Chronic Inflammation

Chronic inflammation is inflammation of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations.

It may follow acute inflammation, as described earlier, or chronic inflammation may begin insidiously, as a low-grade, smoldering response without any manifestation of an acute reaction. This latter type of chronic inflammation is the cause of tissue damage in some of the most common and disabling human diseases, such as rheumatoid arthritis, atherosclerosis, tuberculosis, and pulmonary fibrosis. It has also been implicated in the progression of cancer and in diseases once thought to be purely degenerative, such as Alzheimer disease.
CAUSES OF CHRONIC INFLAMMATION

Chronic inflammation arises in the following settings:

• Persistent infections by microorganisms (mycobacteria)

• Excessive and inappropriate activation of the immune system (auto-antigens evoke a self-perpetuating immune reaction)

• Prolonged exposure to potentially toxic agents, either exogenous or endogenous (asbestosis)
Chronic inflammation is characterized by:

- **Infiltration with mononuclear cells**, which include macrophages, lymphocytes, and plasma cells

- **Tissue destruction**, induced by the persistent offending agent or by the inflammatory cells

- Attempts at healing by connective tissue replacement of damaged tissue, accomplished by proliferation of small blood vessels (angiogenesis) and, in particular, fibrosis
FIGURE 2-22A  A, Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, arrowheads), and (3) replacement by connective tissue (fibrosis, arrows). B, By contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

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FIGURE 2–22B A, Chronic inflammation in the lung, showing all three characteristic histologic features: (1) collection of chronic inflammatory cells (*), (2) destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, arrowheads), and (3) replacement by connective tissue (fibrosis, arrows). B, By contrast, in acute inflammation of the lung (acute bronchopneumonia), neutrophils fill the alveolar spaces and blood vessels are congested.

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The macrophage is the dominant cellular player in chronic inflammation.

The half-life of blood monocytes is about 1 day, whereas the life span of tissue macrophages is several months or years.

Monocytes begin to emigrate into extravascular tissues quite early in acute inflammation, and within 48 hours they may constitute the predominant cell type.
As illustrated in Fig. 2-10, different macrophage populations may serve distinct functions—some may be important for microbial killing and inflammation, and others for repair. Their impressive arsenal of mediators makes macrophages powerful allies in the body's defense against unwanted invaders, but the same weaponry can also induce considerable tissue destruction when macrophages are inappropriately activated. It is because of the activities of these macrophages that tissue destruction is one of the hallmarks of chronic inflammation. The ongoing tissue destruction can itself activate the inflammatory cascade, so that features of both acute and chronic inflammation may coexist in certain circumstances.
The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, and are responsible for much of the tissue injury in chronic inflammation.

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Fibrocytes are mesenchymal cells that arise from monocyte precursors. They are present in injured organs and have both the inflammatory features of macrophages and the tissue remodelling properties of fibroblasts. Chronic inflammatory stimuli mediate the differentiation, trafficking and accumulation of these cells in fibrosing conditions associated with autoimmunity, cardiovascular disease and asthma. This Opinion article discusses the immunological mediators controlling fibrocyte differentiation and recruitment, describes the association of fibrocytes with chronic inflammatory diseases and compares the potential roles of fibrocytes in these disorders with those of macrophages and fibroblasts. It is hoped that this information prompts new opportunities for the study of these unique cells.
Granulomatous inflammation is a distinctive pattern of chronic inflammation that is encountered in a limited number of infectious and some noninfectious conditions.

A granuloma is a cellular attempt to contain an offending agent that is difficult to eradicate. In this attempt there is often strong activation of T lymphocytes leading to macrophage activation, which can cause injury to normal tissues.

Tuberculosis is the prototype of the granulomatous diseases, but sarcoidosis, cat-scratch disease, lymphogranuloma inguinale, leprosy, brucellosis, syphilis, some mycotic infections, berylliosis, reactions of irritant lipids, and some autoimmune diseases are also included.

Recognition of the granulomatous pattern in a biopsy specimen is important because of the limited number of possible conditions that cause it and the significance of the diagnoses associated with the lesions.
Injury to cells and tissues sets in motion a series of events that contain the damage and initiate the healing process. This process can be broadly separated into regeneration and repair (Fig. 3-1).

Regeneration results in the complete restitution of lost or damaged tissue.

Repair may restore some original structures but can cause structural derangements.

In healthy tissues, healing, in the form of regeneration or repair, occurs after practically any insult that causes tissue destruction, and is essential for the survival of the organism.
FIGURE 3-1 Overview of healing responses after injury. Healing after acute injury can occur by regeneration that restores normal tissue structure or by repair with scar formation. Healing in chronic injury involves scar formation and fibrosis. GI, gastrointestinal.

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In mammals, whole organs and complex tissues rarely regenerate after injury, and the term is usually applied to processes such as liver growth after partial resection or necrosis, but these processes consist of compensatory growth rather than true regeneration.

Tissues with high proliferative capacity, such as the hematopoietic system and the epithelia of the skin and gastrointestinal (GI) tract, renew themselves continuously and can regenerate after injury, as long as the stem cells of these tissues are not destroyed.
**Repair**

Most often consists of a combination of regeneration and scar formation by the deposition of collagen.

Scar formation is the predominant healing process that occurs when the extracellular matrix (ECM) framework is damaged by severe injury (Fig. 3-2).

Chronic inflammation that accompanies persistent injury also stimulates scar formation because of local production of growth factors and cytokines that promote fibroblast proliferation and collagen synthesis.

The term fibrosis is used to describe the extensive deposition of collagen that occurs under these situations.
ECM components are essential for wound healing, because they provide the framework for cell migration, maintain the correct cell polarity for the re-assembly of multilayer structures, and participate in the formation of new blood vessels (angiogenesis).

Cells in the ECM (fibroblasts, macrophages, and other cell types) produce growth factors, cytokines, and chemokines that are critical for regeneration and repair. Although repair is a healing process, it may itself cause tissue dysfunction, as, for instance, in the development of atherosclerosis.
Control of Normal Cell Proliferation and Tissue Growth

In adult tissues the size of cell populations is determined by the rates of cell proliferation, differentiation, and death by apoptosis (Fig. 3-3), and increased cell numbers may result from either increased proliferation or decreased cell death.

Differentiated cells incapable of replication are referred to as terminally differentiated cells.

The impact of differentiation depends on the tissue under which it occurs: in some tissues differentiated cells are not replaced, while in others they die but are continuously replaced by new cells generated from stem cells.

FIGURE 3–3 Mechanisms regulating cell populations. Cell numbers can be altered by increased or decreased rates of stem cell input, cell death due to apoptosis, or changes in the rates of proliferation or differentiation.

Cell proliferation is largely controlled by signals (soluble or contact-dependent) from the microenvironment that either stimulate or inhibit proliferation. An excess of stimulators or a deficiency of inhibitors leads to net growth and, in the case of cancer, uncontrolled growth.

http://www.fli-leibniz.de/images/groups/morrison/morrison1n.gif
The tissues of the body are divided into three groups on the basis of the proliferative activity of their cells:

- **continuously dividing** (labile tissues): Such as surface epithelium
- **quiescent** (stable tissues): Such as liver
- **Non-dividing** (permanent tissues): Such as neurons
Stem cells are characterized by their self-renewal properties and by their capacity to generate differentiated cell lineages (Fig. 3-4).

To give rise to these lineages, stem cells need to be maintained during the life of the organism.

Such maintenance is achieved by two mechanisms:

(a) obligatory asymmetric replication, in which with each stem cell division, one of the daughter cells retains its self-renewing capacity while the other enters a differentiation pathway, and

(b) stochastic differentiation, in which a stem cell population is maintained by the balance between stem cell divisions that generate either two self-renewing stem cells or two cells that will differentiate.
**FIGURE 3-4** Stem cell generation and differentiation. The zygote, formed by the union of sperm and egg, divides to form blastocysts, and the inner cell mass of the blastocyst generates the embryo. The cells of the inner cell mass, known as embryonic stem (ES) cells, maintained in culture, can be induced to differentiate into cells of multiple lineages. In the embryo, pluripotent stem cells divide, but the pool of these cells is maintained. As pluripotent cells differentiate, they give rise to cells with more restricted developmental capacity, and finally generate stem cells that are committed to specific lineages.
In adults, stem cells (often referred to as adult stem cells or somatic stem cells) with a more restricted capacity to generate different cell types have been identified in many tissues.

Somatic stem cells for the most part reside in special microenvironments called niches (Fig. 3-5), composed of mesenchymal, endothelial, and other cell types.

It is believed that niche cells generate or transmit stimuli that regulate stem cell self-renewal and the generation of progeny cells.

Recent groundbreaking research has now demonstrated that differentiated cells of rodents and humans can be reprogrammed into pluripotent cells, similar to ES cells, by the transduction of genes encoding ES cell transcription factors. These reprogrammed cells have been named induced pluripotent stem cells (iPS cells).
FIGURE 3–5A Stem cell niches in various tissues. A, Skin stem cells are located in the bulge area of the hair follicle, in sebaceous glands, and in the lower layer of the epidermis. B, Small intestine stem cells located near the base of a crypt, above Paneth cells (stem cells in the small intestine may also be located at the bottom of the crypt). C, Liver stem (progenitor) cells, known as oval cells, are located in the canals of Hering (thick arrow), structures that connect bile ductules (thin arrow) with parenchymal hepatocytes (bile duct and Hering canals are stained for cytokeratin 7). D, Corneal stem cells are located in the limbus region, between the conjunctiva and the cornea.

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FIGURE 3–5C Stem cell niches in various tissues. 

A. Skin stem cells are located in the bulge area of the hair follicle, in sebaceous glands, and in the lower layer of the epidermis. 

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(Courtesy of Tania Roskams, MD, University of Leuven, Leuven, Belgium.)
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(Courtesy of T-T Sun, MD, New York University, New York, NY.)
Healing by Repair, Scar Formation and Fibrosis

If tissue injury is severe or chronic, and results in damage of both parenchymal cells and the stromal framework of the tissue, healing can not be accomplished by regeneration.

Under these conditions, the main healing process is repair by deposition of collagen and other ECM components, causing the formation of a scar.

In contrast to regeneration which involves the restitution of tissue components, repair is a fibroproliferative response that “patches” rather than restores the tissue.

The term scar is most often used in connection to wound healing in the skin, but is also used to describe the replacement of parenchymal cells in any tissue by collagen, as in the heart after myocardial infarction. Repair by connective tissue deposition includes the following basic features:

- inflammation
- angiogenesis,
- migration and proliferation of fibroblasts,
- scar formation
- connective tissue remodeling
The relative contributions of repair and regeneration are influenced by:

(1) the proliferative capacity of the cells of the tissue

(2) the integrity of the extracellular matrix

(3) the resolution or chronicity of the injury and inflammation
Angiogenesis is a fundamental process that affects physiologic reactions (e.g. wound healing, regeneration, the vascularization of ischemic tissues, and menstruation), and pathologic processes, such as tumor development and metastasis, diabetic retinopathy, and chronic inflammation.

**FIGURE 3–15A** Angiogenesis by mobilization of endothelial precursor cells (EPCs) from the bone marrow and from preexisting vessels (capillary growth). A, In angiogenesis from preexisting vessels, endothelial cells from these vessels become motile and proliferate to form capillary sprouts. Regardless of the initiating mechanism, vessel maturation (stabilization) involves the recruitment of pericytes and smooth muscle cells to form the periendothelial layer. B, EPCs are mobilized from the bone marrow and may migrate to a site of injury or tumor growth. At these sites, EPCs differentiate and form a mature network by linking to existing vessels.

Angiogenesis from Preexisting Vessels.

In this type of angiogenesis there is vasodilation and increased permeability of the existing vessels, degradation of ECM, and migration of endothelial cells. The major steps are listed below.

Vasodilation in response to nitric oxide, and VEGF-induced increased permeability of the preexisting vessel

Proteolytic degradation of the basement membrane of the parent vessel by matrix metalloproteinases (MMPs) and disruption of cell-to-cell contact between endothelial cells by plasminogen activator

Migration of endothelial cells toward the angiogenic stimulus

Proliferation of endothelial cells, just behind the leading front of migrating cells

Maturation of endothelial cells, which includes inhibition of growth and remodeling into capillary tubes

Recruitment of periendothelial cells (pericytes and vascular smooth muscle cells) to form the mature vessel
Angiogenesis from Endothelial Precursor Cells (EPCs)

EPCs can be recruited from the bone marrow into tissues to initiate angiogenesis (Fig. 3-15). The nature of the homing mechanism is uncertain.

The number of circulating EPCs increases greatly in patients with ischemic conditions, suggesting that EPCs may influence vascular function and determine the risk of cardiovascular diseases.

FIGURE 3-15B Angiogenesis by mobilization of endothelial precursor cells (EPCs) from the bone marrow and from preexisting vessels (capillary growth). A, In angiogenesis from preexisting vessels, endothelial cells from these vessels become motile and proliferate to form capillary sprouts. Regardless of the initiating mechanism, vessel maturation (stabilization) involves the recruitment of pericytes and smooth muscle cells to form the periendothelial layer. B, EPCs are mobilized from the bone marrow and may migrate to a site of injury or tumor growth. At these sites, EPCs differentiate and form a mature network by linking to existing vessels.

Growth Factor-mediated Proliferation

- **Platelet Derived Growth Factor (PDGF)**
  - promotes the chemotactic migration of fibroblasts and smooth muscles
  - chemotactic for monocytes
  - competence factor that promotes the proliferative response of fibroblasts and smooth muscles upon concurrent stimulation with progression factors

- **Epidermal Growth Factor (EGF)**
  - promotes growth for fibroblasts, endothelial and epithelial cells
  - is a progression factor - promotes cell-cycle progression.

- **Fibroblast Growth Factor (FGF)**
  - promote synthesis of fibronectin and other extracellular matrix proteins
  - chemotactic for fibroblast and endothelial cells
  - promotes angiogenesis
  - links extracellular matrix components (collagen, proteoglycans) and macromolecules (fibrin, heparin) to cell-surface integrins.

- **Transforming Growth Factors (TGFs)**
  - TGF-α - similar to EGF
  - TGF-β - mitosis inhibitor that aids in modulating the repair process. May be responsible for hypertrophy by preventing cell division. Chemotactic for macrophages and fibroblasts

- **Macrophage-derived cytokines (IL-1 and TNF)**
  - promote proliferation of fibroblasts, smooth muscle and endothelial cells
VEGF is the most important growth factor in adult tissues undergoing physiologic angiogenesis (e.g., proliferating endometrium) as well as angiogenesis occurring in chronic inflammation, wound healing, tumors, and diabetic retinopathy.

**FIGURE 3–17** Interactions between Notch and VEGF during angiogenesis. VEGF stimulates delta-like ligand 4 (DLL4)/Notch, which inhibits VEGFR signaling. Compared with unperturbed angiogenesis, DLL4 blockade causes an increase in capillary sprouting and endothelial cell (EC) proliferation, creating vessels that are disorganized and have a small lumen size. VEGF blockade decreases capillary sprouting, and the proliferation and survival of ECs.

(Courtesy of Minhong Yan, Genentech, San Francisco, CA.)
HYPOXIA

• HIF-1 stabilization
• Secretion of pro-angiogenic factors
• Recruitment of CD14+ EPCs

(a)

↓ pO₂ ↓ pO₂

• Disruption of endothelial cell-cell adhesions
• Increased vascular permeability
• Extravasation of EPCs

(b)

↓ pO₂ ↓ pO₂

• Degradation of endothelial basement membrane
• Drilling of pre-capillary tunnels

(c)

• Creation of a pro-angiogenic microenvironment
• Sprouting angiogenesis into capillary-like tunnels

(d)

Key:  
- Endothelial cell
- Endothelial progenitor cell
- White blood cell
A key component of angiogenesis is the motility and directed migration of endothelial cells, required for the formation of new blood vessels. These processes are controlled by several classes of proteins, including:

1. integrins, especially αvβ3, which is critical for the formation and maintenance of newly formed blood vessels

2. matricellular proteins, including thrombospondin 1, SPARC, and tenascin C, which destabilize cell-matrix interactions and therefore promote angiogenesis

3. proteinases, such as the plasminogen activators and MMPs, which are important in tissue remodeling during endothelial invasion. Additionally, these proteinases cleave extracellular proteins, releasing matrix-bound growth factors such as VEGF and FGF-2 that stimulate angiogenesis. Proteinases can also release inhibitors such as endostatin, a small fragment of collagen that inhibits endothelial proliferation and angiogenesis. αVβ3 Integrin expression in endothelial cells is stimulated by hypoxia and has multiple effects on angiogenesis: it interacts with a metalloproteinase (MMP-2, discussed below), it binds to and regulates the activity of VEGFR-2, and it mediates adhesion to ECM components such as fibronectin, thrombospondin, and OPN.[72]
FIGURE 3–12 Main components of the extracellular matrix (ECM), including collagens, proteoglycans, and adhesive glycoproteins. Both epithelial and mesenchymal cells (e.g., fibroblasts) interact with ECM via integrins. Basement membranes and interstitial ECM have different architecture and general composition, although there is some overlap in their constituents. For the sake of simplification, many ECM components (e.g., elastin, fibrillin, hyaluronan, and syndecan) are not included.

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FIGURE 3–13 Mechanisms by which ECM components and growth factors interact and activate signaling pathways. Integrins bind ECM components and interact with the cytoskeleton at focal adhesion complexes (protein aggregates that include vinculin, α-actin, and talin). This can initiate the production of intracellular messengers or can directly mediate nuclear signals. Cell surface receptors for growth factors may activate signal transduction pathways that overlap with those activated by integrins. Signaling from ECM components and growth factors is integrated by the cell to produce various responses, including changes in cell proliferation, locomotion, and differentiation.

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FIGURE 3-14A Proteoglycans, glycosaminoglycans (GAGs), and hyaluronan. A, Regulation of FGF-2 activity by ECM and cellular proteoglycans. Heparan sulfate binds FGF-2 (basic FGF) secreted into the ECM. Syndecan is a cell surface proteoglycan with a transmembrane core protein, extracellular GAG side chains that can bind FGF-2, and a cytoplasmic tail that binds to the actin cytoskeleton. Syndecan side chains bind FGF-2 released by damage to the ECM and facilitate the interaction with cell surface receptors. B, Synthesis of hyaluronan at the inner surface of the plasma membrane. The molecule extends to the extracellular space, while still attached to hyaluronan synthase. C, Hyaluronan chains in the extracellular space are bound to the plasma membrane through the CD44 receptor. Multiple proteoglycans may attach to hyaluronan chains in the ECM.
Figure 3-16C Notch signaling and angiogenesis. A, The Notch receptor binds a ligand (a delta-like ligand, Dll, is shown in the figure) located in an adjacent cell, and undergoes two proteolytic cleavages (the first cleavage by ADAM protease, the second by δ-secretase), releasing a C-terminal fragment known as Notch intracellular domain (Notch-ICD). B, Notch signaling in endothelial cells during angiogenesis, triggered by the binding of the Dll4 ligand in a tip cell to a Notch receptor in a stalk cell. Notch-ICD migrates into the nucleus and activates the transcription of target genes. C, Sprouting angiogenesis, showing a migrating tip cell and stalk cells connected to the endothelial cells of the main vessel.
CUTANEOUS WOUND HEALING

Cutaneous wound healing is divided into three phases: inflammation, proliferation, and maturation (Fig. 3-18).

These phases overlap, and their separation is somewhat arbitrary, but they help to understand the sequence of events that take place in the healing of skin wounds. The initial injury causes platelet adhesion and aggregation and the formation of a clot in the surface of the wound, leading to inflammation.

In the proliferative phase there is formation of granulation tissue, proliferation and migration of connective tissue cells, and re-epithelialization of the wound surface. Maturation involves ECM deposition, tissue remodeling, and wound contraction.
Inflammation
- Clot formation
- Chemotaxis

Proliferation
- Re-epithelialization
- Angiogenesis and granulation tissue
- Provisional matrix

Maturation
- Collagen matrix
- Wound contraction

Days after wounding

FIGURE 3–20B Healing of skin ulcers. A, Pressure ulcer of the skin, commonly found in diabetic patients. The histologic slides show: B, a skin ulcer with a large gap between the edges of the lesion; C, a thin layer of epidermal re-epithelialization and extensive granulation tissue formation in the dermis; and D, continuing re-epithelialization of the epidermis and wound contraction.

(Courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)
FIGURE 3–20C Healing of skin ulcers. **A,** Pressure ulcer of the skin, commonly found in diabetic patients. The histologic slides show: **B,** a skin ulcer with a large gap between the edges of the lesion; **C,** a thin layer of epidermal re-epithelialization and extensive granulation tissue formation in the dermis; and **D,** continuing re-epithelialization of the epidermis and wound contraction.

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(Courtesy of Z. Argenyi, MD, University of Washington, Seattle, WA.)
Stages of Normal Cutaneous Wound Healing

- **Trauma**
- **Haemostasis**
- **Inflammation**
- **Cell Migration**
- **Cell Proliferation**
- **ECM Synthesis**
- **Granulation Tissue**
- **Angiogenesis**
- **Re-epithelialisation**
- **Remodelling**
- **Wound Closure**
- **Contraction**

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**Inflammation**
- Immune infiltration
- Debris clearance
- Neutrophil killing

**Proliferation**
- Fibroblast proliferation
- Scar formation
- Angiogenesis
- Proteoglycan
- Fibroblast
- Collagen

**Remodelling**
- Epithelialization
- ECM remodeling
- Scar maturation/contraction
- Apoptosis
- Epithelium
- Endothelium

**Hemostasis**
- Coagulation
- Platelets
- Fibers

**Wound Healing**
- Injury
- Hours
- Days
- Weeks
- Months
- Years
- Post-injury time

**Time (Days)**
- **Inflammation**
- **Proliferation**
- **Maturation**
- **Wound Contraction**
- **Collagen Accumulation**
Repair Process

• Removal of Debris
  ▪ begins early and initiated by liquefaction and removal of dead cells and other debris

• Formation of Granulation Tissues
  ▪ connective tissue consisting of capillaries and fibroblasts that fills the tissue defect created by removal of debris

• Scarring
  ▪ fibroblasts produce collagen until granulation tissue becomes less vascular and less cellular
  ▪ progressive contraction of the wound occurs, resulting in deformity of original structure
Factors that Impede Repair

• Retention of debris or foreign body
• Impaired circulation
• Persistent infection
• Metabolic disorders
  ▪ diabetes
• Dietary deficiency
  ▪ ascorbic acid
  ▪ protein
Healing and granulation

• Fibroplasia is a response to
  ▪ Damaged connective tissue
  ▪ Parenchymal damage exceeds regenerative capacity
• Hyperplasia of connective tissue
• Neovascularization
• Granulation
  ▪ coordinated proliferation of fibroblasts with a rich bed of capillaries
  ▪ intensely hyperemic with a roughened or granular, glistening surface
  ▪ healthy granulation tissue resists secondary infections
Healing by First Intention

- Clean, surgical incision or other clean narrow cut
- Focal disruption of epithelial basement membrane with little cell damage
- Regeneration dominates fibrosis
- Scabbing with fibrin-clotted blood
- Neutrophils migrate to edges
- Epidermis becomes mitotic and deposits ECM
- Macrophages replace neutrophils
- Vascularization and collagen deposition fills gap
- Contraction of collagen minimizes epidermal regeneration
Healing by Second Intention

- Larger area of tissue injury such as abscess, ulcer, infarction that destroys ECM
- Large clot or scab with fibrin and fibronectin fills gap
- Larger volume of necrotic debris must be removed by more neutrophils and macrophages
  - Opportunity for collateral damage by phagocytes
- Scar tissue formed from vascular cells, fibroblasts, and myofibroblasts
- Contraction of myofibroblasts distorts tissue
- More prone to infection
Debridement
Removal of injured tissue and debris:

Antimicrobial activity:

Chemotaxis and proliferation of fibroblasts and keratinocytes:

Angiogenesis:

Deposition and remodeling of ECM:

- Phagocytosis, collagenase, elastase
- Nitric acid, ROS
- PDGF, TGF-β, TNF, IL-1, KGF-7
- VEGF, FGF-2, PDGF
- TGF-β, PDGF, TNF, OPN, IL-1, collagenase, MMPs

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INJURY

Cellular and vascular response

Stimulus removed (acute injury)

- Parenchymal cell death (intact tissue framework)
- Superficial wounds
- Some inflammatory processes

*REGENERATION*
Restitution of normal structure

Examples:
- Liver regeneration after partial hepatectomy
- Superficial skin wounds
- Resorption of exudate in lobar pneumonia

*REPAIR*
Scar formation

Examples:
- Deep excisional wounds
- Myocardium infarction

*FIBROSIS*
Tissue scar

Examples:
- Chronic inflammatory diseases (cirrhosis, chronic pancreatitis, pulmonary fibrosis)

Persistent tissue damage
FIGURE 3–25 Development of fibrosis in chronic inflammation. The persistent stimulus of chronic inflammation activates macrophages and lymphocytes, leading to the production of growth factors and cytokines, which increase the synthesis of collagen. Deposition of collagen is enhanced by decreased activity of metalloproteinases.

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Keloid—excessive cutaneous fibrosis