Treatment of Paroxysmal Nocturnal Hemoglobinuria with ACTH

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PAROXYSMAL NOCTURNAL HEMOGLOBINURIA is a rare hemolytic disease characterized by intravascular hemolysis and excretion of hemoglobin in the urine during sleep. Crosby,1 in an extensive review of the literature, found reports of 123 cases of this condition and gave credit to Strübing for first recognizing it as an entity in 1882. It was not until another description was published by Marchiafava2 in 1928, however, that the disease became generally recognized.

The real nature of the hemolytic process is still unknown. Van den Bergh, in 1911, discovered that the defect lay in the red cells and that their destruction was increased by exposure to carbonic acid. Subsequently, it was confirmed that the plasma of these patients is normal and that a factor present in normal plasma is essential for the hemolytic action.3 The nocturnal occurrence of hemoglobinuria was explained on the theory that during sleep there is decreased pulmonary ventilation, consequent carbon dioxide retention, and thus a lowered hydrogen ion concentration of the body fluids which would be conducive to hemolysis. The evidence, however, that such a change occurs is not strong. Recently it has been fairly definitely demonstrated4 that the hemolysis does not depend on an antigen-antibody reaction, and that the degree of hemolysis parallels the accelerator-globulin activity (Ac-globulin of Seegers, Factor V of Owren, labile factor of Quick), suggesting that this globulin fraction may be the essential plasma hemolytic factor noted previously. The clinical and pathologic aspects of this disease have been well described in previous reviews by Scott,5 Ross6 and Marks7 and need not be discussed here.

This condition has been classed as an acquired hemolytic disease in the absence of any evidence that the red cell defect is hereditary or congenital. Because of the ineffectiveness of all forms of therapy used in the past8 and in view of recent reports of the beneficial effects of ACTH in acquired hemolytic anemias,9 10 a patient in whom the diagnosis of paroxysmal nocturnal hemoglobinuria was established was recently treated with ACTH. It is the purpose of this communication to describe the results of this therapy.

CASE REPORT

The patient, a 41 year old man, came to the clinic in November 1950. He had been in good health until the spring of 1946 when he had had an episode of acute bacterial pneumonia, treated with sulfonamides. Shortly after an apparently good recovery, he began to notice weakness, fatigue and pallor. Examination at that time revealed a hemoglobin value of 40 per cent. He was studied fully in a hospital and a diagnosis was finally made of "aplastic anemia." He received periodic blood transfusions for the next year. In November 1947 he was studied in another hospital, and it was observed that the urine voided on arising in the morning was deeply colored while that passed during the rest of
the day was normal in color. An acid hemolysis test was then performed and found to be positive. A diagnosis of paroxysmal nocturnal hemoglobinuria was made at that time.

From the early part of 1948 until June 1950 the patient was maintained in a state of moderate well-being by repeated blood transfusions and was able to do light work. Beginning in June 1950 the hemoglobinuria became constant throughout the twenty-four hour period. He became severely anemic and complained of marked weakness and lassitude.

Initial physical examination at the clinic revealed a yellowish pallor and mildly icteric sclerae. The liver and spleen were not palpable. Urinalysis demonstrated plus albuminuria and hemosiderin granules contained within epithelial cells. Throughout the period of observation before treatment all urine specimens passed day and night varied from the color of strong tea to almost black. Examination of the blood revealed the following: hemoglobin 5.6 Gm. per 100 cc., erythrocytes 1,500,000; hematocrit 16 per cent and reticulocytes 22 per cent. The platelets were reduced to 62,000 per cu. mm. The resistance of the erythrocytes to lysis in hypotonic saline solution was normal and the Coombs test was negative. The test for acid hemolysis was positive. Bone marrow smears showed marked normoblastic hyperplasia. The megakaryocytes appeared adequate in number but only 16 per cent were actively forming platelets.

On December 4, 1950, the patient was admitted to the hospital for therapy. He was given infusions of ACTH (Armour) solution intravenously for eleven days, starting with 12.5 mg. per day, increasing to 80 mg., then decreasing to 10 mg., with a total of 437.5 mg. Each infusion was given over a period of eight to twelve hours. Eosinophil counts in the fasting state and after the termination of each infusion were low, the highest count being 25 per cu. mm. In addition, he received five transfusions of washed red cells. Subjectively, there was marked improvement with production of a feeling of well-being. Objectively, however, there was no significant change in the color of the urine and the reticulocyte counts remained essentially at the pretreatment level. The patient was discharged on the thirteenth hospital day.

Three weeks later (January 10, 1951) he was readmitted to the hospital because of severe, generalized, abdominal cramps associated with low grade fever and black urine. During the previous six months he had experienced three similar attacks, all subsiding spontaneously in five to seven days. On this occasion he received three transfusions of whole blood and left the hospital on the fifth day, free of fever and cramping abdominal pain. Five days later, on January 20, 1951, he returned to the hospital, again with severe, generalized, abdominal pains and backache, and requested another course of ACTH. The drug was given intravenously as before, with a total of 410 mg. over twelve days, starting with 20 mg. daily, increasing to 80 mg. and decreasing to 5 mg. Eosinophil counts in the fasting state were variable, the highest being 128 and the lowest 6 per cu. mm. Following each infusion the eosinophil counts were low, in the range of 0 to 10 per cu. mm. Within thirty-six hours of the beginning of therapy his pains had completely subsided and two days after the start of treatment the urine became normal in color. This was associated with a definite rise in hemoglobin and hematocrit, and a marked fall in reticulocytes. The hemosiderinuria and the positive acid hemolysis test, however, remained. Improvement in the blood persisted during the rest of the hospital stay. At the end of the ACTH therapy, cortisone, 50 mg. daily by mouth, was started, and the patient was discharged, feeling well.

The urine remained free of hemoglobin for a total of fifteen days. On the fifth day of cortisone therapy, however, there was a gradual return of hemoglobinuria throughout the twenty-four hour period, associated with a fall in the hemoglobin and the hematocrit reading. The dose of cortisone was increased to 200 mg. per day for two days, then reduced to 150 mg. At this dosage level the urine cleared for two days but again became deeply colored in spite of continued high doses of cortisone. There was a sharp rise in reticulocytes during this period.

On February 26, 1951, for the third time the patient was hospitalized for ACTH treatment. Therapy was again given by the intravenous route as before, with a total of 790 mg. given over seventeen days, starting with 40 mg. daily, increasing to 80 mg., then decreasing to 20 mg. For two days the urine was clear, but following a transfusion it again became deeply colored and this color persisted. As with the first course of therapy, there
was no significant change in the blood picture apart from a slight temporary decrease of reticulocytes. During this period the patient became definitely, although not deeply jaundiced. Because of failure to improve, he became very discouraged and left the hospital on March 17, 1951.

During the next few days the abdominal cramps recurred. There was a sharp drop in the hemoglobin, red cell count and hematocrit values to alarming levels, with a concomitant rise in the reticulocyte count. He was admitted to the hospital for the fifth time on March 29, 1951, and given immediate and repeated transfusions of washed red cells. Shortly after admission, administration of dicumarol was begun in doses sufficient to maintain a plasma level of prothrombin of about 10 to 30 per cent. There was a very rapid drop in the reticulocyte count and a slower rise in hemoglobin and hematocrit levels. Five days after starting treatment the urine became free of hemoglobin. Albuminuria gradually disappeared but hemosiderin persisted. The patient was discharged from the hospital but continued taking dicumarol. When last seen at the clinic his urine had been clear for five weeks. He then returned to his home to continue medication under the supervision of his local physician.

The values of the hemogram are given in figure 1.

**Discussion**

This case illustrates several interesting points with regard to both the disease and the treatment. The hemoglobinuria becomes constant and is as great during the day as during the night. This condition not infrequently occurs in the later stages of the disease. This would seem to argue against the role of a fall in hydrogen ion concentration as the determining factor in the typical nocturnal nature of the hemoglobinuria. As suggested by Crosby and Dameshek, it would be of interest to determine Ac-globulin activity during the day and night in the early stages of the disease.

Leukopenia and thrombocytopenia are found in a considerable number of patients; in this case the platelet count was definitely decreased. The reason
for the occurrence of these cytopenias is not known, although there are several possible explanations. There may be a hypersplenic effect with decreased release of platelets from the marrow or increased destruction in the spleen; the absence of sequestration of cells in the spleen and the failure of patients to improve after splenectomy are possible arguments against this effect. Crosby and Dameshek have suggested that the thrombocytopenia may be due to the withdrawal of platelets from the circulating blood in the formation of the many platelet thrombi commonly found on postmortem examination, or to increased platelet destruction comparable to the red cell lysis.

A third possibility is that there is a primary failure of development of thrombocytes; this is suggested by the fact that among 8 recently reported cases available for review,12-19 in which the platelet count was specifically mentioned, 3 were low,12-14 and of these, 2 were found to have no megakaryocytes in the sternal marrow smears.12-14 In addition, in 4 of 7 postmortem studies in which histologic examination of the bone marrow was performed,5 there were few or no megakaryocytes. In the present case the marrow contained a normal number of megakaryocytes but production of platelets seemed to be depressed.

Treatment of this condition has been unsatisfactory. Various attempts at therapy have included alkalinization of the blood, administration of parasympathomimetic drugs such as pilocarpine, splenectomy and transfusion.8 Each of these methods appeared to be effective for a time but sooner or later, the beneficial effect was lost. Recently the use of dicumarol was tried by Crosby and Dameshek because of its Ac-globulin inhibiting effect, with equivocal results. Blood transfusions at times appeared to produce prolonged remissions, but because the donor blood carries with it a supply of the very factor which is necessary for hemolysis, transfusion is often followed by an acute exacerbation or "intragroup transfusion reaction." For this reason Dacie20 recommended the use of washed red cells rather than whole blood.

The use of ACTH in hematologic conditions has centered around the leukoses and acquired hemolytic anemias with demonstrable antibodies. Although paroxysmal nocturnal hemoglobinuria is considered to be an acquired disease, no abnormal antibodies are demonstrable. Because of the plight of the patient, however, a trial with ACTH was considered worth while. The results in this case have been confusing but of considerable interest. The remission which occurred during the second course of treatment was in all probability due to therapy and not merely coincidental. The long preceding period of constant hemoglobinuria, its sudden complete cessation during therapy and the associated changes in the blood picture all are strongly in favor of such an assumption.

The question then arises as to why the drug was effective on one occasion and apparently without effect on others. The fact that the acid hemolysis test remained positive during the remission indicates that the basic abnormality of the red cells was not altered and that a change must have occurred in the plasma factors or in their relation to the red cells. In recent studies21 on blood coagulation, ACTH was found to have variable effects on the titers and interactions of the elements concerned with clotting. One of the usual results was a lowering in Ac-globulin activity with an average fall from 15 to 9 units per cu. cm. This
would fit in with the suggestion that the hemolytic factor is related to the plasma Ac-globulin. Since it is not known whether the changes in the coagulogram induced by ACTH are constant in a given individual, it is possible that a variation in effect on the Ac-globulin was responsible for the varying clinical results in this patient. Admittedly, the use of ACTH and cortisone is not without danger in this disease which is characterized by intravascular thrombosis as well as hemolysis. Robson has shown that the administration of these hormones gives rise to increased capillary resistance and thrombocytosis, both of which factors favor the development of intravascular thrombosis.

In conformity with the finding in other hematologic conditions that ACTH-induced remissions are not often permanent, the improvement produced in this case persisted for only five days after cessation of therapy. In spite of this brief period of improvement under ACTH and cortisone therapy it would seem to us that these hormones should be added to the list of ineffectual methods of treatment of paroxysmal nocturnal hemoglobinuria.

Dicumarol therapy was tried as a last resort and it coincided with the longest remission yet obtained. It is possible that the transfusions were responsible for the benefit experienced, but many previous transfusions had failed to produce such effects. The dangers involved in the use of anticoagulants in ambulatory treatment are well recognized but in this case it was thought that the risk was justified. How long the remission will last remains to be seen.

**SUMMARY**

A proven case of paroxysmal nocturnal hemoglobinuria is reported in which the patient was treated with ACTH on three occasions. Following an initial failure, the second course of ACTH resulted in a dramatic deceleration of hemolysis which, however, lasted only a short time after the cessation of treatment. A third attempt was again of no avail in relieving the condition. Treatment with dicumarol coincided with a remission of the hemolysis which has lasted, so far, for five weeks.

**REFERENCES**

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