Red blood cells disorders

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Dedication

To the students at Faculty of Health Sciences Elsheikh Abdallah Elbadri University

Acknowledgement:

To our teachers from primary schools to postgraduate level

Introduction

Red blood cells: The blood cells that carry oxygen. Red cells contain hemoglobin and it is the hemoglobin which permits them to transport oxygen (and carbon dioxide). Hemoglobin, aside from being a transport molecule, is a pigment. It gives the cells their red color (and their name).

The abbreviation for red blood cells is RBCs. Red blood cells are sometime simply called red cells. They are also called erythrocytes or, rarely today, red blood corpuscles. [(1)]

Discovery of red cells:

Antoni van Leeuwenhoek is widely credited as the discoverer of red blood cells. In truth, he was not the first person to observe "red particles" in blood but his observations were more detailed and numerous than those (by Malpighi and Swammerdam) that preceded him.

1) Antoni van Leeuwenhoek (1632-1723):
   Leeuwenhoek's first written description of human red blood cells (his own) was in a letter to Constantine Huygens (father of the physicist and astronomer Christiaan Huygens) on April 5, 1674 and later in another letter addressed to Mr. Oldenberg, Secretary of the Royal Society of London on April 5, 1674. The first publication of the observation of globules in blood occurred in April 1674 in the Philosophical Transactions of the Royal Society of London in which Leeuwenhoek published his 1673 observations reported in the letter to Huygens. In a letter dated August 14, 1675, Leeuwenhoek went on to make the remarkable discovery that "those sanguineous globules in a healthy body must be

very flexible and pliant, if they are to pass through the small capillary veins and arteries, and that in their passage they change into an oval figure, reassuming their roundness when they come into a larger room."

The first known drawings of animal red blood cells by Leeuwenhoek were contained in letters dated March 3, 1682 (salmon red blood cells) and July 16, 1683 (frog red blood cells). Leeuwenhoek's first drawing of human red blood cells (long thought to be the first drawing ever of human red blood cells) was contained in a letter dated July 7, 1700. Leeuwenhoek, despite many years of study of red blood cells, continued to mistakenly view them as spheres (globules in his terminology).

2) Marcello Malpighi (1628-1694):

Malpighi was a distinguished anatomist whose name has been applied to the malpighian tubules of insects (their equivalent of a kidney) and to a layer of the epidermis of the skin. Indeed, the first observation of the existence of red blood cells (from a dog) appears to have been made by Malpighi in a March 1661 letter to Borelli (published in 1687) in which he said: "By blood I do not understand the aggregate of the four common humors - both biles, blood and pituita, but all that which flows continuously through the veins and arteries, and which consists of an infinite number of particles." In a 1666 publication, Malpighi described a human blood clot. He noted the redish cells which escaped when one washed the clot. He noted "some very small red particles" which were independent because they "can roll and turn helter-skelter in the little places." Thus Malpighi described (in letter format) red blood cells some 13 years before Leeuwenhoek (1661 vs 1674). Indeed, Malpighi also published observations on human red blood cells some eight years before Leeuwenhoek's 1674 publication on observations of "round globuls" in his own blood.

3) Jan Swammerdam (1637-1680):

Swammerdam was trained as a physician and he visited Leeuwenhoek on several occasions in 1674. Leeuwenhoek wrote of these visits: "Dr. Swammerdam hath again within this fort-night visited me twice, accompanied with a Gentleman, to both of which I have shew'd many of these Microscopical Observations, and of such others as I had formerly spoken to him about; perceiving that his speculations are busy upon this subject, and that probably he will discourse more largely of it than I have done hitherto." Swammerdam used a glass capillary tube (invented by Leeuwenhoek in 1774) to withdraw human blood from a louse and to observe red blood cells. In a January 1678 letter to Thevenot, he refers to these "small globuls" and states "nothing more beautiful is to be seen than that, especially if one lets it run to and fro, as when every globulus separately is revolving like a circle." In this letter he includes the drawing shown in Fig 3, which is the first known illustration of human red blood cells. In a letter in April of the same year (1678), Swammerdam acknowledges learning the use of glass capillary tubes from Leeuwenhoek whom he describes in these terms: "It is impossible to go into discussion with him, as he is biased, and reasons in a very barbarical way, having no academic education." However, the interesting thing, in terms of priority of discovery of red blood cells, is evidence that Swammerdam may have made observations on the red blood cells of the frog in 1663 (or even earlier). Swammerdam is known to have demonstrated frog dissections in 1663 and in an

undated manuscript appended to a 1737-38 book Swammerdam describes "a vast number of orbicular particles, of a flat oval but regular figure" in frog blood. [2]

Red cells formation (erythropoiesis):

Because of the inability of erythrocytes (red blood cells) to divide to replenish their numbers, the old ruptured cells must be replaced by totally new cells. They meet their demise because they don't have the usual specialized intracellular machinery, which controls cell growth and repair, leading to a short life span of 120 days.

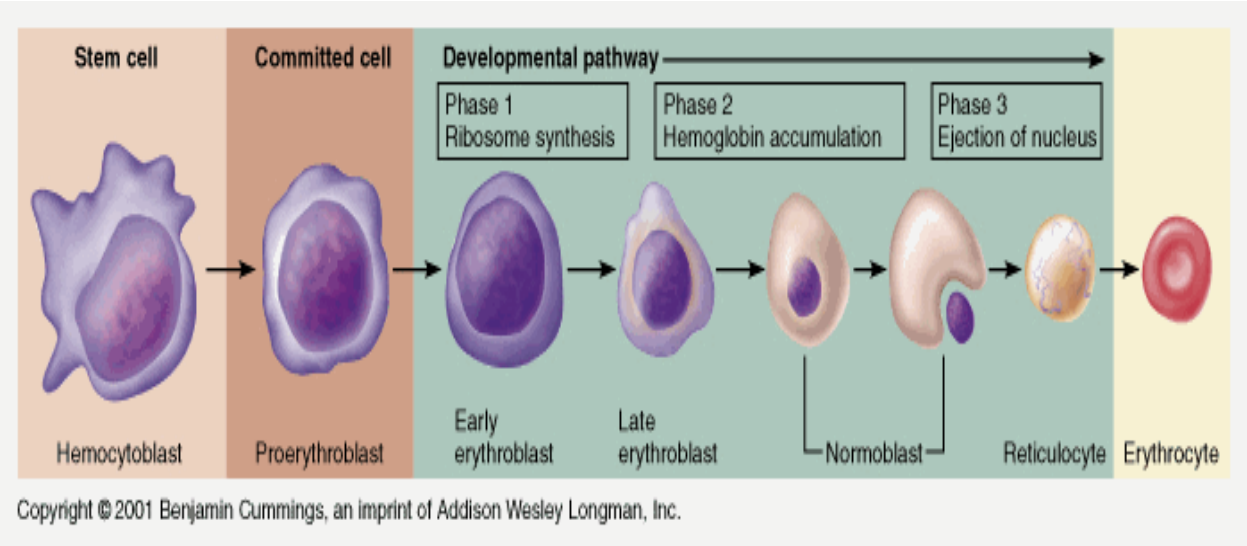
This short life span necessitates the process erythropoiesis, which is the formation of red blood cells. All blood cells are formed in the bone marrow. This is the erythrocyte factory, which is soft, highly cellar tissue that fills the internal cavities of bones.

Red blood cells differentiation:

Erythrocyte differentiation takes place in 8 stages. It is the pathway through which an erythrocyte matures from a hemocytoblast into a full-blown erythrocyte. The first seven all take place within the bone marrow. After stage 7 the cell is then released into the bloodstream as a reticulocyte, where it then matures 1-2 days later into an erythrocyte. The stages are as follows:

Erythrocytes are derived in the red bone marrow from pluripotent stem cells that give rise to all types of blood cells. Myeloid stem cells are partially differentiated cells that give rise to erythrocytes and several other types of blood cells.

Nucleated erythroblasts are committed to becoming mature erythrocytes. These cells extrude their nucleus and organelles, making more room for hemoglobin. Reticulocytes are immature red blood cells that contain organelle remnants. Mature erythrocytes are released into the capillaries..



Distinct Characteristics of Erythrocytes during Erythropoiesis:

These characteristics can be seen during erythrocyte maturation:

•The size of the cell decreases

•The cytoplasm volume increases

•Initially, there is a nucleus and as the cell matures the size of the nucleus decreases until it vanishes with the condensation of the chromatin material. [3]

Erythropoietin:

•*Erythropoietin (EPO) is a hormone produced by the kidney.*

•*Erythropoietin promotes the formation of red blood cells by the bone marrow.*

•*The erythropoietin hormone level can be detected and measured in the blood (the EPO test).*

•*Measurement of the blood erythropoietin level can be used to detect certain medical conditions.*

•*Erythropoietin can be synthesized and used as a treatment of some forms of anemia.*

•*Erythropoietin has been misused as a performance-enhancing drug by some athletes.*

- ✓ Erythropoietin (EPO) is a hormone produced by the kidney that promotes the formation of red blood cells by the bone marrow.
- ✓ The kidney cells that make erythropoietin are sensitive to low oxygen levels in the blood that travels through the kidney. These cells make and release erythropoietin when the oxygen level is too low. A low oxygen level may indicate a diminished number of red blood cells (anemia), or hemoglobin molecules that carry oxygen through the body.

    - ✓ Erythropoietin stimulates the bone marrow to produce more red blood cells. The resulting rise in red cells increases the oxygen-carrying capacity of the blood.
      As the prime regulator of red cell production, erythropoietin's major functions are to:
      1. Promote the development of red blood cells.
      2. Initiate the synthesis of hemoglobin, the molecule within red blood cells that transports oxygen.

      Chemically, erythropoietin a protein with an attached sugar (a glycoprotein). It is one of a number of similar glycoproteins that serve as stimulants for the growth of specific types of blood cells in the bone marrow.

      Erythropoietin is produced to a lesser extent by the liver. Only about 10% of erythropoietin is produced in the liver. The erythropoietin gene has been found on human chromosome 7 (in band 7q21). Different DNA sequences flanking the erythropoietin gene act to control liver versus kidney production of erythropoietin.

The erythropoietin hormone can be detected and measured in the blood. An abnormal level of erythropoietin in the blood can indicate bone marrow disorders, (such as polycythemia, or increased red blood cell production) kidney diseases, or erythropoietin abuse. Testing erythropoietin blood levels is of value if:

•Too little erythropoietin might be responsible for too few red blood cells (anemia), especially anemia related to kidney disease・.

・Too much erythropoietin might be causing too many red blood cells (polycythemia).

・Too much erythropoietin might be evidence for a kidney tumor.

・Too much erythropoietin in an athlete may suggest erythropoietin abuse.

The patient is usually asked to fast for 8-10 hours (overnight) and sometimes to lie quietly and relax for 20 or 30 minutes before the test. The test requires a routine sample of blood, which is sent to the laboratory for analysis. (4)

Red blood cells functions:

The primary function of red blood cells is to transport oxygen to body cells and deliver carbon dioxide to the lungs. A red blood cell has what is known as a biconcave shape. Both sides of the cell's surface curve inward like the interior of a sphere. This shape aids in a red blood cell's ability to maneuver through tiny blood vessels to deliver oxygen to organs and tissues. Red blood cells are also important in determining human blood type. Blood type is determined by the presence or absence of certain identifiers on the surface of red blood cells. These identifiers, also called antigens, help the body's immune system to recognize its own red blood cell type. (5)

Erythrocytes structure:

20 to 30 trillion red blood cells (erythrocytes; RBCs) circulate in the bloodstream of an average adult.

RBCs are small, disc-shaped cells that measure 7 – 8 micrometers (μm) in diameter. As they mature, RBCs extrude their nucleus and fill their cytoplasm with hemoglobin (Hb) molecules, which bind and transport oxygen (O2) and carbon dioxide (CO2).

Mature RBCs are also biconcave in shape, which means they are indented in the middle and raised along the margins. The thinnest area of an RBC normally measures about 1 μm and the thickest area measures 2-3 μm.

Due to their shape, RBCs appear pale in the middle and darker along the edges.

The biconcave shape provides RBCs with more surface area than other spherical cells of the same diameter. The additional surface area increases the rate of gas (O2; CO2) exchange with the tissues and lungs.

The biconcave shape also makes RBCs more flexible, which helps them flow through the narrow openings of the capillaries more easily. [6]

Anemia

Anemia is one type of red blood cell disorder. A lack of the mineral iron in your blood commonly causes this disorder. Your body needs iron to produce the protein hemoglobin, which helps your red blood cells (RBCs) carry oxygen from your lungs to the rest of your body. There are many types of anemia.

Iron deficiency anemia: Iron deficiency anemia occurs when your body does not have enough iron. You may feel tired and short of breath because your RBCs are not carrying enough oxygen to your lungs. Iron supplementation usually cures this type of anemia.

Pernicious anemia: Pernicious anemia is an autoimmune condition in which your body is unable to absorb sufficient amounts of vitamin B-12. This results in a low number of RBCs. It is called "pernicious," meaning dangerous, because it used to be untreatable and often fatal. Now, B-12 injections usually cure this type of anemia.

Aplastic anemia: Aplastic anemia is a rare but serious condition in which your bone marrow stops making enough new blood cells. It can occur suddenly or slowly, and at any age. It can leave you feeling tired and unable to fight off infections or uncontrolled bleeding.

Autoimmune hemolytic anemia (AHA): Autoimmune hemolytic anemia (AHA) causes your immune system to destroy your red blood cells faster than your body can replace them. This results in you having too few RBCs.

Sickle cell anemia: Sickle cell anemia (SCA) is a type of anemia that draws its name from the unusual sickle shape of the affected red blood cells. Due to a genetic mutation, the red blood cells of people with sickle cell anemia contain abnormal hemoglobin molecules, which leave them rigid and curved. The sickle-shaped red blood cells can't carry as much oxygen to your tissues as normal red blood cells can. They may also become stuck in your blood vessels, blocking blood flow to your organs.

Thalassemia:

Thalassemia is a group of inherited blood disorders. These disorders are caused by genetic mutations that prevent the normal production of hemoglobin. When red blood cells do not have enough hemoglobin, oxygen doesn't get to all parts of the body. Organs then do not function properly. These disorders can result in:

- ✓ bone deformities
- ✓ enlarged spleen
- ✓ heart problems
- ✓ Growth and developmental delays in children.

Polycythemia vera:

Polycythemia is a blood cancer caused by a gene mutation. If you have polycythemia, your bone marrow makes too many red blood cells. This causes your blood to thicken and flow more

slowly, putting you at risk for blood clots that can cause heart attacks or strokes. There is no known cure. Treatment involves phlebotomy, or removing blood from your veins, and medication. [7]

Overview:

It is a condition that develops when your blood lacks enough healthy red blood cells or hemoglobin. Hemoglobin is a main part of red blood cells and binds oxygen. If you have too few or abnormal red blood cells, or your hemoglobin is abnormal or low, the cells in your body will not get enough oxygen. Symptoms of anemia -- like fatigue -- occur because organs aren't getting what they need to function properly.

Anemia is the most common blood condition in the U.S. It affects about 3.5 million Americans. Women, young children, and people with chronic diseases are at increased risk of anemia. Important factors to remember are:

•Certain forms of anemia are hereditary and infants may be affected from the time of birth.

•Women in the childbearing years are particularly susceptible to iron-deficiency anemia because of the blood loss from menstruation and the increased blood supply demands during pregnancy.

•Older adults also may have a greater risk of developing anemia because of poor diet and other medical conditions. [8]

<u>Iron deficiency anemia:</u>

Iron is very important in maintaining many body functions, including the production of hemoglobin, the molecule in your blood that carries oxygen. Iron is also necessary to maintain healthy cells, skin, hair, and nails.

Iron from the food you eat is absorbed into the body by the cells that line the gastrointestinal tract; the body only absorbs a small fraction of the iron you ingest. The iron is then released into the blood stream, where a protein called transferrin attaches to it and delivers the iron to the liver. Iron is stored in the liver as ferritin and released as needed to make new red blood cells in the bone marrow. When red blood cells are no longer able to function (after about 120 days in circulation), they are re-absorbed by the spleen. Iron from these old cells can also be recycled by the body.

Iron deficiency is very common, especially among women and in people who have a diet that is low in iron. The following groups of people are at highest risk for iron-deficiency anemia:

•Women who menstruate, particularly if menstrual periods are heavy

•Women who are pregnant or breastfeeding or those who have recently given birth

•People who have undergone major surgery or physical trauma

•People with gastrointestinal diseases such as celiac disease (sprue), inflammatory bowel diseases such as ulcerative colitis, or Crohn disease

•People with peptic ulcer disease

•People who have undergone bariatric procedures, especially gastric bypass operations

•Vegetarians, vegans, and other people whose diets do not include iron-rich foods (Iron from vegetables, even those that are iron-rich, is not absorbed as well as iron from meat, poultry, and fish.)

•Children who drink more than 16 to 24 ounces a day of cow's milk (Cow's milk not only contains little iron, but it can also decrease absorption of iron and irritate the intestinal lining causing chronic blood loss.)

Other less common causes of iron deficiency include:

•Blood loss from the gastrointestinal tract due to gastritis (inflammation of the stomach), esophagitis (inflammation of the esophagus), ulcers in the stomach or bowel, hemorrhoids, angiodysplasia (leaky blood vessels similar to varicose veins in the gastrointestinal tract), infections such as diverticulitis, or tumors in the esophagus, stomach, small bowel, or colon

•Blood loss from chronic nosebleeds

•Blood loss from the kidneys or bladder

•Frequent blood donations

•Intravascular hemolysis, a condition in which red blood cells break down in the blood stream, releasing iron that is then lost in the urine. This sometimes occurs in people who engage in vigorous exercise, particularly jogging. This can cause trauma to small blood vessels in the feet, so called "march hematuria." Intravascular hemolysis can also be seen in other conditions including damaged heart valves or rare disorders such as thrombotic thrombocytopenia purpura (TTP) or diffuse intravascular hemolysis (DIC). [9]

Symptoms of IDA:

Initially, iron deficiency anemia can be so mild that it goes unnoticed. But as the body becomes more deficient in iron and anemia worsens, the signs and symptoms intensify.

Iron deficiency anemia signs and symptoms may include:

•Extreme fatigue

•Weakness

•Pale skin

•Chest pain, fast heartbeat or shortness of breath

•Headache, dizziness or lightheadedness

•Cold hands and feet

•Inflammation or soreness of your tongue

•Brittle nails

•Unusual cravings for non-nutritive substances, such as ice, dirt or starch

•Poor appetite, especially in infants and children with iron deficiency anemia.

Causes:

Iron deficiency anemia occurs when your body doesn't have enough iron to produce hemoglobin. Hemoglobin is the part of red blood cells that gives blood its red color and enables the red blood cells to carry oxygenated blood throughout your body.

Causes of iron deficiency anemia include:

•*Blood loss:* Blood contains iron within red blood cells. So if you lose blood, you lose some iron. Women with heavy periods are at risk of iron deficiency anemia because they lose blood during menstruation. Slow, chronic blood loss within the body — such as from a peptic ulcer, a hiatal hernia, a colon polyp or colorectal cancer — can cause iron deficiency anemia. Gastrointestinal bleeding can result from regular use of some over-the-counter pain relievers, especially aspirin.

•*A lack of iron in your diet:* Your body regularly gets iron from the foods you eat. If you consume too little iron, over time your body can become iron deficient. Examples of iron-rich foods include meat, eggs, leafy green vegetables and iron-fortified foods. For proper growth and development, infants and children need iron from their diets, too.

•*An inability to absorb iron:* Iron from food is absorbed into your bloodstream in your small intestine. An intestinal disorder, such as celiac disease, which affects your intestine's ability to absorb nutrients from digested food, can lead to iron deficiency anemia. If part of your small intestine has been bypassed or removed surgically, that may affect your ability to absorb iron and other nutrients.

•*Pregnancy*: Without iron supplementation, iron deficiency anemia occurs in many pregnant women because their iron stores need to serve their own increased blood volume as well as be a source of hemoglobin for the growing fetus. [(10)]

Diagnosis:

Although the history and physical examination can lead to the recognition of the condition and help establish the etiology, iron deficiency anemia is primarily a laboratory diagnosis.

Useful tests include a complete blood count (CBC); a peripheral smear; serum iron, total iron-binding capacity (TIBC), and serum ferritin; evaluation for hemosiderinuria, hemoglobinuria, and pulmonary hemosiderosis; hemoglobin electrophoresis and measurement of hemoglobin A2 and fetal hemoglobin; and reticulocyte hemoglobin content.

Other laboratory tests (e.g., stool testing, incubated osmotic fragility testing, measurement of lead in tissue, and bone marrow aspiration) are useful for establishing the etiology of iron deficiency anemia and for excluding or establishing a diagnosis of 1 of the other microcytic anemias.

Complete Blood Count:

The CBC documents the severity of the anemia. In chronic iron deficiency anemia, the cellular indices show a microcytic and hypochromic erythropoiesis—that is, both the mean corpuscular volume (MCV) and the mean corpuscular hemoglobin concentration (MCHC) have values below the normal range for the laboratory performing the test. Reference range values for MCV and MCHC are 83-97 fL and 32-36 g/dL, respectively.

Often, the platelet count is elevated (>450,000/µL); this elevation normalizes after iron therapy. The white blood cell (WBC) count is usually within reference ranges (4500-11,000/µL), but it may be elevated.

If the CBC is obtained after blood loss, the cellular indices do not enter the abnormal range until most of the erythrocytes produced before the bleed are destroyed at the end of their normal lifespan (120 d).

Peripheral Smear:

Examination of the peripheral smear is an important part of the workup of patients with anemia. Examination of the erythrocytes shows microcytic and hypochromic red blood cells in chronic iron deficiency anemia. The Microcytosis is apparent in the smear long before the MCV is decreased after an event producing iron deficiency. Platelets usually are increased in this disorder.

In iron deficiency anemia, unlike thalassemia, target cells usually are not present, and Anisocytosis and poikilocytosis are not marked. This condition lacks the intraerythrocytic crystals seen in hemoglobin C disorders.

Combined folate deficiency and iron deficiency are commonplace in areas of the world with little fresh produce and meat. The peripheral smear reveals a population of macrocytes mixed among the microcytic hypochromic cells. This combination can normalize the MCV.

Serum Iron, Total Iron-Binding Capacity, and Serum Ferritin:

Low serum iron and ferritin levels with an elevated TIBC are diagnostic of iron deficiency. While a low serum ferritin is virtually diagnostic of iron deficiency, a normal serum ferritin can be seen in patients who are deficient in iron and have coexistent diseases (e.g., hepatitis or anemia of chronic disorders). These test findings are useful in distinguishing iron deficiency anemia from other microcytic anemias.

Evaluation for Hemosiderinuria, Hemoglobinuria, and Pulmonary Hemosiderosis:

Iron deficiency anemia can occur from loss of body iron in the urine. If a freshly obtained urine specimen appears bloody but contains no red blood cells, suspect hemoglobinuria. Obtain confirmation in the laboratory that the pigment is hemoglobin and not myoglobin. This can be

accomplished easily because 60% ammonium sulfate precipitates hemoglobin but not myoglobin.

Hemoglobinuria classically is ascribed to paroxysmal nocturnal hemoglobinuria, but it can occur with any brisk intravascular hemolytic anemia. In the early days of heart surgery with implantation of artificial valves, this mechanism of producing iron deficiency anemia was commonplace in large university hospitals. Today, with better prostheses, it has become a less frequent clinical problem. With less severe hemolytic disorders, there may be no significant hemoglobinuria.

Investigate renal loss of iron by staining the urine sediment for iron. Hemosiderin is detected intracellularly. Most of these patients have a low or absent plasma haptoglobin. Similarly, pulmonary hemosiderosis can result in sufficient loss of iron as hemosiderin from the lungs.

Hemoglobin Studies:

Hemoglobin electrophoresis and measurement of hemoglobin A:

Hemoglobin electrophoresis and measurement of hemoglobin A2 and fetal hemoglobin are useful in establishing either beta-thalassemia or hemoglobin C or D as the etiology of the microcytic anemia. Unfortunately, simple tests do not exist for alpha-thalassemia in most laboratories, and it is a diagnosis of exclusion.

Reticulocyte hemoglobin content:

Mateos Gonzales et al assessed the diagnostic efficiency of commonly used hematologic and biochemical markers, as well as the reticulocyte hemoglobin content (CHr) in the diagnosis of iron deficiency in children, with or without anemia. The investigators identified CHr and iron serum as the only parameters that were independently associated with iron deficiency ($P < .05$), and CHr was the strongest predictor of iron deficiency and iron deficiency anemia.

Mateos Gonzalez et al concluded that measurement of CHr may be a reliable method to assess deficiencies in tissue iron supply and, in combination with a CBC, may be an alternative to the traditional biochemical panel for the diagnosis of iron deficiency in children.

Stool testing:

Testing stool for the presence of hemoglobin is useful in establishing gastrointestinal (GI) bleeding as the etiology of iron deficiency anemia. Usually, chemical testing that detects more than 20 mL of blood loss daily from the upper GI tract is employed. More sensitive tests are available; however, they produce a high incidence of false-positive results in people who eat meat. Severe iron deficiency anemia can occur in patients with a persistent loss of less than 20 mL/d.

To detect blood loss, the patient can be placed on a strict vegetarian diet for 3-5 days and the stool can be tested for hemoglobin with a benzidine method, or red blood cells (RBCs) can be radiolabeled with radiochromium and retransfused. Stools are collected, and the radioactivity is quantified in a gamma-detector and compared to the radioactivity in a measured quantity of the

patient's blood. An immunologic method of detecting human species-specific hemoglobin in stool is under development and could increase specificity and sensitivity.

Incubated osmotic fragility:

Incubated osmotic fragility is useful. Microspherocytosis may produce a low-normal or slightly abnormal MCV; however, the MCHC usually is elevated rather than decreased, and the peripheral smear shows a lack of central pallor rather than hypochromia. Spherocytosis can normally be separated from iron deficiency anemia by peripheral blood smear.

Tissue lead concentrations:

Measure tissue lead concentrations. Chronic lead poisoning may produce a mild microcytosis. The anemia probably is related to the anemia of chronic disorders. The incidence of lead poisoning is greater in individuals who are iron deficient than in healthy subjects because increased absorption of lead occurs in individuals who are iron deficient. Paint in old houses has been a source of lead poisoning in children and painters.

Bone marrow aspiration:

A bone marrow aspirate can be diagnostic of iron deficiency. The absence of stainable iron in a bone marrow aspirate that contains spicules and a simultaneous control specimen containing stainable iron permit establishment of a diagnosis of iron deficiency without other laboratory tests.

A bone marrow aspirate stained for iron (Perls stain) can be diagnostic of iron deficiency, provided that spicules are present in the smear and that a control specimen containing iron is performed at the same time. Although this test has largely been displaced in the diagnosis of iron deficiency by serum iron, TIBC, and serum ferritin testing, the absence of stainable iron in a bone marrow aspirate is the criterion standard for the diagnosis of iron deficiency.

This test is diagnostic in identifying the sideroblastic anemias by showing ringed sideroblasts in the aspirate stained with Perls stain. Occasionally, it is useful in separating patients with the anemia of chronic disorders or alpha-thalassemia from patients with iron deficiency, and it is useful in identifying patients with both iron deficiency and the anemia of chronic disorders.

Histologic Findings:

The absence of stainable iron in body tissues, including the bone marrow and liver, is the most useful histologic finding in individuals who are iron deficient. Nonspecific abnormalities of epithelial tissues are reported in iron deficiency. These include gastric atrophy and clubbing of the small intestinal villi. While they suggest that iron deficiency is a pantropic disorder, they have little clinical diagnostic value. [(11)]

Iron deficiency anemia in women:

Pregnancy, significant menstrual bleeding, and uterine fibroids are all reasons why women are more likely to experience iron deficiency anemia.

Heavy menstrual bleeding occurs when a woman bleeds more or longer than women typically bleed during menstruation. According to the Centers for Disease Control and Prevention, typical menstrual bleeding lasts for 4 to 5 days and the amount of blood lost ranges from 2 to 3 tablespoons. Women with excess menstrual bleeding typically bleed for more than seven days and lose twice as much blood as normal.

According to the National Heart, Lung, and Blood Institute, an estimated 20 percent of women of childbearing age have iron deficiency anemia. Pregnant women are even more likely to have iron deficiency anemia because they require greater amounts of blood to support their growing babies.

A pelvic ultrasound can help a doctor look for the source of excess bleeding during a woman's period, such as fibroids. Like iron deficiency anemia, uterine fibroids often don't cause symptoms. They occur when muscular tumors grow in the uterus. While they're not usually cancerous, they can cause heavy menstrual bleeding that can lead to iron deficiency anemia.

Complications:

Most cases of iron deficiency anemia are mild and don't cause complications. The condition can usually be corrected easily. However, if anemia or iron deficiency is left untreated, it can lead to other health problems. These include:

Rapid or irregular heartbeat:

When you're anemic, your heart has to pump more blood to make up for the low amount of oxygen. This can lead to irregular heartbeat. In severe cases, it can lead to heart failure or an enlarged heart.

Pregnancy complications:

In severe cases of iron deficiency, a child may be born prematurely or with a low birth weight. Most pregnant women take iron supplements as part of their prenatal care to prevent this from happening.

Delayed growth in infants and children:

Infants and children who are severely deficient in iron may experience delayed growth and development. They may also be more prone to infections. [(12)]

Iron Deficiency Anemia Treatment & Management:

Medical care starts with establishing the diagnosis and reason for the iron deficiency. In most patients, the iron deficiency should be treated with oral iron therapy, and the underlying etiology should be corrected so the deficiency does not recur. However, avoid giving iron to patients who have a microcytic iron-overloading disorder (e.g., thalassemia, sideroblastic anemia). Do not administer parenteral iron therapy to patients who should be treated with oral iron, as anaphylaxis may result.

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Transfer of a patient rarely is required for treatment of simple iron deficiency anemia. However, it may be necessary to identify the etiology of the anemia, such as occult blood loss undetected with chemical testing of stool specimens; for identification of a source of bleeding that requires endoscopic examinations or angiography; or for treatment of an underlying major illness (e.g., neoplasia, ulcerative colitis).

The British Society of Gastroenterology guidelines suggest that all patients require iron supplementation and that parenteral iron can be used if oral preparations are not well tolerated. The guidelines also state that blood transfusions should be reserved for patients who are at risk for, or who have, cardiovascular instability due to their anemia.

Treatment guidelines from the American College of Physicians (ACP) for adult patients with anemia and iron deficiency include the following:

• A restrictive red blood cell transfusion strategy is recommended for hospitalized patients with coronary heart disease, with the trigger hemoglobin threshold lowered to 7-8 g/dL (recommendation: weak; quality of evidence: low).

• Erythropoiesis-stimulating agents are not recommended for patients with mild to moderate anemia and either congestive heart failure or coronary heart disease (recommendation: strong; quality of evidence: moderate).

Iron Therapy:

Oral ferrous iron salts are the most economical and effective medication for the treatment of iron deficiency anemia. Of the various iron salts available, ferrous sulfate is the one most commonly used.

Although the traditional dosage of ferrous sulfate is 325 mg (65 mg of elemental iron) orally three times a day, lower doses (e.g., 15-20 mg of elemental iron daily) may be as effective and cause fewer side effects. To promote absorption, patients should avoid tea and coffee and may take vitamin C (500 units) with the iron pill once daily.

However, a study by Moretti et al suggests that the standard dosing of iron supplements may be counterproductive. Their research focuses on the role of hepcidin, which regulates systemic iron balance, partly in response to plasma iron levels. They found that when a large oral dose of iron is taken in the morning, the resulting increase in the plasma iron level stimulates an increase in hepcidin, which in turn will interfere with the absorption of an iron dose taken later in the day; indeed, suppression of iron absorption could last as long as 48 hours.

In one part of their study, twice-daily doses of 60 mg or greater resulted in an increase in serum hepcidin levels after the first dose and a 35-45% decrease in the amount of iron that was absorbed from the second dose. With increasing doses, study subjects showed an increase in the absolute amount of iron absorbed, but a decrease in the fraction of the dose that was absorbed. A six-fold increase in iron dose (from 40 mg to 240 mg) resulted in only a three-fold increase in iron absorbed. In another part of the study, total iron absorbed from a morning and an afternoon dose on one day plus a morning dose the next day was not significantly greater than absorption from two consecutive morning doses.

Moretti et al concluded that providing lower dosages and avoiding twice-daily dosing will maximize fractional iron absorption. They note that although the short-term effects observed in their study will require confirmation in longer-term studies, their results support supplementation with 40-80 mg of iron taken every other day. A possible additional benefit of this schedule may be that improving absorption will reduce gastrointestinal exposure to unabsorbed iron and thereby reduce adverse effects from supplements.

Claims are made that other iron salts (e.g., ferrous gluconate) are absorbed better than ferrous sulfate and have less morbidity. Generally, the toxicity is proportional to the amount of iron available for absorption. If the quantity of iron in the test dose is decreased, the percentage of the test dose absorbed is increased, but the quantity of iron absorbed is diminished.

Ferric citrate (Auryxia) gained US Food and Drug Administration (FDA) approval in November 2017 for treatment of iron deficiency anemia in adults with chronic kidney disease (CKD) not on dialysis. Each tablet of ferric citrate 1 gram is equivalent to 210 mg of ferric iron. Approval was based on results from a 24-week placebo-controlled phase 3 clinical trial in 234 adults with stage 3-5 non–dialysis-dependent CKD. Trial participants had hemoglobin levels between 9-11.5 g/dL and were intolerant to or had an inadequate response to prior treatment with oral iron supplements. The starting dose in the study was 3 tablets daily with meals; the mean dose was 5 tablets per day. Importantly, during the study, patients were not allowed to receive any intravenous or oral iron, or erythropoiesis-stimulating agents (ESAs). Significant increases in hemoglobin levels of >1 g/dL at any point during the 16-week efficacy period occurred in 52.1% of patients taking ferric citrate compared with 19.1% in the placebo group).

Pernicious anemia:

•Pernicious anemia is defined as a type of vitamin B12 deficiency that results from impaired uptake of vitamin B-12 due to the lack of a substance known as intrinsic factor (IF) produced by the stomach lining.

•Pernicious anemia is a condition caused by too little vitamin B12 in the body. It is one form of vitamin B12 deficiency anemia.

•Vitamin B12 helps the body make healthy red blood cells and helps keep nerve cells healthy. It is found in animal foods, including meat, fish, eggs, milk, and other dairy products.

•The most common cause of pernicious anemia is the loss of stomach cells that make intrinsic factor. Intrinsic factor helps the body absorb vitamin B12 in the intestine. The loss of parietal cells may be due to destruction by the body's own immune system.

•Pernicious anemia can cause permanent damage to nerves and other organs if it goes on for a long time without being treated. It also raises the risk for developing stomach cancer.

•Common signs and symptoms of vitamin B12 deficiency, seen in pernicious anemia are:

◦Feeling tired and weak

◦Tingling and numbness in hands and feet

◦A bright red, smooth tongue

•Pernicious anemia is diagnosed using family history and medical history, a physical exam, and diagnostic tests and procedures.

•Pernicious anemia is easy to treat with vitamin B12 pills or shots as well as diet changes. Life-long treatment is needed.

•Complications caused by untreated pernicious anemia may be reversible with treatment.

•Doctors don't know how to prevent pernicious anemia that is caused by the immune system destroying stomach cells.

•Eating foods high in vitamin B12 and folic acid can help prevent vitamin B12 deficiency caused by a poor diet.

Pernicious anemia is a disease where large, immature, nucleated cells (megaloblasts, which are forerunners of red blood cells) circulate in the blood, and do not function as blood cells; it is a disease caused by impaired uptake of vitamin B-12 due to the lack of intrinsic factor (IF) in the gastric mucosa. It was termed "pernicious" because before it was learned that vitamin B-12 could treat the anemia, most people that developed the disease died from it.

Pernicious anemia is due to an inability to absorb vitamin B-12 (also known as cobalamin or Cbl) from the gastrointestinal tract. Humans get vitamin B-12 from animal products; both meat and dairy products are dietary sources of vitamin B-12. The body is able to store vitamin B-12 for a long time, so inadequate dietary intake must persist for years before a true deficiency of vitamin B-12 is reached. Therefore, the symptoms of pernicious anemia usually do not appear for years. While pernicious anemia is most commonly diagnosed in adults with an average age of 60, a rare, congenital (inborn) type of pernicious anemia has been described.

As with other causes of anemia, symptoms related to decreased oxygen-carrying capacity of the blood can include tiredness and shortness of breath. Vitamin B-12 deficiency also interferes with the function of the nervous system, and symptoms due to nervous system damage may be apparent even before the anemia is discovered.

Pernicious anemia is most common in Caucasian persons of northern European ancestry than in other racial groups. Pernicious anemia also is termed Biermer's or Addison's anemia.

Sometimes, anemias are subclassified based upon the size and microscopic appearance of the red blood cells. In this regard, pernicious anemia is a form of megaloblastic anemia. Megaloblastic anemia refers to an abnormally large type of red blood cell (megaloblast). Megaloblasts are produced in the bone marrow when vitamin B-12 or folic acid levels are low. Megaloblastic anemia also can be caused by other disease of the bone marrow and can be a side effect of some cancer chemotherapy drugs.

Causes:

Pernicious anemia is considered to be an autoimmune disease, in which the body's own immune system mistakenly damages its own tissues. It is believed that the decreased absorption of vitamin B-12 from the gastrointestinal tract in pernicious anemia results from the presence of an autoantibody against intrinsic factor (IF), a protein made in the stomach that is necessary for the absorption of vitamin B-12. Normally, vitamin B-12 binds to intrinsic factor in the stomach, and this facilitates its absorption by the small intestine further along in the digestive process. Along with the autoimmune process that attacks the IF protein and lowers IF levels in stomach secretions, another autoimmune reaction against the stomach lining cells also occurs, resulting in a form of inflammation known as chronic atrophic gastritis.

Pernicious anemia is sometimes associated with other autoimmune diseases such as Graves' diseases, Hashimoto's thyroiditis and vitiligo (depigmentation or blanching of skin areas).

Is pernicious anemia the same as vitamin B-12 deficiency anemia?

No, pernicious anemia is one form of vitamin B-12 deficiency that results from the autoimmune process described above. However, other causes of vitamin B-12 deficiency also can produce the same signs and symptoms as pernicious anemia. Other potential causes of vitamin B-12 deficiency include surgical removal of the stomach or a portion of the stomach (total or partial gastrectomy), other gastrointestinal diseases such as celiac disease or Crohn's disease, infections of the gastrointestinal tract, longstanding use of acid-reducing medications, and poor nutrition.

Symptoms:

True pernicious anemia results from an autoimmune condition that impairs absorption of dietary vitamin B-12, resulting in vitamin B-12 deficiency. Vitamin B-12 deficiency of any cause, including pernicious anemia, will result in anemia and neurologic symptoms. Because the body has large stores of vitamin B-12, a deficiency takes many years to establish.

Vitamin B-12 deficiency affects the nervous system, leading to a variety of symptoms. Sometimes, these may be apparent before symptoms related to the anemia. Neurological symptoms vary and may be nonspecific (meaning that these are symptoms that can be caused by a number of different conditions). Feelings of numbness, tingling, weakness, lack of

coordination, clumsiness, impaired memory, and personality changes can all occur. Both sides of the body are usually affected, and the legs are typically more affected than the arms. A severe deficiency can result in more serious neurological symptoms, including severe weakness, spasticity, paraplegia, and fecal and urinary incontinence.

Symptoms of anemia are due to the reduced oxygen-carrying capacity of the blood. Shortness of breath, fatigue, dizziness, and pale skin can all occur with anemia. In anemia, the heart is placed under stress since it has to work harder to deliver enough oxygen to body tissues. This can result in heart murmurs, fast heartbeats, arrhythmias, an enlarged heart (cardiomegaly), or even heart failure. It is important to note that not all people who have vitamin B-12 deficiency and neurological symptoms also will have anemia.

A deficiency of vitamin B-12 also can alter the surface of the tongue, making it appear shiny or smooth.

Finally, sometimes pernicious anemia is diagnosed in a patient with no symptoms. In these cases, it is usually found incidentally when blood tests are ordered for another reason.

Diagnosis:

The first step is always a thorough history and physical examination by a health care practitioner. The results of this examination are used to help direct further testing. A number of laboratory tests are available that can help diagnose pernicious anemia as well as other causes of vitamin B-12 deficiency. These tests include:

•A complete blood cell count (CBC)

•Examination of a blood smear (peripheral smear) under a microscope, often performed in association with a CBC

•Blood vitamin B-12 level measurements

•Tests for the presence of autoantibodies to intrinsic factor or stomach lining cells

•Blood levels of iron and iron-binding capacity

•Folate levels (which are often reduced when vitamin B-12 levels are low)

•Blood levels of methylmalonic acid or homocysteine, both of which may be sensitive indicators of vitamin B-12 deficiency.

•The Schilling test, a measure of how well the body can absorb vitamin B-12, is less commonly used today than in the past.

•Finally, bone marrow aspiration or bone marrow biopsy may be recommended in some cases if bone marrow disorders are suspected.

Complications:

If untreated, the neurological complications of pernicious anemia can be permanent and end in death, but pernicious anemia is easily and effectively treated by the administration of vitamin B-12. Life-long treatment is required.

People with pernicious anemia have a slightly increased risk of stomach cancer when compared to the normal population. The incidence of stomach cancer in people with pernicious anemia is 2-3 times higher than in the general population of the same age.

Treatment:

The symptoms of pernicious anemia and vitamin B-12 deficiency can be treated by replenishing the vitamin B-12 supply in the body. If a condition other than pernicious anemia is responsible for vitamin B-12 deficiency, treatment also must be directed at the underlying condition. Symptoms of vitamin B-12 deficiency may be improved after just a few days of medical treatment.

Vitamin B-12 is typically given as an intramuscular injection (shot). An injection of 1000 micrograms (1 mg) of vitamin B-12 is generally given every day for one week, followed by 1 mg every week for four weeks and then 1 mg every month thereafter.

Alternative treatments for pernicious anemia include high-dose oral vitamin B-12, since a lower-efficiency absorption system for vitamin B-12 exists in the intestine that does not require the presence of IF. However, the oral dose required for this type of therapy (1 to 2 milligrams/day) is more than 200 times higher than the minimum daily vitamin B-12 requirement for adults and is significantly higher than that available in most standard multivitamins and B-12 supplements. Nasal spray and sublingual (under the tongue) preparations of vitamin B-12 also are available and are under investigation. [(14)]

Aplastic anemia:

Aplastic anemia is a condition that occurs when your body stops producing enough new blood cells. Aplastic anemia leaves you feeling fatigued and with a higher risk of infections and uncontrolled bleeding.

A rare and serious condition, aplastic anemia can develop at any age. Aplastic anemia may occur suddenly, or it can occur slowly and get worse over a long period of time. Treatment for aplastic anemia may include medications, blood transfusions or a stem cell transplant, also known as a bone marrow transplant.

Causes:

Aplastic anemia develops when damage occurs to your bone marrow, slowing or shutting down the production of new blood cells. Bone marrow is a red, spongy material inside your bones that produces stem cells, which give rise to other cells. Stem cells in the bone marrow produce blood cells — red cells, white cells and platelets. In aplastic anemia, the bone marrow is described in

medical terms as aplastic or hypoplastic — meaning that it's empty (aplastic) or contains very few blood cells (hypoplastic).

Factors that can temporarily or permanently injure bone marrow and affect blood cell production include:

•*Radiation and chemotherapy treatments:* While these cancer-fighting therapies kill cancer cells, they can also damage healthy cells, including stem cells in bone marrow. Aplastic anemia can be a temporary side effect of these treatments.

•*Exposure to toxic chemicals:* Exposure to toxic chemicals, such as some used in pesticides and insecticides, may cause aplastic anemia. Exposure to benzene — an ingredient in gasoline — also has been linked to aplastic anemia. This type of anemia may get better on its own if you avoid repeated exposure to the chemicals that caused your initial illness.

- *Use of certain drugs:* Some medications, such as those used to treat rheumatoid arthritis and some antibiotics, can cause aplastic anemia.

•*Autoimmune disorders*: An autoimmune disorder, in which your immune system begins attacking healthy cells, may involve stem cells in your bone marrow.

•*A viral infection*: Viral infections that affect bone marrow may play a role in the development of aplastic anemia in some people. Viruses that have been linked to the development of aplastic anemia include hepatitis, Epstein-Barr, cytomegalovirus, parvovirus B19 and HIV.

•*Pregnancy*: Aplastic anemia that occurs in pregnancy may be related to an autoimmune problem — your immune system may attack your bone marrow during pregnancy.

•*Unknown factors*: In many cases, doctors aren't able to identify the cause of aplastic anemia. This is called idiopathic aplastic anemia.

Confusion with myelodysplastic syndrome:

Aplastic anemia can be mistaken for a condition called myelodysplastic syndrome. In this group of disorders, the bone marrow produces new blood cells, but they're deformed and underdeveloped. The bone marrow in myelodysplastic syndrome is sometimes called hyperplastic — meaning that it's packed with blood cells. But some people with myelodysplastic syndrome have empty marrow that's difficult to distinguish from aplastic anemia.

Connections with other rare disorders:

Some people with aplastic anemia also have a rare disorder known as paroxysmal nocturnal hemoglobinuria. This disorder causes red blood cells to break down too soon. Paroxysmal nocturnal hemoglobinuria can lead to aplastic anemia, or aplastic anemia can evolve into paroxysmal nocturnal hemoglobinuria.

Fanconi's anemia is a rare, inherited disease that leads to aplastic anemia. Children born with it tend to be smaller than average and have birth defects, such as underdeveloped limbs. The disease is diagnosed with the help of blood tests.

Risk factors:

Aplastic anemia is rare. Factors that may increase your risk include:

•Treatment with high-dose radiation or chemotherapy for cancer

•Exposure to toxic chemicals

•The use of some prescription drugs — such as chloramphenicol, which is used to treat bacterial infections, and gold compounds used to treat rheumatoid arthritis

•Certain blood diseases, autoimmune disorders and serious infections

•Pregnancy, rarely. [15]

Symptoms:

Aplastic anemia symptoms may include:

•Fatigue

•Shortness of breath with exertion

•Rapid or irregular heart rate

•Pale skin

•Frequent or prolonged infections

•Unexplained or easy bruising

•Nosebleeds and bleeding gums

•Prolonged bleeding from cuts

•Skin rash

•Dizziness

•Headache.

Aplastic anemia can progress slowly over weeks or months, or it may come on suddenly. The illness may be brief, or it may become chronic. Aplastic anemia can be very severe and even fatal.

Diagnosis:

•Blood tests. Normally, red blood cell, white blood cell and platelet levels stay within a certain range. Your doctor may suspect aplastic anemia when all three of these blood cell levels are very low.

•Bone marrow biopsy. To confirm a diagnosis, you'll need to undergo a bone marrow biopsy. In this procedure, a doctor uses a needle to remove a small sample of bone marrow from a large bone in your body, such as your hipbone. The bone marrow sample is examined under a microscope to rule out other blood-related diseases. In aplastic anemia, bone marrow contains fewer blood cells than normal.

Treatment:

Treatments for aplastic anemia may include observation for mild cases, blood transfusions and medications for more-serious cases, and in severe cases, bone marrow transplantation. Severe aplastic anemia, in which your blood cell counts are extremely low, is life-threatening and requires immediate hospitalization for treatment.

Blood transfusions:

Treatment for aplastic anemia usually involves blood transfusions to control bleeding and relieve anemia symptoms. Blood transfusions aren't a cure for aplastic anemia. But they do relieve signs and symptoms by providing blood cells that your bone marrow isn't producing. A transfusion may include:

•*Red blood cells*: Transfusions of red blood cells raise red blood cell counts. This helps relieve anemia and fatigue.

•*Platelets:* Transfusions of platelets help prevent excessive bleeding.

While there's generally no limit to the number of blood cell transfusions you can have, complications can sometimes arise with multiple transfusions. Transfused red blood cells contain iron that can accumulate in your body and can damage vital organs if an iron overload isn't treated. Medications can help your body get rid of excess iron.

Over time, your body may develop antibodies to transfused blood cells, making them less effective at relieving symptoms. The use of immunosuppressant medication makes this complication less likely.

Stem cell transplant:

A stem cell transplant to rebuild the bone marrow with stem cells from a donor may offer the only successful treatment option for people with severe aplastic anemia. A stem cell transplant, which is also called a bone marrow transplant, is generally the treatment of choice for people who are younger and have a matching donor — most often a sibling.

If a donor is found, your diseased bone marrow is first depleted with radiation or chemotherapy. Healthy stem cells from the donor are filtered from the blood. The healthy stem cells are injected intravenously into your bloodstream, where they migrate to the bone marrow cavities and begin generating new blood cells. The procedure requires a lengthy hospital stay. After the transplant, you'll receive drugs to help prevent rejection of the donated stem cells.

A stem cell transplant carries risks. There's a chance that your body may reject the transplant, leading to life-threatening complications. In addition, not everyone is a candidate for transplantation or can find a suitable donor.

Immunosuppressants:

For people who can't undergo a bone marrow transplant or for those whose aplastic anemia may be due to an autoimmune disorder, treatment may involve drugs that alter or suppress the immune system (immunosuppressants).

Drugs such as cyclosporine (Gengraf, Neoral, Sandimmune) and anti-thymocyte globulin are examples. These drugs suppress the activity of immune cells that are damaging your bone marrow. This helps your bone marrow recover and generate new blood cells. Cyclosporine and anti-thymocyte globulin are often used in combination.

Corticosteroids, such as methylprednisolone (Medrol, Solu-Medrol), are often given at the same time as these drugs.

Immune-suppressing drugs can be very effective at treating aplastic anemia. The downside is that these drugs further weaken your immune system. It's also possible that after you stop taking these drugs, aplastic anemia may return.

Bone marrow stimulants:

Certain drugs — including colony-stimulating factors, such as sargramostim (Leukine), filgrastim (Neupogen) and pegfilgrastim (Neulasta), and epoetin alfa (Epogen, Procrit) — may help stimulate the bone marrow to produce new blood cells. Growth factors are often used in combination with immune-suppressing drugs.

Antibiotics, antivirals:

Having aplastic anemia weakens your immune system. You have fewer white blood cells in circulation to fight off germs. This leaves you susceptible to infections.

At the first sign of infection, such as a fever, see your doctor. You don't want the infection to get worse, because it could prove life-threatening. If you have severe aplastic anemia, your doctor may give you antibiotics or antiviral medications to help prevent infections.

Other treatments:

Aplastic anemia caused by radiation and chemotherapy treatments for cancer usually improves once you complete those treatments. The same is true for most other drugs that induce aplastic anemia.

Pregnant women with aplastic anemia are treated with blood transfusions. For many women, pregnancy-related aplastic anemia improves once the pregnancy ends. If that doesn't happen, treatment is still necessary. [(16)]

Autoimmune hemolytic anemia:

Autoimmune hemolytic anemia is a group of disorders characterized by a malfunction of the immune system that produces autoantibodies, which attack red blood cells as if they were substances foreign to the body.

•Some people have no symptoms, and other people are tired, short of breath, and pale.

•Severe disease may cause jaundice or abdominal discomfort and fullness due to splenomegaly (an enlarged spleen).

•Blood tests are used to detect anemia and determine the cause of the autoimmune reaction.

•Treatment is corticosteroids or other drugs that suppress the immune system and sometimes, splenectomy (surgical removal of the spleen).

Autoimmune hemolytic anemia is an uncommon group of disorders that can occur at any age. These disorders affect women more often than men. About half of the time, the cause of autoimmune hemolytic anemia cannot be determined (idiopathic autoimmune hemolytic anemia). Autoimmune hemolytic anemia can also be caused by or occur with another disorder, such as systemic lupus erythematosus (lupus) or a lymphoma, and it can be due to the use of certain drugs, such as penicillin.

Destruction of red blood cells by autoantibodies may occur suddenly, or it may develop gradually. If caused by a virus, the destruction may stop after a period of time. In other people, red blood cell destruction persists and becomes chronic. There are two main types of autoimmune hemolytic anemia:

•Warm antibody hemolytic anemia: The autoantibodies attach to and destroy red blood cells at normal body temperature.

•Cold antibody hemolytic anemia (cold agglutinin disease): The autoantibodies become most active and attack red blood cells only at temperatures well below normal body temperature

Paroxysmal cold hemoglobinuria (Donath-Landsteiner syndrome) :is a rare type of cold antibody hemolytic anemia. Destruction of red blood cells results from exposure to cold. Red blood cells may be destroyed even when cold exposure is limited to a small area of the body, such as when the person drinks cold water or washes hands in cold water. An antibody binds to red blood cells at low temperatures and causes destruction of red blood cells within arteries and veins after warming. It occurs most often after a viral illness or in otherwise healthy people, although it occurs in some people with syphilis. The severity and rapidity of development of the anemia varies.

Symptoms:

Some people with autoimmune hemolytic anemia may have no symptoms, especially when the destruction of red blood cells is mild and develops gradually. Others have symptoms similar to

those that occur with other types of anemia (such as fatigue, weakness, and paleness), especially when the destruction is more severe or rapid.

Symptoms of severe or rapid destruction of red blood cells may include jaundice (yellowing of the skin and whites of the eyes), fever, chest pain, fainting, heart failure, and even death. When destruction persists for a few months or longer, the spleen may enlarge, resulting in a sense of abdominal fullness and, occasionally, discomfort

In people with cold antibody hemolytic anemia, the hands and feet may be cold or bluish.

When the cause of autoimmune hemolytic anemia is another disorder, symptoms of the underlying disorder, such as swollen and tender lymph nodes and fever, may dominate.

People with paroxysmal cold hemoglobinuria may have severe pain in the back and legs, headache, vomiting, and diarrhea. The urine may be dark brown.

Diagnosis:

•Blood tests:

Once blood tests show a person has anemia, doctors look for the cause. Doctors suspect increased destruction of red blood cells when a blood test shows an increase in the number of red blood cells that are immature (reticulocytes) or there is evidence of blood destruction on a blood smear (a test in which a drop of blood is spread on a slide and examined under a microscope). Alternatively, a blood test may show an increased amount of a substance called bilirubin produced by the destruction of red blood cells and a decreased amount of a protein called haptoglobin, which binds the hemoglobin released from the destroyed red cells.

Autoimmune hemolytic anemia as the cause is confirmed when blood tests detect increased amounts of certain antibodies, either attached to red blood cells (direct antiglobulin or direct Coombs test) or in the liquid portion of the blood (indirect antiglobulin or indirect Coombs test). Other tests sometimes help determine the cause of the autoimmune reaction that is destroying red blood cells.

Treatment:

•Corticosteroids

•Sometimes splenectomy

•For paroxysmal cold hemoglobinuria, avoiding the cold.

•Sometimes immunosuppressants

The best treatment for paroxysmal cold hemoglobinuria is avoidance of exposure to cold. Sometimes immunosuppressants (drugs that suppress the immune system) are also helpful.

A corticosteroid such as prednisone is usually the first choice for treatment. High doses are used at first, followed by a gradual reduction of the dose over many weeks or months.

When people do not respond to corticosteroids or when the corticosteroid causes intolerable side effects, surgery to remove the spleen (splenectomy) is often the next treatment. The spleen is removed because it is the primary place where antibody-coated red blood cells are destroyed. When destruction of red blood cells persists after removal of the spleen or when surgery cannot be done, immunosuppressants, such as cyclosporine, are used.

When red blood cell destruction is severe, blood transfusions are needed, but they do not treat the cause of the anemia and provide only temporary relief. [17]

Sickle cell anemia:

The term sickle cell disease (SCD) describes a group of inherited red blood cell disorders. People with SCD have abnormal hemoglobin, called hemoglobin S or sickle hemoglobin, in their red blood cells.

Hemoglobin is a protein in red blood cells that carries oxygen throughout the body.

“Inherited” means that the disease is passed by genes from parents to their children. SCD is not contagious. A person cannot catch it, like a cold or infection, from someone else.

People who have SCD inherit two abnormal hemoglobin genes, one from each parent. In all forms of SCD, at least one of the two abnormal genes causes a person’s body to make hemoglobin S. When a person has two hemoglobin S genes, Hemoglobin SS, the disease is called sickle cell anemia. This is the most common and often most severe kind of SCD.

Hemoglobin SC disease and hemoglobin Sβ thalassemia (thal-uh-SEE-me-uh) are two other common forms of SCD.

Causes:

Abnormal hemoglobin, called hemoglobin S, causes sickle cell disease (SCD).

The problem in hemoglobin S is caused by a small defect in the gene that directs the production of the beta globin part of hemoglobin. This small defect in the beta globin gene causes a problem in the beta globin part of hemoglobin, changing the way that hemoglobin works.

When the hemoglobin S gene is inherited from only one parent and a normal hemoglobin gene is inherited from the other, a person will have sickle cell trait. People with sickle cell trait are generally healthy.

Only rarely do people with sickle cell trait have complications similar to those seen in people with SCD. But people with sickle cell trait are carriers of a defective hemoglobin S gene. So, they can pass it on when they have a child.

If the child's other parent also has sickle cell trait or another abnormal hemoglobin gene (like thalassemia, hemoglobin C, hemoglobin D, hemoglobin E), that child has a chance of having SCD. [18]

Risk Factors:

Sickle cell disease is more common in certain ethnic groups, including:

•People of African descent, including African-Americans (among whom 1 in 12 carries a sickle cell gene)

•Hispanic-Americans from Central and South America

•People of Middle Eastern, Asian, Indian, and Mediterranean descent.

Because sickle cell disease symptoms can begin by four months of age, early diagnosis is critical. All newborns in the United States are now tested for the disease. Sickle cell disease can be identified before birth by testing a sample of amniotic fluid or tissue from the placenta. People who carry the sickle cell gene can seek genetic counseling before pregnancy to discuss options.

Symptoms:

Signs and symptoms of sickle cell disease can be mild or severe enough to require frequent hospitalizations. They may include:

•Anemia (looking pale)

•Dark urine

•Yellow eyes

•Painful swelling of hands and feet

•Frequent pain episodes

•Stunted growth

•Stroke. [19]

Diagnosis:

A blood test can check for hemoglobin S — the defective form of hemoglobin that underlies sickle cell anemia. In the United States, this blood test is part of routine newborn screening done at the hospital. But older children and adults can be tested, too.

In adults, a blood sample is drawn from a vein in the arm. In young children and babies, the blood sample is usually collected from a finger or heel. The sample is then sent to a laboratory, where it's screened for hemoglobin S.

If the screening test is negative, there is no sickle cell gene present. If the screening test is positive, further tests will be done to determine whether one or two sickle cell genes are presen

Tests to detect sickle cell genes before birth:

Sickle cell disease can be diagnosed in an unborn baby by sampling some of the fluid surrounding the baby in the mother's womb (amniotic fluid) to look for the sickle cell gene. If you or your partner has been diagnosed with sickle cell anemia or sickle cell trait, ask your doctor about whether you should consider this screening. Ask for a referral to a genetic counselor who can help you understand the risk to your baby.

Treatment:

Bone marrow transplant, also known as stem cell transplant, offers the only potential cure for sickle cell anemia. It's usually reserved for people younger than age 16 because the risks increase for people older than 16. Finding a donor is difficult, and the procedure has serious risks associated with it, including death.

As a result, treatment for sickle cell anemia is usually aimed at avoiding crises, relieving symptoms and preventing complications. Babies and children age 2 and younger with sickle cell anemia should make frequent visits to a doctor. Children older than 2 and adults with sickle cell anemia should see a doctor at least once a year, according to the Centers for Disease Control and Prevention.

Treatments might include medications to reduce pain and prevent complications, and blood transfusions, as well as a bone marrow transplant.

Medications:

Medications used to treat sickle cell anemia include:

•Antibiotics. Children with sickle cell anemia may begin taking the antibiotic penicillin when they're about 2 months old and continue taking it until they're at least 5 years old. Doing so helps prevent infections, such as pneumonia, which can be life-threatening to an infant or child with sickle cell anemia.

As an adult, if you've had your spleen removed or had pneumonia, you might need to take penicillin throughout your life.

•Pain-relieving medications. To relieve pain during a sickle cell crisis, your doctor might prescribe pain medications.

•Hydroxyurea (Droxia, Hydrea). When taken daily, hydroxyurea reduces the frequency of painful crises and might reduce the need for blood transfusions and hospitalizations. Hydroxyurea seems to work by stimulating production of fetal hemoglobin — a type of hemoglobin found in newborns that helps prevent the formation of sickle cells.

Hydroxyurea increases your risk of infections, and there is some concern that long-term use of this drug might cause problems later in life for people who take it for many years. More study is needed.

Assessing stroke risk:

Using a special ultrasound machine (transcranial), doctors can learn which children have a higher risk of stroke. This painless test, which uses sound waves to measure blood flow, can be used on children as young as 2 years. Regular blood transfusions can decrease stroke risk.

Vaccinations to prevent infections:

Childhood vaccinations are important for preventing disease in all children. They're even more important for children with sickle cell anemia because their infections can be severe.

Your doctor will make sure your child receives all of the recommended childhood vaccinations. Vaccinations, such as the pneumococcal vaccine and the annual flu shot, are also important for adults with sickle cell anemia.

Blood transfusions:

In a red blood cell transfusion, red blood cells are removed from a supply of donated blood, then given intravenously to a person with sickle cell anemia.

Blood transfusions increase the number of normal red blood cells in circulation, helping to relieve anemia. In children with sickle cell anemia at high risk of stroke, regular blood transfusions can decrease the risk. Transfusions can also be used to treat other complications of sickle cell anemia, or they can be given to prevent complications.

Blood transfusions carry some risk, including infection and excess iron buildup in your body. Because excess iron can damage your heart, liver and other organs, people who undergo regular transfusions might need treatment to reduce iron levels.

Bone marrow transplant:

A bone marrow transplant, also called a stem cell transplant, involves replacing bone marrow affected by sickle cell anemia with healthy bone marrow from a donor. The procedure usually uses a matched donor, such as a sibling, who doesn't have sickle cell anemia. For many, donors aren't available. But stem cells from umbilical cord blood might be an option.

Because of the risks associated with a bone marrow transplant, the procedure is recommended only for people, usually children, who have significant symptoms and problems from sickle cell anemia.

If a donor is found, the person with sickle cell anemia receives radiation or chemotherapy to destroy or reduce his or her bone marrow stem cells. Healthy stem cells from the donor are injected intravenously into the bloodstream of the person with sickle cell anemia, where they migrate to the bone marrow and begin generating new blood cells.

The procedure requires a lengthy hospital stay. After the transplant, you'll receive drugs to help prevent rejection of the donated stem cells. Even so, your body might reject the transplant, leading to life-threatening complications.

Experimental treatments:

Scientists are studying new treatments for sickle cell anemia, including:

•Gene therapy. Researchers are exploring whether inserting a normal gene into the bone marrow of people with sickle cell anemia will result in normal hemoglobin. Scientists are also exploring the possibility of turning off the defective gene while reactivating another gene responsible for the production of fetal hemoglobin — a type of hemoglobin found in newborns that prevents sickle cells from forming.

Potential treatments using gene therapy are a long way off, however.

•Nitric oxide. People with sickle cell anemia have low levels of nitric oxide in their blood. Nitric oxide is a gas that helps keep blood vessels open and reduces the stickiness of red blood cells. Treatment with inhaled nitric oxide might prevent sickle cells from clumping together. Studies on nitric oxide have shown little benefit so far.

•Drugs to boost fetal hemoglobin production. Researchers are studying various drugs to devise a way to boost the production of fetal hemoglobin. This is a type of hemoglobin that stops sickle cells from forming. [20]

Complications:

Hand-Foot Syndrome:

Swelling in the hands and feet usually is the first symptom of SCD. This swelling, often along with a fever, is caused by the sickle cells getting stuck in the blood vessels and blocking the flow of blood in and out of the hands and feet.

Pain “Episode” or “Crisis”:

Pain is the most common complication of SCD, and the number 1 reason that people with SCD go to the emergency room or hospital. When sickle cells travel through small blood vessels, they can get stuck and clog the blood flow. This causes pain that can start suddenly, be mild to severe, and can last for any length of time.

Anemia:

Anemia is a very common complication of SCD. With SCD, the red blood cells die early. This means there are not enough healthy red blood cells to carry oxygen throughout the body. When this happens, a person might have:

•Tiredness

•Irritability

•Dizziness and lightheadedness

•A fast heart rate

•Difficulty breathing

•Pale skin color

•Jaundice (yellow color to the skin and whites of the eyes)

•Slow growth

•Delayed puberty.

Infection:

People with SCD, especially infants and children, are more at risk for infections, especially those due to bacteria with capsules because of damage to the spleen. Pneumonia is a leading cause of death in infants and young children with SCD.

Acute Chest Syndrome:

This can be life-threatening and should be treated in a hospital. Symptoms and signs are similar to pneumonia. Signs and symptoms include chest pain, coughing, difficulty breathing, and fever.

Splenic Sequestration:

This can be life-threatening and should be treated in a hospital. It happens when a large number of sickle cells get trapped in the spleen and cause it to suddenly get large. Symptoms include sudden weakness, pale lips, fast breathing, extreme thirst, abdominal (belly) pain on the left side of body, and fast heartbeat.

Parents of a child with SCD should learn how to feel and measure the size of their child's spleen and seek help if the spleen is enlarged.

Vision Loss:

Vision loss, including blindness, can occur when blood vessels in the eye become blocked with sickle cells and the retina (the thin layer of tissue inside the back of the eye) gets damaged. Some patients develop extra blood vessels in the eye from the lack of oxygen.

Leg Ulcers:

This usually occurs on the lower part of the leg. They happen more often in males than in females and usually appear from 10 through 50 years of age. A combination of factors cause ulcer formation, including trauma, infection, inflammation, and interruption of the circulation in the smallest blood vessels of the leg.

Stroke:

A stroke can happen if sickle cells get stuck in a blood vessel and clog blood flow to the brain. About 10% of children with SCD will have a symptomatic stroke. Stroke can cause learning problems and lifelong disabilities.

Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE):

Sickling of red cells can increase blood coagulation and induce an increased risk of blood clot in a deep vein (DVT), or in the lung (PE) if the blood clot moves from the deep veins. People with SCD have a high chance of developing DVT or PE. DVT and PE can cause serious illness, disability and, in some cases, death.

Other Possible Complications:

•Damage to body organs (like the liver, heart, or kidneys), tissues, or bones because not enough blood is flowing to the affected area(s).

•Malnutrition and growth retardation among adolescents can cause a delayed onset of puberty and, in males, infertility.

•Gallstones.

•Painful erection of the penis, called priapism, can last less than 2 hours or more than 4 hours. If it lasts more than 4 hours, the person should get urgent medical help. It can lead to impotence.

•A very rare form of kidney cancer (renal medullary carcinoma) has been associated with sickle cell trait. [21]

Thalassaemia

Thalassemia is an inherited blood disorder that reduces the production of functional hemoglobin (protein in red blood cells that carries oxygen). This causes a shortage of red blood cells and low levels of oxygen in the bloodstream, leading to a variety of health problems. There are two main types of thalassemia, alpha thalassemia and beta thalassemia. Signs and symptoms vary but may include mild to severe anemia, paleness, fatigue, yellow discoloration of skin (jaundice), and bone problems. Beta thalassemia is caused by changes (mutations) in the HBB gene while alpha thalassemia is caused by mutations in the HBA1 and/or HBA2 genes. Both are inherited in an autosomal recessive manner. Treatment depends on the type and severity of the condition but may include blood transfusions and/or folic acid supplements.

Symptoms:

The signs and symptoms vary depending on the severity of the thalassemia. For example, people affected by milder forms of thalassemia can develop mild anemia or may have no signs or symptoms of the condition at all. Intermediate forms of thalassemia can cause mild to moderate anemia and may be associated with other health problems such as slowed growth, delayed puberty, bone problems and/or an enlarged spleen. In addition to the signs and symptoms seen in intermediate thalassemia, people with severe forms of thalassemia may also experience severe anemia, poor appetite, paleness, dark urine, yellow discoloration of skin (jaundice), and enlarged liver or heart.

Cause:

There are two main types of thalassemia, alpha thalassemia and beta thalassemia, which each affect a different part of hemoglobin (the protein in red blood cells that carries oxygen). Hemoglobin is made up of two different components (subunits): beta globin and alpha globin. The HBB gene provides instructions for making beta globin, while the HBA1 and HBA2 genes provide instructions for making alpha globin. Each person has two copies of each of these genes, one inherited from the mother and one from the father. Changes (mutations) in the HBB gene lead to reduced levels of beta globin and cause beta thalassemia. Loss (deletion) of some or all of the HBA1 and/or HBA2 genes results in a shortage of alpha globin, leading to alpha thalassemia.

Inheritance:

In general, thalassemia is inherited in an autosomal recessive manner; however, the inheritance can be quite complex as multiple genes can influence the production of hemoglobin.

Most people affected by beta thalassemia have mutations in both copies of the HBB gene in each cell. The parents of an affected person usually each carry one mutated copy of the gene and are referred to as carriers. Carriers typically do not show signs or symptoms of the condition; although some carriers of beta thalassemia develop mild anemia. When two carriers of an autosomal recessive condition have children, each child has a 25% (1 in 4) risk to have the

condition, a 50% (1 in 2) risk to be a carrier like each of the parents, and a 25% chance to not have the condition and not be a carrier.

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The inheritance of alpha thalassemia is complicated by the fact that mutations in two different genes (HBA1 and HBA2) are associated with the condition. People have two copies of the HBA1 gene and two copies of the HBA2 gene in each cell. For each gene, one copy is inherited from the mother and one is inherited from the father. If each parent is missing at least one gene copy, their children are at risk for having alpha thalassemia. However, the exact risk and the severity of each child's condition depends on how many gene copies are lost (deleted) and which combination of the HBA1 and HBA2 genes are affected.

Diagnosis:

Most children with moderate to severe thalassemia show signs and symptoms within their first two years of life. If your doctor suspects your child has thalassemia, he or she may confirm a diagnosis using blood tests.

If your child has thalassemia, blood tests may reveal:

•A low level of red blood cells

•Smaller than expected red blood cells

•Pale red blood cells

•Red blood cells that are varied in size and shape

•Red blood cells with uneven hemoglobin distribution, which gives the cells a bull's-eye appearance under the microscope.

Blood tests may also be used to:

•Measure the amount of iron in your child's blood

•Evaluate his or her hemoglobin

•Perform DNA analysis to diagnose thalassemia or to determine if a person is carrying mutated hemoglobin genes.

Prenatal testing:

Testing can be done before a baby is born to find out if he or she has thalassemia and determine how severe it may be. Tests used to diagnose thalassemia in fetuses include:

•Chorionic villus sampling. This test is usually done around the 11th week of pregnancy and involves removing a tiny piece of the placenta for evaluation.

•Amniocentesis. This test is usually done around the 16th week of pregnancy and involves taking a sample of the fluid that surrounds the fetus.

Assisted reproductive technology:

A form of assisted reproductive technology that combines preimplantation genetic diagnosis with in vitro fertilization may help parents who have thalassemia or who are carriers of a defective hemoglobin gene give birth to healthy babies. The procedure involves retrieving mature eggs and fertilizing them with sperm in a dish in a laboratory. The embryos are tested for the defective genes, and only those without genetic defects are implanted into the uterus.

Treatment:

Treatment for thalassemia depends on which type you have and how severe it is.

Treatments for mild thalassemia:

Signs and symptoms are usually mild with thalassemia minor and little, if any, treatment is needed. Occasionally, you may need a blood transfusion, particularly after surgery, after having a baby or to help manage thalassemia complications.

People with severe beta-thalassemia will need blood transfusions. And because this treatment can cause iron overload, they will also need treatment to remove excess iron. An oral medication called deferasirox (Exjade, Jadenu) can help remove the excess iron.

Treatments for moderate to severe thalassemia:

Treatments for moderate to severe thalassemia may include:

•Frequent blood transfusions. More-severe forms of thalassemia often require frequent blood transfusions, possibly every few weeks. Over time, blood transfusions cause a buildup of iron in your blood, which can damage your heart, liver and other organs. To help your body get rid of the extra iron, you may need to take medications that rid your body of extra iron.

•Stem cell transplant. Also called a bone marrow transplant, a stem cell transplant may be an option in select cases, including children born with severe thalassemia. It can eliminate the need for lifelong blood transfusions and drugs to control iron overload.

During this procedure, you receive infusions of stem cells from a compatible donor, usually a sibling. [23]

Polycythemia vera

Polycythemia vera (pol-e-sy-THEE-me-uh VEER-uh) is a slow-growing blood cancer in which your bone marrow makes too many red blood cells. These excess cells thicken your blood, slowing its flow. They also cause complications, such as blood clots, which can lead to a heart attack or stroke.

Polycythemia vera isn't common. It usually develops slowly, and you might have it for years without knowing. Often the condition is found during a blood test done for another reason.

Without treatment, polycythemia vera can be life-threatening. But proper medical care can help ease signs, symptoms and complications of this disease. Over time, in some cases there's a risk of progressing to more-serious blood cancers, such as myelofibrosis or acute leukemia.

Symptoms:

Many people with polycythemia vera don't have signs or symptoms. Others might have:

•Itchiness, especially following a warm bath or shower

•Headache

•Dizziness

•Bleeding or bruising, usually minor

•Weakness

•Fatigue

•Blurred vision

•Excessive sweating

•Painful swelling of one joint, often the big toe

•Shortness of breath

•Numbness, tingling, burning or weakness in your hands, feet, arms or legs

•A feeling of fullness or bloating in your left upper abdomen due to an enlarged spleen

•Fevers

•Unexplained weight loss.

Causes:

Polycythemia vera is one of a group of blood cancers known as myeloproliferative neoplasms. It occurs when a mutation in a gene causes a problem with blood cell production. Normally, your body regulates the number of each of the three types of blood cells you have — red blood cells, white blood cells and platelets. But in polycythemia vera, your bone marrow makes too many of some blood cells.

The mutation that causes polycythemia vera is thought to affect a protein switch that tells the cells to grow. Specifically, it's a mutation in the protein Janus kinase 2 (JAK2). Most people with polycythemia vera have this mutation. The cause of the mutation isn't known, but it's generally not inherited.

Complications:

Possible complications of polycythemia vera include:

- *Blood clots*: Increased blood thickness and decreased blood flow, as well as abnormalities in your platelets, increase your risk of blood clots. Blood clots can cause a stroke, a heart attack or a blockage of an artery in your lungs (pulmonary embolism) or in a vein deep within a muscle (deep vein thrombosis).

•*Enlarged spleen (splenomegaly):* Your spleen helps your body fight infection and filter unwanted material, such as old or damaged blood cells. The increased number of blood cells caused by polycythemia vera makes your spleen work harder than normal, which causes it to enlarge.

•*Problems due to high levels of red blood cells*: Too many red blood cells can lead to a number of other complications, including open sores on the inside lining of your stomach, upper small intestine or esophagus (peptic ulcers) and inflammation in your joints (gout).

•*Other blood disorders*: In rare cases, polycythemia vera can lead to other blood diseases, including a progressive disorder in which bone marrow is replaced with scar tissue (myelofibrosis), a condition in which stem cells don't mature or function properly (myelodysplastic syndrome), or cancer of the blood and bone marrow (acute leukemia). [24]

Diagnosis:

Blood tests

If you have polycythemia vera, blood tests might reveal:

•An increase in the number of red blood cells and, in some cases, an increase in platelets or white blood cells

•Increased percentage of red blood cells that make up total blood volume (hematocrit measurement)

•Elevated levels of the iron-rich protein in red blood cells that carries oxygen (hemoglobin).

•Very low levels of a hormone that stimulates bone marrow to produce new red blood cells (erythropoietin).

Bone marrow aspiration or biopsy:

A needle suctioning out liquid bone marrow from hipbone

A bone marrow aspiration or biopsy to collect a sample of your bone marrow for study. A bone marrow biopsy involves taking a sample of solid bone marrow material.

A bone marrow aspiration is usually done at the same time. During an aspiration, your doctor withdraws a sample of the liquid portion of your marrow.

Tests for the gene mutation that causes polycythemia vera:

If you have polycythemia vera, analysis of your bone marrow or blood also might show the JAK2 mutation in the cells that's associated with the disease.

Treatment:

Polycythemia vera is a chronic condition that can't be cured. Treatment focuses on reducing your amount of blood cells. In many cases, treatment can reduce the risk of complications from polycythemia vera and ease signs and symptoms.

Treatment might include:

•Taking blood out of your veins. Drawing some blood out of your veins in a procedure called phlebotomy is usually the first treatment option for people with polycythemia vera. This reduces the number of blood cells and decreases your blood volume, making it easier for your blood to function. How often you need phlebotomy depends on the severity of your condition.

•Low-dose aspirin. Your doctor may recommend that you take a low dose of aspirin to reduce your risk of blood clots. Low-dose aspirin may also help reduce burning pain in your feet or hands.

•Medication to decrease blood cells. For people with polycythemia vera who aren't helped by phlebotomy alone, medications, such as hydroxyurea (Droxia, Hydrea), to suppress your bone marrow's ability to produce blood cells might be used.

Interferon alpha may be used to stimulate your immune system to fight the overproduction of red blood cells. It might be used for people who don't respond well to hydroxyurea. It's being studied in clinical trials.

•Medication to destroy cancer cells. Ruxolitinib (Jakafi) is approved by the Food and Drug Administration to treat people with polycythemia vera who don't respond to or can't take hydroxyurea. It helps your immune system destroy cancer cells, and can improve some polycythemia vera symptoms.

•Therapy to reduce itching. If you have bothersome itching, your doctor may prescribe medication, such as antihistamines, or recommend ultraviolet light treatment to relieve your discomfort.

Medications that are normally used to treat depression, called selective serotonin reuptake inhibitors (SSRIs), helped relieve itching in clinical trials. Examples of SSRIs include paroxetine (Paxil) or fluoxetine (Prozac). [25]

Morphological abnormalities of red blood cells:

1. The key word for it is biconcave disc, meaning that it is a disc shaped (or circular) cell that is compressed at the centre in both directions. This allows an increased surface area: volume ratio, providing easier avenues for diffusion of oxygen.
   2. They have a typical diameter of 7.2um, however the normal range is between 6.2um and 8.2um.
   3. They have a typical width of 2.0um, although it can range between 2.0um and 2.5um.
   4. They contain no nucleus, to maximize volume of Hb so as to maximize carriage of oxygen.
   5. They are also very flexible, useful for squeezing into thin capillaries to deliver oxygen to tissues.
   Variations in Size:
   We have mentioned under "General Features of Anemia" that the most important red cell index for discussing the variations in size of blood cells is the Mean Corpuscular Volume (MCV). Just to refresh, the MCV is the average volume of a red blood cell. It is reflective of the size of a cell, and thus, a large MCV indicates a large red blood cell, and a small MCV indicates a small red blood cell. Its typical reference value is 80fL – 95fL, though some sources use 100fL as the upper limit.
   Any variation in size of the RBCs is known as anisocytosis, and the degree of anisocytosis in a sample of blood is known as the red cell distribution width (RDW).

   Microcyte:
   A microcyte, is a red blood cell by definition, a small (micro-) mature cell (-cyte). Thank you for making it so simple, greek derivations. In terms of MCV, a microcyte has an MCV below 80fL. Since the reference range of MCV is 80-95, this should be easy to remember.
   In terms of actual diameter, a microcyte is defined as any RBC with a diameter less than 5.0 microns. Compare this to the average of 7.2 microns.

Diseases Associated with Microcytes:

Microcytes indicate some problem with the manufacturing system of red blood cells, for example, by some deficiency. The diseases include:

- Iron Deficiency Anemia ▪Deficiency of iron leads to a scenario where the red blood cell cannot be filled with Hb and thus is an overall smaller cell, since there is less Hb.

- Sideroblastic Anemia ▪Condition where there the bone marrow releases immature red blood cells, sideroblasts, as opposed to mature red blood cells.
- These sideroblasts have rings of iron around their nucleus, and thus the iron is used up on the sideroblasts.

- Thus, for congenital forms of sideroblastic anemia, there is often a defiency of iron leading to red blood cells that do mature, becoming microcytes.
- Thalassemia Minor ▪Beta thalassemias are a group of disorders in which the beta chain of Hb is usually missing or deformed.
- They occur as a result of blockage to the HBB gene.
- HBB blockage over time leads to decreased Beta-chain synthesis. The body's inability to construct new Beta-chains leads to the underproduction of HBA. Reductions in HBA available overall to fill the red blood cells in turn leads to microcytic anemia.
- Lead Poisoning ▪One of the main causes for the pathology of lead is that it interferes with the activity of an essential enzyme called delta-aminolevulinic acid dehydratase, or ALAD, which is important in the biosynthesis of heme, the cofactor found in hemoglobin. Lead also inhibits the enzyme ferrochelatase, another enzyme involved in the formation of heme.
- The important thing to understand is that microcytosis in lead poisoning occurs due to lack of heme, which leads to a lack of Hb and thus a deficiency, causing smaller RBCs.
- Some Hemoglobinopathies
- Occasionally, chronic disease.

Macrocyte:

A macrocyte on the other hand, is a large (macro-) mature cell (-cyte). Wow. In terms of MCV, a macrocyte has an MCV above 95, or above the reference range. It is thus an enlargement of red blood cells with a near constant concentration of hemoglobin.

Diseases/Conditions associated with Macrocytes:

- Liver Disease
- Patients with hepatic disease and obstructive jaundice have macrocytosis that is secondary to increased deposition of cholesterol or phospholipids on the membranes of circulating red blood cells (RBCs).
- Megaloblastic Anemia
- The most common cause of macrocytic anemia is megaloblastic anemia, which is the result of impaired DNA synthesis. Typically, although DNA synthesis is impaired, RNA synthesis is not, and RNA continues to be produced, increasing the nuclear matter within RBCs that is not being converted to DNA. Thus, the cell gradually enlarges due to increased nuclear matter, causing macrocytosis.
- Vitamin B12 deficiency and Folate deficiency ▪Vitamin B12 and folate is very important in the synthesis of Thymidine and Purines, and thus DNA synthesis is impaired in these deficiencies, causing macrocytosis by the aforementioned mechanisms.
- Aplastic Anemia
- Mild macrocytosis is seen in recovery from aplastic anemia, which occurs when there is a bone marrow pathology and a deficiency of all 3 types of blood cells (WBC, RBC, platelets) occurs.
- Neonates.

Variations in Colour:

Remember that the red blood cell consists of hemoglobin that can be in two states: Either oxygenated, in which case it is oxyhemoglobin, or deoxygenated, in which case it is deoxyhemoglobin. Well, the color of a red blood cell is… red. Yes. I don't know where I was going with that.

To be more precise, oxyhemoglobin and deoxyhemoglobin are different shades of red. Oxyhemoglobin is a brilliant scarlet, while deoxyhemoglobin is a darker burgundy-red.

Hypochromia:

Hypochromia is the most common disorder of color that occurs in red blood cells. Hypo-, of course, means "less" and -chromic means "color" so when we describe a cell as hypochromic, we say it has less color.

Hypochromic RBCs are much paler, and the reason for this is because they lack hemoglobin within them. Because of this, they lose their red coloration and appear much paler. Using this concept, recall that the unit to measure the amount of hemoglobin per cell is mean corpuscular hemoglobin, or MCH. The MCH is simply the average amount of hemoglobin in one red blood cell, from a particular sample. Its reference range is 27pg – 31pg, meaning that there is typically between 27pg and 31pg of hemoglobin in a single red blood cell.

The other unit for hemoglobin content of a red blood cell is mean corpuscular hemoglobin concentration (MCHC). The MCHC is reflective of the concentration of packed red blood cells (so blood excluding plasma) that is hemoglobin. It basically translates to the amount of hemoglobin present in the cellular component of blood, and thus excluding plasma. Its reference range is 32g/dL – 36g/dL.

There are two conditions that a RBC must satisfy in order to be classified as a hypochromic cell. These are:

- The central zone of pallor of the RBC must be greater than 1/3 of the diameter of the cell.
- The MCH must be below 27pg/cell and/or the MCHC must be below 32g/dL.

Diseases associated with Hypochromia:

▪Iron Deficiency Anemia ▪Recall that iron is essential in the production of heme, the centerpiece of hemoglobin.

▪Thus a deficiency in iron leads to a deficiency in heme and thus hemoglobin, resulting in lowered MCH values.

▪Also recall that iron deficiency anemia causes microcytosis, and thus iron deficiency anemia causes hypochromic, microcytic anemia.

▪Thalassemias

▪As discussed previously, thalassemia arises by a genetic defect in the HBB gene that codes for beta chains of hemoglobin, causing the absence of, or underproduction of, beta chains. As alpha chains production gradually slows down in the absence of beta chains,

hemoglobin becomes less and less functional. Thus, less oxygen can be held by hemoglobin, and hemoglobin itself becomes destroyed due to destruction of the then non-functional red blood cells by thalassemia. Consequently, MCH decreases and hypochromic anemia results.

- Notice that thalassemia also causes microcytosis as HBA production to replace HBB decreases over time and the red blood cell shrinks.
- Sideroblastic Anemias
- Recall that sideroblast production (very immature red blood cells), with rings of iron around their nucleus is the hallmark of sideroblastic anemias. These cells are known as ringed sideroblasts.
- Because iron is used up in these non-functional rings, proper red blood cells are not formed, and thus proper hemoglobin is not formed adequately. This results in hypochromic cells, that are again, also microcytic.
- Lead Poisoning
- Lead poisoning impairs the functioning of the enzyme, ALAD, and the enzyme ferrochelatase, both important in the production of heme.
- This impairment in the production of heme leads to decreased hemoglobin in red blood cells, thereby reducing MCH and MHCH and causing hypochromia and microcytosis.
- Some cases of chronic inflammation.

Polychromia:

Polychromasia is a medical condition in which there is an abnormally high amount of immature red blood cells being released into the bloodstream. The most significant of these is the reticulocyte, the immediate precursor to the red blood cell. The only difference between the reticulocyte and the red blood cell is the presence of a meshwork of RNA within the reticulocyte, when viewed with special stains such as the new methylene blue stain that must be removed before the reticulocyte can be called a red blood cell.

Polychromasia literally translates to “many colors,” and the reason for this is because the many immature red blood cells being released into the bloodstream are all different shades of a bluish grey.

Diseases Associated with Polychromasia:

Polychromasia is usually a sign of bone marrow stress as well as immature red blood cells. Polychromasia occurs in conditions which call for premature release of red blood cells into the bloodstream, such as in conditions where RBC levels in the bloodstream are severely low. These include:

- Acute and Chronic Hemorrhage
- During hemorrhage, as blood loss from the body occurs, there is a constantly lowered level of RBCs in the bloodstream. Thus the bone marrow opts to increase the RBC levels by increasing production of red blood cells, and increasing release of red blood cells, even if they are immature or not fully mature. In this way, immature cells such as reticulocytes may appear in the bloodstream, causing Polychromasia.

- Hemolysis
- In hemolysis, as red blood cells are destroyed, the body attempts to replace them by increasing production and release of red blood cells, and this results in the release of immature red blood cells such as reticulocytes into the bloodstream.
- Effective treatment for anemia
- Neonates.

Note that polychromasia is mainly associated with normocytic styles of anemia, as there is no change in MCH or MCV in any of these scenarios.

Variations in Shape of Cells:

The term for variations in the shape of cells is poikilocytosis. Thus, any abnormally shaped cell is called a poikilocyte.
Poikilocytes can occur either due to membrane abnormalities or trauma.
The poikilocytes caused by membrane abnormalities are:
1 .Acanthocytes (Spur Cells)
2. Codocytes (Target Cells)
3. Echinocytes and Burr Cells
4. Spherocytes
5. Stomatocytes (Mouth Cells)
6. Drepanocytes (Sickle cells)
7. Degmacytes (”Bite Cells).

The poikilocytes caused by trauma are:
1. Dacrocytes (Teardrop cells)
2. Keratocytes
3. Microspherocytes and Pyropoikilocytes
4. Schistocytes
5. Semilunar Bodies.

Poikilocytes of Membrane Abnormalities:

Acanthocytes (Spur Cells):
The word acantho- means thorns. This should give you a good idea as to what acanthocytes look like. The word literally means thorn cells after all. Thus, acanthocytes can be described as having a spiked cell membrane, due to irregular thorny projections that vary in width, length and number. Notably, they have no central area of pallor.
Acanthocytes typically arise via one of two mechanisms: Alterations in membrane lipids are seen in abetalipoproteinemia and liver dysfunction.

- In liver dysfunction, apolipoprotein A-II deficient lipoprotein accumulates in plasma causing increased cholesterol in the RBC membrane. This causes abnormalities of membrane of RBC causing remodeling in spleen and formation of acanthocytes.
- In abetalipoproteinemia, there is deficiency of lipids and Vitamin E causing abnormal morphology of RBC membranes.

Diseases Associated with Acanthocytes:

- Abetalipoproteinemia ▪This is a rare autosomal recessive condition that affects the absorption of fat, and fat soluble vitamins from food.
- Abetalipoproteinemia affects the absorption of dietary fats, cholesterol, and certain vitamins. People affected by this disorder are not able to make certain lipoproteins (hence the name, abetalipoproteinemia).
- This leads to a multiple vitamin deficiency, affecting the fat-soluble vitamin A, vitamin D, vitamin E, and vitamin K. However, many of the observed effects are due to vitamin E deficiency in particular.
- As explained above, the deficiency of Vitamin E and lipids results in an abnormal membrane layer of the RBC.
- Abnormal lipid concentrations within the blood cause acanthocytosis primarily by inducing concentration gradients with the lipids in the red cell membrane, causing some portions of the membrane to extend outwards as lipids move in or out of them. This gradient is known as membrane stress, and in conditions of abetalipoproteinemia or hypobetalipoproteinemia, the RBC membrane is more vulnerable to membrane stress.

- Vitamin E Deficiency

- Severe Liver Disease

- As explained above, cholesterol buildup in RBCs causes portions of the red cell membrane to extend out the RBC and form thorny extensions, thus producing acanthocytosis.

- Splenectomy

- A major function of the spleen is the clearance of opsonized, deformed, and damaged erythrocytes by splenic macrophages. If splenic macrophage function is abnormal or absent because of splenectomy, altered erythrocytes will not be removed from the circulation efficiently.

- Malabsorption

- Poor reabsorption of lipids and lipid-soluble vitamins has similar effects on RBCs as abetalipoproteinemia.

- Hypothyroidism

- Very rare cause of acanthocytosis.

- Neuroacanthocytosis

- This is a condition including 4 diseases, namely chorea acanthocytosis, McLeod Syndrome, Huntington Disease – like 2 (HDL2) and pantothenate kinase-associated neurodegeneration.

▪In summary, all neuroacanthocytoses affect the basal ganglia and brain and are a group of movement and neurological disorders.

Codocytes (Target Cells):

Codocytes, also known as target cells, look like typical red blood cells, with a central area of pallor and appropriate size. However, they have a dark, red spot in the middle. For this purpose, they are also referred to as bullseye cells.

Diseases Associated with Codocytes:

Diseases associated with codocytes must obviously cause at least one of two things: Either cause a direct increase in surface area by affecting lipid concentrations in the RBC membrane, or by decreasing hemoglobin concentration within the RBCs. Thus, any disease that can cause these two can cause codocytes to be formed. A list of some of these diseases includes:

▪Thalassemia

▪Associated with a decrease in functional hemoglobin.

▪Iron Deficiency Anemia

▪Associated with a decrease in total hemoglobin.

▪LCAT Deficiency

▪LCAT, or lechitin-cholesterol acyltransferase is an enzyme that coverts free cholesterol into cholesteryl ester. In the absence of LCAT, the cholesterol: phospholipid ratio increases, causing cholesterol buildup in the RBC and increasing the size of the membrane of the RBC. Eventually, the surface area rises to abnormally high levels.

▪Obstructive Liver Disease

▪Obstructive liver disease is associated with an LCAT deficiency.

▪Hemoglobin C (and sometimes Hemoglobin S) Disease – Hemoglobinopathies ▪In hemoglobinopathies such as Hemoglobin C and Hemoglobin S (sickle cell anemia) disease, one of the chains in hemoglobin is genetically malformed (contrast with Thalassemias where a chain is underproduced or missing). As a result of this, typically the hemoglobin is reduced and non-functional, and it causes red blood cells to have a shortened lifespan.

▪Thus, codocytes are very typical of all hemoglobinopathies.

▪Splenectomy ▪Associated with removing opsonized of damaged cells, and thus target cells remain in the bloodstream and are not removed.

Echinocytes or Burr Cells:

Echinocytes. Another type of red blood cell disorder. As usual, let's allow our Greek friends to help us out. Echino- arises from the Greek word echinos, which means hedgehog, or sea urchin. Let's look at a hedgehog and see why echinocytes are named after them.

Look at those spikes, quite regular and quite short. Echinocytes are actually quite similar.

Echninocytes are burr-like erythrocyte with short, blunt, evenly spaced projections. It is a red blood cell with an abnormal membrane that, like acanthocytes, has thorny projections. The main difference between the acanthocyte and the echinocyte however, is the shape of the thorny projections. In acanthocytes, the projections are irregularly spaced, and vary in width, length and number. In echinocytes, the projections are all short and evenly spaced. Furthermore, under the Wright Stain, echinocytes even appear to have a central area of pallor. Acanthocytes show little to no central pallor.

Both acanthocytes and echinocytes occur due to membrane abnormalities of the RBC. Recall that acanthocytes arise from either increased cholesterol buildup within the membranes, or general lipid malabsorption that causes increased membrane tension, which is what leads to the irregular projections on its surface.

Echinocytes on the other hand can be produced in vitro by incubation at high pH or in the presence of high calcium concentrations, exposure to glass surfaces, reduced albumin concentrations, and after prolonged storage, and are usually reversible creations. They can be formed during application of EDTA, drying or staining.

They may also occur in hyperlipidemias caused by liver disease, as with acanthocytes. However, the cholesterol does not become incorporated into the lipid membrane as it does with acanthocytes. Instead, it is speculated that cell surface receptors on the red blood cells bind with HDL cholesterol which induces the shape change in echinocytes.

The acanthocyte thorns are much sharper, longer, and random and show no central area of pallor, as opposed to the echinocyte (Burr Cell) that has short, round, very regular thorny projections and show a central area of pallor.

Diseases/Conditions Associated with Echinocytes:

- Uremia
- Pyruvate Kinase Deficiency
- Microangiopathic Hemolytic Anemia
- Neonates (especially premature)
- As artifacts of EDTA, drying or staining.

Spherocytes:

We've really been helped out here. With a name like "Spherocytes" there's no question what the shape of these cells will be. Spherical cells. Yeah. These cells are sphere-shaped rather than the

typical biconcave disc shape expected of a normal red blood cell, and that is their most important feature.

Spherocytes are simple. They appear as spheres under a blood film with no central area of pallor.

You'll notice that macrocytes also have no central area of pallor. To differentiate one from another, you'll notice that the spherocytes are actually smaller than the normal red blood cells, and thus cannot be macrocytes. In contrast, microcytes show a central area of pallor, and thus you should be able to tell the difference between the three. The spherocytes are smaller due to partial loss of their membrane, without any damage to their intracellular content.

Spherocytes are often always indicative of either hereditary spherocytosis or immune-mediated hemolytic anemia.

Hereditary spherocytosis is a genetic disorder, a molecular defect in one or more of the proteins of the red blood cell cytoskeleton, including, spectrin, ankyrin, Band 3, or Protein 4.2. Because the cell skeleton has a defect, the blood cell contracts to its most surface-tension efficient and least flexible configuration, a sphere.

Alternatively, during immune-mediated hemolytic anemia, there is partial phagocytosis of normal red blood cells by phagocytosis due to the presence of antigens on the surface of the red blood cell. The phagocyte destroys the membrane where the antigen was present, destroying some of the surface area of the cell. Thus, the cell must now shape itself into a sphere, decreasing its surface area: volume ratio, since the volume of the cell remains the same. This is known as immune-mediated hemolytic anemia, since the immune system in the form of phagocytes destroys (hemolyses) a portion of the red blood cells, producing spherocytes. Two simple mechanisms.

Though the spherocytes have a smaller surface area through which oxygen and carbon dioxide can be exchanged, they in themselves perform adequately to maintain healthy oxygen supplies. However, they have a high osmotic fragility–when placed into water, they are more likely to burst than normal red blood cells.

Diseases Associated with Spherocytes:

- Hereditary Spherocytosis
- Immune-mediated Hemolytic Anemia
- Haemolytic jaundice of the newborn due to ABO antibodies
- Transfused Cells
- Severe Burns.

Stomatocytes (Mouth Cells):

Stomatocytes are yet another membrane abnormality that occurs within red blood cells. In this condition, several cells, instead of having a central area of pallor, possess a central "slit" of

pallor. For this reason, they look like a mouth, or in particular, “kissing lips.” Even easier to remember is that they look like coffee beans. Take a look at them below:

Basically, stomatocytes result from an increase in the volume of the red blood cell, and consequently a decrease in the surface area: volume ratio, due to some permeability defect in the membrane.

The reason for the production of the mouth shaped slit is actually unknown at this point, but you can at least remember that stomatocytes are mouth shaped by picturing a mouth drinking water, similar to how water and salts move into stomatocytes due to their membrane defect.

Diseases/Conditions Associated with Stomatocytes:

▪Hereditary Stomatocytosis

▪Hereditary stomatocytosis describes a number of inherited autosomal dominant human conditions which affect the red blood cell, in which the membrane or outer coating of the cell ‘leaks’ sodium and potassium ions.

▪Osmosis leads to the red blood cell having a constant tendency to swell and burst. This tendency is countered by manipulating the flow of sodium and potassium ions. A ‘pump’ forces sodium out of the cell and potassium in, and this action is balanced by a process called ‘the passive leak’.

▪In the hereditary stomatocytoses, the passive leak is increased and the cell becomes swamped with salt and water. The cell lyses and a haemolytic anaemia results.

▪Alcoholism

▪Liver Disease

▪Rh Null Phenotype for Blood.

▪Individuals who possess the Rh null phenotype have osmotically fragile red cells, which take the form of stomatocytes.

▪The osmotically fragile red cells are overfilled with water for their size even at water levels that would be normal for a normal erythrocyte.

▪Thus, they appear as stomatocytes in Rh null phenotypes.

▪As an Artifact ▪If only 10% of less of the cells seen are stomatocytes, then they are most likely artifacts.

Degmacytes (Bite Cells):

A degmacyte (aka “bite cell”) is an abnormally shaped red blood cell with one or more semicircular portions removed from the cell margin. These “bites” result from the removal of denatured hemoglobin by macrophages in the spleen. Glucose-6-phosphate dehydrogenase

deficiency (G6PD), in which uncontrolled oxidative stress causes hemoglobin to denature and form Heinz bodies, is a common disorder that leads to the formation of bite cells.

The Heinz Bodies are seen as antigenic and are quickly phagocytosed. Because the Heinz Bodies are derivatives of hemoglobin, they are located inside the cell, and thus phagocytosis takes a significant "bite" out of the cell. This is the difference between the bite cell and the spherocyte, where only the membrane is destroyed.

Diseases Associated with Degmacytes:

▪Glucose-6-phosphate Dehydrogenase Deficiency (G6PD)

Drepanocytes (Sickle Cells):

This is one we all know. Sickle cell anemia is something we're all familiar with. And it is again, a name that gives away what the cell is shaped like. You guessed it – the blade of a sickle, or a crescent. It is an autosomal recessive genetic disorder. The gene defect is a known mutation of a single nucleotide (GAG to GTG) of the β-globin gene, which results in glutamic acid being substituted by valine at position 6. This new hemoglobin is known as Hemoglobin S (HbS).

This is normally a benign mutation, causing no apparent effects on the secondary, tertiary, or quaternary structures of haemoglobin in conditions of normal oxygen concentration. What it does allow for, under conditions of low oxygen concentration, is the polymerization of the HbS itself. The deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices due to the valine. The hydrophobic side chain of the valine residue at position 6 of the beta chain in haemoglobin is able to associate with the hydrophobic patch, causing haemoglobin S molecules to aggregate and form fibrous precipitates.

In this case, as a result of the hydrophobic chains interacting, the red blood cell essentially folds in on itself, producing its unique shape.

Poikilocytes of Trauma:

Dacrocytes (Teardrop Cells):

Teardrop cells is such a cool name. And they are really shaped like teardrops. Thank you to whoever named these morphological abnormalities in cells. Dacrocytes can also be said to be pear shaped. They are usually characteristic of myelofibrosis, and seen with marrow disorders or marrow infiltrations, really because of improper production of blood cells from the bone marrow. In post-splenectomy patients, the number of dacrocytes drastically increases, since the spleen cannot remove the improperly formed cells.

Diseases Associated with Dacrocytes:

▪Myelofibrosis with myeloid metaplasia ▪Myelofibrosis, also known as osteomyelofibrosis, is a rare bone marrow cancer.

- Beta Thalassemia Major

- Myelophthisic anemias

- Myelophthisic anemia (or myelophthisis) is a severe kind of anemia found in some people with diseases that affect the bone marrow. Myelophthisis refers to the displacement of hemopoietic bone-marrow tissue either by fibrosis, tumors or granulomas.

- Extramedullary Hematopoiesis

Schistocytes:

A schistocyte is a fragmented portion of a red blood cell. It is literally a broken piece off a red blood cell. Obviously then, they are irregular shaped, jagged and have pointed extremities, that is, usually 2 pointy ends. There is no central pallor since they are simply fragments of red blood cells.

Schistocyte formation occurs as a result of mechanical destruction (fragmentation hemolysis) of a normal red blood cell. This occurs when there is damage to the blood vessel and a clot begins to form. The formation of the fibrin strands in the vessels occurs as part of the clot formation process. The red blood cells get trapped in the fibrin strands and the sheer force of the blood flow causes the red blood cell to break. The resulting fragmented cell is called the schistocyte.

They are thus very common in hemolytic anemias, obviously since RBCs are hemolysed and broken down in this condition.

Diseases Associated with Schistocytes:

- Microangiopathic hemolytic anemia (disseminated intravascular coagulation)

- Disseminated intravascular coagulation is an activation of the coagulation cascade which is usually a result of an increased exposure to tissue factor.

- The activation of the cascade leads to thrombi formation which causes an accumulation of excess fibrin formation in the intravascular circulation. The excess fibrin strands because mechanical damage to the red blood cells resulting in schistocyte formation and also thrombocytopenia and consumption of clotting factors.

- Schistocyte values between .5% and 1% are usually suggestive of DIC.

- Thrombotic thrombocytopenic purpura

- Thrombotic thrombocytopenic purpura or TTP is caused by primary platelet activation. Thrombotic thrombocytopenic purpura leads to increased amounts of von Willebrand factor which then attach to activated platelets and mediate further platelet aggregation. Platelets end up being removed and the resulting fibrin strand formation remains. These fibrin strands along with the stress from the blood flow cause fragmentation of the red blood cells, leading to schistocyte formation.

- In TTP, a schistocyte count between 3-10% is common, but >1% is suggestive of the disease.

- Hemolytic uremic syndrome

- Haemolytic-uremic syndrome or HUS is haemolytic anaemia, acute kidney failure (uraemia), and thrombocytopenia.

- HUS is caused by E. coli bloody diarrhea and specific strains of shiga toxin. The bacteria in HUS cause damage to the endothelium which results in platelet activation and formation of microthrombi.

- Red cells get trapped in the fibrin strands of the microthrombi and become sheared by the force of blood flow leading to schistocyte formation.

- Severe burns.

Keratocytes:

Keratocytes formation may be associated with trauma, especially cellular damage from contact with fibrin strands within the microvasculature. Other processes that can contribute to microvascular injury include endotoxemia and antigen-antibody reactions. These forms of microangiopathy subsequently may lead to platelet aggregation, fibrin formation, and, ultimately, intravascular coagulation (DIC). As normal erythrocytes encounter a mesh of fibrin strands, they can become entrapped. Sometimes these cells are impaled on fibrin strands. Blood flow then pushes the cell against the strand of fibrin and the cell may bisect. Alternatively, the opposing sides of the cell may adhere to one another around the fibrin strand. When blood flow frees the cell, the opposing sides rejoin forming a pseudovacuole. Cells with pseudovacuoles are called "blister" cells or pre-keratocytes. When the vacuole ruptures (usually within minutes), the remaining cell resembles a helmet with straps or a horned cell that is designated a keratocyte. Prekeratocytes also can form via fusion of injured cell membranes (e.g., administration of doxorubicin6 and some iron deficiency anemias). These new cells are more fragile than the original parent cell and may rupture, forming a keratocyte.

Semilunar Bodies:

Semilunar bodies are types of poikilocytes caused by cell trauma. They are hypochromic, crescent shaped cells, also called ghost corpuscles/cells or phantom cells, with loss of all hemoglobin. This erythrocyte cell is an "empty" red cell membrane (the external structure or "covering") that is left complete or intact after hemolysis, but the cell is dead. In some cases of AIHA/IMHA, semilunar bodies/ghost erythrocytes may be seen with intravascular hemolysis.

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Unique Cases of Poikilocytosis:

These unique cases of poikilocytosis involve two important hemoglobinopathies: Hemoglobin SC disease and Hemoglobin C Crystals. [26]

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