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Paroxysmal Nocturnal Hemoglobinuria—Present Status and Future Prospects

Tenth Annual Paul M. Aggeler Memorial Lecture

Given October 9, 1979
San Francisco General Hospital Medical Center

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These discussions are selected from the weekly staff conferences in the Department of Medicine, University of California, San Francisco. Taken from transcriptions, they are prepared by Drs. David W. Martin, Jr., Professor of Medicine, and James L. Naughton, Assistant Professor of Medicine, under the direction of Dr. Lloyd H. Smith, Jr., Professor of Medicine and Chairman of the Department of Medicine. Requests for reprints should be sent to the Department of Medicine, University of California, San Francisco, San Francisco, CA 94143.

DR. WALLERSTEIN:* *This is the tenth year of our lectures in honor of the late Paul M. Aggeler, a man best known in science for his discovery of factor IX and for his work on qualitative platelet defects. But far more important, he is remembered as a friend, counselor and conscience for many of us. We established this lectureship to honor him as a teacher whose life touched us all in his respect for science, patients, colleagues and students. We have with us Wendell Rosse whose own career so well epitomizes this kind of clinical investigator.*

Wendell graduated from the University of Chicago School of Medicine, pursued his residency training at Duke University, and developed his scientific research skills at the National Cancer Institute and, later, with Dr. J. V. Dacie in London. Dr. Rosse is now Professor of Medicine at Duke and Chief of the Hematology and Oncology Division there. He has held many other prestigious lectureships (perhaps the best known is the Stratton Lecture of the American Society of Hematology in 1976) and has received many honors in American medicine. His areas of interest have been related primarily to red blood cells and their disorders—erythropoietin, complement, cold agglutinins and immune hemoglobinemias. He will discuss paroxysmal nocturnal hemoglobinuria—its present status and future prospects.

DR. ROSSE:† Although I did not know Dr. Aggeler, I and many hematologists of my generation were influenced by him, and others like him who espoused the philosophy that hematology offers an ideal setting in which to apply the burgeoning

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knowledge of the basic sciences to clinical problems. His untimely death cut short his own efflorescence, but what he built and what he stood for remains clearly evident. That, as Horace said, is "A monument more lasting than one of brass."

I shall discuss a complex and fascinating disease, paroxysmal nocturnal hemoglobinuria (PNH). This is an uncommon but not rare disease, and much of what I will discuss has evolved from cases of patients which I have followed. I have studied the blood of some 80 patients with PNH, 40 of whom I have managed clinically. Of these, I am currently following 20 cases on a regular basis in the clinic. Although this obviously represents a nonrandom sampling, it indicates that although PNH is not a public health menace, it remains an important disease.

Much of its importance arises, however, not from its prevalence but, rather, from what it is able to teach us about the physiology of the bone marrow and its products. It was once said that he who understood syphilis understood clinical medicine. Although I make no such grandiose claims for PNH, I will say that when we come to fully understand PNH, we will be much closer to understanding the control of proliferation of marrow cells, the cause of leukemia, the interaction of serum proteins (especially complement) with the cell membrane, and the structure of abnormal cell membranes. This will cut a wide swath across the spectrum of hematologic processes.

Paroxysmal nocturnal hemoglobinuria is misnamed and is usually misclassified. It is misnamed because the occurrence of hemoglobinuria at night is only one of the symptoms associated with PNH, and it is misclassified among the hemolytic anemias because the implications of this disease are much wider than the hemolysis. However, it is not unnatural that this should have happened because hemoglobinuria, when it occurs, is clearly the most dramatic symptom exhibited in patients with PNH. The condition was first described in 1866 by William Gull,[1] a physician at Guy's Hospital, London. In the charming, somewhat chatty manner of clinical reports of that era, he reported the case of a tanner who, remarkably, had "hematinuria" in variable degrees, although usually worse in the morning. Gull recognized that the pigment in the urine was not due to the presence of red blood cells. In the Remarks section of the case report, he described on a day-to-day basis the color of the patient's urine, a luxury that few editors of journals would permit today.

He described the color as going from indigo to mahogany to amber. This classification system is, I think, slightly inferior to one which was developed by a patient of mine who is a wine connoisseur. He described the color of urine as ranging from port through burgundy to claret to rosé and on to chablis. Nevertheless, we can see from Dr. Gull's description that his patient had paroxysms of dark urine, and that one of these episodes followed an infection of the lymph nodes, otherwise undefined. This exacerbation of hemoglobinuria following infections is typical of patients with PNH.

The next description of which we have a clear record was that of Paul Strübing,[2] an exceedingly observant German clinician from a small clinic in Griefswald. In 1882 he reported in the *Deutsche Medizinische Wochenschrift* a patient with paroxysmal hemoglobinuria which, like that in Gull's patient, was worse at night. In addition to a precise description of the clinical setting, Strübing made several fine clinical observations. He noted an exacerbation in response to exercise, as well as increased hemoglobinuria upon drinking beer, a symptom that I have not seen noted since. Perhaps the quantity of beer ingested by subsequent patients has not been sufficient to match that of Strübing's patient. Strübing hypothesized that the abnormality resided in the red blood cells; however, he thought that hemolysis occurred as these abnormal red blood cells circulated through the kidney. He gave his patient iron, which had become a common remedy in those days for any form of anemia, and noticed an exacerbation of hemoglobinuria. He correctly interpreted this on the basis of his theory that the condition was due to the production of new cells that were then hemolyzed. It has only been in recent years that this perspicacious observation and interpretation have been confirmed fully.

Subsequent to Strübing's report, several other descriptions of PNH have appeared. The most famous were those of Marchiafava[3] and Micheli.[4] Their fame rests not so much on any additional information imparted by their observations (in fact, the major contribution appears to be the description of "perpetual hemosiderinuria" by Marchiafava) but, rather, in the fact that their names were seized upon as eponyms—much of the European literature continues to use the name Marchiafava-Micheli syndrome for PNH. Because of the difficulties with the name that was finally adopted, perhaps an eponymous designation is

better. However, in this case it should be called, more correctly, the Gull-Strübing disease rather than the Marchiafava-Micheli syndrome.

The next significant observation was made by the Dutch physician Hijmans-van den Bergh, who is better known for his observations on the detection of bilirubin. In the *Revue de Medecine* (1911), he described a patient with paroxysmal hemoglobinuria in whom he followed up Strübing's suggestion that the red blood cells were abnormal. Thus, he incubated the patient's cells in the patient's own serum, as well as in ABO-compatible serum with and without carbonic acid. He discovered, to his amazement, that the patient's cells were hemolyzed, both in the patient's own serum and in the normal serum, when carbonic acid was present. This was the first acidified-serum lysis test.

In each of these descriptions, a different name was given to the syndrome, which essentially left it without a name. A disease with no name has no standing whatsoever, and it was only after several more clinical descriptions that the name *paroxysmal nocturnal hemoglobinuria* was given by Enneking.[6] As I will argue later, this is an incomplete and somewhat erroneous name, and yet it is by this name that the syndrome is known.

Our understanding and ability to diagnose PNH took a quantum leap forward with the studies in the late 1930's by Thomas Hale Ham.[7,8] In an article that ranks with that of Strübing as a classic in the field, Ham described the acidified-serum lysis test, often referred to as the Ham test in the United States. The test is exceedingly simple. Normal serum that is type compatible is acidified to a pH of 6.4. Under these conditions, PNH cells are hemolyzed, particularly if the serum is supplemented with magnesium. If the serum is heated to destroy complement, the lysis is not seen. Few normal cells or the cells of any other patients, with one minor exception, are lysed in this test. This test has become and remains, in usual clinical laboratories, the test that defines PNH.

Ham made the critical observation that the defect of the red blood cells in PNH consists of an unusual susceptibility to the hemolytic action of complement. We are still trying to answer the questions raised by these observations.

With the use of the acidified-serum lysis test to define patients who have PNH, it became clear that the clinical presentation may be quite different from that described by Strübing. In particular, many patients had abnormal cells as detected by this test, but did not have hemoglobinuria. In fact, some patients had few signs of overt hemolysis; others simply had chronic hemolytic anemia without overt hemoglobinuria; some patients had typical hemoglobinuria that was paroxysmal and nocturnal, and still others had severe hemoglobinuria in which it was often difficult to detect an exacerbation during the night. We now understand more about why such a wide variation in the amount of hemolysis should occur.

Dacie[9] had observed that when the cells that survived acidified-serum lysis were again treated with acidified serum, little or no more hemolysis occurred, and, yet, a proportion of the cells remained unlysed. This suggested that two populations of cells existed, one of which was normal. Red blood cell survival curves that were biphasic, showing a rapid diminution in survival followed by a more normal survival, also suggested the presence of two populations. Dacie and I[10] showed the existence of the two populations more directly in vitro in a series of experiments in which red blood cells from normal persons and PNH patients were hemolyzed by increasing amounts of complement in the presence of excess antibody. The tests indicated that normal cells were extremely resistant to the lytic action of complement in vitro by the fact that large quantities of complement were required for their lysis. In addition, they showed that normal cells consist of a single population by the fact that when the concentration of complement is plotted on a double logarithmic scale against a function of lysis (that is, the fraction lysed divided by the fraction unlysed), a straight line results. The lysis of PNH cells in a similar system disclosed two populations: one of which was virtually normal in its requirements of complement for lysis and the other of which required much less complement to bring about lysis. It is the presence of such a population of cells, which are more sensitive to lysis by complement, that characterizes PNH. A further advantage of using this technique to detect PNH cells is that the proportion of cells in the population may also be calculated.

Further studies disclosed that there were two kinds of complement-sensitive cells, one of which was intermediate in sensitivity between the originally described abnormal population and the normal cells.[11] These populations have been relabeled PNH I, PNH II and PNH III. PNH I designates the normal-appearing cells, PNH II the moderately abnormal cells, and PNH III the particularly abnormal cells (Figure 1). The most common com-

bination is PNH I and PNH III cells, occurring in approximately 80 percent of all patients. PNH II cells are irregularly present and are much less common. Some patients have only PNH I and PNH II cells and some have all three varieties of cells. A few patients have no detectable normal cells and, rarely, a patient has only PNH II cells (Table 1).

The proportion of abnormal cells varies greatly from patient to patient (Figure 2). Most patients with PNH III cells have them in relatively small proportions; however, the proportion of PNH II cells tends to be greater. The degree of hemolysis observed clinically is dependent on two factors: the proportion of abnormal cells and the degree of their abnormality. If few PNH III cells are present, little evidence of hemolysis will be seen. When the amount is between 20 percent and 50 percent, infrequent bouts of hemoglobinuria will usually occur. In patients with more than 50 per-

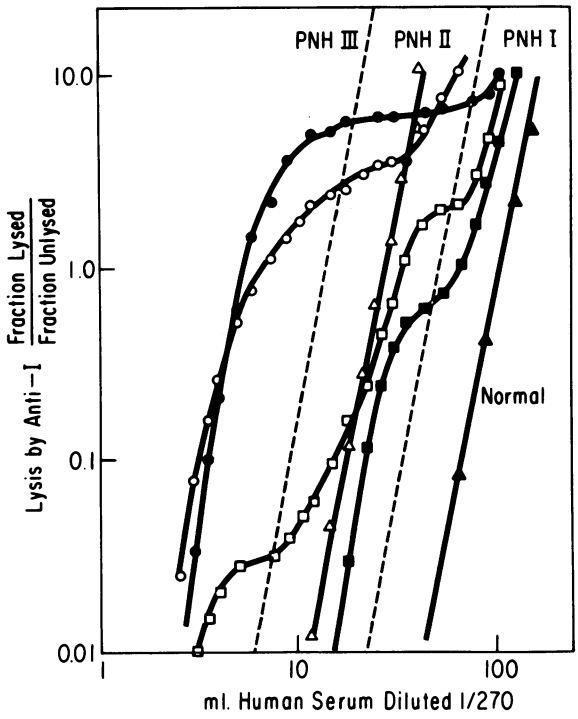

Figure 1.—Complement sensitivity curves of red blood cells of five patients with PNH and a normal control (solid triangles). Cells are sensitized with excess antibody (anti-I) and lysed with limiting amounts of complement as shown on the abscissa. The quotient of the fraction lysed divided by the fraction which is not lysed is shown on the ordinate. Three types of PNH cells are distinguished: PNH I cells which require about the same amount of complement for lysis as normal cells; PNH II cells, requiring somewhat less complement for lysis than normal cells, and PNH III cells which require very much less complement than normal cells for lysis. The presence of two populations in four of the five patients is shown by inflections in the curve; in one patient (shown in open triangles) and in the normal control, the presence of only one population of cells is indicated by the ortholinearity of the curve.

TABLE 1.—*Patients Grouped According to the Types of PNH Red Blood Cells in the Peripheral Blood**

Group	Type of PNH Cells Present I	II	III	Percent of Patients in Group
1	+	..	+	78
2	..	+	+	3
3	+	+	+	9
4	+	+	..	9
5	..	+	..	1

*Blood of 75 patients was examined.

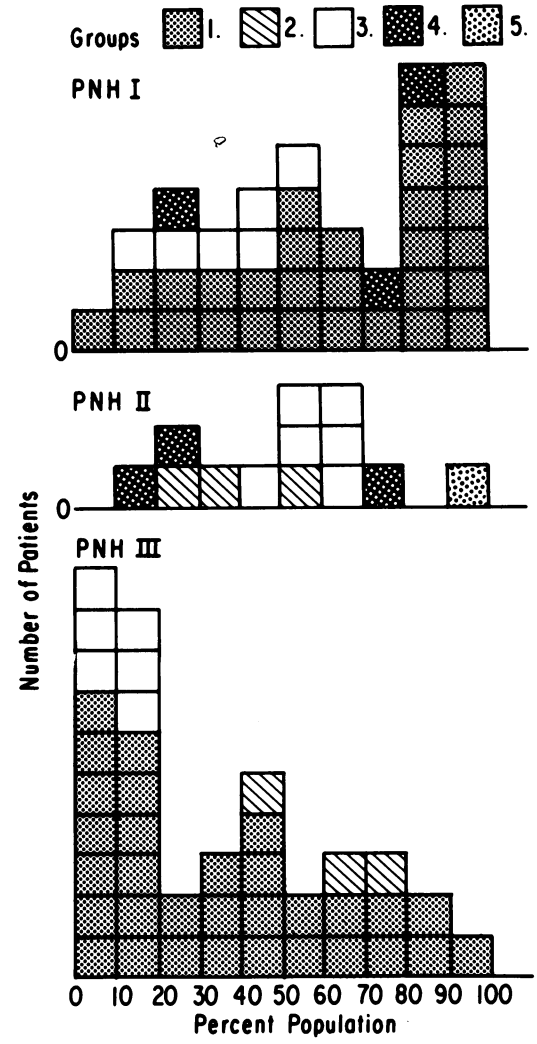

Figure 2.—The distribution of the size of the populations of red blood cells in 44 patients with PNH. The percent of the population in deciles is shown on the abscissa. Each square represents the population of a single patient. (Patient groups are given in Table 1.)

cent PNH III cells, hemoglobinuria will be fairly constant. However, patients with PNH II cells, even in large proportions, often have only intermittent hemoglobinuria. Hence, the variability of presentation can be explained by more detailed knowledge of the illness.

What causes this unusual sensitivity to activation by complement? We have spent considerable time trying to elucidate this question, which has required detailed study of the reactions of complement. Complement is a highly complex group of proteins that interact in a defined sequence to bring about the lysis of cells. It may be activated either by antibody in the classic pathway or by a number of reactions that activate the alternative pathway. Regardless of the pathway activated, PNH cells are more readily lysed. This suggests that the differences between PNH cells and normal cells should be found in the latter steps. We have found this to be the case. When the classic pathway is activated, PNH cells and normal cells fix the same amount of antibody, the same amount of C1, C2 and C4.[12] On the other hand, both PNH III and PNH II cells fix much more C3 than normal cells.[11,12] This is also strikingly true when the alternative pathway is activated: vastly more C3 is fixed to PNH cells than to normal cells. However, this cannot be the entire difference because the severely abnormal PNH III cells are more sensitive than the moderately abnormal PNH II cells.

The lysis by complement is brought about by the intercalation of a protein complex (C5-C9) into the lipid bilayer. This may be in the form of a doughnut, thus resulting in a water-soluble pore, or these components may act as detergent. Either way, free flow of ions occurs and the cell is no longer able to maintain the osmotic relationship between the inside and outside. As a result, a net influx of water occurs and the cell swells and lyses. This complex of protein is visible under an electron microscope as small hydrophilic areas by negative staining. Although many of these complexes are formed on the membrane, few of them are capable of penetrating through the membrane to effect lysis. By assessing carefully the number of such lesions and relating it to the degree of lysis, we have concluded that the number of such detectable lesions on the membrane needed to obtain lysis of PNH cells is about a tenth of that required for normal or PNH II cells.[13] Hence, there appear to be two defects in PNH cells: increase of fixation of C3 (and, perhaps, C5), which is present on both PNH I and PNH III cells, and increased penetrability of the membrane by the complement complex, which is true only for the severely abnormal PNH III cells (Table 2).

TABLE 2.—*Abnormal Reactions of Complement with the Three Kinds of PNH Red Blood Cells*

	PNH I	*PNH II*	*PNH III*
Increased uptake of C3 when complement is activated by the classic or alternative pathway ...	No	Yes	Yes
Increased efficiency of the terminal complex (C5-C9) in penetrating the membrane	No	No	Yes

By my description so far, PNH is not too badly misnamed, although it occurs as a presenting symptom in less than half of the patients. However, there are other clinical features that do not appear to be related to hemolysis at all. One of the most dreaded complications in PNH is the formation of clots in several unusual venous sites. Most commonly, this occurs insidiously in the hepatic veins resulting in a variant of the Budd-Chiari syndrome.[14] Clots in the cerebral veins have been noted. The splenic vein and, in two cases, the veins of the dermis have been involved, the latter resulting in unusual necrotic skin lesions.[15] These clotting events sometimes occur simultaneously with the hemolytic episodes, and it has been suggested that something is liberated by hemolysis that results in intravascular clotting.

It has been shown that the platelets in patients with PNH are abnormally sensitive to lysis by complement.[16] We undertook to determine whether the platelets in PNH have the same membrane abnormality as the red blood cells: for a given amount of the activation of complement, whether by the classic or by the alternative pathway, a greater amount of C3 was fixed to PNH platelets.[17] It has been shown that the fixation of C3 to rabbit platelets causes a release reaction as manifested by the release of serotonin. This is the first step to activation that results in a platelet clot. Normal human platelets did not undergo such a reaction. When we investigated the platelets in PNH, however, they appeared to behave like the rabbit platelets, releasing serotonin upon the fixation of C3. This suggests that the clotting abnormality in PNH may be due to an abnormality of platelets that results in serotonin release and clotting.

It is not clear whether the platelet life span in PNH is diminished; chromium 51 studies have not shown this.[18] However, having worked with plate-

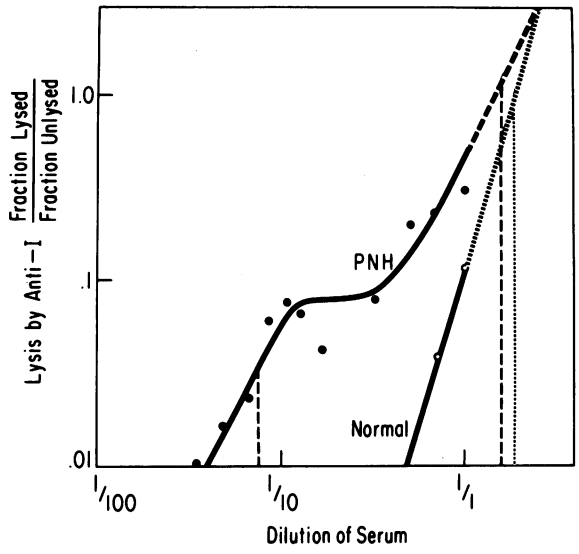

Figure 3.—Demonstration of two cell populations in the granulocytes of a patient with PNH. The test is essentially the same as for red blood cells (see Figure 1). Normal cells exhibit only one population whereas PNH granulocytes appear to be composed of two populations.

lets in vitro and having found them exceedingly difficult to handle, I am willing to consider that the abnormal population of platelets may have been altered during the radioisotope labeling such that the survival time of only the normal population was measured. Clearly, these studies need to be done more carefully. Many patients with PNH have thrombocytopenia, but it is not clear whether this is due to diminished survival, diminished production (see below), or both.

The granulocytes in patients with PNH are also abnormally sensitive to the lytic action of complement (Figure 3).[16] Again, there appear to be populations of cells that differ in their sensitivity.[19] As with the platelets and the red blood cells, the defect appears, at least, to consist of an excessive fixation of the third component of complement. However, the clinical manifestations of this abnormality in the granulocytes are not so apparent as for the other cells. It has been proposed that the cells in patients with PNH have a diminished response to chemotactic activities after exposure to activated complement.[20] These studies also need to be repeated. Granulocytopenia is not uncommon in patients with PNH,[21] but survival studies have given normal results.[22] Again, the possibility that only the normal cells survive the preparation and labeling procedures needs to be considered.

There are still some clinical features that are unexplained but very interesting. Most patients with PNH complain, on questioning, of esophageal tightness. It is particularly prevalent in the morning and during hemolytic episodes. We investigated this complaint in several patients and found it to be due to excessive strength of the muscular contraction. The esophageal peristaltic waves are generated normally, but have seven to ten times the force of normal esophageal waves when this symptom occurs. Thus, swallowing is painful and, on occasion, dangerous; one of our patients swallowed a potato chip without chewing it properly and a large esophageal ulcer developed.

Patients with PNH may also have severe abdominal pain; in two patients in my series it is the main clinical manifestation. This symptom sometimes is confused with an *acute abdomen,* which may result in an abdominal operation—a surgical procedure that is not without complications in patients with PNH. In one such patient, Blum and Gardner found an area of infarcted bowel,[23] and the infarction was thought to be due to venous thrombosis. Usually, however, the cause of the abdominal pain remains mysterious.

Patients with PNH may also have skeletal muscular pain, which may be acute, particularly when it occurs in the lower back. In such a case, it may require narcotics for relief. Recently, however, I have observed two patients who have had a syndrome of chronic muscular pain that occurred only after the diagnosis of PNH was made; a direct relationship was difficult to establish, and yet given the mysterious events that happen in PNH, it is entirely possible that the two syndromes are related.

It should be apparent by now why I believe that PNH is a misnomer. I think that it is misclassified because in almost all textbooks it is included among the hemolytic anemias. I grant that hemolytic anemia is its most obvious symptom; however, it is clear that PNH is much more than a hemolytic anemia, and that the defects are much more wide ranging than in the red blood cells alone.

It can be argued reasonably that PNH is the result of a disorder of the marrow stem cells. A stem cell may be totipotent (capable of producing B lymphocytes as well as the precursors of blood elements), pluripotent (capable of differentiating into any of the blood elements), or committed (sufficiently differentiated so that a single type of cell line can result). Recent studies have applied

the concept that the presence of a given abnormality in all three types of differentiated blood cells indicates that the abnormality exists in at least the pluripotent stem cell. Otherwise, a similar abnormality would have to be postulated as occurring somewhat independently in each of the differentiated cell lines. Similar membrane abnormalities resulting in irregular interactions with complement occur in all three types of differentiated blood cells. It is logical to conclude that the PNH lesion arises in at least a pluripotent stem cell. Both normal and abnormal cells occur simultaneously in most patients, suggesting that a clone of such abnormal stem cells originates from a single event because of some proliferative advantage. Recently, we confirmed the observation of others[24] concerning the clonal nature of abnormal cells in PNH. In a patient heterozygous for glucose-6-phosphate dehydrogenase (G6PD) isoenzymes, we found that the greatly abnormal PNH III cells were all of a single isoenzyme, whereas the PNH I cells contained both isoenzymes. This clone of abnormal cells may arise in an injured marrow of patients with aplastic anemia.[25,26] Its growth may be rapid or may occur over several months. Sometimes the number of abnormal PNH cells remains small and the clinical manifestations are largely those of the aplasia, whereas at other times in other patients the population of abnormal cells predominates with resultant hemolysis and more classic manifestations of PNH. Sometimes the preceding injury is recognized, but more often it is not. As just noted, sometimes only one or another of the marrow-derived blood elements is diminished; however, most patients with PNH have an element of hypoplasia at some point in the course of their disease.

A further clue to the classification of the syndrome is the finding that in a small proportion of patients (five percent to ten percent) acute leukemia eventually develops.[27-29] When this occurs, the abnormal PNH clone disappears. Usually, the condition is acute myeloblastic leukemia, although recently, a patient with PNH was found to have erythroleukemia.

The fact that all three cell lines are affected by the disorder and that the disease might result in leukemia caused Dameshek,[30] ten years ago, to classify PNH among the myeloproliferative disorders. However, there are several other facts that do not fit this classification. All the other diseases of the myeloproliferative syndrome manifest an uncontrolled overproduction of one or another of the cell lines. Although patients with PNH may show a reactive erythroid hyperplasia, this is under physiologic control and, in addition, is frequently less than one would expect for the degree of anemia. Furthermore, as noted previously, PNH frequently arises in patients with aplastic anemia, and elements of aplasia persist.

More recently, the myelodysplastic syndromes, another group of disorders of the bone marrow, have been proposed. Because some investigators believe that the term *myelodysplastic* has been presumed by the neurologists, the term *hematopoietic dysplasia* has been suggested instead. With the understanding that I am not discussing spina bifida, I prefer the term myelodysplastic syndromes.

These syndromes are, like the myeloproliferative syndromes, stem cell disorders. However, they are characterized by hypoproliferation, relative or absolute, of all three cell lines. They consist of abnormal cell products in all three cell lines as well, as one would expect from this kind of disorder. A further difference from the myeloproliferative syndromes has been elucidated recently using cell culture techniques. When bone marrow from patients with the recognized myeloproliferative syndromes are cultured in vitro, they often result in a larger number of colonies than normal.[31,32] In the case of polycythemia vera, the colonies may not require the large doses of erythropoietin that are usually necessary for differentiation of erythroid colonies in vitro. In patients with chronic myelogenous leukemia, large numbers of granulocytic colonies are seen in response to a colony-stimulating factor specific for this cell line. Technology for growing megakaryocytic cells in vitro is still too new to have been tested in patients with essential thrombocythemia. In contrast, the cells from the bone marrow of patients with myelodysplastic syndromes do not proliferate in vitro.[33] In this regard they resemble the cells in the bone marrow of patients with acute leukemia.[34] Finally, like the myeloproliferative syndromes, the myelodysplastic syndromes ultimately result in acute myelogenous leukemia.

Several syndromes have been placed in the category of myelodysplastic syndromes. I will not describe them here, but only mention them for discussion. One of the more common ones is the ill-defined and poorly named syndrome characterized by hypoproliferative bone marrow and abnormal cells that often results in acute leukemia. The French call it "refractory anemia with

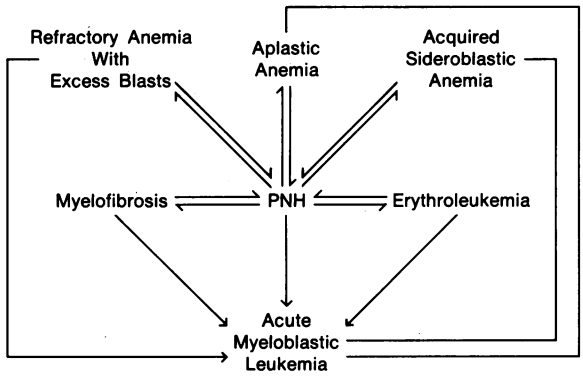

Figure 4.—Relationship of PNH to the other myelodysplastic syndromes. Clinical progression from one syndrome to another is indicated by the direction of the arrows.

excess blasts," but it is also called smouldering leukemia or preleukemia. Di Guglielmo syndrome, often called erythroleukemia, is also a myelodysplastic syndrome. In this disorder there is such dysplastic production of red blood cells that ineffective erythropoiesis is the major finding. Although in many of these patients acute leukemia develops promptly after the discovery of the di Guglielmo syndrome, in others it does not. Patients with acquired sideroblastic anemia may show the features of hematopoietic dysplasia. Although this syndrome is undoubtedly heterogeneous, at least a third of all patients with this syndrome, particularly those that show elements of hypoproliferation in all three cell lines, will eventually have acute leukemia.

Aplastic anemia is listed among the myelodysplastic syndromes. Again, this syndrome is undoubtedly due to heterogeneous causes, some of them thought to be immunologic. Nevertheless, there is also clear evidence that in some instances it is due to a disorder of the stem cell. Although the frequency of conversion to acute leukemia is low, it is well recognized. Finally, myelofibrosis has many of the elements of other myelodysplastic syndromes. In this case, however, some overlap with myeloproliferation is probable. The syndrome has been insufficiently studied to resolve the question.

I should like to concur with Sultan and coworkers[33] that PNH belongs among the myelodysplastic syndromes. It is clearly a stem cell disorder with abnormal products in all three cell lines, and is often characterized by hypoproliferation. We have recently confirmed that the bone marrow in patients with PNH does not proliferate in marrow culture despite the fact that the counts may be relatively normal and the bone marrow may have a normal appearance. Finally, as noted above, PNH results in acute leukemia.

The relationship of PNH to the dysplastic syndromes is further noted by the observed transitions from one to another (Figure 4). Most frequently, PNH emerges from aplastic anemia. On the other hand, patients with myelofibrosis, erythroleukemia, acquired sideroblastic anemia, and refractory anemia with excess blasts have all been shown to have PNH cells. The change is not always unidirectional. On rare occasions, patients with PNH may have the clinical syndrome of aplastic anemia, during which time the evidences of the abnormal population in the peripheral blood disappear. I have observed patients with PNH in whom acquired sideroblastic anemia, myelofibrosis and erythroleukemia develop. When this occurred, the PNH clone also disappeared. As pointed out earlier, all of these syndromes may result in acute leukemia.

Having described PNH in such careful detail, we ought to say something about its treatment. Obviously, the optimal treatment of the stem cell disorder is the replacement of the abnormal stem cell with a normal stem cell. To date, this is only possible with bone marrow transplantation. This has been tried in several patients with PNH, usually in those in whom primarily aplastic anemia is manifested.[35,36] In one interesting case, Thomas and associates[36] transplanted the bone marrow of a healthy identical twin to the other twin with PNH, using the syngenic marrow without previous preparation by radiation or chemotherapy. The PNH disappeared and the patient was cured. In other instances, the PNH cell population was obliterated by treatment before transplantation, and then after engraftment, the PNH was not seen. However, in one startling case, a patient with aplastic anemia who did not have PNH before transplantation was transplanted with presumably normal marrow and acquired PNH as soon as engraftment had occurred. Much remains to be learned about the transplantation of bone marrow in patients with PNH. Obviously, transplantation is not often possible, or even necessary, and patients need to be treated by other means.

Most patients with PNH become iron depleted because of the loss of iron in the urine. Therefore, some form of replacement therapy must be considered. Often, if iron is given at a time when the patient has a low hematocrit, a sudden burst

of hemoglobinuria may result. This was correctly attributed by Strübing to the advent of new cells; such a hemolytic episode can be prevented by either previous transfusion to suppress the wave of erythropoiesis that follows administration of iron to the iron-deficient patient or by the use of prednisone (see below), which suppresses hemolysis.[37]

In the mid 1960's Hartman and associates[38] found that in patients with PNH improvement often is seen after androgenic hormone therapy. The exact manner in which this is brought about is not clear—is it a result of additional stimulus to the dysplastic marrow to produce red blood cells or, as some suppose, is it a result of some effect on serum complement? In any event, at least 50 percent of patients have some improvement with androgenic hormones. At present, we are studying the use of some less androgenizing hormones to determine if certain unpleasant side effects may be avoided, particularly in women.

Prednisone can be effective in the treatment of PNH, but the doses required are often high.[39] I have employed a compromise in which the doses of prednisone are administered on alternate days. Of 16 patients treated, 12 have shown improvement on this regimen. No patient on this schedule has had serious clinical infections, whereas two patients who insisted on taking prednisone every day died of serious intercurrent infections.

With the use of these regimens it is usually possible to obtain at least a reasonable modus vivendi for PNH patients. However, if they fail, transfusion may be required. Although many patients can receive whole blood without incident, it is usually safer to transfuse washed or deglycerolized blood because of the occurrence of well-documented hemolytic episodes in which a patient's cells are hemolyzed after transfusion. This may result from the transfusion of small amounts of activated complement components in the plasma of unwashed blood.

Using these therapeutic regimens, it is often possible for patients with PNH to live a long time during which the PNH cell population can diminish substantially or disappear. While this process is usually very slow, it does offer the hope to PNH patients that they may be able to outlive the disease.[40] It would be a great step forward if other myelodysplastic diseases had a similar prognosis.

By exploring many of the subtle nuances of PNH, I hope that I have conveyed why I believe that this disease is misnamed and misclassified. However, I hope that you can also see how wondrous a disorder it is and how increased knowledge of the disorder may, in turn, help us immeasurably in better understanding the physiology of the bone marrow, the structure of the membrane, and the interaction of that membrane with complement. Clearly, it is the sort of challenge Paul Aggeler would have enjoyed.

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Street Drug Toxicology Laboratories

ABOUT KITS TO RECOGNIZE street drugs: I do not recommend them at all, because when anyone takes the time to put together a kit, by the time they have completed it, the street drugs available in the area have changed significantly. So it would be meaningless. If you really want to do anything about street drugs, I would recommend that you go to the local hospital and convince the head of the pathology department to set up a street drug toxicology laboratory. You can have people anonymously send in samples and you can analyze them and find out what is actually present. You see what they look like and you get some idea of what's going on in your area. . . . By the way, if the people in your area tell you it is illegal: it is not. The Drug Enforcement Administration will give you a license to do it. If you are in a regular hospital, it is no problem at all. . . . I do not recommend you publicize in the newspaper what you find, . . . but you can disseminate the information to the medical community in your area—and that is more important than kits.

—SIDNEY H. SCHNOLL, MD, *Philadelphia*

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