

## HEMOLYTIC ANEMIA

*Hemolytic* refers to the "lysis" or destruction of red cells. Normally, red cells survive in the blood about 100 to 120 days. Considering the red cell has no nucleus with which to replenish its proteins, this is quite an accomplishment. The red cell is constantly being buffeted about as it goes from high pressure and fast flow in arteries to squeezing through very small capillaries and then on to much slower flow in veins. The cells go through all the organs; all this time the cell must carry oxygen from the lungs to the other tissues and, similarly, carry carbon dioxide from the other tissues to the lungs where it is exhaled.

The red cell has a complex membrane (outer cover) that is very pliable, allowing it to squeeze in and out of small places and, yet, strong enough to stand the stresses placed upon it. The red cell also has a very complex system of enzymes to help maintain its own metabolism. In addition, there are small proteins on its surface, some of which are used to identify the cells.

All of these systems must be functioning properly for the red cell to survive and carry out its functions. As the cell ages, the red cell enzymes will decay; as a result, the red cell becomes less functional and is then removed, usually in the spleen. When any one of these systems is deficient or compromised in some way, the cell will die an earlier death. This is called *hemolysis*. Sometimes the hemolysis is mild, and the bone marrow keeps up with it by producing more reticulocytes (*compensated hemolysis*). However, with severe hemolysis, the bone marrow reaches a point where it has reached its limit, and the patient may then develop severe anemia.

When hemolysis is severe or occurs rapidly, it will be fairly obvious to the doctor. The patient will often be quite ill and jaundiced. The hematocrit and hemoglobin will be low, and the reticulocyte count, high, as the bone marrow attempts to compensate for the severe anemia.

When hemolysis is mild or slow, it may be so subtle that other tests are necessary to establish that there is hemolysis. Hemolysis may occur abruptly inside the blood vessels, or it may occur in the spleen. When a red cell is *lysed* in the bloodstream, it releases its hemoglobin. Free hemoglobin, in excess amounts, can be toxic, especially to the kidneys. An example of this is seen when a person receives the wrong type of blood by mistake. In this instance, there will be a dramatic lysis of the red cells, and the large amount of free hemoglobin that is released may cause the kidneys to fail. The amount of free hemoglobin in the blood can be measured.

*Haptoglobin* is another protein in the blood that binds free hemoglobin. In bloodstream hemolysis, a drop in the haptoglobin level occurs since it is binding the free hemoglobin. Often, the iron in free hemoglobin will be excreted by the kidneys as *hemosiderin*. A sample of urine can be stained to look for hemosiderin. With destruction in of red cells in the spleen, the hemoglobin will break down to *bilirubin*, which can be measured in the blood.

The lab tests that are easy to perform are (1) the haptoglobin level; (2) free hemoglobin; (3) urine hemosiderin, and (4) bilirubin. There are other "fancier" tests that are used either for research purposes or in very complicated and obscure problems.

Once it is established that anemia is due to hemolysis, it is necessary to look further and determine the cause. There are many possible causes of Hemolytic Anemia. Doctors attempt to categorize these causes into one of the following: (1) Autoimmune Hemolytic Anemia; (2) abnormal hemoglobins; (3) red cell membrane defects; (4) enzyme abnormalities; and (5) extrinsic non-immune hemolytic anemias. Some of these problems begin at birth (congenital) while others are acquired later in life. It can be helpful to determine if the anemia has been present from birth or occurred later.

SHOULDN'T IT BE OBVIOUS IF THE ANEMIA HAS BEEN PRESENT SINCE BIRTH?

Not necessarily. Sometimes hemolysis and the anemia are subtle; the problem may not be noted until a child is older or even into adulthood.

IF IT WAS HEREDITARY,  
WOULDN'T SOMEONE ELSE IN THE FAMILY HAVE IT?

Often this true, and it is necessary to evaluate other family members for the same type of anemia.

**Note:** Please refer to (1) autoimmune hemolytic anemia; (2) sickle cell anemia; (3) hereditary hemolytic anemia; and/or (4) G-6-PD Deficiency for more specific information regarding those types of hemolytic anemia.

## **AUTOIMMUNE HEMOLYTIC ANEMIA (AIHA)**

Autoimmune Hemolytic Anemia (AIHA) is a condition in which there is *hemolysis* (rupture) of red blood cells caused by *antibodies*. An antibody is a protein that can react with an antigen on the surface of the red cell.

These proteins are called *immunoglobulins* and are types of gamma globulins that, because of their physical structure, can attach to the antigens on the surface of the red cell. There are five types of immunoglobulins. Only two -- IgG and IgM – are involved in Autoimmune Hemolytic Anemia.

Autoimmune Hemolytic Anemia is a rare problem. As mentioned, IgG, or in some cases IgM, antibodies attach to the red cell. The red cells then stick together (*agglutinate*); they rupture (*lyse*) or are destroyed in the spleen. This can start very abruptly, or it can come on slowly. If abrupt, the patient may be quite ill, jaundiced and even develop heart failure. If *hemolysis* (destruction or death of cells) is only slight, the patient may not exhibit any symptoms.

### **WHAT ARE THE CAUSES OF AIHA?**

The causes are divided into three groups. The first is called *idiopathic*, which means there is no obvious cause. In the second group, there is an underlying disease. Very often, this is an autoimmune disease, such as *Systemic Lupus Erythematosus*, or a malignancy, such as *Chronic Lymphocytic Leukemia (CLL)*. The third group is associated with receiving a drug that initiates the process of antibody production. How these diverse conditions lead to antibody production is complex and not completely known.

### **HOW IS THE DIAGNOSIS DETERMINED?**

Patients may feel tired or have a fever, or they may be jaundiced and the patient's urine may get quite dark, i.e., tea-colored. The doctor will notice that the patient is anemic; usually the *reticulocyte* count (new red cells) will be elevated. The test for *haptoglobins* will be reduced (positive). The physician will realize there is hemolysis, and since AIHA is one of the main causes of hemolysis, a Coomb's test will be ordered.

The Coomb's test will identify the antibodies (IgG or IgM) on the surface of red cells in patients with Autoimmune Hemolytic Anemia. The test is very important in blood banking, where it is used to screen units of blood for antibodies so that the patient's body will not destroy the transfused cells, resulting in a sudden severe hemolysis.

### **DOES A POSITIVE COOMB'S TEST ALWAYS MEAN AUTOIMMUNE HEMOLYTIC ANEMIA?**

No. There are occasional false positives, just as there are false negatives. Some people may have a positive Coomb's test without significant hemolysis. However, the Coomb's test is reliable most of the time, especially when one uses it along with all the other information about the patient. That includes inspection of the blood smear, where one may see *spherocytes*, *polychromatophilia* and often *nucleated red cells*, an indication of increased red cell production.

### **WHAT HAPPENS NEXT?**

Essentially two things. The first is to decide if there is an underlying problem such as systemic Lupus or Chronic Lymphocytic Leukemia; it is also important to investigate if the patient has been taking a drug that is known to cause hemolysis.

The second step is to start treatment, especially if the patient is very ill. Treatment will vary depending on the cause of the hemolysis, the severity of the anemia, and on the response of the patient to treatment.

If the cause is felt to be a previously prescribed drug, then treatment may be as simple as stopping the drug. The patient may improve in days to weeks.

If the antibody is an IgG antibody, Cortisone and other drugs that suppress the immune system may be very effective.

Diseases associated with an IgM antibody most often do not respond to treatment with drugs and Cortisone. Folic acid, a vitamin, should be given since the increased production of red cells by the bone marrow can lead to a deficiency of this particular vitamin.

In those cases in which there is an IgM antibody, there may be a relationship to temperature. The IgM antibody may be a so-called cold antibody. This is called Cold Agglutinin Disease. People with this problem have *acrocyanosis*. Acrocyanosis is a purple color of the tips of the fingers, toes, nose and ears when they are exposed to cold. This may also be painful. Treatment of this disease is difficult. It often does not respond to drugs. The best treatment may be to avoid cold temperatures. Even then the patient will usually have a chronic anemia but be able to cope with the problem.

If the hemolysis is so severe that the patient is in danger of heart failure or even dying, it may be necessary to give a blood transfusion. Transfusion in this disease may be hazardous so it is avoided unless it is absolutely necessary. If the hemolysis is mild, it may be prudent just to observe the patient and not treat. This is especially true if the hemolysis is drug related, and the drug can be stopped.

An experienced physician, most often a hematologist, can be very important in the care of patients with Autoimmune Hemolytic Anemia since it can be life-threatening and because it has so many different variations. The disease, however, can be treated, is usually controlled, and can often be cured.

#### IS THERE ANY WAY TO GET RID OF IT?

Sometimes, but not always, it is possible. If an offending drug can be stopped, the anemia will resolve. If it is determined there is an underlying disease, that disease can be treated and may go into remission. In this case, the anemia will improve but may recur if the underlying disease relapses. If the anemia is *idiopathic*, it may disappear with treatment; however, there is also a chance that the anemia can relapse.

#### WHAT HAPPENS UPON RELAPSE?

Other drugs may be used to treat the anemia. On occasion, plasma exchange has been used, but this offers only temporary help since the antibodies continue to be produced. Sometimes it is necessary to remove the spleen. *Splenectomy*, the surgical removal of the spleen, is effective about 50 to 60 percent of the time in

IgG antibody diseases. Splenectomy is of benefit in these people because the spleen behaves like a sieve. If the spleen is removed, there will still be antibodies on the red cells, but they, of course, will no longer get caught up in the spleen. Splenectomy is not usually effective in IgM antibody hemolysis.

#### DOES THE PATIENT HAVE TO TAKE CORTISONE THE REST OF HIS OR HER LIFE?

Usually the patient is started on a relatively high dose of Cortisone and then, as he or she gets better, the dose is cut down to as small a dose as possible. It may be possible to stop the Cortisone altogether. If that drug alone does not work out, other drugs can be combined with the Cortisone. If the hemolysis continues and the side effects of the drugs become a problem, a splenectomy may help. Unfortunately, there is no other good treatment.

#### WHAT ARE THE OTHER DRUGS THAT CAN BE USED?

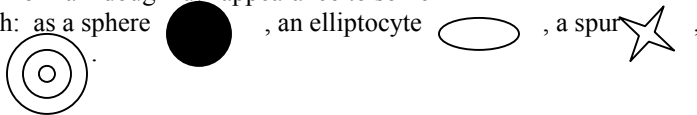
Immunosuppressive drugs, such as cyclophosphamide (Cytoxan) or melphalan, may be used. These drugs are usually used to treat malignant diseases and do have substantial side effects. Still they may be very helpful in treating patients with AIHA.

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### HEREDITARY HEMOLYTIC ANEMIA (HHA)

There are a number of people who inherit a problem with their red cells that can cause *hemolysis* (destruction of cells). A few of these people may be jaundiced and anemic at birth. Most, however, will not exhibit problems until later in childhood or, even later, when they are adults. Others may go through life without ever being diagnosed. Hereditary Hemolytic Anemia (HHA) includes a number of diseases, many of which are quite rare. Basically, HHA can be divided into disorders of the red cell membrane or disorders of red cell metabolism (resulting in the formation of *methemoglobin*).

Red blood cell (RBC) membrane disorders involve a defect in the wall of the red cell, resulting in a change in the shape from the normal "doughnut" appearance to some other form such: as a sphere, an elliptocyte, a spur, or a target cell.



The second type of Hereditary Hemolytic Anemia related to disorders of red cell metabolism is covered separately under Glucose-6- Phosphate Dehydrogenase Deficiency.

Most of the HHA's with abnormal shapes are rare so the disease Hereditary Spherocytosis (HS) will serve as an example. Hereditary Spherocytosis is now known to be a group of diseases. These diseases have a red cell in common that is smaller than the normal red cell and looks like a ball or sphere. Most often, these patients are not very ill and have a mild to moderate anemia although, on occasion, the disease can be severe early in life. The inheritance is variable, but most often it is *autosomal dominant* in which either parent can pass the gene to a child and that child will then have the disease. In a smaller number, the inheritance is *autosomal recessive*, in which both parents would have to pass the gene (*homozygous*) for the offspring to be affected.

The spherocyte, because of its structure, does not survive as well as the normal red cell. *Hemolysis* severe enough to cause jaundice may then be seen, and the patient will be anemic with an increase in their reticulocyte counts (i.e., the new red cells). The spleen is often enlarged. Spherocytes are seen on the blood smear.

The confirmatory lab test is the *osmotic fragility test*, in which the patient's red cells are placed in different concentrations of salt water and compared with normal cells. The spherocyte will not tolerate *hypotonic* (lower salt) solutions as well and will rupture. People with autoimmune hemolytic anemia will also have spherocytes but they will have a positive Coomb's test.

These patients will often have gallstones at a young age. Splenectomy (removal of the spleen) will most often cure the disease.

#### DO ALL PATIENTS NEED TO HAVE A SPLENECTOMY?

No. In some patients the disease is very mild and may not require any treatment. In fact, if possible, it is better to wait until a child is older than 5 or 6 years of age to do a splenectomy since the spleen is important to one's immune system.

#### IS THERE ANY OTHER TREATMENT FOR THIS DISEASE?

No. Neither medication nor any other type of blood manipulation will affect these cells. Even after the spleen is removed, the cells will still appear to be spheres, but the amount of hemolysis will be much less.