiring granulation tissue formation. This process takes more time, resulting in substantial scar tissue, and the final tissue structure differs from the pre-injured state.

LIVER REGENERATION:

Stable tissue

- **Liver can regenerate in 2 ways:**
  1. **Hepatocytes proliferation, post partial hepatectomy**
  2. **Progenitor cells gets activated and proliferate and differentiate**

  Both need growth factors & cytokines and cell matrix interactions

Liver regeneration:

- If liver parenchymal tissue is damaged, regardless of the injurious agent (e.g., trauma or viral infection), the liver has mechanisms to compensate.
- For example, in partial hepatectomy, where a liver lobe is removed due to a tumor, the remaining liver tissue compensates for the lost portion, which may take a few months.
- One way this occurs is through hepatocyte proliferation, where existing liver cells divide to restore liver mass. Another mechanism involves recruiting progenitor cells that enter the liver and eventually differentiate into hepatocytes.
- Growth factors play a crucial role as mediators in inflammation, helping to stimulate cell proliferation and coordinate the healing process.

Summary

Repair by Regeneration

- Different tissues consist of continuously dividing cells (epithelia, hematopoietic tissues), normally quiescent cells that are capable of proliferation (most parenchymal organs), and nondividing cells (neurons, skeletal and cardiac muscle). The regenerative capacity of a tissue depends on the proliferative potential of its constituent cells.
- Cell proliferation is controlled by the cell cycle, and is stimulated by growth factors and interactions of cells with the extracellular matrix.
- Regeneration of the liver is a classic example of repair by regeneration. It is triggered by cytokines and growth factors produced in response to loss of liver mass and inflammation. In different situations, regeneration may occur by proliferation of surviving hepatocytes or repopulation from progenitor cells.

REPAIR BY SCARRING:

- **Large amount of tissue damage**
- **“Patching”, wound healing and scarring**
- **Healing by first and second intention.**
- **Steps:**
  - **Hemostatic plug (platelets)…minutes**
  - **Inflammation (Macs, M1 and M2)…6-48 hours**
  - **Cell proliferation (granulation tissue)…10 days**
  - **Remodeling…. 2-3 weeks**

Repair by Scarring:

- If there is a large amount of tissue loss or damage during an injury, the repair process takes longer. Initially, the wound is patched, and more scar tissue forms as a result.
- In first intention healing, only a small amount of tissue is lost, resulting in minimal scar tissue. In second intention healing, however, there is a larger scar due to extensive tissue loss.
- This repair process is complex:
    1. Initially, platelets are stimulated quickly, creating a hemostatic plug within minutes to prevent further bleeding when an organ is injured.
    2. Next, an inflammatory response is triggered, activating M1 and M2 macrophages.
    3. Cell proliferation then begins, which includes the formation of new blood vessels (angiogenesis). This phase is slower, and any extra material and tissue are cleaned out before strong scar tissue forms, replacing the damaged parenchyma.

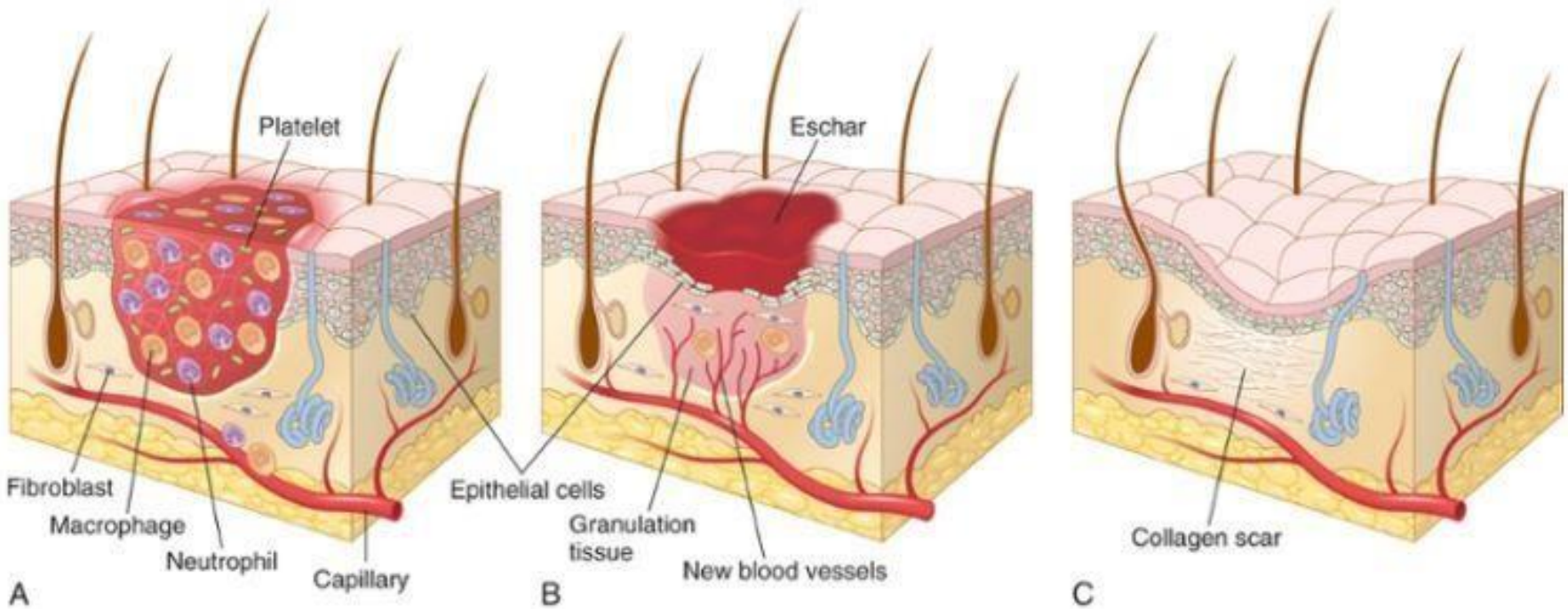


FIG. 3.24 Steps in repair by scar formation: healing of a large wound in the skin. This is …

Interpretation of the previous image:

A. In the case of major tissue injury, blood initially aggregates at the injury site to prevent further bleeding. Matrix components, fibroblasts, and blood vessels play a role in this early phase, while cytokines and growth factors are released to initiate the healing process. Angiogenesis begins at the base of the wound, and growth factors stimulate the epithelium to proliferate and cover the wound surface.

B. A hard, dry clot known as an eschar (a mostly acellular fibrin plug) forms over the lost tissue to prevent further bleeding. The eschar eventually falls off as healing continues beneath it. Meanwhile, angiogenesis and interactions between new blood vessels, growth factors released from the intravascular compartment, the injured area, and the ECM foster the growth of granulation tissue.

C. During the remodeling phase, granulation tissue is replaced by scar tissue, which consists of strong, acellular collagen. The amount of scar tissue formed is proportional to the amount of lost tissue. Over time, scar contraction may occur, causing a dip in the superficial mucosal surface.

Summary Table

Topic	Details
Repair Mechanisms	- Regeneration: Restoration if tissue is capable of regeneration (e.g., mild oral mucosa injuries). - Scar/Fibrosis: For severe injuries (e.g., perianal abscess), where tissues cannot regenerate effectively.
Regeneration	- Requires growth factors, cell-ECM interactions - Types: 1. Proliferating cells (e.g., epithelial cells, bone marrow). 2. Stable tissues (e.g., liver upon stimulation). 3. Permanent cells (e.g., neurons)
Healing Processes	- First Intention: Faster, minimal scarring, tissue back to normal (e.g., clean surgical wounds). - Second Intention: Slower, more scarring (e.g., extensive wounds), interferes with organ function.
Liver Regeneration	- Mechanisms: 1. Hepatocyte proliferation (post-hepatectomy). 2. Activation of progenitor cells (bone marrow recruitment, cytokine, and matrix interactions).
Scar Formation Steps	1. Hemostatic plug (platelets) stops bleeding. 2. Inflammation (macrophages M1/M2) over 6-48 hours. 3. Cell proliferation (angiogenesis, granulation tissue) ~10 days. 4. Remodeling for strong scar tissur.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Robbins & Kumar Basic Pathology, 11th edition, pg. 66,67

لا تنسوا اهل غزة من خالص دعائكم, اللهم ارحمهم وفرج كربهم.
وعن أبي سعيد الخدري أن رسول الله صلى الله عليه وسلم قال: "ما خلق الله من داء إلا وجعل له شفاء علمه من علمه وجهله من جهله إلا السام والسام الموت" رواه ابن ماجه.

واخر دعواهم ان الحمد لله رب العالمين