PARADISE VALLEY
COMMUNITY COLLEGE

16th Annual Science Symposium

Volume I

May 13th, 2010

Paradise Valley College
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Science Symposium
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Foreword

The 16th Annual Science Symposium was held on May 13, 2010. Students enrolled in Organic Chemistry 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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Laxatives:
The Explosive Truth About Laxatives

Prepared for
Dr. Hank Mancini
Instructor
Organic Chemistry 236

Prepared by
Robert Boehland
April 23, 2010
Abstract

The anatomy and functions of the gastrointestinal tract are addressed, and the condition of irritable bowel syndrome (IBS) is linked to bowel dysfunction. The cause of IBS is stated and the different techniques used to treat IBS are used to link the need for laxatives. The different types of laxatives are discussed as well the consequences of laxative abuse. Illustrations are used throughout the paper to assist in the understanding of specific sections.

Introduction

Through the long and complex process of digestion, there are many bodily functions working together as a single unit to simplify the process. This process is straightforward posing limited complications; however, the body is not perfect and is always susceptible to problems. When a dilemma does occur within the gastrointestinal (GI), the side effects may not always be as desirable as one would imagine. On average, most people only experience symptoms of indigestion for short periods of time. However, if an accident does occur, it may change the duration of time of which one will experience symptoms of indigestion. Case studies have shown that injuries related to the spinal cord play a role in bowel dysfunction. Using different methods of therapies as well as appropriate medication can allow those issues to be resolved. One of the most common ways to treat bowel dysfunction is through the application of laxatives. The word laxative comes from the Latin word *laxare* which means loosen and according to the Oxford English Dictionary, it is a drug that stimulates and/or facilitates the evacuation of the bowel. (1) Laxatives may be administered using several different techniques for both oral and rectal applications. The clinical use of these drugs are for the most part manufactured in a lab, but specific diets of certain natural laxatives can also be used to treat symptoms of bowel dysfunction. Consuming too much of a clinically administered laxative may have either a light or severe consequence for abusing the drug. Laxatives are a very useful drug to help relieve pain; however, it is a drug nonetheless and should be used only on a prescription basis.

Gastrointestinal

The gastrointestinal (GI) is the main system in which food is ingested and is broken down by physical and chemical means to provide the body with nutrients which are absorbed for energy. The GI is also responsible for excreting the body of any unwanted waste that is left over from the previous process. Several main organs compose the GI: the stomach, large bowel (large intestine), small bowel (small intestine), appendix, and the rectum, as figure 1 illustrates.

![Gastrointestinal System Diagram](image.png)

**Figure 1 (2)**

**Critical Organs of Gastrointestinal**
Through the process of ingesting food and liquids, all of these organs work as a unit to make the process of the GI operate smoothly. Through the process of ingestion, food is initially broken down physically by chewing then chemically with the saliva secreted in the mouth. As the food passes through the esophagus and enters the stomach, it then is being attacked by enzymes and being further broken down in the stomach acid. The food will then enter the small bowel, where the nutrients are then extracted into the bloodstream and processed by the liver. The large bowel will then remove the liquid from the remaining substance and form the left over waste into stool (feces).

The rectum will then collect the stool and dispose of it at an appropriate time by forming bowel movements. (2) The condition of the GI relies solely on the bowel movements. Normal bowel movement frequencies range from one to three times a day to once to three times a week. Whenever food is passed through the large bowel too fast, the frequencies of the bowel movements occur faster than normal and a condition known as diarrhea occurs. When the food passes through the large bowel too slowly and the frequency of the bowel movements are slower than normal a condition known as constipation then occurs. (3) These conditions are classified as bowel dysfunctions and are caused from many reasons including diet, medications, life style habits, and a condition known as irritable bowel syndrome (IBS). (3)

**Irritable Bowel Syndrome (IBS):**

Bowel movements are all a part of a routine that takes place within the body and whenever there is a disturbance in that routine, a condition known as bowel dysfunction is formed. There are many different forms of bowel dysfunctions; the most common type is a condition known as irritable bowel syndrome (IBS). According to the University of Michigan Health System, IBS is a common chronic disorder causing alteration in one’s bowel habits as well as abdominal discomfort. (3) Several symptoms that occur from this functional bowel disorder include constipation, diarrhea, and an alternation between the two.

IBS can be caused from a considerable amount of different sources. Out of those sources the most frequent occurrences of IBS happen after spinal cord injuries. A study conducted by Scott Glickman and Michael Kamm proves the fact that occurrences of IBS are more common in those who have suffered a spinal cord injury. In this study they issued a very in-depth survey to 115 consecutive outpatients to determine if spinal cord injuries were a main source of IBS. To have the results made obvious, the survey that was conducted was broken into two separate parts, one for pre-injury and one for post-injury. The controlled factor of the study was that the patients were all asked the same questions for pre and post injury. The questions mainly entailed the different methods used for opening the bowel as well as the psychological affect the injury had on the patients. As Figure 2 illustrates the results of the study, it is obvious to point out that post spinal cord injuries have a dramatic effect on the different methods required for opening the bowel. These results may be used to link the need for laxative treatment on those patients who suffer from any kind of spinal cord injury.

In the conclusion of their study, Glickman and Kamm discussed the effects that spinal cord injuries have on both the gastrointestinal functions and the psychological affect on the patient. Out of the 115 patients, 54% of them stated that IBS was the main source of being emotionally unstable. Common symptoms that occurred from the patients suffering from IBS included constipation, diarrhea, and nausea. For the patients who were classified as being emotionally
upset, 65% required longer than 30 minutes to defecate and the remaining percentage required more than 15 minutes. For the patients that were classified as being emotionally stable, 70% of them required only 15 minutes and the remainder required less than 30 minutes. From these results Glickman and Kamm were able to conclude that the emotional status of a person is related to the amount of time it takes one to defecate. (5)

<table>
<thead>
<tr>
<th>Methods of opening bowel</th>
<th>% of patients using method preinjury</th>
<th>% of patients using method postinjury</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Using one or more method</td>
<td>20</td>
<td>95</td>
<td>0.0001</td>
</tr>
<tr>
<td>Sennosides, 25%</td>
<td>9</td>
<td>20</td>
<td>0.01</td>
</tr>
<tr>
<td>Oral laxatives</td>
<td>5</td>
<td>29</td>
<td>0.001</td>
</tr>
<tr>
<td>Suppository fibre</td>
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<td>17</td>
<td>0.001</td>
</tr>
<tr>
<td>Digital stimulation</td>
<td>0</td>
<td>53</td>
<td>0.001</td>
</tr>
<tr>
<td>Manual evacuation</td>
<td>1</td>
<td>68</td>
<td>0.001</td>
</tr>
<tr>
<td>Suppositories</td>
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<td>49</td>
<td>0.001</td>
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<tr>
<td>Enemas</td>
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<tr>
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<td>High-fibre diet</td>
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<td>23</td>
<td>0.001</td>
</tr>
<tr>
<td>Electrical implant</td>
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<td>2</td>
<td>0.5</td>
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<tr>
<td>Other</td>
<td>4</td>
<td>6</td>
<td>0.8</td>
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</tbody>
</table>

**Figure 2 (8)**

Results of Glickman and Kamm’s Study

**Treatment of Irritable Bowel Syndrome (IBS):**

Treatment of IBS all begins with the primary care provider and patient’s relationship. Those patients who suffer from IBS will most likely suffer symptoms of being emotionally upset as well, so it is crucial that the primary care provider takes cases of IBS seriously. In most cases of IBS, the placebo effect of the treatment may increase or decrease depending on the status of that relationship. (9) The different symptoms of IBS will determine if the case is treated with a non-pharmaceutical therapy or pharmacotherapy techniques. Laxative therapy is used for both the non-pharmaceutical and pharmacotherapy techniques; the difference is the type of laxative that is being consumed. The non-pharmaceutical therapies include: diet manipulation, bulking agents, and probiotics. The pharmacotherapy techniques include: antispasmodics, tricyclic antidepressants (TCAs), loperamide, stool softeners, antibiotics, melatonin and chloride channel agonists. (9)

The non-pharmaceutical therapy of diet manipulation will require the patient to exclude specific substances from their diet such as lactose or fructose for a period of time. This diet modification will typically be necessary to enforce for a two to three week period; if little to no improvement is made, the patient will then be reintroduced to the food and placed on a different therapy. The next type non-pharmaceutical therapy are bulking agents which are fiber dietary supplements that help increase flow through the small bowel and allow the volume of stool to increase within the large bowel; this therapy assists in the relief of constipation and abdominal pain. The final type of non-pharmaceutical therapy are probiotics; these supplements help improve the qualitative and quantitative changes in the gut flora. Gut flora are the microorganisms within the gastrointestinal tract that help with the process of digestion. (9)
Antispasmodics are the first type of pharmacotherapy and when this supplement is digested, it is broken up into relaxing agents which smooth out and relax the gut muscles to relieve the abdomen area of pain. Tricyclic Antidepressants (TCAs) are a sedative supplement which facilitates the gastrointestinal and slows its motility to relieve the abdomen of pain. Loperamide is a commonly used supplement to treat diarrhea and urgency for adults. When loperamide is digested, it slows the movement of the large bowel and allows the stool to harden; this therapy treatment often causes nausea, vomiting, urinary retention, and constipation. Stool softeners operate in just the opposite manner; instead of slowing down the movement of the large bowel, this supplement will increase the bowel's frequency and allow the stool to pass through the gastrointestinal quicker than normal. When carbohydrates are not sufficiently digested and begin fermenting within the gastrointestinal causing gas and bloating, pharmacotherapy of antibiotics is used to decrease the gas and bloating. Melatonin is another sedative supplement used to relax the gastrointestinal and smooth out the bowels; it is the substance secreted from the pineal gland when darkness is present. It is the drug responsible for aiding the process of the sleep cycle. The final type of pharmacotherapy is chloride channel agonists; this supplement is categorized as a bicyclic fatty acid derivative known as prostones. (9) "It reacts on the type-2 chloride channels of the gastrointestinal epithelial cells to promote electrolyte secretion and fluid into the small bowel and improve motility."(6)

Laxatives:

According to the New York University Medical Center, "A laxative is a substance that helps you have a bowel movement. Laxatives are used to relieve and prevent constipation, which occurs when it is difficult to have a bowel movement."(7) Laxatives are categorized as either oral laxatives or rectal laxatives and each of those categories may be broken down into smaller sub-categories.

Oral laxatives are those laxative supplements taken by mouth to help facilitate bowel movement and relieve constipation. There are several different kinds of oral laxatives that can be taken, with each one serving a different purpose; it is important to understand each kind and what its function serves. The different kinds of oral laxatives include: bulk-formers, hyperosmotics, lubricants, stimulants, stool softeners (emollients), and combinations of them all. (4)

Bulk-forming laxatives will react with and absorb water as it passes through the bowels, and the liquid will swell to form soft, bulky stool. Once the stool is formed, the regular process of defecation will take place; these types of laxatives will normally be prescribed to treat diarrhea. Metamucil, psyllium seeds, and apples all are consisted of dietary fibers which constitute for great bulk forming agents. (4) Fibers make for great bulk forming laxatives because as the fibers are being digested, they react with the water molecules within the bowels; the fibers will then actually expand and add onto the already existing stool.

Hyperosmotic laxatives, which are the second type of laxative, will stimulate bowel movements and draw water into the bowels from the surrounding tissues. This creates mass soft stool and forces the bowel frequencies to increase. There are three types to hyperosmotics saline, lactulose and polymers. The saline is also known as salt; this is a fast method that is used for rapid emptying of the large bowel. The lactulose is a specialized sugar that operates much of
the same way that the saline does; however, it is a much slower process and is used to treat long term symptoms of constipation. The polymer hyperosmotic laxative is a large molecule that forces water to be retained in the stool. This acts much like a large sponge; it reacts and absorbs much of the water molecules within the bowels resulting in an increase of bowel movements and soft bulky stool. (4) Saline hyperosmotic laxatives are the more common of these three types; in fact in most hyperosmotic laxatives the substance known as Epsom salt will be found. The significant part about Epsom salt is that it possesses the chemical formula MgSO4 * 7H2O. This makes it highly reactive with any form of water, and in most uses of this chemical it is actually used as a drying agent because it absorbs water so well. (4)

The third kind of oral laxatives are lubricant laxatives; these are often an oily substances that coats the bowel walls and the stool masses. This coating allows the stool to remain hydrated and soft, therefore increasing bowel movements as well. (4) These types of laxatives relate closely to the final type of oral laxatives which are stool softeners.

The fourth kind is stimulant laxatives which are very similar to lubricant laxatives in the fact that they act on the bowel walls and increase bowel movements. These stimulant laxatives are those laxatives that increase bowel movement by stimulating the muscle contraction as the stool passes through. (4)

The final category for oral laxatives is stool softeners also known as emollients. These stool softening laxatives react with the stool within the bowels and either softens the stool or maintains the softness of the stool; this type often allows bowel movements to occur without strain. (4) This type is very similar to the lubricant laxatives because both of these kinds are typically oily substances which improve the movement of stool through the bowel. These types of laxatives are typically categorized as lipid fats, which essentially coat the inner walls of the bowels acting as a lubricant for the stool to pass through smoothly. (4) Figure 3 illustrates a commonly found lipid used for both stool softening and lubricant laxatives.

Figure 3 (4)
Organic Illustration of Lipid in Stool Softening and Lubricant Laxatives
Rectal laxatives operate similar to those laxatives that are administered orally. The only few differences are that rectal laxatives are administered through the rectum and these laxatives are meant to treat conditions in short periods of time. The categories of which rectal laxatives are broken down into include all of the same categories as oral laxatives with the only differences being that bulk-forming laxatives pertain only to oral laxatives and carbon dioxide-releasing laxatives pertain only to rectal laxatives. The carbon dioxide-releasing laxatives are suppositories that increase bowel movement with the forming of carbon dioxide gas. This gas resists against the bowel walls causing more muscle contractions to occur as the stool passes along. (4)

Depending on the symptoms of the condition of the patient determines which type of laxative to use; all of these categorized laxatives may be combined to further assist a given condition. Laxatives for the most part are used for clinical purposes and are organically manufactured in a lab; however, there are a multitude of different natural laxatives that are found in daily consumed items, figure 4 illustrates some of the more common types.

```
<table>
<thead>
<tr>
<th>Avocados</th>
<th>Chocolate</th>
<th>Parsley</th>
<th>Rhubarb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Coconut</td>
<td>Peach/Apricots</td>
<td>Soybeans</td>
</tr>
<tr>
<td>Almonds</td>
<td>Coffee</td>
<td>Pears</td>
<td>Spicy Foods</td>
</tr>
<tr>
<td>Aloe Vera</td>
<td>Dandelion</td>
<td>Persimmons</td>
<td>Tumips</td>
</tr>
<tr>
<td>Apple Juice</td>
<td>Dried Apricots</td>
<td>Pineapple</td>
<td>Walnuts</td>
</tr>
<tr>
<td>Chicken Broth (canned)</td>
<td>Molasses</td>
<td>Plums</td>
<td>Watercress</td>
</tr>
<tr>
<td>Chicory</td>
<td>Licorice</td>
<td>Prunes/Prune Juice</td>
<td>Olives</td>
</tr>
<tr>
<td>Mangos</td>
<td>Flaxseed</td>
<td>Hot Tea w/ Lemon</td>
<td>Papayas</td>
</tr>
<tr>
<td></td>
<td>Grapes</td>
<td></td>
<td>Dates</td>
</tr>
</tbody>
</table>
```

**Figure 4 (5)**

**Common Natural Laxatives**

Natural laxatives compared to manufactured laxatives are not nearly as effective because laxatives are precisely chemically organized and specifically structured to a specific condition. The manufactured laxatives will appear as a pure laxative substance which is meant to target a specific condition. Natural laxatives will appear to be impure, yet they will still contain laxative properties however, natural laxatives will also contain substances which do not possess laxative properties. Natural laxatives will still have the same effect as manufactured laxatives; the only differences will be the amount of time it takes the natural laxatives to react and the magnitude of which it affects the person. In the items which are consumed daily by people all over the world, there are a continuous amount of laxatives being digested. Just about any form or fiber, protein or carbohydrate possesses laxatives properties; however, the amount of which those affect people differs on the type of laxative of which it is. When dealing with manufactured laxatives the amount of which it affects the people differs greatly from the affects of natural laxatives. The manufactured laxatives are designed to target specific symptoms of any type of bowel dysfunction. The magnitude of which it affects the person as well as the amount of time
it takes to react all depends on the technique used to administer the drug, whether it be orally or rectally. Manufactured laxatives are similar to every other drug in the sense that only the prescribed amount is sufficient enough for the proper execution. When more than the prescribed amount is consumed, it becomes known as laxative abuse. (5)

According to the University of Maryland Medical Center, laxative abuse is when a person unintentionally or intentionally consumes more than the normal or recommended amount of the laxative. Most cases of child laxative abuse are accidental, but with the majority of cases with adults, laxative abuse is intentional to lose weight. Common symptoms of laxative abuse for both natural and manufactured laxatives from a broad spectrum include: nausea, vomiting, abdominal cramping, and diarrhea. Manufactured laxative abuse will have more severe consequences depending on the type of laxative used. Severe laxative overdose is only found in those laxatives that are manufactured; there are extremely few cases where a person may overdose on those laxatives that are naturally digested. The most severe type of laxative abuse is found when patients consume more than the normal amount of laxative products containing magnesium. A few of the consequences of this type of abuse include: drop in blood pressure, slowed breathing, coma, and even death. (6)

Summary and Conclusion:

The gastrointestinal (GI) is one of the more complex systems in the body being composed of several vital organs. The bowels (intestines) are one of the major factors that assist in the breakdown of food and allow nutrients to be delivered to different locations of the body. Bowel movements are what assist the food through the small bowel into the large bowel. Normal bowel movement frequencies range from one to three times a day to once to three times a week. Whenever there is a disturbance with the bowel movements, a condition known as bowel dysfunction occurs and disrupts the production of digestion. (2)

Irritable bowel syndrome (IBS) is one of the most common types of bowel dysfunctions and there may be many different possible symptoms that arise from IBS. These symptoms are commonly discovered in the form of either constipation or diarrhea or even an alteration of the two. Causes of IBS are usually related to the health of the patient and are caused from the patient's diet, medication, or physical condition. Glickman and Kamm proved in their study that spinal cord injuries are a main cause of IBS and other bowel dysfunctions. Glickman and Kamm also discovered from their study that bowel dysfunction plays a major role in emotional stability. Patients who suffered from bowel dysfunction after the spinal cord injury were found to have more of a struggle when defecating. Their study provided evidence that spinal cord injuries are a main factor for bowel dysfunction which in return is a cause for emotional instability. (3)

The most common treatment for curing conditions of IBS is found to be through the use of laxatives. Laxatives are initially categorized as being either a non-pharmaceutical therapy or pharmacotherapy; these therapies are further categorized as more precise techniques. The non-pharmaceutical therapies include: diet manipulation, bulking agents, and probiotics. The pharmacotherapy techniques include: antispasmodics, tricyclic antidepressants (TCAs), loperamide, stool softeners, antibiotics, melatonin and chloride channel agonists. (6) Outside of the therapies, laxatives are categorized as being either oral or rectal laxatives. Both types of
laxatives aid in the assistance of the bowel movements and relieve the patient of any symptomatic suffering. The difference between the two is the action of how the laxatives are administered; oral laxatives are digested through the mouth. Rectal laxatives are administered through the rectum and are used to treat a condition in a short period of time. (4) Laxatives can be organically manufactured in a lab or they may be found in natural foods which are consumed on a daily basis by people all over the world. (7) The main purpose for laxative use is for treating patients who suffer from forms of bowel dysfunction. Laxatives for the most part are used properly for clinical use; however, when laxatives are used irresponsibly the patient may suffer from laxative abuse. The side effects of laxative abuse can be severe. Manufactured laxatives are a just like any other drug only a sufficient amount is required; any more could be detrimental to the patient. Manufactured laxatives are to be used responsibly and as long as conditions of bowel dysfunctions are present, the use of manufactured laxatives will continue. Laxatives are a drug that cannot be extinct; they are a drug that is needed to help properly execute digestion successfully. This research will be used to help expose the truth about laxatives in several different aspects; it will give an understanding to the purpose for laxatives, differentiate all the different types of laxatives, and highlight the effects that laxatives have on a patient both positively and negatively.
References

Internet Resources


(3) “Constipation.” University of Michigan Health System. 17 March 2010 <http://www.med.umich.edu/1libr/aha/umconstipation.htm


(5) “Natural Laxatives.” University of Michigan Health System. 18 March 2010 <http://www.med.umich.edu/1libr/aha/umlaxative.htm

(6) “Laxative Overdose.” University of Maryland Medical Center. 17 March 2010 <http://www.mmm.edu/ency/article/002586all.htm


Database Journals


Honors Project: Medical Imaging Machines

Student: Robert Bochland

Due Date: 11-30-2009

Course Name: PHY 112- College Physics II

Class #: Lecture- 43132, Lab- 43296

Instructor: Dr. Casey Durandet
Abstract:

Modern medicine requires the use of medical imaging machines because medical imaging machines are what enable doctors to more easily diagnose a patient by looking at the patient’s whole body inside and out. X-ray, fluoroscopy and computed tomography images allow the provider to see the structure of the bones in the body. Positron emission tomography, mammography and ultrasound allow them to see the function of the body, helping diagnose cancerous cells in the early stages. A magnetic resonance imaging machine uses magnetic resonance to provide a computer image of the soft tissue and organs in the body with no radiation. This paper will address the technical side of how each machine works, and the underlying concepts behind physics that contributed to their discoveries.

Introduction:

The knowledge of medical imaging may lead into extensive depth, but the basic knowledge of medical imaging may be understood through simple apparent measures. There are various types of medical imaging machines, some of which are included in common practice and others in which are remotely used. The basis of all medical imaging machines started off with the discovery of the x-ray, which the x-ray’s rules and concepts stand as the starting point of all medical imaging. Since that discovery, medical imaging has played a key role in the advancements made in our accelerating society of medicine and over a short period of time medicine has made compelling improvements. Medical imaging is the leading tool for diagnosing and treating a wide range of diseases. Many of the improvements being made are do to the basic mathematics of physics. The majority of physicists will argue that physics is the backbone and nature of how we live and what we live in. By understanding the basic physics behind medical imaging has lead to the development of many medical imaging machines that are used daily in hospitals around the world to diagnose and treat patients. The discovery of their concepts and technology necessary to create these machines has a long history in physics. Electricity, magnetism, and alternating current are the basic concepts behind these modern machines. Some of the machines that have been developed over this past century include; x-ray (radiography), fluoroscopy, computed tomography, positron emission tomography, magnetic resonance imaging, mammography (thermography), and ultrasounds. These machines continue to be improved and contribute to the development of the newer machines being invented (15-Allen). Each technology has its own special purpose in helping to diagnose and treat patients.

History of Radiography:

Before discussing the physics components in radiography of medical imaging, the history of radiography should be addressed. At the end of the nineteenth century two huge advances were made in the physics world; the discovery of the x-ray, and the understanding of an electron. Both came from the studies of electric discharges in gases at low pressure. These experiments revealed that when metal electrodes were encased in a glass container at atmospheric pressure, and a source of electricity was added, nothing occurred except for when the voltage was high. When the voltage was lowered, the pressure was reduced, and the electric current flowed through the gas. At a pressure of about ten millibars, a steady glow filled the space between the electrodes. If the pressure was reduced further, the glow broke up into bands of light and dark and when reduced even further, the glow disappeared completely, but the glass began to fluoresce brightly (1-Bowers).

In 1859 a German physicist, Plucker, concluded that the fluorescence was due to
something radiating from the electrode or cathode. In 1879, the English physicist, Crookes, put together a series of researches that supported this theory, Crookes showed that cathode rays were emitted normally to the cathode surface and could be deflected by a magnet. When he focused the rays to a point, heat began developing, melting the glass or platinum. After comparing his work to other physicists, he concluded that the rays consisted of negatively charged particles and that the rays were wave motion similar to light. Another physicist Hertz found that cathode rays would pass directly through a thin film of gold or aluminum, but when he died in 1894, Hertz’s successor, Lenard, continued his work. He replicated the same work as Hertz but went a little further, his studies found that the rays still produced fluorescence and could be passed through the hand, but could not travel far at atmospheric pressure. What he failed to notice was that there was a different type of ray involved (1-Bowers).

It was not until 1895 that a professor at Wuerzburg University in Germany, Wilhelm Conrad Roentgen, discovered that the new ray was the x-ray. On November 8, 1895, Roentgen was duplicating the work of Crooke, when he observed a glow of crystals in a container on a table nearby where he was working. He investigated, by shielding the container with heavy black paper and then bringing a sheet coated with barium platin-o-cyanide near. The sheet fluoresced all over and when he put a metallic object in-between, it cast a shadow. He then, concluded that the container was emitting some unknown ray which was passing through the heavier paper and producing fluorescence. In conclusion found out that the ray could pass through most substances casting shadows of solid objects (this is when the first x-ray of a human hand was taken). From his first studies, he concluded that the transparency varied with the density of the substance.

Roentgen reported that he could not obtain reflection or refraction, because the beam of x-rays could not be concentrated by means of mirrors or lenses. He also noted that x-rays originated at the point where the cathode ray beam struck the glass and radiated in all directions, and that x-rays were produced if cathode rays struck aluminum instead of glass (1-Bowers, 2-NDT Resource Center). At that time, he did not fully understand these new rays, but he understood that they traveled in a straight line and were not cathode rays from the main discharge because they were not deflected by the magnet. He also knew that the rays were not ultra-violet because they were not reflected or refracted (1-Bowers).

Once Roentgen’s research was made public, many other physicists became intrigued that there was a wavelength shorter than light. Many stopped their current research efforts to begin similar experimentation so that they could make a discovery for themselves. The majority of the equipment needed to conduct his experiment was readily available in most labs this is why the experiment was easy to duplicate. In fact, the first use of the x-ray was not even for medical use, but for industrial use. It wasn’t until 6 months later, in 1896, that x-rays were being used for the military to locate bullets in wounded soldiers (2-NDT Resource Center). Before the name “x-ray” became established other names were used such as the ‘Roentgen rays’ (which remain today in Germany), “schiagraph”, and “radiographs”. English speaking countries use the terms radiographs and x-rays(1-Bowers).

After Roentgen, there weren’t any major advancements made until an American, Thomas Edison, made a break through. Edison pushed medical facilities to use fluorescent screens rather than photographic plates so fractures could be seen along with other things. Edison was given nearly two hundred thousand elements to test on these plates for the best fluorescence. He concluded that the best influence occurred with calcium tungstate(1-Bowers).

Roentgen then submitted a second paper in March of 1896 stating how air which has been exposed to x-rays can conduct electricity. With the help from physicist, J.J. Thomson,
Roentgen’s theory would then be explained. Thomson was the physicist who discovered a better understanding of the electron. With this, Thomson was able to prove that the x-ray ionizes the air therefore makes it conductive. Roentgen was then able to include a Tesla apparatus in circuit between the induction coil and the x-ray tube. The Tesla made the voltage in the circuit increase, allowing for a more powerful x-ray (1-Bowers). Another advancement was made in 1906 when Snook developed the “interrupter-less transformer”. This allowed voltages high enough to produce x-rays to penetrate the whole body. Also soon after, in 1913, Coolidge developed the hot cathode ray tube. He improved the vacuum to increase the life of the tube and heated the filament to make it a more efficient producer of electrons. This tube became known as the Coolidge Tube. From the early 1900’s until today, many different types of x-rays and x-ray tubes have been utilized and modified.

Background in Physics:

General physics concepts are key to understanding how medical imaging machines work. Just as x-rays are the basis for all other medical imaging machines, electricity and magnetism are fundamentals in physics. Without electricity there would be no computers, telephones or modern medicine. Just with computers alone, this generation is able to store a century of research on a tiny little chip the size of a finger nail. With the discovery of electric forces and electric fields, a multitude of discoveries have been made, which lead to the ability to send messages from one side of the earth to the other within seconds, or arranging the location of atoms (which is key to the operations of radiography and MRI machines).

Electricity was first discovered by the ancient Greeks around 700 B.C. when a fossil material attracted small objects after being rubbed with wool. This phenomenon was later proved with Coulomb’s law, which is the fundamental law of forces between any two stationary charged particles (3-Serway, Vuille & Faughn). There are two forms of electricity the first one being static electricity which is electricity at rest, usually caused by friction. With static electricity, electrons move from one object to another. The second form of electricity is dynamic electricity, which is electricity in motion. For both types, there are three basic fundamentals of how electricity functions; voltage, current and resistance. However, there is another important sub-fundamental that is key to understanding the others, and that is electric charge. Electrical charges are positive or negative and like charges repel one another, and unlike charges attract one another. Most objects usually contain an equal amount of positive and negative charges. When objects have either a net negative or net positive charge, however, electric forces arise. An important characteristic to know about electric charges is that electric charge is always conserved and created only when there is a transfer of negative charges from one object to another. One way to transfer those electrons is through voltage, also known as electric potential. Voltage is the push or pull of electrons, and is considered the driving force of current. Voltage is the product when current and resistance work proportional to one another and the resistance remains constant over wide ranges of voltage or current (\( V = IR \)). This is also known as Ohm’s law.

Current, is the rate at which charges flow through a surface is useful in describing dynamic electricity. Dynamic electricity involves two types of electricity, direct current, and alternating current. Direct current is the flow of electrons in only one direction, and may be found in a uniform direct current or pulsating direct current. In a uniform direct current, the voltage rises, hits a maximum, and remains constant throughout. In a pulsating current, the voltage travels in a constant pattern flow of reaching the maximum and returning back to the minimum. In alternating current, the movement of electrons is constantly changing speed along
with the direction of flow. For this type of current, there needs to be an AC generator and the motion of this flow is sinusoidal and varies with time. The frequency of the generator represents the amount that the voltage changes per second. An important aspect of alternating current is resonant frequency, which occurs when the current is at its maximum value and the impedance is at its minimum. General concepts of alternating current are important to understand when dealing with medical imaging because most machines operate under an alternating current.

Resistance is opposition to the flow of electrons and there is low resistance in conductors and high resistance in insulators. Resistance is the backbone of how static electricity operates. In conductors, electric charges move freely in response to an electric force. Objects receive their charges from either conduction or induction; conduction is the transfer of charge through contact, and the object being charged will result in the same charge as the object doing the charging. Induction is the charging of an object without making contact with the other object. When the object charging is removed, the remainder of electrons is redistributed throughout the charged object. The electric forces of charges are caused by the electric field, which is the region of space around a charged object. This field will exert an electric force on other charged objects within the field. Electric forces are best summarized with Coulomb’s law which states that electric force is directed along a line joining two particles and inversely proportional to the square of separation distance between them. It is proportional to the product of magnitudes of the charges of the two particles and it is attractive if the charges are of opposite sign, and repulsive if charges have the same sign (3-Serway, Vuille & Faughn, 4-Krakos & Percuoco).

Magnetism and electromagnetism are also important fundamental physics concepts to understand and they relate more closely as to how medical imaging machines operate. Magnetism is closely linked with electricity because magnetic fields affect moving charges, which produce magnetic fields. Similar to electric charges, like magnetic poles repel each other, and unlike poles attract each other. The poles on a magnet can be referred to as the North Pole, and South Pole. Due to the earth’s magnetic field, every magnetic object’s North Pole will be directed to the north, and the South Pole will be directed towards the south. When charged particles are moving through a magnetic field, a magnetic force acts on it. The maximum magnetic force is defined as the charge of the particle moving in proportion to the velocity and magnetic field. The maximum field is the force working inversely to the charge and velocity of the particle. The velocity of a charged particle in a magnetic field will be perpendicular to the force of the magnetic field, resulting in the particle moving in a circular motion. The magnetic force will always be directed toward the center of the circular path (3-Serway, Vuille & Faughn).

Electromagnetism is one of the most important parts of physics to understand in relationship to medical imaging machines because electromagnetism waves travel at the speed of light and most machines operate with rays of that speed. The electromagnetic spectrum is made up of different kinds of waves; radio waves, microwaves, infrared waves, visible light, ultraviolet light, x-rays, and gamma rays. Radio waves have the longest waves and are a result of charges through conducting wires. Microwaves are basically just short-wavelength radio waves and are generated by electronic devices, (these waves are suited for aircraft navigation and radar systems). Infrared waves are also known as heat waves because they are produced by hot objects and molecules. Visible waves are the waves that are detected by the human eye, and they are produced by the rearrangement of electrons in atoms and molecules. Ultraviolet light, or UV light, is the light that is absorbed from the sun. X-rays which are the most important type of ray when referring to medical imaging are caused by the bombardment of electrons. The smallest of waves is the gamma ray, which is emitted by radioactive nuclei. The x-ray and the gamma ray
are the only two waves with a sufficient amount of energy to penetrate matter. The biggest side effect that comes along with all of these different electromagnetic waves is electromagnetic radiation (3-Serway, Vuille & Faughn, 4-Krakos & Percuoco). This radiation is an electric and magnetic disturbance traveling through space at the speed of light. The three parameters that almost fully describe this wave form of a photon’s electromagnetic radiation are velocity, frequency and wavelength. The velocity of the photon is equal to the frequency working proportional to the wavelength. Frequency is the cycles that occur every second, and the wavelength is the distance it takes to complete one cycle. The photons will appear to be soft or hard. A soft photon is less penetrating, has lower energy, a longer wavelength and a lower frequency. A hard appearing photon is directly opposite of a soft appearing photon. Long extensive exposure to electromagnetic radiation will cause burning to the skin and even longer exposure may cause multiple types of cancer. Due to the advancements being made with in medical imaging the risk and exposure time for someone has been nearly cut in half (4-Krakos & Percuoco).

**X-Rays & Fluoroscopy:**

An x-ray, also known as a radiograph, is composed of electromagnetic waves that penetrate matter and show the density of a material. x-rays are the basis of all medical imaging. The only two wavelengths they have enough energy to penetrate matter are x-rays and gamma rays. The amount of energy is represented by the frequency of the ray, the higher the frequency, the more penetrating the ray will be. Frequency is used to describe how fast the wavelength is moving up and down in a sinusoidal manner. A typical wavelength for x-rays are about 0.1 nanometers (nm), and the shorter the wavelength, the more penetrating the x-ray is. So, the penetration of an x-ray may be represented by the frequency and the wavelength working proportional to one another. If the frequency rises, the wavelength will shorten, and if the frequency lowers, the wavelength becomes longer. X-rays travel too fast for the human eye to detect, (approximately 186,000 miles per second), and they are delivered in bunches of photons. These photons ionize all of the matter they come into contact with. For example, when a neutral atom is struck an electron gets knocked off and leaves that atom with a net positive charge and a lone pair of electrons. However, an x-ray has a neutral charge and is not affected by electric or magnetic fields. The production of an x-rays comes from the bombardment of electrons accelerating towards a target, and decelerating once in contact with that target. The x-rays are not stored in the matter, but are only absorbed by the heavier denser material. This material is what will show up on a filament that becomes fluoresced, but will only fluoresce on specific radioactive material. Tungsten is the most popular material used in filaments because it gives off the best fluorescence and possesses a very high melting point of 3410_C. The bombardment of electrons that hits the dense material is controlled by a current, and by controlling the current, the heat is also controlled. Heat, in early uses, was one of the biggest problems that technologists faced because the life of the tubes being used were short. This lead to what coined Coolidge’s tube name “hot cathode tube”. With this, a cathode filament is controlled separately than the actual current, allowing a lower voltage, and a lower amount of electrons produced. Now most tubes just have two filaments, a large and a small one, receiving the name “dual filament”. In order to attract the electrons from the cathode filament, there needs to be another material with opposite charge, and that is the anode. The anode is typically made of copper and has a tungsten plate embedded into it. Since an x-ray cannot be focused by a lens, to get a clear picture, a dense material needs to be underneath the object of interest, and the electrons need to be focused. The
thing that is used to focus these electrons is a focusing cup, which is made of molybdenum that has a negative charge. This material condenses the electrons and causes the stream to travel towards the target, by the simple rules of charged particles. Since, this material has a negative charge, and electrons consist of a negative charge, they want to repel each other. As the electrons pass through this cup, they repel against the cup and become focused on the positively charged anode, which has the filament tungsten plate on it. Whatever dense material is in front of that tungsten plate will be the target that is bombarded with electrons, and will appear as a fluoresced image. That image is the definition of what we now know today as to be the basic properties of how the x-ray works (4-Krakos & Percuoco). Digital advancements have been made with radiography. The images produced by the X-rays are transmitted to a computer or digital screen. There are some great advantages that digital radiography has brought to the world of medical imaging. First, elimination of chemical processing films saves time and money. Second, reduced space requirements for storage of images make it more convenient to find old images. Instead of searching through cabinets full of hundreds of small disks, the images can easily be saved on a computer for convenient retrieval. Third, the ability to apply digital image processing to optimize quality and visibility of conditions makes it easier to clear up a bad film taken. With current cutting edge programs, doctors can zoom in and magnify x-rays with the click of a button to more carefully analyze them. Finally, rapid transmissions of images to other locations allow the x-ray to be viewed by one’s colleagues, which makes it convenient for someone who needs a second opinion on something. Also, if a patient moves to another location, the films that have been taken can be sent to that new location within seconds, without having the patient to come in and get them (9-IAEA).

Fluoroscopy works under the same conditions as an x-ray, but the only difference is that fluoroscopy is basically an image intensifier, allowing x-rays to be viewed on a live screen kind of like watching television (12-Reddingier). Fluoroscopy is a live x-ray technique that makes it useful for guiding a variety of diagnostics and being able to explain and actually show the patient what is going on. The ability for a fluoroscopy to function works just like flipping through multiple still pictures making it appear as if there is motion. In a fluoroscopy, pictures are taken at a rate of 25-30 complete images per-second. When images appear that fast, it becomes too fast for the human eye to detect separate stills, making it appear as if those 25-30 still images are in motion. While the exposure of a fluoroscopic image is much smaller than exposure of an x-ray or radiography image, exposure time still needs to be taken into consideration. With fluoroscopic imaging, the x-ray beam is continually being waved over the patient in different areas of the body. An x-ray beam shouldn’t be focused in one spot for an extensive period of time, because the area most exposed results in the highest absorbed dose of radiation in the skin and the underlying organs. This is a primary concern for fluoroscopy for a few reasons. One being that the body is made up of different densities. For example, the amount of x-ray to penetrate the breast is much lower than the x-ray needed to penetrate the thigh. So, precautionary measures should be used when dealing with a highly impacted area, and the amount of radiation that a specific area is being exposed to. High exposure to radiation will cause several types of cancer if there is a high dosage for a long period of time being absorbed by the skin and organs. When using any type of x-ray, positioning the x-ray carefully, shielding the patient with a lead sleeve or vest, and limiting the amount of exposure and intensity of the x-ray is required. With the invention of intensifier tubes and digital flat panel receptors, it became possible to balance the amount of patient exposure along with the clarity of the image. Non-intensified fluoroscopy with
just a fluorescent screen should not be used because of the great amount of time a patient is needed to be exposed for a clear image to appear (9-IAEA).

**Computed Tomography & Positron Emission Tomography:**

Computed tomography (CT) uses the same technology as an x-ray, except a CT breaks apart a three-dimensional image and reproduces it onto a two-dimensional screen. This type of mathematical technique is called reconstruction and is done by a 360° rotation of an x-ray tube around an object. A CT shows slices of the body and varies the thickness of the densities on the two-dimensional screen. It is similar to looking at a map of a mountain with different elevations. The map is flat, but the different colors represent different levels of elevation, or in this case, different densities. To obtain a slice, an x-ray source rotates around the body, while an x-ray detection source rotates opposite the source, on the opposite side of the body. The computer analyzes the number and density of the transmitted x-rays, calculates the coordinates, and assigns a gray scale to individual picture elements that will make the final two-dimensional image appear (11-Bensler, 12-Reddinger).

CT imaging systems are primarily made up of two things: the gantry, which is a cylindrical scanner assembly used so body tissues can be detected for three-dimensional imaging (looks similar to an MRI setup), and the patient table. "The gantry contains x-ray tube including collimators and filters, detectors, data acquisition systems (DAS), rotational components including slip ring systems and all associated electronics such as gantry angulation motors and positioning laser lights. In older CT systems a small generator supplied the power for the x-ray tube and rotational components via cable operation. This type of generator was mounted on the rotational component of the CT system and rotated with the x-ray tube. Some generators remain mounted inside the gantry wall. Some newer scanner designs utilize a generator that is located outside the gantry. Slip ring technology eliminated the need for cables and allows continuous rotation of the gantry components. The inclusion of the slip ring technology into a CT system allows for continuous scanning without interference of cables"(12-Reddinger). It is important to understand the advancements made with the gantry, because before with the generators mounted on the inside, the noise was very loud for the patient, and the cable would cause an interference, meaning longer exposure of x-rays to the patient. The invention of the spiral/helical CT allows for a continuous scan to occur while the patient moves through the gantry only being exposed for approximately 30 to 40 second period.

One of the most important features of a CT machine is that a CT x-ray tube possesses the capability to withstand a lot of heat, which is crucial to the tube life of the machine. The tube must be designed so it can take on high levels of heat generated by the high speed rotation of the anode and the bombardment of electrons upon the anode surface. CT machines will not operate, however, if the maximum heat capacity is reached. The machine will shut down and resume again when the temperature has cooled enough to start up again. This is similar to a radiator on a car (once the heat capacity is reached, it must sit until cooled). A car’s radiator and cooling system are also similar to the functioning of a CT machine. The CT utilizes a combination of oil and air cooling systems to eliminate heat and maintain operational capacity. Also, a CT has a large diameter for the anode plate, which also increases the ability for the anode to take on a lot of heat because there is more area for the heat to dissipate. Most CT machines have more than one focal spot. The smaller the focal spot, the greater the detail, but also the greater the heat. CT machines utilize a bigger filament than most x-ray machines which increases the focal spot. Decreasing the anode angle decreases the size of the effective focal spot. The
average angle for an x-ray anode is 12 and 17 degrees, and a CT anode angle is 7 and 10 degrees. However, CT can afford to use smaller angles and decrease the resolution because with the computer system used to analyze the image, mathematical algorithms are applied to sharpen up the images and make a blurry image clear (12-Reddinger).

To begin the process of a CT, the technologist first selects the setting of thickness that is desired. When this is done, the collimator located on the inside of the x-ray tube is adjusted by either widening or narrowing the beam. Tube filtration and filters are then used to shape the beam intensity by filtering out low energy photons that contribute to the production of scatter. The more fine tuned the beam is, the more accurate the numbers will be for the scan anatomical region. The CT process relies on collecting accurate data and converting it to electrical signal for the computer to pick up and reconstruct. So, to help with that, CT machines are equipped with detectors. A detector is an ionizing gas that when hit by an x-ray, produces light or electrical energy. The two main types of detectors used in CT are, scintillation and xenon gas detectors. The scintillation detectors utilize a crystal that fluoresces when hit by an x-ray photon, which produces light energy. To be able to convert that light energy into analog energy, a photodiode is attached to the scintillation portion of the detector, allowing the computer to pick up the signal. The way xenon gas detectors work is that the ionized tungsten plates are submerged in xenon gas, and the ionization of ions produces an electrical current and that current is picked up as a signal. If the xenon gas detectors are not positioned properly, there is a chance that there will be an inaccurate reading of the signal because the photons may miss the chamber. The detectors read each ray and measure the resultant beam attenuation or ray sum. A set of ray sums is referred as a projection. The DAS system generates and amplifies the analog signal, and coverts the projection totals into digital information. The digital signal is transmitted to an array processor where it takes a multitude of information and arranges it, much like when organizing playing cards to be in order and facing the same direction. The processor then computes the information to convert what once was a three-dimensional image, onto a screen where it is then seen as a two-dimensional image (12-Reddinger). Advancements are being made right now that will enable the image to appear three dimensional allowing a person to walk around the screen and view the entire image as if it were touchable. This will give greater insight as to what is going on with the whole portion of the patient as well as making it simpler to diagnose and analyze (14-Forrest)

CT scans can be used from head to toe including; head (trauma), paranasal sinuses, neck, facial bones, chest, abdomen, pelvis, knee (fractures not cartilage), and calcaneus fracture. A CT cannot distinguish soft tissues or cartilages like an MRI can, so when looking at any kind of joint a CT is looking for the fractures. CT is still the first imaging study to be made before an MRI unless the problem is already known to be a soft tissue. CT also remains the favorite because it is quicker and is less expensive for the patient. Compared to radiography, it allows images to be looked at with fewer overlapping images. However, since every slice does have its own thickness, it may be easy to become fooled when analyzing the data, making it much harder to read than a basic x-ray (11-Bensler).

Positron emission tomography (PET) utilizes most of the same principles as computed tomography, so reiteration is not necessary. The difference, however, between CT and PET is that PET uses one of the most cutting edge and advanced technologies in nuclear medicine. This technology is the use of injecting nuclear medicine into the patient, and having a specified camera called a tracer, tracks the medicine throughout the body. The medicine that is injected into the patient is a radioactive material, and when tracked in the body, it is able to make an
image similar to a CT. PET involves imaging of the metabolic activity of cells within the body. Cancer cells have a much greater metabolic activity than a normal cell does, so a PET is what is able to determine a cancerous cell from a normal cell. The medicine gives off tiny positively charged particles which may be recorded by the camera. A PET shows as much detail as a CT or MRI, but the camera only shows the regions where the medicine is. To be able to derive more complete picture as to what may be the problem, the additional use of a CT scan can be useful. CT and MRI scans show the structure of the body, and PET shows the function of the body. PET scans are mainly used to study metabolic activity and nervous system some common diseases that a PET scan may find are; Alzheimer’s disease, Parkinson’s disease, multiple sclerosis, transient ischemic attack, amyotrophic lateral sclerosis, stroke and schizophrenia. PET scans also find some cancer, especially lymphoma, or cancers of the breast, brain, lung, colon, and prostate. PET is a good way to identify cancer in its early stages. A CT will be able to detect it in its later stages after the cancer has grown and matured. There a many other different types of diseases that PET scans are able to find and with the advancement of nuclear medicine more diseases may be able to be stopped with early diagnosis and treatment.

**Magnetic Resonance Imaging:**

Magnetic Resonance Imaging (MRI) is one of the biggest advances made in today’s world of medical imaging. MRI was first known as nuclear magnetic (NMR), but the name quickly changed because of the word “nuclear”. When thinking or hearing the word nuclear, the thought of radioactivity comes into mind. However, MRI is the one type of medical imaging that uses no radioactivity what so ever. MRI is actually the safest form of medical imaging because there is no radiation. The only hazard to an MRI would be that it may cause claustrophobia when being put through the small cylindrical magnetic tube. Since MRI is the safest form of medical imaging, the question may be why is it not used to treat everything. The answer to that is because MRI only gives a close look at tissue, ligaments, muscle, and cartilage. Also MRI is the most expensive form of medical imaging. Utilizing an MRI will typically only occur when the results are not clear or not obtained from a radiography or tomography scans. The difference between MRI and radiography is in the name of MRI; “magnetic resonance” this means that magnetism is used to align the spinning protons within a magnetic field. The human body is made up of approximately 70% water mass, and a water molecule is made up of two hydrogens for every one oxygen. An organic chemist knows that hydrogens are the most abundant type of molecule, and a hydrogen molecule in organic chemistry is also known as a proton, which is what gets aligned in a magnetic field (5-Wade).

The most commonly used type of magnet used for an MRI machine is one that obeys Faraday’s law of induction. This, in simple terms, is when a magnet is moved through a coil of wire and a current is created. The more turns in the coil, and the faster the magnet moves through the coil, the greater the horizontal magnetic field. A normal MRI machine operates on the scale of 1.5 Tesla (Tesla is the measurement of a magnetic field). More advanced machines can operate on the scale of 3 Tesla, and a scale of 7 Tesla is being experimented with (6-Reddinger). To put into perspective how big 1.5 Tesla really is, it is compared to the magnetic field of the Earth which is only 0.5 Tesla. So, MRI machines are 3 times of what the Earth’s magnetic field is. Having a magnetic force this big allows the protons of the human body to be aligned with little resistance. Since a proton is spinning among its axis when it is placed in a magnetic field, it may take two different positions in the field. It will align in a parallel or anti-parallel direction to the magnetic field, and more protons will align in the parallel direction rather than the anti-
parallel. Protons in the parallel direction are in a low-energy state and protons in anti-parallel are in a high-energy state. The differences between the high-energy and low-energy states represent the strength of the external magnetic field. The higher the magnetic field, the better the alignment is with the low-energy proton. High-energy protons are considered the spin excess (7-Faulkner) and "the magnetic moments of these excess spins add to form the net magnetization." This allows the tissue placed in the magnetic field to become magnetized and the greater the magnetic field, the larger the spin excess is" (7-Faulkner). Having a larger number of spin excess is crucial to MRI because those excess protons are what get computed and reconstructed to form the multi-layers illustrated on an MRI scan. Once the tissue becomes magnetized it will posses either a low or high-energy state, which is known as thermal equilibrium. In the equilibrium, the individual spins are not in phase with one another. This is much like watching television where it is apparent that the individual on the television is talking, but the words that are being said are not matching up with movement of the individual’s mouth, indicating that the sound is not in phase with the picture. In order to get a clear reading for the computer to reconstruct the images, these individual spins need to be put into phase. To do this, the oscillating magnetic field frequency is adjusted to match the precessional frequency of the magnetized protons. When this happens, the nuclei between the two spin states will flip. When the flipping occurs, there is a net absorption of energy which is then picked up electronically by a special computer. This allows the computer to reconstruct the three-dimensional figure onto a two-dimensional screen. The screen image then appears to be a slice of the original figure and the different tissue densities are represented by different colors. A major advantage of the MRI is that it can produce images in all planes, and used with contrast, this can reduce the risk of not noticing a small abnormality.

Mammography, Ultrasounds & Thermography:

Mammography, ultrasounds and thermography technology are the least advanced use of medical imaging, but are all important enough to deserve recognition. Thermograph technology was the first type of technology used that helped lead to the development of mammography. A thermograph relates and operates much like night vision. It absorbs the surrounding radiation of an object and illuminates the different shades of radiation of that object, and the amount of radiation emitted by an object increases with the temperature (6-Reddinger).

Mammography is a very important type of medical imaging machine that helps spot one of the most deadliest cancers out there, breast cancer. Breast cancer is one of the most common types of cancer, it is found in one of every ten women. Mammography’s main use is to spot breast cancer and has become the most popular tool when treating women in health screenings. Studies have been completed that show mammography can help increase the life span of women who are diagnosed with breast cancer (8-Creighton University). Mammography is operated the same way an x-ray is, except with mammography, the intensity of the x-ray being used is substantially less. The tissues of the breast are much less dense than the density of bone, so in order to penetrate the breast tissue, much less of the actual x-rays are needed. If mammography was completed with the same amount of an actual x-ray, then on the x-ray screen it would appear as a dark grey or even black color, making it hard to spot the cancer. The hazards of radiation for mammography are much less than radiography and tomography. The amount of radiation exposure a woman receives from having an annual mammogram is less than the amount they are exposed to from the radiation being emitted from the sun.

Ultrasounds are the safest type of medical imaging modality because it does not use radiation or a magnetic field. It is a useful type of medical imaging for women, mainly used for
those who are pregnant, but is also used to find cysts. Ultrasounds are basically Doppler sonar, which at one point was used by waving a wand over the patient and picking up static. Now ultrasounds have evolved to where there is a live feed as to what is going on within the patient (6-Reddinger). The way an ultrasound operates is that the ultrasound transducer, which is the small electronic device that picks up frequencies, is placed on the patient to pick up the frequency that is traveling within the tissues of the body. A typical frequency level for a diagnostic check operates between 3.5 and 10 million hertz. The frequency that is picked up by the transducer is done in an instant, the returning echoes recorded by the device is transmitted to a screen where they are converted to a gray scale for creation of an ultrasound image (11-Bensler). Ultrasound along with tomography scanning are key parts to the development of the new technique of photo acoustic tomography which in essence will shorten up the time it takes to diagnose a patient. This photacoustic tomography uses the same principles as a CT and ultrasound by reading the pulses of the tissue given off when a laser is shone onto the tissue. This will hopefully someday help determine whether tumors are malignant or not (13-Economist).

Conclusion:

The basic science concepts and understanding of how medical imaging operates is understood through the history of scientific discoveries and the continued advancement in physics. The beginning of all medical imaging began with the discovery of the x-ray. The x-ray was discovered through the hard work of many physicists by applying the rules and laws of physics. With the application of physics, x-rays were able to progress from long harmful treatments, to faster and much safer ones. X-rays went from being single scans of an object to multiple scans of a single object making it possible to more quickly and accurately treat patients. Through more discoveries in physics and the creation of the CT, MRI, and PET, more refined images of the body could be seen. The CT offers slices of X-ray images and produces high quality images to diagnose fractures and broken bones. The MRI offers a less clear picture of bones, but a better image of soft tissue, with no radiation, through magnetic field emissions and radio waves. It is used to analyze the body’s organs and diagnose cancer, blocked blood vessels, tumors, and a multitude of other medical problems. The PET is able to read chemical and metabolic changes in the body, with increased activity analyzed to be cancerous. Ultrasounds and mammograms are most commonly used to observe different stages of pregnancy and diagnose breast cancer respectively. Medical imaging machines have contributed to many saved lives through the early diagnosis of many diseases, and the ability of physicians to accurately identify where fractures and broken bones are so they can be treated. Without the relentless experimentation and ideas developed through physics, the medical imaging machines used in modern medicine would not be available.
Reference List


Birth Control:

An Analysis of Hormonal and Emergency Contraceptives

Vanessa Breguez

April 23, 2010
Abstract

The right to practice birth control is a relatively new right but the knowledge of various methods has been discussed throughout hundreds of years, with a peak in advancement in the last 70 years. The newest methods of birth control include lower dosages of hormonal contraceptives delivered through different courses such as a transdermal patch and a vaginal ring. Another innovative method in pregnancy prevention is the development of emergency contraception, which is discussed in comparison to the other methods of hormonal contraception while examining the public right to this optional safety.

Introduction

Planned Parenthood defines birth control as any method of preventing pregnancy and planning the time of pregnancy.\(^1\) Birth control has come a long way over the years. The first and only method of birth control used was condoms made of animal skin in the 16\(^{th}\) century. It was not until 1844 that rubber was patented and condoms were produced.\(^2\) However, history was not always accepting of controlling birth. In 1873, Congress made it illegal to send and share information about contraceptives through the mail. The law was named the Comstock Act, named after its main advocate Anthony Comstock. Over 20 states passed similar laws, some as strict as prohibiting any drug or instrument from being used as birth control with a fine or imprisonment as punishment for breaking this law.\(^2\)

Today there are over 15 known methods of birth control. Within these 15 methods many varieties are available, such as different types of hormonal pills. Hormonal contraceptives are among the most popular methods of birth control and are regulated by a doctor through prescriptions.\(^1\) One of the newer methods of hormonal birth prevention, emergency contraceptives, also known as the morning after pill, has recently become available to the public without a prescription.\(^3\) The purpose of this report is to analyze the history of birth control, the three most effective hormonal methods available to women today, and compare aspects of these methods with the morning after pill while discussing its open availability to the public.

Background

The use of sponges as a method of pregnancy prevention has been traced to roots in early Egyptian civilizations. These ancient sponges were made of various materials, and they were sometimes drenched in lemon juice or vinegar to act as a spermicide. The sponges used today are synthetic and multiple chemical spermicides are now available.\(^2\)

Condoms are another type of physical barrier that has been used for hundreds of years as a method of birth control. They are reported being used as early as ancient Egyptian civilizations, but they are known to have been used as protection against syphilis in the 16\(^{th}\) century. These early condoms were made of animal intestine and skin, such as chickens or goats.\(^2\) It was not until 1844 that rubber was used to mass produce condoms.

Although by the 19\(^{th}\) century, methods of birth control became more refined, many countries, including the United States, were against these “obscenities” and banned the distribution of birth control.\(^2\) However, against strong oppositions, Scottish-born Dr. Marie Stopes studied
and helped better the world of contraceptives. In 1918 she wrote a guide to birth control called *Wise Parenthood*, and in 1921 opened one of the first birth control clinics in Holloway, London.2

The battle for birth control also continued in the United States. Here, Margaret Sanger watched her mother slowly die after 18 pregnancies and 11 live births. Sanger published a series of articles in her own newspaper *The Woman Rebel* with information about contraception for women.2 However, her actions were challenging the law. The Comstock Act had been passed in 1873 which aimed to stop trade in "obscene literature" and immoral articles, also targeting the exchange of information of birth control devices, sexually transmitted diseases, human sexuality and abortion.4 Sanger continued to challenge this law by opening up the first birth control clinic in America in 1921. However, it was not until 1965 that the Supreme Court repealed the Comstock Law and declared the use of contraceptives as a constitutional right to women and couples.4

The U.S. Food and Drug Administration (FDA) approved Enovid as a treatment for menstrual disorders or infertility. However, this drug was also formulated for birth control, but at the time methods of contraception were still illegal. In 1960 the FDA approved this same formula as the first oral contraceptive. Enovid contained 9.85 milligrams of a progestational hormone and 150 micrograms of an estrogentic hormone, about ten times the amount of progestin and four times the estrogen contained in today's pills.5 This pill worked well as a contraceptive but many users experienced side effects such as nausea, irregular menstrual bleeding and weight gain among others.5 All the trouble that seemed to accompany this pill allowed room for further research.

In 1976 the FDA approved another method of birth control: intrauterine devices (IUDs).2 Many devices were developed and sold between 1964 and 1990. Although IUDs are among one of the most effective methods of birth control,1 the high risk of pelvic inflammation keeps it from being a popular method of contraceptive.2 In 1992, Depo-Provera, the first hormone shot to prevent pregnancy was approved by the FDA. The female condom was also approved for sale during the 1990s.2 The most advancement in birth control, however, has been made between 2000 and 2008, where a hormonal patch became available, as well as a hormonal ring, monthly hormonal injections, and the emergency contraceptive.

**Hormonal Contraceptives**

**Oral Contraceptives**

Oral contraceptives (OCs), also called the "pill," is a method of birth control that utilizes synthetic derivatives of the female hormones, progesterone and estrogen, to prevent ovulation thus preventing pregnancy.1 The two synthetic hormones in OCs deceive the body into thinking it's pregnant, and a high level of progesterone is maintained inhibiting the production of eggs and preventing ovulation.6
Figure 16 - Progesterone and Estrogen, the two female sex hormones that are synthesized and used in OCs for pregnancy prevention.

Today more than 100 million women use OCs. The next most popular methods of birth control are sterilization and IUDs worldwide among married women. For sexually active unmarried women, OCs are the most popular.5

There are two types of oral contraceptives: combined OCs, which contain both synthetic estrogen and progestin (synthetic progesterone) and progestin-only pills.1 Combined OCs (COCs) are the most popular and shown to be the most effective.5

Progesterin-only pills are highly effective for women that are breastfeeding, but outside of this context, they are less effective than COCs; this type of OC has never become widely used. While COCs are usually taken consecutively for 21 days, with a seven day hormone-free interval,6 progestin-only pills are taken continuously with no hormone-free interval between cycles.5

When taken perfectly (not missing pills and following exact instructions), only one in every 1,000 women become pregnant in the first year of use; COCs offer highly effective contraception when taken correctly.5 However, there are several other benefits offered by the used of OCs besides its efficacy in pregnancy prevention.5 OCs also prevents ectopic pregnancy (pregnancy outside of the uterus) which can be very dangerous and life-threatening. This form of contraceptives also aid in preventing iron deficiency or anemia, because of the lighter periods. OCs also provide more regular menstrual cycles, less premenstrual symptoms and dysmenorrheal (pelvic pain during menstruation, which is often accompanied by nausea, vomiting, and diarrhea).5

Some studies have found that endometrial cancer (cancer of the lining of the uterus) and epithelial ovarian cancer are about half as common among OC users as among other women. It is thought that OCs help protect against these cancers by "reducing the rate of cell division in the endometrial lining and the ovaries."2 Other possible health benefits include lowering the risk of loss of bone density (helping prevent osteoporosis), ovarian cysts, benign breast disease and colorectal cancer.5

Today’s COCs contain less than 50 micrograms of estrogen (reduced from 150 micrograms in the first COC). The most popular dosage of estrogen is 30 or 35 micrograms of ethinyl estradiol.5
Progestin doses have also dropped. For example, doses of norethindrone, a popularly used progestin, have dropped from about 10mg to 1.0 or 0.5mg. The reason for such variation in progestin doses is the variation in potency by weight. Also, some types of progestins are more potent than others. The more potent progestins which include levonorgestrel, desogestrel and destodene are used in smaller doses. The different progestins also have different physiological effects on the user, and may interact differently with estrogens. These interactions may modify the effects or both hormones, so it is with careful research these hormones are placed together.

A Serious Health Risk

Although there are several benefits to the usage of hormonal contraceptives, there is one major risk factor associated with continuous use. A study was conducted by the Nurses’ Health Study that assessed the risk of myocardial infarction (MI) and OC in middle aged women (ages 30-55 years). Among past users of contraceptives, no increased risk was found for cardiovascular disease when compared with those who had never used OCs. There was also no association found between the duration of use and cardiovascular diseases; women who had used OCs for over 10 years had the same amount of risk. However, among current OC uses, there was a 2.5 relative increased risk of unfavorable cardiovascular events, including MIs, strokes and cardiovascular death. This difference in risks are believed to be true because of an effect on blood coagulation in a blood vessel (thrombosis), especially since 7 out of 10 of the adverse cardiovascular events occurred in current cigarette smokers.

In testing, when OCs were stopped, the associated risk for cardiovascular events was declined, suggesting reversal of the clotting effect. Multiple other studies using different combinations of progestins and estrogens have shown both a significant and insignificant increase in cardiovascular risks. However, this is indeed a serious risk that must be considered when taking hormonal contraceptives, especially for women over 30 who smoke.
**Figure 4** - Brief Summary of Hormonal Contraceptive Prescribing Guidelines for Women With Elevated Cardiovascular Risk

**The Patch**

A major problem with COCs is women’s difficulty using them consistently and thus effectively. An estimated 2 million unintended pregnancies reflect this problem.

Because of this, a transdermal contraceptive patch was created to deliver the same efficacy as COCs with an improvement in consistency. Clinical studies have found that the patch is comparable in efficacy and cycle control to COCs. It is also shown that women that have switched to the patch are more likely to be adherent.

While the pill is ingested, the patch is a plastic patch that adheres to the skin and delivers hormones through the skin. The patch is applied once a week for three weeks, followed by a patch-free week, aiding to increase in compliance. However, although patch users are more consistent, side effects such as breast tenderness, nausea, headaches and mood changes are reported more often than in women using the pill.

The patch, also known as ORTHO EVRA®-EVRA, its brand name, contains 20 micrograms of the synthetic estrogen ethinyl estradiol (EE) and 150 micrograms of the progestin norelgestromin.

**Contraceptive Vaginal Ring**

Contraceptive vaginal rings (CVR) are another method of hormonal contraception. This is a relatively new method of birth control and only one type of CVR is currently available in the United States; NuvaRing© was developed by Organon and it releases 120 micrograms of etonogestrel (ENG) a day and 15 micrograms of EE per day.

The method of which CVRs deliver these hormones is very unique. The CVR is inserted for three weeks and removed for a week of the month, and each month required a new ring. The steroids are dispersed through the core of the ring homogeneously directly into the blood stream. This method does allow lower doses of steroid due to its immediate entering into the
blood. The lower dose of EE present in NuvaRing has actually shown to reduce “the effects of this synthetic estrogen on the metabolic markers of cardiovascular risk.”

Another advantage to CVRs is the lack of daily attention needed, increasing adhesion and efficacy. However, it can still be difficult for some women to remember when they have to replace the ring or when they are exposed to failure. When used properly, the ring has the same pregnancy rate as COCs.

**Emergency Contraceptives**

**Background**

Emergency contraception (EC) is used after birth control failure or unprotected sexual intercourse to prevent pregnancy. ECs are different than most birth control in that it is used after intercourse instead of prior to the act. ECs are also known as the “morning-after pill” because they have to be administered within 72 hours of such intercourse but the sooner, the better. A woman’s changes of becoming pregnant become higher if the intercourse occurs a few days before or after ovulation. A second dose is taken 12 hours after the first dose for an increase in efficacy; this is known as the Yuzpe regimen. Another option for EC regimen is to take 1.5mg of only levonorgestrel as a single dose.

**ECs vs. Other Hormonal Contraceptives**

ECs contain high doses of the same hormones that are in regular birth control pills. Combined and progestin-only OCs containing the hormone levonorgestrel can be used for emergency contraceptives (ECs). These are not as effective as the regular use of OCs (change of pregnancy is reduced by 75%), but ECs are an option for birth control if there was lack of one during intercourse. Each of the two doses taken contains 100 micrograms of ethinyl estradiol and 0.5mg of levonorgestrel; the total regimen adds up to 200 micrograms of ethinyl estradiol and 1.0mg of levonorgestrel. With the single-dose regimen, 1.5mg of levonorgestrel is administered once, showing similar efficacy and no increase in side effects. Common side effects of ECs are similar to those of birth control pills; they include nausea, fatigue, menstrual changes and abdominal pain.

ECs are sometimes confused with mifepristone, (also known as RU-486 or “the abortion pill”). There is a visible similarity in chemical structure between RU-486, which serves to terminate a pregnancy, and progesterone and progestins. However, the functions of RU-486 and progestins are very different.
RU-486 is a competitive inhibitor of the progesterone receptors in the body; it is an antagonist of progesterone, therefore it is called an “antiprogestrin.” Progesterone is needed for both conception and pregnancy maintenance. This drug works to cease a pregnancy by being accepted by receptors in the female body instead of progesterone. At high doses, RU-486 causes the body to stop secreting natural progesterone completely, which then causes embryo termination. Emergency contraceptives do not serve to terminate pregnancy; ECs contain the same hormones as OCs, but in higher doses to prevent any implantation. RU-486 acts after implantation for termination. These two drugs are distinctively different in function.

Safety

As with any other method of hormonal birth control, blood clotting is also a risk associated with regular use of these contraceptives; ECs are not as effective as ongoing birth control and should not be used routinely instead of birth control.

Emergency contraceptives do not protect against tubal pregnancy as other hormonal methods of birth control do. If a woman who used an EC experiences severe abdominal pain, a health care physician should be contacted immediately because tubal pregnancy is a serious condition, and may be life threatening. However, as noted previously, the use of EC induces side effects as do regular birth control.

Although ECs deliver higher doses of synthetic hormones, it is safe for women to repeatedly use ECs if needed. To be exposed to the same amount of estrogen as a regular low-dose COC, a woman would have to use an EC approximately three times in one month.

Summary and Conclusion

Birth control has an extensive history of usage commencing at ancient Egyptian civilizations. The last 70 years, however, have been the more innovative years for methods of contraception. While in the 1960s methods of birth control were illegal, today multiple contraceptives are widely available to the public. Among the most popular methods of birth control are hormonal contraceptives: combined birth control pills, transdermal contraceptive patch, and contraceptive vaginal ring.

Each method of hormonal contraceptive offers advantages and drawbacks, most varying in adverse effects which are different per combination of hormones. Also, each hormonal
contraceptive is found to be equally efficient when used properly, but this efficacy is found to change due to a difference in ease of adherence with each method.

The main risk factor associated with hormonal contraceptives is the chance of blood clots which may assist in thrombosis and may lead to heart attacks or strokes. This risk increases for women over 35 years of age, especially those who smoke. Discontinuation of OCs will decrease these risks, and long-term use of this method of birth control does not increase risk of adverse cardiac events. However, different combinations of hormones and close health observance allow safe use of hormonal contraceptives, even among those who may have an increased risk, as can be seen in figure 3.8

Multiple studies have shown that women with access to ECs are most likely to use them when needed, working to reduce unintended pregnancies.12 Studies conducted in Europe, where the benefits and availability of ECs are wider than anywhere else in the world, has not shown to lead to an abandonment of other safer methods of birth control.12 It is also conclusive that ECs are not hazardous to women and therefore its use should not be prohibited.12

It is important to note that ECs are not “abortion pills.” ECs serve to prevent implantation, while termination pills serve to prevent progesterone production and terminate the currently implanted embryo. Although there are similarities in molecular structure between the abortion pill and some of the progestin used (even natural progesterone), the function of each drug is very different.

It is widely and scientifically known that no method of birth prevention is infallible. However, EC is an efficient backup whenever routine methods are not used or fail. Other methods of birth control, such as the continuous hormonal contraceptives discussed, should continue to be encouraged and likely will continue to be the most popular form for contraceptive, but ECs are currently the only category of contraception that can be used post-coitally.12

The greater availability of emergency contraceptives continues to expand women autonomy in their reproductive choices. The use of ECs has continuously been proven safe, effective in assisting pregnancy prevention after unprotected coital. This method of birth control, along with education of proper use, can help diminish the number of unplanned pregnancies in the United States, currently at 50 percent of all pregnancies.14 The information accompanying emergency contraceptives, however, should always be thorough and explain completely the correct usage, benefits, and risks involved with using this type or birth control to promote and insure proper usage behavior. Further education on emergency contraception could help decrease the amount of unplanned pregnancies. Diminishing these numbers could possibly assist in decreasing the number of abortions and could help control the fast growing population of today’s world.
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Abstract:

Myostatin, also known as GDF (Growth Differentiation Factor number 8) is a hidden TGF (transforming growth factor beta) beta group member that initiates muscle development and growth (1). There are many different TGF beta subtypes; one of these is the growth differentiation factor. GDF number 8 is called myostatin. Myostatin is the skeletal muscle protein that is associated in muscle production. Before we can understand the outcome and tampering effects of myostatin, we must understand TGF’s main functions is to operate apoptosis in various cell types.

TGF’s (transforming growth factors) operate in two different ways. One of the ways is through SMAD. SMAD’s are proteins that regulate the activity of TGF (1). Another way that TGF operates apoptosis is through DAXX. DAXX is also another protein that regulates TGF (2). Myostatin is mainly made on the skeletal muscles cells. It circulates around the blood and acts on the muscle tissue. It does this by attaching itself to a cell dependent protein molecule called the activin type 2 receptor. Activin type 2 receptors regulate signals on the ligands; these ligands belong to the transformation growth factor beta, which is a family of ligands (2). Activin type II receptors functions are mainly used to control the activin signaling in the Xenopus embryos, although the functions of this behavior is not fully understood (1). This family of ligands includes bone morphogenic proteins, Activin or inhibin, and Nodal. A bone morphogenic protein is a group of growth factors and cytokines. The functions of these proteins are to help the formation of bone, cartilage; they also help construct a group of pivotal morphogenetic signals, and help lead tissue development throughout the body. The gene encrypting myostatin was found around the year 1997 by genetic scientists Alexandra McPherron and Se-Jin Lee (3). This discovery lead to another discovery that a mutation in the myostatin gene is responsible for an increase of muscle mass, this is also known as “double muscling”. Mutations in this gene have found to have a significant increase in muscle size in humans. Scientists hope that further knowledge in the functions of this gene will be used to help treat certain diseases like that of muscular dystrophy, which ruins human muscles. However, other individuals such as athletes may use this knowledge in order to get unfair advantages.

When the scientists Alexandra McPherron and Se-Jin Lee first discovered the gene encrypting of Myostatin, they tested it. The test they incorporated was on mice. They produced a group of mutated mice that lacked the gene. These mice have developed larger muscles than the average mouse. In fact, the mutated mice had muscles about twice the size of average. When the myostatin gene was knocked out Se-Jin Lee commented that the mice “looked like Schwarzenegger mice” (3). These mice went on to be later named “mighty mice”. A few years after this test was concluded, the name mighty mouse went on to be a cartoon.

Here are pictures of the mice that lacked the gene of Myostatin.
The top two pictures that are shown above are of mice with average myostatin levels (4). The bottom two pictures shown above are of mice with lower than average myostatin levels. The picture above is a mouse with average myostatin level (4). The bottom picture shown above is of a mouse that is the myostatin knockout mouse in which there is no myostatin gene.

Myostatin deficiency can be naturally occurring as well. Myostatin mutation at birth can naturally occur as well. This can happen by a mutation of the myostatin gene. Gene mutation is a change in the DNA sequence of a gene. This change is permanent. Mutations can happen in large of small sizes. Mutations that can be large are chromosome mutations. An example of small mutations can be mutations of a single DNA building block, which is also known as the DNA base. Gene mutations can occur in two different ways. One way is that the gene mutation can be acquired from the parents of the species (5). The other way is that it can be acquired during the lifetime of the species (5). Some examples of this naturally occurring gene mutation have been noticed in two different types of cattle. The two different types of cattle are the Belgian Blue and the Piedmontese types. More than a century ago cattle livestock farmers in Asia observed that some of their cattle had more muscles than the others. In this discovery more and more of these super cattle were popping up, this was because the farmers were specifically breeding those cattle. They did this because the cattle were stronger and exhibited an increase of muscle mass more than their cattle peers. These cattle were a mystery to people until the scientists went on to conclude tests on them, later to find that they have lacked the myostatin gene (5). The lacking of the gene is a genetic mutation that occurred in the cattle. Here is a picture of the Belgian Blue bull with a mutated myostatin gene.
A Belgian Blue bull with a very low or no myostatin gene (4).

Here is another picture in which you can see the size of the animal compared to an average human male (4).

After the double muscled cattle and mighty mice experiment was concluded scientist noticed that the myostain gene had the same function in both species of animals. This discovery opened up new doors in futuristic opportunities to develop species that could be of assistance to humans in such jobs as farming and gardening. Myostatin also encourages the growth of skeletal muscles which was also a contributing factor to the doubled muscled mice and cattle. Skeletal muscles are a type of striated muscle tissue that are under the control of the somatic nervous system. Striated muscles are a type of muscles that are in the form of fibers which are combined into fibers that are parallel to each other. Skeletal muscles are one of the three major muscle types, along with the cardiac and smooth muscles. These muscles fibers are made from the fusion of growing myoblasts.

Here is a picture of a skeletal muscle system and muscle fibers that has normal levels of myostatin (5).

Seeing this picture of the normal muscle fiber will be essential to understanding the further tests constructed on myostatin. Scientists later experimented with myostain in reverse ways. They figured if lowering myostatin increases muscle diameters, then increases the myostatin level will
lower the diameter of muscles. A test was conducted by scientist Teresa A. Zimmers on the mice in the year 2002 (5). This test was to see what would happen if a myostatin was given to mice. Knowingly, their hypothesis was that the mice would lose muscle mass and therefore decrease in weight. The AgResearch Ruakure Animal Ethics Committee allowed the animals to be used for this study (5). The type of mouse use for this experiment was the Athymic nude mice. The Athymic nude mouse was the standard laboratory mouse. The Athymic mouse lacks the thymus gland. These mice also have no T-cells and therefore are useful in research because they do not refuse tumor or other cells transplanted from the mice. These mice were kept in a room with the constant room temperature of 20 – 22°C (68-71.6°F). Half the mice were females and half the mice were male. These mice were allowed to have a normal night and day schedule. The mice were also given sterile water and near-sterile food. All mice were property taken care of and treated according the rules and guidelines of SACF (Small Animal Containment Facility) and AgResearch Small Animal Colony Quarantine Manual. The experiment was named the vitro and in vivo of Myostatin-induced cachexia. Here are some samples from the experiment.

As seen under in Section A roman numeral I, II, III, and IV are the CHO (Chinese Hamster Ovary) cells’. In section B that is the diameter of the cells’ under different conditions. In section A Roman numeral I, the size of the cells’ are normal in diameter. In Section A Roman numeral II the cells’ have been recorded after twenty-four hours and, the size of the cells’ are slightly bigger in diameter because of they have been functioning for twenty-four hours before they were recorded. In section A Roman numeral III there was a 3 mille-liter substance added that included myostatin and after twenty-four hours the cells weight dropped because the diameter of cells’ reduced, as you can see from the picture above. In section A roman numeral IV, there was a 10 mille-liter substance added that included myostatin and the cells’ weight dropped even more. Also the cells diameter reduced even more than that of the 3 mille-liters. The CHO cells’ were obtained from a similar experiment done by scientist/doctor Se-Jin Lee (6). This experiment used the same mice and the same conditions for the mice. In this experiment conduct by Se-Jin Lee the mice were injected with cells that had myostatin injected into them. The cells were originally from other mice in the lab that were treated under the same conditions. Se-Jin Lee discovered something interesting during his studies of myostatin and the mice (6). The effect of
Myostatin would be speeded up if there was zinc present. This is only a condition that occurred in mice however. The myostatin could not just be directly injected into the mice. It had to be mixed with a solvent first. Four-to-seven week old mice were given the injection that was included with a myostatin-expressing CHO cell (6). After that four-to-six week old mice were given the injection of just the solvent alone used with mixing the myostatin in just to see if it only would cause changes in the mice. The injection was made at a depth of four millimeters into the right quadriceps femoris muscle of each mouse. Tumors developed at the site of the injection. Tumor sizes were not of any difference in size between all of them (5). Some of the mice were given tap water to drink, and some of the mice were given a sterile twenty-five millimeter solution of ZnSO₄ (Zinc Sulfate) (5). After that the body mass of each mouse was observed frequently. However, the mice that were given the water did not lose much body mass by the sixteen day so the experiment was continued. The experiment was continued till each mouse lost fifteen-twenty percent of their body mass. This occurred at about the thirty day mark with the mice that were given water.

![Graph](image)

The myostatin mice that were given the tap water (closed circles) lost weight slower than the mice that were drinking the zinc. Surprisingly, the myostatin mice that were given tap water until day ten, then zinc water lost weight even faster. These are the closed triangles on the graph. However, none of these mice survived past day fourteen because of severe rapid weight loss (8). The body mass of the mice that were injected with the solvent remained constant over the testing procedure. They are the closed squares. Also, the mice with closed circles were given just water along with the myostatin injection. The weight of these mice remained constant throughout the experiment. The less rapid weight loss in the mice given zinc rather than to mice switching to zinc from water may suggest that mice exposed to greater long durations of high doses of myostatin may somehow make up for the for the increased myostatin signals. So this proves that myostatin can act as a negative regulator of muscle growth (8). But now the question arises, how can myostatin be used for humans?

In 1999, just two years after the “might mice” test. A former professional sprinter gave birth to a baby born in Berlin, Germany. This baby had a mutated myostatin gene. Researchers did not want to release too much information and the family desires to remain private. At four years old the boy was able to hold weights approximately 10 pounds with his arms fully extended. Most adults have difficulties with half that weight. The boy is super muscular showing bulging biceps and calves. His muscle composition is twice as much as normal and his fat composition is about one-half that of normal. He is the ultimate baby, his family says.
An interesting fact, research that was done from the University of Maryland shows that myostatin effects muscle growth in females as well as males (9). The study was done on a group of men and women taking part in a weight lifting program for nine weeks. The muscle growth in the quadriceps (pair on muscles in the upper front of the thigh) was measured and recorded at the end of the study. The myostatin genotype did not seem to be the cause of various rates of muscle development between males and females. The increase of the muscle capacity in the thigh was about twice as much greater in the men than women (9). Although, when only the females were examined, the muscle development in those with fewer common myostatin genes was about seventy percent greater. Changes in the myostatin gene could explain why some people acquire weight from muscle faster than others (9). An example is the muscle fibers in world class bodybuilders, are no larger than in someone who has never picked up a weight in his/her life. Their muscles are bigger because they have much more than average to smaller size fibers. There is a substantiating amount of studies being done in laboratories to invent a drug that can block myostatin and allow development of muscle mass. Furthermore, an invention like this it would be a life saving one. This would help in any life threatening disease where dysfunctioning muscles and wasting is unessential, such as muscular dystrophy (MD). Muscular dystrophy is a disease in which progressive muscles weaken and degenerate, also known as the death of muscles. Some other diseases that it would help are severe muscle atrophy (muscle wasting) and long bed ridden illness. It would also help in long space flights in where the astronauts have trouble using and working out their muscles because of an absence of gravity. Even though these new myostatin blocking drugs are in the testing stage and some labs have conducted small tests studies on people with MD, they still need to pass a moderate amount of safety and ethical procedures to make sure that they are safe to sell. It is also unknown whether a long time on these drugs will be safe, and no other serious side effects will arise. In this scientific world, whenever such information comes out, one can expect some cunning mind to invent a product that will be a solution to the problem. Not surprisingly, a few marketing types have made a product, a ‘natural’ product that can supposedly copy those effects before the pharmaceutical labs can invent them, and also not have any problems or side effects with the product. For example, a replica of this is the myostatin inhibitor states that it has the ability to accomplish the goal of blocking myostatin. But before everyone should rush out and look at this product, note that if this was true shouldn’t this product be nominated or even win a Nobel prize in medicine? Tests done with this have shown that there is no evidence that the product has any effect on muscle growth at all (9). Dr. Mauro Di Pasquale is one of the most influential voices on diet performance and athletic training in the world. Dr. P was a world class athlete for over seventeen years and won world championships in powerlifting. He states “The myostatin products are total hoaxes and a waste of money. The only thing it has going for them is the advertising, which are smooth con jobs.” – Dr. Mauro Di Pasquale. In my opinion I believe that this myostatin should be in the same category as steroids. To me, myostatin and steroids are basically the same exact thing, except for myostatin does not have some of the grueling side effects of those of steroids. I think that the myostatin soon to be products should be used on essential needs only for those who need to lower their myostatin level to survive. I also believe that those who are born with the myostatin dysfunctions should not be able to participate in
professional sports because of their unfair advantage, even if their advantage was not their intention or not. In being an athlete myself, I would be outraged if I found out that I lost to an opponent who had an unfair, unnatural advantage over me. However I do see this being abused in the near future, kind of like that of steroids now. We need to find a way to detect whether an individual is using myostatin to their unfair advantage. I believe we can find a way to do this because we have found a way to do this with steroids. However, how there are some cover up drugs for steroids I believe that those types of cover up drugs will arise in myostatin as well. In this being said when people know how to treat myostatin dysfunction properly to achieve their goal, and are also on a healthy diet. Then more and more of these guys will show up.

A male with little to no myostatin gene (4).
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Accutane: Wonder Drug or Toxic Danger

By: Christian De Anda
Abstract

Accutane was researched and discussed in this paper. The history, controversies regarding the drug, drug synthesis, and biological mechanism of action, are thoroughly encompassed.

Introduction

With every passing day it seems like there is a new treatment to cure America's most hated disease: acne. Whether it is a new face wash, miracle cream or a skin care system such as Proactive, the sufferers with the most severe cases of acne are still not remedied with such products. Turning to the medical community for assistance, many of the afflicted are often prescribed 13-cis retinoic acid, otherwise known as Accutane. From its initial introduction in 1982, 13-cis retinoic acid was often hailed as a gift of science, but within the last 10 years it has been condemned as a scourge of humanity.

Conditions treated

According to the American Board of Dermatology, acne is described as "a common human skin disease, characterized by areas of skin with multiple inflammatory and non-inflammatory pustules." Acne is most prevalently dominant in adolescence, but the disease is known to follow many patients well into their forties. Although many of the causes of acne are under review, the Physicians Desk Reference lists the cause as "the direct result of sebaceous glands becoming clogged with sebum (a naturally occurring oil), and dead skin cells."
Beginning in the 1930s, doctors discovered that high dosages of vitamin A (retinoic acid) notably reduced sebum activity, therefore diminishing acne and decreasing skin turnover rates. This discovery was a direct result of western explorers experiencing the immense implications of eating polar bear liver which contains about 1 million IU of vitamin A per ounce (the RDA for adult humans is only 5000 IU). Consequently, many of the explorers who decided to snack on the bear liver experienced the dreadful "skin peeling" that often occurred after such a large dose.  

This finding not only revolutionized the way acne was treated, but laid the foundation for the development of one of the most controversial prescription medications, Isotretinoin.

**Drug creation and synthesis**

Building upon the discovery that high dosages of vitamin A significantly curtailed sebum production, Roche Pharmaceuticals developed the retinoic acid derivative known as Isotretinoin in 1982. Isotretinoin belongs to a class of drugs known as retinoids, which are chemical compounds related to Vitamin A. Retinoids play a vital role in vision, skin, fetal development, growth, bone metabolism, immune response, and the cellular formation of tissue. According to the book *Contemporary drug synthesis* by Dr. Jack Ji Lee, Isotretinoin is synthesized via the following mechanism:

Dr. Lee summarizes the synthesis in the following way: "Isotretinoin was synthesized via a Wittig Condensation. Phosphonium salt was prepared from direct treatment of vinyl beta-ionol with triphenylphosphonium bromide(Ph3P,HBr) in ethanol solution of cis-beta-formyl crotonic acid to produce Isotretinoin and 2-cis-4-cis-vitamin A acid in a 1:6 ratio."  

**Reasons for development**
Before the development of isotretinoin, a successive number of the afflicted patients found no end in their battle against acne. The majority of the treatments of the time consisted of antibiotics in conjunction with the consistent application of benzoyl peroxide or salicylic acid. In theory, both of the compounds work mutually to reduce the amount of bacteria on the skin, therefore reducing acne, but in application, the treatment is very cumbersome; not only do the effects of the treatment cease once it is discontinued, but the regimen initiates the propagation of antibiotic-resistant bacteria. The proposed therapy of antibiotics and acne inhibiting ointments often rendered a low success rate.

Following its 1982 introduction, the newly developed isotretinoin proved overall better at treating acne. Patients with previously untreatable acne were now being prescribed Accutane. Within the next five years, the drug was applauded as a marvel of medicine, as was demonstrated by its efficacious rate of 75%.

Biological mechanism of action

Accutane has been on the market for 25 years, and for that entire time Roche has specifically stated in the Physician's Desk Reference that the "exact mechanism of action of Accutane is unknown." Roche does not mention that Accutane is a systemic chemotherapy agent that reduces cellular proliferation of the sebaceous glands in the skin (which is why it's so effective against acne). To corroborate the previous statement, scientist James Crandall stated in a study, "These results support the idea that, by human telomerase reverse transcriptase targeting retinoids can induce telomere shortening and cell death and their integration in therapy protocols in cancer treatment must be considered." Human telomerase reverse transcriptase is what maintains the telomeres of eukaryotic chromosomes. In the quote above, it states that retinoids can induce telomere
shortening and cell death. This is how Accutane reduces adult stem cell proliferation in the bone marrow, and how it reduces cell division. The Accutane patient insert claims that “40% of the 13-cis-retinoic acid dosage metabolizes into the all-trans-retinoic acid”\(^6\) other wise known as chemotherapy drug Vesanoid. The pharmacology and toxicology of these two retinoids is similar enough to warrant comparison.

[Fig.4]\(^{11}\)

Research demonstrates that “all-trans retinoic acid down-regulates the human telomerase reverse transcriptase enzyme and, therefore, induces telomere shortening and cell death.”\(^5\) Essentially, both drugs share a similar mechanism of action. Furthermore, cells all over the body are replaced by means of cell division, and there is a limit on the number of times that they may successfully divide. This is known as the Hayflick Limit. Most cells in the body divide about 50 times before they stop dividing and die a natural death.\(^4\) The mechanism that controls this cell division lies within the telomere, which is a cap-like structure on the end of all the different twenty-three pairs of chromosomes. The telomere chain and its length can be thought of as a string of beads with one bead falling off the string each time a cell divides.

[Fig.5]\(^{12}\)

Therefore, the telomere shortens up a little bit every time a cell divides, and again this places a limit on the number of times a cell can replicate itself. Once these beads run out and disappear, the cell stops dividing and undergoes programmed cell death (apoptosis). The constant process of telomeres getting shorter eventually leads to the death of the cell and over time this cumulative cell death leads to one of the major components of the aging process\(^2\). However, the enzyme human telomerase reverse transcriptase acts to repair damage to the telomere, maintain its stability, and extend the length of the telomere beads, thereby overcoming the Hayflick Limit \(^4\). Germ line cells (bacteria) and cancerous
cells continually express telomerase in such ways that they never run out of
telomere beads and therefore remain dividing indefinitely. Telomerase is
naturally expressed more in cells in the body that are the most rapidly dividing,
because these cells undergo more cell division throughout a person's lifetime and
therefore need to have their string of beads repaired and relengthened more often.
In conclusion, Vesanoid and Accutane both cause telomere shortening of cells,
(essentially ceasing mitosis); therefore, it is highly likely that they will have the
same effect on our body's own rapidly dividing cells which is in theory, how
Accutane works to reduce acne.

**Potential Side effects**

Given the nature of the drug, Accutane is not without side effects. First
and foremost, the mitosis inhibiting effects of accutane make it a strong teratogen.
Since Accutane plays a direct role in the division of cellular tissue, forming
fetuses often times experience immense malformations that often require abortion
or at times end in miscarriage. Given the extensive implications, in August of
2005, the Food and Drug Administration introduced the iPLEDGE program. Its
intent is to prevent pregnancy amongst women taking the drug. It requires women
to administer two forms of birth control and submit two negative pregnancy tests
before the prescription can be filled. In addition, another well publicized side
effect of Accutane includes depression. Patients have reported depressive
symptoms while taking Accutane shortly after the drug became legal in 1982.
Whether the drug caused these depressive feelings remains a subject of intense
debate. There are, after all, millions of people taking the drug, and there are bound
to be people experiencing depression among them. Quite a few studies have been
conducted since the drug's introduction. These have included large population-
based studies performed in the United States, the UK, and Canada. The first of
these studies showed no conclusive evidence linking Accutane with depression or
suicide. As the studies mounted, the data continued to show no evidence of a
link. One study published in the New England Journal of Medicine found "431
cases of depression, suicidal ideation, suicide attempts, or suicide in U.S. patients
treated with isotretinoin," within a 10-year period. The article went on to note
that the numbers listed do not exceed the U.S. suicide rate. Then, in 2006,
depression-related behavior was shown in mice injected with the drug. While
animal studies often do not reflect human models, it was marginally intriguing.
But even more provocative was a large case study published in 2008 by
the Journal of Clinical Psychiatry, which was the first controlled study to find a
correlation between Accutane, suicide and depression, albeit relatively minor.

**Personal Opinion**

Since a certain percentage of 13-cis retinoic acid metabolizes into all-
trans retinoic acid and since the ATRA metabolite is how Accutane exerts its
pharmacological actions on the body, there is no doubt that if ATRA causes
telomere shortening then Accutane also causes telomere shortening. If telomere
shortening and down regulation of the telomerase enzyme does take place this could correlate to significant implications for maintaining adequate cell proliferation all over the body during a person’s lifetime. Accutane, being a potent mitosis inhibitor, attacks and damages the cells in the body that are supposed to remain dividing and proliferating for our entire lifetime. If cells have shorter telomere lengths, they get closer to the Hayflick Limit and cannot divide as much or they go on to experience growth arrest and cell death. This is how Accutane reduces acne, and why in some cases, the acne does not come back. Being a systemic chemotherapy agent, Accutane does not know the difference between cancer and the body’s own rapidly dividing cells. With the knowledge that many parts of the human body rely on rapid and plentiful cell division/proliferation to sustain their proper function throughout a person’s lifetime, this information about retinoic acid having a “chemotherapy like” cell division reducing effect becomes extremely important. In essence, if you take too much Accutane for too long of a period of time, you are essentially slowing down or stopping cell division in areas of your body where cells are supposed to remain dividing for your entire lifetime.

**Conclusion**

To conclude, we live in a culture in which not just youth, but beauty is worshipped. Often times, we emphasize the importance of outward appearance, while neglecting the potential internal dangers we cause to our bodies. As is the case with Accutane, mild to severe cases of acne will disappear, but at what cost? As with all medications, the perspective patient and prescribing doctor must weigh the possible side effects with the potential benefits. Nonetheless, patient history, mechanism of action and side effects are just some of the considerations that must be taken into account when administering Accutane.
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Nootropics: Better Memory Through Chemistry
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Abstract
The study of memory and what affects it is ongoing. The different aspects of memory will be summarized. An overview of brain neurochemistry will also be offered. Current research into compounds which assist in the enhancement and/or formation of memory, its usage, focus and protection against or reduction of disease processes will be summarized.

Memory
What is memory? The brain is, after all, the super-computer of the body. It controls, almost every major function from movement, speech, learning, memory, and the processing of all information. Learning utilizes both long and short-term memory. Motor skills are also based on memory, in that repeated neural synapses grow stronger connections. It would seem that everything we are is reduced to our ability to remember, process and utilize information.

Memory involves three major processes: sensory, short-term, and long-term memory. Sensory memory, information from the senses, is stored only as long as it takes the brain to register the information (between 1-4 seconds) and remains mostly unprocessed. Short-term memory contains information in current use. Information is held in short-term memory less than one minute if not rehearsed. Short-term memory is also called working memory, and divides information into three spheres for coding: acoustic, visual and semantic.

Long-term memory involves information remaining for longer than a few minutes. Encoding allows information retrieval, even after long periods of time. The capacity of long-term memory is apparently unlimited. While some scientists believe that neural pathways to information deteriorate over time if they are not used, others believe that everything stored is retrievable forever under the right circumstances. Information is classified by what is being remembered. Episodic memory is for events, semantic memory if for facts, and procedural memory is for skills, sometimes referred to as motor memory.  

![Multi-store model diagram](image)

The “three R’s” of memory are recollection, recall and recognition. Recollection is the type of remembering used in reconstructive memory, where pieces of memories are put together to form a new memory (such as an essay exam). Recall is slightly different, in that no part of the original memory is needed be provided in order to remember it (a fill-in-the-blank exam). The last, recognition, is being able to recall a memory from sensory stimuli involved in it. When it snows, one will recognize the need to wear a coat from recalling that the last time they went out in the same type of weather without one, they froze their butt off.

Neuroanatomy of Memory
There are several major areas of the brain which are involved in memory, from its encoding to recall. The hippocampus and amygdala, part of the limbic system, are related to memory formation and emotional response.

The hippocampus is a major part of the midbrain, and its memory functions include encoding information into long-term memory and topographical "spatial" memory. Spatial memory is important to the ability to find one's way and not get lost, to remember where things are and how to get to them. The hippocampus is among the first areas of the brain damaged in Alzheimer's disease,
leading to the characteristic memory problems and spatial disorientation. Extensive hippocampal damage leads to anterograde amnesia, the inability to form or retain new memories.\(^1\) In one study, temporary deactivation of either hippocampus or caudate nucleus with lidocaine "...affects expression of place and response learning ... indicates the hippocampus may interfere with the acquisition or execution of response strategy."\(^5\) The mammillary bodies, part of the hippocampus, are damaged in alcoholic encephalopathy. The damage is caused by thiamine deficiency. Thiamine deficiency is part of Wernicke-Korsakoff syndrome, which also includes symptoms such as impaired memory and anterograde amnesia.\(^8\)

While the amygdala functions to regulate drives, it is primarily involved with motivation, fear and avoidance conditioning. Many studies suggest the amygdala plays a critical role in emotionally based memory formation.\(^18\) "The amygdala mediates several neuromodulatory systems on memory, including the adrenergic, noradrenergic, cholinergic, opioid, peptidergic and GABAergic systems. Lesions impair acquisition and retention ... Animal investigations showed that β-adrenergic systems and amygdala activation enhance memory consolidation whereas β-adrenergic receptor antagonists block memory-enhancing effects of emotional arousal."\(^29\) The amygdala may also have a role in retrieval of emotional autobiographical information. Mori et al.\(^19\) reported that individuals with Alzheimer's disease were unable to retrieve episodic memories about an earthquake in their city when their amygdala was damaged.

**Neurotransmitters and Other Compounds**

Acetylcholine (often abbreviated ACh) can be called "the" neurotransmitter of motor memory. It functions in both peripheral and central nervous systems, being one of many in the autonomic nervous system and the only neurotransmitter used "in the motor division of the somatic nervous system."\(^31\)

The somatic nervous system processes both sensory and motor memory, except for reflex arcs. Motor neurons release ACh from the axon's terminal knob, which is received by nicotinic receptors; which, in turn, relay stimuli via the ventral root of the spinal cord. Stimuli finally proceed to the neuromuscular junctions of skeletal muscles.\(^31\)

Nicotinic systems in the brain have been experimentally shown over the last decade to play an important role in the cognitive functions of both humans and animals. These ACh receptors are important in the maintenance of optimal memory performance, and they contribute to a variety of disorders, including "addiction to nicotine, Alzheimer's disease, anxiety, autism, depression, epilepsy, Parkinson's disease, schizophrenia, and Tourette's syndrome."\(^2\) Nicotine and other nicotinic agonists improve working memory function in maze studies, and facilitates fear conditioning in the amygdala. It was found, paradoxically, that histamine reverses nicotine and ACh in passive avoidance.\(^2\)

Another major neurotransmitter, dopamine, mainly functions to affect motor response, behavior motivation, and reinforcement. It is well-known to be the pathway of addiction, cravings and pleasure centers of the brain. While these functions are important, they will not be addressed
here, except in that dopamine facilitates memory in the limbic centers already mentioned.

Gamma-aminobutyric acid (GABA) is the "major inhibitory neurotransmitter in both the central and peripheral nervous systems." [28] Consolidation theory assumes that memories are changeable for a short time after acquisition, but become more stable over time. GABA has been shown to have an important role in the consolidation phase (encoding into long-term memory), as well as its excitatory opposites, glutamate and noradrenaline. [28]

Glutamate's contribution in synaptic transmission, mental development and plasticity is "well-established." [27] Research has identified the roles of three specific glutamate receptors, AMPA, NMDA and metabotropic glutamate receptors (mGluR). NMDA receptors have been "overwhelmingly proven" [27] to be involved in actual memory encoding. AMPA receptor function is less clear-cut, but there is evidence that blocking them shuts down neuronal communication, which in turn effects learning and memory. The mGluR receptors have little to do with acquisition of new information, but "memory formation seems to require mGluRs through the modulation of consolidation and recall. Overall, mGluR functions seem variable and dependant on brain structure and the learning task." [25]

Forebrain cholinergic and GABAergic neurons can "directly impact mnemonic function of the hippocampus and other limbic structures". [14] These are functions that are sensitive to decline in aging (spatial learning, memory). As such, they become the logical targets for therapies which improve cognitive ability. Drugs able to enhance ACh (by either increasing ACh itself, or inhibiting it's opposite, acetylcholinesterase, AChE) will improve many different cognitive abilities. "Patients taking AChE inhibitors show increased hippocampal activity and improved performance on explicit memory tasks, demonstrating that these drugs offer clinical benefit. However, this therapeutic avenue in isolation has limitations, as the cognitive enhancing effects of AChE inhibitors in aged individuals are transient; after 3 years, patients with and without AChE inhibitor treatment are cognitively equivalent." [14] Drug therapies which target GABA may offer complementary treatment, specifically GABA (B). The most well-studied GABA (B) receptor antagonist, SGS742, improves performance in water mazes, spatial reference memory and avoidance tasks (hippocampus). In one study, improved memory was associated with decreased hippocampal CREB activity. "The clinical utility of this class of pharmaceuticals is further supported by the wide range of effective doses at which enhanced learning and memory is observed in young subjects and few side effects associated with efficacious doses." [14]

The final system to be mentioned here is the serotonin system. According to King et al., [13] the serotonin system is "implicated in the neurobiological control of learning and memory, both in healthy individuals and pathological disorders, although underlying mechanisms remain elusive." Important features include forebrain innervation, which is derived from fourteen clusters of neurons in the raphe nuclei, located in the brain stem. The function of the raphe nuclei are almost exclusively to produce serotonin. The functions of serotonin are numerous and appear to involve "control of appetite, sleep, memory and learning, temperature regulation, mood, behavior (including hallucinogenetic behavior), cardiovascular and endocrine function, muscle contraction, and depression." [4] The most important clusters in current research seem to include 5-HT1A, 5-HT4 and 5-HT6, all of which are numerous in brain regions associated with learning and memory. Serotonin is implicated in several mood and memory disorders. In addition, selective agonist and antagonistic compounds which bind to their receptor sites modulate similar neurotransmitters, among them GABA, glutamate, and ACh directly. [19] Past research has identified the function of 5-HT1A as being inhibitory in the hippocampus, pyramidal and granule cells, as well as inhibiting somatodendrite receptors. 5-HT4 is abundant in the hippocampus, cortex and striatum, and plays an
important role in controlling ACh release. 5-HT₆ exists in great numbers in the frontal cortex, hippocampus, amygdala, and striatum, where it competes with GABA and indirectly regulates many other neurotransmitters, including ACh, glutamate and dopamine.²

**Nootropics: What They Are and What They Do**

Mosby's Medical Dictionary ²¹ defines the word *nootropic* (no-oh-tropic) to mean "a chemical designed to increase brain metabolism; of, relating to, or promoting the enhancement of cognition and memory and the facilitation of learning: 'smart' drug." While there are dozens of supplements listed on the internet as nootropics, there are very few prescribable drugs. Those include Adderall and its derivatives, Ritalin and Concerta, which are amphetamines used to assist focus in ADHD; and Aricept, an Alzheimer's medication.

Aricept (donepezil HCl) works by inhibiting AChE, the enzyme that breaks down ACh. ACh is in short supply in subjects with Alzheimer's disease. It is FDA approved to treat Alzheimer's, but the drug's manufacturer, Eisai, states this compound is only effective for "mild to moderate" Alzheimer's. Even so, in clinical practice, once a patient is prescribed this medication, they usually take it for the rest of their lives. It's official class is "reversible AChE inhibitor". Donepezil is extensively metabolized to four major metabolites, two of which are active, and a number of minor unidentified metabolites. Donepezil is metabolized by "CYP 450 isoenzymes 2D6 and 3A4" and undergoes glucuronidation. Following administration of ¹⁴C-labeled donepezil, plasma radioactivity was present primarily as intact donepezil (53%) and as 6-O-desmethyldonepezil (11%), which has been reported to inhibit AChE to the same extent as donepezil in vitro and was found in plasma at
concentrations equal to about 20% of donepezil." [9]

Both Ritalin and Concerta are Methylphenidate, which is a Class II CNS stimulant. Both compounds are used to treat ADHD, in which poor impulse control leads to loss of attention and focus. Adderall XR, the most recent addition to this drug line, was patented by Shire Pharmaceuticals and FDA approved in 2001. The "exact mechanism of action has not been established. However, in animals, amphetamines facilitate the action of dopamine and norepi-nephrine by blocking reuptake from the synapse, inhibit the action of monoamine oxidase, and facilitate release of catecholamines." [27] Methylphenidate is a racemic mixture of the D- and L- isomers, with D- being the more biologically active of the pair. [27]

Choline bitartrate, a major precursor to ACh, is the only compound researched that is actually in widespread use today, although most people probably don't know they are taking it. It is an ingredient in both children's and adult's vitamins, along with being added to many energy drinks. Choline is considered to be a cofactor, one of the single most important set of components required to maintain fundamental processes throughout the body. Basic nervous system functions such as neurotransmitter synthesis and healthy cell-to-cell communication would not be possible without the presence of necessary vitamin, mineral and amino acid cofactors. Supplementing a balanced diet with choline has been clinically shown to support healthy nervous system function, healthy cognitive functions such as alertness, concentration, and memory, as well as normal physical performance. In addition, choline may be oxidized in the body to form a metabolite called betaine. Betaine is a source of methyl groups needed for methylation reactions. Methylation reactions convert homocysteine, associated with cardiovascular disease, to methionine in the body. [23]

There are many "supplemental" cognitive enhancers on the internet market today. Some of the main compounds in use today are listed on Table 1. The most well-known supplement, piracetam, is a derivative of GABA and is thought to have an important role in cognitive function. Compounds in research now include vinpocetine, and a myriad of other racetams. As yet, there are no FDA approved nootropic compounds, but there is plenty of monetary motivation to create one that works and get that approval.

Piracetam is very similar in molecular structure to the amino acid pyroglutamate. Piracetam and pyroglutamate have the same "base" chemical structure, the 2-oxo-pyrrolidine, but they differ by the side chain. Pyroglutamate is 2-oxo-pyrrolidine carboxylic acid, and piracetam is 2-oxo-pyrrolidine acetamide. Outside of the U.S., piracetam is used to treat alcoholism, stroke,
vertigo, dementia, sickle cell anemia, seizure, and dyslexia, in addition to its main use as a memory enhancer. One of the most intriguing effects of piracetam is that it promotes the flow of information between the right and left hemispheres of the brain. It is well-known that communication between the two sides of the brain is associated with creativity. This may also be the basis for piracetam's usefulness in the treatment of dyslexia. The effect of piracetam can be increased if taken with DMAE, choline, centrophenoxine, or hydergine. When choline and piracetam are taken together, synergism causes a greater improvement in memory than the sum of each when taken alone.  

Regarding mechanism of action, "no affinity for the alpha 1-, alpha 2-, beta-, muscarinic, 5-HT-, dopamine, adenosine-A1-, mu-opiate, GABA, benzodiazepine and glutamate receptors has been found. Increased turnover of different neurotransmitters has been observed, as well as inhibition of enzymes such as prolylendopeptidase. So far, no generally accepted mechanism of action has been found."[14]

Piracetam is a member of the drug class 'racetams', and they are AMPA receptor modulators. AMPA stands for "a-amin0-3-hydroxy-5-methyl-4-isoxazolepropionic acid" receptor, and mainly mediates glutamate and glutamate analogs throughout the brain. AMPA receptors are the most commonly found receptor in the nervous system, and are integral to plasticity and synaptic transmission. The brain is plastic; when damaged, new dendrites and axons form in order to bypass damage. One of the most thoroughly investigated forms of plasticity in the nervous system is known as long-term potentiation, or LTP. There are two components of LTP - glutamate release and postsynaptic depolarization. When LTP is induced with tetanus stimulation (100Hz for 1 second), there is a sustained excitatory response by neurons. "This response is very intriguing, because it is thought to be the physiological correlate for learning and memory in the cell."[32] In addition, AMPA receptors are composed of four types of subunits, for different dimers of glutamate. "Most AMPARs are heterotetrameric, consisting of symmetric 'dimer of dimers' of GluR2 and either GluR1, GluR3 or GluR4."[16]

Piracetam has also been shown to cross the blood-brain barrier and alter plasma membranes. Animal studies suggest piracetam may improve neuronal efficiency, improve neurotransmitter activity and combat age-related decrease in 5-HT receptors.[17] In sickle cell anemia, it "increases red cell deformability and normalizes aggregation of hyperactive platelets."[33] It has also been shown to have antithrombotic properties (reducing blood clots). "Interaction with membrane phospholipids restores membrane fluidity and could explain its efficacy in various disorders ranging from dementia and vertigo to myoclonus and stroke."[33] In addition, the Israel Ministry of Health, as recently as 2005, studied piracetam's ability to treat tardive dyskinesia in psychiatric patients. While they found it to be effective, a mechanism of action was not identified. Their 9-week double blind crossover study involved giving a 4.8 gram dose of piracetam or placebo to forty psychiatric patients with diagnosed tardive dyskinesia. After four weeks, the piracetam recipients had a "mean decrease of 8.7 points in tardive parkinsonism compared with 0.6 points on placebo."[15] In Switzerland, another study found that piracetam's effects on memory were abolished by adrenalectomy. This led the researchers to study whether steroids affect mechanism of action. They found that "activities mediated by aldosterone receptors might be involved... Blockage of aldosterone receptors, however, does not block effects of cholinomimetics on memory, indicating another mechanism of action."[20]

The adrenal glands produce corticotropin hormones, including steroids (hydrocortisone, cortisol, aldosterone), epinephrine and norepinephrine. The corticosteroids function to control metabolism and inflammatory response. Epinephrine controls "fight or flight" response, increases blood pressure and cardiac output, and converts glycogen to glucose for rapid metabolism.
requirements. Norepinephrine functions as both a neurotransmitter and affects blood pressure, mainly by vasoconstriction.\[10\]

There are also a few supplements that are real medications. Several are approved as nootropics in Europe and other countries, but not in the United States. Vasopressin, for instance, is regulated as an Advanced Cardiac Life Support medication for cardiac arrest. It has the same function as epinephrine, but lasts in the body six times as long. It is one of the most recent (within 5 years) additions to ACLS protocol, but is widely available as a memory enhancer in Europe. It is used to improve memory encoding and increase specific recall and memorization. Vasopressin is made by the posterior lobe of the pituitary gland, and normally functions to constricts blood vessels and reduces urine excretion, mainly during dehydration or stress.\[11\]

Vinpocetine increases circulation and brain metabolism, and can protect against hypoxia related neuron loss. In studies of older adults with dementia, vinpocetine produced "significantly more improvement than placebo in performance on global cognitive tests reflecting attention, memory and concentration."\[17\]

The Aging Brain

There is growing evidence that suggests at least three global changes in the brain that occur with age. Presumed neural benefits of nootropic agents may communicate needs to a population consumed with the neural and physical declines associated with normal aging and specific degeneration related to diseases like Alzheimer's.

First, neurons show several changes simply due to age. Age-related change includes the accumulation of lipofuscin ("wear and tear" pigment); loss of myelin, a fatty substance which surrounds axons, conducting electricity from one neuron to the next; and maybe most importantly, simple shrinkage of the neurons themselves. It may be significant that lipofuscin mainly deposits in the cerebral cortex, and myelin loss is "most notable" in the association areas of the brain, along with the limbic system.

Next, connections between neurons change, the older they become. Dendrites, which connect neurons to each other, reduce in number as the brain ages. This leads to an overall decrease in connections, because dendrite-axon connections are the hubs of neurotransmitter signal. Fewer hubs means less ability to move signals. ACh is one of the most heavily affected by this change, because it so actively involved in the cortex and limbic system.

Finally, it's not just the brain that changes with time. Age-related changes to the cardiovascular system create conditions of lower blood flow; less blood means fewer nutrients, like glucose and oxygen, on which the brain absolutely depends. This is the condition known as ischemia.\[17\]

Amino Acids & Supplements as Natural Nootropics

While there are many supplements available on the internet touted to "improve memory and focus", there are also several that are available in one's normal diet and for purchase over the counter (OTC). These include phospholipids like phosphatidylyserine, lecithin, and citicholine; amino acids,
including acetyl-L-carnitine, taurine, L-tryptophan, L-glutamine; and antioxidants such as vitamins, L-cysteine, L-glutathione, and L-methionone (amino acids which function as antioxidants).

It is interesting to note that several OTC products touted for memory enhancement are also included in energy drinks. Energy drinks are consumed by millions of people every day, in order to feel more "alert and focused". More than five hundred different energy drinks were launched worldwide in 2006 and beverage companies are reaping the financial rewards of the 5.7 billion dollar energy drink industry. In one study, it was noted that 51% of college students drink at least one energy drink per month. The main reasons stated for using energy drinks included insufficient sleep (67%), to increase energy (65%), while studying or completing major course projects (50%), driving for long periods (45%). More than 70% of study participants reported using energy drinks a minimum of one day per week. Improvement of mental functioning is of major interest in college students, and many suffer from sleep deprivation. While sleep deprivation is associated with increased stress and decreased memory performance, the main ingredient in energy drinks, caffeine, has not been quantitatively shown to affect academic performance. Likewise, high glucose levels do not improve reaction times slowed by sleep deprivation. Even current alcoholic drinks that come in a can are playing to college students' needs for alertness by adding ingredients such as taurine, caffeine, and guarana, turning them effectively into energy drink combinations.

Conclusion

There are very few medications FDA-approved to treat memory disorders. To this end, learning and memory is a major area of research in that functioning memory underpins all normal human behavior. In addition, memory disorders are abnormal behavior components in many disorders, ranging from addiction, anxiety, mood disorders such as depression, schizophrenia and several neurodegenerative processes. There are currently no universally effective treatments for these impairments; thus, novel therapeutic approaches, and medications to act on specific neurotransmitters, are strategies that could either reduce cognitive deficits in disease processes or improve normal cognitive function in healthy people.

Although there isn't a lot of U.S.-generated research that most marketed nootropics actually do anything, thousands of people use them. If they were not getting the results they hoped for, they would stop using these supplements. Just because the FDA has not regulated these medications doesn't stop people from taking them. This may constitute 'placebo effect', which is a major factor in ALL medication and treatment modalities. If you think it's going to work, chances are, it will.

The only energy drinks I have ever used have been mostly caffeine (Monster); however, after beginning this research I was impressed by the ingredients of only a few "energy enhancers" that I picked up and tried. What is Playboy's "pleasure enhancer" energy drink's second ingredient? GABA. What is piracetam? A GABA derivative. 5-hour Energy's main ingredients include citicoline and B-complex, and while it didn't have much affect energy wise (for me), it did increase my focus for about four hours. Most other products are just high fructose corn syrup, caffeine, and various B vitamins. Personally, I think it's just a matter of time before one company stumbles on the 'magic formula' that assists learning and focus, and patents it.

They will make a killing, because EVERYONE wants to be the smartest one in the class.
<table>
<thead>
<tr>
<th>Supplement Name</th>
<th>What is it?</th>
<th>Brain Enhancement</th>
<th>What does it do?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piracetam; Racetam's = Pira-, Ani-, Oxi-, Prami- (cetam)</td>
<td>deriv. GABA, chemically related to Pyrrolidine COOH</td>
<td>Frontal Cortex, Striatum, Hippocampus, AMPA receptors, Corpus callosum, Locus Coeruleus</td>
<td>Increases brain metabolism, O2 flow &amp; antioxidant effect, affects neuro-electrical function, stimulates learning, memory, creative thought, hemispheric intercommunication. Boosts ATP, ACa levels.</td>
</tr>
<tr>
<td>L-Huperzine</td>
<td>Plant alkaloid</td>
<td>Increases NMDA receptor &amp; ACh levels, inhibits AChE breakdown</td>
<td>Boosts memory, learning &amp; concentration. Enhances focus.</td>
</tr>
<tr>
<td>Alpha GPC</td>
<td>Choline alfoscerate</td>
<td>Precursor to ACh and Phosphatidyl Choline</td>
<td>Supports brain structure and supports memory.</td>
</tr>
<tr>
<td>Vinpocetine</td>
<td>Deriv. of Vincamine</td>
<td>Amygdala NOT AVAILABLE USA</td>
<td>Brain metabolism, O2 flow &amp; antioxidant effects. Stimulates processing, memory, attention &amp; cortical arousal.</td>
</tr>
<tr>
<td>Theanine</td>
<td>Amino Acid, converts to GABA</td>
<td>Comparative to Paxil</td>
<td>Inhibits stress &amp; anxiety, protects and enhances cognition</td>
</tr>
<tr>
<td>Acetyl-L-Carnitine</td>
<td>Derivative of choline</td>
<td>ACh system</td>
<td>Enhances transport of fatty acids to mitochondria (energy), Maintains ACh</td>
</tr>
<tr>
<td>THA</td>
<td>AChE inhib, related to nerve gas &amp; strychnine</td>
<td>No Data</td>
<td>Memory Enhancer, if dosage too high, causes memory blockade.</td>
</tr>
<tr>
<td>Choline</td>
<td>Precursor to ACh</td>
<td>ACh, limbic system</td>
<td>Memory booster, cell structural enhancer, fat/cholesterol metab.; Can negatively affect mood disorders</td>
</tr>
<tr>
<td>DHEA</td>
<td>Steroid</td>
<td>No Data</td>
<td>Cognitive enhancement, neuronal protection (Alzheimer's)</td>
</tr>
<tr>
<td>Hydergine</td>
<td>Mimics nerve growth factor</td>
<td>Limbic system, cerebral cortex</td>
<td>Enhances blood supply, metabolism, antioxidant function; slows lipofuscin deposits</td>
</tr>
<tr>
<td>Supplement</td>
<td>Class</td>
<td>Availability</td>
<td>Function</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------------</td>
<td>-------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lecithin, CitiCholine</td>
<td>Phospholipids</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Precursor to choline, ACh; Supports communication, neuron membrane protection, healthy brain aging</td>
</tr>
<tr>
<td>Phosphatidylserine</td>
<td>Phospholipids</td>
<td>Dietary, OTC</td>
<td>Enhances neuron membrane surface potentials</td>
</tr>
<tr>
<td>Acetyl-L-carnitine</td>
<td>Amino Acids</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Related to Choline; Increases acetylation of coenzyme A to enhance memory, Increases fatty acid transport (boosts energy)</td>
</tr>
<tr>
<td>L-tryptophan</td>
<td>Amino Acids</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Precursor to serotonin, 5HT Reduces anxiety</td>
</tr>
<tr>
<td>L-Glutamine</td>
<td>Amino Acids</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Converts to Glutamic acid, GABA.</td>
</tr>
<tr>
<td>Taurine</td>
<td>Amino Acids</td>
<td>Dietary, OTC, Energy drinks*</td>
<td>Aids efficient electrical conduction along neuronal pathways</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidants</td>
<td>Dietary, OTC</td>
<td>Protects cell membranes from lipid peroxidation; stops radical formation at PROPAGATION step</td>
</tr>
<tr>
<td>L-Methionone</td>
<td>Antioxidants, Amino Acids</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Lowers histamine, Protects neurons from heavy metal damage. Combines with choline</td>
</tr>
<tr>
<td>L-cysteine</td>
<td>Antioxidants, Amino Acids</td>
<td>Dietary, OTC, Energy Drinks* (Created by taurine metabolism)</td>
<td>Protects cell membranes, prevents neuronal damage from ROH, smoke, Radiation</td>
</tr>
<tr>
<td>L-Glutathione</td>
<td>Antioxidants, Amino Acids</td>
<td>Dietary, OTC ** Preservative for ROH, H2O, soft drinks, gatorade, fruit juice **</td>
<td>Tripeptide (cysteine, glutamic acid &amp; glycine); anti-tumor action, increases brain oxygenation. Anti-microbial function as a preservative.</td>
</tr>
<tr>
<td>B-complex</td>
<td>Vitamins</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>Cell metabolism role; increases energy availability</td>
</tr>
<tr>
<td>Caffeine, &quot;Guarana&quot;, &quot;Ma Huang&quot;</td>
<td>Analieptic</td>
<td>Dietary, OTC, Energy Drinks*</td>
<td>CNS stimulant; improves focus, alertness (limbic effects), electrical conduction, oxygenation; Has negative effects in high doses</td>
</tr>
<tr>
<td>Nicotine [16]</td>
<td>Miscellaneous</td>
<td>Tobacco, OTC stop smoking aids</td>
<td>Affects nicotinic receptors, 5HT; improves working memory</td>
</tr>
</tbody>
</table>
Works Cited


http://library.thinkquest.org/C0110291/basic/brain/sensory.php


Cerebral Vasospasm Following Subarachnoid Hemorrhage

Prepared for
Dr. Hank Mancini
Instructor
Organic Chemistry 236

Prepared by
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April 18, 2010
Abstract

Subarachnoid hemorrhage is a ruptured aneurysm in the brain which allows blood to enter the subarachnoid space. Many patients who survive the treatment may go on to develop cerebral vasospasm. Cerebral vasospasm is the narrowing of the arteries in the brain which decreases blood flow. The paper discusses how subarachnoid hemorrhage and cerebral vasospasm are detected, treated, and current experimental treatments.

Introduction

Subarachnoid hemorrhage is a serious neurological event in which an artery in the brain has ruptured, causing blood to fill the brain space. Treatment for a subarachnoid hemorrhage may be difficult and is on a case-by-case basis. Therefore, the mortality rate for subarachnoid hemorrhage is high. Patients who have survived the subarachnoid hemorrhage and repair may develop cerebral vasospasm, where the arteries in the brain close and prevents blood from flowing to parts of the brain. This can lead to other neurological disorders such as epilepsy. At this point in time, doctors and researchers do not have an exact cause or mechanism for cerebral vasospasm. They do, however, have an understanding of the series of events that may lead up to and the treatment of cerebral vasospasm.

Subarachnoid Hemorrhage (SAH)

Subarachnoid hemorrhage is defined as a rupture of a brain aneurysm into the subarachnoid space of the brain and affects approximately 1 in 10,000 Americans annually. The aneurysm, thin spot of an artery, may have been present in the brain from birth, or may have developed recently. When the rupture occurs, the patient may have been involved in some sort of physical activity, such as heavy lifting or bending. Often times, the patient may have a sudden headache and may describe it as the worst headache they have ever felt or it is as if someone hit them over the head with a baseball bat or hammer. Some patients may become confused or even lose consciousness. Most cases can prove to be fatal. Of these fatal cases, 60% of patients die immediately after the rupture, before arriving at the hospital, and 80% of patients die within 24 hours after being admitted to the hospital. Due to the infrequent number of cases, doctors may find it difficult to recognize. Once the doctors are able to recognize a subarachnoid hemorrhage, the patient may be graded based on the Glasgow Coma Scale as proposed by the World Federation of Neurosurgical Societies.

Detecting Subarachnoid Hemorrhage (SAH)

A CT scan may be used to detect a recent SAH. The aneurysm itself is not seen on a CT scan. However, an area where blood has collected will show up on a CT scan and may lead doctors in the correct area of the aneurysm. Testing of the cerebrospinal fluid for xanthochromia has a better accuracy for detecting an SAH. Xanthochromia creates a yellow color in the cerebrospinal fluid caused by the breakdown products of hemoglobin and can be detected as early as six hours after an SAH. To determine what course of treatment to provide, cerebral angiography can be

![Figure 1](image.png)

Figure 1

Angiogram of carotid artery
performed to locate the source of the bleed once SAH has been diagnosed. During an angiograph, a contrast medium is injected into the arteries and will show up dark on an angiogram as it follows the path of the artery. Once the contrast comes across the rupture, the dark line will spread and fade.

**Glasgow Coma Scale**

The Glasgow Coma Scale is a 15 point scale which measures the patient's eye opening, verbal, and motor responses. The final score is added up and those who score 13-15 are said to be in a mild state. Those who score 9-12 have moderate disability and may have some physical or cognitive impairments which may be corrected through rehabilitation. Those who score 3-8 have severe disability and are said to be in a coma with no response or controlled movements. Those who score less than 3 are said to be in a vegetative state where they do not interact with those around them and have no response to pain.

**I. Motor Response**
6 - Obeys commands fully  
5 - Localizes to noxious stimuli  
4 - Withdraws from noxious stimuli  
3 - Abnormal flexion, i.e. decorticate posturing  
2 - Extensor response, i.e. decerebrate posturing  
1 - No response

**II. Verbal Response**
5 - Alert and Oriented  
4 - Confused, yet coherent, speech  
3 - Inappropriate words and jumbled phrases consisting of words  
2 - Incomprehensible sounds  
1 - No sounds

**III. Eye Opening**
4 - Spontaneous eye opening  
3 - Eyes open to speech  
2 - Eyes open to pain  
1 - No eye opening

**Figure 2**
Points according to response of Glasgow Coma Scale

**Treating Subarachnoid Hemorrhage (SAH)**

Due to the infrequent number of cases, treatment can vary. Some patients may improve over time without any intervention. However, treatment of a patient who arrives at the hospital in a comatose state may be difficult because the comatose state may be from hydrocephalus, swelling of the brain ventricles, rather than the aneurysm itself. Some doctors may place an external ventricular drain into the brain to relieve fluid and pressure build-up in the ventricles. To repair the ruptured aneurysm, doctors may place an aneurysm coil or clip, depending on the size and
location of the aneurysm. If the aneurysm is relatively small, an aneurysm coil may be placed. Surgeons insert a flexible wire into the artery and feed it until it reaches the aneurysm. Once it reaches the aneurysm, the wire coils into a ball and allows a blood clot to form that prevents blood from exiting through the aneurysm. If the aneurysm is larger or may be in a difficult spot for the coil, an aneurysm clip may be surgically placed. This procedure is much more invasive since the surgeons have to open the skull in order to place the metal clip.

![Figure 3 - Aneurysm coil](image1)
![Figure 4 - Aneurysm clip](image2)

**Cerebral Vasospasm**

Cerebral vasospasm is defined as the narrowing of a cerebral artery or blood vessel. "Vaso" refers to blood vessel and "spasm" refers to the vessel's spastic activity which causes the artery to narrow. While the artery is narrowed, blood has a difficult time getting to certain areas of the brain and may cause the brain to die. Cerebral vasospasm begins to occur a few days after a subarachnoid hemorrhage and can last anywhere from a few days to about three weeks. Cerebral vasospasm can be detected by cerebral angiography, physical observation from a doctor, CAT scan, MRI, or transcranial Doppler ultrasound. Cerebral vasospasm can be classified into three types: subangiographic, angiographic, and clinical. Although the exact mechanism for cerebral vasospasm is not known, doctors and researchers have discovered the order of events that lead to vasospasm.

![NORMAL ARTERY](image3)
![VASOSPASTIC ARTERY](image4)

**Figure 5 - Vasospastic vs. Normal Artery**

**Detecting Cerebral Vasospasm**

Cerebral vasospasm is said to be detected best through cerebral angiography. This process is similar to detecting subarachnoid hemorrhage. An opaque contrast is injected into the patient's blood stream. When passed through an x ray, dark areas appear where the contrast is present. If cerebral vasospasm is present, the angiogram would show very thin lines of dark contrast.
A CAT scan may show if the patient has suffered any strokes during vasospasm. Whereas an MRI is used to show how badly the brain tissue has been affected by vasospasm. Transcranial Doppler ultrasound can be done bedside to determine blood flow through the arteries. During Transcranial Doppler ultrasound, the blood's velocity is measured.\(^7\)

**Classification of Cerebral Vasospasm**

Subangiographic vasospasm cannot be detected by cerebral angiography. This type of vasospasm occurs at the physical level but cannot be seen. This can be difficult to see on a cerebral angiogram if the narrowing of the artery is too mild or is occurring in an area of the brain where the arteries branch off in multiple directions. Unlike clinical vasospasm, subangiographic vasospasm cannot be detected bedside by a doctor. Although subangiographic vasospasm may be mild or occur at an area involving many small arteries, some patients may suffer the same symptoms as clinical vasospasm patients.

Angiographic vasospasm can be detected by cerebral angiography. A patient may or may not be able to be evaluated for angiographic vasospasm bedside by a doctor. This may be due to the differences in the individual's brain circulation. Angiographic vasospasm affects the area closest to the site of the ruptured aneurysm. However, it may be possible that vasospasm may be located in distant arteries.

Clinical vasospasm may be detected bedside by a doctor as well as by cerebral angiography.

**Functional Component of Cerebral Vasospasm**

Vasospasm begins with the breakdown of the hemoglobin in red blood cells to oxyhemoglobin. This breakdown product then generates the "reactive oxygen species"\(^6\) superoxide. Reactive oxygen species are toxic and damage cells throughout the blood vessel. These affect the endothelial cells, smooth muscle cells, fibroblasts, and nerve fibers in the blood vessel. In doing so, the artery's normal relaxation-contraction cycle shuts down or acts out of order.

**Molecular Component of Cerebral Vasospasm**

Relaxation and contraction cycles are controlled by mediators which tell the blood vessels when to relax and when to contract. During vasospasm, vasodilators which keep the artery open becomes underactive. Such vasodilators include nitric oxide and prostacyclin. In contrast, vasoconstrictors which cause the blood vessels to contract become overactive and force the blood vessel to close. Such vasoconstrictors include endothelin-1 and thromboxane A\(_2\). Calcium channels are also thought to contribute to vasospasm. To counteract the effects of the calcium channel, calcium channel blockers such as nimodipine prevents smooth muscle contraction and increase vasodilation.\(^8\)

**Structural Component of Cerebral Vasospasm**

Vasospasm may become an inflammatory reaction.\(^7\) In addition to the attack of the walls of the blood vessel, the walls can become filled with white blood cells, the smooth muscle layer can get
thicker, and the smooth muscle layers can become stiff. This allows vasospasm to continue for extended periods of time.

**Treating Cerebral Vasospasm**

Although there has not been a clear cut cure for vasospasm, there have been many attempts to ease the management process. As stated earlier, calcium channel blockers allow the arteries to dilate. This is because it prevents calcium ions from entering into the smooth muscle cells.

Another management process is hypovolemic-hypertensive-hemodilution therapy. During this therapy treatment, the patient's fluids, blood pressure, and arterial pressure were raised. Whereas the blood viscosity was lowered. The process, as adopted by the Barrow Neurological Institute, includes central venous pressure, that was raised and closely monitored at 10-12 mm Hg, hematocrit was lowered and monitored at 33-38%, and systolic arterial pressure was monitored at 160-200 mm Hg if the aneurysm was repaired, 120-150 mm Hg if not.⁹

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**Flow chart of Barrow Neurological Institute's management protocol**

If the cerebral vasospasm is severe, doctors may perform mechanical angioplasty. During this, doctors surgically place a balloon-tip catheter into the narrow artery to force the artery to remain open. However, the artery may rupture during the procedure.

An experimental treatment is to introduce a gene vector that contains nitric oxide synthase into the area where the patient is experiencing vasospasm. Doctors believe that this opens the artery by creating an abundance of nitric oxide into the vasospastic area. In low concentrations, nitric oxide acts as a signal to regulate blood flow, neurotransmission, learning, and memory.¹⁰
Another experimental treatment includes cervical spinal cord stimulation. Spinal cord stimulation helps to improve any neurological dysfunctions caused by vasospasm. Hosobuchi discovered that cerebral blood flow was increased under cervical spinal stimulation. During this procedure, as tested on New Zealand albino rabbits, a wire electrode was surgically inserted under the second cervical vertebrae. The position of the wire was checked by an x-ray, then connected to a Nihon Kohden Electronic Stimulator SEN 33001 and stimulation was applied continuously for 20 minutes at 210 ms impulse duration, 80 Hz frequency, and 2/3 motor threshold intensity. During this experiment, neurological dysfunction and cerebral blood flow were increased.

Summary and Conclusions

Subarachnoid hemorrhage is a very serious, and potentially fatal, neurological event that affects 1 in 10,000 Americans annually. A subarachnoid hemorrhage (SAH) is when a brain aneurysm ruptures and blood begins to enter the subarachnoid region of the brain. Most patients who suffer from a subarachnoid hemorrhage die. Of those that die, 60% die immediately after the rupture occurs. Of the fatal cases, 80% die within 24 hours of being admitted to the hospital.

Subarachnoid hemorrhages can be detected either by a CT scan or cerebral angiography. During a cerebral angiography, a contrast is injected into the blood stream and shows up dark on an x-ray. The approximate area of the rupture is where the dark line is no longer a distinct line. The aneurysm can be repaired surgically by an aneurysm coil or clip. Some cases may heal on their own, with the aid of an external ventricular drain to relieve fluid and pressure build-up in the brain.

In most cases, patients with subarachnoid hemorrhages may develop cerebral vasospasm. Cerebral vasospasm can be detected in some cases bedside by a doctor, through a cerebral angiography, CAT scan, MRI, or transcranial Doppler ultrasound. Cerebral vasospasm is caused by the underactive vasodilators nitric oxide and prostacyclin which prevents the arteries from remaining open and the overactive vasoconstrictors endothelin-1 and thromboxane A2 which forces the artery to close. To help off-set this process, hypervolemic-hypertensive-hemodilution therapy is used. During this therapy, the patient's fluid levels, blood pressure, and arterial pressure is increased and the blood's viscosity is decreased.

Another experimental treatment for cerebral vasospasm include introducing a gene vector that contains nitric oxide into the area of the vasospasm to increase nitric oxide production and force the artery open. Another experimental treatment is cervical spinal cord stimulation by inserting a metal electrode under the second cervical vertebrae and apply electrical stimulation to the area to increase blood flow and neurological dysfunction.

In 1986, my mother suffered from a minor subarachnoid hemorrhage while she was pregnant with me. The aneurysm was clipped, and she made a full recovery and delivered a healthy, full-term baby. In 2008, she suffered a more severe subarachnoid hemorrhage and immediately fell into a coma. She was taken to John C. Lincoln hospital, diagnosed, then sent to Barrow Neurological Institute for treatment. There, the aneurysm was clipped and another, smaller aneurysm was found near the one from 1986 and clipped before it could rupture. A month later, a shunt was surgically placed in her brain to drain any cerebrospinal fluid that may build-up in the
ventricles into her abdomen. This time, she went into mild to moderate vasospasm and came out of that within a week. However, a few days after recovering from the vasospasm and getting ready to be sent off to rehabilitation, she began having epileptic seizures. The doctors informed us of the chance of vasospasm, but not the chance of epileptic seizures. Therefore, the doctors were treating for the vasospasm, but not the seizures. After two pentobarbital-induced comas, and several anti-epileptic drugs, the seizures have been controlled. However, the damage had already been done. She is now in a skilled nursing facility in a minimally conscious state. Meaning, she is able to open her eyes and look around, can respond to pain, but cannot talk or follow commands. Although it is fairly uncommon for patients to develop epileptic seizures as a result of cerebral vasospasm, it would be nice if doctors begin administering anti-seizure medications when they start treating for vasospasm. If anti-seizure medications may counter-act the medications used in treating vasospasm, at least have the neurology department involved and monitor the electrical activities of the brain with electroencephalogram, EEG, rather than treat subarachnoid hemorrhage strictly as a surgical case.
References


Pharmacogenetics
A Basic Overview

Ibeji, Goziechukwu

Organic Chemistry
Dr. Hank Mancini
April 23, 2010
Abstract: Cardiac surgery patients get precisely the right dose of blood thinners to avoid clotting. Glaucoma patients use the least costly, most effective eye drops that lower pressure in their eyes. Diabetics get the therapy they need, based on their genetics, to avoid amputations (Anderson 30). These are the benefits that can be associated with pharmacogenetics, also known as personalized medicine. Pharmacogenetics is the study of the human genetic information and pairing each individual to medications that are best suited to the genetic information. This is by understanding the effects of genetic variation on human drugs and the responses exhibited. An in-depth knowledge of this will lead to a future where there will not be a generic drug for each symptom expressed rather; the medication prescribed will be suited to the specific individual the drug is prescribed to.

The term pharmacogenetics can be used interchangeable with the term Pharmacogenomics. The term pharmacogenetics can be used to describe the effects of individual genes on drug and what the responses are while pharmacogenomics deals with the effect of variants genes on drug response. The understanding of the variation in the genetic information and the process by which it affects us was first noticed in the testing of Phenylihiourea (PTU) (Garima Jarmal et al 78). The taste blindness of the chemical due to the individual genetic make-up gave an insight into the genetic response to different drugs. This then led to the understanding that the concept of drug metabolism could be the groundbreaking discovery on personalized medicine that could lead to better healthcare. The topic of pharmacogenetics has only started to gain recent publication and scrutiny due to the understanding of some of the benefits that could transpire from its use. The Food and Drug Administration has started to understand the potential benefits and have approved some of the available drugs that are categorized as pharmacogenetic drugs. This is a step that will provide many the personalized care that is needed in order to match them their specific health needs. There are many benefits associated with personalized benefit. There is the possibility of reduction in side effects due to matching individuals to the treatment that is personally meant for them. It would also eliminate the problem of banning drugs. There have been cases where certain drugs have had to be banned and taken off the market due to individuals reacting to the drug and experiencing side effects that are detrimental to their health. Personalized medicine will wipe this out due to the fact that there will not be a need to create generic drugs, each drug will be engineered to match the genetic definition of different individuals. This will also lead to a case where there will be a database containing the certain genetic make-up that can respond negatively to the drug and hence, will advise physicians on what treatment to prescribe to their patients. In 2005 the first drug developed to treat a particular subgroup, Bidil, was released (Cuticchia 6). This is a combination of Isosorbide dinitrate and hydralazine hydrochloride (Rxlist).

\[
\begin{align*}
\text{O}_2\text{NO} & + \text{NHNN}_2^+ \\
\text{ONO}_2 & = \text{Bidil}
\end{align*}
\]

So how does pharmacogenetics works? The basic concept behind it is that the human genome consists of approximately 3 billion base pairs, and the sequence of these varies among
individuals. These variations include single nucleotide polymorphisms (SNPs), base insertions or deletions, copy-number variations, and variable numbers of tandem repeats. Because these variations can change the function of proteins that interact with a drug, the response to a drug may differ among individuals. Understanding how these variations influence drug response could help in tailoring drug therapy based on an individual's genetic makeup. (cite)

About a 100 polymorphic traits in human drug response has been identified. This assembly of traits, most of which had been ascribed to genetic polymorphisms of the drug metabolizing enzymes, is mainly responsible for shaping the development of pharmacogenetics. The use of molecular genetics techniques was also gaining momentum in many laboratories in the mid-1980s, making it possible to identify the polymorphic genes that encode them, and express them. Characterization of the naturally occurring variants of these enzymes isolated from tissues, or expressed in heterologous systems, revealed they occurred as high or low (or null) variants that might alter the susceptibility of individuals to toxicity from drugs and other exogenous chemicals. (cite)

Although pharmacogenetic markers have been hailed as promising tools, these proclamations are based mainly on associations rather than their evaluation as predictors. To put the expectations of the promise of pharmacogenetics in a realistic perspective, we review three examples. First, warfarin pharmacogenetics, wherein although the validity of the genetic variant dose is established and there is a validity of genetic variant–hemorrhage association, the clinical utility of testing is not clear. Second, the influences of CYP2D6 on tamoxifen efficacy, a model candidate with potential clinical utility but unclear validity. These examples highlight both the challenges and opportunities of pharmacogenomics. First, establishing a valid association between a genetic variation and drug response; second, doing so for a clinically meaningful outcome; and third, providing solid evidence or rationale for improvement in patient outcomes compared with current standard of care. (Lindt and Veenstra 10)

When a drug is ingested, it interacts with molecules encoded by the genome, which is made of DNA. These molecules may be involved in the absorption, distribution, metabolism and excretion of the drug (the pharmacokinetics or PK program the body does to the drug), or may be the target of the drug and the place where it exerts its therapeutic or toxic effects (the pharmacodynamics or PD program—what the drug does to the body). The most important molecules that interact with drugs are usually proteins that are encoded in the genome. Although 99.7% of the human genome is shared among all people, the remaining 0.3% accounts for much of the variation in physical traits and physiology. Drug response is a direct result of physiology, and so variation in molecules involved in drug response can result in variation in the physiological response to drugs. Variation in the DNA sequence can change the resulting physical characteristics of the encoded molecules, or it can change the timing of their creation/destruction or its magnitude. Genetic variation contributes to inter-patient differences in drug response. Such variations may occur for drug metabolism, drug transporter and drug target proteins. Most of the variations occurring in the human genome are single nucleotide polymorphism (SNPs) with an occurrence rate of at least one every 1000 base pairs.

Genes contain instructions for making proteins, including those which interact with drugs. Any change in a gene can result in changes in the associated protein involved. Individuals get one
copy of a gene from each parent, but each of those copies may have a change or mutation. Mutation can result in production of an enzyme with reduced function or no enzyme may be produced at all. Depending on whether a Person has 0, 1 or 2 normal copies of genes, he or she may be grouped as poor, intermediate or rapid metabolizer. The less normal copies a person has, the poorer the metabolism, and hence, higher blood levels of the drug. This may result in greater effectiveness or more likely greater side effects (Garima Jarmal et al 78).

The research that is currently going on involves gathering DNA information and using that information for research on the effects of the different diseases rather than the application of the genetic geared drugs. There are relatively few examples of genetic variation influencing drug dosage that are well validated across different racial/ethnic/geographic groups as with the case of warfarin (Limdi and Veenstra 10). The current application of warfarin is based on a “one drug for all” model in which the same prescription is being given to all in need of the medication. Documented research has shown though that the response to the drug is very different for different ethnic, racial and geographic groups. Hence the response to the drug varies for each person with a patient potentially reacting adversely to the medication or the medication not being enough to make a difference for the patient. The application of pharmacogenetics will enhance the results of this and help in articulating the required dosage needed by each patient. Statistically, it has been recorded that Caucasians and Asians react more favorable to the drug than the responses of African Americans (Limdi and Veenstra 10).

Based on the presented data above, it can be recognized that the pharmacogenetic approach has had a better response from the patients all round. In order to understand the research better, it is important that the role of warfarin is understood. Warfarin is an anticoagulant and it has also been used as a blood thinner in surgery. It was previous used as a pesticide for rats and mice’s. Warfarin acts on two fundamental enzymes in the body - the CYP2C9 and (VKORC1). These two enzymes have a direct correlation on the response of genes to the warfarin and the understanding of the specific roles of each has brought about the understanding of the dangers of a “one for all” drugs. Within the CYP2C9 gene there have been 13 polymorphisms identified, of which two variants are common: CYP2C9*2 and CYP2C9*3 (Gage and Milligan 55-59). These two variants have been understood to have a slow response to warfarin and have a risk to hemorrhage. The frequency of either the CYP2C9*2 and CYP2C9*3 variants combined is 20% in Caucasians, 6% in African populations, and 2% in Asian populations (Gage and Milligan 55-
This therefore gives the indication that the same dosage might not be beneficial to an African as would be beneficial to an Asian. The V\textit{KORC1} was also studied in order to understand its role and it is recognized that it has different responses from the SNP and so having a clear understanding of its role can lead to better application of treatment.

The Cytochrome P-450 enzyme, a super family of microsomal drug metabolizing enzymes, is the most important of enzymes which catalyze drug metabolism reactions (Garima Jarmal et al 78). One member of this family, CYP2D6 (cytochrome P-450 2D6), has been the most intensively studied and is the best example of Pharmacogenetic variation in drug metabolism (Garima et al 78). The CYP2D6 gene, involved in the metabolism of pesticides and more than 30% of drugs like antidepressants, antipsychotics, antiarrhythmics is one of the most polymorphic and counts for more than 80 allelic variants described with their subvariants (Laura Riccardi et al 485). The CYP2D6 genetic polymorphism was originally discovered as a result of striking difference in the pharmacokinetics and therapeutic effects of drugs metabolized by this enzyme. Drugs as diverse as codeine, dextromethophan, metaprolol and tricytline are all metabolized by this enzyme. People who have low enzyme count in the body metabolize drugs slowing while those with high enzyme count or rapid metabolizers process the drugs that they need quicker and faster through the body. There are different metabolizers that are activated by the CYP2D6 enzyme and there are those that are not activated by the enzyme. Tamoxifen is a prodrug that undergoes extensive first-pass oxidative metabolism by various cytochrome P450 enzymes to active metabolites. Briefly, tamoxifen is hydrolyzed or demethylated to various intermediates by CYP2D6, 2B6, 2C9, 2C19, and 3A (Limdi and Veenstra 10). It has been shown through clinical test how different women respond to the drug due to whether they are high metabolizers or low metabolizers. Studies by Nowell et al. and Wegman et al. indicated CYP2D6 poor metabolizers had an increase in disease-free survival (Limdi and Veenstra 10). This goes to suggest the importance of CYP2D6 enzyme in the body. It plays direct role with our response to the drugs which it metabolizes and through pharmacogenetics, the different metabolizers that are activated by the CYP2D6 enzyme and those that are not activated can be studied and understood.

Association of CYP2D6 and survival among patients with breast cancer on tamoxifen therapy (Limdi and Veenstra 10).

<table>
<thead>
<tr>
<th>Study</th>
<th>Size (n)</th>
<th>Poor metabolizers (%)</th>
<th>DFS HR_{adj} (95% CI)</th>
<th>OS HR_{adj} (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goetz et al., 2007</td>
<td>180</td>
<td>36^{a}</td>
<td>1.60 (1.06, 2.43)</td>
<td>1.34 (0.83, 2.16)</td>
</tr>
<tr>
<td>Schroth et al., 2007</td>
<td>206</td>
<td>40^{b}</td>
<td>1.89 (1.10, 3.25)</td>
<td>1.73 (0.88, 3.41)</td>
</tr>
<tr>
<td>Nowell et al., 2005</td>
<td>162</td>
<td>30^{c}</td>
<td>0.77 (0.32, 1.81)</td>
<td>n/a</td>
</tr>
<tr>
<td>Study</td>
<td>Size (n)</td>
<td>Poor metabolizers (%)</td>
<td>DFS HR$_{adj}$ (95% CI)</td>
<td>OS HR$_{adj}$ (95% CI)</td>
</tr>
<tr>
<td>----------------</td>
<td>---------</td>
<td>-----------------------</td>
<td>---------------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>Wegman 2007</td>
<td>111</td>
<td>29</td>
<td>0.33 (0.08, 1.43)</td>
<td>n/a</td>
</tr>
</tbody>
</table>

*Abbreviations:* DFS, disease-free survival; HR$_{adj}$, adjusted hazard ratio; OS, overall survival; n/a, data not available.

- $^a$ One or more *4 alleles or CYP2D6 inhibitor.
- $^b$ One or more *4, *5, *10, or *41 alleles.
- $^c$ One or more *4 alleles. (Limdi and Veenstra 10).

Even though there has been so much promise to the advancement of personalized medicine, there have also been some ethical issues that are attached to this issue. These issues are fundamental to the development of personalized medicine because to alleviate them is to enhance the advancement of personalized medicine. The ethical issues/concerns that are attached include: privacy concerns, economic considerations and potential malpractice litigation (Cuticchia 6). These issues arise due to the switch from the traditional practices that have always been applied. The traditional practice of medicine has been the application of drugs and medication based on the age, weight, and different environmental factors. The change from these definitions to the definition of genetic make-up and the information can lead to these concerns.

The biggest issue with privacy is the spread of information across channels. Since there has been a limited sharing of genetic information across channels, with the conception of pharmacogenetics, there will be the influx of genetic sharing across medical channels in order to facilitate which genotype is best suited to a particular medication. This might also include the creation of a database into which the information and this will be a violation of privacy information it is argued (Cuticchia 6). With the HIPAA responsible for the control and protection of medical information, the database that will be created might require be under the control a separate medical institution and the release of patient information into such databases might violate both the consent and privacy of the patients.

The NIH invests approximately 30.5 billion dollars throughout institutions for different medical research programs (nih.gov). In 2005 the industry group PhRMA reported pharmaceutical research spending of $39 billion. When combined with non-PhRMA members, the total drug research expenditures exceeded $51 billion, nearly twice that of NIH. While this might seem like a large investment, the expected cost of bringing a drug into the market is in excess of $880 million (Cuticchia 6). This amount is definitely above the available budget for the development of pharmacogenetic drugs. And even though the expected sale of a blockbuster drug is expected to be in the range of $1 billion, Pharmaceutical industries have been loath to invest in this avenue. This is so because it is believed this will take away their avenue of being able to reach a wider passage of patients due to a generic drug. The development of personalized medicine will require the investment of different drugs for each genotype and so will require much investment. There has also been the suggestion that once a personalized is produced that serves a high
percentage of the public, there will be a stoppage of the manufacturing of the drug to fit a different genotype. And this will not eliminate the problem of the “one drug for all” currently being experienced.

Also the potential of possible litigation, there will always be uncertainty with the introduction of a new drug into the market. Even though personalized medicine has been advertised as matching a person’s genotype to the specific drug, there might unforeseen circumstance that might arise after the drug has been marketed to a diverse population. An example of this litigation is the case against Merck & Co. for their release of Vioxx. In Ernst v. Merck, a Texas jury awarded the widow of Robert Ernst $253.4 million in damages on August 19, 2005 due to the accusation of potential damage from the use of Vioxx (Cuticchia 6). Even though this case went up for an appeal and it the judgment was overturned, the damage had already been done. There were already accusations that the drug company did test sufficiently for side effects all round. This is a potential damage that Pharmaceutical companies want to avoid and with the introduction of pharmacogenetic drugs for the first time, there might be side effects that were not foreseen which might arise as the drug reaches different groups of people.

Conclusion

MOLECULAR FOUNDATIONS

GENOMIC ANATOMY
(DNA sequencing)
Person-to-person & ethno-geographic variation

PATTERNS OF EXPRESSION
(RNAs, proteins, metabolites)
Physiological, pathological & developmental variation

PRINCIPLES & TECHNIQUES

DRUG SUSCEPTIBILITY PROFILES

Genotype — phenotype correlations
[Proteins: Cellular location, Mechanisms, Pathways, Networks]

OBJECTIVES

INDIVIDUALIZED THERAPY

DISCOVERY & CLINICAL TRIAL OF NEW DRUGS

(Weber 1)

These are both the challenges and obstacles that face pharmacogenetics. There is so much promise in the practice of this but there are still some gray areas that have to be understood in order for the program to be effective. Like in the structure above, it gives the benefit of having each individual genotype identified and then matching the person to the drug that is right for
them. It has the potential of wiping the numerous side effects that accompany many drugs today. It could reduce the cost of genetic testing and enhance the value of treatment that is gotten (Masahiro Hiratsuka et al 177). The Food and Drug administration have shown their support for the research of pharmacogenetically geared drugs and have set tentative policies on the use of such drugs. The program of Pharmacogenetics is still in its developmental phase. There is still a lot of work to be done and understanding the role of the environment, a person’s diet and their overall health can influence how they respond to drugs. We will have to understand what other enzyme is responsible for the metabolization of drugs as they enter the body. It is understand that Scandinavians Countries currently practice pharmacogenetics to some level and this suggests the that this might actually be a better option of treatment (Garima Jarmal et al 78). It is the most widely used application for genotyping CYP2D6 when treating psychiatric illness. There is so much promise in the future of pharmacogenetics and as Pharmaceutical companies continue to work on this, I would not be surprised to see more pharmacogenetically geared drugs in the market 10 – 15 years from now. It holds so much promise and it is a promise that can be realized.
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Tyrosine Kinase Inhibitors

By: Alex Kar

April 23, 2010
The world is in a constant metamorphosis requiring new advances and directions towards the treatment from acute bacterial infections to cardiac problems to cancer. Cancer is described by many definitions; Webster’s dictionary states that the definition is ‘a malignant tumor of potentially unlimited growth that expands locally by invasion and systemically by metastasis.’ As new types of cancers are discovered, more treatments for them are developed as used to help cure or slow down the effects. Cancers such as breast cancer, renal cell carcinoma and leukemia are very much present and being diagnosed in patients. With developments in modern medicine, new hope is brought to these patients towards a better outlook on life. These cancers flourish with the use of a protein called tyrosine kinase which is a specific protein in the human body that allows the cancer to use towards its progression. Some medications today were and are still being created to inhibit the activity of this protein therefore affecting the cancer’s ability to increase and multiply, these are called Tyrosine Kinase Inhibitors (TKI). The drugs such as Tykerb (Lapatinib) for treatment of Advanced/Metastatic Breast Cancer, Votrient (Pazopanib) for the treatment of Advanced Renal Cell Carcinoma and Gleevec (Imatinib) used to treat a leukemia type known as CML (Chronic Myeloid Leukemia). Many patients that given a death sentence from their diagnosis are now shown a new opportunity towards the attack against these diseases that have affected many. It is through the drug advancements of today that allows for new age battle towards giving an extension for some one’s life.

The protein that causes the development of cancer is called tyrosine kinase. There are more than 50 tyrosine kinase receptors known. This protein is an enzyme that is part of the transferring of ATP to different receptors that play an important role with cell development in the human body. The protein kinase more specifically moves a phosphate group from one protein to another through its activity that leads to signal transductions of molecules. Through phosphorylation of these molecules of the tyrosine residues, the growths of tumors are significant. By this activity cell division, cellular differentiation and morphogenesis or organism shape development is affected. When other outside factors are brought in that would cause the cancers that are ultimately affected by the enzymes activity, this causes the protein to increase work which then concludes to increase cell division and therefore there is abundance. These certain factors that are associated with the cancers in which cause the proteins to act incorrectly which then requires the need for an inhibitor. By inhibiting the proteins action there is a better control of cell division, cellular differentiation and morphogenesis. The inhibiting of the TK receptors help to reduce tumor growths which therefore slow down cancer spreading. Although there are many receptors of tyrosine kinase, only few receptors have medications that are specifically targeting in order to provide a direct approach toward treatment. The following have directly targeted medication therapies; EGFR(Epidermal Growth Factor Receptor) which includes the HER subfamilies, PDGFR(Platelet-Derived Growth Factor Receptor), VEGFR (Vascular Endothelial Growth Factor Receptor), c-kit/stem cell factor receptor and Bcr-Abl and active cytoplasmic kinase and hepatocyte growth factor receptor (HGF).
A chromosomal problem was found to be associated with Chronic Myeloid Leukemia which made the protein always in the 'ON' position when working and therefore in this case CML is associated with increased white blood count. The increase of white blood count is then indirectly related to the working efforts of the proteins. This chromosomal problem is more commonly called Philadelphia chromosome. This causes the increase activity of the Bcr-Abl, c-kit and PDGFR receptors, which ultimately causes the startup of Leukemia to develop in one's body. Gleevec developed by Novartis Pharmaceuticals with an initial U.S. Approval year of 2001. It was a much innovated type development towards treatment of mainly Leukemia, but can also be used to treat other types of cancer. This medication inhibits the receptors Brc-Abl, c-kit, PDGFR that causes the cell production that would cause the overproduction of white blood cells consistent with a Leukemia diagnosis. Therefore the overproduction is slowed down and white blood cell counts start to decrease over the time of the medication therapy. Graph 2 shows the progression free survival (PFS) through the treatment of patients receiving Gleevec or Interferon (IFN). There were three groups of patients from the clinical trials. Some patients were censored from the data for the trials. These factors were patients having progression, discontinuation or at last follow-up. The fact of progression is
defined as moving to an accelerated phase or blast crisis of leukemia stage, death, loss of Complete Response or Major complete response under the treatment of Gleevec. Over 84 months in the ITT (Intention to Treat) numbers, the progression free was about 81.2% of the Gleevec treated patients and 60.6% of the patients that were treated with IFN. The general response while being treated over the 84 Months was as followed under the treatment of Gleevec. The hematologic response was 96.6% of the 553 patients treated with Gleevec. There were 74.7% or 413 patients that had complete cytogenetic response, meaning there are 0% metaphases of the Philadelphia+ chromosomes. The Major Cytogenetic Response under the therapy of Gleevec was 85.4% which includes the complete and partial response which ranges from 0-35% metaphases by the Philadelphia+ chromosomes that increases the white blood cell growth attributed to the disease. These numbers were confirmed through bone marrow testing on the patients receiving treatment. The patients being treated under IFN were as follows hematologic response 56.6%, Complete Response 6.5% and Major Response 16.8% of the 553 patients that were given this treatment.

**Molecular Formula:** $C_{21}H_{23}N_7O_2S \cdot HCl$

**Votrient**

Advanced Renal Carcinoma is cancer of the kidneys that is considered quite common. This cancer attacks the kidneys through tumor development, which sometimes can be either just one larger tumor or many smaller tumors that could be found not only one kidney but in both kidneys at the same time. Through the use of multiple kinase inhibitors, ARC is being treated. The most promising targeted receptor has been the VEGFR. Votrient a relatively newer drug initially U.S. Approval of 2009 is still in its infancy towards successful treatment in patient that has been diagnosed with Advanced Renal Carcinoma (ARC). This medication is a multiple tyrosine kinase inhibitor, and targets many receptors towards the treatment of this cancer. More promising was seen through VEGFR specific treatment, although more recent studies don’t include Votrient in the trials, through other inhibitor medication, this type of treatment shows the most promising towards patient’s success rates. Through the drug maker GlaxoSmithKline, the clinic studies shown through their phase studies are shown in the following table:
Table 1 - Efficacy Results

<table>
<thead>
<tr>
<th>Endpoint/Study Population</th>
<th>VOTRIENT</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall ITT</td>
<td>N = 290</td>
<td>N = 145</td>
<td>0.46*</td>
</tr>
<tr>
<td>Median (months)</td>
<td>9.2</td>
<td>4.2</td>
<td>(0.34, 0.62)</td>
</tr>
<tr>
<td>Treatment-naive subgroup</td>
<td>N = 155 (53%)</td>
<td>N = 78 (54%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Median (months)</td>
<td>11.1</td>
<td>2.8</td>
<td>(0.27, 0.60)</td>
</tr>
<tr>
<td>Cytokine pre-treated subgroup</td>
<td>N = 135 (47%)</td>
<td>N = 67 (46%)</td>
<td>0.54</td>
</tr>
<tr>
<td>Median (months)</td>
<td>7.4</td>
<td>4.2</td>
<td>(0.35, 0.84)</td>
</tr>
<tr>
<td>Response Rate (CR + PR) %</td>
<td>N = 290</td>
<td>N = 145</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>30 (25.1, 35.6)</td>
<td>3 (0.5, 6.4)</td>
<td></td>
</tr>
<tr>
<td>Duration of response</td>
<td>Median (weeks) (95% CI)</td>
<td>Median (weeks) (95% CI)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>58.7 (52.1, 68.1)</td>
<td>46.5 (40.1, 52.9)</td>
<td></td>
</tr>
</tbody>
</table>

The data of Table 1 shows the patients treated by the Votrient or given a placebo respectively by their columns. Overall there were 435 patients that we investigated in this trial with the figures indicated by the "N" value listed in the table. In this study, there were two subgroups to this trial. The "Treatment-naive subgroup" had had no previous treatment for their disease. The "Cytokine pre-treated subgroup" had had one prior therapy of IL-2 or IFNα. Over the trial 290 patients were treated with Votrient and 145 being treated with Placebo. The median progression free under the treatment of Votrient was 9.2 months, meaning there was no progression or the disease became worse for 9.2 months from the start date of the treatment. Under the placebo, this number was 4.2 months, with a hazard ratio of 0.46. The hazard ratio is the comparison of the two groups, those patients being treated by Votrient and those by the placebo. Out of everyone treated overall 0.54 of 54% of the patients treated with Votrient had a 9.2 months median of being progression free in their disease. As we see when the groups are broken down based off previously therapy or not, the numbers are slightly better with those not having any type of treatment prior to clinical treatment under the therapy of Votrient. Figure 1 shows the data in line graph version, with the expectation of good results of therapy to show a gap between the patient being treated by the investigation drug and placebo or other therapy being tested. In Figure 1 we see good expectation of the medication therapy seen through the gap over time of being progression free.
Molecular Formula: C_{29}H_{26}ClF_{4}N_{4}O_{4}S (C_{7}H_{8}O_{3}S)_{2} \cdot H_{2}O

The developing of Tykerb was initially U.S approved in 2007. Through the development of new and better medication like Tykerb, this has provided a chance of a better survival rate for women and men affected.\textsuperscript{9} Tykerb a TKI is used in combination with another medication for a therapeutic treatment for patients. The use of capecitabine (Xeloda) a medication developed by Roche Pharmaceuticals is used in conjunction with Tykerb.\textsuperscript{7} This TKI (Tyrosine Kinase Inhibitor) inhibits the EGFR and HER2 receptors. Tykerb is also used with another medication called letorozole (tradename: Femara) with patients that have a positive hormone receptor metastatic breast cancer. In this case cell growth is targeted where hormone production takes place and can cause normal and abnormal cell growth to occur in women. This treatment is typically indicated for women that are postmenopausal although production of hormones is no longer in ovaries; estrogen is still produced through a conversion of another hormone that is produced by adrenal glands. Therefore postmenopausal women are still at risk for this type of breast cancer.\textsuperscript{8} Since these cells are estrogen fuelled, the combination of anti-estrogen medication Femara is used to help slow down cell production with the use of Tykerb indication of inhibiting the kinase receptors. The table below shows the results from clinic trials ran by providers listed under the investigator assessment and then a follow up analysis of the same data listed under the independent assessment. In this clinic trial there were 399 patients that were involved with 198 under the therapy of Tykerb and Xeloda (capecitabine), and 201 patients under the therapy of just Xeloda, but at a slightly higher dose when treated under the combination therapy with Tykerb.\textsuperscript{7}

### Table 2-Efficacy Results

<table>
<thead>
<tr>
<th></th>
<th><strong>Independent Assessment</strong></th>
<th><strong>Investigator Assessment</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TYKERB 1,250 mg/day +</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Capcitabine 2,500 mg/m²/day</strong></td>
<td>(N = 198)</td>
<td>(N = 201)</td>
</tr>
<tr>
<td><strong>Capcitabine 2,000 mg/m²/day</strong></td>
<td>(N = 201)</td>
<td>(N = 201)</td>
</tr>
<tr>
<td><strong>Capcitabine 2,000 mg/m²/day</strong></td>
<td>(N = 201)</td>
<td>(N = 201)</td>
</tr>
<tr>
<td><strong>Number of TTP events</strong></td>
<td>82</td>
<td>102</td>
</tr>
<tr>
<td><strong>Median TTP, weeks (25%, 75%, Percentile), weeks</strong></td>
<td>27.1 (17.4, 49.4)</td>
<td>18.6 (9.1, 36.9)</td>
</tr>
<tr>
<td><strong>Hazard Ratio (95% CI)</strong></td>
<td>0.57 (0.43, 0.77)</td>
<td>0.72 (0.56, 0.92)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
<td>0.00013</td>
<td>0.00762</td>
</tr>
<tr>
<td><strong>Response Rate (%) (95% CI)</strong></td>
<td>23.7 (18.0, 30.3)</td>
<td>13.9 (9.5, 19.5)</td>
</tr>
<tr>
<td></td>
<td>31.8 (25.4, 38.8)</td>
<td>17.4 (12.4, 23.4)</td>
</tr>
</tbody>
</table>

TTP = Time to progression.
The analysis shows that under the combination therapy of Tykerb and Xeloda the median TTP (time to progression) was 27.1 weeks from the beginning of treatment. In comparison to just the therapy of Xeloda given to patients, there was almost a 9 week decrease that progression would be present in patients when compared to the Tykerb and Xeloda combination therapy. The hazard ratio of clinical trials shows that 43% had success in achieving the 27.1 weeks of time to progression in their diagnosis. Figure 2 shows the data from the Independent Assessment analysis of the clinical trials. We can see quite a gap between the Tykerb+C combination therapy versus the Xeloda therapy by itself. This gap is consistent to showing promising results towards progression free when patients are under the treatment of Tykerb+C combo.

Figure 2—Graph of Independent Assessment

![Graph of Independent Assessment](image)

Figure 3—Graph of Investigator Assessment

![Graph of Investigator Assessment](image)

Figure 3 shows the graph of the data analysis provided directly from the Investigator's Assessment of the clinical trials in which they were running. Through this analysis on a graph platform there is slight decrease in the gap presented within the data from the trials. Therefore the analysis shows that there is a slight decrease in time frame until progression of the disease will occurred.

<table>
<thead>
<tr>
<th></th>
<th>TYKERB 1,250 mg/day + Capcitabine 2,000 mg/m²/day (N = 207)</th>
<th>Capcitabine 2,500 mg/m²/day (N = 201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Survival</td>
<td>Died 76%</td>
<td>82%</td>
</tr>
<tr>
<td>Median Overall Survival (weeks)</td>
<td>75.0</td>
<td>65.9</td>
</tr>
<tr>
<td>Hazard ratio, 95% CI (P value)</td>
<td>0.89 (0.71, 1.10)</td>
<td>0.276</td>
</tr>
</tbody>
</table>

CI = confidence interval

Table 3 shows the data from overall survival of patients that were under the targeted treatment of Tykerb and Xeloda. This data was followed for 2 additional years following trials with some data including patients that eventually crossed over when
being unblended of those only having mono-therapy of Xeloda. 


Through this data there an improvement is seen through combination drug therapy than just the single drug therapy of Xeloda.

<table>
<thead>
<tr>
<th>Table 4—Efficacy Results of Tykerb Treatment and Letrozole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HER2(+) Population</strong></td>
</tr>
<tr>
<td><strong>TYKERB 1500 mg/day + Letrozole 2.5 mg/day</strong> (N = 111)</td>
</tr>
<tr>
<td><strong>LETRAZOLE 2.5 mg/day</strong> (N = 108)</td>
</tr>
<tr>
<td>Median PFS, weeks (95% CI)</td>
</tr>
<tr>
<td>32.8 (24.7, 43.1)</td>
</tr>
<tr>
<td>59.7 (44.8, 68.9)</td>
</tr>
<tr>
<td><strong>P value</strong></td>
</tr>
<tr>
<td>0.019</td>
</tr>
<tr>
<td>0.10</td>
</tr>
</tbody>
</table>

PFS = progression-free survival; CI = confidence interval.

The development of advanced metastatic breast cancer has been associated with postmenopausal woman having a hormone receptor positive. With having a hormone receptor positive, patients have estrogen levels that are associated with cell growth that can be abnormal and consist with breast cancer. In Table 4, there is data showing that the use of HER2(+) with positive hormone receptors under the therapy of Tykerb and Letrozole show a Progression Free Survival (PFS) of 35.4 weeks having 29% Hazard ratio of being successful towards that length of progression free from disease. Under a hormone positive receptor with a HER2(-), there is no significant improvement in the treatment of the condition when treating with a combination therapy of Tykerb and Letrozole versus Letrozole by itself as the primary therapy for patients.

**Figure 4—Graph of Efficacy Results of HER2(+) Population**

In figure 4, the data lines show good success towards Progression Free Survival up until around 60 weeks. This improvement although slight does allow for better success than through just a mono-therapy of anti-estrogens of Letrozole (Femara).

The diagnosis of cancer is very much present through the United States and the entire world. Everyday there is new and improved medical advances in medication that have allowed for patients to be given a new light towards survival as cancer patients. Some patients don't like to take medication, because sometimes we just don't know why medication work they do. As we can see through our advancement of diagnostics of
patients, pharmaceutical companies have been given greater chance for providing specific therapy that we see through Tyrosine Kinase Inhibitors. Over the past year, I've personally been affected and have seen the great aspects to treatment through these medications. With my father's diagnosis with Chronic Myeloid Leukemia, he was given a new hope and light through his treatment given under the Gleevec therapy. The Gleevec therapy has given my father a second chance of life and reducing one's worse fears of having leukemia or cancer for that matter.

**Mechanisms**

Gleevec\textsuperscript{13}
Mechanisms for Votrient and Tykerb

Unable to located chemical structure mechanisms for drug preparations through multiple resources of information.
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10. Mike Kar. Oncology Pharmaceutical Representative. GlaxoSmithKline, Personal Interview
Chocolate Benefits:

"The Sweet Truth about Chocolate and Your Heart"1

Prepared for
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Abstract

Eating dark chocolate is beneficial to the human body in different ways. This is due to the existence of a unique type of antioxidant called flavonoid. The flavonoid level is much higher in dark chocolate than any other types. It helps regulate blood pressure and affects blood vessel function. Therefore, it lowers the chance of having a heart attack.

Introduction

Between all the candies available for consumers, chocolate is one of the choices that most of the people do not stop purchasing and enjoy eating even after they grow up. There is no age limit for loving chocolate. In fact the love between chocolate and the consumer grows bigger and stronger through their aging process. They love and enjoy eating chocolate even more as they become older. There are many different kinds of chocolate; which one to eat is a question whether they want the benefits or just the taste of chocolate. Scientists realize that flavonoids are beneficial to the human body after years of research. Flavonoids are beneficial in many known ways such as making blood vessels function a lot faster, lowering blood pressure, helping to prevent heart attack, or at least lowering the chance of having one.

Types of Chocolate and Substances Inside

There is a range of products which come from cocoa (cacao), mixed with fat and powdered sugar to produce the well known chocolate. There are different types of chocolate such as dark, milk, semisweet, bittersweet, and white. Which one to eat and enjoy is a personal preference and depends on the taste of the individual. Dark chocolate is produced by mixing cacao, sugar, and fat. There is no milk added to dark chocolate. On the other hand, milk chocolate, as the name describes, is chocolate with milk powder. Semisweet chocolate is the same as dark chocolate with half of the sugar, and bittersweet is a third sugar. The white chocolate does not have cocoa solids as one of the ingredients and because of that, some people do not even include white chocolate as a part of the chocolate family.

Flavonoids, also collectively known as Vitamin P, are a class of plant secondary metabolites. According to the IUPAC nomenclature, they can be classified into:

1. Flavonoids: derived from 2-phenylchromen-4-one (2-phenyl-1,4-benzopyrone) structure (examples: quercetin, rutin).
2. Isoflavonoids: derived from 3-phenylchromen-4-one (3-phenyl-1,4-benzopyrone) structure
3. Neoflavonoids: derived from 4-phenylcoumarine (4-phenyl-1, 2-benzopyrone) structure.

![Figure 1: IUPAC Flavonoids Classification](image-url)
<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
<th>Structural formula</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flavone</td>
<td>2-phenylchromen-4-one</td>
<td></td>
<td>Luteolin, Apigenin, Tangeritin</td>
</tr>
<tr>
<td>Flavonol or 3-hydroxyflavone</td>
<td>3-hydroxy-2-phenylchromen-4-one</td>
<td></td>
<td>Quercetin, Kaempferol, Myricetin, Fisetin, Isoflavonol, Pachypodol, Rhizmazin</td>
</tr>
<tr>
<td>Flavanone</td>
<td>2,3-dihydro-2-phenylchromen-4-one</td>
<td></td>
<td>Hesperidin, Hesperetin, Eriodictyol, Homoseoeidictyol</td>
</tr>
<tr>
<td>Flavanoneol or 3-hydroxyflavone</td>
<td>3-hydroxy-2,3-dihydro-2-phenylchromen-4-one</td>
<td></td>
<td>Taxifolin (or Dihydroquercetin), Dihydrokaempferol</td>
</tr>
</tbody>
</table>

Figure 2: Flavones Types

Dark chocolate is one of the types of chocolate with the most amount of flavonoids because of a higher percentage of cocoa use.

**Circulatory System**

In order to understand the effects of flavonoids on the blood vessel functions and the heart, it is better to first discuss the actual circulatory system and see how it works.

The circulatory system is an organ system that is similar to streets and highways with cars going to work or coming back from work. Instead of cars, there are blood cells, nutrients, such as amino acids and electrolytes, hormones, gases, etc. Some of them go to the cells just like going to work, and some of them come out of the cells. The one main difference is they all return to the heart as their main home to refresh and go back to work again. Their main job is to fight diseases and maintain homeostasis by stabilizing body temperature and pH.

The main components of the human cardiovascular system are the heart, blood, and blood vessels. It is very important for the heart to have clean and clear blood vessels in order for it to pump blood through by repeated, rhythmic contractions. Just like humans the cells need oxygen to live and function. One of the major jobs for heart is to pump the oxygenated blood to the cells. When people have physical activities their heart starts beating faster due to a lack of oxygen in the active area.
A problem occurs when one of the blood vessels is blocked because of high blood cholesterol or high blood pressure. If it's a vein or artery anywhere in the body, the human body starts making new ways to transfer the blood but if it is one of the veins or arteries that transfer the blood to the actual heart muscle, people can have a heart attack. What actually is happening is oxygenated blood cannot get into the muscle tissues and cells on time, and they die and eventually the heart loses its rhythmic beat and stops beating.

Figure 3: Heart Anatomy

The blood vessels are divided into three different types: arteries, veins, and capillaries. They are not similar anatomically. There is smooth muscle around both arteries and veins with the difference of having a much thicker layer in arteries and more elastic fibers. The largest artery is the aorta that is leaving the heart. Arteries have to expand in order to accept the blood being forced into them from the heart. Arteries have the property of elasticity, meaning that they can expand to accept a volume of blood, and then contract and squeeze back to their original size after the pressure is released. "If the arteries did not have this property, your blood pressure would be more like 120/0, instead of the 120/80 that is more normal."

Figure 4: Blood Vessel Anatomy
Benefits of Chocolate

There have been many researchers working on the benefits of chocolate to the heart and the virtue of flavonoids. It is known that an intake of flavonoids can help reduce the chance of having a heart attack; it makes blood vessels respond faster in contractions and relaxation, and also regulates blood pressure. As Joan Aragone states in her article, "UCSF scientists are publishing sweet results of a study examining chocolate's effects on blood vessel function in healthy people." The study was randomized, placebo-controlled, giving 11 people 46 grams of dark, flavonoid-rich chocolate every day for two weeks, while 10 others received dark chocolate with low-flavonoid content. "At the end of the two-week trial, the group with flavonoid-rich chocolate had 1.3 percent dilation increase in their blood vessels versus the group with low-flavonoid that had 1 percent decrease." After computing the statistics, the lead author Mary Engler, PhD RN, professor of physiological nursing in the USCF School of Nursing and her team came to the following conclusion: "Improvements in endothelial function [the ability of the artery to dilate] are indicative of improved vascular health and a lower risk for heart disease," Engler says. "Arteries that are able to dilate more have increased blood flow, and this is especially important for the heart." 

Effects of eating Chocolate

Eating chocolate can be beneficial in many ways; one of them is helping lower the chance of having a heart attack. As Lee Bowman states, "There's more evidence that cocoa rich in cholesterol-battling antioxidants helps ward off some of the factors associated with heart attacks and stroke, scientists lecturing here Friday during the annual meeting of the American Association for the Advancement of Science said." But one thing that researchers found is that not all the flavonoids are created equal. As Carl Keen, chairman of the nutrition department at the University of California-Davis, said: "What we're finding, though, is that all flavonoids are not created equal. There are some foods that are richer in them, and seem to be more biologically active, and cocoa is right up there." He compared the reactions of platelets to a flavanol-rich cocoa drink and a blood-thinning, 81-milligram dose of aspirin, and found similar reactions in a group of 20- to 40-year-olds.

"What we don't know is just what the dose-effect of this might be over a longer period of time," Keen said. "We have some research that shows eating foods high in flavonols is good for the arteries, but we don't yet know what the minimum amount is you can consume to have the effect you want, or what happens if you consume at these levels for weeks or months." Another chocolate researcher, Dr. Norman Hollenberg of Brigham and Women's Hospital, reported findings that flavanols may be associated with controlling another chemical that regulates the arteries, nitric oxide. The compound is critical for healthy blood flow and pressure, Hollenberg said. "If our research results continue to support a link between consumption of flavanol-rich cocoa and nitric oxide synthesis, there could be significant implications for public health." In addition to having antioxidant qualities, research indicates that flavanols have other positive influences on vascular health, such as lowering blood pressure and improving blood flow to the brain and heart, making blood platelets less sticky and able to clot, and lowering cholesterol.
Fat in Chocolate

Chocolate manufacturers do not use the type of fat that is unhealthy for human body. Essentially comprised of cocoa butter and equal amounts of oleic acid, \((\text{CH}_3 (\text{CH}_2)_7 \text{CH} = \text{CH} (\text{CH}_2)_7 \text{COOH})\) \(^8\), a heart-healthy monounsaturated fat is found in olive oil. There are also other types of acid being used in the chocolate industry that comes from saturated fat such as stearic acid. As it was mentioned at Cleveland Clinic website, "Research shows that stearic acid appears to have a neutral effect on cholesterol, neither raising nor lowering it." \(^1\)

![Oleic acid, a monounsaturated fatty acid. Note that the double bond is cis; this is the common natural configuration.](image)

![Stearic acid, a saturated fatty acid](image)

**Figure 5**: Oleic Acid Structure

**Figure 6**: Stearic Acid Structure

Summary and Conclusions

Chocolate and the antioxidant inside called flavonoid show benefits to the heart and blood vessels by lowering blood pressure and even lowering bad cholesterol. It is not necessary to eat a great deal of dark chocolate to be healthy, but it is definitely a better choice eating dark chocolate over other types of chocolate and especially other types of candies. The hearts role in the human body is extremely important, at the same time, taking good care of it is very easy. In fact, by simply doing some cardiovascular exercises, changing the eating habits and including dark chocolate in the daily menu reduces the chance of a heart attack. After all, we all want to live a longer life with fewer diseases and with properly functioning organs. We could help achieve some of this by eating dark chocolate!
References


Insomnia:
The Struggle of Mind over Mattress

Jared Kaufer
Abstract

Insomnia is among the most common medical complaints; while suffering from insomnia, patients will awaken with low energy, often in bad moods. This condition will also affect the individual’s work performance, health and the quality in which he lives his life. Common symptoms of insomnia include the inability to sleep although very tired, daytime tiredness, anxiety as bedtime approaches and tension headaches. Many causes of insomnia exist such as substance abuse, anxiety, and depression. Although millions of people suffer from insomnia every night, they can take steps in order to battle this disease. Among the treatments available for insomnia, prescription medications are the most popular; however, numerous doctors recommend that their patients participate in non-medical treatments such as cognitive therapy and sleep hygiene therapy.

Introduction

Every day, patients all over the world go to see their primary care physicians with the most common complaint being the patients cannot fall asleep at night. The Mayo Clinic describes insomnia as the inability to fall or stay asleep. This can take a toll on patient’s energy levels, mood, and work performance. With this being one of the top diagnosed diseases in America, the estimate in 2009 was 50-70 million Americans who suffer from insomnia, while about 10 percent of that population reported that it does not receive enough sleep to function efficiently during the day due to lack of sleep. Also, According to the University of Maryland Medical Center, 40-60 percent of those people diagnosed with insomnia show signs of depression. While this may be the case, significantly important as well is that about 50 percent of insomnia cases have no identifiable cause. Much of today's pharmacological business comes from prescription medications intended to help patients receive a full night of sleep. Of the top 100 drugs prescribed today, a number of different medications purport to treat insomnia including Klonopin®, Ativan®, Valium®, Ambien®, Lunesta®, and Restoril®.

Different types of insomnia have different effects on patients. The least worrisome type of insomnia is called primary insomnia. Primary insomnia is the inability to fall and stay asleep with no relation to other medical conditions such as depression, anxiety, and fibromyalgia, among others. However, if no other medical conditions seemingly influence a patient’s insomnia, the diagnosis is Co-morbid insomnia. Co-morbid insomnia is the most common form of insomnia. Patients with this form also experience everything from anxiety, pain, and depression to restless leg syndrome and sleep apnea. Restless leg syndrome is a central nervous system disorder in which patients experience twitching and strange sensations in their legs. Sleep apnea occurs when the patient stops breathing temporarily during sleep due to the blockage of the airways in his throat because the muscle fails to relax. This will cause the patient to wake up several times a night to catch his breath, even though he rarely is aware of what just happened to them. The last type of insomnia is Chronic insomnia in which patients experience lack of sleep almost every night of the week, which can also occur due to medical problems or bad sleeping habits.
Biochemistry of Insomnia

The human body takes on a method that helps put the person asleep; the driving force for this process is the body’s ability to produce serotonin. The cause for insomnia in patients who suffer multiple times a month is the result of the body not being able to produce sufficient amounts of the neurotransmitter melatonin. According to Dr. Plesman, melatonin is “a hormone produced in the brain by the pineal gland from the amino acid tryptophan.” Melatonin is dependent on light, meaning that the synthesis of melatonin will only happen if it is dark. In most people, the highest levels of melatonin in the blood are just prior to bedtime, thus being the chemical that gives a sleepy or tired feeling. This is a reason that a number of doctors recommend patients do not read or watch television before they go to bed, as with the lights on, the body is not producing the necessary melatonin to fall asleep.

In order for the body to create melatonin, it must start with tryptophan. Tryptophan is one of the ten essential amino acids that the body uses to synthesize the necessary proteins. The body then converts the amino acid tryptophan into serotonin. Serotonin is a hormone found in all animals, mainly in the pineal gland. This hormone is a messenger that transmits nerve signals and decides whether to narrow the blood vessels or not. Serotonin converts into melatonin in the pineal gland of the body, which creates the feeling of tiredness.

![Tryptophan to Serotonin and Melatonin](image)

Treating insomnia and treating depression are often very similar in that both diseases are effects of an imbalance of serotonin, and may also result from anxiety. The root of the insomnia biochemistry problem is that in order for the body to get sufficient amounts of melatonin, the body must absorb plenty of Vitamin B6, Magnesium, and Vitamin D in order to convert serotonin from tryptophan. If the body cannot produce serotonin, it is impossible for the body to then create the necessary melatonin for sleep. In addition, if the body has a deficiency of Vitamin B3, which is known as Niacin, this will cause the body to use all of the available tryptophan to convert it to Niacin to replace the lack of this vitamin. The end result is little to no tryptophan left over for conversion to serotonin.

Various sources lead to insomnia, from drug abuse to chemical imbalances in the body. During restless nights in which people cannot achieve sleep, environmental stresses and excitement are often the cause. With environmental stress, the body naturally produces adrenaline and/or cortisol; both of these chemicals interfere with the body’s production of serotonin.
Insomnia also has an effect on the heart. In a recent study conducted at the Universite de Montreal, published in the journal *Sleep* found that “people who suffer from insomnia have heightened nighttime blood pressure, which can lead to cardiac problems." This study measured the 24 hour blood pressures of sound sleepers and that of insomniacs. Dr. Paola Lanfranchi, a professor at the Universite, said, “Whereas blood pressure decreases in regular sleepers and gives their heart a rest, insomnia provokes higher nighttime blood pressure that can cause long-term cardiovascular risks and damage to the heart.” This is important because blood pressure and cardiovascular problems are common conditions among the American population. This means that insomnia is very important to treat before the patients become victims of high blood pressure and have to start going on blood pressure medications in addition to insomnia medication.

**Causes of Insomnia**

The most common and dangerous cause for insomnia starts with substance abuse. With addicts everyday looking for new ways to get high, they increase the risks of not only insomnia, but often experience more life threatening effects. One category of drugs commonly abused is stimulants. Stimulants are drugs “that elevate mood, increase feelings of well-being, and increase energy and alertness.” Stimulants are psychoactive drugs that induce temporary improvements in physical or mental function by enhancing activity of the central and peripheral nervous systems. The most common stimulants include caffeine, nicotine, alcohol and sugar.

Among the more serious stimulants that are not only illegal, but very dangerous and addictive include ecstasy and cocaine. Ecstasy has the chemical name of 3,4-ethylenedioxythoamphetamine, but most know it as MDMA. The drug works by binding to serotonin transporters, which in turn, terminates the signal between neurons.

Another illegal stimulant is benzoylecgonine, also known as cocaine. Cocaine comes in a powder form from the coca plant but also comes in a smokable form, called “crack” on the streets. Cocaine has the same effect as Ecstasy as it targets and stimulates the central nervous system, therefore opening the door for insomnia troubles. Another drug commonly abused but often overlooked as a drug by the average person is alcohol. Alcohol is a depressant, which is a drug that temporarily diminishes the function or activity of the brain. While alcohol acts as a sedative that helps a person fall asleep, alcohol “prevents deeper stages of sleep and often causes a person to awaken in the middle of the night”. These are the most common dangerous drugs to take due to their effects on the body. Also, if people are experiencing sleep issues, they should take a look at what they eat and drink every day, and they will be able to identify something that they may be able to change that will help them get sufficient sleep.

While substance abuse is the most recognizable cause of insomnia, other medical conditions can affect a person’s ability to get
a good night’s sleep. A physical condition that doctors often point to is fibromyalgia. Fibromyalgia is a condition in which patients have tender spots at various places in their bodies, such as their necks, shoulders, backs, and arms, and these points will cause pain if these areas experience pressure. This condition causes insomnia because patients cannot find a comfortable position to lie in while trying to get rest. No matter where they lie, they will apply pressure to one of those tender spots causing the patient pain throughout the whole night, preventing successful sleep. In cases of extreme insomnia, people must be aware of sleep apnea. This is a common disorder when patients experience shallow breaths or pauses in breathing while a patient is sleeping. This can occur for anywhere from a few seconds to a few minutes. This happens when the airway becomes obstructed, or completely blocked, causing the blood oxygen levels to lower until the brain detects it and sends the signal to the body to twitch and wake up. People usually will wake up due to having to catch their breath, which often takes the form of a big gasp. For this reason, extreme cases of sleep apnea can keep someone up all night long as the brain will keep the person awake in order for the blood oxygen levels to stay at a standard level.

Along with physical conditions, psychiatric conditions also play a major role in determining if a person has insomnia. Anxiety and Depression are both very common conditions that affect people across America every day. The Surgeon General of America describes anxiety as “a group of conditions that share extreme or pathological anxiety as the principal disturbance of mood or emotional tone.” Anxiety is closely related to the concept of fear in that when people feel anxiety, it is a result of disturbances of mood, thinking, physiological activity, and behavior. For these reasons, people who suffer from anxiety clearly have difficulty falling or staying asleep. Another psychological condition that millions of Americans suffer from is depression. Depression occurs when chemical imbalances in the brain exist. Depression can also accompany anxiety in that worrying what will happen the next day or what happened that day will keep someone tossing and turning all night long. While both of these psychological conditions are the most common causes of insomnia, branches of both of these mental illnesses can cause people severe troubles in addition to disrupting their sleep cycles.

While many people in America suffer from insomnia, science and technology have allowed scientists to synthesize drugs such as benzodiazepines and non-benzodiazepines to help treat people who suffer from insomnia.

**Benzodiazepines**

Benzodiazepines are a family of medications, within the same branch as depressants, which therapeutically induce sleep, relieve anxiety, relieve muscle spasms, and prevent seizures. These drugs act as a hypnotic in high doses and sedatives in low doses. Benzodiazepines are among the most marketed and most commonly prescribed medications that affect the central nervous system.
When prescribing benzodiazepines, some drugs treat sleep-onset insomnia, for patients with insomnia but who have no daytime anxiety. Among the drugs in this group are temazepam (Restoril®), flurazepam (Dalmane®), stazolam (ProSom®), and triazolam (Halcion®). The drug triazolam is a very potent drug and recently the government passed a law that outlawed the drug to be packaged in quantities higher than 10 tablets. This was passed because people using triazolam were often found suffering from dementia, and was lethal if overdosed on.

There are also benzodiazepines that are used in patients who suffer from not only insomnia troubles, but also daytime anxiety. These drugs include alprazolam (Xanax®), diazepam (Valium®), clonazepam (Klonopin®), lorazepam (Ativan®). Under the Controlled Substance Act (CSA), benzodiazepines are depressants and are schedule III medications. With repeated use of these drugs in high doses, even in therapeutic doses of these medications, they can cause patients amnesia, hostility, irritability, and disturbing and vivid dreams on top of tolerance and physical dependence. Withdrawal from these medications can cause the patient severe side-effects, causing the patient to seek treatment from a hospital. If the doctor wants to take a patient off the medication, he will usually tamper down the doses over a time period to lessen the withdrawal symptoms.

**Non-Benzodiazepines**

Often the first step of treatments for patients with insomnia is this class of medications. Along with treatment for insomnia, doctors use non-benzodiazepines during surgical anesthesia. These medications, along with benzodiazepines, can be addictive and users must be careful and responsible.

One of the more commonly prescribed drugs for insomnia is Eszopiclone, brand name Lunesta®. This drug is one of the safest drugs to use for insomnia, as it has the smallest chance of becoming addictive, and has no use for recreation as it doesn’t cause the user to achieve a “high.” Common side effects of Lunesta® are loss of coordination, dizziness, and metallic taste in the mouth.

Ramelteon (Rozerem®) is a fairly new drug that scientists developed which selectively binds to melatonin receptors and is the only sleep aid that is not scheduled with the CSA. The FDA has approved this drug to control long-term treatment for insomnia, and it works best for patients who have the case of delayed sleep onset.

The most common drug used for treatment of insomnia of all the classes of medications is the drug Zolpidem Tartrate (Ambien®). Zolpidem Tartrate comes in two strengths, 5mg and 10mg; however, it is
available as the name brand Ambien for the controlled release 12.5mg tablets. Zolpidem Tartrate is for short term treatment of insomnia and also has a side treatment for restless leg syndrome. This drug can become addictive if taken for a long time and produce hallucinations, delusions, anterograde amnesia, and impaired judgment. 

Nonpharmacologic Management of Insomnia

Science has advanced in the synthesis of new drugs to help patients get through all sorts of problems they face throughout their lives. All sorts of different drugs are available for different conditions - from drugs that help children who suffer from Attention Deficit Disorder, to more mature patients who suffer from common conditions such as high cholesterol, and high blood pressure. However, many people wish to stay as far away from these medications as they can because of the potential side effects these drugs present. In the treatment of insomnia, people can try various methods before reverting to any of these [non]benzodiazepine drugs.

One of the therapies that have proven to lessen the effects of insomnia is Cognitive Therapy. The goal of this is to “break the cycle of insomnia, emotional distress, dysfunctional beliefs, and further sleep disturbances.” This therapy starts with taking control of the patient’s dysfunctional beliefs about sleep, challenging the legitimacy of them, and replacing them with better substitutes. While this technique works better with older patients, it is effective in people of all ages. An example of this concept is that the patient will talk with his physician about the patient’s realistic expectations about his sleep requirements, the outcomes of his insomnia, and realistic and healthy strategies to help promote sleep for the patient.

Sleep Hygiene Education has become popular with a great number of physicians lately. This is the education of the physician’s patients about good sleeping habits. Such good sleeping habits include avoiding drinking caffeine in the evening and avoiding eating heavy meals within two hours of bedtime. Another point that the physicians make to their patients is to not drink many fluids before bedtime in order to avoid nighttime urination. As far as exercise goes, it is very important that the patients take part in some sort of exercise activity during the day and avoid exercising at nighttime in order to get the heart rate and blood pressure under control to promote good sleeping. Lastly, when waking up in the morning, doctors recommend that patients get at least a half an hour of daytime light. These are all techniques proven to work in patients who suffer from insomnia.

Lastly, science has proven stimulus control to be the most effective therapy for treating insomnia. Doctors teach the patients to eliminate distractions in the bedroom and associate only sex and sleep for bedroom use. If the patient wants to watch television or read, the patient should go to another room other than the bedroom. The patient will also learn to go to sleep when he is tired, and if he does not fall asleep within 15-20 minutes, he should remove himself from the room and go get a drink of water or do something else relaxing. Stimulus control also teaches that patients can no longer take naps, and waking up at the same time each day is necessary. Using one or most of the above techniques often prevents a patient’s need for prescription medications.
**Personal Opinion**

Working in a pharmacy has opened my eyes to many problems that patients face every day. Among the ‘fast movers’ that my pharmacy dispenses, are Ambien®, Restoril®, Lunesta®, alprazolam, lorazepam, clonazepam, and diazepam. All of these medications treat patients who suffer from insomnia. Often times these patients will obviously develop an addiction to these medications, especially the Xanax, calling to request more 10-15 days before they are due for their refill. Not only this, but I have caught plenty of times people writing in refills on the hardcopy their doctor gave them when the doctor didn’t intend to give any refills. Due to this, I would recommend that a person try out some of the nonpharmacologic means to treat insomnia. Cognitive therapy, sleep hygiene education, and stimulus control are all very effective means to achieving that good night’s rest. A safer option is for insomniacs to talk to their doctors about alternative means for treating their condition before asking the doctor for these scheduled and addictive medications.

**Conclusion**

In conclusion, about 50 percent of Americans deal with the effects of insomnia. The body needs to produce the necessary serotonin to help the body fall asleep. A variety of causes can prevent that from occurring, leading to insomnia. These causes may include substance abuse, other medical conditions, anxiety, and depression. Scientists were able to synthesize drugs through research that help insomniacs get the sleep that they need. Different drugs treat the condition – most of the most common are Zolpidem (Ambien®), and Alprazolam (Xanax®). Since some undesirable side effects to many of these medications exist, physicians have come up with alternative means for treating insomnia, such as cognitive therapy, sleep hygiene education, and stimulus control. These are effective alternatives to drugs. With millions of Americans suffering from insomnia, doctors must take the necessary steps to diagnose the right type of insomnia in their patients, and give them the right pathways to curing or treating their insomnia problems, whether it is with a prescription medication, or through alternative means.
References:


The New Age of Medicine and Patient Health Care
Valerie Kerchner
April 22, 2010
Abstract

The world of medicine is evolving with evidence of new applications supplied from the Human Genome Project. Disease can now be classified into subgroups of the population using personalized medicine and genomics to target a gene's specific response to a drug on the market. Preventive health care can come into effect before symptoms are apparent due to individual human genomes, and new drug therapies can be applied throughout the drug development process.

It was recognized by Sir William Osler (1849-1919) that "variability is the law of life, and as no two faces are the same, no two bodies are alike, and no two individuals react alike, and behave alike under the abnormal conditions we know as disease" (1). In understanding Osler, it is unrealistic to assume that all individuals are to be subjected to identical medical treatment. However, this is what the pharmaceutical industry has been supporting throughout its development. The treatments are appealing to the masses of the population and the medicine is not personalized to the individual. So for that matter, what is personalized medicine? The most widely used definition is 'the right drug for the right patient', for clarification of this simple motto, undoubtedly no physician would knowingly prescribe the wrong medicine (2). The President's Council of Advisors on Science and Technology (PCAST) published a more comprehensive definition in their "Priorities for Personalized Medicine " report as follows:

'Personalized medicine refers to the tailoring of medical treatment to the individual characteristics of each patient. It does not literally mean the creation of drugs or medical devices that are unique to a patient rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease of their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and side effects for those who will not.'(2)

Personalized medicine makes the assumption that our current standard of diagnosis of human diseases and patient responses to both disease and therapeutic intervention are incomplete (2). The key piece of evidence that supports this is the variability in responses of patients to standard drug treatments (2). When listening to the radio or watching TV, a commercial for a new prescription drug on the market is often advertised. It begins by describing what the drug treats and some depiction of how it will make your life easier or better. By this time your full attention is centered on the ad and you start thinking it will fit you perfectly. Then at the end of the advertisement an endless list of side effects is brought forth. Suddenly the risks outweigh the benefits and that prescription drug doesn't seem so promising.

That unappealing list of side effects that include possible dangerous complications is a byproduct of the industry producing for the majority of the population. This brings forth a new attempt to individualize health care with specific emphasis on the Human Genome Project. Genomic medicine is the use of information from genomes (from humans and other organisms) and their derivatives (RNA, proteins, etc.) to guide medical decision making (1). Personalized medicine uses genomic medicine to take advantage of a molecular understanding of disease to optimize preventive health care strategies and drug therapies while people are still well or at the earliest stages of disease (1). Genetic variations give rise to the variable responses in individuals to any given drug treatment (1). Pharmacogenomics use genomic technologies to identify molecular patterns of response, drug disposition, and drug targets or conversely the effect of a drug on gene expression (1). A physician's access to an individual's genome ensues strategic selection of drug candidates that will produce a positive response and begin the treatment process at much earlier stages of a disease.
The current drug development process is what is known as linear where there is little availability for feedback or improvement until the later stages of development(3). Examples can be taken from recent and past reports regarding the unexpected side effects displayed by drugs already widely tested before being marketed(4). If the drug was efficiently tested, then there are variability factors in individuals that were not accounted for during drug testing, and proves the effectiveness of the drug only pertains to certain groups of the population. A new approach to the future drug discovery will involve a series of research feedback loops. Therefore the early stages of discovery, including selection and validation of drug targets, small-molecule screening and chemistry, and preclinical assessment of compounds, will be linked to the later stages of clinical development(3). This way at each stage of development of a drug new genomic markers and improvements can be made throughout the process of clinical trials in order to successfully apply a new drug for FDA approval.

Traditional drug discovery. Linear approach where feedback and improvements are not available until Phase IV(3).

Future drug discovery. Circular approach where new data is involved in developing a new drug throughout the stages of development(3).

One of the most sensitive drugs to individual variability is presumably Warfarin, Warfarin is an oral anticoagulant that is prescribed for the long-term treatment and prevention of thromboembolic events (clotting of blood in the blood vessel), with more than 21 million prescriptions annually in the U.S. alone(1). However, because of the drug’s narrow therapeutic index, a variety of complications is associated with its treatment, even after dose adjustment according to age, gender, weight, disease state, diet, and concomitant medications(1). The time to stable dosing with Warfarin can be many months, and thus patients can be at risk of excessive bleeding if the initiating doses are too high, or ineffective clot control if the doses are too low(5). Warfarin acts as a vitamin K antagonist by inhibiting the regeneration of reduced vitamin K, vitamin K epoxide reductase complex 1 (VKORC1), an essential cofactor of clotting(5). VKORC1 catalyzes the rate-limiting step of the vitamin K cycle and is inhibited by anticoagulants(5). The administered drug is a racemic mixture of S and R enantiomers, with the S enantiomer accounting for the majority of the therapeutic effect(5). Whereas R-warfarin utilizes several metabolic clearance pathways, S-Warfarin at therapeutic concentrations is metabolized predominantly by the enzyme CYP2C9, which converts the drug to 7-hydroxy and 6-hydroxy
A meta-analysis of nine studies involving almost 3,000 Warfarin patients indicates that carriers of the CYP2C9*2 and *3 alleles are at significantly higher risk of bleeding because they metabolize S-Warfarin more slowly (5). By combining patient clinical characteristics with knowledge of CYP2C9 and VKORC1 genotypes, as much as 60% of the variability in Warfarin dose requirements can be explained (5).

**Mechanism of action of Warfarin and roles of CYP2C9 and VKORC1 in modulating anticoagulation.** Warfarin exerts its pharmacological effect by inhibiting VKORC1. VKORC1 is the vitamin K cycle enzyme controlling regeneration of reduced vitamin K, an essential cofactor that drives formation of the clotting factors. CYP2C9 is the major P450 enzyme that metabolizes S-Warfarin to inactive metabolites. CYP2C9, Cytochrome P4502C9; VKORC1, vitamin K epoxide reductase complex 1, GGCX, gamma-glutamyl carboxylase (5).

The treatment response rates in cancer are amongst the lowest for any major disease, and this, coupled with now well-established genomic basis of cancer pathology, has long put cancer research in the vanguard of personalized medicine (2). Oncology has delivered key success in personalized medicine: the examples provided by Herceptin in breast cancer and Gleevec in chronic myeloid leukemia (CML) have long carried the mantle for individualized therapy (2). A humanized monoclonal antibody directed against the extracellular domain of the HER-2 receptor tyrosine kinase, Herceptin (Trastuzumab) is marketed solely for the subset of patients (about 10%) who over express the HER2/neu (2). The drug manufacturer Genentech knew that from its market research early on that the market would be limited to women with the HER-2 mutation, about 20% to 25% of breast cancer patients. The drug was approved for the HER-2 positive patients in the most advanced stages in 1998 and approved for the early diagnosis stage in November 2006 (6).

Gleevec (Imatinib), which was approved in 2001, is an inhibitor of the ABL tyrosine kinase that has become the primary therapeutic intervention for CML (2). Like Herceptin before it, Gleevec exemplifies how improved molecular classification of disease not only provides improved diagnostic information but also enables the development of therapies targeted towards these specific disease subsets (2). Imatinib was obtained through the addition of a methylpiperazine group to the para position of the benzamide, which greatly enhanced the water solubility and physicochemical properties of the
compound(7). Imatinib crystal structure reveals that it possesses a conserved hydrogen-bond pair between the ligand. There is one hydrogen bond with the side chain of a conserved glutamic acid and the other with the backbone amide of aspartic acid(7).

In figure b the structure of Imatinib is in green and the red fractured lines represent the hydrogen bonds.

Despite the early success of Herceptin and Gleevec, there was little encouragement for personalized medicine advocates in the area of targeted therapies for many years. Indeed, the failure of key drugs such as AstraZeneca’s Iressa (Gefitinib) undermined the rationale(2). Iressa, an inhibitor of the epidermal growth factor receptor tyrosine kinase that was approved by the FDA in 2003 based on phase II of drug discovery data in a non-small lung carcinoma (NSCLC), seemed to hold promise for personalized therapy(2). However, in 2005 its use was restricted to patients already benefiting or those enrolled in clinical studies in relapsing or refractory NSCLC(2). Although Iressa showed benefit in subsets of patients (notably women, Asians and non-smokers), it showed inconsistent response across the broader population(2). AstraZeneca did not give up on Iressa, however, they have pursued the efficacy in Asian populations with several large-scale studies in Asia(2).

Drug manufacturers have been loath to surrender broad markets and efficient marketing campaigns for more targeted patient populations(6). Drug companies are slowly coming around to the potential benefits of targeting certain treatments to smaller patient populations who genetic tests show will be more receptive to them(6). The list of diagnostic tests on the label for drugs approved by the FDA is growing as has the number of pharmaceutical products with package inserts recommending a genetic test for prescription selection or dosage. Now more than 200 product labels either recommend genetic testing or point to the influence of genetic variation on drug response or safety(1). The blockbuster approach, the idea of producing a drug for the masses of the population, does not bode well for big companies grappling with personalized medicine, according to Garth Powis, who chairs the department of experimental therapies at M.D. Anderson(8). Powis says,"If you think about it, the
blockbuster drug mentality that a lot of drug companies still have is unsustainable. If you have a blockbuster drug, you have to treat a lot of patients. If you're treating only 10% of lung cancer patients, you don't have a blockbuster drug"(8). John Sninsky, vice president of discovery research at Celera says,"Targeted practices have been going on for a long time, we just haven't been using the molecular information that has emerged in recent years with the sequencing of the human genome and transcription analyses"(8).

Even though there is recent progress in pinpointing a number of drugs that cater to subsets of the population there are still hurdles and skepticism in the pathway of personalized medicine. The access to the sequencing of the human genome is a tremendous step in the right direction but we're talking about identifying the responses of millions of genes to find which take part in a particular disease. This concept is going to take some time if implemented in the future, but the benefits that come about from this research is evidence enough. It will be worth the time taken to effectively document genes that have responses to marketed drugs in order to tailor medicine to the individual, slowly but surely it can be completed. There is another issue of having access to optimal relevant tissues, which for many diseases may not be possible(3). This is understandable and we're not talking about finding medicine for all the diseases in the world, although it might be desirable, we are simply just putting our foot through the door of personalized medicine. With a new way of viewing from a molecular standpoint a drug and the response that the body has on it, we can manufacture drugs that are specific to an individual.

Notably one of the most influential doubts of personalized medicine both from the professionals and the public is the cost. In the interest of the pharmaceutical industry ten to fifteen years ago the cost of developing a new drug was $300 million to $400 million, versus more than $1 billion today(6). That's money down the drain if a drug fails to get regulatory approval says Ross Miken, director of health-care services and technology research at Deutsche Bank Securities(6). Dr. Robert Epstein, Medco's chief medical officer, cites other kinds of drugs that have sold better when paired with a companion diagnostic test(6). One example is the generic drug Abacavir, an oral treatment for HIV, to which 6% of patients had a hypersensitivity reaction(6). Once a certain gene was uncovered that predicts with more than 99% certainty which patients will have the reaction--and the findings were published in The New England Journal of Medicine in February 2008, urging doctors not to prescribe the drug to that subgroup--sales of the drug increased 28% worldwide over the next eight months(6). Therefore drug companies that are concerned with losing money by marketing drugs to the subsets of the population can reevaluate the drugs they have previously released where adverse reactions were present. They then can develop a companion diagnostic test comparing specific gene responses to the drug and release new findings and advisories to enhance the efficacy of the existing drug. The advantages of personalized medicine to the pharmaceutical industry include increased efficiency and reduced costs of target and lead discovery, reduced time lines and costs of clinical trials, emergence of new gene targets for drug discovery, and product differentiation in the market(3).

In terms of the public, they aren't waiting. Awareness of personalized medicine is increasing with the rise in news coverage of technologies for early cancer detection and determining genetic aptness for diseases(8). Do-it-yourself testing kits are now available, and private companies offer routine screening(8). For example a company named Navigenics, a California-based genomics testing service charges $2,500 for an initial genetic scan and counseling session(8). Indeed this is a lot of money now because it is not widely used presently, however with the advancement in personalized medicine a genome of each individual would be necessary in order to perform a thorough analysis for drug therapy in the preventative stages. There are even reimbursement policies enacted that support genomic and personalized medicine to protect the public. The Advanced Laboratory Act of 2006
ensures that the payment system more accurately reflects the value of molecular diagnostic tests and their potential to reduce health care costs in the long run(1). The American Association of Health Plans advocates a policy of encouraging genetic testing and preventive care, even for presymptomatic individuals when those tests can lead to improvements in care(1). The Center for Disease Control ACCE Project is a model process for evaluating data on emerging genetic tests based on analytic validity, clinical validity, clinical utility, and associated ethical, legal, and social issues(1). The Evaluation of Genomic Applications in Practice and Prevention is an evaluation of genetic and genomic tests and establish standards for what constitutes adequate evidence for insurance coverage(1). The advantages of personalized medicine to patients and clinicians include higher probability of desired outcome with a drug, low probability of untoward side effects, preventive strategies, focused therapies, reduced costs, and better health and better health care(3).

![Diagram of the course of a chronic disease over time (red curve), illustrating the opportunities (over time) to use various molecular and clinical tools to refine risk of developing disease as well as screening, diagnosis, prognosis, and therapeutic selection.](image)

The government is also taking a stand to encourage personalized medicine with legislative policies that support it. The Genetic Information Non-Discrimination Act (GINA) ensures that all genetic information will be protected against misuse in health insurance and employment(1). Health and Human Services Personalized Health Care Initiative is designed to improve the safety, quality, and effectiveness of health care for every patient in the United States(1). The Genomics and Personalized Act is developing the potential of personalized medicine to improve the quality of health care and the policy changes needed to create a more accommodating landscape for it to thrive(1).

More than 100,000 deaths per year are attributed to adverse drug reactions(3). Personalized medicine promises to offer treatment for the right patient at the right time(3). There is clear evidence that the traditional trial-and-error practice of medicine is eroding in favor of more precise marker-assisted diagnosis and treatment(3). For the patient, the benefits are clear: safer and more effective treatment of disease(3). For industry there appears an equally desirable outcome of this approach: increased efficiency, productivity and better product lines(3). Society as a whole will also realize a benefit: more focused application of precious health care resources to those in need of them(3).

Personalized medicine will revolutionize the world of medicine. New treatments, new drugs, new therapies, so many things about how drug development is done today will shift to a preventive status in the early stages rather than the later stages. With all the talk of health care reform for the population, what the people want out of their health services, personalized medicine is the way to the future. Genomics can now be used to identify the response that specific genes have on certain drugs from a molecular standpoint and drugs can be modified to fit individual circumstances. With the success in cancer treatments it can now be seen that personalized medicince has promise, although this advancement has hurdles to overcome both in the scientific process and in society, it has established itself in the new age of medicine.


Treatments of Hyperthyroidism in the Feline Patient

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Abstract

In both humans and animals the thyroid glands play a key role in regulating metabolism. When the thyroid ceases to function normally the metabolism can either slow down (hypothyroidism) or speed up (hyperthyroidism) dramatically. This drastic change in metabolism can also affect other systems in the body including heart rate, vision, and kidney function, if left untreated. Treatments for hyperthyroidism include medication therapy, surgery, and radioactive iodine. This paper explores how hyperthyroidism affects the domestic feline, and the efficacy of the current treatments of this disease.

What are the Thyroid Glands?

The thyroid glands are part of the endocrine system and consist of two lobes which are located just below the larynx, next to the trachea. Their major functions are the synthesis and regulation of thyroxine (T\textsubscript{4}) and triiodothyronine (T\textsubscript{3}) hormones. These hormones are iodine containing amino acid derivatives of thyronine, and are instrumental in the regulation of growth and metabolism. Physiologically, the synthesis of these hormones begins in the hypothalamus. From there, thyroid releasing hormone moves to the pituitary gland where thyroid stimulating hormone (TSH) is produced. TSH activates the thyroid glands to synthesize and release T\textsubscript{4} and T\textsubscript{3}. The thyroid glands contain thyroglobulin, which is also responsible for the production and release of these hormones. Historically it was thought that the thyroid glands contained a lubricating fluid for the trachea. It was also believed that because women’s thyroid glands are larger than men’s, they functioned cosmetically to enhance the contour of the neck. Their large blood supply led others to conclude that the glands provided a pathway for increased blood flow to the brain. These early ideas led one scientist in 1820 to conclude the female’s larger glands were

“necessary to guard the female system from the influence of the more numerous causes of irritation and vexation of mind to which they are exposed than the male sex.”

This theory was argued by a man named Hofrichter:

“If it were indeed true that the thyroid contains more blood at some times than others, this effect would be visible to the naked eye; in this case women would certainly have long ceased to go about with bare necks, for husbands would have learned to recognize the swelling of this gland as a danger signal of threatening trouble from their better halves.”

In 1895 it was published that the enlargement of the thyroid glands was associated with changes in the heart and eyes. The work of Graves and Basedow, published in 1835 and 1840, also showed similar conclusions. In 1961 it was discovered that the thyroid glands are also responsible for the regulation of calcium.

\[ \text{HO} \quad \text{CH}_2\text{CH(NH}_{3}^+\text{)}\text{COO}^- \]

Fig. 1 Thyronine
The two most recognized diseases of the thyroid glands are hypothyroidism and hyperthyroidism. Hypothyroidism is characterized by under active thyroid glands, and is attributed to atrophy, or deterioration of one or both of the thyroid glands, or a decreased production of thyroxine and triiodothyronine hormones. The associated symptoms include the slowing of metabolism which generally leads to weight gain. This can be easily treated with oral thyroxine hormone supplements. Hyperthyroidism, or over active thyroid glands, is attributed to enlarged thyroid glands and an overproduction of the thyroxine and triiodothyronine hormones. Symptoms of hyperthyroidism are more complex than hypothyroidism and usually include increased appetite, weight loss, and high blood pressure. If left untreated, the increase in metabolism caused by hyperthyroidism may eventually lead to heart failure, and blindness due to retinal detachment. The most common treatments of hyperthyroidism include oral medication, thyroidectomy, or surgical removal of the thyroid gland, and radioactive iodine therapy.²

Hyperthyroidism in the Feline Patient

Hyperthyroidism is the most common endocrine disease in cats. Most cats that are affected are greater than 10 years old, but evidence shows that any age group over 2 years can be affected. A large percentage (98 to 99%) of hyperthyroid felines have adenomas, or benign tumors of the thyroid gland, and fewer than 2% have adenocarcinomas, or malignant tumors. The
cause of hyperthyroidism remains unknown, but some studies suggest that cats that eat canned food or use litter boxes are at an increased risk. This may be due to the fact that fish or liver flavored foods have high concentrations of iodine.\(^3\)

In the feline patient, hyperthyroidism is formally diagnosed with a blood test that shows an increased serum total thyroxine (T\(_4\)) concentration. The patient usually presents with clinical signs such as polyphagia, or increased appetite, weight loss, and a greasy or unkempt hair coat. Occasionally hyperactivity or aggression is also noted. Upon physical examination an enlarged thyroid gland may be palpable, and hypertension may be noted, but the normal clinical signs are enough to warrant blood screening. In the event that the serum total T\(_4\) concentration appears to be borderline high in the reference range, a serum free T\(_4\) concentration should also be measured. More thorough blood tests should be preformed if the clinical signs of hyperthyroidism are present, but total and free T\(_4\) concentrations are normal to low. This is because concurrent kidney disease may falsely lower these results. Diagnosis of hyperthyroidism can also be achieved by thyroid scintigraphy, where radioactive technetium 99m is injected into the patient, and concentrates in the thyroid gland. This diagnostic tool is the most definitive, but due to cost and safety, it is not normally preformed in standard veterinary practices.\(^3\)

![Visible Thyroid Growth](image1.png)

![Thyroid Scintigraphy](image2.png)

**Medicinal Therapy**

Treatment of hyperthyroidism in cats is similar to that of human patients. Upon a positive diagnosis of the disease, the first step in treatment is oral or transdermal antithyroid medication. There are two antithyroid medications that can be used in cats; methimazole and propylthiouracil. These medications directly affect the production of thyroid hormones by inhibiting thyroid peroxidase, which is the catalyst that helps monoiodotyrosine and diiodothyrosine bind together to form thyroxine and triiodothyronine.\(^4\)

Methimazole is the most common antithyroid medication prescribed to feline patients. It is usually administered orally in a tablet form, and usually takes seven to ten days to take effect. Methimazole can also be compounded into a gel that is applied to the skin inside of the ear flap. The transdermal method is preferred by most owners and their feline companions, but can take up to 3 to 4 weeks to take effect.\(^3\)
Adverse effects of methimazole drug therapy can range from mild to severe. Oral administration can cause decreased appetite and vomiting, and transdermal administration can cause dermatitis and ear infections. Other adverse effects noted are a decrease in red and white blood cell counts, lethargy, self induced skin abrasions due to itching, and rarely, severe toxic liver disease. Most of the more mild symptoms resolve themselves over time, and the more severe symptoms can be alleviated by discontinuing administration of the drug.

It is very important to monitor blood chemistry values often in order to determine proper dosing of the medication. Kidney failure, while common in older cats, can mask hyperthyroidism, and thorough blood screening will detect this as well. If kidney failure is diagnosed, a balanced treatment plan to alleviate the symptoms of both diseases needs to be implemented. Serum T₄ concentrations should be checked one to two weeks after medication therapy is begun, and every three to six months for long term use. Most cats show signs of normal thyroid function after about two weeks while taking methimazole, but if a cat has severe adverse reactions to methimazole, then propylthiouracil is recommended.

Treatment with oral propylthiouracil has proven to be effective at controlling hyperthyroidism, but is not commonly used in veterinary medicine today. This is because the incidence of adverse effects in cats is much greater than those associated with methimazole. It is important to note that medication therapy with either of these drugs does not cure hyperthyroidism, but only alleviates the symptoms by blocking the synthesis of new thyroid hormones. These medications must be given over the lifetime of the feline patient and combined with frequent visits to the veterinarian and periodic blood screening, this method of treatment can become quite costly.

**Surgical Treatment**

If antithyroid medication does not control hyperthyroidism, or the feline cannot tolerate it, then thyroidectomy may be indicated. Thyroidectomy is the surgical removal of one or both of the thyroid glands. This procedure has the ability to cure hyperthyroidism, but is not always successful, and also not without risks. Removal of either one or both thyroid glands is a
procedure best left to surgical specialists. The feline's overall health must be thoroughly accessed, and age must be considered, prior to any anesthetic procedure. Some surgeons suggest removing one thyroid gland at a time in order to prevent the incidence of hypocalcemia. The removal of both glands simultaneously can disrupt the regulation of calcium and cause decreased concentration in the blood stream, which can be life threatening. It is also important to preserve the parathyroid glands for this reason. Common procedure is to remove the parathyroid glands, and transplant them into the muscles of the abdomen, where they will regain normal function.\(^7\)

Hypocalcemia, laryngeal paralysis, and anesthesia are the most life threatening risks of thyroidectomy. Another risk of the removal of the thyroid glands is hypothyroidism, where not enough thyroid hormone is being produced. This can be controlled with oral thyroid hormone supplements. A recurrence of hyperthyroidism is also a possibility if both thyroid glands are not removed, or some residual thyroid tissue is left behind. In rare cases where the feline has a malignant tumor adjacent to the thyroid gland(s), thyroidectomy may not be possible.\(^7\)

Prior to thyroidectomy, the feline patient should be given methimazole for one to three weeks and blood chemistries should be evaluated to ensure the symptoms of hyperthyroidism and/or underlying kidney disease are under control. Because this disease is associated with hypertension, it is important to be sure the heart is in good enough condition to withstand anesthesia and the stress of healing. For this reason, radiographs, or x-rays, are taken of the chest and an echocardiogram, or ultrasound of the heart, is preformed. Intravenous fluids are administered prior to, during and post surgery to maintain hydration and proper concentrations of calcium, potassium and sodium in the blood stream.\(^7\)

**Alternative Treatments**

If the benefits of thyroidectomy do not outweigh the risks, or the symptoms of hyperthyroidism recur, then radioactive iodine therapy can be considered as a means of curing hyperthyroidism. This treatment employs the use of the \(^{131}\)I isotope, which is injected into the patient either subcutaneously, under the skin, or intravenously, into a vein. Most studies show that greater than 95% of feline patients return to normal thyroid function within one to two weeks of the first injection, and fewer than 5% require a second injection. \(^{131}\)I treatment has proven to be the most effective and least invasive means of curing this disease.\(^8\)

After injection, \(^{131}\)I concentrates in the thyroid tissue where it destroys the hyperfunctioning cells with minimal damage to the normal cells. This isotope has a half life of eight days and radiation is almost completely depleted within 56 days. Its radiation is composed of beta rays which work directly to destroy the affected cells, and x-rays which pass through the tissue. Because this treatment emits radiation, it carries a minimal risk to the personnel that are handling and administrating the treatment, therefore veterinary facilities that offer this treatment are not abundant. These treatment centers are found mostly at veterinary colleges or specialty clinics. Decreased availability of these facilities and the radioactive nature of the treatment cause this to be an expensive method for curing hyperthyroidism.\(^8\)

Because \(^{131}\)I spares the normally functioning cells of the thyroid, this treatment does not have the life threatening risks associated with thyroidectomy. In a small amount of patients, hypothyroidism occurs and is then treated with thyroid hormone supplements, but the benefits of this treatment outweigh the risks. Studies have indicated that a large percentage of felines
continue to have normal thyroid function six years after $^{131}$I treatment. Anesthesia is not normally required for this procedure, making it ideal for elderly felines, or those not healthy enough to tolerate anesthesia and surgery. The biggest disadvantages of radioactive iodine treatment are the stress of travel and hospitalization on the feline, and the large expense for the owner. Depending on which state the facility is located in, the amount of time the feline must remain hospitalized in a clinic varies. This is because each state has its own laws and guidelines that dictate when a publicly safe level of radiation is being emitted by the patient.

Currently chemical ablation is being tested as a treatment for hyperthyroidism. The process involves injecting 100% ethanol directly into the thyroid glands, and must be preformed with the feline patient anesthetized. Ultrasonography is used to find the diseased tissue of the thyroid and to guide the needle to the proper injection site. Studies have shown that one or more treatments have been successful in eliminating the symptoms of hyperthyroidism, but the long term effects are still under investigation. As with thyroidectomy, disadvantages to this form of treatment are the possibility of laryngeal paralysis, and anesthetic risks.

The Future

As the human population continues to grow, the pet population will grow with it. All over the world feline companions are becoming a larger part of people’s lives, and the need for thorough veterinary care is rising. The advancements made in veterinary medicine over the last few decades have made it possible for our four legged friends to live longer and healthier lives, and the current trend of employers offering pet health insurance has made it more affordable for many people to reap the benefits of their pets receiving the best medical treatment possible.

Because there are more households with cats in America than ever before, the incidence of many diseases including hyperthyroidism is much higher. With more people visiting their veterinarians regularly, many of these diseases are diagnosed in their early stages when they can be treated and controlled with greater success, but choosing the best treatment option can be a difficult decision. It is important to weigh the benefits and risks of each treatment depending on each individual circumstance.

Age is an extremely important consideration when deciding the best treatment for hyperthyroidism. Most of the felines diagnosed with this disease are geriatric, which increases the likelihood of concurrent diseases such as heart or kidney failure. These diseases can complicate treatment by thyroidectomy and chemical ablation because anesthesia is required. Elderly felines are usually less tolerant to stress, making the long hospital stays proceeding radioactive iodine treatment difficult to endure. These procedures can be expensive to the owner, and the quality of the feline’s life should be considered, making medication therapy a suitable treatment.

The overall health of the feline should also be considered. Many of the felines diagnosed with hyperthyroidism have no concurrent diseases and can undergo any of these treatments. For these patients the most effective treatment for hyperthyroidism is radioactive iodine therapy. This treatment alleviates the stress of receiving daily medication and periodic blood screenings. It avoids risks associated with anesthetic procedures and surgery, such as hypocalcemia and laryngeal paralysis. Radioactive iodine therapy is the least invasive treatment for
hyperthyroidism, requiring only one or two injections that return the thyroid glands to their normal functioning state.

As advancements in veterinary medicine continue, the number of facilities that offer radioactive iodine therapy is increasing. Currently this treatment is only offered at highly specialized veterinary hospitals and veterinary medical college teaching hospitals, but knowledge of the efficacy of this treatment is spreading throughout the public as well as the veterinary community. In the near future this treatment option will become more available to standard veterinary practices and less expensive for pet owners, making it the ideal option for the treatment of feline hyperthyroidism.
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Illustrations

Fig. 1 “Structure of Thyronione” <http://www.chem.qmul.ac.uk/iupac/AminoAcid/AAap2.html>

Fig. 2 “Structure of Thyroxine”<http://www.speciation.net/Public/Objects/Glossary/index.html?rb_select_l=1>

Fig.3 “Structure of Triiodothyronine” <https://cornellbiochem.wikispaces.com/Hypothyroidism>

Fig. 4 “The Thyroid Glands”< http://www.albanyvet.com/hypert.html>

Fig. 5 “Visible Thyroid Growth”<http://www.berwickvet.com.au/pages/services/radioiodine.html>

Fig. 6 “Thyroid Scintigrapy” <http://www.fabeats.org/owners/hyperthyroidism/info.html>

Fig. 7 “Structure of Methimazole”<http://www.medicineonline.com/drugs/M/3671/Methimazole-Tablets-USP.html>

Fig. 8 “Structure of Propylthiouracil” <http://www.rxlist.com/propylthiouracil-drug.htm>
Alcohol Abuse and its Negative Effects

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Organic Chemistry II
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Abstract

The intention of this project is to express an opinion about the effects of alcohol abuse. Alcohol itself is not a problem; however, alcohol abuse will bring multiple negative consequences to both nondrinkers and alcohol abusers. One of the most dangerous consequences of alcohol abuse is possible permanent brain damage. In addition, alcohol abuse will have a direct impact at home, at job settings and in society. Therefore, it is important to handle alcohol consumption properly and safely.

Warning

Due to the sensitivity of this topic, and to respect the readers and everybody’s decisions and beliefs, this material is being presented in two different parts. The first part is a combination of both the writer’s opinion and facts. The second part is more detailed and involves science, visual, and graphic material. The following information is not considered a treatment for alcohol abuse. It is just the writer’s opinion and general information about alcohol and alcohol abuse.

Several years ago, alcohol consumption was legalized for the good of society. Later on, throughout human history, some people around the world incorporated alcohol beverages as part of their meals and even as part of their special meetings or holidays. It is well known some particular cultures such as Italians and Jews do not overuse or abuse the ingestion of alcohol. It is important to keep in mind that alcohol was legalized to benefit everybody, at least in the United States. Unfortunately, some individuals due to different factors, have been trapped into the most common drug use of all the times: alcohol consumption. American history explains the reasons alcohol was legalized. It was mainly to stop illegal activities and crime. Alcohol abuse is a concern in today’s society due to an out of control alcohol consumption. A solution to stop and manage alcohol abuse is education. “Alcohol has been part of societies for thousands of years, as shown by this representation of the ancient Greek god of grape growing and wines, Bacchus.” Alcohol abuse affects everybody therefore; education should be everybody’s responsibility.

Education, being such a positive approach, could start right where the problem could potentially develop with young people and teens. It is important to educate youth at an early age about alcohol consumption. Alcohol being part of society plays a role in human gatherings; it gives a sense of happiness, and is affordable. Obviously, some people ignore or refuse to recognize that alcohol is intoxicating. How to approach alcohol consumption depends on each individual because alcohol abuse can become an addiction. Along with it comes possible brain damage, drastic life changes and it can furthermore create dysfunctional members in our society due to alcohol dependence. Once again, there is nothing wrong with consuming alcohol but there are ways of knowing if it is acceptable to drink and how much. Conflicting messages, combined by misunderstandings and misinformation are usually the main reason some people make wrong decisions when consuming alcohol.
Introduction

From a medical and scientific view, alcohol is not a drug but acts like one. Alcohol is classified as a drug in the context of abuse. Alcohol is considered a depressant but it has drug effects as it slows down the central nervous system. According to the Dietary Guidelines for Americans, there is no light drinking and there is only one safe way to drink alcohol. It is recommended that women consume one drink per day and men no more than two drinks. Alcohol consumption mainly depends on a person’s age and health. Alcohol addiction is identify by, craving for alcohol, the inability to limit drinking, physical illness when the person stops drinking, and the need to increase the amount drunk to feel the effects.

Excess of alcohol will cause difficulty in walking, unclear vision, slurred speech, slowed reaction times, and impaired memory. How alcohol abuse permanently damages the brain is not precisely known yet, but it is well known that it happens. Studies being conducted on a regular basis help scientists in better understanding the effects of alcohol on the brain. Blackouts and memory lapses are also impairments in memory any heavy drinker will experience. Technology that uses computerized tomography is the way studies can tell if a person has already suffered brain damage. An indicator of brain damage is brain shrinkage.

Family members suffered the pain that alcohol abuse brings home. Emotional and economic abuse is only a portion of the whole problem. Children are more sensitive to this problem and suffer long-lasting emotional trauma caused by an alcoholic. Alcohol abuse is a serious psychological problem that requires family therapy to all family members including minors. Alcohol abusers tend to divorce and have constant problems with domestic violence. A drinking problem becomes everybody’s problem.

Job settings battle with economic and production losses cause by alcohol abuse. Alcohol abuse is treated as a disease by many jobs. Therefore, alcoholics do not lose their jobs. Some employers suggest professional help and follow up with their employees to be aware of their progress. This involves a cost, which in many cases is covered, by the employer. During this process absenteeism, time, and effort affects production which also brings less revenue and losses to the businesses. At times, alcoholics following a rehab treatment still get paid under sick leave benefits. After all, alcoholics are responsible for their own rehabilitation, recovery, and performance at work.

Alcohol abuse harms society in many ways but mainly financially. Medical treatments are the only way to go about alcohol abuse. The first step is counseling, however, many insurance plans do not even cover this service. In the mean time, treatment for alcohol abuse is not an option. If done, it is paid by nondrinkers who will absorb every single service require to treat alcoholics.
What is Alcohol?

To understand the effects of alcohol it is recommended to understand alcohol as a chemical. Some of the main properties of alcohol are: ⁵

Alcohol is always found as a clear liquid at room temperature

Alcohol is dense and evaporates at lower temperature. This property allows it to be distilled

Alcohol dissolves easily in water

Alcohol is flammable

Alcohol can be made in three different ways:

Fermentation of fruits or grain mixture: ⁵

\[ \text{C6H12O6} \rightarrow 2 \text{CH3CH2OH} + 2 \text{CO2} \]

Most Ethanol used in industries is made by and addition reaction between ethane and steam:

\[ \text{C2H4} + \text{H2O} = \text{C2H5OH} \]

Chemical modification of fossil fuels such as oil, natural gas or coal

\[ 3\text{H2} + \text{N2} = 2\text{NH3} \]

Chemical combination of hydrogen with carbon monoxide (methanol or wood alcohol)

Methanol is prepared by a process called destructive distillation of wood. This kind of methanol is for commercial use and is prepared as follows: ⁷

\[ \text{CO(g)} + 2\text{H2(g)} \xrightarrow{\text{ZnO + Cr2O3, High temperature, pressure}} \text{CH3OH(l)} \]

Ethyl Alcohol

This is the type of alcohol found in foods and alcoholic beverages. The molecular structure of ethanol is.

\[
\begin{array}{cccccc}
 & & H & & & \\
H3 & C & - & C & - & O & - & H \\
& & H & & & 
\end{array}
\]
Ethanol Concentration

<table>
<thead>
<tr>
<th>Drink</th>
<th>Alcohol Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beer</td>
<td>0.54 oz. (30 ml)</td>
</tr>
<tr>
<td>Malt liquor -12 oz. (355 ml)</td>
<td>1.00 oz. (21 ml)</td>
</tr>
<tr>
<td>Whiskey Sour/Highball</td>
<td>0.60 oz. (18 ml)</td>
</tr>
<tr>
<td>Table Wine - 5 oz. (148 ml)</td>
<td>0.55 oz. (16 ml)</td>
</tr>
<tr>
<td>Beer - 12 oz. (355 ml)</td>
<td>0.54 oz. (16 ml)</td>
</tr>
</tbody>
</table>

The U.S. Department of Health and Human Services is very clear about its recommendations on alcohol consumption. One drink for women and two drinks for men per day are recommended. According to the Surgeon general women should not drink alcohol beverages during pregnancy because of the risk of birth defects.⁸

How Alcohol Enters the Body

When a person drinks an alcoholic beverage, alcohol is mainly absorbed into the small intestine. Alcohol then enters body tissues in proportion of their water content this is why more ethanol goes into the blood and the brain. Ethanol is very toxic therefore, the body disposes it immediately. The following chemical reaction explains how this process is done.⁹

\[
\text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{-C-H} + 2\text{H}
\]

In the liver, alcohol dehydrogenizes enzymes and converts ethanol into acetaldehyde which is also toxic.⁹ Acetaldehyde is also destroyed by the aldehyde dehydrogenize enzyme, which converts it to acetate ion as follows:⁹

\[
\text{CH}_3\text{-C-H} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{-C-O} + 3\text{H}
\]

The concentration of alcohol depends in the beverage. Higher concentration of alcohol cause faster absorption.

The type of drink. Carbonated alcohol beverages like beer and some wines are absorbed by the body faster than others.

Empty stomach. Food in the stomach slows down alcohol absorption.
How the Body Responds to Alcohol

The psychological and behavioral changes associated with alcohol intoxication, reflex its effects mainly in various parts of the brain.\textsuperscript{10} Normally, alcohol is transported to water containing portions of the body. Therefore more alcohol concentration goes into the blood and in the brain. In the brain, alcohol acts primarily on the nerve cells. Once in the brain, alcohol takes effect first in the cerebral cortex. The cerebral cortex controls memory, attention, language and awareness.\textsuperscript{10} The normal work process of the cerebral cortex is altered which causes poor judgment and no coordination. In the limbic system, alcohol consumption causes memory loss and emotion changes. The cerebellum coordinates body movements. In this part of the brain alcohol affects the nerves that coordinate sensory receptions, coordination, and motor control. Hypothalamus and Pituitary Gland coordinates automatic functions though the medulla. Alcohol consumption affects the Hypothalamus which controls sexual desire and performance. This is exactly what alcohol abuse does in the brain. Alcohol abuse primarily affects the human brain which makes it a serious concern because the brain gives the power to think, plan and speak.

Brain Disorders

Heavy drinking accelerates brain shrinkage. This means atrophy or actual damage of the brain which is a critical determinant neurodegenerative change and cognitive decline in aging.\textsuperscript{11} Other major changes related to alcohol brain disorders include loss of neurons. Studies only support this fact in chronic alcohol use. Alcohol abuse is also a cause of alcohol dementia. Methanol toxicity can also cause brain edema and necrosis. Putaminal necrosis and hemorrhage is cause by methanol metabolites and metabolic acidosis.\textsuperscript{11}

MRI, PET, and SPECT scans in the past several years allow scientists to study how alcohol abuse affects teen’s brain.\textsuperscript{12} Brain damage in teens is critical due to the brain not being fully developed (gray matter in the image means a fully developed brain).\textsuperscript{12} A study done on two 15 years old teens, one a non-drinker and the other a heavy drinker showed the teen the alcohol abuse problem as having poor brain activity during a memory task.\textsuperscript{12} Some studies that involve the use of sophisticated imaging technology have proved brain damage is more serious than memory loss.
Alcohol at Home

Alcohol abuse tears families apart. Most alcohol abusers are irresponsible individuals who bring home problems like violence, marital conflicts, infidelity, jealousy, economic insecurity, and divorce. Schools report alcoholic parents do not meet their children’s educational, developmental, social, and emotional needs. An estimated 15% of the total children in the United States, between the ages of 17 and younger, live with an adult diagnosed with alcohol abuse. Alcohol abuse causes a vicious cycle at home that increases family problems and as family problems increase, alcohol consume increases as well.

Alcohol at Work

Alcohol abusers bring their alcohol abuse problem into the workplace causing accidents, low production, and in general a negative morale to job settings. According to NIAAA and other government health agencies the estimated economic costs American businesses paid for alcohol abuse were in 1992 about $106,999,000.00 and $134,206,000.00 in 1998. This analysis proved that alcohol abuse remains as one of the highest expenses paid by American businesses. Alcohol use at work reported 20 to 30 percent of the total ER visits during the year 2000. Employers pay the price in different ways for alcohol abuse issues. It could be in health care premiums, tardiness, absenteeism, workers compensation and disability claims, and mainly in decrease productivity. Strong and clear work policies could reduce alcohol problems at work and reduce the high cost of work expenses caused by alcohol abuse.

Alcohol and Society

Two studies done by the NIAAA and the White House Office of Drug Control Policy done in 2002, reported $328 billion dollars as the total economic cost of drug abuse. More than half or 56.3% was estimated to be on alcohol abuse. This is not the only concern society has to deal with. The main problems are alcohol abuser’s behavioral changes or mood swings. Since alcohol abuse affects the brain, a person develops personality changes. Alcohol abusers tend to be passive and when upset become overly emotional. Defensiveness leads a person to blame or claim to be victimized. Alcohol abusers have a tendency to manipulate people by making excuses for failure or find other people to handle or solve their problems or responsibilities. Lack of self discipline, is also one of many behavior problems displayed by alcohol abusers. This means the inability to follow rules and complete assignments, work related duties, and keep commitments. Alcohol abusers who display aggressive behaviors create unhealthy relationships at work and in public. Alcoholism is a disease no society should tolerate. There is no room for alcohol abuse in people’s lives. An ordinary person has a family, friends, a job and/or a single responsibility that requires being free from alcohol abuse. Alcohol in excess prevents a person from fulfilling personal and public obligations. Behavior changes due to alcohol abuse directly impact society in many ways, therefore, alcohol ingestion should be moderate and with limits.
Conclusion

Throughout history, alcohol abuse has been a problem for human beings. Sociologists and psychologists and their study of different cultures and historical eras have noticed people’s drinking habits. The most predominant factor in these studies centered on how people drink and continue drinking as the result of what they are exposed to. Basically, the way to go from alcohol abuse to a normal alcohol drinking habit is through changing or stopping the way one drinks and/or behavior. Once again, alcohol abuse has a straight connection with how alcohol is advertised and presented. A very popular thought about alcohol is to reduce the amount of alcohol a society consumes to stop alcohol abuse. However, it is proved that this had very little to do with alcohol abuse. It is remarkable how little correspondence there is between the amount of alcohol consumed (per person) in different societies and the problems alcohol consumption generates.

Ethnicity and cultural aspects play either a positive or negative role towards alcohol consumption. Both areas have to do with some source of education or social behaviors displayed by group of individuals. It is a fact, people develop patterns of belief and behavior based on what is being observed or learned. In addition, most humans realize there are rewards with making the right decisions. The way family and society communicate norms, ties and values is how people make decisions, approach alcohol, and deal with life in general. The environment associated with drinking also play a crucial role in the addictive process. It is important to remember that every person is responsible and has the right to live in a proper and acceptable environment. No one should be forced to live under uncomfortable circumstances.

Sometimes external forces contribute to someone’s decision and responsibility comes down to an internal factor (choice) which individuals should base their decisions. For most people, it is relatively easy to modulate ethanol intake but it is the person’s responsibility to remember how far to go. As a person chooses to drink more regularly, the brain adapts quickly adapts to the increasing amounts of ethanol. Once the limit is passed, alcohol can take over and poison the body and/or addiction results.

Throughout human history, great scientists have changed the world with knowledge towards technology, science or health. As human’s wants and needs evolved, new knowledge is necessary to make life fit and placent. While many research studies are being done, it is great that college students have the opportunity to incorporate their knowledge, input, and suggestions that very well could provide an opportunity or a change in someone’s life. It is challenging and fascinating to come up with new achievements, however, it is also important to reinforce what is already available. Alcohol abuse and its negative effects have damaged life in many ways. There is plenty of information and help available to enjoy and avoid alcohol abuse. It is everybody’s responsibility to remain healthy, as good or bad decisions reach others as a natural consequence. Alcohol consumption is part of today’s society, and abuse can be prevented and reduced as much as 3% per year and up to 12% in the next five years. A proposal to achieve this goal could be obtained by following the following three steps: These steps involve activities that any person of any age can participate as the main idea is to educate the public future’s generations.
Proposal

1. Celebrate Alcohol History as a Society

2. Conduct Annual alcohol awareness events at school with active participation by students, parents, and instructors.

3. Alcohol distributor’s participation to promote alcohol warnings and healthy drinking habits involving communities and education centers.

The actual percentages of alcohol consumption are presented in the first picture. The proposal results are calculated in the second graph. Information contain in the first picture is data collected from a study done in December 2006 by NIDA, National Institute on Drug Abuse. The changes in decreases are calculated by using basic math and statistics. The three steps provided in the proposal should reduce alcohol abuse. As basic steps reinforce with consistency makes a difference in the long run. Consumers will have the opportunity to make the right choice when consuming or approaching alcohol beverages. Percentages of alcohol abuse are decreased as the percentages of non-drinkers increases. It does not require much to take care of alcohol abuse as the numbers and percentages prove it. Obviously much needs to be done to present the discussion on how to approach and incorporate these steps into the public. Policies will be required to present and support this plan as well as being ready to deal with challenges from such a large society that have enjoyed different kinds of freedom. Impressions will change as positive results are plotted in graphs that prove the effectively of this proposal. Americans society is wants to include treatment for addictions to be incorporated into the new health reform as people believe addiction is seen as a chronic disease rather than being considered as a personal failing. It is great to know that Americans are concerned about alcohol and drug addiction because it shows there is a degree of concern about doing something towards addictions, instead of minimizing the problem.
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Wheat You Cannot Eat
Celiac Disease

Kristin McLeod
April 23, 2010
Dr. Mancini
Abstract

Celiac disease is a genetically linked autoimmune disease with an environmental trigger. One percent of Americans are affected by celiac disease which destroys the villi lining the small intestine whenever the body detects the presence of gluten. Antibody and genetic testing are used to identify a possibility of the disease but only a biopsy can officially diagnose celiac disease. Upon diagnosis following a gluten-free diet is the only known treatment and allows the intestine to heal and resume its normal functions. Medical advancements are being made that may one day lead to forms of treatment other than diet and may also answer the mystery behind this disease, along with other autoimmune disorders.

Background

Celiac disease is an inherited autoimmune disorder. Autoimmune disorders are conditions in which a person's immune system attacks and destroys healthy body tissue. There are more than eighty autoimmune disorders. Rheumatoid arthritis, Type 1 diabetes, Multiple Sclerosis, Systemic Lupus, and Grave's disease are a few commonly recognized autoimmune disorders. Typically, white blood cells help to protect the body from harmful substances. These harmful substances, or antigens, include bacteria, viruses, cancer cells, and blood or tissues from another person or species. In response to these harmful substances the body produces antibodies to destroy them. Individuals with autoimmune disorders have immune systems which mistakenly identify healthy tissues as antigens. This results in an immune response destroying the normal healthy body tissues.

The cause for the immune system being unable to detect the difference between antigens and healthy body tissues is still unknown. Autoimmune disorders can result in destruction of one or more types of body tissue, changes in organ function, and/or abnormal growth of an organ. Some of the organs and tissues that may be affected by an autoimmune disorder include muscles, joints, skin, blood vessels, connective tissues, red blood cells, and endocrine glands such as the thyroid or pancreas. The symptoms and treatment depend on the specific autoimmune disorder a person is diagnosed with and there is no known prevention for autoimmune disorders. Celiac disease differs slightly from all other autoimmune disorders because with celiac disease the environmental precipitant is known.

Intolerances

Many people think that celiac disease is an allergy but this is not true. Wheat allergies, gluten intolerance, and celiac disease are all food intolerances. Food intolerances are broken down into several classifications including food allergy, autoimmune-mediated, congenital digestive disorders, and metabolic diseases. Food allergies like a wheat allergy occur when a trigger food causes an immune response toward the particular food protein. The symptoms produced by the body are time limited and don't cause long term harm to tissues of the body, minus the exception which is an immediate response causing anaphylactic shock like peanuts. Food allergies can be temporary and may even be outgrown by the age of five. Gluten intolerance differs because the negative reaction, induced by food, does not involve the immune system. Gluten intolerances cause a reaction within the digestive tract which produces gastrointestinal symptoms.
Autoimmune disorders are affected by genetics, and the body destroys its own tissues which can result in other disorders or complications. Celiac disease is an autoimmune-mediated disorder.  

<table>
<thead>
<tr>
<th>Type of Condition</th>
<th>Immune System Involvement?</th>
<th>Genetic Risk</th>
<th>Permanent Tissue Damage?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Food Allergy</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Intolerance</td>
<td>No</td>
<td>Yes*</td>
<td>No</td>
</tr>
<tr>
<td>Celiac Disease</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*No gene has been identified in the medical literature as being responsible for the development of gluten intolerance.

Table from 3

**History**

Celiac disease has been around for thousands of years. 10,000 years ago in the Middle East the birth of agriculture occurred when people observed that new plants arose from seeds falling to the ground from other plants. Domestication of crops was quickly learned and crossbreeding of different grass plants began creating staple grains such as wheat, barley, and rye. This advancement also came at a price as an illness emerged killing mostly children. Beginning in 250 A.D., a man by the name of Aretaeus of Cappadocia, described an unnamed disease in his writings. In these writings he described patients as “koiliakos”, which translates to “suffering in the bowels”. The observations of Cappadocia were later translated from Greek to English by Francis Adams. Adams translated them in 1856 for the Syndenham Society of England and coined the moniker as “celiacs”. In 1888, Dr. Samuel Gee of the United Kingdom recounted cases of celiac disease affecting both children and adults. Gee presented about these cases stating that “to regulate the food was the main point in treatment. The allowance of farinaceous foods must be small, but if the patient can be cured at all, it must be by means of diet”. This precise statement is credited to Gee as the first link between celiac treatment and diet. Even September 13th has been designated as National Celiac Disease Awareness Day in honor of Gee’s birthday. Despite his discoveries, Gee was slightly off as his suggestion for treatment was thinly sliced bread, toasted on both sides. During the 1920’s, a man by the name of Sidney Haas, claimed to have “clinically cured” the disease through the banana diet. In the treatment of ten children, the two children who did not follow the banana diet died while the others returned to healthy children. The banana diet was based on the principal that carbohydrates were the culprit. This diet included the elimination of all bread, crackers, potatoes, and cereals. In 1952, a Dutch pediatrician by the name of Dr. Willem Karel Dicke recognized that the ingestion of wheat proteins is what causes the disease, not carbohydrates. Dicke noticed that after World War II, the war related shortage of bread led to a significant decrease (35% to almost zero) in the number of deaths in children with celiac disease. He also noted that once wheat was again available the rates returned to their previous levels. By studying fecal content, Dicke and his colleagues identified gluten as the trigger for celiac disease, and the gluten-free diet became standard treatment. Dicke’s doctoral thesis for the University of Utrecht was based around this theory and Dicke, along with Charlotte Anderson, and a number of other colleagues in
Birmingham, England went on to link and describe the damage to the villi of the small intestine that occurs with individuals diagnosed with celiac disease in 1954\textsuperscript{6}. Two years later, a definitive form of diagnosis done through a biopsy was developed by Margot Shiner, a gastroenterologist\textsuperscript{7}.

**Celiac Disease**

Originally believed to be a rare childhood syndrome existing outside of Europe, today celiac disease is known to be a common genetic disorder. Also referred to as celiac sprue, nontropical sprue, and gluten-sensitive enteropathy, approximately 1 in 133 people (roughly 3 million) have celiac disease in the United States. Of these three million individuals only three percent have actually been diagnosed. Celiac disease is a lifelong inherited autoimmune disorder of the digestive system in which the villi of the small intestine are destroyed by the immune system in response to the consumption of gluten preventing proper absorption of nutrients by the body\textsuperscript{5,8}.

![Prevalence of celiac disease in the U.S.](image)

Table from 3

Gluten refers to a rubbery mass that consists of storage proteins that linger after starch has been washed from wheat-flour dough\textsuperscript{9}. The type of protein in each grain varies. Gliadin in wheat, hordain in barley, secalin in rye, avenin in oats, zein in corn, and oryzenin is rice are all slightly different. The gluten found within wheat, barley, rye, and sometimes oats contain particular amino acid sequences which may be harmful to individuals with celiac disease\textsuperscript{5}. The peculiar structure of gluten is unusually rich in the amino acids glutamine and proline. This property of gluten prevents it from being completely broken down and leaves behind small fragments or peptides. In a healthy person these peptides remain within the gastrointestinal tract and are typically excreted before the immune system even notices\textsuperscript{5}.

When individuals who have celiac disease consume gluten their bodies respond to it as if it is an invader and this affects the digestive process of the small intestine. The small intestine attaches to the stomach and is broken into three parts. The first parts of the small intestine, the duodenum and the jejunum, are where celiac disease is commonly found\textsuperscript{3}. The immune system specifically damages and destroys the villi lining the small intestine. Villi are tiny fingerlike projections found along the surface of the small intestine which normally serve to absorb
nutrients through the walls of the small intestine into the bloodstream\(^2,4,6^8\).

Celiac disease is influenced by both genetic and environmental factors. Genetically, celiac disease patients possess either the gene HLA-DQ2 or HLA-DQ8. HLA-DQ2 and HLA-DQ8 proteins are made by antigen-presenting cells\(^3,10\). The job of these is to serve as immune sentinels who gobble up foreign organisms and proteins, break them up and fit selected fragments into the grooves present on the HLA molecules, and place the resulting complexes on the cell surface where immune system helper cells called T lymphocytes can peruse. In individuals with celiac disease the intestinal epithelial cells release tissue transglutaminase which attaches to undigested gluten and modifies the peptides enabling them to bond to the HLA-DQ2 and HLA-DQ8 proteins. The result of this is when antigen-presenting cells under intestinal epithelial cells take up the complexes of tissue transglutaminase and gluten, the cells join the gluten to the HLA's and dispatch them to the cell surface, where they activate the T lymphocytes. When the T cells are activated they induce the release of chemicals cytokines and chemokines causing further immune activity. Typically, the presence of these chemicals along with the enhanced immune defenses would be helpful in the event of a microbial attack. In individuals with celiac disease these chemicals and increased immune defense do not help, instead they harm the intestinal cells which are responsible for absorbing nutrients\(^5\).

Besides these genetic factors several environmental factors may play a role in celiac disease. Celiac disease is believed to surface in many situations as a result of an environmental trigger\(^4,8\). These triggers could be surgery, pregnancy, childbirth, viral infection, or severe emotional stress\(^8\). In infants the occurrence of gastrointestinal infections, such as rotaviral infection, can increase the risk of celiac developing. Changes in infant feeding practices may also play a role in the development of celiac disease. Epidemiologic studies have shown that there is a protective effect from breast-feeding and the introduction of gluten in relation to weaning. When gluten is given to infants before the age of 4 months it is associated with an increased risk of disease development and when given after 7 months of age there is a marginal risk. If the introduction of gluten overlaps with breastfeeding the risk may be minimized\(^6\).

**Symptoms**

There are a multitude of symptoms for celiac disease. Celiac disease is a multi-system, multi-symptom disorder and symptoms can be varied and even mimic other bowel disorders\(^2\). Different people may experience different symptoms and many people never experience any symptoms at all. Symptoms may appear at anytime during a person's life and can be triggered for the first time from events such as surgery, pregnancy or childbirth, viral infection, or severe emotional stress. Even though celiac disease affects the digestive system, symptoms may occur in the digestive system or other areas of the body. Infants and young children typically have digestive symptoms which may include abdominal bleeding, pale, foul-smelling, fatty stool, vomiting, constipation, chronic diarrhea, irritability, and weight loss. Children and infants with celiac disease are commonly malnourished due to impairment of the small intestine when celiac is untreated. Since nutrition is critical in growth and development, failure to thrive may occur in infants along with delayed growth and stature, delayed puberty, and dental enamel defects of the permanent teeth. Unlike children, adults are less likely to experience digestive symptoms. Instead adults may experience fatigue, bone or joint pain, anemia, arthritis, seizures, depression or anxiety, canker sores inside the mouth, tingling numbness in hands or feet, infertility or
recurrent miscarriage, or an itchy skin rash called dermatitis herpetiformis\textsuperscript{2,3,6,8}. The most common sign of celiac disease in adults is iron deficiency anemia that does not respond to treatment with iron therapy\textsuperscript{3}. Individuals experiencing any of these symptoms may require further testing to determine if the cause is celiac disease.

There are also individuals who experience no symptoms at all. These people, even though symptomless, can still develop complications from the disease over time. If untreated long term complications may include malnutrition which can lead to anemia, osteoporosis, and miscarriage. Liver disease and cancer of the intestine can also occur\textsuperscript{3}.

**Diagnosis**

The only way to officially confirm that someone has celiac disease is through a biopsy of the small intestine. Prior to a biopsy antibody or genetic testing is used. Depending on the situation dictates whether DNA testing or antibody testing is required. Genetic testing is used for two main reasons. The first is to rule out celiac disease and the second is to test someone who has not had a biopsy because they have been following a gluten free diet. For individuals who have been following a gluten free diet for an extended period of time this is the only way to determine if symptoms may be a result of celiac disease. DNA testing is done through a blood test or cheek swab and it determines whether and at-risk person carries the genes which are responsible for the development of celiac disease\textsuperscript{5}. Certain gene variants encoding proteins known as histocompatibility leukocyte antigens (HLA’s) play a role\textsuperscript{5}. HLA-DQ2 and HLA-DQ8 are both genes located on the HLA-class II complex. Almost all, ninety-five percent of individuals with celiac disease have been shown to carry these “haplotypes”, whereas just thirty to forty percent of the general population has one of these versions\textsuperscript{2,5}. As a result an individual who tests negative cannot develop celiac disease while a positive indicates the possibility of celiac. Genetic testing does not diagnose celiac disease it only places people into an “at-risk” group for the disease indicating they should be closely monitored through antibody testing in the future\textsuperscript{2}.

Antibody testing can only be used for individuals who have been consuming gluten in their diet. Research has shown that people with celiac disease who eat gluten have a higher than normal level of certain antibodies in their blood. Antibodies act like warning signals being produced by the immune system when the body perceives a substance as threatening. With celiac disease the body sends out warning signals for the proteins in wheat, rye, and barley generically known as gluten which are supposed to be safe. With antibody testing, blood is first tested to measure the levels of the antibodies known as anti-endomysium (EMA) and anti-tissue transglutaminase (tTGA). There are several antibody tests including Endomysial antibody (EMA-IgA), Tissue transglutaminase antibody (tTG-IgA/IgG), Anti-gliadin antibody (AGA-IgG, AGA-IgA), and Total serum IgA. A positive test result is not a diagnosis in itself it means that a biopsy is required\textsuperscript{2,3,6,8}.

If antibody testing, genetic testing, or symptoms suggest celiac disease a biopsy of the small intestine is performed to establish the diagnosis. Tiny pieces of the small intestine must be obtained to check for damage to the villi. Because the damage caused by celiac disease is microscopic, in the majority of the cases it is not possible to confirm the diagnosis of celiac disease just by looking at the walls of the intestine. This is why biopsies are needed. The biopsy is endoscopic and it is performed by a gastroenterologist most often in an outpatient
surgical suite. Sedation and local anesthesia are used and the procedure lasts less than a half hour. A long thin tube with a camera on the end is inserted into the patient’s mouth, down the throat, and into the esophagus. Once the tube reaches the stomach the physician locates the entryway into the small intestine (the duodenum) and inserts the tube there. Through this whole process the camera at the end of the tube is sending video images to a monitor in the procedure room. Gastritis or other inflammation such as acid reflux can be visually assessed through the monitor. A tiny surgical instrument is then inserted down the tube where five to six areas of the small intestine are biopsied. The biopsy is taken by grasping very small sections of tissue and slicing them gently away from the walls of the intestine. These samples will be examined to check for damage to the villi. Taking multiple samples is important because celiac disease can cause patchy lesions and if only one to two samples are obtained it may be missed. There are no nerve endings in the intestine, so the procedure is relatively pain free in the gut. Some patients will experience a sore throat, but the majority has no recollection of the procedure. Results from the biopsy will confirm if the patient has celiac disease³.

Diagnosis and treatment are very important because it can prevent complications of celiac disease and decrease chances of developing another autoimmune disorder. Not only individuals who possess symptoms should be tested for celiac disease. Anyone over the age of three, regardless of symptoms should be tested if related to a close relative with biopsy confirmed celiac disease. A close relative is defined as a parent, sibling, or child. Celiac is hereditary and four to twelve percent of an affected person’s first-degree relatives will also have the disease. They wait until the age of three typically because children under three years of age may not always have accurate antibody testing. Also, children need to be eating wheat or barley based cereals for up to a year before than can generate an autoimmune response to gluten and have their blood tested. Besides individuals with a close relative who has celiac any individual who has a related autoimmune disorder, regardless of celiac symptoms, should be tested. Even if the test comes back negative they should continue to be tested on a periodic basis. Anyone with Down Syndrome or Turner’s Syndrome should be tested on a periodic basis and also any individual who has experienced persistent miscarriage or infertility where medical cause cannot be found should be tested for celiac disease³.

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Chance of developing autoimmune condition</th>
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<tbody>
<tr>
<td>4 - 12 yrs of age</td>
<td>16.7%</td>
</tr>
<tr>
<td>12 - 20 yrs of age</td>
<td>27%</td>
</tr>
<tr>
<td>Over 20 yrs of age</td>
<td>34%</td>
</tr>
</tbody>
</table>

Table from 3

Research has shown the advantages of diagnosing celiac disease at an early age and how it can affect the chance of developing another autoimmune disorder. Children diagnosed before the age of
four are at a greatly reduced risk for developing other autoimmune disorders. Children between the ages of 4 and 12 have a 17% risk. The percent risk continues to grow as age increases and individuals age 12-20 years of old have a 27% risk. Above the age of 20 a person’s risk increases to 34% chance for developing another autoimmune disorder.3

Once testing and diagnosis have occurred, follow-up antibody testing should continue. Follow-up testing is necessary to confirm that antibody levels are returning to normal, which is indicative of the intestine healing from the gluten free diet. These follow-up tests can help individuals with celiac know if their diet is working effectively and can also help identify if other health conditions such as joint pain are related to the disease. A person newly diagnosed with celiac disease should go for follow-up testing two times in the first year of diagnosis. The first appointment should be scheduled three to six months after the diagnosis and the second appointment should take place after following the gluten free diet for one full year. Yearly follow-up testing should continue from this point on as the most serious complications resulting from celiac disease occur within the first 5 years after diagnosis.3

Treatment

The only known treatment for celiac disease is to follow a gluten-free diet. A gluten-free diet means avoiding all foods containing wheat (including kamut, spelt, and triticale), rye, and barley. Many foods and household products contain gluten making this a difficult task at first.2,3,6,8,10 Gluten can be expected to be found in products such as breads, pastas, cookies, and other obvious grain products, though it is also hidden in many processed foods like frozen french fries, ice cream (wheat is often added to prevent crystallization), chili powder (wheat added to prevent clumping but not listed on the label), soy sauce, and rice cereals. Even many non-food items like cosmetics and household cleansers contain gluten. Other items containing gluten include the glue used on lickable envelopes and stamps, self stick stickers and labels, art supplies such as paints, clay, play-doh, and glue, personal items such as lipstick, lip balm, sun screen, shampoo, soap, skin lotions, toothpaste, mouthwash, and detergents. Latex or rubber gloves are often powdered with wheat or oat flour so at the dentist or doctor, etc someone with celiac must request unpowdered ones. Even medications can be dangerous and it is important to inform the pharmacist if you have celiac disease as gluten may be used as a binder, pills may be dusted with flour during manufacturing, and capsules may have gluten present in the oil inside. Making this more difficult, the term gluten is rarely used on product labeling or it is left out because food manufacturers are not currently required to list the ingredients used in “packaging”. Therefore chewing gum or chocolate may have been on a conveyor belt dusted with flour to keep it from sticking and now it is contaminated, but by just looking at the label this is unknown.10

Plain meat, fish, rice, fruits, and vegetables do not contain gluten, and people with celiac can consume as much as they would like. Potato, rice, soy, amaranth, quinoa, buckwheat, or bean flour can be substituted for wheat.5 A dietician can be very helpful in teaching people with celiac about the new diet and food selection, label reading, and other helpful strategies for managing the disease. Fortunately the growth in diagnoses for celiac has encouraged many gluten free products to be developed, sold, and readily available. Many restaurants now cater to people with celiac disease. P.F. Changs, Outback, Flemings, Red Robin, Z-Tejas, and Pasta Pomodoro are a few of the restaurants that have a menu which possesses gluten-free items.
Phoenix, Arizona even has a gluten-free bakery demonstrating the impact this disease has had on America already.

For most people adhering to a gluten-free diet will stop symptoms, heal existing intestinal damage, and prevent further damage. Within weeks of following the diet improvements will be observed and typically within 6-18 months the small intestine is completely healed with the villi intact and working\(^3\). The gluten-free diet must be followed for the remainder of a person’s life, ingesting even the smallest amount of gluten can damage the small intestine. A very small amount of people show no improvement on the gluten-free diet. The most common reason for this is that small amounts of gluten are still being consumed. This could be attributed to hidden sources of gluten such as modified food starch, preservatives, binders, excipients, fillers, malt, and stabilizers made with wheat\(^2\). Also, many corn and rice products are produced in factories which also manufacture wheat products and there is a possibility of cross contamination\(^10\). Rarely, the intestinal injury will continue despite following a very strict gluten free diet. Individuals in this situation have a condition known as refractory celiac disease. People with refractory celiac disease have severely damaged intestines that cannot heal. In this case their intestines are unable to absorb enough nutrients and therefore they require intravenous nutrients to supplement\(^8\).

**Advancements**

There are currently several drug treatments being evaluated for celiac disease. Researchers are studying enzyme combinations and proteins that aid chemical reactions in the body which might detoxify gluten before it enters into the small intestine. Many clinical trials exist which test new nondietary therapies for celiac disease. Al-vine Pharmaceuticals in San Carlos, California has developed an oral protein-enzyme therapy that completely breaks down gluten peptides normally resistant to digestion. Other investigators are looking into ways in which tissue transglutaminase can be inhibited so it would be unable to chemically modify undigested gluten fragments into the form where they bind so effectively to HLA-DQ2 and HLA-DQ8 proteins. In addition, and Australian company Nexpep is working on a vaccine that would expose the immune system to small amounts of strongly immunogenic forms of gluten. The theory behind this idea is that repeated small exposures would ultimately induce the immune system to tolerate gluten\(^7\).

In 2000, Dr. Alessio Fasano at the University of Maryland School of Medicine discovered that the human protein zonulin which regulates the permeability of the intestine, is found in increased levels during the acute phase of celiac disease. Fasano said, “Zonlin works like the traffic conductor or gatekeeper of our body’s tissues. Our largest gateway is the intestine with its billions of cells. Zonulin opens the spaces between cells allowing some substances to pass through while keeping harmful bacteria and toxins out. We could never figure out how a big protein like gluten was getting through to the immune system but now we know people with celiac disease have increased levels of zonulin which opens the junctions between cells. In essence the gateways are stuck open, allowing gluten and other allergens into the immune system where they are attacked by the antibodies\(^11\)” In 2009 zonulin was further identified by Fasano and his team as a molecule in the human body called haptoglobin 2 precursor. The precursor haptoglobin 2 matures into haptoglobin. Previously the precursor was believed to have no purpose except to mature into the mature molecule. Haptoglobin 2 is the first precursor molecule that serves another function entirely - opening a gateway in the gut, or intestines, to let gluten in.
It is believed that this molecule zonulin/pre-haptoglobin 2 could be the missing piece and possible solution to celiac disease\textsuperscript{12}.

Fassano has since helped to co-found Alba Therapeutics which is currently exploring the value of Larazotide, a zonulin inhibitor.

Larazotide has already been tested in two human trials to check for safety, tolerability, and efficacy in celiac patients who ate gluten. Thus far the tests have shown no excess of side effects and demonstrated that the agent reduced gluten-induced intestinal barrier dysfunction, production of inflammatory molecules, and gastrointestinal symptoms in celiac patients. Larazotide marks the first time a drug has stopped an autoimmune process, interfering specifically with an autoimmune response against a particular molecule made by the body. This advancement has since received approval by the FDA to expand its studies and try Larazotide on other autoimmune disorders including Crohn’s disease and type 1 diabetes\textsuperscript{5}.

**Conclusion**

Celiac disease is a unique model of autoimmunity in which some of the genes involved, the target autoantigen, and the environmental trigger are all known. Caused by ingesting gluten, the gluten free diet is currently the only effective treatment for individuals with celiac disease. Diagnosed through an intestinal biopsy, celiac disease destroys the tiny villi that line the small intestine which prevents proper absorption of nutrients. A better understanding of the complexity of the genetic/environmental interaction responsible for celiac disease has opened the way to explore alternative therapeutic treatments. Effective treatments other than dietary restrictions are still some ways off but growth in awareness and diagnoses has brought this disease out of hiding and the discoveries being made may soon unveil a solution to both celiac disease and other autoimmune disorders.
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Depression:
The Drugs and How It Affects the Body

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Abstract

Depression, a mental and social problem, was researched and discussed in this paper. The specific areas of the central nervous system are discussed, along with the processes that are involved for a person being depressed. In addition, treatments including the different drugs are used to interact with the central nervous system, and other treatments are used to help cure this manic psychological disease. In this paper, images of the nomenclature for some of the medication and mechanisms will be used to help illustrate how the drug structure is drawn and how they are carried out in the body.

Introduction

A psychologist's work is to help people cope with any mental imbalances. One of the more common psychological issues psychologists and physicians face is the many different forms of depression. Depression is the psychological condition of people who feel saddened and the withdrawn from society due to personal and social uncertainty. Depression is not an "overnight" occurrence; the development of depression occurs through many months, even years, of constant negative feelings. Depression usually occurs in teenagers, war veterans, and senior citizens, even though it can occur in anybody at any age. In addition, the percentage of people diagnosed with depression does vary between genders. According to research conducted in the University of Michigan Depression Center, "Some studies report that perhaps as many as 25% of women and 15% of men have experienced a depressive disorder of some sort at some time in their lives,"¹ and "University of Michigan research shows that as many as 15 percent of all college students may have symptoms of depression, and about 10 percent of college students arrive on campus with a history of the illness."² As the research shows, the numbers of people affected by this disease are severe through the various age groups and genders.

There are many different types of depression psychologists and other health professionals use to diagnose patients. The first type is called depression, and it is the lowest and least serious form, yet it is the most common and most expressed form of depression. If depression worsens, the psychologists would diagnose a patient with dysthymia (chronic depression). Dysthymia occurs when the mood swings occur more often and for a long period of time. According to the research identified in Harvey Simon's article, it "afflicts 3 - 6% of the general population and is characterized by many of the same symptoms that occur in major depression..."³. The research shows that this occurs in a lower number of the population, but the symptoms are the same. Finally, the last major type of depression people are diagnosed with is Bipolar disorder, known as manic depression disorder. In this disorder, patients are usually struggling between moods of being happy and being sad. In this disorder, people could be happy and energetic, then end up being depressed. Bipolar disorder is the more complex form of depression and the mood swings are random.
Biochemistry of Depression

The biochemistry of depression, like other processes of the human body, is a long sequence of events in a body that triggers the event. When referring to depression in a biochemical point of view, the central nervous system triggers the events of depression. The central nervous system consists of the brain, spinal cords, and the optic nerves. The brain is the specific part in which depression begins. To better understand the biochemistry of the brain, there are a few parts of the brain that help regulate and release the various hormones in the human body, such as the hypothalamus, which all make up the limbic system. According to the authors of Brain Explorer, a website created by the Lundbeck Institute company who are world leading in research discovery, “The hypothalamus and the pituitary gland may also play a role in depression, as they are involved in hormonal control, and increased levels of some hormones may play a role in maintaining a depressed state.”

One of the neurotransmitters that help regulate depression is Serotonin. A neurotransmitter is a chemical that moves on the synapse to another part of the body, such as a muscle or another nerve. Serotonin, also known as 5-Hydroxytryptamine, is a neurotransmitter released in the body that is involved with many mood behaviors a person exhibits. Cortisol is another biochemical hormone that affects depression.

Another hormone that affects the brain and possibly puts a person through depression is cortisol. Cortisol is a chemical that is created when a person goes through any type of stress. When the body is under stress and the brain signals for the production of cortisol, the brain may produce too much of the chemical which causes the person to become depressed. When the brain is under the influence of too much cortisol at a given time, it may produce depression in the body. According to Alexander Pickett, a contributing writer for Harvard University’s Crimson newsletter, “Paul A. Ardayfio, a graduate student at the Harvard Medical School who ran these experiments as part of his dissertation, explained that ‘we’ve known for over a century that chronically high levels of cortisol were linked to depression, so we decided to test whether or not cortisol directly caused some symptoms of depression.’ The study found that chronic exposure to cortisol may cause some symptoms of depression, but did not find evidence that it causes depression itself.”

The study proved that cortisol produces symptoms of depression based on the results the experiment produced. In this section, the biochemistry was described to have a background on what chemical imbalances are produced in the brain to cause depression. Other than the lack of the neurotransmitter serotonin in the brain, the lack of the neurotransmitters norepinephrine, epinephrine, and dopamine also have a significant effect on state of the brain, which leads to depression.
The synthesis of 5-Hydroxytryptamine

**Causes and Effects of Depression and Drug Therapy**

The causes of depression are limited to one cause but sometimes it is the combination of different causes that results in a depressive state. One of the more common ways people become depressed is due to the genetic traits a person contains. Depression, like any other disease, could become hereditary, through a parent or both parents, to be passed on the offspring. Scientists have linked the small allele of “5-HTT,” a gene that regulates serotonin, to be a major factor of depression. According to Paul Recker, a journalist for *Mental Health Today* and whom followed the experiments completed by doctors at the University of Wisconsin, “Depression was diagnosed in about 33 percent of the study subjects who had at least one short 5-HTT gene copy and who had experienced four traumatic events over a five-year period. Among those with two copies of the long form of 5-HTT, only 17 percent were diagnosed with depression after four traumatic events. Researchers said tests showed that those with even one copy of the short 5-HTT gene were almost three times more likely to think or attempt suicide than those with only the long 5-HTT.”

According to the experiment researched, the patients with the short allele of “5-HTT” were showing symptoms of depression and its destructive behaviors. The genetics could also be a cause of the problem, especially with losing a loved one, experiencing another illness and other stressful situations.

Also, DNA (Deoxyribose Nucleic Acid) is a big part of the cause of depression and lack of serotonin. Research shows that there is certain information from a gene that creates cells to create serotonin. When that information is missing from the DNA, the cells are not created and the individual won’t produce many serotonin neurotransmitters. According to Gila Z. Reckess, a reporter for Washington University at St. Louis, “These results suggest that while the two genes overlap and share a similar function, *Lmx1b* works at an earlier step than *Pet1* and controls development of all serotonin-producing cells. Because *Pet1* only is involved in development of about three-fourths of these cells, *Lmx1b* must control other genes and pathways.”

The results
from Dr. Yu-Qiang Ding’s experiment proved that the mice without those cells, due to the lack of the Lmx1b gene, have less serotonin in their bodies than those of the other mice.

Depression could also exist within social situations especially with teenagers and the starting of puberty. Growing up, one of the biggest challenges teenagers face is appearance and how they are seen by other people. One of the common groups of adolescents that are affected by depressions is the obese groups. According to a report by Amy Levey, a member of the American Psychological Association (APA), “A recent University of Minnesota study reveals that children who were teased about being overweight were more likely to have poor body image, low self-esteem, and symptoms of depression. The study found that 26 percent of teens who were teased at school and home reported they had considered suicide, and 9 percent had attempted it.” The study showed that obese children showed to have depression and have a poor outlook on themselves. Social situations, among others like genetics, diet, and stress are some of the common causes of depression, and scientists are even discovering more causes as more experiments are conducted. These causes have mostly negative effects associated with them both socially and physically. Due to depression, a person’s self-esteem drops, patients lack the willingness to take care of themselves, and possibly experience relationship issues in the future. Depressed people also cause physical harm to themselves by suicide or even cause harm in their bodies.

One of the common and popular treatments among physicians is drug therapy, in which physicians prescribe anti-depressant medication. Anti-depressants come in many different categories. Among these categories are Tricyclics, MAOIs, SSRIs, and SNRIs. Each type of medications will be described and talked about in the upcoming pages.

**Tricyclics (TCAs)**

Tricyclics Anti-depressants, also known as TCAs, are the oldest and less used anti-depressant category created. These classes of drugs are named after the similarities of three cyclic rings being attached to each other. The rings could be either heterocyclic, a normal ring (which only contains carbon and could be a benzene or aromatic ring), or a mixture of both. According to Dr. Robert Aucker, the author of *Pharmacology and the Nursing Process*, “Cyclic antidepressants (tricyclics and tetracyclics) are believed to work by correcting the imbalance by correcting the imbalance in the neurotransmitter concentrations at the verve endings in the CNS.
(the biogenic amine hypothesis). This is accomplished by blocking the reuptake of the neurotransmitters to accumulate at the nerve endings.11 The mechanism of TCA is simple to understand. TCA drugs increase the amount of neurotransmitters in the nerve endings to correct a chemical imbalance. The reason doctors don’t use TCAs as a first resort is due to the large amount of side-effects and the high toxicity levels in most of the TCAs. According to a case study done at the University of Pittsburg Medical School of Pathology, “CNS manifestations of toxicity include agitation, stupor, coma, seizure, and maniac excitement. Cardiovascular toxicities include potentially fatal arrhythmia, hypotension, hypertension, and congested heart failure. Acute poisoning with TCAs is common and potentially life-threatening.”12 Due to the conditions stated above, like hypertension (high blood pressure) and seizures, TCAs are proven to be dangerous to consume. Due to these side-effects, scientists tried come up with another category of drugs that attempted to determine the same goal safely.

**MonoAmine Oxidase Inhibitor (MAOIs)**

According to the research conducted by Rashmi Nemade, the author of article Medications for Major Depression, “Monoamine oxidases are enzymes that break down serotonin, norepinephrine, and dopamine. By preventing these enzymes from working, MAOI medications allow neurotransmitters to remain in the synaptic gap longer, which gives them more opportunity to activate the post-synaptic neuron’s receptors, creating a greater stimulation of the post-synaptic recipient neuron. Increasing someone’s serotonin, norepinephrine, and/or dopamine levels tends to have an antidepressant effect.”13

The second category of drugs that were created to replace TCAs is MonoAmine Oxidase Inhibitor (MAOIs). MAOIs are one of the more powerful and effective anti-depressants that are available for patients with depression. Due to the mechanism listed above, MAOI drugs (like Effexor), are able to block the enzyme, Monoamine Oxidases, from destroying serotonin, norepinephrine, and dopamine. Once the levels of those hormones increase, the depression in most people will settle down. Due to the side-effects, doctors use MOAI’s as a last resort drug for treating of depression. The drug to drug interaction and interactions with certain foods make it more dangerous to use than TCA. The next drug category doctors use is SSRIs.

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

Selective Serotonin Reuptake Inhibitors, also known as SSRIs, are another type of anti-depressions physicians use to treat depression and other depression related diseases. They are the more preferred drug type to use because they are less toxic to the human body and through constant experimentation, people taking them experienced less side effects than the other types of drugs. The drugs are called “Selective” because the neurotransmitter that is being focused on is Serotonin. Sometimes the cells that make serotonin reabsorb the chemical, which causes the
lack of serotonin in the brain. The main purpose of these drugs is that they are designed to make the cells that make serotonin more available in the brain. Recent findings have found the mechanism, in which the pills work in the body. According to Dr. Sheldon H. Preskorn, who is the author of the book Clinical Pharmacology of SSRI's, "That SOA may be, by way of example but not limited to, an uptake pump, an enzyme, or a receptor. The drug ‘recognizes’ and binds to that SOA. The activation or inhibition of a specific site is termed the drug's mechanism of action (MOA). For example, a drug may be an agonist or antagonist at a specific serotonin receptor." Once the drug finds the specific site, in this case the reuptake pump on a serotonin creating cell, the drug will bind to that site and block it from absorbing the serotonin it creates. Also, when the pump is stopped from absorbing the serotonin, the serotonin level in the brain will increase and remove any chemical imbalances that were caused.

More research conducted by Dr. Sheldon H. Preskorn indicates that "Racemic fluoxetine produces racemic norfluoxetine. While S-fluoxetine, R-fluoxetine, and S-norfluoxetine are potent and selective inhibitors of serotonin uptake in vitro and in vivo, that is not true for R-norfluoxetine." Under steady-state conditions, the plasma levels of racemic fluoxetine and norfluoxetine are comparable. Thus, studies attempting to correlate the plasma levels of fluoxetine and norfluoxetine should ideally take into account the relative inactivity of the R-norfluoxetine in terms of the inhibition of serotonin uptake. The R-enantiomers of fluoxetine and norfluoxetine are also weaker inhibitors of CYP 2D6 than are the S-enantiomers. Thus, failure to distinguish between these enantiomers in studies attempting to correlate plasma levels of fluoxetine and norfluoxetine with the inhibition of the metabolism of CYP 2D6-dependent substrates will hamper the ability to establish such a relationship.

The success of the drug that binds with certain SOA (referred to as site of action) does depend on the enantiomers formed when the drug is made. When comparing the results of an experiment Dr. Preskorn conducted for citalopram and fluoxetine, two of the most commonly prescribed anti-depressants showed that there is a significant difference between the S-enantiomers and the R-enantiomers. The study he conducted proved that out of all four enantiomers found that worked for CYP 2D6, the R-norfluoxetine proved to be the weakest.
addition, the R-nortriptyline and R-fluoxetine proved to be weaker compared to the “S-“ versions of the chemicals.

Physicians commonly prescribe SSRIs because they are one of the few drug groups that have very little side effects. Some side effects could be controlled while others cannot be controlled. One of side effects that could be controlled is called Serotonin Syndrome. Serotonin Syndrome (SS) is when there is a high level of serotonin in the body. It occurs when SSRIs or SNRIs are mixed with other drugs that produce serotonin. Even though this side effect could be controlled, it is fatal if it remains untreated. Another side effect that occurs with SSRI, like any other class of anti-depressant, is Discontinuation Syndrome. According to the AAFP, “Antidepressant discontinuation syndrome occurs in approximately 20 percent of patients after abrupt discontinuation of an antidepressant medication that was taken for at least six weeks.”15 This occurs when the patients are suddenly taken off the anti-depressants after a short period of time.

**Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)**

Serotonin–Norepinephrine Reuptake Inhibitor, also known as SNRIs, is the final type of anti-depressants that physicians prescribe to treat depression and other related diseases. Since this is a new type of medication, the full mechanism are still being researched and studied. Due to current research, scientists have theorized that SNRI drugs work similar to SSRI drugs. Unlike SSRIs, SNRIs focus on two neurotransmitters, serotonin and norepinephrine. The drugs in this group focus on the nerve cells, which create both serotonin and norepinephrine, and stop the reabsorbing process of those cells. Scientists were also able to find out that SNRIs have the similar side effects compared to SSRIs.

**Other Treatment Options**

When it comes to treating depression, there are more safe and natural alternatives to drugs. The first alternative treatment for depression is living a healthy lifestyle. Exercises, like swimming, running, and basketball, encourage the production of the hormone, endorphins. Endorphins are neurotransmitters, which are created in the limbic system that help muscles relax, which causes people to become happier. A combination of meditation and music are other natural alternatives to drugs. Meditation with the right music can help calm a person down and reduce a person’s stress level. Other alternatives to drugs are having a proper diet and the proper amount of sleep. A proper diet helps the production of chemicals that help create serotonin. While a proper amount of sleep helps reduce stress levels in the body. Those are some alternative treatment to drugs that are natural and reduce the chances of experiencing negative side-effects
**Personal Opinion**

I believe that the alternative ways of curing depression are much better than taking pills to help solve the problems with major depression. Naturally, through combinations of exercise and proper diet, people can create hormones that make themselves more relaxed and happy. In addition to psychotherapy, patients talk about their stresses which in turn will calm them down. I believe that in the future rather than prescribing medications to the patients, doctors will work with their patients to find a successful plan to solve their problems naturally to cause less or no side effects.

**Conclusion**

In conclusion, depression is a mental illness that affects roughly 20% of the American population and higher percentages in third-world countries. In this paper, the biochemistry of depression was discussed to provide information about the body, which eventually becomes part of the causes of depression in depressive people. After the cause of the problem was identified, scientists created drugs (in the categories of TCAs, MAOIs, SSRIs, and SNRIs) to help solve the chemical imbalance in the brain. The earlier created drugs, TCAs and MAOIs, were proven that they are ineffective and in some cases worsen the depression symptoms. For these reason, some doctors don’t prescribe these drugs or prescribe them as a last resort. It wasn’t until the creation of the SSRIs and SNRIs that those physicians saw improvements in patients’ conditions. Though recent medications have shown improvement in psychological conditions, there are a lot of side effects that accompany those improvements. As mentioned earlier, if physicians work with their patients to create a natural alternative than prescribing medication, then people will have a cure that will have the least amount of side-effects possible.
References


“Music to Our Ears: The Mechanics of Sound”
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Course: PHY111 #56491
Instructor: Dr. Casey Durandet
Abstract

Music in its entirety has many aspects: the production of sound, the sound waves, the construction of instruments, the performance by musicians, and the cultural differences and similarities in instrumentation. These concepts will be discussed in greater detail along with information from an interview with a professional musician and from a tour of the Musical Instrument Museum.

Physics Behind Music

In order to understand the way sound is produced, a couple of terms and concepts have to be defined. The first is the definition of waves.

One definition of a traveling wave is "a transfer of energy without the transfer of matter." An example of this would be if two people were holding a jump rope fairly taut. If one person began moving the string back and forth, energy would travel down the rope to the other person but the rope itself would not be transferred (Lapp). This applies to music because what we hear constantly are sound waves when they reach our ear.

There are two types of waves that will be discussed: Transverse and Longitudinal waves. Transverse waves are easier to visualize because they look like a wave of the ocean or the jump rope in the previous example. A transverse wave is one in which "the particles of the disturbed medium move in a direction perpendicular to the wave velocity." (Serway)

Alternatively, longitudinal waves are defined as having "the elements of the medium undergo displacements parallel to the direction of wave motion." (Serway) This type of wave can be seen with a stretched slinky. By compressing the slinky on one end, areas of compression and rarefaction are formed along the length of the slinky (Serway). The basis of sound has to do with vibration. Compression and rarefaction are used to express the density of the air molecules. An example that the College Physics textbook uses is with a tuning fork. As shown in the picture, compression is an area with high density and rarefaction is an area with decreased density. (Serway).

Other terms that need to be defined are frequency, wavelength, amplitude and period.
Frequency \( f \equiv \frac{1}{T} \), which is measured in Hertz, is measured in cycles per second (s\(^{-1}\)). Period \( T \) is measured in seconds as the time per cycle. Amplitude \( A \) is the greatest distance that an object moves from the equilibrium point. Wavelength \( \lambda \) is "the distance between two successive points that behave identically." (Serway) depends upon the medium through which the wave is traveling and its frequency. (Loy).

To demonstrate the relationship between wave speed and wavelength and frequency, we will use the following equation:

\[
\text{wave speed } v = \frac{\Delta x}{\Delta t}
\]

Since \( \lambda \) is a measure of wavelength, \( \Delta x \) can be replaced by \( \lambda \) and \( \Delta t \) can be replaced by \( T \) which stands for period or time to complete a cycle.

\[
v = \frac{\lambda}{T}
\]

By replacing \( \frac{1}{T} \) with \( f \) we get the equation for wave speed:

\[
v = f \lambda
\]

(Serway)

The equation for the speed of waves on strings is:

\[
\text{wave speed } v = \sqrt{\frac{F}{\mu}}
\]

\( F \) is the tension in the string and \( \mu \) is the mass of the string per unit length.

By changing the tension in the string \( F \) one can tune the string to a particular frequency. (Serway)

The speed of sound can also be measured. In a fluid and gas, the speed of sound is:

\[
v = \sqrt{\frac{B}{\rho}}
\]

where \( B \) is the bulk modulus which is "the response of a substance to uniform squeezing" and \( \rho \) is the density. (Serway)

Another form of this equation is called the speed of a longitudinal wave is a solid rod:

\[
v = \sqrt{\frac{E}{\rho}}
\]

(Serway)

Constructive interference occurs when the crest of one wave passes through another. This also means that they are in phase with each other.
Destructive interference occurs when two waves are out of phase and cancel each other out when they overlap.

Beats occur when two waves vibrate in and out of phase with each other creating "an alternation in loudness." (Serway) In the picture above the beats occur where the waves interact. "Sour notes" are notes that have frequencies close to each other, which create more beats. (Serway)

"A node occurs where the two traveling waves always have the same magnitude of displacement but the opposite sign, so the net displacement is zero at that point." (Serway).

An antinode is where the string has the greatest amplitude and is located between two nodes. (Serway)

\[ f_i = \frac{v}{\lambda_i} = \frac{v}{2L} \]

In the previous equation \( L \) is the length of the string. Since we know \( v = \sqrt{(F/\mu)} \) then we can write \( f_i = 1/2L(\sqrt{(F/\mu)}) \)

A harmonic is a "multiple of the fundamental frequency of a vibrating object." (Loy) The 1st harmonic has the same wavelength as the string or vibrating and the second is half of the wavelength as the first and so on. Each harmonic can be determined by the number of node-antinode pairs and each frequency is a multiple of the first harmonic. Overtones are not necessarily harmonics but any resonating frequency (Overtones and Harmonics). The first overtone of a string would be the second harmonic.
There are various musical scales used throughout the world. The most common are the Western scales which include the major scale and three minor scales.

**History of Instruments**

One of the oldest instruments found to be playable is a nine-thousand year-old bone flute which was found in Jiahu, China. After many tests such as carbon-14 dating, United States Chemist Garman Harbottle and Jiahu researchers were able to date one flute to nine thousand years-old. (Genzer)

By 1700, the first piano had been built by Bartolomeo Cristofori who was an instrument maker for the prince of Tuscany. (4) What made the piano different from its predecessors was its ability to produce soft and loud sounds, hence the original name, piano et forte, which is Italian for “soft and loud”. Before the piano, there were harpsichords though they could not vary the volume therefore the need of the alternating intensities in volume initiated the invention of the piano. (Patrikis)

The way the piano works is it has hammers that hit the strings when a key is pressed on the keyboard, thus vibrating the string to produce a tone. A perfectly detailed description of the function of Cristofori’s piano is from the publication, Piano Roles.

“Action of the Cristofori piano in the Musical Instrument Museum, Leipzig. Depressing the key raises the jack to push up the lip under the intermediate lever, the left end of which touches the hammer shank, pivoted at the left. The lever pushes the hammer shank hard enough to send the hammer flying to the string. As the key rises, the spring on the jack (under the key) and the key’s motion combine to move the jack sideways so that it misses (“escapes”) the lip’s return to rest. When the key is released, the spring returns
the jack to its position under the lip. The check catches the hammer as it falls back from the string, releasing it when the key is released. The right end of the key as it rises pushes up the damper from the string.” (Patrikis)

**MIM tour**

Recently, the Musical Instrument Museum was opened in Phoenix. It was a really great experience to be able to tour it. There were so many instruments from around the world, hundreds of years old. There were many incredible exhibits, especially the guitar. They featured a wide array of guitars throughout the centuries.

Once you make your way upstairs, you put on the headphones that they gave you and walk from country to country as music from that are streams into your ears. They display instruments from that country. We started in Africa and right away I noticed many percussion instruments. There were many drums. In the United States, they show several all the instruments and styles of music which led to the diversity of American music. The percussion that was popular in Africa was brought in with the blues style. It was incredible to be able to trace the lines of music which led to popular music of today.

The similarities between the instruments of the countries were remarkable. There was so much to see and learn and listen to through the tour. It is a tour worth seeing twice.

Below is a Strothiol from Paris, France and it is a horn fiddle.

![Image of a Strothiol](image)

**Interview**

I had the opportunity to interview a professional musician and discover her line of work and why she chose that career path. Her name is Katrina King and she is the Principal Flutist in the Symphony of the Southwest Orchestra. She first began playing the flute when she was in fourth grade when the band teacher at her elementary school allowed her to try the flute. When she put her lips to the mouthpiece, she produced a sound and she knew that was the instrument for her. She participated in her school bands but did not receive lessons until the age of 16.

For college, she attended Grand Canyon University and earned Bachelors Degree in Music Education. She was unhappy with the music program at the school but learned a lot during private lessons from Joe Corral, a flutist of the Phoenix Symphony Orchestra.
About 10 years ago, she saw an opening in the Symphony of the Southwest for a flutist and saw the opportunity to audition. There were fifteen who auditioned and of all of them she was chosen to join the orchestra.

Her favorite composer is Claude Debussy because of his tendency to include flute solos in his pieces. She is looking forward to performing *Prelude to the Afternoon of a Faun* at an upcoming performance, in which she has a solo.

She is currently certified to teach in schools but enjoys her schedule of teaching privately three days a week and performing with different groups for private gatherings. (Katrina King)

She seems to really enjoy her career and has a supportive and kind personality that is ideal for a private instructor.
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