INFLAMMATIONS IV

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Chronic Inflammation

- **Definition:**
- *Chronic inflammation is a tissue response to injury of prolonged duration (weeks or months) in which inflammation, tissue injury, and attempts at repair coexist, in varying combinations.*
- *It may follow acute inflammation, or may begin insidiously, or a progressive process without any signs of a preceding acute reaction.*

- ***Chronic inflammation can develop by one of the following 3 ways:***

1. ***Chronic inflammation following acute occurs when:***

- The tissue destruction is extensive, or
- The bacteria survive and persist in small numbers at the site of acute inflammation, e.g. in osteomyelitis, pneumonia terminating in lung abscess.

2. ***Recurrent attacks of acute inflammation:***

- *When repeated bouts of acute inflammation culminate in chronicity e.g. in:*
- Recurrent urinary tract infection leading to chronic pyelonephritis,
- Repeated acute infection of gallbladder leading to chronic cholecystitis.

3. ***Chronic inflammation starting de novo:***

- When the infection with organisms of low pathogenicity is chronic from the beginning, e.g. *TB*.

Causes of Chronic Inflammation

A. ***Persistent infections*** *by microorganisms that are difficult to be eradicated, such as TB, certain viruses, fungi, and parasites.*

- These organisms often evoke an immune reaction called ***delayed-type hypersensitivity***.
- The inflammatory response sometimes takes a specific pattern called ***granulomatous inflammation***.
- In other cases, ***unresolved acute inflammation*** evolves into chronic inflammation e.g., pneumonia progresses to chronic lung abscess.

B. ***Hypersensitivity diseases:***

- Chronic inflammation caused by excessive and inappropriate activation of the immune system, e.g.,:

1. ***In allergic diseases:*** *chronic inflammation is due to excessive immune response against environmental substances, as in bronchial asthma.*
2. ***In autoimmune diseases:*** *Auto/self-antigens evoke a self-immune reaction → chronic inflammation and tissue damage; as in rheumatoid arthritis and multiple sclerosis.*

- Autoimmune and allergic reactions are triggered against antigens that are normally harmless, so *serve no useful purpose and only cause disease.*
- Such diseases show morphologic patterns of *mixed acute and chronic inflammation*.
- ***Fibrosis*** may dominate the late stages.

c. ***Prolonged exposure to potentially toxic agents, either exogenous or endogenous.***

- An exogenous agent like silica; a non-degradable material that, when inhaled for prolonged periods, results in ***silicosis***.
- ***Atherosclerosis*** is a chronic inflammatory disease that is thought to be induced, at least in part, by excessive production and tissue deposition of endogenous cholesterol and other lipids.

- Chronic inflammation may be important in the ***pathogenesis of diseases*** that are not thought of as inflammatory disorders.
- ***These include:***
  1. Neurodegenerative diseases such as Alzheimer disease,
  2. Metabolic syndrome and the associated type 2 diabetes, and
  3. Certain cancers in which inflammatory reactions promote tumor development.

Morphologic Features of Chronic Inflammation

- Though there may be *differences* in chronic inflammatory response depending upon *the tissue involved and the causative organisms,* there are some basic *similarities* amongst various types of chronic inflammation.
- In contrast to acute inflammation, which is manifested by vascular changes, edema, and predominantly neutrophilic infiltration, ***chronic inflammation is characterized by the following:***

1. **Mononuclear cell infiltration:**

- *The cellular exudate takes either a diffuse or a perivascular arrangement.*
- *Chronic inflammatory lesions are infiltrated by mononuclear inflammatory cells e.g., macrophages, lymphocytes, and plasma cells, sometimes, eosinophils and mast cells.*
- ***Macrophages comprise the most important cells in chronic inflammation.***
- *They are represented by circulating monocytes, tissue macrophages, epithelioid cells and, multinucleated giant cells.*
- The inflammatory fluid exudate is scanty.

- ***Macrophages at the site of chronic inflammation come from:***
  i. Chemotactic factors and adhesion molecules → continued macrophages infiltration;
  ii. Local proliferation of macrophages; and
  iii. Longer survival of macrophages at the site of inflammation.
- *On reaching the extravascular space blood monocytes transform into tissue macrophages.*
- *Besides their in phagocytosis,* macrophages may get activated in response to *cytokines (lymphokines)* and *bacterial endotoxins.*

- ***On activation,*** macrophages release several biologically active substances e.g. *acid and neutral proteases, ROS and cytokines → tissue destruction, neovascularisation and fibrosis.*
- ***In chronic inflammation, macrophages and lymphocytes influence each other and release mediators of inflammation.***

2. **Tissue destruction or necrosis:**

- *Tissue destruction and necrosis are central features of chronic inflammation.*
- ***This is induced by:***

A. *Persistent offending agent*, or
B. *Activated macrophages* which release a variety of biologically active substances e.g. protease, elastase, collagenase, lipase, ROS, cytokines (IL-1, IL-8, TNF-α), nitric oxide, and angiogenesis growth factor.

3. **Proliferative changes and attempts at healing:**

- As a result of necrosis, *proliferation of small blood vessels; angiogenesis,* and *fibroblasts is stimulated → formation of inflammatory granulation tissue.*
- Later on the small arteries and arterioles show *thickening* and *narrowing* due to proliferation of the *sub-intimal connective tissue → "end arteritis obliterans".*
- *Healing by fibrosis occurs and collagen laying takes place.*

Systemic Effects of Chronic Inflammation

- ***Chronic inflammation is associated with the following systemic features:***

1. **Fever:** Mild fever, often with loss of weight and weakness.
2. **Anemia:** Chronic inflammation is usually accompanied by anemia of varying degree.
3. **Leucocytosis:** In contrast to acute inflammation, chronic inflammation has leucocytosis with relative lymphocytosis.

4. **ESR:** ESR is elevated in all cases of chronic inflammation.
5. **Amyloidosis:** Long-term cases of *chronic suppurative inflammation* may develop *secondary systemic (AA) amyloidosis.*

Cells and Mediators of Chronic Inflammation

- *The combination of leukocyte infiltration, tissue damage, and fibrosis that characterize chronic inflammation is due to local activation of several cells and production of mediators.*

Macrophages Origin and Sites

- ***Macrophages*** are derived from ***hematopoietic stem cells*** in the ***bone marrow*** and from ***progenitors*** in the ***embryonic yolk sac*** and ***fetal liver*** during early development.
- *In the steady state (in the absence of tissue injury or inflammation), they populate the tissues, stay for long periods, and are replenished mainly by proliferation of resident cells.*
- Circulating cells of this lineage are known as ***monocytes.***

- ***Tissue macrophages are:***
  1. *Kupffer cells in the liver,*
  2. *Alveolar macrophages in the lungs,*
  3. *Littoral cells in the spleen,*
  4. *Sinus histiocytes in lymph nodes, and*
  5. *Microglial cells in the CNS.*
- These cells comprise the ***mononuclear phagocyte system,*** known by the older and inaccurate name ***reticulo-endothelial system.***
- *The half-life of blood monocytes is about one day, whereas the life span of the tissue macrophages is several months or years.*

- *In inflammatory reactions, progenitors in the bone marrow give rise to monocytes, which enter the blood, migrate into various tissues, and differentiate into macrophages.*
- Entry of blood monocytes into the tissues is governed by the same factors that are involved in neutrophil *emigration,* such as *adhesion molecules and chemokines.*
- *Macrophages often become the dominant cell population in any inflammatory reactions within 48 hours of onset.*

Role of Macrophages in Chronic Inflammations

- *Macrophages are the dominant cells in most chronic inflammations.*
- They also function as ***effector cells*** that eliminate microbes in ***cellular*** and ***humoral immune responses***.
- They serve roles in acute ***inflammation*** and ***repair***.
- *They secrete cytokines and growth factors →:*

1. Destroying foreign invaders and tissues, and
2. *Activating* other cells, mainly *T lymphocytes*.

- *Macrophages and their mediators are powerful in the body's defense against unwanted invaders, but can also induce considerable tissue destruction when inappropriately or excessively activated.*
- *Tissue destruction* is one of the *hallmarks* of chronic inflammation.
- *If the irritant is eliminated, macrophages eventually disappear (either dying off or making their way via lymphatics into the lymph nodes).*

- *Sometimes macrophage accumulation persists, as a result of continuous recruitment from the circulation and local proliferation at the site of inflammation.*
- ***There are two major pathways of macrophage activation, called classical and alternative pathways.***
- *Which of these is taken by a given macrophage depends on the nature of the activating signals.*

1. ***Classical macrophage activation*** is induced by:
   A. Microbial products such as endotoxin, which engage TLRs, and
   B. T cell-derived signals, e.g, cytokine IFN-γ, in immune responses.

- ***Classically activated macrophages (M1)*** *produce NO and ROS and up-regulate lysosomal enzymes.*
- *Secreted NO and ROS enhance the ability of macrophages to kill the ingested organisms, and secrete cytokines that stimulate inflammation.*

2. ***Alternative macrophage activation*** is induced by cytokines other than IFN-γ, e.g., IL-4 and IL-13, produced by *T lymphocytes*.
   - These macrophages are *not actively microbicidal.*
   - The principal function of ***alternatively activated (M2) macrophages*** is tissue *repair.*
   - They secrete growth factors that promote *angiogenesis, activate fibroblasts, and stimulate collagen synthesis.*

- *In response to most injurious stimuli, the first activation pathway is the classical one, designed to destroy the offending agents, and this is followed by alternative activation, which initiates tissue repair.*
- *However, the sequence is not documented in most inflammatory reactions.*
- *Numerous other macrophage subpopulations have been described and the M1 and M2 subsets are also not fixed.*

- *In addition to elimination of injurious agents such as microbes and initiation of repair, macrophages are also responsible for:*

A. *Much of the tissue injury in chronic inflammation.*
B. *Persistence of chronic inflammation and the accompanying tissue injury., e.g.,*

- ***Both effects are due to their secreted mediators*** e.g., cytokines (TNF, IL-1, and chemokines) and eicosanoids.
- Thus, macrophages are central to the *initiation and propagation of inflammatory reactions.*

- ***Macrophages display antigens to T lymphocytes and respond to signals from T cells.***
- This sets up a feedback that is essential for defense against many microbes by *cell-mediated immune responses.*

Classical and Alternative Macrophage Activation

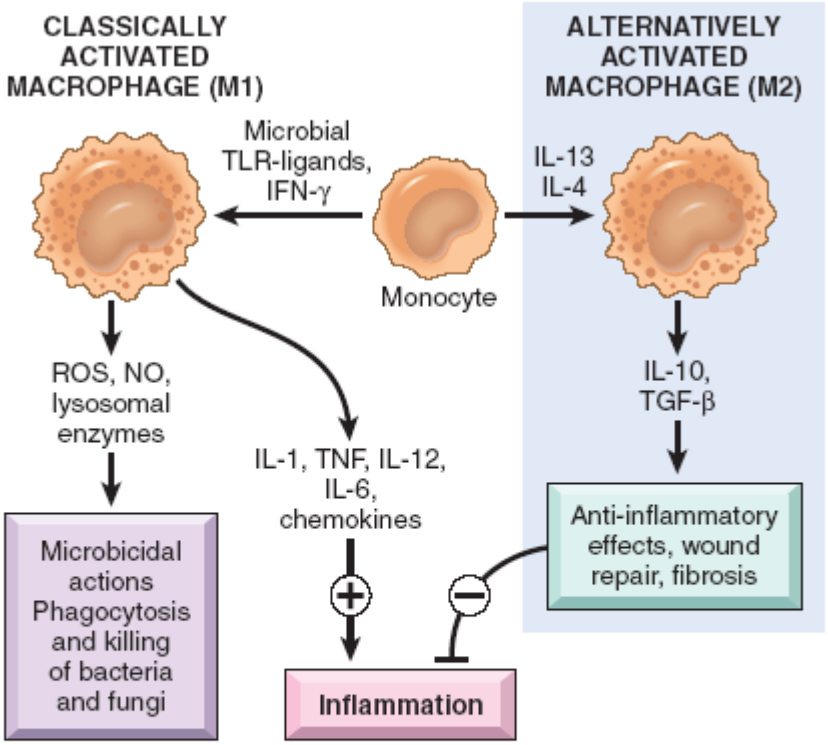

Fig. 3.19 Classical and alternative macrophage activation. Different stimuli activate monocytes/macrophages to develop into functionally distinct populations. Classically activated macrophages are induced by microbial products and cytokines, particularly IFN-γ. They phagocytose and destroy microbes and dead tissues and can potentiate inflammatory reactions. Alternatively activated macrophages are induced by other cytokines and are important in tissue repair and the resolution of inflammation.

Lymphocytes Role in Chronic Inflammation

- *Microbes and other environmental antigens activate T and B lymphocytes, which amplify and propagate chronic inflammation.*
- *Although the major function of these lymphocytes is as **mediators of adaptive immunity** against infectious pathogens, these cells are often present in chronic inflammation and, when they are activated, the inflammation tends to be persistent and severe.*

- *Granulomatous inflammation,* are dependent on lymphocyte responses.
- Lymphocytes may be the dominant population in chronic inflammation seen *in autoimmune diseases and hypersensitivity reactions.*
- CD4+ T lymphocytes secrete cytokines, that promote inflammation and influence the nature of the inflammatory reaction.
- These T cells greatly ***amplify*** the early inflammatory reaction induced by recognition of microbes and dead cells as a part of the ***innate immune response.***

- There are ***three subsets of CD4+ T cells*** that secrete different cytokines and elicit different types of inflammation:

1. ***TH1 cells produce the cytokine IFN-γ,*** which activates macrophages by the classical pathway.
2. ***TH2 cells secrete IL-4, IL-5, and IL-13,*** which recruit and activate eosinophils and are responsible for the alternative pathway of macrophage activation.
3. ***TH17 cells secrete IL-17*** which induce the secretion of chemokines responsible for recruiting neutrophils into the reaction.

- *Both **TH1 and TH17 cells** are involved in defense against many types of bacteria and viruses and in autoimmune diseases.*
- ***TH2 cells*** are important in *allergic inflammation and in* defense against *helminthic parasites.*
- ***Lymphocytes and macrophages interact in a bidirectional way.***
- These interactions play an important role in propagating chronic inflammation.
- *Macrophages display antigens to T cells, express membrane molecules (called co-stimulators) that activate T cells, and produce cytokines (IL-12 and others) that also stimulate T cell responses.*

- *Activated T lymphocytes, in turn, produce cytokines, which recruit and activate macrophages, promoting more antigen presentation and cytokine secretion.*
- The result is a cycle of cellular reactions that sustain chronic inflammation.
- *Activated B lymphocytes and antibody-producing plasma cells are often present at sites of chronic inflammation.*
- *The antibodies may be specific for persistent foreign or self antigens in the inflammatory site or against altered tissue components.*

- *However, the specificity and even the importance of antibodies in most chronic inflammatory disorders are unclear.*
- In some chronic inflammatory reactions, *the accumulated lymphocytes, antigen-presenting cells, and plasma cells cluster together to form lymphoid structures resembling the follicles found in lymph nodes.*
- These are called ***tertiary lymphoid organs***.

- This type of ***lymphoid organogenesis*** is seen in:
  1. *The synovium of patients with longstanding rheumatoid arthritis,*
  2. *Hashimoto thyroiditis, and*
  3. *Gastric mucosa in H pylori infection.*
- *The local formation of lymphoid organs may maintain the immune reaction, but their significance not established.*

Macrophage–lymphocyte interactions in chronic inflammation

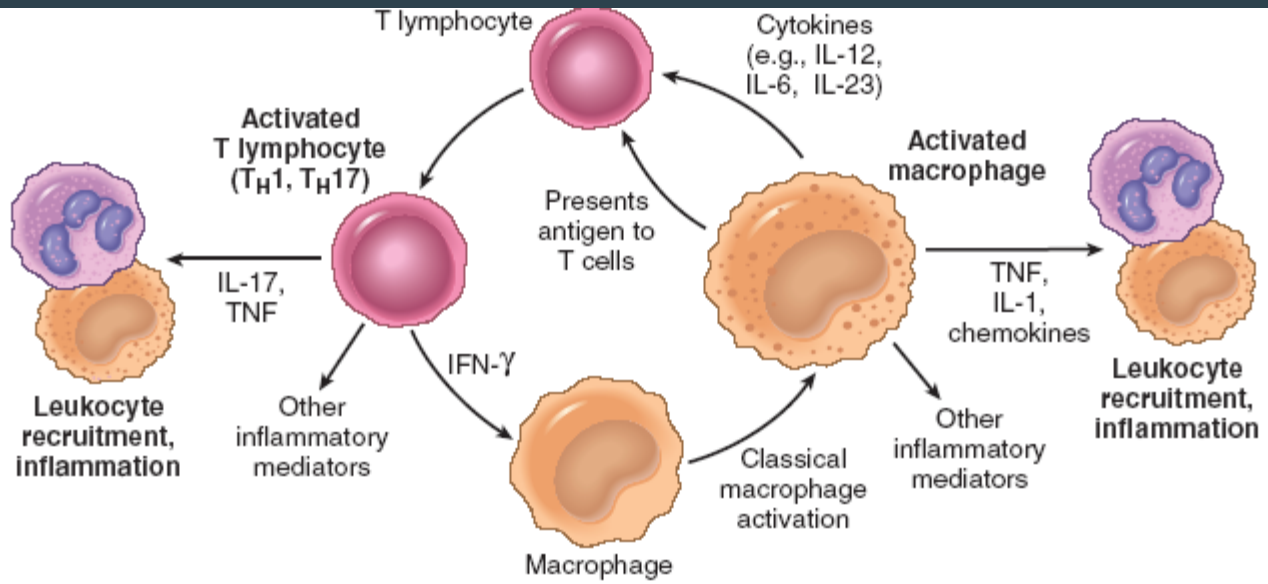

Fig. 3.20 Macrophage–lymphocyte interactions in chronic inflammation. Activated T cells produce cytokines that recruit macrophages (TNF, IL-17, chemokines) and others that activate macrophages (IFN-γ). Activated macrophages in turn stimulate T cells by presenting antigens and via cytokines such as IL-12.

Other Cells in Chronic Inflammation
Eosinophils

- ***Eosinophils*** are abundant in immune reactions mediated by ***IgE antibody*** and in parasitic infections.
- Their recruitment is driven by adhesion molecules similar to those used by neutrophils, and by specific *chemokines (e.g., eotaxin)* derived from leukocytes and epithelial cells.

- ***Eosinophils*** *have granules that contain major basic protein, a highly cationic protein that is toxic to the parasites but also injures host epithelial cells.*
- This is why eosinophils are of benefit in *controlling parasitic infections*.
- It also contribute to *tissue damage* in immune reactions such as ***allergies.***

Mast cells

- ***Mast cells*** are widely distributed in the connective tissues and participate in both *acute and chronic* inflammation.
- Mast cells arise from *precursors in the bone marrow.*
- They have many similarities with circulating basophils.
- *They are tissue-resident, and therefore play more significant roles in inflammatory reactions in tissues than basophils do.*

- Mast cells and basophils express on their surface the receptor ***FcεRI,*** which binds the ***Fc portion of IgE antibody.***
- *In immediate hypersensitivity reactions, IgE bound to the mast cells' Fc receptors, specifically recognizes antigen, and in response the cells de-granulate and release mediators, such as histamine and prostaglandins.*
- This type of response occurs during allergic reactions to foods, insect venom, or drugs, sometimes *with catastrophic results (e.g., anaphylactic shock).*

- *Mast cells are also present in chronic inflammation, and because they secrete a plethora of cytokines, they can promote inflammatory reactions.*

- Many forms of chronic inflammation, show large numbers of ***neutrophils***, induced either by:

1. *Persistent microbes, or*
2. *By cytokines and other mediators produced by activated macrophages and T lymphocytes.*

- In chronic osteomyelitis, a neutrophilic exudate can persist for many months.
- Neutrophils are important in chronic damage induced in lungs by *smoking and other irritant.*
- This pattern of inflammation has been called ***acute on chronic*.**

Types of chronic inflammation

- *For descriptive classification, histological features are used for classifying chronic inflammation into 2 types:*

1. **Chronic non-specific inflammation:**

- Different irritants produce inflammatory reactions of the same microscopic picture.
- This is characterized by formation of granulation tissue and healing by fibrosis.
- This type of chronic inflammation may follow acute inflammation, e.g. chronic abscess, chronic osteomyelitis and chronic pyelonephritis.
- A variant of this type is ***chronic suppurative inflammation*** in which infiltration by PML and abscess formation are additional features e.g. actinomycosis.

2. **Chronic specific (granulomatous) inflammation:**

- Each irritant or injurious agent produces inflammation having a characteristic microscopic picture.
- *It is characterized by formation of granulomas e.g. tuberculosis, sarcoidosis, leprosy, syphilis, actinomycosis, and bilharziasis.*

Granulomatous Inflammation

- Granulomatous inflammation is a form of chronic inflammation characterized by *collections of activated macrophages,* often with *T lymphocytes*, *and sometimes associated with central necrosis.*
- *The activated macrophages may develop abundant cytoplasm and begin to resemble epithelial cells, and are called* ***epithelioid cells*****.**

- Some activated macrophages may fuse, forming multinucleate ***giant cells***.
- ***Granuloma*** formation 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 the normal tissues.

GRANULOMAS

- **Definition:**
- *Granuloma is a type of chronic specific inflammation characterized by focal accumulation of large number of macrophages together with lymphocytes, plasma cells, giant cells and fibroblasts forming tiny granules which fuse to form tumor-like masses.*

- The word ***'granuloma'*** is derived from *granule* meaning circumscribed granule-like lesion, and -*oma* which is a suffix means a mass or lump.

- ***There are 3 types of granuloma according to the etiology:***

1. **Infective granuloma:**
   A. Bacterial: e.g. tuberculosis, leprosy and syphilis.
   B. Parasitic: e.g. bilharziasis and leishmaniasis.
   C. Fungal: e.g. madura foot.

2. **Non infective granuloma (foreign body granuloma):**
   A. Silicosis and asbestosis.
   B. Foreign body granuloma formed around pieces of wood or glass, catgut and talc powder.
3. **Granuloma of unknown cause:**
   A. **S**arcoidosis
   B. Regional enteritis; Crohn's disease.

- ***There are two types of granulomas according to their different pathogenesis:***

1. ***Immune granulomas*** are caused by a variety of agents that are capable of inducing *a persistent T cell-mediated immune response.*

- This type of immune response produces granulomas usually when the *inciting agent cannot be readily eliminated,* such as persistent microbe or self antigen.
- *Macrophages activate T cells to produce cytokines, such as IL-2, which activates other T cells, perpetuating the response, and IFN-γ, which activates the macrophages.*

2. ***Foreign body granulomas*** are seen in response to relatively inert foreign bodies, in the *absence of T cell-mediated immune responses.*

- Typically, foreign body granulomas form *around materials such as talc*, sutures, or other fibers that are *large enough to preclude phagocytosis by a macrophage but are not immunogenic.*
- ***Epithelioid cells*** and ***giant cells*** are apposed to the surface of the foreign body.
- The foreign material can usually be identified in the center of the granuloma, particularly if viewed with ***polarized light***, in which it may appear refractile.

Pathogenesis of Granuloma

- Formation of granuloma is caused by type IV hypersensitivity reaction.
- It is a protective defense by the host but it causes tissue destruction due to persistence of a poorly digestible antigen e.g. *TB, leprae bacilli, sutures, and talc powder.*
- ***The sequence in evolution of granuloma is as follows:***

1. **Engulfment by macrophages:**
- *Macrophages and monocytes engulf the antigen and try to destroy it.*
- *Since the antigen is poorly degradable, these cells fail to digest and degrade it, and instead undergo morphologic changes to epithelioid cells.*
2. **CD4+ T cells:**
- *Macrophages, being antigen-presenting cells, having failed to deal with the antigen, present it to CD4+ T lymphocytes.*
- *These lymphocytes get activated and elaborate lymphokines (IL-1, IL-2, interferon-γ, TNF-α).*

3. Cytokines:

- *Cytokines formed by activated CD4+ T cells and also by activated macrophages perform the following roles:*

I. *IL-1 and IL-2 stimulate proliferation of more T cells.*
II. *Interferon-γ activates macrophages.*
III. *TNF-α promotes fibroblast proliferation and activates endothelium to secrete prostaglandins which have role in vascular response to inflammation.*
IV. *Growth factors (TGF-β, platelet derived growth factor) elaborated by activated macrophages stimulate fibroblast growth.*

- *A granuloma is formed of macrophages modified as epithelioid cells in the center, with some interspersed multinucleate giant cells, surrounded peripherally by lymphocytes (mainly T cells), and healing by fibroblasts or collagen depending upon the age of granuloma.*

Morphology and Composition of Granuloma

- *Granuloma has the following structural composition:*

1. **Epithelioid cells:**

- They are modified macrophages/histiocytes that have epithelial cell-like appearance.
- They are elongated, have vesicular lightly-stained, slipper-shaped nucleus, and abundant *pink granular cytoplasm with indistinct cell boundaries*.
- *Epithelioid cells are weakly phagocytic.*

2. Multinucleate giant cells:

- They are *40 to 50 µm in diameter,* formed by fusion of adjacent epithelioid cells and may have 20 or more nuclei.
- These nuclei may be arranged at the periphery like horseshoe or ring, or are clustered at the two poles ***(Langhans' giant cells),*** or they may be present centrally ***(foreign body giant cells).***
- The former are commonly seen in TB while the latter are common in foreign body reactions.
- Like epithelioid cells, these giant cells are *weakly phagocytic* but *produce secretory products which help in removing the invading agents.*

3. **Lymphoid cells:**

- *The host response by lymphocytes in granuloma develops as a feature of cell mediated immune reaction to the inciting antigen.*
- Plasma cells indicative of accelerated humoral immune response are present in some types of granulomas.

4. **Necrosis:**

- *Granulomas associated with certain infectious organisms (classically TB) often contain a central zone of necrosis.*
- ***Grossly,** this has a granular, cheese-like appearance and consistency and is therefore called **caseous necrosis.***
- ***Microscopically,** this necrotic material appears as amorphous, structureless, eosinophilic granular debris, with loss of cellular details.*

- *The granulomas in Crohn's disease, sarcoidosis, and foreign body reactions tend to not have necrotic centers, so called* ***non-caseating.***

5. **Fibrosis:**

- *Healing of granulomas is accompanied by **fibrosis** that may be extensive.*
- *It starts by proliferating fibroblasts at the periphery of granuloma*

- The classical example of granulomatous inflammation is the tissue response to tubercle bacilli which is called ***tubercle***.
- ***TB*** should always be excluded as the cause when granulomas are identified.
- A fully-developed tubercle is about 1 mm in diameter with central area of caseation, surrounded by epithelioid cells and one to several multinucleated giant cells *(commonly Langhans' type)*, surrounded at the periphery by lymphocytes and bounded by fibroblasts and fibrous tissue.

- In this disease the granuloma is referred to as a ***tubercle.***
- The morphologic patterns in various granulomatous diseases may be sufficiently different to allow accurate diagnosis.
- Granulomas may also develop in some immune-mediated inflammatory diseases, specially ***Crohn's disease,*** and in a disease of unknown etiology called ***sarcoidosis.***

Examples of Diseases With Granulomatous Inflammation

Table 3.9 Examples of Diseases With Granulomatous Inflammation

Disease	Cause	Tissue Reaction
Tuberculosis	*Mycobacterium tuberculosis*	Caseating granuloma (tubercle): focus of activated macrophages (epithelioid cells), rimmed by fibroblasts, lymphocytes, histiocytes, occasional Langhans giant cells; central necrosis with amorphous granular debris; acid-fast bacilli
Leprosy	*Mycobacterium leprae*	Acid-fast bacilli in macrophages; noncaseating granulomas
Syphilis	*Treponema pallidum*	Gumma: microscopic to grossly visible lesion, enclosing wall of macrophages; plasma cell infiltrate; central cells are necrotic without loss of cellular outline; organisms difficult to identify in tissue
Cat-scratch disease	Gram-negative bacillus	Rounded or stellate granuloma containing central granular debris and recognizable neutrophils; giant cells uncommon
Sarcoidosis	Unknown etiology	Noncaseating granulomas with abundant activated macrophages
Crohn disease (inflammatory bowel disease)	Immune reaction against undefined gut microbes and, possibly, self antigens	Occasional noncaseating granulomas in the wall of the intestine, with dense chronic inflammatory infiltrate

Differences between Acute and Chronic Inflammation

- *Comparison between acute and chronic inflammation is shown in the following table:*

Features	Acute inflammation	Chronic inflammation
• **Irritant**	• Mild, moderate or severe	• Mild irritant
• **Onset**	• Sudden	• Gradual
• **Duration**	• Short (days-weeks)	• Long (weeks-months)
• **Inflammatory cells**	• PML, pus cells and macrophages	• Lymphocytes, plasma cells, macrophages and giant cells
• **Vascular changes**	• Marked	• Mild
• **Blood vessels**	• Thin dilated congested capillaries	• Thick walled arteries and arterioles (end arteritis)
• **Fluid exudates**	• Present	• Scanty or absent
• **Toxemia**	• Acute toxemia	• Chronic toxemia
• **Fibrosis**	• Absent or mild	• Marked
• **Types**	• Suppurative • Non suppurative	• Non specific • Specific
• **Fate**	• Resolution or chronicity	• Fibrosis and its complications


Thank You