30: TISSUE TYPES and EPITHELIAL TISSUE (part 1)

Now that we've finished our study of cells, we are ready to see how cells cooperate to form tissues. Tissues will then combine together to form organs. Organs are connected in various ways to make our major body systems such as the respiratory system or the digestive system. Finally, the systems are all interconnected so that they all function together as a unit— a whole body.

All cells in the body (except egg and sperm cells) can be classified into one of four categories. Just four! With all the many different types of cells, you'd think there would be more categories. Admittedly, it's a stretch for a few of the classifications, especially blood cells. However, this classification system works well enough that it probably won't change any time soon.

The four main tissue types are: ***epithelial, connective, muscle, and nervous***.

Epithelial tissue is used as a covering, both outside and inside. The top layer of skin, the ***epidermis***, is epithelial tissue, and so is the lining of the lungs and the digestive tract. Epithelial tissue is designed to replaced often so it can take the wear and tear of touching and rubbing against things. It will also absorb things from the environment, both nutrients and toxins.

Connective tissue is used to bind and support body parts. By definition, connective tissue occurs in a ***matrix***. This means the cells are in some kind of solid, liquid, or gel. Connective tissue includes ligaments, tendons and cartilage, but it also includes bone, blood and fat cells. You might be able to guess that bone will be in a solid matrix and blood will be in a liquid matrix.

Muscle tissue is designed for movement. Protein cables called actin and myosin will work together to cause cell fibers to slide past each other. Muscles cells are very strange, forming long "megacells" with hundreds of nuclei. There are three types of muscles tissue: ***voluntary*** (the ones you can move), ***involuntary*** (the ones you have no control over, like in your intestines) and ***cardiac*** (in the heart).

Nervous tissue is made of cells called ***neurons***. This type of tissue is designed for communication and uses electricity to pass signals from cell to cell. Nervous tissue is found in the brain, the spinal cord and the peripheral nerves (nerves in the body).

Epithelial tissue is our exterior covering, both inside and out. ("Epi" means "on," and "thele" means "teat or nipple." So originally, back in the early 1700s, the word epithelial meant just the skin around the nipple area, which looks different from regular skin. Eventually, scientists realized that the two types of skin were basically the same and the word was adopted for all skin areas.) Epithelial cells come in three basic shapes: ***squamous*** (flat and wide), ***cuboidal*** (like a cube), and ***columnar*** (like a column). Each type of cell is very good in a certain application, as we will see in the newt lesson. A specialized type of columnar cells is the ***goblet cell*** that produces mucus.

All epithelial tissue is built on ***basement membrane***, which is a layer of protein cables of different types. The connections found in the basement membrane are very mechanical— great examples of protein gadgets. The epithelial cells themselves are held together by adhesion junctions that use ***desmosomes***. Desmosomes have ***attachment plaques*** on the inside of the plasma membrane so that the protein cables won't pop out of the membrane. The plaques help to spread out the pulling force over a larger surface area, thus reducing the pressure at any one point. (Remember, the consistency of the plasma membrane is similar to olive oil— soft and fluid.) The cables that go across between the plaques are actually half-cables coming out from each side. The half-cables meet in the middle, with a connection that might be thought of as biological Velcro®. (Cells can dissolve and rebuild desmosomes very quickly. We'll see this again in later lessons.) On the inside, the plaques are attached to the cytoskeleton that runs all over the inside. Thus, again, we see pulling and stretching forces being spread out over a large area to prevent tearing at any one point. NOTE: There might also be gap junctions present so that the cells can communicate.)

On the bottom, there are ***hemidesmosomes*** (half-desmosomes) that attach to the basement membrane. The basement membrane is not made of cells, but of protein cables. Mostly, these cables are made of a type of protein called ***collagen***. We will take a look at the molecular structure of collagen in a future lesson. There are different kinds of collagens and they are known by Roman numerals. Some sources say that there are 16 types of collagen, but others will say up to 28 have been discovered. Here we see collagens I, III, IV and VII. The top layer of basement membrane is called the ***basal lamina*** and it has two layers: a top layer consisting of protein hooks and a bottom layer made of fibers of collagen. (These hooks are made of proteins called ***laminins***.) Under the basal lamina there is a layer called the ***reticular lamina***. (Remember, "rete" is Latin for "net," so when you see a word starting with "reti-" expect to see some kind of network.) The reticular lamina is made of more collagen fibers, and looping fibers woven throughout it, connecting up to the laminin hooks. The basal lamina and the reticular lamina together make the basement membrane.

Beneath the basement membrane, you will often find another layer of connective tissue. In the skin, it will be the dermis layer. Remember that skin is made of two layers, the epidermis and the dermis, with the basement membrane in between. Only the epidermis is made of epithelial cells. The basement membrane in skin is often where a blister will form. Those protein cables get broken as your skin rubs back and forth against something (such as a rake handle). The epidermis separates from the dermis and a space opens up between the two. The immune system senses damage and immediately fills the space with fluid that has many immune cells in it. As the blister heals, new epithelial cells and new basement membrane will grow and will replace the old, damaged ones.

31: EPITHELIAL TISSUE (part 2)

Epithelial tissues are classified using basically two characteristics: the shape of the cells and how deep they are stacked. Each type of tissue is just what is needed in certain areas of the body. Notice that all types of epithelial tissue are anchored to basement membrane.

The first category we will consider is the "simple" category. Simple means that there is only one layer of cells.
Simple squamous tissue is a single layer of squamous cells. Squamous cells are very flat, so a single layer of these cells is perfect for places where you want to transfer gases and nutrients from one side of the cells to the other. Two places where you would find this type of tissue are the lining of the lungs (where you want to transfer oxygen and carbon dioxide) and the walls of capillaries (where you want to transfer oxygen, carbon dioxide, nutrients and wastes). Epithelium in blood vessels has a special name: ***endothelium***. The endothelial cells don't form perfect water-tight bonds between themselves. These cracks between the cells will allow small things to leak through. This leakiness is helpful in many situations, as we will see in future lessons. However, the capillaries of the brain are different; they do not leak. This lack of leakiness is called the "blood-brain barrier." These tighter junctions in the brain capillaries is to make it very difficult (hopefully impossible) for bacteria, viruses and harmful large molecules to get into the brain.

Simple cuboidal tissue has one layer of cuboidal cells. Since these cells are thicker than squamous cells, you don't expect them to do much transferring of gases or nutrients. Cuboidal cells are usually specialized for secretion and absorption. Secretion means they make some kind of product, and absorption means they take something in. This type of tissue is found in glands and in the lining of the tiny tubules in the kidneys. Some simple cuboidal cells have microvilli. ("Villi" means "little fingers.") The purpose of the microvilli is to increase surface area. This is especially helpful to cells that are involved in absorption of some kind.

Simple columnar tissue often has goblet cells, microvilli, and/or cilia. Goblet cells produce mucus. Microvilli, as we've already stated, serve to increase the surface are of the cell. Cilia are tiny hair-like structures that can move. The cilia "beat" in rhythm producing a sweeping effect. This is most clearly seen inside the Fallopian tubes where the ovum must be swept along, down the tubes and toward the uterus. Simple columnar is also found along the inside of the digestive tract.

Stratified tissues have more than one layer. ***Stratified squamous,*** the type of tissue found in the ***epidermis*** of the skin and in the lining of the mouth, has many layers of cells, with the youngest cells at the bottom and the older cells at the top. The bottom layers, just above the basement membrane, keep making more cells all the time and these cells gradually move upwards.

There are two types of stratified squamous tissue: 1) ***keratinized***, and 2) ***non-keratinized***. ***Keratin*** is the name of one of the proteins found in the cytoskeleton. Remember, there are three sizes of cytoskeleton fibers: the large microtubules, the intermediate filaments, and the tiny microfilaments. Keratin is an intermediate filament. It is keratin fibers to which the desmosomes attach. In keratinized tissue, the cells begin to fill up with keratin as they rise to the surface. By the time they reach the surface, the cells have lost most or all of their organelles, including the nucleus, and they are basically an empty shell stuffed full of keratin. Since keratin is a waxy substance, the keratin-filled cells give the surface of the skin a fairly waterproof texture. In non-keratinized epithelium, the cells stay alive all the way to the top and do not fill up with keratin. The top cells still flake off easily, though, and are constantly being replaced, just like in keratinized epithelium. An example of non-keratinized epithelium is the inside of the mouth.

Stratified cuboidal tissue is found primarily in glands such as salivary glands and mammary (milk-producing) glands because this type of tissue is very good at secretion. It is usually only two cells thick, unlike stratified squamous.

Stratified columnar tissue is not as common as the other types of epithelial tissue. It is harder to find examples of this type, but it can be found in small amounts in the eye, the throat, the uterus, the urethra (tube leading out of urinary bladder) and the salivary glands. As with simple columnar tissue, stratified columnar is good for secretion, and it is also good for protection, as it is several layers thick.

Pseudostratified columnar tissue is a major feature of the lining of the ***trachea*** (pipe leading down into lungs). "Pseudo" means "false," so pseudostratified looks like it is stratified, but it isn't. In true stratified tissue, cells are stacked on top of cells so that the cells in the top layer are not touching the basement membrane. Pseudostratified isn't stratified because each and every cell in pseudostratified is touching the basement membrane, even if it does not look like it. (The fact that their nuclei are at various levels adds to the illusion that they are stratified.) We've got to trust the professional biologists who have examined these tissues under an electron microscope and can assure us that all the cells are touching the basement membrane. Most of the cells in pseudostratified are either goblet cells or are ciliated cells. The mucus and the cilia work together to be a kind of housekeeping service, sweeping dust and dirt up and away from the lungs. When the mucus gets to the top, you either swallow it or cough it up. (Those goblet cells really starting cranking out the mucus if you get some irritating particles down your airway. Soon after you start coughing, you find that suddenly there's a large volume of mucus to cough up!)

Transitional epithelial tissue is found in the urinary bladder. It is designed to stretch and then snap back to normal again. As the bladder fills up, tiny nerves sense the stretching that is going on and send signals to your brain that tell you that you need to empty your bladder soon.

32: CONECTIVE TISSUE OVERVIEW, and COLLAGEN

The definition of a connective tissue isn't that it must connect something; some types of connective tissue do connect things. The definition of connective tissue comes from the microscopic view of these tissues. Connective tissues are made of three things: 1) specialized cells, 2) ground substance, and 3) protein fibers. In general, the ***specialized cells*** create the protein fibers and much of the ground substance. In other words, the specialized cells create the environment in which they live. The ***ground substance*** is the "background stuff" that everything is immersed in, and can be a solid, liquid or gel. ***Protein fibers*** can be ***collagen, elastin, or reticular fibers***. (Reticular fibers are basically very thin threads of collagen.)

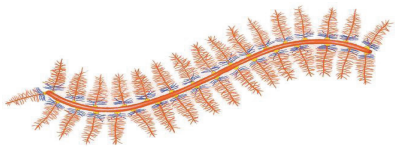
There are three types of connective tissue, with three subcategories under each. (The number three shows up a lot, as you will see!) ***Fibrous*** connective tissue is divided into ***loose*** (areolar), ***dense***, and ***adipose*** (fat). ***Cartilaginous*** connective tissues are ***hyaline, elastic or fibrocartilage***. The last category is a catch-all for everything else, and I have called it "other." These others include ***bone, blood and lymph***. (Don't worry that you don't know what all these tissues are. The important thing right now is to get this chart written so that you can come back to it later on, as we study each kind of connective tissue.)

Let's start with a close-up look at ***collagen***. The word collagen comes from the Greek word "kolla" which means "glue," and "gen," which means "to make." So collagen is...a glue-maker? Actually, this name makes sense when you think that for centuries, scrapings from animal hides were used to make glue, and skin has a lot of collagen in it. Collagen from animal hides is used today to make gelatin ("Jello") which is very gummy and sticky, like glue.

The smallest unit of collagen is a polypeptide (chain of amino acids) in an alpha helix shape. Three of these alpha helices are bound together to form the complete triple-helix collagen protein. (Every third amino acid in the chain is ***glycine***, the smallest amino acid. Its small size helps the strands wind together very tightly.) The triple-helix proteins are assembled inside the endoplasmic reticulum of cells called fibroblasts. In order for the stapler enzyme inside the ER to be able to do its job and assemble these proteins, it needs a molecule of vitamin C (ascorbic acid) to attach to its active site. An extra molecule that is necessary for an enzyme to be able to do its job is called a ***coenzyme*** or ***cofactor.*** If there is a shortage of vitamin C, a condition called ***scurvy*** can result. Many sailors died of scurvy in past centuries, before nutrition was recognized as a possible cause of disease.

The triple-helix collagen proteins exit the ER in vesicles and go over to a Golgi body where they are tagged with sugar tags that mean "put me outside the cell." The collagen proteins exit the Golgi and are taken (inside vesicles) to the plasma membrane where exocytosis occurs and they are put outside. Once outside the cell, collagen proteins begin to link up with each other and make larger strands. The first larger stand they make is called a ***microfibril.*** Then some microfibrils join together to make a ***fibril***, and finally some fibrils are bound together to make a ***fiber***. (Sometimes the fibers are bound into even bigger bundles.) This "bundles of bundles of bundles" organization is used in other tissue types, too, such as muscle. It is the ideal structure for achieving great strength.

Fibroblasts are cells that make collagen. Since they also secrete most of the things that form the ground substance, the fibroblasts really create their entire environment. The ground substance is made of 90 percent water 10 percent something called ***proteoglycans***. The "proteo" part means "protein" and the "glycan" part means "sugar" (like "gluco"). A proteoglycan molecule that looks a bit like a bottle brush. (This picture shows many proteoglycans attached to a long "rope" molecule.) The "hairs" of these "brushes" are long chains of sugars that are very hydrophilic. Thus, they attract lots of water molecules to the area. That is where the 90 percent water comes from. The proteoglycan molecules draw the water in and hold it there. The high water content of the dermal layer of skin (under the basement membrane) is partly what makes the skin so soft and resilient. (One of the first symptoms of serious dehydration is that the skin doesn't bounce back after you press it.) One of these brush molecules is called ***chondroitin sulfate***, a very popular nutritional supplement that you can find in any pharmacy or grocery store.



The little brushy things are the proteoglycans. The orange stripe in the middle is hyaluronic acid.

The long "rope" molecule that all the bottle brush molecules are attached to is called ***hyaluronic acid.*** *(Hi-ah-lure-ON-ic)* The ends of the hyaluronic acid molecules are fastened to the collagen fibers. In many parts of the body, the space around the cells is filled with these ropes and bottle brushes. This space, all around the cells, is often called the ***extracellular matrix***. "Extra" means "outside" in this case. Other things can float around in the extracellular matrix, too. White blood cells are often found here.

Hyaluronic acid is sometimes taken as a nutritional supplement by people who are wishing to avoid problems with connective tissue. The theory is that by supplying plenty of hyaluronic acid, the connective tissues will take these molecules in and use them to build extracellular matrix. This is thought to help the connective tissues stay young and healthy. Is this true? One researcher in Japan believes it is. He moved to Yuzurihara, a small town north of Tokyo, in order to study its population of exceptionally healthy and long-living people. The elderly in this town look youthful, rarely get sick, and often live to be over 100. The researcher concluded that besides having an excellent diet and lifestyle, these people also happen to have available an ideal food source for longevity: a species of potato that is very high in hyaluronic acid. A lifetime of eating a diet high in hyaluronic acid (and also lots of green vegetables) has made diseases of aging very rare. Many elderly people in this village reach their 90s without ever having been in a hospital. (Cosmetic companies have found a way to make hyaluronic acid into a facial cream. Claims are made that using these creams will slow down or reverse wrinkling.)

33: LOOSE CONNECTIVE TISSUE
(part 1 of FIBROUS)

Loose connective tissue is very abundant in the body. Skin is the most obvious example of where loose connective tissue is found, but you can also find it surrounding blood vessels, nerves and all organs. It is the connecting link between epithelial tissue and muscle tissue, and it lies just beneath the surface in your lungs and intestines. The word ***areolar*** *("air-ree-OH-lar," or "a-REE-oh-lar")* is often used to describe loose connective tissue because this word means "airy" and, as you will see, there seems to be lots of open space in this tissue. This space is actually filled with ***proteoglycans*** (those bottle brush molecules) that hold lots of water. Some of the immune cells are able to swim around in this watery space, a bit like protozoans do in a pond.

Fibroblasts are the specialized cells in all types of fibrous connective tissue, including loose connective tissue. They secrete both the protein fibers and the ground substance. There are three types of protein fibers in loose connective tissue: ***1) collagen fibers, 2) elastic fibers, and 3) reticular fibers***. Collagen fibers are very strong. Elastic fibers (as their name implies) are stretchy. Collagen and elastin together make this tissue both strong and flexible. Reticular fibers are very thin and form a delicate network for capillaries, nerves, and immune cells. (Remember, "rete" means "net.") Without this reticular network, all these parts would either slosh around or fall down to the bottom because of gravity. The reticular fibers keep the cells in place. (Reticular fibers are actually very thin collagen fibers.)

The ground substance in this type of tissue is the same as we saw in the last drawing. The fibroblasts make all the ***proteoglycans*** ("bottle brush" molecules) that are attached to long "ropes" made of ***hyaluronic acid***. Proteoglycans are very small and can't be seen with a regular microscope like fibroblasts and collagen fibers can. The proteoglycans are like sponges and soak up lots of water. This means that the "empty space" you see in this drawing is actually full of water (not air, despite the fact that areolar means "airy").

Adipose cells (***adipocytes***) can be found in and around loose connective tissue. (Adipose means "fat" so we can also call them fat cells.) Fat cells are cells that have HUGE storage vacuoles (vesicles) filled with triglycerides. (A vacuole and vesicle are basically the same thing: a sphere made of phospholipid membrane. When a vesicle is very large and is filled water, air, or fat, it is often called a vacuole.) Remember those 3-legged lipid molecules from lesson 3? That's what is inside these vacuoles. The vacuole gets so large that it just about fills the entire cell. The other organelles are still there, but they are all pushed to one side and squished into a small space. The primary job of an adipocyte is to store energy. Because of this stored energy, the body can go for a fairly long time without taking in food. Secondarily, adipose cells provide protective padding around delicate parts of the body.

The cells that float or move around in loose connective tissue are cells of the immune system—white blood cells. We will study these in greater detail when we get to the lessons on blood cells, but this is a good place to introduce a few of them.

Macrophages are "big eaters." ("Macro" means "big," and "phage" means "eat.") They eat pretty much anything that you don't want in your body: bacteria, viruses, dead or injured cells, and dirt. Macrophages know not to eat normal, healthy cells, but will gobble up just about anything else. They are your body's recycling unit. They can move around like an amoeba, oozing about by stretching out blobby "arms." They eat things by using the process of endocytosis. They "patrol" in this type of tissue, looking for invaders or garbage that needs to be dealt with.

Neutrophils are also "eaters" though their name does not have "phage" in it. We'll find out what their name means in a future lesson. Neutrophils are one of the "first responders" at the scene of an injury. They are there immediately, ready to gobble up any foreign invaders that try to take advantage of the injury to enter the body. Neutrophils have a very strange multi-lobed nucleus that allows them to get through the thin cracks between the endothelial cells.

Lymphocytes come in two varieties: T cells and B cells. These two types of cells work together to identify and tag foreign invaders. Some types of T and B cells are memory cells that can remember how to fight pathogens you've encountered before. (A pathogen is something that makes you sick.) T and B cells look identical under a microscope.

Mast cells are the most notable immune cells in loose connective tissue. They are responsible for starting the ***inflammatory*** process. Though excess inflammation can be a problem, a normal amount of inflammation is necessary to get the healing process started. Swelling helps to keep the injured area isolated and to reduce blood loss. The cells that kick off the inflammatory process are the mast cells. They contain thousands of tiny vesicles filled with a chemical called ***histamine***. When some of the mast cell's surface receptors receive signals that there is trouble in the area, their vesicles all go through rapid exocytosis, meaning they burst open at the cell's surface and spill out their contents—histamine and cytokines. The histamine causes the capillaries to dilate (get bigger) and become leaky. Lots of water and proteins leak out of the capillaries and produce the swelling. The histamine also stimulates nerve cells and makes them send messages of pain (and sometimes itching) to the brain. The ***cytokines*** are chemical messages that go out to other immune cells, telling them to come to this area and help out. We'll meet these other immune cells in future lessons.

These vesicles filled with histamine are often called ***granules***. There are several kinds of immune cells that look like they are filled with little blobs, or "grains," and they are classified as "granular" cells. The mast cell is one of these granular cells. We will meet other granular cells in future lessons. Right now you just need to know that when we talk about granules we mean these little vesicles filled with chemicals. You are likely to meet the word granules in books and websites about immune cells.

34: DENSE AND ADIPOSE FIBROUS CONNECTIVE TISSUE and CARTILAGINOUS CONNECTIVE TISSUE

Before you start this drawing, go back and look at the top of drawing 32. Look at the three categories of connective tissues. They are fibrous, cartilaginous and other. Notice that there are three categories under each of these categories. In drawing 32 we looked at just the first category of fibrous tissue: loose, or areolar, tissue. In this drawing we will finish the other two types of fibrous tissue, then do all three types of cartilaginous tissues. All these tissues will seem very similar to you and might be hard to keep categorized properly in your mind. It is helpful to remember that FIBROUS tissues have specialized cells called FIBROBLASTS, and CARTILAGINOUS tissues have specialized cells called CHONDROCYTES. Look for the word root "fibro" in the first pair, and then notice that the words in the second pair both start with the letter "C."

Fibrous connective tissues have ***fibroblasts***. We met the fibroblast cell in the last lesson in the loose connective tissue, so you already know that these cells produce the protein fibers and ground substance that surround them. They make both collagen and elastin, but in proportions that are appropriate for their location in the body. Tissues that need to be very strong and just a little flexible have a lot of collagen and less elastin. Tissues that need to be very stretchy have more elastin than collagen.

Dense fibrous connective tissue can be either ***regular*** or ***irregular.*** The word regular is being used here to mean something like "straight and orderly." The collagen fibers in ***regular dense*** tissue are mostly parallel, going in just one direction. This makes these tissues very strong in one direction—the direction in which the fibers run. They can sustain a pulling force in that one direction, so they are perfect for tendons and ligaments. ***Tendons*** connect bone to muscle and ***ligaments*** connect bone to bone. There are very few elastin fibers in tendons and ligaments; they are mostly collagen. Another place you find dense regular tissue is in a protective layer that surrounds the brain. (This layer is called the ***dura mater***, which is Latin for "tough mother.")

Dense irregular tissue has fibers that are less parallel and go in several directions. It is not super strong in any one direction, but it is still fairly strong in all directions. Again, it is mostly collagen with only a little elastin. You find this kind of tissue as a protective layer around bones and muscles. (We will see when we study muscles that they are all in bags. The ends of the bags become tendons.) Dense irregular is also found in the dermis layer of skin. As we will see when we draw skin, the top layer of the dermis is loose (areolar) connective tissue and the bottom layer of the dermis is dense irregular tissue. The dense irregular layer is what gives skin its strength. Small tears in the collagen fibers of this layer result in permanent stretch marks visible on the surface of the skin.

The third type of fibrous connective tissue is ***adipose tissue***. This is actually a variation on loose connective tissue (remember, we saw adipose cells there!) but when there are many adipose cells in a large clump, it is called adipose tissue. There are actually two types of specialized cells in adipose tissue: fibroblasts that make collagen fibers and ***adipocytes*** that store fat. Adipocytes far out number the fibroblasts. An adipocyte is a real cell and has a nucleus and other organelles, though they are squished off to one side. The most prominent organelle is the ***storage vacuole*** (a large vesicle) that is filled with triglycerides (those little hangers with three fatty acids hanging down). The adipocytes take extra fatty acids that the body doesn't need to burn immediately, and puts them into storage. Adipose tissue can be found under the skin and around the internal organs where it provides insulation and protection. It also provides padding on places that need it (like where you sit down). Females have more adipose tissue than males; the extra adipose padding is part of what defines a face or a body as feminine.

CARTILAGINOUS

The specialized cells in cartilaginous tissue are called ***chondrocytes*** *(KON-dro-sites)*. Each chondrocyte is surrounded by a little "pool" called a ***lacuna***. (To help remember this name, try associating it with the word "lagoon," which is a ring of water around an island.) Cartilaginous tissue, unlike fibrous, has no capillaries and no nerves. This type of tissue occurs in places where there is a lot of rubbing, so you really would not want nerves here. The three types of cartilaginous are hyaline, elastic, and fibrocartilage.

Hyaline cartilage looks shiny and sort of a clear white color. (The word root "hyalus" came from Greek and means "glass.") If you've ever looked at the ends of chicken bones, you'll have seen this cartilage. Hyaline is found on the ends of long bones, the ends of ribs, and also in the nose and the trachea. That hard tube in your neck (the trachea) is made out of hyaline cartilage. Also, during embryonic development, the bones begin as hyaline cartilage. During the fourth month of pregnancy, the baby's cartilage bones begin hardening. Minerals such as calcium, magnesium and phosphorus are brought into the cartilage, transforming it into bone.

Elastic tissue has a lot of elastin protein and not much collagen. Obviously, this makes it very flexible. Elastic tissue is what makes the underlying structure of our ears. It is also found in the epiglottis, that flap that covers our trachea (windpipe) as we swallow, so that food does not get into our lungs. (Obviously, you have nerves in your ears, but they are found in the fibrous connective tissue that surrounds the cartilage.)

Fibrocartilage is very tough. It is an excellent shock absorber. You'll find fibrocartilage between the vertebrae bones in the spine and also in the crack where the pelvic bones come together in the front. In these two places you need a tissue that can withstand a lot of compression (being pushed together). The fact that the pelvic bone has a gap filled with cartilage is very important in females. During pregnancy, hormones cause cartilage to soften, allowing for stretching and bending of places like this crack in the pelvis. Otherwise, the bones might break.

35: BONE CELLS and the OSTEON

Though bone may not seem like a connective tissue, we will see that it does indeed qualify according to our three requirements. Bone has specialized cells called ***osteoblasts*** and ***osteocytes***. ("Osteo" means "bone.") These specialized cells secrete ***collagen fibers,*** just like fibroblasts and chondrocytes do. The ground substance in bone is a ***solid***. (In the loose and fibrous connective tissue the ground substance was more of a gel.) The solid texture in bone comes from the minerals that are deposited between all the collagen fibers. The two main minerals that you find here in bone are ***calcium*** and ***phosphorus***.

Osteoblast cells are very similar to fibroblasts because they secrete collagen. Their secretion is more "organized," though, because they can make layers of fibers that are all going in the same direction. They can alternate the directions of the layers forming something like plywood, where you find alternating layers of wood grain going in perpendicular directions. This alternation of directional layers is what gives plywood its strength. The alternating layers of collagen fibers in bone also provide a great deal of strength. The collagen fibers in bone could also be likened to the steel "rebar" rods that are put into concrete. The rebar allows concrete to survive small amounts of bending without cracking the cement. Collagen in bone also provides some flexibility in the midst of a mineral "cement."

Osteoblasts work as a team. They are fastened together by both gap junctions and tight junctions. The gap junctions allow for communication and the tight junctions give a leak-proof barrier. As the osteoblasts move along they leave a web of collagen fibers behind them. The minerals don't fill in immediately, so for a short time there is an area called ***osteoid*** that is not solid yet. The osteoblasts also secrete another specialized protein that attracts minerals and causes them to solidify into that collagen web.

Once in a while, one of the osteoblasts will get left behind and become stuck in the solid bone and will change its shape so that it has very thin finger-like projections. After this happens, the cell is no longer called an osteoblast but is called an ***osteocyte***. Osteocytes are surrounded by a ***lacuna***, just like chondrocytes are. (This is another similarity between cartilage and bone.) The lacuna goes all the way around the osteocyte, even around its long projections. The areas of the lacuna that surround these projections are called the ***canaliculi,*** or "little canals." The finger-like projections of osteocytes reach out until they touch the projections of other cells. Since the osteocytes are stuck in the solid bone, the contact they have with other cells through these projections is the only contact they have with the "outside world." The osteocytes can communicate with each other through these projections, and they can also share oxygen and nutrients. Osteocytes near blood vessels pick up the nutrients and pass them along to osteocytes that are further away from the vessels.

Osteocytes arrange themselves into concentric rings (rings inside of rings). The rings are called ***lamellae***. A set of rings is called an ***osteon***. The osteon is considered to be the basic unit of solid bone. In the center of an osteon is a space reserved for blood vessels. This space is called the ***central canal***, or the ***Haversian canal*** (named after the discoverer, Mr. Havers). A tiny vein and artery share the space with a lymph vessel and a tiny nerve. Since there are nerves running through osteons, bones can experience pain. The lymph vessels help to get rid of wastes. (The small lymph vessels eventually connect to the larger lymph network which dumps the lymph fluid back into the blood system.) The tiny vein and artery bring oxygen and nutrients to the bone cells, but it is only the cells closest to the vessels that actually absorb the nutrients. Those inner osteocytes then have to pass the nutrients along to the cells in the outer rings. This system works okay on a small scale, but there is a limit to how far nutrients can be transported. The maximum size of an osteon seems to be about 200 microns, about the same size as an egg cell (the largest human cell).

Osteons are constantly being re-built. The minerals stored in compact bone can be taken back out again and put into the blood stream if necessary. The calcium level in the blood must be kept at a constant level, and if calcium is not being supplied through the food that is coming into the stomach, the body must get the calcium from somewhere else. There are special cells called osteoclasts (which we will meet in a future lesson) that dissolve the minerals out of the collagen and put them back into circulation. After the osteoclasts have destroyed an area of bone, osteoblasts must move it and replace it. This cycle of destroying and rebuilding bone tissue is called ***bone remodeling*** and it happens continuously throughout your life. Newer osteons form complete circles. Older ones get covered over by the new ones so they no longer look perfectly round. Remember, also, that ostens are more like tubes than circles. The lamellae are cylindrical, like straws.

36: BONES MAKE BLOOD CELLS

The ends of the long bones contain ***red marrow***. Red marrow is the site for blood cell production. In babies, red marrow fills all the bones, so all bones are involved in blood production. As we grow up, the marrow in the middle of our long bones changes to become yellow marrow, made of mostly adipose cells, but the ends of the bones remain full of red marrow throughout our life. Other bones that have blood-producing marrow are the ribs, vertebrae and pelvic bones.

The red marrow is found within an intricate network of bone, called ***trabecular bone***. ("Trabecula" is Latin for "little beam.") Trabecular bone looks very much like a sponge that has become hard, so it is often called ***spongy bone***. Red marrow fills all the empty space in spongy bone. Like all bone, spongy (trabecular) bone is manufactured by osteoblasts, some of whom become trapped and turn into osteocytes.

Red marrow contains many different kinds of cells. There are some adipose cells, but not nearly as many as in yellow marrow. The most important kind of cell in red marrow is the multipotent stem cell called the ***hematopoietic*** stem cell. ("Hema" is Greek for "blood," and "poiein" is a Greek word meaning "makes.") From the hematopoietic stem cell come all the different types of blood cells. Where did the hematopoietic stem cells come from? They've been there from earliest days, when the embryo was only a few weeks old. Some of the embryonic cells differentiated into these stem cells and have stayed as stem cells ever since. The stem cells never get used up because they themselves don't become other cells. They make clones that then turn into other cells.

The first decision a hematopoietic stem cells makes is whether to become a ***myeloid*** stem cell or a ***lymphoid*** stem cell.

The ***myeloid stem cell*** can differentiate into more types of stem cells. (Remember that every time a stem cell differentiates, it takes a step "down." There is no going back—there's no un-differentiating.) One option the myeloid cell has is to become a ***mast cell***. We've already seen this cell in action. It is found in loose connective tissue, close to the capillaries. The mast cell has lots of vesicles filled with histamine. When injury occurs, the mast cell releases its histamine. The histamine acts on the cells of the capillaries (the endothelial cells) and causes the capillary to expand and to leak. Water and proteins leak out and create swelling (edema). This is part of the normal inflammatory response and is necessary for healing.

Another option open to the myeloid stem cell is to become a ***megakaryoctye***. ("Mega" means "large," and "karyo" means "nucleus" so these cells have a large nucleus.) Ironically, these large-nucleus cells will form tiny cells with no nucleus. These tiny cells, called ***platelets***, are actually classified as cell fragments, not actual cells. Platelets are essential to blood clotting and without them we would bleed to death from even a tiny cut. The technical name for platelets is ***thrombocytes*.**

The myeloid stem cell also has the option of turning into an ***erythrocyte***. ("Erythro" is Greek for "red" so in English we would just say "red cell.") Like platelets, erythrocytes have no nucleus, but unlike platelets, erythrocytes are actual cells, not fragments. There are very strange cells, though, because the nucleus and other organelles disappear in order to make the red cell more efficient at its job (carrying oxygen from the lungs and delivering it to cells). We will learn more about red cells in drawing 39.

Another option for a myeloid stem cell is to turn into a type of stem cells that will produce three different cells: ***basophils, eosinophils, and neutrophils***. These three cells look a bit similar but have distinctly different jobs. The word "phil" on the end of these names is one you have seen many times already. You will remember that it means "love." So what do these cells love? Stains. They tend to soak up either acidic or basic (alkaline) stains. Basophils soak up basic (alkaline) stains and as a result turn blue. Eosinophils soak up a stain called eosin which is acidic, turning them bright red. Neutrophils don't soak up either very well, leaving them light pink. Basophils are very similar to mast cells. In fact, they are pretty much the same cell, except that mast cells are found in tissues and basophils are found in the blood. Basophils are also responsible for allergic responses. Both basophils and eosinophils are key players in fighting parasites. Yes, it is a yucky thought, but sometimes bodies can be invaded by tiny parasitic worms. Eosinophils are the number one parasite fighters of the immune system. Neutrophils have a much different role — they are a type of phagocyte ("eating cell"). They float through the blood, looking for invaders to gobble up. They are part of your immediate response to pathogens. Many of them go to sites of infection, then end up as "pus." (Pus is mostly dead neutrophils.)

The myeloid cell can also become a ***monocyte***. Monocytes then differentiate into either **macrophages** ("big eaters") or **dendritic cells** ("dendros" is Greek for "branch"). We saw macrophages in loose connective tissue. Dendritic cells have a similar job, eating up pathogens, and then presenting pieces of these invaders to the T cells. We'll learn more about this soon.

The ***lymphoid stem cells*** can turn into ***dendritic cells***, or they can become another type of stem cell which will produce cells we call ***lymphocytes***. ***B cells*** are so named because they mature right there in the Bone. Some B cells will become "memory" cells because they retain information about how to attack viruses and bacteria you have come into contact with in the past. (This is what gives us our immunity to viruses after we have had them once.) ***T cells*** leave the bone and mature in the Thymus, a gland in the upper part of your chest, in front of your heart and lungs but under your ribcage. There are several kinds of T cells, including killer Ts, helper Ts and suppressor Ts (also known as regulatory Ts). ***NK cells*** are ***Natural Killer*** cells. They are also part of your immediate response to invaders. We will learn more about lymphatic cells in future drawings.

One last vocabulary word you should know is ***granular***. Some white cells look like they are filled with little particles, or granules. (The granules are little vesicles.) These include basophils, eosinophils, neutrophils and mast cells. They are sometimes called *granulocytes*. The other cells, those without granules, are called *agranular*, meaning "without granules."

37: BLOOD (as a tissue)

Blood can be classified as a connective tissue because it has specialized cells, ground substance and protein fibers. The specialized cells are numerous (as we saw in drawing 36) and include red cells, white cells, and platelets. The ground substance in blood is liquid, and we call it ***plasma***. For the protein fibers, we actually have to stretch the definition a bit. Yes, there are fibers, called ***fibrinogen***, but these proteins are made in the liver, not by the blood cells. There are also non-fibrous proteins in blood, too.

In order to see what is in blood, a machine called a ***centrifuge*** is used. A centrifuge is a bit like the carnival ride where you sit in swings that spin around and up, but the centrigue spins the test tubes about about 2000 revolutions per minute, whereas the carnival ride does about 5 rpm. The elements of blood settle out according to their density. Plasma is at the top, red cells go to the bottom, and white cells and platelets end up as a narrow band in the middle. About 55% of blood is plasma, 45% is red cells and less than 1% is white cells and platelets. Sometimes people are very surprised to learn what a small percentage of blood is white cells because they are so important in fighting infection. But the system works!

In the last drawing we did a survey of blood's specialized cells. In this drawing we will look at the other elements of blood. The ground substance that all the cells are floating in is called ***plasma***. Plasma is 91% water. About 7% of plasma is various proteins, and about 2% is "solutes." Solutes are tiny molecules such as nutrients (such as glucose), wastes (such as urea and ammonium), gases (such as oxygen and carbon dioxide), vitamins (water soluble ones), and some minerals.

The proteins in blood fall into basically four categories: 1) ***fibrinogen***, 2) ***clotting factors***, 3) ***albumins***, and 4) ***globulins***.

1) Fibrinogen, as its name suggests ("gen" is Greek for "create"), creates ***fibrin***. Fibrin is made of protein "strings" which are used to form blood clots. "Blood clots" sounds like something you don't want to have. You may know people who take medications to prevent blood clots. However, blood clots are a natural body defense. If blood did not clot, a tiny cut would keep on bleeding until all our blood was gone. Clotting is necessary to keep our blood inside. When the body tries to keep the blood inside, this is called ***hemostasis*** ("hemo" is blood, and "stasis" means to keep steady). In hemostasis, blood stays in. We will learn more about clotting in the next drawing. We will see the ***clotting factors*** at work, too, using a chain reaction known as a ***cascade***.

2) ***Clotting factors*** are tiny proteins that activate fibrinogen and platelets. The clotting factors themselves need to be activated by chemical messages from injured cells. When an injury message goes out, the clotting factors then initiate the clotting process. Because the clotting factors are not active until they receive a signal, they can safely float in the blood alongside fibrinogen and platelets without activating them. The clotting factor we will meet here is ***thrombin***, which activates fibrinogen.

3) The ***albumin*** proteins are like little taxi cars, transporting things through the blood. About half of all blood proteins fall into this category. Why would you need taxis in the blood? Hydrophobic substances are "afraid" of water, and since plasma is 91% water, we have a problem. Hydrophobic substances include fats, hormones, some ions, and some proteins (such as bilirubin, which we will meet later). These substances need a way to go through the blood without touching water. Albumins have little "pockets" where hydrophobic substance can tuck in and hide while they ride through the blood.

4) The ***globulins*** are of several different kinds: ***alpha, beta and gamma***. (Greek letters A, B and G.) Globulins do look somewhat like a "glob" because their shape is not linear, like fibers, but more round, like a blob. (The albumins also look fairly blobby.) The alpha and beta globulins are very similar. Like the albumins, they act like little taxis for substances that don't like being in the watery blood. They transport things like fats, cholesterol, hormones, and mineral ions. The beta globulins have another role, and that is to help dissolve clots once they are not needed anymore. HDL (high density lipoprotein) is an alpha globulin that transports fats back to the liver. LDL is a beta globulin that takes fats away from the liver. You want more HDL than LDL (more fats being returned to the liver) so HDL is often called the "good" fat and LDL is seen as "bad." LDL isn't really bad, but must be kept in balance.

Gamma globulins are also known as ***immunoglobulins*** or ***antibodies***. "Anti" means "against" so they must be against some kind of bodies. The bodies they are against are any bodies (foreign particles) that do not belong to your body. Antibodies are made by B cells and act a bit like tags that say "NOT SELF" and can be stuck onto invaders. You can have antibodies to just about anything: viruses, bacteria, parasites, pollens, and even foods. It is then up to other kinds of white cells (such as T cells and macrophages) to actually destroy the invaders.

More about fibrinogen:

Fibrinogen, blood's little fibers, are short proteins that have the capability, under the right conditions, of joining together to make large, strong fibers called ***fibrin***. The shape of fibrinogen is a bit like a barbell, having a narrow middle and large ends. Fibrinogen fibers can only be activated by clotting factors, notably ***thrombin***. When there is an injury to a vessel, a signal will go out that activates a whole series of clotting factors, causing a chain reaction which, as a final result, changes the fibrinogen molecule. The protein called thrombin will activate sites on the middle of the fibrinogen molecules, allowing them to stick together. Immediately, strands of fibrin begin to form. Fibrin will become a strong mesh that will catch and hold platelets and blood cells, forming a clot. On the surface, where we can see the clot, we often call it a scab (especially when it dries out).

38: BLOOD: THE CLOTTING CASCADE

Hemo**sta**sis is the mechanism by which our blood **sta**ys in our bodies. ("Hemo" is Greek for "blood.") When a blood vessel is injured, our cells react immediately, forming a clot that plugs up the hole. The clot stays in place until the surrounding cells have repaired the damage. Then the clot dissolves so blood can start flowing again. Hemostasis has two steps: a "Platelet Plug" then a "Fibrin Fabric."

NOTE: Some sources will give three steps, adding "vasoconstriction" before the platelet plug. This means the muscles around the vessel contract, shrinking the diameter of the vessel. Less blood flows through, so less blood is lost.

Step 1: Platelet Plug (Primary Hemostasis)

When endothelial cells (the epithelial cells that line the inside of blood vessels) are injured, the connective tissues underneath are suddenly exposed. Normally, collagen never comes into contact with blood. The only time that collagen comes into contact with blood is when something goes wrong.

Floating in the blood are platelets and clotting factors. (We saw in a previous drawing that platelets are pieces of a larger cell called a megakaryocyte. The clotting factors were made by the ***liver.***) The platelets have little receptors on their surface that function like hooks that can grab onto collagen. Normally, platelets do not come into contact with collagen, so these receptors are not active. When something does go wrong, and collagen is exposed, platelets begin sticking to the collagen strands. Enough platelets stick that a clump, or "plug," begins to form. One of the clotting factors, called ***von Willebrand Factor,*** is very helpful at this point. It acts like a glue between the platelets and the collagen. The plug is much stronger with vWF there to help out.

Another important event in this stage is ***platelet activation***. When the receptors on the outside the platelets sense that they are grabbing onto something, several changes occur. The most obvious change is their shape. The platelets grows arm-like things that we might call "branches." In Greek, "dendros" means "branch," so we call their new shape their ***dendritic form***. These arms will help them stick together. While their shape is changing, they are also releasing chemicals that they have been storing in vesicles: calcium ions, and clotting factors including thrombin. ***Calcium*** is needed to activate thrombin. Note that we get some thrombin here, but will get a lot more at the end of step 2.) Additionally, inactive receptors on their surface become activated so they can hold on to collagen and to other platelets even more strongly.

Step 2: Fibrin "Fabric" (Secondary Hemostasis)

In the second step, the tissues will form a proper clot, which will be strengthened by fibrin stands. The net of fibrin strands will begin to catch other kinds of cells, besides platelets. It will catch red cells, and some white cells. The presence of red cells is what gives a clot (or scab) its reddish color. The arrival of white cells will be helpful because they will kill germs that have gotten into the cut. If the population of white cells (especially neutrophils) becomes so large that we can see it, we call it "pus."

As we know, to make fibrin out of single fibrinogen units, a protein factor named ***thrombin*** is necessary. Thrombin activates quite a few other proteins and it even activates molecules called ***antithrombin*** and ***Protein C***, which will begin to undo what thrombin has done. During the healing process, the clot will need to be dissolved. Thrombin is "thinking ahead" to that time, and has already begun producing the factors necessary for that process.

The complicated process that leads to the formation of thrombin is called the ***coagulation cascade***. Outside of biology, "cascade" means "waterfall." Waterfalls begin small at the top, and then spill down, getting bigger at each level. In biological cascades, there are just a few molecules at the beginning of the process, then, at each step, more and more molecules are affected. The first molecule undergoes a change that affects a second molecule. That second molecule changes the third, the third changes a fourth, and so on. It can be helpful to think of a "domino rally" where you set up a line of dominoes and then knock over the first domino. Each domino falls against its neighbor and, one by one, the whole row goes down. In the coagulation cascade, the "dominoes" are proteins called ***coagulation factors*** and are known not by names but by Roman numerals. Instead of getting knocked down, they are "activated." Activation often involves a change to the shape of the molecule. When activated, each factor goes and activates the next factor down the line. The final result of the coagulation cascade is the activation of thrombin which turns fibrinogen into fibrin. The thick strands of fibrin then form the sticky "fabric" that holds the clot together.

There are two "streams" that join together in the coagulation cascade. The shorter branch starts outside the vessel, with the release of a protein called ***tissue factor***, also known as factor III (3), from the surface of body cells near the injured vessel. Tissue factor combines with factor VIIa (7a) and they activate factor X (10). This stream is the "quick start" of the system and occurs outside of the vessel. Once things are rolling, thrombin itself can begin activating factors 7, 10 and 11. It is important at this point to note that several of these factors, namely 2, 8, 10 and 11, require a cofactor (a helper molecule) to function properly. This cofactor is ***vitamin K***, a vitamin found in dark green leafy vegetables. The action of vitamin K can be blocked by a chemical called ***warfarin*** (named after the Wisconsin Alumni Research Foundation, the group that sponsored its discovery in 1940). In high doses, warfarin has been used as a rat poison. The rats bleed to death, but hopefully back in their nest, not on your back porch. In small doses, warfarin can be used as a medicine to prevent life-threatening blood clots. The most common warfarin drug is called ***Coumadin***. It is very likely that someone you know takes Coumadin, as it is a widely used medication.

If your body can't make factors 8, 9 or 11, you will have a disease called ***hemophilia*** in which you can bleed to death even from a small cut. This disease is often called "the royal disease" because Queen Victoria of England carried the gene for it and passed it to several of her children who then married into other royal families around Europe. (Nowadays patients can get injections of the missing clotting factors.)

The longer pathway, the one that starts with factor XII (12) is also kicked off by injury that exposes the collagen that surrounds the blood vessel. This pathway occurs inside the vessel, so it is often called the "intrinsic" pathway.

Why this complicated system? Why can't factor 12 just activate thrombin? The cascade allows for a ***geometric increase***. At each level, there is a huge increase. If factor 12 had to activate all the thrombins, the process would go too slowly. The cascade actually works faster than factor 12 alone. Speed is important when your body is racing to stop bleeding.

39: RED BLOOD CELLS (ERYTHROCYTES)

We've already met erythrocytes in lessons 36 and 37. We know that they come from stem cells that were produced by the hematopoietic stem cell. (Erythrocytes are sort of like the "great-grandchildren" of the hematopoietic stem cell.) As the erythrocytes mature, they begin to lose their organelles. When fully mature, red cells have no nucleus (and therefore no DNA), no ER, no Golgi bodies and no mitochondria. (Mitochondria use oxygen for their electron transport chains, so mitochondria would be a detriment to the purpose of red cells, which is to carry oxgyen.) Surprisingly, though, they can live like this, with no organelles, for about 3 months. After about 100 days, the red cells begin to express protein "tags" on the surface of their plasma membrane that mark them as old cells. As the cells pass through the liver and spleen, they go past macrophages that are looking for these tags. The macrophages grab the old red cells and eat them. The erythrocyte's parts are recycled and used to build new cell parts, perhaps even new red cells.

The number of erythrocytes that the bone marrow produces is controlled primarily by the kidneys. Since all the blood filters through the kidneys many times per hour, this is a good location to have an oxygen monitoring system. Special cells in the kidney can sense the oxygen level in the blood, and if it begins to fall, a substance called ***erythropoietin*** will begin to be produced. The erythropoietin is taken (via the blood) to the bone marrow where it affects the hematopoietic stem cells. It tells these stem cells to begin producing more erythrocytes. More red cells will mean more "vehicles" to carry oxygen. (This process takes several days.) Athletes can take advantage of this, training at high altitudes, then competing at lower altitudes. Bone marrow can make about 2 million red cells per second, giving you a total of about 20 trillion red cells in your blood at any given time.

An erythrocyte contains about 250 million molecules of ***hemoglobin***. Hemoglobin is a protein make of four separate proteins joined together in a square-looking quaternary structure. The "-globin" part of the word refers to these globular proteins. The "hemo-" part of the word refers to "***heme***," a molecule that holds an iron (Fe) atom. Each of the four proteins in hemoglobin holds one heme molecule and each heme molecules holds one iron atom. (These iron atoms are what makes your blood red.)

The structure of heme is very similar to the structure of chlorophyll. Chlorophyll has a magnesium atom where heme has an iron atom. The magnesium atom in chlorophyll is the "action site" where the energy from a photon of light can be transfered to electrons. For some types of anemia (low iron level in blood) patients are given chlorophyll as a nutritional supplement. The body can pop out the magnesium and transform the chlorophyll in to heme.

The iron atom in heme can loosely hold a molecule of oxygen, O_2. (Oxygen always goes around in pairs.) It is important that the oxygen is only loosely held because it must be able to "jump off" quickly when it gets to a place that needs oxygen.

When hemoglobin is recycled, the globin part is reduced to amino acids. The heme molecule is removed and the iron atom is taken out. The iron goes into a "taxi" (a betaglobulin) called ***transferrin***, which circulates in the blood, making the iron atoms available to any cells that need them. The rest of the heme begins to be broken down by cells in the liver. After the first "break" heme becomes ***bilirubin,*** a yellow molecules that gives bruises their yellow color. Bilirubin is broken down further into molecules that are yellow and brown. These are eventually excreted in urine and feces and are what give them their characteristic colors.

Erythrocytes express hundreds proteins on their outer surface. Most of these proteins don't affect medical procedures such as blood transfusions, but a few of them are critically important. The most important proteins are called A, B, and Rh. A cell that expresses A proteins on its surface will also have antibodies to protein B in the plasma. A cell that expresses B proteins on its surface will have antibodies to protein A. An antibody is a tag designed to stick to a foreign particle that gets into the body. (The foreign particle is often called the ***antigen***.) So the anti-B antibodies will cling to the B proteins on a cell that expresses B. The A antibodies will stick to the A proteins. This can cause quite a mess. The mess is called ***agglutination*** and on a microscope slide it looks like clumping or coagulation of the blood.

A person whose cells express both A and B proteins on the surfaces is said to have AB type blood. The AB's won't make either kind of antibody. A person whose red cells don't express either A or B is said to have type O blood and will have both A and B antibodies in their plasma. Your blood type is something you inherit from your parents. It is one of the most studied topics in genetics and lots info is available online if you want to know more.

The ***Rh*** protein was first discovered in the ***Rhesus*** monkey. Biologically, humans are primates and thus share many biological similarities with apes and monkeys. A red cell either has the protein, or doesn't. If it has the Rh protein, it is said to be "Rh positive." If the protein is missing, you are "Rh negative." A person who is Rh negative won't automatically produce anti-Rh antibodies, though. The antibodies will only be produced if the immune system comes into contact with Rh positive red cells. The two occasions where this might happen are transfusions and pregnancy. (Nowadays, it never happens in transfusions because donated blood is carefully typed ahead of time.)

If an Rh negative mother is carrying an Rh positive baby, there is a chance that a few of the baby's red cells might leak into the mother's bloodstream, causing her immune system to start producing Rh antibodies. (Normally, the placenta does keep the blood system separate, but if even a few cells leak over, that is enough to sensitize the mother. Also, during the messy birth process, it is fairly easy for the blood to get mixed up.) If the mother's Rh antibodies got into the baby's blood, they would attack the baby's red cells, endangering the baby. This can be prevented by giving the mother an injection of artificial antibodies that "cover up" the Rh factors on any of the baby's cells that might leak over. The mother's immune cells won't "see" the Rh proteins since they are covered up, and thus no antibodies will be made.

40: LEUCOCYTES (part 1): GRANULOCYTES

First, notice the spelling difference between this title and the title on the template page. Here is a word that can, and is, spelled both ways with equal frequency. It doesn't matter whether you use a "c" or a "k" in the word leucocyte/leukocyte. Some people claim that this is a British/American difference, but apparently both spellings show up on both sides of the Atlantic. So you can choose which way you think looks nicest and go with it. Personally, I am partial to the "c" spelling, (for no logical reason at all) but I might use both at various times in this course. (NOTE: A few words require one or the other, such as the word "leukemia" which must be spelled with a "k.")

The hematopoietic stem cells differentiate into myeloid stem cells, and then one option that the myeloid cell has it to become a granulocyte cell. These cells are called ***granulocytes*** because when you look at them under the microscope they have little dots, or granules inside them. Technically, these structures are vesicles, and are filled with chemicals waiting to be released.

All the granulocytes have very strange-looking nuclei. They have 2 or more ***lobes***, with thin strands connecting them. This arrangement is probably to help them get through tight spaces. Immune cells move around among other cells, and can even leave the blood and go into tissues by squeezing through the tiny cracks between the epithelial cells. Having the nucleus split up into two or more small sections probably makes it easier for the cell to move in narrow spaces.

Basophils were discovered in 1879 by a German physician named Paul Erlich. A year earlier, Erlich had discovered the mast cell, which is very similar to the basophil. The name "basophil" means "base lover," as these cells will take up an alkaline (basic) stain, turning them dark blue. The basophil's granules (vesicles) are filled with several chemicals, of which the most important to know is ***histamine***. Histamine kicks off the inflammatory response, by dilating blood vessels so that plasma and proteins leak out into the tissues. (If this happens to much and too fast, your blood pressure can drop suddenly, causing you to faint.) Histamine also makes you itch because it irritates the nearby nerve cells. Basophils also make a chemical called ***heparin***, which slows down the clotting process. The ***basophil*** normally floats around in the blood and does not permanently reside in tissues like the mast cells does. However, if there is trouble in a tissue somewhere, the basophils can be called in to help. They can squeeze out of the capillaries and get into tissue if needed. However, to keep things straight in your mind, think of basophils in blood, and mast cells in tissues.

Antibodies called ***IgE***s stick to the outside of basophils. (B cell lymphocytes make these antibodies.) The bottom portion ("base" of the Y) sticks to the cell, and the top "v" part attracts antigens. (The word ***antigen*** means something from outside the body--"not self." When the body attacks one of its own parts that part is called an auto-antigen. "Auto" means "self.") Often, substances like food molecules, mold spores or pollen grains can stick to these IgEs and cause the basophil to release its histamine. Thus, basophils are involved in allergic reactions. Basophils, along with mast cells, are responsible for the intense "anaphylactic" (life-threating) allergic reaction that is often associated with allergens like bee stings and peanuts.

The ***mast cell*** was officially discovered and named by Paul Erlich, but had definitely been observed by several scientists in previous years. Erlich thought maybe this cell had something to do with being well-nourished so he named it in honor of the fattening food (mast) that farmers gave their livestock. (Even famous scientists can make mistakes!)

We've already met the mast cell in loose connective tissue, which is where it lives all the time. It does not float around in the blood like basophils do. Mast cells start the inflammatory process by releasing histamine, which dilates blood vessels and makes them leak. Histamine also irritates your nerve endings, causing them to itch. Mast cells are covered with IgE antibodies (made by B cells). When antigens stick to the antibodies, the mast cell begins to release histamine. Mast cells can also be triggered by any kind of trauma, even something as simple as slapping your skin or pressing something hot against it. Mast cells, like all immune cells, release chemicals called cytokines that act as messages to other cells.

Eosinophils got their named from their "love" of an acidic stain called eosin. (Some people prefer to call them ***acidophils***.) Erlich was the person who stained and named these cells in the 1870s, but they had already been noticed by microscopists for several decades. Though Erlich was wrong about the function of mast cells, he guessed correctly the function of the eosinophils and the role that the granules played.

Eosinophils are best known for their role in fighting parasites, especially worms. Yes, worms. Worms have been a reality of life for humans for thousands of years, and still are a reality for millions of people today. Eosinophils attack worms and their eggs. (You can see an actual video of this on the YouTube playlist.) When a parasite is discovered, chemical messages go out to recruit eosinophils to that site and to tell the bone marrow to start producing extra eosinophils. Hundreds (or thousands) of eosinophils will surround the parasite, releasing toxic chemicals as close to the worm as possible, hoping to cause damage.

Eosinophils migrate quickly out of the blood and into tissue. Their favorite places to hang out are in the digestive system, the lungs, and the skin. People who have overactive eosinophils often have problems with these body parts. (Eosinophils seem to play a significant role in asthma, but their exact role is still not completely understood.) It's strange that these cells could stir up trouble, because overall their role is to counteract histamine and help to clean up the "mess" that basophils and mast cells make. The counteracting substance is called ***histaminase***, which neutralizes histamine.

41: LEUCOCYTES (part 2): NEUTROPHILS

Neutrophils, as their name suggests, are fairly neutral when it comes to stain that microscopists pour over them. They don't particularly "love" either basic or acidic stains. They prefer to stay as neutral as possible. Though they do look a bit pink after the lab technicians are done with them. Like the other granulocytes, neutrophils also have a multi-lobed nucleus that will allow the cell to slip through tight cracks and narrow spaces.

Neutrophils are very abundant, as high as 65 percent of the white cells in your blood. (NOTE: If you do some online searches, you will find that these percentages will vary. The percentages quoted here are the most commonly used ones.) Our bone marrow makes about 100 billion neutrophils every day. The marrow keeps a reserve ready in case of emergency, storing up to five times as many neutrophils as there are in circulation. These cells have a very short life span of only a few days. (If you've ever seen "pus" you've seen billions of dead neutrophils.) Neutrophils can eat up to about 50 bacteria in their short lifetime. When neutrophils die, macrophages come and eat them, recycling all the parts.

Neutrophils float around in the blood almost as if they are a police force on patrol, constantly scanning for trouble spots where they might be needed. Our cartoon neutrophil has a red cross on its forehead, reminding us that it is a "first responder" and is very often the first leucocyte at the scene of an infection. Often, the neutrophils clean up the infection while it is very small and we never know what happened. Sometimes an infection will progress to the point that we become aware of it, but there are many tiny invasions every day that are taken care of by our neutrophils without our knowledge.

Our cartoon neutrophil has hair made of little bumps that represent receptors. All cells have numerous receptors, of course, but we are emphasizing them here because the neutrophil's specialized receptors allow it to sense all kinds of pathogens. Cells don't have eyes, of course, so the only way they can know what is in their environment is through their receptors. A neutrophil needs to be able to "smell" bad things around it and go after them. Other parts of the immune system help the neutrophil to know what needs to be eaten by tagging pathogens with ***opsonins***. This word comes from the Greek "opsonein" which means "getting ready to eat." In ancient Greece, side-dishes were knows as "opsons," and the Greeks thought of them as helping you to get ready to eat the main course. The immune system opsonins are tiny chemical tags that "taste good" to neutrophils. Neutrophils will eat anything covered with opsonins. Antibodies are a type of opsonin, and the IgG is especially useful as an opsonin. The two prongs of the Y stick to the pathogen and the base of the Y matches a receptor on the neutrophil. (Remember, B cells make Ig antibodies.) Other opsonizing molecules are made by the liver, and are part of a system called "complement" which we'll talk about in a later lesson. A protein called ***C3b*** is the most well-known protein opsonin made by the liver.

Neutrophils normally float around in the blood. When body cells outside the capillaries are under attack by invaders, they can bring neutrophils to the area by the following process. The nearby endothelial cells put out "hooks" that can grab the passing neutrophils. Once the neutrophils are stopped, they begin squeezing through the cracks between the endothelial cells. They can make enzymes that dissolves the junctions between cells, opening the gap even wider. (Then the endothelial cells go to work fixing the gap.) Once in the ***interstitial space*** (the space between body cells) the neutrophils begin "sniffing out" the invaders. Neutrophils can move on their own, a bit like an amoeba, so they can actually chase down the pathogens. They can "smell" both opsonins that may have been attached to the invaders, and also chemical trails being left by the invaders themselves. Once they get close enough, they engulf the pathogen by the process of ***phagocytosis*** (endocytosis of large things). This process brings the pathogen into the cell inside a vesicle. Vesicles containing engulfed pathogens are called ***phagosomes***.

Once the pathogen-containing phagosome is brought inside the neutrophil, chemical weapons are employed. The neutrophils makes several kinds of chemical weapons, most of which involve oxygen. A general term for these oxygen-based weapons is Reactive Oxygen Species (ROS). The "bullets" on these weapons are often called ***free radicals***.

1) Super-oxide: This is an oxygen molecule, O_2, with an extra electron stuck onto it. A special enzyme sticks on this electron. The electron is like a bullet that will go flying off, damaging whatever it hits.

2) H_2O_2 (hydrogen peroxide): You can see that if we took off one oxygen, we'd have water, H_2O, a very stable molecule. So how does that extra oxygen even stay on the molecule? Not very well, and it can go flying off very easily as a bullet called "singlet oxygen." A single oxygen is a very unhappy atom and wants to steal two electrons from anything it bumps into. In this case, stealing electrons from a pathogen will help to destroy the pathogen.

3) HOCl: (hypochlorous oxide, a form of bleach) Hydrochloric acid, HCl is a relatively stable molecule, so, again, we have a single oxygen that can fall off very easily. The enzyme robot that makes this molecule is light green in color. Since this weapon is made particularly in response to bacteria, if your mucus is greenish, it is likely that you are fighting a bacteria rather than a virus.

4) Digestive enzymes: Like all cells, neutrophils have lysosomes that are filled with digestive enzymes that can dissolve just about anything. If a lysosome merges (joins) with a phagosome, its enzymes get dumped all over the pathogen helping to destroy it.

5) Hiding iron: Neutrophils can gather up iron atoms so that the bacteria can't use them. Bacteria need iron for many of their cellular processes, as do most forms of life. (The Lyme disease bacteria *B. Burgdorferi* is a rare exception—it uses manganese.)

NOTE: A few types of bacteria can survive being in a phagosome by preventing the neutrophil from dumping in those chemicals. (Survival tricks like this are called ***virulence factors***. Often, virulence factors can be shared with other bacteria, like secret information being passed around.) Fortunately, most bacteria can't survive being in a phagosome.

ADDITIONAL NOTE: Free radicals can damage body cells, too, not just pathogens. The body must have ways to protect its own cells from free radical damage. Substances that can absorb free radicals are called ***antioxidants*** ("against oxygen"). Some natural substances can be antioxidants, such as vitamins C and E, and the mineral selenium. Your body makes a powerful antioxidant molecule called ***glutathione***. Glutathione is able to absorb dangerous electrons and not be destoyed itself.

42: LEUCOCYTES (part 3): MACROPHAGES

Macrophages start out as ***monocytes***. We saw monocytes listed in our chart of blood cells back in lesson 36; it came from the myeloid stem cell. Half of our body's supply of monocytes are stored in the spleen and the other half are found in the blood. Monocytes can eat pathogens the way that neutrophils can (and they even have chemical weapons inside) but they are not as efficient at eating compared to neutrophils. (In other words, they eat more slowly.) The monocyte's main job isn't eating, so it's okay if it's slow. Its main job is to turn into either a ***dendritic cell*** or a ***macrophage***.

So here's the pathway for making a dendritic cell: hematopoietic stem cell, myeloid stem cell, monocyte, dendritic cell. Dendritic cells get their name from their long skinny branches. They stay small, only about 10-15 microns, about the same size as the other white cells. The dendritic cell's job is to eat pathogens, digest them, then put tiny pieces of the pathogen in little clips pinned to its outer surface so that T cells can come and look at them. (Or rather, feel them, since T cells don't have eyes!) This process of eating pathogens then showing their pieces to T cells is called ***antigen presentation***. Cells that do this are called ***Antigen Presenting Cells***, or ***APCs***. Often they will even be called "professional" APCs. (Where the amateurs are is anyone guess!) Dendritic cells are found in large numbers in the skin and in the digestive tract, two areas that come into contact with things from the outside world, which is a good place to have cells that process antigens. Dendritic cells are also found in lymph nodes, which makes sense because this is where T cells hang out, too, and the antigens are being presented primarily for T cells.

The other option for monocytes is to turn into a macrophage. We met a macrophage back in the drawing on loose connective tissue. So we know that macrophages can be found in body tissues. Macrophages can even adapt themselves to inhabit certain types of tissues. Of course, this requires that scientists make up new names for them so that you can have more terms to learn. When we meet them in the lungs, they are called "dust cells." In the liver, macrophages are called Kupffer cells, in the skin they are Langerhans cells, and in the brain they are called microglia. Some scientists think that a type of bone cell called an osteoclast is also a type of macrophage but this is being debated. Osteoclasts are the opposite of osteoblasts, since they destroy bone and dissolve the minerals out of them, whereas the osteoblasts build bone and add minerals to them. Since osteoclasts spend their lives eating and recycling bone tissue, we can at least say the are certainly "big eaters" like macrophages. More on osteoclasts in the next module!

Macrophages have lots of lysosomes so they can digest almost anything that gets into your body. They will even try to eat things that they can't digest. Macrophages are your body's bottom line when it comes to cleaning up. If a macrophage can't deal with it, you are in big trouble. One thing macrophages can't break down is the mineral asbestos. Asbestos fibers are fireproof, so in past decades there were used extensively for insulation in buildings or inside appliances. Little did anyone know back then, but when microscopic asbestos fibers get into the lungs, they cause permanent and devastating damage. The poor macrophages get skewered by the sharp asbestos fibers. Since they can't digest them, those fibers stay in the tissues, stabbing all cells they come into contact with. People with asbestos fibers in their lungs often end up getting lung cancer eventually. Nowadays, asbestos is never used in places where people might get exposed to it.

Macrophages have basically three jobs. (This is over-simplifying, of course.) First, as we already know, they are "eaters." They eat pathogens of all kinds, old erythrocytes (this takes place in the liver), dirt, debris, all cellular messes, and old or sick cells, especially neutrophils. Remember, neutrophils only live a few days and if they've been fighting germs, at the end of those days they are filled with dead (or maybe even still living) pathogens. What happens to the old neutrophils that are full of germs? Macrophages are enough larger than neutrophils that they can engulf them and digest them. (Macrophages can grow to be 40 to 50 microns, compared to 10-15 for a neutrophil. For really big pathogens, macrophages can merge together to make a super macrophage that is over 100 microns in diameter.)

Macrophages determine whether a neutrophil needs to be eaten by requiring what we are calling the "CD31 handshake." (This term is our own, and you won't see it in a book.) The "handshake" uses those CD31 hooks we drew on both the neutrophil and macrophage. A macrophage can "catch" a neutrophil by using this hook. It holds the neutrophil there, as if in a strong handshake, and won't let it go unles the neutrophil can give the correct chemical password. If the neutrophil is young and healthy, it will be able to give the correct chemical response and the macrophage will let it go unharmed. If the neutrophil is old or sick (or full of pathogens) it will have trouble giving the chemical response. If it fails to give the response, the neutrophil is engulfed and digested.

The second job of the macrophage is to present antigens to T cells. Like dendritic cells, macrophages are "professional" APCs. They digest pathogens and then put the tiny pieces on their outer membrance so that T cells can examine them. The little protein gadget clip used to post the pieces on the membrane is called the Major Histocompatibilty Complex, or ***MHC***. We will learn more about this molecule in the next few lessons. Since MHCs are also used by body cells to display samples of proteins inside of them, we can help ourselves remember what MHC does by using the mnemonic "My House Cleaning." These clips show what is going on inside the cell.

Lastly, macrophages secrete a lot of cytokine messages in order to communicate with other cells. Messages that are passed between white cells are called ***interleukins*** ("Inter" means "between," and "leuko" means "white.") Interleukins 4 and 12 are especially important when macrophages are talking to T cells. They will tell the helper T cells what kind of helper to turn into.

43: LEUCOCYTES (part 4): LYMPHOCYTES: B CELLS

We've met antibodies in several lessons already. Now it is time to meet the cells that make them: ***B cells***. B cells are lymphoid cells, which means they came from lymphoid stem cells. (You can look back at the chart in lesson 36 if you want to make sure you remember the lymphoid and myeloid stem cells.)

B cells stay in the **B**one marrow to mature. (Oddly enough, technically, the "B" is not for "Bone," but for "Bursa," an organ found in birds, where B cell maturation was discovered 1956.) Before they mature they are called "naïve," which means they have no experience and don't know what to do yet. (Those double dots over the "i" means you pronounce the "i" separate from the "a.") Maturing just means that they become capable of making one particular kind of antibody. One B cell makes one kind of antibody. Just one. It can make a million of them, but they will all be identical "clones." In fact, a whole bunch of identical antibodies are called monoclonal antibodies. (Medicine names that end in "-mab" are made of monoclonal antibodies. Example: Rituximab is an antibody that attaches to a protein called CD20, which is found on the outside of B cells. The antibody sticks to the B cells so that macrophages will eat them. This medicine is used to reduce the total number of B cells in the body.) B cells, as a group, can produce over 10 million different shapes of antibodies, but each B cells makes only one shape. Most antibody shapes will not find anything to match up with and will never be used. Only a few will fit with an antigen. Once a fit is found, that B cell will be told to produce a lot of them.

Antibodies are protein gadgets. They are very small, too small to see without an electron microscope. When we draw them as Y's sticking to things, they are WAY out of scale! Antibodies are made the same way any protein is made, by transcribing sequences from the DNA, then having ribosomes translate them into protein chains. The difference between antibodies and any other protein is that the transcribing process allows for some mutations to occur. Only B cells have this special process where the bases C, G, T, and A are allowed to be scrambled randomly. When mutations occur in regular cells, or in other parts of the B cell, it is very bad for the cell. Cells have machinery akin to spell checkers and editors that try to eliminate mutations. But here, mutations are allowed because each B cell must produce an antibody with a unique shape. The only way this can happen is to use the process of random mutations.

Antibodies are made of 4 pieces of protein. The two longer ones are called ***heavy chains*** and the two smaller ones are called ***light chains***. The base of the antibody Y is called the ***constant region*** and does not change. There are 5 different types of bases: A, D, E, G and M, and each one is used for a different purpose in the body. (We've already met IgEs and we know that the E base sticks to basophils and mast cells. None of the other bases stick to cells.) The top "V" part of the Y is the ***variable region***, so this part varies from B cell to B cell. (This is where the mutation was allowed.) The top of the variable region is called the ***antigen binding site***, the part that sticks to the antigen (not-self). The antigen sticks as a result of shape matching, like a piece going into a puzzle, or a key into a lock.

Antibodies have more than one function. First, they can act as an annoyance to a pathogen, but sticking to it. One antibody isn't annoying, but if you are completely covered in them, that's very annoying. (Imagine having 5,000 clothespins clipped to your body and clothes and you can't get them off.) Second, antibodies can cause clumping, called ***agglutination***. Clusters of antibodies and antigens get stuck together, making the antigens non-functional. These clusters can be called ***immune complexes***. The body will then try to get rid of these clusters. Large clusters will probably have to be eaten and digested by macrophages. Third, antibodies can attract neutrophils and macrophages. When they do this, we call them "***opsonins***," after the Greek word "opsonein," meaning "getting ready to eat." Neutrophils and macrophages love to eat things with opsonins (in this case, Ig's) stuck to them. The Ig's act like little candies.

After the B cells are mature and capable of producing their antibody, they mostly migrate to lymph nodes, but might also end up in the spleen (which is like a large lymph node) or the tonsils (or a few other minor places that you don't have to remember). They sit and wait. For what? For a T cell to come and let them know if their antibody is needed. We'll see this happen in a future lesson.

44: LEUCOCYTES (part 5): T CELLS

First, more information about how regular body cells function.

To understand how T cells work, we first need to learn a little more about how body cells work. Cells are like little houses with no windows. How will their neighbors know what is going on inside? What if a thief is inside? (e.g., a virus)

The body has a roaming police force that constantly scans for trouble. The police cells (killer T's and NK cells) will kill any cell that cannot prove that everything is okay inside. Body cells must "clean house" and cover their outer membranes with samples of the proteins that are floating around inside. If the cellular police detect an intruder or a sickness (such a virus or a cancer cell) they will kill the cell so the problem does not spread to other cells.

There are always proteins floating around in the cytosol of the cell. They are part of the cytoplasm. A tiny shredder machine called a ***proteasome*** chops these proteins into tiny bits. (This is the same shredder machine that recycles mis-folded proteins have have been scrapped.) The little shredded pieces might be as small as only 5-10 amino acids. Then these protein bits go through a portal and into the ER (endoplasmic reticulum). Meanwhile, a ribosome is making a polypeptide and "spitting" it into the ER. This protein will fold up to become a protein gadget clip, called ***MHC***. This little MHC clip is designed to hold a piece of shredded protein. Once this clip is loaded with a sample of protein, it is put into a vesicle and shipped to the surface of the plasma membrane. The clip inserts into the membrane and sits there, displayed the piece of protein it is holding.

MHC stands for ***Major Histocompatibilty Complex***. "Major" means big or important, "histo" means "tissue," "compatibility" means "getting along together," and "complex," in this sense, means a clump made of several smaller parts. There are two kinds of MHCs, and they are usually numbered with Roman numerals 1 and 2: **I and II.** Regular body cells make and use MHC I. We'll see soon that antigen presenting cells use MHC II. It is the interaction of these two MHCs that allows the immune system to know what is going on inside a cell and also to identify intruders.

MHC II is found only on ***"professional" antigen-presenting cells (APCs)*** which include macrophages, dendritic cells and some B cells. We will see how MHC II works in the next lesson.

An important side note about MHC I is that it is responsible for rejection of transplanted organs. The MHC molecule can have a lot of minor variations that don't affect its functionality. Each person can have as many as 50 different variations of MHC. You might want to think of MHC as being made of colored beads. There would be lots of ways you can arrange the colors and still have a functional MHC molecule. Each person has their own unique selection of colors and patterns. The closer you can get to matching the MHC patterns of the transplanted organ to the MHC patterns of the patient who is receiving it, the better. You really want to fool the immune system, if possible, into thinking that the transplanted organ should be accepted as part of the body. You may have seen registry opportunities where people can give a tissue sample that will go into a national database. The donor's MHC pattern will be analyzed and recorded. Then, doctors can use this database to try to find a good match for their patients. (Obviously, these database can only be used for things like bone marrow transplants, where the donor doesn't have to die or give up an organ!)

NOTE: Just in case you see this term and wonder what it is, "HLA," Human Leukocyte Antigen, is another name for MHC.

45: LEUCOCYTES (part 6): T CELLS, continued

Now we need to learn about the MHC clip on the APCs (Antigen Presenting Cells). The APCs are macrophages, dendritic cells and sometimes B cells, but here we will focus on the macrophages since they have a special relationship with T cells.

First, let's see how macrophages present pathogen samples to T cells. The macrophage eats a pathogen and begins digesting with by merging the phagosome with a lysosome. With neutrophils, we saw chemical weapons getting poured into the phagosome, but here we don't want to damage the pathogen's molecules. We just want to chop the pathogen into tiny bits. The merged vesicle is called a ***phagolysosome***. (Textbooks make a big deal about knowing this term.) Meanwhile, an MHC II clip is being manufactured by the ER (similar to what we saw in the last drawing). What is different about MHC II manufacturing is that, unlike MHC I, the MHC II must have a safety clip attached to it so it does not pick up any stray proteins. When the vesicle holding the MHC II merges with the phagolysosome, then the safety clip comes off and a piece of pathogen sticks to the binding site on the MHC II. The process then proceeds the same way as before, with the vesicle merging with the plasma membrane so that the MHC is then stuck to the outside of the cell.

T cells have receptors that look a lot like antibodies. ***TCRs*** (T Cell Receptors) can stick to a piece of pathogen if the piece happens to exactly match the shape of the receptor. The probability of a T cell finding a match for its receptor are actually very low. Most T cells will never find a match and, thus, never be used. However, a few will find a match. These few will then begin rapid mitosis so there are a lot more of them with a correct match.

A T cell is able to sense either MHC I or MHC II (not both). Some T cells have a specialized protein called ***CD4***, which matches MHC II. ("CD" stands for "Cluster of Differentiation" which is just a fancy science way of saying "clump we've identified." They kept finding little clumps of proteins on the outsides of certain types of cells, and started numbering them. This was the 4th.) T cells with this CD4 protein are able to "feel" MHC II, and "know" that there is a macrophage behind the protein sample. Remember, cells don't have eyes or brains. They can't see the macrophage and they don't know that the bit of pathogen protein they are feeling isn't part of an actual pathogen. They have to sense the MHC II clip. CD4 cells are often called "T helper" cells because their role will be to help other T cells and also B cells to become activated. T helpers are not able to directly kill pathogens themselves.

Other T cells have a protein called ***CD8***. (Apparently proteins 5, 6 and 7 were discovered in the interim.) CD8 matches with MHC I, so a T cell with this CD8 gadget will "know" it is touching a body cell. This type of T cell has often been called a "killer" cell because it has a weapon that shoots perforin "bullets" that puncture a hole in the cell membrane. Additionally, this T cell can then shoot toxins into the cell through this hole, so recently scientists have begun calling them "cytotoxic" T cells instead of just "killers."

The main thing to remember from this lesson is that CD4 T cells are called "helpers" and they recognize MHC II on antigen-presenting cells such as macrophages. CD8 T cells are called "killers" or "cytotoxic" and they recognize MHC I on body cells. CD8 cells are capable of killing infected body cells directly, using "bullets" and toxins that we will meet in lesson 47.

NOTE: Sometimes they put a little + sign next to the 4 and 8, like this: $CD4^+$ $CD8^+$ This plus sign just means that they would test "positive" for this protein if you tested them in a lab.

NOTE: As long as we have some extra space, this might be a good place to add a general note about all this complicated stuff we are learning. Why learn all this? Isn't this a bit too much? Actually, there's a good chance you might actually use this information at some point in the future, even if you won't be going on to study medical science. For example, you or a family member might have to make a decision about how to deal with an autoimmune illness and you'll need to know how certain medications work on the immune system. You'll have to decide what kind of doctor to go to and whether you want to try natural alternatives to pharmaceuticals that have lots of side effects. Or perhaps you'll find that knowing some of the immune basics will prevent you from being scammed by someone selling a supplement that they claim fixes the immune system. If you can see that their science is bad, don't waste your money. If nothing else, you'll have an appreciation for how incredibly complex the body is. It's far more complex than what is being presented here. Some researchers spend their entire career investigating one small part of the immune system and still don't know even half of what there is to know. Every time a new discovery is made, we find out how much more we don't know!

46: LEUCOCYTES (part 7): T CELLS, continued again

Like all blood cells, T cells are "born" in the bone marrow. They come from the hematopoietic stem stem after it has differentiated into a lympoid stem cell. After T cells mature (meaning they've developed their T cell receptors and become capable of recognizing MHC) they migrate to the ***thymus***. The thymus is a lesser-known organ and many people are unaware of its existence. This is partly due to the fact that in adults it is not very active any more. Most of its activity is during childhood.

The thymus is located under the ribcage, just above the heart. It has a blobby shape, but usually looks like it has two lobes, left and right. During childhood it is very large, but as we grow older, it shrinks and starts to become more "fatty" and less active. Inside the thymus are several types of specialized cells. One type is designed to catch T cells as they float by in the blood. This is how the T cells "migrate" to the thymus. They are carried along in the blood until they are "grabbed" by these cells in the thymus. Other specialized cells check to see if each T cell can recognize an antigen. If a T cell is defective and not capable of recognizing antigens, it will be destroyed and recycled. Other cells check the T cells to see if they will react to body cells that are presenting normal body proteins. If the T cells react to normal body proteins, they are also destroyed. (NOTE: Sometimes errors occur and T cells that react to body protein escape. These T cells are called ***auto-reactive*** because they react to "self" ("auto" means "self"). This causes ***auto-immune*** reactions where T cells go around attacking body cells.) What happens in the thymus is often called "training" of T cells, but in fact it is more like "screening." About 98 percent of all T cells fail the screening process and are destroyed.

After leaving the thymus, T cells go to lymph nodes and sit there waiting until they are needed. Since they have not yet been activated, and "have no experience," they are called ***naïve T cells***. The CD8 T cell has something that the CD4 does not. It has what we are calling a "perforin gun." The CD8 has the ability to shoot tiny proteins like bullets, puncturing a hole in the plasma membrane. After the hole is punctured, it can also shoot toxin molecules through this hole and into the cell. We will learn more about this in the next lesson.

Now, a note about pathogens. Pathogens can live inside or outside of body cells. (Some can do both, but more often they choose one or the other.) You can see the list of ***extracellular*** and ***intracellular*** pathogens on the drawing page. The body needs to know where a pathogen is lurking so that it can launch the appropriate response.

The decision of where to look for the pathogen is made by the macrophages who ate and presented the pathogen. (The science of exactly how this happens is still being researched.) Somehow, the macrophage "knows" where the pathogen is, and is able to pass this information along to the T cells. When a CD4 T helper cell comes along that has a receptor that matches the pathogen sample (being held in the MHC II clip) it will "lock on" to it and then wait for a signal from the macrophage. The macrophage will then secrete a ***cytokine*** (messenger molecule) that somehow tells the T helper where the pathogen is located, either outside or inside the body cells.

If the cytokine message tells the T helper that the pathogen is hiding inside the body cells, the T helper will then go and alert T killer cells. (We call this kind of T helper "1" and can write: Th1.) If the cytokine message tells the T helper that the pathogen is located outside the body cells, the T helper will then go and alert B cells. (We call this kind of T helper "2" and can write: Th2.) As we already know, the B cells make antibodies that will attach to the pathogens, causing clumping and also attracting phage cells to eat them. The response of the B cells is called the ***humoral response*** because it occurs in a "humor" which is an old-fashioned word for body fluid. (More on this in the next lesson.)

An interesting side note about the Th1 versus Th2 response is in the disease known as leprosy, caused by a bacteria called *Mycobacterium leprae*. This bacteria likes to live inside of cells, so the best immune response would be to use Th1 helper cells that go and alert killer T's to kill infected cells. When this happens, the disease is very mild and usually the person's immune system is able to fight it off adequately. However, some people's immune systems make a mistake and use the Th2 pathway instead. This means that B cells will be alerted to make antibodies. Antibodies can't get into cells, so antibodies are pointless when the pathogen is hiding inside cells. When a body makes this mistake and uses the Th2 response to leprosy, the result is the devastating form of the disease that we are more familiar with.

47: LEUCOCYTES (part 8): How T cells work with B cells

We start with a review of how macrophages work. They eat pathogens, digest them, and put the pieces onto MHC II clips on the outside of the cell so that T cells can come and inspect them. The type of T cell that interacts wtih macrophages is usually the naive *(nie-eev)* helper (CD4) T cell. (Note: Both "naive" and "naïve" are correct spellings.) The cell is naive because it does not have a job yet. If the naive helper's receptor matches the piece of pathogen, it will then begin to change. What it turns into will depend on a signal from the macrophage.

The T cell will need to know whether the pathogen is an intracellular or extracellular pathogen. If the pathogen is intracellular and is hiding inside of body cells, the T helper will need to alert killer T cells who can kill infected body cells. This is called the ***cell mediated response***. If the pathogen is extracellular and is located outside of the body cells, the helper T will go to the B cells and tell them to flood the body fluids with antibodies. This is called the ***humoral response***. (Textbooks emphasis these terms, so it is good to know them.) The term "humoral" comes from the word "humor," a Medieval word for body fluids. In the Middle Ages they believed that there were four essential body fluids: blood, phlegm, black and yellow bile. These controlled not only your health but also your personality. They had awful remedies for getting rid of "excess" fluids. (Even as late as the 1700s, doctors killed George Washington by letting him bleed, in order to get rid of "extra" blood.) We don't use the word "humor" anymore for body fluids, but it does show up in several anatomy terms, such as "humoral."

In the cell mediated pathway, the naive Th0 (T helper zero) differentiates into a Th1 (T helper 1) and finds a cytotoxic (Tc) killer T that is waiting for instructions. A killer T recognizes bad proteins on the MHC I on body cells. It "knows" this is probably an infected cell that needs to be killed, but it waits for confirmation from a helper T. If the helper T has also recognized this bad protein, it will send a cytokine message to the killer T that says to go ahead and kill the cell. The Th1 cell also sends cytokine messages back to the macrophage encouraging it to speed up, and also cytokine messages to itself telling itself to make many clones. The killer T cells also begin making many clones. Most of these clones will be active killers, but a few will become memory cells.

Killer T cells do their killing by releasing chemicals very near to the surface of the cell membrane. One of these chemicals is called ***perforin*** and is released as individual sub-units that will self-assemble into a tube. It's like an instant hole that puts itself together automatically. Once there is a hole in the cell membrane, chemicals (often called "toxins") known as ***granzymes*** go through the hole and into the cell. The granzymes start a cascade process where one molecule affects another, which affects another, which affects another until the final molecule is released. This final molecule is a DNA shredder, and it destroys all the DNA in the nucleus. Once the DNA is gone, the cell can no longer make proteins and it slowly dies. Slow and contained cell death is ideal because then the surrounded healthy cells are not disturbed. (Then who comes along and cleans up the mess? Macrophages, of course.)

The virus that causes HIV AIDS attacks cells that have CD4 on their surface. This is mainly T helper cells, although macrophages and dendritic cells also express small amounts of CD4. As the population of T helpers begins to shrink, there are fewer and fewer helpers to interact with the T killers. The T killers find infected cells and are waiting to kill them, but without the helpers to give the "Go!" signal, they never get around to killing the bad cells. Thus, pathogens start taking over.

If the macrophage tells the naive Th0 cell that the pathogens are extracellular, the T cell will then turn into a Th2 and begin interacting with B cells. This strategy makes sense because B cells make antibodies that are released into body fluids and this is where extracellular pathogens are. B cells will have already discovered the pathogens and will have started making IgM antibodies against them. IgMs are made of a group of 5 antibodies attached at their stems. This large, somewhat clunky-looking shape is good for the initial stage of finding and binding antigens, but in the long run, the IgG form will be better. An IgG looks like a single Y. To ramp up the fight against the pathogen, the B cell should switch from making IgMs to making IgGs. However, it will not make this switch unless it gets a signal from a Th2 cell. The Th2 send cytokine messages to the B cell, allowing to start "class switching." Once the B cell switches over to IgGs, it will no longer be able to make IgMs. It is a permanent switch.

The B cell also begins to make many clones of itself. Most of the clones will be ***plasma cells***, actively making antibodies. A few will become memory cells so that if this pathogen is ever encountered again, the immune system will be better prepared to deal with it. Usually, we are never aware that our body encounters the pathogen a second time. The pathogen is dealt with so quickly that we never actually "come down with" the infection. B memory cells are very long-lived, often enduring for our entire lifetime.

There are some other options for naive T cells, not just Th1 and Th2. Occassionally they will turn into T regulatory cells, which used to be called T suppressors. Tregs tell the killers to stop attacking once the infection is under control. The Th0 might also turn into a Th17. Th17 cells are the opposite of Tregs—they encourage inflammation and immune activity. Th17s used to be thought of as a malfunction of the immune system, but now they are seen as a cell that plays a helpful role in some situations. Th3 cells encourage B cells to make IgA antibodies. IgAs are like two Y's joined at their bases. They can't stick to body cells, so they can't cause inflammation. Their purpose seems mainly to be washing out antigens from the respiratory tract and the digestive tract. IgA antibodies bind and hold antigens, then get washed out with mucus secretions.

48: IMMUNE SYSTEM OVERVIEW

The body has several layers of defenses against pathogens. The first layer consists of physical barriers that attempt to keep germs out. The most obvious barrier is the skin. The epidermis does a pretty good job of keeping bacteria and parasites from entering the body. It is usually only when we get a cut or scrape that invaders get in. The lining of the respiratory tract (nose, trachea, lungs) keeps germs out by secreting a mucus layer. In the trachea the cells also have cilia that sweep the mucus up and away from the lungs. The digestive tract has a mucosal layer, as well. The stomach secretes a strong acid that can kill most pathogens. In the eyes, tears flush out germs, and the tears themselves have some anti-microbial properties. The nose, with its constant mucus production, does quite a good job of washing out not only pathogens but dust and dirt particles, too.

The second layer of defense is called the innate immune system. The root word "nat" means "born" so this is the system you are born with. The innate system is all set up and ready to go and does not need any training. (Since the T cells are trained in the thymus, they would not be part of this system.) The cells that are usually considered to be part of the innate (non-trained) system are the basophil, the eosinophil, the mast cell, the neutrophil, the NK (natural killer) cells, and usually the macrophages and dendritic cells, as well. Some texts also include the liver as part of this system, since it produces proteins that help the other cells do their jobs.

The NK (natural killer) cell is a lymphocyte, like the T and B cells. In fact, some scientists considered it to be basically another type of T cell. Its physical appearance and function are a lot like the killer T cells. The NK cell's main job is to feel the outside of body cells, checking for MHC I. It can detect bad proteins attached to MHC I and then directly kill the cell. NK cells do not need to check with T helpers first, the way killer T cells do. Perhaps that is why they are called "natural killers." NK cells can do something that Tc cells can't do—they can detect the absence of MHC I. If a cell is sick it might not be able to manufacture normal tags such as MHC. Also, some viruses can cause cells to stop expressing MHC I. (Perhaps the virus thinks this is a way to hide from the immune system?) The NK cell "feels" the surface of the body cell and if it does not feel any MHC I, it will kill the cell. (The HIV virus is very sneaky, because it causes the cell to put out just enough MHCs so that the NK cell does not get suspicious.) The NK kills cells the same way that the killer T does, using a ***perforin*** "gun." The perforin makes a hole in the cell, then the ***granzymes*** (the "toxins") go in and start a cascade process that ends with the DNA in the nucleus being shredded. This is called ***programmed cell death***, or ***apoptosis***.

The macrophages and dendritic cells are special members of the innate team because they are also sort of members of the adaptive team, as well. We've already seen how these cells work, presenting antigens to the T cells. The liver is also often listed as a member of the innate immune system. We'll discuss it in just a minute.

The adaptive system has three names, which can be very confusing. These three names are used equally, and you have to be familiar with all of them and know that they are the same thing: ***adaptive, specific, acquired***. "Adaptive" means that this system adapts and changes over time. "Specific" means that its function aims at specific pathogens, not all pathogens in general. "Acquired" means that you gradually acquire it over time, as your body comes into contact with various pathogens in your environment. We've already met the members of the adaptive immune system: the T cells and B cells. We've learned how they are able to react to a very specific pathogen, through the recognition of the T cell receptors and the B cell's antibodies. Remember, antibodies are very specific and can only attach to one particular molecular shape. We've got millions of T cells and B cells, each one with a slightly different shape on its receptor or antibody. Hopefully, when a pathogen comes along, one of the shapes will match. What allows you to acquire and keep this system over time are the memory cells that are produced.

The liver produces many different kinds of proteins that help the immune system to be more efficient. These proteins, as a group, are called ***complement***. (It is strange that they use this word in the singular form, instead of saying complements. However, strange as it is, that's the way it is.) The complement proteins are numbered using the letter C; C1, C2, C3, etc. These proteins will function in a chain reaction manner, somewhat similar to the chain reactions we see in the coagulation cascade and in apoptosis. Just like coagulation proteins, these complement proteins float in the blood in their inactive form and are not activated unless they are needed.

Complement proteins accomplish four things:

1) They can activate mast cells.
2) They make ***Membrane Attack Complexes*** (similar to the ring that perforin makes).
3) They can act like opsonins, making macrophages and neutrophils want to eat them (and whatever they are stuck to).
4) They can stick pathogens together in a clump so that they are easier for the phagocytic cells to eat. ***(agglutination***)

C3 is the only complement protein we'll take a close look at. C3 has two sections, **a** and **b**. A scissor enzyme can come along and separate C3a from C3b. C3a can go over and stick to mast cells, beginning the inflammation process. C3b goes and attaches to the plasma membrane and attracts C5, C6, C7, C8 and C9. These molecules self-assemble and form a ring, much the same way that the perforin molecules do. The ring formed by these complement proteins is called the ***membrane attack complex***. The main difference is that the membrane attack complex is not followed up by toxins. There aren't any granzymes here, just a big hole. If lots of membrane attack complexes are launched, hopefully the pathogen's membrane will end up with enough holes that it will collapse.

49: THE NEURON

Nervous tissue is designed for basically one function: transmitting electrical signals. The cells that actually do the work of transmitting are called ***neurons***. Neurons need lots of help, so they have a whole crew of supporting cells that protect them, nourish them, and repair them. In this lesson we will look at the anatomy of just the neuron and one supporting cell.

The neuron we've drawn is a generic ***motor neuron***. This means that it will likely be attached at one end to a ***muscle fiber***. ("Motor" means "movement.") Neurons shown in textbooks are almost always motor neurons. This type of neuron is only found in the ***peripheral*** nervous system, which means everything outside of the brain and spine. ***Sensory neurons*** are also found in the peripheral nervous system. Some sensory nerves take in information directly, such as pain and pressure sensors. Pain sensors have free nerve endings that are easily irritated and result in signals being sent to the brain that are interpreted as pain. Pressure sensors have some padding around them so that they don't register signals as pain. Some sensory neurons connect to specialized cells that can sense things like light, smell and taste. The sensory cells then transmit a signal to the sensory neuron. Sensory neurons usually have their cell body in the middle (this is called a ***unipolar*** arrangement).

Neurons have basically three parts: a cell body called the ***soma,*** some ***dendrites***, and an ***axon***. The soma contains the nucleus, ER, Golgis, mitochondria, lysosome, ribosomes, etc. The dendrites are often long and skinny and look a bit like tree branches, which is how they got their name. The job of the dendrites is to sense in-coming electrical signals. The axon is long and thin and can be anywhere from a few millimeters long to almost a meter long. (The place where you find very long axons is in your leg, running from the base of your spine down to your toes.) Axons carry electrical signals all the way to the ends of the cell. The end of the cell branches out, but not is not quite as branch-like as the dendrite end. At the end of each branch is a little knob-like thing. This knob doesn't have an official name and goes by quite a few names: terminal knob, synaptic knob, terminal button, axon terminal, synaptic terminal. Take your pick; all of these seem to be used equally. Here, we'll use the term ***terminal knob***. The terminal knobs are full of mitochondria and also vesicles waiting to release their chemicals. Terminal knobs are usually connected to either a muscle fiber or the dendrites of another neuron. We will talk more about the terminal knobs in a future lesson.

The axons of neurons found in the body (not in the brain or spine) have their axons surrounded by ***Schwann cells***. These protective cells are incredibly thin and very long, and are rolled around the axon like a piece of paper can be rolled around a pencil. One end of the Schwann cell is thicker because it contains the nucleus and organelles. The thick end stays on the outside. The thin part of the cell is so thin that it is basically nothing more than the plasma membranes with a lot of fat (mostly cholesterol) molecules in the middle. This line-up of protective Schwann cells is known as the ***myelin sheath***. You hear the term myelin sheath more often than you hear about Schwann cells. It can be easy to forget that the sheath is actually made of cells! The Schwann cells have two jobs. First, they insulate the axon the way electrical wires are insulated by their plastic or rubber coatings. The neuron's job is to conduct electricity (like a metal wire) so it needs to be insulted. Second, the Schwann cells can help an axon to regrow if it gets severed. The Schwann cells will stay place and acts as tubes to guide the severed ends of the axon back together, if possible. This healing process is slow and can take weeks or months.

If an axon begins to lose part of all of its myelin covering, the neuron will not be able to transmit electrical signals. One result can be that muscles are no longer able to move properly. The disease known as Multiple Sclerosis involves a breakdown of myelin.

The mitochondria in a neuron are critically important to their functioning. They start out in the soma (cell body) and travel down the axon to the terminal knobs. Then, after a while, they are transported back up the axon and return to the cell body where they are recycled and made into new mitochondria. This transport of mitochondria up and down the axon is done by those tiny motor proteins that look like they are walking. They carry the mitochondria along the microtubule "roads." Microtubules (part of the cytoskeleton) go all the way down through the axon. Also, vesicles filled with chemicals are manufactured in the ER and Golgi bodies and then carried down to the knobs by the motor proteins. Researchers think the vesicles can also be taken back up and recycled, but this is a very new discovery and there is still a lot they don't know.

When mitochondria are not properly transported up and down the axon, the results can be devastating. This is one of the things that goes wrong in neurological diseases such as ALS (Lou Gehrig's disease). Even if the problem seems very small, like the mitochondria not being able to get turned around in the knob, big problems can be the result. (There is a special molecule whose job it is to get the mitochondria from the "down track" to the "up track." If this molecule is not produced, the neuron will malfunction.)

50: NERVOUS TISSUE in the PNS

The big divide in classification of nervous tissue is the PNS versus the CNS. These abbreviations are standardly used in all texts. ***PNS*** stands for ***Peripheral Nervous System*** and ***CNS*** stands for ***Central Nervous System***. The central nervous system is the brain and the spinal cord. The peripheral nervous system is everything else (arms, legs, chest, face, etc.). Each type of nervous tissue has special features that help it to maximize its efficiency.

Neurons in the PNS have slightly different shapes according to what they do. They all have the same three parts (soma, dendrites and axon) but these parts can be arranged differently. The ***motor neuron*** has the dendrites coming off the soma, and the axon going out one side. Many motor neurons have their cell bodies inside the spinal cord, and their axon terminals attached to a muscle fiber. Their job is to rely signals from the brain that are telling the muscle fiber to contract. This is the type of neuron we drew in the last lesson. Neurons that have multiple "processes" (i.e. "things") sticking off the soma are called ***multipolar*** neurons. Another vocabulary word associated with this type of neuron (as if we needed another one) is the word ***efferent***. Efferent means taking information from the brain and relaying it out to the body. The opposite of this is ***afferent*** (as if we needed another similar word). Afferent neurons take messages from the body to the brain. (If you are planning on studying anatomy at the college level, "efferent" and "afferent" are words you should know. If you won't be studying this stuff at college level, these are words that you can get along without. The main point is that you know that some neurons take info from body to brain and others take info from brain to body.)

A ***sensory neuron***'s job is to pick up information from the outside world and carry it to the brain. Sensory neurons have dendrites that are adapted to one of the senses. For example, the dendrites of some sensory neurons are found in skin and receive signals that are interpreted by the brain has pain, pressure, cold or heat. Sensory dendrites in the nose and tongue and are activated when certain chemicals touch the receptor cells. Sensory dendrites in the eye are connected to other cells that are activated by light. In the ear, there are several types of sensory dendrites, as the ear is involved in not only hearing sounds, but balance, too. The cell body of a sensory neuron is located in the middle of the cell, which gives it a rather odd appearance. Neurons that look like this are called either ***bipolar*** or ***unipolar***, depending on whether there are two things sticking off the cell body (bipolar) or only one (unipolar). (NOTE: Bipolar neurons have no connection with the brain syndrome called Bipolar Disorder. "Bipolar" is a general term that means something with two sides.) NOTE: Recently, scientists have begun to call unipolar cells ***pseudounipolar,*** because on close inspection it is more complicated than seeing just "one thing" sticking off the soma. (If you are not going to be studying anatomy in the future, don't worry too much about learning these terms.)

Axons can be very long. The longest axon in the body runs from the base of the spine all the way down to the foot. Each axon only controls a very small muscle fiber, so you must have millions of axons in order to control your millions of muscle fibers. Instead of having these millions of axons running every which way all over your body, the axons are bundled together in a very organized way.

The term ***nerve fiber*** is used when we talk about an axon and its coverings. (Technically, the "axon" is just the long skinny part of a neuron and does not include any wrappings.) Of course, we already know that most axons in the PNS are surrounded by a Schwann cells that protects and insulates. Around the Schwann cells there is another protective layer called the ***endoneurium***. (Here is another word you don't need to memorize unless you will be studying anatomy in the future.) The endoneurium is made of connective tissue. It's like the paper wrapper around a sandwich and serves to hold everything in place. (When we studied connective tissue we mentioned that it is found all over the body; this is a place that is rarely mentioned.) So a nerve fiber is an axon with its myelin sheath (Schwann cells) and its connective tissue covering.

Nerve fibers are then bundled together into ***fascicles*** *(FASS-ick-uls).* The fascicle also has a connective tissue covering, very similar to the one surrounding the nerve fiber. The covering around the fascicle is called the ***perineurium*** ("peri" means "around"). Again, not a word you need to worry about unless you will be going on to study anatomy in greater depth. The fascicles are then bundled together to make ***nerves***. Nerves also contain some tiny blood vessels and connective tissue to hold everything together, and they have a covering called the ***epineurium*** ("epi" means "on top"). Nerves can contain nerve fibers (axons) from both efferent and afferent neurons.

Nerves are often found running alongside blood vessels. A "neurovascular bundle" is a nerve, an artery and a vein held together by connective tissue. When a nerve is cut, some of the special fluid found inside these connective tissue coverings can leak out. This fluid can be sensed by MRI imaging, making it possible for doctors to determine the location and extent of damage to nerves.

A ***reflex arc*** is an arrangement of motor and sensory neurons that allows fast reaction time by processing the signal in the spine instead of going all the way to the brain. A sensory neuron picks up a signal, relays it to the spinal cord where an interneuron connects it to a motor neuron that then sends a signal out to a muscle. For example, if your finger touches a hot stove, the hot and pain sensors are triggered and the signal is sent to the spine, through the interneuron and over to the motor neuron which is connected to a muscle that immediately moves in order to get your finger away from danger. Another signal is sent to the brain so that you will realize what happened, but by the time your brain understands what just happened, your finger will have already pulled away from the heat.

You can see in the cross section of the spine that the cell bodies of the sensory neurons are all located in the same area, creating a lump that we call a ***ganglion***. Since this ganglion is attached to the dorsal (back) part of the spinal cord, we call this lump the ***dorsal ganglion***. There isn't a matching ganglion in the front because the cell bodies of the motor neurons are located inside the spinal tissue. Can you see the lump that they form inside the spinal cord?

51: NERVOUS TISSUE in the CNS

The ***CNS (Central Nervous System)*** consists of the brain and the spinal cord. This drawing shows a slice of brain tissue. You would find similar cells in the spinal cord but they would be arranged differently. Neurons are the primary cells of the CNS, but they are quite outnumbered by the supporting cells all around them. The supporting cells are called ***neuroglia***. ("Glia" means "glue.") Some of these supporting cells really do act like glue, keeping the neurons tightly in place.

In the coloring demonstration, the neuron was colored green. In some places you can see (green) dendrites coming very close to some (green) axon terminals. These connections between dendrites and axon terminals will be discussed in the next lesson. This is where the electric signal is passed from neuron to neuron, though the signal must be translated into chemicals in order to jump the gap.

These neurons look like they have Schwann cells along their axons, but in fact these cells are called ***oligodendrocytes***. ("Oligo" means "few.") In the demo we colored them blue. Oligodendrocytes have a few "arms" that reach out and grab sections of axon, covering and insulating them. The oligodendrocytes also help to stabilize the neurons and prevent them from moving around. Despite their name ("few branches") some oligodendrocytes have been observed to be holding on to as many as 50 neurons. At birth, only some of your neurons have oligodendrocytes around them. The process of ***myelination*** (putting myelin sheaths around all the axons) isn't complete until you reach 25-30 years of age.

The cells that are best at stabilizing the neurons are the ***astrocytes***. ("Astro" means "star.") In the demo, we colored these cells yellow. The astrocytes use their "arms" to hold not only the somas and axons in place, but also, very importantly, those connections between dendrites and axon terminals. The astrocytes surround these connections and keep them from slipping apart. If these connections were to get torn apart, there would be disastrous consequences for the body—it would be like tearing the electrical wiring out of a building. The elevators and light would not work. In the body, it's not elevators and lights—it's things like muscles and memories. The astrocytes are also responsible for feeding the neurons and taking away their wastes. They do this by connecting some of their "arms" to a blood vessel so that they can absorb oxygen, water, and nutrients. These substances travel though the astrocyte and then go out through other arms that are touching neurons.

The cells that we've colored orange are called ***microglia***, and are the only neuroglial cells that have "glia" in their name. This is a bit ironic because these glial cells don't act like glue at all. Microglia are the macrophages of the brain, and are constantly moving around, looking for pathogens to gobble up. Microglia are the only immune cells found in the brain; you won't find neutrophils or T cells or basophils or any of the other immune cells found in the rest of the body. Microglia have extra receptors that normal macrophages don't have, allowing them to be more efficient at recognizing and eating pathogens. When microglia aren't eating, their arms look very skinny and branch-like. Once they get activated and start into eating mode, the branches disappear and they look much more like regular macrophages (kind of blobby).

Like macrophages, the microglia are also responsible for all clean up jobs. They digest damaged cells and get rid of any molecular debris they find in the interstitial spaces (between cells). They also help to "prune" the "electrical wiring" by eating old connections that have not been used and are therefore deemed unnecessary. Getting rid of unused connections makes the neuronal network more efficient. Some researchers have observed microglia doing what looks like "tapping" on neurons and their connections, as if to inspect them. The more we learn about microglia, the more intelligent they seem to be!

Ependymal cells *(eh-PEND-i-mahl)* form the lining of fluid-filled spaces called ***ventricles***. We will learn more about ventricles when we take a look at the brain as a whole. Ventricles are "empty spaces" in the brain that are filled with a fluid which is produced, in part, by ependymal cells. The ependymal cells have cilia on the side that faces the ventricle. The cilia are used to move the fluid around. The fluid flows in and out of four ventricles, and then goes out to the spaces around the outside of the brain and spinal cord. Eventually, the fluid is reabsorbed back into the body and the water and minerals are recycled.

The brain is full of blood vessels. Large vessels come in, then split off into smaller and smaller branches, eventually forming tiny, microscopic capillaries. The capillaries are where the gas and nutrient exchange occurs. Astrocytes attach themselves to the outside of the capillaries to absorb nutrients. Another type of cell also attaches itself to the capillaries. ***Pericytes*** wrap around the capillaries in order to help control blood flow and also to help keep large things from leaking out. They are like helper cells for the endothelial cells. The endothelial cells and the pericytes together form what is known as the ***Blood Brain Barrier (BBB)***. The endothelial cells in the brain are stitched together very tightly, much tighter than in the rest of the body. In body tissues, the capillaries are often exposed to histamine from mast cells that causes them to dilate and get leaky. This should never happen in the brain. (Good thing there are no mast cells in the brain!) Tiny molecules such as glucose and amino acids are absorbed from the blood by the endothelial cells, then transfered to the astrocytes, who then transfer them to the neurons. The essential things that neurons need are all small enough to be obtained in this way. The BBB keeps harmful substances out of the brain. In the rare case of a pathogen getting into the brain and causing a condition that needs medical treatment, doctors must give the patient a substance that will cause the brain capillaries to be a little bit leaky so that medicines can get into the brain tissues. This is only done in an emergency, as you really don't want to disturb the BBB. Because the BBB is so efficient, it is difficult to find medicines to treat long-term brain problems.

52: THE ACTION POTENTIAL and THE SYNAPSE

Neurons are the focal point of both the PNS and the CNS since they are the ones that carry the electrical impulses that go back and forth between the brain and the body. There are several basic mechanisms in the neuron's axon that work together to accomplish the task of transmitting an impulse: the sodium-potassium pump, ion channels, and neurotransmitters in the synapse.

All along the axon's plasma membrane there are many sodium-potassium pumps. These pumps use one ATP every time they pump. One complete pumping action pumps 3 Na^+ ions outside the membrane and brings 2 K^+ ions inside. The net result is one more positive ion outside than inside. This means that eventually there will be more positive charges outside than inside. Another way of looking at it is that the inside is now more negative than the outside. Therefore, you often see the inside of the axon labeled with a negative sign and the outside with a positive. This is confusing to students when they see that both ions being pumped having positive charges. The negative charge on the inside is <u>in comparison to</u> the outside, which has even more positive ions. What the ion pumps have done is set up a gradient. Remember, atoms want to be equally distributed everywhere. Now that we have most (but probably not all) the Na^+ ions on one side and the K^+ ions on the other, what will happen if we open ion channels that will let them travel across the membrane? Yes, the Na^+ ions will rush in through ***sodium gates***, and the K^+ ions will rush out via ***potassium gates***. This rushing in and out is called the ***action potential***. This active rushing of ions <u>IS</u> the electrical signal we keep talking about neurons carrying.

After the Na^+ ions have all rushed across the membrane, we now have the reverse situation—we have the inside of the axon being positive and the outside being negative. Once the K^+ gates open and the K^+ ions rush across, we no longer have a positive inside, but we are not quite back to where we started. To be able to do another action potential, the axon must restore the original amount of negativity inside. So the sodium-potassium pumps go to work and start pumping $Na^{+\,i}$ ions out and K^+ ions in. Once everything is back to where we started, this is called the ***resting potential***. The resting potential is when the axon is all set and ready to go for another action potential. The word "potential" is appropriate here because in this state, the axon has the potential to carry a signal, but has not done so yet. (For those of you who like details, in this resting state, a very precise voltmeter will register the inside of the axon at about -70 millivolts, mV. After the action potential has fired, the outside will then register at about +40 mV.)

The axon we are showing here doesn't have any Schwann cells around it. Something very interesting happens under the Schwann cells. The action potential can kind of "jump" through the insulated Schwann areas, without having to do all the rushing in and out of ions. The rushing of ions occurs only at the nodes of Ranvier, where there are gaps between the Schwann cells. Since it seems that the action potential can "jump" from node to node, the Latin word for jumping, "saltare," was used to form a word for this neuron action: ***saltatory***. Since we also use the word "conduct" for electricity, the complete term for this jumping of the action potential from node to node is ***saltatory conduction***. (For a visual demonstration of this, see the video listed on the lesson page.)

When the action potential has gone all the way down the axon it ends in the terminal knobs. This electrical impulse, the action potential, cannot jump the gap that exists between the terminal knobs and the dendrites of the next neuron. (This area where knobs meet the next neuron is called the ***synapse***. The actual empty space between is called the ***synaptic cleft***.) Instead, the action potential causes calcium ions to rush into the knobs and thereby causing the waiting vesicles to fuse with the membrane and spill their contents into the gap. (We saw this use of calcium in module 1 when we studied fertilization of the ovum. Calcium ions cause vesicles to do exocytosis.) The neurotransmitter chemicals in the vesicles can be of various types. (For more information on neurotransmitters, see the additional info on the lesson page.) Each transmitter will have a matching receptor on the sides of an ion channel embedded in that dendritic plasma membrane. (NOTE: Sometimes axon terminals touch the soma, too, not just dendrites.)

Some neurotransmitters fit into receptors on Na^+ channels. Others stick to receptors on K^+ receptors. If two neurotransmitter molecules stick to a Na+ channel it will open to allow an influx of Na+ ions. Since this is what happens in an action potential, the result will be that this next neuron will be encouraged to start a new action potential. (Mulitple Na^+ gates have to open to have a new action potential start. One is probably not enough.) If neurotransmitters stick to a K^+ channel, then K^+ ions will flow in and... nothing will happen because having a lot of K+ on the inside is part of the resting potential, not the action potential. This action of K^+ ions is called an ***inhibitory*** response because it discourages, or inhibits, the next neuron from beginning a signal. The action of the Na^+ ions is called an ***excitatory*** response because it encourages, or excites, the next neuron into action. If enough Na^+ ions flow into this next neuron, an action potential will begin in the hillock and move down into the axon. One role of the soma is to collect all the various inputs coming from all these ion channels and sort of "sum them up" and then generate—or <u>not</u> generate—a new signal.

This process is, of course, more complicated than described here. For exaxmple, there are a number of neurotransmitter chemicals that have different actions in the synapses. Also, there are ***enzymes*** waiting in and around the synapses that capture and either destroy or recycle the neurotransmitters. The neurotransmitters have to be disposed of immetiately so they don't keep acting after the signal is finished. They, also, need to be reset every time. And all this (this whole lesson) happens in a fraction of a second!

CUT OFF THIS BOTTOM SECTION ALONG DOTTED LINE

Here are patterns for two action potential sliders. You'll only need one, but the extra is provided in case of multiple students, or in case you make a mistake and need an extra. The blank rectangles fold around the axon (make sure they are loose enough to slide). The action potential rectangle is glued on top. (The video will show you how to assemble them.)

53: MUSCLE FIBERS and the NEUROMUSCULAR JUNCTION

Muscles follow the same organizational format we've already seen several times now: bundles of bundles of bundles. The largest bundle is what we know as a "muscle." A muscle is surrounded by a connective tissue bag called a ***fascia*** *(FASH-ah)* that gets thick at one end and turns into a ***tendon***. The tendon is what attaches to a bone. The muscle itself is made of bundles of ***fascicles***, *(FASS-i-kuhls)* which are, in turn, made of bundles of ***muscle fibers***. A single muscle fiber is very small and you'd need a microscope to see it. Muscle fibers are made of very, very tiny filaments called ***myofibrils***. Myofibrils are made of protein "ropes" called ***actin*** and ***myosin***. We've actually met actin already, as it is the smallest of the cytoskeleton filaments. (To see actin and myosin you need an electron microscope.) The next lesson has more information about actin and myosin.

Motor neurons (the kind we drew in lesson 49) attach to muscle fibers. The axon terminals of one neuron can connect to just a few muscle fibers or as many as 30-50, depending on how big the muscle is and where it is located. (The cell bodies of these motor neurons are usually found in the spinal cord, as you might remember from drawing 50.) A motor neuron and the muscle fibers to which it is attached are called a ***motor unit***. They are a unit because the neuron will make all of them work together at the same time.

There aren't any individual muscle cells. During embryonic development, all individual muscle cells fused together to create very long "super cells" with lots of nuclei. So a long muscle fiber actually IS a muscle cell. Sort of. Muscle fibers have all the usual cell parts, especially lots of mitochondria for producing ATPs.

Muscle fibers have some features that other body cells do not:

1) myofibrils filled with actin and myosin
2) a plasma membrane that dips down forming tubes (known as T tubules)
3) an adapted smooth endoplasmic reticulum that looks very different from the smooth ER found in other body cells

Since muscle fibers are so different from other cells, scientists felt compelled to make up different names for their cells parts. The Greek word roots they choose for muscle stuff are "myo" meaning "muscle," and "sarco" meaning "flesh" (similar to "meat"). The plasma membrane was renamed as the ***sarcolemma***, the cytoplasm became the ***sarcoplasm***, and the smooth ER was named the ***sarcoplasmic reticulum***. The places where the sarcolemma (plasma membrane) dips down are called ***T tubules***. ("T" stands for "transverse," with "trans" meaning "across.") The T tubules are going to carry the action potential down into the interior of the fiber. As we will see, muscle cells are similar to neurons in that they are equipped to carry an action potential across their membrane. This means that the sarcolemma must be equipped with sodium-potassium pumps, to maintain the resting potential where the outside is more positive than the inside (because of all the sodium ion that have been pumped out).

NOTE: The sarcoplasmic reticulum is not shown in the middle drawing. It would make the drawing too complicated. The SR is shown in the bottom drawing.

The place where an axon terminal connects to a muscle fiber is called the ***neuromuscular junction***. Just as with neurons, we have a ***synaptic cleft***, a little gap, where neurotransmitter chemicals must cross and start a new action potential on the other side. The neurotransmitter chemical we find inside the vesicles in these axon terminals is called ***acetylcholine, ACh***. There are also little enzymes lurking in the gap that will destroy acetylcholine as soon as it has done its job. You would not want ACh building up, as this would make the muscle fibers contract continually, causing a muscle to be unable to relax, even for a second. In fact, this is what happens with some poisons. The poison molecules interfere with the breakdown process and you get too much ACh in the synapse. The muscles go into extreme cramping, even the heart muscle, which causes death. Another poison, ***curare***, which is made from a plant that grows in South American (and is used to make poisoned arrow tips), prevents ACh from being able to bind to the receptors on the muscle side of the cleft. This means that the muscles can't contract at all. The muscles become paralyzed and the heart stops beating.

After the vesicles in the axon terminal release ACh into the gap, the ACh molecules stick to binding sites on the sodium channels on the muscle side of the gap. The sodium channels open to allow sodium ions to enter, thus starting a new action potential. However, this action potential will do something different in the muscle fiber. The T tubules (which carry the action potential since they are part of the sarcolemma) lie along thick parts of the sarcoplasmic reticulum that are storing calcium ions. The action potential will cause the SR to release its calcium ions. These ions will flow into the myofibrils and attach themselves to the actin filaments, something will see in more detail in the next lesson.

54: ACTIN and MYOSIN

Muscle fibers (cells) are made of myofibrils. Myofibrils are made of two types of protein chains: ***actin*** and ***myosin***. We've actually met actin before when we studied the cytoskeleton in module 1. The smallest filaments of the cytoskeleton are basically made of actin. Myosin filaments are thicker than actin and they have little paddle-like projections sticking off. Sometimes actin and myosin are referred to as thin and thick filaments.

The actin and myosin filaments are organized into short units called ***sarcomeres***. Sarcomeres give myofibrils a striped appearance. Each sarcomere is an individual unit that contracts, and when all of the sarcomeres contract at the same time this is what makes the whole muscle contract. All of the myofibrils in a muscle fiber are connected to the same neuron, so they all function together, contracting at the same time. The ends of a sarcomere are called the ***Z lines***. They look like thin lines on the sarcomere and they act as scaffolds to which actin and myosin are secured by even tinier protein ropes. The thicker band in the middle is called the ***A band***, and it is the area where the myosin fibers are found. This band is darker because of the density of both actin and myosin filaments. Motion (contraction) will happen when the actin and myosin filaments slide past each other and shorten the whole sarcomere.

Actin looks like two ropes twisted together. The ropes are protein gadgets, of course. Sometimes actin is drawn as lines or ropes, but when shown close up, actin is usually drawn to look like two bead necklaces twisted together. On each "bead" there is a binding site where one of the myosin "heads" can bind if the conditions are right. These binding sites are covered by a protein thread called ***tropomyosin***. A protein called ***troponin*** is attached to tropomyosin helps in this covering process. Troponin is sort like the release button that will allow the tropomyosin threads to roll off the binding sites. When a calcium ion binds to troponin, this triggers the troponin to open up the binding sites by moving tropomyosin out of the way. Where do the calcium ions come from? From the sarcoplasmic reticulum where they are stored. What caused the SR to release the calcium? The release was triggered by the action potential that came down through the T tubules. Where did the action potential come from? It started when the neurotransmitter ACh crossed the synaptic cleft at the neuromuscular junction.

ATPs are used as the energy source for muscle contraction. When an ATP binds to the myosin head, it then splits into ADP and P. When the calcium ions come along, the myosin heads bind to the binding sites on the actin. After they bind, the ADP and the P leave the myosin head. As they leave, this causes a shape change in the myosin head that results in it pushing the actin filament. All the myosin heads do this at the same time, causing the entire actin filament to slide over. This sliding action causes the sarcomere to get shorter (to contract). After this motion happens, a fresh ATP comes over and binds to the myosin head, causing it to let go and go back to its original position. Then the cycle can repeat.

ATPs for muscle contraction come from three places. The first place is NOT the mitochondria, as you might guess. The first source that muscles use is from a molecule called ***creatine***. Creatine can hold onto a phosphate, P. An enzyme robot called ***creatine kinase*** can take the P off creatine and put it onto an ADP, making it into ATP. (A "kinase" is any protein gadget that can take phosphates on and off.) This seems like a very easy and simple way to create ATP— just have an enzyme do the whole thing in one step! So why do we even need mitochondria and their complicated electron transport chains? Both are necessary in the grand scheme of life. ATP from creatine can only last about 5-10 minutes, then it is gone. This is long enough to let you do a short sprint, go up the stairs, carry some heavy boxes, and other short, intense daily tasks. However, if you walk, jog, or swim for over 10 minutes, you will need those ATPs made by the mitochondria. The mitos are really good at cranking out lots of ATPs as long as oxygen is available. That's the thing to remember about cellular respiration (the ETC)-- it needs oxygen. (Creatine does not need oxygen.)

It is possible to exercise harder and longer than your mitochondria can keep up with, depleting the available oxygen in the muscles. Then your muscles will need an alternative energy source. "Plan C" is called ***lactic acid fermentation***. Glycolysis splits glucose into 2 pyruvate molecules. The pyruvates will go into the Krebs cycle if oxygen is present. If not, they will pile up in the cytoplasm. Also, after a lot of glycolysis has happened (because of no oxygen), all the NADH "trucks" will be full. (Remember, glycolysis produces not only 2 ATPs but also 2 NADH, also.) With no trucks available, glycolysis will stop.

As a result of the chemical process whereby pyruvates are turned into lactic acid, some NADH trucks are emptied and made available so that glycolysis can continue to take place. The downside to this process is that lactic acid in your muscles does not feel good; it produces that burning sensation. Therefore, lactic acid also serves as a warning signal, letting you know that your muscles are truly running out of oxygen. You feel enough pain that you stop over-doing it and let your muscles replenish their supply of creatine and ATPs in the mitochondria.