Paroxysmal Nocturnal Hemoglobinuria Treated with ACTH without Benefit

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Paroxysmal Nocturnal Hemoglobinuria is one of the rarer forms of chronic hemolytic anemia. It is characterized by exacerbations of increased intravascular erythrocytic destruction during sleep to an extent that the level of plasma hemoglobin concentration exceeds the renal threshold, thereby resulting in hemoglobinuria. The physiologic mechanism of such an erythrocytic reaction remains undetermined and therapy to date is symptomatic.

Hijmans Van den Bergh⁴ was the first to point out, by means of an acid fragility test, that the fault in paroxysmal nocturnal hemoglobinuria resides in the erythrocyte rather than in the plasma. Ham⁵ concluded that the fundamental defect in this disease was in the erythrocyte, which was more susceptible to destruction when the pH of the blood was lowered during sleep. Buell and Mettier⁶ demonstrated that the fundamental disturbance appears to be in red cells that had become sensitized to a lysin normally present in human sera. During 1943 a case of paroxysmal nocturnal hemoglobinuria was reported⁴ in which the severity of the hemoglobinuria was decreased by separate trial periods of Adrenalin and Eschatin (Parke, Davis & Co.), the aqueous extracts of the medullary and cortical portions of the adrenal gland. Synthetic epi-nephrine (Suprarenin, Winthrop & Co.) and desoxycorticosterone did not alter the nocturnal spilling of hemoglobin in the urine.

The recent isolation of the pituitary adrenocorticotropic hormone in adequate quantities for therapeutic use indicated a trial of this material in nocturnal hemoglobinuria, especially because of the striking results that had been obtained in some cases of acquired auto-immune hemolytic anemia. Therapy was carried out on the same case reported in 1943.⁴

Case Report

C. W., white male, age 37, had anemia since 1934, although the diagnosis of paroxysmal nocturnal hemoglobinuria was not made until 1939. Positive physical findings were confined to pallor and limited physical endurance commensurate with the existing degree of anemia. Splenomegaly was never found. During 1939 the significant laboratory findings were: erythrocytic count 2,570,000, hemoglobin 8.7 Gm., leukocyte count of 4,650 with a normal differential; reticulocytes varying from 20 to 25 per cent. Westergren sedimentation rate of 70 mm. in one hour, Wintrobe sedimentation rate corrected for anemia 46 mm. in one hour; icterus index 17 units with .18 mg. of direct acting bilirubin and 1.7 mg. total bilirubin. Normal fragility of the erythrocytes when suspended in hypotonic solutions of sodium chloride; and urinary urobilinogen values of 1:30 as determined by the method of Wallace and Diamond using Ehrlich's reagent. Spectroscopic examination of the urine revealed absorption bands characteristic of oxyhemoglobin.

The patient received a number of transfusions without reaction between 1937 and 1942. After this he suffered severe reactions characterized by hyperpyrexia, accentuation of the hemoglobinuria and generalized aching and debility with each transfusion.

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On re-study during September 1950, the patient had an erythrocyte count of 1,800,000 with 5 Gm. of hemoglobin, a leukocyte count of 3,200 with a normal differential percentage, 153,000 platelets, a total eosinophil count of 37 per cu. mm., 14 per cent reticulocytes, a Westergren sedimentation time of 135 mm., positive heat and acid reactions, positive acid-thrombin reaction as described by Crosby and a negative direct Coombs test. The patient's serum contained Rh antibodies in a titer of 1:256 when tested with albumen as a serum diluent and cell suspending medium.

ACTH (Armour's) therapy in a dosage of 10 mg. each 6 hours was started September 5, 1950 (fig. 1, section A) and maintained for three days without apparent change, either clinically or hematologically, of the cellular blood levels. On the fourth day the dosage of ACTH was increased to 20 mg. each 6 hours for a daily total quantity of 80 mg. On the fifth day the blood counts were: erythrocytes 1,600,000, leukocytes 2,800, eosinophils 28 per cu. mm., and 9 per cent reticulocytes with a Westergren sedimentation rate of 55 mm. per hour, (fig. 1., section B). Generally he did not feel well and was somewhat depressed, yet there was no specific pain. By the end of the fifth day his feeling of discomfort was sufficient to warrant a decrease in the amount of ACTH to 10 mg. each 6 hours. This was followed by a reduction to 5 mg. each 6 hours on the seventh and eighth days for a total daily dosage of 20 mg. and then one single 10 mg. injection on the ninth and tenth days. A total of 380 mg. of ACTH was administered during the ten day period. As the dosage was decreased, the patient felt much better, was less depressed, and at the end of two weeks he was his usual self.

The Coombs test continued to give a negative direct reaction. The eosinophil count dropped to 6 on the seventh day of ACTH administration and the sedimentation rate was consistently lower (Fig. 1, section B). The blood platelets remained at the same level.

![Fig. 1.—Hematologic findings during ACTH therapy.](image-url)
of 150,000 to 200,000 and no gross hemoglobinuria occurred during this period of ACTH administration. The clotting time, as determined by the capillary tube method, was approximately 2 minutes before therapy and remained between 2 and 3 minutes during and after the use of ACTH.

**DISCUSSION**

This patient with chronic paroxysmal nocturnal hemoglobinuria derived no detectable clinical benefit from a therapeutic trial with corticotropin. The erythrocyte and leukocyte counts and hemoglobin determinations were consistently a little lower even though this was within the range of normal variation (fig. 1, section C and D). However, in the case of the reticulocytes there was a slight but distinct drop from 14 to 9 per cent during the first three days of ACTH administration. This was followed by stabilization at an average level of 10 to 11 per cent during the remaining period of ACTH therapy. The erythrocyte sedimentation rate was improved, dropping from an initial level of 135 mm. in one hour to 45 mm. per hour by the seventh day of therapy. This was followed by a gradual return to 100 mm. per hour as the hormone was decreased to 10 mg. on the tenth day. On the seventh day the circulating eosinophil count dropped to a level of 6 per cu. mm. as compared with pre-therapy levels of 37 per cu. mm., thus indicating the eosinopenic effect of ACTH.

Recently Dameshek et al. have observed 5 cases in which remissions occurred with the use of ACTH in both "symptomatic" and "idiopathic" types of hemolytic anemia. The Coombs test was positive before and after therapy in all of their cases. The diminution or disappearance of hemagglutinins suggested that ACTH exerted a favorable influence on the hemolytic disease by altering the pathologic antibody mechanism of the lymphoid tissue.

The negative Coombs reaction in paroxysmal nocturnal hemoglobinuria and the failure of this disease to be benefited from ACTH lends further support to the suggestion that the defect in paroxysmal nocturnal hemoglobinuria is not caused by an acquired globulin antibody attached to the surface of the erythrocyte. On the contrary, these reactions would add to the concept of Buell and Mettier who were among the first to indicate that the mechanism of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria is due to a defective red cell unduly sensitive to a lysin normally present in plasma and to the more recent work of Crosby and Dameshek that the hemolytic activity is an enzyme-like reaction related to the coagulation mechanism of the blood.

**CONCLUSIONS**

A case of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria is reported in which ACTH was administered for a ten day period without apparent clinical benefit. The erythrocytic, leukocytic, and hemoglobin levels were not significantly altered. The reticulocyte percentage was slightly but definitely decreased and the erythrocytic sedimentation rate temporarily improved.

**REFERENCES**

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