LESSON 1: VIRUS MORPHOLOGY and ANATOMY

Don't let the word "morphology" scare you. It has a simple meaning. It is the study of the shape of something. That's right, scientists could have said "let's look at the shape" but they had to make up a complicated word that uses a Greek word so it would sound more "science-y." Here's the tricky part, though. Most people think "morph" means "to change." That's partly due to television shows like the Mighty Morphin' Power Rangers, who say, "It's morphin' time!" and then change into super-heroes. So now we have to re-educate young people and let them know that "meta" means "change" and "morph" means "shape." For example, when an insect goes through metamorphosis, it changes (meta) shape (morph). Morphology is actually one of the easiest things to study, because it doesn't involve any chemistry. We just look at shapes, often naming them and classifying them into groups.

Viruses come in three basic shapes, although these shapes are not what scientists use to classify viruses. (Classification is done by looking at the genome: the DNA or RNA.) The shape categories virologists use are:

1) RODS (also known as HELICES) The most well-known virus in this group is the Tobacco Mosaic Virus, or TMV. It was the first virus ever discovered. It is a long, thin cylinder, like a drinking straw. The cylinder is made of a long strand of protein curled around and around and around, sort of like twisting a piece of thick wire around a pencil. The shape of the circular wrapping is called a helix. "Helices" is the plural form of the world helix. The TMV's genetic material, RNA, is wrapped up in a helix shape also, and adheres to the inside of the tube.

The rabies virus is usually put into this category, too, although it is a very short cylinder and has a rounded end, making it look like a bullet. The Ebolavirus doesn't fit into any category very well, but it fits into this one better than the others. It is like a long, thin snake. The ends are not open, like the TMV, but are sealed. It might look like a worm, but it's not living and can't move.

2) ICOSAHEDRAL (includes spheres) Most viruses fall into this category. An icosahedron is a 20-sided shape made of triangles. There is a scientific reason why viruses so often take this shape. The virus is made of many individual protein pieces that fit together. It turns out that the icosahedron is the most efficient way for these pieces to come together because it requires the least amount of energy. This is universal pattern that we see everywhere in nature— things try to be at the lowest possible energy level. The smallest icosahedron is made of 60 identical proteins, with three proteins forming a triangle. Bigger icosahedrons will have more proteins, but mostly in multiples of 60 (commonly 180, 240 and). Sometimes the icosahedron will be hiding inside a spherical outer envelope, but even that is likely to based on this same geometry. The glycoprotein spikes sticking out are often, but not always, found at places where the triangles meet.

3) COMPLEX This is a catch-all category for viruses that don't fit into the first two categories. Bacteriophages (or just "phages") attack only bacteria, not plants or animals. They look a bit like lunar modules from the moon landings of the 1970s. The top part is an icosahedron, which can look spherical or oval in some phages. Most phages have names like T2, T4 and T7. The T stands for "type." (The Greek word root "phage" means "to eat.") The things that look like legs are called tail fibers and allow it to stick to the outside of a bacteria cell.

Recently, some really huge viruses have been found. They are far too big to follow icosahedral geometry, so they end up as giant oval shapes. For example, the Pandoravirus looks a bit like a flask with a stopper. The discoverer of this virus was reminded of the Greek myth about Pandora, whose curiosity got the better of her and she opened a flask she was told not to open, and out of the flask came all the evils of the world. In this case, the evil would be the virus's RNA, which invades a tiny ameba and causes it to make more Pandoraviruses.

WHAT IS INSIDE A VIRUS?

Viruses can vary a lot, but the two things they all have in common are 1) a **capsid** made of protein, and 2) a **genome** made of either DNA or RNA. Other structures that might be present are an outer **envelope** made of lipid membrane (stolen from the host cell the virus came out of), spikes and knobs made of **glycoprotein** (sugar-proteins) that allow it to attach to cells, tiny **protein gadgets** that will play a part in the reproduction process, and sometimes a thin layer of protein called the **matrix**, which adheres to the fatty lipid layer and gives it a bit more strength.

WHAT IS PROTEIN?

We keep saying that things are made of protein. Do you remember what protein is made of? The individual building block of protein is the amino acid. Aminos are made of atoms arranged around a central carbon atom. When we want to show al long chain of amino acids, they are usually drawn as circles with a letters written on them. Many aminos strung together form a polypeptide. The long polypeptide chain folds up into a particular shape and we call it a protein.

WHAT IS GENETIC MATERIAL?

Genetic material is either DNA or RNA and both have a "backbone" (the long edge of the ladder) made of alternating sugar and phosphate molecules, and rungs made of "bases." DNA has Adenine, Thymine, Cytosine, and Guanine. RNA replaces Thymine with Uracil (which is very much like thymine). DNA in most cells is always double-sided like a ladder, and RNA is always single-sided. In viruses, DNA and RNA can both be either single or double sided.

LESSON 2: SIZE and PREVALENCE

We start with two more great vocabulary words: prevalence and ubiquitous. Prevalence means how much there is of something. Ubiquitous means found everywhere.

We learn about three units of measure: the millimeter, the micron (or micrometer) and the nanometer. If you cut a millimeter into a thousand parts you get a micron, if you cut a micron into a thousand parts you get a nanometer. (If we wanted to go the next step down, we'd use the word "pico." So a picometer would be 1/1000 of a nanometer.)

Microns are used to measure things like cells and protozoans. Cells range in size from 30 to 150 microns. Protozoans range in size from 10 to 500 microns. The width of a human hair is about 80 to 100 microns, which makes it surprising that we can see it. Hair has color, reflects light very well, and is very long, all of which make it more visible. Spider silk is also only microns wide but can be seen because it reflects light so well.

Here are the viruses we drew:

Pandora: The largest virus ever discovered, at 1,000 nm (one micron). It infects single-celled amebas.
Pox family: This family includes smallpox, cowpox and monkeypox. Cowpox was used for the first vaccine, which is where we get the word vaccine. "Vacca" is the Latin word for "cow."
Parvo: Causes severe illness in dogs, but some strains infect humans, also, causing what is called Fifth disease, which gets its name from the fact that it was number five in a list of childhood illnesses. Fifth disease causes rash and fever. Dogs are vaccinated against parvovirus when they get their annual shots at the vet.
Polio: Most often a mild disease, but can also be severe in some cases and attack the nervous system causing permanent paralysis. We vaccinate people against this disease now, but the virus is still out there.
Hepatitis B: Causes an infection of the liver, but can only be transmitted from person to person by contact with body fluids, most commonly blood. It can be passed from mothers to unborn babies, or through blood transfusions or from the use of dirty injection needles. There is now a vaccine for it.
Zika: This infection is transmitted by mosquitoes that live in the tropics or subtropics. Brazil and the Caribbean were the sites of the most recent outbreaks. It causes only mild symptoms in adults. The big concern is that when pregnant women catch it, their unborn children can acquire a birth defect called microcephaly, which means their head and brain grow too slowly and end up being so small that the baby will have many disabilities.
Papilloma: This virus attacks skin. There are different strains of papilloma, some causing the warts we get on our hands and feet. If you walk across floors in locker rooms, you are treading on millions of papilloma viruses. Other strains will attack soft tissues of the urogenital tract (the parts we use privately in the bathroom) but these are harder to catch than the wart kind.
Rotavirus: Vomiting and diarrhea. Yuck. Most of us have had one of these viruses at least once. They are highly contagious, but usually last only a few days.
Adenovirus: These cause upper respiratory infections, the ones we often catch during winter "cold and flu season." Though these viruses are not fun to catch, they are milder than the influenza viruses.
Influenza: These are the nasty flus that people sometimes die from. The most famous flu was the epidemic of 1918, right after World War I. The 1918 flu strain was unusual in that it hit younger people harder than older people.
HIV: Human Immunodeficiency Virus, which causes AIDS. It was unknown before the 1980s, and began as a disease prevalent only in the homosexual community, but it soon spread into Africa as a disease of heterosexuals. It can only be spread by contact with body fluids such as blood, urine, and other secretions. Unfortunately, unborn babies can be infected by their mothers. There are medicines now to treat this disease, so it is not as deadly as it used to be (if you have access to those medicines).
Coronavirus: Causes flu-like symptoms. The name "corona" comes from the way it looks, with a haze of light-colored rays going out from it, reminding us of how the sun looks during an eclipse, when you can see its corona.
Measles: Holds the record for being the most contagious of all viruses. Causes rash and fever. There is a vaccine for it.
Rabies: A disease that can infect both animals and humans. We have our dogs and cats vaccinated against it, which protects the human population. Rabies attacks the nervous system and is always fatal. Fortunately, it is slow and there is a several week window of opportunity to get a vaccination if you are bitten by a rabid animal.
Herpes: This is a whole family of viruses. Some strains cause ulcers in and around the mouth. Others cause chickenpox and shingles. Most everyone in the world is infected with several kinds of Herpes, usually picked up during infancy or childhood. They stay in your body for the rest of your life, but usually stay dormant (not active).
Ebola: A virus originating near the Ebola River in west Africa. Passed through blood contact. You don't want to hear symptoms.
TMV: Tobacco Mosaic Virus, the first virus ever discovered. Infects many plants besides tobacco.
Mimivirus: Considered a "megavirus" because of its huge size. It infects amebas, in both fresh and ocean water. "Mimi" is short for "mimicking microbe" meaning that it fooled its discovers into thinking it was a bacteria.

Most of what we learned about prevalence is written on the activity sheet and doesn't need further explanation.

LESSON 4: BACTERIOPHAGES

The history of the discovery of phages was briefly mentioned in our time line, and we'll give more of the story in the next lesson. In this lesson we will focus on just the anatomy and physiology of phages. (Scientists like to use "phage" as it is shorter than "bacteriophage.")

The T4 phage is about 200 nm tall, and belongs to a group of phages called the "tailed" pages. What looks to you like a stem is called the tail. The head is the capsid, and it does look like a head. Some phages have a collar right below the head, and some even have some whiskers coming out from the collar. (The whiskers do act like animal whiskers, somehow sensing the environment and pulling the tail fibers up if conditions are not right for successfully landing on a bacteria.) The stem part of the tail is called the "sheath." At the bottom of the sheath is a baseplate and attached to the baseplate are six tail fibers, which look very much like legs. The fibers have special shapes at their tips that match the shapes of certain parts on the surface of a bacteria, and this is what lets them find and latch on to the type of bacteria they can infect. Phages can't infect all bacteria, just one type. The receptors will only fit into one particular part in one species of bacteria. (Phage receptors never match any of the surface parts on human cells, nor any types of plant or animal.)

The capsid is packed full of DNA. It was packed under great pressure, so it is sort of "spring loaded" and ready to come streaming out when given a chance. The DNA is fairly long, but not the longest in the viral kingdom. The DNA has 169,000 "rungs" on its ladder. Each rung is called a **base pair** because it is made of two molecules called **bases**. The length of DNA is often written in bas pairs, like this: 169,000 bp, or even 169 kbp, where "k" stands for 1,000. The base pairs that make the rungs are [Adenine and Thymine] and [Cytosine, and Guanine]. They are arranged in a very particular order, so that they spell out a secret code that can be read by a little machine called a **ribosome**. (But wait-- T4 doesn't have any ribosomes, so what good is all that code? Hmm... it might have to borrow some ribosomes.)

Not all phages look like T4. Some have no tail or a very short one. Some have no tail fibers, or a long curly one. One phage is a long thin tube, looking more like the Tobacco Mosaic Virus than T4. All phages have names that are just letters and numbers. Besides T4 there's T2, T3, and so on up through T17. There's also a P series, an M series.

The T4 phage infects a very common bacteria called *E. coli*. ("E" is for "Escherichia." *ESH-er-RICK-ee-ah)* We have a type of *E. coli* living in our intestines and it is very helpful as long as the population doesn't get too large. However, there is also a type of *E. coli* that causes food poisoning. (By the way, did you notice that *E. coli* is always written in italic (slanty) letters? That's how scientists tell you that's their official classification name, using genus and species.)

E. coli is a rod-shaped bacteria that often has one or more tails called **flagella**. It has two membranes as a covering, and some poisonous strings of sugars sticking off the outside. These sugar chains have a very long name (lipopolysaccharides)so often they are called **endotoxins**. When a lot of *E. coli* die all at once and fall apart, these sugar chains can circulate in our bodies and make us sick. The T4 likes these toxic sugar chains, though, because that is one of the places it can get a grip on the bacteria.

Inside the bacteria we find: 1) a clump of DNA, 2) an almost invisible network of fine threads called the **cytoskeleton**, and, 3) most importantly, RIBOSOMES! Ribosomes are little machines that can read copies of DNA code. They are like factories can turn the DNA instructions into usable proteins that will become parts for the structure of a cell. Other types of proteins become additional machines, called enzymes. Enzymes are like little robots that only do one task. They might put two molecules together or take things apart.

After the T4's tail fibers latch on, the tail sheath contracts and out comes a protein needle to punch a hole in the bacteria's membranes, and also some packets of enzymes that will digest the "peptidoglycan" barrier in the middle, that is made of sugars and proteins. Then the DNA comes shooting out and goes inside the bacteria.

Once inside, the T4 DNA will follow the **lytic** cycle. The DNA will be read by little enzyme "robots" that will unzip the DNA and start making copies of one side. This copy of one side is called messenger RNA, mRNA. There will also be enzyme workers who will direct this process, telling the copier where to start and stop. The T4 DNA has 289 sections of code (called "genes") that each code for a different protein. There are even codes for making enzyme workers that will help very long protein strings fold up into their correct shapes. The shape of a protein is critical. Some enzymes are "inspectors" who find proteins that are folded wrong and get rid of them. And, most importantly, complete copies of the viral DNA are made.

When all the proteins have been made, they start to go together to make the virus parts: capsid, tail sheath, baseplate, tail fibers. Before the capsid is attached to the sheath, a little molecular motor on the bottom of the capsid pushes one of the DNA copies up into it. If we scaled up the motor to something we could see, this motor would be as powerful as a car engine! When about 100 to 150 new viruses have been assembled, the bacterial cell wall bursts open and all the viruses escape, ready to go off and infect 100 to 150 new cells. (This whole process takes only about 30 minutes.)

Other viruses follow a different path of infection, called the **lysogenic** cycle. The goal of this process is to have the viral genome hide for a long time, perhaps even years, but be ready to pop out at an opportune time, whenever that might be. The virus has instructions its DNA for how to fool the bacteria into adding the virus's DNA to its own DNA. A little enzyme machine cuts and stitches the two genomes to make one larger one. So when the bacteria begins to divide and make a copy of itself (the fission process), it copies that new version of the DNA with the viral genome in it. Presto, you then have two bacteria with viral genomes hiding inside. Then those two bacteria split, making four bacteria with viral genomes inside. And so on. At some point in the future, the viral DNA can come back out and start into the lytic cycle, where actual viruses are made.

LESSON 5(a): HOW VIRUSES ENTER CELLS

There are three basic steps that a virus must go through to enter a cell. The first step is to attach securely to the cell. The second is to somehow get their payload of DNA or RNA into the cell. The third step is only for enveloped viruses because in this step they merge their envelope with the cell's membrane.

The first step is to attach to the cell. The surface of all cells is a "forest" of tiny proteins sticking up everywhere. Most of these proteins are receptors of some kind. Some are like ID tags and function to identify the cell as "self," meaning belonging to the body. Some are used for attachment to other cells. Some are there to take in nutrients that the cells needs, or to receive chemical messages sent out by other cells. Some receptors are actually not receiving but sending messages but we call them receptors anyway. Chemical messages are in the form of hormones made of lipids (fats), or proteins, sugars, or even small ions such as calcium atoms.

The first feature we draw is actually a mechanism that cells don't attach to: the proton pump. This little "machine" constantly pumps positively charged protons from the inside to the outside of the cell. (The protons probably came from a hydrogen atom that lost its electron. Hydrogen's nucleus is nothing but a proton, so when it loses its electron the nucleus floats around as a single proton.) The proton pump is a key factor for many viruses in their entry process.

Another feature on the cell surface that is not a major target of virus attachment is MHC 1 (also known as HLA) which looks like a little flag and is used to identify the cell as belonging to the body. Immune system cells called NK (natural killer) cells patrol the body, feeling the surface of cells, looking for those ID tags. If they don't find them, they kill the cell with a little protein "gun" that shoots a hole in the cell. Cells that are infected with viruses often are not able to put their flags out, so they are killed by the NKs.

Cell receptors that are commonly known as viruses receptors are:

1) Sialic acid: a tiny sugar found on the ends of many long glycoprotein chains, especially on cells found in the respiratory tract.
2) ACE2 (Angiotensin Converting Enzyme 2): part of the blood pressure regulation system, it tells arteries to relax and open, thus lowering blood pressure. (ACE is the opposite and works to constrict vessels and raise blood pressure.) ACE2 receptors are found in the lungs, heart, blood vessels, and intestines. The coronavirus attaches to ACE2, so it can enter anywhere these receptors are found, including the intestines. This is why people are told to wash their hands thoroughly, so corona is not swallowed.
3) CD155, also known as **PVR** (Polio Virus Receptor): used as a connection between cells, found mainly in epithelial cells in the skin, lungs and intestines. (CD stands for Cluster of Differentiation, a technical-sounding way to say "clump that is different.")
4) CD4: a receptor found on T cells allowing the T cells to communicate with macrophages. Both of these cells are types of white blood cells and are part of your infection-fighting immune system. HIV attacks T cells and enters using CD4. This is why HIV is such a serious disease-- it disables germ-fighting cells.
5) CAR: Coxsackie-B Adenovirus Receptor, which is not designed for these viruses, but for body processes such as proper formation of the heart during embryonic development, and for cells to attach to each other in the heart and lungs.

We also drew a 7-pass receptor, as they are a very common feature found in the membrane. Most 7-pass receptors are also called G-Protein Coupled Receptors. This type of receptor has some very complicated and interesting mechanical features under the surface of the membrane. About half of all prescription medicines are designed to target some type of GCPR.

The most important concept to understand in drawing 1, is that viruses are able to latch on to a receptor because their protein spike or knob just happens to fit perfectly into a receptor. It is all about shape matching. Sometimes the phrase "lock and key" is used to describe it. The virus (unfortunately) has a copy of the correct key shape to open the lock.

Viruses need to get their genome into the cell. Some naked viruses, like polio, open a small pore right at one of the vertices (corners) of their icosahedral capsid, using a fusion protein, and the genome threads through the hole and into the cell.

Other naked viruses wait until they are taken into the cell, inside a "bubble" called an endosome. The endosome is made of a piece of membrane, so it still has proton pumps in it. The pumps are still pumping protons, so the endosome begins to fill with protons. This causes the pH to drop, and the endosome becomes acidic. This is just what the virus needs, as the low pH causes the capsid to disassemble and the endosome to burst open.

If a virus has a lipid envelope, it will need to merge the envelope with the cell membrane. Since the virus's membrane is actually stolen cell membrane (from the cell it came out of) the two membranes will merge naturally if they can be brought together. Some viruses merge their membranes at, or close to, the surface. Others wait until they are in an endosome. In either case, a fusion protein will be needed.

The fusion protein is not accessible (hidden) until the virus attaches to the receptor. The attachment of the receptor triggers the release of the fusion protein and it sticks down into the cell membrane. Again, the low (acidic) pH inside the endosome is a key to making this happen. When the viral membrane fuses to the endosome, the result is sort of a C shape, and the genome suddenly finds itself outside the endosome, in the cytoplasm of the cell. Influenza virus is the best example of this, so we will study the influenza process in lesson 5(b).

LESSON 5(b): HOW INFLUENZA ENTERS CELLS

The very first viral receptor ever discovered was the one that influenza uses: **sialic acid**. We learned in the last lesson that sialic acid is the very last sugar on many long chains. The chains can be made of nothing but sugar molecules, (such as glucose, or galactose), or the chain might include some amino acids. Chains that include both sugars and amino acids are called **glycoproteins**. "Glyco" means "sugar." The word glycoprotein is a very general word and can be used to describe very small structures or very large structures like the spikes we see on influenza. If a scientists were to list the basic parts of influenza, it would read like this: capsid, genome, lipid envelope, glycoproteins.

The glycoproteins we find sticking out of influenza's capsid are not all the same. If we look closely, we will see that there are two distinctly different shapes. Both shapes look a bit like clubs, with a "head" and a "stalk." The larger shape is called **hemagglutinin** (HE-mah-GLUE-tin-in) and the smaller one is called **neuraminidase** (noor-ah-MIN-i-dase).

Hemagglutinin (HA) gets its name from two words: "heme," meaning "blood," and "agglutinate," meaning "to clump." Why the reference to blood? Remember from lesson 3, we learned about a test that was developed in 1940, when they discovered that some viruses will cause red blood cells to clump. Red blood cells are covered with tiny glycoproteins that have sugar strings hanging off. The last sugar on the string is sialic acid so influenza is one of the viruses that will stick to red blood cells. This doesn't do the virus any good, though, as red blood cells don't have a nucleus. The influenza genome must enter a nucleus in order to replicate. So any viruses that stick to red blood cells will be "duds" that never reproduce. Cells in the trachea and lungs also have sialic acid sugars attached to them, and they, and they will be the cells that become infected.

The other glycoprotein, **neuraminidase** (NA), is like a little pair of scissors that only cuts one thing. It trims off the sialic acid sugar from the end of a chain. This will come in handy when the new virus tries to leave the cell. It doesn't want to be stuck to the cell it is coming out of. The NA trims off any sialic acids it touches, clearing the way for the virus to escape.

During the billions of times that viruses are replicated, small mistakes will be made. The result can be that the shape of HA or NA can change just a tiny bit. These changes may or may not affect the ability of the virus to cause infection. The successful changes are the ones that become permanent. Scientists have found (so far) 16 different shapes that HA can take. The first one ever discovered was called H1. The second was H2, and so on. The same holds true for NA. The first shape they discovered was called N1, then there was N2, N3, etc. up to N9. The famous flu pandemic of 1918 was a variety of influenza that had H1 and N1. (H1N1 still circulates today, but it is less dangerous than it was in 1918.) H2N2 caused the Asian flu outbreak of 1957. H5N1 caused the Bird Flu epidemic of 2004.

Influenza's capsid is surrounded by a lipid membrane that it took from the cell it came out of. The capsid itself is made of proteins. Embedded in the wall of the capsid are a few proton channels called M2. These channels will allow protons to come inside the capsid after the virus is inside an endosome in the cell.

Inside the capsid we find the viral RNA, broken into 8 pieces. At the end of each piece of RNA we find a little clump of proteins stuck to it. These proteins are copying machines that the RNA will need as soon as it gets into the host cell nucleus. There are also two small proteins that ride around with the genome. One is called NEP (Nuclear Exit Protein) which is like a copy of the password that all messenger RNAs need to get out of the cell nucleus. (Everything must pass through a heavily guarded exit pore.) The other small protein is NS1 (Non-Structural 1), and it prevents the cell from making its own RNAs, especially messenger RNAs that will be used to manufacture anti-viral "weapons" (such as Interferon).

Influenza is taken into cells by a process called "clathrin-mediated endocytosis." (Mediated means controlled, and endocytosis means "bringing things inside the cell.") **Clathrin** is a substance made of proteins that form a sort of scaffolding outside the endosome, like the temporary scaffolding on a building while it is being built. Little 3-armed proteins (triskelions) snap together on the under side of the membrane and work to pull the membrane down into a round shape. Another related protein curls around the top where it is getting narrow, and pinches it off like you pinch the end of a balloon after blowing it up. Then the endosome is cut free and is ready to travel.

Nothing moves on its own inside a cell. All movement is done by little "taxi" proteins called **motor proteins**. These amazing proteins have little "feet" that "walk" along "roads" made of long fibers called **microtubules**. Imagine a tightrope walker holding a house on his back as he slowly walks the rope-- that's pretty much what these motor proteins look like. They haul the endosome over to the nucleus.

While the endosome is riding along, the proton pumps in its membrane continue to pump, making the inside of the endosome more acidic. (About 5 on the pH scale for those of you who know about pH.) This lowering of pH is the trigger for HA to change its shape. (The technical term for this is a "conformational change." Scientists like long words.) The shape change will let a fusion protein pop out and stick into the cell membrane. Then the shape will change even more, and HA will begin to bend in half. When three HAs all do this together, the result is what they call "hair-pinning," meaning a very sharp bend in the membrane. The end result is that the membranes fuse together forming a hole from which the viral RNA can escape.

The pieces of viral RNA suddenly find themselves released right near the nucleus. They will be taken through the tiny pores that guard entry to the nucleus. Inside the nucleus they will begin to direct the manufacturing of viral proteins.

NOTE: Not all viruses must go to the nucleus. Some stay outside and use the ribosomes in the cytoplasm

LESSON 6: INSIDE A CELL

Cells are like little cities. They are surrounded by a wall, like ancient human cities were. The wall has portals and gates that let certain things in and out at certain times. They have power plants that provide energy for factories, vehicles, and tools. They have a library full of coded information. They have roads on which molecular taxis travel. They have recycling centers. They have factories that build most of the structures (and tools as well).

If a virus were a person, what would be its thoughts about cells? Viruses do not have the ability to reproduce on their own. They will need to rely on a lot of the machines and structures inside their host cell. Outside of a cell, viruses have no source of energy. Without energy, nothing can move or change. Viruses also don't have the right machines for making proteins. They carry instructions for making proteins, but have no way to actually make them.

Before we can discuss how a virus takes over a cell, we need to be familiar with the parts of a cell, and know what types of raw material and energy will become available to the virus. Cells contain structures called organelles, which means "little organs."

NUCLEUS: This is like the library of the cell and contains most of the cell's DNA (mitochondria also have a little DNA). Inside the nucleus you find the genome (the DNA that contains every bit of information necessary for building the body the cell is part of). The nucleus has tiny holes, or portals, that restrict what can go in and out. The DNA always stays inside.

NUCLEOLUS: This is an area inside the nucleus where RNA is made that will be folded up to make ribosomes. The RNA leaves the nucleus unfolded because the portal holes in the nucleus are so tiny. After it is out, the RNA will fold up to make ribosomes.

MITOCHONDRIA: This is where the ATP "batteries" are recharged. ATP is a molecule with three phosphates (PO4) on the end. When the third phosphate pops off, energy is released. The mitochondria uses energy from food molecules to power little machines that put the third phosphate back on ATP making it usable again. Everything in the cell that needs energy uses ATP (or a similar molecule called GTP).

LYSOSOMES: The are the recyclers of the cell. They can chop and recycle just about anything, whether it is made of sugars, lipids, proteins, or nucleotides.

RIBOSOMES: These are the factories where amino acids are assembled into proteins using instructions from messenger RNA.

GOLGI BODIES: This is where final touches are put onto many structures, and labels (made of sugars) are added. The labels often tell where the structure should be taken, like a mailing label.

ENDOPLASMIC RETICULUM; This is a series of tubes outside the nucleus and is made of membrane, the same stuff the outer wall is made of. Many proteins start their assembly inside this tube because they will eventually need to be enclosed in a bag made of membrane. The ER puts bags around them and usually sends those bags off to the Golgi bodies for final processing.

Things you find in a cell mainly fall into four categories:

INSTRUCTIONS: This is the DNA or RNA; both are made of nucleotides (sections of "ladder"). The information is found in the arrangement of the amino acids (the pattern they form). The information itself is non-physical and lies in the realm of ideas

RAW MATERIALS: Besides tiny atoms and molecules such as water and oxygen, there are four main types of materials:
1) Amino acids: These string together to make proteins. There are 20 different kinds.
2) Sugars: These are simple sugars such as glucose, fructose, galactose and mannose.
3) Lipids: (fats) These are long chains of carbon atoms, often attached to a "hanger" molecule called glycerol.
4) Nucleotides: These make half a "rung" on a DNA ladder, or a whole rung on RNA. Besides the rung they also have a piece of the side of the ladder, so all you need to do is string them together.

TOOLS/WORKERS: Cells have lots of "gadgets" that are usually made of protein. Some of them function much like tools we are familiar with such as scissors, staplers, folding machines, shredders, motors, vehicles, pumps, keys, clips, and copy machines. Most of these tools need energy in order to operate, just like our tools need electricity, batteries, or muscle power. Cellular tools use rechargeable batteries called ATP (briefly explained in the section above on mitochondria).

STRUCTURES: The instructions, raw materials, and tools are used to build structures. Often these structures are made of protein but can have added features made of sugars or lipids. Many cellular structures function like structure we are familiar with, such as cables, string, walls, , flags, hooks, anchors, mailboxes, letters, labels, walls, bags, tubes, and gates (we did not draw gates).

The division between tools and structures is a bit blurry. (Is a key a tool or a structure?)

LESSON 7: INSIDE A CAPSID, and CLASSIFYING VIRUSES

We've already learned the basic parts of a virus, but now let's take a closer look at the inside parts. We'll have to be very general in our descriptions because no virus is exactly like any other.

Inside a virus we find basically two things: 1) a genome in the form of either DNA or RNA, and 2) one or more tiny protein "tools" that the virus will need upon entering the cell. Some viruses, like polio, are too small to carry extra proteins and will borrow or make everything once inside a cell. Other viruses, like smallpox, are very large and have room to carry over a hundred protein tools inside their capsid.

Genome length is measured in base pairs (rungs of the DNA or RNA ladder). Parvovirus has one of the smallest genomes, at less than 3,000 base pairs. Polio is also fairly small, at about 8,000. Coronavirus has one of the largest RNA genomes at almost 30,000 base pairs. When genomes are larger than about 10,000 base pairs, they begin to be fragile. You will find larger genomes wound around protein strings, rods, or spools, to protect them from damage. The entire structure (genome plus proteins) is called the **nucleocapsid**.

Genomes can be either DNA or RNA. For DNA genomes, it can be the usual double-stranded DNA (the same stuff found in the nucleus of all cells), or it can be single-stranded DNA (a ladder with just one side).

-- Double-stranded (ds) DNA viruses include many we are familiar with such as adenovirus, papilloma (warts), all the herpes viruses, and the pox family of viruses. Viruses with dsDNA can use the host cell's copying machines in the nucleus.

-- Single-stranded (ss) DNA viruses are on the small side and include parvo, circo, and anello, and many plant viruses. When a single-stranded viral genome comes into the nucleus of a host cell, the cell's DNA machinery thinks that the viral DNA needs to be repaired, and it will go to work making a matching strand, and thus turning it into dsDNA, which is great for the virus because all the cell's machine are made for dsDNA.

--Another variation on DNA is the "gapped" DNA viruses. Their DNA is generally circular, with most of it double-stranded, but gaps were it is only single stranded. The cell machinery sees the gaps and "fixes" them, thus allowing the viral DNA to be able to use the cellular copying machines. Examples of gapped DNA viruses included Hepatitis C and feline (cat) leukemia.

RNA genomes can be either "positive sense" or "negative sense." Both DNA and RNA are directional, meaning that it makes a difference which end you start from. It's like having a right side and a left side, except that right and left doesn't make sense. The two ends are called 5' (five prime) and 3' (three prime). These numbers come from the arrangement of the 5 carbon atoms in the ribose sugar found in the "backbone" (sides of the ladder). Scientists decided that RNA that can be fed into ribosomes (mRNA) would be called "positive sense." (Ribosomes read RNA starting with the 5' end.) RNA that is read the other direction, staring with the 3' end would be called "negative sense." When "positive" and "negative" are used in this way, there is no electrical meaning at all. It's simply a way to keep track of the directionality of the molecule.

--Positive sense RNA viruses are the only viruses whose genome can be read by ribosomes. RNA(+) viruses include the caliciviruses (the ones the whales poop out), coronaviruses, flaviviruses (yellow fever), and the Picorna family (members include polio, rhinovirus (causes colds), and Coxsackie B).

--Negative sense RNA viruses are just as successful as positive sense ones, despite the fact that they have to have a more complicated system for making mRNA to feed to ribosomes. They have to carry the code for making a copying machine that uses RNA to make RNA. Cells don't have this type of copy machine. Some RNA(-) viruses not only carry the code in their genome, they also carry the actual protein machine inside their capsid. Influenza has an RNA polymerase protein stuck onto the ends of each one of its 8 RNA segments.

--Some viral genomes have doubled-stranded RNA, looking very much like DNA, but having A, U, C and G, as their bases, instead of the ones found in DNA: A, T, C, and G. The Reovirus family has dsRNA. If you've ever had a "stomach flu" you might have had an encounter with a rotavirus, a member of this group.

--The retroviruses have RNA(+) but are in a group all to themselves because they have a very different strategy. They have a special copying machine called "reverse transcriptase" which lets them make DNA from their RNA. They then insert this DNA copy into the genome of the host cell, so it becomes a permanent part of the cell's genome. The most well-known member of this group is HIV (Human Immunodeficiency Virus). Reverse transcriptase was discovered by David Baltimore, the same person who invented this classification system for viruses.

Genomes are very orderly in their arrangement of information. At one end you find all the coding for the structures such as capsid, spikes, or matrix. At the other end you find the coding for how to build copy machines and other tools (scissors, staplers, folders, etc.). The purpose of some tools is to damage cellular machines. In many viral genomes you also find codes that tell when certain proteins are to be made or used. The genome is generally read from the 3' prime first, where all the tool information is. The structural proteins come last.

There are key items that all viruses need but <u>none</u> of them have: **ribosomes, raw materials, and a source of energy**. All viruses must use the cell's ribosomes to make their protein structures from the cell's supply of amino acids, and all viruses must rely on the cell's production of ATP energy.

LESSON 8(a): HERPES SIMPLEX-- A DNA VIRUS

Every virus has its own unique life cycle pattern, so what you learn here may or may not apply even to other DNA viruses. However, herpes simplex is a very good example to use because we'll see quite a few key features of viral replication.

The herpes family of viruses gets its name from the Greek word "herpein," which means "to creep." This is thought to refer to the way the rashes produced by herpes creep along the skin. Herpes viruses enter the body though epithelial cells, primarily skin cells. The outer layer of skin is actually a layer of dead cells, which herpes cannot attach to. The skin must be cut or damaged in some way for the virus to enter. Many herpes viruses causes rashes or sores on the skin, but they can produce other symptoms, as well.

There are hundreds of herpes viruses which infect a wide range of animals. There are 8 types that infect humans:

1) HSV-1: herpes simplex 1, which causes sores in and around the mouth
2) HSV-2: herpes simplex 2, which causes warts and sores in and around the genital region
3) VZV: Varicella zoster, or "chickenpox" which causes fever and pox-like sores on the skin
4) EBV: Epstein-Barr virus, a
5) HCMV: Human Cytomegalovirus, often causes no symptoms, but can also cause pneumonia and rash
6) HHV-6: ("Roseola," a common and mild infection in infants and toddlers)
7) HHV-7: a relatively mild virus unless the person's immune system is not working well
8) HHV-8: causes Karposi's sarcoma (skin tumor)

Herpes viruses are relatively large, from 150 to 200 nanometers in diameter. They have very large genomes (from 120,000 to 240,000 base pairs) made of double-stranded DNA.

A major feature of herpes viruses is their ability to become latent (dormant). After initial infection, they will often travel to the nearest sensory neuron and hide inside the cell body of the neuron. The circle of DNA might or might now become part of the host cell genome, but even if it does not, the cell still can't ever rid itself of the viral DNA. A very well-known example of this is the varicella zoster virus which, in its initial infection causes "chickenpox." Then it goes into neurons and lies dormant for decades. If it comes out again, this time the infection will be called "shingles" and will involve both neurons and skin cells. Because of neuron involvement, the virus causes more pain than it did the first time around. The triggers for varicella becoming lytic again are not well understood, though the probability does increase with age.

Almost every adult on the planet carries at least one type of herpes. Most people are exposed to HSV-1 during childhood and 67 percent will go on to test positive for it as adults. If you or someone you know gets small, white mouth sores from time to time, HSV-1 is the likely cause. HSV-2 is a concern for people who are sexually active since that is how it is passed from person to person. Women who are infected with HSV-2 run a greater risk of getting cervical cancer. A large section of the population carries cytomegalovirus (HCMV) though they've never had any symptoms. HCMV doesn't cause problems for people with healthy immune systems. Roseola (HSV-6) is a very common childhood disease, and mild enough that making a vaccine for it is very low priority.

After doing this drawing and seeing how complex the assembly process is, you might wonder if anything ever goes wrong. The answer is yes, things often go wrong and with some viruses, only one in several hundred attempts at creating a virion will actually produce a perfect virion capable of future infection. However, the infected cell is churning out thousands of virions, so it doesn't matter if not all of them work.

LESSON 8(b): POLIO-- AN RNA VIRUS

Polio is a "naked" (no envelope) positive sense (+) RNA virus, and is a member of the "Picorna" family, one of the Group 4 viral families in the Baltimore classification system. Other members of the Picorna family include rhinovirus (common cold) and Coxsackie B. (Coxsackie is always capitalized because it is named after Coxsackie, New York, where it was first isolated.) There are two stories about the name "Picorna." One says that each letter stands for one of the original viruses put into this group. The other idea is that "pico" means "small" and "rna" stands for "RNA." This would suggest that all the viruses in this group have small RNA genomes (less than 10,000 base pairs).

Polio can also be classified as an "enterovirus" because it enters the body through the digestive system and attaches to the cells that line the intestines. After they replicate and make billions more of themselves, the virions eventually get into the blood. In about 1% of people infected with polio, the virus will begin invading nerve cells called motor neurons. The bodies of these cells are located in the spinal cord. Whenever there is inflammation in the spinal cord, this is called myelitis (mi-eh-LIE-tis), so when polio gets into the spine we call the disease "poliomyelitis."

Since polio has RNA(+) and reads the same as mRNA, it doesn't go into the nucleus and it doesn't bring any of its own tools. The genome is small and the capsid is small, too, only about 30 nanometers. Polio has been heavily researched for decades and its genome was completely mapped back in the early 1980s. That means they made a list of every A, U, C and G, and had a pretty good idea of which parts of the code made certain proteins. Of course, you remember from lesson 3 that Jonas Salk made a vaccine in 1955. A researcher named Albert Sabin perfected the vaccine in the 1960s, making it even more effective.

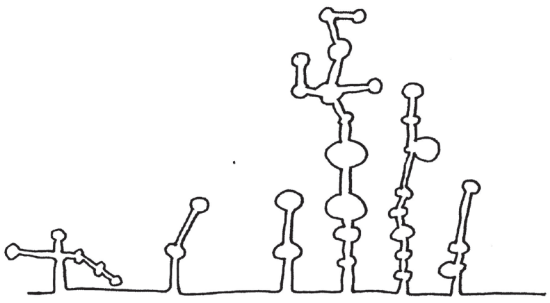
Here are the stages of polio virus infection of a cell:

1) Attachment to Poliovirus Receptor (PVR) also known as CD155.
2) Entry and uncoating--the RNA goes into the cytosol. (Some diagrams show this happening at the surface, other diagrams show the virion inside a small endosome.)
3) Ribosomes read the polio RNA like it is a cellular mRNA, and a very long protein chain is made. This "polyprotein" chain contains all the virus's proteins in one long line.
4) Two of polio's proteins are proteases ("scissors") and will cut the polyprotein into its smaller units.
5) Host Shut Off: One of the scissors is the right shape for snipping an important cellular protein tool ("EIF4G"), which is the first protein to attach to a mRNA. A group of tiny proteins has to cooperate to make a big clump that is just the right shape to stick to a ribosome. If you get rid of the first protein, the rest won't attach and no mRNA will be translated. This prevents the cell from making its own proteins.

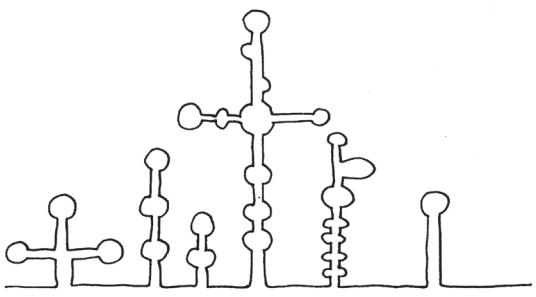
5a) But wait-- if polio just got rid of all the starter proteins for using a ribosome, then how is polio going to use the ribosomes? Turns out that one section of the polio RNA will coil up into a 3D shape that will mimic the shape of that group of starter proteins, and the ribosome will be fooled into attaching to the polio RNA! (If you want to know more about this topic, you can search using the term IRES, which stands for Internal Ribosomal Entry Site).

6) Formation of "replication complexes": As the cell becomes stressed its ER and Golgi bodies lose their shape and turn into small blobs (vesicles). The polio RNA polymerase ("RdRp") copy machines will attach themselves to the edges of these vesicles and then start making gazillions of copies of the polio genome. The original genome is positive sense, so it takes two rounds of copying to produce a new genome. (POSITIVE copies to NEGATIVE, which copies back to POSITIVE)
7) Ribosomes start manufacturing polio capsids and new virions assemble themselves.
8) The cell ruptures (this is called "lysis") and all the new virions exit.

Poliovirus is being used to treat a very difficult form of brain cancer. The brain tumor cells happen to express CD155 on their surface, whereas normal brain cells don't. That gave some researchers the idea to use poliovirus to destroy those tumor cells. They cut and pasted a different IRES area into some polio viruses, using an IRES from another Picorna virus-- the rhinovirus (common cold). The adapted polio (with the rhino IRES) would be unable to cause an actual polio infection in the patient receiving the treatment, but the virus would attack the tumor cells. The immune system would then be alerted to the need to destroy those bad cells and they would start helping to destroy the tumor cells. This treatment has been successful in several patients.



IRES from poliovirus



IRES from rhinovirus

LESSON 9: THE BODY FIGHTS BACK

This lesson is not a complete description of the immune system. If you want to know more about how the immune system works, there are nine drawing lessons devoted to this topic in module 3 of my Mapping the Body with Art curriculum, available on my website. Here in this lesson, I will just mention a few aspects of the immune system that are aimed at viruses.

The first layer of defense is physical barriers that block viruses from entering. Skin does a great job of keeping viruses out, because the top layer of skin is made of dead cells. Viruses can only enter living cells that have receptors. Dead cells are like a brick wall to a virus. The surface layer of cells in moist places like the mouth, nose, throat, lungs, and intestines, have specialized cells that can make mucus. Viruses can get stuck in mucus and be unable to function. Mucus mostly ends up going to the stomach (as we swallow mucus that we sniff or cough up) and the acid in the stomach can kills many viruses. (Of course, some viruses like to be in the stomach, but most do not.)

If a virus gets past the physical barriers and enters cells, the next layer of defense kicks in. There are phagocytes ("eating cells") roaming around, eating every foreign object in their path. The biggest eater is called the **macrophage**. ("Macro" means "big," and "phage" means "eater.") A similar cell is the **dendritic cell**, which gets its name from its long branch-like arms. ("Dendri" means "branch.") Both of these cells engulf all particles they come across. If a virus is taken in by one of these eaters, it will not have a chance to do its usual attachment-and-entry routine, it will not be able to uncoat and replicate, and will be digested inside one of the eater cell's lysosomes. (**Lysosomes** are big endosomes filled with digestive enzymes.) These eating cells will also put some of the digested pieces onto their own type of MHC clip (MHC-2) and post them on their surface.

If the virus gets past the phagocytes, it will likely be able to enter one of the body cells. However, cells have sensing devices floating around in their cytoplasm that can detect viral RNA. (Examples include RIG-1 and MDA5.) Usually they sense double-stranded RNA, which is never made by a cell. Even if a virus doesn't have a dsRNA genome, it will produce some dsRNA as a temporary by-product of genome replication. When a sensor molecule comes into contact with the viral RNA, it will change shape (a "conformational change") and this will then cause it to be able to interact with another cellular protein. This reaction will allow another reaction, and then another, like a chain reaction, with the end result being the production of a protein message called **interferon** (IFN). There are three types of interferon: alpha, beta and gamma. They all cause the cell to produce many anti-viral proteins, but can do so in a slightly different way. (These anti-viral proteins have been discovered so recently that it is hard to find out details about them.) Interferon also acts as a message to other cells to warn them that one of their neighbors has been infected, and to call immune system cells to come to the site of infection.

MDA5 can detect uncapped RNA, which is why influenza does its "cap-snatching." The measles virus has a way to block the action of MDA5. Toll-like receptors (TLRs) are located on the outside surface of macrophages and dendritic cells. TLR-3 is the best at sensing viral RNA. When activated, TLR-3 will start that complicated chain reaction that will lead to interferon production.

If the virus gets past ask these defense system, and finds a body cell with a receptor it can attach to, it will enter the cell and start to replicate. But little pieces of viral protein will start appearing in the clips in the MHC-1 flags of that the cell, as it constantly sends flags to the surface. A white blood cell called a Natural Killer (NK) is able to "feel" what the clips are holding. If it is not a body protein (or it is a bad body protein such as cancer), the NK cell will use **perforin** to kill the cell. Imagine a tiny gun shooting bullets that, when they land, assemble themselves into a ring. The ring builds itself on the surface of the cell, so you end up with a hole in the cell membrane. Along with the proteins for the hole, there are also proteins called **granzymes**, which are classified as toxins because they cause cell death. The granzymes go down through the hole and into the cell where they begin a chain of events that ends with the DNA being shredded to bits. With no DNA, the cell can't do anything and it slowly shrivels and disintegrates. (Macrophages then come and eat up the pieces.) When a cell dies in this way, we call it **apoptosis**. Many cells in your body are programmed to live only a short time then die. Programmed cell death is one of the ways your body stays healthy.

If the virus tries to trick the NK cell and prevent the viral-protein-carrying flags from going to the surface (like we saw with herpes) the NK cell can still detect that something is wrong. It can count the number of flags on the surface and if there are none, or very few, it will assume something is wrong and kill the cell. (A few viruses have ways to make the cell put up fake flags!)

All the defense strategies we have discussed so far are part of the body's non-specific, or "innate" system. This system reacts the same way to all pathogens. If the virus gets past the innate system, it meets the "adaptive" immune system. This system acts specifically to individual pathogens. These cells can tell influenza from coronavirus. The system involves interaction between macrophages, dendritic cells, T cells and B cells.

Macrophages and dendritic cells have flags called MHC-2. They put samples of what they have eaten into the clips on MHC-2. Helper T cells come along and "feel" these samples. Each T cell "knows" a sample pattern that does not belong to the body. If the helper T has a match to the viral protein, it will be activated. It will hopefully come across a killer T cell that has found that same pattern sticking to a cell's MHC-1 clip. The killer T "gets permission" from the helper T, and then the killer T uses perforin to kill the cell.

B cells make Y-shaped proteins called **antibodies**. Each B cell is capable of matching one particular protein shape that might be found on a pathogen. If it runs into a helper T cell that has been activated by a macrophage, and the helper T's sample matches the shape of the B cell's antibody, the B cell will be told to make thousands of its antibodies. The antibodies might match a virus's glycoproteins and stick to them, preventing the virus from attaching. Or the antibodies could stick to the capsid proteins. In both cases, macrophages will eat anything with antibodies stick to it, so they gobble up viruses with antibodies.

LESSON 10: VACCINES and ANTI-VIRALS

The goal of a vaccine is to imitate the natural process of recovering from a viral infection, without actually experiencing the infection. When we recover from an infection, most of our B cells will receive signals from other immune cells to stop producing antibodies and to go through the process of apoptosis (programmed cell death). However, a small number of B cells will turn into memory cells, and will live on for years, ready to be activated if the need should arise. The first time the B cells are activated to attack a new virus, the process can take up to two weeks. The next time around, the memory B cells can shorten the activation time to just a few days, and the virus will be overwhelmed with antibodies before it can do any damage. Our immune system deals with pathogens (viruses, bacteria) every day, and most of the time we just go about our activities unaware of all the battles our immune system is winning.

A vaccine simulates infection by delivering whole viruses, or pieces of virus, to macrophage cells. The macrophages roam around looking for things to eat, so anything you inject will eventually end up being discovered by macrophages. The macrophages process the viral proteins and then present them to T helper cells who then find the matching B cells. These B cells will start producing antibodies (but not quite to the degree necessary for a real infection). Most importantly, some B cells will turn into memory cells.

Vaccines are classified as either active ("live") or inactive. Active vaccines are whole viruses that have been weakened, or "attenuated." Usually this means that their genome has mutated, as we saw with polio. Albert Sabin discovered a natural mutation of one letter in the IRES part of polio's RNA genome. We call these "live" vaccines even though viruses are non-living, because the virus retains a substantial part of its ability to replicate. What it can't do is actually cause harmful disease. In the case of polio, the virus in the Sabin vaccine could still infect the intestinal cells, but it could not attack nerve cells. In the intestines, polio is harmless. You don't even know it is there. It's when it travels to the neurons that you begin to see poliomyelitis symptoms. Other active vaccines include measles, mumps, rubella, yellow fever, and chickenpox.

Inactive vaccines are either whole viruses that have been "killed" by chemicals, or just small pieces (fractions) of viral protein such as bits of spike or capsid. The first inactive vaccine was the polio vaccine invented by Jonas Salk. He used a chemical called formalin to damage the viruses so badly that they no longer functioned. He found that the immune cells would still react the same way to these inactivated viruses. Using just tiny pieces of viral protein removes any concern that the vaccination will be able to actually cause disease. Recently, advanced genetic techniques have allowed virologists to make plants cells or yeast cells produce either empty capsids, or pieces of viral genome, which can be used for a vaccine that can't possibly cause disease. These vaccines are called "recombinant."

Sometimes, a vaccine that contains only pieces of a virus will not cause a strong enough response to get B memory cells produced. Virologists have found that if they add something to the vaccine to cause a microscopic amount of inflammation, this can trigger the desired memory response. Added substances are called "adjuvants." A common adjuvant is alum (aluminum hydroxide). Another option is to use inactivated bits of bacteria that fit into those TLR sensors.

In the past few years, some researchers have raised concerns about whether aluminum adjuvants can have side effects. They are generally considered safe by the FDA, but aluminum has been suggested as a possible contributing factor to the development of Alzheimer's in elderly people. Veterinarians have noticed that (a small number of) cats can develop tumors in the places where they receive shots, though there isn't any obvious reason why this should be so. It doesn't happen in dogs.

Anti-virals are medications you take after you come down with a virus. The tricky part is to find a chemical that will harm the virus without harming body cells. Viruses are made of the same stuff we are (proteins, lipids, DNA, RNA), and a general toxin would kill the host cell as well as the virus. You have to find a molecule that will stick to a particular viral shape, a shape not found in body cells. Before virologists were able to map out the exact shape of a virus, it was a matter of trial and error, collecting and experimenting with any new substance they could find. The would take samples of anything--dirt, plants, bacteria, fungi, minerals-- and do an assay to see if they killed viruses. Amazingly enough, they found a chemical from a Caribbean sea sponge that would stop herpes viruses! They did not know it at the time, but this chemical, which they sold under the name Acyclovir, was so similar to the guanine rung in DNA or RNA that the virus would use Acyclovir instead of the real guanine. Acyclovir had no attachment point for the next rung, and thus genome replication would come to a halt. Many anti-virals work like this, being an analogue (a mimic) of a nucleoside (A, T, U, C, G).

The strategy used to treat influenza infections is a chemical that sticks to the NA, neuraminidase, and prevents it from cleaving (cutting) the HA spike free as the virus is trying to leave the cell by the process of budding. The medicines molecules (sold as Tamiflu or Relenza) bind to the active site of NA, preventing its scissor action. The influenza viruses are stuck. (They will eventually be digested by macrophages.) The protein shape of NA is complicated and various drug binding sites can be used.

One of the many anti-virals that is used against HIV is called Fuzeon. It is a protein containing only 127 amino acids (short enough to be called a "peptide"). It binds to HIV's spike at just the right place so that it is not able to connect to the cell receptor that allows it to expose its fusion protein and join with the cell membrane.

A strategy that worked for a while on influenza was a chemical (sold as "Amantadine") that locked onto the M2 channel and blocked it. Unfortunately, influenza mutates quite quickly because of its segmented genome and the lack of a spell checker, and soon a new version of influenze arose where the shape of the M2 channel was just enough different that the chemical was no longer able to lock onto it.