Host Reaction to Biomaterials

- **Biomaterials are commonly used**
  - **as implants and other tissue-contacting medical devices over a wide range of applications such as**
    - *prostheses* in cardiovascular, orthopedic, dental, ophthalmological, and reconstructive surgery
  - **in minimally invasive interventions** such as
    - stent placement in the biliary tree or in the blood vessels
  - **in extracorporeal devices** such as
    - hemodialysis membranes, in surgical sutures or bioadhesives
  - **in controlled drug-release devices**.

- Most implants serve their recipients well for extended periods by alleviating the conditions for which they were implanted.

- However, **some implants and extracorporeal devices ultimately develop complications – adverse interactions of the patient with the device or *vice versa* – which constitute device failure, and thereby may cause harm to or death of the patient.**

- **Effects of both the implant on the host tissues and the host on the implant are important in mediating complications and device failure**

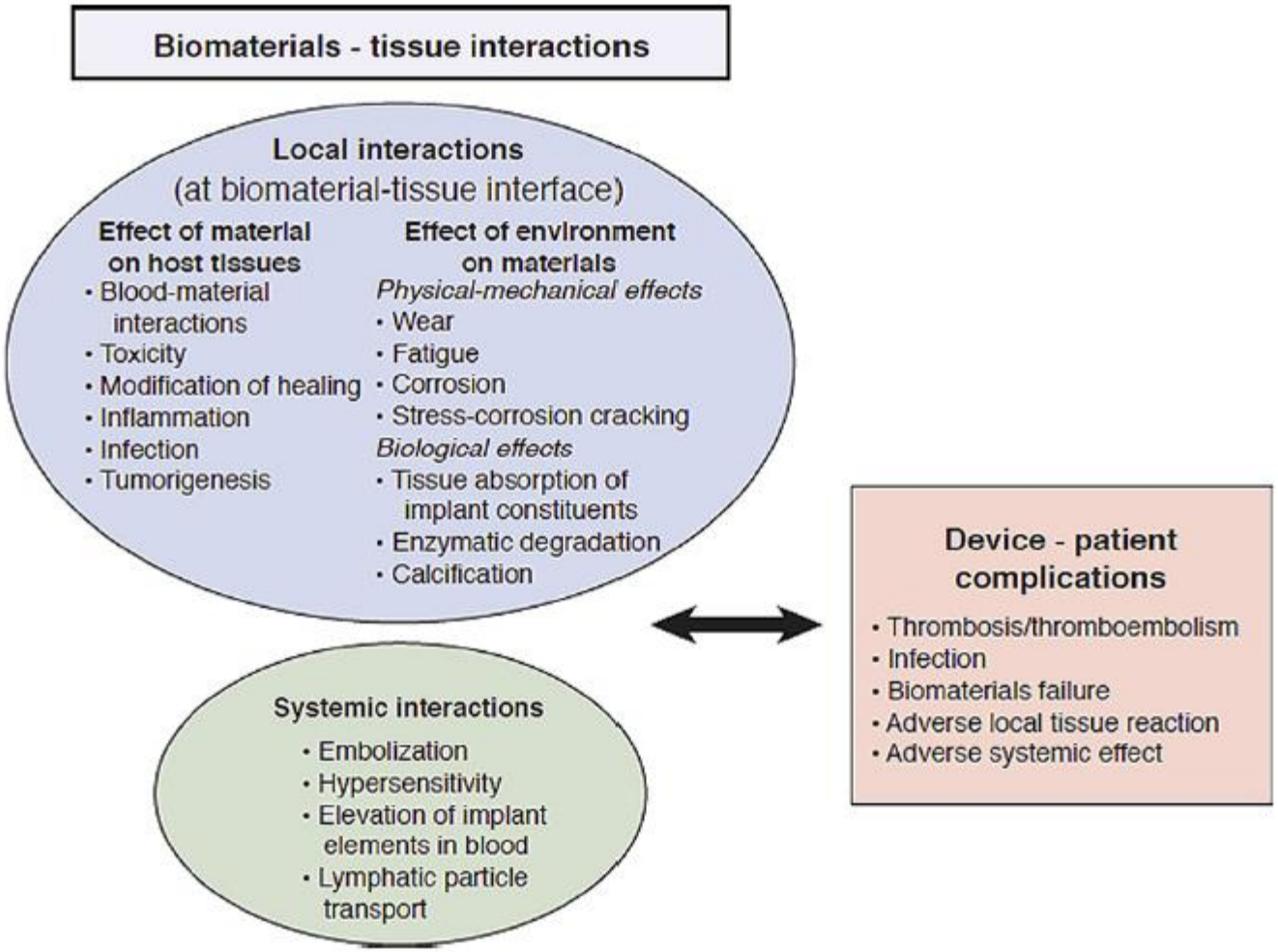


FIGURE II.2.1.1 Biomaterials–tissue interactions. (Reproduced from Schoen, F. J. (2002). Prosthetic-materials: Past, present and future. In: *Advances in Cardiovascular Medicine* (Harvey 1602–2002 Symposium, on the 4th Centenary of William Harvey's Graduation at the University of Padua), Thiene, G., & Pessina, A. C. (Eds.), Universita degli Studi di Padova, pp. 289–307 and Schoen, F. J. & Padera, R. (2012). Cardiovascular Pathology. In: *Cardiac Surgery in the Adult*, 4th edn., Cohn, L. H. & Edmunds, L. H. (Eds.). McGraw–Hill, pp. 95–148.)

INFLAMMATION, **WOUND HEALING, AND THE FOREIGN-BODY RESPONSE**

- Inflammation, wound healing, and foreign-body reaction are generally considered as parts of the tissue or cellular host responses to injury.

TABLE II.2.2.1	Sequence/Continuum of Host Reactions Following Implantation of Medical Devices
Injury	
Blood–material interactions	
Provisional matrix formation	
Acute inflammation	
Chronic inflammation	
Granulation tissue	
Foreign-body reaction	
Fibrosis/fibrous capsule development	

- **Overlap and simultaneous occurrence of these events should be considered.**
    - the foreign-body reaction at the implant interface may be initiated with the onset of acute and chronic inflammation.

- From a biomaterials perspective, placing a biomaterial in the *in vivo* environment requires

    - **Injection**
    - **Insertion**
    - **Surgical implantation**

    all of which injure the tissues or organs involved.

- The placement procedure **initiates a response** to injury by the tissue, organ or body, and mechanisms are activated **to maintain homeostasis**.

- The degrees to which the homeostatic mechanisms are perturbed, and the extent to which pathophysiologic conditions are created and undergo resolution, are a measure of the host reactions to the biomaterial and may ultimately determine its biocompatibility.

OVERVIEW

- **Inflammation is generally defined as the reaction of vascularized living tissue to local injury**. **It sets a series of events** that may heal and reconstitute the implant site through replacement of the injured tissue by regeneration of

  - native parenchymal cells
  - formation of fibroblastic scar tissue

  or

  a combination of these two processes.

- **Immediately following injury, there are changes in vascular flow, caliber, and permeability**. Fluid, proteins, and blood cells escape from the vascular system into the injured tissue in a process called **exudation**.

  - Following changes in the vascular system, which also **include changes induced in blood and its components, cellular events occur.**

    - **Regardless of the tissue or organ into which a biomaterial is implanted, the initial inflammatory response is activated by injury to vascularized connective tissue**

TABLE II.2.2.2	Cells and Components of Vascularized Connective Tissue
Intravascular (Blood) Cells	
Erythrocytes (RBC)	
Neutrophils (PMNs, polymorphonuclear leukocytes)	
Monocytes	
Eosinophils	
Lymphocytes	
Plasma cells	
Basophils	
Platelets	
Connective Tissue Cells	
Mast cells	
Fibroblasts	
Macrophages	
Lymphocytes	
Extracellular Matrix Components	
Collagens	
Elastin	
Proteoglycans	
Fibronectin	
Laminin	

- **Thrombus or blood clot formation on the surface of a biomaterial is related to the well-known Vroman effect** in which a hierarchical and dynamic series of collision, absorption, and exchange processes, determined by protein mobility and concentration, regulate early time-dependent changes in blood protein adsorption.

- **Injury to vascularized tissue in the implantation procedure leads to immediate development of the provisional matrix at the implant site within minutes to hours following implantation of a medical device.**

- **This provisional matrix consists of**

  - **fibrin** produced by activation of the coagulation and thrombosis systems
  - **inflammatory products** released by the complement system, activated platelets, inflammatory cells, and endothelial cells

- **The provisional matrix may be viewed as a naturally derived, biodegradable, sustained release system in which mitogens, chemoattractants, cytokines, and growth factors are released to control subsequent wound-healing processes.**

- **Components within or released from the provisional matrix, i.e., fibrin network (thrombosis or clot), initiate**

    - the resolution
    - Reorganization
    - repair processes such as inflammatory cell and fibroblast recruitment.

- The complex three-dimensional structure of the fibrin network with attached adhesive proteins provides a substrate for cell adhesion and migration.

- **The predominant cell type** present in the inflammatory response varies with the age of the inflammatory injury

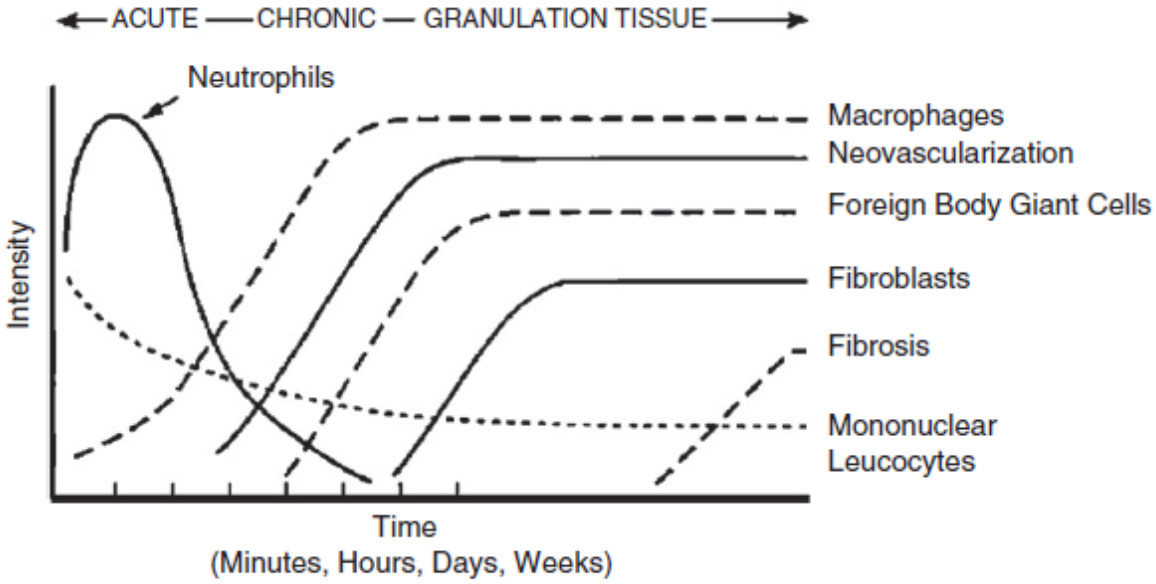


FIGURE II.2.2.1 The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

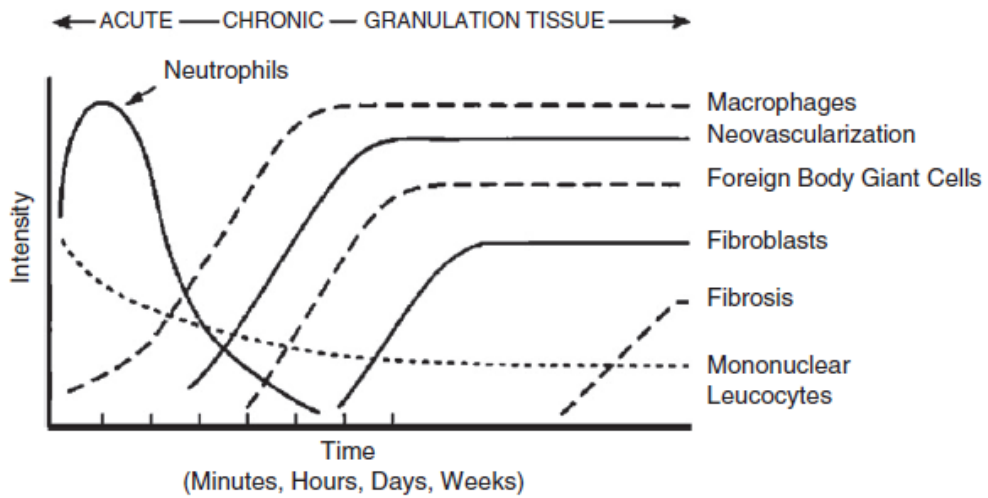


FIGURE II.2.2.1 The temporal variation in the acute inflammatory response, chronic inflammatory response, granulation tissue development, and foreign-body reaction to implanted biomaterials. The intensity and time variables are dependent upon the extent of injury created in the implantation and the size, shape, topography, and chemical and physical properties of the biomaterial.

- **neutrophils predominate during the first several days following injury and then are replaced by monocytes as the predominant cell type.**

- Following emigration from the vasculature, **monocytes differentiate into macrophages and these cells are very long-lived (up to months).**

- **Monocyte emigration may continue for days to weeks, depending on the injury and implanted biomaterial, and chemotactic factors for monocytes are activated over longer periods of time.**

- The size, shape, and chemical and physical properties of the biomaterial may be responsible for variations in the intensity and duration of the inflammatory or wound-healing process. Thus, **intensity and/or time duration of the inflammatory reaction may characterize the biocompatibility of a biomaterial.**

- **While injury initiates the inflammatory response, the chemicals released from plasma, cells or injured tissue mediate the inflammatory response. Important classes of chemical mediators of inflammation are:**

video

TABLE II.2.2.3 Important Chemical Mediators of Inflammation Derived from Plasma, Cells or Injured Tissue

Mediators	Examples
Vasoactive Agents	Histamines, serotonin, adenosine, endothelial-derived relaxing factor (EDRF), prostacyclin, endothelin, thromboxane α_2
Plasma Proteases	
Kinin system	Bradykinin, kallikrein
Complement system	C3a, C5a, C3b, C5b–C9
Coagulation/fibrinolytic system	Fibrin degradation products, activated Hageman factor (FXIIA), tissue plasminogen activator (tPA)
Leukotrienes	Leukotriene B_4 (LTB_4), hydroxyeicosatetranoic acid (HETE)
Lysosomal proteases	Collagenase, elastase
Oxygen-derived free radicals	H_2O_2, superoxide anion
Platelet activating factors	Cell membrane lipids
Cytokines	Interleukin 1 (IL-1), tumor necrosis factor (TNF)
Growth factors	Platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor TGF-α or (TGF-β), epithelial growth factor (EGF)

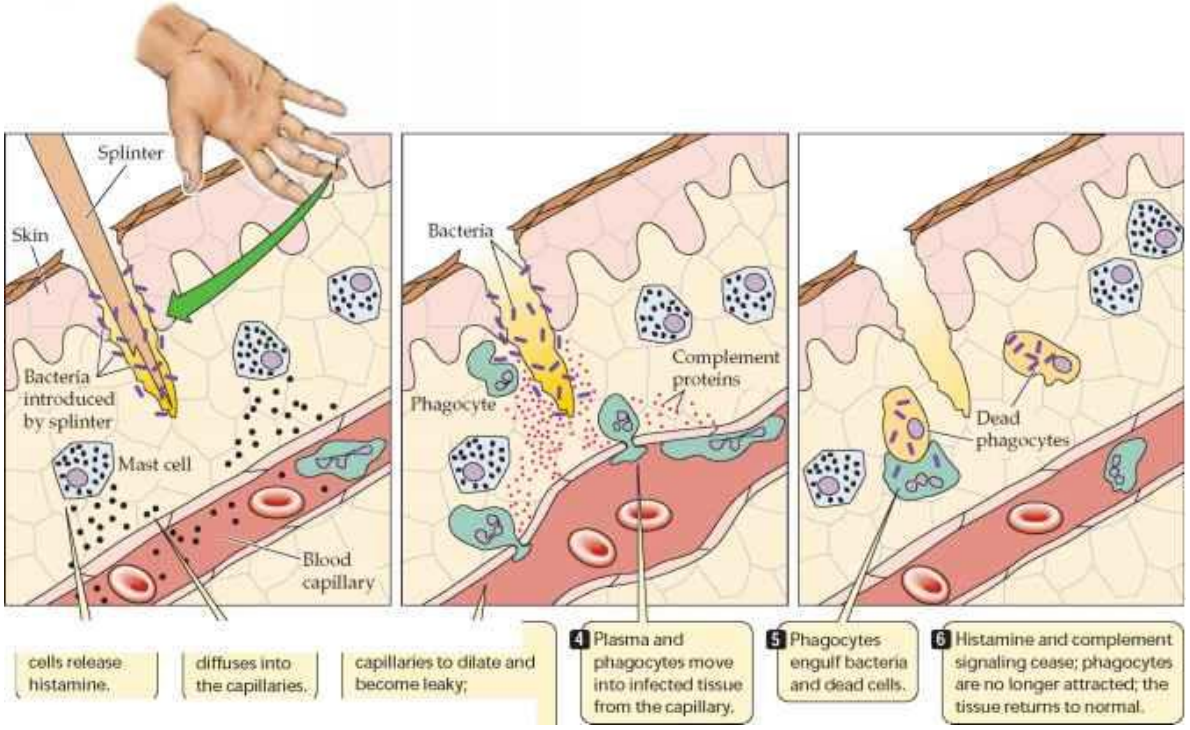
ACUTE INFLAMMATION

- Acute inflammation is of relatively short duration, lasting for minutes to hours to days, depending on the extent of injury.

- Its main characteristics are the exudation of fluid and plasma proteins (edema) and the emigration of leukocytes (predominantly neutrophils).

- **Neutrophils (polymorphonuclear leukocytes, PMNs) and other motile white cells emigrate or move from the blood vessels to the perivascular tissues and the injury (implant) site.**

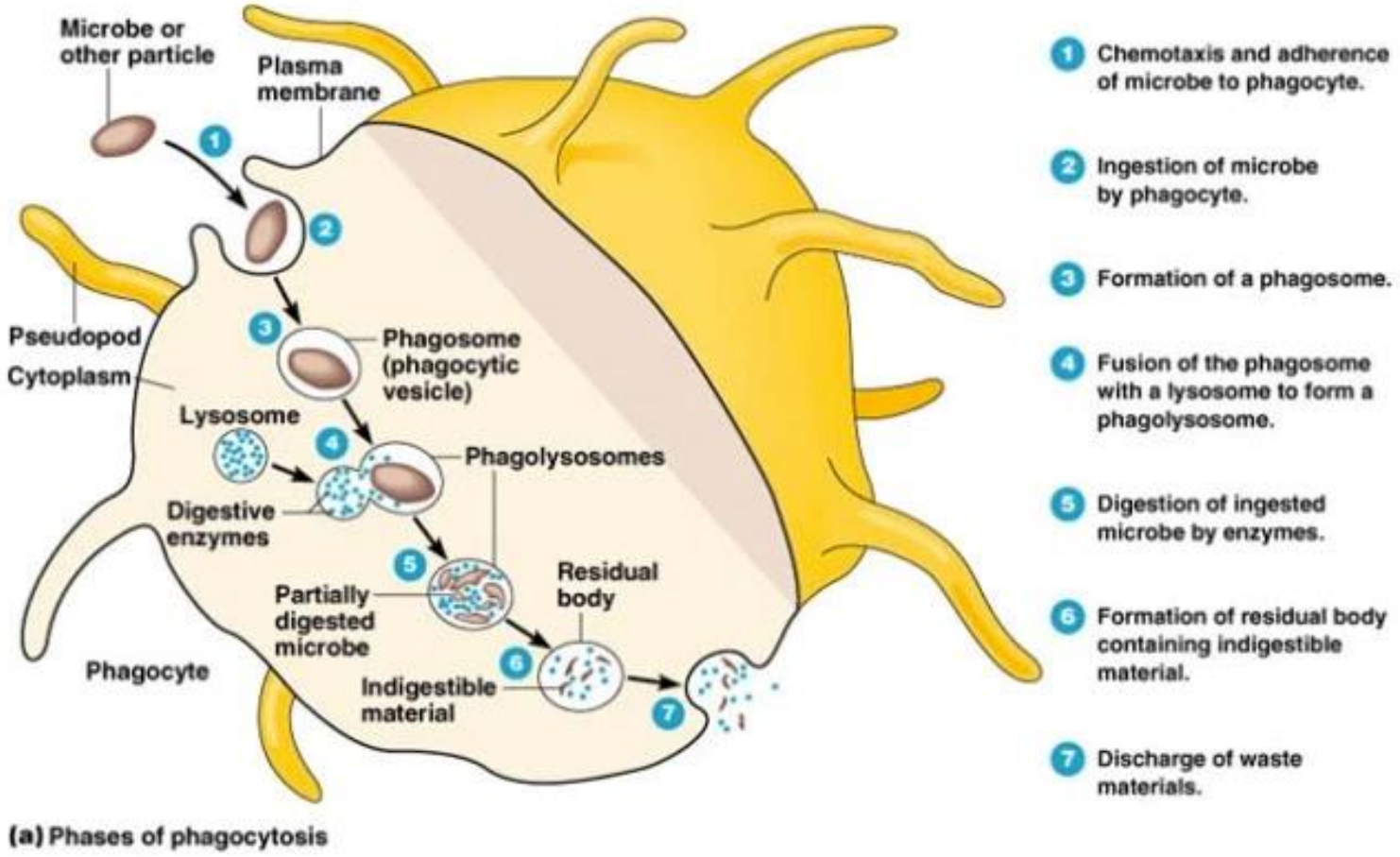
    - Leukocyte emigration is assisted by "adhesion molecules" present on leukocyte and endothelial surfaces. Specific receptors for chemotactic agents on the cell membranes of leukocytes are important in the emigration or movement of leukocytes.



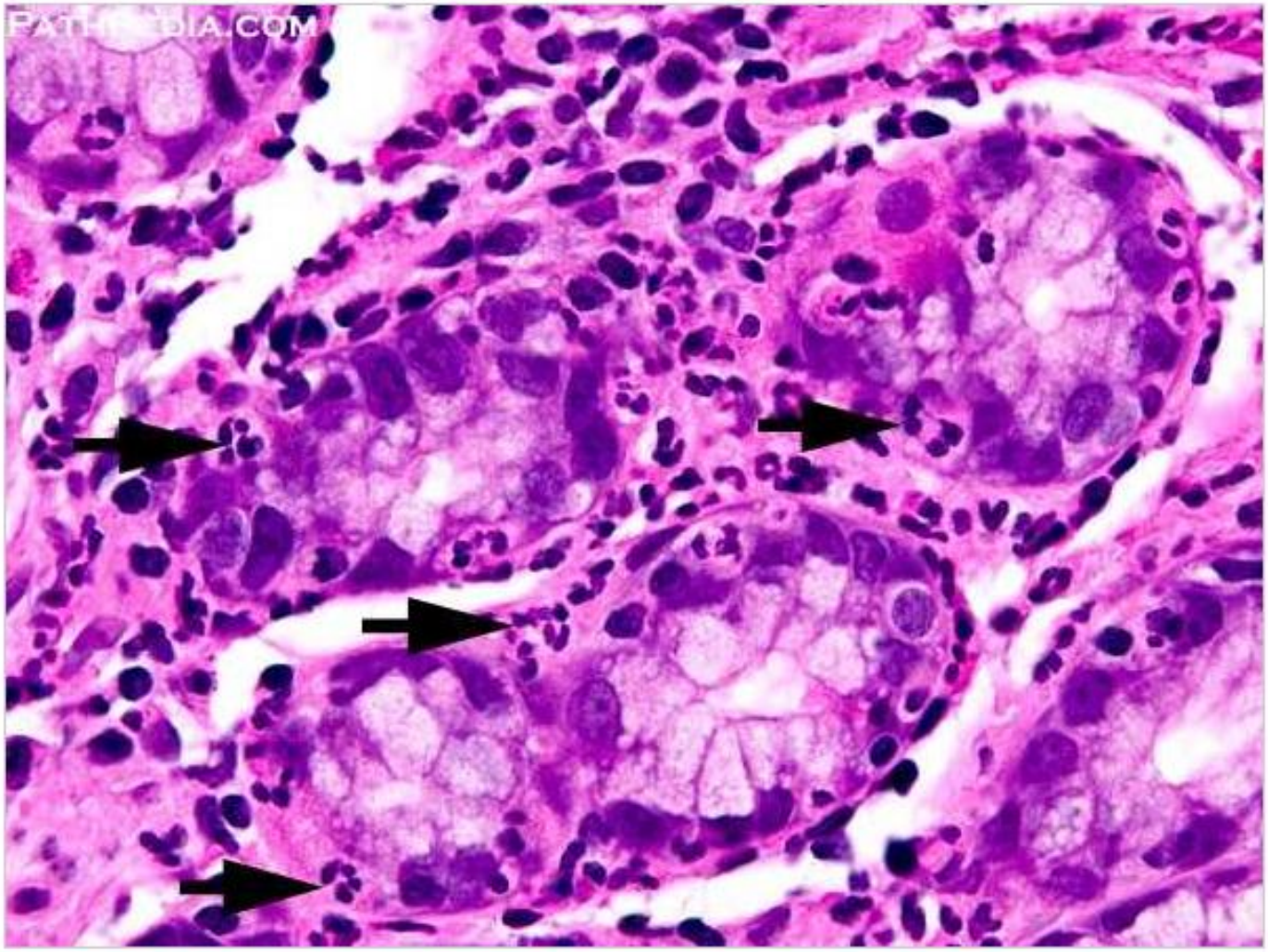
- **Following localization of leukocytes at the injury (implant) site, phagocytosis and the release of enzymes occur following activation of neutrophils and macrophages.**

- **The major role of the neutrophil** in acute inflammation is to phagocytose microorganisms and foreign materials.

    - **Phagocytosis is seen as a three-step process in which the injurious agent undergoes recognition and neutrophil attachment, engulfment, and killing or degradation**

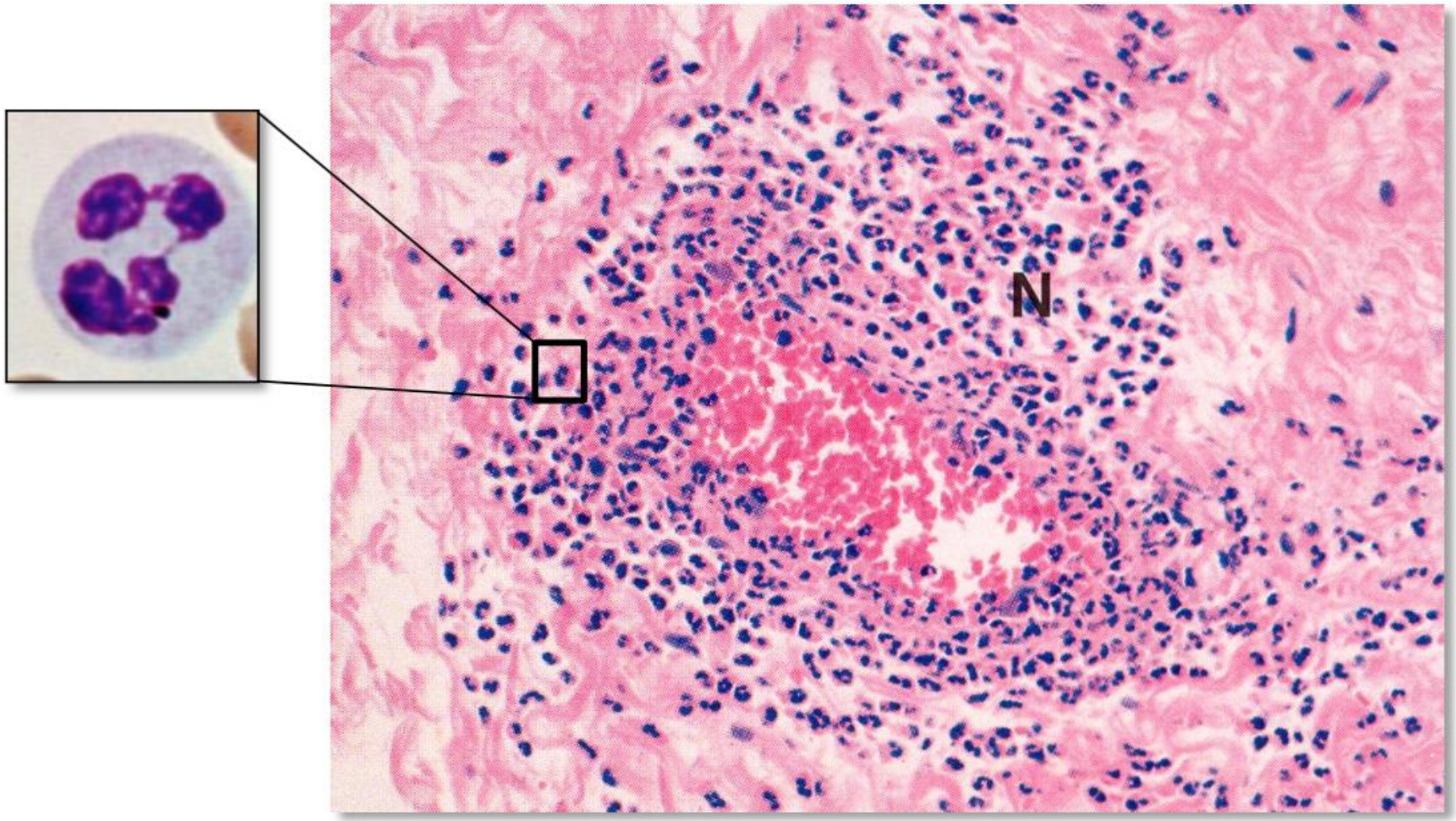


- **biomaterials are not generally phagocytosed by neutrophils or macrophages but certain events in phagocytosis may occur.**
    - The process of recognition and attachment is expedited when the injurious agent is coated by naturally occurring serum factors called “opsonins’’.
    - The two major opsonins are immunoglobulin G (IgG) and the complement-activated fragment, C3b.
    - Both of these plasma-derived proteins are known to adsorb to biomaterials, and neutrophils and macrophages have corresponding cell-membrane receptors for these opsonization proteins.
    - Other blood proteins such as fibrinogen, fibronectin, and vitronectin may also facilitate cell adhesion to biomaterial surfaces.
    - This process does not involve engulfment of the biomaterial, but does cause the extracellular release of leukocyte products in an attempt to degrade the biomaterial.
- **Acute inflammation normally resolves quickly, usually less than 1 week, depending on the extent of injury at the implant site.**
    - the presence of acute inflammation at the tissue/implant interface at time periods beyond 1 week (i.e., weeks, months, or years) suggests the presence of an infection



[ACUTE INFLAMMATION]. Acute inflammation is a quick natural response of the host to tissue injuries and certain foreign injurious agents. The response is mediated by neutrophils and certain plasma proteins and other chemicals. The response is aimed at containing the injurious insult and repairing the damage. Neutrophils are recruited from blood to the site of injury in a series of steps beginning with the release of certain substances at the site of injury that help guide the neutrophils exodus. Acute inflammation may last for hours to several days. This photomicrograph shows acute gastritis with many neutrophils in and around the gastric glands.

Histologically, acute inflammation presents as an abundance of neutrophils accumulated around venules within connective tissue



CHRONIC INFLAMMATION

- Chronic inflammation is characterized by the presence of macrophages, monocytes, and lymphocytes, with the proliferation of blood vessels and connective tissue.

  - **chemical and physical properties of the biomaterial**
  - **motion in the implant site by the biomaterial**
  - **Infection**

  may lead to chronic inflammation.

- The presence of mononuclear cells, including lymphocytes and plasma cells, is considered chronic inflammation

- Chronic inflammation with the presence of collections of lymphocytes and monocytes at extended implant times (weeks, months, years) may also suggest the presence of a long-standing infection

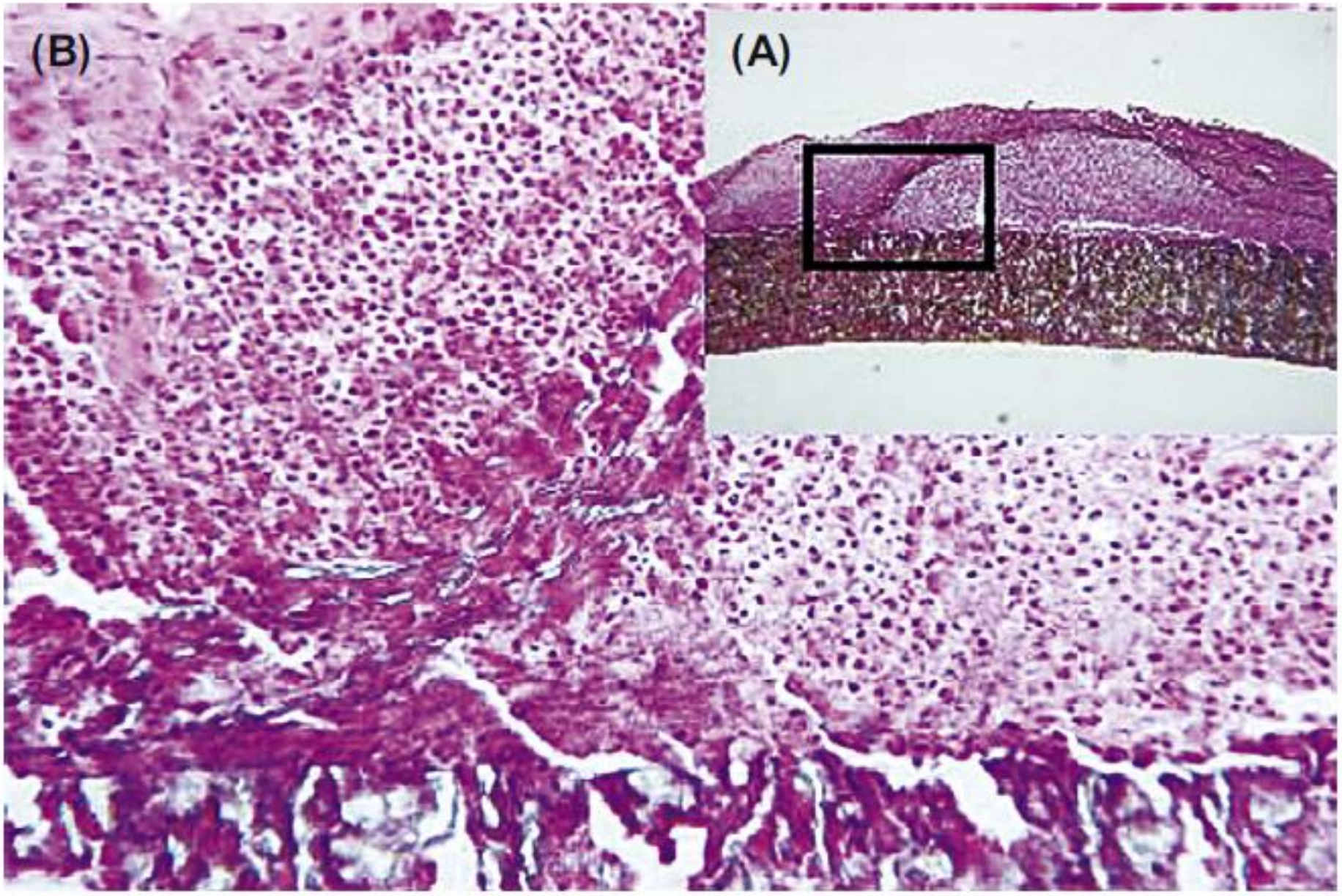
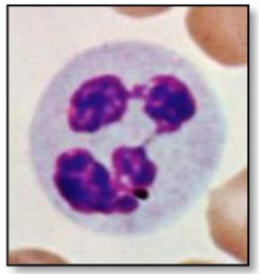
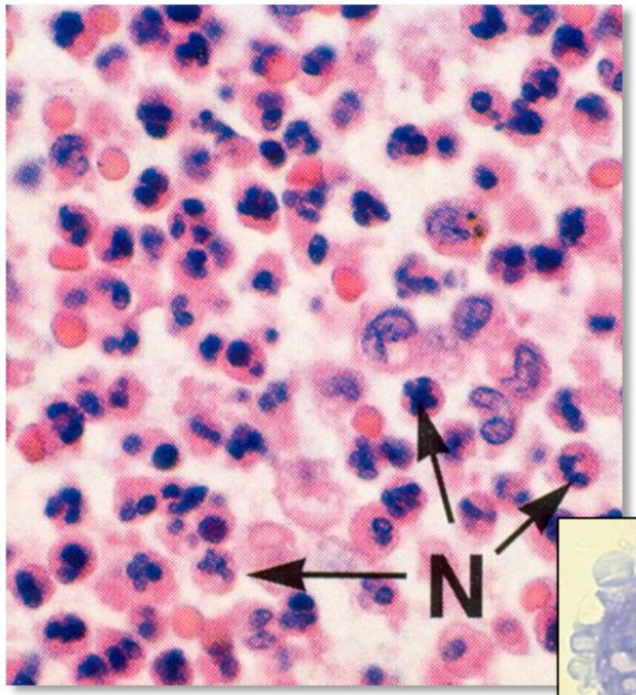
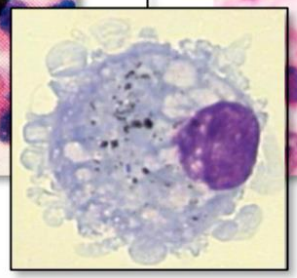


FIGURE II.2.2.3 Chronic inflammation, secondary to infection, of an ePTFE arteriovenous shunt for renal dialysis. (A) Low-magnification view of a focal zone of chronic inflammation. (B) High-magnification view of the outer surface with the presence of monocytes and lymphocytes at an area where the outer PTFE wrap had peeled away from the vascular graft. Hematoxylin and eosin stain. Original magnification (A) 4 ×, (B) 20 ×.

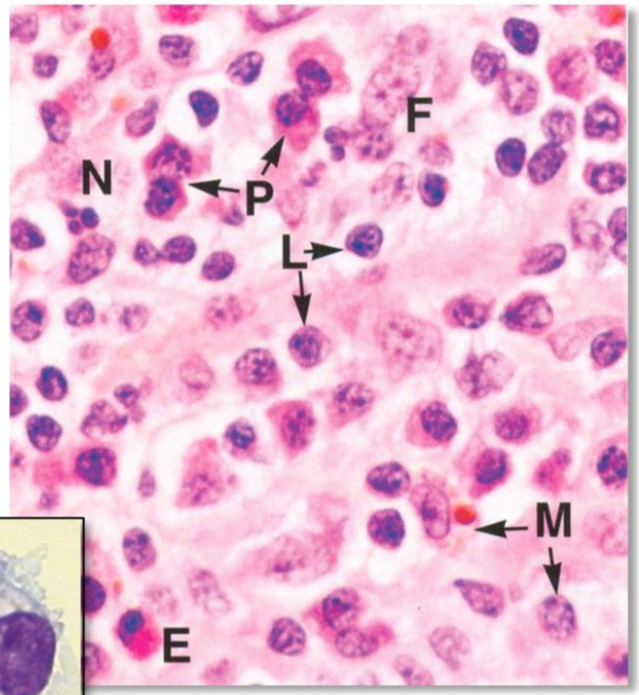
Acute inflammatory exudate

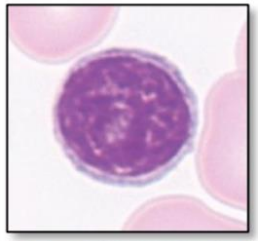


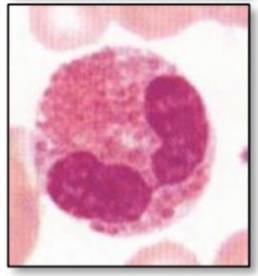


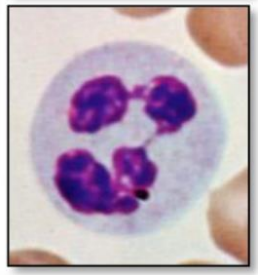


Chronic inflammatory exudate

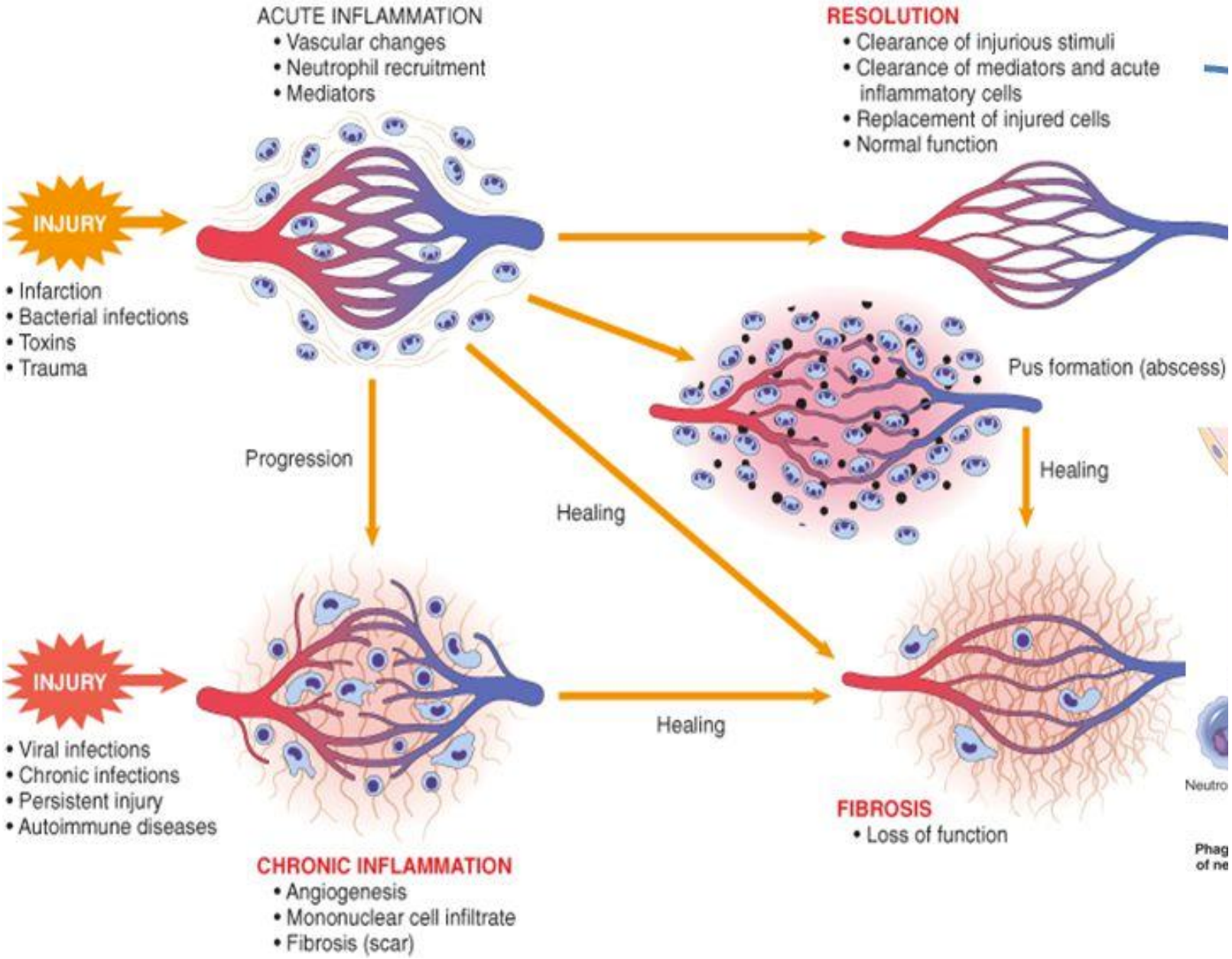








Outcomes of acute inflammation: Resolution, healing by fibrosis, or chronic inflammation



- **The macrophage is probably the most important cell in chronic inflammation, because of the great number of biologically active products it can produce.**

- Growth factors such as

  - platelet-derived growth factor (PDGF)
  - fibroblast growth factor (FGF)
  - transforming growth factor-β (TGF-β)
  - TGF-α/epidermal growth factor (EGF)
  - interleukin-1 (IL-1) or tumor necrosis factor (TNF-α)

  are important to the growth of fibroblasts and blood vessels, and the regeneration of epithelial cells.

- Growth factors released by activated cells can stimulate production of a wide variety of cells; initiate cell migration, differentiation, and tissue remodeling; and may be involved in various stages of wound healing.

	ACUTE	CHRONIC
ONSET	IMMEDIATE	DELAYED
DURATION	FEW DAYS	UPTO MONTHS, YEARS
CAUSATIVE AGENTS	BACTERIA INJURED TISSUES	PERSISTENT ACUTE , FOREIGN BODY , VIRAL AUTOIMMUNE
MAJOR CELLS	NEUTROPHILS ,BASOPHILS MONOCYTESMACROPHAGES	MONONUCLEAR CELLS MONO,LYMHPHOCYTES PLASMA CELLS FIBROBLASTS
PRIMARY MEDIATORS	VASOACTIVE AMINES	EICOSANOIDS
OUTCOMES	RESOLUTION ABSCESS FORMATION CHRONIC INFLAMMATION	TISSUE DESTRUCTION FIBROSIS NECROSIS

GRANULATION TISSUE

- **Within one day following implantation of a biomaterial (i.e., injury), the healing response is initiated by the action of monocytes and macrophages.**

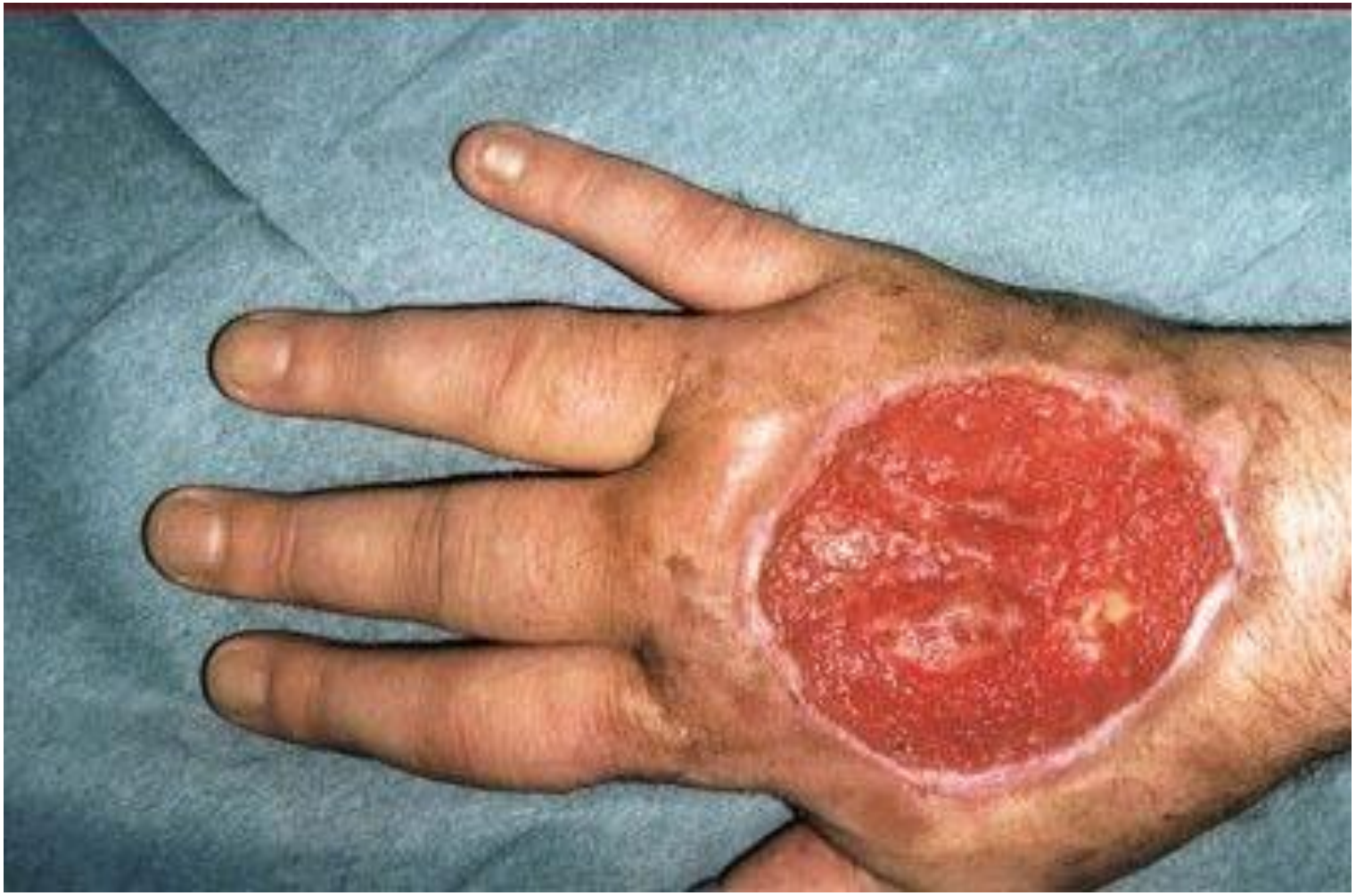
- **Fibroblasts and vascular endothelial cells in the implant site proliferate and begin to form granulation tissue, which is the specialized type of tissue**

- **The new small blood vessels are formed in a process known as neovascularization or angiogenesis**.

- **Fibroblasts also proliferate in developing granulation tissue, and are active in synthesizing collagen and proteoglycans**.

- In the early stages of granulation tissue development, proteoglycans predominate but later collagen, especially type III collagen, predominates and forms the fibrous capsule.

- **Macrophages are almost always present in granulation tissue. Other cells may also be present if chemotactic stimuli are generated**



- **The wound-healing response is generally dependent on the extent or degree of injury or defect created by the implantation procedure.**

  - **Wound healing by primary union** or first intention is the healing of clean, surgical incisions in which the wound edges have been approximated by surgical sutures. Healing under these conditions occurs without significant bacterial contamination, and with a minimal loss of tissue.

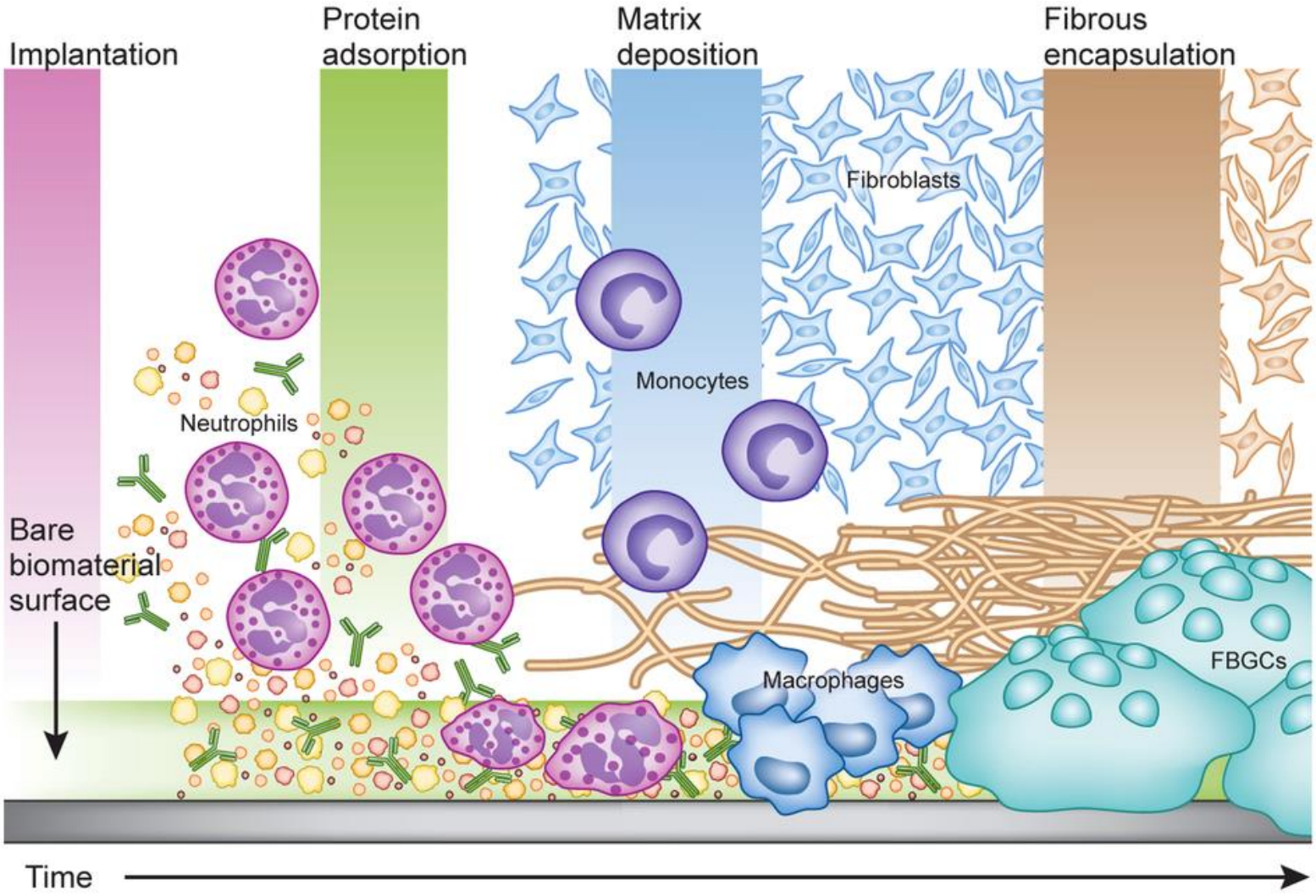
  - **Wound healing by secondary union** or second intention occurs when there is a large tissue defect that must be filled or there is extensive loss of cells and tissue.

    - Regeneration of parenchymal cells cannot completely reconstitute the original architecture, and much larger amounts of granulation tissue are formed that result in larger areas of fibrosis or scar formation.

FOREIGN-BODY REACTION

- The foreign-body reaction to biomaterials is composed of foreign-body giant cells.

- **Foreign body giant cells are formed by the fusion of monocytes and macrophages to phagocytose the material**



- The foreign-body reaction depending upon the form and topography of the implanted material

    - **Relatively flat and smooth surfaces such** as those found on breast prostheses have a foreign-body reaction that is composed of a layer **of macrophages one-to-two cells in thickness.**
    - **Relatively rough surfaces** such as those found on the outer surfaces of expanded poly tetrafluoroethylene (ePTFE) or Dacron vascular prostheses have a foreign-body reaction composed of **macrophages and foreign-body giant cells at the surface.**

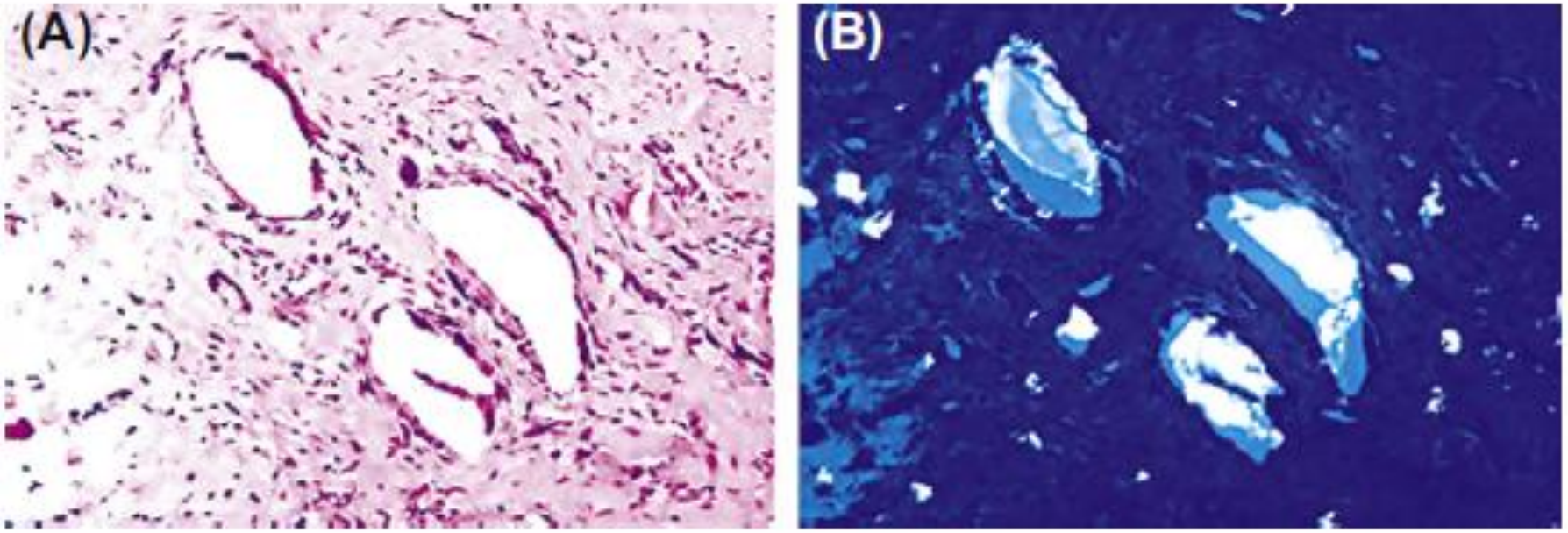


FIGURE II.2.2.6 (A) Focal foreign-body reaction to polyethylene wear particulate from a total knee prosthesis. Macrophages and foreign-body giant cells are identified within the tissue and lining the apparent void spaces indicative of polyethylene particulate. Hematoxylin and eosin stain. Original magnification 20 ×. (B) Partial polarized light view. Polyethylene particulate is identified within the void spaces commonly seen under normal light microscopy. Hematoxylin and eosin stain. Original magnification 20 ×.

video

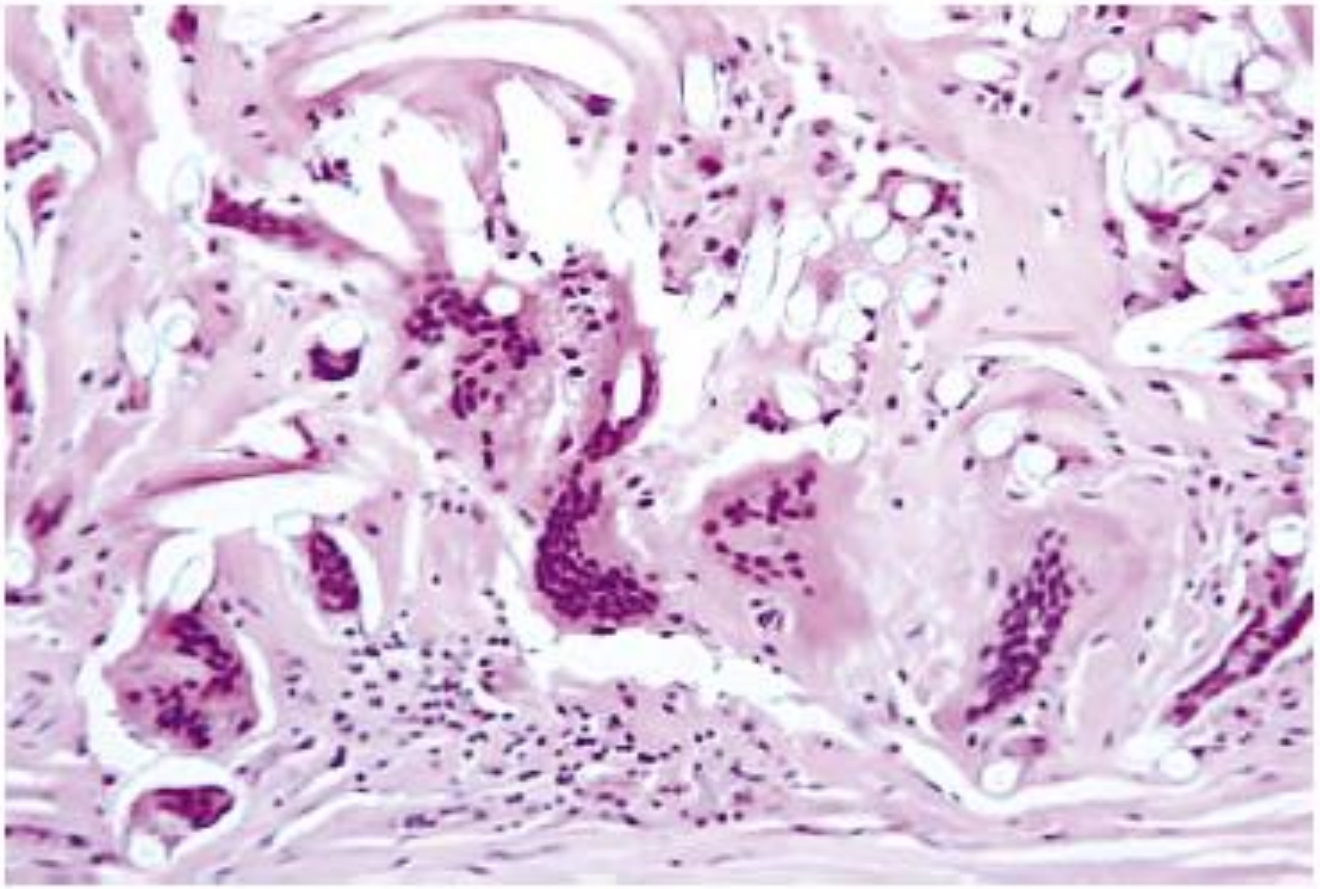


FIGURE II.2.2.7 Foreign-body reaction with multinucleated foreign body giant cells and macrophages at the periadventitial (outer) surface of a Dacron vascular graft. Fibers from the Dacron vascular graft are identified as clear oval voids. Hematoxylin and eosin stain. Original magnification 20 ×.

FIBROSIS/FIBROUS ENCAPSULATION

- **The end-stage healing response to biomaterials is generally fibrosis or fibrous encapsulation**

- Repair of implant sites can involve two distinct processes:

  - **regeneration,** which is the replacement of injured tissue by parenchymal cells of the same type
  - **replacement by connective tissue** that constitutes the fibrous capsule.

- **The regenerative capacity of cells allows them to be classified into three groups:**

  - labile : continue to proliferate throughout life (e.g. **epithelial cells, lymphoid and hematopoietic cells)**

  - stable (or expanding) : retain this capacity but do not normally replicate **parenchymal cells of the liver, kidney, and pancreas); mesenchymal cells (e.g., fibroblasts, smooth muscle cells, osteoblasts, and chondroblasts)**

  - permanent (or static) : cannot reproduce themselves after birth (nerve cells and cardiac muscle cells)

- **Perfect repair with restitution of normal structure can theoretically occur only in tissues consisting of stable and labile cells, whereas all injuries to tissues composed of permanent cells may give rise to fibrosis and fibrous capsule formation with very little restitution of the normal tissue or organ structure.**