PNH
Basic Explanations

This publication provides general information for patients and their families. Although the AA&MDSIF tries to provide the most accurate and updated information it does not warrant or guarantee information contained herein. Patients should always seek medical advice from a qualified hematologist and discuss these materials, individual questions and concerns with their physician.

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Dear Friend,

Like most people you probably had never heard of PNH, aplastic anemia or myelodysplastic syndromes until you or a loved one was diagnosed with this condition. Now you face the challenge of understanding and coping with this very complex illness as well as the many emotions that go with it. However, you don't have to face this alone.

The Aplastic Anemia & MDS International Foundation is here to help you. We will answer your questions, give you the latest in medical research information, and put you in touch with other patients who will share their treatment experiences. All of our services are free of charge because we are a nonprofit 501(c)(3) organization as recognized by the Internal Revenue Service.

We hope this brochure will help you to better understand myelodysplastic syndromes by explaining basic information about this bone marrow failure disorder. While this information is not intended as a substitute for the advice of a physician, it is vitally important that you learn as much as you can about the disease, medical research findings, and all treatment options available to you. We also offer many other free publications and newsletters that provide information on managing the disease, medical updates, and foundation events.

Since 1983, AA&MDSIF has been leading the fight against bone marrow failure disease with the help of a distinguished medical board, a dedicated board of directors, and hundreds of devoted volunteers around the world. Please help us assist others in their struggle—we dearly need your support.

Contact us today for someone to talk to, discuss our free services, or to help us to help others. We look forward to hearing from you.

Good luck and best wishes,

Marilyn Baker
Executive Director

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Preface

Chapter One of this brochure explains how paroxysmal nocturnal hemoglobinuria, (PNH) develops, how it is treated, and what to expect if you or your loved one is affected by it. In Chapter Two you will find a detailed explanation on how the body's blood system works, both under normal circumstances and in cases of PNH or other bone marrow failure disorders. Chapter Two will also provide an expanded look at the physical processes discussed in the first chapter, and will give you a fuller understanding of how the body produces blood and fights infection. At the end of the brochures is a glossary giving brief definitions of terms related to PNH and the blood system.

As you read the chapters, you will find most terms explained, but you may wish to consult the glossary to clarify some of the medical terms. You will notice in Chapter Two that key terms are underlined which makes them easier to find in the glossary. Two closely related diseases, aplastic anemia and myelodysplastic syndromes are described in other brochures from the AA & MDS International Foundation.

Chapter 1

INTRODUCTION

PNH is a rare but potentially serious blood disease affecting people of all ages. Although some of the features of this disease, such as hemolysis inside of the blood vessels or appearance of red urine, have been known for over 100 years, many aspects of PNH remain a mystery. As with other "orphan" diseases, the progress in their understanding is slow. For physicians and scientists who study this disease, it is often frustrating that they are only able to give limited answers and explanations to many of the questions that PNH patients have.

Only recently have we learned the complicated mechanisms and pathologic relationships leading to the development of this disease. Despite recent advances, much more research is needed to fully clarify all the aspects of this disease. Many specialists believe that research on the development of PNH in the bone marrow will also be helpful in understanding other diseases of the blood system such as aplastic anemia and leukemias. Because PNH is such a rare disease, rigorous clinical trials at institutions seeing numerous PNH patients produce the best chance of developing effective treatments and cure. This is why it is important that patients participate in the clinical trials whenever possible.

PNH EXPLAINED

First one must understand the mechanisms of PNH in order to understand the symptoms. PNH is not inheritable. It develops from an acquired mutation in the genetic material of the most immature bone marrow cells called stem cells. These bone marrow stem cells are responsible for the steady supply of blood cells because they produce three types of blood cells: RED CELLS which deliver oxygen to the tissues; WHITE CELLS which fight infections, and PLATELETS which clot the blood.

In PNH, the mutation in the genetic material of a stem cell affects a specific gene called PIG-A. Due to this mutation, the enzyme required for attaching many important proteins on the surface of the blood cells is missing, and the affected stem cell is producing defective mature blood cells that "spread" the disease. Red cells, white cells, and platelets produced by the diseased stem cell all carry the defect that causes symptoms associated with this disease. We do not know what causes the mutation of the stem cell in PNH. We also do not know why the defective PNH stem cell outgrows "normal stem cells that allow the diseased blood cells to progressively replace normal cells."

SYMPTOMS EXPLAINED

General. The presence of defective marrow and blood cells are responsible for the symptoms in PNH. PNH produces a variety of clinical symptoms but not all patients will experience every possible complication and the disease may show different degrees of severity in each patient. It is very important that patients understand the course of their disease and individual prognosis can be difficult to predict. Generally, low red cell count with low hemoglobin levels (in conjunction with low platelet and white cell count) can either be a result of increased destruction of blood cells, or a decreased production in the marrow (a hallmark of marrow failure states). While in PNH, the destruction of red blood cells is the most important factor leading to anemia; in some patients, production of red cells in the marrow is impaired and destroyed red cells are not sufficiently replaced.

Hemolysis. Lack of certain proteins on the surface of red cells (produced by the mutated bone marrow stem cell) makes the cells susceptible to being more easily destroyed (hemolysis). This process is mediated by a complicated system of serum proteins called "complement." Under normal circumstances, complement serves as an antimicrobial defense factor and kills microorganisms. Healthy red cells are equipped with surface proteins that make them resistant to the action of complement. However, in

PNH, red cells lack these proteins and are susceptible to the destruction by complement. When PNH red cells are destroyed, they release hemoglobin, which is the red pigment of blood. Hemoglobin is excreted in the urine causing its red or coca-like discoloration, which is a characteristic sign of PNH. More importantly, this destruction of red cells can result in anemia. Depending on the severity of hemolysis, patients may experience headaches, ear ringing, palpitations, heart racing, fatigue and sleepiness. Severe anemia may result in fainting spells and could possibly lead to a heart attack. Usually, destruction of PNH red cells continues at a certain individual rate and the bone marrow can compensate for it with an increased production. Unfortunately, the bone marrow of some PNH patients may not be able to produce enough red cells so patients experience more severe anemia and may even require transfusions. In addition to ongoing hemolysis, several unknown factors may cause a dramatic increase in destruction of PNH cells, often referred as to a hemolytic crisis. Some known factors to cause hemolytic crisis are other diseases and stress.

Blood clots. Because PNH stem cells can also produce defective platelets, PNH platelets can be a source of serious and often fatal complications. It is believed that in PNH, the lack of certain (currently still unknown) proteins from PNH platelets increases their propensity to form undesired blood clots— a condition termed thrombosis. Clots can be carried by the blood flow to the lungs resulting in a very serious condition called lung embolism. Blood clots may also lead to serious complications and possible death when they block the blood flow in vital organs such as liver, spleen, intestine or brain. The symptoms of blood clots in legs or arms include pain, swelling and redness or bluish discoloration. Symptoms of clots in internal organs depend upon the organ affected. Clots in the liver may cause abdominal pain, feeling of fullness, chest pain and yellow discoloration of skin and eyes. A blood clot that has traveled to the lungs can cause shortness of breath, cough with bloody sputum chest pain, palpitations, and pain when a patient takes deep breaths.

Formation of blood clots in PNH is very unpredictable; some patients may experience these clots quite frequently while other patients never have any. As the exact mechanism leading to thrombosis is not known, there are no ways to predict who is at greatest risk. Clearly, patients who had an episode of thrombosis in the past have a greater risk to experience repeated episodes.

Marrow failure/defective blood production. In many PNH patients, the marrow will sufficiently compensate for the destruction of red cells in the blood stream. These patients will also show an adequate production of platelets or white cells. However, many studies have demonstrated that PNH marrow is not working properly even if the decrease in blood counts is not evident. PNH patients may develop more or less severe marrow failure similar to those of aplastic anemia. The reasons for the marrow failure in PNH are not clear. However, we know that PNH occurs frequently as a complication of aplastic anemia (in earlier estimates up 10% of AA patients) and many patients (30-40%) with aplastic anemia may harbor PNH stem cells and produce PNH blood cells. Evidence for PNH cells can be also detected in some patients with MDS.

Impaired production of platelets will result in a decreased platelet count, also referred to as thrombocytopenia, which depending on its severity, may lead to bleeding and bruising. External bleeding may cause blood loss and anemia while internal bleeding may result in serious complications such as a stroke.

Decreased white cell production impairs the body's ability to fight infections. The risk for serious bacterial and fungal infections dramatically increases when the number of granulocytes in blood decreased to below 500 per per uL. Patients with low numbers of white cells have to be aware that they need to seek medical attention when they experience fever or other symptoms of infection. For a PNH patient, a quick administration of antibiotics during an infection may be life saving.

PNH AND APLASTIC ANEMIA

As mentioned above, PNH is closely related to aplastic anemia. Many aplastic patients have different degrees of PNH involvement. PNH may develop from aplastic anemia, or aplastic anemia and low counts might be a complication of PNH. Specialists believe that aplastic anemia sets the conditions which are advantageous for the growth of PNH stem cells and allows for the development of PNH. It is possible that the clarification as to why PNH and aplastic anemia so frequently occur together might help us to understand the causes for these diseases, and hopefully, develop new specific treatments.

DIAGNOSIS

Symptoms of hemolysis and anemia, together with the discoloration of urine especially evident in the morning, are characteristic signs of PNH. However, in the setting of low blood counts, the diagnosis may be more difficult. Historically, diagnosis of PNH was established by using the Ham test. In this test, destruction of patient's red cells by complement in a test tube is measured. Because in patients with ongoing hemolysis most of the PNH red cells are destroyed in the blood stream, Ham test is very insensitive. Currently, new more sensitive tests are being used which rely on the measurement of missing proteins on patient's white cells using an instrument called flow cytometer (PNH flow cytometry). These advanced testing techniques can identify even a tiny number of PNH cells. In addition to helping with diagnosis, these tests have helped doctors recognize that PNH cells may be found much more frequently than previously thought, and that many patients with aplastic anemia show evidence of asymptomatic PNH.

In addition to the specific diagnostic tests for PNH, measurements of numbers of red blood cells and hemoglobin levels are important for the determination of the severity of hemolysis, blood loss or bone marrow dysfunction. All these factors may affect the hemoglobin levels and the severity of anemia. However, in order to know whether the anemia is due to hemolysis or impaired red cell production, reticulocyte count should be measured. Reticulocytes are young red cells and their numbers, when high, will tell you and your doctor that your marrow is working properly and anemia is this setting is most likely due to the red cell destruction. While the number of platelets will be helpful to see whether a patient is at risk for bleeding, decreased platelet production in PNH also is a sign for the defective function of bone marrow. Similarly, if marrow is not working properly, the number of white cells will be decreased. Severe depression in white blood cell count may predispose to life-threatening infections (the detailed description of thrombocytopenia and low white cell counts can be found in the specific brochure devoted to aplastic anemia).

Other blood tests may also be useful. The severity of ongoing hemolysis may be measured using LDH — a protein that is set free when red cells are destroyed. High LDH values are consistent with hemolysis. Similarly, low levels of a protein, called haptoglobin, are also indicative of hemolysis. In addition, it is also important to determine iron levels to establish whether a patient is iron deficient or in an iron overload state.

TREATMENTS

Because PNH is rare, there are only very few scientifically established facts about the best way of treating this disease. Generally, there are 2 ways of treatment — bone marrow transplantation and of conservative treatments. The decision of which treatment option to use should be discussed in great detail between the doctor and patient. The AA&MDSIF brochure, "Managing Treatment Decisions" will be of value in asking questions about treatments.

Conservative treatment. Principally, there are no specific agents to treat PNH. Care management of patients with hemolysis, with and without signs of bone marrow failure, may differ. In patients with typical hemolytic form, many doctors advocate that flare up of hemolysis should be treated with courses of steroid hormones, such as prednisone. There are no scientific proofs that this strategy is really effective, but it is believed that steroids may decrease the destruction rate of red cells. Chronic usage of steroids is even more controversial as such therapy has many toxic side effects. In any case, if administered on chronic basis, all attempts should be made to use the lowest possible dose and to limit the duration of treatment. Transfusions may be needed for acute decreases in hemoglobin or on a periodic basis when the patient's decrease in hemoglobin level is steady. Transfusion is a routine procedure and its toxicity may be less than that of a chronic steroid administration. However, many patients feel emotional resistance towards transfusions. The risks involved in a single transfusion are very low and administration of blood is not a "magic mark" that indicates progression to a more advanced and severe stage of the disease."

As explained above, PNH may increase the propensity for blood clots. Generally, routine blood thinners are not uniformly recommended unless patients have experienced an episode of thrombosis because many patients may never have this complication. Generally, thromboses are treated with infusion of the blood thinners (such as heparin) into the vein and, after acute symptoms have resolved, with chronic administration of oral blood thinners such as coumadin. Most doctors will recommend long-term blood thinner therapy with coumadin but it is not entirely clear whether such therapy is really effective in preventing further blood clots. In addition, blood thinners may be complicated in patients whose platelet count is low as in such situation; the risk of bleeding may be higher than that of thrombosis.

Immunosuppressive therapy may be of benefit to patients whose blood counts are low due to the decreased blood cell production (and / or whose marrow

is empty). As explained in the previous paragraphs, low reticulocyte count (reticulocytes are immature red cells which indicate that marrow is working) can show that marrow is not working properly; hemolysis with normal compensatory red cell production would be otherwise accompanied by a high reticulocyte count. Other signs of defective marrow function include low platelet and white cell count. Under such circumstances, similar as in the typical aplastic anemia, immunosuppressive treatments may be beneficial. These treatments include anti-thymocyte globulin (ATG) and cyclosporine. Cyclosporine given alone has not been very effective. Immunosuppressive treatments do not eliminate the PNH cells, but may improve the function of the bone marrow and help to compensate for the destruction of the blood cells. More information on this therapy can be found in the AA&MDSIF brochure "AA Basic Explanations" or from the AA&MDSIF website. Good supportive care is very important and may affect the comfort of living and survival. In addition to the direct treatment of hemolysis, folic acid and iron may help bone marrow to replace destroyed red cells. Many PNH patients loose large amounts of iron in urine, which can result in iron-deficiency. On the other extreme, if they receive many transfusions, they can develop iron overload. This is why it is important that the iron status be continually monitored and appropriate therapy instituted when needed.

Bone marrow transplantation. Bone marrow transplantation offers the only known curative therapy for PNH. However, the decision to undergo this complicated procedure must be thoroughly researched and all potential risks discussed between the doctor and patient. Many aspects influence the success of this procedure; therefore, each case must be individually evaluated to determine if it is a viable treatment option. There are several types of transplants and each have different prognosis. Best results are achieved in younger patients with a matched sibling donor. Unfortunately, only a minority of patients will have such a donor. Other types of transplantation performed with marrow from unrelated donors have a much greater risk of serious and chronic complications. Patients must decide for themselves if they want to risk a transplant or continue their current conservative care based on the severity of their symptoms.

PROGNOSIS

The course of PNH may vary in patients. PNH may be chronic with only mild symptoms or it can be a disabling disease with frequent hemolytic crises and regular need for transfusions. Of course, unexpected complications such as development of aplastic anemia or occurrence of blood clots, may affect survival. The most common deadly complication of PNH is occurrence of blood clots in vital organs. With a good supportive care PNH patients can live with their disease for many years.

WELLNESS

Apart from specific treatments and medications, there are some actions you can take to have the optimum level of wellness possible for you.

Do not take any over the counter medications, prescription medications, supplements, vitamins or herbs without first consulting with your doctor. If you have low red cell counts you should avoid excessive exercise, going to high altitudes or any activity that causes chest pain, severe shortness of breath or heart racing. Some doctors believe that heavy anaerobic exercise may contribute to acidification of blood and induce hemolysis. If you have low platelet count or are taking blood thinners, you should avoid activities that could result in straining or injuries. If you develop headache or persistent pain anywhere, which could indicate a bleeding problem, you should notify your doctor. If you have low white cell counts you may be more likely to catch bacterial infection. Be alert to any symptoms of infection–fever or increased fatigue can be warning signs, and you should report these promptly to your doctor.

EMOTIONAL ISSUES

When you are diagnosed with this disease, you may feel shock, anger and fear, and even relief at learning what is wrong. You will need to make time for medical treatment and administration. Everyday life must go on for you and your family. PNH is a chronic disease and you should not schedule your entire life around the disease. Although this may seem overwhelming and impossible, many other patients with the same condition have come through to lead full lives often becoming stronger as individuals and as families. We publish 2 booklets that can help: "Families coping with AA and MDS" and "Managing and Treatment Decisions".

TAKING ACTION

Here are some important first steps that will help you to feel more in control with your disease and its treatment:

- Find a doctor who is an experienced expert in treating your disease. Make sure that your doctor takes time to clearly answer your questions, explain all of your treatment options and include you in the decision making process. Be comfortable with your doctor and avoid overconfident but also insecure physicians. Choosing a medical institution that offers clinical trials will give you the best chance of receiving the best advice and your case may contribute to the medical progress which can result only from a collective experience.

- Learn all you can about the disease and possible treatment options. The Internet, publications of AA&MDS International Foundation and other patients may be good sources of information.

- Ask questions of your doctor and other health professionals. For serious treatment decisions, obtain second opinion to feel more comfortable about you choice. Remember that the selection of the treatment may be influenced by the institutional bias especially if there is no established treatment standard. Do not be afraid to keep asking questions until you fully understand the answers and request a written reference material whenever possible. Ask about all possible treatment options and about research studies available at your institution and other institutions.

- Start keeping track of all your medical information in a notebook or computer. A logbook will help you to document your disease and provide your doctor with useful information.

Chapter 2

Blood is a "circulating tissue" of the body. It is composed of many specialized cells suspended in **plasma**. Two of its main functions are to transport oxygen and nutritive materials to the tissues of the body and to transfer waste products to disposal sites. Blood also transports the body's defense cells to areas damaged through injury or infection. There are three major types of blood cells: (1) Red Blood Cells (RBCs) or **erythrocytes**; (2) White Blood Cells (WBCs) or **leukocytes**; (3) Platelets. The bone marrow in a healthy adult produces and releases about 2.5 billion red blood cells (RBCs), 2.0 billion platelets, and 1 billion white blood cells (WBCs) for every kilogram (2.2 lbs.) of body weight every day.

PRODUCTION OF BLOOD CELLS

Blood cell production is called **hematopoiesis** and occurs in both the liver and the spleen of the **fetus**. After birth, blood cells are produced in the spongy tissue filling the center of the bones, the **bone marrow**. The bone marrow produces **stem cells**, which are the "parent cells" for more mature blood cells. Stem cells respond to chemical signals (**cytokines**) that are produced by the body to increase a specific population of blood cells as needed. The stem cell undergoes proliferation by dividing into two cells again and again, making more duplicates as well as immature **blast cells**. The blasts will then **differentiate**, that is grow up and specialize, to make mature red blood cells, white cells, or platelets.

COMPLETE BLOOD COUNT (CBC)

The CBC is a laboratory test that is performed on a small amount of blood usually taken from an arm vein. It provides detailed information about the quantity and quality of each of the blood cell types a person has. The CBC includes a measurement of the number of each of the three major formed blood elements (the red, white and platelet blood cells) and a measure of the **hemoglobin** (the oxygen-carrying component of the blood) and the **hematocrit**, (the percentage of the blood that consists of red blood cells). The quantity of each of the blood cells is expressed as the number of that particular element in a given volume of blood, usually a mm3 (which is a very small droplet, about one five thousandth of a teaspoon) or a liter (which is a little more than a quart). The hemoglobin is usually expressed as the weight of hemoglobin in grams (there are about 30 grams in one ounce) found in a deciliter of blood (one tenth of a liter, or a little more than one tenth of a quart).

1. **WBCs.** These cells fight infection, produce cytokines and are responsible for most immune responses;

2. ***RBCs***. These cells contain hemoglobin (the protein that carries oxygen to tissues) and gives blood its red color;

3. **Hemoglobin (Hgb)**. The red protein in the red blood cells that carries oxygen from the lungs to the tissues and carries carbon dioxide, a waste product, from the tissues to the lungs;

4. **Hematocrit (HCT)**. This is the percentage of the total blood volume due to the RBC; and

5. **Platelet**. These stop bleeding by helping to form blood clots.

NORMAL (Mean) ADULT BLOOD VALUES*
mm3 (cubic millimeter) — g/dL (grams per deciliter) —% (percentage)

	WBC (x103/mm3)	Neutrophils (x103/mm3)	Hgb	Hematocrit	Reticulocyte	Platelets (x103/mm3)
Male	7.4	4.4	15.5 g / dL	47%	0.8-2.5	150-350
Female	7.4	4.4	14.0 g / dL	41%	0.8-4.1	150-350

NORMAL (Mean) CHILDREN'S BLOOD VALUES*
mm3 (cubic millimeter) — g/dL (grams per deciliter) —% (percentage)

	WBC (x103/mm3)	Neutrophils (x103/mm3)	Hgb	Hematocrit	Reticulocyte	Platelets (x103/mm3)
1 month	10.8	3.8	13.9 g / dL	44%	0.1-1.7	—
6 month	11.9	3.8	12.6 g / dL	36%	0.7-2.3	—
6 mo-2 yrs	10.6	3.5	12.0 g / dL	36%	—	150-350
2-6 yrs	8.5	3.8	12.5 g / dL	37%	0.5-1.0	150-350
6-12 yrs	8.1	4.4	13.5 g / dL	40%	0.5-1.0	150-350
12-18 years						
male	7.8	4.4	14.5 g / dL	43%	0.5-1.0	150-350
female	7.8	4.4	14.0 g / dL	41%	0.5-1.0	150-350

*** data from *Harriet Lane Handbook*, 15th Edition, ed. Siberry and Iannone, C.V. Mosby, 2000.**

Note: The table above displays the mean (average) values for different blood components; normal lab results involve a range rather than a single value. Individual normal values may be higher or lower; for instance, blood counts typically decrease with age.

RED BLOOD CELLS

RBCs are the most plentiful cells in the blood. They give the blood its red color and are primarily responsible for carrying oxygen to tissues. The life span of each RBC is about 120 days. A **reticulocyte** is a very young RBC. Reticulocytosis (many reticulocytes in the blood) is usually a sign of an increase in the red cell production by the bone marrow. This elevation indicates that the bone marrow is responding appropriately to an increase in the need for total red blood cell mass. A normal reticulocyte count is 1%-2% of the total RBC count.

PLATELETS

Platelets (**thrombocytes**) are the smallest blood cells. The main function of the platelet is to rush to an area of injury, such as a cut on your finger. The platelets will stick to a torn blood vessel wall and form a plug that temporarily seals off the leak. Eventually a clot forms at the same site to stop the bleeding.

Platelets originate from megakaryocytes, which are very large cells present in the bone marrow. The megakaryocytes break apart and each tiny fragment forms a platelet. After platelets leave the bone marrow they are taken up by the spleen for storage and released slowly according to the needs of the body. Platelets live for about 8 to 10 days.

When a body does not have enough platelets (**thrombocytopenia**) a person may bleed uncontrollably from either a large vessel or from microscopic blood vessels called capillaries. Bleeding into the tissue becomes visible in the form of a bruise. Bleeding from capillaries causes pinpoint red dots called **petechiae**. When the platelet count falls below 5000 per cubic millimeter, bleeding frequently occurs spontaneously anywhere in the body even without a fall or cut. Some patients experience spontaneous or increased bleeding at platelet levels above 5,000 up to 20-30,000.

Each patient may respond differently to low levels of platelet counts. The trigger level at which a platelet transfusion may be required will differ with age, other health problems, the site of bleeding, the extent of bleeding, and the approach to aplastic anemia agreed upon by the patient and the physician.

WHITE BLOOD CELLS

WBCs are part of the body's immune system and clear the body of harmful material. They are produced and reside in the bone marrow and the **lymphatic system** and are composed of many different cell types.

WBCs defend the body against organisms that cause infections. They destroy invading bacteria and viruses, and may help remove abnormal cells originating within the body itself. WBCs also remove dead or injured cells in the body.

WBCs may also participate in harmful processes such as allergies, transplant rejection, graft-versus-host disease after a bone marrow transplant, and autoimmune diseases. In these special instances the WBCs react against the patient's own tissues. In many individuals with aplastic anemia the patient's immune system begins suppressing the cells of the bone marrow. In other patients drugs or other toxins directly inhibit bone marrow production. Regardless of the mechanisms causing marrow suppression, the trigger for marrow failure is unknown (or **idiopathic**) in more than 50% of all cases.

WBCs are classified or named according to their structure and function. The **granulocytes** have granules that contain **enzymes** that are capable of killing microorganisms, and breaking down (**catabolizing)** debris that is ingested by **phagocytosis**. The granulocytes are called neutrophils, basophils, or eosinophils according to the types of granules they have.

The major granulocyte is the **neutrophil**. It is the most numerous and comprises about 55% of the total adult WBC count. The neutrophils "eat" bacteria present in the body and help fight infections. A mature neutrophil may also be called a "**poly**" or PMN, and young polys are called "**bands**" or stabs.

The **absolute neutrophil count** (ANC) is a measure of the actual number of WBCs that are mature neutrophils. This is a reliable measure of a body's susceptibility to infection: the higher the ANC, the greater the resistance to infection. The number of WBCs, the percentage of polys, and the percentage of bands must be known to calculate the ANC. To calculate the ANC, first add the percentage of the polys and the bands together. Next, take that number and multiply it by the number of WBCs. Remember too, the lab value of the WBCs is usually in thousands per mm3 and one must move the decimal three places to the right for the actual number.

Another granulocyte is the eosinophil, which may participate in allergic reactions. It comprises 1-4% of the total WBC count. The least abundant granulocyte is the basophil. It is usually less than 1% of the total adult WBC count.

Other WBCs contain few or no granules. The monocytes are blood borne phagocytes that participate in immune and inflammatory responses, and may develop into macrophages. They also ingest dead or defective cells, especially blood cells, and are major producers of cytokines.

The **lymphocytes** usually represent 1/3 to 1/2 of the total WBCs and are the primary cells of the immune response. The majority of the lymphocytes are produced in the **lymph** nodes and thymus gland. The number of lymphocytes is generally not affected in a patient with aplastic anemia because it is a bone marrow disease. However, if the patient is undergoing **immunosuppressive** therapy, the lymphocytes may be decreased. The life span of different types of lymphocytes can be days, months, or years.

The **lymphocytes** include a special population of cells known as natural killer cells. The main function of the natural killer cell is to exert direct **cytotoxic** or cytolytic effects on targeted nonself cells. It appears that the natural killer cells are also effective in destroying unhealthy or abnormal self cells. Natural killer cells participate in the destruction of nonself cells from other individuals or animals. Usually these actions are beneficial to the individual, but can also cause the rejection of grafts and transplanted organs.

THE IMMUNE SYSTEM

The immune system of a normal adult is continually challenged by a spectrum of substances that it recognizes as being foreign or "nonself." These foreign substances are called antigens, which are often proteins present on the surface of cells. Our bodies are usually tolerant of the antigens on our own cells.

The body's reaction to foreign substances is called the Immune Response. When this response occurs the body activates immune cells (immunocytes). There are two major types of immunocytes (B and T cells) that are capable of recognizing and destroying antigens. B-cells produce antibodies which incapacitate the antigen, and the T-cells attack the antigen directly. Once the B and T cells have been exposed to a particular antigen, some of these cells, called "memory cells," become capable of remembering the antigen and can act even faster if the antigen re-enters the body.

When a foreign cell enters the body it will eventually reach a lymph node. There it will stimulate B-cells to produce specific antibodies. This antigen-antibody pair is as specific as a lock and key because each antibody usually only fights against or binds to one type of antigen.

BLOOD DISORDERS

Disorders of the blood system can involve problems in the production, function or destruction of any of the cellular components of the blood. Depending on the specific problem, patients may have minimal disruption of their daily activities or may experience potentially life-threatening events.

Anemia is defined as a decrease in the number of RBCs or the quantity of hemoglobin or hematocrit. This leads to a reduction in the amount of oxygen the blood can carry. Anemia may be due to a variety of causes.

There are many different types of anemia. Some anemias are caused by a nutritional deficiency and can be corrected by a change in the diet and / or the addition of specific supplements. However, in patients with aplastic anemia, myelodysplastic syndromes and PNH, these supplements will not correct the anemia because these patients do not have a healthy bone marrow capable of producing blood cells (AA, MDS, PNH) or cells are prematurely destroyed on circulation (PNH).

Aplastic anemia (AA) results from an injury to the stem cells in the bone marrow which decreases the production of all three types of blood cells: red cells, white cells, and platelets. Bone marrow damage may be caused by exposure to toxins, chemicals, viruses, or drugs. In most cases the cause is not known.

Myelodysplastic syndromes (MDS) are a group of bone marrow failure disorders that are similar to aplastic anemia. There is a reduction of the blood cells produced by the bone marrow, and some of the cells may be abnormal, or immature. Chromosomal abnormalities are often present in MDS but not in aplastic anemia. Advanced MDS may progress to a cancer of the blood (acute leukemia). Myelodysplastic syndromes are classified by **morphology** or appearance of blood and bone marrow cells under the microscope.

According to the **FAB criteria**, there are five subtypes of MDS:

1. Refractory anemia (RA)
2. Refractory anemia with ringed sideroblasts (RARS)
3. Refractory anemia with excess of blasts (RAEB)
4. Refractory anemia with excess of blasts in transformation (RAEB-t)
5. Chronic myelomonocytic leukemia (CMML)

Paroxysmal nocturnal hemoglobinuria (PNH) is a rare but potentially serious blood disease affecting people of all ages. It develops from an acquired mutation in the genetic material of the most immature bone marrow cells called stem cells. Mutated stem cells produce defective blood cells of all lineages. Due to the PNH defect, diseased red cells are prematurely destroyed in the blood, a process called hemolysis. In addition, bone marrow is not working properly and PNH patients may show similar symptoms as patients with AA and MDS.

BONE MARROW EXAMINATION

In a patient with suspected aplastic anemia or MDS, a bone marrow aspiration is necessary to examine the actual marrow. In a bone marrow aspiration a small amount of the bone marrow is removed from a bone through a needle. Bone marrow aspiration provides important information on cell types, iron stores, and the presence or absence of abnormal cells. Chromosome studies to detect possible malignant cells may also be performed on the marrow sample. Because aspiration disturbs the marrow structure, the degree of bone marrow cellularity (the quantity and quality of the bone marrow cells) cannot be accurately determined.

In a bone marrow biopsy, a small piece of the marrow is removed intact. This provides the most reliable and specific information regarding the degree of bone marrow cellularity (how well the bone marrow is producing cells). Marrow biopsy is more difficult and expensive than marrow aspiration.

RED BLOOD CELL TRANSFUSIONS

Transfusions of red blood cells are often needed for the temporary relief of anemia in patients with AA, MDS and PNH. Usually, some of the plasma (the fluid surrounding the blood cells) is removed to make the red blood cells easier to give; this more concentrated blood product is known as packed RBCs or PRBCs. Transfusions may relieve fatigue, allowing the heart to work at a slower rate. Before a transfusion is given, blood specimens must be obtained for cross-matching. Cross-matching is testing of donor's blood and recipient's plasma for compatibility. **Vital signs**, including temperature, must be checked before and during the transfusion. RBC transfusions usually take three to four hours to complete. If a serious transfusion reaction occurs, the signs are usually seen within the first 15-20 minutes.

One drawback to the use of repeated transfusions is related to our bodies' inability to eliminate excess iron. Iron is carried by hemoglobin inside the red cells. When the red cells break down, iron is released and stored in critical organs such as the liver and the heart. Under normal conditions there are approximately 4-6 grams of iron in the body. Each unit of blood for

transfusion contains approximately 200-250mg of iron. This means that a patient receiving two units of blood per month could accumulate 5-6 grams of iron in one year. Years of red cell transfusion result in the accumulation of iron known as **hemochromatosis** or "iron overload" eventually causing dysfunction and death. Diagnosis involves measurement of the serum iron and transferrin saturation, as well as the ferritin level. This can sometimes be obtained from a bone marrow aspirate or more accurately from a liver biopsy. An indirect measure of body iron may be obtained by measuring storage iron (serum ferritin) in the blood.

Excess iron can then be removed from the body using desferrioxamine (Desferal), an **iron chelator**. Chelators bind iron and eliminate it from the body in the urine and stool. Desferal, the only iron chelating agent approved in the US, is usually given via a slow **subcutaneous** infusion by syringe pump, at least four to six days of the week. Intravenous administration during blood transfusions is useful for patients who comply poorly with treatment. Most hematologists agree that chelation therapy should be started before organ damage has a chance to occur, some suggesting treatment after as few as 15 transfusions, or when the serum ferritin level has reached 1000ng / ml (normal is 40-160).

The most common side effect from subcutaneous infusion of Desferal is pain and swelling at the injection site, usually subsiding after 24 hours. Warm compresses applied to the site are often helpful.

A recent alternative to continuous subcutaneous infusion of desferrioxamine is a rapid (bolus) injection of the same drug twice daily. This was found to be equally effective, does not induce serious side effects and is better accepted by many patients. An oral chelator has been tried in Europe but has not been approved in this country because of some detrimental side effects.

IRRADIATED BLOOD

Many doctors recommend that blood be irradiated before being transfused into patients. This inactivates the lymphocytes and prevents graft-versus-host disease. The use of leukocyte filters (also called leukopor filters) and irradiated blood is recommended by doctors for patients who repeatedly receive blood transfusions. This double precaution helps those who are transfusion-dependent from building up antibodies against platelets, transplantation proteins, and other antigens.

PLATELET TRANSFUSIONS

The normal life span of a platelet is quite short, only 8-10 days. Patients may need regular platelet transfusions or they may elect to not use platelet transfusions unless they have bleeding. Because platelets carry specific antigens, a patient's body may recognize transfused platelets as foreign and produce antibodies that rapidly destroy the transfused platelets. In those patients adequate responses to platelet transfusions may be restored by giving platelets that are matched with the patient for histocompatibility (HLA) antigens.

WHITE BLOOD CELL TRANSFUSIONS

White blood cells are usually not transfused to patients. Their life span is extremely short (only a few hours) so their use is reserved for individuals with severe infections who do not respond to antibiotics.

TRANSFUSION REACTIONS

Common transfusion reactions include fever, chills, and allergic reactions (itching, hives). Diphenhydramine (Benadryl) or acetaminophen (Tylenol) can be used both to treat or to prevent recurrent transfusion reactions. Severe transfusion reactions, due to infusion of incompatible red blood cells, may cause shortness of breath, back pain, low blood pressure, and decreased urine output.

RISKS OF TRANSFUSION CONTAMINATION

Contamination of blood products for transfusion is rare. Although it is not possible to completely eliminate all risk, recent advances in the testing of blood products have reduced the possibility of contamination from viruses such as HIV and hepatitis to a point where the risk to the patient is extremely low.

TOPICAL ANESTHETIC

For those people who are very sensitive to pain, your doctor may suggest a topical anesthetic called EMLA (idocaine & prilocaine.) It is a prescription gel that comes with its own bandaids. It is applied to the area of puncture at least one hour before needle insertion takes place. The result is decreased discomfort with the needle insertion.

Appendix: Glossary

Absolute Neutrophil Count—*A measure of the actual number of neutrophils present in the blood per unit volume.*

Allergen—*A substance that causes an allergic reaction.*

Anemia—*Any condition involving a decrease in the hemoglobin level of the blood below normal.*

Antigen—*A body substance, usually a protein, that can stimulate an immune reaction.*

Aplastic—*Involving the absence or defective development of a tissue or organ.*

Band—*A young neutrophil.*

Blast Cells—*Immature cells that mature into various blood cells.*

Bone Marrow—*Soft tissue occupying the inner cavities of bones responsible for blood cell production.*

Catabolize—*To break down complex chemical compounds into simpler ones.*

Cytokines—*Hormone-like proteins secreted by many different cell types which regulate cell proliferation and function.*

Cytopenia—*A deficiency of cells in the blood.*

Cytotoxic—*Destructive to cells.*

Differentiate—*To develop into a different (usually more mature, and specialized) characteristic or function than the original.*

Enzyme—*A protein that acts as a catalyst to induce chemical changes in other substances.*

Erythrocyte—*A mature red blood cell.*

FAB Criteria—*Criteria used for classifying leukemia and myelodysplastic syndromes which were developed and agreed upon by a group of French, American and British scientists.*

Febrile—*Feverish; involving an elevated body temperature.*

Granulocyte—*One of the three types of white blood cells (the others being monocytes and lymphocytes), so called because they have granules that contain enzymes that help fight infection.*

Hematocrit—*The percentage of a volume of blood occupied by red blood cells.*

Hematopoiesis—*The production of blood cells.*

Hemochromatosis—*An excess of iron deposits in the body, also known as "iron overload."*

Hemoglobin—*The red blood cell protein-iron compound responsible for transporting oxygen from the lungs to the cells, and carbon dioxide from the cells to the lungs.*

Hyperplastic—*Involving an increased number of cells.*

Hypersensitivity—*An abnormal sensitivity to a stimulus.*

Hypoplastic—*Involving a decreased number of cells.*

Idiopathic—*Usually refers to any condition with no known cause.*

Immunosuppressive—*Being capable of inhibiting immune responses.*

Iron Chelator—*A substance which binds iron and then eliminates it from the body in the urine and stool.*

Leukocyte—*White blood cells, important in defending against infection and clearing the body of harmful material, of which there are several types: granulocytes, monocytes and lymphocytes.*

Lymph—*A clear, transparent filtrate of plasma that is collected from tissues throughout the body and eventually flows to the lymphatic system.*

Lymphatic System—*An important aspect of the body's immune system, consisting of vessels that carry lymph fluid from tissues throughout the body through the lymph nodes to the venous blood circulation.*

Lymphocyte—*One of the three types of white blood cells (the others being granulocytes and monocytes), and the primary cell of the immune response, responsible for attacking antigens; divided into two forms, B cells and T cells.*

Monocyte—*One of the three types of white blood cells (the others being granulocytes and lymphocytes), normally constituting 3-7% of the blood.*

Morphology—*The study of the structure and form of an organism.*

Neutropenia—*A deficiency of neutrophils in the blood.*

Neutrophil—*The most numerous of the white blood cells, important for helping the body fight infections.*

Pancytopenia—*A deficiency of all types of blood cells.*

Petechiae—*Pinpoint hemorrhagic spots in the skin.*

Phagocytize—*To engulf and destroy dangerous microorganisms or cells, a function performed by certain white blood cells.*

Poly—*A mature neutrophil.*

Plasma—*The fluid (noncellular) portion of the circulating blood.*

Platelet—*The smallest cells in the blood, essential for blood clotting.*

Proliferation—*Growth by reproduction of similar cells.*

Reticulocyte—*An immature red blood cell.*

Reticulocyte Count—*The number of reticulocytes usually expressed as the percent of red blood cells.*

Stem Cells—*Cells that give rise to any of the different blood cells.*

Subcutaneous—*Beneath the skin.*

Synthesis—*A building up, putting together, or composition.*

Thrombocyte—*Platelet.*

Thrombocytopenia—*A deficiency in the number of platelets.*

T-lymphocyte—*A lymphocyte that is important in the immune response, but which in aplastic anemia suppresses the stem cells; also known as a T cell lymphocyte.*

Transferrin—*A protein that binds iron and thus regulates iron absorption and transports iron in the body.*

Vital Signs—*The temperature, pulse, respiration, and blood pressure.*

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