



SHEET NO. 13+14



PATHOLOGY

DOCTOR 2019 | MEDICINE | JU

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The first 2 ½ pages of this lecture will be revision of lecture 12.

Recap:

- If there is a large amount of damaged tissue, repair process (of either the epithelium or the parenchymal cell) won't be able to regenerate and replace the lost tissue. So instead, repair will occur by **fibrosis**.
- **Fibrosis** includes: patching(ترقيع) the lost tissue of the injured area → healing the wound → replacing the lost tissue especially if the scarring in the tissue is large.
- Healing by first intention:
 - ✓ Occurs whenever you have small amount of tissue loss/ small epithelial injury,
 - ✓ Repair by regeneration, **quick**,
 - ✓ Such as; surgical scar, when the surgeon cuts the abdomen or cuts the skin of the leg, and then approximates the tissue, and sutures it. by this the replacement of the tissue will be quicker and more accurate.
- Healing by second intention:
 - ✓ Large amount of tissue damage,
 - ✓ Repair by scar formation, **slow**,
 - ✓ Requires extensive granulation tissue formation,
 - ✓ Requires extensive angiogenesis process; to prepare the ground for building a very strong scar tissue, which covers and protects the rest (non-injured) tissue.
- In cases of severe tissue damage, second intention will be the way of healing, and this takes place through the following steps:

All have the same meaning:
*scar formation
*fibrosis *fibrous tissue
*fibrous scar *scaring

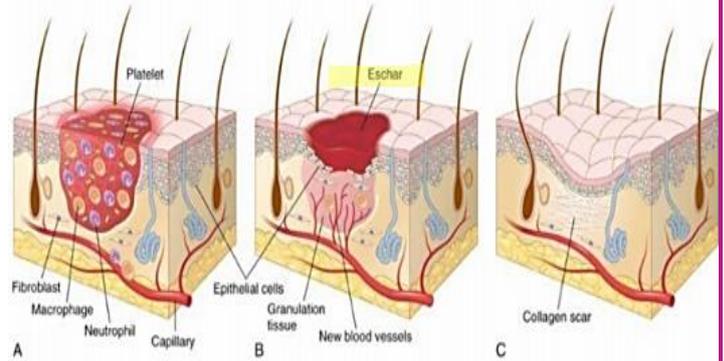
1) Hemostatic plug (platelets): <ul style="list-style-type: none">♦ formation of platelets/hemostatic plug♦ this plug forms quickly (minutes after injury)♦ if the patient uptake anti-platelets/coagulation drugs, forming platelets will occupy much more time.	2) Inflammation process: <ul style="list-style-type: none">♦ activation of the macrophages (M1, M2)♦ starts 6 hours after the injury and continues till 48 hours. (6-48 hrs.)	3) Cell proliferation: <ul style="list-style-type: none">♦ Including angiogenesis and fibroblast migration and proliferation♦ takes 10 days to be completed.	4) The remodeling process: <ul style="list-style-type: none">♦ starts 2-3 weeks after injury♦ it takes 6 months to be completed (100% remodeling).
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Hemostatic → development of something, in order to prevent bleeding and insure homeostasis.

Remodeling: cleaning up extra tissue and proteins and cell debris from the site of injury.

- A cartoon from the skin and subcutaneous tissue, where an injury caused damage and loss of the tissue, explanation:

In (A): initially, blood will fill in the gap with lots of hematopoietic blood elements which gets activated and secretes inflammatory chemical mediators. **Platelets** get recruited and stimulated to aggregate on the surface of the well of fresh blood.



-Here we can see that there is a discontinuity/big gap in the epithelium, the basement membrane has been destroyed by the injurious agent.

Underneath this damage, there is an artery feeding the tissue, which will get stimulated to start **angiogenesis**.

In (B): after a while, this platelet plug will dry out, become acellular forming “**Eschar**”.

After healing process is done, Eschar will fall out and drop

Angiogenesis process starts from the underneath artery, building up new capillaries, that will creep into the cavity, supporting epithelial and basement membrane proliferation, angiogenesis occurs through fibroblasts migration from new capillaries to the site of injury, to undergo fibrosis, forming **granulation tissue**. Fibroblasts along with ECM, and ECM proteins, at the end form **mature scar tissue**.

In (C): mature scar tissue is formed through:

-cross linking collagen (removing collagen type III, replacing it by collagen type I); to provide the scar tissue with adequate strength that protects the integrity between the new tissue, and the tissue that it belongs to.

- **Angiogenesis process:**

- ✓ an extremely important process in repair by scarring,
- ✓ part of the initial formation of the granulation tissue,
- ✓ multi steps process, each step needs its own GFs, stimulators, inhibitors and enzymes (specifically enzymes of remodeling at the end stages of angiogenesis),
- ✓ there is a strong interaction between newly formed blood vessels and inflammatory cells and ECM and its cells and proteins.
- ✓ This process starts by: Notch signaling (sprouting/branch)
- ✓ The major GFs: **VEGF-A**, **FGFs** mainly **FGF2** and **TGF-β**

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- **Activation of fibroblasts and deposition of connective tissue:**
 - ✓ It is the following process after angiogenesis and granulation tissue forming,
 - ✓ What happens? fibroblasts migrate and proliferate in the site of injury, and then they get activated and start to deposit ECM proteins that are needed in tissue scar formation,
 - ✓ The major GFs and cytokines needed for fibroblasts activation and proliferation: **PDGF, FGF2, TGF-β**
 - ✓ Fibroblasts can differentiate into a cell with contractile muscle features, called: **myofibroblasts** which stimulates laying down more collagen to close the gap.

- **Remodeling of connective tissue:**
 - ✓ After connective tissues synthesis and deposition, the connective tissue in the scar continues to be modified and remodeled; **to strengthen** the scar tissue.
 - ✓ This process mainly represents: **cross linking of collagen (switching from type III → I)**
 - ✓ This process is mainly done by certain mediator: Matrix Metalloproteinases (**MMPs**), which degrade collagen and stimulates its conversion into type I.
 - ✓ MMPs have an inhibitor called **TIMP** (tissue inhibitor of MP)
 - ✓ When is TIMP activated? When we don't need MMPs any more, because if MMP is always active, then **all** what we have built during fibrosis will be degraded (along with the degradation of collagen type III by MMP). **Otherwise**, TIMP will help keeping the balance between synthesis (fibrosis) and degradation (remodeling).

FACTORS THAT IMPAIR TISSUE REPAIR (IMPORTANT):

Reparative process is affected by multiple factors that impact its speed, intensity, degree and perfection, an individual may suffer from only one or multiple factors:

<p>1. Infection:</p>	<ul style="list-style-type: none"> - the enemy of surgeons and patients who undergo a surgery. - if the wound gets infected → all the reparative process will be interrupted → the proper healing process will be delayed. - it prolongs inflammation and potentially increases the local tissue injury. - Antibiotics are used as an infection-avoidance in cases of *severe acute injury or *high-risk surgery or *intra-abdominal surgery; where the risk of infection or post-operation infection is high. - In case of surgeries, patients are covered eight hours before surgery by antibiotics to prevent infections.
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<p>2. Diabetes mellitus: most important example on comorbidities (الأمراض المصاحبة)</p>	<ul style="list-style-type: none"> - Diabetes have short- and long-term complications, that negatively impact the reparative process. - Patients suffering from diabetes/glycosylation of the blood stream → <ul style="list-style-type: none"> *need extra time for healing, *need more support, *experience delay in their reparative process, *experience negative impact on GFs & mediator's activation. - The more you control diabetes → the more you provide proper healing.
<p>3. Nutritional status:</p>	<ul style="list-style-type: none"> - Proper nutrition is important for proper healing. - Patients who are debilitated(منهك), lost a lot of weight, suffering malnutrition, need parenteral nutrition (PN/مغذّي/مصل) before doing any surgery/medical intervention for them; to raise up their immunity. - Patients who are well-nourished will have proper reparative process.
<p>4. Steroids: strong anti-inflammatory drug</p>	<ul style="list-style-type: none"> - Number of people uptaking steroids is increasing. - A very critical drug, causes delay in the reparative processes (instead of 1-2 weeks). - Steroids are inhibitors in the main stem (phospholipase A2) of the arachidonic acid metabolism. - In case of surgeries you should prevent the patient from uptaking steroids; since in addition to slow healing process, steroids cause low immunity, so the chance of infections is higher. - If Patients uptaking steroids had a severe tissue damage, you must properly think about the treatment.
<p>5. Mechanical factors:</p>	<ul style="list-style-type: none"> - Such as increased local pressure or torsion, Causing improper healing process. - Ex: a smoker patient suffering from obesity, chronic obstructive lung disease, continuous coughing, needed a major surgery in their abdomen, <ul style="list-style-type: none"> → you must take care of their abdominal wound; because the surgery causes intra-abdominal pressure that may result in: improper healing and sometimes: Wound Dehiscence. <div style="border: 1px solid black; padding: 5px; margin-top: 10px;"> <p>Wound Dehiscence: when a surgical incision reopens either internally or externally.</p> </div>

<p>6. Poor Perfusion: important</p>	<ul style="list-style-type: none"> - Poor perfusion occurs due to any of these: sever ischemia, atherosclerosis, hypertension, hyperlipidemia. - Patients suffering from poor perfusion, and undergo surgery → <ul style="list-style-type: none"> *need more time for healing *need more attention concerning their nutrients. - Antibiotics help in improving the healing process even if it takes longer time.
<p>7. Foreign bodies:</p>	<ul style="list-style-type: none"> - Such as fragments of steel, glass, needle, medical equipment, or even bone, all impede healing process. - After every single surgery you must remove all of such foreign bodies. - Sometimes removing a foreign body from the tissue causes more damage than keeping it inside, so you can either keep it inside for a while and remove it later, or keeping it forever (if it is too small and removing it will cause more damage, and the body is able to repair with its existence).
<p>8. Type and extent of tissue injury:</p>	<ul style="list-style-type: none"> - A facial wound or an incision in the face of a 15-yr-old child will quickly heal (a couple of days), i.e. Sometimes you remove the suture in the 5th/6th day. - On the other hand, if a 75-yr-old smoker with sever atherosclerosis, peripheral vascular disease, had to do a varicose vein surgery or bypass surgery, then the wound will take longer time; because the type of the injury is more extent and the location of injury is different.
<p>9. Site of injury:</p>	<ul style="list-style-type: none"> - Ex: abdominal wounds heal slower than facial/in the head/in the tongue wounds. - All injuries and wounds depend on the site of injury and the extent of the injury.

ABNORMAL HEALING

Not all repair processes are completely perfect, **problems** in healing processes can occur and if so, they will lead to abnormal healing, such problems are:

- 1) Deficient scar formation
- 2) Excessive repair
- 3) Contractures

We will only talk about the first 2 problems.

1st: DEFICIENT HEALING/SCAR FORMATION

- sometimes the formed scar is deficient and weak, and this deficiency leads to serious complications such as; wound dehiscence.

Wound dehiscence: when the wound is opened because of increased intra-abdominal pressure.

- ★ Those sutures are okay.
- ★ The wound here has been opened because the sutures could not stand the increased mechanical intra-abdominal pressure.



- ★ in cases of wound dehiscence:
 - We have to provide antiseptic environment and protect the wound from infection.
 - **Treatment/prevention:** At the moment of opening the wound you cannot go back and close it, **you have to let it heal by granulation tissue** from the bottom to the surface, and this takes long time (weeks and months).
 - When dealing with wounds of patients suffering from obesity, cough and COPV, we must be ready and put stronger sutures, keep adding gauze and dressing and keeping it for longer time to prevent this (dehiscence) from happening.
 - It could occur in another place other than the abdomen.

- Examples are mainly ulcers; every type of ulcers has a different pathophysiology and different underlying mechanism:

A. Venous leg ulcers

- ✓ They are superficial and dusky,
- ✓ Classic Venous ulcer,
- ✓ Occur due to excessive venous insufficiency and stagnation of the venous system in the lower limb,
- ✓ The common area of these ulcers is: The medial area of the lower leg,
- ✓ They are grey to blue.



B. Arterial ulcers

- ✓ Deep,
- ✓ Occur due to severe ischemia in the blood supply of certain branches of an artery.



C. Diabetic ulcers

- ✓ Deep arterial ulcer,
- ✓ Occur in **diabetic patients**; due to **peripheral neuropathy** (diabetes affects all the organs including the neural sensory neurons). So, they will develop what we call “**Diabetic foot**”, which represents gangrenes and ulcers in the diabetic-patient foot. Nowadays, there are a lot of clinics taking care of the diabetic foot of these patients.



D. Pressure sores/Bed ulcers

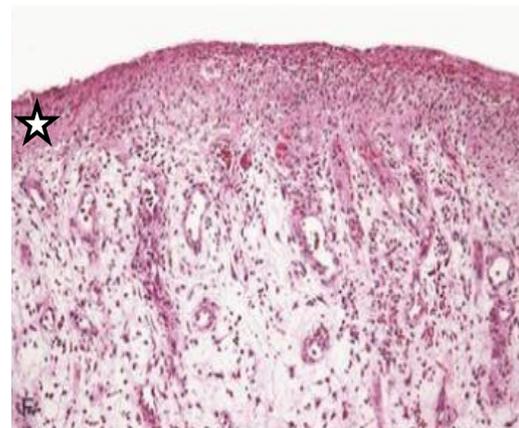
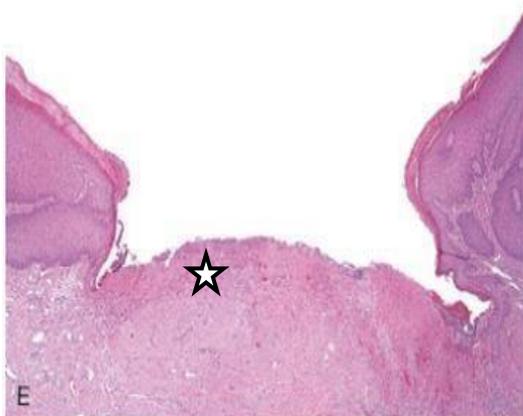
- ✓ The picture shows a back of a patient who **stayed in the bed for a long time**,
- ✓ Occur in patients with **quadriplegia or severe CNS illness**,
- ✓ due to the pressure on their back which leads to ischemia to that area, followed by **deep ulcers**,
- ✓ Nowadays, such ulcer type is considered as a significance of malpractice and bad nursing care,
- ✓ The protocol followed for such patients is: mobilizing them every 15-30 mins. Now, new and specific beds are manufactured for such patients, with multiple bubbles that electrically move up and down, trying to distribute the pressure on the patients back, **so the best treatment is by prevention, through those beds or good nursing.**



A cross section of any of these ulcers will look like this:

E: Discontinuity, big deep ulcer in the squamous mucosal epithelium surface of the skin.

★ **F: The floor of the ulcer:** angiogenetic granulation tissue, occurs as a response to this ulcerative morphology of the inflammatory response.



2nd: EXCESSIVE SCARRING

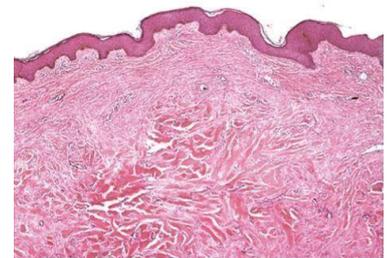
● Hypertrophic scar:

- ✓ Subcutaneous,
- ✓ Treatment: **-excision** (استئصال); trying to clean up the scar tissue by certain surgical types. Or **-utilizing some local anti-inflammatory medications** like steroid cream; to decrease the amount of scar tissue.
- ✓ In cases of surgery: the patient will have instead of a small, insipient, inapparent scar, there will be more scar formation (hypertrophic scar) due to some reasons.



● Keloid:

- ✓ Subcutaneous,
- ✓ A specific type of hypertrophic scar,
- ✓ Occurs more in **dark pigmented people**; that any small surgery can induce big excessive scar tissue like keloid.
- ✓ Sometimes it is really difficult to treat,
- ✓ It runs through families,
- ✓ The picture shows: a lot of fresh, large scars of simple cutaneous tumors → healing by exuberant keloid material.
- ✓ basically, if you take a section from this and examine it under the microscope, you see **abundant dense bundles of collagen type I**, abnormally located causing squamous cell elevation. The more you manipulate them surgically, the more scars you will have.
- ✓ sometimes it is hard to differentiate between keloid and hypertrophic ulcers under the microscope, so you depend on the family history and the pigment of the patient whether it is dark or light.



Both Hypertrophic scar and Keloid, are cosmetically not nice, and can also affect the function if it involves in a joint or in an area which is sensitive for movement.

● Exuberant granulation tissue (proud flesh):

- ✓ Rare.

● Aggressive fibromatosis (desmoid tumor):

- ✓ Subcutaneous/ deep.

● Contractures

FIBROSIS OF ORGANS

The changes which we have talked about concerning fibrosis **in tissues**, can occur **in vital organs**. Info:

- ❖ A very serious condition,
- ❖ Sometimes it causes increase in morbidity or mortality probability,
- ❖ Due to: **excessive deposition of collagen and ECM proteins**.
i.e.: after continuous infections or continuous immunologic injury, whether this injury is in the liver/kidney/pancreas/spleen, this leads to:
inflammation→repair, inflammation→repair, inflammation→repair
this results in: more formation of scar tissue. After 5/10/15/20 years, excessive fibrosis in that particular organ will impact the **vital functions** of that organ.
- ❖ **TGF-β** is the most important mediator in fibrosis,
- ❖ Scar tissue formation and fibrosis in vital organs causes diseases, mainly:

1) Liver Cirrhosis

- ❖ Severe fibrosis, almost end stage,
- ❖ Almost 95% of livers tissue is replaced by fibrosis, causing liver failure,
- ❖ The patient must be treated, if not, they will die,
- ❖ Treatment: either transplantation or stopping the process of fibrosis,
- ❖ Liver failure with no transplantation increases mortality probability,
- ❖ In the west region, the most common cause of liver cirrhosis is alcoholism,
- ❖ In our region, the most common cause is chronic hepatitis C.

2) Idiopathic lung fibrosis

- ❖ Interstitial lung fibrosis,
- ❖ These patients represent lung fibrosis with unknown reason (etiology), that's why it is called 'idiopathic'
- ❖ The whole lung will be replaced by fibrosis scar tissue,
- ❖ The patient cannot breathe or utilize their lungs,
- ❖ some undergo lung transplantation, if not, the mortality probability is high.

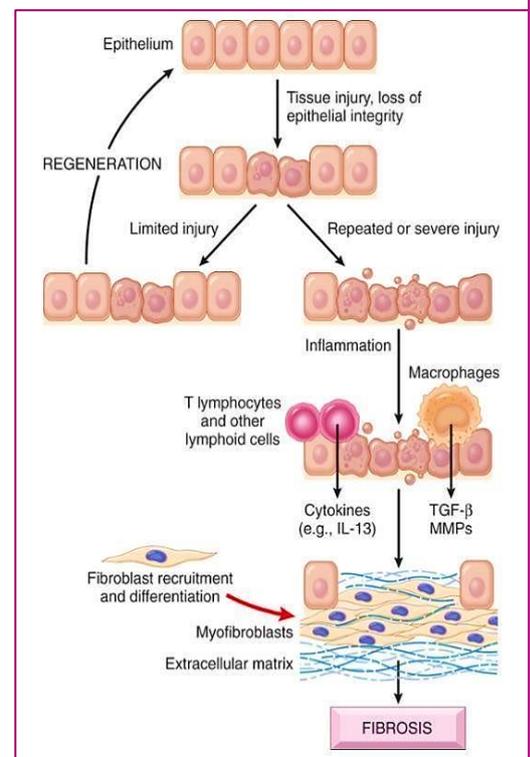
3) ESKD (end stage kidney disease), the last stage of long-term (chronic) kidney disease.

- ❖ If a patient is diagnosed with chronic renal disease, and is already suffering from hypertension (hypertensive nephropathy, a kidney disease caused by damage from hypertension) or diabetes (diabetic nephropathy, a serious kidney-related complication of type 1 diabetes and type 2 diabetes), such patient needs continuous follow up by their clinicians to get sure that the impact of the underlying disease (hypertension/diabetes) gets decreased by close follow up, so that ESKD gets delayed or treated very early.

- ❖ A lot of diseases that affect the kidney end up in causing severe and marked parenchymal renal fibrosis,
- ❖ under the microscope at late stages we can describe the biopsy by: “end stage kidney disease”,
- ❖ diagnosis with ESKD requires collaboration between **pathologists** (looking at the renal biopsy, seeing severe fibrosis in the kidney) and **clinicians** (following up the patient to identify if the patient had history with untreated diabetes or hypertension or glomerulonephritis... (since those diseases increase the probability of ESKD)).

A cartoon explaining excessive scar fibrosis, which leads to loss of function in some of these vital organs:

- If the injury is very small and the extent is limited → regeneration will occur quickly, and the tissue goes back to its original normal state.
- But in cases of severe tissue injury **or** repeated attacks of severe injury such as; repeated attacks of hepatitis C in the liver, this is the result →
 - *inflammation and recruitment of inflammatory cells,
 - *repair by scar formation induced by **TGF- β**,
 - *forming more fibrous tissue, instead of regeneration,
 - * the same cycle keeps repeating again and again and again, within couple of years, depending on the intensity of the injury, this will lead to severe fibrosis in that organ, if:
 - liver→ liver cirrhosis
 - kidney→ ESKD
 - lung→ Idiopathic interstitial lung fibrosis.



Summary

Cutaneous Wound Healing and Pathologic Aspects of Repair

- The main phases of cutaneous wound healing are inflammation, formation of granulation tissue, and ECM remodeling.
- Cutaneous wounds can heal by primary union (first intention) or secondary union (secondary intention); secondary healing involves more extensive scarring and wound contraction.
- Wound healing can be altered by many conditions, particularly infection and diabetes; the type, volume, and location of the injury are important factors that influence the healing process.
- Excessive production of ECM can cause keloids in the skin.
- Persistent stimulation of collagen synthesis in chronic inflammatory diseases leads to tissue fibrosis, often with extensive loss of the tissue and functional impairment.

If you
made it
till here

Then you
are a
super hero

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