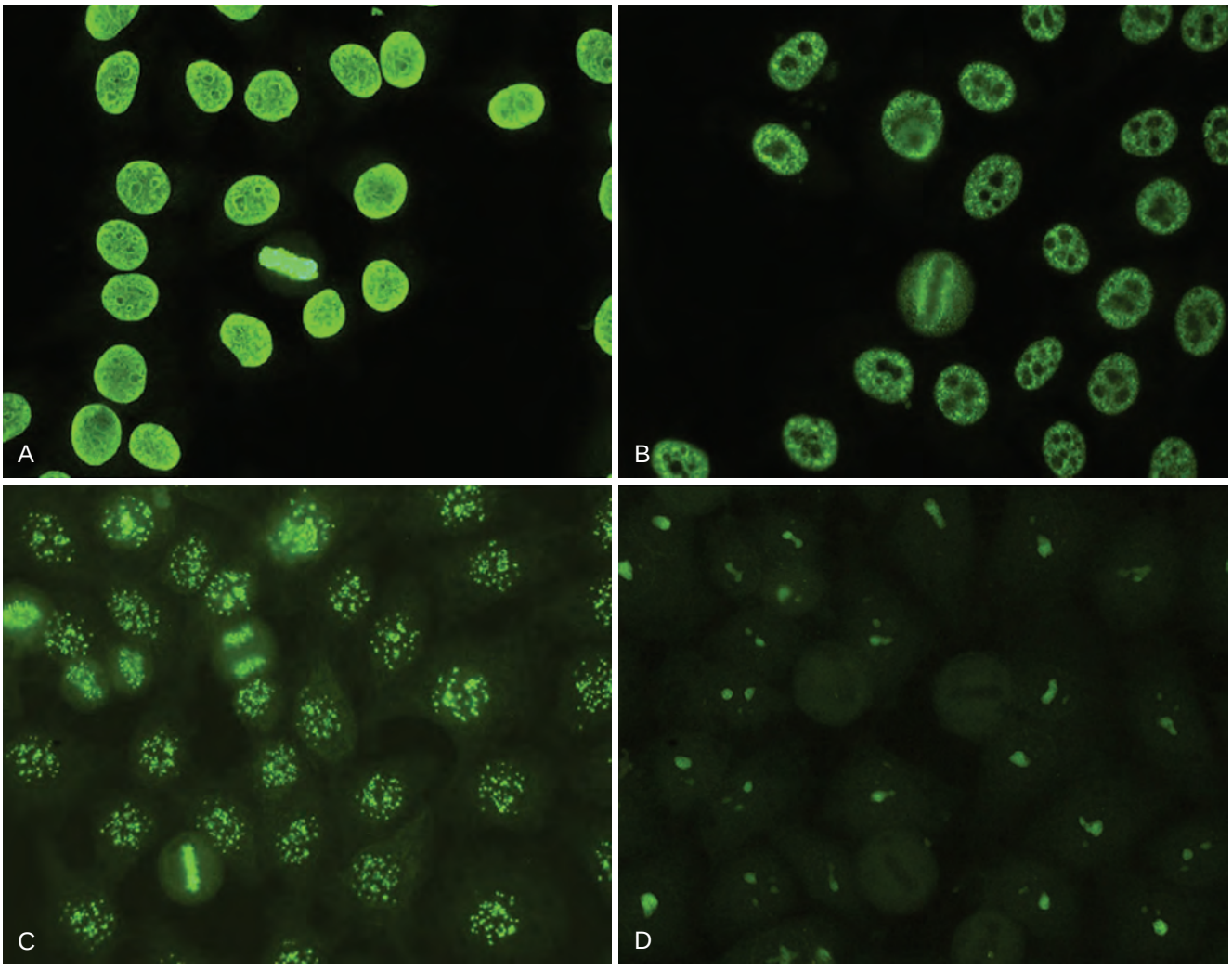

Figure 6-24 Staining patterns of antinuclear antibodies. **A,** Homogeneous or diffuse staining of nuclei is typical of antibodies reactive with dsDNA, nucleosomes and histones, and is common in SLE. **B,** Speckled pattern is seen with antibodies against various nuclear antigens, including Sm and RNPs. **C,** The pattern of staining of anti-centromere antibodies is seen in some cases of systemic sclerosis, Sjogren syndrome, and other diseases. **D,** Nucleolar pattern is typical of antibodies against nucleolar proteins. (Images reproduced from Wiik AS, et al, J. Autoimm. 35:276, 2010, with permission.)

autoantibodies. Specific alleles of the *HLA-DQ* locus have been linked to the production of anti–double-stranded DNA, anti-Sm, and antiphospholipid antibodies, although the relative risk is small.

- Some lupus patients have inherited deficiencies of early complement components, such as C2, C4, or C1q. Lack of complement may impair removal of circulating immune complexes by the mononuclear phagocyte system, thus favoring tissue deposition. Knockout mice lacking C4 or certain complement receptors are also prone to develop lupus-like autoimmunity. Various mechanisms have been invoked, including failure to clear immune complexes and loss of B-cell self-tolerance. It has also been proposed that deficiency of C1q results in defective phagocytic clearance of apoptotic cells. Many cells normally undergo apoptosis, and if they are not cleared their nuclear components may elicit immune responses.
- Genome-wide association studies have identified several genetic loci that may be associated with the disease. Many of these loci encode proteins involved in lymphocyte signaling and interferon responses, both of which may play a role in lupus pathogenesis, as discussed later. The relative risk for each locus is small, and even taken together these loci account for 20% or less of the genetic predisposition, suggesting an important role for environmental factors, discussed later.

Immunologic Factors. Recent studies in animal models and patients have revealed several immunologic aberrations that collectively may result in the persistence and uncontrolled activation of self-reactive lymphocytes.

- **Failure of self-tolerance in B cells** results from defective elimination of self-reactive B cells in the bone marrow or defects in peripheral tolerance mechanisms.
- **CD4+ helper T cells** specific for nucleosomal antigens also escape tolerance and contribute to the production of high-affinity pathogenic autoantibodies. The autoantibodies in SLE show characteristics of T cell-dependent antibodies produced in germinal centers, and increased