17th Annual
Science Symposium
Volume I
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Paradise Valley College
Foreword

The 17th Annual Science Symposium was held on May 12, 2011. Students enrolled in my Organic Chemistry classes and Dr. Casey Durandet's Physics classes from Paradise Valley Community College (PVCC) participated in the event. Each contributor was responsible for selecting and researching their topic and preparing a paper. A few orally presented their project to their peers. This booklet contains each of those papers.

As an instructor and faculty advisor for this symposium, I want to thank and congratulate each participant for their effort, courage and dedication. By participating, these individuals perpetuate this event annually. I am both proud and honored to present the work of these individuals.

William L. "Hank" Mancini, PhD
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Tay-Sachs Disease:

The search for a cure

By: Ali Azar
Organic Chemistry 236
Dr. Hank Mancini
Paradise Valley Community College
April 21, 2011
Abstract

Tay-Sachs is an inherited autosomal disease in a recessive pattern, affecting primarily people with Ashkenazi Jewish heritage. The disease occurs when excessive amounts of fatty acid derivatives named gangliosides accumulate in the brain. This causes an unrelenting deterioration of the mental and physical abilities in patients beginning around six months of age, usually resulting in death by the age of four. The primary cause of the disease is genetic mutation of the Hex-A gene on chromosome 15. Currently, preventative measures such as screening and education are the primary methods of minimizing the impact of this tragic disease.

Background

Tay-Sachs disease is an inherited neurological disorder in which there is progressive destruction of nerve cells in the brain and spinal cord. It can appear in three forms: Classical Infantile, Juvenile, and Late Onset, which is also known as Chronic Tay-Sachs. The Classical Infantile is the most common and severe form. For those who are affected by Tay-Sachs, the enzyme hexosaminidase A is either missing or has very decreased functioning. This causes an accumulation of a lipid, or fatty substance, to deposit in the nervous system. Tragically, there is no treatment or cure for Tay-Sachs, and those with the Classical Infantile form suffer severe disability and death by age four.

The disease was named ‘Tay-Sachs’ because of two individuals that made large contributions in its discovery. Warren Tay was a British ophthalmologist who noticed a cherry-red spot (one of the first symptoms) on the retina of an affected individual in 1881. Several years later, Bernard Sachs, a New York neurologist, began studying numerous cases of the disease. By doing this, he provided the first description of the cellular changes that occur and identified that the disorder seemed to be familial in nature, and in 1896, he named the condition “Amaurotic Family Idiocy”. He also noticed that a large majority of these cases involved individuals of Eastern European Jewish origin. Sachs developed many theories to explain the disorder, including breastmilk, which was quickly discredited as many of his patients had not been nursed by their own mothers. Soon thereafter, the disease was re-named “Tay-Sachs”, giving credit to the observations and ideas of both Tay and Sachs that laid the foundation for further research. It was not until the late 1960s, with the acceptance of Mendelian genetics, that an understanding began to form for this disease.

Historically, the discovery also led to an immense amount of intolerance and racism against Eastern European Jews. When Sachs noticed that a large majority of his cases involved what he referred to as “Hebrews” primarily from Russia, he influenced a generalization that the disease was strictly “Jewish”. Though the disease does primarily affect this population, and it was not his intention (as he himself was Jewish), at the time the lack of understanding developed into extreme prejudice. Assumptions quickly surfaced that Jews were biologically inferior and resulted in harsh discrimination. Many Jews, attempting to escape the extreme poverty of their native countries in the early 20th century, were not welcomed in their attempts to immigrate to the United States. As Nancy Stepan explains, “fear was growing that degeneration within civilized peoples threatened civilization itself”. 
Pathophysiology

The enzyme Hexosaminidase A (Hex-A) is vital to proper neurological functioning. If one has little to none of this important enzyme, a fatty substance (lipid) called GM2 ganglioside will be accumulated in nerve cells (especially in the brain) at abnormally high levels. For an unaffected individual, a normal amount of Hex-A continuously breaks down gangliosides, keeping an appropriate balance in the body. Tay-Sachs is a lysosomal storage disease because the Hex-A enzyme resides in lysosomes, which function to break down toxins and be the recycling centers of the cell. High accumulation of GM2 gangliosides progressively damages cells by blocking other cell processes. The continuation of this process eventually leads to the cell being killed and destroyed. Serious damage can be caused to the nervous system by the buildup of neurons with GM2 ganglioside present. The result can be observed in the symptoms of individuals suffering from Tay-Sachs disease. The accumulation of GM2 gangliosides in neurons is so severe that the brain mass of Tay-Sachs individuals living for more than one year can display an increase in weight by more than 50%.

Chromosome number 15 carries the Tay-Sachs gene, also called the hexosaminidase A (Hex-A) gene. Specifically, the Hex-A gene is located on chromosome 15’s long arm, between the positions of 23 and 24. The Hex-A gene directs cells to make the alpha subunit part of the enzyme hexosaminidase A. Eventually, the alpha subunit comes together with a beta subunit which has been made by a beta-polypeptide gene, also known as hexosaminidase (Hex-B) gene. When the alpha and beta subunits come together, a functioning enzyme is formed.
Tay-Sachs disease is a recessive disorder, requiring two defective genes: one from the mother, and one from the father; each carriers of the gene. A carrier is an individual who has one defective gene and one normal gene. If a carrier and a non-carrier have children, their children will not have Tay-Sachs. However, it is highly probable that 50% of their children will end up being carriers of the gene. For couples who are each carriers, there is a 1 in 4 chance of having a child with Tay-Sachs. According to the World Health Organization, in the United States 1 in every 27 people with Ashkenazi Jewish heritage of Eastern European origin are carriers. The same risk (1 in 27) exists for North Americans who are French-Canadian or of the Cajun community in Louisiana. Irish Americans also have a higher risk; about 1 in 50 are carriers. The rest of the population, including Jews of Sephardic origin, and the non-Jewish population, the carrier rate is about 1 in 250 people.

Classical Infantile Tay-Sachs is the most common form of the disease. Individuals have two null alleles; meaning hexosaminidase-A enzyme activity is little to none. Until about six months of age, babies with this disease will seem to develop normally. One of the first signs is that the babies will stop interacting with others and develop a staring gaze. They will become abnormally startled by normal levels of noise. Within the first year, peripheral vision will become lost, eventually leading to complete blindness. This is always associated with a retinal “cherry-red spot” found in the eye(s), shown in figure 4 to the left. Affected children will also have abnormally large heads. Their motor skills will either plateau or start to regress between the 8th and 10th months of age. They will lose the ability to crawl, turn over, sit, or reach out. This is due to their muscles becoming very weak and floppy (muscle atrophy) and increasing ataxia (loss of

Fig. 3 Inheritance Pattern; Autosomal Recessive Inheritance pattern of Tay-Sachs Disease.

Fig. 4 Cherry-red spot, located on the retina, is associated with vision loss.
coordination). Complete loss of voluntary movement occurs in the second year of life. Between ages one and two, children suffer recurrent seizures and diminishing mental function. At the end of their second year, they will suffer worse seizures, will be unable to swallow and have difficulty breathing. All of these symptoms lead to them being mentally retarded, paralyzed, and in a non-responsive, vegetative state. Death normally occurs between ages two and four.\textsuperscript{1,5,8}

Fig. 5 Cerebrum; Tay-Sachs Disease Histology.\textsuperscript{12}  
Fig. 6 Spinal Cord; Tay-Sachs Histology.\textsuperscript{13}

The Juvenile and Chronic forms of Tay-Sachs are characterized by an individual usually having compound heterozygotes; having inherited a null Hex-A allele as well as an allele that has low Hex-A activity. Those with these forms of the disease have very low to moderately low levels of Hex-A. Higher levels of Hex-A will result in slower onset of symptoms and disease progression. Juvenile-onset normally begins between ages two and five, resulting in very low levels of Hex-A. The symptoms of these children resemble those of the Classical Infantile form. A cherry-red spot may not be present, but loss of vision does eventually occur. Even though disease progression is slower, death usually occurs by late adolescence or in the early 20’s. If symptoms start after age 5, this is due to slightly higher levels of Hex-A, resulting in milder symptoms and slower disease progression. Mental abilities, hearing, and vision may remain fairly normal. Unfortunately, individuals will most likely continue suffer from ataxia, dysarthria (slurred speech), muscle atrophy, cramps, and tremors. Those with Late-Onset, or Chronic Tay-Sachs, will likely have moderate amounts of the Hex-A enzyme. Symptoms will present later, usually in late adolescence, and may include spinocerebellar degeneration, motor neuron disease, psychiatric abnormalities, and progressive dystonia (uncontrollable muscle contractions, causing twisting and abnormal postures). Normally, vision is not affected. Within each form of the disease, severity will range, and each individual experience may be different.\textsuperscript{1,8}

**Diagnosis and Prevention**

For those with Classic Infantile Tay-Sachs, normally the first, unofficial form of diagnosis comes from examining the eyes for the characteristic cherry-red spot, located in the retinal area. Diagnosis for these babies, as well as for those with the Juvenile and Chronic forms,
can be done through measuring the amount of hexosaminidase A, either by testing blood serum, white blood cells, or in a skin fibroblast.⁹

Tay-Sachs carrier testing is available, and encouraged, for individuals that come from high-risk backgrounds. In addition to the populations of high-risk previously mentioned, there is some data that also suggests elevated risks for those with Pennsylvania Dutch background, as well as those from the British Isles and of Italian decent. Due to Tay-Sachs being such a tragic disease, individuals should be tested before they consider conceiving. It is also recommended that individuals of high-risk backgrounds be tested even if they don’t plan on conceiving or are beyond childbearing years. Their carrier status is still very important in relation to their close relatives, such as siblings, cousins, aunts, uncles, and children, who must be notified if they are in fact a carrier, in order to be tested also. The same goes for families with a child who is already affected, even if they aren’t of a high-risk background. Close relatives to the parents of this child may potentially be carriers as well.¹¹

Pre-natal testing can be done for those who may have a baby at risk. There are two procedures that can be used: Amniocentesis and Chorionic Villus Sampling (CVS). Amniocentesis can be performed between the 15th through 20th weeks of pregnancy. During this procedure, a long needle is inserted into the mother’s abdomen, and a sample of the fluid surrounding the unborn baby is taken. Chorionic Villus Sampling can be done between the 10th and 12th weeks of pregnancy.⁹ This is currently more commonly used than Amniocentesis because it can be done earlier. It is ideal because it can allow parents more time to prepare, or for some, to seek an earlier elective abortion. In this procedure, chorionic villus cells are obtained from the placenta. These cells contain the same genetic material as the baby, and collecting a sample may be obtained by one of two methods. One method involves inserting a thin, flexible catheter tube through the vagina and cervix, up to the placenta. The other method can be done by using a long, thin needle (similar to the one used in Amniocentesis) through the mother’s abdomen and into the placenta. In both Chorionic Villus Sampling and Amniocentesis, an ultrasound must be used in order to guide the catheter or needle to the correct location.¹⁵

Another effective preventative method is through mate selection. Individuals at risk of passing along the Tay-Sachs gene can be anonymously screened through special programs offered through local hospitals and Jewish organizations. Through these programs, prospective
couples who are likely to conceive a child with Tay-Sachs or another genetic disorder can avoid marriage. This type of anonymous testing is useful in that it eliminates the stigma of carriehship, while decreasing the rate of homozygosity in this population.16

Other Screening methods such as Preimplantation Genetic Diagnosis (PGD) can also be a useful tool in preventing the occurrence of Tay-Sachs. In the past, PGD was primarily used to prevent diseases such as Sickle Cell Anemia, Huntington’s Disease, Beta-Thalassemia as well as Cystic Fibrosis. More recently, this same process has been used to also screen for Tay-Sachs disease. The process involves the in-vitro fertilization of the mother’s egg, and testing the embryo prior to implantation. The embryo is then screened and only healthy specimens are selected for transfer into the mother’s womb.17

Management

Currently, there is no cure for Tay-Sachs disease. The goal is to try and make the patient comfortable. Respiratory care is important for those with the disease because mucus frequently will accumulate in their lungs. This creates a high risk for development of respiratory infections leading to breathing problems. One way to reduce this mucus is a method called chest physiotherapy, which can be taught to families to administer to the child at home. The decreased ability to properly swallow food and liquids may lead to aspiration (the food or drink ends up in the lungs). This can also cause respiratory problems. In order to combat this, assistive feeding devices may be needed. A feeding tube may be inserted through the nose into the stomach, or surgically placed through the abdomen into the stomach (a more permanent route). Medications to help with pain, control muscle spasms, and to reduce seizures are normally prescribed. Affected individuals may also receive physical therapy, in which someone physically moves the affected body parts to help keep joints flexible, and allow as much range of motion as possible. It may also help to delay loss of muscle function and pain from muscle contractions. Families with children who have Tay-Sachs disease are especially in need of support resources, information, and education.18

Research Trends

Research exploring Tay-Sachs therapy approaches is currently being investigated in laboratories. The medication Zavesca (miglustat) was developed to treat adults with mild to moderate Type 1 Gaucher disease. As a substrate reduction drug, it has shown promise in slowing the disease’s progression and lowering the accumulation of lipids in the central nervous system.

Providing the missing Hex-A through enzyme replacement therapy has been explored but has come up against a significant obstacle. The brain cells affected by the disease are protected by the blood-brain barrier, which blocks the replacement Hex-A enzyme from traveling to the brain through blood as they are too big in size.

Using stem cells found the umbilical cord blood has been investigated in young children, but there isn’t enough information about how to specifically reverse or slow the damage caused
to the nervous system. Research is also being done in the fields of gene therapy and pharmacological chaperone therapy.\textsuperscript{11}

Fig. 8 Zavesca (Miglustat) Molecular Structure.\textsuperscript{19}

Fig. 9 Macrophage Cell; Zavesca has shown promise in controlling Tay-Sachs disease symptoms.\textsuperscript{26}

The idea behind gene therapy is to augment the mutated gene by introducing a functional gene, either as free DNA, in a lipid coat, or as a viral vector (a modified virus that is harmless carries the missing enzyme to the brain). Pharmacological chaperone therapy is very recent, and involves having a chaperone molecule bind to those with defected enzymes that are misfolded due to their mutation. The chaperone molecule would then help the enzyme fold into its correct, three-dimensional shape. The idea behind this is to help increase functional enzymes to be distributed in the lysosomes.

**Conclusion**

The diagnosis of a baby with Tay-Sachs is a devastating experience for affected families, knowing that there is no cure, and that their situation will worsen until they lose their baby. For the affected person, the situation is even more desperate and heart-breaking. The pain resulting from the diseases can be at times simply unbearable. Prevention is the key to minimizing the frequency of these tragedies. Education about Tay-Sachs for every population, especially those with elevated risks, is the first step in prevention. Arming the population at risk with knowledge about risk factors and screening methods will hopefully result in more responsible action. This can include promoting preventative measures such as getting tested for having the carrier gene. Education will also help to create a concerned interest in others to help find and fund possible treatments and cures. Hopefully someday, we will be able to say that Tay-Sachs is a disease of the past.


6. Ganglioside Mechanism, Fig.1 [Internet]. Davidson (NC): Davidson College; [cited 2011 Apr 2]. Available from: http://www.bio.davidson.edu/Courses/Molbio/MolStudents/spring2003/Holmberg/HEXA.html


10. Inheritance Pattern, Fig.3 [Internet]. Provo (UT): Dr. Edward Labanca; [cited 2011 Apr 2]. Available from: http://geneticsf.labanca.net/?attachment_id=758

11. Cherry-red Spot, Fig.4 [Internet]. Columbus (OH): The McGraw-Hill Companies; [cited 2011 Apr 11]. Available from: http://accessmedicine.net/search/searchAMResultImg.aspx?searchStr=biers+spots&searchType=2&fullTextStr=biers+spots&resourceID=4&narrowing=yes


20. Macrophage Cell, Fig.9 [Internet]. San Francisco (CA): Actelion Pharmaceuticals US, Inc. [cited 2011 Apr 11]. Available from: http://65.61.169.141/P_SRT.html
Tsunami: An Elaborate Catastrophe

By Caress G. Bernardo

November, 29 2010

Physics 111

Section MW66070

Dr. Casey Durandet
Abstract

The world has been the stage of a plethora of natural phenomena such as earthquakes, volcanic eruptions, tornados, and tsunami. The fundamentals of physics have been related to these phenomena since the dawn of time. This paper will address the physics behind tsunami waves and how they are generated throughout our world. This will include the fundamentals of physics such as kinetic energy, potential energy, wave speed, wave length, compression waves, Newton's laws of motion, and many other elements of physics. This essay will elucidate on the documentation, history, characteristics, and how tsunami waves form; along with the actions as well as advancements we humans have done to predict tsunami in order to save lives and prevent catastrophe.

Introduction

Living in the Philippines, which is composed of islands in Southeast Asia, I have heard of tsunami that have occurred in my country and other countries as well. The amount of destructive force generated by a tsunami is emphasized by a lot of people in my country, but I'm sure it has been in other countries as well. After reading and doing research pertaining to tsunami, it shed a lot of insight on to how they form and what are the elements that work behind the scenes that make them possible. The word tsunami comes from the "Japanese word represented by two characters: 'tsu' and 'nami'. The character 'tsu' means harbor, while the character 'nami' means wave" (4). Just as what the English translation implies, a tsunami is a series of waves. These series of waves form after being "caused by large-scale disturbances of the ocean" such as earthquakes, landslides, volcanic eruptions, explosions, and meteorites which adequately form "ocean waves with very long wavelengths" depending on the disturbance (15). One can wonder if how much force is generated by a tsunami or how exactly does it gain acceleration and how do these tsunami react when approaching land? As physicists, we can address these questions through physics and by knowing what its components such as force, acceleration, amplitude, wave motion, and Sir Isaac Newton's laws of motion have to do with it, we gain elaboration on the phenomenon we call the tsunami.

History of the Tsunami

Tsunami have occurred throughout history and have actually been mentioned in ancient history. In fact, in 426 B.C., the Greek historian Thucydides inquired in his book History of the Peloponnesian War about the causes of tsunami, and was the first to argue that ocean earthquakes must be the cause. Thucydides wrote "the earthquake, where it was very great, did there send off the sea; and the sea returning on a sudden, caused the water to come on with greater violence. And it seemed unto me that without an earthquake such an accident could never happen" (5, 32). This excerpt illustrates the catastrophic impact that tsunami have in our history. Furthermore, in 1912, a scientist named Thomas A. Jaggar founded the Hawaiian Volcano Observatory (HVO) and acted as its director until 1940. In 1923, he first witnessed the relationship between earthquakes and tsunami. After receiving data via seismograph that an earthquake has occurred, Jaggar immediately calculated the quake's point of origin, which was 2,500 miles away under the ocean. Seven hours later, large waves started to hit the Hilo Bay of Hawaii after the earthquake occurred 2,500 miles away in the Aleutians. Because of Jaggar's findings, a meteorologist named R.H. Finch spoke at a scientific meeting in Sydney the same
year pertaining to the relationship of seismic (earthquake) waves to tsunami waves, seismic waves being able to travel faster from the earthquake’s point of origin (25). These turn of events led to further investigation on the mechanism and accurate prediction of tsunami. The Japanese term tsunami or harbor wave was adopted to classify this phenomenon in 1963 by an international scientific conference and has been used ever since. Tsunami have been mistaken as wind generated waves or tidal waves, which are not of relation to the phenomena. Tsunami do not submit to lunar, solar, and planetary gravitational influences like normal ocean waves, but are formed due to a displacement of water caused by a disturbance (4). Due to tsunami having the ability to create much havoc such as the tsunami wave that hit Istanbul, Papua New Guinea on July 17th of 1988, eradicated three villages and unfortunately killed 2,100 people who were near the shore at the time. Due to that calamity, coastal engineers from the University of California (USC), along with a team of tsunami specialists such as scientists, geologists, a seismologist, computer modelers, and hydraulic engineers went to the site of the tsunami in order to dig up some understanding pertaining to disaster. The use of computer models and hydraulics has been a new field of methodology when studying tsunami at the time. These methods are used in order to map out tsunami activity and early-warning systems in order to prevent unwanted casualties since earthquakes are phenomenon that cannot be predicted (28). Scientists and researchers use the aid of historic tsunami records and numerical models in order to gain insight to when and where tsunami might occur more frequently such as the estimation that major Pacific wide tsunami only occur every 10 to 12 years (4).

**Disturbances that Form Tsunami**

The main and most common disturbance that generates a tsunami is an earthquake, more specifically, submarine (underwater) earthquakes. Earthquakes are implosions that occur beneath the earth’s surface and therefore causes shockwaves to travel from the point where it first occurred, which is the focus point or hypocenter. The shockwaves that originate from this point are called seismic waves and would eventually reach the point above the hypocenter, which is the epicenter. Hypocenters are distinguished between shallow (less than 70km below the surface), intermediate (between 70 and 300km), and deep (300km and below). Earthquakes are measured through the Mercalli Intensity scale gauges from I (detectable via seismograph) through XII, which is characterized as catastrophic. Seismologists measure the actual magnitude by referring to the Richter scale (1). The Richter scale was invented by an American seismologist named Charles F. Richter in 1935. It is used to measure the magnitude of seismic waves from an earthquake occurring anywhere in the world. Earthquakes with a magnitude of 7 or more are considered severe, which can destroy structures and generate major tsunami. Estimating the magnitude and the distance from the seismograph to the origin of an earthquake is done by doing calculations on the seismic waves recorded by a seismograph. Seismic waves travel like ripples that resonate after a pebble is dropped on still water. The Mercalli scale on the other hand, was developed by an Italian seismologist named Giuseppe Mercalli and is often used to measure the severity of an earthquake pertaining to how much it affects a population within an area (21). The comparison of intensities or seismic data in different areas through the Mercalli scale enables seismologists to locate the earthquake’s point of origin as well (1). Tsunami are formed due to tectonic earthquakes that occur under the ocean and are associated with the movement of the earth’s crust. The water above a fracture occurring under the ocean will be displaced due to the elevation or subduction of tectonic plates. Subduction is the term used to describe the event when
an oceanic plate subsides or slips under a continental plate. Accordingly, subduction will produce an earthquake and are classified as subduction earthquakes, which are the common cause of tsunami (6). After an interview with Dr. Harry Birkmann, a professor of geology, I have noted from him that the theory pertaining to plate tectonics is that it is the continuous movement of the earth’s lithosphere or crust composed of tectonic plates due to the magma beneath. This movement enables these tectonic plates to converge at a fault line, a crack in the earth’s crust due to displacement. This convergence will then generate an earthquake depending on what kind of fault occurs such as subduction, normal, and reverse faults (32). Earthquakes with vertical displacements are the most effective in generating tsunami due to the sudden upward disturbance done by two converging plates, rather than horizontal displacements which also generate a vertical displacement depending on the sloping of the ocean floor (30). Furthermore, the displacement of water above a generated earthquake will then create waves on the surface, but due to gravity, the mass of displaced water is forced back into its equilibrium position (6). Tsunami are not only exclusive to earthquakes, but by any disturbance that causes a huge displacement of water. A tsunami is generated when the surrounding water around a disturbance is agitated. With this in mind, one can find that submarine volcanoes and as well as landslides can generate a tsunami. An eruption of a submarine volcano will cause water to be forced upwards and thus creates a disturbance in the water’s equilibrium. On the other hand, debris from a landslide that falls from above the surface of the water will cause a significant disturbance as the debris hit the water. This is similar to the rare meteor impacts when a large cosmic body hits the water from above, but these kinds of disturbances only generates tsunami that only lasts for a short duration and often does not reach coastlines far from the disturbance’s point of origin, unlike submarine earthquakes, which can create tsunami waves that can reach distant shores and create havoc elsewhere (7).

Characteristics of a Tsunami

The characteristics of a tsunami begin with the fact that it is commonly caused by submarine earthquake that causes the seafloor to vertically deform and displaces the equilibrium of the water. The displacement of a large mass of water creates a depression at the surface of the water. Water, as a liquid, will rush to fill that depression and in turn, will spread out at right angles to create an oscillatory wave motion, a motion which happens repetitively from the origin of the disturbance. Furthermore, tsunami waves with large wavelengths are generated and move away from the disturbance (2). The term wavelength is simply the distance between successive waves, while wave period is the time measured in seconds between waves (23, 32). The wave frequency is the measure when a number of waves passing a given point during a second and is measured in hertz (24). Tsunami waves can have wavelengths that stretch for hundreds of kilometers and wave periods with durations from 20 minutes to several hours. The speed of a tsunami depends on the depth of the water where a wave travels (2). As I worked with Dr. Birkmann on the tsunami wave tank, he mentioned that the water rushes back and then move forward when a sudden vertical force exerts from below to the surface as the sea floor deforms as free floating sediments of the ocean floor are carried away by the wave (32).
When a Tsunami Approaches and Hits Land

When a tsunami that travels hundreds of mile per hour approaches the shore, its wave speed will decrease due to the increase of height of the sea floor as the wave approaches the shoreline. Its wavelength will then be compressed as the large volume of stored energy in the wavelength is shifted to wave height, transforming a 3-foot wave tsunami wave to a colossal wave with a height of several feet and meters (see Figure A). The phenomenon when a tsunami wave pass through shallower water and lose wave speed, but gains wave height is called the shoaling effect. Once a wave reaches a point over the average sea-level, it is called the run-up. The average run-up for a tsunami wave exceeds 10 meters (30 feet) and may even reach over 40 meters (130 feet) in a few cases. Shallow water forces the wave height of a tsunami to increase and inflict destruction when it curls as it hits the shore. Coastlines that are more vulnerable to tsunami are gulfs, bay, estuaries which are funnel-shape entrances that amplify waves into a gigantic wall of water called a bore that weighs billions of tons and devastates shores with sheer destructive power. Speaking of destructive power, a tsunami is not only just one wave, but a series of waves called a tsunami wave train which can lead to further damage to structures and jeopardize people who thought the tsunami has ended and have returned to their homes, not knowing that another wave may hit.

Figure A

This increase of wave height can be calculated by the given formula below:

\[ \frac{h_v}{h_d} = \left( \frac{H_d}{H_a} \right)^{1/4} \]

Wave heights in shallow water are represented by \( h_v \), while \( h_d \) represents the wave height in deep water. \( H_t \) and \( H_d \) represents the depths of shallow and deep water within a body of water. If applied, a 1 meter tsunami wave travelling in waters 4,000 meters deeps would have a wave height of 4 to 5 meters in water which are 4 to 5 meters deep. Even though wave lose energy like normal waves, even with the loss of energy, tsunami are able devastate shores with colossal waves. A tsunami may arrive at the shore with either its crest or trough as it may appear as a rapid rising tide. The run up of a tsunami is measured by a wave’s vertical height above sea level and would reach a several meters.

Calculating the Speed of a Tsunami
Tsunami are characterized as shallow-water waves because their wave lengths are much longer compared to the depth of the ocean where it travels. Tsunami wavelengths can reach up to 10 to 500km and wave periods of up to an hour.

All Shallow-water waves move at a speed \( c \), which is dependent upon the depth of the water the waves travels on and is determined by the formula:

\[
c = \sqrt{gH}
\]

The acceleration due to gravity is represented by \( g = 9.8\text{m/s}^2 \) and \( H \) as the depth of the water the wave travels in.

The typical water depth is of the ocean is around 4000 meters, so a tsunami will travel at around 200 m/s [200m/s \( \times 60\times 60/1,000 \), or 720 km/h (450 mph) [divided by 1.609 to convert to miles per hour]. As seen on the table below, other parts of the ocean such as the Mariana Trench will enable tsunami waves to travel up to 1,000 or more kilometers per hour (15, 13).

Table 2: Ocean depth information with average speed of tsunami wave

<table>
<thead>
<tr>
<th>Ocean</th>
<th>Average depth (m)</th>
<th>Deepest depth (m)</th>
<th>Speed of tsunami waves, ( v ) (km/h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pacific Ocean</td>
<td>4,637</td>
<td>Mariana Trench = 11,033</td>
<td>766.8 &lt; ( v ) &lt; 1184.4</td>
</tr>
<tr>
<td>Atlantic Ocean</td>
<td>3,926</td>
<td>Puerto Rico Trench</td>
<td>705.6 &lt; ( v ) &lt; 1044.0</td>
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<td></td>
<td></td>
<td>8,605</td>
<td></td>
</tr>
<tr>
<td>Indian Ocean</td>
<td>3,963</td>
<td>Java Trench = 7,725</td>
<td>709.2 &lt; ( v ) &lt; 900.0</td>
</tr>
<tr>
<td>Southern Ocean</td>
<td>4,000 to 5,000</td>
<td>The southern end of the Southern Sandwich Trench = 7,235</td>
<td>712.8 &lt; ( v ) &lt; 957.6</td>
</tr>
<tr>
<td>Arctic Ocean</td>
<td>1,205</td>
<td>Eurasia Basin = 5,450</td>
<td>388.8 &lt; ( v ) &lt; 831.6</td>
</tr>
</tbody>
</table>

Table 1\(^{(13)}\)

The Pacific Ocean has waters that are typically 3 miles or more in depth and can cause tsunami waves to travel at 435 mph (700km/h) or more, but with wave heights of only a few feet or meters. This is why ships out in the ocean are not affected by the passing of a tsunami wave (2). The amplitude generated by submarine earthquakes is determined by the amount of sea floor displaced after the convergence of plates (15). Amplitude is simply the displacement in waves (24). Accordingly, the shape of the underwater disturbance affects the wavelength and wave period of a tsunami wave. Tsunami can travel long distances without significant energy loss until the waves can reach the shore. As they head toward the shore, the crest or upper part of the wave will undergo bending or refractions, caused by the different parts of the wave moving at different speeds.\(^{(15)}\)
The Indian Ocean Tsunami of 26th December 2004

The day after Christmas, a submarine earthquake with a magnitude of 9.3 occurred at the northern western tip of Sumatra, which produced a tsunami that caused one of the most catastrophic disasters in history. A series of tsunami waves have hit dozens of nations’ coastlines and killed more than 230,000 people, including 168,000 in the Aceh province of Indonesia, near the epicenter of the earthquake (27). The tragedy left 5 million homeless and 500,000 people injured, not only in south Asia, but also in the eastern nations of Africa (17). As seen on figure A above, the earthquake generated tsunami waves that have reached shores not only in Southern Asia, but reached African nations such as South Africa, Kenya, and Somalia 4,500 kilometers away. It took the waves from 15 minutes to 7 hours to reach shores on their path (15, 16). The India Plate converged with the Burma Plate and then the India Plate started to slip under the opposite plate, creating a subduction earthquake along a faultline (8). The large vertical thrust when the India Plate submerged under the Burma tectonic plate, generating an earthquake powerful enough to send tsunami waves across the vast Indian Ocean (15). Although the Pacific Ocean is a seismically active zone due to the Pacific Ring of Fire, the Indian Ocean is dangerous due to low lying coasts and the Indian Plate being active at both its east and west margins making tsunami more severe if it occurs (22). A tsunami researcher named Vasily Titov said: “When our team was first notified of the Sumatra earthquake, our computer models indicated that a small-scale tsunami would be produced. As better data came in about the size and strength of the earthquake, the models forecasted a more and more devastating tsunami.” This is why tsunami have been studied for the purpose of finding more ways to be accurate when it comes to forecasting the phenomenon in order to prevent disasters such as the 2004 Indian Ocean Tsunami (29).

Force, Velocity, Acceleration, and Newton’s Laws of Motion

Sir Isaac Newton was not only known as a brilliant mathematician, astronomer, philosopher, and chemist, but he was also known as the father of physics. He formulated the relationship between force and motion in his three laws of motion. The first law states that “a body at rest tends to remain at rest or a body in motion tends to remain in motion at a constant speed in a straight line unless acted on by an outside force”. The second law then states that “the acceleration $a$ of a mass $m$ by an unbalanced force $F$ is directly proportional to the force and inversely proportional to the mass, or $a = F/m$”. Then finally, the third law notions that “for every action there is an equal and opposite reaction. The third law implies that the total momentum of a system of bodies not acted on by an external force remains constant”. The third law is exemplified by the resonance or repetition of a tsunami wave as it goes in motion through a body of water due to a force exerted upon it. Motion is defined as the “change of position of one body with respect to another” (29). Force is a vector quantity, which has both magnitude and direction, “that changes the motion, size, and shape of a body”, but when two forces act upon each other, such as the downward force exerted by gravity and the upward force generated by the earth under a person’s feet is an example of equilibrium (19). Another vector quantity is acceleration, which is the change of velocity through time and is generated when force is applied to a body. This is elaborated by the second law of motion where the force $F$ must be equivalent to original force and velocity, $F=ma$ (18). Sir Isaac Newton left knowledge and more insight pertaining to worldly things relating to physics which surround us, from throwing a Frisbee to the generation of a tsunami.
Physics behind Tsunami

The physics behind tsunami begins with earthquakes that may occur from volcanic activity, explosions, cosmic impacts, and the tectonic plate movement due to magma. As the movement of plate tectonics, being the common cause of earthquakes that generate tsunami. Submarine earthquakes that occur from the sudden divergence of plate tectonics where plates shifts vertically underwater which produces huge energy that pushes up an upward wave towards the surface of the ocean, creating maximum amplitude as it resonates. This phenomenon is called the waterberg phenomenon. To better understand this concept, the use of geophysics in order to find the energy $E$ produced by an earthquake is essential. The formula in order to determine this energy is $E \approx 10^X$, where $X$ is equal to $4.8 + 1.5M_L$. The relationship between Richter magnitudes $M_L$ is relative to a certain amount of energy $E$ measured in Joule or J as seen on the figure B below (8, 9).

![Energy vs Richter Magnitude Graph](image)

**Figure B**

The figure above shows the relationship of the supposed 9.2 magnitude $M_L$, of the 2004 Sumatran earthquake to the amount of mechanical energy $E$ produced. When a magnitude of $M_L = 9.2$ is inputted into the formula $E \approx 10^X$, the amount of energy $E$ produced would be $4 \text{ exajoules}$ or $4 \times 10^{18}$ J. To better understand how much energy is produced, $4 \text{ exajoules}$ can be compared to 80,000 Hiroshima atomic bombs used in World War II. A single Hiroshima bomb can produce an explosion equal to 12.5 kilotons of TNT (trinitrotoluene). Now back to the waterberg phenomena, due to the displacement of the seafloor when tectonic plates converged, an energy generating earthquake is manifested. A submarine earthquake with a certain magnitude occurring along a faultline will generate a sudden upward wave to the surface of the water (see figure C) (8, 10). Mechanical energy, as the sum of kinetic energy which is associated with motion and potential energy which acts as a stored energy associated with relative position is generated accordingly (3). It is assumed that the amount of mechanical energy produced will be the same with the respect of the distribution of potential $U$ and kinetic energy $K$. In the waterberg phenomenon, the volume of water that shifts vertically is called the waterberg. Since water is
under buoyant equilibrium, estimating the stored energy or potential energy $U$ of the box-shaped waterberg is the only approach needed. Referring to the figure below, knowing that $d$ is the vertical increase in height, $h$ represents the depth of the ocean, lambda or $\lambda$ represents the wavelength inside the box-shaped waterberg, and $L$ as the length of the box. We can estimate how much potential energy $U$ is generated out of the Indian Ocean earthquake when data from the actual earthquake is used with the formula:

$$U_w = \frac{1}{2} \rho_w g L \lambda d^2$$

The water's density is represented by rho $\rho_w \approx 1000$kg m$^{-3}$. In physics laws, the conservation of energy explains that the waterberg with a similar dimension in the sea floor will have equivalent potential energy $U$. Data from the 2004 Sumatran earthquake provided that $L \approx 1200$km and the wavelength $\lambda$ of the waterberg is 150km, along with a $d$ of 5 meters. According to standard gravity acceleration, $g$ is equal to 9.8 m/s$^2$. When the data is then inputted in the equation, we find that the total potential energy $U$ deposited by the earthquake was $E_w \approx U_w \approx 2 \times 10^{16}$ or 20 petajoules (8, 11).

The maximum potential energy $U$ pushes the waterberg box upwards. The waterberg is being pushed by the maximum potential energy $U$ and minimum kinetic energy $K$. According to the conservation of energy, where energy cannot be destroyed and can be transferred. The water ratio of percentage of the energy produced in the water and earthquake energy is $E_w/E \approx 1\%$. This ratio illustrates that the 1% (20 petajoules of potential energy $U$) of the total energy generated by the earthquake is used generate the upward-wave that causes a significant disturbance in the water's equilibrium and in turn, created the series of tsunami waves that resonated and crossed the Indian Ocean causing havoc on shores along its wave's path. 1% was used but what happened to the other 99% of radiation energy, what happened is that the energy got transferred to different kinds of energy such as heat, absorbed by the lithosphere under the ocean, and of course kinetic energy (8).
Tsunami Warning Systems and Mechanism

Two tsunami warning systems are being run by the U.S. The Pacific Tsunami Warning Center based in Hawaii and the West Coast and Alaska Tsunami Warning Center in Alaska. Other stations have also been established by other countries such as Japan’s Meteorological Agency which runs multiple warning systems due to their history of tsunami occurrences. Following the 2004 Sumatran Earthquake, warning centers have been established in countries such as Indonesia, New Zealand, and Australia. In 2006, after the Indian Ocean Tsunami, the United Nations Educational, Scientific, and Cultural Organization (UNESCO) announced that a global tsunami warning system will be established and funding on more equipment will be done (26). With the continuous establishment of warning systems, it is not certain how many are in operation as of now (14). Scientists or seismologists take advantage of the fact that seismic waves and tsunami waves are related. Being able to predict the emergence of a tsunami is a breakthrough for coastal safety in various places around the world. Pacific-wide tsunami are commonly caused by faulting on ocean floor due to the convergence of plate tectonics. Seismographs record seismic waves when earthquakes do occur and a system or network of seismograph stations comprise the Tsunami Warning System that relay information to each other in order to determine the epicenter and magnitude of an earthquake. This way, they are able to anticipate if a tsunami will be generated because of that earthquake since a submarine earthquake with a magnitude of 7 or greater can almost always generate a major tsunami. Seismic alarms are set to alarm when a 6.5 magnitude and above earthquake occurs anywhere in the Pacific. Scientists will then rush to their seismographs and record seismic data from their seismograms. The information will then be relayed to the Honolulu Observatory or other stations that request data where their staff will determine the epicenter and magnitude of the earthquake that has occurred (22). If an earthquake is adequate enough to form a tsunami, a Tsunami Watch is issued. If the emergence of a tsunami is confirmed, a Tsunami Warning will be declared as security institutions such as police departments are preparing for evacuation procedures (25). Other forms of detecting seismic waves have been introduced such as the Global Positioning System (GPS) equipment that reads land movement on shores on shorelines could forecast or provide warnings almost as well as a warning system with seismographs, buoys, and satellites at a station’s disposal (31).

Conclusion

Tsunami have been the cause of much destruction throughout history and it is imperative that we learn from it. Even though science as of now cannot predict when earthquakes may happen, but when a submarine earthquake or a significant disturbance occurs, a tsunami can be generated and then predicted. That is why scientists are further studying the phenomenon to become more adept at forecasting it and then save lives in process. Severe tsunami are caused by vertical displacements since the energy and force generated by an earthquake will send an upward wave that will cause a large amplitude on the surface of the water cause tsunami waves to resonate. Tsunami act as shallow-water waves and their speed depends upon the depth they travel in. They are indeed shallow-waves because their wavelengths are longer than the depth of the water. Tsunami are said to be the wrath of Mother Nature as it destroys, kills, and cause strife, but it is an elaborate phenomenon that has occurred ever since water-displacing disturbances and water have existed. All we can do is learn from it and hope for the best since a natural phenomenon is simply natural.
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Type 1 Diabetes:
Controlling and Working Towards a Cure

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Instructor
Organic Chemistry 236

Prepared by:
Aaron Brown
April 22, 2011
Abstract

Each year Diabetes affects more people and causes more deaths in the United States than breast cancer and AIDS combined. Diabetes is also the seventh leading cause of death in the country with almost 200,000 reported deaths a year. There are four different types of diabetes, which are Gestational Diabetes, Secondary Diabetes, Type 2 Diabetes, and Type 1 Diabetes. Type 1 Diabetes is also known as Insulin-Dependent Diabetes and formerly referred to as Juvenile Diabetes. There are three main diagnostic tests that can be done to diagnose diabetes, which are an A1C test, fasting plasma glucose test (FGP), Oral Glucose Tolerance Test (OGTT). There are multiple types of insulin that can be used by Type 1 Diabetics, which include rapid-acting, short-acting, intermediate-acting, and long-acting insulin. Insulin can be administered into the body through syringes, insulin pens, or insulin pumps. Research is being done to create new ways of administering insulin that does not involve painful injections and hopefully finding a cure for the disease. Some of these experiments include pancreas transplants, islet transplants, insulin inhalers, insulin patches, and stem-cell research.

Introduction

Diabetes is a growing disease throughout the world. There are 25.8 million children and adults in the United States which accounts for 8.3% of the population that live with some form of diabetes. There are four different forms of diabetes, which are Gestational Diabetes, Secondary Diabetes, Type 2 Diabetes, and Type 1 Diabetes which is also known as Insulin-Dependent Diabetes or formerly known as Juvenile Diabetes. Gestational Diabetes is usually diagnosed in women who are in or around their twenty-eighth week of pregnancy, but goes away at the end of their pregnancy. Secondary Diabetes occurs due to another medical condition or treatment of another condition, for example it can occur in Cystic Fibrosis. Type 2 Diabetes is the most common form of the disease. A patient develops Type 2 Diabetes by having an unhealthy diet or lifestyle and genetics that put them more at risk for developing the disease. On the other hand Type 1 Diabetes is an autoimmune disease that is usually diagnosed at a young age. This form of diabetes affects the body by the destruction of insulin producing cells, known as beta cells or islet cells, by the immune system of the body. This occurs because the body’s immune system recognizes the cells that produce insulin as foreign and destroys them. Therefore, patients with Type 1 Diabetes lack the ability to produce the amounts of insulin needed to maintain homeostasis of the blood sugar levels in the body. This type of diabetes is a lot less common and is only seen in about 5% of the people diagnosed with diabetes. Insulin is a hormone that helps the body absorb sugars, starches and other food and converts them into energy. When the body absorbs the sugar into the blood stream instead of the cells, it can lead to cell death and many other complications throughout the body associated with diabetes.

Diagnosis

Unlike Gestational Diabetes and Type 2 Diabetes, Type 1 Diabetes can often go on for a while before being diagnosed, because many of the symptoms of Type 1 Diabetes seem very harmless. For example, some of the symptoms include polyuria (frequent urination), polydipsia (excessive thirst), polyphagia (extreme hunger), unusual weight loss, extreme fatigue and irritability, and a fruity, sweet, or wine-like odor on breath. It is very important to get checked if you think you may have multiple symptoms, because the longer diabetes goes untreated the more harm that can
come to your body. Having untreated diabetes can lead to problems, including hyperglycemia (high blood sugar), hypoglycemia (low blood sugar), ketoacidosis (high levels of ketones in blood), or eventually lead to coma or death.\(^2\) Also, having high blood sugar over many years can lead to serious damage to the body’s organ systems, for example, it can cause complications that effect the heart, nerves, kidneys, eyes, and other parts of the body.

There are multiple ways to test for diabetes. One test that a doctor can do is to check the patients A1C level. Doing an A1C test checks the patient’s average blood glucose over the past two to three months and determines a percentage of sugar in their blood over that time period. The A1C test measures the amount of glycosylated hemoglobin in the body. Hemoglobin becomes glycosylated when the blood sugar is too high by having sugar molecules attach to the hemoglobin, which is a protein found in red blood cells. These sugar molecules stay attached to the hemoglobin for the lifespan of the blood cell, which is about 120 days.\(^7\) A different test a doctor can do is run a fasting plasma glucose test (FPG).\(^11\) To do this test, patients need to fast for at least eight hours, have their blood drawn, and then have the blood analyzed in a lab for the blood sugar level. The normal blood sugar range for a non diabetic patient is between 70 and 100 milligrams per deciliter (mg/dL). The average diabetes diagnosis is made when two separate blood tests show that the patients fasting blood sugar is higher than or equal to 126 mg/dL.\(^4\) A third test that can be done to check for diabetes is called an Oral Glucose Tolerance Test (OGTT).\(^11\) This test is similar to the FPG test, but after the patient fasts for at least eight hours, they are given 75 to 100 grams of sugar to consume, then blood samples are taken, and analyzed in a lab for blood sugar levels.\(^4\) Another way a patient can test whether he or she may have diabetes is using a glucometer. A glucometer is like little computer that read the patient’s blood sugar levels and shows the number on the screen. The average person’s blood sugar should be from 70 mg/dL to 120 mg/dL. If it is substantially above that range or below that range than the patient should get checked out immediately. For example, a blood sugar level greater than 200 mg/dL may be a sign of diabetes.\(^4\) Another test that can be preformed is called a Ketone test. This test uses the patient’s urine and checks for unusual amounts of ketones in the urine. Ketones are a product created from the body breaking down fat to use for energy when there is no sugar being put into the cells as a result of insufficient insulin or no reaction from the cells to the insulin.\(^1\)

![Diabetes Blood Levels](image)

**Figure 1:** The normal, pre-diabetes, and diabetes blood levels for the A1C, FPG and OGTT test.\(^11\)
Current Treatments

After being diagnosed with diabetes patients then have to decide how they want to manage their disease. This is usually done by injecting insulin into the subcutaneous tissue before a meal to counteract and balance the sugar consumption. Insulin is also needed to control blood sugar levels throughout the day. In addition to administering insulin, diabetics have to prick their fingers multiple times throughout the day to check their blood sugar levels. Although eating food and then injecting insulin sounds very easy, the hard part is knowing how much insulin the person needs for that meal. Many factors can change the amount of insulin needed, because it is different from person to person. Some factors that could influence how much insulin someone could need to balance out their sugar from their meal could be the type of food he or she is eating (if it is high in sugar or low in sugar), the foods absorption rate (how quick it gets absorbed into the blood), the persons absorption rate, as well as stress, illness, and exercise.²

There are many different types of insulin’s that have been developed. There is Rapid-acting, Short acting, intermediate-acting, long-acting, and pre-mixed insulin’s.¹² Rapid-acting insulin is usually used for covering meals that that cannot be accounted for by the patients long-acting insulin alone. Short-acting insulin is usually used for meals that are going to be eaten within a half hour to an hour from the insulin being injected. Short-acting is also used in many insulin pumps, because it is delivered into the body in small increments throughout the day and night. Intermediate-acting insulin is insulin that is used by a patient either over night or half of the day and is usually combined with rapid- or short-acting insulin’s to control the blood sugar better. Long-acting insulin is active throughout the entire day to help keep blood sugar levels stable and can sometimes be given mixed with rapid- or short-acting insulin’s depending on the types of insulin. Pre-mixed insulin is usually taken two times a day and normally before a meal to account for carbohydrates being consumed and stabilizing blood glucose levels over a period of time.¹²

<table>
<thead>
<tr>
<th>Type of Insulin &amp; Brand Names</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Role in Blood Sugar Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Humalog or lispro</td>
<td>15-30 min.</td>
<td>30-90 min.</td>
<td>3-5 hours</td>
<td>Rapid-acting insulin covers insulin needs for meals eaten at the same time as the injection. This type of insulin is used with longer-acting insulin.</td>
</tr>
<tr>
<td>Novolog or aspart</td>
<td>10-20 min.</td>
<td>40-50 min.</td>
<td>3-5 hours</td>
<td></td>
</tr>
<tr>
<td>Apidra or glulisine</td>
<td>20-30 min.</td>
<td>30-90 min.</td>
<td>1-2½ hours</td>
<td></td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular (R) humulin or novolin</td>
<td>30 min. -1 hour</td>
<td>2-5 hours</td>
<td>5-8 hours</td>
<td>Short-acting insulin covers insulin needs for meals eaten within 30-60 minutes</td>
</tr>
<tr>
<td>Velosulin (for use in the insulin pump)</td>
<td>30 min.-1 hour</td>
<td>2-3 hours</td>
<td>2-3 hours</td>
<td></td>
</tr>
<tr>
<td><strong>Intermediate-Acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH (N)</td>
<td>1-2 hours</td>
<td>4-12 hours</td>
<td>18-24 hours</td>
<td>Intermediate-acting insulin covers insulin needs for about half the day or overnight.</td>
</tr>
<tr>
<td>Type</td>
<td>Start Duration</td>
<td>Peak Duration</td>
<td>End Duration</td>
<td>Notes</td>
</tr>
<tr>
<td>--------------</td>
<td>----------------</td>
<td>---------------</td>
<td>--------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lente (L)</td>
<td>1-2½ hours</td>
<td>3-10 hours</td>
<td>18-24 hours</td>
<td>This type of insulin is often combined with rapid- or short-acting insulin.</td>
</tr>
<tr>
<td>Ultralente (U)</td>
<td>30 min.-3 hours</td>
<td>10-20 hours</td>
<td>20-36 hours</td>
<td>Long-acting insulin covers insulin needs for about one full day. This type of insulin is often combined, when needed, with rapid- or short-acting insulin.</td>
</tr>
<tr>
<td>Lantus</td>
<td>1-1½ hour</td>
<td>No peak time; insulin is delivered at a steady level</td>
<td>20-24 hours</td>
<td></td>
</tr>
<tr>
<td>Leveimir or detemir (FDA approved June 2005)</td>
<td>1-2 hours</td>
<td>6-8 hours</td>
<td>Up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Pre-Mixed*</td>
<td></td>
<td></td>
<td></td>
<td>These products are generally taken twice a day before mealtime.</td>
</tr>
<tr>
<td>Humulin 70/30</td>
<td>30 min.</td>
<td>2-4 hours</td>
<td>14-24 hours</td>
<td></td>
</tr>
<tr>
<td>Novolin 70/30</td>
<td>30 min.</td>
<td>2-12 hours</td>
<td>Up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Novolog 70/30</td>
<td>10-20 min.</td>
<td>1-4 hours</td>
<td>Up to 24 hours</td>
<td></td>
</tr>
<tr>
<td>Humulin 50/50</td>
<td>30 min.</td>
<td>2-5 hours</td>
<td>18-24 hours</td>
<td></td>
</tr>
<tr>
<td>Humalog mix 75/25</td>
<td>15 min.</td>
<td>30 min.-2½ hours</td>
<td>16-20 hours</td>
<td></td>
</tr>
</tbody>
</table>

*Premixed insulins are a combination of specific proportions of intermediate-acting and short-acting insulin in one bottle or insulin pen (the numbers following the brand name indicate the percentage of each type of insulin).

Chart 1: Onset, peak, duration, and role of blood sugar management of the different kinds of insulins used for the treatment of Type 1 Diabetes.  

For a Type 1 Diabetic there are multiple ways of administering insulin needed. One way of administration is just by using a syringe to draw up insulin from a multi-dose vial and injecting the insulin into the body’s subcutaneous tissue though the syringe. A second way to administer insulin is using an insulin pen, which is a prefilled pen-like device that you screw a needed onto the end and dial in how much insulin you want to administer and inject it into the body. There are many different types of pens, with some having fast acting insulin and others having long acting insulin. The names of some of these pens are Lantus SoloStar pens (long acting insulin), Apidra SoloStar pens (rapid acting insulin), Humalog KwikPen, Levemir FlexPen, NovoLog FlexPen, etc. The third way to administer insulin into the body is to use an insulin pump. An insulin
pump is a pocket sized computer that feeds the patient insulin throughout the day and night when needed through a cannula, or a tiny flexible tube, that is in the subcutaneous tissue. The insulin pump can help keep blood sugar levels closer to the normal range throughout the day, a lot better than if the patient was injecting themselves with insulin multiple times a day. This is because people may give themselves too much insulin over multiple shots a day which usually ends up in having big swings in blood sugar. Not only does the insulin pump help control the blood sugars better but, many people also prefer using the insulin pump over insulin syringes and insulin pens because if the person is out eating somewhere they don’t have to pull out a syringe and insulin and inject themselves in front of everyone. Instead with an insulin pump the patient can just punch in how many units of insulin they need and the pump just puts it in their blood for them because they already have a needle in them. Another reason many people like to use insulin pumps is because instead of giving themselves multiple shots throughout the day the only have the change out the needle one every two to three days.

Research and Future Treatments

There are many research facilities and foundations that are looking for a cure for Type 1 Diabetes as well as finding out new and improved ways to check and control blood glucose levels and different methods of administering insulin. Some of these experiments include pancreas transplants, islet transplants, insulin inhalers, insulin patches, and stem-cell research.

The pancreas transplant seems like a logical fix to a Type 1 Diabetic, because a Type 1 Diabetics’ pancreas has stopped producing insulin resulting in the need to inject themselves with insulin to control blood sugar levels. However, transplanting the pancreas can sometimes be worse than the disease itself. This is because the body is so complex that it knows its own parts from foreign objects, therefore, to have this be a successful transplantation, the patient must take immunosuppressive drugs that decrease the strength of the immune system, so that the body is more likely to accept the transplanted organ. However, the risks that are associated with weakening the immune system are higher risk for infection or disease and can possibly result in death. There is also a possibility that after taking the immunosuppressive drugs that the pancreas could still be rejected by the body, resulting in the patient becoming diabetic again. With a successful transplantation and acceptance of the organ by the body, the patient will no longer have diabetes or the need to receive insulin injections or to check blood sugar levels any longer. There is about 1,300 people each year that have Type 1 Diabetes that receive a pancreas transplant and after a year 83% of those patients have no more symptoms of diabetes, no longer have to take insulin, and have the ability to keep normal blood sugar levels.

The islet transplant is another type of transplantation that can be done to help patients with Type 1 Diabetes.
This transplant includes taking a cluster of beta cells from a pancreas that makes insulin and putting them in the patient's liver. Doctors like this procedure more than the pancreas transplant, because it is much safer and easier to perform. Doctors have also found a new procedure to do this called the Edmonton Protocol, which takes only about an hour to perform. The Edmonton Protocol is a procedure that requires specialized enzymes to remove the islets from a donor pancreas. A regular islet transplant for a normal sized person requires about one million islet cells, which requires about two donor pancreases, because the islets are so fragile. Once the islets are transplanted into the patient it still takes time for the cells to attach themselves to the new blood vessels and to begin producing and releasing insulin. As a result, the patient's blood sugar will still have to be check periodically until the blood sugar is controlled.

The insulin inhaler is a product that is being worked on currently as another alternative to taking sometimes painful insulin injections. These products would allow diabetics to administer their medication by breathing in insulin through inhalers similar to ones used for asthmatic patients. Scientists have been having some difficulties however while trying to create these new products, because they have to figure out exactly how much insulin is needed to achieve the best results and how much will actually be absorbed into the body when breathing it in. One insulin inhaler called Oral-Lyn™ has already been approved by the Ecuadorian Ministry of Public Health for commercial sales in Ecuador. Now, the drug company is just trying to get approval by the FDA, but have yet to do so.

Insulin patches are also a developing method for administering insulin into diabetic patients. Patches are commonly used to transfer nicotine into people who are attempting to quit smoking, however, it has been difficult for researchers to develop a patch for insulin, because the insulin molecule is larger than nicotine and is difficult to absorb through the skin. Researchers have had to become creative in their ways to try to make insulin absorb through the skin, which includes using chemicals to help insulin be absorbed, and ultrasound or electrical currents. One scientist, Samir Mitragotri, who is funded by the American Diabetes Association, is developing a drug that incorporates the patch idea into it. He is creating a drug that once it is in the intestines will release patches that attach to the wall of the intestines. These patches will then release insulin at a slow rate to help control blood sugar levels. These drugs have not been completely developed yet and more research is still needed.

Stem-Cell research is the one thing that scientists believe holds the cure for Type 1 Diabetes. It is believed that embryonic stem cells, which come from embryos, are going to be the type of stem cell that will be needed to create insulin producing cells that may cure Type 1 Diabetes. Research is being done to learn how to direct stem cells to do what is need to help cure the disease. A positive note for stem cell transplantation is that it is believed that if insulin producing cells created through stem cells could be made, they could make the cells out of material that would
not lead to an immune response, which would decrease the likelihood of rejection and patients would not have to take immunosuppressant drugs. Even though stem cell research is controversial it could lead to a cure for diabetes and prevent complications shown in chronic diabetes.⁶

Summary and Conclusion

Type 1 Diabetes may not be the most prevalent form of diabetes; however it still affects millions of people throughout the world. This autoimmune disease is a challenging disease for people, because blood sugar levels are consistently changing and patients have to continue to fine tune their treatment for optimal stability of blood glucose levels. A Type 1 Diabetics response to everyday life events can affect their blood sugar levels by putting stress on the body, which makes it difficult to create stability in their disease. Insulin injections and pumps are currently the options for Type 1 Diabetics to treat their disease, but these treatments can be very painful and a hassle to include in their everyday routines. Creation of new methods for treating diabetes could result in better quality of life for diabetics and better control of their disease, which would result in less complications that occur from instability in blood sugar levels. Research on new methods for treatments are coming closer to being put on the market, however, it is a long process that researchers have to go through, but when the end product comes through it can help diabetics in managing their disease. The optimal outcome for research on Type 1 Diabetes would be to find a cure, however this may be far in the future. Stem cell research at the moment seems like diabetics best hope for finding a cure, however, this research is controversial and many people disagree with these types of research, which may be hindering the process of finding a cure if at all possible.
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Environmentally Safe Plastics

Robert Campbell

April 22, 2011
Abstract:

Our world is littered with immeasurable amounts of non-biodegradable plastics. They fill our landfills; litter our streets and neighborhoods; and pollute our oceans. Marine life is devastated by floating debris which floats in our oceans. Already the undertaking required to clean up the trash already produce in past generations would take trillions of dollars, millions of labor hours, and many decades. With such harmful effects of these non-biodegradable, non-recyclable plastics it is necessary to evolve production techniques to use materials which can be reused and/or be capable of safely degrading in a short amount of time. It is up to the inhabitants of this world we call home to make changes in our lifestyles and society to protect the only home we have.

Introduction:

A product which is biodegradable is defined as a material that has the ability to break down into basic components consistently, safely and in a relatively short amount of time. In nature everything is designed to break down and be used again in a cycle of life. Nature has perfected this system and we as a society need to be able to learn how to utilize this ability to reuse materials without a byproduct waste. Everyday commercial production produces millions of tons of trash that is non recyclable. This diminishes our natural resource, bears economical burden and devastates the Earth’s environment.

Environmental Impact of Plastics:

The first polymers were produced in labs in the early 1920’s. As these polymers were produce and developed the plastics produced were viewed negatively if the product showed signs of performance determination with time. So plastic products where manufactured from extremely durable and long lived plastics; with no concern for their disposability or recyclability in the future. Nearly a century later and products are still consistently made with non-biodegradable materials and recycling techniques have only recently been sought for recently from political pressure from environmental activists. Everyday consumer products that we purchase in our day to day lives have biodegradable times in the years. A small chart has been provided with some
Details on the amount of time required for everyday material to decompose of natural causes without the intervention of human or mechanical assistance. Composted paper has a relatively short period of decomposition but products such as soda cans, can take up towards a 100 years and glass bottles not recycled have a shelf life of 1 million years. Many of these materials are discarded where they end up in landfills and in many cases in second and third world countries are illegally dumped into the world’s oceans. The environmental factors alone should be considered alarming indicators that a new approach for the production of consumer and commercial products is required.

Anyone can go to a Taco Bell in the late evening and order from their menu a large variety of items such as bean burritos, Baja chalupas or even a standard crunchy taco. All this items come in a seemingly harmless plastic wrapper. These wrappers for the most part are produced in Asia and are imported over seas to thriving American fast food chain\textsuperscript{1}. In 2000 a research ship named the Alquita discovered a 10-mile-wide flotilla of the disposable sacks, an estimated 6 million of them destined for Taco Bells around the country. This flotilla of taco bell wrappers that never made it to their destination is now on their way to the center of the pacific to join the ever growing “Great Garbage Patch”. The Great Garbage Patch is a suitable name for the collection of trash that is collected by ocean currents and mashed to together between several
main current systems. The pile of trash was in 2000 estimated to be twice the size of Texas and growing. A collection of old commercial fishing nets, water bottles, qt oil jugs, plastic bags, foam packaging and just about any floating trash debris which is tossed into the ocean. Sea turtles and large fish mistake plastic grocery bags for jellyfish. Thousands of dolphins, sharks and seals die every year from being entangled in discarded commercial fishing nets where they are left to drown or starve. Sea birds not only get trapped by old six-pack rings but mistake old lighters and toothbrushes for small fish and end up choking. Bits of Polymer plastics only break down into smaller pieces of plastic which are consumed by jelly fish, plankton, and other small fish. When the bottom of an ecosystems food chain is affected a domino effect occurs affecting every organism higher up the food chain. Plastic polymers are now in fact being found in fish produce from the oceans that we buy at the supermarket and place on our dinner tables at home. As horrendous as this sounds most people would be all for the process of cleaning up this environmental disaster.

The truth of the matter is that no country wants to claim responsibility for the Great Garbage Patch. The cost of such an undertaking would be staggering. The cost of fuel used to run the boats that would be able to skim for large debris and micro plastics and man labor hours is more then anyone wants to pay. This all adds up to a bigger challenge than even sifting beach sand to remove bits of marine debris. In some areas where marine debris concentrates, so does marine life. This makes simple skimming the debris risky—more harm than good can be caused. Much of our ocean life is in the microscopic size range. Straining ocean waters for items such as microplastics would capture the plankton that is the base of the marine food web and responsible for 50% of the photosynthesis on Earth. This is the same amount of photosynthesis produced by all terrestrial plants on Earth. Also due to the sheer size of the Pacific Ocean it would takes hundreds of ships a hundred of years to thoroughly clean up the trash in the pacific. This is but one example of the affects of not using biodegradable products has on our environment. What we need are materials that can be recycled easily and remain cost effective or materials that can be left to biodegrade in a relatively short amount of time.

**Environmental Friendly Plastics:**

Two types of Eco-Friendly plastics are Bioplastics which easily biodegrade and Thermal based film plastics which can easily be recycled and reused. Bioplastics are also referred to as starch based plastics which are composed from corn, soy or potatoes. Bioplastics meet the required standards set by the American Society for Testing Material for biodegradability. Which means that in the presence of water, heat, and aeration the bioplastics can break down 60% or more within 180 days. The erosion and degradation of a polymer describes how the polymer physically loses mass. The two common erosion mechanisms are surface and bulk erosion. Surface eroding polymers do not allow water to penetrate into the material. They erode layer by layer, like a throat lozenge. Bulk eroding polymers take in water like a sponge throughout the whole material and erode inside and on the surface of the polymer. Bulk eroding materials are preferred to the surface eroding materials when it comes to producing something with a short life necessity. Vice versa a surface eroding material is better suited for products which need to last
longer. Figure 2 below shows how organic components of some compounds can be broken down into smaller parts with the exposure to moisture. Bioplastics are also very encouraged because the basic components are made from easily replenished crops which can be grown every year. Bioplastics do tend to be more expensive to manufacture than the traditional polymer plastics out on the market due to the lack factors equipped to manufacture on a large scale basis. Another downside to bioplastics is that most bioplastics end up in landfills where they are denied one of the 3 requirements for proper decomposition. When trashed it can be exposed to moisture and heat but does not receive any aeration to complete the process. Bioplastics very easily go through the process of decomposition but unfortunately are not capable of being recycled. What this means is that there is less of an impact on the environment because discarded bioplastics can simply biodegrade instead of floating around the world’s oceans where marine life can be injured or killed. At the same time since bioplastics aren’t capable of being recycled we are not able to reuse any of the original materials to produce additional products. This would make bioplastics excellent for the manufacturing of fast food wrappers, grocery bags, shipping peanuts, and any other plastics that are short used and do not need to be water resistant.

**Water Soluble Bioplastic Compounds**

Figure 2.

A.

\[
\begin{align*}
R_1\text{-}C\text{-}X\text{-}R_2 & \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad R_1\text{-}C\text{-}O\text{-}H & \quad + \quad HX\text{-}R_2
\end{align*}
\]

*Where X = O, N, S*

Examples:

- Ester
  \[
  R_1\text{-}C\text{-}O\text{-}R_2
  \]

- Amide
  \[
  R_1\text{-}C\text{-}NH\text{-}R_2
  \]

- Thioester
  \[
  R_1\text{-}C\text{-}S\text{-}R_2
  \]

B.

\[
\begin{align*}
R_1\text{-}X\text{-}C\text{-}X'\text{-}R_2 & \quad \overset{\text{H}_2\text{O}}{\longrightarrow} \quad R_1\text{-}X\text{-}C\text{-}O\text{-}H & \quad + \quad HX'\text{-}R_2
\end{align*}
\]

*Where X and X' = O, N, S*
Examples:

\[ R_1-O-\overset{\text{Carbonate}}{\text{C}}-O-R_2 \]  
\[ R_1-\text{NH} \underset{\text{Urethane}}{\text{C}}-O-R_2 \]  
\[ R_1-\text{NH} \underset{\text{Urea}}{\text{C}}-\text{NH}-R_2 \]

C.

\[ R_1-\overset{\text{H}_2\text{O}}{\text{C}}-X-\overset{\text{C}}{\text{C}}-R_2 \rightarrow \overset{\text{C}}{\text{C}}-\text{OH} \quad \text{and} \quad HX-\overset{\text{C}}{\text{C}}-R_2 \]

Where \( X \) and \( X' = O, N, S \)

Examples:

\[ R_1-\overset{\text{Imide}}{\text{C}}-\text{NH}-\overset{\text{C}}{\text{C}}-R_2 \]  
\[ R_1-\overset{\text{Anhydride}}{\text{C}}-O-\overset{\text{C}}{\text{C}}-R_2 \]

Now another type of eco friendly plastics is referred to as thermal based film plastics. Thermal based biodegradable plastics are produce with an additive that causes it to break down when exposed to high temperatures. These plastics can be melted down and reused to from new plastic products. These plastics are safe for food because there are non-toxic and can be recycled several times without loss of much product. Now the down side to these thermal based plastics is that they are heat sensitive. Some more than others but some garbage bag manufactures who produce their products from these thermal based plastics will put a warning label on the packaging warning the consumer to keep the product away from heat. Two types of thermal plastics are oxo- and hydro-biodegradable. Oxo-biodegradable plastic is the less expensive of the two and requires oxygen to begin the process of decomposition. Oxo- plastics are also very easy to manufacture because they can be produced in the some machinery used to produce conventional plastics. When exposed to air oxo-plastics will break down into biodegradable compounds over the time frame of a few months to a few years depending on the composition, size, and air exposure of material. Hydro- bio degradable thermal plastics are quicker to decompose into biodegradable compounds when they are exposed to water. Hydro-plastics are more expensive to manufacture because the machinery needed to produce this plastics has yet to be developed on a large scale. But with either type of thermal plastic there is an advantage in the fact that they are extremely easy to recycle into more reusable plastics. By melting the plastics
they maintain composition but are converted into a liquid state. Once they have been melted they are easily remolded and cooled to form new shapes and sizes with very little loss of structural integrity.

**Companies Leading the Way:**

Many companies when accused of producing environmentally harmful plastics have made public statements that it is not their responsibility as a company to make sure that potentially harmful plastics are disposed of correctly by rather it is solely up to the consumer to take these measures. Now I agree that the consumer should take a sense of responsibility when it comes to properly recycling or composting old discarded plastic products; it still important that companies who produce large amounts of plastic should produce products which can be recycled and/or composted. Some companies have recognized the need and value of responsible production of their plastic based products. Companies such as Paper mate® have taken measures to be more eco friendly®. The company has started producing their pens from a plastic which is composed of more than 50% of renewable vegetable based material which can easily be replenished. The company uses a material called Mirel® to produce their pens which is a compound similar to that of conventional plastics³. The company even includes easy instructions on how to discard old pens by disassembling them, discarding the very little bit of product which is non-recyclable, and simply burying the rest of the pen where it will degrade naturally over a short period of time. The result is a product which has a relatively short life necessity but won’t pollute our environment with non-biodegradable by-product.

Another eco-friendly company taking the lead in recyclable products is a small Swedish shoe company called OAT Shoes®. While most sneakers are not very eco-friendly due to the nature of the processes and materials used to make them, the creators of OAT Shoes have produce a more environmentally friendly shoe made from already recycled materials⁴. Their efforts have resulted in the creation of a shoe that not only is made from recycled material but can also be planted when the shoe is longer new. From where the shoe is planted small plants and flowers will grow from seeds imbedded in the biodegradable soles of the shoes. Once the wearer outgrows them, they can just plant them in their garden rather than chuck them in the garbage.

**Conclusion:**

The importance of evolving in a society that is more eco-friendly is not a luxury. The environmental impact that discarded, non-biodegradable, non-recyclable products have on our oceans is alarming. In the Pacific alone there are thousands of dolphins, seals, and sea lions
entangled in discarded commercial fishing nets that drown; the tens of thousands of birds, turtles and fish each year that consume plastic bags, old lighters, and toothbrushes which they end up choking on; and the countless billions of floating micro plastics that kill off organisms at the bottom of the food chain which in turn can devastate whole ecosystems can break even the coldest of hearts. Why do we pollute our oceans and pack full our landfills when there are many alternative solutions we can explore and utilize. Bioplastics which can remove millions of pounds of discarded trash from the earth by producing simple everyday short-lived biodegradable plastics. We don’t need a subway® sub bag to last decades when the longest we may use them is the short drive home where we remove our sub and immediately discard the bag. There are thermoplastics which can easily be recycled by the process of melting them down and remolding new plastics with the same material. Even if the thermoplastic is not recycled properly there is little environmental impact due to the fact that the plastic can decompose eventually over a short period of time with exposure to air or water. It is a responsibility that companies should undertake to make sure that their consumer products leave little if no impact on our environment by producing such plastics that can decompose or recycle. Yet it is also our responsibility as consumers to properly dispose and sort potentially recyclable materials. We cannot begin to decrease the quantities of trash we pollute the earth with until we have first mastered the ability to dispose of and/or recycle the trash that we do produce. Only then can we truly protect the planet we call home and all of its inhabitants. It’s not just the responsibility of one man, one company, or one country. But the burden lies on everyone to do their part to create a cleaner, safer world for generations to come.
Works Cited


Epigenetic Change and Cancer

By Shane Cook
Abstract

This paper summarizes how traditional genetic mechanisms determine the expression of a gene. Epigenetic changes to DNA are introduced and known mechanisms for epigenetic change are discussed. Epigenetic changes to cancer related genes are introduced. Drugs currently being used against epigenetically caused cancer are also discussed.

Traditional Mendelian genetics explains the inheritance and expression of genes. A gene is a unit of DNA found in the nucleus of the cell that directs the manufacture of proteins in the body thus displaying various traits. The types of genes found in an organism are referred to as a genotype and the traits displayed as a result of the genes are called a phenotype. Many genes are referred to as being either dominant or recessive. If the dominant gene is inherited then it will be displayed in the phenotype. A simple example would be the inheritance of the color red in a flower. The dominant gene for red color is denoted as “R” and the recessive gene is denoted as “r”. Each offspring inherits one gene from each parent for a total of two genes. A flower that inherits the genotypes RR or Rr will be red in color and their genotypes would be homozygous dominant and heterozygous dominant respectively. A flower with the genotype rr will not display the red color phenotype and will instead be white. The rr flower would have a homozygous recessive genotype (Raven 2007).

Genetic changes occur when the structure of the DNA changes. Changes to DNA structure are called mutations and can occur during cell replication. When a mutation occurs and the DNA sequence is altered, the expression of a gene can also be altered. For example, if the dominant R gene from each parent were to be altered or damaged, the resulting offspring would all be white. Mutations can also occur if DNA is exposed to radiation. Deletion is a type of chromosomal mutation in which part of the chromosome is lost. Another chromosomal mutation is inversion. As inversion occurs when a
segment of a chromosome is broken off, reversed, and then put back together. These mutations can alter the appearance of a gene and thus alter the phenotype expressed in the organism (Raven 2007).

Epigenetic changes are not changes or mutations that occur to the DNA itself but rather environmental or chemical changes that affect the expression of a gene. Epigenetic change can silence or activate the expression of a gene (Riddihough and Zahn et al. 2010). One of the more recent and well-known experiments showing epigenetic change is the case of the agouti mice. The agouti gene in mice governs what color fur the mouse has. The mice that are homozygous dominant or heterozygous dominant for the agouti gene have yellow fur.

The yellow furred mice have a tendency to be obese and have a higher rate of diabetes and cancer. The mice that are homozygous recessive for the agouti gene have brown fur, are not obese and tend to live longer than the yellow furred mice (Watters et al. 2006). In the experiment, a group of yellow furred pregnant females were fed a normal diet. About 60% of the group’s offspring had yellow coats. Another group of yellow furred pregnant females were fed a high methyl diet, their food was enriched with vitamin B12 and folic acid. About 60% of the offspring from the group with a high methyl diet were brown furred. The brown furred mice should have displayed a yellow coat according to their statistical genotype. It would appear that a change in the diet of the parent could have an effect on whether or not a gene is displayed. In the case of the agouti mice, the gene to display a yellow coat was suppressed by a methyl-enriched diet (Gibbs et al. 2003).

The epigenetic mechanism seen with the agouti mice is known as DNA methylation. DNA methylation is the most prominent known mechanism for epigenetic change (Brower et al. 2011). DNA is comprised of the nucleotides adenine, thymine, cytosine and guanine. The nucleotides adenine and thymine are bonded together to form a base pair (AT). And the nucleotides guanine and cytosine bond together to form a base pair (CG). Genes are comprised of specific sequences of these base pairs. For a gene to function properly, the DNA must be able to open up and send messages for protein synthesis. The gene sends messages by opening up and forming messenger RNA or
mRNA. If the DNA is unable to open up or the formation of mRNA is blocked then the gene can be silenced. If DNA opens up too frequently the result can be an overactive gene.

DNA methylation takes place at the CG base pair. The methyl group, CH$_3$, is attracted to the cytosine nucleotide and bonds to it.

![Diagram](image)

Generally, DNA methylation is a naturally occurring process and is not harmful. DNA methylation becomes problematic when it occurs too frequently or not often enough. Too many methyl groups added to DNA is known as hypermethylation. When there are too few methyl groups it is known as hypomethylation. When hypomethylation occurs a gene can become overactive. When hypermethylation occurs the gene can become inactive or suppressed. By hyperactivating or suppressing a gene, DNA methylation can alter the phenotype of an organism without altering the DNA or the gene sequence thus an epigenetic change occurs (Minkel et al. 2010).

DNA methylation plays a role in the development of cancer specifically, when reacting with oncogenes. An oncogene is a type of gene that regulates cell division and growth. The two main types of oncogenes are proto-oncogenes and tumor suppressing oncogenes. Proto-oncogenes produce proteins that signal for cell division. Proto-oncogenes are responsible for initiating cell division. Tumor suppressing oncogenes produce proteins that stop cell growth and division. Tumor suppressing oncogenes are responsible for the termination of cell division. The two types of oncogenes work in tandem to regulate cell growth. Cancerous growth may arise if a proto-oncogene becomes hyperactive and causes excess cell division. Cancer can also arise if the tumor suppressing oncogene is damaged or rendered inactive and cell division continues unregulated. When a tumor suppressing oncogene becomes hypermethylated, the excess methyl groups hinder the genes ability to form mRNA and send messages resulting in a silenced gene (Cavenee and White et al. 1995). If the tumor suppressing oncogene becomes silenced, then the cell division initiated by the proto-oncogene can continue unregulated leading to excess growth. Analyses of solid tumors shows that hypermethylation of tumor suppressing oncogenes is prevalent.
It is thought that if a gene can be silenced by hypermethylation then the reverse should be true. A gene can be reactivated by removing methyl groups or, demethylation. There aren't currently any drugs available to help solve the hypomethylation of an oncogene but there are some drugs being used to treat the hypermethylation of an oncogene with varying degrees of success. Currently, studies are being conducted using demethylating drugs to reactivate silenced tumor suppressing oncogenes. One of the more prominent drugs being studied currently is azacitidine, which is sold under the trade name Vidaza. The way azacitidine works is by mimicking the cytosine nucleotide and inserting itself into the DNA strand during replication. The azacitidine molecule then traps DNA methyltransferases, which are the enzymes responsible for methylating DNA; the binding of the methyltransferases prevents the methylation of the DNA strand. The newly formed, unmethylated DNA should not have any suppressed genes and should be able to regulate cell growth (Kaiser et al. 2010).

Another drug that has seen some success in controlling DNA methylation is the drug decitabine. Decitabine is used to reduce hypermethylation of DNA. In low doses the drug strips the methyl groups off of DNA. Some studies have show that the reactivated tumor suppression oncogene allows the cell to regain control of cell division. Often when the cell regains control it will undergo apoptosis or, cell death. Through apoptosis, the division and spreading of cancerous can be halted (Al-Romaith et al. 2008).
Cancer can arise from genetic changes such as mutations to DNA. But cancer can also occur through epigenetic change whereby the structure of the DNA and genes remain intact but are either hyperactive or suppressed. An individual may not be genetically susceptible to cancer, meaning their DNA is not programmed for it, it is possible that epigenetic changes such as DNA methylation can give rise to cancerous cells. DNA methylation is one of the major mechanisms in epigenetic change. By silencing the tumor suppressing oncogene, cell division and growth can continue unregulated. Currently the drugs azacitidine and decitabine, which are both DNA methyltransferase inhibitors, are being studied to treat cancer arising from DNA methylation. Hopefully, the continued study of epigenetics will lead to a better understanding of how cancer arises and how to cure it.
References


Rheumatoid Arthritis and the medications of the past, present and future

Amanda Crozier

CHM 236
Dr. Hank Mancini
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Abstract

This paper reviews the specificities of the disorder Rheumatoid arthritis (RA) and the medications used to treat Rheumatoid arthritis in the past 100 years and the medications currently used in the medical field, as well as the medications that are being developed and tested for this disorder. The cause of Rheumatoid arthritis is still unknown to this day and consequently a cure has not been developed. However the affects of Rheumatoid arthritis on the human body are known even down to the microscopic level and is the current direction of the treatment for the disorder. Unfortunately this means the medications are treating the effects and not the cause.

Rheumatoid arthritis is not a recently discovered disorder, due to its extreme disfiguring of joints and bones, but even with modern science the exact cause is still unknown. The symptoms of early Rheumatoid arthritis include: fatigue, loss of appetite, low fever, swollen glands and weakness but those symptoms are often seen in many other sicknesses or disorders and make early detection of Rheumatoid arthritis almost impossible (Borigini and Zieve 2010a). As the disorder progresses the symptoms become more severe and include:

- Morning stiffness
- Joint pain that is felt on both sides of the body
- Joints become swollen and spongy
- Finally over time the joints lose their range of motion and joint deformity may occur (Borigini and Zieve 2010a).

![Rheumatoid arthritis (late stage)](/image)

Boutonniere deformity of thumb
Ulnar deviation of metacarpophalangeal joints
Swan-neck deformity of fingers

Image was found on PubMed Health website (Borigini and Zieve 2010a)
As seen in the image above Rheumatoid arthritis in its later stages can be devastating to an individuals joints and render them ineffective to do even the most simplest of tasks. This deformity can affect many joints in the body but research show smaller joints are affected first, these include: joints of the wrist, hands, ankles and feet but as the disease progresses the shoulders, elbows, knees, hips, jaw and neck can be affected as well (Mayoclinic 2009). The damage to the joints also appear to be symmetrical in patients, for instance both hands would have the same level of deformity.

Rheumatoid arthritis is believed to be an autoimmune disease in which the bodies own antibodies attack healthy tissue and in most cases the synovial joint. The synovial membrane is a fluid filled sack that provides lubrication and nourishment for the joint and as the immune system attacks it the synovial membrane produces excess fluid. White blood cells enter the synovial membrane and cause inflammation which in turn causes the synovial membrane to thicken and release enzymes that destroy cartilage and bone tissues (Harvard Medical College 2005). As the cartilage and bone is destroyed the joint losses range of motion and may become disfigured.

It is also important to know the difference between rheumatoid arthritis and Osteoarthritis. Osteoarthritis is the deterioration of the cartilage between joints through wear and tear. This condition occurs through the repetitive use of a joint over time and can look very similar to the earlier stages of rheumatoid arthritis. Rheumatoid arthritis is not caused through use of the joint and may occur at any age but most commonly between the ages of 40 and 60 (Mayo clinic 2009). Osteoarthritis affects almost everyone over the age of 70 but ranges in severity (Borigini and Zieve 2010b). Osteoarthritis is not caused by an autoimmune disease and there for is not treated in the same way. Osteoarthritis is treated with medications such as Acetaminophen (Tylenol), NSAIDs (Aspirin, Ibuprofen, Naproxen) (Borigini and Zieve 2010b).

Rheumatoid arthritis medications have advanced much throughout the past 100 years. Originally Rheumatoid arthritis was treated in very much the same way as
Osteoarthritis with medication like Acetaminophen (Tylenol), NSAIDs (Aspirin, Ibuprofen, and Naproxen). Aspirin was one of the first drugs used to treat Rheumatoid arthritis. The origins of aspirin can be traced back to 400BC where it was extracted from the bark of the willow tree. Aspirin works by blocking an enzyme called cyclooxygenase-2 (COX-2) which causes inflammation, pain and fever. One of the side effects to this reaction is that aspirin also blocks a similar enzyme called cyclooxygenase-1 (COX-1) which is necessary for stomach and kidney health (Penn State 2010). This is why the most common side effect is stomach lining issues and kidney damage.

Image was located on (Penn State 2010) website.

The above image is the mechanism for the production of Acetylsalicylic acid (Aspirin)

This production of aspirin is pretty straight forward; the Salicylic acid has an OH group on it which attacks the one of the strained carbons on the acetic anhydride. When the bond is formed there is a positive charge on the oxygen and the hydrogen leaves with a base to balance the molecule. The bond to the carbon causes the oxygen on the other side to break its double bond which causes it to have a negative charge. The electron pair
swing back to form the double bond again which pushes the other oxygen on the molecule off. The result is Acetylsalicylic acid or aspirin.

This image was found on (Penn State 2010) website

The above reaction shows how cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) convert arachidonic acid, which is from membrane phospholipids, into cyclic prostaglandins. Prostaglandins are compounds that control "blood pressure, inflammation, fever, platelet aggregation during clotting, gastric secretions, kidney functions and several other important processes" (Penn State 2010). The anti-inflammation and pain reducing effects of aspirin coming from inhibiting the enzyme cyclooxygenase-2 (COX-2). Unfortunately aspirin will inhibit cyclooxygenase-1 (COX-1) as well which is where the antithrombic and ulcerogenic properties come from.

Though aspirin helped with the inflammation and pain associated with Rheumatoid arthritis it did not help prevent the progression of the disease. Methotrexate is now considered the first-line disease modifying anti-rheumatic drug (DMARD) medication for individuals with Rheumatoid arthritis (Matsumoto, M.D and Bathon, M.D). Other DMARDs include leflunomide (Arava), hydroxychloroquine (Plaquinil), sulfasalazine (Azulfidine), and finally minocycline (Dynacin, Minocin) (Mayo Clinic 2009). Methotrexate (MTX) was originally synthesized in the 1940s and was designed to inhibit dihydrofolate reductase. "Reduced folate (tetrahydrofolate) is the proximal single carbon donor in several reactions involved in the de novo synthetic pathways for purine and pyrimidine precursors of DNA and RNA required for cell proliferation" (M Cutolo and A Sulli et al 2001). Methotrexate was not used for Rheumatoid arthritis until 1951 where its abilities to inhibit the generation of lymphocytes and other cells that cause inflammation in the joint. Methotrexate also inhibits monocytes and macrophages that are believed to be a critical part of the Rheumatoid arthritis pathophysiology and inflammatory synovitis (M Cutolo and A Sulli et al 2001).
The above image was found on (M Cutolo and A Sulli et al 2001) website

This image shows how low doses of methotrexate interacts within a cell to decrease the inflammatory response caused by Rheumatoid arthritis. Methotrexate decreases the production of monocytes, which are large phagocytic white blood cells, and causes monocytes to undergo apoptosis. Apoptosis is a process where a cell destroys itself and is commonly known as cell death. Methotrexate also decreases the production of Lymphocyte Th2 and the known proinflammatory Lymphocyte Th1. Cyclooxygenase-2 (COX-2) is also inhibited by methotrexate, which was also a benefit of aspirin. Its is also observed that methotrexate reduces that amount of synovial fibroblast that is produced which in turn reduces the amount of metalloproteinase (MMP) produced. Metalloproteinase (MMP) is a protein that is speculated to be a cause of synovial joint damage (M Cutolo and A Sulli et al 2001). “Recent data have already suggested that the disruption of the cell cycle caused by high dose MTX treatment may be the initial step of the apoptotic sequence of dying cells and may explain the antiproliferative effects of the drug” (M Cutolo and A Sulli et al 2001). In other words methotrexate may be similar to another chemical in the body that initiates cell death in specific cells. Recent finding also suggest that methotrexate might inhibit the movement of immature and inflammatory monocytes into the inflamed sites and reduces the survival of cells already in the
inflamed synovial joint (M Cutolo and A Sulli et al 2001). Basically this means that methotrexate not only blocks the production of inflammatory cells and but also destroys inflammatory cells already present in the affected areas.

The above intercellular reactions show the complexity of the chemical reactions that occur with methotrexate. The reaction starts in the top left where methotrexate (MTX) affects the production of FGAR and the production of FAICAR, which causes an influx of AICAR production. The accumulation of AICAR inhibits the AMP and ADA, which in turn causes an increase of Adenosine. The intracellular increase of Adenosine causes the Adenosine to move across the cell membrane. The Adenosine then attaches to specific receptor proteins A1 and A2 where cyclic adenosine monophosphate (cAMP) is released into the cell. Cyclic adenosine monophosphate (cAMP) then leads to an immunosuppression response (M Cutolo and A Sulli et al 2001). This covers both the anti-inflammatory and immunosuppression properties of methotrexate.

The most recent type of medication available for Rheumatoid arthritis patients is Biologic Response Modifiers (Biologic DMARDs). “Biologic response modifiers are drugs made from living cells” (University of Maryland Medical Center 2011). This type of medication targets specific parts of the immune system that cause the inflammation and joint damage in Rheumatoid arthritis patients.

The current biologic DMARDs include:
- Etanercept (Enbrel) approved 1998
- Infliximab (Remicade) approved 1999
- Adalimumab (Humira) approved 2002
- Anakinra (Kineret) approved 2001
- Abatacept (Orencia) approved 2005
- Rituximab (Rituxan) approved 2006

(University of Maryland Medical Center 2011)

Biologic DMARDS are the current first line treatment for Rheumatoid arthritis but they can be used in combination with other DMARD. Biologic DMARDS can not be used together due to the increase chance of infection due to the suppression of the immune system (University of Maryland Medical Center 2011). “In recent trials, some patients have achieved remission using methotrexate in combination with infliximab, adalimumab, or rituximab” (University of Maryland Medical Center 2011).

Molecular model of Humira found on Abbott Laboratories website

Adalimumab (Humira) is the recombinant IgG1 monoclonal antibody that is unique for human tumor necrosis fact (TNF) (Edwards 2003). “The drug binds specifically to TNF-alpha and blocks its interaction with the p55 and p75 cell surface TNF receptors” (Edwards 2003). The unique component of biologic DMARDS are that they are living antibodies that are created in a lab.

Rituximab (Rituxan) is the most recent medication approved by the FDA to treat Rheumatoid arthritis. Rituximab (Rituxan) is “a genetically engineered human-mouse chimeric monoclonal antibody against the CD20 antigen, has been used successfully in the treatment of B Cell malignacies” (Singh and Robinson 2005). Genetic engineering is the future for medications for Rheumatoid arthritis. Genetically engineered antibodies are created from sequences of DNA or RNA that are spliced together using specific enzymes and place in phages, which are bacteria host that replicate extremely fast. Then the bacteria are destroyed and the antibodies are removed and tested.

Conclusion

There may not be a cure for Rheumatoid arthritis but the medications have come a long way from simple aspirin to genetically engineered antibodies. The future medications for Rheumatoid arthritis will no longer be compounds created in labs but
living cells that are biologically programmed. Unfortunately even these complex medications do nothing to cure the disease and if the individual stops taking them the symptoms will return. The real breakthrough will be when the cause of the Rheumatoid arthritis is found and if it's a genetic defect or abnormality then genetic engineering will be able to eventually cure it. Gene therapy is the use of genetic engineering to place healthy genes into the DNA of an individual with genetic disorders.
The Environmental Effects of the Use of Chemical Dispersants in Response to Marine Oil Spills

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April 22, 2011
Abstract

In 2010, industry and the United States Federal Government were caught off guard by an explosion in BP’s Deepwater Horizon oilrig that resulted in the spilling of millions of gallons of crude oil into the Gulf of Mexico. The response to the Deepwater Horizon spill was marked by the unprecedented use of chemical dispersants. This paper is an analysis of the use of dispersants, the chemical composition of the dispersant used in the Deepwater Horizon response, Corexit 9527 and Corexit 9500, and toxicology studies associated with the Corexit products. This is followed by a discussion on the environmental impact of using, as opposed to not using, dispersants.

Deepwater Horizon

The year 2010 marked the occurrence of one of the worst environmental disasters in the United States’ history and “the largest accidental oil spill in history.” On April 20, 2010, global energy company BP’s Deepwater Horizon oilrig, located in the Gulf of Mexico “42 miles off the coast of Louisiana,” suffered from an explosion that caused the death of 11 rig workers and an “underwater [oil] geyser” that was to continuously spew crude oil over the next 85 days. Over that time, multiple attempts at stopping the spewing well were made, and it was not until five months after the explosion that the well was definitively declared dead. According to researchers at Columbia University, over the course of the Deepwater Horizon oil spill, as much at 185 million gallons of oil had been released as a result of the damaged well. Following the blowout, various methods of oil clean up were employed, including: “situ burning, sorbents, herding, chemically dispersing, booming off sensitive areas, and mechanical removal.” While many of the methods used were non-controversial, one method that was used was surrounded by some controversy. Over the course of the clean up, BP, with the permission of the United States Environmental Protection Agency (EPA), acting under the direction of the Obama Administration, came under fire for the heavy use of chemical dispersants. The dispersants in question were Corexit 9527 and Corexit 9500, chemical dispersants manufactured by Nalco Company. The Corexit products have been in use for the past 20 years and are approved by many developed countries as a suitable method for at sea oil dispersal. The problem with its use during the Deepwater Horizon cleanup was in response to the 2 million gallons of Corexit products used. When used at this scale some felt it could create serious toxicological effects. According to Nalco “All of the ingredients contained in Nalco’s dispersants are
safe,” citing that all are compounds that can be found in household products⁸. However, while these compounds may be predominantly toxicologically inert in small amounts, studies have shown that in large amounts the compounds can cause adverse effects on both the flora and fauna inhabiting marine environments⁷. Dispersants are used on oil slicks formed at the surface of the water by dispersing the oil into the water column thereby speeding the natural decomposition of the oil⁹. What follows will be an overview of the reasons for and methods of the use of dispersants, an overview of the dispersant, Corexit, that was used in the Deepwater Horizon cleanup followed by a discussion on the toxicological effects in marine environmental ecosystems and the environmental cost of using and not using dispersants.

**Use of Dispersants**

When oil is spilled into marine environments it floats to the surface of the water and forms what are known as surface oil slicks¹⁰. These slicks can be several inches thick depending on the compositions of the crude oil, the ambient temperature and the movement of wind and water currents¹¹. Oil is not formed from a single compound; rather it is a mixture of hydrocarbons that behave differently when in contact with a marine environment¹¹. Following the release of the oil, the “more volatile components begin to separate and disperse into the atmosphere”¹¹. The fate of the remaining compounds is what is significant to the discussion and use of chemical dispersants. Oil is insoluble in water and, depending on the composition of the portion of oil being observed, behaves in various ways¹¹. The components that make up crude oil separate with a rapidity based on the wave action and temperature (warmer temperature induces faster dispersal) at the location of the spill¹¹. The lighter components separate and “form thin films” leaving behind thicker masses of oil which form thick layers of oil¹⁰. These differing layers of oil can be dispersed into the water column by the wave action of the marine environment¹¹. The oil from the spill can adversely affect the live inhabitants of marine environment in several ways. When oil spills occur, the most visible aspect of the impact on marine fauna is the visible coating of oil on large marine animals¹¹. In the case of marine birds, the coating of oil on their feathers renders the waterproof quality of their feathers useless¹¹. Marine mammals are chemically affected not only by the coating of oil on their skin but also by the intake of toxic fumes from the oil vapors¹¹. The think layer of oil can break off in chunks called “tar balls” which can be ingested by animals, causing internal harm¹⁰. Due to wave action, the oil slick can form emulsions with the seawater¹¹. This emulsion can have detrimental effects on
coastal habitats\textsuperscript{11}. This problem occurs when the emulsion "coat[s] plants and benthic animals, [such as] corals, crabs and shell fish, preventing photosynthesis and breathing and blocking filter feeding mechanisms\textsuperscript{11}.

In the case of Deepwater Horizon, the oil slick formed by the spill was a threat to the gulf's coastal grass estuaries, which harbored a wide variety of commercially utilized animal species including shelled and bony fishes\textsuperscript{11}. The oil that reaches the shore, especially in the shallow coastal gulf waters, form a sediment that can take years to biodegrade\textsuperscript{11}. The issue of concern in the instance of the Deep Water Horizon spill was, that due to the shallow nature of the Gulf, the oil would "cover hundreds of square miles of coastal habitat" forming both an environmental and commercial disaster\textsuperscript{11}.

Due to these devastating effects of an oil spill on the marine and coastal environments, every effort is made to stop the dispersion of an oil slick in as short a time as possible. A method of halting the progression of the slicks towards the coast as well as a method for speeding the biodegradation of the spilled oil is through the use of chemical dispersants\textsuperscript{9}. Dispersants are used to break the oil slick into small droplets, which in, combination with natural wave action, distribute the oil into the water column\textsuperscript{9}. Dispersants are a group of chemicals that are a combination of surfactants and solvents, which speed the natural dispersion of oil into the water column\textsuperscript{9}. The solvent penetrates through the oil slick where it "transports and distributes the surfactant to the oil/water interface"\textsuperscript{9}. The transport of the surfactant to the bottom of the oil layer is essential due to the composition of the surfactant. Surfactants are molecules composed of "an oleophilic part and a hydrophilic part"\textsuperscript{9}. The interaction between the surfactant and the oil/water layer results in a reduction in surface tension and the formation of small oil droplets\textsuperscript{9}. The
droplets occur as the oleophilic end of the surfactant interacts with the oil, while the hydrophilic end interacts with the water (see Figure 3). These droplets are no longer connected to the oil slick and are easily dispersed into the water column by wave action. The reformation of the oil slick is thereby reduced as the droplets are quickly separated from each other. Once in droplet form, the oil is more easily biodegraded, primarily by microorganisms. The dispersion of oil is beneficial as it reduces the concentration of oil in a location to levels that are considerably less toxic that that found in an oil slick. As mentioned previously, when crude oil first spills, the more volatile components are evaporated out. As this occurs the viscosity of the remaining oil increases. This viscosity is detrimental to the use of dispersants as the solvents must be able to penetrate to the oil/water interface. Due to this consideration, dispersants must be used within the “[first few] hours to [the first] few days” of the formation of the oil slick. The increased viscosity further hampers the dispersion due to the mechanical inability of the wave action to assist with dispersion. The action of the dispersant is almost immediate and is easily observable (see Figure 4 on previous page). The result is a dark brown “coffee-colored” plume visible beneath the surface. Because most of the testing done with dispersants is conducted in laboratory experiments, without the influence of natural marine conditions, such as wave action and temperature, there is no set amount of dispersant that is used for dispersion of a given amount of oil. The usual amount of dispersant applied begins with a ratio of 1:20 dispersant to oil. From that point, visual observation is used to determine whether the oil has been dispersed or not. The formation of a brown oil plume seen beneath the surface indicates effective dispersal. The formation of a white plume indicates that the dispersant is either used in excess amounts or is unable to penetrate the oil slick and is running off into the water. In both cases, the application of the dispersants is halted as the dispersant has already been effective or will not be effective in the given situation. As noted, the dispersant is usually applied to oil slicks on the surface of the water. This is accomplished by spraying the dispersant from boats and from planes. In the case of the Deepwater Horizon spill, dispersant was also applied to the oil gushing form the wellhead located on the sea floor, in an attempt to reduce the amount of oil that reached the surface. While the use of dispersants effectively removes the slick from the surface and makes it more readily available to micro-organisms to metabolize and for natural dissolution of the oil over time, the dispersants are additional chemicals that are added to an ecosystem in addition to the already toxic oil. Because the Corexit products are considered the most effective over a wide range of conditions, they are the most frequently utilized dispersant. For this reason the following discussion will focus primarily on the Corexit products as dispersants.

Corexit Products, Toxicology and Oil Biodegradation

Chemical Composition

The exact chemical composition of the Corexit products was not publicly available until June 2010, as companies are not legally required to release proprietary information about their products. Prior to that date, Nalco released only a Material Safety Data Sheet (MSDS) with a few of the ingredients being disclosed. However, due to pressure for the public over the secrecy of the ingredients of the Corexit Products used in the Deepwater
Horizon response, Nalco publically released the ingredients for both Corexit 9527 and 9500\textsuperscript{3,13}. The composition of the Corexit products is shown in Table 1 (see next page).

The 2-butoxyethanol used in Corexit 9627 and the petroleum distillates in the Corexit 9500 are both used as solvents\textsuperscript{3} to transport the surfactants through the oil slick\textsuperscript{3}. Corexit 9527 was used at the beginning of the clean up and was replaced by Corexit 9500 shortly after the clean up began\textsuperscript{13}. The sorbitans and 2-sulfo-1,4-bis(2-ethylhexyl) ester, sodium salt are a mixture of surfactants\textsuperscript{3,10} which interact with the water oil interface to form the easily-dispersed, small oil droplets\textsuperscript{9}. At the time of the Deepwater Horizon spill, there was little information regarding the “fate and biological effects” of the various components of the Corexit products beyond that supplied by Nalco’s MSDS sheets for Corexit 9527 and Corexit 9500\textsuperscript{10}. Now there are many toxicology studies that have been conducted, however they reflect what can be accomplished in a lab and, as the use of dispersants had not been conducted on the scale as of Deepwater Horizon, the long term effects of the use of dispersants in the ecosystem, especially in the Gulf of Mexico, cannot be accurately determined\textsuperscript{15}

<table>
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<tr>
<th>CAS Registry Number</th>
<th>Name</th>
<th>Chemical Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1338-43-8</td>
<td>Sorbitan, mono-(9Z)-9-octadecenoate</td>
<td><img src="image1" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>9005-65-6</td>
<td>Sorbitan, mono-(9Z)-9-octadecenoate, poly(oxy 1,2-ethanediyl) derivs.</td>
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<tr>
<td>9005-70-3</td>
<td>Sorbitan, tri-(9Z)-9-octadecenoate, poly(oxy-1,2-ethanediyl) derivs</td>
<td><img src="image3" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>577-11-7</td>
<td>* Butanedioic acid, 2-sulfo-1,4-bis(2-ethylhexyl) ester, sodium salt (1:1)</td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>29911-28-2</td>
<td>Propanol, 1-(2-butoxy-1-methylethoxy)</td>
<td><img src="image5" alt="Chemical Structure" /></td>
</tr>
<tr>
<td>64742-47-8</td>
<td>Distillates (petroleum), hydrotreated light</td>
<td>N/A</td>
</tr>
<tr>
<td>111-76-2</td>
<td>** 2-butoxyethylol</td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

Table 1: Ingredient list for Corexit 9527 and Corexit 9500\textsuperscript{13}.

\* Contains 2-Propanediol

** ... (Ethanol, 2-butoxy-)... [not] included in the composition of COREEXIT 9500\textsuperscript{13}
Toxicology Studies Concerning Corexit 9500 and Marine Organisms

The use of Corexit 9527 in the Deepwater Horizon response was phased out by mid response in favor of Corexit 9500, due primarily to the content of 2-butoxyethanol\(^3\). Therefore the toxicology tests that follow were conducted using Corexit 9500. One method for determining the toxicity of a compound is called Lethal Concentration (LC\(_{50}\)) values\(^3\). These values “reflect the ‘lethal concentration’ required to kill 50% of the test organisms” over a given time period\(^3\). The EPA conducted a series of peer edited LC\(_{50}\) toxicity tests on several species of marine organisms, which inhabit the Gulf of Mexico\(^5\). Those organisms tested were the “mystid shrimp, Americanmysis bahia, an aquatic invertebrate... and the inland silverside, Menidia beryllina, a small estuarine fish”\(^15\). Part of the concern with the use of the Corexit products was the possibility that a less toxic dispersant could be used\(^15\). Therefore the tests were conducted using eight different dispersants “Dispersit SPC 1000; Nokomis 3-F4; Nokomis 3-AA; ZI 400; SAFRONGOLD; Sea Brat #4; Corexit 9500 A; JD 2000” all of which were selected from the EPA’s list of fourteen approved dispersants and with the criteria that the selected eight were of known lower toxicity\(^13\). When testing the toxicology of dispersants, the following procedure was conducted. Samples of varying concentrations of “dispersants, dispersants-oil mixtures, and oil alone” were used in the exposure of the two species\(^15\). The fate of the organisms in the afore mentioned solutions was compared to that of the species “kept in clean, untreated seawater”\(^15\). It is important to note that many of the toxicology studies conducted are conducted in laboratory conditions\(^15\) that do not necessarily reflect the actual toxicology of the dispersants in the marine environment\(^3\). This is due to the fact that the concentrations of substances used in LC\(_{50}\) tests are “at sustained concentrations much higher than what [is] actually see[n]” in the constantly moving marine environment\(^3\). In the natural environment an organism’s contact with dispersants and oil is acute rather than chronic, as is found in the studies conducted in laboratory situations\(^10\). Also the differing compounds can affect organisms differently based on several factors such as “species...[and] stage of development (adult versus larval)”\(^15\). Despite this the tests are useful starting points for determining toxicity\(^15\). The results of the study conducted by the EPA are as follows.

For all eight dispersants in both test species, the dispersants alone were less toxic than the dispersant-oil mixture. Oil alone was found to be more toxic to mystid shrimp than the eight dispersants when tested alone. Oil alone had similar toxicity to mystid shrimp as the dispersant-oil mixtures, with exception of the mixture of Nokomis 3-AA and oil, which was found to be more toxic. The oil results for small fish were inconclusive.\(^15\)

The study was inconclusive for Menidia beryllina as only 7% of the test organisms died\(^15\). Importantly the study concluded that the dispersant “Corexit 9500 was no more or less toxic than the other available alternatives” for acute exposure\(^15\).

Biodegradation of Oil, Corexit 9500 and Oil/Corexit Mixtures

Although the exact means by which spilled oil is broken down and processed by marine ecosystem is unknown, it is known that there is significant biodegradation by microbes\(^3\). The primary purpose of using dispersants is to speed the biodegradation of the spilled oil\(^15\). The results of studies conducted on the subject conclude that mixtures of oil
with Corexit 9500 do speed the biodegradation process\textsuperscript{15}. The half-life of the oil from the Deepwater horizon spill was considered to be “12-70 days in seawater”\textsuperscript{15}. Studies concerning the half-life and rate of biodegradation of Corexit 9500 are lacking\textsuperscript{15}. However the fate of dispersed oil is somewhat more studied. According to studies published by the EPA concerning the “biodegradation of dispersed oil,” the use of Corexit 9500 to disperse oil results in a 50% increase in the rate of biodegradation of spilled oil\textsuperscript{15}.

Environmental Costs of Using and Not Using Dispersants

The use of dispersants comes with an environmental tradeoff. Is it better to allow the oil slick to remain on the surface or is it better if the oil is dispersed in the water column? Is the benefits of putting chemical dispersants, about which little is known, into the ecosystem in order to speed the biodegradation of the oil? The answer is not a simple one.

The most important concept regarding the use of dispersants is that the oil is simply moved from the surface into the water column\textsuperscript{3}. It is not gone. The primary reason for using dispersants in the Deepwater Horizon response was to protect ecologically “fragile wetlands,” including “mangroves and salt marshes” and to protect the shoreline on the Gulf Coast (see Figure 5 on next page)\textsuperscript{15}. By protecting the shoreline, the habitat, and the species that inhabit it can be protected\textsuperscript{15}. The use of dispersants also helps to reduce the thick oil slicks which adversely affect marine mammals and birds\textsuperscript{3}. There are downsides to the dispersed oil droplets though. The small size of the droplets make the oil appear as a food source to small zooplankton, which, if killed, effect the entire food chain as they are “crucial to the marine food web”\textsuperscript{3}. Although the purpose for the use of dispersants is to make the contents of the oil slick more readily available to be metabolized by microbes, this does come with a down side\textsuperscript{3}. The microbes are anaerobic and their metabolism of the oil results in a drop in the oxygen levels in the surrounding waters, which can result in negative effects for surrounding aerobic organisms\textsuperscript{3}. This effect can be monitored by testing the waters for dissolved oxygen content and reducing the use of dispersants when dissolved oxygen content is at levels less than 2mg/L (normal content is 4mg/L)\textsuperscript{15}. While the use of dispersants helps to protect shorelines, the dispersed oil has the potential to adversely effect flora and fauna located underwater (see Figure 5 on next page)\textsuperscript{3}. For this reason dispersants should be used with caution in shallow waters and are more suitable for open seas\textsuperscript{3}.

While the effects of dispersed oil are many, and generally include a trade off between the oil effecting the shore line and being degraded slowly to the oil affecting the lower levels of the sea and degrading in some cases too quickly, the most concerning aspect of the use of dispersants is the lack of long term studies concerning their use\textsuperscript{3}. Unfortunately while toxicology tests may indicate the results of acute exposure the information regarding the “sub-lethal effects...[such as]... changes in reproduction or immune function” is glaringly lacking\textsuperscript{3}.
Figure 5: "Floating oil will not affect coral or sea grass, but it can devastate coastlines. Dispersed oil, on the other hand, becomes far more available to underwater organisms but largely spares coastal ecosystems."  

Conclusion

The use of dispersants is not a new practice. The difficulty arises in that, due to industry rights to confidentiality, adequate studies concerning the effects and degradability of dispersants, namely the Corexit products, on the marine environment are lacking. Based on the studies that have been conducted on the toxicity of Corexit 9500, the use of Corexit 9500 in response to oil spills especially of the magnitude of the Deepwater Horizon spill, the use of dispersants can be an effective method of reducing environmental damage. While dispersants are an additional chemical added to the environment with little knowledge of their long term effects, the use of dispersants in the open seas and when used in amounts that are regulated, can be beneficial. The oil spilled during the Deepwater Horizon catastrophe was such a great quantity that the 2 million gallons of Corexit products was small in comparison and the dispersant was of less toxicity than the oil. The benefit of using dispersants in the open sea to speed the biodegradation of oil to 6-35 days compared to the normal 12-70 days, albeit anaerobic and possibly harmful to aerobic aquatic life, is preferable to the extremely slow, in some cases decades long, aerobic breakdown which occurs when oil is metabolized on shoreline and in muddy sediment environments. Due to what little knowledge there was at the time of the Deepwater Horizon spill, the use of dispersants can be seen as the best response method. However due to the increased interest in the fate and use of dispersants and the unintentional opportunity to study the effects of dispersed oil provided by the Deepwater Horizon response, it is a suitable time to study the long term effects of chemical dispersants on the marine environment to determine whether the use of dispersants in the future is the correct and most environmentally conscious decision.
References


Baycol® (Cerivastatin Sodium):
A Look into What Went Wrong

Prepared for
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Organic Chemistry 236

Prepared by
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April 21, 2011
Abstract

Hypercholesterolemia or high cholesterol is a major health concern for many people. If not maintained accordingly, imbalanced cholesterol levels can lead to heart attack, stroke, and other vascular diseases. Prescription strengthen drugs called statins were developed to help control cholesterol levels and allow patients to lead healthy, productive lives. One statin in particular was Baycol® (Cerivastatin Sodium) tablets. Baycol®, said to be above the rest in treating Hypercholesterolemia, was approved by the FDA and marketed for the treatment of high cholesterol. This paper includes the overview of Hypercholesterolemia and the rise and fall of Baycol® (Cerivastatin Sodium), a once promising statin that went on to become more infamous than it was helpful. All images support the information reflected in the text.

Introduction

Since the late 1980’s, a slew of new drugs called Statins have flooded the pharmaceutical market. These miracle drugs, used originally for the treatment of Hypercholesterolemia and the reduction of low-density cholesterol (LDL), contested against coronary artery disease (CAD) and cardiovascular disease (CVD). Statins gave millions of people around the world a helping hand in the fight against vascular disease, heart attack, and stroke. Due to their revolutionary nature in the pharmaceutical world, the long-term risks of Statins, like many new drugs, went unknown for many years. It was not until long-term patients taking these so-called “wonder-drugs” began to fall ill and develop extremely rare myopathic disorders that the long-term risks of Statins became known. One statin in particular, Baycol® (Cerivastatin Sodium), raised several concerns after patients' ailments turned into more serious medical matters and in the end resulted in death for some.

Cholesterol Production and Statins

Statins are categorized as a class of drugs used to lower lipids and reduce cholesterol levels in patients with high levels of cholesterol. Cholesterol, in normal amounts, can be a good resource for the body. A major role of high-density cholesterol (HDL), the good cholesterol, is to support the cells that make up the internal organs and muscular tissues. HDL cholesterol is a building block for hormones and is also associated with the transportation of low-density cholesterol (LDL). LDL cholesterol accounts for most of the cholesterol issues that currently plague the lives of 36 million Americans.¹

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**Figure 1**
Production of Cholesterol
Statins lower LDL cholesterol by allowing some of the built up cholesterol on the walls of a patient’s arteries, due to diet or family history, to be reabsorbed. This reabsorption process will in turn strengthen the walls of those same arteries that were once plagued by cholesterol plaques.²

The mechanisms in which most statins follow begin with the blocking or inhibiting of HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase, the major enzyme in cholesterol production. The human body creates cholesterol by using reductase to transition through the Mevalonate pathways. These pathways give way to the production of dimethylallyl pyrophosphates (DMAPP) and isopentenyl propanophosphates (IPP). Once the DMAPP and IPP pathways have been laid, the synthesis of cholesterol can occur. Statins go in and act as HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors. These inhibitors follow the Mevalonate pathways just as the body’s own reductase do; however, the statins work to stop the reaction needed to form excess cholesterol from occurring by removing the catalyst (reductase) from the situation. Without the reductase, which helps to catalyze the DMAPP and IPP pathways, the production of excess cholesterol is stunted.³

**Baycol® (Cerivastatin Sodium)**

Organically Baycol’s main ingredient, Cerivastatin Sodium, has an empirical formula of C26H33FNNaO5 and can be named as [S-R*,S*(E)]-7-[44-(4-fluorophenyl)-5-methoxymethyl]-2,6bis(1-methylethyl)-3-pyridinyl]-3,5-dihydroxy-6-heptenoate.⁴

![Figure 2](image.png)

**Organic Structure of Cerivastatin Sodium C26H33FNNaO5**

Florophenyl compounds, like the ones found in Baycol®, are used to help with the acceptance of the drug by the body after being ingested, allowing for it to be metabolized. Once this occurs the drug can go on to make the intended corrections to the patient’s system.⁵

The clinical pharmacology of Baycol® (Cerivastatin Sodium), as enacted by the FDA, states that in “patients with Hypercholesterolemia (IIa and IIb), Baycol® has been shown to reduce plasma total cholesterol, LDL-C, and apolipoprotein B as an adjunct to a change in diet.” The FDA goes on to say that Baycol® can also reduce “plasma triglycerides and increase plasma HDL-C.” In
its reports the FDA concluded that Baycol® had no consistent effects on plasma. Results also stated that the effects of Baycol® on cardiovascular morbidity and mortality were unknown.4

Entrance of Baycol® to the Pharmaceutical Market

On February 18, 1998, Baycol® (Cerivastatin Sodium) was introduced by the Bayer Corporation onto the pharmaceutical market. The introduction was made after Bayer received approval for doses of Baycol® up to 0.3mg by the US Food and Drug Administration (FDA) on June 26, 1997. FDA endorsement came after a period of tests and clinical trials that would seem short by most clinical standards, especially for a statin. The Bayer Corporation marketed Baycol® as an effective new statin that was “simple and safe” with claims of less side effects and a greater reduction of LDL cholesterol deposits and triglycerides than in comparison to the other statins on the market. Baycol® was also said to have greater patient tolerance and cause less interactions with other medications. Baycol® was quickly promoted to Physicians as a way to strategize recognition and product growth. As its popularity grew, Baycol® was taken back to the FDA by Bayer and granted approval on two new dosing options; making Baycol available in 0.3mg, 0.4mg, and 0.08mg. Due to quick marketing tactics and a strong new client-base, Baycol® became a huge success for the Bayer Corporation.6

In 2000, Baycol® was the third largest drug sold in the history of the company with sales reaching $554 million and projected sales of 2001 at over $800 million. Baycol® was a hit with insurance providers like HMOs. This was because it was the cheapest statin on the market at that time.7

Clinical Trials for Baycol®

The Bayer Corporation conducted clinical trials for Baycol® (Cerivastatin Sodium) tablets in North America, Israel, and South Africa. The controlled studies conducted were reviewed by the FDA and went on to show that Baycol® did in fact lower the plasma totals and LDL cholesterol of those studied with Hypercholesterolemia and mixed Hyperlipidemia. Over 2,800 patients took part in the testing, a relatively small amount for pharmaceutical testing, over a period of 4 to 104 weeks. The trial was a random, double-blind study where a control group was given a placebo. From those tested the results showed that patients with Ila Hypercholesterolemia (genetically induced) and Iib Hypercholesterolemia (diet induced) reacted well to the 0.05 – 0.3mg doses of Baycol® they were given. The results showed substantial reductions in patients overall cholesterol levels after the first week along with lower levels of plasma triglycerides (TG) and promotion of HDL cholesterol.4
The FDA approval for Baycol® came after the Bayer Corporation conducted clinical trials consisting of about 3,000 people, a lesser amount than should have been tested for a drug with such potential potency. This accelerated approval process helps to shorten the time it takes drug companies to receive clinical data from the new drugs being tested, increasing the risk by keeping the drug from being fully examined and the side effects unknown. This quick to market method is what ultimately lead to the failure of Baycol®.

<table>
<thead>
<tr>
<th>Dosage</th>
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<th>Total-C</th>
<th>LDL-C</th>
<th>HDL-C</th>
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<tr>
<td>Placebo</td>
<td>137*</td>
<td>+1.7</td>
<td>+1.8</td>
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<tr>
<td>0.2 mg qd**</td>
<td>143†</td>
<td>-17.4</td>
<td>-25.3</td>
<td>+10.4</td>
<td>-10.7</td>
<td>-18.7</td>
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<tr>
<td>0.3 mg qd**</td>
<td>135‡</td>
<td>-19.4</td>
<td>-28.2</td>
<td>+10.3</td>
<td>-12.7</td>
<td>-20.5</td>
</tr>
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* 137 patients were evaluated for all parameters except LDL-C which had 136 patients.
† 143 patients were evaluated for Total-C, HDL-C and TG. For LDL-C and Apo-B there were 140 and 141 patients evaluated, respectively.
‡ 135 patients were evaluated for all parameters except LDL-C which had 134 patients.
** qd = once daily

In a separate dose-scheduling study, BAYCOL® (cerivastatin sodium tablets) was given as either a 0.2-mg dose once daily with dinner or at bedtime or as a 0.1-mg dose twice daily (morning and evening). Mean LDL-C reduction in response to BAYCOL® dosed once with dinner or at bedtime was about 4% greater than the mean reduction in response to twice daily (divided) dosing (p<0.05).

After the prior market approval of Baycol®, the FDA released an adverse event report warning consumers of the direct connection between rhabdomyolysis and statin use, especially with Cerivastatin. The FDA’s warning stated that although rare, the occurrence of rhabdomyolysis could lead to increased levels of plasma creatine levels and kidney failure.

On August 18, 2001, the Bayer Pharmaceutical Division withdrew Baycol® (Cerivastatin Sodium) from the market. The withdrawal came after reports surfaced that many Baycol® patients began to develop myotoxicity leading to the FDA’s investigation and official consumer warning.

**Statin Induced Myotoxicity & Rhabdomyolysis**

Myotoxicity is the buildup of toxins in the muscles which can cause pain, weakness, discomfort, and in extreme cases muscle degeneration. This severe case of myotoxicity is known as rhabdomyolysis.

Symptoms of statin-induced myotoxicity and statin-related rhabdomyolysis have been seen in patients as early as one week after starting statin use. The diagnosis of statin-related myotoxicity can be seen in patients who experience and report myalgia (muscle pain), weakness,
or who are tested and found to have elevated concentrations of Creatine Kinase (CK) in their blood. The normal resting levels of CK for men are between 55 to 170 units per liter (U·L⁻¹) and 30 to 135 units per liter (U·L⁻¹) for women. Excess levels of CK can result in myositis or muscle pain that is directly correlated to abnormal increases CK levels. More serious increases in CK levels can lead to rhabdomyolysis.

Rhabdomyolysis occurs when a patient’s CK levels are 10 times the highest normal limits stated above. In situations like these, patients experience tremendous pain, due to the degeneration of muscle tissues and the leaking of myoglobin, a heme protein associated with the storing of oxygen within the muscles into the muscles and bloodstream. Due to the patient’s compromised condition, the release of myoglobin is too great and the over-oxidation of muscle tissues lead to degeneration, acute renal (kidney) injury or failure, and in some cases death.

** Fallout of Baycol® **

As a direct result of the Aug. 18, 2001 withdrawal of Baycol®, the Bayer Corporation suffered major economic and public consequences for the failure of Baycol®. Shares within the Bayer Companies fell by 43%, there was a 6.5% decline in sales for the first quarter of 2002, and the company overall operating profit dropped a staggering 46%. Bayer’s once promising and extremely affluent asset was now the expensive thorn in their side. The withdrawal of Baycol® cost the Bayer Corporation over $575 million and 1,800 Bayer employees their jobs. Fifteen
manufacturing plants were also compromised to help the monetary balance after the massive explosion.¹²

Out of the 871 cases, 31.9% were in correlation with Cerivastatin use. This statistic later became bleaker when further results showed 38 consumers died from the complications caused by Baycol®.⁸

At the time of the recall, Baycol® was being distributed in over 63 countries. The death toll reached 52 by 2001. Months after this information was released, Bayer said that the actual death toll from Baycol® was over 100. Since 1997, Baycol® was the 12th prescription drug pulled from the U.S. market due to extremely dangerous side effects.¹³

**Bayer Corporation Lawsuits**

As if their economic struggles weren’t enough, the Baycol® backlashes lead the Bayer Corporation to legal troubles as well. As many as 40,000 patients filed complaints within the U.S. alone, leading to a staggering 600 trials. While in Europe, 400 complaints were filed in 2001 alone.¹²

**Summary and Conclusion**

Hypercholesterolemia is a serious disease that plagues the U.S. population as well as many others across the world. Medicines like statins, when fully understood can bring longevity and knowledge to vast amounts of people. Baycol® had what looked to be a promising future as a top drug worldwide; however, due to the corporate push to get it on the market and the lack of knowledge on its long-term effects, Baycol® was withdrawn and blacklisted for the deaths of over 100 peoples name. The ill-fated outcomes that stemmed from the withdrawal of the Bayer Corporations Baycol® (Cerivastatin Sodium) tablets were unfortunate and could have been prevented if the proper time and surveillance was put into the clinical trials of the drug. It is an injustice done to anyone who puts their trust in the competence and their lives in the hands of the pharmaceutical drug companies.
References


Canine Parvo Virus

Ashley Forshee

April 2011
ABSTRACT

Canine Parvo Virus is a serious gastrointestinal disease that is expensive, exhausting and time consuming to treat, but can be very easily prevented with modern vaccinations and simple awareness. This virus is actively evolving and has become increasingly resilient, capable of living in the environment outside its host cell for many months and is not easily deactivated by household cleaning products. CPV most commonly effects dogs and puppies under 6 months but is capable of infecting any animal that is exposed and vulnerable. Treatment and prevention have evolved along with the virus over the past many years and continue to evolve as the virus changes and becomes more immune to the technology designed to fight it.

CONTENT

The Parvo Virus is a nonenveloped virus composed of single stranded DNA. Canine Parvo Virus (CPV) is present in two main strains, CPV-1 which is most commonly associated with gastroenteritis in young dogs, and CPV-2 which is the widely known disease responsible for most parvoviral enteritis leading to death in dogs today (8). Within this second class, two strains have evolved over the last 20 years, CPV-2a and CPV-2b. CPV-2b is the strain most commonly found in the United States, while both strains are still seen in Europe. The evolution of the Canine Parvo Virus has lead to an extremely stable form that spreads more effectively and is unaffected by most environmental conditions (5). CPV is most commonly seen in young puppies under 6 months of age but can infect most canines and even some felines. Breeds more prone to CPV include Rottweilers, German Shepherd Dogs, American Pit Bull Terriers, Doberman Pinschers, Laborador Retrievers, and English Springer Spaniels (5). Males tend to be more prone to contracting this virus then females, although infected mother dogs can pass the virus on to entire litters.

Like most viruses, the Canine Parvo Virus spreads by infecting rapidly dividing cells of its host, and using those cells machinery to replicate and form new viruses (2). Figure 1 represents an epithelial cell that has been infected with CPV. The cell has lysed and is releasing newly formed viruses into the extracellular space (4). Figure 2 shows a single parvo virus on the left and cluster of parvo viruses on the right (1). CPV normally attacks the cells of the lymph nodes first and spreads to cells of the intestines, bone marrow and lymphoid tissues after only two to four days (6). Localized infection in the intestines affects primarily the epithelium lining of the entire digestive tract; tongue, esophagus, small intestine and lymphoid tissue (5). Once the virus has localized in the intestines, it degrades the microvilli lining the intestines, leading to dehydration, bloody diarrhea and vomiting (8). Secondary infections from bacteria present in the intestines often then enter the blood stream through degraded tissue, leading to more serious clinical signs such as myocarditis, or inflammation of the heart tissues, and sepsis (5). Degradation of the lining of the intestines prevents the animal from absorbing water and nutrients, and most often results in bloody diarrhea and vomiting, as well as loss of appetite and dehydration.
Infected animals shed large amounts of viral particles in their feces both during illness and up to 10 days after. CPV is then transmitted to other animals through direct contact with infected feces. CPV is extremely stable and is capable of living free in the environment for many months. It is easily transferred to its surroundings and can be carried on humans, instruments, cage or kennel surfaces, and even insects. CPV can live on surfaces for as long as five months, infecting any animal that comes in contact with it. The best way to clean surfaces is with sodium hypochlorite (bleach) since most detergents are ineffective at inactivating the virus (5). Animal shelters, boarding kennels, breeding facilities and veterinary hospitals must take special precautions in recognizing CPV and then taking the appropriate steps to prevent further infection of other animals. Dog owners should be wary of public dog parks and places where dogs of unknown origin may frequent due to lack of knowledge of other pets vaccination history.

Many times animals do not show clinical signs until several days after infection has set in. Most animals are presented to veterinary clinics with symptoms such as lethargy, diarrhea, vomiting, loss of appetite and weight loss (10). Very young puppies may appear to go into shock induced by myocarditis, or swelling of the heart tissues. Normally entire litters are affected, and the virus can be contracted in utero (8). New born pups are often found dead within 24 hours of
the first signs due to the sudden onset of heart failure caused by myocarditis (5). Severe anorexia and abdominal discomfort upon palpation are often noted along with enlarged lymph nodes and an irregular body temperature (10). Abdominal radiographs often show signs of gas or fluid in the intestines which can be misleading to veterinarians as these things are often present in healthy dogs as well (5).

The most accurate in-house diagnostic test is the fecal enzyme-linked immunosorbent assay (ELISA) which tests fecal samples for antigens specific to CPV. The most effective samples are collected rectally, since antigens are seldom detectable after 10-12 days of infection (5). A CBC analysis of blood samples may indicate lymphopenia, leucopenia or neutropenia; lack of white blood cells which are used to fight infections (10)(11).

Treatment for CPV is mostly supportive and is similar to treatment for any gastrointestinal enteritis. Serious cases should be hospitalized to allow for intravenous fluid and electrolyte therapy, as well as constant monitoring by professional care takers which should be continued until vomiting and diarrhea cease (6). Fluid and electrolyte therapy depend on the severity and specificity of the individual case. If the dog is hyponatremic, meaning the sodium content in the blood serum is low, a saline based fluid is administered to boost sodium content in the blood stream. Hyponatremia usually occurs due to lack of water intake. Sodium content in the blood stream is normally regulated naturally by the stimulation of thirst due to the secretion of the antidiuretic hormone (ADH) (3). Often in cases of CPV hyponatremia occurs due to loss of water because of consistent vomiting and diarrhea, so even if the animal is drinking water it may still be losing a sufficient amount of nutrients. If the animal is not hyponatremic, meaning the sodium serum levels remain normal, then a fluid therapy of lactated Ringer’s is administered intravenously. A supplement of potassium is often added to the fluid therapy as an extra boost, along with 2.5% glucose to aid in the regulation of the blood sugar. Fluids and medications are given intravenously so as to allow direct contact with the blood stream. Subcutaneous fluids are often inadequate and can lead to shedding of large amounts of skin as the cellular content of the body is compromised, especially in animals suffering from the loss of white blood cells (6). Blood plasma or blood transfusions are necessary when very young puppies become anemic or hypoalbuminemic, meaning serum albumins in the blood stream are very low. Colloid and crystalloid therapy is helpful in stable puppies that are hypoproteinemnic, or protein levels in their blood stream are low. Colloid therapy refers to fluids that do not readily pass through the intravenous membrane due to molecular size and therefore retain blood pressure in the veins and arteries. In contrast, crystalloid therapy refers to fluids that pass readily through the membrane and into the extracellular space. These fluids are usually composed of sodium chloride and help to reinstate the sodium balance in the extracellular fluids (7).

Aside from fluid support many dogs are also treated with antibiotics to ward of secondary infections caused by bacteria in the intestines (6). The large amount of degradation of the lining of the intestines causes bacteria to enter the bloodstream, known as sepsis, and can be detrimental without the aid of antibiotics, sometimes resulting in a severe drop in blood pressure
leading to septic shock (9). Symptoms of vomiting and diarrhea are also treated to help prevent dehydration. Medications that curb nausea, such as metoclopramide, are administered and food is often withheld until vomiting and diarrhea have ceased for at least 24 hours, after which a bland diet of rice, chicken, or commercial veterinary diets may be integrated back into the routine at very small increments (6). Still, once the animal has shown significant signs of recovery and may be discharged from the care of a hospital, it should be kept secluded from other animals for 2 to 4 weeks since viral particles may still be shed in the feces for 10 days or more post infection (8).

Prevention is the best way to keep the Canine Parvo Virus at bay. Vaccinations should be administered to healthy puppies starting between 6 and 10 weeks of age with the last booster vaccine given around 12 weeks. Vaccinations may be incapable of surviving in adult females due to their immune system. These immunities may also be passed on to their litters. Like any vaccine, the Parvo vaccine should be boosted up to 3 times at 3 to 4 week intervals, until the dog is 16 weeks of age, to ensure the immunity takes effect immediately after the maternal immunities have diminished. Even adult dogs should receive booster vaccines if it is unknown whether or not they have received vaccines in the past. After the initial boosters have been completed the vaccine should be boosted annually for the remainder of the animals life (8).

These vaccines are available as two different types; modified live, and inactivated. A modified live vaccine contains living viral entities and tends to last much longer in the animals immune system, however live vaccines should not be used in very young puppies under 5 weeks of age as they may cause severe reactions due to low levels of immunity already present in the animals system. An inactivated vaccine is often used in pregnant or nursing mothers and in puppies under 5 weeks of age (6). These vaccines are safe to use in combination with other viral vaccinations. Vaccines often result in acute infections of the virus and viral particles are shed in the feces for up to 10 days. These components are not dangerous as they do not occur in the large amounts that a virus obtained from the environment will (5).

For dogs previously cured of the Parvo Virus, recontamination from its surroundings is the biggest issue. As mentioned before, CPV can live for many months outside of a host and is not readily destroyed by most household detergents. The best way to cleans an infected area is with household bleach diluted 1:32 parts. Even so, dogs should be kept away from contaminated areas and other animals until vaccinations are completed (8). Most dogs that survive the Canine Parvo Virus develop immunities to it that may last the remainder of their lives. However, this does not mean these dogs do not need to be vaccinated as it is unproven whether or not this immunity is effective for all dogs and against all CPV strains. CPV is continuously evolving to form new strains and vaccination technology is only one step behind it.

As vaccination technology evolves and the public becomes more educated about CPV and other canine viruses, the occurrence of the virus in house hold pets should hopefully diminish. However, most animal hospitals and veterinary clinics see cases of CPV coming from
pets adopted as strays that were found on the street or adopted out of shelters. With the ever increasing population of homeless pets in animal shelters it is impractical for organizations such as the humane society to treat each and every sickness that walks through its doors, especially with a disease such as Canine Parvo Virus, Canine Distemper Virus, and Canine Corona Virus, which can become very expensive to treat. Therefore, many animals that show signs of CPV or other severe sicknesses in the shelter are simply euthanized before they are able to be adopted. Animals that do not readily show signs are vaccinated and adopted out, but occasionally turn up at a veterinary clinic with a disease such as CPV. In these instances, the shelters are notified and the owner is given the option to return the dog, but they are informed that the animal will most likely be euthanized upon return. Any remaining sibling of that litter is generally euthanized as well to prevent further infection to the rest of the residents at the shelter. Here is where the importance of spaying and neutering yours pets becomes apparent. The fewer stray animals in the streets contracting viruses, the fewer disease ridden animals end up adopted out of shelters and into our homes.
BIBLIOGRAPHY


Thalidomide: Beneficially Wicked

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April 22, 2011
Abstract

Thalidomide is one of the most notorious drugs in medical history. Until recently, thalidomide was remembered only for its ability to create horrendous birth defects after it was taken by women as a sedative and by pregnant women to relieve morning sickness in the late 1950's. The affected children had missing or drastically shortened arms or legs, often reduced to flipper-like appendages. Even today, the phrase "Thalidomide Baby" evokes pure horror. More recently, thalidomide was found to be a useful treatment for leprosy and is Food and Drug Administration (FDA) approved for that purpose in the United States. In addition, it is being used in the treatment of certain types of cancer.  

With definite pros and cons, thalidomide can be described as beneficially wicked.

Chemistry and Mechanisms

Thalidomide is an immunomodulatory agent. An immunomodulatory agent is a drug that may be an immunosuppressant or an immunostimulator based on its effect on the immune system.

The empirical formula for thalidomide is C₁₃H₁₀N₂O₄ and the gram molecular weight is 258.2.

Chemical Structure

![Chemical Structure of Thalidomide]

Thalidomide is an off-white to white, odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. It contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S-(-) or R-(+). It is an equal mixture of the S-(-) and R-(+) forms and, therefore has a net optical rotation of zero.

Mechanism

The mechanism of action of thalidomide is not fully understood. Thalidomide possesses immunomodulatory, antiinflammatory and antiangiogenic properties. Available data from in vitro studies and clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration.

Although thalidomide was initially developed as a sedative, it has a multitude of other effects that were not evident when it first came to market. The first discovery was its teratogenic, the ability to cause birth defects, when taken by pregnant women.
Most recently, there have been studies showing that the treatment of multiple myeloma, an incurable bone marrow cancer that accounts for two percent of cancer-related deaths, is another possible use for the drug. In a study conducted in 1998 at the University of Arkansas, one-third of the 84 patients who had failed to respond to other therapies improved, and two went into complete remission. The possible mechanisms of action of thalidomide, its in vitro metabolites, or both, in myeloma are being extensively studied. It has been found that thalidomide may directly inhibit the growth and survival of myeloma cells, bone marrow stromal cells, or both. This may be accomplished through oxidative damage to DNA mediated by free radicals, which probably has a role in the teratogenicity of thalidomide. A second mechanism involves the finding that adhesion of myeloma cells to bone marrow stromal cells triggers the secretion of cytokines that increase the growth and survival of myeloma cells, and induces them to be resistant to drugs.⁷

**History of Thalidomide**

Thalidomide, one of the most notorious drugs in the world, was first developed and sold in Europe in the 1950s as a tranquilizer. A West German company brought it to market, and it was eventually sold by 14 companies in 46 countries. Doctors in those countries prescribed it to pregnant women as a relief for morning sickness, not knowing of the drug’s horrible effect on their fetuses.⁶ It was found that mothers who had taken the drug during the first trimester, when the limb buds of the fetus are formed, produced children with a wide range of deformities. The most well known pattern was phocomelia which is the absence of a portion of the arm with the hands extending as flipper-like appendages from the shoulders. Another frequent arm malformation was radial aplasia, defined as the absence of the thumb and the adjoining bone in the lower arm. Similar limb malformations occurred in the lower extremities. The babies almost always had both sides affected and often had both the arms and the legs malformed. Besides the limbs, the drug caused malformations of the eyes, ears, heart, genitals, kidneys, digestive tract (including lips and mouth), and nervous system⁵. Between 20% and 90% of pregnant women exposed to even one dose of the drug bore children with these defects.⁷

Thalidomide was never approved by the Food and Drug Administration (FDA) for use in the United States, and therein lies one of the FDA’s greatest success stories. In November of 1960, Dr. Francis Kelsey, the FDA official charged with overseeing thalidomide’s New Drug Application (NDA), was concerned that thalidomide might cause neuropathy, a nerve disease, in some users. She decided that the thalidomide NDA was incomplete and refused to approve it. This kept thalidomide tied up just long enough, since in 1961 the drug’s effect on newborn children became known. In 1962, President Kennedy presented Dr. Kelsey with a gold medal, the Distinguished Federal Civil Service Award, for her efforts.⁶
To deal with the diverse applications for which thalidomide was being tested, the FDA in 1994 established the Thalidomide Working Group to provide consistency among the reviewing of the studies. Members of the Thalidomide Victims Association of Canada (TVAC) were outraged at the idea that the licensing of thalidomide was being considered. The TVAC reluctantly recognized that strict regulation would be preferable to illegal distribution on the black market. According to Randy Warren, the chief operating officer of the TVAC:

"We’re forced to prefer regulated thalidomide over illegal thalidomide available on street corners, without warnings. We who know suffering cannot deny quality of life or longer life to others who suffer. We demand mandatory compliance with strict distribution systems. Thalidomide must never be a drug of choice, but always of need or last resort. We demand forced research into new analogs to replace thalidomide, with all of the benefits but without the teratogenic and disconcerting nerve damage side effects. When the new analog or drug is developed, we demand the removal of thalidomide from this planet. Thalidomide must always be called thalidomide – no glory names, just thalidomide."  

In 1998, the use of thalidomide to treat erythema nodosum leprosum was approved by the FDA. Although the FDA established very strict control of its use, thalidomide’s approval led to greater availability and increased interest in the drug. As a result, thalidomide is now a very useful drug in the treatment of a large number of disorders from erythema nodosum leprosum to multiple myeloma. Today, despite its many uses, thalidomide remains the most strictly regulated drug in the world.  

**Indications, Usage, and Administration**

**Erythema Nodosum Leprosum**

Erythema nodosum leprosum (ENL), also known as type-2 reaction, is characterized by brightly red, raised, tender nodules and plaques of varying sizes. They are warmer than the surrounding skin and they go pale on light touch. The severe form is more common in Caucasians and Mongolians. Necrotic and ulcerative forms are the rare presentations of severe ENL. Thalidomide is indicated for the acute treatment of the cutaneous manifestations of moderate to severe ENL and is also indicated as maintenance therapy for prevention and suppression of the cutaneous manifestations of ENL recurrence. The initial dose is 100 to 300mg per day, preferably one hour after the evening meal. If 400mg per day is needed, give at bedtime or in divided doses at least one hour after meals to patients with severe cutaneous ENL reaction or to those who have previously required higher doses to control the reaction.

**Multiple Myeloma**

Multiple myeloma is a cancer of the plasma cells, a type of white blood cell present in bone marrow. Plasma cells normally make proteins called antibodies to help fight infections. Thalidomide in combination with dexamethasone is indicated for the
treatment of patients with newly diagnosed multiple myeloma. Adults with multiple myeloma initially take 200mg per day, divided at bedtime and at least one hour after the evening meal. Dexamethasone 40mg is also administered on days one to four, days nine to 12 and days 17 to 20 every 28 days.

Side Effects and Risks

When a physician chooses to prescribe thalidomide, the benefits must obviously outweigh the risk, and the risks are great. The major risk is severe, life-threatening birth defects. It must not be taken by women who are pregnant or who could become pregnant while taking this medication. Even a single dose of thalidomide taken during pregnancy can cause severe birth defects. For men taking thalidomide, this medication is present in the semen so sperm donation is prohibited while taking the drug. If thalidomide is being used to treat multiple myeloma, there is a risk of blood clots forming in the arms, legs and/or lungs. This risk is greater when thalidomide is used along with other chemotherapy medications such as dexamethasone. To help decrease the risk of blood clots forming, the physician may also prescribe an anticoagulant, a blood thinner.

Side effects include but are not limited to:

- Drowsiness
- Dizziness
- Confusion
- Anxiety
- Depression or mood changes
- Difficulty falling asleep or staying asleep
- Bone, muscle, joint or back pain
- Weakness
- Headache
- Changes in appetite
- Weight changes
- Nausea
- Constipation
- Dry mouth
- Dry skin
- Pale skin
- Itching
- Uncontrollable shaking of a body part
- Swelling of the hands, feet, ankles, or lower legs
- Difficulty achieving or maintaining an erection

S.T.E.P.S.® Program

In 1975, the FDA created guidelines for drug companies to follow in regards to labeling medications about their affects on reproduction and pregnancy. Thalidomide is rated category X, which is contraindicated in pregnancy. With drugs in the X category, studies in animals or humans, or investigational or post-marketing reports, have demonstrated positive evidence of fetal abnormalities or risk which clearly outweighs any possible benefit to the patient. A program called System for Thalidomide Education and Prescribing Safety (S.T.E.P.S.®) has been approved by the FDA to make sure that pregnant women do not take thalidomide and those women do not become pregnant while taking thalidomide. All individuals who are prescribed thalidomide, including men and women who cannot become pregnant, must be registered with S.T.E.P.S.®, have a
thalidomide prescription from a doctor who is registered with S.T.E.P.S.®, and have the prescription filled at a pharmacy that is registered with S.T.E.P.S.® in order to receive this medication.

A physician’s visit is required every month during treatment to talk about the diagnosis and any side effects being experienced. At each visit, the physician may give a prescription for up to a 28-day supply of medication with no refills. This prescription must be filled within 7 days.

Donating blood during thalidomide therapy is prohibited. Sharing medication is also prohibited even though someone may have the same symptoms.³

*Women and Thalidomide*

If a woman can become pregnant, she will need to meet certain requirements during her treatment with thalidomide. She needs to meet these requirements even if she may have a history of not being able to become pregnant. She may be excused from meeting these requirements only if she has not menstruated for 24 months in a row, or if she has had a hysterectomy.

A woman must use two acceptable forms of birth control for four weeks before she begins to take thalidomide, during her treatment, and for four weeks after her treatment. Her doctor will tell her which forms of birth control are acceptable. She must use these two forms of birth control at all times unless she can guarantee that she will not have any sexual contact with a male for four weeks before treatment, during treatment, and for four weeks after treatment.

A woman must have a negative pregnancy test within the 24 hours before beginning treatment with thalidomide. She will also need to be tested for pregnancy in a laboratory weekly during the first four weeks of treatment and then once every four weeks if she has regular menstrual cycles or once every two weeks if she has irregular menstrual cycles.

If a woman believes she may be pregnant or if she has a late, irregular or missed menstrual period, she should call her physician immediately. The physician should also be made aware of intercourse if two forms of birth control are not used. If a woman becomes pregnant during thalidomide therapy, the physician is required by law to call the FDA and the manufacturer, Celgene Corporation. The physician will also refer the woman to a physician who specializes in problems during pregnancy who can help make choices that are best for her and the baby.³

*Men and Thalidomide*

Since thalidomide is present in semen, a man taking thalidomide must either use a latex condom or completely avoid any sexual contact with a woman who is pregnant or may become pregnant for four weeks after he starts treatment. This is required even if he has had a vasectomy. A man should tell his physician immediately if he has had unprotected
sex with a woman who can become pregnant or if he think for any reason that his partner is pregnant. The donation of sperm is also prohibited during thalidomide treatment.9

A Thalidomide Love Story

Through all of the tragedy and devastation thalidomide has caused, there are truly remarkable stories of happiness and hope surfacing over fifty years later. Louise Medus, 46 and Darren Mansell, 47 dated as teenagers. Darren first proposed to Louise when she was just 19. Feeling she was too young to marry, Louise turned him down and the two went their separate ways. Both later married other people, had children and separated from their respective partners. But, in 2002, the two reunited by a chance meeting. Determined not to throw away what they both recognized was a second chance, they began dating again. When Darren proposed for a second time, Louise happily accepted.

Both Darren and Louise were thalidomide babies, and have endured more than 40 years of stigma as a result of their condition. In the news article, Louise states concern with thalidomide being approved for the use of treating cancer. She says, “I am horrified that thalidomide has recently returned as a treatment for cancer. I, of all people, know the dangers, and I would never inflict what I have suffered on more potential victims. It is still an extremely dangerous drug.” However, knowing what some of her thalidomide peers are going through, she is quick to point out that she is very lucky. She has shortened arms, legs and feet and Darren has shortened arms.

Soon after birth, Louise was placed in a home for disabled children because her parents were told she would live for only a few weeks. She spent most of her childhood in the home, returning to her family only for occasional holidays. She went on to become one of the best-known thalidomide children, largely thanks to her father and his campaign to secure compensation for victims of the drug. Louise says she does not blame her family for being kept in a home most of her life. She says things were different then and disabled children were not seen much in the community. Due to the lack of knowledge about thalidomide back then, doctors thought children affected by the drug would only have a couple of months, then a few years, and eventually said if the children were lucky, they would make it out of their 20’s.

Despite the restrictions she faced, Louise says her childhood was happy. It was not until she was watching her own children grow that she realized how much she had missed out on. Louise separated from her first husband in 1994 but with the help of 24-hour caregivers, who she still relies on today, she has managed to raise her children on her own and is extremely proud of herself. At age 35, she faced another obstacle. She became ill with polycystic kidney disease, a hereditary condition which was worsened by her disability. After nearly dying, Louise became the first thalidomide victim to have a kidney transplant in 2002 and went on to make a full recovery.
Like Louise, Maggie Boyd, 45, was a thalidomide victim. She also was put into a home shortly after her birth. Maggie has shortened legs and limited use of her thumbs. She barely saw her mother after her placement in the home. She states her father was absent from the family as her parents had divorced before she was born. Her mother only visited her twice when she was a little older, once bringing her younger sister but her mother never told her sister that Maggie was her child too. Maggie says, “I think my mother felt guilty and ashamed of me.” She didn’t have a bad childhood but there was a huge emotional cost. For instance, she married far too quickly only because she wanted someone to love her. She later divorced but has gone on to raise her four children.

Like many other thalidomide victims, Maggie devotes part of her time to an ongoing battle for compensation from the drug’s German makers and German government. Compensation deals made in the 1970’s and now worn by inflation are no longer adequate to provide the degree of care needed by victims. Maggie, who is wheelchair bound, says having an independent life is expensive. Cars and houses have to be specially adapted and victims are not necessarily able to work. She states, “No one is asking for millions of dollars. We just want enough to ensure we can survive.”

With the passing of the 50th anniversary since thalidomide was launched in the United Kingdom, the love story of Louise and Darren and the strength and independence of Maggie are proof that happiness can be uncovered from this unique human tragedy. 11

Conclusion

The lessons of thalidomide have not been, nor should they ever be forgotten. The FDA is a stronger agency because of it, and to this day cites the impact the thalidomide tragedy has had on policy. The pressure to push through approval of thalidomide and the consequences that would have resulted had the FDA given in are used as a defense of the strict approval system that is in place. Although the system is often attacked for being too slow and preventing new experimental drugs from being used as soon as possible, the risks of being too hasty are quite clearly seen from the thalidomide case.

It is clear that the thalidomide tragedy is very much on the minds of officials, and is still having an impact on policy. Perhaps this idea is best expressed by Sol Barer, the chief executive officer of the Celgene Corporation: “There has never been a drug that has so profoundly affected drug development around the world as has thalidomide. It altered attitudes about drug regulation, it significantly broadened FDA authority, it affected all drug development. It changed history.” 7

Nowadays, the FDA is constantly faced with the challenge of weighing the risks and benefits associated with drugs and their side effects and determining if and when they can be approved for use. Dealing with the new uses that are being found for thalidomide is a particularly delicate situation, considering the significant impact of its history. The approach taken thus far is one of cautious approval coupled with the strictest distribution rules ever issued. Until new uses for the drug are found which provide the same
beneficial effects without the horrific negative effects, we can only hope that the guidelines will work.
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Korinne Frey

Was I Born Gay?

April 20th, 2011
Abstract

The big question today in society whether it be in a social or political setting, is whether or not homosexuals are born gay. It seems that if there was a “gay” gene discovered it could change things in society as we know it. While many homosexuals feel that they were born the way they are, is it really true? In the past years, there have been many studies done and there are many theories out there whether or not homosexuals are born gay. This paper will take a look at those studies and theories.

For a very long time the American Psychiatric Associations defined homosexuality as a mental illness. It took a very long time, and for many doctors to do research and studies to be done for the American Psychiatric Association to remove homosexuality from its list of mental illnesses in 1980. (Facts.) So if homosexuality is not a mental illness, what is it? That is what many doctors, scientists and psychologist have tried to determine what it is. Some people believe that it all begins in the womb during development. There is no doubt that during development men’s and women’s brains develop differently. The sex hormones that are prevalent in men and women are a form of steroid hormones. The two main hormones are testosterone and estrogen. Testosterone and estrogen are both derivates of cholesterol. Below are the chemical structures of cholesterol, testosterone, and estrogen respectively.

\[ \text{Chemical structure of cholesterol} \]

\[ \text{Chemical structure of testosterone} \]

\[ \text{Chemical structure of estrogen} \]
After looking at all three structures it is easy to tell that testosterone and estrogen are the derivatives of cholesterol. Since cholesterol is usually a constituent of the cell membrane, the sex hormones are as well. Cholesterol also has a waxy cell membrane that allows it to pass through other cell membranes. The sex cells have this same characteristic too. The receptor cells for the sex hormones are actually located inside the cell. (Dynes 1990)

Below are the mechanisms for testosterone and estrogen.
If the testosterone stops outside of the cell there is a chemical relay in the cytoplasm that does several different things. It changes the cell chemistry, initiates hormone release, blocks cell death, and gets the cell from a resting stage to the growth phase of it's life cycle. Inside the cell, the testosterone attaches the receptor in the nucleus and begins to activate the protein producing genes. (Hormones)

(Estrogen)

In the mechanism for the estrogen, it too can bind with surface receptors. If it does this then is begins a chemical relay in the cytoplasm which triggers nitric oxide production. The production of this will either flood the cell with calcium or trigger hormone release. When the estrogen binds with the receptors inside the cell, it moves into the nucleus and activates protein producing genes. (Hormones)

The testes are the main source for producing testosterone. The ovaries are the main source for producing estrogen. Each gonad also produces trace amounts of the other sex hormone as well. This happens because the structures of each hormone are so similar to each other. In the developing brain, the brain becomes masculinized by testosterone
after it is converted to estrogen within the cells of the brain by the enzyme aromatase. In order to prevent masculinization the brain, all embryos and fetuses produce an estrogen binding protein called alpha-fetoprotein. The alpha-fetoprotein captures an estrogen that comes into contact with it, and leaves the testosterone unaffected. This then enters the brain cells and is converted into estradiol with in the neurons. (Development) Once this is done sex differentiation is complete within the brain. While this describes what makes males different from females from a brain prospective, it does not talk about the differences between heterosexuals and homosexuals. Throughout time homosexuality has been studied, but only a handful of people have tried to prove that homosexuality is because of a biological factor.

Homosexuality has been around for hundred of years, and as long as it has been around it has been studied. The first time that homosexuality was studied was with Aristotle. While he did not come right out and say whether or not people were homosexual, he had his own theories on love and friendship. He also noted that while males sometimes played the role of women, anal sex was not normal. Since during this time there was not a real study of psychology, a different realm of science tried to explain homosexuality. In Alexandria, the school of astrologoy took a look at homosexuality and tried to explain what they thought it was. They used the influence of the planet’s position to Venus and the person’s horoscope to explain this. In this time period it was expected of women to be passive. If the women was aggressive in a heterosexual relationship then she was then placed into the same category as lesbians because she did not fit the mold. The scientist during this time period based homosexual activity on the planets and what was going on in the environment instead of any biological or social factors. (Dynes 1990)

The next time period that homosexuality was studied was during the 4th century. A man named Caelius Aurelianus was the first person to say that homosexuality was not actually a disease but a problem with unrestrained libido. He believed that a man with an unrestrained libido did not care who he had sex with as long as he was having sex. By this behavior it made him behave less like a man and more like a woman. (Dynes 1990)

In the 18th century more writings were done on the study of homosexuality. Most of the writings dealt with the fact that homosexuals were acting on their own wills and that they could control the urges if they wanted to. In 1857, Benedict Auguste Morel defined the term degeneration. (Dynes 1990) Degeneration is, “a lowering of effective power, vitality, or essential quality to an enfeebled and worsened kind or state, also, a progressive deterioration of physical characters from a level representing the norm of earlier generations or forms”. (Merriam-Webster) After defining the term degeneration, Morel determined that the hypothesis of homosexuality is, “many mental states could be explained by the degeneration of the central nervous system”. (Dynes 1990) Also during this time, Ernst von Feuchtersleben defined the term psychopathy. Von Feuchtersleben defined the term as “pathological state of mind without a legion of the brain or central nervous system”. (Merriam-Webster) Today we know the term psychopathy to mean “mental disorder especially when marked by egocentric and antisocial activity”.

(Merriam-Webster)

The first two people to make major headway in studying homosexuals were Karl Heinrich Ulrichs and Karoly Maria Kertbeny. During the 1800’s they tried to do as many studies as possible on homosexuals but had a difficult time finding subjects to study.
These studies also did not hold much weight in the academic world because they usually found only one or two people to study and these people were usually from prison or an insane asylum. (Dynes 1990) Up until this time most doctors and psychoanalysts believed that homosexuality was pathological. Sigmund Freud on the other hand did not. He believed that everybody was born bisexual. Freud said that whether a person turned out to be heterosexual or homosexual depended on the experiences that person had with their parents and other people. Because of this, Freud believed that homosexuality should not be viewed as a form of pathology. After Freud, many psychoanalysts rejected his theories and argued that homosexuality was indeed pathological that stemmed from family relationships. (Facts) Below I will be discussing more recent studies that have been done to try to determine whether or not a person is born gay.

The first modern study that was done on homosexuals was in 1985 by Richard C. Pillard and James D. Weinrich of Boston University. They studied twins and family DNA to see if homosexuality was inherited. Since their study, five other twin studies have been done. The data of their study shows that 57% of identical male twins, 24% of fraternal twins, and 13% of brothers of gay men were also gay. The study also showed that 50% of identical female twins, 16% of fraternal twins, and 13% of lesbians with lesbian sisters were gay. When looking at all of the information that was collected family clustering could be seen. (Hamer and LeVay 1994) To say the these results are conclusive would be incorrect. The main problem with this study is that if homosexuality was genetically linked then 100% of the identical twins would have received this gene. Also another problem with this study was that is was not a random group of twins. The men put ads out asking for people to be in the study. This is not fair because the twins who participated in this study may have had their own objectives. Finally there were similar twin studies that were done that did not produce the same results. The twin study that was done seemed to show more of an environmental influence in homosexuality than biological. (Harrub et.al 2003)

Another study that was done was in 1992 by Laura S. Allen and Roger A. Gorski. In their study they looked at sexual orientation and the size of the anterior commissure in the human brain. The anterior commissure is a fiber tract that is located in the midsagittal area of the brain. They took 90 postmortem brains from homosexual men, heterosexual men, and heterosexual women. After doing all of their tests, they determined that the anterior commissure was 18% larger in homosexual men than in heterosexual women, and 34% larger than in heterosexual men. One major factor that played a role in this was that 24 homosexual men died of AIDS as did 6 heterosexual men. While this may seem to lead to the reason why the anterior commissure was larger, they determined that it had no effect on the outcome because AIDS related neuropathologies are normally related to neural atrophy. They also determined that it did not matter if the homosexual males died of AIDS or not because the numbers of men without AIDS still showed that the anterior commissure was still larger. While this study seemed to show that there was a correlation between the anterior commissure and homosexual men, the major problem with this study was that there was really no way to tell for sure if the men were telling the truth on whether or not they were homosexual or heterosexual. For the time that this study was done it seemed that this was proof that there was a biological difference and reason that people were born gay. This theory though did not hold up and this study was never
Another study that was done involved women. This study was done by Sheri A. Berenbaum. She studied women that had congenital adrenal hyperplasia. Known as CAH, it is a "genetic disease that results in high levels of androgens beginning early in gestation and continuation until development until treatment is initiated". (Berenbaum 1998) Females with CAH are exposed to higher levels of androgens than that of typical girls and boys. They are also exposed to the typical amount of female ovarian hormones. While girls with CAH identify as girls and are raised as girls along with their unaffected sisters, they have very different social experiences. Females that have CAH are behaviorally masculinized and defeminized. Effects of CAH are the following; girls are more aggressive, have greater spatial ability, more likely to be left handed, play with boys’ toys and less with girls’ toys, more likely to choose boys as playmates, less interested in infants, motherhood, feminine appearance, more likely to have homosexual or bisexual fantasies. Most of the women with CAH have female typical gender identities. (Berenbaum 1998) Only a small percent of these women have gender identity conflict or live as a man. This study included 24 girls with CAH, 16 unaffected sister, 18 boys with CAH and 24 unaffected brothers. There was a test performed in 1990 that some of these women still have some of the sex-atypical behaviors in adulthood that they did when they were children. Problems with this study was the it was never replicated. Also, many of these women had to think back to their childhood to answer these questions. No woman could be one hundred percent correct about their memories from the past. In this study the mothers of these women were called on to answer questions about their daughters when they were young. Sometimes there were two different answers between the daughters and the mothers. While this study does not define that homosexuality is from a biological factor, it does show that different levels of androgens affected children differently. (Berenbaum 1998)

A famous study that was done by Simon LeVay looked at the medial preoptic area of the hypothalamus and sexual behavior. The group of cells that they looked at were located in the anterior hypothalamus. The hypothalamus is a very important part of the brain that is responsible for many of the regulatory functions of the human body. One of the functions of the hypothalamus is the control of sexual behavior and reproduction. This group of cells is called the INAH3. LeVay formed his hypothesis that the INAH3 was larger in homosexual men then heterosexual men. He took autopsy specimens from 19 homosexual men who died of AIDS, 16 heterosexual men who died of AIDS and 6 women with an unknown sexual orientation. He took the hypothalamus and stained it to mark the neuronal cell groups and encoded the specimens to eliminate bias. LeVay used a microscope to measure their cross sectional area. He then measured the area and thickness and then calculated the volume of the INAH3. After determining this, he did the same for the INAH1, INAH2, and INAH4. He noticed that the INAH3 was absent in some gay men all together. LeVay also noted that there was no difference in size between homosexual men and the women. At the time, many critics disregarded this because of what AIDS can do to the human body. LeVay found though that there was no volume difference between the homosexual men who had AIDS and the heterosexual men who had died AIDS. After the study was done, LeVay looked at one homosexual man who did not die of AIDS and found very similar results. (Hamer and LeVay 1994) While for
the 1990's, this seemed to be a major breakthrough, there are many problems that we see today with this study. The first major problem with this study is that since it was done it has never been replicated. Also, the INAH3 in the men who died of AIDS would have been smaller anyway because AIDS decreases the amount of testosterone that is present. He also did not have complete medical histories of the men and women. There could have been other biological problems that he did not know about. The last major problem of LeVay's study like the rest of the studies, was that there was no way for him to be sure the heterosexual men who died of AIDS were actually heterosexual, they could have lied at the beginning of the study. (Harrub et.al 2003)

   Even though none of these theories and studies played out, they have made people really think about where homosexuality comes from. More recently, people have not only turned to biologically factors but by social factors as well. Daryl J Bem has a theory that combines both genes and the way children are raised. He believes that there is no specific gay gene but rather genes that influence temperament such as their aggression and activity. It is much like the females that have CAH. It is easy to see that children play sports based on their temperament, and that children play with other children who are like them. Bem used information from a large scale study that was done at the Kinsey Institute for Sex Research. The study found that 71% of homosexual men and 70% of homosexual women felt different from same sex peers during childhood and adolescence. This study like some of the others relied on information and past feelings from their childhood. This study though did have participants that were relativity young so their memories were better. Using this information from this study Bem determined his theory that exotic become erotic. He said that “exotic becomes erotic because feeling different from a class of peers in childhood produces heightened nonspecific physiological arousal which is subsequently transformed into erotic attraction” (Bem 2000)

   For me being a homosexual woman, I have always felt that I was born this way. Looking back at my childhood there was nothing different about it from any other child that I grew up around. I have a younger sister and she is heterosexual. Growing up I always wanted to play sports and play with the boys at school, while she wanted to play with her Barbies and have sleepovers. My parents never discouraged us from doing certain things, they always encouraged us to do what we enjoyed. As much as I want to say that is a gay gene, after doing all of the research it is hard to say that such a gene exists. Much of the research that was done is outdated and not replicated. There is no hard evidence that one exists. The studies that say that our genes influence our temperament in development and actions along with our social upbringing make the most sense. Thinking back to my childhood and how I was these theories seem to fit. My parents never pushed me in one direction or another, they just allowed me to be me. Although a gay gene could mean that I was born this way and can not be changed, I can say that I am very comfortable with who I am and I would not want to change myself for anything or anyone.

   If one was to ask any homosexual person if they believed that they were born gay many of them would say yes. There is no denying that how one views their own personal sexuality is a natural feeling. The possibility of a gay gene could open so many doors and new possibilities. If it were proven that there was a gay gene then it would make people more understanding and tolerating. Also, it would possibly change the government’s
view of homosexuality and equal rights for all no matter what sexual orientation. While there are studies that have been done in the past to relate biological factors to sexuality there is no definitive proof that homosexuals are born that way. Until there are studies that are repeated and more definitive evidence found, there is no way to say for sure that homosexuals are born that way. The strongest evidence is that hormones play a role in temperament along with the social upbringing.
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The Underlying Hidden Effects of Lipitor and Crestor

Michael Frieh

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The Underlying Effects of Lipitor and Crestor

There is a very thin line between life and death, quality of life and survival, and benefits and consequences. The growing rate for heart disease is astronomical here in the United States; over 25 million people have some form of cardiac disease and still growing. Life is becoming more difficult to survive and so the levels of stress for the people have no plans on coming to a halt. If anything, it will continue to increase, and the world of medicine, more particularly the pharmaceutical industry, is very well aware of this. Statins have been a “miracle” drug to some and a life changing experience for others, from healthy to unable to walk or sleep. Two cholesterol reducing drugs are currently covering the majority of the world’s most chosen method of reducing cholesterol, Lipitor and Crestor. The questions is, are their side effects, and more importantly, their underlying effects not being focused upon by the physicians and big dogs themselves worth the risk just to reduce your cholesterol?

As we all know, life is very fragile. One little problem can sway one’s life in a completely different direction. Being born unhealthy or being born healthy and developing unhealthy habits as a child through adulthood, may result in disastrous attacks on the human body. People in this world contend with the negative forces of nature every day, every month, and every year of their lives. Just the thought of daily stresses can ache the heart of a person. Why do people allow this to happen? Well, there can be many answers to that question. In the world of evolution, the formula to what we are and what we become is based on genetics times the environment we are raised in. Many adverse events and diseases come into play based on this. More specifically, here in America, heart disease plays an active role, and because of this, the major pharmaceutical industries continuously play their role in extending their hands and noses into the public’s lives.

The United States in particular has an ever-growing rate of depression, obesity, diabetes, cancer, and more particularly heart disease. According to the statistics of the Center of Disease Control, “Heart Disease is the Number One Cause of Death. About every 25 seconds, an American will have a coronary event.” Heart disease is the primary killer and continues to affect the lives of many people who are at risk and have coronary problems, as well as their friends and family members. The weakness of the heart is a great attack on the human body for the functionality of the human body depends on the heart’s ability to divide the nonoxygenated and oxygenated blood away from each other and continually pump nutrients and oxygen to the rest of the body. Our heart is an engine connected by a large infrastructural network built of highways such as the body’s arteries, capillaries, and veins. Using its red blood cells as delivery trucks to transport and deliver what the rest of the body needs to survive, its life span calls for important changes to our diets and lifestyles in order to keep transportation and delivery at an optimum condition. Just like in every day rush hour traffic, if one path is closed off due to congestion, traffic may slow down or even come to a halt. The daily stress of survival may cause many to do things that are unhealthy for their hearts, yet the heart cannot deliver a warning message until it may be too late. Yearly physicals are recommended by doctors in order to review any changes occurring in one’s health. For men especially, testicular, colon and prostate health can be deadly if left unchecked. Of course aside from those health issues, weight, blood pressure, triglycerides and cholesterol levels should always be looked after since they may become high due to hereditary. Diet and exercise may be the best preventative measures to keeping the risk of heart disease low. Nonetheless, some may not be able to manage the changes needed to keep their health in optimal condition. In today’s day and age, we have the pharmaceutical world to thank for extending many lives and giving many a second, perhaps even a third or fourth, chance to live.

The Center of Disease Control states that, “Heart disease is the leading cause of death in the United States and is a major cause of disability. The most common heart disease in the United States is
coronary heart disease, which often appears as a heart attack. In 2010, an estimated 785,000 Americans had a new coronary attack, and about 470,000 had a recurrent attack. About every 25 seconds, an American will have a coronary event, and about one every minute will die from one.” Genetics may install the programming for heart disease yet the environmental pressures of life are all that is needed to apply the great physical stress needed to activate the programming. Different people handle stress differently, some using the positive and healthy methods available to us such as exercise, a parent playing with their kids, walking their dog, or even more complex methods such as meditation, yoga, and martial arts. Although this is all available to the majority of us, it is not the usual norm of releasing the stress for others.

Smoking, indulging in alcoholic beverages, and illegal drug use have been seen all over the world and the side-effects of their temporary “escape” can cause many more serious health problems, pertaining to the catch phrase: “If it’s not one thing, it’s another.” Smoking, along with the dangerous chemicals that are combusted and ingested, within its nature can cause devastating effects to the heart, as well as the rest of the body. Alcohol and drugs both have similar effects, slowly rotting away components our body needs in order to function properly. Everyday adolescents get turned onto those dangerous forms of “enjoyment and stress relief,” possibly for the rest of their lives. The human heart is in constant use and must pump all day and night for the rest of our lives. Without this muscle continuously pumping, we would not be able to live another second. Many people are indeed aware of all this, but most of us have lives where it is rather difficult to implement healthier changes or stop bad habits that have formed from earlier years. The pharmaceutical industry, of course, is aware of all this.

The world of pharmacology was implemented in order to create and produce medicinal solutions and treatments to help cure, prevent and/or reduce the effects of illness, though it also has turned into a world of massive revenue production and television advertisement madness. There is practically a drug to treat almost everything man has come across. Are they safe? Are they effective? Will I have to be on it for the rest of my life? How much will they cost me? Will this medication better or make my life worse? Questions that most patients ask themselves when they prepare to take on a product of the pharmaceutical world can be quite overwhelming. Of course, the bigger the selection of drugs to treat one issue, plus the misunderstanding of the drugs’ role and chemical interactions, may cause patients to just take their doctor’s word for it. There are many different drugs available for preventing heart disease called statins; two specific prescription drugs, Lipitor and Crestor, and their effects will be discussed.

As the Italian philosopher and poet (1265-1321) Dante once said, “The more perfect a thing is, the more susceptible to good and bad treatment it is.” This philosophy can also apply to medicine, for
the fact that a medication may treat, cure, or prevent one symptom or illness may also give way for a new ailment one to make its debut. The medication Atorvastatin calcium, brand named Lipitor, was synthesized in 1985 in a lab in Ann Arbor, Michigan by an organic chemist, Bruce Roth. It was supposed to be an inhibitor of the enzyme HMG-CoA reductase, which causes a change to the body's production of cholesterol. In December of 1996, the FDA had finally approved Lipitor as a medication to help reduce blood cholesterol (dyslipidemia) and help prevent cardiovascular disease. With its patent due to expire in June of 2011, Pfizer and Ranbaxy Laboratories had agreed to delaying the generic launch within the United States until November 2011. Lipitor was the top sold pharmaceutical in the world in 2008 with sales skyrocketing to $12.4 billion. It is quite a long carbon chain; full of benzene rings with a molecular formula C_{33}H_{43}F_{5}N_{5}O_{3} and molecular weight of 558.64g/mole. “In recent years, the use of “statins”, cholesterol-lowering drugs, has elicited tremendous controversy.” Doctors who believe in natural approaches to disease prevention have suggested that statin drugs are poison that should be avoided altogether. Pharmaceutical company-influenced cardiologists, on the other hand, have stated that virtually everyone over age 40 should be on a statin drug” (Arizona Center for Advanced Medicine).

![Chemical structure of Lipitor](image)

When it comes to medications, the difference between a medicine and a poison is dosage. This applies to both Lipitor and Crestor. Although Crestor has released four different doses in smaller amounts than Lipitor did. Lipitor has released four different doses approved by the FDA as a potentially safe amount to ingest, there are long term problematic effects that occur with taking such medications to insure longevity. Now the questions begin? What is Lipitor doing exactly to reduce my cholesterol and prevent heart disease from occurring? What else is Lipitor doing to my body? Will I feel different after beginning treatment with Lipitor? Is my doctor being a hundred percent honest with me about Lipitor being okay for me to take? Those questions are completely valid and patients should ask their doctors if Lipitor is the right medication for their high levels of cholesterol compared to the rest of the other medications? Well to begin, Lipitor has released four different approved doses, 10mg, 20mg, 40mg, and 80mg, as well as a lower dosage for children. Even children with high levels of cholesterol may take Lipitor. In 2002, the chewable children dose was approved in the United States, eight years later, following its debut into Europe after the European Union approved the New York-based company Pfizer to release its “wonderful” creation. In general, a jump from a dosage of 10mg up to 8 times the amount as a “maximum strength” version should be alarming. The maximum strength is meant for those who have had a major heart attack, recurring heart attacks, or after a stent was installed but has recently been prescribed to many who do not have severe cardiac issues.

The main purpose of Lipitor, atorvastatin, is to lower levels of LDL cholesterol along with diet and exercise. Based on Lipitor’s official website, “Along with diet and exercise, LIPITOR is proven to lower "bad" cholesterol by 39%-60% (average effect depending on dose). And LIPITOR, along with diet, is clinically proven to reduce the risk of heart attack and stroke in patients with heart disease or several common risk factors for heart disease. Common risk factors include family history of early heart disease, high blood pressure, low good cholesterol, age, and smoking. LIPITOR is the #1 prescribed branded cholesterol-lowering medicines in the world.” (Lipitor.com). What should catch the attention of patients is that diet and exercise are proven methods of reducing LDL and have been for centuries. Lipitor is only an expensive accessory with unsultry side effects to complete the prescription
drug package. Lipitor is in fact the #1 most prescribed brand in the world, with sales in 2009 in at $13 billion. Does this mean it's safe? "In an effort to boost profits, Pfizer is convincing doctors to prescribe the strongest, riskiest, and most expensive dose of Lipitor® to more and more patients – despite concerns about its safety and efficacy" (Arizona Center for Advanced Medicine).

Crestor, generically named rosuvastatin but actually rosvastatin calcium, one of Lipitor’s competitors, and the newest of the six recently released statins, is also in the business of reducing LDL cholesterols and prevention of cardiac disease. Crestor is manufactured by AstraZeneca. It was approved by the FDA August of 2003, approved in 154 countries, and launched in 56 countries in 2004. Rosuvastatin, C_{27}H_{38}FN_{2}O_{6}S, also synthetically made, shares a similar chemical structure as the rest of the synthetic statins have; only rosuvastatin contains sulfur, whereas the others do not. It too reduces the production of cholesterol by inhibiting the HMG-CoA reductase. Rosuvastatin is also to be taken while getting on a special diet low in saturated fats and low cholesterol. In addition to all this, exercise is indeed required, at least 30 minutes a day, every day, or as frequent as possible. Crestor comes in 5, 10, 20, and 40mg doses, unlike Lipitor which is offered in 80mg as its maximum dose. Both Lipitor and Crestor come in a tablet form and its elimination half-life is approximately 19 hours. Rosuvastatin was approved by the FDA in February of 2010 as a medication to help prevent cardiac disease.

When a conversation about prescription drugs arises, there is often a known purpose to taking them and an unknown effect to how it is completing its purpose and what it is doing to the rest of the body. The purpose of statins is to increase clearance of low-density lipoprotein (LDL). Statin use decreases the risk of heart attack, stroke, and other arterial diseases that are related to high cholesterol levels in the body (Emedicinehealth.com). What is cholesterol?

Cholesterol is a soft, waxy substance that is usually synthesized in the liver naturally for hormonal formation and functions, but can also be absorbed from diet. Its chemical formula is C_{27}H_{46}O with a molar mass of 386.65g/mol and a melting range of 148-150°C (WebMD.com). It is a structural component essential to provide proper cell membrane permeability and fluidity. The body compensates for its 200-300mg daily intake from diet by reducing the amount synthesized. It also has a purpose in manufacturing bile acid, sterol hormones and vitamin D. As one may suspect, we do indeed need cholesterols. Cholesterol is a natural part of the mammalian functionality and lifestyle. So why does having high levels of cholesterol reduce the quality of a person’s life?
There is a difference in cholesterols, for there is bad LDL (low-density lipoprotein) cholesterol that builds up as a plaque against the arterial walls and good (HDL) cholesterol. LDL cholesterol can build up and over time cause the blood vessel to become less flexible than it should be. When enough LDL cholesterol has narrowed an already narrowing artery, potentially blocking off the blood supply, a stroke or myocardial infarction (heart attack) may occur. The total cholesterol count consists of these two lipids, Lp(a) cholesterol, and triglycerides in the body, and the amount can be determined by going to the doctor for a blood test at least once a year. The process of synthesizing cholesterol begins with one molecule of acetyl CoA and one molecule of acetoacetyl-CoA, which are dehydrated to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA). This next step is regulated, rate-limiting and irreversible for this molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase. This is the site of inhibition for the statin drugs. This causes heart disease; although there are different types of heart disease cholesterol can trigger, the most common is coronary heart disease, the narrowing and clogging of an artery preventing the heart from getting its precious oxygen and nutrients.

The underlying effect of Lipitor and Crestor is that they drain the muscles of the body of Coenzyme Q10. A compound naturally found in the mitochondria, or the power house of the cell. It is required for the process of synthesis of adenosine triphosphate (ATP). Muscle contraction, production of proteins and a number of other processes depend on ATP. Unfortunately, while many may want to treat their high cholesterol, they may be trading in their subtle levels of youth for it. According to University of Maryland Medical Center, "Levels of CoQ10 tend to be lower in people with high cholesterol compared to healthy individuals of the same age. In addition, certain cholesterol-lowering drugs called statins (such as atorvastatin, cerivastatin, lovastatin, pravastatin, simvastatin) appear to deplete natural levels of CoQ10 in the body. Taking CoQ10 supplements can correct the deficiency caused by statin medications without affecting the medication's positive effects on cholesterol levels. Plus, studies show that CoQ10 supplementation may decrease the muscle pain associated with statin treatment" (Umm.edu). Also, Scientists believe free radicals contribute to the aging process, as well as the development of a number of health problems, including heart disease and cancer. Antioxidants, such as CoQ10, can neutralize free radicals and may reduce or even help prevent some of the damage they cause (Umm.edu). The CoQ10 is then used to bind to the cholesterol which results in a reaction where the cholesterol’s melting range is reduced to a lower range, thus allowing more to deplete into
the blood and out of the arteries. This method of reducing cholesterol may be effective, but also has some flaws in that the coenzyme Q10 may not be replenished right away. Symptoms of low levels of coenzyme Q10 can cause chronic fatigue syndrome, depression, autonomic and neurocognitive symptoms.

Some people even complained that they or their family member taking a statin, such as Lipitor or Crestor, seemed to be aging much faster or feeling “old.” A homeopathic medication site mentions that, “CoQ10 is an antioxidant, meaning that it can absorb free radicals found in the body. Free radicals can damage DNA and kill cells, and are thought to be major contributors to the aging process. Antioxidants can help prevent this damage from occurring by destroying free radicals” (naturalremedies.org). This can cause a problem for diagnosis as to why are they feeling that way if the patient is around their golden years and has been on a statin for a year or so “due to the fact of the body naturally starts to produce less coenzyme Q10 as it ages” (naturalremedies.org). It can be a contribution of stress, metabolic ailment, or some other severe biological disturbance in a person’s health, but if relatively healthy, though with high cholesterol and taking a statin, the problem might lie in the low levels of coenzyme Q10.

The side effects of Lipitor listed off Lipitor’s official website includes: headache, weakness, insomnia, dizziness, chest pain, peripheral edema, rash, abdominal pain, constipation, diarrhea, dyspepsia, flatulence, nausea, urinary tract infection, arthralgia, myalgia, back pain, arthritis, sinusitis, pharyngitis, bronchitis, rhinitis, infection, flu-like syndrome, and allergic reaction. According to the medical journal article, “Cholesterol-Lowering Drugs May do More Harm Than Good,” “among the side effects listed are muscle cramps, loss of libido, dysfunction of certain cranial nerves (including alteration of taste and impairment of extraocular movement), facial paralysis, breast enlargement, incontinence, sweating, acne, and uterine hemorrhage.” The article continues to say, “Active liver disease or unexplained persistent elevations of serum transaminases” tops the list of contraindications in one leading simvastatin drug. “Liver Dysfunction—HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function” is
listed as a warning on an atorvastatin calcium drug. The warning goes on to say that jaundice developed in one patient in clinical trials.”

Crestor is also very capable of a long list of side effects including: Rosuvastatin may cause side effects. Tell your doctor if any of these symptoms are severe or do not go away: constipation, heartburn, dizziness, difficulty sleeping, difficulty staying asleep, depression, joint pain, and cough. The list does not end there, it also continues with lesser common effects such as: muscle pain, tenderness/weakness, lack of energy, fever, chest pain, yellowing of the skin or eyes (jaundice), nausea, pain in the upper right part of the abdomen, extreme fatigue, unusual bleeding or bruising, loss of appetite, flu-like symptoms, sore throat, chills, or other signs of infection (due to a reduced immune system). It can also affect the integumentary system such as the skin with rash, hives, itching, difficulty breathing or swallowing, swelling of the face, throat, tongue, lips, eyes, hands, feet, ankles, or lower legs, hoarseness, and numbness or tingling in the fingers or toes. Crestor was different from the rest of the statins because of its toxicity and ability to cause renal kidney failure. Five months into its debut, a 39 year old woman died from kidney failure. Patients on the maximum dose were experiencing hematuria (blood in the urine), and proteinuria (protein in their urine). The FDA had this to say, “An FDA medical officer reviewing rosuvastatin had sobering comments on the cases of kidney problems with the drug:

These three cases of renal insufficiency of unknown etiology are of concern because they present with a clinical pattern, which is similar to the renal disease seen with rosvastatin in these clinical trials. There is mild proteinuria associated with hematuria and the suggestion of tubular inflammation or necrosis [death of cells]. All cases occurred at the 80 mg dose which was also associated with the greatest number of patients with abnormal renal findings in these clinical trials. Proteinuria and hematuria could be potentially managed with regular urinalysis screening. However, if they are the signals for the potential progression to renal failure in a small number of patients, this may represent an unacceptable risk since currently approved statins do not have similar renal effects.”

It was also stated, “AstraZeneca attempted to "spin" the drug's potential for causing elevated protein levels in the urine by claiming that it was due to a previously unobserved effect of the statin family of drugs. However, the research submitted by AstraZeneca to the FDA did not show a similar degree urine protein elevation with any of the other statins.” The solution to this problem was clear that it was just to monitor the patients at high doses. Worstpills.org stated in their article, “The Endocrinologic and Metabolic Drugs Advisory Committee recommended that kidney monitoring be required for patients taking 40 milligrams of rosvastatin per day. The FDA failed to take this advice, rather, the agency approved this puzzling statement in the Laboratory Tests section of the drug's professional product labeling or package insert:

In the rosvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosvastatin treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosvastatin 40 mg, when compared to lower doses of rosvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing.”

With the medication’s own label warning about all these adverse effects, and all the people continuing to take this cholesterol-lowering medication, the percentage of adverse effects may continue to increase, as well as possibly uncovering new adverse effects in children from parents who have been on
atorvastatin. In a personal online article titled “Nerve Problem with Lipitor and Crestor: Ann’s Story,” a 63 year old woman describes her experience while on Crestor, when she changed to Lipitor, and finally when she quit both. She states that while on Crestor, only 13 pills into her prescription, she lost the ability to walk associated to neurological side effects of Crestor. Her doctor later prescribed her Lipitor, and she was walking normally with Lipitor, but other symptoms emerged. She experienced what she describes as tingliness and numbness in her hands and feet. She stopped feeling hot and cold sensation and had itching, burning, and shooting pains throughout her feet. She later went in for testing, and after being cleared from diabetes and any other disease to cause these effects, she told her neurologist about Lipitor. Her neurologist told her to try and stop taking any form of statins, including Lipitor due to its “documented connection.” A month after deciding to stop taking Lipitor, she went back in for neurological testing, only to show that the sensation in her feet began its process of healing back to normal and after her third test, she was fine again with only minor neurological nerve damage from Lipitor’s damaging effects. She stated, “My energy level has soared and now I actually feel like walking for exercise and do so regularly. I feel younger, more flexible. Next I tried not taking an anti-anxiety medication that had been prescribed for the heart palpitations and breathing issues that I also had experienced while taking Lipitor. To my surprise those symptoms were also gone. I am a different person today from one year ago. I am so glad that I decided that my quality of life was more important than being afraid of dying because of the high cholesterol issue.” Going back to the catch phrase “if it’s not one thing, it’s another”, this personal testimonial further supports why Lipitor and Crestor may be more harmful than helpful due to their underlying and hidden effects Pfizer keeps tucked away in order for profits to rise. Lipitor and Crestor indeed began to affect people’s lives in unfavorable ways, and unfortunately, due to the patient’s trust in their physician and in the pharmaceutical companies, many people may be suffering more from the adverse side effects than from the high cholesterol itself.

In June of 2006, lawsuits were filed claiming that the company Pfizer has “failed to warn” doctors and patients about serious possible side effects of the cholesterol-lowering drug. Both lawsuits claimed that Lipitor caused the men lasting, debilitating muscle and nerve problems as well as memory loss. A 60 year old man from Atlanta claimed that Lipitor had damaged his nervous system, causing burning hands and feet, memory loss, and fatigue, even three years after he stopped taking Lipitor. A 47 year old man from New York was left with debilitating muscle damage and extensive memory loss. Pfizer has been in the news for quite some time since their start due to Lipitor damaging people rather than helping them. In other cases, the elderly and their family members have suffered from using Lipitor. According to an article published in the Canadian Medical Association Journal, “Statins may increase risk of postoperative delirium in elderly patients…” Delirium is a sudden and severe change in cognitive function causing confusion, inability to concentrate, and sometimes hallucinations. Postoperative delirium is observed in many people over the age of 70. Delirium can leave the patient with anxiety, delayed recovery, and increased hospital costs. Unfortunately, some have never recovered from it, resulting in a permanent state of delirium. This questions whether statins were designed with thought, consideration, and care, or whether it was merely another strategic marketing scheme in order to increase and boost sales off of a growing health issue. The profits the pharmaceutical companies have collected from these drugs are increasing by the year. Pfizer had even asked for an extension on their patent for Lipitor from 2009 until 2011.

Lipitor, in terms of research and longevity, has been around much longer than Crestor, yet they both seem to have affected many people’s lives dramatically. It is rather sad for all these side effects and disastrous life changing events, but with proper diet and exercise, change in lifestyles, and perhaps a reduced amount of statins for a longer amount of time may help reduce cholesterol and still allow the patient to live a happy lifestyle. Many are not educated on what the FDA approves and does not approve. Is the trade for longevity worth risking the youth of our body and the quality of life? Well that
is up to the person, to some longevity is worth every pill, and to others, they rather just enjoy what they have.
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The Chemistry of the Cell Cycle, the Relationship to Cancer, and the Addition of Virotherapy to the Arsenal of Cancer Treatments

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Organic Chemistry 236

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The Chemistry of the Cell Cycle, the Relationship to Cancer, and the Addition of Virotherapy to the Arsenal of Cancer Treatments

Abstract

The cell cycle is an intricate part of every working function within the human body. The malfunction of its processes are central in the development of cancer. Traditional treatment methods fail to produce measurable results and are often toxic. This inadequacy has led to a renewed search in the understanding and advancement of virotherapy as an alternative approach towards the treatment of cancer.

Introduction

Cancer is among one of the most evasive diseases known to affect the human population. It is listed as the second leading cause of death within the United States by the Centers for Disease Control and Prevention (CDC).\(^1\) Along with being one of the leading causes of death, the disease is also one of the most systemically invasive diseases known. Cancer is not just one disease, but a large group of diseases affecting many different areas of the human body.\(^2\) To date, there has been a multitude of treatment strategies developed which include different variations of surgery, chemotherapy, radiation, and/or a combination of all three. However, many of these treatments are accompanied with severely adverse side effects that can lead to other medical conditions and illnesses. Even with a plethora of different treatment strategies, cancer remains a leading cause of death. This being said, the lack of effective treatments for the various forms of cancer demand a need to develop new strategies, such as virotherapy, that can be used either separately or in conjunction with current treatment methods.

Cancer - What is it?

The main characteristics of cancer are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and spread to distant sites within the body via the blood and lymph systems.\(^2\) Each form of cancer is distinguished by the nature, site, or clinical course of the lesion. The basis of cancer is believed to reside in mutated alterations of genetic material (DNA) that normally function to control both the growth and death of a cell. Many factors may contribute to the mutation of genetic material leading to cancer. These factors include both environmental and lifestyle aspects such as tobacco use, exposure to ultraviolet radiation, exposure to carcinogens, inherited genetic alterations, and exposure to certain viruses.\(^3\)

Cancer and the Cell Cycle

In order to understand the various approaches toward the treatment of cancer, it is essential that the somatic cell cycle is first understood. The basis of all cancer begins on a cellular level with the malfunction of various cellular growth regulators. Normal cells propagate at a controlled rate dictated by internal growth regulators and are kept in check by a series of cell cycle checkpoints. The normal cell cycle is divided into five phases: G\(_1\) (gap phase 1), S (synthesis), G\(_2\) (gap phase 2), M (mitosis), and C (cytokinesis).
G₁, S, and G₂ phases are collectively known as ‘interphase’. The processes that occur during interphase are essential not only for the advancement into the next phase (mitosis) of the cell cycle, but these processes also create the machinery that ensures completion of mitosis. During the interphase stage, the cell is in a diploid state. The vast majority of cell growth will occur during the G₁ phase. This is also where the cell’s commitment to divide is made. The presence of nuclear proteins (i.e. Histone H1) is a primary indicator of DNA replication, marking the transition between the G₁ and the S phase of the cell cycle.

The S phase is where DNA replication takes place and is the only stage where DNA is replicated. Here, the chromosomes are replicated via the histone proteins where an identical chromatin structure is created by depositing the proteins onto the daughter DNA. Upon completion, the cell then enters into the G₂ phase of the cell cycle.

In G₂, many proteins and cell organelles are synthesized. These processes are meant for the development of organelles like mitochondria, as well as for the condensation of chromosomes. There are several proteins produced in this phase that are used in the final condensation of the chromosomes, and though the final condensation occurs early in mitosis, these proteins must be present for mitosis to continue. The synthesis of centrioles and tubulin – the proteins necessary for separation of the chromosomes - are also synthesized in this phase to be used at a later time within the cell cycle.

Mitosis, the M phase, occurs after interphase has been concluded. Like interphase, mitosis consists of several stages: prophase, prometaphase, metaphase, anaphase, and telophase. Within mitosis, the somatic cell divides via nuclear division in which the previously duplicated chromosomes separate to form two genetically identical daughter nuclei. The figure below provides a graphic explanation of the events occurring during the various stages of mitosis.

<table>
<thead>
<tr>
<th>Interphase</th>
<th>Prophase</th>
<th>Prometaphase</th>
<th>Metaphase</th>
<th>Anaphase</th>
<th>Telophase</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Interphase" /></td>
<td><img src="image2" alt="Prophase" /></td>
<td><img src="image3" alt="Prometaphase" /></td>
<td><img src="image4" alt="Metaphase" /></td>
<td><img src="image5" alt="Anaphase" /></td>
<td><img src="image6" alt="Telophase" /></td>
</tr>
</tbody>
</table>

**DNA Replicates**
- Chromosomes condense, the spindle forms, and the nuclear envelope disintegrates. Each chromosome has two chromatids.
- Chromosomes align independently at metaphase plate.
- Chromatids separate.
- The nuclear envelope reforms and the cell now divides (cytokinesis).

*Figure 1. Stages of mitosis.*

The final stage of the cell cycle is cytokinesis, or the C phase. By definition, cytokinesis is the division of the cytoplasm following nuclear division, thus rendering a fully duplicated pair of cells that, upon completion, will both begin a new cell cycle.
Biochemistry of Cell Cycle Control

In a normal cell, the cell cycle is regulated by a series of checkpoints: the G1/S checkpoint, the G2/M checkpoint, and the spindle checkpoint. Each of these events is biochemically regulated by a variety of interactions with cyclin-dependent protein-kinases (CDK). The enzymatic activity of CDK is highly specialized, reacting only when activated by specific cyclins (positive regulatory subunits) that bind to the CDK molecules, controlling their ability to phosphorylate target proteins. Progression through the various phases of the cell cycle is accomplished by fluctuating synthesis and degradation of phase-specific cyclin proteins, CDK inhibitors (CKI), and reversible phosphorylation. Any disruption in the routine regulation of this cycle will either halt the cell cycle until repairs are made, cause cell death, or lead to genetic mutations that cause uncontrolled cellular proliferation. Damage to tumor suppressor genes p53, p15\textsuperscript{ink4a}, p16\textsuperscript{ink4a}, p18\textsuperscript{ink4c}, p19\textsuperscript{ink4d}, p21, p27\textsuperscript{Kip1}, and pRb (retinoblastoma susceptibility protein) are of particular interest in this event, as damage to these molecules contributes to tumor formation.

The mechanisms of cell cycle control become activated upon contact with growth factor proteins, such as Ras, that bind to cell surface receptors. These receptors send mitogenic signals into the cell through a series of transductional pathways resulting in activation of cytoplasmic signaling cascades. In response, proteins turn on the machinery necessary to mediate cellular proliferation processes. Ras activation induces transcription of Cyclin-D in the G1 phase through a Ras-responsive element in the cyclin-D gene promoter. Cyclin-D then associates with CDK4 and/or CDK6 to form active complexes that phosphorylate specific genes at a serine, threonine, or tyrosine site, leading to further transcriptional processes. The mechanisms of this phosphorylation are shown below.

![Figure 2. Mechanisms of phosphorylation.](image-url)
When pRb is associated with E2F transcriptional factors (protein regulators), it is in an inactive state.\textsuperscript{9} The Cylin-D/CDK4 complex phosphorylates pRb, dissociating it from E2F and activating transcription of Cylcin-E.\textsuperscript{6,7} In turn, Cylcin-E reacts with CDK2 to allow progression from the G\textsubscript{1} phase into the S phase of the cell cycle.\textsuperscript{6,7} The new Cylcin-E/CDK2 complex phosphorylates pRb yet again, triggering synthesis of Cylcin-A. Cylcin-A then complexes with its associated protein, CDK2. Cylcin-B is synthesized in both the G\textsubscript{2} and M phases. It complexes with CDK1 to form MPF (M-phase promoting factor), the protein complex responsible for progression into mitosis. It is also the protein kinase responsible for stimulating degradation of the Cylcin-B complex, an event required for mitotic exit. Figure 3 is a depiction of cyclin-kinase mechanisms taking place as the cell cycle progresses.

![Diagram](image)

**Figure 3.** Progressive phosphorylation regulates cell cycle progression.

**Impacting cancer**

The cellular checkpoints just described are only part of a very large, very complex set of cellular pathways. Considering their complexity, it is reasonable to speculate that defects may alter these pathways therefore increasing the inability for cellular response to sense and repair damage. Cells with intact damage response mechanisms, such as the p53 and pRb pathways, have three means of resolution in attempt to prevent oncogenesis: repair, cell cycle arrest, or apoptosis (cell death). Mutations in any of these damage response pathways may permit the continued growth of cells with genomic abnormalities leading to malignant transformation. For researchers, determining the specific pathways that are important in affecting the predisposition to malignancies versus those that are not may provide invaluable insights into the mechanistic approach towards treatment.

![Diagram](image)

**Figure 4.** Schematic diagram of the p53 pathway leading to cell cycle arrest, DNA repair, and apoptosis.
Current Treatments

There are many treatments available today in the attempt to combat cancer. The most broadly known treatments include surgery, radiation, and chemotherapy. Of all the treatments available, surgery is the oldest and most common form. Surgery involves removal of affected tissues as a diagnostic, curative, and preventative measure in treatment of cancer. Advancements in technology have expanded the realm of surgical techniques from the traditional excisional methods to include laser surgery, electrosurgery, and cryosurgery. Common side effects of surgery include pain, bruising, swelling, and drainage around the site of the surgery, as well as fatigue, loss of appetite, bleeding and infection. Lymphedema is another possible side effect that can cause severe pain and swelling due to insufficient drainage of lymphatic fluid. Surgery, however, is rarely used as a stand-alone treatment. It is not uncommon to combine surgical treatments with radiation therapy and/or chemotherapy.

Radiation therapy is the medical use of high energy ionizing beams (i.e. X-rays, electron beams, gamma rays, neutron beams and proton beams) with intent to control proliferating cancer cells. Radiation therapy works by damaging the DNA inside the cell nucleus. High energy radiation deposits energy in living tissues through a process called ionization, which creates positively and negatively charged particles. The ions cause a chain of chemical reaction within cells. Next, the process of oxidation forms high reactive free radicals. These free radicals diffuse (spread) to the nucleus of the cell and cause DNA damage. As the cells die, the chemical effect of radiation is evidenced by the eventual shrinkage of tumors. Both normal cells and cancer cells are affected by radiation. However, the more slowly dividing cells can repair themselves much more efficiently than the rapidly dividing cancer cells. Because the normal cells recover, a therapeutic or differential effect is created. Cancer cells generally do not recover and are therefore eradicated by radiation therapy.

Many side effects occur in response to treatment with radiation therapy. These reactions can be acute or chronic. Because treatment is administered locally, side effects are generally restricted to the area of treatment. Acute side effects are common and occur as an immediate response to the administration of treatment. The side effects experienced are dependent upon the organ systems present within the region of the body where treatment is applied. For example, if a patient’s abdominal region is treated, they are likely to experience changes within the gastrointestinal tract, such as diarrhea. Likewise, irradiation of the head and neck structures may lead to nausea, vomiting, and/or hair loss. It is normal for patient’s to experience peeling, discoloration, and burning of the skin within the region of treatment.

Chronic side effects may also occur as a result of irradiation. Chronic side effects are rare, but when they do exist, they can be serious. Severe fatigue is the most common chronic complaint. The duration of side effects experienced as a result of radiation therapy can last for several weeks to several months following completion of treatment. In addition, acute side effects, such as skin irritation, always run the risk of becoming chronic problems.
Chemotherapy is the treatment of cancer through pharmaceutical drugs. It is normally used in combination with surgery and/or radiation therapy. Chemotherapy is an effective treatment strategy in fighting cancerous cells that have already spread to other parts of the body and that cannot be treated with any other method. There are dozens of cancer drugs available that use a wide variety of mechanisms to eliminate cancer cells. Most focus on the interruption of cell cycle processes during cell division by blocking DNA replication, directly damaging the DNA itself, or interfering with the source enzymes necessary to build the DNA. In many cases, drugs utilizing different mechanisms are used together simultaneously to maximize their effect. The specific drug classes (along with the associated applicability) can be defined as follows:

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Function</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agents</td>
<td>Cause DNA strands to incorrectly cross-link</td>
<td>Melphalan</td>
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<tr>
<td>Platinum Analogs</td>
<td>platinum-DNA crosslinks</td>
<td>Oxaliplatin</td>
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<td><img src="attachment" alt="Oxaliplatin" /></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>Interfere with folate production</td>
<td>Cytarabine</td>
</tr>
<tr>
<td></td>
<td></td>
<td><img src="attachment" alt="Cytarabine" /></td>
</tr>
</tbody>
</table>
| Topoisomerase Inhibitors | Block enzymes for unwinding DNA<sup>15</sup> | Topotecan
\[ \text{N(CH}_3\text{)}_2\text{HCl} \]
|-------------------------|-----------------------------------------|----------------------------------|
| Antimicrotubules        | Blocks assembly/disassembly of microtubules and scaffolding for chromosome migration<sup>15</sup> | Paclitaxel

Table 1. Cytotoxic drugs used in chemotherapy treatment.

The side effects of chemotherapy include bone marrow suppression leading to low counts of white blood cells, red blood cells, and platelets. This increases the risk of infection, reduces blood oxygen transport, and decreases the platelets clotting ability, thereby increasing the risk of uncontrolled bleeding. Similar to radiation therapy, chemotherapy side effects also include fatigue, loss of appetite, nausea, vomiting, hair loss, and diarrhea. It may also affect an individual’s fertility.

Virotherapy

Virotherapy is a unique approach towards the treatment of cancer. Treatment with virotherapy involves exploitation of the viral replication process, using a modified viral vector to specifically target, infect, and destroy cancer cells from the inside out. The concept is not a new concept, but has gained momentum in recent years among the vast technological advances in modern research and medicine.

The adenovirus has been the most widely studied of all potential viral vectors. The reason for this is because the adenovirus is simply everywhere. They are what one could consider as the ‘universal’ human virus. There are at least 43 (of more than 100) different serotypes that have been found in humans.<sup>16</sup> This allows the virus the ability to infect a very broad range of cells.<sup>16</sup> This is of great importance considering cancer can occur in nearly all types of cells within the human body. Additional features that make the adenovirus an ideal candidate for use in viral therapy are that the virus has shown low pathogenicity in humans, it can carry large amounts of DNA, it is capable of horizontal gene transfer (HGT), its genome does not undergo a high rate of rearrangement, and it is easy to manipulate via recombinant DNA techniques.<sup>16</sup>

Transductional and transcriptional targeting are the two foremost methods utilized for attack on cancer cells in virotherapy. Transductional targeting requires modification of the vector’s capsid
proteins, or 'arms', to ensure that it is only able to react with the receptors found on malignant cells. Reaction at the receptor site allows entry into the cell, where the virus then inserts its DNA into the nucleus, hijacking the cell's replication machinery for its own proliferation. It then multiplies itself inside the cell until it reaches capacity leading to lysis. The newly replicated and released viruses then go on to attack the surrounding cells, repeating the process all over again. This methodology targets the unwanted malignancies on a cellular level, prevents entry into healthy cells, and therefore limits the potential side effects of the treatment. An example is shown below.

Figure 6. Oncolytic transductional targeting.

Transcriptional targeting is very similar to transductional targeting in that it uses the cancer cell to replicate itself leading to cell lysis. The methods differ, however, in that transcriptional
targeting involves genetic manipulation of viral DNA versus the manufacturing of specific capsid proteins. In this approach, tumor-specific promoter genes are spliced into the viral genome.17 The purpose of these genes is to activate the replication of the virus, however they are unable to activate within normal healthy cells. This is because the healthy cells do not contain the mutations that cause a cell to become carcinogenic. In contrast, once they enter the mutated cancer cell, they react with those mutations to initiate the encoding of proteins that trigger the replication that inevitably leads to the death of the host cell. So although transcriptional targeting will allow viral entry into normal cells, the virus will remain inactive and unable to cause harm.

Figure 7. Oncolytic transcriptional targeting.17
What the Future Holds in Cancer Treatment Therapies

When compared to traditional treatment methods, the relevance in understanding the mechanisms of virotherapy lies in the fact that this approach not only exploits already naturally occurring processes (cellular and viral replication), but this approach further allows exploitation of anticancer mechanisms utilizing some common characteristics found in a large variety of cancer (i.e. inactivated p53 and pRb pathways). In addition, virotherapy provides a more targeted mechanism to seek out and destroy cancer cells while dramatically minimizing damaging side effects to surrounding tissues. This modality of treatment can be taken even further by combing treatments. Chemotherapy treatments may make a perfect partner with transductional virotherapy as the viral capsid can be hollowed out and designed to carry the cytotoxic drugs that kill cancer. Because the capsid proteins are programmed to react only with receptors found on carcinogenic cells, the toxicity normally associated with chemotherapy is thus reduced while increasing treatment efficacy.

As for the current treatments, they will continue to be utilized until more effective treatments are developed. For many decades, and the majority of the century, virotherapy has been generally dismissed as a modality of treatment. However, with new technologies researchers have discovered new ways to manipulate and reprogram the viruses to behave in specific ways. In this aspect, and because of the natural ability of the virus to seek and enter cells, it would be a great disservice not to continue the development of virotherapy in search for a more effective treatment strategy. Within the realm of virotherapy lies the smoking gun of cancer treatment. It is up to us to find it.
Bibliography


Primary Immunodeficiency: The Immune System’s Enemy

Natalia Habbo
April 22, 2011
Abstract: Primary Immunodeficiency is a group of diseases which directly affect a person's immunity. There are several different aspects of the immune system affected by Primary Immunodeficiency depending on the particular diseases inherited. There are several signs and symptoms, diagnoses, treatments, and people affected by PI.

Primary immunodeficiency (PI) is a group of several different diseases which are usually inherited, and directly affect the immune system\(^1\). The immune system is defined as "A complex system comprised of many organs and cells that defends the body against viruses, bacteria and other foreign substances."\(^1\) They are considered to be primarily single-gene disorders of the immune system\(^2\). In primary immunodeficiency the genes of the cells which make up the immune system are missing or dysfunctional. Genetic disorders, such as PI are caused by the mutations, or change, in a specific gene or set of genes. They are unlike secondary, or acquired, immunodeficiency's, such as HIV or aids virus, in that they cannot be caught or passed on, unless it is genetically to offspring\(^2\). That being said, primary immunodeficiency causes a person to be greatly susceptible to infections and other diseases. It is usually seen early on in life, due to excessive illness and/or infections\(^1\). The disease is not considered to be rare, presents at any age and in some cases does not present itself with severe infections\(^3\), yet if not treated effectively or early enough it can be fatal\(^4\). This group of diseases causes many different types of symptoms, effects a range of people, though it is most common in infants and children, and effects different cells in the body, depending on the specific disease in the category\(^3\).

The immune system, the body’s defense against foreign invaders, is mostly comprised of the thymus, liver, bone marrow, tonsils, lymph nodes, spleen, and blood. These elements of the body all work together to do exactly what they are meant to do, fight off germs or pathogens. They are important in keeping a healthy human being stay healthy. The special cells which make up the immune system are white blood cells found in the thymus, bone marrow and complements of the blood. The white blood cells consist of T-cells, B-cells and phagocytes, and the complements are the proteins in the blood stream that help protect against infections\(^1\). PI diseases are classified according to the affected components of the immune system, whether they are antibody deficient or combined B- and T-cell deficient, have defective phagocytes or have complement defects\(^4\). In Primary immunodeficiency, the gene cells of this network are deficient and cause the immune system to work improperly. Once specific deficient gene cell is identified, research is done to find out the normal functionality of the gene, what protein it makes, and how it contributes to the immune system. Recently, the genes which are responsible for many PI diseases have been identified\(^5\).

Antibody deficiencies make up about half of the diseases which are called primary immunodeficiencies. They are caused by too few antibody-producing B cells or B cells which do no function properly\(^4\). This causes inadequate production of antigen-specific antibodies and in some cases no antibodies being made. These disorders show their effects with recurrent sinus and pulmonary infections and septicemias with bacteria\(^4\).

X-linked Agammaglobulinemia (XLA) is an X-linked disease, X-linked because the mutated gene which is responsible for the disease is located on the X chromosome\(^5\). X-linked diseases are characterized by the woman carrier passing the defective X-linked mutation on to her offspring causing the disease to show up in the male recipient. This disease causes youngsters to make no antibodies which cause them to have little or no
mature B cells of antibody-secreting plasma cells. Baby boys who have inherited XLA are healthy in their first few months of life because they are protected by IgG they received from their mother's placenta. As the IgG from their mother's fades, they start to develop infections caused by bacteria and viruses. The bacteria and viruses which would have normally been controlled by antibodies are able to flourish, causing many other diseases. XLA cannot be cured, but can be controlled by immunoglobulin therapy in large doses, causing children to live fairly normal lives.

Common Variable immunodeficiency (CVID) is a name for a group of disorders characterized by low levels of gammaglobulin and too few IgA antibodies. People with CVID have normal numbers of B cells, but their B cells are defected, and their T cells show defects as well. This disease is most commonly seen in people in their twenties, but can also show up in children. It affects men and women with no family history of CVID. The disease causes frequent bacterial infections, influences the development of immune system illnesses such as anemia and rheumatoid arthritis, and an increased risk of cancer. Antibiotics are helpful in treating the infections of this disease, but the most effective treatment for CVID is gammaglobulin therapy. The gammaglobulin raises antibody levels, fights infections and allows people with CVID to live normal lives.

Hyper-IgM Syndrome shows up in children, and is caused by high levels of IgM, no IgA, and very low levels IgG. They also have very low levels of white blood cells called neutrophils. In the X-linked form of Hyper-IgM Syndrome, the defective gene is unable to encode a molecule which normally permits the T cells and B cells. This causes the B cells making IgM to miss the signal from the T cells telling them to switch to making IgA and IgG. Children may start contracting bacterial infections or developing sores inside their mouths before their first birthday. Another aspect of Hyper-IgM is autoimmune disease, causing an even larger risk of infection, because the immune system is fighting itself. The treatment for Hyper-IgM is IVIG, which contributes missing IgG antibodies, and lowers the IgM antibodies causing children with this syndrome to live normally.

Selective IgA Deficiency is a deficiency of the immunoglobulin in body secretions and mucus membrane linings. It usually guards the body at body entrances, blocking bacteria, viruses, toxins, and certain food components. The B cells of someone with IgA deficiency appear to be normal, but are incapable of maturing to secrete IgA antibodies. It is the most common immunodeficiency, occurring in as many as 1 of every 333 Caucasian Americans, although the cause is unknown. Most people never know they have it because they stay fairly healthy. The number of infections for people with Selective IgA Deficiency is fairly close to the number of infections people with no immunodeficiency, yet they are more susceptible to more health problems, such as allergies, asthma, autoimmune diseases, and neurological diseases. The treatment consists of mainly antibiotics and periodical checkups.

IgG Subclass Deficiency is caused by the missing antibody subclasses of IgG, IgG1, IgG2, IgG3, and IgG4. Each subclass has its own role. In this particular deficiency the IgG levels may be normal, but further evaluation would have to take place to determine if there would be deficiencies in the subclasses. Patients with this disease do not have as severe of infections as other immunoglobulin deficiencies. Antibiotics are used to treat IgG Subclass Deficiency, and IVIG is also used for children who do not respond to antibiotics.
Combined B- and T-Cell deficiencies are much more serious than the B cell/antibody deficiencies, because both the body's major immune system defenses are defective. They constitute approximately 20% of Primary Immunodeficiency diseases. The severity of Combined B- and T-cell deficiencies is evident in the most known PI disease called Severe combined Immunodeficiency (SCID). It is rare, occurring in 1 of every 500,000 births, and until recently, was considered to be fatal. The syndrome is caused by mutations in at least 13 different genes, and is inherited as either an X-linked, or autosomal recessive defect. In the X-linked form, boys have lymphocytes, white blood cells, which cannot grow, develop or communicate with B cells. They tend to have low numbers of T cells or natural killer cells, so their B cells cannot function, and their immunoglobulin levels are low. In the autosomal recessive form of SCID, adenosine deaminase (ADA) deficiency causes the SCID. ADA causes infants to lack the ADA enzyme necessary for T cell survival. It is usually seen in infancy with severe infections. These infections trigger other complications such as pneumonia and chronic diarrhea. Infants tend to lack all immune defenses needed for survival. When diagnosed, the current infections are brought under control, and then IVIG is used to boost the immune system. A physician can also diagnose SCID at birth is SCID runs in the family. SCID can be treated with enzyme replacement therapy called PED-ADA, immunoglobulin replacement, and gene therapy has been found to be successful. The most effective form of treatment currently is bone marrow transplantation, and in more severe cases, chemotherapy followed by bone marrow transplantation is used for treatment.

T Cell deficiencies are caused by defects in T cell maturation or function. They contribute to 10% of Primary Immunodeficiency diseases. A known form of T cell deficiency is DiGeorge Anomaly. It is the result of a birth defect which occurs in the fetus. These defects affect the face, parts of the brain, and the heart, as well as the thymus. These defects are not necessarily in every case of DiGeorge Anomaly, each case is specific to each person and the organs which are affected. Many children with this anomaly have very small thymuses and some children have a missing thymus. The T cells mature in the thymus, so the missing T cells, or too few T cells cause the B cells dependent on them not to develop, causing infections. It is diagnosed soon after birth because of the distinct characteristics. Treatments are usually used to treat the defects of DiGeorge, and the rest of the treatments are used to supply T cells which can work independently of the thymus. The main cause of death for DiGeorge Anomaly is the congenital heart defect, and the second cause of death is the immune deficiency.

Defective Phagocytes are the cause of Primary Immunodeficiency's which cause an inability of cells that engulf and kill invaders to remove pathogens or infected cells of the body. Phagocytic defects account for 18% of all PI cases. Chronic Granulomatous Disease (CGD) is type of phagocytic defect disease in which phagocytes are unable to produce the oxygen-transporting compounds that they need to kill certain types of germs. There are four types of CGD, each type associated with a different gene protein that in combination work together to allow phagocytes to work properly. It is found generally within the first couple years in a child's life. It is found by the typical signs of PI such as infections, and illnesses. Most all youngsters develop lung disease, pneumonia, and a distinct condition which forms tumors of white blood cells called granulomas. Theses granulomas collect in areas of infection and continue to form even after infection. Prompt diagnosis is the most important method to managing the disease.
Like other PI diseases, managing the current infection with regular antibiotics is important. Regular injections of gamma interferon are also important and help to regulate the disease. Due to the fact that phagocytes deal mostly with bacteria, people with CGD are encouraged to keep their skin as clean as possible to protect from germs. Serious infections are very common, yet good health with good treatment is common for people with CGD³.

Complement deficiencies are the least common Primary Immunodeficiency, and occur less frequently⁴. The complement system consists of proteins that usually attach to antibody-coated foreign invaders and bacteria. Diseases such as C2 deficiency have a defect on the gene for the complement protein which helps attach to the antigen. In the case of C2 deficiency, the protein C2 is deficient⁴. It causes severe infections like meningitis, and causes a susceptibility to autoimmune diseases. Terminal complement protein deficiencies occurring with complement proteins C6 through C8 are associated with severe infections such as N. gonorrhoeae⁴. There are no cures for complement deficiencies and there are no specific therapies. There are new investigations on ways to manage complement deficiencies such complement concentrates which replace the deficient complement proteins⁵.

### International

**Classification of Immunodeficiency Defects**

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**Major Immunodeficiency Groups**

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**Total: 20,091**

**Source: Survey of Jeffrey Modell Centers**

**Chart 1: Eight major categories of Primary Immunodeficiencies**

The Jeffrey Modell Foundation conducted a five study experiment on early diagnosis and management of Primary Immunodeficiency's. Surveys were distributed to physician experts at the Jeffrey Modell Diagnostic, Research, and Referral Centers worldwide. The studies included 304 physicians at 138 academic hospitals and medical schools, in 39 countries and 120 cities⁶. They provided information on several different aspects of the diseases including the total number of patients followed, and the number of patients with specific PI defects. In the study about 37,544 patients were reported as being followed
with suspected PI disorder and 30,283 patients were identified with specific PI defects. The charts above, internationally (not in the United States), and below, United States, show the total numbers of patients with PI diseases. Each patient was categorized into a particular Primary Immunodeficiency group depending on their specific condition. The values show the prevalence of some PI disease over others and give a general overview of PI in the global sense. The first chart shows the international patients with PI. About 20,091 people were followed, and 50% of them had Antibody deficiencies. About 0.2% was found to have defects in innate immunity, which are non-specific deficiencies. In the second chart the United States patients are exhibited. About 10,192 patients were followed, and of that total about 60% had predominantly Antibody deficiencies. The least common showed to be the innate immunity. These charts show a correlation to the evidence published, that the most common types of PI are the Antibody deficient diseases.

### United States

<table>
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<th>Classification of Immunodeficiency Defects</th>
<th>Major Immunodeficiency Groups</th>
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<tr>
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| Source: Survey of Jeffrey Modell Centers   | Chart 2: Total of 20,091 patients internationally (outside the United States) identified with specific PI defects

The signs and symptoms of primary immunodeficiency can range from a variety of different things. The signs and symptoms can also vary from children to adults. There are several warning signs associated with children with PI, and it is said that if a child exhibits two or more of the warning signs they should be taken to a physician for further examination. According to immunedisease.com the warning signs for children are as follows:

1. Four or more new ear infections within one year
2. Two or more serious sinus infections within one year
3. Two or more months on antibiotics with little effect
4. Two or more pneumonias within one year
5. Failure of an infant to gain weight or grow normally
6. Recurrent, deep skin or organ abscesses
7. Persistent thrush in mouth or fungal infections on skin
8. Need for intravenous antibiotics to clear infections
9. Two or more deep-seated infections including septicemia
10. A family history of primary immunodeficiency

The warning signs for adults are very similar but vary slightly from the warning signs associated with children with PI, they are as follows:
1. Two or more new ear infections within one year
2. Two or more new sinus infections within one year, in the absence of allergy
3. One pneumonia per year for more than one year
4. Chronic diarrhea with weight loss
5. Recurrent viral infections (colds, herpes, warts, condyloma)
6. Recurrent need for intravenous antibiotics to clear infections
7. Recurrent, deep abscesses of skin or internal organs
8. Persistent thrush or fungal infection on skin or elsewhere
9. Infection with normally harmless tuberculosis-like bacteria
10. A family history of PI

The warning signs give a good indication that something is occurring abnormally in the body. Once the warning signs have become evident further testing is done to find the exact problem.

The testing involved in diagnosing Primary immunodeficiency is usually done using a blood sample. It is important to evaluate if the correct immune cells are present, and in adequate numbers, and if they are working properly. To determine if all factors are present testing is done. A blood cell count is taken of red blood cells, white blood cells and platelets. A quantitative immunoglobulins test measures the immunoglobulin levels in the blood for IgG, IgM, and IgA. Antibody responses are checked to see if the immunoglobulins are working correctly. This is done using a blood test to examine the antibodies present to the usual childhood immunizations. A complement test is done to see how the complement system is working in the blood. Skin tests are done to determine how well T cells are operating. Miniature amounts of standard reaction-provoking antigens are injected into the skin, and the response is swelling if T cells are working properly. There are also stages in testing due to the different factors relating to the immune system. The 4 stages are:

1. History and physical examination (height and weight), CBC and differential, Quantitative Immunoglobulin levels IgG, IgM, IgA
2. Specific antibody responses (tetanus, diphtheria), Response to pneumococcal vaccine (in ages 3 and up), IgG subclass analysis
3. Candida and Tetanus skin tests, Lymphocyte surface markers, Mononuclear, lymphocyte proliferation studies, Neutrophil oxidation burst (if indicated)
4. Complement screening, Enzyme measurements, Phagocyte studies, NK cytotoxicity studies, Further complement studies, Neot antigen to test antibody production, Other surface/ cytoplasmic molecules, Cytokine receptor studies, Family/ genetic studies

Usually to diagnose PI detailed medical history is needed, physical examinations are conducted, blood tests are done to check red and white blood cell counts, antibody levels, B and T cell function, and the complement system, and skin tests are performed to show
if T cells are working properly\(^1\). Once the diagnosis is complete, treatment is needed for Primary Immunodeficiency. Treatment is specialized to each disease in the PI group of diseases.

Newborn screening is important in some of the more severe cases of PI\(^5\). The first year of life is usually cut short for infants who are not treated or diagnosed early enough, thus newborn screening is crucial for survival in certain cases of PI disease\(^5\). There is a population-based newborn screening (NBS) which began in the 1960's, originally used to determine if children had the disorder PKU\(^5\). Now, the NBS test is used to screen for 4 to 30 different disorders within a few days of birth. The screening is done by taking a blood specimen from a baby's heel, spotting it onto filter paper, and sending it to a public health lab. The CDC created a program to help improve the quality of their testing using NBS. It also is used to regulate, and monitor the NBS laboratories\(^5\). This helps to collect data, and determine the effectiveness of early screening and detection of certain diseases and disorders, including PI.

![Inherited Immune Syndromes](image)

**Graph 1:**

The above graph\(^9\) shows the years after bone marrow transplantation and the survival percentage of 35 people under the age of 18 years\(^9\).

Two technologies for the treatment of Primary Immunodeficiency are gene therapy and hematopoietic cell transplantation (HCT)\(^10\). The two therapies are potentially the only significant ways to cure genetic disorders, such as PI. Gene therapy is used to correct the missing or malfunctioning gene by introducing a functional copy of the defective gene into the appropriate cells\(^10\). If successful, the cell is directed to produce the missing protein. In 1990, two girls with SCID due to ADA deficiency were treated
with gene therapy. T cells were removed, treated to become active, and the T cells carrying the new gene for ADA were reinjected into the girls, while still getting their regular treatments for ADA. HCT is used to cure/treat severe cases of PI. Over 45,000 hematopoietic cell transplantations are conducted a year. HCT transplantations refer to transplants such as bone marrow, or cord blood transplants. The most effective way to treat a more severe form of PI is bone marrow transplantation. This means life is possible for infants diagnosed with SCID and other severe forms of PI.
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   http://emedicine.medscape.com/article/135711-overview#a0199

   Available from:
   http://www.info4pi.org/Documents/Publications/JMFGenoPhenoFinal_20100113_163924.pdf (chart 1 and chart 2)

Medicinal Marijuana

By Paula Hawley

April 22, 2011
Abstract

Just recently AZ proposition 203 was passed in the state of Arizona prompting many questions about marijuana’s medical efficacy and safety. The law allows the legal selling and possession of marijuana for therapeutic purposes. The therapeutic uses, efficacy and delivery methods of marijuana are herein discussed along with the historical and legal significance of the drug.

Introduction

Marijuana, the common name for cannabis, is a plant that can be used for medicinal purposes and illegally for leisure uses. Attempts to legalize this drug for medicinal purposes have stimulated different political, ethical and social issues and debates. The argument is divided between those that are attempting to legalize marijuana and those opposing it (primarily the government). It is important to understand all aspects of marijuana and why it could be used medicinally.

Marijuana has been used for therapeutic purposes dating back possibly more than 2,000 years (Johnson, 2009) in Europe, Asia and Africa. The earliest traces of cannabis use are the use of seeds as therapeutic resources in Chinese cultures (Zuardi, 2006). The uses ranged from anesthetic purposes to rheumatic pain relievers. It is currently still used by the Chinese as a laxative. There is also historical evidence that in India it was used for therapeutic and religious purposes.

During the late 1800’s physicians in America began understanding the potential benefits of medical marijuana. The first noted conference was held in Ohio in 1860 (Zuardi, 2006). At this time the use of therapeutic marijuana was legal at the federal and state level. For 90+ years it was considered a legitimate medication by the US Pharmacopoeia (Johnson, 2009). Later, other drugs like aspirin and morphine began taking precedence causing marijuana to lose its appeal. During the 1930’s the U.S. Federal Bureau of Narcotics began what would eventually become a successful campaign against the legal use of marijuana.

When The Marihuana Tax Act of 1937 was passed it allowed the federal government to regulate marijuana (Johnson, 2009). This taxed anyone using marijuana and eventually required proper documentation as well. If not properly followed, the law resulted in possible imprisonment for those convicted. By this time almost every state in the US had laws regulating marijuana as well. Eventually cannabis was banned throughout the entire US and by the 1940’s was officially taken out of the US Pharmacopoeia (Zuardi, 2009). Few agencies other than the American Medical Association (AMA) argued against the ban of marijuana. In the 1970’s the Controlled Substances Act was enacted later becoming the Comprehensive Drug Abuse Prevention and Control law that placed Marijuana in a class of drugs known as schedule I. Other drugs in this class include heroin and LSD (Johnson, 2009). The drugs in this class are thought to be drugs that under no circumstances can be used for medical purposes, whereas drugs like cocaine,
opiates and amphetamines are legal for medical uses and are considered schedule 2 drugs (Johnson, 2009).

On a federal level the debate goes on regarding legalization of medical marijuana pharmacies and dispensaries. The federal governments' enforcement of marijuana prohibition is by means of the Drug Enforcement Agency (DEA). The DEA monitors and occasionally targets medical marijuana facilities however the laws are enforced more frequently by the states individually (McMahon and Largen, 2003). Thus far about 12 states have legalized marijuana for medicinal purposes (Johnson, 2009). One of the toughest questions currently facing Congress is the severity of punishment for convicted marijuana users and distributors (Johnson, 2009). One state that has recently joined the ranks of legalizing marijuana for medical purposes is the state of Arizona. In Arizona the law will allow possession, distribution or selling as a pharmacy when indicated by a physician. These dispensaries would be considered non-profit organizations and each patient must have a certification rather than prescription when picking up the marijuana. Regardless, it is still considered against federal laws to grow or be in possession of marijuana.

The Food and Drug Administration (FDA) has also played a major role in opposing marijuana as a therapeutic mediator. In 2006 the FDA indicated it’s disapproval of smoked marijuana as a means of medical therapy. The FDA does not condone or approve that smoked marijuana has medicinal benefits. Therefore those physicians currently prescribing it are doing so against FDA regulations (Johnson, 2009). The Institute of Medicine (IOM) has stated that risks of smoking marijuana have not yet been definitively determined. The IOM did divulge scientific evidence indicating cannabinoid drugs as potentially having therapeutic affects but suggested smoking it should not be used for medicinal purposes (Johnson, 2009).

Currently the only standard legal form of marijuana is something known as Marinol (Ford, 1997), which contains synthetic tetrahydrocannabinol (THC) in pill form for medicinal purposes. This synthetic pill is made to imitate the function of smoked marijuana on the central nervous system and brain (Ford, 1997) and is the only federally legal (when prescribed by a doctor) substitute for medicinal marijuana. This drug has not had the same efficacy as shown by smoking the substance. Many of the symptoms thought to be addressed with smoked marijuana cannot be handled the same way by Marinol. Not only is it difficult to subside nausea, a common side effect suggested to be addressed by medicinal marijuana for a patient undergoing chemo, but to attempt to have them swallow a pill and prevent it from leaving in emesis, can be a difficult feat (Ford, 1997). According to reports by the IOM, synthetic cannabinoid drugs have a better potential than the smoked form. However the IOM also indicates that more research is required as to the mechanism and safety of these drugs (Johnson, 2009).

The human brain contains cannabinoid receptors (Johnson, 2009) located in the hippocampus which is found in the frontal lobe. The cannabinoid receptors interact with the ligands known as endocannabinoids. The receptors are participants in pain control of the body as well as controlling emotions (limbic system), appetite, vomiting reflex, motor skills and memory.
(cerebellum and basal ganglia) (Johnson, 2009). The neurotransmitters the body naturally uses to activate the cannabinoid receptors are called anandamides (Benson, Joy and Watson, 1999). Although not proven, it is believed that anandamides which are synthesized from N-arachidonoyl phosphatidylethanolamine, one of the most abundant phospholipids found in animals, have the ability to alter other neurotransmitters such as endorphins, serotonin and dopamine (Benson, Joy and Watson, 1999). According to Benson, Joy and Watson, the lack of these cannabinoid receptors located in the pons and medulla contribute to the rare occurrence of lethality caused by overdosing from marijuana (1999).

![Cannabinoid Receptor Sites](image)

Diagram and location of hippocampus in the brain (Bonsor, 2001)

The main substance found in the plant cannabis is THC which is the component that has the ability to interact with cannabinoid receptors. The reason for THC's effectiveness is that once in the brain it can act identically on the cannabinoid receptors as the naturally occurring neurotransmitter anandamide (Benson, Joy and Watson, 1999). The article written by Bonsor explains how the chemical portions of THC are so potent and fast acting that within seconds, it circulates from lungs to blood stream where it is carried to the brain and begins to act on the cannabinoid receptors. Therefore, within seconds it has the potential to affect vomiting reflexes, or altering emotion and appetite (Bonsor, 2001).
THC as separated from cannabis is classified as a schedule 2 drug currently allowing it to be used medicinally, however not in a form that can be smoked, in which case it is prescribed as Marinol, the synthetic pill form previously mentioned. The purpose of the classifications is to indicate which drugs might act as a "gateway" drug, the potential of abuse and the affects of the drugs. For a quick comparison drugs also classified with Marijuana in the schedule 1 include lysergic acid diethylamide (LSD) historically used as a method of psychoactive treatment and known for its extensive hallucinogenic affects. Heroin is also classified as a schedule 1 drug. This drug is used in other countries as a legal derivative of morphine for managing pain. It is considered highly addictive with regular use and is associated with HIV because the most common use of delivery is via intravenous injections. Chronic users of this drug often are left with collapsed lungs, cellulitis and liver disease. The potency and negative side effects of the drugs classified alongside marijuana are far greater than anything proven by the use of marijuana.

The diseases thought to benefit from the effects of marijuana include, but are not limited to, those suffering from AIDS, undergoing chemotherapy, as well as anorexia, glaucoma, neuropathic pain, and multiple sclerosis (MS) (Johnson, 2009).

The treatments used when battling cancer or AIDs/HIV often cause nausea and vomiting which in turn result in a loss-of-appetite and weight loss. It is imperative to avoid malnutrition when undergoing these types of therapies. From the current research marijuana has been shown to subdue nausea in these patients and even the synthetic forms of cannabinoids indicate an improvement in nausea (Crawford et al, 2007). As noted earlier, the benefit of smoked marijuana for nausea circumvents the need to orally digest something when one is highly nauseous.

Spasticity is a side effect of multiple sclerosis, an autoimmune disorder that is caused by the damage to myelin sheaths on nerves (Ford, 2007), that has been tested for therapeutic marijuana uses. The ability of THC to bind to the receptors in the basal ganglia is the mechanism for which it is beneficial. The spasms experienced are unconscious movements caused by spasms of the muscle; the effect of marijuana lessens the movement of uncontrollable muscle spasms.
Although people that struggle with MS often experience difficulties with coordination, it is not thought that this would be relieved by marijuana. The goal is that with a decrease in spasticity one might have better coordination (Bonsor, 2001).

Glaucoma is another disease that has shown possible relief from symptoms by marijuana. Glaucoma is a condition caused by abundant fluid accumulations in the eye which create intraocular pressure (Ford, 2007). This pressure can lead to eventual blindness if the optic nerve becomes damaged from the pressure buildup within the eye. Marijuana has been shown to decrease this intraocular eye pressure.

Other symptoms likely to be alleviated from therapeutically smoked marijuana are pain, sleep disorders and psychiatric symptoms including depression, bipolar and anxiety disorders (Johnson, 2009).

While it is frequently argued that smoked marijuana is beneficial for many different conditions and symptoms this route of administration causes much debate. The IOM finds synthetic cannabinoid drugs (tablet) to be more advantageous than smoked marijuana. The IOM reports “For patients such as those with AIDS or who are undergoing chemotherapy, and who suffer simultaneously from severe pain, nausea and appetite loss, cannabinoid drugs might offer broad spectrum relief not found in any other single medication” (Johnson, 2009 p.36). Opponents of smoked marijuana claim it causes harm to the cardiovascular system and lungs. At this point, there is not enough data to prove this theory. Likewise there is no significant evidence that marijuana does not contribute to cardiovascular and lung damage. The research conducted by the AMA declares that smoked marijuana had a higher rate of efficacy to counteract nausea and emesis for chemotherapy treated patients as well as a better rate of relief from those suffering from spasticity and pain. Another possible solution for smoking marijuana would be to increase its potency therefore requiring less smoking and less damage to the organs. To counter this argument the damage of higher potency to the bodies receptors would need to be researched (Johnson, 2009). Also developed to avoid smoking have been the invention of vaporizers. Vaporizers have the ability to deliver the drug similarly to that of smoking without having to smoke or ingest a pill (Johnson, 2009).

The only debate that doesn’t require clinical data to determine the efficacy of smoked vs. synthetic marijuana is from the patient’s perspective. The IOM believes a terminally ill cancer patient is an exception to the rule. Regardless of benefit or harm from smoking marijuana it is believed that a terminally ill patient needs quality of life rather than weighing benefits of a treatment (Johnson, 2009). Currently there are 8 terminally ill patients that receive joints monthly. It is sent to them through federal government due to the IND Compassionate Access Program. This program was initiated in 1978 and allows that select number of people to carry and use marijuana without suffering any consequences. These patients were deemed ill enough by the federal government. This is not legal for anyone else in the country (Johnson, 2009).
Equally controversial in the debate over legalizing medicinal marijuana is whether it would increase recreational use and the ability to obtain it for non-clinical use. The only way to prove or disprove this theory would be to assess the change in numbers of recreational users after legalization. This is a topic used in large part by the pharmaceutical companies as their argument for dismissal.

Making marijuana legal would also have financial implications for many parties involved including the state, the owners of the dispensaries and the tobacco companies. An expense for the state would be to employ law enforcement for applying and verifying adherence of citizens with this law similar to the way alcohol is monitored. There would however be revenue from taxing the substance. The actual generating and selling of the product would employ many people. Eventually pharmaceutical companies would establish types of marijuana creating competition within the market, therein creating revenue. The substance would be taxed and closely monitored to ensure all funds made are accounted for. California has already began to see revenue from taxing legal marijuana (Legality and Profitability of “Medical” Marijuana). In order to obtain a license for running and operating a dispensary a lawyer must be hired to assist in completing the application. It is costly to get certified and the certificates would are limited. Each state would regulate this individually. Arizona will regulate it by only allowing so many licenses to be distributed and each dispensary must be located so many miles apart to be considered legitimate.

Conclusion

More research and information needs to be obtained in order to understand the extensive nature of this drug and its potential harms/benefits. Currently, few researchers have the funds to conduct studies with large enough pools of participants to make an impact on the notion of its therapeutic effects. Marijuana is a drug and therefore it will have side effects as do all drugs whether legal or not. As there is potential to benefit many people suffering from debilitating diseases it is worth putting time, effort and money into addressing current issues and working toward legalization of medicinal marijuana.

Opinion

I personally believe there are many positive aspects to legalizing marijuana. My reasoning stems from the many facts that I learned while conducting the research for this paper as well as having worked in an oncology ward with many terminally ill patients. It is difficult to understand why someone with stage 4 brain cancer would be worried about the effects of smoke to their lungs, especially when there is no proven link between the two. Another factor is that pharmaceutical companies have historically been opposed to legalizing marijuana. It is a very low cost drug that thus far has proven to be mildly effective for a range of symptoms. Pharmaceutical companies are major providers in the pain management sector. Marijuana could threaten the market for many of the pain medications like opiates and sleep aids just to name a few. It would also
reduce the market for synthetic marijuana. In many instances it seems that the resistance from the established pharmaceutical community is biased so that facts and proof are not taking priority. Finally, it is very difficult to understand why the penalties for someone in possession of marijuana can exceed those whose crimes are far more dangerous to society. In general I believe legalizing something tends to result in having greater control over it. Prohibition is a perfect example of how difficult it is to monitor a drug when it is illegal. Granted, there is potential that recreational users would have less difficulty getting marijuana however this risk seems minor when one takes into account the already large number of recreational users. Hopefully more research and proof of benefits would result in the legalization of marijuana on the federal level and resulting control on the state level.
References


Fertility Drugs: Do the benefits outweigh the physical, emotional, and monetary costs?

Sarah Hylton

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Abstract:

Infertility is a problem that affects a large population of the world’s men and women, 6.1 million individuals in fact. There are many drugs and treatment options available today. The physical, emotional, and monetary costs of each option are very high, yet many men and women want nothing more than to hold a new child in their arms. So the question asked is: does the benefit of having a child truly outweigh the risks involved?

What is infertility? Infertility is a condition of the reproductive system that impairs the conception of children. It affects approximately 6.1 million individuals throughout the United States. The diagnosis of infertility is usually given to couples who have been attempting to conceive for at least 1 year without success. Conception and pregnancy are complicated processes that depend upon many factors including the production of healthy sperm by the man, healthy eggs produced by the woman, unblocked fallopian tubes that allow the sperm to reach the egg, the sperm’s ability to fertilize the egg when they meet, the ability of the fertilized egg to become implanted in the woman’s uterus, and sufficient embryo quality. Finally, for the pregnancy to continue to full term, the embryo must be healthy and the woman’s hormonal environment must be adequate for its development. When just one of these factors is impaired, infertility can result.

The most common causes of infertility include egg quality and production, blocked tubes, and the male problems. Problems in eggs quality and production are the result of poor egg quality, irregular ovulation or failure to ovulate because of hormonal deficiencies or imbalances. Another cause can also be polycystic ovarian syndrome, which is a condition in which a hormonal imbalance prevents the egg-containing follicles on the ovaries from the maturing and releasing of an egg, instead forming often painful ovarian cysts. Blocked fallopian tubes are the result of scar tissue, adhesions, and damaged tube ends. Another common cause is endometriosis, which is the growth of endometrial cells outside the uterus, most often on the ovaries, Fallopian tubes, or the exterior of the uterus. About 10 to 15 percent of women of childbearing age have this condition. Many of these women will never show symptoms. Even if a woman ovulates regularly, blocked tubes make pregnancy next to impossible, since the egg is unable to reach the uterus. In men, infertility can be the result of a blocked vas deferens, poor sperm quality, low sperm motility, a semen deficiency, or not having enough, or any sperm to begin with. The most common solution is to undergo an operation to clear the blocked tubes. However, if the operation is unable to cure a man’s infertility, fertility drugs may boost sperm production, or a man’s sperm can be used to artificially inseminate his partner.

Infertility has several treatment options, most commonly prescribed are fertility drugs. Fertility drugs work by promoting ovulation by stimulating hormones in a woman’s brain to get an egg ready and release it from her ovaries each month. Many fertility drugs have been used safely and successfully for more than 30 years. Unlike many other infertility solutions, such as in vitro fertilization, fertility drugs won’t increase the chance of multiple births beyond 5 to 15 percent.

Today women almost take fertility drugs for granted. Anyone who has trouble having a baby knows that there are specialists and treatments available to help her.
And women are even more aware that the success rates today are quite high. Fertility drugs and treatments have not always been readily available, though. Many steps were made over the years to obtain the know how to help fertilize a woman.

In fact, the first steps toward modern fertility miracles began more than 80 years ago. In the 1920’s and 30’s, reproductive hormones were discovered. First, estrogen, the female hormone, was discovered in 1923. In 1935, the male hormone, testosterone, was discovered. The two hormones were key towards modern fertility treatments. In the 1940s and 1950s, the first synthetic hormones intended to increase fertility were created. In the 1960’s the ovary-stimulating drug Clomid and hMG were made available in the United States. These two drugs improved the likelihood of ovulation by up to 80 percent and conception improved to 40 percent. In the 1970’s and 1980’s fertility drugs were used to stimulate ovulation for egg retrieval. The first “test tube babies” resulted in live births in both Europe and the United States. In the 1990’s and today fertility drugs have become very commonplace. By 2002, almost 12 percent of married women had used some form of fertility drug treatment³.

There are nine most common brands of fertility drugs that are prescribed to women today. The first one is called clomiphene. The brand names include Clomid and Serophene. Clomiphene, taken in pill form daily, stimulates the pituitary gland to produce follicle-stimulating hormones, which are the hormones that trigger ovulation. It prompts the ovaries to prepare a number of eggs for ovulation. Women who ovulate irregularly or not at all commonly use Clomiphene. About 70 to 90 percent of women who take Clomiphene will ovulate, and of those who ovulate, 20 to 60 percent will get pregnant⁴. The drug human chorionic gonadotropin or hCG is usually given in conjunction with this drug. hCG stimulates the follicle to release an egg.

The third drug, Human Menopausal Gonadotropin (hMG) consists of purified follicle stimulating hormone. When injected into the body, FSH causes a woman to develop egg follicles. After seven to twelve days of shots, the woman receives an injection of human chorionic gonadotropin that stimulates the ovaries to release the egg or eggs that it has just developed. HMG is most often given to women with low estrogen levels who have not responded to Clomiphene. Possible side effects from hMG include abdominal tenderness and weight gain. In rare cases, less than 5 percent of the time, women develop hyperstimulated ovaries, a potentially fatal condition signaled by sudden onset of severe pelvic pain, nausea, vomiting, or weight gain. Due to an excessive number of eggs, the ovaries rapidly swell to several times their size and may leak fluid into the abdominal cavity. Even with careful monitoring, multiple pregnancies and ovarian hyperstimulation can occur. The rate of multiple births is close to 20 percent. About 70 to 90 percent of women who take hGM will ovulate, and of those who ovulate, 20 to 60 percent will get pregnant⁴.

Another method of stimulating the cycle of the ovaries is simply through the use of receiving FSH independently, without any other medication. The brand names include Gonal-F and Bravexelle. A prescriber commonly gives a prescription of FSH, and a second one for hCG. These two are often used in combination.

If the cause of infertility is a menstrual cycle that's irregular or erratic, then Gn-RH, known as Gonadotropin-releasing hormone analogs, can be prescribed.
This specific treatment is quite often used for those women who ovulate prematurely, or a woman that has her period before the lead follicle is mature enough. This form of treatment supplies the pituitary gland with the Gn-RH, enabling the doctor then to induce follicle growth through the use of FSH.

Another medication that may be given orally is called Metformin, which the brand name is Glucophage. It's recommended when a physician believes that infertility is caused by insulin resistance. Insulin resistance is suspected as a cause in the development of polycystic ovarian syndrome.

If the menstrual cycle is irregular because there are higher than normal levels of prolactin in a woman's system then the medication Bromocriptinecin is prescribed. Bromocriptine, which can be taken orally or as a vaginal pill, reduces the pituitary gland's production of the hormone prolactin. Excess prolactin reduces estrogen levels and inhibits ovulation. Women who take Bromocriptine suffer from hyperprolactinemic amenorrhea. Side effects from Bromocriptine include nausea, dizziness, low blood pressure, and headaches. Patients who take the drug vaginally often report fewer side effects. 90 percent of the women who take Bromocriptine will ovulate as long as they continue taking the drug. Of the women who ovulate, 65 to 85 percent will get pregnant. Sold under the name of Parlodel, this is the hormone which triggers milk production in women who have just given birth.

A doctor may want to prescribe a medication called an aromatase inhibitor. This class of medication, which includes letrozole and anastrozole, has not been approved by the U.S. Food and Drug Administration for use for the problem of infertility. Aromatase inhibitors are drugs made specifically for breast cancer. Many doctors though, prescribe it when clomiphene citrate is not effective. This is reserved for women who can't ovulate on their own. The manufacturer itself has warned physicians to refrain from using this. Its use may cause adverse health effects including birth defects and miscarriages.

The number one prescribed fertility treatment is the oral clomiphene citrate. Clomiphene is used to induce ovulation in women who do not produce eggs but wish to become pregnant. Clomiphene is in a class of medications called ovulatory stimulants. It works similarly to estrogen, a female hormone that causes eggs to develop in the ovaries and be released. Clomiphene comes as a tablet to take by mouth. It is usually taken once a day for 5 days, beginning on or about day 5 of the cycle. To help remember to take clomiphene, it should be taken around the same time every day. Clomiphene must be taken exactly as directed, absolutely no more or no less that prescribed by a doctor.

To understand how Clomid works, it is necessary to have a basic understanding of the hormonal feedback mechanism operating in the ovulatory cycle. The hypothalamus is a small gland at the base of the brain which indirectly regulates the levels of follicle stimulating hormone (FSH), luteinizing hormone (LH) and others via the pituitary gland. It can be thought of as a thermostat that varies hormonal levels based primarily upon the levels of FSH and estrogen. Gonadotropin releasing hormone (GnRH) is produced by the hypothalamus and travels to the pituitary where it stimulates the production of FSH. FSH directly stimulates the recruitment and growth of the ovarian follicles, each of which contains an egg. If FSH levels remain high, as is the case with injectable FSH medications, numerous follicles will develop and mature.
As healthy follicles develop, they produce estrogen which travels through the bloodstream to the hypothalamus. The hypothalamus monitors the level of estrogen and varies the production on GnRH accordingly. High estrogen levels signal that the follicles are mature, which causes the production GnRH to decrease thus lowering the levels of FSH.

Clomid works by "competing" with the estrogen receptors at the hypothalamus. It occupies receptors that would normally "sense" estrogen making it seem that estrogen levels are low. This "competing" action causes the hypothalamus to produce more GnRH with stimulates the pituitary to increase production of FSH.

Eighty percent of patients that are prescribed Clomid will ovulate and 40 % of those patients will conceive. Once ovulation occurs on Clomid, there is no value in increasing the dosage. In general, Clomid should only be used for a maximum of six cycles, and it has been studied that there is no significant advantage of treating for more than 4 cycles. Numerous studies demonstrate that if pregnancy will occur on Clomid, seventy-five percent will occur within three to four cycles.

When Clomid is being prescribed without artificial insemination and pregnancy has not resulted after three cycles, intrauterine insemination (IUI) may be added for the remaining three cycles to increase the chance of pregnancy. However, when seeing an Infertility Specialist, it is usually recommended that FSH (injectable fertility drugs) be used to directly stimulate the ovaries. If the patient fails to conceive on Clomid, with IUI, after a maximum of three to four cycles, gonadotropin cycles with IUI will often be attempted. If a patient fails to conceive on FSH and IUI, in vitro fertilization (IVF) is usually the next step. Each couples treatment protocol is different and based upon the specific cause of the infertility.

The common side effects of Clomiphene include flushing, upset stomach, vomiting, breast discomfort, headache, and abnormal vaginal bleeding. Less common side effects, but ones that should be taken very seriously if they occur are, ovarian enlargement, blurred vision, visual spots or flashes, double vision, lower stomach pain, stomach swelling, weight gain, and shortness of breath. Clomiphene should not be used for more then 6 cycles; studies have shown that long term use of the drug can increase the risk of ovarian cancer.

Another important side effect to take into account is the fetal and neonatal abnormalities that were reported during postmarket surveillance of Clomiphene, some of which include: delayed development; abnormal bone development, including skeletal malformations of the skull, face, nasal passages, jaw, hand, limb, foot, and joints; tissue malformations including imperforated anus, tracheoesophageal fistula, diaphragmatic hernia, renal agenesis and dysgenesis; and malformations of the eye and lens, ear, lung, heart, and genitalia; as well as dwarfism, deafness, mental retardation, chromosomal disorders, and neural tube defects.

Clomiphene:

2-(4-(2-chloro-1,2-diphenylethenyl) phenoxy)-N,N-diethyl-ethanamine
Molecular Formula: $C_{26}H_{23}CINO$

Structure:

Clomiphene is a mixture of two geometric isomers, enclomiphene (E-clomiphene) and zucclomiphene (Z-clomiphene).

![Molecular Structure Diagram]

Enclomifene  Zucclomifene

Preparation:

To prepare clomiphene, three raw materials are used: citric acid monohydrate, diethyl carbonate, and 4-Hydroxybenzophenone.

4-Hydroxybenzophenone is condensed with 2-(diethylamino)ethyl chloride in toluene in the presence of alkali. The 4-[2-diethylamino]ethoxy]benzophenone formed is then grignardized with benzyl chloride, and the tertiary carbonyl produced is then dehydrated to give 2-[p-(1,2-diphenylvinyl)phenoxy]triethylamine. The compound is chlorinated to yield clomiphene and then reacted with an equimolar quantity of citric acid. Clomiphene citrate is a mixture of (E)- and (Z)- geometric isomer containing 30-50 percent of the (Z)-isomer.

Solubility:

Clomiphene is sparingly soluble in alcohol, and slightly soluble in water or chloroform, and is insoluble in ether.

Physical Description:

Clomiphene is a white to pale yellow powder when synthesized. It is essentially odorless. Clomiphene melts at about 118 degrees Celsius with decomposition.
One major concern surrounding fertility drugs is the whether or not fertility drugs are safe. Fertility drugs are often pointed to as a risk factor for ovarian cancer. There are several factors that may increase a woman's risk of ovarian cancer. One factor is that an increased number of uninterrupted ovulations in a woman's lifetime increase her chance of developing ovarian cancer. This also explains why events that interrupt the constant cycle of ovulations, such as pregnancy, breastfeeding, and oral contraceptive use, are associated with a decreased risk of ovarian cancer. Another factor is that increased levels of certain hormones associated with ovulation, such as human chorionic gonadotropin, increase the risk of ovarian cancer. Fertility drugs can increase both the number of ovulations and the levels of hormones associated with ovulation. A conflicting study states that women who take ovulation-inducing drugs in conjunction with IVF are not at an increased risk of developing breast, ovarian, or uterine cancer. However, women who seek treatment but do not take fertility drugs have more than twice the expected incidence of uterine cancer, and women with unexplained infertility have elevated rates of uterine an ovarian cancer. This study was based on 29,700 women who registered for treatment at 10 IVF clinics in Australia. The study only refers to increasing the risk of cancers when fertility drugs are taken with IVF, and not the risk of cancer when drugs are taken by themselves.

Other concerns are the likelihood of multiple births that arise from fertility drug use. Multiple births occur in about 50 percent of cases, especially among women in their early 30s or younger. In most cases, risks can be lowered through careful monitoring and controlling dosages of medications. For IVF, if a high number of eggs are seen developing on the ultrasound, doctors are able to remove them and place back two or three embryos. If too many eggs are seen, the patient may be advised to not attempt to get pregnant. Couples sometimes are hesitant to cancel the cycle because they have so much invested in it, both financially and emotionally. In addition, if the couple does not cancel the cycle and four or more embryos implant, the newborn babies have a high risk of neurological complications if they survive. Multiple births are also risky because they can result in the birth of sickly, premature babies. Premature babies face serious complications, including lung problems and bleeding of the head, which can cause long-term physical and mental impairment.

The costs of fertility are not just physical. The costs of fertility treatment are very expensive. Plus, there are no guarantees. Spending more money on infertility may give more chances at conception, but there is still no assurance that a biological child will develop.

Clomid is one type of fertility medication, and it makes up the major cost of the treatment cycle. Clomid or other gonadotropin injections ranges from $50 to $4,000, depending on the treatment plan, the drugs involved, and the patients cycle. A doctor may suggest artificial insemination to the patient. If the doctor injects sperm into the uterus, it can cost $250 to $750 per injection. A sperm was, a fertility procedure that removes weak and unhealthy sperm, costs an average of $150. Ovulation induction costs around $1,600 for office visits, injection training, baseline FSH test, and estrogen and ultrasound monitoring throughout the cycle. The $1,600 doesn’t include fertility drugs, making the cost of this infertility procedure fairly high. The $1,600 pricetag is the per month cost for the course of the treatment.
For invitro fertilization, the average cost of removing eggs from a woman’s ovaries, mixing them with her partner’s sperm and implanting the resulting embryos into her uterus ranges from $7,000-$15,000. The cost of this procedure includes office visits, baseline tests, estrogen and ultrasounds monitoring, hospital costs, embryo freezing, and physician costs, but it does not include the costs of the fertility drugs⁹.

Receiving donor eggs is another option. The cost of donor eggs is between $10,000-$50,000. This is a cash price, because the donor’s eggs and egg retrieval are never covered by insurance. A final option is finding a surrogate. A surrogate in not covered by medical insurance and can cost anywhere from $15,000-$60,000. The money goes to lawyers agencies, and the surrogates’ medical expenses⁹.

Other costs involved in fertility procedures that are often not calculated into the initial price are blood work, lab tests, various medical procedures, sonograms, office visits, anesthesia, and surgeries involved in child birth. Each of these expenses can run from $300-$10,000 of additional costs.

While the possibility of multiple children may seem like a good alternative to remaining childless for many couples, each couple must weigh the risks and benefits of using fertility drugs to have these children. Fertility drugs can cause serious physical damage and have long-term effects on the mother and the child. Each patient must consult their doctor and follow his/her recommendations to ensure that the use of a fertility drug is safe for the parents and the child. In addition, due to the cost of fertility drugs, it is often upper and middle class parents that are able to choose this option. It is not truly an option for all.

The use of fertility drugs also has many social and ethical implications. It implies that parents are interested in having offspring that are genetically related to them. There are many options available to infertile couples, and fertility drugs are just one solution. Childlessness can also be resolved by a method that is physically safe for all parties: adoption. Adoption is a choice open to infertile parents, yet adoption has many social stigmas attached to it that often prevents many couple from choosing adoption over fertility drugs.

After weighing both the benefits, having a child of my own, and the risks, ovarian cancer and possible complications and effects on my body and baby, and also weighing the costs of the treatment, I have decided that if I am found to be infertile, I would choose the first steps of fertility treatment to attempt to get pregnant. If I were not to get pregnant after the use of Clomiphene, and possible FSH shots, I would choose adoption. The costs and emotional draining involved in the long process of becoming pregnant is just too high for myself. But I also understand why people would choose the option to continue with the fertility treatments as well. A newborn child is one of the world’s most precious gifts. Having a child is very important part of life for most people. Choosing fertility options is a choice that should be discussed in depth with both the partner and a doctor. And the chance that a baby may not develop from the process is a cost that the patient must be willing to live with. I believe, overall, fertility drugs are an effective solution to infertility for many couples, yet it comes with very high physical, emotional, and monetary costs, that cannot be taken lightly.
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Sounds of Silence, the Science of Speakers

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Sounds of Silence, the Science of Speakers

This paper serves to introduce the science of sound and how a speaker produces soundwaves. It begins with a description of waves in general and then explores sound waves in particular. The functioning of an electrodynamic speaker is then discussed followed by a brief introduction to emerging technologies.

If a tree falls in the forest and no one is around to hear it does it make a sound? The existential ramifications of this question will probably confound people forever, much like Schrödinger's cat. If a cat that is both alive and dead in a sealed box meows did it in fact make a sound? Existentialism aside the answer to these two questions, is both yes and no. The exact answer depends upon which definition of sound one uses (Everest, 2000). The sensation humans call sound is the result of mechanical vibrations exciting the ear drum causing electrical impulses to be sent to the brain. If this is the definition of sound one wants to use then the answer is no. There was no ear drum to be excited and therefore no sound was created. However the second definition of sound refers to the vibrations created in the air and does not require an observer. This definition means there was in fact a sound.

Sound starts with a vibrating object which creates disturbances in the surrounding medium. In the case of the tree its motion creates vibrations in the atmosphere resulting in a phenomenon known as sound. In order for sound waves to propagate two things are required of the surrounding medium. The first is elasticity and the second is inertia (Everest, 2000). The reason these properties are necessary will become clear in the following paragraphs concerning the various characteristics of waves.

Waves can best be understood through examples, and for this discussion of sound waves the idea of a tuning fork will be used. The two most basic characteristics of waves are compression and rarefaction. Figure 1 shows a tuning fork and the resultant compressions and rarefactions it creates in the air once it is set into motion.

The first picture (a) shows the tuning fork at rest and the uniform appearance of the surrounding air. The middle picture (b) shows a zone of compression where the outward motion of the tuning fork has forced the molecules in the air to move closer together. This creates an area of higher pressure with respect to normal atmospheric pressure as well as higher molecular density (Serway & Vuille, 2009). The third example (c) is of rarefactions. Here the inward motion of the tuning fork creates a region of air with reduced molecular density and lower pressure (Serway & Vuille, 2009). The ideas of elasticity and inertia now come into play.

As the air molecules are pushed together in a compression, the elastic nature of air acts to pull the molecules back to their original position. The inertia of the molecules forces them to overshoot the original position and

![Figure 1: Compression and Rarefaction](image)
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they are pushed past it once again calling elasticity in to play (Everest, 2000). This continues until the forces of inertia and elasticity fade away. The caption of Figure 1 describes sound as a longitudinal wave. Longitudinal as well as transverse are two additional ways to characterize a wave.

Longitudinal waves occur when a vibrating object moves the individual particles of the medium in the same direction as the wave is moving (Serway & Vuille, 2009). As the wave moves away from the tuning fork it is easy to see that the lines (representing individual molecules) move back and forth in the same direction. Transverse waves occur when the vibrating particles move at right angles to the direction of the wave (Serway & Vuille, 2009). To imagine this type of motion think of dropping something into water. As the waves move outward from the source of impact the individual water particles move up and down creating ripples. Transverse waves do not concern the propagation or production of sound in air because air does not posses the properties necessary for transverse waves to occur. However diagrams of transverse waves make the explanation of longitudinal waves easier to understand. The next few paragraphs will introduce ideas related to sound waves that can be quantified with variables allowing mathematical analysis.

![Wave Diagram](image)

The first variable of interest in describing the action of a sound wave is frequency. Frequency describes the number of times the tines of the tuning fork complete one cycle of motion per unit of time and by extension the waves created by the tuning fork. Starting from an arbitrary position of \( x = 0 \) and moving through the maximum positive position (\( x = A \)) back through the origin to the minimum negative position (\( x = -A \)) and back to \( x = 0 \) describes one cycle (see Figure 2). Frequency (\( f \)) is measured in Hertz (Hz) or cycles per second, and is defined mathematically as: \( f = v / \lambda \) where \( v \) = wave speed, and \( \lambda \) = wavelength (Serway & Vuille, 2009). Wavelength is the distance over which a waves shape repeats, in other words it is the length of one cycle. The reciprocal of frequency is the period (\( T \)) or: \( T = 1 / f \) (Serway & Vuille, 2009). The period is the time it takes for one wavelength to complete its cycle. In Figure 2 the horizontal line represents the \( x \) axis. The crests correspond to the maximum positive position (A) and the troughs represent the minimum negative position (-A). This figure illustrates a transverse wave as well as a longitudinal wave. If one considers the curved line to be the motion of the particles, a transverse wave is shown. However, if one considers the curved line to be variations in pressure it describes a longitudinal wave. An important aspect of frequency, the natural frequency of a system is the next topic of discussion.

The natural frequency also known as a resonant frequency of a vibrating system is the frequency that the system vibrates at once set into motion, with no further outside interference. It is easy to get a system to vibrate at its natural frequency because the system will pick out its
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natural frequencies and discard any other frequencies present (Nave, 2010). This phenomenon is known as resonance. All vibrating systems have at least one natural frequency and often times more than one (Serway & Vuille, 2009). In regards to sound, the lowest natural frequency is called the fundamental frequency or \( f_0 = f \) (Serway & Vuille, 2009). Integer multiples of the fundamental frequency are also natural frequencies ie: \( f_1 = 2(f) \), \( f_2 = 3(f) \) and so on. These other natural frequencies are known as harmonics (Serway & Vuille, 2009). A sound wave that has no harmonics and is composed of only one frequency takes the familiar shape of a sine wave. Harmonics are important with respect to sound because they allow the ear to differentiate between the sound of a flute for example and a trombone (Everest, 2000). The two instruments may be playing the same note but it is easy to distinguish between them because of their differing harmonics.

Phase is commonly used when describing the interaction of two individual sound waves. If the two waves in question are in phase their individual peaks and valleys occur at the same time. Phase will be discussed in more detail later when the topic of interference is explored.

The next variable of interest in the description of waves is amplitude. Amplitude is the maximum distance the wave moves in either the positive or negative direction (Serway & Vuille, 2009), it is the \( \pm A \) used to describe one cycle in the discussion of frequency. It is important to note that it is either plus or minus A and not both. The distance from 0 to a crest or trough is the amplitude of the wave. These variables are sufficient to describe basic waves and the discussion now turns to the differing types of waves.

Sound waves occur across a spectrum like light waves, and fall into three categories: audible, ultrasonic, and infrasonic (Serway & Vuille, 2009). Audible waves as the name might suggest have frequencies humans can hear. Infrasonic waves have frequencies below the threshold of human hearing. Earthquake waves while sometimes heard are an example of infrasonic waves (Serway & Vuille, 2009). Ultrasonic waves have frequencies that are above the upper limit of human perception (Serway & Vuille, 2009). This report will focus on audible waves since these waves are the desired output of a sound system.

Waves can be further classified as spherical or plane waves (Serway & Vuille, 2009). Light and sound waves are generally spherical, unless the source of the waves is confining and directing the emitting wave, as in a flashlight, or a hypersonic speaker which will be discussed later. Spherical waves project energy in all directions from the source (Serway & Vuille, 2009). Their intensity (I) is defined as the average power divided by the area or: \( I = P / A \). The area of a spherical wave is the same as the area for a sphere: \( 4 \pi r^2 \) making the equation \( I = P / 4 \pi r^2 \) (Serway & Vuille, 2009). As the spherical wave moves farther from the source the curved nature of the wave fronts seem to flatten out and can then be considered plane waves (Serway & Vuille, 2009). To make this concept clearer think of the surface of the Earth, the Earth is definitely round but when one is standing in a large clear field it appears flat. The intensity of spherical sound waves typically dissipates rather quickly because the area of a sphere grows exponentially. The intensity of sound will be discussed in more detail later. Next the motion of waves and wave interference comes to the fore.
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An interesting phenomenon of wave motion is the standing wave. A standing wave can be demonstrated with a string attached at one end to a stationary point while the opposite end is connected to a vibrating object. When the vibrations reach the resonant frequency of the string, the waves moving along the string appear to stop moving (Serway & Vuille, 2009), hence the name standing wave, and the string looks similar to the curved line in Figure 2. Another more exciting display of a standing wave can be seen using a Rubens tube.

As seen on the Discovery Channel show Mythbusters, a Rubens tube is a section of pipe closed at one end by a speaker, and sealed at the other end. A gas pipeline is installed at the sealed end and holes are drilled in equal distances along the top of the pipe. The gas is turned on and ignited along the top as seen in Figure 3. When a sound is played by the speaker a standing wave is generated inside the pipe and the flames provide a visual display of the wave.

Figure 3: A Rubens tube

A standing wave occurs when the initial wave reaches the fixed end of the string (or pipe) and is reflected back toward the source. Nodes and anti-nodes are used to help understand the nature of standing waves. A node occurs on a standing wave where the initial wave and the reflected wave's amplitudes are equal but opposite in direction (Serway & Vuille, 2009). On a string, the nodes are the part of the string that don't appear to be moving, in the Rubens tube the nodes are the points where the flames are the smallest. The anti-nodes, as the name might suggest, occur halfway between each node (Serway & Vuille, 2009). They are the points on the Rubens tube where the flames are the largest. Even in a tube with an open end, standing waves are created because the wave is partially reflected at the open end (Serway & Vuille, 2009). Standing waves are important to the discussion of sound because they allow instruments such as flutes and organs to produce sound. Another important characteristic of waves is the Doppler effect.

The Doppler effect occurs when the source of a sound, the listener of a sound or both, are moving (Serway & Vuille, 2009). It is a phenomenon with an easily identifiable example: that of an emergency vehicle. As the emergency vehicle with lights on and sirens blaring roars past an observer, the person observing seems to hear a change in the siren's frequency. It either seems to get higher or lower depending on whether the vehicle is moving towards or away from the observer. This occurs because the sound waves are forced closer together in front of the moving source and spread apart behind it (Serway & Vuille, 2009). In an extreme example of the Doppler effect, when an object moves faster than the speed of sound the wave fronts in front of the object all collapse onto one another and are heard all at once, in a sonic boom (Serway & Vuille, 2009).
Constructive and Destructive Interference occurs when two waves encounter each other, see Figure 4. Constructive interference happens when the two waves are in phase, the peaks and valleys of each wave falling in line with each other, peak to peak and valley to valley ("Interference," 1999). Destructive interference occurs any time the two waves in question are not in phase. If the waves meet peak to valley and they have the same amplitude and frequency theoretically they would cancel each other out completely and there would be no sound at all ("Interference," 1999).

However, in the real world because it is almost impossible to have two waves meet perfectly in this situation silence is rarely the end result ("Interference," 1999).

Taking a look at Figure 4, we see an example of constructive and destructive interference. Example (a) shows the result of constructive interference, each waves amplitude is added together resulting in a wave with the same frequency, but double the amplitude. The second example (b) shows the result of destructive interference; the two waves cancel each other out. In line with the idea of interference is the concept of beats. These beats do not refer to the rhythmic beating of a drum in a song, but rather the rhythmic beats that occur when two waves alternate between constructive and destructive interference with each other. The volume of the two sounds seems to go up and down creating audible "beats" this can be seen in Figure 5 (Serway & Vuille, 2009).

The equation for the speed of sound in an ideal gas is: \( v = \sqrt{\gamma RT/M} \), where \( \gamma = \) adiabatic constant of the gas in question, \( R = \) the universal gas constant, \( T = \) the absolute temperature and \( M = \) the molecular mass (Nave, 2010). The speed of sound in air is approximately \( v = 331.4 + 0.6 T \), measured in meters per second (Nave, 2010). The general equation for the speed of a traveling wave is \( v = \sqrt{(B / \rho)\gamma} \), where \( B = \) the bulk modulus of the medium and \( \rho = \) the density of the medium (Serway & Vuille, 2009). This is useful in determining the speed of sound in water which, at 20°C is 1483 m/s (Nave, 2010).

The speed of sound is useful not only in calculating the frequency but also the intensity of a sound wave. The equation for intensity of a sound wave (I) is: \( I = P / A \), where \( P = \) power and \( A = \) area, intensity is measured in watts per meter squared (Serway & Vuille, 2009). \( P \) can be further simplified to \( F(v) \), where \( F = \) force and \( v = \) speed. Intensity is important because it can be used to find the Decibel (dB) level of a sound. Decibels are a better measure of sound because it is based on a logarithmic scale which approximates the way the ear processes sound.
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(Serway & Vuille, 2009). The equation of a Decibel is: $\beta = 10 \log_{10} \left( \frac{I}{I_0} \right)$, where $\beta =$ Decibel level, and $I_0 = 1.0 \times 10^{-12}$ W/m$^2$ (the threshold of hearing). This means that a sound at the threshold of hearing ($I = I_0$) corresponds to a dB level of $0 = \beta = 10 \log_{10} \left( \frac{I}{I_0} \right)$

The first definition of sound relates to human perception of sound. It is not entirely accurate to say that humans “hear” sounds, but more like we feel them. The vibrations of low frequency sounds can be easily felt at a concert, or near a car with booming bass. In fact some of the frequencies of the sound being created by the speakers can sometimes only be felt and not heard. Earthquakes are another example of sound waves that can definitely be felt but not always heard. The human ear has developed the ability to feel vibrations that occur between about 0 dB and 120 dB (Serway & Vuille, 2009), (from the discussion of dB level earlier the difference in intensity between 0 and 120dB is $1.0 \times 10^{12}$ or one trillion) and as will be explained transmit this information to our brains where it is “heard.”

The ear consists of three regions: the outer ear, the middle ear, and the inner ear. The outer ear is made up of the familiar part of the ear that sticks out from the head, and the ear canal (“Hearing loss,” 2009). The ear canal terminates at the tympanum or ear drum. The middle ear consists of the ossicles a set of three small bones. These bones are called the hammer, anvil and stirrup and are so named because of their shapes. The inner ear consists of the fluid filled cochlea. It is inside this fluid that the vibrations of sound are turned into electrical impulses that the brain can then interpret (“Hearing loss,” 2009).

As sound waves approach the ear the outer ear acts to both filter and distort the sound making it easier to hear certain frequencies (Serway & Vuille, 2009). Generally the ear favors sounds within the range of normal human speech. The waves travel down the ear canal and cause the tympanum to vibrate. These vibrations are picked up by the hammer and transmitted via the anvil to the stirrup which moves the oval window. The various sizes of the ossicles as well as the relative difference in the size of the ear drum and oval window allow the ear to magnify the sounds (Serway & Vuille, 2009). Once the vibrations pass the oval window a standing wave is set up inside the cochlea. The interior of the cochlea not only contains fluid but also the basilar membrane. This membrane is covered in tiny hairs that each have distinct natural frequencies which they respond to (“Hearing loss,” 2009). It is here that sound is transformed into electrical impulses that are sent to the brain. The interesting thing about this process is that the ear separates the sounds according to frequency and then re-integrates them when they reach the brain. Damage to the tiny hairs on the basilar membrane is often the reason for hearing loss from exposure to loud, intense sounds. Hearing loss can occur gradually over time from repeated exposure to loud sounds, or can occur suddenly with exposure to a sufficiently loud sound (“Hearing loss,” 2009).
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The current design of electrodynamic loudspeakers is based on work dating back to the late 1800's ("History and"). Not much has changed in its design since then. The idea was initially described by Werner Von Siemens in 1877 but the technology to amplify the electrical signals and produce a useful speaker did not exist at that time ("History and"). It was not until 1921 that two researchers, C.W. Rice of General Electric and E.W. Kellogg of AT&T were able to produce an amplification system and the modern electrodynamic loudspeaker was born ("History and").

The electrodynamic loudspeaker's design has not changed since it was first described by Siemens in the late 1800's ("History and"). The following description of parts comes from a video clip from the show How It's Made, entitled Loudspeakers. A loudspeaker is composed of a moving diaphragm powered by electromagnetic principles. The diaphragm, also known as the speaker cone is the part of the speaker that is responsible for moving the air around it and creates the actual vibrations that we perceive as sounds. The diaphragm is driven back and forth by the action of the voice coil. It is a light tube wrapped with a conductive wire and together with the permanent magnet turns the electrical impulses of music or speech into the mechanical motion the diaphragm relies on to do its job. The permanent magnet is necessary to complement the electro-magnet that is created by current running through the wires of the voice coil. The magnet that is created when the voice coil is under current is alternately attracted to and repelled by the permanent magnet thus creating motion. The dust cap covers the voice coil and as its name suggests keeps dust from entering the voice coil which could adversely affect the voice coil's ability to move over time. The spider and suspension of the speaker each perform the same job, the spider attaches the voice coil to the basket while the suspension attaches the diaphragm to the basket. They both provide suspension to the moving parts of the speaker, keeping the voice coil and diaphragm properly aligned as they move up and down. The basket is connected to the magnet and gives the upper suspension a surface to mount to as well as providing a place for the electrical contacts and mounting screws to be attached to.

These types of electromagnetic speakers come in a variety of sizes, each size having particular advantages or disadvantages over the others. In the audio world the differently sized speakers are often referred to as high-range (tweeters), mid-range or low-range (woofers and sub-woofers) (Rio & Buono, 2009). It is necessary to have different sizes of speakers because of resonance. Each type of speaker responds to a different range of frequencies. The high pitch sounds tweeters produce require a small light weight diaphragm, while the low range produced by woofers requires a large diaphragm to move a sufficient amount of air characteristic of low frequency sounds (Rio & Buono, 2009).
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There are many different types of speakers on the market many of which rely upon a diaphragm to create vibrations. Another type of diaphragm dependent speaker is the electrostatic type as seen in Figure 8. Here a thin, lightweight diaphragm is coated with a conductive material and suspended between two electrified plates (“FAQ”). The sound signal is sent to the diaphragm causing it to vibrate as it is attracted to and repelled by the electrified plates. These speakers are very good at reproducing sound but because of the lightweight nature of the diaphragm but usually require traditional electrodynamic subwoofers to reproduce low frequency sounds (“FAQ”).

Hypersonic speakers take a departure from the traditional diaphragm model. This technology makes use of ultrasonic waves. As mentioned earlier ultrasonic waves are outside the range of human hearing, so how is this possible? It has to do with distortion and interference of waves. These speakers create two sets of ultrasonic waves and project them in a relatively straight line (Maney, 2003). When the two waves come into contact with and object or a person they interfere with each other producing audible sound waves (Maney, 2003). Ultrasonic waves, by their very nature can travel farther than audible waves and also stay more focused. This means that these new speakers can project sound farther than traditional speakers without losing as much volume and can be heard over 100 yards away even in a noisy environment (Maney, 2003).

Another type of diaphragm speaker has been developed by Warwick Audio Technologies in the United Kingdom. From an article about this new type of speaker on cnet.com: “The technology behind the FFL assembles thin conducting and insulating materials, resulting in the development of a flexible laminate. When activated by an electrical signal, the laminate will vibrate and produce sound.” This new type of speaker is less than a quarter of a millimeter thick and can be used in many different types of applications. These speakers could be painted or printed on thereby concealing them to look like a picture for instance.

Carbon nanotube speakers like hypersonic speakers do not use a diaphragm to generate vibrations in the surrounding medium (H. E.). These speakers utilize heat to create pressure...
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waves in the medium thereby creating sound (H. E.). One of the more useful properties of carbon nanotubes is the fact that they are hydrophobic, which means they repel water (H.E.). These speakers can be used in water without the added worry of the nanotubes being degraded (H. E.). Another benefit of these speakers is that they generate sound comparable to commercial speakers (H.E.).

Any discussion of new technology would be incomplete without taking a look at what is happening in the retail world with the age old electrodynamic speaker. Bose's website has a wealth of information concerning their various technological innovation. They decided to take a look at the unassuming electrodynamic driver and see if it was possible to create great sound without resorting to an array of differently sized drivers and all the extra equipment necessary to power such speakers. In the mid-1980's they developed Waveguide technology. Using the properties of resonance of standing waves in a tube the engineers at Bose discovered they could amplify the sound of a small speaker without introducing distortion or losing low frequencies. The real breakthrough for them however, was when they discovered they could bend the tube at certain points without sacrificing the sound. This allowed them to develop the Wave radio (Figure 11) that, while under one foot tall packs in a tube over seven feet long!

All of this new technology is a wonderful addition to the audio market, but it doesn't look like traditional audio setups are going to be going anywhere soon. With that in mind the discussion now turns to the tried and true technologies that have been around since just about the beginning of the speaker itself. The following information on audio equipment was provided by Nave, C. at the HyperPhysics website.

An amplifier is used to increase the signal being sent to a speaker. Electrical circuits present resistance to the signal being transmitted through them, making an amplifier necessary. Sub-woofer and woofers in general favor low frequencies and are well suited to produce them, however, a large amount of power is required to drive them not only because they are responsible for moving larger amounts of air, but also because they have larger, heavier magnets.

Another necessary piece of equipment is a crossover. The crossover takes an input signal and separates it into two or more signals tailored to certain frequency ranges. For example, a two way crossover, generally splits the signal into a high/mid-range signal meant for tweeters and mid-range speakers and a low-range signal, meant for the woofers. Crossovers can be installed in a speaker cabinet by the manufacturer especially if it is a two or three way speaker. A two-way speaker has one driver for low frequencies, and another for mid and high range. A three-way speaker adds a separate mid-range driver freeing up the tweeter to focus on high frequency vibrations. They can also be purchased separately and installed as part of the stereo rack in a home system or placed somewhere in a car audio system.
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In order to customize an audio system further it is often a good idea to integrate an equalizer. The equalizer allows one to increase or decrease the volume of a specific set of frequencies while leaving the other frequencies present alone. It can be used to accentuate voices, or decrease the amount of bass being produced. Together these three components allow one to customize the listening experience and in some cases, such as the amplifier, are necessary for the system to function as intended. These three pieces of equipment are usually present in car audio systems, and depending upon how important sound is to a person may or may not be present in a home system.

It is hard to imagine that for the past hundred years or so speaker technology has not changed much. Bose began the process of innovation in the mid-1980's and in the past couple of decades many other companies have jumped on the bandwagon to improve the design of the traditional speaker and in some cases radically change the way speakers operate. It is certainly an exciting time in the field of acoustics and who knows what the future will bring.
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REFERENCES


Cocaine: Ancient Affliction, Modern Addiction

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Abstract

The use of cocaine dates back to over 2,000 years. It is known for the euphoric feeling it produces. Cocaine inhibits the dopamine transporters, which prevents the transportation of dopamine from the synapse cleft and back into the cytosol. Three human enzymes are known to metabolize cocaine: human carboxylesterase 1 (hCE1), intestinal CE (human CE2), and serum butyrylcholinesterase (hBuChE) (Bencharit, 2003). Both intestinal CE and hBuChE hydrolyze the large benzoyl ester linkage on the cocaine, while only hCE1 hydrolyzes the methyl ester linkage to produce benzoylecongonine, which is the primary urinary metabolite.

Background Information

The use of coca leaves for psychoactive purposes can be traced back to over 2,000 years ago in what is now Peru (Palmer, 2010). The villagers in the area would chew on the leaves in order to release the cocaine alkaloids into their bodies, a practice which continues to this day. This is still widely practiced in the region today, but has since been replaced with the relatively new method of administration via insufflation. This was made possible by German scientists in the late 19th century, who were able to successfully isolate the cocaine alkaloid for the first time in modern history (Gaedke, 1855). The molecular classification for cocaine is: C17H21NO4 and has a molecular weight of 303.4g/mol. Cocaine comes in two forms, both (+) and (-) however, (-)-cocaine is the naturally occurring (Figure 1). The drug was now more concentrated which meant a more powerful high for users and thus increasing the likelihood of addiction and dependence.

Figure 1

![Structures of (-)-cocaine and (+)-cocaine](image)

Cocaine has traditionally been more of a “luxury” drug due to its relatively high price tag when compared to other illicit substances. This has somewhat changed with the advent of crack cocaine in the 1980s. Suddenly lower income Americans, particularly minority neighborhoods, became ravaged by what was referred to as an epidemic for about 10 years. This surge of cocaine presence in inner-city communities had a rippling effect across the nation in the urban centers of America in the late 1980’s and early 1990’s. From violence to theft to an overall
diminishing of the social fabric in communities plagued by the drug, Americans were reminded of how vicious cocaine addiction can truly be. Fortunately, use and abuse of this substance has largely subsided since its peak about two decades ago, as shown by a recent report sponsored by the White House, conducted by the Office of National Drug Control Policy. According to the 2008 ONDCP study, of the 38 million Americans who had used cocaine in their lives, only about 0.7% of them had done so in the past month. That is of course not to say that other factors weren’t involved. Cocaine use is declining largely in part to the rise of a synthetic drug with similar effects, but cheaper and more efficient in terms of potency and duration: methamphetamine.

**Mechanism for cocaine blocking the transport of dopamine across membrane.**

Cocaine has been recognized throughout the years as one of the most abused psychoactive drugs, afflicting millions of people worldwide. Natural binding sites in the brain tissues of both humans and rodents have been discovered. The binding of cocaine and cocaine-like compounds to these sites inhibit dopamine uptake, thus creating their effect by changing the flow of dopamine, which means a more powerful high for users and an increase of neurotransmitters. However, recent studies have found that in both *in vivo* and *in vitro*, cocaine increases the cell surface distribution of dopamine transporters (DAT) which could be associated with increases in altered dopamine (DA). These DAT’s are crucial sites for cocaine and are thought to be the cause of cocaine abuse (Daws et al 2002). Studies have also shown that the primary attack for cocaine on the human body is the dopamine transporters (DAT). Cocaine is a high-affinity inhibitor of DAT and is thought that its binding to DAT causes increasing levels of extracellular dopamine. Cocaine analog, (-)-2β-carbomethoxy-3β-(4-iodophenyl) tropane was identified to be competing with substrate dopamine to bind with DAT.

DAT are integral membrane proteins that are responsible for the pumping of neurotransmitter dopamine out of the synapse cleft and back into the cytosol, terminating the sight of neurotransmitters. DAT functions as a symporters, and is a member of the neurotransmitter sodium symporters (NSS), which moves dopamine across the cells by coupling the movement of sodium ions, which move from areas of high concentration to low. DAT also requires the binding of two NA+ ions and one Cl- ion with the dopamine substrate. The driving force for the reuptake of dopamine is the concentration gradient of Na+K+ ATPase (Huang et al 2009). Dopamine plays a critical role in our mental and physical health. It acts as a chemical messenger, which is similar to adrenaline. It affects brain processes that control movement, emotional responses and our ability to experience pleasure and pain. The affects of dopamine are controlled by dopamine receptors, which are G protein–coupled receptors. These receptors are responsible for the signaling of release of dopamine into the synapse cleft to control emotion, cognition and locomotion (Missale et al 1998).

On the DAT, there is a substrate entry tunnel for dopamine to enter into the binding site, which is through a funnel-like tunnel between the various helices in the structure. Along this
tunnel, are gates that form the bottom of the extracellular reception area. An inhibitor, like cocaine and its analogs, which have limited structural diversity, can use these reception areas as an alternative binding site. Once dopamine has bound to the DAT, these gates will slowly close and the structure will undergo conformational change to transport the dopamine across the membrane to the intracellular side. However, before DAT can undergo this conformational change from the extracellular opening, a cocaine molecule can be captured which prevents any changes in the structure, thus preventing the transportation of dopamine. Further attractions via hydrophobic interaction from the amino acids may direct the benzyol ester group of the cocaine to move towards the bottom of reception area. Due to cocaine's electrostatic and hydrophobic characteristics of the cationic headgroup, side chains near EL-4 may be attracted and cover the cocaine headgroup (Figure 2).

Cocaine can be considered as a noncompeting inhibitor due to its ability to bind with DAT and DAT-DA (dopamine bound to DAT). By binding to the DAT with the absence of dopamine, cocaine can block the formation of the DAT-dopamine complex because it blocks the dopamine-entry tunnel, thus preventing dopamine from binding. Cocaine can accomplish this by entering either the initial binding site or the overlap binding side. However, since both dopamine and cocaine are positively charged, electrostatic repulsion between the two makes cocaine less likely to bind to DAT-DA and more likely to bind to DAT. Cocaine has two methods for inhibiting the transportation of dopamine: through blocking the initial binding of dopamine to DAT, or by preventing the conformational change in the structure of DAT after the dopamine is bound.

![Figure 2](image)

**The Metabolism of Cocaine:**

Three human enzymes are known to metabolize cocaine: human carboxylesterase 1 (hCE1), intestinal CE (human CE2), and serum butyrylcholinesterase (hBuChE) (Bencharit, 2003). Both intestinal CE and hBuChE hydrolyze the large benzyol ester linkage on the cocaine. However, only hCE1 hydrolyzes the methyl ester linkage to produce benzoylecgonine, which is the primary urinary metabolite. When ethanol is present with cocaine, transesterification is conducted and the toxin cocaethylene metabolite is produced (Bencharit, 2003).
Human carboxylesterase is a serine hydrolases found in the liver, small intestine, kidney and circulatory plasma. It hydrolyzes esters, amides, and thioesters and plays an important role in the metabolism of cocaine. Crystal structures of hCE1 in concert with the cocaine analog homatropine are used for the metabolism of cocaine. The reaction site on the homatropine where the methyl ester linkage on the R-stereoisomer of cocaine is oriented towards the small ridge pocket while both the benzoyl and tropine groups of the homatropine are packed within the large pocket of the enzyme. A mix of both R- and S-homatropines are used in the crystallization and while both bind to the second surface of the ligand binding site of the hCE1, only the R-stereoisomer is witnessed in the active site on the enzyme. This shows how the enzyme is both site and stereospecific in order to undergo hydrolysis and transesterification on the methyl ester linkage (Bencharit, et al 2003). The conversion of cocaine R-cocaine to benzoylecgonine requires water and hCE1, which removes the methyl group off the methoxy. However, in the hydrolysis of cocaine in the presence of ethanol a two-step hydrolysis occurs. First, hCE1 forms a covalent acyl-enzyme intermediate at the carboxylic methyl ester, this is followed by an attack by ethanol which creates cocaethylene (Figure 4). Since the human brain has only C-terminal forms of hCE1 enzymes, it cannot produce cocaethylene despite the amount of alcohol in its presence.

As mentioned previously, there are two other enzymes that are involved in metabolizing cocaine: intestinal CE (human CE2), and serum butyrylcholinesterase (hBuChE). Both of these enzymes function in a similar manner, in that they both hydrolyze the benzoyl ester linkage and produce ecgonine methyl ester and benzoic acid (Bencharit et al 2003), (Gao et al 2010). Wild-type hBuChE is known to have a low catalytic efficiency against natural (-)-cocaine, which is the only biologically active cocaine (Huang et al 2010). However, 20 naturally occurring hBuChE mutants have been identified with an increase of hBuChE plasma activity (Zhan et al 2003). It has been reported, that the toxicity of cocaine can be greatly reduced when high levels of plasma hBuChe are present. Large quantities of this enzyme have been known to protect monkeys and
rodents against cocaine toxins (Sun et al 2002). Therefore, the dominant metabolic pathway for breaking down cocaine is hBuChE-catalyzed hydrolysis (Gao et al 2006). It has also been found that this enzyme significantly decreases the cocaine half-life (Gao et al 2006). Hydrolysis accounts for 95% of cocaine metabolism, in which hBuChE is the principle enzyme used. The other 5% is oxidized in the liver via the microsomal cytochrome P450 system producing norcocaine, a hepatotoxin and local anesthetic (Gao et al 2006), (Zhan et al 2003). Studies have also revealed the binding of hBuChE-(−)-cocaine involves two different complexes: nonprereactive and the prereactive. The nonprereactive is the initial enzyme-substrate (ES) binding complex where chemical reactions do not occur. In the prereactive, (−)-cocaine lies horizontally at the bottom of the substrate binding gorge, with its benzoyl ester group located near the catalytic site which consists of catalytic triad residues S198-H438-E2325 of enzymes (Huang 2010).

The proposed hydrolysis of cocaine consists of acylation and deacylation stages demonstrated by the ester hydrolysis by serine hydrolases (Zhan et al 2003). Achemy is started by SER198 attacking the carbonyl carbon on the cocaine benzoyl ester to form a tetrahedral intermediate (INT1) through the first transition state. During the intermediate formation, C-O bonds between the carbonyl carbon and Ser-198 slowly form, while Ser-198 transfers its proton to imidazole N atom of His-438, which acts as a base. The second step involves the decomposition of the intermediate to the metabolite ecgonine methyl ester and acyl-BChE (INT2a) through the second transition state. During the change from INT1 to INT2a, a proton gets transferred to the benzoyl ester oxygen while the C-O bond breaks between the carbonyl carbon and the ester oxygen. Figure 6 shows the reaction process step-wise while Figure 4 shows the basic equation.
Physical effects of cocaine on the body.

Cocaine users experience effects similar to those who chew on the leaves, but just on a more intensified scale. It should be noted that this is not always due to changes in administration or molecules but rather the presence of additives in isolated cocaine. For example it is common for both Coca leave consumers and cocaine users to experience a numbing/tingling sensation in their mouths and faces. Although this is due to certain chemical properties in the drug itself, cocaine users typically experience this with more intensity due to the popular additive of
lidocaine and other similar numbing agents present in cocaine which are usually added by dealers to increase profits.

Numbness is only one of the effects of cocaine, taking a backseat to more prominent features such as the sense of all-encompassing euphoria most users report feeling within a few short minutes after taking the drug. This is due in part to the fact that the drug blocks vital neurotransmitters such as: dopamine, serotonin, nor epinephrine as well as a host of others (WebMD). So by blocking some of the body’s intricate processes, cocaine basically tricks the user into thinking they are happy when in reality this may not be the case and is often the exact opposite. This feeling of irrational happiness is short-lived (although this stage can last up to 30 minutes it typically lasts about half that time), and is commonly accompanied by an equally intense “low” where users suffer from negative feelings ranging from anger and depression, to thoughts of suicide. This feature adds to the cycle of dependence, with addicts seeking to chase that “feel-good” sensation as opposed to the agonizing withdrawal.

Cocaine also acts in a way which speeds up the heart rate, leading to a number of other side effects. Combined with the aforementioned feeling of euphoria, someone with a rapidly beating heart may feel “sped up” and act accordingly. Usually this manifests itself in the form of talkativeness, an unusually high amount of self confidence, and an overall physical and mental “rush”. This is similar to someone experiencing a sudden burst of adrenaline. Some of the negative side effects of this aspect include: restlessness, insomnia, irregular heartbeats, as well as overall itchiness (due to the increased presence of blood at the surface of the user’s skin). As with any state of increased heart rate, one is likely to also experience a heightened level of sweating while on the drug (Rehab today, 2008). Going back to the Peruvian example, the ancient villagers used coca in no small part due to the heart rate-increasing effects of the drug. This facilitated daily life, especially as it related to working, in a high altitude area where blood vessels become easily constricted.

Cocaine is extremely addictive, in part due the manipulation of the brain’s reward centers which occurs upon first use. Multiple studies have shown that laboratory animals will often choose cocaine over food and water. Furthermore, such animals have been known to choose cocaine administration even when a punishment is given for such behavior. One such study highlighted the drug’s addictive potential, when a number of rats would repeatedly press a button 10,000 times to receive a single dosage (Cocaine Withdrawal, 2011). This partially explains the behavior of humans, who will also continue to use the substance regardless of the negative implications for their own lives (i.e. family/relationship issues, monetary problems, employment issues, legal trouble etc.). This addiction is mostly psychological and not so much physical like other drugs such as opiates like Heroin. That is not to say however that there is no physical component to this affliction, especially as it relates to the withdrawal phase. Some of the physical symptoms of cocaine withdrawal include: fatigue, nausea, muscle cramps, and an increased appetite (Cocaine Withdrawal, 2011). The most unpleasant symptoms associated with cocaine withdrawal come from the sudden lack of dopamine which is released upon
administering the drug. Dopamine is one of the primary catecholamine neurotransmitters responsible for producing feelings, such as pleasure. Thus when cocaine acts to release a great deal of dopamine, one is likely to perceive their situation as being more favorable than when they are not using the drug. Simply put: this feature of cocaine makes using the drug seemingly more appealing than being sober. Chronic use of the drug can lead to a chemical imbalance in the area of the brain’s reward center, leading to negative symptoms such as anxiety and depression even years after the complete cessation of use.

One does not need to have used the drug over the course of years in order to have developed a serious addiction/dependency to the substance. One study, conducted on 17 participants, found that only 12 minutes after administering the drug to them, feelings of craving and addiction began to take hold and indeed peak (Breiter, 1997). As with other drugs, repeated use of cocaine leads to a tolerance, meaning one must take increasingly large doses in order to “enjoy” similar effects to those once felt on lower amounts. Though this psychological tolerance occurs fairly quickly, one does not easily become physically tolerant which can be a dangerous combination often leading to overdose.

Typically when one overdoses on cocaine, they are likely to suffer a number of symptoms directly related to the blood thinning/heart rate increasing effects of the drug. These symptoms typically manifest in the form of: nausea, vomiting, panic attacks, increased blood pressure, vomiting, faintness, hypothermia, unconsciousness, and of course can lead to death. In order to determine the amount of a particular drug needed to overdose, scientists have developed a system known as “LD-50”. This is referring to the dosage which proved lethal to 50% of the test subjects (usually rats). As it relates to cocaine, the ld-50 is said to be about 95.1 mg. This essentially means that in order for a human to potentially encounter an overdose, they would have to ingest 95.1 milligrams per kilogram of bodyweight.

Given all of these rather adverse aspects of the drug, it is still important to note that cocaine was once widely respected and even prescribed by the medical community. At the turn of the 20th century, multiple academics from various professions within medicine hailed cocaine as a wonder drug of sorts. Famous Austrian psychoanalyst Sigmund Freud not only encouraged its use to his patients, but frequently consumed the substance himself and even documented his use in a journal. Ironically enough it was even used to taper people off of their morphine and alcohol addictions. The commercial use of cocaine was not always limited to medicine, but also a wide array of other industries. From tonic to chocolate tablets, cocaine was at one point available in nearly every section of one’s pharmacy or market. Perhaps the most famous example of the illicit drug being used for commercial purposes is the titan of the soda industry: Coca Cola. Though the name still contains a hint to this now illicit past, the notorious ingredient has since been removed.

Currently cocaine is illegal in just about every country in the world. However it is rather difficult to enforce the production of the drug as coca tends to grow rather rapidly around the
equator. Also, cartels have gotten very powerful in many of the 3rd world nations where the drug is most often produced, leading to some criminal organizations enjoying de facto autonomy to manufacture and distribute their product. The negative effects the drug has not only on the individual but also society at large are often overlooked by locals who benefit directly from the production of the substance. For example a villager in Columbia making the equivalent of a dollar a day selling produce etc. would benefit tremendously in terms of quality of life if they were to work in a cocaine producing factory for double the pay. In many ways, cocaine has become one of the most powerful industries in South America.
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Transmissible Spongiform Encephalopathies
Science Symposium 2011
Written by: Azam Khan
For Dr. Mancini, Chem 236
Abstract:
Proteins are the building blocks of many organisms, and the function of these proteins can mean the difference between life and death. The reason these proteins are so unique is due to their implication for being mutated due to their nature of their chemical, structural, and molecular make up. With a few theories describing the infection and onset of the disease, they mostly all agree on the similarity of the fact that these proteins can be induced to change by an altered prion protein. Many advancements are still being made on the progress to understand and possibly cure this disease, though there are currently only measures taken to prevent it.

Introduction and definitions:
Prions are normal proteins of animal tissues that can misfold and become infectious. Typically in the noninfectious state, these proteins may be involved in cell-to-cell communication. Prions are associated with a group of diseases called Transmissible Spongiform Encephalopathies. TSEs are unique to the medical community in that they are unlike anything previously seen, as they are not cellular organisms or viruses. The diseases which are caused result in irreversible neurodegeneration, and can are transmissible between species. Sadly at the onset of symptoms there is typically only a few months before the disease leads to death.

Prions are extremely resistant to heat, even beyond 100°C, and chemical disinfectants have cannot inactivate prions adequately. They are difficult to decompose biologically and can live in the soil for several years. The prototype agent, scrapie, is highly resistant to disinfectants, heat, ultraviolet radiation, ionizing radiation and formalin.

Prions have a predominant characteristic of creating vacuoles in which the amyloid protein, or the prion, appears in the gray brain matter making it appear histologically spongy. They are typically found only in the brain, spinal cord, and retina.

Types of species affected and diseases:
TSE’s have been able to be experimentally transmitted to cats, mink, mice, pigs, sheep, goats, marmosets and cynomolgus monkeys. They have been found in captive wild cats, including tigers, a puma, an ocelot and a cheetah. Exotic ruminants has been seen in captive nyalas, gemsbok, Arabian oryx, eland, kudu, scimitar-horned oryx, ankole and bison.

In humans there can be a few different forms of TSEs. There is a classic CJD, in which die in their late sixties after developing relatively slow-onset mental deterioration. Compare this to variant CJD, and the difference that most deaths have occurred among young adults in their late twenties and are often preceded by sudden behavior changes initially diagnosed as psychiatric illness.

Bovine spongiform encephalopathy (BSE), feline spongiform encephalopathy (FSE), variant Creutzfeldt-Jakob disease (vCJD) and spongiform encephalopathy of exotic ruminants appear to be related diseases. Meat infected with mad cow disease (BSE) is thought to trigger a fatal human variant of the illness- known as variant Creutzfeld-Jacob Disease (vCJD).

History of illness:
Since 1986, more than 180,000 cases of BSE have occurred in the U.K.in cattle, particularly dairy cattle. The USDA implemented precautions to prevent any incidences of BSE in the
United States. Such precautions included restricting the importation of ruminants and certain ruminant products from all European countries from all European countries\textsuperscript{2}. In 1997 a ban forbade the practice of feeding rendered bovine meat or bone meal to US livestock\textsuperscript{2}.

Surveillance and testing started in the United States in 1990, and there were no reported animals which were infected until December 2003. The detected animal was a cow slaughtered on a farm near Yakima, Washington was confirmed to have a positive test for BSE\textsuperscript{2}. The cow was non-ambulatory at slaughter, also known as a downer\textsuperscript{2}, which caused it to be included in the United States Department of Agriculture (USDA's) targeted BSE surveillance program\textsuperscript{2}.

Some 57,000 cattle\textsuperscript{2} have been tested using the criteria set forth by the targeted surveillance approach designed to test high-risk animals for BSE\textsuperscript{2}. High risk animals were defined as downer animals, animals that die on the farm, older animals and animals exhibiting signs of neurological distress\textsuperscript{2}.

Etiology:

Agents previously suspected in causing the disease included bacteria, virus, and parasites or other infectious agent known to cause disease\textsuperscript{2}. Realistically the agent causing TSE is not known, though it is thought to be due to the feeding of rendered bovine meat and bone meal to young calves\textsuperscript{2}. Changes in the rendering practices for livestock feed may have allowed infectious meat or bone meal from scrapie-infected sheep to be fed to cattle\textsuperscript{3}. Rendering of contaminated cattle carcasses and wastes seems to have amplified the agent\textsuperscript{3}. The source of infection in felines was thought to be pet food that contained cattle offal. Wild cats in zoos may have been infected when they were fed cattle carcasses\textsuperscript{3}.

The agents which are theorized to be responsible are the mis-folded prions. Bovine Spongiform Encephalopathy (BSE), also known as "mad cow" disease, appears to be caused by the same agent\textsuperscript{6}. A minority opinion is that they may be caused by virinos or retroviruses\textsuperscript{3} though it is not typically favored.

Diagnosis:

Typically diagnosis has been slow to be understood in patients affected by the disease. Recent developments have allowed progressive movements to be able to be made to help the diagnosis of Transmissible Spongiform Encephalopathies. Preliminary diagnoses of vCJD are based on patient history, clinical symptoms, and magnetic resonance imaging of the brain\textsuperscript{4}. Periodic electroencephalography or 14-3-3 protein detection in spinal fluid is helpful for clinical diagnosis\textsuperscript{4}. Neuronal vacuolation and non-inflammatory spongiform changes in the gray matter are pathognomonic\textsuperscript{3}.

TSE's can be diagnosed by histopathology in animals by detecting PrPSc (a disease-specific isoform of the membrane protein PrP) in the brain\textsuperscript{3}. It is found in unfixed brain extracts by immunoblotting and in fixed brains by immunohistochemistry\textsuperscript{3}. The test is confirmed by finding characteristic fibrils of PrPSc (scrapie-associated fibrils) with electron microscopy in brain extracts\textsuperscript{3} being found and then diagnosed by transmission tests in mice\textsuperscript{3}. However, an incubation period of several months often makes this technique impractical\textsuperscript{3}. As of recent there
has been a modified immunoblot, which is a chemiluminescent ELISA test, a sandwich immunoassay and a two-site noncompetitive immunometric procedure\(^3\).

When considering diagnosis in humans, vCJD is typically confirmed by microscopic examination of brain tissue, usually at necropsy\(^3\). There will be the presence of amyloid plaques surrounded by vacuoles are found; such plaques are seen in only 5 to 10% of cases of classic CJD\(^3\). Also performing a tonsil biopsy by Western blot and immunohistocchemistry can show the presence of the prion protein\(^3\).

A company called Prionics based out of the United Kingdom has developed several tests which are extremely more rapid than the typical assays currently used. All of the tests are based on a single sample-preparation procedure\(^1\) and are extremely suitable for routine analysis of large sample numbers and are absolutely reliable, even under rough, high-throughput conditions\(^1\). The most notable of which is the WESTERN, which has assumed the golden standard of testing. Other tests include LIA, PrioSTRIP, and the PrioSTRIP SR\(^1\).

Clinical Manifestations and Symptoms:
The amyloid plaques will present themselves via formation of "daisy-shaped" areas of damage in the central nervous system\(^6\). With in the areas vacuolization, or the formation of holes\(^6\), there is believed to be a build-up of the abnormally shaped prion proteins causing the observed neurodegeneration\(^6\). There can be a very long period of time elapses between infection and the appearance of the first clinical symptoms: typically 2-4 years in sheep, 3-6 years in cattle and more than 10 years in humans\(^1\).

Humans will display psychiatric problems, have processing problems with basic information as well as with speaking, and eventually neurological signs appear accompanied by unpleasant sensations in the limbs and face\(^3\). Signs are usually psychiatric symptoms, including anxiety, depression, and social withdrawal\(^1\). After a course of several months humans will display gait disturbances, ataxia, incoordination, slurring of speech and tremor\(^3\). Chorea, dystonia, myoclonus and dementia typically develop late in the course of disease\(^3\). Many Spongiform Encephalopathies display similar symptoms amongst their respective infected individuals, many of the times leading to progressive unsteadiness and clumsiness, visual deterioration, and/or muscle twitching\(^2\).

Animals will display a variety of symptoms seen here in Table 1.

### Table 1: Clinical Manifestations and Symptoms Seen in Animals\(^3\)

<table>
<thead>
<tr>
<th>BSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>The clinical signs of BSE may include hyperesthesia, hindlimb ataxia, pelvic swaying, hypermetria, tremors, falling, recumbency, and behavioral changes such as apprehension, nervousness, and occasionally frenzy. Intense pruritus is not usually seen.</td>
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<tr>
<td></td>
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<tr>
<td>Decreased rumination, bradycardia, and altered heart rhythms have also been reported. progresses to recumbency and coma, and death occurs from weeks to months later. Rare cases may develop acutely and progress rapidly within days.</td>
</tr>
</tbody>
</table>

*Spongiform encephalopathy of exotic ruminants*
In exotic ruminants, the clinical signs may include loss of condition, unsteadiness, incoordination, and self-mutilation by biting.

Appears to progress more rapidly than most spongiform encephalopathies; the mean period from the onset of symptoms to euthanasia is 13.5 days.

**FSE**
The clinical signs of FSE can include behavioral changes, tremors, and ataxia. Cats may become aggressive or tend to creep aimlessly around their home and hide.

Somnolence is common and convulsions may occur. Excessive salivation, hyper-responsiveness to loud noises, and dilated pupils have also been seen.

Death occurs in approximately 6 to 8 weeks.

Transmission and Communicability:
BSE, FSE, and vCJD are all suspected of transmitting themselves orally through the intake of food. BSE is thought to have mutated from the scrapie agent, found in sheep. The agent is found mainly in nervous tissues. The agent has not been found in muscle, blood, or milk, nor does lateral infection seem to occur; though suspected increased prevalence due to vertical transmission is present to offspring of BSE-infected cattle.

Exotic Ruminants SE is very similar in transmission to that of BSE. Experimentally, this spongiform encephalopathy can be transmitted both orally and parenterally. Vertical transmission is uncertain, though two offspring of affected animals developed the disease, but vertical transmission has not been seen in experimental infections.

Prions are thought to be absorbed into the body during digestion where they begin the process of changing their normal protein counterparts into abnormal proteins. There are some associated foods that are higher in prevalence to present the presence of prions. The key to food protection is obtaining bovine meat and meat byproducts from animals not infected with BSE and protecting against contamination of food with high risk tissues, especially brain and spinal cord tissue.

High risk tissues include cattle's skull, brain, trigeminal ganglia (nerves attached to the brain, eyes, tonsils, spinal cord, dorsal root ganglia (nerves attached to the spinal cord), and the distal ileum (part of the small intestine). Gelatin, derived from the hides and bones of cattle, appears to be very low risk potential contamination in foods, including dietary supplements. There is currently no known means of reconditioning contaminated foods.

Communicability has not been observed in humans based on casual contact, though classic CJD has been transmitted during medical procedures such as corneal and dura mater grafts. It may also be possible to spread CJD by liver transplants, blood transfusions, pituitary-derived human growth hormone injections and contaminated brain electrodes. Communicability in animals has not been observed.

Morbidity and Mortality:
In humans a worldwide rate of approximately one case per million people each year\(^2\). 138 cases of vCJD were reported worldwide from 1993 to October 2002\(^3\). The mortality rate is 100\%\(^3\). Animal models of morbidity and mortality are not entirely accurate but are suspected to be fairly low.

Geographic Distribution and Frequency

The global distribution of TSE's is diverse in pattern, and spread. TSEs occur world-wide, but the highest prevalence of BSE is in Europe, whereas CWD is most commonly found in North America\(^1\). BSE is found in Liechtenstein, the Falkland Islands and Canada, Israel, Japan, as well as numerous European countries, including Portugal, Ireland, Switzerland, Belgium, Spain, Germany, France, Slovakia, Italy, the Netherlands, Denmark, Slovenia, Greece, the Czech Republic, Finland, Austria and Poland, Albania, Bulgaria, Croatia, Cyprus Republic, Estonia, Hungary, Latvia, Lithuania, Luxembourg, Romania, San Marino Republic and Turkey\(^3\). One reported case of BSE in the U.S. which appears to be the result of importing cattle from Canada that may have been exposed to feed which contained meat and bone meal from rendered cattle\(^6\).

Other forms of TSEs have their localized spread of infection as well. Feline SE for example is found exclusively in the United Kingdom, with a single isolated case in a cat in Norway\(^3\). vCJD has predominantly been seen to occur in the United Kingdom, although there have been six cases occur in France, as well as one case in Italy, another in Ireland, and one here in the United States\(^3\).

The woman who lived in the United States\(^6\) lived in the United Kingdom from 1979 to 1992 and was probably infected there during the BSE epidemic\(^5\).

BSE has not been detected in Australia, New Zealand, or South America\(^3\).

Target Populations:

All cases of vCJD to date have occurred in individuals of a single human genotype\(^1\) that is methionine homozygous at codon 129 of the prion protein\(^3,6\). About 40\% of the total human population belongs to this methionine-methionine homozygous state\(^3\).

Functional and Molecular component:
Human Health Risk:
The primary risk of humans developing the new variant form of Creutzfeldt-Jakob Disease (vCJD) is through eating BSE-contaminated food products\(^1\). Infection may be spread via blood, transplantation, injection of human growth hormone or surgical instruments\(^1\). There can also be iatrogenic Transmission, which is from humans to humans\(^1\).

Economic Impact:
An economic impact can be implicated in the killing and complete destruction (culling) of the cohort animals\(^1\). Simply dealing with the disposal of the infected animals and material has high costs associated with it\(^1\). Lastly, the meat industry export restrictions from affected areas will have a negative impact\(^1\).

Treatment and Therapy Research:
As of today, there is no treatment or prophylaxis\(^2\), nor is there a vaccine\(^3\) for either humans or animals. The possible benefits of Quinacrine are being investigated\(^3\). Quinacrine has been previously used to treat other diseases such as malaria; however, it was found to have serious side effects and is no longer licensed in the United Kingdom\(^20\). The evidence to date for any possible clinical benefit is very scarce\(^20\). The demonstrated efficacy of quinacrine in cell culture, its relative safety and well known side-effects in the clinical setting, and the universal fatality of CJD justify quinacrine as an immediate candidate for the treatment of CJD\(^10, 11\).

Disinfection:
Effective disinfection is possible with a single porous load autoclave cycle of 134-138°C for 18 minutes\(^3\). Infectious tissues should either be autoclaved under the same conditions or incinerated\(^3\). A 4% sodium hydroxide or 10% sodium hypochlorite solution is effective if it is applied for more than 1 hour at 20°C\(^3\). Overnight disinfection is recommended for equipment\(^3\).

Prevention
The Harvard Center for Risk Assessment concluded that this ruminant feed rule provides a major defense against BSE and vCJD in the US\(^2\). Current reevaluation of the BSE screening program is attempting to be able to get more rapid tests similar to the ones currently being used in Europe\(^2\).
Table 2: Measures to Minimize the Risk

<table>
<thead>
<tr>
<th>Testing program for the identification and elimination of BSE-infected animals: A study carried out by Prionics in 1998 using its BSE test showed for the first time that BSE can enter the food chain. Subsequent studies underlined these findings and led to the institution of compulsory rapid post mortem testing of slaughtered cattle older than 30 months.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A ban on feeding mammalian protein to cows, sheep and goats to halt the spread of BSE.</td>
</tr>
<tr>
<td>The removal of tissues known to harbor particularly high amounts of infectivity (specified risk materials, SRM) such as brain, spinal cord and intestines from cattle at slaughter.</td>
</tr>
</tbody>
</table>

Conclusion:
This relatively unseen illness is the result of a mutated protein which has no cure, difficulty in preventing, and is becoming more pronounced in clinical manifestation and transmission. With epidemiology consistently being redefined, and new aspects about the functional, structural, and molecular components being continually found it makes for a difficult disease to claim to completely understand. Through proper preventative measures, and thorough regulation the disease can be limited, and even expected to wane down. With exposure to the diseased, many regulating bodies can make proper guidelines to be able to limit its spread. Concurrently studies of the disease and the amyloid plaques should be done, and possibly multidisciplinary such that other neurological diseases with similar mechanism can be better understood.
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Prescription Waste and its Effects on us

Johnathan Kuntz
4/21/2011
Abstract:

PPCP (pharmaceuticals and personal care products as pollutants) is and developing issue that has potential to cause serious lasting harm. PPCP are contaminating our water supplies around the world, and studies show that increases PPCP levels are beginning to affect ecosystems and aquatic life forms. This paper outlines What some of the top prescription medication PPCPs are, how they are getting into our water ways, and what can be done to help prevent it.

Introduction:

The current issue facing Governments, Pharmaceutical companies, and the general populous is the growing concern of pharmaceutical waste contaminating our drinking water supply. Currently the FDA (Food and Drug Administration) and EPA (Environmental Protection Agency) has no set standard for what is the official “safe” level of PPCPs (pharmaceuticals and personal care products as pollutants). Because of this, there is no official system in place to monitor the increasing contamination levels.

Pharmaceuticals and Personal Care Products (PPCPs)

The EPA defines PPCPs to be, “any product used by individuals for personal health or cosmetic reasons or used by agribusiness to enhance growth or health of livestock. PPCPs comprise a diverse collection of thousands of chemical substances, including prescription and over-the-counter therapeutic drugs, veterinary drugs, fragrances (perfumes and colognes), lotions, and cosmetics.”(E.P.A.)

Studies done by the EPA have been able to identify that the source of the PPCPs and how PPCPs get into our water supplies. This also takes into account some of the top medications found throughout our nations water supplies.

I. Sources of PPCPs:

- Human Activity (bathing, shaving, swimming)
- Illicit drugs
- Veterinary drug (ie: antibiotics, steroids)
- Agribusiness
- Residues from pharmaceutical manufacturing
- Residues from hospitals (waste)

II. How PPCPs get into ground water:

- Medication residues pass out of the body and into sewer lines.
- Externally applied drugs / personal care products are washed down shower or sink drains after use (ie: lotions, ointments, liniments, personal hygiene products)
- Unused or expired medication that are placed in the trash, or flushed down toilets
- PPCPs that end up in landfills eventually will be absorbed into soil where rain water is then able to wash it into ground water sources.

### III. Top Pharmaceutical Contaminates:

- **Premarin:** Is a medication which is used for estrogen replacement therapies for women experiencing menopause. Premarin works by binding to estrogen receptors, which then allow for developing and maintaining female sex characteristics. Some of the side effects linked with this medication include thromboembolism, retinal thrombosis, stroke, Breast cancer, ovarian cancer, pancreatitis, depression, dementia, chorea seizure and asthma exacerbation. The chemical name of this medication is, (8R,9S,13S,14S,17R)-17-ethynyl-13-methyl-7,8,9,11,12,14,15,16-octahydro-6H-cyclopenta[a]phenanthrene-3,17-diol.

- **Diazepam (valium):** Diazepam works by binding to benzodiazepine receptors, and enhancing GABA (Gamma-Amino Butyric acid) effects. GABA is an amino acid which acts as a neurotransmitter in the central nervous system. It inhibits nerve transmission in the brain, calming nervous activity. This medication can be used to treat a wide variety of conditions, including, anxiety, alcohol withdrawal, muscle spasms, seizure disorders, and can be used as a sedative before surgery. This medication has also been linked with such side effects as, respiratory depression, addiction, suicidal tendencies, cardiovascular collapse, and paradoxical CNS (central nervous system) stimulation. The chemical name for the medication is, 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one

- **Bleomycin (Blenoxane):** The exact mechanism of action for this medication is still unknown, it is thought to work by inhibiting DNA synthesis as well as RNA and protein synthesis on a lower level. This medication is used in chemo-therapy to treat Hodgkin Lymphoma, Squamous cell cancer, and Testicular cancer. Side effect includes pneumonitis, pulmonary fibrosis, hypotension, mental confusion, fever, chills, wheezing, cerebral
arthritis, and death. The chemical name for this medication is N1-[3-
(dimethylsulphonio)propyl]Bleomycin-amide.

- **Hydrocodone / Acetaminophen (Vicodin):** This is a combination medication of Hydrocodone and Acetaminophen. The exact mechanism for Acetaminophen is unknown. However, Acetaminophen is known to produces analgesia and anti-pyretic effects. The mechanism for Hydrocodone (8) binds to various opioid receptors, which produces analgesia and sedation. This medication is used to treat moderate to severe pain and chronic pain. Side effects associated with this medication include; lightheadedness, dizziness, sedation, nausea / vomiting, constipation, drowsiness, psychomotor impairment, rash, pruritus, and addiction. Several serious reactions to this medication that can potentially be life threatening are respiratory depression, and hepatotoxicity (If medications containing Acetaminophen are take in excess of 4000mg per day, liver damage / liver failure can result from use of the medication). The chemical name for this medication is 4,5α-epoxy-3-methoxy-17-methylmorphinan-6-one.

- **Prozac:** This medication functions by selectively inhibiting serotonin reuptake. This medication a psycho-therapeutic medication that is typically used to treat depression, OCD (obsessive-compulsive disorder), bulimia nervosa, panic disorders, and bipolar disorder. Severe side effects have been linked to this medication and include; depression worsening, suicidal tendencies, withdrawal syndrome from stopping medication, mania, seizures, hyponatremia, hypoglycemia, vasculitis, anaphylactoid reactions, severe rash, abnormal bleeding / altered (2) platelets function.
The chemical name (2) of this medication is (dl)-N-Methyl-3-phenyl-3-(alpha,alpha,alpha-trifluoro-p-tolyloxy)propylamine hydrochloride.

- **Azithromycin (Zithromax):** This medication’s mechanism is bacteriostatic, or more specifically the medication binds to the (P) site of 50S ribosomal subunit, this then interferes with protein synthesis. Azithromycin is an antibiotic use in treating a variety of bacterial infections including, pneumonia, chancroid infection, acute salmonellosis, and typhoid fever. Several serious side effect to this medication include; angioedema, anaphylaxis (penicillin based medication), hepatotoxicity, toxic epidermal necrolysis, and myasthenia gravis exacerbation. (8)

![Chemical Structure](image)

**Scientific Concern:**

Currently there is debate not just on how can this issue be dealt with, but is this even an issue we need to concern ourselves with. As stated by Dr. Mercola, “despite extensive purification treatments used by water companies, traces of bleomycin, a chemotherapy drug, and diazepam, a sedative, have been found in the drinking water. Though experts say the drug levels are too low to pose a direct health risk, concerns have been raised about exposing pregnant woman to drugs, which could harm an unborn child.”(7) Granted the amounts of PPCPs being recorded are low, and there is debate on how sever this issue is, and because our technological advances have only now begun to pick up these trace amounts of PPCPs, there is only enough data to determine that if left untreated, this issue has the potential to spiral out of control on an exponential scale.

Even though experts have stated that the PPCPs are in “low” concentrations. It is now being reported that even the lowest concentrations, water ways containing trace amounts
Premarin are all beginning to have a major ecological impact. A Swedish team at Uppsala University discovered that estrogen replacement therapy medications, as well as other estrogen-like contaminants are affecting aquatic life by forcing an intersex change, or more simply defined as the conversion from male to female.

The team designed and performed an experiment in which two species of frogs, "the northern leopard frog (Rana pipiens) from US and Canada and the European common frog (Rana temporaria) were exposed to the same (5) trace amounts of estrogen found in natural waters in Europe, the United States and Canada. In the control groups, the females represented fewer than 50% of the total number of adults, a normal ratio, but the sex ratio in frog groups raised in water with various estrogen levels was very different. "Earlier studies in the United States linked a similar sex-reversal of Rana pipiens male frogs -- one of the two species used in the experiment -- in the wild to a pesticide that produced estrogen-like compounds. Pesticides and other industrial chemicals have the ability to act like estrogen in the body," Berg said. "Some of sex-altered males became fully functioning females, but other had ovaries but no oviducts, making them sterile," Berg explained. "The study does not measure the potential impact of pollutant-driven sex change for frog species, but the implications are disquieting. Obviously if all the frogs become female it could have a detrimental effect on the population," she said. "The only immediate remedy would be to improve sewage treatment in areas where frogs and other amphibians might be affected to filter out estrogen concentrations coming from contraceptive pills and from industrial pollutants."

Similar studies have been performed in the US by examining how trace amounts of estrogen have been recorded to have similar affects of fish in our rivers and streams. The results indicated that as with the frogs, the fish exposed to estrogen compounds, can result in an intersex change. Not only do such facts show just how potentially hazardous PPCPs can be, it also should serve as warning to us, that the PPCPs levels are increasing, and with more and more prescriptions being sold each year, it is only a matter of time until PPCP levels are able to affect us if nothing is done to remove them.
Short and Long Term Solutions:

The long term goal is to upgrade water treatment facilities with technologies that are able to detect PPCPs. This is because our current facilities only separate solids and liquid and then sanitize the liquid portion and release it back into the water source. (1) By so doing, we would be ensuring that our water remains safe for use/consumption, and the ecosystems around the world remain clean and uncontaminated by our waste products.

However, we are still a long way off from implementing such a long term solution since we are just beginning to understand the issue at hand. To offset this, many short term solutions are being used to help manage PPCP contaminants. Currently, pharmacists and other health care professionals are helping to educate the public about this situation and are helping to collect and set up collection facilities and programs to safely destroy old or unused medication and other potential PPCPs. Such programs and facilities include,

- Pharmaceutical take-back programs or household hazardous waste collection programs that accept pharmaceuticals.
- Follow any specific disposal instructions that may be printed on the prescription/medication label.
- Taking unused/expired medications to your local pharmacy to be disposed of properly.
- Attending education seminars to increase awareness of how to dispose of PPCPs yourself and how to help dilute them so they cause less of an impact.

Another recommended short term solution that is gaining popularity is to purchase a reverse-osmosis water filtration system for your home. These water filtration systems have been shown to remove PPCPs to the best as seen in the chart below, reverse osmosis filter are able to filter out a wide range of particulates and PPCPs currently found in drinking water.

**TYPICAL REJECTION CHARACTERISTICS OF R.O. MEMBRANES**

Elements and the Percent R.O. Membranes will remove

<table>
<thead>
<tr>
<th>Element</th>
<th>Percentage Removal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>85 - 94%</td>
</tr>
<tr>
<td>Sulfate</td>
<td>96 - 98%</td>
</tr>
<tr>
<td>Calcium</td>
<td>94 - 98%</td>
</tr>
<tr>
<td>Potassium</td>
<td>85 - 95%</td>
</tr>
<tr>
<td>Nitrate</td>
<td>60 - 75%</td>
</tr>
<tr>
<td>Iron</td>
<td>94 - 98%</td>
</tr>
<tr>
<td>Zinc</td>
<td>95 - 98%</td>
</tr>
<tr>
<td>Mercury</td>
<td>94 - 96%</td>
</tr>
<tr>
<td>Selenium</td>
<td>96 - 98%</td>
</tr>
<tr>
<td>Phosphate</td>
<td>92 - 96%</td>
</tr>
<tr>
<td>Lead</td>
<td>94 - 98%</td>
</tr>
<tr>
<td>Arsenic</td>
<td>96 - 98%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>85 - 92%</td>
</tr>
<tr>
<td></td>
<td>94 - 98%</td>
</tr>
</tbody>
</table>
Nickel 95 – 98%
Fluoride 95 – 98%
Manganese 84 – 92%
Cadmium 85 – 92%
Barium
Cyanide
Chloride
% may vary based on membrane type, water pressure, temperature & TDS

Conclusion:

The overall conclusion that should be drawn from this paper is that PPCPs are not an issue to be taken lightly. PPCPs are detrimental to the health of our ecosystems as well as to ourselves. We need to take active steps to educate both ourselves and people we know about this issue, and by taking active steps as the ones indicated in this paper, it will be possible to help control and reduce contamination levels of PPCPs before any lasting harm can come to our environment.
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Dentally Derived Stem Cells:
Not Just a Treatment, But a Cure

Marc Lebowitz

April 18, 2011
Abstract

Research on dental stem cells is expanding at an unprecedented rate and new developments have created an environment in which dentists will be in the position to assume the leading role in the treatment sequence of medical disease. Although the full extent of the potential of dental stem cells has yet to be uncovered, clinical treatments for various situations are already being conduct. This paper gives an overall idea about dentally derived stem cells and what makes them so unique. Everything from what they are to where they are found, the benefits, practical dental and medical applications, and obstacle to overcome are discussed in great detail.

Introduction

Stem cells are primitive cells that have the remarkable ability to develop into many different cell types in the body. Stem cells are distinguished from other cell types by two important characteristics. First, they are unspecialized cells capable of renewing themselves through cell division, sometimes after long periods of inactivity. Second, under certain physiologic or experimental conditions, they can differentiate into many specialized cell types and organs such as the heart, lung, skin, sperm, eggs as well as other tissues.

In general, there are two broad types of stem cells, embryonic stem cells and somatic (adult) stem cells. Embryonic stem cells are pluripotent, which mean that they have the ability to form most, if not all cell types. Embryonic stem cells are found in embryos between four and five days old, and form the three germ layers which give rise to the entire body of the organism. When first discovered, scientists were enthusiastic that embryonic stem cells would provide a way to cure, not just treat, many diseases. However, this has been proven to be difficult in practice for many reasons. First, in order to obtain embryonic stem cells the embryo must be destroyed. This entails the destruction of a potential life which poses the ethical and legal dilemma of determining the rights of the embryos, and whether government funding should be available to support this field of research. Second, there are significant medical and engineering challenges to using these cells including inadequate cell numbers, immuno-rejection, and tumor development.

The other broad category of stem cell is the somatic stem cell. The role of these cells is to generate replacements for cells that are lost through normal wear and tear, injury, or disease. Somatic stem cells have been identified in many organs and tissues, including the brain, bone marrow, muscle, and umbilical cord blood. Somatic stem cells are known as multipotent stem cells because their potential is normally limited to one or more lineages of specialized cells. However, a special type of multipotent stem cell that is found in bone marrow and dental pulp, called mesenchymal stem cells, possess the ability to produce a multitude of different cell types. Mesenchymal stem cells also have a so called homing property, meaning that when they are delivered systemically they migrate to the site of injury.

In recent years scientists have found somatic stem cells in many more tissues than they once thought possible, including teeth. Given their unique regenerative abilities, research on dentally derived somatic stem cells has generated a great deal of excitement. For years scientists all over the world have been working on possibilities of using these stem cells to regenerate human cells that have been damaged due to illness, developmental defects and injury. These cells offer new
potential for treating a variety of diseases such as arthritis, diabetes, heart disease, and many others. However, much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease.

Development of Teeth and Dental Stem Cells

The existence of stem cells in teeth is a robust phenomenon and are required for the development of teeth. Early in fetal development, teeth arise from the neural crest through a series of interactions between neural, mesenchymal, and epithelial tissues and proceed through five distinct morphological stages: bud, cap, bell, crown, and root. In the first stage of tooth development, the dental epithelium forms a bud that extends into the underlying dental mesenchyme. Then, the dental epithelium undergoes significant proliferative activity, extending around the periphery to form a cap-like structure. During this process, epithelial cells organize themselves into three distinct regions, namely the outer epithelium, the inner epithelium, and central cell layers. Next, cells of the dental papilla condense and give rise to dentin and pulp tissues. The dental follicle forms around the enamel organ and dental papilla, eventually forming the periodontal tissues. The bell stage is characterized by continued proliferation and differentiation of the dental epithelium forming the dentin matrix and the enamel matrix for.

Finally, the crown of the tooth forms, and at this point the tooth root structures develop and form the dentin, cementum, periodontal ligament and alveolar bone.

The developed tooth can be thought of as an encapsulated population of dormant stem cells. Of all the somatic stem cells, dental stem cells are the most accessible, and like all craniofacial stem cells, originate from neural crest cells and mesenchymal stem cells during development. Dental stem cells are found in the pulp, periodontal ligament, follicle and apical papilla of both deciduous (primary) and permanent teeth. Scientists have found that the cells from these structures are rich in a variety of different stem cell types including; chondrocytes, which have the ability to regenerate cartilage and plays an important role in the treatment of arthritis and joint diseases. Osteoblasts, which have the ability to regenerate bone. Adipocytes, which have the ability to repair damaged cardiac tissue. And mesenchymal stem cells, the most potent among all tissue stem cells and have the ability to differentiate into various types of reparative cells. The relatively recent discovery, that dental pulp tissue contains a population of multipotent mesenchymal stem cells, has revolutionized dental research and opened new avenues in particular for reparative and reconstructive dentistry, and tissue engineering in general.
What Makes Dental Stem Cells So Unique

Dentally derived stem cells differ from other stem cells in a variety of ways. First of all, they are plentiful, non-invasive, and easy to collect. Unlike harvesting bone marrow stem cells which requires invasive surgery to retrieve or umbilical cord stem cells which are only available at birth, dental stem cells can be collected from deciduous teeth which naturally fall out on their own, or from permanent teeth that are extracted during routine dental procedures, such as extracted wisdom teeth. These teeth, which would otherwise be discarded, provide a great and easily accessible source of stem cells which can be harvested and stored for future use. Also, obtaining dental stem cells is far less expensive compared to other stem cell sources. Second, dental stem cells are able to regenerate solid tissue types that cord blood cannot. Some of the potential tissue types the dental cells can regenerate include connective tissue, bone, muscle, cartilage, dental tissue, and neuronal tissue, while umbilical cord blood stem cells are typically limited to treating blood cancers and genetic diseases of the blood. Dental stem cells produce a host of beneficial neurotrophic factors, which promote nerve cell survival. Researchers believed this to be due to their lineage from the neural crest.

Additionally, dental stem cells are about ten times easier than commonly used skin fibroblasts to be reprogrammed to induced pluripotent stem cells. The advantage of induced pluripotent stem cells is that they behave like embryonic stem cells but without many of the challenges that embryonic stem cells face, like the controversial use of embryos. Once reprogrammed, they can be guided to differentiate into most of the cell types in the body, therefore making them extremely useful for tissue regeneration. Using harvested stem cells from one's own body to regenerate tissues and organs, compared to donated tissues, is a major advantage. It drastically decreases the likeliness of the body rejecting the tissue. Therefore, the patient will not need to be given a heavy dose of immuno-suppressants, sparing them from additional discomfort and suffering.

Banking of Stem Cells

The concept of banking dental stem cells for future clinical uses was considered shortly after they were discovered. Private companies are now marketing dental stem cell banks as hedges against future illness in the hopes that research will continue to refine the techniques and procedures that will eventually provide not just treatment options, but a cure to different diseases. With continued research and new discoveries, storing dental stem cells in the bank has the potential to be more valuable than putting money in the bank.

The banking of dental stem cells has become more prevalent in recent years for a variety of reasons. One reason is that stem cells are more potent the younger they are, so if umbilical cord blood was not saved at birth, the next best time to obtain stem cells, without unnecessary invasive surgery, is from deciduous or wisdom teeth. Adolescents have two excellent opportunities for banking their dental stem cells. The first may occur following extraction of bicuspids teeth for orthodontic treatment. The bicuspids teeth are not fully formed until between the ages of 12 to 14 years. Occasionally, these teeth are extracted for orthodontic reasons before the roots are fully formed, which ensures a better chance for success of harvesting viable stem cell. The second opportunity occurs when their wisdom teeth are extracted. The roots of the
 wisdom teeth are not fully formed until after the age of 18; extracting these teeth during the
teenage years helps to ensure the greatest abundance of proliferative stem cells.

Another reason dental stem cells are stored is because some people see it as sort of a biological
insurance in the event of an unforeseen illness. Other people have chosen to store their stem
cells because of their family history and a hereditary propensity for a particular disease. Lastly,
the obtaining and storing of dental stem cells are relatively effortless for both the patient and the
dentist. All the patient has to do is enroll with one of the many private companies that store stem
cells such as StemSave or Store-A-Tooth, who will then ship a collection and transport kit to the
dentist or oral surgeon prior to the patient’s appointment. On the day of the appointment, the
dentist extracts the tooth or teeth and rather than being discarded, is placed into the kit and
shipped to lab. Once in the lab, the teeth are cracked open and inspected for stem cells.
Biomarker validation is a critical tool to confirm the presence, and type of stem cells in tooth.
Upon validation, the dental pulp containing the stem cells is then harvested, processed, and
cryogenically stored until needed. Cryopreservation is a process where cells or whole tissues are
preserved by cooling to low sub-zero temperatures, typically -196 °C, the boiling point of liquid
nitrogen. Rapid freezing is necessary to prevent ice from forming around or inside the cells and
to prevent dehydration, as these would cause cell damage and death. At these low temperatures,
any biological activity, including the biochemical reactions that would lead to cell death is
effectively stopped.

Dental and Medical Applications

Dental stem cells can potentially be used in a variety of dental and medical applications, from
repairing and replacing teeth to regenerating tissue and organ development. Research has
revealed that there are three key components to replace lost or damaged tissue for all tissue
engineering and regenerative medicine procedures. The first component is the stem cells, which
were harvested from the patient at an earlier date and properly stored to preserve the integrity of
the cell membranes. The next component is morphogenetic signals such as growth factors and
differentiation factors. Growth factors are naturally occurring substances, typically a protein or a
steroid hormone, that play an important role in the multiplication and differentiation of stem cells
into the specifically needed type of cells. They act as signaling molecules between cells. Bone
morphogenetic proteins and cytokines play an intricate role in organogenesis, and in the dental
aspect specifically GDF-11 (growth/differentiation factor-11) plays a major role in differentiating
dental pulp stem cells into odontoblasts which is the corner stone in teeth tissue engineering³.
The last component is the scaffolding. A 3-dimensional scaffold of extracellular matrix
provides the differentiated stem cells with a mold and the environment to grow and function into
the intended type of tissue or organ. Rather than the cells adhering on the external surface of the
scaffolding, the cells actually migrate into the cavities inside the scaffolding structure. And after
about 30 days of culture, the cells hook into the cavities where these cells quickly start to secrete
the extracellular matrix and differentiate.

Dental stem cells have already been used in the dental field in a few different ways to treat
humans, although most treatments are still in the laboratory or animal trial phase. One of the
current uses of dental stem cells is alveolar bone regeneration, where defects of the alveolar ridge
are filled with a construct of dental stem cells and seeded onto a collagen matrix. Results for this
procedure have shown that within a year, the gap was filled with bone\(^4\). Research in animal models has shown that dentally derived stem cells can be used to re-grow tooth roots in the presence of proper growth factors and a biologically compatible scaffold. Also, stem cells extracted from the dental pulp of a tooth have been harvested, then directly implanted into the pulp chamber of a severely injured tooth. The goal is to regenerate the pulp inside the damaged tooth, preventing the need for endodontic treatment\(^5,7\). Stem cells derived from the periodontal ligament may offer promise for regenerating the periodontal ligament and other supporting structures of the periodontium that have been destroyed by gingival disease, providing an alternative approach to traditional clinical therapies.

Researchers believe that dental stem cells and related bioengineering technologies in future years, will transform dentistry in a magnitude far greater than was previously ever conceived. Dentally derived stem cells have the potential to make the currently used dental treatments such as metallic alloys, composites, and even titanium implants obsolete. Regenerative therapy is less invasive than surgical implantation, and early animal studies suggest comparable results in strength and function of the biological implant as compared to a traditional dental implant\(^4\). Years from now dental stem cells will hopefully be able to correct cleft palates, sparing children from multiple surgeries, stem cells will also have the potential to save injured teeth and jaw bones, correct periodontal defects, and most strikingly bioengineering entire teeth structures, known as third dentin, is on the horizon. A method has been developed in the lab to regenerate tooth buds in a single procedure by combining dental pulp and bone marrow on a scaffold and implanting this into surgically created defects. The construct led to organized dentin, enamel, pulp, cementum, and periodontal ligament surrounded by regenerated alveolar bone, suggesting a method that could translate directly to humans in years to come\(^5\).

Perhaps the most important potential application of dentally derived stem cells is the generation of cells and tissues that could be used for cell-based therapies. Today, donated organs and tissues are often used to replace ailing or destroyed tissue, but the need for transplantable tissues and organs far outweighs the available supply. Stem cells, directed to differentiate into specific cell types, offer the possibility of a renewable source of replacement cells and tissues to treat diseases including Parkinson’s disease, Alzheimer’s diseases, spinal cord injury, burns, cardiovascular diseases, diabetes, osteoarthritis, and rheumatoid arthritis\(^6\). The expression of neural markers in dental stem cells elicits imagination of their potential use in neural regeneration, as in the treatment of Parkinson’s disease, for which there is currently no cure. Adult dental stem cells have been and are being investigated to treat Parkinson’s disease, which currently affects an estimated 1 million people in the United States, as well as to treat related neurological diseases and spinal cord injuries\(^1\). In addition, they appear to replace dead neural...
cells and support degenerating neural cells. Stem cells are also being investigated for the
development of myocardial cells to repair damaged heart muscle following cardiac infarct. Heart
failure affects more than 5 million people in the United States alone. Mesenchymal stem cells
have been found to be able to differentiate into myocardial cells and vascular epithelium, as well
as to release molecules that are protective for cardiac cells¹. Patients have already been treated
with dentally derived mesenchymal stem cells following cardiac infarcts to regenerate heart
muscle and improve function.

Dental stem cells are also believed to alter the immune system and are currently being
investigated for use in the treatment of graft-versus-host disease, Crohn’s disease and lupus¹.
Stem cells isolated from dental pulp have been found to exhibit immuno-regulatory and immuno-
suppressive properties. Other potential uses include stem cell derived insulin producing cells to
treat diabetes and mesenchymal stem cells for tissue regeneration following radiation-induced
damage. Clinical manipulation of stem cells’ DNA is also leading to the development of gene
therapies².

Another prospective application of dental stem cells is that they could be used to test new drugs.
For example, new medications could be tested for safety on specific differentiated cells lines.
Other kinds of cell lines are already used in this way. Cancer cell lines, for example, are used to
screen potential anti-tumor drugs⁷. Dental stem cells could provide an abundant supply of
multipotent stem cells that would allow drug testing in a wider range of cell types.

Obstacles to Overcome

Differentiating dental stem cells into usable cells while avoiding transplant rejection are just a
few of the hurdles that researchers still face. Although, the possibility of rejection has been
minimized due to the nature of dental stem cells, it is still a very real possibility. Also, much of
the potential treatments for dental stem cells that are in clinical trials are performed on animals.
And even if successful, does not necessarily translate to human treatment with the same success
rate. The growth factors that are typically used in these animal trials are specifically selected for
the animal the research is conducted on, which would again, alter the results when translated to
human treatments.

As for dental applications, whole tooth regeneration has a few obstacles of its own to overcome
before it replaces the role of titanium implants, bridges, and dentures. These challenges include
the lack of formation of normal tooth size, the lack of consistent root formation, and a lack of
evidence of complete eruption into functional occlusion, the manner in which the upper and
lower teeth come together when the mouth is closed⁷,⁸. Researchers are working on ways to
control the size, cusp width, and cusp position⁹. It would not make sense to go through the
trouble of bioengineering to have regenerative teeth that were either too big or too small for the
recipient’s mouth or to have the new teeth coming in sideways and disrupt adjoining teeth and
possibly tongue movement. Once this process is perfected and ready for human use, it could
replace bridges, inserts and dentures. The process would not be entirely painless since the rotten
tooth would still need to be pulled. Once the site of the former tooth healed, then an oral surgeon
would have to drill down in the bone to set the tooth germ and sew up the area. It would take a
month or more for the new tooth to come in. The tooth, of course, would arrive just like all teeth
do, by splitting the gum.
There are also a few challenges in regard to testing drugs on dentally derived stem cells. In order to screen drugs effectively, the conditions must be identical when comparing different drugs. Therefore, scientists will have to be able to precisely control the differentiation of stem cells into the specific cell type on which drugs will be tested. Current knowledge of the signals controlling differentiation falls short of being able to mimic these conditions precisely enough to generate pure populations of differentiated cells for each drug being tested.

Additionally, a clear challenge in the field of dental stem cells is the need to have more dentists understand the value of these cells and the important role dentists can play in educating their patients. Every year millions of healthy teeth that possess stem cells are routinely discarded as medical waste. If more patients were informed about the vast potential dental stem cells contain, maybe more they would considered saving them in the event of an unexpected illness in the future. At the very least, the dental stem cells could be harvested and used in clinical trials and research in an effort to further develop practical applications.

Conclusion

It is clear from this brief overview that there is tremendous clinical potential for the use of dental stem cells in treatments involving not just dentistry, but many medical applications. Despite some progress, there still remain some major obstacles to formulating safe, simple and reproducible cell-based approaches for tooth repair and regeneration that could be used on patients. Research suggests that dental stem cells have many advantages compared to other stem cell sources, and are a viable source of somatic mesenchymal stem cells.

The research surrounding stem cells is very exciting and although the full possibilities of dentally derived stem cells are not yet known, it may be possible in the near future to create organs or part of organs such as heart, liver, kidney, bone and even teeth. These tissues would much more likely to be accepted by the body, compared to embryonic stem cells, as they are grown from the patient’s own cells, thus eliminating the need to put patients on heavy immuno-suppressive medicines currently given to organ transplant patients. Ultimately, the use of these dental stem cells over other sources of mesenchymal stem cells for therapeutic use will not only depend on ease of use and accessibility, but also on the efficiency and quality of repair in relation to cost. Dental stem cells offer exciting promise for future therapies, but significant technical hurdles remain that will only be overcome through years of intensive research.
Bibliography


Omega-3 Fatty Acids:

Analyzing DHA, EPA, and ALA Fatty Acids

Jaziel Llanes

April 22, 2011
Abstract

When it comes to the human body things can be complicated. Even with this being true, our body works in an almost perfect manner. There are of course thousands of different features in our body such as red blood cells, glands, and all different sorts of organs. One of the greatest features of our body is the production of fatty acids. Fatty acids are actually broken down fats that our body will form after we ingest food. Our body will break down these fats into fatty acids in order for them to be able to be absorbed into our bloodstream. There are many different types of fatty acids in our body but one that has been fascinating in health and medicine is termed the Omega-3 fatty acid. The Omega-3 fatty acid is considered an essential fatty acid. Being an essential fatty acid means that the human body is not able to synthesize Omega-3 without outside sources. Questions that arise from the topic of Omega-3 range from; what is it, how does it work, where is it found, is it natural, and is it produced in the lab? Omega-3 has also been popularized more in the society because of its health benefits and its presence in many fish. Omega-3 can be a great tool for our body to function at the top most level.

Introduction

Omega-3 fatty acids are classified as polyunsaturated. This mainly means a carbon chain with double bonded carbons. Omega-3 fatty acids are especially important in their roles in forming our central nervous system. Omega-3 actually is what helps build cell membranes in our brain. Besides building cell membranes in the brain it is also responsible for some blood clotting control. These fatty acids are of course essential and must be taken from outside sources. There are three main types of the Omega-3 fatty acids. The three different types are DHA, EPA, and ALA. All are known to be fatty acids and their functions are not much different, but their structure does change in each Omega-3 fatty acid (Ehrlich 2009).

DHA

First is the DHA fatty acid. The DHA fatty acid stands for Docosahexaenoic acid. DHA has been talked about a lot because of it being present in fish. Fish such as salmon and blue fin tuna have great amounts of DHA. DHA is essentially what you will swallow if you take fish oil supplements. DHA is not limited to fish only, but is also found in seaweed. DHA is a fatty acid that can be synthesized but only with the presence of ALA. Because of this it is considered an essential fatty acid. Our body will produce a small amount of DHA, but only from ALA which we must get from outside sources. New babies that are born will need DHA because it will aid in the development of their nervous system, and visual system. Newborns get much of their DHA from breast feeding. DHA has numerous functions and uses that it can be applied towards. First DHA shows that heart disease can be prevented and also helps patients with signs of heart disease. DHA from fish oil helps remove some amounts of plaque in our arteries, as well as lowering blood pressure. DHA has also proven to reduce menstrual pain but only when it is taken at a regular basis (Ehrlich 2009). The American Heart Association took part in a study and they found with this project that consuming two servings of fish with DHA might help prevent or reduce the risks of heart disease (Framingham Heart Study 2011).
The image shown of the next page is a Blue fin tuna, which is one of the many fishes that contain great amounts of DHA and EPA. This fish is found in the Atlantic Ocean ranging from coasts of Brazil to Norway (MarineBio 2011).

The chemical structure of DHA Omega-3 can be defined as conjugated. DHA molecule is termed conjugated because there are double bonds in between carbons. In chemistry a conjugated system is a really good molecule in terms of stability. The molecule is stabilized because of the inductive effect which is when neighboring carbons help stabilize each other by a partial sharing of electrons, this leads to delocalization. In delocalization the pi electrons (which are the two electrons in the double bonds) will delocalize or move throughout the molecule helping stabilize the molecule overall. The DHA molecule also has a carboxylic acid functional group at the end of the carbon chain (DHA/EPA Omega-3 Institute 2010).

![Docosahexaenoic Acid (DHA) (22:6 n-3)](image)

**EPA**

EPA is another type of Omega-3 fatty acid that is also helpful to our body. EPA, which stands for eicosapentaenoic acid is similar to DHA in many ways. Like DHA EPA is also found in many of the same sources. EPA is found in cold water fish just like DHA. Many people fear of ingesting fish because of its mercury content, but the Food and Drug Administration has found that consuming several servings of fish a week poses no real threat to health if the person has no health problems (Simopoulos 2009). EPA is also found in breast milk but it is found at much lower levels. Like DHA EPA is also synthesized by our body from ALA.
The structure of EPA is very much like DHA but there are three carbons with single bonds following the carboxylic acid functional group. Just like DHA EPA is a conjugated molecule having double bonded carbons split by single bonded carbons. The structure of EPA is also stable because of the delocalization of the molecule.

![Eicosapentaenoic Acid (EPA) (20:5 n-3)](image)

**ALA**

ALA is the last type of Omega-3 fatty acid and it is also responsible for synthesizing the other types of fatty acids. ALA, which is an abbreviation for Alpha-linolenic acid, has been mostly talked about because it can actually be used to synthesize DHA and EPA. This would definitely be the way a vegetarian can get his or hers omega-3. Since ALA is found in many different oils such as canola oil, and also in nuts. Just like DHA and ALA omega-3 poses many health benefits to our body. ALA is only different because it can synthesize DHA and EPA once in our body (Simopoulos 2009).

The chemical structure of ALA is drawn out below.

![Alpha-Linolenic Acid (omega-3)](image)

The structure like the other structures is similar in having conjugated double bonds. This structure is also different in the way that there are only three pi bonds or double bonds. It also still has the carboxylic acid group on the tail of the molecule.

Studies such as The Nurses Health Study, took 76,000 women for ten years and gave them an average of 1.4 grams per day of flax seed, showed that they had half the risk of dying from a heart attack than those who only took and consumed about 0.7 grams per day of flax seed. This shows how it might benefit to take ALA but when this study was done on men it turned out
bad. When the study was done on men they were followed for 14 years, they only reduced their risk of developing heart disease by 11 percent. The bad part of this study was that those men who consumed the more ALA would be twice as likely to develop prostate cancer (Shardt 2005).

Omega-3 has made a big impact in the United States. It has also caused many opportunities for entrepreneurs. Omega-3 has become so popular with people because of the studies that have been done and stated to the public. Since these studies took long, about ten or more years, people have trusted the studies and are now willing to take the supplement form of Omega-3. About every year omega-3 is mentioned in the news. With this happening people are producing different forms of the supplement (Nightline 2010). The question is, are they all the same?

Fish oil supplements are usually made from salmon, tuna, mackerel, and even seal blubber. Also with the fish oil supplements you will most likely find vitamins (A,B1,B2,C) and minerals added just so you can have all you need in the Omega-3 supplement. Another thing with the supplements is that they will usually add the vitamin E. The vitamin E is added for the purpose of preventing the spoilage of the product (Shardt 2005). Some of the many types of fish oil brands out there include Nature Made and Kirkland Fish Oil. Besides the pure fish oil capsules for everyone, they also offer prenatal vitamins that include Omega-3 DHA such as One A Day. There are thousands of Fish Oil supplements out there but not all are 100 percent fish oil. Many times the supplements will only include a minuscule amount of fish oil, therefore the buyer will be paying for the other chemicals and not the Omega-3. This information can easily be read on the bottle. Basically if you are deciding to take Fish Oil supplements what should be read and looked upon is the actual content of Omega-3 per pill or capsule.

Nature Made Omega-3 Capsules  Prenatal Vitamins With the essential fatty acid Omega-3 DHA.

In general Omega-3 has undergone many studies that have been done for the purpose of finding its effect on different diseases. Some of the diseases that it has been tested to have an effect towards include rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. These studies were mostly done with little number of people but did show signs to either fish oil
being effective or it not being effective. One of the first studies that were done was the study to see if Omega-3 had an effect in patients who suffered from rheumatoid arthritis.

**Research Studies**

Rheumatoid arthritis is known as an autoimmune disease where the body’s immune system attacks healthy tissues and cells. The effect is usually shown more on hands, knees, feet and can be seen by twisted and bent like tissue. In the patients with rheumatoid arthritis, there were 12 who were chosen in a study that was done by a team formed by James MJ and Cleland LG. These twelve patients were chosen and they were given 3.6 g of EPA and 2.4 g of DHA every day for six weeks. After their trials were completed they were analyzed to see any differences in their daily activity since they had taken the DHA and EPA. in this study they all reported decreased symptoms of their tender joints. After these clinical trials and tests were completed the researchers concluded that the intake of Omega-3 in the form of DHA and EPA, should be taken especially, by people who have a genetic probability of acquiring the disease. They have recommended that it should become part of the dietary cycle of most vulnerable patients. Even though the study has only been done in small numbers they have found the results to be the same, thus concluding that Omega-3 does and might help towards reducing the symptoms and effects, that rheumatoid arthritis has on many patients (Borigini 2010).

**Male with a severe case of Rheumatoid Arthritis**

The Next disease that has been tested to see if Omega-3 might have an effect towards it is inflammatory bowel disease. Inflammatory bowel disease is known as the disease to cause red swelling in your large and small intestines. The direct cause of this disease is not fully understood but studies show that it has to do mainly with diet and also genetics. The disease itself is not contagious but has been shown to be passed down in the family. This disease will create open sores in the intestines, which in turn put the intestines at a vulnerable state to infection. Patients who took Omega-3 showed a reduction of LTB4 which is high in patients who carry the inflammatory bowel disease. Belluzzi et al showed that the relapse of inflammatory bowel disease rate was reduced in patients who consumed a supplementation of 2.7 g of Omega-3 a day. These studies towards inflammatory bowel disease showed that there is some relevance towards the disease and Omega-3 supplements (Kelley 2010).
Psoriasis is the disease where there is redness irritated flaky skin. This disease is found regularly on people suffering from AIDS, and autoimmune disorders such as rheumatoid arthritis. Psoriasis is a disease that is passed down by family. It has also been found that it is an autoimmune disease. With this disease the body’s own immune system mistakes healthy cells for intruder cells and attacks these healthy cells. Omega-3 has been shown to show that people taking their medication and Omega-3 at the same time showed improvements on their symptoms. This study was conducted on 40 people with psoriasis. This research study was also conducted on lithium induced psoriasis. This means that not all Psoriasis patients may experience relief to their symptoms just from taking Omega-3 (Kevin Berman 2010).

Another disease that affects millions today is Asthma. Asthma is known for the coughing and wheezing disease. This disease is an inflammatory disease in which the airways are affected. Asthma is caused mainly by the inflammation of the airways and can be triggered by allergens, severe exercise, and pollen. One clinical study was conducted with a group of 29 children who took supplements of EPA and DHA Omega-3. These children after ten months of taking the supplements showed that their symptoms had been reduced after they had taken the supplements for 10 months. They also had a placebo group who did not show any signs of reduced symptoms after taking the placebo (AHRQ 2011).
The image on the left shows a regular bronchiole compared to an inflamed one on the right.

Omega-3 has also been interesting in animal science. Many researchers have said that Omega-3 is in fact a great way to reduce inflammatory diseases in canines and other types of animals. Studies have shown that dogs fed with DHA and EPA enriched foods were showing less signs of arrhythmia. Canines is specific had their heart beating at a balanced pace after exercising. Also they showed better signs of not having arthritis, allergies, and skin infections. Omega-3 is not just an essential fatty acid in humans but also for house pets such as dogs in this case (Hall, Henry, Skinner, Jewell, Wander 2005).

**Conclusion**

In this paper we have mentioned what Omega-3 is, where it is found, its chemical structure, benefits, and studies that it has gone through. First, Omega-3 is classified as an essential fatty acid is a great chemical that does wonders in our bodies, an essential fatty acid solely means that it can’t be synthesized or made from our body. Also we learned where we can find omega-3. Omega-3 is found in the three types, which include DHA, EPA, and ALA. We know that DHA and EPA are only found in meat sources such as the Blue Fin tuna and Salmon. We also know that ALA can be found in many plants and grains including flax seed and sea weeds. Also if you own a chia pet, you could actually eat it! Chia seeds contain high amounts of Alpha Linolenic Acid. ALA is also the one Omega-3 fatty acid responsible for synthesizing DHA and EPA in your body, or of course obtaining DHA and EPA without needing to make it with ALA, from fish. We also conclude by examining the structure of Fatty acids that they are all unsaturated, meaning double carbon to carbon bonds, also organic molecules, and they are classified as conjugated because of the way the carbons are separated with alternating double bonds on the carbons. All of the Omega-3 fatty acids also include a carboxylic acid functional group at the tail of the carbon chain molecule.

The benefits of Omega-3 included all health benefits. We saw that Omega-3 is essential for a newborns development of the nervous system, and their visual system. Knowing this, it is crucial that newborns get breast fed since that will be the primary way to get their DHA and EPA, and if breast feeding is not available due to sickness of the mother or some other issue then formula will be the best way to get DHA or EPA. When picking the right formula for the
newborn you must read the ingredients and make sure it will contain Omega-3. Another big thing we can say about Omega-3 being beneficial is how it works out in helping heart. With heart disease being one of the big killers in today’s world, there are many people trying to find ways to help them out. With Omega-3 we know that it will help in removing plaque stuck in arteries thus preventing any sort of heart disease or heart attack. Besides these benefits Omega-3 has also been proven to help the growth of the brains cell membranes.

There have also been many studies such as the studies towards the different diseases that include rheumatoid arthritis, inflammatory bowel disease, psoriasis, and asthma. At this point we can’t say that Omega-3 has extreme effects and results towards these diseases but they do no harm and will work in other forms such as stated above in the growth of the brain cells.

Omega-3, DHA, ALA, EPA is a great area of study that has been discovered and should have more researchers dedicated to finding new and useful information of what more it can do and long term effects of its consumption. With research we could find much more information of its benefits and even if it is helpful in preventing some major sicknesses that will ultimately lead to killing patients. Omega-3 shows promising results, if researched more. Eventually, it could be a key to new treatments in the medicine field.
Cited References


