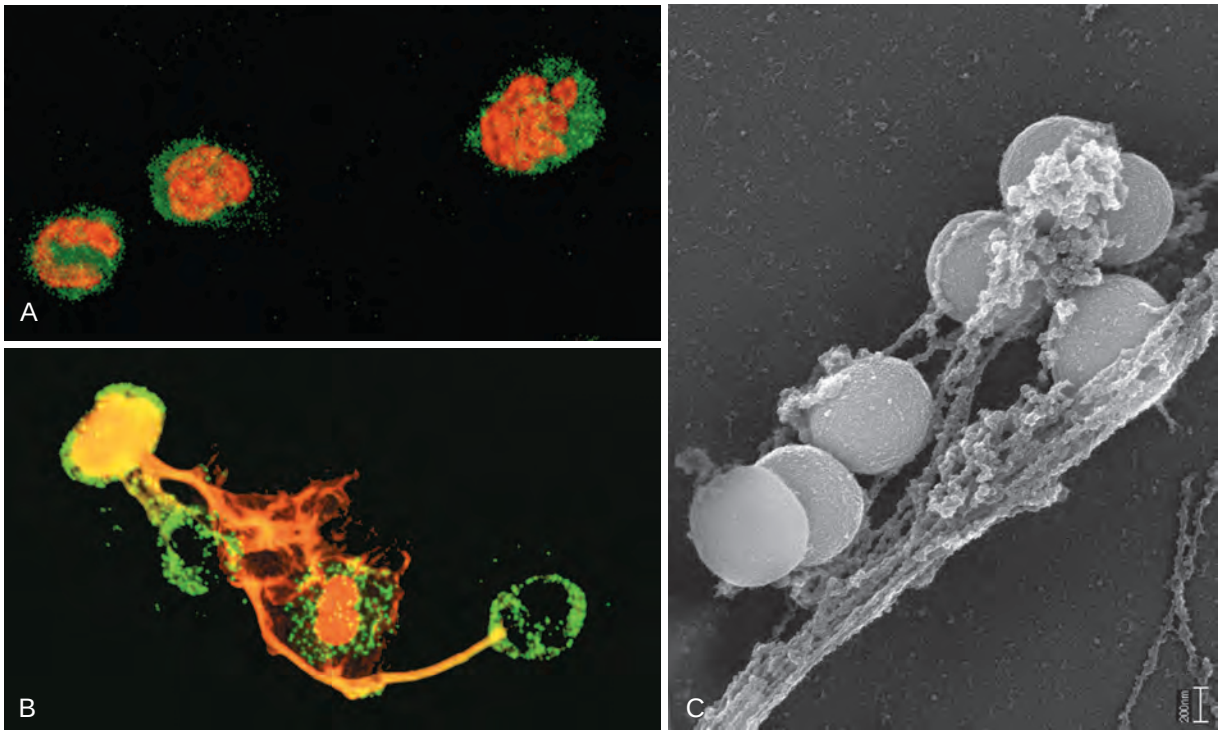

Figure 3-9 Neutrophil extracellular traps (NETs). **A,** Healthy neutrophils with nuclei stained red and cytoplasm green. **B,** Release of nuclear material from neutrophils (note that two have lost their nuclei), forming extracellular traps. **C,** An electron micrograph of bacteria (staphylococci) trapped in NETs. (From Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. Nat Rev Microbiol 2007;5:577, with permission.)

complement proteins directly, yielding anaphylatoxins, and release a kinin-like peptide from kininogen. Neutrophil elastase has been shown to degrade virulence factors of bacteria and thus combat bacterial infections. Macrophages also contain acid hydrolases, collagenase, elastase, phospholipase, and plasminogen activator.

Because of the destructive effects of lysosomal enzymes, the initial leukocytic infiltration, if unchecked, can potentiate further inflammation by damaging tissues. These harmful proteases, however, are normally controlled by a system of *antiproteases* in the serum and tissue fluids. Foremost among these is α_1-antitrypsin, which is the major inhibitor of neutrophil elastase. A deficiency of these inhibitors may lead to sustained action of leukocyte proteases, as is the case in patients with α_1-antitrypsin deficiency (Chapter 15). α_2-Macroglobulin is another antiprotease found in serum and various secretions.

Other microbicidal granule contents include *defensins*, cationic arginine-rich granule peptides that are toxic to microbes; *cathelicidins*, antimicrobial proteins found in neutrophils and other cells; *lysozyme*, which hydrolyzes the muramic acid-*N*-acetylglucosamine bond, found in the glycopeptide coat of all bacteria; *lactoferrin*, an iron-binding protein present in specific granules; and *major basic protein*, a cationic protein of eosinophils, which has limited bactericidal activity but is cytotoxic to many parasites.

Neutrophil Extracellular Traps

Neutrophil extracellular traps (NETs) are extracellular fibrillar networks that provide a high concentration of antimicrobial substances at sites of infection and prevent the spread of the microbes by trapping them in the fibrils. They are produced by neutrophils in response to infectious pathogens (mainly bacteria and fungi) and inflammatory mediators (e.g., chemokines, cytokines [mainly interferons], complement proteins, and ROS). The extracellular traps consist of a viscous meshwork of of nuclear chromatin that binds and concentrates granule proteins such as antimicrobial peptides and enzymes (Fig. 3-9). In the process of NET formation, the nuclei of the neutrophils are lost, leading to death of the cells. NETs have also been detected in the blood during sepsis, and it is believed that their formation in the circulation is dependent on platelet activation. The nuclear chromatin in the NETs, which includes histones and associated DNA, has been postulated to be a source of nuclear antigens in systemic autoimmune diseases, particularly lupus, in which individuals react against their own DNA and nucleoproteins (Chapter 6).

Leukocyte-Mediated Tissue Injury

Leukocytes are important causes of injury to normal cells and tissues under several circumstances:

- As part of a normal defense reaction against infectious microbes, when adjacent tissues suffer collateral damage. In some infections that are difficult to eradicate, such as tuberculosis and certain viral diseases, the prolonged host response contributes more to the pathology than does the microbe itself.
- When the inflammatory response is inappropriately directed against host tissues, as in certain autoimmune diseases.
- When the host reacts excessively against usually harmless environmental substances, as in allergic diseases, including asthma.