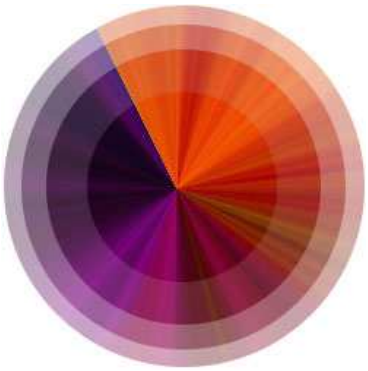


Wound Healing

Sunday 28 Oct 2007 , Dr.Qattan

❤ we would like to send **a Deep Thank You** for Ohoud Al-saedi & Lamees Almutlaq for writing this lecture & the Dr's notes.. if it wasn't for their kindness we wouldn't have papers for this lecture .

These are some guiding signs :

(!) : Important note .

☒ : The Dr didn't mention this at all but it was found in the slides .

★ : Is a risk question --> The Dr said that this point was important or asked a question about it .

- Have Q's ? found errors ? send them at : surgeryqueens@gmail.com

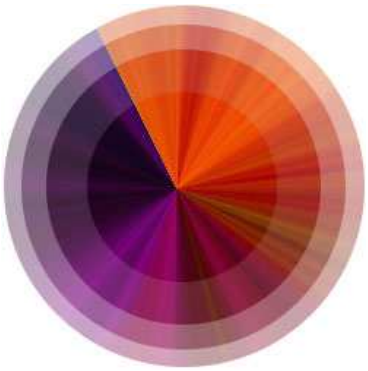
Before starting I just want to make a couple of things clear:

- The skin is of three layers : epidermis (upper), dermis (under), subcutaneous (the lowest).
- The dermis contains the fibroblasts that form collagen.
- Collagen is what makes the dermal layer join and close.

Wound healing is of two types: *(what are the differences between the two?)*

A)Healing by Primary Intention:

- This occurs when there is a small cut and the epithelial edges are not far apart so these edges are brought together and joined by suturing to close the wound.
- This takes about 1-2 days (so we tell the patient that it's ok to take a shower after two days because there will be no infection since the wound is closed).
- While the upper layer "epithelium or epidermis" has been joined and closed, the lower layer "dermis" is slower than the epidermis and needs a long time to form collagen and close (takes about 4 days to form collagen and about 7 days to make the collagen strong), so if we remove the sutures on the second day the wound will open again because even though the epidermis has closed, the dermis hasn't healed yet (so the sutures can be taken out on 5^{th}-7^{th} day).
- If the wound is under tension we should wait longer before removing the stitches because collagen in that case needs to be stronger.



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(!) Summary :

* Occurs in small cuts with epithelial edges near each other
* Fast (1-2 days)
* The epidermis is closed but the dermis takes time.
* The wound is closed by SUTURES.
* This type of healing is what we see in surgical wounds (wounds that have been cut by surgeons E.g. : during surgeries).
* It is good healing with minimal scars.

B) Healing by Secondary Intention:

- This type occurs when the epithelial edges are far apart and are not joined together by sutures so the epithelial edges will grow only few millimeters &won't close, in this case the DERMIS is the one that's going to bring the epidermis together and joins the edges..

  (How?)
- The bed of the wound (the dermis) starts forming granulation tissue that contains (vessels, fibroblasts, collagen, & inflammatory cells)..so the collagen in the dermis will contract to bring the edges of the dermis together and thereby the edges of the epidermis above together (How? I'll explain it in details later!).
- This type takes longer time.

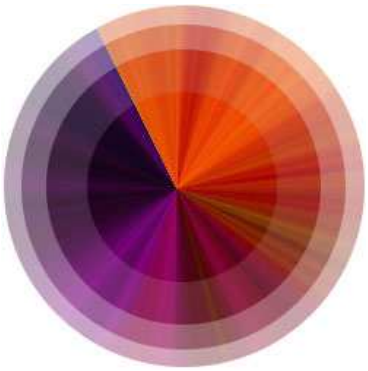
(!) Summary :

* Occurs in large wounds with far apart epithelial edges.
* Takes long time.
* The dermis closes before the epidermis and causes the epidermis to close.
* It's not the sutures that bring the wound together , it's the [Collagen + Granulation tissue] .

Phases of wound healing:

Phases of wound healing: (they are the same in both Primary and Secondary Intention)

1) Vascular phase
2) Cellular phase
3) Remodeling



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1) Vascular phase: (two parts: vasoconstriction & vasodilatation)

A) Vasoconstriction: (This is to stop the bleeding)

a) Due to sympathetic supply.

b) From thromboxane that is secreted from platelets

There is a process of action in which platelets come and start secreting thromboxane , so what is that process? I'll explain exactly what happens when a wound occurs right from the start :)

One) When a wound is cut, the vessels in the dermis are also cut → they start bleeding → immediate vasoconstriction occurs by sympathetic supply. Another thing also occurs which is that the extrinsic factors of the wound activate the coagulation cascade that ends by forming **Fibrin**.

Two) (what's the coagulation cascade?)

Coagulation Cascade: prothrombin --------> thrombin

↓ (stimulates)

fibrinogen ----------> fibrin ----------> stable fibrin

↑ (stimulates)

factor 13

(★ If there is any deficiency in factor 13 there will be abnormal wound healing)

Three) Fibrin has an important role which is that it's the **primary 1st blanket** for platelets to stick on and start secreting aggregating factors to call more platelets to come, these aggregating factors are:

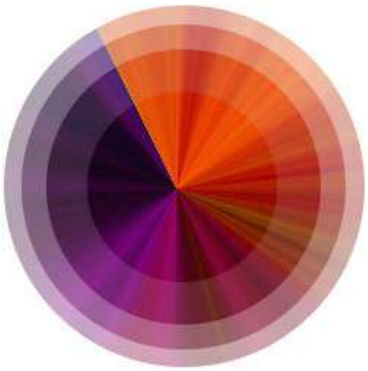
1) **Fibronectin :** which is a bigger blanket for the platelets (because fibrin can only hold the initial platelets so these platelets secrete a bigger blanket for the newly coming platelets, and these newly coming platelets also form more fibronectin and more aggregating factors) *"ya3ny it's like an ongoing cycle"..*
2) **Thromboxane :** all platelets secrete thromboxane and as platelets increase in amount by aggregation at the site of the wound, more thromboxane is being secreted until enough thromboxane will cause vasoconstriction helping the sympathetic initial vasoconstriction.

B) Vasodilatation: (This is to increase the blood supply to the wound so that it can heal)

(How can blood help In wound healing?)

Blood has:

1- Mast cells that secrete histamine .
2- Platelets that secrete serotonin.
3- Other inflammatory cells that secrete prostaglandins and nitric oxide (NO).



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➔ These four secretions will cause vasodilatation and therefore more recruitment of inflammatory cells to heal the crack. *(also a cycle)*

(!) Summing up vascular phase:

✳ It's made of : Vasoconstriction + Vasodilatation.

✳ It occurs [immediately].

✳ Vasoconstriction to stop the bleeding then vasodilatation to increase blood supply → achieving hemostasis.

✳ FIBRIN IS NOT SECRETED FROM PLATELETS but as an [END PRODUCT] of the coagulation cascade.

✳ Fibrin is the first blanket for platelets to aggregate and form a plug.

✳ Platelets in vasoconstriction secrete: 1-thromboxane 2-fibronectin.

✳ Platelets in vasodilatation secrete: serotonin.

✳ Fibronectin is the [bigger] platelet blanket.

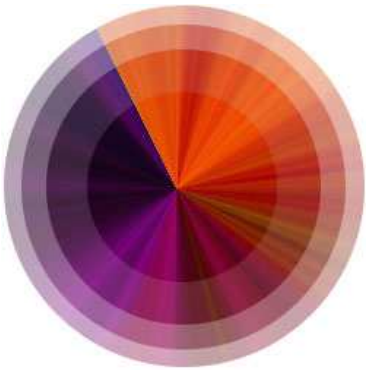
2)Cellular phase: *(Three parts: inflammatory neutrophilic, inflammatory macrophagic, fibroblasia)*

- After vasodilatation, more inflammatory cells come.
- Even though fibroblasts are the ones that produce collagen that is responsible for wound healing, the Inflammatory cells are needed [before] healing to:
  1) Clean out the wound (from bacteria).
  2) To stimulate fibroblasts to produce collagen.
- Inflammatory cells go out of the capillaries into the wound by:
  1) Margination .
  2) Adhesion.
  3) Migration.

A) Inflammatory neutrophilic phase:

- **This phase takes 2 days.**
- **Adhesion of neutrophils occur by:** the Louis Antigen on the neutrophils binds to **P-SELECTIN** on endothelial cells of the capillary. After that endothelial cells start gaping and migration occurs.
- **Migration occurs by:** binding of Integrin on the neutrophils to ICAM (inter-cellular-adhesion-molecule) on the surface of the capillary endothelial cells facing the gap.

(!) Note: The first inflammatory cells to enter are the neutrophils because the first adhesion molecule to be expressed is P-selectin.



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- After migration of neutrophils (The Soldiers) to the wound site they have 3 main functions :
  1) Phagocytosis.
  2) Production of free radicals to kill bacteria.
  3) Production of [proteinases] to break the edges of the collagen already present at the wound so that the newly formed collagen can stick to the old one.
- After finishing their function the neutrophils die by apoptosis.

(!) Summary :

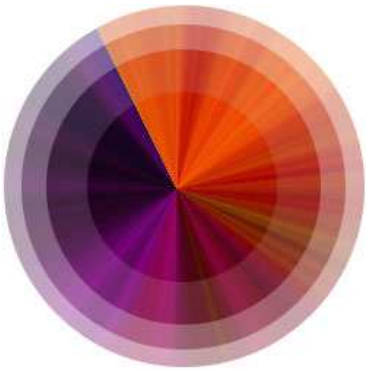
[In 2 days] : [Adhesion :Louis antigen + p – selectin], [Migration : ICAM + integrin] ,[Clean up the wound : phagocytosis , free radicals , proteinases] , [Finally : neutrophil DEATH (apoptosis)]

B) Inflammatory macrophage phase:

- Starts after the neutrophils die.
- Takes another 2 days.
- **Adhesion of macrophages occurs by:** binding of an antigen next to the Louis antigen on the macrophages to the **E-SELECTIN** on the epithelial cells of the capillary.
- **Migration is by :** binding of Integrin on macrophages to the ICAM on the endothelial cells.

(!) Note : Macrophages are the 2nd cells that enter to the wound.

- Function of macrophages (The General → the big guy):
  A. Same as neutrophils :
     1) Phagocytosis (to clean the debris of dead neutrophils – the dead soldiers)
     2) Free radical production.
     3) Proteinases.
  B. If macrophages are doing the same neutrophil function then why are they here ? So they have two more functions :
     4) *Production of cytokines.
     5) *Production of growth factors.
- **(!) The growth factors macrophages produce (extremely important)**:
  1) (★)TGF beta (transforming growth factor beta) stimulates the fibroblasts to produce collagen**.[most important]**
  2) Epidermal (epithelium)growth factor
  3) Keratinocyte (epithelium) growth factor — Stimulate epithelial growth and closure of wound .
  4) FGF basic (fibroblast growth factor basic) — Stimulate angiogenesis (capillary formation) .



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5) Vascular endothelial growth factor
6) Platelet derived growth factor (secreted by both platelets and macrophages): **(!) IT HELPS IN ALL STEPS OF WOUND HEALING** = everything : endothelial, fibroblasts, angiogenesis stimulation .

(!) Summary of Growth Factors : [Epithelium : 2 growth factors] , [Vessels : 2 growth factors] , [Fibroblasts : 1 growth factor] , [Everything : 1 growth factor]

C) Fibroplasias phase:

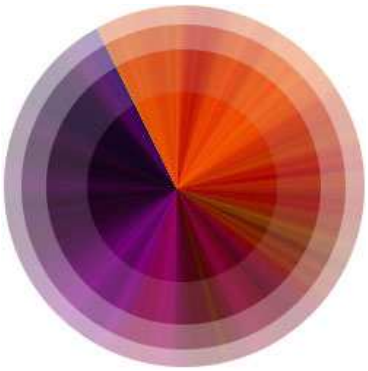
After macrophages have finished their function, fibroblasts start forming collagen .

**what is collagen?*

- **Collagen:** a protein that causes wound healing.
- Is called tropocollagen because there are 3 polypeptide chains in one molecule of collagen.
- Each polypeptide chain is made of 1000 amino acids so the tropocollagen which is one molecule of collagen (with the 3 polypeptides) has 3000 amino acids.
- Each polypeptide chain is a helix and intertwines with the other two and it turns every 3rd amino acid -> so there are 333 turns per chain.
- The area of joining of the 3 helixes is tight so we need a very small amino acid → (**GLYCINE)**.
- So glycine can be found in every 3rd amino acid → it's the most abundant amino acid in collagen.
- In one tropocollagen there are 999 molecules of glycine (333 X 3 chains).

Steps of collagen synthesis in fibroblasts:

1. **Hydroxylation** of lysine and proline: *(It's a very important step because we only eat non-hydroxylated lysine and proline)*
2. Formation of **PROcollagen** [It's a tropocollagen with an extra piece]then this piece is broken and it's secreted outside the fibroblast in the extracellular matrix.
3. The tropocollagen then will **cross link .**
   - The most important cross linking enzyme is "Lysine Oxydase".
   - This cross linking of collagen will form long sheets that will contract..how does this contraction occur? When macrophages see that the wound hasn't healed yet they start producing very large amounts of **TGF beta** that instead of stimulating fibroblasts to form collagen → they cause fibroblast to mutate into **myofibroblasts** that will start producing actin & myosin (like a muscle cell)→This will cause the contraction of cell.



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But if these actin and myosin contract in the myofibroblast, only the myofibroblastic cell will contract without the contraction of the surrounding cells and tissue so there must be something that will transmit the myofibroblastic contraction to the surrounding wound tissue

So these myofibroblasts produce a receptor called "**fibroneksis**". This receptor will attach to [fibronectin] already present in the wound *(remember this? It was the big blanket for platelets)* and the fibronectin attaches to collagen→so now we formed a rope [fibroneksis on myofibroblasts---fibronectin---collagen].

So now when actin and myosin in the myofibroblasts contract they cause contraction of collagen , therefore the whole wound.

- But actin and myosin need a stimulus for them to contract.. in muscles the stimulus was from the nerves but here there are no nerves so the contraction here is stimulated by LPA (lysophosphatitic acid) that is produced from platelets.

(!) Summary :

⁕ If the wound edges are close , there is no problem , the cross link collagen will heal the wound . But if the wound is not closed , (although formation of collagen & cross linkage) →macrophages produce too much TGF-ß → fibroblasts become myofibroblasts → produce actin + myosin → connect to receptor (fibroneksis) →which is attached to fibronectin → which is attached to collagen → whole wound contracts .

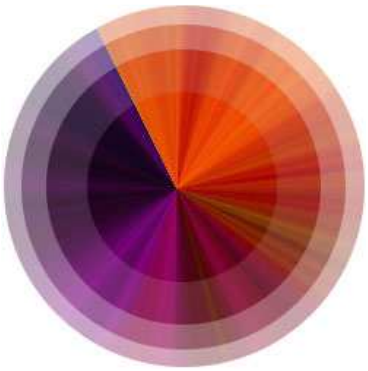
⁕ To remember collagen synthesis : Hydroxy – Pro – Cross.

3)Remodeling: *(after the wound has healed)*

- Collagen initially when produced are not parallel to each other so there will be:
  1) Organization of collagen to be parallel.
  2) More cross linking.
  3) Production of stronger collagen of type I (because the initially formed collagen is of type III).

This is **All & Exactly Everything** that the doctor mentioned during the lecture .. There are no added points .. & there is nothing mentioned from the last year lecture notes after comparing the two lectures , & actually there are differeneces in the phases & their sequences ,so you should stick to th doctor's words .

- Surgery Queens



Wound Healing

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Revision Notes :

- The dermis → collagen.
- Primary wound healing → suture wound together.
- Fibronectin → platelet adhesion (IMP!!)
- Platelets → thromboxin A2
- Aggregation → by platelet factor → CLOT
- Fibrin is coagulation cascade.
- Deficiency in factor 13 → cannot heal bcuz it's the 1st blanket.
- ICAM→ inter cellular adhesion molecule.
- Integrin attaches to ICAM

1st inf. Cells → neutrophils bcuz of P-selectin then after migration they phagocytose and free radicals clean the wound and produce protieneases then apoptosis (2 days)

2nd inf. Cells→ macrophages → E-selectin , this happens at 2 days → cleans again (phagocytoses neutrophils, free radicals and protienease factors).

- Macrophages have 2 more functions (growth factors, cytokines).

growth factor B, TGFB→ stimulates fibroblasts to secrete collagen .

- They also produce EGF & keratinocyte GF and vascular EGF and fibroblasts , & platelet derived growth (has overall action).

✱ Fibroplasia phase :

- Collagen is poly peptide chain .
- Collagen molecule = tropocollagen .
- 1000 amino acids in each chain X3 .
- Area of joining → glycine .
- Most abundant → glycine.
- Lysyl oxidase (IMP!!!)
- Hydroxyl - pro - cross