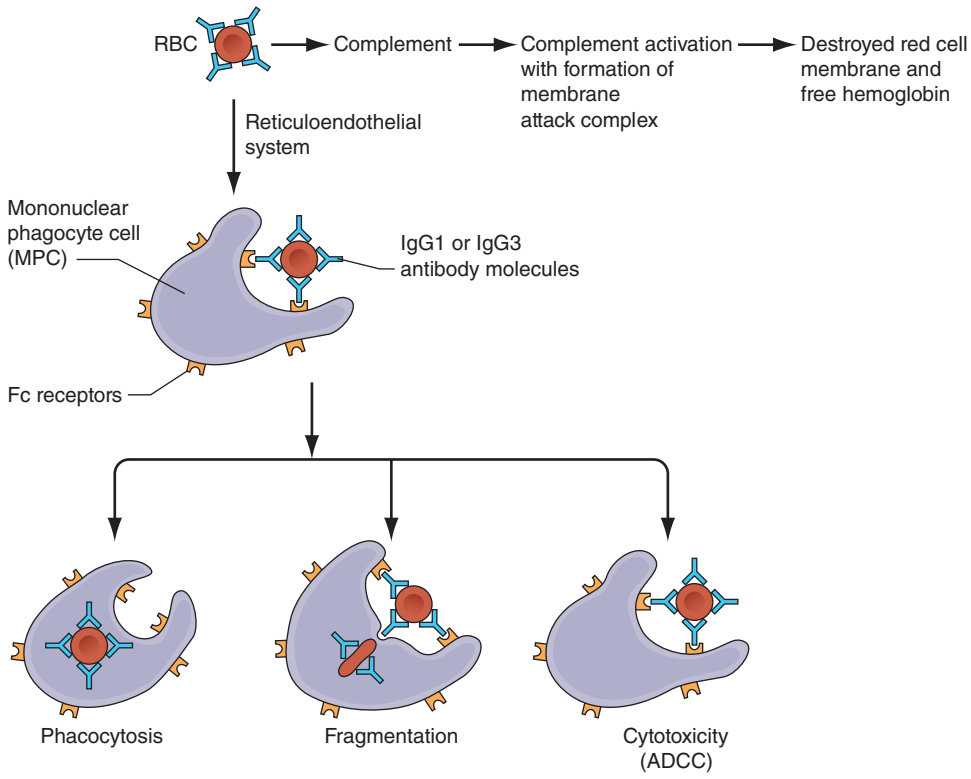

FIGURE 129-8 Mechanism of antibody-mediated immune destruction of red blood cells (RBCs). ADCC, antibody-dependent cell-mediated cytotoxicity. *(From N Young et al: Clinical Hematology. Philadelphia, Elsevier, 2006; with permission.)*

PAROXYSMAL COLD HEMOGLOBINURIA (PCH) PCH is a rather rare form of AIHA occurring mostly in children, usually triggered by a viral infection, usually self-limited, and characterized by the involvement of the so-called Donath-Landsteiner antibody. In vitro, this antibody has unique serologic features; it has anti-P specificity and binds to red cells only at a low temperature (optimally at 4°C), but when the temperature is shifted to 37°C, lysis of red cells takes place in the presence of complement. Consequently, in vivo there is intravascular hemolysis, resulting in hemoglobinuria. Clinically the differential diagnosis must include other causes of hemoglobinuria (Table 129-6), but the presence of the Donath-Landsteiner antibody will prove PCH. Active supportive treatment, including blood transfusion, is needed to control the anemia; subsequently, recovery is the rule.

COLD AGGLUTININ DISEASE (CAD) This designation is used for a form of chronic AIHA that usually affects the elderly and has special clinical and pathologic features. First, 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. The antibody is usually 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). Second, the antibody is produced by an expanded clone of B lymphocytes, and sometimes its concentration in the plasma is high enough to show up as a spike in plasma protein electrophoresis, i.e., as a monoclonal gammopathy. Third, because the antibody is IgM, CAD is related to Waldenström's macroglobulinemia (WM) **(Chap. 136)**, although in most cases, the other clinical features of this disease are not present. Thus, CAD must be regarded as a form of WM (i.e., as a low-grade mature B cell lymphoma) that manifests at an earlier stage precisely because the unique biologic properties of the IgM that it produces give the clinical picture of chronic HA.

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. Blood transfusion is not very effective because donor red cells are I positive and will be rapidly removed. Immunosuppressive/cytotoxic treatment with azathioprine or cyclophosphamide can reduce the antibody titer, but clinical efficacy is limited, and in view of the chronic nature of the disease, the side effects may prove unacceptable. Unlike in AIHA, prednisone and splenectomy are ineffective. Plasma exchange will remove antibody and is, therefore, in theory, a rational approach, but it is laborious and must be carried out at frequent intervals if it is to be beneficial. The management of CAD has changed significantly with the advent of rituximab; although its impact on CAD is not as great as on AIHA, up to 60% of patients respond, and remissions may be more durable with a rituximab-fludarabine combination. Given the long clinical course of CAD, it remains to be seen with what schedule or periodicity these agents will need to be administered.

Toxic Agents and Drugs A number of chemicals with oxidative potential, whether medicinal or not, can cause hemolysis even in people who are not G6PD deficient (see above). Examples are hyperbaric oxygen (or 100% oxygen), nitrates, chlorates, methylene blue, dapsone, cisplatin, and numerous aromatic (cyclic) compounds. Other chemicals may be hemolytic through nonoxidative, largely unknown mechanisms; examples include arsine, stibine, copper, and lead. The HA caused by lead poisoning is characterized by basophilic stippling; it is in fact a phenocopy of that seen in P5N deficiency (see above), suggesting it is mediated at least in part by lead inhibiting this enzyme.

In these cases, hemolysis appears to be mediated by a direct chemical action on red cells. But drugs can cause hemolysis through at least two other mechanisms. (1) A drug can behave as a hapten and induce antibody production; in rare subjects, this happens, for instance, with penicillin. Upon a subsequent exposure, red cells are caught, as innocent bystanders, in the reaction between penicillin and antipenicillin antibodies. Hemolysis will subside as soon as penicillin administration is stopped. (2) A drug can trigger, perhaps through mimicry, the production of an antibody against a red cell antigen. The best known example is methyldopa, an antihypertensive agent no longer in use, which in a small fraction of patients stimulated the production of the