Wound Healing

Wound Healing

- same events,
- in the same order,
- in every healing process

regardless

- tissue type
- inciting injury

Wound Healing

Wound repair

is the effort of tissues to restore normal function and structure after injury.

- To reform barriers to fluid loss and infection,
- Limit further entry of foreign organisms and material,
- re-establish normal blood and lymphatic flow patterns,
- restore the mechanical integrity of the injured system,
- perfect reorganization is sacrificed for urgent return to function.

Regeneration,

is the perfect restoration of the preexisting tissue architecture in the absence of scar information.

- Ideal wound healing,
- Only found in embryonic development,
- in lower organisms, such as the stone crab and the salamander,
- in certain tissue compartments, such as bone and liver.

Wound Healing

- accuracy of regeneration is traded for the speed of repair.
- divided into specific stages
- phases overlap in both
  - time
  - activity.

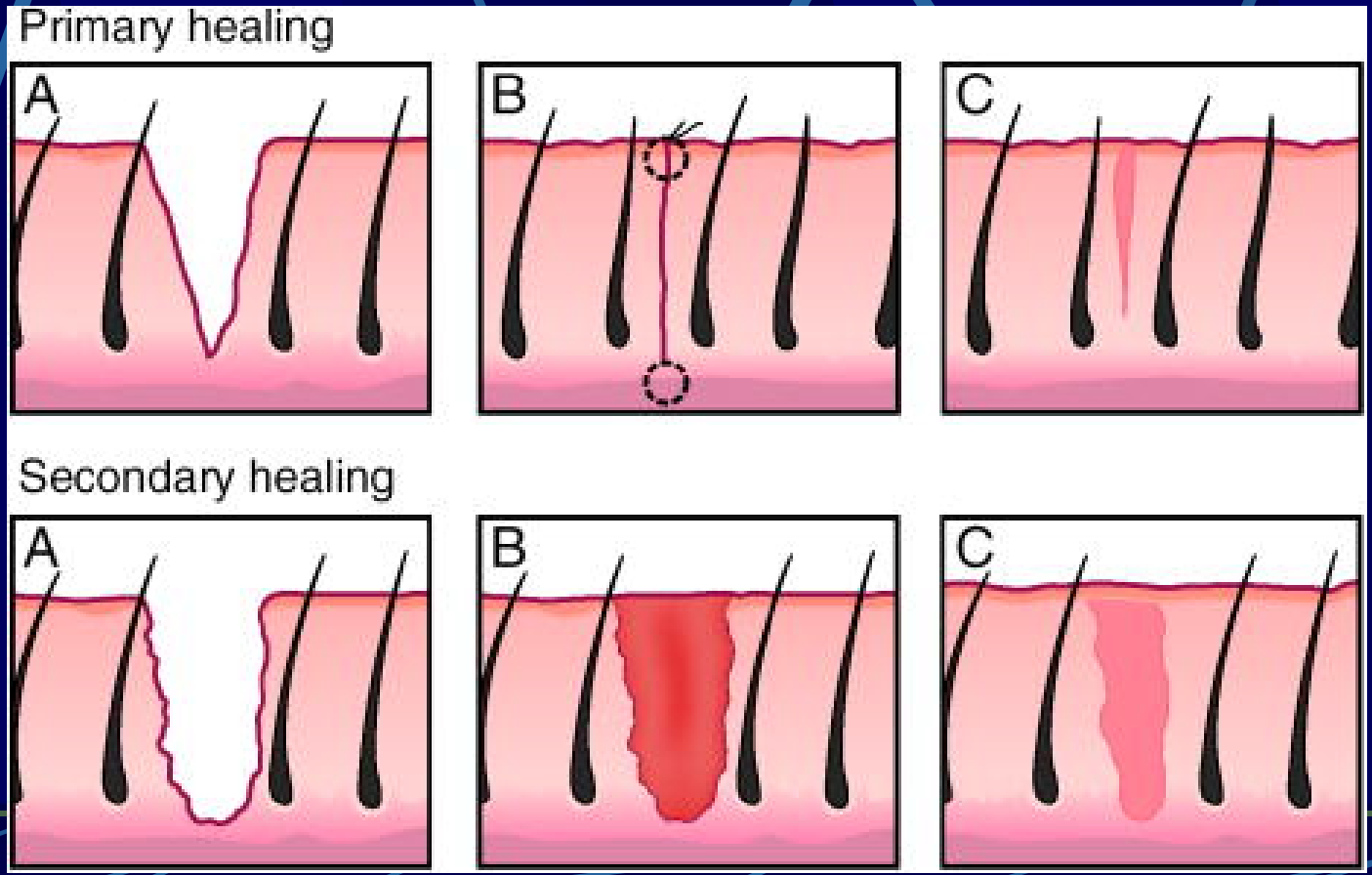
Acute wounds

- orderly and timely reparative process
- to achieve sustained restoration of structure and function.

Chronic wound,

- does not proceed to a restoration of functional integrity.
- stalled in the inflammatory phase
- variety of etiologies
- does not proceed to closure.

Wound Healing *primary*, *secondary*, *tertiary* repair



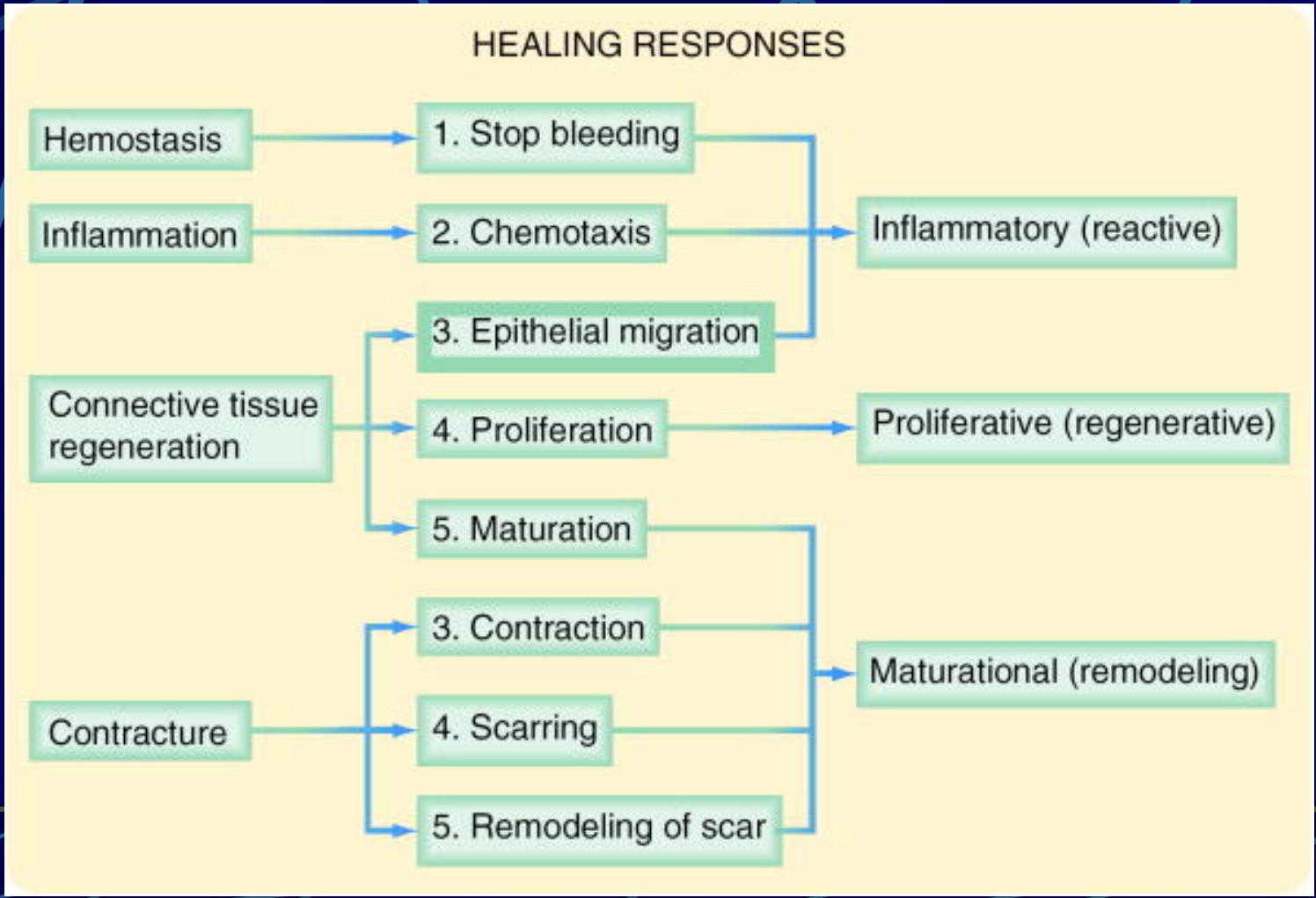
Wound Healing

Primary,
or first-intention, closures are those wounds that are immediately sealed with simple suturing, skin graft placement, or flap closure, such as the closure of the wound at the end of a surgical procedure.

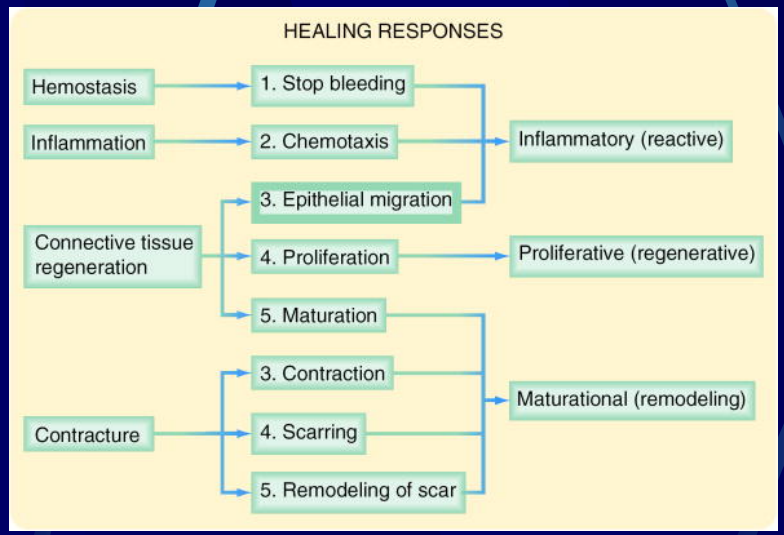
Secondary,
or spontaneous, intention involves no active intent to seal the wound. Generally, this type of closure is represented by the highly contaminated wound, which will close by reepithelialization and contraction of the wound.

T*ertiary* intention = *delayed primary closure*.
A contaminated wound is initially treated with repeated débridement and perhaps systemic or topical antibiotics for several days to control infection. Once it is assessed as ready for closure, surgical intervention, such as suturing, skin graft placement, or flap design, is performed.

Wound Healing Phases



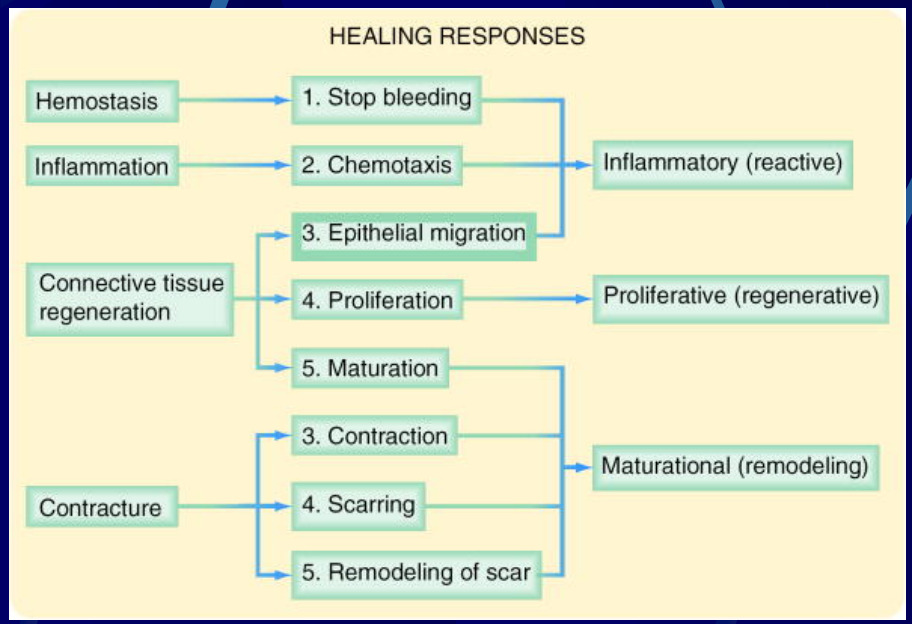
Wound Healing Phases



- *inflammatory* (*reactive*)
  the body's defenses are aimed at limiting the amount of damage and preventing further injury.
- *proliferative* (*regenerative* or *reparative*)
  is the reparative process with
  - reepithelialization,
  - matrix synthesis,
  - neovascularization

  to relieve the ischemia of the trauma itself.
- *maturational* (*remodeling*)
  is the period of scar contraction with
  - collagen cross-linking,
  - shrinking,
  - loss of edema.

Wound Healing Phases in a Large Wound



i.e. pressure sore

- eschar or fibrinous exudate *inflammatory phase*;
- granulation tissue *proliferative phase*;
- the contracting or advancing edge *maturational phase*.

All three phases may occur simultaneously,

Phases with their individual processes may overlap

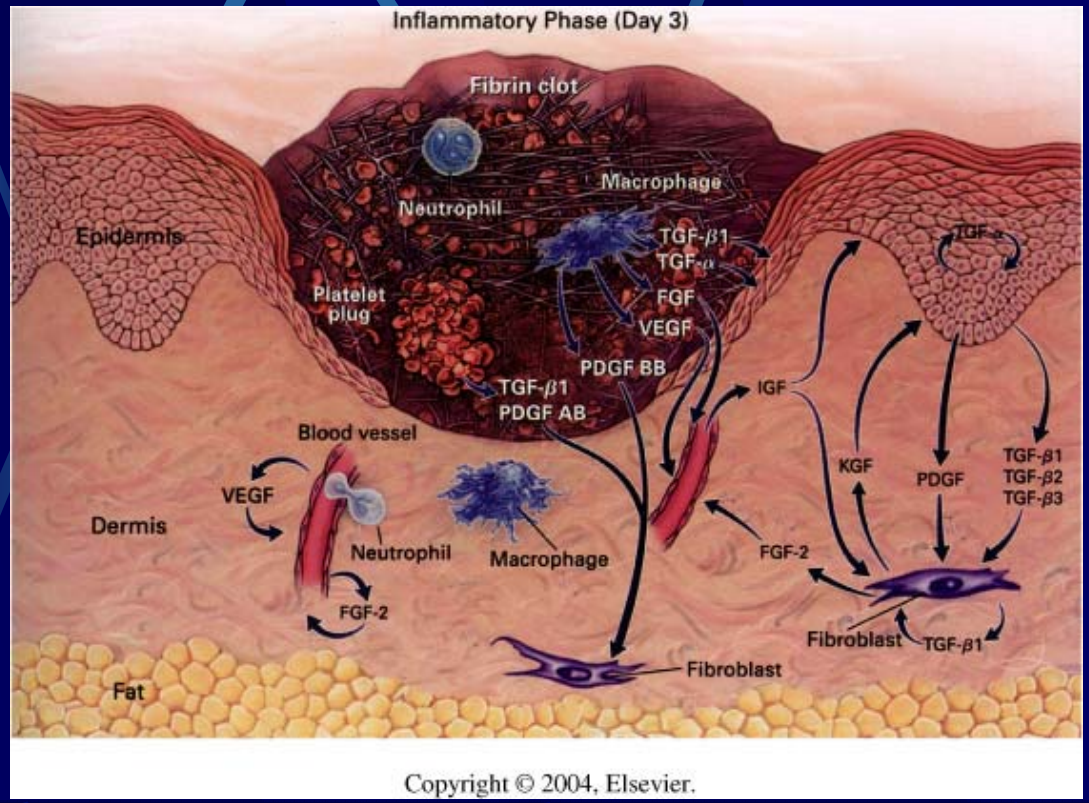
Inflammatory Phase

Hemostasis and inflammation

- tissue's attempt to limit damage
- stopping the bleeding,
- sealing the surface of the wound,
- removing any necrotic tissue, foreign debris, or bacteria

Characterized by

- increased vascular permeability,
- migration of cells into the wound by chemotaxis,
- secretion of cytokines and growth factors into the wound,
- activation of the migrating cells



Hemostasis and Inflammation

Blood vessel damage →

- exposure of subendothelial collagen to platelets, →
  - platelet aggregation and
  - activation of the coagulation pathway.

Initial intense local vasoconstriction of arterioles and capillaries

- followed by vasodilation and increased vascular permeability.

Cessation of hemorrhage is aided by plugging of capillaries with erythrocytes and platelets, which adhere to the damaged capillary endothelium.

Exposure of types IV and V collagen promotes platelet aggregation as platelets bind to these proteins and become activated.

The initial contact between platelets and collagen requires the von Willebrand factor (vWF) VIII

Hemostasis and Inflammation

Platelet adhesion to the endothelium

- interaction between high-affinity glycoprotein receptors and the integrin receptor GPIIb-IIIa (αIIbβ_3).
- platelets express other integrin receptors
  - direct binding of collagen, laminin,
  - indirectly by attaching to subendothelial matrix-bound fibronectin, vitronectin, and other ligands.

The clotting cascade initiated by:

- intrinsic
- extrinsic pathways.

The fibrin strands trap red blood cells, forming the clot, and seal

Lattice framework will be the scaffold for

- endothelial cells,
- inflammatory cells,
- fibroblasts.

Thromboxane A2 and prostaglandin F2 α, assist with platelet aggregation and vasoconstriction.

Hemostasis and Inflammation

Increased Vascular Permeability

- Platelet binding → changes in conformation
  → intracellular signal transduction pathways
  → platelet activation and the release of biologically active proteins.
  α granules and, dense bodies
- Mast cells:
  - release histamine and serotonin, → permeability of endothelial cells → leakage of plasma from the intravascular space to the extracellular compartment.

Hemostasis and Inflammation

Polymorphonuclear Cells

- adherence, chemoattraction:
  - Complement factors: C5a, leukotriene B_4
- Adhesion by Plt-aggregating factor:
  - thrombin +
  - leukotriene C_4 and D_4
- endothelial-neutrophil adherence:
  Monocytes and endothelial cells inflammatory mediators:
  - interleukin (IL)-1
  - tumor necrosis factor (TNF)-α

All these facilitates:

- diapedesis of neutrophils into the inflammatory site

Neutrophils begin their migration:

- release the contents of their lysosomes and enzymes
- elastase and other proteases into the extracellular matrix (ECM), facilitating the migration of the neutrophils.

Hemostasis and Inflammation

intense vasodilation

increased vascular permeability

Clinical findings:

- *rubor* (redness),
- *tumor* (swelling),
- *calor* (heat),
- *dolor* (pain)
- *functio lesa* (loss of function)

Hemostasis and Inflammation

Following migration of the PMNs :

- Functional activation:
- may induce new cell surface antigen expression,
- increased cytotoxicity,
- increased production and release of cytokines.

- Activated neutrophils:
  - scavenge necrotic debris, foreign material, and bacteria.
- Stimulated neutrophils
  - generate free oxygen radicals with electrons donated by the NADPH
  - electrons across the membrane into lysosomes
  - superoxide anion (O_2^-) is formed
  - superoxide dismutase catalyzes formation of H_2O_2, degraded by myeloperoxidase in the azurophilic

Hemostasis and Inflammation

Macrophages

- The macrophage is central to wound healing
  - orchestrates the release of cytokines and
  - stimulate many of the subsequent processes of wound healing
- appear at the same time that neutrophils disappear
- induce PMN apoptosis
- Chemotaxis of migrating blood monocytes occurs within 24 to 48 hours.

Chemotactic factors specific for monocytes:

- bacterial products,
- complement degradation products (C5a),
- thrombin,
- fibronectin,
- collagen,
- TGF-β, and
- PGDF-BB.
- also facilitated by the interaction of the integrin receptors on the monocyte surface with ECM proteins, such as fibrin and fibronectin.

Hemostasis and Inflammation

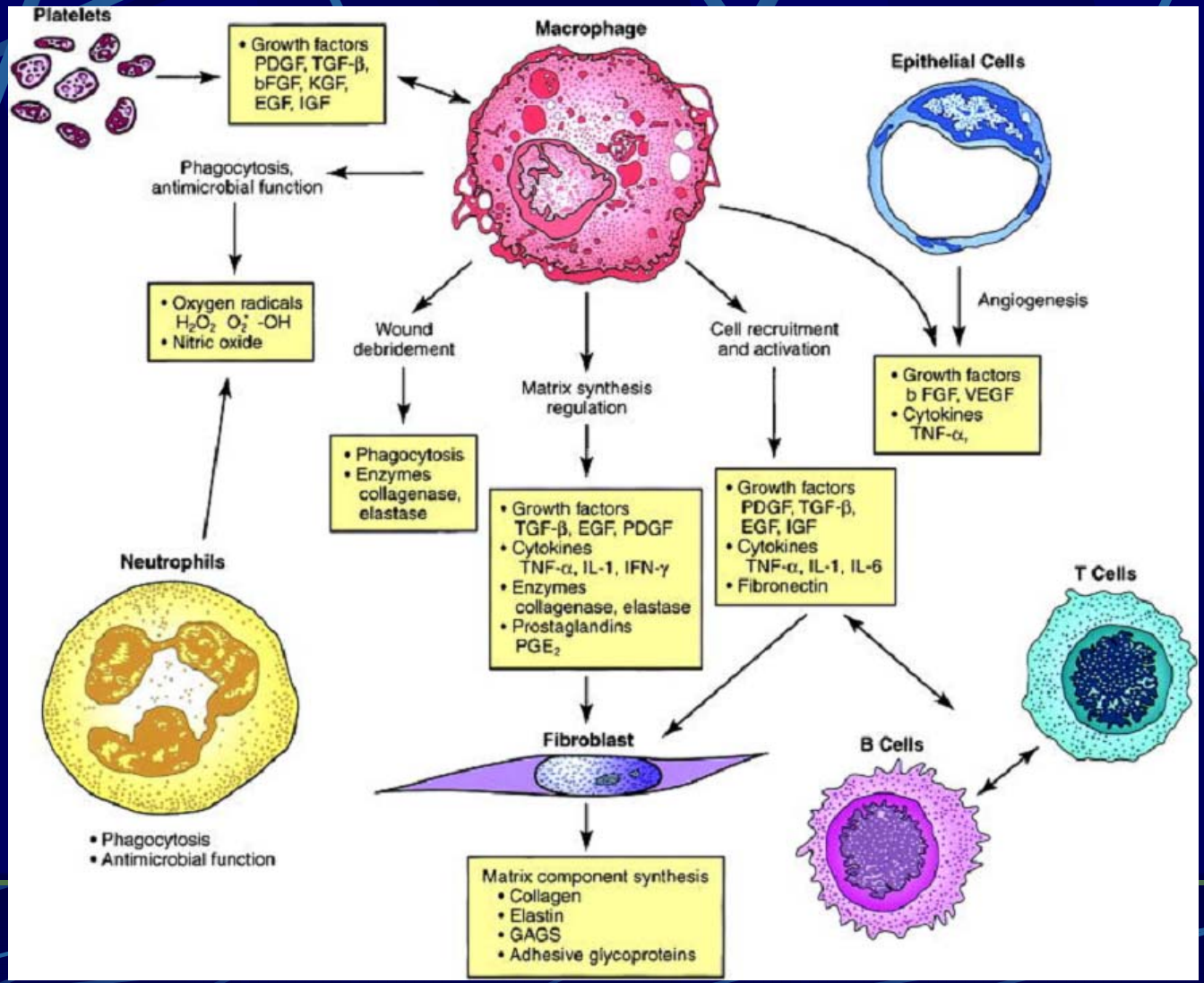


TABLE 8-1 -- Cytokine Activity in Wound Healing		
Cytokine	**Cell Source**	**Biological Activity**
Proinflammatory Cytokines		
TNF-α	Macrophages	PMN margination and cytotox., ± collagen synth.; prov. metab. subst.
IL-1	Macrophages	Fibroblast and keratinocyte chemotaxis, collagen synthesis
	Keratinocytes	
IL-2	T lymphocytes	Increases fibroblast infiltration and metabolism
IL-6	Macrophages	Fibroblast proliferation, hepatic acute-phase protein synthesis
	PMNs	
	Fibroblasts	
IL-8	Macrophages	Macrophage and PMN chemotaxis, keratinocyte maturation
	Fibroblasts	
IFN-γ	T lymphocytes	Macrophage and PMN activation; retards collagen synthesis and cross-linking; stimulates collagenase activity
	Macrophages	
Anti-inflammatory Cytokines		
IL-4	T lymphocytes	Inhibition of TNF, IL-1, IL-6 production; fibroblast prolif., collagen synth.
	Basophils	
	Mast cells	
IL-10	T lymphocytes	Inhibition of TNF, IL-1, IL-6 prod.; inhib. macrophage and PMN activ.
	Macrophages	
	Keratinocytes	

TABLE 8-2 -- Cytokines that Affect Wound Healing

Cytokine	Abbreviation	Source	Functions
Platelet-derived growth factor	PDGF	Platelets, macrophages, endothelial cells, keratinocytes	Chemotactic for PMNs, macrophages, fibroblasts, and smooth muscle cells; activates PMNs, macroph., and fibrobl.; mitogenic for fibrobl., endoth. cells; stim. Prod. of MMPs, fibronectin, and HA; stim. angiogenesis and wound contraction; remodeling
Transforming growth factor-beta (including isoforms β_1 , β_2 , and β_3)	TGF-β	Platelets, T lymphocytes, macrophages, endothelial cells, keratinocytes, fibroblasts	Chemotactic for PMNs, macrophages, lymphocytes, fibroblasts; stim. TIMP synthesis, keratinocyte migration, angiogenesis, and fibroplasia; inhib. Prod. of MMPs and keratinocyte proliferation; induces TGF-β production
Epidermal growth factor	EGF	Platelets, macrophages	Mitogenic for keratinocytes and fibroblasts; stimulates keratinocyte migration
Transforming growth factor-alpha	TGF-α	Macrophages, T lymphoc., keratinocytes	Similar to EGF
Fibroblast growth factor-1 and -2 family	FGF	Macrophages, mast cells, T lymphocytes, endoth. cells, fibroblasts	Chemotactic for fibroblasts; mitogenic for fibroblasts and keratinocytes; stimulates keratinocyte migration, angiogenesis, wound contraction, and matrix deposition
Keratinocyte growth factor (also called FGF-7)	KGF	Fibroblasts	Stimulates keratinocyte migration, proliferation, and differentiation
Insulin-like growth factor	IGF-1	Macrophages, fibroblasts	Stimulates synthesis of sulfated proteoglycans, collagen, keratinocyte migration, and fibroblast proliferation; endocrine effects similar to those of growth hormone
Vascular endothelial cell growth factor	VEGF	Keratinocytes	Increases vasopermeability; mitogenic for endoth. cells

HA, hyaluronic acid; MMPs, matrix metalloproteinases; PMNs, polymorphonuclear leukocytes; TIMP, tissue inhibitor of matrix metalloproteinase.

Hemostasis and Inflammation

Lymphocytes

- Appear 5th day,
- peak at around the 7th day.
- Initially, lymphocytes were thought to play a minimal role in acute wound healing

B lymphocytes:

- downregulating healing as the wound closes.

Effects on fibroblasts

- stimulatory cytokines
  - IL-2 and fibrobl. activ. factor
- inhibitory cytokines:
  - TGF-β, TNF-α, and IFN-γ.

T cells produce IFN-γ,

- Stim. the macroph. to release a cascade of cytokines TNF-α and IL-1
- decreased synthesis of prostaglandins, which enhances the effect of inflam. mediators.
- suppresses collagen synthesis
- inhibits macrophages from leaving the site of injury.
- IFN-γ appears to be an important mediator of the chronic nonhealing wound

Hemostasis and Inflammation

Role of lymphocytes

cyclosporine, tacrolimus and steroids

- suppress T-lymphocyte function and proliferation
- impair wound healing in experimental wound models
  - possibly through decreased nitric oxide synthesis.

In vivo

- lymphocyte depletion suggests the existence of an incompletely characterized T-cell lymphocyte population
- neither $CD4^+$ nor $CD8^+$
- this subset that seems to be responsible for the promotion of wound healing

Proliferative Phase

- acute responses of hemostasis and inflammation begin to resolve
- scaffolding is laid for repair of the wound:
  - angiogenesis,
  - fibroplasia,
  - epithelialization.
- characterized by formation of granulation tissue:
  - capillary bed,
  - fibroblasts,
  - macrophages,
  - loose arrangement of collagen, fibronectin, and hyaluronic acid.

Proliferative Phase

Angiogenesis

- Activated endothelial cells degrade the basement membrane of postcapillary venules, allowing migration of cells through this gap
- Division of these migrating endothelial cells results in tubule or lumen formation
- Eventually, deposition of the basement membrane occurs, resulting in capillary maturation
- Appears to be stimulated and manipulated by a variety of cytokines, predominantly produced by macrophages and platelets

Proliferative Phase

Fibroplasia

Fibroblasts differentiate from resting mesenchymal cells in connective tissue;

- the normally quiescent and sparse fibroblasts are chemoattracted to the inflammatory site
- they divide and produce the components of the ECM

Fibroblast, normally arrested in the G_0 phase undergoes replication and proliferation after stimulation by macrophage and platelet-derived cytokines and growth factors

Proliferative Phase

Fibroblasts

- primary function to synthesize collagen
- they begin to produce collagen during the cellular phase of inflamm.
- *lag phase:* time required for undifferentiated mesenchymal cells to differentiate into highly specialized fibroblasts
  - delay between injury and the appearance of collag. in a healing wound
  - generally 3 to 5 days depending on the type of tissue injured
- migrate in response to chemotactic substances,
  - growth factors (PDGF, TGF-β), C5 fragments, thrombin, TNF-α, eicosanoids, elastin fragments, leukotriene B_4 , and fragments of collagen and fibronectin
- Collagen synthesis rates decline after 4 weeks, eventually balancing the rate of collagen destruction by collagenase (MMP-1).
- At that point, the wound enters a phase of collagen maturation.

Proliferative Phase

Epithelialization

- epidermis serves as a physical barrier to prevent fluid loss and bacterial invasion
- tight cell junctions contribute to its impermeability
- the basement membrane zone
  - gives structural support
  - attachment between the epidermis and the dermis

The basement membrane zone:

- (1) the lamina lucida (electron clear), laminin and heparan sulfate;
- (2) lamina densa (electron dense), type IV collagen;
- (3) anchoring fibrils, type IV collagen,
  secure the epidermodermal interface
  connect from the lamina densa into the dermis.

The basal layer of the epidermis attaches to the basement membrane zone by hemidesmosomes.

Proliferative Phase

- Re-epithelialization of wounds begins within hours after injury.
- the wound is rapidly sealed by clot formation
- then by epithelial (epidermal) cell migration across the defect.
- Keratinocytes migrate to resurface the wound:
  - basal layer of the residual epidermis
  - in the depths of epithelium-lined dermal appendages.
- Epithelialization involves a sequence of changes in wound keratinocytes:
  - detachment,
  - migration,
  - proliferation,
  - differentiation,
  - stratification.
- If the basement membrane zone is intact, epithelialization proceeds more rapidly.

Proliferative Phase

- The epithelial cells move in a leapfrog and tumbling fashion
- They move until the edges establish contact.
- If the basement membrane zone is not intact, it will be repaired first.
- The absence of neighbor cells at the margin may be a signal for the migration and proliferation of epidermal cells
- After the wound is completely re-epithelialized,
  - the cells become columnar and stratified again,
  - while firmly attaching to the re-established basement membrane and underlying dermis.

Proliferative Phase

Extracellular Matrix

The ECM exists as a scaffold

- to stabilize the physical structure of tissues
- complex role by regulating the behavior of the cells that contact it.

Cells within it produce the macromolecular constituents,

- (1) glycosaminoglycans (GAGs), polysaccharide chains, usually found covalently linked to protein in the form of proteoglycans;
- (2) fibrous proteins, such as collagen, elastin, fibronectin, and laminin.

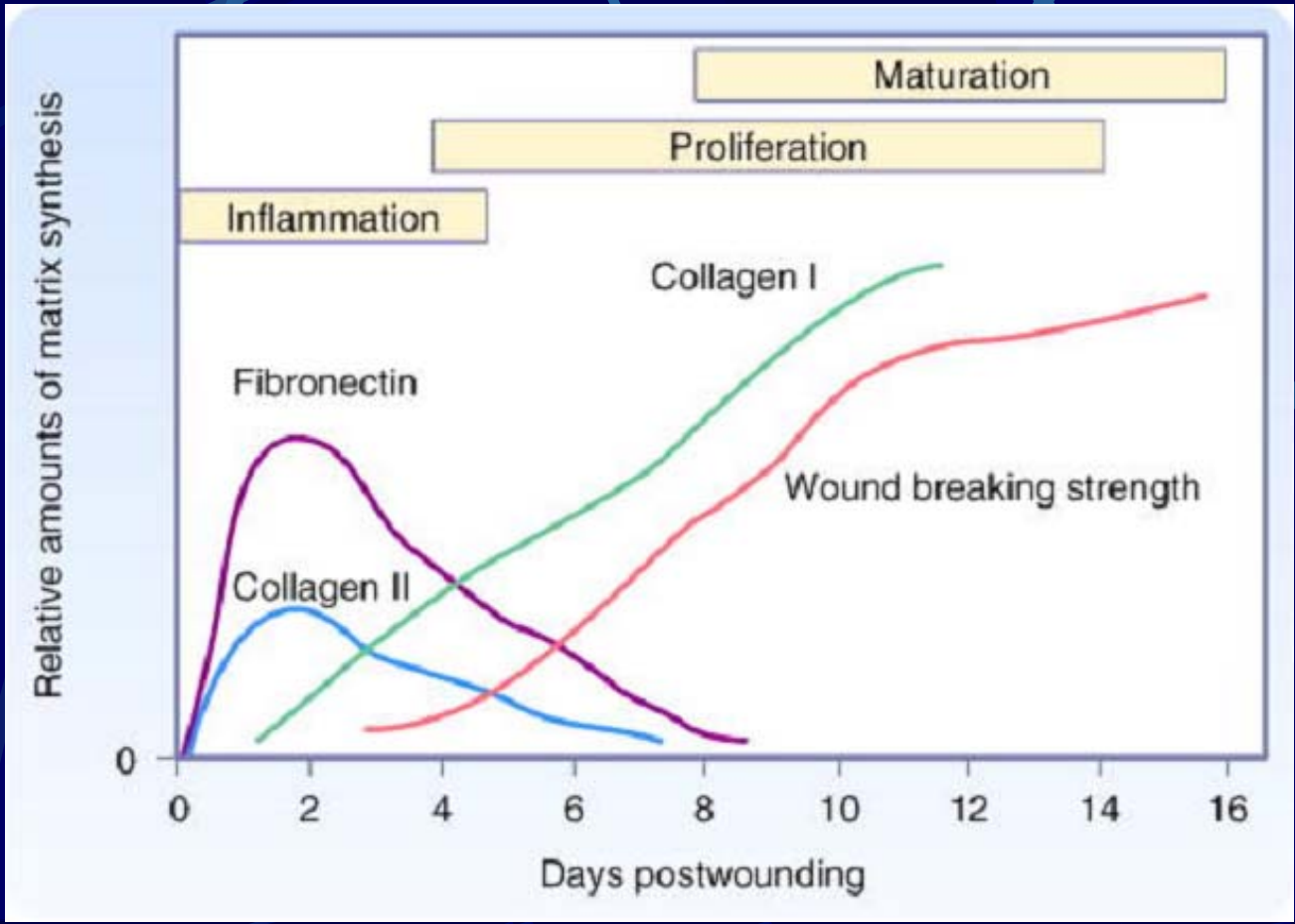
Proliferative Phase

- Proteoglycan molecules: a gel-like “ground substance.”
  - highly hydrated gel
  - allows the matrix to withstand compressive forces
  - while permitting between the blood and the tissue cells the rapid diffusion of:
    - nutrients,
    - metabolites,
    - hormones
- Collagen fibers to organize and strengthen it
- Elastin fibers to give resilience
- Matrix proteins to have adhesive functions

Proliferative Phase

- As the wound matrix accumulates, it is changing in composition as healing progresses,
  - balanced between new deposition and degradation.
- The provisional matrix is a scaffold for cellular migration
  - fibrin,
  - fibrinogen,
  - fibronectin,
  - vitronectin.
- GAGs and proteoglycans are synthesized next,
  - supporting further matrix deposition and remodeling.
- Collagens, the predominant scar proteins,
  - are the end result.
- Attachment proteins, such as fibrin and fibronectin, provide linkage to the ECM through binding to cell surface integrin receptors.

Proliferative Phase



Wound matrix deposition over time.

Fibronectin and type III collagen constitute the early matrix.

Type I collagen accumulates later and corresponds to the increase in wound-breaking strength.

Proliferative Phase

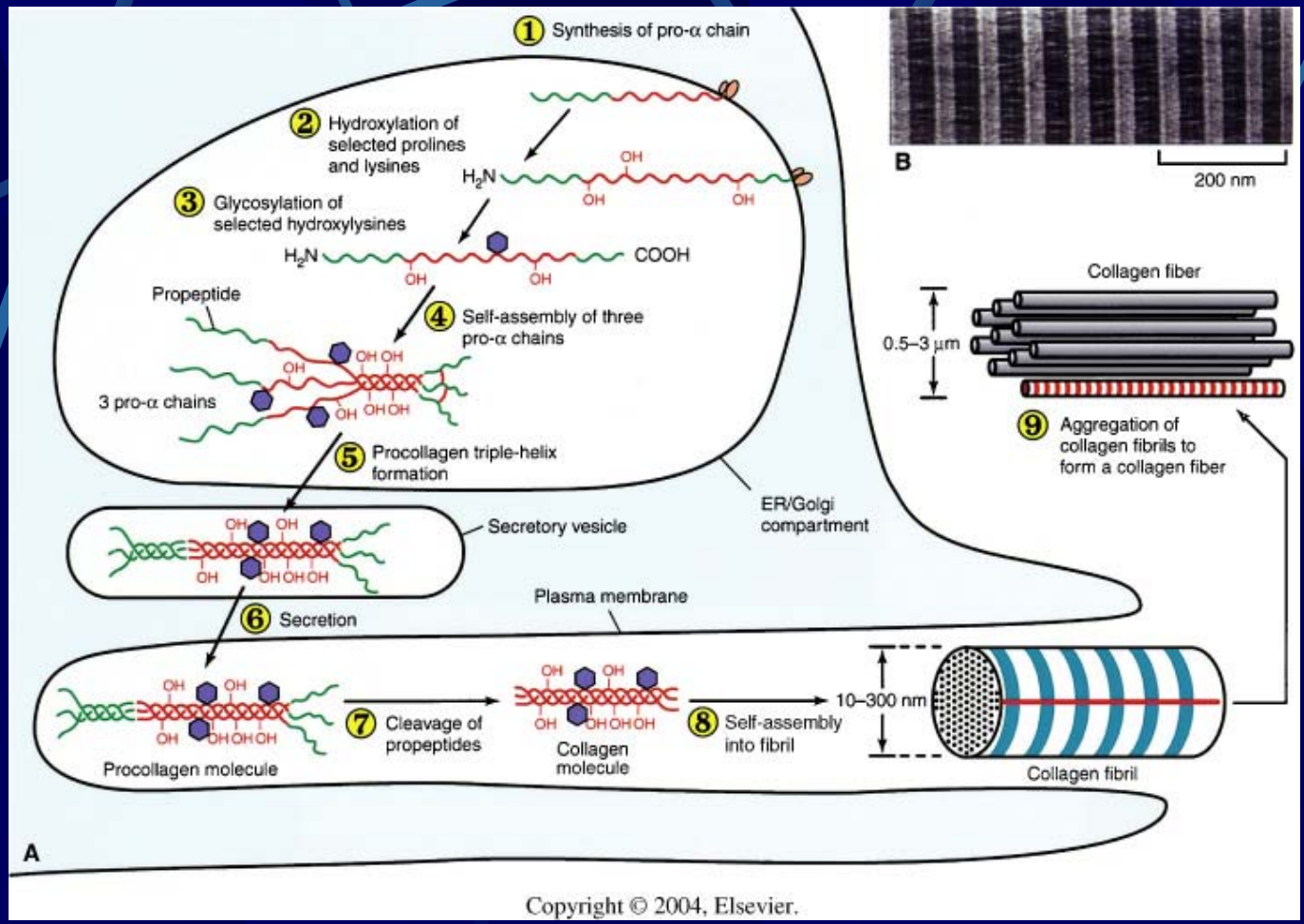
Collagen Structure

- secreted by a variety of cell types.
- major component of skin and bone
- 25% of the total protein mass in mammals.

The collagen molecule

- proline and glycine-rich
- long, stiff, triple-stranded helical structure,
- comprises three collagen polypeptide α chains wound around one another in a ropelike superhelix.
- proline (ring) provides stability to the helical conformation,
- glycine, (small size) allows tight packing of the three alpha chains to form the final superhelix.
- There are at least 20 types of collagen;
- main of connective tissue are types I, II, III, V, and XI

Proliferative Phase



The formation of a collagen fibril.
Collagen fibrils assembling in the extracellular space contained within a large infolding in the plasma membrane.

Proliferative Phase

Collagen

- Type I is the principal collagen of skin and bone, the most common.
- In the adult, the skin is approximately 80% type I and 20% type III.
- In newborns, the content of type III collagen is greater than that found in the adult.
- In early wound healing, there is also an increased expression of type III
- Type I collagens are the fibrillar collagens, or the fibril-forming collagens.
  - They are secreted into the extracellular space where they assemble into collagen fibrils (10 to 300 nm in diameter), which then aggregate into larger, cablelike bundles called collagen fibers (several micrometers in diameter).

Proliferative Phase

Collagen

- collagen synthesis increased:
  - Vitamin C (ascorbic acid),
  - TransformingGF-β,
  - Insulin like GF-1, and IGF-2.
- collagen synthesis decreased
  - IFN-γ type I procollagen mRNA synthesis,
  - glucocorticoids inhibit procollagen gene transcription
- Genetic disorders:
  - *osteogenesis imperfecta*, deletion of one procollagen α_1 allele results in weak and easily fractured bones.
  - Ehlers-Danlos syndrome is a result of mutations affecting type III collagen and is characterized by fragile skin and blood vessels and hypermobile joints.

Proliferative Phase

Elastic Fibers

- skin, blood vessels, and lungs require strength and elasticity to function, for recoil after transient stretch.
- Elastic fibers are predominantly composed of elastin,
  - highly hydrophobic protein (about 750 amino acids long).
- Soluble tropoelastin is secreted into the extracellular space where it forms lysine cross-links to generate a large network of elastin fibers and sheets.
- The predominant theory is that the elastin polypeptide chain adopts a “random coil” conformation that allows the network to stretch and recoil like a rubber band.
- Elastic fibers consist of an elastin core covered with a sheath of microfibrils (fibrillin), essential for the integrity of the elastic fibers.
- Elastin is produced early in life, stabilizes, and does not undergo much further synthesis or degradation, with a turnover that approaches the life span
- Fibrillin gene mutations result in Marfan’s syndrome; severely affected individuals are prone to aortic rupture

Proliferative Phase

Glycosaminoglycans and Proteoglycans

- GAGs are unbranched polysaccharide chains composed of repeating disaccharide units:
  - a sulfated amino sugar (*N*-acetylglucosamine or *N*-acetylgalactosamine),
  - uronic acid (glucuronic or iduronic).
- The GAGs are highly negatively charged because of the sulfate or carboxyl groups on most of their sugars.
- Four types of GAGS exist:
  - (1) hyaluronan (HA),
  - (2) chondroitin sulfate and dermatan sulfate,
  - (3) heparan sulfate,
  - (4) keratan sulfate.

Proliferative Phase

- The GAGs in connective tissue usually constitute less than 10% of the weight of the fibrous proteins.
- highly negative charge attracts osmotically active cations, such as Na^+
  - causing large amounts of water to be incorporated into the matrix.
- This results in porous hydrated gels and is responsible for the turgor that enables the matrix to withstand compressive forces.
- Hyaluronan is the simplest of the GAGs.
  - prevalent in fetal tissues, is believed to be a factor in the scarless wound healing seen in fetal tissues.
  - during wound healing facilitates cell migration by physically expanding the ECM
  - creates a cell-free space for cell migration, during embryogenesis and formation of the heart and other organs.
  - when cell migration finishes, the excess HA is degraded by hyaluronidase.

Proliferative Phase

Proteoglycans

- diverse group with functions mediated by both their core proteins and GAG chains.
- provide hydrated space around and between cells.
- form gels of different pore size and charge density to regulate movement of cells and molecules.
  - Perlecan, a heparan sulfate proteoglycan, serves this role in the basal lamina of the kidney glomerulus. Decreased levels of perlecan are believed to play a role in diabetic albuminuria.
- bind signal molecules (growth factors), proteases and protease inhibitors.
  - (1) immobilizing the protein and restricting its range of action;
  - (2) providing a reservoir of the protein for delayed release;
  - (3) altering the protein, more effective presentation to cell surface recept.
  - (4) prolonging the protein's action by protecting it from degradation;
  - (5) blocking the activity of the protein

Proliferative Phase

Basal Lamina

- flexible, thin (40- to 120-nm thick) mats of specialized ECM
- separate cells and epithelia from the underlying or surrounding connective tissue.
- functions;
  - (1) as a molecular filter, preventing passage of macromolecules (i.e., in kidney glomerulus);
  - (2) as a selective barrier to certain cells (i.e., the lamina beneath the epithelium prevents fibroblasts from contacting epithelial cells, but does not stop macrophages or lymphocytes);
  - (3) as a scaffold for regenerating cells to migrate;
  - (4) is important in tissue regeneration where the basal lamina survives.

Proliferative Phase

Basal Lamina

- In the skin, the basal lamina is tethered to the underlying connective tissue by specialized anchoring fibrils. This composite of basal lamina and collagen is the basement membrane.
- Most mature basal laminae contain type IV collagen, perlecan, and the glycoproteins laminin and nidogen.
- Mice lacking the laminin-γ_1 chain die during embryogenesis because they cannot make a basal lamina.

Maturational Phase

- Wound ***contraction*** is the centripetal movement of the whole thickness of the surrounding skin, reducing the amount of disorganized scar.
- Wound ***contracture*****,** in contrast, is a physical constriction or limitation of function and is the result of the process of wound contraction.
- Contractures occur when excessive scar exceeds normal wound contraction and results in a functional disability.
- Scars that traverse joints and prevent extension or scars that involve the eyelid or mouth and cause ectropions
- Wound contraction appears to occur by a complex interaction of the extracellular materials and the fibroblast (not completely understood)
- *Myofibroblasts:* fibroblasts in a contracting wound, which undergo change for stimulation
  - both function and structure in common with fibroblasts and smooth muscle cells

Maturational Phase

Remodeling

- The fibroblast population decreases and the dense capillary network regresses.
- Wound strength increases rapidly within 1 to 6 weeks and then appears to plateau up to 1 year after the injury
- Compared with unwounded skin, the tensile strength is only 30% in the scar.
- There is an increase in breaking strength after approximately 21 days, which is mostly a result of cross-linking. Although collagen cross-linking causes further wound contraction and increase in strength, it also results in a scar that is more brittle and less elastic than normal skin.
- Unlike normal skin the epidermodermal interface in the healed wound is devoid of rete pegs, the undulating projections of epidermis that penetrate into the papillary dermis. Loss of this anchorage results in increased fragility and predisposes the neoepidermis to avulsion after minor trauma.

Abnormal Wound Healing

Factors that Inhibit Wound Healing

- Infection
- Ischemia
  - Circulation
  - Respiration
  - Local tension
- Diabetes mellitus
- Ionizing radiation
- Advanced age
- Malnutrition
- Vitamin deficiencies
  - Vitamin C
  - Vitamin A
- Mineral deficiencies
  - Zinc
  - Iron
- Exogenous drugs
  - Doxorubicin (Adriamycin)
- Glucocorticosteroids

Hypertrophic Scars and Keloids

Both keloids and hypertrophic scars are characterized by excessive collagen deposition versus collagen degradation.

Keloids are defined as scars that grow beyond the borders of the original wounds

- rarely regress with time.
- more prevalent among patients with darker pigmented skin, occurring in 15% to 20% of African Americans, Asians, and Hispanics.
- appears to have a genetic predisposition.
- tends to occur above the clavicles on the trunk, in the upper extremities, and on the face.
- cannot be prevented at this time and are refractory to medical and surgical intervention.
- have thicker, more abundant collagen bundles that form acellular nodelike structures in the deep dermal portion of the keloid lesion.

Hypertrophic Scars and Keloids

Hypertrophic scars, are raised scars that remain within the confines of the original wound

- frequently regress spontaneously.
- can occur anywhere on the body.
- differ histologically from normal scars.
- in many cases preventable
- Prolonged inflammation and insufficient resurfacing, such as can occur with a burn wound, lead to hypertrophic scar.
- It appears that the tension that signals formation of activated fibroblasts also causes deposition of excessive collagen.

Hypertrophic Scars and Keloids

- Both keloids and hypertrophic scars have stretched collagen bundles aligned in the same plane as the epidermis as opposed to normal scar tissue, where the collagen bundles are randomly arrayed and relaxed.
- The center of keloid lesions also contains a paucity of cells compared to that of the hypertrophic scar that has islands composed of aggregates of fibroblasts, small vessels, and collagen fibers throughout the dermis.

Chronic Nonhealing Wounds

- Chronic wounds, like other abnormal wounds, appear to have derangements in various stages of wound healing and unusually elevated or depressed levels of cytokines, growth factors, or proteinases.
- Chronic wound fluid, unlike acute wound fluid, has been demonstrated to have greater levels of IL-1, IL-6, and TNF-α;
- Levels of these proinflammatory cytokines decreased as the wound healed.
- An inverse relationship between TNF-α and essential growth factors such as EGF and PDGF has been demonstrated.

Chronic Nonhealing Wounds

- Wounds that are chronically inflamed and do not proceed to closure can develop squamous cell carcinoma
  - chronic burn scars, Marjolin
  - osteomyelitis,
  - pressure sores,
  - venous stasis ulcers,
  - hidradenitis.
- The wound appears irregular, raised above the surface, with a white, pearly discoloration.
- premalignant state is pseudoepitheliomatous hyperplasia.
- The above biopsy result, biopsy should be repeated because there may be squamous cell carcinoma present in other areas

Chronic Nonhealing Wounds

Infection

- Probably the most common cause of healing delays is wound infection.
- If the bacterial count in the wound exceeds 10^5 organisms per gram of tissue,
- if any β-hemolytic streptococci are present

Chronic Nonhealing Wounds

Hypoxia

- Molecular oxygen is essential for collagen formation.
- Ischemia can be caused by atherosclerosis, cardiac failure, or simple wound tension preventing localized perfusion.
- glycolysis may be sufficient to initiate collagen synthesis,
- presence of molecular oxygen is critical for the post-translational hydroxylation of prolyl and lysyl residues required for triple-helix formation and cross-linking of collagen fibrils.
- Use of tobacco products has a similar impact on wound healing due to
  - vasoconstriction that occurs with smoking
  - the elevated carbon monoxide serum levels that can limit the oxygen-carrying capacity of the blood

Chronic Nonhealing Wounds

Diabetes

- impairs wound healing at all stages of the process.
- associated neuropathy and atherosclerosis is prone to tissue ischemia, repetitive trauma, and infection.
  - large-vessel disease,
  - microvascular level.
- basement membrane of the capillaries is thickened, causing decreased perfusion in the microenvironment,
- increased perivascular localization of albumin, suggesting that these capillaries are leaky.
- diabetic patients are prone to repeated trauma as a result of the diabetic neuropathy that affects both sensory and motor functions both in somatic and autonomic pathways.

Chronic Nonhealing Wounds

Diabetes

- susceptible to infection because of an attenuated inflammatory response, impaired chemotaxis, and inefficient bacterial killing.
- Infection also increases local tissue metabolism, further imposing a burden on an already tenuous blood supply
- lymphocyte and leukocyte function is impaired,
- increased collagen degradation and decreased collagen deposition.
- The collagen that is formed is more brittle than normal collagen,

Chronic Nonhealing Wounds

Ionizing Radiation

- causes endothelial cell injury with endarteritis resulting in atrophy, fibrosis, and delayed tissue repair.
- unlike most hypoxic wound beds, angiogenesis is not initiated.
- greatest effect is on cells in the G_2 through M phase, rapidly dividing cell populations are most sensitive to radiation:
  - keratinocytes
  - fibroblasts
- impairing epithelialization and granulation tissue formation.

Chronic Nonhealing Wounds

Aging

- elderly patients are more likely to have surgical wound ruptures and delayed healing
- the same patient as he or she ages will heal more slowly.
- collagen undergoes qualitative and quantitative changes.
- dermal collagen content decreases
- aging collagen fibers show distorted architecture and organization
- decreased re-epithelialization, depressed collagen synthesis, and impaired angiogenesis with decreased levels of multiple growth factors
- impaired macrophage activity, with reduced phagocytosis and delayed infiltration of macrophages and B lymphocytes into wounds
- decrease in response to hypoxia

Chronic Nonhealing Wounds

MalNutrition

- protein catabolism can result in a delay in wound healing.
- hypoalbuminemic patient can experience wound healing delay or even dehiscence, (below 2.0 g/dL)
- Vitamin deficiencies primarily owing to their effect as cofactors:
  - 3 months of vitamin C deprivation
  - vitamin A impedes monocyte activation, fibronectin deposition that further affects cellular adhesion, and impairment of the TGF-β receptors.
  - vitamin K deficiency is to limit the synthesis of prothrombin and factors VII, IX, and X.
  - Vitamin K metabolism is impeded by antibiotics. Those patients who have chronic or recurrent infections should have their clotting parameters checked before surgical procedures.

Chronic Nonhealing Wounds

Malnutrition

- Minerals:
  - Zinc deficiency is rare, except in cases such as large burns, severe multiple trauma, and hepatic cirrhosis.
  - Zinc deficiency results in early wound healing delays
  - Iron deficiency anemia is a debatable cause of wound healing delay.
  - Although the ferrous ion is a cofactor necessary to convert hydroxyproline to proline, there are conflicting reports as to the effects that acute and chronic anemia have on wound healing

Chronic Nonhealing Wounds

Drugs

- Some directly inhibit wound healing.
  - Doxorubicin (Adriamycin) is a potent inhibitor
- clinical studies show little impairment, experimental models:
  - nitrogen mustard, cyclophosphamide, methotrexate, bis-chloroethyl-nitrosourea (BCNU), and doxorubicin are the most potent wound inhibitors.
- Tamoxifen, an antiestrogen:
  - decrease cellular proliferation
  - dose-dependent decrease in wound breaking strength
- Glucocorticosteroid
  - impairs fibroblast proliferation and collagen synthesis.
  - amount of granulation tissue formed is also decreased.
- Steroids stabilize the lysosomal membranes, can be reversed by the administration of vitamin A.

Fetal Wound Healing

- heal rapidly and without the scarring and inflammation
- re-epithelialize faster with less neovascularization and faster increase in strength.
- differ from adults
  - in inflammatory responses,
  - ECM components,
  - growth factor expression and responses.
- gestational-age and wound-size dependent
- wounds created early in gestation heal scarlessly and with dermal appendages