production and formation of immune complexes that deposit in vessels. The vascular lesions resemble those found in experimental immune complex–mediated disorders, such as the Arthus phenomenon and serum sickness, and in many cases contain readily identifiable antibody and complement. Often, however, this type of vasculitis presents a number of diagnostic challenges. Only rarely is the specific antigen responsible for immune complex formation identified. Also, in most cases it is not clear whether the pathogenic antigen-antibody complexes are deposited from the circulation or form in situ. Indeed, the sensitivity and specificity of circulating immune complex assays in such diseases are extremely low. In many suspected cases, even the antigen-antibody deposits are scarce. In such instances, the immune complexes may have been degraded by the time of biopsy; alternatively, other mechanisms may underlie such "pauci-immune" vasculitides.

Immune complex deposition is also implicated in the following vasculitides:

- *Drug hypersensitivity vasculitis*. In some cases (e.g., penicillin), drugs act as haptens by binding to serum proteins or vessel wall constituents; other agents are themselves foreign proteins (e.g., streptokinase). Regardless, antibodies directed against the drug-modified proteins or foreign molecules result in immune complex formation. The clinical manifestations can be mild and self-limiting, or severe and even fatal; skin lesions are most common. It is always important to consider drug hypersensitivity as a cause of vasculitis since discontinuation of the offending agent usually leads to resolution.
- *Vasculitis secondary to infections*. Antibodies to microbial constituents can form immune complexes that circulate and deposit in vascular lesions. In up to 30% of patients with polyarteritis nodosa (see later), the vasculitis is attributable to immune complexes composed of hepatitis B surface antigens (HBsAg) and anti-HBsAg antibody.

Antineutrophil Cytoplasmic Antibodies

Many patients with vasculitis have circulating antibodies that react with neutrophil cytoplasmic antigens, so-called *antineutrophil cytoplasmic antibodies (ANCAs)*. ANCAs are a heterogeneous group of autoantibodies directed against constituents (mainly enzymes) of neutrophil primary granules, monocyte lysosomes, and endothelial cells. ANCAs are very useful diagnostic markers; their titers generally mirror clinical severity, and a rise in titers after periods of quiescence is predictive of disease recurrence. Although a number of ANCAs have been described, two are most important. These were previously grouped according to the intracellular distribution of the target antigens (cytoplasmic [c-ANCA] or perinuclear [p-ANCA]), but are now classified according to their antigen specificity:

- *Anti-proteinase-3 (PR3-ANCA, previously c-ANCA)*. PR3 is a neutrophil azurophilic granule constituent that shares homology with numerous microbial peptides, raising the possibility that the generation of PR3-ANCAs is triggered by certain infections. PR3-ANCAs are associated with polyangiitis (see later).
- *Anti-myeloperoxidase (MPO-ANCA, previously p-ANCA)*. MPO is a lysosomal granule constituent involved in oxygen free radical generation (Chapter 3). MPO-ANCAs are induced by several therapeutic agents, particularly propylthiouracil. MPO-ANCAs are associated with microscopic polyangiitis and Churg-Strauss syndrome (see later).

The close association between ANCA titers and disease activity suggests a pathogenic role for these antibodies. Of note, ANCAs can directly activate neutrophils, stimulating the release of reactive oxygen species and proteolytic enzymes; in vascular beds, such activation also leads to destructive interactions between inflammatory cells and endothelial cells. While the antigenic targets of ANCA are primarily intracellular (and therefore not usually accessible to circulating antibodies), it is now clear that ANCA antigens (especially PR3) are either constitutively expressed at low levels on the plasma membrane or are translocated to the cell surface in activated and apoptotic leukocytes.

A plausible mechanism for ANCA vasculitis is the following:

- Drugs or cross-reactive microbial antigens induce ANCA formation; alternatively, leukocyte surface expression or release of PR3 and MPO (in the setting of infections) incites ANCA development in a susceptible host.
- Subsequent infection, endotoxin exposure, or inflammatory stimulus elicits cytokines such as TNF that upregulate the surface expression of PR3 and MPO on neutrophils and other cell types.
- ANCAs react with these cytokine-activated cells, causing either direct injury (e.g., to endothelial cells) or further activation (e.g., of neutrophils).
- ANCA-activated neutrophils cause tissue injury by releasing granule contents and reactive oxygen species.

Since ANCA autoantibodies are directed against cellular constituents and do not form circulating immune complexes, the vascular lesions do not typically contain demonstrable antibody and complement. Thus, ANCA-associated vasculitides are often described as "pauci-immune." Interestingly, ANCA directed against proteins other than PR3 and MPO are often seen in patients with nonvasculitic inflammatory disorders, such as inflammatory bowel disease, sclerosing cholangitis, and rheumatoid arthritis.

Antiendothelial Cell Antibodies

Antibodies to endothelial cells, perhaps induced by defects in immune regulation, may predispose to certain vasculitides, for example, Kawasaki disease (see later).

The following discussion presents several of the best characterized and generally recognized vasculitides; there is substantial overlap among the different entities. Moreover, it should be kept in mind that some patients with vasculitis do not have a classic constellation of findings that allows them to be neatly pigeon-holed into one specific diagnosis.

Giant Cell (Temporal) Arteritis

Giant cell (temporal) arteritis is the most common form of vasculitis among older individuals in the United States