



# ***Pathology***

**Subject : Pathology**

**Lec no : Lec 14**

**Done By : Jana Alqhaiwi**

وَقُلْ رَبِّ زِدْنِي عِلْمًا

خلونا يا جماعة قبل ما نبلش بالمحاضرة نعطيكم طريقة تكسبوا فيها أجر  
وانتو قاعدين بمحلكم

طب يلا اتحمسنا شو هي طريقة؟

الموضوع هو كالاتي التبرع برصيد الطباعة تبعكم للطلاب المحتاجة  
الأغلب عنا يستخدم ايباد وما يحتاج هاد الرصيد فليش ما تكسب أجر وتعطيه لناس  
محتاجيته

طب خلص أنا اقتنعت وبدي اتبرع شو أعمل؟

الموضوع جدا بسيط عزيزي الطالب كل يلي عليك عمله هي أنه تتأكد أول اشي أنه  
عندك رصيد طب كيف؟ سهلة بتروح على  
بوابة < خدمات أخرى > رصيد الطباعة

إذا أعطاك (لا يوجد أي حركات طباعه حاليا) معناها رصيدكم موجود وفيكم تتبرعوا

طب تأكدت كيف أتبرع هسا؟

من البوابة < خدمات أخرى > الدخول لشبكة الانترنت (المختبرات واللاسلكية)  
بتأخذ اسم المستخدم (ويلي هو رقمك الجامعي) ويتنسخ كلمة السر  
وأخر اشي بتدخل على QR CODE يلي تحت ويتعبي فورم تبع التبرع بالرصيد

وبس كده انتهت القصة شفتوا قديش سهلة ويتكسب فيها  
أجر كل حدا رح يدرس من الورق يلي اتبرعت فيه

قال -صلى الله عليه وسلم-: (صنائع المعروف تقي مصارع السوء و  
الأفات و الهلكات، وأهل المعروف في الدنيا هم أهل المعروف في الآخرة)

يلا روحواكملوا المحاضرة  
يعطيكم العاقبه



# Functions of ECM

- ① **(1) Mechanical support for Cell anchorage (fixation) + migration**  
③ ± Maintenance of cell polarity. ما يتقدر تحافظ على its polarity تكون ضعيفة
- ② **(2) Control of cell growth.**  
ECM components can regulate cell proliferation. By presentation of many growth factors that are very important in cell growth
- (3) Maintenance of cell differentiation.** Effect the degree of differentiation  
Type of ECM proteins affects the degree of differentiation of the cells in the tissue, acting via cellular receptor of integrin family.
- (4) Scaffolding for tissue renewal.** مثل الصفاة تجديد الخلايا ورجوعها لشكلها الطبيعي  
The maintenance of normal tissue structure requires BM for stromal scaffold. هو اضر Scaffolding repair is the restoration of tissue architecture and function after an injury
- (5) BM acts as a boundary between epithelium & underlying connective tissue.** → That's why epithelium rest on BM in a fixed way and between it there is interstitial tissue وبتكون مترابطة ومرتبطة مع بعضها
- (6) Storage & presentation of GFs like FGF & HGF, both are excreted & stored in the ECM in some tissues.**  
FGF : fibroblast growth factor  
HGF : hepatocyte growth factor



**ECM is component of tissue which provide thickness and rigidity of soft tissue & bone**

**ECM** تتكون من اكثر من **component** و اهم واحد فيها هو collagen

و ايضا تتكون من **interstitial matrix** تربط الخلايا بال **underlining connective tissue** و عندنا **basement membrane of endothelial cell and lining epithelium**

مستقرة و مرتبطة بها عن طريق **adhesive molecule**

# ① Collagen

Which of the following is true about collagen?

هذا السؤال يحفظ (المهم)

This is the most abundant of the matrix protein, it is synthesized by the fibroblasts & osteoblasts.

Collagens are fibrous structural proteins, that confer tensile strength. القوة التي تظلت بسبب collagen

The collagens are composed of three separate polypeptide chains braided into rope-like triple helix. More than 30 types have been identified, some of which are unique to specific cells & tissues. مختلفة بمكان الجسم

Can be fibrillar collagen like type I, II, III, & V.

Collagen types I & III form a major proportion of the connective tissue in healing wounds & particularly in scars.

الشرح بالسلايد يلي بيده

The tensile strength of the fibrillar collagen derives from their cross-linking, which is the result of covalent bonds catalyzed by the enzyme lysyl-oxidase, his process requires vitamin C. important in collagen synthesis

مهم

That is why individuals with vitamin C deficiency have skeletal deformities.

Other are non-fibrillar & may form:

- (a) BM (type IV)
- (b) or be component of other structures like intervertebral discs (type IX), or dermal-epidermal junctions (type VII).

is a genetic or heritable disease in which bones fracture (break) easily, often with no obvious cause or minimal injury.

Genetic defects in collagen causes diseases like osteogenesis Imperfecta &

② Ehlers-Danlos syndrome. Disease that weakens the connective tissue of the body.

The cross-linking of fibrillar collagen fibers is essential for providing tensile strength to tissues. This cross-linking process involves the formation of covalent bonds between specific amino acids within the collagen molecules.

The enzyme responsible for catalyzing these covalent bonds is called lysyl oxidase. Lysyl oxidase acts by oxidizing specific lysine and hydroxylysine residues within collagen, allowing them to form cross-links with neighboring collagen molecules.

An interesting fact is that this process of cross-linking collagen fibers requires the presence of vitamin C. Vitamin C, also known as ascorbic acid, is a cofactor for the enzyme lysyl hydroxylase, which is involved in the hydroxylation of lysine and proline residues in collagen. Without sufficient vitamin C, the hydroxylation step is disrupted, leading to defective collagen synthesis and impaired cross-linking.

2

# ELASTIN

لعشاني بروتين



When blood vessels exposed to stress, elastin contribute to return its baseline structure

After physical stress, the ability of tissue to recoil & return to a baseline structure is conferred by elastic tissue, especially in the walls of large blood vessel (e.g aorta, which must accommodate recurrent pulsatile blood flow), uterus, skin, & ligaments. Morphologically elastic fibers consist central core of elastin surrounded by meshwork of **fibrillin glycoprotein**. Defects in fibrillin synthesis leads to weakening of arterial walls & skeletal deformities like **Marfan's syndrome**.

Q: Marfan's syndrome is defect in which of the following  
↳ Fibrillin

## 3) PROTEOGLYCANS & HYALURONAN (gel-like material)

These are highly hydrated compressible gel

1) [conferring **resilience** and **lubrication** such as cartilage in joints.]

2) They consist of long polysaccharides, called **glycosaminoglycans**, or **mucopolysaccharides**, (examples are dermatan sulfate & heparan sulfate)

3) Also serve as **reservoirs** for Growth Factors secreted into the ECM (e.g Fibroblast Growth Factor).

# Adhesive Glycoprotein, & Adhesion Receptors → <sup>حاضرة ١٤</sup> Part of ECM

Both are involved in:

- ✓ (1) cell-cell adhesion
- ✓ (2) the linkage between cells & ECM, &
- ✓ (3) binding between ECM components.

هون بنحكي عن ال adhesive receptors و مهمتها

● The adhesive glycoproteins include: → <sup>Binds the components of ECM together</sup>

adhesion molecule

(a) **fibronectin** (major component of the <sup>1</sup> interstitial ECM) <sup>2</sup>, synthesized by **fibroblasts** **monocytes** & <sup>3</sup> **endothelial cells**. It binds the extracellular matrix components together also attach to integrins & to fibrin in blood clot, necessary in healing.

(b) **laminin** (major constituent of BM).

The **adhesion receptors**, also known as cell **adhesion molecules** (CAMs), can modulate cell proliferation, differentiation & motility . .



هسة احنا بنعرف انه ال **epithelial cells** بترتكز على ال **basement membrane** ، لكن هذا الارتكاز ما يكون اعتباطي بكون عبارة عن **integrin adhesion molecules** ، وهاي ال **integrins** هي لنفس عائلة ال **entegins** الموجودة على ال **leukocyte** يلي اخذناها بمادة الميد طيب هاي ال **integrins** بشو بتفيدنا ؟  
- **selectin** ال بعمله ال **rolling** انتبهوا ال **in firm adhesion** -

**adhesion molecules (CAMs), can modulate cell proliferation, differentiation & motility . .**

لعمري هاي الجمل مراجعة صر ونزومة .. لربك رح  
ا حس هاي ..

ال **laminin** بربط الخلية بالوسط المحيط فيها فيعني هو يلي حيعطي اشارة للخلية انه يلا انقسمي او يلا اتمايزي وهيك يعني ، يعني هي بالنهاية **receptors** اما في ما يخص الحركة ، فاحنا حكيننا انه ال **rolling** بصير بواسطة هاي المواد

محلولة حرمه .. هاي ال **receptors** حو وجود ر بكو ال خلايا ال (RBC) و بالتالي ال (RBC) حو رح - متأثر بال- (Chemotaxis) لانه حو على ال **receptor**

الدكتورة غششتنا سؤال للعملي ، ،

انه بتجيبك صورة لل **basement membrane** وبتحكيلك شو ال

**major component** ، فانت لازم تعرف انه المكونات الاساسية هي

1-laminin 2-collagen 3-proteoglycan

الدكتورة رجعت لهاد السلايد ←

Slide 157

Interstitial matrix

كيف يرتبطوا مع بعض  
عن طريق fibronectin

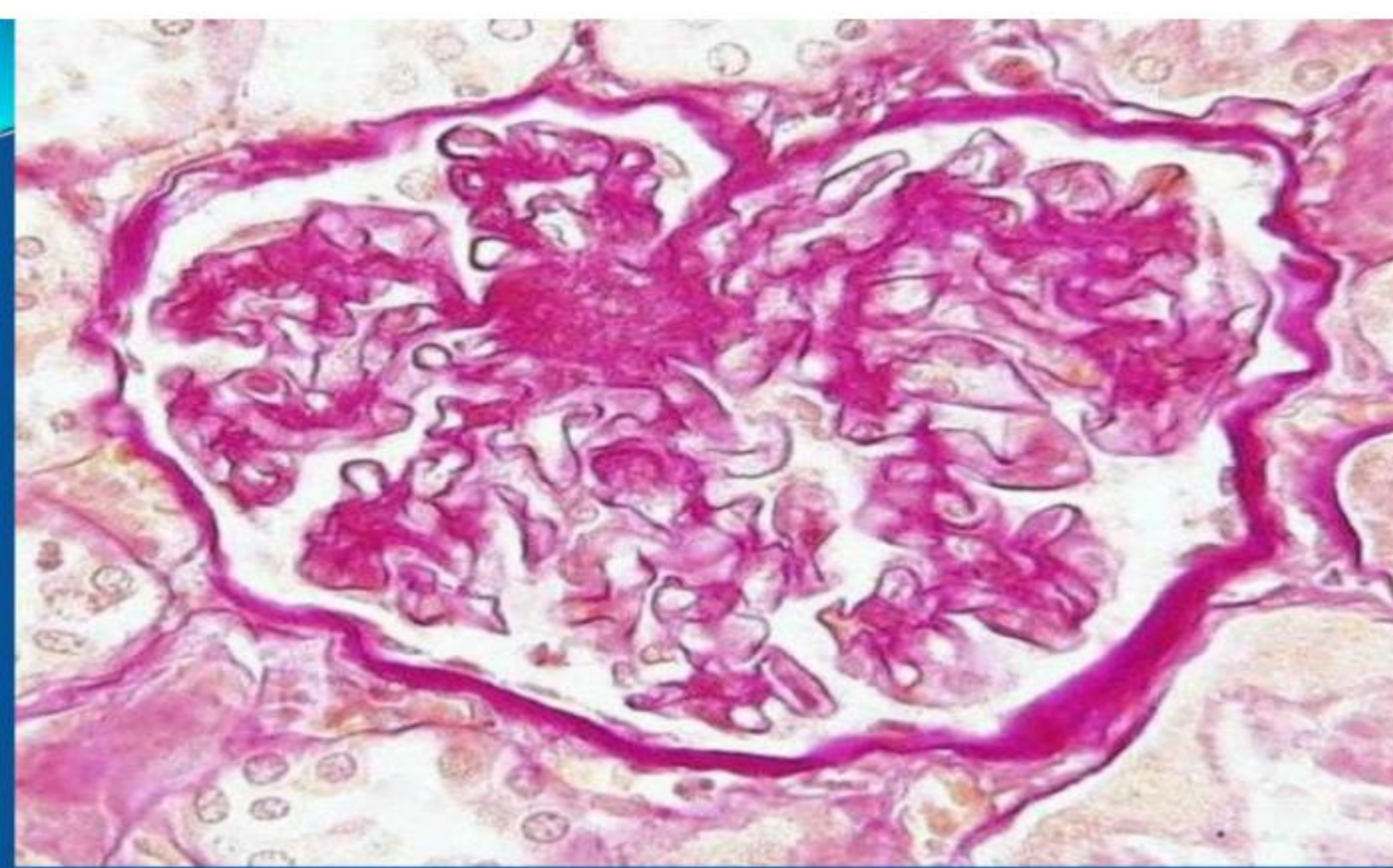


Figure 62 : Renal glomerulus showing basement membrane (pink colored)

150

## Basement membrane

- Collagen form
- Non fibrillin collagen form
- Laminin
- Proteoglycan

**INTEGRINS** → موجوده بكل الخلايا ما عدا RBC → It is an adhesive molecule

Are a family of transmembrane glycoproteins that are the main cellular receptor for ECM components, like fibronectins & laminins. Integrins are present in the plasma membrane of most animal cells, with the exception of RBCs.

They bind to many ECM components initiating signaling cascades that can affect cell locomotion, proliferation, & differentiation.

## Integrins

هي عبارة عن receptors و اي اشارة يستقبلها هاد receptor حتأثر على الخلية ، و احدى أهم المواد اللي بتتفرز هي growth factor , و يلي بدك تعرفه عنها مجموعة من الشغلات يلي هي, ال GF تعتبر short lived يعني تأثيرها لا يدوم لفترة طويلة و يشتغل locally مش زي الهرمونات يعني GF is not hormone الهرمونات تنفرز من الخلية للدم و تتأثر على مكان بعيد

علا بباله وحدة

اما ال GF اله ٣ طرق للانتقال



Chemical substances acts on different receptors

## Autocrine signaling:

In which a soluble mediator **acts predominantly on the cell that secretes it.** →

chemical substance  
يعني الخلية نفسها تفرز  
receptor  
و عنفس الخلية

① This pathway is important in the immune response (eg lymphocyte proliferation induced by some cytokines), & ② in compensatory epithelial hyperplasia (e.g. liver regeneration).

Hepatocyte secrete growth factor which works on itself to helps in proliferation

## Paracrine signaling:

In which, a substance affect cells **in the immediate vicinity of the cell that released the agent.**

This pathway is important for recruiting inflammatory cells to the site of infection, and in wound healing.

example: macrophage and lymphocyte → Lymphocyte has interferon which activates macrophage

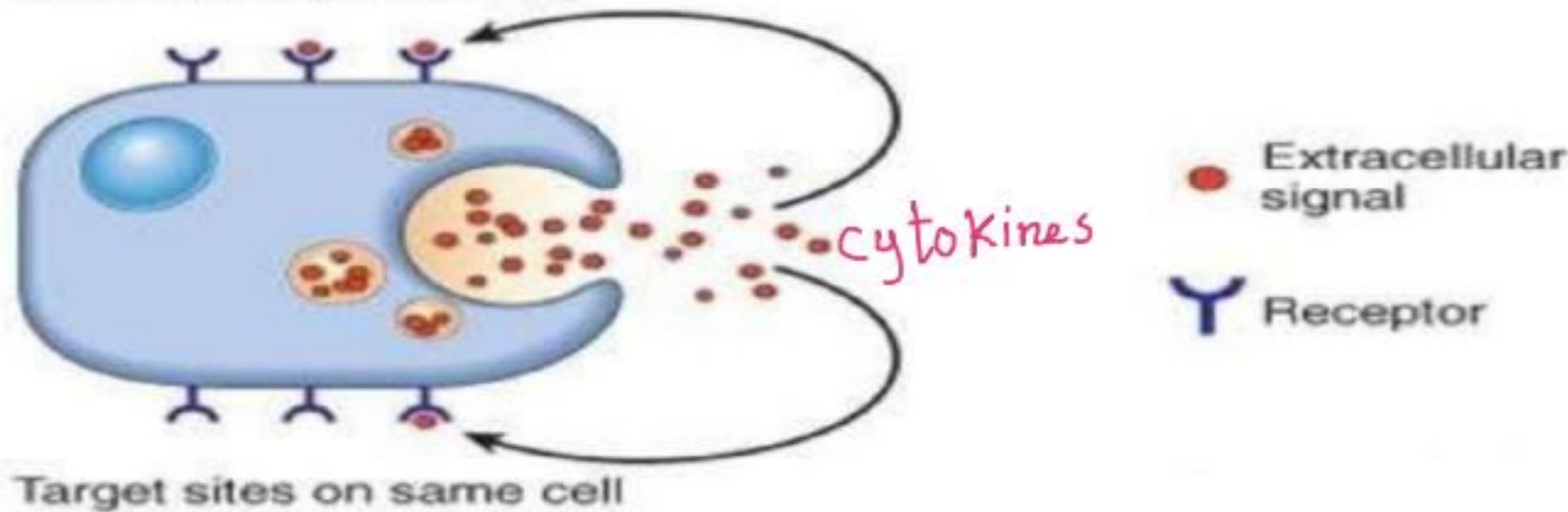
## Endocrine signaling :

In which a regulatory substance, such as a **hormone**, is released into the blood stream & **acts on target cells at a distance.** →

Example : pituitary gland secrete TSH, TSH acts on thyroid

Every chemical substance has its receptor to transduct signaling

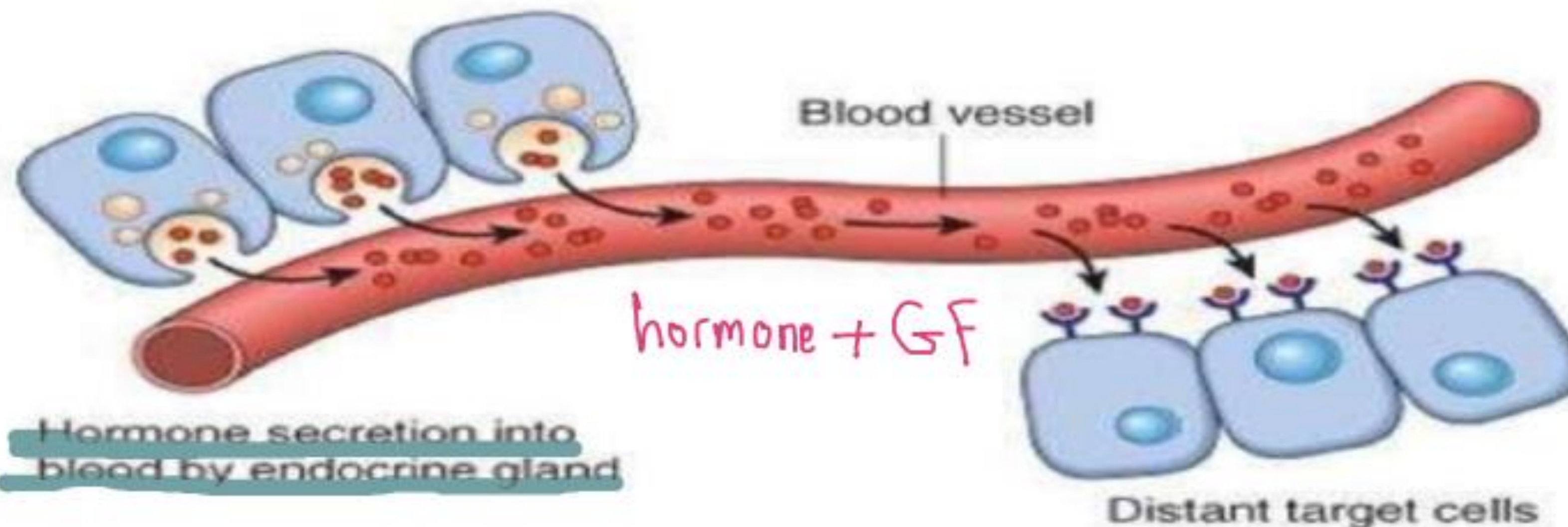
### AUTOCRINE SIGNALING



### PARACRINE SIGNALING



### ENDOCRINE SIGNALING



F 65: Patterns of extracellular signaling of growth factors .

# GROWTH Factors

شغلها بشبه الهرمونات  
بس هي مش هرمون

موجود جزأ من

- They are small glycoproteins ,which generally considered as a subset of cytokines, **refer to the diffusible signaling proteins that stimulate cell growth, differentiation, survival, inflammation, and tissue repair.**
- They can be secreted by neighboring cells, distant tissues and glands, or even tumor cells themselves.
- Normal cells show a requirement for several growth factors to maintain proliferation and viability.
- Growth factor can exert their stimulation through endocrine, paracrine or autocrine mechanisms.
- Due to their short half-lives and slow diffusion in intercellular spaces, growth factors usually act locally.
- Typically, the signal transduction of growth factors is initiated by binding to their receptors on the surface of target cells.

Autocrine,  
paracrine  
signaling



— Hormones are originally secreted from glands , & consist of proteins ->can consider as growth factor  
Not all hormone is growth factor

— Growth factor is natural diffused proteins which is secreted by neighbour cell, cancer cells, gland which helps in wound healing , angiogenesis, and cell growth.

some hormones may consist of cholesterol like steroid

**Growth factor is protein , not fat**



## Growth factors & cytokines involved in regeneration & wound healing are :

- Epidermal growth factor : (EGF) : هاي الصفحة مش للحفظ  
بدن اعرفوا عاودين  
Released from activated macrophages , keratinocytes & other cells. It is mitogenic for keratinocytes & fibroblasts , stimulates keratinocytes migration and stimulates granulation tissue formation.
- Transforming growth factor alfa : (TGF- $\alpha$ )  
Released from activated macrophages, T lymphocytes & keratinocytes & other cells. It stimulates replication of hepatocytes & epithelial cells.
- Hepatocyte growth factor (HGF) (scatter factor)  
Released from fibroblasts, stromal cells in the liver & endothelial cells . Enhances proliferation of hepatocytes & other epithelial cells , and enhance cell mobility.

## Vascular endothelial cell factor (VEGF) (isoform A,B,C,D)

Released from mesenchymal cells . It stimulates

- ① proliferation of endothelial cells &
- ② increases vascular permeability.

کای حفظ

## Platelets-derived growth factor (PDGF)

Released from platelets , macrophages , endothelial cells , keratinocytes & smooth muscle cells. It is chemotactic to neutrophils , macrophages , fibroblasts & smooth muscle cells. Stimulates the production of extra cellular matrix protein. — which of the following stimulate the development of fibrosis? PDGF

## Fibroblast growth factor (FGF)1&2:

Released from macrophages, mast cells, T lymphocytes , endothelial cells & other cells.

It is chemotactic & mitogenic for fibroblasts , & keratinocytes. It stimulates keratinocytes migration , angiogenesis , wound contraction & matrix deposition.

\* and (VEGF) and (FGF) factors → angiogenesis

Cancer ليساعد على نمو Blood vessels تصنيع ال

Drug inhibit FGf/VEGF علاج

is the most potent chemotactic agent

\* → الالتهاب ← CBA

التهاب الالتهاب الالتهاب الالتهاب

## Transforming growth factor beta (TGF- $\beta$ )

Released from platelets , T lymphocytes , macrophages , endothelial cells , fibroblasts & smooth muscle cells.

It is chemotactic for neutrophils , macrophages , lymphocytes fibroblasts & smooth muscle cells & stimulates ECM synthesis & suppresses acute inflammation .

## Keratinocyte growth factor (KGF)

Released from fibroblasts.

It stimulates keratinocyte migration , proliferation & differentiation.

كل يلى اظنانه لسة عان نضم كيف ال tissue يتغير



بعض ال امثلة :-

1. type of tissue
2. severity and duration of the injury

# Regeneration & repair

Depends on cell capacity to proliferate

The relative roles of *regeneration & repair* vary between the type of tissues affected and also depends on the nature, the severity & the duration of the injury.

**I - Type of tissue :** stable or labile or permanent cells باعتد على انواع الخلايا

The “**Proliferative Potential of Different tissues**” is based on the proliferative capacity & thereby, the ability of tissues to repair themselves.

The ability of the surviving cells to divide is the key factor in this response .

## II- Severity & duration of injury:

Mild injury may be followed by complete restoration of normal cellular architecture , especially in tissues having labile or stable cells like skin & liver.

The liver cells have a remarkable capacity to regenerate .

In experimental animals up to 90% of liver can be removed surgically and the remaining parenchyma will regenerate to the original mass having normal cellular structure & function.

**living-donor transplantation** in which portion of the liver is resected from a normal individual & is transplanted into a recipient with end-stage liver disease .

هذا الحكي كله مار معنا ، ، بعد كم سلايد كاتب ملاحظات

Patients with liver tumor, treated by **partial hepatectomy**, in both conditions the tissue resection triggers a dramatic, proliferative response of the remaining hepatocytes (which are normally quiescent) & the subsequent replication of the surgical removal of 40% to 60% of the liver, in hepatic cells.

لاحظ هون بحكيك ال hepatocyte تضررت كثير بس ال ECM ما انصر ، و بيهاي الحالة بقدر ارجع ال liver زي ما كان

In humans when there is massive central necrosis of hepatocytes , with minimal collapse of the matrix as in viral hepatitis , however, in most cases the hepatocytes regenerative responses ensure restoration of the liver architecture and function when infection subsides.

باختصار قدرة ال liver . على انه يعمل repair بتعتمد على نوع الاصابة ،

طبعاً هذا الاشي انا موضحة بعد كم سنلايد



While in chronic liver cell injury, when the amount of fibrosis is quite substantial, the regeneration develops in form of regenerating nodules surrounded by fibrous tissue as in liver cirrhosis.

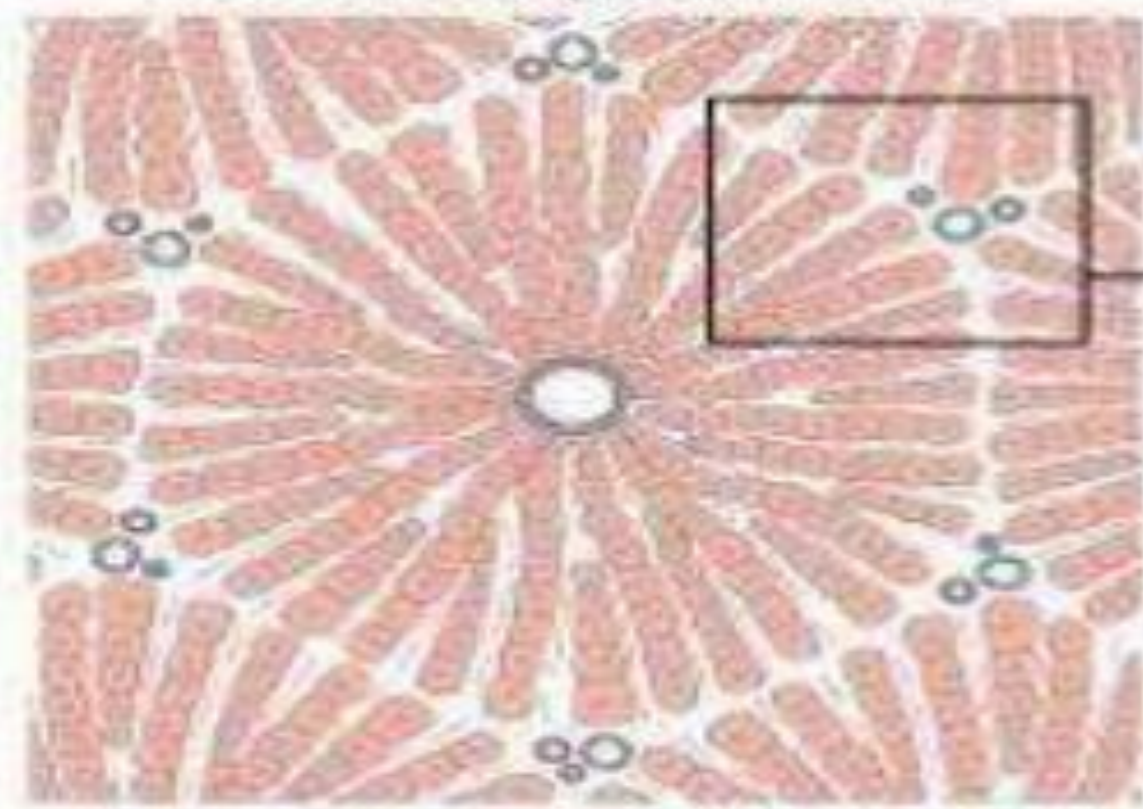
↳ in regenerative nodules (scar tissue)

It seems that the tendency of chronic inflammatory process to produce excessive fibrosis is related to continuing production of macrophages & lymphocytic-derived cytokines like interleukin-6 (IL-6) & tumor necrosis factor (TNF) & growth factors like HGF & EGF & TGF- $\alpha$  which act as a mediator of the healing process.

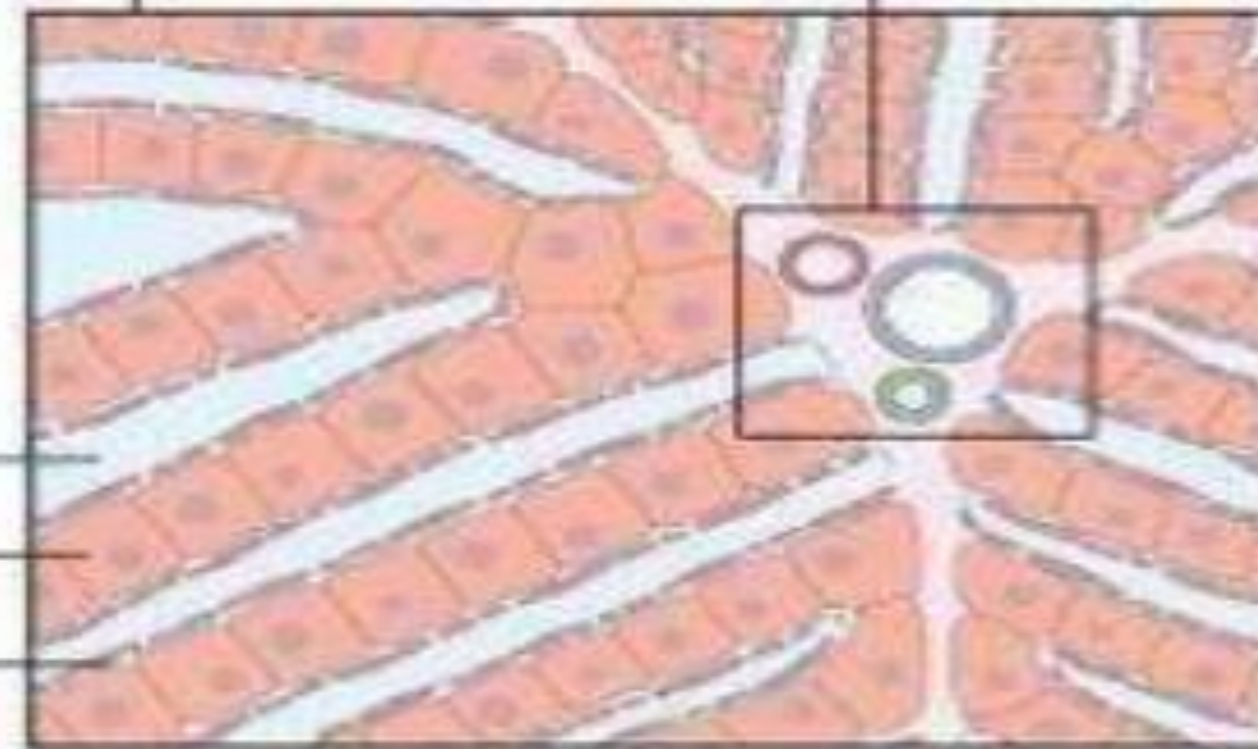
TNF and IL1 are master cytokines

كل المذكور هون هي سغلات بتعمل تحفيز لعملية الـ fibrosis

Normal hepatic lobule



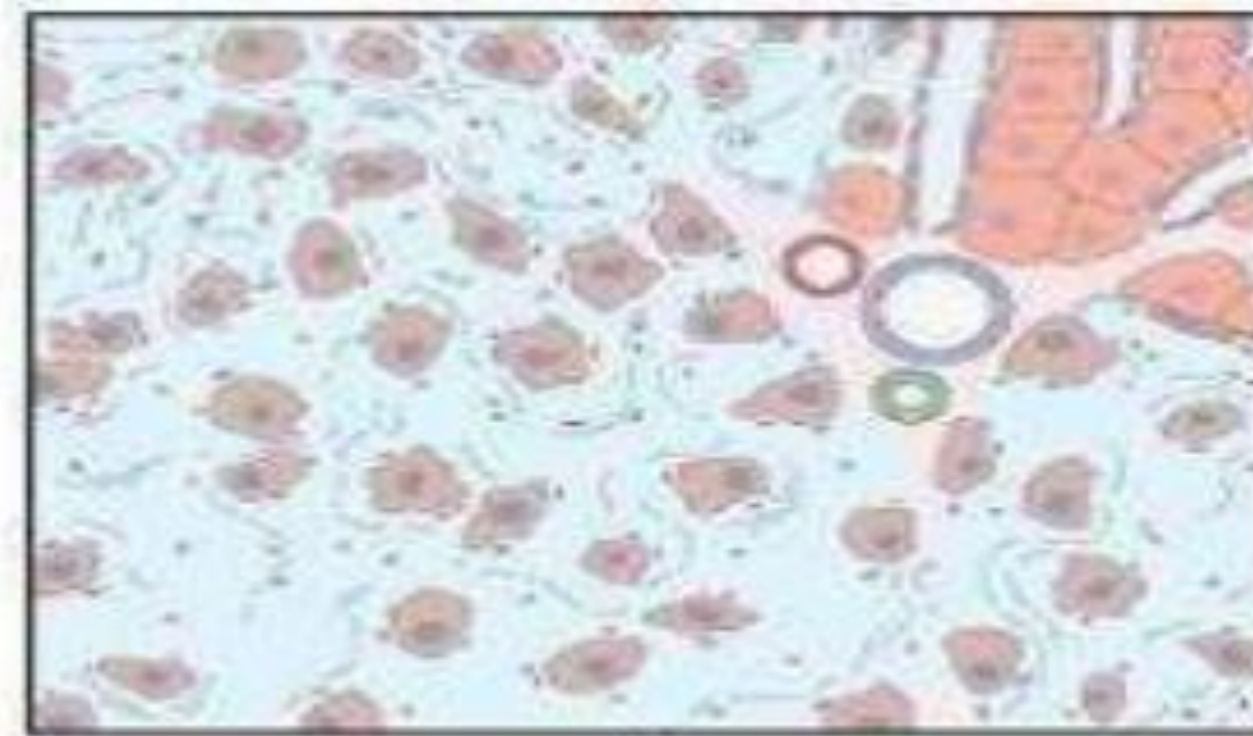
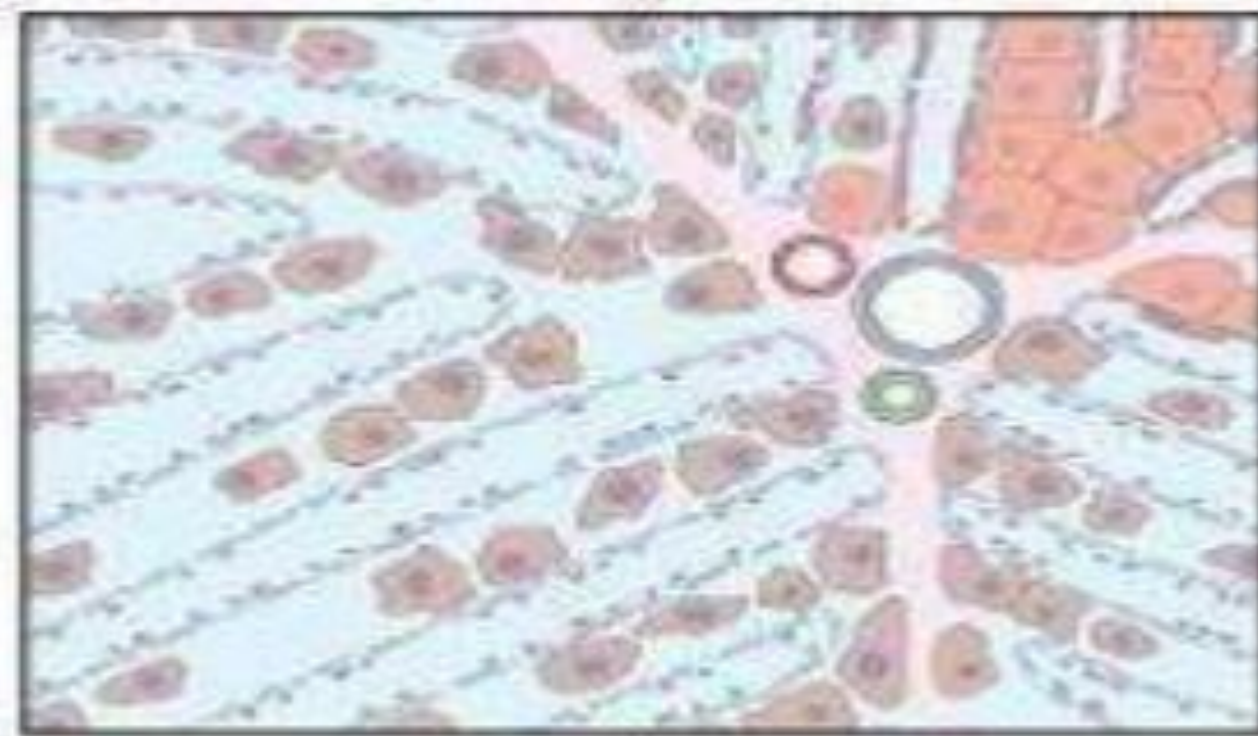
Portal triad:  
hepatic artery, portal  
vein, bile duct



Sinusoid  
Hepatocyte  
Connective tissue  
reticular fibers

Injury to cells

Injury to cells and matrix

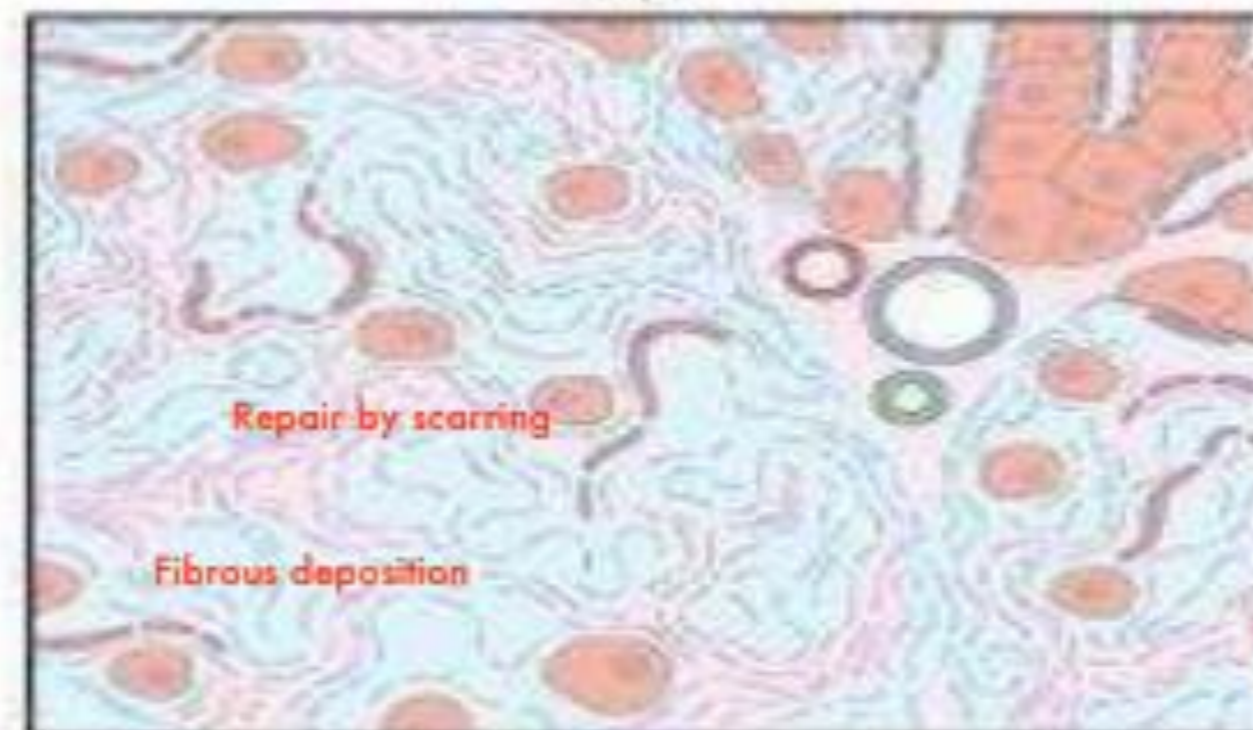


Proliferation of residual cells  
within intact matrix

Deposition of connective tissue;  
proliferation of residual cells  
within disrupted matrix



**Regeneration**



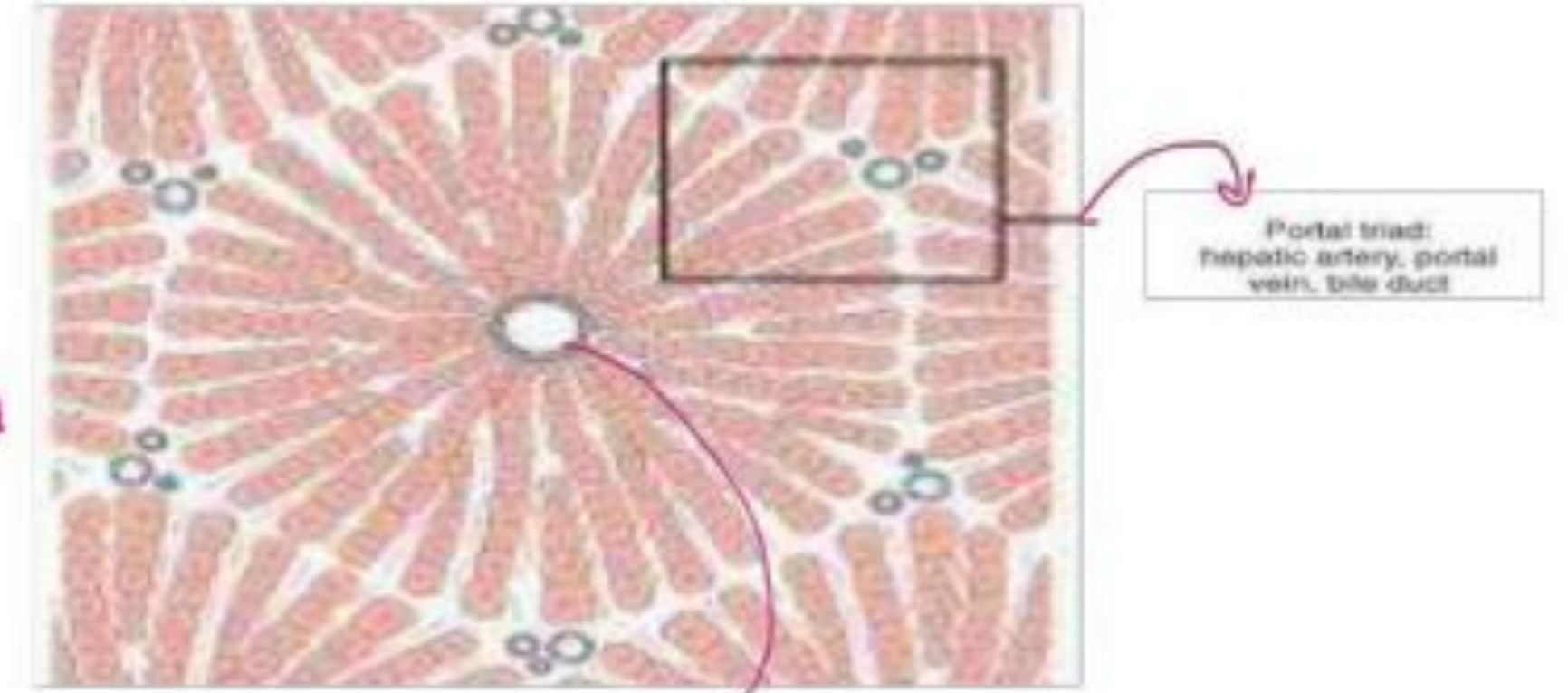
Repair by scarring

Fibrous deposition

**F 67 : Mechanisms of tissue repair. In this example, injury to the liver is repaired by regeneration if only the hepatocytes are damaged, or by laying down of fibrous tissue (scarring) if the matrix is also injured.**

*extensive damage*

بذلك تعرف بأنه الكبد مكون  
من lobules هذا الشكل هذا يعبر واحد منهم



Central vein

severe/Long duration

ال Damage في ال liver يا اما بأثر على ال hepatocyte فقط وهاي عادي بتتعوض ، او ال damage بصيب ال ECM and hepatocyte و هون بصير fibrosis .. يعني التعوض بسلامتك ..

عشان هيك قلنا سابقا انه ال lobule اذا انشال كله ما بتقدر تعوضه لانه احنا شلنا ال ECM و شلنا الخلايا و شلنا كل اشئ شو بدنا  
تعوض لنعوض

مهمة

Hepatitis A is not chronic inflammation, but hepatitis B and C are considered chronic ,So, they will cause liver cirrhosis

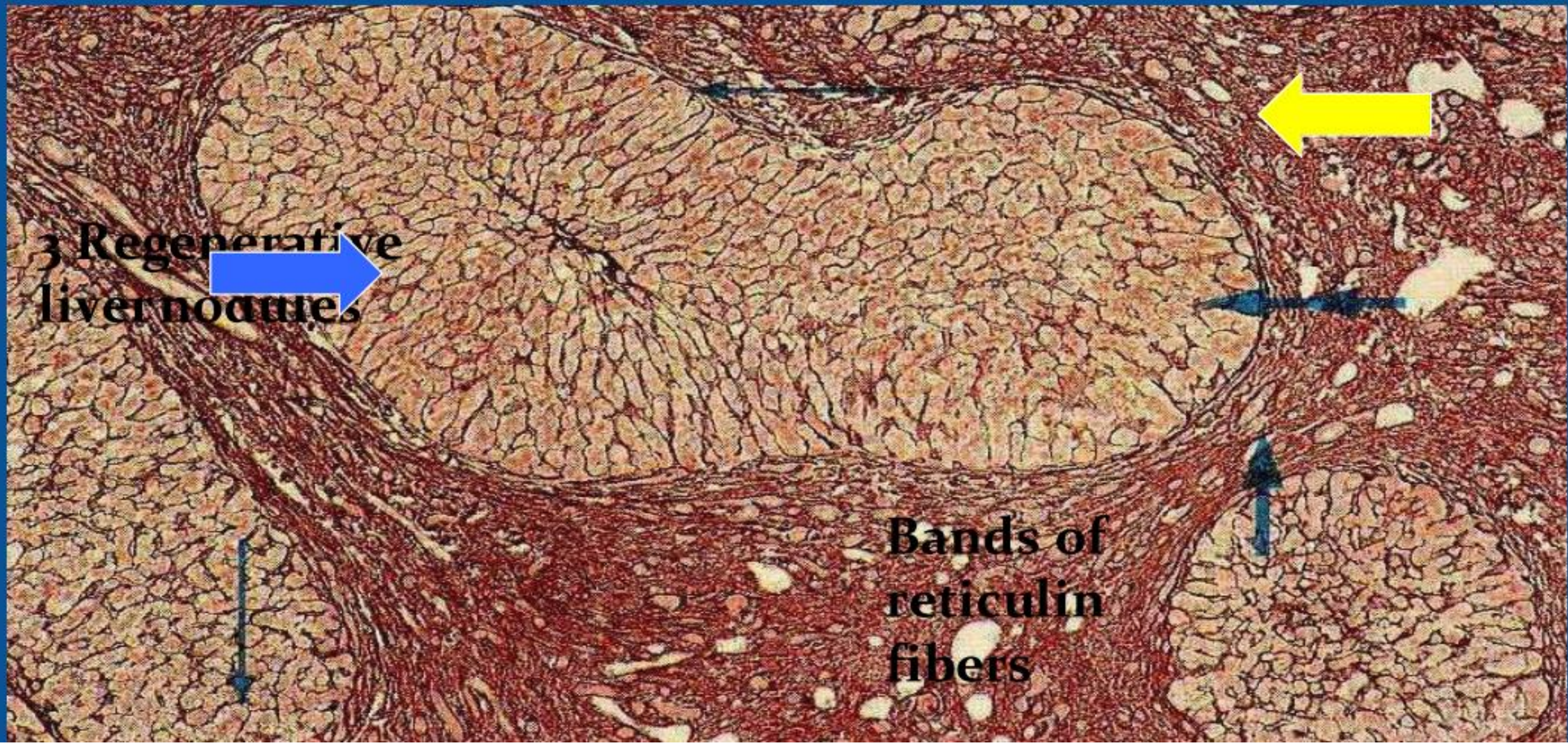
سؤال  
عملي

This picture represents what?

Figure 68 : Liver cirrhosis : Liver section stained by **reticulin stain**

There are three regenerative liver nodules (double arrow),  
separated by broad bands of reticulin fibers (thick arrow). An  
example of healing by **combine** regeneration & fibrosis which  
follows injury to the liver cells & stroma .

↑  
ملاحظة



## Repair for skin wounds



نبلش حكي عن ال **primary** ، حكيانا انه يكون نظيف ، ما يكون في خسارة كبيرة للأنسجة و يكون في **minimal formation of granulation tissue and fibrosis** .

شو هو ال **granulation tissue** و متى بتكون ؟

- بتكون بعد اليوم الثالث و بتكون من **macrophage** و **fibroblast** و **ECM** و من **new blood vessels**

طيب شو اسم العملية يلي من خلالها بنكون **blood vessels**

- اسمها **angiogenesis**

الـ angiogenesis ← هاي العملية مهمة كثير و زي ما الها فوائد الها مضار ، لانه صح انا بحتاجها بالـ wounds repair لكن برضه الـ tumor من خلال هاي الآلية بتقدر تنتشر و تضرنا أكثر ..

و مع ذلك بتضها عملية مهمة و مفيدة بكثير جوانب ، الجانب الاول حكيينا عنه ، اما الجانب الثاني بدي اياك تتذكر بالاناتومي اخذنا اشبي اسمه collateral circulation و حكيينا انه من خلاله اذا صار عندي لـ artery thrombosis معين ، الدم ممكن يسلك طريق ثاني و يوصل الدم للـ organ و وقتها أخذنا مثال العين فيها collateral circulation ..

الدكتورة اعطت مثال انه بالـ atherosclerosis بصير عنا collateral circulation

كيف بنهد هاي العملية ؟

رح احكي بشكل عام لكن لازم تنزلوا تبصموا شغللات تحت اولاشي بصير عندي vasodilation بتأثير من GF ، و رح تزيد الالنفاذية و بعدين حيتكسر الـ basement membrane و يخلي الـ epithelial cells تطلع و تكون tube جديد و بعدها هذا الـ tube رح يتجمع حويله كل المكونات يلي بتحيط بأيـ vessels زي basement membrane و pericyte و smooth muscle و غيدها

# Angiogenesis :

Is a process of new blood vessel development from existing vessel, primarily venules

It is critical in healing at site of injury , in development of collateral circulation at sites of ischemia , & in allowing tumors to increase in size beyond the constraints of their original blood supply .

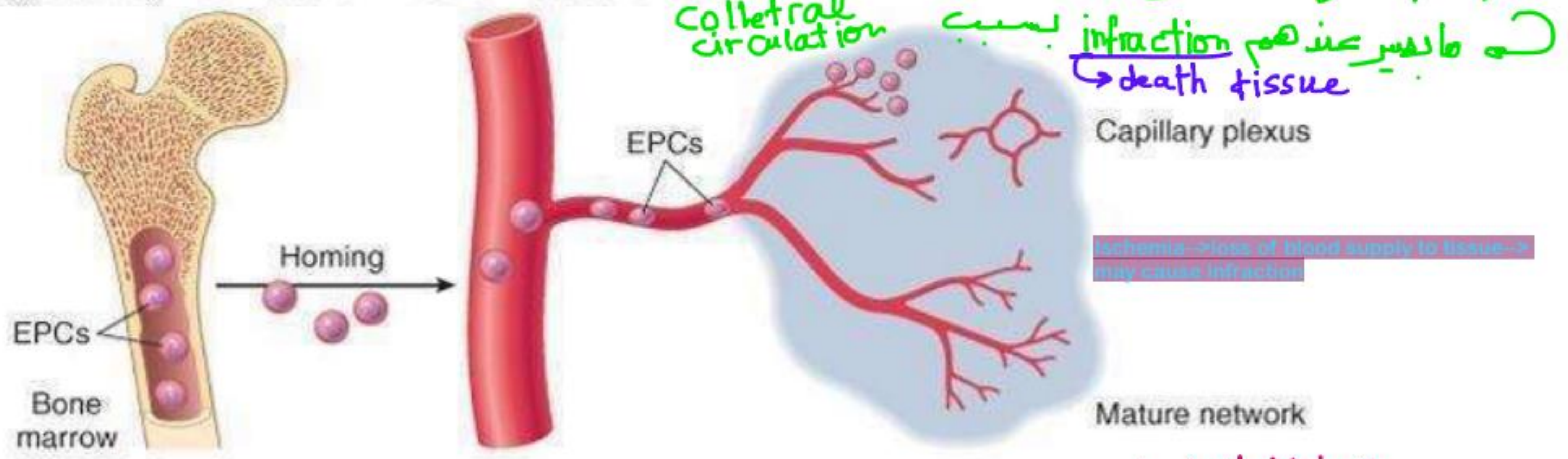
## Steps of angiogenesis include :

- 1 **Vasodilation** occurring in response to NO & increased permeability induced by vascular endothelial growth factor (VEGF) .
- 2 **Migration of proliferating endothelial cells** from pre-existing blood vessels towards the area of tissue injury forming solid tube .
- 3 **Remodelling of proliferating endothelial cells into capillary tubes** attached to the lumen of the pre-existing vessel .
- 4 **Recruitment of periendothelial cells ( pericytes) & smooth muscle cells** around the new capillaries .
- 5 **Suppression of endothelial cells proliferation & deposition of basement membrane.**

📌 **The major growth factors involved in angiogenesis : the most important are vascular endothelial growth factor (VEGF) & basic fibroblast growth factors ( basic FGF) .**

That's why old age people

A. Angiogenesis by mobilization of EPCs from the bone marrow



B. Angiogenesis from preexisting vessels

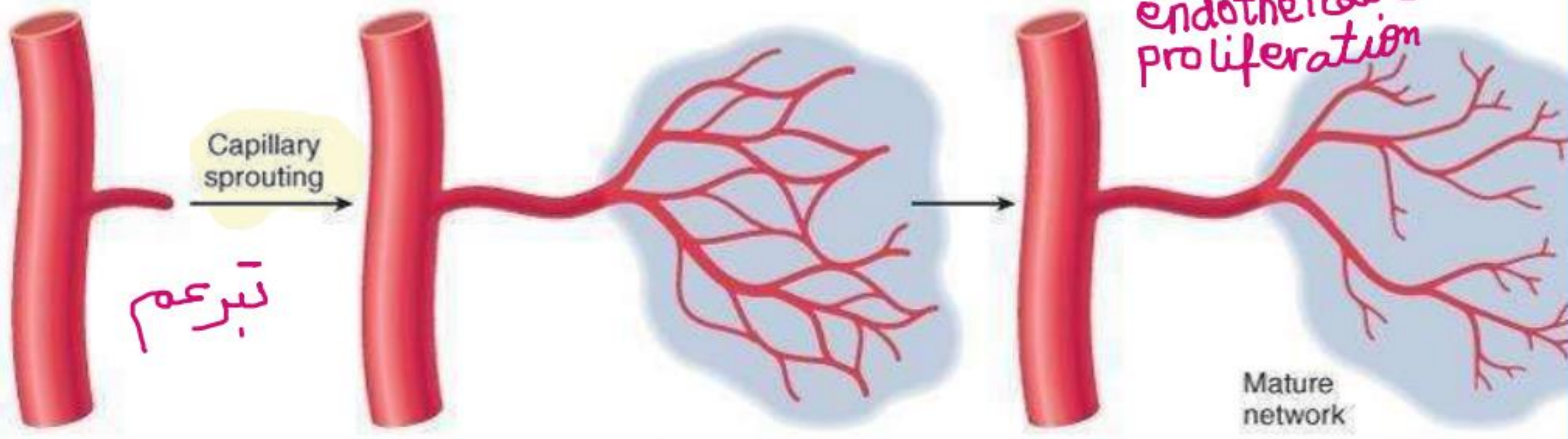


Figure 69 : Diagrammatic demonstration of steps of angiogenesis .



مهم جدا ... بييجي عليه كثير اسئلة بالامتحان

## HEALING OF SKIN WOUND (Ulcer و Surgical wound)

Here, we specifically describe the healing of skin wounds.

As it involves both epithelial regeneration & the formation of connective tissue scar, it is thus illustrative of the general principles that apply to wound healing in all tissues.

Healing of skin wounds : Either  
labile cell (ability to proliferate)

- I. Healing by Primary intention.  
( Primary union) Or
- II. Healing by secondary intention ( Secondary union)

## Healing by Primary Intention

جرح يكون نظيف

Occurs in an **uninfected clean sterile wound without tissue loss** as in surgical incision approximated by surgical sutures .

The incision causes only focal disruption (loss of continuity) of epithelial BM & death of relatively few epithelial & connective tissue cells.

As a result, epithelial regeneration predominates over fibrosis.

A **small scar** is formed , but there is **minimal wound contraction**.

Loss of skin substance

Very focal disruption of tissue



granulation tissue, fibrous scar تكون

Regeneration predominates over fibrosis



Suture enhance the process of healing

When an incision is made in the skin & subcutaneous tissue, blood escapes from the cut vessels, it clots on the wound surface & fills the gap between the wound edges, which is narrow in sutured wound .

Within **24 hours**: **neutrophils** are seen at the incision margin, migrating toward the fibrin clot.

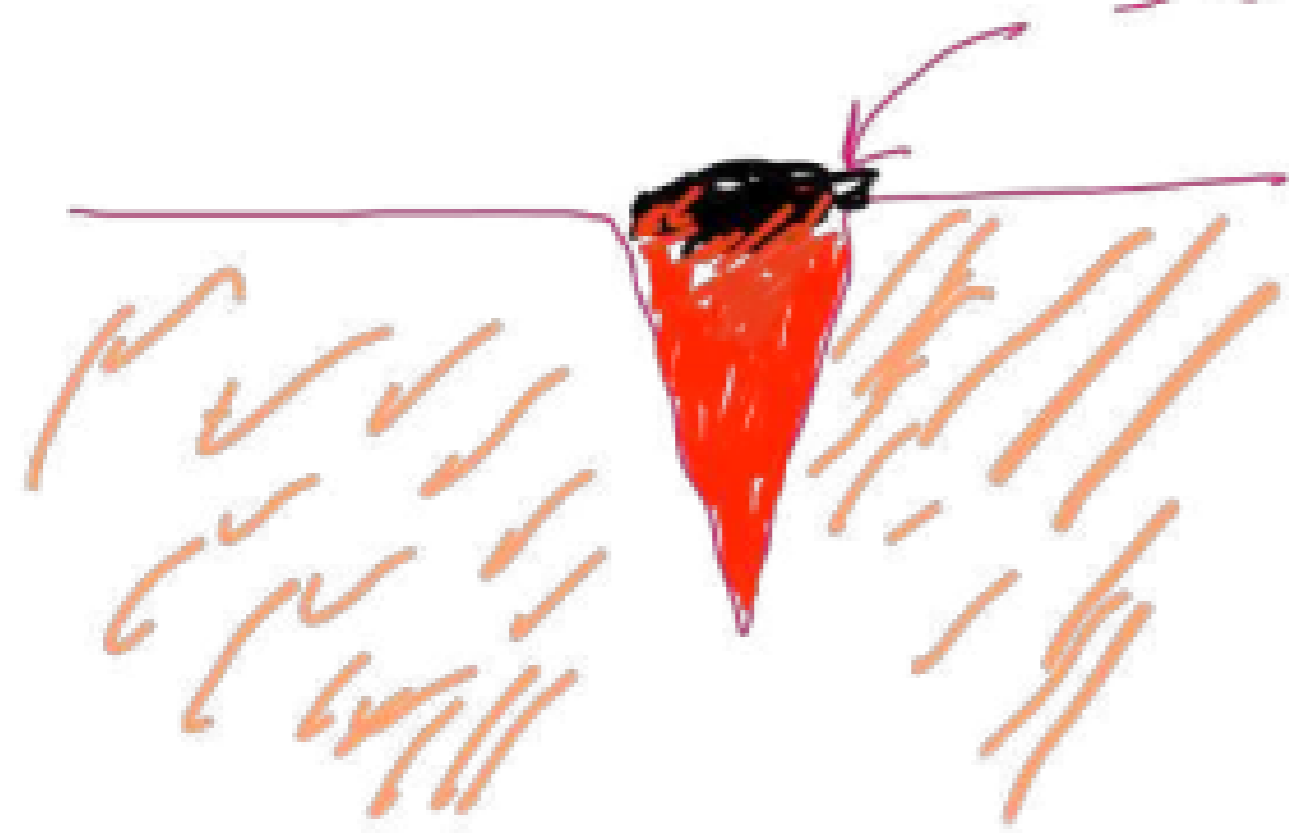
This is called **traumatic inflammatory response** .

Meanwhile the **Basal cells** at the cut edge of the epidermis begin to exhibit mitotic activity. . .

Within **24 to 48 hours** , epithelial cells from both edges have begun to migrate & proliferate along the dermis, depositing basement membrane components as they progress .

- لما يهر في جرح في ال skin أو Subcutaneous tissues  
 الدم يتجمع داخل هذا الجرح و يجعل خثرة

- خلال ٢٤ ساعة يتيجي ال Neutrophils عند مكان  
 الجرح ← هاي العملية اسمها : scab (granulation tissue)

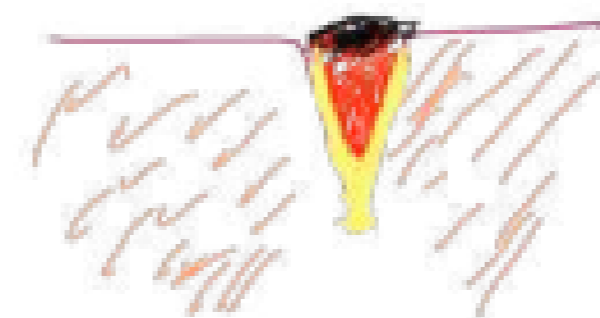


traumatic inflammatory response

- بعدها يتبلس ال Basal cells لتقسم

Basal cells are found at the bottom of the epidermis – the outermost layer of skin.

- خلال (٢٤ - ٢٨) ساعة يتبلس تكون epithelial cells جديدة  
 على الطرف الجرح



\* الالهز اعتبروه خلايا جديدة

ملاحظة: - ال times ١٠٠٠ حاجي في ال مكان

Scab is easy to bleed , because it is granulation tissue

٩٦  
جای  
بالا متجان

The cells meet in the midline beneath the surface **scab** , yielding a thin but continuous epithelial layer . The basal cell proliferation stops by **contact inhibition** .

By day 3 neutrophils have been largely replaced by **macrophages** , followed by **angiogenesis & granulation tissue** , which consists of **proliferating capillaries & fibroblasts** progressively invades the incision space .

**Collagen fibers** being layed down by the **fibroblasts** are now evident at the incision margins, but these are vertically oriented & do not bridge the incision .

**Epithelial cell proliferation continues** , yielding a thickened epidermal covering layer.

في اليوم الثالث ، (عص)

- ال Macrophages بتيجي بدل ال neutrophils

- و بيلع عندي angiogenesis

- و بيلع في عندي ال Granulation tissue

- بيلس يتجمع ال Collagen

و اعرف انه ال epithelial proliferation

بفل مسند لهاي اللحظة

**By day 5**, angiogenesis reaches its peak as **granulation tissue** fills the incisional space & collagen fibrils become more abundant & begin to bridge the incision.

The epidermis recovers its normal thickness as differentiation of surface cells yields a mature epidermal architecture with surface keratinization.

### **During the second week:**

There is continued collagen accumulation & fibroblasts proliferation. The WBC infiltrate, edema, & the vascularity are substantially diminished. The long process of "blanching" (pallor) begins, accomplished by: collagen deposition within the incisional scar & the regression of vascular channels.

**By the end of the first month** the scar comprises acellular connective tissue, devoid of inflammatory cells & covered by an essentially normal epidermis.

Hair follicles & sebaceous glands which are destroyed in the line of incision are permanently lost. →

Can't be replaced  
when destroyed

Collagen deposition → Acellular connective tissue

\* في اليوم الخامس :

- الـ angiogenesis يوجد لأكثر إحتي يمكن تحله

- ملاحظة: بعد اسبوع في العملية يشيلوا الحيط .. ليس إنتبه  
انه يتكون قوة النسيج 1.1 من قوته الأولية  
لم عشان مايفتح الجرح

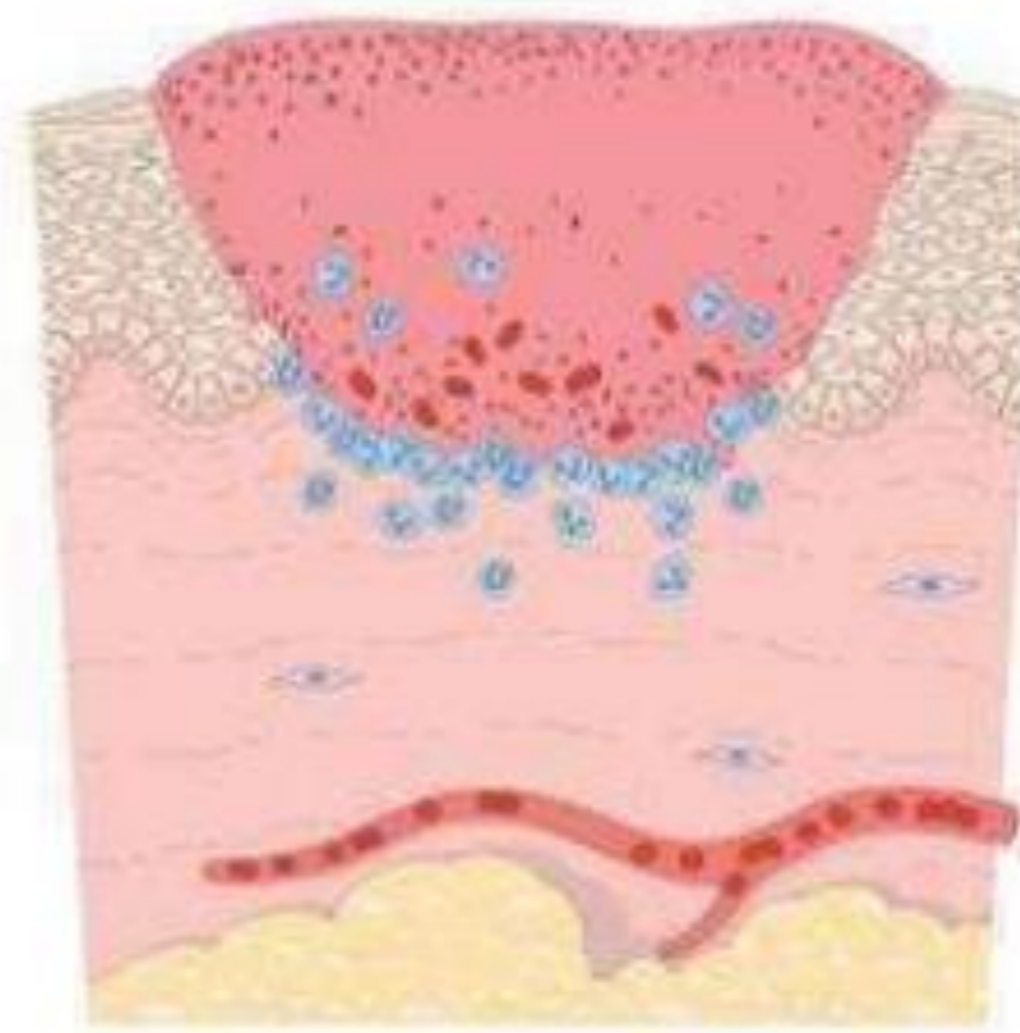
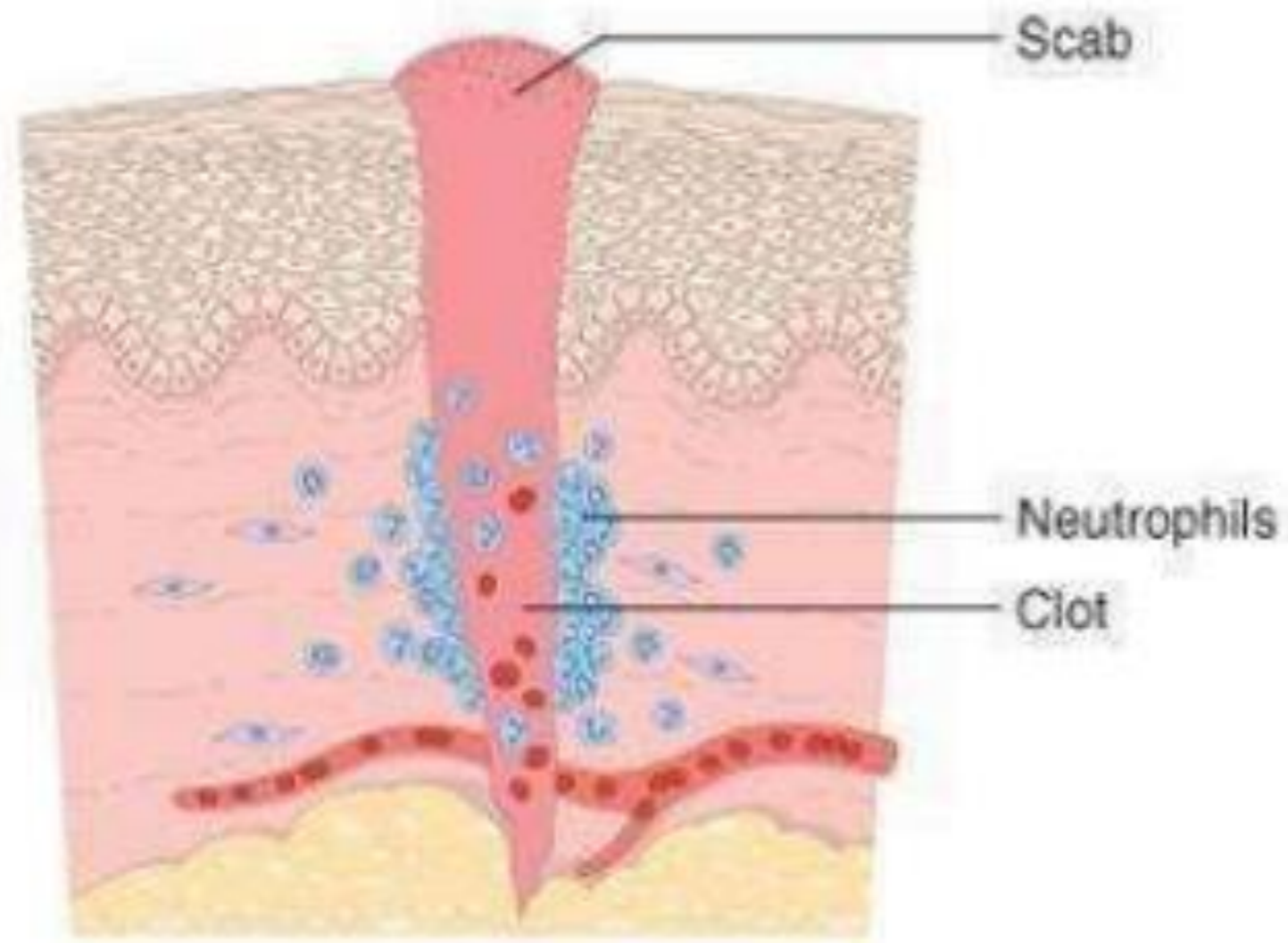
— الفريق بين primary, secondary substance  
هو (loss of skin substance ( skin contraction) )



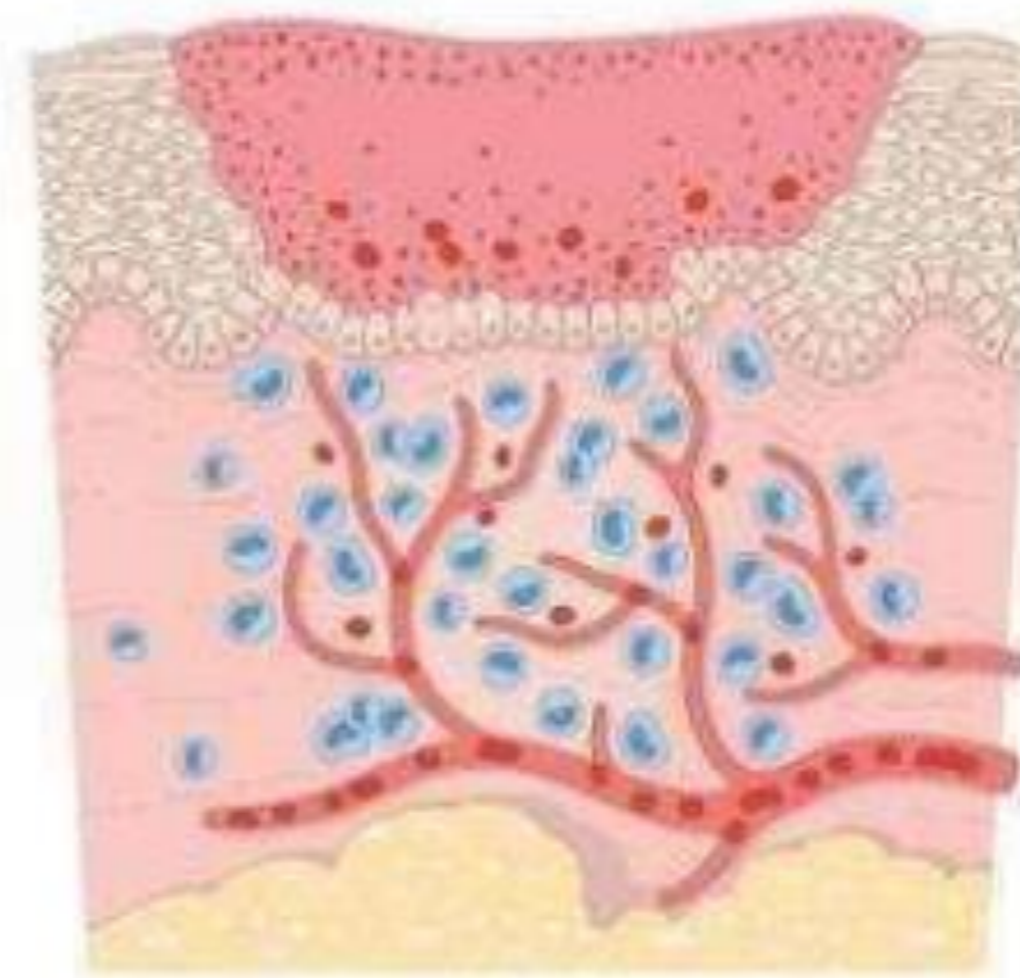
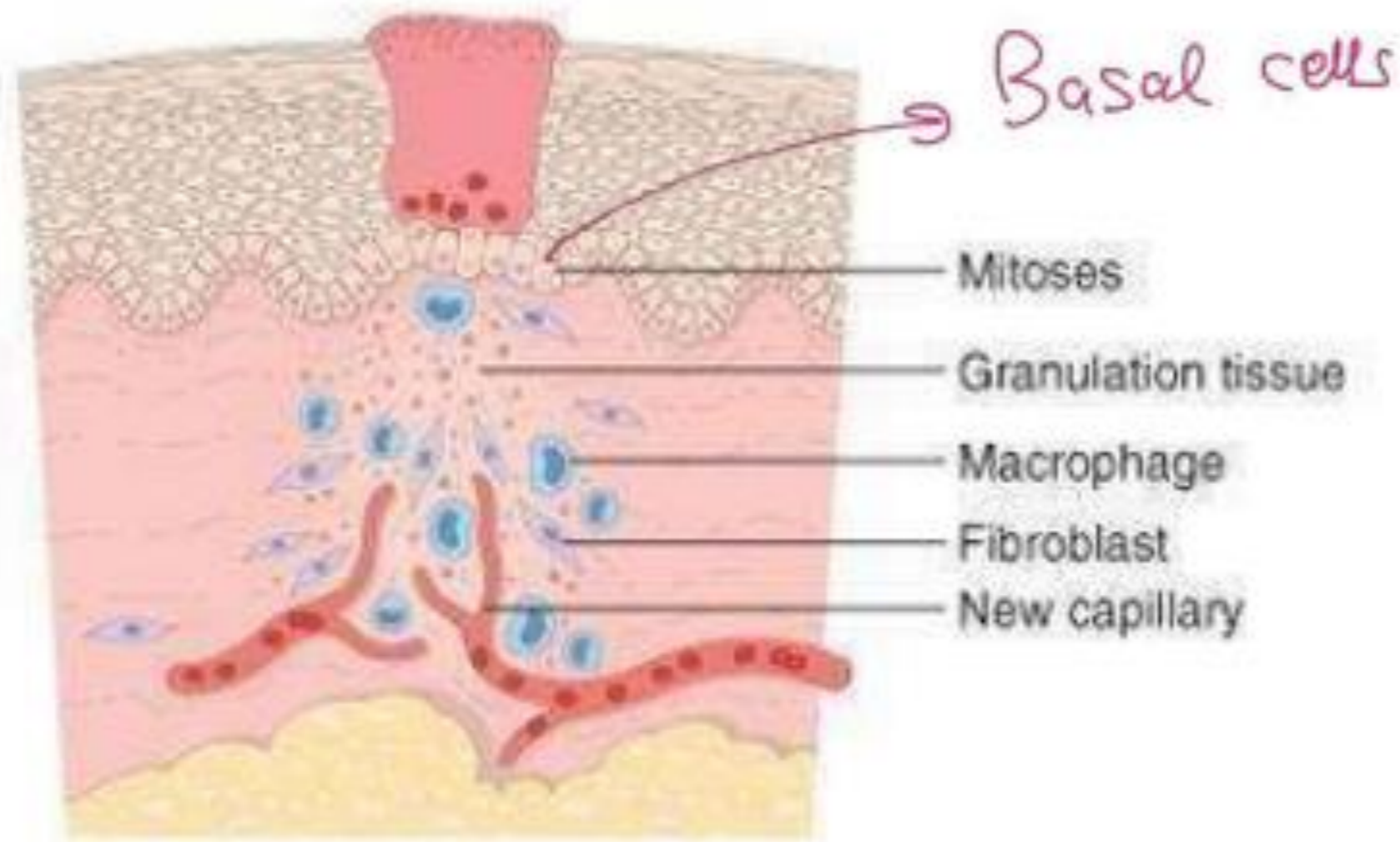
HEALING BY FIRST INTENTION

HEALING BY SECOND INTENTION

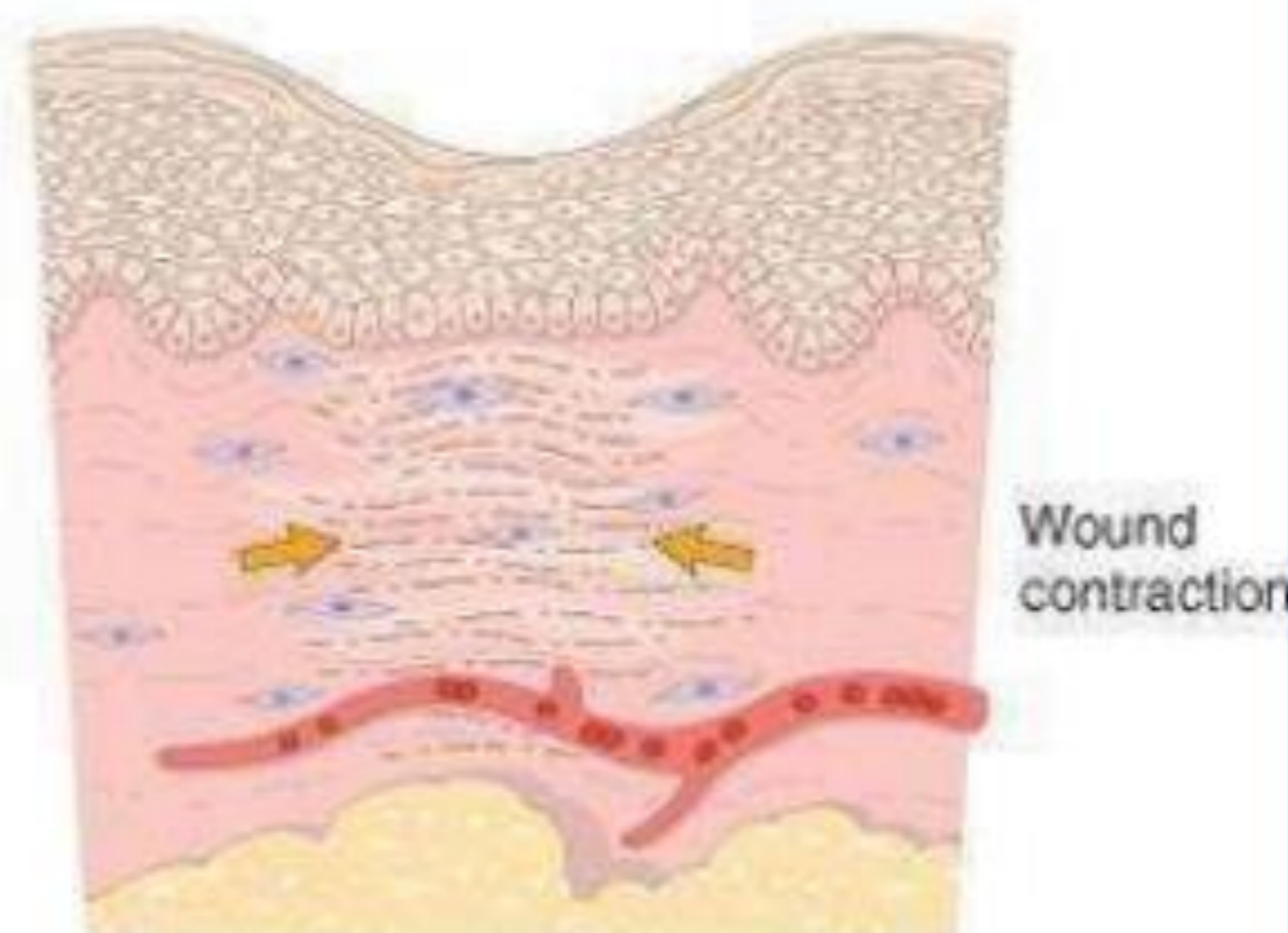
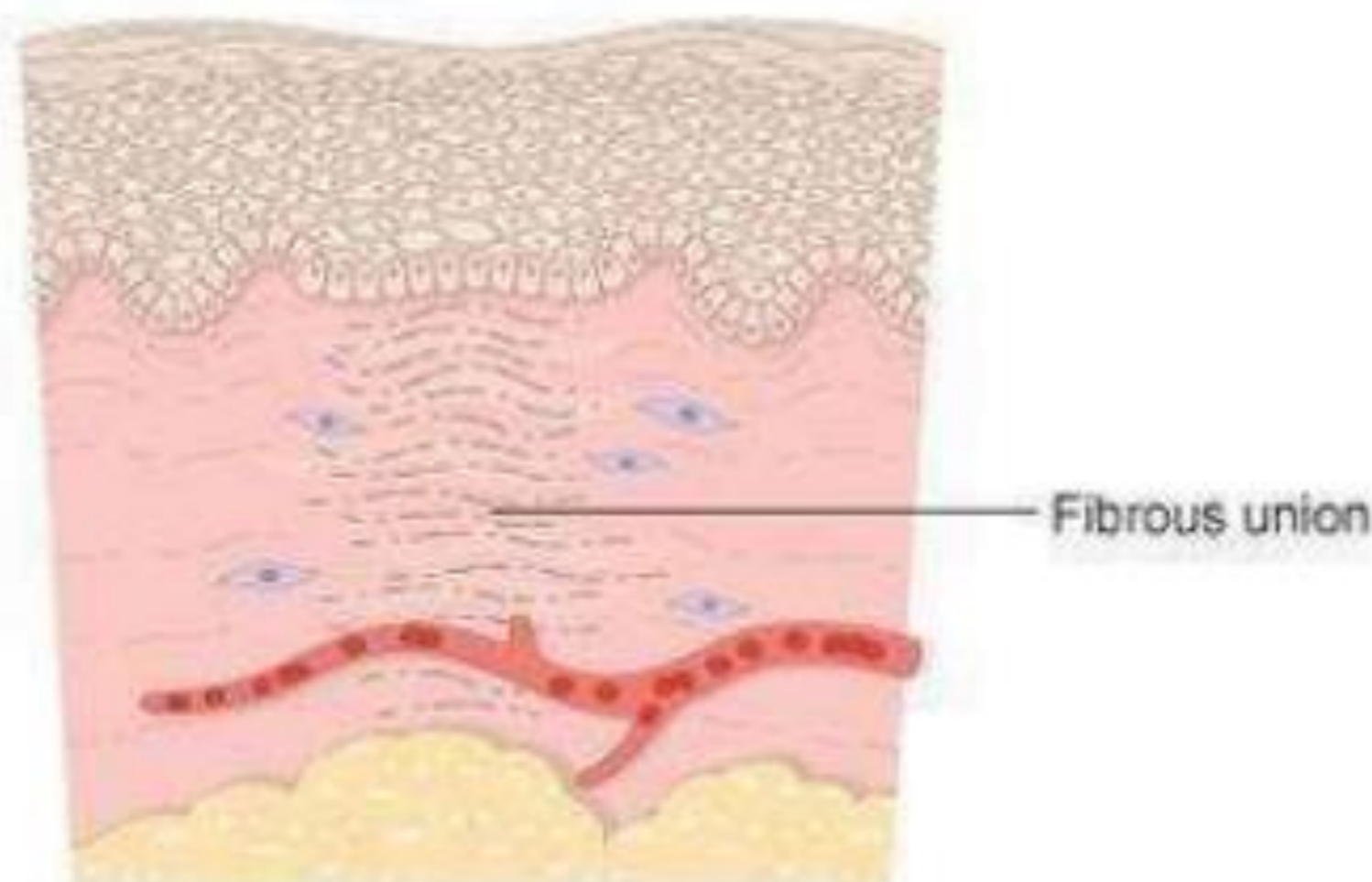
24 hours



3 to 7 days

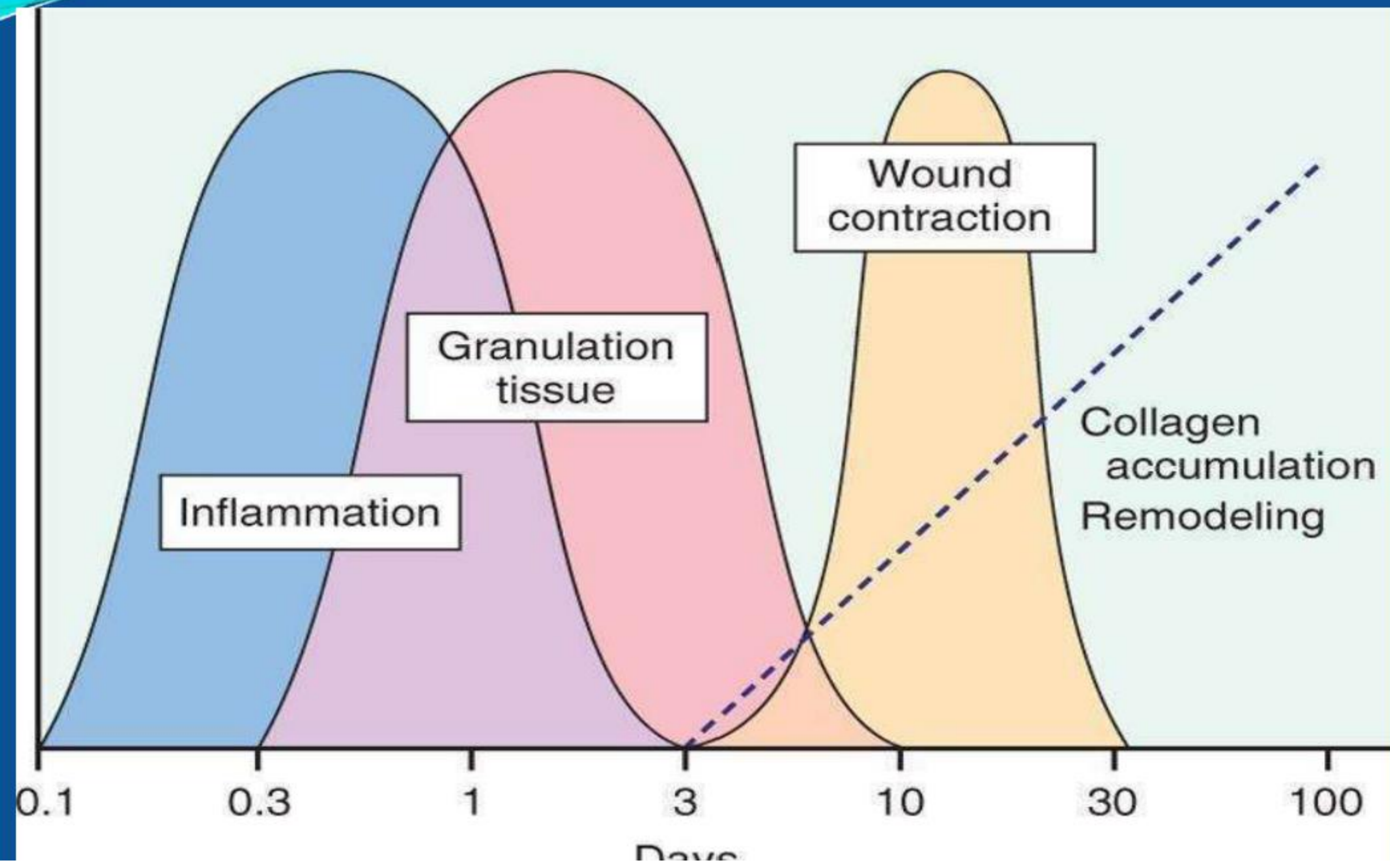


Weeks



**F 70 : Steps of wound healing by first intention (left) & second intention (right). In the latter, note the large amount of granulation tissue & wound contraction**

# F 71 : Phases of wound healing



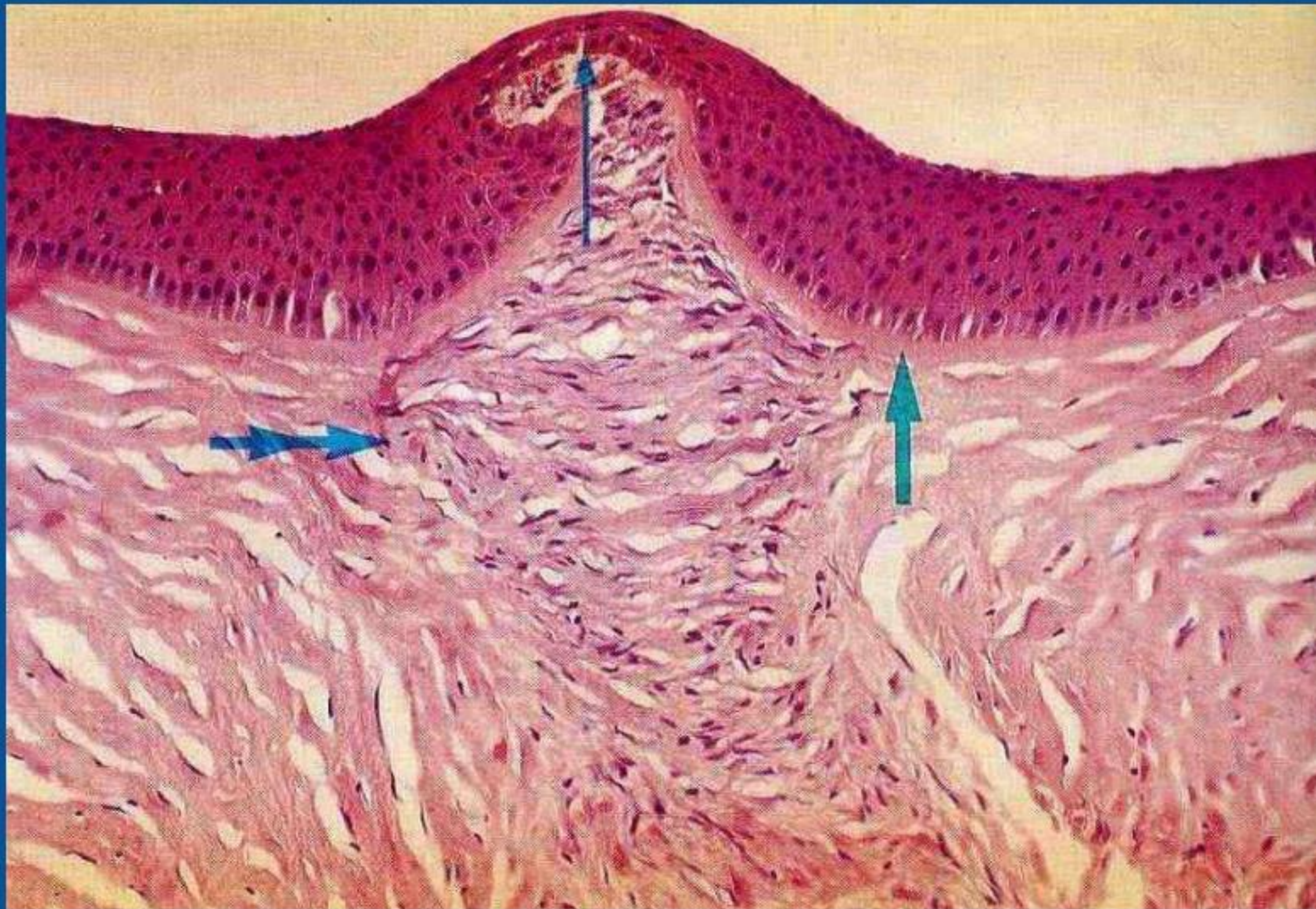
Spot  
diagnosis

Surgical wound  
healed by  
primary  
intention



**Figure 72 :Healing of surgical wound by primary intention or union**

Figure 73 : Healed wound: Cornea . The healed wound is visible as a 'gap' in the stroma, filled with a connective tissue & many fibrocytes (double A), the epithelium covering the gap in it (thin A) is much thinner than the normal epithelium on each side of the wound.

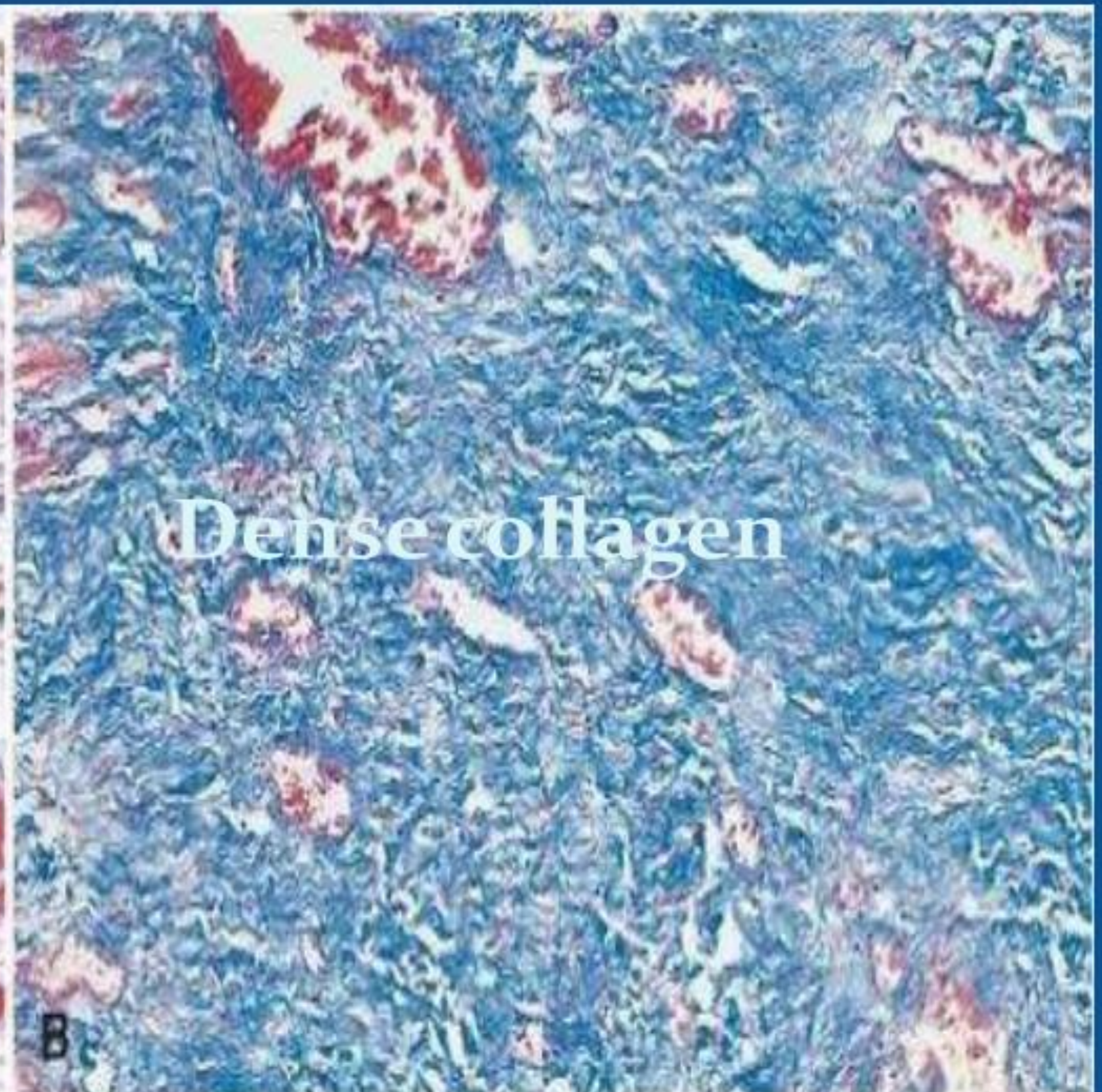
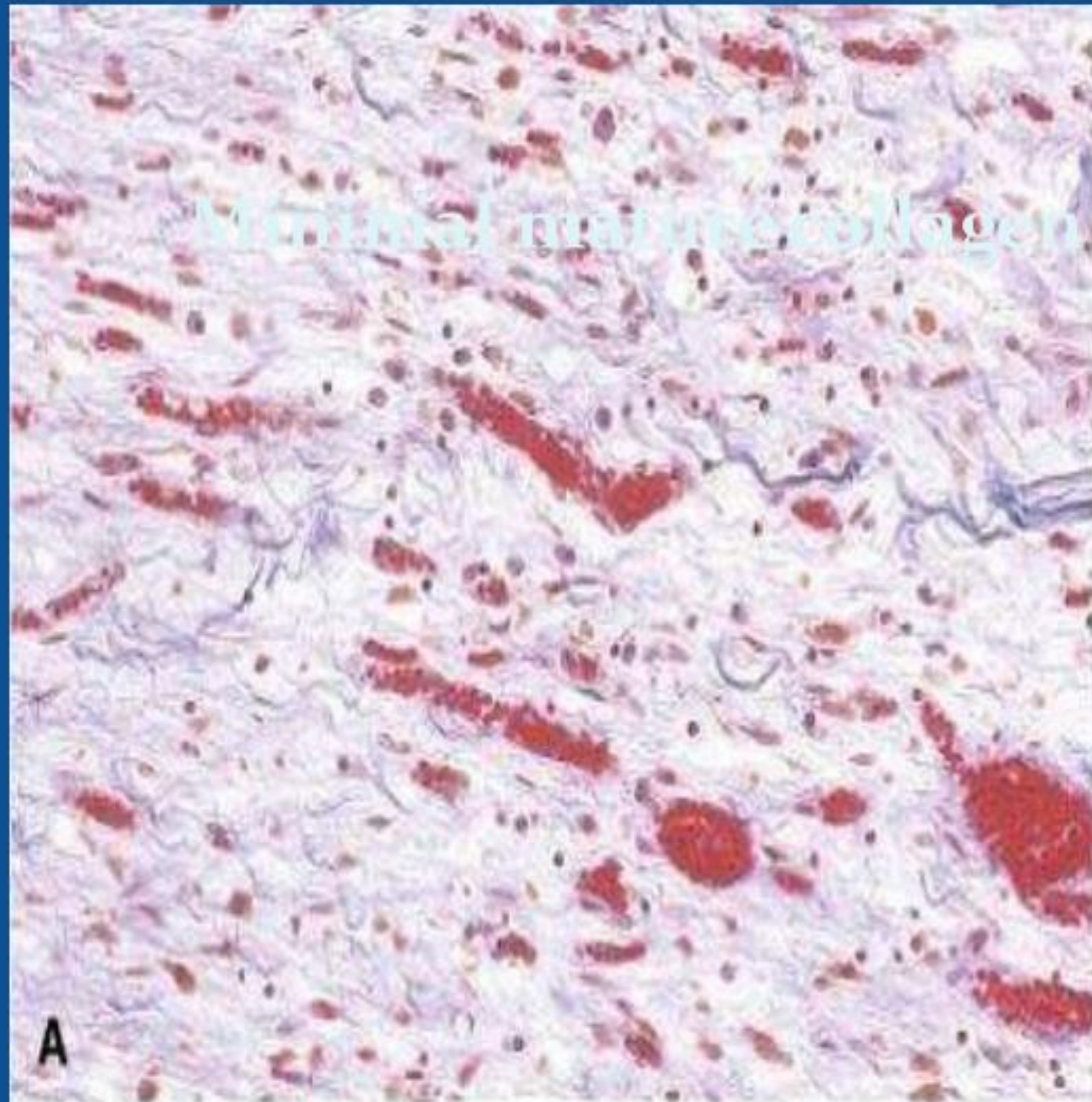


The epithelium is much thinner than normal.

و بعمره ما  
برجع الجلد  
بعد الجرح  
لقوته بنسبة  
مئة بالمية  
بس ممكن  
بعد 3 اشهر  
يرجع 70%

Figure 74 : A, Granulation tissue showing numerous blood vessels, edema, & a loose ECM ; minimal mature collagen .

B, **Trichrome stain** of mature scar, showing dense collagen(blue) with only scattered vascular channels.



# Healing by Secondary Intention (which of the following is seen in secondary intention?)

When cell or tissue loss is more extensive, as in Infarction, Abscess, Ulcer or Large wound, the reparative process is more complex.

That's why healing in secondary intention is irregular

The regeneration of parenchymal cells alone cannot restore the original architecture, therefore, there is an extensive ingrowth of granulation tissue from the wound margins, followed by ECM accumulation & scarring.

This is called **secondary union or healing by second intention**

What is the most important difference between primary and secondary intention? Wound contraction

## Secondary union differs from the primary in several aspects:

(1) A larger clot or scab rich in fibrin and fibronectin forms at the surface of the wound.

(2) **Inflammation** is more intense because large tissue defects have a greater volume of necrotic debris, exudate, and fibrin that must be removed.

Consequently large defects have a greater potential for secondary inflammation – mediated injury.

(3) Larger defects require greater volume of granulation tissue to fill in the gaps & provide the underlying framework for the regrowth of tissues epithelium. A greater volume of granulation tissue generally results in a greater mass of scar tissue.

→ the most important difference

## (4) Secondary healing involves wound contraction.

(greater in secondary)

Within **6 weeks** large skin defects may be reduced to **5%-10%** of their original size largely by **contraction**.

يتقلص حجم الجلد

This process is due to the presence of myofibroblasts, a modified fibroblasts exhibiting many of the ultrastructural & functional features of contractile smooth muscle cells.

Remember: "Myo" is related to muscle and one of its characteristics is ability to contract





**Figure 75 : Healing by secondary intention of a large wound with excessive tissue necrosis .**

Initial



Area: 111.00 cm<sup>2</sup>

Intermediate



Area: 25.90 cm<sup>2</sup>

Most Recent



Area: 7.87 cm<sup>2</sup>

Figure 76 :Healing of skin wound by secondary intention



Scar predominate regeneration in secondary healing



Figure 77 : Healing by secondary intention : showing a large **irregular permanent scar** .

# Wound Strength

Carefully sutured wounds have <sup>النسب المطلوبة</sup> approximately 70% of the strength of unwounded skin, largely because of the placement of the sutures.

When sutures removed after one week, wound strength is approximately 10% of that of unwounded skin, but this increases rapidly during the next 4 weeks . <sup>يبدأ يتقوى أكثر →</sup>

The recovery of tensile strength results from:

(1) Collagen synthesis exceeding degradation during **the first 2 months**, & from

(2) structural modifications of collagen (e . g cross-linking & increased fiber size) when synthesis declines at later times . <sup>يترتب بطريقة أكثر فائدة للجرح ↷</sup>

<sup>\* مريض</sup> Wound strength reaches 70% to 80% of normal by 3 months , but usually does not improve beyond that point. → <sup>ما يتوصل 100% healed skin</sup>

# Factors that cause delay of healing process :

In wound healing, normal cell growth & fibrosis may be altered by a variety of factors, frequently reducing the quality or adequacy of the reparative process:

1 **Infection**, <sup>مسبب</sup> is the single most important cause of delay in healing, by prolonging the inflammation phase of the process, & potentially increases the local tissue injury.

2 **Nutrition** has <sup>عميق</sup> profound effects on wound healing, for example protein deficiency & especially, vitamin C deficiency, inhibit collagen synthesis & retard healing.

↳ Scurvy

↳ if it is given for a long period of time

3 **Glucocorticoids** (steroids): have well-documented anti-inflammatory effects, & their administration may result in poor wound strength owing to diminished fibrosis.

\* Diabetic patients has many factors contribute to delay healing such as atherosclerosis, unhealthy tissue especially uncontrolled one, poor blood perfusion

4. **Mechanical factors** such as <sup>Locally</sup> increased local pressure or torsion <sup>①</sup> may cause wounds to pull apart (separate), <sup>②</sup> or dehisce (e. g abdominal wound dehiscence after laporatomy). →

لما يفتتح الجرح بسبب الضغط و السكري احد الاسباب

5. **Poor blood perfusion**, due either to <sup>①</sup> atherosclerosis (which reduce arterial blood supply), or to <sup>②</sup> obstructed venous drainage, e. g varicose veins, both impairs healing. →

الذي هو الدوالي التي يطلع على الرجلين بسبب الوقوف الطويل يقلل

6. **Foreign bodies** <sup>at the site of suture</sup> such as fragments of steel (e. g gun-shot , glass, wood, or even bone, impede (delay) healing process .

شئنا suture ليس ضل منه جزء ياتي هو nodules, mass بصير مكان suture .  
ماي الخالة من ضمن Foreign bodies و بسببها suture granuloma

مهم ( سؤال  
اجي باحد  
الامتحانات)

When there is large damage to the skin

Healing wounds may also generate excessive granulation tissue that protrudes above the level of the surrounding skin & in fact, prevent re-epithelialization. This is called **exuberant granulation, or proud flesh**.

☞ Sometimes, the accumulation of excessive amounts of collagen can give rise to **prominent raised scars known as Keloids**, more commonly seen in blacks

Keloid is irregular ugly looking scar developed when there is injury to skin & is not painful, but emotionally stress

هو بصير اكثر اشي بالي بشرتهم  
سمراء بس برضه ممكن بشكل اقل  
يصير عند البيض

↳ genetic & environmental factor

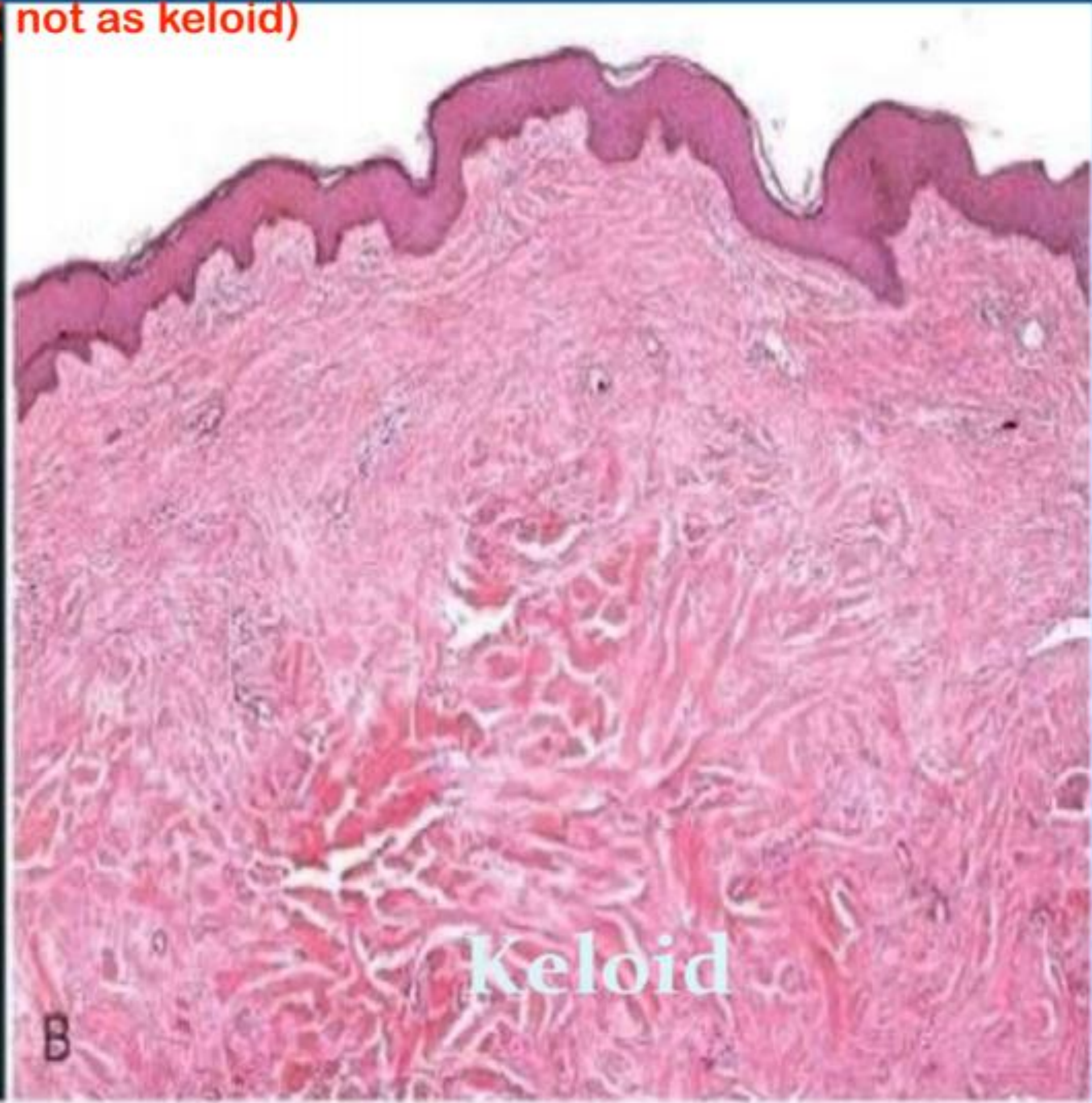
F 78 : Keloid.

A, Excess collagen deposition in the skin forming a raised scar known as a keloid. B, Thick collagen deposition in the dermis ( pink color).

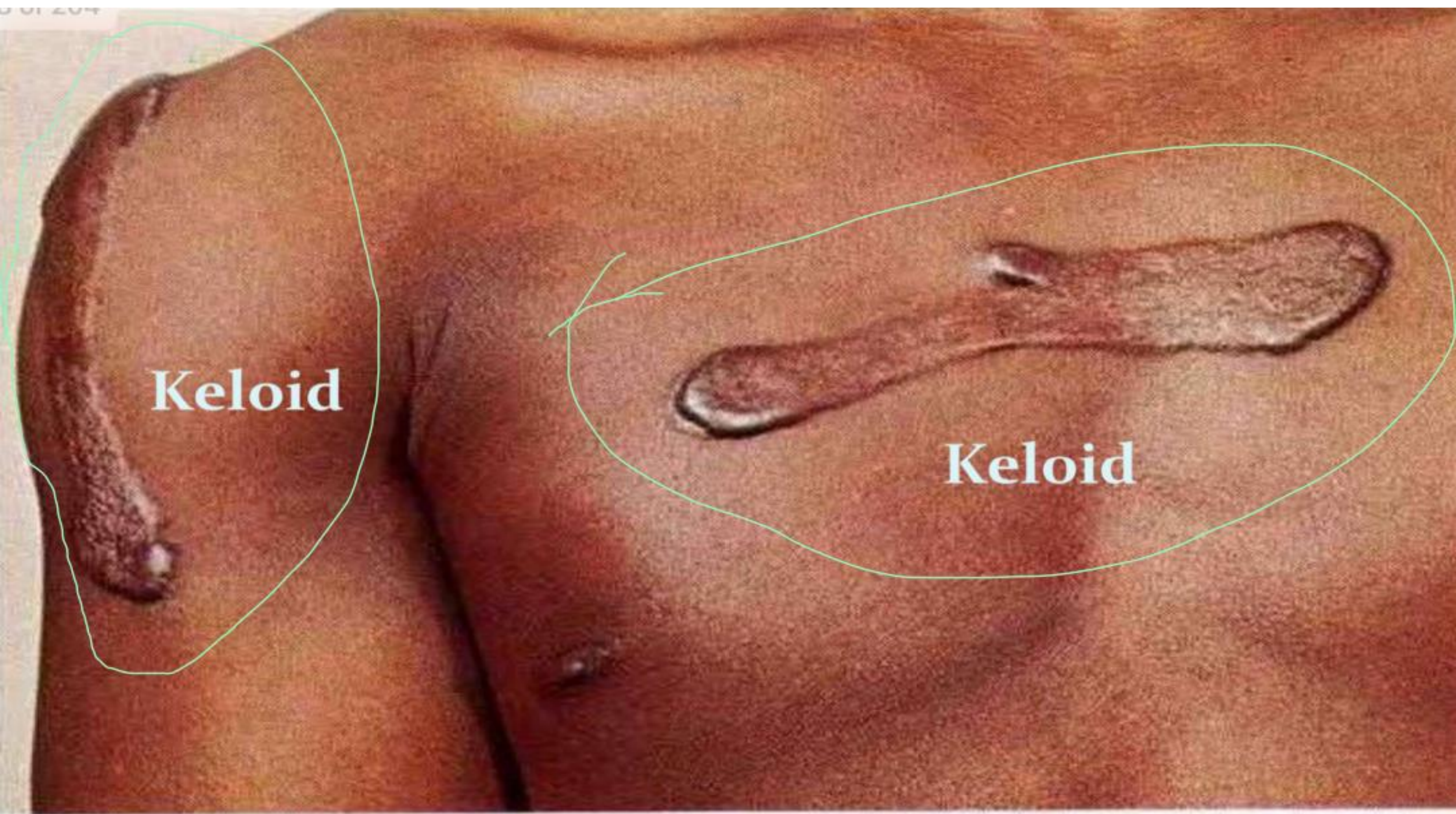
Collagen in Hypertrophic scar is wavy , regular and regress over time ( not as keloid)



Should be treated





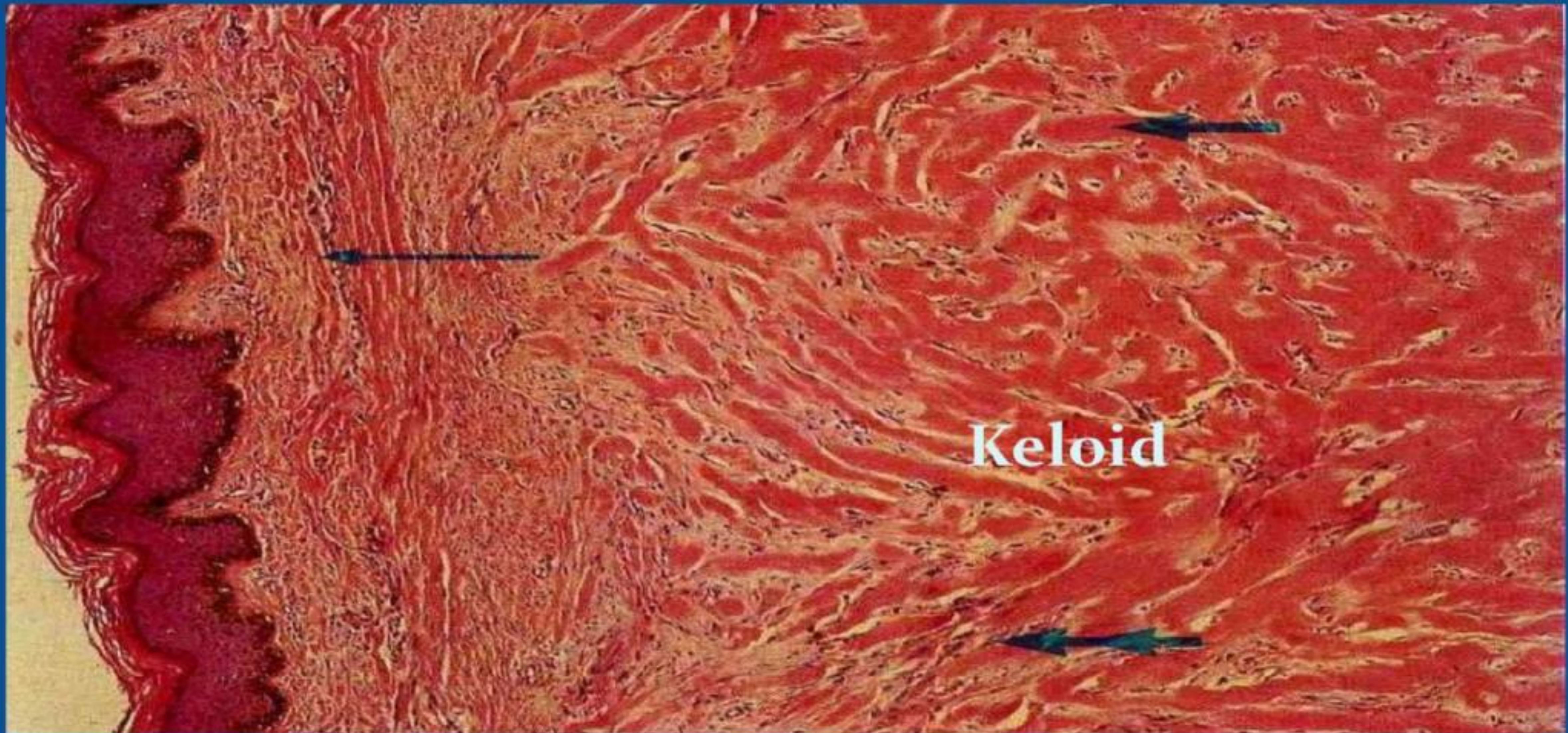


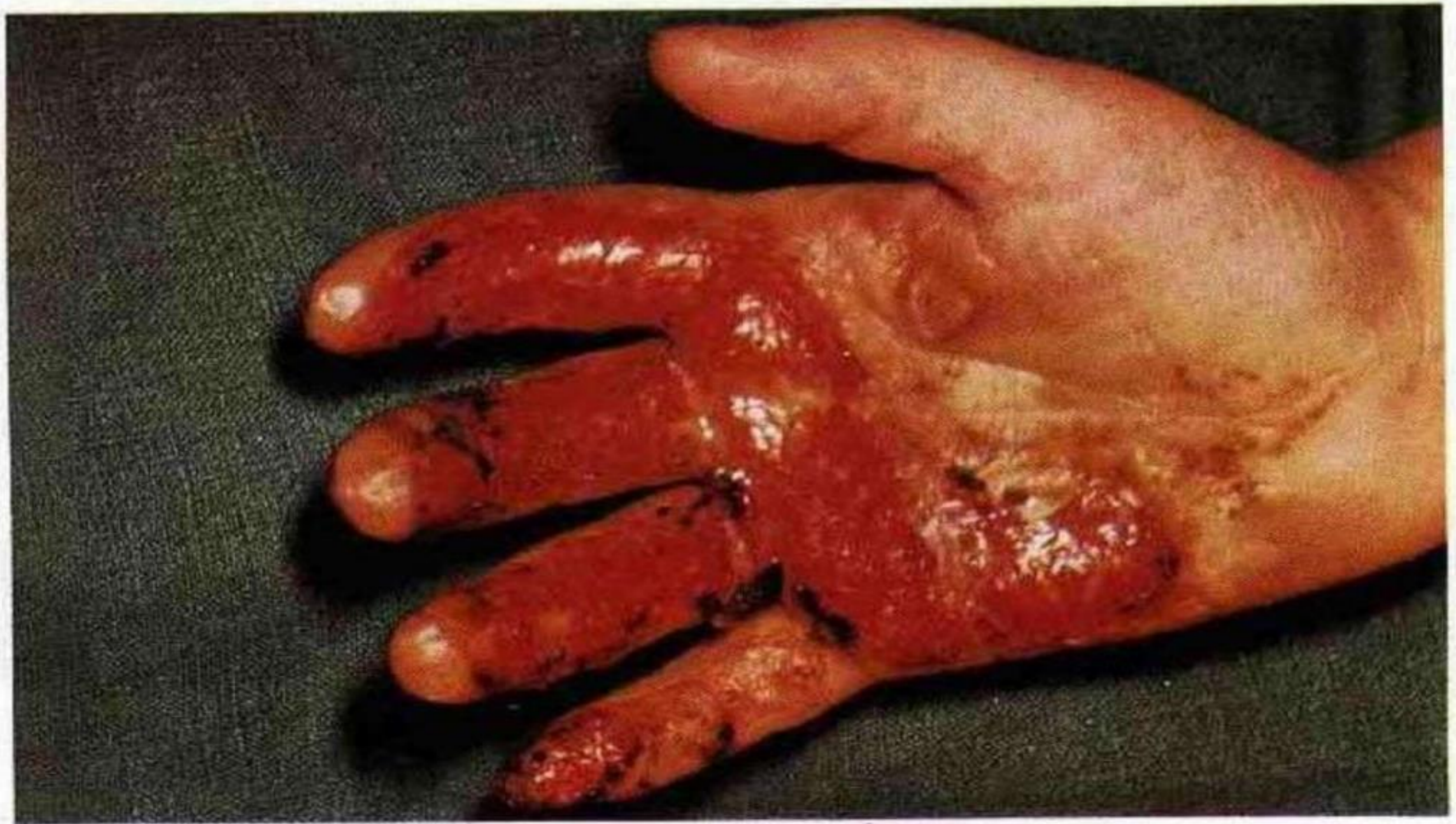
14.5 Keloid

Figure 79 : Keloid → از الله بسكل خاص وليس جراحياً surgically

سؤال اجب باصقان العملي  
Figure 80 : Keloid in a healed wound in the Skin.

The epidermis & dermis (thin arrow) appear normal, but the deeper dermis & subcutaneous tissues are replaced by very broad bands of hyaline eosinophilic collagen (thick arrow) .



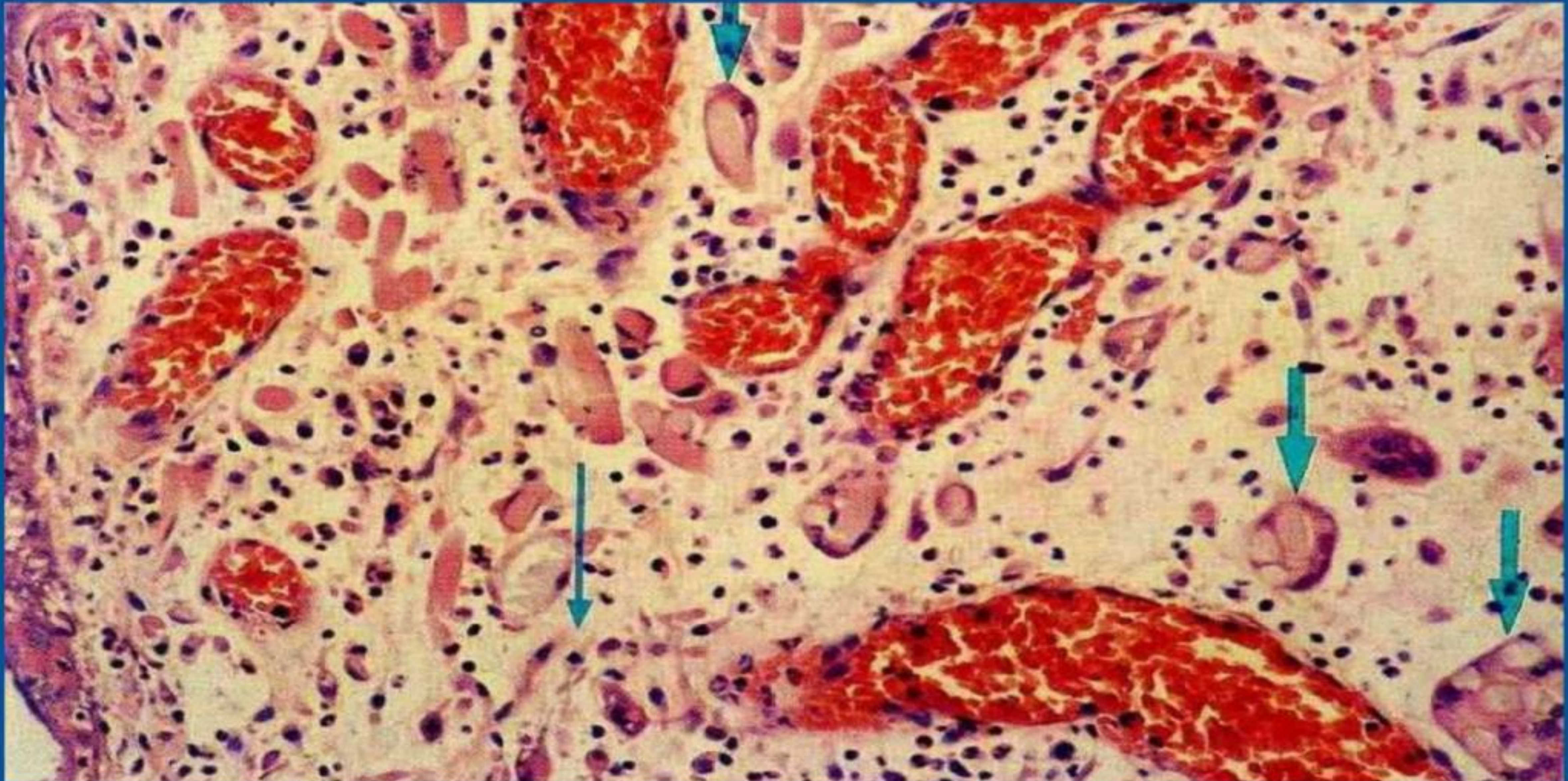


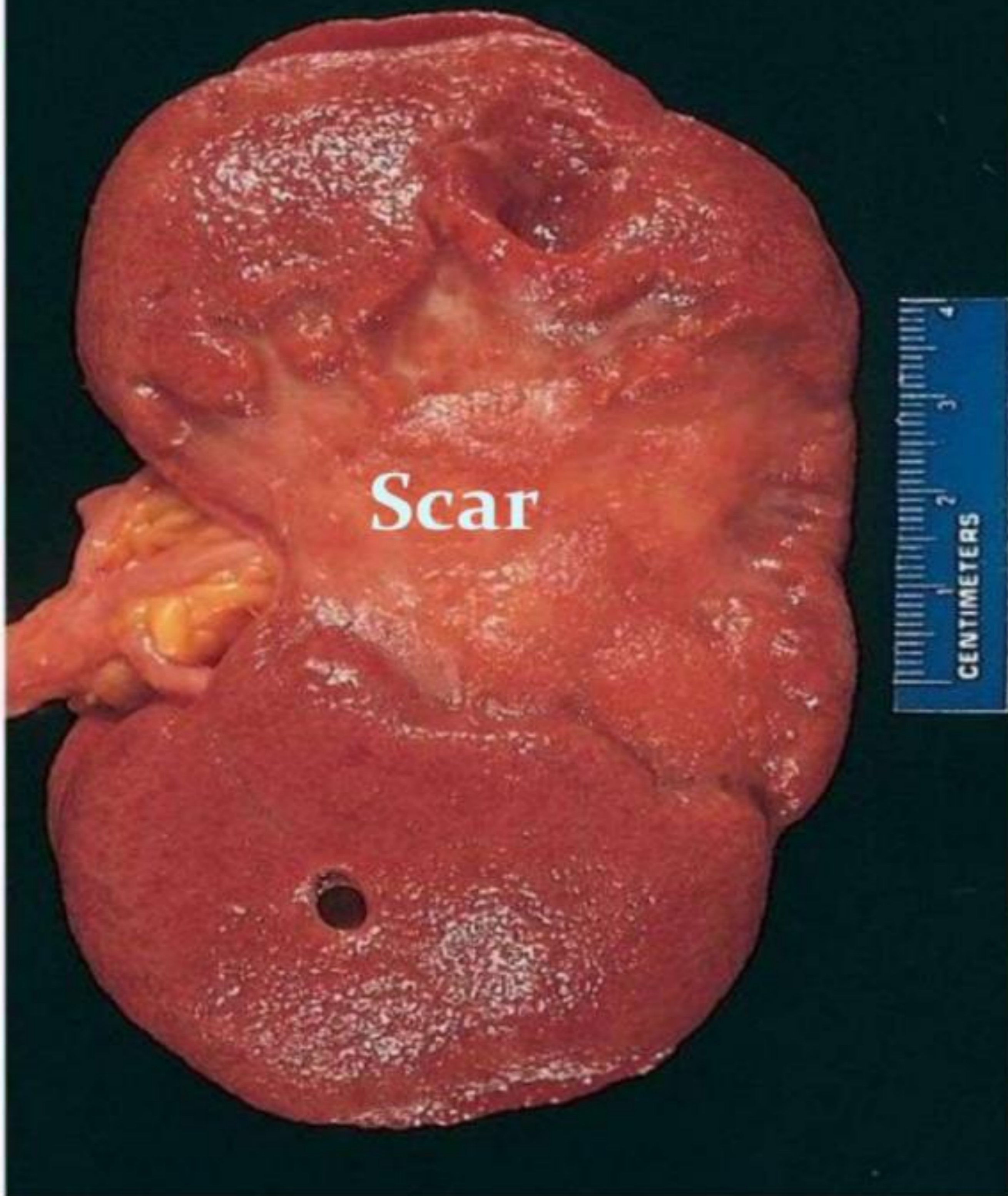
1.12 Granulating burn

Figure 81 : Exuberant granulation tissue. Proud flesh

**Figure 82 : Foreign-body granuloma : healed wound of skin , showing granulation tissue, consisting of (1) large & greatly dilated capillaries, (2) lymphocytes & plasma cells, (3) fibroblasts (thin arrow), (4) very large giant cells enclosing nylon suture material, (thick arrow ) from the original surgical incision**

*Nodule on site of suture*



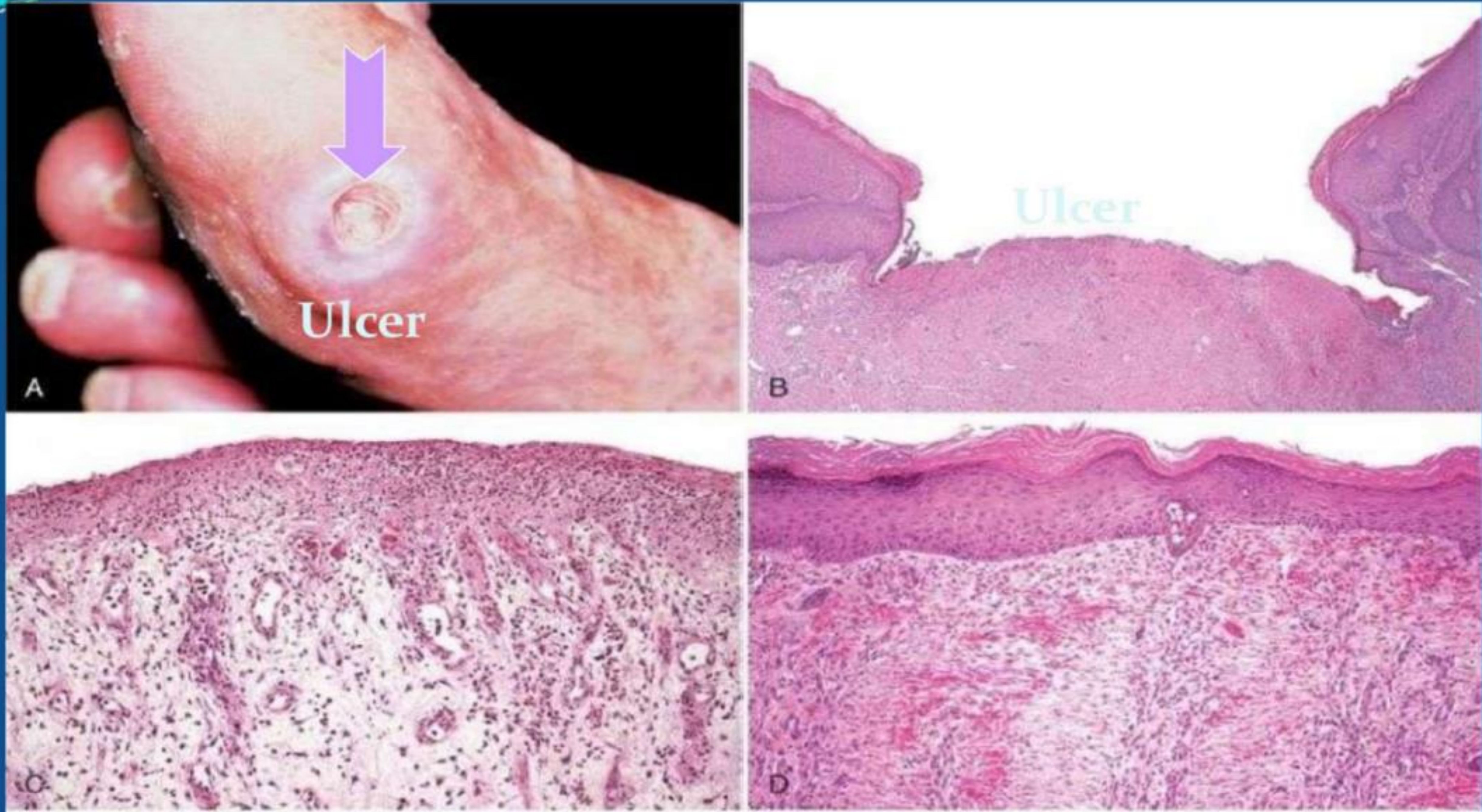


Scar ← Ischemia of renal tissue ← renal artery انسداد

**F 83 : Large old kidney infarct, now replaced by a large fibrotic scar.**

↓  
Mature collagen fiber

# Figure 84 : Healing of diabetic skin ulcer.



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**Granulation tissue**