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The Human Immune System and Application of Bioengineering

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I teach AP Biology and General Science at Cooperative Arts & Humanities Magnet High School. This is a performing arts magnet school, located in the city of New Haven, CT. Being a magnet school we draw 30% of our students from surrounding districts that are a mix of urban and suburban school systems. We utilize a block schedule with four 90 minute periods a day.

I teach AP Biology as a sophomore year class. Though the content appears vast the underlying focus is on the application of science to the living world. This class is about teaching students how the mysteries of life are described and understood with critical and creative thinking.

The content of this unit, the human immune system and disease will cover the immune system along with infectious diseases and autoimmune diseases. The unit will also present information about medicines in development to usher in a new era of immune system bioengineering to correct immune system defects and restore competence of our complex defense system.

The human immune system is extremely complex, but easily understood when one focuses on the roles of the different components. This unit is tailored to provide enough content to allow for a deeper understanding of the immune system, but at times, may be too in depth for the average biology class. Information about infectious diseases and autoimmune diseases is presented solely to exemplify the functions of the immune system and not as a content bank about specific diseases. Personal hygiene and antibiotic use is discussed in terms of the human microbiota. Lastly, content about disease remedies using nanotechnology is presented to augment classroom discussion about immunity and elicit a deeper understanding about how the immune system functions. The ultimate goal is to frame the immune system's shortcomings and malfunction as the cause of disease through which the remedy can be found.

Connecting to the real world

People have the internet in their front pocket, or more likely, right in front of their face as they text a friend. Unfortunately, though we think we are well informed and knowledgeable about important topics like disease prevention often we are not. Our students are not. They have likely heard about more complex issues, drug trials, rare diseases, and genetic disorders because of the internet, but that does not substitute for understanding. Even more seriously, they do not have instruction in school about how to navigate the bombardment of campaigns about health and hygiene. Students need a more comprehensive understanding about vaccinations, the immune system, and disease to make informed decisions about their lives. Unfortunately the campaigns to promote major public issues like vaccines are easily usurped by a single voice because the nature of the internet being a public realm and of course because of social media. The implications of being misinformed and uneducated are dire.

As educators we need to reframe an understanding of the human immune system to students. We must inform students about how diseases are transmitted, how they can protect themselves, and how their decisions affect other people and themselves for years to come. As educators, we must go beyond basic textbook instruction about how the immune system functions. It is important for students to realize that public health issues such as disease can be remedied through engineering. Engineering not just as it relates to the production of new medicines, but also how it relates to targeted corrections and re-engineering of our immune systems to cure diseases.

Content Objectives

The content objectives of this unit are the role of the human immune system in maintaining a disease free status; how infection happens and how can effective treatments be designed against microbes; method of infection and treatment of viruses; actions of an autoimmune disease; our relationship with our microbiota; and the application of nanotechnology to engineer the human immune system.

Teaching Strategies

Content is covered through reading, lecture, and discussion. The understanding of the content is fostered by activities that require collaboration, modeling, and justification. It is necessary to first instruct students about the human immune system before engaging them in activities related to the understanding of how the body acquires a disease. Throughout the unit I will offer examples about how to relate the logical design of the immune system to that of a comprehensive defense strategy that a nation, state, or building would employ to guard its resources.

Innate and Acquired Immunity

The human immune system is easily divided into two components, innate immunity and acquired immunity. More specifically the division is cell mediated and humoral immunity, innate and acquired respectively. Innate immunity, as the name implies, are immune functions that exist and function the same in every person. It is comprised of structural features, chemical secretions, and non-discrete white blood cells. Understanding innate immunity can help students to think about their body's activities from a perspective of the body protecting itself. Innate immunity is typified as a general response to invasive particles, molecules or other foreign material. Acquired immunity encompasses the facets of the immune system that are either received from the child's mother or developed through life. This is also referred to as adaptive immunity because it allows the body to constantly adapt to new invasions. This is an evolutionary advantage allowing humans to combat pathogens that pass the innate immune system. This component includes antibodies and cell-mediated defense pathways. Acquired immunity protects us from specific invaders, in particular, ones that have been previously encountered by either ourselves or our mothers. The body has a wonderfully complicated and efficient method of maintaining homeostasis and avoiding a disease state.

Innate Immunity

Innate immunity can be thought of as design elements common to all humans. This is the set of defense structures that passively defend the body as well as cells that actively respond automatically to anything that is nonself. Nonself refers to molecules, particles, cells, and even multicellular things that come into contact with the human body. The body has secretions and structures that limit the crossing of foreign matter of the epithelial cells that line the exterior of the body.

Innate Immunity: External Body Surfaces

External, in the case of the body, not only refers to the skin that you see but also includes the linings of organs that are exposed to the outer-body world. For example, the mouth, though it seems that something that passes into the mouth has passed into the body, it has not. The mouth is lined with a layer of cells called epithelial cells. This barrier of cells is a first line of separation between the outside world and the body. Epithelial tissue is the layer of tightly packed epithelial cells that form the barrier. This tight packing prevents pathogens from entering the body, along with other functions such as fluid retention and protection from mechanical injury.

Consider a fence around private property. It is a barrier, but not impenetrable. Furthermore it has to include a door for entry and exit.

Epithelial tissue, skin, is in constant contact with the outside world. Any instance of contact with material, whether it is a door knob, food, another person, puts the person in contact with bacteria, fungi, viruses, chemicals, and even parasites. Furthermore bacteria, and fungal spores, are in the air, water, and soil. Unless a person has just recently sterilized section of epithelium it is covered with bacteria. We live our lives in close association with bacteria but the epithelial lining keeps these single celled organisms out of the body. The epithelial lining does a remarkable job at being a physical barrier against minute invaders. Different types of epithelium line different parts of the body, but in general the tight junctions serve the function of innate

immunity.

Epithelial tissues are strong enough to help prevent mechanical injury while still retaining major flexibility. Skin must be flexible enough to allow for muscular movement but strong enough to resist being punctured. Light abrasions do not compromise the epithelial layer thus presenting a point of entry to the body by foreign matter. At times abrasions will compromise the external tissue and the body has defenses for this situation that will be addressed later both within the realm of innate immunity and more thoroughly encompassed by acquired immunity.

Innate Immunity: Mucous Membrane and Secretions

The mucous membrane is found contiguous with epithelial tissues as well as below. These are specialized cells and glands that secret a fluid called mucus. Mucus secretion is integral to the prevention of colonization and possible infiltration by foreign organisms via destruction and/or removal. The mucus that is found in your respiratory tract traps foreign matter and then the ciliated epithelial cells help to sweep the secretion, with its trapped matter, up and out of the body. Tears provide a washing action to sweep would be invaders away, preventing colonization.

Consider a door mat at the entrance to a building. Designed to remove and trap debris, keeping it from entering the building.

Mucus as well as tears and saliva contain lysozyme. Lysozyme can destroy microbes, such as bacteria. Lysozyme's action is on the cell wall of bacteria, causing the rupture of the cell wall and subsequent death.

The stomach secretes a gastric juice. This is a mixture of enzymes, mucus, and hydrochloric acid, creating a barrier for microbes that are ingested in our food or mucus. This highly acidic environment solid barrier for all but the most specialized bacteria.

Secretions of sebaceous glands and sweat glands help to keep the skin coated with an acidic environment. Microorganisms are prevented from colonizing the skin thus keeping the tissue free of pathogenic bacterial growth. It must be noted that the skin is home to bacteria, but this bacteria, like most all bacteria is non-pathogenic. A skin swab will reveal the existence of countless symbiotic bacteria that live in harmony with us. Later I will discuss this intimate relationship between humans and symbiotic flora. The acidic environment helps to keep large colonies of bacteria from forming and posing a threat to the body.

Consider spilling something on your kitchen floor. If you leave it there it will attract bugs, trap dirt, or even stain the linoleum. You need to clean your floor frequently to avoid the accumulation of matter that may ultimately affect the integrity of the material.

Innate Immunity: Skin Shed

Lastly, concerning epithelial tissue, the process of constant regeneration of the epithelium helps to keep the body free of pathogens. As new epithelial cells are generated the old ones are shed. The epithelial lining of the body is constantly being turned over. This prevents bacteria from taking up long term residence as they, with their microenvironment, are discarded as new growth occurs. For example the rate of turnover for "the (epithelial) cells lining the small intestine is every 4 to 6 days for humans." [1]

Just like skin is shed, people change clothes. We must change our clothing frequently to avoid the build of smells and grime.

Innate Immunity: External Barrier Breach

In the event of the external barrier being compromised and breached by microbes or foreign matter there exist innate internal defenses. A system that relies on first the detection and recognition of nonself matter infiltration and the subsequent destruction and removal of said invaders. Leukocytes, a type of white blood cell, work in concert with the lymphocytes, another type of white blood cell, of the acquired immune system. Recall that the overarching theme is that of maintaining homeostasis. Internal innate defenses primarily incorporate phagocytosis of invading microbes and chemical pathways that elicit multicellular reactions such as inflammation that serve to remediate the problem quickly.

Innate Immunity: Inflammation

Inflammation of tissue, the swelling, redness, and heat associated with tissue comprise. This helps to protect the body from a diseased state. The redness results from the increased blood flow that has been encouraged by damaged cells. Damaged cells release a chemical messenger called histamine that initiates the inflammatory response. Mast cells help amplifying the response through the release of more histamine. Mast cells are found in connective tissue and epithelial tissue. Chemicals released by these cells will attract other immune cells to the area, thus helping to mediate the response. The more blood flow to the area caused by the dilation of blood vessels also results in more white blood cells to help mediate the invasion and return the body to a normal state. The increased blood flow also results in the swelling. The pain is felt because of the swelling and subsequent pressure that is created and sensed by local neurons. Pain and itchiness is also associated with direct action of mast cells. The increased temperature associated with inflammation is also a result of the increased blood flow.

Consider that when a fire breaks out, the firemen rush to area and drench it with water. This connection seems like a stretch, but the accumulation of firemen in one area along with the action of changing the environment to an extreme, temporarily, is the same idea. The necessary professionals are attracted to the problem area and as a result of mitigating a problem, the local environment changes temporarily.

Innate Immunity: Fever

Fever is an immune response that results in an increased body temperature. It is easily mistaken as being the cause of disease when in fact it is the result. It is a calculated compromise of the body to raise its temperature to increase metabolic activity to hasten the immune response. It also helps by surpassing a threshold temperature for some pathogens, a temperature maximum, wherein beyond which they cannot survive thus resulting in death. It is a compromise because the body also has a temperature threshold that if passed will result in tissue damage and subsequent problems. It is a temporary therapeutic response that is mediated by the hypothalamus in response to infection.

Imagine when a school has to go into lock down. Every person is alert and aware of the fact that an intruder if present. The whole building affected because the actions of one are a threat to the whole system.

Innate Immunity: Leukocytes

Circulating in the blood, in interstitial fluids, and the lymph systems are leukocytes. These defenders of the body range from large macrophages to comparably small granulocytes. These are cells that recognize microbes and foreign matter and are able to respond to protect the body from a diseased state. Unlike the white blood cells associated with acquired immunity, these defenders do not have memory and responding to

signals from the humoral immune system or directly to cells that present themselves as nonself. As will be discussed later, the cell mediated responses do not act in isolation and are typically activated by signals from the humoral immune system lymphocytes. Furthermore, autoimmunity will be covered wherein some of these same players are overreacting to non-threatening foreign matter or in some cases inappropriately attacking self-cells that have been accidently determined to be foreign.

Leukocytes respond to signals generated by lymphocytes or markers on microbes that identify the microbe as being of foreign origin. You can equate this response as a sort of validation process wherein the leukocyte will respond to specific molecules that it "knows" are of bacterial origin or are signals generated by the immune system such as antibodies. The latter would be signals that result in a host of responses specific to the type of phagocyte. In contrast leukocytes screen self-cells and are able to recognize them as such and take no action. In the event that a self-cell is infected or comprised a leukocyte can identify it as such because of changes to surface level proteins of the infected cell and take the necessary action against the cell. Our cells are able to communicate with the immune system when they have been compromised and in the interest of maintaining homeostasis the cell can signal that it must be destroyed. Normally a cell will present parts of the proteins that it is manufacturing, in the case that a cell has been infected it will presenting proteins that are nonself, thus eliciting a response from the leukocyte. A major roll of leukocytes is to act in response to antibodies generated and released by B-lymphocytes of the humoral immune system. In the case of invasion by foreign matter, it is the macrophage, of the innate immune system that teaches the B-lymphocytes of the acquired immune system, what is nonself. This is done with antigen presentation. In subsequent attacks by the same foreign invader the humoral immune system can now recognize the invader as well, resulting in a quicker immune response. This complex interaction will be covered in subsequent sections and was discussed here to reinforce that cell mediated and humoral immunity work in concert to protect the body.

Leukocytes that will be covered in this unit are macrophages, granulocytes (neutrophils, eosinophils, and basophils), dendritic cells, and natural killer cells. The mode of action for these leukocytes is primarily phagocytosis. Antimicrobial proteins including interferons and the complement system will also be discussed. These proteins will attack pathogens directly as well as mitigate by impeding reproduction of the microbe.

The connection between leukocytes and varying levels of security guards will be made to illustrate the necessary differences of these white blood cells.

Innate Immunity: Leukocytes: Macrophages

Macrophages are large phagocytic cells that as the descriptor phagocytic implies, consume microbes and foreign invaders. They are found migrating throughout the body in the blood and interstitial spaces. They are also found in organs and within the lymphatic system. Dense populations of macrophages are found in lymph nodes and in the spleen. Both are filtering points for lymph and blood respectively. Microbes are trapped in these organs and consumed by the resident macrophages.

Though macrophages can immediately sequester and destroy invading microbes, it is their relationship and communication with lymphocytes that is most important. Macrophages are antigen presenting cells. Antigen is a general term for any molecule that is identified as foreign to the body. These are commonly proteins or polysaccharides that are specific to the invading microbe. An antigen can also be a toxin found in extracellular fluids. The antigen is essentially the identifier. Macrophages consume foreign matter and then present that matter on their surface in order to show it to T-lymphocytes, important white blood cells of the acquired immune system. This communication between the two systems is integral to the learning process of humoral immunity. Ultimately antibodies are created for each specific antigen and protect the body by "binding to

antigens they find, the antibodies can neutralize them or precipitate (antigen) destruction by complement enzymes or by scavenging cells." [2]

Macrophages also release cytokines and chemokines that will initiate the inflammatory response. They do this in response to infection. This is another way that the macrophage is operating as a player within a bigger network or immune response cells and pathways. Macrophages can be activated by the release of proteins from infected cells, proteins such as interferon that will be discussed shortly.

You can equate the macrophage to a security guard. A security guard that knows who belongs and who does not and is big enough to sequester an intruder. This security guard will then alert the police about the intruder and share identifying information.

Innate Immunity: Leukocytes: Granulocytes

There are three granulocytes that we currently know of, neutrophils, eosinophils, and basophils. These are first responder cells and though part of innate immunity their action can be in response to antibody presence, antibodies are created by lymphocytes. Phagocytic action is the mode for some of them and they are known for consuming invaders until they die. The yellowy white fluid associated with an infection, pus, is primarily dead granulocytes.

These granulocytes are differentiated but share the common characteristic of being first responders in the event of infection. Neutrophils respond to chemoattractants released by bacteria, inflamed cells, or dead and dying cells. They utilize phagocytosis to neutralize affected cells. Eosinophils are associated with attack of multicellular invaders. Lastly basophils are associated with allergic responses and parasitic attacks.

These are the first responders to an accident. A good analogy is a paramedic, they respond quickly and deal with the situation the best they can.

Innate Immunity: Leukocytes: Dendritic Cells

Dendritic cells are phagocytic and will also present antigens. Antigen presentation is a primary function of these leukocytes, helping to strengthen the humoral immune response. They differ from macrophages in that they are capable of initiating attacks on pathogens. Wherein a macrophage will consume and present, a dendritic cell will go further and activate other phagocytes to remedy a problem. Dendritic cells are found all throughout the body and largely around epithelial barriers.

Think of an armed security guard. This is a defender that has weapons to defend the territory and the discretion to judge a threat and carry out the needed response. This guard will also recruit others to join in. This guard will communicate with the police as well.

Innate Immunity: Leukocytes: Natural Killers

Natural killer cells are uniquely developed to identify and kill virus infected cells. They are also known to attack cancer cells. There mode of action is to release a chemical attack that results in apoptosis of the infected cell. Apoptosis is cascade of pathways that is set in motion resulting the death of a cell, it is considered programmed cell death.

This is a specialized soldier guard that will neutralize threats according to a certain protocol. The type of protection needed to identify a domestic threat such as a terror cell that has set up residence.

Innate Immunity: Antimicrobial Proteins: Interferons

Interferon is considered an antimicrobial protein because its use by infected cells will trigger events that result in an immune response. Interferon can be thought of a distress signal that is released by a cell in response to viruses, bacteria, parasites, and even cancer cells. This warning can signal leukocytes to action as well as warn nearby cells to prepare and produce defense chemicals. Though interferons cannot directly mitigate a response against a pathogen, their role of warning the rest of the immune system and neighboring cells is pivotal in the maintenance of homeostasis.

Any properly defended building will have an alarm system with a series of sensors that can respond to abnormal activity and notify the guards.

Innate Immunity: Antimicrobial Proteins: Complement Cascade

The complement cascade or complement system involves about 25 to 30 proteins that participate in the immune response. They work by aiding in the destruction and removal of bacteria and antigens. They circulate within the blood in an inactive state and are activated by antibodies. Different cascades will result in the destruction of a bacterial invader through a chain reaction of events initiated by the activation of the first protein in the cascade. Other cascades result in the inflammatory response, while still others will increase the susceptibility of microbes to phagocytosis.

This is a low level, unarmed security guard that is relegated to doing rounds. This is an active guard that circulates the building for suspicious activity. This guard has radio or whistle to alert other guards of a disturbance.

Innate Immunity: Summary

What is defined as the human innate immune system ranges from structural facets of the body to tissue responses to bodily secretions to cell level action all the way down to antimicrobial protein action. This system does not stand alone and cannot defend the body from all attacks. Innate immunity is intertwined with acquired immunity yet is defined by immediate call to action in response to foreign material. As will be discussed, acquired immunity, though more targeted and effective, relies on presentation of antigens by the leukocytes and subsequent production of antibodies. These antibodies are produced onsite in response to new antigens as well as by memory cells from a previous encounter or via maternal acquisition. This is a loop though and antibody action within body stimulates many components of the innate immune system.

Acquired Immunity

Acquired immunity, as the name implies, encompasses the white blood cells, lymphocytes, which manage the defense against pathogens based through antigen recognition with antibodies. The information that is used is either presented to the lymphocytes by leukocytes or has been transferred to the person via maternal methods. In more understandable terms, acquired immunity is actively developed by exposure to pathogens or vaccinations. Falling under the definition of passive acquired immunity is immunity that develops because of transfer of lymphocytes or antibodies from a donor.

There are two general types of cells involved in this immune system, B-cells and T-cells. B-cells, or B-lymphocytes, are produced in the bone marrow and T-lymphocytes in the thymus. Their roles are remarkably different but inherently intertwined in the effective defense against disease.

Acquired Immunity: T-Lymphocytes

T-lymphocytes aid in the discovery of antigens and the subsequent presentation of them to B-lymphocytes. The B-lymphocytes create and release the antibodies. T-lymphocytes search for antigens. They find them being presented by leukocytes as well as infected cells. In the case of leukocyte presentation, the white blood cell has consumed a pathogen and then presented an antigen on its surface for the T-cell to discover. Furthermore, antigens can be found by T-cells when presented by diseased cells. For example, a cell that has been co-opted by a virus will be producing viral proteins. Fragments of those viral proteins will be presented by the cell and the T-cells will discover them. The presentation of the antigen is done with a special molecule called a major histocompatibility complex (MHC) protein. T-lymphocytes also aid in the destruction of pathogens. T-cells are further differentiated into two classes, helper T-cells and killer T-cells.

Acquired Immunity: T-Lymphocytes: Helper T-Cells

The helper T-cell is the type that communicates with leukocytes. Leukocytes share the antigen with the cells along with how to neutralize an attack from the pathogen. The binding of the T-cell receptor with an antigen that has been presented by another cell on and MHC complex serves to activate the T-cell into an effector cell. The effector cell multiplies and carries out two vital processes. One process is that the effector cells communicate information about the antigen to B-lymphocytes. This is information that leads to antigen specific antibody creation as well as about how the antigen is neutralized. In the case of an antigen that the body already recognizes, the effector cells are activating memory B-cells to produce the necessary antibodies. Secondly, the effector cells will signal killer T-cells, also known as cytotoxic cells, as well as macrophages. Helper T-cells are important both in the immediate response and mitigation of a pathogen as well as future responses by sharing antigen information with B-lymphocytes.

Acquired Immunity: T-Lymphocytes: Killer T-Cells

Killer T-cells also have receptors for antigens and are activated by antigen binding. When activated they are considered effector cells. Cytotoxic cells are effective at killing cells that have intracellular pathogens such as viruses, bacteria, or parasites. Intracellular action is beyond the reach of the antibody. Cytotoxic cells kill by inducing apoptosis in the infected cell. "Once bound to its target cell, a can employ at least two strategies to kill the target, both of which operate by inducing the target cell to kill itself by undergoing ." [3]

Acquired Immunity: B-Lymphocytes

B-cells are white blood cells that begin as naïve plasma cells. A single B-cell that has been generated by the bone marrow is considered naïve until it is activated by a helper T-cell that presents an antigen. The antibodies, immunoglobulin molecules, produced by the B-cell are specific to the antigen. Any given B-cell can only produce one type of antibody and because of possible variations in the structure of the antibody and specialized enzymes that can add DNA to the antibody coding section, the combinations are nearly infinite. This means that the human body has the potential to create antibodies for nearly any molecule. This can be good and bad as will be discussed later concerning autoimmune diseases. The antibodies themselves do not necessarily destroy pathogens but more help to make pathogens visible to the components of the innate immune system for destruction. The creation of memory B-cells results from the initial interaction of a naïve B-cell with an antigen.

Antibodies are the crucial component of the B-cell. Antibodies are receptor molecules. These molecules have

antigen binding sites of near infinite variation. Any given B-cell will only produce one specific antibody. That being said, antibodies of different class are produced by the same B-cell. These all bind the same antigen but have different roles such as surface receptor for antigens; allergen binder to promote the allergic response; secreted antibodies that have differing functions in the extracellular space.

With primary introduction of an antigen the humoral response is slow. Once binding of antigen to antibody occurs the B-cell is activated and it will proliferate creating plasma cells as well as memory B-cells. When this antigen is presented again at a later date the immune system already has memory B-cells to be activated. Before the initial pathogen infection there is a limited number of B-cells specific to the antigen that the pathogen has. After this initial interaction there exist memory B-cell clones. With more cells present that can recognize a given pathogen a quicker response occurs. Once the immune system is taught about a pathogen it is prepared for any subsequent attacks by the pathogen.

The ability to teach the immune system which antibodies are important is fundamental to our ability use vaccines to protect ourselves from infection. It is not so much that getting a vaccination for measles prevents the body from encountering measles, but instead that when measles do enter the body the pathogen is recognized and the defense is already prepared. This prepping of the immune system is what keeps us free of those diseases that we have vaccines for.

Acquired Immunity: Summary

This was very brief description of the acquired immune system. It is typified by its ability to learn about new pathogens and tailor specific responses against them. The learning allows for an effective strategy of having the response ready and waiting for a possible attack. The acquired immune system does not work as an isolated entity, instead it is interwoven with innate immunity to protect the body from a disease state.

Consider how the police and other armed forces can work together to keep track of dangerous people. There is a lot of communication among the different forces and they respond to known threats as identified by previous encounters. The police and army are geared up and ready for known threats that have been encountered before or that they have been warned about.

The Lymphatic System

Immunity as a process to keep the body healthy and maintain homeostasis cannot be discussed without addressing the lymphatic system. The thymus, where T-cells are produced, is part of the lymphatic system. This is a network of tubes that permeate the body to collect extracellular fluids for filtering, sampling, replacement, and removal. The arterial capillaries of the circulatory system are permeable, allowing blood cells, water, and other small constituents pass out of the circulatory system into the extracellular space. Some of this fluid is recovered by venous capillaries. The remaining fluid is collected by lymph vessels to flow through the lymphatic system. Within this fluid are pathogens and antigens as well as cellular waste. Fluid, and its constituents, found in the lymph system is called lymph.

As lymph is passed through the lymph vessels it must pass through lymph nodes. Lymph nodes house lymphocytes and leukocytes giving these white blood cells a chance to screen the molecules, cells, and microbes that are in the lymph. Phagocytic activity is high in lymph nodes. T-lymphocytes are also conveniently located here in this advantageous location. T-cells that are activated can continue in the lymph vessels and enter into the circulatory system via the left and right subclavian veins or be transported to the organs and structures that the lymph system is associated with. The structures associated with the lymph

system are the thymus, adenoids, tonsils, appendix, spleen, and Peyer's patches.

The lymphatic system can be equated to the sewer system and processing plants that a major city will have. This is a network of structures that are in place to handle the waste of the population.

Why We Get Sick

Despite the highly efficient and capable immune system of the human, we still get sick. What will be discussed in this section is how and why disease is prevalent. Disease is the result of the immune system malfunctioning or being overwhelmed or subverted.

Bacterial Diseases

It is common practice now to sanitize our hands and common surfaces frequently. This is done so to target the "less than 1 percent of the different types (of bacteria that) make people sick. Many are helpful. Some bacteria help to digest food, destroy disease-causing cells, and give the body needed vitamins." [4] How do we deal with an opponent that his hiding amongst friends?

The human body, at any given time, is host to 10 times more bacterial cells than human cells. This is referred to as the microbiota. There is a deep seated commensal relationship between bacteria and humans. The process of vaginal birth exposes the newborn to their first bacteria. As the baby is exposed to the world more and more bacteria are acquired and they take residence on the different epithelial tissues of the body. This is the key, the bacteria are confined to the external body surfaces. There is, as discussed earlier, ample innate immune defenses to keep microbes out of the body. Even when some do breach, it is likely they are not virulent. Issues arise when the virulent microbes enter the body and get a foot hold.

If a virulent microbe is able to circumvent or overwhelm the immune system the body will become diseased. This is achieved with virulence factors that give the bacteria an advantage against the immune system. Pathogenic bacteria may quickly populate normally sterile tissue, release toxins, and damage cells. The medical marvel of the 20 th century was the discovery of antibiotics. These are chemicals that kill bacteria but do not harm our cells. This is due to structural differences between the prokaryotic bacteria and eukaryotic cell of humans. Antibiotics are very effective if you infected but are not a prophylactic and have not residual effect on bacteria.

Lately the use of antibiotics is concerning the public and professionals for two reasons. They encourage the proliferation of antibiotic-resistant strains of bacteria by selecting for them. Through random mutation progeny of a bacterium may, by chance, be resistant to an antibiotic. If this is a virulent bacteria and the disease is being treated with antibiotics, the individuals that are resistant will have an advantage and go on to proliferate. The second concern is that antibiotics are commonly broad spectrum. This means that they kill any number of different species of bacteria and not just the single virulent species that is inflicting the person. The ramifications of this are not understood, but considering our relationship with a microbiota it is not hard to believe that killing off our good bacteria with an antibiotic is a good sound practice.

Bacterial Diseases: Virulence Factors

Bacterial disease results from a failure of the immune system to respond appropriately to virulent bacteria. Often bacteria are able to infect the body because the immune system is compromised already or suppressed. Pathogenic bacteria often have unique traits that give them an advantage. These traits are called virulence factors and they help bacteria to infect a host, cause disease, and get by host defenses.

Virulence Factors:

- Adherence Factors: Many pathogenic bacteria colonize mucosal sites by using *pili* (fimbriae) to adhere to cells.

- Invasion Factors: Surface components that allow the bacterium to invade host cells can be encoded on plasmids, but more often are on the chromosome.

- Capsules: Many bacteria are surrounded by capsules that protect them from opsonization and phagocytosis.

- Endotoxins: The lipopolysaccharide endotoxins on Gram-negative bacteria cause fever, changes in blood pressure, inflammation, lethal shock, and many other toxic events.

- Exotoxins: Exotoxins include several types of protein toxins and enzymes produced and/or secreted from pathogenic bacteria. Major categories include cytotoxins, neurotoxins, and enterotoxins.

- Siderophores: Siderophores are iron-binding factors that allow some bacteria to compete with the host for iron, which is bound to hemoglobin, transferrin, and lactoferrin. [5]

Viral Diseases

A virus is non-living pathogen. Viruses are protein packages of RNA or DNA that require a host to reproduce and manufacture its proteins. A virus that can infect a human has receptors for proteins expressed on human cells. This also helps explain why viruses do not commonly jump from one species to another, because cells of one species are inherently different from another. Furthermore it makes sense that viruses transmit more frequently among more closely related species. For example, it is more likely that a virus will transmit from a monkey to a human than from an oak tree to a human. The method of a viral infection makes them a difficult adversary for the immune system because they are hiding within cells. By the time a lymphocyte or leukocyte detects one it has already infected a cell and began manufacturing proteins. As mentioned early, byproducts of the viral molecules will be presented on the host cell, available for detection by phagocytes and helper T-cells.

Viruses make us sick because they destroy cells. Once the body realizes that it is infected with a virus the immune system is set to action. The immune response is the sickness that is associated with the virus. As the viral infection destroys cells making copies of itself the immune system responds. The symptoms of a virus are the actions of the immune system. Unfortunately there are not many antiviral medications and the body is left to fight the virus on its own. In general we can treat the symptoms but not the cause. The antibiotic that works against a bacterial infection is useless without a bacterial target. Taking antibiotics to treat viral infection may make matters worse as they destroy many commensal bacteria and select for antibiotic resistant virulent strains.

Though there are not many options once a viral infection has occurred, we can limit the spread of the virus to other people. Limiting the transmission of any given virus requires that we understand the mode of transmission for the virus. For example, if the virus requires blood to blood contact from an infected individual

to a healthy individual we can limit transmission by avoiding blood contact. The most contagious viruses are the ones that transmit through the air wherein you can be in the same room as an infected person and catch the disease. The best way to protect ourselves against viral infections is with vaccines, a prophylactic.

Vaccinations were discovered in the 19 th century through work with cowpox virus. A virus that inflicts cows and is similar to the human virus smallpox led to the discovery that people can become immune to a virus. Though scientists of the time did not know all of the details about how vaccinations were working they did know that if a person was exposed to cowpox they were protected against smallpox. This is the human immune system working, the secret to vaccinations are the lymphocytes, particularly the memory B-cells. The cowpox virus is not dangerous to humans, but the immune system still identifies it as foreign and responds to the antigen. In this case, the antigen is the same as the smallpox antigen, thus giving the immune system a chance to learn how to recognize the antigen without the threat of getting infected. Subsequent encounters with the smallpox virus are neutralized by the immune system because it is prepared for the attack and can move swiftly enough to neutralize the infection. Many more vaccinations have been developed using the same principals and natural action humoral immunity.

Autoimmune Diseases

Autoimmune diseases are remarkably different from an infectious disease concerning the cause and treatment but share commonality as a problem with the immune system. There are some 80 known autoimmune diseases, and as the name implies, these are diseases wherein the immune system is attacking the body. The reason is that the immune system is incorrectly recognizing body cells as antigens. As the white blood cells try to neutralize the perceived threat other immune responses are elicited. The person feels sick because of the symptoms.

Scientists do not know yet why autoimmune diseases develop and for the most part treatments are limited to treating symptoms. It is, however, understood now that autoimmunity begins when the immune system turns on the body and that can happen for many reasons including error, self cells looking like bacteria or viruses "mimicry" or simply an over exaggerated immune response. One complication is that many of diseases present similarly as general immune responses. For example, fever, inflammation, swelling, and redness. Though the cause can be very specific it is difficult to determine what pseudo antigen is causing the immune response. Autoimmune diseases are similar to allergies in that the immune system is responding inappropriately to a non-threatening antigen. At some time the immune system incorrectly learned that an innocuous antigen was pathogenic and it is just carrying out its normal processes to neutralize the threat.

Engineering Immune System Solutions and the System Itself

Understanding how the immune system works is the key to finding solutions for diseases. Rather than treating symptoms the goal of medicine is to treat the problem. If the complexity of the immune system is understood by the students they can think appropriately about how medicines work and what future medicines need to do. With knowledge of the inner workings of the immune system students are able to understand antibiotics, hygiene, vaccinations, and future solutions for diseases. Through understanding of the immune system students can study it from the appropriate perspective, one in which the diseases that inflict humans are the result of immune system failures. This allows them to think about novel solutions to the problem, using the innate intricacies of the system to remedy disease. Ultimately, the goal, is that students understand that engineering is at the core of the solution, engineering that is guided by actions of the existing immune system that has served human kind so well for hundreds of thousands of years.

Immune system failures are not a modern day problem in so much as they are just be exacerbated by modern technology. Diseases have been around for as long as humans have been in existence, but aspects of the modern life may be amplifying the impact of any single disease. Today we have global travel; we live in large cities; we eat exotic foods; stress our bodies with pollution; and use antibiotics. Our exposure to and ability to deal with microbes are both affected by these actions. Consider living in a city with air pollution wherein your immune system is constantly expending energy and resources to maintain a healthy body. This increases the possibility for infection because the immune system is compromised. Consider the impact of cities, millions of people living in close proximity to each other, the perfect environment of a contagious disease.

Viruses to Fight Cancer

There is current research and preliminary successes using viruses to fight cancer. The ability of a virus to enter a cell and wreak havoc can be used against cancerous cells. Imagine a medicine that is a virus. Imagine infecting oneself with a virus with a cancer cell host in order to cure a cancer.

Viruses to Fight Cancer: Measles

The insidious measles virus, nearly eradicated in this country the with effective use of vaccines, may hold be solution to tumors. "Measles virus offers an ideal platform from which to build a new generation of safe, effective oncolytic viruses." [6] The virus needs to gain access to the cell, it does so by happening to have a receptor for a surface level protein on the targeted cell. Cancer cells do not express the common access protein that measles uses, but by chance mutation attenuated measles strains have a receptor for a different protein that is more prevalent on tumor cells than non-tumor cells. This is a non-harmful form of measles that targets tumor cells. The original virulent form of measles infects cells through a different receptor. A problem with this solution is that most people are vaccinated for measles and the immune system still recognizes the attenuated form of measles and defends against it. The ultimate solution may involve suppressing the immune, which as discussed may result in other diseases, or by circumventing the immune system by sneaking the virus past the lymphocytes in a cell carrier.

It is important to expose students to these new methods of disease control. Initially it sounds ridiculous that a person suffering from cancer will find sanctity in measles because of our general knowledge about this highly virulent disease. Exposing our students to such methods of cancer relief through a deep understanding of the immune system results in a more informed student that can think more appropriately about how diseases will be remedied in the future. One need only imagine the reaction of the general public to news about measles being given to cancer patients and how this can manifest into deeper misunderstandings of the immune system and how diseases operate.

Nanotechnology

Some of the latest developments in medicine are occurring within the realm of nanotechnology. Scientists are engineering drug delivery tools that are beyond microscopic. The particles made at the nano scale are so small that they must be viewed using scanning equipment that construct images of objects as small as 1/1,000,000,000 of a meter. The invention of such technology is pivotal to the development of nanotechnology. Furthermore nano probe development is fostering advances in diagnostics: "the ability to monitor antibody binding and sense the cellular immune response in real time with readily available technology should facilitate widespread diagnostic applications." [7] This brings immunology to whole new realm wherein immunologists can see the immune system in action at a molecular level.

Nanotechnology: Effective and Localized Delivery of Medicines

Nano scale is that of molecules. This allows us to engineer medicines at a molecular level, small enough to pass directly into cells. These molecules are small enough to allow us to communicate with the immune system via antigens. Scientists are experimenting with packaging molecules inside nano scale vessels. These vessels can be made to mimic bacteria in shape and with antigen presentation. This gives them the ability to send a package to T-lymphocytes in order to program them. If for example, you want to teach the immune system about an antigen you have to present the antigen to the immune system first. If you package the desired virulent antigen into a vessel that is readily perceived by the immune system as pathogenic the leukocytes and lymphocytes will act accordingly and neutralize the perceived threat. This delivers the virulent antigen directly to the immune system in a safe package. The result is that the humoral immune system will develop a memory for the antigen, protecting the body from possible future attack. A superior approach to vaccination that by nature has the potential to be more effective, less expensive, and easier. A major downfall of vaccinations is shelf-life, nanotechnology solutions can overcome that barrier because of their relative stability and ease of transport and storage.

Nano particles made of ploy lactic-co-glycolic acid (PLGA) are being produced to encapsulate medicines for delivery in the body. These are important because the biodegradable polymer of the capsule can be manipulated to have varying breakdown rates. "a wide variety of agents—from extremely hydrophobic to highly hydrophilic—can be encapsulated in PLGA nanoparticles, drug release rates can be tailored to particular applications, and size and loading are easily manipulated to provide further control over drug delivery." [8] Imagine that you have some leftovers in your refrigerator. That rotting food is stinking up the kitchen. Now imagine that you soaked your kitchen in Clorox to remedy the situation. Sure, it may work, but what is the collateral damage? Instead you are able to target the offender, delivering the necessary cleaning protocol directly to the food and container. The drugs of today are not dissimilar to the analogy. Though they may work to remedy a situation, they must delivered in such a fashion that they affect many non-target areas and must be taken on a time schedule maintain a concentration in the body. Solutions with PLGA encapsulated drugs may be coming soon. This is a probable solution that can solve multiple problems with one eloquent answer, nanotechnology.

Nanotechnology: Engineering the System

Engineering a better immune system will likely be the outcome of nanotechnology as it applies to vaccinations. The teaching and re-teaching of the immune system is in essence a form of engineering wherein the immune system is improved through science and technology.

The teaching of the immune system is paramount to our defense against current and future viral attacks. There may be answers to treating those infected with a virus as well. The re-teaching of the immune system is critical at this time wherein modern day plagues are those of autoimmune nature. Immune system malfunctions wherein lymphocytes have incorrectly associated cells of the self as pathogenic. The answer to fixing autoimmune disease may be in the reprogramming of lymphocytes. Now that we are in a new era wherein we can communicate directly with the immune system we can operate under a different paradigm that treats the immune system as bank of information that can be modified. Abandoning previous methods wherein the solution was to augment or suppress the system and instead strengthen it with information.

Classroom Activities

In my classes I often employ activities involving models. This provides the students the opportunity to have discussions and engage in a creative process. This also allows me to circulate the room and have discussions with the students. Modeling also requires that students justify their work. This is vital to assessing their understanding of a concept. As you move about the room you can ask students to defend the nuances of their models, thus forcing them to justify their creation and be reflective about their understanding.

Comparing the Immune System to the Defense Strategy of a Nation

An easy to do activity is have students compare the components of the innate and acquired immune system to that of the defense strategy of a nation. That being said you can apply this to a state, city, or even just a building and are not bound to using a nation as the model. The importance is that students make connections between the logic of defense that humans use to that of the logic of the immune system. For example, castles have walls which can be equated to skin. This barrier, though hard to penetrate, must have some compromises. This is a modeling activity wherein students create drawings or three dimensional models and justify them. This helps to reinforce the intricacies of the immune system and the specificity of cellular roles and actions. By requiring the students to incorporate different components, as listed below in bullets, the complexity of the activity can be modulated.

Components of an effective defense:

- Physical barrier
- Cross-barrier transport
- Gate keepers
- Structural defenses of vulnerable areas
- Identification system for inhabitants
- Universal warning system
- Internal and external defensive weapons
- Systems for neutralization of invaders
- Information systems for communicating about invaders
- Descriptions of possible invaders
- Plans for sequestering large invaders
- Strategy for cataloging past invaders
- Interior monitoring of members
- Rapid internal transport mechanisms
- Hierarchical roles of defenders
- Sewer/Waste system
- Messages from other nations

Modeling Lymphocyte Activity

I have black lab tables in my room. These are perfect for drawing on with chalk, particularly regular, cheap, dusty chalk. Students really enjoy being encouraged to draw on the desk for a change and I use this method throughout the year to model a number of different complex concepts that involve pathways and relationships among many components.

Provide students with the article "Life, Death and the Immune System" and encourage them to use their notes and text book. Group them in threes and instruct them draw the process that occurs within the body when a new antigen has been presented by a macrophage. This is another modeling activity and you can assess them

on the level of detail that they incorporate. I use a baseline requirement of including a macrophage, MHC protein, helper T-cell, killer T-cell, B-cell, memory B-cell, antigen, and antibody.

This activity is designed to take one class period with time to clean the desks after the model has been justified. In the case of a large class I have students defend their models to other students rather than to me. I circulate and grade them on this process to instill some accountability. I must note thought that I do not do peer to peer model justification until the class has had sufficient practice with the process. Sufficient practice is typically four to five times prior wherein they defend the model to me individually or to the class as a whole in presentation format.

Adaptive Immunity Activity

This activity takes one class period, the learning outcome is an understanding of the limits and functionality of adaptive immunity is. The incorporation of vaccines helps players to conceptualize how vaccines work.

The class is dividing into two teams, the "pathogens" and the "immune system". On the blank side of 50 note cards, using a marker, write two capital letters. Do not repeat any two letters. For example, you may write "TS" or "WK". The letters are arbitrary. Cut all cards in half lengthwise, leaving yourself with 50 bottoms and 50 tops. Give the tops, these are antigens, to the pathogens and the bottoms, the antigen receptors on T cells, to the immune system. Instruct the pathogens to exit the classroom. They will be entering one at a time with a randomly selected top, they are acting as antigen presenting cells. The immune system must find the complementary base for the top in their collection of cards. Once found the pathogen leaves with the top card. The bottom complement is taped to the door frame. If in subsequent pathogen entry the same top was randomly selected the pathogen is stopped at the door, modeling adaptive immunity. This may go on for several rounds, each time the pathogens are selecting random cards from the full deck. An extension is to ask the students how to model vaccinations.

This activity is simply to model how fast the adaptive immune system responds to antigens that have been encountered before. Conversely how long it takes for the immune system to deal with antigens it has not encountered.

Fostering Critical Thinking

Gone is the paradigm that the role of the teacher is to impart knowledge. That the sole role of an instructor is to present content and then test the acquisition of the content. The modern teacher is tasked with motivating students to learn. This shift is not solely occurring pursuant a mandate but a direct result of the students that are in our classrooms. Students are not engaged, more and more they are not motivated to learn. This is not to say that grades are not a motivating factor, but unfortunately they are the only factor for many children. There seems to be a pervasive attitude among students to seek a discrete answer to everything. Motivated solely by what will be on a test.

Teaching a unit that incorporates the principles of engineering as the solution to a problem engages students in critical thinking. To understand how this process applies to the immune system necessitates that the

student understand the immune system. Teaching about current solutions to real problems, such as autoimmune diseases, exposes the student to the need for understanding immunology.

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Student Resources

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Implementing District Standards

S1. D31 Describe the similarities and differences between bacteria and viruses.

S2. D32 Describe how bacterial and viral infectious diseases are transmitted, and explain the roles of sanitation, vaccination and antibiotic medications in the prevention and treatment of infectious diseases.

S3. D42 Describe how structural and behavioral adaptations increase the chances for organisms to survive in their environments.

S4. D45 Explain how technological advances have affected the size and growth rate of human populations throughout history.
