Paroxysmal Nocturnal Hemoglobinuria: Report Of Two Cases With Atypical Features, Autopsy Findings, And Review Of Pathophysiology

Alexander S. Ullman
Robert C. Horn Jr.
Joseph P. Abraham
Ellis J. VanSlyck

Follow this and additional works at: https://scholarlycommons.henryford.com/hfhmedjournal

Part of the Life Sciences Commons, Medical Specialties Commons, and the Public Health Commons

Recommended Citation
Available at: https://scholarlycommons.henryford.com/hfhmedjournal/vol11/iss2/3

This Article is brought to you for free and open access by Henry Ford Health System Scholarly Commons. It has been accepted for inclusion in Henry Ford Hospital Medical Journal by an authorized editor of Henry Ford Health System Scholarly Commons.
PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

Report of Two Cases with Atypical Features, Autopsy Findings, and Review of Pathophysiology

ALEXANDER S. ULLMANN, M.D., ROBERT C. HORN, JR., M.D.,
JOSEPH P. ABRAHAM, M.D., AND ELLIS J. VANSLYCK, M.D. F.A.C.P.

Paroxysmal nocturnal hemoglobinuria (P.N.H.) is a rare and fascinating hemolytic disease of insidious onset and chronic course. It is characterized by an intracorpuscular erythrocytic defect rendering the red cells unusually susceptible to hemolysis both in vitro and in vivo. This is usually manifested by anemia, weakness, dark urine, and abdominal pain, accompanied by hemoglobinemia, hemoglobinuria, and hemosiderinuria. Infection, bleeding, and thrombosis are notable complications. However, attention may first be directed to atypical features of the illness, leading to delay in diagnosis. This is well demonstrated in the two cases to be discussed. The first of these was thought to have aplastic anemia throughout much of her illness, while the second was initially admitted with a tentative diagnosis of gastro-intestinal bleeding.

CASE REPORTS

CASE 1 (Z. D.) — A 49-year-old obese, white female whose illness began in July, 1959, with an episode of dizziness and weakness ascribed to pills she had been taking for hypertension. She developed dyspnea and leg pains which caused progressive disability. Thereafter, severe menorrhagia was noted, and a D & C revealed no specific findings.

In August, 1959, she was admitted to another hospital where her laboratory studies indicated 11.2 grams of hemoglobin per 100 ml. with 4.1 million red cells per cubic millimeter; hematocrit 36 vol. per cent; MCV 88 cubic microns; MCHC 31.1 per cent. The white blood cell count was 3500 per cubic millimeter with a differential of 2 bands, 21 segmented neutrophils, 22 large lymphocytes, 44 small lymphocytes, 8 monocytes, 1 myelocyte and 2 metamyelocytes. The platelets were moderately decreased in number. The reticulocyte count was 3 per cent. The sternal marrow was hypocellular. The myeloid-erythroid ratio was 1 to 10. Erythroid cells were increased, and megakaryocytes were decreased. Further determinations included normal serum protein, 1.5 mg. per 100 ml. total bilirubin, a negative Coombs' test, and an absence of cold agglutinins. The chest x-ray was negative. Repeated laboratory studies in the same hospital in October and December, 1959, were essentially similar. It was concluded that the bone marrow picture was compatible with the diagnosis of toxic pancytopenia. At the end of 1959 she noted episodes of nausea, vomiting, right upper quadrant pain, chills and cramps. Gallbladder x-rays revealed cholelithiasis.

*Resident in Pathology.
*Chairman, Department of Pathology.
**Associate Physicians, Division of Hematology.
Her first admission to Henry Ford Hospital was on January 3, 1960. At that time, there was generalized pain and tenderness in the abdomen, more marked in the right upper quadrant. There was no guarding or rebound tenderness. No adenopathy was noted. The remainder of the physical examination was negative. During hospitalization she had numerous tarry stools and continued to have generalized abdominal tenderness.

Laboratory reports included a normal serum alkaline phosphatase, bilirubin, calcium, amylase, lipase, urea nitrogen, and blood sugar. The hemoglobin on admission was 11 grams per 100 ml.; hematocrit 30 vol. per cent; the white cell count was 3,300 per cubic millimeter with 5 bands, 39 neutrophils, 1 eosinophil, 36 lymphocytes and 19 monocytes; 4.4 per cent reticulocytes were noted. The VDRL was non-reactive. Stool guaiac was strongly positive. Her urine was characterized by hemoglobinuria, methemoglobinuria and hemosiderin. The pigments showed only a few red cells, although a benzidine test was strongly positive. The pigments in the urine were identified as oxyhemoglobin, methemoglobin and hemosiderin. The hemoglobin dropped to 8 grams per 100 ml., and at this time the total serum bilirubin increased to 2.24 mg. per 100 ml. Repeated urinalyses showed hemoglobin to be consistently present in the urine. Both direct and indirect Coombs' tests were negative. The reticulocyte count was 11.4 per cent. During hospitalization, the serum hemoglobin rose from 88 mg. per 100 ml. to 220 mg. per 100 ml. The peripheral blood smear showed decreased platelets, neutropenia, and a pleomorphic red cell picture with many nucleated erythrocytes and a few pear-shaped macrocytes. The bone marrow smear was hypocellular with decreased platelets, neutrophilia, and a pleomorphic red cell picture with many nucleated erythrocytes and a few pear-shaped macrocytes. The bone marrow smear was hypocellular with a myeloid-erythroid ratio of 1.3 to 1. There was an increase in normoblasts with a slight increase in alpha globulin. Electrocardiogram, chest x-ray, bone survey, and upper GI series were negative. She was discharged with the diagnosis of suspected aplastic anemia. Medication at this time included methyl testosterone and prednisone.

She was readmitted to the hospital in February, 1960, for painful, bleeding, thrombosed, internal hemorrhoids. She had become "Cushingoid" in appearance. Moderate enlargement of her spleen was noted on physical examination at this time. She was treated conservatively for the hemorrhoids. Now it was first noted that her urine was black. Examination showed only a few red cells, although a benzidine test was strongly positive. The pigments in the urine were identified as oxyhemoglobin, methemoglobin and hemosiderin. The hemoglobin dropped to 7.5 grams per 100 ml. and the hematocrit to 25 vol. per cent. BSP showed 11 per cent retention in 45 minutes, and the total cholesterol 174 mg. per 100 ml. Widal and Brucella agglutinations were negative. The platelet count remained in the range of 12,000 to 27,000 per cubic millimeter. Repeated LE tests were negative. The sternal bone marrow aspirate contained one hypercellular particle. This showed a myeloid-erythroid ratio of 1.3 to 1. There was an increase in normoblasts with a few macronormoblasts and megaloblasts; 6.4 per cent plasmacytes were present. Serum protein electrophoresis showed 5.4 grams of total protein with 2.3 grams of albumin and a slight increase in alpha globulin. Electrocardiogram, chest x-ray, bone survey, and upper GI series were negative. She was discharged with the diagnosis of suspected aplastic anemia. Medication at this time included methyl testosterone and prednisone.

In September, 1960, she accidently sustained a three-inch laceration on the right anterior tibial area. Two days later the wound appeared infected, and her temperature reached 105°F. Under treatment at home she was comatose for more than a week.

She was readmitted to Henry Ford Hospital on October 1, 1960, complaining of dizziness, headache, epigastric distress, cramps, gas pains and general malaise. Physical examination showed multiple ecchymotic areas and slightly icteric sclerae. The lungs and heart were negative. A split-thickness skin graft was applied to the large infected ulceration on the right leg. Before and after surgery, the patient received several transfusions of packed red cells. Post-operatively, the patient complained of nausea and vomiting, and later severe urinary urgency and frequency. At cystoscopy under local anesthesia on November 3rd, the bladder mucosa was noted to be edematous and diffusely hemorrhagic with large areas of necrotic tissue. A diagnosis of acute necrotizing cystitis was made. Gynecological examination under anesthesia showed discoloration, hemorrhagic vaginal walls and a necrotic appearing external cervical os. Cervical and vaginal biopsies showed a marked inflammatory change with multiple thrombi. The patient's general toxicity increased, and she became unresponsive. Dextan was given intravenously with no apparent improvement. During the night of November 6th, the patient's temperature rose to 104°; her breathing became irregular and shallow, and she expired on November 7, 1960.

Autopsy (A60-568) was performed 5½ hours after death. Only the positive findings are reported here. Gross examination showed 150 cc. of blood-stained fluid in the left pleural cavity. There were several large ulcerated areas in the ecum and the ascending colon, the largest one measuring 3 x 2 cm. These ulcers were filled with blood clots and the surrounding tissue showed hemorrhagic necrosis (Fig. 1). There was extensive hemorrhage in the perinephric and peripelvic adipose tissue and in the pancreas. The kidney surfaces were
Figure 1
Ulceration with hemorrhagic necrosis in cecum and ascending colon.

Figure 2
Mahogany brown kidneys with hemorrhages in both pelves and ureters; hemorrhagic necrosis of the bladder wall.
Figure 3
Fresh thrombi in the blood vessels of the cecum; infarction and hemorrhage into the submucosa and ulceration of the mucosa. H & E stain; Magnification X 20.

Figure 4
Hemosiderin deposition in the cells of the convoluted tubules. The glomeruli are not involved. H & E stain; Magnification X 115.
Hemosiderin deposition in tubular epithelium. Iron stain; Magnification X 325. (Insert: Magnification X 700)

depth mahogany brown with small areas of subcapsular petechial hemorrhage. The cut surfaces showed the same mahogany color. A strongly positive Prussian blue reaction was demonstrated. There were several hemorrhagic areas in the calyces and pelves and in both ureters. The bladder wall was markedly thickened and its mucosal surface completely covered by necrotic hemorrhagic material. The wall was hemorrhagic in its entire thickness and similar, hemorrhagic, necrotic areas were found in the surrounding adipose tissue (Figure 2). The posterior and lateral vaginal walls showed purplish discoloration caused by extensive submucosal hemorrhage.

On microscopic examination the lung showed small atelectatic areas with marked congestion and numerous red cells in the alveoli. The spleen was extremely congested and contained numerous macrophages loaded with hemosiderin. The trabecular veins were thrombosed and the trabeculae were infiltrated by lymphocytes and plasma cells. The liver sinusoids showed marked engorgement with small areas of necrosis around the central veins. Heavy hemosiderin deposits were present. The cecum and ascending colon revealed fresh unorganized thrombi in all the veins with infarction and extensive hemorrhage into the submucosa and ulceration of the mucosa (Figure 3). The omentum showed numerous venous thrombi in varying stages of organization with hemorrhagic necrosis in the surrounding areas. There was deposition of abundant hemosiderin in the cells of the convoluted tubules of both kidneys. The glomeruli were not involved (Figures 4 and 5). The peripelvic veins showed extensive thromboses with large hemorrhagic areas which were surrounded by inflammatory cells, largely lymphocytes and plasma cells, but including a thin zone of polymorphonuclear cells. The entire bladder wall was hemorrhagic and necrotic. All veins appeared to be thrombosed. The hemorrhagic necrosis extended into the surrounding adipose tissue. These areas were surrounded by numerous inflammatory cells. The cervix showed extensive thrombosis of the veins with large necrotic areas and numerous microscopic abscesses (Figure 6). The bone marrow was hypocellular and all of its elements except normoblasts were depressed.
Figure 6
Thrombosis in the veins of the cervix; large necrotic areas and microscopic abscesses. H & E stain; Magnification X 17.

Final Anatomical Diagnoses

1. Paroxysmal nocturnal hemoglobinuria.
2. Venous thrombi with hemorrhages into
   a. Kidneys
   b. Bladder (hemorrhagic necrotic cystitis)
   c. Pancreas, tail
3. Necrosis and inflammation with multiple thrombi of
   a. Cervix
   b. Cecum and ascending colon
4. Hemothorax, left
5. Skin graft, right anterior tibial region.

CASE 2 (L. N.) — A 21-year-old white female who presented at this hospital on April 14, 1958, with complaints of weakness, fatigue and recurrent headaches accompanied by nausea and vomiting. Symptoms were of about nine months duration.

The initial physical examination revealed a temperature of 98°F, a pulse of 80 per min., respirations of 18 per min. The weight was 135½ pounds, and the blood pressure was 120/80 mm. Hg. She was well developed and nourished. There was striking skin pallor and a generally sallow complexion. There was no scleral icterus; a few small posterior cervical nodes were noted. There was a grade II apical systolic murmur. A sharp liver edge was
palpated 4 cm. below the right costal margin. The spleen extended 2 cm. below the left costal margin.

Laboratory data: The hemoglobin was 8.8 grams per 100 ml., red blood count 2.58 million per cubic millimeter, white blood count 4,500 per cubic millimeter with 49 neutrophils, 2 eosinophils, 1 basophil, 38 lymphocytes and 10 monocytes. The red blood cells were microcytic and hypochromic. There was moderate polychromasia and poikilocytosis, numerous elliptical forms and some target cells. The urine revealed 1+ albumin, 0-3 leukocytes and 0-2 red cells per high power field. The photofluorogram of the chest was negative; barium enema and upper gastro-intestinal x-rays were negative. Stools were consistently negative for occult blood, and proctoscopy revealed no abnormality. The reticulocyte count was 8.9 per cent, platelet count 57,500 per cubic millimeter, direct and indirect Coombs' test negative, total bilirubin 0.62 mg. per 100 ml., direct bilirubin 0.12 mg. per 100 ml., sedimentation rate 22 mm. per hour, hematocrit 28 vol. per cent, and progress hemoglobin 7.9 grams per 100 ml. The quantitative fecal urobilinogen was 629 mg. per cent, alkaline phosphatase 1.6 Bodansky units, cholesterol 185 mg. per 100 ml. with 54 per cent esters, heterophile agglutination titre 1:14, blood urea nitrogen 12 mg. per 100 ml., non-protein nitrogen 28 mg. per 100 ml. The serum protein electrophoresis was within normal range. The serum iron was 57 mcgm. per 100 ml. Gastric analysis revealed free acid in all specimens. Hemoglobin electrophoresis indicated hemoglobin A only, and alkali denaturation indicated less than 2 per cent alkali stable hemoglobin. Cephalin cholesterol flocculation was 3+, thymol turbidity 5 units, thymol flocculation 2+. The bromsulfalein test indicated 3 per cent retention in forty-five minutes. The urine sediment contained numerous golden yellow granules which stained black upon the addition of ammonium sulfide and gave a positive reaction with the Prussian blue reagent. Plasma hemoglobin was 232 mg. per 100 ml. Cold agglutinin titre was 1:128. The sternal marrow aspirate revealed a myeloid-erythroid ratio of 0.9:1; the marrow smears were at the upper limits of normal cellularity. The chief abnormality was a marked increase in normoblasts and their mitoses. LE tests were consistently negative. The presumptive acid hemolysis test of Ham was positive, and the confirmatory complete Ham test was also positive. The patient received repeated transfusions of packed red blood cells with a satisfactory rise in hemoglobin and symptomatic improvement.

On July 26th, she returned complaining of episodic headaches followed by nausea and weakness, recurring at about two-week intervals. A brief trial of an alkaline ash diet was of no benefit in relieving symptoms or progression of anemia. Reticulocyte count remained in the range of 3 to 7 per cent. She was readmitted to the hospital on October 1, with recurrence of the anemia.

On this admission, physical findings were essentially as before. There was again striking pallor and a palpable spleen and liver. The hemoglobin was 5.9 grams per 100 ml., white blood count 4.450 per cubic millimeter, non-protein nitrogen 32 mg. per 100 ml. Other laboratory data was essentially as noted on the first admission. The patient responded satisfactorily to transfusions of packed red cells.

The next admission was in late March, 1959, because of abdominal pain, weakness, and the passage of dark urine. The hemoglobin was 9.6 grams per 100 ml., white blood count 4.850 per cubic millimeter, and blood urea nitrogen 15 mg. per 100 ml. The total bilirubin was 1.92 mg. per 100 ml., direct bilirubin 0.32 mg. per 100 ml. The plasma hemoglobin was 54.8 mg. per 100 ml. The quantitative fecal urobilinogen was 417 mg. per 100 ml., reticulocyte count 8 per cent. The peripheral blood morphology was essentially as before. On this occasion, the patient was started on an anti-coagulant, phenprocoumon (Marcumar), and this has been continued since that time. There was no appreciable subjective change, though satisfactory hypoprothrombinemia was obtained. The next admission was on December 4, 1959 for further treatment with blood transfusion. Subsequent to that time, transfusions of packed red blood cells have been required at approximately three-month intervals.

DISCUSSION

The unique initial findings in both these cases serve to emphasize the fact that this illness, though it produces striking physiologic changes, is not always readily detected. It should be considered in the differential diagnosis of any obscure chronic anemia.

The persistent finding of pancytopenia and a hypoplastic marrow (as in Case 1) can readily lead to the erroneous diagnosis of aplastic anemia.
The second patient was originally thought to have a blood loss anemia in view of the microcytic hypochromic red cells and the low serum iron. Because of the frequently associated abdominal pain, one might conclude that such a patient had a bleeding gastro-intestinal lesion. This misleading situation results from the depletion of iron stores by the increased renal excretion of iron.

Other vagaries of the disease include the fact that hemoglobinuria may not be prominent and may readily escape detection. Further, it is not limited to nocturnal occurrence.

In essence, the diagnosis is suggested by the finding of anemia (usually with leukopenia and thrombocytopenia), signs of hemolysis, hemosiderinuria, hemoglobinuria, and hemoglobinemia. Final confirmation is achieved by the acid hemolysin test of Ham, the thrombin test of Crosby, and the heat resistance test of Hegelin and Maier.

**Review of Pathologic Physiology in P.N.H.**

Paroxysmal nocturnal hemoglobinuria as a disease entity was first described by Paul Struebing in 1882. He recognized that the disease was a new entity and characterized it by careful description of his patient and by the citation of earlier cases. This early discovery had been forgotten until it was rediscovered and described independently by Marchiafava and Micheli in 1928 and 1931. The disease became known as the “Marchiafava-Micheli syndrome”. Ham, Dacie, Dameshek and Crosby have done much to devise methods for its diagnosis and to clarify the pathogenesis.

There is general agreement that the basic abnormality in P.N.H. is a defect of the erythrocyte. Ham showed that the P.N.H. red blood cells were abnormally sensitive to slight changes in hydrogen ion concentration. Lowering the pH, even within the physiologic range, increased hemolysis, and raising the pH reduced or eliminated hemolysis. This fact is utilized in the performance of a specific test for hemolysis with acidified serum (Ham’s test). It has been suggested that the occurrence of hemoglobinuria during sleep might be due to the effect of depressed respiration with retention of carbon dioxide and consequent lowering of pH of the blood.

Correlated with the defective erythrocyte is the marked reduction in red cell survival time. It has been shown in several studies that the erythrocytes of patients with P.N.H. survived only about thirty days. When P.N.H. red cells are transfused into normal recipients, there is a very rapid initial destruction, often followed by normal survival of approximately 20% of the transfused P.N.H. cells, indicating that not all the P.N.H. cells are defective.

The biochemical and structural nature of the defect of the P.N.H. red cells has recently been the subject of extensive study. Though the etiology of the disease is still unknown, it is generally accepted that the defect is localized in the stroma of the erythrocytes. DeSandre observed that in patients with P.N.H., the red cell acetylcholinesterase activity is significantly lower than that in normal adults or in
patients with other anemias. Metz and his collaborators\textsuperscript{20} recently found that the reduction of acetylcholinesterase activity of the erythrocytes appears to be a regular finding in severe cases of P.N.H. The acetylcholinesterase content of the erythrocyte population in P.N.H. varies, and some of the cells have a normal amount of the enzyme. The esterase content of the reticulocyte-rich upper layer of the centrifuged P.N.H. blood is often lower than that of the blood as a whole.\textsuperscript{21} This suggests that the most affected cells in P.N.H. do not survive in the circulation beyond the reticulocyte stage. According to Holland and Greig\textsuperscript{22} the formation and breakdown of acetylcholine is related to cell permeability. When the enzyme is inactive, the cell presumably loses its selective permeability and undergoes hemolysis.

Among other alterations of the P.N.H. erythrocytes, an increase in total cholesterol and phospholipids has been found.\textsuperscript{23,24} Although the ratio between lecithins, cephalins, and sphingolipids was normal, the total amount was found to be increased. When the stroma of a normal red cell was compared to that of a P.N.H. erythrocyte by electron microscopy, the latter showed a morphologic abnormality (patchy appearance with many clefts).\textsuperscript{14,25} Dameshek\textsuperscript{26} proposed that the erythrocyte defect in P.N.H. may be due to an immunologic mechanism as yet undiscovered. Whatever the exact nature of the defect in the red cells may be, it renders these cells more susceptible to hemolysis than the normal erythrocytes, even though the usual osmotic fragility tests are normal.

The hemolytic mechanism acting upon the susceptible P.N.H. cells is present in any normal plasma and is known as the properdin system. Properdin is a serum euglobulin which is not in itself lytic to P.N.H. cells. However, in the presence of complement and magnesium ion, at an optimum pH of 6.8-7.0, it causes lysis of these abnormal red blood cells.\textsuperscript{27} This system consists of a heat stable and a heat labile inhibitor with corresponding heat stable and labile accelerators. A significant aspect of the properdin system is the sensitivity of the stable inhibitory factor to the activity of thrombin. A small amount of thrombin can greatly increase the hemolysis that occurs in vitro by destroying this inhibitor. This reaction to thrombin is so striking that it has been used as another diagnostic test for P.N.H. (the Crosby test). The effect ofbishydroxycumarin (Dicumarol) or related anticoagulants in preventing hemolytic episodes in P.N.H. patients depends upon the decrease of prothrombin and thus thrombin, thereby sparing the thrombin-sensitive inhibitor. Heparin, which does not reduce the amount of prothrombin or thrombin in the blood, does not have a similar beneficial effect, but on the contrary, is thought to cause increased hemolysis by impeding the thrombin-labile inhibitor of the properdin system.

In view of the leukopenia and thrombocytopenia frequently seen in P.N.H., it is thought that a defect in stromal protein also exists in these elements, and that they, too, are liable to lysis by the P.N.H. hemolytic system.\textsuperscript{28} It has been demonstrated in vitro that the white cells and platelets of P.N.H. are more susceptible to destruction during incubation than normal ones. The postulated defect of the platelets leads to Crosby's "vicious cycle". This relates the blood coagulation system to the P.N.H. hemolytic mechanism. The accelerated destruction of P.N.H. platelets liberates.
thromboplastin, resulting in an increased thrombin level in the blood. This, in turn, activates the hemolytic enzymes by destroying the heat-stable inhibitor, thus causing increased hemolysis. This reaction, which brings about destruction of the P.N.H. red cells, also affects and destroys again more P.N.H. platelets, creating a cycle that causes production of more thrombin. This vicious cycle can be broken by Dicumarol which reduces the amount of circulating prothrombin, and thus thrombin. Therefore, the administration of Dicumarol, which has no effect on normal platelets, often causes significant elevation of the platelet count in P.N.H. The leukopenia may explain the susceptibility of these patients to infection. In one of our patients (Z.D.) Rebuck and associates examined leukocytic function in serial cover slip preparations of an experimental skin lesion. They found marked decrease of the cytoplasmic alkaline phosphatase activity of the migrated neutrophils and less obvious, but similar depressed activity of the lymphocytes. They concluded that this depression of both exudative leukocytic numbers and enzymatic activity might be a reflection of impaired function in general. Their conclusions are supported by our necropsy findings, wherein the necrosed areas around the infarcts were surrounded only by a thin zone of leukocytes in contrast to the usual thick zone.

The frequent thromboses are related to the proclivity of P.N.H. platelets to agglutinate. These thromboses often result in headaches and abdominal pain, which may be improved by the use of bishydroxycumarin.

A fundamental feature of the disease is hemoglobinemia which is the result of intravascular hemolysis. Normally there is less than 10 mg. per 100 ml. of hemoglobin in the plasma. When the hemoglobin level rises to 50-100 mg. per 100 ml., the haptoglobin binding capacity is exceeded and hemoglobinuria ensues. Some of the free hemoglobin in the plasma is converted to hematin which is combined with serum albumin to form methemalbumin, a golden brown pigment, which is not excreted in the urine. A rather simple and reliable test for detection of intravascular hemolysis is the determination of methemalbumin (at 558 microns on the absorption band) by a hand spectroscope. The performance of this test may direct attention to the possibility of P.N.H. and obviate the need for less definitive tests. Whenever hemoglobin is filtered by the glomeruli, the renal tubules take up part of the hemoglobin and convert the iron to a colloidal sol of ferric iron, called hemosiderin, which can be detected easily in the urine sediment. Because of the continuous exfoliation of hemosiderin-laden renal tubular epithelium, hemosiderinuria is a constant feature of P.N.H. and therefore provides a more useful screening test.

**SUMMARY**

Unusual features of P.N.H. are exemplified in two new cases herein reported. The first case closely mimicked aplastic anemia for several months. The second had findings suggestive of iron deficiency anemia.

The classic observations on pathologic physiology of P.N.H. have been reviewed, as well as recent observations on specific structural, chemical, and enzymatic defects of the P.N.H. erythrocyte. The important diagnostic features of the disease have been discussed.
NOCTURNAL HEMOGLOBINURIA

REFERENCES
