Paroxysmal Nocturnal Hemoglobinuria

With Two New Case Reports

By Samuel K. McIlvanie, M.D.* and Marion F. Beard, M.D.

Chronic Hemolytic Anemia with intermittent nocturnal hemoglobinuria and constant hemosiderinuria is a relatively rare disorder which was recently reviewed by Marks, who added 3 new cases, bringing the total reported to 76. Apparently the first description was by Chauffard and Troisier (1908), yet the first clear-cut accounts were reported by Marchiafava (1928) and Micheli (1931).

Ham's studies of acid hemolysis did much to enhance exact diagnosis of the disease. Further work by Ham and Dingle revealed not only a primary defect in the erythrocytes, which were hemolyzed in the presence of human complement, but that hemolysis was increased with acidification. Red cell sensitization, as measured by the Coombs test, has been reported to be negative. Dacie, in a recent report, has postulated that hemolysins of low activity are present in all sera, and that in paroxysmal nocturnal hemoglobinuria the erythrocytic surface has a greater affinity for hemolysins, with resultant cell destruction. Crosby and Dameshek showed that the normal plasma factor which is capable of destroying the abnormal P.N.H. cells, appears to be the activated coagulation accelerator which exists in plasma as an inert proenzyme and which may be activated by thrombin.

The general hemolytic character of the anemia is evidenced by reticulocytosis, bone marrow erythrocytic hyperplasia without maturation arrest, hyperbilirubinemia of the delayed type, elevated urinary urobilinogen, absence of urinary bile and macrocytosis usually proportional to reticulocytosis. More or less specific accompaniments of P.N.H., in addition to the above, are leukopenia, occasional thrombocytopenia, constant hemosiderinuria, nearly constant methemalbuminemia, intermittent hemoglobinuria increased during sleep and normal osmotic fragility.

Satisfactory treatment has not been developed although the most recent report by Marks shows reduction in "hematuria" following pilocarpine nitrate therapy. The drug had to be discontinued, however, because of undesirable side effects. This report includes observations on 2 new patients, which increases the total reported to 79. Our observations include changes of blood pH during the night and day, effects of parasympathomimetic drugs, brief experiments with hapten and electrophoretic studies of the hemoglobin.

Case Reports

Case Report 1: Patient S. H. (1794970), a 42 year old white woman, was first seen in Louisville General Hospital February 14, 1949 with the chief complaint of progressive weak-

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ness. Eleven years previously she complained of prolonged weakness following tonsillitis. She gradually improved and felt fairly well for five years. She then experienced gross "hematuria" and was hospitalized. A genito-urinary examination, including an intravenous pyelogram, was negative. She was placed on therapy for "pernicious anemia" but continued in a weakened state until the present admission. When questioned, she revealed that the early morning urine occasionally was rather dark brown in color, but never red. Her family history is noncontributory. She had 5 normal children.

On examination, she was well developed, but chronically ill. The skin showed a peculiar, slightly ashen pallor, and there was no icterus. The liver was not enlarged, but the spleen was palpable two fingers below the infracostal margin. There was 1 plus pretilial pitting edema. A neurologic examination was normal except for a questionable stocking-glove hypalgesia.

Laboratory data revealed: leukocytes 2,500, erythrocytes 1.56 M., hemoglobin 4 Gm., platelets 287,000 and reticulocytes 16.2 per cent. Bone marrow aspiration was difficult and only a few particles could be obtained. Microscopically, however, the particles were consist-

ent with hemolytic anemia. Intravenous pyelogram, chest x-ray, fragility, sickle cell preparation, bleeding and clotting time were all normal. The cephalin flocculation was 2 plus with a thymol turbidity of 2.4 units. The heat resistance test was consistently positive. There was hemosiderinuria. The Donath-Landsteiner test and tests for cold hemagglutinins were negative. The blood serum revealed nearly constant methemalbuminemia and intermittent hemoglobinemia.

The patient was given 9 Gm. daily of ammonium chloride which changed the plasma pH of 7.48 with CO₂ combining power of 51.7 volumes per cent to a pH of 7.41 with CO₂ of 39.86. At the close of this test the serum showed hemolysis at room temperature as well as after heating. The patient was given a trial of prostigmine for two months and the results are noted below. Her clinical course is shown in figure 1, covering the 12 month period beginning February 14, 1949. Her 5 children, both male and female, and her mother showed no anemia and had negative heat resistance tests.

Case Report 2: Patient O. E., #193691, a 42 year old white woman, was admitted to Louisville General Hospital February 6, 1950, because of severe anemia, splenomegaly and jaundice. In 1942 the patient developed jaundice, weakness and anemia. She gave no spontaneous history of urinary changes but recalled one time when her urine was a little pink before it became dark brown in association with jaundice. That episode lasted about six weeks and was accompanied by marked weakness. She had received no treatment. From 1942
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until 1949 she had had no acute episodes, yet her strength was reduced and she fatigued easily. In 1949 she had had a second acute episode lasting approximately six weeks. The third attack began approximately one month prior to the present admission when she was first seen by her private physician.* At that time the leucocyte count was 8,400, erythrocytes 1.5 M., hemoglobin 22 per cent and hypotonic saline fragility was normal. Bilirubin was 0.4 mg. direct and 3.1 mg. delayed. She was given blood transfusions.

When first seen on January 31, the blood counts were as follows: RBC 3.14 M., hemoglobin 11.2 Gm., PCV 35%, MCV 111.5, MCH 35.4, MCHC 31.8, reticulocytes 5.8 per cent, 163,000 platelets and 4,000 leucocytes with a normal differential. The bone marrow showed a marked hyperplasia of the erythroid series with a left shift and typical megaloblasts, but without maturation arrest. The bone marrow differential count was 12 per cent segmentated granulocytes, 17 per cent band forms, 14 per cent myelocytes, 3 per cent eosinophilic granulocytes, 6 per cent reticulocytes, 3 per cent plasma cells, 41 per cent erythro-normoblasts, and 4 per cent proerythroblasts. Blood and urinary chemistry was as follows: 4.8 mg. urinaly urobilinogen in 2 hours, total cholesterol 231 mg. with 161 mg. as cholesterol esters, cephalin flocculation 3 plus, thymol turbidity 3.0 units, “one-minute” bilirubin 1.7 and “delayed” bilirubin 2.6 mg. per cent. X-ray studies of the gall bladder and gastrointestinal tract were negative. Examination of the stools revealed no occult blood.

On examination, the patient appeared chronically ill. Her skin showed a muddy icterus. The liver was tender and palpable four fingers below the rib margin in the parasternal line. The spleen was enlarged, nontender, and extended three fingers below the infracostal margin. As her jaundice cleared a metallic skin discoloration was readily seen.

The laboratory data are shown in table 1, indicating that the patient’s cells were hemolyzed in an acidified normal and in her own serum, but not after heat inactivation. They also showed that hemolysis occurred upon exposure to heat (37 C.). The Coombs test was negative.† The patient was studied with regard to changes in pH during waking and sleeping hours. The effects of pilocarpine nitrate are shown in table 2.

1. Analysis of Cases

Symptoms and Diagnosis: Emphasis on the name is misleading in that probably less than half of the patients present themselves with a history of paroxysmal hemoglobinuria. Marks in reviewing 73 cases found the following incidence of presenting symptoms: hemoglobinuria, 33; jaundice, 27; lumbar pain, 7; anemia or associated symptoms, 30; abdominal pain, 5; splenomegaly, 2. Our 2 patients were unaware of a chronic urinary abnormality until advised to observe color changes. Periods of freedom from acute episodes are common. The patients may adjust to low levels of hemoglobin so that only close questioning reveals a history of nearly continuous weakness, easy fatigue, and even states of semi-invalidism existing between overt hemolytic phases. From a clinical standpoint we have not been impressed with the hemoglobinuria, which is frequently lacking, nor with the paroxysms which may be years apart as in patients O. E. and S. H. We have been impressed, however, with the metallic skin pallor, moderately severe chronic anemia which is usually macrocytic, and with the chronic, unremitting fatigue associated with low grade hemosiderinuria, leukopenia and reticulocytosis. Chronic illness, not paroxysmal, has been the outstanding characteristic of the disease in our patients.

During acute episodes, frank “hematuria” may lead to complete genitourinary investigations as in patient S. H., especially when the lumbar pain is marked. Liver tenderness may be present during acute phases as in O. E. Some degree of liver dysfunction may occur as a result of chronic anoxemia and lead

* Patient kindly referred to us by Dr. William P. Hall, Paducah, Ky.
to degenerative changes in liver epithelial cells, resulting in increased one minute
as well as delayed bilirubin, as in O. E. Central zonal necrosis with thrombosis of
small portal veins has been reported by several investigators. The cephalin flocculation test may be positive; however, the associated anemia with reticulocyto-
sis and the history help to direct attention to a primary hemolytic process.
Particularly important is the frequent association of acute hemolysis with upper respiratory infections. This apparently initiated the clinical history of patient S. H. although she had been singularly free of any febrile illnesses in the

| Table 1.—Summary of Diagnostic Data in 2 New Patients with Paroxysmal Nocturnal Hemoglobinuria |
|---|---|---|---|---|
| Patient | Urinary hemoglobin | Acid hemolysis | Heat inactivated acidified normal and patient's serum plus patient's cells | Coombs test | Heat resistance test |
| O. E. | Constant | Positive | No Hemolysis | Negative | Wine Red Hemolysis |
| S. H. | Constant | Positive | No Hemolysis | Negative | Wine Red Hemolysis |

subsequent eleven years, except for influenza at the close of prostigmine treatment noted below.

2. Experimental Observations

A. The Acid Hemolysis Test. Hemolysis has not always occurred in tube 1 of Ham's test (patient's cells and patient's serum) although it has always been present in the acidified tubes. We do not believe that in a positive test all tubes containing the patient's cells will show hemolysis; further, such a requirement could lead to confusion in making the diagnosis. In addition, such an interpretation is not in line with Ham's original presentation of the test. An interesting phenomenon is that frequently tube 1 above shows no hemolysis, yet hemolysis is constantly present in the simultaneous heat resistance test. The principal difference between the two tubes is that the cells in tube 1 of Ham's test have been affected by defibrination, by washing in normal saline and possibly by changes in pH.

Ham noted no difference in the degree of hemolysis of cells washed 3 times in normal saline as compared with washing 6 times. He also noted that saline dilution of the serum reduced hemolysis. Crosby's finding that serum accelerator globulin is the hemolytic factor explains the occasional absence of hemolysis in tube 1 of the Ham test and also the constant occurrence of hemolysis in the heat resistance test performed simultaneously, since in the latter test clotting and incubation increased the amount of Ac-globulin. We had examined this discrepancy with the Coombs test prior to the publications of Crosby and Dameshek by washing red cells, 1, 2 and 3 times and by using sedimented cells in the Ham's test. The Coombs test was negative in each instance which seemed to eliminate the possibility of a light globulin coating which may have rendered the cells more sensitive to hemolysis.

Dacie has suggested that heat inactivated (56 C. for 30 minutes) acidified serum should also be included in testing the erythrocytes of possible P. N. H.
patients. Erythrocytes from O. E. and S. H. were so tested and hemolysis did not occur. Actually, the discovery\textsuperscript{13, 14} of the role of serum accelerator globulin seems to increase the value of the heat resistance test and possibly makes unnecessary the heat inactivation modification.

B. Blood pH. There is no question but that the hemolysis is accelerated in vitro by increasing the acidity; however, there is reason to doubt its importance in vivo. A decrease in nocturnal blood pH has been postulated in association with decreased pulmonary ventilation and slight elevation of carbon dioxide tension of the alveolar air. Hastings is quoted by Ham\textsuperscript{3} as noting such a decrease, and it was also reported by Kleitman.\textsuperscript{9} Ham\textsuperscript{5} found no significant changes in 1 patient's arterial blood pH during waking and sleeping hours. Hoffman and Kracke\textsuperscript{10} found the patient's blood more alkaline during sleep, but postulated that the blood in the spleen may actually become more acid, although no proof was offered. Removal of the spleen in Ham's Case 4,\textsuperscript{5} however, had no effect on the unrelenting course of the disease, even though the nocturnal phase of hemoglobinuria was apparently removed. It simply became constant with essentially the same results.

Kleitman's\textsuperscript{8} review of the physiology of sleep serves to emphasize the large number of factors which might be of significance in elucidating the effect of sleep in this disease. To list a few of the changes: the blood pressure falls, heart rate slows, blood sugar rise following a feeding of glucose is lessened, titratable urinary acidity is increased, muscular relaxation occurs, phosphate excretion is increased, vascular dilatation is constant and unaffected by adrenalin. There is no change in alkaline reserve and the blood is thinner and contains less protein.

We have studied changes in blood pH taken from the antecubital vein in 2 of our patients (O. E. and S. H.) and 1 control. A Coleman pH meter with a micro electrode was used so that readings could be made directly and immediately upon the aspirated blood. Readings taken upon blood withdrawn into vials and allowed to stand, if only for a few minutes, probably do not represent the in vivo pH even when careful techniques have been used. Our results are shown in figure 2. The venous blood pH did not become more acid during sleep, rather, there was a tendency towards increased alkalinity, particularly in patient S. H. Blood sodium levels taken at the same time on patient S. H. showed no significant changes throughout the three days and nights studied. Webster, et al.\textsuperscript{31} made the interesting observation that excretion of hemoglobin perfused into the frog kidney was accelerated by increasing the acidity. However, local acidity in the kidney during sleep (associated with increased acidity of the urine) as an explanation for the nocturnal hemoglobinuria, appears to be eliminated since plasma levels of hemoglobin are increased during sleep.\textsuperscript{4–10} Marks\textsuperscript{4} reported no therapeutic results in treatment of one case with potassium citrate, 120 grains/day, and sodium bicarbonate, 120 grains/day. Therapy based on altering blood pH has not been of value in improving the anemia.

C. Therapy with Parasympathomimetic Drugs. Hoffman and Kracke\textsuperscript{10} investigated sympathomimetic and parasympathomimetic drugs, using adrenalin in oil (Parke-Davis Co. 1:1000) and prostigmine (1 cc. of 1:4000 solution) given at 9:00 p.m. and 3:00 a.m. and showed a reduction in nocturnal hemoglobinuria with the urine becoming clear. However, the anemia was not improved over a
period of two weeks and the bone marrow stress, as judged by reticulocytosis, was unaffected. The patient claimed to feel better. After two months with light amber urines free of hemoglobin, on an aqueous extract of adrenal cortex (Exchotin), the hemogram showed no improvement. Marks\(^1\) used pilocarpine nitrate gr. 1 10 at 8:00 p.m. and 2:00 a.m. and also noticed clearing of hemoglobinuria; however, the drug had to be discontinued because of side effects.

![Figure 2](image-url)

**Fig. 2.—Venous blood pH changes in paroxysmal nocturnal hemoglobinuria.**

![Figure 3](image-url)

**Fig. 3.—Patient S.H.: Effects of prostigmine bromide.**

We used oral prostigmine bromide on patient S. H. for a two month period with gradually increasing doses to 15 mg. at 9:00 p.m. and 1:00 a.m. The results are shown in figure 3. There was some reduction in the usual dark amber morning urine, although no specimen tested ever approached a normal light straw color and hemosiderin was present in all random tests. Her hemogram was basically unaltered and for the week prior to discontinuing the drug she became progressively weaker. Whether the severe reticulocytosis (40 per cent) in S. H. noted shortly after hospitalization was due to stopping the drug or not is difficult to determine since she also developed influenza. The disease does not run a constant course and any evaluation of short term effects is associated with some error. As
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with Hoffman's patient, we observed no real hematologic improvement which is the necessary criterion of successful therapy and of more value than brief changes in hemoglobinuria which we have found quite variable.

Pilocarpine has been tried on patients O. E. and S. H. and the results are shown in table 2, in which we have used as indices of blood destruction the urinary quantitative urobilinogen, bilirubin levels, plasma hemoglobin (patient S. H.), plus daily erythrocyte, hemoglobin and reticulocyte estimations. Pilo-

<table>
<thead>
<tr>
<th>Date</th>
<th>Bilirubin mg.</th>
<th>Urinary urobilinogen—2 hrs.</th>
<th>Erythrocytes (M.)</th>
<th>Reticulocytes (%)</th>
<th>Urinary hemosiderin</th>
<th>Plasma hemoglobin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient O. E.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/7/50</td>
<td>2.9</td>
<td>11.1 mg.</td>
<td>3.09</td>
<td>8.6</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>2/13/50</td>
<td>3.1</td>
<td>4.1</td>
<td>2.80</td>
<td>12.0</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td><strong>Pilocarpine Nitrate Begun Here</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2/14/50</td>
<td>2.6</td>
<td>4.48</td>
<td>2.90</td>
<td>11.8</td>
<td>2 Plus</td>
<td>—</td>
</tr>
<tr>
<td>2/15/50</td>
<td>2.6</td>
<td>5.46</td>
<td>2.85</td>
<td>10.8</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>2/16/50</td>
<td>2.6</td>
<td>5.28</td>
<td>2.60</td>
<td>10.2</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>Patient S. H.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/20/50</td>
<td>.7</td>
<td>1.40</td>
<td>2.41</td>
<td>4.4</td>
<td>Positive</td>
<td>86 mg. per cent</td>
</tr>
<tr>
<td>3/22/50</td>
<td>.85</td>
<td>.72</td>
<td>2.80</td>
<td>4.2</td>
<td>Positive</td>
<td>93</td>
</tr>
<tr>
<td>3/23/50</td>
<td>.80</td>
<td>.99</td>
<td>2.95</td>
<td>4.2</td>
<td>Positive</td>
<td>92</td>
</tr>
<tr>
<td>3/24/50</td>
<td>1.05</td>
<td>.64</td>
<td>3.08</td>
<td>3.2</td>
<td>Positive</td>
<td>105</td>
</tr>
<tr>
<td>3/25/50</td>
<td>1.00</td>
<td>—</td>
<td>3.11</td>
<td>2.0</td>
<td>Positive</td>
<td>100</td>
</tr>
<tr>
<td><strong>Pilocarpine HCl Begun Here (3/27/50)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/27/50</td>
<td>.80</td>
<td>1.52</td>
<td>3.05</td>
<td>4.2</td>
<td>Positive</td>
<td>88</td>
</tr>
<tr>
<td>3/28/50</td>
<td>1.30</td>
<td>1.30</td>
<td>—</td>
<td>—</td>
<td>Positive</td>
<td>90</td>
</tr>
<tr>
<td>3/29/50</td>
<td>.85</td>
<td>1.05</td>
<td>3.50</td>
<td>4.6</td>
<td>Positive</td>
<td>91</td>
</tr>
<tr>
<td>3/30/50</td>
<td>1.00</td>
<td>.48</td>
<td>3.48</td>
<td>6.0</td>
<td>Positive</td>
<td>91</td>
</tr>
<tr>
<td>3/31/50</td>
<td>1.15</td>
<td>1.04</td>
<td>3.50</td>
<td>6.0</td>
<td>Positive</td>
<td>114</td>
</tr>
<tr>
<td>4/3/50</td>
<td>—</td>
<td>1.11</td>
<td>3.00</td>
<td>5.0</td>
<td>Positive</td>
<td>—</td>
</tr>
<tr>
<td>4/13/50</td>
<td>—</td>
<td>3.63</td>
<td>2.82</td>
<td>7.2</td>
<td>Positive</td>
<td>—</td>
</tr>
</tbody>
</table>

* Pilocarpine nitrate 6 mg. at 9:00 p.m. and 2:00 a.m. in patient O.E. Pilocarpine HCl 6 mg. at 9:00 p.m. and 2:00 a.m. in patient S.H.

carpine nitrate and hydrochloride (6 mg.) were given subcutaneously at 9:00 p.m. and 1:00 a.m. Even though night urines cleared moderately, hemosiderin was constantly present and the hemogram was not improved. Patient O. E. was discharged to her private doctor for further trial on pilocarpine therapy. Patient S. H. showed no evidence of improvement on pilocarpine therapy after treatment for three weeks and gradually began a decline while still receiving the drug. We believe the data thus far hold little encouragement for treatment of paroxysmal nocturnal hemoglobinuria with parasympathomimetic drugs.

D. Experiments with Hapten*. In view of Dacie's finding of hemolysins in

* Assistance of Dr. Hames G. Shaffer, Department of Bacteriology, University of Louisville School of Medicine, in this experiment is gratefully acknowledged.
normal sera, we investigated the possible therapeutic value of hapten. Whether the waxy-resinous substance obtained, using the method of Carter, is actually hapten is open to question. However, it is said to prevent agglutination of RH+ sensitized O cells when set up against a potent anti RH0 serum in vitro. Our preparation was tested by this method and found to be active. A series of experiments were then set up as follows: (1) Whole blood of the patient and control were mixed immediately with varying amounts of hapten in alcohol and normal saline solutions and in the free lipid state. These tubes were placed in the water-bath at 37 C. and read as in the heat resistance test. Hemolysis was unaffected.

(2) The Ham test was modified by adding hapten in 20 and 40 per cent alcohol solutions to the tubes containing erythrocytes from control and the patient. Sera of the control and patient were first incubated at 37 C. for 15 minutes with hapten prior to adding to the cells in the Ham test and hemolysis was not altered.

In view of our negative data in vitro we did not believe it worthy of a trial in vivo.

E. Electrophoretic Studies. In view of the very interesting discovery by Pauling of the structurally abnormal hemoglobin in sickle cell disease, it was thought of interest to study this possibility in P.N.H.* The electrophoretic mobility of carbonmonoxyhemoglobin at pH 6.91 buffer ionic strength 0.1 was as follows:

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ns.</th>
<th>Mobility</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. H.</td>
<td>179470</td>
<td>$-0.12 \times 10^{-4}$ cm$^2$ sec$^{-1}$ volt$^{-1}$</td>
</tr>
<tr>
<td>O. E.</td>
<td>193691</td>
<td>$-0.11 \times 10^{-4}$</td>
</tr>
</tbody>
</table>

Mixture of O. E. and normal carbonmonoxyhemoglobin: $-0.10 \times 10^{-4}$

The mobilities agree with that of previous normal carbonmonoxyhemoglobin and no evidence of abnormality in the hemoglobin is seen. Thus, although the defect is in the erythrocyte, it does not appear to be related to structural or molecular abnormalities of the hemoglobin. Changes in the cell surface are more likely involved in the hemolytic sensitivity.

To date the only satisfactory treatment is the giving of washed red cells whenever symptoms require alleviation. This is usually at erythrocyte levels below 2.0 M. per cu. mm. Other forms of treatment appear unnecessary. In the realm of speculation it is possible that nocturnal vasodilatation and stasis may in some way increase small amounts of $\alpha$-globulin and thus explain the increased hemolysis during sleep in this most perplexing disease.

**SUMMARY AND CONCLUSIONS**

1. Two patients with paroxysmal nocturnal hemoglobinuria are reported. The chronicity of the hemolytic process is stressed.

2. Venous blood pH was found to be generally more alkaline during sleep and we believe that the nocturnal hemolytic process is not due to increased acidity per se.

3. A trial with (1) oral prostigmine bromide for two months, and (2) with subcutaneous pilocarpine nitrate and pilocarpine hydrochloride showed no evidence of reduced erythrocyte destruction and the anemia was unaffected.

* We are grateful to Dr. Linus Pauling and Dr. Harvey Itano, Gates and Crellin Laboratories, for carrying out these determinations.
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4. There was no effect with hapten upon in vitro hemolysis.
5. The hemoglobin structure of the erythrocyte in this disease is normal as measured by the electrophoretic method.

REFERENCES

Paroxysmal Nocturnal Hemoglobinuria With Two New Case Reports

SAMUEL K. MCILVANIE and MARION F. BEARD