EDITORIAL

The Hemolytic Crisis

THE HEMOLYTIC crisis which occurs so suddenly in cases of familial hemolytic jaundice (familial spherocytosis) has excited interest but its pathogenesis has remained a mystery since it was first described as "crise de déglobulization." Adding to its mystery is its fairly frequent occurence in successive members of the same family, the cases usually appearing within a few days of each other.[1–3]

During the crisis there is a precipitous reduction in the red cell count, accompanied by such constitutional symptoms as fever, vomiting and malaise. Some blood findings have received relatively scant attention, although occasional observers have noted the rather paradoxical reductions in leukocytes, platelets and reticulocytes which may be present—paradoxical because in excessive blood destruction one expects regenerative efforts on the part of the bone marrow with resultant increases in reticulocytes, leukocytes and platelets. What is more, reticulocytosis is considered almost as pathognomonic a finding of the disease as spherocytosis.

Some years ago, I remarked on the pancytopenia which occurred in three cases of familial crisis[1] and stated that "one may speculate as to whether this . . . is due to a hormonal influence of the spleen on the marrow, with the result that the maturation or delivery of cells to the circulation becomes inhibited." In studying a recent case* Bloom and I found, during the crisis, marked pancytopenia with a complete lack of reticulocytes for four days. Simultaneously, the marrow showed maturation arrest of the nucleated red cells at the primitive or erythrogone level. When the arrested maturation was spontaneously re-established, reticulocytosis took place in the peripheral blood and the blood counts then returned to pre-crisis levels. We have interpreted the events occurring in crisis as due largely to "hypersplenic" effects with resultant hyperhemolysis, as well as inhibitory effects upon the marrow, the latter resulting in maturation arrest and diminished delivery of marrow cells to the blood.

Owren, whose comprehensive article on the hemolytic crisis appears in this issue, submits a different interpretation for the same set of data. He states that there is no evidence for increased hemolysis during crisis but that the extreme reductions in red cells, leukocytes, platelets and reticulocytes are due to a sudden hypoplastic or aplastic disturbance in the marrow. On the other hand, the extreme spherocytosis of the crisis, the drop in red cell count of from 1.0 to 3.0 millions within a day or two of onset and the remarkably quick response in all the various blood cellular constituents which occurs with splenectomy, would seem to argue against Owren's thesis. Nevertheless, Owen's observations are of unusual interest and should serve to provoke further work on the pathogenesis of the crisis, and, indeed, on the fundamental mechanisms of familial hemolytic spherocytosis as well. It is likely that

* Dameshek, William and Bloom, Marvin S.: The Events in the Hemolytic Crisis with Particular Reference to Reticulocytopenia. To be published in one of the forthcoming issues of *Blood* dedicated to Dr. George R. Minot.

two mechanisms, acting simultaneously, are responsible for the extremely rapid drops in red cell count: (1) maturation arrest and (2) hyperhemolysis.

The development of extreme spherocytosis in the crisis might indicate that this was due to the activity of some extrinisic hemolytic factor acting upon mature red cells, thus causing their rapid destruction. If this is true for the crisis, in which we have occasionally found the presence of a serum auto-hemolysin, it is also a possibility for the less marked spherocytosis and anemia during the long periods between crises. In other words, is congenital spherocytosis really due to a fundamental defect in erythropoiesis as most observers maintain, or is it dependent upon the action of some hemolytic factor which may be specific for the individual's own red cells? In favor of this concept is the relatively large size of the polychromatophilic reticulocytes, which are quite in contrast with the more mature orthochromatic spherocytes. This might indicate that "hemolysin" has converted normal non-nucleated reticulocytes to injured red cells, i.e. the spherocytes. This would take the disease out of the bone marrow and into some vascular or intravascular site. Be that as it may, there are still many unsolved problems in this, the first described and best known form of hemolytic anemia, and a portent of work to come.

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REFERENCES

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