Analytical Review

Paroxysmal Nocturnal Hemoglobinuria: Current Concepts of Certain Pathophysiologic Features

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There are certain disorders which even though rare are of disproportionately great interest since their study can provide insight into many pathophysiologic mechanisms. In the field of hematology one such disorder is paroxysmal nocturnal hemoglobinuria (PNH). Among the features of PNH making it an important “clue” disease are: an acquired erythrocyte abnormality associated with a known stromal enzyme deficiency and marked sensitivity to complement-induced hemolysis; chronic intravascular hemolysis providing a unique study model of hemoglobinemia, haptoglobin kinetics and the renal excretion of filtered hemoglobin; changes in iron metabolism associated with this process; and the tendency to thrombotic complications observed in the setting of chronic intravascular hemolysis and thrombocytopenia.

A number of reviews on PNH have been written within the past decade.1-5 Historic accounts and the typical clinical features are well documented in these papers. It is not our purpose to duplicate these reviews or to provide an all-inclusive treatise. Rather the discussion will be limited to current concepts regarding certain important pathophysiologic features of PNH. The review will be based upon the work of many investigators as well as upon analyses made possible by our own unusual opportunity to carry out long-term studies on 8 patients during the past 7 years.

Etiology

Although it is well established that the basic abnormality in this chronic hemolytic anemia resides in the red cell, the precise nature of the erythrocyte defect in PNH remains unknown. The more recent description of a deficiency in erythrocyte acetylcholinesterase (AChE) activity6-8 suggests the presence of a genetic alteration. There is, however, no evidence of familial involvement by history, serologic studies for PNH or erythrocyte AChE determinations.6-8 The identical twin of 1 PNH patient has remained free of any signs of the disorder for 2 decades following the diagnosis in her sibling.6,10 In view of such considerations the possibility of a somatic mutation existing in PNH has been raised.5

In addition to the established hemolytic nature of the disorder, an important question to be answered is the relationship of PNH to aplastic ane-
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Clinically the pancytopenia observed may mimic aplastic anemia. Furthermore, a number of instances of hypocellularity of the marrow either preceding the onset of PNH or intervening during the course of the disease have been reported. In most patients, however, the bone marrow is very cellular. In view of the present ready availability of trephine needle biopsies, further studies of the marrow in various stages of this disorder would be most helpful in evaluating the frequency and significance of marrow aplasia in PNH.

Seeming marrow unresponsiveness could be due to causes other than aplasia. Such causes, which will be discussed in subsequent sections, include: iron deficiency; a “ceiling” on the response to iron therapy due to precipitation of hemolytic crisis by this treatment; or selective destruction of very young red cells. Results of ferrokinetic studies have generally been more consistent with destruction of young red cells than with true marrow hypoplasia. Furthermore, some patients on iron and androgen therapy have been able to maintain normal or near-normal hematocrit values even when the red cell life span was shortened, indicating an appreciable degree of marrow reserve capacity.

DIAGNOSIS

The failure to make the diagnosis of PNH usually results from not considering the disorder in patients with atypical features. Thus the diagnosis should probably be considered in any patient with a puzzling anemia particularly if unexplained hemolytic anemia, pancytopenia, or a history of frequent transfusion reactions exists. The classic story of hemoglobinuria on arising with subsequent clearing during the day usually presents little diagnostic difficulty. However, many patients with PNH when first seen do not give a history of hemoglobinuria, because the hemoglobinuria is truly occult, or because they have failed to observe its presence. In the latter case, inspection of a morning urine specimen by the physician may reveal definite hemoglobinuria.

Once considered clinically, the diagnosis of PNH can be easily established in the laboratory. Marked hemolysis in the serum obtained from clotted blood incubated at 37 C. for 1 to several hours (positive “heat test” or “autohemolysis test”), particularly if coupled with a strong Perl’s Prussian blue reaction for hemosiderin in the urinary sediment, constitutes good presumptive evidence for PNH. If either of these tests is positive, the more specific acid hemolysis and thrombin tests should be carried out.

RED CELL DEFECT

Van den Bergh’s observation in 1911 that the PNH erythrocyte is peculiarly susceptible to hemolysis in acidified serum still defies explanation in terms of the basic red cell defect. The demonstration by electron microscopy of an abnormally patchy and granular erythrocyte stroma in PNH has not always been confirmed. The severity of this morphologic defect may vary with the degree of in vivo or in vitro hemolysis and may also depend in part on methods of preparation. Somewhat similar changes
have been reported in cells undergoing immune hemolysis in vitro\textsuperscript{24} as well as in experimental immune hemolytic anemia in animals.\textsuperscript{25} Thus these morphologic changes which are not necessarily specific for PNH may merely be the result of hemolytic damage\textsuperscript{20,24} and could conceivably go undetected during periods of minimal hemolysis.

Much work has been done regarding red cell lipids in PNH,\textsuperscript{26-32} but there is no agreement as to whether any defect exists, or if present what its nature is. It has been pointed out that both methodology and type of dietary fat may greatly influence results of red cell lipid analyses.\textsuperscript{20,30} Moreover, treatment to absorb lipids from the stroma of normal red cells did not render them susceptible to hemolysis in acidified serum.\textsuperscript{33}

A few studies of high energy phosphate turnover in PNH have appeared. The rate of entry and efflux of $^32P$ in PNH cells has been reported to be reduced.\textsuperscript{34,35} Unpublished studies from our laboratory employing a somewhat different method have shown a normal $^32P$ uptake. An increased turnover of the labile phosphate of ATP and decreased stability of erythrocyte ATP has also been noted,\textsuperscript{34} but phosphorylation of ADP has been reported normal.\textsuperscript{36}

Decreased \textit{acetylcholinesterase} (AChE) activity has been the most consistently demonstrated biochemical abnormality in the PNH erythrocytes.\textsuperscript{4,6-8,37} With certain exceptions, the degree of enzyme deficiency has paralleled the clinical severity and in mild cases the enzyme value may be normal.\textsuperscript{6-8,37} In normal blood the highest AChE values are found in young cells, particularly in reticulocytes. In PNH, however, the young red cells share the AChE deficiency, and in some patients the values in young cells have been reported to be lower than in older cells.\textsuperscript{6-8,37} The reported increased susceptibility to hemolysis on the part of PNH reticulocytes\textsuperscript{38} may possibly correlate with the reported increased susceptibility to hemolysis of PNH cells with lower AChE values.\textsuperscript{37} However, such correlation does not prove that AChE deficiency of and by itself leads to increased susceptibility to hemolysis.

There is no evidence that AChE deficiency reflects any "general poverty" of enzymes in the PNH erythrocyte. Various other enzymes have been found to be normal or increased, the increase probably reflecting the presence of many young red cells.\textsuperscript{6,39,40} DPNase—like AChE, a \textit{stromal-bound} enzyme—has also been found to be normal in our laboratory. On the other hand, Vaccari and Baldini have reported a marked reduction in the thiol groups in PNH erythrocytes which may indicate a profound structural alteration in the cellular stroma.\textsuperscript{41} However, the linking of this observation to any alteration in erythrocyte enzymes was not confirmed in their work and requires further study.

The function of AChE in erythrocytes remains unknown. A role in maintaining normal cellular permeability has been postulated.\textsuperscript{42} In addition AChE has been thought to protect the normal erythrocyte from the deleterious effects of low pH ("enzyme buffer" hypothesis). The latter view was largely derived from experiments in which normal red cells with AChE activity suppressed by drugs were incubated in solutions of isotonic choline esters.\textsuperscript{42}
However, repetition of such experiments employing enzyme-deficient PNH cells has not confirmed either of these postulated functions of erythrocyte AChE.\textsuperscript{43,44}

There is no evidence that in vivo depression of AChE in otherwise normal erythrocytes brings about accelerated hemolysis. Inhibition of red cell AChE activity by accidental insecticide poisoning or by deliberate ingestion of AChE inhibitors\textsuperscript{45,47} has not resulted in overt hemolysis or shortened red cell life span. Work in our laboratory indicated that there is probably no significant, simultaneous inhibition of the serum hemolytic system to account for these negative results. Furthermore, familial deficiency of red cell AChE is not associated with hemolysis or positive serologic tests for PNH.\textsuperscript{46}

Some decrease in erythrocyte AChE activity has been noted in occasional patients with a variety of hematologic disorders.\textsuperscript{6} However, both the frequency and degree of enzyme defect have not usually approached that seen in severe PNH. Moderately severe reductions in enzyme activity have more recently been reported in some cases of ABO hemolytic disease of the newborn\textsuperscript{47} and in Coombs positive autoimmune hemolytic anemia.\textsuperscript{48} In addition treatment of normal red cells with various proteolytic enzymes has resulted in “pseudo-PNH” cells with low AChE\textsuperscript{44} and similar though not identical susceptibility to hemolysis in acidified serum.\textsuperscript{33,46,48}

The foregoing implies that decreased erythrocyte AChE is not specific for PNH. The low enzyme values may simply reflect damage to the PNH red cell. A similar type of erythrocyte damage might account for the decreased AChE seen in certain other hematologic disorders. The extreme deficiency seen in some PNH patients may reflect a greater degree of stromal damage. It is possible that both deficient AChE activity and the reported electron microscopy defect of the PNH red cell reflect cellular damage since both have also been observed in experimental immune hemolytic anemia.\textsuperscript{25} However, a failure to incorporate AChE into the PNH red cell stroma during production still cannot be excluded.

\section*{Serum Hemolytic System}

The nature of the serum factors, present in both normal and PNH serum and required for the in vitro PNH acid hemolysis reaction, has been the subject of considerable investigation. Ham and Dingle concluded that although complement was probably required, this did not seem to be the sole hemolytic agent since PNH hemolytic potential could be removed from serum without depleting complement.\textsuperscript{50} However, no erythrocyte antibody has been demonstrated.

Hinz and co-workers showed that treatment of serum to remove each of the four classical components of complement resulted in each instance in removal of PNH hemolytic activity.\textsuperscript{51} In addition treatment of serum at 18 C. with zymosan also removed PNH hemolytic activity. This latter maneuver removes properdin, and the addition of either crude or highly purified properdin to such serum restores PNH hemolytic activity.\textsuperscript{51,52} Although controversy exists regarding the exact nature and general biologic role of properdin,\textsuperscript{53} its requirement in the PNH acid hemolysis reaction has been
The sequence of the interaction between properdin and components of complement in PNH hemolysis is not known.

There are a number of ways in which PNH acid hemolysis has appeared to differ from classical complement systems: the absence of a demonstrable antibody, the lack of detectable complement fixation (i.e., utilization), the absence of hemolysis in serum diluted 1/4 or greater, the lack of an absolute requirement for calcium, and more recently, the enhancement of PNH hemolysis by polyinosinic acid (poly I), a synthetic polynucleotide which inhibits classical complement systems.

The lack of detectable complement fixation may be a reflection of the great susceptibility of PNH red cells to complement injury such that usual technics of complement fixation do not detect the small amounts of complement utilized. In this regard recent work has demonstrated the presence of complement on the unlysed cells following PNH acid hemolysis.

The lack of calcium requirement for PNH hemolysis can no longer be cited as evidence for a difference between PNH hemolysis and classical complement hemolysis. As Yachnin and Ruthenberg have recently shown, classical complement hemolysis can also occur in the absence of calcium provided the reaction is run in undiluted serum as is the case in the PNH acid hemolysis reaction. The very interesting observation by these same authors that polyinosinic acid enhances the PNH acid hemolysis reaction has suggested to them that the initial steps of this reaction may take place in the fluid (serum) phase rather than entirely on the red cell surface as is the case in antibody complement hemolytic reactions.

The relationship of these in vitro observations to in vivo PNH hemolysis is not known. In contrast to the antibody-induced hemolytic anemias with complement-dependent in vitro hemolytic systems, the serum complement in PNH, when measured, has been normal and the direct antiglobulin test almost always negative. The significance of the occasional instances of positive antiglobulin reactions in PNH is not clear. These could represent either superimposed autoimmune reactions or simply intervals in which it is possible to detect complement proteins on the red cell. Further observations on the antiglobulin reaction in the long-term study of PNH, particularly during severe hemolytic episodes, seem warranted.

The mechanism by which hemolysis is accentuated during sleep or during acute hemolytic episodes is not known. Nor is it known why infections, certain antisera and drugs, and even menstruation may precipitate hemolytic crises. One difficulty in carrying out meaningful in vitro studies with respect to factors augmenting hemolysis clinically is that the in vitro tests have not always correlated well with changes in the degree of clinical hemolysis.

A most dramatic precipitation of hemolysis of the patient’s own cells may follow the transfusion of whole blood into PNH patients. Originally this was thought due to the infusion of additional plasma hemolytic factors. A more recent interpretation suggests that the reaction might be triggered by leukoagglutinins present in the previously transfused patient. However, this reaction in PNH has even been seen with the very first unit of whole blood given. Fortunately, the reaction can be prevented or minimized by wash-
In view of the thrombotic tendency observed clinically (see below), investigations have been carried out to determine whether coagulation factors might interact with the PNH hemolytic system. Originally factor V was thought to be involved in PNH hemolysis but this was not confirmed. Crude bovine thrombin was also observed to enhance in vitro PNH hemolysis. Whether this enhancement is due to the presence of thrombin clotting activity or of natural antibodies in commercial thrombin has been disputed. Recent studies in our laboratory have shown that the natural antibodies contained in crude bovine thrombin are capable of fixing complement to normal and PNH cells as well as enhancing PNH hemolysis. Removal of impurities from commercial thrombin by absorption with normal cells or cation exchange chromatography markedly reduces but does not abolish the ability of thrombin to enhance PNH hemolysis when these reactions are carried out over a wide range of pH. Heating at 56 C. for sufficient time to remove all thrombin clotting activity does not diminish the ability of crude thrombin or chromatographically purified thrombin to enhance PNH hemolysis. Based on these observations it is our present opinion that enhancement of PNH hemolysis by various preparations of crude or purified bovine thrombin is not due to thrombin clotting activity but instead is due to the presence of contaminants in these thrombin preparations. Final assessment of the mechanism of enhancement of PNH hemolysis by thrombin awaits the availability of thrombin preparations of even greater purity.

THROMBOTIC TENDENCY

The well-known thrombotic tendency in PNH constitutes a serious complication and a frequent cause of death. There is a general consensus that these thrombotic episodes usually follow periods of accentuated hemolysis. Thus attention has naturally focused on the means by which PNH hemolysis might affect platelets or the blood coagulation system and lead to thrombosis.

Platelets

Despite the fact that most PNH patients have thrombocytopenia at some time during their disease, hemorrhagic phenomena are infrequent and bleeding time and capillary fragility tests are usually normal. To explain the presence of both thrombocytopenia and a thrombotic tendency, the thesis has been advanced that thrombocytopenia results from platelet lysis in vivo (by the same system which lyses the PNH red cells) and that the thrombotic tendency is a result of circulating platelet products. This thesis is supported in part by the report that platelet-poor plasma from PNH patients generated virtually as much thrombin as did PNH platelet-rich plasma. However, not all workers have confirmed these latter findings. Furthermore, the intravenous injection of platelet extracts into experimental animals has been reported to have no influence on blood coagulation modalities.

A very sensitive in vitro measure of platelet integrity is the clot retraction test. PNH platelets when concentrated appropriately in plasma produce nor-
mal clot retraction.72 In unpublished studies in our laboratory the clot retraction function of PNH, as well as of normal platelets, was not impaired when they were incubated with PNH red cells in a modified acid hemolysis reaction mixture. These normal in vitro tests might reflect that the PNH platelets which are damaged in vivo are removed from the circulation and thus are not available for in vitro testing. However, platelet life span was found normal in 2 patients in 1 study74 and in 5 of 6 of our PNH patients. In our patients episodes of severe hemolysis and thromboses have not been associated with significant changes in the platelet count.

Clot-Promoting Effect of PNH Erythrocytes

There is general agreement that plasma obtained from PNH blood which has been incubated at 37 C. for 1 hour possesses increased thromboplastic activity in the thrombin generation test.71,75,76 This effect, attributed to the release of “non-haemolytic thromboplastic activity” from the erythrocytes of PNH, was detected in other hemolytic anemias as well.71 The phenomenon was particularly marked with reticulocytes and with PNH red cells and did not appear to be due to the hemoglobin released.71,75

The critical question is whether this effect occurs in vivo to an extent sufficient to play a role in the development of thrombosis. Thus, the determination of thrombin generation in fresh, unincubated PNH plasma is of critical importance for the detection of circulating “non-haemolytic thromboplastic activity.” Results have been conflicting. Subnormal,71,77 normal72,78 and increased thrombin generation75,76 have all been reported. Differences in technic as well as variations in the clinical status may account for these divergent results, and further studies are indicated. In the interpretation of such studies it should be noted that infusions of tissue thromboplastin into experimental animals can produce variable results (i.e., large thrombi, a coagulation defect or no ostensible effect) depending on the amount and rate of infusion.79

Other Coagulation Studies

The results of other coagulation studies have been variable. Abnormalities reported in PNH include: reduced Factor XI activity,80-82 elevated Factor VIII and fibrinogen values82 and a nocturnal increase in Factor V and VII activities interpreted as the cause for the nocturnal accentuation of PNH hemolysis.83 In contrast, studies in normals have revealed no alteration in blood coagulation during sleep,84 and normal thromboplastin generation using PNH plasma and serum has been reported.85

Although a thrombotic tendency in PNH is undeniable and that it usually follows episodes of severe hemolysis seems reasonably certain, it is obvious that much remains to be done to resolve the conflicting results of coagulation studies reported to date.

Susceptibility to Infections

An increased susceptibility to infections in PNH has been reported, and, prior to the antibiotic era, infections were a frequently listed cause of death.1
There are few critical studies on this aspect of the disease. One possible explanation for this susceptibility might be the frequently observed leukopenia. A tendency to chronic leukopenia has been observed in 5 of our 8 patients. However, acute episodes of severe infection or thrombosis in our patients have usually been accompanied by leukocyte counts greater than 10,000 per cu. mm.\textsuperscript{13}

Functional abnormalities in PNH leukocytes may also exist. Leukocyte alkaline phosphatase\textsuperscript{6,66} and acetylcholinesterase\textsuperscript{12} have been found to be low in PNH. Studies of cellular exudative response by Rebuff and his associates using the coverslip technic have revealed a marked decrease in cellularity of the exudate in 1 patient and a marked depression of the leukocyte alkaline phosphatase activity in the exudate in another.\textsuperscript{87} Furthermore, an abnormally thin zone of leukocyte margination surrounding an area of infarction in the uterine cervix was noted in 1 of these patients. The cellular exudative response has also been found to be abnormal in chronic granulocytic leukemia,\textsuperscript{88} in which low leukocyte alkaline phosphatase likewise occurs. In this latter state cytogenetic studies usually reveal chromosomal abnormalities. To date, however, cytogenetic studies in PNH have been normal.\textsuperscript{12,89}

The effect of the chronic hemolytic process in PNH on serum or reticuloendothelial factors necessary in host defense against infections has not been fully assessed. In our patients serum electrophoretic patterns have been normal. With the use of more refined technics, however, gamma globulin abnormalities have been detected.\textsuperscript{90} Recent work in animals has pointed to an increased susceptibility to infections in mice following experimentally induced hemolysis. The mechanism for this increased susceptibility is not established but may relate to decreased bacteriocidal capacity of reticuloendothelial cells for phagocytized bacteria.\textsuperscript{91}

** MANAGEMENT **

**Iron Therapy**

One would logically expect iron deficiency to be frequent in PNH in view of the marked loss of iron in the urine due to the hemoglobinuria and persistent hemosiderinuria.\textsuperscript{11,92} Frank hypochromia of the red cells has been only occasionally documented in PNH.\textsuperscript{1,92} There are several reasons why the magnitude of iron deficiency in PNH may not be fully appreciated. These include: (1) the liberal use of transfusions in recent years tending to replace lost iron, (2) possible masking of low serum iron values by the hyperferremic effect of hemolytic crises, and (3) the hesitancy to use iron therapy because of its reported ability to precipitate hemolytic crises.

One of our PNH patients with classical hematologic and ferrokinetic findings of iron deficiency has experienced complete relief of his severe anemia on oral iron therapy alone.\textsuperscript{13} This treatment did not precipitate hemoglobinuric crisis although there remains other evidence for a continuing

\*Dr. Eric Engel, Department of Medicine, Vanderbilt Medical School, kindly carried out cytogenetic studies on 6 of our PNH patients and also found them to be normal.
chronic, low grade hemolytic process. In another patient 11 months of oral therapy alone produced no effect on the anemia as well as no precipitation of gross hemoglobinuria. In a third patient 4 weeks of oral iron therapy had no effect on the anemia but was followed by gross hemoglobinuria, the first such episode in a number of months. In still another patient oral iron therapy resulted in a rise in hematocrit from 28 to 41 per cent within 4 weeks, but at this time gross hemoglobinuria began and became steadily worse. The hematocrit fell progressively to 26 per cent within the next month. In a fifth patient there was suggestive evidence that a single intramuscular injection of 500 mg. of iron accentuated on-going, chronic and moderately severe hemoglobinuria.

It thus seems that iron therapy can precipitate gross hemoglobinuria but not in all PNH patients. In some instances the mechanism may be pathophysiologic rather than pharmacologic as follows: In some iron-deficient PNH patients, iron therapy may result in an outpouring of young erythrocytes and even temporary improvement in the degree of anemia. After a certain period of time, a sufficient number of “sensitive” erythrocytes may accumulate, and hemolysis may then be triggered on a large scale. Earlier opinions that PNH patients could not tolerate a hemoglobin concentration above a certain critical value (in the absence of transfusions) without gross hemoglobinuria may relate to a similar mechanism.

On the other hand, in still other cases of PNH with iron deficiency, all of the young red cells produced in response to iron therapy may be so “sensitive” as to be quickly destroyed. Hickey and Malley reported 1 patient with episodes of gross hemoglobinuria about 1 week after the institution of oral iron therapy on multiple occasions.93

*Androgen and Iron Therapy*

Gardner and Pringle94 noted improvement in the anemia of 1 of 3 PNH patients treated with androgen, and Weisman and Hinz6 noted similar improvement in 1 patient using androgen with parenteral iron. Six of our patients have been treated during the past 3 years with oral androgen (fluoxymesterone,* 15 to 60 mg. daily) and oral iron therapy.13 Responses have been classified as poor in 1, fair in another and good in 4. In these latter 4 patients anemia has been partially or completely relieved for long periods of time and hemolysis has been distinctly less. Although urinary iron loss diminished in intensity, the 4 patients with good response manifested hypoferrremia and other evidence of iron deficiency, particularly during intervals when iron therapy was temporarily withdrawn.

These findings suggest that androgen in addition to its postulated classical role of stimulating the marrow may also diminish the chronic hemolytic process in PNH. In 1 patient, androgen seemed to have some protective effect against precipitation of hemoglobinuric crisis by oral iron therapy. In 2 others, gross hemoglobinuria developed shortly after the abrupt

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*Kindly supplied as Halotestin® by Dr. Paul C. Schwallie, the Upjohn Co., Kalamazoo, Michigan.*
withdrawal of androgen. On the other hand, the use of a large dose of androgen in 1 patient had no immediate influence on an established hemoglobinuric crisis. The seeming frequency of iron deficiency in our patients in recent years may relate in part to a decreased need for transfusions resulting from androgen therapy.

Other Measures

Because of the great variability and periodicity in the clinical course of PNH, evaluation of therapy is difficult. There is a paucity of detailed data on long-term follow-up studies. Many therapeutic measures initially advocated with enthusiasm have been disappointing with long-term evaluation. Although a few cases have ameliorated with the passage of time, there is no known curative therapy.

Splenectomy has at times been advocated and might deserve consideration in a patient with an unusual degree of splenomegaly and evidence suggesting "hypersplenism." In most instances, however, splenectomy has produced little or no improvement, and serious and even fatal postoperative thrombotic episodes have been frequent.

In view of the possible inter-relationship between coagulation factors and the PNH hemolytic system, long-term anticoagulation with coumarin derivatives has been considered as a means to suppress hemolysis. The results of this therapy have been disappointing. Use of anticoagulant drugs in patients with a marked thrombotic tendency is another matter to be decided on the basis of the individual case.

Adrenocortical steroid drugs have also been tried but generally have not been effective. Nonetheless, steroids might be considered in the occasional patient who develops a positive Coombs antiglobulin test, possibly representing an autoimmune hemolytic process superimposed on the basic PNH disorder.

For maintenance transfusion therapy red blood cells adequately washed to remove the plasma (and white cells) should be used in order to minimize or prevent the reactions frequently seen with whole blood.

Acute Hemolytic Episodes

There are no specific measures available to halt an acute hemolytic crisis in PNH. Control of precipitating factors by removing suspect drugs or treating infections is indicated but usually will not dramatically halt a severe hemolytic episode once it has started.

Forcing fluids to assure good urine output during episodes of marked hemoglobinuria seems warranted although acute renal failure with hemolytic crises in PNH is extremely rare compared to the frequency of this complication following hemoglobinuria from isoimmune transfusion reactions. To illustrate, 1 of our patients maintained a urine output of greater than 1800 ml. per day with no change in serum urea nitrogen during 3 days of extreme hemoglobinuria accompanied by a fall in hematocrit from 39 per cent to 17 per cent.

Transfusions of washed red blood cells in addition to correcting anemia
may at times dramatically suppress hemolysis although this is not invariably true.\textsuperscript{2,13} The mechanism for this suppression is not known.

Based on the observation that it inhibited PNH hemolysis in vitro, dextran has been used successfully to suppress hemolytic crises in PNH.\textsuperscript{95} Despite the acute suppression there may be a return of hemolysis after 1 to 2 days. Although the chronic use of dextran is prohibited by possible hemorrhagic complications,\textsuperscript{95} the acute suppression of hemolysis by dextran may serve to tide the patient over a crisis until a chronic steady state returns.

In view of the marked tendency to thrombosis following a severe hemolytic episode, anticoagulant drugs should be used during this time at the slightest suggestion of thrombosis, and perhaps even prophylactically. Coumarin derivatives are usually employed in this situation until the danger of thrombosis has passed. However, caution is urged in the combined use of coumarin derivatives and dextran in the PNH patient with thrombocytopenia since such might lead to a significant hemorrhagic state.

The use of heparin in PNH has been controversial. In addition to its anticoagulant effect, heparin also inhibits PNH hemolysis in vitro.\textsuperscript{56} Clinically, heparin has been alleged to inhibit PNH hemolysis dramatically,\textsuperscript{83} although others have found it of no basic therapeutic value,\textsuperscript{41} and still other workers have stated that heparin actually precipitates hemolytic crises.\textsuperscript{1,96} Further work on this question seems indicated, especially since heparin might be an excellent anticoagulant choice in PNH during times of increased susceptibility to thromboses.

\textbf{Surgery in PNH}

The problems of managing patients through major surgery make elective surgery inadvisable in most patients with PNH. The three major concerns in this regard are: (1) transfusions, (2) precipitation of hemolysis and (3) thromboses. Transfusion should ideally be with washed red cells. If plasma expansion is also needed, albumin or dextran may be given at the same time. If whole blood or packed cells must be given because of shock or lack of time to wash red cells, dextran given at the same time may protect from transfusion-induced PNH hemolysis. Although little work has been done on the effect of anesthesia on PNH hemolysis, special attention should be given to avoid acidosis and hypoxia. In view of the marked thrombotic tendency in PNH, prophylactic anticoagulation should be considered postoperatively once healing is sufficient to permit such therapy, particularly if prolonged immobilization is anticipated.

\textbf{REFERENCES}

5. Dacie, J. V.: Paroxysmal nocturnal


10. —: Personal communication.


60. Weisman, R., and Hinz, C. F., Jr.: Personal communication.


73. Epstein, E., and Quick, A. J.: Effect...
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