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Treatment of Hemolytic Anemias with Associated Intracorpuscular Defect

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ANEMIA BY DEFINITION is a clinically significant reduction of the red cell mass to levels below normal. It may result from inadequate production of red cells or from decreased life span of the red cells.[5] Hemolytic anemia belongs in the latter category; in all hereditary hemolytic anemias, the short life span of the red cell is a consequence of some intrinsic fault.[4] The cell is faultily constructed in such a way that it is incapable of surviving normally in the normal blood stream. Transfuse the blood from such a patient into a normal recipient and the red cells are quickly destroyed. Transfuse normal red cells into the patient with hereditary spherocytosis and they survive normally. It is the red cell itself, not its environment, that is fundamentally at fault. Yet, fortunately, the environment can sometimes be altered in such a way that even the abnormal red cells can survive, and, in spite of the abnormality, the hemolytic disease is corrected.

Treatment of anemia involves two principles: (1) to increase the production of red cells when inadequate and (2) to prolong the life span of red cells when too short. In hemolytic disease, and also in hemorrhage, a normal bone marrow compensates for the short life span by increasing the output of red cells.[6] The life span can be one-eighth of normal and the erythropoietic marrow, by producing eight times the normal number of red cells, prevents anemia. Any further decrease in life span usually results in anemia because the marrow is unable to make the additional effort. The degree of anemia which results depends on the difference between the requirement for red cells and the amount produced: The shorter the life span, the worse the anemia. In this situation, the severity of anemia may be critical and therapy imperative. If it is not possible to correct the hemolytic disease, treatment by blood transfusion can augment the effort of the marrow. The aim of transfusion so employed is not to correct the anemia but to prevent invalidism or death from lack of oxygen-carrying capacity of the blood.

In most kinds of hereditary hemolytic anemia, the average life span of the red cells is from 10–20 days, or about 8–15 per cent of the normal 120 days.

HEREDITARY SPHEROCYTOSIS (HS)[9]

The hemolytic disease of hereditary spherocytosis (HS) can be cured by splenectomy. The short life span of the spherocyte is the consequence of a genetically determined defect of cellular metabolism which results in premature destruction by the spleen.[16] With the spleen removed, the abnormality of the red cells remains, but the cells are able to survive normally. Rare recurrences following splenectomy have resulted from splenosis or massive hypertrophy of an accessory spleen. Unless there are overbearing contraindications, it is a good practice to recommend splenectomy whenever the diagnosis of HS is made. The cure rate is practically 100 per cent, the risk is small, and the complications of HS in unsplenectomized patients are dangerous. The possible exception to this recommendation is in the case of children less than 1 year old, and this is discussed below. We have encountered patients with HS whose anemia became troublesome at 75–85 years of age; splenectomy was recommended and performed with the usual gratifying cure of the patient's disease.

Corticosteroids and other hormones, hematinics, and other replacement or supportive therapy are without value in HS unless there is a specific indication for them which is unrelated to the hereditary disease, e.g., iron deficiency or pernicious anemia.

Aregenerative crisis is an abrupt temporary obliteration of the erythropoietic marrow.[15] The crisis is thought to be a reaction to viral infection, and it may attack one member after another in a family with HS. Red cell production stops, usually for about 10 days. The production of granulocytes and platelets may also be interfered with, but rarely to the extent of causing purpura or the agranulocytic syndrome. However, the anemia is a serious, even life-threatening problem. The turnover of red cells in HS is ordinarily so rapid that interrupting the supply of replacements even for a few days results in rapid development of severe anemia. Consider the difference between a normal human and a patient with HS under these conditions, when erythropoietic activity is stopped for 10 days.[4] The average life span of normal red cells is 120 days; after the resupply of red cells has been halted for 10 days the total red cell mass will have shrunk by an inconsequential 8 per cent. The average life span of hereditary spherocytes may be about 12 days; after resupply has been halted 10 days, the red cell mass will have shrunk by more than 75 per cent of the original. After splenectomy, the patient with HS behaves normally because the life span of red cells is sufficiently lengthened to override the short-lived crisis.

Treatment of the crisis is transfusion of either whole blood or red cells. The normal red cells survive normally and serve to sustain the patient

through the period of aregeneration. The amount of transfusion should be sufficient to prevent physiologic embarrassment from peripheral hypoxia. The crisis is characterized by reticulocytopenia, and the end of the crisis is heralded by a flood of reticulocytes. There is no reason to use corticosteroids or other bone marrow "stimulants" or hematinics. Splenectomy is recommended as soon as the patient is "out of the woods."

Hemolytic crisis is a relatively rare complication of HS in which an acquired hemolytic process (usually autoimmune) is superimposed on the hereditary disease.[4, 19] The life span of the spherocytes becomes even shorter and the anemia proportionately more severe. The signs of hemolytic disease are exaggerated: the reticulocytosis increases, the spleen may expand, and there may even be hemoglobinuria. The Coombs' test has been found to be positive and autoagglutination and autohemolysis have also been observed. The marrow is not aplastic, as in the aregenerative crisis. The crises which have been described have been short-lived and appear to be a consequence of intercurrent infection, in some cases infectious mononucleosis.

Treatment of the crisis is fundamentally supportive in nature and consists of the appropriate use of blood transfusion. In this circumstance, the donor cells are susceptible to the acquired hemolytic process and their short survival means that the transfusion program may have to be more intense than it is in the aregenerative crisis. The patient's physiologic requirement for oxygen-carrying capacity should be the indicator of adequacy. If the transfusion of 2 or 3 units blood/day is insufficient to maintain an adequate concentration of hemoglobin, the use of corticosteroids is indicated to damp the acquired hemolytic process. The initial dose should be large enough to assure prompt improvement if the process is susceptible to steroid therapy, i.e., 100–150 mg./day of cortisone or its equivalent. The dose should be promptly tapered to the lowest level which controls hemolysis and withdrawn altogether when the patient can maintain his hemoglobin at an adequate concentration without corticosteroids.

The anemia of HS may become more severe during pregnancy. If the complication is severe and if it involves an aregenerative reaction of the marrow, one should consider the advisability of splenectomy to improve the life span of whatever red cells the marrow is capable of producing. The second trimester is the best time for such intervention. Careful hematologic studies should be made to determine whether or not the patient has iron deficiency. Megaloblastic anemia of pregnancy has been reported in women with HS[18] and other forms of hereditary hemolytic disease.[20] Supplemental iron and folic acid are usually sufficient to correct these deficiency states.

Gallstones develop in almost all patients with HS. To prevent this

complication is one important reason for recommending early splenectomy. In *any* case, the gallbladder should be examined prior to splenectomy, and when stones are present the surgical incision should be planned to permit removal of both gallbladder and spleen.

Infection following splenectomy has been reported to be a serious problem in young children, and the subject is still being debated.[13, 17] The original warnings were based almost entirely on cases of severe hematologic disease, such as Cooley's anemia. It has not been and at present cannot be determined whether infants with HS are placed at any increased risk of infection by removal of the spleen. Beyond the age of 1 year, it seems certain they are not. The decision of whether or not to recommend splenectomy for children in the first year of life requires careful judgment, weighing the risk of the operation and the *possibility* of increased risk of infection against the dangers of the disease. In the author's experience, the problem has been resolved by recommending splenectomy for HS when the infant is anemic or has had an anemic crisis.

HEREDITARY NONSPHEROCYTIC HEMOLYTIC ANEMIA[1, 2, 11]

This is a *group* of diseases as yet not clearly separable one from another but different from HS because of lack of spherocytosis and because of failure of splenectomy to cure the hemolytic anemia.

Treatment of benefit to the patient consists of supporting him through anemic crises by blood transfusion, as in HS. At the present time, it seems wise to forego other therapeutic trials, especially steroids and splenectomy, which have been proved of no value. There is one variety of this disease in which the red cells demonstrate a deficiency of glucose 6-phosphate dehydrogenase.[18] Patients with hereditary nonspherocytic hemolytic anemia should all be tested for absence of this enzyme; those who are found to possess the fault should be protected against the classes of drugs which induce hemolysis in the anemic crises due to "primaquine sensitivity." (See article by Anderson and Swisher in this Symposium.)

HEREDITARY ELLIPTOCYTOSIS[20, 24, 25]

This is a group of diseases of varying pathogenicity. There is one form in which the morphologic abnormality is not associated with shortened red cell life span, and an intermediate form in which red cell life span is moderately shortened without anemia, a completely compensated hemolytic disease. Elliptocytosis with hemolytic anemia resembles HS in many respects. Osmotic fragility is increased, autohemolysis of blood incubated in vitro is abnormally high, there is splenomegaly, and the

hemolytic disease is cured by splenectomy. The disease might be classified as an elliptocytic variant of HS or a spherocytic variety of hereditary elliptocytosis. A precise nosologic classification awaits definition of the faults which produce the red cell deformities and diminished life span.

Treatment of hereditary elliptocytosis is not indicated when there is no disease. With hemolytic anemia, splenectomy is recommended. Complications are treated as in HS. Care should be taken to exclude the possibility of the ovalocytic variety of thalassemia minor, which may be mistaken for elliptocytosis but is not benefited by splenectomy.

PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare, chronic, incurable hemolytic disease, probably acquired, which may appear early or late in life, and may be mild, severe, or variable in its course. Of its etiology nothing is known, and no specific or permanently beneficial treatment is available. The term "hemolytic" applied to PNH has a broader meaning than usual, for not only are red cells destroyed prematurely but there is reason to believe that the white cells and platelets are similarly involved. The hemolytic anemia is characterized by chronic hemoglobinemia which varies in intensity from day to night, rising while the patient sleeps and falling when he wakes. "Nocturnal" hemoglobinuria occurs when the plasmal level rises enough during sleep to top the renal threshold for hemoglobin. Patients with PNH are especially prone to infections, a susceptibility which may reflect an inadequacy of their leukocytes, and they are apt to develop thrombosis, perhaps because of their sensitive platelets. There are crises of increased hemolysis with severe hemoglobinuria, and at these times the danger of thrombosis is magnified. When death occurs, it is usually during such crises.

The onset of the disease is often insidious. Symptoms of anemia take the patient to his doctor, and not infrequently attempts at therapy precipitate the first bout of hemoglobinuria. The early years of the illness are often the worst, with many crises, many bouts of infection, and much pain due probably to minor infarction. If the patient survives these years, he not infrequently develops an ability to live with his illness and may go for years without serious difficulty.

The cause of death is usually one of three complications. Thrombosis, either of the brain or portal system, is the most common. Acute anemia during severe crises is second; third is infection, a complication which has diminished considerably as a cause of death since the development of antibiotics.

Treatment of PNH is difficult. The usual hematinics are worthless at

best, and usually harmful. The use of iron, even by mouth, not infrequently provokes hemoglobinuria. The steroid hormones are generally contraindicated by their tendency to cause thrombosis. Several patients have died from cortisone-induced thromboses, and others have not been helped. However, should a patient develop a hemolytic crisis due to autoimmunization with antibodies against his own red cells, the use of steroids may be of value. If steroids are to be given, it is advisable to preface therapy with Dicumarol, and thereby counteract the tendency to thrombosis. Splenectomy is generally of no value in PNH. The spleen is seldom much enlarged and the operation is not often recommended. Rarely, the spleen becomes massive and "hypersplenic," at which time splenectomy is justified even though the organ may be a site of myeloid metaplasia.

Therapy for these patients is best kept to a minimum. They should be encouraged to learn to live with their anemia. When the anemia is severe or becomes severe during crises, the patient should be given transfusions. If he develops reactions to the transfusions, the plasma should be removed from the blood and the red cells washed with saline before they are transfused. Reactions to compatible blood are common in PNH and are usually followed in several hours by hemoglobinuria due to destruction of the patient's own red cells. This is apparently a reaction to plasma of the transfused blood and may be avoided by using washed red cells. During severe crises of anemia, one must continue transfusion despite these reactions to prevent death.

Dextran, a polymer of dextrose which is used as a plasma volume expander, is somehow able to interfere with the PNH hemolytic system;[7] infusions of 500 ml. of 6 per cent dextran have been helpful in controlling crises. Long-term use of dextran is not recommended because it may induce a tendency to bleed.

The use of Dicumarol in the treatment of PNH may be of limited benefit. It helps prevent thrombosis and is therefore recommended during crises. In some patients, Dicumarol also impedes hemolysis and the anemia is benefited. However, it does not prevent or halt hemolytic crises, even though it may prevent thrombosis during the crisis. Once Dicumarol is started it should not be suddenly withdrawn. The tendency to thrombosis that it holds in check may abruptly reassert itself. The long-term administration of Dicumarol may relieve a patient suffering from frequent pains of PNH, and at the same time diminish his need for transfusions. It goes without saying that Dicumarol must not be used without adequate control of the patient's prothrombin activity, which should be kept at about 20 per cent of normal.

Heparin can increase PNH hemolysis and should not be used, especially during hemolytic crises.

It is difficult to make a prognosis in PNH because of the danger of sudden fatal thrombosis. Some patients have been known to live for 35 years, while others, in whom the disease was abrupt and violent, have died in a few months. When one surveys the damage that has been caused by ill considered efforts at therapy in PNH, one cannot help feeling that life expectancy would be improved if the patients were neglected.

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