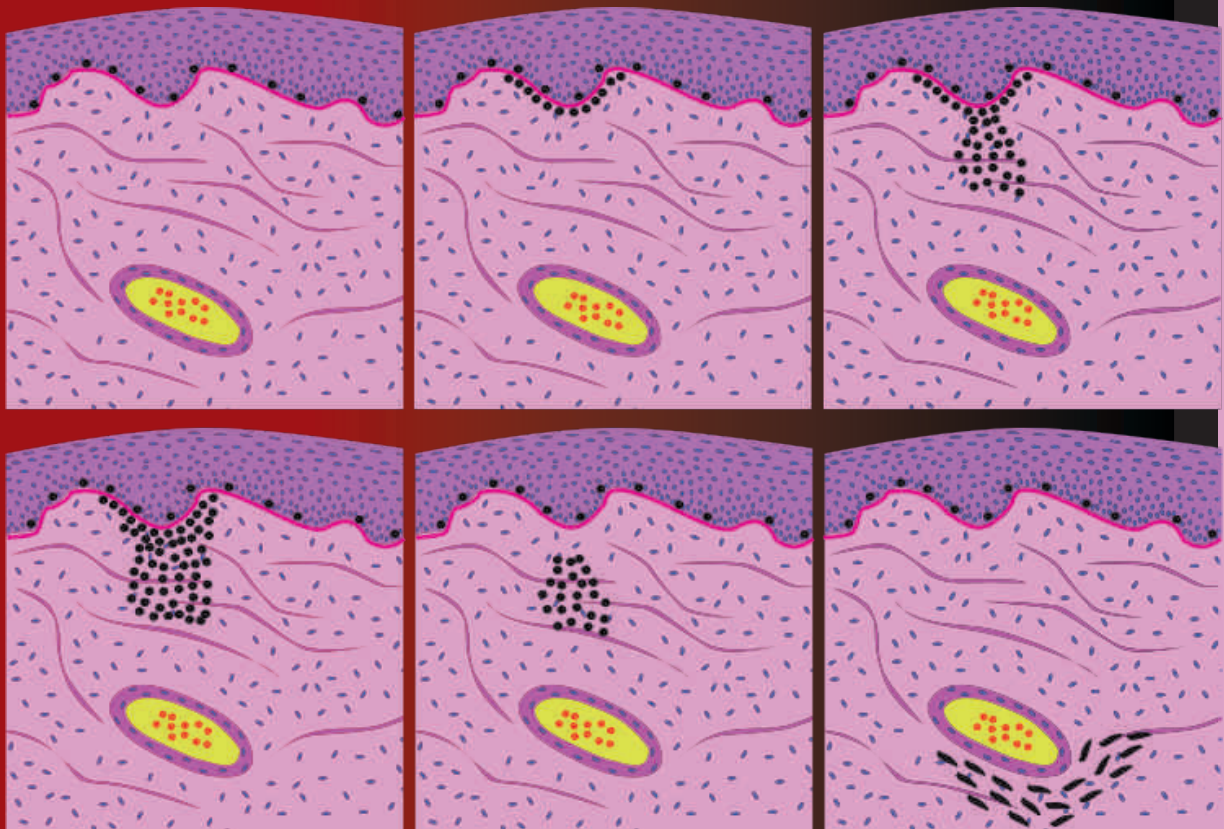


# General Pathology For Dental Students: A Concise Text



Adel M Abdel-Azim

Edition 1



# **General Pathology for Dental Students: A Concise Text**

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Medical knowledge is constantly changing. As new information become available, changes in treatment, procedures, equipment and the use of drugs become necessary. Readers are strongly recommended to follow up recent medical information.

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## **Preface**

The aim of this book is to offer an overview of aspects of pathology, with an emphasis on basic facts in general practice. Intended outcomes are that, having read this book, readers should be more aware of the immediate steps needed to make the diagnosis and arrange patient management.

The amount of knowledge that must be assimilated by the student of today makes it important to present the basic facts in as simple and concise a manner as possible. Each year more is added to the sum of knowledge whilst the available time to learn for examination purposes is not increased.

The material presented is somewhat comprehensive, but still concise. The highlights of the book are brief outlines summarizing the features of each disease. These summary statements serve as take-home messages and could only facilitate learning. Composite drawings of clinical signs and symptoms, summarizing the principal clinical findings in important diseases or their complications are yet another highlight. Structural writing makes the book easier to use and contribute to its esthetic appeal. The book has a clinical orientation and the pathology findings are frequently correlated with the clinical data. This is especially well done in the chapters dealing with general pathology.



## Course Description

This course has been designed to provide you with a practical approach to general and systemic pathology. The lectures and laboratories provide information and practice needed to develop an introductory level of proficiency in formulating differential diagnoses through the interpretation of gross and microscopic changes in various organs and their correlation with clinical, radiologic and laboratory tests.

Overall, the goals of the labs are to build your knowledge, skills and abilities in:

1. Developing a medical vocabulary in order to converse with other health professionals.
2. Synthesizing lecture material with clinical information, laboratory, and radiographic examinations of systemic diseases and their etiology, pathogenesis and prognosis.

Learning Objectives Upon completion of this course you will be able to:

1. Formulate an orderly differential diagnosis of possible causes for a patient's problem, including the correct etiology, plus the other most likely and pertinent etiologies.
2. Prioritize the list of possible causes in your differential diagnosis based on clinical history, physical examination findings, radiographs and laboratory work.
3. Suggest further medical tests to help distinguish between your different diagnostic choices.
4. Explain how this disease will affect your dental practices.
5. Describe the basic pathogenesis of various disease entities.
6. Recognize general medical terms utilized in pathology.

## **Recommended Text Books**

Kumar, V. (Ed.), Cotran, R. S., Robbins, S. L. (2007). Basic Pathology (8th ed.). Philadelphia, PA: W.B. Saunders. To enhance the meaning of the lectures, the student is expected to read the pertinent text material PRIOR to the lecture.

# 2 Acute and Chronic Inflammation

## *Chapter Overview*

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- 2.1 Definition
  - 2.2 Terminology
  - 2.3 Main Types of Inflammation
  - 2.4 Types of Inflammatory Cells
  - 2.5 Acute Inflammation
  - 2.6 Chronic Inflammation
  - 2.7 Mixed Acute & Chronic Inflammation
  - 2.8 Granulomatous Inflammation
- 

## **2.1 Definition**

Inflammation is the tissue reaction against injury or irritant. Inflammation is not a synonym for infection. Inflammation occurs only in living tissue.

## **2.2 Terminology**

Greek root + -itis

gingivitis, metritis, pulpitis, nephritis and son on .....

## 2.3 Main Types of Inflammation

Could be classified according to the severity, onset and duration into:

**Peracute:** Very rapid onset and fulminating

**Acute:** Rapid onset and of shorter duration

**Subacute:** Slower onset with longer duration than acute

**Chronic:** Slowest onset with protracted duration

It should be noted that each one can progress or regress into other types. The differences between acute and chronic inflammation are summarized in table (2.1)

**Table 2.1:** Differences between acute and chronic inflammation:

Differences between Acute and Chronic Inflammation		
Item	Acute	Chronic
Causative agent	Pathogens, injured tissues	Persistent inflammation due to non-degradable pathogens, persistent foreign bodies, or autoimmune reactions
Onset	Immediate	Delayed
Duration	Few days	Up to many months, or years
Major cells involved	Neutrophils, macrophages	lymphocytes, plasma cells, macrophages, fibroblasts
Primary mediators	Vasoactive amines (Histamine and serotonin)	IFN- $\gamma$ and other cytokines, growth factors, hydrolytic enzymes
Outcomes	Resolution, abscess formation, chronic inflammation	Tissue destruction, fibrosis, acute exacerbation

## 2.4 Types of Inflammatory Cells

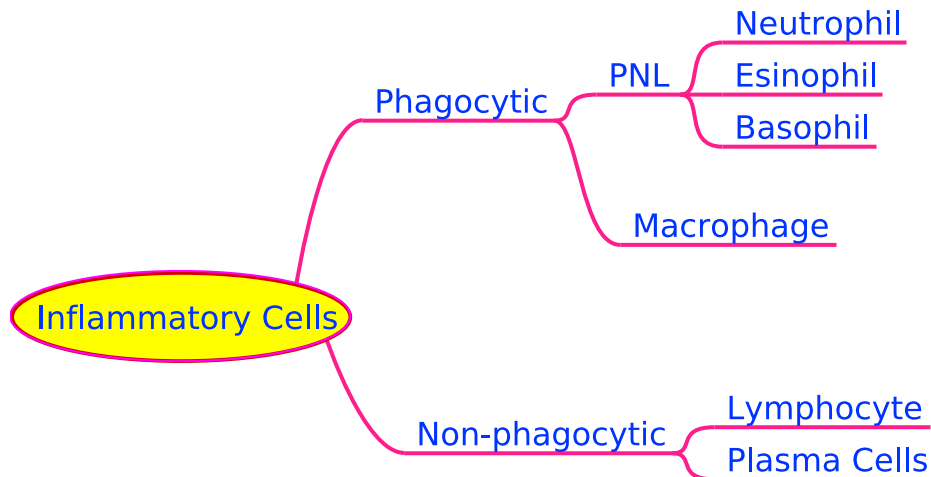
Inflammatory cells are classified based on the following basis, see also figure (2.1):

1. Presence of absence of microscopic cytoplasmic granules:
  - a) Granulocytes
    - ◆ Polymorph nuclear leukocytes (PNL)
      - i. Neutrophils
      - ii. Eosinophils
      - iii. Basophils
  - b) Agranulocytes
    - i. Monocytes (histiocytes, macrophages)
    - ii. Lymphocytes
    - iii. Plasma cells
2. Function (phagocytosis)
  - a) Phagocytic cells
    - i. Monocytes (histiocytes, macrophages)
    - ii. PNL (particularly neutrophils)
  - b) Non-phagocytic cells
    - i. Lymphocytes
    - ii. Plasma cells

## 2.5 Acute Inflammation

### 2.5.1 Definition

A rapid and transient response to injury or irritant

**Figure 2.1:** Types of Inflammatory Cells

## 2.5.2 Cardinal Signs of Inflammation

classical 5 symptoms (Celsus 1st c. B.C., Virchow 19th c. A.D.)

1. **calor** heat, resulting from vasodilation of blood vessels
2. **rubor** redness, resulting from vasodilation of blood vessels
3. **tumor** swelling, resulting from edema
4. **dolor** pain. resulting from local release of prostaglandin and kinins
5. **functio laesa** loss (or impairment) of function

## 2.5.3 Causes of Acute Inflammation

1. Infections (e.g., bacterial or viral infection)
2. Immune reactions (e.g., reaction to a bee sting)
3. Other stimuli
  - ◆ Tissue necrosis (e.g., acute myocardial infarction)
  - ◆ Trauma, radiation, burns, foreign body (e.g., glass, splinter)

### 2.5.4 Aims of Inflammation

- ◆ Is the inflammation beneficial?
- ◆ Yes, inflammation aims at elimination of the noxious agents and restoration of tissue integrity.
- ◆ But sometimes, one has to pay for this benefit. This payment may be represented in a form of residual scarring or other forms of inflammatory complications. Always remember that “nothing in life comes for free and that there are sacrifices that seem worthwhile”.
- ◆ Inflammation may be harmful as in hypersensitivity, rheumatoid arthritis, anaphylactic reaction and atherosclerosis.

### 2.5.5 Classification (Other Types of Inflammation)

#### Types of Inflammation Based on Exudate:

1. Suppurative (purulent) inflammation: pus
  - ◆ Localized proliferation of pus-forming organisms, such as *Staphylococcus aureus* (e.g., skin abscess).
  - ◆ *S. aureus* contains coagulase. which cleaves fibrinogen into fibrin and traps bacteria and neutrophils
  - ◆ Pyogenic bacteria, eg, staphylococci, streptococci, gramnegative bacilli, anaerobes.
2. Serous inflammation: effusion
  - ◆ Thin, watery exudate
  - ◆ Insufficient amount of fibrinogen to produce fibrin
  - ◆ Example blister in second-degree burns, viral pleuritis
3. Catarrhal inflammation (inflammation of mucous membranes)
  - ◆ Marked secretion of mucus.
  - ◆ Infections, e.g., common cold (rhinovirus); allergy (eg, hay fever).
4. Fibrinous inflammation: fibrinogen → fibrin

- ◆ Due to increased vessel permeability. with deposition of a fibrin-rich exudate
  - ◆ Often occurs on the serosal lining of the pericardium, peritoneum, or pleura
  - ◆ Danger of adhesions
  - ◆ Example fibrinous pericarditis
5. Pseudomembranous inflammation: surface necrosis
- ◆ Bacterial toxins damage mucosal lining, producing a membrane composed of necrotic tissue
  - ◆ Example pseudomembranes associated with *Corynebacterium diphtheriae* produces a toxin causing pseudomembrane formation in the pharynx and trachea.
6. Necrotizing inflammation:
- ◆ Marked tissue necrosis
  - ◆ Highly virulent organisms (bacterial, viral, fungal), eg, plague (*Yersinia pestis*), anthrax (*Bacillus anthracis*), mucormycosis.
7. Hemorrhagic inflammation:
- ◆ Destruction of blood vessel walls resulting in leakage of a large number of red blood cells resulting in the red coloration of inflammatory exudate.
  - ◆ Example Epidemic hemorrhagic fever, Leptospirosis and Plague.
8. Ulcerative inflammation:
- ◆ Necrosis on or near the surface leads to loss of tissue and creation of a local defect (ulcer)
  - ◆ Example Ulcerative colitis
9. Granulomatous inflammation:
- ◆ Is a distinct type of chronic inflammation characterized by formation of granuloma
  - ◆ Example TB, syphilis, actinomycosis and leprosy

### Types of Inflammation Based on Histological Features

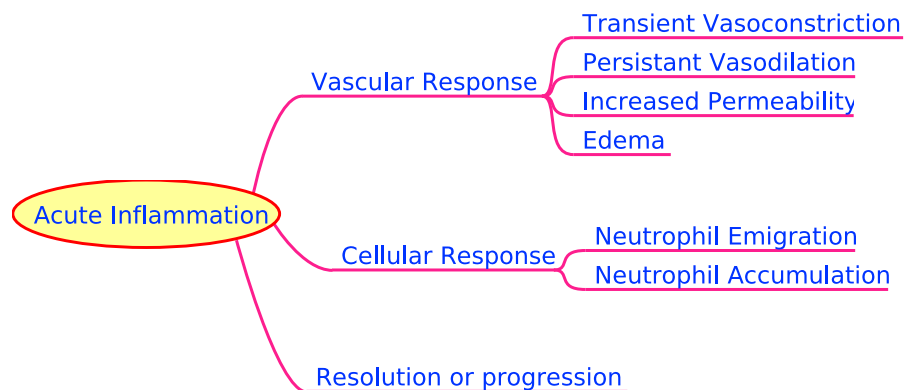
1. Nonspecific: Produce non-specific histologic picture
2. Specific: Produce a specific histologic picture that is peculiar to that type of infection e.g. TB.

### Types of Inflammation Based on Causative Agent

1. Aseptic (sterile) chemical substances, radiation
2. Septic (caused by living organisms)

## 2.5.6 Stages of Acute Inflammation

The process of acute inflammation occurs in stages (see figure (2.2)).



**Figure 2.2:** Stages of Acute Inflammation

These stages are summarized in the following paragraph.

1. Transient vasoconstriction
2. Persistent vasodilatation
3. Increased Permeability of vessel walls

4. Fluid exudate (edema), (the passage of a large amount of fluid from the circulation into the interstitial tissue producing swelling)
5. Cellular exudate (Neutrophil emigration & accumulation)
6. Resolution or progression

**Table 2.2:** Exudate Versus Transudate

Always Remember

- ◆ Exudation should be distinguished from transudation. Transudation (transudate) denotes increased passage of fluid into tissues through vessels of normal permeability. The force that causes outward passage of fluid from the microcirculation into the tissues is either increased hydrostatic pressure or decreased plasma colloid osmotic pressure. A transudate has a composition similar to that of an ultrafiltrate of plasma.
- ◆ On the other hand, Exudate is the passage of blood fluids into the interstitial tissue due to defective permeability of the vascular walls as in acute inflammation.



### Transient Vasoconstriction

Results from neurogenic reflex that lasts only seconds

### Persistent Vasodilatation and Stasis

- ◆ Histamine and other vasodilators (e.g., nitric oxide) relax vascular smooth muscle, causing initial increase in blood flow (*hyperemia*).
- ◆ As fluid is lost into the exudate (see below), *stasis* may supervene, with very sluggish blood flow due to increased vessel caliber and increased blood viscosity.
- ◆ The postcapillary venule is dilated and has swollen endothelial cells.
- ◆ Postcapillary venules generally show the greatest change.

### Increased Permeability of Vessel Walls

- ◆ Histamine and other mediators contract endothelial cells producing endothelial gaps.
- ◆ Tight junctions are simpler in venules than arterioles.
- ◆ A transudate (protein and cell-poor fluid) moves into the interstitial tissue.

### Fluid Exudate and Formation of Edema

- ◆ The passage of a large amount of fluid from the circulation into the interstitial tissue produces swelling (inflammatory *edema*).
- ◆ Increased passage of fluid out of the circulation because of increased vascular permeability is termed exudation.
- ◆ Exudation helps combat the offending agent by:
  1. diluting it
  2. causing increased lymphatic flow
  3. flooding the area with plasma, which contains numerous defensive proteins such as immunoglobulins and complement.
  4. Provides opsonins (IgG, C3b) to assist in phagocytosis

### Cellular Exudate (Neutrophil Emigration & Accumulation)

1. Types of Cells Involved
  - a) Acute inflammation is characterized by the active emigration of inflammatory cells from the blood into the area of injury.
  - b) Neutrophils (polymorphonuclear leukocytes) dominate the early phase (first 24 hours). After the first 24-48 hours, macrophage and immunologically active cells such as lymphocytes and plasma cells enter the area.
  - c) Neutrophils remain predominant for several days.
2. Margination

- a) Neutrophils are pushed from the central axial column to the periphery (margination)
  - b) RBCs aggregate into rouleaux ("stacks of coins") in venules.
3. Rolling
- a) Due to activation of selectin adhesion molecules on the surface of neutrophils and endothelial cells
  - b) Neutrophils loosely bind to selectins and "roll" along the endothelium.
4. Adhesion
- Adhesion molecules firmly bind neutrophils to endothelial cells.
5. Transmigration (diapedesis)
- a) Neutrophils dissolve the basement membrane and enter interstitial tissue.
  - b) Fluid rich in proteins and cells (i.e., exudate) accumulates in interstitial tissue.
6. Chemotaxis
- a) Neutrophils follow chemical gradients that lead to the infection site.
  - b) Chemotactic mediators bind to neutrophil receptors.
  - c) Mediators include C5a, LTB<sub>4</sub>, bacterial products, and interleukin.
  - d) Binding causes the release of calcium, which increases neutrophil motility.
7. Phagocytosis
- a) Multistep process, consisting of three steps
    - i. Opsonization
    - ii. Ingestion
    - iii. Killing
  - b) Opsonization
    - i. Opsonins attach to bacteria (or foreign bodies),

- A. Opsonins include IgG, C3b fragment of complement, and other proteins (e.g., C-reactive protein).
- B. Neutrophils have membrane receptors for IgG and C3b.
- ii. Opsonization enhances neutrophil recognition and attachment to bacteria.
- c) Ingestion
  - i. Neutrophils engulf (phagocytose) and then trap bacteria in phagocytic vacuoles.
  - ii. Primary lysosomes empty hydrolytic enzymes into phagocytic vacuoles producing phagolysosomes.
- d) Bacterial killing
  - i. O<sub>2</sub>-dependent myeloperoxidase (MPO) system
    - A. Production of superoxide free radicals (O<sub>2</sub><sup>-</sup>)
    - B. Production of peroxide (H<sub>2</sub>O<sub>2</sub>)
    - C. Production of bleach (HOCl)
    - D. Chronic granulomatous disease are examples of diseases that have a defect in the O<sub>2</sub>-dependent system.
  - ii. O<sub>2</sub>-independent system
    - A. Refers to bacterial killing from substances located in leukocyte granules
    - B. Examples lactoferrin (binds iron necessary for bacterial reproduction)

### **Resolution or progression**

In uncomplicated acute inflammation, tissue returns to normal in a process of resolution (Chapter Healing & Repair), in which the exudate and cellular debris are liquefied and removed by macrophages and lymphatic flow.

### 2.5.7 Chemical Mediators of Inflammation

1. They derive from plasma, leukocytes, local tissue, bacterial products.  
Example arachidonic acid mediators are released from membrane phospholipids in macrophages, endothelial cells, and platelets).
2. They have short half-lives (e.g., seconds to minutes).
3. They may have local and systemic effects.  
Example histamine may produce local signs of itching or systemic signs of anaphylaxis.
4. They have diverse functions:
  - a) Vasodilation; Examples histamine, nitric oxide.
  - b) Vasoconstriction; Example thromboxane.
  - c) Increase vessel permeability; Example histamine, bradykinin.
  - d) Produce pain; Example bradykinin
  - e) Produce fever; Examples IL-1, T N F
  - f) Chemotactic; Examples IL8

### 2.5.8 Factors Involved in the Termination of Acute Inflammation

Usually, when the causative agents are removed, inflammation resolves spontaneously due to the action of the following factors:

1. Short half-life of inflammatory mediators
2. Lipoxins
  - a) Anti-inflammatory mediators
  - b) Derive from arachidonic acid metabolites
  - c) Inhibit transmigration and chemotaxis
  - d) Signal macrophages to phagocytose apoptotic bodies
3. Resolvins
  - a) Synthesized from omega-3 fatty acids

- b) Inhibit production and recruitment of inflammatory cells to the site of inflammation
- 4. Clearance of neutrophils by apoptosis

### **2.5.9 Outcomes (Consequences) of acute inflammation**

1. Resolution The inflammatory exudate is reabsorbed and the tissue restored to normal, e.g. lobar pneumonia. This presumes that there has been minimum or no tissue destruction.
2. Healing by repair or regeneration where tissue has been destroyed, scar may be formed.
3. Progression into chronic inflammation.
4. Spread
  - a) Direct-e.g. cellulitis
  - b) Lymphaticlymphangitis progressing to acute lymphadenitis
  - c) Blood vessels
    - i. Pyaemia-spread of pyogenic organisms in infected micro-thrombi via the blood stream possibly giving rise to secondary (metastatic) abscesses
    - ii. Septicaemia-multiplication of organisms in the blood stream in the absence of adequate host defenses
5. Death resulting from
  - a) Toxemia, e.g. endotoxic shock and its complications
  - b) Involvement of vital organs, e.g. encephalitis, myocarditis

### **2.5.10 Systemic Manifestations of Inflammation**

#### **(General Responses To Inflammation)**

Occurs mainly in severe or prolonged inflammation:

1. Pyrexia (fever) resulting from the effects on the temperature regulation centre in the hypothalamus of a small molecular weight protein, endogenous pyrogen. Endogenous pyrogen is produced by polymorphs and cells of the mononuclear phagocyte system after they have been activated by:
  - a) Phagocytosis
  - b) Infective agents
  - c) Endotoxins
  - d) Pyrogenic steroids
  - e) Indirectly by immune-complexes

The endogenous pyrogen is then released into the circulation and acts on the hypothalamus. Body temperature rises as a consequence of heat conservation and increased production.

2. Negative nitrogen balance
3. Increased erythrocyte sedimentation rate
4. Anemia as a result of:
  - a) Blood loss from inflammatory lesions
  - b) Haemolysis
  - c) Toxic depression of the bone marrow
5. Leucocytosis:
  - a) Neutrophilia in
    - i. Pyogenic infections
    - ii. Tissue breakdown-myocardial infarction, mesenteric infarction
  - b) Eosinophilia in
    - i. Allergic disorders-hay fever, drug allergy
    - ii. Parasitic infestation-trichinosis, schistosomiasis, filariasis, hydatid disease, strongyloides
    - iii. Skin diseases-some cases of exfoliative dermatitis, dermatitis herpetiformis, pemphigus, eczema, psoriasis, scabies
    - iv. Pulmonary eosinophilia-Loeffler's syndrome (simple pulmonary eosinophilia), prolonged pulmonary eosinophilia, tropical eosinophilia

- v. Polyarteritis nodosa
- c) Lymphocytosis in
  - i. Chronic infection-tuberculosis, secondary syphilis, brucellosis, typhoid fever
  - ii. Viral infection-influenza, rubella, mumps, measles, chicken-pox, infectious mononucleosis
  - iii. Whooping-cough
  - iv. Acute infectious lymphocytosis
- d) Monocytosis in some cases of
  - i. Bacterial infections-tuberculosis, typhoid fever, brucellosis, sub-acute bacterial endocarditis
  - ii. Protozoal and rickettsial infections-malaria, leishmaniasis, trypanosomiasis, Rocky Mountain spotted fever
- 6. Reactive hyperplasia of the reticuloendothelial and lymphoid systems (especially with chronic inflammation)
  - a) Enlargement of regional lymph nodes
  - b) Hepatomegaly (and 'non-specific reactive hepatitis')
  - c) Splenomegaly
- 7. Degenerative changes in other organs as a result of persistent toxemia, e.g. fatty change and hydropic vacuolation in the liver
- 8. Constitutional symptoms-malaise, anorexia, headache, loss of weight, etc.

## 2.6 Chronic Inflammation

### 2.6.1 Definition

Is the persistence of inflammation with attempts of repair resulting from persistence of the injurious agent.

### 2.6.2 Causes

1. Persisting infection or prolonged exposure to irritants (intracellular surviving of agents e.g. TB)
2. Repeated acute inflammations (otitis, rhinitis)
3. Primary chronic inflammation low virulence, sterile inflammations (silicosis)
4. Autoimmune reactions (rheumatoid arthritis, glomerulonephritis, multiple sclerosis)

### 2.6.3 Mechanisms

The injurious agent may persist because:

1. There is a defective acute inflammatory response
  - a) Poor blood supply
  - b) Poor general nutrition
  - c) Abnormal neutrophil function
  - d) Anti-inflammatory drugs, especially corticosteroids
2. The agent is resistant to phagocytosis and/or intracellular destruction
  - a) Intracellular infectious agents, e.g. tuberculosis, salmonellosis, brucellosis, viral infections
  - b) Foreign-body reactions. These act as a nidus for persistent infection or as tissue irritants which directly provoke a chronic inflammatory reaction. Such irritants can be divided into: a. Endogenous, e.g. necrotic adipose tissue, cholesterol crystals, uric acid crystals in gout b. Exogenous, e.g. suture material, metallic fragments, silica, asbestos fibers
3. The provoking agent is a body constituent as in:
  - a) Auto-immune diseases, e.g. diffuse lymphocytic thyroiditis (Hashimoto's disease), auto-immune atrophic gastritis, adrenal atrophy, etc.
  - b) Reactions to altered self-antigens, e.g. contact dermatitis to rubber, nickel, etc.

### 2.6.4 Classification

1. Clinical
  - a) Following acute inflammation, e.g. chronic osteomyelitis
  - b) Arising de novo, e.g. brucellosis, tuberculosis
2. Histological
  - a) Specific having a reproducible histological pattern, e.g. tuberculosis, syphilis, leprosy
  - b) Non-specific showing only the general features of inflammation, e.g. chronic pulpitis, chronic cholecystitis, chronic pyelonephritis

### 2.6.5 General Features

1. Continuing some features of acute inflammation
  - a) Polymorph infiltration
  - b) Fibrinous exudation
  - c) Increased vascularity
2. Features of healing-repair and/or regeneration (formation of granulation tissue)
3. Infiltration by chronic inflammatory cells
  - a) Lymphocytes
  - b) Plasma cells
  - c) Macrophages
  - d) Eosinophils

### 2.6.6 Cells of Chronic Inflammation

#### A. Lymphocytes and plasma cells

Small lymphocytes can be divided into two reactive populations

1. T-lymphocytes which are thymus dependent and are responsible for cell-mediated immunity
2. B-lymphocytes which are responsible for antibody mediated (humoral) immunity

On contact with the appropriate antigen both types of lymphocyte, if already primed or sensitized, will undergo blast cell transformation. B-cells develop into plasma cells which then produce the corresponding antibody, and T-cells produce soluble factors, lymphokines, which are important in the mediation of chronic inflammation. There is co-operation between T-cells and macrophages in the recognition, concentration and processing of antigen prior to a B-cell response.

A third population of lymphocytes does not give conventional results in tests for T and B cells and these cells have been designated 'null cells'. This population also includes cells capable of antibody dependent cytotoxicity (K cells) and natural killer cells (NK cells) which spontaneously destroy tumor cells in vitro.

**1T-lymphocyte sub-populations** In the normal individual about 75% of the peripheral blood lymphocytes are T-cells. About 2/3 of these belong to the helper/inducer subset, and the other 1/3 are of the cytotoxic or suppressor type.

For normal development T-lymphocytes require a period of maturation in the thymus. Precursor cells originating in the bone marrow arrive in the thymus pass through three maturation stages before appearing in the peripheral blood as small lymphocytes.

**2Lymphokines** These are soluble products of varying molecular weight secreted by sensitized T-cells when they react with antigen. They function as an amplification system in the cellular immune response and have the following actions:

1. Recruitment of macrophages
  - a) Monocyte Chemotactic factor attracts monocytes out of the circulation to the site of chronic inflammation

- b) Macrophage Migration Inhibition Factor retains monocytes/macrophages at the inflammatory site
  - c) Macrophage Activation Factors enhance the phagocytosis and killing of bacteria
  - d) Macrophage Arming Factors enhance the cells cytotoxic effects
  - e) Lymphokines augment macrophage secretion of complement components and prostaglandins
2. Recruitment of other lymphocytes
    - a) Lymphocyte Mitogenic Factor stimulates other noncommitted lymphocytes to produce lymphokines at the inflammatory site
    - b) Lymphocyte potentiators augment the reaction of other sensitized lymphocytes to specific antigens
  3. Production of interferon In addition to the synthesis of interferon by lymphocytes as a direct response to viral stimulation, a lymphokine is released which enhances macrophage production of interferon.

**3. B-cell stimulation** Certain antigens are capable of directly stimulating B-lymphocytes to undergo blast transformation. Such antigens, for example bacterial lipo-polysaccharides, are termed T-independent antigens. The majority of antigens, however, require co-operation between macrophages, T and B lymphocytes to produce a response (T-dependent antigens). One possible mode of co-operation is that macrophages phagocytose antigen and present it to helper T-cells by direct cell-to-cell interaction. Such interaction is controlled by the major histocompatibility genes. Processed antigen on the T-cell surface is then presented to the B-cell by antigen bridging, and this induces B-cell transformation.

Alternatively, a factor may be secreted by sensitized helper lymphocytes following their interaction with macrophages which induces a reaction in B-lymphocytes.

#### **4. Role of antibodies in chronic inflammation**

1. Antigen binding followed by complement activation

2. Bacterial agglutination
3. Opsonization of bacteria or foreign cells via Fc binding of phagocytic cells
4. Neutralization of toxins and virus infectivity

## **B. Macrophages**

Although monocyte emigration is a feature of the later stages of acute inflammation, their accumulation in chronic inflammation is frequently conspicuous and they may constitute the predominant cell type. When macrophages are the dominant cell, and in particular when they are found in circumscribed aggregates, the inflammatory reaction is termed granulomatous. The aggregates themselves are termed granulomas. Granulomas with a high turnover of cells recruit macrophages from the circulating monocyte pool. The demands of low-turnover granulomas can be met by proliferation of local tissue macrophages.

### **The mononuclear phagocytic system**

- ◆ A system composed of macrophages and their precursors
- ◆ Osteoclasts and other multinucleated giant cells are derived from this system

## **2. Functions of the macrophage**

1. Phagocytosis
  - a) Ingestion and destruction of bacteria (particularly after a lymphokine response)
  - b) Removal of effete cells or necrotic cell debris
  - c) Storage of irritant substances, e.g. carbon particles
2. Antigen handling
  - a) Uptake and processing of antigen with production of fragments (? coupled with RNA) which are stimulatory for helper lymphocytes
  - b) Direct cell-to-cell binding with specifically sensitized T-lymphocytes

### 3. Enzyme production

- a) Neutral proteases Collagenase Elastase Plasminogen activator Angiotensin convertase
- b) Acid hydrolases Lipases Acid proteases Ribonucleases Phosphatases Glycosidases Sulphatases
- c) Lysozyme (anti-bacterial activity)

### 4. Synthesis

- a) Complement components
- b) Arachidonic acid metabolites Prostaglandins Thromboxane Leukotrienes
- c) Binding proteins Fibronectin Transferrin Transcobalamin
- d) Endogenous pyrogens
- e) Enzyme inhibitors Plasmin inhibitors  $\alpha_2$ -macroglobulin

### 5. Growth promoting factors for

- a) Lymphocytes
- b) Fibroblasts
- c) Endothelial cells
- d) Erythroid and myeloid precursors

### 6. Production of interferon

## 3. Special forms of macrophage

1. Epithelioid cells-enlarged macrophages with finely granular eosinophilic cytoplasm found in tuberculosis, sarcoidosis, Crohn's granulomas, etc.
2. Siderophages-macrophages laden with hemosiderin and found in: a. Areas of hemorrhage b. Chronic venous congestion of the lung (heart failure cells') c. Hemosiderosis
3. Melanophages-melanin-laden macrophages found in the interstices of a malignant melanoma, pigmented nevus, etc.
4. Lipophages-macrophages with 'ground-glass' cytoplasm after phagocytosis of: a. Altered fat, e.g. in traumatic fat necrosis b. Cholesterol, e.g. in atherosclerosis, cholesterosis of the gall-bladder, etc.

5. Muciphages-macrophages which have ingested mucin following its release from damaged epithelium, e.g. in the lamina propria of the large intestine after an episode of inflammatory bowel disease

#### 4. Giant cells

- ◆ In some circumstances macrophages fuse and give rise to multinucleated giant-cells
- ◆ Examples are:
  1. Specific infections
    - a) Tuberculosis (Langhans giant cells)
    - b) Syphilis
    - c) Fungal infections
  2. Foreign body reactions
  3. Lipid phagocytosis (Touton giant-cells) in xanthogranuloma, fibro-histiocytoma, etc.
  4. Collagen diseases
    - a) Rheumatic fever (Aschoff giant-cells)
    - b) Rheumatoid nodules
    - c) Giant-cell arteritis
  5. Granulomatous diseases of unknown aetiology
    - a) Sarcoidosis
    - b) Crohn's disease
    - c) Wegener's granulomatosis

#### C. Eosinophils

Whilst eosinophils are seen in certain acute inflammatory responses such as atopic hypersensitivity reactions, they are more characteristic of chronic inflammation. They are poorly phagocytic cells whose granules have a high content of an arginine-

rich cationic protein in addition to the usual granulocyte enzymes. They possess receptors for IgG, C3b and C3d.

### **1 Functions (possible)**

1. Neutralization of leukotrienes
2. Inhibition of histamine release from mast cells via the cyclic AMP system, probably by production of E, and E2 prostaglandins
3. Production of enzymes capable of killing helminths
4. Killing of antibody-coated cells

### **2 Chemotaxis and Eosinophils**

- ◆ Eosinophils respond to the same chemotactic factors as neutrophil polymorphs with the following important additions:
  1. Eosinophil chemotactic factor of anaphylaxis (ECF-A) released from sensitized tissues on exposure to antigen
  2. A specific eosinophil chemotactic factor produced by sensitized T-lymphocytes on exposure to antigen
  3. A pre-formed factor released from mast-cell granules (ECG-M) which may be identical with ECG-A
  4. A complement dependent factor found in guinea-pig serum, ECG-C

### **D. Basophils**

Basophils are the least common of the granulocytes, representing about 0.01% to 0.3% of circulating leukocytes (white blood cells).

They contain large cytoplasmic granules which obscure the cell nucleus under the microscope.

### **Functions (possible)**

- ◆ Releases histamine, proteoglycans (e.g. heparin and chondroitin), and proteolytic enzymes (e.g. elastase and lysophospholipase).
- ◆ They also secrete leukotrienes, and several cytokines.
- ◆ Basopenia (a low basophil count) is difficult to demonstrate as the normal basophil count is so low; it has been reported in association with autoimmune urticaria (a chronic itching condition).
- ◆ Basophilia is also uncommon but may be seen in some forms of leukaemia or lymphoma.

## 2.7 Mixed Acute & Chronic Inflammation

Features of both types of inflammation may coexist in certain circumstances, as in chronic suppurative inflammation and recurring acute inflammation. Two examples will follow:

### 2.7.1 Chronic Suppurative Inflammation

- ◆ It is difficult to remove the large amounts of pus associated with chronic suppurative inflammation. Infectious agents in pus are basically inaccessible to the actions of antimicrobial drugs and host defense mechanisms because the pus material is avascular.
- ◆ The surrounding viable tissue responds with a longstanding inflammatory process in which areas of suppuration (liquefied necrotic tissue and neutrophils) alternate with areas of chronic inflammation (lymphocytes, plasma cells, macrophages) and fibrosis. Such a pattern occurs in chronic suppurative osteomyelitis and pyelonephritis.
- ◆ If the area of suppuration localizes to an abscess that remains over a long period, a fibrous wall of increasing thickness forms. The difference between an acute and a chronic abscess lies in the thickness of the fibrous wall; both forms are filled with pus.

### 2.7.2 Recurrent Acute Inflammation

- ◆ Repeated attacks of acute inflammation may occur if there is a predisposing cause, eg, in the gallbladder when there are gallstones.
- ◆ Each attack of acute inflammation is followed by incomplete resolution that leads to a progressively increasing number of chronic inflammatory cells and fibrosis.
- ◆ Depending on the time of examination, the picture may be mainly that of chronic inflammation or of acute superimposed on chronic inflammation.
- ◆ The terms subacute inflammation and acute-on-chronic inflammation are also used to denote this pattern.

## 2.8 Granulomatous Inflammation

### 2.8.1 Definition

- ◆ Granulomatous inflammation is a distinct pattern of chronic inflammation characterized by formation of granulation tissue.
- ◆ It is a protective response to chronic infection or foreign material, preventing dissemination and restricting inflammation.
- ◆ Some autoimmune diseases such as rheumatoid arthritis and Crohn's disease are also associated with granulomas.

### 2.8.2 What is a Granuloma

Basically, a granuloma is a localized mass of granulation tissue with aggregations of chronic inflammatory cells.

### 2.8.3 Causes of Granulomatous Inflammation

- ◆ Bacteria: Tuberculosis, Leprosy, Syphilis, Actinomycosis

- ◆ Parasites: Schistosomiasis
- ◆ Fungi: Histoplasmosis, Blastomycosis
- ◆ Foreign body Granulomas
  - \* Endogenous ( keratin, necrotic bone or adipose tissue uric acid crystals)
  - \* Exogenous (wood, silica, asbestos, silicone, suture)
- ◆ Unknown cause such as sarcoidosis

#### **2.8.4 Mechanism of Granuloma Formation**

The classic example for the immune granuloma is that caused by the bacillus of tuberculosis. In this disease, the granuloma is referred to as a tubercle and is classically characterized by the presence of central caseous necrosis. Caseating necrosis is rare in other granulomatous diseases.

There are many atypical presentations that it is always necessary to identify the specific etiologic agent by: special stains for organisms (acid-fast stains for tubercle bacilli), culture methods (tuberculosis, fungal disease), and serologic studies (syphilis). In sarcoidosis, the etiologic agent is unknown.

Granuloma: bacilli are inhaled by droplets

↓

Bacteria are phagocytosed by alveolar macrophages. Macrophages fail to digest the phagocytosed bacteria and accumulate at the site of injury.

↓

A localized inflammatory response recruits more mononuclear cells

↓

The granuloma consists of a kernel of infected macrophages surrounded by foamy macrophages and a ring of lymphocytes and a fibrous cuff.

↓

The granuloma may caseates, ruptures and spills into the airway



# 3 Healing and Repair

## *Chapter Overview*

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- 3.1 Definitions
  - 3.2 Major Causes of Tissue Destruction
  - 3.3 Regeneration
  - 3.4 Repair
  - 3.5 Wound Healing
- 

### 3.1 Definitions

Healing is the replacement of destroyed or lost tissue by viable tissue. Healing is achieved in two ways:

1. **Regeneration:** Is the replacement of the damaged tissue by the same tissue type as was originally there.
2. **Repair:** The proliferation and migration of connective tissue cells leading to fibrosis and scar formation.

Most organs will heal using a mixture of both mechanisms.

### 3.2 Major Causes of Tissue Destruction

1. Loss of blood supply (ischemic) necrosis

2. Inflammatory agents
  - a) By direct physical or toxic effects
  - b) Indirectly as a result of the host response
3. Traumatic excision
  - a) Accidental
  - b) Surgical
4. Radiotherapy

### 3.3 Regeneration

The capacity of damaged tissue to respond by regeneration varies considerably. Tissues can be allocated to one of three categories, see table (3.1):

1. Labile cells (*intermitotic*) which continue to proliferate throughout life, e.g. epidermis, lining epithelia, endothelium, connective tissue, haemopoietic tissue, endothelial cells
2. Stable cells (*reversibly postmitotic*) which retain the capacity to regenerate and occasionally exhibit mitoses by virtue of normal cell-turnover, e.g. , liver, renal tubular epithelium, smooth muscle
3. Permanent cells (*irreversibly postmitotic*) which cannot reproduce themselves after attaining maturity, e.g. neurones of the C.N.S., sensory organs, renal glomeruli, striated muscle, adrenal medulla.

Labile tissues heal by regeneration with little or no repair. Permanent tissues are incapable of regeneration and heal entirely by repair. Most organs show evidence of both processes.

#### 3.3.1 Control of Regeneration

Regeneration appears to be controlled by stimulatory and inhibitory factors. Stimulation is a two-stage process:

**Table 3.1:** Classification of Cells on the Basis of Their Regenerative Capacity

Cell Types	Mitotic Capacity	Examples
Labile (intermitotic)	Short $G_0$ phase; almost always in mitotic cell cycle	Hematopoietic stem cells Basal cells of epithelium Hair follicle cells
Stable (reversibly postmitotic)	Long $G_0$ phase; can divide actively when stimulated	Osteoblast Chondrocyte Fibroblast Endothelial cell Liver
Permanent (irreversibly postmitotic)	None (cannot divide)	Neurons Ganglion cells Cardiac muscle <sup>1</sup> Skeletal muscle <sup>1</sup>

<sup>1</sup>Cardiac and skeletal muscle cells demonstrate limited mitotic capability in experimental settings. In humans, they are functionally permanent cells.

1. **Initiation.** Cells in growth arrested phase ( $G_0$ ) are primed for progression to cell division. Initiation is brought about by tissue-specific growth factors such as Epidermal Growth Factor (EGF) and Platelet Derived Growth Factor (PDGF).
2. **Potentiation** by general (non-specific) growth factors such as insulin, hydrocortisone, and growth-hormone. These potentiators stimulate cells which have already been primed by the appropriate initiator to enter S phase.

### 3.3.2 Cell cycle

Phases of the cell cycle

1.  $G_0$  phase  
Resting phase of stable parenchymal cells
2.  $G_1$  phase

Synthesis of RNA, protein, organelles, and cyclin D

3. S (synthesis) phase

Synthesis of DNA, RNA, protein

4. G<sub>2</sub> phase

Synthesis of tubulin, which is necessary for formation of the mitotic spindle

5. M (mitotic) phase

Two daughter cells are produced.

## 3.4 Repair

Before discussing the nature of repair, it is necessary to appreciate the role of the fibroblast in the biosynthesis of proteoglycans and collagen.

### 3.4.1 Biosynthesis of proteoglycans

The proteoglycans or “ground substance” of connective tissues are, as their name implies, macromolecules composed of a protein core to which carbohydrate is attached. The carbohydrate moieties take the form of long linear polysaccharides which are attached radially around the protein molecule. They can be divided into sulphated and non-sulphated types:

**Sulphated:**

Heparan sulphate, Keratan sulphate, Chondroitin sulphates A, B, and C

**Non-sulphated:**

Hyaluronic acid Chondroitin

The protein moiety is synthesis ed in the rough ER of the fibroblast and to this core the hexose sugars are sequentially added to form the polysaccharide attachments. Sulphation follows as a separate step.

### 3.4.2 Biosynthesis of collagen

Collagen is the most abundant protein in the body and forms the major structural component of many organs. Collagen molecules consist of three polypeptide chains arranged in a triple helix and whilst the basic polypeptide structure is straightforward, the molecule undergoes a complex series of post-translational modifications and interactions with proteoglycans which greatly modifies its properties.

### 3.4.3 Types of collagen

There are seven types of collagen chain and these have been designated  $\alpha 1$  (I-V) and  $\alpha 2$  (1) and (11). They are combined to form at least five isotypes of collagen:

Type 1 : bone, tendon, skin, fascia, cornea

Type 2 : cartilage ( including hyaline ), vitreous body

Type 3 ( reticulin ) : skin, blood vessel, uterous, granualtion tissue

Type 4 : basement membrane or basal lamina

Type 5: cells surfaces, hair and placenta

Mnemonic: Collegen "types" go from hard to soft.

Type I = bone, type II = cartilage, type III (in addition to type I) = skin, type IV = basement membrane.

### 3.4.4 Induction of Repair

Injury to tissues is followed by a complex series of reactions embracing the coagulation, complement and kinin systems. In addition the attachment of platelets to exposed collagen is followed by release of platelet-derived growth factor from

their granules. This factor initiates fibroblast replication which is the predominant feature of early repair. Repair involves two overlapping processes:

1. Organization
2. Progressive fibrosis

### 1. Organization

- ◆ This is the replacement of dead tissue or hematoma by granulation tissue.
- ◆ Organization is seen in:
  1. Hematomas in wound and fracture healing
  2. Thrombi
  3. Infarcts
  4. Fibrinous exudates

#### **Granulation tissue:**

1. Demolition. Monocytes migrate into the area, take on the properties of macrophages, and phagocytose cell debris, fibrin and red blood cells. Clearance of dead tissue is facilitated by the secretion of proteolytic enzymes by macrophages (e.g. collagenase, elastase) and other secretory products are important in promoting repair, e.g. fibronectin
2. Fibroblast activity. Local resting fibroblasts (fibrocytes) proliferate rapidly and migrate into the area where they continue to divide and commence synthetic activity. Initially the activated fibroblasts produce proteoglycans but as they mature switch over to collagen synthesis. At the same time, some fibroblasts develop bundles of microfilaments in their cytoplasm and acquire contractile properties. Such modified fibroblasts are termed myofibroblasts.
3. Ingrowth of capillaries. Endothelial cells in the severed blood vessels of surrounding viable tissue undergo rapid proliferation and grow into the area as solid cords. These endothelial 'buds':

- a) Link up to form arcades
- b) Canalize. This occurs within hours of formation
- c) Become freely permeable to plasma, RBCs, leukocytes and platelets
- d) Differentiate into arterioles and venules

## 2. Progressive fibrosis

- ◆ Continued accumulation of intercellular collagen and diminution of vascularity and cellularity
  1. Collagen re-orientation along lines of stress-remodeling
  2. Diminished cellularity
  3. Formation of an avascular, hypocellular scar
- ◆ Further changes in scars:
  1. Cicatrization -a late diminution in size resulting in deformity
  2. Calcification
  3. Ossification

## 3.4.5 Cell-Matrix Interactions

Whilst it has long been appreciated that certain cells require to be attached to a substrate before they can proliferate normally, it has only recently been established that such attachment is brought about by a series of specific binding proteins. These proteins are particularly important in the proliferation of connective tissue cells:

1. Fibronectin attaches fibroblasts to collagen
2. Chondronectin binds chondrocytes to Type II collagen, the matrix of cartilage
3. Laminin binds epithelial cells to the Type IV collagen of basement membranes

4. Osteonectin binds hydroxy-apatite and calcium ions to Type I collagen (bone matrix) and initiates mineralization

## 3.5 Wound Healing

In considering the healing of a skin wound two types are usually distinguished:

1. A clean wound with closely apposed margins-an incised wound (healing by first intention)
2. An open or excised wound (healing by second intention).

There are no fundamental differences between these two types, they merely differ in the degree to which the various stages apply (healing by second intention).

### 3.5.1 Stages in wound healing

1. Escape of blood and exudate
2. Acute inflammatory response at the margins
3. Hardening of the surface forming a scab
4. Demolition by macrophages with phagocytosis of cellular debris and removal of dead tissue. In addition macrophages secrete products which are important in the early stages of repair such as prostaglandins and fibronectin.
5. Organization:
  - a) Platelet derived growth factor initiates fibroblastic proliferation
  - b) Activated fibroblasts secrete proteoglycans and fibronectin
  - c) Fibroblasts produce Type III collagen (reticulin) fibers and migrate along this "scaffold".
  - d) Fibronectin-mediated attachment of fibroblasts to collagen is followed by enhanced proliferation
  - e) Simultaneous proliferation and migration of endothelial cells

6. Epidermal proliferation. By mitotic activity and migration, epidermal cells grow in from the margins and undermine the surface scab. When they meet in the centre of the wound, mitosis and migration cease presumably as a result of some cell-to-cell signal. This phenomenon is known as “contact inhibition”.
7. Contraction of the wound an early diminution in size brought about by the inward movement of the skin margins which greatly reduces the volume of repair tissue required for healing. Myofibroblasts are thought to be responsible for wound contraction, and the same cells provide the tensile strength of the wound at this stage
8. Progressive increase in collagen fibers
9. Loss of vascularity and shrinkage of the scar

### 3.5.2 Healing by First Intention:

- ◆ Occurs in small wounds that close easily.
- ◆ Epithelial regeneration predominates over fibrosis
- ◆ Healing is fast, with minimal scarring/infection
- ◆ Examples:
  - \* Paper cuts
  - \* Well-approximated surgical incisions
  - \* Replaced periodontal flaps

### 3.5.3 Healing by second Intention:

There is a substantial loss of tissue in the wound requiring formation of large quantity of granulation tissue with subsequent scar formation

The healing of an excised wound differs from that of an incised wound in that there is:

1. Greater tissue loss

2. More inflammatory exudate and necrotic tissue to remove
3. Wound contraction is necessary
4. More granulation tissue is required, a bigger scar is formed and this may result in deformity
5. Slower process
6. Increased liability to infection

**Key Facts For Healing by Second Intention:**

- ◆ Occurs in larger wounds that have gaps between wound margins
- ◆ Fibrosis predominates over epithelial regeneration
- ◆ Healing is slower, with more inflammation and granulation tissue formation, and more scarring
- ◆ Examples: large burns and ulcers, extraction sockets, external-bevel gingivectomies

### 3.5.4 Factors influencing wound healing

#### Local factors adversely affecting healing

1. Type of wounding agent; blunt, crushing, tearing etc.
2. Infection
3. Foreign bodies in wound
4. Poor blood supply
5. Excessive movement
6. Poor apposition of margins, e.g. large hematoma formation
7. Poor wound contraction due to tissue tethering, e.g. skin over tibia
8. Infiltration by tumor
9. Previous irradiation

**General factors adversely affecting healing**

1. Poor nutrition
  - a) Deficiency of protein. This results in a lack of the sulfur-containing amino acids methionine and cysteine which are essential for the synthesis of collagen
  - b) Lack of ascorbic acid (vitamin C) results in abnormal granulation tissue and deficient collagen production
  - c) Zinc deficiency
2. Excessive glucocorticosteroid production or administration
3. Fall in temperature
4. Jaundice

**3.5.5 Factors accelerating wound healing**

1. Ultraviolet light
2. Administration of anabolic steroids, deoxycorticosterone acetate, and growth hormone
3. Rise in temperature
4. Hyperbaric oxygen

**3.5.6 Complications of wound healing**

1. Wound rupture
2. Infection
3. Implantation of epidermal cells giving rise to keratin-filled epidermoid cyst
4. Weak scars with possible development of incisional hernia
5. Cicatrization and deformity
6. Keloid formation: The production of an elevated scar by excessive fibrosis

7. Proud flesh: The swollen flesh that surrounds a healing wound, caused by excessive granulation tissue. May result from persistence of foreign bodies or contamination with some bacteria or fungi.
8. Malignant change. The development of squamous carcinoma in old healed incisions is a recognized but rare complication

### 3.5.7 Healing of Fractures

Steps in the healing of a fractured long bone are:

1. Hemorrhage: This is due to torn blood vessels.
2. Hematoma formation
3. Transient inflammatory reaction: This is due to damage of the cells. This reaction should subside within few days otherwise complications will result
4. Organization of the clot: In which granulation tissue will begin to invade the clot
5. Osteoclastic activity: To remove the sharp edges and bone debris, this action is responsible for widening of the fracture line after 2 weeks of the trauma.
6. Osteoid tissue formation: In which undifferentiated mesenchymal cells differentiate into osteoblasts. Osteoblasts begin to lay down the special bone matrix named osteoid which consists of a ground substance and a special type of collagen, collagen type I.
7. Calcification of osteoid: Once osteoid tissue is calcified it is termed callus. Callus consists of woven bone.
8. Remodeling: In which callus is resorbed and replaced by lamellar bone.

### 3.5.8 Healing of tooth socket

Healing of tooth socket is considered as a healing by second intention. The steps of healing will be as follows:

1. Following extraction of a tooth, the socket fills with extravasated blood which then colts
2. The blood clot is organized to form granulation tissue
3. Transient inflammatory reaction which should subside within few days otherwise complications will result
4. Osteoclastic resorption of the crestal bone and small specules of bone detached during extraction commences at this time
5. Gingival epithelial proliferation and migration occurs across the defect. Epithelial continuity is restored 10-14 days after extraction
6. Osteoblasts begin to appear in the granulation tissue toward the base of the socket and the granulation tissue is gradually replaced by woven bone
7. After approximately 6 weeks, the outline of the socket can be viewed both histologically and radiographically
8. Woven bone is remodeled with the formation of cortical and cancellous bone and disappearance of the lamina dura. Remodeling also includes a reduction in the height of the alveolar bone in the area of the extraction
9. Radiographically, the socket is generally obliterated between 20 and 30 weeks after extraction.

### **3.5.9 Complications of fracture healing**

1. Delayed union
2. Mal-union
  - a) Angulation
  - b) Shortening
3. Fibrous union resulting from
  - a) Excessive movement which may lead to the development of a false joint (pseudoarthrosis)
  - b) Infection which may also give rise to osteomyelitis
  - c) Ischemia.

4. Non-union if soft-tissues such as muscle or fat are interposed between the severed ends

### **3.5.10 Pathological Fractures**

These are fractures occurring spontaneously (that is with normal stresses) because of intrinsic disease of the bone.

**Causes:**

1. Osteoporosis, especially steroid induced
2. Metastatic tumors
3. Primary tumors (benign and malignant)
4. Paget's disease
5. Bone lesions of hyperparathyroidism
6. Osteogenesis imperfecta