# Section Three: Chapter 15: Blood

## What is Blood and what does it do?

**Blood** is a fluid connective tissue that is pumped throughout the body and heart, flowing through all the blood vessels of the body. It delivers oxygen ($O_2$), nutrients and warmth to the tissues, and removes carbon dioxide ($CO_2$) and metabolic wastes from cells. Healthy, clean, easy flowing blood is key to good health. Blood also has a vital role in circuiting cells, hormones and other signal molecules that aid in communication, as well as in the protection, repair, defense, and maintenance of homeostasis in the body.

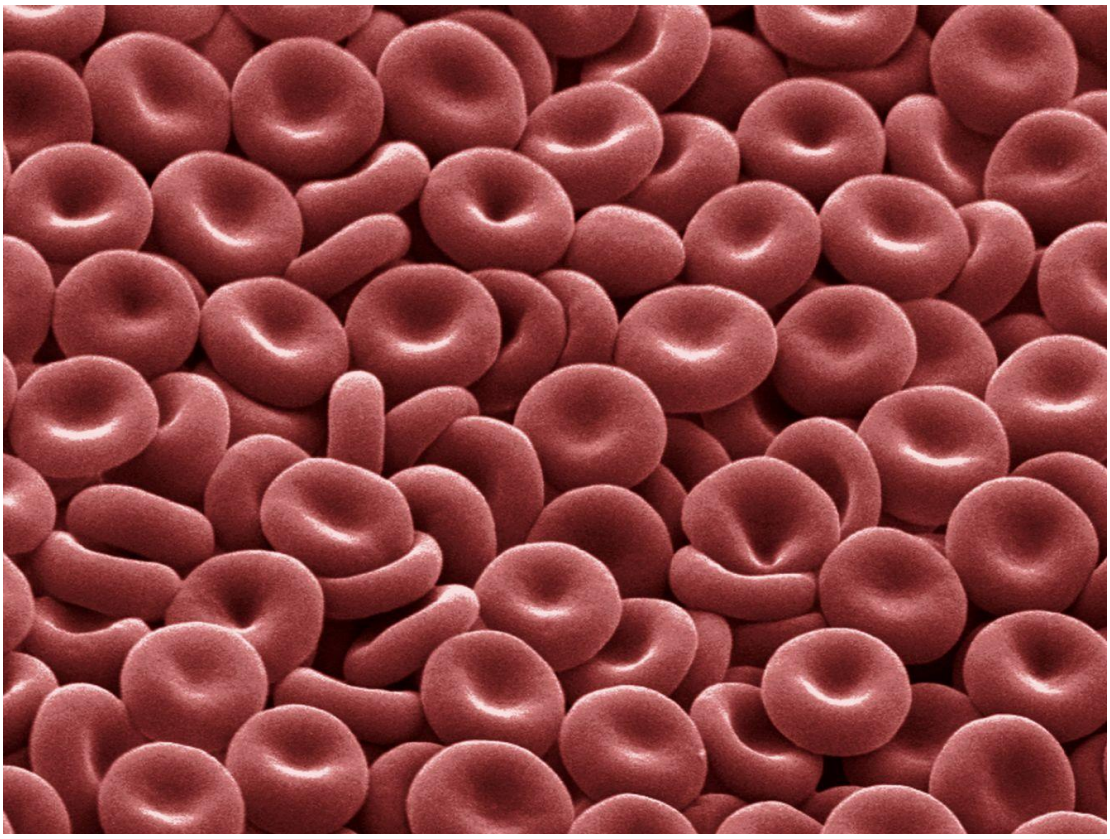


**Figure 15.1** Seen in the picture above are erythrocytes or red blood cells in blood. These relatively small biconcave shaped cells represent the vast majority of cells in the blood. Aren't they wonderful?

## What are the Components of Blood?

To qualify as a connective tissue, blood must have **cells**, **fibers** and **ground substance**. It has all of these and one of the best ways to consider blood is to view it as having two main elements. **Cellular** and **Fluid**. If we take a test tube of blood and spin it in a centrifuge at high speeds it will separate out into two parts: The **Cellular** (or **Formed**) **elements**, and the fluid component of blood which is called **Plasma**.

The Cellular of Formed elements of blood are the cells that are normally circulated around the body within the blood, which include **erythrocytes** or red blood cells (**RBCs**), **leukocytes** or white blood cells (**WBCs**), and **platelets** which are fragments of cells. The **plasma** is the straw colored fluid that sits on top of the spun sample, called the supernatant. It contains a vast array of important substances that are critical to the body. About 92% of plasma is water which suspends all of the other elements of the blood. See the figure below of the spun sample of blood in the test tube for the list of amazing substances normally found in plasma.

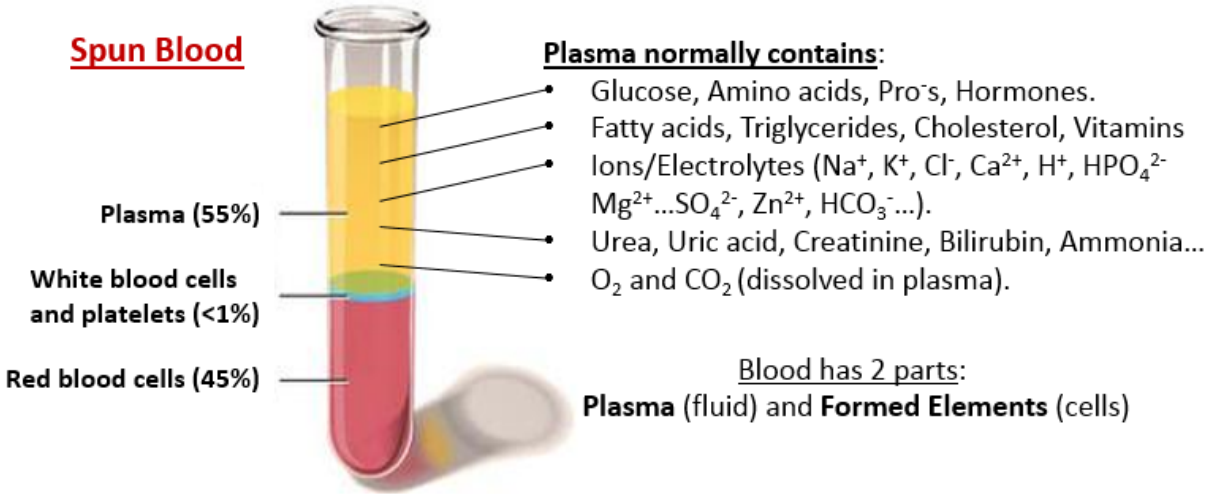



**Figure 15.2** A sample of spun blood showing plasma with all its components, white blood cells and red blood cells.

Blood pH ranges from **7.35 to 7.45**. Typically, arterial blood has a higher pH (average of 7.41, so it is more basic), whereas venous blood has a lower pH (average 7.35, so it is more acidic). The blood is more acidic (lower pH) in venous blood because there is more dissolved $CO_2$, which forms carbonic acid.

**What is an ABG?** Arterial Blood Gases (**ABG**) is the most accurate representation of a person's clinical status with regard to a blood test that measures the **pH**, levels of oxygen (**$O_2$**) and carbon dioxide (**$CO_2$**) from an artery. The test is used to check the function of a person's cardiopulmonary system and their ability to deliver $O_2$ and remove $CO_2$.

Blood brings **warmth** to wherever it flow. Blood is slightly warmer than normal body temperature ($T_b$), it's about 38°C (or 100.4 °F), compared to 37.1°C (or 98.6 °F) for an average internal $T_b$ reading. As blood flows along blood vessels friction and resistance are experienced, producing plenty of heat.

**Blood and Plasma Viscosity**

Viscosity of any fluid is defined as the density (thickness) of the fluid which can also be expressed as resistance to flow. Which do you think is more viscous, blood or water? Turns out **blood** is about 5 to 6 times more viscous than water, so it is thicker after all. It is primarily the cells that are present in whole blood that make it so much more viscous than water.

As we will see, the fluid component of blood (the plasma) contains **mostly water** but the proteins and all of the other substances in it (described below) make it more viscous. When **plasma** is at body temperature (98.6°F or 37°C) is about 1.8 times more viscous than water at the same temperature. Therefore, blood is more viscus than plasma, which is more viscous than water.

## Composition of Blood

**Blood** is a specialized fluid connective tissue in the body that transports nutrients, $O_2$, $CO_2$ and waste products around the body inside blood vessels. Your body constantly circulates blood to ensure growth, repair, protection, and to maintain homeostasis across the entire body. Blood usually constitutes about **8%** of adult body weight, with males having between 5 to 6 L and females having between 4–5 liters of blood.

Blood is contained in the closed circulatory system and although the total volume of blood can vary depending on several factors, it is kept remarkably stable via multiple feedback mechanisms to maintain homeostasis of this critical body fluid.

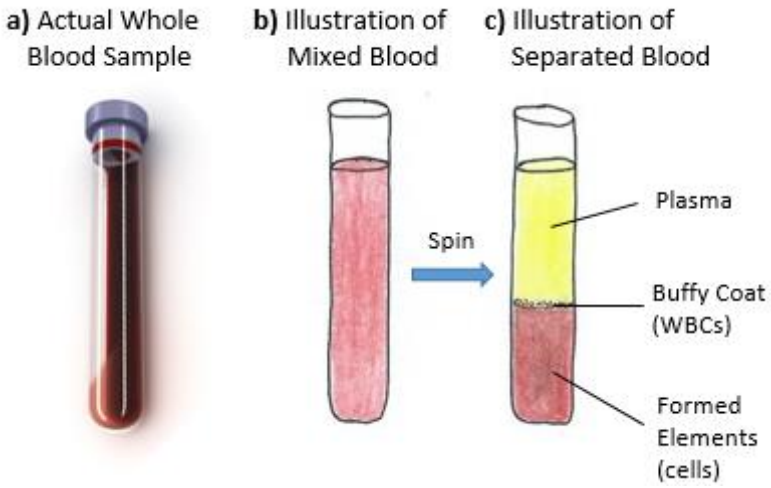



**Figure 15.3** This shows **a)** and actual sample of real whole blood, **b)** an illustration of whole or mixed blood, and **c)** an illustration of separated blood after having been spun at high speeds in a centrifuge. In the spun blood we can see the 2 major components of blood, the plasma, which is the supernatant on top and the heavier formed cellular elements on the bottom.

As shown in **Figure 15.3** above, when the blood is spun at high speeds in a centrifuge, it separates into its two major portions and below are some basic information about these two components.

**1)** The liquid portion called ***plasma*** (~55% of blood volume). This fluid portion contains glucose, amino acids, protein, hormones, ions (electrolytes), etc., as well as dissolved $O_2$ and $CO_2$.

**2)** The formed elements or ***blood cells*** (~45% of blood volume). The vast majority of cells are **erythrocytes** (red blood cells or **RBC**s), also **leukocytes** (white blood cells or **WBC**s) and platelet cells.

**General Characteristics of Blood**

In its natural flowing state, blood is homogenized, meaning its diverse elements are **thoroughly mixed**, uniformly and evenly distributed. The color of blood is not always the same and ultimately it can indicate its level of **oxygenation**. Blood is typically bright **red** in its highly oxygenated state, this is due to the binding of oxygen ($O_2$) to the **heme** containing portion of the pigmented molecule **hemoglobin** (**Hb**) inside red blood cells. When there is less $O_2$ bound to these sites, the color of blood becomes dusky **red/purple** and with even less $O_2$ the color can become more **blue**. This is why images depicting the systemic circuit show most arteries containing red blood and most veins containing blue blood, indicating the $O_2$ content of the blood.

**Blood Viscosity, Blood Flow and Blood Pressure**

Blood is viscous fluid, meaning it is 'thick' and dense. As mentioned, the viscosity of blood is about <u>five (5) to six (6) times greater than that of water</u>. This is primarily due to the presence of plasma proteins and various cells within the blood. Since viscosity is a measure of resistance to flow, the high viscosity of blood has a significant impact on **blood flow** and **blood pressure**. Imagine if you were trying to drink water through a straw and compare that to drinking honey through the same sized straw. Which would be easier and why? The water, because it is less viscus, thus less resistant to flow.

## The Blood Plasma

Like other fluids in the body, plasma is composed primarily of water: In fact, it is about 92% water. Dissolved or suspended within this water is a mixture of substances, most of which are proteins. There are literally hundreds of substances dissolved or suspended in the plasma, though many of them are found only in very small quantities. Note: **Serum** is a fluid that remains after the clotting factors have been removed from plasma.

### Plasma Proteins

Plasma is about **92%** water, and essentially the rest of plasma volume is made of proteins, about 7%. There are three (3) major groups of plasma proteins, plus regulatory proteins, as follows:

- **Albumin** - most abundant plasma protein accounts for about **60%** of all plasma proteins. It is made by the **liver** and delivered to blood by way of the sinusoidal capillaries in the liver. Albumin is what egg whites are made of, a slippery and thick fluid, and helps explain how plasma proteins contribute to blood viscosity. These molecules serve as transport binding proteins for insoluble lipids (fatty acids and cholesterol), to facilitate transport of hydrophobic lipids in the watery plasma. Albumin is the most significant contributor to the osmotic pressure of blood (COP), the force generated in solution by proteins that can draw water across blood vessel walls from tissues into the bloodstream. This in turn helps to maintain both blood volume and blood pressure.

- **Globulins** – make up about **35%** of plasma proteins in three subgroups: alpha, beta, and gamma globulins. The **alpha** and **beta** are made in the **liver** and transport iron, lipids, and fat-soluble vitamins A, D, E, and K to cells. **Gamma globulins** are **antibodies** (**immunoglobulins**) involved in immunity and the only plasma proteins not made by the liver, but by **leukocytes** (plasma cells).

- **Fibrinogen** – only accounting for about **5%** of the plasma proteins, it is essential for blood clotting. Fibrinogen is an inert (inactive) enzyme made by the **liver**. It is cleaved into the active **fibrin** during the coagulation phase of hemostasis.

  - ***Regulatory*** - Less than **1%** of the total plasma proteins. These are enzymes, proenzymes and hormones that are circulated by various tissues in the body at any one time. Levels of these change constantly and often described separately to the 3 plasma proteins categories listed above.

**Note regarding the differences between the various Plasma Proteins**.

There are two types of **alpha globulins** made in the liver, alpha 1 and 2. Essentially they carry out the same function: Acting as enzymes and transporters for hormones, cholesterol, and copper (Cu) through the bloodstream. They also work to help or facilitate or inhibit the actions of other enzymes.

There are two types of **beta globulins** (beta 1, and 2). Like alpha, they transport hormones, lipids and minerals. However, they do not participate in enzymatic activities, but instead assist in immune responses against bacteria and parasites.

The **gamma globulins**, unlike alpha and beta, are *made by immune cells*, lymphocytes and plasma cells, to act as antibodies or immunoglobulins. Lymphocytes and plasma cells produce these antibodies or immunoglobulins, to interact with antigens that arise externally. Thus, gamma globulins (immunoglobulins) are involved in the immune response.

## Lipids in Plasma

Lipids are an important and a critical nutrient for the human body, we have already seen its vital role in membranes across all systems. The also act as great insulators, and many function as signal molecules and hormones.

### There are 2 Essential Fatty Acids

Just as there are essential amino acids, there are two fatty acids that are essential, meaning that your body cannot make them and they must be obtained from your diet!

1. Alpha-linolenic acid, an **omega-3 fatty acid**.
2. Linoleic acid, an **omega-6 fatty acid**.

### Transport of Lipids in Blood

When discussing the lipids in the blood, it is important to recall that most lipids are **hydrophobic** and plasma (which is 92% water) is **hydrophilic**. Therefore, most lipids require special mechanisms for **transport** through the blood to and from the tissues.

#### The Lipoproteins in the Blood

If we want to answer the question "How are these lipids transported in the blood"? The answer is that this is done with **lipoproteins**. These are protein transporters that shuttle large amounts of lipids in the plasma to and from various tissues all around the body. They can be likened to boats for lipids that need to take a trip across the water-like plasma to their destination.

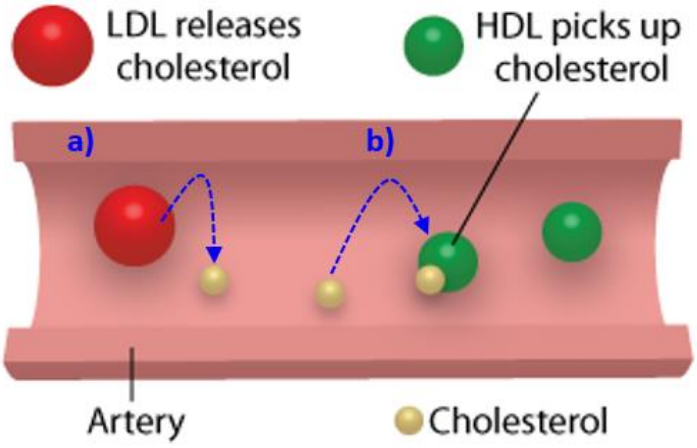



**Figure 15.4** This shows **a)** the LDL releasing cholesterol into the blood for delivery to nearby tissues. The opposite is seen in **b)** as the HDL picks up any excess cholesterol in the blood and returns it to

1. **Ultra Low-Density Lipoproteins**, these are also known as **chylomicrons** and consist of a phospholipid bubble that contains triglycerides, phospholipids, cholesterol, and proteins. They transport **dietary lipids** from the small intestines to other locations in the body.

2. **Very Low Density Lipoproteins** (**VLDLs**) are made in **liver,** they contain mostly **triglycerides** (~50%). These travel around the body and return **triglycerides** to liver. They can be converted into LDLs.

3. **Low Density Lipoproteins** (**LDLs**) these carry mostly **cholesterol** (~50%). They circulate in the blood and release lipids to cells of the body that need them, as they are required for membranes, hormones, insulators, etc. **The Liver removes LDL from circulation**.

4. **High Density Lipoproteins** (**HDLs**) these **transport cholesterol** from the **cells** back to the **liver** for recycling or disposal.

**The Importance of Lipids in the Body**

In summary, all of these lipids are vital to maintaining healthy functions in the body. This is why all of these carriers for them exist. It is especially important not to buy into the vilification of lipids, especially referring to the LDLs a "lethal" because they deliver cholesterol or HDL's as "healthy" because they take it away. Cholesterol cannot be bad, besides, the LDLs and HDLs are **carriers of cholesterol**, do not assign them labels of 'Bad 'or 'Good' cholesterol, it is silly and irrelevant. Elevated cholesterol is not the cause of cardiovascular disease - that is a scientific fact. It is a sign that something is wrong. The very elegant and functional transport system between the LDLs and the HDLs is a perfect example of the balance found in physiology.

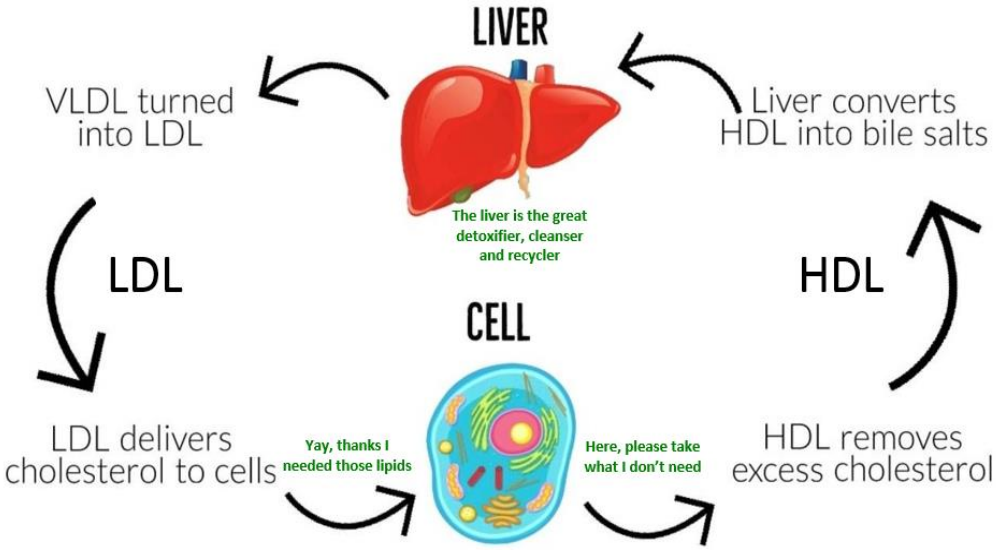



**Figure 15.5** This graphic shows the cyclic and balanced pattern of delivery and removal of cholesterol to and from the body's tissues. Very Low Density Lipoproteins (VLDL) are made in liver, convert into Low Density Lipoproteins (LDLs) which circulate lipids to tissues. The High Density Lipoproteins (HDL) transport cholesterol from the cells back to the liver for recycling or disposal.

## The Fat and Cholesterol Myth

It might be apropos to touch on the tyranny of the medical myths (widely held beliefs that are not true) about how bad fat and especially cholesterol is for your health. By now we should know that fat is a natural healthy part of your body.

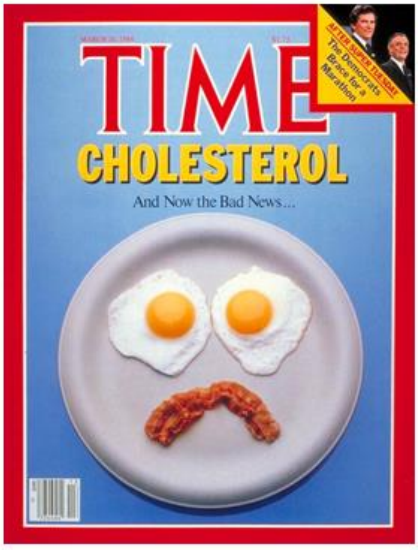
**The Seven Countries Study**

The trend to significantly reduce fats in our diet, especially saturated animal fats, took hold in the early 1960's due to the studies overseen by Dr. Ancel Keys called "The Seven Countries Study" purporting to find a causal link between diets high in animal fat and cardiovascular disease. The study was **deeply flawed** even by scientific standards at the time, but that has not stopped it from becoming the most cited study in human nutrition. Thankfully many genuine health mavericks, have been warning all for some time that blaming animal fat consumption for our poor nutritional health was absurd. Worse, not only was removing beneficial saturated fats from our diets very deleterious to human health, so too was the substitution of poly-unsaturated vegetable oils for those natural fats.

Now, 60 years after the initial findings were heavily promoted by all of the powerful health and medical groups, it is common knowledge that the information was not scientifically accurate. The truth is that saturated fats like butter and coconut oil are very nutrient rich and extremely beneficial to human health.

Read the article '**7 Reasons Why Butter is Good for You**' posted on the website. It may be time to break the scary programming. Still to this day, despite it being on the cover of Time Magazine in 2014 that "**Scientists Got it Wrong**", this mythos that fat causes heart disease continues to be an accepted lie. This lie is repeated in just about every textbook around, just one good reason to write your own textbook!


**Ancel Keys** cover of Time Magazine in **1961**. He claimed that saturated fats in the diet clogged arteries and caused heart disease.



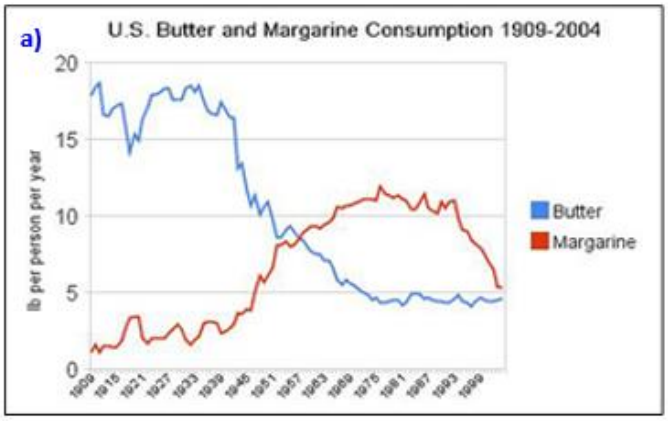

Time Magazine Cover from **1984** still busy blaming cholesterol and saturated fats as a cause of heart disease.


Time cover story in **2014**. Only now scientists had to admit they were wrong about saturated fats. They don't cause heart disease after all, they are actually good for you!

**Figure 15.6** Shows Time Magazine covers of: **a)** Dr. Ancel Keys in 1961 claiming saturated fats and caused heart disease; **b)** Perpetuation of the 'Bad Cholesterol' Myth in the 1980's; and finally **c)** a published 'correction' of labeling "Fat the Enemy" in 2014.

**Did Eating less Fat Reduce Cardiovascular Disease?**

Are you surprised that the answer to "Did eating less fat reduce cardiovascular disease" is No? As the below graphs in **Figure 15.7** indicate, the campaign to taint animal fats (like butter) as bad for your health has been a success! In addition, there was and still is a force that also encouraged American's to replace butter with heavily processed toxic **margarine**, containing hydrogenated vegetable oils which are toxic trans **fats** (read the article '**Margarine vs Butter**' posted on the website to see how margarine is made).



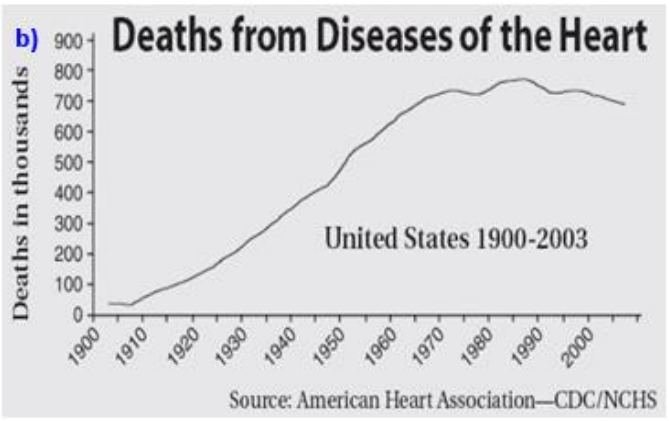




**Figure 15.7** Shows **a)** the rates of butter and margarine consumption per capita per year, and **b)** the number of deaths from diseases of the heart from the turn of the 20th century.

There was the removal of something good and beneficial (saturated fats) and the replacement of it with something toxic and deleterious (trans fats). Please note the time frame of the graph **a)** on the right in **Figure 15.7** above. At the same time that the consumption or butter and margarine were swapped out, the successful eradication of heart disease did **not** occur as the model that blamed animal fat for cardiovascular disease predicted. In fact, and has not occurred and likely never will occur - even the American Heart Association has to show on graph **b)** that the numbers for heart disease have gone up. In fact, **Heart Disease is the number one killer of Americans**. Number one. If the "Fat causes heart disease" myth were true, we would certainly not expect the numbers of people dying from heart disease to continue to **rise**.

But wait, there's more to the story. Not only was there an abandonment of healthy fats in the diets of adults in the United States, but there has also been a steady increase in the consumption of refined sugar over the last 300 hundred years, with an ***exponential increase in sugar intake*** over the last hundred or so years (see graph **b** in **Fig. 15.8**). It should be painfully obvious to anyone what the 'probable cause' for the skyrocketing rates of heart disease are in this and others countries. How much longer until more people embrace the truth of this health situation, and many other simple truths hiding in plain sight? Hopefully more and more will understand the truth, but people must seek out the truth in order to find it.

**The Replacement of Fats with Sugar**

As a nation, we have embarked on this low dietary fat crusade for 60 years now, and if heart disease has continued to be a major health issue, then are we at least less fat? Surely, as a result of the reduction in the percentage and types of fats in our diet, we are less fat as a result of eating less fat? The answer is No - Darn it! See **Figure 15.8** below. Americans are actually fatter because of it! How is that possible? It's possible by the simple fact that if you remove good healthy fats from your diet and replace them with refined highly processed carbohydrates (like sugars and starchy grains) the result will be more fat people. Any excess carbohydrates in the diet will be converted almost immediately in your body to, you guessed it, **FAT**. So the truth of the matter is you can eat zero fat and still gain weight in fat.

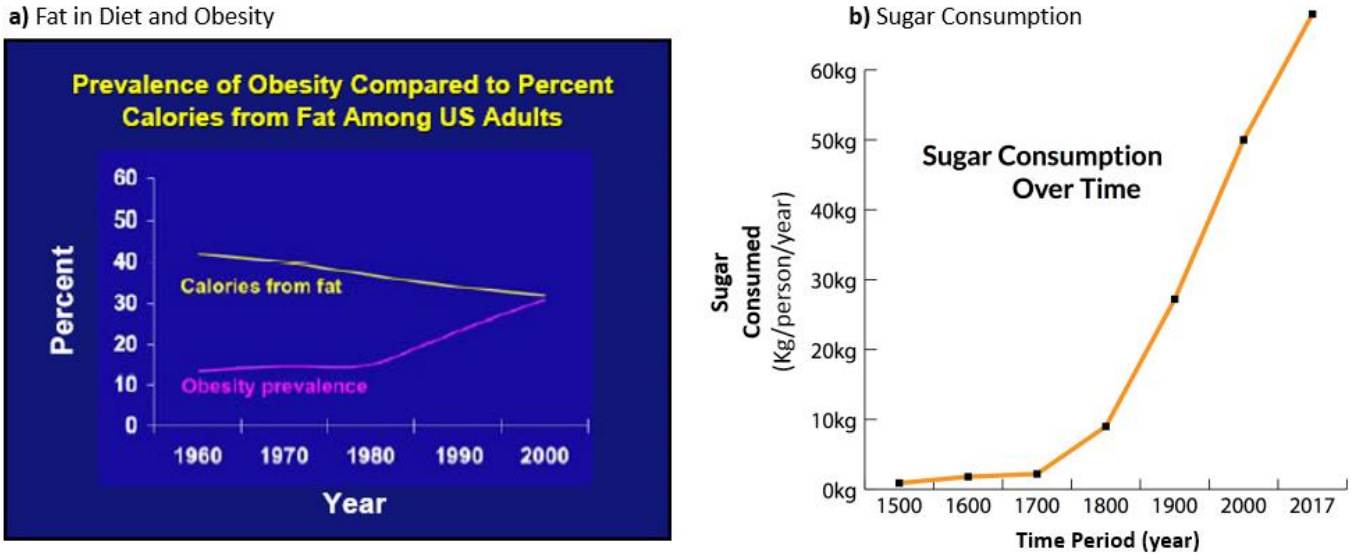



**Figure 15.8.** In graph **a)** it can be seen that although calories from fat decreased by about 10% starting from the 1960's, the prevalence of obesity did not decline. There is a notable incline in obesity during the mid-1980's coinciding with the introduction of High Fructose Corn Syrup (HFCS) to many beverages and the introduction of Diet Sodas, containing artificial sweeteners. In graph **b**) it can be seen that American's are now consuming more than 150 lbs (70 Kg) of sugar each a year. This is over twice the amount consumed compared to about 100 years ago.

**Other Solutes Dissolved in Plasma**

In addition to proteins, plasma contains a wide variety of other substances that are essential to a healthy functioning body. These include: glucose, amino acids, vitamins, fatty acids, triglycerides, cholesterol, ions/electrolytes ($Na^+$, $K^+$, $Cl^-$, $Ca^{2+}$, $H^+$, $HPO_4^{2-}Mg^{2+}$…$SO_4^{2-}$, $Zn^{2+}$, $HCO_3^-$…) urea, uric acid, creatinine, bilirubin, ammonia and dissolved gases $O_2$ and $CO_2$.

## Blood Cell Formation Overview

All blood cells (red and white) are produced in the red bone marrow by a process of **hematopoiesis**.

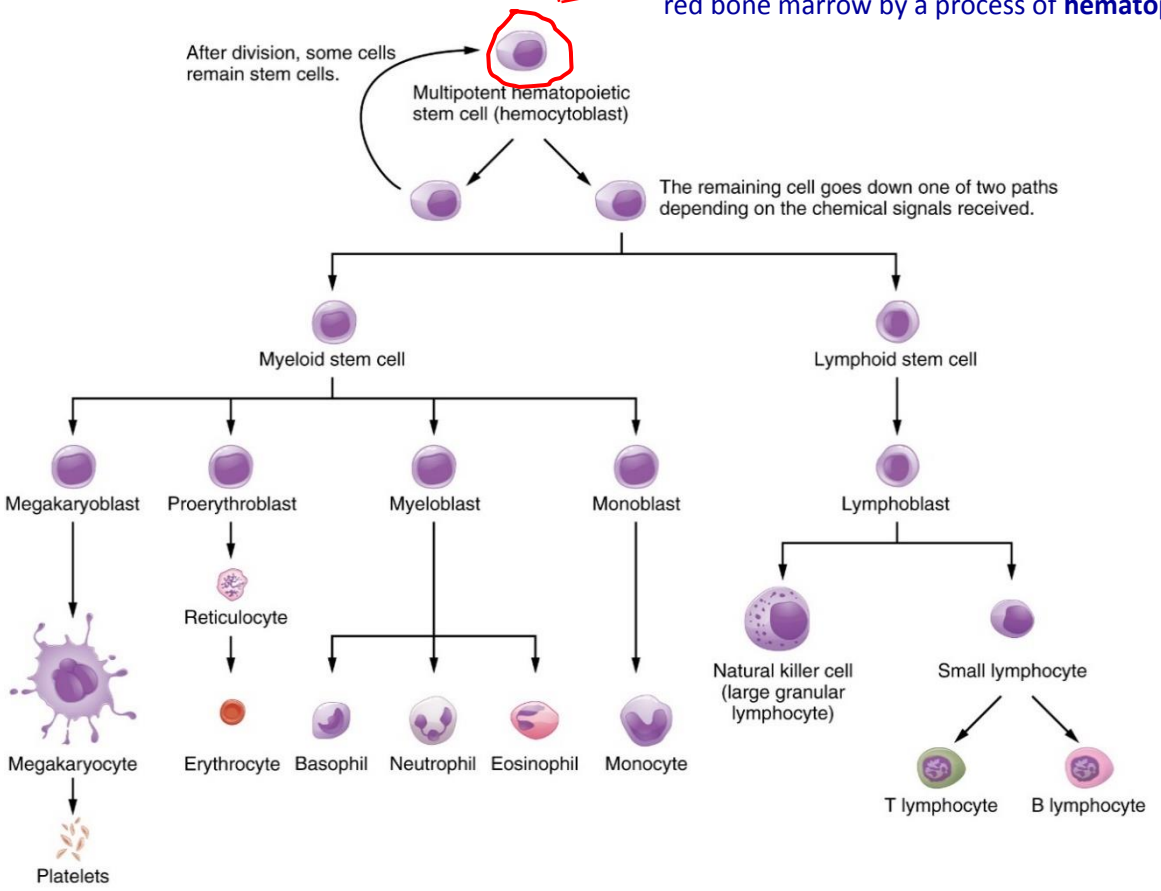



**Figure 15.9.** This chart shows the stem cell lineage of all blood cells that originate from the multipotent hematopoietic stem cell. The two main lines are the myeloid stem cell which yields platelets, erythrocytes, basophils, neutrophils eosinophils and the monocytes. The lymphoid stem cell generate the lymphocytes, the natural killer (NK) cells, T cells and B cells.

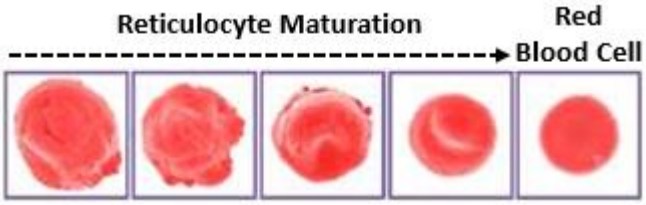
All blood cells, red, white, or platelets start with the exact same **hematopoietic stem cells**. As shown in the flow chart in **Figure 15.9** above, the multipotent hematopoietic stem cell (hemocytoblast) generates all blood cells. Hematopoiesis means 'making/generating blood' and we will discuss the lineage of each group along the way as we examine each type of cell separately.

## The Red Blood Cells (Erythrocytes)

As seen in the figure above, the myeloid stem cell generates 4 cells, one of which is the **pro-erythroblast,** the stem cells for RBCs. The name is a nice indication that it come before the erythrocyte. As these cells mature they begin to extrude the nucleus (kick it out!) and the cell then begins to fill with **hemoglobin** and they become **reticulocytes** - which are immature red blood cells. These cells then become the mature

bright red **erythrocytes** ready to squeeze from the red bone marrow and enter into the circulation via capillaries to begin their journey around the body.

In a blood sample, the reticulocytes can be distinguished from mature RBCs because they still contain portions of their nucleus (see image on previous page). Within a few days they become full-fledged RBCs. Therefore, a **reticulocyte count** of your blood will indicate your rate of **erythropoiesis**, or RBC production. The values for normal **RBC count** in blood ranges from 4.2 to 5.4 million/µL for females and 4.7 to 6.1 million/µL for males. This range for children is generally from 4.6 to 4.8 million/µL.




**Erythrocyte Sedimentation Rate** (**ESR**) is a measure of how fast red blood cells (erythrocytes) settle to the bottom of a tube over a given period of time. It is a test used to detect and monitor inflammation in the body. Normal sedimentation rates are 0-15 mm/hr for males and 0-20 mm/hr for females. Inflammation will *increase* sedimentation rate (i.e., RBCs will fall faster) while polycythemia (excessive RBCs) will *decrease* sedimentation rate (i.e., RBCs will fall more slowly).

**The RBC's are Special for many Reasons**

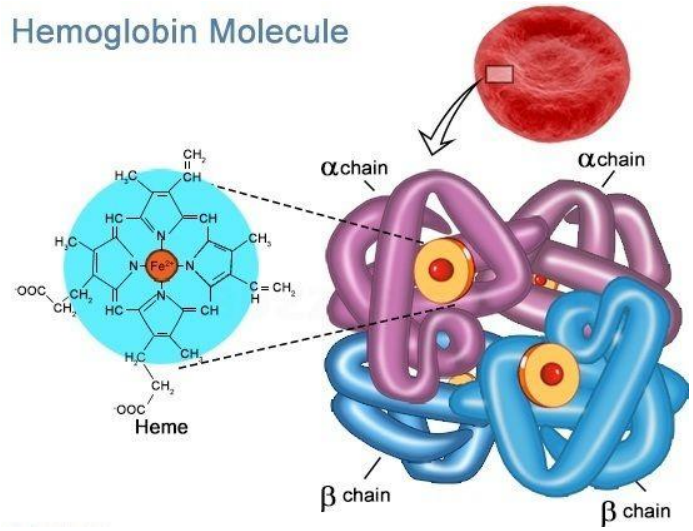
Firstly, RBCs are the most abundant type of blood cell, in fact, more than **99%** of all cells in blood are RBCs. This cell is what gives blood its deep red color.

The RBC is highly specialized for its purpose, which is to transport gases, Oxygen ($O_2$) and some Carbon Dioxide ($CO_2$). These cells lack many of the organelles found in most cells – they have **no nucleus**, **no ribosomes**, and **no mitochondria**. With so few organelles, these leaves a lot more room for more hemoglobin (Hb) molecules. Each RBC contains about **250 million** hemoglobin molecules, which helps transport $O_2$ and $CO_2$ in the body.

RBCs are very small cells, in fact they are the **smallest** blood cell in terms of diameter, ranging from **7 to 8 µm**. They are also are very **flexible** cells because they contain the membrane protein **spectrin**, which gives elasticity to the cell, enabling it to squeeze through the smallest blood vessels. This cell can almost fold in half when traversing very narrow vessels.

An important reason RBC do not have any mitochondria is because they do not want to use the $O_2$ they are carrying, and the mitochondria are for making ATP – in the presence of $O_2$. RBCs still need ATP, but they generate it anaerobically (without using $O_2$). In order to do this they need to contain enzymes in their cytosol for glycolysis, so they can to make limited ATP w/out using the $O_2$ they are transporting. The cell markers (antigens) on the external surface of the RBC are made from glycoproteins and glycolipids and determines your **blood type** (discussed later).

The **red bone marrow** makes all blood cells, including RBCs. There are about **2.5** million RBCs per sec produced and released into the circulation.




One RBC contains about **250 million** Hb molecules. This works out to be that 1 RBC can carry as many as 1 billion molecules of oxygen ($O_2$). Whoa, that's a lot of oxygen! The Hb binds and transports Oxygen ($O_2$) and some Carbon Dioxide ($CO_2$) in the body. The Hb molecule contains **4 globin portions** (2 α and 2 β chains). At the center of each globin is an iron (Fe) containing **Heme** molecule.

If there are about 2.5 million RBCs per sec produced and released into the circulation, then if we count to two: 1 one thousand, 2 one thousand – you've made about 5 million RBCs in that time span.

**Figure 15.10** There are millions of hemoglobin (Hb) molecules found inside every red blood cell. A single Hb molecule is composed of four globin amino acid chains (two alpha and two beta), with a heme containing molecule at the center of each globin. It is the heme portion that binds the oxygen ($O_2$) and transports it in the blood.

## Limited Life Span of RBCs

As a consequence of their specializations, RBCs have a limited life span and can circulate around the body for up to **120 days**, until they become worn out. With no real organelles inside the cell, they have limited repair capability. The older or damaged RBCs are culled (removed) from circulation by specialized cells (macrophages) in the **spleen** and **liver**. If 2.5 million RBCs are being *made* per second to maintain homeostasis, this means approximately 2.5 million RBCs are being *removed* from circulation each second. If there is a need for more RBCs, the kidneys release the hormone **erythropoietin** (means 'red cell maker') to stimulate RBC production in the red bone marrow.

In a lab it is measured by spinning a sample of blood in a hematocrit tube with a high speed centrifuge. In the process the heavier elements (cells) separate from the lighter (fluid) plasma, with the formed elements settling at the bottom of the hematocrit tube. Suspended on the top of the sample is the straw colored liquid that is plasma, which can also be called the **supernatant** - this comes from a Latin word meaning 'to swim above' or to 'float on the surface'. In between these two separated portions of spun blood is a layer called the **buffy coat**. This is due to its opaque color. It normally constitutes less than 1% of a blood sample and is composed of the white blood cells (WBCs) also called **leukocytes**, and the **platelets**, (also called **thrombocytes**) which are actually cell fragments. A *thrombus* means blood clot, and platelets are involved in clotting of the blood, so this name is a great indicator of function.

## Hematocrit

The blood hematocrit is the percentage volume of red blood cells in blood. Blood **hematocrit** can be measured from the spun blood sample, and it can also be referred to as is the **packed red blood cell volume** or packed cell volume (PCV) of blood. Basically it measures the % of RBCs in the total volume of blood. Normally, in a healthy person about **45%** of a blood sample is erythrocytes.

**Hematocrit** can vary because like all other physiological parameters, it exists in a range. In general, it can range from about 36 to 50%, but there are important factors that influence that range, including gender, age, geographical location and other conditional factors.

- Normal hematocrit for **females**: Range **37** to **47%** (average **41%**).
- Normal hematocrit for **males**: Ranges **42** to **52%** (average **47%**).


The values for the other cells present in blood (WBCs and platelets), is so small that it's not normally considered with the hematocrit value.

If a person's hematocrit is low, it's possible to increase it by increasing the consumption of red meat, especially liver, fish and shellfish (oysters, clams, shrimp, and scallops), dried fruit (apricots, prunes, and peaches), and green leafy vegetables, all are rich in iron.

**Figure 15.11** Shown here is the centrifuge (left) and the hematocrit reading (right) as a percentage of the whole blood.

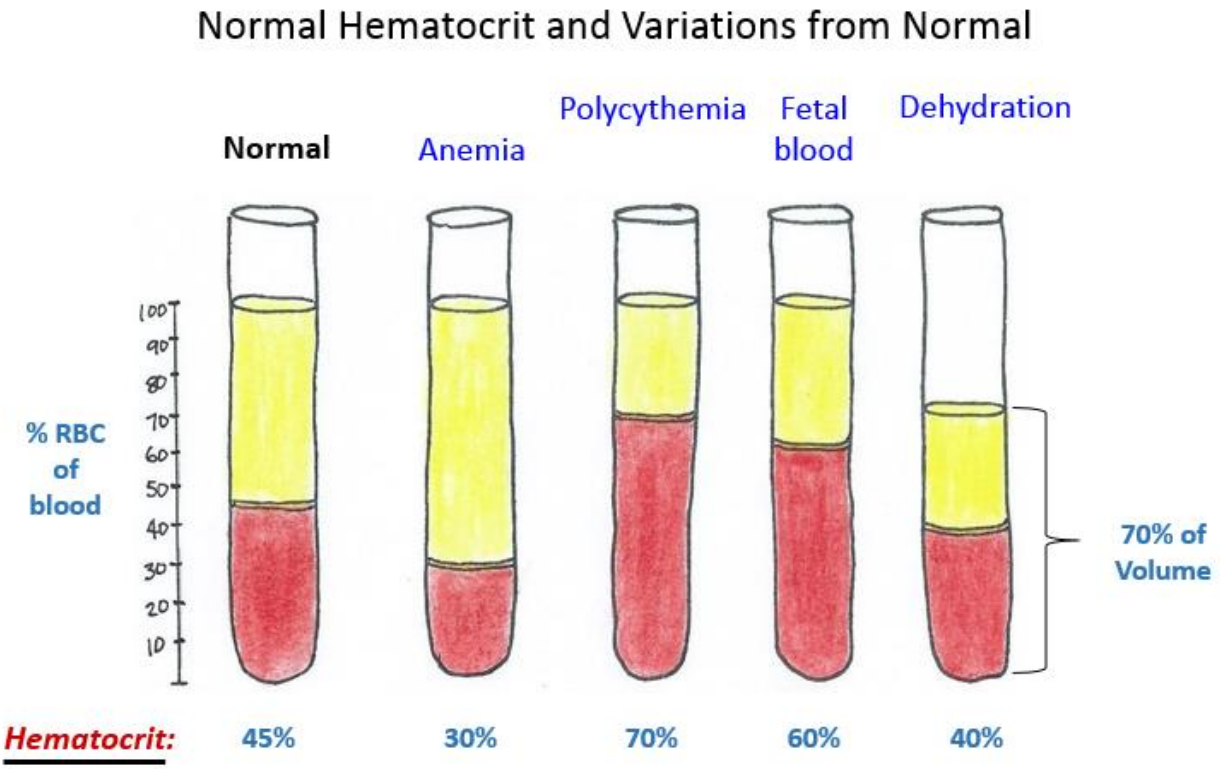



**Figure 15.12** Here we have a comparison of normal blood hematocrit (45%) to various conditions such as anemia, and polycythemia. Also shown is typical hematocrit for fetal blood, and during periods of dehydration.

## What is Anemia?

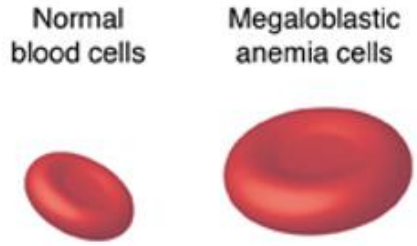
**Anemia** is a condition in which there is a deficiency in the $O_2$ carrying capacity of blood that is due to a decrease in RBCs or hemoglobin. There are many forms of anemia, and regardless of the form it commonly results in pallor (paleness), weakness and weariness.

### There are 3 basic Categories of Anemia

Anemia is a general term and often a fuller descriptor is provided by the inclusion of the category of anemia, which is really a description of how the state of anemia arouse. The three broad categories are below.

### 1) Inadequate Erythropoiesis

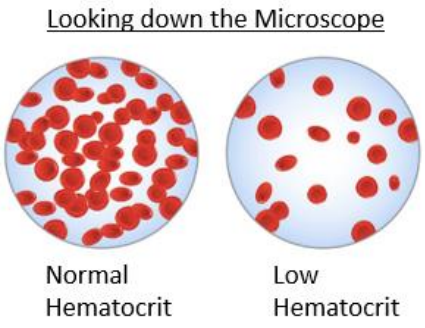
The term **poiesis** means to generate or make, so erythropoiesis means to make erythrocytes or red blood cells (RBC's). This condition of inadequate RBC production can arise in several ways, leading to the problem of not making enough healthy red blood cells. A common way it can be caused is from inadequate nutrition, for example an **iron deficiency** will prevent enough heme from being available for the hemoglobin molecule which is carried by the RBC's. A deficiency in the **vitamin $B_{12}$** (folate) will lead to '**pernicious anemia**'. This deficiency in $B_{12}$ causes the body to produce abnormally large red blood cells (called **megaloblastic** cells) that cannot function properly (see above).

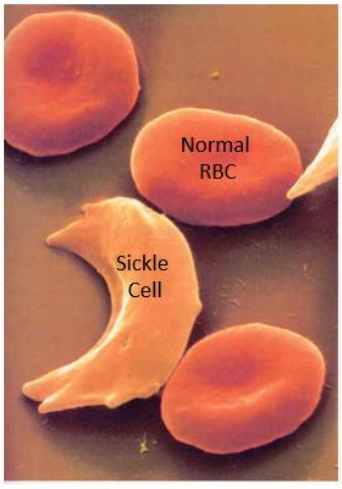



Another example of inadequate erythropoiesis occurs when the hormone **erythropoietin** (meaning 'erythrocyte maker') that is released from the kidneys is too low to make stimulate sufficient RBC production in the red bone marrow. This results in lower than normal RBC count or a **low hematocrit**.

### 2) Hemolytic Anemia

The term hemolytic means to lyse (cut) blood cells. This category refers to the abnormal breakdown of RBCs. The types of inherited hemolytic anemia include sickle cell disease and thalassemia. **Sickle cell anemia** (within a group of disorders called sickle cell disease, is a genetic blood disorder in which the β subunit of the globin portion of the Hb has a mutation, and this causes malformed RBCs leading to deformed RBCs that take on a characteristic sickle shape. These inflexible misshaped cells block small blood vessels causing pain and hampering gas exchange. In this condition there aren't enough healthy red blood cells to carry adequate oxygen ($O_2$) throughout the body. This is caused by the substitution of single amino acid in a chain of 126 amino acids. At position 6 in the beta-globin, **valine** replaces **glutamic acid**. This results in the production of abnormal beta-chains, called 'S hemoglobin'.



Sickle Cell Anemia

**Thalassemia** is a genetic disorder which leads to the destruction of RBC and anemia. It is caused by an inadequate amount or an abnormal form of Hb in the red blood cells. The term 'thala' comes from the Greek word for 'sea' as it was first known around the Mediterranean, and of course 'emia' means blood.

**3) Hemorrhagic Anemia** is a loss of blood volume. This can occur with **physical trauma** that involves laceration (tearing) of a blood vessel and blood loss (either internally or externally). It can occur due to a disease state, for example a blood vessel with an aneurysm (weakening of a vessel wall) could rupture, again leading to blood loss form he closed circulatory system. Finally, it could involve **hemophilia**, which is usually an inherited disorder in which the blood does not clot properly. It can lead to spontaneous excessive bleeding, in addition to bleeding after an injury or surgery. Having too little of factors VIII (8) or IX (9) is what causes hemophilia. A person with hemophilia will lack only one factor, either factor VIII or factor IX, but not both. There are two major kinds of hemophilia: hemophilia A, which is a factor VIII deficiency; and hemophilia B, which is a factor IX deficiency.

**Some useful Terms and Definitions for this Section:**

**Hypoxia** - state in which the $O_2$ is insufficient for normal life functions.
**Hypoxemia** - occurs when arterial $O_2$ supply is below normal, typically below **95% $O_2$** saturation.
**Oxyhemoglobin** - compound formed when $O_2$ is bound to hemoglobin, becomes $HbO_2$.
**Carbaminohemoglobin** - compound when $CO_2$ binds Hb. About 10% of $CO_2$ in blood carried this way.
**Carboxyhemoglobin** - complex of **carbon monoxide** (CO) and Hb that forms in red blood cells.
**Polycythemia** - elevated hematocrit (too many RBCs in blood); can be adaptive or pathological.

## The White Blood Cells or Leukocytes

The leukocytes, or white blood cells (WBC's) are the others cells in blood (they reside in the buffy coat when blood is spun). These cells are a part of the body's phenomenal immune system. They protect and assist the body when it is fighting an infection and other diseases. The two broad types of white blood cells are the granular leucocytes (neutrophils, eosinophils, and basophils), and the agranular leucocytes (monocytes, and lymphocytes – including natural killer cells, T cells and B cells).

### The Histology of White Blood Cells

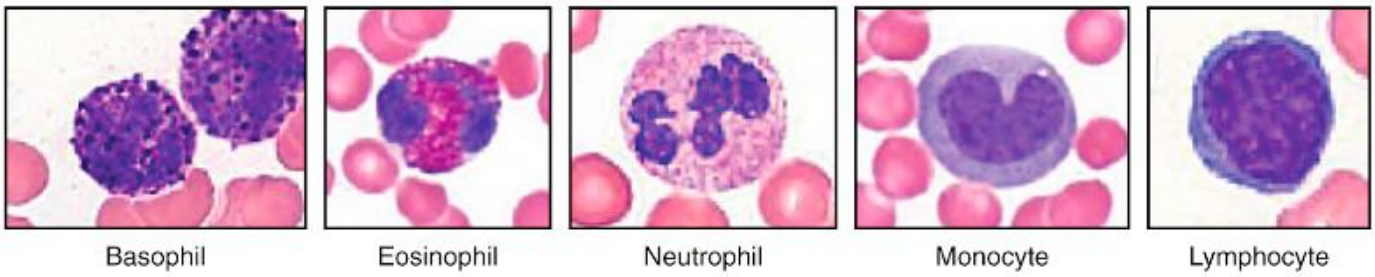



**Figure 15.13** This shows a blood sample of **a)** whole (or mixed) blood, and **b)** separated blood after having been spun at high speeds in a centrifuge. In the spun blood we can see the 2 major components of blood, the plasma, which is the supernatant on top and the heavier formed cellular elements on the bottom.

### Granular Leukocytes

These are leukocytes that have cytoplasmic granules that contain very powerful enzymes & substances for defense. They 'degranulate' and release the contents of the granules when triggered.

**Neutrophils** make up 60-70% of total leukocyte count in human blood. These are very active in **phagocytosing** bacteria, their activity and death in large numbers forms the pus of wounds. They defend against bacterial and fungal infection.

**Eosinophils** primarily deal with **parasitic** infections and are also the predominant inflammatory cells in **allergic** reaction (e.g. asthma, hay fever and hives). They engulf and destroy foreign cells.

**Basophils** are responsible for allergic and antigen responses by releasing ***histamine*** at the site of tissue injury causing vasodilation, and for release ***heparin*** to limit the size of a forming blood clot.

### Agranular Leukocytes

These leukocytes do not contains granules in their cytoplasm. **Lymphocytes** are formed in red bone marrow but they arise from **lymphoid stem cells** and are much more common in the **lymphatic system** where much of their differentiation occurs. Lymphocytes are normally 20 to 30% of the total WBC count, making them the second most abundant type of WBC. In general, they engulf and destroy viruses and release antibodies. The blood has three types of lymphocytes: **Natural Killer (NK) cells, T cells and B cells.**

- **Natural killer (NK) cells** are capable of recognizing foreign cells that are not "self", as indicated by cell markers or proteins or abnormal markers on their plasma membrane. These cells can detect cancerous cells and those infected with a virus, and other anomalies. These NK cells provide a general, non-specific immunity. In terms of identifying them in histology slides, if a lymphocyte is a big larger, typically they will be NK cells.

- The **T cells** undergo maturation in the thymus (where they get their 'T' name), and T cells provide cellular-level immunity by physically attacking foreign or diseased cells directly.

- The **B cells** undergo a maturation process in the bone marrow (where they get their 'B' name). A form of B cell (plasma cells) produces **antibodies** (immunoglobulins) that bind to specific foreign or abnormal components of plasma membranes. This is also referred to as humoral (body fluid) immunity.

**Monocytes** in the blood phagocytose (engulf and destroy) microorganisms, cancerous cells, dead leukocytes and cellular debris. They also present pathogens to T cells for recognition so that an antibody response may be mounted. Unlike neutrophils, monocytes are able to replace their lysosomal contents and have a longer active life. Eventually monocytes leave the bloodstream to become tissue ***macrophages*** which remove dead cell debris as well as attacking microorganisms.

**Leukocytosis** is used to describe a high WBC count, whereas **leukemia** is caner of the WBCs. **Leukopenia** is low WBC count, which is almost always related to a decrease in neutrophils

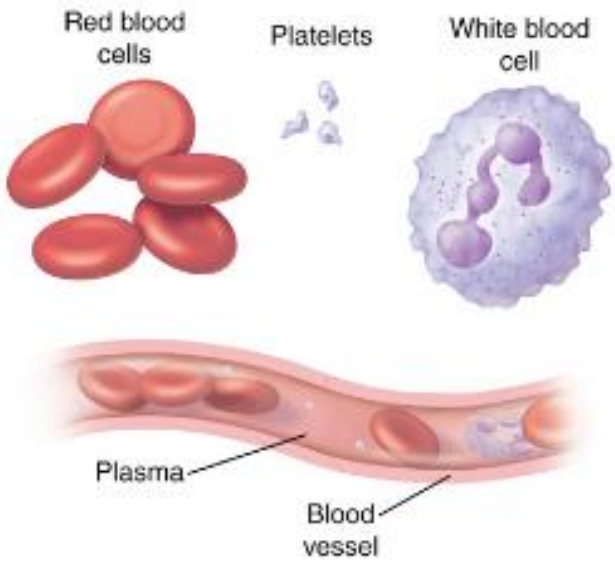
**Platelet cells** are very small and they are not actually cells, but are fragments of a larger type of cell called a **megakaryocyte**. **Platelet** cells are also called **thrombocytes**. Because they play a significant role in thrombosis (formation of a blood clot). The function of platelet cells is to prevent blood loss by starting a chain reaction that leads to initiation of blood clotting.

Platelet are *very small*, being 2-3 µm in diameter. Compare that to a RBC that is from 7-8 µm. Most platelets are biconvex discoid (lens) shaped cell fragments that have many granules but no nuclei. These cells play a major role in blood clotting (hemostasis). Between **150,000** and **400,000** are found in each cubic millimeter ($mm^3$) or micro liter (µL) of blood.

The condition of having a low blood platelet count is called **thrombocytopenia**, since platelets are also called thrombocytes and -penia means deficiency. Thrombocytopenia might result due to disorders, such as leukemia of from excessive toxicity of bone marrow or the immune system. Characterized by easy or excessive bruising (purpura), and bleeding into the superficial skin regions, yielding reddish-purple spots (petechiae) often on the lower legs.

### General Life Spans of the various Blood Cells

With limited repair capability, RBCs have a limited life span (120 days). Worn, older and damaged RBCs are removed from the circulation in the sinusoidal capillaries by **macrophages** in the spleen and liver.




Red blood cells (RBCs) have a life span of about **120 days** and white blood cells (WBCs) have a life span that ranges from **13 to 20 days**. Platelet cells have a very short lifespan, normally just **5-9 days**, predominantly because they are expended in clotting and do not carry on extensive metabolic activity. The normal number of leukocytes (WBCs) in blood is **5,000** to **10,000** per cubic millimeter ($mm^3$) or micro liter (µL).

If more RBCs are needed, the kidneys release the hormone **erythropoietin** to stimulate RBC production in the red bone marrow.

**Figure 15.14** Illustrated in the drawing above are the relative sizes of blood cells, comparing erythrocytes, leukocytes and platelets (which are not cells but fragments of megakaryocytes. It also shows how these cells travel within the plasma (fluid portion of blood) through the smallest of the blood vessels, the capillary.

## Overview of ABO Blood Groups (Types)

A blood type (also called a blood group) is a classification of blood based on the presence or absence of genetically determined 'flags' or cell markers on the surfaces of RBCs called ***antigens*** (also referred to as **agglutinogens**). It is the plasma of blood that contains ***antibodies*** (also called **agglutinins**).

The **Antigens - these determine blood type.** The ABO blood group is based on two antigens called **A** and **B** (see below). Individuals whose RBCs display only antigen A, have blood type A. Individuals who display only antigen B have blood type B. If both **A** and **B** antigens are displayed, the result is type AB blood.

The absence of both A and B antigens results in type O blood. Fill in the blood types for the RBCs in **Figure 15.15** below:

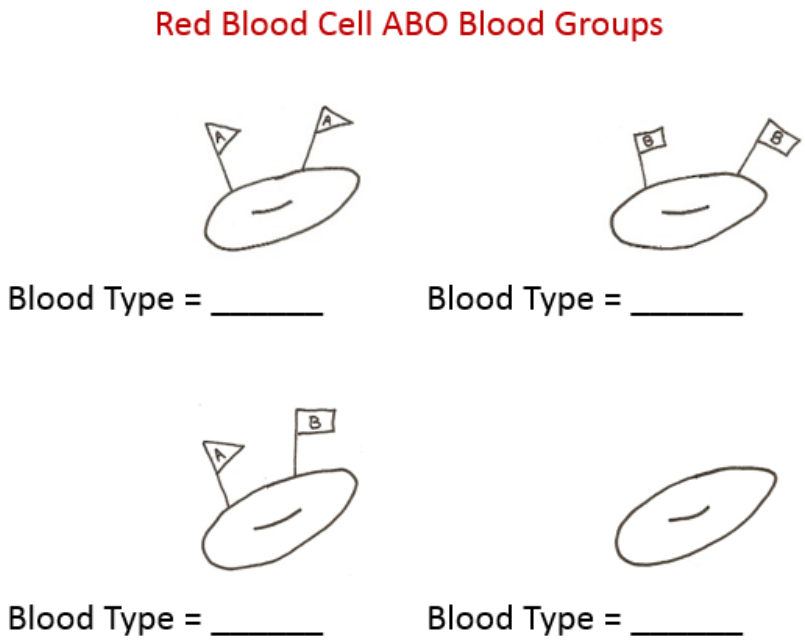


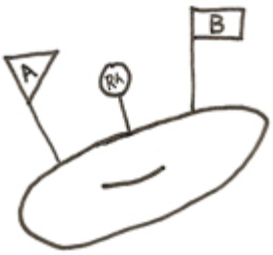

**Figure 15.15** In this illustration, the exercise is to examine the 'flags' (cell markers) on each of the red blood cells and from the presence or absence of flags determine the general blood type (A, B , AB or O) for each of the cells.

### The Natural Antibodies

There are natural ***antibodies*** in blood plasma. The anti-A antibody reacts with and attacks antigen A, and the anti-B antibody reacts with and attacks antigen B. Therefore, a person cannot have antibodies in their plasma that match their blood type because the antibodies would attack the antigens of their own red blood cells and may clump. Hence, if you have an A on your RBC, then your plasma has only B antibodies, no A antibodies. This is because if a RBC carrying an antigen were to mix with plasma that contains the corresponding antibodies - **agglutination** or '**clumping'** of blood would occur. This is bad if you want blood to flow and help keep you alive. As you can imagine, **antigens** and **antibodies** are of critical importance in blood transfusions. If certain bloods are mixed, agglutinated cells become lodged in small capillaries throughout the body and, over a period of hours, the cells can swell, rupture, and release hemoglobin into the blood, this is called **hemolysis**. Therefore, certain blood types cannot be mixed!

### Rh Blood Group

The Rh system is the second most significant blood-group system that is commonly used. It is much more involved than this, but simply put the Rh factor is another RBC marker and you either have the Rh antigen (Rh positive or $Rh^+$), or you do not (Rh negative or $Rh^-$). Together with the **ABO** blood typing, the absence or presence of the Rh factor is also included in the comprehensive blood grouping. For instance, if a person has type A antigen on their red blood cell and no Rh factor, then their blood type is $A^-$ (A negative).




How would you name the Blood Type on the RBC shown to the upper right? = _____

A compelling analogy for the 8 blood types is the picture to the right of the 8 donuts. The type of icing on each donut represents the A antigen (brown) and the B (pink) antigen. Note the lack of an antigen O is represented as a plain donut with no icing. The sprinkles represent the having the additional Rh factor or not (no sprinkles). Interestingly, if you look up the Note how the plain donut, without any sprinkles even, represents type $O^-$ blood!

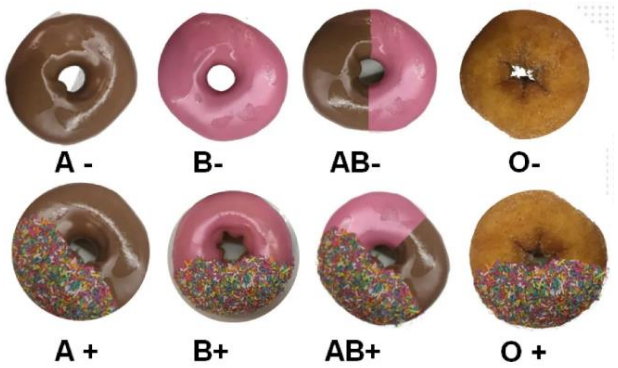



**Figure 15.16** The donuts to the right represent the eight blood type categories indicated. Brown icing is A and pink icing is B. No sprinkles is - for Rh factor and sprinkles present means + for Rh.

**Hemolytic Disease of the Newborn** (**HDN**)

The Rh factor can be important during a second pregnancy and childbirth. Under normal circumstances, human plasma does not contain anti-Rh antibodies. If, however, a woman who is $Rh^-$ becomes pregnant with an $Rh^+$ child, then her blood *may* produce antibodies that will react with the blood of a subsequent child. The first child is unaffected, as the mother's body has not yet produced antibodies. This can lead to a reaction and **hemolysis** may occur in the fetal blood, produced by fetal maternal incompatibility called ***hemolytic disease of the newborn*** *(or fetus)*, and could be fatal for the newborn infant.

## Hemostasis - Stopping Blood Loss.

The word hemostasis indicates the function (hemo = blood, stasis= stationary) = stopping blood. This is the process in the body that prevents **hemorrhage**, which is excessive bleeding leading to loss of blood volume. This is a protective measure, to prevent excessive blood loss and tissue damage.

**There are 3 Steps for Hemostasis to Occur**

1. **Vascular spasm**
2. **Platelet plug formation**
3. **Coagulation (blood clotting)**

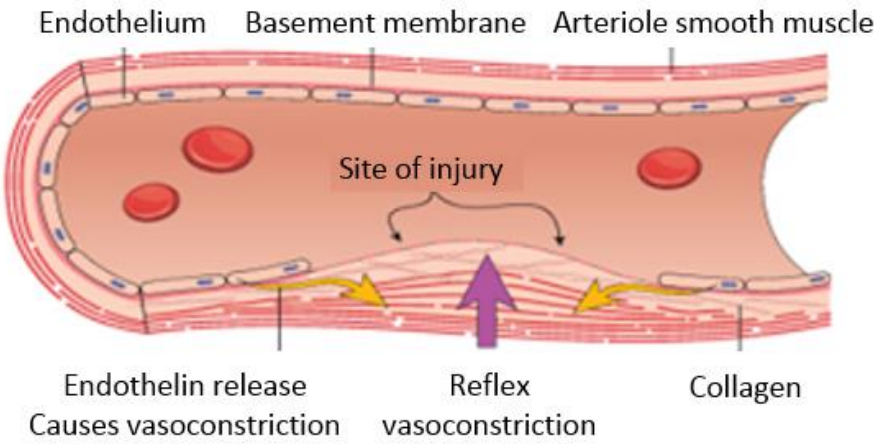



**Figure 15.17** An injury to a small arteriole will reflexively involve a vascular spasm, which is the vasoconstriction of the vessel from the release of the nearby paracrines endothelin from the endothelial cells that line the blood vessel. The next step after vascular spasm is the formation of the platelet plug, which is commenced by the exposure of collagen fibers to the interior vessel surface.

**1) Vascular Spasm**

Vascular smooth muscle (VSM) in walls of ruptured/damaged blood vessel **contract** – pain receptors are the signal and endothelial cells release **endothelin**, a vasoconstrictor! This reduces blood flow/loss. This is illustrated in **Fig. 15.17** above and also in **Fig. 15.18** below. Interestingly, all endothelial cells of vessels have an outer coating of **prostacyclin**, a platelet cell repellant! Only when endothelial cells are damaged and this layer is gone, can platelets cells become activated.

**2) Platelet Plug** - this occurs as **platelet cells are activated** accumulate and **adhere** at the site of vessel injury. A damaged (ruptured) vessel exposes **collagen** – this triggers platelet cells (via pseudopods) to stick to damaged vessel. Then platelets degranulate releasing: **Serotonin** (yes, the NT!) here it acts as a vasoconstrictor; **Prostaglandins**, vasoconstrictors; **ADP**, this attracts and degranulates more platelets.

*All of this causes **platelet cell aggregation** (a positive feedback loop) and the cycle continues until it is broken when the small vessel is sealed.*

**3) Coagulation** (blood clotting) - this part is complex and it the final crescendo in reducing bleeding. It involves the conversion of the plasma protein **fibrinogen** into insoluble **fibrin** threads which create a net-like framework necessary for blood clotting to occur. Pro-coagulants (clotting factors) activate the steps to form a series of **reaction cascades**.

There are three pathways involved in Coagulation:

- ❑ Extrinsic Pathway: Factors released by damaged tissues begin the cascade.
- ❑ Intrinsic Pathway: Factors found in blood begin cascade (platelet degranulation).
- ❑ Common Pathway: Both the intrinsic and extrinsic pathways lead to the common pathway, in which fibrin is produced to seal off the vessel.

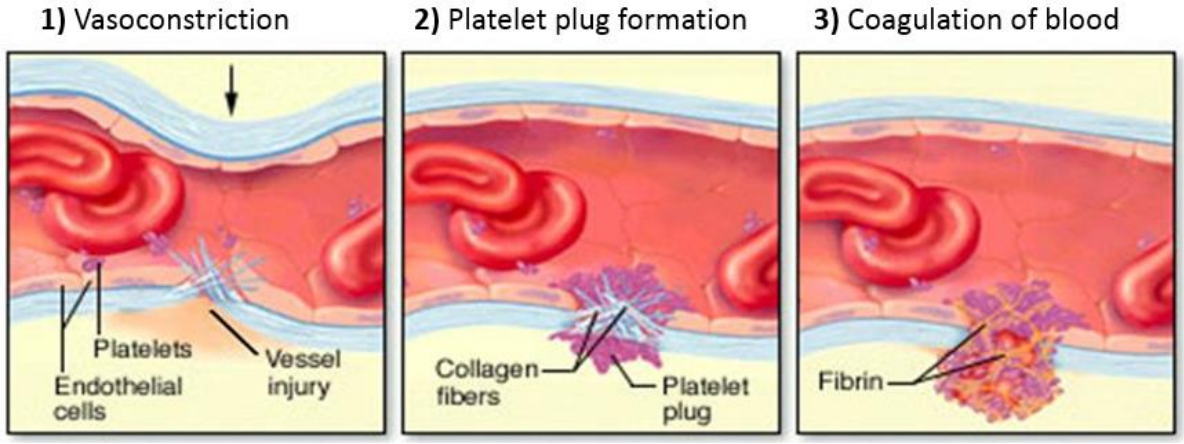



**Figure 15.18** In summary, the three steps are distinct: **1)** vasoconstriction, the vessel contracts to reduce blood flow; **2)** platelet plug formation to adhere to the site of injury, and **3)** coagulation with fibrin to reduce bleeding.

**Common Pathway**

Once factor X has been activated by either the intrinsic or extrinsic pathway, the enzyme prothrombinase converts factor II, the inactive enzyme prothrombin, into the active enzyme **thrombin**. Then, thrombin converts factor I, the soluble **fibrinogen**, into the insoluble **fibrin** protein strands. Factor XIII then stabilizes the fibrin clot. There's a whole other series of enzymes to dissolve the clot when no it's longer required.

## Blood Glucose Levels

The glucose in blood is called 'blood sugar' or 'blood glucose'. Glucose is a simple sugar (monosaccharide) and is used as a fuel for the body's cellular activities. Therefore, glucose levels in our blood are homeostatically controlled in our body: if blood glucose gets **too low**, mechanism exist to **increase it**; if blood glucose gets **too high**, mechanism exist to **decrease it**. Hence, this parameter is tightly regulated by a negative feedback loop. The regulation of blood glucose involves the endocrine system and two hormones with opposing (antagonistic) actions, **Insulin** and **Glucagon**. In **Table 15.1** below, the basic values for blood glucose are given for various states, showing the pattern of what occurs to blood glucose levels when fasting and after eating.

For a 150 lb (70 kg) person about 4 grams of glucose (about a teaspoon) is circulating in the blood at any time. **Glycogen** is the storage molecule for glucose and provides a source for glucose when it is low in the body. Both **skeletal muscle** and **liver** cells store glycogen as a reserve for glucose (the **uterus** also stores glycogen). These stores are quickly hydrolyzed liberating free glucose into the bloodstream during periods of fasting in order to maintain blood glucose at a constant level. Neurons in the nervous system consume about 60% of blood glucose in fasting, sedentary individuals, thus nervous tissue relies heavily on glucose to remain functional. This is why maintaining stable levels of blood glucose is so vital.

**Table 15.1** Comparison of various blood glucose levels and what they indicate.

| What Blood Glucose Levels Likely Indicate | | | |
|---|---|---|---|
| mg/dL | Fasting | After Eating | 2-3 hours After Eating |
| Normal | 70 - 100 | 170 - 200 | 120 - 140 |
| Impaired Glucose | 110 - 125 | 190 - 230 | 140 – 160 |
| Diabetic | 130+ | 220 - 300 | 200+ |

### Hyperglycemia and Hypoglycemia

Persistently elevated levels of blood glucose is referred to as **hyperglycemia**; (*hyper* =higher than normal; *glyc* = glucose; *emia* = blood). Whereas, persistently low levels of glucose in the blood are referred to as **hypoglycemia** (*hypo* ='lower than normal', *glyc* = glucose, *emia* = blood). The occurrence of hyper- or hypoglycemia may be in direct response to activity or substances ingested, or may indicate an abnormal imbalance in the body. Circadian patterns for glucose levels typically are lowest in the morning, especially after cortisol levels fall (after 11am) prior to eating the first meal of the day, and rise after meals for an hour or two. Physical activity also lowers blood glucose. Alcohol intake causes an initial surge in blood sugar, and later tends to cause levels to fall. Also, certain drugs can increase or decrease glucose levels. Two hormones released from the **pancreas** are **insulin** and **glucagon**, they act together to balance metabolic activities and blood glucose levels.

**Insulin** is made by beta cells in pancreatic islets of the pancreas and favors *anabolic reactions by* storing energy and producing proteins and glycogen. Insulin **decreases blood glucose** by inserting **Glut-4 transporters** into cells to import glucose. The more Glut-4 transporters inserted, the more glucose is imported into cells, lowering glucose levels in blood.

**Glucagon** is made by alpha cells in the pancreatic islets and favors *catabolic reactions* by hydrolyzing stored glycogen, lipids and protein. Inducing glycogenolysis (breaking down glycogen) liberates glucose into blood, **elevating blood levels**. It also stimulates gluconeogenesis, ('making new glucose') which makes glucose from lipids and proteins (non-carbohydrate sources), sparing available glucose for neurons.

### What is Diabetes Mellitus?

**Diabetes Mellitus** (DM) is a disorder characterized by persistent hyperglycemia which may occur for several reasons. It is the most prominent disease associated with an inability to regulate blood glucose levels. There are two types of DM, Type 1 DM and Type 2 DM (see below). Diabetes Mellitus ranks as #7 in the top leading causes of death in the U.S. This is thought-provoking when we understand that that the vast majority of DM cases, about 90% (see below), are caused by lifestyle choices (e.g., diet and exercise) and can be completely 100% reversed without any drugs at all.

**Type 1 Diabetes Mellitus**

The type 1 diabetes mellitus (DM) is also called "juvenile-onset" or "insulin-dependent" diabetes, as symptoms appear during childhood (in two age ranges, between 4 and 7, and 10 and 14 years of age). The insulin decedent term is because insulin injections are used to treat it. Only about **10%** of DM cases are type 1. This type is caused by an **autoimmune disorder** in which **the immune cells of the body attack the beta cells of the pancreas until they are destroyed**. Since the beta cells of the pancreas make **insulin**, gradually the insulin levels will diminish below normal, and ultimately insulin cannot be made at all. As a consequence, the body cannot utilize the glucose that is circulating in the blood, and blood glucose levels remain high, resulting in **hyperglycemia**. Although the initial cause of hyperglycemia in type 1 is created by a different mechanism to type 2, the long term effects and consequences of type 1 and 2 diabetes mellitus are virtually identical.

**Type 2 Diabetes Mellitus**

The type 2 diabetes mellitus is also called "non-insulin-dependent", and is much more common than type 1, accounting for about **90%** of cases. This is caused by **life-style choices**. The main culprit is the choice to indulge in a **poor diet**. The condition of type 2 DM is created by consuming excessive amounts of refined carbohydrates (**especially sugars**) over a long period of time. This includes **simple carbohydrates** (breads and cereals), as well as candy and soda. Another huge impact is the level of physical activity a person regularly engages in. The more sedentary (inactive) the life style the much higher the risk of DM. Other life-style factors such as drinking alcohol and smoking also elevate the risks.

In type 2 DM when glucose levels are chronically elevated in the blood, insulin levels must also be very high in order to handle this continuous excess load of sugar in the blood. As a consequence, **insulin receptors on target cells of the body experience down-regulation due to overstimulation by insulin**. This ultimately brings about a ***desensitization*** of the body's cells to insulin. The result is elevated blood glucose while many cells in the body starve because they cannot use the glucose that is in abundance in the blood vessels. In addition to this, the pancreas must produce massive amounts of insulin, as more and more is required since the cells have lost their sensitivity to it - this causes the pancreas to become exhausted and become unable to meet the excessive demands.

Most searches online about what the main risk factors are for type 2 DM will show a list like this:
*Weight; Fat distribution; Inactivity; Gender; Family history; Race and ethnicity; Blood lipid levels; Age; Prediabetes…*

See anything covertly missing on that list above? Yes, what you eat! The first risk factors 'weight' and 'fat distribution' are related to what? They are predominantly related to diet and exercise levels. The factors of gender, race and age etc., will not be independent to any life-style, which is a choice. No person will get DM if they have a healthy diet and are active like a human should be. Many cultures have the practice of taking a walk after dinner or a large meal. It may be surprising for some to know that the contraction of skeletal muscle lowers blood glucose. In fact, skeletal muscle activity does this to a large degree that is independent of insulin levels (see skeletal muscle chapter 13). This therefore reduces the insulin released in response to the meal, and this is key to not becoming diabetic.

**Steady Increase in Diabetes Mellitus**

The incidence of diabetes mellitus in the U.S. has been steadily rising the last 6 decades, as shown in the graph in **Figure 15.19** below. This condition is recognized as a serious health problem that can de debilitating if it becomes chronic (long term). Importantly, diabetes mellitus is also linked with other serious co-morbidities in the latter stages, as discussed below.

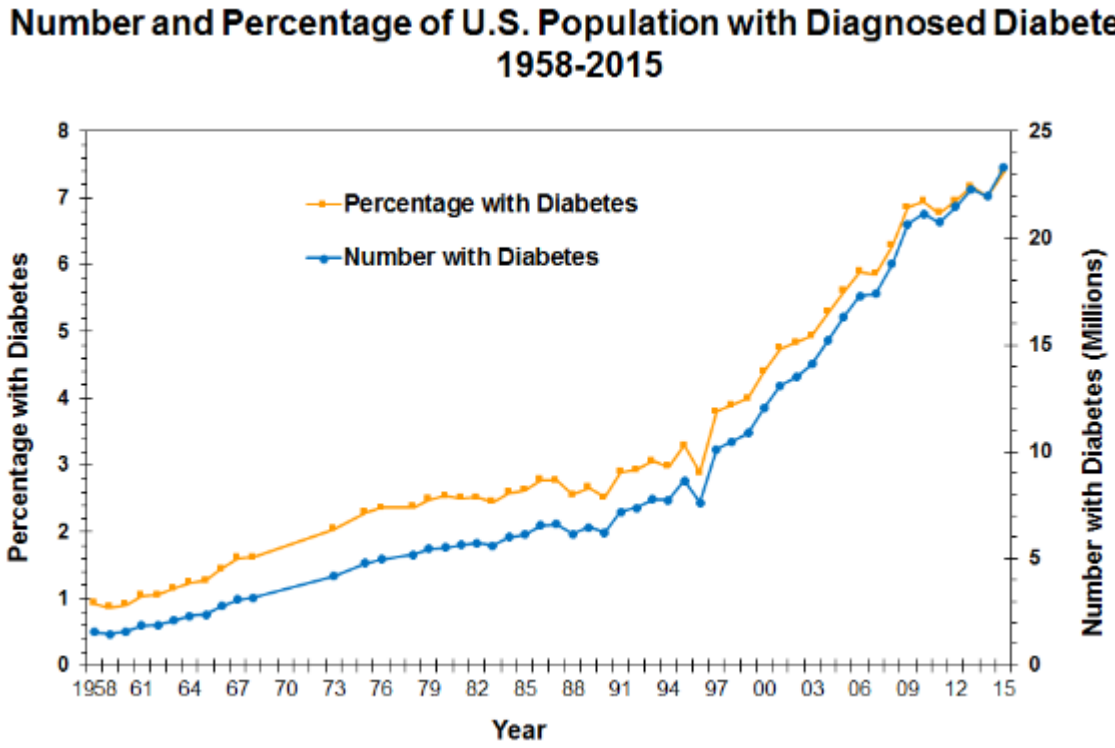



**Figure 15.19** This graph shows the trend in diagnosed diabetes mellitus (type 2) in the United States from 1958 through 2015. The prevalence of type 2 diabetes increased from 0.93% in 1958 to 7.40% in 2015. In 2015, 23.4 million people had diagnosed diabetes, compared to only 1.6 million in 1958. From CDC's Division of Diabetes.

## Symptoms and Consequences of Chronic Diabetes Mellitus

Although type 1 and 2 diabetes mellitus have different causes, after the onset, both types have the same symptoms. These **symptoms** include: Hyperglycemia, glycosuria (glucose in urine), polyuria (excessive urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue and dehydration.

When the condition is chronic, the excess blood glucose also attaches non-enzymatically to plasma proteins in the blood and red blood cells e.g., hemoglobin (**Hb**), and results in ***Advanced Glycated End-Products*** (**AGE's**). These AGE's have many deleterious effects, particularly harmful is poor circulation and the reduction of $O_2$ delivery to many tissues which can lead to significant damage.

**Chronic diabetes mellitus can lead to the following**:

**Eye Problems**: Most common vision disease retinopathy: Blood vessels to retina leak, bleed and become blocked; this can cause partial loss of vision or permanent blindness. There is also an increased risk for cataracts and glaucoma, both can be debilitating.

**Heart Disease**: Chronically elevated blood glucose is linked to plaque formation in coronary arteries (atherosclerosis). Diabetics have twice the risk of heart disease.

**Peripheral Arterial Disease (PAD):** Atherosclerosis in extremities, causing leg pain, poor circulation. Gangrene can occur as a consequence, which can causes tissue necrosis (death) and may result in below the knee amputations (BKA's).

**Neuropathy**: Peripheral, affects hands and feet; tingling, burning, numbness or complete loss of feeling. Also in organs, can slow digestion, cause constipation and decreased sexual response.

**Chronic Kidney Disease & Kidney Failure (Nephropathy)**: The additional load on the kidneys from glycosuria, polyuria and dehydration are extremely taxing on the renal system, primarily causing glomerulosclerosis, which is a hardening of the glomerulus where filtration of the blood occurs. Diabetes is the leading cause of kidney failure among Americans.

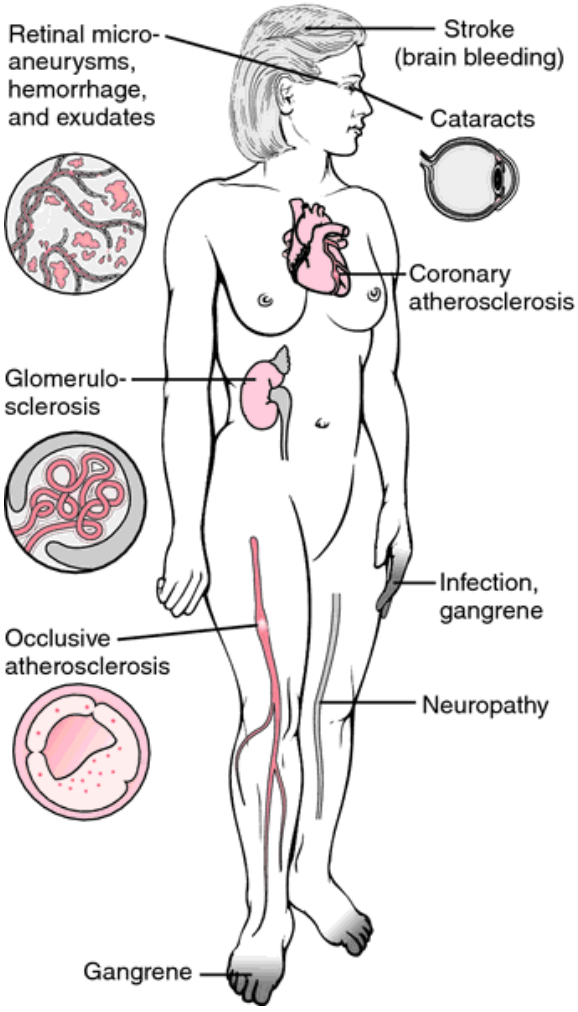



**Figure 15.20** Shows the various pathologies associated with chronic diabetes mellitus.

**Stroke:** This is also called a cerebrovascular accident (CVA) and can occur when the blood supply to part of the brain is interrupted or reduced, which prevents brain tissue from getting adequate $O_2$ and nutrients. Brain cells can be damaged or die in minutes. Most strokes are form blood clot that block blood vessels in the brain or neck. Those with diabetes have a 1.5 times higher risk of stroke than those without diabetes.

After taking a closer look at diabetes mellitus we can see that this condition is association with many other chronic disease states (**Fig. 15.20**). Many are on the top 10 list for causes of death and all significantly impair health. It is critical to be aware of how to be healthy and how to remain healthy. Never having any of these conditions is better than any cure for them.

## Testing and Measuring Blood Glucose Levels

The **Oral Glucose Tolerance Test** (**OGTT**) measures the body's ability to use glucose, and can be used to diagnose **diabetes mellitus** and **prediabetes**, or **gestational diabetes** associated with pregnancy. The **glucose tolerance test** is a medical test in which a weight-standardized dose of **glucose** is given orally and blood samples are taken over time to determine the rate of glucose clearance from the blood. Samples may be taken from every 30 min, or only once after either one hour or 2 hours. In general, after an overnight fast (8 hours) normal blood glucose ranges from **70 to 100 mg/dL**.

**Here are Some Examples of Glucose Testing that are commonly used:**

- **Random Glucose** - measured anytime regardless of last meal.
  Range: 70-120 mg/dL, **normal**.

- **Fasting Plasma Glucose** - measured at least 8 hours post meal.
  Range: 60-110, should be below 110 mg/dL.
  If fasting levels from 110 and 125 mg/dL, considered 'impaired fasting glycaemia'.
  If fasting levels repeatedly at or above **126** mg/dL, diagnostic of diabetes.

- **1 hour GTT (Glucose Tolerance Test)** - measured 60 mins post glucose ingestion.
  Range: Below 180 mg/dL, considered **normal**.

- **2 hour GTT (Glucose Tolerance Test)** - measured 120 min post glucose ingestion.
  Range: Below 140 mg/dL, **normal**.
  Range: Higher from 140 to 200 mg/dL, indicates **hyperglycemia**.
  Range: Above **200** mg/dL at 2 hours, confirm "impaired glucose tolerance" of **diabetes mellitus**.

**The A1C Test for Glycated Hemoglobin**

The **A1C** blood test provides info regarding the average blood glucose levels **over the past 3 months!** Used to diagnose **Type 2 diabetes** and prediabetes. Also called hemoglobin A1C, HbA1c or ***glycated hemoglobin** test, because **Glucose** attaches non-enzymatically with **hemoglobin** (**Hb**) in RBCs. Higher the blood glucose, more glucose attached to Hb. **A1C** test measures amount of **Hb** with attached glucose, reported as a **%**. The higher the %, the higher your blood glucose levels have been over last 3 months. An illustration of this concept is seen in **Figure 15.21** below.

**Scale**:
Below **5.7%** = normal.
From **5.7** to **6.4%** = pre-diabetes.
At **6.5%** or higher = diabetic.

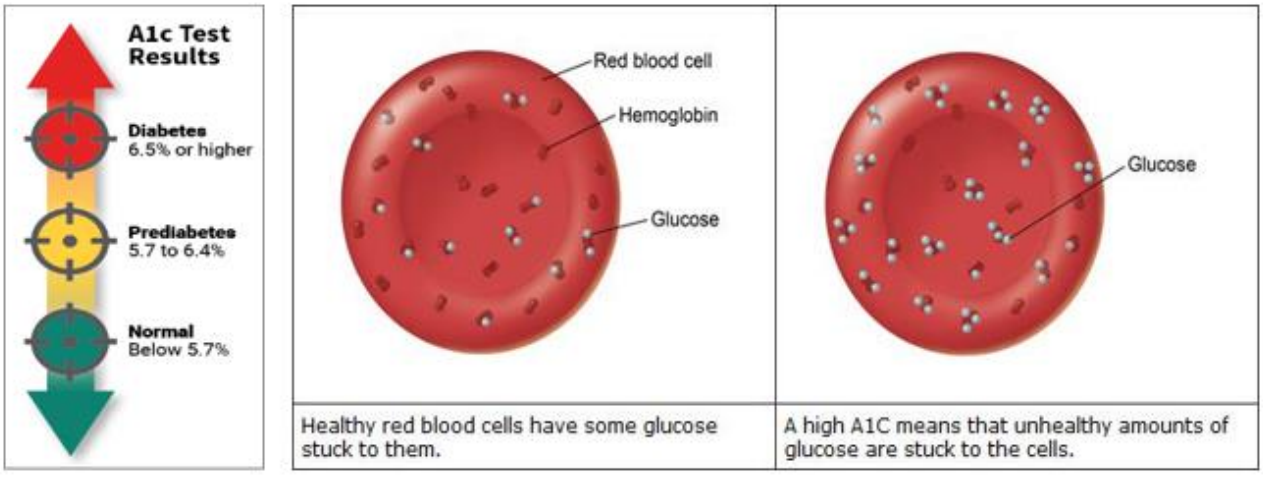



**Figure 15.21** The graphic above shows a healthy red blood cells (left) with a normal amount of glucose attached to the hemoglobin (Hb) portion, and what an unhealthy amount of glucose would look like (right) in an A1C test. Rather than detecting recent glucose in blood, this approach reveals the probable glucose levels over the past three months and can be used to assess diabetes mellitus.

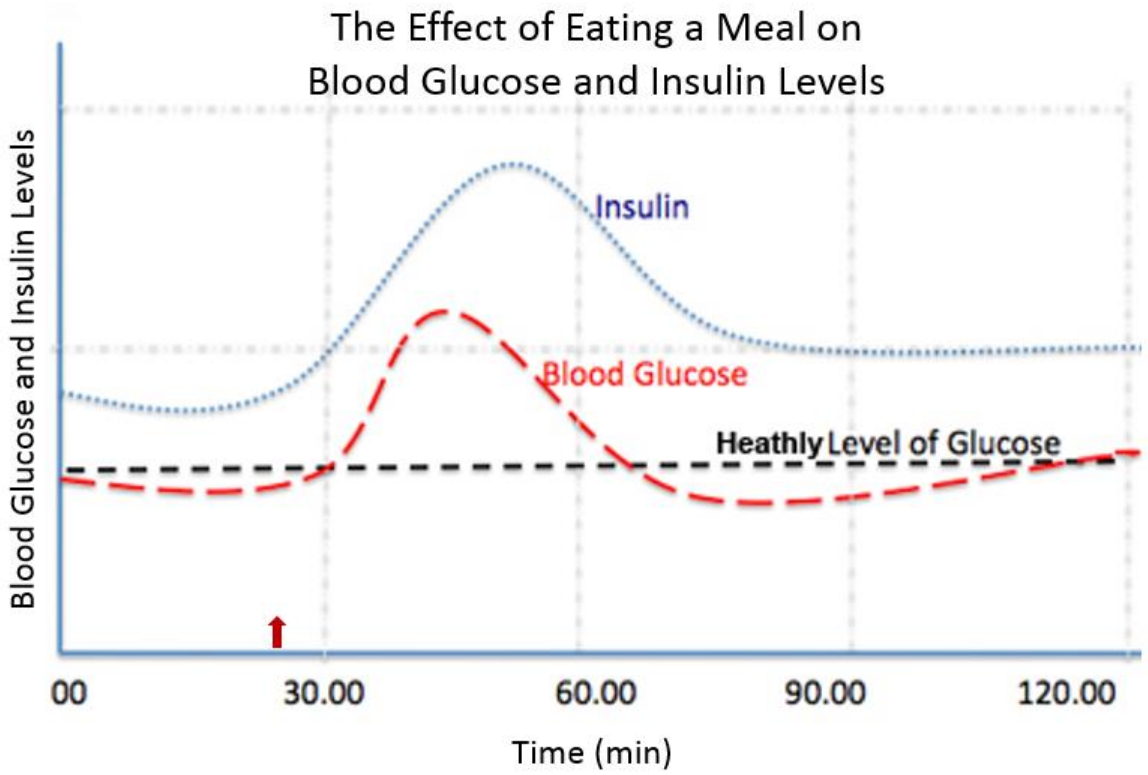



**Figure 15.22** This graph shows blood glucose levels before and after a subject eats a meal (at read arrow) and how blood glucose is temporarily elevated afterward. It also shows the almost immediate concurrent response of insulin increasing in order to promote the reduction of blood glucose.

- **Glycemic Index** (GI) indicates how quickly a certain food turns into sugar in a person's body.
- **Glycemic Load** (GL) indicates the total amount of glucose in the food.

**Table 15.2** Comparison of general and specific high and low glycemic index foods.

| Higher Glycemic Index Foods | Lower Glycemic Index Foods |
|---|---|
| **Refined Processed Foods**<br><br>Highly packaged, stripped of any real nutrients. | **Whole Foods**<br><br>At or close to original state of food, nutrient rich. |
| White Bread, White Rice | Brown Rice or Quinoa |
| Candy and Soda | Complex Organic Vegetables |
| Low fat Yogurt (there's no point) | Nuts and Legumes |
| Girl Scout Cookies (sorry) | Fibrous Organic Fruits |

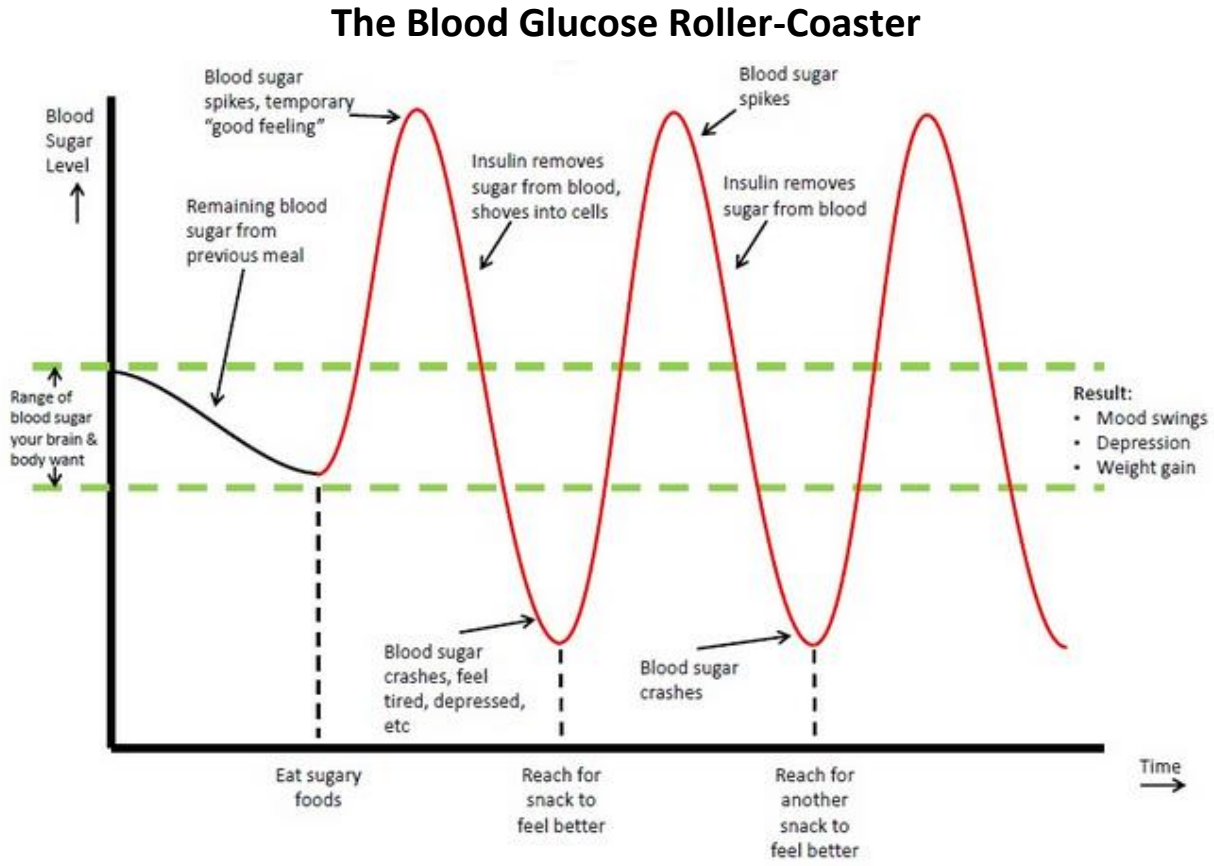



**Figure 15.23** This shows the problem with the "Rollercoaster" of spikes and troughs of Blood glucose levels from consuming a diet with a lot of refined carbohydrates.

**How to get off the Blood Glucose Roller-Coaster**

Those with insulin resistance from diabetes mellitus type 2 have gotten to this stage of insulin insensitivity because of long term 'spikes' in blood sugar caused by routinely eating highly refined sugary foods. See the graph in **Figure 15.23** above. On the x-axis where it says "Eat sugary foods" we see this causes the quick and high peak (spike) in blood glucose.

When spikes in blood glucose like this occur, insulin must be released in large amounts to lower this elevated blood glucose back into its normal range (set point). This large release of insulin causes a dip in blood glucose, which leads to hypoglycemia. Oddly a person now feels hungry again because of lowered blood glucose. This 'crash' in blood glucose really lowers energy and alertness and the easiest fix for that is usually, yes, another sugary snack to get that blood sugar nice and high again. Any additional spike in blood glucose will require another massive quantity of insulin to bring it back down, which will bring another crash in glucose, which triggers another need to have another snack to bring it back up… This is the roller-coaster ride of **diabetes mellitus type 2**. The spikes in blood glucose cause a spike in blood insulin, both of which are detrimental to your body.

Many studies have found a correlation between the amount of insulin release and the delirious effects of aging. More insulin, faster aging. If you want to stay looking and feeling and acting young, don't get on this rollercoaster.

During the glucose roller-coaster ride many people will experience **sugar cravings, night sweats, irritability, palpitations, dizziness, fatigue and weight gain**. Staying on this unstable roller coaster increases the risk of developing a variety of age-related and obesity-related diseases, including type 2 diabetes. In addition, extreme fluctuations in blood sugar levels can cause a lot of emotional disturbance like depression, agitation, feelings of irritability, anxiety, and lack of energy, easy fatigability, and uncontrollable temper. In other words it kind of sucks to feel this way and it is not necessary.

The best solution is to take responsibility for your health right now and make positive changes that will dramatically improve your health, your emotional and mental outlook, and of course your spirit.

## Review Questions for Chapter 15: Blood

**1.** The process by which all blood cells are formed is called
- **a)** hemocytoblastosis
- **b)** erythropoiesis
- **c)** hemopoiesis
- **d)** leukocytosis
- **e)** monocytosis

**2.** An inability of body cells to receive adequate amounts of oxygen may indicate a malfunction of
- **a)** neutrophils
- **b)** leukocytes
- **c)** lymphocytes
- **d)** eosinophils
- **e)** erythrocytes

**3.** Megakaryocytes are derived directly from
- **a)** myeloid stem cells
- **b)** monoblast
- **c)** megakaryoblast
- **d)** thrombocytes
- **e)** myeloblast

**4.** The name of the test procedure giving information about the rate of erythropoiesis is called the
- **a)** differential WBC count
- **b)** sedimentation rate
- **c)** hemoglobin count
- **d)** reticulocyte count

**5.** Normal RBC count per cubic millimeter ($mm^3$) or micro liter (µL) in males is between ___million
- **a)** 200 to 250
- **b)** 10 to 15
- **c)** 2.5 to 4.5
- **d)** 4.7 to 6.1
- **e)** 4.2 to 5.4

**6.** The normal number of leukocytes per cubic millimeter ($mm^3$) or micro liter (µL) is
- **a)** 5,000 to 10,000
- **b)** 8,000 to 12,000
- **c)** 2,000 to 4000
- **d)** over 15,000
- **e)** 4,000 to 6,000

**7.** Hemolysis produced by fetal-maternal incompatibility of blood cells is called
- **a)** infantile necrosis
- **b)** newborn polycythemia
- **c)** fetal hemolysis
- **d)** hemolytic disease of newborn

**8.** The term for a high white blood cell count is:
- **a)** leukopenia
- **b)** leukocytosis
- **c)** hematocrit
- **d)** polycythemia
- **e)** leukemia

**9.** Platelets are formed from small fragments of a special cell called
- **a)** megakaryocytes
- **b)** eosinophils
- **c)** hemocytoblasts
- **d)** monocytes
- **e)** platelets

**10.** Under the microscope, red blood cells appear as
- **a)** circular discs with a central nucleus
- **b)** circular discs with lobed nuclei
- **c)** biconcave discs without nuclei
- **d)** oval discs with many nuclei
- **e)** bi-lobed nucleus cells

*Answers in Appendix B*