

Clinical Examples of Leukocyte-Induced Injury

Acute

- Acute respiratory distress syndrome
- Acute transplant rejection
- Reperfusion injury
- Septic shock
- Vasculitis

Chronic

- Arthritis
- Asthma
- Atherosclerosis
- Glomerulonephritis
- Chronic lung disease
- Chronic rejection

Defects in Leukocyte Function

- Defects in leukocyte function, both genetic and acquired, lead to increased vulnerability to infections:
 - *Defects in leukocyte adhesion*
 - *Defects in phagolysosome function.* One such disorder is *Chédiak-Higashi syndrome*, an autosomal recessive condition characterized by neutropenia (decreased numbers of neutrophils), defective degranulation, and delayed microbial killing
 - *Defects in microbicidal activity.* The importance of oxygen-dependent bactericidal mechanisms is shown by the existence of a group of congenital disorders with defects in bacterial killing called *chronic granulomatous disease*

Defects in Leukocyte Function

Genetic

- Leukocyte adhesion deficiency 1
 - β chain of CD11/CD18 integrins
- Leukocyte adhesion deficiency 2
 - Fucosyl transferase required for synthesis of sialylated oligosaccharide (receptor for selectin)
- Chronic granulomatous disease
 - Decreased oxidative burst
 - X-linked
 - NADPH oxidase (membrane component)
 - Autosomal recessive
 - NADPH oxidase (cytoplasmic components)
 - Myeloperoxidase deficiency
 - Absent MPO-H₂O₂ system
- Chédiak-Higashi syndrome
 - Protein involved in organelle membrane fusion

Defects in Leukocyte Function

Acquired

- Thermal injury, diabetes, malignancy, sepsis, immunodeficiencies
 - Chemotaxis
- Hemodialysis, diabetes mellitus
 - Adhesion
- Leukemia, anemia, sepsis, diabetes, neonates, malnutrition
 - Phagocytosis and microbicidal activity

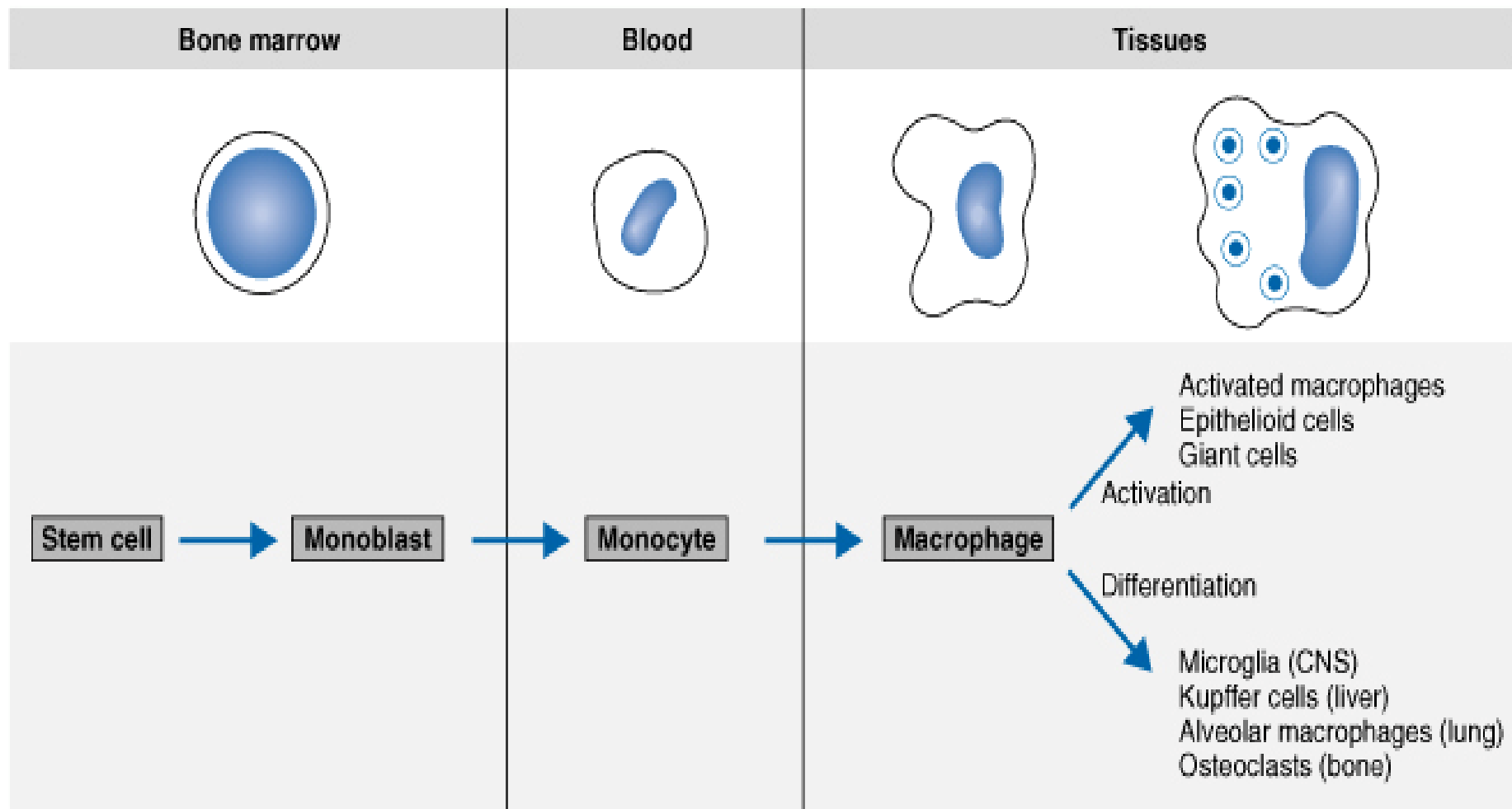
MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION

- *Infiltration with mononuclear cells* include
 - Macrophages
 - Lymphocytes
 - Plasma cells
 - Eosinophils
- *Tissue destruction*
 - induced by the persistent offending agent or by the inflammatory cells.
- *Healing*
 - *by connective tissue replacement of damaged tissue, accomplished by proliferation of small blood vessels (angiogenesis) and, in particular, fibrosis*

MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION

- ***MONONUCLEAR CELL
INFILTRATION***
 - The macrophage is the dominant cellular player in chronic inflammation
 - The mononuclear phagocyte system (sometimes called reticuloendothelial system) consists of closely related cells of bone marrow origin, including blood monocytes and tissue macrophages

mononuclear phagocyte system



–monocytes begin to emigrate into extravascular tissues quite early in acute inflammation and within 48 hours they may constitute the predominant cell type

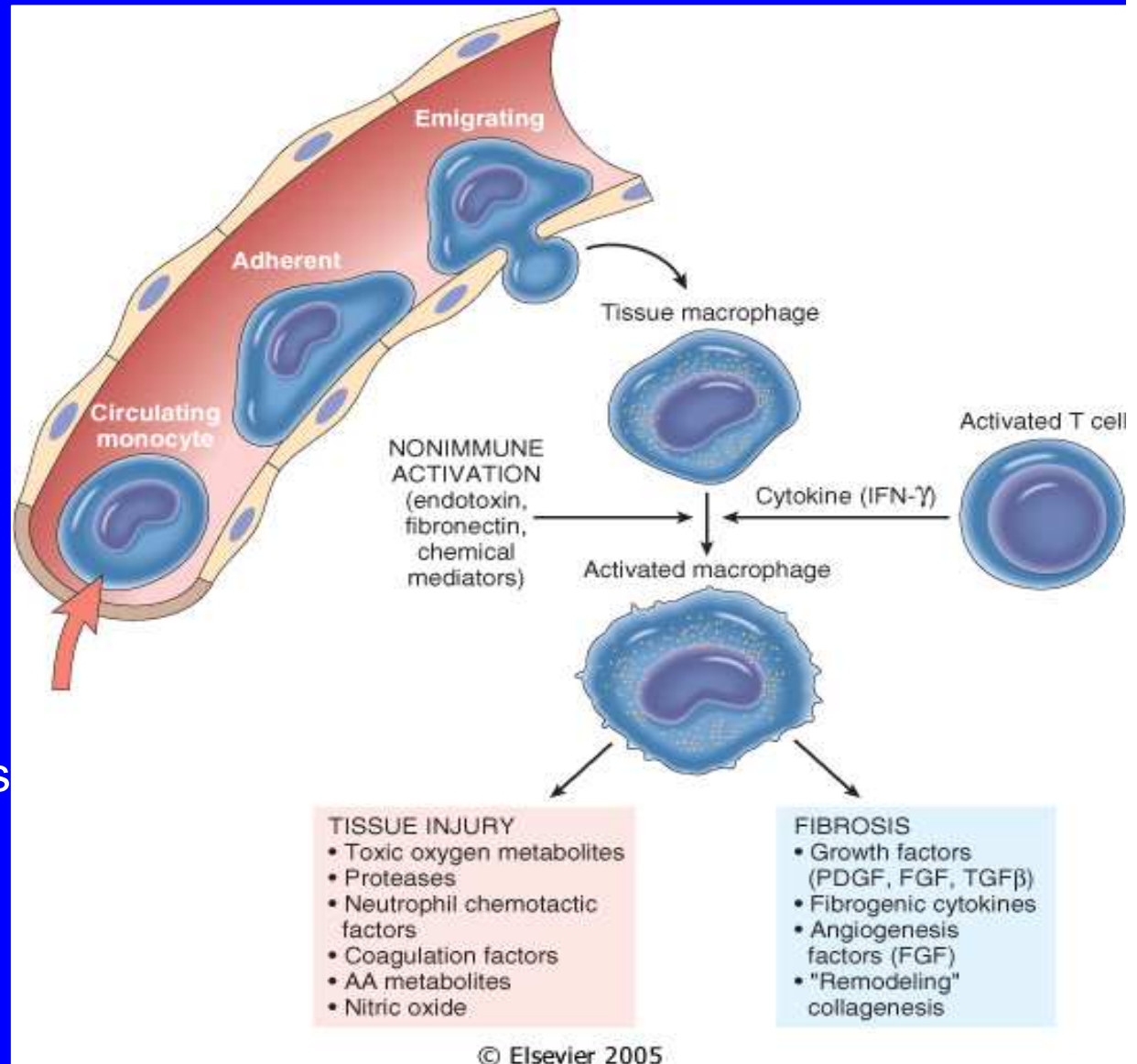
MONONUCLEAR CELL INFILTRATION

- Macrophages may be *activated* by a variety of stimuli, including
 - cytokines (e.g., IFN- γ) secreted by sensitized T lymphocytes and by NK cells
 - bacterial endotoxins
 - other chemical mediators
- Activation results in
 - increased cell size
 - increased levels of lysosomal enzymes
 - more active metabolism
 - greater ability to phagocytose and kill ingested microbes.
- *Activated macrophages secrete a wide variety of biologically active products* that, if unchecked, result in the tissue injury and fibrosis

The roles of activated macrophages in chronic inflammation.

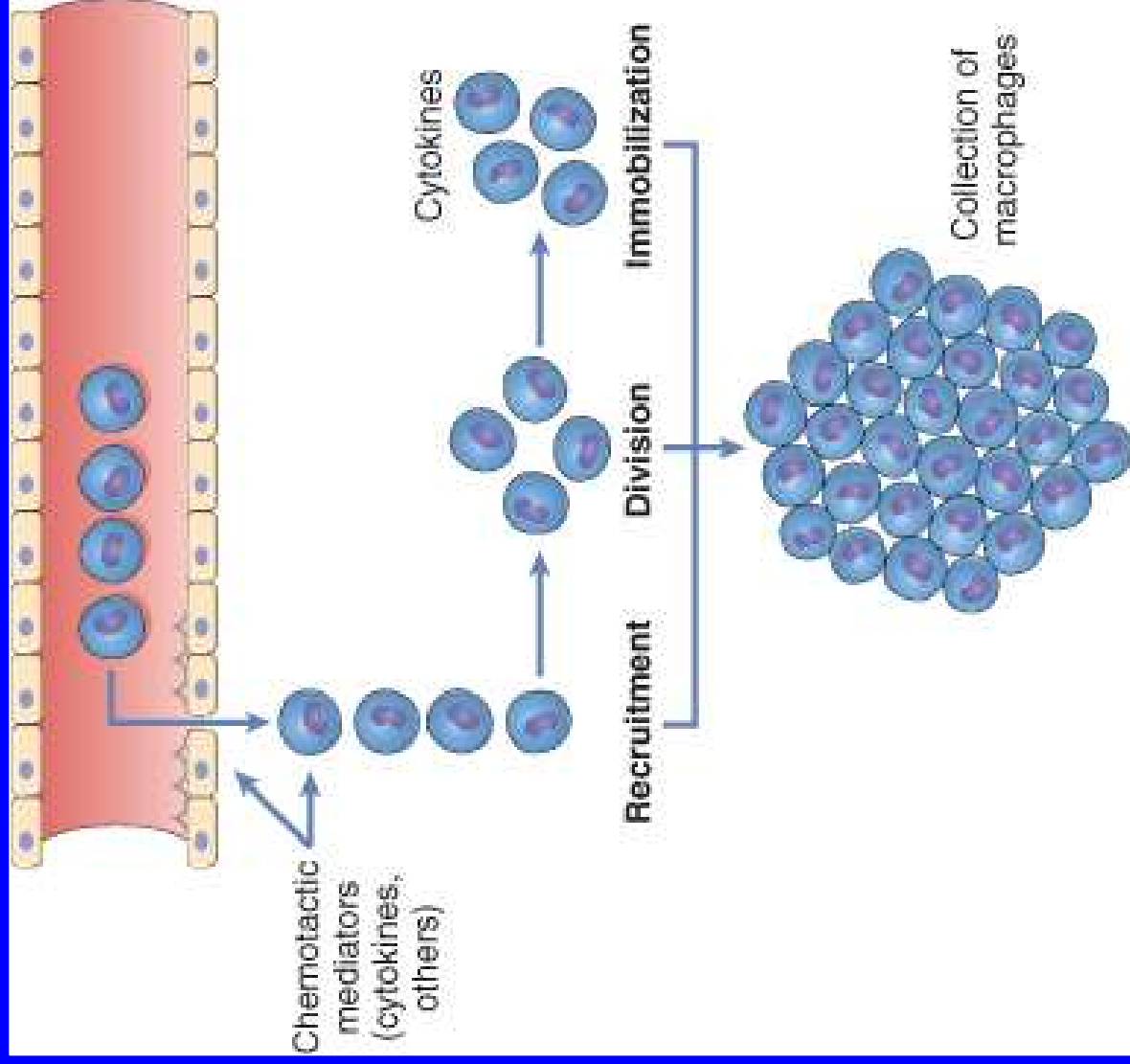
Products of macrophages

1. Acid and neutral proteases
2. Chemotactic factors
3. Reactive oxygen metabolites
4. Complement components
5. Coagulation factors
6. Growth promoting factors for fibroblasts, blood vessels and myeloid progenitor cells
7. Cytokines : IL-1, TNF
8. Other biologic active agents (PAF, interferon, AA metabolites)



MORPHOLOGIC FEATURES OF CHRONIC INFLAMMATION

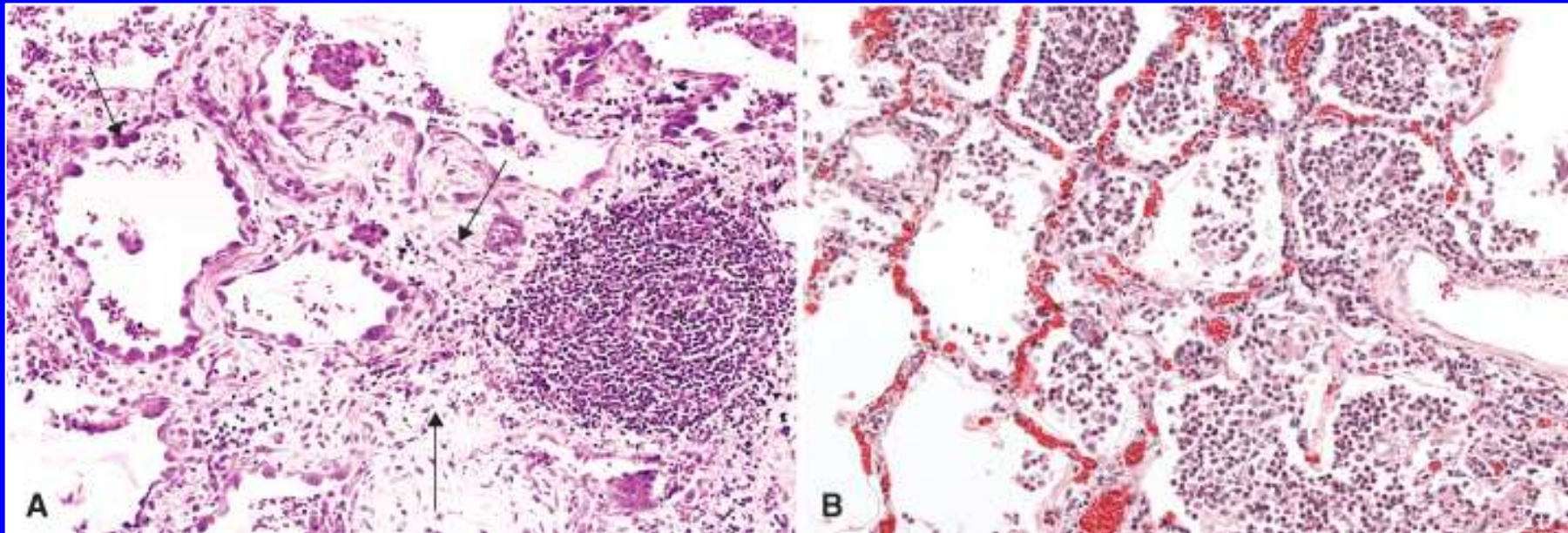
- The products of activated macrophages serve to eliminate injurious agents such as microbes and to initiate the process of repair, and are responsible for much of the tissue injury in chronic inflammation
- In chronic inflammation, macrophage accumulation persists, this is mediated by different mechanisms:
 1. *Recruitment of monocytes from the circulation*, which results from the expression of adhesion molecules and chemotactic factors
 2. *Local proliferation of macrophages* after their emigration from the bloodstream
 3. *Immobilization of macrophages* within the site of inflammation
- ongoing tissue destruction can activate the inflammatory cascade by diverse mechanisms, so that features of both acute and chronic inflammation may coexist



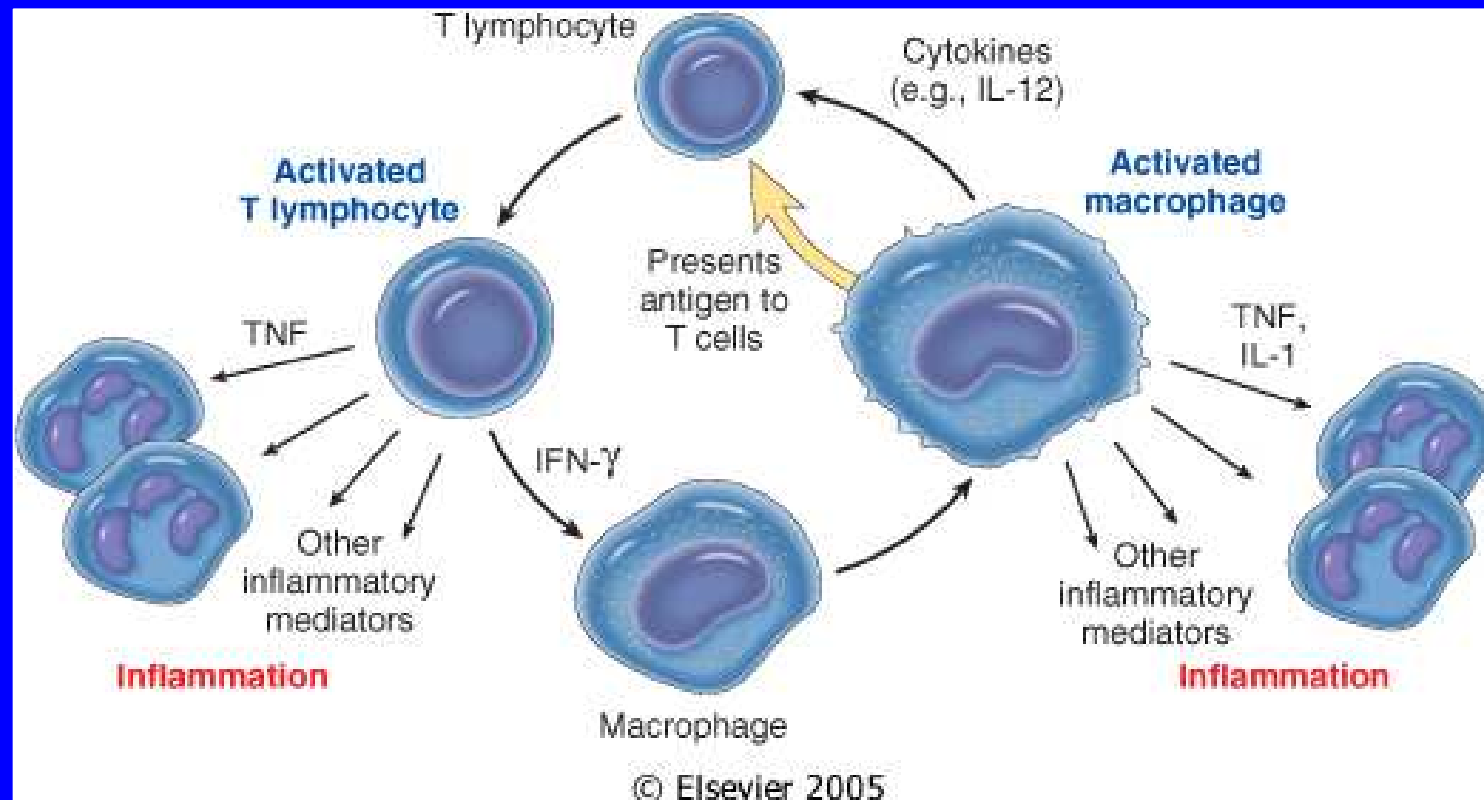
OTHER CELLS IN CHRONIC INFLAMMATION

- **Lymphocytes**

- *Both T & B Lymphocytes migrates into inflammation site*



–Lymphocytes and macrophages interact in a bidirectional way, and these reactions play an important role in chronic inflammation

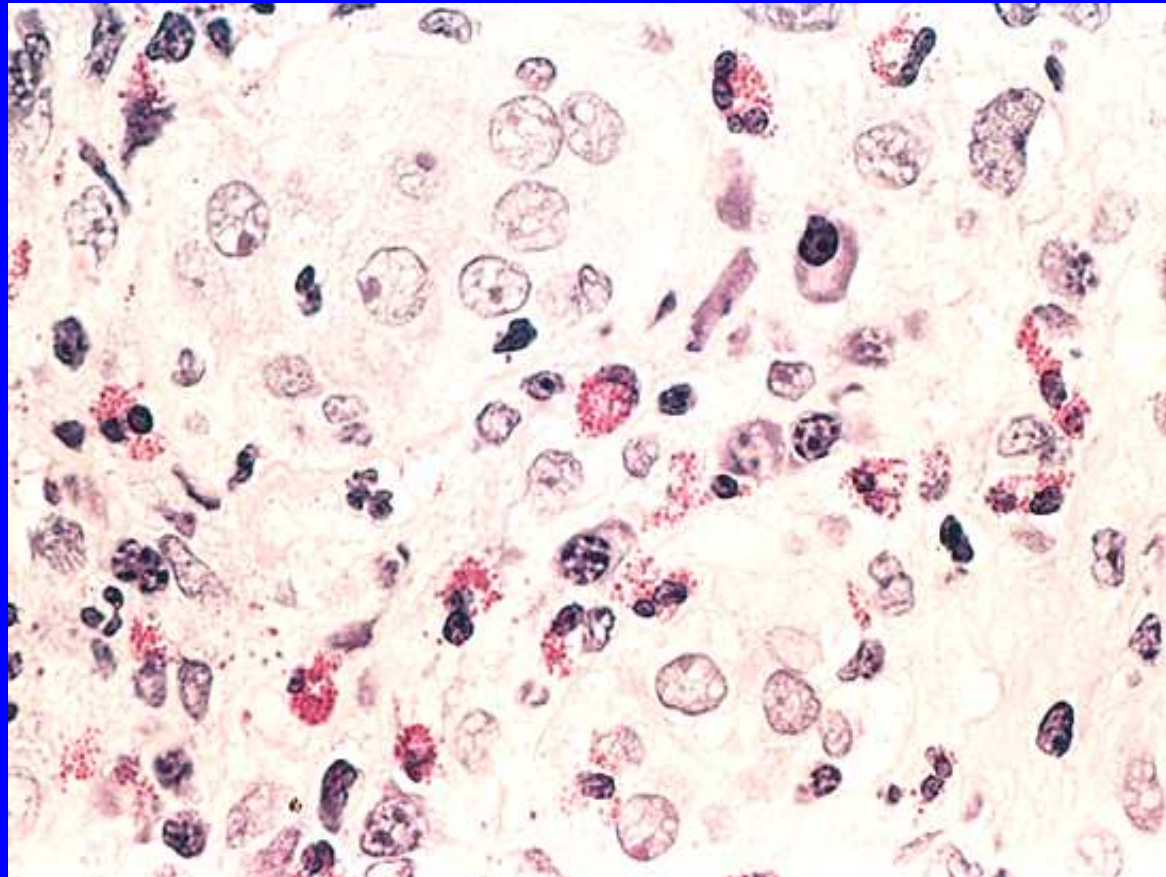


Activated lymphocytes and macrophages influence each other and also release inflammatory mediators that affect other cells.

• *Eosinophils*

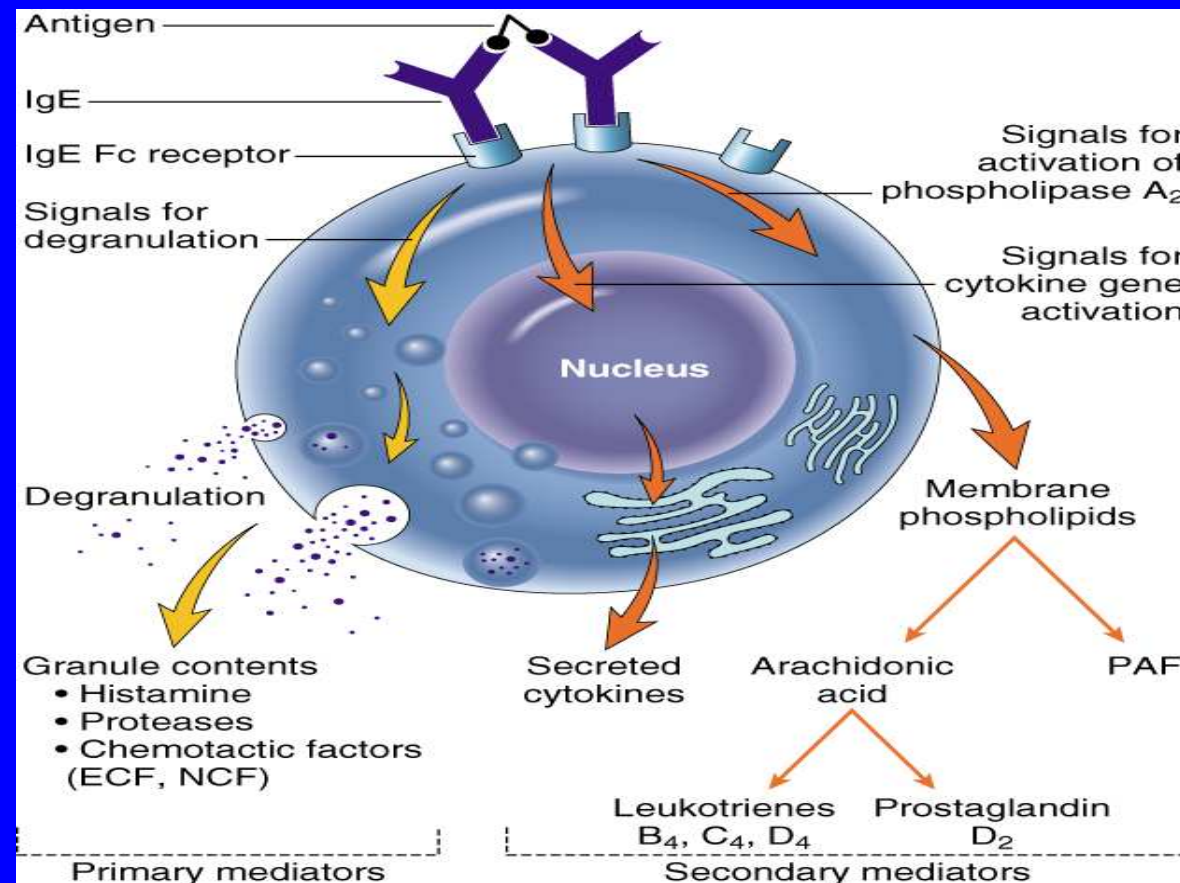
are abundant in immune reactions mediated by IgE and in parasitic infections

- respond to chemotactic agents derived largely from mast cells
- Granules contain major basic protein: toxic to parasites and lead to lysis of mammalian epithelial cells



- **Mast cells**

- are widely distributed in connective tissues
- Mast cells express on their surface the receptor that binds the Fc portion of IgE antibody ,
 - IgE antibodies bound to the cells' Fc receptors specifically recognize antigen, and the cells degranulate and release mediators, such as histamine and products of AA oxidation



OTHER CELLS IN CHRONIC INFLAMMATION

- ***GRANULOMATOUS INFLAMMATION***
 - ***Granulomatous inflammation is a distinctive pattern of chronic inflammatory reaction characterized by focal accumulations of activated macrophages, which often develop an epithelial-like (epithelioid) appearance***

