



Surveillance Errors and Disease

Curriculum Unit 15.04.02
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Introduction

Ask a student to name diseases that affect the human body and they can develop a pretty lengthy list of infectious and chronic conditions. Large portions of popular media and news are dedicated to showcasing any number of ailments. Given the widespread coverage of recent epidemics like Ebola and listeria, many students are able to explain how someone can catch a disease. Many students can also start to explain the underlying causes behind some non-communicable diseases like Alzheimer's and diabetes. It is easy to understand how foreign bodies like bacteria, viruses, and parasites can cause problems in our bodies. These particles do not belong and, as such, can cause devastating effects to our tissues. It is the formation of non-communicable diseases—diseases that form when our bodies fail or are unable to maintain themselves—that are more difficult to understand.

However, what is the actual process behind 'getting sick'? Is it something that just happens to us or are there underlying reasons that lead to the development of disease? More importantly, what stops us from getting sick in the first place... or keeps illness at bay until the end stages of our life?

Our bodies are at attention, keeping an eye out for potential trouble makers whether they come from the outside like allergies and bacteria or from within the cells of our bodies like cancer. Several methods of surveillance work together to keep our bodies in homeostasis—to keep our body systems operating and healthy.

But what happens when those surveillance systems fail?

Rationale

I am a high school science teacher at a small magnet school. Our health science and sports medicine magnet theme is aimed at providing students with the background materials necessary to pursue careers in the medical and health fields. Many of our students take multiple biomedical science courses each year depending

on the track they have decided to follow.

One of the courses that I teach is a health science class where students step into the role of various medical professionals to diagnose patients based off of their medical files. Students study the body systems through the lens of a doctor attempting to diagnose and treat their patient. As a result, students need to learn what does and does not constitute “normal” within the human body and how a change can create problems. In a final, year-end project, students are responsible for creating their own medical case based off of a disease that they pick.

Since we are a small school, many of these students have had me for previous classes, including a course with strong microbiology and epidemiology units. As a result, many students associate me with communicable diseases and are comfortable with discussing their transmission and development. Next year, this will not be the case as most students will have me for the first time. Even so, a quick poll of the students in the pre-requisite class confirmed the same idea: students are comfortable with the idea of a transmittable disease.

The course I currently teach puts the focus on non-communicable diseases which students are not comfortable explaining. Many students do not understand how their bodies, which excel at maintaining homeostasis, can be the direct cause of several devastating diseases. I am frequently asked, “How can I catch this?” when the real culprit has been lurking inside them all along. Explaining this idea was a never ending source of frustration for both myself and my students.

This unit was developed with the goal of teaching students how the body is able to keep itself health through regulation mechanisms and the catastrophic results when those checks are out of balance or overwhelmed. A large portion of this unit will be a quick survey of some of the many mechanisms that the human body uses as quality control checkpoints. We will be specifically talking about the surveillance involved with the formation of new DNA, fixing broken DNA in the cell, removing proteins that are misfolded, and the immune system’s ability to recognize self vs. non-self. After, these surveillance mechanisms will be demonstrated using various non-communicable diseases.

At the end of this unit, students will be able to explain how the body’s own system can be responsible for the development of chronic, degenerative diseases. This unit will allow students to move into patient case files and explore with more confidence the cause of the disease. My goal in providing this content is to demonstrate the various causes of non-communicable diseases. I believe that by providing a wide variety of samples, teachers and students will grasp a better understanding of how these various disease mechanisms function.

Curriculum Content

Diseases: Communicable and Chronic

As previously mentioned, students seem to have difficulty differentiating between communicable diseases and diseases that originate from ‘self’ tissues. For this reason, it is important to address the idea of disease itself. The first part of this unit discusses what constitutes disease, a small primer on the immune system, and how disease can originate from a foreign agent or from a fault in our own tissues.

Look up the list of diseases and conditions hosted by the Center of Disease Control and you can find every malady imaginable from chronic kidney disease to Ebola. So what exactly qualifies as a disease? One could argue that a disease is any condition that disrupts the body's normal optimum conditions, homeostasis, outside of physical trauma or injury. However, for the purpose of this paper, a disease or a disorder will refer to any ailment that causes damage or interferes with the body's ability to function resulting in a failure of a part of or the whole body. ¹

It is important for students to understand the distinction between disease and injury. Take, for example, the symptoms of an allergy sufferer in early spring and compare it to a person who is cleaning and stirs up dust. Both might exhibit sneezing, watery eyes, and general tissue irritation, however only the person who suffers allergies has a condition that could be qualified as a disease. Diseases and injuries can both causes long lasting damage to the body, may have similar symptoms, or may share identical treatments. The body responds atypically to the allergen, responding by releasing histamines and setting off the chemical cascades that correspond to an allergy attack. This is a defined change that disrupts the normal physiological conditions of the body. Unlike diseases, injuries usually occur from an outside source of trauma, accident, unexpected event. They can be enduring—a person who is in a car accident may have damage that lasts years—but usually occur because of a single event. ²

This curriculum unit further breaks down diseases into several categories to allow for an easier understanding. While the majority of this paper will delve into chronic conditions that develop from within the body, I will also provide a brief refresher on communicable diseases, particularly those of bacterial and viral origin. For a more in depth review of these concepts, and a survey of current emerging infectious diseases, please reference *Emerging and Reemerging Infectious Diseases* , a curriculum unit written in 2014.

Communicable Diseases

A communicable disease is one that can, if given the opportunity, pass from one unfortunate host to another in an act called transmission. In recent years, news of bacterial and viral infections has taken center stage in the infectious disease world. On any given day, a quick visit to the Office of Infectious Diseases hosted by the Center for Disease Control can quickly provide a running list of current epidemics and outbreaks in the United States and internationally.

Bacterial and viral infections are not quite as simple as common media would have them pictured. Transmissions are often highly specific-- Ebola can only spread through infected fluid like blood and semen, not by air or water-- and the body has a built in surveillance system constantly on the lookout for anything that could qualify as "not self". ³ Regardless of the mode of transmission, bacterial and viral particles cause disease through several common methods.

Once inside the host body, bacteria and viruses both continue their lifecycle by undergoing replication. Bacterial cells replicate by splitting through a process called binary fission. As bacteria grow and replicate, they may directly damage tissues through the release of cytotoxins and other dangerous compounds. For example, *Streptococcus pyogenes*, releases a hyaluronidases and proteases that cause soft tissue inflammation of the throat in a disease known as strep throat. ⁴ In other species, the actual act of destroying the bacteria may be responsible for releasing toxins into the host tissues.

Viruses also use their hosts as a tool for replication. The virus life cycle can go via two routes. The more immediate route involves replication through the lytic cycle where the virus hijacks the host cell's machinery

as a tool for creating many viral particles before lysing (breaking out) or otherwise leaving the host cell. The lysogenic life cycle is similar in that it does eventually result in the lysis of infected cells, the main difference being that prior to this stage the virus acts as a sleeper agent hiding among its host's DNA and slowly replicating every time the host divides.

The lysogenic cycle, while taking longer to complete, can produce many more viral particles for this reason. This particular life cycle may also cause many problems in addition to the viral infection. Many viruses do not have a specific part of the host DNA that they insert themselves into. As a result, a virus may insert their DNA into a part of the DNA that is responsible for maintaining the healthy condition of the cell. In human papilloma virus infections, the virus might insert its DNA into a region that disrupts a gene that codes for proteins responsible for suppressing tumors. ⁵ More information about HPV is found in below when we discuss instances where surveillance is turned off or broken.

Non-Communicable Diseases

A portion of this unit will focus on non-communicable diseases caused by surveillance errors. A non-communicable disease (NCD) is any ailment that is unable to be transmitted from one person to another via direct or indirect contact. Non-communicable diseases progress slowly over the lifespan, as seen in cases like arthritis and chronic pulmonary obstructive disorder (COPD). These diseases often require long term treatment plans to mitigate any symptoms as they appear.

Other NCDs have a rapid onset, and may cause a quick fatality depending on the type of disease. For example, an allergy sufferer may have a sudden "attack" during peak seasons. In this instance, the disease has rapid onset and the person usually recovers in a matter of hours. Some cancers, on the other hand, can present quickly in a patient and cause rapid degeneration and eventual death. According to the WHO, NCDs kill about 38 million people annually with nearly half of those deaths due to cardiovascular diseases. ⁶

There are some connections between communicable and non-communicable diseases. Scientists are discovering more connections between communicable pathogens and what were traditionally believed to be chronic diseases. For example, there are a number of diseases, like cancers and Type 1 Diabetes, which have connections to viruses. As previously mentioned, viruses DNA insertions into the host DNA may turn deactivate genes that are responsible for surveillance. A few examples of autoimmune surveillance errors and their connection to viruses are discussed in the section about what happens when surveillance makes a mistake.

Our Body's Surveillance and Regulation

Before we can start discussing NCDs specifically, it is important to understand how the human body maintains homeostasis. Homeostasis is the body's ability regulate the internal conditions of the body despite change. For example, your body maintains a constant temperature, pH, and O₂ saturation level that is vital to keeping tissues healthy. In addition to the systems that are responsible for maintaining physiological conditions in the body, the body is constantly being sampled to identify problems that are happening inside the body. The second portion of this unit will be dedicated to demonstrating the various ways that the body is able to recognize mistakes in DNA, proteins, and microorganisms.

DNA Replication Self Editing

DNA replication is crucial in the replication of cells. All proteins in the body are derived from the genes found

in the body's cells and each cell contains identical copies of DNA. It is important for DNA to have the ability to self-edit and catch replication errors as these can lead to malformation of important proteins. If the error is not caught, it will be passed along through mitosis to all subsequent generations of daughter cells.

If DNA errors are present, they can cause mutations in the formation of proteins that are essential for maintaining homeostasis. For example, an insertion or a deletion in a gene may cause a frame shift mutation, rendering the protein that it codes for. This sort of mutation is seen in familial hypocholesteremia, where a frameshift mutation alters the structure of the LDL receptor proteins.⁷ Point mutations, where the wrong nucleotide is inserted into the DNA instead of the complimentary nucleotide base, can also be devastating. One type of basal breast cancer is caused by a point mutation in the PIK3CA gene which alters its function. A single error is enough to activate this oncogene.⁸ Using these techniques described below, DNA fidelity is very high, with only one error per every 10^9 bases.⁹ A high fidelity rate in DNA synthesis is important because errors in replication are inherited by daughter cells.

DNA replication has several built in checkpoints. First, DNA base pairs are complementary only to another specific nucleic acid-- adenosine pairing with thymine and cytosine pairing with guanine. As the DNA strand unwinds and unzips for replication, DNA polymerase attaches at the strand at the 5' end at a primer. This enzyme attaches to the old DNA strand joins new amino acids together as it forms the complementary strand. This process is efficient because complementary base pairs have a higher affinity to one another than other nucleic acid residues. As the correct nucleic acid enters the DNA polymerase and binds with the complementary nucleotide, a conformational change occurs within the enzyme, allowing it to move forward on the chain. If an incorrect nucleotide were to enter into the sequence, it is unlikely that the conformational change in the enzyme would occur before the nucleotide is covalently bonded into the chain.^{ix} This process acts as a way to check the complementary DNA strand as it is being formed.

If an incorrect nucleotide is bonded into the forming complementary DNA chain, a secondary check takes place using a proofreading exonuclease. When a non-complementary nucleotide attaches, it disrupts the -OH end of the primer strand, shifting the conformation of the DNA strand and inhibiting the addition of new nucleotides.⁹ Essentially, this ends up dislodging the polymerase which prevents additional nucleotides from being added to the strand. When this happens, the cell takes time to correct the nucleotide mistake. A special molecule called a 3' to 5' exonuclease breaks the covalent bond and removes the incorrect nucleotide. Once this step occur, DNA polymerase is able to continue strand elongation.⁹

If a mistake is overlooked by either of the two processes previously mentioned, a third system is in place called strand directed mismatch repair.¹⁰ This process works by identifying distortions in the sugar-phosphate backbone of DNA caused by non-complementary base pairs. Usually, an incorrectly selected nucleotide will cause the backbone to bow out or to pull in. This irregularity in the width of the double helix can be identified by the cell. Once a distortion has been identified, the backbone is nicked by an enzyme. At the same time, MutS, a protein that travels along the DNA strand checking for errors, binds to the incorrect base pair that is causing the distortion. MutS binds to MutL which causes MutH recruitment.¹⁰ This in turn causes the helix to fold like a hair pin as MutH cuts the backbone. One this occurs, the piece of DNA with the incorrect nucleotide can undergo degradation. After, the gap can be filled in using DNA polymerase III, correcting the error. This process is only able to occur within a very narrow window of time while the newly synthesized strand is unmethylated.¹⁰ At this point, the DNA double helix is considered to be hemi-methylated. After methylation has occurred on the newly formed strand, these control proteins are no longer able to recognize which is the original template.¹⁰

DNA Double Strand Break Repair

There are many things that can cause DNA strands to break, including mechanical stress and ionizing radiation from x-rays. Once a DNA strand is broken, there are repair mechanisms in place to help reassemble damaged strands. It is important that damaged DNA be repaired in order to prevent the loss of the chromosome, recombination that trigger oncogene activation, or creating critical errors that will cause the cell to be marked for destruction. ¹¹ There are two main mechanisms for strand break repair in eukaryotic cells: homologous recombination of DNA strands and non-homologous DNA end joining. ¹¹

In homologous recombination, the damaged strand of DNA will form a bond with a comparable DNA. ¹² Sticky ends of the damaged strand will invade a full strand of DNA looking for homologous sites forming connections called Holliday Junctions. ¹² Once the damaged DNA strands are connected with the template DNA strands at these sites, DNA synthesis can occur. DNA polymerases will use the template strand to fill in the damaged strand, resulting in repaired DNA.

In non-homologous DNA end joining, the protein Ku binds to the break site. At this point, a nuclease is able to attract nuclease attachment. ¹³ These nucleases cut a sticky end overhang in the DNA where polymerases can bind. Once bound, this forms a full complex that the ligase can bind to. At this point, the ligase can rejoin the strands of DNA, and complete the template. ¹³ While the integrity of the DNA is repaired, this method of repair damages the sequence of the original strand which may cause harm later.

Protein Misfolding and Degradation

In addition to checking the DNA of an organism, it is also important to look for errors that are found in the products that the DNA is producing. Proteins can also have errors that reduce their function or cause entirely new problems to occur as a result of how it interacts with a substrate. In order to reduce the amount of non-functioning or mis-functioning proteins, there are several checkpoints that collect these products and dispose of them through degradation.

Proteins are created through the translation process by ribosomes. Ribosomes are responsible for reading the codons of mRNA and constructing proteins. In order to ensure that the proteins being created are able to function correctly, there are multiple forms of control that are used during translation of new proteins. One example of quality control that occurs during translation is the kinetic favorability of anti-codons that match the correct mRNA codon. Non-cognate anticodon pairings, i.e. those that do not match, inhibit GTP hydrolysis and A site entry—two necessary steps to adding an amino acid to a growing peptide chain. ¹⁴

After the initial stringing of the protein's amino acid chain, secondary, tertiary, and even quaternary structures start to form. One of the key quality control points used in the surveillance of proteins is recognition of which proteins are and which are not folded. Folded proteins have a high affinity for a carrier protein that will pick them up and transport them for packaging, leaving unfolded or misfolded proteins where they are tagged by another protein for removal. ¹⁵ In the endoplasmic reticulum, the targeted protein is transported to the Sec61 translocon where it is degraded. ¹⁶

Other protein machinery exists to differentiate between correctly folded proteins and those that must be targeted for and degradation. Chaperone proteins, also known as heat shock proteins, assist with the folding of complex amino acid chains into their tertiary and quaternary forms. When a cell undergoes stress, the products that they make might be damaged. Excessive heat is able to cause proteins to unfold or to fold

incorrectly, denaturing them.¹⁵ One chaperone protein—HSP70— assists proteins with folding and refolding denatured proteins. After HSP70 attaches to a protein that is folding correctly, HSP70 recruits two co-chaperones which in turn, recruits additional proteins like HSP90 that further facilitate folding.¹⁵ If the protein takes too long to refold, HSP70 recruits two other chaperones which ubiquitinate the misfolded protein thereby targeting it for degradation.¹⁵

The Immune System: Self vs. Non-self

In many diseases, especially those involving a foreign agent such as a bacteria or a virus, the ability of the body to recognize which cells belong and which are intruders is crucial in maintaining health. This concept is often tied into immune surveillance, as this is the primary tool for dealing with potential outside threats.

Cells carry special marker proteins embedded in their membranes that allow for communication and identification within the body. The cells of our immune system are able to recognize these specific marker molecules and will leave them alone. When a foreign molecule enters into the environment, the lymphocytes are unable to recognize the epitopes on the surfaces of the invading cell membrane. The presence of these unknown epitopes acts as an antigenic trigger, which can stimulate the immune system into responding.

It is for this reason that blood transfusions are only possible between compatible donor-recipient pairs. Blood cells also carry epitopes on the surface of their membranes: A, B, O and Rhesus polypeptide factors. The erythrocytes in a person carry special sugar markers on their cell surface. These markers, or antigens, have two forms A or B. The presentation of these marks on the surface of the cell is what grants a person A, B, or AB blood type. If a person lacks these markers altogether, then they are type O blood.¹⁷

If A positive blood was introduced into the body of a B negative recipient, the immune system would quickly recognize the antigens related to the A blood phenotype as well as the presence of the Rhesus polypeptide. As such, their body would launch an immune attack on the foreign blood, causing coagulation, hemolysis, and ultimately rejection of the transfused tissue.²⁸

This same principle explains why organ donors must be matched to a recipient before a transplant. The cells of our tissues have special markers that indicate that they are self. These markers are called HLA markers. The specific structure of these proteins is different for every person, depending on the alleles that they possess¹⁸. As T-cells patrol the tissues, they are able to identify cells that are coated in specific HLA markers. If other major histocompatibility complexes are present that do not belong, then the immune system will react.¹⁸ HLA proteins interact with specific receptors on T cells. If these two receptors are able to interact appropriately, then the T cell continues on its way.

HLA proteins also present, or hold onto, proteins from within the cell. This allows T cells to monitor what is going on within the cell.¹⁸ If the protein is normal, then the T cells do not react. However, if a foreign antigen is presented by autosomal HLA cells, then the small differences in the interaction between the two receptors triggers an immune response.¹⁸

In order for organ donation to be successful, doctors identify candidates with similar major histocompatibility complex profiles to their patient.¹⁸ Highly similar profiles are less likely to trigger an immune response from the T cells, forcing rejection of the organ.

Diseases of Surveillance Failure

Degenerative diseases occur through several overarching mechanisms. Errors happen all the time, either spontaneously or through promotion due to an outside factor such as UV radiation or chemicals. Usually, the body is able to catch these errors as they occur and prevent them from piling up, using some of the mechanisms already outlined above. There are several instances where the body's surveillance mechanisms do not work as expected, which can cause errors.

These errors in surveillance can be classified into four major groups. The first example of a surveillance error is when that surveillance system is reduced. Surveillance can also become overwhelmed and, thus, ineffective. Surveillance mechanisms can make mistakes in what it is they are targeting, such as those observed in auto-immune diseases. Finally, surveillance can become overexcited. In the course of my class, students will explore many different NCDs. As such, I have decided to showcase only a few diseases in this introductory unit as examples that highlight and model how these specific errors can cause disease.

It is also important to note that these errors do not always fit neatly into a category. Many times, there are multiple levels of surveillance error at work that lends itself to the formation of a particular disease. As such, some diseases may be mentioned multiple times. Each particular disease must be studied *in situ* to determine the specific mechanisms that may cause it to arise.

Surveillance is Turned off or Broken

Errors are constantly being made in the body, however the various surveillance protocols in place are able to catch and repair a majority of these mistakes before they become an issue. As a person ages, the surveillance mechanisms lose efficiency or are turned off. This process of cell mortality is called senescence. Encoded in the cells that are responsible for maintaining surveillance of our bodies are specialized sections called telomeres. Every time a cell divides, the telomere shortens. Over time, surveillance begins to break down, as do the rest of a person's cells, resulting in aging.¹⁹

This process allows more and more errors to accumulate until eventually the body is no longer removing offending proteins. For example, through-out a person's lifetime the body is constantly making the amyloid proteins that are responsible for the plaques associated with Alzheimer's disease.¹⁹ These proteins, however, are targeted for degradation by surveillance mechanisms and are removed before they can aggregate and cause real damage.

In human papilloma virus (HPV), surveillance is turned off through another method. HPV infects squamous epithelial cells of the cervix where it can cause cervical cancers. HPV-16, the strain that is most representative in cervical cancers—integrates into the host DNA.²⁰ Along with the other genes in the viral genome, it also has two oncogenes which, when translated, destroy the human tumor suppressor gene p53.²⁰

Tumor suppressor genes like p53 are important quality control proteins used to halt cellular division when there are errors in the DNA. In the cell cycle, it is important for DNA to be error free when it is being copied. If there are mistakes in the copying of DNA or if part of the genome is missing or damaged, there can be deleterious effects on the daughter cells.²⁰ P53 causes cell cycle arrest. If the damage is unable to be fixed, p53 will then mark the cell for apoptosis, preventing the error from being passed into the daughter cells.²⁰ When p53 is down-regulated, mutations can accumulate, leading to the formation of cancerous cells.

HPV, and other cancers, can turn off this quality control mechanism either by expressing proteins that cause p53 to be destroyed or by preventing p53 from forming correctly. In HPV, one of the viral genes E6 binds to an ubiquitin ligase which in turn bind to p53.²⁰ This complex is then destroyed by a proteasome complex in the host cell.

Surveillance is Overwhelmed

One example of the surveillance system becoming overwhelmed is with the introduction of advanced glycation end products (AGEs) or glycotoxins. AGEs, can be found in most modern diets if they contain processed food items. These compounds are found in animal-derived products that are higher in fat and protein content. As the foods are cooked, more of these compounds are developed and, eventually consumed. These glycotoxins can also form within the human body through a multi-step process ²¹

AGEs develop when a sugar reacts with a protein. This forms when the glucose binds to a lysine or arginine found in a compound like a lipid, protein, or even DNA. This develops a Schiff base-- a complex that has a carbon-nitrogen double bond. The Schiff bond then forms a secondary compound called an Amadori product which has the ability to form crosslinks with other proteins. ²² This is a slow process that can take months and it is irreversible. These compounds are especially dangerous because they accumulate within the cell and inhibit normal cellular function. Within the tissues of the body, they can cause inflammation.

These compounds are known to cause several different NCDs including diabetic nephropathy ²³ , cardiovascular disease ²⁴ , and the formation of amyloid beta proteins found in Alzheimer's disease ²⁵ . In diabetic nephropathy, AGEs bind to the receptors on the cell surface, limiting the ability of nerve bundles inhibiting their normal function. ²⁶ This may lead to many of the neurological complications of diabetes including loss of vision and painful tingling in the extremities. The link between cardiovascular disease and AGEs involve the ability of AGEs to form stiff cross-linked structures with collagen. In the arteries, AGEs bind to the walls, decreasing their elasticity which can lead to heart failure. ²⁷ In Alzheimer's disease, AGE modifies the amyloid beta seeds, which increases the aggregation of these plaques in the brain. ²⁸

A key way to prevent the formation and possibly break the bonds between AGEs and their linked compounds is through the use of AGE-inhibitors. Currently, ALT-711 has been found to increase elasticity in cardiac tissue, improve the hydration of the epidermis, and potentially prevent secondary diabetes related conditions like renal failure.²⁷ While it is unlikely ALT-711 will completely undo the damage caused by AGEs on the body's tissues, it may restore some of the functionality of affected areas.²⁷

A second series of diseases that deal with the overwhelming of surveillance mechanisms are those dealing with protein misfolding and recruitment. Proteostasis, the combination of the words protein and homeostasis, is responsible for the suppression of protein aggregations or plaques ²⁹ . This series of pathways is responsible for removing proteins that are misfolded. As previously mentioned, one of the pathway is the ER unfolding response that is responsible for tagging misfolded or unfolded proteins for removal and degradation. When these proteins are not removed and enter into the body tissues, they can overwhelm the correct phenotypes, causing disease.

There are many different types of diseases that are related to protein folding mistakes including cystic fibrosis, Huntington's, and the previous disease we covered Alzheimer's. ³⁰ Unlike Alzheimer's, which occurs when the surveillance mechanisms are turned off over time, the proteostasis diseases that follow occur when the network is overwhelmed and is unable to keep up with the removal of misfolded proteins. As these

proteins build up in the tissues, they overwhelm the correctly folded protein and cause disease.

Two very similar examples of proteostasis diseases that overwhelm the body's surveillance mechanisms are Kuru or new variant Creutzfeldt-Jacob's Disease (nvCJD). In both of these diseases, the patient come into contact with a misfolded protein called a prion. A prion is more stable the native protein and yet it is in a shape that rarely occurs by itself. Most native proteins are only weakly stable, probably to allow for functional degradation by the cell.³¹ However, prions are highly resistant to degradation because of the repeating side chains that form beta sheets. This makes it difficult to remove prion proteins from the body. Furthermore, when the normal protein comes into contact with the disease shape, this ends up converting the native protein into more of the disease shape.³¹

In these diseases, a person comes into contact with tissue that has prion proteins—human brain tissue in Kuru or tainted beef in nvCJD-- that contains these prion proteins. These prion proteins migrate to the brain in a currently unknown mechanism where they act as a "seed", recruiting healthy brain proteins to refold into prion protein amyloid plaques.³¹ This process does not happen automatically—it may take years for the formation of these amyloid plaques. However, when it does occur, it is a rapid process which overwhelms the body's ability degrade proteins and is often difficult if not impossible to treat.

Surveillance is Hypersensitive

Allergies are an example of the body's surveillance system becoming overexcited. The immune system, as previously explained, is constantly surveying the internal environment for any harmful particles that do not belong. If a person is exposed to a particular particle, or antigen, over time they may develop a hypersensitivity to it even if that particle is not harmful. Particles that cause hypersensitivity might be exogenous like pollen or dander, or endogenous like the tissues in your cells or a piece of peanut that was eaten.³² Normally, these particles would interact with the body and not trigger any problems with the immune system. In people with allergies, or Type 1 hypersensitivity, contact with a particle that they have become sensitized to triggers a number of reactions.³²

When an allergen enters the body, it is identified by B cells. These B cells begin producing IgE, a type of immunoglobulin that is released to protect against parasites and other foreign agents. IgE will then interact with mast cells. When this happens, mast cells react by releasing histamine. Histamines cause an inflammatory response in tissues, causing the area to swell.³² This response usually happens a few minutes after exposure to the antigen. A few hours after the exposure, cytokines also enter the tissue, which may cause additional swelling.³² Depending on the severity of the hypersensitivity, a person may experience a wide variety of symptoms from itchy, runny eyes to anaphylaxis.

Surveillance Makes a Mistake

As previously discussed, part of our body's natural defense system is the ability to recognize self vs non-self. This step is crucial in the recognition of foreign antigens and removing them before they can cause harm to tissues. The immune system does a decent job at targeting molecules that have foreign antigens and developing strategies for dealing with the same infection should it reappear. However, the immune system can become overzealous in its duty and may actually attack normal, healthy somatic cells due to a case of mistaken identity. This type of reaction is very similar to the reactions shown above in hyperactive surveillance. Just like with allergies, the body mistakes a protein as harmful when it isn't, triggering an immune response. This type of sensitization is classified as Type 2 hypersensitivity or autoimmune cytotoxic events. In autoimmune diseases, the body turns on itself and attempts to damage healthy tissue after

mistaking it as foreign.

Autoimmune diseases form for a variety of reasons. If the immune system is exposed to a bacteria or a virus that presents an antigen, it develops antibodies that are targeted to that specific epitope. After the foreign agent is removed from the body, the memory of that antigen remains, preparing the body to respond should infection by the same agent recur. ³³ The trouble lies with antigens that have epitopes that are very similar to the protein markers embedded in body tissue. In the case of autoimmune diseases, the body is now over-sensitive to these markers and, instead of recognizing them as 'self' tissue and leaving them alone, attack those tissues. This can lead to a number of autoimmune conditions, depending on the particular disease.

One example of this occurs as through a combination of a primary infection with the sexually transmitted infectious agent chlamydia in persons with the presence of genetic factor HLA-B27. ³⁴ *Chlamydia trachomatis* bacteria are passed between an infected individual and their partner during sex. This bacterium can cause burning, itching sensations in the genitals and is often treated using antibiotics.³⁴ The immune system also responds to the infection by producing T cells that interact with infected cells and lymphocytes that respond to the epitopes that are found on the bacteria's surface.³⁴ This infection leads to long term immune memory against the particular antibodies found on chlamydia by the adaptive immune system. CD4+ T cells, a special subset of the immune T cells, circulate through the body looking for chlamydia after the infection has been cleared up as a way to defend the body against further attack.³⁴ Unfortunately, in a disorder known as Reiter's syndrome, these T cells cause a reactive response by these same cells against synovial joints in the body, causing arthritis.³⁴

There is a similar relationship between diabetes and an enterovirus like Coxsackievirus. The exact relationship between viruses and type 1 diabetes is not fully understood and there are still conflicting theories about the exact involvement, however it is believed that the specific CVB4 enterovirus plays a role in activating the immune system. In fact, one experiment was able to use isolated CVB4 from a type 1 diabetic and induce diabetes in mice. ³⁵ It is believed that CVB4 infects the islet cells of the pancreas using receptors that are on the cell's surface. After the infection is cleared it, it is believed that the T cells are still primed and now attack the cells of the pancreas, inhibiting their ability to produce insulin. ³⁵ Much is still unknown about this exact process.

Strategies and Methods for Teaching

The activities and strategies listed here are an example of what I plan to use in my classroom during this unit. Each of these activities can be modified to increase the rigor or to provide more scaffolding for students. In addition to the activities that I have listed below, I will support student learning through the use of jig-saw reading activities, guided lectures, quizzes and tests.

Disease Word Sort

One activity that will be helpful for students is to provide a series of 20 cards with various diseases that they have hypothetically been exposed to, such as Ebola, hypocholesteremia, Alzheimer's, cancer, and the flu. Students can sort these diseases into different categories of their choosing according to the following criteria: there must be more than 2 words in each grouping to qualify and they must be able to explain their rationale

behind the category. The students should then be asked to discuss their different category choices with the class and identify common trends. Did students choose to sort them according to whether they are communicable or not? Did they sort diseases by those that are easy to treat and those that aren't? This activity can lead into a discussion for how different diseases are classified or, as a further extension, how certain diseases can be treated.

Symptoms, Two Different Ways

Symptoms, Two Different Ways is an activity I developed to help students think critically about the differences between diseases and injuries. A secondary objective for this assignment is to illustrate that many diseases may have similar symptoms. In this activity, students will be paired up and provided a list of several symptoms. They will be asked to work with a partner to create two different scenarios for their symptoms—one that illustrates a disease and one that demonstrates an injury. These scenarios will be presented in a patient case history report, where they (the patient) is describing the onset, duration, and severity of their symptoms. Patient histories may also include other pieces of information, including family history. After student groups have created these casefiles, they will exchange folders with a neighboring group and decide which story demonstrates an injury and which case file represents a disease.

This activity can also be expanded in several ways, depending on the ability levels of the students and the depth with which this information is covered. One modification to this activity is to have students go a step further with their identification. If they have decided that the patient is demonstrating a disease and not an injury, based on the patient casefile history, they should attempt a diagnosis. After diagnosis, students can then take it one step further and identify the type of disease it is: communicable or non-communicable.

Model Building

In order to help my students understand the complex interactions between molecules, I plan on using modeling. There are a few types of modeling that I would like to use-- physical models and virtual models. One model activity that I plan to use was created by Brian White at University of Massachusetts to demonstrate protein folding. I have modified this activity below for a high school class, but the full resource with activity documents is listed under Teacher Resources.

Students will be given about 3 feet of 18 gauge armature wire and asked to create a 6 amino acid chain.³⁶ Students will be asked to fold side chains into their model by twisting the wire. Hydrophobic side chains, those that do not like to be surrounded by water, are large loops that can fit 2 fingers while hydrophilic side chains can be represented by 4 twists (positive charge) or 2 twists (negative charge).³⁶ Students will be asked to make at least one of each in their chain.

Students will then be asked to 'fold their protein', keeping in mind the particular nature of their protein. After students have folded their own individual chains and draw or photograph the shape, I will have them denature, or stretch out the backbone of their model. They will exchange their chain with a partner who will then see if their folding is similar to the initial one created by the student. Finally, students can link their protein together with a partner's by twisting the wire at the ends together to make one long strand.³⁶ Together with their partner, they will be asked to refold their protein and see if the overall shape changes. As an end result, each group will work together to answer several key questions including a discussion of how side chains affect the shape of a folded protein.

Demonstrating Surveillance Errors

In class, we will be examining how surveillance is turned off in old age. For this demonstration, I will make a large string spider web in the back of the room. Four students will be provided with scissors and instructed to cut the strings in the web. The rest of the class will be asked to tie the strings back together as the cuts are being made. Make a string network half of the class is cutting things half of them are tying them together all the time. At first, the “surveillance” and repair team will be able to keep up with the damage being done. However, as time goes by, I will tap students to sit down. . Soon the “surveillance and repair” system becomes overwhelmed and cannot keep up with the amount of “damage” accumulating in the system causing system failure. This activity is analogous to the turning off surveillance of old age.

This same model can also be altered to demonstrate an overwhelming of surveillance. In this case, there are 5 students who are asked to serve as the surveillance and repair system of the body. One student acts as “damage” and cuts the strings. As in the previous model, the surveillance team is able to prevent damage from being done to the overall system. After a minute or so of this, add a large number (no more than 14) of students to the one already acting as act as damage to the system. This will result in an overburdening of the surveillance system who, after time, will not be able to keep up with the damage.

Discussing Disease

For a final project, students will be responsible for creating a presentation about how an error in surveillance is responsible for a specific disease. In order to facilitate students with this project, I will create a list of diseases that fit neatly into one of the four categories. Each group of four will choose one of the diseases from the list and they will need to explain which surveillance error it fits into and why.

First, students will describe the symptoms and epidemiology of the disease, including any common demographics where it can be found. After describing the disease itself, each group will look deeper and discuss the specific mechanism that causes the disease. Once they have described this mechanism, they will need to provide evidence that supports this disease as an example of one of the four surveillance errors.

This assignment allows me to evaluate students in three areas—two pedagogical and one content knowledge, which I have already described. One of the pedagogical skills that I emphasize in my classes are verbal and non-verbal speaking skills. As each group presents, I do not grade them on their written work during the presentation—that comes after when I look through it after class. Instead, I watch the body language and listen to how each student speaks and grade them based on a verbal-nonverbal rubric. Some of the skills that I focus on are speaking out towards the audience instead of reading, speaking loudly, and using good body language.

The second pedagogical area that I will be focusing is argumentation. In their presentation, students are asked to justify their selection for the type of surveillance mechanism and support their reasoning using evidence from the method behind the disease.

Resources for Teachers

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Implementing Standards

This unit can be used to meet any number of standards from both the common core and from Next Generation Science Standards.

Next Generation Science Standards

HS-LS1-1. Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.

HS-LS1-3. Plan and conduct an investigation to provide evidence that feedback mechanisms maintain homeostasis.

HS-LS3-2. Make and defend a claim based on evidence that inheritable genetic variations may result from: (1) new genetic combinations through meiosis, (2) viable errors occurring during replication, and/or (3) mutations caused by environmental factors.

Common Core State Standards

ELA-Literacy.RST.9-10.1: Cite specific textual evidence to support analysis of science and technical texts, attending to the precise details of explanations or descriptions

ELA-Literacy.RST.9-10.2: Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept provide and accurate summary of text

ELA-Literacy.RST.9-10.3: Follow precisely a complex multistep procedure when carrying out experiments, taking measurements, or performing technical tasks, attending to special cases or exceptions defined in the text

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