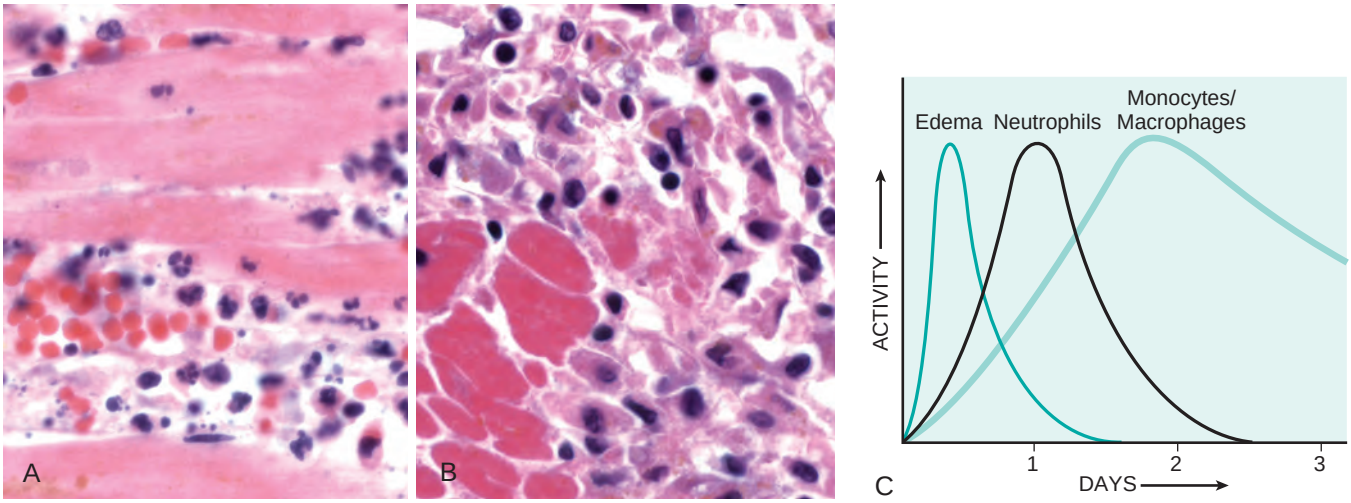

Figure 3-6 Nature of leukocyte infiltrates in inflammatory reactions. The photomicrographs show an inflammatory reaction in the myocardium after ischemic necrosis (infarction). **A,** Early (neutrophilic) infiltrates and congested blood vessels. **B,** Later (mononuclear) cellular infiltrates. **C,** The approximate kinetics of edema and cellular infiltration. For simplicity, edema is shown as an acute transient response, although secondary waves of delayed edema and neutrophil infiltration can also occur.

by selectins); firm attachment to endothelium (mediated by integrins); and migration through interendothelial spaces.

- Various cytokines promote expression of selectins and integrin ligands on endothelium (TNF, IL-1), increase the avidity of integrins for their ligands (chemokines), and promote directional migration of leukocytes (also chemokines); many of these cytokines are produced by tissue macrophages and other cells responding to the pathogens or damaged tissues.
- Neutrophils predominate in the early inflammatory infiltrate and are later replaced by monocytes and macrophages.

Once leukocytes (particularly neutrophils and monocytes) have been recruited to a site of infection or cell death, they must be activated to perform their functions. The responses of these leukocytes consist of (1) recognition of the offending agents by TLRs and other receptors, described earlier, which deliver signals that (2) activate the leukocytes to phagocytose and destroy the offending agents.

Phagocytosis and Clearance of the Offending Agent

Recognition of microbes or dead cells induces several responses in leukocytes that are collectively called *leukocyte activation* (Fig. 3-7). Activation results from signaling pathways that are triggered in leukocytes, resulting in increases in cytosolic Ca^{2+} and activation of enzymes such as protein kinase C and phospholipase A_2. The functional responses that are most important for destruction of microbes and other offenders are phagocytosis and intracellular killing. Several other responses aid in the defensive functions of inflammation and may contribute to its injurious consequences.

Phagocytosis

Phagocytosis involves three sequential steps (Fig. 3-8): (1) *recognition* and *attachment* of the particle to be ingested by the leukocyte; (2) *engulfment*, with subsequent formation of a phagocytic vacuole; and (3) *killing* or *degradation* of the ingested material.

Phagocytic Receptors. **Mannose receptors, scavenger receptors, and receptors for various opsonins bind and ingest microbes.** The macrophage *mannose receptor* is a lectin that binds terminal mannose and fucose residues of glycoproteins and glycolipids. These sugars are typically part of molecules found on microbial cell walls, whereas mammalian glycoproteins and glycolipids contain terminal sialic acid or *N*-acetylgalactosamine. Therefore, the mannose receptor recognizes microbes and not host cells. *Scavenger receptors* were originally defined as molecules that bind and mediate endocytosis of oxidized or acetylated low-density lipoprotein (LDL) particles that can no longer interact with the conventional LDL receptor. Macrophage scavenger receptors bind a variety of microbes in addition to modified LDL particles. Macrophage integrins, notably Mac-1 (CD11b/CD18), may also bind microbes for phagocytosis. The efficiency of phagocytosis is greatly enhanced when microbes are opsonized by specific proteins (opsonins) for which the phagocytes express high-affinity receptors. The major opsonins are IgG antibodies, the C3b breakdown product of complement, and certain plasma lectins, notably mannose-binding lectin, all of which are recognized by specific receptors on leukocytes.

Engulfment. After a particle is bound to phagocyte receptors, extensions of the cytoplasm (pseudopods) flow around it, and the plasma membrane pinches off to form a vesicle (phagosome) that encloses the particle. The phagosome then fuses with a lysosomal granule, resulting in discharge of the granule's contents into the phagolysosome (Fig. 3-8). During this process the phagocyte may also release granule contents into the extracellular space.