EDITORIAL

Auto-immunization

BETWEEN 1907 and 1914, the French workers Chauffard,[1] Widal[2] and their collaborators discriminated sharply between hereditary and acquired types of hemolytic anemia. The rivalry between these two groups was keen, but from it sprang many new concepts and diagnostic tests. Widal, Abrami, and Brulé found auto-agglutinins in each of their cases of acquired hemolytic anemia and pointed to the diagnostic value of this finding. The significance of their observations was lost for many years, and for a long period (approximately between 1920 to 1940) many observers stated that no real distinction could be made between hereditary and acquired forms. In the last decade, however, observations have accumulated which not only prove that hemolytic anemia may be acquired but which go far towards indicating some of the mechanisms involved.

The finding of an immune type of iso-hemolysin in three cases of acute hemolytic anemia led us to suspect that this was etiologically related to the excessive degree of hemolysis present.[3] This was borne out by experimental observations with hetero-hemolysins.[4] Guinea pig red cells, injected into rabbits, resulted in the development of anti-guinea pig hemolytic serum. When this serum was then injected in guinea-pigs, spherocytosis and acute hemolytic anemia developed. The observation was made that the small spherocytes were mature red cells and that the large red cells present were reticulocytes. This "biphasic" type of red cell population was considered to be distinctive for hemolytic anemia and the deduction was made that it was due to (a) hemolytic activity of hemolysin acting on mature red cells and producing spherocytosis, and (b) to regenerative activity on the part of the marrow, resulting in reticulocytosis. The disease hemolytic anemia was considered to be an "active" rather than a "passive" process, and not due to a marrow dysfunction.

Later, when the mechanisms for acute hemolytic disease of the newborn (erythroblastosis fetalis) were studied, it was apparent that Rh iso-antibody as developed by the Rh negative mother was responsible for injuring and thus destroying the Rh positive red cells of the fetus. Some Rh antibodies could be detected in salt solution, whereas in other cases, bovine albumin or plasma had to be used to demonstrate the agglutinin ("blocking" or "univalent" antibodies). With the use of another test developed later by Coombs, Mourant, and Race,[5] it was apparent that antibody was firmly affixed ("coated") to the red cell and could not be readily removed even with repeated washings of salt solution.

Hetero-immunization is rather readily understood; red cells from one species of animal (X-antigen) are injected into the circulation of another species; the second animal builds up a hetero-antibody (anti-X); this antibody can then injure the red cells of animals of the X-type and cause hemolytic anemia. Iso-immunization, too, seems fairly simple to comprehend, at least in its superficial aspects. Here, an individual lacking a specific factor (such as Rh) can be immunized by the red cells (antigen) of another individual of the same species, with the production of

an antibody. When this antibody (anti-Rh) is then re-injected into the circulation of an individual with Rh positive red cells, antibody is adsorbed by the red cells. These become injured, i.e., spherocytic, or agglutinated, and are then removed from the circulation either by way of mechanical trauma or by splenic hemolysis.

In most cases of acquired hemolytic anemia other than in the type seen in the newborn, *auto*-immunization appears to be the central feature. The cause for this phenomenon, in which the individual's own red cells apparently develop antigenic qualities, thus producing an auto-antibody, is quite obscure. In any event, there can be little doubt that in practically all cases of acquired hemolytic anemia not due specifically to bacteria, parasites, chemicals or other definite factors, i.e., in the idiopathic cases, the plasma contains an *auto*-antibody which acts against the individual's own red cells. This is also an *iso*-antibody, since it reacts against all types of human red cells and can be detected both by the use of bovine albumin as a testing fluid and by the Coombs anti-globulin technic. Evidence is at hand indicating that this antibody causes a shortening of red cell survival time of "foreign" transfused red cells and of the individual's as well. Recent studies in our laboratory reveal a striking correlation between three tests: (1) iso- and auto-antibody as detected by the bovine albumin technic, (2) the anti-globulin test, and (3) the red cell survival time as determined by the Ashby technic. We find that auto-antibody is often higher in concentration than is iso-antibody.

Auto-immunization appears to be the prime factor in acquired hemolytic anemia. It occurs not only in the idiopathic cases, but in the "symptomatic" hemolytic anemia of such conditions as chronic lymphocytic leukemia. In the last three cases of this disorder we have observed, an auto-antibody of agglutinin type was demonstrable. As a result of auto-immunization, various types of antibodies may develop. It appears probable that antibody, affixing itself to the mature red cells of the affected individual, causes agglutination and other disturbances of the red cell membrane with resultant spherocytosis. The highest concentrations of antibody are associated with the greatest degrees of spherocytosis. These "sensitized" red cells are then acted upon either by complement, causing hemolysis, or more often are destroyed by the mechanical trauma of the circulation or selectively removed from the circulation by the spleen

Splenectomy in acquired hemolytic anemia may or may not remove the largest single production center for auto-antibody formation; in any event, the chief spherocyte-destroying organ is removed. It is well to realize that splenectomy may be either wholly or partially ineffective, since continued production of antibody may occur. Future progress in acquired hemolytic anemia, which seems to be on the increase, lies in determining why auto-immunization develops and how it may be controlled

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