wAIHA. First, cold agglutinin disease (CAD) is a chronic and more frequently indolent condition—in contrast to the abrupt onset of warm antibody AIHA. Second, the term *cold* refers to the fact that the autoantibody involved reacts with red cells poorly or not at all at 37°C, whereas it reacts strongly at lower temperatures. As a result, hemolysis is more prominent the more the body is exposed to the cold. Third, the antibody is produced by a clone of autoreactive B lymphocytes. Sometimes the antibody concentration in the serum is high enough to show up as a spike in plasma protein electrophoresis, thus qualifying CAD as an IgM monoclonal gammopathy; however, it differs from Waldenström macroglobulinemia by not having the characteristic *MYD88* mutation (see **Chap. 111**): there is instead, in the B-cell clone of a majority of CAD patients, a somatic mutation in the *KMT2D* gene, encoding a lysine histone methylase that seems to favor proliferation. The antibody produced by the B-cell clone is IgM; usually it has an anti-I specificity (the I antigen is present on the red cells of almost everybody), and it may have a very high titer (1:100,000 or more has been observed). IgM, when bound to red cells, is a powerful activator of the complement cascade, with ultimate formation of the membrane attack complex (see Fig. 100-9): this will directly cause destruction of red cells (*intravascular hemolysis:* indeed, CAD patients may present with hemoglobinuria). In addition, once complement is activated C3b will bind to red cells that, thus opsonized, will be destroyed by macrophages (*extravascular hemolysis*); unlike in AIHA, there is no predominance of the spleen in this process.

In mild forms of CAD, avoidance of exposure to cold may be all that is needed to enable the patient to have a reasonably comfortable quality of life; but in more severe forms, the management of CAD is not easy. Plasma exchange will remove antibodies and is, therefore, in theory, a rational approach in severe cases. However, the management of CAD has changed significantly with the advent of the anti-CD20 antibody rituximab: up to 60% of patients respond. If remission is followed by relapse, a new course of rituximab may be again effective, and remissions may be more durable with a rituximab-fludarabine combination, in particular in