Treatment of Paroxysmal Nocturnal Hemoglobinuria

By Wendell F. Rosse

Paroxysmal nocturnal hemoglobinuria (PNH) is a complex stem cell disorder that is manifested by hemolytic anemia with hemoglobinuria, unusual venous thromboses, and episodes of severe pain in the abdomen and back. In some patients, the bone marrow is relatively or absolutely hypoplastic with the resultant reticulocytopenia, leukopenia, and thrombocytopenia. In rare instances, the syndrome eventuates in acute myeloblastic leukemia.

The major clinical manifestations of PNH appear to be ultimately due to a dysplastic process of the marrow that results in a population of abnormal cells of all three cell lines of the peripheral blood. This population is, in each case, characterized by an unusually great fixation of the terminal components of complement and by an abnormal susceptibility of the membrane to rupture by these components. Thus, in the red cell, activation of serum complement results in hemolysis; in the platelet, such activation may result in the initiation of the platelet release phenomenon, leading to thrombosis.

The ideal treatment of PNH would be the replacement of the abnormal stem cells with stem cells capable of proliferating normally and producing normal cellular descendants. This has been accomplished by transplantation in several cases, particularly when marrow hypoplasia is an important clinical manifestation of the disorder. The patients have been prepared for transplantation by the usual therapy for the ablation of the recipient's marrow, including the abnormal population. When the donor marrow was infused, the PNH population did not recur. In two patients, pretreatment with cytotoxic drugs or irradiation was omitted; nevertheless, upon infusion of syngeneic bone marrow from an identical twin, the abnormal population of PNH cells disappeared.

Because PNH may be very chronic and long-lasting and because of the difficulties of marrow transplantation, even in allogeneic transplantation between HLA-identical siblings, this treatment continues to be fraught with considerable morbidity and some mortality, and bone marrow transplantation does not appear at this time to have a clear-cut role in the treatment of PNH, save in those patients with a markedly hypoplastic marrow.

Iron Therapy

Considerable iron is lost because of the hemoglobinuria, which is usually manifest at some time or other by patients with PNH. Many patients do not have overt hemoglobinuria but, nevertheless, lose large amounts of hemosiderin as iron-laden renal cells are sloughed. As much as 22 g of hemoglobin and 20 mg of iron as hemosiderin may be lost in a single day. When iron losses are severe, they usually cannot be made up from dietary iron sources, and hence, these must be supplemented.

Paul Strübing, in his classic description of the disorder, recognized that giving iron to patients with PNH might result in exacerbation of hemoglobinuria. This was at one time thought to be due to the toxic effect of the iron itself, but it is now recognized that the hemoglobinuria that follows iron therapy in the iron-deficient PNH patient is due to the delivery to the circulation of a cohort of cells susceptible to the lytic action of complement. This cohort results from the burst of erythropoiesis that follows iron replenishment. If erythropoiesis is suppressed by transfusion or if the patient is not iron deficient, the burst of erythropoiesis and the paroxysm of hemoglobinuria will not occur.

This reaction to iron therapy has led some physicians to withhold iron even in the iron-deficient PNH patient. In most cases, however, iron may be given safely either orally or parenterally. Oral administration is usually accompanied by less severe hemolytic reaction, but the iron losses in the urine may be so great that oral therapy cannot compensate for them. Parenteral iron therapy using iron dextran (Imferon) is equally efficient; it is more likely to result in a hemolytic episode, since iron is rapidly delivered to the marrow. Iron in this form is delivered to the erythron at variable rates; some of the least available iron may not be mobilized sufficiently rapidly, resulting in iron-deficient erythropoiesis at a time when granules of iron are visible in the macrophages of the bone marrow. If a hemolytic episode should occur following iron therapy,
it can be treated with either suppression of erythropoiesis by transfusion or suppression of hemolysis by prednisone (see below).

**ANDROGEN TREATMENT**

Hartmann and associates first found that many patients with PNH had an improvement in their hemoglobin and total clinical status upon treatment with androgenic hormones. Methyltestosterone, parenteral androgens (testosterone enanthate, Durabolin, etc.), and semisynthetic androgens (flouxymesterone and oxymethalone) have all been used with success.

The mode of action of the androgenic steroids is uncertain; although it has been suggested that these drugs have inhibitory action on complement or its activation, most investigators believe that they act as they do in aplastic anemia in stimulating the bone marrow to greater red cell production. Granulocyte and platelet numbers are seldom increased if they are low.

The patients who benefit most from androgen therapy are, in general, those patients with a degree of bone marrow hypoplasia. In such patients, the increase in the production of red cells may result in an increase in hemoglobinuria despite an amelioration of the anemia. This, as in the case of iron repletion, is due to the increased production of both normal and abnormal cells. The normal cells survive, but the abnormal cells are lysed by complement.

These androgenic steroids are not without side effects. Frequently, in the doses used, virilizing effects occur in women. In men, prostatism has been reported. Some androgens have an adverse effect on the liver, causing either cholestatic jaundice or, in some cases, peliosis hepatis; this latter complication has not been observed in patients with PNH. One of the recently recognized complications of PNH is an insidious form of hepatic venous thrombosis (insidious Budd-Chiari syndrome). It has been suggested that androgen therapy may be a predisposing cause of this disorder, but the data are not definite on this point.

Since it is difficult to determine prior to treatment which patients will respond to androgen therapy, a trial of flouxymesterone (5–20 mg/day) or oxymetholone (10–50 mg/day) is worthwhile. A period of 6–8 wk should be allowed to determine whether a response has resulted. If androgens are not clearly useful, their use probably should be discontinued in view of possible hepatotoxicity.

**PREDNISONE THERAPY**

The use of prednisone in the treatment of PNH was assessed shortly after the introduction of the adrenocorticosteroid drugs. It was found that, in some cases, hemolysis could be suppressed but that the doses of steroids that were required were often greater than were tolerable on a daily basis. Because of the great incidence of catastrophic side effects from high doses of adrenocorticosteroids given for long periods of time, a virtual interdict on their use has been promulgated.

However, in recent years, better understanding of the use of steroids has resulted in the revived interest in their use.

The mode of action of adrenocorticosteroids is not at all clear. The cells of the patients are not rendered less sensitive to the lytic action of complement as measured by the available in vitro assays. The serum of recipients of prednisone is not rendered less capable of bringing about the lysis of PNH cells when complement is activated either by antibody or by acidification (this data must be interpreted with caution, since these means of activation of complement are much stronger than those that activate complement in vivo). Perhaps steroids inhibit the activation of complement by the alternative pathway.

Whatever the mechanism, steroids can, in some patients, be strikingly useful in preventing hemolysis. The action is rapid; if prednisone is given at 6:00 p.m., to a patient able to respond, the nocturnal hemolytic episode is aborted. In one severe hemolytic episode, the addition of 60 mg of prednisone to the therapeutic regimen abruptly brought the hemoglobin excretion from 22 g/day to less than 500 mg/day over a period of 36 hr.

The doses of prednisone required to produce a beneficial effect are high. In general, 20–60 mg (0.25 to 1 mg/kg/day) are required. Since this amount of drug cannot be tolerated on a daily basis without ill effects (particularly, an increased incidence of infections) we have treated our patients with prednisone on alternate days in doses ranging from 15 to 40 mg every other day.

On such a regimen, 12 out of 18 patients have shown a significant clinical response. Patients manifesting primarily hypoplastic bone marrow do not gain benefit unless erythropoiesis can be stimulated with androgenic steroids. Patients with little hemolysis likewise do not benefit. Other than these factors, it is not possible to predict the patient’s response to prednisone. If no clear-cut benefit is derived after a period of 6 wk, prednisone should be discontinued.

While taking prednisone, patients tend to have hemolysis on the day that the prednisone is omitted. During exacerbations of hemolysis, this hemolysis is exaggerated and considerable hemolysis may even occur on the day the prednisone is taken. During these
times, many patients gain benefit from an increase in the dose to 40–60 mg every day for a short period (1 wk).

In treating 15 patients with prednisone by this technique for a period ranging from 2 to 7 yr, few complications have arisen. One patient had bilateral lenticular opacities. No patient had a serious infection. In contrast, 3 of 3 patients who were taking prednisone on a daily basis had serious bacterial and fungal infections; two of these patients died.

In summary, prednisone in doses of 15–40 mg/day, given on alternate days, may be a useful adjunct in the treatment of patients with PNH who have a large population of susceptible cells. It must be emphasized that this drug should not be given to these patients on a daily basis except for short intervals. On the alternate day regimen, few side effects have been noted.

TRANFUSIONS

When the treatment of PNH by medication is not possible or is not successful, the patient may require transfusion. In some patients, the transfusion of whole blood or even packed red cells leads to hemolysis of the patient’s complement-susceptible cells.23 This is often confused with a hemolytic transfusion reaction due to the destruction of the transfused cells by alloantibodies. The reason for the hemolysis of the patient’s cells is not known. Alloantibodies in the donor plasma against red cell antigens of the patient do not appear to account for it. The presence of white cells in the transfused blood that are able to react with alloantibodies in the recipient, thus activating complement, has been suggested to be the cause, but this has not been rigorously proven. It is most likely that the hemolysis is due to the infusion of activated complement components present in the plasma in the stored blood, which are then able to activate the patient’s serum complement, bringing about hemolysis.

In any event, this hemolytic reaction in most cases can be prevented by the transfusion of washed or frozen-reconstituted red cells. This procedure is apparently not necessary for all patients, but when it is required, it removes a great deal of apprehension and confusion surrounding transfusion.

THE TREATMENT OF ACUTE COMPLICATIONS OF PNH

The Hemolytic Crisis

The clinical course of many patients with PNH is punctuated by episodes of increased hemolysis. Not infrequently, these episodes are initiated by infections, viral or bacterial. The episode is characterized by darker urine, which remains markedly hemoglobinuric throughout the day. Patients often complain of malaise and fatigue and may have abdominal pain (see below).

The treatment of a hemolytic episode should aim at diminishing hemolysis and preventing complications. Hemolysis may, on occasion, be diminished by giving prednisone in high doses; if the patient is taking prednisone on alternate days, the dose may be increased and the frequency may be increased to daily; daily prednisone should not be maintained for more than 7 days. Transfusion may ameliorate a hemolytic crisis by suppressing the production of complement-sensitive cells.

A major complication of a hemolytic episode is acute renal failure. Many patients may have striking hemoglobinuria without impairment of renal function, but with a hemolytic episode, they may become dehydrated and acute but reversible renal failure may ensure. Patients should be urged to maintain hydration during these episodes; intravenous hydration may be required.

Venous Thrombosis

Patients with PNH frequently have venous thromboses involving particularly the hepatic veins, other intraabdominal veins, and the cerebral veins.22–24 This often results in insidious and confusing clinical syndromes. The cause of this thrombosis may be the abnormal platelet in PNH.8

Anticoagulation is indicated in these clinical syndromes; however, some caution must be exercised in the use of heparin. Clear-cut hemolytic episodes have been recorded after treatment with heparin.25 On the other hand, many patients are given heparin without consequence. The reason for the biphasic reaction may reside in the fact that heparin activates the alternative pathway of complement at low concentrations but inhibits the activation of complement at higher concentrations.26 Successful anticoagulation with coumarin and its cogeners is without special attendant risk. Treatment with the coumarin compounds probably should be initiated as quickly as possible after the recognition of the syndrome.

Acute hepatic vein thrombosis should be treated aggressively with high doses of heparin given intravenously. The otherwise dismal outcome amply warrants the risk.24

Chronic venous thrombosis of the hepatic veins (Budd-Chiari syndrome) is reasonably common in patients with PNH and tends to be long lasting with exacerbations. It has been successfully controlled by a
combination of anticoagulation and prednisone therapy.

### Painful Episodes

Patients with PNH may be subject to recurrent attacks of abdominal pain. This is severe, colicky, and may be an acute process that would seem to require surgery. The cause of this complication is not clear: in one case only, thrombosis of the mesenteric veins was found. Patients with this syndrome frequently must be hospitalized and treated with narcotics and rehydration. At the present time, there is no specific therapy.

### SUMMARY

Patients with PNH may be treated with a number of known agents. As in all patients with a chronic disease, a regimen tolerable over a long period of time must be selected. Knowledge and anticipation of complications and their proper treatment are essential parts in the treatment. When these principals are used, many patients may live reasonable lives for very long periods of time.

### REFERENCES

Treatment of paroxysmal nocturnal hemoglobinuria

WF Rosse