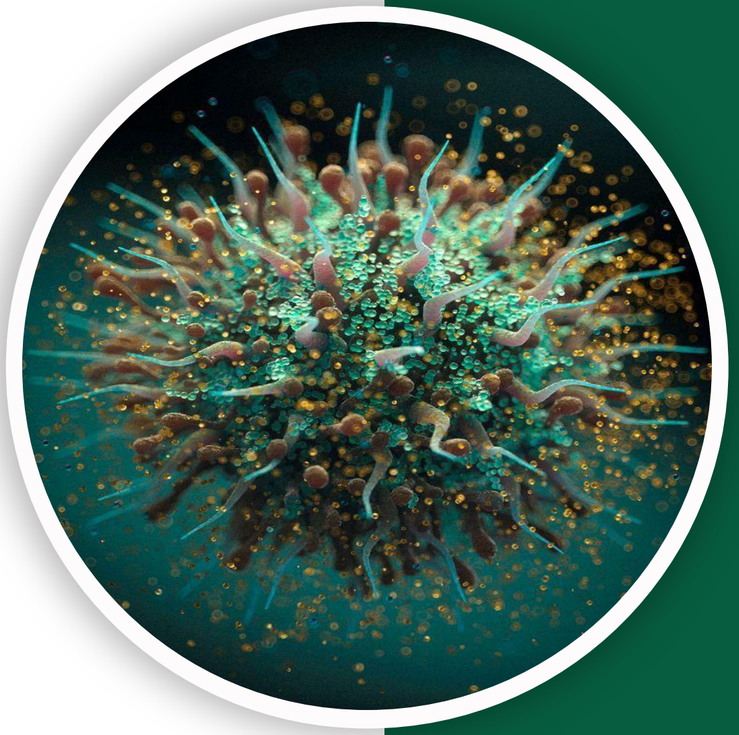
بسم الله الرحمـٰن الرحيم

(وَفَوْقَ كُلِّ ذِي عِلْمٍ عَلِيمٌ)

Pathology | Final 2

Repair (Pt.2)



Written by : DST

Reviewed by : Leen Alzoubi

NST

وَلِلَّهِ الْأَسْمَاءُ الْحُسْنَى فَادْعُوهُ بِهَا

المعنى: الخالق المالك المدَبّر، المربّي جميع خلقه بنِعَمه، ويُربيّ أولياءه بما يُصلح قلوبهم، ولا يجوز إطلاق اسم الرب على غير الله تعالى إلا مضافاً، كرب الأسرة.

الورود: ورد في القرآن (٩٠٠) مرة.

الشاهد: ﴿ ٱلْحَمْدُ لِلَّهِ رَبِّ ٱلْعَٰلَمِينَ ﴾ [الفاتحة:١].

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اضغط هنا لشرحٍ أكثر تفصيلًا

- **This table contains the key points mentioned by the doctor..**

Aspect	Healing by First Intention	Healing by Second Intention
Tissue Damage	Minimal tissue damage (e.g., small surgical cuts)	Extensive tissue damage (e.g., large wounds, trauma)
Healing Process	Rapid and accurate healing with minimal scarring	Requires extensive granulation tissue, angiogenesis, and scarring
Hemostasis	Quick formation of a hemostatic plug to stop bleeding	Formation of a hemostatic plug within minutes
Inflammation Phase	Short, limited inflammation	Prolonged inflammation lasting 6 hours to 2 days
Proliferation Phase	Fast epithelial regeneration and wound closure	Includes angiogenesis, fibroblast migration, and tissue proliferation (up to 10 days)
Remodeling Phase	Minimal, rapid remodeling	Extensive remodeling lasting up to 3 weeks, sometimes 6 months
Scar Formation	Minimal scarring	Significant scarring; collagen remodeling (Type 3 to Type 1)
Wound Closure	Tissue approximated, minimal gap	Larger gap, requires filling with granulation tissue
Capillary Growth	Limited angiogenesis	Extensive angiogenesis to provide nutrients to healing tissue

Lecture 8

ANGIOGENESIS:

- **Angiogenesis** is extremely important and represents a key part of the initial formation of granulation tissue during wound healing.
- It is a multi-step biological process, and each step requires specific stimulators, inhibitors, and growth factors (GFs).

- **Central role in healing**
- **Requires multiple steps; signaling pathways, growth factors, cell-matrix interactions and enzymes of remodeling**
  - **GF: VEGF-A, FGFs mainly FGF-2, TGF-ß**
  - **Notch signaling: sprouting**
  - **ECM proteins**
  - **Enzymes for final remodeling**

Major growth factors (GFs):

A) VEGF-A: (vascular endothelial growth factor)
B) FGFS-2 (Fibroblast growth factors family)
C) TGF-B (transforming growth factor beta) one of the most potent fibrogenic or scar-forming mediator.

1. Angiogenesis Initiation
- The angiogenesis process is initiated and regulated by the Notch signaling pathway, which coordinates new blood vessel formation.

2. ECM Protein Production
- ECM proteins are produced and gradually accumulate in the wound area.
- These proteins help lay down the structural foundation needed for future scar formation.

3. Enzymes for Final Remodeling
- In the final stage of healing, specific enzymes contribute to remodeling

this is a quiescent or normal blood vessel (quiescent equilibrium state)

- Blood vessels stand still
- the endothelial cells covering the blood vessels from inside toward the lumen , lying on or buildup on basement membrane(BM)

Basement membrane

- composed of mainly collagen type 4 and laminin , and this is surrounded by pericytes

Pericyte

- single layer of delicate cells

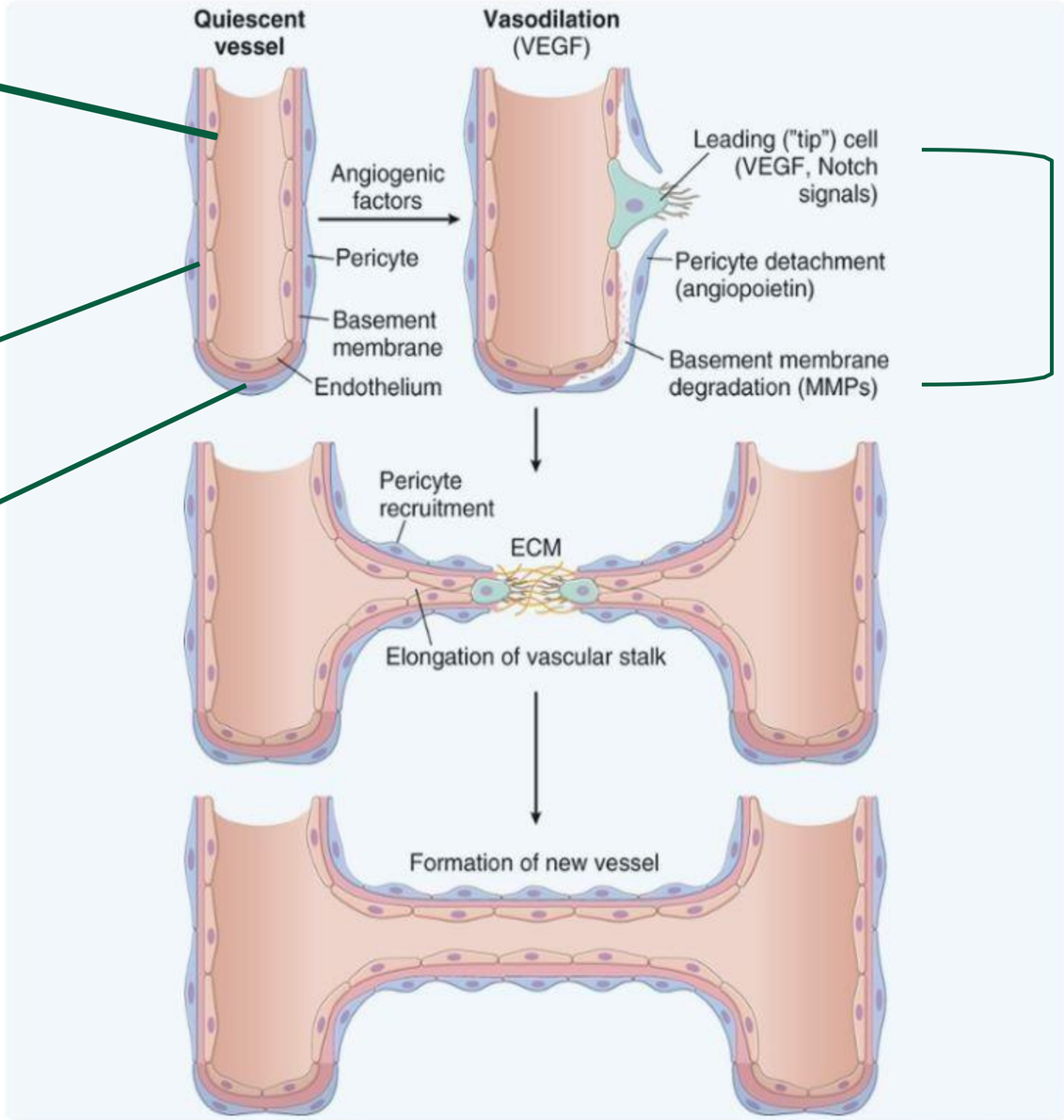

FIG. 3.25 Angiogenesis. In tissue repair, angiogenesis occurs mainly by the sprouting o…

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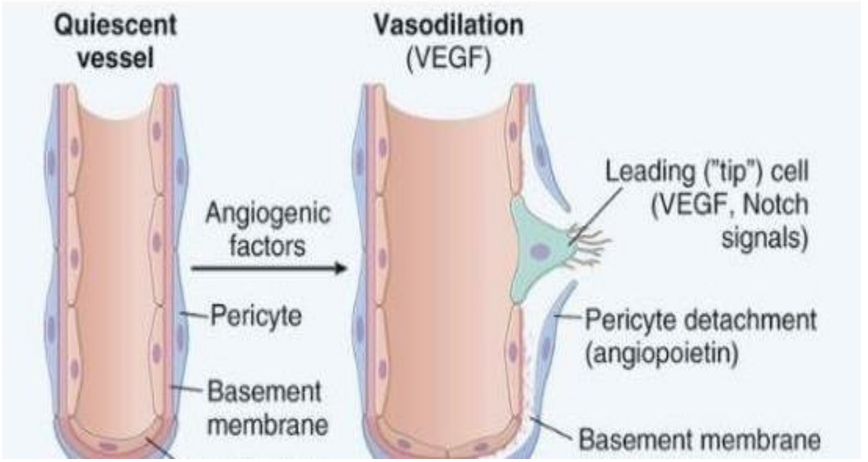
1. Initiation of the Process:

· The process begins with the separation or detachment of pericytes.

· This detachment is mediated by a factor called angiopoietin, which stimulates the separation of pericytes.



2. Exposure of Endothelial Cells:

· The detachment of pericytes leaves the endothelial cells uncovered or exposed.

· This exposure makes the endothelial cells susceptible to additional factors, specifically the vascular endothelial growth factor (VEGF).

3. Activation of Endothelial Cells:

· VEGF initiates the process of sprouting (or notching) by activating the endothelial cells.

· The endothelial cells become metabolically active and begin extending their cytoplasmic membrane into the surrounding tissue.

4. Degradation of the Basement Membrane:

· Concurrently (at the same time) , the basement membrane undergoes degradation.

· This step is facilitated by metalloproteinases, enzymes that degrade components like collagen type IV and laminin.

· The degradation of the basement membrane creates space, enabling the endothelial cells to sprout and extend out of the main blood vessel.

5. Extension and Sprouting:

· The same process occurs in a nearby blood vessel:

· Extension of endothelial cells , Extension of pericytes.

· Then the sprouting activated endothelial cells produce extracellular matrix proteins.

6. Interaction of Cellular Components:

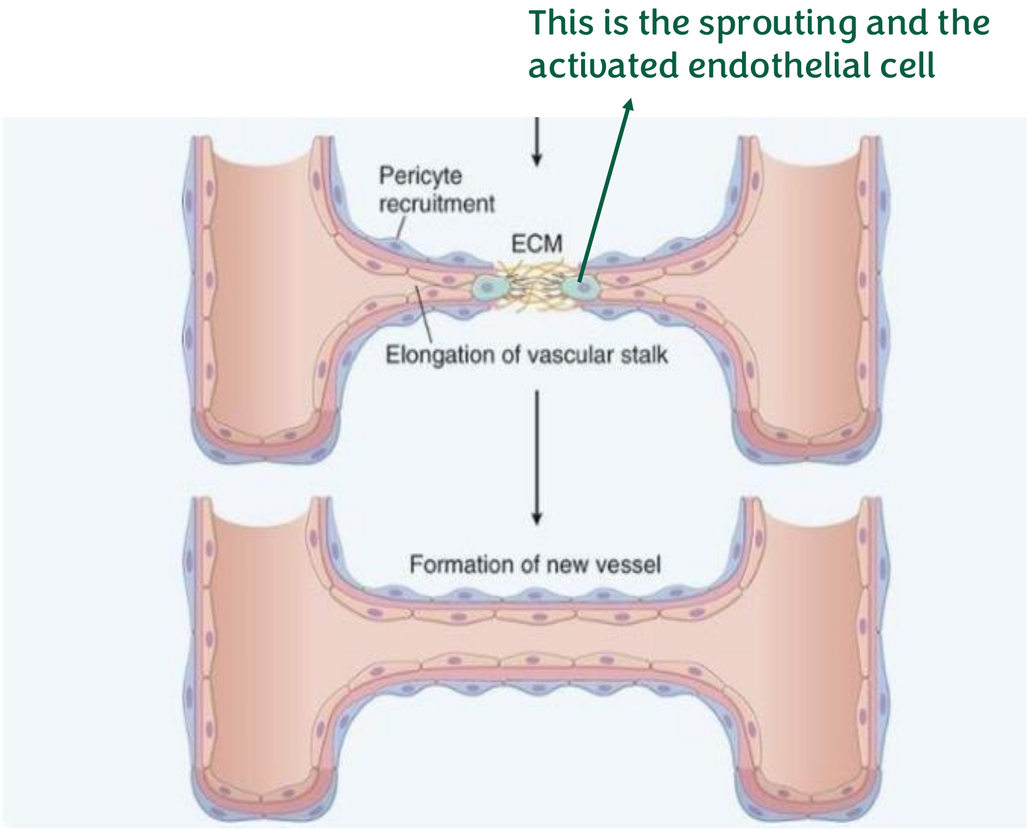
· The interaction between endothelial cells, pericytes, extracellular matrix proteins, and the basement membrane is critical.

· This interaction facilitates the movement and coordination of the cellular system and the basement membrane toward the tip of a similar sprouting process in the adjacent blood vessel.

7. Formation of Stalks:

· As the process continues, the stalks formed by endothelial cells and pericytes on both sides begin to elongate.

· These stalks approximate and move closer to one another until the gap
between them is fully closed.



8. Connection and Completion:

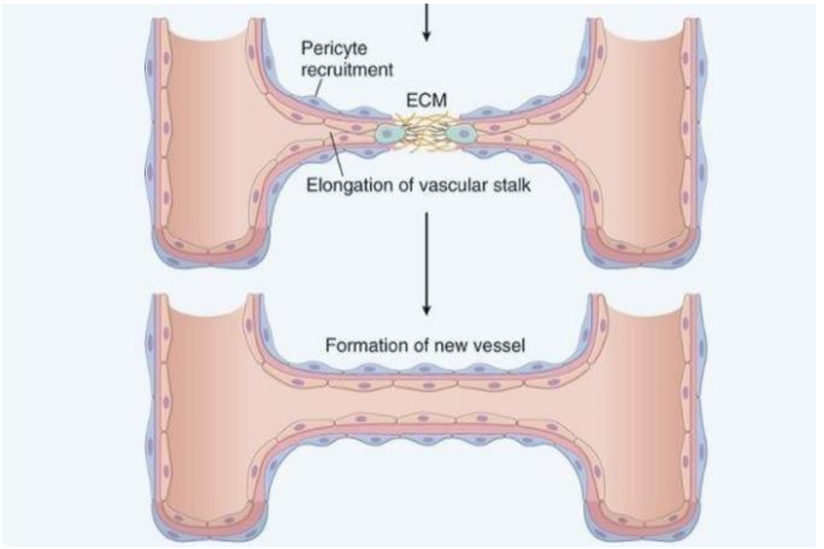
· Once the stalks meet, the following events occur:

· Pericytes attach to each other.

· The basement membrane connects seamlessly.

· Endothelial cells establish organized connections.

· These steps result in the formation of a new channel and the completion of the angiogenesis process, creating a new blood vessel.



9. Scale of Angiogenesis:

· This process is repeated thousands of times (e.g., 1,000, 2,000, or 5,000 instances), resulting in the formation of numerous capillaries and vascular structures.

Impact of Tissue Vascularity on Healing:

· The efficiency of angiogenesis depends on the vascularity of the tissue:

· In individuals with good blood supply and no ischemia or chronic atherosclerosis, angiogenesis occurs more quickly, In patients with ischemic heart disease or atherosclerosis, the process is slower, which negatively affects healing and repair.· Thus, vascularity of tissue is a critical factor influencing the speed and effectiveness of tissue healing and repair.

ACTIVATION OF FIBROBLASTS AND DEPOSITION OF MATRIX:

- **2 STEPS:**
  - **Migrations and proliferation of fibroblasts** to the site of injury
  - **Deposition of ECM proteins by these cells**

Once fibroblasts are active, they start laying down extracellular matrix (ECM) proteins necessary for scar tissue formation.

- **Need cytokines and GFs: PDGF, FGF-2, TGF-ß**
- **Fibroblasts and myofibroblasts help lay down collagen to close the gap**
- **TGF-ß is the most important**

Some fibroblasts differentiate into myofibroblasts, which exhibit contractile features similar to muscle cells.

· **Myofibroblasts are:** Slightly more epithelial and less elongated than fibroblasts.

· More effective at laying down collagen and helping to close gaps in lost tissue, such as in the pancreas.

After collagen has been laid down and the new granulation tissue has been formed to establish a young scar tissue (this is not enough), additional remodeling processes are needed in this connective tissue to strengthen the scar tissue

REMODELING OF CONNECTIVE TISSUE:

Type III collagen is weaker and more fragile than type I collagen (stronger and more durable)

After collagen has been laid down and granulation tissue has matured into young scar tissue, additional remodeling processes are required to strengthen the scar.

- **It is needed to make the scar strong and contract it**
- Remodeling involves the **Cross linking of collagen ,** the replacement and the
- **Switching of type III to type I collagen**
- **Degradation of collagen by Matrix Metalloproteinases (MMPs) and balanced by their inhibitors (TIMPs)**

MMPs are responsible for:

·Degrading collagen.

·Inducing cross-linking.

·Facilitating the transition from Type III to Type I collagen.

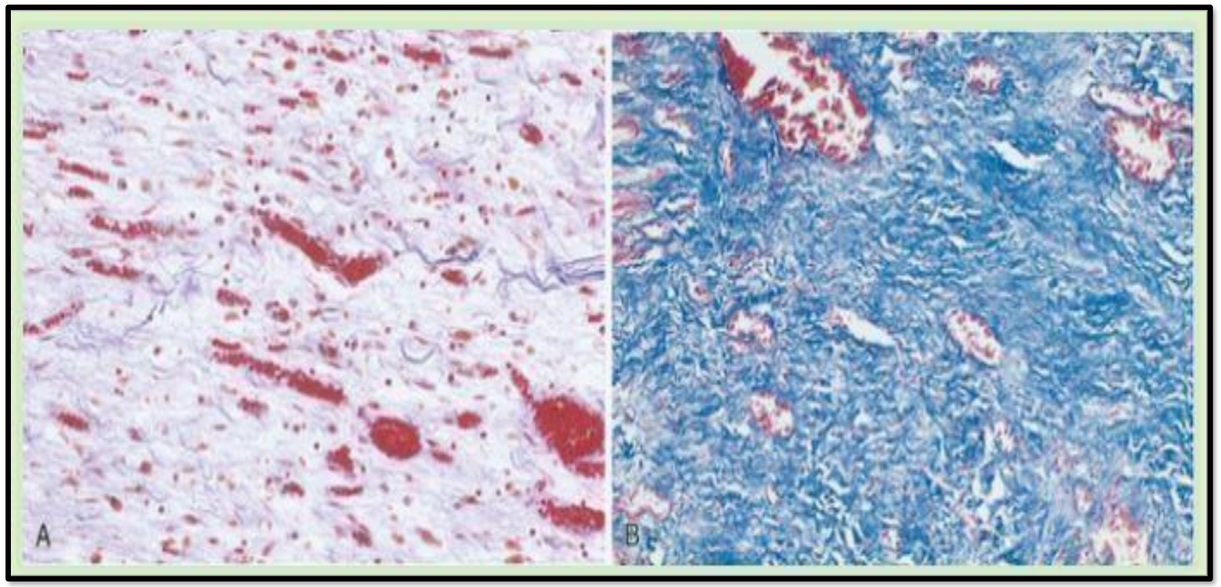
- Excessive MMP activity could compromise the structural integrity of the scar tissue.

-To maintain balance, the body produces Tissue Inhibitors of Metalloproteinases (TIMPs), which:

·Inhibit MMPs.

·Ensure a proper balance between fibrosis and remodeling, preserving what has already been built.

GRANULATIONS TISSUE VS MATURE SCAR



Young Early Granulation Tissue:

· Histologically, is characterized by:

· Hundreds to thousands of small capillaries and blood vessels.

· The presence of collagen type III, which is weaker and less durable than collagen type I (in blue)

Mature scar

During the remodeling process, collagen type III is replaced by collagen type I, which is stronger and more suitable for long-term repair. This transition marks the progression from early granulation tissue to mature scar tissue.

· A trichrome stain is used to highlight collagen type I in blue.

· Strong scar tissue, predominantly composed of collagen type I, appears blue.

· The number of blood vessels is significantly reduced compared to early granulation tissue.

· The abundance of collagen type I is markedly increased

comparing early granulation tissue and mature scar tissue:

Feature	Early Granulation Tissue	Mature Scar Tissue
Collagen Type	Predominantly **Type III** (weaker, less durable).	Predominantly **Type I** (stronger, more durable).
Blood Vessels	Numerous small capillaries and blood vessels.	Fewer blood vessels compared to early granulation tissue.
Strength	Weaker structural integrity.	Stronger and more stable.
Appearance on Trichrome Stain	Collagen not prominently stained.	**Type I collagen** appears **blue**.
Tissue Composition	Rich in cellular and vascular components.	Dense with extracellular matrix, mainly collagen type I.
Functionality	Initial stage of wound healing.	Final stage of tissue repair, providing stability and strength.

Summary

Repair by Scar Formation

- Repair occurs by deposition of connective tissue and scar formation if the injured tissue is not capable of regeneration or if the structural framework is damaged and cannot support regeneration.
- The main steps in repair by scarring are clot formation, inflammation, angiogenesis and formation of granulation tissue, migration and proliferation of fibroblasts, collagen synthesis, and connective tissue remodeling.
- Macrophages are critical for orchestrating the repair process, by eliminating offending agents and producing cytokines and growth factors that stimulate the proliferation of the cell types involved in repair.
- TGF-β is a potent fibrogenic agent; ECM deposition depends on the balance among fibrogenic agents, matrix metalloproteinases (MMPs) that digest ECM, and the tissue inhibitors of MMPs (TIMPs).

FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT):

The reparative process in any tissue is influenced by several factors that determine the efficiency and quality of repair. These factors can either support or hinder the process.

1. Infections
2. Diabetes mellitus
3. Nutritional status
4. Steroids
5. Mechanical factors
6. Poor perfusion
7. Foreign body
8. Type and extent of tissue injury
9. Site of injury

These factors often occur together. For example, a single patient may suffer from infections, diabetes, and other factors simultaneously, complicating the healing process.

All of them can be in the Same patient

1. Infections

· Infections are the enemy of surgeons and patients undergoing surgery , they are one of the most important factors affecting repair.

· If a wound becomes infected:

1) The reparative process is interrupted.

2) Proper healing is delayed.

3) There is a higher risk of complications and improper scar formation.

· During severe acute injuries, patients are often covered with antibiotics.

· In high-risk surgeries (e.g., intra-abdominal surgeries), antibiotics are given 8 hours before surgery to reduce infection risks.

· Dirty wounds must be cleaned and cleared of infection-causing factors to promote proper healing.

2. Comorbidities – Diabetes Mellitus

· Diabetes is a critical comorbidity that delays the reparative process and increases the time needed for healing.

· Effects of diabetes include:

1) Impaired blood vessel function (angiogenesis).

2) Disruption of growth factor activation and mediator signaling.

3) Glycosylation of tissues and blood vessels, which is toxic and negatively impacts healing.

· Patients with poorly controlled diabetes face a higher risk of complications and impaired healing.

· Proper control of diabetes can mitigate complications and improve the healing process.

· Poorly managed diabetes, with its short-term and long-term complications, impacts the entire healing cascade, particularly angiogenesis.

I need you to pay attention to :

3. Nutritional Status

· Not common in our region but occurs in patients with chronic diseases or after surgeries (e.g., small intestine resection).

· if you have a patient who is debilitated , lost a lot of weight , malnourished and you need to expose him to major surgery, we utilize what we call parenteral nutrition where we give them high-calorie, high-protein compounds in his blood vessels to build up his immunity before we expose him to major surgery.

• Outcome:

· Well-nourished individuals have a smoother, quicker healing process.

4. Steroid Use

· Steroids are strong anti-inflammatory drugs that inhibit the arachidonic acid pathway.

· Their use delays the healing process (e.g., healing may take three weeks instead of one week).

- Impact on Patients:

· Patients on steroids are immunocompromised, increasing the risk of infections.

· Tissue damage in these patients is harder to repair.

- Management of Steroid Use:

· If possible, discontinue steroids before surgery.

· Pay attention to other factors to ensure proper healing.

· Provide preventive measures (e.g., infection control)

for patients with severe tissue damage and steroid use

5. Mechanical Factors

· The presence of foreign bodies delays healing and can result in improper healing, Whenever possible, foreign bodies should be removed from the injury site before closing or cleaning the wound.

Example:

Obesity and Smoking

-Obese and smokers patients ,especially those with chronic obstructive lung disease (COPD), can face additional mechanical challenges during healing:

-A patient undergoing abdominal surgery may experience complications due to increased intra-abdominal pressure from obesity or chronic coughing (as seen in smokers with COPD).

- These factors can result in wound dehiscence (separation of a wound), negatively affecting the healing process.

Management: Special care is required for such patients to monitor the wound closely and manage the increased pressure.

6. Poor perfusion

· Poor perfusion, often due to conditions such as severe ischemia, atherosclerosis, hypertension, and peripheral vascular disease will delay the healing process.

• Example:

Patients with these conditions who undergo surgery, especially in the peripheral areas (e.g., foot or hands), require more time for healing.

They may also need additional care, including proper nutrition, antibiotics, and more time for recovery.

• Management: Ensuring proper blood supply and perfusion is essential for effective healing and for activating the reparative process.

7.Foreign Body in Wound

· The presence of foreign bodies inside a wound, such as needles, scissors, or forceps, is highly dangerous and considered malpractice if overlooked.

• Management:

- All foreign bodies should be removed during surgery or wound closure to ensure proper healing.

• Exceptions: In some cases, removing a foreign object could cause more damage, so it may be kept in place temporarily or permanently (e.g., small needles in soft tissue).

The body can encapsulate such foreign bodies over time with scar tissue, but in general, foreign bodies impede the healing process.

8. Type and Extent of Tissue Injury

· its impact the healing process.

• Example:

-Facial Wounds in a Young Patient:

· A 15-year-old with a facial wound or incision will heal quickly, often within a couple of days. Sutures may be removed as early as the fifth or sixth day.

-Severe Peripheral Wounds in an Older Patient:

· A 75-year-old smoker with severe atherosclerosis and peripheral vascular disease undergoing vein surgery or bypass surgery will experience delayed healing. The wound takes longer to heal due to the severity and location of the injury.

9. Site of Injury

Wounds in certain areas of the body heal at different rates depending on the tissue type and blood supply.

- Examples:

-Quick-Healing Areas:

Injuries to the face, head, or tongue heal faster due to richer blood supply.

-Slower-Healing Areas:

Abdominal wounds take longer to heal than facial wounds.

Peripheral lower limb injuries require even more time due to poorer blood circulation in these regions.

Factor	Primary Impact on Healing	Unique Consideration	Examples
1. Infections	Delays healing, increases complications	Can lead to improper scar formation; requires antibiotics pre- and post-surgery in high-risk cases	Wound infections after surgery
2. Comorbidities	Slows reparative processes	Diabetes impacts angiogenesis, blood vessels, and overall repair	Diabetic patients with poor control
3. Nutritional Status	Impairs tissue repair and immunity	Malnutrition affects healing; parenteral nutrition may be needed for malnourished patients before major surgery	Malnutrition in post-surgical patients
4. Steroid Use	Suppresses inflammation and delays healing	Increases risk of infection and prolonged healing; may require discontinuation before surgery	Patients on chronic steroids
5. Mechanical Factors	Interrupts wound integrity	Includes foreign bodies, high intra-abdominal pressure, or coughing leading to wound dehiscence	Obese smokers with abdominal surgery
6. Blood Supply	Critical for oxygen and nutrient delivery	Poor perfusion from ischemia, atherosclerosis, or peripheral vascular disease slows repair	Peripheral wounds in patients with PVD
7. Foreign Bodies	Triggers chronic inflammation and delays healing	Small foreign bodies can sometimes remain if removal causes more damage	Retained needle in soft tissue
8. Type of Injury	Influences healing time based on severity	Larger, deeper injuries take longer to heal	Vein surgery in elderly patients
9. Site of Injury	Healing varies by tissue type and blood supply	Facial wounds heal faster than abdominal or lower limb wounds	Head vs. peripheral limb injuries

PAST PAPERS:

1) **Found in mature scars:**
A. cross-linked collagen 1
B. Granulation tissue
C. a lot of thin-walled capillaries
D. collagen 3 only
E. collagen 2 only

2) **Secondary repair -compared with initial repair- has:**
A. more scar and more tissue injury
B. always associated with tissue granuloma
C. very small tissue lost
D. maintained the function of the repaired tissue

3)In contrast to repair after acute inflammation, repair after chronic inflammation is characterized by: A.Lesser activity of vascular endothelial growth factor
B. Lesser amount of collagen type 1
C. granulation tissue and scar formation
D. quick and simple with no need for mediators

4) Microscopic examination of granulation tissue and early immature scar formation will show?
A. numerous young capillaries and heavy mixed inflammation cell infiltrate
B. complete re-epithelialization of the surface
C. heavy eosinophilic and mast cell infiltrate
D. Abundant cross-linked collagen type 1 fibers
E. numerous foreign-body type giant cells granulomas

Additional Resources:

رسالة من الفريق العلمي:

﴿ يَأْتِ بِهَا الله إن الله لطِيفٌ خَبِير ﴾

"Allah will bring it about. Indeed, Allah is Subtle and All-Aware."

ثُم تأتي إرادةُ الله , فتتيسر مُعسراتك وتتمهد الطُرق، وتفتح مغاليقُها ,وتهيأ اسبابها
وتتجمل لتأتيكَ كاملة تامة مصحوبة بجَميل عطاءِ ربُّك.
فلا يغُرنك تشتتُها الآن، ولاتحزن لإستحلاتها، فوالله لوّكانَ بينك وبينها عوامقُ البحار
وشواهق الجبال يآت بها الله.

Then comes the will of God — and what was once difficult becomes easy, the paths are
— smoothed, the locked doors are opened, the means are prepared, and everything aligns
arriving to you complete and perfect, wrapped in the beautiful generosity of your Lord
So don't be deceived by its current scattering, and don't be saddened by how impossible it seems
By God, even if vast oceans and towering mountains stood between you and it — God would
still bring it to you

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			