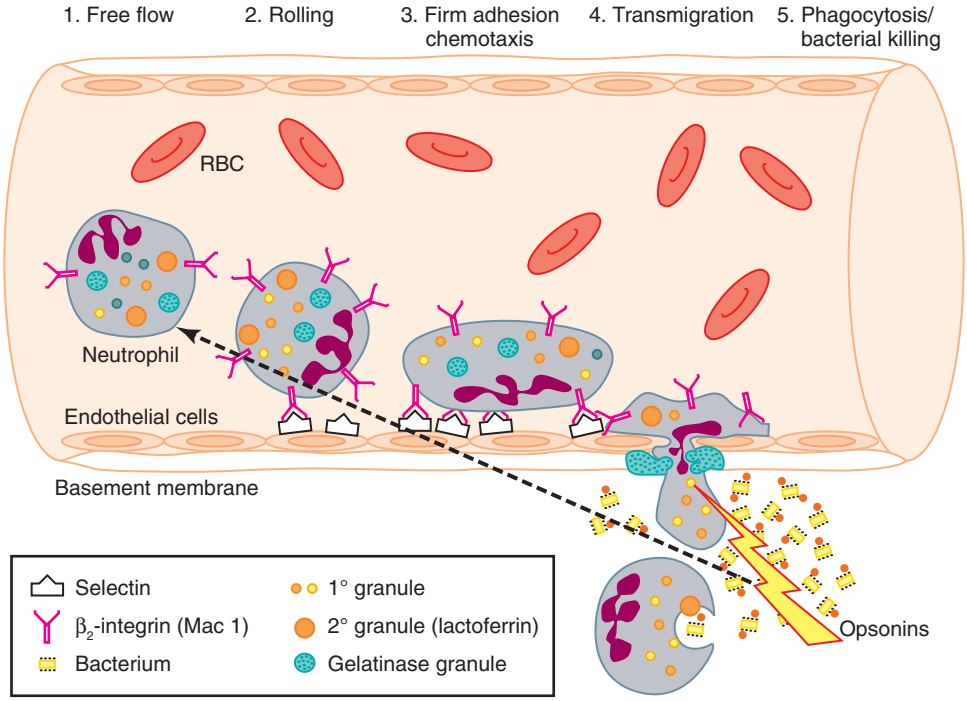

FIGURE 48-2 Sequence of neutrophil activation shows the process of rolling, engagement with the vessel wall, attachment, diapedesis, and phagocytosis. Mac 1, Macrophage antigen 1 (CDI Ib/CD18); RBC, red blood cell.

Intracellular killing occurs by oxygen-dependent and oxygen-independent mechanisms. Contents of the primary granules, including cathepsin G, defensins, and lysozyme, break down the bacterial cell wall and kill the target organism. However, the major mechanism of bacterial killing is the *respiratory burst.* Stimulation of the neutrophil activates a membrane-bound oxidase complex, which generates superoxide through the transfer of an electron from reduced nicotinamide-adenine dinucleotide phosphate (NADPH). The interaction of superoxide with water generates hydroxyl ions. Myeloperoxidase catalyzes the formation of hypochlorite ion from hydrogen peroxide and chloride. The NADPH oxidase is a multisubunit enzyme. Absence or decreased activity of any one subunit impairs bacterial killing and results in chronic granulomatous disease, a congenital illness in which patients are predisposed to life-threatening bacterial infections.

Neutrophil granules give neutrophils their characteristic appearance and have important functions in neutrophil-mediated activation and killing. *Primary granules* arise early in myeloid differentiation and are found in neutrophils and monocytes. They contain a large number of proteins, including myeloperoxidase, acid hydrolases, and neutral proteases. These granules fuse with the phagocytic vacuole and aid in the digestion of ingested bacteria. *Secondary granules* arise later in the differentiation pathway and give the neutrophil its characteristic granular (electron-dense) appearance. These granules contain lactoferrin, transcobalamin, and the matrix-modifying enzymes collagenase and gelatinase. On neutrophil stimulation, the granules are released into the extracellular space. Lactoferrin and transcobalamin act as antibacterial proteins by sequestering iron and vitamin B_{12} away from bacteria, and collagenase and gelatinase break down connective tissues at the site of inflammation.

Abnormalities in neutrophil granules have been described in rare clinical syndromes. Absence of myeloperoxidase produces surprisingly mild symptoms and may be associated with defects in control of fungal infections. Secondary granule deficiency is rare and is associated with a slight increase in the risk of bacterial infections.

For a deeper discussion of these topics, please see Chapter 169, "Disorders of Phagocyte Function," in Goldman-Cecil Medicine, *25th Edition.*

Eosinophils and Basophils

Eosinophils and basophils arise from myeloid precursors in the bone marrow. They transit rapidly from the marrow to the blood and into the peripheral tissues, where they play a role in allergic and inflammatory reactions. Like neutrophils, they have secondary granules that give them a characteristic appearance and are functionally important. Both cell types occur in small numbers under normal conditions.

Although eosinophils are capable of phagocytosis, most of the activity of these cells is mediated through the release of granule contents. The eosinophil numbers are elevated in parasitic and helminthic infections, in which these cells are thought to play a role in the allergic response to those organisms. Cell numbers are also elevated in allergic reactions and in collagen vascular diseases, linking their function to immunomodulation. Hypereosinophilic syndromes, in which extremely high levels of eosinophils can be seen, are rare, and hypereosinophilia can be associated with damage to the lung, peripheral nervous system, and endocardial tissues. The differential diagnosis of eosinophilia is outlined in Table 48-1.