Tissue Repair and Wound Healing

Healing (repair):

Host response to tissue injuries. The latter may result in cell death and tissue destruction.

Healing including:

1. **Regeneration:** which indicates the replacement of injured tissue by proliferation of surviving specialized parenchymal cells.

2. **Connective tissue response:** which is characterized by replacement of the damaged tissue by granulation tissue and its subsequent maturation into fibrous tissue and scar formation.

The relative contribution of the above two processes vary according to the:

a. Type of the tissue involved by the damage.
b. Nature, severity and duration of the injury.

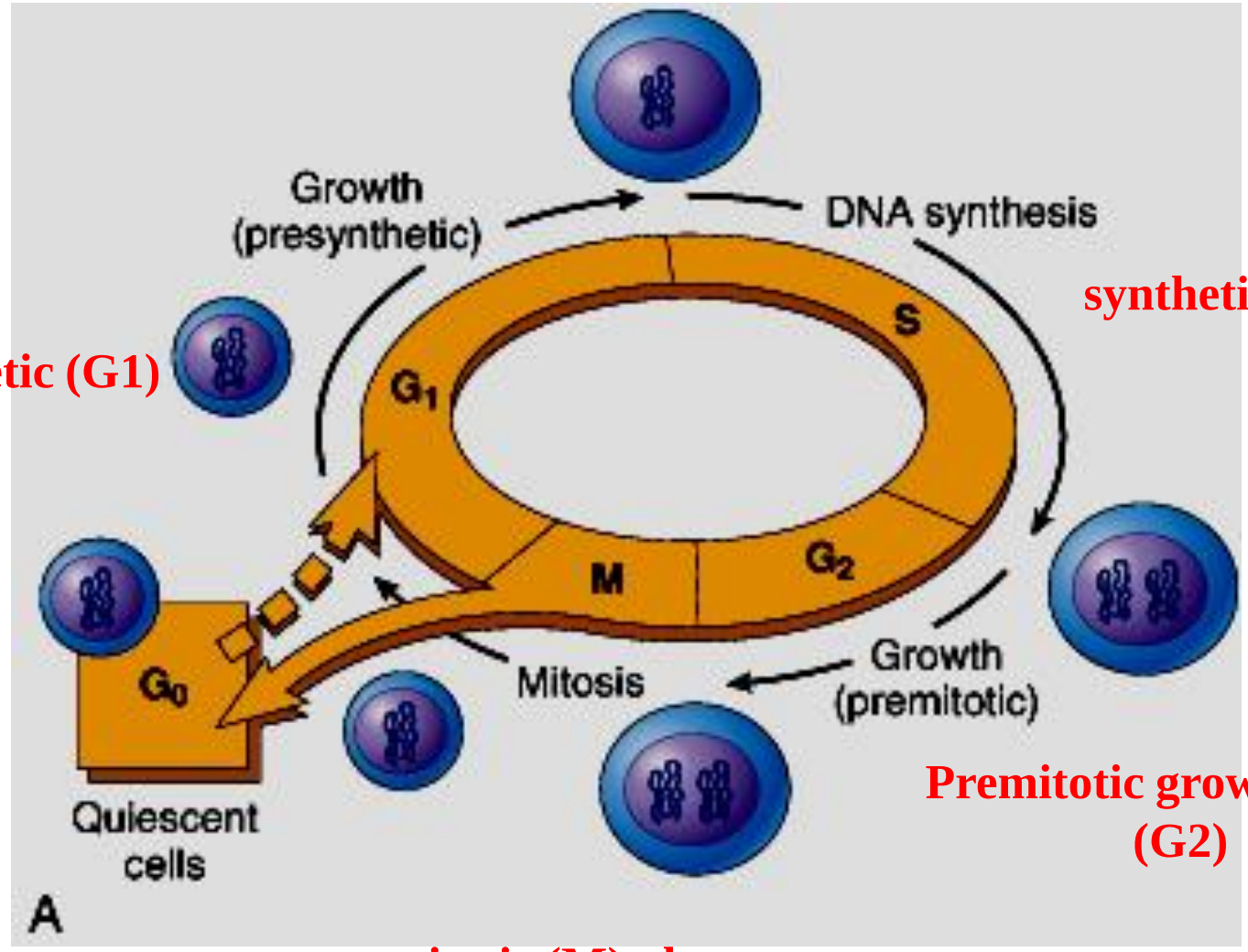
Understanding the process of repair requires some knowledge of the control of cell proliferation and the extracellular matrix (ECM) and its. functions .

Normal cell proliferation — The cell cycle

The cell cycle consists of:

1. Presynthetic growth phase **(G1)**
2. DNA-synthetic phase **(S)**
3. Premitotic growth phase **(G2)**
4. Mitotic phase **(M)**

Stages of cell cycle



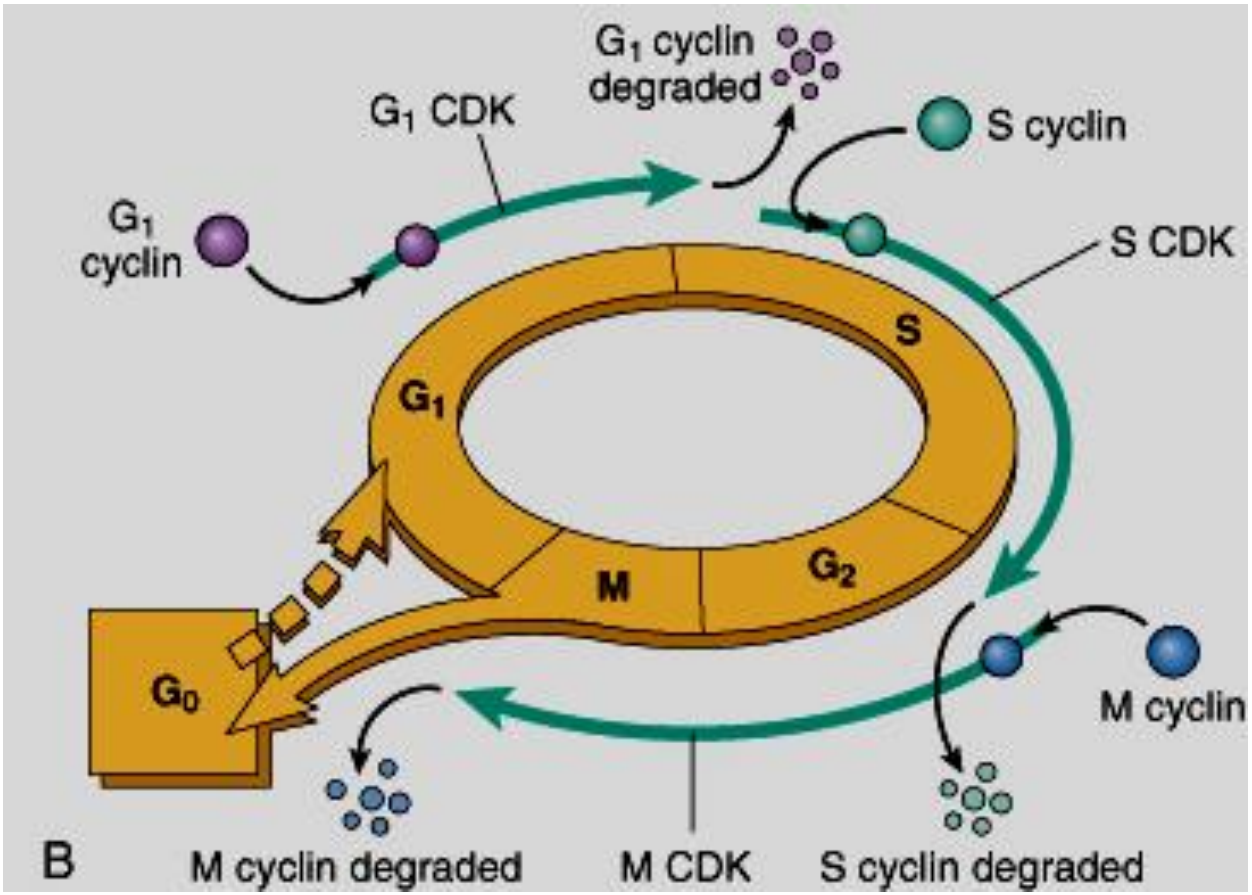
Presynthetic (G1)

synthetic (S)

Premitotic growth phase (G2)

mitotic (M) phase

Control of cell cycle progression



CDKs are constitutively synthesized but are activated only when complexed with cyclins. The cyclins (indicated as globular proteins) are synthesized only at certain stages of the cell cycle and then are degraded as the cycle progresses into the next phase; as they are degraded the relevant CDK becomes inactive.

* Entry and progression of cells through the cell cycle are controlled by changes in the levels and activities of a family of proteins called **Cyclins.**

* The levels of the **various cyclins** increase at specific stages of the cell cycle, after which they are rapidly degraded as the cell moves on through the cycle.

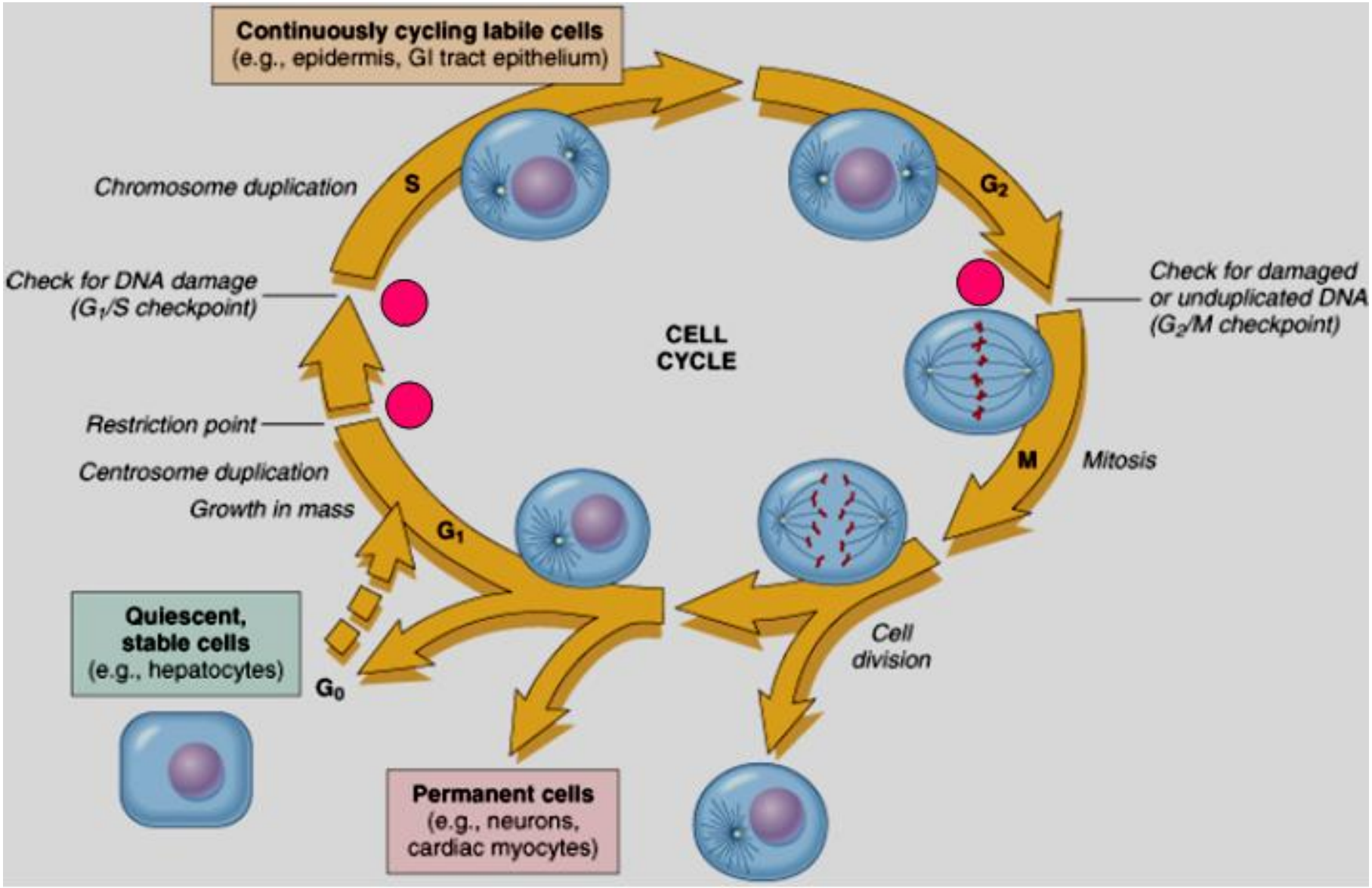
* Cyclins accomplish their regulatory functions by phosphorylating a selected group of protein substrates, and then activating the cyclin-dependent kinases **(CDKs).**

* CDKs are constitutively synthesized but are activated only when complexed with cyclins. The cyclins (indicated as globular proteins) are synthesized only at certain stages of the cell cycle and then are degraded as the cycle progresses into the next phase; as they are degraded the relevant CDK becomes inactive.

* Cyclin-CDK complexes are also regulated by the binding of **CDK inhibitors.** These are particularly important in regulating cell cycle checkpoints **(G1—S and G2—M),** which are points at which cell DNA is replicated and all mistakes repaired before progressing.

* When DNA is damaged e.g. by ultraviolet irradiation, the tumor suppressor protein **TP53** (policeman gene) is stabilized and induces the transcription of a CDK inhibitor CDKN1A (formerly called p21).This arrests the cells in G1 or G2 until the DNA can be repaired, at that point the TP53 levels fall, CDKN1A diminishes and the cells can proceed through the checkpoint.

* If the DNA damage is too extensive, TP53 will initiate a cascade of events by which the cell will undergo **apoptosis.** The latter term refers to a **programmed active cell death.**



G1 restriction point, and the G1/S and G2/M checkpoints

The cells of the body are divided into **three groups** depending on their relationship to cell cycle.

1- Labile cells: These under normal (physiological) conditions are in continuous division and death. They include the:

1. The hemopoietic cells in the bone marrow.
2. The majority of surface epithelial cells including:
   a. stratified squamous surface of the skin, oral cavity, vagina, and cervix.
   b. cuboidal epithelium of the ducts draining exocrine organs (salivary glands, pancreas, biliary tract).
   c. columnar epithelium of G.I.T., uterus, and fallopian tubes.
   d. transitional epithelium of the urinary tract.

These tissues have special cells, called **stem cells** that are programmed to divide continuously.

2- Stable cells (quiescent) :

These are considered to be **quiescent** or have only low-levels of replicative capacity in their normal state. However, they are capable of undergoing rapid division in response to injury e.g. parenchymal cells of most solid glandular tissues **including the liver, kidney, and pancreas, as well as endothelial cells lining blood vessels, and mesenchymal cells such as fibroblasts and smooth muscle cells.**

3- Permanent cells:

These are specialized, terminally differentiated cells. They show no proliferative activities in postnatal life i.e. if lost; they cannot be replaced by identical cells. Examples include: **neurons, cardiac muscle cells, and the cells of the lens.** If these cells are injured, they will be replaced by scar tissue.

Extracellular matrix (ECM) :

ECM is a dynamic, constantly remodeling macro-molecular complexes, synthesized locally and constituting a significant proportion of any tissue.

ECM is synthesized by mesenchymal cells e.g. fibroblasts; these form a three-dimensional amorphous gel. Its major components are fibrillar and nonfibrillar collagens, with proteoglycan and glycoprotein elements.

ECM has the following functions:

The ECM is much more than a space filler around cells. Its various functions include:

1. **Provides mechanical support** for the cells and in the absence of adhesion most cells die.

2. Determines cell orientation (polarity). Basolateral (bottom and sides) versus apical (top) are important for the proper functions of most cells e.g. absorption of nutrients from G.I.T. or release of digestive enzymes in the pancreas.

3. Controls cell growth.

4. Regulates cell growth and differentiation.

These are regulated by cell adhesion and cell shape. Generally the more adherent a cell is the more proliferative and less synthetic it will be.

5. Provides scaffolding for tissue renewal.

6. Important for storage and presentation of regulatory molecules.

ECM occurs in two basic forms:

1- Interstitial matrix .

2- Basement membrane .

1- Interstitial matrix :

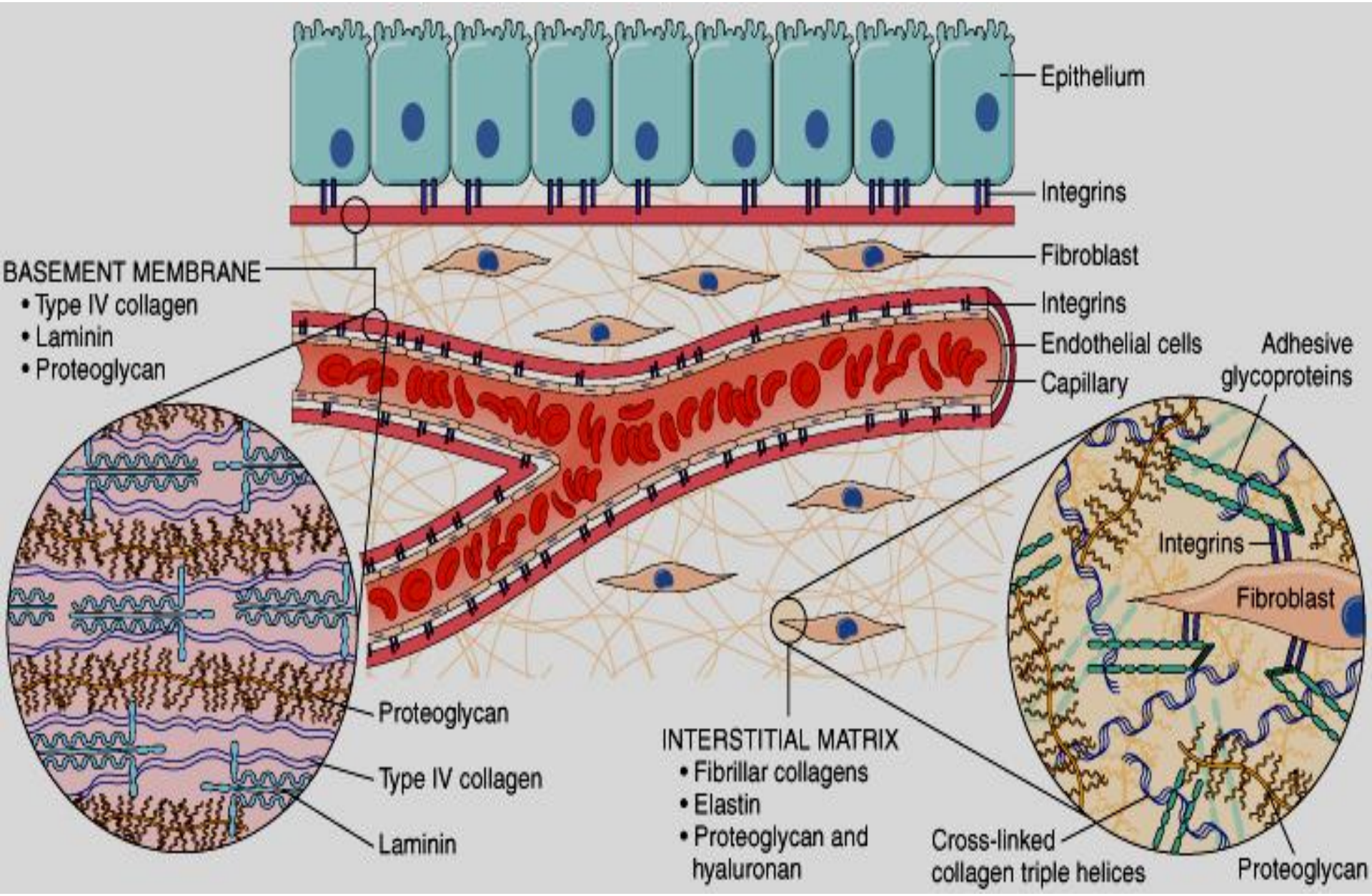
a. present in the spaces between cells in connective tissues

b. present in the spaces between Epithelium and supportive vascular and smooth muscle structures.

It is synthesized by mesenchymal cells e.g. fibroblasts; these form a three-dimensional amorphous gel. Its major components are fibrillar and nonfibrillar collagens, with proteoglycan and glycoprotein elements.

2- Basement membrane:

The basement membrane sits beneath the epithelium; it acts as a boundary between the epithelium and underlying connective tissues. It is synthesized by the epithelium as well as the underlying mesenchymal cells. It consists of amorphous nonfibrillar **type IV collagen and adhesive glycoproteins.**


Epithelium
Integrins
Fibroblast
BASEMENT MEMBRANE
• Type IV collagen
• Laminin
• Proteoglycan
Integrins
Endothelial cells
Capillary
Adhesive glycoproteins
Integrins
Fibroblast
Proteoglycan
Type IV collagen
Laminin
INTERSTITIAL MATRIX
• Fibrillar collagens
• Elastin
• Proteoglycan and hyaluronan
Cross-linked collagen triple helices
Proteoglycan

There are three basic components of ECM:

1. Fibrous structural proteins that provides tensile strength and recoil (collagen).
2. Adhesive glycoproteins.
3. Water-hydrated gels that permit resilience and lubrication.

1- Collagen:

This is the most abundant of the matrix proteins; it confers tensile strength. It is composed of a triple helical structure formed from three peptide chains **(**α chain**)**.

Fibroblasts are the principle cells involved in the synthesis of collagens. This process starts by secretion of procollagen molecules, which are modified by the removal of peptides from the amino- and carboxyl- terminal ends by a specific peptidases.

The resultant collagen molecules align to form **collagen fibrils,** which have beaded appearance on electron microscopy; these contribute to the strength of the fibrils. This is reinforced by cross-linking of collagen molecules by covalent bonding.

Collagen fibers are formed by aggregation of several collagen fibrils. There are **18** types of collagen and the predominant type of collagen varies in different tissues. The tensile strength of the fibrillar collagens derives from their cross-linking; a process dependent on **Vitamin C; thus children with ascorbate deficiency will have :**

- skeletal deformities.

- Bleed easily because of weak vascular wall basement membrane.

- Show poor healing of injuries.

Collagen Types

I	Major interstitial collagen 90% : skin, bone, tendon, cornea.
II	Cartilage, intervertebral disc, vitreous body.
III	Interstitial collagen: skin, internal organs.
IV	Basement membranes.
V	Minor interstitial collagen as in III.
VI	Interstitial microfibrils; widespread distribution.
VII	Anchoring fibrils at dermo -epidermal junction.

Individual fibrils often contain more than one collagen type; **type I and III commonly** coexist.

2- Adhesive glycoproteins:

These are of high molecular weight and function as matrix adhesion molecules, the most abundant of which is **Fibronectin .**

Fibronectin exists in two forms (plasma and tissue). This protein has binding sites for other matrix proteins, such as collagen and also for cell surface integrins. Accordingly it acts as a link between cells and matrix and controls the structure of the extra cellular matrix.

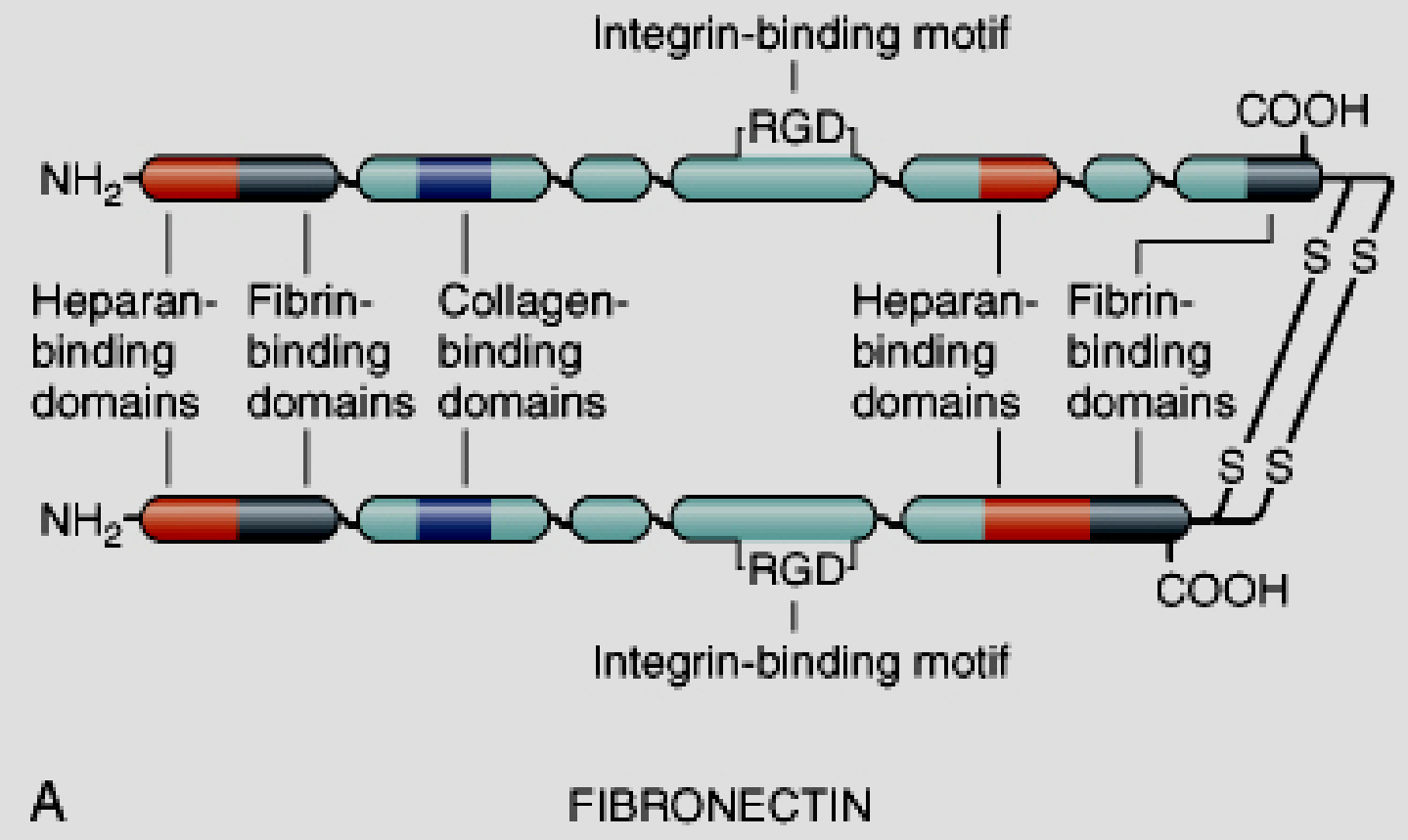
3- Glycosaminoglycans:

These are water-hydrated gel and negatively charged polysaccharide chains, that permit resilience and lubrication.

The most abundant of glycosaminoglycans are:

1. Hyaluronic acid
2. Chondroitin sulphate
3. Dermatan sulphate
4. Heparin sulphate
5. Keratin sulphate.

Fibronectin molecule



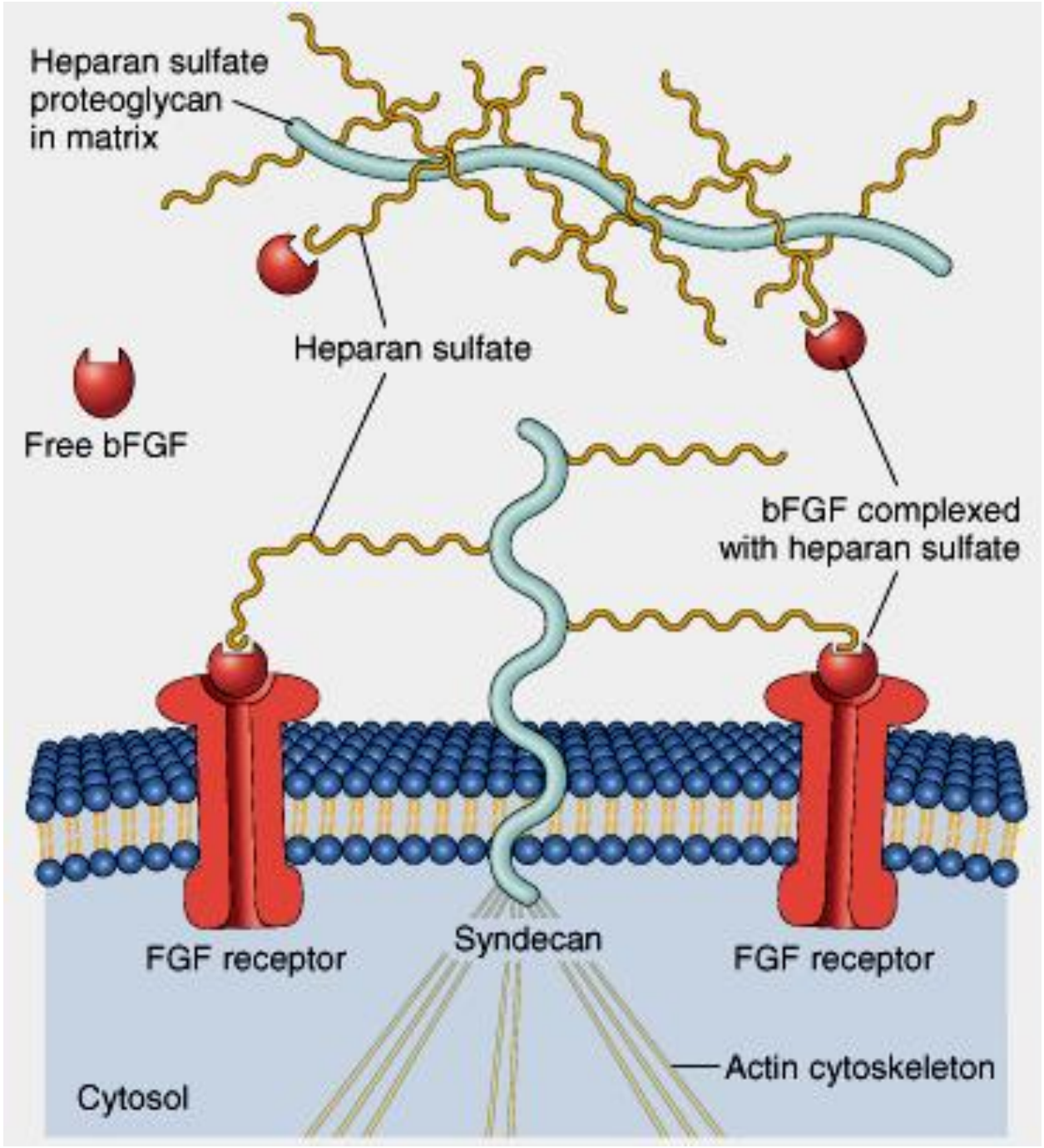
The molecule consists of a disulfide-liked dimer with various domains that bind to ECM components, as well as the integrin-binding domain.

Proteoglycans in the ECM and on cells act as reservoirs for growth factors. Heparan sulfate binds basic fibroblast growth factor (bFGF) secreted into the ECM.

Any subsequent injury to the ECM can release bFGF, which can then stimulate recruitment of inflammatory cells, fibroblast activation, and new blood vessel formation.

Syndecan is a cell surface proteoglycan with a transmembrane core protein and attached extracellular glycosaminoglycan side chains.

The glycosaminoglycan chains can also bind free bFGF from the ECM and thereby mediate improved interactions with cell surface FGF receptors. The cytoplasmic tail of syndecan attaches to the intracellular actin cytoskeleton and helps maintain the morphology of epithelial sheets.


Heparan sulfate proteoglycan in matrix
Heparan sulfate
Free bFGF
bFGF complexed with heparan sulfate
FGF receptor
Syndecan
FGF receptor
Actin cytoskeleton
Cytosol

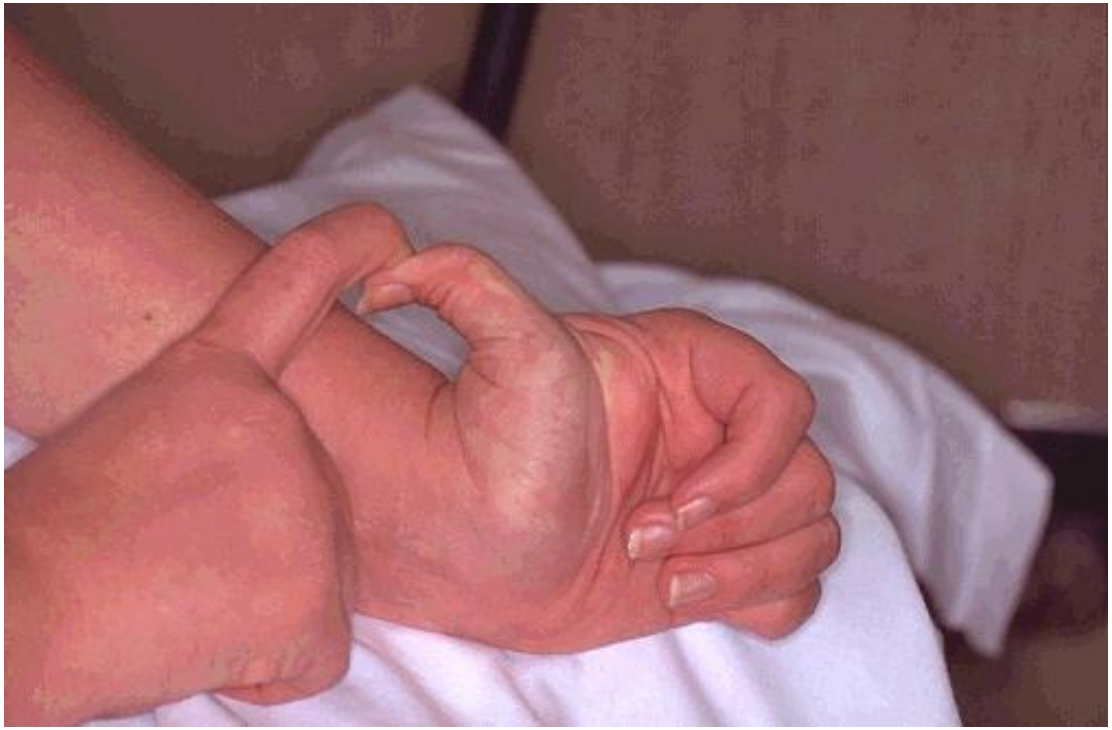
Their relative amounts vary from tissue to tissue. Their molecules are hydrophilic; therefore they serve to provide tissue turgor by attracting water and acting as a hydrated gel. They also have the capacity to bind to collagens and fibronectin and may participate in the structural organization of the extra cellular matrix.

Elastin:

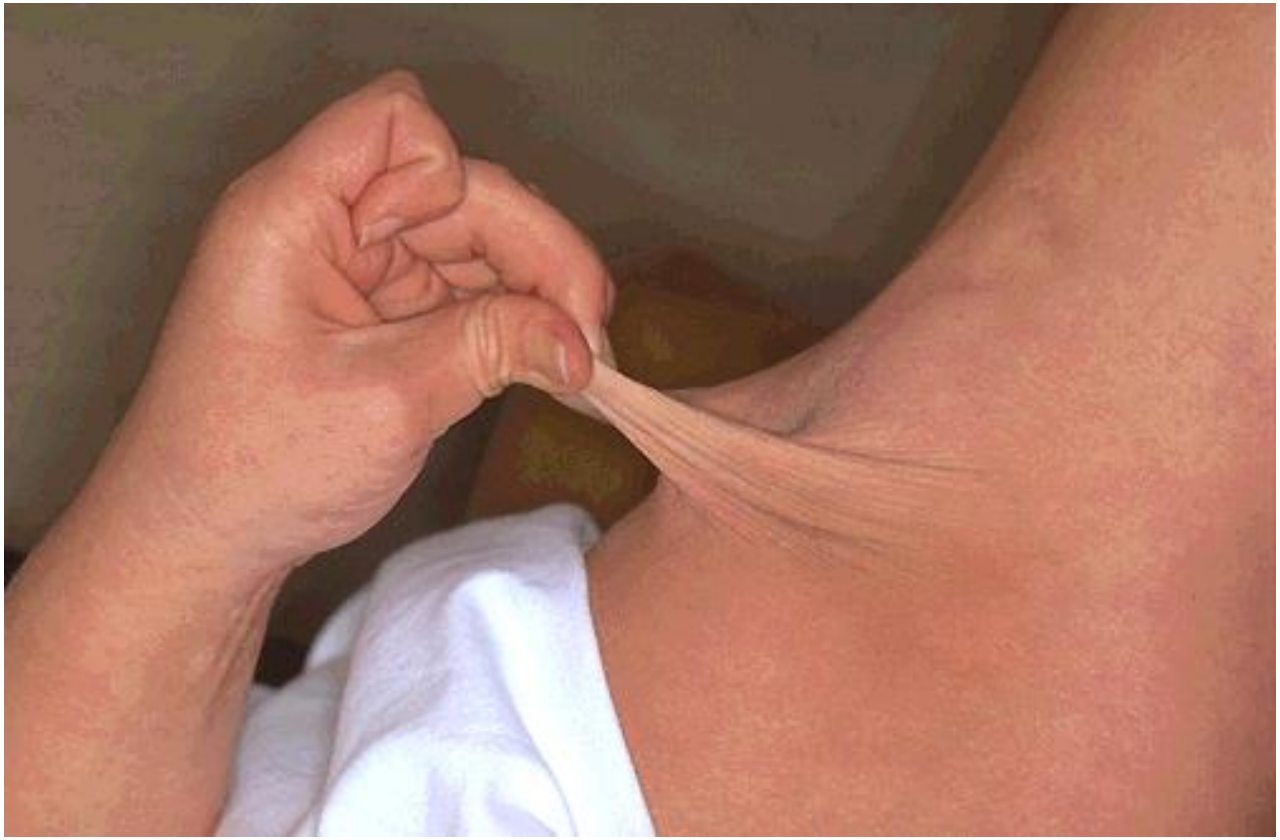
This is a protein, which forms the core of elastic fibers.
Elastin molecules are extensively cross-linked producing random coils, which give the elastic fibers the property of recoil after transient stretching. Elastic fibers are most abundant in tissues in which there is a need for recoil, e.g.

1. Large arteries such as the aorta.
2. The dermis of skin.
3. Ligaments.
4. Uterus.

Defects in elastic fibers lead to skeletal abnormalities and weakened aortic wall (Marfan syndrome).



This is **Ehlers-Danlos syndrome** (EDS), a connective tissue disease in which there is a disorder of collagen synthesis. There are several types with various inheritance patterns.. Pictured here is a hyper-extensible, hypermobile joint typical of EDS



The skin can be stretched considerably with **Ehlers-Danlos syndrome** (EDS). The skin with EDS is also very fragile and easily traumatized

Growth factors

- Growth factors are chemical mediators that affect cell growth by binding to specific receptors on the cell surface or intracellularly.
  * Stimulate cellular proliferation.
  * Influence cell migration & cell differentiation .
  * Influence tissue remodeling .

- Induce cell proliferation by affecting the expression of **Protooncogens** (genes involved in normal growth control pathways).

- Alterations in the structure or expression of protooncogenes can convert them into **Oncogens** (contribute to uncontrolled growth of cancers).

Growth Factors and Cytokines Involved in Regeneration and Wound Healing

Cytokine	Symbol	Source	Functions
Epidermal growth factor	EGF	Activated macrophages, salivary glands, keratinocytes, & many other cells	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration and granulation tissue formation
Transforming growth factor α	TGF-α	Activated macrophages, T lymphocytes, keratinocytes, and many other cells	Similar to EGF; stimulates replication of hepatocytes and many epithelial cells
Hepatocyte growth factor (scatter factor)	HGF	Mesenchymal cells	Enhances proliferation of epithelial and endothelial cells, and of hepatocytes; increases cell motility
Vascular endothelial cell growth factor (isoforms A, B, C, D)	VEGF	Mesenchymal cells	Increases vascular permeability; mitogenic for endothelial cells

Cytokine	Symbol	Source	Functions
Platelet-derived growth factor (isoforms A, B, C, D)	PDGF	Platelets, macrophages, endothelial cells, keratinocytes, smooth muscle cells	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macrophages, and fibroblasts; mitogenic for fibroblasts, endothelial cells, and smooth muscles cells; stimulates production of MMPs, fibronectin, and HA; stimulates angiogenesis and wound remodeling; regulates integrin expression
Fibroblast growth factor 1 (acidic), -2 (basic), and family	FGF-1, -2	Macrophages, mast cells, T lymphocytes, endothelial cells, fibroblasts, and many tissues	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition

Cytokine	Symbol	Source	Functions
Transforming growth factor β(isoforms 1, 2, 3)	TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, smooth muscle cells, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts, and smooth muscle cells; stimulates TIMP synthesis, angiogenesis, and fibroplasia; inhibits production of MMPs and keratinocyte proliferation; regulates integrin expression and other cytokines
Keratinocyte growth factor (FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation

Growth inhibition

- Contact inhibition.

- Cell-matrix interaction.

- Some growth factors (e.g. TGF-β) .

- ?Growth arrest genes and ?Tumor suppressor genes.

Mechanisms of tissue repair

I- Repair by Regeneration.

II- Repair by connective tissue deposition (Fibrosis)

Repair by regeneration

- Replacing injured tissue by same type of original tissue cells.

- Labile & stable cells.

- Involves two tissue components:

  * Cellular proliferation, which is regulated by growth factors & growth inhibitors.
  * Extracellular matrix (ECM) & cell-matrix interaction.

- An intact basement membrane directs epithelial cell polarity & is essential for its orderly regeneration.

Tissue regeneration can occur in parenchymal organs with stable cell populations, but with the exception of the liver, this is usually a limited process. Pancreas, adrenal, thyroid, and lung tissues have some regenerative capacity.

The surgical removal of a kidney elicits in the **contralateral kidney** a compensatory response that consists of both hypertrophy and hyperplasia of proximal duct cells. The mechanisms underlying this response are not understood.

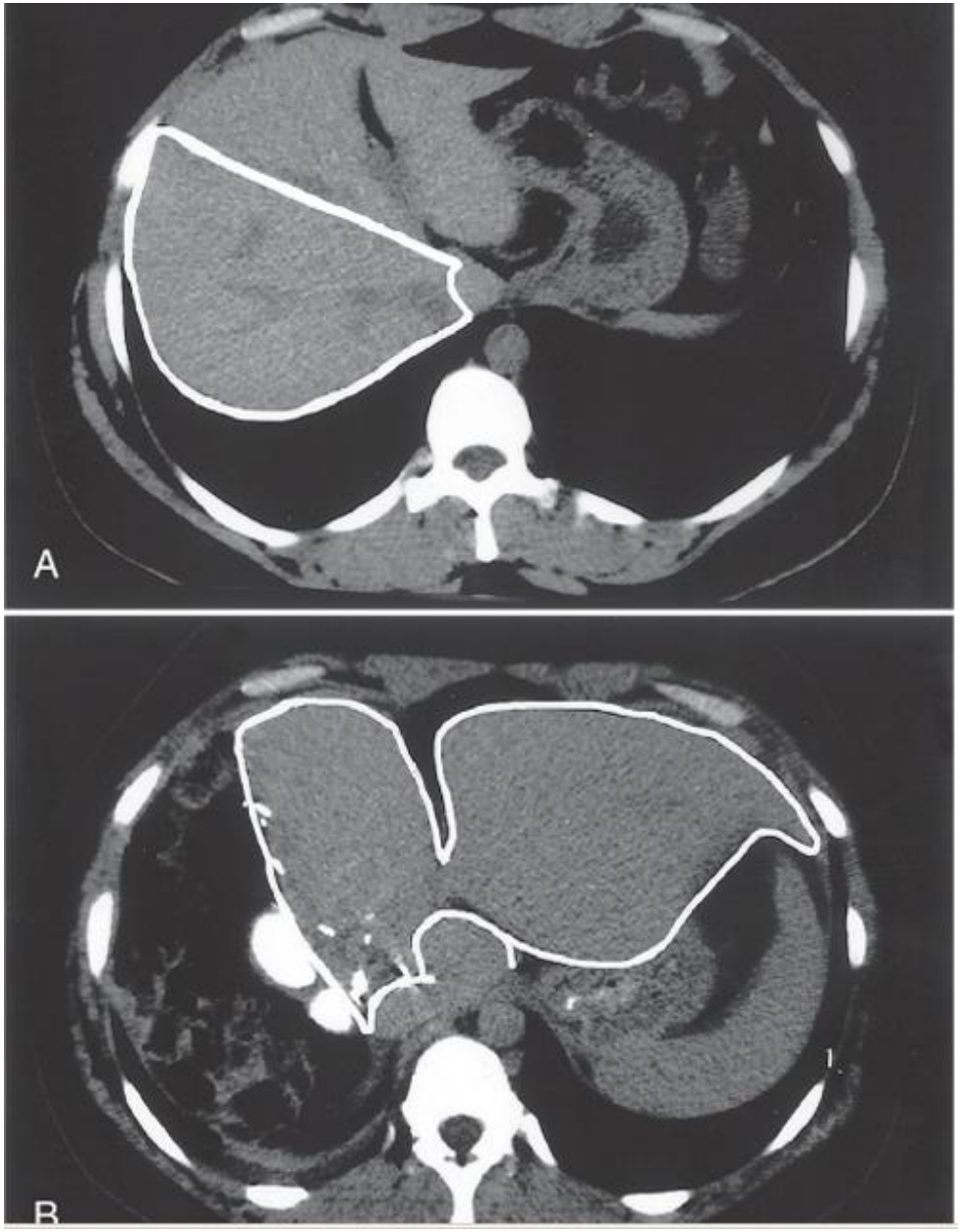
Much more dramatic, however, is the regenerative response of the **liver** that occurs after surgical removal of hepatic tissue.
As much as 40% to 60% of the liver may be removed in a procedure called living-donor transplantation, in which a portion of the liver is resected from a normal individual and is transplanted into a recipient with end-stage liver disease, or after partial hepatectomies performed for tumor removal.

Regeneration of human liver

Computed tomography scans of the donor liver in living-donor liver transplantation.

A- The liver of the donor before the operation. Note the right lobe (outline), which will be resected and used as a transplant.

B- Scan of the same liver 1 week after resection of the right lobe; note the enlargement of the left lobe (outline) without regrowth of the right lobe.



In all of these situations, the tissue resection triggers a proliferative response of the remaining hepatocytes (which are normally quiescent), and the subsequent replication of hepatic nonparenchymal cells.

In experimental systems, hepatocyte replication after partial hepatectomy is initiated by **cytokines (e.g., tumor necrosis factor (TNF) and interleukin 6 (IL-6)** that "prime" the cells for replication by stimulating the transition from G0 to G1 in the cell cycle.

Progression through the cell cycle is dependent on the activity of growth factors such as *HGF and the EGF family of factors, which includes transforming growth factor α.*
HGF is produced by fibroblasts, endothelial cells, and liver nonparenchymal cells. It induces proliferation of hepatocytes and most epithelial cells, including those in the skin, mammary gland, and lungs.

- HGF binds to a specific tyrosine kinase receptor (MET), which is frequently overexpressed in human cancers. *EGF and TGF-α* share a common receptor (epidermal growth factor receptor, or EGFR) with intrinsic tyrosine kinase activity.

- The "EGFR" is actually a family of receptors that respond to EGF, TGF-α, and other ligands of the EGF family.

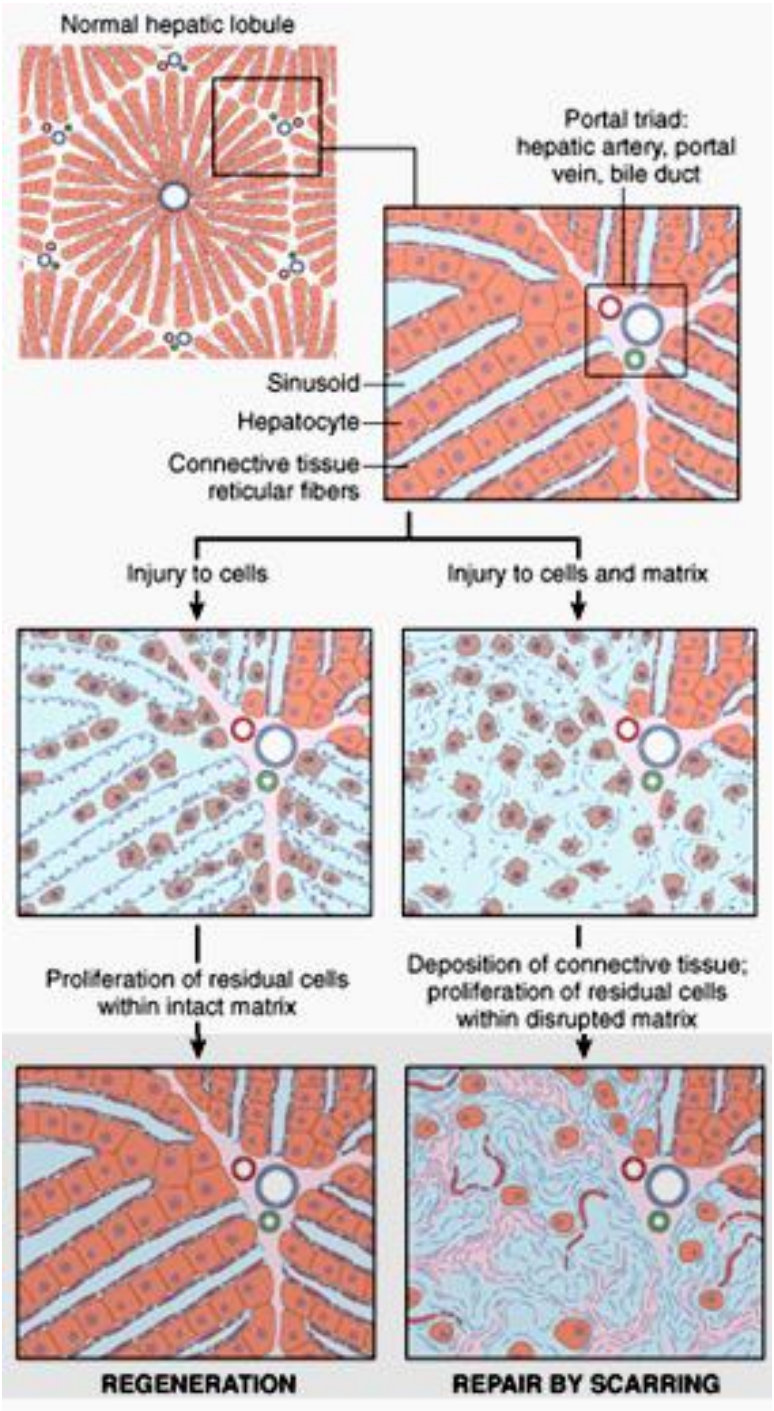
- EGF/TGF-α is mitogenic for hepatocytes and most epithelial cells, including keratinocytes. In cutaneous wound healing EGF is produced by keratinocytes, macrophages, and other inflammatory cells. The main EGFR (referred to as EGFR1 or ERB B1) is frequently overexpressed in lung and some brain tumors and is an important therapeutic target for the treatment of these conditions. ERB B2 (also known as HER-2/NEU) has received great attention because of its overexpression in breast cancers, in which it is a target for effective cancer control.

I- Repair by Regeneration

injury to the liver is repaired by regeneration if only the hepatocytes are damaged,

or

by laying down of fibrous tissue if the matrix is also injured.

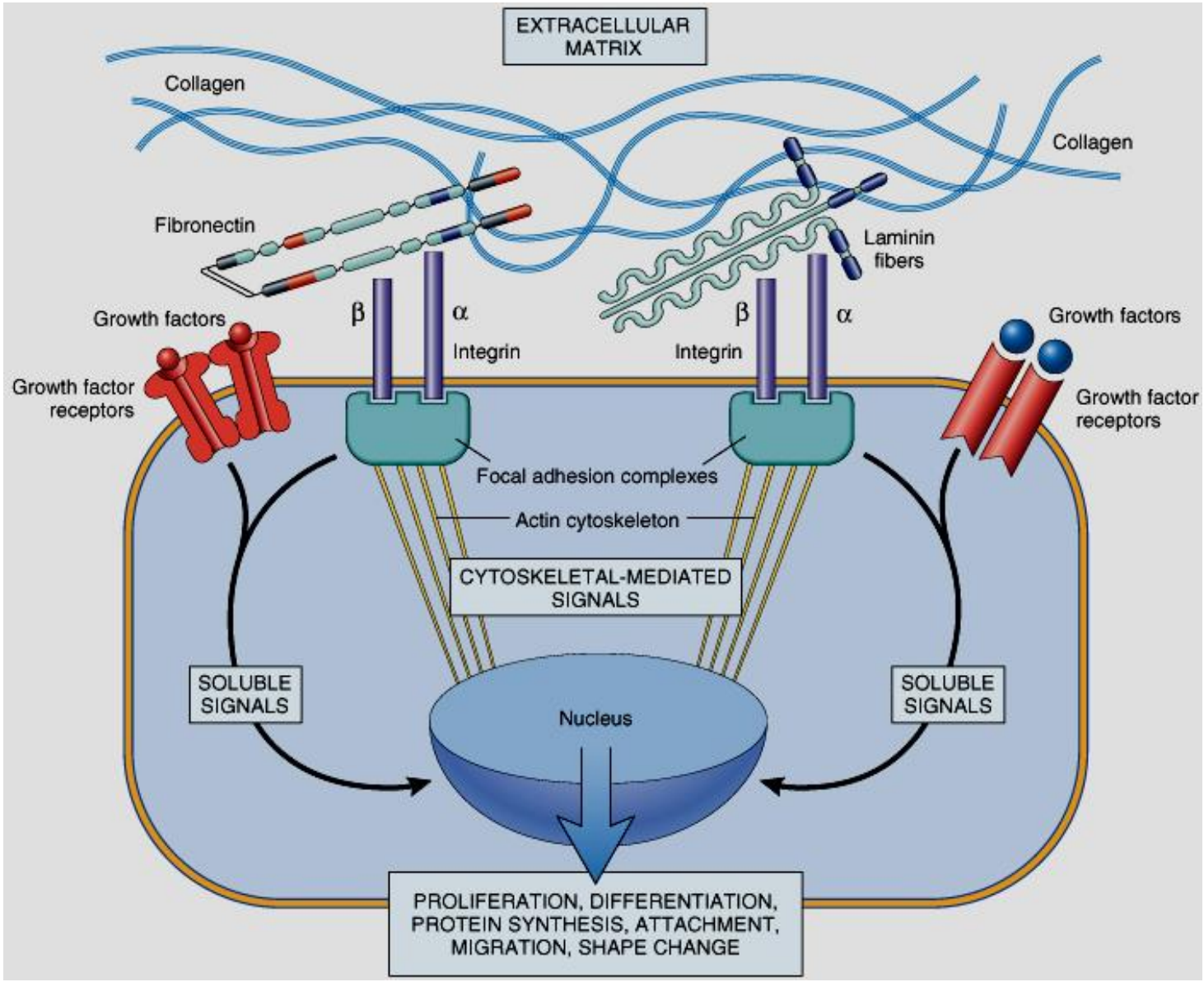


- Integrins bind ECM and interact with the cytoskeleton at focal adhesion complexes (protein aggregates that include vinculin, α-actinin, and talin).

- This can initiate the production of intracellular second messengers or can directly mediate nuclear signals.
- Cell surface receptors for growth factors also initiate second signals.

-Together, these are integrated by the cell to yield various responses, including changes in cell growth, locomotion, and differentiation.

ECM interactions and growth factors can influence cell growth, motility differentiation, and protein synthesis.



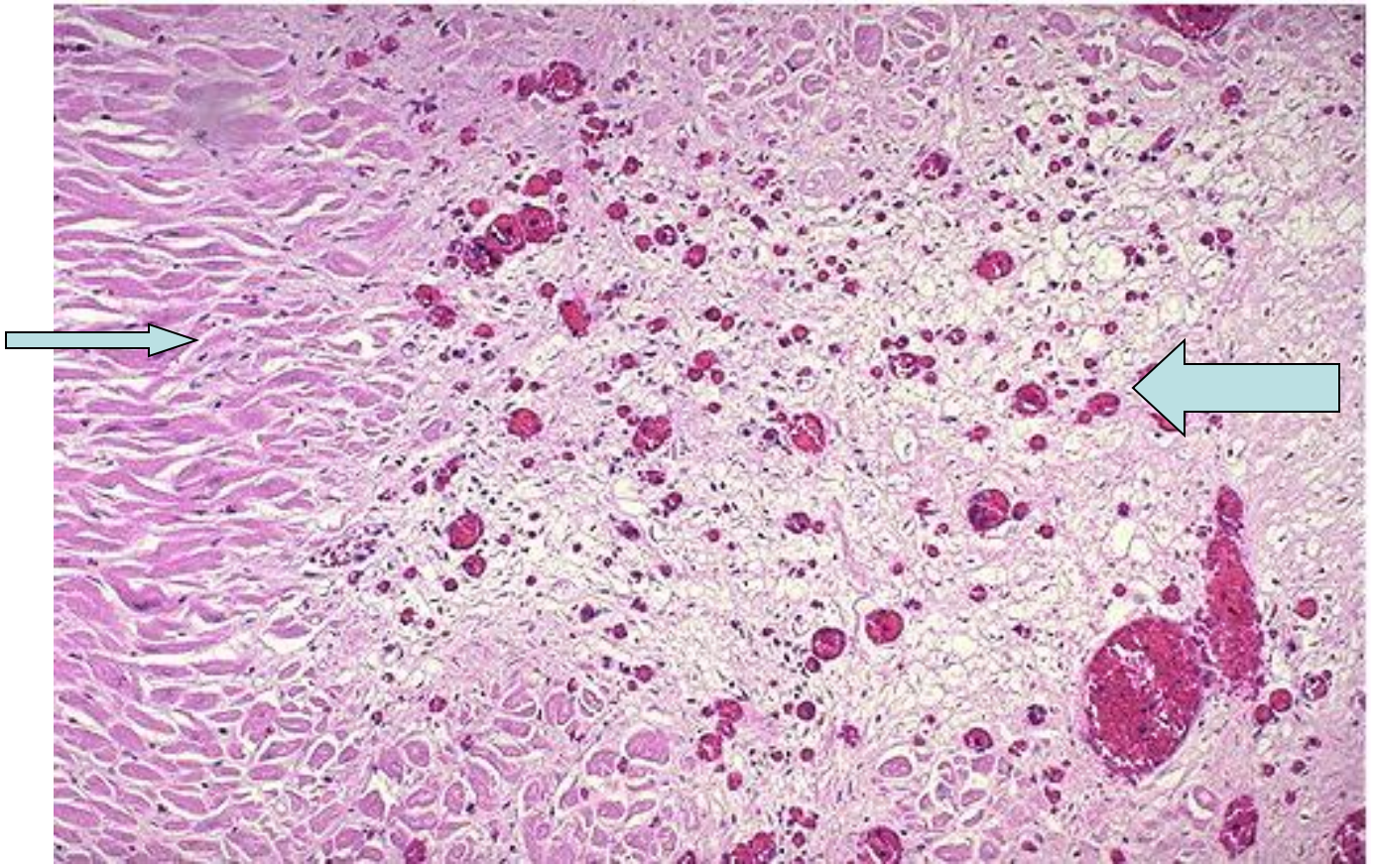
Molecular control of the healing process

Healing involves:

1. Regeneration and migration of specialized cells.
2. Angiogenesis.
3. Proliferation of fibroblasts.
4. Matrix protein synthesis .
5. Cessation of these processes.

These processes are controlled and mediated by growth factors, which are low molecular weight polypeptides. They bind to specific receptors on cell membranes, generate second messengers and initiate a series of intra-cellular events, resulting in cell proliferation.

Healing of myocardial infarction



Replacement of a zone of infarcted myocardium by granulation tissue with production of collagen (scarring) Thick arrow. There is no regeneration of the damaged myocardial cells. Non-infarcted myocardium is present at the far left (thin arrow).

2- Angiogenesis

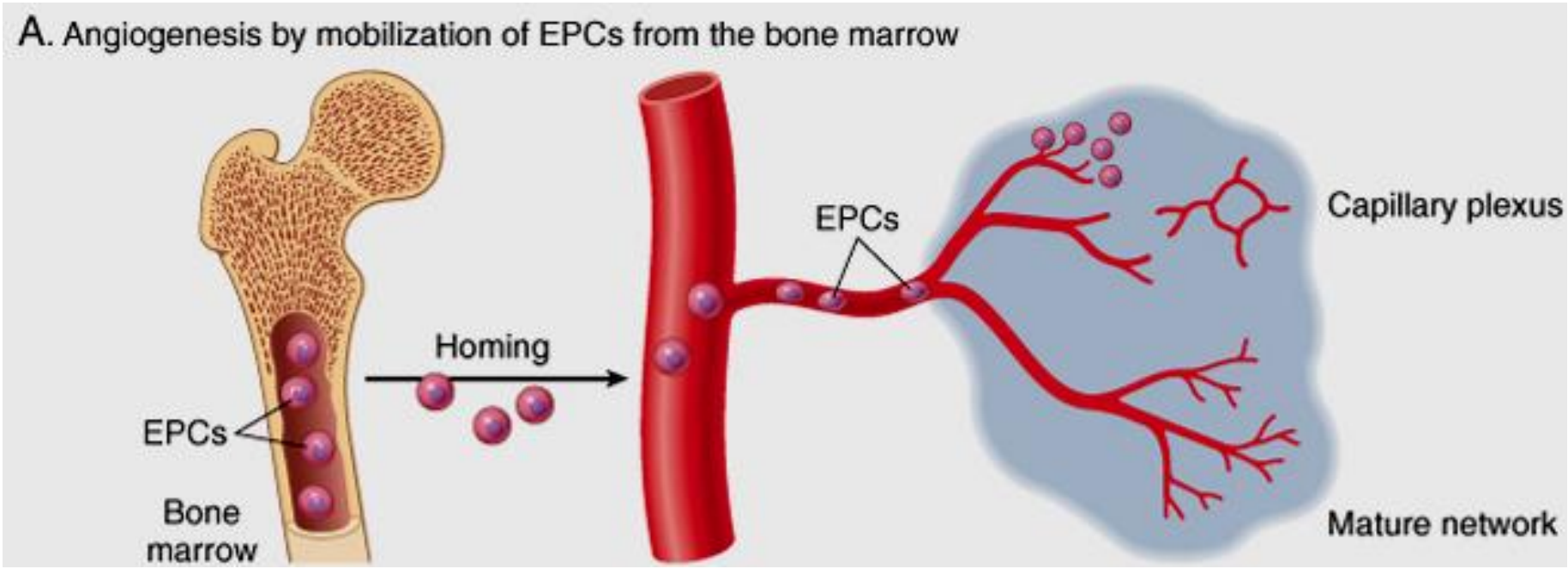
Angiogenesis resulting from:

A- Mobilization of bone marrow endothelial precursor cells.
(EPCs), EPCs can be mobilized from the bone marrow and migrate to a site of injury or tumor growth. At these sites EPCs differentiate and form a mature network by linking with preexisting vessels.

B- From preexisting vessels at the site of injury.
In angiogenesis from preexisting vessels, endothelial cells from these vessels become motile and proliferate to form capillary sprouts.

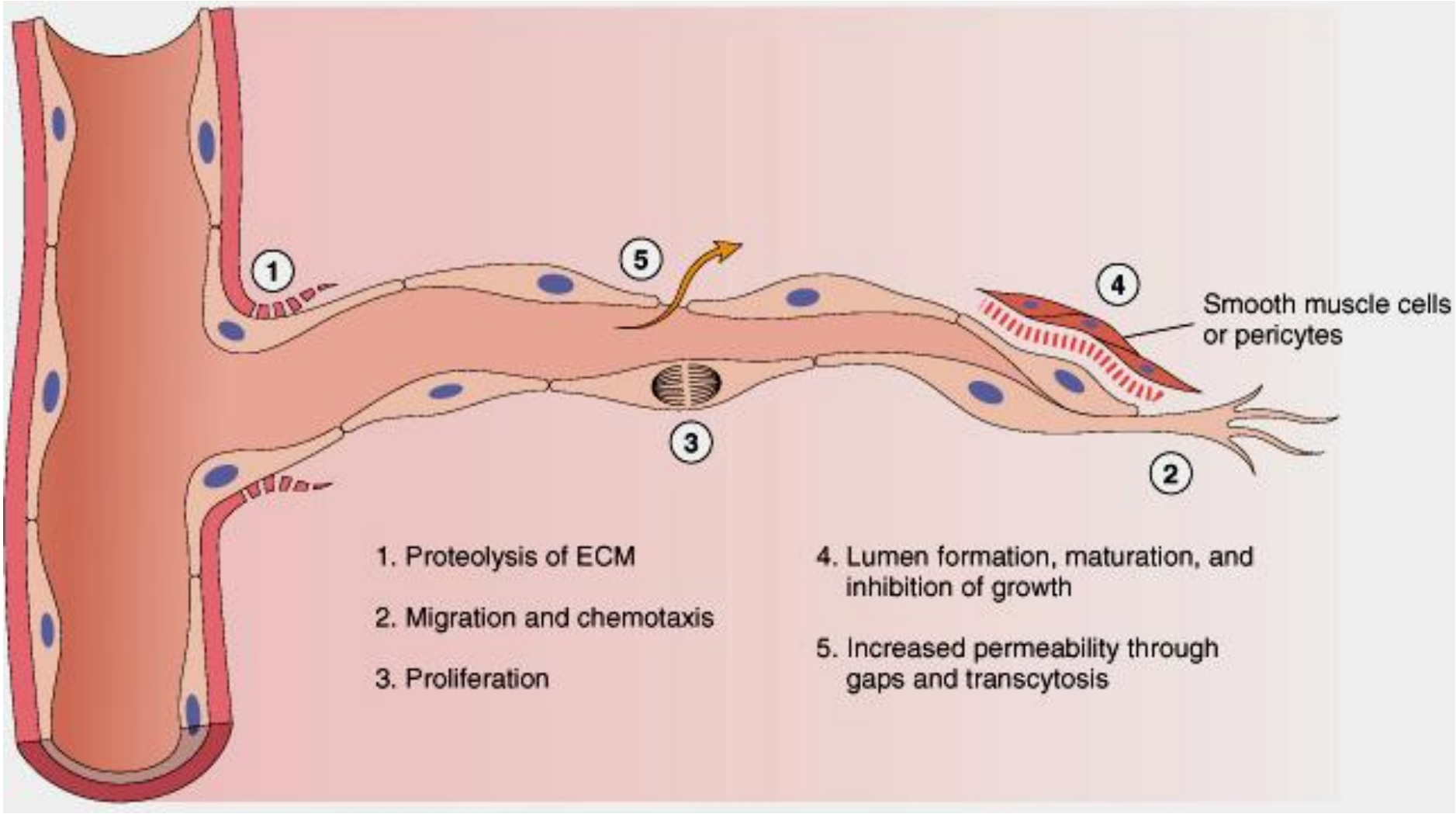
Regardless of the mechanism of angiogenesis, vessel maturation requires the recruitment of pericytes and smooth muscle cells to form the periendothelial layer.

A- Mobilization of bone marrow endothelial precursor cells



Endothelial precursor cells

B- From preexisting vessels at the site of injury



Steps in the process of angiogenesis:

(1) Basement membrane and extracellular matrix (ECM) degradation.

(2) endothelial migration.

(3) endothelial proliferation (mitosis).

(4) organization and maturation including the recruitment of vascular pericytes or smooth muscle cells.

(5) indicates the increased permeability due to intercellular gaps and increased transcytosis. This increased permeability allows deposition of plasma proteins (e.g., fibrinogen) in the extracellular matrix and provides a provisional stroma for fibroblast and endothelial cell ingrowth; it also leads to the edema that occurs in granulation tissue.

growth factors involved in angiogenesis

- **VEGFs** (Vascular endothelial growth factor) constitute a family of growth factors that include VEGF-A, -B, -C, and -D. VEGF-A is generally referred to as VEGF; VEGF-C selectively regulates lymphoid vasculature.

- Several agents can induce VEGFs, *the most important being hypoxia.* Other inducers are platelet-derived growth factor (PDGF), TGF-β, and TGF-α.

- **Basic fibroblast growth factor (FGF-2).** It also promotes the migration of macrophages and fibroblasts to the damaged area, and stimulates epithelial cell migration to cover epidermal wounds.

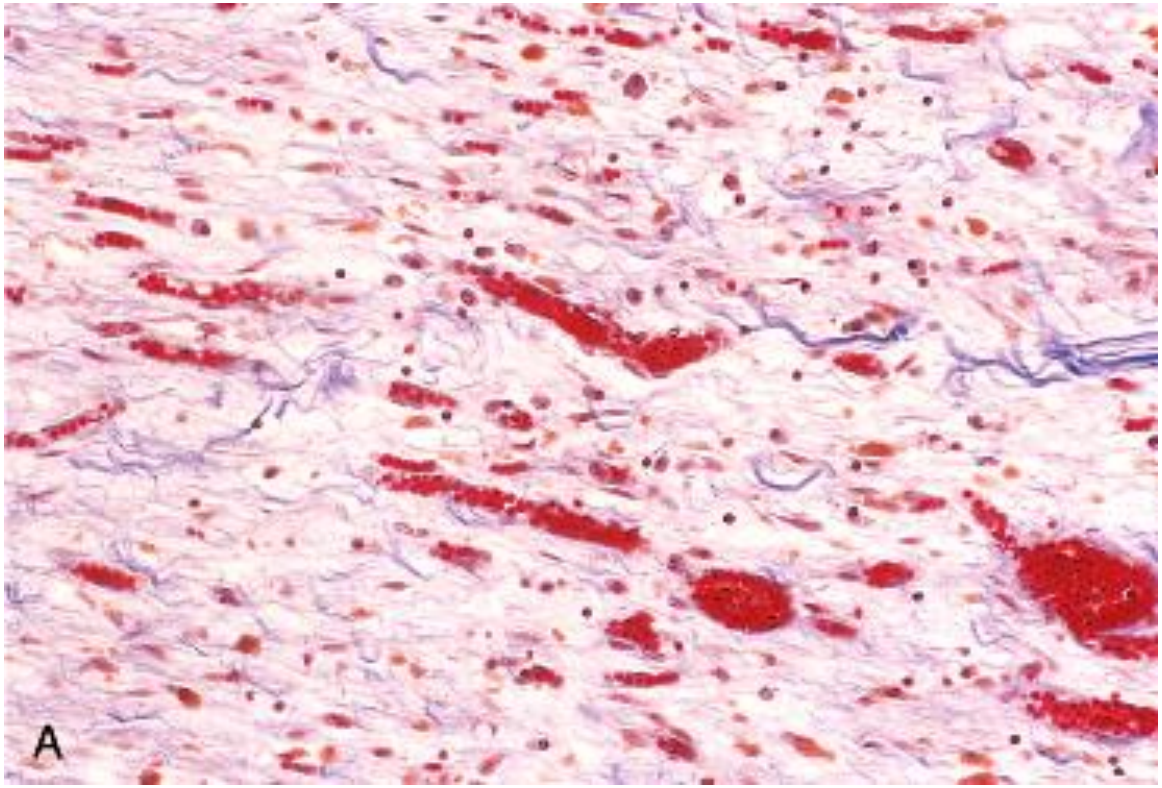
3&4 - Fibrosis & ECM deposition

- The pre-existing capillaries in the undamaged tissue form new capillaries by budding that extend into the damaged area, which is also infiltrated by macrophages, fibroblasts and myofibroblasts.

- Macrophages phagocytose inflammatory exudates and dead tissue. So at this stage we see the **vascular granulation tissue,** which is a fragile complex of interconnecting capillaries, macrophages, and support cells (fibroblasts), which replaces the area of damaged tissue. collagen synthesis by fibroblasts (type III) begins early in wound healing (days 3 to 5) and continues for several weeks, depending on the size of the wound.
- The process whereby the inflammatory exudate is replaced by granulation tissue is called **organization.**

- The fibroblasts initially are large and plump, but subsequently become in arresting status with a scant cytoplasm and an elongated spindle-shaped nucleus. These inactive fibroblasts are known as fibrocytes.

Vascular granulation tissue



A- Granulation tissue showing numerous blood vessels, edema, and a loose ECM containing occasional inflammatory cells.
This is a **trichrome stain** that stains collagen blue; minimal mature collagen can be seen at this point.

- The above stage is followed by progressive growth of fibroblasts and myofibroblasts, with a complex capillary network, and few residual macrophages **(Fibrovascular granulation tissue).**

- The proliferating fibroblasts actively synthesize collagen mainly **type III**, in addition to fibronectin and proteoglycans. Then many of the newly formed capillaries regress until a small number of vascular channels remains, providing nutrients for the fibroblasts. Some of the persisting vessels acquire smooth muscle in their walls, and remain as venules and arterioles.

- The intervening spaces between the vessels become progressively filled with fibroblasts synthesizing collagen **(Fibrous granulation tissue).**

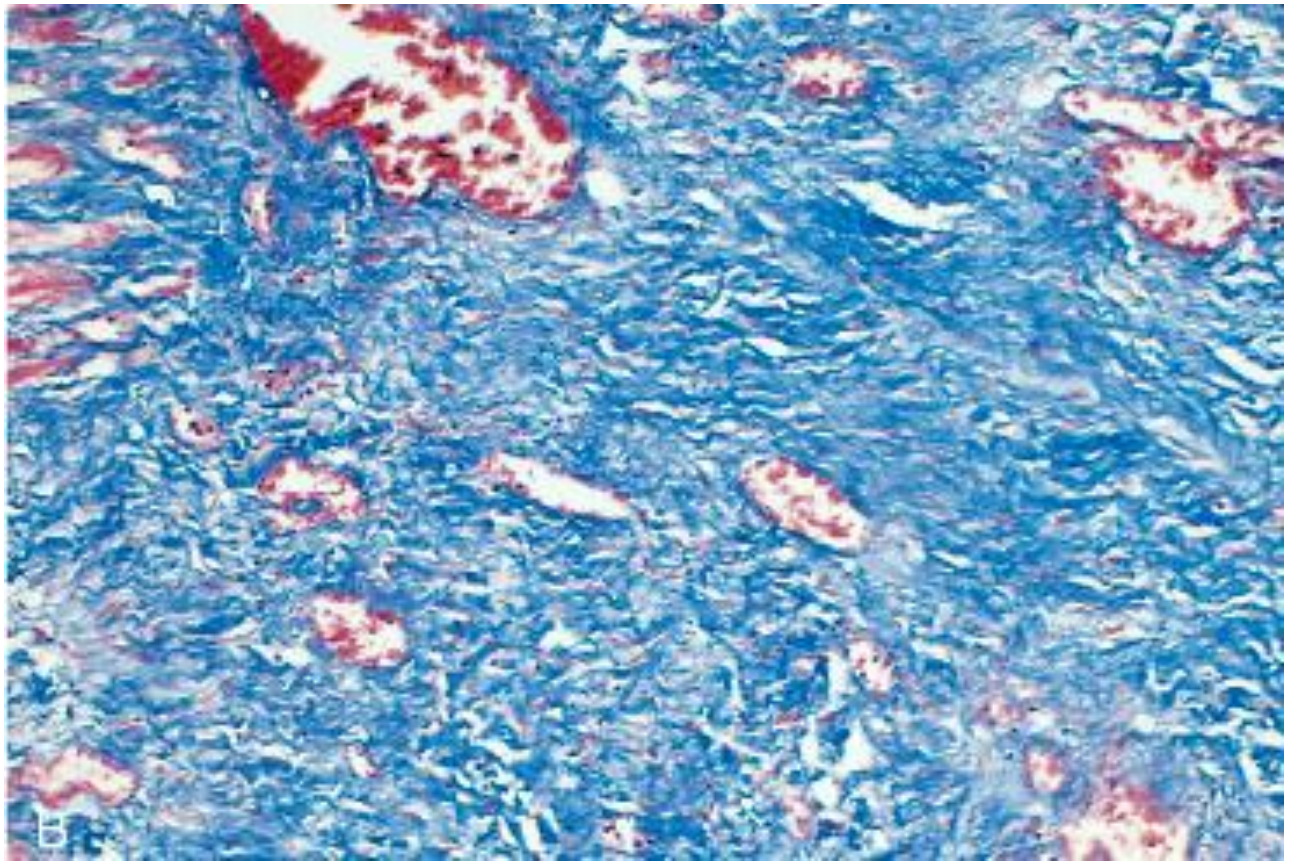
Scar formation builds on the granulation tissue framework of new vessels and loose ECM that develop early at the repair site.

It occurs in two steps:

(1) migration and proliferation of fibroblasts into the site of injury.

(2) deposition of ECM by these cells. The recruitment and stimulation of fibroblasts is driven by many growth factors, *including PDGF, FGF-2, and TGF-β.*

- Over a period of weeks collagen **type I** becomes the most abundant protein, which is responsible for the strength of the matrix in a scar.
- Contraction of the area of granulation tissue occurs through the contractile effects of the myofibroblasts. The size of the damaged area is thus reduced. Production of dense collagen by the fibroblasts forms collagenous scar.



B- Trichrome stain of mature scar, showing dense collagen, with only scattered vascular channels.

- One source of these factors is the activated endothelium, but more importantly, growth factors are also elaborated by inflammatory cells.

- Macrophages, in particular, are important cellular constituents of granulation tissue, and besides clearing extracellular debris and fibrin at the site of injury, they elaborate a host of mediators that induce fibroblast proliferation and ECM production.

- Sites of inflammation are also rich in mast cells, and with the appropriate chemotactic milieu lymphocytes may also be present.

- Each of these can contribute directly or indirectly to fibroblast proliferation and activation.

5- ECM and Tissue Remodeling

- The *degradation* of collagens and other ECM components is accomplished by a family of matrix metalloproteinases (MMPs), which are dependent on *zinc ions* for their activity.

- MMPs should be distinguished from neutrophil elastase, cathepsin G, plasmin, and other *serine proteinases* that can also degrade ECM but are not metalloenzymes.

- MMPs include *interstitial collagenases*, which cleave fibrillar collagen (MMP-1,-2 and -3); *gelatinases* (MMP-2 and 9), which degrade amorphous collagen and fibronectin; and *stromelysins* (MMP-3, -10, and -11), which degrade a variety of ECM constituents, including proteoglycans, laminin, fibronectin, and amorphous collagen.

- MMPs are produced by a variety of cell types fibroblasts,macrophages, neutrophils, synovial cells, and some epithelial cells, and their synthesis and secretion are regulated by growth factors, cytokines, and other agents . **Figure**

- Their synthesis is inhibited by:

1- TGF-β and may be suppressed pharmacologically with steroids.

2- MMPs are produced as inactive (*zymogen*) precursors that must be first activated; this is accomplished by certain chemicals or proteases (e.g., plasmin) likely to be present only at sites of injury. **Figure**

3- activated collagenases can be rapidly inhibited by specific tissue inhibitors of metalloproteinases (*TIMPs*), produced by most mesenchymal cells. MMPs and their inhibitors are spatially and temporally regulated in healing wounds. They are essential in the debridement of injured sites and in the remodeling of the ECM.

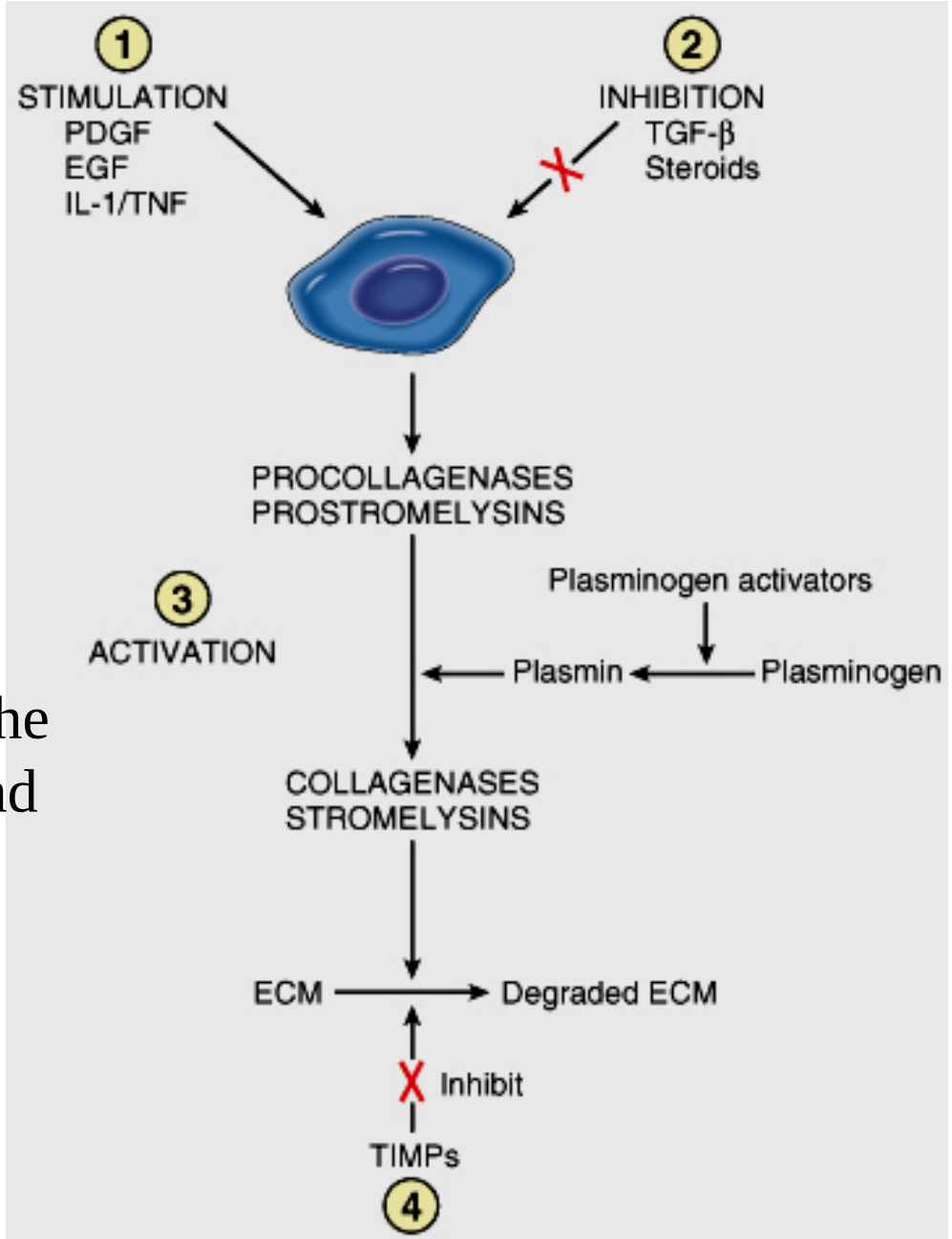
Matrix metalloproteinase (MMP) regulation

(1) regulation of synthesis by a variety of growth factors or cytokines,

(2) inhibition of synthesis by corticosteroids or transforming growth factor β (TGF-β),

(3) regulation of the activation of the secreted but inactive precursors, and

(4) blockade of the enzymes by specific tissue inhibitors of metalloproteinases (TIMPs).



Healing of Skin Wounds (Cutaneous wound healing)

Healing of Skin Wounds (Cutaneous wound healing)

1- Clean, uninfected surgical wounds.

Healing of clean, uninfected surgical wounds, in which adjacent surfaces are closely apposed and held together by stitches, is by **first intention (Primary union).** There is a minimal amount of dead tissue. It is a rapid process resulting in minimal scarring.

2- Open wounds, with extensive tissue loss.

On the contrary, healing of open wounds, with extensive tissue loss and large tissue defect, is by **second intention (secondary union),** which takes longer time and leads to formation of large amount of granulation tissue and prominent scarring.

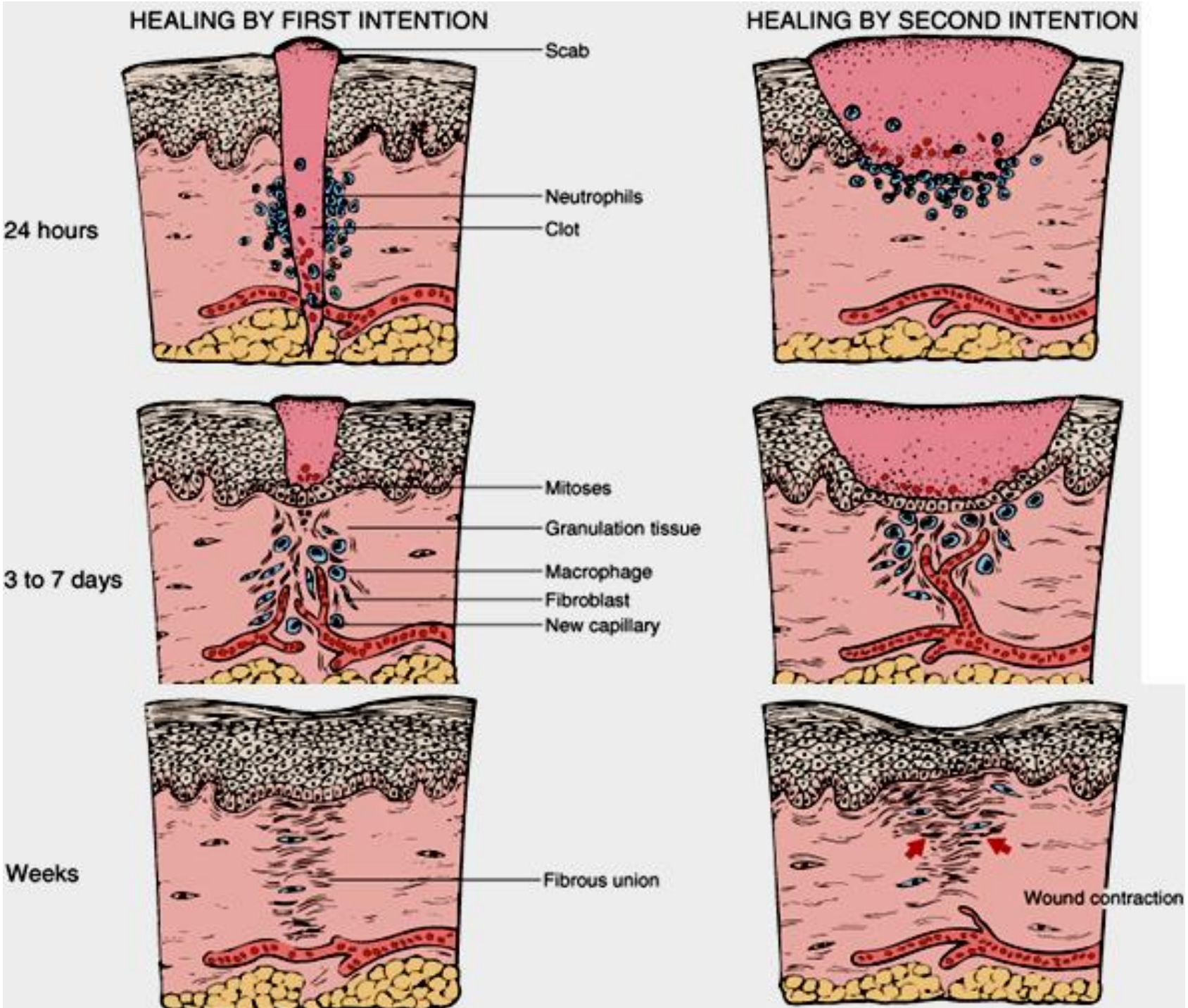
The difference between primary and secondary union are quantitative, not qualitative i.e. the same elements are involved but their proportions are different.

Primary union (Healing by first intention)

1- Narrow incisional space resulting in a limited inflammatory reaction
2- Granulation tissue invades incision space
3- Limited amount of wound contraction

Secondary union (Healing by secondary intention)

1- Large tissue defect resulting in a more intense inflammatory reaction
2- Larger amount of granulation tissue
3- Wound contraction


HEALING BY FIRST INTENTION
HEALING BY SECOND INTENTION
Scab
Neutrophils
Clot
24 hours
Mitoses
Granulation tissue
Macrophage
Fibroblast
New capillary
3 to 7 days
Fibrous union
Weeks
Wound contraction

Healing by secondary union (second intention):

- More extensive tissue loss as in an open wounds & large surface ulcers.

- It takes longer period of time, & requires larger amount of granulation tissue to fill the gap between the edges of the wounds.

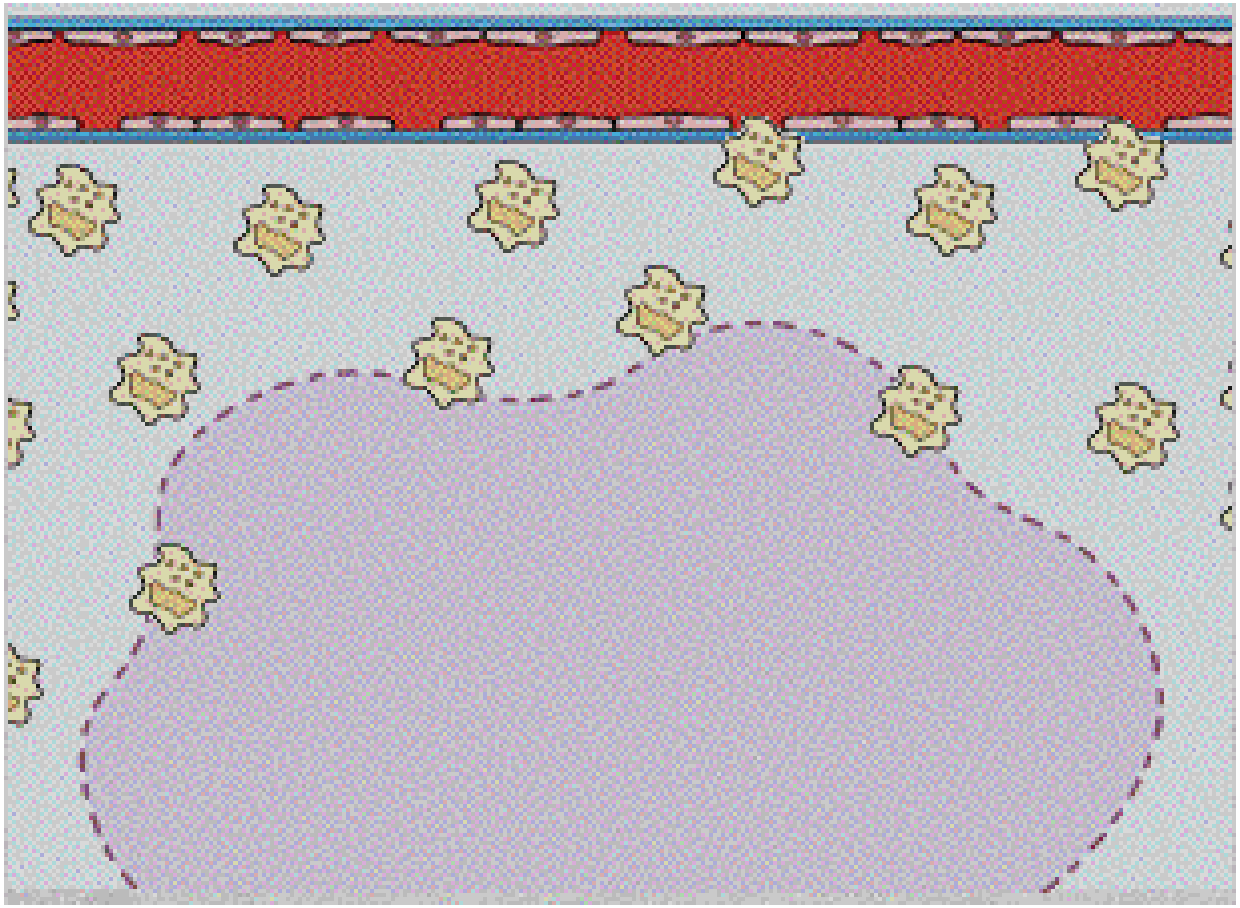
- First hemorrhage and exudation of fibrin from the cut surfaces,which is soon followed by a more intense inflammatory reaction, with migration of neutrophils and subsequently monocytes.

- Epithelial cells proliferate; basal layer at the margins then migrate producing a sheet of cells that form tongue-like projections on the wound surface. But they cannot cover completely the wound surface because the denuded area is large. This happens when the granulation tissue from the base fills the wound space.

- As soon as the wound surface is covered, epithelial migration ceases & proliferation, stratification & keratinization are rapidly completed, but rate ridges are not reformed. Within few days of injury and through a process of angiogenesis a network of new capillaries occurs this is associated with the presence of macrophages & migration of fibroblasts. The latter starts active synthesis of collagens (fibrovascular granulation).

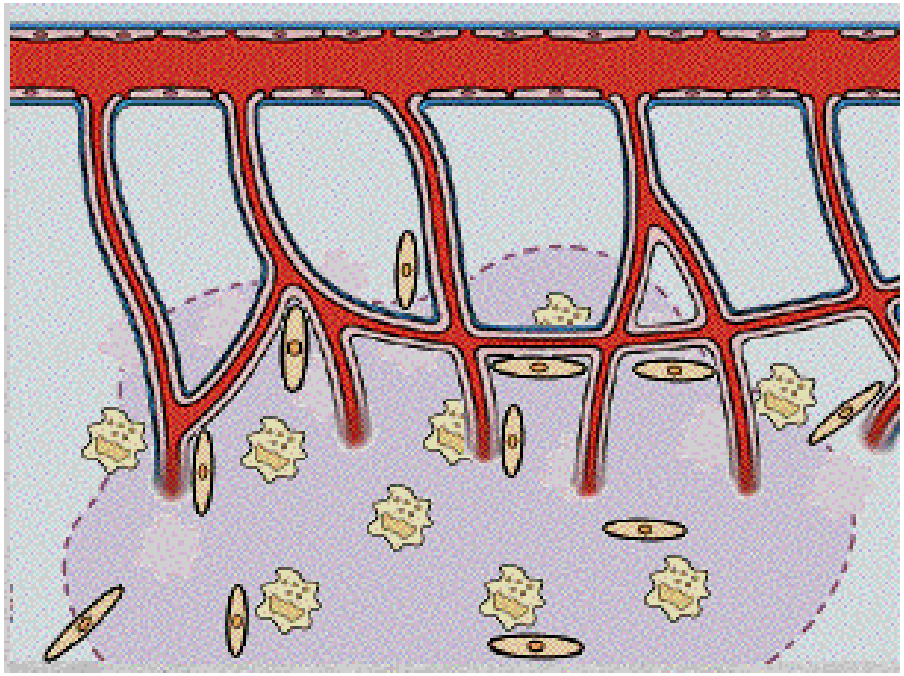
- Then the inflammatory reaction subsides, with disappearance of some of the new blood vessels and the gap is replaced by collagen fibers, which in a period of months will undergo further cross-linking and remodeling and become progressively less cellular. This is followed by contraction of the wound i.e. the defect is markedly reduced in size, due to contraction of myofibroblasts.

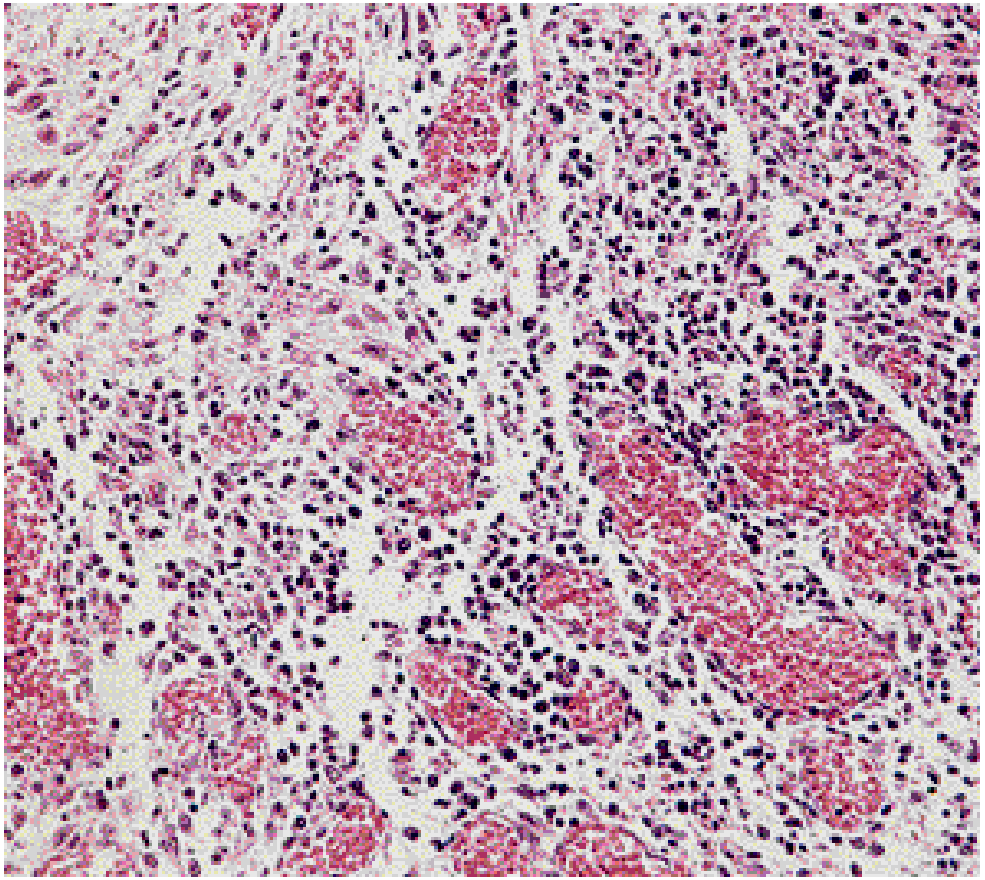
Histological Stages of wound healing

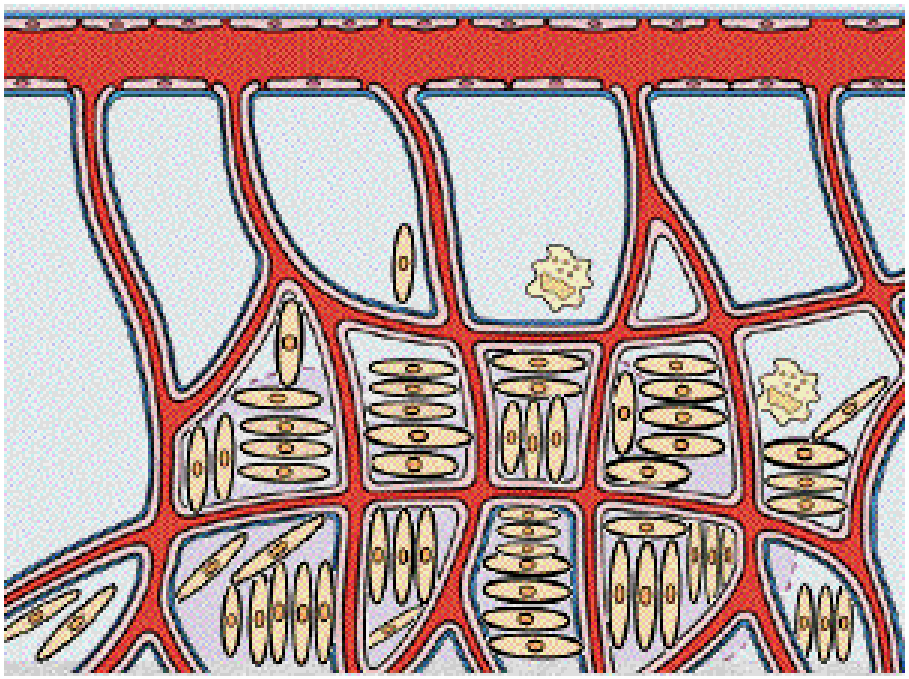


1- Removal of debris by macrophages

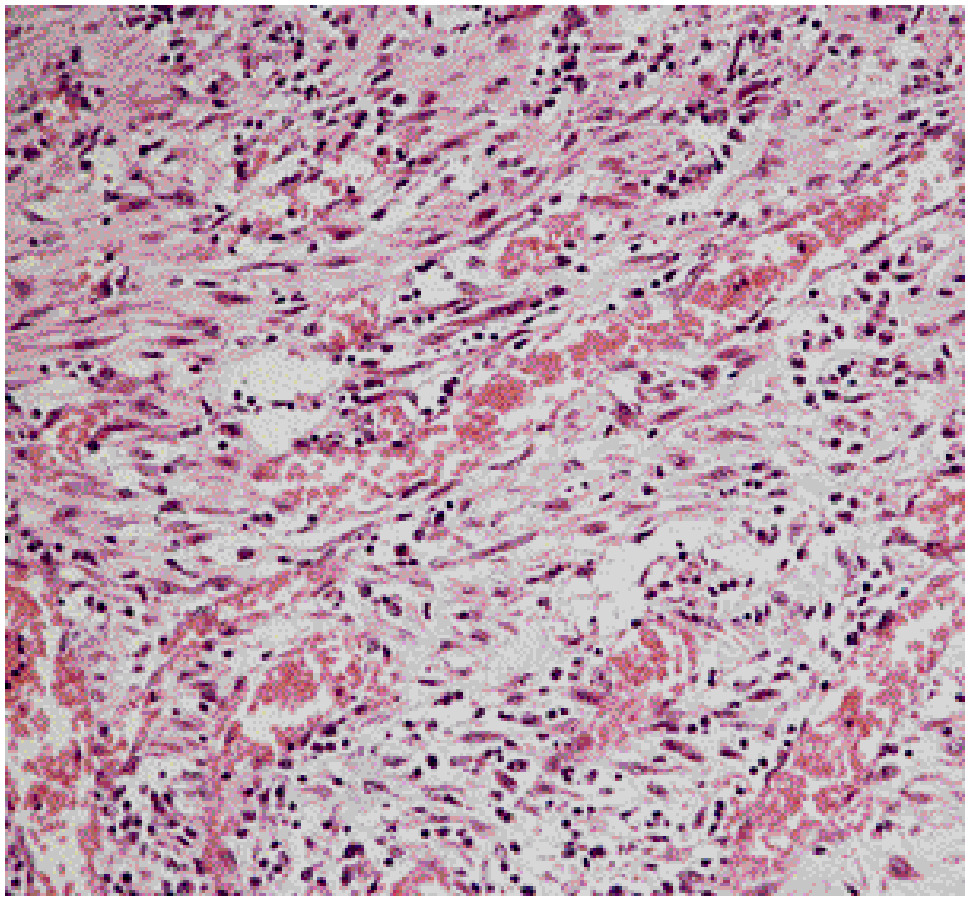
2- vascular granulation tissue



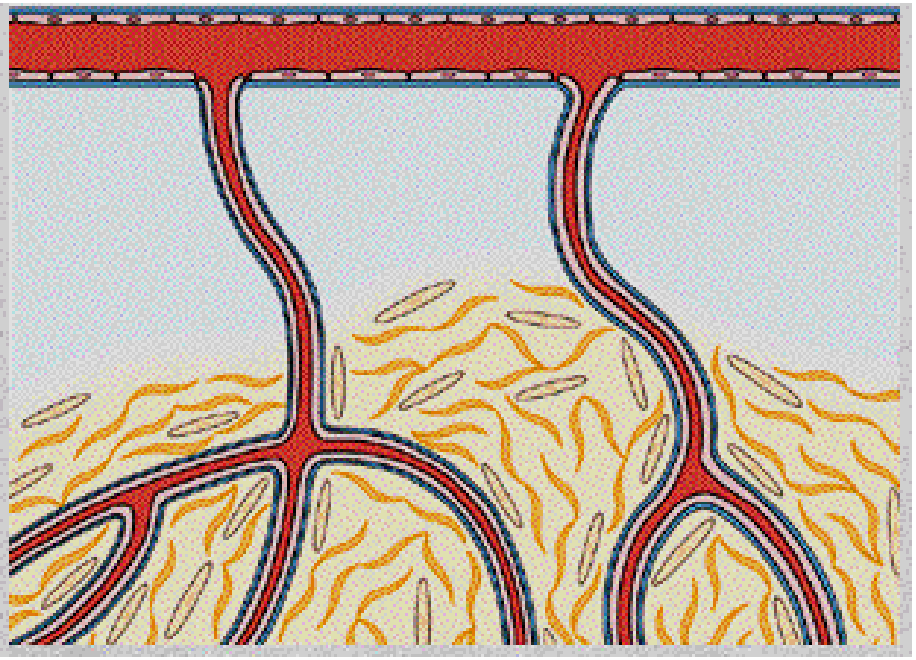


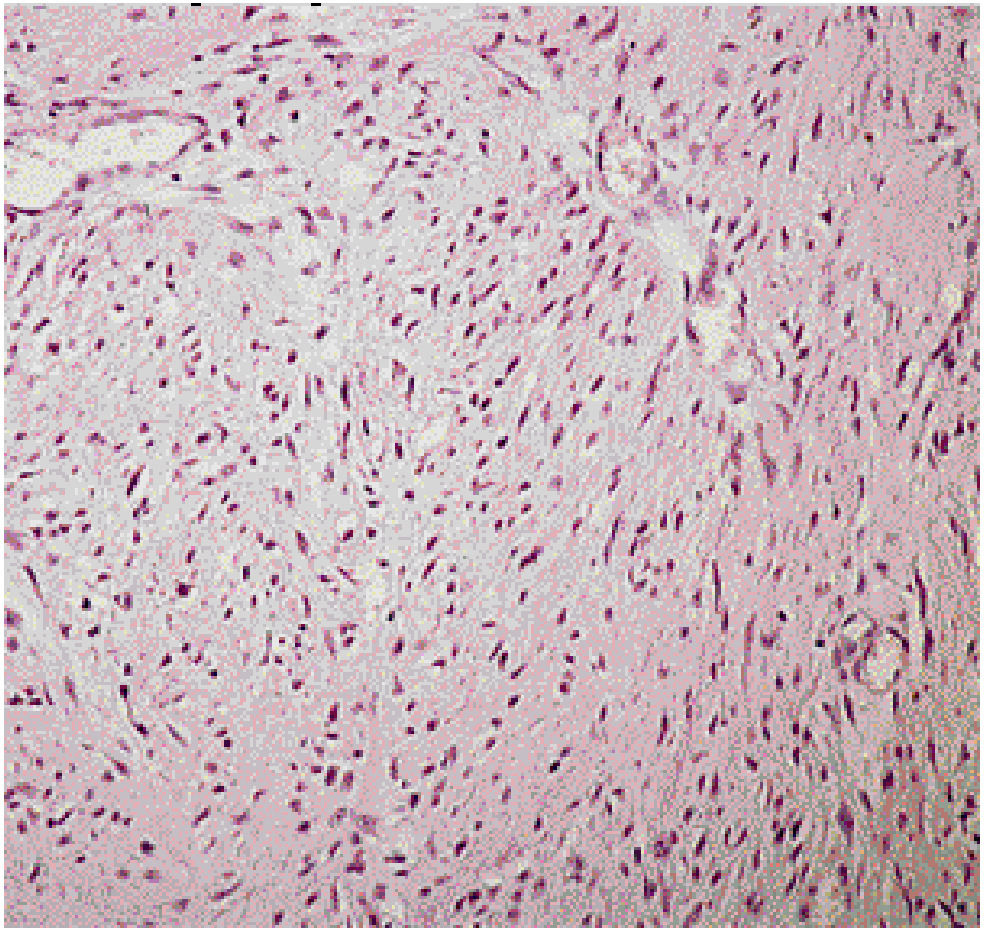


3- fibro-vascular granulation tissue

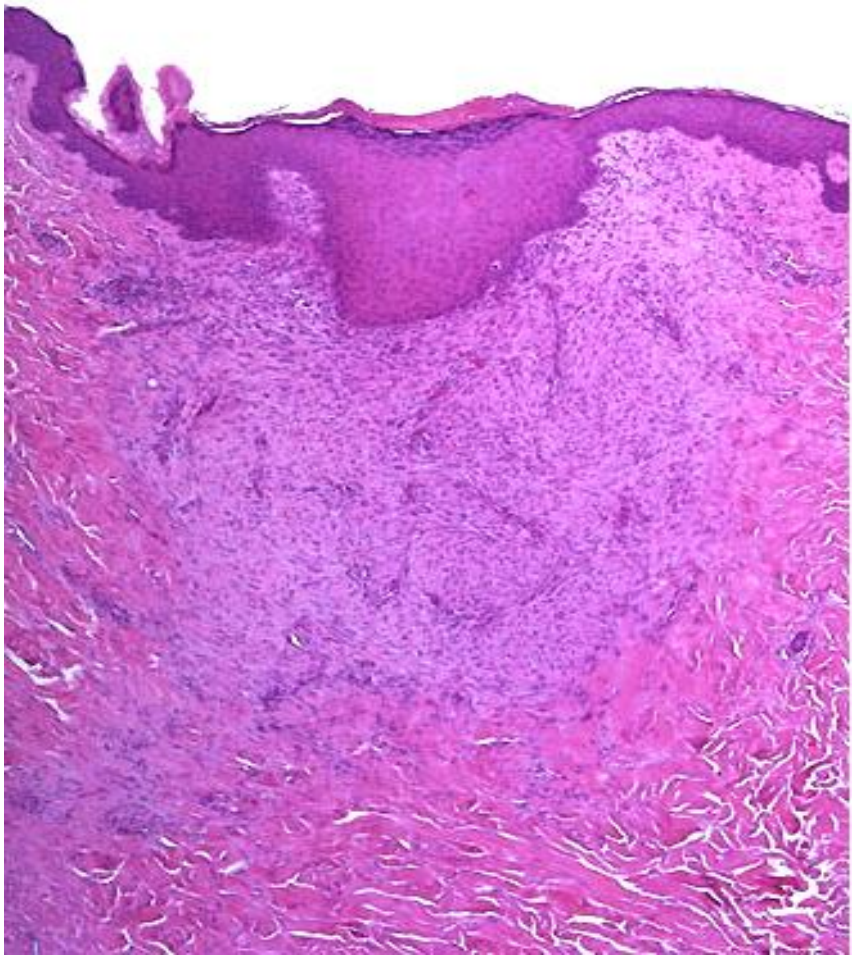


4- collagenous scar formation





Healing scar, skin



This is a healing biopsy site on the skin seen a week following the excision, The skin surface has re-epithelialized, and below this is granulation tissue with small capillaries and fibroblasts forming collagen. After a month, just a small collagenous scar will remain.

Factors influencing wound healing:

A. Local:

1. Type, size & location of wound.
2. Adequacy of blood supply.
3. Infection.
4. Movement.
5. Presence of foreign body material.
6. Exposure to ionizing radiation, & ultraviolet light.

B. Systemic:

1. Circulatory status.
2. Metabolic status.
3. Systemic infection.
4. Diabetes mellitus.
5. Hormones.
6. Hematological diseases; neutropenia.
7. Renal failure.
8. Tumor cachexia.

Local factors:

1- Type, size and location of the wound:

A clean, aseptic surgical wound heals faster than a wound produced by blunt trauma with abundant necrosis and irregular edges. Small wounds heal faster than large ones.

Wounds that occur in richly vascularized areas such as the face heal faster than those that occur in poorly vascularized areas such as the foot. Adhesion to bony surfaces (as in wounds over the tibia) prevents contraction and adequate apposition of the edges.

2- Adequacy of blood supply: Wound with poor blood supply heal slowly e.g.

- Leg wounds in patients with varicose veins.
- Ischemia due to pressure produces bedsores. The same mechanism (pressure) prevents their healing.
- Ischemia due to arterial obstruction also prevents healing.

3- Infection:

Wounds provide a portal of entry for microorganisms. Infection delays or prevents healing. This promotes formation of excessive granulation tissue, and may result in a large deforming scar.

4- Movement:

Early motion subjects the wound to persistent trauma. Exercise also increases the circulating levels of glucocorticoids, which inhibit repair.

5- Exposure to ionizing radiation & ultraviolet light:

Irradiation of the wound blocks cell proliferation, retards granulation tissue formation & interferes with blood supply. The outcome is slow healing. Exposure of wounds to ultraviolet light accelerates the rate of healing.

Systemic factors:

1- Cardiovascular status:

determines the blood supply to the injured area, which is important for wound healing. Poor healing attributed to old age is often due largely to impaired circulation.

2- Metabolic status:

a. Protein calorie malnutrition impairs healing.

b. Vit. C deficiency (scurvy) impairs wound healing. This is because vit.c is involved in synthesis of collagen as well as in intracellular hydroxylation of procollagen. Thus in vit.c deficiency the collagen fibers show less cross-linking than normal & is more readily degraded. The wound shows also less vascular proliferation.

c. Zinc is required for collagen synthesis, so its deficiency will lead to delay wound healing.

3- Systemic infection: Leads to delay wound healing (multifactorial).

4- Diabetes mellitus:

Wounds in diabetics often become infected & in turn, infection makes the control of diabetes difficult, resulting in sever retardation or failure of healing.

5- Hormones: Corticosteroides impair wound healing due to:

a. inhibition of collagen synthesis.

b. general depression of protein synthesis .

c. anti-inflammatory effect, with scanty macrophage infiltrates and so lack of macrophage-derived growth factors.

Complications of wound healing:

1. Wound dehiscence and Incisional hernias

A wound after a laparotomy may burst open. This occurs in 0.5-5% of all abdominal operations. Increased mechanical stress on the wound from vomiting, coughing, or ileus is a factor in over 90% of cases. Systemic factors also operate including poor metabolic status, such as vit.c deficiency, hypoproteinemia, and neoplasia. Incisional hernia is a late consequence of a weak abdominal scar.

2. Ulceration

Wounds ulcerate because of inadequate blood supply & vascularization. For example, leg wounds typically ulcerate. Non-healing wounds develop in areas devoid of sensation, such as trophic or neuropathic ulcers, which may be seen in patients with spinal cord injury, tertiary syphilis (tabes dorsalis) and leprosy.

3. Excessive scar formation (Keloid)

An excessive deposition of extra cellular matrix at the wound site results in hypertrophic scar or keloid. Histologically, there are abundant, broad & irregular collagen bundles, with more capillaries and fibroblasts than would be expected for a scar of the same age.

4. Excessive contraction (contracture).

A decrease in wound size depends on the presence of myofibroblasts. An exaggeration of this process is termed contracture.

This results in sever deformity of wound and surrounding tissues. It is particularly found in healing of skin burns, especially second & third degree burns.

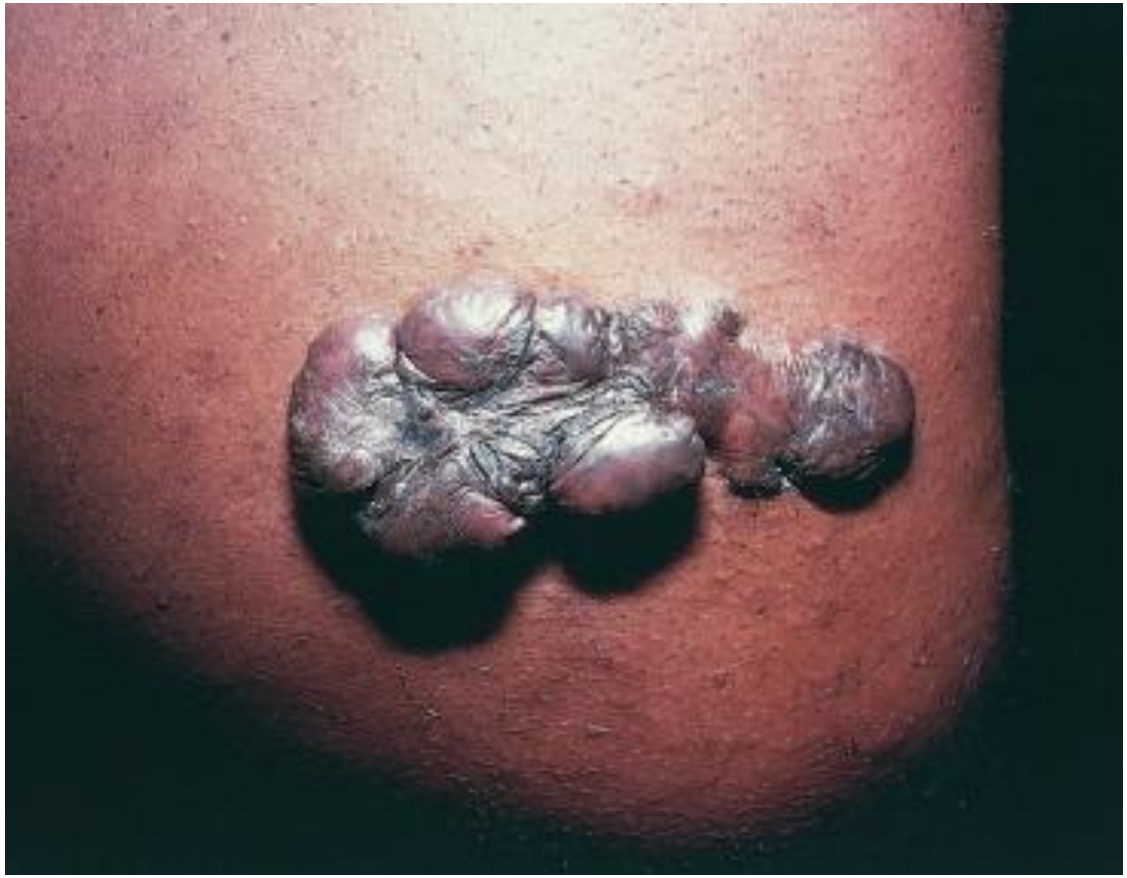
A contracture can be severe enough as to block joints. In G.I.T it may lead to constrictive rings e.g. esophageal stricture following the ingestion of caustic chemicals.

Several diseases are characterized by contracture and irreversible fibrosis of superficial fascia, including Dupuytren's disease (palmar contracture), planter contracture & Peyronie's disease (contracture of the cavernous tissues of the penis). In these diseases there is no known precipitating injury, even though the basic process is similar to contracture in wound healing.

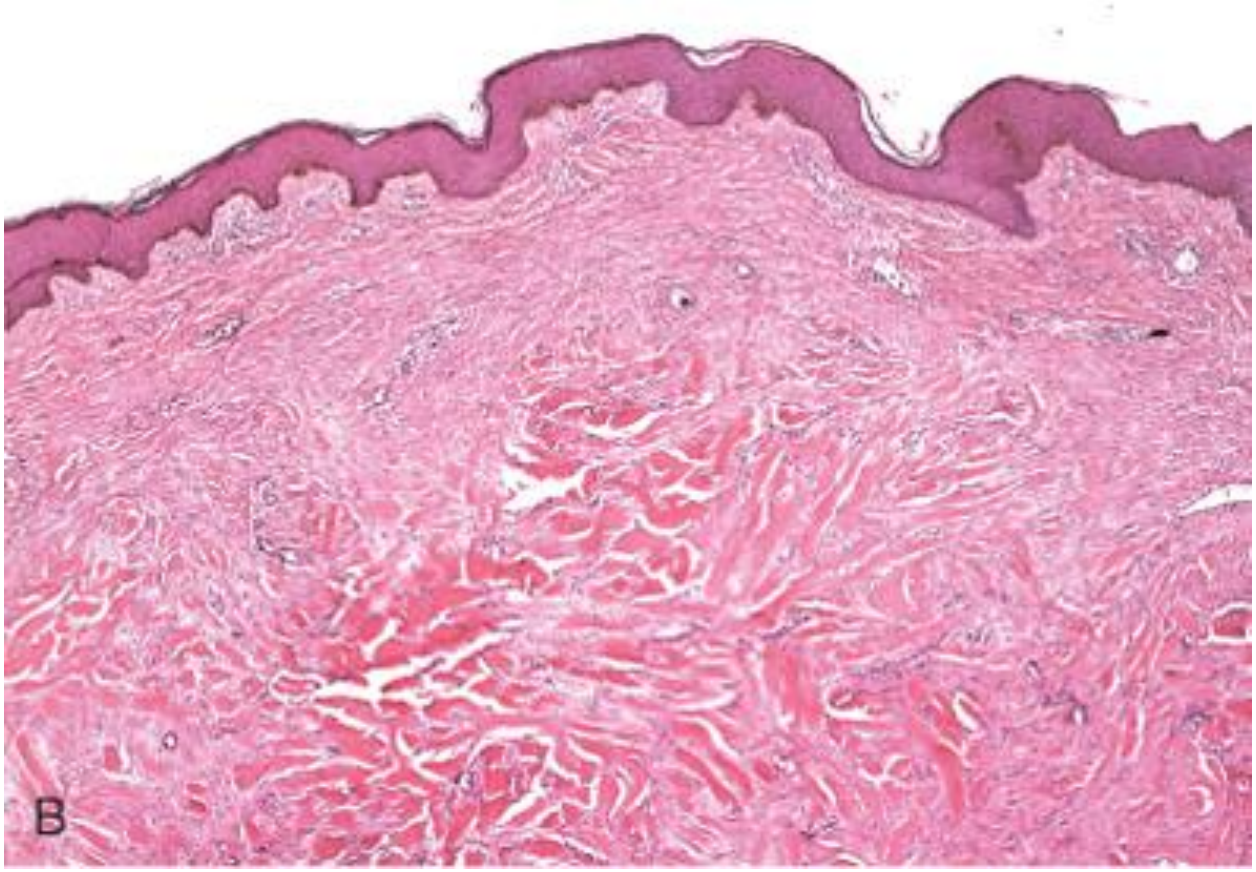
5. Desmoid tumor (aggressive fibromatosis):

Rare massive fibroblastic proliferation which may follow incisional scars or traumatic injuries .

Keloid

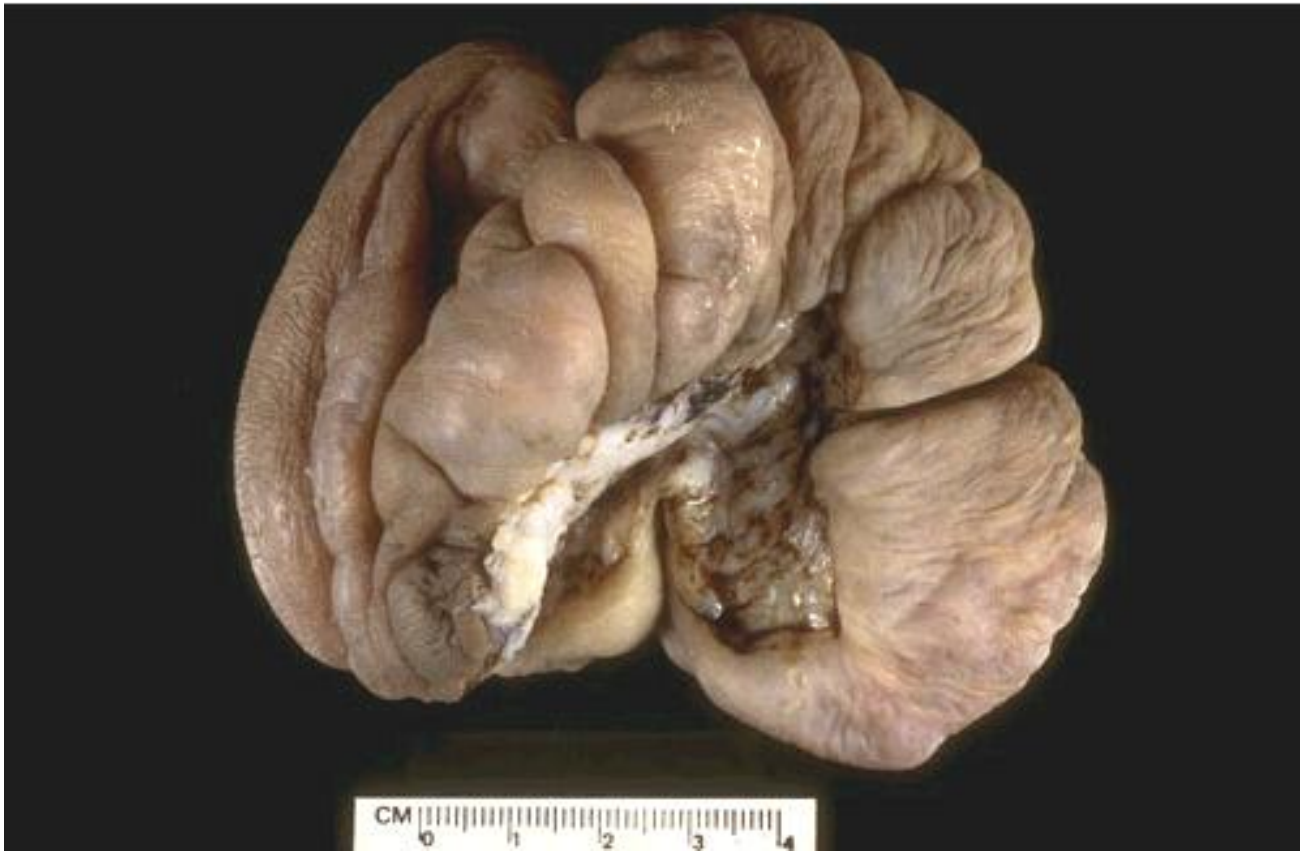


A, Excess collagen deposition in the skin forming a raised scar known as a keloid



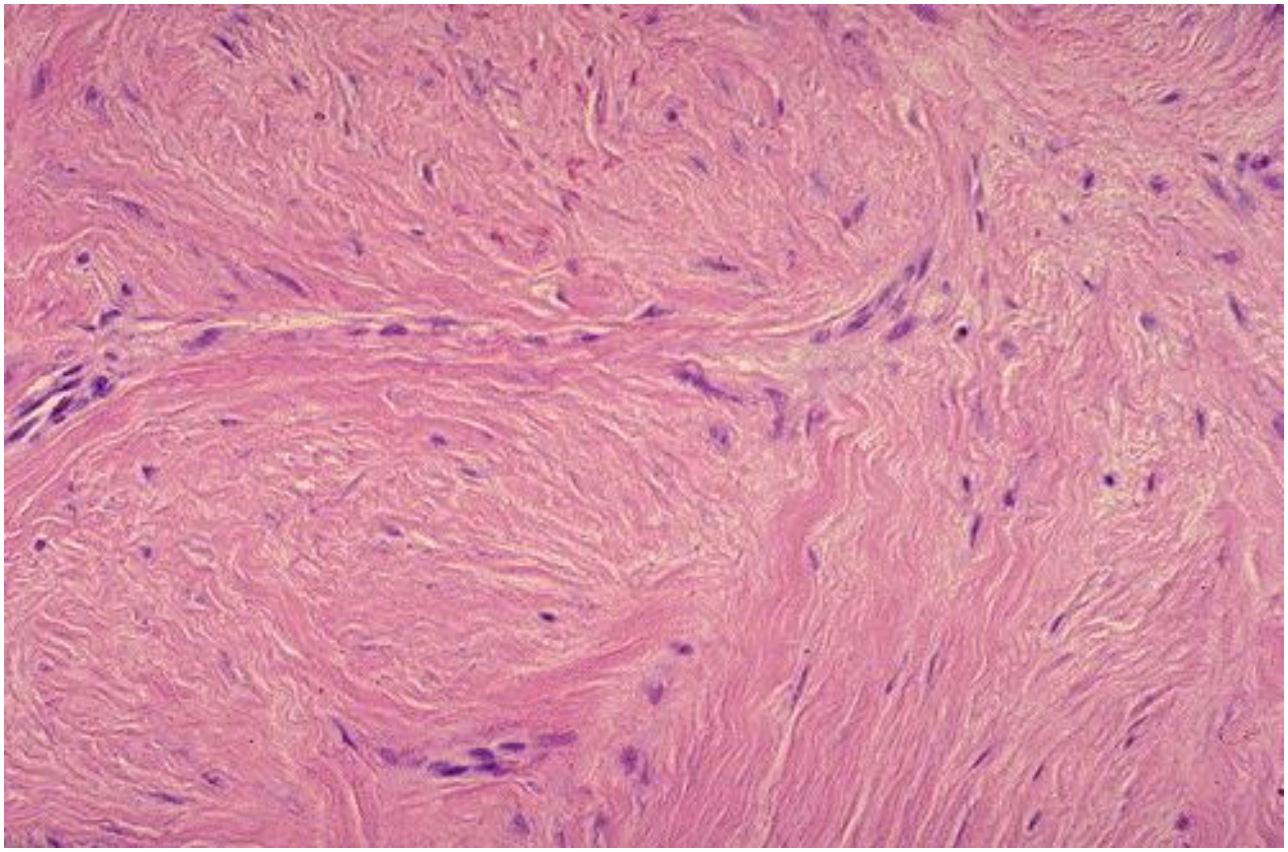
B, Thick connective tissue deposition in the dermis

Keloid – Gross



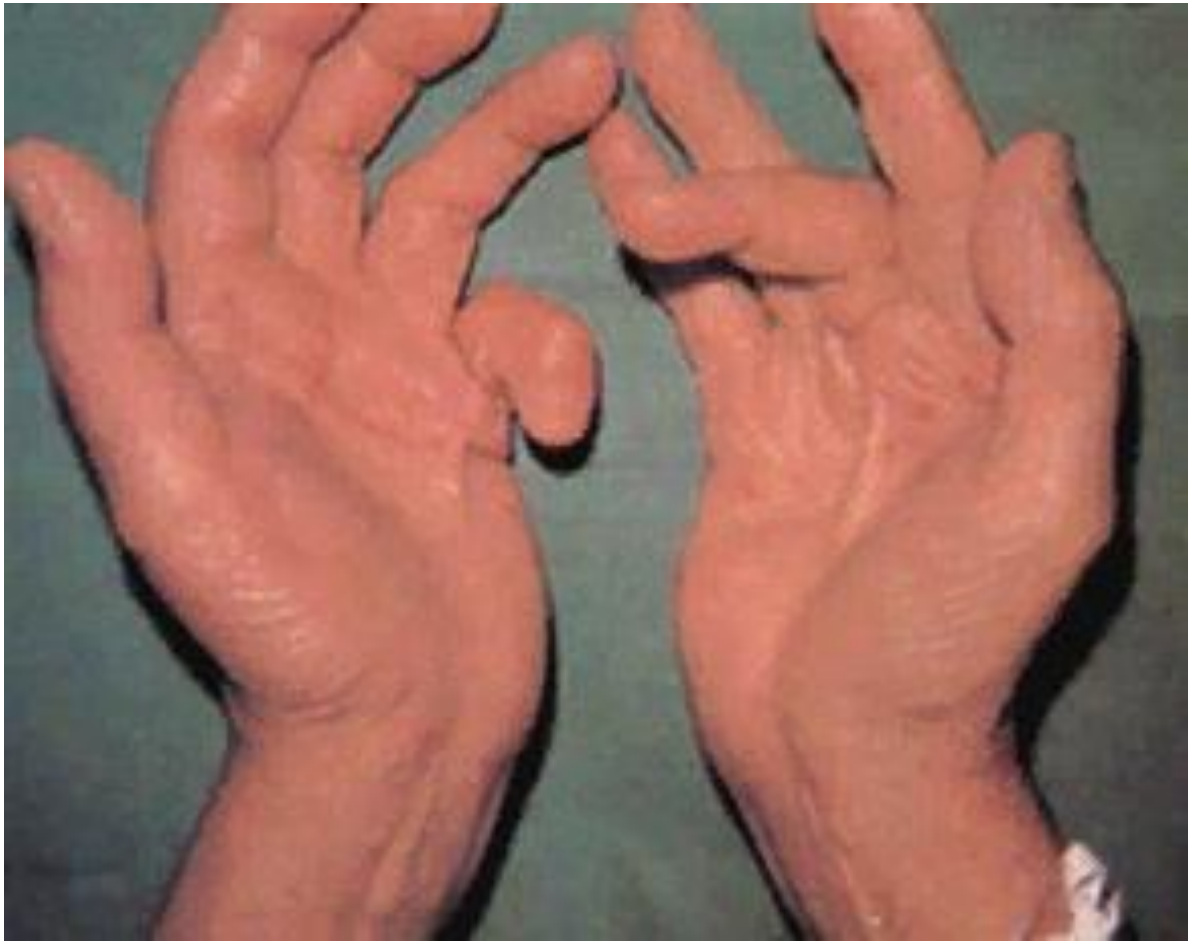
This large nodular mass is a keloid excised from the ear in a young male who had previously incurred trauma with laceration. Ear piercing in women may promote keloid formation. A keloid is an overgrowth of dermal scar tissue that forms over months following the injury.

Keloid - Microscopical section



Bundles of dense collagen form the keloid as seen here microscopically.

Dupuytren's contracture



Contracture of the palmar fascial bands produces flexion deformity of the Lt. little and Rt. middle fingers.