Immune by Philipp Dettmer

1 What Is the Immune System?

- Scientists study the immune system by looking at the tree of life and examining the immune systems of animals that are still around today.
    - The father separated two creatures are on the tree and still share a single trait of the immune system, the older the trait is.
- *Humoral Immunity*: protein-based “stuff” floating through bodily fluids outside of the cells of animal that kills outsider microorganisms.
- *Cell-mediated Immunity*: cells that specialize in defense.
- The immune system is not a singular thing; it is complex and composed of hundreds of different parts and billions of cells.
- The core of the immune system is that it is essentially a tool to distinguish the other from the self.
- The goal of the immune is system is maintaining and establishing homeostasis (equilibrium between all elements of the body).
    - It’s a BALANCE.

2 What Is There to Defend?

- The real weak points to infections are our mucous membranes (the surface that lines the windpipe and lungs, eyelids, mouth, nose, stomach, intestines, reproductive tracts, and bladder.
    - The mucous membranes are part of our outsides - we are nothing more than a complex tube.
- The average human body has 40 TRILLION cells.

3 What Are Your Cells?

- Cells are the smallest units of life, essentially biological robots driven by biochemical reactions guided by even smaller parts.
- Cells have organelles, like the nucleus, which is the information center for the cell.
- Cells are mostly made from proteins, the most fundamental organic building blocks and tools of all living things.
- Proteins are 3-dimensional puzzle pieces made from chains of amino acids, tiny building blocks that come in 20 different varieties.
- The order these blocks are put in are based on what DNA, a long sequence of instructions made

up of building manuals called genes.

- Special proteins read the information on the DNA string and convert it to a messenger molecule called mRNA, the language the DNA uses to communicate instructions.
    - mRNA molecules are transported from the nucleus to the ribosome, which specializes in producing proteins.
    - The mRNA is read and translated into amino acids that are ordered accordingly and formed into a protein.
- Shape of proteins determines everything, and determines how proteins interact with each other.
    - *Biological pathways*: a series of interactions between individual things that lead to change in a cell.
- Proteins can be used as messengers and construction materials.
- The complex interaction between dumb proteins create a less dumb cell, which creates complex interactions between other less dumb cells, which eventually creates a pretty smart immune system.

4 The Empires and Kingdoms of the Immune System

- The immune system can be split into two parts:
    - *Innate Immune System*: contains all the defenses you are both with and can be employed right when an invasion occurs.
        - Basic defenses that can tell self from other.
        - Not tailored to any specific enemies, but good for most.
    - *Adaptive Immune System*: contains specialized super cells that coordinate and support the first line of defense.
        - It is very specific, and knows all there is to know about every single potential threat on the planet.
        - It is not ready when you are born, and needs to be trained.
            - Starts weak and gets weak again in old age.

5 Meet Your Enemies

- *Pathogen*: any microorganism that causes disease.
- Bacteria are among the oldest living things on the planet and are the smallest things we consider alive.

6 The Desert Kingdom of the Skin

- Skin cells begin 1 millimeter deep.
- In the basal layer, stem cells do nothing but multiply.
- Skin cells produce keratin, a tough protein that makes up the hard part of skin, nails, and hair.
- Each generation of skin cells pushes the older generation up.
- When skin cells mature, they develop long spikes and interlock with other cells. Then, they create lamellar bodies (tiny bags of fat to create a waterproof coat covering the cells).
    - The lamellar bodies act as a physical wall and are filled with *defensins*, natural antibiotics that kill enemies.
- The skin cells at the surface are all dead and are essentially a wall of corpses that keeps on shedding.
- Sweat adds a lot of salt on your skin which kills microbes.
- The skin has an *acid mantle*, a mixture of sweat and other substances that makes you slightly acidic enough to be unappealing to microorganisms.
- pH = POWER OF HYDROGEN
    - The higher the power, the fewer the hydrogen ions (more hydrogen = more acidic).
- Bacteria lives all over your skin like barbarians on the outskirts of a massive wall. Most tribes are peaceful and help by just taking up space so other bad bacteria can't stay.
    - Some even kill other bad bacteria!

7 The Cut

- When you receive a cut:
    1. The Innate Immune System reacts immediately by sending out *Macrophages*, the largest immune cells in your body. They devour dead cells and live enemies, coordinate new defenses, and heal wounds.
    2. Macrophages then call *Neutrophils*, crazy killer monkey suicide cells that attack everything in site.
    3. *Platelets*, fragments of another cell called a megakaryocytic appear and try to create a barrier on the cut part of your skin.
    4. Then, the immune system orders the blood vessels to open up and unleash a warm fluid stream to squeeze nerve cells and let the brain know something's up (pain). Also, they unleash a silent killer...
    5. The *Dendritic Cell* appears and absorbs enemies and researches them, and then goes somewhere else to deliver that information.

8 The Soldiers of the Innate Immune System:

Macrophages and Neutrophils

- Macrophages and Neutrophils make up a class of cells called *phagocytes* (eating cells).
  - Eat like Majin Buu absorbs.
- *Phagocytosis* involves a cell grabbing on to a pathogen, trapping it in a compartment filled with acid, breaking it up and eating it. Then, spitting out the rest for other cells to eat.
- Macrophages regularly eat parts of you that die.
  - Cells die regularly in a process called *apoptosis*, where they commit suicide and let the body know.
- Tattoos are stored in macrophages!
- Macrophages also shut down immune responses after a while!
- Macrophages live up to several months, Neutrophils only live a few days.
- Neutrophils can cast nets of their own DNA to trap enemies and kill them - and then still live somehow and keep killing! Called a *Neutrophil Extracellular Trap (NET)*.

9 Inflammation: Playing with Fire

- Any time your body is in danger - perceived or real - it uses inflammation.
- Chronic inflammation is involved in more than half of all deaths each year because its present in so many diseases.
- Inflammation releases a tsunami wave of all sorts of special attack proteins to combat enemies.
- Inflammation is marked by redness, heat, swelling, pain, and loss of function.
- When a cell dies through apoptosis, it's a very neat and organized suicide that doesn't set of any alarms. When it isn't neat, the body knows the cell died unnaturally and may set of inflammation.
- The *Mast Cell* is a large cell that explodes if irritated and releases chemicals that causes massive inflammation.

10 Naked, Blind, and Afraid: How Do Cells Know Where to Go?

- Cells use *cytokines* to smell where to go. Those are small proteins used to convey information.
  - For example, cells like Macrophages can release a bunch of cytokines warning the body that enemies are around.
  - Some cytokines called chemokines are used purely for navigational purposes.
- The closer to the origin of the source of a smell a cell is, the more cytokines it will pick up.
- Cells have a bunch of noses called *receptors* all over their body to be as precise as possible when determining direction.

    - Once a receptor picks up on a cytokine, it can let the genes inside of the cell know what happened.
- The more cytokines a cell's nose picks up, the more it will react.
- If too many cytokines break through in a *cytokine storm*, more and more immune cells will respond causing harm.

11 Smelling the Building Blocks of Life

- The reason the immune system has evolved to combat all types of bacteria and bacteria has not evolved to stop it is because of *microbial pattern recognition*:
    - Bacteria always needs specific types of proteins to be bacteria.
        - An example is the flagellum, the wavy tail that sperm cells also has. If a microorganism has one, the immune system knows to target it.
            - Which is why there needs to be many quick sperm cells!
    - The immune system has a recipe for defense for each of these proteins.
        - Through their *Toll-Like Receptors*.
            - Every animal has them, making it one of the oldest parts of the immune system.

12 The Invisible Killer Army: The Complement System

- The complement system is one of the oldest parts of the immune system.

> ...we are going to brush over a lot of details because we can and life is too short for stuff like this.

- The complement system is a group of over 30 different proteins that work together to stop bacteria.
    - They flow in through inflammation!
- There are about 15 quintillion complement proteins in every fluid in our bodies.
- Complement proteins normally just all float around passively.
- The first protein that is usually activated - seemingly at random - is called C3, and activates the rest in turn.
- Complement proteins constantly change their shape.
- C3 breaks apart into two parts - C3a and C3b.
    - C3a acts very similar to cytokines and alerts phagocytes about the threat.
    - C3b attaches itself to the nearest bacteria, changes shape, draws in other complement proteins (C3 Convertase), and cripples the bacteria.
        - All these complement proteins on the bacteria also act as an easy way for phagocytes

to absorb the bacteria - *opsonization*
        - Bacteria and phagocytes are both negatively charged, complement proteins are positively charged!
    - C3b proteins can form Membrane Attack Complexes that include complement proteins that turn into large spears that penetrate the bacteria, causing it to gush out its insides.
- Complement proteins are most useful against viruses, which need to travel from cell to cell. Complements intercept them before they latch on!

13 Cell Intelligence: The Dendritic Cell

- Many pathogenic bacteria actually don't care about the complement system.
- Dendritic Cells have long starfish-like arms that flop around everywhere.
- Dendritic Cells identify what kind of enemy is infecting you.
    - They absorb bacteria much like phagocytes, but they spit them back out once they get an idea what they're dealing with.
- They also make the decision to activate the adaptive immune system.

Superhighways and Megacities

- The *Lymphatic System* is a network of superhighways and megacities.
- *Lymphatic vessels* are miles long and covers the entire body.
- The lymphatic system is responsible for transporting excess blood back into blood vessels after it's been sent to your cells.
    - It constantly drains your body of excess fluids.
- Blood vessels are insanely speedy, while lymphatic vessels are much slower and calmer.
- The yellowish-white fluid transported through the lymphatic system is called *lymph*.
- The lymphatic system is also our waste management and alarm system.
    - The system picks up all sorts of garbage and dead cells everywhere.
- The organs of the lymphatic system are called *lymph nodes*.
    - We have about 600 of them around our bodies.
    - It's where adaptive immune cells go to look for matches.
    - It's also where Dendritic Cells are go when they're reporting their findings from an infection!
- The *spleen* is a large lymph node that filters dying blood cells.
    - It also stores an emergency reserve of blood, red blood cells, and platelets.
- *Monocytes* are reinforcement immune cells that can turn into Macrophages.
    - They arrive when they hear that Macrophages are losing.

    - Half flow through the blood and half are stored in your spleen for emergencies.
        - They also can help you with heart attacks!
- *Tonsils* are another center for immune system intelligence that actively sample what comes in your body.
    - Microfilm cells grab stuff from your mouth and show it off here to other immune cells.
    - Helps the immune system recognize what kind of foods you eat.
    - Helps produce weapons against invaders.
- The spleen and tonsils can be removed due to injury or chronic inflammation; it's not life-threatening, but it does remove some of this great help.

15 The Arrival of the Superweapons

- *Helper T Cells* are specialized cells from the Adaptive Immune System that were created for specific instances of immune resistance.
    - They re-energize tired Macrophages through cytokines!
- *Antibodies*, specialized assassins also created in the Adaptive Immune System arrive and take out any leftover bacteria by maiming them and stringing them together for the re-energized Macrophages to eat.
- Some of the Helper T cells remain after the battle is won and make sure there is no future attack and new civilian cells can regrow.

16 The Largest Library in the Universe

- Bacteria are constantly evolving, much faster than humans.
- The immune system comes pre-installed with hundreds of millions of adapted immune cells ready to fight any possible threat we could ever encounter.

17 Cooking Tasty Receptor Recipes

- An *antigen* is any protein piece that can be recognized by the immune system.
- Even though the human genome has only about 20k-25k genes, through the different combinations, the immune system has the potential to recognize any possible antigen in the known universe!

18 The Murder University of the Thymus

- The *Thymus* is a collection of tissue that trains *T Cells* (literally Thymus Cells).

- T Cells each have only ONE specific type of receptor that is able to recognize ONE specific antigen.
- T cells are trained in the Thymus through three different tests:
    1. First, to see if they have functioning receptors.
    2. Second, to see if they are able to communicate with other immune cells (*positive selection*).
    3. Lastly, to see if they recognize cells within the body (*negative selection*). If they don't, they pass!
        - This is because if they were able to, they would target our own cells and destroy them! What leads to autoimmune diseases...
- If T cells fail in any test, they die. Very few survive, but that's still enough to produce 10-20 million T Cells daily.
- The Thymus shrinks and loses tissue as you age. When you're about 85, your Thymus is basically gone, which is why older people are so susceptible to disease!
    - They're left with the T Cells they've trained up to that point.
    - Researchers are working to figure out how to regrew tissue in the Thymus or reduce the shrinking - anti-aging!

19 Presenting Information on a Gold Platter: Antigen Presentation

- The Dendritic Cell is an *antigen presenting cell*, which means it covers itself with the antigens of bacteria and uses that to convey to Helper T cells in the Adaptive Immune System what's going on.
- *Major Histocompatibility Complex class II (MHC class II)* molecules are like mini hotdog buns that grab and hold onto antigens.
- Helper T cells are extremely careful about reacting to antigen presentation; the Dendritic Cell must:
    - 1) Have antigens captured in MHC class II molecules
    - 2) Gently touch/kiss the Helper T Cell which confirms that the antigens are real
- The Dendritic Cell has about a week before it dies, so it has to find the right T Cell by then.
- MHC II molecules are unique to everyone, with different presentation capabilities.
    - This is extremely important because this means no pathogen can easily wipe us out!
    - MHC II molecules give of a distinct smell in everyone; we are more attracted to mates that give off a smell indicating they have different MHC II molecules than us! Which allows production of a baby with a more varied MHC II molecule pool.
        - Which is why family members smell the same at the MHC class II level!

20 Awakening the Adaptive Immune System: T cells

- There are multiple classes of T Cells: Helper, Killer, and Regulatory.
- T Cells start their growth in the bone marrow , where they mix and match gene fragments that create their unique receptors.
- Then, they visit the Thymus, where they go through the 3 step test to see if they get activated.
- Once the right Dendritic Cell finds them in a lymph node, they become a Helper T Cell.
    - T Cells are constantly traveling throughout the body, looking for the right Dendritic Cell.
- Once the Helper T Cell is activated, it splits in two, then does it again and again until there are thousands.
    - This is called *Clonal Selection Theory* and it won a Nobel Prize!
- After there are enough, the cells break into two groups. The first group heads to the site of infection using the cytokine signals in the lymph.
    - Takes about 5 days to a week!
- Helper T Cells re-energize and amplify Macrophages, over and over again until the bacteria are all defeated.
    - This means that these cells also shut the immune response down once the battle is over.
- Most of the T Cells kill themselves with the rest of the Macrophages, but few stick around and become **Memory Helper Cells**.
    - In case of another infection, there is no need for the Dendritic Cell to go to the lymph node and start the whole process again.
        - This is what being immune to a disease means!
            - Basically, most pathogens only have a single chance to infect you because of this.

21 Weapon Factories and Sniper Rifles: B cells and Antibodies

- B Cells are large immune cells similar to T Cells in that they also originate in the bone marrow (but are educated directly there instead of the Thymus) and also have one specific receptor to recognize one specific antigen.
- B Cells release *Antibodies* that act as both receptors for the B Cell and a weapon that strikes down antigens.
    - First the Antibodies stick to the B Cell until it sticks to an antigen and actives the B Cell.
    - Then the B Cell releases thousands of new Antibodies per second to attack.
- Lymph cleans up residue and dead cells and bacteria from the site of infection and is carried away to lymph nodes, where B Cells hang around.
- The B Cells get right in the middle of the lymph coming in and explore all the antigens coming

through.

- Once the B Cell finds the right one, the first activation signal is given off.
- The reason B Cells don't need a Dendritic Cell or any other antigen-presenting cell is because B Cell receptors can pick up much larger antigens than T Cells can (with their MHC Class II molecules).
- Complement proteins that were part of the bacteria flowing in from the lymph help the B Cells recognize antigens much easier.
- Once a B Cell has been given the first activation signal, it starts cloning itself by splitting in two over and over again until it has about 20k copies. These B Cell copies produce Antibodies that use the blood to head to the infection site.
    - These initial Antibodies are weaker than ones yet to come!
- If these B Cells don't receive another activation signal, they die within a day, because they assume the infection wasn't that bad.
    - Immune system really saves resources!
- The second activation signal is given by the second group of Helper T Cells.
- The B Cells have to become antigen-presenting cells to receive the Helper T Cells.
    - They chew up antigens and bring the parts out on their own MHC molecules on their bodies.
        - Can do many at once!
    - The Helper T Cell examines these antigen chunks and finds the right B Cell match.
- Once the B Cell receives the second signal from the Helper T Cell, it transforms into a *Plasma Cell*, a super-powered version of its original self.
    - The *Plasma Cell* sends out high quality antibodies that are like missiles and fires them at enemies through the lymph and blood.

22 The Dance of the T and the B

- The lower quality antibodies produced initially by the B Cells are made to be just good enough; the B Cells don't look for exact matches when taking in lymph.
- The antibodies are perfected after Helper T Cells come in and provide that second signal to B Cells.
- When B Cells transform to Plasma, it's called *Somatic Hypermutation* or *Affinity Maturation*. In this process, the cell mutates its gene fragments to be perfectly specific for the enemy at hand.
- Only the B Cells that make a mutation that works; if it is worse than the lower quality antibodies from before, it won't receive more signals from the T Cells and kill itself.
- The best B Cells survive and go into the battle and wreck all enemies.

23 Antibodies

- Antibodies are protein bundles that can stick to antigens.
- They are extremely small and very specific.
- Antibodies have two pincers and a long… butt.
- Antibodies grab onto antigens, slows, hurts, and opsonizes them, similar to complement proteins.
    - Like complements, this makes the antigens easy to target by Macrophages and Neutrophils.
    - Before antibodies grab a bacterium, their butts are “deactivated” so that immune cells aren’t attracted to them until they’re on an enemy.
- Antibodies can also activate complements.
- There are four class of antibodies:
    1. *IgM Antibodies* - the majority of antibodies first produced; the lower quality ones. They are basically 5 antibodies merged together.
        - They can activate complements!
        - Their main job is to buy time until better Antibodies are available.
    2. *IgG Antibodies* - these come in a few different types. They can activate compliments, but not as well as IgM Antibodies.
        - Useful for longer term infections; they are unable to activate complements to limit inflammation.
        - They are the only Antibodies to pass from the blood of a mother into the blood of an unborn fetus.
        - They are the longest to decay.
    3. *IgA Antibodies* - the most abundant antibody in the body. Their main job is to clean your mucosa.
        - Primarily inhabits the respiratory tract, primary sex organs, and the digestive tract.
        - Protects the entrances to your body.
        - Snot from a cost is full of IgA giving viruses and bacteria a hard time!
        - Can’t activate complements and therefore can’t order inflammation.
        - Can clump chunks of bacteria together and get them step away by snot or mucus or feces.
    4. *IgE Antibodies* - they make you have allergic reactions!
- B Cells know what type of Antibodies to make based on context from Helper T Cells.
- B Cells aren’t locked into making one type of Antibodies throughout their lifespan.

24 The Swamp Kingdom of the Mucosa

- The lungs, guts, mouth and respiratory and reproductive tracts are basically just the outsides wrapped up in the insides, called the *Mucosa*.
- Because so many outside invaders pass through the Mucosa, some good and some bad, the immune system needs to be very balanced here.
- The first line of defense the Mucosa uses is *mucus*, a slippery substance that looks like watery gel.
    - The stuff in your nose when you have a cold!
- Mucus is produced by *Goblet Cells*.
- Mucus is basically a physical barrier so intruders have a difficult time reaching cells behind the barrier.
    - It contains all sorts of salts and enzymes that defend it - including IgA Antibodies!
- Mucus is moved constantly by *cilia*, tiny organelles that look like hair that cover the outside of *Epithelial Cells* that make up the first layer of the mucous membrane.
    - Epithelial Cells are your inside skin cells!
        - They can activate the immune system and call for help with cytokines.

25 The Weird and Special Immune System of Your Gut

- 30-40 trillion bacteria from thousands of species and thousands of viruses make up the gut microbiota.
    - The viruses hunt the bacteria and are not interested in us.
- Once food is broken down by saliva, it is sent through the intestine, where over 90% of its nutrients are absorbed.
    - A lot of the friendly bacteria living here, called *commensal bacteria*, help break down the food in exchange for getting to stay there!
        - They live on top of the mucus layer, and if they try to go past the mucus layer, they will be killed by either defensins (the needles on the skin) or other proteins.
        - They can't be too good at their job, because food still needs to pass through and we need nutrients!
- Below the mucus layer are the intestinal epithelial cells, which are extremely well connected to each other by special proteins.
    - This layer is only one cell thick!
- The third layer beneath that contains the *Lamina Propria*, the home of the immune system of the gut. There, special Macrophages, B Cells, and Dendritic Cells stand guard.
    - None of cells can cause inflammation (or call Neutrophils) though, to prevent diarrhea.
    - The Dendritic Cells squeeze their long arms through the epithelial cells to sample different commensal bacteria flowing through to always be ready.

    - The B Cells produce large amounts of IgA Antibodies, which are good at clumping bacteria together, which gets thrown out with your poop.
- To catch serious enemies, the gut has a special lymph node called *Peyer's patches* that are integrated with the intestines.
- *Microfold Cells*, located in the tonsils, reach into the intestines and take samples of things they think could be interesting for the immune system to look at.
    - They transfer bacteria into the Peyer's patch where it can be analyzed by the adaptive immune cells.

26 What Is a Virus?

- Viruses are the simplest of all self-replicating living things, literally just a few lines of genetic code and a few proteins.
    - They completely rely on other living things.
- It is estimated that there are 10^31 viruses on Earth, making it the most successful entity on the planet!
- The main thing a virus needs to do to thrive is get inside cells.
    - They do this by connecting to specific receptors.
        - Only about 200 different species of virus can infect us.
- Viruses essentially enter cells, take over the membrane and force it reproduce more of the virus, then explode the cell from within using all the new viruses.
- Nothing multiplies as fast as viruses, because they are extremely reckless and don't care if mutations are positive or negative.
    - Brute-force evolution!
- Viruses are smaller and harder to detect than bacteria and can use cells to trick the immune system to stand down.

27 The Immune System of Your Lungs

- The lungs are some of the most exposed places of the whole body.
- Defenses of the respiratory system begin in the nose where your nose hair keeps out large particles.
- Mucus expels intruders with sneezes.
- There is no mucus in the deeper parts of your lungs so that *alveoli* (tiny sacs full of air) aren't covered and can allow you to breath.
    - The only thing protecting you here is a single layer of epithelial cells!
- *Alveolar Macrophages* roam around the surface of the lungs to pick up trash.

- They are very chill and hard to provoke.
- They can't cause inflammation.

28 The Flu—The "Harmless" Virus You Don't Respect Enough

- *Influenza A* viruses lead to the flu.
  - Named from "influence" in Italian, stemming from the Middle Ages where people thought the flu was caused by astronomical events.
  - Is the most powerful strain of the family of *Orthomyxoviridae*.
  - Specializes in infecting epithelial cells of the respiratory systems in mammals.
- Influenza A has been responsible for four major pandemics in the 20th century alone!
- The viruses only have a few hours to reach the epithelial cells before our immune system kills them with various proteins or antibodies.
- Once a single virus reaches a cell, it connects to the specific receptor with its spike protein.
  - The epithelial cells are clueless and just take in the virus after connecting to its spike protein.
  - The cell wraps the virus inside, where mayhem occurs and more viruses are created.
  - The viruses take over the RNA molecules, which previously took DNA and delivered it to the protein production factory of the cell. Now, it creates more viruses.
- Viruses spread extremely quickly to other cells!
  - On average, a virus infecting a single cell by Influenza A is able to produce enough viruses to infect 22 new cells before the first victim cell dies.
  - They will spread to millions of cells (which isn't too much physical space overall, but relative to the size of a cell, is a lot!
- Viruses are very discreet compared to bacteria, and often our bodies don't know what's going on until quite a few cells have been infected.

29 Chemical Warfare: Interferons, Interfere!

- Epithelial cells have a bunch of different receptors that check their insides for red flags, like viruses.
- If a cell realizes it's been invaded by a virus, it releases emergency cytokines to surrounding cells and to the immune system.
  - Many different types are released, but an important one are called *interferons*.
    - Interferons are like a mobile alarm that run through and tell other cells that something is afoot and that they need to shut down all production.

        - No production of protein means no replication of viruses!
        - Sometimes they are so good that they can stop a virus by themselves.
- It's impossible for the body to deduct how many viruses are there and how many cells are compromised.
- Some viruses, like influenza A, has adapted special attack proteins to stop interferons from getting out.
    - It's very good at delaying the immune system from finding out about what's going on, but it can't stay hidden forever.
- *Plasmacytoid Dendritic Cells* are special Dendritic Cells that move through the blood and lymphatic network specifically searching for viruses.
    - Once found, they ooze out tons and tons of interferons.
    - They are very sensitive to virus signals.
- We lose our appetite when we're sick because cytokines signal the brain that a serious defense is ongoing and the body needs to conserve its energy for that; digesting food requires a lot of energy!
    - Better short-term, not long-term.
- Once a virus is found, Macrophages and Neutrophils will come help (though Neutrophils aren't helpful because they can't fight viruses well and only trigger more inflammation).
- During the battle, the immune cells realize another type of cytokine called *Pyrogens* that trigger chemicals that cause fever in your body; the brain may generate heat through shivering (which makes the muscles contract quickly) or by contracting blood vessels close to the surface of the body, which reduces the heat that escapes through the skin (which is why you get cold!).
- An increased body temp is fine for your own cells, which can run normally and often even at higher speeds in the heat, but not good for intruders.
    - At the cost of burning more calories! Fevers are energy-expensive.
- The flu falls under the category of *Acute Upper Respiratory tract viral infections*, the most common disease that humanity has to deal with.
- Fun fact: the color of the snot does not tell you if you have a cold or flu, it's how severe the inflammatory reaction inside your nose is! Not what caused it.
    - The more colorful, the more Neutrophils have given their life.
- The best way to kill a lot of viruses is to destroy infected cells and the viruses inside them. But how does the immune system do this without causing damage to you?

30 The Window into the Soul of Cells

- *MHC Class I* molecules present antigens, similar to MHC Class II molecules, but on top on every single cell with a nucleus (which means no red blood cells).

- MHC Class I molecules provide a window into the proteins that are being produced inside of a cell, so that if a virus is producing bad proteins, the immune system can see it from the outside.
- There can be more than one MHC Class I molecules on a cell, and cells may produce more if a virus is detected so the immune system knows what's going every step of the way.
- Fun fact: the reason organ transplants are so harmful is because the transplanted organ has the MHC molecules of the previous host, so the new host's immune system recognizes it as *other* and attacks it.
    - This is why people with transplants need to be put on immunosuppresents, which stop the immune system from attacking.
        - Leaves people much more vulnerable to infections.

31 The Murder Specialists — Killer T Cells

- **Killer T Cells** are the siblings of Helper T Cells that kill without mercy.
- Around 40% of the body is made up of Killer T Cells.
- Killer T Cells use MHC Class I molecules (instead of Class II like Helper T Cells) to be activated.
- Dendritic Cells can do something called **cross-presentation**, which enables them to present some antigens through MHC Class II molecules and some through MHC Class I.
    - This way, they can activate both Helper and Killer T Cells.
- Killer T Cells need a second signal to activate; until they get it, they are working a bit sluggishly and kill themselves quickly.
    - They get the second signal from Helper T Cells.
    - Once they receive a second signal, the Killer T Cells constantly clone themselves and goes around finding cells that are infected by a virus.
        - Which they know through the cells' MHC Class I molecules!
        - Once an infected cell has been found, the Killer T Cell tells the cell to kill itself using apoptosis.
            - Macrophages then clean the remnants.
        - The whole process is called **serial killing**.

32 Natural Killers

- Many viruses have adapted and are able to prevent cells from creating MHC Class I windows.
- **Natural Killer Cells** are related to T Cells, except they branched off and are more like army grunts over trained assassins.
- They simply check if a given cell has an MHC Class I molecule. If it does, they're free to go. Otherwise, they are told to kill themselves!

- This concept of looking for the “absence of self” is called **The Missing-Self Hypothesis**.
- Natural Killer Cells can also detect if a cell is under stress, meaning something is going on with it that’s not immediately clear.
- IgG Antibodies work together with Natural Killer Cells to catch pesky viruses.

33 How a Viral Infection Is Eradicated

- So to summarize:
    1. A virus enters the body and starts to infect epithelial cells and hiding their MHC Class I molecules.
    2. Different responses begin, including Macrophages, Monocytes, Neutrophils, and the production of more mucus to cough virus particles out from your body.
    3. In about 2-3 days, Natural Killer Cells arrive and find cells that have no MHC Class I windows.
    4. Thousands of Dendritic Cells, after sampling the battlefield, put the virus particles in their MHC Class I and II molecules and take them to lymph nodes, where they activate Helper and Killer T Cells.
    5. Half the Helper T Cells go on to activate B Cells that send over Antibodies and go through affinity maturation.
    6. After a week, Killer T Cells arrive and wreak havoc together with the Antibodies from the Plasma B Cells.
- The reason we don’t have better medication against viruses is because:
    - Creating antibiotics that fit the receptors for viruses mean creating antibiotics that fit the receptors for our own cells, which would mean attacking ourselves.
    - Viruses hide in our own cells, so it would be extremely difficult tracking them down.
- Bacteria, on the other hand, has cell walls (which we don’t have) so it’s easy to target those.
    - Also has a special bacterial ribosome that we can target.

34 Shutting the Immune System Down

- The immune system is essentially a long line of activation signals.
    - The chain perpetuates as long as each link continues to receive a signal from its previous chain.
- Once fewer battle cytokines are released, fewer immune cells are simulated, which means as old cells die, fewer new ones take their place.
- **Regulatory T Cells** make about 5% of all T Cells and work to calm down the immune response after a battle.

    - They order Dendritic Cells to become worse at activating the Adaptive Immune System and make Helper T Cells slower.
    - They end immune reactions to achieve homeostasis once more!
    - They are especially helpful in the gut, where we can't have our immune systems destroy everything.
    - They are extremely important when combatting autoimmune diseases.

35 Immune—How Your Immune System Remembers an Enemy Forever

- There are about 100 billion **Memory Cells** in your body.
- While some B Cells turn into attacking Plasma Cells after being activated, some will turn into different kinds of Memory Cells.
    - One group is called **Long-Lived Plasma Cells** that go into your bone marrow for months to years and constantly produce Antibodies for the specific antigen they were activated for.
    - The other group are called **Memory B Cells**, which settle down in your lymph nodes and do nothing until the same antigen returns one day.
        - These are extremely useful because they need no activation and can start up right away next time.
- T Cells mostly kill themselves after a fight, but about 10% will stick around and become **Tissue-Resident Memory T Cells**, where they stick around the infected area in case the antigen returns.
- T Cells also can become **Effector Memory T Cells**. These patrol the lymphatic system and the blood, and search for past enemies.
- The final T Cell group include the **Central Memory T Cells**, which stick around lymph nodes, doing nothing but waiting for past antigens.
    - Once they are found, the Central Memory T Cells produce Effector Memory T Cells to go kill.
- Measles is of the worst diseases out there because it kills your memory cells, making you much weaker to past disease again!

36 Vaccines and Artificial Immunization

- We realized that getting a disease makes us immune to it a long time ago.
    - We first came up with the idea of **variolation**, an attempt to artificially give people immunity by injecting a tiny bit of diseased scabs from an infected person and putting it in a healthy person.
        - This helped, but a lot of people still got pretty sick from it.

- The first vaccine was developed to combat smallpox.
    - The big change was that we realized we don't have to use the actual smallpox disease to infect healthy people, but instead cowpox, a much more mild version of smallpox.
- The challenge in making vaccines is to create one that activates the necessary steps in the immune system that lead to memory cells being created.
- There are a few different methods of vaccination:
    - **Passive Immunization** involves borrowing immunity against a disease from someone else who survived it.
        - For instance, if a snake bites you and injects its venom into you, we have produced antivenoms, derived from injecting sequential doses of venom into animals (not enough to kill them) and then extracting their blood and separating the Antibodies.
        - This also occurs naturally during pregnancy, through the placenta or through breast milk.
        - We can also harvest antibodies from human to human in a process called IGIV.
        - This is temporary however, as the Antibodies will eventually decay.
    - **Active Immunization** is allowing the immune system to create memory cells to combat specific pathogens.
        - **Natural active immunization** is when a disease infects you and your immune system naturally creates the memory cells.
        - **Live-attenuated vaccines** involve the process of putting the weak but real version of a disease into our bodies to create immunity.
        - **Inactivated vaccines** involve killing the pathogen and adding mild chemicals (just enough to get the immune system going) before putting it in our bodies.
        - **Subunit vaccines** involve injecting only a part of a pathogen into the body, so it can be easily recognized by T or B Cells.
        - **mRNA vaccines** involves injecting ourselves with mRNA that results in our own cells producing antigens that the immune system can then recognize.

37 When Your Immune System Is Too Weak: HIV and AIDS

- The **Human Immunodeficiency Virus (HIV)** targets Helper T Cells.
- HIV is transmitted through bodily fluids, often through blood or sexual intercourse.
- HIV enters the Helper T Cells via receptors called "CD4".
- HIV is a **retrovirus**, which means that it merges with genetic code and becomes a part of you forever.
    - We are all pretty much 8% virus because of retroviruses.
- HIV infections happen like so:

1. First, the **acute phase**, in which Dendritic Cells are infected by the virus. The Dendritic Cells take the virus unknowingly to the lymph nodes, where all the T Cells are.
2. HIV spreads sneakily throughout, infecting numerous T Cells that are busy fighting the the identified parts of the virus like normal.
    - The earliest symptoms of HIV are all normal: fatigue, low fever, sore throat. Usually HIV isn't identified until months or years after.
3. Next, the **chronic phase** begins. HIV doesn't make cells explode to clone itself; instead it uses **immunological synapses**, the method of communication many cells have with each other where they use their little fingers (called pseudopodia) to check each other's receptors.
    - This is very effective for the virus, as the immune system would never know what's going on.
    - HIV can also just hide and do nothing in cells until it finds the right time to become active.
4. Once Helper T Cells are activated, HIV starts spreading rapidly. Every time HIV clones itself, it makes a copy of itself with an error. That error is a mutation that can make the virus either more or less effective. Because it clones literally billions of times a day, this is extremely deadly.
5. The Adaptive Immune System spends years in a constant battle with this incredible enemy, all while killing its own cells in the process because Killer T Cells are killing infected Helper T Cells.
6. One day, the Adaptive Immune System can't handle any more and collapses, entering **profound immunosuppression**, leading to the **Acquired Immune Deficiency Syndrome (AIDS)**, in which your Adaptive Immune System is basically out of order and all the pathogens and viruses that weren't that big of a deal before can now attack and kill you.

- HIV treatments work by targeting the different stages of virus development so HIV never turns to AIDS.

38 When the Immune System Is Too Aggressive: Allergies

- Being allergic to something means that the immune system is massively overreacting to something that is probably not that dangerous.
    - This is called **immediate hypersensitivity**.
- In the context of allergies, antigens are called **allergens**, short pieces of proteins that are recognized by the adaptive immune cells and antibodies.
- The IgE Antibody is the one reacts to allergens.
    - Produced by B Cells in your skin, lungs, and intestines.

- The first time you experience something, your B Cells might recognize them as allergens and produce IgE Antibodies.
    - The next time you are exposed to that thing, the IgE Antibodies will latch onto Mast Cells, which explosively release **histamine** and other chemicals that end up causing massive inflammation.
        - Process called **degranulation**
        - The release of histamine may cause a dangerous loss of blood pressure and make breathing very difficult.
- Mast Cells aren't the only culprits - **Basophils** are special cells that patrol the blood and are charged up by IgE Antibodies.
    - They make sure the Mast Cells keep exploding and causing inflammation.
- **Eosinophils** are also apart of this process; they are activated by cytokines from Mast Cells and Basophils and make sure the symptoms of the allergic reaction stay around.

39 Parasites and How Your Immune System Might Miss Them

- The reason we go through allergic reactions might be because of parasites.
- There are about 300 kinds of parasitic worms that can infect humans.
    - They still infect about 2 billion people in the world (all in low income countries) and can remain chronic for up to 20 years.
- Parasitic worms lay eggs that leave the body in our poop.
- The allergic reactions described in the previous chapter make a lot more sense in the context of attacking these parasitic worms.
- Because higher income countries have done away with parasites, the theory is that the immune system, which built up defenses against worms over time, still expects them to be a thing.

40 Autoimmune Disease

- In autoimmunity, your T and B Cells are able to recognize your own antigens - **self-antigens**.
- We can all get autoimmune diseases, but genetically speaking, some have it as a higher risk than others.
- While T and B Cells have receptors that specialize in one particular antigen, they can still work with other antigens, just less effectively. If an antigen matches the shape of a self-antigen, it may recognize an enemy within if an infection with that similar-shaped antigen invades.
    - This is called **molecular mimicry**.
        - This is an evolutionary trait, similar reasons to camouflage.

    - This also requires the thymus to have made a mistake and send through T Cells that are **autoreactive** (they recognize the body).
- If T Cells recognize self-antigens, they will kill the body's own cells and eventually produce Memory Killer T Cells and Long-Lived Plasma Cells (which will constantly pump out antibodies that are fighting against our own bodies).
- Symptoms for autoimmune diseases include many common ones, including fatigue or trashes or fever.
    - They are rarely lethal.
- Dendritic Cells are always floating around, even with no infection around, and providing reports to the lymph nodes on what's floating around the body.
    - If they find autoreactive T Cells, they can shut them down by giving them one kiss/signal instead of the usual two.

41 The Hygiene Hypothesis and Old Friends

- There's been an odd trend in higher income countries in the past few decades - as diseases like smallpox, mumps, and measles died down due to advances in antibiotics, we've seen a huge rise in allergies and autoimmune diseases.
- The **Hygiene Hypothesis** is a popular theory that because humans had become too clean and sterile and going against nature, we were suffering immune disorders.
    - Just because something isn't natural doesn't mean it's wrong - in fact, it's most often better.
- Most of the diseases we experienced in the past are eradicated; all the diseases we face now are new and have blown up because we all have been living in close proximity to each other for the past ten thousand years.
- While the realization that hygiene is extremely effective at keeping us healthy, we also realized that our immune system needs to be trained by more harmless bacteria - the **"Old Friends" Hypothesis**.
- Our bodies have communities of **commensal microorganisms** that train our immunity and live in mutual trust with out bodies.
- Our early phases of live require the collection of "data" so our immune system knows what's around it.
    - Vaginal birth and breastmilk are important to transfer the mother's bacteria to the child!
        - Rise in C-sections and lack of breastfeeding are correlated with higher rates of immune disorders and allergies.
- Our diets nowadays also contain a lot less fiber, and fiber is required for commensal bacteria to thrive.
- Basically - be hygienic, but also play in the dirt from time to time!

42 How to Boost Your Immune System

- There really isn't a way to "boost" your immune system.
  - A stronger immune system will just make the different parts of it too aggressive, which is not the goal - homeostasis is!
- Every product claiming to boost your immune system is a scam.
- The only way to have a more effective immune system is to eat healthy and exercise.

43 Stress and the Immune System

- Having less stress is the biggest thing anyone can actually do to make their immune systems work more effectively.

44 Cancer and the Immune System

- There are two major categories of cancer:
  1. When cancer cells form in solid tissue and create tumors.
     - Tumors can be benign, which might still be dangerous, but ultimately removable.
  2. When cancel cells form in bodily liquids like blood or lymph (leukemia).
- For cancer to happen, three major things need to take place:
  1. A mutation has to take place in your **oncogenes**, which are the genes that monitor your growth.
     - Prominent in early ages but then shut off as you get older.
  2. Your **tumor suppressor genes**, the genes that constantly scan your DNA for errors, break.
  3. Your cells lose the ability to kill themselves in apoptosis.
- Cancer is basically a cell that stops working for the collective and starts doing its own thing.
- Statistically, it's almost certain for you to get cancer the older and older you get, but other things will probably kill you first.
- Because cancer takes place after your reproductive age, evolution hasn't solved it yet.
- Your body makes cancer cells routinely, but the immune system usually handles it in three phases in a process called **immunoediting**:
  1. **The Elimination Phase** - cancer cells divide and multiply haphazardly and are mostly quickly taken care of the immune system's innate and adaptive components.
  2. **The Equilibrium Phase** - the cancer cells that survive reproduce and their sneaky instincts are passed on.
     - One of these instincts involves cancer cells targeting the **inhibitor receptors** of Killer T

Cells and Natural Killer Cells. These are the receptors that allow these cells to kill other cells.

3. **The Escape Phase** - the new cancer cells create a better world, called a **cancer microenvironment**, that makes it much much more difficult for the immune system to fight them.

- Smoking basically slows down your entire immune system and makes your respiratory system hell.

45 The Coronavirus Pandemic

- Both the past **SARS coronavirus** and **MERS coronavirus** had really high mortality rates but were much less infectious than COVID-19.
- Coronaviruses target the **ACE2** receptor in cells. This receptor regulates blood pressure and is prominent in epithelial cells in the lungs.
- Coronaviruses are also really good at shutting down interferons, which means the virus does not slow down and more and more immune cells are added to the battle, resulting in heavy inflammation in the lungs.
- People's experience with COVID-19 differs because of different MHC molecules and genes.
- COVID-19 can also lead to blood clotting, leading to a lack of oxygen supply in your organs, possibly leading to strokes or heart attacks.